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Unsymmetrical Ferrocenylethylamine-Derived Monophosphoramidites: Highly Efficient Chiral Ligands for Rh-Catalyzed Enantioselective Hydrogenation of Enamides and α-Dehydroamino Acid Derivatives

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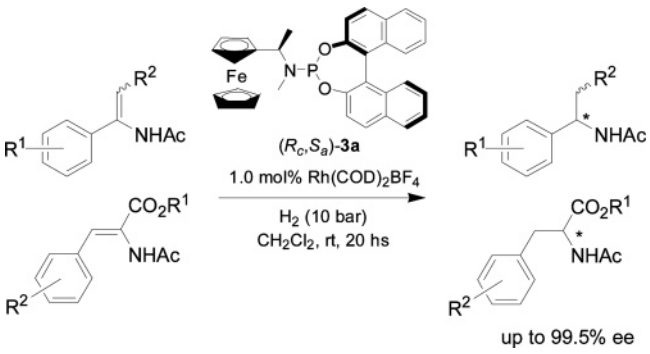

A new family of unsymmetrical ferrocenylethylamine-derived monophosphoramidites were synthesized and successfully applied in the Rh-catalyzed enantioselective hydrogenation of a range of enamides and α-dehydroamino acid esters, and ee values of up to 99.5% were obtained for both types of substrate. These results suggest that unsymmetrical amine-derived monophosphoramidites can also exhibit excellent enantioselectivity for a broad range of substrates, comparable to or higher than those of the most efficient symmetrical amine-derived monophosphoramidites reported thus far.

Asymmetric hydrogenations catalyzed by chiral metal−ligand complexes are among the most powerful tools for obtaining enantiomerically enriched compounds.[1] Despite the encouraging performance of many bidentate P-chelate ligands, the past few years have witnessed a renewed interest in the development of chiral monodentate phosphorus-containing ligands for use in rhodium-catalyzed asymmetric hydrogenation reactions. This resurgence in monodentate ligands is due to the ready accessibility of a range of diverse ligand structures, and their often lower cost when compared to bidentate ligands. Following the pioneering studies from the groups of Pringle,[2a] Reetz,[2b] and Feringa[2c] and more recently Chan[2d] and Zhou,[2e] a large number of chiral monodentate phosphonite, phosphite, and phosphoramidite ligands have been found to induce excellent enantioselectivities in rhodium-catalyzed asymmetric hydrogenation reactions, comparable to or exceeding those obtained with bidentate ligands.[3] Among the chiral monodentate phosphorus ligands developed to date, MonoPhos (**1**), the simplest member of the monodentate phosphoramidites based on axially chiral 2,2′-binaphthol, has held an especially important position.[4] In addition to exhibiting high efficiency in the rhodium-catalyzed hydrogenation of α-dehydroamino acids and esters, aromatic enamides, and itaconic acid derivatives, the MonoPhos (**1**) ligand architecture can be readily modified to optimize the hydrogenation of substrates that do not give good results with Monophos itself. Structural modification of the MonoPhos backbone can be carried out either by introducing substituents onto the binaphthyl moiety or by replacing the dimethylamino group with other C_2-symmetric amines. However, introduction of substituents onto the binaphthyl moiety of MonoPhos has usually resulted in diminished enantioselectivities and reaction rates. In contrast, replacement of the dimethylamino group with other C_2-symmetrical amines has proven to be more successful. For example, in the Rh-catalyzed enantioselective hydrogenation of enamides, good enantioselectivity (96% ee) was obtained with

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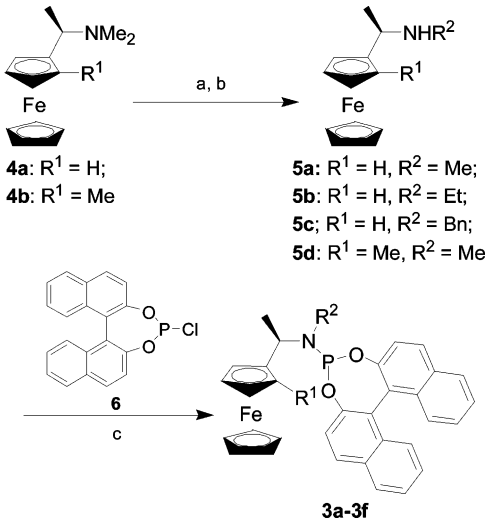
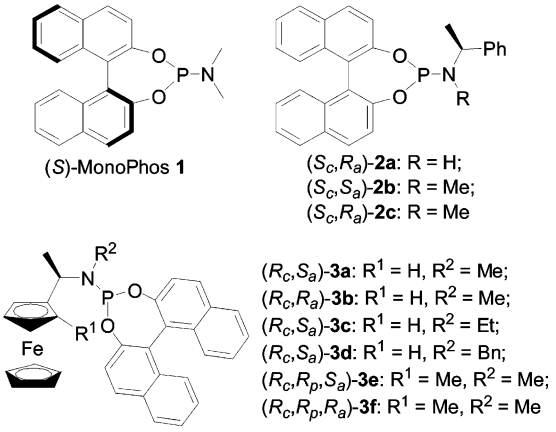
SCHEME 1. Synthesis of Ferrocenylethylamine-Derived Monophosphoramidites 3a−f[a]



[a] Reagents and conditions: (a) MeI, acetone, 0 °C to room temperature; (b) R^2NH_2, MeOH or CH_3CN, room temperature; (c) **6**, Et_3N, toluene, 0 °C to room temperature.

the use of MonoPhos only when the reaction was performed at low temperature (−20 °C).[5] Simply by replacing the dimethylamino group of MonoPhos with a diethylamino group, the enantioselectivity was increased to 99.6% ee at a higher temperature (5 °C).[2e] When the dimethylamino group of MonoPhos was replaced by a piperidyl or morpholine moiety, the enantioselectivities for the hydrogenation of a broad range of substrates could also be increased.[6] Interestingly, replacement of the dimethylamino group with an unsymmetrical amino moiety has not been investigated as thoroughly, and has usually resulted in dramatically diminished enantioselectivity.[7] To the best of our knowledge, with the exception of a recent report showing that α-phenylethylamine-derived monophosphoramidite **2a** displayed excellent enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of *β*-dehydroamino acid esters,[8] few monodentate phosphoramidites with unsymmetrical amino groups have exhibited high enantioselectivities in catalytic asymmetric hydrogenation.

Prompted by our recent success in the development of unsymmetrical ligands for asymmetric catalysis,[9] we initiated a study of the synthesis of a series of monodentate phosphoramidites derived from unsymmetrical amines, and investigated their efficiency in Rh-catalyzed asymmetric hydrogenation. Herein, we report the results of this study, and describe the development of α-ferrocenylethylamine-derived monophosphoramidites **3**. We demonstrate that unsymmetrical amine derived monophosphoramidites are also able to exhibit excellent enantioselectivities for a broad range of substrates, including α-dehydroamino acids esters and aromatic enamides. Furthermore, the hydrogenation reaction conditions used in this study are much milder than those typically reported.



The synthesis of the monodentate ligands **3** is straightforward as outlined in Scheme 1. α-Ferrocenylethylamines **5** can be prepared from the corresponding *N*,*N*-dimethylamino precursor **4** through a two-step transformation in high yields and with retention of configuration at the stereogenic carbon center.[10] The BINOL-derived chlorophosphite **6** was obtained in quantitative yield by heating (*S*)- or (*R*)-BINOL in neat PCl_3 at reflux, evaporation of excess reagents, azeotropic distillation of the residue with toluene, and finally recrystallization from *n*-hexane.[11] Simple treatment of the chlorophosphite **6** with a series of α-ferrocenylethylamines **5** in toluene at 0 to 25 °C in the presence of triethylamine gave rise to the monophosphoramidite ligands **3** in good to excellent yields. The resulting monophosphoramidites **3** are stable and can be kept under Ar atmosphere for extended periods.

With these ferrocenylethylamine-derived monophosphoramidites **3** in hand, we next proceeded to test their efficiency in Rh-catalyzed asymmetric hydrogenation. In the first set of experiments, *N*-(1-phenylethenyl)acetamide **7a** was used as a test substrate. Hydrogenation was conducted at room temperature under a H_2 pressure of 10 bar in the presence of 1 mol % of catalyst prepared in situ from $Rh(COD)_2BF_4$ and 2.2 mol % of chiral ligand, and the results are summarized in Table 1. As a comparison, α-phenylethylamine-derived monophosphoramidites **2b** and **2c** were also evaluated in this test reaction. Rh/(S_c,S_a)-**2b** complex showed no catalytic activity in this reaction (entry 1), while its distereoisomer (S_c,R_a)-**2c** exhibited good enantioselective induction, giving the hydrogenation product in 93% ee (entry 2). Use of the corresponding ferrocenylethylamine-derived ligand (R_c,S_a)-**3a** dramatically improved the enantioselectivity and gave the product in 99%

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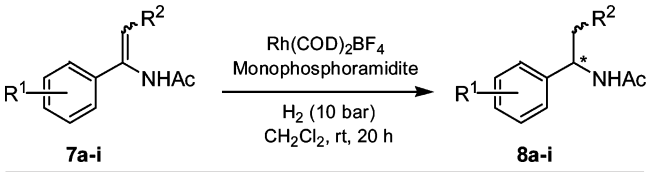
TABLE 1. Rh-Catalyzed Asymmetric Hydrogenation of Enamides 7a−i[a]



7a-i **8a-i**

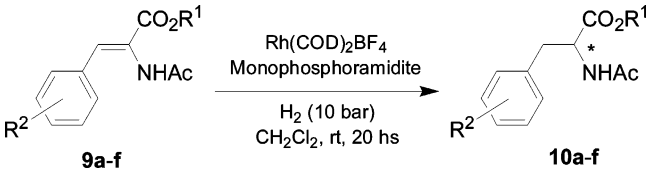
entry	ligand	substrate	R^1	R^2	solvent	conv (%)	ee (%)[b] (config.)[c]
1	**2b**	**7a**	H	H	CH_2Cl_2	N.R.	N.R.
2	**2c**	**7a**	H	H	CH_2Cl_2	100	93 (*S*)
3	**3a**	**7a**	H	H	CH_2Cl_2	100	99 (*R*)
4	**3b**	**7a**	H	H	CH_2Cl_2	100	86 (*S*)
5	**3c**	**7a**	H	H	CH_2Cl_2	100	53 (*R*)
6	**3d**	**7a**	H	H	CH_2Cl_2	N.R.	N.R.
7	**3e**	**7a**	H	H	CH_2Cl_2	100	92 (*R*)
8	**3f**	**7a**	H	H	CH_2Cl_2	100	15 (*S*)
9	**3b**	**7a**	H	H	MeOH	78	99 (*R*)
10	**3b**	**7a**	H	H	EtOAc	95	>99 (*R*)
11	**3b**	**7a**	H	H	toluene	100	63 (*R*)
12	**3b**	**7b**	4-CF_3	H	CH_2Cl_2	100	99 (*R*)
13	**3b**	**7c**	4-Cl	H	CH_2Cl_2	100	99 (*R*)
14	**3b**	**7d**	4-Br	H	CH_2Cl_2	100	99 (*R*)
15	**3b**	**7e**	4-Me	H	CH_2Cl_2	100	>99 (*R*)
16	**3b**	**7f**	4-OMe	H	CH_2Cl_2	100	98 (*R*)
17	**3b**	**7g**	3-OMe	H	CH_2Cl_2	100	**99.5** (*R*)
18	**3b**	**7h**	H	Me	CH_2Cl_2	100	94 (*R*)
19	**3b**	**7i**	H	Et	CH_2Cl_2	100	96 (*R*)

[a] Reactions were performed with 0.5 mmol of substrate and 1 mol % of catalyst (L/Rh = 2.2/1) in 3 mL of solvent at room temperature and with an H_2 pressure of 10 bar. [b] Enantiomeric excesses were determined by GC, using a Chiral Select 1000 capillary (0.25 mm × 30 m) column. [c] Determined by comparing the optical rotations with reported value.

ee, which is comparable to the best results obtained by those monophosphoramidites containing a symmetrical amine moiety, but under much milder conditions (entry 3). However, complex (R_c,R_a)-**3b** containing a (R_a)-binaphthyl moiety only gave the product in 86% ee and with opposite absolute configuration (entry 4). These results indicated that the binaphthyl moiety in the ligand controls the chirality of the hydrogenation product and the matched stereogenic elements are (R_c)-central and (S_a)-axial absolute configurations.

We next investigated the effect of amine moiety on the reaction and found that the substitutent in the amine had a dramatic influence on both the enantioselectivity and catalytic activity. The results indicated that the rhodium complex of a ligand containing a bulkier substituent in the amino moiety tended to show lower catalytic activity and provided lower levels of enantioselectivity (entries 3, 5, and 6). Thus, replacing the methyl group of (R_c,S_a)-**3a** with an ethyl group dramatically decreased the enantioselectivity to 53% ee (entry 5). The rhodium catalyst derived from ligand **3d** containing a benzyl group surprisingly showed no catalytic activity in the reaction (entry 6). The presence of planar chirality in the ferrocene ring did not improve the enantioselectivity, and an ee of 92% was obtained by the use of (R_c,R_p,S_a)-**3e** (entries 7 and 8). The nature of the solvent had a significant effect, and CH_2Cl_2 proved to be the best solvent for the reaction (entries 9−11). Under the optimized conditions, the hydrogenation of a variety of aromatic enamides with ligand (R_c,S_a)-**3a** was then performed. Excellent enantioselectivities were obtained in each case regardless of the electronic properties of the aryl group on the substrate (entries 12−17), and the best result was obtained for *N*-[1-(3-methoxy)-phenylethyl]acetamide **7g** (99.5% ee) (entry 17). Furthermore,

TABLE 2. Rh-Catalyzed Asymmetric Hydrogenation of α-Dehydroamino Acid Esters 9[a]



9a-f **10a-f**

entry	ligand	substrate	R^1	R^2	solvent	ee (%)[b] (config.)[c]
1	**3a**	**9a**	Me	H	CH_2Cl_2	98 (*R*)
2	**3b**	**9a**	Me	H	CH_2Cl_2	91 (*S*)
3	**3c**	**9a**	Me	H	CH_2Cl_2	85 (*R*)
4	**3d**	**9a**	Me	H	CH_2Cl_2	60 (*R*)
5	**3e**	**9a**	Me	H	CH_2Cl_2	98 (*S*)
6	**3f**	**9a**	Me	H	CH_2Cl_2	70 (*R*)
7	**3b**	**9a**	Me	H	MeOH	97 (*R*)
8	**3b**	**9a**	Me	H	EtOAc	94 (*R*)
9	**3b**	**9b**	Me	4-OMe	CH_2Cl_2	>99 (*R*)
10	**3b**	**9c**	Me	2-OMe	CH_2Cl_2	**99.5** (*R*)
11	**3b**	**9d**	Me	4-Cl	CH_2Cl_2	99 (*R*)
12	**3b**	**9e**	Me	2-Cl	CH_2Cl_2	97 (*R*)
13	**3b**	**9f**	Et	H	CH_2Cl_2	>99 (*R*)

[a] Reactions were performed with 0.5 mmol of substrate and 1 mol % of catalyst (L/Rh = 2.2/1) in 3 mL of solvent at room temperature and with an H_2 pressure of 10 bar. Full conversions were achieved in all cases. [b] Enantiomeric excesses were determined by GC, using a CP-Chiralsil-L-Val capillary (0.25 mm × 30 m) column. [c] Determined by comparing the optical rotations with reported value.

Rh/(R_c,S_a)-**3a** complex also exhibited high efficiency in the hydrogenation of *E*/*Z* mixtures of β-substituted enamides **7h**−**i**, giving the products with up to 96% ee (entries 18 and 19), thereby demonstrating the wide scope of the present Rh/monophosphoramidite catalyst in the hydrogenation of enamides.

To further show the synthetic utility of these unsymmetrical ferrocenylethylamine-derived monophosphoramidites, we then investigated their efficiency in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters **9**. Remarkable enantioselectivities and catalytic activities were also observed in this reaction, and the results were summarized in Table 2. The most efficient catalyst was prepared in situ from Rh(COD)$_2$BF$_4$ and (R_c,S_a)-**3a** or (R_c,R_p,S_a)-**3e**, which provided the products in 98% ee under standard conditions employed in the hydrogenation of enamides **7** (entries 1 and 5). The reaction was weakly solvent dependent and proceeded smoothly in all of the solvents tested to give the product in good enantioselectivities (entries 1, 7, and 8), with the best solvent being CH_2Cl_2 (entry 1). The rhodium complex of the ligand (R_c,S_a)-**3a** was particularly effective for the hydrogenation of α-dehydroamino acid esters. All of the substrates were hydrogenated in very high enantioselectivities (entries 9−13), and the best results were obtained in the hydrogenation of substrate **9c**, which provided ee values of up to 99.5% (entry 10).

Although the precise mode of stereoinduction for these ferrocenylethylamine-derived monophosphoramidites is not clear, the presence of additional central chirality should have some impact on the enantiodiscrimination step. Compared with C_2-symmetrical monophosphoramidites such as Monophos (**1**), chiral ferrocenylethylamine-derived monophosphoramidite (R_c,S_a)-**3a** appears to provide a more effective chiral environment around the Rh atom due to the presence of additional central chirality, resulting in improved enantioselectivities. The mismatched central and axial chiralities in (R_c,R_a)-**3b** render the

chiral environment around the Rh atom less effective, resulting in decreased enantioselectivities. The replacement of R^2 groups on the nitrogen atom of ligands **3** from methyl (**3a**) to bulkier ethyl (**3c**) and benzyl (**3d**) or by the introduction of a methyl group (R^1) onto the ferrocenyl ring (**3e** and **3f**) led to decreased enantioselectivities, which is possibly the result of steric effects as reported by other groups.[3g,3t]

In summary, we have explored a new family of unsymmetrical amine-derived monodentate phosphoramidites and investigated their efficacy in Rh-catalyzed asymmetric hydrogenation. Simply by changing the dimethylamino group of Monophos (**1**) into an unsymmetrical ferrocenylethylamine moiety, the selectivities in the hydrogenation of a broad range of substrates could be increased dramatically. Thus, *N*-methyl ferrocenylethamine-derived monophosphoramidite **3a** is broadly applicable and demonstrates extremely high selectivity in the catalytic hydrogenation of both enamides and α-dehydroamino acid esters, comparable to or exceeding those reached by monophosphoramidites containing a symmetrical amine moiety reported thus far. Furthermore, the air-stable ligands can be readily prepared in three steps from readily available *N*,*N*-dimethyl-1-ferrocenylethylamine and BINOL, which offers the benefits of simple procedures and low cost. Further applications of these ligands are in progress.

Experimental Section

General Procedure for the Synthesis of Chiral Ferrocenylethylamine-Derived Monophosphoramidites. To a stirred solution of ferrocenylethylamine (**5a**−**d**) (10 mmol) and triethylamine (50 mmol) in 100 mL of toluene was added dropwise a solution of BINOL-based chlorophosphite (3.8 g, 11 mmol) in 30 mL of toluene at 0 °C under a N_2 atmosphere over 30 min. The resulting mixture was allowed to stand at room temperature overnight. The precipitate was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography to give the crude product, which can be further purified by recrystallization from hexane/dichloromethane.

***N*-Methyl-*N*-[(*R*)-1-ferrocenylethyl]-(*S*)-1,1′-bi-2-naphthyl phosphoramidite (R_c,S_a)-3a:** orange solid; $[\alpha]^{20}_D$ +17.5 (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, J = 6.8 Hz, 3H), 2.00 (d, J = 5.6 Hz, 3H), 4.01 (s, 4H), 4.13−4.15 (m, 2H), 4.22 (s, 1H), 4.52 (s, 1H), 4.69−4.73 (q, 1H), 7.13−7.97 (m, 12H); ^{13}C NMR δ 18.4, 26.7, 52.2, 52.6, 67.7, 67.9, 68.8, 69.4, 69.8, 77.4, 77.7, 78.0, 89.9, 122.7, 123.1, 124.6, 125.2, 125.4, 126.7, 127.5, 127.7, 128.8, 129.0, 130.4, 130.9, 131.2, 132.0, 133.2, 133.5, 150.2, 150.9; ^{31}P NMR δ 148.0; HRMS(*m*/*z*) calcd for $C_{33}H_{29}FeNO_2P$ + H 558.1279, found 558.1254.

General Procedure for Asymmetric Hydrogenation and Determination of Enantiomeric Excesses. In a nitrogen-filled glovebox, a stainless steel autoclave was charged with $Rh(COD)_2BF_4$ (2.0 mg, 0.5×10^{-2} mmol) and monophosphoramidite ligand **3** (1.1×10^{-2} mmol) in 1.5 mL of a degassed solvent. After the solution was stirred for 10 min at room temperature, the substrate (0.5 mmol) in 1.5 mL of the same solvent was added to the reaction mixture. Hydrogenation was then performed under 10 bar of H_2 pressure for 20 h at room temperature. The reaction mixture was passed through a short silica gel column to remove the catalyst. After evaporation of the solvent, the crude reaction mixture was analyzed by chiral GC to determine the conversion and enantiomeric excesses.

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Supporting Information Available: Experimental procedure, characterization data, and spectroscopic data for all ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

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