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A versatile synthesis of phosphine–aminophosphine ligands for asymmetric catalysis

Neil W. Boaz,* James A. Ponasik, Jr. and Shannon E. Large

Research Laboratories, Eastman Chemical Company, PO Box 1972, Kingsport, TN 37662, USA

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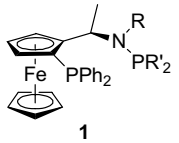
Abstract—A new and versatile synthesis of phosphine–aminophosphine ligands allows the incorporation of a wide range of nitrogen and phosphorus substituents into these ligands, several of which exhibit improved properties for rhodium-catalyzed asymmetric hydrogenation reactions. This synthesis also allows the preparation of mixed phosphine–phosphoramidite species.

1. Introduction

Asymmetric catalysis is a powerful technology for generating single enantiomer materials. Of the asymmetric catalytic reactions, asymmetric hydrogenation is perhaps the most powerful, as it utilizes an inexpensive reagent (hydrogen) with an often relatively inexpensive unsaturated substrate to afford a high value single enantiomer product. The catalysis is usually performed with precious metals complexed to chiral ligands, which enforce the enantioselectivity. There have been a large number of chiral ligands prepared for asymmetric catalysis.[1] In general, the most easily designed and most abundant ligands are C_2-symmetrical bis-phosphines due to their stereochemical redundancy. Significantly lesser in number are other arrangements, such as bidentate bis-aminophosphines,[2] bis-phosphites,[3] bis-phosphinites,[4] bis-phosphonites,[5] and mixed ligands such as phosphine-phosphite,[6] aminophosphine-phosphinite,[7] phosphine-phosphonite,[8] phosphine-phosphoramidite,[9] and phosphonite-phosphite[10] systems.

Perhaps the most noteworthy of the nonsymmetric chiral bidentate ligands possessing a ferrocenyl backbone, with a number of highly enantioselective species have found prominence.[11] Among these is a series of phosphinoferrocenyl-aminophosphine ligands that have recently been reported as useful species for asymmetric catalysis.[12] The rhodium complexes of these BoPhoz™ ligands **1** exhibit high activities and enantioselectivities for the asymmetric hydrogenation of a wide variety of dehydroamino acids, itaconates, and α-ketoesters. In addition, these species demonstrate outstanding air stability and are designed to avoid any extreme conditions in their preparation. Thus, this ligand family combines a number of characteristics that make them uniquely attractive for asymmetric catalysis.



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2. Results and discussion

It was noted at an early stage that a limited variation of the substituents on the nitrogen and phosphorus atoms of the aminophosphine portion of **1** resulted in significant modulation of the reactivity characteristics of these ligands. Unfortunately, a wider nitrogen and phosphorus substituent variation was not viable using the original synthesis. Variation of the nitrogen substituent was limited by the steric hindrance around the final intermediate **2**, such that when R was larger than *n*-propyl, the final reaction with a chlorodiarylphosphine failed, affording none of the desired product **1** under the standard reaction conditions. Stronger conditions led only to reagent decomposition. Variation of the phosphorus substituents was more feasible, although there are few commercially available chlorophosphines, and the preparation of these types of species is tedious.

* Corresponding author. Tel.: +1 423 229 8105; fax: +1 423 224 7582; e-mail: nwboaz@eastman.com

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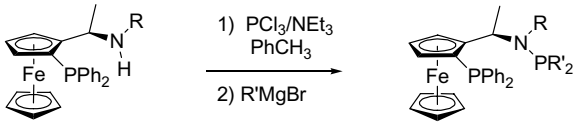
It was apparent that a modification of the synthetic route was required to allow the preparation of a wider variety of ligands **1**. The most attractive strategy involved exploiting the steric hindrance of **2** as an advantage. This was achieved by utilizing the small electrophile phosphorus trichloride in place of the larger chlorodiphenylphosphine (or other disubstituted chlorophosphine). Under normal circumstances, a statistical mixture of compounds with one, two, or three amines on the phosphorus would be anticipated. However, the steric bulk of **2** is such that with a 1:1 mixture of PCl_3 and **2** only the monoadduct was formed, with no indication of diaminochlorophosphine (or products therefrom) or triaminophosphine present. Subsequent reaction of the dichloroaminophosphine with a nucleophile such as a Grignard reagent can afford the desired species **1**. The viability of this synthesis was initially examined for the preparation of the parent species **1a** where R is methyl and R′ is phenyl. The reaction was performed under moderate conditions (0 °C to ambient temperature) and afforded the desired **1a** in 83% isolated yield.[13] With this proof of principle, a wide variety of ligands were prepared with numerous substituents on both the nitrogen and phosphorus (Table 1). The latitude of this procedure is exemplified by the fact that even the *N*-*tert*-butyl species **1d** can be prepared, albeit in moderate yield. The main impurities observed in these reactions were aryl coupling compounds from the aryl Grignard reagents. These were removed and the ligands purified by either chromatography or crystallization.

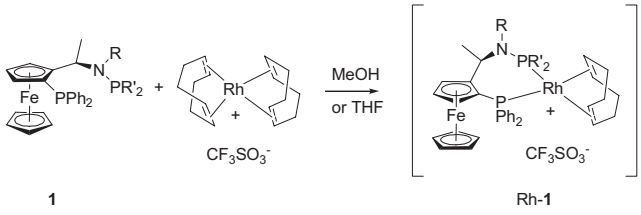
Table 1. Ligands prepared



2 **1**

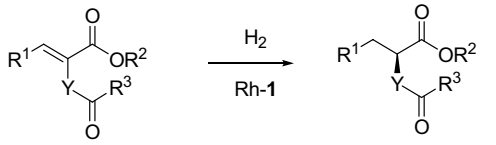
Compound	R	R′	Yield (%)
a	Me	Ph	83
b	*i*-Pr	Ph	67
c	Neopentyl	Ph	13
d	*t*-Bu	Ph	48
e	Ph	Ph	77
f	$PhCH_2$	Ph	64
g	(*S*)-Phenethyl	Ph	75
h	(*R*)-Phenethyl	Ph	83
i	Me	4-$MeOC_6H_4$	73
j	Me	4-MeC_6H_4	52
k	Me	3,5-$Me_2C_6H_3$	61
m	Me	4-FC_6H_4	81
n	Me	4-ClC_6H_4	35
o	Me	3-FC_6H_4	83
p	Me	3,4-$F_2C_6H_3$	84
q	Me	3,4-$Cl_2C_6H_3$	85
r	Me	3,5-$F_2C_6H_3$	77
s	Me	3,5-$Cl_2C_6H_3$	58

Rhodium complexes of these new ligands were prepared as indicated below (Fig. 1) and examined in situ for the asymmetric hydrogenation of a variety of substrates (Fig. 2).



1 Rh-**1**

Figure 1. Preparation of rhodium complex of **1**.



3 **4**

a: R^1 = Ph, R^2 = R^3 = Me, Y = NH
b: R^1 = Ph, R^2 =H, R^3 = Me, Y = NH
c: R^1 = R^2 = H, R^3 = Me, Y = NH
d: R^1 = 2-naphthyl, R^2 = R^3 = Me, Y = NH
e: R1 = cyclopropyl, R^2 = Bn, R^3 = Boc,Y = NH
f: R^1 = H, R^2 = Me, R^3 = OMe, Y = CH_2
g: R^1 = R^2 = H, R^3 = OH, Y = CH_2

Figure 2. Asymmetric hydrogenation reactions.

As indicated in Table 2, replacing the R group of **1** with a substituent larger than methyl had in general a negative effect on the enantioselectivity of the asymmetric hydrogenation of a variety of dehydroamino acids and itaconates. These results validate the previous limited study, which indicated that the *N*-methyl group was superior to other nitrogen substituents such as ethyl or *n*-propyl.[12] The inclusion of a second center of asymmetry in the substituent did not overcome the deleterious effect of the added bulk, although moderate match and mis-match effects were observed (ligands **1g** and **1h**).

Table 2. Nitrogen substituent effects on the asymmetric hydrogenations of substrates **3** with Rh-**1**[a]

Ligand	% ee						
	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
1a	99.1	99.4	96.1	98.1	98.6	94.0	97.4
1b	91.8	17.4	68.3	90.0	32.9	50.2	90.9
1c	70.7	81.2	93.6	47.6	26.8	5.5	16.4
1d	60.4	75.6	93.4	57.0	38.4	15.8	21.6
1e	89.8	94.0	93.4	88.9	67.8	0.8	66.4
1f	88.3	93.4	13.6	86.3	70.6	44.0	83.3
1g	94.2	82.8	95.4	92.6	46.8	20.6	11.4
1h	73.0	86.0	79.6	70.9	19.4	28.6	21.7

[a] Hydrogenations were run at 0.1 M concentration in THF or methanol with 1 mol % catalyst at 10 psig for 6 h.

Variation of the phosphorus substituents resulted in a number of ligands that afforded very high enantioselectivities for the asymmetric hydrogenation of dehydroamino acids and itaconates (Table 3), in many cases matching and sometimes surpassing the parent ligand **1a**. The data indicate that electron-withdrawing groups

on the aromatic ring generally enhance the enantioselectivity, while electron-donating groups have a slightly negative effect. This may be due to an enhanced difference between a more electron-poor aminophosphine and the electron-rich ferrocenyl phosphine, perhaps resulting in more ordered and tighter substrate binding. This is particularly noteworthy for the itaconate substrates **3f** and **3g**, as a number of ligands with electron-withdrawing substituents afford higher enantioselectivities with these substrates than the parent **1a**. Indeed, the best overall ligand **1o** has 3-fluorophenyl substituents on the phosphine, and affords hydrogenation results (as the rhodium complex) that are comparable or superior to **1a**. This ligand provides 2-methylsuccinic acid in 99.0% ee, the best result obtained to date for this substrate using ligands **1**.

Table 3. Phosphorus substituent effects on the asymmetric hydrogenations of substrates **3** with Rh-**1**[a]

Ligand	% ee						
	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
1a	99.1	99.4	96.1	98.1	98.6	94.0	97.6
1i	97.8	98.3	94.0	96.7	98.1	92.2	94.1
1j	97.7	98.8	84.3	97.5	98.2	91.6	96.0
1k	98.2	82.9	50.2	97.9	95.3	96.2	98.9
1m	98.7	98.8	96.7	98.3	98.8	96.8	97.6
1n	98.7	99.0	95.6	98.5	98.4	93.3	97.5
1o	98.8	99.2	97.6	98.5	99.0	97.4	99.0
1p	99.0	97.2	94.8	98.5	99.4	94.2	98.4
1q	98.9	99.2	43.0	98.6	98.8	95.4	98.6
1r	98.8	99.1	15.2	98.6	99.2	94.3	98.6
1s	98.7	99.1	20.0	98.4	98.8	96.5	98.8

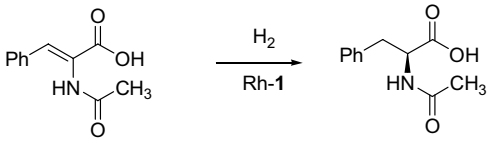
[a] Hydrogenations were run at 0.1 M concentration in THF or methanol with 1 mol % catalyst at 10 psig for 6 h.

The activity of homogeneous catalysts is of great practical consequence, as highly active species usually require less of the expensive catalyst. The rhodium complex of ligand **1a** is particularly highly active, which compounds its utility for asymmetric hydrogenation reactions.[12]

It was of interest to determine the activity of the rhodium complexes of these newly generated ligands **1**, in particular the ligands with varying phosphorus substituents, as they could provide insight into both steric and electronic effects (and in general afford hydrogenation products with high enantioselectivity). The turnover frequencies of these species were determined from their initial rates of hydrogenation of a test substrate, 2-acetamidocinnamic acid (**3b**).[12b] There was no obvious correlation of rate with either substituent electronic nature or steric constraints (Table 4). However, most of the rhodium complexes of these ligands are highly active for the asymmetric hydrogenation of **3b**, with only **1n** failing to crest a turnover frequency of 10,000 h^{-1}. Thus, any of these ligands will afford useful practical species for asymmetric hydrogenation.

The modified synthetic procedure outlined above also allows the use of other nucleophiles in place of Grignard reagents. In particular, phenols can be used as nucleophiles in the second step of the reaction (with triethylamine as base) to afford mixed phosphine–phosphoramidites **5**. A variety of species were prepared encompassing electron-donating and electron-withdrawing groups as well as auxiliary chirality as indicated in Figure 3.

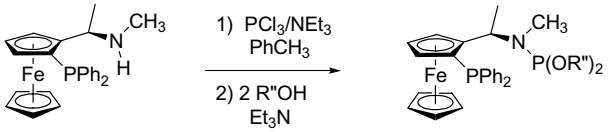
Table 4. Catalytic activities for the asymmetric hydrogenation of **3b** with Rh-**1**[a]



3b **4b**

Ligand	ee (%)	Conversion (%)	TOF (h^{-1})[c]
1a	98.8	99.6	49,900
1i	91.5	99.8	25,000
1j[c]	94.8	99.0	16,100
1k[c]	97.6	99.5	46,700
1m	98.6	99.8	42,000
1n	97.1	99.8	9,100
1o	99.2	99.9	27,900
1p	98.5	99.8	17,800
1q	99.0	99.8	20,600
1r	99.0	99.8	17,800
1s[b]	98.4	99.5	14,500

[a] Reactions run at 0.75 M concentration in methanol with 40 psig hydrogen at a S:C ratio of 3000:1 unless otherwise noted.
[b] The methodology for determining the turnover frequency is as described in Ref. 12b.
[c] Reaction run at a S:C ratio of 5000:1.



2 **5**

a: R" = Ph (79%)
b: R" = 4-MeOPh (65%)
c: R" = 4-CF_3Ph (55%)
d: R" = *R*-1,1'-Binaphthyl-2,2'-diyl (71%)
e: R" = *S*-1,1'-Binaphthyl-2,2'-diyl (51%)

Figure 3. Phosphine–phosphoramidite ligand preparation (isolated yields in parentheses).

Asymmetric hydrogenation results using these species are shown in Table 5, and indicate that the rhodium complexes of phosphine–phosphoramidites **5** afford high enantioselectivites in some cases, but are not nearly as general as the phosphine–aminophosphines **1**.

Of particular interest are the BINOL-substituted species **5d** and **5e** wherein the BINOL functionality spans both P–O valencies. Reports from other research groups concerning these species appeared concurrent with our investigations, although the ligands were prepared using slightly different methodologies.[9b–d] These reports indicate that species **5d** in particular affords high enantioselectivities for a variety of asymmetric hydrogenation reactions. Our work agrees with these reports, particularly for substrate **3b**, wherein the (*R*)-BINOL derivative

Table 5. Asymmetric hydrogenations of substrates **3** with Rh-**5**[a]

Ligand	% ee					
	3a	**3b**	**3c**	**3e**	**3f**	**3g**
5a	92.9	97.0	53.8	nr[b]	6.9	64.8
5b	95.2	98.2	92.6	54.2	7.8	63.6
5c	91.0	97.8	90.0	46.6	23.2	75.8
5d	99.1	99.9	67.1	nr[b]	35.6	95.7
5e	17.5	54.1	85.6	81.2	5.0	92.6

[a] Hydrogenations were run at 0.5 M concentration in THF or methanol with 1 mol % catalyst at 10 psig for 6 h.
[b] No hydrogenation was observed.

5d affords near enantiomeric purity. There is also a significant stereochemical match–mismatch effect with most substrates between the diastereomers. The high enantioselectivity generated from the rhodium complex of **5d** is likely due to the axial chirality of the BINOL and not just the cyclic nature of the phosphoramidite diol portion, as ligand prepared from the enantiomers of hydrobenzoin and diethyl tartrate afforded consistently poor enantioselectivities for asymmetric hydrogenations. The kinetics of the hydrogenations utilizing the rhodium complexes of **5d** and **5e** were examined with substrate **3b** as above, and indicated 5300 and 12,800 catalytic turnovers per hour, respectively, while maintaining exceedingly high enantioselectivity with **5d** (99.8% ee). Thus, the rhodium complexes of these ligands, although substantially slower than the best phosphine–aminophosphines **1**, show activities comparable to many other ligands.[12b] Unfortunately, the exceedingly high enantioselectivities with the rhodium complex of **5d** are not particularly broad, as the reactions with **3c** and **3f** gave poor results.

3. Conclusion

A new and general methodology has been developed to prepare a wide variety of phosphine–aminophosphine and phosphine–phosphoramidite ligands. Many of these species afford excellent results as rhodium catalysts for asymmetric hydrogenation reactions.

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13. A typical synthetic procedure is exemplified for the preparation of **1a**: Toluene (10 mL) was added to a 100-mL three-necked flask, which was cooled in ice to below 5 °C. Phosphorus trichloride (0.26 mL; 3.0 mmol; 1.0 equiv) was added followed by triethylamine (0.50 mL; 3.6 mmol; 1.2 equiv). (*R*)-*N*-Methyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]-ethylamine **2a** (1.26 g; 3.0 mmol) dissolved in 10 mL of toluene was added over about 5 min such that the temperature remained below 10 °C. The reaction mixture was allowed to warm to ambient temperature over 30 min and then stirred at ambient temperature for 2 h. The reaction mixture was cooled in ice to below 5 °C and a 3.0 M ethereal solution of phenylmagnesium bromide (3.5 mL; 10.5 mmol; 3.5 equiv) was added over ca. 10 min such that the temperature remained below 10 °C. The reaction mixture was allowed to warm to ambient temperature overnight to completely consume **2a** according to TLC analysis. The mixture was cooled in ice-water and saturated aqueous sodium bicarbonate solution (20 mL) added at a rate such that the temperature remained below 15 °C. The layers were separated, the aqueous solution was filtered to remove insolubles, and it was further extracted with ethyl acetate. The combined organic extracts were dried with sodium sulfate and concentrated. The crude product was filtered through a pad of neutral alumina and eluted with 1:9 ethyl acetate–heptane with 5% added triethylamine to afford 1.52 g (83%) of **1a**. ^{1}H NMR ($CDCl_3$) δ 7.65 (m, 2H); 7.4–7.0 (m, 14H); 6.82 (m, 4H); 5.006 (m, 1H); 4.502 (br s, 1H); 4.40 (m, 1H); 4.15 (m, 1H); 3.798 (s, 5H); 2.148 (d, 3H, J = 3.30 Hz); 1.471 (d, 3H, J = 6.87 Hz). ^{13}C NMR ($CDCl_3$) δ 142.4 (d, J_{C-P} = 9 Hz); 140.3 (d, J_{C-P} = 24 Hz); 140.0 (d, J_{C-P} = 10 Hz); 139.5 (d, J_{C-P} = 7 Hz); 135.9 (d, J_{C-P} = 22 Hz); 134.1 (d, J_{C-P} = 22 Hz); 132.3 (d, J_{C-P} = 17 Hz); 131.7 (d, J_{C-P} = 18 Hz); 129.3 (s); 128.8 (s); 128.1–127.2; 97.9 (dd, J_{C-P} = 14, 28 Hz); 75.7 (d, J_{C-P} = 14 Hz); 72.1 (d, J_{C-P} = 5 Hz); 70.5 (s); 69.9 (s); 69.8 (s); 58.4 (dd, J_{C-P} = 9, 39 Hz); 30.6 (d, J_{C-P} = 11 Hz); 18.5 (d, J_{C-P} = 6 Hz). ^{31}P NMR (CD_2Cl_2) δ 58.8 (d, J_{P-P} = 7.7 Hz); −25.3 (d, J_{P-P} = 7.7 Hz). Chiral HPLC (250 × 4.6 mm Chiralpak AD-H, 99:1 hexane–isopropanol, 1 mL/min, λ = 254 nm): t_R (*S*,*R*-**1a**) 10.4 min, t_R (*R*,*S*-**1a**) 11.6 min. HRMS *m*/*z* calcd for $C_{37}H_{35}FeNP_2$ (M^+) 611.15942, found 611.16429. $[\alpha]_D^{24} = -257$ (*c* 0.96, toluene).