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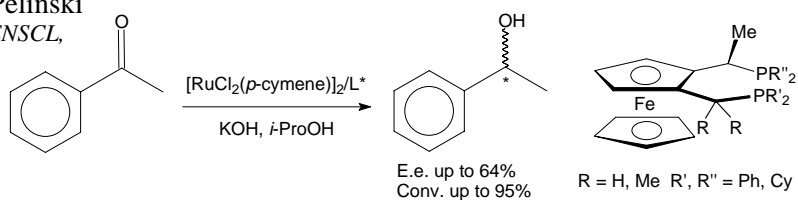
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Chiral ferrocenyl diphosphines for asymmetric transfer hydrogenation of acetophenone

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Chiral Ferrocenyl Diphosphines for Asymmetric Transfer Hydrogenation of Acetophenone

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Abstract— The synthesis of new optically pure ferrocenyl diphosphines have been realized from (*R*)-(+)-*N,N*-dimethylaminoethylferrocene. Particularly, dissymmetric ferrocenyl diphosphines have been synthesized. The diphosphines have been used as ligands in asymmetric transfer hydrogenation of acetophenone in the presence of Ru catalysts. © 2006 Elsevier Science. All rights reserved

Catalytic asymmetric hydrogenation of prochiral ketones to chiral alcohols using transition metal complexes has gained increasing interest during recent years.¹ In particular, ruthenium-catalyzed asymmetric transfer hydrogenation using 2-propanol under basic conditions presents the advantages of a low cost, ease of handling and high solubility of 2-propanol as hydrogen donor reagent.² Noyori developed an efficient and highly enantioselective ruthenium catalyst using diamines as chiral ligands.³ Other types of ligands such as amino alcohols,⁴ aminooxazolines,⁵ aminophosphines,⁶ diureas,⁷ and phosphine oxides⁸ have also been used with various levels of rates, yields and selectivities. In particular, only ferrocenyl ligands possessing oxazoline/phosphines,⁹ triphosphines,¹⁰ amino alcohols¹¹ imine/phosphines,¹² and diamines¹³ have been studied. Also, to our best knowledge, the involvement of ferrocenyl diphosphines has not been reported so far. Moreover, Genêt reported a series of dibromodiphosphinoruthenium catalysts ([RuP*₂Br₂], where P*=diphosphine) for transfer hydrogenation of ketones, achieving good conversion in short reaction times.¹⁴ However, only moderate enantioselectivities (7–52% ee) has been obtained.

We have had an ongoing interest in the synthesis and use of optically active ligands in asymmetric catalysis, especially ferrocenyl amino alcohols.¹⁵ Herein we present the synthesis of new ferrocenyl diphosphines **1–5** (Figure 1)

and the first results for asymmetric transfer hydrogenation of acetophenone catalyzed by Ru(II) complexes of these bidentate ligand system. Our initial efforts focused on screening a variety of ferrocenyl compounds in which chelating groups and stereogenic centers were varied in order to ascertain their effects on the reaction.

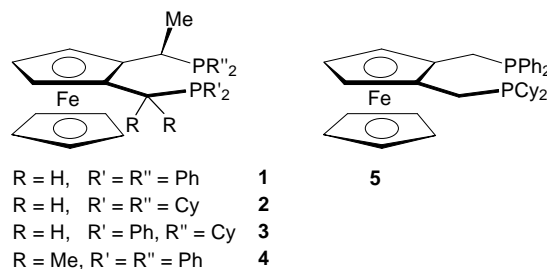
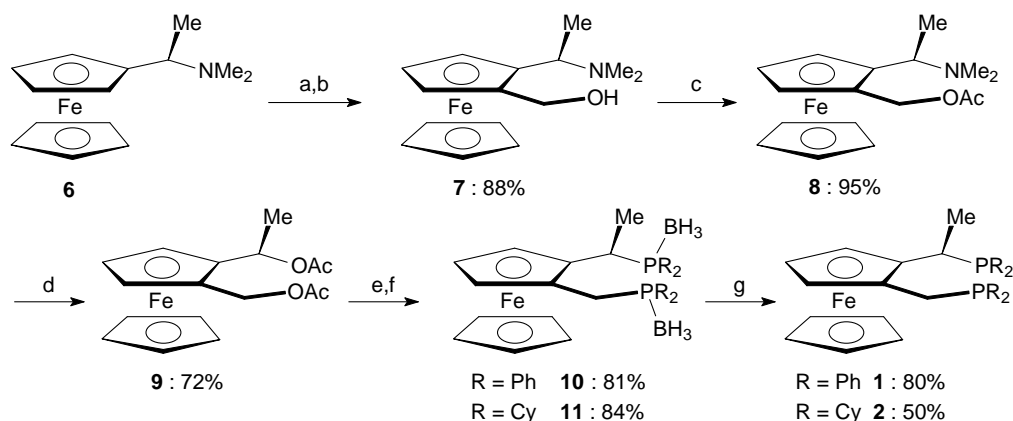


Figure 1.

Following a similar procedure as described by Fukuzawa,¹⁶ the ferrocenyl diphosphines **1** and **2** have been synthesized from (*R*)-*N,N*-dimethyl-1-ferrocenylethyl amine **6** (Scheme 1).¹⁷ Thus, the commercial ferrocenyl amine **6** has been converted to the amino alcohol **7** in two steps in a global yield of 88%. The ortholithiation of **6** by *t*-BuLi followed by addition of DMF and the reduction by NaBH₄ of the aldehyde led to **7**. The acylation of the alcohol group was carried out in acetic anhydride in the presence of dimethylaminopyridine and triethylamine at room temperature to give **8** in 95% yield. The dimethylamino group was then substituted by an acetoxy residue in the

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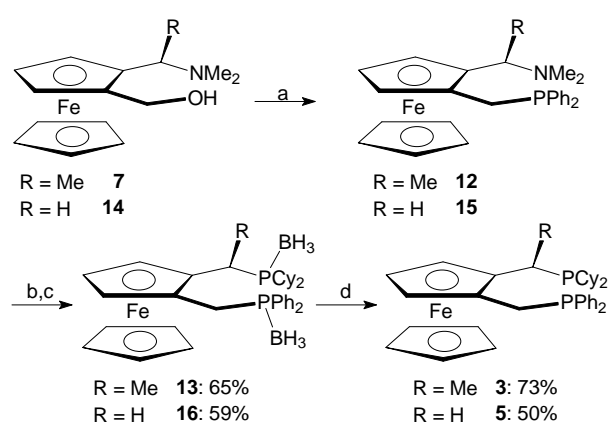


Scheme 1 Reagents and conditions: a) *t*-Buli, Et₂O then DMF; b) NaBH₄, MeOH; c) Ac₂O, DMAP, NEt₃, RT, 1 h; d) Ac₂O, 100°C, 45 min; e) HBF₄, CH₂Cl₂ then HPR₂, CH₂Cl₂, RT; f) BH₃.Me₂S, THF, RT, 1 h; g) Morpholine for **1** or HBF₄.OEt₂, RT for **2**, 12h.

presence of acetic anhydride at 100°C providing **9** in 72% yield. The diacetoxyferrocene **9** was then converted into diphosphines in the presence of HBF₄ followed by addition of HPR₂ in CH₂Cl₂ at room temperature. A protection of the diphosphines was necessary for a purification by silica gel column chromatography. Ferrocenyl protected diphosphines **10** and **11** were obtained in 81 and 84% global yield respectively. The deprotection of the diphosphines by morpholine or HBF₄.OEt₂ yielding respectively **1** and **2** was carried out just before use in catalysis.

The synthesis of the ferrocenyl diphosphine **3**¹⁸ was carried out from the amino alcohol **7** (Scheme 2). Thus, the alcohol function was first transformed to diphenylphosphine group in the presence of HBF₄ following by addition of HPPh₂ at room temperature providing to aminophosphine **12**. After substitution of dimethylamino group by PCy₂ and protection by BH₃, the protected diphosphine **13** was obtained in 65% global yield for the three steps. The deprotection of the diphosphine by HBF₄.OEt₂ led to **3** in 73% yield.

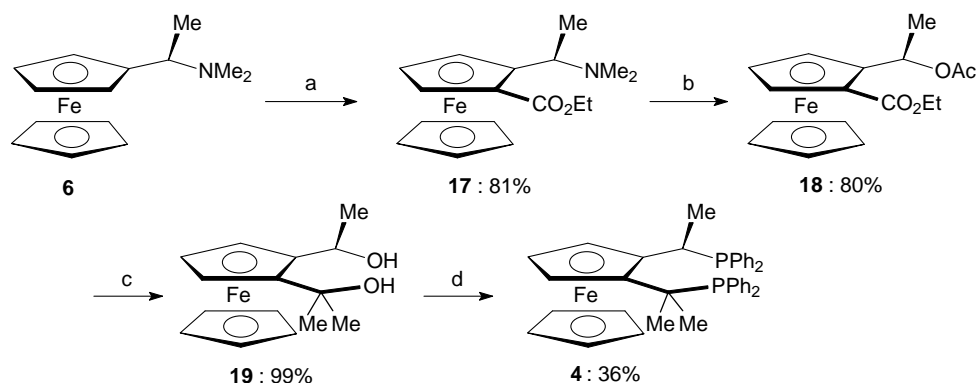
According to the literature method,¹⁹ the optically pure amino alcohol **14**, possessing only planar chirality, has been synthesized from *N,N*-dimethylaminomethylferrocene. Then, the analogous reactions as described previously for **3**, have been realized from ferrocenyl compound **14** (Scheme 2). The protected diphosphine **16** has been obtained in 59% global yield. The deprotection by HBF₄.OEt₂ of **16** leads to **5** in 50% yield.²⁰



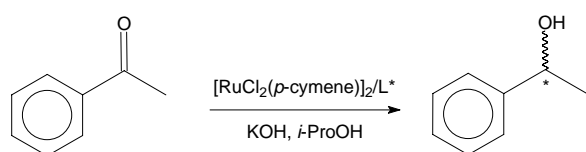
Scheme 2 Reagents and conditions: a) HBF₄, CH₂Cl₂ then HPPh₂, CH₂Cl₂; b) HPCy₂, AcOH, for R = Me, 90°C, 1.45 h and for R = H, 120°C, 3 h; c) BH₃.Me₂S, THF, RT, 1 h; d) HBF₄.OEt₂, RT, 12h.

The ferrocenyl diphosphines **4** has been synthesized from (*R*)-*N,N*-dimethyl-1-ferrocenylethylamine **6** (Scheme 3).²¹ Thus, the ortholithiation of **6** by *t*-BuLi followed by addition of diethylcarbonate led to **17** in 81% yield. The dimethylamino group was then substituted by an acetoxy residue in the presence of acetic anhydride at 100°C providing **18** in 80% yield. The ferrocenyl dialcohol **19** was obtained quantitatively by the addition of an excess of MeLi on **18**. The dialcohol was then converted into diphosphine **4** in the presence of HBF₄ followed by addition of HPPh₂ in CH₂Cl₂ at room temperature. The diphosphine **4** has been obtained in 36% yield.

In order to examine the catalytic behavior of these new ferrocenyl ligands, transfer hydrogenation of acetophenone, using [RuCl₂(*p*-cymene)]₂ and *i*-PrOH/KOH mixture as the base, has been first investigated (Scheme 4).²² The preliminary results are summarized in Table 1.



Scheme 3 Reagents and conditions: a) *t*-Buli, Et₂O then CO(OEt)₂; b) Ac₂O, 100°C, 1 h; c) MeLi (6 eq); d) HBF₄, CH₂Cl₂ then HPPH₂, CH₂Cl₂, RT



Scheme 4

Table 1. Asymmetric transfer hydrogenation of acetophenone in the presence of ligands **1-5**^a

Entry	L*	Time min	Conversion ^b %	Ee ^c %	Config. ^d
1	1	10	30	61	<i>R</i>
2	1	50	60	55	<i>R</i>
3 ^e	1	2	95	40	<i>R</i>
4 ^f	1	10	51	64	<i>R</i>
5	2	60	66	19 ^g	<i>S</i>
6	3	12	41	20	<i>S</i>
7	4	130	71	50	<i>R</i>
8	5	270	5	29	<i>S</i>

^a Reactions were carried out by using 2 mmol of acetophenone in the presence of [Ru(*p*-cymene)Cl₂]₂ (substrate/Ru = 100), the ligand (ligand/Ru = 2) and KOH (0.1 mmol). For details see reference 16.

^b The progression of the reaction was monitored by GC analysis with a Chiraldex capillary column.

^c Determined by GC analysis with a Chiraldex capillary column.

^d Absolute configurations were determined by comparing the sign of the optical rotations with the literature ones.

^e Reaction performed at 80°C.

^f Reaction performed in using ligand/Ru = 1.

^g Maximal e.e.

The first catalytic system investigated was carried out in the presence of ligand **1**, presenting carbon centered and planar chiralities. As shown in Table 1, a modest enantioselectivity (61% ee, entry 1) was observed in presence of ferrocenyl diphosphine **1**. Moreover, only 30% of conversion was obtained after 10 min.

The reversibility of the asymmetric transfer hydrogenation of ketones to secondary alcohols with 2-propanol frequently deteriorates the enantiomeric purity of the chiral products. Indeed, a decrease of enantiomeric excess was observed during the reaction time in presence of ligand **1**. 61% ee was obtained after 10 min and 55% ee after 50 min (entries 1 and 2).

Performing the hydrogenation at 80°C led to a decrease of the enantioselectivity and an increase of activity providing 1-phenylethanol with 40% ee and 95% yield after only 2 min (entry 3).

The enantioselectivity was practically unaffected by changing the ratio ligand/Ru from 2 to 1 (compare entries 2 and 4).

It appears that the presence of the diphenyl group in the ligand is essential for a good enantioselectivity. Replacement of the diphenyl by a dicyclohexyl group on the phosphorus atom led to a reduction of the enantioselectivity and inverted the sense of the induction. As such, (*S*) 1-phenylethanol was obtained in 19% of ee in the presence of ligand **2** (entry 5). This value corresponds to the maximal enantiomeric excess at 60 min.

In ligand **4**, the replacement of the hydrogen atom on the lateral chain by two methyl groups induced a diminution of enantioselectivity (compare entries 1 and 7, 61% ee for **1** vs 50% ee for **4**).

It also seems that, for this type of ligand, the presence of a chiral center adjacent to the diphosphino group has a major influence on the catalytic activity. Thus, a low activity (5% after 270 min, entry 8) has been obtained in the presence of the ferrocenyl diphosphine **5**, possessing only planar chirality.

In summary, this paper describes the synthesis of a series of new ferrocenyl diphosphines and their use as ligands for asymmetric transfer hydrogenation of acetophenone catalyzed by Ru(II) complexes. The results obtained for the ligand **1** represents the best one from the literature with this type of catalytic system using ferrocenyl diphosphines as

ligands. The improvement of the ligand design is under study.

Acknowledgments

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- 1:** ^1H NMR (CDCl_3) δ 7.5-7.0 (m, 20H), 4.1 (s, 5H), 4.0 (m, 1H), 3.9 (m, 1H), 3.8 (m, 1H), 3.3 (m, 1H), 2.6 (d, J = 15.5 Hz, 1H), 2.0 (dd, J = 15.5 and 4.2 Hz, 1H), 1.5 (dd, J = 7.1 and 13.9 Hz, 3H). ^{31}P NMR (CDCl_3) δ 5.8, -18.2.
2: ^1H NMR (CDCl_3) δ 4.3 (m, 1H), 4.1 (s, 5H), 4.0 (m, 1H), 3.9 (m, 1H), 2.8 (m, 1H), 2.6-2.4 (m, 2H), 2.0-1.0 (m, 47H). ^{31}P NMR (CDCl_3) δ 12.2, 7.9.
- 3:** ^1H NMR (CDCl_3) δ 7.5-7.2 (m, 10H), 4.0 (s, 5H), 4.0 (m, 1H), 3.9 (m, 2H), 3.4 (m, 1H), 3.1 (m, 1H), 2.9 (m, 1H), 1.9-1.0 (m, 25H). ^{31}P NMR (CDCl_3) δ 12.0, -17.5.
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- 5:** ^1H NMR (CDCl_3) δ 7.5-7.2 (m, 10H), 4.1 (m, 1H), 4.0 (s, 5H), 3.8 (m, 1H), 3.7 (m, 1H), 3.2 (d, J = 14.4 Hz, 1H), 3.1 (d, J = 14.4 Hz, 1H), 2.5 (dd, J = 15.2 and 1.7 Hz, 1H), 2.3 (dd, J = 15.2 and 1.7 Hz, 1H), 1.8-1.1 (m, 22H). ^{31}P NMR (CDCl_3) δ -5.1, -16.0.
- 4:** ^1H NMR (CDCl_3) δ 7.7-6.9 (m, 20H), 4.1 (s, 5H), 4.1 (m, 1H), 4.0 (m, 1H), 3.9 (m, 1H), 3.2 (m, 1H), 1.6 (d, J = 14.2 Hz, 3H), 1.5 (m, 3H), 1.4 (d, J = 3.4 Hz, 3H). ^{31}P NMR (CDCl_3) δ 12.9, 6.8.
- Typical experimental procedure: the appropriate amount of ligand (0.02 mmol) was added to the catalyst precursor (0.01 mmol) $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ in dry freshly distilled 2-propanol (5 mL) and stirred at 80°C for 20 min under nitrogen. After allowing the orange solution to cool to room temperature, a solution of acetophenone (2 mmol) in 2-propanol (14 mL) and KOH (1 mL, 0.1 M in 2-propanol) was added. The resulting solution was stirred at 20°C and the reaction was monitored by GC.