

Chiral ferrocenyl diphosphines for asymmetric transfer hydrogenation of acetophenone

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Received 22 November 2004; revised 13 December 2004; accepted 14 December 2004
Available online 8 January 2005

Abstract—The synthesis of new optically pure ferrocenyl diphosphines have been realized from (*R*)-(+)-*N,N*-dimethylaminoethyl-ferrocene. 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.

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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 alcohols,¹¹ 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** (Fig. 1)

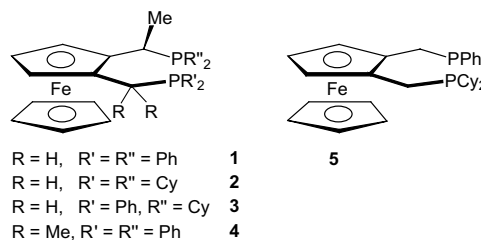


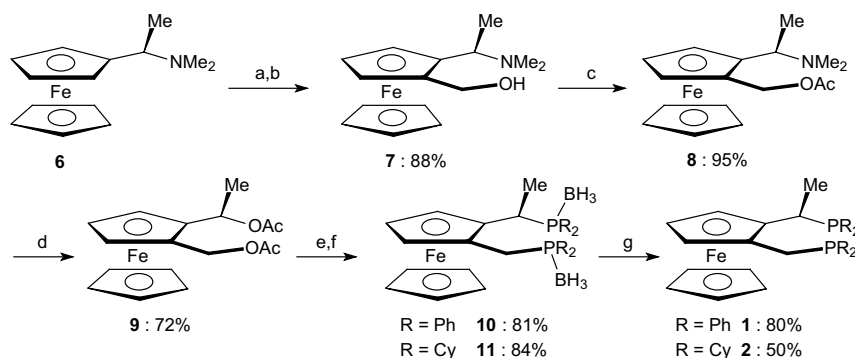
Figure 1.

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.

Following a similar procedure as described by Fukuzawa et al.,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 *tert*-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 presence of acetic anhydride at 100 °C providing **9** in 72% yield. The diacetoxyferrocene

Keywords: Diphosphines; Ferrocene; Transfer hydrogenation.

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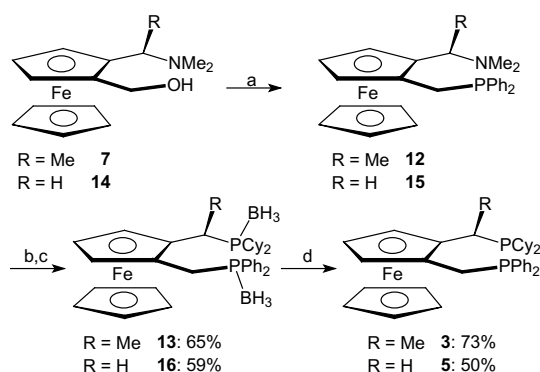


Scheme 1. Reagents and conditions: (a) *t*-BuLi, Et₂O then DMF; (b) NaBH₄, MeOH; (c) Ac₂O, DMAP, Et₃N, rt, 1 h; (d) Ac₂O, 100 °C, 45 min; (e) HBF₄, CH₂Cl₂ then HPR₂, CH₂Cl₂, rt; (f) BH₃·Me₂S, THF, rt, 1 h; (g) Morpholine for **1** or HBF₄·OEt₂, rt for **2**, 12 h.

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.

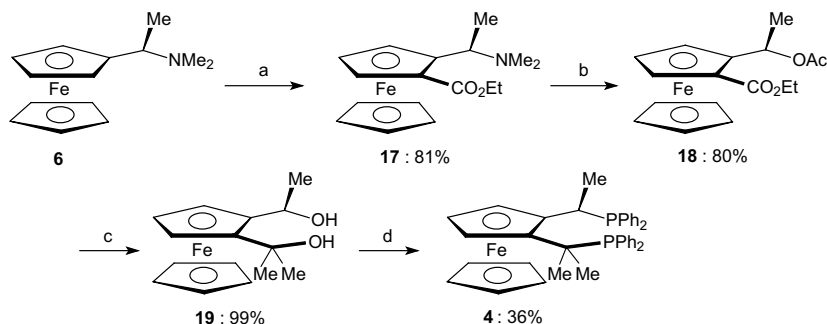
The synthesis of the ferrocenyl diphosphine **3**¹⁸ was carried out from the amino alcohol **7** (Scheme 2). Thus, the alcohol function was first transformed to diphenylphosphine group in the presence of HBF₄ following by the addition of HPPH₂ at room temperature providing to aminophosphine **12**. After 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

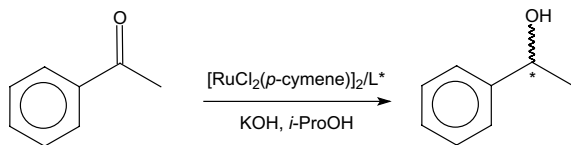


Scheme 2. Reagents and conditions: (a) HBF₄, CH₂Cl₂ then HPPH₂, CH₂Cl₂; (b) HPCy₂, AcOH, for R = Me, 90 °C, 1.45 h and for R = H, 120 °C, 3 h; (c) BH₃·Me₂S, THF, rt, 1 h; (d) HBF₄·OEt₂, rt, 12 h.

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 residu 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.



Scheme 3. Reagents and conditions: (a) *t*-BuLi, Et₂O then CO(OEt)₂; (b) Ac₂O, 100 °C, 1 h; (c) MeLi (6 equiv); (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 Ref. 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 ee.

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.

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 the 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 the presence of ligand **1**. Ee (61%) 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.

Acknowledgements

The authors gratefully thank the 'Ministère de la Recherche et de la Technologie' and the 'Centre National de la Recherche Scientifique' for financial support and Francine Agbossou-Niedercorn and Isabelle Suisse for helpful discussions.

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17. **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.
18. **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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20. **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.
21. **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.
22. 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.