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Letter: Preliminary Communication

Synthesis and applications of new chiral diphosphines bearing a diphenylphosphino group and a phenylcyclohexylphosphino group

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Abstract

Chiral diphosphines derived from Diop and BPPM and bearing a phenylcyclohexylphosphinogroup and a diphenylphosphinogroup were prepared. These ligands, and especially the BPPM analog, in association with rhodium complexes, exhibited high enantioselectivities, up to 93%, and activities in the reduction of various unsaturated substrates although they were used as a mixture 50/50 of two epimers.

Keywords: Chiral phosphine; Rhodium complex; Hydrogenation; Enantioselectivity

The hydrogenation of prochiral olefins with chiral rhodium phosphane complexes as catalysts under homogeneous conditions is now a well established reaction [1–4]. Most of the reported chiral phosphorus ligands have chiral carbon(s) in their molecular structures. Chiral phosphine ligands bearing chiral phosphorus atom(s), which should be more effective in enantioselectivity due to the close proximity of the stereogenic center to the reaction site, are less common [5,6]. Some chiral diphosphines having chirality both on phosphorus atoms and in the carbon skeleton have also been described [7–13]. However, most of these ligands beared two diarylphosphino groups. More recent work focused on the preparation of bisphosphine ligands with one diarylphosphino group and one dicyclohexylphosphino group, according to the 'Respective Control Concept' developed by Inoguchi et al. (Ref. [14] and references therein); these ligands show a higher activity than their bis(diarylphosphino) analogues in asymmetric hydrogenation of prochiral unsaturated substrates.

We were interested in the synthesis of a new class of diphosphines, bearing one diphenylphosphino group and one phenylalkylphosphino group. These diphosphines were expected to follow the 'Respective Control Concept' of Achiwa; they also present a new stereogenic phosphorus atom, which allow the eventual preparation of a matched (or mismatched) bis-

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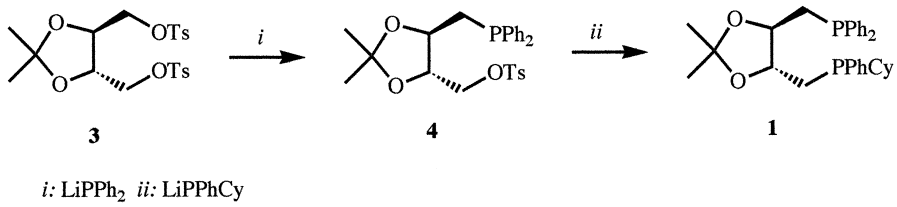


Scheme 1.

phosphine ligand. We present in this communication preliminary results in this field.

The two chiral diphosphines, [(4*R*,5*R*)-4-diphenylphosphinomethyl-5-(cyclohexylphenyl)-phosphinomethyl-2,2-dimethyl-1,3-dioxolane] **1** and (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-cyclohexyl phenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine **2**, were prepared according to Schemes 1 and 2. Selective phosphination of the ditosylate **3** [15] with lithium diphenylphosphide in THF gave the monophosphine **4** in 46% yield. Subsequent phosphination of **4** using lithium phenylcyclohexylphosphide in THF, obtained from cyclohexyldiphenylphosphine and lithium in THF, afforded the diphosphine **1** [1] in 78% yield as a mixture of two epimers in a ratio 50/50.

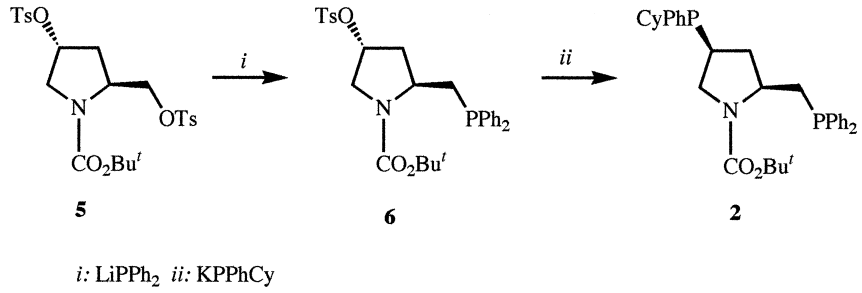
Diphenylphosphination of the chiral pyrrolidine ditosylate **5** [16] with lithium diphenylphosphide in THF at room temperature gave the monophosphine **6** in 29% yield. Subsequent phosphination of **6** using diphenylcyclohexylphosphine prepared by cleavage of diphenylcyclohexylphosphine with potassium–sodium alloy in dioxane afforded the diphosphine **2** [1] in 68% yield as a mixture 50/50 of the two epimers at phosphorus.

[1] Selected data for phosphines **1** and **2**. **1**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–1.20 (m, 5H, CH_2), 1.30 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.50–1.80 (m, 5H, CH_2), 2.00 (m, 1H, CH), 2.10–2.35 (m, 4H, CH_2), 3.70–3.90 (m, 2H, CH), 7.20–7.50 (m, 15H, C_6H_5); ^{31}P (80 MHz, $CDCl_3$) δ −22.9 (s), −22.5 (s), −20.6 (s), −18.0 (s). **2**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80–1.30 (m, 5H, CH_2), 1.40 (s, 9H, CMe_3), 1.40–1.60 (s, 6H, CH_2), 1.60–2.30 (m, 4H, CH_2), 3.15 (m, 1H, CHN), 3.40 (m, 1H, CHP), 3.80 (m, 2H, CHN), 7.20–7.60 (m, 15H, C_6H_5); ^{31}P (80 MHz, $CDCl_3$) δ −22.0 (s, 2P), −8.2 (s, 1P), −7.4 (s 1P).

Cationic rhodium(1) complexes of these two diphosphines can be prepared following the conventional method. Namely the cationic complex [Rh(COD)(**1**)]ClO_4 was obtained by treating [Rh(COD)(acac)] with $HClO_4$ and addition of ligand **1**, and [Rh(COD)(**2**)]PF_6 by treating [$Rh(COD)_2$]PF_6 with ligand **2**. These complexes were characterized by ^{31}P NMR spectra: [Rh(COD)(**1**)]ClO_4 exhibited two doublets of doublet for each diastereoisomer at δ 10.8 ($J_{Rh,P}$ = 140 Hz and $J_{P,P}$ = 35 Hz) and 13.4 ppm (J = 143 and $J_{P,P}$ = 35 Hz), and δ 10.9 and 13.5 ppm, respectively; [Rh(COD)(**2**)]PF_6 exhibited a doublet of doublet at δ 19.9 Hz ($J_{Rh,P}$ = 148 Hz and $J_{P,P}$ = 69 Hz) for the diphenylphosphino group of the two epimers, and two doublets of doublets at δ 27.1 and 27.3 ppm ($J_{Rh,P}$ = 155 Hz and $J_{P,P}$ = 69 Hz) for the phenylcyclohexylphosphino group.

These rhodium complexes were used in the reduction of some unsaturated prochiral substrates such as dehydroaminoacids and esters, itaconic acid and its dimethylester. The results are summarized in Table 1. Reduction of the various prochiral substrates using [Rh(COD)(**1**)]ClO_4 as the catalyst gave lower enantioselectivities than those generally obtained using DIOP as the ligand, except for itaconic acid which gave quite similar e.e. (49%). The use of the phosphine **1** as a mixture of the two epimers at the phosphorus seems disadvantageous for obtaining high enantioselectivities in this case.

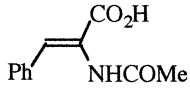
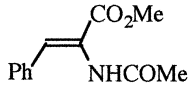
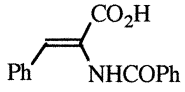
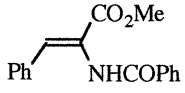
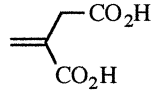
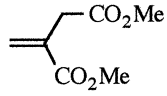
However the results are completely different using [Rh(COD)(**2**)]PF_6 as the catalyst. In the reduction of α-acetamidocinnamic acid and its methyl ester, e.e. up to 84 and 93%, respec-



Scheme 2.

tively, were obtained without added amine. These results are quite similar to the values already published using BPPM as the ligand (91.6% and 95.2%, respectively) [16], and higher than the values published using diphosphine BCPM [(2*S*,4*S*)-*N*-*tert*-butoxycarbonyl)-4-(di-

Table 1
Catalytic hydrogenation of some prochiral substrates by rhodium complexes of **1** and **2**[a]

Entry	Substrate	e.e. % (Config.) Ligand **1**	Ligand **2**
1		50 *(S)*[b]	84 *(R)*[b]
2		23 *(S)*[b]	93 *(R)*[b]
3		46 *(S)*[c]	81 *(R)*[c]
4		21 *(S)*[c]	40 *(R)*[c]
5		49 *(R)*[c] 38 *(R)* [c,d]	83 *(S)*[c] 83 *(S)*[c]
6		36 *(S)*[c]	10 *(S)*[c]

[a] Conditions: [substrate]/[catalyst] = 100; [substrate] = 0.067 mol l^{-1}; CH_3OH 7.5 ml; 25°C; p_{H_2} 1 atm; 24 h.
[b] Determined by gas chromatography using XE-60-L-valine-*tert*-butylamide (10 m) as the column, after esterification with diazomethane in the case of the acid.
[c] Calculated using the reported optical rotations of pure enantiomers: *N*-benzoyl-(*S*)-phenylalanine $[\alpha]_D^{27}$ −40.3 (*c* 1.0, CH_3OH) [17]; *N*-benzoyl-(*S*)-phenylalanine methyl ester $[\alpha]_D^{27}$ −45.3 (*c* 1.3, C_2H_5OH) [18]; (*R*)-methylsuccinic acid $[\alpha]_D^{25}$ +16.88 (*c* 4, C_2H_5OH) [19]; (*R*)-methylsuccinic acid dimethyl ester $[\alpha]_D^{25}$ +4.2 (*c* 5, $CHCl_3$) [20].
[d] Et_3N (1 equivalent) was added.

cyclohexylphosphino)-2-[(diphenylphosphino)-methyl]pyrrolidine (only 37% e.e. in the reduction of the unsaturated acid) (Ref. [14] and references therein). We could also notice the higher activity of this catalyst with a half-time reaction of 3 and 4 min for the acid and the ester, respectively. In the case of the reduction of α-benzamidocinnamic acid, the obtained enantioselectivity (81%) was again close to the value described using BPPM as the ligand (84%) [16].

Finally reduction of itaconic acid and its dimethyl ester gave enantioselectivities up to 83% and 10%, respectively. These results are quite similar to the values obtained using BPPM or BCPM as the ligand (Ref. [14] and references therein). One could notice than high enantioselectivity was obtain using **2** as the ligand in the reduction of itaconic acid in the presence or not of triethylamine; under the same conditions, the use of BCPM as the ligand gave low enantioselectivity without triethylamine added (26%), the high e.e. being restored in the presence of this amine (92%). For the reduction of the dimethyl ester of itaconic acid, enantioselectivities of 5% and 16% were obtained using BPPM and BCPM, respectively, as the chiral ligand (Ref. [14] and references therein).

In conclusion, the use of the new diphosphine **2** bearing a diphenylphosphino and a cyclohexylphenylphosphino groups as ligand in the reduction of prochiral unsaturated substrates gave enantiomeric excess quite similar to those obtained with BPPM as the ligand, although it was a 50/50 mixture of the two epimers at phosphorous, and with quite high activities. This ligand seems to fulfill the 'Respective Control Concept' of Achiwa. Work is in progress actually to separate the two epimers, in order to know the reasons of the high enantioselectivity obtained, and to use these ligands in the reduction of other substrates such as ketoesters as well as in other reactions.

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