Chinese Journal of Chemistry, **2004**, *22*, 1456—1458 **Note**

Synthesis of Diphosphites from *trans,trans*-Spiro[4.4]nonane-1,6-diol and Their Application in Rh-catalyzed Asymmetric Hydroformylation of Styrene

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Chiral diphosphite ligands were prepared by the reaction of (1*R*,5*S*,6*R*)-(*trans,trans*)-spiro[4.4]nonane-1,6-diol with chlorophosphites. The rhodium(I) complexes containing these ligands were tested in the asymmetric hydroformylation of styrene and moderate enantioselectivity (up to 49% *ee*) was obtained. A pair of diastereomers **5a** and **5b** gave the opposite configuration of the product, which implies that the sense of enantioface selection is mainly dictated by the configuration of the terminal group on the ligand.

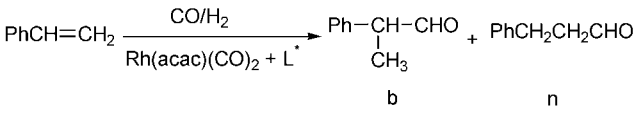
Keywords catalyst, chiral diphosphite, hydroformylation

Introduction

Catalytic asymmetric hydroformylation of olefins is a method for the preparation of optically pure aldehydes, which are important precursors for the synthesis of pharmaceuticals.[1] A variety of chiral ligands and catalyst systems have been reported,[2,3] which were expected to provide high regio- and stereo-selectivity in the hydroformylation of olefins. There has been growing interest in the use of phosphite ligands since van Leeuwen's report on the high catalytic activity of phosphite ligands in rhodium catalyzed hydroformylation.[3] Up to 95% *ee* was obtained by Nozaki in the hydroformylation of styrene with the phosphine-phosphite ligands with excellent chemo- and regio-selectivity.[4]

Bisphosphinite derived from *cis,cis*-spiro[4.4]-nonane-1,6-diol (abbreviated as spirol) was found to be an efficient chiral ligand for the catalytic asymmetric hydrogenation of enamides.[5] Since phosphite-Rh(I) complexes often showed high catalytic activity and good enantioselectivity in hydroformylation, and the phosphites were readily prepared from spirol, we wish to synthesize diphosphites from spirol and use them as chiral ligands in hydroformylation. Unfortunately, diphosphite derived from *cis,cis*-spirol can not be obtained due to the steric constraits between the bulky substituents on bisphenol moieties.[6] Chiral diphosphites from *cis,trans*-spirol have been synthesized, and their diphosphite-Rh(I) catalyst systems showed moderate enantioselectivity (65% *ee*) and high regioselectivity (b/n＝97/3) in hydroformylation of styrene (Scheme 1).[7] Here we sought to extend our studies to other diphosphite ligands derived from *trans,trans*-spirol.

Scheme 1



Results and discussion

Optically pure *trans,trans*-spirol was obtained by asymmetric reduction of racemic spiro[4.4]nonane-1,6-dione using chiral oxazaborolidine as catalyst.[8] This procedure provided 99% *ee* of *trans,trans*-spirol, which was used as starting material for the synthesis of our chiral ligands. Diphosphites **3** and **5** were synthesized by the reaction of (1*R*,5*S*,6*R*)-*trans,trans*-spirol **1** with the corresponding chlorophosphites in benzene in the presence of pyridine (Scheme 2). Diastereomers **5a** and **5b** were used to observe the chiral cooperative effect. The catalyst species in hydroformylation were prepared *in situ* by simply mixing $Rh(acac)(CO)_2$ and 1.5 equivaents of diphosphites. A little excess of ligands was useful for preventing the background reaction catalyzed by unmodified rhodium species.[9] It is known that an incubation period is necessary for the formation of $RhH(L)(CO)_2$ from $Rh(acac)(CO)_2$ and diphosphite.[10] In order to improve reaction rate, the catalyst was prepared under the typical conditions [40 ℃, 10 atm of syn gas, 10 h] before substrate was added. The results of the asymmetric hydroformylation of styrene are summarized in Table 1.

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Scheme 2

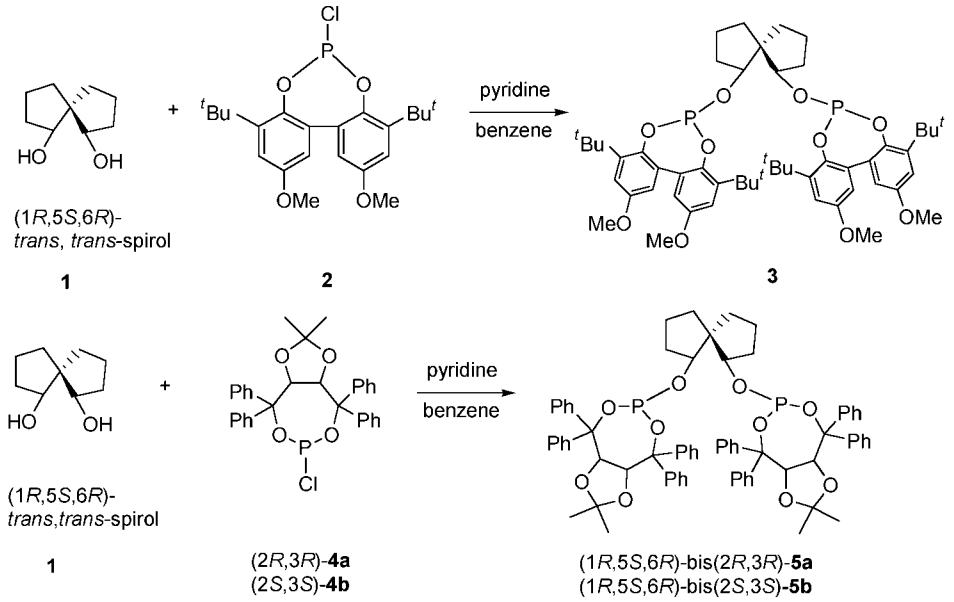

Table 1 Asymmetric hydroformylation of styrene catalyzed by diphosphite-Rh(I) complexes [a]

Entry	Ligand	*T*/℃	*p*/atm	Solvent	Yield[b]/%	b/n[b]	*ee*[c]/%
1	**3**	40	40	toluent	30	95/5	30(*S*)
2		40	20	toluent	50	95/5	32(*S*)
3		40	10	toluent	66	95/5	26(*S*)
4		25	10	toluent	31	95/5	33(*S*)
5		40	20	THF	42	95/5	35(*S*)
6		40	20	CH_2Cl_2	35	95/5	29(*S*)
7	**5a**	40	20	toluent	19	82/18	32(*S*)
8	**5b**	40	20	toluent	47	75/25	41(*R*)
9[d]		40	20	toluent	38	75/25	49(*R*)
10[d]		50	20	toluent	62	77/23	47(*R*)

[a] Reactions were carried out in a 40 mL autoclave under the reaction conditions [syn gas (CO/H_2=1/1), S/C=500, L/Rh=1.5, 10 h]. The complex was incubated under 10 atm of syn gas at 40 ℃ for 10 h before the substrate was added. [b] Yields and b/n ratios were determined by GC using *cis*-decahydronaphthane as internal standard. [c] Enantiomeric excesses were determined by GC analysis (β-236M, 0.25 mm×25 m) of the corresponding acid. Configurations were drawn in parentheses according to the sign of optical rotation of the corresponding aldehyde. [d] L/Rh=2.5.

The catalysis was carried out to give a mixture of the branched (b, 2-phenylpropanal) and the normal (n, 3-phenylpropanal) products (Scheme 1). Up to 95/5 of the b/n ratio was obtained when the catalyst containing ligand **3** was used in hydroformylation of styrene. Little influence on the enantioselectivity was observed on varying pressure of syn gas (Entries 1—3). The yields of product decreased with increasing pressure of syn gas. When the reaction temperature decreased from 40 to 25 ℃, the enantiomeric excess was slightly increased. However, the yield of product decreased markedly (Entry 3 vs. 4). As a solvent, THF and CH_2Cl_2 gave comparable regioselectivity and enantioselectivity in this catalyst system.

Ligands **5a** and **5b** were also evaluated under the typical reaction conditions (40 ℃, 20 atm, 10 h). The catalyst containing **5a** gave 32% *ee* of the branched aldehyde with 19% yield, while diastereomer **5b** gave the desired aldehyde with higher enantioselectivity (41% *ee*) and higher yield (47%). These results may suggest that there is a cooperative effect between the chirality of the terminal group and the central chirality of the spiro backbone. This pair of diastereomers **5a** and **5b** gave the opposite configuration of product, which implies that the sense of enantioface selection was mainly dictated by the configuration of the terminal group on the ligand. The enantiomeric excess was increased from 41% to 49% *ee* when the ratio of L/Rh was increased to 2.5 (Entry 8 vs. 9). Ligands **5a** and **5b** show lower b/n ratios than ligand **3**. High b/n ratios were obtained using ligand **3** and this might be attributed to large bulky substituents on the terminal group. [11]

Conclusion

New chiral diphosphites derived from (1*R*,5*S*,6*R*)-*trans*,*trans*-spirol **1** for the catalytic asymmetric hydroformylation of styrene have been synthesized. The rhodium(I) complexes containing these ligands gave the desired aldehyde with up to 49% *ee*.

Experimental

General

All reactions were carried out in oven-dried glassware using Schlenk techniques under pure nitrogen. Toluene and THF were distilled from sodium-benzophenone, and pyridine from CaH_2. PCl_3 and styrene

were distilled before use and stored under pure nitrogen. Melting points were determined on a Southend SS25PH apparatus and are uncorrected. Elemental analyses were recorded on a Carloerba-1106 instrument. Gas chromatographic analyses were performed by SC-7 gas chromatography. ^{31}P NMR spectra were obtained on a Varian FT-80A using H_3PO_4 (85%) as an internal standard and ^1H NMR spectra on a Bruker 300 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Enantiomeric excesses were measured after Jones oxidation of the aldehyde to the corresponding acids on an SC-7 gas chromatograph with a Chrompack *β*-236M, 0.25 mm×25 m chiral capillary column. Hydroformylation reactions were carried out in a laboratory-made stainless-steel autoclave (40 mL).

Preparation of compound 3

6,6'-Di-*tert*-butyl-4,4'-dimethoxy-2,2'-bis(phenol) (540 mg, 1.5 mmol) was dissolved in benzene (10 mL) and pyridine (0.5 mL) . This solution was added dropwise to a cooled solution of PCl_3 (0.2 mL) and pyridine (0.5 mL) at 0 ℃. The reaction mixture was stirred for 6 h at 60 ℃. The solvent and excess of PCl_3 were removed under vacuum. The remained trace of PCl_3 in the residue was removed by benzene (3 mL) under reduced pressure and this procedure was repeated three times. Compound **2** formed *in situ* was dissolved in benzene (6 mL) and pyridine (0.5 mL). (1*R*,5*S*,6*R*)-*trans*,*trans*-spiro[4.4]-nonane-1,6-diol (93 mg, 0.6 mmol) dissolved in benzene (3 mL) was added dropwise to the solution of compound **2** at 0 ℃ . The reaction mixture was stirred overnight at room temperature. The resulting pyridine salts were filtered off. Evaporation of the solvent gave a white plaster which was purified by flash column chromatography using toluene as eluent. A white foam (378 mg, 68%) was obtained. m.p. 101－103 ℃; $[\alpha]_D^{20}$ ＋10.4 (0.40, CH_2Cl_2); ^1H NMR (CD_3COCD_3, 300 MHz) *δ*: 7.20—7.12 (m, 4H), 6.76—6.74 (m, 4H), 4.80 (m, 2H), 3.37 (s, 12H), 2.16—1.43 (m, 48H); ^{31}P NMR (CD_3COCD_3) *δ*: 146.78. Anal. calcd for $C_{53}H_{70}O_{10}P_2$: C 68.52, H 7.25; found C 68.11, H 7.24.

Preparation of compound 5a

Treatment of (－)-TADDOL (700 mg, 1.5 mmol) and (1*R*,5*S*,6*R*)-*trans*,*trans*-spiro[4.4]nonane-1,6-diol (93 mg, 0.6 mmol) as described as compound **3** afforded compound **5a** (379 mg, 55%). m.p. 94—95 ℃; $[\alpha]_D^{20}$ ＋122.1 (0.84, CH_2Cl_2); ^1H NMR (CD_3COCD_3, 300 MHz) *δ*: 7.61—7.23 (m, 40H), 5.15 (m, 4H), 4.85 (m, 2H), 2.06—1.32 (m, 12H), 1.15 (s, 6H), 0.46 (s, 6H); ^{31}P NMR ($CDCl_3$) *δ*: 135.99. Anal. calcd for $C_{71}H_{70}O_{10}P_2$: C 74.35, H 6.11; found C 74.54, H 6.31.

Preparation of compound 5b

Treatment of (＋)-TADDOL (700 mg, 1.5 mmol) and (1*R*,5*S*,6*R*)-*trans*,*trans*-spiro[4.4]nonane-1,6-diol (93 mg, 0.6 mmol) as described as compound **3** afforded compound **5b** (419 mg, 61%). m.p. 97—98; $[\alpha]_D^{20}$ － 142.2 (0.66, CH_2Cl_2); ^1H NMR (CD_3COCD_3, 300MHz) *δ*: 7.66—7.22 (m, 40H), 5.14 (m, 4H), 4.71 (m, 2H), 2.08—1.33 (m, 12H), 1.12 (s, 6H), 0.46 (s, 6H); ^{31}P NMR ($CDCl_3$) *δ*: 135.76. Anal. calcd for $C_{71}H_{70}O_{10}P_2$: C 74.35, H 6.11; found C 74.49, H 6.26.

Procedure for the asymmetric hydroformylation

The autoclave filled with $Rh(acac)(CO)_2$ (0.0085 mmol) and diphosphite (0.025 mmol) was purged three times with syn gas ($CO : H_2 = 1 : 1$), then toluene (1.5 mL) was added and pressurised to 10 atm of syn gas. The reaction mixture was stirred for 10 h at 40 ℃ to form the active catalyst. Styrene (4.25 mmol) and toluene (1 mL) were placed in the autoclave under the atmospheric pressure and the syn gas was introduced until the desired pressure was reached. After the desired reaction time, the autoclave was cooled to room temperature and depressurised. *cis*-Decahydronaphthalene as an internal standard was added. The mixture was filtered on silica gel and the filtrate was analysed by GC for the determination of yield and regioselectivity. A sample of the filtrate was oxidised to acid by Jones oxidation and analysed by GC for determination of the enantiomeric excess.

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