Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4701–4707

TETRAHEDRON:
ASYMMETRY

A new ligand containing a unique combination of backbone- and P-centered chirality: synthesis, resolution and asymmetric catalysis using a chiral enantiopure 2,2′-biphospholene

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Received 11 October 1999; accepted 26 November 1999

Abstract

Enantiopure 2,2'-bi(1-phenyl-3,4-dimethyl-2,5-dihydro-1*H*-phosphole) has been synthesized and tested in the rhodium-catalyzed asymmetric hydrogenation of α-acetamidocinnamic acid. Enantioselectivities up to 75% have been achieved. The absolute configuration of the biphospholene was determined by X-ray diffraction methods on a crystalline tungsten carbonyl derivative.

1. Introduction

Chirality can be introduced into a ligand structure in many different ways.[1] The most successful concepts in the field of (di)phosphine ligand design are P-centered chirality,[2,3] backbone chirality[4] and the introduction of chiral groups rendering the phosphorus atom non-stereogenic and chirotopic, as in the phospholane-based ligands of the DuPHOS series.[5]

Our laboratory has recently synthesized ligands containing 2-substituted 3-phospholene skeletons.[6] Their preparation has been facilitated by the discovery of a particularly straightforward access to a unique C_2-symmetric biphospholene structure, through the coupling of appropriately substituted phospholes (Scheme 1).[7,8]

An unusual feature of these C_2-symmetric ligands is the combination of two different types of chirality, which are localized within the backbone and at the phosphorus atom. These ligands are more electron-rich than the commonly used triarylphosphines and, being dialkylaryl- or trialkylphosphines, are comparable with ligands of the DuPHOS/BPE series.[5] Unlike DuPHOS, they have structures which should be relatively easy to vary at the aryl moiety.

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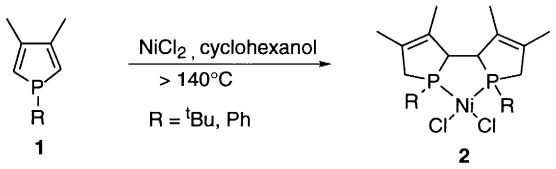
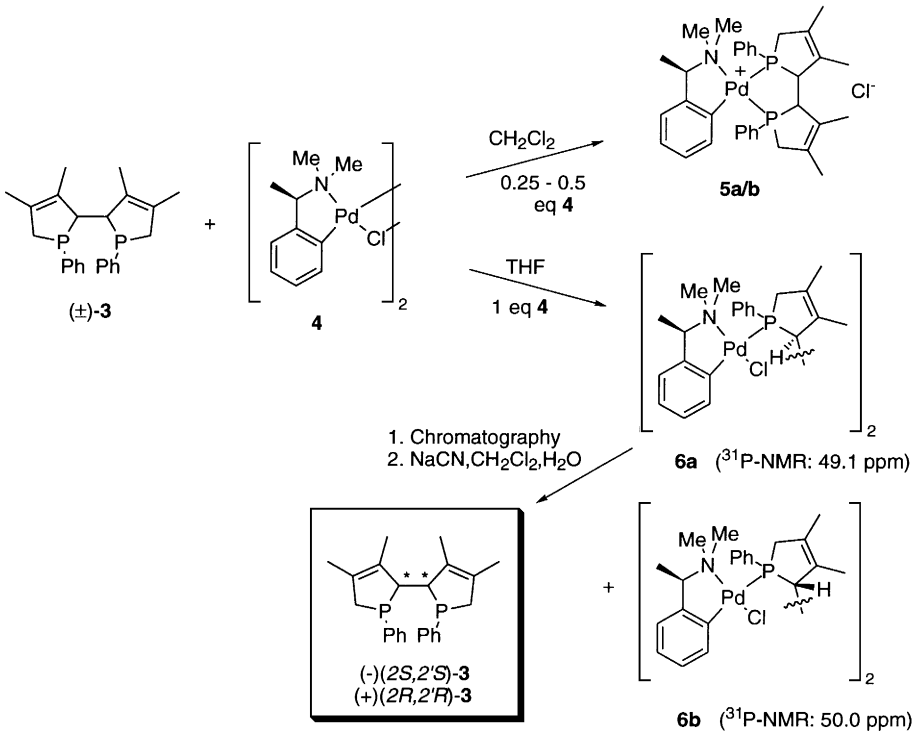
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00547-9



Scheme 1.

2. Results and discussion

We employed the well-known palladium complex (+)-(*R*)-**4**[9] to separate the two enantiomers of biphospholene **3**. Complexation using 0.25 equivalents of complex **4** in dichloromethane at 0°C gave a mixture containing the two diastereomeric complexes **5a**/**b** in a ratio close to 1:1 (Scheme 2), along with uncomplexed biphospholene **3**. Hence, a kinetic resolution or enrichment of one enantiomer is not feasible. As anticipated, complexation using half an equivalent of complex **4** cleanly gave the chelate complexes **5a**/**b**, as shown by ^{31}P NMR spectra (two AB systems with doublets of 20 Hz coupling each at 78.2, 76.3, 56.5, 54.6).



Scheme 2.

Unfortunately, attempts to separate the two diastereomers on silica (using CH_2Cl_2/EtOAc or EtOAc/toluene mixtures) failed. Attempted crystallizations from several solvent mixtures, after anion exchange with KPF_6, were also unsuccessful.

Eventually, complexation of biphospholene **3** to 1 equivalent of palladium dimer **4** in THF was attempted. The two diastereomeric bridged dinuclear palladium complexes **6a**/**b** which were formed in high yield showed broad singlets at 50.0 and 49.1 ppm in the ^{31}P NMR spectra.

These two complexes were easily separated by flash chromatography on silica using toluene:EtOAc (80:20) as eluent. Complex **6a** (49.1 ppm) was eluted first. Decomplexation using NaCN in a biphasic CH_2Cl_2/water mixture yielded pure samples of the two enantiomers (+)- and (−)-**3**, $[\alpha]_D^{25}=\pm 125$, as colourless crystals.

In order to obtain a crystalline derivative for the determination of the absolute configuration, enantiopure (+)-**3**, derived from diastereomer **6b**, was reacted with $[(CO)_5W(THF)]$. (+)-(**3**)$W(CO)_4$ could be isolated as the only complex after recrystallization from toluene/$CHCl_3$ as a crystalline solid, suitable for X-ray structural analysis (Fig. 1).[10] Its absolute configuration was shown to be (+)-(2*R*,2′*R*).

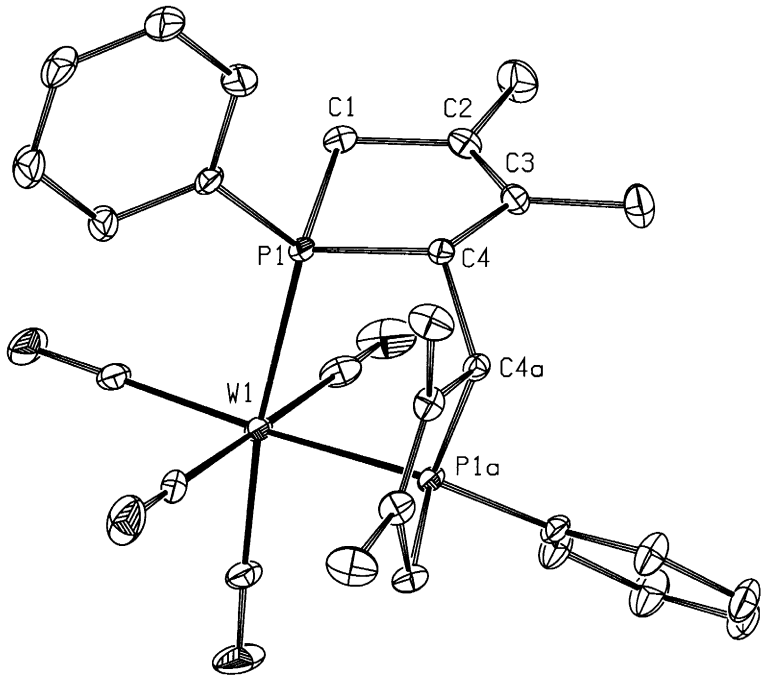
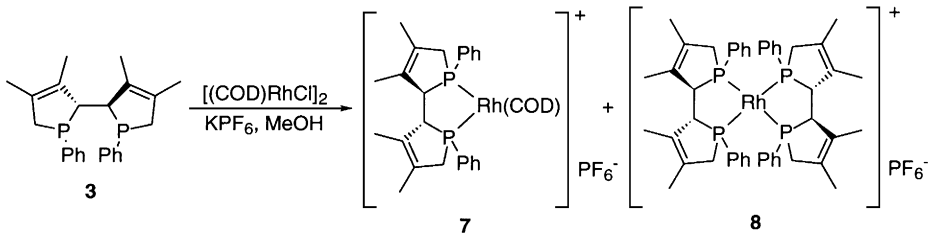


Fig. 1.

The addition of a solution of ligand **3** to a suspension of $[(COD)RhCl]_2/KPF_6$ in methanol gave a mixture of cationic complexes **7** (^{31}P NMR: δ=77.8 ppm, J_{Rh-P}=147 Hz) and **8** (^{31}P NMR: δ=78.9 ppm, J_{Rh-P}=129 Hz) in a ratio close to 1:1 (Scheme 3).

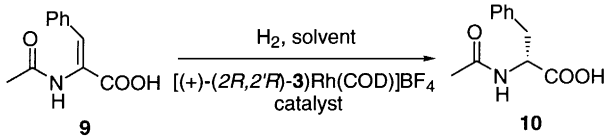


Scheme 3.

Bis(diphosphine)rhodium complexes are not usually active hydrogenation catalysts, so complexation to other rhodium precursors was tested to obtain higher yields of **7**. Coordination using acidified (HBF_4) solutions of (acac)Rh(COD) in THF cleanly yielded catalyst precursor **7** (BF_4 as anion).[11] Compound **7**

separated as an orange, air sensitive oil upon evaporation of most of the solvent and addition of diethyl ether. It solidified after several weeks.

Initial hydrogenations were performed using α-acetamidocinnamic acid **9** (Scheme 4). Results are shown in Table 1.



Scheme 4.

Table 1
Asymmetric hydrogenation of α-acetamidocinnamic acid **9** using biphospholene rhodium complex **7**

entry	reaction conditions[1)]	conv. (%)	ee (%)
1	MeOH / 7 atm / RT / 0.3 % / 1 h	100	69
2	MeOH / 40 atm / RT / 0.3 % / 30 min	100	65
3	MeOH / 7 atm / 6°C / 0.5 % / 1.5 h	60	75
4	^{i}PrOH / 7 atm / RT / 0.3 % / 1.5 h	100	59
5	C_6H_6 / 7 atm / RT / 0.3 % / 3 h	15	40

1) solvent / hydrogenation pressure / temperature / catalyst loading / reaction time.

Under standard conditions (entry 1) the (2*R*,2′*R*)-catalyst gave (*R*)-*N*-acetylphenylalanine in 69% ee. Increasing the pressure to 40 atm had little effect upon selectivity (entry 2). However, the enantiomeric excess could be increased slightly to 75% when lowering the temperature to 6°C (entry 3). The use of solvents such as ^{i}PrOH or benzene gave selectivities of 59 and 40% ee, respectively (entries 4 and 5).

3. Conclusion

An enantiopure 2,2′-biphospholene (**3**) having a unique combination of backbone and P-centered chirality can be obtained through chromatographic separation of the diastereomeric palladium complexes **6a**/**b**. Inital tests in the rhodium-catalyzed asymmetric hydrogenation of α-acetamidocinnamic acid have shown good activity and enantioselectivities up to 75%.

We are currently synthesizing more ligands based on the 2,2′-biphospholene scaffold and investigating them in a range of processes. Further elaboration of this basic ligand structure is envisaged.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AC 200 SY spectrometer operating at 200.13 MHz for ^{1}H, 50.32 MHz for ^{13}C and 81.01 MHz for ^{31}P NMR. Chemical shifts are expressed in parts per million (ppm) downfield from external tetramethylsilane (^{1}H and ^{13}C) and 85% aqueous H_3PO_4 (^{31}P).

Due to their sensitivity to air, all manipulations with the free ligand **3** and the corresponding rhodium complex **7** were conducted with freshly degassed solvents under dry argon. In contrast, the apparently air-stable palladium complexes **6a**/**b** can be chromatographed without any precautions.

4.2. Synthesis and separation of the two diastereomeric complexes *6a* and *6b*

To a solution of 910 mg (2.4 mmol) 2,2′-bi(1-phenyl-3,4-dimethyl-2,5-dihydro-1*H*-phosphole) **3**[7] in 10 ml THF were added 1.4 g (2.4 mmol) bis{μ-chloro[(*R*)-*N*,*N*-dimethyl(α-methylbenzyl)amino-2-*C*,*N*]palladium(II)} **4**[9] and the solution was allowed to stir at room temperature for 15 min. Complete formation of the two diastereomeric complexes can be monitored by ^{31}P NMR ((THF): δ (ppm)=50.0, 49.1 (broader peak)). The solvent was removed in vacuo and the oily product was chromatographed on silica (270 g). The diastereomer characterized by the broader peak in the ^{31}P NMR at 49.1 ppm was eluted first with toluene:EtOAc (80:20) as solvent (yield: 955 mg; 83%); that showing the less broad peak at 50.0 ppm was eluted second with toluene:EtOAc (60:40) as solvent (yield: 820 mg; 76%).

Compound **6a**: ^{1}H NMR ($CDCl_3$): δ (ppm)=7.70–7.60 (m, 2H), 7.35–7.10 (m, 3H), 6.85–6.50 (m, 4H), 4.80–4.55 (m, 1H), 3.95–3.75 (m, 1H), 3.70–3.45 (m, 1H), 2.87 (s, 3H), 2.80–2.65 (m, 1H), 2.64 (s, 3H), 2.31 (s, 3H), 1.68 (s, 3H), 1.51 (d, J=7 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm)=153.5, 137.8 (d, J=7 Hz), 134.8, 134.0, 132.3, 132.1, 132.0, 131.8, 130.2, 128.5, 128.4, 128.3, 126.1, 124.4, 122.4, 60.3, 52.4, 49.8, 45.2, 42.7, 42.0, 17.1, 17.0, 16.9, 16.7. ^{31}P NMR (THF): δ (ppm)=49.1. $[\alpha]_D^{25}=-103$ (c=1.0, $CHCl_3$).

Compound **6b**: ^{1}H NMR ($CDCl_3$): δ (ppm)=7.85–6.50 (m, 9H), 4.70 (s, 1H), 4.15–3.90 (m, 1H), 3.71–3.45 (m, 1H), 2.87 (s, 3H), 2.80–2.65 (m, 1H), 2.60 (s, 3H), 2.31 (s, 3H), 1.70 (s, 3H), 1.51 (d, J=6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm)=152.4, 149.4, 137.0 (t, J=6 Hz), 134.7–133.2 (m), 132.1 (t, J=7 Hz), 131.9, 131.6, 128.3 (t, J=5 Hz), 126.0, 124.2, 122.7, 60.2, 52.2 (t, J=16 Hz), 49.0, 43.3, 42.4 (t, J=17 Hz), 17.2 (t, J=5 Hz), 16.7 (t, J=4 Hz), 15.6. ^{31}P NMR (THF): δ (ppm)=50.0. $[\alpha]_D^{25}=+82$ (c=0.96, $CHCl_3$).

4.3. Decomplexation of *6a* and *6b*

To a solution of 410 mg (0.43 mmol) of complex **6b** in 4 ml dichloromethane were added 2 ml of an aqueous saturated NaCN solution. The mixture was shaken vigourously for 30 min, water (10 ml) was added and the organic phase was separated. The aqueous phase was extracted twice with dichloromethane (2 ml). The combined organic phases were dried over magnesium sulfate, filtered and the solvent was removed in vacuo. The crude product was eluted over silica (2 g) with dichloromethane as solvent. Evaporation of the solvent afforded 110 mg (0.29 mmol, 67% yield) of the ligand as a colourless solid. ^{1}H NMR ($CDCl_3$): δ (ppm)=7.50–7.22 (m, 5H, Ph), 3.30–2.85 (m, 2H, CH_2), 2.60–2.45 (d, J=17 Hz, 1H, CH), 1.84 (s, 3H, CH_3), 1.84 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm)=142.3 (ψt, J=7 Hz, C_{ipso}), 132.5 (s), 132.3 (s), 131.8, 131.6, 131.4, 128.3, 128.2, 128.1, 59.5 (ψt, J=10 Hz), 38.5, 17.0, 14.6. ^{31}P NMR (CH_2Cl_2): δ (ppm)=−25.5. (+)-(2*R*,2′*R*)-**3** $[\alpha]_D^{25}=+125$ (c=0.71, CH_2Cl_2). From **6a**: (−)-(2*S*,2′*S*)-**3** $[\alpha]_D^{25}=-125$ (c=0.70, CH_2Cl_2).

4.4. Synthesis of tungsten complex ((+)-(R)-*3*)W(CO)$_4$

A mixture of $(CO)_5W(THF)$ (prepared from 350 mg (1 mmol) $W(CO)_6$ in 50 ml THF under UV irradiation for 1.5 h) and 190 mg (0.5 mmol) diphosphine (+)-**3** were stirred overnight at room

temperature. The solvent was removed in vacuo and the residue was chromatographed over silica with hexane:dichloromethane 80:20, affording 300 mg (86%) of ((+)-(*R*)-**3**)$W(CO)_4$ as white crystals. The product was recrystallized from $CDCl_3$:toluene 50:50. ^{1}H NMR ($CDCl_3$): δ (ppm)=7.70–7.55 (m, 2H, Ph), 7.45–7.25 (m, 3H, Ph), 3.90–3.52 (m, 1H), 3.28–2.83 (m, 2H), 1.60 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm)=208.4 m, CO), 201.4 (m, CO), 136.6 (ψt, J=17 Hz), 131.8 (t, J=3 Hz), 130.8, 130.1, 129.7 (t, J=5 Hz), 128.6 (d, J=5Hz), 57.8 (t, J=22 Hz), 45.3 (m), 16.5 (d, J=5 Hz), 14.9 (d, J=3 Hz). ^{31}P NMR ($CDCl_3$): δ (ppm)=52.2 ($^1J_{P-W}$=226 Hz). $[\alpha]_D^{25}$=+246 (c=1.32, $CDCl_3$).

*4.5. Synthesis of rhodium complex **7***

To a solution of 62 mg (0.2 mmol) (acetylacetonato)(1,5-cyclooctadiene)rhodium and 48 mg (0.3 mmol) tetrafluoroboric acid diethyl etherate in 2 ml THF was added a solution of 76 mg (0.2 mmol) 2,2′-bi(1-phenyl-3,4-dimethyl-2,5-dihydro-1*H*-phosphole) **3** in 1 ml THF dropwise over a period of 5 min. After stirring for 30 min, most of the solvent was removed in vacuo and diethyl ether (2 ml) was added to precipitate complex **7**. The upper layer was decanted, the residue was again washed with 2 ml diethyl ether and finally dried in vacuo. ^{31}P NMR (THF): δ=78.4 ppm (d, J_{Rh-P}=146 Hz).

*4.6. Hydrogenation of α-acetamidocinnamic acid **9***

To a 0.2 molar solution of 410 mg (2 mmol) α-acetamidocinnamic acid **9** in freshly degassed methanol was added 0.3–0.5 mol% of catalyst precursor **7**. The solution was subsequently transferred by means of a syringe into a hydrogenation bomb, previously purged three times with 7 atm hydrogen and stirred under 7 atm hydrogen for the indicated time. The pressure was released and the solvent was removed in vacuo. The conversion was determined from ^{1}H NMR spectra of the crude product in d_6-DMSO. A small sample was converted into its methyl ester with trimethylsilyldiazomethane in hexane:2-propanol=90:10, and the enantiomeric excess was determined by HPLC analysis using a Daicel column Chiralcel OD (hexane:2-propanol=90:10, 1 ml/min; retention times: 9.7 min (*R*), 12.3 min (*S*)).

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