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Enantiopure 1-*r*-*H*-2-*c*,5-*t*-diphenylphospholane as ligand in Rh-catalyzed asymmetric hydrogenation

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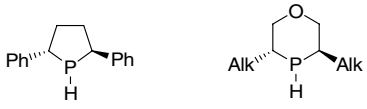
Abstract—Chiral enantiopure secondary phospholane 1-*r*-*H*-2-*c*,5-*t*-diphenylphospholane and the corresponding oxide are unusual and efficient ligands in the rhodium catalyzed hydrogenation of olefins.

1. Introduction

Enantiomerically pure phosphines have been—and still are—widely used as chiral ligands in a variety of metal-catalyzed enantioselective reactions.[1] Among them, binaphthyl-, ferrocenyl and phospholanyl-containing frameworks are important structures, which give good results in a broad range of applications.[2] However, all these are tertiary phosphines with three P–C bonds. The only example of using a secondary phosphine in asymmetric catalysis was described by Helmchen and co-workers.[3] The authors reported the synthesis and use of secondary phosphinane **2** in asymmetric hydrogenation (Fig. 1). Furthermore, chiral secondary phospholanes were found to be unknown as ligands.



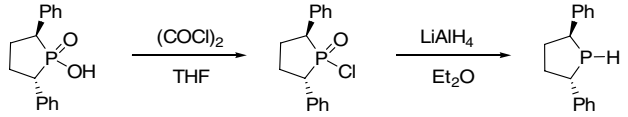
(*S*,*S*)-**1** **2**

Figure 1.

As part of our efforts to synthesize new, enantiopure 2,5-diphenylphospholane ligands,[4] we decided to fill this void and examined the potential of secondary (*S*,*S*)-1-*H*-2,5-diphenylphospholane **1** as a ligand. Herein we report that secondary phospholane, which may be considered as the parent of P-substituted-2,5-diphenylphospholane family offers good activity and enantioselectivity in Rh-catalyzed hydrogenations.

2. Results and discussion

The synthesis of **1** was carried out from the chiral enantiopure phospholanic acid **3**.[5] The acid was transformed quantitatively into phosphinyl chloride **4** using oxalyl chloride. Reduction of **4** with lithium aluminium hydride gave the expected phospholane **1** in an enantiopure form and quantitative yield (Scheme 1). This easy procedure offers an efficient and rapid pathway to this simple ligand.



(*S*,*S*)-**3** **4** (*S*,*S*)-**1**

Scheme 1. Synthesis of secondary phospholane **1**.

Due to the sensitivity of **1** towards oxidation, we decided to protect the ligand as a rhodium complex $Rh(COD)P_2BF_4$ **5**. This complex was prepared from $Rh(COD)_2BF_4$ precursor and 2 equiv of (*S*,*S*)-**1** in dichloromethane, as a brown, air-stable powder (Scheme 2).

The ^{31}P NMR analysis of complex **5** showed one clean sharp doublet ($\delta = 27.2$ ppm, $J = 142$ Hz), revealing the

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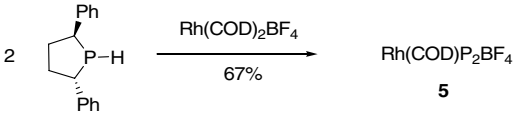
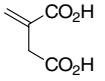
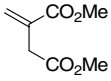
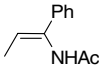
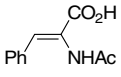
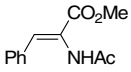
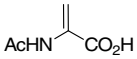
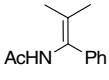
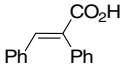
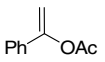


Scheme 2. Synthesis of (*S*,*S*)-**1** rhodium complex **5**.

formation of the C_2-symmetric [Rh(COD)(P^*)$_2$] complex. The results of asymmetric hydrogenation of activated olefins **6**–**14** catalyzed by the new chiral complex **5** are reported in Table 1.

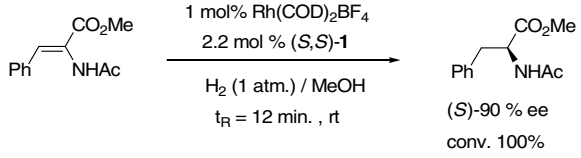
Table 1. Catalytic asymmetric hydrogenation using **1**-Rh complex[a]

	Substrate	H_2 (bar)	Conversion[b] (%)	$t_{1/2}$ (min)	ee[c] (%)
6		1	100	30	52 (*R*)
7		1	100	8	39 (*R*)
8		1	95	—[d]	28 (*R*)
9		1	100	8	68 (*S*)
10		1	100	23	82 (*S*)
11		1	100	4	58 (*S*)
12		1 40	0 62	— —[e]	— 8 (*S*)
13		1 40	0 0	— —	— —
14		1	0	—	—

[a] All reactions were carried out in methanol at room temperature in the presence of 1 mol % of complex **5** under one atmosphere of dihydrogen unless otherwise noted.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC or CPG analysis using Chiralcel OD-H or Chiraldex β-PM column, respectively.
[d] The reaction was carried out for 24 h under dihydrogen.
[e] The reaction was carried out for 5 days under dihydrogen.

We observed an excellent reactivity of the secondary phosphine complex for substrates **6**–**11**. A total conversion was obtained in most cases in less than 1 h reaction time under an atmospheric pressure of dihydrogen at room temperature. The reactions were rapid, with the exception of substrates **8**, **12**, **13** and **14**. Compound **8** needed 24 h of reaction time to reach 95% conversion. The tetrasubstituted compound **12** was not hydrogenated under atmospheric pressure of dihydrogen. A moderate conversion (62%) was obtained under pressure after 24 h reaction time. This result could be explained by the steric hindrance of the substrate. However the less sterically hindered compound **13** did not react, either at a low or a higher pressure. This suggests that steric hindrance is not solely responsible for the low reactivity. A common feature for substrates **8**, **12**, **13** and **14** is the presence of an α-phenyl substituent, which could inhibit the reactivity. The lack of reactivity of the simple substrate **14** seems to confirm this hypothesis. However, compound **10** reacted readily to give quantitatively the hydrogenated product with good enantioselectivity (82% ee).

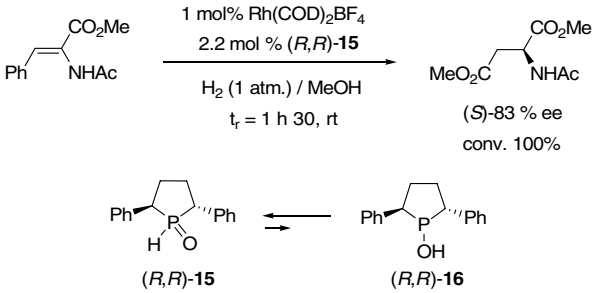
Under the same reaction conditions, compound **10** was hydrogenated in the presence of 1 mol % of Rh(COD)$_2$BF$_4$ and 2.2 mol % of (*S*,*S*)-**1** to generate the catalytic active species in situ, under rigorous exclusion of oxygen. Only 12 min were required for the total conversion, and the product was obtained in 90% ee (Scheme 3).



Scheme 3. Catalyzed hydrogenation reaction with (*S*,*S*)-**1** and Rh(COD)$_2$BF$_4$.

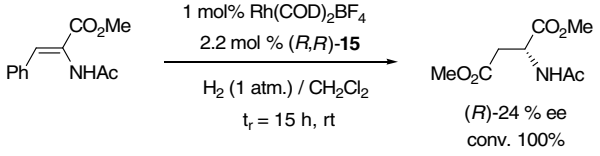
This result indicated that the secondary phospholane **1** is an efficient ligand in rhodium catalyzed hydrogenations. Compound **1** offers enantioselectivities, which compare well with P-substituted-2,5-diphenylphospholane.[6]

The corresponding oxidized analogue of (*R*,*R*)-**1** is the secondary phospholane oxide **15**. This compound described in our previous paper,[5] has been used in Ir-catalyzed asymmetric hydrogenation of imines.[7] It offers the advantage of not being sensitive towards oxygen. Considering the well-known equilibrium[8] between the secondary phosphine oxide and the hydroxy phosphine **16** it is suggested that **15** could be the precursor of the active species **16** as ligand. The Rh-catalyzed hydrogenation of (*Z*)-methyl-acetamidocinnamate **10** gave the product with total conversion and 83% ee (Scheme 4).



Scheme 4. Rh-catalyzed hydrogenation reaction with (*R*,*R*)-**15** and Rh(COD)$_2$BF$_4$ in methanol.

In dichloromethane, the same catalyst gave the product with only 24% ee as the (*R*)-enantiomer. This surprising inversion of configuration and the longer reaction time suggest a different mechanism and stereochemical course for hydrogenation in methanol or dichloromethane (Scheme 5). This could be the result of a different equilibrium of ligands **15** and **16**.



Scheme 5. Catalyzed hydrogenation reaction with (*R*,*R*)-**15** and $Rh(COD)_2BF_4$ in dichloromethane.

3. Conclusions

In conclusion, we have shown that a simple synthesis allows us to obtain the monodentate, secondary phosphine **1**. This simple compound appears as an active ligand for Rh-catalyzed hydrogenation of olefinic compounds. Investigations on the ability of **1** to give active chiral transition-metal complexes for the catalysis in other reactions are currently underway.

4. Experimental

Proton NMR spectra were recorded on Bruker 250, 360 or 400 MHz spectrometers. ^1H and ^{13}C NMR analyses of sensitive phosphorus compound **1** were realized under an argon atmosphere. Proton chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as internal reference (TMS, $\delta = 0.0$). *J* values are given in hertz (Hz). Carbon NMR spectra were recorded on Bruker 250 MHz (62.9 MHz) or 300 MHz (75.45 MHz) spectrometers with complete proton decoupling. Phosphorus NMR spectra were recorded at 101.2 MHz spectrometer with complete proton decoupling. The corresponding chemical shifts are reported in parts per million (δ) relative to the residual deuterated solvent or external phosphoric acid (H_3PO_4, $\delta = 0.0$). Flash column chromatography was performed using silica gel Merck (0.04–0.063 μm). Optical rotations were recorded at the sodium D line with a Perkin Elmer 341 polarimeter. The specific rotation [α] is given without the units (understood to be deg cm^2 g^{-1}). High-resolution mass spectra were obtained with a MAT95 Thermo-Finnigan spectrometer using electrospray or GC analysis. All reactions were carried out in Schlenk tubes under an argon atmosphere. All solvents were distilled from appropriate drying agents prior to use. The synthesis and experimental data of (*R*,*R*)-1-oxo-2,5-diphenylphospholane **15** were reported in our previous paper.[5]

4.1. (2*S*,5*S*)-(+)-2,5-Diphenylphospholane 1

(2*S*,5*S*)-(−)-1-Chloro-1-oxo-2,5-diphenylphospholane **2** (1 mmol) was suspended in freshly distilled diethyl ether (10 mL) after sonication and cooled at 0 °C. Lithium aluminium hydride (1.5 mmol) was added portionwise. The solution was stirred at room temperature for 16 h, then hydrolyzed with a minimum of water and filtered under argon to give a colourless solution. The solvent was removed in vacuo and phospholane **1** was obtained as a white solid and used without further purification. $[\alpha]_D^{20} = +104$ (*c* 0.95, $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): $\delta = 7.25$ (9H, m), 7.10 (1H, m), 3.90 (1H, m), 3.35 (1H, ddd, $J_{PH} = 190$ Hz, $J_{HH} = 11$ Hz and 11 Hz), 3.35 (1H, m), 2.45–2.55 (2H, m), 2.00–2.15 (1H, m), 1.75–1.90 (1H, m). ^{31}P NMR (101.2 MHz, $CDCl_3$): $\delta = -17.8$ (d, $J_{PH} = 190$ Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 38.8$ (d, $J_{PC} = 5$ Hz), 39 (s), 41.10 (d, $J_{PC} = 9$ Hz), 44.80 (d, $J_{PC} = 12$ Hz), 126.00 (d, $J_{PC} = 13$ Hz), 127.15 (d, $J_{PC} = 14$ Hz), 127.65 (d, $J_{PC} = 8$ Hz), 128.55 (s). HRMS (IE): $m/z = 240.1063$ found. Calcd for $C_{16}H_{17}P$: 240.1068.

4.2. Bis((*S*,*S*)-2,5-*trans*-diphenylphospholane)(cyclo-octa-1,5-diene)rhodium tetrafluoroborate 5

A Schlenk tube was charged with the desired enantiopure (*S*,*S*)-*trans*-2,5-diphenylphospholane **1** (1.7 mmol) in freshly distilled DCM (15 mL). A solution of $Rh(COD)_2BF_4$ (347 mg, 0.8 mmol) in DCM (5 mL) was then added at room temperature via cannula. The mixture was stirred for 3 h and the solvent was removed under reduced pressure to give an orange solid. This was washed with cold diethyl ether giving the complex as a powder (443 mg, 67%). ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 7.4$–7.0 (m, 20H, Ph); 5.6 (m, 1H, CH Bn); 5.0 (m, 2H, CH alkene); 4.4 (m, 2H, CH alkene); 4.3 (m, 2H, CH Bn); 3.3–3.2 (m, 1H, CH Bn); 2.7–2.6 (m, 4H, CH_2 phosphine); 2.3–2.1 (m, 4H, CH_2 phosphine); 2.1–1.5 (m, 8H, CH_2 (COD)). ^{31}P NMR (101.2 MHz, CD_2Cl_2), $\delta = 27.2$ (d, $J_{Rh-P} = 142$ Hz). ^{13}C NMR (62.9 MHz, CD_2Cl_2, δ ppm): 141.3 (Cquat), 138.0 (Cquat), 134.8 (Cquat), 129.8 (CHPh), 129.4 (CHPh), 129.0 (CHPh), 128.8 (CHPh), 128.4 (CHPh), 128.1 (CHPh), 127.5 (CHPh), 99.2 (CH=CH), 95.4 (CH=CH), 43.5 (CH phosphine), 43.3 (CH phosphine), 43.1 (CH phosphine), 42.8 (CH phosphine), 38.5 (CH_2 phosphine), 34.8 (CH_2 phosphine), 32.7 (CH_2 (COD)), 30.0 (CH_2 (COD)), 27.8 (CH (COD)). HRMS (Electrospray): $m/z =$ found: 691.2123. Calcd for $C_{40}H_{46}P_2Rh$: 691.2130.

4.3. Rhodium-catalyzed asymmetric hydrogenation: general procedure

A Schlenk tube placed in a glove box was charged with (*S*,*S*)-**1** (5.3 mg, 22 μmol) and bis(cyclooctadiene)rhodium tetrafluoroborate (4.1 mg, 10 μmol). The tube was then taken out of the glove box and charged with 5 mL of degassed, anhydrous methanol. The mixture was stirred for 20 min, and the yellow solution obtained was cannulated into a Schlenk tube containing 1 mmol of the chosen substrate under a hydrogen atmosphere. The uptake of hydrogen began immediately upon stirring. After completion of the reaction (no further hydrogen uptake), the resulting solution was concentrated in vacuo, taken up in dichloromethane (10 mL) and stirred with activated carbon for 1.5 h. Filtration over Celite and removal of the solvent afforded the hydrogenated product. Enantiomeric excesses

were determined by chiral HPLC on a Chiralcel OD-H column, with hexane/*i*-PrOH (90/10) as eluent or by chiral capillary GC using Chiraldex β-PM column.

Acknowledgements

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