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A FACILE METHOD FOR THE PREPARATION OF 2,4-BIS(DIPHENYLPHOSPHINO)PENTANE (BDPP) ENANTIOMERS AND THEIR APPLICATION IN ASYMMETRIC HYDROGENATION *

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Summary

Asymmetric heterogeneous hydrogenation of acetylacetone was applied for the preparation of both enantiomers (2*R*,4*R* and 2*S*,4*S*) of 2,4-bis(diphenylphosphino)pentane (BDPP). Among the chiral phosphines prepared up to now BDPP appears to be unique in the sense that its rhodium(I) complexes serve as effective homogeneous asymmetric hydrogenation catalysts not only for the reduction of *Z*-α-amidoacrylic acids but also for the reduction of α-ethylstyrene, acetophenone, and acetophenonebenzylimine. The analogous phosphinite ligand BDPOP yields a less selective catalyst.

Introduction

We have recently reported a convenient and efficient method for the preparation of the pure enantiomers of 2,4-bis[(diphenylphosphinyl)oxy]pentane (BDPOP) [1]. Rhodium complexes of this bidentate phosphinite were moderately effective in performing the catalytic asymmetric hydrogenation of olefinic precursors of α-amino acids. The corresponding diphosphine BDPP could not be obtained sufficiently pure at that time.

Simultaneous with our investigations a few 1,3-diphosphines have been prepared also by other groups [2,3] and because of their special interest the enantiomers of 2,4-bis(diphenylphosphino)pentane have been studied by Bosnich and his group in detail [3] **. They obtained these compounds only as oils however, and in poor yields. The reported method of preparation involved the separation of racemic

* Dedicated to Prof. J. Halpern.

** Bosnich's group has termed these compounds skewphos but in agreement with the nomenclature we used in our foregoing publication [1] the abbreviation BDPP will be used in this paper.

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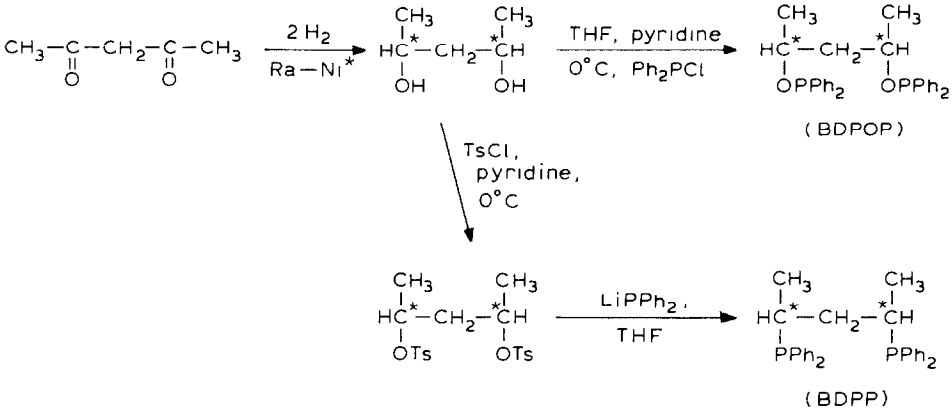
2,4-pentanediol from the *meso* form by fractional distillation of the sulfite esters and the separation of the two diastereomers of the bis(camphorsulfonate-d_{10} ester) of the racemic 2,4-pentanediol.

Now we report in detail the preparation of both enantiomers (2*R*,4*R* and 2*S*,4*S*) of 2,4-bis(diphenylphosphino)pentane (BDPP) starting from acetylacetone and using asymmetric heterogeneous hydrogenation over Raney-nickel modified with a mixture of tartaric acid and NaBr [4,5]. The 2,4-pentanediol enantiomers obtained in this way can be transformed with Ph_2PCl not only to the corresponding enantiomers of BDPOP [1] but also in the usual way via ditosylate to the corresponding enantiomers of BDPP which are obtained as crystalline materials in pure form (Scheme 1).

SCHEME 1



Experimental

Chemicals and apparatus

(−)-(2*R*,4*R*)- and (+)-(2*S*,4*S*)-2,4-pentanediol were prepared by hydrogenating acetylacetone in the presence of Raney-nickel catalyst modified with an aqueous solution of tartaric acid (the (*R*, *R*) or (*S*,*S*) enantiomer, respectively) and NaBr [1]. This preparative method was found to be reproducible and furnished the enantiomeric diols with 40–60% yields (10 experiments).

THF and benzene were distilled over sodium benzophenoneketyl, pyridine was distilled from BaO.

^1H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Tesla BS 487 C spectrometer at 80 MHz, and ^{13}C NMR spectra in $CDCl_3$ at 20 MHz, ^{31}P NMR spectra at 32.1 MHz on a Varian-CFT-20 spectrometer. The optical rotations of the products were measured on a Schmidt Haensch LM visual polarimeter. The optical yields were calculated using reported values for the optical rotations of the pure products [6–8].

Preparation of (−)-(2R,4R)-2,4-pentanediol ditosylate

To a mixture of 1.04 g (10 mmol) of (−)-(2*R*,4*R*)-2,4-pentanediol (optical purity above 97%) and 8.1 ml (100 mmol) of dry pyridine cooled to 0 °C, 4.78 g (25 mmol)

of *p*-toluenesulfonyl chloride was slowly added. The resulting suspension was allowed to stand for a night and then added to 100 ml of crushed ice with vigorous stirring. The organic layer was washed with diluted hydrochloric acid, an aqueous solution of Na_2CO_3, water and then dried over $MgSO_4$. The solvent was removed under reduced pressure leaving 3.7 g (90%) of a white crystalline solid, $[\alpha]_D^{20}$ −6.5° (*c* 3.17, $CHCl_3$). Anal. Found: C, 54.2; H, 5.9. $C_{19}H_{24}O_6S_2$ calcd.: C, 55.0; H, 5.8%.

^1H NMR (δ, ppm): CH_3 at 1.15 (d, *J* 6 Hz), CH_2 at 1.8 (t, *J* 6 Hz), CH_3(Ph) at 2.35 (s), CH at 4.63 (sext., *J* 6 Hz), H(aromatic) at 7.25 and 7.69 (d, d, *J* 8 Hz).

^{13}C NMR (δ, ppm): CH_3 21.2, (Ph) CH_3 21.5, CH_2 43.7, CH 76.7, aromatic carbons 145.3, 127.8, 130.0 132.9.

A completely analogous procedure was used to convert (+)-(2*S*,4*S*)-pentanediol into (+)-(2*S*,4*S*)-pentanediolbis(*p*-toluenesulfonate), $[\alpha]_D^{20}$ + 6.5° (*c* 3.79, $CHCl_3$).

(−)-(2S,4S)-2,4-bis(diphenylphosphino)pentane (BDPP)

To a magnetically stirred solution of 8.9 ml (50 mmol) of Ph_2PCl in dry THF (60 ml) finely cut strips of lithium (0.76 g, 110 mmol) were added. The mixture was refluxed for 3 h during which time the solution turned deep red. The phosphide solution was cooled to 0 °C and then 8.3 g (20 mmol) of (−)-(2*R*,4*R*)-pentanediolbis(*p*-toluenesulfonate) in 30 ml of dry THF was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. The light yellow solution was treated with 100 ml of deoxygenated water, THF removed at 30–40 °C (20 mmHg) and the aqueous layer extracted with 3 × 100 ml of ether. The etheral solution was worked up using the method of Bosnich and co-workers [3]. The product is a white crystalline solid, 3.95–4.20 g (45–48%, calculated for pentanediolbis(*p*-toluenesulfonate)), m.p. 81 °C, $[\alpha]_D^{20}$ −124° (*c* 3.0, $CHCl_3$) Anal. Found: C, 78.9; H, 6.91; P, 14.0. $C_{29}H_{30}P_2$ calcd.: C, 79.1; H, 6.82; P, 14.1%.

The ^1H NMR spectrum (in C_6D_6 at 25 °C, δ, ppm) of BDPP shows three well resolved resonances with the expected intensity for the aliphatic protons. A series of selective homonuclear decoupling experiments were performed to determine the coupling constants: CH_3 at 0.88 (dd, *J*(PCCH) 14 Hz, *J*(HH) 7 Hz), CH_2 at 1.52 (quint., *J*(PCCH) 7 Hz, *J*(HH) 7 Hz), CH at 2.41 (sept., *J*(PCH) 7 Hz, *J*(HH) 7 Hz).

^{13}C NMR (δ, ppm): CH_3 15.7 (d, *J*(PCC) 16.5 Hz), CH 27.2 (t, *J*(PC) 11 Hz, *J*(PCCC) −11 Hz), CH_2 36.4 (t, *J*(PCC) 18.5 Hz); aromatic carbons: C(1) 137.0 (d, *J*(PC) 14.9 Hz) 136.7 (d, *J*(PC) 14.0 Hz), C(2) 133.5 (d, *J*(PCC) 9.4 Hz), C(3) 128.2 (d, *J*(PCCC) 7.1 Hz), C(4) 128.7 (s).

^{31}P NMR (δ, ppm): −0.5 (s), upfield from external 85% phosphoric acid.

Mass spectrum (75 eV): $M^{\cdot+}$, *m/e* 440 (10%); $[M - C_6H_5]^+$ 363 (100%); $[M - P(C_6H_5)_2]^+$ 255 (10%); $[P(C_6H_5)_2]^+$ 185 (13%).

A completely analogous procedure was used to convert (+)-(2*S*,4*S*)-pentanediolbis(*p*-toluenesulfonate) into (+)-(2*R*,4*R*)-bis(diphenylphosphino)pentane, (m.p. 78 °C), $[\alpha]_D^{20}$ + 124° (*c* 4.0, $CHCl_3$). Anal. Found: C, 78.8; H, 6.91; P, 13.9. $C_{29}H_{30}P_2$ calcd.: C, 79.1; H, 6.82; P, 14.1%.

[Rh(NBD)-(+)-(2R,4R)-BDPP]ClO_4

A solution of 300 mg (0.68 mmol) of (+)-(2*R*,4*R*)-BDPP in 30 ml of methanol was added dropwise to a stirred solution of 142.8 mg (0.31 mmol) of $[Rh(NBD)Cl]_2$ in 80 ml of methanol. The orange-red solution was stirred for a further hour and then treated with a solution of 1.5 g of $NaClO_4 \cdot H_2O$ in 60 ml of deoxygenated

water. The resulting red orange precipitate was washed with water and diethyl ether and dried in vacuo to give 400 mg (88%) of product. Anal. Found: C, 56.3; H, 5.2; P, 8.4. $C_{36}H_{38}P_2ClO_4Rh$ calcd.: C, 58.8; H, 5.2; P, 8.4%.

^{31}P NMR: 24 ppm (d, J(Rh–P) 149 Hz).

Hydrogenation experiments

The rhodium complex and the appropiate amount of phosphine were dissolved under Ar. In the case of in situ catalyst systems composed of $[Rh(NBD)Cl]_2$ + BDPOP or BDPP the solution was prehydrogenated for 40 min at room temperature. Hydrogenations were performed in a glass reactor at atmospheric pressure or in 20 ml stainless steel autoclaves at 70 bar under the reaction conditions given in Tables 1–3.

Amino acid products were worked up by literature methods [9]. Products obtained from acetophenone or Schiff-base hydrogenations were separated from the catalyst by distillation and conversions were determined by GLC.

Results and discussion

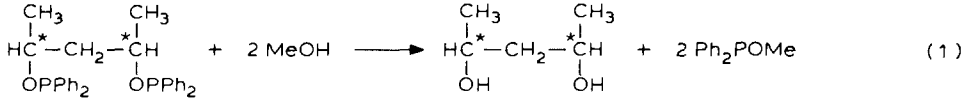
The method for the preparation of BDPP described in the experimental section is simpler than the earlier one reported for the same ligand in the literature [3] and gives a crystalline product with an overall yield of 16–26% (calculated for acetylacetone). In addition the pentanediol enantiomers obtained as intermediates can be transformed almost quantitatively into the corresponding enantiomers of BDPOP [1].

Catalytic hydrogenation of dehydroamino acids was carried out under ambient conditions. The results compiled in Table 1 show that BDPP gave higher enantioselectivities than BDPOP.

The values are in good agreement with those found by Bosnich and his coworkers [3] for the skewphos (BDPP) containing catalyst. As already described for similar systems [10] optical yields were independent of whether cationic or in situ catalysts obtained from $[Rh(NBD)Cl]_2$ + ligand were used, but the rates were lower with the latter systems. In general, higher optical yields were obtained with substrates containing stronger electron-withdrawing groups (COOH > COOMe, Ph > H, PhCO > MeCO). In the case of BDPOP the products had the same configuration as the ligand, with BDPP the opposite enantiomers were formed.

The complexes formed from BDPP were not only selective but also rather active catalysts: turnover numbers between $1–30 \times 10^{-2}$ s^{-1} could be obtained in the hydrogenation of Z-α-amidoacrylic acids. Accordingly this ligand yields catalysts which are almost as active as those formed in the presence of prophos [11] and compare very favorably with similar catalysts based on the structurally analogous chiraphos ligand (turnover numbers $0.06–2 \times 10^{-2}$ s^{-1} [7]).

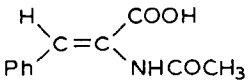
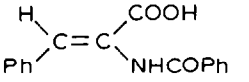
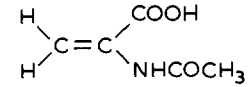
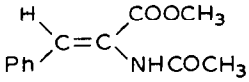
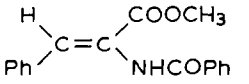
The enantioselectivity of the BDPOP-containing catalysts did not depend on the solvent (Table 1). This proves, that methanol does not solvolyze the chiral phosphinite (eq. 1) to yield achiral catalysts.



(1)

TABLE 1

HYDROGENATION OF DEHYDROAMINO ACIDS [a]. OPTICAL YIELDS (%)

Substrate	$[Rh(NBD)(BDPP)]^+ ClO_4^-$ [b]	$[Rh(NBD)Cl]_2$ + BDPOP [c,d]	$[Rh(NBD)_2]^+ BF_4^-$ + BDPOP [b,d]
	96	68	67
	88	78	78
	90	53	52
	72	48	48
	79	71	68

[a] Reaction conditions: 30 °C, 1 bar H_2; 2.5 mmol of substrate; substrate/Rh = 100/1; 10 ml of solvent; conversion: 100%. [b] In methanol or THF. [c] In benzene/methanol 1/1. [d] P/Rh 2.2/1.

TABLE 2

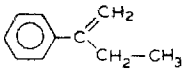
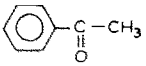
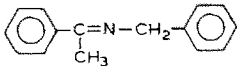
INFLUENCE OF REACTION TEMPERATURE ON OPTICAL YIELD AND TURNOVER NUMBER [a] IN HYDROGENATION OF (Z)-$C_6H_5CH{=}C(NHCOCH_3)COOH$ [b]

Temperature	Catalyst (S,S)-BDPP + $[Rh(NBD)_2]^+ BF_4^-$		Catalyst (R,R)-BDPOP + $[Rh(NBD)_2]^+ BF_4^-$	
	Optical yield % [c]	Turnover number $10^{-2}\ s^{-1}$	Optical yield % [c]	Turnover number $10^{-2}\ s^{-1}$
−50	–	–	76	0.4
−20	98	2.8	74	1.4
0	97	8.3	73	6.9
30	95	16.8	71	16.7
40	95	27.8	–	–
50	94	37.5	–	–
60	91	30.6	69	22.2
70	92	27.8	–	–

[a] At 50% conversion. [b] Reaction conditions: substrate/Rh/P 100/1/2.2; 1 bar H_2; solvent: 10 ml of ethanol, conversion: 100%. [c] Prevailing enantiomer: (R)-(−).

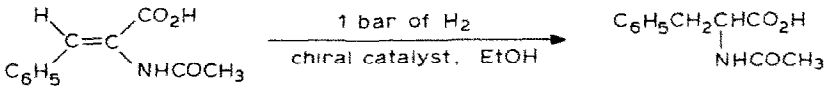
TABLE 3

ASYMMETRIC HYDROGENATION OF C=C, C=O AND C=N DOUBLE BONDS [a]

Substrates	Catalyst $[Rh(NBD)Cl]_2$ + (*S*,*S*)-BDPP		Catalyst $[Rh(NBD)Cl]_2$ + (*R*,*R*)-BDPOP	
	Optical yield (%) (configuration)	Conversion (%)	Optical yield (%) (configuration)	Conversion (%)
	54 [b] (*S*)	95	27 [c] (*S*)	100
	82 [d] (*S*)	72	50 [e] (*S*)	46
	73 [f] (*R*)	96	8 [g] (*S*)	98

[a] Substrate/Rh/P 100/1/2.2, 10 ml of solvent. [b] Benzene/methanol 1/1, 30 °C, 1 bar H_2, 20 h, Et_2N/Rh 2.0, 10 mmol of substrate. [c] Ethanol, 30 °C, 1 bar H_2, 20 h, 10 mmol of substrate. [d] Methanol, 50 °C, 70 bar H_2, 24 h, Et_3N/Rh 5.0, 5 mmol of substrate. Optical yield was determined by using the optically active NMR shift reagent tris[(3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III). [e] Benzene/methanol 1/1, 50 °C, 70 bar H_2, 24 h, Et_3N/Rh 2.0. [f] Methanol, 20 °C, 70 bar H_2, 6 h, Et_3N/Rh 8.0, 5 mmol of substrate. [g] Methanol, 30 °C, 70 bar H_2; 6 h, 5 mmol of substrate.

The temperature dependence of optical yields with BDPOP and BDPP-containing catalyst systems was determined for reaction 2.



(2)

Due to the high activity of the catalysts, data over an unusually broad temperature range could be obtained. The results are compiled in Table 2. These show that the selectivity of both catalysts is rather insensitive to temperature. Considering the high flexibility of 6- and 8-membered rings this results was somewhat unexpected.

The enantioselectivity of the BDPP-containing catalyst decreased with increasing hydrogen pressure. At 50 bar and 0 °C the optical yield obtained in the hydrogenation of *Z*-α-acetamidocinnamic acid was 82%. Such an effect of pressure has already been observed with several other chiral phosphines [12–14] and has been explained by Halpern [15].

A notable feature of the BDPP-containing catalyst is its relatively high enantioselectivity in the hydrogenation of simple olefins, ketones and Schiff bases (Table 3). Although the catalyst is much less active for reduction of the substrates mentioned above than for dehydroamino acids, nevertheless under adequate conditions reasonable activities could be achieved.

The 54% optical yield in the hydrogenation of α-ethylstyrene is much higher than

that observed with DIOP and closely approaches the best value (60%) reported for this substrate up to now [16]. In the case of acetophenone the optical yield shown in Table 3 (82%) is to our knowledge the highest value ever obtained for this substrate [17]. Finally, the 73% enantiomeric excess observed in the asymmetric hydrogenation of acetophenone benzylimine is the highest value obtained up till now with a Schiff base [8,18,19].

These results shown that BDPP is a unique ligand in the sense that it is suitable for the efficient asymmetric hydrogenation of not only *Z*-α-amidoacrylic acids but also of such simple unsaturated substrates which have no additional functional groups that could lead to a secondary interaction between the substrate and the catalyst. Actually, a survey of relevant literature data [7–9, 11–14, 20–25] shows, that BDPP apparently surpasses all chiral phosphine ligands known in enantioselectivity if a broad range of substrates is considered.

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