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Aminophosphine phosphinites of propranolol analogues as ligands for Rh-catalyzed asymmetric hydrogenation

H.W. Krause *, U. Schmidt, S. Taudien, B. Costisella [1], M. Michalik

Institut für Organische Katalyseforschung an der Universität Rostock e.V., Buchbinderstr. 5/6, 18055 Rostock, Germany

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Abstract

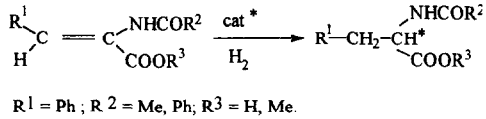
Chiral aminophosphine phosphinites of a series of propranolol derivatives have been prepared and their Rh chelates tested in the asymmetric hydrogenation of standard amino acid precursors. In order to optimize the stereoselectivity of the catalyst the N-substituents of the starting 1,2-amino alcohols were varied to introduce various steric and electronic effects. Direct correlations to steric constants, values of pK_a or data from ^{31}P-NMR and ^{13}C-NMR could not be discerned. This concerns especially the pronounced difference in ee between the *N*-methyl **4** and *N*-isopropyl derivative **5**. ^{31}P NMR spectra hint at the electronic effect of the N-substituent.

Keywords: Chiral Rh complexes; Aminophosphine; Phosphinites; Propranolol; Asymmetric hydrogenation; Steric influence; NMR data

1. Introduction

In the series of ligands L used in the Rh(I)-catalyzed asymmetric hydrogenation of dehydroamino acids chiral bidentate aminophosphine phosphinites of several optically active 1,2-amino alcohols have been found to give highly active catalysts in reaction 1 [1–5,7].

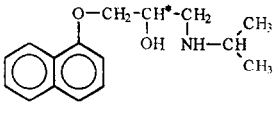
Among these, the derivatives of the readily available β-adrenolytically active propranolol, I, proved to be suitable for the asymmetric hydrogenation according to reaction 1 [6]



(1)

R^1 = Ph ; R^2 = Me, Ph; R^3 = H, Me.

giving rise to an enantiomeric excess of about 76–94%. **19** applied to other similar substrates reacts also with high enantiomeric excess [9–12]. On the assumption that the selectivity is caused mainly by the steric or electronic influence of the N-substituent R^4 (instead of the isopropyl group) we decided to prepare further optically active analogues of propranolol, their aminophosphine phosphinites and their rhodium complexes in order to optimize the enantio-differentiation of the catalyst and to seek for possible correlations with measures of steric and electronic effects and NMR data.



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* Corresponding author.

[1] Institut für Angewandte Chemie, Abtl. Analytik, Berlin-Adlershof.

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This concept was stimulated by results of Hatat et al. [8,13] who have shown the selectivity and activity in the hydrogenation of diketones to be influenced mainly by the aminophosphine group.

2. Experimental

2.1. Apparatus

Optical rotations were measured by the electrical polarimeter Polamat A (Carl Zeiss, Jena) or a Gyromat HP (Fa. Kernchen). ^{31}P NMR taken proton decoupled on a Varian CFT-20. ^{13}C NMR spectra were recorded on Bruker ARX-300 spectrometer. The enantiomeric excess was determined directly by GLC using a Hewlett Packard 5880 A chromatograph fitted with 12 m fused silica capillary column deactivated by Carbowax 20 M for acetyl phenylalanine methyl ester (150°C) or a 4.30 m capillary column for benzoyl phenylalanine methyl ester (175°C) XE 60 both coated with L-valine-tert.butylamide. FID, split 1:60. HPLC analysis was performed as described in [14]. All preparations were carried out under argon, the solvents were purified and dried where possible with Na/benzophenone and stored under argon. The hydrogenation reaction was performed under normal pressure as described in [15].

2.2. Chemicals

Dehydroamino acids were prepared by known methods as cited in [6].

1(1-Naphthyloxy)-2-hydroxy-3-methylaminopropane hydrochloride was prepared according to [16,17]. M.p. 183°C, o.p. = 96.8%

*(S)-1(1-Naphthyloxy)-2-hydroxy-3(α-phenylbenzylamino)propane hydrochloride. (S)-**6**·HCl*

To NaH (1.2 g) in DMF(40 ml) it was added a solution of α-naphthol (6.1 g, 43.3 mmol) in DMF (20 ml). After 30 min (*S*)-(+)-glycidyl tosylate (9.2 g) was added and the solution stirred for 4 h at room temperature. It was diluted with water and several times extracted with ether. The dried ether was removed yielding a brown oil. This was used without further purification in the next step. Al_2O_3 (neutral, activity 1, Greiz-Dölau) (37.5 g) was dispersed in ether to which α-phenylbenzylamine (1.5 g) was added and stirred. After 5 minutes the naphthyloxyepoxypropane (1 g) was added and the course of the reaction followed by TLC (approximately 32 h). Methanol was added, the Al_2O_3 filtered off, the solvent removed in vacuo and the residue dissolved in isopropanol. Isopropanol containing HCl was added to give an acidic solution. The hydrochloride fast precipitating was recrystallized two times from isopropanol. The product was checked by HPLC and analyzed. Colorless crystals M.p. 191–197°C, $[\alpha]_D^{25}$ −8.6 (*c* 1.18, MeOH), o.p. 75.9%. $C_{26}H_{26}NOCl$ (419.93). Calcd. C 74.36 H 6.24 N 3.34. Found C 74.39 H 6.15 N 3.31.

*(S)-1(1-Naphthyloxy)-2-hydroxy-3(3-pentylamino)propane, (S)-**7**·HCl*

The 1(1-Naphthyloxy)epoxypropane was obtained similarly to the procedure given above from NaH (0.44 g), α-naphthol (1.8 g) in DMF (6 ml), and (*S*)-(+)-glycidyltosylate (2.6 g) in DMF (6 ml). To the epoxide 3-pentylamine (10 g) and water (1.1 ml) were added and heated with stirring for 4 h at 90°C. The cooled mixture was diluted with water (25 ml) and extracted with ether (3×) the ether washed subsequently with 1 N NaOH, brine and dried. Removal of the solvent gave an oil transformed to the hydrochloride as above. Yield: 2.2 g. M.p. 149–152°C. $[\alpha]_D^{25}$ −18.2 (*c* 1.06, MeOH), o.p. 81.7%; $C_{18}H_{26}NO_2Cl$ (323.85). Calcd. C 66.75 H 8.09 N 4.33. Found C 66.56 H 7.90 N 4.58.

*(S)-1(1-Naphthyloxy)-2-hydroxy-3-cyclopentylaminopropane hydrochloride. (S)-**8**·HCl*

1(1-Naphthyloxy)epoxypropane was prepared similarly to the procedure given above from NaH (0.44 g)in DMF (11.7 ml), α-naphthol (1.8 g) in DMF (6 ml) and (*S*)-(+)-glycidyltosylate (2.6 g) in DMF (6 ml). The cyclopentylamine (9.8 g = 11.4 ml) and water were added as outlined in (*S*)-**7**. Yield: 2.2 g. M.p. 223–226°C.

$[\alpha]_D^{20}$ −20.2 (*c* 1, MeOH), o.p. 92.8% $C_{18}H_{24}NO_2Cl$ (321.86). Calcd. C 67.17 H 7.50 N 4.3. Found C 66.95 H 7.64 N 4.49.

*(S)-1(1-Naphthyloxy)-2-hydroxy-3-cyclohexylaminopropane hydrochloride. (S)-**9**·HCl*

A procedure similar that of (*S*)-**8**·HCl was used, using cyclohexylamine (11.4 g = 13.1 ml) and water (1.1 ml). Yield: 2.1 g. M.p. 223–228°C. $[\alpha]_D^{20}$ −28.1 (*c* 1, MeOH), o.p. 95.3%. $C_{19}H_{26}NO_2Cl$ (335.86). Calcd. C 67.94 H 7.80 N 4.17. Found C 67.49 N 4.32.

*(S)-1(1-Naphthyloxy)-2-hydroxy-3-aminopropane hydrochloride. (S)-**10**·HCl*

The glycidyl derivative was prepared similarly to (*S*)-**6** starting with α-naphthol (6.1 g). The epoxide was dissolved in toluene washed with water and dried. The toluene was evaporated in vacuo and to the yellow oily residue phthalimide (5.2 g) and potassium phthalimide (1 g) added. The mixture was heated to 180°C for 30 min. and the deep red product recrystallized from EtOH. The phthalimide (0.9 g) was suspended in EtOH (10 ml) and hydrazine hydrate (25%, 1 ml) was added. The mixture was heated to 50°C for 30 min. whereby a colorless gelatinous precipitate was formed. 1 N HCl was added and the mixture heated becoming clear but soon especially on cooling a precipitate was formed which was filtered off. The solution was made alkaline and extracted several times with ether. After drying the solvent was removed in vacuo and the amine transformed to the hydrochloride as described above. Recrystallization from isopropanol. Colorless crystals M.p. 212–222°C. $[\alpha]_D^{25}$ −18.7 (*c* 1.02, MeOH), o.p. 96.8%. $C_{13}H_{16}NO_2Cl$ (253.72). Calcd. C 61.54 H 6.36 N 5.52. Found C 61.75 H 6.18 N 5.50.

*1-(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3-methylaminopropane, **11** rac.*

To **4**·HCl (2.7 g) in benzene (30 ml) was added Et_3N (8.5 ml). The mixture was heated to 50°C with stirring. Within one hour chlorodiphenylphosphine (3.9 ml) in benzene (20 ml) was added dropwise and heating continued at 80°C for further 3 h. After standing for 12 h the formed salt was filtered off over glass wool and Celite 545 (Ferrak, Berlin) and the filtrate concentrated. The resulting oil was dried by heating for three hours at 50°C and 133.3 Pa.

$C_{38}H_{35}NO_2P_2$ (599.62). Calcd. C 76.11 H 5.88 N 2.34 P 10.33. Found C 75.81 H 5.99 N 2.53 P 10.21. MS: *m/e* 599 (M^+), 386 (impurity PPh_2–PPh_2O), 472, 262, 201.

*1-(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3-methylaminopropanerhodium (1,5-cyclooctadiene)tetrafluoroborate, (S)-**18**, rac.*

11 (2.3 g) and RhCOD(acac) (1.16 g) were dissolved in abs. THF (8 ml) by stirring for 5 min. HBF_4 (0.7 ml, 40%) was added and stirring continued for 30 min. To the clear red solution ether (1–3 ml) was added and the crystallisation carried out in a refrigerator yielding a fine powdered yellow–brown complex which was filtered, washed with ether and dried.

$C_{46}H_{47}NO_2P_2BF_4Rh$ (897.53). Calcd. C 61.55 H 5.28 N 1.56 P 6.90. Found C 60.91 H 5.57 N 1.64 P 6.16

*(S)-(+)-1(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3-methylaminopropane, (S)-**11***

A procedure similar that of **11** rac. was used, starting with (*S*)-(−)-**4** (2.7 g hydrochloride). Yield: 6.2 g (88%) weakly yellow oil, $[\alpha]_D^{23}$ 64.9 (*c* 2.41, benzene). $C_{38}H_{35}NO_2P_2$ (599.62). Calcd. C 76.11 H 5.88 N 2.34 P 10.33. Found C 76.40 H 5.94 N 2.35 P 10.20. ^{1}H-NMR ($CDCl_3$): 2.42 (d, $^3J_{(HP)} = 5$ Hz (CH_3); 3.46 (dd, $^3J_{(HH)} = 6$ Hz; $^3J_{(HP)} = 12$ Hz (CH_2), 4.12 (m, O–CH_2), 4.46 (m,O–CH), 6.3–7.5 (m, aromatic).

*(S)-1(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3-methylaminopropanerhodium (1,5-cyclooctadiene)tetrafluoroborate, (S)-**18***

A procedure similar that of **18** rac. was used, starting with (*S*)-(+)-**11** (5 g), RhCOD(acac) (2.5 g), THF (18.7 ml), HBF_4 (1.52 ml, 40%) yielded the complex (3.5 g, 46.8%) as a fine orange–red powder.

$C_{46}H_{47}NO_2P_2BF_4Rh$ (897.53). Calcd. C 61.55 H 5.28 N 1.56 P 6.90 Rh 11.47. Found C 60.77 H 5.52 N 1.54 P 6.02 Rh 11.57.

*(S)-1(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3(3-pentylamino)propane, (S)-**14***

Using a procedure similar that of **11** rac., (*S*)-**7** (0.7 g hydrochloride), benzene (6.5 ml), Et_3N (2.3 ml), chlorodiphenylphosphine (0.8 ml) in benzene (4.3 ml), gave the product as an oil. $C_{42}H_{43}NO_2P_2$ (655.72). Calcd.C 76.93 H 6.61 N 2.14. Found C 76.56 H 6.94 N 2.20, $[\alpha]_D^{23}$ +35.1 (*c* 0.62, benzene).

*(S)-1(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3(3-pentylamino)propanerhodium (1,5-cyclooctadiene)tetrafluoroborate, (S)-**21***

A procedure similar that of **18** was used, starting with (*S*)-**14** (3.1 g), RhCOD(acac) (1.4 g) in THF (3 ml), HBF_4 (0.84 ml, 40%). Orange–red crystals. $C_{50}H_{55}NO_2P_2RhBF_4$ (953.63). Calcd. C 6297 H 5.81 N 1.47 P 6.50 Rh 10.79. Found C 62.95 H 5.83 N 1.39 P 6.87 Rh 10.81.

*(S)-1(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3-cyclopentylaminopropane, (S)-**15***

According to (*S*)-**11** starting with (*S*)-**8** (1.5 g hydrochloride), benzene (14 ml), Et_3N (3.9 ml) and chlorodiphenylphosphine (1.8 ml) in benzene (9.3 ml). $C_{42}H_{41}NO_2P_2$ (653.70). Calcd. C 77.16 H 6.32 N 2.14 P 9.4. Found C 75.55 H 6.42 N 2.41 P 9.51. $[\alpha]_D^{20}$ +60.8 (c 0.76, benzene).

*(S)-1(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3-cyclopentylaminopropanerhodium (1,5-cyclooctadiene)tetrafluoroborate, (S)-**22***

According to **18** starting with (*S*)-(+)-**15** (2 g), RhCOD(acac) (0.9 g) in THF (1.9 ml) and HBF_4 (0.543 ml, 40%). Orange–red crystals. $C_{50}H_{53}NO_2P_2RhBF_4$ (951.61). Calcd. C 63.10 H 5.61 N 1.47 P 6.51 Rh 10.81. Found C 62.77 H 5.56 N 1.54 P 6.67 Rh 10.27.

*(S)-(+)-1(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3-cyclohexylaminopropane, (S)-**16***

According to (*S*)-**11** starting with (*S*)-**9** (1.5 g hydrochloride), benzene (13.4 ml), Et_3N (3.8 ml) and chlorodiphenylphosphine (1.74 ml) in benzene (8.9 ml). $C_{43}H_{43}NO_2P_2$ (667.73), Calcd. C 77.34 H 6.49 N 2.10 P 9.2. Found C 75.94 H 6.61 N 2.29 P 8.68. $[\alpha]_D^{22}$ +68.5 (*c* 1, benzene).

*(S)-1(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3-cyclohexylaminopropanerhodium (1,5-cyclooctadiene)tetrafluoroborate, (S)-**23***

A procedure similar that of (*S*)-**22** was used, starting with (*S*)-**16** (2.1 g), RhCOD(acac) (0.9 g), THF (2 ml), HBF_4 (0.55 ml, 40%). Orange–red crystals. $C_{51}H_{55}NO_2P_2RhBF_4$ (965.64). Calcd. C 63.43 H 5.74 N 1.45 P 6.42 Rh 10.66. Found C 63.30 H 5.71 N 1.53 P 5.94 Rh 10.31.

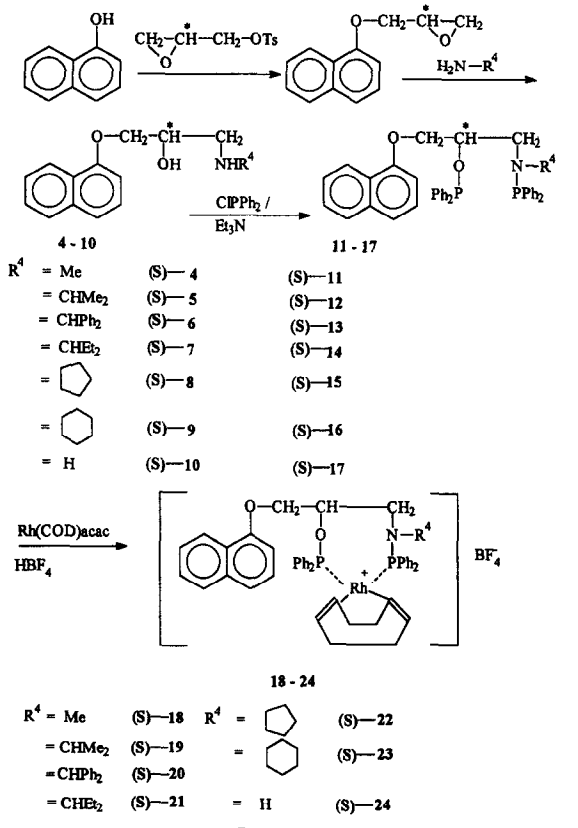
*(S)-1(1-Naphthyloxy)-2,3-O,N-bis(diphenylphosphino)-2-hydroxy-3-aminopropane, (S)-**17***

From (*S*)-**10** using a procedure similar to that of **11** rac. (*S*)-**7** (0.9 g) in benzene (11 ml), Et_3N (3 ml) chlorodiphenylphosphine (1.4 ml) in benzene (7.1 ml). Oil. $C_{37}H_{33}NO_2P_2$ (585.59). Calcd. C 75.88 H 5.68 N 2.39 P 10.58. Found C 76.17 H 5.89 N 2.29 P 10.54. $[\alpha]_D^{23}$ +26.2 (*c* 1.46, benzene).

3. Results and discussion

The propranolol analogues **4**, **6–10**, which may be also of interest in respect of their potential cardiovascular properties, were prepared by the reaction sequence shown in Scheme 1. Steric and electronic effects were modified by introducing *N*-methyl ($R^4 = Me$) **4**; *N*-diphenylmethyl ($R^4 = Ph_2CH$) **6**; *N*-diethylmethyl ($R^4 = Et_2CH$) **7**; *N*-cyclopentyl (R^4 = cyclopentyl) **8**; and *N*-cyclohexyl (R^4 = cyclohexyl) **9** residues. The primary amino alcohol **10** was also prepared.

As shown in Scheme 1 the racemic amino alcohol **4** was made from the racemic epoxide. Resolution with 2,3-ditoluoyltartaric acid provided the enantiomers of **4**, which were also prepared starting from the optically active glycidyl tosylates and sodium naphtholate. The ring-opening reaction with methylamine in this case proceeds with retention of configuration, but takes place with inversion of the configuration on C2 when the optically active epichlorohydrin is used instead of the tosylate. For **6–10** only the route via the tosylates was used. The reaction of the epoxide with the amines was carried out with an excess of the latter what was later removed by distillation. During this process some racemisation was observed, especially when higher temperatures and longer heating periods were necessary, as in the synthesis of **6** and **7**. The optical purities of the amino alcohols were checked by HPLC (see Table 3) [14]. Compound **10** was made by the Gabriel synthesis [18]. Ring-opening proceeds in the presence of potassium phthalimide, care must be taken to maintain alkaline conditions. Hydrazine hydrate cleavage affords the free amine [19].



Scheme 1.

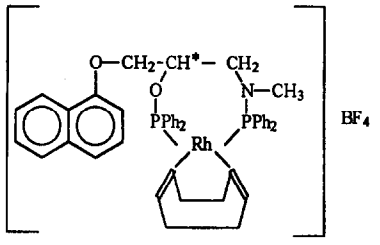
3.1. Ligand synthesis

The course of the subsequent reactions with chlorodiphenylphosphine to obtain the ligands depends on the steric properties and the basicity of the amino alcohols. Whereas **4** and **10** react within 3 h without complication, others behave differently. For example after 3 h **14** displays an O–P (δ 112.9 ppm) and a N–P (δ 44.3 ppm) signal in ^{31}P NMR and a second one (δ 114.3 ppm) arising from only O-phosphinylation. This shows that O-phosphinylation is favoured, as already observed by Petit et al. [13]. Monophosphinylation occurs nearly exclusively in the cases of the *N*-tert.butyl and *N*-diphenylmethyl derivatives because of the bulkiness of the substituents.

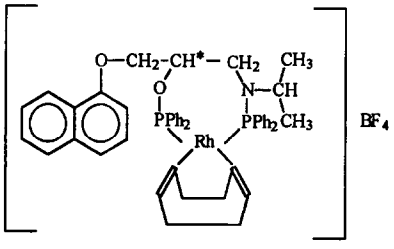
3.2. Catalyst synthesis

The rhodium catalysts **18–24** are easily made from the ligands **11–17** (except from **13**). Proprapphos **19** has been prepared formerly [6] by addition of HBF_4 to the equimolar mixtures of the ligands and RhCOD(acac). Except for **24** which was used in situ, the Rh complexes gave orange crystals relatively stable in air. Complexes **18**, either racemic or optically active turned out to be less soluble in THF than the analogous proprapphos–Rh complex **19**,

Table 1
Catalytic asymmetric hydrogenation of dehydroamino acids and esters catalyzed by the cationic (*S*)-Rh complexes **18** and **19** (substrate: (*Z*)-R–CH=C(NHCOR′)–COOR″)



18



19

Entry	Complex	R	R′	R″	Substrate/Rh	*t*/2 min	ee %
1	18	Ph	Me	H	100	1.9	45
2	**18**	Ph	Me	Me	100	1.8	47
3	**18**	Ph	Ph	H	100	2.4	41
4	**18**	Ph	Ph	Me	100	3.8	40
5	**18**	Ph	Me	H	1000	40.0	9
6	**18**	Ph	Ph	H	1000	40.0	3
7	**18**	Ph	Me	Me	100	7.0	40 [a]
8	**19**	Ph	Me	H	100	2.0	87
9	**19**	Ph	Me	Me	100	2.0	87
10	**19**	Ph	Ph	H	100	~1.0	89
11	**19**	Ph	Ph	Me	100	~1.0	89

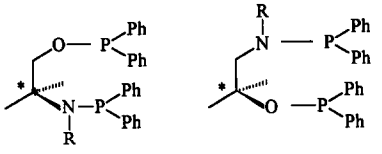
Conditions: Substrate 1 mmol (entry 5 and 6 = 10 mmol), Rh complex 0.01 mmol, methanol 15 ml, 25°C, 0.1 MPa H_2, conversion 100%, configuration (*R*).
[a] Catalyst prepared in situ.

3.3. Asymmetric hydrogenation

Table 1 shows the results of the catalytic asymmetric hydrogenation of N-protected aminoacrylic acid derivatives in the presence of cationic Rh complexes **18** and **19**.

The most striking feature is the drastic fall in enantioselectivity from ≥ 80% ee (Table 1, entry 8–11) to 40–50% ee (entry 1–7) on going from **19** to **18** and this is accompanied by a fall in rate, especially in the case of the neutral complexes as summarized in Table 2.

The result is in contrast to those observed in the series of OP–NP ligands derived from amino acids [2] such as (*S*)-AlaNOP to (*S*)-LeuNOP for which variation of R in N–R results in the sequence Me > Me_2CH > (*S*)-Et(Me)CH > Me_2CHCH_2 of decreasing ee% (configuration *R*). Examination of the two structures shown below (II)

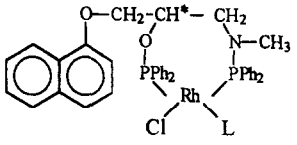


normal iso

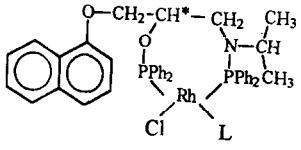
II

reveals that increase in the size of R in the neighbourhood of the stereo-controlling position probably reduces the stability of the first intermediate between the Rh complex and the substrate. For the 'iso' series, on the other hand, the preference for a distinct conformation is raised by increasing the N-basicity combined with increasing steric effect of R. The higher basicity of P(N) compared with P(O) in the aminophosphine phosphinites result in the double bond of the substrates to be bound trans to P(N), because the basic P(N) donor allows better matching with the higher π-acceptor character of the C=C double bond than with that of the C=O bond. From the theoretical two pairs of the catalyst–substrate complexes (each a major and minor complex) the two P(N)–C=C complexes should be prevailing. Indeed, recently carried out ^{31}P NMR experiments allowed the identification of three species (the fourth could not be seen) at lower temperatures in the case of dimethyl itaconate, showing the trans P(N)–C=C bound species to be in great excess [23]. Thus an arrangement as in III, with P(N) trans to the olefin may also predominate with the dehydroamino acid derivatives.

Table 2
Catalytic asymmetric hydrogenation of dehydroamino acids and esters catalyzed by the neutral (*S*)-Rh complex **18** and **19** (substrate: (Z)-R-CH=C(NHCOR')COOR")



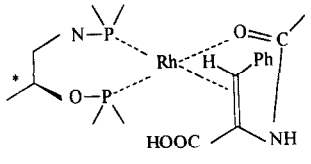
18



19

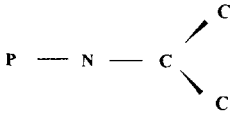
Entry [a]	Complex	R	R'	R"	Substrate/Rh	*t*/2 min	ee %
1	**18**	Ph	Me	H	100	15	20
2	**18**	Ph	Ph	H	100	12	24
3	**18**	Ph	Me	Me	100	20	47
4	**18**	Ph	Ph	Me	100	21	41
5	**19**	Ph	Me	H	100	7	88
6	**19**	Ph	Ph	H	1000	15	89

[a] For conditions see Table 1.



III

Because of the N,O exchange in the AlaNOP to the iso AlaNOP series (see II) the latter provides the opposite configuration of the emerging amino acids. This is in good agreement with the work by Hatat et al. [8], who also found the exchange of configuration during the hydrogenation of ketones. In their case they suppose the hydrogen being arranged trans to P(N) and thus gaining an increased hydride character. It is of interest that computer modelling of the interaction of propraphos–Rh **19** with benzamidocinnamic acid shows that one of the energetically most favored positions involves the arrangement III. The O–P bond cis to the double bond provides the stereo control in terms of the 'respective control concept' advanced by Achiwa [20,21]. Table 3 shows the results for the hydrogenation of dehydroamino acids and their esters in the presence of whole series of the cationic Rh complexes **18–24**. It seems that the diethylmethyl derivative **21** and the cyclic analog **22** are the most selective catalysts when the optical purity of the starting amino alcohol is taken into account. Table 3 shows the E_s values for R as well as pK_a of the applied bases. A simple correlation either with steric effects or basicity alone would be surprising and does not exist. In view of the increase in E_s on going from $C(CH_3)_3 = -1.54$ to $CH(Ph)_2 = -1.76$, it might seem that the nonformation of **13** (and consequently of **20**) is due to the steric effect, but on the other hand **7** which shows an even larger E_s ($CHEt_2 = -1.98$) forms **14**, and consequently also the Rh complex **21**. This underlines the only limited signification of steric substitution constants E_s or Charton's υ constants [22] for a comparison in this case. In view of the stereoselection the only significant difference lies between *N*-methyl **18** and the following four compounds **19–23** having a β-branched aza carbon framework bound to the phosphorus:



which provokes considerable steric repulsion with the hydrogen atoms of the P phenyl groups and thereby restricts the conformative mobility. But this picture, surely, is simplified since a more detailed kinetic study in the hydrogenation of dimethyl itaconate revealed e.g. strong differences between **19** and **23** [23] which are believed to exist in the hydrogenation of dehydroamino acids, too. There is also no correlation to the pK_a of the bases used in the preparation of **4–10**. Thus,

Table 3 shows that on going from **18**, substrate B, ee 41%, to **23**, substrate B, ee 92%, the strong change of stereoselectivity although the pK_a is 10.66 in both cases. In Tables 1–3 the ligands and Rh complexes of (*S*) configuration were used. In the catalytic reaction (*R*) amino acid derivatives are formed. The only exception displays (*S*)-**24** using acidic substrates (Table 3) which give (*S*) product. On the other hand the bulkier ester groups in C and D furnish 35 and 27% ee (*R*), respectively (Table 3). The configurations of the amino acids are in accordance with the general accepted rules for seven-membered Rh complexes taking into account that the above mentioned 'iso' structure gives rise to a change in configuration [13]. Table 3 shows that the reaction rate remains rather constant. All catalysts are highly active. The *N*-benzoyl group of the substrate has a small but measurable influence.

^{31}P-NMR

The drastic difference in ee between **18** and **19** is reflected looking at the chemical shifts of the two phosphorous atoms in the ^{31}P NMR spectra (Table 4). Between the rhodium complex **18** and the ligand **11** and the rhodium complex **19** and **12**,

Table 4
^{31}P NMR chemical shifts δ (ppm), ^{103}Rh–^{31}P and ^{31}P–^{31}P coupling constants *J* (Hz; in parentheses), and differences in chemical shifts Δδ of aminophosphine phosphinites **11–17** and their Rh chelates **18–24**

R^4	**11–17** [a]		**18–24** [a]		Δδ	
	$\delta_{P(O)}$	$\delta_{P(N)}$	$\delta_{P(O)}$	$\delta_{P(N)}$	$\delta_{P(O)}$ [b]	$\delta_{P(N)}$ [b]
H	114.9	43.0				
Me	111.9	67.5	122.4 dd (172; 28)	87.9 dd (161; 28)	10.5	20.4
$CHMe_2$	112.5	49.0	126.4 dd (173; 26)	80.7 dd (159; 26)	13.9	31.7
$CHEt_2$	112.9	44.3	127.4 dd (174; 26)	79.0 dd (159; 26)	14.5	34.7
	113.1	52.9	124.4 dd (172; 30)	83.2 dd (159; 30)	11.3	30.3
	113.1	52.9	125.1 dd (173; 27)	83.0 dd (159; 27)	12.0	30.1

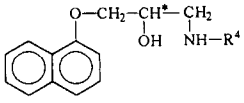
[a] Without **13** and **20**.
[b] $\delta_{P(O)}$ **11–17**/$\delta_{P(O)}$ **18–24**. $\delta_{P(N)}$ **11–17**/$\delta_{P(N)}$ **18–24**.

Table 3
Catalytic asymmetric hydrogenation of amino acid precursors by aminophosphine phosphinite Rh chelates **18–24**. Chelate configuration (*S*) (product configuration (*R*) if not indicated otherwise)

Substrate	o.p. [a] %	A		B		C		D		E_s	pK_a [e]
–N–R^4		*t*/2 min	ee %	*t*/2 min	ee %	*t*/2 min	ee %	t/2 min	ee %		
H	96.8	12	2 [b,c]	16	8 [b,c]	11	35	2	27	–	9.23
Me	96.8	2	45	3	41	2	47	4	40	0 [d]	10.66
$CHMe_2$	98.0	2	87	15	89 [f]	2	87	40	81 [f]	−0.47	10.63
$CHEt_2$	81.7	2	87	4	88	2	85	2	87	−1.98	10.12
Cyclopent.	92.8	2	91	2	94	2	89	2	92	−0.51	9.95 [g]
Cyclohex.	95.3	2	89	2	92	2	86	2	88	−0.79	10.66
$CH(Ph)_2$	75.9	[h]								−1.76	8.3
CMe_3	–	[h]								−1.54	

For conditions see Table 1.
[a] Optical purity of **4–10**.
[b] Configuration (*S*).
[c] Catalyst formed in situ.
[d] Reference data.
[e] pK_a of the amines used in synthesis.
[f] Substrate: Rh = 1000.
[g] 50% EtOH.
[h] No hydrogenation. A = acetamidocinnamic acid, B = benzamidocinnamic acid, C = methyl acetamidocinnamate, D = methyl benzamidocinnamate.

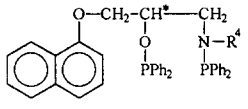
Table 5
^{13}C NMR chemical shifts δ (ppm) of amino alcohols in DMSO-d_6 and $CDCl_3$ (in parentheses)



R^4	Me	$CHMe_2$	$CHEt_2$	H	H
	4	**5**	**7**	**8**	**9**
OCH_2	69.8 (69.8)	69.9(69.7)	69.8	69.8	69.8(69.7)
OCH	64.8 (66.1)	65.2(65.9)	65.1	65.1	65.1(65.8)
NCH_2	50.9 (49.2)	46.9(48.6)	47.2	48.9	46.7(48.6)
R^4:NCH	–	49.8(51.7)	59.6	58.5	56.2(58.5)
NCH_3	32.8 (29.7)	–	–	–	–
CH_2	–	–	21.6; 21.3	28.7; 23.4	[a]
CH_3		18.5(19.2) 18.0(19.1)	9.2; 9.0	–	–

[a] 28.4, 27.9 (C-2′); 23.8 (C-3′); 24.6 (C-4′); (29.22, 29.19 (C-2′); 24.4 (C-3′); 24.7 (C-4′)).

Table 6
^{13}C NMR chemical shifts δ (ppm) and coupling constants J (Hz; in parentheses) of the ligands **11–16** in $CDCl_3$



R^4	Me	$CHMe_2$	$CHEt_2$	H	H
	11	**12**	**14**	**15**	**16**
OCH_2	69.6 d (4.9)	69.6 d (4.8)	[a]	69.8 d (4.7)	69.6 d (4.7)
OCH	78.5 dd (18.0; 7.5)	79.1 dd (18.1; 2.9)	79.5 d (19.1)	79.5 d (18.1)	79.2 dd (18.1; 1.8)
NCH_2	59.3 dd (32.0; 4.9)	49.6 dd (5.7; 5.7)	49.2 d (10)	51.5 d (15)	51.9 d (5.8)
R^4:NCH	–	51.7 d (14.3)	59.8 d (7.3)	63.0 d (8.3)	60.6 d (16.3)
NCH_3	38.2 d (2.9)	–	–	–	–
CH_2	–	–	[a]	[a]	[a]
CH_3	–	[a]	[a]	–	–

[a] Not assigned due to overlapping with signals of by-products.

respectively, the $\Delta\delta_{P(O)}$ is 10.5 and 13.9 ppm and increases to 20.4 and > 30 ppm at the P(N) phosphorous. No differences could be observed in the series of coupling constants of P(O)–Rh and P(N)–Rh. The lower chemical shift of the P(N) atom in the free ligand **12** with respect to $\delta_{P(O)}$ compared with the values of **11** is caused by the greater shielding of the N-function and the higher basicity. One result of the complex formation is the greater deshielding (low field shift) of the N-bound phosphorous of **19** against **18**. It is caused by the greater donor activity of the isopropyl group which in turn should gives rise to an increased stability of the catalyst–substrate complex III.

^{13}C NMR spectra

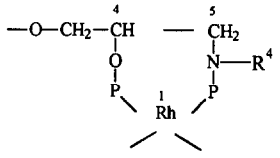
Tables 5–7 show the NMR data of the C atoms in question $-OCH_2-$, $-C^*HO-$, $-CH_2N-$, $-N-R^4$ and R^4 as well as for the amino alcohols, their aminophosphine phosphinites and their rhodium complexes $[Rh(COD)L]BF_4$.

The differences in the chemical shifts of **19** and **21–23** to **18** are less pronounced than in their ^{31}P NMR spectra. In general the chemical shifts

Table 7
^{13}C NMR chemical shifts and coupling constants (in parentheses) of the Rh complexes $[Rh(COD)L]BF_4$ **18–23** in $CDCl_3$

R^4	Me	$CHMe_2$	$CHEt_2$	H	H
	18	**19**	**21**	**22**	**23**
OCH_2	67.8 d (8.7)	68.6 d (6.6)	68.7 d (5.8)	68.0 d (4.9)	68.2 d (5.5)
OCH	76.0 d (3.4)	78.6 d (4.3)	78.7 d (4.8)	79.1 dd (2.4; 2.4)	79.0 dd (2.5; 2.5)
NCH_2	55.7 dd (14.4; 4.1)	45.8 dd (10.8; 3.6)	47.9 dd (10.5; 3.9)	47.3 dd (13.0; 5.4)	47.5 dd (12.8; 5.1)
R^4:NCH	–	51.7 dd (7.0; 1.8)	63.6 d (8.6)	63.0 dd (6.6; 1.2)	61.1 dd (7.0; 1.3)
NCH_3	41.7 dd (5.4; 1.1)	–	–	–	–
CH_2	–	–	28.5 d- (3.2) 27.6 s	31.0 d- (2.4) 30.7 d- (2.8); 24.1; 23.6	32.5; 31.7 26.1; 25.9; 25.2
CH_3	–	21.3 d- (3.7); 20.8 s	12.0; 11.9	–	–

between the amino alcohols and their phosphinylated analogues are characterized by a strong low field shift on $-C^*HO-$ and $-N-CH_2-$ whereas no changes on $-OCH_2-$ and surprisingly on $-N-R^4$ (N–CH–) exist. On going to the metal complexes a small high field shift occurs once more concerning $-C^*$ and $-N-CH_2-$ in case of **18**. Since from chelation a seven-membered ring follows, mainly the atoms 4 and 5 are influenced within the ring, an effect, which may be interpreted by the known γ effect. No pronounced distinction between **19** and **18** is detectable.



4. Conclusion

In a series of aminophosphine phosphinites derived from propranolol analogues the enantiodifferentiation is influenced by the N-substituent. Apart from R^4 = methyl the % ee and rate of the asymmetric hydrogenations using other N-substituted derivatives are within a narrow range, but neither measures of steric nor of electronic effects are suitable for correlations. The optimal enantioselectivity is reached with N-derivatives substituted by the diethylmethyl or cyclopentyl groups. Especially between these two amines the E_s is totally different showing that simple comparisons make no sense. The reaction rate in the series of catalysts is high and under the experimental conditions rather constant.

From ^{31}P NMR spectra the pronounced differences in the enantiomeric excess between the *N*-methyl **18** and *N*-isopropyl **19** derivative are indicated by different $\Delta\delta$ values, the ^{13}C NMR data on the other hand do not provide any relations.

In future for electronic effects *N*-*p*-substituted phenyl derivatives are envisaged, the steric influence has been elucidated by investigating diastereomeric ligands [24].

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