Tetrahedron Vol. 34, pp. 2405–2408
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0040-4020/78/0901-2405/$02.00/0

STRUCTURAL REQUIREMENTS IN CHIRAL DIPHOSPHINE-RHODIUM COMPLEXES—XI[1]

ASYMMETRIC HOMOGENEOUS HYDROGENATION OF Z-α-ACYLAMINOCINNAMIC ACIDS AND ESTERS WITH (1S, 2S)-*TRANS*-1,2-BIS(DIPHENYLPHOSPHINOMETHYL) CYCLOHEXANE/RHODIUM(I) COMPLEXES

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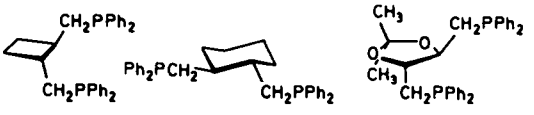
(*Received in UK 20 February 1978; accepted for publication 28 February 1978*)

Abstract—Z-α-acylaminocinnamate esters were hydrogenated with neutral rhodium(I) complexes containing (1S, 2S)-*trans*-1,2-bis(diphenylphosphinomethyl)cyclohexane. Increasing the steric bulk of the alcohol moiety of the ester function results in increased enantioface differentiation in favor of the re-si prochiral face to yield an excess of the S-amino acid derivatives. In the series of N-acetylphenylalanine ester products (resulting from hydrogenation of Z-α-acetamidocinnamate esters) the optical purity increased from 1% ee-(R) [Me]; 20% ee-(S) [Et]; 47% ee-(S) [i-Pr]; to 58% ee-(S) [t-Bu]. Increasing the steric bulk of the acyl function (NHCOR, where R is an alkyl moiety) favors the reduction of the si-re prochiral face [in the methyl ester substrates] to yield an excess of the R-amino acid derivatives. In the series of N-acylphenylalanine methyl ester products (resulting from hydrogenation of Z-methyl α-acylaminocinnamates) the optical purity increased from 1% ee-(R) [Me]; 13% ee-(R) [i-Pr]; to 15% ee-(R) [t-Bu and 1-adamantyl]. The α-formamido and α-benzamido substrates gave hydrogenation products having 22% ee-(R) [H] and 35% ee-(R) [Ph]. In the corresponding free acids, increasing the steric bulk of the acyl function (NHCOR, where R is an alkyl moiety) results in almost no change in the optical purity of the reduction products. In the series of N-acylphenyl-alanine products (resulting from hydrogenation of Z-α-acylaminocinnamic acids) the optical purity was 35% ee-(S) [Me]; 31% ee-(S) [i-Pr]; 33% ee-(S) [t-Bu]; and 35% ee-(S) [1-adamantyl]. The α-benzamido substrate gave a hydrogenation product having 8% ee-(S).

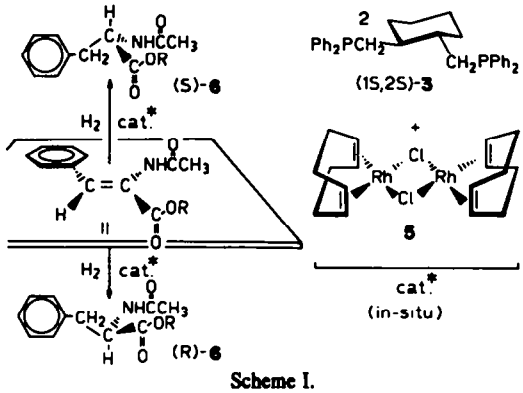
The (1R, 2R) - *trans* - 1,2 - bis(diphenylphosphinomethyl)cyclobutane (1) chiral chelating diphosphine was recently investigated in rhodium(I) complexes used for the asymmetric hydrogenation of Z-α-acetamidocinnamate esters (2).[1] It was decided to continue this study using the analogous (1S, 2S)-*trans*-1,2-bis(diphenylphosphinomethyl)cyclohexane (3). The two above-mentioned chiral diphosphines are carbocyclic analogues of the heterocyclic 2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane[2,3] (DIOP) (4) (Fig. 1).



1 3 4

Fig. 1.

Neutral Rh(I) catalysts were prepared *in-situ* from chloro(1,5-cyclooctadiene)rhodium(I) dimer (5) and the chiral diphosphine in benzene. The homogeneous catalysts were used in the asymmetric hydrogenation of Z-α-acetamidocinnamate esters (2) to yield the corresponding N-acetylphenylalanine esters (6) (Scheme 1). The results of these investigations (performed in abs EtOH/benzene = 2.3) are reported in Table 1. Increasing the steric bulk of the alcohol moiety of the ester function results in increased enantioface differentiation in favor of the re-si prochiral face to yield more of an excess of the S-amino ester derivatives. In the series of increasing steric bulk within the alcohol moiety of the ester, the optical yield of the product changed dramatically: 1% enantiomeric excess (ee)-(R) [Me]; 20% ee-(S) [Et]; 47% ee-(S) [i-Pr]; and 58% ee-(S) [t-Bu]. The corresponding free acid gave 35% ee-(S) under the same reaction conditions.[1]



Scheme I.

Rh(I) complexes of the (1R, 2R)-cyclobutane diphosphine analogue (1) showed a relative lack of sensitivity to the alcohol moiety bulk (in the asymmetric hydrogenation of the same series of ester substrates): 44% ee-(R) [Me]; 42% ee-(R) [Et]; 41% ee-(R) [i-Pr]; 40% ee-(R) [t-Bu]; and 86% ee-(R) for the free acid.[1] A somewhat similar lack of sensitivity was shown by Rh(I) hydrogenation complexes of the heterocyclic diphosphine (2R, 3R)-DIOP (4): 69% ee-(R) [Me]; 72% ee-(R) [Et]; 76% ee-(R) [i-Pr]; 77% ee-(R) [t-Bu]; and 82% ee-(R) for the free acid.[4] It can be seen that the carbocyclic cyclohexyl diphosphine (3) behaves differently than the carbocyclic cyclobutane analogue (1) and DIOP (4) in the Rh(I) catalyzed hydrogenation of the unsaturated esters (2). The carbocyclic cyclohexyl diphos-

phine (3) also behaved differently than the cyclopentyl, cyclobutyl and DIOP diphosphines in the Rh(I) catalyzed hydrogenation of N-acetyldehydroalanine: 72% ee-(R) [(1R, 2R)-cyclobutane]; 72% ee-(R) [(1R, 2R)-cyclopentane]; 40% ee-(S) [(1S, 2S)-cyclohexane]; and 73% ee-(R) [(2R, 3R)-DIOP].[5]

The relatively large dependence of the ester reduction product (6) optical purity upon the alcohol steric bulk (for the cyclohexyl analogue 3 compared to the cyclobutyl analogue 1 and to DIOP 4) can be interpreted as resulting from a more flexible 7-membered chelating ring that is 1,2-*trans* fused to the diphosphine cycle. Thus, an increase in alcohol moiety steric bulk in the substrate could increase the population of a particular chelate ring chiral conformer. This reduction in conformational possibilities could result in the reaction products having higher optical purity. If the 7-membered chelate ring is already fairly rigid and exists in mainly one chiral conformation, then the series of unsaturated esters (2) and the N-acetyldehydroalanine might show a different type of behavior compared to the more flexible case.

In addition, as in the case of the cyclobutane analogue (1) and contrary to that with DIOP (4), there is a much larger difference between the degree of enantioface selectivity exhibited by the prochiral free acid compared to the unsaturated methyl ester. It is likely that this is indicative of differences in the polar character of the ester moiety compared to that of the carboxyl group.

In a similar manner, a series of N-acylphenylalanine free acids and methyl esters were produced via hydrogenation of the corresponding unsaturated substrates. From Table 2 it can be seen that increasing the steric bulk of the acylamino function (NHCOR, where R is an alkyl moiety) favors the reduction of the si-re prochiral face [in the methyl ester substrates] to yield an excess of the R-amino acid derivatives. In the series of N-acylphenylalanine methyl ester products (resulting from the corresponding Z-methyl α-acylaminocinnamates) the optical purity increased from 1% ee-(R) [Me]; 13% ee-(R) [i-Pr]; to 15% ee-(R) [t-Bu and 1-adamantyl]. The α-formamido and α-benzamido substrates gave hydrogenation products having 22% ee-(R) [H] and 35% ee-(R)

Table 1. Asymmetric hydrogenation of Z-α-acetamidocinnamate esters [C_6H_5CH=$C(NHCOCH_3)COOR$] Catalyzed by neutral chlororhodium(I)/(1S, 2S)-*trans*-1,2-bis(diphenylphosphinomethyl)cyclohexane complexes[a]

R	$[\alpha]_D^{25}$[b]	% opt. purity[c]	abs. config.
H	+16.4[d]	35[e]	S
Me	- 1.2[f]	1[g]	R
Et	+17.5[f]	20[h]	S
i-Pr	+35.7[f]	47[i]	S
t-Bu	+43.4[f]	58[j]	S

Table 2. Asymmetric hydrogenation of Z-α-acylaminocinnamic acids and methyl esters [C_6H_5CH=$C(NHCOR)COOH$ and C_6H_5CH=$C(NHCOR)COOCH_3$] catalyzed by neutral chlorohodium(I)/(1S, 2S)-*trans*-1,2-bis(diphenylphosphinomethyl)cyclohexane complexes[a]

	free acids[k]			methyl esters		
R	$[\alpha]_D^{25}$[b]	% opt. purity[c]	abs. config.	$[\alpha]_D^{25}$[b]	% opt. purity[c]	abs. config.
H	-[m]	-	-	+21.8[f]	22[l]	R
Me	+16.4[d]	35[e]	S	- 1.2[f]	1[g]	R
i-Pr	+28.0[f]	31[n]	S	-11.7[f]	13[n]	R
t-Bu	+24.1[f]	33[o]	S	-11.1[f]	15[o]	R
1-Ada	+22.6[f]	35[p]	S	- 9.5[f]	15[p]	R
Ph	- 3.8[d]	8[q]	S	+15.8[d]	35[q]	R

[a] [Rh] = 3.0 mmol l^{-1}; [diphosphine]/[Rh] = 1.1; [substrate]/[Rh] = 25; [abs. EtOH]/[benzene] = 2.3; total volume 10 ml; 1 atm. H_2; 25°C; and ~100% conversion (unless stated otherwise). [b] $10^{-1} \times [\alpha]$ = degree g^{-1} cm^2. [c] % enantiomeric excess, ± 1%. [d] (C 1.0, 95% EtOH). [e] Based upon N-acetyl-(S)-phenylalanine: $[\alpha]_D^{25}$ +46.5° (C 1.0, 95% EtOH), Ref. 4; lit.[17] $[\alpha]_D^{25}$ +46.8° (C 1.06, 95% EtOH). [f] (C 1.0, $CHCl_3$). [g] Based upon N-acetyl-(S)-phenylalanine ethyl ester: $[\alpha]_D^{25}$ +101.3° (C 1.0, $CHCl_3$), Ref. 4. [h] Based upon N-acetyl-(S)-phenylalanine ethyl ester: $[\alpha]_D^{25}$ +85.9° (C 1.0, $CHCl_3$), Ref. 4. [i] Based upon N-acetyl-(S)-phenylalanine i-propyl ester: $[\alpha]_D^{25}$ +76.1° (C 1.0, $CHCl_3$), Ref. 4. [j] Based upon N-acetyl-(S)-phenylalanine t-butyl ester: $[\alpha]_D^{25}$ +74.4° (C 1.0, $CHCl_3$), Ref. 4. [k] Free acid reduction products converted to methyl esters via diazomethane prior to determination of optical purity (with the exception of R = Me). [l] Based upon N-formyl-(S)-phenylalanine methyl ester: $[\alpha]_D^{25}$ +99.0° (C 1.0, $CHCl_3$), Ref. 6. [m] ~40% conversion, optical rotation not determined. [n] Based upon N-isobutyryl-(S)-phenylalanine methyl ester: $[\alpha]_D^{25}$ +90.8° (C1.0, $CHCl_3$), Ref. 6. [o] Based upon N-pivaloyl-(S)-phenylalanine methyl ester: $[\alpha]_D^{25}$ +73.2° (C 1.0, $CHCl_3$). [p] Based upon N-adamantyl-1-carbonyl-(S)-phenylalanine methyl ester: $[\alpha]_D^{25}$ +63.9° (C 1.0, $CHCl_3$). [q] Based upon N-benzoyl-(S)-phenylalanine methyl ester: $[\alpha]_D^{25}$ −45.3° (C 1.3, 95% EtOH), Ref. 17.

[Ph]. Rh(I) complexes of (2S, 3S)-DIOP gave a similar increase in the amount of attack on the si-re prochiral face upon increase in the steric bulk of the alkyl group within the acylamino function.[6] Thus, in this case the corresponding reduction products showed 69% ee-(S) [Me]; 15% ee-(S) [i-Pr]; to 0% ee [t-Bu and 1-adamantyl].[6] The α-formamido and α-benzamido substrates gave hydrogenation products having 58% ee-(S) [H] and 36% ee-(S) [Ph] using DIOP.[6] A comparison between the Rh(I) complexes containing DIOP and the cyclohexyl analogue (3) show that in both catalytic systems the formamide shows increased attack on the re-si prochiral face [less (S)-product] relative to the acetamide analogue.

It is clear that the formamido group is smaller in steric size than the acetamido group. Yet, inspection of the optical purity data for the N-acylphenylalanine methyl esters (produced by Rh(I) complexes containing either DIOP or the cyclohexyl analogue) show that steric considerations alone cannot explain the results of the formamido substrate *vis-à-vis* the rest of the series. By ^{1}H NMR it has been shown that in $CDCl_3$, the formamide substrate exists in both *trans* and *cis*-amide conformations, while the acetamido substrate only exhibits signals corresponding to the *trans*-amide conformer.[7] One must be cautioned with regard to the significance of the ^{1}H NMR data since it has yet to be shown that the optical purity of the reduction product may be effected by the existence of *cis*/*trans*-amide conformational equilibria within the α-acylamino moiety of the olefinic substrate. This point is currently under active investigation.

Another reason for special behavior of the formamides may well be the difference in the electronic nature of the substituent adjacent to the CO carbon within the α-acylamino group of the olefin. This appears to be reasonable since the trifluoromethyl group [in α-trifluoroacetamido substrates] exerts a very definite electronic influence upon the optical purity of the reduction product.[6,8] When the α-trifluoroacetamido analogue (both the methyl ester and the free acid) is reduced with Rh(I)-DIOP complexes, there is a considerably greater reduction of the si-re prochiral face than is comensurate with the steric size of the trifluoromethyl group alone.[6,8] In this particular case the steric size effect can be efficiently estimated since the Van der Waals diameter of CF_3 is intermediate between that of Me and t-Bu.[9] It is reasonable to state that C atom substituents adjacent to the CO carbon atom of the α-acylamino group are more efficient in their ability to push electrons towards the partially positive carbon center than either the trifluoromethyl group or the proton moiety.

If we look at the optical purity of the N-acylphenylalanine methyl esters in which the acylamino moiety contains an alkyl group adjacent to the CO, it is seen that there is a larger difference in the values for the acetamide vs the isobutyramide than there is for the isobutyramide vs the pivalylamide (Δ% ee = 12 and 2, respectively). Similar results were also found when the diphosphine used in the catalyst was the cyclobutane analogue (1) of DIOP.[8] This can be interpreted more in terms of a masking of the polar character of the acylamino function rather than just a steric effect alone. In addition, simple steric considerations also seem insufficient to explain the relatively high optical purity of 35% ee-(R) shown by the N-benzamidophenylalanine methyl ester. Polar factors effecting the CO are most likely at work here, perhaps even some type of π-π interaction with the phenyl rings of the catalyst itself. This point is under current investigation.

The series of N-acylphenylaline free acids gives interesting results in Table 2. The size of the alkyl group in the α-acylamino function of the unsaturated substrate appears not to effect the optical purity of the reduction product. The importance of the carboxylic acid function is indicated by these results. Again, it is evident that the relatively low value of 8% ee-(R) for the benzamido analogue compared to the 31–35% ee-(R) for the acetamido-pivalylamido substrates cannot be explained on the basis of steric effects alone.

The above experiments with α-acylaminocinnamic acids and methyl esters are most indicative of the importance of polar effects upon the enantioface differentiation step in the asymmetric hydrogenation of dehydroamino acid derivatives. Further investigations are in progress on this subject.

EXPERIMENTAL

Hydrogenations were carried out in a glass atmospheric pressure apparatus at 25.0 ± 0.5° according to the method described in Ref. 4, 10. Neutral rhodium(I) complexes were prepared from chloro(1,5-cyclooctadiene)rhodium(I) [dimer purchased from Strem Chemicals Inc.] according to the method described in Ref. 4, 10. All mg pts are uncorrected. Microanalyses were performed at the Hebrew University of Jerusalem.

(1S, 2S) - Trans - 1,2 - Bis(diphenylphosphinomethyl)cyclohexane. Racemic *trans*-1,2-cyclobexanedicarboxylic acid, m.p. 220–221° (lit.[11] 227–229°), was prepared from *cis*-1,2-cyclohexanedicarboxylic anhydride (Aldrich Chemical Co.) via the method of Applequist and Werner.[11] (1S, 2S)-*trans*-1,2-cyclohexanedicarboxylic acid, m.p. 173–175° and $[\alpha]_D^{25}$ +20.3° (*c* 2.0, acetone) [lit. m.p. 183.5–185.0° and $[\alpha]_D^{30}$ +22.3° (*c* 5.3, acetone),[11] m.p. 179–180° and $[\alpha]_{578}$ +22.4° (*c* 0.214, acetone), ref. 12; m.p. 182–185° and $[\alpha]_D^{24}$ +20.8° (*c* 5.0, acetone),[13] and $[\alpha]_D^{25}$ +20.9° (*c* 3.5, acetone,[14]], was obtained via resolution with cinchonidine according to the method of Armarego and Kobayashi.[12] Conversion to the methyl di-ester via reaction with diazomethane was followed by reduction with LAH to yield (1S, 2S)-*trans*-1,2-bis(hydroxymethyl)cyclohexane, m.p. 66–67° and $[\alpha]_D^{24}$ −19.8° (2, benzene) [lit. m.p. 63–64° and $[\alpha]_D^{24}$ −20.2° (*c* 4.0, benzene), ref. 12; m.p. 61–62° and $[\alpha]_D^{24}$ +21.4° (*c* 4.0, benzene) for the (1R, 2R)-enantiomer.[15] Reaction with *p*-toluenesulfonyl chloride in pyridine afforded the (1S, 2S)-*trans*-1, 2-bis(hydroxymethyl)cyclohexane di-*p*-toluenesulfonate, m.p. 112–113° and $[\alpha]_D^{21.5}$ +24.2° (*c* 4.0, benzene) [lit. m.p. 109–109.7° and $[\alpha]_D^{28}$ +25.0° (*c* 5.0, benzene),[11] m.p. 109–110° and $[\alpha]_D^{21.5}$ −24.8° (*c* 5, benzene) for the (1R, 2R)-enantiomer.[15] Finally, reaction with lithium diphenylphosphide according to the method of Aguiar *et al.*[16] gave a solid which was recrystallized from MeOH to yield (1S, 2S)-*trans*-1,2-bis(diphenylphosphinomethyl)cyclohexane hydrate as a crystalline solid, m.p. 55–56° and $[\alpha]_D^{25}$ +52.7° (*c* 1.0, benzene). The IR spectrum (KBr pellet) showed absorptions at 3280 cm^{-1} (broad w) O-H stretch; 2940 cm^{-1} (s) C–H stretch; 1545 cm^{-1} (w) C=C stretch; 1455 cm^{-1} (s) C–H bending; 1405 cm^{-1} (s) P-phenyl stretch; 705 and 690 cm^{-1} (s) monosubstituted benzene ring. The ^{1}H NMR 100 MHz spectrum in $CDCl_3$/TMS showed a multiplet at 7.20 ± 0.10 δ, 20H aromatic protons; a crude doublet at 2.34 δ, J ~ 12 Hz, 2H CH_2P; a crude doublet at 1.99 δ, J ~ 12 Hz, 2H, CH_2P; and a multiplet at 1.30 ± 0.50 δ, 10H, cyclohexyl protons. (Found: C, 77.36; H, 7.12. Calcd. for $C_{32}H_{34}P_2 \cdot H_2O$: C, 77.09; H, 7.28%).

The synthesis of the Z-α-acetamidocinnamate esters and appropriate N-acetylphenylalanine ester optically-pure standards has been described previously.[4] The synthesis of the Z-α-acylaminocinnamic acids and methyl esters as well as the appropriate N-acylphenylalanine methyl ester optically-pure standards will be described elsewhere.[8] All new compounds exhibited satis-

factory elemental analyses, and their proposed structures were all in agreement with the observed IR and ^{1}H NMR spectra.

All reactions were terminated after 24 hr. After evaporation of the solvent *in vacuo*, the percent conversion was determined by ^{1}H NMR using a Varian XL-100 spectrometer. The percent conversion of esters was also determined by analysis on a Varian model 2100 gas chromatograph using a column of 6% Carbowax 20-M coated on Chromosorb W AW/DMCS (60–70 mesh), 1.0 m length, and 1/4-in. o.d. glass tubing. The operating conditions were: column temp. 180°, injector and detector temp. 250°, and a N_2 carrier gas flow rate of 75 ml/min.

Residues of crude product mixtures (from the free acid substrates) were directly treated with diazomethane in ether. The resulting methyl esters were analyzed by gas chromatography to determine the percent conversion. All the crude esters (including those prepared via diazomethane) were taken up in a minimum quantity of $CHCl_3$, and chromatographed on a silica-gel column (prepared in petroleum-ether 60–80°-eluted with an increasing gradient of EtOAc in petroleum-ether 60–80°). The purified N-acylphenylalanine ester products were stored in a desiccator *in vacuo* over P_2O_5 prior to determination of the optical rotation in a Perkin-Elmer MC-141 polarimeter. The rotation was measured at three wavelengths: 589 (Na-D), 434.75 and 334.15 nm; 25° and a concentration of 1.0×10^{-2} g ml^{-1} in $CHCl_3$ (unless otherwise noted). Each experiment was performed at least twice, and the optical rotation of at least two samples from each experiment were determined.

Validity of diazomethane treatment of crude free acid raction product mixtures. Z-α-acetamidocinnamic acid yields N-acetylphenylalanine [82% ee-(S)] when hydrogenated in abs EtOH/benzene 2.3:1 using a neutral chlororhodium(I)/(2S, 3S)-DIOP complex.[3,4] The determination of free acid product optical purity was performed via polarimetry after the crude product mixture had been chromatographed on a silica-gel column.[4] A sample of the crude free acid product mixture was treated with diazomethane in ether and then chromatographed on a silica-gel column. The purified N-acetylphenylalanine methyl ester gave $[\alpha]_D^{25}$ +84.3° (*c* 1.0, $CHCl_3$) for 83% ee-(S), based upon $[\alpha]_D^{25}$ +101.3° (*c* 1.0, $CHCl_3$) for the pure (S)-enantiomer.

Acknowledgements—The authors wish to express their thanks to Prof. U. Schöllkopf and Dr. R. Meyer for their genorous gift of the α-formamido substrate.

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