Tetrahedron Letters No. 52, pp 4639 - 4642, 1977. Pergamon Press. Printed in Great Britain.

STRUCTURAL REQUIREMENTS IN CHIRAL DIPHOSPHINE-RHODIUM COMPLEXES. X[1]. ASYMMETRIC HOMOGENEOUS HYDROGENATION OF Z-N-ACETYLDEHYDROAMINO ACIDS AND ESTERS WITH (1R,2R)-TRANS-1,2-BIS(DIPHENYLPHOSPHINOMETHYL)CYCLOBUTANE/RHODIUM(I) COMPLEXES.

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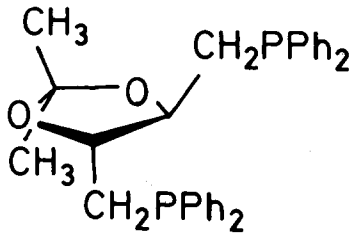
(Received in UK 14 September 1977; accepted for publication 3 November 1977)

Summary: Z-α-acetamidocinnamate esters were hydrogenated with neutral rhodium(I) complexes containing (1R,2R)-trans-1,2-bis(diphenylphosphinomethyl)cyclobutane. Increasing the steric bulk of the alcohol moiety in the unsaturated esters had little influence upon the optical purity of the N-acetylphanylalanine ester products. In the series Me, Et, i-Pr, and t-Bu the optical purity decreased from 44 % ee-(R) [Me] to 40 % ee-(R) [t-Bu]. The chiral cyclobutane diphosphine appears to be only slightly more effective than the heterocyclic DIOP when ring-substituted Z-α-acetamidocinnamic acids are hydrogenated with neutral rhodium(I) complexes without the addition of triethylamine. Addition of triethylamine to the solvent blend seems to be more beneficial to the cyclobutane analogue than to DIOP.

The chiral cyclobutane, cyclopentane, and cyclohexane carbocyclic analogues of 2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane[2a,b] (DIOP) (I) were recently investigated in rhodium(I) complexes for the asymmetric hydrogenation of N-acetyldehydroalanine and Z-N-acetyldehydrophenylalanine.[1e] As a result of this preliminary study, it was decided to systematically investigate the structural requisites in rhodium(I) hydrogenation complexes containing each of the above-mentioned chiral diphosphines.

The (1R,2R)-trans-1,2-bis(diphenylphosphinomethyl)cyclobutane (II) analogue of DIOP was first prepared by Rhone Poulenc S.A.[3] and later in our laboratories.[4] Neutral Rh(I) catalysts were prepared in-situ from chloro(1,5-cyclooctadiene)rhodium(I) dimer and the appropriate chiral diphosphine (I-II) in benzene. The homogeneous catalysts were used in the asymmetric hydrogenation of Z-α-acetamidocinnamate esters to yield the corresponding N-acetylphenylalanine esters. The results of these investigations (performed in [abs. EtOH]/[benzene] = 2.3) are reported in Table 1. In the series of increasing steric bulk within the alcohol moiety of the ester, the optical yield of the product changed very little: 44 % enantiomeric excess (ee)-(R) [Me]; 42 % ee-(R) [Et]; 41 % ee-(R) [i-Pr]; and 40 % ee-(R) [t-Bu]. The corresponding free acid gave 86 % ee-(R) under the same reaction conditions.[1e] Rh(I) hydrogenation complexes of the heterocyclic diphosphine (2R,3R)-DIOP showed a somewhat similar lack of sensitivity in the asymmetric hydrogenation of the same series of ester substrates: 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. It is seen that the general trend of the change in optical purity of the reduction products as a function of the



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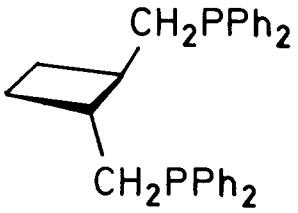

II

increasing steric bulk of the alcohol moiety is not the same for the two diphosphines (I-II). In addition, there is a much larger difference between the degree of enantioface selectivity exhibited by the prochiral free acid compared to the methyl ester when the cyclobutane diphosphine analogue is used instead of DIOP.

The higher optical purity obtained for the reduction product of Z-α-acetamidocinnamic acid using the cyclobutane diphosphine (II) [86 % ee] vs. DIOP (I) [82 % ee] is real but not large. The original Rhone Poulenc S.A. data[3] show a lower optical purity for the N-acetylphenylalanine [78 % ee] obtained via the cyclobutane diphosphine/Rh(I) complex (when performed without the addition of triethylamine to the solvent blend).

In Table 2 are listed the data for the asymmetric hydrogenation of ring-substituted N-acetylphenylalanine precursors using the cyclobutane diphosphine/Rh(I) complex. Again, the cyclobutane diphosphine analogue of DIOP is only slightly more effective than DIOP when the dehydroamino acid derivatives are hydrogenated without the addition of triethylamine. Addition of triethylamine to the solvent blend appears to be more beneficial to the cyclobutane diphosphine analogue (II) than to DIOP.

The ring-substituted N-acetylphenylalanine precursors did not show a great variation of reduction product optical purity vs. the electronic nature of the ring substituent. This result is in line with that found for the reduction of para-substituted Z-(1R,3R,4S)-menthyl-α-acetamidocinnamates with (2S,3S)-DIOP/Rh(I) complexes. In the case of DIOP, the relationship between the electronic character of the p-substituent and the percent diastereomeric excess of the corresponding N-acetylphenylalanine menthyl ester reaction products is suggestive of an insignificant substituent effect: 77.2 % diastereomeric excess (d.e.)-(S,3R) [p-H]; 79.7 % d.e.-(S,3R) [p-CH_3]; 79.5 % d.e.-(S,3R) [p-Cl]; and 81.0 % d.e.-(S,3R) [p-OAc].[5]

X-ray crystallographic structure determination has shown that the β-phenyl substituent in Z-α-benzamidocinnamic acid is not coplanar with the olefinic bond.[6] C.P.K. space filling models show steric hindrance between the β-phenyl ring and the amido-proton of the benzamide group. One can speculate that in the asymmetric induction step [of the hydrogenation reaction] perhaps a similar non-coplanar relationship might be found in the α-acetamido substrate analogues within the DIOP•Rh hydrogenation complex. This non-coplanarity between the β-phenyl ring and the olefinic bond might thus account for the above-mentioned results with the ring-substituted N-acetylphenylalanine precursors. However, it is clear that more conclusive evidence is needed.

Based upon our hydrogenation results, the optical purity of the chiral cyclobutane diphosphine (II) used in our experiments seems to be as pure as that described by Rhone Poulenc S.A.[3]

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

R	$[\alpha]_D^{25}$[b]	% opt. purity[c]		abs. config.
H	-40.0[d]	86[e]	(82)[f]	R
Me	-44.9[g]	44[h]	(69)[f]	R
Et	-36.2[g]	42[i]	(72)[f]	R
i-Pr	-31.2[g]	41[j]	(76)[f]	R
t-Bu	-29.8[g]	40[k]	(77)[f]	R

Table 2. Asymmetric hydrogenation of Z-N-acetyldehydroamino acids [$RCH=C(NHCOCH_3)COOH$] catalyzed by neutral chlororhodium(I)/(1R,2R)-trans-1,2-bis(diphenylphosphinomethyl)-cyclobutane complexes.[a]

R	$[\alpha]_D$[b]	% opt. purity[c]		abs. config.	$[Et_3N]/[Rh]$
C_6H_5	-40.0[d,l]	86[e,m]	(82)[f]	R	0
3',4'-OCH_2O-C_6H_3	-42.5[n]	80[o]	(79)[p]	R	0
4'-AcO-C_6H_4	-42.2[d]	85[q]	-	R	0
3'-MeO-4'-AcO-C_6H_3	-35.4[r]	87[s]	(84)[t]	R	0
C_6H_5[u]	-42.1[d]	91[e,v]	(79)[p]	R	3
3',4'-OCH_2O-C_6H_3	-45.5[n]	85[o,w]	(76)[x]	R	3

footnotes for Tables 1 and 2: [a][Rh] = 3.0 mmol l^{-1}; [diphosphine]/[Rh] = 1.1; [substrate]/[Rh] = 50 (acids) 25 (esters); [abs. EtOH]/[benzene] = 2.3; total vol. 10 ml; 1 atm H_2; 25°C and ∿100% conversion. (1R,2R)-trans-1,2-bis(diphenylphosphinomethyl)cyclobutane: $[\alpha]_D^{20}$ - 17.0° (C 1.0, benzene) and mp 107° lit.[3] $[\alpha]_D^{20}$ - 18.6° (C 1.0, benzene) and mp 107°; satisfactory elemental analysis. [b]10^{-1} × [α] = degree g^{-1} cm^2. [c]% enantiomeric excess: ±1%; values in parenthesis are for diphosphine = (2R,3R)-DIOP. [d]25°C, (C 1.0, 95% EtOH). [e]based upon N-acetyl-(S)-phenylalanine $[\alpha]_D^{25}$ + 46.5° (C 1.0, 95% EtOH) lit.[7] $[\alpha]_D^{25}$ + 46.8° (C 1.06, 95% EtOH). [f]data taken from ref. 1a. [g](C 1.0, $CHCl_3$). [h]based upon N-acetyl-(S)-phenylalanine methyl ester $[\alpha]_D^{25}$ + 101.3° (C 1.0, $CHCl_3$), ref. 1a. [i]based upon N-acetyl-(S)-phenylalanine ethyl ester $[\alpha]_D^{25}$ + 85.9° (C 1.0, $CHCl_3$), ref. 1a. [j]based upon N-acetyl-(S)-phenylalanine i-propyl ester $[\alpha]_D^{25}$ + 76.1° (C 1.0, CHCl), ref. 1a. [k]based upon N-acetyl-(S)-phenylalanine t-butyl ester $[\alpha]_D^{25}$ + 74.4° (C 1.0, $CHCl_3$), ref. 1a. [l]$[\alpha]_D^{25}$ - 39.5° for reaction performed in [abs. EtOH]/[benzene] = 2.0 lit.[3] $[\alpha]_D^{22}$ - 36.3°. [m]85% ee for reaction performed in [abs. EtOH]/[benzene] = 2.0 lit.[3] 78% ee. [n]18°C, (C 1.0, 95% EtOH). [o]based upon N-acetyl-(R)-3',4'-methylenedioxyphenylalanine $[\alpha]_D^{18}$ - 53.4° (C 1.8, EtOH), ref. 8. [p]data taken from ref. 2b. [q]based upon N,O-diacetyl-(S)-tyrosine $[\alpha]_D^{25}$ + 49.9° (C 1.0, 95% EtOH). [r]20°C, (C 1.0, MeOH). [s]based upon N-acetyl-(S)-3'-methoxy-4'-acetoxyphenylalanine $[\alpha]_D^{20}$ + 40.8° (C 1.0, MeOH), ref. 9. [t]data taken from ref. 10. [u]reaction performed in [abs. EtOH]/[benzene] = 2.0. [v]lit.[3] 89% ee. [x]data taken from ref. 3.

Thus, in Table 2 it is shown that for the N-acetylphenylalanine precursor our results are either higher [without added Et_3N] or identical [with added Et_3N] compared to the Rhone Poulenc results: 86 vs. 78 % ee, and 91 vs. 91 % ee, respectively. It is conceivable that the difference in the specific rotation of the chiral cyclobutane diphosphine (II) determined in our laboratory versus that stated by Rhone Poulenc S.A.[3] {$[\alpha]_D^{20}$ - 17.0° vs. lit.[3] -18.6°, both (C 1.0, benzene)} might be due to determination errors (especially when one considers the low magnitude of the values obtained).

Further experiments are in progress to determine the nature of the steric and polar effects that influence the interactions between the prochiral olefinic substrate in the chiral diphosphine/Rh(I) hydrogenation complex.

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