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ASYMMETRIC HYDROGENATIONS CATALYSED BY DIPHOSPHINITE RHODIUM COMPLEXES DERIVED FROM NATURAL TARTARIC ACID

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Summary

Two chiral diphosphinites, derived from natural tartaric acid, have been prepared and used as ligands for the preparation of two asymmetric hydrogenation catalysts, which were isolated in a crystalline state. After several weeks storage, these catalysts are still effective in the asymmetric hydrogenation of α-acetamido- and α-benzamido-cinnamic acid, citraconic acid, 2-phenyl-1-butene. In the hydrogenation of amino acid precursors the optical yields ranged from 14 to 44%. Starting from a given substrate, each of the two enantiomers can be obtained by appropriate choice of one of our two catalysts, which are thus complementary to each other. The influence on the optical yield of various factors in the hydrogenations are considered.

Organophosphorus species have commonly been used as ligands in soluble Wilkinson's type catalysts which are key reagents in the homogeneous reduction of double prochiral bonds. Catalysts involving phosphine asymmetric ligands were first studied, and these complexes, in which the asymmetry arises either from an asymmetric phosphorus center or a chiral hydrocarbon substituent, in most cases gave very good optical yields, especially in the hydrogenation of amino acid precursors. Such soluble rhodium catalysts can also be obtained by using as ligands diphosphinites which are derived from asymmetric phenols or alcohols [2—11], the alcohols often being sugar derivatives.

We have now prepared two chiral diphosphinites which are derivatives of tartaric acid, and from these the corresponding rhodium complexes. We describe below studies of the use of these compounds in asymmetric hydrogenation of the carbon—carbon double bond in various substrates.

Results

Synthesis of diphosphinites and derivated rhodium complexes

Starting from natural tartaric acid or ester, we prepared two hydrogenation

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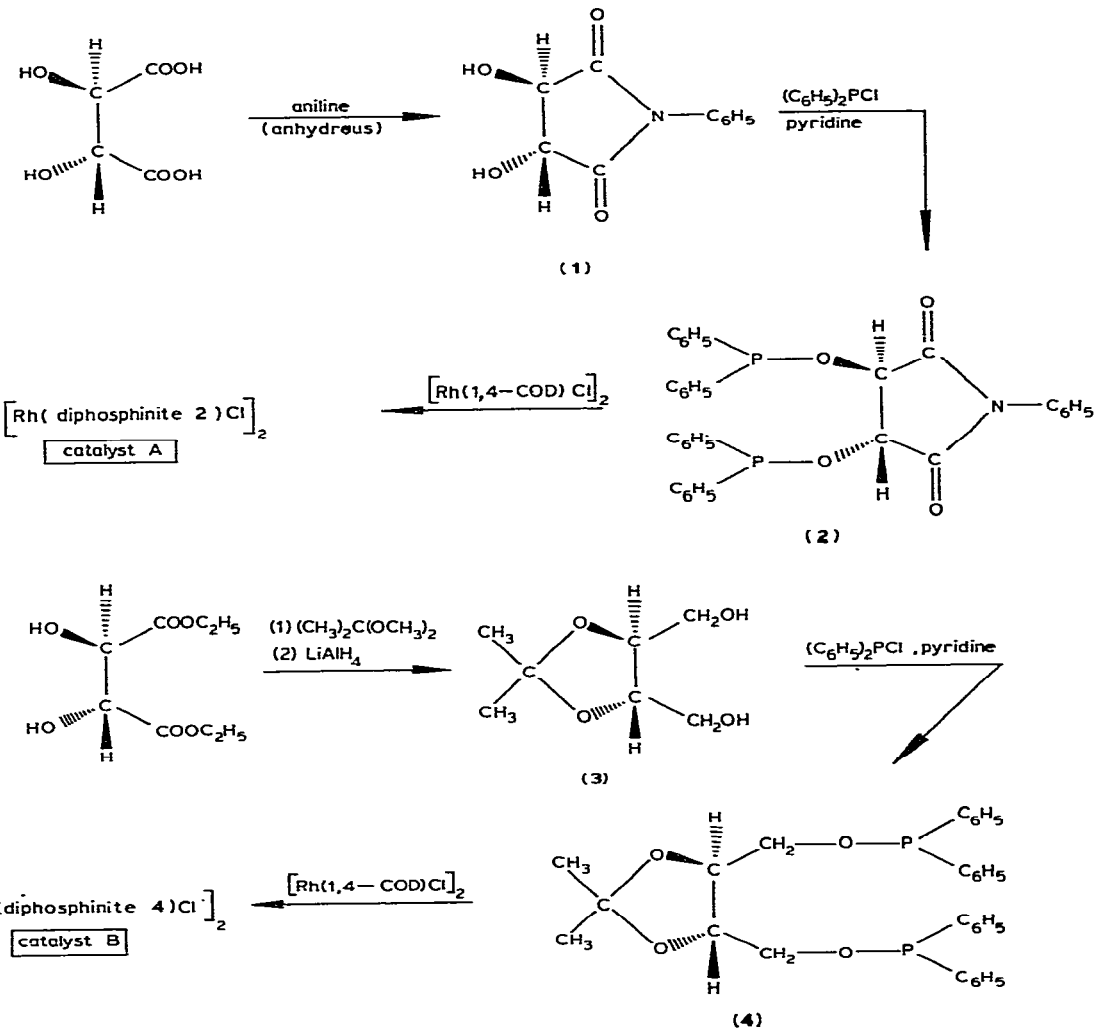
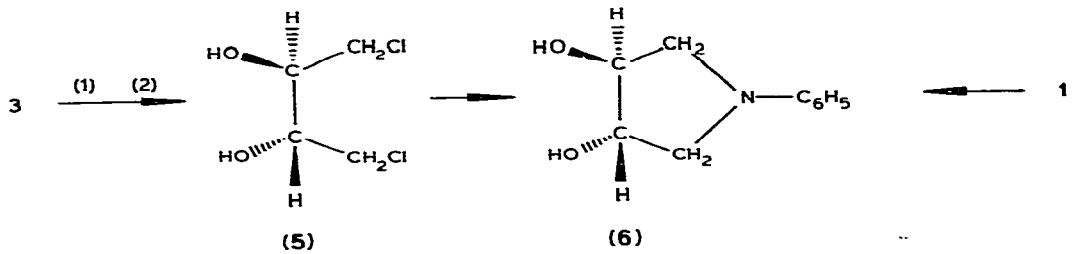
catalysts as follows:



While a report on this was in the press [12], catalyst A was also mentioned in the proceedings of a Hungarian symposium on rhodium in homogeneous catalysis [13], but we have been unable to obtain further details from the authors concerned.

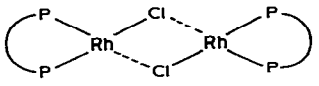
We made pyrrolidine **6** as a chiral compound (the first such preparation to our knowledge) from **1** or **3** as follows:



A third rhodium catalyst, obtained from the corresponding diphosphinite, gave only poor optical yields and was not further studied.

Catalytic compounds A and B were obtained as chlorides in a crystalline state. Elementary analyses agree with the empirical formula (Rh(diphosphinite)Cl), but they are probably dimeric species $(Rh(diphosphinite)Cl)_2$, as are the rhodium catalyst precursors [14].

This formulation is not in agreement with the literature reports. Catalysts with diphosphinite ligands are usually formulated as the (Rh(diphosphinite)-diene) anion, with rhodium coordinated to a second dienic ligand. But such suggested structures usually refer to diphosphine complexes prepared "in situ", and a compound of this type has been isolated in only one case [4]. In our catalytic complexes, rhodium is not coordinated to a second bidentate ligand or a diene, and the complexes must be regarded as:



A similar conclusion was drawn by Selke [13] for diphosphinites derived from carbohydrates.

Asymmetric hydrogenations

Catalysts A and B are very efficient for the hydrogenation of α-acetamido and α-benzamidocinnamic acids, citraconic acid and 2-phenyl-1-butene. They are complementary catalysts as for the same substrate, opposite results are obtained from the two catalysts.

Acetophenone and 2-ethyl-1-hexene do not undergo hydrogenation with these catalysts.

Discussion

The results show that catalyst A is more efficient than catalyst B, in both chemical reduction and asymmetric induction. The latter feature can be explained in terms of the greater proximity of both the phosphorous (and thus of the rhodium atom) to chiral C atoms in the first catalyst, and the more rigid structure in this case may also contribute.

Catalyst B with its two phosphinite ligands is the analogue of Kagan's DIOP with phosphine ligands [15]. Consideration of the distance from the chiral centers, which are closer to rhodium in DIOP, similarly explains the good optical yields on use of the latter for the same substrates.

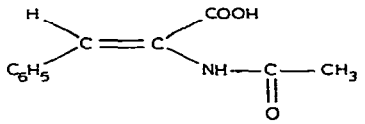
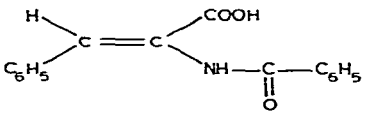
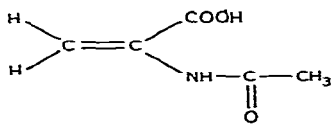
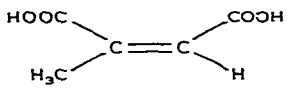
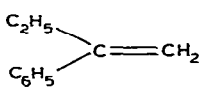
Various experimental conditions have been described for the use of diphosphinite rhodium complexes, and their influences on the course of the reaction are not clearly established. Thus it was of interest to study the effects of varying the conditions used in the present work.

Reaction time

At 50 atm of hydrogen and room temperature, hydrogenation of acylamido acid precursors goes to completion after 1 h and in some cases after only 15 min. A similar reaction time was recently reported for a diphosphinite glucose

TABLE 1

EXPERIMENTAL RESULTS [a]

Substrate	Catalyst	Molar amount subs/Rh	P_{H_2} (atm)	Reaction time	Optical yield (%)	Configuration
	A	230	50 25	15 min 60 min	36	*S*
	B	270	50	60 min	15	*R*
	A	110	10	60 min	44	*S*
	B	100	50	60 min	17	*R*
	A	230	10	15 min	26	*S*
	B	260	55	60 min	14	*R*
	A	100	55	17 h	24	*S*
	B	100	55	no reaction	—	—
	A	140	50	15 h	37	*R*
	B	150	50	15 h [b]	1	*S*

[a] Optical yields are calculated on the basis of reported maximum rotations: *N*-acetyl-(*R*)-phenylalanine: $(\alpha)_D^{26} = -51.8°$ (*c* = 1, EtOH) [15]; *N*-acetyl-(*S*)-phenylalanine: $(\alpha)_D^{26} = +46.0°$ (*c* = 1, EtOH) [16]; *N*-benzoyl-(*R*)-phenylalanine: $(\alpha)_D^{24} = -19.8°$ (*c* = 8.8, 0.4 *N* NaOH) [17]; *N*-benzoyl-(*S*)-phenylalanine: $(\alpha)_D^{27} = -40.3°$ (*c* = 1, MeOH) [18]; *N*-acetyl-(*R*)-alanine: $(\alpha)_D^{26} = +66.5°$ (*c* = 2, H_2O) [19]; *N*-acetyl-(*S*)-alanine: $(\alpha)_D^{26} = -66.2°$ (*c* = 2, H_2O) [19]; (*S*)-methylsuccinic acid: $(\alpha)_D^{22} = -12.4°$ (*c* = 1.3, MeOH) [20]; (*R*)-phenyl-2-butane: $(\alpha)_D^{23} = -24.3°$ (1 dm, neat) [21]. [b] Chemical yield = 40%.

derivative [4]. In most cases with diphosphinite ligands complete chemical reduction requires 24 hours.

Hydrogen pressure effect

Ojima [22] reports that in the case of phosphine ligands used for the reduction of 2-benzamidocinnamic acid, the optical yields decrease sharply as the hydrogen pressure is increased. For the same substrate and catalyst A, we found no significant variation in the optical yield with hydrogen pressure ranging from 4 to 60 atm. We observed a longer reaction time only in the case of low pressures. Similar conclusions have been drawn for other diphosphinites [9].

Effect of the catalyst complex anion

Some authors have reported a significant variation in the optical yield according to the nature of the anion of the diphosphinite rhodium complex [4,11]. In

our work, when ClO_4^- or BF_4^- was used in place of Cl^- no significant change in optical yield was observed in the case of catalyst A.

Effect of the substrate/Rh ratio

All the present hydrogenation reactions were carried out with substrate/Rh ratios between 100 and 250. We examined the influence of this ratio for the hydrogenation of acetamidocinnamic acid with catalyst A. No variation in the optical yield (36%) was observed for molar substrate/Rh ratios ranging from 70 to 350 (10 to 50 mg of catalyst for 1 g substrate). At a ratio of 700 the optical yield decreases (30%).

Solvent effect

For hydrogenation of aminoacid precursors with catalysts A and B, benzene, dichloromethane and isopropyl alcohol are poor solvents, and the reaction is incomplete or does not take place. This is probably related to the poor solubility of the catalyst in these solvents.

Methanol and ethanol are better solvents for these catalysts. However the limit of the catalyst concentration is 0.7 mg/ml: above this value the partly undissolved catalyst is recovered after the reaction.

Although methanol and ethanol were chosen as the only available solvents for our reactions, we found that they have a negative influence on the asymmetric induction by the catalysts. Thus when the acetamidocinnamic acid hydrogenation is monitored by UV spectroscopy for the chemical reduction and by polarimetry for the asymmetric induction, the rotatory power quickly reaches a limiting value while the chemical reduction is still far from complete.

A significant part of the substrate is thus reduced without asymmetric induction. Since no precipitation of metallic rhodium is observed in this intermediate stage of reaction, we assume that the latter part of the reaction is catalysed by a modified or new complex. This transformation of the original complex may involve alcoholysis of a ligand. This is supported by observation that when diphosphinite **2** is boiled for a short time in absolute alcohol it is transformed into diol **1**.

Experimental section

The ^1H NMR spectra were recorded on a Perkin-Elmer R-32 spectrometer. UV spectra were obtained with a Unicam SP 1800 spectrometer. Optical rotations were determined with a Perkin-Elmer 241 automatic polarimeter. Hydrogenations were performed in a steel bomb purchased from the Paly company, Vitry (France), Merck methanol was used without further purification. The new products described gave analyses, which were carried out in the CNRS microanalysis laboratory.

N-Phenyltartrimide, **1**

The product obtained as described by Barrow and Atkinson [23] was crystallized from nitromethane and then from water. Any tartaric dianilide is thus removed: yield = 40%. The two products may be distinguished by their different IR carbonyl bands: tartrimide: double band 1710 and 1730 cm^{-1}; dianilide:

1680 cm^{-1}. The identity of *N*-phenyltartrimide was confirmed by analysis, m.p. (255°C) (α_D^{25} = +130° (*c* = 1.5, MeOH) (see ref. 23), mass spectra (*M* = 207) and ^1H NMR in CF_3COOH, ppm): 7.2—7.7 (m, 5 H) 5.25 (s, 2 H).

(2S,3S)-2,3-o-isopropylidene-1,2,3,4-tetrahydroxybutane, **3**

The method reported in ref. 24 was used for the preparation of this compound.

(2R,3R)-1,4-dichloro-2,3-dihydroxybutane, **5**

The product was obtained by treatment of **3** with $SOCl_2$ in pyridine and subsequent hydrolysis of the cetal function by warming in 1*N* H_2SO_4 on the water bath. Final crystallisation in $CHCl_3$/hexane (2/1) gave a product identical with that described by Feit [25]. M.p. = 67°C, $(\alpha)_D^{20}$ = +16.3° (*c* = 0.2, MeOH). ^1H NMR ($CDCl_3$, ppm): 3.5—4 (m, 6 H) 2.65 (s, 2 H).

(3S,4S)-3,4-dihydroxy-1-phenyl pyrrolidine, **6**

(i) By reduction of **1** by $LiAlH_4$ in THF. The initial oil crystallized in C_6H_6, yield = 41%.

(ii) Condensation of aniline with **5** as described for the racemic product by Robert and Ross [26]. White crystals m.p. 154°C; mass spectra: *M* = 179. Ditosyl derivative: m.p. = 128°C.

Other characteristic data for **6**: $(\alpha)_D^{25}$ = +45° (*c* = 0.2, $CHCl_3$). ^1H NMR (C_5D_5N, ppm): 7.05—7.5 (q, 2 H) 6.5—6.9 (m, 5 H) 4.7 (s, 2 H), quadruplets centered to 3.68 and 3.72 ppm, *J* = 10 Hz (4 H).

(2S,3S)-2,3-o-bis(diphenylphosphino)-N-phenyltartrimide, **2**

Diol **1** (4.15 g, 0.02 mol) is dissolved in 50 ml of pyridine (Merck) and 9 g of $(C_6H_5)_2PCl$ are added stepwise with vigorous stirring. A precipitate is observed at half addition and then the mixture again becomes fluid. The mixture is then warmed to 45°C for 3 hours, under nitrogen. After cooling and addition of a further 5 g of $(C_6H_5)_2PCl$, the procedure is repeated. The mixture is then set aside for 12 hours in the cold. The precipitate is collected and washed 3 times with absolute ethanol to remove pyridinium hydrochloride. The diphosphinite **2** is then dried in the cold and used without further purification. M.p. = 240°C, yield: 22% = 2.5 g. Satisfactory C, H, N and P analyses for $C_{34}H_{27}NO_4P_2$ were obtained.

IR: ν(CO) = 1710 cm^{-1}; $(\alpha)_D^{23}$ = +106° (*c* = 1.2, pyridine). ^1H NMR (CF_3COOH; partial decomposition, ppm): 8—8.8 (m, 25 H) 4.08 (s, 2 H). In some cases another product, m.p. = 205°C, ν(CO) = 1694 cm^{-1}, isolated and this was identified from its analysis and mass spectra as the monophosphinite.

(2S,3S)-2,3-o-isopropylidene-2,3-dihydroxy-1,4-(diphenylphosphinoxy)butane, **4**

Diol **3** (4.2 g) is dissolved under nitrogen with magnetic stirring in 40 ml of pyridine. Then 13.2 ml (20% excess) of chlorodiphenylphosphine are added stepwise during 20 min; a white precipitate of pyridinium hydrochloride appears. Stirring is continued for 2 hours. The mixture is then filtered under nitrogen and evaporated, and the residue is distilled under reduced pressure (10^{-4} mmHg). Diphosphinite **4** is collected between 240 and 250°C; yield: 9 g (56%). Satis-

factory C, H, and P analyses for $C_{31}H_{32}O_4P_2$ were obtained. ^1H NMR ($CDCl_3$ ppm): 7.31 (m, 20 H) 4.07 (m, 4 H) 3.91 (m, 2 H) 1.32 (s, 6 H). No rotatory power was recorded because the value varies rapidly in solution.

Catalyst A

Under nitrogen and with magnetic stirring, 0.5 g $[Rh(COD)Cl]_2$ [14] is dissolved in a mixture of methanol (5 ml) and isopropanol (7 ml). After 20 min stirring, 1.27 g diphosphinite 2 is added in one lot and stirring is continued for 20 hours. The colour of the mixture goes from bright yellow to orange-yellow. The progress of the reaction can be observed for samples under the microscope: the long needles of the diphosphinite disappear and are replaced by small crystals of the catalyst. The catalyst is filtered off under nitrogen and washed 3 times with 3 ml of methanol/isopropanol (2/3); yield: 1.4 g (97%). M.p. = 170—180°C (dec.). Analysis. Found: C, 57.14; H, 4.42; Cl, 4.85; N, 1.99; P, 8.44. Calcd. for $RhC_{34}H_{27}ClNO_4P_2$: C, 57.19; H, 3.78; Cl, 4.98; N, 1.96; P, 8.44%.

Catalyst B

The complex $[Rh(COD)Cl]_2$ (0.99 g) is added to 10 ml methanol under nitrogen with magnetic stirring. To this suspension is added dropwise (30 min) a solution of 2.2 g diphosphinite 4 in 15 ml isopropanol. The mixture is stirred in the cold for 12 hours, the colour changing from bright yellow to orange-yellow. The precipitate is collected under nitrogen, washed 3 times with 1 ml isopropanol, then dried upon $CaCl_2$. Yield = 1.5 g (56%); m.p. = 138°C (dec.). Analysis. Found: C, 56.32; H, 5.22; P, 9.09. Calcd. for $RhC_{31}H_{32}ClO_4P_2$: C, 55.66; H, 4.79; P, 9.28%.

Hydrogenation procedures

General. Hydrogen pressure, reaction time, and results are indicated in Table 1. Solvent and substrate are introduced into a 250 ml steel bomb equipped with a magnetic stirrer. The mixture is first purged by nitrogen bubbling and the reactor atmosphere then purged three times with hydrogen before the final hydrogen pressure was established.

a) *Amino acid precursors*: solvent: 40 ml methanol, substrate 0.5 g, catalyst: 6 to 14 mg, room temperature.

At the end of the reaction, the UV spectra show whether the reaction is complete. The mixture is then boiled with 0.5 g of vegetable charcoal in order to take up the catalyst and residual traces of its precursor. The solution is evaporated and the solid residue of amino acid dried to constant weight. The rotatory power is then determined in a suitable solvent.

UV characteristic absorptions: λ_{max} (nm):

N-acetylphenylalanine 259
α-acetamidocinnamic acid 278
N-benzoylphenylalanine <240
α-benzamidocinnamic acid 280
N-acetylalanine <230
α-acetamidoacrylic acid 242.

b) *Citraconic acid*: solvent: 60 ml benzene, substrate: 2 g, catalyst A: 110 mg, temperature: 75°C.

At the end of the reaction, the solution is diluted with 40 ml methanol, filtered through a short silica column and boiled with 0.5 g charcoal. The filtrate is concentrated and the residual oily methylsuccinic acid distilled under reduced pressure (B.p. = 60°C, 1 mmHg). A viscous liquid is initially obtained but soon crystallizes.

c) *2-Phenyl-1-butane*: solvent: 30 ml benzene, substrate: 2 ml, catalyst A: 55 mg, temperature: 50°C. Completion of the reaction is confirmed by VPC. The catalyst is precipitated with a hexane/ether (3/1) mixture. After filtration through a short silica column, the solvent is removed and the oily residue distilled (M.p. = 173°C), giving 2-phenyl-1-butane.

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