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ASYMMETRIC HYDROGENATION OF ACETOPHENONE WITH RHODIUM(I) COMPLEXES OF NEW CHIRAL PHOSPHINES DERIVED FROM AMINO ACIDS. AN UNUSUAL MODIFICATION OF THE CATALYST SYSTEM

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Summary

Chiral, *N*-substituted diphenylphosphinoacetamides were prepared by the acylation of L-aminoacid esters and L-α-phenylethylamine with diphenylphosphinoacetic acid. These compounds were used as ligands in Rh^I complex catalysts for hydrogenation of acetophenone and styrene. In the presence of strong, sterically hindered bases the complexes showed low to moderate hydrogenating activity and enantioselectivity. The catalytic activity is enhanced significantly in the presence of a separate aqueous phase.

Introduction

Despite successes in the practice and theory of asymmetric homogeneous catalysis, the preparation of new types of catalysts remains one of the main tasks in this field of study. We have prepared a series of chiral amides containing the diphenylphosphino (Ph_2P) moiety by the following reaction:

$$Ph_2PCH_2COOH + R^1\overset{*}{C}H(NH_2)-R^2 \xrightarrow[CHCl_3]{DCCI} Ph_2PCH_2C(=O)NH\overset{*}{C}H(R^1)-R^2 \qquad (1)$$

DCCI = dicyclohexylcarbodiimide

(R^1 and R^2 are shown in Table 1.)

Here we report on the preparation and properties of these compounds and their use as ligands in Rh^I complex catalysts for homogeneous hydrogenation of acetophenone and styrene. An unusual effect of added water is also discussed.

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TABLE 1

ANALYTICAL DATA FOR $Ph_2PCH_2CONHCHR^1R^2$ COMPOUNDS

Starting amine (abbreviation of product)	R^1	R^2	$\nu(CO)$ [a] ester (cm^{-1})	$\nu(CO)$ [a] amide (cm^{-1})	$[\alpha]_D^{20}$ [b] (deg.)	Analysis Found (calcd.) (%)			M.p. (°C)
						C	H	N	
L-Proline (PT)	CH_2-CH_2 / CH_2 / $CH-R^2$ / N	-$COOBu^t$	1741	1639	−52.9	69.61 (69.51)	7.01 (7.10)	3.68 (3.52)	110—113
L-Valine (VT)	Pr^i	-$COOBu^t$	1732	1624 1545	−7.4	69.81 (69.98)	7.84 (7.80)	3.88 (3.50)	94—97
L-Phenylalanine (FAT)	-CH_2Ph	-$COOBu^t$	1730	1655 1510	+49.5	72.61 (72.47)	6.58 (6.76)	3.31 (3.13)	78—82
(FAE)	-CH_2Ph	-COOEt	1734	1649 1531	+53.7	71.52 (71.76)	5.95 (6.02)	3.45 (3.36)	120—123
L-α-Phenylethylamine (FEA)	-Me	-Ph	—	1629 1543	−33.5	76.01 (76.06)	6.22 (6.38)	4.01 (4.03)	122—125

[a] In KBr. [b] c = 1.5—2 g/100 ml; $CHCl_3$.

Results and discussion

For the preparation of diphenylphosphinoacetamides (eq. 1) L-α-phenylethylamine and esters of L-aminoacids were used as chiral amines. Some of the characteristics of the new compounds are listed in Table 1. Since diphenylphosphinoacetic acid (or the analogous phosphinocarboxylic acids) can be prepared relatively easily, this reaction offers a convenient route to a range of chiral phosphines. Somewhat similar compounds have already been prepared [1] from the acylation of 2,2'-bis(diphenylphosphinoethyl)amine with various carboxylic acids, including chiral ones. The coordination chemical properties of diphenylphosphinoacetic acid and its esters have also been investigated [2].

Catalytic hydrogenations

Rh^I complexes formed (in situ) from $[Rh(COD)Cl]_2$ (COD = cyclooctadiene) and the new phosphines catalyze the hydrogenation of styrene and acetophenone in the presence of bases, viz. triethylamine (TEA), dicyclohexylamine (DCA) and 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN), at 323 K and 1 bar total pressure.

Hydrogenation of acetophenone

Only the Rh^I-complexes of PT and FEA (for abbreviations see Table 1) were examined in detail, since the other phosphines gave only slightly active catalysts under the same conditions. The results are summarized in Table 2. For compariso use of PPh_3 as ligand was also studied. When benzene/methanol mixtures were used as solvent no hydrogenation occurred, and so the reactions were carried

TABLE 2

HYDROGENATION OF ACETOPHENONE WITH Rh^I-PHOSPHINOACETAMIDE AND Rh^I-PPh_3 COMPLEXES

No.	Ligand	Base	Base/Rh	H_2O (v/v %)	Initial rate (mol H_2/mol Rh h)	Optical yield [e] (%)
1	PPh_3	TEA	2	—	2 5 [c]	
2	PPh_3	TEA	2	20	19 0	
3	PPh_3	DBN	2	—	5 0	
4	FEA	TEA	1	—	— [d]	
5	FEA	TEA	2	20	3 5	15
6	FEA [a]	TEA	2	20	6 0	22
7	FEA [b]	TEA	2	20		19
8	FEA	DBN	1	—	2 4	10
9	FEA	DBN	2	—	2 4 [c]	9
10	PT	TEA	1	—	0 7	
11	PT	TEA	1	20	6 0	10
12	PT [a]	TEA	1	20	7 1	22
13	PT	DBN	1	—	2 5	
14	PT	DBN	2	—	5 0	15
15	PT	DBN	8	—	4 0	12

Conditions T = 323 K, P_{total} = 1 bar, [Rh] = 20 mM, [L]/[Rh] = 3, S/Rh = 435 (in acetophenone) [a] [S]/[Rh] = 200 (solvent benzene) [b] [S]/[Rh] = 200 (solvent: benzene), [L]/[Rh] = 2 [c] 1 v/v % water does not influence the rate [d] Not measurable. [e] Optical yield of (*R*)-(+)-α-phenyl-ethanol $[\alpha]_D^{20}$ = 43 5—52.8° (for the calculations $[\alpha]_D^{20}$ = 44° was used throughout)

out in benzene or with acetophenone itself as solvent.

The rates (max. 7.1 mol H_2/mol Rh h) and the optical yields (9—22%) of acetophenone hydrogenation catalyzed by Rh^I-FEA and -PT complexes are low to moderate. The highest optical yields were achieved using benzene solutions (as in ref. 3), entries 6 and 12; L/Rh = 3. The highest initial rate was observed with the same L/Rh ratio (Fig. 1). This finding is somewhat contradictory to the usual observations according to which the catalytic activity and enantioselectivity vary in an opposite manner. By virtue of the amide (and ester) oxygen, the phosphines may be able to coordinate as bidentate ligands to the central rhodium ion, as was shown in analogous complexes [2,4], retaining the optical selectivity of the catalyst even at relatively low [P]/[Rh] ratios.

The nature and amount of the applied bases have significant effects on the reaction rate. The sterically hindered, non-coordinating, so-called superbase, DBN, gives higher rates than TEA (entries 1, 3; 4, 8; 10, 13). The [base]/[Rh] ratio does not seem crucial (entries 8, 9 and 13—15), though there is a slight maximum in the effect at [base]/[Rh] = 2. The optical yield is similarly influenced.

The most interesting changes in the reaction rate are produced by the addition of water. Though in homogeneous solutions a small amount of water has no appreciable effect (entries 1 and 9), in the presence of a separate aqueous phase of relatively large volume (e.g. 20 v/v %), the rate of hydrogenation increases by approx. an order of magnitude. (In DBN-containing solutions precipitation occurred on the addition of water, therefore for the two-phase hydrogenations TEA was always used.)

Hydrogenation of styrene

These results are summarized in Table 3.

In the absence of bases, $RhClP_3$-type catalysts derived in situ from [RhCl-

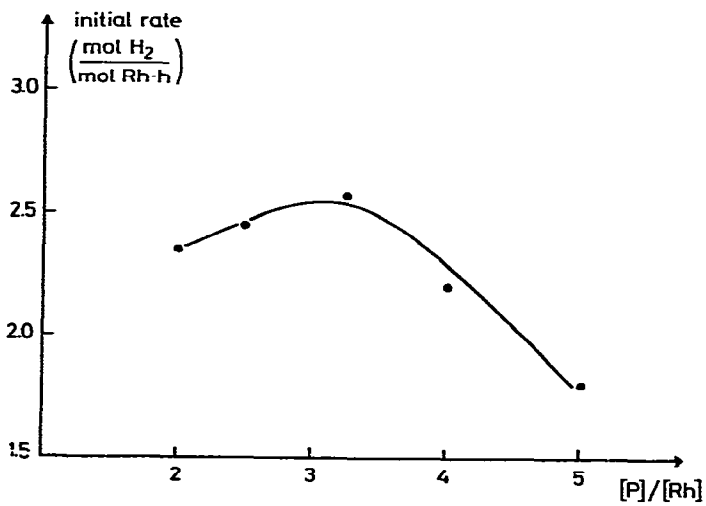

Fig. 1. Initial rate of acetophenone hydrogenation as a function of the [P]/[Rh] ratio, in the presence of an aqueous phase (20 v/v %). Ligand: FEA, T = 323 K, P_{total} = 1 bar, [Rh] = 10 mM, [S]/[Rh] = 100 (solvent benzene). TEA/Rh = 1.

TABLE 3

HYDROGENATION OF STYRENE WITH Rh^{I}-PHOSPHINOACETAMIDE AND Rh^{I}-PPh_3 COMPLEXES

No.	Ligand	Base	H_2O (v/v %)	Initial rate (mol H_2/mol Rh h)
1	PPh_3 [a]	—	—	23 0
2	PPh_3 [a]	TEA	—	35.0
3	PPh_3 [a]	TEA	20	37.5
4	FEA [b]	TEA	—	0.5
5	FEA [b]	DCA	—	1.5
6	FEA [b]	DBN	—	2.5 [d]
7	FEA [b]	TEA	20	38.0
8	PT [c]	TEA	20	66.0
9	FAE [b]	TEA	20	2 5 [e]
10	VT [b]	TEA	20	4.7 [e]

Conditions: L/Rh = 3 throughout, solvent benzene, T = 323 K, P_{total} = 1 bar [a] [Rh] = 2 5 mM, S/Rh = 100, base/Rh = 4 [b] [Rh] = 10 mM, S/Rh = 25, base/Rh = 4 [c] [Rh] = 10 mM, S/Rh = 25, base/Rh = 1 [d] 1 v/v % water does not influence the rate [e] Not measurable in the absence of an aqueous phase.

$(COD)]_2$ and the phosphinoacetamides showed low or no activity in styrene hydrogenation. The increase in rate is rather small on addition of bases, DBN again giving the highest rate. Similarly, the catalytic activity of $RhCl(PPh_3)_3$ is somewhat increased by TEA. The rate is not influenced by addition of a small amount of H_2O, up to the solubility limit (approx. 1 v/v % under our experimental conditions). However, a large increase in the rate is observed, if the reaction mixture is stirred with a separate aqueous phase (entries 7—10), and the activity of the Rh^{I}-PT and -FEA complexes becomes higher than, or equal to, respectively, that of $RhCl(PPh_3)_3$.

The effect of water

There are numerous reports in the literature that the addition of water to different homogeneous hydrogenation systems results in changes in the rate and selectivity (including enantioselectivity) of the given reaction (see examples cited in refs. 5 and 6), and in some cases the phenomenon remain unexplained [7].

However, our observations suggest a previously unconsidered, non-chemical origin of the effect of water. Figure 2 shows the rate of acetophenone hydrogenation as a function of the volume of the aqueous phase. Since the influence of water can be observed only in the presence of bases, we suggest the following mechanism:

$$RhClP_3 \overset{+H_2}{\underset{-H_2}{\rightleftharpoons}} H_2RhClP_3$$

$$H_2RhClP_3 + NR_3 \rightleftharpoons HRhP_3 + NR_3 \cdot HCl$$

organic phase

aqueous phase

$$R_3NH^+ + Cl^-$$

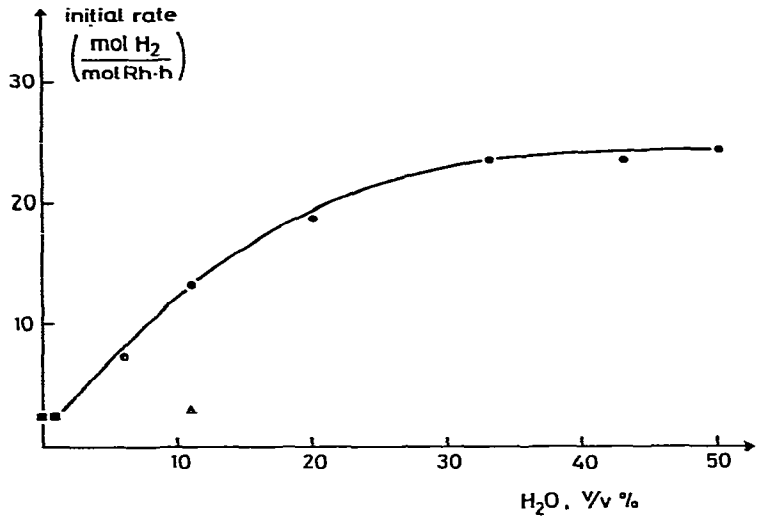

Fig. 2. Initial rate of acetophenone hydrogenation as a function of the relative amount of the aqueous phase. Ligand: PPh_3, T = 323 K, P_{total} = 1 bar [Rh] = 20 mM, [L]/[Rh] = 3, [S]/[Rh] = 435 (without solvent, TEA/Rh = 2) homogeneous solution; separate aqueous and non-aqueous phases; 0.5 M TEA · Cl solution instead of water (▲).

The first two processes are generally recognized to operate in hydrogenations in the presence of bases [8,9], and 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) was shown to be an effective dehydrohalogenating agent in reactions with Ru, Os, and Pt hydrides [10]. In accord with reports in ref. 3, we have found that the stereoselectivity is higher in benzene solutions than in the more polar acetophenone itself, which may suggest that in benzene no other reaction contributes significantly to the formation of catalytically active intermediates. However, the slow rates in benzene can be increased if the second equilibrium is shifted to the right by extracting the base hydrochloride into the aqueous phase. This suggestion is further supported by the fact, that when 0.5 M TEA · HCl solution was used instead of water no increase in the rate was observed (Fig. 2). Moreover, 50—85% of the theoretically required chloride could be determined in the aqueous phases by titration with $Hg(NO_3)_2$, depending on the phosphine used and the experimental conditions. The modification of the catalyst systems by this extraction method may help in developing more effective enantioselective procedures which avoid the disadvantageous effect of certain additives (e.g. alcohols, especially at high [base]/[Rh] ratios). We have found that benzene solutions of the catalysts, after prehydrogenation, extraction, phase-separation and drying over Na_2SO_4 could be used under anhydrous conditions. The activity of these pre-formed catalyst solutions was approximately the same as that of those prepared in situ in two-phase catalytic systems.

Experimental

Materials

The L-aminoacid-esters (Reanal), L-α-phenylethylamine (Merck) and DCCI (Fluka) were of highest purity and were used as received. Solvents and substrates

were purified by standard procedures and were distilled and stored under purified N_2. Diphenylphosphinoacetic acid Na [11] was prepared by treating ethyl chloroacetate with sodium diphenylphosphide in liquid NH_3 and hydrolysis of the resulting ester in alcoholic NaOH solution [12]. Acidification of aqueous solutions of the crude product gives the free acid, which can be recrystallized from alcohol/water mixtures.

Preparation of the phosphinoacetamides

To a solution of 10 mmol of the aminoacid ester or amine in 30 ml $CHCl_3$ 2.44 g (10 mmol) of diphenylphosphinoacetic acid was added, followed by a slow, dropwise addition of 2.06 g (10 mmol) of DCCI in 20 ml $CHCl_3$. During the addition of DCCI the mixture was well stirred and the temperature was kept at about 0°C. After 20 hours standing at room temperature (3 hours in case of L-proline Bu^t ester), the dicyclohexylcarbamide was filtered from the ice-cooled solution, and the filtrate was evaporated to dryness at 40°C. The residue was recrystallized from 96% ethanol (FAE, FEA), diethyl ether (PT) or ethanol/water mixtures (FAT, VT). Yields varied from 50% (PT) to 75% (VT). It is beneficial (though not crucial) to prepare the compounds under nitrogen to avoid oxidation. The products are white, crystalline substances. Their purities were checked by TLC on silica gel (solvent: benzene/acetone = 1/1). Analytical and spectroscopic data are given in Table 1.

Hydrogenation experiments

$[RhCl(COD)]_2$ (0.02—0.1 mmol Rh) and the required amount of the phosphine were dissolved in the reaction medium (benzene solutions of acetophenone or styrene, or acetophenone alone) under hydrogen, in a thermostatted reaction vessel equipped with a serum cap and connected to a gas burette. Appropriate amounts of bases and water were added with hypodermic syringes. The reaction mixture was stirred magnetically at 50.0 ± 0.1°C, and the hydrogen consumption was followed at a constant total pressure of 1 bar. In hydrogenation of acetophenone the resulting solution was vacuum distilled and the extent of reaction was also determined by GLC analysis of the distillate (HP 5840A, 10% Carbowax 20M on Chromosorb WDMCS 80—100 mesh). Optical rotations were determined on a Perkin Elmer 241 direct reading polarimeter at 589 nm.

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