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ASYMMETRIC HYDROGENATION, HYDROFORMYLATION AND HYDROCARBALKOXYLATION OF OLEFINS BY TRANSITION METAL COMPLEXES WITH STEROIDAL PHOSPHINES

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Summary

Two new optically active phosphines, 3α-diphenylphosphino-5α-cholestane [(+)-DICOL] and 2,3-*O*-(5′α-cholestan-3′,3′-ylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane [(−)-DIOCOL] have been prepared and used as ligands in transition metal catalyzed asymmetric processes. In CO-insertion reactions, especially in the Pd promoted hydrocarbalkoxylation,(+)-DICOL-based complexes displayed a remarkable catalytic activity and a very high regioselectivity, but a poor stereoselectivity. Optical yields of up to 93% and up to 34%, respectively, were obtained in asymmetric hydrogenation and hydroformylation catalyzed by rhodium complexes with (−)-DIOCOL.

Introduction

Asymmetric additions to carbon–carbon double bond, catalyzed by transition metal complexes, such as hydrogenation, hydroformylation and hydrocarbalkoxylation, have received considerable attention in the past decade. Asymmetric hydrogenation has mainly been carried out with rhodium [1] and ruthenium [2] catalysts, the hydroformylation with rhodium and platinum catalysts [3], and the hydrocarbalkoxylation with palladium complexes [4].

Tertiary optically active phosphines chiral either at phosphorus or at carbon(s) have usually been employed as the chiral ligands in the above mentioned asymmetric processes, and the optical yields reached are often very high, especially in the hydrogenation. They are less satisfactory, however, in CO insertions, where they are normally lower than those in hydrogenation and in other catalytic additions to carbon–carbon double bond, such as carbenoid cyclopropanation and hydrosilylation [5]. The maximum values of asymmetric induction achieved in hydroformylation and hydrocarbalkoxylation are 95% [6] and 69% [7], respectively, and both these results were obtained by use of the chiral ligand (−)-DIPHOL, the bis(dibenzophosphole) analogue of the more popular (−)-DIOP. However, ten years after the first

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demonstration of asymmetric hydroformylation the choice of the chiral ligand in CO-insertion reactions catalyzed by transition metal complexes is still largely empirical since, in spite of the considerable work done in this area, adequate understanding of the factors controlling the stereoselectivity of these reactions is still lacking. This prompted us to see whether the introduction of a bulky substituent with several chiral centers in the phosphine framework might enhance the stereodifferentiating ability of the catalyst, particularly in carbonylations of olefinic substrates.

In spite of the large number of chiral ligands derived from easily available optically active natural products, no phosphines chiral at a carbon of a steroidal moiety have been described in the literature (cholesteryldiphenylphosphine has been mentioned in a patent [8], but without any detail of its preparation or use in asymmetric reactions). In the present paper we describe the preparation and the characterization of two new phosphines derived from cholesterol, and report the results obtained in some transition metal catalyzed asymmetric processes employing these ligands.

Results and discussion

Synthesis of the chiral phosphines

The two chiral phosphines were prepared using cholesterol as starting product.

3α-Diphenylphosphino-5α-cholestane [(+)-DICOL] was synthesized by the reaction sequence depicted in Scheme 1. Pure cholesterol was catalytically hydrogenated to give 5α-cholestan-3β-ol [9] which was converted into the *p*-toluensulfonate [10]. Reaction of the latter compound with sodium diphenylphosphide in THF/dioxane required 72 h at room temperature for completion. The phosphine was purified by crystallization from ether/methanol: it is rather sensitive to air oxidation in solution, but can be stored in the crystalline form without appreciable change.

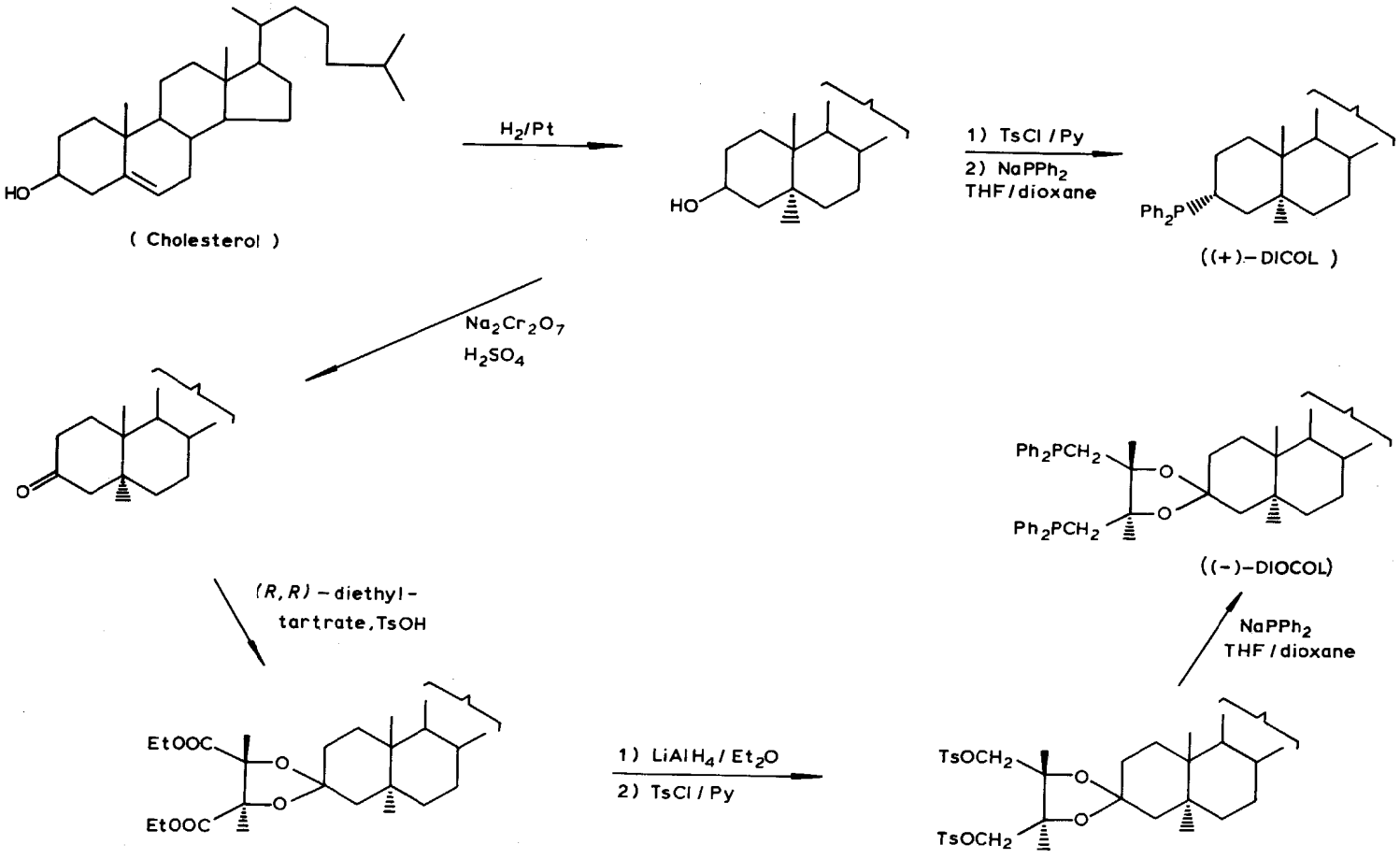
The overall yield from cholesterol to (+)-DICOL in a typical preparation was 28–30%.

For the preparation of 2,3-*O*-(5′α-cholestan-3′,3′-ylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane [(−)-DIOCOL], 5α-cholestan-3-one, easily available from cholesterol [11], was used as the carbonyl component in the ketalization of (*R*,*R*)-diethyltartrate (Scheme 1). The $LiAlH_4$ reduction of this ketal afforded 2,3-*O*-(5′α-cholestan-3′,3′-ylidene)-L-threitol, which was converted into (−)-DIOCOL in 70% yield by reaction with *p*-toluenesulfonyl chloride in pyridine, followed by treatment at room temperature with sodium diphenylphosphide in THF/dioxane. The yield based on 5α-cholestan-3β-ol was 25%. The phosphine is rather easily oxidized in solution, but stable in the crystalline form.

Asymmetric hydrogenation

The catalysts for asymmetric hydrogenation were prepared in situ from $[Rh(COD)Cl]_2$ (COD = cyclooctadiene) and (+)-DICOL or (−)-DIOCOL, using a P/Rh mol ratio of 2.2/1. As these catalysts were found to be almost inactive at low pressure, hydrogenation experiments were performed under 70 atm of hydrogen. The reactions were carried out at room temperature overnight in a 1/1 benzene/methanol solution, with α,β-unsaturated acids or esters as substrates and a substrate/catalyst ratio of 200/1. Under these conditions reduction of carbon–carbon double bond

SCHEME 1


HO
(Cholesterol)
H_2/Pt
HO
1) TsCl / Py
2) $NaPPh_2$
THF / dioxane
Ph_2P
((+)-DICOL)
$Na_2Cr_2O_7$
H_2SO_4
O
Ph_2PCH_2
Ph_2PCH_2
O
O
((-)-DIOCOL)
(R, R) - diethyl -
tartrate, TsOH
$NaPPh_2$
THF / dioxane
EtOOC
EtOOC
O
O
1) $LiAlH_4$ / Et_2O
2) TsCl / Py
$TsOCH_2$
$TsOCH_2$
O
O

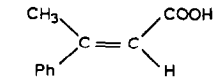
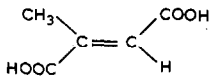
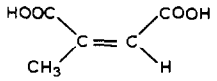
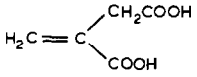
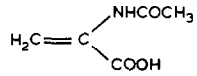
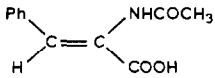
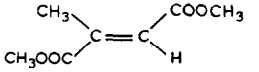
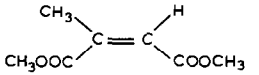
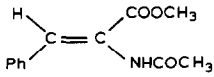
occurred with complete selectivity, and the products were isolated in high yield either by distillation or by acid-base work up. The results obtained are reported in Table 1.

The products from the hydrogenation of (*Z*)-α-acetylaminocinnamic acid and (*E*)-β-methylcinnamic acid in the presence of the (+)-DICOL based catalyst were optically inactive, and so this ligand was not further employed.

With (−)-DIOCOL, the highest asymmetric induction was obtained in the hydrogenation of (*Z*)-α-acetylaminocinnamic acid, which gave *N*-acetyl (*R*)-phenylalanine in 91–93% optical yield, depending on the conditions employed (Table 1).

TABLE 1

ASYMMETRIC HYDROGENATION OF α,β-UNSATURATED ACIDS AND ESTERS CATALYZED BY $[Rh(COD)Cl]_2$/(−)-DIOCOL (P/Rh molar ratio 2.2/1; substrate: 5×10^{-3} mol; benzene/methanol (1/1) 40 ml; substrate/catalyst 200/1; hydrogen pressure 70 atm; reaction temperature 25°C; reaction time 16 h)

Run	Substrate	Conversion (%)	Configuration	Optical yield [a] (%)
1		98	(*R*)	10.8
2		75	(*R*)	9.2
3		95	(*S*)	2.7
4		98	(*S*)	9.8
5		95	(*R*)	30
6		96–98	(*R*)	93.3 [b] 91 92.9 [b,c]
7		75	–	–
8		95	–	–
9		98	(*R*)	13

[a] Calculated on the following basis: (+)-(*S*)-3-phenylbutanoic acid: α_D^{25} +58.5° [12]; (+)-(*R*)-2-methylsuccinic acid: $[\alpha]_D^{25}$ +17.1 (EtOH) [13]; (+)-(*R*)-*N*-acetylalanine: $[\alpha]_D^{25}$ +66.5 ($c = 2$, H_2O) [14]; (−)-(*R*)-*N*-acetylphenylalanine: $[\alpha]_D^{25}$ −46 ($c = 1$, EtOH) [15]; (−)-(*R*)-*N*-acetylphenylalanine methyl ester: $[\alpha]_D^{25}$ −21.4 ($c = 1.9$, MeOH) [16]. [b] Substrate/catalyst ratio 100/1. [c] In the presence of triethylamine (2 mmol).

Optical yields much lower than these were obtained with the other acids, while, with one exception, esters gave only racemic products.

Asymmetric hydroformylation

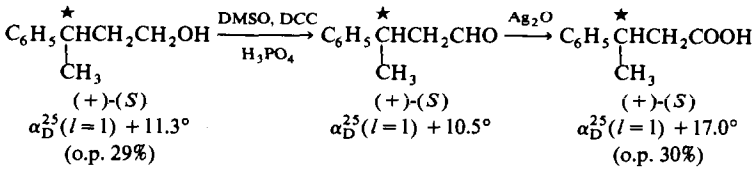
The hydroformylation of prochiral olefins was carried out using as catalytic systems rhodium phosphine complexes prepared in situ from rhodiumhydrido-carbonyl-tris(triphenylphosphine) and (+)-DICOL or (−)-DIOCOL, respectively (P/Rh mole ratio 3/1). The results are reported in Table 2.

The catalytic complex formed from (+)-DICOL showed good activity and selectivity in hydroformylation but a poor stereoselectivity, since optical yields were never higher than 1%. The regioselectivity for the formation of the linear aldehyde is in the range observed using conventional monodentate phosphine ligands [17,18]. No isomerization of the substrate was observed during the reaction, in agreement with results for other catalytic systems based on rhodium phosphine complexes [19].

The $HRh(CO)(PPh_3)_3$/(−)-DIOCOL catalyst was less active than the corresponding one formed from the monodentate phosphine (+)-DICOL; a slight preference towards the formation of the less branched isomer was also observed. The optical yields are always higher than those obtained with (+)-DICOL, but only in the hydroformylation of isoprene did they reach a satisfactory value (~ 34%). In the case of styrene the optical yield was not improved by lowering the reaction temperature and the gas pressure. No isomerization of the starting olefins was observed in the presence of the (−)-DIOCOL based catalyst.

As the relationships between the sign of the optical rotation and the absolute configuration and that between the value of the rotation and the optical purity were unknown for 3-phenylbutanal, this aldehyde was stereochemically correlated both with the known (+)-(*S*)-3-phenyl-1-butanol [12], from which it was prepared through DMSO-oxidation [20], and with the corresponding acid [12] obtained by Ag_2O-oxidation (Scheme 2). As no appreciable racemization is expected in the reactions reported in Scheme 2, it was possible to extrapolate for the optically pure (+)-(*S*)-3-phenylbutanal an optical rotation $\alpha_D^{25} + 34.8°$ (neat, $l = 1$, minimum value).

SCHEME 2



Asymmetric hydrocarbalkoxylation

The results obtained in the olefin hydrocarbalkoxylation catalyzed by $PdCl_2$/(+)-DICOL and $PdCl_2$/(−)-DIOCOL complexes (P/Pd mole ratio 2/1) are reported in Table 3.

The most striking feature of the behaviour of the (+)-DICOL derived catalyst is its high activity: using styrene as substrate, the corresponding ester was obtained in 63% yield after 274 h under 90 atm of CO pressure even at room temperature. The carbonylation rate was strongly depressed by the presence of bulky substituents on

(Continued on p. 296)

TABLE 2

ASYMMETRIC HYDROFORMYLATION OF OLEFINS (substrate: 0.1 mol; benzene: 40 ml; $HRh(CO)(PPh_3)_3$/olefin ~ 1/500; P_{tot} 80–90 atm at 25°C (CO/H_2 1/1)

Run	Substrate	Reaction temp. (°C)	Reaction time (h)	Conversion [b] (%)	Yield [c] (%)	Optically active compound			
						Name	A [a]	Configuration	Optical yield [g] (%)
In the presence of (+)-DICOL (metal/phosphine 1/3)									
1	1-butene	60	16	99	90	2-methylbutanoic acid	40	(*S*)	1
2	*cis*-butene	80	n.d.	99	91	2-methylbutanoic acid	100	–	0
3	2,5-dihydrofurane	60	30	99	90	3-tetrahydrofuroic acid	100	–	0
4	3,3-dimethyl-1-butene	60	24	93	80	2,3,3-trimethylbutanal	7	(*S*)	1
5	styrene	80	4	45	30	2-phenylpropanoic acid	89	(*R*)	1
6	2-phenylpropene	90	110	66	52	3-phenylbutanal	95	(*R*)	1
In the presence of (−)-DIOCOL (metal/phosphine 1/1.5)									
7	1-butene	60	65	98	91	2-methylbutanoic acid	13	(*R*)	3.8
8	*cis*-butene [d]	90	n.d.	98	90	2-methylbutanal	100	(*S*)	1
9 [e]	2,5-dihydrofurane	60	44	99	93	3-tetrahydrofuroic acid	100	(*R*)	3.3
10	2,3,3-trimethyl-1-butene	100	n.d.	65	50	3,4,4-trimethylpentanoic acid	100	(*R*)	1.1
11	styrene	80	16	92	85	2-phenylpropanoic acid	68	(*R*)	6.3
12 [f]	styrene	40	93	8	–	2-phenylpropanoic acid	62	(*R*)	4.6
13	2-phenylpropene	90	240	55	50	3-phenylbutanal	95	(*S*)	1
14	isoprene	80	140	98	30	3-methylpentanoic acid	–	(*S*)	34.2

[a] A = % of chiral aldehyde in the recovered reaction product. [b] Determined by GLC. [c] Mol of aldehydes recovered/mol of starting olefin. [d] Solvent: mesitylene (40 ml). [e] P_{tot} 110 atm at 25°C (CO/H_2 1/1). [f] Experiment at atmospheric pressure (CO/H_2 1/1). [g] Calculated on the following bases: (+)-(*S*)-2-methylbutanoic acid: $[\alpha]_D^{25}$ +19.8 [21]; (−)-(*S*)-3-tetrahydrofuroic acid: $[\alpha]_D^{25}$ −14.1 (acetone) [22]; (+)-(*S*)-2,3,3-trimethylbutanal: $[\alpha]_D^{25}$ +84.5 (*n*-heptane) [23]; (−)-(*R*)-2-phenylpropanoic acid: $[\alpha]_D^{25}$ −91.2 [24]; (+)-(*S*)-2-methylbutanal: $[\alpha]_D^{25}$ +36.5 [25]; (+)-(*R*)-3,4,4-trimethylpentanoic acid: $[\alpha]_D^{20}$ +20.6 (ethanol) [26]; (+)-(*S*)-3-methylpentanoic acid: $[\alpha]_D^{25}$ +8.83 [27].

TABLE 3

ASYMMETRIC HYDROCARBETHOXYLATION OF OLEFINS (substrate 0.1 mol; benzene/EtOH 4/1, 50 ml; $PdCl_2$/olefin ~ 1/500)

Run	Substrate	Reaction temp. (°C)	Reaction time (h)	P_{CO} [b] (atm)	Conversion [c] (%)	Yield [d] (%)	Optically active compound			
							Name	A [a]	Configuration	Optical yield [g] (%)
In the presence of (+)-DICOL (metal/phosphine 1/2)										
1	1-butene	70	18	140	80	65	ethyl 2-methylbutanoate	59	(*S*)	2
2	*cis*-butene	70	41	140	85	72	ethyl 2-methylbutanoate	98	(*R*)	1
3 [e]	3,3-dimethyl-1-butene	100	60	80	93	n.d.	methyl 2,3,3-trimethylbutanoate	11	(*R*)	2.6 [f]
4	2,3,3-trimethyl-1-butene	100	164	80	n.d.	33	ethyl 3,4,4-trimethylpentanoate	100	(*R*)	2.5 [f]
5	styrene	80	96	90	99	96	ethyl 2-phenylpropanoate	100	(*S*)	1.6
6	styrene	50	18	90	80	72	ethyl 2-phenylpropanoate	100	(*S*)	1.4
7	styrene	25	274	90	63	50	ethyl 2-phenylpropanoate	100	(*S*)	1.5
8	2-phenylpropene	100	24	95	85	80	–	0	–	–
In the presence of (−)-DIOCOL (metal/phosphine 1/1)										
9	1-butene	90	15	150	98	88	ethyl 2-methylbutanoate	27	(*S*)	4.3
10	*cis*-butene	100	12	140	99	91	ethyl 2-methylbutanoate	59	(*R*)	2.1
11	2,3,3-trimethyl-1-butene	100	72	80	75	68	ethyl 3,4,4-trimethylpentanoate	100	(*S*)	12.5 [f]
12	styrene	70	47	100	99	80	ethyl 2-phenylpropanoate	44	(*S*)	6.7
13	2-phenylpropene	120	24	80	99	95	ethyl 3-phenylbutanoate	100	(*S*)	1.3 [f]

[a] A = % of the chiral ester in the recovered reaction product. [b] Measured at room temperature. [c] Determined by GLC. [d] Mol of esters recovered/mol of starting olefin. [e] Solvent: benzene/MeOH 4/1. [f] Determined on the corresponding acid obtained by saponification. [g] Calculated on the following bases: (+)-(*S*) ethyl 2-methylbutanoate α_D^{25} +17.3° (*l* = 1) [30]; (−)-(*R*)-2,3,3-trimethylbutanoic acid $[\alpha]_D^{25}$ +41.0 [31]; (+)-(*R*)-3,4,4-trimethylpentanoic acid $[\alpha]_D^{20}$ +20.6 [26]; (+)-(*S*) ethyl 2-phenylpropanoate α_D^{25} +71.2° (*l* = 1) [32]; (+)-(*S*)-3-phenylbutanoic acid: α_D^{25} +58.5° (*l* = 1) [12].

the olefinic carbons, as in the case of t-butylethylene which was carbonylated only to a moderate extent even at 100°C (Table 3, run 4).

As previously reported for other monodentate phosphines [28,29], (+)-DICOL promotes the formation of the more branched ester: ethyl 2-phenylbutanoate was regiospecifically obtained in the hydrocarbethoxylation of styrene irrespective of the reaction temperature (Table 3, runs 5,6 and 7). 2-Phenylpropene was carbonylated almost exclusively at the α-position, giving rise to an achiral ester containing a quaternary carbon atom (Table 3, run 8). Very low optical yields were recorded for the chiral products (up to 2.6%). It is noteworthy that in the case of styrene the extent of the asymmetric induction is unaffected by change in the reaction temperature (Table 3, runs 5, 6 and 7).

As expected [28,29], the hydrocarbethoxylation of the same olefins catalyzed by $PdCl_2$/(−)-DIOCOL complex brings about the formation of the less branched ester: for example, 2-phenylpropene gave only ethyl 3-phenylbutanoate, arising from the regioselective addition of the carbethoxyl group to the β-position (Table 3, run 13). Only in the case of 2,3,3-trimethyl-1-butene did (+)-DICOL and (−)-DIOCOL give the same ester (Table 3, runs 4 and 11).

Conclusions

The (+)-DICOL based catalysts gave unsatisfactory stereoselectivity results in the asymmetric transition metal catalyzed processes, particularly in the hydrogenation, where in two cases the recovered products were optically inactive. The bulky steroidal group bound to the phosphorus seems to exert only a weak influence on the steric course of these reactions, at least with the substrates we have tested. The behaviour of (+)-DICOL derived complexes towards asymmetric hydroformylation is comparable with that of other catalysts derived from monodentate tertiary phosphines chiral at carbon such as neomenthyl- [18] and 2-methylbutyl- [17] diphenylphosphine.

Some interesting results for both the catalytic activity and the regioselectivity were obtained in the hydrocarbalkoxylation catalyzed by $PdCl_2$/(+)-DICOL, and this process may be of considerable synthetic value, particularly for the preparation of chiral esters from arylsubstituted ethylenes.

The bidentate ligand (−)-DIOCOL provides asymmetric inductions that are always higher than those observed with (+)-DICOL, and in most of the CO-insertion reactions the optical purities of the chiral products obtained are similar to those obtained from the same processes catalyzed by (−)-DIOP complexes.

The asymmetric inductions obtained in the hydrogenation experiments with (−)-DIOCOL are usually somewhat lower than from those using (−)-DIOP. It is possible that this may due to some extent to the different conditions (catalytic precursor, pressure, etc.) employed in the experiments carried out with (−)-DIOP. In all cases, in the hydrogenation of (*Z*)-*N*-acetylaminocinnamic acid, the (−)-DIOCOL-based catalyst behaves better than any (−)-DIOP derived catalyst [15], giving *N*-acetylphenylalanine in an optical yield (93%) which is in the range of the best results ever obtained for this substrate.

The data reported in Table 4 show that, with one exception, (−)-DIOCOL and (−)-DIOP give always rise to products of the same predominant configuration. This is consistent with previous results obtained with (−)-DIOP related ligands, which

indicate that only structural modifications to the phosphorus substituents affect both the extent and the type of asymmetric induction for asymmetric hydrogenation [15] and carbonylation [33]. The only exception to this rule observed in our set of experiments refers to the hydroformylation of 2-phenylpropene, in which, under comparable reaction conditions, (−)-DIOCOL gave 3-phenylbutanal of opposite configuration to that produced by (−)-DIOP. Peculiar behaviour of this olefin in the asymmetric hydroformylation is not unprecedented [33].

As for the hydrocarbalkoxylation, no change in the configuration of the relevant ester was observed when (−)-DIOCOL was used instead of (−)-DIOP. In the case of styrene and 2,3,3-trimethyl-1-butene optical yields were higher with the

TABLE 4

COMPARISON BETWEEN (−)-DIOP AND (−)-DIOCOL AS LIGANDS IN METAL CATALYZED ASYMMETRIC PROCESSES

Substrate	Ligand	Branched/ linear	Configuration	Optical yield (%)	Reference
Asymmetric rhodium-catalyzed hydrogenation					
(*Z*)-*N*-acetylamino-	(−)-DIOP		(*R*)	81	[15]
cinnamic acid	(−)-DIOCOL		(*R*)	93	
(*Z*)-methyl *N*-acetyl-	(+)-DIOP		(*S*)	49	[34]
minocinnamate	(−)-DIOCOL		(*R*)	13	
N-acetylamino	(−)-DIOP		(*R*)	73	[15]
acrylic acid	(−)-DIOCOL		(*R*)	30	
(*E*)-β-methylcin--	(−)-DIOP		(*R*)	24	[15]
namic acid	(−)-DIOCOL		(*R*)	10.8	
Asymmetric rhodium-catalyzed hydroformylation					
1-butene	(−)-DIOP	15/85	(*R*)	1.4	[17]
	(−)-DIOCOL	13/87	(*R*)	3.8	
cis-butene	(−)-DIOP	only branched	(*S*)	8.1	[35]
	(−)-DIOCOL	only branched	(*S*)	1.0	
styrene	(−)-DIOP	82/18	(*R*)	1.3	[36]
	(−)-DIOCOL	68/32	(*R*)	6.3	
2-phenylpropene	(−)-DIOP	5/95	(*R*)	2.1	[17]
	(−)-DIOCOL	5/95	(*S*)	1.0	
2,5-dihydrofurane	(−)-DIOP	only 3-isomer	(*R*)	3.8	[37]
	(−)-DIOCOL	only 3-isomer	(*R*)	3.3	
isoprene	(−)-DIOP	[a]	(*S*)	32.3	[38]
	(−)-DIOCOL	[a]	(*S*)	34.2	
Asymmetric palladium-catalyzed hydrocarbalkoxylation					
1-butene	(−)-DIOP	25/75	(*S*)	7.6	[30]
	(−)-DIOCOL	27/73	(*S*)	4.3	
cis-butene	(−)-DIOP	20/80	(*R*)	7.2	[30]
	(−)-DIOCOL	59/41	(*R*)	2.1	
2,3,3-trimethyl-	(−)-DIOP	0/100	(*S*)	9.8	
1-butene	(−)-DIOCOL	0/100	(*S*)	12.0	
styrene	(−)-DIOP	n.d.	(*S*)	2.3	[30]
	(−)-DIOCOL	44/56	(*S*)	6.7	
2-phenylpropene	(−)-DIOP	1/99	(*S*)	6.3	[39]
	(−)-DIOCOL	0/100	(*S*)	1.3	

[a] Mixture of 3-methyl- and 4-methyl-pentanal.

$PdCl_2$/(−)-DIOCOL than with the $PdCl_2$/(−)-DIOP catalytic system (Table 4).

Finally, it is noteworthy that 2-phenylpropene can be almost regiospecifically converted into either ethyl 2-methyl-2-phenyl propanoate or ethyl 3-phenyl-butanoate by hydrocarbethoxylation in the presence of $PdCl_2$/(+)-DICOL or $PdCl_2$/(−)-DIOCOL, respectively. Similar behaviour can reasonably be expected for other 1-aryl-1-alkylethylenes.

Experimental

Materials

All the olefins were obtained commercially (Fluka) and distilled before use. The $RhCl_3$ and $HRh(CO)(PPh_3)_3$ (Strem Chemicals) and $PdCl_2$ (Fluka) were used as received. 5α-Cholestan-3β-ol [9] and 5α-cholestan-3-one [11] were prepared by known procedures starting from cholesterol. α,β-Unsaturated acids were commercial products, and their methyl esters were prepared by use of diazomethane. Carbon monoxide was obtained from GMBH (Ludwighafen, West Germany) and hydrogen from NIGS (Porto Torres, Italy).

$[Rh(COD)Cl]_2$ was prepared according to the literature [40].

The identities of the reaction products were confirmed by comparison with authentical samples.

General procedures

NMR spectra were recorded on a Varian T-60 spectrometer in $CDCl_3$ solution using TMS as internal standard ($\delta = 0$). Optical rotations were obtained with a Perkin–Elmer 241 polarimeter. GLC analyses were performed on a Perkin–Elmer 3920 B instrument using a 6 ft column of 15% Carbowax 20M on Chromosorb W. TLC analyses were performed on Merck 0.25 mm silica gel plates and the spots were made visible by spraying the plates with 1/1 H_2SO_4/EtOH solution and then warming them for a few minutes at 110°C. Mass spectra were recorded on a Hitachi Perkin–Elmer RMU-6L mass spectrometer. Elemental analysis were obtained with a Perkin–Elmer Elemental Analyzer 240B.

Preparation of 3α-diphenylphosphino-5α-cholestane [(+)-DICOL]

All manipulations were carried out in anhydrous solvents under nitrogen.

A solution of 5α-cholestan-3β-ol tosylate [10] (25 g; 0.046 mol) was added dropwise to a 2/1 dioxane/THF solution (150 ml) of sodium diphenylphosphide obtained from chlorodiphenylphosphine (14.13 g; 0.064 mol) and metallic sodium (7.06 g; 0.307 mol) following a reported procedure [41]. The mixture was stirred at room temperature for 72 h and, after addition of diethyl ether (50 ml), filtered to remove the inorganic salts. The filtrate was evaporated under reduced pressure and the residue was taken up with ether (200 ml). The solution was filtered and methanol (120 ml) was added. The solution was then concentrated until precipitation occurred. The solid was collected under nitrogen and recrystallized twice from ether/methanol to give pure (+)-DICOL (10 g; 39% yield); m.p. 129–131°C; $[\alpha]_D^{20}$ + 22.0 (*c* 0.968; dioxane); ^1H NMR (most significant peaks): δ (ppm) 7.62–7.12 (m, 10H, aromatic); 2.81–2.5 (m, 1H, 3β-hydrogen). Mass spectrum M^+ 556 (Rel. int. 100%). (Found: C, 84.1; H, 10.24. $C_{39}H_{57}P$ calcd.: C, 84.1; H, 10.3%).

Preparation of diethyl 2,3-O-(5'α-cholestan-3',3'-ylidene)-L-tartrate

A solution of 5α-cholestan-3-one (50 g; 0.13 mol) and diethyl L-(+)-tartrate (100 ml, 0.58 mol) in benzene (4000 ml) containing TsOH (100 mg) was refluxed in a flask equipped with a Dean-Stark apparatus for 18 h. After the theoretical amount of water had been collected, the solution was cooled and neutralized (pyridine), and the solvent was removed in vacuo. The residue was washed with water then filtered off and crystallized twice from CH_2Cl_2/MeOH in the presence of few drops of pyridine to give 2,3-*O*-(5'α-cholestan-3',3'-ylidene)-L-tartrate (55.6 g; 75% yield), homogeneous to TLC (benzene/acetone 9/1); m.p. 103–104°C, $[\alpha]_D^{20}$ + 4.24 (c = 1; dioxane). Mass spectrum M^+ 574 (rel. int. 21%) (Found: C, 73.1; H, 10.3. $C_{35}H_{58}O_6$ calcd.: C, 73.1; H, 10.2%).

Preparation of 2,3-O-(5'α-cholestan-3',3'-ylidene)-L-threitol

An ethereal solution of diethyl 2,3-*O*-(5'α-cholestan-3',3'-ylidene)-L-tartrate (42 g; 0.073 mol in 350 ml) was added dropwise under nitrogen to a suspension of $LiAlH_4$ (7 g; 0.184 mol) in anhydrous ether (350 ml). After 4 h refluxing the mixture was cooled, and water (7 ml) was slowly added followed by 15% NaOH (7 ml). The inorganic precipitate was filtered off and washed with ether. The combined filtrate and washings were evaporated, and the residue was crystallized from CH_2Cl_2/MeOH.

An additional crystallization from ether/hexane gave 2,3-*O*-(5'α-cholestan-3',3'-ylidene)-L-threitol (21.5 g; 60% yield) homogeneous to TLC (benzene/acetone 7/3); m.p. 199–200°C, $[\alpha]_D^{20}$ + 13.88 (c = 1, dioxane). Mass spectrum M^+ 490 (rel. int. 17%) (Found: C, 75.6; H, 11.2. $C_{31}H_{54}O_4$ calcd.: C, 75.9; H, 11.1%).

Preparation of 2,3-O-(5'α-cholestan-3',3'-ylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane [(−)-DIOCOL]

All manipulations were carried out under nitrogen.

A solution of 2,3-*O*-(5'α-cholestan-3',3'-ylidene)-L-threitol 1,4-bis-*p*-toluensulfonate (23.4 g; 0.0295 mol) ((m.p. 122–125°C), prepared in 95% yield from the diol by treatment with TsCl in pyridine) in anhydrous THF (65 ml) was added dropwise (10 min) at room temperature to a stirred 2/1 dioxane/THF solution (120 ml) of sodium diphenylphosphide prepared from chlorodiphenylphosphine (17 g; 0.077 mol) and metallic sodium (7.5 g; 0.325 mol). The solution was stirred at room temperature for 48 h and then quenched by dropwise addition of absolute EtOH (50 ml). The solvents were removed under reduced pressure and the residue was washed with degassed water then sucked dry. The solid was washed with EtOH, dried in vacuo, dissolved in anhydrous ether, and the solution was dried (Na_2SO_4). The solid obtained by evaporation of the ether was crystallized twice from ether/EtOH giving pure (−)-DIOCOL (18 g; 74% yield) homogeneous to TLC (benzene/ether 8/2); m.p. 137–140°C; $[\alpha]_D^{25}$ −17.7 (c = 1.51; dioxane). ^{1}H NMR most significant peaks: 7.45–7.05 (m, 20H, aromatic); 3.98–3.81 (m, 2H, CH–O); 2.61–2.15 (m, 4H, CH_2–P). (Found: C, 79.6; H, 8.8. $C_{55}H_{72}O_2P_2$ calcd.: C, 79.9; H, 8.8%).

Hydrogenation experiments: general procedure

In a typical experiment $[Rh(COD)Cl]_2$ (2.5×10^{-5} mol) and the phosphine (P/Rh ratio 2.2/1) were placed in a stainless steel autoclave. The autoclave was rocked and the air was removed. A solution of the substrate (5×10^{-3} mol) in 1/1

benzene/methanol mixture (40 ml) was introduced by suction, then the vessel was pressurized with hydrogen (70 atm), and shaken overnight at room temperature.

The products were separated from the catalyst as follows.

In the case of acids the residue obtained after removal of the solvent was taken up in 5% aqueous $NaHCO_3$ and the solution was extracted with ether. The aqueous phase was acidified with a 10% aqueous HCl and extracted again with ether. The solution was dried (Na_2SO_4) then evaporated to give the product.

In the case of esters, the products were isolated either by short path distillation or by chromatography on a silica gel column.

The results are reported in Table 1.

High pressure hydroformylation experiments: general procedure

The complex $HRh(CO)(PPh_3)_3$ ($1-2 \times 10^{-4}$ mol) and the phosphine (Rh/P ratio 1/3) were placed in a stainless steel autoclave. The autoclave was rocked and the air was removed (0.1 mmHg). A solution of the olefin (0.1 mol) in benzene (40 ml) was introduced by suction and the vessel was pressurized with 1/1 CO/H_2 at 80–90 atm at room temperature then heated in an oil bath at the appropriate temperature (60–100°C) until a satisfactory conversion (GLC) was reached. Products were purified either by distillation or by Ag_2O oxidation to the corresponding acids.

Hydroformylation products obtained from isoprene were isolated and purified by the procedure previously reported [38]. The results are reported in Table 2.

Hydroformylation of styrene at atmospheric pressure

Styrene (52 g, 0.5 mol), $HRh(CO)(PPh_3)_3$ (94.1 mg, 1.14×10^{-4} mol) and (−)-DIOCOL (160 mg, 1.93×10^{-4} mol) were placed in a two-necked flask connected to a gas reservoir containing an equimolar mixture of H_2 and CO maintained at atmospheric pressure. The air was evacuated and the system was flushed three times with the gas mixture. The reaction was then carried out at 40 ± 1°C for 93 h (8% conversion by GLC). High vacuum distillation gave 7 ml of an aldehyde mixture (60% of 2-phenylpropanal and 40% of 3-phenylpropanal) containing some styrene. This mixture was oxidized with Ag_2O and the acids isolated by the usual work up were purified by distillation. The optical purity of (−)-(*R*)-2-phenylpropanoic acid was determined on a mixture containing 38% of 3-phenylpropanoic acid, and a value for the pure compound of $\alpha_D^{25} - 4.2°$ was obtained by extrapolation, corresponding to an optical purity of 4.6% [24].

Hydrocarbalkoxylation experiments: general procedure

In a typical experiment $PdCl_2$ (2×10^{-4} mol) and the phosphine (Pd/P ratio 1/2) were introduced in a stainless steel autoclave which was then rocked. The air was removed and a solution of the olefin (0.1 mol) in 4/1 benzene/ethanol was introduced by suction. The vessel was pressurized with CO (about 140 atm) at room temperature and then heated in an oil bath at the appropriate temperature (usually 80–100°C) until the gas uptake ceased. The products were recovered, distilled off, after removal of the solvent, and were purified by further distillation. The results are reported in Table 3.

Oxidation of (+)-(S)-3-phenylbutan-1-ol to (+)-(S)-3-phenylbutanal

(+)-(*S*)-3-Phenylbutan-1-ol (7.12 g, 0.047 mol), $\alpha_D^{25} + 11.3°$ ($l = 1$, neat) (corre-

sponding to an optical purity [12] of 29%) was added dropwise to a solution of dicyclohexylcarbodiimide (28.9 g, 0.14 mol) in 47.5 ml of freshly distilled dimethylsulfoxide (DMSO), 25 ml of benzene, and 1 ml of $5M$ H_3PO_4 in DMSO. The resulting suspension was stirred for 3 h, then ethyl acetate (120 ml) and formic acid (12 g) in methanol (25 ml) were added cautiously so as to control the gas evolution. After an additional one hour of stirring, the precipitated dicyclohexylurea was filtered off and extracted with ethyl ether. The ethereal extract was washed with water, dried (Na_2SO_4) and (+)-(*S*)-3-phenylbutanal was isolated by distillation under reduced pressure: 6 g (80% yield); b.p. 62°C at 0.05 mmHg, α_D^{25} +10.5° ($l = 1$, neat).

Oxidation of (+)-(S)-3-phenylbutanal to (+)-(S)-3-phenylbutanoic acid

(+)-(*S*)-3-Phenylbutanal (2 g, 0.013 mol) α_D^{25} +10.5° ($l = 1$, neat) was added dropwise to a well stirred suspension of Ag_2O (4.63 g, 0.02 mol) in 20 ml of 6% aqueous NaOH. The suspension was stirred overnight and the mixture was worked up in the usual way to give pure (+)-(*S*)-3-phenylbutanoic acid (1.8 g, 80% yield), which showed α_D^{25} +17.0° ($l = 1$, neat), corresponding to 30% minimum optical purity [12].

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