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HYDROCARBOALKOXYLATION OF *N*-VINYLPHTHALIMIDE CATALYZED BY PALLADIUM COMPLEXES

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Summary

The hydrocarboalkoxylation of *N*-vinylphthalimide catalyzed by palladium tertiary phosphine complexes occurs with high selectivity towards the linear isomer when the alcohol is used also as the solvent but towards the branched isomer in the presence of an additional solvent. When triphenylphosphine is employed as the ligand, the yield and the regioselectivity towards the branched isomer increase with increasing p_{CO} or decreasing concentration of the phosphine. Reaction in the presence of molecular hydrogen leads to higher yields, with minor changes in regioselectivity. High regioselectivities towards either the linear or the branched isomer are observed also in the presence of chiral di- or mono-phosphines, but the degree of asymmetric induction is very low.

Introduction

The recent increasing interest in palladium-catalyzed hydrocarboalkoxylation is due to the fact that it occurs under relatively mild conditions and is highly regioselective [1]. For example, in the presence of $PdCl_2(PPh_3)_2$ in combination with $SnCl_2$, terminal olefins are easily carbonylated at 70—80°C, 10—130 atm with a regioselectivity up to 90% for the linear isomer in a solvent of intermediate polarity, such as a ketone [2], or in the alcohol itself as solvent [3]. Very recently it was shown that a $PdCl_2(PPh_3)_2/PPh_3$-based catalyst promotes the carbonylation of propene with predominant formation of the linear product when the alcohol is also the solvent, while in the presence of a different solvent, preferably a ketone, the branched isomer predominates [3,4]. While in most cases the linear isomer is the desired product, there might some-

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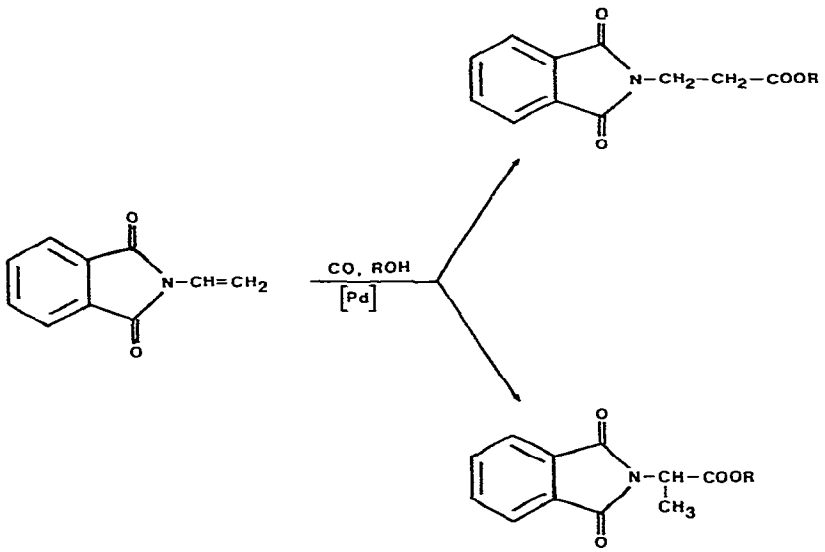
times be more interest in the other isomer. Thus, in the hydrocarboalkoxylation of terminal prochiral olefins using an optically active catalyst, the branched isomers are required if enantiomerically enriched products are desired.

In order to ascertain whether the regioselectivity control found in the hydrocarboalkoxylation of propene with the $PdCl_2(PPh_3)_2/PPh_3$-based catalyst is found with other prochiral substrates containing the vinyl group, we have undertaken a study on the hydrocarboalkoxylation of *N*-vinylphthalimide (NVP) (Scheme 1). This substrate was chosen as the model compound because it is a



SCHEME 1

convenient precursor for alanine derivatives [5]. We also carried out some hydrocarboalkoxylation experiments in the presence of chiral palladium catalysts formed in situ from $PdCl_2$ and mono- and bi-dentate optically active tertiary phosphines in order to investigate the dependence of the regio- and stereoselectivity on the structure of the ligand.

Results and discussion

a) Hydrocarboalkoxylation of NVP with achiral catalysts

Most of the experiments were carried out using methyl ethyl ketone (MEK) as solvent and MeOH as the hydrogen donor, and with $PdCl_2(PPh_3)_2/PPh_3$ in the ratio P/Pd = 3/1 as the catalyst precursor, under p_{CO} = 130 atm at 110°C for four hours. Triphenylphosphine was added because it was found to prevent decomposition to metallic palladium, which is inactive unless HCl is present [6].

The results obtained in a set of experiments are listed in Table 1. With MeOH as the solvent the main product (run 1) is the linear isomer. About 92% of the NVP undergoes conversion and ca. 27% of the reaction products consists of *N*-1′-methoxyethylphthalimide, formed by Markovnikov addition of alcohol to the vinylic double bond. Under the same reaction conditions, but with MEK as

TABLE 1

HYDROCARBOALKOXYLATION OF *N*-VINYLPHTHALIMIDE [a] (NVP)

Run	Catalyst	Conversion (%) [b]	Selectivity (%) [c]	Regioselectivity (%) [d]
1 [e]	$PdCl_2(PPh_3)_2/PPh_3$ (1/1)	92.2	73.2	83.5/16.5
2	$PdCl_2(PPh_3)_2/PPh_3$ (1/1)	92.2	95.7	11.8/88.2
3 [f]	$PdCl_2(PPh_3)_2/PPh_3$ (1/1)	80	94.7	22/78
4 [g]	$PdCl_2(PPh_3)_2/PPh_3$ (1/1)	99	95.7	8.7/91.3
5 [g, h]	$PdCl_2(PPh_3)_2/PPh_3$ (1/1)	79.6	95.2	6/94
6 [h]	$PdCl_2(PPh_3)_2/PPh_3$ (1/1)	70.6	95.3	8/92
7 [i]	$PdCl_2(PPh_3)_2/PPh_3$ (1/1)	40	91	56/44
8	$PdCl_2(PPh_3)_2/PPh_3$ (1/2)	90	94.2	16/84
9	$PdCl_2(PPh_3)_2/LiCl$ (1/20)	88	95	8/92
10 [j]	$PdCl_2(PPh_3)_2/SnCl_2$ (2/1)	30	30	65/35
11 [k]	$PdCl_2$(DBP)	29.6	97.1	98.5/1.5

[a] Reaction conditions: 110°C; p_{CO}: 100 atm at 25°C; 10 mmol of substrate in 10 ml of a 9/1 mixture of MEK/MeOH; substrate to catalyst ratio: 100/1; 4 h. [b] Determined by GLC. [c] Calculated as moles of esters/moles of reacted substrate × 100. [d] % Linear/% branched isomer. [e] Solvent: MeOH (10 ml). [f] Solvent: MEK/EtOH (8/2). [g] Reaction carried out in the presence of hydrogen (20 atm at 25°C). [h] Reaction time 2 h. [i] p_{CO}: 20 atm at 25°C. [j] Reaction temperature: 70°C. [k] DBP: 1,4-bis-diphenylphosphinobutane. Reaction time 88 h.

the solvent (run 2), the branched isomer greatly predominates and the amount of the by-product at the same NVP conversion is strongly reduced (~4%) compared with that in run 1. It is noteworthy that the regioselectivity of the methylacrylate insertion into *trans*-$PtH(NO_3)(Et_3P)_2$ is similarly influenced by such solvents [7].

Comparable results are obtained when EtOH is used instead of MeOH (run 3): the lower ratio of branched to straight isomer obtained is probably due to the lower MEK/alcohol ratio used in this case [3].

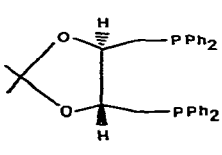
These results are in keeping with those obtained in the carbonylation of propene using the same catalytic precursor. In the latter case, it was found that the rate could be increased, with minor effects on the regioselectivity, by carrying out the reaction in the presence of molecular hydrogen. Under these conditions the reaction is quite selective towards the ester without formation of aldehyde. The same beneficial hydrogen effect was observed for reactions of NVP; the esters are formed in almost quantitative yields and the amount of the by-product is <5% (run 4). Under these conditions the conversion of NVP after two hours almost reaches that found after four hours in the absence of hydrogen (compare runs 5 and 2).

As a general trend, the regioselectivity slightly decreases with an increasing degree of conversion of NVP (compare runs 4 and 5, 2 and 6). This fact may be due to a variation of the relative concentrations of the active species as the reaction progresses.

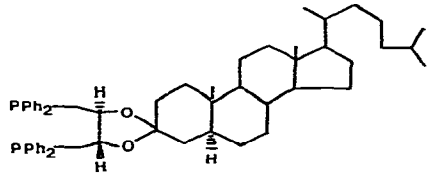
With aliphatic terminal olefins the yield and the regioselectivity were found to increase on increasing p_{CO} or on decreasing the concentration of free PPh_3 [3,4,5]. This was mainly attributed to steric effects, since in the presence of a higher concentration of PPh_3 or at low p_{CO} the equilibria in solution are shifted towards less active and bulkier catalytic species which favour formation of the

linear isomers. Analogous behaviour was observed on varying p_{CO} and the concentration of free PPh_3 with NVP as substrate (compare runs 2 and 7, and 2 and 8, respectively). The effect of p_{CO} is rather pronounced; for example, the branched/linear isomer ratio falls from 7.5 to 0.78 when p_{CO} is decreased from 130 to 27 atm, and under low p_{CO} a large amount of by-product is formed.

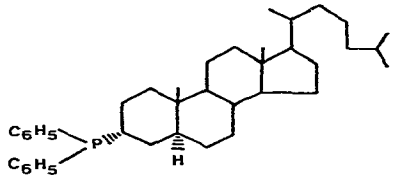
Finally, the activity of some modified catalyst precursors was explored. In the presence of LiCl, which is known to enhance the rate of formation of the branched isomer in the carbonylation of aliphatic terminal olefins [3,8], the regioselectivity is slightly improved (run 9). Conversely, the linear isomer predominates when the reaction is carried out at 70°C with $PdCl_2(PPh_3)_2$ in combination with $SnCl_2$ as the catalyst precursor (run 10). In this case, however, the main product is that arising from the addition of MeOH to the double bond of NVP. A comparably low reaction rate was found using $PdCl_2$(DBP) as the catalyst (run 11); as reported by other authors [9,10], a high linear/branched isomer ratio was observed.



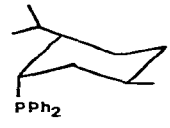
(−)-DIOP



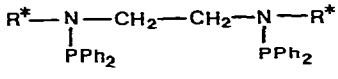
(−)-DIOCOL



(+)-DICOL



(+)-NMDPP



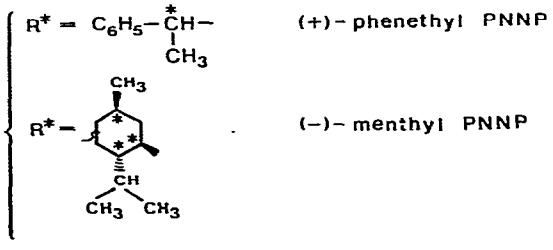


Fig. 1. Chiral phosphines used.

b) Hydrocarboalkoxylation of NVP with chiral catalysts

The reactions were carried out in a 4/1 MEK/EtOH solution at 100°C under p_{CO} = 150 atm (initial pressure) in the presence of $PdCl_2$ and the mono- and bi-dentate phosphines listed in Fig. 1 (P/Pd = 2/1). The results of these experiments are shown in Table 2.

Only in the presence of a monodentate phosphine such as (+)-DICOL and (—)-(*R*)-s-butyldiphenylphosphine were high reaction rates observed (runs 14 and 18, respectively). When a chelating ligand was employed, the activity of the catalytic system was lowered. The (—)-menthyl-PNNP-based catalyst was completely ineffective in promoting the carbonylation (run 16). Analogous results were obtained by Stille and coworkers [11] in the hydrocarboalkoxylation of NVP at 70°C and 100 atm with $PdCl_2$/DIPHOL, $PdCl_2$/CAMP and $PdCl_2$/DIPAMP catalytic systems.

The selectivity of all the hydrocarboalkoxylation reactions was >75% except in the case of (+)-phenethyl-PNNP (run 15), the main concurrent reaction being the addition of ethanol across the reactive double bond of NVP.

The chelating phosphines gave rise to a very poor regioselectivity towards the formation of the chiral ester (runs 12 and 13); on the other hand, monodentate phosphines, such as (+)-DICOL and (+)-NMDP, gave a catalyst which produced the branched isomer with a high regioselectivity, but with a negligible optical yield (≤2%).

In conclusion, the palladium-catalyzed hydrocarboalkoxylation of unsaturated amides or imides constitutes a valuable synthetic tool for the preparation of simple esters either of β-amino acids or of racemic α-amino acids, depending on the phosphine employed as the ligand. At present this process does not seem satisfactory for making optically active α-amino acids because of the unsatisfactory regio- and stereo-selectivity displayed by chelating phosphine-based catalytic systems, which are the very effective in other asymmetric processes, such as hydrogenation.

Experimental

Materials

NVP was prepared as described [12]. The phthalimido ethyl esters were isolated from the reaction mixture by crystallization from benzene/hexane (linear isomer; m.p. 75—76°C; lit. m.p. 74°C [13]) or by column chromatography on alumina (branched isomer; m.p. 59—60°C; lit. m.p. 58—60°C [14]). Their structures were confirmed by comparison of their ^1H NMR and mass spectra with those of authentical samples prepared from phthalic anhydride and α- and β-alanine ethyl ester.

N-1′-Ethoxyethylphthalimide, obtained as by-product in the reactions carried out in the presence of EtOH, was identified by comparison with an authentic sample prepared as described in ref. 13. The catalyst $PdCl_2(PPh_3)_2$ was prepared by a published procedure [15], while $PdCl_2$ supplied by Fluka AG was used as received. (—)-DIOP was purchased from Strem Chemicals. (—)-DIOCOL and (+)-DICOL were prepared as described elsewhere [17].

We thank Dr. G.M. Giongo (Assoreni, Monterotondo) for providing samples of (+)-phenethyl- and (—)-menthyl-PNNP; Dr. P. Frediani (Cattedra di Chimica

TABLE 2

ASYMMETRIC HYDROCARBALKOXYLATION OF *N*-VINYLPHTHALIMIDE (NVP) [a]

Run	Catalyst	Reaction time (h)	Conversion(%) [b]	Selectivity (%) [c]	Regioselect. (%) [d]	Opt. yield [e, f] (%) (Conf.)
12	$PdCl_2$/(−)-DIOP, 1/1	40	99	88	97.5/2.5	—
13	$PdCl_2$/(−)-DIOCOL, 1/1	20	99	86	93.5/6.5	—
14	$PdCl_2$/(+)-DICOL, 1/2	4	99	91	12/88	2 (*R*)
15 [g]	$PdCl_2$/(+)-phenethyl-PNNP, 1/1	70 [h]	54	28	67/33	—
16 [g]	$PdCl_2$/(−)-menthyl-PNNP, 1/1	26 [i]	65	0	—	—
17	$PdCl_2$/(+)-NMDPP, 1/2 [k]	34	94	92	1/99	1.3 (*S*)
18 [g]	$Pd(Cl_2$/(−)-(*R*)-s-butyldiphenylphosphine [j], 1/2	14	87	75	54/46	~0

[a] Substrate: 15 mmol in 20 ml of 4/1 mixture of MEK/EtOH; substrate to catalyst ratio 100/1; *T*: 100°C; p_{CO}: 150 atm at 25°C. [b] Determined by GLC. [c] Calculated as mol of esters/mol of substrate reacted X 100; [d] % linear/% branched isomer. [e] (*c* 10, EtOH). [f] Calculated taking for optically pure (—)-(*S*)-ethyl-2-phthalimidopropionate, $[\alpha]_D^{20} = -19.0$ [16]. [g] *T*: 115°C; p_{CO}: 100—120 atm at 25°C. [h] Plus 40 h at 165°C. [i] Plus 190 h at 140°C. [j] The ligand employed was 75% optically pure. [k] *T*: 100°C; p_{CO}: 120 atm.

Industriale, University of Florence) for a sample of (+)-NMDPP and Dr. R. Lazzaroni (Centro di Studio del CNR per le Macromolecole Stereoordinate ed Otticamente Attive, University of Pisa) for a sample of (—)-(*R*)-s-butylphosphine.

General procedure

Yields and compositions of products were determined by GLC, using a Hewlett-Packard Gas chromatograph model 5830A equipped with a Hewlett-Packard GLC terminal model 18850. Analyses were performed on a 6 ft column of SE-30 25% on Chromosorb P at 170°C with helium as carrier gas.

NMR spectra were recorded on a Varian T-60 instrument in $CDCl_3$ solution using TMS as internal standard (δ = 0 ppm). Optical rotations were measured in ethanolic solution (c = 10) in 1 dm tubes on a Perkin Elmer 241 polarimeter. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L spectrometer.

Experimental procedure

Hydrocarboalkoxylation of NVP with achiral ligands. Carbonylation experiments were carried in a 100 ml stainless steel, stirred autoclave, contained in a thermostated oil bath. Catalyst, ligand and substrate were placed in a Pyrex bottle in the autoclave to prevent contamination from other metallic species and to avoid effects of the metal surface of the autoclave. Carbon monoxide pressure was maintained approximately constant throughout the experiments by introducing carbon monoxide equivalent to the total pressure drop observed.

In a typical experiment, 0.1 mmol of $PdCl_2(PPh_3)_2$, 0.1 mmol of PPh_3. 0.01 mol of NVP, 0.021 mol of alcohol, and the solvent (total volume 10 ml) were introduced into a Pyrex bottle placed in the autoclave, and the free volume was reduced to ca. 50 ml. The autoclave was rocked, cooled in a ice bath and purged five times with carbon monoxide (10 atm each time). Carbon monoxide was then introduced (100 atm) and the autoclave was placed in a thermostated oil bath, where it reached the working temperature in ca. 10 min.

At the end of the reaction the autoclave was cooled in an ice bath and slowly depressurized. The reaction mixture was analyzed after the usual work up.

Results are reported in Table 1.

Asymmetric hydrocarboalkoxylation of NVP

NVP (15 mmol), $PdCl_2$ (0.15 mmol) and the ligand (P/Pd = 2/1) were placed in a stainless steel autoclave of 50 ml. The autoclave was closed and the air was removed (0.1 mmHg). A 4/1 solution of MEK/EtOH (20 ml) was introduced by suction and the vessel was pressurized with CO (ca. 150 atm) at room temperature and then heated in an oil bath at 100—115°C until the gas uptake ceased (see Table 2). Products were recovered from the reaction mixture either by crystallization (linear isomer) or by column chromatography on alumina (branched isomer) with diethyl ether as eluant.

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