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Chemoselectivity in the rhodium-catalyzed hydroformylation of 4-vinylpyridine: crucial role of phosphine ligand in promoting carbonylation instead of hydrogenation

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Abstract

Hydroformylation of 4-vinylpyridine (**4VP**) in benzene with $Rh_4(CO)_{12}/PMe_2Ph$ or Rh_4CO_{12} as catalytic precursor shows completely different chemoselectivity, carbonylation product (branched aldehyde) largely prevailing with the first catalyst, hydrogenation product 4-ethylpyridine (**4EP**) with the second one. Different phosphines and P/Rh ratios were also used, and a comparison with 3-vinylpyridine (**3VP**) under the same experimental conditions was made too. In all the experiments **3VP** exclusively gives aldehidic products. In the case of **4VP**, hydrogenation prevails on carbonylation at low P/Rh ratio (< 0.5), while for higher values more than 80% of carbonylation product is obtained. The strong electron-donor phosphine ligand changes the polarization of the carbon–rhodium bond making this carbon suitable for the migratory insertion process and hence determining the acyl–metal intermediate formation precursor of the aldehyde.

Keywords: Hydroformylation; Phosphines; Vinylpyridines; Rhodium; Chemoselectivity; Catalysis

1. Introduction

The rhodium-catalyzed hydroformylation of unsaturated substrates usually gives aldehydic products with a high chemoselectivity [1]. This occurs both with aliphatic substrates, such as 1-hexene [2], and aromatic ones, such as styrenes [3], vinylfurans [4] and vinylpyrroles [5], whose hydroformylation almost exclusively gives the expected aldehydic products.

Nevertheless there are some exceptions to this trend, such as α,β-unsaturated aldehydes and ketones that undergo only a hydrogenation process under oxo conditions [6]. Also vinylidenic olefins containing one or two pyridyl moieties give rise to a relatively high amount of hydrogenation product when they are hydroformylated in the presence of rhodium catalysts [7]. The reason for this behavior is still obscure.

We recently reported that the rhodium-catalyzed hydroformylation of 4-vinylpyridine (**4VP**) led to the exclusive formation of 4-ethylpyridine (**4EP**); this result was in contrast to the one that observed for 3-vinylpyridine (**3VP**), whose hydroformylation under the same experimental conditions gave the corresponding aldehydic branched isomer **3α** with very high chemo- and regioselectivity [8] (Scheme 1). The different behavior of the two vinylpyridine isomers was explained on the basis of the different charge density on 3- and 4-positions in the pyridine ring, which influences the polarity of the carbon-rhodium bond in the branched alkyl–rhodium intermediates, determining their different evolution [8].

As in the above investigation unmodified $Rh_4(CO)_{12}$ was used as catalytic precursor, it was interesting to see if in the case of **4VP** the use of rhodium catalytic systems modified with an auxiliary phosphorus ligand (**L**) could vary the electronic situation onto the alkyl metal intermediates and then encourage the formation

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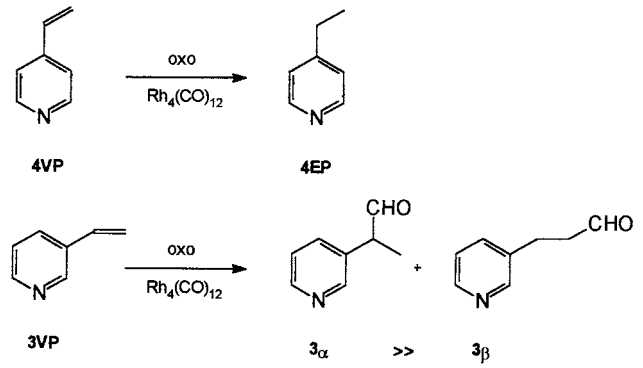
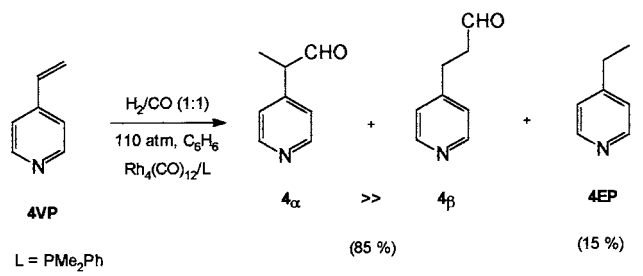


Scheme 1.



Scheme 2.

of the corresponding aldehydic products, instead of hydrogenation compounds. Different phosphines and P/Rh ratios were used in order to determine their influence on the selectivity of the process. 3-Vinylpyridine was also investigated under the same experimental conditions; the purpose was to compare the reciprocal behavior of these vinylpyridine isomers, characterized by the above-mentioned different electronic situations [8].

We surprisingly found that in the presence of phosphorus ligands, **4VP** gave a high chemoselectivity into aldehydes and an almost complete regioselectivity into the branched isomer **4α** (Schemes 2 and 3, Fig. 1). In these conditions **3VP** and **4VP** behaved in a very similar manner.

2. Results

The hydroformylation reactions were carried out in benzene at partial substrate conversion, in a stainless steel autoclave, using $Rh_4(CO)_{12}$ as catalyst precursor, both in the absence and in the presence of phosphines. The composition of the reaction mixtures was evaluated by GC analysis, using *o*-xylene as internal standard.

A set of runs was carried out for **4VP** with $Rh_4(CO)_{12}$ in the presence of PMe_2Ph by varying the P/Rh ratio. This ranged from 0.25 to 9, at 100°C and 110 atm total pressure ($CO/H_2 = 1:1$). The reaction was also investigated at different temperatures, in the range 60–120°C, by using P/Rh = 4. The results obtained are summarized in Tables 1 and 2 and in Fig. 1. Analogous experiments carried out on **3VP** are reported in Tables 1 and 2.

A set of experiments was carried out on **4VP** in the presence of $Rh_4(CO)_{12}$ modified with various phosphorus ligands (P/Rh = 6), differing from each other in electronic properties and steric hindrance. All the reactions were carried out at 100°C and at 110 atm gas pressure ($CO/H_2 = 1:1$). The results obtained are summarized in Table 3.

It was observed that the reaction times were shorter than those observed in the case of unmodified $Rh_4(CO)_{12}$ for both the substrates, but they tend to increase with the increase of P/Rh ratio.

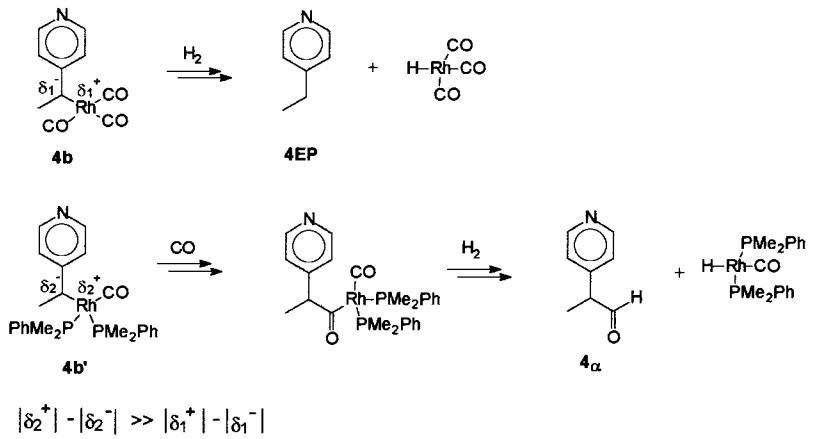
For **4VP**, by increasing the P/Rh ratio, the amount of the hydrogenation product 4-ethylpyridine (**4EP**) quickly decreases from 70% at P/Rh = 0.25 to 15% at P/Rh = 2, reaching 10% at P/Rh = 9, whilst the percentage of the branched aldehyde **4α** on the total of aldehydic products is always very high, rising from 92% at P/Rh = 0.25 to 98% at P/Rh = 2 and being constant for higher ratios. The reaction selectivity does not change with increasing temperature, at least in the range 60–120°C (P/Rh = 4). All the phosphorus ligands used give a chemoselectivity into aldehydic products greater than 80% and a regioselectivity into branched aldehyde **4α** greater than 95% for most cases, not significantly depending on the electronic and steric character of the phosphine.

For **3VP**, by increasing the P/Rh ratio, the chemoselectivity into aldehydic products always stays very high (ca. 99%), while the α-regioselectivity tends to increase from 86% at P/Rh = 0 to 96% at P/Rh = 6 (see Table 4). Also for this isomer, the increase of temperature at a fixed P/Rh ratio (P/Rh = 4) does not affect the selectivity of the process.

2-(4-pyridyl)propanal (**4α**), the predominant isomer, has been identified from the ^{1}H-NMR spectrum of the crude hydroformylation mixture[1]. 3-(4-pyridyl)propanal (**4β**), the minor product of the reaction, has been characterized by comparison with an authentic sample obtained by oxidation of 3-(4-pyridyl)propanol [9][2]. The aldehydes **3α** and **3β**, deriving from the hydroformylation of **3VP**, had already been characterized in a previous work [8].

[1] ^{1}H-NMR spectrum of **4α** in C_6D_6 (TMS) shows as characteristic signals a doublet at 0.92 ppm (CH_3), a quartet at 2.80 ppm (CH) and a doublet at 9.12 ppm (CHO); any attempt at isolation through the usual techniques (distillation, liquid chromatography, etc.) failed because of its instability.

[2] ^{1}H-NMR spectrum of 4β in C_6D_6 shows as characteristic signals two triplets at 2.05 ppm and at 2.36 ppm, respectively (CH_2) and a doublet at 9.19 ppm (CHO).



Scheme 3.

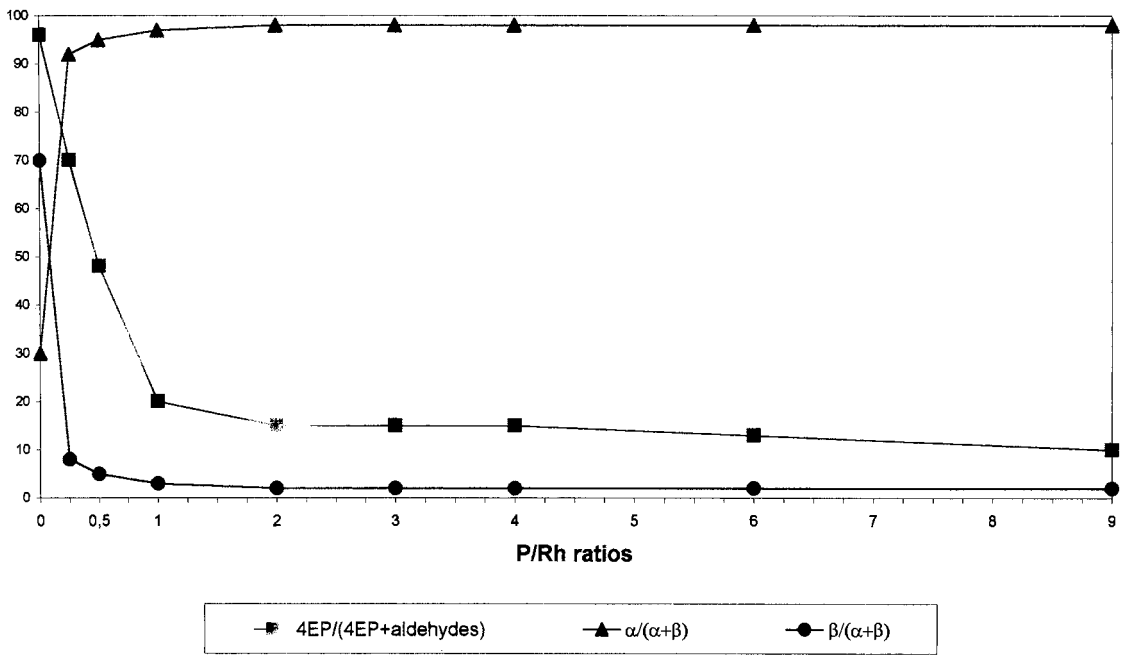
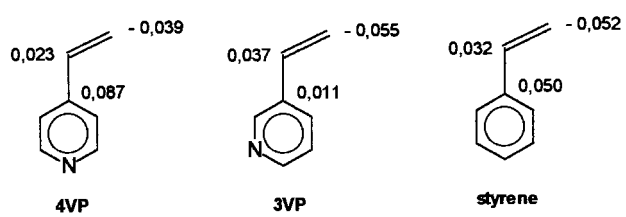


Fig. 1. Rhodium-catalyzed hydroformylation of 4-vinylpyridine (**4VP**) at complete substrate conversion in the presence of $Rh_4(CO)_{12}/PMe_2Ph$ as catalyst precursor: influence of P/Rh ratio on the reaction selectivity.

3. Discussion and conclusions

In a previous paper [8] on the hydroformylation of **3VP** and **4VP** it was clearly emphasized that in the presence of unmodified $Rh_4(CO)_{12}$ **4VP** almost exclusively gives the hydrogenation of the olefinic double bond instead of the carbonylation process. This behavior was attributed to the electron-poor character of the pyridine ring and, in particular, to the high positive charge localized on the position 4 (CNDO calculations) [10]. This feature determines a strong decrease of the nucleophilic character of the carbon bonded to the rhodium, which is not able to give the migratory insertion on the CO coordinated to the metal and hence undergoes only a slow dihydrogen addition.



The dramatic change of chemoselectivity caused by the addition of a phosphine ligand is likely due to the increase of Rh–C bond polarization. Indeed the inductive electron-donor effect of phosphine could be transmitted through the rhodium to the adjacent carbon, which becomes sufficiently nucleophilic to give the migratory insertion on CO, hence evolving to the acyl intermediate, precursor of the branched aldehyde (**4α**). In addition it should be pointed out that a high

Table 1
Rhodium-catalyzed hydroformylation of vinylpyridine isomers (***n*VP**) at complete substrate conversion in the presence of $Rh_4(CO)_{12}/PMe_2Ph$ as catalyst precursor: influence of P/Rh ratio on products distribution [a]

Substrate	P/Rh	Time (min)	Hydrogenation [b] (yield%)	Hydroformylation [b] (yield%)	α:β [b]
3VP	0	120	1	99	86:14
3VP	1	20	1	99	91:9
3VP	3	45	1	99	95:5
3VP	6	200	1	99	96:4
4VP	0	240	98	2	30:70
4VP	0.25	71	70	30	92:8
4VP	0.5	30	53	47	95:5
4VP	1	15	19	81	97:3
4VP	2	30	15	85	98:2
4VP	3	40	15	85	98:2
4VP	4	60	15	85	98:2
4VP	6	60	13	87	98:2
4VP	9	70	10	90	98:2

[a] Reaction conditions: 4.64 mmol of ***n*VP**, 5 ml of benzene, 0.004 mmol of $Rh_4(CO)_{12}$; autoclave volume 25 ml; 100°C temperature; 110 atm total pressure (1:1 H_2/CO).
[b] Percentage determined via GC on the total reaction products of the crude reaction mixtures, using *o*-xylene as internal standard.

Table 2
Rhodium-catalyzed hydroformylation of vinylpyridine isomers (***n*VP**), at complete substrate conversion at different temperatures in the presence of $Rh_4(CO)_{12}/PMe_2Ph$ as catalyst precursor [a]

Substrate	Temperature	Time (min)	Hydrogenation [b] (yield%)	Hydroformylation [b] (yield%)	α:β [b]
3VP	60	960	1	99	96:4
3VP	80	420	1	99	96:4
3VP	100	120	1	99	95:5
3VP	120	60	1	99	95:5
4VP	60	600	16	84	99:1
4VP	80	60	16	84	98:2
4VP	100	60	15	85	98:2
4VP	120	20	15	85	97:3

[a] Reaction conditions: 4.64 mmol of ***n*VP**, 5 ml of benzene, 0.004 mmol of $Rh_4(CO)_{12}$, 0.064 mmol of PMe_2Ph (P/Rh = 4); autoclave volume 25 ml; 110 atm total pressure (1:1 H_2/CO).
[b] Percentage determined via GC on the total reaction products of the crude reaction mixtures, using *o*-xylene as internal standard.

Table 3
Rhodium-catalyzed hydroformylation of 4-vinylpyridine (**4VP**) at complete substrate conversion in the presence of $Rh_4(CO)_{12}$ modified with different phosphorus ligands [a]

Phosphorus ligand	Time (min)	Hydrogenation [b] yield (%)	Hydroformylation [b] yield (%)	4α:4β [b]
PPh_3	30	9	91	95:5
$PMePh_2$	35	10	90	96:4
PMe_2Ph	55	13	87	98:2
PMe_3	60	12	88	98:2
PEt_3	30	12	88	96:4
$P(nBu)_3$	30	11	81	96:4
DPPE	30	20	80	96:4
DPPP	50	9	91	98:2

[a] Reaction conditions: 4.64 mmol of 4-vinylpyridine, 5 ml of benzene, 0.004 mmol of $Rh_4(CO)_{12}$, 0.096 mmol of P (P/Rh = 6); autoclave volume 25 ml; 100°C temperature; 110 atm total pressure (1:1 H_2/CO).
[b] Percentage determined via GC on the total reaction products of the crude reaction mixtures, using *o*-xylene as internal standard.

chemoselectivity into aldehydes (always greater than 80%) is also observed by using other phosphines, showing that this is a general trend due to the well-known σ-donor property of phosphorus ligands.

In the case of **3VP** the positive charge density on position 3 of the pyridine ring is much lower [10] so the carbon atom in Rh–C bond is sufficiently nucleophilic both with unmodified and phosphine-modified

Table 4
Rhodium-catalyzed hydroformylation of vinylpyridine isomers (***n*VP**) and styrene at complete substrate conversion: a comparison between $Rh_4(CO)_{12}$ and $Rh_4(CO)_{12}/PMe_2Ph$ [a]

Substrate	Catalyst precursor	Time (min)	Hydrogenation [b] (yield%)	Hydroformylation [b] (yield%)	α:β [b]
Styrene	[Rh]	20	1	99	79:21
3VP	[Rh]	120	1	99	86:14
4VP	[Rh]	240	98	2	30:70
Styrene	[Rh/L]	60	1	99	94:6
3VP	[Rh/L]	45	1	99	96:4
4VP	[Rh/L]	60	15	85	98:2

[a] Reaction conditions: 4.64 mmol of substrate, 5 ml of benzene, 0.004 mmol of $Rh_4(CO)_{12}$, 0.064 mmol of PMe_2Ph (**L**) (P/Rh = 4); 100°C temperature; autoclave volume 25 ml; 110 atm total pressure (1:1 H_2/CO).
[b] Percentage determined via GC on the total reaction products of the crude reaction mixtures, using *o*-xylene as internal standard.

$Rh_4(CO)_{12}$. Thus the chemoselectivity into aldehydic products is always almost complete.

The high α-regioselectivity observed for the branched aldehydic isomers **4α** and **3α** should derive from the preferential formation of the branched alkyl–metal intermediates with respect to the linear ones, due to the electron-withdrawing character of the pyridine ring. This feature had already been discussed in a previous paper on the hydroformylation of styrene [3] and vinylpyridines [11].

The results summarized in Table 2 indicate that temperature does not affect the selectivity of the reaction in the presence of phosphine either with **4VP** or with **3VP**. This could be explained taking into account what has already been reported in the case of styrene and of vinylpyrroles: it is likely that the presence of phosphine ligands on the metal inhibits the β-hydride elimination process and hence prevents the interconversion of alkyl–metal species. So the isomeric ratio between the aldehydic products directly reflects the one of isomeric alkyl–rhodium intermediates [3].

In conclusion, the above findings clearly show the dramatic influence of electronic factors on the selectivity of the hydroformylation reactions of vinylpyridines, depending both on the different position of the double bond with respect to the annular nitrogen atom and on the electronic properties of the catalytic system.

4. Experimental

Benzene was dried over molecular sieves and distilled under nitrogen. The starting compound 4-vinylpyridine (**4VP**) was commercially available and was distilled before use. 3-vinylpyridine (**3VP**) [12] and $Rh_4(CO)_{12}$ [13] were prepared as reported in literature. GC analyses of the reaction mixtures were performed on a Perkin–Elmer 8500 chromatograph equipped with a 12 m × 0.22 mm BP1 capillary column, using helium as carrier gas. ^{1}H-NMR spectra were measured on a Varian VXR 300 spectrometer. Chemical shifts were referred to TMS.

4.1. Hydroformylation of vinylpyridines: general procedure

A solution of ***n*VP** (0.5 ml, 4.64 mmol), $Rh_4(CO)_{12}$ (3 mg, 0.004 mmol), phosphine (corresponding to the desired P/Rh molar ratio) and *o*-xylene (0.5 ml) in benzene (5 ml) was introduced by suction into an evacuated 25 ml stainless steel autoclave. Carbon monoxide was introduced, the autoclave was stirred and heated to 100°C, and dihydrogen was rapidly introduced up to 110 atm total pressure ($CO/H_2 = 1:1$). When the gas absorption reached the value corresponding to the desired conversion, the reaction mixture was siphoned out. The degree of conversion was measured by GLC analysis, using *o*-xylene as internal standard.

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