Rhodium-Catalyzed Hydroformylation of 4-Vinylpyridine: 4-Ethylpyridine Formation via an Unusual Cleavage of the Rh−C Bond by the Enolic Form of the Oxo Product

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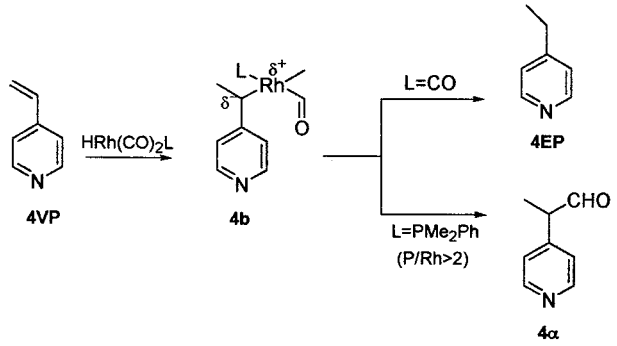
The hydroformylation of 4-vinylpyridine (**4VP**) with rhodium catalyst $Rh_4(CO)_{12}$ modified with phosphine ligands (PMe_2Ph) is not completely chemoselective to the branched aldehyde 2-(4-pyridyl)propanal (**4α**), the corresponding hydrogenation product 4-ethylpyridine (**4EP**) always being formed. A series of experiments carried out at different concentrations of rhodium catalyst and **4VP** as well as at various degrees of conversion indicate that the amount of hydrogenation product increases with increasing concentration and conversion of the substrate but is only slightly affected by the catalyst concentration. Deuterioformylation experiments carried out in the presence of the phosphine-modified catalyst have established the origin of the hydrogenation product. The recovered **4EP** is monodeuterated, the deuterium atom appearing exclusively in the methyl group of **4EP**. All the observations are consistent with cleavage of the rhodium−carbon bond in the branched alkyl-metal intermediate by the acidic proton of aldehyde **4α** in its enolic form.

Introduction

Hydroformylation, the well-known reaction that consists of a CO/H_2 addition to unsaturated substrates promoted by transition metal hydrido carbonyls, is characterized by an almost complete chemoselectivity into aldehydic products. The side processes occurring under "oxo" conditions, such as hydrogenation, isomerization, and polymerization, usually are of secondary importance.[1] However, there are some interesting exceptions. For instance the hydroformylation of vinyl compounds conjugated with a carbonyl moiety does not lead to the expected aldehydic products; in this case only hydrogenation of the olefinic double bond takes place.[1b,2]

As far as vinyl aromatic and vinyl heteroaromatic substrates are concerned, a very high chemoselectivity to aldehydes is obtained, with the exception of 4-vinylpyridine (**4VP**) and 2-vinylpyridine (**2VP**), which give hydrogenation or hydroformylation products depending on the catalyst employed.[3] In particular, in the presence of unmodified $Rh_4(CO)_{12}$, **4VP** provides the hydrogenation product 4-ethylpyridine (**4EP**) almost exclusively, while by using a phosphine-modified rhodium precursor the chemoselectivity to aldehydes is high. In addition, the regioselectivity is almost complete toward the branched aldehydic isomer 2-(4-pyridyl)propanal (**4α**)[4] (Scheme 1).

Scheme 1



The peculiar behavior of **4VP** and **2VP** has been attributed to the different polarization of the Rh−C bond in the branched alkyl rhodium intermediates, when unmodified or phosphine-modified catalyst precursors, respectively, are employed.[4] In the case of the unmodi-

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(1) (a) Wender, I.; Pino, P. *Organic Synthesis via Metal Carbonyls*; Wiley: New York, 1968. (b) Pruett, R. L. *Adv. Organomet. Chem.* **1979**, *17*, 1. (c) Pino, P. *J. Organomet. Chem.* **1980**, *200*, 223. (d) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal., A: Chem.* **1995**, *104*, 17. (e) Ungváry, F. *Coord. Chem. Rev.* **1999**, *188*, 263. (f) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329. (g) van Leeuwen, P. W. N. M.; Claver, C. In *Rhodium Catalyzed Hydroformylation*; Kluwer Academic Publishers: Dordrecht, 2000.

(2) Kwok, T. J.; Wink, D. J. *Organometallics* **1993**, *12*, 1954.

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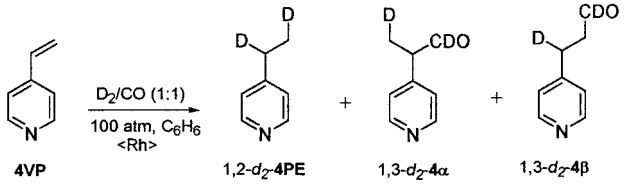
Scheme 2



fied catalyst system the high positive charge localized at position 4 of the pyridine ring causes a strong decrease of the nucleophilic character of the carbon bonded to the rhodium in the alkyl-metal species; thus the migratory insertion process on the CO coordinated to rhodium is strongly prevented and the above intermediate undergoes only a slow dihydrogen addition (Scheme 1).

The electron donor effect of the phosphine ligand on the Rh−C bond makes the carbon atom nucleophilic enough to undergo migratory insertion onto a CO coordinated to the metal, leading to the branched aldehydic isomer. On this basis it is surprising that a considerable amount (10−20%) of hydrogenation product is formed, even in the case of modified catalyst with phosphine ligands; indeed, neither the type of ligand nor an increasing P/Rh ratio influences significantly the amount of **4EP**. Since this result is not easily explainable on the basis of the previously reported hypothesis, it seemed worthwhile to gain a better insight into the problem through deuterioformylation experiments, which, in the case of other vinylaromatic substrates, have proved to be very useful in determining the nature and the fate of the corresponding alkyl-rhodium intermediates. Thus we carried out deuterioformylation runs on **4VP** with both catalyst systems, i.e., unmodified $Rh_4(CO)_{12}$ and $Rh_4(CO)_{12}$ modified with PMe_2Ph (**L**) (Scheme 2).

Particular attention was devoted to the recovery and characterization of the deuterated **4EP** obtained in both the presence and absence of phosphine. In addition the influence on the chemoselectivity of (a) the extent of substrate conversion and (b) the concentration of both **4VP** and phosphine-modified rhodium catalyst was investigated.

Results

Deuterioformylation reactions were carried out in benzene at partial substrate conversion (20−30%), in a stainless steel autoclave (25 mL), at 100 °C and 100 atm total pressure (CO/D_2 = 1:1). $Rh_4(CO)_{12}$ was used as catalyst precursor,[6] both in the absence and in the presence of PMe_2Ph (**L**). In a typical experiment, 4 mL of benzene, 0.80 g (7.6 mmol) of **4VP**, and a **4VP**/Rh/**L** molar ratio of 475:1:4 were employed. The crude reaction mixtures were analyzed by GC analysis, using *o*-xylene as internal standard, by GC−MS spectrometry, and then by ^{1}H NMR and ^{2}H NMR spectroscopy.

(5) (a) Uccello-Barretta, G.; Lazzaroni, R.; Settambolo, R.; Salvadori, P. *J. Organomet. Chem.* **1991**, *417*, 111. (b) Lazzaroni, R.; Uccello-Barretta, G.; Scamuzzi, S.; Settambolo, R.; Caiazzo, A. *Organometallics* **1996**, *15*, 4657. (c) Lazzaroni, R.; Settambolo, R.; Uccello-Barretta, G.; Caiazzo, A.; Scamuzzi, S. *J. Mol. Catal., A: Chem.* **1999**, *143*, 123.

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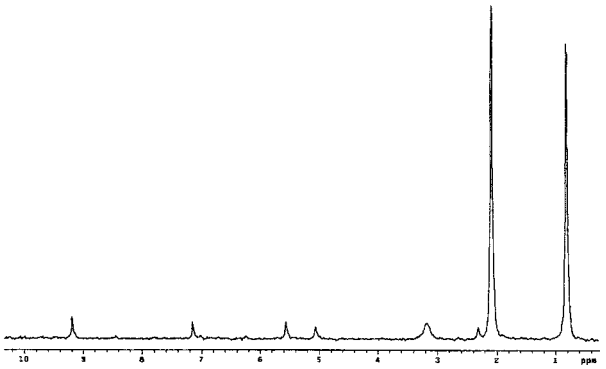


Figure 1. ^{2}H NMR spectrum (46 MHz) of the crude reaction mixture in benzene, obtained by deuterioformylation of 4-vinylpyridine (**4VP**) at 100 °C in the presence of unmodified $Rh_4(CO)_{12}$.

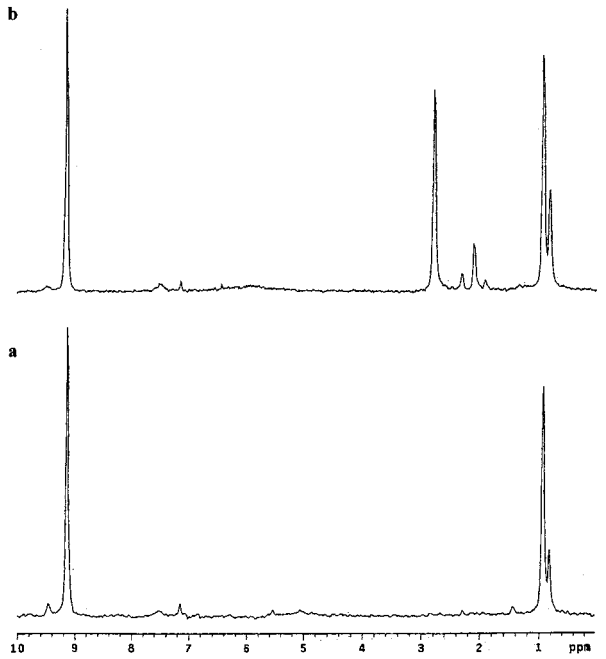
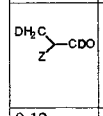
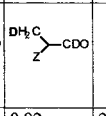
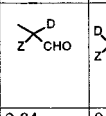
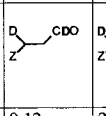
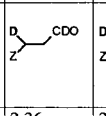
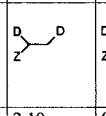
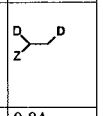


Figure 2. ^{2}H NMR spectrum (46 MHz) of the crude reaction mixture in benzene recovered by deuterioformylation of 4-vinylpyridine (**4VP**) with $Rh_4(CO)_{12}/PMe_2Ph$ (1:4) at (a) 26% and (b) 100% substrate conversion.

The ^{2}H NMR spectrum from the run carried out in the presence of unmodified $Rh_4(CO)_{12}$ at total substrate conversion (Figure 1) shows the expected signals for the almost exclusive reaction product, 1,2-dideuterio-1-(4-pyridyl)ethane (1,2-d_2-**4PE**: δ 0.84 ppm for CH_2D and 2.10 ppm for CHD, in 1:1 intensity ratio). The olefinic signals due to the geometrical isomers of (*Z*)-2-deuterio-1-(4-pyridyl)ethene (δ 5.00 ppm) and (*E*)-2-deuterio-1-(4-pyridyl)ethene (δ 5.48 ppm) are also present but with very low intensity (<5%) relative to the **4PE** signals. The β-hydride elimination process involving the branched alkyl-metal intermediate is responsible for the incorporation of the deuterium into the vinyl moiety.[5] The ^{2}H NMR spectrum from the run carried out in the presence of $Rh_4(CO)_{12}/PMe_2Ph$ (P/Rh = 4) after 15 min (26% substrate conversion) (Figure 2a) clearly shows the signals for the branched aldehydic isomer 1,3-d_2-**4α**, obtained as the main reaction product (δ 9.12 ppm for CDO and 0.92 ppm for CH_2D). As far as the hydrogenation product is concerned, the CH_2D signal at 0.84 ppm

Table 1. ^{2}H NMR Chemical Shifts[a] of the Deuterated Products[b] Arising from the Deuterioformylation of 4-Vinylpyridine (4VP)

1,3-d_2-4α	1,3-d_2-4α	2-d_1-4α	1,3-d_2-4β	1,3-d_2-4β	1,2-d_2-**4PE**	1,2-d_2-**4PE**
						
9.12	0.92	2.84	9.12	2.36	2.10	0.84

[a] Referred to C_6D_6 as external standard, benzene as solvent, 46 MHz. [b] Z = 4-pyridyl

is present, but surprisingly the corresponding CHD signal at 2.10 ppm shows a very low intensity. No signal due to deuterated olefin is present. In Table 1 the ^{2}H NMR chemical shifts of the deuterated products arising from the above deuterioformylation runs are reported.

The amount of the hydrogenation product was found to be higher than in the corresponding hydroformylation (**4EP**: 25% for D_2 oxo, **4EP**: 15% for H_2 oxo), while the regioselectivity toward the branched aldehyde was the same (96:4).[4]

Deuterioformylation of **4VP** with phosphine-modified rhodium catalysts was also examined in runs carried out at 85% and 100% substrate conversion. The ^{2}H NMR spectrum of the crude reaction mixture after 45 min (85% substrate conversion) shows the presence of two additional signals at 2.84 and 2.10 ppm. The former is due to the deuterium atom on carbon atom C2 of **4α** aldehyde. Its intensity increases with time and after 3 h (100% substrate conversion) reaches the same intensity as the signals at 9.12 and 0.92 ppm (Figure 2b). The resonance at δ 2.10 ppm is due to the deuterium atom on carbon atom C1 of 1,2-d_2-**4PE**, the relative intensities of the signals due to deuterium on carbon atoms C1 and C2 being 0.4:1. Therefore, at complete substrate conversion partially deuterated 1,2-d_2-**4PE** and the trideuterated product 1,2,3-trideuterio-2-(4-pyridyl)propanal (1,2,3-d_3-**4α**) have been formed. A weak signal at δ 2.36 ppm due to the deuterium in the α position of the pyridine ring of the linear aldehyde 1,3-d_2-3-(4-pyridyl)propanal (1,3-d_2-***4β***) is also present (Figure 2b). To analyze more precisely the content of deuterium in **4PE**, both in the presence and in the absence of phosphine, the corresponding reaction mixtures were distilled; the hydrogenation products were collected as head fractions and characterized by GC−MS, ^{1}H NMR, ^{2}H NMR, and ^{13}C NMR spectroscopy. In the case of **4PE** coming from the unmodified catalyst run, it was observed that

(i) The GC−MS spectrum shows a 109 molecular ion peak.

(ii) The ^{1}H NMR spectrum shows two signals at δ 2.62 and 1.23 ppm, with a 1:2 relative intensity.

(iii) The ^{2}H NMR spectrum shows two peaks (1:1 intensity) at δ 2.10 and 0.84 ppm (Figure 3a).

(iv) The ^{13}C NMR spectrum shows two triplets at δ 27.8 and 13.9 ppm (J_{C-D} 19 Hz).

These observations confirm the presence of two deuteriums, one each for the two carbons of the ethyl moiety (1,2-d_2-**4PE**). In the case of **4PE** coming from the **L**-modified catalyst run, it was observed that

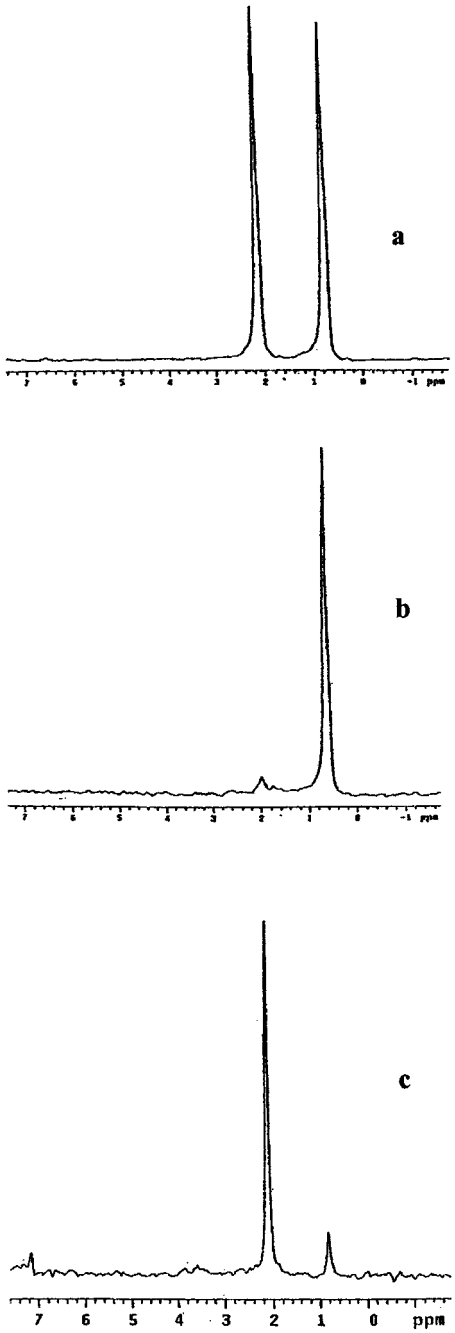


Figure 3. ^{2}H NMR spectrum (46 MHz) of 4-ethylpyridine (**4EP**) recovered by distillation from (a) deuterioformylation of 4-vinylpyridine (**4VP**) at total substrate conversion with $Rh_4(CO)_{12}$, (b) deuterioformylation of 4-vinylpyridine (**4VP**) at 26% substrate conversion with $Rh_4(CO)_{12}$/PMe_2Ph (1:4), and (c) hydroformylation of 4-vinylpyridine (**4VP**) at 26% substrate conversion in the presence of 2-d_1-2-(4-pyridyl)propanal (2-d_1-**4α**).

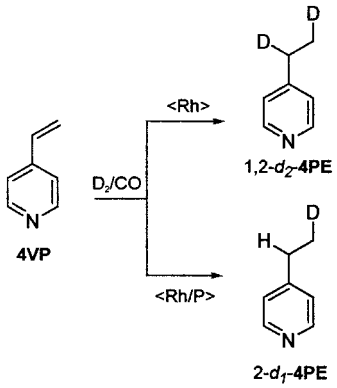
(i) The GC−MS spectrum shows a 108 molecular ion peak

(ii) The ^{1}H NMR spectrum shows two signals at δ 2.62 and 1.23 ppm, with a 1:1 relative intensity.

(iii) The ^{2}H NMR spectrum shows a strong peak at δ 0.84 ppm and a very low intensity peak at δ 2.10 ppm (Figure 3b).

(iv) The ^{13}C NMR spectrum shows a triplet at δ 13.9 ppm (J_{C-D} 19 Hz) and a singlet at 27.8 ppm.

Scheme 3



These observations suggest the presence of one deuterium located almost exclusively on the 2-carbon atom of the ethyl group in 2-d_1-**4PE**.

Discussion

The most surprising result obtained from the rhodium-catalyzed hydroformylation of **4VP** is the different amount of deuterium incorporated into 4-ethylpyridine depending on the type of catalyst employed. The analysis of the isolated **4PE** derived from deuterioformylation mixtures showed that, with the use of unmodified $Rh_4(CO)_{12}$, **4PE** contained two deuteriums, one each for the two carbons of the ethyl moiety, while in the case of phosphine-modified $Rh_4(CO)_{12}$ at low substrate conversion the corresponding **4PE** contained about one deuterium, almost exclusively on the β-carbon of the ethyl group (Scheme 3).

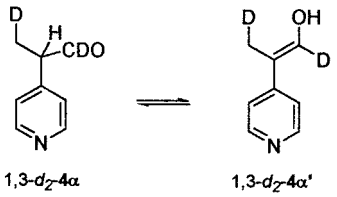
In the case of unmodified $Rh_4(CO)_{12}$, a slow oxidative addition of D_2 to the branched alkyl-rhodium intermediate accounts for the formation of the expected dideuterated product 1,2-d_2-**4PE**.

To account for the formation of monodeuterated 2-d_1-**4PE** in the experiments carried out in the presence of phosphine-modified catalyst, several hypotheses could be advanced; for example (a) two different catalytic systems could be present in the reaction mixture, one promoting hydrogenation and the other hydroformylation, and (b) decarbonylation of the branched aldehyde **4**α could occur under oxo conditions. As the amount of hydrogenation product is independent of the type of phosphine and of the P/Rh molar ratio,[4] at least in the range 4−10, it can be assumed that all the rhodium catalyst is complexed by the phosphine and hence the presence of unmodified rhodium catalyst can be excluded (hypothesis a). Hypothesis b can be excluded too on the basis of deuterioformylation experiments. According to the mechanism proposed for decarbonylation,[7] a dideuterated species would be expected, but not a monodeuterated one as found experimentally.

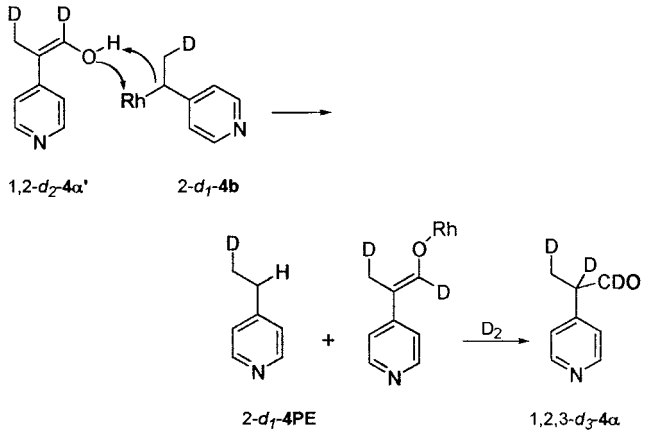
To account for the formation of monodeuterated **4PE**, it must be noted that the main reaction product, the branched aldehydic species 1,3-d_2-**4**α, is in equilibrium with the corresponding enolic form 1,3-d_2-**4**α' (Scheme 4).

The ^{1}H NMR spectrum in C_6D_6 of **4**α shows only resonances due to the keto form, in contrast with the corresponding isomer in the position 2 (**2**α) (whose enolic tautomer **2**α' predominates and is easily recognizable[3a]). However, the hydrogen in the α position with respect to CDO is quite acidic, as shown by the following observations.

Scheme 4



Scheme 5



(i) By prolonged heating of deuterioformylation mixtures a complete scrambling of the above proton with deuterium is observed (^{2}H NMR analysis, δ 2.84 ppm) and trideuterated aldehyde 1,2,3-d_3-**4**α (Figure 2b) is obtained. Analogously, on treating the crude reaction mixture from **4VP** hydroformylation with D_2/CO, the undeuterated aldehyde **4**α is transformed quantitatively into the monodeuterated one, 2-d_1-2-(4-pyridyl)propanal (2-d_1-**4**α) (^{2}H NMR analysis δ 2.88 ppm).

(ii) By treating the above hydroformylation mixture with D_2O the α-proton exchanges with deuterium (^{2}H NMR analysis, δ 2.84 ppm).

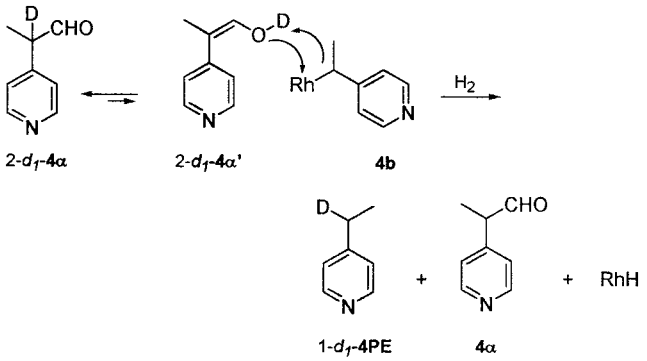
On this basis we propose that the branched alkyl-rhodium intermediate can react under oxo conditions by (a) a migratory insertion to a coordinated CO, leading to a rhodium acyl species and thence to the branched aldehyde (Scheme 1), (b) a cleavage of the rhodium−carbon bond by the OH group of the enolic form of the aldehyde 1,3-d_2-**4**α', with formation of the monodeuterated hydrogenation product 2-d_1-**4PE** and the trideuterated aldehyde 1,2,3-d_3-**4**α (Scheme 5).[8]

This hypothesis was confirmed by the following experiments. When **4VP** is hydroformylated at partial substrate conversion (26%) in the presence of an equimolar amount of aldehyde 2-d_1-**4**α monodeuterated in the α position, the hydrogenation product recovered by distillation from the reaction mixture is monodeuterated in the α position with respect to the pyridine ring and hence monodeuterated 1-d_1-1-(4-pyridyl)ethane (1-d_1-

(7) Prince, R. H.; Raspin, K. A. *J. Chem. Soc., A* **1969**, 612.

(8) The enolic form of the aldehyde d_1-**4**α can exchange deuterium in two ways: (i) by cleavage of the rhodium−carbon bond (Scheme 5) and (ii) by direct exchange with rhodium carbonyl hydride, giving a rhodium deuteride and undeuterated aldehyde **4**α. Thus the amount of deuterium released by d_1-**4**α is greater than that incorporated into 1-d_1-**4PE**.

Scheme 6



4PE) is formed, as clearly shown by the ^{2}H NMR spectrum (Figure 3c). The deuterium appearing in 1-d_1-**4PE** must come from 2-d_1-**4α** aldehyde, because this is the only source of deuterium in the reaction mixture (Scheme 6).

A quantitative evaluation of deuterium transfer from 2-d_1-**4α** to 1-d_1-**4PE** was carried out by examining the crude reaction mixture via ^{2}H NMR and by using hexadeuteriobenzene as an internal standard. For 1 mol of deuterium atom incorporated into 1-d_1-**4PE**, about 1.3 mol of deuterium is released by 2-d_1-**4α** aldehyde.[8] An analogous experiment in which **4VP** is deuterioformylated in the presence of the same monodeuterated aldehyde 2-d_1-**4α** gives 1,2-d_2-(4-pyridyl)ethane, partially deuterated also in position 1, the deuterium atoms in 1 and 2 position being in the ratio 0.85:1. Thus we can conclude that **4EP** obtained by hydroformylation of **4VP** with the Rh/P catalytic system originates from a bimolecular reaction involving the enolic form of aldehyde and the branched alkyl rhodium intermediates.

In principle this process must be influenced by the concentration of the reagents. A series of experiments was carried out at different concentrations of **4VP** and Rh catalyst (in all cases the ratio Rh/P used was 1:4) and also at various degrees of conversion. The concentration of rhodium catalyst has only a slight effect on the chemoselectivity of the reaction, at least in the range examined. A modest increase in the yield of hydrogenation product **4EP** from 12 to 15% as the rhodium concentration is increased from 0.27 to 2.46 mmol·dm^{-3} was observed. In contrast, the **4VP** concentration strongly influences the distribution of the reaction products: the chemoselectivity to aldehydes is complete at low **4VP** concentration (<0.86 mol/L), while the amount of the hydrogenation product **4EP** strongly increases with increasing **4VP** concentration (Table 2). These results prompted us to investigate **4VP** hydroformylation at different degrees of substrate conversion. In the experiment carried out at high **4VP** concentration, the amount of **4EP** strongly increases with increasing conversion and hence with increasing aldehyde concentration in the reaction mixture (Table 3). These observations clearly demonstrate that the reaction product, the branched aldehyde **4α** in its enolic form, is involved in a cascade process which determines the outcome as the reaction proceeds toward full conversion. To see if the enolic form of aldehyde **4α′** is able to cleave the rhodium−carbon bond in the alkyl-metal intermediate generated from unmodified catalyst, we deuterioformylated **4VP** with $Rh_4(CO)_{12}$ in the presence of an equimolar amount of undeuterated aldehyde **4α**. The reaction is much slower, giving complete conversion after 3 h. The ^{2}H NMR spectrum of the crude reaction mixture at partial substrate conversion (45%) shows two resonances of the same intensity at δ 0.84 and 2.10 ppm, as expected for the classic deuterated species. The signal at δ 2.84 ppm typical of 2-d_1-**4α** arising from hydrogen−deuterium exchange of the α proton of the aldehyde is also present, as previously observed with the phosphine-modified catalytic system. Because of the low polarity of the Rh−C bond previously discussed, the alkylrhodium intermediate undergoes neither migratory insertion nor cleavage by the enolic form of aldehyde but only gives **4EP** as a consequence of slow oxidative addition of H_2 or D_2 to rhodium and transfer to the vinylic moiety. This result is very interesting because it confirms the different behavior of the Rh−C bond when the catalytic system is a simple rhodium carbonyl hydride or a rhodium carbonyl hydride modified with an electron donor phosphine ligand.

In conclusion, the results obtained in the hydroformylation of vinylpyridine isomers, catalyzed by either unmodified or phosphine-modified $Rh_4(CO)_{12}$, clearly show the peculiar behavior of these substrates, which is very different from that shown by other aromatic (styrene and substituted styrenes) and heteroaromatic substrates (vinylpyrroles and vinylfurans). The electron-poor character of the pyridine ring plays a crucial role by modifying the C−Rh bond polarity and increasing the acidity of the benzylic proton in the branched aldehyde **4α**.

Table 2. Rhodium-Catalyzed Hydroformylation of 4-Vinylpyridine (4VP) in the Presence of $Rh_4(CO)_{12}$/PMe_2Ph as Catalyst Precursor: Influence of 4VP Concentration on Product Distribution[a]

entry	[4VP] mol·dm^{-3}	hydrogenation (yield %)	hydroformylation (yield %)	α:β[b]
1	0.23	<1	>99	98:2
2	0.83	1	99	98:2
3	1.06	4	96	98:2
4	1.24	7	93	98:2
5	1.42	10	90	98:2
6	1.59	15	85	97:3
7	1.90	19	81	96:4
8	2.60	34	66	96:4

[a] Reaction conditions: 0.82 mmol·dm^{-3} of $Rh_4(CO)_{12}$, 13 mmol·dm^{-3} of PMe_2Ph, solvent benzene (4 mL), vessel volume 25 mL, temperature 100 °C, 100 atm total pressure (H_2/CO, 1:1), reaction time 70 min, conversion >97%. [b] Percentage determined on the total reaction products via GC analysis of the crude reaction mixture, using *o*-xylene as internal standard.

Table 3. Rhodium-Catalyzed Hydroformylation of 4-Vinylpyridine (4VP) in the Presence of $Rh_4(CO)_{12}$/PMe_2Ph as Catalyst Precursor: Influence of Substrate Conversion on Product Distribution[a]

entry	time (min)	conversion (%)	hydrogenation (yield %)	hydroformylation (yield %)
8a	11	15	13	87
8b	16	34	19	81
8c	70	>97	34	66
2a	20	43	1	99
2b	70	>97	1	99

[a] Reaction conditions: see Table 2.

Finally, as is well documented in several recent publications,[9] it should be noted the fundamental role played by ^{2}H NMR analysis of the deuterioformylation product in elucidating the behavior of the alkyl rhodium intermediate during the reaction. It must be stressed that in this case the classical approach based only on analysis of the distribution of the reaction products would not have provided evidence for the pathway leading to the hydrogenation product formed in the presence of phosphine-modified catalysts. In our case, without the deuterioformylation approach, it would have been very difficult to rationalize the results obtained in the hydroformylation of **4VP**.

Experimental Section

Benzene was dried over molecular sieves and distilled under nitrogen. $Rh_4(CO)_{12}$ was prepared as reported in the literature.[6] 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 and ^{2}H NMR spectra were measured on a Varian VXR 300 spectrometer. Chemical shifts were referred to TMS.

Hydroformylation or Deuterioformylation of 4-Vinylpyridine (4VP): General Procedure. In a typical experiment, a solution of **4VP** (0.8 mL, 7.42 mmol), $Rh_4(CO)_{12}$ (3 mg, 0.004 mmol), and PMe_2Ph (9.0 mg, 0.064 mmol) in benzene (4 mL) was introduced by suction into an evacuated 25 mL stainless steel autoclave equipped with a magnetic stirrer. The reactor was transferred to an oil bath, and carbon monoxide was introduced; the autoclave was then heated to 100 °C (45 atm), and H_2 (or D_2) was rapidly introduced up to 100 atm total pressure (CO/H_2 or D_2 = 1:1). When the gas absorption reached the value (8−10 atm) corresponding to the desired partial conversion (25−30%), the reactor was rapidly cooled and a sample of the reaction mixture was siphoned out. In the experiment carried out at total substrate conversion the drop of pressure was restored by injection of a carbon monoxide−deuterium (hydrogen) mixture (1:1 from a high-pressure container). The degree of conversion was measured by GLC analysis, using *o*-xylene as internal standard. Deuterated (4-pyridyl)ethane (**4PE**) was isolated from the crude reaction mixture by distillation as a colorless oil (80 °C, 20 mmHg).

2-*d*$_1$-2-(4-Pyridyl)propanal [2-*d*$_1$-4α]. A 2.4 g sample of **4VP** in benzene (20 mL) was hydroformylated in a 50 mL stainless steel reactor as described above. GC analysis of a siphonated sample of the reaction mixture after 75 min showed that **4VP** had been completely transformed into branched and linear aldehydes (96:4 isomeric ratio), the amount of hydrogenation product being less than 2%. The reactor was cooled and the CO/H_2 gas mixture replaced with CO/D_2. The reaction mixture was heated at 100 °C for an additional 3 h. The deuterium−hydrogen exchange at carbon atom C2 was complete, as shown by GC−MS analysis and the ^{2}H NMR spectrum of the crude reaction mixture. After evaporation of the solvent, a pure sample of 2-*d*$_1$-**4α** (δ = 2.84 ppm) was obtained as a yellow-green oil by distillation of the crude product at reduced pressure (0.1 mmHg, 120−125 °C).

1,2-*d*$_2$-1-(4-Pyridyl)ethane [1,2-*d*$_2$-4PE]. ^{1}H NMR ($CDCl_3$, TMS): δ 1.23 (m, 2H), 2.62 (m, 1H), 7.10 (d, 2H, *J* 5.0 Hz), 8.48 (d, 2H, *J* 5.0 Hz). ^{2}H NMR (C_6H_6): δ 0.84 (1D), 2.10 (1D). ^{13}C NMR ($CDCl_3$, TMS): δ 13.9 (t, J_{C-D} 19 Hz), 27.8 (t, J_{C-D} 19 Hz), 123.5 (s), 149.8 (s). GC−MS: 109 (M^+, 100), 108 (71), 93 (95), 80 (42), 79 (44), 66 (97).

2-*d*$_1$-1-(4-Pyridyl)ethane [2-*d*$_1$-4PE]. ^{1}H NMR ($CDCl_3$, TMS): δ 1.23 (m, 2H), 2.62 (t, 2H, *J* 7.2 Hz), 7.10 (d, 2H, *J* 5.0 Hz), 8.48 (d, 2H, *J* 5.0 Hz). ^{2}H NMR (C_6H_6): δ 0.84 (1D), 2.10 (traces). ^{13}C NMR ($CDCl_3$, TMS): δ 13.9 (t, J_{C-D} 19 Hz), 27.8 (s), 123.5 (s), 149.8 (s). GC−MS: 108 (M^+, 100), 107 (75), 92 (73), 80 (36), 79 (43), 65 (57).

1-*d*$_1$-1-(4-Pyridyl)ethane [1-*d*$_1$-4PE]. ^{1}H NMR ($CDCl_3$, TMS): δ 1.21 (d, 3H, *J* 7.1 Hz), 2.62 (m, 1H), 7.10 (d, 2H, *J* 5.0 Hz), 8.48 (d, 2H, *J* 5.0 Hz). ^{2}H NMR (C_6H_6): δ 0.84 (1D), 2.10 (traces). ^{13}C NMR ($CDCl_3$, TMS): δ 13.9 (s), 27.8 (t, J_{C-D} 19 Hz), 123.5 (s), 149.8 (s). GC−MS: 108 (M^+, 100), 107 (73), 93 (94), 80 (43), 79 (41), 66 (95).

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