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# **Amino-phosphanes in Rh(I)-catalyzed hydroformylation: New mechanistic insights using D<sub>2</sub>O as deuterium-labeling agent**

Jacques Andrieu\*<sup>a</sup>, Jean-Michel Camus<sup>a</sup>, Cédric Balan<sup>a</sup> and Rinaldo Poli\*<sup>b</sup>

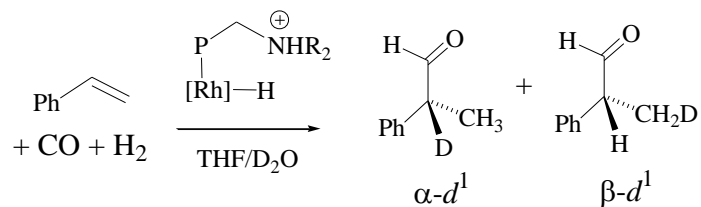
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## Synopsis

The dangling ammonium function in Rh- $\alpha$ -P,N catalytic systems induces, as a function of its pK<sub>a</sub>, a Rh-acyl racemization which affects the enantioselectivity in styrene hydroformylation.

## Keywords

Rhodium(I), aminophosphine ligands, H/D isotopic exchange, hydroformylation catalysis, enantioselectivity

## Abstract

In previous work, we have demonstrated that the dangling amino group in aminophosphine ligands increases the rate of Rh-catalyzed styrene hydroformylation as a function of the amino group basicity and of the distance between the P and N functions. We now report additional stereochemical and mechanistic insights resulting from new catalytic experiments performed with Rh- $\alpha$ -P,N catalytic systems in the presence of D<sub>2</sub>O. In addition to the expected D<sub>0</sub> product, the formation of the  $\beta$ -D<sub>1</sub> aldehyde, PhCH(CH<sub>2</sub>D)CHO was observed in all cases by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, indicating that H/D exchange occurs for the rhodium-hydride complex. Minor amounts of a  $\beta$ -D<sub>2</sub> product, PhCH(CHD<sub>2</sub>)CHO, were also formed under certain conditions, demonstrating the reversibility of the olefin coordination step. The composition of the aldehyde mixture is slightly affected by the nature of the catalytic precursor or the P,N ligand used. In the specific case of the  $\alpha$ -P,N ligand [ $\alpha$ -P,N = (*S*<sub>Ar</sub>,*S*<sub>C</sub>)-Ph<sub>2</sub>PCH(*o*-C<sub>6</sub>H<sub>4</sub>Cl(Cr(CO)<sub>3</sub>))NPh], in combination with the [RhCl(COD)]<sub>2</sub> precatalyst, products PhCD(CH<sub>3</sub>)CHO ( $\alpha$ -D<sub>1</sub>) and PhCD(CH<sub>2</sub>D)CHO ( $\alpha$ , $\beta$ -D<sub>2</sub>) were also produced. This result suggests a reversible deprotonation assisted by an intramolecular H-bonding interaction between the dangling ammonium function and the carbonyl moiety. This isotopic exchange process decreases the asymmetric induction from 14 to 7% e.e. when using the enantiopure version of this ligand. Aldehydes bearing a D atom on the formyl group, e.g. PhCH(CH<sub>3</sub>)CDO, were never observed. The latter observation excludes protonolysis of the rhodium-acyl intermediate as the aldehyde forming step. In addition, it also excludes a bimolecular reaction involving the rhodium-acyl and rhodium-hydride intermediates.

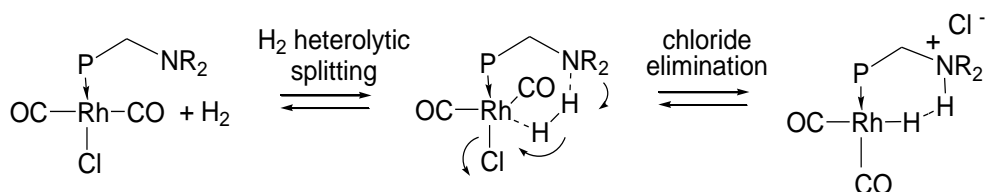
## Introduction

Metal complexes containing P,N bifunctional phosphines have attracted considerable attention in the field of homogeneous catalysis, in particular with transition metals like Ni<sup>1</sup>,

Pd<sup>2,3</sup>, Pt<sup>4</sup>, Ru<sup>5,6</sup>, Rh<sup>3,7</sup> and Ir.<sup>8-10</sup> These ligands can be either  $\kappa^1:P$  or  $\kappa^2:P,N$  coordinated and each coordination mode can modify the catalytic properties. For example, when a pyridinylphosphine is only P-coordinated in a Pd(II) complex, the dangling amine function acts then as a “proton messenger” in alkyne methoxycarbonylation catalysis<sup>2</sup>, whereas a selective P,N chelation of a chiral phosphinediamine induces an effective chiral field in rhodium complex leading to a higher selectivity in asymmetric hydrogenation of acrylic acid.<sup>7</sup>

In our laboratory, we have developed different access ways to chiral  $\alpha$ -<sup>11</sup> or  $\beta$ -P,N<sup>12,13</sup> and mixed  $\alpha,\beta$ - and  $\beta,\gamma$ -P,P,N<sup>14</sup> ligands and their coordination properties have been explored in copper(I)<sup>15</sup>, palladium(II)<sup>13,16</sup> and rhodium(I) complexes<sup>14,17,18</sup> Recently, we have examined the coordination properties of various P,N ligands in rhodium catalyzed hydroformylation and demonstrated the hemilabile character of  $\beta$  or  $\gamma$ -P,N ligands under CO pressure. Therefore, under these conditions, these ligands behave like their related  $\alpha$ -P,N monophosphine ligands, for which the chelating mode is not observed under any operating conditions.<sup>18</sup> The presence of a dangling nitrogen group close to the rhodium metal center could promote the activation of dihydrogen by heterolytic cleavage (see scheme 1). In this interaction, the Rh center acts as a Lewis acid, accepting H<sup>-</sup>, whereas the nearby amine function acts as a Lewis base, capturing the proton.

**Scheme 1**



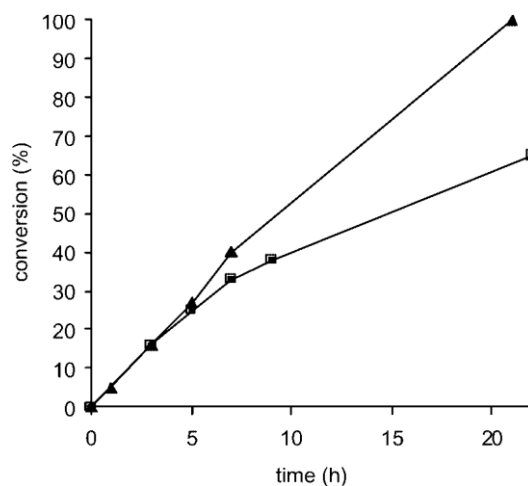
Nevertheless, even in the presence of chiral  $\alpha$ -<sup>17</sup>,  $\beta$ -P,N<sup>12</sup> or other P,N ligands<sup>19,20</sup>, the enantioselectivity of branched aldehydes formed in styrene hydroformylation were very low

(<14%). We decided to further investigate the mechanistic details of the enantioselective process by additional experiments based on H/D isotopic exchanges using D<sub>2</sub>O as a deuterium source. Indeed, deuterioformylations performed in the presence of D<sub>2</sub> instead of H<sub>2</sub> have been most effective for elucidating mechanistic details in catalytic processes, for instance the degree of reversibility for the olefins insertion reactions into the Rh-H bond,<sup>21-23</sup> or the different behavior of primary, secondary, and tertiary Rh-alkyl intermediates under hydroformylation conditions.<sup>24</sup> In addition, the use of deuterated reagents like D<sub>2</sub>, EtOD, or (*S*)-CH<sub>3</sub>-CH(Ph)OD have also provided mechanistic information, respectively, in iridium-catalyzed alkane dehydrogenation<sup>25</sup>, in palladium-catalyzed styrene hydroalkoxy-carbonylation<sup>26</sup> or in metal-catalyzed hydrogen transfer from alcohols to ketones.<sup>27</sup> Our choice of heavy water, D<sub>2</sub>O, as the source of the deuterium label was suggested by the proposed implication of ammonium functionalities, with potentially exchangeable protons, near the catalytic center, as shown in Scheme 1. Furthermore, its use would allow us not only to follow the D-incorporation into organic compounds during the catalysis, but also to obtain useful information on the stability and/or reactivity of our Rh-P,N catalysts in aqueous media.<sup>28-30</sup> We could then evaluate their potential for extension to biphasic conditions.<sup>31</sup>

## Results and Discussion

The catalytic runs were carried out using [RhCl(COD)]<sub>2</sub> or [Rh(acac)(CO)<sub>2</sub>] as precatalyst, with an equimolar amount of the  $\alpha$ -P,N ligands Ph<sub>2</sub>PCH<sub>2</sub>NR<sub>2</sub> (R = Me, Ph) or Ph<sub>2</sub>PCH(Ar)NPh [Ar =  $\eta^6(o\text{-C}_6\text{H}_4\text{Cl})\text{Cr}(\text{CO})_3$ ], in the presence of one thousand equivalents of D<sub>2</sub>O and styrene. Control experiments were also carried out with PPh<sub>3</sub> and in the absence of phosphine ligand. In a previous contribution, we have reported the catalytic activity and linear/branched selectivity of the above systems in dry CHCl<sub>3</sub>.<sup>18</sup> The hydroformylation experiments in the presence of D<sub>2</sub>O, reported in this paper, were carried out under similar

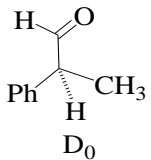
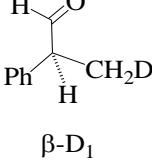
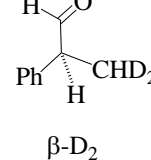
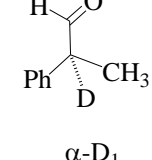
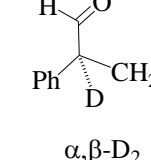
conditions with the exception of the solvent, which was changed from  $\text{CHCl}_3$  to THF in order to insure homogenous conditions in the presence of water. In Figure 1, we compare the activity of the same Rh-P,N precatalyst under the two different solvent conditions.



**Figure 1** Conversion for the catalyzed styrene hydroformylation as a function of time: ■, in THF-D<sub>2</sub>O, ▲, in CHCl<sub>3</sub>. Both experiments have been performed using the catalytic conditions described for run 5, Table 1.

Neither the branched/linear regioselectivity (91/9),<sup>18</sup> nor the turnover frequency at the beginning of the catalytic process are affected by this solvent change. However, the catalyst starts to lose activity after ca. five hours. Conversions of 65% and 100% were obtained respectively after one and two days, whereas a complete conversion was achieved in CHCl<sub>3</sub> after only one day (see figure 1). Therefore, the loss of activity seems related to catalyst decay due to the presence of the large excess of water. Since a complete conversion was achieved after two days, we decided to analyze the crude aldehyde mixture by NMR spectroscopy after this period for all catalytic runs. The nature and relative proportions of the branched aldehydes are summarized in Table 1. The small relative amounts of linear aldehyde did not permit the analysis of the deuterium incorporation and these data are therefore excluded from Table 1.

**Table 1.** Effect of the P,N ligand on the composition of deuterated aldehydes.

Run <sup>a</sup>	Catalytic Precursor	Ligand (1 equiv.)					
			D <sub>0</sub>	β-D <sub>1</sub>	β-D <sub>2</sub>	α-D <sub>1</sub>	α,β-D <sub>2</sub>
1	[RhCl(COD)] <sub>2</sub>	no	44%	44%	12%	-	-
2	[RhCl(COD)] <sub>2</sub>	PPh <sub>3</sub>	73%	27%	-	-	-
3	Rh(acac)(CO) <sub>2</sub>	PPh <sub>3</sub>	87%	13%	-	-	-
4	[RhCl(COD)] <sub>2</sub>	Ph <sub>2</sub> PCH <sub>2</sub> NPh <sub>2</sub>	51%	41%	9%	-	-
5	[RhCl(COD)] <sub>2</sub>	Ph <sub>2</sub> PCH(Ar)NHPPh <sup>b</sup>	60%	20%	-	15%	5%
6	[RhCl(COD)] <sub>2</sub>	Ph <sub>2</sub> PCH(Ar)NHPPh <sup>b</sup> + NEt <sub>3</sub> <sup>c</sup>	73%	23%	-	4%	-
7	Rh(acac)(CO) <sub>2</sub>	Ph <sub>2</sub> PCH(Ar)NHPPh <sup>b</sup>	75%	25%	-	-	-
8	[RhCl(COD)] <sub>2</sub>	Ph <sub>2</sub> PCH <sub>2</sub> NEt <sub>2</sub>	83%	17%	-	-	-
9	Rh(acac)(CO) <sub>2</sub>	Ph <sub>2</sub> PCH <sub>2</sub> NEt <sub>2</sub>	77%	23%	-	-	-

<sup>a</sup> Conditions: [RhCl(COD)]<sub>2</sub> (2.62 x 10<sup>-2</sup> mmol) or [Rh(acac)(CO)<sub>2</sub>] (5.23 x 10<sup>-2</sup> mmol), styrene/Rh and D<sub>2</sub>O/Rh = 1000, plus ligand, THF

(35 ml), 55°C, P(syngas) = 600 psi, two days. <sup>b</sup> Ar = η<sup>6</sup>(*o*-C<sub>6</sub>H<sub>4</sub>Cl)Cr(CO)<sub>3</sub>. <sup>c</sup> P,N/NEt<sub>3</sub> ratio = 1.



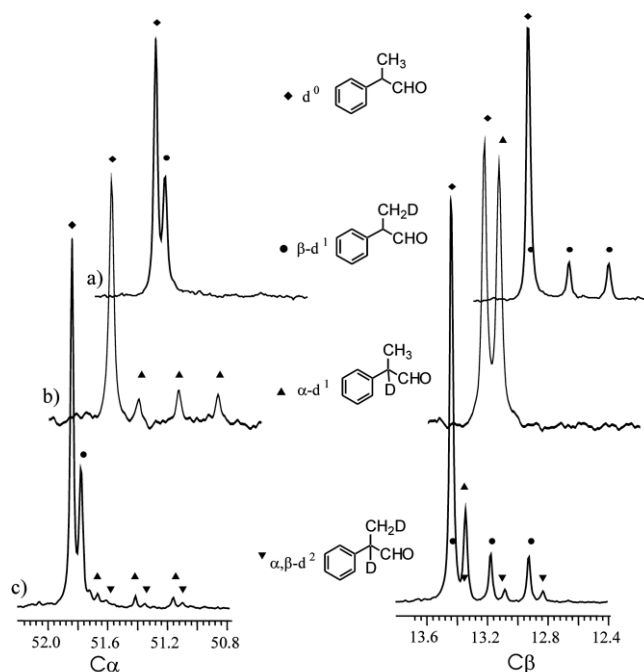
The incorporation of the deuterium atoms either in the terminal methyl group or in the internal methyne group of the branched aldehydes was determined unambiguously by careful analysis of the primary and secondary isotope shifts and of the  $J_{CD}$  patterns for the  $\alpha$ - and  $\beta$ -C resonances in the  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum (see Table 2). The relative amounts of the various products were quantified by integration of the  $^{13}\text{C}\{^1\text{H}\}$  resonances affected by the secondary isotope shift, since the Overhauser effect does not depend on the substitution pattern at the adjacent C atom.<sup>32-34</sup> Thus, for instance, the relative proportion of compounds  $\text{PhCH}(\text{CH}_3)\text{CHO}$  and  $\text{PhCH}(\text{CH}_2\text{D})\text{CHO}$  were obtained by integration of the two proton-decoupled methyne signals, whereas the relative proportions of compounds  $\text{PhCH}(\text{CH}_3)\text{CHO}$  and  $\text{PhCD}(\text{CH}_3)\text{CHO}$  were obtained by integration of the two proton-decoupled methyl signals.

**Table 2:** Selected  $^{13}\text{C}$ -NMR data and  $J_{CD}$  coupling constants of deuterated compounds

compounds	$\text{C}_\alpha$ $\delta$ in ppm ( $J_{CD}$ in Hz)	$\text{C}_\beta$ $\delta$ in ppm ( $J_{CD}$ in Hz)
$\text{D}_0$	51.82	13.43
$\beta\text{-D}_1$	51.77	13.18(19)
$\beta\text{-D}_2$	51.72	signal too weak
$\alpha\text{-D}_1$	51.41 (20)	13.34
$\alpha,\beta\text{-D}_2$	51.36 (20)	13.08(19)

Figure 2 shows the  $^{13}\text{C}$  NMR spectra for three representative product mixtures. The mixture obtained from run 7 (Figure 2a), as well as most other runs (see Table 1) shows only the  $\beta\text{-D}_1$  compound in addition to the regular  $\text{D}_0$  product, whereas run 5 produces a more complex mixture of deuterated aldehydes (Figure 2c). The spectrum in Figure 2b corresponds to a control mixture of  $\text{D}_0$

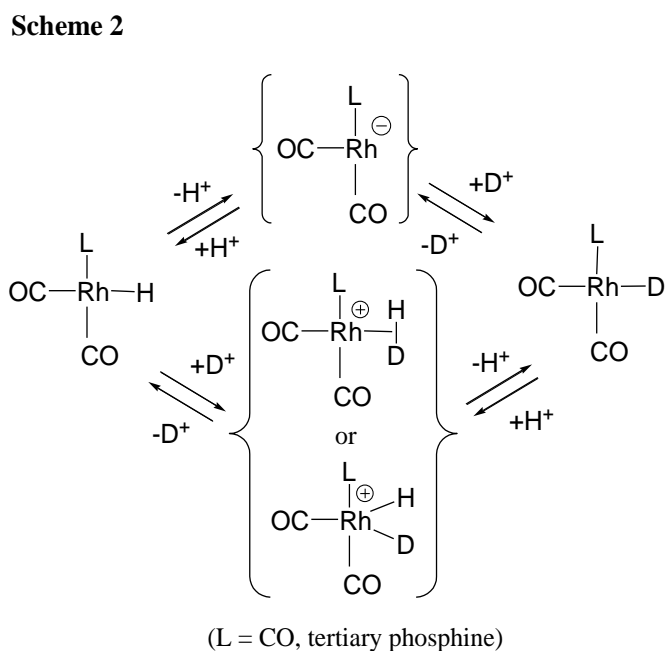
and  $\alpha$ -D<sub>1</sub> products, which was obtained by direct isotopic exchange between the D<sub>0</sub> aldehyde and [PhND<sub>3</sub>]<sup>+</sup>[BF<sub>4</sub>]<sup>-</sup>. It is to be remarked that in none of the runs was any deuterium atom found on the aldehyde function, *i.e.* PhCH(CH<sub>3</sub>)CDO.



**Figure 2** <sup>13</sup>C{<sup>1</sup>H} NMR spectra of partially deuterated aldehydes mixtures. Only the peaks of the branched aldehydes are shown for clarity. C<sub>α</sub> and C<sub>β</sub> correspond respectively to the methyne and methyl carbon atoms. (a) From run 7, after complete conversion. (b) from the reaction between D<sub>0</sub> aldehyde and 0.3 equivalent of [PhND<sub>3</sub><sup>+</sup>](BF<sub>4</sub><sup>-</sup>), after 24 hrs, under catalytic conditions described in Table 1 without rhodium catalyst. (c) From run 5, after complete conversion.

The ubiquitous formation of the β-D<sub>1</sub> derivative is clear indication that D<sup>+</sup> finds its way into the hydride position during the catalytic cycle. Since the decayed catalyst (Figure 1) yields no (or a much lower amount of) new aldehyde, and since the aldehyde does not incorporate D under these conditions in the absence of the catalyst (*vide infra*), we can conclude that the isotopic distribution measured at the end of the experiment is not affected by the catalyst decomposition process. As this β-D<sub>1</sub> incorporation phenomenon occurs also when the phosphine ligand carries no amine

function (runs 2 and 3) and even in the absence of any phosphine (run 1), a direct acid dissociation of the hydride intermediate in the protic medium or a reversible protonation to generate a dihydrogen complex or a classical dihydride intermediate (Scheme 2) appear as the most logical mechanisms for this H/D exchange.



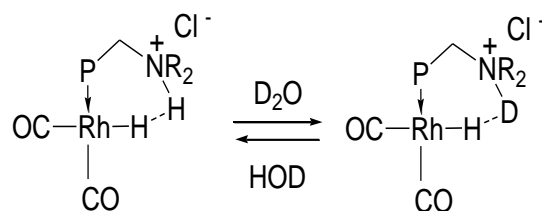
The observation that all experiments where a phosphine ligand is present (runs 2-9) provided a greater  $D_0/\beta\text{-}D_1$  ratio ( $\approx 3$ ) than run 1 appear in better agreement with the hypothesis of acid dissociation. Note that the  $D_0/\beta\text{-}D_1$  ratio is not greatly affected by the phosphine nature. For other processes, on the other hand, the amount of D incorporation by exchange with  $D_2O$  was shown to greatly depend on the nature of the phosphine ligand and substrate.<sup>30,35</sup>

The formation of the  $\beta\text{-}D_2$  product is observed only in the absence of phosphine ligand (run 1) and for run 4, using the  $Ph_2PCH_2NPh_2$  ligand. The presence of this product must be the consequence of reversibility for the styrene insertion step. It is to be remarked that H elimination from the  $\beta\text{-}D_1$ -1-phenylethyl insertion product should be favored over D elimination by a kinetic isotope effect, since the C-H/D vibrational modes are stronger than those of the  $C\cdots H/D$  and  $Rh\cdots H/D$  interactions in the transition state.<sup>36</sup> The reversibility of the styrene coordination step is

further confirmed by the recovery of free  $\beta$ -D<sub>1</sub>-styrene, *i.e.* PhCH=CHD, when a catalytic experiment carried out under the same condition of run 1 was quenched and the organic phase analyzed after 30 % conversion. The absence of  $\alpha$ -D<sub>1</sub>-styrene, *i.e.* PhCD=CH<sub>2</sub>, indicates that the 1,2 insertion leading to the  $\eta^1$ -2-phenylethyl rhodium complex (precursor of the linear aldehyde) is irreversible. This is consistent with other previously reported results.<sup>22,37,38</sup> Reversible 2,1 styrene insertion has previously been evidenced for hydroformylation experiments carried out under D<sub>2</sub> with Rh<sub>4</sub>(CO)<sub>12</sub> as catalyst (without phosphine ligands) or with [Rh(acac)(CO)<sub>2</sub>] in presence of mono-, di-phosphines, or (*R,S*)-binaphos ligand.<sup>21,23,37,38</sup> With the latter Rh-binaphos catalytic system, the amount of  $\alpha$ -plus  $\beta$ -D<sub>1</sub>-styrene was observed to increase significantly from 2 to 30% when the syngas pressure was increased from one to one hundred atm. Our results indicate that the styrene insertion becomes less reversible in the presence of phosphine ligands, with the exception of run 4. The latter leads to quite comparable results to those of run 1 and to those of the process conducted with tetranuclear rhodium precatalysts in the absence of phosphine ligands.<sup>38</sup> In other previous work based on the use of mono or di-phosphine ligands, the amount of deuterium label found in styrene was reported to be very minor and to vary only slightly (from 0.1 to a few %) as a function of the phosphine nature.<sup>21</sup> The unusually high proportion of  $\beta$ -d<sup>2</sup> in run 4 could be due to a ligand dissociation, but we have no further evidence to confirm or refute this assumption at this time.

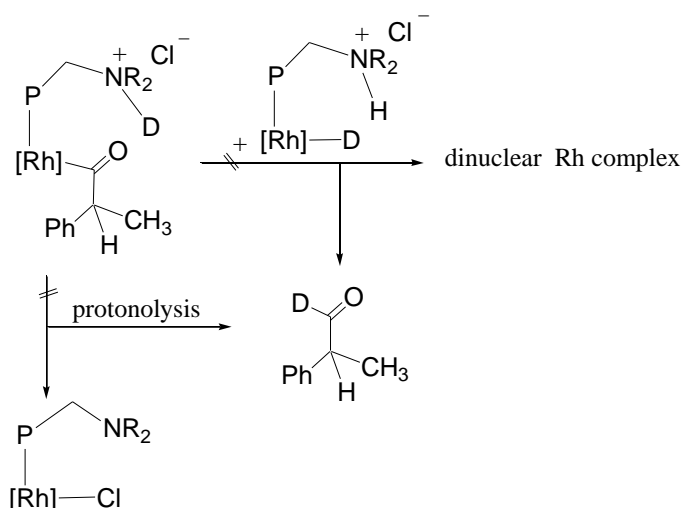
The absence of any observable deuterium incorporation into the formyl group has very important implications. As discussed above, an HCl equivalent is generated during the catalyst activation process when using the [RhCl(COD)]<sub>2</sub> precursor. This by-product will presumably be trapped by the internal amine function (see Scheme 1), since amines are more basic than water (pK<sub>a</sub>  $\approx$  4.8 for PhNH<sub>2</sub>Me<sup>+</sup> and 10.7 for NHEt<sub>3</sub><sup>+</sup>). The ammonium protons of the resulting Rh-ammonium species are likely to be exchanged by D<sup>+</sup> in the presence of D<sub>2</sub>O, see Scheme 3.

### Scheme 3



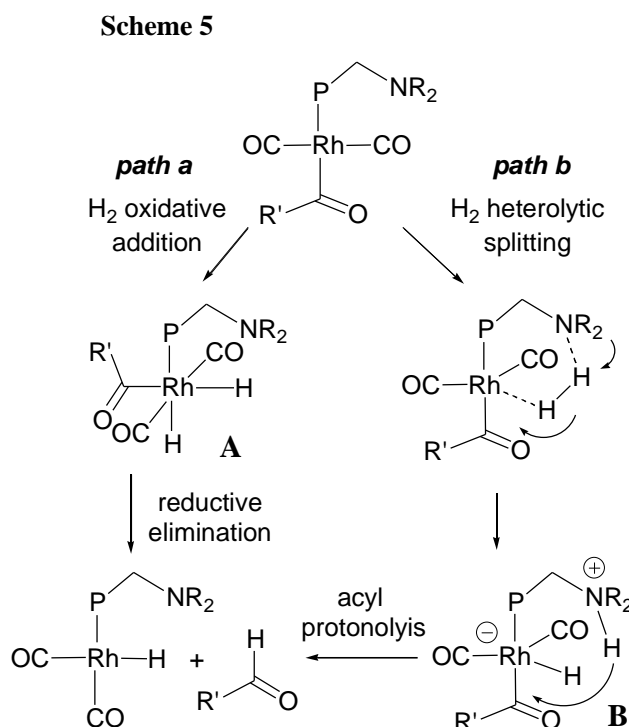
Therefore, the outcome of the catalytic runs in the presence of D<sub>2</sub>O excludes Rh-acyl protonolysis by the ammonium function as the aldehyde forming step (see Scheme 4). In other words, the aminophosphine ligand does not act as a “proton messenger”, unlike the pyridinylphosphine ligand in the palladium catalyzed alkyne methoxy-carbonylation process.<sup>2</sup> Furthermore, this result also excludes the possibility of a binuclear aldehyde elimination process between a rhodium acyl and a rhodium hydride species,<sup>39,40</sup> for this system. These observations are summarized in Scheme 4.

### Scheme 4



The hydrogen atom that becomes part of the formyl group must derive from the H<sub>2</sub> molecule involved in the hydrogenolysis step. As discussed in our recent contribution,<sup>18</sup> hydrogenolysis could occur either by H<sub>2</sub> oxidative addition followed by aldehyde reductive elimination with a Rh(III) dihydride intermediate (A), or by H<sub>2</sub> heterolytic splitting via a zwitterionic ammonium-hydride

complex (**B**), see Scheme 5. In either case, the aldehyde release from the intermediate must be faster than the H/D exchange at the site that ultimately delivers the H atom to the formyl unit.



The most unexpected result of our investigation, however, is the observation of the  $\alpha$ -D<sub>1</sub> and  $\alpha,\beta$ -D<sub>2</sub> products for the [RhCl(COD)]<sub>2</sub>/Ph<sub>2</sub>PCH(Ar)NPh catalytic system (Table 1, runs 5 and 6). A possible pathway for the D-incorporation from D<sub>2</sub>O at the  $\alpha$ -position could in principle involve a  $\beta$ -elimination reaction from the Rh-acyl complex leading to a ketene-hydride intermediate. After Rh-H/Rh-D isotopic exchange with D<sub>2</sub>O and subsequent ketene insertion, the Rh-acyl complex with deuterium atom at the  $\alpha$ -position could be obtained. However, this mechanism is unlikely for three different reasons. The first one is that the high reactivity of ketene toward water<sup>41</sup> should lead to the related acid, which is not detected in NMR spectra. The second reason is that such a mechanism should lead to aldehydes without any e.e.

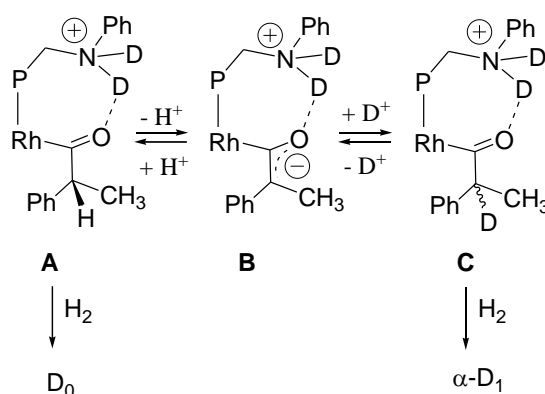
Additional catalytic runs were performed with complexes RhCl(COD)(*S,S*- $\alpha$ -P,N) and Rh(acac)(CO)(*S,S*- $\alpha$ -P,N) prepared *in situ* from the chiral ligand [*S,S*- $\alpha$ -P,N = (*S*<sub>Ar</sub>,*S*<sub>C</sub>)-Ph<sub>2</sub>PCH(*o*-C<sub>6</sub>H<sub>4</sub>Cl(Cr(CO)<sub>3</sub>))NPh]<sup>17</sup> and the rhodium precatalysts [RhCl(COD)]<sub>2</sub> and

Rh(acac)(CO)<sub>2</sub>, respectively. These tests, run either with RhCl(COD)(*S,S*- $\alpha$ -P,N) in CHCl<sub>3</sub> or with Rh(acac)(CO)(*S,S*- $\alpha$ -P,N) in C<sub>6</sub>H<sub>6</sub>, gave (*S*)-2-phenylpropanal with 7% and 14% e.e., respectively. In order to verify that the low e.e. are not merely the consequence of racemization under our catalytic conditions, (*R*)-2-phenylpropanal was heated at 55°C in CHCl<sub>3</sub> for one day. No significant change of the e.e. was observed. Thirdly, it is not possible to easily rationalize why the H/D exchange at the  $\alpha$  position via the ketene intermediate would only be promoted by the [RhCl(COD)]<sub>2</sub>/Ph<sub>2</sub>PCH(Ar)NHPPh combination. Note that changing the P,N ligand to a more basic one (run 8), or changing the precursor to the acetylacetonate complex (run 7) suppresses this phenomenon.

The catalyst modifications alluded to above have an effect on the state of protonation of the dangling nitrogen atom, thus suggesting a direct role of this function in the H/D exchange at the  $\alpha$  position. Therefore, a possible pathway for the formation of the  $\alpha$ -D<sub>1</sub> and  $\alpha,\beta$ -D<sub>2</sub> products in runs 5 and 6 could be based on the equilibrium between the Rh-acyl intermediate and its related enolate form (**A** and **B** in Scheme 6), with assistance by the ammonium function via hydrogen bonding. This assistance requires the presence of a proton-bearing ammonium functionality with sufficient acidity, thereby explaining the absence of this phenomenon when using the acetylacetonate precatalyst (the dangling amine is not protonated) or for more basic P,N ligand (insufficient acidity for the resulting ammonium function). The decreased amount of  $\alpha$ -D<sub>1</sub> aldehyde from 15 to 4% when an addition external base is added to this catalytic system (from run 5 to run 6) is also consistent with this mechanistic proposal. A control experiment carried out under the same temperature and pressure conditions of run 5, in the presence of a catalytic amount of [PhND<sub>3</sub>][BF<sub>4</sub>] (0.1% vs the aldehyde), but without the rhodium complex and the phosphine, shows no observable  $\alpha$ -D incorporation. However, ca. 50% conversion to the  $\alpha$ -D<sub>1</sub> aldehyde occurred when a higher amount of deuterated ammonium salt (20% vs the aldehyde) was used under similar conditions (see Figure 2b). Thus, H/D exchange at the  $\alpha$  position can indeed occur in the presence of a sufficiently strong acid. Note that PhND<sub>3</sub><sup>+</sup> is a stronger acid than the dangling Ph<sub>2</sub>PCH(Ar)NPhH<sub>2</sub><sup>+</sup> function and

yet it is a less effective H/D exchange catalyst than the protonated, rhodium-coordinated aminophosphine. This suggests cooperativity between the ammonium function and the metal center.

**Scheme 6**



At this point, the enolate anion **B** can be protonated by either  $\text{H}^+$  or  $\text{D}^+$ , originating from water or from the  $-\text{ND}_2\text{Ph}^+$  fragment, leading to **A** or **C**. Further hydrogenolysis liberates the  $\text{D}_0$  and  $\alpha\text{-D}_1$  aldehydes, respectively. On the basis of the basic properties of the dangling amine function, one would expect that the  $[\text{RhCl}(\text{COD})]_2/\text{Ph}_2\text{PCH}_2\text{NPh}_2$  (run 4) should also lead to H/D exchange at the  $\alpha$  position, whereas no  $\alpha\text{-D}_1$  product is observed in this case. This result is probably associated with the insufficient basicity of the N atom (*e.g.* the  $\text{pK}_a$  of  $\text{Ph}_2\text{NH}_2^+$  is 0.8 vs 4.85 for  $\text{PhNH}_2\text{Me}^+$ ). Thus, the liberated HCl would be trapped by the aqueous solvent in this case, rather than by the dangling amine group.

It is to be noted that Rh-enolate intermediates have also been proposed in catalytic aldolisation reactions or in one-pot catalytic tandem/aldol condensation, but in both cases the enolate moiety adopts a  $\eta^1\text{-O}$  coordination mode rather than a  $\eta^1\text{-C}$  one.<sup>42,43</sup> The H/D exchange process on the Rh-acyl, according to the proposed scheme 6, must necessarily be associated to an intramolecular racemization before the aldehyde liberation by hydrogenolysis. In this respect, there is a correlation between the production of  $\alpha\text{-D}_1$  aldehyde for run 5 (and its absence for run 7) in



Table 1 and the reduced enantioselectivity observed with the  $\text{RhCl}(\text{COD})(S,S\text{-}\alpha\text{-P,N})$  precatalyst vs the  $\text{Rh}(\text{acac})(\text{CO})(S,S\text{-}\alpha\text{-P,N})$  precatalyst in chloroform (discussed above).

## Conclusion

The isotopic composition of aldehyde, obtained by styrene hydroformylation using  $\text{Rh}\text{-}\alpha\text{-P,N}$  catalytic systems in the presence of  $\text{D}_2\text{O}$ , allows us to draw new stereochemical and mechanistic information of this catalytic reaction. Specifically, the absence of  $\text{PhCH}(\text{CDO})\text{CH}_3$  in all cases shows that the rhodium-acyl intermediate does not release the aldehyde product by a protonolysis process, nor by bimetallic reductive elimination. The presence of  $\text{PhCD}(\text{CHO})\text{CH}_3$  in only one catalytic experiment shows, for the first time, that a Rh-acyl racemization may be catalyzed in the presence of certain ligands. An intramolecular H-interaction between the ammonium and Rh-enolate moieties is proposed to be responsible for this process, leading to M-acyl racemization before the reductive elimination step. This is a new phenomenon to be considered for the design of new ligands for use in the efficient and highly enantioselective branched hydroformylation process. It should also be considered for the extension of existing rhodium catalyzed asymmetric hydroformylation processes to ionic liquid media such as imidazolium or ammonium salts.

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## Experimental Section

### General procedures

All manipulations were carried out under purified argon and in the dark using standard Schlenk techniques. All solvents were dried and deoxygenated by standard methods and distilled under dinitrogen prior to use.  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR measurements were carried out with a Bruker AC300 spectrometer. The peak positions are reported with positive shifts in ppm downfield of TMS as calculated from the residual solvent peaks. The commercial compounds  $\text{PPh}_3$ ,  $\text{Ph}_2\text{NH}$ ,  $[\text{RhCl}(\text{COD})]_2$ ,  $[\text{Rh}(\text{acac})(\text{CO})_2]$  and  $[\text{Rh}(\text{CO})_2\text{Cl}]_2$  were used as received without further purification. The ligands  $\text{Ph}_2\text{PCH}_2\text{NEt}_2$ ,  $\text{Ph}_2\text{PCH}_2\text{NPh}_2$ ,  $\text{Ph}_2\text{PCH}(\text{Ar})\text{NHPH}$  [ $\text{Ar} = o\text{-C}_6\text{H}_4\text{Cl}(\text{Cr}(\text{CO})_3)$ ], were prepared according to the literature.<sup>11,15,44,45</sup> The preparation of optically pure version of the latter ligand, (*S,S*)-**1**, has been previously reported<sup>11</sup> The synthesis of complex  $[\text{RhCl}(\text{COD})(\alpha\text{-P,N})]$  **1** with  $\alpha\text{-P,N} = \text{Ph}_2\text{PCH}(o\text{-C}_6\text{H}_4\text{Cl}[\text{Cr}(\text{CO})_3])\text{NHPH}$  has previously been described.<sup>17</sup> The (*R*)-2-phenylpropanal was prepared by oxidation reaction using the Dess-Martin reagent<sup>46</sup> from commercially available (*R*)-2-phenyl-1-propanol (Aldrich) according to a previously described procedure<sup>47</sup> (e.e. = 93% by use of the NMR chiral shift reagent  $[\text{Eu}(\text{hfc})_3]$ , according to the literature<sup>48</sup>).

### Catalytic runs

The hydroformylation reactions were carried out in a 300-mL stainless-steel Parr autoclave equipped with a magnetic drive, an internal glass vessel, and an immersion tube connected to a valve for solution withdrawals under pressure. The temperature was controlled by a rigid heating mantle and a single loop cooling coil. The autoclave was purged three times under vacuum/argon before introducing the catalytic solution (see Table 1). The 1:1  $\text{CO}/\text{H}_2$  mixture was prepared by mixing the pure gases in a 500-ml stainless steel cylinder before introduction into the autoclave at the desired pressure (see Table 1). The zero time for kinetic runs was considered as the time at which the desired pressure was reached inside the autoclave. In order to maintain temperature and pressure conditions as constant as possible during each kinetic run, only a few mL of catalytic

solution mixture were carefully withdrawn each time from the autoclave. The THF solvent was then rotary evaporated at room temperature and the yellow-orange residue was analyzed by proton and carbon NMR spectroscopies. For the product obtained in the presence of the optically active catalyst, the *e.e.* as well as the absolute configuration of the enantiomer were determined by use of the NMR chiral shift reagent [Eu(hfc)<sub>3</sub>], according to the literature.<sup>48</sup>

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