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Ruthenium catalyzed regioselective hydrophosphination of propargyl alcohols

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Received (in Cambridge, UK) 17th December 2002, Accepted 5th February 2003
First published as an Advance Article on the web 17th February 2003

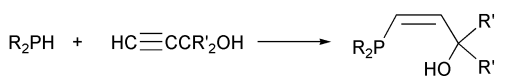
Catalytic hydrophosphination of propargyl alcohols by ruthenium complexes $RuCl(cod)(C_5Me_5)$ and $RuCl(PPh_3)_2(C_5Me_5)$ leads to the formation of functionalized vinylphosphines, with linkage of the phosphorus atom to the terminal alkyne carbon, *via* a ruthenium vinylidene intermediate.

Alkenylphosphines are attracting interest as building blocks in organic synthesis and as useful ligand precursors for catalysis.[1,2] The synthesis of vinylphosphines is generally achieved by the reaction of halophosphines with vinylmagnesium or lithium derivatives which do not tolerate functional groups.[3] Two alternatives have been described: the direct addition of secondary phosphines to alkynes which requires prolonged heating and leads to isomer mixtures, and radical chains reactions.[3] Recently, metal-catalysed additions of P–H bonds to alkynes have offered control over both regio- and stereoselectivity leading to alkenylphosphines.[4] Palladium and platinum catalysts favour the anti-Markovnikov addition of diphenylphosphine oxide to alkynes,[5] and the regioselectivity is reversed by addition of phosphinic acid $R_2P(O)OH$,[6] whereas rhodium(I) catalysts lead to the formation of *E*-alkenylphosphine oxides or phosphonates.[7] The catalytic addition of secondary phosphines HPR_2 to non-functional alkynes is just emerging. It is performed by lanthanides,[8] palladium and nickel catalysts,[9] for the preferred production of alkenylphosphines with addition of the phosphorus atom to the internal alkyne carbon. All the above hydrophosphinylation and hydrophosphination processes were shown to take place *via* insertion of the alkyne into M–H or M–PR_2 bonds. To our knowledge, no example of catalytic hydrophosphination of functional alkynes has been reported in spite of its potential for a new direct route to a wide range of polydentate ligands.

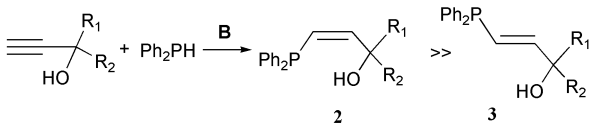
We now report the first example of direct hydrophosphination of propargyl alcohols in the presence of diphenylphosphine catalysed by ruthenium complexes $RuCl(PPh_3)_2(C_5Me_5)$ (**A**) and $RuCl(cod)(C_5Me_5)$ (**B**). This highly regioselective reaction affords in one step functionalised vinylphosphines with P–CH= bond formation *via* a vinylidene ruthenium intermediate (Scheme 1).

Whereas most ruthenium(II) complexes activate propargyl alcohols *via* metal allenylidene intermediates $Ru{=}C{=}C{=}CR_2$,[10] $RuCl(PPh_3)_2(C_5Me_5)$ (**A**), in the presence of NH_4PF_6, stoichiometrically reacts with propargyl alcohols to give the vinylidene derivative $Ru(=C=CHCR_2OH)(PPh_3)_2(C_5Me_5)$-$PF_6$[11] and ruthenium vinylidene intermediates are well known to favour nucleophilic addition to the Ru=C carbon atom.[12] Consequently, the addition of diphenyphosphine to *in situ* generated vinylidene has been attempted.

1-Ethynyl-1-cyclohexanol **1a** was reacted with 1.2 equivalents of diphenylphosphine in previously neutralised chloroform, by treatment with Na_2CO_3, in the presence of 5 mol% of complex (**A**) and NH_4PF_6. After 24 hours at reflux, complete



Scheme 1



	yield [%][b]	2a-d (Z) / 3a-d (E)[c]
1a: $R_1 = R_2 = -(CH_2)_5-$	70	95 / 5
1b: $R_1 = R_2 =$ Me	81	75 / 25
1c: $R_1 = R_2 =$ Et	55	75 / 25
1d: R_1 = Me; $R_2 = i$Bu	50	80 / 20

[a] Complete GC conversion after 20-24h
[b] Isolated yields of **2** and **3** after SiO_2 chromatography
[c] ratio *Z*/*E* was determined by ^{1}HNMR
B = $RuCl(cod)(C_5Me_5)$

Scheme 2

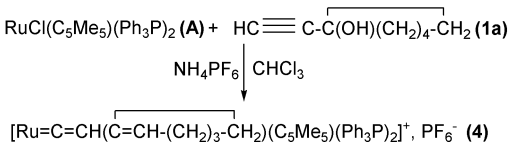
conversion of **1a** led to a mixture of the stereoisomers **2a** and **3a** (*Z*/*E* = 85/15).

Several catalytic systems such as $RuCl(L)_2(C_5R_5)$ (R = H, Me) (L = PPh_3, cod) and diphenylphosphine with $NaPF_6$, NH_4PF_6 or Na_2CO_3 were tested, and we rapidly observed that $RuCl(cod)(C_5Me_5)$, with diphenylphosphine in the presence of Na_2CO_3 in chloroform, generated the best catalyst system for this hydrophosphination.

The reaction of propargyl alcohols **1a**–**d** with diphenylphosphine in $CHCl_3$, in the presence of catalytic amounts of $RuCl(cod)(C_5Me_5)$ (**B**) (5 mol%) and Na_2CO_3 (10 mol%), leads after 20–24 h at reflux to complete conversion of **1** and the production of the two stereoisomer vinylphosphines **2a**–**d** (*Z*) and **3a**–**d** (*E*) (Scheme 2).[13] The ratio *Z*/*E* was determined by ^{1}H NMR. Only P–CH= bond formation was observed demonstrating the selective anti-Markovnikov addition of the H–P(III) bond across the alkyne. The reaction is also stereoselective as the *Z* isomer is always preferentially formed. For the derivative **2** with *Z* configuration, ^{1}H NMR spectroscopy indicates an O–H···P interaction between the hydroxy group proton and the phosphorus atom (**2a**, δ = 3.18 ppm and J(H,P) = 11.7 Hz for the hydroxy proton). Chromatography of the **2**–**3** mixture led to an increase of the *E*/*Z* ratio, and by using silica gel or basic and neutral alumina a fast complete isomerisation of **2** to **3** was observed. Monitoring the transformation of **2d**/**3d** by ^{1}H NMR showed that a *Z*/*E* ratio of 4/1 is approximately constant during the reaction.

In order to gather information about the reaction mechanism several experiments were carried out. $RuCl(cod)(C_5Me_5)$ (**B**) in the presence of two equivalents of $HPPh_2$ and NH_4PF_6 in chloroform at room temperature has its cod ligand displaced and gives $[Ru(C_5Me_5)(Ph_2PH)_2]^+PF_6^-$ $(\mathbf{C})^+$. The intermediate $(\mathbf{C})^+$ formation was monitored by ^{31}P NMR: after a few minutes of reaction in chloroform, we observed the complete coordination of the two secondary phosphines on the ruthenium center (δ = +37.8 ppm *vs.* δ = −39 ppm for the free secondary phosphine). The stoichiometric reaction of (**A**) with **1a** and NH_4PF_6 in chloroform led to the isolation of vinylidene complex (**4**) resulting from the dehydration of the ruthenium activated propargyl alcohol (Scheme 3).

DOI: 10.1039/b212408d



Scheme 3

This observation shows the role of Na_2CO_3 is simply to inhibit dehydration of the vinylidene intermediate in the catalytic cycle. The complex (**4**) is also catalytically active under the general reaction conditions (Scheme 2) with 10% Na_2CO_3.

Based on these results, the catalytic cycle from precursor (**B**) is likely to proceed as indicated in Scheme 4: i) formation of intermediate $[Ru(C_5Me_5)(Ph_2PH)_2]^+X^-$ (**C**)$^+$, identified by spectroscopy for $X^- = PF_6^-$, ii) formation of the unstable vinylidene (**D**), analogous to the dehydrated isolated complex (**4**) arising from (**A**), iii) addition of an external Ph_2PH to the electrophilic vinylidene carbon of (**D**).

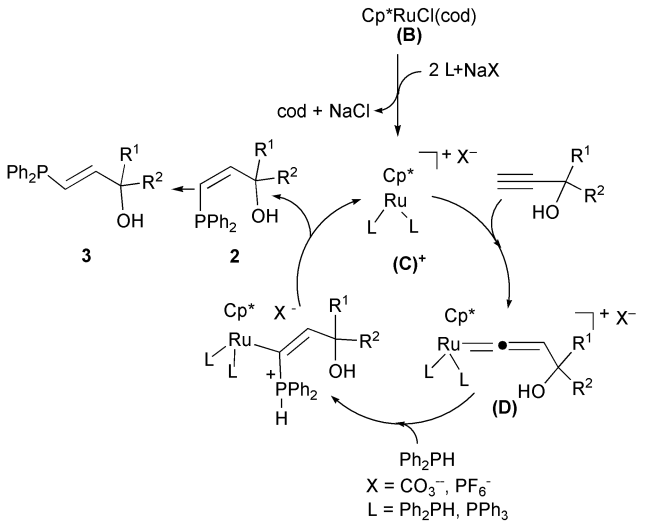
The stereoselectivity of the reaction dramatically depends on the nature of the propargylic alcohol substituents R_1 and R_2 and on the nature of the ruthenium(II) catalyst precursors. With the Cp^*RuXL_2 catalyst precursors (**A**) and (**B**), the *Z* isomer is always obtained as the major product, whereas in the case of $CpRuXL_2$ precursors we observed by contrast the major formation of the *E* isomer (Table 1).

This difference of stereoselectivity is likely due to the steric hindrance of the C_5R_5 group and also of the propargyl alcohol groups. Indeed, the Scheme 2 results indicate that the bulkier cyclohexyl substituent leads to the higher **2a**/**3a** ratio (95/5).

In order to show that the reaction is not restricted to propargyl alcohols but can also be performed with vinylidene precursors, an initial study of the hydrophosphination of terminal alkynes RC≡CH (R = Ph, Bu, $SiMe_3$) has been carried out. It also leads to the corresponding alkenylphosphines $Ph_2PCH{=}CHR$ with stereoselective formation of the *Z* isomer (*Z*/*E* = 93/7 for R = Ph).

However the corresponding hydrophosphination of alkynes with internal C≡C bonds cannot be achieved (*e.g.* CH_3–C≡C–C_6H_5), thus again supporting the vinylidene intermediate.

The above results show a novel catalytic method to prepare alkenylphosphines with hydroxy functionality *via* regioselective hydrophosphination of propargyl alcohols. This reaction, that is catalysed by $RuX(L)_2C_5Me_5$ complexes and proceeds *via* the formation of a vinylidene intermediate, has potential for access to new bifunctional phosphorus ligands.



Scheme 4

Table 1 Influence of the catalyst on the hydrophosphination of **1a**[a]

Catalyst	Selectivity **2a**/**3a**[b]
$RuCl(C_5Me_5)(cod)$	95/5
$Ru(C_5Me_5)(CH_3CN)_3PF_6$	80/20
$RuCl(C_5Me_5)(PPh_3)_2$	85/15
$Ru(C_5H_5)(CH_3CN)_3PF_6$	35/65
$RuCl(C_5H_5)(PPh_3)_2$	45/55

[a] Conditions as in Scheme 2. Complete GC conversion after 20–24 h. [b] Ratio *Z*/*E* was determined by ^{1}H NMR.

This work was supported by the CNRS and the Ministère de la Recherche. The authors are grateful to the latter for a PhD grant to F. M. and to the European Union for support *via* the Cost Program D17 and Socrates Program Exchange for H. L. with the University of Poznan (Poland).

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13 Selected data: **2a** :^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.23–7.44 (m, 10H, Ph), 6.58 (dd, *J*(H,H) = 12.3 Hz, *J*(H,P) = 27.5 Hz, 1H; CH), 6.19 (dd, *J*(H,H) = 12.3 Hz, *J*(H,P) = 3.4 Hz, 1H; CH), 3.18 (d, *J*(H,P) = 12.1 Hz, 1H; OH), 1.38–1.79 (m, 10H, $(CH_2)_5$). ^{31}P NMR (81 MHz, $CDCl_3$, 25 °C) δ = −28.3 ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ = 21.9 (s, CH_2), 25.3(s, CH_2), 38.9 (s, CH_2), 74.2 (s, C–OH), 125.3 (d, *J*(C,P) = 12.2 Hz; CH=), 128.6 (d, *J*(C,P) = 7.2 Hz; Ph), 128.6 (s, Ph), 132.6 (d, *J*(C,P) = 18.3 Hz; Ph), 138.9 (d, *J*(C,P) = 7.3 Hz; Ph), 154.3 (d, *J*(C,P) = 16.0 Hz; –CH=). **3a**: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ = 7.22–7.50 (m, 10H, Ph), 6.49 (dd, *J*(H,H) = 16.8 Hz, *J*(H,P) = 6.9 Hz, 1H; CH), 6.27 (dd, *J*(H,H) = 16.8 Hz, *J*(H,P) = 14.8 Hz, 1H; CH), 1.39–1.81 (m, 10H, $(CH_2)_5$). ^{31}P NMR (81 MHz, $CDCl_3$, 25 °C) δ = −12.9 ppm. HRMS calcd. for $C_{20}H_{23}OP$ 310.14865, found 310.14794.