Hydrophilic (η^6-arene)-ruthenium(II) complexes with P-OH ligands as catalysts for the isomerization of allyl-benzenes and C-H bond arylation reactions in water

Rebeca González-Fernández, Pascale Crochet,* and Victorio Cadierno*

Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Centro de Innovación en Química Avanzada (ORFEO-CINQA), Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles", Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain

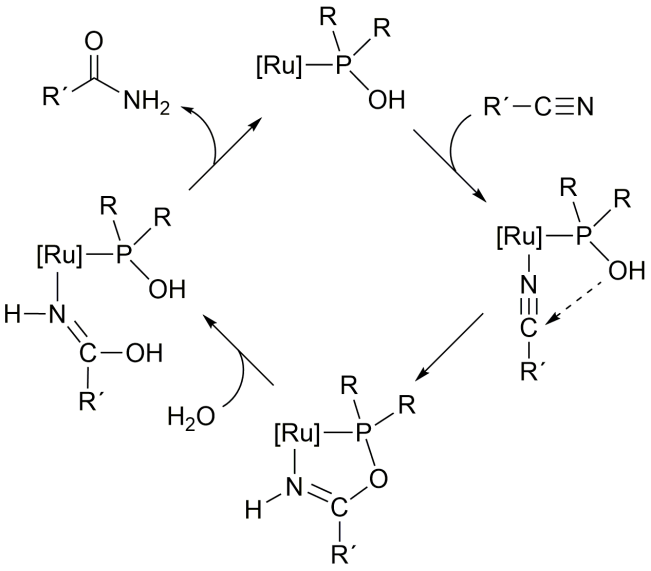
* To whom correspondence should be addressed. E-mail: crochetpascale@uniovi.es (P.C.); vcm@uniovi.es (V.C.).

Abstract

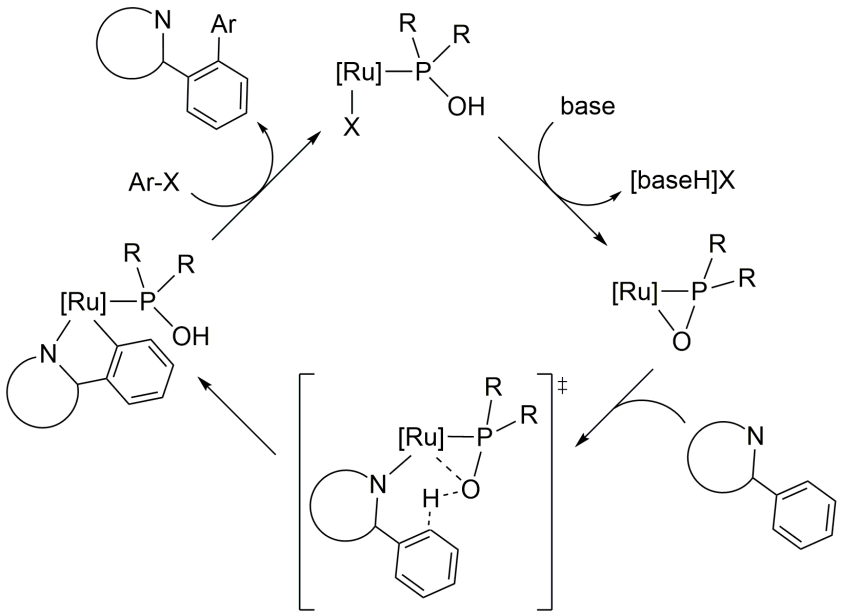
Half-sandwich ruthenium(II) complexes containing η^6-coordinated 3-phenylpropanol and phosphinous acid-type ligands, namely [$RuCl_2$(η^6-$C_6H_5CH_2CH_2CH_2OH$){$P(OH)R_2$}] (R = Me (**2a**), Ph (**2b**), 4-$C_6H_4CF_3$ (**2c**), 4-C_6H_4OMe (**2d**), OMe (**2e**), OEt (**2f**), OPh (**2g**)), have been synthesized in 44-88% yield by reacting [$RuCl_2${η^6:κ^1*(O)*-$C_6H_5CH_2CH_2CH_2OH$}] (**1**) with the appropriate pentavalent phosphorous oxide $R_2P(=O)H$. The structure of [$RuCl_2$(η^6-$C_6H_5CH_2CH_2CH_2OH$){$P(OH)Me_2$}] (**2a**) was unequivocally confirmed by X-ray diffraction methods. Compounds **2a-g** proved to be catalytically active in the isomerization of allylbenzenes into the corresponding (1-propenyl)benzene derivatives employing water as the sole reaction solvent, with [$RuCl_2$(η^6-$C_6H_5CH_2CH_2CH_2OH$){$P(OH)(OPh)_2$}] (**2g**) showing the best performance and a broad substrate scope (73-93% isolated yields with *E/Z* ratios around 90:10 employing 1 mol% of **2g**, 3 mol% of K_2CO_3, and performing the catalytic reactions at 80 ºC for 4-24 h). The results herein presented show for the first time the utility of phosphinous acids as auxiliary ligands for metal-catalyzed olefin isomerization processes, reactions in which a cooperative role for the P-OH unit is proposed. On the other hand, the utility of complexes **2a**-**g** as catalysts for *ortho*-arylation reactions of 2-phenylpyridine in water is also briefly discussed.

Introduction

Phosphinous acids PR_2OH (R = alkyl or aryl groups) and their heteroatom-substituted counterparts, *i.e.* compounds $P(OR)_2OH$ and $P(NR_2)_2OH$, have emerged in recent years as a useful class of auxiliary ligands in homogeneous catalysis.[1] In particular, ruthenium complexes containing this type of ligands have led to relevant results in catalytic nitrile hydration reactions[2] and directing-group-assisted C-H bond arylation processes,[3] with mechanistic investigations pointing to a cooperative effect of the P-OH ligands in both transformations.[4] Thus, density functional theory (DFT) calculations on the ruthenium-catalyzed nitrile hydrations indicated that the reactions proceed through the initial formation of a five-membered metallacyclic intermediate by intramolecular addition of the phosphinous acid to the ruthenium-coordinated nitrile, the subsequent hydrolysis of the metallacycle leading to the final amide product (Scheme 1).[2b,d,5] In the case of the C-H bond arylation processes, computational studies performed by Ackermann and co-workers revealed that the phosphinous acid ligands facilitate the key C-H cleavage step.[3d] Thus, as shown in Scheme 2, under the basic conditions required in this type of reactions, the phosphinous acid is transformed into the corresponding phosphinito anion PR_2O^-, which is responsible for the abstraction of the *ortho*-aryl proton.

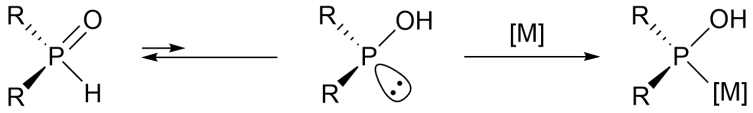


Scheme 1. The cooperative effect of phosphinous acid ligands in Ru-catalyzed nitrile hydration.



Scheme 2. Cooperative effect of PR_2OH ligands in Ru-catalyzed C-H bond arylation processes.

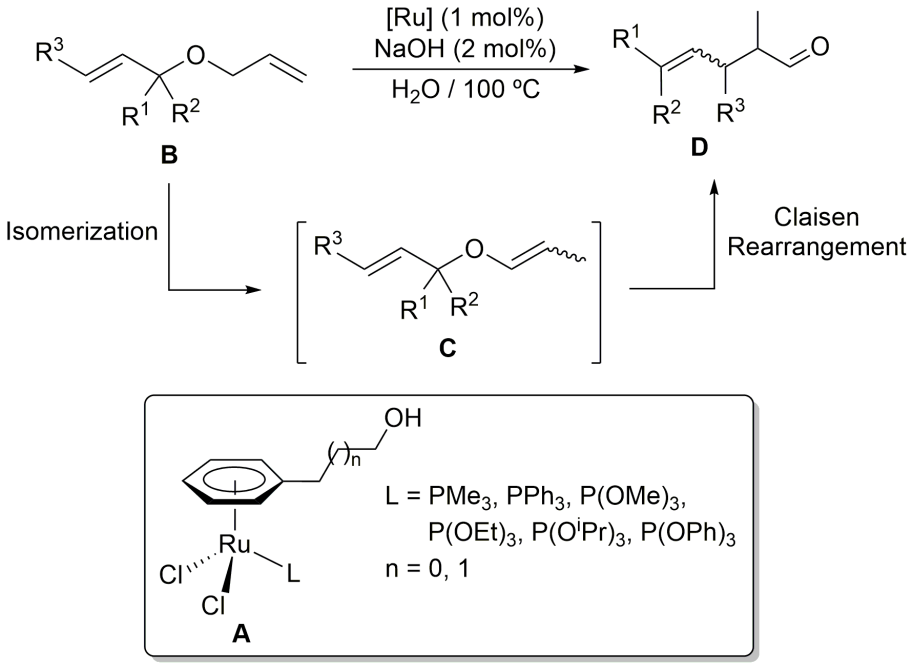
Concerning their preparation, transition metal complexes with phosphinous acids and related P-OH ligands are usually generated by reacting the appropriate metallic precursor with a pentavalent phosphorous oxide (Scheme 3).[1,4,6] In solution, these air-stable compounds exist in equilibrium with their trivalent tautomers, which is driven towards the latter by coordination to the metal center. Although much less employed, alternative methods of synthesis involving the hydrolysis of P-C, P-Cl, P-N or P-OR bonds in coordinated phosphines, chlorophosphines, aminophosphines and phosphites, respectively, are also known.[4,7]



Scheme 3. Synthesis of metal complexes with phosphinous acid ligands from secondary phosphine oxides.

Very recently, we reported that hydrophilic arene-ruthenium(II) complexes containing η^6-coordinated 2-phenylethanol and 3-phenylpropanol ligands [$RuCl_2\{\eta^6$-$C_6H_5CH_2(CH_2)_nCH_2OH\}(L)$] (n = 0, 1; L = phosphine or phosphite; **A**) are able to catalyze, in combination with NaOH, the transformation of diallyl ether derivatives **B** into synthetically useful γ,δ-unsaturated aldehydes **D** in water (Scheme 4).[8] The process

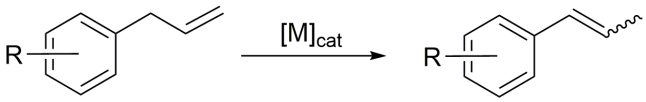
involves the initial Ru-catalyzed isomerization of the diallyl ether substrates **B** into the corresponding allyl vinyl ethers **C**, followed by a thermal Claisen rearrangement of **C** into the final products **D**.



Scheme 4. Ru-catalyzed isomerization/Claisen rearrangement of diallyl ethers in water.

Of the different ruthenium complexes **A** employed as catalysts, those containing phosphite ligands $P(OR)_3$ resulted more effective than their phosphine PR_3 counterparts.[8] NMR experiments carried out with aqueous solutions of these compounds evidenced a different behavior upon addition of NaOH. Thus, while the phosphite-containing complexes evolved into metallic species containing coordinated $P(OR)_2OH$ units, due to the base-promoted hydrolysis of the $P(OR)_3$ ligands, the addition of NaOH to aqueous solutions of the phosphine ones led mainly to Cl^-/OH^- metathesis processes. Accordingly, we assumed that the higher catalytic activity of the phosphite derivatives was related with the *in situ* formation of $P(OR)_2OH$-containing complexes which could act as the real active species for the initial C=C bond migration step. This fact, along with the lack of previous investigations on the application of phosphinous acids as ligands in metal-catalyzed olefin isomerization processes,[1] prompted us to synthesize analogous arene-ruthenium(II) complexes with this type of ligands and evaluate their catalytic potential. The isomerization of allylbenzene derivatives (Scheme 5) was

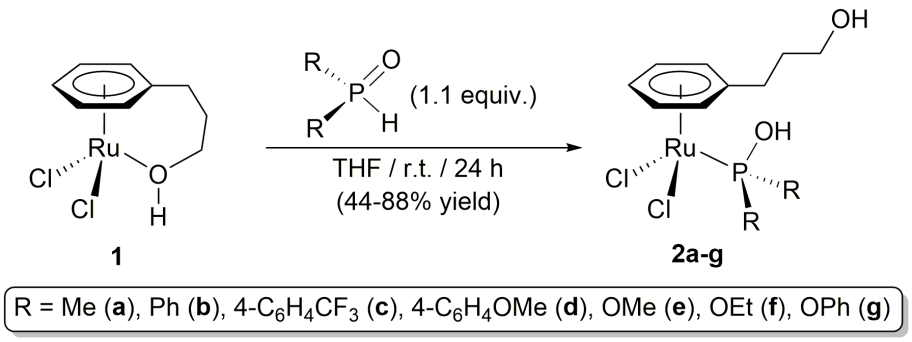
chosen as model reaction given their ease of access and the high interest of the process from both academic and industrial points of view, because the resulting (1-propenyl)benzene products are relevant synthetic intermediates in organic chemistry, and also because they usually feature biological activity and applicability in the production of pesticides, fragrances, cosmetics, flavors and pharmaceuticals.[9] The catalytic behavior of the synthesized Ru(II) complexes in the *ortho*-arylation of 2-phenylpyridine was also evaluated, employing for both catalytic transformations environmentally friendly water as solvent. The results derived from these studies are presented herein.



Scheme 5. The metal-catalyzed isomerization of allylbenzenes.

Results and Discussion

In our previous work on the isomerization/Claisen rearrangement of diallyl ethers **B** using the ruthenium(II) derivatives **A** as catalysts (Scheme 4), we found that the nature of the η^6-coordinated arene ligand, *i.e.* 2-phenylethanol (n = 0) or 3-phenylpropanol (n = 1), did not exert any effect on the catalytic activity of the complexes.[8] That is why in the present study we focused exclusively on η^6-3-phenylpropanol derivatives given the more convenient and higher-yield access to the corresponding precursor [$RuCl_2\{\eta^6$:κ^1*(O)*-$C_6H_5CH_2CH_2CH_2OH\}$] (**1**).[10] Thus, as shown in Scheme 6, a series of [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)R_2\}$] complexes containing symmetrically substituted phosphinous (**2a-d**) and phosphorous acid (**2e-g**) ligands could be synthesized by treatment of THF solutions of **1** with the corresponding secondary phosphine oxide or *H*-phosphonate, respectively, the reactions involving the previously commented P(=O)H to P-OH tautomerization process (Scheme 3). As expected due to the presence of two OH groups in their structures, compounds **2a-g**, which were isolated as air-stable orange solids in moderate to high yield (44-88%), are perfectly soluble in water and other polar solvents, such as alcohols, DMSO or acetone,[11a] and completely insoluble in *n*-alkanes or diethyl ether.



Scheme 6. Synthesis of the arene-ruthenium(II) complexes **2a-g**.

Complexes **2a-g** were characterized by elemental analyses, IR, and multinuclear NMR spectroscopy (details are given in the Experimental Section).[11b] In this regard, the $^{31}P\{^{1}H\}$ NMR spectra evidenced the clean formation of a unique phosphorus-containing product, featuring a singlet resonance strongly deshielded ($\Delta\delta$ = 84.7-114.6 ppm) with respect to that of the starting ligand precursor $R_2P(=O)H$ (see Table 1). As previously found in the related complexes **A** (Scheme 4),[8] the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **2a-g** showed the equivalence of the CH_{ortho} and CH_{meta} protons and carbons of the η^6-coordinated 3-phenylpropanol units, consistent with the presence of a symmetry plane in the complexes. A broad resonance at δ_H 2.90-3.40 ppm, assigned to the OH group of the 3-phenylpropanol ligand, was also observed in the ^{1}H NMR spectra of all these compounds, not finding on the contrary those corresponding to the P-OH units.[12] Nonetheless, two distinguishable ν(OH) absorption bands (in the range 3207-3421 cm^{-1}) were found in their IR spectra.

Table 1. $^{31}P\{^{1}H\}$ NMR data for compounds $R_2P(=O)H$ and complexes **2a-g**.

$R_2P(=O)H$	δ_P[a]	Complex **2**	δ_P[b]
$Me_2P(=O)H$	23.2 ppm	**2a**	118.9 ppm
$Ph_2P(=O)H$	21.8 ppm	**2b**	106.9 ppm
$(4\text{-}C_6H_4CF_3)_2P(=O)H$	17.9 ppm	**2c**	102.6 ppm
$(4\text{-}C_6H_4OMe)_2P(=O)H$	21.0 ppm	**2d**	106.0 ppm
$(MeO)_2P(=O)H$	10.6 ppm	**2e**	118.8 ppm
$(EtO)_2P(=O)H$	7.4 ppm	**2f**	114.7 ppm
$(PhO)_2P(=O)H$	0.4 ppm	**2g**	115.0 ppm

[a] Spectra recorded in $CDCl_3$ at 25 ºC. [b] Spectra recorded in acetone-d_6 at 25 ºC.

A single-crystal X-ray diffraction study on complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)Me_2\}$] (**2a**) unequivocally confirmed the molecular structures proposed for compounds **2a-g**. ORTEP views are shown in Figure 1 along with selected structural parameters.

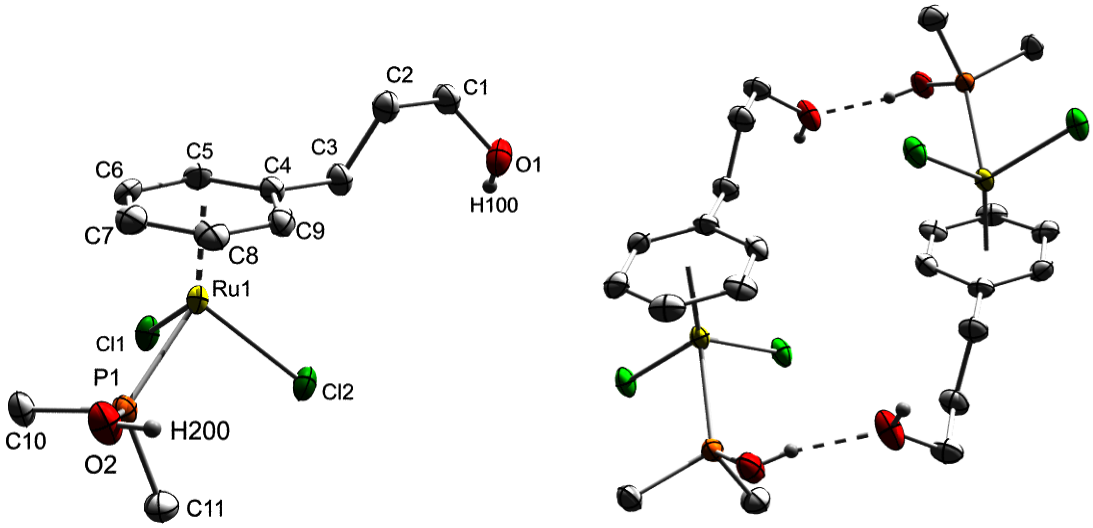


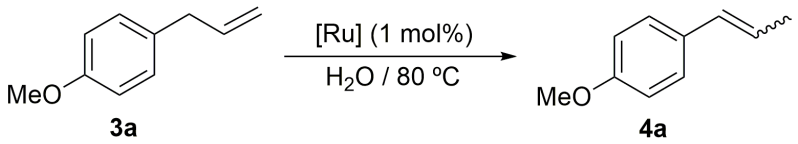
Figure 1. ORTEP-type views of the structure of complex **2a** showing the crystallographic labelling scheme (left) and the intermolecular H-bonding interactions (right). Hydrogen atoms, except those on O(1) and O(2), have been omitted for clarity. Thermal ellipsoids are drawn at the 40% probability level. Selected bond distances (Å) and angles (deg): Ru-C* = 1.6943(3); Ru-Cl(1) = 2.4013(9); Ru-Cl(2) = 2.4270(9); Ru-P(1) = 2.3004(9); P(1)-C(10) = 1.811(4); P(1)-C(11) = 1.797(4); P(1)-O(2) = 1.592(3); C(1)-O(1) = 1.423(5); C*-Ru-P(1) = 128.61(3); C*-Ru-Cl(1) = 126.54(3); C*-Ru-Cl(2) = 125.98(3); Cl(1)-Ru-Cl(2) = 87.16(3); Cl(1)-Ru-P(1) = 84.69(3); Cl(2)-Ru-P(1) = 90.34(3); Ru-P(1)-O(2) = 116.4(1); Ru-P(1)-C(10) = 114.0(1); Ru-P(1)-C(11) = 116.6(2); C(10)-P(1)-C(11) = 103.7(2); C(10)-P(1)-O(2) = 98.8(2); C(11)-P(1)-O(2) = 105.1(2); C* denotes the centroid of arene unit (C(4), C(5), C(6), C(7), C(8) and C(9)).

The complex features a typical three-legged piano-stool geometry, with the ruthenium atom surrounded by the η^6-bonded 3-phenylpropanol molecule, two chlorides, and the phosphorous atom of the dimethylphosphinous acid ligand. The Ru-P(1) and P(1)-O(2) bond lengths observed (2.3004(9) and 1.592(3) Å, respectively) were comparable to those found in the crystal structure of the related species [$RuCl_2(\eta^6$-*p*-cymene)$\{P(OH)Me_2\}$] (Ru-P = 2.3078(1) Å and P-O = 1.613(3) Å).[2a] It is also worthy

of note that, in marked contrast to what is usually observed in the solid state crystal structures of ruthenium(II) complexes of type [$RuCl_2(\eta^6$-arene){$P(OH)R_2$}],[2a,3e,13] no intramolecular H-bonding of the hydroxyl group of the phosphinous acid with the chloride ligands was present in this case. Instead, the P-OH unit is involved in an intermolecular hydrogen bond with the hydroxyl group of the 3-phenylpropanol ligand, thus leading to the formation of dimeric aggregates in the solid state (Figure 1). According to the classification of Jeffrey,[14] the distances and angle of the O(2)-H(200)···O(1) contact (O(2)-H(200) = 0.81(6) Å; O(1)-H(200) = 1.86(6) Å; O(1)-O(2) = 2.645(4) Å; O(2)-H(200)-O(1) = 165(6)º) allow it to be classified as "moderate", basically electrostatic in nature, among the H-bonds considered most common in chemical systems.

With compounds **2a-g** in hands, we next studied their catalytic potential for the isomerization of allyl-benzene derivatives employing estragole **3a** as model substrate (Table 2). A first series of experiments, performed in water at 80 ºC with 1 mol% of **2a-g** and in the absence of any additive, indicated that all of them are catalytically active, providing anethole **4a** as the unique reaction product in ≥ 83% yield after 8 h (entries 1-7).[15] In particular, the best results were obtained with [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH$){$P(OH)(OPh)_2$}] (**2g**), which generated **4a** in almost quantitative yield and with a very high *trans* selectivity (93%; entry 7).[16] In order to determine to what extent the presence of an OH group in the *P*-donor ligand is beneficial for the process, the catalytic behavior of the triphenylphosphite complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH$){$P(OPh)_3$}] (**5**) was explored under identical reaction conditions. As shown in entry 8, although it also turned out to be an active catalyst, its effectiveness was much lower than that of [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH$){$P(OH)(OPh)_2$}] (**2g**). Thus, after 8 h of heating, only 50% conversion of **3a** into **4a** was reached. Interestingly, the kinetic profile of this reaction is characterized by the presence of an induction period, absent in the case of complex **2g**, indicating the slow formation of the real active species in the catalytic cycle (see Figure 2). On the basis of our previous work,[8] we assume that this induction period is associated with the hydrolysis of the coordinated phosphite ligand $P(OPh)_3$ into $P(OH)(OPh)_2$,[17] a slow process at neutral pH that can be accelerated in basic media. In full agreement with this last point, when the aqueous solution containing **5** was pretreated with NaOH (3 equiv.) prior to the addition of the estragole substrate, the profile of the catalytic reaction drastically changed and the conversion of **3a** into **4a** was faster (see Figure 2).

Table 2. Catalytic estragole (**3a**) to anethole (**4a**) isomerization in water using complexes $[RuCl_2(\eta^6\text{-}C_6H_5CH_2CH_2CH_2OH)(L)]$ as catalysts.[a]



3a **4a**

Entry	Catalyst	Time (h)	Yield of **4a** (%)[b]	*E/Z* ratio[b]
1	**2a** (L = $P(OH)Me_2$)	2	29	89:11
		4	56	90:10
		8	83	92:8
2	**2b** (L = $P(OH)Ph_2$)	2	59	85:15
		4	82	88:12
		8	94	89:11
3	**2c** (L = $P(OH)(4\text{-}C_6H_4CF_3)_2$)	2	43	91:9
		4	78	91:9
		8	94	93:7
4	**2d** (L = $P(OH)(4\text{-}C_6H_4OMe)_2$)	2	50	86:14
		4	81	88:12
		8	93	89:11
5	**2e** (L = $P(OH)(OMe)_2$)	2	27	90:10
		4	53	91:9
		8	87	92:8
6	**2f** (L = $P(OH)(OEt)_2$)	2	28	89:11
		4	54	91:9
		8	83	93:7
7	**2g** (L = $P(OH)(OPh)_2$)	2	55	91:9
		4	83	93:7
		8	> 99	93:7
8	**5** (L = $P(OPh)_3$)	2	4	80:20
		4	12	83:17
		8	50	87:13

[a] Reactions performed under argon atmosphere using 2 mmol of **3a**, 0.02 mmol of the corresponding ruthenium complex, and 1 mL of water. [b] Determined by GC (uncorrected GC areas).

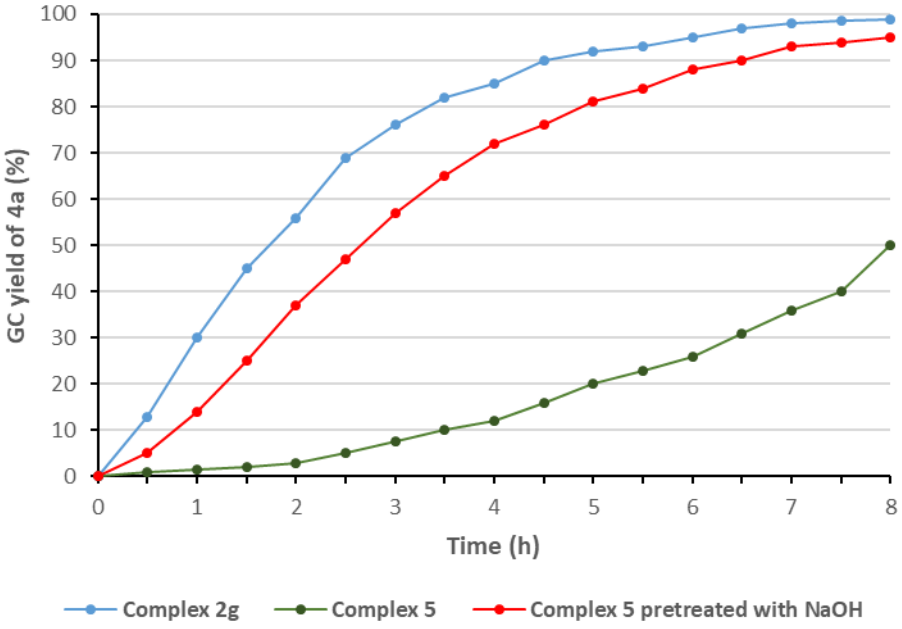
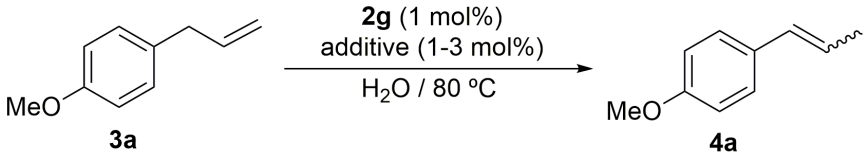


Figure 2. Isomerization of estragole (**3a**) into anethole (**4a**) in water catalyzed by complexes **2g** and **5** as a function of time.

The effect of different additives on the catalytic behavior of the most active complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)(OPh)_2\}$] (**2g**) was next explored, employing again estragole **3a** as model substrate (Table 3). Thus, as shown in entries 1-2, we found that the effectiveness of **2g** is not affected by the addition of the chloride abstractor $AgPF_6$ (1-2 mol%). These observations, along with fact that the isomerization of **3a** into **4a** employing a saturated $NaCl_{(aq)}$ solution as the solvent proceeds with the same efficiency as in pure water (entry 3), seem to indicate that dissociation of the chloride ligands is not required for the binding of the substrate to the metal center.[18] On the other hand, while the addition of HCl to the reaction medium did not lead to significant changes in the activity of **2g** (entries 4 and 5), faster conversions were observed in the presence of NaOH (entries 6-9). In particular, employing 3 mol% of NaOH, quantitative conversion of **3a** into **4a** was reached in only 5 h (entry 8), with a further increase in the NaOH:Ru ratio leading to the same results (entry 9). In additional experiments, the effect of other bases (3 mol%) on the reaction was investigated (see Table S1 in the Supporting Information file), and we found that the use of K_2CO_3 makes possible to shorten in one hour the time needed to completely transform **3a** into **4a**

(entry 10).[19] At this point it should also be noted that, in all the reactions listed in Tables 3 and S1, the *trans*-selectivity at the maximum conversion was almost identical regardless of the additive employed (93-94%).

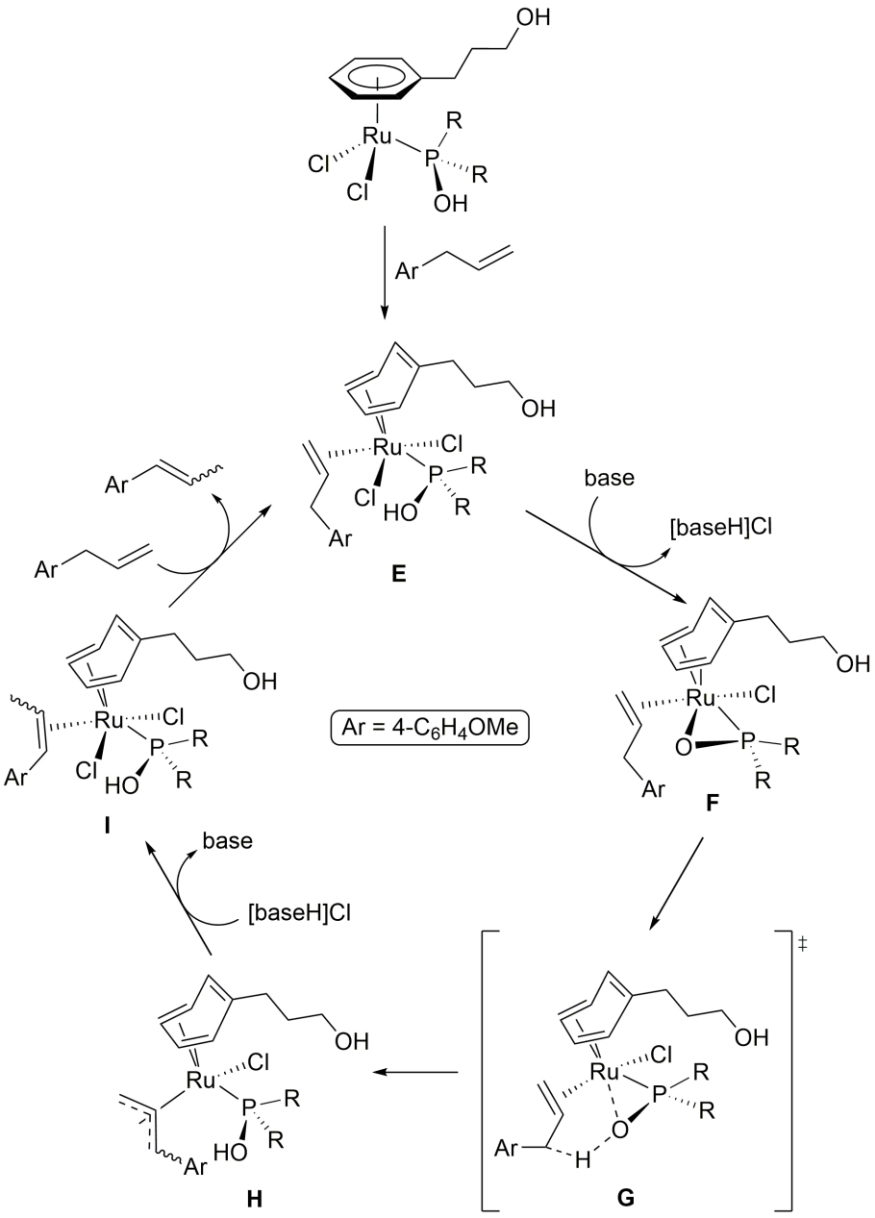
Table 3. Catalytic estragole (**3a**) to anethole (**4a**) isomerization in water using complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)(OPh)_2\}$] (**2g**) as catalyst: Effect of additives.[a]



Entry	Additive	Time (h)	Yield of **4a** (%)[b]	*E/Z* ratio[b]
1	$AgPF_6$ (1 mol%)	2	53	91:9
		4	83	92:8
		8	96	93:7
2	$AgPF_6$ (2 mol%)	2	45	91:9
		4	77	92:8
		8	94	93:7
3[c]	NaCl	2	58	91:9
		4	87	92:8
		8	99	93:7
4	HCl (1 mol%)	2	47	92:8
		4	79	92:8
		8	95	93:7
5	HCl (2 mol%)	2	49	92:8
		4	81	92:8
		8	94	93:7
6	NaOH (1 mol%)	2	69	91:9
		4	92	92:8
		7	> 99	93:7
7	NaOH (2 mol%)	2	79	92:8
		4	96	93:7
		6	> 99	93:7
8	NaOH (3 mol%)	2	86	92:8
		4	98	93:7

		5	> 99	93:7
9	NaOH (4 mol%)	2	87	91:9
		4	98	93:7
		5	> 99	93:7
10	K_2CO_3 (3 mol%)	2	90	93:7
		4	> 99	94:6

[a] Reactions performed under argon atmosphere using 2 mmol of **3a**, 0.02 mmol of complex **2g**, and 1 mL of water. [b] Determined by GC (uncorrected GC areas). [c] A saturated $NaCl_{(aq)}$ solution was employed as solvent.

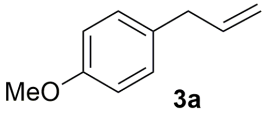
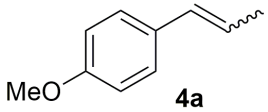
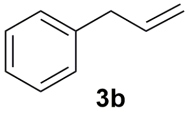
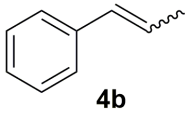
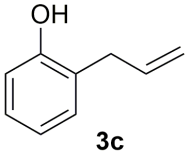
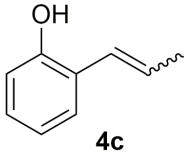
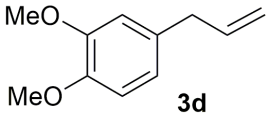
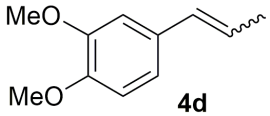
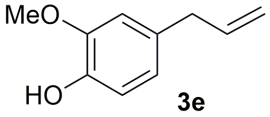
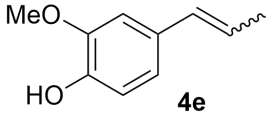
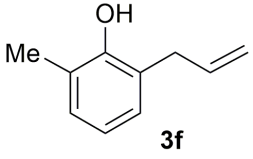
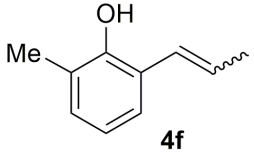


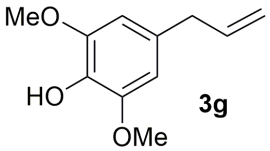
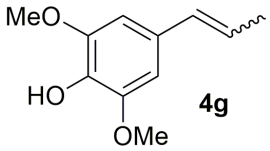
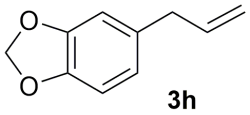
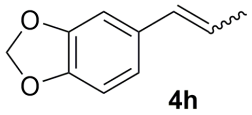
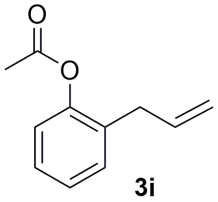
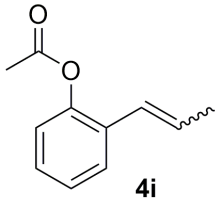
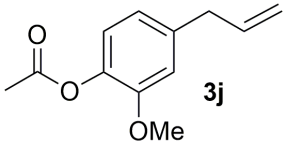
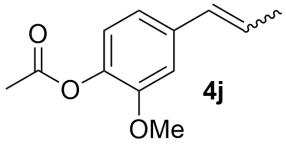
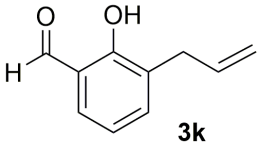
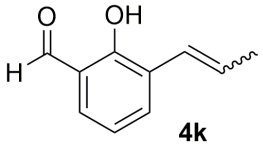
Scheme 7. Proposed mechanism for the estragole to anethole isomerization catalyzed by **2a-g**.

On the basis of these results and the previous findings on the cooperative effect of phosphinous acid-type ligands in the Ru-catalyzed C-H bond arylation processes shown in Scheme 2, the reaction pathway depicted in Scheme 7 could be tentatively proposed for the present C=C bond isomerization reaction. We assume that initial coordination of the estragole substrate to the ruthenium center proceeds through a change in the hapticity of the arene ligand (from η^6 to η^4), leading to intermediate π-olefin complex **E**, which evolves into the phosphinito derivative **F** by elimination of HCl. This step is obviously favored in basic medium, and explains the rates acceleration observed when a base is added to the reaction mixture.[20] Then, the π-allyl intermediate **H** could be generated from **F** by abstraction of one of the methylenic protons by the phosphinito anion PR_2O^- (transition state **G**). Final protonation of **H** would lead to **I** from which the anethole molecule is displaced by another molecule of the substrate.

The ability of complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)(OPh)_2\}$] (**2g**) to promote the isomerization of other commercially available allylbenzene derivatives **3b-k** was subsequently evaluated under the optimized reaction conditions described above, *i.e.* in water at 80 ºC employing 1 mol% of **2g** in combination with 3 mol% of K_2CO_3 (see Table 4). To our delight, the process proved to be general and, as was the case with estragole **3a** (entry 1), all tested substrates could be converted into the corresponding (1-propenyl)benzenes **4b-k** in almost quantitative GC yield and with a high *trans*-selectivity (*E/Z* ratios from 88:12 to 97:3). As a general trend, those allylbenzenes containing exclusively electron-donor substituents, *i.e.* hydroxy or alkoxy groups, in the aromatic ring required of short times (4-6 h) to be completely isomerized (compounds **3a,c-f,h**; entries 1, 3-6 and 8). A fast reaction was also observed when the parent allylbenzene **3b** (entry 2) was employed as substrate. Conversely, when electron-withdrawing substituents, *i.e.* acetoxy or formyl groups, were introduced, longer reaction times were needed to attain full conversion (compounds **3i-k**; entries 9-11). The only exception found was that of 4-allyl-2,6-dimethoxyphenol **3g**, for which a slow isomerization was observed (entry 7). The higher steric hindrance associated with the trisubstitution of the aromatic ring could be behind this anomalous behavior. Also of note is the fact that the (1-propenyl)benzene products **4a-k** can be easily isolated from the aqueous reaction medium by a simple extraction with dichloromethane (see details in Experimental Section), with complex **2g** remaining dissolved in the aqueous phase.[21]

Table 4. Isomerization of the allylbenzene derivatives **3a-k** by complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)(OPh)_2\}$] (**2g**) in water.[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]	*E/Z* ratio[c]
1	 **3a**	 **4a**	4	> 99 (93)	94:6
2	 **3b**	 **4b**	4	> 99 (85)	95:5
3	 **3c**	 **4c**	4	99 (74)	88:12
4	 **3d**	 **4d**	4	> 99 (75)	95:5
5	 **3e**	 **4e**	6	99 (93)	88:12
6	 **3f**	 **4f**	4	> 99 (81)	88:12

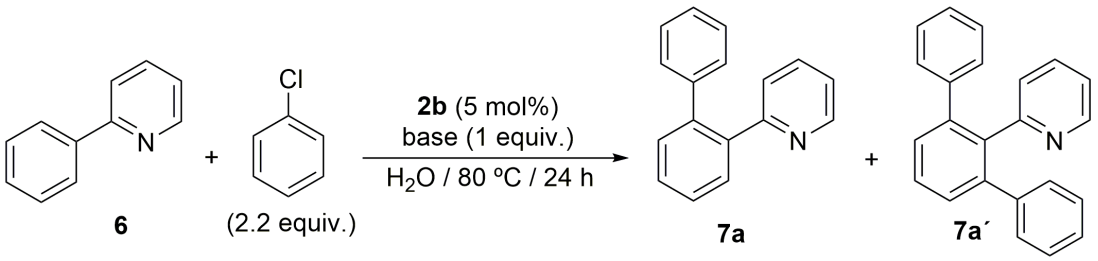
7	 **3g**	 **4g**	24 30	92 97 (89)	91:9 97:3
8	 **3h**	 **4h**	4	> 99 (76)	96:4
9	 **3i**	 **4i**	8 24	91 > 99 (73)	90:10 91:9
10	 **3j**	 **4j**	12	99 (86)	94:6
11	 **3k**	 **4k**	16	99 (93)	92:8

[a] Reactions performed under argon atmosphere using 2 mmol of the corresponding allylbenzene **3**, 0.02 mmol of the Ru(II) complex **2g**, 0.06 mmol of K_2CO_3, and 1 mL of water. [b] Yields determined by GC (uncorrected GC areas). Isolated yields after workup are given in brackets. [c] *E*/*Z* ratios were determined by GC or by ^{1}H NMR spectroscopy.

On the other hand, as previously commented in the Introduction Section, Ru(II) complexes with phosphinous acid-type ligands, both preformed or generated *in situ* by mixing the appropriate ruthenium precursor with a pentavalent phosphorous oxide, have proven to be useful catalysts for C-C coupling reactions through directing-group-assisted C(sp^2)-H activation processes (see Scheme 2).[3] However, despite the growing interest in developing these C-H bond functionalization reactions employing environmentally friendly water as solvent,[22] to date all works involving phosphinous acids have been carried out in organic media (in most of them, toxic *N*-methyl-2-pyrrolidinone (NMP) was used as solvent).[3] This fact prompted us to evaluate the catalytic potential of the hydrophilic complexes **2a-g** for C-H bond arylations in water. Thus, in a first series of experiments, we investigated the *ortho*-phenylation of 2-phenylpyridine **6** with an excess of chlorobenzene (2.2 equiv.) employing complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)Ph_2\}$] (**2b**) as model catalyst (5 mol%). As shown in Table 5, when the mixture was heated in water at 80 ºC for 24 h, the monoarylated product **7a** was generated in very low yield (entry 1). As expected, the addition of one equivalent of base to the reaction medium allowed to improve the performance of complex **2b** (entries 2-10). In particular, the best results were obtained with Cs_2CO_3 (entry 5), the reaction leading to the formation of the mono- and diarylated derivatives **7a** and **7a´** in 79% overall yield, with excellent selectivity towards the monoarylated one (**7a:7a´** ratio of 91:9). The ^{1}H NMR spectrum of the crude indicated that no side-products are generated in the process. Further increase in the yield (> 96%) was achieved when 2 or 3 equivalents of Cs_2CO_3 were employed, but the selectivity towards the monoarylated product **7a** was in these cases lower (entries 11 and 12). Conversely, the use of a substoichiometric amount of Cs_2CO_3 (0.5 equiv.) significantly decreased the efficiency of the arylation process (entry 13), confirming that at least one equivalent of base is needed to attain a high conversion. On the other hand, as shown in entry 14, a reduction of the amount of chlorobenzene to only one equivalent did not lead to significant losses of activity or selectivity. At this point we would like also to emphasize that the results obtained with [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)Ph_2\}$] (**2b**) in water compare favourably with those described by Clavier and co-workers for the same reaction when employing the closely related diphenylphosphinous acid complex [$RuCl_2(\eta^6$-*p*-cymene)$\{P(OH)Ph_2\}$] as catalyst in NMP.[3e] Thus, using 5 mol%

of this complex, in combination with K_2CO_3 (3 mol%), an almost equimolar mixture of **7a** and **7a´** was obtained in 49% yield after 24 h of heating at 80 ºC.

Table 5. Catalytic arylation of 2-phenylpyridine (**6**) in water using chlorobenzene and complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)Ph_2\}$] (**2b**) as catalyst: Screening of different bases.[a]

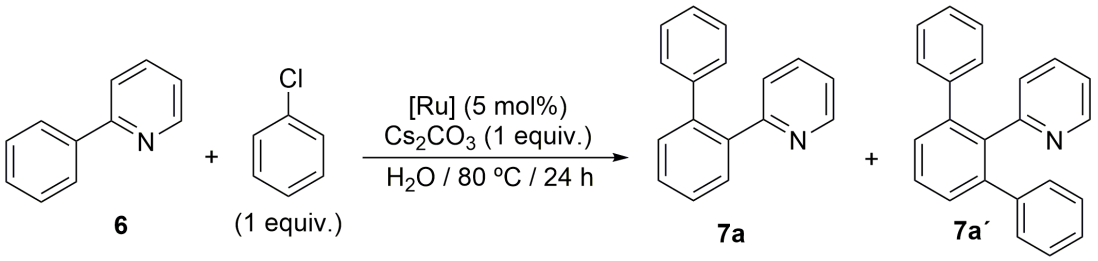


Entry	Base	Yield (%)[b]	**7a:7a´** ratio[b]
1	-----	22	100:0
2	Li_2CO_3	70	83:17
3	Na_2CO_3	69	80:20
4	K_2CO_3	61	80:20
5	Cs_2CO_3	79	91:9
6	LiOH	50	91:9
7	NaOH	52	89:11
8	KOH	47	91:9
9	$CsOH·H_2O$	51	92:8
10	$NaCO_2H$	31	100:0
11[c]	Cs_2CO_3	96	70:30
12[d]	Cs_2CO_3	> 99	67:33
13[e]	Cs_2CO_3	40	90:10
14[f]	Cs_2CO_3	76	92:8

[a] Reactions performed under argon atmosphere using 1 mmol of **6**, 2.2 mmol of chlorobenzene, 0.05 mmol of complex **2b**, 1 mmol of the corresponding base and 2 mL of water. [b] Determined by ^{1}H NMR spectroscopy. [c] Reaction performed with 2 equiv. of Cs_2CO_3. [d] Reaction performed with 3 equiv. of Cs_2CO_3. [e] Reaction performed with 0.5 equiv. of Cs_2CO_3. [f] Reaction performed with 1 equiv. of Cs_2CO_3 and 1 equiv. of chlorobenzene.

The catalytic performance of the other synthesized complexes in the *ortho*-phenylation of **6** was next explored using 1 equivalent of both PhCl and Cs_2CO_3. As shown in Table 6, all of them proved to be catalytically active delivering predominantly the monoarylated product **7a** (**7a:7a´** ratios from 88:12 to 92:8) in high yield. The best compromise in yield and selectivity was achieved with complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)(OMe)_2\}$] (**2e**) which led to a 91:9 mixture of **7a/7a´** in 81% overall yield (entry 5).

Table 6. Catalytic arylation of 2-phenylpyridine (**6**) in water using chlorobenzene: Comparative performances of complexes [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)(L)$].[a]



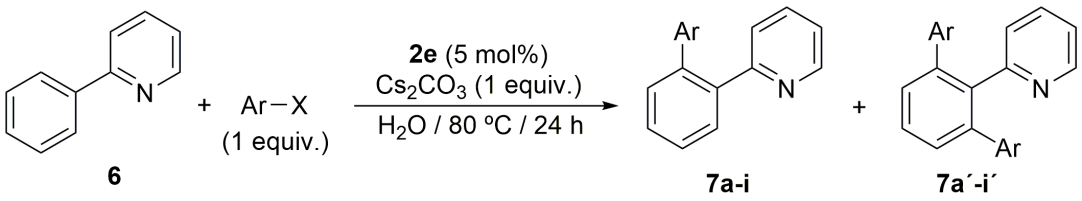
Entry	Catalyst	Yield (%)[b]	**7a:7a´** ratio[b]
1	**2a** (L = $P(OH)Me_2$)	73	92:8
2	**2b** (L = $P(OH)Ph_2$)	76	92:8
3	**2c** (L = $P(OH)(4\text{-}C_6H_4CF_3)_2$)	70	89:11
4	**2d** (L = $P(OH)(4\text{-}C_6H_4OMe)_2$)	74	92:8
5	**2e** (L = $P(OH)(OMe)_2$)	81	91:9
6	**2f** (L = $P(OH)(OEt)_2$)	84	88:12
7	**2g** (L = $P(OH)(OPh)_2$)	80	88:12

[a] Reactions performed under argon atmosphere using 1 mmol of **6**, 1 mmol of chlorobenzene, 0.05 mmol of the corresponding ruthenium complex, 1 mmol of Cs_2CO_3 and 2 mL of water. [b] Determined by ^{1}H NMR spectroscopy.

Finally, the ability of [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)(OMe)_2\}$] (**2e**) to catalyze the arylation of **6** with other aryl halides was briefly explored (see Table 7). In this regard, the process was found to be equally effective when bromo- or iodobenzene were employed as the electrophilic coupling partners, with only minor differences in reactivity and selectivity when compared to the reaction carried out with chlorobenzene

(entries 2-3 *vs* entry 1). On the other hand, as shown in entries 4-11, different arylchlorides could also be satisfactorily employed. In general, high yields (> 70%) and a remarkable selectivity towards the monoarylated products were observed, regardless of the electronic nature or substitution pattern of the aromatic ring. Nonetheless, we should note that *ortho*-substituted arylchlorides led to poorer results in comparison to their *meta*- or *para*-substituted counterparts (entry 6 *vs* entries 4-5 and entry 8 *vs* 7), a not surprising fact on the basis of steric grounds.

Table 7. Different arylation reactions of 2-phenylpyridine (**6**) in water using complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)(OMe)_2\}$] (**2e**) as catalyst.[a]



6 **7a-i** **7a´-i´**

Entry	Ar	X	Yield (%)[b]	**7:7´** ratio[b]
1	Ph	Cl	81	91:9 (**7a/7a´**)
2	Ph	Br	86	81:19 (**7a/7a´**)
3	Ph	I	76	87:13 (**7a/7a´**)
4	4-C_6H_4OMe	Cl	77	100:0 (**7b/7b´**)
5	3-C_6H_4OMe	Cl	78	91:9 (**7c/7c´**)
6	2-C_6H_4OMe	Cl	15	100:0 (**7d/7d´**)
7	4-C_6H_4Me	Cl	77	91:9 (**7e/7e´**)
8	2-C_6H_4Me	Cl	57	82:18 (**7f/7f´**)
9	4-C_6H_4C(=O)Me	Cl	77	89:11 (**7g/7g´**)
10	3-C_6H_4C(=O)Me	Cl	71	89:11 (**7h/7h´**)
11	4-$C_6H_4CF_3$	Cl	75	92:8 (**7i/7i´**)

[a] Reactions performed under argon atmosphere using 1 mmol of **6**, 1 mmol of the corresponding aryl halide, 0.05 mmol of complex **2e**, 1 mmol of Cs_2CO_3 and 2 mL of water. [b] Determined by ^{1}H NMR spectroscopy.

Conclusion

In summary, different half-sandwich ruthenium(II) complexes containing hydrophilic 3-phenylpropanol and phosphinous acid-type ligands, *i.e.* compounds [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)R_2\}$] (**2a-g**), have been synthesized and their effectiveness as catalysts for the isomerization of allylbenzene derivatives, as well as for the *ortho*-C-H bond arylation of 2-phenylpyridine, in environmentally friendly aqueous media demonstrated. In general, high activities and selectivities towards the formation of the corresponding (*E*)-(1-propenyl)benzene and monoarylated products, respectively, were observed. The results herein presented show for the first time (*i*) the utility of $P(OH)R_2$ compounds as auxiliary ligands in metal-catalyzed olefin isomerization processes and (*ii*) the ability of ruthenium(II)-$P(OH)R_2$ complexes to promote C-H activation process in water. Overall, this work gives new evidences for the enormous potential of phosphinous acid-type ligands in homogenous catalysis.

Experimental Section

Synthetic procedures were performed under an atmosphere of dry argon using vacuum-line and standard Schlenk or sealed-tube techniques. Organic solvents were dried by standard methods and distilled under argon before use.[23] All reagents were obtained from commercial suppliers and used without further purification with the exception of the ruthenium complexes [$RuCl_2\{\eta^6$:κ^1*(O)*-$C_6H_5CH_2CH_2CH_2OH\}$] (**1**)[10] and [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OPh)_3\}$] (**5**),[24] and the secondary phosphine oxides $R_2P(=O)H$ (R = Me,[25] Ph,[26] 4-$C_6H_4CF_3$,[26] 4-C_6H_4OMe[26]), which were prepared by following the methods reported in the literature. Infrared spectra were recorded on a Perkin-Elmer 1720-XFT spectrometer. NMR spectra were recorded at 25 °C on Bruker DPX-300 or AV400 instruments. $^{13}C\{^1H\}$ and ^1H chemical shifts were referenced to the residual signal of deuterated solvent. All data are reported in ppm downfield from $(CH_3)_4Si$. For $^{19}F\{^1H\}$ NMR spectra, the chemical shifts were referenced to the $CFCl_3$ standard. DEPT experiments have been carried out for all the compounds reported in this paper. GC measurements were made on a Hewlett Packard HP6890 apparatus (Supelco Beta-Dex™ 120 column, 30 m length, 250 μm diameter). Elemental analyses were provided by the Analytical Service of the Instituto de Investigaciones Químicas (IIQ-CSIC) of Seville. For column chromatography, Merck silica gel 60 (230-400 mesh) was employed.

General procedure for the preparation of complexes [$RuCl_2$(η^6-$C_6H_5CH_2CH_2CH_2OH$){P(OH)R_2}] (R = Me (2a), Ph (2b), 4-$C_6H_4CF_3$ (2c), 4-C_6H_4OMe (2d), OMe (2e), OEt (2f), OPh (2g)). A suspension of complex [$RuCl_2${η^6:κ^1*(O)*-$C_6H_5CH_2CH_2CH_2OH$}] (**1**) (0.308 g, 1 mmol) and the corresponding $R_2P(=O)H$ derivative (1.1 mmol) in THF (50 mL) was stirred 24 h at room temperature. The reaction mixture was then evaporated to dryness, the oily residue formed dissolved in the minimum amount of CH_2Cl_2 (*ca.* 5 mL), and the product precipitated by adding 30 mL of a diethyl ether/hexane mixture (1:1 v/v). The same precipitation procedure was repeated twice more and the reddish orange solid was finally washed with diethyl ether (5 mL) and dried *in vacuo*. **(2a):** Yield: 0.266 g (69%). IR (KBr): ν = 3416 and 3349 (br, O-H) cm^{-1}. $^{31}P\{^1H\}$ NMR (acetone-d_6): δ = 118.9 (s) ppm. ^1H NMR (acetone-d_6): δ = 5.70 (td, 2H, $^3J_{HH}$ = 5.6 Hz, $^3J_{PH}$ = 1.8 Hz, CH_{meta}), 5.52 (d, 2H, $^3J_{HH}$ = 5.6 Hz, CH_{ortho}), 5.32 (t, 1H, $^3J_{HH}$ = 5.6 Hz, CH_{para}), 3.65 (t, 2H, $^3J_{HH}$ = 6.3 Hz, C*H*$_2$OH), 2.90 (br s, 1H, CH_2O*H*), 2.56 (t, 2H, $^3J_{HH}$ = 7.5 Hz, C*H*$_2$Ph), 1.92-1.83 (m, 2H, C*H*$_2CH_2$Ph), 1.87 (d, 6H, $^2J_{PH}$ = 10.5 Hz, Me) ppm; P-OH signal not observed. $^{13}C\{^1H\}$ NMR (acetone-d_6): δ = 111.2 (s, C_{ipso}), 87.8 (s, CH_{ortho} or CH_{meta}), 87.4 (d, $^2J_{PC}$ = 6.4 Hz, CH_{ortho} or CH_{meta}), 78.9 (s, CH_{para}), 60.6 (s, CH_2OH), 32.2 and 29.4 (s, *C*H_2*C*H_2Ph), 20.7 (d, $^1J_{PC}$ = 36.9 Hz, Me) ppm. Elemental analysis calcd. (%) for $C_{11}H_{19}Cl_2O_2PRu$: C 34.21, H 4.96; found: C 34.33, H 4.94. **(2b):** Yield: 0.388 g (76%). IR (KBr): ν = 3381 and 3285 (br, O-H) cm^{-1}. $^{31}P\{^1H\}$ NMR (acetone-d_6): δ = 106.9 (s) ppm. ^1H NMR (acetone-d_6): δ = 7.80-7.73 (m, 4H, PPh), 7.52-7.49 (m, 6H, PPh), 5.57-5.49 (m, 4H, CH_{meta} and CH_{ortho}), 4.96 (t, 1H, $^3J_{HH}$ = 5.1 Hz, CH_{para}), 3.62 (t, 2H, $^3J_{HH}$ = 6.0 Hz, C*H*$_2$OH), 2.94 (br s, 1H, OH), 2.58 (t, 2H, $^3J_{HH}$ = 7.5 Hz, C*H*$_2$Ph), 1.88-1.79 (m, 2H, C*H*$_2CH_2$Ph) ppm; P-OH signal not observed. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 137.5 (d, $^1J_{PC}$ = 60.3 Hz, C_{ipso} of PPh), 131.5 (d, J_{PC} = 11.3 Hz, CH_{ortho} or CH_{meta} of PPh), 131.3 (s, CH_{para} of PPh), 128.4 (d, J_{PC} = 10.5 Hz, CH_{ortho} or CH_{meta} of PPh), 113.2 (s, C_{ipso}), 88.2 and 87.9 (s, CH_{ortho} and CH_{meta}), 80.3 (s, CH_{para}), 61.4 (s, CH_2OH), 31.0 and 29.0 (s, *C*H_2*C*H_2Ph) ppm. Elemental analysis calcd. (%) for $C_{21}H_{23}Cl_2O_2PRu$: C 49.42, H 4.54; found: C 49.29, H 4.50. **(2c):** Yield: 0.569 g (88%). IR (KBr): ν = 3420 and 3284 (br, O-H) cm^{-1}. $^{31}P\{^1H\}$ NMR (acetone-d_6): δ = 102.6 (s) ppm. $^{19}F\{^1H\}$ NMR (acetone-d_6): δ = -63.5 (s) ppm. ^1H NMR (acetone-d_6): δ = 8.09 (dd, 4H, $^3J_{PH}$ = 7.2 Hz, $^3J_{HH}$ = 7.2 Hz, CH_{ortho} of $C_6H_4CF_3$), 7.80 (d, 4H, $^3J_{HH}$ = 7.2 Hz, CH_{meta} of $C_6H_4CF_3$), 5.69-5.66 (m, 2H, CH_{meta}), 5.59 (d, 2H, $^3J_{HH}$ = 6.0 Hz, CH_{ortho}), 5.18 (t, 1H, $^3J_{HH}$ = 4.5 Hz, CH_{para}), 3.64 (t,

2H, $^{3}J_{HH}$ = 6.3 Hz, CH_2OH), 2.97 (br s, 1H, OH), 2.61 (t, 2H, $^{3}J_{HH}$ = 7.5 Hz, CH_2Ph), 1.90-1.81 (m, 2H, CH_2CH$_2$Ph) ppm; P-OH signal not observed. ^{13}C{^{1}H} NMR (acetone d_6): δ = 142.9 (d, $^{1}J_{PC}$ = 53.5 Hz, C_{ipso} of $C_6H_4CF_3$), 132.3 (d, $^{2}J_{PC}$ = 11.9 Hz, CH_{ortho} of $C_6H_4CF_3$), 131.6 (q, $^{2}J_{FC}$ = 34.3 Hz, C_{para} of $C_6H_4CF_3$), 124.6 (m, CH_{meta} of $C_6H_4CF_3$), 124.0 (q, $^{1}J_{FC}$ = 271.8 Hz, CF_3), 113.9 (d, $^{2}J_{PC}$ = 5.9 Hz, C_{ipso}), 89.2 (s, CH_{ortho} or CH_{meta}), 88.7 (d, $^{2}J_{PC}$ = 6.4 Hz, CH_{ortho} or CH_{meta}), 81.0 (s, CH_{para}), 60.6 (s, CH_2OH), 31.9 and 29.5 (s, *C*H$_2$*C*H$_2$Ph) ppm. Elemental analysis calcd. (%) for $C_{23}H_{21}F_6Cl_2O_2PRu$: C 42.74, H 3.27; found: C 42.81, H 3.45. **(2d):** Yield: 0.399 g (70%). IR (KBr): ν = 3411 and 3254 (br, O-H) cm^{-1}. ^{31}P{^{1}H} NMR (acetone-d_6): δ = 106.0 (s) ppm. ^{1}H NMR (acetone-d_6): δ = 7.68 (dd, 4H, $^{3}J_{PH}$ = 10.5 Hz, $^{3}J_{HH}$ = 8.7 Hz, CH_{ortho} of C_6H_4OMe), 7.04 (dd, 4H, $^{3}J_{HH}$ = 8.7 Hz, $^{4}J_{PH}$ = 1.8 Hz, CH_{meta} of C_6H_4OMe), 5.51-5.46 (m, 4H, CH_{meta} and CH_{ortho}), 4.93 (t, 1H, $^{3}J_{HH}$ = 5.1 Hz, CH_{para}), 3.88 (s, 6H, OMe), 3.62 (t, 2H, $^{3}J_{HH}$ = 6.0 Hz, CH_2OH), 3.06 (br s, 1H, OH), 2.58 (t, 2H, $^{3}J_{HH}$ = 7.5 Hz, CH_2Ph), 1.85-1.80 (m, 2H, CH_2CH$_2$Ph) ppm; P-OH signal not observed. ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 161.9 (s, C_{para} of C_6H_4OMe), 133.5 (d, J_{PC} = 12.9 Hz, CH_{ortho} or CH_{meta} of C_6H_4OMe), 129.1 (d, $^{1}J_{PC}$ = 65.6 Hz, C_{ipso} of C_6H_4OMe), 113.9 (d, J_{PC} = 11.8 Hz, CH_{ortho} or CH_{meta} of C_6H_4OMe), 113.1 (s, C_{ipso}), 88.1 (d, $^{2}J_{PC}$ = 5.8 Hz, CH_{ortho} or CH_{meta}), 87.9 (s, CH_{ortho} or CH_{meta}), 80.3 (s, CH_{para}), 61.4 (s, CH_2OH), 55.5 (s, OMe), 31.2 and 29.1 (s, *C*H$_2$*C*H$_2$Ph) ppm. Elemental analysis calcd. (%) for $C_{23}H_{27}O_4Cl_2PRu$: C 48.43, H 4.77; found: C 48.51, H 4.81. **(2e):** Yield: 0.276 g (66%). IR (KBr): ν = 3417 and 3212 (br, O-H) cm^{-1}. ^{31}P{^{1}H} NMR (acetone-d_6): δ = 118.8 (s) ppm. ^{1}H NMR (acetone-d_6): δ = 5.76 (td, 2H, $^{3}J_{HH}$ = 5.9 Hz, $^{3}J_{PH}$ = 1.8 Hz, CH_{meta}), 5.63 (d, 2H, $^{3}J_{HH}$ = 5.9 Hz, CH_{ortho}), 5.47 (t, 1H, $^{3}J_{HH}$ = 5.9 Hz, CH_{para}), 3.77 (d, 6H, $^{3}J_{PH}$ = 11.1 Hz, OCH_3), 3.64 (t, 2H, $^{3}J_{HH}$ = 6.6 Hz, CH_2OH), 3.20 (br s, 1H, OH), 2.60 (t, 2H, $^{3}J_{HH}$ = 7.5 Hz, CH_2Ph), 1.93-1.84 (m, 2H, CH_2CH$_2$Ph) ppm; P-OH signal not observed. ^{13}C{^{1}H} NMR (acetone-d_6): δ = 113.0 (d, $^{2}J_{PC}$ = 6.7 Hz, C_{ipso}), 89.0 (d, $^{2}J_{PC}$ = 7.5 Hz, CH_{meta} or CH_{ortho}), 88.8 (s, CH_{meta} or CH_{ortho}), 80.1 (s, CH_{para}), 60.5 (s, CH_2OH), 52.6 (d, $^{2}J_{PC}$ = 7.0 Hz, OCH_3), 32.0 and 29.3 (s, *C*H$_2$*C*H$_2$Ph) ppm. Elemental analysis calcd. (%) for $C_{11}H_{19}O_4Cl_2PRu$: C 31.59, H 4.58; found: C 31.65, H 4.51. **(2f):** Yield: 0.196 g (44%). IR (KBr): ν = 3421 and 3224 (br, O-H) cm^{-1}. ^{31}P{^{1}H} NMR (acetone-d_6): δ = 114.7 (s) ppm. ^{1}H NMR (acetone-d_6): δ = 5.73 (t, 2H, $^{3}J_{HH}$ = 4.8 Hz, CH_{meta}), 5.61 (d, 2H, $^{3}J_{HH}$ = 5.1 Hz, CH_{ortho}), 5.44 (t, 1H, $^{3}J_{HH}$ = 4.5 Hz, CH_{para}), 4.21-4.12 (m, 4H, OCH_2CH$_3$), 3.64 (t, 2H, $^{3}J_{HH}$ = 5.7 Hz, CH_2OH), 3.46 (br s, 1H, OH), 2.59 (t, 2H, $^{3}J_{HH}$ = 7.5 Hz, CH_2Ph), 1.91-1.85 (m, 2H, CH_2CH$_2$Ph), 1.31 (t, 6H, $^{3}J_{HH}$ = 6.9 Hz, OCH$_2$CH_3) ppm; P-OH

signal not observed. $^{13}C\{^1H\}$ NMR (acetone-d_6): δ = 112.5 (s, C_{ipso}), 88.9 (d, $^2J_{PC}$ = 7.1 Hz, CH_{meta} or CH_{ortho}), 88.8 (s, CH_{meta} or CH_{ortho}), 81.3 (s, CH_{para}), 68.4 (s, OCH_2CH_3), 60.5 (s, CH_2OH), 32.1 and 28.6 (s, CH_2CH_2Ph), 15.8 (s, OCH_2CH_3) ppm. Elemental analysis calcd. (%) for $C_{13}H_{23}O_4Cl_2PRu$: C 34.99, H 5.20; found: C 35.06, H 5.19. **(2g):** Yield: 0.325 g (60%). IR (KBr): ν = 3408 and 3207 (br, O-H) cm^{-1}. $^{31}P\{^1H\}$ NMR (acetone-d_6): δ = 115.0 (s) ppm. ^1H NMR (acetone-d_6): δ = 7.43-7.24 (m, 10H, OPh), 5.59-5.55 (m, 2H, CH_{meta}), 5.44 (d, 2H, $^3J_{HH}$ = 5.7 Hz, CH_{ortho}), 5.00 (t, 1H, $^3J_{HH}$ = 5.1 Hz, CH_{para}), 3.60 (t, 2H, $^3J_{HH}$ = 6.0 Hz, CH_2OH), 3.40 (br s, 1H, OH), 2.51 (t, 2H, $^3J_{HH}$ = 7.8 Hz, CH_2Ph), 1.86-1.76 (m, 2H, CH_2CH_2Ph) ppm; P-OH signal not observed. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 151.2 (d, $^2J_{PC}$ = 11.0 Hz, C_{ipso} of OPh), 129.8 (s, CH_{meta} of OPh), 125.2 (s, CH_{para} of OPh), 121.5 (d, $^3J_{PC}$ = 3.5 Hz, CH_{ortho} of OPh), 114.3 (d, $^2J_{PC}$ = 6.9 Hz, C_{ipso}), 89.3 (d, $^2J_{PC}$ = 7.6 Hz, CH_{meta} or CH_{ortho}), 88.8 (s, CH_{meta} or CH_{ortho}), 80.3 (s, CH_{para}), 61.4 (s, CH_2OH), 30.9 and 29.2 (s, CH_2CH_2Ph) ppm. Elemental analysis calcd. (%) for $C_{21}H_{23}O_4Cl_2PRu$: C 46.51, H 4.27; found: C 46.63, H 4.30.

General procedure for the isomerization of the allylbenzene derivatives 3a-h catalyzed by complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)(OPh)_2\}$] (2g): Under argon atmosphere, the corresponding allylbenzene **3a-k** (2 mmol), water (1 mL), the ruthenium(II) complex **2g** (0.011 g, 0.02 mmol; 1 mol%) and K_2CO_3 (0.008 g, 0.06 mmol; 3 mol%) were introduced into a Teflon-capped sealed tube, and the reaction mixture stirred at 80 °C for the indicated time (see Table 4). The course of the reaction was monitored by taking regularly samples of *ca.* 10 μL which, after extraction with CH_2Cl_2 (3 mL), were analyzed by GC. Once the maximum conversion of the starting substrate is reached, the resulting aqueous solution was allowed to reach room temperature and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and evaporated to dryness, yielding the corresponding (1-propenyl)benzene products **4a-k** as oily materials. The identity of compounds **4a-k** was confirmed by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy (copies of the NMR spectra have been included in the Supporting Information file).

General procedure for the *ortho*-arylation reactions of 2-phenylpyridine catalyzed by complex [$RuCl_2(\eta^6$-$C_6H_5CH_2CH_2CH_2OH)\{P(OH)(OMe)_2\}$] (2e): Under argon atmosphere, 2-phenylpyridine **6** (143 μL, 1 mmol), the corresponding aryl

halide (1 mmol), water (2 mL), the ruthenium(II) complex **2e** (0.021 g, 0.05 mmol; 5 mol%) and Cs_2CO_3 (0.327 g, 1 mmol) were introduced into a Teflon-capped sealed tube, and the reaction mixture stirred at 80 °C for 24 h. After this time, the aqueous reaction mixture was cooled to room temperature and extracted with diethyl ether (4 x 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The oily residue was dissolved in $CDCl_3$, and the reaction yield and ratio between the mono- and diarylated products were determined by ^{1}H NMR spectroscopy, through the integration of the signals of the C(5)-H pyridinic protons for the starting material **6** and the products **7a-i** and **7a´-i´**. Copies of the NMR spectra of the experiments collected in Table 7 have been included in the Supporting Information file.

X-ray crystal structure determination of compound 2a. Crystals of **2a** suitable for X-ray diffraction analysis were obtained by slow diffusion of *n*-hexane into a saturated solution of the complex in dichloromethane. The most relevant crystal and refinement data are collected in Table S2 (see the Supporting Information). Data collection was performed with a Rigaku-Oxford Diffraction Xcalibur Onyx Nova single-crystal diffractometer using Cu-Kα radiation (λ = 1.5418 Å). Images were collected at a fixed crystal-to-detector distance of 62 mm using the oscillation method, with 1.30° oscillation and 2.5-6.0 s variable exposure time per image. Data collection strategy was calculated with the program CrysAlis^{Pro} CCD.[27] Data reduction and cell refinement were performed with the program CrysAlis^{Pro} RED.[27] An empirical absorption correction was applied using the SCALE3 ABSPACK algorithm as implemented in the program CrysAlis^{Pro} RED.[27] The software package WINGX was used for space group determination, structure solution, and refinement.[28] The structure was solved by Patterson interpretation and phase expansion using SIR2014.[29] Isotropic least-squares refinement on F^2 using SHELXL97 was performed.[30] During the final stages of the refinements, all the positional parameters and the anisotropic temperature factors of all non-H atoms were refined. All H atoms were geometrically located and their coordinates were refined riding on their parent atoms. The function minimized was $\{\Sigma[\omega(F_o^2 - F_c^2)^2]/\Sigma[\omega(F_o^2)^2]\}^{1/2}$ where $\omega = 1/[\sigma^2(F_o^2) + (0.0499P)^2]$ with $\sigma(F_o^2)$ from counting statistics and $P = [\max(F_o^2, 0) + 2F_c^2]/3$. Atomic scattering factors were taken from International Tables for X-ray Crystallography, Volume C.[31] Geometrical

calculations related to the centroid C* were made with PARST.[32] The crystallographic plots were made with DIAMOND.[33]

Supporting Information. Tables with the screening of different bases in the estragole-to-anethole isomerization catalyzed by complex **2g**, and the crystallographic information of compound **2a**. NMR spectra of the ruthenium complexes **2a-g** and the isolated (1-propenyl)benzene derivatives **4a-k**, and ^{1}H NMR spectra of the arylation reactions collected in Table 7.

Accession Code. CCDC 1937935 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Acknowledgements. Financial support from the Spanish Ministry of Economy, Industry and Competitiveness (MINECO project CTQ2016-75986-P) and the University of Oviedo (project PAPI-18-GR-2011-0032) is gratefully acknowledged. R.G.-F. thanks MECD of Spain for the award of a FPU fellowship. Prakash Chemicals (Budaun, India) is also acknowledged for the generous gift of the estragole employed in this work. This article is dedicated to Professor Ferenc Joó on the occasion of his 70th birthday.

Notes. The authors declare no competing financial interest.

References

(1) For review articles covering the field, see: (a) Dubrovina, N. V.; Börner, A. Enantioselective catalysis with chiral phosphine oxide preligands. *Angew. Chem. Int. Ed.* **2004**, *43*, 5883-5886. (b) Ackermann, L. Air- and moisture-stable secondary phosphine oxides as preligands in catalysis. *Synthesis* **2006**, 1557-1571. (c) Catalytic arylations with challenging substrates: From air-stable HASPO preligands to indole syntheses and C-H-bond functionalizations. *Synlett* **2007**, 507-526. (d) Ackermann, L.

Air-stable bifunctional HASPO preligands for metal-catalyzed cross-couplings and direct C-H bond arylations. *Isr. J. Chem.* **2010**, *50*, 652-663. (e) Shaikh, T. M.; Weng, C.-M.; Hong, F.-E. Secondary phosphine oxides: Versatile ligands in transition metal-catalyzed cross-coupling reactions. *Coord. Chem. Rev.* **2012**, *256*, 771-803. (f) Achard, T. Advances in homogeneous catalysis using secondary phosphine oxides (SPOs): Pre-ligands for metal complexes. *Chimia* **2016**, *70*, 8-19.

(2) See, for example: (a) Knapp, S. M. M.; Sherbow, T. J.; Yelle, R. B.; Juliette, J. J.; Tyler, D. R. Catalytic nitrile hydration with [Ru(η^6-*p*-cymene)Cl_2(PR_2R')] complexes: Secondary coordination sphere effects with phosphine oxide and phosphinite ligands. *Organometallics* **2013**, *32*, 3744-3752. (b) Tomás-Mendivil, E.; Cadierno, V.; Menéndez, M. I.; López, R. Unmasking the action of phosphinous acid ligands in nitrile hydration reactions catalyzed by arene-ruthenium(II) complexes. *Chem. Eur. J.* **2015**, *21*, 16874-16886. (c) Tomás-Mendivil, E.; Francos, J.; González-Fernández, R.; González-Liste, P. J.; Borge, J.; Cadierno, V. Bis(allyl)-ruthenium(IV) complexes with phosphinous acid ligands as catalysts for nitrile hydration reactions. *Dalton Trans.* **2016**, *45*, 13590-13603. (d) González-Fernández, R.; Crochet, P.; Cadierno, V.; Menéndez, M. I.; López, R. Phosphinous acid-assisted hydration of nitriles: Understanding the controversial reactivity of osmium and ruthenium catalysts. *Chem. Eur. J.* **2017**, *23*, 15210-15221. (e) Liardo, E.; González-Fernández, R.; Ríos-Lombardía, N.; Morís, F.; García-Álvarez, J.; Cadierno, V.; Crochet, P.; Rebolledo, F.; González-Sabín, J. Strengthening the combination between enzymes and metals in aqueous medium: Concurrent ruthenium-catalyzed nitrile hydration – asymmetric ketone bioreduction. *ChemCatChem* **2018**, *10*, 4676-4682.

(3) See, for example: (a) Ackermann, L. Phosphine oxides as preligands in ruthenium-catalyzed arylations via C-H bond functionalization using aryl chlorides. *Org. Lett.* **2005**, *7*, 3123-3125. (b) Ackermann, L.; Althammer, A.; Born, R. Catalytic arylation reactions by C-H bond activation with aryl tosylates. *Angew. Chem. Int. Ed.* **2006**, *45*, 2619-2622. (c) Ackermann, L.; Mulzer, M. Dehydrative direct arylations of arenes with phenols via ruthenium-catalyzed C-H and C-OH bond functionalizations. *Org. Lett.* **2008**, *10*, 5043-5045. (d) Zell, D.; Warratz, S.; Gelman, D.; Garden, S. J.; Ackermann, L. Single-component phosphinous acid ruthenium(II) catalysts for versatile C-H activation by metal-ligand cooperation. *Chem. Eur. J.* **2016**, *22*, 1248-1252. (e) Graux,

L. V.; Giorgi, M.; Buono, G.; Clavier, H. [$RuCl_2(\eta^6$-*p*-cymene)] complexes bearing phosphinous acid ligands: preparation, application in C-H bond functionalization and mechanistic investigations. *Dalton Trans.* **2016**, *45*, 6491-6502.

(4) For a recent review article covering the chemistry of ruthenium complexes with phosphinous acid ligands, see: Francos, J.; Elorriaga, D.; Crochet, P.; Cadierno, V. The chemistry of Group 8 metal complexes with phosphinous acids and related P-OH ligands. *Coord. Chem. Rev.* **2019**, *387*, 199-234.

(5) A related reaction pathway has also been proposed for nitrile hydration reactions catalyzed by the well-known Parkins platinum catalyst [$PtH\{(PMe_2O)_2H\}(PMe_2OH)$]: (a) Ghaffar, T.; Parkins, A. W. A new homogeneous platinum containing catalyst for the hydrolysis of nitriles. *Tetrahedron Lett.* **1995**, *36*, 8657-8660. (b) Cadierno, V. Synthetic applications of the Parkins nitrile hydration catalyst [$PtH\{(PMe_2O)_2H\}(PMe_2OH)$]: A review. *Appl. Sci.* **2015**, *5*, 380-401.

(6) Walther, B. The coordination chemistry of secondary phosphine chalcogenides and their conjugate bases. *Coord. Chem. Rev.* **1984**, *60*, 67-105.

(7) See, for example: (a) Roundhill, D. M.; Sperline, R. P.; Beaulieu, W. B. Metal complexes of substituted phosphinites and secondary phosphites. *Coord. Chem. Rev.* **1978**, *26*, 263-279. (b) Appleby, T.; Woollins, J. D. Inorganic backbone phosphines. *Coord. Chem. Rev.* **2002**, *235*, 121-140. (c) Gledbach, T. J.; Pregosin, P. S. η^1 to η^6 Ru-arene π complexation: New bonding modes and P-C bond cleavage chemistry. *Eur. J. Inorg. Chem.* **2002**, 1907-1918.

(8) Lastra-Barreira, B.; Francos, J.; Crochet, P.; Cadierno, V. Ruthenium(II) complexes with η^6-coordinated 3-phenylpropanol and 2-phenylethanol as catalysts for the tandem isomerization/Claisen rearrangement of diallyl ethers in water. *Organometallics* **2018**, *37*, 3465-3474.

(9) For a review article covering this catalytic transformation and highlighting its industrial relevance, see: Hassam, M.; Taher, A.; Arnott, G. E.; Green, I. R.; van Otterlo, W. A. L. Isomerization of allylbenzenes. *Chem. Rev.* **2015**, *115*, 5462-5569.

(10) (a) Miyaki, Y.; Onishi, T.; Kurosawa, H. Synthesis and reaction of ruthenium(II) complexes containing heteroatom donor (O, N, and P) tethered to η^6-arene ring. *Inorg. Chim. Acta* **2000**, *300-302*, 369-377. (b) Although complex **1** was initially formulated by Kurosawa and co-workers as a dimer, *i.e.* [{RuCl(μ-Cl)(η^6-$C_6H_5CH_2CH_2CH_2OH$)}$_2$], X-ray diffraction studies confirmed its monomeric tethered structure: Čubrilo, J.; Hartenbach, I.; Schleid, T.; Winter, R. F. Tethering versus non-coordination of hydroxy and methoxy side chains in arene half sandwich dichloro ruthenium complexes. *Z. Anorg. Allg. Chem.* **2006**, *632*, 400-408.

(11) (a) As a representative example the measured solubility of complex [$RuCl_2$(η^6-$C_6H_5CH_2CH_2CH_2OH$){P(OH)Me_2}] (**2a**) in water was 23 mg/mL at room temperature. (b) Despite being soluble in water, acetone-d_6 or $CDCl_3$ were employed as solvents for NMR measurements since, as previously observed for related phosphine and phosphite complexes [$RuCl_2$(η^6-$C_6H_5CH_2CH_2CH_2OH$)(PR_3)] (see reference 24 below), D_2O solutions of compounds [$RuCl_2$(η^6-$C_6H_5CH_2CH_2CH_2OH$){P(OH)R_2}] (**2a-g**) contain three species in equilibrium: (*i*) the starting materials **2a-g**, (*ii*) the aquo-complexes [RuCl(η^6-$C_6H_5CH_2CH_2CH_2OH$){P(OH)R_2}(D_2O)][Cl], generated by dissociation of one of chloride ligands and subsequent coordination of a water molecule, and (*iii*) the tethered species [RuCl(η^6:κ^1(*O*)-$C_6H_5CH_2CH_2CH_2OH$){P(OH)R_2}][Cl], resulting from chloride dissociation and intramolecular coordination of the OH group of the 3-phenylpropanol ligand to ruthenium. The chloride ligand dissociation processes are completely inhibited when an excess of NaCl is added to the aqueous solutions.

(12) According to the data reported for related [$RuCl_2$(η^6-*p*-cymene){P(OH)R_2}] species a lower field resonance (δ_H = 5-7 ppm) should be expected for the P-OH units. See, for example, references 2b and 3e.

(13) (a) Krafczyk, R.; Thönnessen, H.; Jones, P. G.; Schmutzler, R. Chemistry of bis(pentafluorobenzyl) phosphines and phosphine oxides. Single-crystal X-ray diffraction study of η^6-mesitylene-dichloro-[bis(pentafluorobenzyl)phosphinous acid]-ruthenium(II) and of 1,2-bis(pentafluorophenyl)ethane. *J. Fluorine Chem.* **1997**, *83*, 159-166. (b) González-Fernández, R.; González-Liste, P. J.; Borge, J.; Crochet, P.; Cadierno, V. Chlorophosphines as auxiliary ligands in ruthenium-catalyzed nitrile

hydration reactions: application to the preparation of *β*-ketoamides. *Catal. Sci. Technol.* **2016**, *6*, 4398-4409.

(14) (a) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, U.K., 1997. (b) Steiner, T. The hydrogen bond in solid state. *Angew. Chem. Int. Ed.* **2002**, *41*, 48-76.

(15) One reviewer suggested a Brønsted acid catalysis by proton release from complexes **2a-g** when dissolved in water. This possibility can be completely ruled out since in an independent experiment carried out, under identical experimental conditions, with 1 mol% HCl, and in the absence of ruthenium, no conversion of **3a** into **4a** was observed after 8 h of heating.

(16) As it can be seen in all the entries of Table 2, a slight increase in the *E/Z* ratio of the anethole product with time was observed. In accord with this general trend, when the reaction shown in entry 7 was extended to 24 h a *trans*-selectivity of 95% could be achieved.

(17) No major difference in activity was found when the isomerization of **3a** catalyzed by the triphenylphosphite complex **5** was performed in the presence of mercury. This fact discards that the induction period observed is related with the generation of catalytically active ruthenium nanoparticles.

(18) (a) When the isomerization of **3a** with complex **2g** was performed in the presence of free 3-phenylpropanol (20 equiv. per Ru), the performance shown by this catalyst remained unaffected, thus allowing to discard also that the vacant coordination sites on the metal are generated by dissociation of the η^6-coordinated arene ligand. (b) Additional experiments performed with aqueous solutions of complexes **2a-g** at 80 ºC confirmed the robustness of the ruthenium-arene bond in these compounds. In particular, after a 4-hour heating and subsequent evaporation of the solvent, complexes **2a-g** were recovered unchanged as evidenced from the corresponding $^{31}P\{^1H\}$ and ^1H NMR spectra recorded in acetone-d_6.

(19) We have measured the initial pH of the aqueous solution employed for the catalytic experiment collected in entry 1 of Table 2. The solution is acidic (pH around 3). When the same reaction was performed at pH 7 employing a phosphate buffer, **4a** was generated in 95% yield (*E/Z* ratio = 93:7) after 8 h. This reaction rate increase with pH is consistent with the beneficial effect exerted by the bases in this catalytic transformation.

(20) Given the different acidity of the two OH groups present in complexes **2a-g** (the pKa of 3-phenylpropanol is 15.0 while that of $(PhO)_2P$-OH is 6.5), a reaction pathway involving the deprotonation of the OH group dangling on the η^6-coordinated arene ligand does not seem very likely.

(21) The aqueous phase containing **2g** (and the K_2CO_3 base) can be reused, albeit featuring a reduced effectiveness. For example, its reuse in the estragole-to-anethole isomerization led to only 70% conversion after 4 h at 80 ºC (to be compared with the result collected in entry 1 of Table 4).

(22) For reviews covering this topic, see: (a) Li, B.; Dixneuf, P. H. sp^2 C-H bond activation in water and catalytic cross-coupling reactions. *Chem. Soc. Rev.* **2013**, *42*, 5744-5767. (b) Gandeepan, P.; Kaplaneris, N.; Santoro, S.; Vaccaro, L.; Ackermann, L. Biomass-derived solvents for sustainable transition-metal catalyzed C-H activation. *ACS Sustainable Chem. Eng.* **2019**, *7*, 8023-8040.

(23) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5th ed.; Butterworth-Heinemann: Oxford, U.K., 2003.

(24) Lastra-Barreira, B.; Díez, J.; Crochet, P.; Fernández, I. Functionalized arene-ruthenium(II) complexes: Dangling *vs.* tethering side chain. *Dalton Trans.* **2013**, *42*, 5412-5420.

(25) Hays, H. R. The reaction of diethyl phosphonate with methyl and ethyl Grignard reagents. *J. Org. Chem.* **1968**, *33*, 3690-3694.

(26) Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Hrapchak, M.; Latli, B.; Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C. H. A superior method for the reduction of secondary phosphine oxides. *Org. Lett.* **2005**, *7*, 4277-4280.

(27) *CrysAlis^{Pro} CCD & CrysAlis^{Pro} RED*; Oxford Diffraction Ltd., Oxford, U.K., 2008.

(28) Farrugia, L. J. WinGX and ORTEP for Windows: an update. *J. Appl. Cryst.* **2012**, *45*, 849-854.

(29) Burla, M. C.; Caliandro, R.; Carrozzini, B.; Cascarano, G. L.; Cuocci, C.; Giacovazzo, C.; Mallamo, M.; Mazzone, A.; Polidori, G. Crystal structure determination and refinement via SIR2014. *J. Appl. Cryst.* **2015**, *48*, 306-309.

(30) Sheldrick, G. M. *SHELXL97: Program for the Refinement of Crystal Structures*; University of Göttingen, Göttingen, Germany, 1997.

(31) *International Tables for X-ray Crystallography*, *Volume C*; Wilson, A. J. C., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992.

(32) Nardelli, M. PARST: A system of FORTRAN routines for calculating molecular structure parameters from results of crystal structure analyses. *Comput. Chem.* **1983**, *7*, 95-98.

(33) Brandenburg, K.; Putz, H. *DIAMOND*; Crystal Impact GbR, Bonn, Germany, 1999.

FOR TABLE OF CONTENTS USE ONLY

Hydrophilic (η^6-arene)-ruthenium(II) complexes with P-OH ligands as catalysts for the isomerization of allyl-benzenes and C-H bond arylation reactions in water

Rebeca González-Fernández, Pascale Crochet,* and Victorio Cadierno*