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Expanding the Range of Pyrenylphosphines and Their Derived Ru(II)-Arene Complexes

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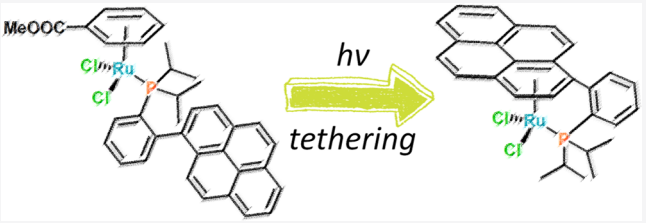
ABSTRACT: The precursor $\mathbf{PPyrCl_2}$ (Pyr = 1-pyrenyl) has been used to prepare a number of novel 1-pyrenylphosphines. Treatment of $\mathbf{PPyrCl_2}$ with methylmagnesium chloride has provided the phosphine $PPyrMe_2$, with methanol/triethylamine, the phosphonite $PPyr(OMe)_2$ (**1**), with dimethylamine/triethylamine, the diaminophosphine $PPyr(NMe_2)_2$ (**2**), and with lithium aluminum hydride, $PPyrH_2$ (**3**). From this primary phosphine, phosphirane $PPyr(CH_2CH_2)$ (**5**) has been obtained. The phosphine $PPyr_2Ph$ (**6**) has been synthesized from 1-bromopyrene, while 1-bromo-2-(1-pyrenyl)benzene has been used to prepare Ph-PyrPhos (**7**) and *i*-Pr-PyrPhos (**8**). The new phosphines have subsequently been used to obtain the corresponding $[RuCl_2(\eta^6\text{-arene})(PPyrR_2)]$ complexes $\mathbf{C1^{Cym}}$–$\mathbf{C3^{Cym}}$ and $\mathbf{C6^{Cym}}$–$\mathbf{C8^{Cym}}$ (arene = *p*-cymene; Cym) and $\mathbf{C1^{Mba}}$–$\mathbf{C3^{Mba}}$ and $\mathbf{C6^{Mba}}$–$\mathbf{C8^{Mba}}$ (arene = methyl benzoate; Mba), which have been fully characterized; the crystal structures of $\mathbf{C1^{Cym}}$, $\mathbf{C1^{Mba}}$, $\mathbf{C2^{Cym}}$, $\mathbf{C2^{Mba}}$, $\mathbf{C6^{Mba}}$, and $\mathbf{C7^{Cym}}$ were determined by X-ray diffraction. Substitution of the methyl benzoate fragment of complexes $\mathbf{C7^{Mba}}$ and $\mathbf{C8^{Mba}}$ by the η^6-coordinated pyrenyl group of the coordinated phosphine was achieved photochemically, giving the tethered complexes $\mathbf{C7^{Tet}}$ and $\mathbf{C8^{Tet}}$. In these two complexes the phosphine acts as a κ^1,η^6-coordinated ligand, as evidenced by the X-ray structure of $\mathbf{C8^{Tet}}$. The antineoplastic activities of the piano-stool Ru compounds revealed that they are highly phosphine dependent and two compounds, namely $\mathbf{C1^{Cym}}$ and $\mathbf{C2^{Cym}}$, exhibit interesting biological properties.



INTRODUCTION

D_{2h}-Symmetric pyrene (Pyr) has interesting properties and broad applications.[1] Pyrene is one of the simplest polycyclic aromatic hydrocarbons (PAHs) and constitutes the smallest peri-fused aromatic hydrocarbon. It is formed in small quantities by incomplete combustion of organic compounds, and although it has 16 π electrons and does not follow Hückel's rule, it is aromatic.[2] This feature gives pyrene very particular electronic and photophysical properties, including an exceptionally long lived fluorescence, which have been exploited to great effect in many fields, such as in organic electronics.[3] In addition, pyrene's flat aromatic system is ideal for studies on π–π interactions, intercalation chemistry, and supramolecular systems.[1] Thanks to these remarkable properties, a large variety of pyrenylated molecules (and materials) are widely used in chemical, physical, and biological studies.

Phosphorus-supported pyrene-containing molecules are no exception. Figure 1 shows a few selected examples of previously described 1-pyrenylphosphines and ruthenium derivatives. It should be noted that most derivatives of pyrene are functionalized at position 1, which is the most reactive. Functionalization of the other positions is much less frequent and requires specific methodologies.[4]

Quian, Huang, Yang, and co-workers[5] reported several air-stable pyrenylphosphine oxides ($\mathbf{P(O)PyrR_2}$) and found that $\mathbf{P(O)Pyr_3}$ exhibits a prominent temperature-dependent fluorescence intensity, suggesting its potential use as a molecular thermometer. Shortly after, Baker, Walensky, and co-workers[6] revisited this chemistry and expanded the fluorescence spectroscopy studies to other tris(1-pyrenyl)-pnictogens and their oxide and sulfide derivatives. Other more elaborated phosphine oxides (not bearing the pyrenyl ring directly bound to the phosphorus atom) have also been described.[7]

Several 1-pyrenylphosphines ($\mathbf{PPyrR_2}$) are also known, which are usually prepared by lithiation of 1-bromopyrene and phosphination with a chlorophosphine. Diphenyl-1-pyrenylphosphine ($\mathbf{PPyrPh_2}$)[8] has been known for some time,[9] since it is used as a fluorescent probe to detect the presence of oxidizing agents in lipids. This phosphine, which is

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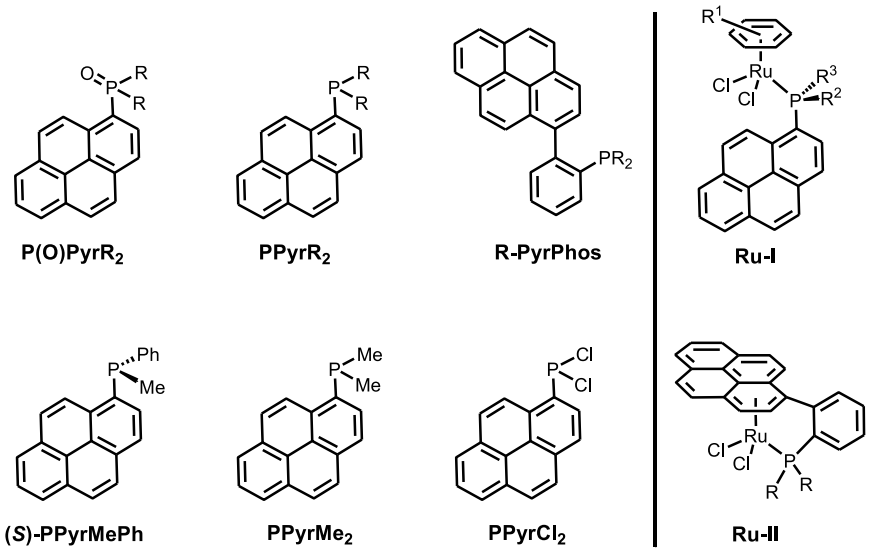
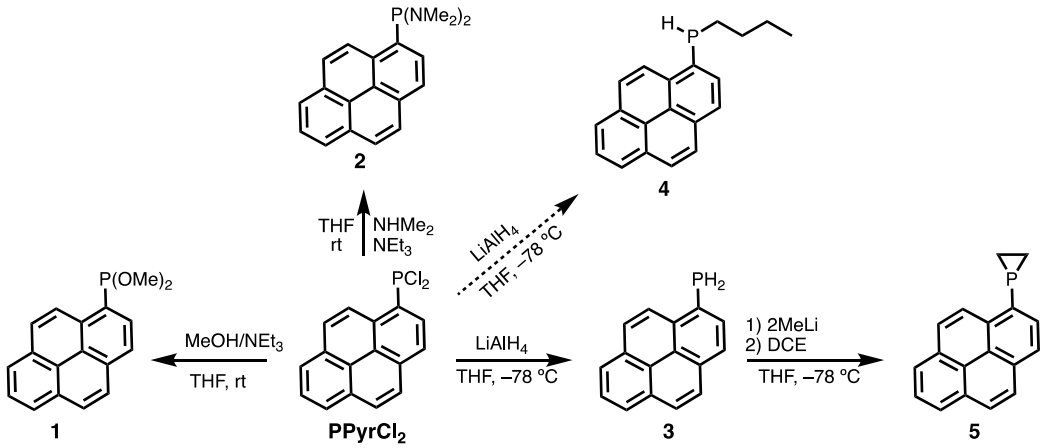


Figure 1. Selected 1-pyrenylphosphines and two derived families of Ru(II)-arene complexes.

Scheme 1. Preparation of 1-Pyrenylphosphines from $PPyrCl_2$



commercially available, is not fluorescent but the oxide is; therefore, it provides a sensitive method for the detection of oxidants, especially by HPLC.[10] Yip and co-workers[11] found that this phosphine and 1,6-bis(diphenylphosphino)pyrene could be metalated by [MCl(dppm)] (M = Pd, Pt; dppm = 1,1-bis(diphenylphosphino)methane) and studied the phosphorescence of the resulting complexes. This diphosphine ligand was used by the same group to explore the formation of Ag(I) and Cu(I) metallacyclophanes.[12]

Ionkin and co-workers[13] described the bulky **PPyr(*t*-Bu)$_2$** as a ligand for Pd-catalyzed Suzuki–Miyaura couplings and isolated a dimeric cyclometalated palladium complex. König and his co-worker[8b] used **PPyr$_3$** and **PPyrPh$_2$** to accelerate Pd-catalyzed cross-couplings under UV light. Yamakawa and co-workers[14] described **Cy-*t*-Bu-PyrPhos**, which was an efficient ligand in Pd-catalyzed aminations.

Our own interest in developing new monophosphine ligands for catalytic applications[15] led to the preparation of the first *P*-stereogenic 1-pyrenylphosphines (Figure 1), which were used in Pd-[16] and Ru-catalyzed[16,17] asymmetric reactions, although they provided low enantioselectivities. In contrast, some Ru-η^6-arene complexes of 1-pyrenylphoshines (**Ru-I**, Figure 1) were found to show potent cytotoxic activities,[18] especially with **PPyrMe$_2$**, which was described for the first time. Some structure–activity relationships (SARs) could be uncovered in that study. It can be mentioned here that numerous piano-stool Ru complexes have been reported which show remarkable anticancer properties.[19] For instance, [Ru(η^6-arene)Cl$_2$(pta)] RAPTA-type compounds (pta = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane) were found to exhibit interesting antimetastatic properties.[20]

In this context, a report of Baumgartner and co-workers[21] caught our attention because it described the preparation of **PPyrCl$_2$** in the course of their studies to synthesize PAH-functionalized dithienophospholes. Given the central role of dichlorophosphines in the preparation of heteroleptic (PRR′$_2$) phosphines,[22] we reasoned that **PPyrCl$_2$** should be an ideal precursor to expand the currently limited range of 1-pyrenylphosphines.

In the present paper, we describe the preparation of several novel 1-pyrenyphosphines starting from the precursor **PPyrCl$_2$** and of two families of their Ru-η^6-arene complexes. In addition, we also describe the preparation of a new member of the PyrPhos family and some derived ruthenium complexes, including the unprecedented tethered **Ru-II**-type complexes (Figure 1), bearing a η^6-coordinated pyrene substituent. Finally, preliminary cell-viability studies of the complexes are also presented, which reveal that two of the piano-stool Ru

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compounds exhibit interesting cytotoxic properties, in the 10 μM range.

RESULTS AND DISCUSSION

Synthesis of Pyrenylphosphines. *1-Pyrenylphosphines.* The synthesis of the new 1-pyrenylphosphines started with the preparation of dichloro(1-pyrenylphosphine) (**PPyrCl$_2$**), following the method of Baumgartner and co-workers[21] (Scheme 1).

PPyrCl$_2$ (δ_P +165.1 ppm)[21] was prepared by lithiation of 1-bromopyrene, followed by phosphination of the organolithium with chlorobis(diethylamino)phosphine to give PPyr(NEt$_2$)$_2$ (δ_P +100.1 ppm) and subsequent acidolysis of the P−N bonds by treatment with hydrogen chloride in diethyl ether. **PPyrCl$_2$** is a bright yellow solid that is stable under an inert atmosphere but very reactive to nucleophiles, allowing the preparation of 1-pyrenylphosphines.

We started our research by developing a new and more effective synthetic route to **PPyrMe$_2$**, which was recently reported to generate very cytotoxic Ru-arene complexes.[18] The previous method produced the ligand by reaction of 1-lithiopyrene with chlorodimethylphosphine; however, the latter reagent is very expensive, volatile, and violently pyrophoric, which make the method unsuitable for the large-scale preparation of **PPyrMe$_2$**. In contrast, it was found that **PPyrCl$_2$** reacted smoothly with 2 equiv of nonpyrophoric methylmagnesium chloride[23] to produce the desired ligand (δ_P −59.3 ppm).

Next, the reactivity of **PPyrCl$_2$** in condensation reactions with alcohols and amines was examined. The reaction of **PPyrCl$_2$** with methanol at room temperature, in the presence of an excess of triethylamine as a proton scavenger, produced the expected phosphonite **PPyr(OMe)$_2$** (**1**) in good yield. Initially, the reaction was performed in dichloromethane, as reported for other compounds,[23] but triethylammonium chloride was generated as a very fine solid, which greatly hindered the filtration. In contrast, in THF, the ammonium salt was formed as a nicely crystalline solid that could easily be removed by filtration. Phosphonite **1** is a yellow solid with a $^{31}P\{^1H\}$ NMR chemical shift of +158.3 ppm. In the ^1H and $^{13}C\{^1H\}$ NMR spectra, the expected sharp doublets of the methyls of the equivalent methoxy groups appear at 3.38 ($^3J_{HP}$ = 10.8 Hz) and 53.6 ($^2J_{CP}$ = 9.8 Hz) ppm, respectively.

The condensation of **PPyrCl$_2$** with a commercial THF solution of dimethylamine,[23,24] in the presence of triethylamine, produced the diaminophosphine **PPyr(NMe$_2$)$_2$** (**2**) as a yellow solid in very good yield. The compound showed the characteristic $^{31}P\{^1H\}$ NMR shift (δ_P +100.9 ppm) for arylbis(diethylamino)phosphines,[23,25] and in the ^1H and $^{13}C\{^1H\}$ NMR spectra, the four methyl groups of the ligand appeared as being equivalent.

The primary phosphine 1-pyrenylphosphine **PPyrH$_2$** (**3**) was next synthesized. Primary phosphines are often prepared by reduction of dichlorophosphines with lithium aluminum hydride; this method has indeed been applied to obtain some primary phosphines with PAH substituents such as 1-naphthylphosphine[26] and 9-anthracenylphosphine.[27] Therefore, **PPyrCl$_2$** was treated with slightly more than 2 equiv of lithium aluminum hydride and after an aqueous workup, under strict anaerobic conditions, 1-pyrenylphosphine was obtained as a yellow semisolid, together with a slight amount of an unexpected secondary phosphine (**4**), as discussed later. The $^{31}P\{^1H\}$ spectrum of **3** presents a singlet at −127.9 ppm, which becomes a triplet of doublets of triplets in the H-coupled ^{31}P spectrum (Figure 2).

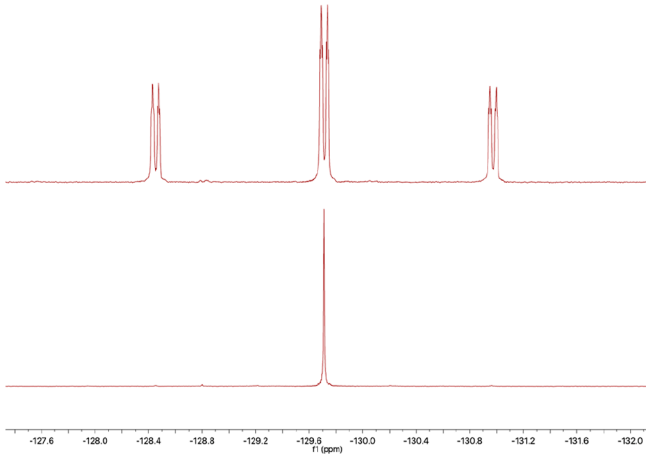


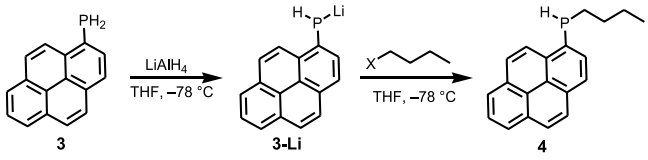
Figure 2. $^{31}P\{^1H\}$ (bottom) and ^{31}P (top) NMR spectra of **3** ($CDCl_3$, 162 MHz).

The high-field shift is typical of primary phosphines, as is the large $^1J_{PH}$ value,[26−28] reaching 204 Hz for **3**. The fine structure of the triplet is due to the coupling of the phosphorus atom with the H^2 of pyrene, giving a doublet ($^3J_{PH^2}$ = 7.3 Hz) and then to H^3 and H^{10}, with a small $^4J_{PH^{3,10}}$ value of 1.1 Hz. Schmidbaur and co-workers[26] reported similar values for $^1J_{PH}$ and $^3J_{PH}$ in 1-naphthylphosphine. In the ^1H NMR spectrum of **3**, the large doublet of the PH$_2$ protons appears at 4.45 ppm, a chemical shift in line with those of other primary arylphosphines.[26,27]

Primary phosphines have the gruesome reputation of being dangerously pyrophoric and evil-smelling compounds,[28a,c,29] although some of them are stable and are gaining interest as synthetic intermediates in organophosphorus chemistry.[23,30] In this respect, **3** is relatively well behaved, as it can be stored for months under strict exclusion of dioxygen. In solution, however, it quickly degrades on exposure to air and presents the foul, unmistakably *garlicky* smell characteristic of volatile phosphines.[29]

In the course of our studies, the synthesis of **3** was repeated a few times and, in some cases, the secondary phosphine PPyr(*n*-Bu)H (**4**) was obtained instead as a main product (Scheme 2). This compound was identified by a sharp doublet

Scheme 2. Proposed Formation of Phosphine 4



in its H-coupled ^{31}P NMR spectrum (δ_P −59.3 ppm, $^1J_{PH}$ = 210.4 Hz) and by the characteristic NMR features of a *n*-butyl group in the ^1H and $^{13}C\{^1H\}$ NMR spectra (see the Experimental Section and Figures S17−S19). The *n*-butyl group must come from the *n*-butyllithium solution employed to prepare **PPyrCl$_2$**, which was not purified. A possibility is that **3**, once formed, is deprotonated by lithium aluminum

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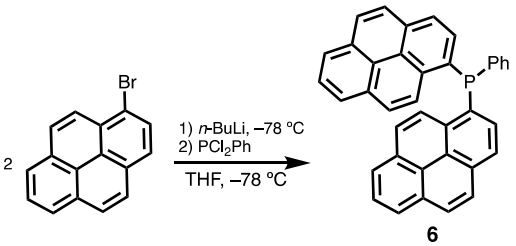
hydride, forming a very nucleophilic phosphide (**3-Li**), which is alkylated by a butyl electrophile (Scheme 2).

The preparation of **PPyrCl$_2$** involves the lithiation of 1-bromopyrene, which generates 1 equiv of 1-bromobutane. This compound, however, cannot be the alkylating agent to generate **4**, since it was also present in the successful preparations of **3**. It appears that the commercial source of the *n*-BuLi solution is important (see the Experimental Section for details). It seems that an unidentified species in the *n*-BuLi solution from one of the suppliers is the source of a *n*-butyl electrophile that is responsible for the different reactivity observed (generation of **4** instead of **3** and *vice versa*).

Primary phosphines are versatile precursors and have been used to prepare three-membered phosphorus heterocycles: viz., phosphiranes.[31] Phosphine **3** was treated with 2 equiv of methyllithium to generate a dark purple solution of the extremely nucleophilic lithium 1-pyrenylphosphide dianion, which afforded **5** in good yield by treatment with 1,2-dichloroethane. Phosphirane **5** is a yellow solid whose most characteristic feature is its specific $^{31}P\{^1H\}$ chemical shift of −235.8 ppm. This is a normal value for a phosphirane[23,27b,30c,31b] and reflects the greater s character of the lone-pair orbital, due to the highly strained nature of the three-membered ring.[30c] Phosphiranes, with some exceptions,[30c,32] are unstable toward ring opening, causing their decomposition and polymerization.[30c,31a] Although it has been reported that extended π conjugation is beneficial for the stability of phosphiranes,[30c] the 1-pyrenyl substituent is apparently not enough to render **5** stable, since it was found to decompose after a few weeks stored pure under a dinitrogen atmosphere or within minutes when it is dissolved in chloroform and exposed to direct sunlight. The $^{31}P\{^1H\}$ spectrum exhibits many sharp peaks between −60 and +10 ppm, ascribed to decomposition and polymerized species (see Figure S20).

Tris(1-pyrenyl)phosphine has been described and fully characterized,[6,8b] but bis(1-pyrenyl)phosphines have been very rarely reported. Ung and co-workers[33] recently described the synthesis of ethylbis(1-pyrenyl)phosphinite, but the sole example of a bis(1-pyrenyl)phosphine is phenylbis(1-pyrenyl)-phosphine (**6**), which was prepared for comparison purposes without experimental details[8a] or as a synthetic intermediate,[5] without being isolated. Therefore, it was deemed interesting to report the detailed synthesis and characterization of this compound (Scheme 3).

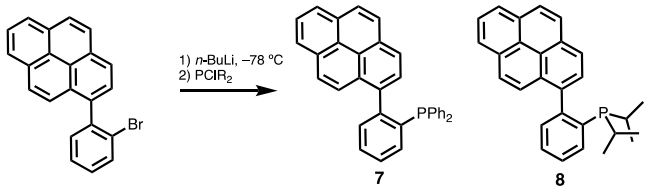
Scheme 3. Preparation of 6



The reaction of 2 equiv of 1-lithiopyrene with dichlorophenylphosphine successfully afforded **6** in good yield as an air-sensitive yellow substance that showed a sharp singlet at −21.5 ppm in the $^{31}P\{^1H\}$ NMR spectrum, in agreement with the reported value.[8a]

2-(1-Pyrenyl)phenylphosphines. A few years ago, we reported the preparation of several *P*-stereogenic (2-arylphenyl)phosphines and their application in the ruthenium-catalyzed asymmetric reduction of ketones.[34] It was found that these ligands were able to act as a $\kappa P,\eta^6$-donor ligands by photochemical displacement of a η^6-coordinated arene from the ruthenium atom. The preparation of similar ligands bearing a 1-pyrenyl moiety was then envisaged (Scheme 4).

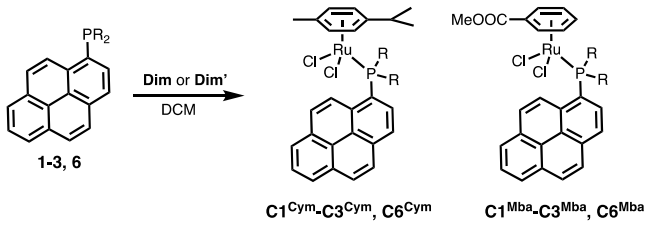
Scheme 4. Preparation of PyrPhos ligands 7 and 8



Yamakawa and co-workers[14] described analogous (2-(1-pyrenyl)phenyl)phosphines with cyclohexyl and *tert*-butyl groups for palladium-catalyzed aminations and coined the name *PyrPhos* for them. Bouit, Nyulászi, Hissler, and co-workers[35] prepared phosphine **7** as an intermediate of pyrenebenzo[*b*]phosphole, without reporting its full characterization. 1-Bromo-2-(1-pyrenyl)benzene[36] was subjected to the standard lithiation−phosphination sequence,[14,34] giving the expected ligands **7** (δ_P −14.0 ppm) and **8** (δ_P −4.8, −5.4 ppm). The fact that two resonances were observed for **8** in its $^{31}P\{^1H\}$ NMR spectrum (Figure S31) reflects the presence of two species in solution, arising from the restricted rotation of the phenyl−pyrenyl bond. A similar phenomenon has been observed for other (2-arylphenyl)phosphines[34,37] and other bulky phosphines.[8b,38]

Ruthenium(II)-Arene Complexes. *Complexes with 1-Pyrenylphosphines.* Approximately 2 equiv of phosphines **1**−**3** and **6** were added to solutions of [RuCl(μ-Cl)(η^6-*p*-cymene)]$_2$ (**Dim**) and [RuCl(μ-Cl)(η^6-methyl benzoate)]$_2$ (**Dim′**) in dichloromethane, generating two families of complexes with different arenes, namely **C1^{Cym}**−**C3^{Cym}**, **C6^{Cym}** and **C1^{Mba}**−**C3^{Mba}**, **C6^{Mba}** (Scheme 5), through dimer splitting.[15b,16,18]

Scheme 5. Preparation of Complexes Derived from Ligands 1−3 and 6[a]



[a]**Cym** stands for *p*-cymene and **Mba** for methyl benzoate.

The complexes were obtained as orange or red solids in low to moderate yields after a single recrystallization. Further recrystallizations were detrimental to both the yield and purity of the complexes, due to limited stability in solution. Once they were isolated, the complexes were stable in the solid state except for **C3^{Cym}** and **C3^{Mba}**, which slowly decomposed on exposure to air. The complexes are soluble in dichloromethane, chloroform, and dmso, poorly soluble in alcohols, and completely insoluble in alkanes or water. In solution, NMR spectroscopy showed that all of the complexes are unstable

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with time, since decomposition products could be detected from hours to days depending on the case. The decomposition is due to arene decoordination and phosphine decoordination. The former process is much faster for the more labile methyl benzoate,[18] especially if the solution is not protected from light.[34] Interestingly, the arene decoordination rate depends on the P-ligand: when dmso-d_6 solutions of **C1**^{Mba} and **C2**^{Mba} were monitored by ^{1}H NMR spectroscopy in the dark (see Figures S82 and S83), almost complete decoordination of methyl benzoate was found after 24 h for **C1**^{Mba}, while more than 72 h was required for **C2**^{Mba}.

Dichloromethane solutions of methyl benzoate complexes gradually become cloudy due to the formation of a precipitate of the highly insoluble $[RuCl(\mu\text{-}Cl)(\eta^6\text{-methyl benzoate})]_2$, implying decoordination (and subsequent oxidation/hydrolysis) of the P-ligand.

Analytical and spectroscopic data support the proposed formulation of the compounds. In particular, successful coordination of the ligands was evidenced by the shifts of the $^{31}P\{^1H\}$ signals (Table 1).

Table 1. $^{31}P\{^1H\}$ Chemical Shifts (in ppm, See the Experimental Section for the Solvent) of Phosphines and Their Corresponding Ru Complexes

	δ_P		
ligand X	ligand X	**CX**^{Cym}	**CX**^{Mba}
1	+158.3	+145.5	+142.1
2	+100.9	+103.3	+99.6
3	−129.7	−27.0	−28.9
6	−21.5	+32.8	+31.1

As expected,[18] the two families of complexes, namely **CX**^{Cym} and **CX**^{Mba} (Scheme 5), presented very little difference in the ^{31}P chemical shifts with the same ligand. In contrast, the chemical shift differences between the uncoordinated and coordinated ligands depended strongly on its nature.

Counterintuitively, the ^{31}P signal for phosphonite **1** shifted upfield upon coordination, a feature that has also been observed with other phosphonites coordinated to $[RuCl_2(\eta^6\text{-}p\text{-cymene})]$ moieties.[39] For example, the chemical shift of diethylphenylphosphonite changes from +157.0 ppm for the free ligand[40] to +138.2 ppm on coordination.[39d]

Interestingly, the ^{31}P chemical shift of diaminophosphine **2** is almost unaffected upon coordination. Unfortunately, this fact cannot be compared to other ligands, as there is only one reported diaminophosphine ligand coordinated to $[RuCl_2(\eta^6\text{-}p\text{-cymene})]$, i.e. dipyrrolylphosphine, which is electronically distinct (in comparison to **2**).[41] However, Higham and coworkers[23] reported the coordination of 1,1′-binaphthyl-*N*,*N*,*N*′,*N*′-tetramethyldiaminophosphine to a Pd(allyl)Cl moiety, observing a similar small change in ^{31}P chemical shift of the ligand upon coordination.

A significant 100 ppm downfield shift of the $^{31}P\{^1H\}$ resonance is observed upon coordination of the primary phosphine **3**. In addition, the $^1J_{PH}$ coupling constant increases from 204.3 Hz for the free ligand to 391.1 and 404.4 Hz for **C3**^{Cym} and **C3**^{Mba}, respectively. This can be attributed to the increased s orbital character of the P−H bonds;[42] such a feature has been observed in the very few reported complexes of primary phosphines coordinated to $[RuCl_2(\eta^6\text{-arene})]$ units.[42b,43]

A more moderate downfield shift was observed in the case of the coordination of triarylphosphine **6**, as is usually observed for tertiary phosphines.[18,34] The peaks of **C6**^{Cym} and **C6**^{Mba} are very broad, which is not surprising given the bulkiness of dipyrenylphosphine **6**.

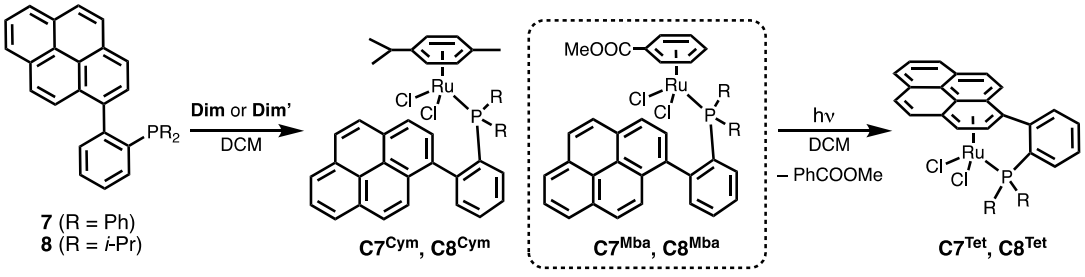
The ^{1}H NMR spectra agreed with the proposed structures of the complexes; in the case of complexes **C2**^{Cym}, **C2**^{Mba}, **C6**^{Cym}, and **C6**^{Mba} the very wide signals observed can be explained by their steric hindrance; it is very likely that the η^6-arene fragment and the phosphine groups rotate slowly on the NMR time scale. Such a phenomenon has been observed previously.[18,34]

Complexes with 2-(1-Pyrenyl)phenylphosphines. The coordination of 2-(1-pyrenyl)phenylphosphines **7** and **8** to ruthenium was performed in the same way as previously described. The obtained complexes are shown in Scheme 6.

All of the complexes were obtained as orange solids in yields better than those of the aforementioned complexes, most likely as the result of the higher stability of phosphines **7** and **8**. The complexes were soluble in chloroform and dichloromethane and insoluble in pentane, hexane, and water. The characterization data agreed with the proposed structures and also illustrated the bulkiness of the coordinated phosphine. This was indeed evidenced in the $^{31}P\{^1H\}$ NMR spectra, which showed very wide peaks, so that in the case of the bulkiest complex **C8**^{Cym}, the ^{31}P signal could not even be located (Figure S68). We therefore carried out low-temperature NMR experiments in deuterated chloroform, which allowed us to observe the missing peak at δ +49.5 ppm on cooling below 260 K (see Figure S69). The ^{1}H NMR spectra were more complicated than expected, suggesting the presence of several species in solution, for instance involving different orientations of the η^6-coordinated arene rings, and showed little variation upon lowering the temperature.

Following methods given in previous studies,[34] solutions of complexes **C7**^{Mba} and **C8**^{Mba} were irradiated with a conventional 9 W fluorescent desk lamp, to perform the photochemical displacement of the methyl benzoate ring by the 2-

Scheme 6. Preparation of Complexes C7^{Cym}, C7^{Mba}, C7^{Tet}, C8^{Cym}, C8^{Mba}, and C8^{Tet}



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(1-pyrenyl)phenyl group of the phosphines. The solutions rapidly became darker, and from them the desired tethered complexes $\mathbf{C7}^{\mathbf{Tet}}$ and $\mathbf{C8}^{\mathbf{Tet}}$ could be isolated in low yields (36 and 20%, respectively) as dark brown solids after 6 h of irradiation. The complexes are soluble in dichloromethane or chloroform and completely insoluble in pentane, hexane, and water. The HRMS of the complexes showed an intense peak corresponding to the $[M - Cl]^+$ ion (Figures S84–S89). Their ^{31}P NMR spectra showed sharp signals (Figures S77 and S79), in contrast to their nontethered counterparts, probably due to the increased rigidity brought by the phosphine, coordinated in a κ^1,η^6 fashion. As expected, a large downfield shift was observed in the $^{31}P\{^1H\}$ NMR spectra.[34] The tethered complexes are chiral, and this is reflected in the ^1H NMR of $\mathbf{C8}^{\mathbf{Tet}}$, in which the methyl groups of the isopropyl moieties appear as four well-separated doublets of doublets (see the Experimental Section and Figure S81). No temperature effect was noted by $^{31}P\{^1H\}$ NMR spectroscopy (Figure S80). When the same tethering reaction was carried out with the *p*-cymene complex $\mathbf{C7}^{\mathbf{Cym}}$ or $\mathbf{C8}^{\mathbf{Cym}}$, up to 4 days was required to achieve full conversion, and very low (<10%) yields were obtained. While an analogous reaction was described by some of us with complexes bearing *P*-stereogenic (2-arylphenyl)phosphines (aryl = phenyl, biphenyl, naphthyl),[34] the results presented here prove that the reaction can be generalized to ligands in which the aryl group is a peri-fused polycyclic aromatic hydrocarbon, such as pyrene.

To study the tethering reaction by UV–vis spectroscopy, a solution of $\mathbf{C7}^{\mathbf{Mba}}$ was irradiated with white light by the spectrophotometer's lamp during short intervals and the UV–vis spectra were collected (Figure 3).

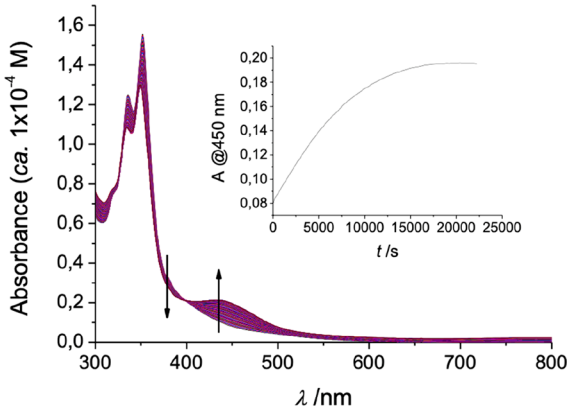

Figure 3. Time-resolved UV–vis spectra of a ca. 1.0×10^{-4} M dichloromethane solution of $\mathbf{C7}^{\mathbf{Mba}}$ irradiated with white light (190–1100 nm) for 0.5 at 60 s intervals. Inset: absorbance at 450 nm vs time.

The spectral changes occurring over about 6 h are illustrative of clean tethering of $\mathbf{C7}^{\mathbf{Mba}}$ to $\mathbf{C7}^{\mathbf{Tet}}$ (5 min of direct irradiation by the spectrophotometer's lamp and continuous "open-compartment" light). If the experiment is performed under continuous irradiation (Figure S90), a more intricate process, including decomposition, occurs. A similar time-dependent behavior is observed upon continuous irradiation of a solution of $\mathbf{C7}^{\mathbf{Tet}}$ (Figure S91), which evolves with time. Time-resolved static measurements under indirect sunlight produce a rather similar pattern of UV–vis spectral changes (Figure S92). Analogous comportments were observed for $\mathbf{C8}^{\mathbf{Mba}}$ and for the *p*-cymene complexes $\mathbf{C7}^{\mathbf{Cym}}$ and $\mathbf{C8}^{\mathbf{Cym}}$; however, for the latter, the changes need longer times and/or more intense irradiations and they are accompanied by increased decomposition, in line with the very low yields obtained.

The tethered complexes $\mathbf{C7}^{\mathbf{Tet}}$ and $\mathbf{C8}^{\mathbf{Tet}}$ are interesting because although in the literature there are several Ru(II) complexes bearing a η^6-coordinated pyrene,[44] they mostly contain the *all organometallic* $[Ru(\eta^6\text{-pyrene})Cp]^+$ cations, without any phosphorus or tethered ligand. Interestingly, Loughrey and co-workers[44d] showed that some of these complexes are quite cytotoxic.

Crystal Structures. Single crystals, suitable for X-ray diffraction studies, were obtained for $\mathbf{C1}^{\mathbf{Cym}}$, $\mathbf{C1}^{\mathbf{Mba}}$, $\mathbf{C2}^{\mathbf{Cym}}$, $\mathbf{C2}^{\mathbf{Mba}}$, $\mathbf{C6}^{\mathbf{Mba}}$, and $\mathbf{C7}^{\mathbf{Cym}}$ and also for the tethered complex $\mathbf{C8}^{\mathbf{Tet}}$ by slow diffusion of hexane or diethyl ether in concentrated solutions of the corresponding complexes in dichloromethane. Crystallographic and refinement parameters are summarized in Table S1 ($\mathbf{C1}^{\mathbf{Cym}}$ and $\mathbf{C1}^{\mathbf{Mba}}$), Table S2 ($\mathbf{C2}^{\mathbf{Cym}}$ and $\mathbf{C2}^{\mathbf{Mba}}$), Table S4 ($\mathbf{C6}^{\mathbf{Mba}}$ and $\mathbf{C7}^{\mathbf{Cym}}$), and Table S6 ($\mathbf{C8}^{\mathbf{Tet}}$). As illustrated in Figures S1–S3, all of the complexes exhibit the typical piano-stool geometry around the metal center (see also Figure 4), including tethered $\mathbf{C8}^{\mathbf{Tet}}$.

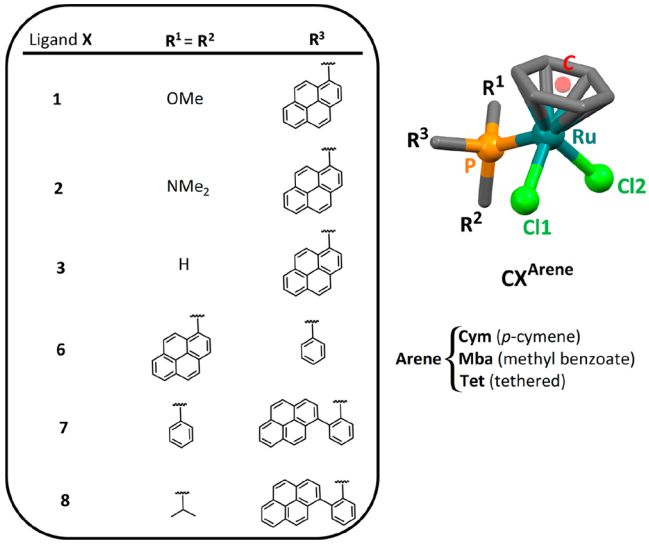

Figure 4. Schematic representation of the piano-stool ruthenium(II) complexes $\mathbf{CX}^{\mathbf{Arene}}$ prepared in the present study, where **X** represents the monophosphine ligand $PR^1R^2R^3$ and **Arene** stands for the η^6-arene ligand, namely *p*-cymene (**Cym**), methyl benzoate (**Mba**), or the tethered ligand (**Tet**). ***C*** symbolizes the centroid of the η^6-arene ligand.

Selected coordination bond distances and angles are given in Table S3 ($\mathbf{C1}^{\mathbf{Cym}}$, $\mathbf{C1}^{\mathbf{Mba}}$, $\mathbf{C2}^{\mathbf{Cym}}$ and $\mathbf{C2}^{\mathbf{Mba}}$), Table S5 ($\mathbf{C6}^{\mathbf{Mba}}$ and $\mathbf{C7}^{\mathbf{Cym}}$), and Table S7 ($\mathbf{C8}^{\mathbf{Tet}}$). The Ru–***C*** distances (***C*** = centroid of the η^6-arene ring; Figure 4) in the range 1.69–1.72 Å are normal. The Ru–Cl and Ru–P bond lengths, varying from 2.37 to 2.42 Å and from 2.28 to 2.39 Å, respectively, are also in normal ranges for such Ru compounds. The angles around the Ru ion are typical, with Cl–Ru–Cl and Cl–Ru–P values ranging from 85 to 90° and from 87 to 90°, respectively. The ***C***–Ru–Cl and ***C***–Ru–P angles are in normal ranges as well: 122–127° and 123–130°, respectively.

Cytotoxicity. The ability of the Ru compounds to inhibit cell growth and/or induce cell death was evaluated in A549 cells (lung adenocarcinoma) at a fixed complex concentration

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of 10 μM. The corresponding cell viability data, after incubation for 24 h, are given in Table 2. In general, the

Table 2. Cell Viability Values (%)[a] of the 14 Ru Compounds Prepared, at a Fixed Concentration of 10 μM, for A549 (Lung Adenocarcinoma) Human Cells, after Incubation of 24 h at 37 °C

ligand X	CX^{Cym}	CX^{Mba}	CX^{Tet}
1	51 ± 6	77 ± 24	
2	53 ± 10	66 ± 9	
3	98 ± 18	106 ± 15	
6	102 ± 5	105 ± 4	
7	96 ± 3	83 ± 4	94 ± 3
8	94 ± 2	90 ± 2	96 ± 2

[a]The results are expressed as mean values ± SD out of three independent experiments.

complexes are not very active. Only $\mathbf{C1}^{Cym}$, $\mathbf{C1}^{Mba}$, $\mathbf{C2}^{Cym}$, and $\mathbf{C2}^{Mba}$ show some interesting cytotoxic activity. In particular, the *p*-cymene-based complexes $\mathbf{C1}^{Cym}$ and $\mathbf{C2}^{Cym}$ give rise to cell viabilities of around 50% after 24 h incubation at 37 °C (Table 2); hence, these compounds have a half-maximum inhibitory concentration (IC_{50} value) of about 10 μM, which is in the range of that observed for related complexes from the ligand dimethyl(1-pyrenyl)phosphine (whose improved synthesis is described herein), reported earlier.[18] Thus, replacement of methyl substituents by methoxy or dimethylamino groups does not improve the cytotoxic properties of the corresponding Ru compounds or worsen them. In contrast, the use of the primary phosphine **3** does not generate active compounds (Table 2). Similarly, functionalization of the phosphine ligand with additional aryl groups (in addition to the pyrenyl unit), i.e. ligands **6** and **7**, also gives inactive compounds, as does the use of isopropyl groups combined with a 2-(1-pyrenyl)phenyl substituent: viz., ligand **8**. Tethering complexes $\mathbf{C7}^{Mba}$ and $\mathbf{C8}^{Mba}$ by photoinduced η^6-coordination of the pyrenyl ring of ligands **7** and **8**, respectively, does not lead to compounds, viz. $\mathbf{C7}^{Tet}$ and $\mathbf{C8}^{Tet}$, with improved cytotoxic properties (Table 2).

The NMR studies (see above) have shown that the complexes evolve in dmso-d_6; it is therefore reasonable to consider that these complexes are also altered in aqueous solution. Unfortunately, the actual species responsible for the cytotoxicity remains unknown due to the poor aqueous solubility of the complexes, which precluded NMR studies either in neat water or in water/dmso mixtures, without a large excess of dmso. In-depth studies are currently being carried out with related complexes, including more robust 1-pyrenylphosphines, with the objective of unveiling the nature of the cytotoxic species.

CONCLUSIONS

The present study has allowed us to demonstrate that the dichlorophosphine $\mathbf{PPyrCl_2}$ is a highly versatile precursor for the preparation of 1-pyrenyl-based phosphines. A few new members of such ligands have been prepared, including the primary phosphine **3** and its derived phosphirane, **5**. In addition, a new and efficient method for the preparation of the dimethylphosphine $\mathbf{PPyrMe_2}$ avoiding pyrophoric reagents has been developed. A series of no less than 14 different pyrenyl-containing ruthenium complexes has hence been prepared from 6 distinct phosphine ligands and characterized. The Ru(II) complexes with PyrPhos ligands **7** and **8** can readily be photochemically modified through exchange of the η^6-methyl benzoate ligand by the 2-(1-pyrenyl)phenyl substituent of the coordinated phosphine, producing tethered complexes $\mathbf{C7}^{Tet}$ and $\mathbf{C8}^{Tet}$.

Exploratory cytotoxicity studies allowed us to show that the biological activities of the complexes drastically depend on the nature of the coordinated phosphine ligand, the Ru compounds being completely inactive or exhibiting significant cell toxicities. For instance, 10 μM solutions of $\mathbf{C1}^{Cym}$ and $\mathbf{C2}^{Cym}$ were capable of decreasing 50% cell viability of A549 (lung adenocarcinoma) cells, after 24 h of incubation at 37 °C.

EXPERIMENTAL SECTION

General Considerations. All compounds were prepared under a purified dinitrogen atmosphere using standard Schlenk and vacuum-line techniques. The solvents were purified by a solvent purification system or by standard procedures[45] and stored under dinitrogen. ^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H}, and ^{1}H–^{13}C HSQC NMR spectra were recorded at room temperature with 400 MHz spectrometers using $CDCl_3$ as solvent unless otherwise specified. The fields were 400 MHz (^{1}H), 101 MHz (^{13}C), and 162 MHz (^{31}P). Chemical shifts are reported downfield from standards, and the coupling constants are given in Hz. High-resolution mass analyses (HRMS) were carried out using electrospray ionization (ESI). The dichlorophosphine $\mathbf{PPyrCl_2}$[21] and ruthenium dimer **Dim′**[46] were prepared following literature protocols. 1-Bromo-2-(1-pyrenyl)benzene,[36] $\mathbf{PPyrMe_2}$,[18] **6**,[5,8a] and **7**[35] have been described previously but with different procedures or with few details of their characterization; for this reason, their detailed preparation and characterization are given herein. The ligands and especially the complexes contain small amounts of residual solvents (THF, dichloromethane, hexane, pentane) despite extensive drying under reduced pressure. The ^{1}H NMR peaks of these solvents have been marked in the spectra in the Supporting Information and can be easily identified from the literature data.[47] Despite many attempts, reasonable elemental analyses for the complexes with ligands **7** and **8** could not be obtained; therefore, they are not included. Note on safety: the phosphines and derivatives described here are malodorous compounds. The stench is especially notorious with the more volatile phosphines $\mathbf{PPyrMe_2}$, **3**, **4**, *and* **5**. *These foul-smelling substances should be prepared, characterized, used, and stored with utmost care following the recommendations for the manipulation of volatile organophosphorus compounds.*[29]

Precursors. *1-Bromo-2-(1-pyrenyl)benzene.* This compound was prepared by a modification of a literature procedure,[36a] following our previously developed method to prepare 1-bromo-2-arylbenzenes.[34] Tris(dibenzylideneacetone)dipalladium(0) (343 mg, 0.375 mmol) and triphenylphosphine (787 mg, 3 mmol) were dissolved in 80 mL of 1,2-dimethoxyethane to obtain the catalyst. The mixture was stirred for 10 min, and then 1-bromo-2-iodobenzene (642 μL, 5 mmol) was rapidly added. After 15 min of reaction, the mixture had become greenish and a suspension of 1-pyrenylboronic acid (1.23 g, 5 mmol) in 80 mL of a deoxygenated 2 M aqueous sodium carbonate solution was added. The resulting biphasic mixture was refluxed for 12 h at 95 °C. The mixture was cooled to room temperature and extracted with dichloromethane (2 × 100 mL), and the combined organic phase was washed with water, dried over anhydrous sodium sulfate, and filtered. The solvents were removed under reduced pressure, leaving a dark brown pasty solid, which was purified by column chromatography (silica flash, hexane). The solvent was removed under reduced pressure, giving the title compound as a white solid. Yield: 1.55 g (87%). The characterization data matched those reported earlier for this compound.[36]

1-Pyrenylphosphines. *$\mathbf{PPyrMe_2}$.* The dichlorophosphine $\mathbf{PPyrCl_2}$ (1.51 g, 5.0 mmol) was dissolved in 50 mL of THF, and the yellow solution was cooled to −78 °C. A 3 M THF solution of methylmagnesium chloride (4.0 mL, 12.0 mmol) was added dropwise, and the mixture was warmed to room temperature over 3 h. At this

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point, 1 mL of MeOH was added to quench the remaining Grignard reagent. A $^{31}P\{^{1}H\}$ NMR spectrum of the solution was recorded, which showed the clean formation of **PPyrMe$_2$** (δ_P −59.3 ppm).[18] From this solution and following our previously reported procedures,[18] the free phosphine **PPyrMe$_2$**, its borane adduct **PPyrMe$_2$·BH$_3$**, or the known complexes [RuCl$_2$(η^6-*p*-cymene)(**PPyrMe$_2$**)] and [RuCl$_2$(η^6-methyl benzoate)(**PPyrMe$_2$**)] can be obtained.[18]

PPyr(OMe)$_2$ (1). The dichlorophosphine **PPyrCl$_2$** (758 mg, 2.5 mmol) was dissolved in 50 mL of THF, and triethylamine (2.1 mL, 15.0 mmol) was added. The addition of methanol (250 μL, 6.2 mmol) caused the formation of a cloudy mixture that was stirred for 2 h. The solution was filtered and brought to dryness, leaving the title product as a yellow solid. Yield: 582 mg (79%).

^{1}H NMR (C_6D_6): 9.01 (dd, J = 9.2, 3.2 $1H_{Ar}$), 8.59 (dd, J = 8.4, 3.2, $1H_{Ar}$), 8.02−7.70 (m, $6H_{Ar}$), 3.38 (d, J = 10.8, 6H). $^{13}C\{^{1}H\}$ NMR: 133.2−123.8 (m, C_{Ar}, CH_{Ar}), 53.6 (d, J_{CP} = 9.8, CH_3). $^{31}P\{^{1}H\}$ NMR (C_6D_6): +158.3 (s).

PPyr(NMe$_2$)$_2$ (2). The dichlorophosphine **PPyrCl$_2$** (758 mg, 2.5 mmol) was dissolved in 50 mL of THF, and triethylamine (2.1 mL, 15.0 mmol) was added, at room temperature. The addition of a 2 M THF solution of dimethylamine (2.6 mL, 5.2 mmol) caused the formation of a cloudy mixture that was stirred for 14 h. The solution was filtered and brought to dryness, leaving the title product as a yellow solid. Yield: 755 mg (92%).

^{1}H NMR: 8.58 (d, J = 9.2, $1H_{Ar}$), 8.23−7.98 (m, $8H_{Ar}$), 2.86 (d, J = 8.8, 12H). $^{13}C\{^{1}H\}$ NMR: 135.0−124.4 (m, C_{Ar}, CH_{Ar}), 41.7 (d, J_{CP} = 16.2, CH_3). $^{31}P\{^{1}H\}$ NMR: +100.9 (s).

PPyrH$_2$ (3). *For the preparation of this compound, a 1.6 M n-BuLi solution in hexanes from Sigma-Aldrich (now Merck), product reference number 186171, was used to prepare the precursor dichlorophosphine* ***PPyrCl$_2$***.

To a suspension of lithium aluminum hydride (417 mg, 11.0 mmol) in 50 mL of THF, precooled to −78 °C, was added a solution of **PPyrCl$_2$** (1.51 g, 5.0 mmol) in 30 mL of THF dropwise during 2 h, and the mixture was warmed to room temperature overnight. To the brown suspension was carefully added 25 mL of saturated solution of a thoroughly degassed aqueous ammonium chloride (*dihydrogen evolution!*), and the THF was eliminated under reduced pressure. The aqueous suspension was extracted with dichloromethane (3 × 20 mL), the combined organic phase was dried with sodium sulfate and filtered, and the solvent was removed under reduced pressure, yielding the primary phosphine as a malodorous, yellow semisolid. Yield: 888 mg (76%).

^{1}H NMR: 8.41 (dd, J = 9.2, 2.0, $1H_{Ar}$), 8.23−8.01 (m, $8H_{Ar}$), 4.45 (d, J_{HP} = 204.0, 2H). $^{13}C\{^{1}H\}$ NMR: 133.9−125.1 (m, C_{Ar}, CH_{Ar}). $^{31}P\{^{1}H\}$ NMR: −129.7 (s). ^{31}P NMR: −129.7 (tdt, J_{PH} = 204.3, 7.3, 1.1).

PPyr(n-Bu)H (4). *This secondary phosphine was unexpectedly obtained when the precursor dichlorophosphine* ***PPyrCl$_2$*** *was prepared using 1.6 M n-BuLi solution in hexanes from Acros Organics, product reference number 181271000.*

The procedure to prepare **3** was followed, yielding the secondary phosphine **4** as a white resin that was slightly impure since some amount of **3** (∼8%) was present as well. Yield: 1.16 g (80%).

^{1}H NMR (C_6D_6): 8.72 (dd, J = 9.2, 3.6, $1H_{Ar}$), 8.07 (dd, J = 7.6, 5.2, $1H_{Ar}$), 7.93−7.71 (m, $8H_{Ar}$), 4.54 (dt, J_{HP} = 210.8, J_{HH} = 7.2, 1H), 1.96−1.84 (m, 1H), 1.79−1.69 (m, 1H), 1.41−1.32 (m, 2H), 1.23−1.17 (m, 2H), 0.72 (t, J = 7.2, H). $^{13}C\{^{1}H\}$ NMR: 133.9−118.6 (m, C_{Ar}, CH_{Ar}), 26.8 (d, J_{CP} = 2.7, CH_2), 23.8 (d, J_{CP} = 12.7, CH_2), 23.4 (d, J_{CP} = 35.0, CH_2), 13.6 (CH_3). $^{31}P\{^{1}H\}$ NMR (C_6D_6): −59.3 (s). ^{31}P NMR (C_6D_6): −59.3 (d, J_{PH} = 210.4).

PPyr(CH$_2$CH$_2$) (5). Phosphine **3** (468 mg, 2.0 mmol) was dissolved in 10 mL of THF, and the yellow solution was cooled to −78 °C. A 1.6 M methyllithium solution in diethyl ether (2.6 mL, 4.2 mmol) was added, and the dark purple mixture was stirred for 30 min. To this mixture was added 1,2-dichloroethane (180 μL, 2.28 mmol), and the reaction mixture was stirred overnight. The reaction was subsequently quenched with 1 mL of methanol, and the solvents were eliminated under reduced pressure. The crude product was treated with 10 mL of dichloromethane and 10 mL of water, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phase was dried with sodium sulfate and filtered and the solvent removed under reduced pressure to yield the desired phosphirane as a yellow solid. Yield: 452 mg (87%).

^{1}H NMR (C_6D_6): 9.01 (dd, J = 9.2, 2.8, $1H_{Ar}$), 7.91−7.67 (m, $8H_{Ar}$), 1.29−1.25 (m, 2H), 1.16−1.08 (m, 2H). $^{13}C\{^{1}H\}$ NMR (C_6D_6): 136.8−124.7 (m, C_{Ar}, CH_{Ar}), 10.7 (d, J_{CP} = 40.8, CH_2). $^{31}P\{^{1}H\}$ NMR (C_6D_6): −235.8 (s).

PPyr$_2$Ph (6). 1-Bromopyrene (1.41 g, 5.0 mmol) was dissolved in 40 mL of THF, and the solution was cooled to −78 °C. A 1.6 M *n*-BuLi solution (3.2 mL, 5.0 mmol) was added, and the solution was stirred for 2 h. Dichlorophenylphosphine (339 μL, 2.5 mmol) was added at −78 °C, and the mixture was warmed to room temperature overnight. A 20 mL portion of water was then added, and the THF was removed under reduced pressure. The suspension was extracted with dichloromethane (3 × 20 mL) under dinitrogen, and the combined organic phase was dried with anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure, and the crude product was recrystallized in dichloromethane/ethanol to provide the desired compound as a yellow semisolid. Yield: 1.02 g (80%).

^{1}H NMR (C_6D_6): 9.18 (dd, J = 9.2, 4.8, $1H_{Ar}$), 8.01−7.58 (m, $18H_{Ar}$), 7.53−7.49 (m, $1H_{Ar}$), 7.10−7.03 (m, $3H_{Ar}$). $^{13}C\{^{1}H\}$ NMR (C_6D_6): 135.0−125.4 (m, C_{Ar}, CH_{Ar}). $^{31}P\{^{1}H\}$ NMR (C_6D_6): −21.5 (s).[8a]

2-(1-Pyrenyl)phenylphosphines. *P(PyrPh)Ph$_2$ (7).* 1-Bromo-2-(1-pyrenyl)benzene (357 mg, 1.0 mmol) was dissolved in 5 mL of THF, and the solution was cooled to −78 °C. A 1.6 M *n*-BuLi solution (625 μL, 1.0 mmol) was added, and the solution was stirred for 2 h. Chlorodiphenylphosphine (185 μL, 1.0 mmol) was added at −78 °C, and the mixture was warmed to room temperature overnight. A 5 mL portion of water was added, and the THF was removed under reduced pressure. The suspension was extracted with dichloromethane (5 × 10 mL), and the combined organic phase was dried with anhydrous sodium sulfate and filtered. The evacuation of the solvent under reduced pressure furnished the desired compound as a pasty, yellowish solid. Yield: 333 mg (72%).

^{1}H NMR (C_6D_6): 7.94−7.82 (m, $3H_{Ar}$), 7.82−7.72 (m, $5H_{Ar}$), 7.56−7.34 (m, $3H_{Ar}$), 7.30−7.18 (m, $4H_{Ar}$), 7.05−6.88 (m, $8H_{Ar}$). $^{13}C\{^{1}H\}$ NMR (C_6D_6): 139.1−124.3 (m, C_{Ar}, CH_{Ar}). $^{31}P\{^{1}H\}$ NMR (C_6D_6): −14.0 (s).[35]

P(PyrPh)^{i}Pr$_2$ (8). The procedure used to prepare phosphine **7** was followed, but employing chlorodiisopropylphosphine (159 μL, 1.0 mmol). Yield: 264 mg (67%).

^{1}H NMR (C_6D_6): 8.01−7.81 (m, $5H_{Ar}$), 7.73 (t, J = 8.0, $1H_{Ar}$), 7.57 (dt, J = 7.2, 2.0, $1H_{Ar}$), 7.41−7.37 (m, $2H_{Ar}$), 7.32−7.23 (m, $2H_{Ar}$), 7.06−7.03 (m, $2H_{Ar}$), 1.90−1.74 (m, 2H), 0.99 (dd, J = 10.8, 7.2, 3H), 0.96 (dd, J = 12.0, 7.2, 3H), 0.93 (dd, J = 6.8, 4.4, 3H), 0.77 (dd, J = 14.4, 6.8, 3H). $^{13}C\{^{1}H\}$ NMR: 149.7−124.2 (m, C_{Ar}, CH_{Ar}), 25.5 (d, J_{CP} = 16.4, CH), 24.3 (d, J_{CP} = 15.4, CH), 20.8 (d, J_{CP} = 19.3, CH_3), 20.4 (d, J_{CP} = 11.2, CH_3), 20.1 (d, J_{CP} = 1.8, CH_3), 19.7 (d, J_{CP} = 9.2, CH_3). $^{31}P\{^{1}H\}$ NMR (C_6D_6): −4.8 (s), −5.4 (s).

Ruthenium Complexes. *C1^{Cym}*. Phosphonite **1** (147 mg, 0.5 mmol) was dissolved in 40 mL of dichloromethane, and the ruthenium precursor **Dim** (122 mg, 0.20 mmol) was added; the resulting mixture was stirred for 3 h protected from light. The solution was brought to dryness, and the crude product was recrystallized in dichloromethane/hexane to give the title product as a red solid. Yield: 101 mg (42%).

^{1}H NMR: 9.11 (d, J = 9.2, $1H_{Ar}$), 8.46 (dd, J = 10.0, 8.0, $1H_{Ar}$), 8.31−8.08 (m, $7H_{Ar}$), 5.27 (d, J = 6.4, 2H), 4.86 (d, J = 6.0, 2H), 4.01 (d, J = 11.2, 6H), 2.74 (sept, J = 6.8, 1H), 1.76 (s, 3H), 1.01 (d, J = 6.8, 6H). $^{13}C\{^{1}H\}$ NMR: 133.8−123.8 (m, C_{Ar}, CH_{Ar}), 107.5 (C), 98.5 (C), 92.2 (d, J_{CP} = 6.5, 2CH), 89.2 (br, 2CH), 55.9 (d, J_{CP} = 8.9, $2CH_3$), 30.0 (CH), 21.7 ($2CH_3$), 18.1 (CH_3). $^{31}P\{^{1}H\}$ NMR: +145.5 (s). IR: 3017, 2943, 1622, 1457, 1378, 1023, 851, 639 cm^{-1}. HRMS: $[M - Cl]^+$ calcd for $C_{28}H_{29}ClO_2PRu$, 565.0631; found, 565.0645. Anal. Calcd for $C_{28}H_{29}Cl_2O_2PRu$: C, 56.01; H, 4.87. Found: C, 55.65; H, 5.12.

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***C1*^{Mba}**. Phosphonite **1** (147 mg, 0.5 mmol) was dissolved in 40 mL of dichloromethane, and the ruthenium precursor **Dim′** (154 mg, 0.25 mmol) was added; the resulting mixture was stirred for 3 h protected from light. The mixture was then filtered to eliminate any remaining **Dim′** and subsequently brought to dryness. The crude product was recrystallized in dichloromethane/hexane to give the title product as a red solid. Yield: 72 mg (24%).

^{1}H NMR: 9.03 (d, J = 9.2, 1H$_{Ar}$), 8.53 (dd, J = 10.4, 8.0, 1H$_{Ar}$), 8.32−8.21 (m, 5H$_{Ar}$), 8.15−8.08 (m, 2H$_{Ar}$), 6.38 (d, J = 6.0, 2H), 5.50 (br, t, J = 5.6, 1H), 5.31 (t, J = 6.0, 2H), 3.99 (d, J = 11.2, 6H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR: 164.4 (C = O), 134.2−124.1 (m, C$_{Ar}$, CH$_{Ar}$), 96.5 (d, J_{CP} = 5.1, 2CH), 91.8 (CH), 87.3 (d, J_{CP} = 5.3, 2CH), 86.2 (d, J_{CP} = 5.4, 2C), 56.2 (d, J_{CP} = 8.6, 2CH$_3$), 53.2 (CH$_3$), 52.2 (CH$_3$). ^{31}P{^{1}H} NMR: +142.1 (s). IR: 3021, 2943, 1731 (ν(C═O)), 1268, 955, 714 cm^{-1}. HRMS: [M + NH$_4$]$^+$ calcd for $C_{26}H_{27}Cl_2NO_4PRu$, 620.0092; found, 620.0097. Anal. Calcd for $C_{26}H_{23}Cl_2O_4PRu$: C, 51.84; H, 3.85. Found: C, 52.43; H, 4.39.

***C2*^{Cym}**. The procedure used to prepare **C1**^{Cym} was followed but using aminophosphine **2**. Yield: 123 mg (49%).

^{1}H NMR: 9.17 (d, J = 9.6, 1H$_{Ar}$), 8.32−8.24 (m, 5H$_{Ar}$), 8.20 (d, J = 9.2, 1H$_{Ar}$), 8.14 (d, J = 8.8, 1H$_{Ar}$), 8.09 (t, J = 7.6, 1H$_{Ar}$), ∼ 5.5−4.0 (vbr, 4H$_{p\text{-cymene}}$), ∼3.2−2.4 (vbr, 13H$_{NMe+p\text{-cymene}}$), 1.61 (s, 3H), 1.12 (br s, 6H$_{p\text{-cymene}}$). ^{13}C{^{1}H} NMR: 133.8−123.8 (m, C$_{Ar}$, CH$_{Ar}$), 113.8 (d, J_{CP} = 7.3, C), 97.7 (C), 86.9 (vbr, 4CH), 86.9 (vbr, 4CH$_3$), 30.5 (CH), 22.1 (br, 2CH$_3$), 17.7 (CH$_3$). ^{31}P{^{1}H} NMR: + 103.3 (s). IR: 3013, 2921, 2853, 2813, 2786, 1567, 1440, 1279, 1185, 967, 853, 667, 627 cm^{-1}. HRMS: [M − Cl]$^+$ calcd for $C_{30}H_{35}ClN_2PRu$, 591.1264; found, 591.1241. Anal. Calcd for $C_{30}H_{35}Cl_2N_2PRu$: C, 57.51; H, 5.63. Found: C, 56.52; H, 5.95.

***C2*^{Mba}**. The procedure used to prepare **C1**^{Mba} was followed but using aminophosphine **2**. Yield: 132 mg (42%).

^{1}H NMR: 9.06 (d, J = 9.2, 1H$_{Ar}$), 8.35−8.28 (m, 3H$_{Ar}$), 8.23−8.03 (m, 5H$_{Ar}$), 6.24 (s, br, 2H), 5.55 (br t, J = 5.2, 1H), 4.43−4.40 (m, 2H), 3.95 (s, 3H), ∼ 3.2−2.5 (vbr, 12H). ^{31}P{^{1}H} NMR: +99.6 (s). IR: 3033, 2853, 2720, 1732 (ν(C═O)), 1267, 1179, 966, 850, 767, 699, 630 cm^{-1}. HRMS: [M − Cl]$^+$ calcd for $C_{28}H_{29}ClN_2O_2PRu$, 593.0693; found, 593.0692. Anal. Calcd for $C_{28}H_{29}Cl_2N_2O_2PRu$: C, 53.51; H, 4.65. Found: C, 53.21; H, 4.10.

***C3*^{Cym}**. The procedure used to prepare **C1**^{Cym} was followed but using the primary phosphine **3**. Yield: 121 mg (56%).

^{1}H NMR: 8.56 (d, J = 8.8, 1H$_{Ar}$), 8.37−8.10 (m, 8H$_{Ar}$), 6.15 (d, J_{HP} = 391.2, 2H), 5.23 (d, J = 5.6, 2H), 4.99 (d, J = 5.6, 2H), 2.65 (sept, J = 7.2, 1H), 1.99 (s, 3H), 1.12 (d, J = 6.8, 6H). ^{13}C{^{1}H} NMR: 134.0−123.4 (m, C$_{Ar}$, CH$_{Ar}$), 105.3 (C), 100.7 (C), 87.6 (d, J_{CP} = 5.8, 2CH), 86.7 (d, J_{CP} = 4.6, 2CH), 30.7 (CH), 22.2 (2CH$_3$), 18.6 (CH$_3$). ^{31}P{^{1}H} NMR: −27.0 (s). ^{31}P NMR: −27.0 (td, J_{PH} = 391.1, 13.6). HRMS: [M − Cl]$^+$ calcd for $C_{26}H_{25}ClPRu$, 505.0420; found, 505.0412; [M + NH$_4$]$^+$ calcd for $C_{26}H_{29}Cl_2NPRu$, 558.0452; found, 558.0452. Anal. Calcd for $C_{26}H_{25}Cl_2PRu$: C, 57.78; H, 4.66. Found: C, 57.53; H, 5.02.

***C3*^{Mba}**. The procedure used to prepare **C1**^{Mba} was followed but using the primary phosphine **3**. Yield: 73 mg (27%).

^{1}H NMR: 8.47 (d, J = 9.2, 1H$_{Ar}$), 8.35 (dd, J = 14.0, 8.0, 1H$_{Ar}$), 8.26−8.15 (m, 5H$_{Ar}$), 8.07−8.02 (m, 2H$_{Ar}$), 6.24 (br, d, J = 4.4, 2H), 6.15 (d, J_{HP} = 405.6, 2H), 5.58 (br, t, J = 6.0, 1H), 5.32 (t, J = 6.0, 2H), 3.65 (s, 3H). ^{31}P{^{1}H} NMR: −28.9 (s). ^{31}P NMR: −28.9 (td, J_{PH} = 404.4, 13.9). IR: 3014, 2904, 2780, 1728 (ν(C═O)), 1562, 1397, 1267, 1091, 842, 767, 727, 649 cm^{-1}. HRMS: [M + NH$_4$]$^+$ calcd for $C_{24}H_{23}Cl_2NO_2PRu$, 559.9881; found, 559.9901. Anal. Calcd for $C_{24}H_{19}Cl_2O_2PRu$: C, 53.15; H, 3.53. Found: C, 52.89; H, 3.44.

***C6*^{Cym}**. The procedure used to prepare **C1**^{Cym} was followed but using phosphine **6**. Yield: 72 mg (22%).

^{1}H NMR: 9.13 (d, J = 9.2, 1H$_{Ar}$), 8.28−7.03 (m, 22H$_{Ar}$), 5.92 (d, J = 6.0, 1H), 5.75 (d, J = 6.0, 1H), 5.48 (d, J = 6.0, 1H), 5.34 (d, J = 6.0, 1H), 3.2 (m, 1H), 1.76 (s, 3H), 1.34−1.28 (m, 6H). ^{31}P{^{1}H} NMR: +32.8 (br, s). HRMS: [M − 2Cl − H]$^+$ calcd for $C_{48}H_{36}PRu$, 745.1592; found, 745.1605. Anal. Calcd for $C_{48}H_{37}Cl_2PRu$: C, 70.59; H, 4.57. Found: C, 69.69; H, 4.90.

***C6*^{Mba}**. The procedure used to prepare **C1**^{Mba} was followed but using phosphine **6**. Yield: 123 mg (30%).

^{1}H NMR: 9.40 (vbr, 1H$_{Ar}$), 8.48−7.08 (m, 22H$_{Ar}$), 6.56−6.28 (vbr, 3H), 4.86 (br, s, 2H), 3.98 (s, 3H). ^{31}P{^{1}H} NMR: +31.1 (br, s). HRMS: [M − 2Cl − H]$^+$ calcd for $C_{46}H_{30}O_2PRu$, 747.1021; found, 747.1021. Anal. Calcd for $C_{46}H_{31}Cl_2O_2PRu$: C, 67.49; H, 3.82. Found: C, 66.12; H, 3.90.

***C7*^{Cym}**. The procedure used to prepare **C1**^{Cym} was followed but using phosphine **7**. The product was obtained as a dark orange solid. Yield: 240 mg (78%).

^{1}H NMR: 9.12 (d, J = 14.4, 8.0, 1H$_{Ar}$), 8.14−6.90 (m, 19H$_{Ar}$), 6.04 (td, J = 7.6, 2.4, 2H$_{Ar}$), 5.88 (t, J = 7.2, 1H$_{Ar}$), 5.19 (d, J = 6.0, 1H), 5.17 (d, J = 6.0, 1H), 4.99 (d, J = 5.2, 1H), 4.90 (br, s, 1H), 4.62 (br, d, J = 6.0, 1H), 2.85 (sept, J = 6.8, 1H), 2.70 (sept, J = 7.2, 1H), 1.86 (s, 3H), 1.68 (s, 3H), 1.10 (d, J = 7.2, 6H), 1.03 (d, J = 6.8, 6H). ^{13}C{^{1}H} NMR: 143.9−122.8 (m, C$_{Ar}$, CH$_{Ar}$), 111.5 (d, J_{CP} = 3.5, C), 110.1 (d, J_{CP} = 1.0, C), 96.1 (C), 90.1 (d, J_{CP} = 2.7, CH), 89.2 (d, J_{CP} = 3.1, CH), 87.3 (d, J_{CP} = 5.6, CH), 87.0 (d, J_{CP} = 7.3, CH), 30.4 (CH), 30.2 (CH), 22.8 (2CH$_3$), 22.0 (2CH$_3$), 17.9 (CH$_3$), 17.1 (CH$_3$). ^{31}P{^{1}H} NMR: ∼+18 (vbr). IR: 3062, 2945, 1583, 1092, 848, 744, 694 cm^{-1}. HRMS: [M − Cl]$^+$ calcd for $C_{44}H_{37}ClPRu$, 733.1359; found, 733.1360.

***C7*^{Mba}**. The procedure used to prepare **C1**^{Mba} was followed but using phosphine **7**. The product was obtained as a light orange solid. Yield: 285 mg (74%).

^{1}H NMR: 8.90 (br, s, 1H$_{Ar}$), 8.14−7.05 (m, 22H$_{Ar}$), 6.47 (d, J = 6.0, 1H), 6.41 (d, J = 6.4, 1H), 6.3 (br, 1H), 6.08 (t, J = 8.0, 2H), 5.89 (br, 1H), 5.18 (dd, J = 9.6, 5.2, 1H), 5.07 (t, J = 5.6, 1H), 5.00 (br, s, 1H), 4.76 (br, 1H), 3.96 (s, 3H), 3.94 (s, 3H). ^{13}C{^{1}H} NMR: 164.4 (C═O), 134.3−123.0 (m, C$_{Ar}$, CH$_{Ar}$), 95.6 (d, J_{CP} = 3.8, CH), 89.1 (s, CH), 85.2 (d, J_{CP} = 2.4, CH), 53.44 (CH$_3$), 53.41 (CH$_3$). ^{31}P{^{1}H} NMR: ∼+26 (vbr). IR: 3057, 1727 (ν(C═O)), 1512, 1463, 1433, 1293, 1274, 1986, 1109, 1093, 949, 848, 833, 768, 746, 724, 693 cm^{-1}. HRMS: [M + NH$_4$]$^+$ calcd for $C_{42}H_{35}Cl_2NO_2PRu$, 788.0820; found, 788.0831.

***C8*^{Cym}**. The procedure used to prepare **C1**^{Cym} was followed but using phosphine **8**. The product was obtained as a dark orange solid. Yield: 126 mg (45%).

^{1}H NMR: 7.85−7.80 (m, 5H$_{Ar}$), 7.41−7.33 (m, 8H$_{Ar}$), 5.47 (d, J = 6.0, 2H), 5.34 (d, J = 6.0, 2H), 5.19 (d, J = 6.0, 2H), 4.98 (dd, J = 6.4, 1.6, 1H), 2.96−2.81 (m, 3H), 2.69−2.56 (m, 1H), 2.16 (s, 3H), 1.86 (s, 3H), 1.37−1.26 (m, 12H), 1.28 (d, J = 6.8, 6H), 1.10 (d, J = 7.2, 6H). ^{13}C{^{1}H} NMR: 134.5−123.8 (m, C$_{Ar}$, CH$_{Ar}$), 111.3 (d, J_{CP} = 3.3, C), 96.1 (C), 89.2 (d, J_{CP} = 3.2, CH), 87.2 (d, J_{CP} = 5.5, CH), 81.4 (CH), 80.7 (CH), 30.4 (CH), 30.7 (CH), 30.4 (CH), 27.1 (d, J_{CP} = 22.7, CH), 22.3 (2CH$_3$), 22.0 (2CH$_3$), 20.1−19.4 (m, CH$_3$), 19.1 (CH$_3$), 17.9 (CH$_3$). ^{31}P{^{1}H} NMR (218 K): +49.5 (s, br). IR: 3048, 2960, 2869, 1470, 1435, 1388, 1092, 1056, 1033, 850, 743, 695. HRMS: [M − arene − Cl + 2H]$^+$ calcd for $C_{28}H_{29}ClPRu$, 533.0733; found, 533.0734.

***C8*^{Mba}**. The procedure used to prepare **C1**^{Mba} was followed but using phosphine **8**. The product was obtained as a light orange solid. Yield: 221 mg (63%).

^{1}H NMR: 7.76−7.71 (m, 5H$_{Ar}$), 7.46−7.37 (m, 8H$_{Ar}$), 6.42 (d, J = 6.4, 2H), 5.36−5.29 (m 1H), 5.08 (t, J = 6.0, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.22−3.16 (m 1H), 2.69−2.63 (m, 1H), 1.50−0.80 (m, 1H). ^{13}C{^{1}H} NMR: 164.5 (C═O), 134.3−124.8 (m, C$_{Ar}$, CH$_{Ar}$), 95.6 (d, J_{CP} = 3.8, 2CH), 89.0 (s, CH), 85.2 (d, J_{CP} = 2.4, 2CH), 53.54 (CH$_3$), 53.46 (CH$_3$), 20.1.14.2 (m, 4CH$_3$). ^{31}P{^{1}H} NMR: +50.7 (s, br). IR: 3056, 2955, 2870, 1724 (ν(C═O)), 1522, 1433, 1272, 1986, 1108, 848, 768, 696 cm^{-1}. HRMS: [M + NH$_4$]$^+$ calcd for $C_{36}H_{39}Cl_2NO_2PRu$, 720.1133; found, 720.1132.

***C7*^{Tet}**. Complex **C7**^{Mba} (193 mg, 0.25 mmol) was dissolved in 20 mL of dichloromethane, and the solution was stirred for 6 h exposed to the light of a conventional desk lamp. The solvent was eliminated under reduced pressure, and the crude product was recrystallized in dichloromethane/hexane, giving the title product as a dark brown solid. Yield: 57 mg (36%).

^{1}H NMR (CD_2Cl_2): 8.13 (dd, J = 9.2, 1.6, 1H$_{Ar}$), 8.03 (d, J = 8.8, 1H$_{Ar}$), 7.98−7.17 (m, 19H$_{Ar}$), 6.64 (d, J = 9.6, 1H), 6.54 (d, J = 6.0, 1H). ^{31}P{^{1}H} NMR (CD_2Cl_2): +63.1 (s). IR: 3053, 1586, 1482,

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1434, 1093, 996, 843, 690. HRMS: $[M - Cl]^+$ calcd for $C_{34}H_{23}ClPRu$, 599.0263; found, 599.0262.

***C8*^{Tet}**. The procedure used to prepare **C7^{Tet}** was followed but using complex **C8^{Mba}**. The product was obtained as a dark brown solid. Yield: 28 mg (20%).

^{1}H NMR (CD_2Cl_2): 7.94−7.32 (m, 11H$_{Ar}$), 6.52 (d, J = 9.6, 1H), 6.44 (d, J = 6.0, 1H), 2.84−2.73 (m, 2H), 1.32 (dd, J = 14.0, 7.2, 3H), 1.12 (dd, J = 17.6, 7.2, 3H), 0.96 (dd, J = 15.6, 6.8, 3H), 0.88 (dd, J = 16.8, 6.8, 3H). ^{31}P{^{1}H} NMR (CD_2Cl_2): +82.6 (s). IR: 3051, 2936, 2867, 1435, 1275, 1094, 1036, 864, 753, 625. HRMS: $[M-Cl]^+$ calcd. for $C_{28}H_{27}ClPRu$, 531.0576; found, 531.0580.

Single-Crystal X-ray Diffraction. Data for compounds **C1^{Cym}**, **C2^{Cym}**, **C2^{Mba}**, **C6^{Mba}**, **C7^{Cym}**, and **C8^{Tet}** (see the Supporting Information) were collected on a Bruker APEX II QUAZAR diffractometer equipped with a microfocus multilayer monochromator with Mo Kα radiation (λ = 0.71073 Å). Data for compound **C1^{mba}** were collected using a Bruker D8 diffractometer with Photon II detector on the Advanced Light Source beamline 12.2.1 at Lawrence Berkeley National Laboratory, from a silicon 111 monochromator (λ = 0.7288 Å). Data reduction and absorption corrections were performed by using SAINT and SADABS, respectively.[48] The structures were solved using SHELXT[49] and refined with full-matrix least- squares on F^2 by using SHELXL-2014.[49] For compounds **C2^{Cym}** and **C6^{Mba}**, a void containing only diffuse electron density was analyzed and taken into account with Olex2/Solvent Mask.[50] An estimated content of four and three diffuse lattice CH_2Cl_2 molecules were deduced, respectively, and included in the formula. All details can be found in CCDC 1999290−1999296, which contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via https://summary.ccdc.cam.ac.uk/structure-summary-form.

Cell Culture. A549 cells were cultured in DMEM medium (Biological Industries, Beit Haemek, Israel) supplemented with 10% heat-inactivated fetal bovine serum (FBS; Life Technologies, Carlsbad, CA), 100 U/mL penicillin, 100 μg/mL streptomycin, and 2 mM L-glutamine, all from Biological Industries. Cells were grown at 37 °C under a 5% CO_2 atmosphere.

Cell Viability Assays. Cell viability was determined by the MTT assay. Briefly, cells (1×10^5 cells/mL) were seeded in 96-well plates and allowed to grow for 24 h. Afterward, 10 μM of each compound was added for 24 h. DMSO (diluent) was added in control cells at 1% (v/v). After treatment, 10 μM of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma-Aldrich) was added to each well for an additional 4 h. The medium was removed, and the blue MTT formazan precipitate was dissolved in 100 μL of DMSO. The absorbance at 570 nm was measured on a Multiskan FC multiwell plate reader (Thermo Scientific Inc., Waltham, MA). The cell viability was expressed as a percentage of control cells. The data are shown as the mean value ± standard deviation of three independent experiments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00302.

Crystallographic tables and representations of the crystal structures for **C1^{Cym}**, **C1^{Mba}**, **C2^{Cym}**, **C2^{Mba}**, **C6^{Mba}**, **C7^{Cym}**, and **C8^{Tet}**, multinuclear NMR spectra of the ligands and complexes, time-resolved ^{1}H NMR spectra of **C1^{Mba}** and **C2^{Mba}** in dmso-d_6, experimental and simulated mass spectra of **C7^{Tet}** and **C8^{Tet}**, and time-resolved UV−vis spectra of the tethering reaction depicted on the right-hand side of Scheme 6. (PDF)

Accession Codes

CCDC 1999290−1999296 contain 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.

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Notes

The authors declare no competing financial interest.

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