Facile Method to Obtain Functionalised η6-Bound Arenes in Ru(II) and Os(II) Half-Sandwich Complexes

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RESEARCH ARTICLE

Facile Method to Obtain Functionalised η⁶-Bound Arenes in Ru(II) and Os(II) Half-Sandwich Complexes

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Abstract: Half-sandwich Ru(II)- and Os(II)-arene complexes have great potential for catalytic and biological applications. The possibility of fine-tuning their chemical reactivity by including modifications in the ligands around the metal adds to their many advantages. However, structural modifications at the n⁶-bound arene have had significant synthetic limitations, particularly in the design of Os(II)-tethered complexes. For the first time, we have employed a practical C(sp^3)-C(sp^2) coupling to obtain 28 new Ru(II) and Os(II) η⁶-arene half-sandwich complexes with a wide variety of arene functionalities, including those that enable the formation of tether rings, such as quinoline and coumarin. The introduction of novel functional groups at the arene in Ru(II)- and Os(II) half-sandwich complexes can broaden the synthetic scope of this type of organometallic complexes, and help to take full advantage of their structural diversity, especially in intracellular catalysis.

Introduction

Organometallic Ru(II) and Os(II) half-sandwich complexes with piano-stool geometry of general formula [Ru/Os(η⁶-arene)XYZ] are very attractive for their applications in catalysis[1] and in biology as antibacterial[1b] and anticancer agents.[2] Recent applications as intracellular catalysts highlight the great potential of these molecules in medicine.[3] Their advantages include the mild reaction conditions required for their synthesis and high yields.[1b] These complexes can be seen as composed of three main building blocks: the η⁶-bound arene, the metal centre, and (often polydentate) ligands X, Y and Z. One of their most attractive features is that their chemical reactivity can be fine-tuned by varying each of these building blocks, which allows for the modification of key thermodynamic and kinetic parameters.[4] Among the components, the arene plays an essential role stabilising the metal in its +2 oxidation state. It also possesses a high *trans* effect that significantly influences the lability of the X, Y and/or Z ligands.[5] It also provides the molecule with a hydrophobic face that has been exploited to improve biomolecular recognition and the transport of the organometallic compound across cell membranes in biological applications.[4] The arene can also be designed to facilitate the formation of tethered complexes, where a functionalised arene effectively works as a hemilabile bidentate ligand. As such, the η⁶-bound ring is strongly anchored to the metal, while the σ-bond between the pendant functionality and the metal centre can be dissociated under specific stimuli.[6] The chelate effect of the tether ring can be advantageous in terms of stability, and beneficial in the stereo-differentiation processes of asymmetric catalysis.[7] Hemilability in this type of complexes – whereby a vacancy in the first coordination sphere of the metal can be purposely created– is particularly attractive for both catalytic and biological applications, since it allows for controlled metal-centred reactivity inside the cell.[6, 8]

Despite the impact of the arene on the chemistry of half-sandwich metal-arene compounds, versatility on arene functionalisation has been modest. This is particularly critical in the case of osmium complexes, with just a few reported examples different from the well-known [Os(η⁶-*p*-cymene)XYZ] complexes. Among these examples, there are Os-arenes bearing alcohols and acids reported by us,[6, 9] and those bearing η⁶-biphenyl ligand, reported by Sadler.[10] The lack of structural variation is undoubtedly attributed to the limitations imposed by the synthetic methodology to attach the arene to the Os(II) core, most of which are not shared by Ru(II).

A common way to obtain a functionalised η⁶-bound arene in half-sandwich ruthenium complexes is by an arene-exchange reaction under strong heating (>120 °C) or UV radiation.[11] The arene ligand in the dimer precursor, preferably bearing electron-withdrawing groups, is replaced by the desired incoming arene.[12] Ethyl or methyl benzoate dimers, of formula [Ru(η⁶-Et/Me-benzoate)Cl_2]$_2$, are some of the most common precursors,[6, 11c] yet also other substituted arene Ru(II) dimers, such as *p*-cymene, have been employed, producing significantly lower yields.[13] Nevertheless, the synthetic application of this ligand exchange reaction is often complicated by the formation of equilibrium mixtures between products and starting material.[11a] In addition, due to the harsh conditions, the arene exchange is sometimes accompanied by decomposition, which further decreases the yield of the target product.[11a] However, perhaps the greatest limitation of the arene-exchange method is that it is ineffective with osmium. Theoretical data and quantum-mechanical calculations indicate that the strength of metal-arene bond increases in the series Fe → Ru → Os and Re → W → Os; consequently, osmium can be one of the most inert metals regarding ligand exchange reactions.[11a] The failure of carrying out arene-exchange reactions by our group using the [Os(η⁶-Et-benzoate)Cl_2]$_2$ analogue as a suitable dimer precursor, adds to this observation.[6, 14]

To date, the conventional path to synthesise osmium-arene complexes is by the redox reaction between hydrated $OsCl_3$

(analogous to $RuCl_3 \cdot nH_2O$) with a cyclohexadiene derivative (the reduced version of the target arene), to obtain chlorido-bridged dimers $[Os(\eta^6\text{-arene})(\mu\text{-Cl})Cl]_2$ or dichlorido tether monomers $[Os(\eta^6{:}\kappa^1\text{-areneZ})Cl_2]$ that are generally air stable and can further react and substitute the chlorido ligands with a wide variety of ligands.[12] This means that for every $Os(\eta^6\text{-arene})$ complex that needs to be synthesised, there are not many options other than to prepare the reduced version of the desired arene. In other words, the main obstacle to generate novel half-sandwich structures rich in arene functionalities is the synthetic challenges presented by the preparation of their cyclohexadiene (reduced) counterparts.

The traditional way to synthesise cyclohexadiene derivatives is through the Birch reduction, which dearomatizes arenes using lithium or sodium in liquid ammonia at ≤−78 °C.[15] However, there are a number of difficulties and restrictions associated with this reaction, such as the kind of substrates that can be reduced and/or whose reduction is impractical, due to the possible loss of the functional group, low yields and over-reduction, among others. Examples of challenging and/or impossible substrates for the Birch reduction include phenols, aromatic amines/ethers/esters/ketones, as well as certain aromatic polynuclear and di-/tri-phenyl compounds, especially functionalised ones.[16] Other important limitations of the Birch reduction include poor chemoselectivity and laborious experimental procedure.[17] A more concerning difficulty is the use of liquid ammonia, which must be prepared with an elaborate set-up and carefully dissipated after the reaction is complete. In order to avoid the hazards involved in working with liquid ammonia, different ammonia-free methods have been developed. Some examples include the use of alkali alloys in silica gel,[18] samarium reagents,[19] photo-,[20] or electro-reduction,[21] sodium dispersion (SD)[22] and SD together with a crown ether.[17, 22b] Two impactful works recently reported by Baran[23] and Koide,[24] show a chemical reduction inspired by Li-ion battery technology,[23] and a scalable Birch reduction using lithium and ethylenediamine,[24] respectively. However, limitations such as low yields, over-reduction, scaling up difficulties and/or the need for expensive reagents or specialised equipment mean that, despite its complications, the Birch reduction using liquid ammonia remains the gold standard in the preparation of novel half-sandwich arenes of Ru and Os.[24]

In summary, both the arene-exchange reaction and the preparation of cyclohexadiene derivatives are often unpractical –or even unfeasible– to easily decorate the η^6-arene building block in Ru(II)/Os(II) tether and non-tether half-sandwich complexes, especially in the case of Os. This has particularly impacted the lack of synthetic versatility in Os-tethers. In fact, the first purposely synthesised Os tether complexes have been recently reported by us.[6, 9] Therefore, a synthetic method is needed that allows arenes to be functionalised through mild and less hazardous conditions, with accessible reagents and materials, and with a wide variety of possible substituents, including those that allow the formation of tether rings (e.g., N,[11c, 25] O,[6, 8, 26] S,[27] donors).

Here, we present a $C(sp^3)$-$C(sp^2)$ coupling synthetic method to derivatise cyclohexadienes,[28] which has never been applied before to obtain functionalised arene precursors for the synthesis of half-sandwich complexes, or any other type of organometallic compound (Figure 1). From one reduced arene, we obtained a variety of non-tether and tethered Ru(II) and Os(II) half-sandwich complexes, some of which present unique structures (especially for osmium), which would be very difficult –perhaps even impossible– to obtain with any other methodology.

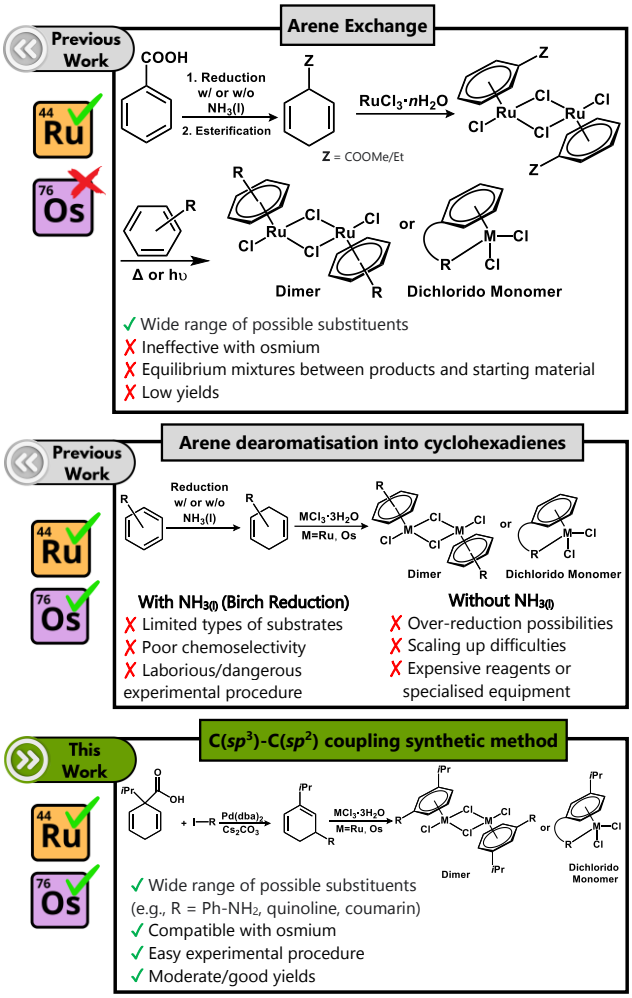
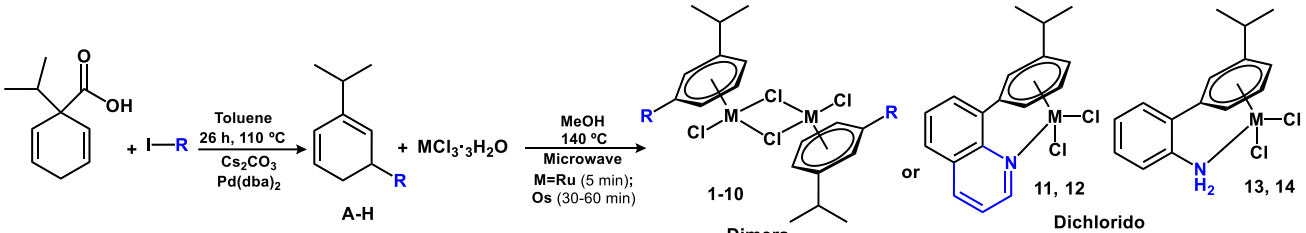
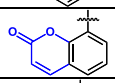
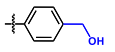
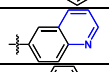


Figure 1. Advantages and disadvantages of the conventional ways to functionalise η^6-arene precursors in half-sandwich complexes, in contrast to the methodology of this work.

Results and Discussion

Eight arene precursors **A**–**H** were synthesised following the reaction path showed in Scheme 1. Six of the compounds (**B**–**G**) are new. 1-Isopropylcyclohexa-2,5-diene-1-carboxylic acid was reduced through a Birch reduction,[29] although other ammonia-free alternatives are available.[23, 24] This compound was *m*-coupled with an iodobenzene derivative, through a simplified version of a stereospecific Pd-catalysed arylation of cyclohexadienyl carboxylic acids.[28] With this methodology, the aryl iodide (I–R) is the reagent responsible for functionalising the reduced arene, so a great variety of reduced compounds are obtained without the need of multiple reductions reactions. The main advantage of aryl iodide derivatives is that they are commercially available in a wide variety at affordable costs and/or



Arene Precursor		Metal Complexes			
Code	R	*Dimer*	*Dichlorido Monomer*	*bpy Monomer*	M
A		1	-	15	Ru
		2	-	16	Os
B		3	-	17	Ru
		4	-	18	Os
C		5	-	19	Ru
		6	-	20	Os
D		7	-	21	Ru
E		8	-	22	Ru
F		9	-	23	Ru
		10	-	24	Os
G		-	11	25	Ru
		-	12	26	Os
H		-	13	27	Ru
		-	14	28	Os

Scheme 1. Synthetic routes and chemical structures of the organometallic ruthenium(II)- and osmium(II)-arene complexes reported in this work.

can be synthesised by conventional organic synthesis. Additionally, regarding the organometallic structure, the coupled phenyl ring elongates the carbon chain from the η^6-arene carbon to facilitate the formation of 5- or 6-membered tether structures. In general, better yields were obtained with aryl iodides bearing strong electron-donating substituents (such as NH_2), while iodobenzene derivatives with weaker electron-donating groups (e.g., alkyl) were less reactive and the reaction yield decreased, in agreement with reported observations for these coupling reactions.[28] Likewise, the size of the α-substituent influenced the reaction outcome,[28] as higher yields were achieved with the isopropyl substituted acid, with respect to the unsubstituted one.

Another advantage of this methodology is that it is possible to further derivatise the functional groups of newly synthesized reduced arenes. A variety of groups, such as ethynyltrimethylsilane, alcohol (**D**) and amine (**H**) were easily converted into alkyne (**I**), azide (**J**) and azobenzene (**K**) groups, respectively (details in the Supporting Information). This gave them an added value, since the groups in **I**, **J** and **K** are highly attractive for many types of reactions and applications; for example, click reactions for azide and alkyne, or photo-responsive applications, in the case of azobenzene.[30] The structures of all the organic compounds obtained in this work are shown in Figure 2.

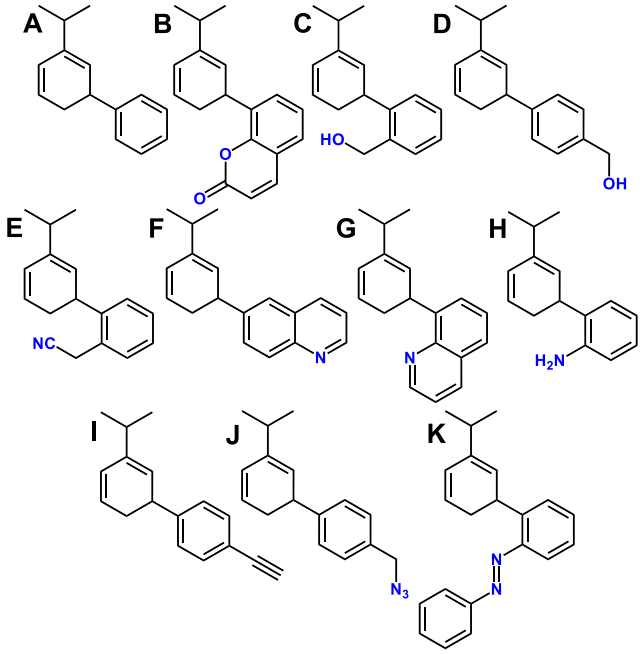


Figure 2. Chemical structures of the arene precursors synthesised in this work: **A**–**H** were synthesised through the C(sp^3)-C(sp^2)coupling reaction,[28] while **I**, **J** and **K** were obtained from the derivatisation of trimethylsilane, alcohol (**D**) and amine (**H**) groups, respectively.

Mixing an excess of compounds **A**–**H** with $MCl_3 \cdot 3H_2O$ (M = Ru or Os) in methanol, and heating the mixture in the microwave synthesiser for 5 min (Ru) or 30-60 min (Os), leads to the corresponding organometallic precursors **1**–**14** (Scheme 1 and SI), which alternatively can be obtained by conventional heating (reflux) for longer reaction times (usually between 1–3 days).[12] Depending on the R group, dimers (**1**–**10**) or dichlorido monomers (**11**–**14**) were obtained. When the pendant functionality can result in a tether compound, that is, it can chelate the metal due to both its metal-binding capabilities and the right accessibility through space (ligands **G** and **H**), our results showed formation of tether compounds [Ru/Os(η^6:κ^1-arene)Cl_2], as previously reported.[6, 8, 11c] The general tendency is that functionalities with N-donors such as NH_2, pyridines or quinolines, tend to form dichlorido monomers, whereas other pendant groups (e.g., OH) result in dimer formation. It is important to emphasise that the metal must be accessible to interact with the donor atom, otherwise the tether will not be formed. For example, **F** forms non-tether complexes **9** and **10** (and **23** and **24**), as the interaction between the metal and the N atom of the quinoline is not spatially possible. Conversely, isomer **G** results in tether complex **11** and **12** (and **25** and **26** derivatives, vide infra).

A way to help discern a dimer from a dichlorido monomer, is experimentally contrasting both reactivities. Both precursors undergo replacement of two chlorido ligands in the first coordination sphere of the metal by a bidentate chelating ligand, which in this work was N,N-bipyridine (2,2'-bpy, used to represent a common XY chelating ligand). Compared to dimers, dichlorido monomers tend to be less reactive in subsequent substitution reactions. For example, the reaction between dichlorido monomers **11** and **12** and bpy required more time and the use of silver salts (details in the SI), when compared to that of dimers **1**–**10**.

The desired target monomers (Chart 1) with general formula [M(η^6-C_6H_4(^{i}Pr)(R))(bipyridine)Cl]Cl (M = Ru(II), **15**, **17**, **19**, **21**, **22**, **23** and **27**; or Os(II), **16**, **18**, **20**, **24** and **28**) were obtained by dissolving the corresponding precursor (**1**–**10**, **13**, **14**) and bpy in methanol at room temperature (Scheme 1 and details in the SI). These +1 cations were isolated as their chloride salts. For complexes [M(η^6:κ^1-C_6H_4(^{i}Pr)(quinoline))(bpy)]$(PF_6)_2$ (M = Ru(II), **25** and Os(II)**, 26**), it was necessary to remove the chlorido ligands from their respective precursors **11** and **12** with $AgPF_6$ in methanol, before adding the bpy. The resulting +2 cations were isolated as PF_6^- salts. All monomers **15**–**28** were obtained in good yields (56-93%), from their respective dimer/dichlorido precursor.

Compounds **B**–**G** and **I**–**K** were characterised by ^{1}H and ^{13}C{^{1}H} NMR, with signals analogous to those already reported for **A** and **H** compounds (Figures S1–S9 in SI).[28] Additionally, compounds **I**–**K** were characterised by FT-IR (Figure S10). New complexes **1**–**28** were characterised by 1D ^{1}H and ^{13}C{^{1}H} NMR, and 2D [^{1}H,^{1}H] COSY and ^{1}H-decoupled [^{1}H,^{13}C] HMQC NMR spectroscopy, as well as by mass spectrometry (ESI-MS) and CHN elemental analysis for bpy monomers (Figures S11–S38). Single crystal X-ray diffraction structures were obtained for complexes **11**, **12**, **13**, **15·PF$_6$**, **25** and **26** (Figure 3 and Figure S39).

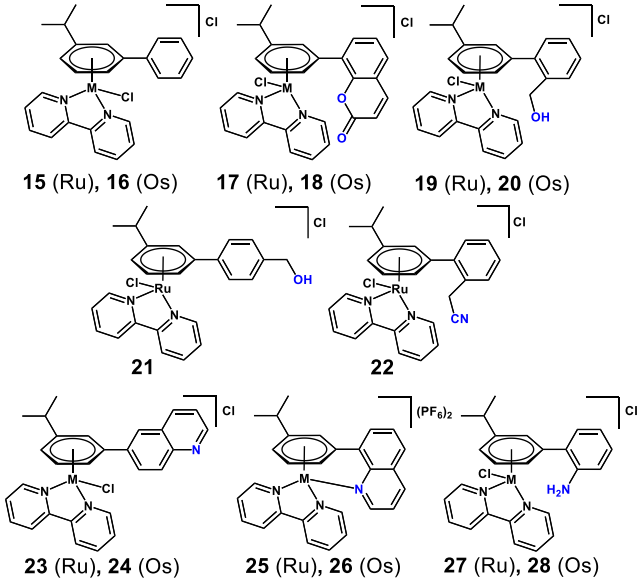


Chart 1. New bpy-Ru(II)-and Os(II) half-sandwich complexes synthesised in this work.

The ^{1}H NMR spectra of complexes **1**–**28** were in agreement with those of previously reported ruthenium and osmium analogues,[6, 11c, 31] where the general trend is that in open-tether/non-tether complexes (dimers **1**–**10** and monomers **15**–**24**, **27** and **28**), the most shielded η^6-proton signal tends to be more shifted to low field, with respect to closed-tether complexes (dichlorido monomers **11**–**14**, and bpy monomers **25** and **26**). This tendency is attributed to the restricted rotation of the η^6-bound arene along the M-centroid axis in closed-tether complexes.[6] In consequence, the span between the least and most shielded proton of the arene is larger in closed-tether complexes. In our case, the Δδ of the bound arene spans between 0.18–0.61 ppm in open-tether/non-tether complexes and 0.61–1.02 ppm in closed-tether complexes. All η^6-arene proton shifts for each complex are summarised in Table S1.

The X-ray crystal structures of tether complexes **11**, **12**, **13**, **25** and **26** (Figure 3) and non-tether complex **15·PF$_6$** (Figure S39) unambiguously confirmed our characterisation. Complexes **11**, **12**, **26** and **27** are the first Ru/Os-arenes X-ray structures to be reported with a tethered quinoline.

Some interesting features of our tethered compounds were observed in their X-ray structures, especially in comparison with non-tethered complex **15·PF$_6$**. Among those, the offset of C7 toward the metal with respect to the plane that contains the η^6-arene. In closed-tether complexes **11**, **12**, **13**, **25** and **26** this value is in the range 0.455–0.489 Å (comparable to that of other Ru(II) and Os(II) similar compounds),[6, 11c, 31] while for the non-tether complex **15·PF$_6$**, C7-offset is considerably lower (0.071 Å). We also measured the arene tilt angle (M-centroid-C6). In non-tether and open tether complexes it tends to be equal or greater than 90°,[6] as in **15·PF$_6$** (90.02°), while in all closed-tether complexes the angle is less than 90° (85.50°–86.68°). The tether ring torsion was observed in the propeller twist of the pendant ring plane, with respect to the one containing the coordinated arene. In non-tether complex **15·PF$_6$**, this twist angle was only 14.66°, whereas for tethered complexes **11**, **12**, **13**, **25** and **26** the angle was almost square, in the range 81.71°–89.45° (this is in agreement with

similar complexes).[11c] It is also interesting to observe that the ring tension has an impact on the synthetic reactivity and outcome of these structures, as for example both closed-tether dichlorido monomers **13** and **14** result in open-tether complexes **27** and **28** upon bpy chelation.

Contrasting Ru and Os analogues **11** vs **12**, and **25** vs **26**, no significant differences were found for most of the selected angles and distances (Table S2), except for the bite angle formed between the N atoms of the chelate ligand and the metal (∠X–M–Y), and each of the angles between these N atoms and the nitrogen (N1) of the pendant ring (∠X–M–N1 and ∠Y–M–N1). In all three cases, these angles were smaller in the Os complex.

Crystallographic data (Table S3), as well as distances and angles of hydrogen-bonding interactions in complex **13** (Figure S40 and Table S4), are shown and discussed in detail in the Supporting Information of this manuscript.

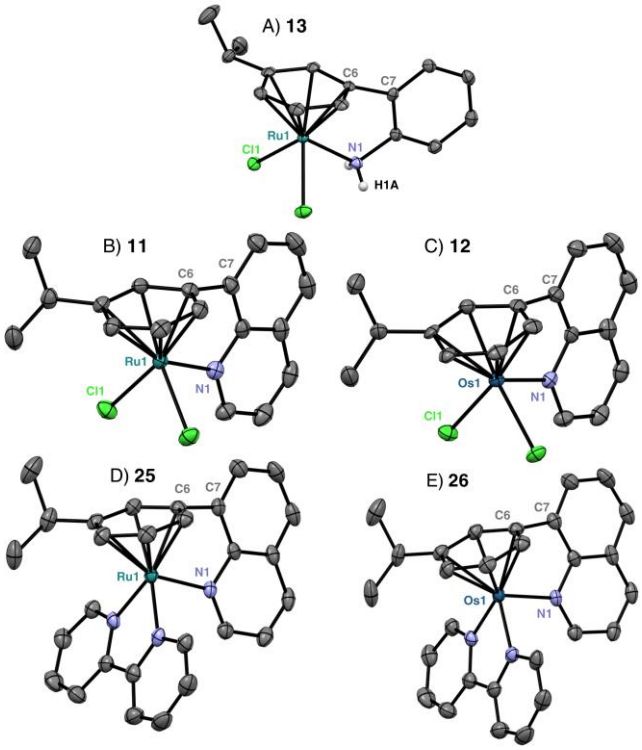


Figure 3. ORTEP diagrams and atom numbering schemes for closed-tether compounds: A) **13** [Ru(η^6:κ^1-C$_6$H$_4$(^{i}Pr)((C$_6$H$_4$)NH$_2$))Cl$_2$], B) **11** [Ru(η^6:κ^1-C$_6$H$_4$(^{i}Pr)(quinoline))Cl$_2$], C) **12** [Os(η^6:κ^1-C$_6$H$_4$(^{i}Pr)(quinoline))Cl$_2$], D) **25** [Ru(η^6:κ^1-C$_6$H$_4$(^{i}Pr)(quinoline))(bpy)](PF$_6$)$_2$ and E) **26** [Os(η^6:κ^1-C$_6$H$_4$(^{i}Pr)(quinoline))(bpy)](PF$_6$)$_2$ (50% probability ellipsoids). The H atoms (except those on the nitrogen in the tether ring in **13**) and the PF$_6^-$ counterions in **25** and **26** have been omitted for clarity.

Conclusion

Arene-derivatisation for the design of new Ru/Os half-sandwich complexes can have significant limitations including laborious/hazardous experimental procedures (especially for the Birch reduction due to the use of liquid ammonia), the need for specialised and/or expensive reagents or equipment, and limited substituent types, among others. With this method, only one reduction reaction –with or without liquefied NH_3– is needed; and from that product, it is possible to synthesise a great range of precursors of arene ligands (hemilabile and non-hemilabile). This enables the synthesis of tether and non-tether Ru(II) and Os(II) half-sandwich complexes with useful and interesting functional groups, which would be very difficult, or perhaps impossible, to synthesise through methods currently used to derivatise cyclohexadienes. A conventional alternative to obtain half-sandwich complexes is the arene exchange,[32] but unlike our method, it is ineffective with osmium.

We present a novel methodology for the facile derivatisation of the arene moiety in ruthenium and osmium half-sandwich compounds. We synthesised eleven cyclohexadiene derivatives (nine of them new) and some of their respective precursors, Ru/Os(II) dimers/dichlorido monomers, to get fourteen Ru(II) and Os(II) half-sandwich complexes, using bipyridine as the bidentate ligand (XY=bpy), with general formulae [Ru/Os(η^6-C$_6$H$_4$(^{i}Pr)(R))(bpy)Cl]Cl (**15**–**24**, **27** and **28**) and [Ru/Os(η^6:κ^1-C$_6$H$_4$(^{i}Pr)(quinoline))(bpy)](PF$_6$)$_2$ (**25** and **26**). This is a promising methodology with which we can avoid carrying out a reduction reaction every time a reduced functionalised arene is designed, and an alternative to the well-exploited arene-exchange reduction for Ru(II)-arenes.

Our work enables to fine-tune the molecular design for Ru/Os-arene organometallics by varying the arene substituents, depending on the application for which the compound is aimed at. For example, incorporating substitutes that allows coupling and click reactions, including biological labelling (e.g., coumarin moiety, obtained in this work),[33] the synthesis of metalloenzymes,[34] and biocatalysts,[35] among other useful applications.

Supporting Information

The authors have cited additional references within the Supporting Information.[36] SI includes further information about experimental procedures, characterisation spectra and crystallographic data.

Author Contributions

A. M. P. conceived and designed the study. C. C. developed the synthetic methodology, synthesised and characterised the compounds. A. M. P. and C. C. discussed the findings and contributed towards writing the manuscript.

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Keywords: Half-sandwich complexes • tethered complexes • ruthenium • osmium • arene

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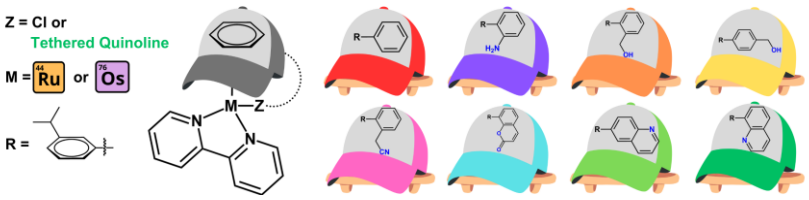

We pioneer the use of a practical C(sp^3)-C(sp^2) coupling to obtain Ru(II)- and Os(II)-η^6-arene half-sandwich complexes with a wide variety of arene functionalities, including those that enable the formation of tether rings. We synthesise 28 new complexes bearing eight different substituents, mostly unreported for Ru(II) or Os(II) half-sandwich complexes, such as quinoline (tethered and non-tethered) and coumarin.