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Review

Functionalised η^6-arene ruthenium complexes

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Contents

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ABSTRACT

η^6-Arene ruthenium complexes have been known for more than 30 years, and their chemistry has been extensively studied for unfunctionalised arenes such as benzene, *para*-cymene and hexamethylbenzene. However, little is known about η^6-arene ruthenium complexes in which the arene ligand is not merely an aromatic hydrocarbon but contains chemical functions as substituents. This review gives an overview of functionalised η^6-arene ruthenium complexes, their syntheses and structures, as well as their intrinsic potential ranging from biological applications to applications as nano-materials.

1. Historical background

The 1950s were crucial for the emergence of organometallic chemistry as an independent field of research. Major discoveries such as the Wittig reaction [1], the Ziegler–Natta process [2,3] or the preparation of π-allyl palladium complexes [4] were achieved during that prolific time. Moreover, the early 1950s saw the synthesis of the first sandwich complexes, ferrocene $(\eta^5\text{-}C_5H_5)_2Fe$, by Pauson in 1951 [5]. The structure, erroneously assigned by Pauson, was correctly addressed a year later by Wilkinson and Woodward [6]. It was soon after the preparation of ferrocene that Wilkinson synthesised the corresponding ruthenocene derivative [7]. Since this pioneering work, a multitude of π-systems incorporating

Abbreviations: Cy, cyclohexyl; dapta, 3,7-diacetyl-1,3,5-triaza-5-phosphabicyclo[3.3.1]nonane; de, diastereomeric excess; dmf, *N*,*N*-dimethylformamide; dmso, dimethylsulfoxide; dppf, 1,1′-bis(diphenylphosphino)ferrocene; en, ethylenediamine; ee, enantiomeric excess; IC_{50}, drug concentration necessary to attain 50% inhibition of cell viability; Ph, phenyl; ^{i}Pr, isopropyl; ROMP, ring opening metathesis polymerisation; pta, 1,3,5-triaza-7-phosphaadamantane; thf, tetrahydrofuran; tpp, 5,10,15,20-tetra(4-pyridyl)porphyrin; [9]aneS_3, 1,4,7-trithiacyclononane.

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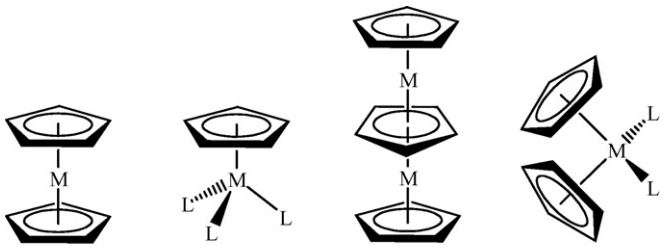
cyclopentadienyl ligands with different transition metals were synthesised. Other than sandwich complexes, half-sandwich, multidecker and tilted sandwich complexes were prepared as well [8]:

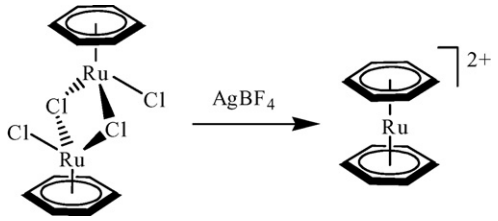


sandwich half-sandwich multidecker tilted

The first rational synthesis of the neutral isoelectronic C_6H_6 metallocene was developed by Fischer and Hafner in 1955 [9]. Bis(benzene)chromium, $(\eta^6\text{-}C_6H_6)_2Cr$, was obtained by the reaction of $CrCl_3$ with benzene and aluminium powder as reducing agent in the presence of $AlCl_3$:

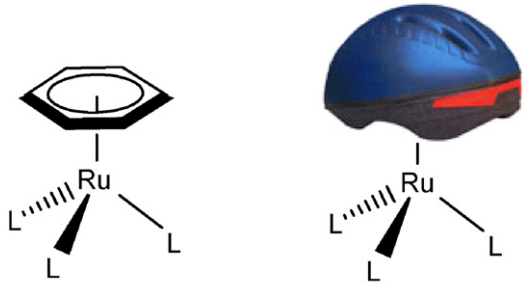
$$CrCl_3 + C_6H_6 \xrightarrow[H_2O]{Al,AlCl_3} [(\eta^6\text{-}C_6H_6)_2Cr]^{+} \xrightarrow[KOH]{Na_2S_2O_4} (\eta^6\text{-}C_6H_6)_2Cr$$

The ruthenium analogue was synthesised in a similar manner using $RuCl_3{\cdot}nH_2O$, benzene, $AlBr_3$ and aluminium [10]. A superior method giving better yields and allowing as well the synthesis of mixed bis-arene ruthenium salts was developed a few years later by Bennett and Matheson [11]. Bis(arene)ruthenium complexes were the first η^6-arene ruthenium compounds, but many others followed:



2. Introduction

Within the large family of η^6-arene ruthenium complexes, piano-stool complexes are undeniably the most studied ones. They have found applications in catalysis, supramolecular assemblies, molecular devices, and have shown antiviral, antibiotic, and anticancer activities. These three-legged piano-stool complexes possess a pseudo-octahedral geometry at the ruthenium(II) atom, the arene ligand occupying three coordinating sites (the seat) with three other ligands (the legs). Therefore, the octahedral geometry can be viewed as pseudo-tetrahedral, thus limiting the number of possible isomers:

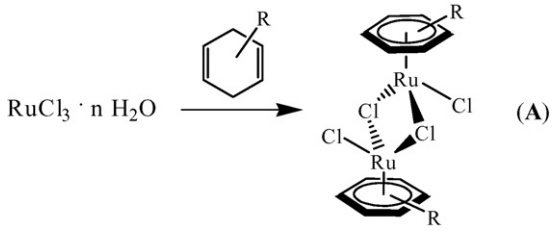


3 remaining coordination sites for ligands L

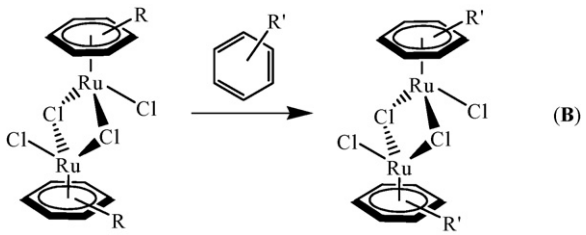
The presence of the aromatic π-ligand stabilises and protects the metal centre, preventing rapid oxidation to ruthenium(III). Moreover, the arene ligands are relatively inert towards substitution reactions and consequently are often considered as spectator ligands. However, the arene moiety which is strongly coordinated to the ruthenium atom can be customised by simply attaching different substituents. These functionalised substituents can be modified to tune the properties of the arene-ruthenium complexes. The three remaining coordination sites opposite to the arene ligand can be used to introduce a wide variety of ligands with N-, O-, S- or P-donor atoms. The resulting complexes are neutral, mono- or dicationic, and often these ligands are labile. This tendency to exchange ligands in solution is crucial in self-assemblies [12] and catalytic processes [13].

3. Synthetic methods

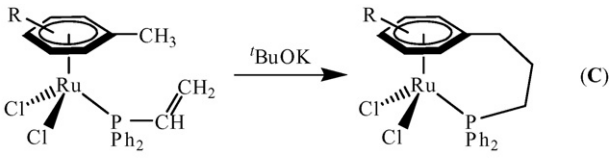
Introduced by Winkhaus and Singer [14] and later improved by other groups [15,16], the most commonly used preparation of arene ruthenium complexes is by reaction of $RuCl_3{\cdot}nH_2O$ with a cyclohexadiene derivative in an EtOH–H_2O solvent mixture (route **A**). The resulting chloro-bridged dimers are generally air stable and can react with a wide variety of ligands, by means of cleavage of the chloro-bridged, to afford in excellent yield mononuclear half-sandwich complexes [17]:

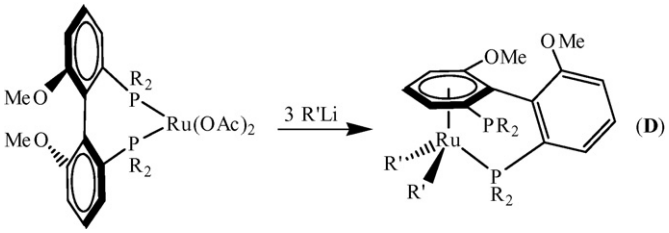


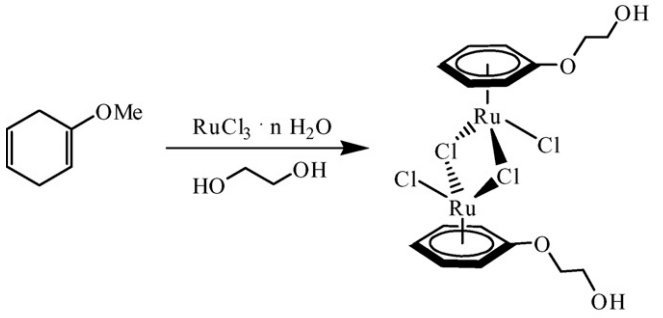
A second route to generate arene ruthenium complexes involves the exchange of the π-ligand at elevated temperature (**B**) [18]. These arene exchange processes were extensively studied by Mutterties [19]. The arene exchange happens either in a concerted- or a stepwise fashion with the incoming arene: The arene ligand is progressively removed from the coordination sphere passing from η^6 to η^4 to η^2 and finally being released before or during the insertion of the new arene ligand. Arene ligands possessing electron-withdrawing groups are more easily replaced, while the most stable arene ruthenium moiety is the electron-rich hexamethylbenzene ruthenium derivative:



In the preparation of tethered half sandwich η^6-arene ruthenium complexes two other strategies were also employed. The first one implies an intramolecular base-promoted Michael addition reaction between the connecting tethered arm and the η^6-arene ligand (**C**) [20], while the second uses the propensity for the ruthenium atom to coordinate one face of a biaryl ligand (**D**) [21]:

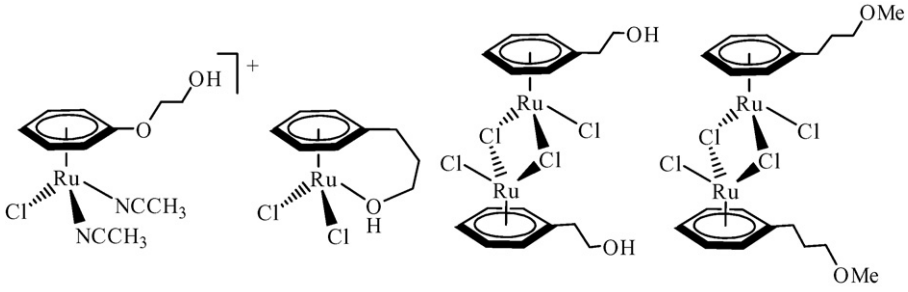






1

The dinuclear complex **1** reacts with NH_4PF_6 in acetonitrile to afford the mononuclear complex $[(\eta^6\text{-}C_6H_5OCH_2CH_2OH)RuCl(CH_3CN)_2]PF_6$ (**2**) which possesses two coordinated acetonitrile molecules [23]:



2 **3** **4** **5**

Several synthetic pathways coupled with relatively easily accessible materials have contributed to the rich chemistry of functionalised η^6-arene ruthenium complexes. The following chapters describe the synthesis, structure and potential application of functionalised η^6-arene ruthenium complexes.

4. Simple functionalised derivatives

The reaction of commercially available 1-methoxy-1,4-cyclohexadiene with ruthenium chloride hydrate affords in methanol the expected dinuclear compound $[(\eta^6\text{-}C_6H_5OCH_3)Ru(\mu\text{-}Cl)Cl]_2$ [18]. However, if the reaction is carried out in ethanol, or 1,2-ethanediol an alkoxy exchange is observed [22], giving rise to the formation of OR functionalised arene ruthenium complexes. The alkoxy exchange is promoted by the methoxy group through an acid-catalysed mechanism:

Functionalised arene ruthenium complexes possessing a hydroxyalkyl (hydroxypropyl (**3**) and hydroxyethyl (**4**)) or methyl ether arm (**5**) have also been synthesised [24]. Interestingly, the hydroxypropyl derivative **3** turned out to be a mononuclear compound in the solid state instead of the expected dinuclear complex, the terminal hydroxy group of the pendant arm being coordinated as well to the ruthenium atom. Several phosphine derivatives were prepared from **4** and **5**, including PCy_3, P^iPr_3 and the water-soluble $P(CH_2OH)_3$ complex. The electrochemistry of the phosphines derivatives were studied, showing a chemically reversible oxidation at positive potentials which was assigned to the Ru(II/III) couple [24].

In order to generate metal containing liquid crystals, mono- and di-functionalised arene ruthenium complexes containing ester substituents have been prepared [25]. The dinuclear complexes $[\{\eta^6\text{-}C_6H_5(CH_2)_3OCO\text{-}p\text{-}C_6H_4\text{-}OC_8H_{17}\}Ru(\mu\text{-}Cl)Cl]_2$ (**6**) and $[\{\eta^6\text{-}p\text{-}C_6H_4(CH_2COOCH_2CH_3)_2\}Ru(\mu\text{-}Cl)Cl]_2$ (**8**) were obtained in good yield from the corresponding cyclohexadiene derivatives. Moreover, their corresponding mononuclear triphenylphosphine derivatives were as well isolated and characterised, $[\{\eta^6\text{-}C_6H_5(CH_2)_3OCO\text{-}p\text{-}C_6H_4\text{-}OC_8H_{17}\}Ru(PPh_3)Cl_2]$ (**7**) and [{η^6-

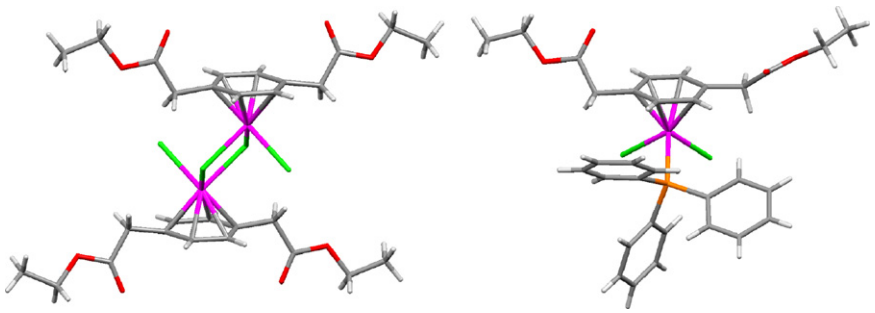
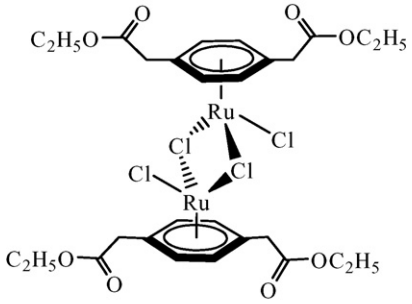


Fig. 1. Molecular structures of **6** (left) and **7** (right) [25].

p-$C_6H_4(CH_2COOCH_2CH_3)_2\}Ru(PPh_3)Cl_2]$ (**9**), respectively:



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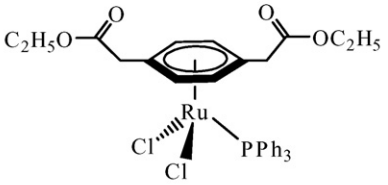

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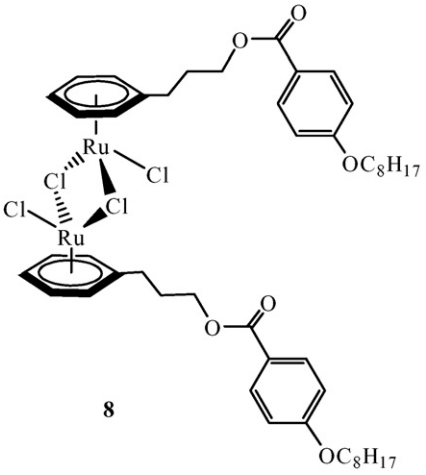

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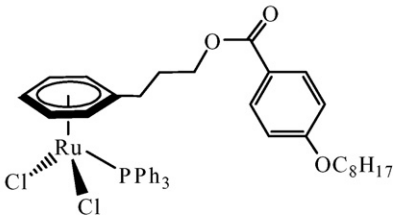


9

The molecular structures of **6** and **7** were established by single-crystal X-ray structure analysis, see Fig. 1. In **6**, the tethered arms point away from the aromatic plane and despite the presence of these two side arms, slipped-parallel π-stacking interactions were observed between the phenyl rings of the arene ligand, thus forming infinite one-dimensional chains in the crystal. In **7**, no such π-stacking interactions were observed, instead weak hydrogen bonds were observed between two neighbouring molecules, thus forming in the solid state a dimer. The total distance between the two ruthenium atoms was 5.547(2) Å.

The thermal behaviour of **8** and **9** were studied in view of possible mesomorphic properties. However, both complexes have shown decomposition without the appearance of liquid crystalline phases. The orange complex **8** decomposed at 205 °C to give a black solid, while in **9**, the decomposition occurred at 155 °C and was accompanied by the emergence of dark red bubbles in the liquid phase, suggesting cleavage of the tethered ester chain and formation of a ruthenium compound which was then soaked in the organic liquid phase.

5. Tethered derivatives

The configurational stability of coordinatively unsaturated two-legged piano-stool complexes is a critical aspect in the prospective of using a chiral-at-metal η^6-arene ruthenium complex as a catalyst for enantioselective transformations [26]. Theoretical studies suggest that the inversion barrier of the pyramidal ground state geometries of the catalytic active species is low (<15 kcal mol^{-1}), thus hampering their use as enantioselective catalysts, see Fig. 2 [27].

Therefore, anchoring the metal centre in a cyclic framework would significantly raise the inversion barrier, thus preventing

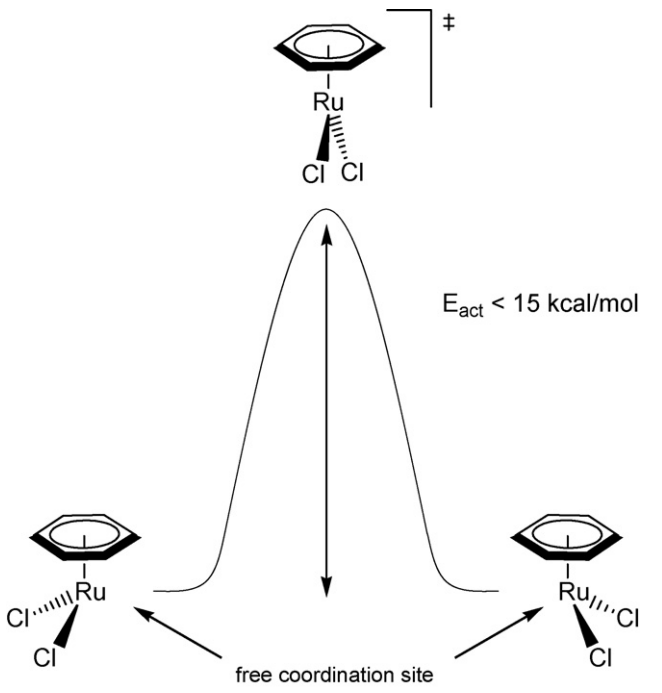
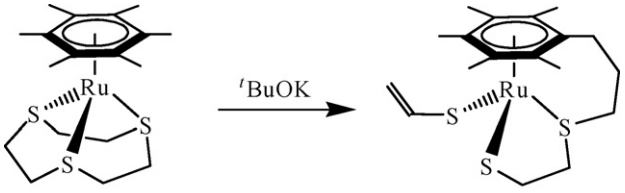


Fig. 2. Inversion of a C_1-symmetric intermediate (16-electron) via a C_s-symmetric transition state [27].

rapid racemisation. Moreover, tethered arene complexes offer the possibility of stabilising arene coordination for a range of oxidation states. This chapter focuses on the synthesis and stability of the different tethered arene ruthenium complexes. The catalytic applications of some of these different compounds will be discussed in Chapter 8.

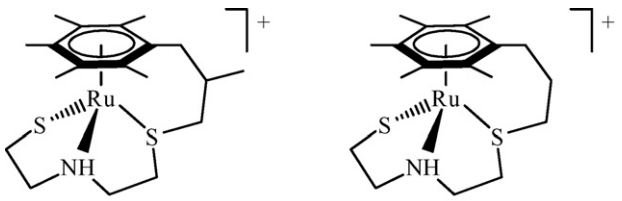
π-Complexation of aromatic ligands by transition metal has a powerful effect on the reactivity of the arene [28]. One major feature is the enhancement of the acidity of benzylic protons, which could lead to the alkylation and functionalisation of methylated aromatic compounds. The most studied reactions consist of deprotonation of a methyl substituent with an excess of a base and subsequent alkylation of the methylene group by alkyl or aryl halides. This approach was used to synthesise the first tethered η^6-arene ruthenium complex, in which successive deprotonation on treatment with an excess of potassium ^{t}butoxide at the cationic complex $[(\eta^6\text{-}C_6Me_6)Ru([9]aneS_3)](PF_6)_2$ ([9]aneS$_3$ = 1,4,7-trithiacyclononane) led to the formation of $[\{\eta^6{:}\eta^2\text{-}C_6Me_5(CH_2)_3S(CH_2)_2S\}Ru(SCHCH_2)]$ (**10**) [29]. It was demonstrated that the formation of **10** involves stepwise fragmentation of $[(\eta^6\text{-}C_6Me_6)Ru([9]aneS_3)](PF_6)_2$ through C–S bond cleavage under basic conditions:



10

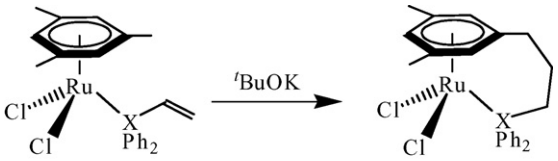
A similar reaction was employed twelve years later to synthesise the cationic tetradentate complexes $[\{\eta^6{:}\eta^3\text{-}C_6Me_5CH_2CH(Me)CH_2S(CH_2)_2NH(CH_2)_2S\}Ru]^+$ (**11**) and $[\{\eta^6{:}\eta^3\text{-}C_6Me_5(CH_2)_3S(CH_2)_2NH(CH_2)_2S\}Ru]^+$ (**12**) [30].

The 1,4,7-trithiacyclononane ligand was replaced by the NS_2 derivative bis(2-mercaptoethyl)amine. However, in basic conditions the reactivity remains almost the same, C–S bond cleavage followed by arene tethering through S-alkylation. The only difference is that in this present case a second deprotonation step to give a terminal S-allyl derivative, similar to **10**, is not feasible. It appears that C–S cleavage cannot occur in the $NH(CH_2)_2S$ linkages of **11** and **12**:



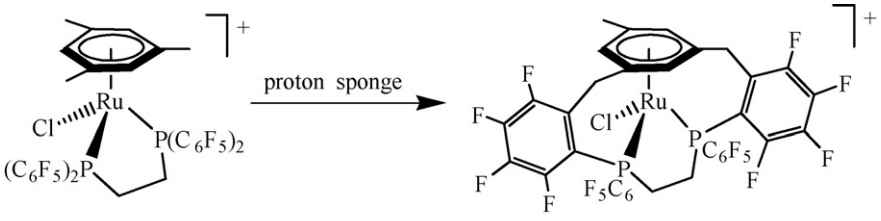
11 **12**

Several chelating phosphine and arsinopropyl-arene ligands such as $[\{\eta^6{:}\eta^1\text{-}1,3,5\text{-}C_6H_3(CH_3)_2(CH_2CH_2XPh_2)\}RuCl_2]$ (X = P, **13**; or As, **14**) formed by base-promoted intramolecular hydroalkylations were synthesised using the same strategy [20,31]. The novelty of this approach is the unusual reaction between a vinyl moiety on the coordinated phosphine or arsine ligand and a methyl group of the η^6-arene ligand. The terminal vinylic carbon atom forms a new C–C bond to the methyl group with a concomitant C–H bond cleavage and formation of a new C–H bond on the carbon α to the phosphorus atom. This reaction is formally a base-catalysed hydroalkylations of a C–C double bond:



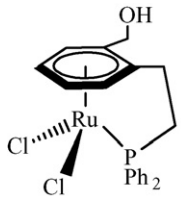
13; X = As
14; X = P

In a similar strategy, in which the acidity of the benzylic protons of an arene ruthenium ligand is coupled with a dehydrofluorinative C–C coupling reaction, a chiral-at-metal di-strapped arene ruthenium complex $[\{\eta^6{:}\eta^1{:}\eta^1\text{-}C_6H_3Me\text{-}5\text{-}[CH_2\text{-}2\text{-}C_6F_4P(C_6F_5)CH_2]_2\text{-}1,3\}RuCl]^+$ (**15**) is synthesised [32]. The mesitylene ruthenium complex which possess a bidentate 1,2-bis{bis(perfluorophenyl)phosphino}ethane ligand reacts with two equivalents of 1,8-bis(dimethylamino)naphthalene (proton sponge) to give complex **15** in excellent yield. In situ NMR experiments based on $^{31}P\{^1H\}$ NMR data have suggested strongly that the intermediate is $[\{\eta^6{:}\eta^1{:}\eta^1\text{-}C_6H_3Me_2\text{-}3,5\text{-}CH_2\text{-}2\text{-}C_6F_4P(C_6F_5)CH_2CH_2P(C_6F_5)_2\}RuCl]^+$. The $^{31}P\{^1H\}$ NMR spectrum shows resonances at δ = 80.2 and 55.3 ppm, corresponding to $P(C_6F_5)C_6F_4CH_2$ and $P(C_6F_5)_2$, respectively:

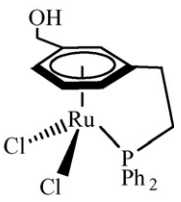


15

The displacement of an electron-poor arene was employed to synthesise a series of tethered phosphine derivatives [33]. The phosphine alcohol complexes $[\{\eta^6{:}\eta^1\text{-}1,2\text{-}C_6H_4(CH_2OH)(CH_2CH_2PPh_2)\}RuCl_2]$ (**16**) and $[\{\eta^6{:}\eta^1\text{-}1,2\text{-}C_6H_4(CH_2OH)(CH_2CH_2PPh_2)\}RuCl_2]$ (**17**) were obtained in excellent yield. Complexes **16** and **17** were obtained by treatment of the dinuclear complex $[(\eta^6\text{-}C_6H_5CO_2Et)RuCl_2]_2$ with the corresponding phosphino alcohol ligand followed by replacement of the electron-poor arene $\eta^6\text{-}C_6H_5CO_2Et$ at elevated temperature. The formation of **16** and **17** was easily monitored by $^{31}P\{^1H\}$ NMR spectroscopy. However, all attempts to functionalise the alcohol group to a phosphinite or phosphite, albeit using many different bases, were unsuccessful. The lack of reactivity of the alcohol function was eventually rationalised by extended Hückel calculations: The absence of oxygen contributions in the highest lying occupied molecular orbitals did not favour attack at the alcohol position, despite a high-negative charge located on the oxygen:



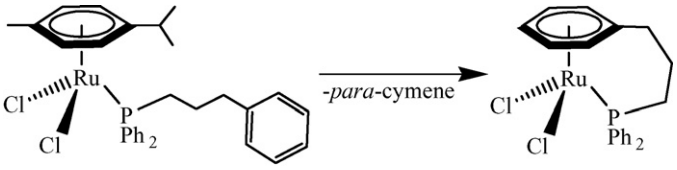
16



17

The molecular structures of **16** and **17** were determined by single-crystal X-ray structure analysis, see Fig. 3. Both structures are staggered rather than eclipsed with C_{arene}–C_{CH_2}–C_{CH_2}–P dihedral angles of 40.4(4)° for **16** and 44.4(5)° for **17**. In the regioisomers **16** and **17**, the coordinated η^6-arene ligand is essentially planar, although incorporation of the tethered phosphine tends to force the *ipso* carbon toward the metal centre. The oxygen points away from the ruthenium atom in **16** and toward the ruthenium atom in **17**, thus setting the oxygen atom at 4.241(3) and 3.761(4) Å from the metal, respectively.

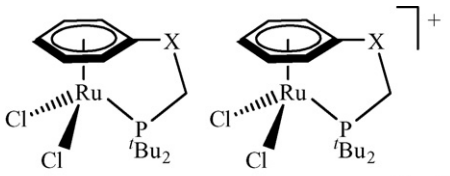
A few months later, Smith and Wright synthesised a similar tethered phosphine arene ruthenium complex [{η^6:η^1-$C_6H_5(CH_2)_3PPh_2$}$RuCl_2$] (**18**) in which the *para*-cymene ligand was replaced after 18 h at 130 °C in refluxing chlorobenzene [34]. The synthesis of **18** exploited arene exchange at high temperature and chelating effect after coordination to the ruthenium atom of the phosphine ligand. The molecular structure of **18** has shown that the coordinated ring was pushed across the face of the metal so that the free end of the ring was significantly lifted away from the ruthenium. Electrochemical cyclovoltammetric studies of **18** in acetonitrile have shown the formation of [{η^1-$C_6H_5(CH_2)_3PPh_2$}$RuCl_2(CH_3CN)_3$], in which the η^6-C_6H_5-ring was substituted by three coordinated acetonitrile molecules:



18

Reactions of **18** with NH_4PF_6 in the presence of a variety of neutral two-electron donor ligands afforded a series of cationic complexes of the general formula [{η^6:η^1-$C_6H_5(CH_2)_3PPh_2$}RuLCl]$^+$ (L = $P(OPh)_3$, $P(OMe)_3$, PPh_3, PMe_3, NCMe, NC_5H_5) [35]. The exchange of a chloride for the ligands L generates a chiral-at-metal centre as a racemic mixture of enantiomers.

A series of tethered arene ruthenium complexes containing the bulky trialkylphosphines $^tBu_2PCH_2XC_6H_5$ ligands (X = OCH_2, CH_2) has been prepared [36]. The neutral complexes [(η^6:η^1-$C_6H_5XCH_2P^tBu_2$)$RuCl_2$] (**19**) react with different donor ligands to afford the cationic complexes [(η^6:η^1-$C_6H_5XCH_2P^tBu_2$)RuLCl]$^+$ (**20**) (L = NCMe, $OCMe_2$, PMe_3). Allenylidene derivatives were synthesised as well from **19** and HC≡CC(OH)Ph_2:



19 20

X = OCH_2, CH_2
L = NCMe, $OCMe_2$, PMe_3

In a similar way, in order to stabilise the arene ligand in oxidised species, Bennett et al. synthesised a series of η^6:η^1-phosphine arene ruthenium complexes (**21** and **22**) [37]. The methyl *o*-toluate complex [(η^6-1,2-$MeC_6H_4CO_2Me$)$RuCl_2$]$_2$ was a suitable labile precursor to form tethered arene ruthenium complexes in which the η^6-1,2-$MeC_6H_4CO_2Me$ ligand was replaced by the aromatic ring of the phosphine ligand after 24–72 h at 120 °C in thf. The electrochemical stability of the complexes was studied by cyclic voltammetry. All tethered complexes showed reversible one-electron Ru(II)/Ru(III) redox steps in dichloromethane:

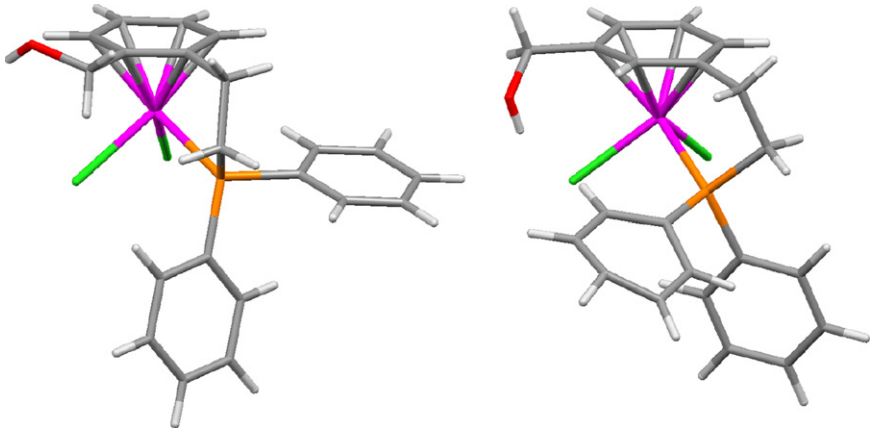


Fig. 3. Molecular structures of **16** and **17** [33].

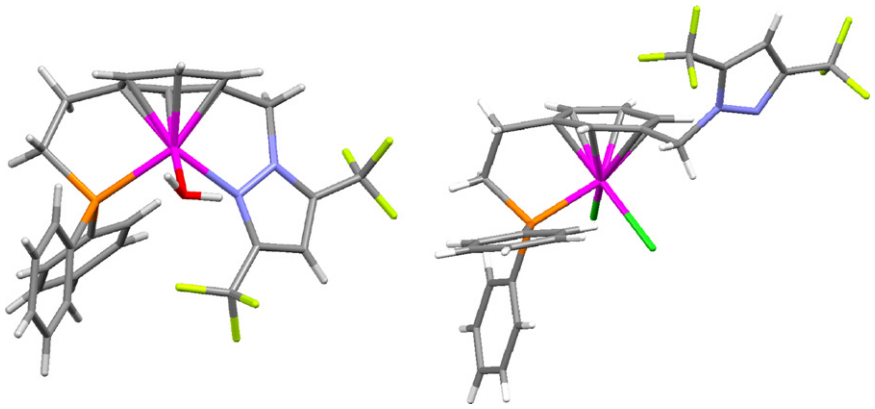
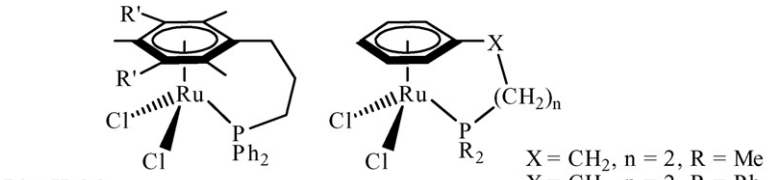
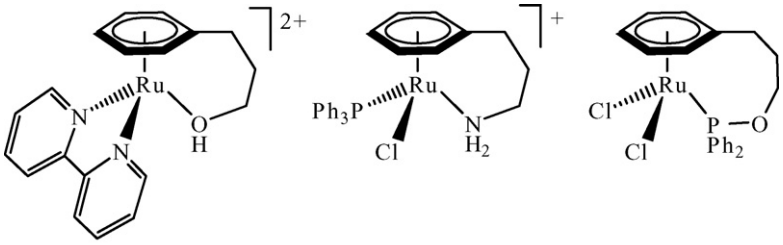


Fig. 4. Molecular structures of ($S_{Ru}R$)-**26** and **27** [40].



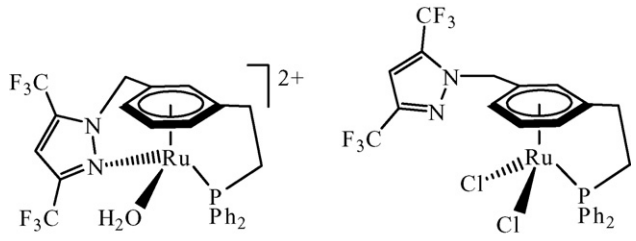
21 **22**

The synthesis of ruthenium complexes chelated by an oxygen [{η^6:η^1-$C_6H_5(CH_2)_3OH$}(2,2′-bipyridine)Ru]$^{2+}$ (**23**), nitrogen [{η^6:η^1-$C_6H_5(CH_2)_3NH_2$}$(PPh_3)RuCl]^+$ (**24**) or phosphorous [{η^6:η^1-$C_6H_5(CH_2)_3OPPh_2$}$RuCl_2$] (**25**) donor atom and η^6-arene ligand has been studied by Kurosawa [38]. The chelate effect exerted by the η^6-arene ligand and the pendant arm is responsible for the stabilisation of otherwise labile binding atoms to the ruthenium centre. The synthesis and properties of these moderately stable tethered complexes were of potential interest to develop and understand catalytic processes:



23 **24** **25**

Inspired by Tröger's base [39], a configurationally stable piano-stool complex with chirality at the metal centre was synthesised by anchoring the ruthenium metal centre in a rigid bicyclic framework [40]. The enantiopure ($R_{Ru}S$)- and ($S_{Ru}R$)-[{η^6:η^1:η^1-(PArN)}$Ru(OH_2)$]$(CF_3SO_3)_2$ (**26**) (PArN = 1-[3-(2-diphenylphosphanyl-ethyl)-benzyl]-3,5-bis-trifluoromethyl-1*H*-pyrazole) were prepared after separation of the racemic intermediate [{η^6:η^1-(PArN)}$RuCl_2$] (**27**) on chiral preparative HPLC. The stereochemical stability of these complexes was remarkable. All attempts to racemise the enantiopure complexes **26** and **27** have failed, yielding decomposition products rather than a racemic mixture of products. It was clear from the CD spectra of **26** and **27** that the configuration at the ruthenium centre was encoded by the planar chirality resulting from the η^6-coordination of the prochiral arene moiety. Related complexes with an enantiopure auxiliary incorporated in the PArN* ligand (PArN* = 2-[3-(2-di-phenylphosphanyl-ethyl)-benzyl]-7,8,8-trimethyl-4,5,6,7-tetrahydro-2*H*-4,7-methano-indazole), facilitating analysis and separation, were prepared in a similar manner [41]:

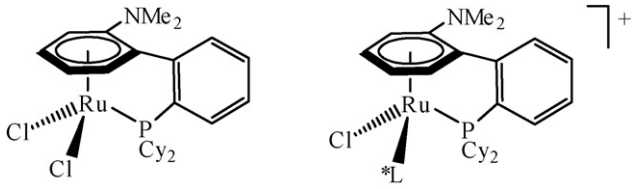


($R_{Ru}S$)-**26** **27**

The molecular structures of ($S_{Ru}R$)-**26** and -**27** were determined by single-crystal X-ray structure analysis, see Fig. 4. Upon coordination of the tethered pyrazole ring to the ruthenium atom in **26** as compared to **27**, the Ru–P bond lengthens by 0.065 Å, while the

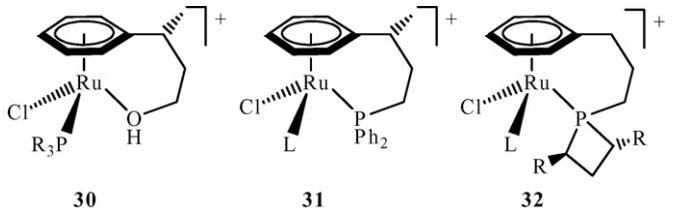
Ru–arene$_{centroid}$ length shortens by 0.030 Å. In **26**, the piano-stool geometry around the ruthenium is slightly distorted, the P–Ru–N angle being 102.0(1)°, reflecting the large bite angle imposed by the 1,3-substitution pattern of the tethered arms on the arene.

Tethered arene ruthenium complexes can also be obtained from biphenyl unit in which the conformational freedom of the tether is restricted. Indeed, (2-dicyclohexylphosphino)-biphenyl derivatives react with $[(\eta^6\text{-}C_6H_6)Ru(\mu\text{-}Cl)Cl]_2$ in dmf at 100 °C to give the tethered complex $[\{\eta^6\text{-}\eta^1\text{-}C_6H_4(NMe_2)(C_6H_4PCy_2)\}RuCl_2]$ (**28**) [42]. Despite the presence of the 2′-dimethylamino group in **28**, which makes the molecule chiral, resolution of the planar chiral enantiomers was unsuccessful. Therefore abstraction of a chloride from **28** to create a chiral-at-metal centre, thus giving rise to diastereoisomers, was very tempting. However, the separation of the diastereoisomers in complexes of the type $[\{\eta^6\text{-}\eta^1\text{-}C_6H_4(NMe_2)(C_6H_4PCy_2)\}RuClL^*]^+$ (**29**) (L* = chiral ligand) was unsuccessful as well. The authors finally succeed by coordinating an achiral phosphine ligand (PPh_3) to the metal centre which gives rise to the diastereoisomers $[\{\eta^6\text{-}\eta^1\text{-}C_6H_4(NMe_2)(C_6H_4PCy_2)\}(PPh_3)RuCl]^+$ which after separation of the diastereoisomers underwent spontaneous resolution upon crystallisation. It was a rare example of a planar chiral, tethered, late transition metal compound isolated in its enantiopure form:



28 **29**

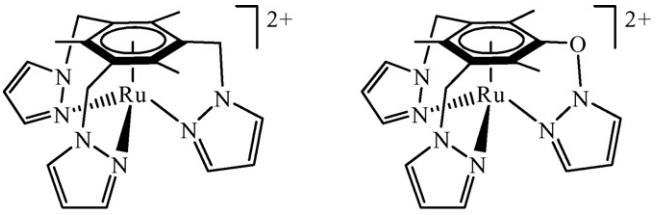
In view of forming chiral-at-metal compounds, Zenneck and co-workers synthesised a series of O- and P-tethered arene ruthenium complexes incorporating the (*R*)-3-phenylbutyl moiety; $[\{\eta^6\text{-}\eta^1\text{-}C_6H_5CH(CH_3)CH_2CH_2OH\}(PR_3)RuCl]^+$ (**30**) and $[\{\eta^6\text{-}\eta^1\text{-}C_6H_5CH(CH_3)\text{-}CH_2CH_2PPh_2\}RuLCl]^+$ (**31**) [43]. These complexes were isolated and characterised as their tetrafluoroborate salts. The chelation of the pendant arm and substitution of a chloride by another ligand (L) creates the desired chiral-at-metal complexes **30** and **31**. While the hydroxyl derivative was obtained as an almost 1:1 mixture of diastereoisomers, the phosphine derivative was enriched in one diastereoisomers with de (de = diastereomeric excess) up to 90%. This discrepancy between the formations of the two diastereoisomers allowed isolation upon crystallisation of the major diastereoisomer:



30 **31** **32**

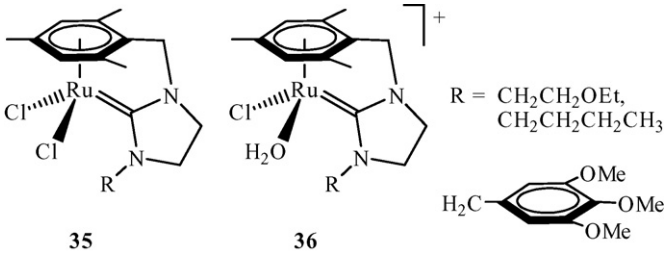
Similarly, the same group has synthesised chiral-at-metal complexes by introduction of an enantiopure tethered phosphine to the pendant arm of an arene ligand, thus generating a single pair of diastereoisomers upon coordination of the phosphine moiety and replacement of a chloro ligand. Complexes of the type $[\{\eta^6\text{-}\eta^1\text{-}C_6H_5CH_2CH_2CH_2P(\text{–}CHRCH_2CHR\text{–})\}RuLCl]^+$ (**32**) (R = Cy, ^{i}Pr, ^{t}Bu, Bz, Me) were obtained in excellent yield and as single diastereoisomer [44]. Due to the low-conformational flexibility of the four-membered ring, a positive effect on asymmetric processes was expected by the authors. However, no catalytic results have been published so far.

The reaction of $[Ru(dmso)_4Cl_2]$ with polyheteroaryl-substituted tripodal ligands [1,1′,1″-(2,4,6-trimethylbenzene-1,3,5-triyl)tris (methylene)tris(1*H*-pyrazole) and 1,1′-(5-(1*H*-pyrazol-1-yloxy)-2,4,6-trimethyl-1,3-phenylene)bis(methylene)bis(1*H*-pyrazole)] in ethanol/water at reflux gives the encapsulated arene ruthenium complexes **33** and **34**, respectively [45]. The encapsulation of a ruthenium atom by a η^6-arene ligand linked to three nitrogen-containing groups was prepared for the first time:



33 **34**

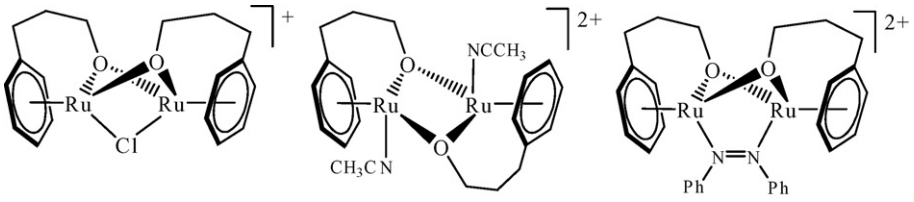
Electron-rich olefins that contain one or two arylmethylene groups attached to a nitrogen atom were treated with $[(\eta^6\text{-}1,4\text{-}^iPrC_6H_4Me)Ru(\mu\text{-}Cl)Cl]_2$ in toluene at 100 °C for 4 h to generate a series of tethered carbene ruthenium complexes (**35**) [46]. Extraction of one chloride ion from **35** with $AgCF_3SO_3$ in water affords the aqua complexes **36**. The molecular structures of some of these carbene complexes show short Ru–C bond lengths ranging from 1.996(3) to 2.058(3) Å:



35 **36**

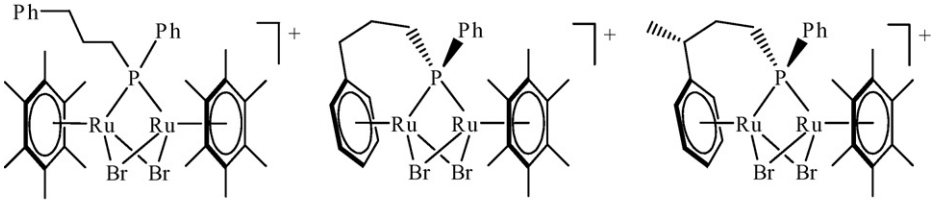
6. Tethered-bridged derivatives

Functionalised η^6-arene ruthenium complexes in which the pendant arms are used as a bridging ligand were reported for the first time by Kurosawa and co-workers [47]. Deprotonation of the alcohol function of a pendant arm tethered to the arene ligand affords in the appropriate conditions a cationic bridging alkoxo derivative $[\{\eta^6\text{:}\eta^1\text{:}\mu\text{-}C_6H_5(CH_2)_3O\}_2Ru_2Cl]^+$ (**37**). *cis*-Azobenzene and acetonitrile react with [**37**]BF_4 to form the dimeric species $[\{\eta^6\text{:}\eta^1\text{:}\mu\text{-}C_6H_5(CH_2)_3O\}_2Ru_2(CH_3CN)_2]^{2+}$ (**38**) and $[\{\eta^6\text{:}\eta^1\text{:}\mu\text{-}C_6H_5(CH_2)_3O\}_2Ru_2(azobenzene)]^{2+}$ (**39**), respectively. The bridging chloride atom in **37** can be replaced as well with disulfide, pyridazine and pyridine. However, [**37**]BF_4 reacts with bipyridine to form exclusively the mononuclear alkoxo complex $[\{\eta^6\text{:}\eta^1\text{-}C_6H_5(CH_2)_3O\}Ru(bipyridine)]^+$:



37 **38** **39**

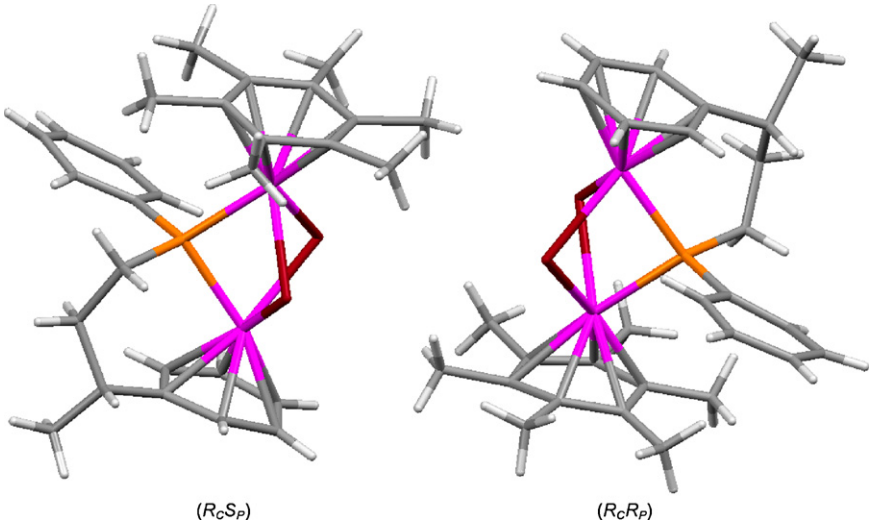
We have synthesised several chiral-at-phosphorus diruthenium phosphido complexes from the dibromo-phosphido bridged dinuclear arene ruthenium complex **40** and have shown that an intramolecular ligand exchange between one arene ligand at ruthenium and a phenyl substituent at the side arm of the phosphido-bridge leads to chiral-at-the-phosphorous tethered derivatives **41** [48]. Introduction of a stereogenic carbon atom within the pendant arm of the phosphido bridging ligand gives rise to the formation of diastereomeric complexes **42**:



40 (R_P)-**41** (R_C,R_P)-**42**

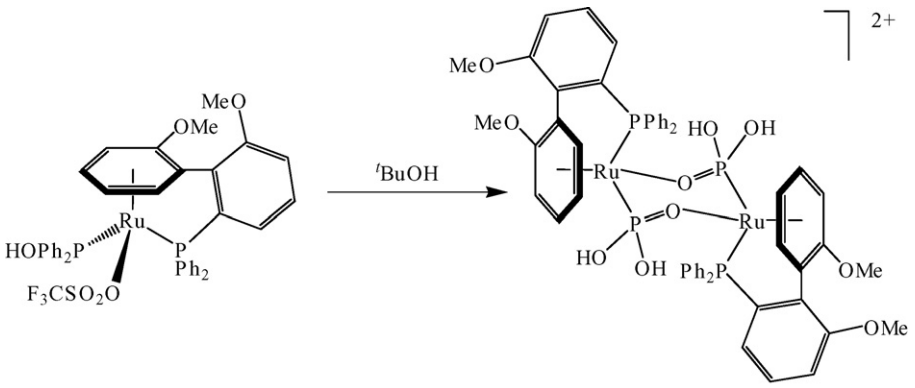
The two diastereomers (R_CS_P)-**42** and (R_CR_P)-**42** are distinguishable in the ^{1}H NMR spectrum, which has shown two doublets of almost equal intensity for the η^6-C_6Me_6 protons at $\delta = 1.95$ and 1.94 ppm. Single crystals suitable for a X-ray structure analysis were obtained by slow diffusion of ether in a concentrated acetone solution of [**42**]BF_4. Both diastereomers, (R_CR_P)-**42** and (R_CS_P)-**42**, were found in the crystal, and the X-ray structure analysis revealed that the two ruthenium atoms are in a distorted octahedral geometry in which the metal centres are bridged by two bromo and a tethered-phosphido ligands, see Fig. 5. Surprisingly, two conformations are observed for the six-membered metallacycle formed upon coordination of the phenyl ring of the pendant arm of the phosphido ligand, a chair-like (R_CS_P) and a half-twist-like (R_CR_P) conformation for the diastereomers of **42**.

The reaction of hydroxydiphenylphosphine arene ruthenium derivatives with ^{t}butyl alcohol in a thf/H_2O solution affords dimeric complexes in which the P=O moiety bridges two ruthenium centres (**43**) [21]. The phosphonato compound is due to solvolysis from traces of water. The molecular structure of **43** is based on mass spectroscopy, NMR, and microanalytical data. It is the first Ru-complex containing an anion of phosphorous acid, $P(=O)(OH)_2$ as ligand:



(R_CS_P) (R_CR_P)

Fig. 5. The molecular structure of the diastereomers of cation **42** [48].

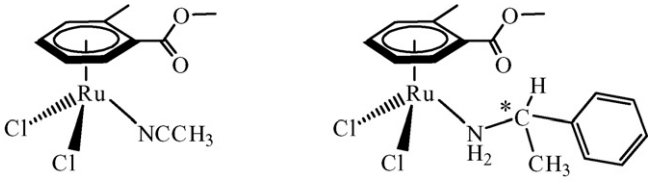


43

7. Chiral derivatives

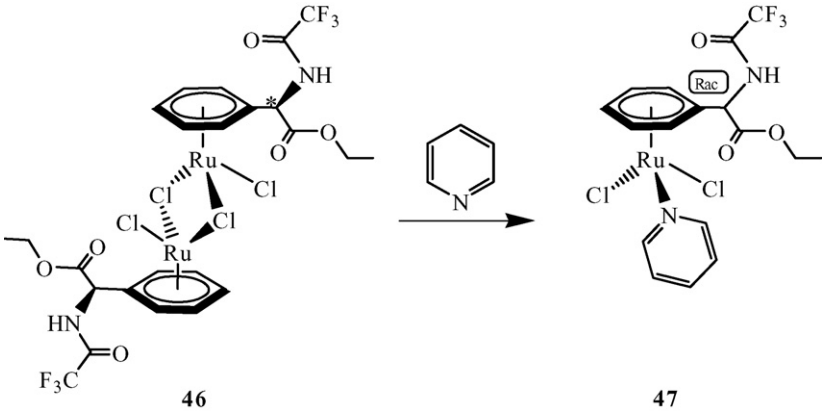
The synthesis and resolution of chiral organometallic complexes is a challenging aspect of organo-transition metal chemistry, especially in the context of asymmetric synthesis. Arene ruthenium compounds were employed as catalysts in asymmetric synthesis. The three-legged piano-stool complexes with three different ligands possess metal-centred chirality, however, too often the resolution of the enantiomers remains a difficult task [49]. Therefore, to bypass these difficulties different research groups have used the arene ligand to introduced a second element of chirality, thus giving rise to diastereoisomers and allowing an easier separation. The first strategy is to use planar chirality as a second element of chirality while the second possibility is to introduce an enantiomerically pure auxiliary group tethered to the arene ligand.

It is known that an arene ligand bearing two non equivalent substituents in 1,2 or 1,3 positions or three equivalent substituents in 1,2,4 positions relative to each other, coordinated in an η^6-fashion to a transition metal, generates planar chirality at the metal with respect to the face of the coordinated arene [50]. Planar chirality of arene ruthenium complexes was studied first by Bennett and co-workers [51]. The mononuclear complex **44** was obtained as a racemic mixture, and under replacement of the weakly coordinated acetonitrile molecule with an enantiopure chiral amine ((*S*)-1-phenylethylamine) a pair of diastereoisomers was formed. Fractional crystallisation of **45** from methanol-diethyl ether gave a solid containing 90% of the more insoluble diastereomer:



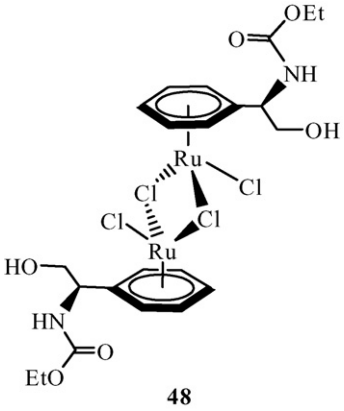
44 45

Introduction of an enantiomerically pure auxiliary group tethered to the arene ligand possesses advantages over planar chirality. Indeed, if the role of chirality at the metal centre is to be probed without a bias, the presence of planar chirality is undesirable. Moreover, in many cases, after separation of the diastereomers, the chiral auxiliary can be chemically removed without destruction of the catalyst which is not possible with an arene ligand possessing planar chirality. Among other chiral arene ruthenium complex in which the chiral element is inserted in a pendant arm of the arene ligand, a D-phenyl-glycine derivative has been synthesised (**46**) [52]. However, racemisation at the α-carbon, leading to a 1:1 mixture of enantiomers, occurs when the dinuclear complex reacts with pyridine to form the mononuclear complex [{η^6-phenylglycine}$RuCl_2$(pyridine)] (**47**):



46 47

To avoid racemisation at the α-carbon, we have synthesised the analogous derivatives **48** and **49**, in which a methylene group instead of an ester function at the α-position of the chiral auxiliary group has prevented the racemisation of the asymmetric carbon [53]. In both cases they have shown that no racemisation occurs at the α-carbon atom:



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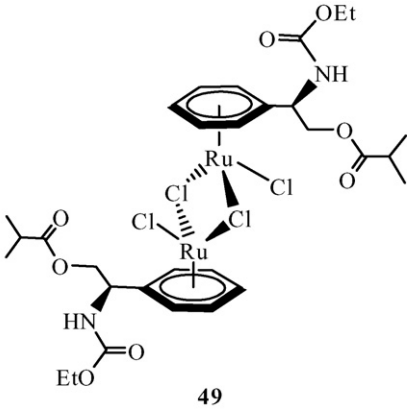
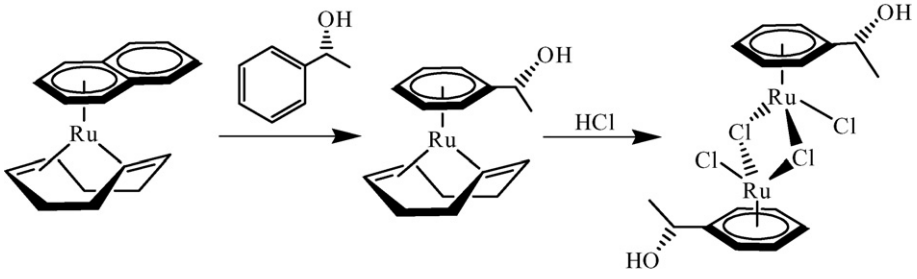


49

We have also synthesised the chiral chloro-bridged dimer (*RR*)-[(1-phenylethanol)$RuCl_2$]$_2$ (**50**) [53]. In this case, a different synthetic method was used to avoid loss of chirality during the Birch reduction of (*R*)-1-phenylethanol, because the use of metallic sodium in liquid ammonia can cleave the C–O bond of the OH substituent to give ethylcyclohexadiene with loss of the chiral centre [54]. Therefore, complex **50** was synthesised by naphthalene displacement in [Ru(C_8H_{12})($C_{10}H_{18}$)] [55] and followed by reaction with HCl [56], an alternative way to prepare chloro-bridged arene ruthenium dimers:



50

The insertion of an enantiopure auxiliary to the pendant arm of an arene ruthenium complex has been used for the resolution of configurationally stable piano-stool complexes. Tethering a phosphine and an enantiopure pyrazole to an arene yields a chiral 10-electron donor ligand (PArN*) [41]. An enantiopure camphorpyrazole group was used to generate the enantiopure PArN* ligand (PArN* = 2-[3-(2-diphenylphosphanyl-ethyl)-benzyl]-7,8,8-trimethyl-4,5,6,7-tetrahydro-2*H*-4,7-methano-indazole). Therefore, upon η^6:η^1:η^1-coordination of PArN* to Ru(II), a chiral-at-metal complex is generated, [(η^6:η^1:η^1-PArN*)RuL]$^{2+}$ (L = weakly bound solvent). The insertion of a chiral auxiliary has facilitated analysis and diastereomer separation. Suitable crystals for X-ray structure analysis were obtained for both diastereomers of the aqua derivative [(η^6:η^1:η^1-PArN*)Ru(OH_2)][CF_3SO_3]$_2$ (cations (RR_PS_{Ru})-[**51**]$^{2+}$ and (RS_PR_{Ru})-[**51**]$^{2+}$), see Fig. 6.

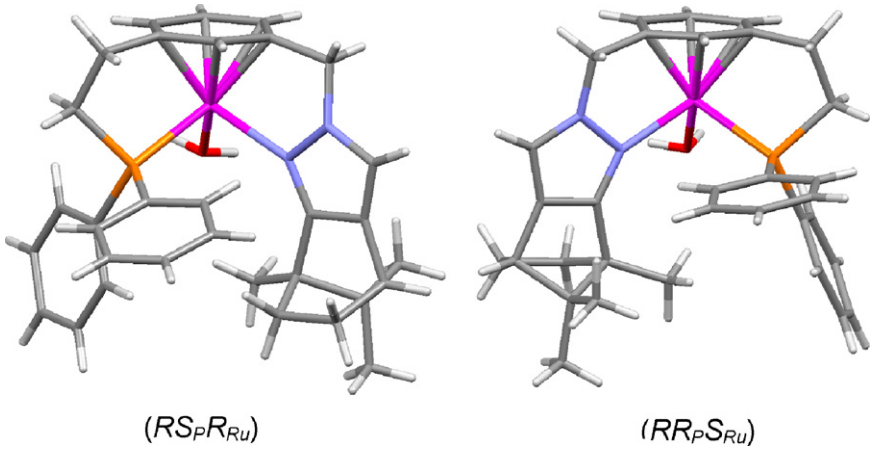


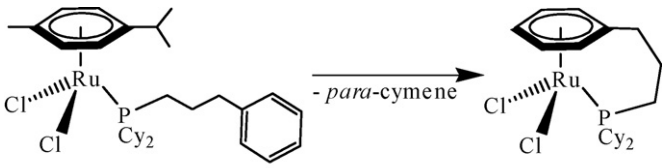
Fig. 6. The molecular structure of the diastereomers of cation **51** [41].

On the basis of molecular models, one can anticipate clashing between $C(CH_3)_2$-bridge and CH_3 of bridgehead of camphor with the phenyl groups of the phosphine. Indeed, the steric clash is reflected in the angles around the ruthenium atom. For (RR_PS_{Ru})-**51**, both N–Ru–P and O–Ru–P bite angles (101.1(2)° and 99.0(1)°) are significantly larger than those for (RS_PR_{Ru})-**51** (99.4(1)° and 90.4(1)°). The 1,3-substitution pattern of the tethered phosphine-imine groups on the arene ligand imposed rather large N–Ru–P bite angles (101.1(2)° and 99.4(1)°), although the η^6-arene remained essentially planar.

8. Catalytically active complexes

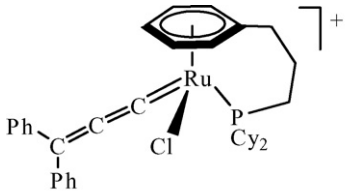
Arene ruthenium complexes were shown to be catalytically active in hydrogenation [57], transfer-hydrogenation [58] Diels-Alder reactions [59], olefin metathesis [60], olefin cyclopropanation [61] and atom-transfer radical polymerisation [62]. In most cases, the ruthenium catalyst precursor possesses a hydrocarbon η^6-arene ligand with nitrogen or phosphorus donor ligands. In general, the catalytic activities and selectivities are good and are strongly affected by the nature of the arene ligand. In most cases the mechanism of these catalytic reactions remains a debatable point, and the role of the arene ligand is unclear. For instance, in the transfer hydrogenation of ketones, the arene moiety is assumed to be a spectator ligand, while for olefin metathesis and atom-transfer radical polymerisation, the catalytic activity results from arene displacement. It is as well known that *in situ* formation of nanoclusters or metal nanoparticle catalysts is common under reducing conditions [63]. Therefore, in some cases it is crucial to form a robust molecular arene ruthenium catalyst to avoid arene exchange, while in other cases arene displacement is an essential step in the catalytic cycle.

During the cyclopropanation of olefins with ethyl diazoacetate, the displacement of the *para*-cymene ligand to form a chelating complex such as [{η^6:η^1-$C_6H_5(CH_2)_3PCy_2$}$RuCl_2$] (**52**) is a key intermediate in the catalytic process [64]. The release of one or more ligand(s) is essential to generate sites, which allows coordination of the substrate and therefore for the reaction to take place. The yield of the reaction is clearly affected by the temperature, while the *cis*/*trans* or *endo*/*exo* ratio is not influenced by an increase of temperature:



52

The same complex **52** was used as precursor for the synthesis of an allenylidene catalyst [{η^6:η^1-$C_6H_5(CH_2)_3PCy_2$}$RuCl(=C=C=CPh_2)]CF_3SO_3$ (**53**) for ring closing olefin metathesis [65]. However, despite satisfactory catalytic activity the reaction rates were lower than those of the non-chelated analogue [(η^6-*p*-Pr^iC_6H_4Me)$RuCl(=C=C=CPh_2)(PCy_3)]PF_6$. The molecular structure of **53** revealed that the C=C double bonds of the allenylidene moiety are of different length, the one closer to the ruthenium being 0.12(3) Å shorter. Furthermore, the trimethylene chelated arm does not change the geometry around the metal centre as compared to that of the dimethylene bridged tethers **16** and **17** [33]:



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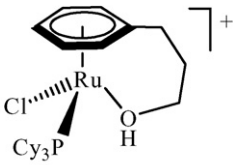
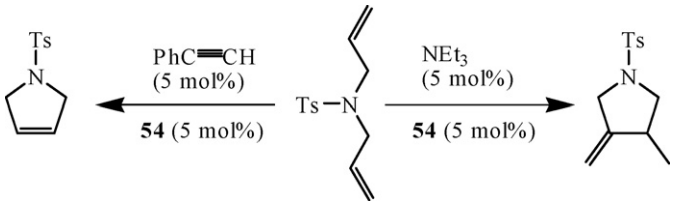
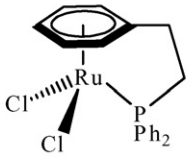


54

A similar alcohol chelate complex [{η^6:η^1-$C_6H_5(CH_2)_3OH$}$RuCl(PCy_3)]^+$ (**54**) has been used as a precursor catalyst in the cycloisomerisation and ring closing metathesis (RCM) of α,ω-dienes in the presence of co-catalysts [66]. In the presence of 5 mol% of **54** and 5 mol% of triethylamine as co-catalyst in refluxing dichloromethane, tosylated diallylamine (*N*,*N*-diallyl-4-methylbenzenesulfonamide) gives in excellent yield the *exo*-methylene pyrrolidine derivative, while 2*H*-pyrroline is obtained in excellent yields if the co-catalyst is replaced by 5 mol% of phenylacetylene. Interestingly, as compared to non-tethered systems such as the benzene analogue [(η^6-C_6H_6)$RuCl(PCy_3)]_2(BF_4)_2$, the catalytic activity increases in the presence of a chelating side arm:



A series of tertiary phosphine ligands with pendant arenes were synthesised and converted to the corresponding chelating ruthenium complexes [(η^6-η^1-$C_6H_5CH_2CH_2PPh_2$)$RuCl_2$] (**55**), [(η^6-η^1-$C_6H_5CH_2CH_2PCy_2$)$RuCl_2$] (**56**), [{η^6-η^1-$C_6H_5CH(C_6H_5)CH_2PPh_2$}$RuCl_2$] (**57**) and [{$\eta^6$-$\eta^1$-$C_6H_5CH(C_6H_5)CH_2PCy_2$}$RuCl_2$] (**58**) in view of using them as precursor catalysts for ring opening metathesis polymerisation (ROMP) of norbornene [67]. In the presence of trimethylsilyldiazomethane the η^6-arene ligand is displaced, giving rise to very active catalytic species. In methanol the carbene precursor was produced by oxidative addition of methanol to the ruthenium centre, without decomplexation of the arene moiety. The activity was significantly lowered, but a better control over the *cis*/*trans* ratio was obtained, suggesting that the use of a rigid framework may provide a useful tool to influence the structure of ROMP polymers:



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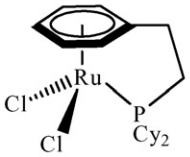

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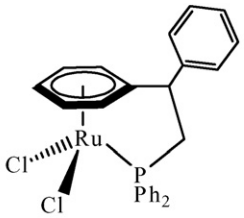

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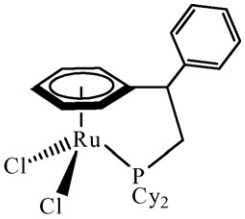
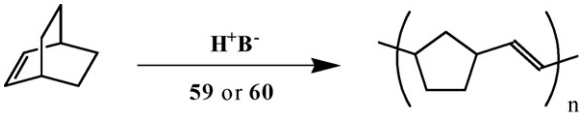
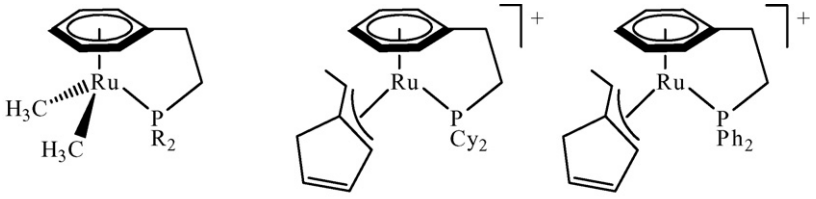


58

More recently, the reactions of [{η⁶:η¹-$C_6H_5(CH_2)_2PR_2$}Ru(CH_3)$_2$] (R = Cy (**59**), Ph (**60**)) with boron activators ([$H(Et_2O)_2$][B{3,5-$C_6H_3(CF_3)_2$}$_4$], $\mathbf{H^+B^-}$) in the presence of CO, acetylene, ethylene and norbornene were studied [68]. If an excess of norbornene is used, ring-opened polynorbornene is obtained, thus suggesting a ring opening metathesis polymerisation process at the ruthenium centre without decomplexation of the arene ligand. The same complexes react in dichloromethane and $\mathbf{H^+B^-}$ in the presence of acetylene to afford polyacetylene and the complexes [{η⁶:η¹-$C_6H_5(CH_2)_2PR_2$}Ru(η³-$CH_3CHC_5H_5$)]$^+$ (R = Cy (**61**), Ph (**62**)). Cations **61** and **62** have been characterised by X-ray structure analysis of their [B{3,5-$C_6H_3(CF_3)_2$}$_4$] salts:

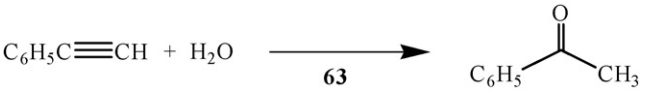


The same derivatives **59** were considered as potential ruthenium-based Ziegler–Natta catalyst precursors for the polymerisation of ethylene [69]. The authors have shown that the tethered complexes were thermally more stable than non-tethered analogues. However, no activity was observed toward the polymerisation of ethylene:

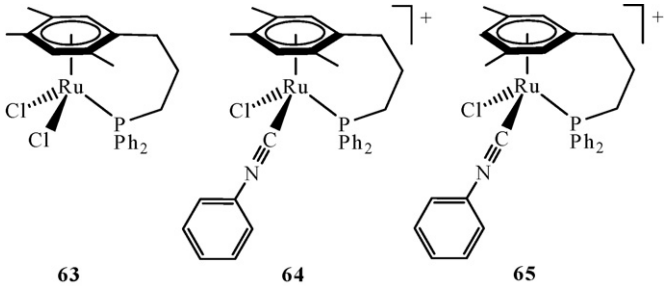


R = Cy (**59**); R = Ph (**60**) **61** **62**

The catalytic hydration of phenylacetylene to generate acetophenone was conducted with the precursor [{η⁶:η¹-1,2,4,5-$C_6H_2(CH_3)_3(CH_2CH_2CH_2PPh_2)$}$RuCl_2$] (**63**) [70]. Phenylacetylene was reached with 2.5 mol% of **63** in refluxing ethanol (95%) for 24 h. Complete conversion was obtained by using the water present in the solvent, thus affording acetophenone in 45–66% yield. The results show a good conversion and similar reactivity of both the tethered and non-tethered complexes. However, the intermediate following the protonation step in the production of ketones remained unclear:

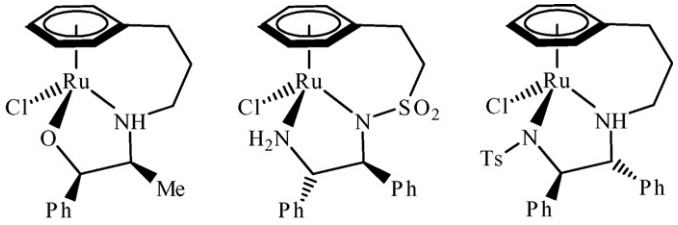


The reaction of **63** or the [{η⁶:η¹-1,3,5-$C_6H_3(CH_3)_2(CH_2CH_2CH_2PPh_2)$}$RuCl_2$] analogue with an excess of phenylisocyanide and $NaPF_6$ in methanol–dichloromethane solution gave the phenylisocyanide complexes **64** and **65**, respectively. All attempts to synthesise aminocarbenes from **64** or **65** gave in the conditions tested recovery of the starting materials or only decomposition products:



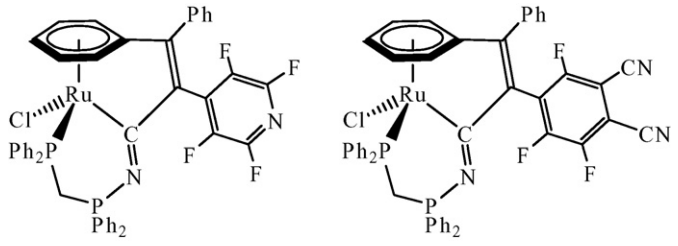
63 **64** **65**

In order to form stable ruthenium catalysts for asymmetric transfer hydrogenation reactions, an amino alcohol and a monotosylated diamine moiety were tethered to an arene ligand [71]. The two complexes **66** and **67** were tested as catalysts in asymmetric transfer hydrogenation reactions of aromatic ketones. In particular, complex **67** (0.25 mol%) reduces acetophenone to give 1-phenylethanol in >99% yield and 96% ee (*R*) after a reaction time of 21 h at room temperature, while complex **68** (0.5 mol%) gives 1-phenylethanol in >99% yield and 96% ee (*S*) of the opposite enantiomer. A series of control reactions showed that the reaction was catalysed by a tethered compound and not a non-tethered component or ruthenium nanoparticles. Moreover, it was later demonstrated that for the substrate ^{t}Bu-phenyl-ketone, only the tethered complex **68** gives the corresponding alcohol [72]:



66 **67** **68**

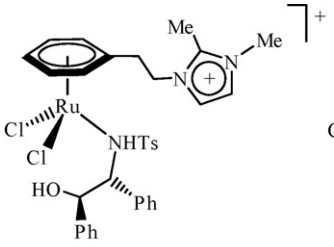
A series of similar η⁶:η¹:η¹-arene ruthenium complexes (**69** and **70**) with P and C donor atoms were synthesised by reaction of iminophosphorane complexes with an excess of 1,1-diphenyl-2-propyn-1-ol in CH_2Cl_2 at room temperature [73]. Surprisingly displacement of the *para*-cymene ligand was achieved at low temperature. The formation of **69** and **70** resulted from coupling of the uncoordinated iminophosphorane unit with the allenylidene chain with concomitant exchange of the *para*-cymene ligand by one phenyl group of the alkynol. Moreover, migration of the fluoroaromatic substituent from the imino group to the C_β of the allenylidene chain took place as well. The involvement of allenylidene species was confirmed by using a closely related mesitylene ruthenium complex. However, the catalytic performance of these complexes remains to be studied:



69 **70**

Cationic arene ruthenium complexes with pendant imidazolium tags were synthesised to study their potential as catalysts in biphasic ionic liquid transfer hydrogenation [74]. The catalytic activity of **71** and **72** has been evaluated in the biphasic, enantioselective

transfer hydrogenation of acetophenone. With 2-propanol/KOH, the effect of additional charged groups in terms of catalyst retention and recycling was beneficial, while with formic acid, conventional catalysts afforded better results due to a necessary extraction step with water. Despite a quantitative conversion to 1-phenylethanol and an excellent enantioselectivity in the condition used the results were not satisfactory in terms of catalyst reuse. Further studies to optimise the reaction conditions and to use these systems to other catalytic reactions such as, biphasic olefin metathesis are currently underway:



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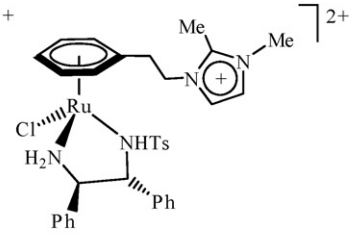
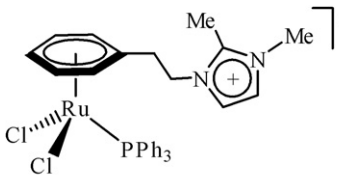


72

Therefore, the same group has turned their attention to the biphasic hydrogenation reaction of CO_2 with a series of related arene ruthenium complexes (**73**–**75**) [75]. The catalytic hydrogenation of carbon dioxide into useful products is a major challenge. The activity of these compounds in aqueous CO_2 reduction was low, and it was suggested that the presence of water was required to generate the catalytically active species. However, the advantage of the imidazolium functionalised arene ruthenium systems lies in the fact that they can be easily derivatised with a large range of ligands and the arene ligand modified to give to the system the desired solubility properties:

$$CO_2 + H_2 \xrightarrow{\text{catalyst}} HCOOH$$



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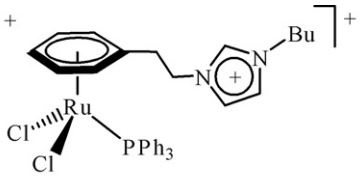
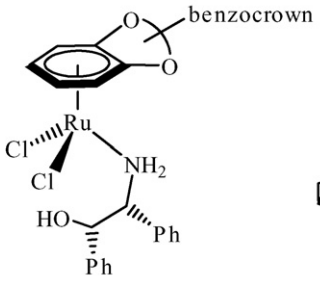
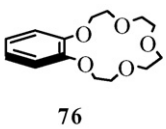


74

Following the same goal, to generate an efficient homogeneous catalyst that provide facile access to numerous products in excellent yield and selectivity, with a good catalyst separation and reuse in an easy way, a series of complexes containing crownether moieties were synthesised [76]. They were studied as potential precursors in biphasic catalytic processes. These complexes offer the possibility to attach and detach a charge and then transfer the complex back and forth between different solvent phases such as ionic liquids and organic solvents. The benzocrownether complexes were reacted with (1*S*, 2*R*)-2-amino-1,2-diphenylethanol and the corresponding chiral complexes (**76**–**79**) were tested as pre-catalysts in the enantioselective reaction of acetophenone with 2-propanol. The catalytic activity was good, while the enantioselectivity was only modest:





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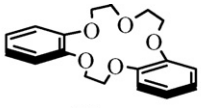

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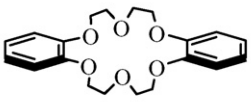
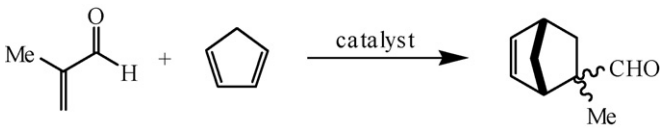


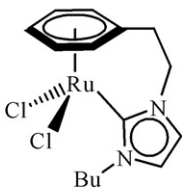
78

79

Three-legged piano-stool complexes with three different ligands possess metal-centred chirality [49] and therefore they have been studied as potential catalysts in asymmetric Diels-Alder reactions. However, application of those complexes was limited to stochiometric reactions, since racemisation at the chiral metal centre often took place during the catalytic reactions [27]. During a catalytic reaction, the unsaturated two-legged piano-stool intermediate possesses an inversion barrier of <15 kcal mol^{-1}, this low-energy inversion barrier has a dramatic effect on the enantiomeric excess of the resulting products as the catalyst would rapidly racemise, thus affording essentially racemic products. Thus, controlling and keeping the metal-centred chirality remains an extensive field of research:



Recently Faller's group has synthesised a series of cationic chiral-at-metal tethered arene ruthenium complexes (**80**) [42]. The tethered phosphine arm allows a greater stability of the catalyst, and despite the introduction of an enantiopure chiral ligand (L*) on the ruthenium atom, the separation of the diastereomers were unsuccessful. However, the different catalysts have shown good *exo*/*endo* diastereoselectivity and good conversion (>95%) with modest enantioselectivity. The nature of the active catalyst is formally a 16-electron complex that may interact with adventitious water molecule or substrate. It would yield a stereogenic metal centre in which the stereochemistry would probably be controlled by steric factors:



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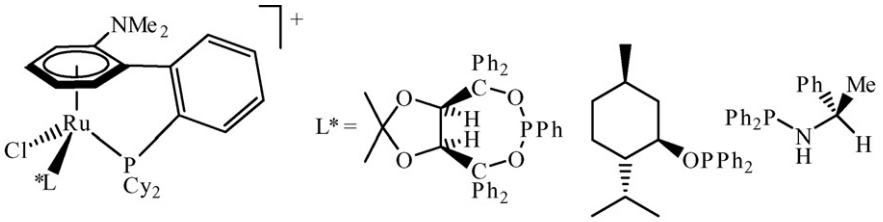
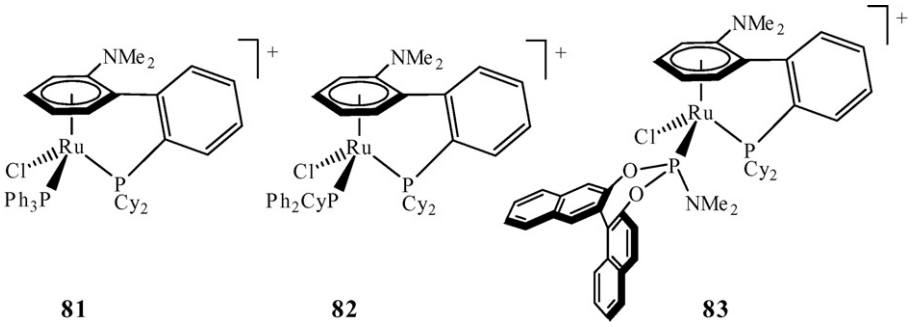


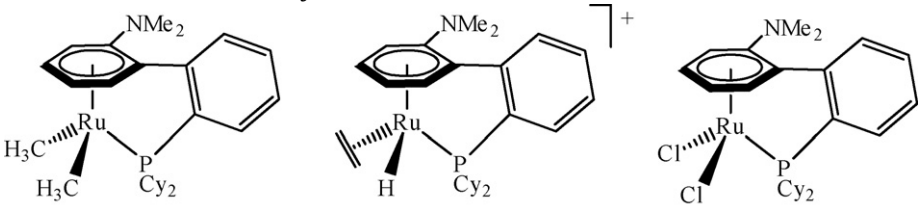
80

The triphenylphosphine and cyclohexyldiphenylphosphine derivatives were isolated as single diastereomers by spontaneous resolution upon fractional crystallisation. Therefore, the enantiopure tethered precatalyst **81** and **82** were tested as asymmetric Lewis-acid-catalysts in Diels-Alder reaction of methacrolein and cyclopentadiene [77]. The most selective catalyst (10 mol% at −25 °C) was complex **82** which catalysed the reaction with 94% de (*exo*) and 40% ee. The chirality at the metal centre was mainly controlled by the chirality of the tethered ligand, the NMe_2 group directing the orientation of the bulky phosphine ligand to the *anti*-binding site. Replacement of the achiral trialkyl phosphine with the enantiopure phosphoramidite (*S*)-monophos ligand (**83**) allowed the catalytic reaction to reach *exo* selectivity up to 93% with ee up to 70%:



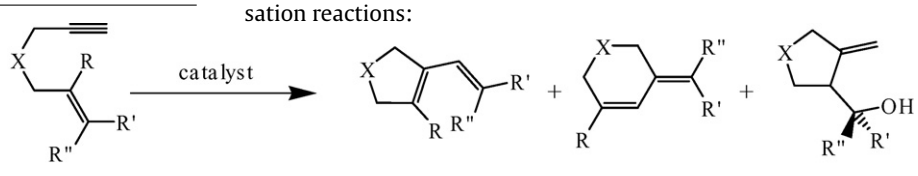
81 82 83

A similar system with planar chirality has been used to form an enantiopure cationic ethylene hydride complex $[(\eta^6{:}\eta^1\text{-}1,2\text{-}Me_2NC_6H_4C_6H_4PCy_2)(CH_2{=}CH_2)RuH]^+$ (**85**) [78]. The stereoselective formation of **85** was rationalised by the directing influence of the NMe_2 group. The cationic complex **85** is obtained in high yield from the neutral dimethyl precursor $[(\eta^6{:}\eta^1\text{-}1,2\text{-}Me_2NC_6H_4C_6H_4PCy_2)Ru(CH_3)_2]$ (**84**) upon addition of CPh_3PF_6. This reaction is believed to be initiated by hydrogen abstraction from one methyl group, forming a carbene species that undergoes an insertion of the remaining methyl group, forming a 16-electron ethyl intermediate [79]. The formation of **85** would then result from a β-hydride elimination of the ethyl species. The diastereomeric olefin hydride complex **85** was observed to exhibit two fluxional processes: a facile olefin rotation and another process that results in the exchange of the hydride and an olefin proton. As the rate of diastereomer interconversion is much slower than that of olefin insertion, the studies have suggested that the latter exchange takes place through an agnostic species which undergoes dynamic methyl rotation:



84 85 86

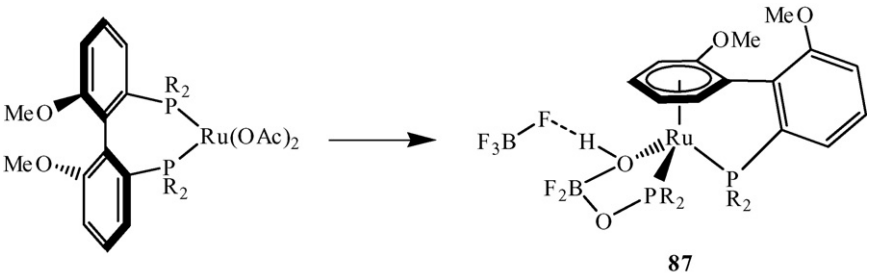
The dichloro derivative $[(\eta^6{:}\eta^1\text{-}1,2\text{-}Me_2NC_6H_4C_6H_4PCy_2)RuCl_2]$ (**86**) was a catalyst precursor for enyne cycloisomerisations and hydroxycyclisations [78a]. The resulting products were due to skeletal rearrangement processes, including an unusual cyclisation to form six-membered ring compounds. Other applications of this catalyst are under investigation, such as alkyne activation in different substrates and desymmetrisation reactions:



X = $C(CO_2Me)_2$

R = H, Me; R' = H, Me, Ph; R" = H, Me

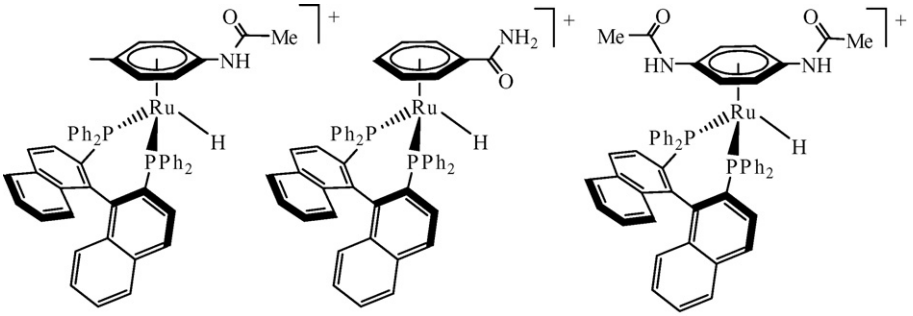
A series of chelating tertiary phosphane complexes originating from $[Ru(OAc)_2(MeO\text{-}biphep)]$ (MeO-biphep = 6,6′-dimethoxybiphenyl-2,2′-diylbis(diarylphosphine)) was obtained in good yield via P–C bond cleavage [80]. A series of ^{31}P and ^{19}F NMR experiments have suggested that the P–C bond-breaking reaction involved monofluorophosphine (PR_2F) intermediates, the fluoride being extracted from a BF_4 anion. These chiral-at-metal complexes such as **87** were evaluated as enantioselective homogeneous catalysts:



87

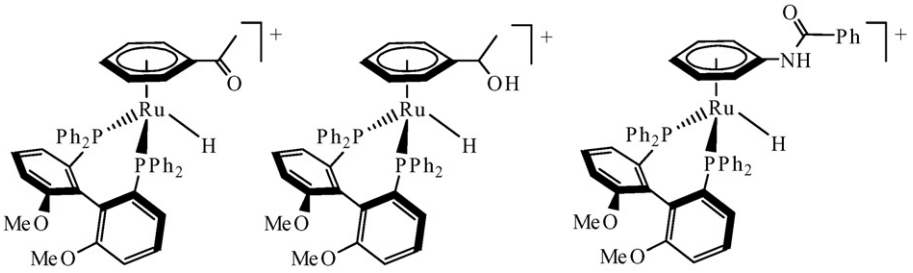
R = 3,5-di-^{t}Bu-phenyl; phenyl; *p*-tolyl

A series of phosphino arene ruthenium complexes derived from binap (**88**–**90**) {2,2′-bis(diphenylphosphino)-1,1′-binaphthalene} or MeO-biphep (**91**–**93**) were prepared by Pregosin in view of their use in transfer-hydrogenation catalysis [81]. The non-functionalised arene ruthenium complexes are not active, while those with readily deprotonated groups are quite active. The MeO-biphep derivatives show faster rates than the binap analogues, but the rates are independent to the nature of the arene. These observations suggest that the active catalyst possesses a structure that differs notably from the starting compounds:



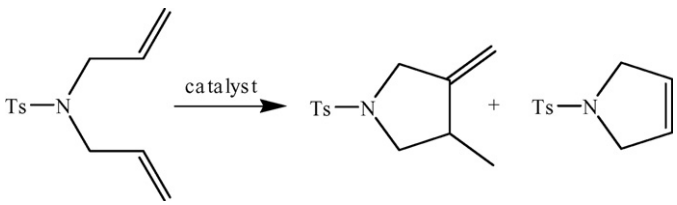
88 **89** **90**

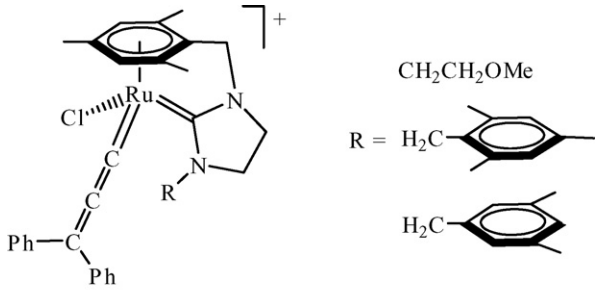
It was demonstrated later that under catalytic conditions (2.5 equiv. KOH, 90 °C, 20 min) **88** decomposes to give quantitatively a new species that arises from deprotonation of the N atom. Moreover, decomplexation of the arene ligand was clearly shown by NMR measurements in ^{i}PrOH-d_8 [82]:



91 **92** **93**

Chelated arene-carbene ruthenium complexes of the type **35** have been used as catalytic precursors for alkene metathesis and cycloisomerisation [83]. It was found that the catalyst precursors, after *in situ* formation of the corresponding allenylidene derivatives (**94**), were active for the catalytic ring-closing metathesis transformation of dienes (*N*,*N*-diallyl-4-methylbenzenesulfonamide, diethyl 2,2-diallylmalonate, 2,2-diallylmalononitrile) in chlorobenzene or toluene at 80 °C:

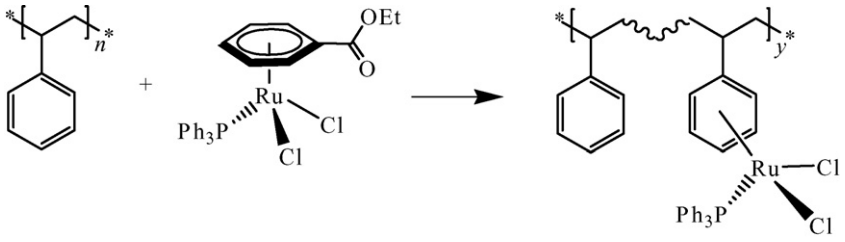




94

9. Immobilised complexes

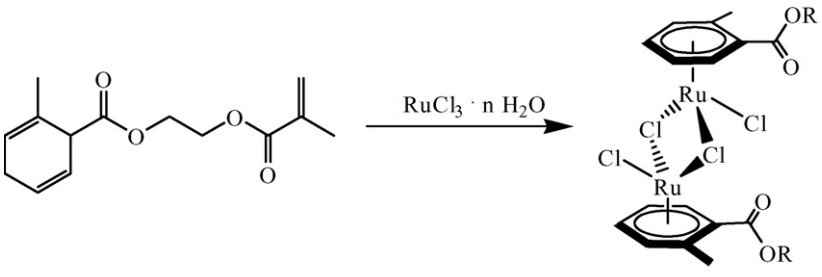
Given the practical advantages of heterogeneous catalysts with respect to homogeneous ones, various methods to immobilise arene ruthenium complexes have been developed [84]. In most cases the arene ruthenium moiety is coordinatively attached by mono- or bidentate ligands covalently bound to the support. Alternatively, the catalytic metal centre can be attached to the support through the arene ligand, a strategy which was first reported by Akiyama and Kobayashi [85]. The polymer-supported arene ruthenium system was thus obtained by arene displacement of the mononuclear complex [{η^6-$C_6H_5COOCH_2CH_3$}$RuCl_2(PPh_3)$] (**95**) [33] at high temperature in the presence of the polymer. The supported catalyst **96** was then successfully used in ring-closing olefin metathesis reaction:



95 96

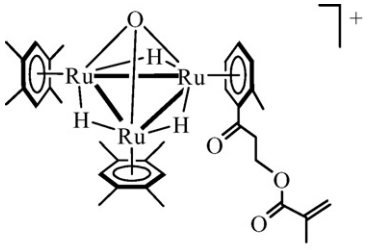
The same polymer-supported arene ruthenium catalyst **96** was successfully used for the hydrogenation of acetophenone to give the corresponding alcohol in high yield, as well as for imino aldol reactions, aza Diels-Alder reactions, cyanation reactions, allylation reactions, Mannich-type reactions, Strecker reactions and quinoline synthesis [86].

In a different approach, Severin et al. have immobilised an arene ruthenium catalyst through a polymerisable side chain that was directly attached to the arene ligand [87]. In this case the reaction conditions are mild with respect to those of an arene displacement reaction. The synthesis of the arene ruthenium precursor was obtained by standard reaction of $RuCl_3 \cdot nH_2O$ with the cyclohexadiene derivative in ethanol:



97

The dinuclear complex **97** and the mononuclear triphenylphosphine derivative [{η^6-1,2-$MeC_6H_4COOCH_2CH_2OC(O)C(CH_3)$=$CH_2$}$RuCl_2(PPh_3)$] were copolymerised with divinylbenzene or ethyleneglycol dimethacrylate to generate a series of polymer-supported arene ruthenium catalysts. These polymers containing arene ruthenium units were used as heterogeneous catalysts in asymmetric transfer hydrogenation of aromatic ketones. The results showed that immobilised arene ruthenium complexes can be easily prepared, and that they are of considerable interest in terms of catalyst–substrate separation and catalyst reusability:



98

In order to immobilise a cationic trinuclear arene ruthenium cluster to a polymer, the cluster derivative **98** containing a polymerisable side chain has been synthesised [88]. The molecular structure was determined by X-ray diffraction study of the tetrafluoroborate salt ([**98**]BF_4), see Fig. 7.

Cation **98** is chiral, due to the planar chirality of the arene ruthenium moiety, but it crystallises as a racemic mixture of both enantiomers. In the solid state, the methacrylate side arm points away from the metallic core and shows only weak interactions with neighbouring molecules. The benzene ring of the methacrylate ligand and a durene ligand of a neighbouring molecule form π-stacking interactions in the crystal packing.

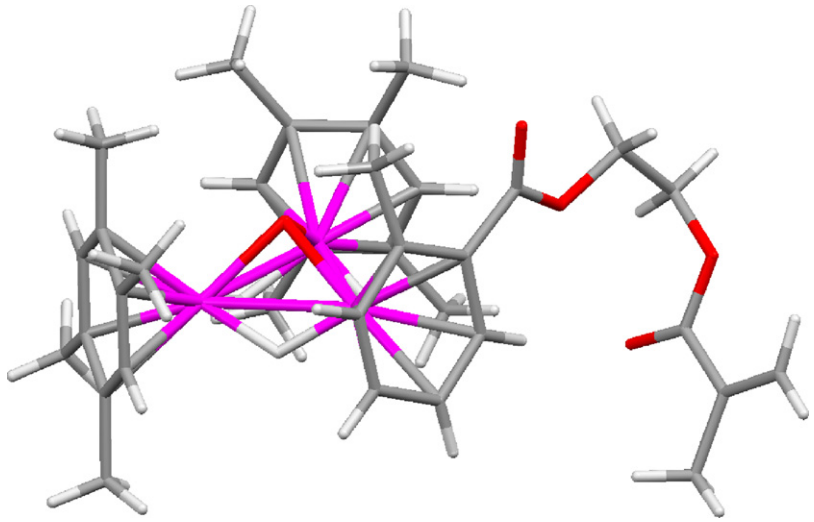


Fig. 7. The molecular structure of **98** [88].

10. Heteronuclear complexes

Heteronuclear ruthenium ferrocene complexes such as $[Ru(NH_3)_5(NCFc)]^{2+}$ (Fc = ferrocenyl) have been known for 25 years [89]. Ferrocenyl groups bonded to a ruthenium atom containing a coordinated arene ligand were reported for the first time by Bruce et al. in 1988 [90]. Since then, other complexes containing ferrocene and arene-ruthenium units were synthesised either by coordination of a sulphido, phosphido or amido ferrocene [91], or by coordination of ferrocene alkynes to an arene ruthenium unit [92]. Nevertheless, while the functionalisation of a cyclopentadienyl ligand by a ferrocenyl group has received some attention by different groups [93], the functionalisation of a η^6-arene ligand by a ferrocenyl group has been studied only by our group [94].

Two different strategies were used in order to tether a ferrocenyl moiety to a η^6-arene ligand coordinated to a ruthenium atom. Both imply a classical esterification reaction, in which the esterification is done either prior to the coordination of the arene ligand or after the arene coordination. A series of η^6-arene ruthenium complexes with ferrocenylated side arms were synthesised using these methods. For example, the dinuclear ruthenium complex $[RuCl_2\{\eta^6\text{-}C_6H_5(CH_2)_2O(CO)Fc\}]_2$ reacts with two equivalents of $FcPPh_2$, PPh_3 or with one equivalent of dppf (1,1′-bis(diphenylphosphino)ferrocene) in dichloromethane to give quantitatively the heteronuclear complexes $[\{\eta^6\text{-}C_6H_5(CH_2)_2OC(O)Fc\}RuCl_2(FcPPh_2)]$ (**99**), $[\{\eta^6\text{-}C_6H_5(CH_2)_2OC(O)Fc\}RuCl_2(PPh_3)]$ (**100**) and the ferrocene bridged, pentanuclear complex $[(\mu\text{-dppf})\{(\eta^6\text{-}C_6H_5(CH_2)_2OC(O)Fc)_2RuCl_2\}]$ (**101**), respectively. The electrochemical behaviour of these complexes with ferrocenylated side arms display the expected cyclic voltammograms, two *independent* reversible one-electron waves of the Ru(II)/Ru(III) and Fe(II)/Fe(III) redox couples:

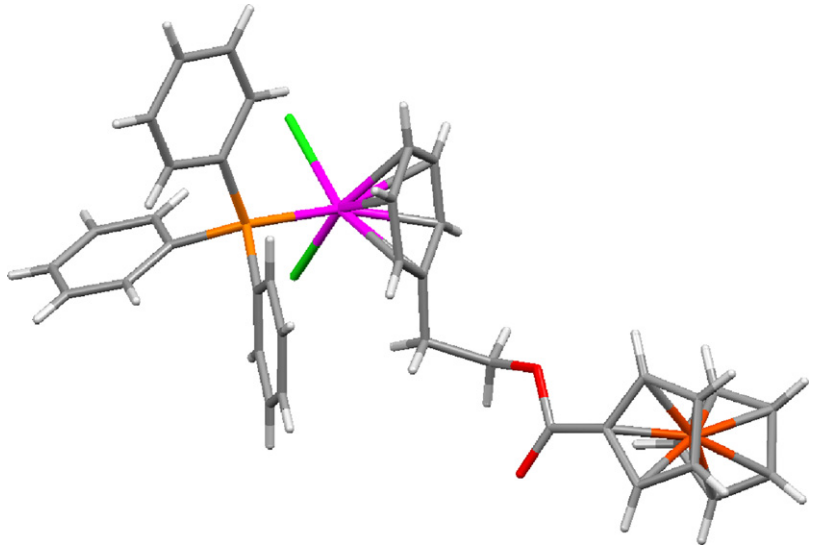
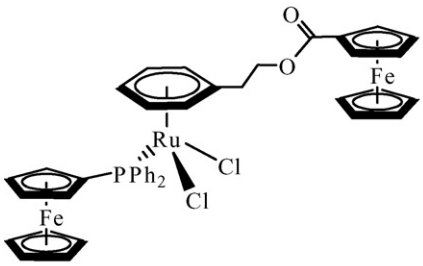
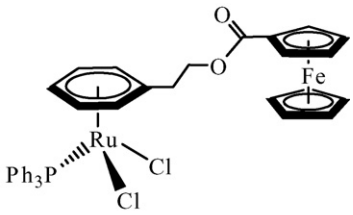


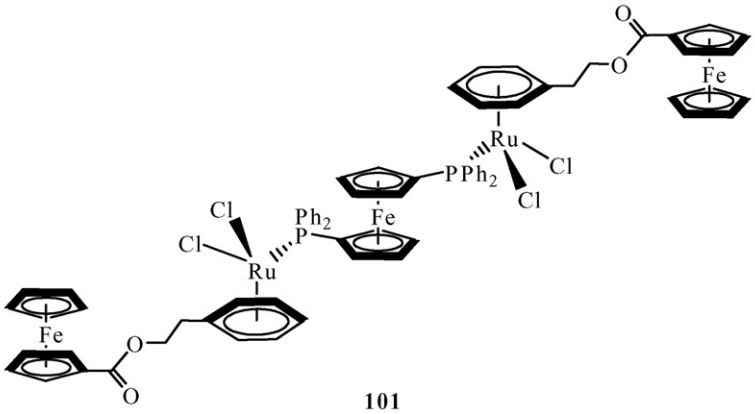
Fig. 8. The molecular structure of **100** [94].



99



100

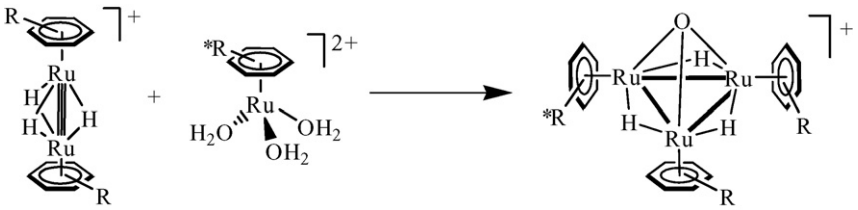


101

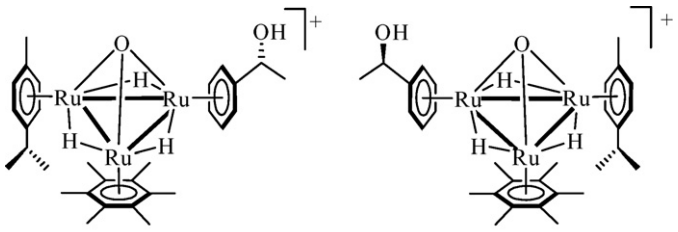
The molecular structure of **100** was determined by single-crystal X-ray structure analysis, see Fig. 8. The ferrocene moiety was in the eclipsed conformation and the phenyl ethyl substituent was rotated out of the ester plane by 75.5(9)°, allowing no π-interaction between the Cp ring and the η^6-arene ligand. The C=O distance was shorter than that of ferrocenecarboxylic acid benzotriazole ester which is known to have a weak and reactive ester bond [95], thus explaining the stability of the ester function in these complexes.

11. Clusters

The reaction of dinuclear cation $[(\eta^6\text{-arene})_2Ru_2(\mu_2\text{-H})_3]^+$ with mononuclear cations $[(\eta^6\text{-arene}^*)Ru(H_2O)_3]^{2+}$ in aqueous solution results in the formation of trinuclear cluster cations of the type $[(\eta^6\text{-arene}^*)(\eta^6\text{-arene})_2Ru_3(\mu_2\text{-H})_3(\mu_3\text{-O})]^+$ [96]. The triruthenium framework is capped by a μ_3-oxo ligand stemming from an aqua ligand. The arene ligands in the trinuclear cluster cations obtained by this reaction can be varied a great deal. Indeed, introduction of three different arene ligands generates a chiral Ru_3O core:



Several intrinsically chiral cluster cations containing a chiral auxiliary group R* at one of the arene ligands have been prepared in view to separate intrinsically chiral Ru_3O cluster core [53]. The chiral phenylethanol chloro-bridged dimer **50** was used to synthesise a trinuclear ruthenium cluster cation with framework chirality and a chiral auxiliary tethered to an arene ligand. A mixture of diastereomers was obtained (*SR*)-**102** and (*RR*)-**102** which, however, could not be separated:



(*SR*)-**102** (*RR*)-**102**

The single-crystal analysis of [**102**]BF_4 showed both diastereomers to be present in the same crystal in a 1:1 ratio, see Fig. 9. The two diastereomeric clusters (*SR*)-**102** and (*RR*)-**102** differ by the existence of an intra-hydrogen bond in the solid state for (*RR*)-**102**. The presence of a $CHCH_3OH$ side arm allows (*RR*)-**102** to form an intramolecular hydrogen bond with the μ_3-oxo ligand, the O···O distance being 2.727(4) Å. No such intramolecular hydrogen bond is observed in (*SR*)-**102**.

Similarly, the chiral aminoester chloro-bridged dimer **48** was used to synthesise trinuclear ruthenium cluster cations with double intrinsic chirality. As for [**102**]BF_4, a mixture of diastereomers was obtained (*SS*)-**103** and (*RS*)-**103**, which could not be separated, too. In order to confirm that no racemisation at the α-position of the chiral auxiliary group occurs during the synthesis of the diastereomeric cluster cation **103**, the enantiopure trinuclear cation (*S*)-**104**

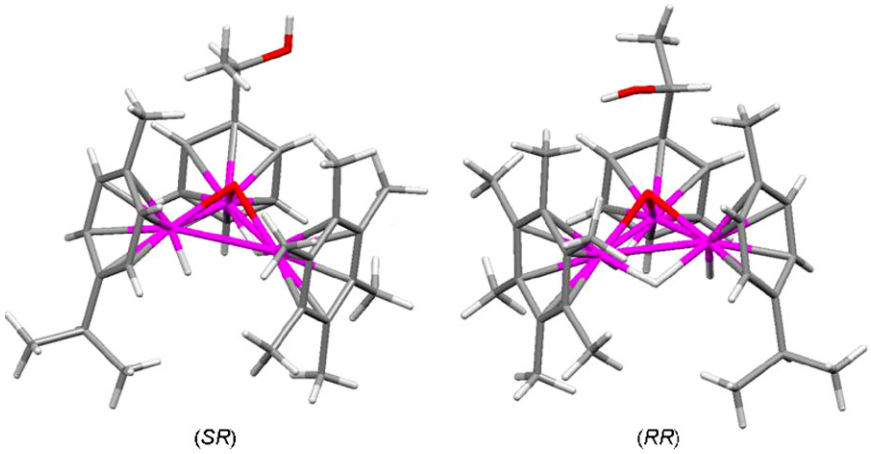
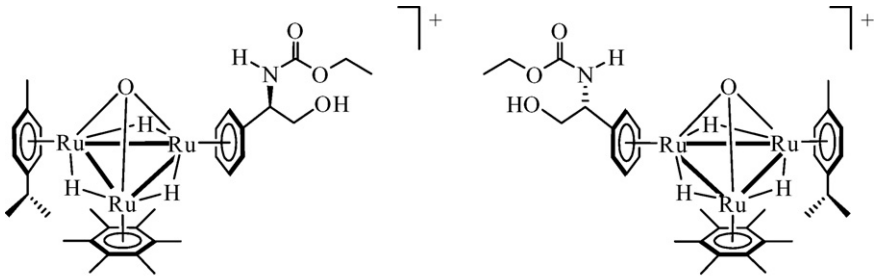


Fig. 9. The molecular structure of the diastereomers of cation **102** [53].

was synthesised, and its molecular structure determined. Complex **104** possesses an achiral Ru_3O framework and only the chiral carbon atom of the functionalised side arm:



(*SS*)-**103** (*RS*)-**103**

The enantiopure structure of (*S*)-[(η^6-C_6Me_6)$_2${η^6-C_6H_5(CH(NHCO$_2$Et)-CH$_2$OH)}$Ru_3(\mu_2$-H)$_3(\mu_3$-O)]$^+$ (**104**) was confirmed by X-ray molecular structure of its tetrafluoroborate salt, see Fig. 10. The structure reveals the presence of strong intramolecular hydrogen bonds between the hydroxo proton and the oxo cap (distance O···O = 2.648 Å) as well as between the amido proton and the oxygen atom of the CH_2OH moiety (distance O···O = 2.722 Å), stabilising the molecular edifice in the solid state.

The diastereomeric separation was finally successful in the case of [{η^6-C_6H_5(S-CH(NHCO$_2$Et)CH$_2$OCO^{i}Pr)}(η^6-C_6Me_6)(η^6-1,4-^{i}PrC_6H_4Me)$Ru_3(\mu_2$-H)$_3(\mu_3$-O)]$^+$ (**105**), in which the chiral dimer **49** was used as starting material. The diastereomers $R_{Ru_3O}S$ and $S_{Ru_3O}S$ were separated by thin-layer chromatography on silica

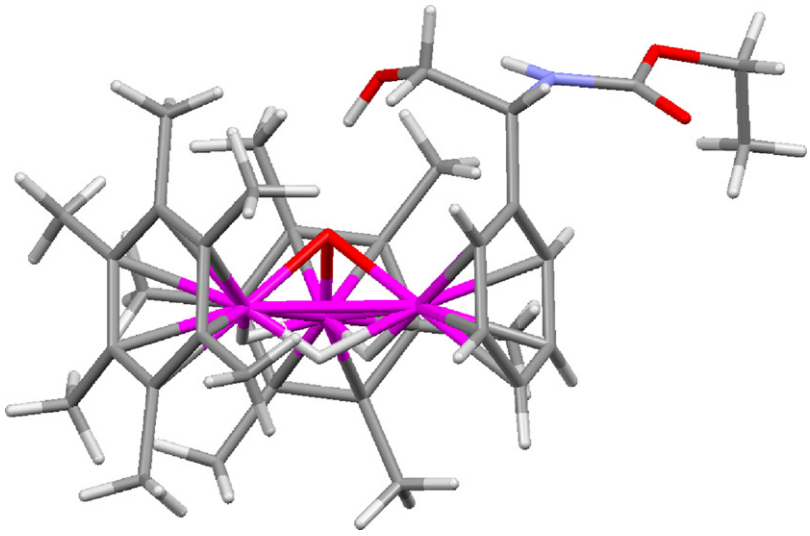


Fig. 10. The molecular structure of the enantiopure cation (*S*)-**104** [53].

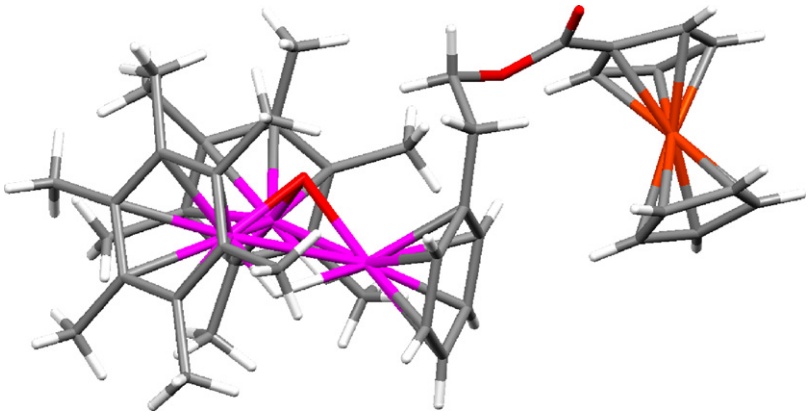
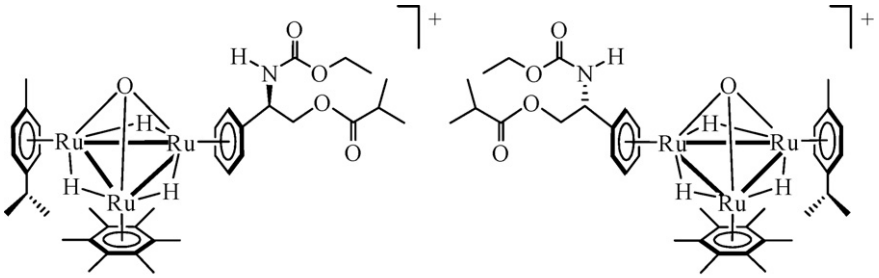


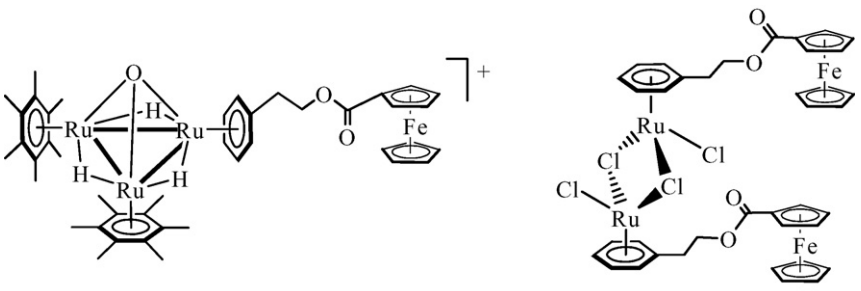
Fig. 11. The molecular structure of **106** [97].

gel [53]. This was the first case where an intrinsically chiral Ru_3O cluster was enantiotopically resolved:



(*SS*)-**105** (*RS*)-**105**

The trinuclear cluster cation **106** containing a ferrocenyl moiety was synthesised using the dinuclear ruthenium complex [{η^6-$C_6H_5(CH_2)_2O(CO)Fc$}$RuCl_2$]$_2$ (**107**). The cluster is stable in water, and crystallised in acetone. The molecular structure was determined by X-ray structure analysis of the tetrafluoroborate salt, [**106**]BF_4, see Fig. 11:



106 **107**

In cluster **106**, the triruthenium framework is comparable to other trinuclear arene ruthenium clusters [97], showing similar geometric parameters, differences appear only at the periphery. The ferrocene moiety, which is in the eclipsed conformation, is surrounded by acetone solvent molecules and tetrafluoroborate ions.

In an effort to get insight in the catalytic mechanism involved in the hydrogenation of benzene to cyclohexane under biphasic conditions by water-soluble cluster cations of the type [(η^6-arene)$_3Ru_3(\mu_2$-H)$_3(\mu_3$-O)]$^+$, a series of trinuclear arene ruthenium clusters possessing a functionalised arene moiety have been synthesised. As the catalytic hydrogenation of benzene was believed to take place in the hydrophobic pocket of the trinuclear cluster, hypothesis which turned out to be wrong [98], two derivatives in which an aromatic substrate was attached to the catalyst were prepared [99]. The length and flexibility of the side arm chain was modified to allow the phenyl group to be hydrogenated via an intra- or inter-molecular process. The water-soluble cluster cations [{η^6-$C_6H_5(CH_2)_2OC(O)C_6H_5$}($\eta^6$-$C_6Me_6$)$_2Ru_3(\mu_2$-H)$_3(\mu_3$-O)]$^+$ (**108**) and [{η^6-$C_6H_5(CH_2)_2OC(O)(CH_2)_3C_6H_5$}($\eta^6$-$C_6Me_6$)$_2Ru_3(\mu_2$-H)$_3(\mu_3$-O)]$^+$ (**109**) were synthesised:

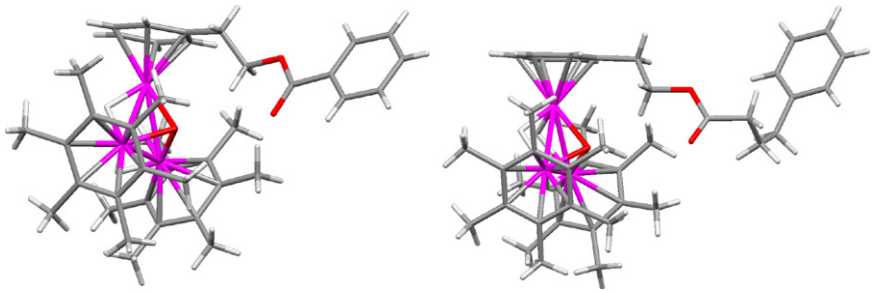
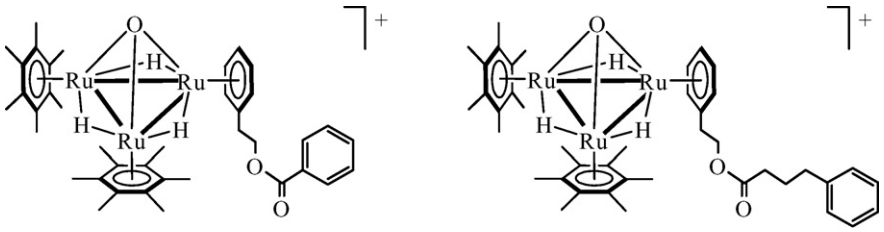


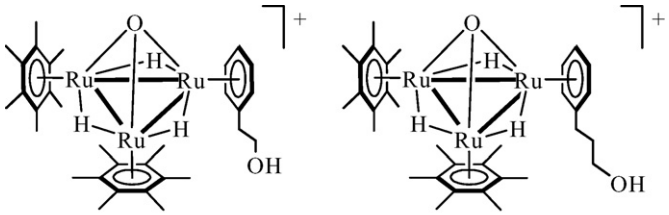
Fig. 12. The molecular structures of **108** (left) and **109** (right) [99].



108 **109**

However, these two complexes **108** and **109** were inactive for the hydrogenation of the phenylester group in water, showing only partial decomposition without hydrogenation under the conditions; 50–110 °C, 60 bar H_2 for 12–72 h. The X-ray structure analyses of [**108**]BF_4 and [**109**]BF_4 (see Fig. 12) show in both complexes, the phenylester moiety to have no interaction with the triruthenium framework, only an intramolecular hydrogen contact is observed between a hydrogen atom of the C**H**$_2$OCO and the oxygen atom of the μ_3-oxo cap.

The cationic trinuclear arene ruthenium clusters showed interesting host-guest properties [100]. Indeed, the μ_3-oxo ligand was a strong acceptor which can form hydrogen bonds, while the hydrophobic pocket spanned by the three arene ligands acts as a bowl to host different molecules. Two derivatives containing a $(CH_2)_n$OH (n = 2 (**110**); n = 3 (**111**)) side arm attached to one of the three arene ligand were prepared:

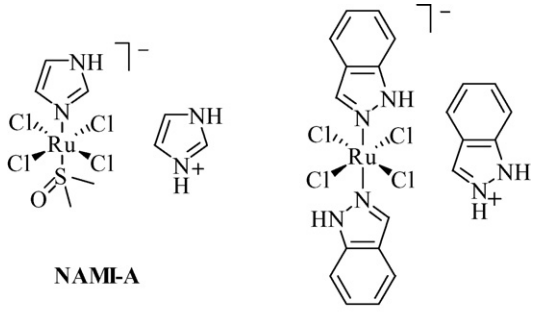


110 **111**

Interestingly, in the presence of benzene, they both crystallise with a benzene molecule held inside the hydrophobic pocket, see Fig. 13. The guest molecule interacts weakly with the host only by hydrophobic and van der Waals contacts. In **110**, the hydroxyl group forms a strong intramolecular hydrogen bond with the μ_3-oxo ligand, while in **111**, the hydroxyl group forms in the solid state an intermolecular hydrogen bonded dimer with a neighbouring cluster molecule and two water molecules.

12. Biologically active complexes

Recently it was shown that ruthenium possesses several favourable chemical properties, suggesting that it may be a strong candidate to replace platinum and to form a basis for rational anticancer drug design [101]. A number of ruthenium complexes show high *in vitro* and *in vivo* antitumor activity and two of them have successfully completed phase I of clinical trials, NAMI-A [102] and KP1019 [103]. The synthesis of ruthenium complexes is relatively easy and the metal possesses the ability under physiological conditions to adopt a large range of oxidation states (Ru^{II}, Ru^{III} and Ru^{IV}), an important feature for metal-based anticancer drugs. In addition, ruthenium is less toxic than platinum and it is believed that the remarkable anticancer activity of ruthenium resides in its ability to mimic iron in binding to several biomolecules, including serum transferrin and albumin:



NAMI-A **KP1019**

Like other classes of ruthenium compounds, organometallic ruthenium complexes bearing η^6-arene ligands have been intensively studied as potential anticancer drug candidates. The arene

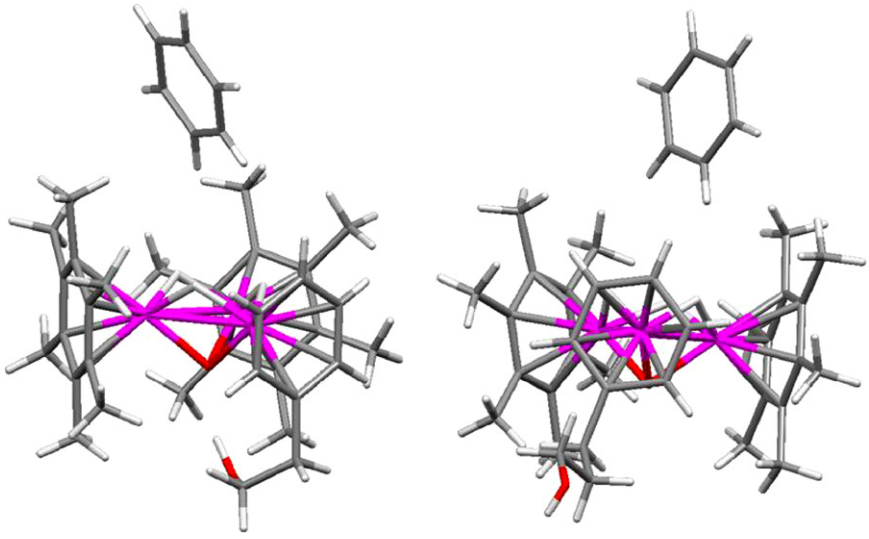
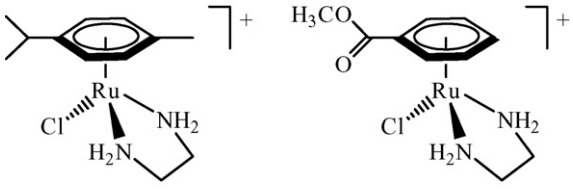


Fig. 13. The molecular structures of [$C_6H_6 \subset$ **110**] (left) and [$C_6H_6 \subset$ **111**] (right) [100].

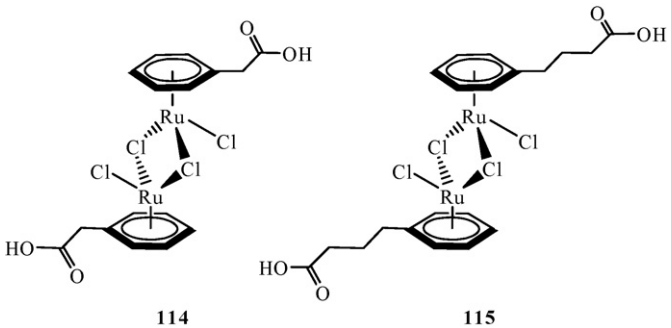
ligand not only provides a lipophilic side to the complex but also stabilises the ruthenium atom in the oxidation state II. Several studies revealed that this type of complexes binds covalently to DNA via the N atom of purines and causes cytoxicity by inhibiting cellular DNA synthesis [104]. So far, the arene ligands seem to play only a minor role in the cytotoxicity effect of arene ruthenium drugs. However, it is obvious from the number of recent publications that functionalised arene ruthenium complexes possessing a biological active substituent is an emerging field of research. The attached bio-sensor can act as carriers, active agents, bio-markers or recognition sites and therefore pave the way for a multitude of potentially new research projects with interesting applications. While DNA interactions cannot be ruled out as the principal target and principal mechanism to focus on for the development of new arene ruthenium anticancer agents, other potential targets, involving different mechanisms, clearly need to be investigated to produce a new generation of metal-based drugs with higher selectivity and cytotoxicity.

One of the earliest example of an arene ruthenium complex investigated as anticancer drug candidates was [(η^6-C_6H_6)Ru(dmso)Cl_2] [105]. It has been suggested by the authors that the dmso derivative strongly inhibit topoisomerase II activity by cleavage complex formation via interaction with DNA and crosslink formation with topoisomerase II. Arene ruthenium complexes containing ethylenediamine ligand (en) or its derivatives [(η^6-arene)Ru(en)Cl]$^+$ showed high *in vitro* cytotoxicity, comparable to that of cisplatin [106]. It appears that extended arene ligands, such as biphenyl and tetrahydroanthracene, improve the cytotoxicity of the drug, while the introduction of an electron-withdrawing group at the arene moieties such as $COOCH_3$ result in complexes with poor cytotoxicity. Indeed, the cationic complex [(η^6-$C_6H_5COOCH_3$)RuCl(en)]$^+$ **112**, isolated as its hexafluorophosphate salt, showed a moderate activity on A2780 ovarian cancer cells (IC_{50} = 55 μM), because the presence of an electron-withdrawing group at the arene ligand reduces the activity of the complex, as compared to the *para*-cymene analogue [(η^6-^{i}Pr$C_6H_4CH_3$)RuCl(en)]PF_6 ([**113**]PF_6) (IC_{50} = 9 μM) [106]:



112 **113**

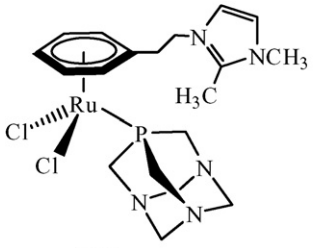
The introduction of carboxylato groups into a pendant arm tethered to the arene ligand has been used for N-terminal labelling of α-amino acids and peptides [107]. The dinuclear complexes [{η^6-$C_6H_5(CH_2)_nCOOH$}Ru(μ-Cl)Cl]$_2$ {n = 1 (**114**) and n = 3 (**115**)} were prepared by dehydrogenation of the appropriate cyclohexadiene with $RuCl_3 \cdot nH_2O$, and their reactivity was studied, which demonstrated that the pendant arm fragment {η^6-$C_6H_5(CH_2)_3COOH$}Ru^{2+} is suitable for both η^6- and N-terminal labelling of amino acids and peptides. Moreover, it was suggested that the formation of chelate κ*O*-coordinated species through the tethered carboxylate function was a key aspect in the stronger affinity of {η^6-$C_6H_5(CH_2)_3COOH$}Ru^{2+} with *N*-acetyltryptophan, as compared to the analogous *para*-cymene fragment:



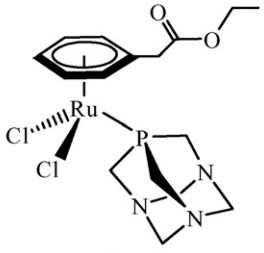
114 **115**

The *in vitro* and *in vivo* assessment of a series of η^6-arene ruthenium complexes containing a pta ligand (pta = 1,3,5-triaza-7-phosphaadamantane) were evaluated as anticancer agents [108]. In addition to the benzene, toluene, *para*-cymene and hexamethylbenzene derivatives, three systems with functionalised arene ligands were tested, complexes **116**, **117** and **118**. All pta complexes were found to cause pH-dependent DNA damage, in such a way that DNA was damaged at the typical pH of hypoxic tumour cells, whereas little or no damage was observed at characteristic pH values of healthy cells. This behaviour was attributed to the pta ligand, which can be protonated at low pH, and the protonated form was considered to be the active agent. Therefore, the introduction of functionalised pendant arms on the arene ligand, such as in **116**, **117** and **118**, did not show any significant improvement in the cytotoxicity of the compounds (IC_{50} (TS/A cells) = 66 μM, **116**; 103 μM, **117**; 159 μM, **118**) as compared to the η^6-aromatic hydrocarbon systems:

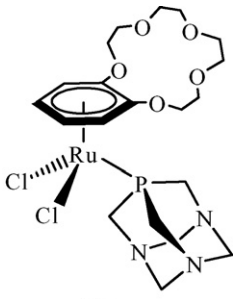
Recently, a new series of organometallic arene ruthenium complexes with potential hydrogen-bonding groups attached to the pendant arm of the arene ligand have been prepared and studied for their antitumor activity [109]. The pta and dapta ligands (dapta = 3,7-diacetyl-1,3,5-triaza-5-phosphabicyclo[3.3.1]nonane) were used to obtain the neutral and cationic mononuclear arene ruthenium complexes **119**–**125**. The cytotoxicity of these functionalised arene ruthenium complexes showed no enhancement of the cytotoxicity toward the cancer cell lines screened, as compared to the analogous arene ruthenium complexes without hydrogen-bonding substituent, namely toluene, *para*-cymene, hexamethylbenzene [109]. While the presence of substituents that can potentially hydrogen bond to DNA at the aromatic rings in titatocene-type drugs increase markedly their cytotoxicity [110], it is striking to note that in the case of these arene ruthenium complexes the effect of the hydrogen-bonding function is actually the opposite. The origins of this unexpected effect were not clearly identified:



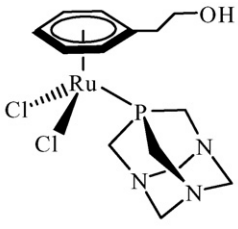
116



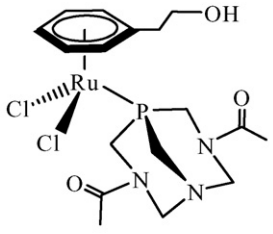
117



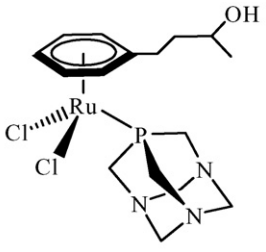
118



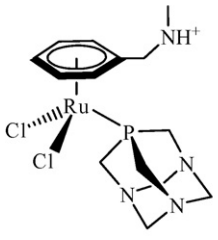
119



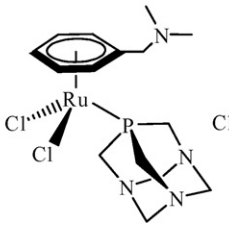
120



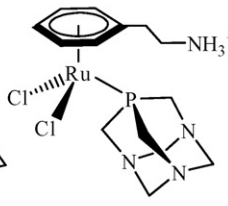
121



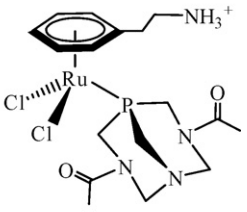
122



123



124



125

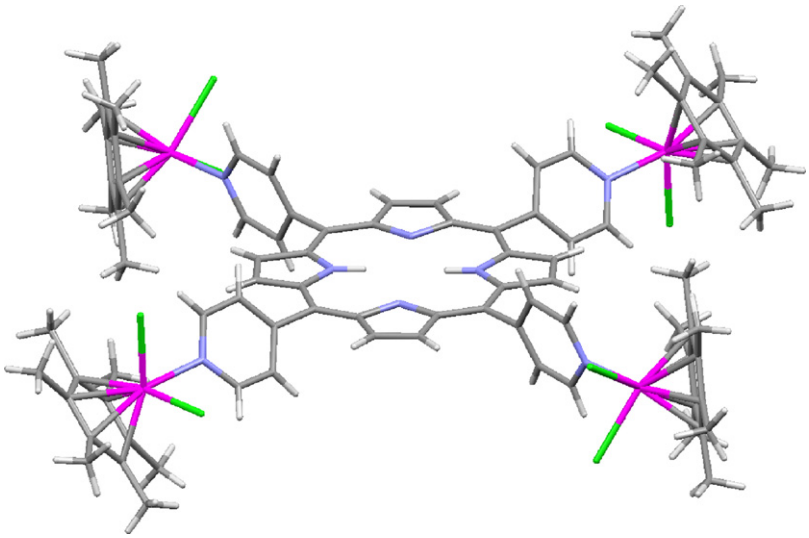
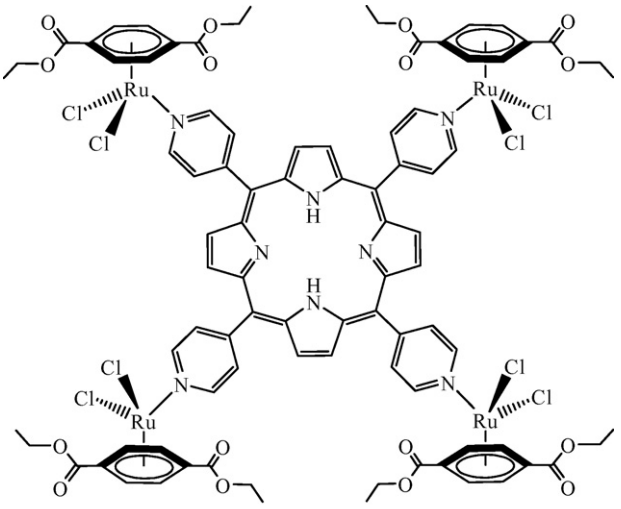


Fig. 14. Molecular structure of $[Ru_4(\eta^6\text{-}C_6Me_6)_4(tpp)Cl_8]$ (**126**) [111].

In order to combine the phototoxicity of porphyrin moieties with the cytotoxicity of arene ruthenium complexes, we recently synthesised a series of arene ruthenium derivatives coordinated to 5,10,15,20-tetra(4-pyridyl)porphyrin (tpp), and the *in vitro* tumour cell growth inhibition effects has been assessed [111]. Among them, the di-ester derivative $[Ru_4\{\eta^6\text{-}1,4\text{-}C_6H_4(COOEt)_2\}_4(tpp)Cl_8]$ (**126**) was synthesised and characterised, this compound shows a strong cytotoxicity before and after exposure to light, as compared to the toluene or *para*-cymene derivatives that show only strong photocytotoxicity. Given the importance of photodynamic therapy for cancer treatment, this type of system offers a high potential in terms of future drug and phototoxicity optimisation:



126

The structure of **126** was confirmed by the single-crystal X-ray structure analysis of the hexamethylbenzene analogue $[Ru_4(\eta^6\text{-}C_6Me_6)_4(tpp)Cl_8]$, see Fig. 14. The structure shows the four pyridyl rings to be perpendicular to the porphyrin core and the four chloride atoms of two adjacent metals to share the same quadrant. The adjacent metal–metal distances are 13.697(2) and 14.254(2) Å. These observations are in agreement with those in the related compounds $[Ru_4(NO)_4(tpp)Cl_{16}]^{4-}$ [112] and $[Ir_4(\eta^5\text{-}C_5Me_5)_4(Zn\text{-}tpp)\{S_2C_2(B_{10}H_{10})\}_4(thf)_2]$ [113].

13. Conclusions and outlook

So far, functionalised η^6-arene ruthenium complexes have been mainly used to develop new catalytically active systems. However, as emphasised throughout this review, functionalised η^6-arene ruthenium derivatives can find many other applications.

Especially useful in drug design, additional functions can be attached to the arene moiety to improve uptake, solubility or even activity of arene ruthenium metal-based drugs. Chiral functional groups can be attached to the arene moiety, if an auxiliary chiral element is needed for chiral separation or chiral recognition. Functional groups can be used to tether arene ruthenium moieties to nanoparticles or to fix arene ruthenium catalyst to support. The purview of this chemistry is only limited by the chemist's imagination.

A search on the Cambridge Structural Database for X-ray structures possessing at least one arene ruthenium unit gave 1767 hits (December 2007). This huge number of hits confirms the interest in η^6-arene ruthenium complexes in chemistry. Their intrinsic potential ranging from biological applications to applications as nano-materials, as emphasised in this review, suggests that the functionalisation of the arene moiety will give to this family of compound new perspectives and create a new era for these versatile complexes.

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