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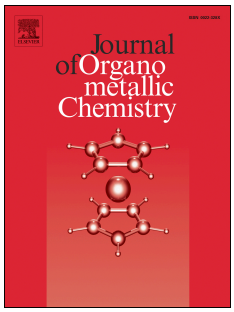

Synthesis and characterization of ruthenium compounds incorporating keto-amine ligands. The applications of catalytic transfer hydrogenation and cancer cell inhibition

Tzung-Han Lin, Kuheli Das, Amitabha Datta, Wohn-Jenn Leu, Hung-Chang Hsiao, Chia-Her Lin, Jih-Hwa Guh, Jui-Hsien Huang

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Synopsis for the Graphical Abstract

Synthesis and characterization of ruthenium compounds incorporating keto-amine ligands. The applications of catalytic transfer hydrogenation and cancer cell inhibition

Tzung-Han Lin [a], Kuheli Das [a], Amitabha Datta [a], Wohn-Jenn Leu [c], Hung-Chang Hsiao [a], Chia-Her Lin [b], Jih-Hwa Guh [c], Jui-Hsien Huang [a,*]

A series of ruthenium compounds containing keto-amine bidentate ligands were synthesized and their potential anti-cancer activity and transfer hydrogenation activity were also studied.

Pictogram for the Graphical Abstract

Synthesis and characterization of ruthenium compounds incorporating keto-amine ligands. The applications of catalytic transfer hydrogenation and cancer cell inhibition

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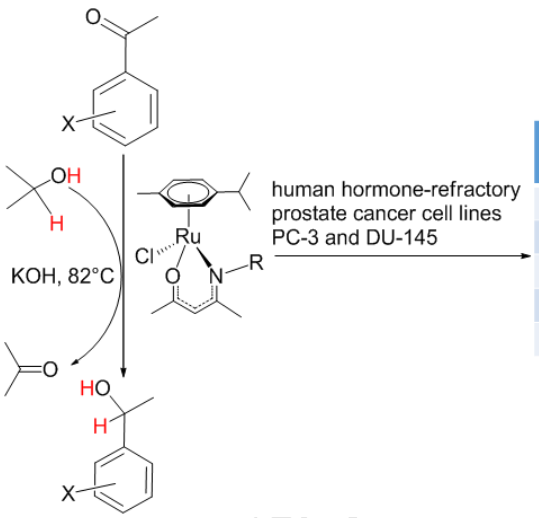

Compound	SRB assay (GI_{50}, μM)	
	PC-3 cells (N=3)	DU-145 cells (N=3)
6	14.54 ± 1.30	21.64 ± 2.46
7	4.25 ± 0.42	5.48 ± 0.35
8	5.34 ± 0.17	5.65 ± 0.14
9	19.68 ± 0.65	20.93 ± 2.69
10	12.39 ± 1.51	14.31 ± 0.90

Synthesis and characterization of ruthenium compounds incorporating keto-amine ligands. The applications of catalytic transfer hydrogenation and cancer cell inhibition

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ABSTRACT

A series of keto-amine bidentate precursors **1**-**5**, $OCCH_3CHCCH_3NHR$ (where **1**, R = C_6H_3-2,6-$^{i}Pr_2$; **2**, R = C_6H_2-2,4,6-Me_3; **3**, R = C_6H_4-2-^{t}Bu; **4**, R =C_6H_4-2-OMe; **5**, R = C_6H_4-2-OMe-5-Me) were synthesized and combined with $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ to generate the monomeric arene-Ru derivatives, $[Ru(\eta^6\text{-}p\text{-cymene})(OCCH_3CHCCH_3NR)Cl]$ (where **6**, R = C_6H_3-2,6-$^{i}Pr_2$; **7**, R = C_6H_2-2,4,6-Me_3; **8**, R = C_6H_4-2-^{t}Bu; **9**, R = C_6H_4-2-OMe; **10**, R = C_6H_4-2-OMe-5-Me) in moderate yield. The ruthenium derivatives effectively catalyzed the conversion rate in transfer hydrogenation of substituted acetophenone. The molecular structures of **2**, **6**-**10** were determined by single crystal X-ray diffractometry in the solid state, revealing a four-coordination environment around the Ru atom. The potential anti-cancer activity of ruthenium derivatives against human hormone-refractory metastatic prostate cancer (HRMPC) cell lines was also studied.

Introduction

The chemistry of η^6-arene ruthenium compounds has received considerable attention in recent years, since a large number of applications in supramolecular [1-5] and medicinal chemistry [6-11] have been developed with excellent or promising results. Ruthenium arene-chloride dimeric complexes, $[(\eta^6\text{-arene})RuCl_2]_2$ [12-14], are good starting materials that could generate a variety of ruthenium derivatives to be used as anti-cancer drugs [15-24] and homogeneous catalysts [25-27]. The distinctive features of the ruthenium arene compounds include (i) the variability of η^6-arene fragments, (ii) substitution of the chloride with mono- or multi-dentate anionic ligands, and (iii) the ability to adjoin mono- or multi-dentate ligands to arene ruthenium compounds as shown in **Scheme 1**. The η^6-arene fragment in ruthenium compounds includes alkyl substituted arenes [28], tethered amines, phosphines, and NHC carbine arenes [29-30], etc. Similarly, mono- and multi-dentate anionic ligands as well as neutral ligands have been applied to form new organo-ruthenium derivatives (see **Scheme 1**).

Catalytic asymmetric transfer hydrogenation of ketones has recently emerged as a viable means for synthesizing chiral alcohols [31]. Due to its operational simplicity, the easy availability of reductants, and the high

enantioselectivities, the catalytic enantioselective reduction of ketones has been extensively studied during the last decade. The [Ru(η^6-arene)-(chelating-ligand)Cl]-type compounds exhibit the characteristic "piano stool" structure, with the unreactive arene as a "spectator ligand" in the metal coordination sphere and the chloride as a suitable "leaving group" [32]. These structural features seem favorable to afford sequential reactions involved in catalysis. Recently, Williams et al. [33] reported the synthesis of water-soluble aminosulfonamide ligands and their applications in the Ru(II)-catalyzed enantioselective transfer hydrogenation of aromatic ketones.

In the search for new organo-ruthenium compounds, we developed a series of bidentate keto-amine ligands and have subjected these precursors into [Ru(η^6-*p*-cymene)Cl_2]$_2$ to form new monomeric ruthenium derivatives. By changing the sterically hindered alkyl substituents on the keto-amine moiety, we are able to tune the stereogeometries of the ruthenium compounds and to study the Ru-catalyzed transfer hydrogenation. We also investigated the potential of the Ru derivatives as anticancer agents against HRMPC PC-3 and DU-145 cells.

Results and discussion

Synthesis and characterization of compounds 1-10

A series of keto-amine ligands **1**-**5**, $OCCH_3CHCCH_3NHR$ (where **1**, R = C_6H_3-2,6-$^iPr_2$; **2**, R = C_6H_2-2,4,6-Me_3; **3**, R = C_6H_4-2-^{t}Bu; **4**, R = C_6H_4-2- OMe; **5**, R = C_6H_4-2-OMe-5-Me) were synthesized according to a modified procedure [34] by the reaction between an arylamine and 2,4-pentanedione in methanol with a small amount of formic acid (**Scheme 2**). The amine N*H* protons for compounds **1**-**5** were involved in intramolecular hydrogen bonding with the keto (C=O) oxygen to form a six-membered chelate ring and the ^{1}H NMR spectra were relatively similar, showing broad *NH* signals at ca. δ 12.0. The methine protons of the keto-amine backbone for compounds **1**-**5** all displayed characteristic sharp singlets at *ca*. δ 4.7~5.1. In the ^{1}H NMR spectrum, the chemical shift of the methine proton is usually monitored to screen for the complexation of keto-amine ligands with metals. The keto-amine ligands **1**-**5** were converted to their corresponding lithium salts by adding one equivalent of Li^{n}Bu and then were subjected to a THF solution of [Ru(η^6-*p*-cymene)Cl_2]$_2$ [35] at 0 °C. After workup, complexes [Ru(η^6-*p*-cymene)($OCCH_3CHCCH_3NR$)Cl] (where **6**, R = C_6H_3-2,6-$^iPr_2$; **7**, R = C_6H_2-2,4,6-Me_3; **8**, R = C_6H_4-2-^{t}Bu; **9**, R =

C_6H_4-2-OMe; **10**, R = C_6H_4-2-OMe-5-Me) were isolated in moderate yield (see **Scheme 2**) and characterized by ^{1}H and ^{13}C NMR spectra. The characteristic methine proton for the keto-amine backbone of complexes **6**-**10** showed the typical ^{1}H NMR signal at ca. δ 4.66~4.77, a more up-field shifted signal than observed for the corresponding keto-amine ligands. This upfield shift was presumably due to the electron shielding from the ruthenium atom. It is worth noting that the steric hindrance between the cymene isopropyl group [36] and the substituted aryl group of the keto-amine ligands resulted in a slow rotation of the amine-aryl C-N bond as shown in **Scheme 3**. This criterion is quite distinct for larger steric hindrance among aryl rings of the keto-amine for compounds **6** and **7**. At room temperature, *i.e*., the slow limit, compound **6** showed two septets (δ 3.78 and 3.09) and four doublets (δ 1.42, 1.31, 1.29, and 1.27) for the two corresponding isopropyl fragments. Compound **7** likely displayed two singlets (δ 2.37 and 2.14) for two methyl groups at *ortho* positions of the 2,4,6-trimethylphenyl fragment. These resonances were broadened when the ^{1}H NMR spectra were taken at elevated temperature (see supporting information). The energy barriers for C-N bond rotation of compounds **6** and **7** were estimated at 60.9 and 59.8 KJ/mol, respectively [37].

For compounds **8**-**10**, the ^{1}H and ^{13}C NMR spectra corresponded well with the predicted molecular geometries.

Molecular geometries of compounds 2 and 6-10

The summary of X-ray crystal data collection and the selected bond lengths and angles for compounds **2** and **6**-**10** are shown in **Table 1** and **Table 2**, respectively. The crystals of organic keto-amine compound **2** were obtained from a saturated methylene chloride solution at -20 ℃ and its molecular geometry is depicted in **Figure 1**. Compound **2** showed a planar keto-amine backbone architecture with conjugated bond lengths [38-39]. The corresponding bond lengths for C=O and C-N were 1.2438(15) and 1.3409(15) Å, respectively. Crystals of compounds **6**-**10** were obtained from concentrated toluene solutions at -20 ℃. The molecular geometri es of **6**-**10** are depicted in **Figures 2-6** and could be best described as three-legged piano stool structures with the cymene as the base and the oxygen and nitrogen atoms from the keto-amine frame and the chloride serving as the three legs.

The corresponding bond lengths between ruthenium and the center of the cymene ring belong at ca. 1.67 Å [40-43]. In general, the keto-amine backbone

was coordinated with the ruthenium atom to form a six-membered chelated ring where the ruthenium atom deviated from the keto-amine plane at ca. 0.53 Å. The Ru-N_{amine} and Ru-O_{keto} bond lengths were at ca. 2.11 and 2.05 Å, respectively. As showed in **Scheme 3**, the isopropyl and methyl fragments of the phenyl rings for compounds **6** and **7** showed steric hindrance with the cymene isopropyl groups.

Transfer hydrogenation using ruthenium catalysts

The transfer hydrogenation reaction applied to the reduction of ketones has been explored in detail in recent years. Homogeneous asymmetric hydrogenation of olefins and ketones catalyzed by chiral transition metal complexes has provided a powerful means for preparing optically active organic compounds. The reduction of carbonyl [C=O] groups to pure secondary alcohols is a reaction of fundamental importance, more particularly the asymmetric reduction of ketone to enantiomeric secondary alcohols in modern synthetic chemistry. The most commonly used metal catalysts are ruthenium-based compounds, usually with (+2) as the formal oxidation state of Ru atom. In hydrogenation, the hydrido metal compounds ($MH(L)_n$) may be

generated as the catalyst which can accelerate the reduction of ketone in the catalytic cycle where a reducing equivalent-H may be supplied by the reducing solvent (like isopropanol) or from other reducing agents. In Scheme 4, compounds **6**-**10** were used as catalysts for transfer hydrogenation in the isopropyl alcohol system, proceeding as -C=O- $\rightarrow$ -CH(OH)-. The results of the studies are shown in Table 3. The transfer hydrogenation reactions for acetophenone and isoproplyl alcohol displayed high conversion yields regardless of the nature of the substituents on the aryl rings of the catalysts. When 4-methyl acetophenone was used, the conversion yields were lower than those obtained when acetophenone was used and no transfer hydrogenation reactions were observed while the 2,4,6-trimethyl-acetophenones were used. All these results showed that the steric hindrance of the substituted acetophenone is the key factor for the transfer hydrogenation conversion yield, regardless of the steric geometries of the ruthenium catalysts.

Anti-proliferative activities of ruthenium compounds

The discovery of compounds to combat prostate cancer is one of the main challenges found in clinical oncology. The demand for therapeutic drugs is particularly high because of the poor prognosis for patients with hormone-refractory metastatic prostate cancer (HRMPC). The majority of human prostate cancer cell lines, including the two "classical" cell lines DU-145 and PC-3, are reported to be androgen receptor (AR)-negative. Due to this unmet medical need, prostate cancer is the target of a significant proportion of both basic and clinical research. The anti-proliferative activities of ruthenium compounds have been examined using sulforhodamine B assay, a standard screening test used for *in vitro* anticancer drug screens at the U.S. National Cancer Institute. The data in Table 4 confirmed that the ruthenium compounds are effective in inhibiting the cell proliferation in both HRMPC PC-3 and DU-145 cells. We also listed the screening data of cisplatin, [(η^6-p-cymene)Ru^{II}(L)Cl]Cl [44], and [Ru(η^6 -cymene)Cl(η^2-dppm)]PF_6 [45] for their in vitro antitumour activity. The *in vitro* cytotoxicities (GI_{50}) for PC-3 and DU-145 cells using compounds **6**-**10** were all less than 30 μM, ranging from 4.25-19.68 μM and 5.48-20.93 μM, respectively. Compound **7** showed the best result with values of 4.25 and 5.48 μM for PC-3 and DU-145, respectively. Comparing the steric hindrance and electronic effects of the substituted phenyl

keto-amine ligands, compounds with the bulky 2,6-diisoproproylphenyl group (compound **6**) or the strong electron donating 2-methoxylphenyl group (compounds **9** and **10**) displayed lower cytotoxicity than those with the 2,4,6-trimethyl or 2-^{t}butyl phenyl substituents (compounds **7** and **8**). This results indicate that suitable steric hindrance and electron donating ability are crucial for the ruthenium compounds to perform as good anti-cancer reagents. Therefore, fine tuning of the substituents of the phenyl keto-amine ligands and the use of different ligand systems are the main targets in the search for new organometallic anticancer reagents.

Conclusion

Herein, we have reported the synthesis of a series of arene-ruthenium compounds prepared from keto-amine bi-dentate precursors and their structures are discussed. All the compounds were well characterized by ^{1}H and ^{13}C NMR spectroscopy. The electronic and steric effects of the substituted phenyl keto-amine ligands on the ruthenium compounds showed minimal effects in the transfer hydrogenation reduction of acetophenone. However, the substituents on the acetophenone made significant contributions to catalytic

reduction. Furthermore, the anti-proliferative activities of Ru-derivatives were tested on HRMPC cell lines, namely PC-3 and DU-145. Compounds **7** and **8** were the most influential candidates that displayed effective anticancer activity against HRMPCs. Further investigations with Ru-derivatives prepared from new bidentate organic precursors and their potential effects on apoptosis in different human cells are currently being carried out.

Experimental Section

Materials and physical techniques

All reactions were performed under a nitrogen atmosphere using standard Schlenk techniques or in glove box. Tetrahydrofuran and toluene were dried by refluxing over sodium benzophenone ketyl. Solvents were distilled and stored in solvent reservoirs that contained 4-Å molecular sieves and were purged with nitrogen. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance 300 spectrometer and the chemical shifts were recorded in ppm relative to the residual protons of $CDCl_3$ (δ = 7.24, 77.0 ppm). Elemental analyses were performed using a Heraeus CHN-OS Rapid Elemental Analyzer at the

Instrument Center of the NCHU. Ligands 1-5 and [Ru(η^6-p-cymene)Cl_2]$_2$ were prepared using a modified procedure [35].

*Synthesis of compounds **1**-**5**, $OCCH_3CHCCH_3NHR$.*

A general method for synthesis of compounds **1**-**5** was described as follows. A round bottom flask charged with 2,4-pentanedione and 30 mL of methanol was added aryl amine slowly. A small amount of formic acid was used as catalyst. The solution was stirred for overnight and solvent was removed over vaccum to yield the final product.

Compound 1:

2,4-pentanedione (5.0 g, 49.9 mmol), 2,6-diisopropylaniline (8.85 g, 49.9 mmol), gave 11.8 g of brown solid product, 93% yield. ^{1}H NMR (δ, $CDCl_3$): 1.05 (d, 6H, C*H*Me_2), 1.11 (d, 6H, C*H*Me_2), 1.53 (s, 3H, *Me*), 2.00 (s, 3H, *Me*), 2.95 (sept, 1H, C*H*Me_2), 5.12 (s, 1H, C=C*H*C), 7.06 (m, 2H, P*H*), 7.17 (m, 1H, P*H*),12.02 (br, 1H,N*H*). ^{13}C NMR (δ, $CDCl_3$): 18.8, 22.4, 24.3, 28.2, 28.7, 95.4, 123.3, 128.1, 133.3, 146.0, 162.8, 195.5.

Compound 2:

2,4-pentanedione (10.0 g, 99.8 mmol), 2,4,6-trimethylaniline (13.5 g, 99.8 mmol), gave 18.6 g of yellowish solid product, 86% yield. ^{1}H NMR (δ, $CDCl_3$): 1.57 (s, 3H, *Me*), 2.04 (s, 3H, *Me*), 2.10 (s, 6H, *Me*), 2.22 (s, 3H, *Me*), 5.15 (s, 1H, C=C*H*C), 6.88 (s, 2H, *Ph*), 11.82 (br, 1H, N*H*). ^{13}C NMR (δ, $CDCl_3$): 17.1, 17.8, 20.0, 27.9, 94.91, 128.1, 133.1, 134.7, 136.1, 162.1, 194.5. Anal. Calcd: C, 77.50; H, 8.24; N, 6.78. Found: C, 77.37; H, 8.81; N, 6.44%.

Compound 3:

2,4-pentanedione (3.00 g, 29.9 mmol), 2-^{t}butylaniline (4.47 g, 29.9 mmol), gave 6.78 g of reddish oily product, 98% yield. ^{1}H NMR (δ, $CDCl_3$): 1.11 (s, 9H, ^{t}*Bu*), 1.50 (s, 3H, *Me*), 1.81 (s, 3H, *Me*), 4.92 (s, 1H, C=C*H*C), 6.66 (m, 1H, *Ph*), 6.88 (m, 2H, *Ph*), 7.14 (m, 1H, *Ph*), 12.31 (br, 1H,N*H*). ^{13}C NMR (δ, $CDCl_3$): 12.9, 28.2, 29.9, 34.2, 96.4, 125.8, 126.2, 126.3, 129.0, 136.3, 144.9, 160.4, 167.6. Anal. Calcd: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.37; H, 9.76; N, 6.42%.

Compound 4:

2,4-pentanedione (5.0 g, 49.9 mmol), 2-methoxyaniline (6.85 g, 49.9 mmol),

gave 10.61 g of brown oily product, 98% yield. ^{1}H NMR (δ, $CDCl_3$): 1.52 (d, 3H, *Me*), 1.65 (d, 3H, *Me*), 3.18 (s, 3H, *OMe*), 4.75 (s, 1H, C=C*H*C), 6.45 (m, 2H, P*H*), 6.67 (m, 2H, P*H*), 12.00 (br, 1H, N*H*). ^{13}C NMR (δ, $CDCl_3$): 18.6, 27.9, 54.4, 96.8, 110.3, 119.3, 123.6, 125.1, 126.9, 151.5, 158.9, 194.2.

Compound 5:

2,4-pentanedione (5.0 g, 49.9 mmol), 2-methoxy-5-methylaniline (6.85 g, 49.9 mmol), gave 10.38 g of dark black oily product, 94% yield. ^{1}H NMR (δ, $CDCl_3$): 1.72 (d, 3H, *Me*), 1.84 (s, 3H, *Me*), 2.01 (s, 3H, *Me*), 3.53 (s, 3H, O*Me*), 4.94 (s, 1H, C=C*H*C), 6.55 (m, 1H, *Ph*), 6.69 (m, 2H, *Ph*), 12.11 (br, 1H, N*H*). ^{13}C NMR (δ, $CDCl_3$): 18.9, 19.7, 28.1, 54.8, 96.8, 124.9, 125.9, 126.8, 128.9, 150.0, 150.7, 194.5.

*Synthesis of compounds **6**-**10***

A general method for synthesis of compounds **6** - **10** was described as follows. A Schlenk flask charged with keto-imine and 10 mL of THF was cooled to 0℃ and added Li^{n}Bu slowly. The resulting solution was added to another flask which contains $[Ru(\eta^6\text{-p-cymene})Cl_2]_2$ and 10 mL of THF at room

temperature. After stirring for 3 hours, THF was removed and the residue was extracted. The extraction was filtered through celite and the filtrate was concentrated to a small amount and stored at -20℃ to yield the final product.

{Ru(η^6-p-cymene)[$OCCH_3CHCCH_3N(C_6H_3$-2,6-$^iPr_2$)]Cl} (***6***)

Compound **1** (0.40 g, 1.54 mmol), Li^{n}Bu (2.5 M in hexane, 0.61 mL, 1.54 mmol), and [Ru(η^6-p-cymene)Cl_2]$_2$ (0.47 g, 0.77 mmol) were used and the final product was obtained from a saturated toluene solution to yield 0.473 g of deep red crystals (57%). ^{1}H NMR (δ, $CDCl_3$): 1.03 (br, 6H, CH*Me*$_2$), 1.31 (br, 12H, CH*Me*$_2$), 1.56 (s, 3H, *Me*), 1.77 (s, 3H, *Me*), 1.97 (s, 3H, *Me*), 2.62 (sept, 1H, C*H*Me$_2$), 3.16 (br, 1H, C*H*Me$_2$), 3.84 (br, 1H, C*H*Me$_2$), 4.05 (br, 1H, cymene), 4.75 (s, 1H, CC*H*C), 4.81 (br, 1H, cymene), 5.26 (br, 1H, cymene), 5.31 (br, 1H, cymene), 7.21 (d, 3H, *Ph*). ^{13}C NMR (δ, $CDCl_3$): 17.8, 21.5, 23.3, 25.0, 25.3, 25.5, 26.1, 27.5, 27.9, 30.6, 82.0, 84.2, 86.8, 95.0, 97.4, 103.5, 123.4, 125.0, 126.4, 142.0, 144.0, 151.5, 166.2, 177.6. Anal. Calcd: C, 61.41; H, 7.06; N, 2.65. Found: C, 61.77; H, 7.29; N, 2.92%.

{Ru(η^6-p-cymene)[$OCCH_3CHCCH_3N(C_6H_2$-2,4,6-Me_3)]Cl} (***7***)

Compound **2** (0.40 g, 1.84 mmol), Li^{n}Bu (2.5 M in hexane, 0.73 mL, 1.84

mmol), and [Ru(η^6-p-cymene)Cl_2]$_2$ (0.56 g, 0.92 mmol) were used and the final product was obtained from a saturated toluene solution to yield 0.33 g of red crystals (36.7%). ^{1}H NMR (δ, $CDCl_3$): 1.20 (br, 6H, CH*Me*$_2$), 1.47 (s, 3H, *Me*), 1.96 (s, 3H, *Me*), 2.00 (s, 3H, *Me*), 2.14 (br, 3H, *Me*), 2.32 (s, 3H, *Me*), 2.39 (br, 3H, Me), 2.74 (sept, 1H, C*H*Me$_2$), 3.74 (br, 1H, cymene), 4.73 (br, 1H, cymene), 4.76 (s, 1H, CC*H*C), 5.03 (br, 1H, cymene), 5.27 (br, 1H, cymene), 6.93 (s, 2H, *Ph*). ^{13}C NMR (δ, $CDCl_3$): 17.8, 20.9, 22.4, 22.9, 26.2, 30.9, 92.5, 97.4, 103.7, 134.7, 152.4, 152.4, 164.6, 178.4. Anal. Calcd: C, 59.19; H, 6.62; N, 2.88. Found: C, 58.82; H, 6.75; N, 2.65%.

{Ru(η^6-p-cymene)[OCCH$_3$CHCCH$_3$N(C$_6$H$_4$-2-^{t}Bu)]Cl} (***8***)

Compound **3** (0.30 g, 1.28 mmol), Li^{n}Bu (2.5 M in hexane, 0.51 mL, 1.28 mmol), and [Ru(η^6-p-cymene)Cl_2]$_2$ (0.39 g, 0.64 mmol) were used and the final product was obtained from a saturated toluene solution to yield 0.33 g of red crystals (51.2%). ^{1}H NMR (δ, $CDCl_3$): 1.19 (m, 6H, CH*Me*$_2$), 1.45 (s, 9H, ^{t}*Bu*), 1.54 (s, 3H, *Me*), 1.80 (s, 3H, *Me*), 1.95 (s, 3H, *Me*), 2.65 (sept, 1H, C*H*Me$_2$), 4.06 (d, 1H, cymene), 4.69 (s, 1H, CC*H*C), 5.00 (d, 1H, cymene), 5.07 (d, 1H, cymene), 5.41 (d, 1H, cymene), 7.15 (m, 2H, *Ph*), 7.45 (d, 1H, *Ph*), 7.63 (d, 1H, *Ph*). ^{13}C NMR (δ, $CDCl_3$): 17.36, 21.20, 22.85, 25.02, 25.57, 30.48, 33.57,

36.34, 74.55, 81.37, 87.74, 88.83, 91.47, 96.84, 105.22, 125.51, 126.91, 128.89, 129.58, 140.23, 154.83, 167.13, 177.24. Anal. Calcd: C, 59.93; H, 6.84; N, 2.80. Found: C, 60.13; H, 6.49; N, 2.99%.

{Ru(η^6-p-cymene)[$OCCH_3CHCCH_3N(C_6H_4$-2-OMe)]Cl} (***9***)

Compound **4** (0.40 g, 1.95 mmol), Li^{n}Bu (2.5 M in hexane, 0.78 mL, 1.95 mmol), and [Ru(η^6-p-cymene)$Cl_2]_2$ (0.60 g, 0.975 mmol) were used and the final product was obtained from a saturated toluene solution to yield 0.44 g of red crystals (47.2%). ^{1}H NMR (δ, $CDCl_3$): 1.16 (d, 6H, CH*Me*$_2$), 1.57 (s, 3H, *Me*), 1.92 (s, 3H, *Me*), 1.98 (s, 3H, *Me*), 2.59 (sept, 1H, C*H*Me_2), 3.58 (d, 1H, cymene), 3.91 (s, 3H, O*Me*), 4.72 (s, 1H, CC*H*C), 5.05 (d, 1H, cymene), 5.11 (d, 1H, cymene), 5.28 (d, 1H, cymene), 6.95 (m, 2H, *Ph*), 7.14 (d, 1H, *Ph*), 7.69 (d, 1H, *Ph*). ^{13}C NMR (δ, $CDCl_3$): 18.25, 20.86, 23.26, 23.28, 26.32, 30.40, 55.20, 54.57, 77.35, 77.75, 85.96, 95.13, 96.06, 100.76, 110.26, 121.49, 126.41, 127.78, 146.61, 151.67, 164.78, 176.87. Anal. Calcd: C, 53.59; H, 6.13; N, 2.84. Found: C, 53.70; H, 6.04; N, 2.97%.

{Ru(η^6-p-cymene)[$OCCH_3CHCCH_3N(C_6H_2$-2-OMe-5-Me)]Cl} (***10***).

Compound **5** (0.40 g, 1.80 mmol), Li^{n}Bu (2.5 M in hexane, 0.72 mL, 1.80

mmol), and [Ru(η^6-p-cymene)Cl_2]$_2$ (0.55 g, 0.90 mmol) were used and the final product was obtained from a saturated toluene solution to yield 0.35 g of red crystals (40.4%). ^{1}H NMR (δ, $CDCl_3$): 1.20 (m, 6H, CH*Me*$_2$), 1.63 (s, 3H, *Me*), 1.97 (s, 3H, *Me*), 2.02 (s, 3H, *Me*), 2.30 (s, 3H, *Me*), 2.63 (sept, 1H, C*H*Me$_2$), 3.67 (d, 1H, cymene), 3.93 (s, 3H, O*Me*), 4.66 (br, 2H, H_2O) 4.76 (s, 1H, CC*H*C), 5.03(d, 1H, cymene), 5.16 (d, 1H, cymene), 5.33 (d, 1H, cymene), 6.87 (m, 2H, *Ph*), 6.98 (m, 1H, *Ph*), 7.55 (d, 1H, *Ph*). ^{13}C NMR (δ, $CDCl_3$): 18.1, 20.5, 20.7, 23.2, 26.3, 30.3, 55.2, 55.2, 77.1, 84.7, 86.3, 86.8, 94.3, 95.9, 101.0, 110.9, 126.6, 128.0, 146.2, 149.4, 164.5, 176.6. Anal. Calcd: C, 56.44; H, 6.18; N, 2.86. Found: C, 56.77; H, 6.46; N, 3.05%.

Cell lines and cell culture

Human hormone-refractory prostate cancer cell lines PC-3 and DU-145 were collected from American Type Culture Collection (Rockville, MD). Cells were cultured in RPMI 1640 medium with 10% FBS (v/v) and penicillin (100 U/ml)/streptomycin (100 μg/ml). Cultures were maintained in a humidified incubator at 37 ^{o}C in 5% CO_2/95% air.

Sulforhodamine B (SRB) assays

Cells were seeded in 96-well plates in medium with 5% FBS. After 24 hours, cells were fixed with 10% TCA to represent cell population at the time of drug addition (T_0). After additional incubation of DMSO or the compound for 48 hours (PC-3 cells) or 72 hours (DU145 cells), cells were fixed with 10% TCA and SRB at 0.4% (w/v) in 1% acetic acid was added to stain cells. Unbound SRB was washed out by 1% acetic acid and SRB bound cells were solubilized with 10 mM Trizma base. The absorbance was read at a wavelength of 515 nm. Using the following absorbance measurements, such as time zero (T_0), control growth (C), and cell growth in the presence of the compound (Tx), the percentage growth was calculated at each of the compound concentrations levels. Percentage growth inhibition was calculated as: $[1-(Tx-T_0)/(C-T_0)]$ x 100%. Growth inhibition of 50% (IC_{50}) is determined at the compound concentration which results in 50% reduction of total protein increase in control cells during the compound incubation. Data are expressed as mean±SEM of three to five determinations.

X-ray crystallography

Suitable crystals of compounds **2**, **6**-**10** were attached to a fine glass fiber with paratone oil and mounted in goniostat for data collection. Data collections were performed at 150 K under liquid nitrogen vapor for all complexes. Data were collected on a Bruker SMART CCD diffractometer with graphite monochromated Mo-K_α radiation. No significant crystal decay was found. Data were corrected for absorption empirically by means of ψ scans. All non-hydrogen atoms were refined with anisotropic displacement parameters. For all the structures, the hydrogen atom positions were calculated and they were constrained to idealized geometries and treated as riding where the H atom displacement parameter was calculated from the equivalent isotropic displacement parameter of the bound atom. An absorption correction was performed with the program SADABS [46] and the structures of both complexes were determined by direct methods procedures in SHELXS [47] and refined by full-matrix least-squares methods, on F^2's, in SHELXL [48]. All the relevant crystallographic data and structure refinement parameters are summarized in **Table 1**. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. CCDC-1056020 (**2**), CCDC-1056021 (**6**),

CCDC-1056022 (**7**), CCDC-1056023 (**8**), CCDC-1056024 (**9**) and CCDC-1056025 (**10**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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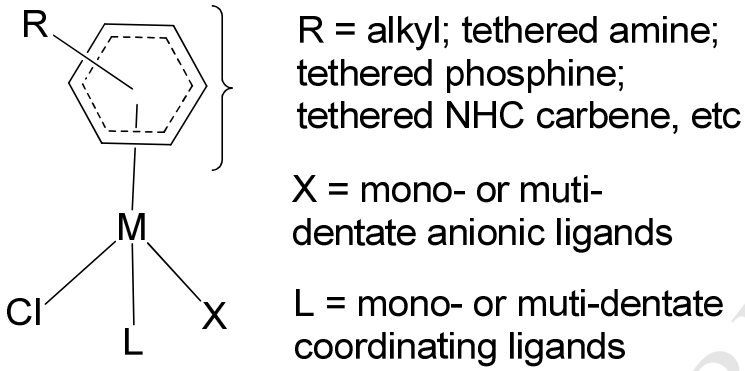
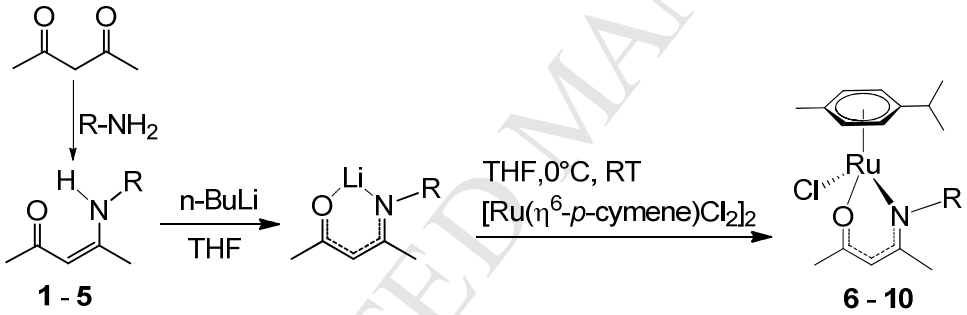
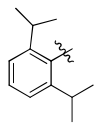
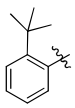
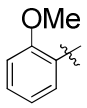
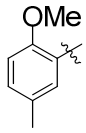
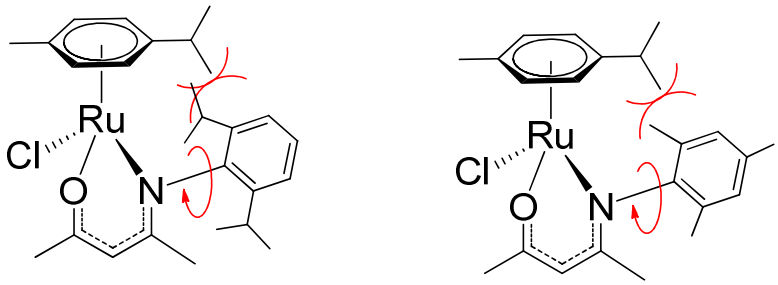


Scheme 1. The variation of η^6-arene ruthenium complexes

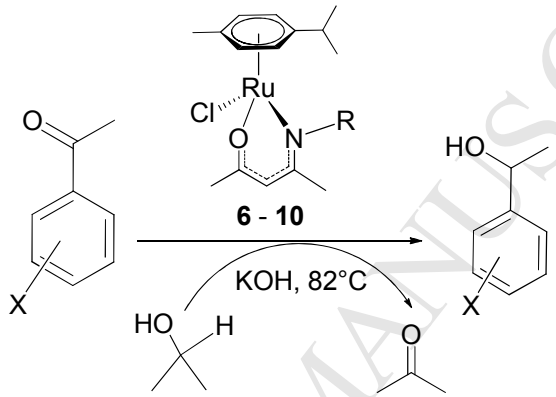


compound	**1, 6**	**2, 7**	**3, 8**	**4, 9**	**5, 10**
R					

Scheme 2. Synthesis of compounds **1** – **10**



Scheme 3. The steric hindrance of N-Aryl bond rotation of compounds **6** and **7**



Scheme 4. Catalytic transfer hydrogenation of substituted acetophenone in the presence of isopropyl alcohol and ruthenium catalysts.

Captions for Figures

Figure 1.The molecular structure of compound **2**. Thermal ellipsoids are drawn at 30% probability level.

Figure 2. Molecular geometry of compound **6**. Thermal ellipsoids are drawn at 30% probability level and all the hydrogen atoms are omitted for clarity.

Figure 3. Molecular geometry of compound **7**. Thermal ellipsoids are drawn at 30% probability level and all the hydrogen atoms are omitted for clarity.

Figure 4. Molecular geometry of compound **8**. Thermal ellipsoids are drawn at 30% probability level and all the hydrogen atoms are omitted for clarity.

Figure 5. Molecular geometry of compound **9**. Thermal ellipsoids are drawn at 30% probability level and all the hydrogen atoms are omitted for clarity.

Figure 6. Molecular geometry of compound **10**. Thermal ellipsoids are drawn at 30% probability leveland all the hydrogen atoms are omitted for clarity.

Figure 1.

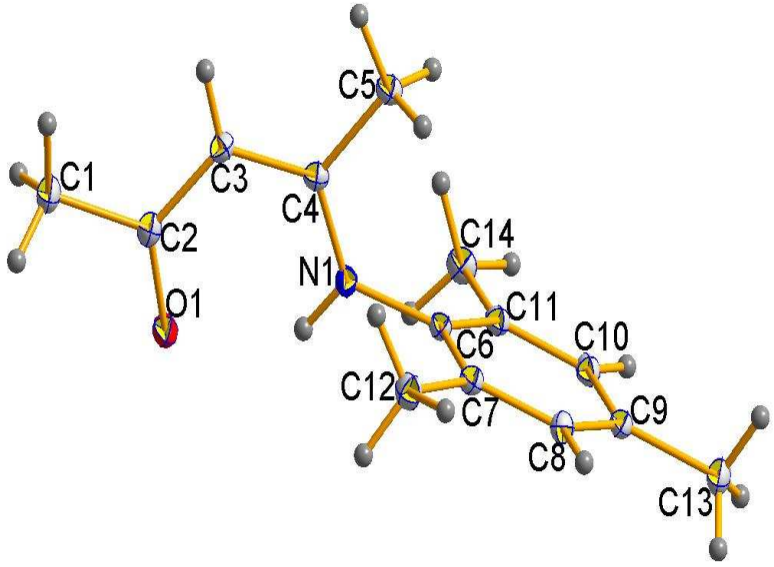


Figure 2.

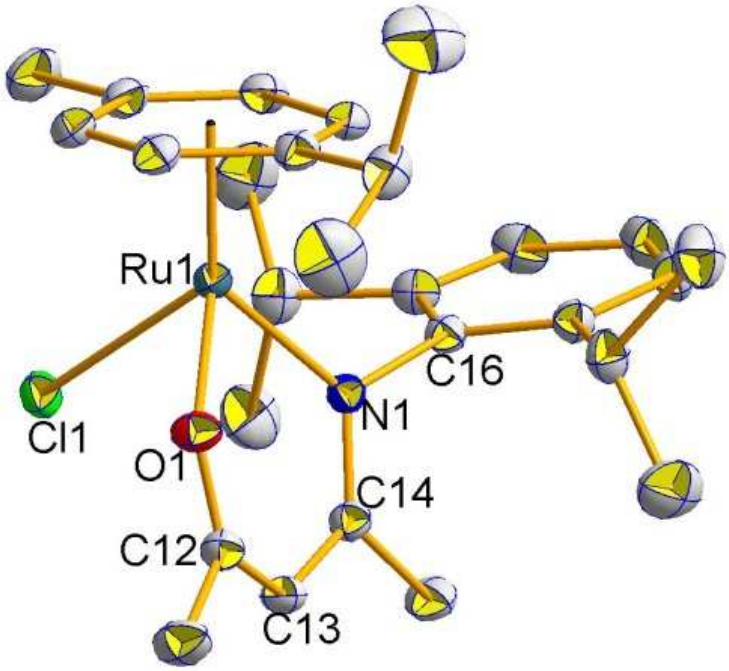


Figure 3.

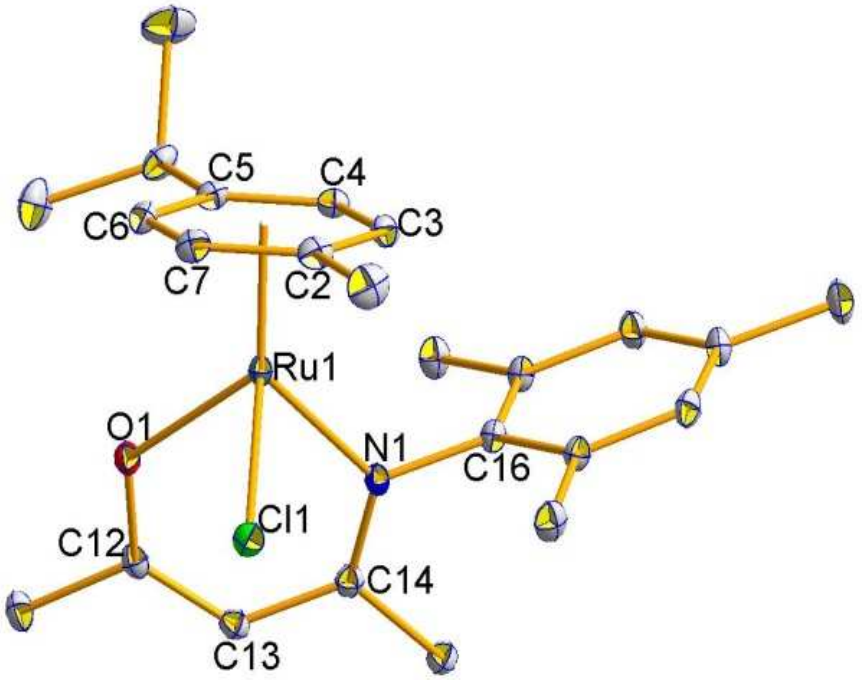


Figure 4.

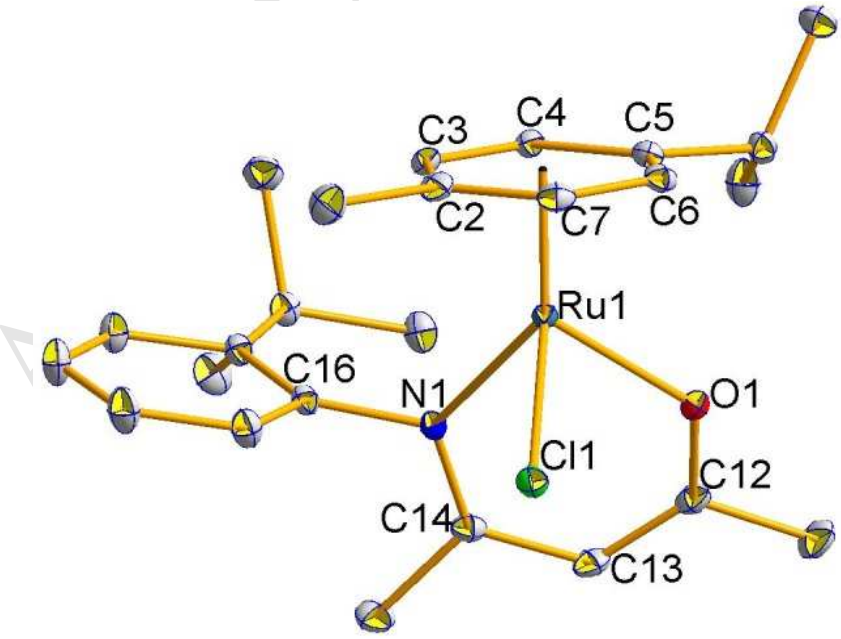


Figure 5.

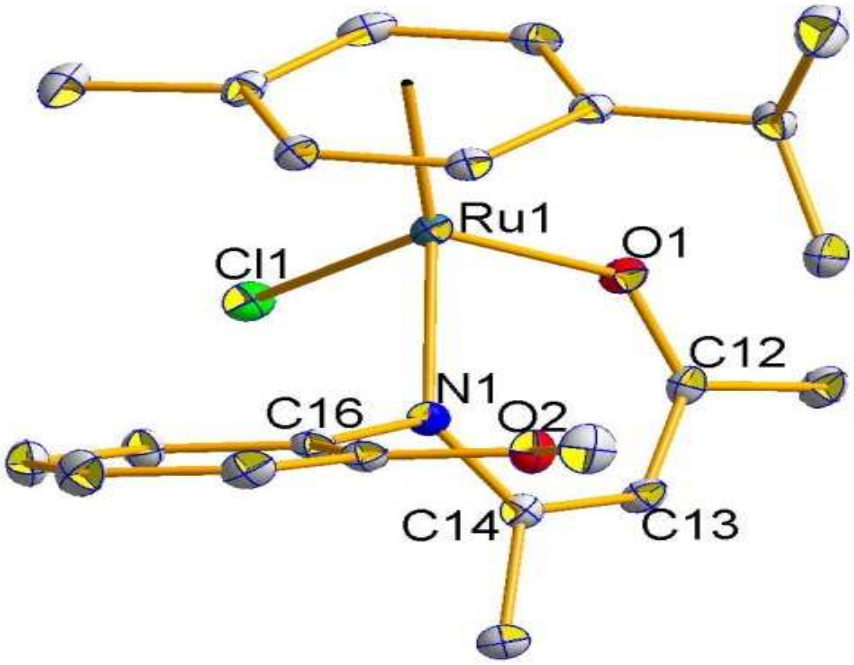


Figure 6.

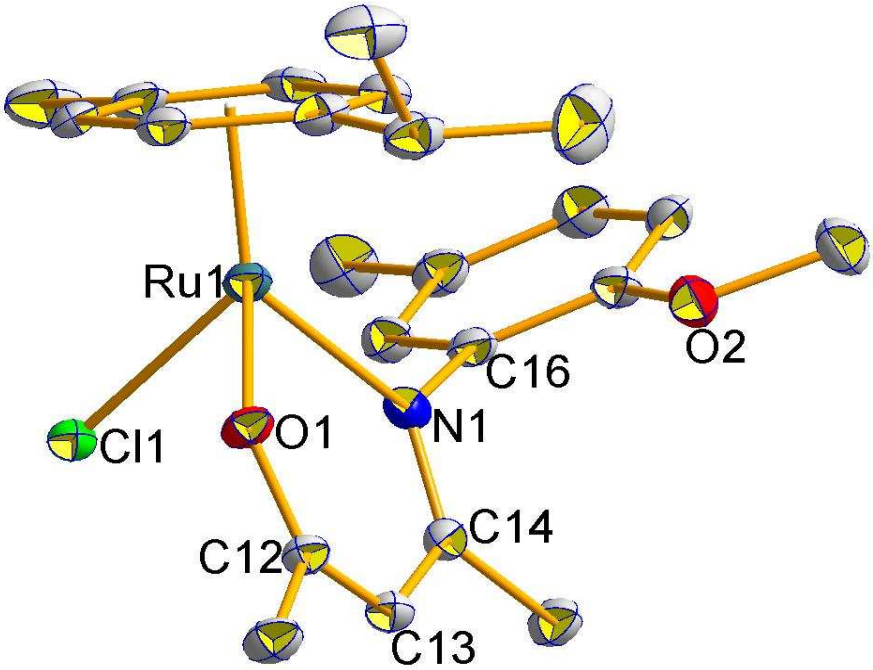


Table 1. The summary of X-ray crystal data collection of compounds **2** and **6**-**10**

	2	**6**	**7**	**8**	**9**	**10**
formula	$C_{14}H_{19}NO$	$C_{27}H_{38}ClNORu$	$C_{24}H_{32}ClNORu$	$C_{25}H_{34}ClNORu$	$C_{22}H_{28}ClNO_2Ru$	$C_{23}H_{30}ClNO_2Ru$
FW	217.30	529.10	487.03	501.05	474.97	489.00
T [K]	150(2)	150(2)	150(2)	150(2)	150(2)	150(2)
crystal system	Monoclinic	Triclinic	Triclinic	Monoclinic	Triclinic	Triclinic
space group	$P2_1/n$	P-1	P-1	$P2_1/c$	P-1	P-1
a [Å]	9.974(3)	9.8238(9)	10.6266(4)	11.6711(6)	10.6866(3)	10.5943(14)
b [Å]	9.876(3)	10.6251(10)	11.2924(4)	11.6622(5)	10.7282(3)	11.0844(14)
c [Å]	12.793(4)	13.7941(19)	11.3439(7)	17.3387(8)	11.2684(4)	11.4173(14)
α [º]	90	97.333(6)	111.732(3)	90	73.677(2)	64.901(7)

β [º]	99.218(5)	96.866(7)	97.596(3)	97.473(3)	62.312(2)	64.994(8)
γ [º]	90	113.163(5)	110.759(2)	90	64.145(2)	75.836(8)
V [Å^3]	1244.0(7)	1290.0(2)	1126.74(9)	2339.94(19)	1024.46(5)	1096.8(2)
Z	4	2	2	4	2	2
ρ_c [Mg m^{-3}]	1.160	1.365	1.438	1.422	1.543	1.484
μ[mm-^{1}]	0.072	0.729	0.828	0.800	0.912	0.855
F(000)	472	554	506	1040	490	506
rflns collected	15234	18351	15541	33231	14164	12051
independent rflns	3080[R_{int}=0.0459]	6378[R_{int}=0.0203]	5567[R_{int}=0.0305]	6054[R_{int}=0.0289]	5063[R_{int}=0.0206]	5437[R_{int}=0.0580]
data/restraints/parameters	3080 / 0 / 154	6378 / 0 / 289	5567 / 0 / 261	6054 / 0 / 270	5063 / 0 / 250	5437 / 0 / 260
goodness-of-fit on F^2	0.943	0.925	0.944	0.747	1.005	1.029

R_1, wR_2 (I>2σ(I))	R_1 = 0.0457 wR_2 = 0.1327	R_1 = 0.0253, wR_2 = 0.0700	R_1 = 0.0381, wR_2 = 0.1008	R_1 = 0.0203, wR_2 = 0.0802	R_1 = 0.0267, wR_2 = 0.0639	R_1 = 0.0639, wR_2 = 0.1526
R_1, wR_2 (all data)	R_1 = 0.0510, wR_2 = 0.1389	R_1 = 0.0289, wR_2 = 0.0728	R_1 = 0.0421, wR_2 = 0.1063	R_1 = 0.0227, wR_2 = 0.0862	R_1 = 0.0323, wR_2 = 0.0682	R_1 = 0.0943, wR_2 = 0.1862
largest diff. peak, hole [eÅ^{-3}]	0.274 and -0.300	0.333and-0.557	2.317 and -1.280	0.384 and -0.633	0.875 and -0.888	2.036 and -2.211

Table 2. Selected bond lengths (Å) and angles (º) for compounds **2** and **6-10**.

2			
O(1)-C(2)	1.2438(15)	N(1)-C(4)	1.3409(15)
N(1)-C(6)	1.4330(14)	C(2)-C(3)	1.4283(17)
C(3)-C(4)	1.3833(16)		
C(4)-C(3)-C(2)	123.07(11)	C(3)-C(2)-C(1)	118.67(11)
6			
Ru(1)-O(1)	2.0546(13)	Ru(1)-N(1)	2.1143(14)
Ru(1)-Cl(1)	2.4434(5)	Ru(1)-Cymene$_{center}$	1.672
O(1)-C(12)	1.284(2)	N(1)-C(14)	1.325(2)
N(1)-C(16)	1.445(2)	C(13)-C(12)	1.371(3)
C(14)-C(13)	1.405(2)		
O(1)-Ru(1)-N(1)	88.08(5)	N(1)-Ru(1)-Cl(1)	85.35(4)
O(1)-Ru(1)-Cl(1)	84.13(4)	C(12)-C(13)-C(14)	126.42(17)
7			
Ru(1)-O(1)	2.0653(17)	Ru(1)-N(1)	2.105(2)
Ru(1)-Cl(1)	2.4326(6)	Ru(1)-Cymene$_{center}$	1.676
O(1)-C(12)	1.286(3)	N(1)-C(14)	1.319(3)
N(1)-C(16)	1.438(3)	C(12)-C(13)	1.373(3)

C(13)-C(14)	1.419(3)	O(1)-Ru(1)-Cl(1)	84.07(5)
O(1)-Ru(1)-N(1)	88.20(7)	N(1)-Ru(1)-Cl(1)	85.51(6)

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Ru(1)-O(1)	2.0641(10)	Ru(1)-N(1)	2.1006(11)
Ru(1)-Cl(1)	2.4276(4)	Ru(1)-Cymene$_{center}$	1.671
O(1)-C(12)	1.2870(17)	C(14)-C(13)	1.415(2)
C(12)-C(13)	1.377(2)	N(1)-C(14)	1.3146(17)
C(16)-N(1)	1.4405(17)	O(1)-Ru(1)-N(1)	89.17(4)
N(1)-Ru(1)-Cl(1)	83.47(3)	O(1)-Ru(1)-Cl(1)	84.83(3)

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Ru(1)-O(1)	2.0663(14)	Ru(1)-N(1)	2.0929(17)
Ru(1)-Cl(1)	2.4366(5)	Ru(1)-Cymene$_{center}$	1.669
N(1)-C(14)	1.314(3)	N(1)-C(16)	1.428(2)
O(1)-C(12)	1.283(3)	C(12)-C(13)	1.373(3)
C(13)-C(14)	1.422(3)	O(1)-Ru(1)-N(1)	88.36(6)
O(1)-Ru(1)-Cl(1)	85.62(4)	N(1)-Ru(1)-Cl(1)	85.09(5)

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Ru(1)-O(1)	2.075(3)	Ru(1)-N(1)	2.079(5)
Ru(1)-Cl(1)	2.4245(14)	Ru(1)-Cymene$_{center}$	1.667

C(12)-C(13)	1.363(8)	O(1)-C(12)	O(1)-C(12)
N(1)-C(16)	1.434(7)	N(1)-C(14)	1.317(7)
C(13)-C(14)	C(13)-C(14)	O(1)-Ru(1)-N(1)	88.17(16)
O(1)-Ru(1)-Cl(1)	86.72(11)	N(1)-Ru(1)-Cl(1)	83.59(12)

Table 3. Transfer hydrogenation of ketone using isopropyl alcohol in the presents of ruthenium catalysts

Cat.	X^a = H	X^a = 4-Me	X^b = 2, 4, 6-Me_3
6	96.5	63.8	trace
7	93.6	81.6	trace
8	96.3	54.3	trace
9	88.2	54.7	trace
10	94.6	46.3	trace
blank	55.6	17.5	trace

[a]reaction time: 3 hours; [b]reaction time: 12 hours

Table 4. In vitro cytotoxicity of **6**-**10** and related compounds for human hormone-refractory prostate cancer cell lines PC-3 and DU-145

Compound	**SRB assay (GI_{50}, μM)**	
	PC-3 cells (N=3)	DU-145 cells (N=3)
6	14.54 ± 1.30	21.64 ± 2.46
7	4.25 ± 0.42	5.48 ± 0.35
8	5.34 ± 0.17	5.65 ± 0.14
9	19.68 ± 0.65	20.93 ± 2.69
10	12.39 ± 1.51	14.31 ± 0.90
Cisplatin	> 30	> 30
$[(\eta^6\text{-p-cymene})Ru^{II}(L_1)Cl]Cl$[a]		44.9
$[(\eta^6\text{-p-cymene})Ru^{II}(L_2)Cl]Cl$[b]		> 80
$[Ru(\eta^6\text{-cymene})Cl(\eta^2\text{-dppm})]PF_6$	1.9	
$[Ru(\eta^6\text{-cymene})Cl(\eta^2\text{-dppmO})]PF_6$	> 100	

[a]: L_1 = bis(3,5-dimethylpyrazolyl)parabenzoic acid; [b]: L_2= bis(3,5-dimethylpyrazolyl)metabenzoic acid

- A series of arene ruthenium compounds containing keto-amine bidentate ligands were synthesized
- potential anti-cancer activity of ruthenium derivatives against human hormone-refractory metastatic prostate cancer (HRMPC) cell lines
- The ruthenium derivatives effectively catalyzed the conversion rate in transfer hydrogenation of substituted acetophenone