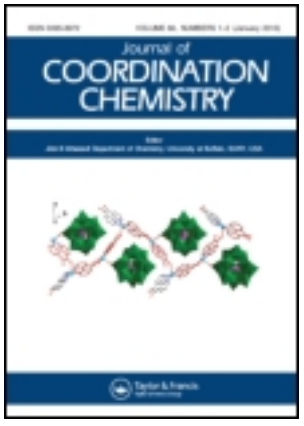

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Catalytic and anticancer activities of sawhorse-type diruthenium tetracarbonyl complexes derived from fluorinated fatty acids

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Catalytic and anticancer activities of sawhorse-type diruthenium tetracarbonyl complexes derived from fluorinated fatty acids

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The reaction of fluorinated fatty acids, perfluorobutyric acid ($C_3F_7CO_2H$), and perfluorododecanoic acid ($C_{11}F_{23}CO_2H$), with dodecacarbonyltriruthenium ($Ru_3(CO)_{12}$) under reflux in tetrahydrofuran, followed by addition of two-electron donors (L) such as pyridine, 1,3,5-triaza-7-phosphatricyclo [3.3.1.1]decane, or triphenylphosphine, gives stable diruthenium complexes $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3F_7)_2(L)_2$ (**1a**, L = C_5H_5N; **1b**, L = PTA; **1c**, L = PPh_3) and $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}F_{23})_2(L)_2$ (**2a**, L = C_5H_5N; **2b**, L = PTA; **2c**, L = PPh_3). The catalytic activity of the complexes for hydrogenation of styrene under supercritical carbon dioxide has been assessed and compared to the analogous triphenylphosphine complexes with non-fluorinated carboxylato groups $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3H_7)_2(PPh_3)_2$ (**3**) and $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}H_{23})_2(PPh_3)_2$ (**4**). In addition, the cytotoxicities of the fluorinated complexes **1** were also evaluated on several human cancer cell lines (A2780, A549, Me300, HeLa). The complexes appear to be moderately cytotoxic, showing greater activity on the Me300 melanoma cells. Single-crystal X-ray structure analyses of **1a** and **3** show the typical sawhorse-type arrangement of the diruthenium tetracarbonyl backbone with two bridging carboxylates and two terminal ligands occupying the axial positions.

Keywords: Dinuclear complexes; Carbonyl ligands; Fluorinated fatty acids; Carboxylato bridges; Ruthenium; Supercritical carbon dioxide

1. Introduction

Supercritical carbon dioxide ($scCO_2$) is an interesting reaction medium for homogenous catalysis due to its inertness in most catalytic reactions. The $scCO_2$ is abundant, non-toxic, non-flammable, readily available, and inexpensive and thus considered to be one of the best ecologically friendly alternatives to conventional solvents [1]. However, metal complexes are in general poorly soluble in $scCO_2$. This major obstacle has been overcome by using fluorinated derivatives, which remarkably improved the solubility of metal

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complexes in $scCO_2$ [2]. These fluorinated derivatives have been tested for different catalytic reactions such as hydrogenation, oxidation, and hydroformylation [2].

Carbon monoxide has been recognized as an important signaling molecule in mammals. It is produced by oxidation of heme by heme oxygenase, and evidence has been found that CO possesses anti-inflammatory, vasodilatory, anti-apoptotic, anti-proliferative, and anti-hypoxia therapeutic effects [3]. Notably, among chemotherapeutic metals, ruthenium is now considered one of the most promising chemotherapeutic agents because of its low toxicity and ability to mimic iron in living systems [4]. Consequently, ruthenium carbonyl complexes have attracted considerable attention, and the biological role of such complexes has been investigated by several research groups [5].

Recently, we evaluated the potential of sawhorse-type diruthenium tetracarbonyl complexes as biological agents [6]. First reported by Lewis and co-workers in 1969 [7], sawhorse-type diruthenium tetracarbonyl complexes are quite robust and are known to catalyze various reactions [8]. Herein, we report the synthesis of sawhorse-type complexes containing carboxylates derived from saturated fluorinated fatty acids (perfluorobutyric acid, perfluorododecanoic acid) with a variety of axial ligands (pyridine, 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane, triphenylphosphine). The complexes were tested as catalysts for the hydrogenation of styrene under $scCO_2$ conditions, and the anticancer activities of the perfluorobutyric acid derivatives were evaluated on human cancer cell lines A2780, Me300, A549 and HeLa.

2. Results and discussion

Dodecacarbonyltriruthenium ($Ru_3(CO)_{12}$) reacts with an excess of saturated fluorinated fatty acids, perfluorobutyric acid ($C_3F_7CO_2H$), or perfluorododecanoic acid ($C_{11}F_{23}CO_2H$), in THF under reflux and high pressure to yield a solution containing the THF intermediates $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3F_7)_2(THF)_2$ and $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}F_{23})_2(THF)_2$, respectively. These labile dinuclear THF intermediates further react with two-electron donors (L), such as pyridine (NC_5H_5) (**a**), 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane (PTA) (**b**), or triphenylphosphine (PPh_3) (**c**), to generate in reasonable yields the stable dinuclear complexes $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3F_7)_2(L)_2$ (**1a**, L = C_5H_5N; **1b**, L = PTA; **1c**, L = PPh_3) and $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}F_{23})_2(L)_2$ (**2a**, L = C_5H_5N; **2b**, L = PTA; **2c**, L = PPh_3) (figure 1).

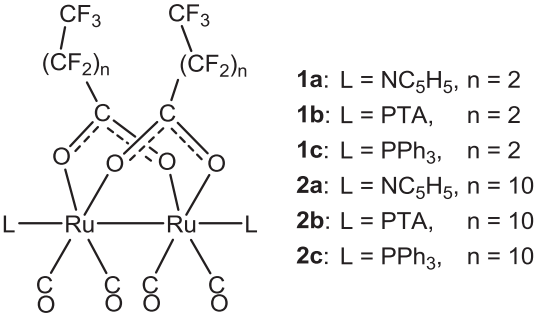


Figure 1. Molecular structures of the dinuclear complexes $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3F_7)_2(L)_2$ (**1**) and $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}F_{23})_2(L)_2$ (**2**).

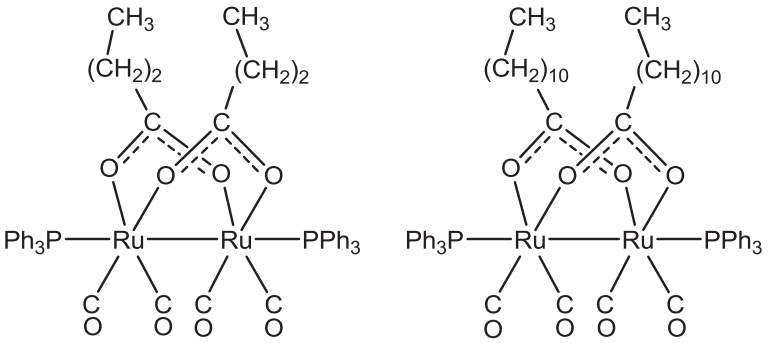


Figure 2. Molecular structures of the dinuclear complexes $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3H_7)_2(PPh_3)_2$ (**3**) and $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}H_{23})_2(PPh_3)_2$ (**4**).

The same synthetic method was used to prepare the parent complexes $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3H_7)_2(PPh_3)_2$ (**3**) and $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}H_{23})_2(PPh_3)_2$ (**4**), containing non-fluorinated alkyl chains and triphenylphosphine axial ligands (figure 2).

These sawhorse-type dinuclear tetracarbonyl complexes are air-stable yellow crystalline powders and have been completely characterized by infrared, NMR, mass spectrometry, and elemental analysis. All complexes exhibit in the $\nu_{(CO)}$ region of their infrared spectrum the characteristic three bands around 2000 cm^{-1} for the terminal carbonyl groups [8], and the strong and broad band for symmetric and asymmetric $\nu_{(OCO)}$ vibrations of the bridging carboxylato groups around 1660 cm^{-1}. In the non-fluorinated derivatives **3** and **4**, this asymmetric $\nu_{(OCO)}$ vibration band is observed at 1560 cm^{-1}. In **1** and **2**, all ^1H NMR spectra show the expected resonances for the axial ligands. For example, in **1a** and **2a**, the protons of the pyridines are at $\delta = 7.5$, 7.9, and 8.6 ppm in a 2:1:2 integration, while for the PTA complexes **1b** and **2b** two multiplets of equal integrations at 4.3 and 4.6 ppm are observed. In **1c**, **2c**, **3**, and **4**, three multiplets are observed in the aromatic region for the axial PPh_3, while in **3** and **4** additional signals corresponding to the alkyl chains are also observed. In the ^{19}F NMR spectra of **1**, three distinct signals are observed and easily assigned, while for **2** several additional signals corresponding to CF_2 groups appear between -120 and -125 ppm. For **1b** and **2b**, sharp singlets are observed at $\delta \approx -54$ ppm in their $^{31}P\{^1H\}$ NMR spectra, while in **1c**, **2c**, **3**, and **4** a sharp singlet appears at $\delta \approx$ 15 ppm, both in accord with coordination of PTA and PPh_3 in the axial positions of sawhorse-type diruthenium tetracarbonyl complexes [9].

Crystals of **1a** and **3** were obtained by slow diffusion of pentane into a dichloromethane solution of the corresponding complex. The single-crystal structure analyses of **1a** and **3** show the $Ru_2(CO)_4$ sawhorse backbone with two pyridines (**1a**) or triphenylphosphines (**3**) in the axial positions and the carboxylato bridges in the equatorial positions (figure 3). The Ru–Ru distances [**1a**: 2.694(1) Å, **3**: 2.7477(5) Å] are in the range of a ruthenium–ruthenium single bond, as observed in analogous complexes [9]. The OCO bond angles of the carboxylato bridges [**1a**: 129.2(5)°, **3**: 125.3(3)°] differ only slightly from those observed in other $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CR)_2L_2$ complexes [9]. In **3**, the Ru–P distance is 2.4524(8) Å, consistent with Ru–P distances observed in analogous complexes [9]. The remaining structural parameters appear to be normal for this type of complex [8]. Selected bond lengths and angles for **1a** and **3** are listed in the caption of figure 3.

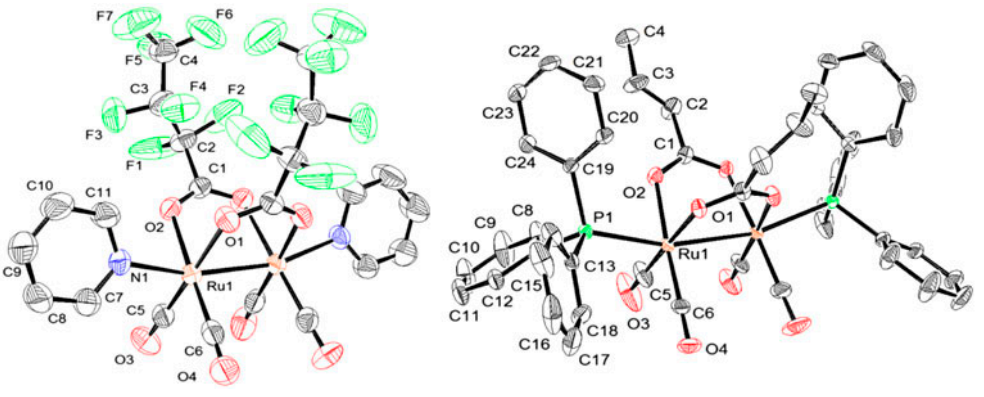
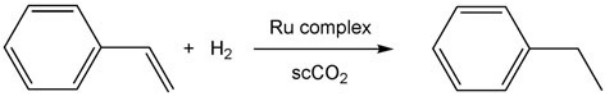


Figure 3. ORTEP representation of **1a** and **3** showing ellipsoids at the 35% probability level with hydrogens omitted for clarity (symmetry code: $i = -x, y, \frac{1}{2}-z$). Selected bond lengths (Å) and angles (°): **1a**, Ru1–Ru1^i 2.694(1), Ru1–N1 2.218(4), Ru1–O1 2.151(4), Ru1–O2 2.149(4), O1–C1–O2^i 129.2(5), N1–Ru1–Ru1^i 165.79 (13), O1–Ru1–O2 83.52(18); **3**, Ru1–Ru1^i 2.7477(5), Ru1–P1 2.4524(8), Ru1–O1 2.130(2), Ru1–O2 2.124(2), O1–C1–O2^i 125.3(3), P1–Ru1–Ru1^i 163.97(2), O1–Ru1–O2 87.66(10).

2.1. *Catalytic evaluation*

Several studies have reported the use of sawhorse-type diruthenium tetracarbonyl complexes as efficient catalysts for isomerization, hydrogenation, carbonylation, and coupling reactions. This aspect of the chemistry of sawhorse-type ruthenium complexes has been detailed in a recent review [8]. The preparation in good yields of such new complexes containing carboxylate ligands derived from saturated fluorinated fatty acids has motivated interest to evaluate their catalytic properties under supercritical conditions of carbon dioxide. Indeed, ligands modified with perfluoroalkyl ponytails are known to exhibit a great CO_2-philic character, and thus, they have been used to increase the solubility of homogeneous catalysts in $scCO_2$ [10]. In this preliminary catalytic study, selected sawhorse-type diruthenium complexes with short (**1b** and **1c**) and long (**2c**) fluorinated alkyl chains were considered as catalyst for the hydrogenation of styrene in $scCO_2$ conditions (equation (1)), and their activities were also compared with those obtained with non-fluorinated analogs (**3** and **4**) and $Ru_3(CO)_{12}$.



(1)

Catalytic data are summarized in table 1. The sawhorse-type diruthenium complexes are very poor catalysts for hydrogenation of styrene. The conversions of styrene into ethyl benzene are always below 15% regardless of the length of the fluorinated alkyl chains and the nature of the axial ligands (PPh_3 axial ligands seem to be the most suitable). In addition, the yield in ethyl benzene is not increased by supercritical conditions of carbon dioxide (entries 2 and 4). The incorporation of fluorinated alkyl chains leads finally to a moderate benefit. In previous studies, the addition of a co-solvent, such as methanol, has been reported to be helpful for increasing the catalytic activity of transition metal catalysts under $scCO_2$ conditions [11]. Herein, for the same complex (**1c**), we only observe a weak positive effect with the presence of methanol (entries 2 and 3). In fact, the best conversion

Table 1. Hydrogenation of styrene under supercritical carbon dioxide conditions.

Entry	Catalyst	Medium	Conversion (%)	Product
1	**3**	H_2[a]/CO_2[b]	07	Ethyl benzene
2	**1c**	H_2[a]/CO_2[b]	06	Ethyl benzene
3	**1c**	H_2[a]/CO_2[b]/CH_3OH[c]	10	Ethyl benzene
4	**1c**	H_2[a]	12	Ethyl benzene
5	**1b**	H_2[a]/CO_2[b]	04	Ethyl benzene
6	**4**	H_2[a]/CO_2[b]/CH_3OH[c]	03	Ethyl benzene
7	**2c**	H_2[a]/CO_2[b]/CH_3OH[c]	06	Ethyl benzene
8	**2c**	H_2[a]	06	Ethyl benzene
9	$Ru_3(CO)_{12}$	H_2[a]/CO_2[b]	22	Ethyl benzene
10	$Ru_3(CO)_{12}$	H_2[a]	71	Ethyl benzene
11	recovery of entry 10	H_2[a]	95	Ethyl benzene

Reaction conditions: Amount of catalyst = 0.02 mmol, substrate/catalyst = 500, T = 65 °C, reaction time = 16 h.
[a]P_{H2} = 10 bar. [b]P_{total} = 120 bar. [c]1 mL.

Table 2. Cytotoxicity of **1** after 72 h exposure of human cancer cells.

	IC_{50} [μM]		
Cell lines	**1a**	**1b**	**1c**
HeLa	199 ± 9	179 ± 1	178 ± 2
A549	190 ± 9	184 ± 5	190 ± 2
Me300	73 ± 1	61 ± 8	63 ± 1
A2780	124 ± 1	111 ± 1	129 ± 1

is obtained using $Ru_3(CO)_{12}$ as catalyst (entry 9). The conversion is further enhanced when the reaction is only carried out in the presence of H_2 (entries 10 and 11). However, the degradation of the catalyst is also observed, leading to a final black precipitate suspected to correspond to ruthenium nanoparticles [12]. Thus, the low activity recorded with these sawhorse-type diruthenium tetracarbonyl complexes can be rationalized by the stability and preservation of the starting ruthenium species in the $scCO_2$ reaction medium.

2.2. *Biological studies*

The cytotoxicity of **1** was evaluated *in vitro* on human cancer cell lines: HeLa cervix, A549 pulmonary, Me300 melanoma, A2780 ovarian. Unfortunately, the poor solubility of **2**, **3**, and **4** did not allow their assessment. Cells were exposed for 72 h to increasing concentrations of **1a**-**1c**, and their survival was determined using the MTT assay (MTT = 3-(4,5-dimethyl-2-thiazoyl)-2,5-diphenyltetrazolium bromide). In all cell lines, the complexes show similar cytotoxicity with an IC_{50} ranging from 60 to 200 μM depending on the cell line tested (table 2). These results suggest that the nature of the axial ligands plays only a minor role on the overall cytotoxicity. Among the cell lines tested, Me300 melanoma cells were the most sensitive cells to all complexes. This is important since melanoma tumors are aggressive and resistant to common chemotherapeutic treatments [13].

3. Conclusion

A series of sawhorse-type complexes containing carboxylates derived from saturated fluorinated fatty acids have been prepared and evaluated as catalysts for the hydrogenation of

styrene under supercritical CO_2 condition and as anticancer agents on various human cancer cell lines. Despite the lack of catalytic activity, the dinuclear complexes $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3F_7)_2(L)_2$ (**1**) show moderate cytotoxicity *in vitro*. The observed cytotoxicity on Me300 melanoma cells is encouraging, and further investigation on the biological potential of these perfluorinated sawhorse-type diruthenium tetracarbonyl complexes is in progress.

4. Experimental

4.1. *General remarks*

All manipulations were carried out under a nitrogen atmosphere. Organic solvents were degassed and saturated with nitrogen prior to use. $Ru_3(CO)_{12}$ was prepared according to published methods [14], while butyric acid, perfluorbutyric acid, dodecanoic acid, perfluorododecanoic acid, pyridine, 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane, and triphenylphosphine were purchased from Sigma-Aldrich and used as received. NMR spectra were recorded on a Bruker 400 MHz spectrometer. IR spectra were recorded as KBr pellets on a PerkinElmer 1720x FT-IR spectrometer (4000–400 cm^{-1}). Electro-spray mass spectra were obtained in positive-ion mode with an LCQ Finnigan mass spectrometer. Elemental analyzes were performed by the Mikroelementarisches Laboratorium, ETH Zürich (Switzerland). Column chromatography was performed using silica gel 60 (63–200, 60 Å, Brunschwig).

4.2. *Preparation of sawhorse-type diruthenium tetracarbonyl complexes*

A solution of $Ru_3(CO)_{12}$ and three equivalents of the appropriate fluorinated fatty acids in dry tetrahydrofuran (20 mL) was heated at 110 °C in a pressure Schlenk tube for 15 h. Then, addition of three equivalents of the axial ligand [(L = NC_5H_5); (L = PTA); (L = PPh_3)] under stirring at room temperature for 2 h afforded the final products. After evaporation of the tetrahydrofuran, the complexes were isolated from the residue by precipitation from dichloromethane/pentane. In order to improve the purity, the crude products were subjected to chromatography on silica gel using a dichloromethane/pentane mixture as eluent (for **1b** and **2b** a dichloromethane/ethanol mixture was used), and the solid obtained was dried under vacuum.

$Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3F_7)_2(NC_5H_5)_2$ (**1a**)
Yield: 200 mg (71%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.46$–7.50 (m, 4 H, H_{C5H5N}), 7.90 (tt, 2 H, $^3J = 8$ Hz, $^4J = 2$ Hz, H_{C5H5N}), 8.62–8.64 (m, 4 H, H_{C5H5N}). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) $\delta = -81.7$ (6 F), -118.8 (4 F), -128.1 (4 F). IR (KBr, cm^{-1}) $\nu_{(OCO)}$ 1650.9 vs. $\nu_{(CO)}$ 1967.4 vs. (ν_{CO}) 1992.7 m, (ν_{CO}) 2041.6 vs. ESI-MS (positive mode): $m/z = 935.58$ $[M + 2\ H_2O + H]^+$. Anal. Calcd for $C_{22}H_{10}N_2O_8F_{14}Ru_2 \cdot C_5H_{12}$ (970.59) C 33.41, H 2.28, N 2.89; Found: C 33.69, H 1.88, N 3.06%.

$Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3F_7)_2(PTA)_2$ (**1b**)
Yield: 97 mg (59%) ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.25$ (br-m, 12 H, H_{PTA}), 4.62 (m, 12 H, H_{PTA}). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) $\delta = -54.68$ ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) $\delta = -81.7$ (6 F), -118.6 (4 F), -128.4 (4 F). IR (KBr, cm^{-1}) $\nu_{(OCO)}$ 1663.0 vs. $\nu_{(CO)}$ 1967.8 vs. (ν_{CO}) 1991.6 m, (ν_{CO}) 2037.4 vs. ESI-MS (positive mode): $m/z = 1055.90$ $[M + H]^+$. Anal. Calcd for $C_{24}H_{24}N_6O_8F_{14}P_2Ru_2 \cdot C_2H_5OH \cdot CH_2Cl_2$ (1365.45) C 27.35, H 2.72, N 7.09; Found: C 27.62, H 2.66, N 6.63%.

$Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3F_7)_2(PPh_3)_2$ (**1c**)
Yield: 150 mg (76%) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$–7.45 (m, 18 H, H_{PPh3}), 7.48–7.55 (m, 12 H, H_{PPh3}). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) $\delta = 15.23$ ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) $\delta = -82.0$ (6 F), -118.6 (4 F), -128.3 (4 F). IR (KBr, cm^{-1}) $\nu_{(OCO)}$ 1658.9 vs. $\nu_{(CO)}$ 1966.4 vs. (ν_{CO}) 1991.1 m, (ν_{CO}) 2030.9 vs. ESI-MS (positive mode): *m/z* = 1183.96 $[M - 3\ CO + H]^+$. Anal. Calcd for $C_{48}H_{30}O_8F_{14}P_2Ru_2$ (1264.81) C 45.58, H 2.39; Found: C 45.84, H 2.56%.

$Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}F_{23})_2(NC_5H_5)_2$ (**2a**)
Yield: 153 mg (67%) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.45$–7.49 (m, 4 H, H_{C5H5N}), 7.90 (tt, 2 H, $^3J = 8$ Hz, $^4J = 2$ Hz, H_{C5H5N}), 8.62–8.64 (m, 4 H, H_{C5H5N}). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) $\delta = -81.8$ (6 F), -117.8 (4 F), -122.5 (4 F), -122.9 (20 F), -123.8 (8 F), -127.2 (4 F). IR (KBr, cm^{-1}) $\nu_{(OCO)}$ 1667.4 vs. $\nu_{(CO)}$ 1964.0 vs. (ν_{CO}) 1984.2 m, (ν_{CO}) 2046.5 vs. ESI-MS (positive mode): *m/z* = 980.97 $[M - C_{12}F_{23}O_2 - C_5H_5N - CO + H]^+$. Anal. Calcd for $C_{38}H_{10}F_{46}N_2O_8Ru_2$ (1698.56) C 26.87, H 0.59, N 1.65; Found: C 26.58, H 0.72, N 2.04%.

$Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}F_{23})_2(PTA)_2$ (**2b**)
Yield: 56 mg (26%) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.25$ (br-m, 12 H, H_{PTA}), 4.62 (m, 12 H, H_{PTA}). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) $\delta = -54.70$ ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) $\delta = -81.8$ (6 F), -117.6 (4 F), -122.6 (4 F), -122.8 (16 F), -123.0 (4 F), -123.8 (4 F), -124.0 (4 F), -127.2 (4 F). IR (KBr, cm^{-1}) $\nu_{(OCO)}$ 1662.3 vs. $\nu_{(CO)}$ 1960.6 vs. (ν_{CO}) 1982.5 m, (ν_{CO}) 2038.0 vs. ESI-MS (positive mode): *m/z* = 1856.77 $[M + H]^+$. Anal. Calcd for $C_{40}H_{24}N_6O_8F_{46}P_2Ru_2{\cdot}C_2H_5OH$ (1900.74) C 26.54, H 1.59, N 4.42; Found: C 26.59, H 1.57, N 4.31%.

$Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}F_{23})_2(PPh_3)_2$ (**2c**)
Yield: 60 mg (54%) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.44 (m, 18 H, H_{PPh3}), 7.46–7.50 (m, 12 H, H_{PPh3}). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) $\delta = 15.24$ ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) $\delta = -81.8$ (6 F), -117.57 (4 F), -122.9 (24 F), -123.8 (8 F), -127.2 (4 F). IR (KBr, cm^{-1}) $\nu_{(OCO)}$ 1658.9 vs. $\nu_{(CO)}$ 1966.8 vs. (ν_{CO}) 1991.3 m, (ν_{CO}) 2031.9 vs. ESI-MS (positive mode): *m/z* = 1692.86 $[M - PPh_3 - 4\ CO + H]^+$. Anal. Calcd for $C_{64}H_{30}F_{46}O_8P_2Ru_2$ (2064.93) C 37.23, H 1.46; Found: C 37.19, H 1.55%.

$Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_3H_7)_2(PPh_3)_2$ (**3**)
Yield: 80 mg (52%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.60$ (t, 6 H, $^3J = 7$ Hz, CH_3), 1.10–1.17 (m, 4 H, CH_2), 1.92 (t, 4 H, $^3J = 7$ Hz, CH_2), 7.36–7.41 (m, 18 H, H_{PPh3}), 7.54–7.57 (m, 12 H, H_{PPh3}). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) $\delta = 14.11$ ppm. IR (KBr, cm^{-1}) $\nu_{(OCO)}$ 1564.1 vs. $\nu_{(CO)}$ 1941.1 vs. (ν_{CO}) 1975.9 m, (ν_{CO}) 2018.4 vs. ESI-MS (positive mode): *m/z* = 987.04 $[M - CO + H]^+$. Anal. Calcd for $C_{48}H_{44}O_8P_2Ru_2$ (1012.95) C 56.91, H 4.38; Found: C 56.41, H 4.40%.

$Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{11}H_{23})_2(PPh_3)_2$ (**4**)
Yield: 108 mg (56%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (t, 6 H, $^3J = 7$ Hz, CH_3), 1.00–1.11 (m, 16 H, CH_2), 1.22–1.29 (m, 20 H, CH_2), 1.92 (t, 4 H, $^3J = 7$ Hz, CH_2) 7.36–7.40 (m, 18 H, H_{PPh3}), 7.54–7.55 (m, 12 H, H_{PPh3}). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) $\delta = 14.21$ ppm. IR (KBr, cm^{-1}) $\nu_{(OCO)}$ 1567.6 vs. $\nu_{(CO)}$ 1952.4 vs. (ν_{CO}) 1981.5 m, (ν_{CO}) 2031.1 vs. ESI-MS (positive mode): *m/z* = 1238.33 $[M]^+$. Anal. Calcd for $C_{64}H_{76}O_8P_2Ru_2$ (1237.37) C 62.12, H 6.19; Found: C 62.00, H 6.12%.

4.3. *Catalytic experiments*

4.3.1. Safety warning. Experiments involving pressurized gasses can be hazardous and must only be conducted with suitable equipment and following appropriate safety conditions [15].

General procedure for hydrogenation of styrene in supercritical carbon dioxide: the reaction was carried out in a 125 mL stainless steel reactor equipped with a magnetic stirrer. The reactor was purged with argon prior to the introduction of Ru-catalyst and styrene (amount of catalyst = 0.02 mmol, substrate/catalyst ratio = 500) via a cannula transfer. When methanol was used as co-solvent, catalysts were prior dissolved in 1 mL of degassed methanol. After introduction of H_2 (10 bar), CO_2 was admitted, leading to a total reaction pressure of 120 bar. The reaction temperature was controlled by an internal thermocouple. After a reaction time of 16 h, the reactor was cooled down to 0 °C, the pressure was gently released, and the liquid phase was transferred to a Schlenk tube. Trap-to-trap distillation under *vacuum* at ambient temperature allowed separation of volatile compounds that were quantitatively analyzed by GC (Thermo Scientific FOCUS GC, TR-Wax 30 m capillary column, FID detector).

4.4. *Cell culture*

Human lung (A549) and cervix (HeLa) cancer cells were obtained from the American Tissue Type Culture Collection (Manassas, VA, USA). A2780s ovarian cancer cells were obtained from the ECACC (Salisbury, UK). Human Me300 melanoma cells were kindly provided by D. Rimoldi, Ludwig Institute of Cancer Research, Lausanne branch. HeLa and A549 cells were routinely grown in Dulbecco's modified Eagle's medium containing 4.5 g/L glucose, while A2780 and Me300 were grown in RPMI 1640 medium both supplemented with 10% heat-inactivated fetal calf serum and antibiotics (all from Gibco, Basel, Switzerland).

4.5. *Evaluation of the cytotoxicity of the sawhorse-type diruthenium tetracarbonyl complexes*

Cells in 96-well plates (Costar, Corning, USA) were exposed at 37 °C to increasing concentrations of complexes in complete culture medium for 72 h (5 mM stock solution in DMSO). After washing with phosphate-buffered saline (PBS), the supernatants were replaced with fresh medium and cell survival was measured using the 3-(4,5-dimethyl-2-thiazoyl)-2,5-diphenyltetrazolium bromide (MTT) test. MTT (Merck) was added at 250 μg/mL and incubation was continued for 2 h, as previously described [16]. Then, the cell culture supernatants were removed, the cell layer was dissolved in isopropanol/0.04 N HCl, and the absorbance at 540 nm was measured in a 96-well multiwell-plate reader (iEMS Reader MF, Labsystems, Bioconcept, Switzerland) and compared with the values of control cells incubated without complexes. Experiments were conducted in triplicate wells and repeated three times.

4.6. *Single-crystal X-ray structure analyses*

Crystals of **1a** and **3**, prepared by slow diffusion of pentane in a dichloromethane solution of **1a** and **3**, were mounted on a Stoe Image Plate Diffraction system equipped with a ϕ

Table 3. Crystallographic and structure refinement parameters for **1a** and **3**.

	1a	**3**
Chemical formula	$C_{22}H_{10}F_{14}N_2O_8Ru_2$	$C_{48}H_{44}O_8P_2Ru_2$
Formula weight	898.46	1012.91
Crystal system	Monoclinic	Monoclinic
Space group	*C* 2/*c* (No. 15)	*C* 2/*c* (No. 15)
Crystal color and shape	Yellow block	Yellow block
Crystal size	0.24 × 0.20 × 0.17	0.25 × 0.23 × 0.18
a (Å)	15.630(3)	24.7037(11)
b (Å)	17.900(4)	9.5100(3)
c (Å)	10.860(2)	18.9324(9)
β (°)	106.41(3)	102.530(4)
V (Å^3)	2914.6(10)	4341.9(3)
Z	4	4
T (K)	293(2)	173(2)
D_c (g cm^{-3})	2.048	1.550
μ (mm^{-1})	1.175	0.824
Scan range (°)	$2.28 < \theta < 26.10$	$1.69 < \theta < 29.22$
Unique reflections	2797	5854
Observed refls. [$I > 2\sigma(I)$]	1918	4532
R_{int}	0.0441	0.0842
Final *R* indices [$I > 2\sigma(I)$]*	0.0440, wR_2 0.1231	0.0491, wR_2 0.0876
R indices (all data)	0.0616, wR_2 0.1304	0.0734, wR_2 0.0944
Goodness-of-fit	0.998	1.044
Max, Min $\Delta\rho$/e (Å^{-3})	1.053, −0.531	0.896, −0.799

*Structures were refined on F_o^2: $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma w(F_o^2)^2]^{1/2}$, where $w^{-1} = [\Sigma(F_o^2) + (aP)^2 + bP]$ and $P = [\max(F_o^2, 0) + 2F_c^2]/3$.

circle goniometer using Mo-Kα graphite monochromated radiation (λ = 0.71073 Å) with ϕ range 0–200°. The structures were solved by direct methods using SHELXS-97, while the refinement and all further calculations were carried out using SHELXL-97 [17]. Hydrogens were included in calculated positions and treated as riding atoms using the SHELXL default parameters. The non-H atoms were refined anisotropically using weighted full-matrix least-squares on F^2. In **3**, the two butyryl chains were disordered, pointing away from each other, with a 50:50 occupancy ratio. Crystallographic details are summarized in table 3. figure 3 was drawn with ORTEP [18].

Supplementary material

CCDC-914514 **1a** and 914515 **3** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internet.)+441223/336033; Email: deposit@ccdc.cam.ac.uk].

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