A General Strategy to Add Diversity to Ruthenium Arene Complexes with Bioactive Organic Compounds via a Coordinated (4-Hydroxyphenyl)diphenylphosphine Ligand

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Supporting Information

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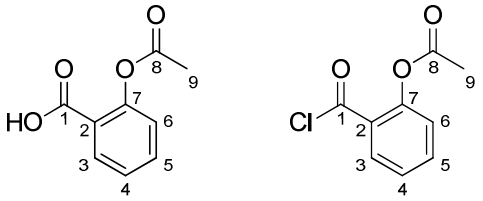
General experimental details

$RuCl_3 \cdot 3H_2O$ (99.9%) was purchased from Strem and the organic reactants were obtained from Alfa Aesar, Sigma Aldrich or TCI Europe and were of the highest purity available. The following reagents were stored under nitrogen or argon as received: aspirin (ASP-CO_2H), ethacrynic acid (EA-CO_2H), 4-bromophenol (under protection from the light), *tert*-butyldimethylsilyl chloride (TBDMSCl), chlorodiphenylphosphine, oxalyl chloride (4°C), butyl lithium (2.5 M in hexanes; 4°C), tetrabutylammonium fluoride (TBAF, 1 M in THF; 4°C), triethylamine and ethyl(diisopropylamino)carboxydiimide hydrochloride (EDCI·HCl; –20°C). Tributylamine was distilled from BaO and stored under nitrogen. $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ was prepared according to a literature method.[1] All reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques and solvents distilled from appropriate drying agents. Once isolated, *p*-$C_6H_4Br(OSiMe_2{}^tBu)$, $PPh_2(4\text{-}C_6H_4OSiMe_2{}^tBu)$, $PPh_2(4\text{-}C_6H_4OH)$, **L2** and **L4** were stored under nitrogen, all of the other products being air stable. Silica gel (Merck, 70-230 mesh) was dried at 150 °C overnight and stored under nitrogen. NMR spectra were recorded at 298 K on a Bruker Avance II DRX400 instrument equipped with a BBFO broadband probe. Chemical shifts (expressed in parts per million) are referenced to the residual solvent peaks (^1H, ^{13}C) or to external standard (^{31}P to 85% H_3PO_4). Spectra were assigned with the assistance of $^1H\{^{31}P\}$, DEPT-135 spectra and ^1H-^1H (COSY), ^1H-^{13}C (*gs*-HSQC and *gs*-HMBC) correlation experiments.[2] Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer equipped with a UATR sampling accessory. Infrared spectra of CH_2Cl_2 solutions were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with a CaF_2 liquid transmission cell. Carbon, hydrogen and nitrogen analysis was performed on a Carlo Erba mod. 1106 instrument. Melting points were determined on a STMP3 Stuart scientific instrument with a capillary apparatus.

IR and NMR spectra of bioactive acids and their corresponding acyl chlorides

Aspirin (ASP-CO_2H) and Aspirin acyl chloride (ASP-COCl)

Chart S1. Structures of ASP-CO_2H (left) and ASP-COCl (right) (numbering refers to carbon atoms).

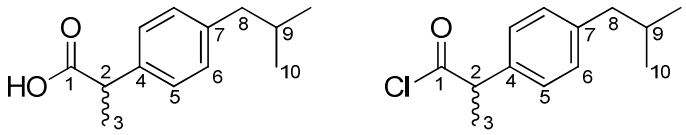


ASP-CO_2H. Colourless solid. IR (solid state): $\tilde{\upsilon}$/cm^{-1} = 3200-2700w-br, 2869w, 2832w, 2697w, 2658w, 2586w, 2545w, 1750s ($\nu_{C8=O}$), 1681s ($\nu_{C1=O}$), 1605s, 1575w, 1483w, 1456s, 1436w, 1418m, 1369m, 1304s, 1291s, 1258m, 1218s, 1184s, 1135m, 1093m, 1086m-sh, 1038m, 1012m, 970m, 915s, 885m-sh, 839s, 803s, 789m, 753s, 704s, 666m. IR (CH_2Cl_2): $\tilde{\upsilon}$/cm^{-1} = 3625w, 1770s ($\nu_{C8=O}$), 1738m ($\nu_{C1=O}$), 1701s, 1608m, 1487sh, 1370m, 1222s-sh, 1189s, 1086w, 1068w, 1017m. ^{1}H NMR ($CDCl_3$): δ/ppm = 10.7 (br, 1H, OH), 8.13 (d, $^3J_{HH}$ = 7.7 Hz, 1H, C3-H), 7.63 (t, $^3J_{HH}$ = 7.6 Hz, 1H, C5-H), 7.36 (t, $^3J_{HH}$ = 7.6 Hz, 1H, C4-H), 7.14 (d, $^3J_{HH}$ = 8.0 Hz, 1H, C6-H), 2.35 (s, 3H, C9-H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ/ppm = 170.3 (C1 or C8), 169.9 (C1 or C8), 151.4 (C7), 135.0 (C5), 132.7 (C3), 126.3 (C4), 124.1 (C6), 122.4 (C2), 21.1 (C9).

ASP-COCl. Colourless solid. IR (CH_2Cl_2): $\tilde{\upsilon}$/cm^{-1} = 1780s-sh ($\nu_{C1=O}$), 1768s ($\nu_{C8=O}$), 1675w, 1603m, 1577w, 1477m-sh, 1451m-sh, 1371m, 1123m-sh, 1193s, 1162m, 1115w, 1101w. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.25 (d, $^3J_{HH}$ = 7.9 Hz, 1H, C3-H), 7.70 (m, 1H, C5-H), 7.43 (m, 1H, C4-H), 7.18 (d, $^3J_{HH}$ = 7.9 Hz, 1H, C6-H), 2.35 (s, 3H, C9-H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ/ppm = 169.2 (C8), 164.7 (C1), 150.4 (C7), 136.1 (C5), 134.4 (C3), 126.6 (C4), 126.5 (C6), 124.4 (C2), 20.8 (C9) ppm.

Ibuprofen (IBU-CO_2H) and Ibuprofen acyl chloride (IBU-COCl)

Chart S2. Structures of IBU-CO_2H (left) and IBU-COCl (right) (numbering refers to carbon atoms).



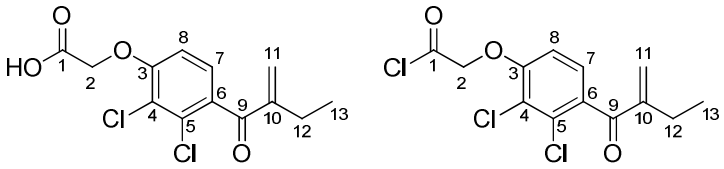
IBU-CO_2H. Crystalline colourless solid. IR (solid state): $\tilde{\upsilon}$/cm^{-1} = 3090w, 3045w, 3020m, 2992m, 2980m, 2954m, 2922m, 2869m, 2728w, 2632w, 2602w, 2542w, 1712s ($\nu_{C=O}$), 1507m, 1462m,

1450m, 1442w, 1418s, 1379m, 1365w, 1329m-sh, 1321m, 1268m, 1230s, 1183s, 1168m, 1123m, 1092w, 1073m, 1008m, 970w, 935m, 879w, 865s, 849m, 834w, 820w, 779s, 747w, 691w, 667s. IR (CH_2Cl_2): $\tilde{\upsilon}/cm^{-1}$ = 2870m, 1747w and 1708s ($\nu_{C=O}$), 1513w. ^1H NMR ($CDCl_3$): δ/ppm = 10.5 (br, 1H, OH), 7.23 (d, $^3J_{HH}$ = 8.0 Hz, 2H, C5-H), 7.11 (d, $^3J_{HH}$ = 8.0 Hz, 2H, C6-H), 3.71 (q, $^3J_{HH}$ = 7.2 Hz, 1H, C2-H), 2.45 (d, $^3J_{HH}$ = 7.2 Hz, 2H, C8-H), 1.85 (non, $^3J_{HH}$ = 6.7 Hz, 1H, C9-H), 1.51 (d, $^3J_{HH}$ = 7.2 Hz, 3H, C3-H), 0.90 (d, $^3J_{HH}$ = 6.6 Hz, 6H, C10-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 180.9 (C1), 141.0 (C7), 137.1 (C4), 129.5 (C6), 127.4 (C5), 45.2 (C8), 45.1 (C2), 30.3 (C9), 22.5 (C10), 18.2 (C3).

IBU-COCl. Colourless liquid. IR (CH_2Cl_2): $\tilde{\upsilon}/cm^{-1}$ = 1785s ($\nu_{C=O}$), 1513w.

Ethacrynic acid (EA-CO_2H) and Ethacrynic acyl chloride (EA-COCl)

Chart S3. Structures of EA-CO_2H (left) and EA-COCl (right) (numbering refers to carbon atoms).

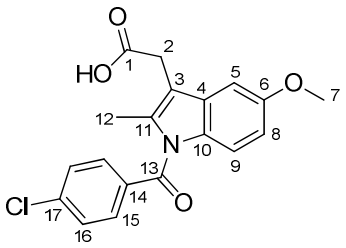
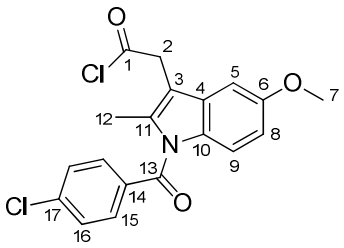


EA-CO_2H. Colourless solid. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3300-2550w-br, 2968m, 2938w, 2882w, 1724s ($\nu_{C1=O}$), 1671s and 1661s ($\nu_{C9=O}$), 1622w, 1585s ($\nu_{C10=C11}$), 1556w-sh, 1474s, 1455m-sh, 1424m, 1387m, 1370m, 1360m, 1340w, 1307m-sh, 1279s, 1265s, 1249s, 1205s, 1124m, 1078s, 1005m, 956m-sh, 945s, 930m, 909s, 849w, 825w, 799s, 768s, 736w, 721m, 690m. IR (CH_2Cl_2): $\tilde{\upsilon}/cm^{-1}$ = 3500-3400w-br, 1780m, 1761m and 1741s ($\nu_{C1=O}$), 1667s ($\nu_{C9=O}$), 1588s ($\nu_{C10=C11}$), 1470s-sh, 1385m-sh, 1340w, 1123w, 1083s. ^1H NMR ($CDCl_3$): δ/ppm = 7.75 (s-br, 1H, OH), 7.15 (d, $^3J_{HH}$ = 5.3 Hz, 1H, C7-H), 6.81 (d, $^3J_{HH}$ = 4.9 Hz, 1H, C8-H), 5.95 (s, 1H, C11-H), 5.60 (s, 1H, C11-H'), 4.80 (s, 2H, C2-H), 2.46 (q, $^3J_{HH}$ = 7.1 Hz, 2H, C12-H), 1.14 (t, $^3J_{HH}$ = 7.3 Hz, 3H, C13-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 196.2 (C9), 172.6 (C1), 155.2 (C3), 150.3 (C10), 134.2 (C4), 131.7 (C5), 129.1 (C11), 127.0 (C7), 123.5 (C6), 111.0 (C8), 65.9 (C2), 23.5 (C12), 12.5 (C13).

EA-COCl. Pale yellow liquid. IR (CH_2Cl_2): $\tilde{\upsilon}/cm^{-1}$ = 1848m and 1806s ($\nu_{C1=O}$), 1668s ($\nu_{C9=O}$), 1587s ($\nu_{C10=C11}$), 1468s-sh, 1385m-sh, 1340w, 1216m-sh, 1127w, 1088m, 1049m.

Indomethacin (IM-CO_2H) and Indomethacin acyl chloride (IM-COCl)

Chart S4. Structures of IM-CO_2H (left) and IM-COCl (right) (numbering refers to carbon atoms).

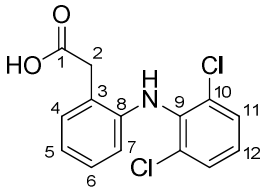
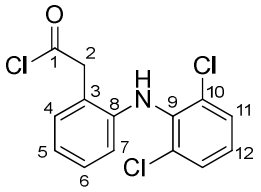



IM-CO_2H. Colourless solid. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3024w, 2967w, 2928w, 2832w, 1713s ($\nu_{C1=O}$), 1689s ($\nu_{C13=O}$), 1614w, 1603w, 1588w, 1478m, 1455m, 1426w, 1412w, 1396w, 1371m-sh, 1359m, 1306s, 1290m-sh, 1261w, 1233s-sh, 1222s, 1189m, 1148m, 1085m, 1067s, 1028m, 1012w, 925w, 906w, 854w, 838m, 832s, 769w, 752s, 736w, 702w, 691w, 658w. IR (CH_2Cl_2): $\tilde{\upsilon}/cm^{-1}$ = 1713s ($\nu_{C1=O}$), 1685s ($\nu_{C13=O}$), 1595m, 1479s-sh, 1369m, 1358m, 1315s-sh, 1090m, 1068w, 1036w, 1015w. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.66 (d, $^3J_{HH}$ = 8.5 Hz, 2H, C15-H), 7.47 (d, $^3J_{HH}$ = 8.5 Hz, 2H, C16-H), 6.95 (d, $^4J_{HH}$ = 2.4 Hz, 1H, C5-H), 6.85 (d, $^3J_{HH}$ = 9.0 Hz, 1H, C9-H), 6.67 (dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, C8-H), 3.82 (s, 3H, C7-H), 3.69 (s, 2H, C2-H), 2.38 (s, 3H, C12-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 176.8 (C1), 168.4 (C13), 156.2 (C6), 139.5 (C17), 136.4 (C4), 133.9 (C14), 131.3 (C15), 130.9 (C10 or C11), 130.6 (C10 or C11), 129.3 (C16), 115.1 (C9), 111.9 (C3), 111.8 (C8), 101.4 (C5), 55.9 (C7), 30.1 (C2), 13.4 (C12).

IM-COCl. Pale yellow solid. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3097w, 3072w, 3060w, 3038w, 3000w, 2967w, 2941w, 2903w, 2835w, 1790s ($\nu_{C1=O}$), 1683s ($\nu_{C13=O}$), 1621w, 1597m, 1488w-sh, 1477m, 1465s, 1442m, 1434m, 1402w, 1371w, 1349s, 1324s, 1291m, 1260m, 1229s, 1213s, 1192w, 1178w, 1153s, 1139m, 1085s, 1066s, 1034s, 1013s, 991s, 947s, 898m, 850m, 825m, 800s, 789s, 755s, 740m, 714m, 691s, 657w. IR (CH_2Cl_2): $\tilde{\upsilon}/cm^{-1}$ = 1795m ($\nu_{C1=O}$), 1687s ($\nu_{C13=O}$), 1595m, 1479s-sh, 1371m, 1357m, 1315s-sh, 1091s, 1069w, 1037w, 1015m.

Diclofenac (DF-CO_2H) and Diclofenac acyl chloride (DF-COCl)

Chart S5. Structures of DF-CO_2H (left) and DF-COCl (right) (numbering refers to carbon atoms).

DF-CO_2H. Colourless solid. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3500-3100w-br, 3322m (ν_{NH}), 3071w, 3030w, 2971m, 2927w, 2882w, 2724w, 2636w, 2609w, 2584w, 2562w, 1690s ($\nu_{C=O}$), 1587m, 1577m, 1568m, 1506s, 1495m-sh, 1479m, 1452s, 1421s, 1412s, 1380m, 1321m, 1303s, 1281s, 1272s, 1199m, 1158s, 1130m, 1092m, 1070w, 1045w, 936s, 890w, 861m, 835m, 817w, 775m,

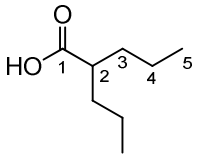
765s, 751m, 739s, 709s. ^{1}H NMR (Acetone-d^{6}): δ/ppm = 10.8 (br, 1H, OH), 7.46 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H, C11-H), 7.29 (d, $^{3}J_{HH}$ = 7.3 Hz, 1H, C4-H), 7.20 (s, 1H, NH), 7.17–7.08 (m, 2H, C6-H and C12-H), 6.94 (t, $^{3}J_{HH}$ = 7.3 Hz, 1H, C5-H), 6.47 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, C7-H), 3.82 (s, 2H, C2-H). ^{13}C{^{1}H} NMR (Acetone-d^{6}): δ/ppm = 173.9 (C1), 143.9 (C8), 138.8 (C9), 131.8 (C4), 130.4 (C10), 129.9 (C11), 128.6 (C6), 125.8 (C3), 125.6 (C12), 122.6 (C5), 118.3 (C7), 38.6 (C2).

DF-COCl. In a 50 mL schlenk tube, $(COCl)_2$ (0.10 mL, 1.2 mmol) was added to a solution of DF-CO_2H (73 mg, 0.25 mmol) in CH_2Cl_2 (6 mL). The resulting colourless suspension was stirred at room temperature for 1.5 hours and the progress of reaction was monitored by TLC. Therefore, volatiles were carefully removed in vacuo (60°C) and a pale yellow solid was obtained. IR (solid state): $\tilde{\upsilon}$/cm^{-1} = 1731s ($\nu_{C=O}$), 1613m, 1563w, 1489m, 1461m-sh, 1455m, 1436m, 1361m, 1317w, 1302m, 1239m, 1205w, 1191m, 1171m, 1148m, 951m, 859w, 781s, 748s, 670m. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.51 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, C11-H), 7.40-7.32 (m, 2H, C4-H and C6-H), 7.21 (t, $^{3}J_{HH}$ = 7.6 Hz, 1H, C12-H), 7.10 (t, $^{3}J_{HH}$ = 7.4 Hz, 1H, C5-H), 6.41 (d, $^{3}J_{HH}$ = 7.7 Hz, 1H, C7-H), 3.78 (s, 2H, C2-H). ^{13}C NMR ($CDCl_3$): δ/ppm = 173.7 (C1), 143.4 (C8), 135.6 (C9), 130.9 (C4), 130.6 (C10), 129.1 (C11), 128.0 (C6), 124.9 (C12), 124.4 (C3), 123.2 (C5), 109.2 (C7), 35.8 (C2).

Reactions of **1** with DF-COCl and Et_3N under different experimental conditions led to mixtures of products that did not contain **6**.

Valproic acid (VP-CO_2H)

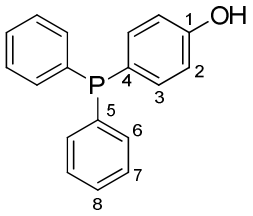
Chart S6. Structure of VP-CO_2H (numbering refers to carbon atoms).



Colourless liquid. IR (liquid film): $\tilde{\upsilon}$/cm^{-1} = 3300-2800w-br, 2959m, 2935m, 2874m, 1702s ($\nu_{C=O}$), 1466w, 1416w, 1381w, 1344w, 1290w, 1279w, 1251m, 1213m, 1153w, 1108w, 941w, 820w, 770w-sh, 748w. ^{1}H NMR ($CDCl_3$): δ/ppm = 11.4 (s-br, 1H, OH), 2.37 (m, *J* = 9.2, 5.2 Hz, 1H, C2-H), 1.68–1.55 (m, 2H) and 1.50–1.40 (m, 2H, C3-H), 1.40–1.27 (m, 4H, C4-H), 0.91 (t, $^{3}J_{HH}$ = 7.2 Hz, 6H, C5-H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ/ppm =183.6 (C1), 45.3 (C2), 34.5 (C3), 20.7 (C4), 14.1 (C5)

Synthesis of $PPh_2(4\text{-}C_6H_4OH)$, L1

Chart S7. Structure of $PPh_2(4\text{-}C_6H_4OH)$ (numbering refers to carbon atoms).



The three-step procedure for the synthesis of $PPh_2(4\text{-}C_6H_4OH)$ was adapted from the literature.

Step 1.[3] In a 100 mL Schlenk tube, Et_3N (2.0 mL, 14 mmol) and TBDMSCl (2.36 g, 15.7 mmol) were added to a solution of 4-bromophenol (2.20 g, 12.7 mmol) in CH_2Cl_2 (20 mL). The pale yellow suspension was stirred at room temperature for 18 hours under protection from the light and the progress of reaction was monitored by TLC. The resulting mixture (pale yellow solution/colourless suspension) was extracted with H_2O (50 mL), the organic phase was separated and volatiles removed in vacuo. The residue was redissolved in hexane (15 mL) and extracted with H_2O (2x50 mL). The organic phase was dried with Na_2SO_4, filtered and volatiles were removed in vacuo (40°C). The compound $p\text{-}C_6H_4Br(OSiMe_2{}^tBu)$ was obtained as a colourless liquid. Yield: 3.49 g, 96%. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.32 (d, $^3J_{HH}$ = 8.6 Hz, 2H, CH), 6.71 (d, $^3J_{HH}$ = 8.6 Hz, 2H, CH), 0.97 (s, 9H, C*Me*$_3$), 0.18 (s, 6H, Si*Me*$_2$).

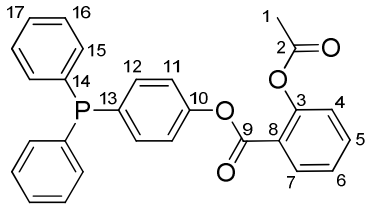
Step 2.[4] In a 100 mL schlenk tube, ^{n}BuLi (2.5 M in hexanes; 5.0 mL, 12.5 mmol) was slowly added (15 min) to a solution of $p\text{-}C_6H_4Br(OSiMe_2{}^tBu)$ (3.49 g, 12.1 mmol) in Et_2O (35 mL) at 0°C under vigorous stirring. The resulting pale yellow solution was allowed to heat to room temperature and stirred for 1.5 hours then Ph_2PCl (2.4 mL, 13 mmol) was slowly added (15 min) at 0°C. The resulting suspension was allowed to heat to room temperature and stirred for 18 hours. Therefore the reaction mixture was loaded on top of a SiO_2 column (h 4.5, d 4.5 cm) and eluted with Et_2O (80 mL). Volatiles were removed in vacuo and $PPh_2(4\text{-}C_6H_4OSiMe_2{}^tBu)$ was obtained as a colourless solid. Yield: 3.82 g, 80%. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.38 (s, 10H, Ph_2), 7.32 (*pseudo*-t, $^3J_{HH}$ = $^3J_{HP}$ = 7.0 Hz, 2H, CH), 6.93 (d, $^3J_{HH}$ = 8.1 Hz, 2H, CH), 1.08 (s, 9H, C*Me*$_3$), 0.30 (s, 6H, Si*Me*$_2$). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ/ppm = -6.8.

Step 3.[4] In a 100 mL round-bottom schlenk flask, TBAF (1 M in THF; 15 mL, 15 mmol) was slowly added (15 min) to a solution of $PPh_2(4\text{-}C_6H_4OSiMe_2{}^tBu)$ (3.40 g, 8.66 mmol) in Et_2O (20 mL) at 0°C under vigorous stirring. The resulting pale yellow solution was allowed to heat to room temperature and stirred for 16 hours then 37% HCl (1.3 mL, *ca.* 16 mmol) was added dropwise at 0°C. The reaction mixture was allowed to heat to room temperature and stirred for 5 hours, therefore volatiles were removed in vacuo. The oily residue was dissolved in Et_2O (10 mL) and the

solution was extracted with H_2O (3x25 mL). The organic phase was separated, reduced to a small volume in vacuo and loaded on top of a SiO_2 column (h 6, d 4.5 cm). The title compound was eluted with Et_2O (100 mL) then volatiles were removed in vacuo. The resulting oily residue was re-dissolved in a small volume of hexane and dried in vacuo, yielding $PPh_2(4\text{-}C_6H_4OH)$ as a colourless solid. Yield: 1.72 g, 71%. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3400-3100w-br (ν_{OH}), 3070w, 3054w, 2918w, 2850w, 1598m, 1582m, 1498m, 1477w, 1434m, 1362w, 1329w, 1174m, 822s, 743s, 695s. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.41–7.30 (m, 10H, Ph), 7.26 (t, $^3J_{HH} = {}^3J_{HP}$ = 8.1 Hz, 2H, C3-H), 6.88 (d, $^3J_{HH}$ = 8.4 Hz, 2H, C2-H), 5.96 (s-br, 1H, OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 156.5 (C1), 137.5 (d, $^1J_{CP}$ = 9.0 Hz, C5), 135.9 (d, $^2J_{CP}$ = 21.1 Hz, C3), 133.4 (d, $^2J_{CP}$ = 18.9 Hz, C6), 128.7 (C8), 128.5 (d, $^3J_{CP}$ = 6.9 Hz, C7), 115.9 (d, $^3J_{CP}$ = 8.2 Hz, C2). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ/ppm = –6.8 ppm.

Synthesis of $PPh_2(4\text{-}C_6H_4OCO\text{-}ASP)$, L2

Chart S8. Structure of **L2** (numbering refers to carbon atoms).



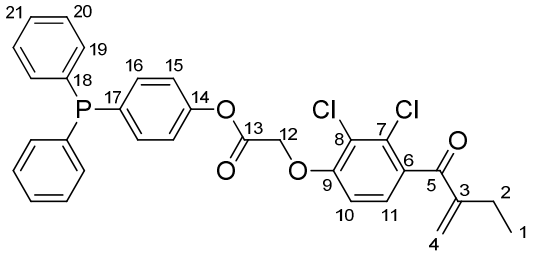
In order to prepare ASP-COCl,[5] in a 50 mL schlenk tube $(COCl)_2$ (0.25 mL, 2.9 mmol) and one drop of DMF were added to a solution of ASP-CO_2H (119 mg, 0.658 mmol) in CH_2Cl_2 (7 mL). The resulting colourless solution was stirred at room temperature for 1 hour then volatiles were carefully removed in vacuo (50°C). The colourless solid obtained was dissolved in CH_2Cl_2 (7 mL); IR spectrum of this solution confirmed the complete conversion to the acyl chloride (ASP-COCl). Therefore $PPh_2(4\text{-}C_6H_4OH)$ (190 mg, 0.68 mmol) and Et_3N (0.11 mL, 0.79 mmol) were introduced. The resulting pale yellow-brown solution was stirred at room temperature for 20 hours then volatiles were removed in vacuo. The colourless solid residue was suspended in Et_2O (20 mL) and extracted with O_2-free H_2O (4x20 mL). The phases were separated and volatiles were removed in vacuo from the organic phase. The residue was dissolved in a small volume of Et_2O and loaded on top of a SiO_2 column, followed by elution with hexane:Et_2O (1:1 *v*/*v*). The title compound was obtained as an extremely-air sensitive, colourless solid after solvent removal in vacuo (RT), along with some non P-containing by-products. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.21 (d, $^3J_{HH}$ = 7.9 Hz, 1H, C7-H), 7.69–7.61 (m, 1H, C5-H), 7.44–7.29 (m, 12H, Ph_2P + C12-H), 7.21 –7.15 (m, 3H, C11-H and C6-H), 7.08 (d, $^3J_{HH}$ = 8.8 Hz, 1H, C4-H), 2.32 (s, 3H, C1-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 169.9 (C2), 162.9 (C9), 151.4 (C3 or C10), 151.3 (C3 or C10), 137.1 (d, $^1J_{CP}$ = 10.5 Hz, C14), 134.8 (C5), 135.2 (d, $^2J_{CP}$ = 20.6 Hz, C12), 133.9 (d, $^2J_{CP}$ = 19.6 Hz, C15), 132.8 (C7), 129.0

(C17), 128.7 (d, $^{3}J_{CP}$ = 6.9 Hz, C16), 126.4 (C6), 124.2 (C4), 122.6 (C8), 122.0 (d, $^{3}J_{CP}$ = 7.5 Hz, C11), 21.2 (C1). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ/ppm = –6.1 ppm.

The compound completely converted into the corresponding phosphine oxide ($^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ/ppm = 31.7) and other by-products upon 20 minutes of air exposition of the solid.

Synthesis of $PPh_2PPh_2(4\text{-}C_6H_4OCO\text{-}EA)$, L4

Chart S9. Structure of **L4** (numbering refers to carbon atoms).

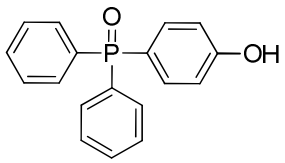


A solution of $PPh_2(4\text{-}C_6H_4OH)$ (190 mg, 0.68 mmol) and EA-CO_2H (233 mg, 0.768 mmol) in CH_2Cl_2 (15 mL) was treated with EDCI·HCl (200 mg, 1.04 mmol) and then with DMAP (16 mg, 0.13 mmol). The resulting colourless solution was stirred at room temperature for 24 hours. Volatiles were removed in vacuo (RT) and a colourless foamy solid was obtained. The solid was suspended in Et_2O (20 mL) for 1 hour, then the liquid was transferred into another flask; the extraction procedure was repeated three times. The title compound was obtained as an extremely-air sensitive, colourless solid after solvent removal in vacuo (RT), along with some non P-containing by-products. Yield: 230 mg, 60%. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.39–7.28 (m, 12H, Ph_2P + C16-H), 7.18 (d, $^{3}J_{HH}$ = 8.5 Hz, 1H, C11-H), 7.13 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, C15-H), 6.91 (d, $^{3}J_{HH}$ = 8.5 Hz, 1H, C10-H), 5.97 (s, 1H, C4-H), 5.62 (s, 1H, C4-H'), 5.02 (s, 2H, C12-H), 2.49 (q, $^{3}J_{HH}$ = 7.2 Hz, 2H, C2-H), 1.17 (t, $^{3}J_{HH}$ = 7.4 Hz, 3H, C1-H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ/ppm = 195.9 (C5), 166.3 (C13), 155.4 (C9), 150.5 (C3 or C14), 150.3 (C3 or C14), 136.9 (d, $^{1}J_{CP}$ = 10.3 Hz, C18), 135.2 (d, $^{2}J_{CP}$ = 20.4 Hz, C16), 134.4 (C8), 133.8 (d, $^{2}J_{CP}$ = 19.5 Hz, C19), 131.8 (C7), 129.8 (C21), 128.9 (C4), 128.8 (d, $^{3}J_{CP}$ = 6.8 Hz, C20), 126.9 (C11), 123.7 (C6), 121.4 (d, $^{3}J_{CP}$ = 7.1 Hz, C15), 111.2 (C10), 66.5 (C12), 23.5 (C2), 12.5 (C1). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ/ppm = -6.3.

The compound rapidly converted into the corresponding phosphine oxide ($^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ/ppm = 28.2) and other by-products upon brief air exposition of the solid.

Synthesis of $O{=}PPh_2(4\text{-}C_6H_4OH)$[6]

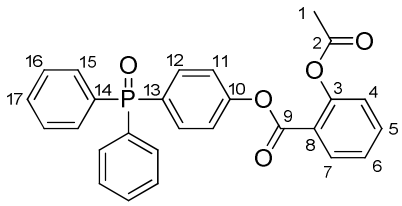
Chart S10. Structure of $O{=}PPh_2(4\text{-}C_6H_4OH)$ (numbering refers to carbon atoms).



A solution of $PPh_2(4\text{-}C_6H_4OH)$ (240 mg, 0.86 mmol) in acetonitrile (15 mL) was treated with an excess of $H_2O_{2,aq}$ (30% w/w, ca. 15 mmol), and the resulting mixture was allowed to stir at room temperature for 24 hours. Then the volatiles were removed in vacuo, and the colourless residue was dried in vacuo over P_2O_5 for 5 hours. Yield 202 mg, 80%. ^{1}H NMR (CH_3OD): δ/ppm = 7.67–7.62, 7.58-7.53, 7.47-7.42, 6.95-6.92 (m, 14H, arom CH). $^{31}P\{^1H\}$ NMR (CH_3OD): δ/ppm = 33.1.

Synthesis of $O{=}PPh_2(4\text{-}C_6H_4OCO\text{-}ASP)$, O=L2

Chart S11. Structure of **O=L2** (numbering refers to carbon atoms).

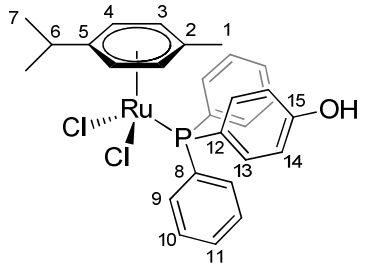


A suspension of $O{=}PPh_2(4\text{-}C_6H_4OH)$ (150 mg, 0.510 mmol) in CH_2Cl_2 (20 mL) was treated with Et_3N (0.10 mL, 0.72 mmol) and ASP-COCl, freshly prepared from ASP-CO_2H (110 mg, 0.611 mmol) as described above for the synthesis of **L2**. The mixture was allowed to stir at room temperature for 20 hours, then the volatiles were removed in vacuo. The residue was charged on a silica column: after washings with petroleum ether/diethyl ether, the fraction corresponding to **O=L2** was collected by using a mixture of diethyl ether and acetone (1:1 *v*/*v*) as eluent. The product was isolated as a colourless sticky solid after removal of the volatile materials in vacuo. Yield 175 mg, 75%. Anal. calcd. for $C_{27}H_{21}O_5P$: C, 71.05; H, 4.64. Found: C, 70.66; H, 4.75. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3058w, 2981w, 1766m ($\nu_{C9=O}$), 1742s ($\nu_{C2=O}$), 1605m, 1592m, 1484m, 1451w-m, 1437m, 1397w, 1367w-m, 1287m, 1244s, 1185vs, 1166vs ($\nu_{P=O}$), 1118vs, 1070s, 1038vs, 1015s, 961w, 914s, 884m, 841w, 804w, 787w, 750m, 726s, 694vs. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.23 (m, 1H, C7-H), 7.79–7.66 (m, 7H, arom CH), 7.59 (m, 2H, arom CH), 7.50 (m, 4H, arom CH), 7.41 (m, 1H, arom CH), 7.31 (m, 2H, arom CH), 7.20 (m, 1H, arom CH), 2.32 (s, 3H, C1-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 169.6 (C2), 162.4, (C9), 153.5, 151.3 (C10 and C3), 135.0 (C6), 133.8 (d, $^2J_{CP}$ = 10.4 Hz, C12), 132.1 (d, $^2J_{CP}$ = 8.9 Hz, C15), 132.0 (d, $^1J_{CP}$ = 104 Hz, C14), 130.3 (d, $^1J_{CP}$ = 106 Hz, C13), 128.6 (C17), 128.1 (C16), 126.3 (C4), 124.2 (C5), 122.0 (d, $^3J_{CP}$ = 13.4 Hz, C11), 21.0 (C1). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 28.7.

Synthesis and characterization of ruthenium compounds

Synthesis of [(η^6-*p*-cymene)$RuCl_2$(κP-PPh_2(4-C_6H_4OH))], 1

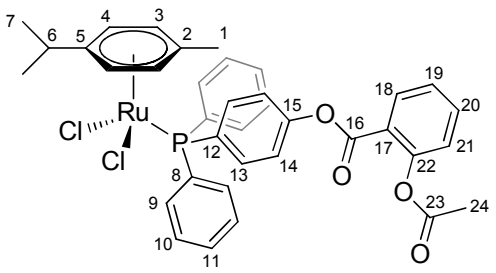
Chart S12. Structure of **1** (numbering refers to carbon atoms).



The title compound was prepared according to a slightly modified literature procedure.[7] In a 100 mL round bottom flask, PPh_2(4-C_6H_4OH) (500 mg, 1.80 mmol), [(η^6-*p*-cymene)$RuCl_2$]$_2$ (516 mg, 0.843 mmol) and CH_2Cl_2 (20 mL) were introduced. The resulting brick red solution was stirred at room temperature and the precipitation of an orange compound began shortly afterwards. After 14 hours, the suspension was rapidly filtered and the orange solid was washed with Et_2O and dried in vacuo (45°C). Yield: 895 mg, 91%. Orange crystals of **1**·H_2O·DMSO were grown in a DMSO or a DMSO/Me_2CO solution settled aside at room temperature. Orange crystals of **1**·$CHCl_3$ were obtained by slow hexane diffusion in a chloroform solution of **4** settled aside at room temperature. The compound is soluble in DMSO, scarcely soluble (CH_2Cl_2, MeOH, acetone) or completely insoluble (Et_2O, hexane) in other common organic solvents. Anal. calcd. for $C_{28}H_{29}Cl_2OP_2Ru$: C, 54.64; H, 4.75. Found: C, 54.49; H, 4.80. Melting point: 148°C (dec.). IR (solid state): $\tilde{\upsilon}$/cm^{-1} = 3267w-br (ν_{OH}), 3094-3047w, 2981m, 2971m, 2872w, 1597s, 1579m, 1541w, 1499s, 1481m, 1470m, 1438m, 1419m, 1388m, 1381m, 1360w, 1270s, 1206m, 1178s, 1159w, 1114w, 1088s, 1057m, 1033w, 998w, 965w, 938w, 898w, 869w, 860w, 833s, 816m, 802w, 747m, 704m-sh, 696s. ^{1}H NMR (DMSO-d_6): δ/ppm = 9.98 (s, 1H, OH), 7.78-7.65 (m, 4H, C9-H), 7.57 (*pseudo*-t, $^3J_{HH}$ = $^3J_{HP}$ = 8.3 Hz, 2H, C13-H), 7.48-7.28 (m, 6H, C10-H and C11-H), 6.79 (d, $^3J_{HH}$ = 7.4 Hz, 2H, C14-H), 5.29 (d, $^3J_{HH}$ = 6.1 Hz, 2H, C4), 5.20 (d, $^3J_{HH}$ = 5.8 Hz, 2H, C3), 2.48* (hept, $^3J_{HH}$ = 6.7 Hz, C6-H), 1.75 (s, 3H, C1-H), 0.95 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H). *partially overlapped with DMSO signal. ^{13}C{^{1}H} NMR (DMSO-d_6): δ/ppm = 159.2 (C15), 136.1 (d, $^2J_{CP}$ = 10.6 Hz, C13), 134.9 (d, $^1J_{CP}$ = 44.8 Hz, C8), 133.8 (d, $^2J_{CP}$ = 9.2 Hz, C9), 129.8 (C11), 127.6 (d, $^3J_{CP}$ = 9.6 Hz, C10), 122.2 (d, $^1J_{CP}$ = 50.9 Hz, C12), 114.8 (d, $^3J_{CP}$ = 10.7 Hz, C14), 108.4 (C5), 95.1 (C2), 89.3 (C3), 86.6 (d, $^2J_{CP}$ = 4.8 Hz, C4), 29.7 (C6), 21.4 (C7), 17.1 (C1). ^{31}P{^{1}H} NMR (DMSO-d_6): δ/ppm = 22.9 ppm.

Synthesis of [(η^6-*p*-cymene)$RuCl_2$(κP-PPh_2(4-C_6H_4OCO-ASP))], 2

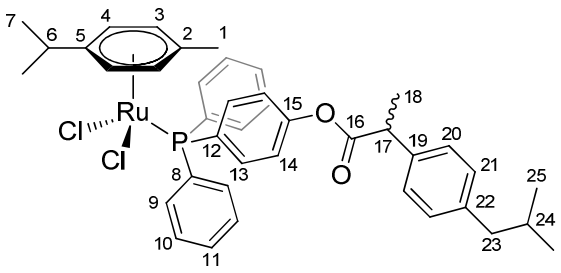
Chart S13. Structure of **2** (numbering refers to carbon atoms).



A CH_2Cl_2 solution (15 mL) of ASP-COCl (129 mg, 0.650 mmol), freshly prepared according to the procedure described above for the synthesis of **L2**, was treated with **1** (320 mg, 0.547 mmol) and then with Bu_3N (0.19 mL, 0.813 mmol). The orange suspension quickly turned into a dark red solution. After 24 hours, the product was precipitated with diethyl ether (ca. 30 mL) and isolated; the volatiles were removed in vacuo, thus affording a dark orange oily residue. The residue was charged on a silica column: Et_2O was eluted in order to remove impurities, then a red band, corresponding to **2**, was collected by using neat CH_2Cl_2 as eluent. The product was recovered as a red powder upon removal of the volatiles under reduced pressure. Yield 236 mg, 58%. Crystals suitable for X-ray analysis were collected from a dichloromethane solution layered with diethyl ether and stored at −30 °C. The compound is soluble in DMSO and chlorinated solvents and insoluble in hexane and water. Anal. calcd. for $C_{37}H_{35}Cl_2O_4PRu$: C, 59.52; H, 4.72. Found: C, 59.6; H, 4.8. Melting point: 125°C (dec.). IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3057w, 2961w, 1765m-sh ($\nu_{C16=O}$), 1741s-br ($\nu_{C23=O}$), 1606w, 1589w, 1482m, 1450w-m, 1434m, 1367w-m, 1286m, 1243m-s, 1206s, 1188vs, 1168vs, 1111w, 1091m, 1037m, 1013w-m, 913w-m, 883w, 841w, 800w, 748m-s, 726w, 695vs, 655w. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.15 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, C18-H), 7.90 (dd, *J* = 9.8, 8.9 Hz, 2H, C13-H), 7.84 (ddd, *J* = 10.3, 7.8, 1.6 Hz, 4H, C9-H), 7.62 (td, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, C20-H), 7.42–7.33 (m, 7H, C10-H, C11-H and C19-H), 7.17–7.13 (m, 3H, C14-H and C21-H), 5.20 (d, $^3J_{HH}$ = 6.1 Hz, 2H, C4-H), 5.02 (d, $^3J_{HH}$ = 5.5 Hz, 2H, C3-H), 2.81 (hept, $^3J_{HH}$ = 6.9 Hz, 1H, C6-H), 2.28 (s, 3H, C24-H), 1.86 (s, 3H, C1-H), 1.09 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ/ppm = 169.7 (C23), 162.6 (C16), 152.1 (d, $^4J_{CP}$ = 2.3 Hz, C15), 151.3 (C22), 136.2 (d, $^2J_{CP}$ = 10.4 Hz, C13), 134.8 (C20), 134.3 (d, $^2J_{CP}$ = 9.5 Hz, C9), 134.0 (d, $^1J_{CP}$ = 46.1 Hz, C8), 132.3 (C18), 131.1 (d, $^1J_{CP}$ = 46.9 Hz, C12), 130.5 (d, $^4J_{CP}$ = 2.0 Hz, C11), 128.2 (d, $^3J_{CP}$ = 10.0 Hz, C10), 126.3 (C19), 124.2 (C21), 122.5 (C17), 121.2 (d, $^3J_{CP}$ = 10.8 Hz, C14), 111.2 (d, $^2J_{CP}$ = 2.8 Hz, C5), 96.3 (C2), 89.3 (d, $^2J_{CP}$ = 3.3 Hz, C3), 87.3 (d, $^2J_{CP}$ = 5.6 Hz, C4), 30.4 (C6), 22.0 (C7), 21.1 (C24), 17.8 (C1). ^{31}P{^{1}H} NMR ($CDCl_3$): δ/ppm = 23.7 ppm.

Synthesis of [(η^6-*p*-cymene)RuCl$_2$(κ*P*-PPh$_2$(4-C$_6$H$_4$OCO-IBU))], 3

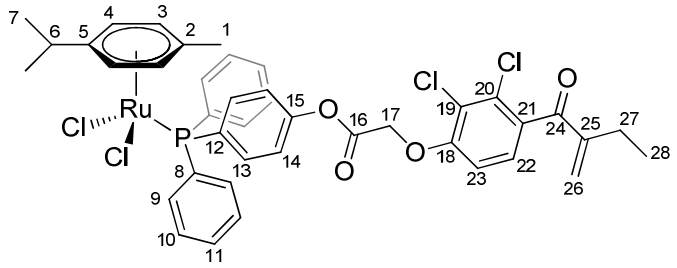
Chart S14. Structure of **3** (numbering refers to carbon atoms).



In a 50 mL schlenk tube, $(COCl)_2$ (0.25 mL, 2.8 mmol) was added to a solution of IBU-CO_2H (122 mg, 0.590 mmol) in CH_2Cl_2 (7 mL). The resulting colourless solution was stirred at room temperature for 2 hours, then volatiles were carefully removed in vacuo (60°C). The colourless liquid obtained was dissolved in CH_2Cl_2 (10 mL); IR analysis of this solution confirmed the complete conversion to the acyl chloride (IBU-COCl). Therefore **1** (175 mg, 0.299 mmol) was introduced and an orange suspension was obtained. Addition of Et_3N (130 µL, 0.93 mmol) caused immediate formation of a deep red solution. The solution was stirred at room temperature overnight and the formation of a soluble Ru compound was assessed by TLC and ^{31}P NMR. The solution was then extracted with H_2O (3x20 mL) and volatiles were removed in vacuo from the organic phase. The residue was dissolved in a small volume of Et_2O. Hexane addition under stirring caused the precipitation of the title compound as a red-brown powder. The suspension was filtered and the solid was washed with hexane and dried in vacuo (45°C). Yield: 137 mg, 59%. The compound is soluble in DMSO and chlorinated solvents, less soluble in Et_2O and insoluble in hexane and water. Anal. calcd. for $C_{41}H_{45}Cl_2O_2PRu$: C, 63.73; H, 5.87. Found: C, 63.4; H, 5.8. IR (solid state): $\tilde{\nu}/cm^{-1}$ = 3055w, 2957m, 2927w, 2868w, 1755s ($\nu_{C=O}$), 1590w, 1579w-sh, 1512w-sh, 1495m, 1483m, 1465m, 1435m, 1398w, 1382w, 1366w, 1331w, 1316w, 1280w, 1261w, 1208m, 1169s, 1134s, 1119s-sh, 1092s, 1069m, 1018m, 999w, 923w, 895w, 846m, 800m, 746m, 695s. ^1H NMR ($CDCl_3$): δ/ppm = 7.84–7.76 (m, 6H, C9-H and C13-H), 7.41–7.32 (m, 6H, C10-H and C11-H), 7.26 (d, $^3J_{HH}$ = 7.8 Hz, 2H, C20-H), 7.12 (d, $^3J_{HH}$ = 7.9 Hz, 2H, C21-H), 6.99 (d, $^3J_{HH}$ = 7.4 Hz, 2H, C14-H), 5.18 (d, $^3J_{HH}$ = 3.2 Hz, 2H, C4-H), 4.98 (d, $^3J_{HH}$ = 5.0 Hz, 2H, C3-H), 3.91 (q, $^3J_{HH}$ = 7.1 Hz, 1H, C17-H), 2.83 (hept, $^3J_{HH}$ = 6.8 Hz, 1H, C6-H), 2.45 (d, $^3J_{HH}$ = 7.1 Hz, 2H, C23-H), 1.84 (s, 3H, C1-H), 1.90–1.80 (m, $^3J_{HH}$ = 6.6 Hz, 1H, C24-H), 1.58 (d, $^3J_{HH}$ = 7.1 Hz, 3H, C18-H), 1.09 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H), 0.90 (d, $^3J_{HH}$ = 6.6 Hz, 6H, C25-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 172.9 (C16), 152.5 (d, $^4J_{CP}$ = 2.9 Hz, C15), 141.1 (C22), 137.0 (C19), 135.9 (d, $^2J_{CP}$ = 10.4 Hz, C13), 134.3 (d, $^2J_{CP}$ = 9.4 Hz, C9), 134.0 (d, $^1J_{CP}$ = 45.5 Hz, C8), 130.8 (d, $^1J_{CP}$ = 47.4 Hz, C12), 130.4 (d, $^4J_{CP}$ = 1.1 Hz, C11), 129.7 (C21), 128.1 (d, $^3J_{CP}$ = 9.9 Hz, C10), 127.3 (C20), 121.1 (d, $^3J_{CP}$ = 10.7 Hz, C14), 111.3 (d, $^2J_{CP}$ = 2.7 Hz, C5), 96.2 (C2), 89.3–89.2 (m, C3), 87.4– 87.2 (m, C4), 45.4 (C17), 45.1 (C23), 30.4 (C6 or C24), 30.3 (C6 or C24), 22.5 (C25), 22.0 (C7), 18.5 (C18), 17.9 (C1). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 23.6.

Synthesis of [(η^6-*p*-cymene)$RuCl_2$(κ*P*-PPh_2(4-C_6H_4OCO-EA))], 4

Chart S15. Structure of **4** (numbering refers to carbon atoms).



Preparation via acyl chloride. In a 50 mL Schlenk tube $(COCl)_2$ (0.10 mL, 1.2 mmol) was added to a solution of EA-CO_2H (65 mg, 0.21 mmol) in $CHCl_3$ (7 mL). The colourless solution was heated under reflux for 1 hour then volatiles were carefully removed in vacuo (50°C). The pale yellow oily residue obtained was dissolved in CH_2Cl_2 (10 mL); IR analysis of this solution confirmed the complete conversion to the acyl chloride (EA-COCl). Therefore **1** (103 mg, 0.176 mmol) was introduced and an orange suspension was obtained. Addition of Et_3N (50 µL, 0.36 mmol) led to the formation of a red solution in 20 minutes. The reaction mixture was stirred at room temperature overnight then volatiles were removed in vacuo. The residue was dissolved in a small volume of CH_2Cl_2/^{i}PrOH (1:1 *v*/*v*) then hexane was added under stirring. The title compound precipitated as a brown-red powder. The suspension was filtered and the solid was washed with Et_2O and dried in vacuo (40°C). Yield: 98 mg, 64%.

Preparation via EDCI-mediated coupling: In a 25 mL Schlenk tube, EA-CO_2H (108 mg, 0.355 mmol), **1** (84 mg, 0.143 mmol), CH_2Cl_2 (7 mL), EDCI·HCl (86 mg, 0.554 mmol) and DMAP (5 mg, 0.041 mmol) were introduced in this order. The resulting orange suspension turned into a red solution in a few minutes. The solution was stirred at room temperature for 24 hours and the formation of a soluble Ru compound was assessed by TLC. Therefore volatiles were removed in vacuo. The residue was dissolved in CH_2Cl_2 and extracted with H_2O (3x30mL). Volatiles were removed in vacuo from the organic phase and the residue was suspended in Et_2O (20 mL). The suspension was filtered and the resulting brown solid was washed with Et_2O and dried in vacuo (40°C). Yield: 77 mg, 64%.

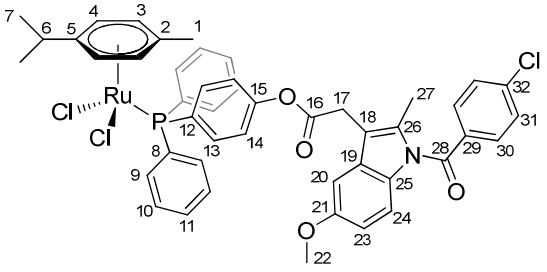
Preparation via coordination of phosphinoester ligand: In a 50 mL round bottom flask, **L4** (275 mg, 0.488 mmol), [(η^6-*p*-cymene)$RuCl_2$]$_2$ (119 mg, 0.194 mmol) and $CHCl_3$ (20 mL) were introduced and the resulting brick red solution was heated at reflux for 30 hours. The final dark red solution was cooled to room temperature and then volatiles were removed in vacuo. The residue was suspended in Et_2O (15 mL) with vigorous stirring and filtered. The solid was re-dissolved in a

small volume of CH_2Cl_2 then ^{i}PrOH (1-2 mL) and hexane were added with intense stirring. The title compound precipitated as a brown powder. The suspension was filtered and the solid was washed with hexane and dried in vacuo (40°C). Yield: 219 mg, 65%.

The compound is soluble in chlorinated solvents and DMSO, less soluble in ^{i}PrOH and Et_2O, insoluble in hexane and water. Anal. calcd. for $C_{41}H_{39}Cl_4O_4PRu$: C, 56.63; H, 4.52. Found: C, 56.4; H, 4.5. Melting point: 114°C (dec.). IR (solid state): $\tilde{\upsilon}$/cm^{-1} = 3057w, 2981s, 2972s-sh, 2889m, 1778m ($\nu_{C16=O}$), 1664m ($\nu_{C24=O}$), 1584m ($\nu_{C25=C26}$), 1494m-sh, 1495w-sh, 1482m-sh, 1469m, 1435m, 1383s, 1339w, 1293m, 1259m, 1206m, 1169s, 1157s, 1120m, 1074s, 1017m, 1000m, 952m, 895w, 843w, 801m, 770w-sh, 747m, 695s, 666w. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.88 (*pseudo*-t, $^{3}J_{HH} = {}^{3}J_{HP}$ = 9 Hz, 2H, C13-H), 7.82 (*pseudo*-t, $^{3}J_{HH} = {}^{3}J_{HP}$ = 9 Hz, 4H, C9-H), 7.45–7.32 (m, 6H, C10-H and C11-H), 7.15 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H, C22-H), 7.12-7.07 (m, 2H, C14-H), 6.87 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H, C23-H), 5.93 (s, 1H, C26-H), 5.58 (s, 1H, C26-H'), 5.19 (d, $^{3}J_{HH}$ = 5.0, 2H, C4-H), 5.00 (d, $^{3}J_{HH}$ = 5.0 Hz, 2H, C3-H), 4.97 (s, 2H, C17), 2.80 (hept, $^{3}J_{HH}$ = 6.1 Hz, 1H, C6-H), 2.44 (q, $^{3}J_{HH}$ = 6.9 Hz, 2H, C27-H), 1.84 (s, 3H, C1-H), 1.12 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H, C28-H), 1.08 (d, $^{3}J_{HH}$ = 5.9 Hz, 6H, C7-H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ/ppm = 195.7 (C24), 165.9 (C16), 155.2 (C18), 151.2 (C15), 150.0 (C25), 136.1 (d, $^{2}J_{CP}$ = 10.3 Hz, C13), 134.1 (d, $^{2}J_{CP}$ = 9.5 Hz, C9), 134.0 (C19), 133.8 (d, $^{1}J_{CP}$ = 47.7 Hz, C8), 131.5 (C20), 131.3 (d, $^{1}J_{CP}$ = 46.0 Hz, C12), 130.5 (C11), 128.8 (C26), 128.1 (d, $^{3}J_{CP}$ = 9.8 Hz, C10), 126.9 (C22), 123.4 (C21), 120.6 (d, $^{3}J_{CP}$ = 10.3 Hz, C14), 111.3 (C23), 111.1 (C5), 96.2 (C2), 89.1 (C3), 87.2 (d, $^{2}J_{CP}$ = 4.8 Hz, C4), 66.5 (C17), 30.2 (C6), 23.3 (C27), 21.8 (C7), 17.8 (C1), 12.4 (C28). ^{31}P{^{1}H} NMR ($CDCl_3$): δ/ppm = 24.0.

Synthesis of [(η^6-*p*-cymene)RuCl$_2$(κ*P*-PPh$_2$(4-C$_6$H$_4$OCO-IM))], 5

Chart S16. Structure of **5** (numbering refers to carbon atoms).

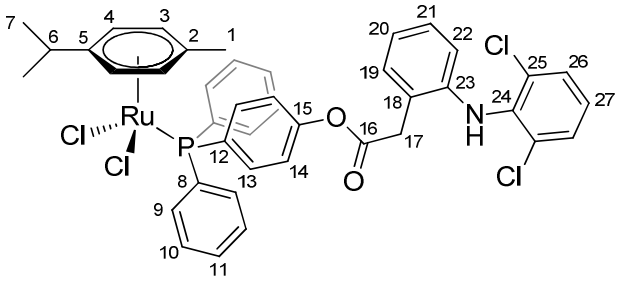


In a 50 mL schlenk tube $(COCl)_2$ (0.15 mL, 1.7 mmol) was added to a solution of IM-CO_2H (109 mg, 0.304 mmol) in CH_2Cl_2 (7 mL). The resulting pale yellow solution was stirred at room temperature for 2 hours. Volatiles were then carefully removed in vacuo (50 °C), thus yielding a pale yellow solid. IR analysis of this material (solid state and CH_2Cl_2 solution) confirmed the complete conversion of IM-CO_2H into the corresponding acyl chloride (IM-COCl). Therefore **1**

(146 mg, 0.249 mmol) and CH_2Cl_2 (8 mL) were introduced and an orange suspension was obtained. Addition of Et_3N (88 μL, 0.63 mmol) caused immediate formation of a deep red solution. The solution was stirred at room temperature overnight and the formation of a soluble Ru compound was assessed by TLC and ^{31}P NMR. Therefore, the solution was extracted with HCl 10^{-3} M in H_2O (3x20 mL). Volatiles were removed in vacuo from the organic phase and the residue was suspended in Et_2O/hexane (1:1 *v*/*v*, 20 mL). The suspension was filtered and the brown-red powder was washed with hexane and dried in vacuo (45°C). Yield: 179 mg, 78%. The compound is soluble in chlorinated solvents and DMSO, less soluble in Et_2O, insoluble in hexane and water. Anal. calcd. for $C_{47}H_{43}Cl_3NO_4PRu$: C, 61.08; H, 4.69. Found: C, 61.2; H, 4.7. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3056w, 2960w, 2928w, 2872w, 2833w, 1960w, 1756m ($\nu_{C16=O}$), 1681s ($\nu_{C28=O}$), 1590m, 1608m-sh, 1478s, 1456m, 1435s, 1398m, 1369m-sh, 1356s, 1317s, 1290m-sh, 1210s, 1169s, 1121s, 1088s, 1065s, 1033m, 1014s, 996m, 924m, 913m, 835m, 801m, 753s, 728m-sh, 694s. ^1H NMR ($CDCl_3$): δ/ppm = 7.87–7.77 (m, 6H, C9-H and C13-H), 7.66 (d, $^3J_{HH}$ = 8.4 Hz, 2H, C30-H), 7.47 (d, $^3J_{HH}$ = 8.4 Hz, 2H, C31-H), 7.42–7.34 (m, 6H, C10-H and C11-H), 7.04 (d, $^3J_{HH}$ = 7.6 Hz, 2H, C14-H), 7.01 (d, $^4J_{HH}$ = 2.3 Hz, 1H, C20-H), 6.87 (d, $^3J_{HH}$ = 9.0 Hz, 1H, C24-H), 6.67 (dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 2.3 Hz, 1H, C23-H), 5.19 (d, $^3J_{HH}$ = 5.8 Hz, 2H, C3-H or C4-H), 4.98 (d, $^3J_{HH}$ = 5.6 Hz, 2H, C3-H or C4-H), 3.88 (s, 2H, C17-H), 3.82 (s, 3H, C22-H), 2.82 (hept, $^3J_{HH}$ = 6.8 Hz, 1H, C6-H), 2.43 (s, 3H, C27-H), 1.85 (s, 3H, C1-H), 1.09 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 168.9 (C16 or C28), 168.4 (C16 or C28), 156.3 (C21), 152.2 (C15), 139.5 (C32), 136.3 (C19), 136.1 (d, $^2J_{CP}$ = 10.4 Hz, C13-H), 134.3 (d, $^2J_{CP}$ = 9.3 Hz, C9-H), 134.0 (d, $^1J_{CP}$ = 45.4 Hz, C8-H), 133.9 (C29), 131.3 (C30), 131.0 (C26), 130.5 (C25), 130.4 (C11), 129.3 (C31), 128.2 (d, $^3J_{CP}$ = 9.9 Hz, C10), 120.9 (d, $^3J_{CP}$ = 10.8 Hz, C14), 115.1 (C24), 111.9 (C18), 111.8 (C23), 111.3 (C5), 101.4 (C20), 96.3 (C2), 89.2 (d, $^2J_{CP}$ = 2.0 Hz, C3 or C4), 87.3 (d, $^2J_{CP}$ = 5.3 Hz, C3 or C4), 55.9 (C22), 30.7 (C17), 30.4 (C6), 22.0 (C7), 17.9 (C1), 13.5 (C27). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 23.8.

Synthesis of [(η^6-*p*-cymene)RuCl$_2$(κ*P*-PPh$_2$(4-C$_6$H$_4$OCO-DF))], 6

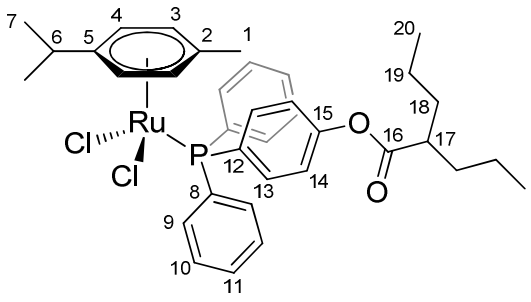
Chart S17. Structure of **6** (numbering refers to carbon atoms).



A solution of DF-CO_2H (134 mg, 0.452 mmol) in CH_2Cl_2 (10 mL) was treated with **1** (250 mg, 0.428 mmol), EDCI·HCl (104 mg, 0.543 mmol) and DMAP (8.0 mg, 0.068 mmol) in the order given. The orange suspension quickly turned into a dark red solution. After 24 hours, the volatiles were removed in vacuo and the residue was charged on a silica column. Mixtures of petroleum ether and Et_2O were used to elute impurities, then an orange band, corresponding to **6**, was collected by using neat CH_2Cl_2 as eluent. The product was recovered as an orange powder upon removal of the solvent in vacuo. Yield 221 mg, 60%. The compound is soluble in DMSO and chlorinated solvents and insoluble in hexane and water. Anal. calcd. for $C_{42}H_{38}Cl_4NO_2PRu$: C, 58.48; H, 4.44. Found: C, 58.4; H, 4.3. Melting point: 127°C (dec.). IR (solid state): ν = 3351br (ν_{NH}), 3056w, 2957w, 2124w, 1746m ($\nu_{C=O}$), 1588w-m, 1495m-s, 1451s, 1435s,1292w-m, 1207s, 1168vs, 1129vs, 1092s, 1017m-s, 1013w-m, 922w, 846w-m, 799w-m, 774m-s, 745vs, 695vs, 663w-m cm^{-1}. ^1H NMR ($CDCl_3$): δ/ppm = 7.88–7.78 (m, 6H, C9-H and C13-H), 7.41–7.30 (m, 9H, C10-H, C11-H, C19-H and C26-H), 7.15 (td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, C21-H), 7.10 (dd, $^3J_{HH}$ = 8.5 Hz, J = 1.3 Hz, 2H, C14-H), 7.00 (t, $^3J_{HH}$ = 7.4 Hz, 1H, C27-H), 6.98 (t, $^3J_{HH}$ = 8.0 Hz, 1H, C20-H), 6.65 (s, 1H, NH), 6.57 (d, $^3J_{HH}$ = 8.2 Hz, 1H, C22-H), 5.18 (d, $^3J_{HH}$ = 6.0 Hz, 2H, C3-H or C4-H), 5.00 (d, $^3J_{HH}$ = 5.7 Hz, 2H, C3-H or C4-H), 4.03 (s, 2H, C17-H), 2.82 (hept, $^3J_{HH}$ = 6.7 Hz, 1H, C6-H), 1.86 (s, 3H, C1-H), 1.09 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 170.3 (C16), 152.2 (d, $^4J_{CP}$ = 2.2 Hz, C15), 142.8 (C23), 137.9 (C24), 135.9 (d, $^2J_{CP}$ = 10.4 Hz, C13), 134.4 (d, $^2J_{CP}$ = 9.5 Hz, C9), 133.9 (d, $^1J_{CP}$ = 45.6 Hz, C8), 132.0 (d, $^1J_{CP}$ = 45.6 Hz, C12), 131.1 (C19), 130.5 (d, $^4J_{CP}$ = 2.1 Hz, C11), 129.6 (C25), 129.0 (C26), 128.5 (C21), 128.2 (d, $^3J_{CP}$ = 8.0 Hz, C10), 124.3 (C27), 123.9 (C18), 122.5 (C20), 121.1 (d, $^3J_{CP}$ = 10.6 Hz, C14), 118.8 (C22), 111.3 (C5), 96.2 (C2), 89.3 (d, $^2J_{CP}$ = 3.2 Hz, C3 or C4), 87.2 (d, $^2J_{CP}$ = 5.4 Hz, C4 or C4), 38.7 (C17), 30.4 (C6), 22.0 (C7), 17.9 (C1). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 23.6.

Synthesis of [(η^6-*p*-cymene)$RuCl_2$(κ*P*-PPh_2(4-C_6H_4OCO-VP))], 7

Chart S18. Structure of **7** (numbering refers to carbon atoms).



In a 25 mL Schlenk tube, CH_2Cl_2 (7 mL), VP-CO_2H (55 μL, 0.35 mmol), **1** (82 mg, 0.087 mmol), EDCI·HCl (85 mg, 0.54 mmol) and DMAP (5 mg, 0.04 mmol) were introduced in the order given.

The resulting orange suspension turned into a red solution in a few minutes. The solution was stirred at room temperature for additional 24 hours, and the formation of a soluble Ru compound was assessed by TLC. Therefore volatiles were removed in vacuo; the residue was dissolved in CH_2Cl_2 and extracted with H_2O (3x30mL). Volatiles were removed in vacuo from the organic phase and the residue was suspended in hexane (20 mL). The suspension was cooled to -20°C, then filtered and the resulting red-brown solid was washed with a small volume of cold hexane and dried in vacuo (40°C). Yield: 70 mg, 71%. The compound is soluble in DMSO, chlorinated solvents and Et_2O, less soluble in hexane and insoluble in water. Anal. calcd. for $C_{36}H_{43}Cl_2O_2PRu$: C, 60.84; H, 6.10. Found: C, 60.9; H, 6.2. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3055w, 2958m, 2931m, 2871m, 1751s ($\nu_{C=O}$), 1621w, 1590m, 1577w-sh, 1540w, 1495m, 1483m, 1465m, 1435s, 1397w, 1377m, 1261w, 1209m, 1193m, 1169s, 1147m-sh, 1094s, 1067m-sh, 1056m-sh, 1028m, 1017m, 999m, 975w, 923w, 873m, 848w, 800m, 746s, 695s. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.89–7.79 (m, 6H, C9-H and C13-H), 7.43–7.34 (m, 6H, C10-H and C11-H), 7.06 (d, $^3J_{HH}$ = 7.9 Hz, 2H, C14-H), 5.20 (d, $^3J_{HH}$ = 5.9 Hz, 2H, C4-H), 5.00 (d, $^3J_{HH}$ = 5.7 Hz, 2H, C3-H), 2.84 (hept, $^3J_{HH}$ = 6.8 Hz, 1H, C6-H), 2.59 (m, *J* = 14.1, 9.3, 5.3 Hz, 1H, C17-H), 1.87 (s, 3H, C1-H), 1.78–1.66 (m, 2H, C18-H), 1.59–1.48 (m, 2H, C18-H), 1.40 (sex, $^3J_{HH}$ = 7.1 Hz, 4H, C19-H), 1.10 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H), 0.94 (t, $^3J_{HH}$ = 7.2 Hz, 6H, C20-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 174.8 (C16), 152.5 (d, $^4J_{CP}$ = 2.7 Hz, C15), 136.0 (d, $^2J_{CP}$ = 10.4 Hz, C13), 134.3 (d, $^2J_{CP}$ = 9.5 Hz, C9), 134.1 (d, $^1J_{CP}$ = 46.4 Hz, C8), 130.7 (d, $^1J_{CP}$ = 45.9 Hz, C12), 130.4 (C11), 128.2 (d, $^3J_{CP}$ = 9.9 Hz, C10), 121.2 (d, $^3J_{CP}$ = 10.6 Hz, C14), 111.4 (d, $^2J_{CP}$ = 3.2 Hz, C5), 96.2 (C2), 89.2 (d, $^2J_{CP}$ = 2.8 Hz, C3), 87.3 (d, $^2J_{CP}$ = 5.5 Hz, C4), 45.5 (C17), 34.7 (C18), 30.4 (C6), 22.0 (C7), 20.8 (C19), 17.9 (C1), 14.1 (C20). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 23.6.

Table S1. Comparison of IR and NMR data for complexes **1-7** and related compounds.

IR band[a] or NMR signal[b] / Compound	ν(C=O) / cm^{-1} ester moiety	^{1}H δ(OH) / ppm	^{13}C δ(CO_2) / ppm ester moiety	^{31}P δ(PR_3) / ppm
$PPh_2(4\text{-}C_6H_4OH)$	-	5.96 s-br	-	-6.8
1	-	9.98 s	-	22.9
ASP-CO_2H	1681s	10.7 br	170.3 / 169.9	-
2	1741m-sh	-	162.6	23.7
IBU-CO_2H	1712s	10.5 br	180.9	-
3	1755s	-	172.9	23.6
EA-CO_2H	1724s	7.75 s-br	172.6	-
4	1778m	-	165.9	24.0
IM-CO_2H	1713s	n.d.	176.8	-
5	1756m	-	168.9 / 168.4	23.8
DF-CO_2H	1690s	10.8 br	173.9	-
6	1746m	-	170.3	23.6
VP-CO_2H	1702s	11.4 s-br	183.6	-
7	1751s	-	174.8	23.6

[a] Solid-state or liquid film (VP-CO_2H).

[b] $CDCl_3$ solution except **1** (DMSO-d_6 solution) and DF-CO_2H (acetone-d_6 solution)

X-ray crystallography

The diffraction experiments were carried out on a Bruker APEX II diffractometer equipped with a CCD detector and using Mo-Kα radiation (Table SI2). Data were corrected for Lorentz polarization and absorption effects (empirical absorption correction SADABS [8]). The structures were solved by direct methods and refined by full-matrix least-squares based on all data using F^2.[9] Hydrogen atoms were fixed at calculated positions and refined by a riding model, except O-bonded hydrogens of **1·Me$_2$SO·H$_2$O** that have been located in the Fourier map and refined isotropically using the 1.5 fold U_{iso} value of the parent atoms. The O-H distances were restrained to 0.84 Å (s.u. 0.02). All non-hydrogen atoms were refined with anisotropic displacement parameters.

Table S2. Crystal data and experimental details for **1·Me$_2$SO·H$_2$O** and **2**.

	1·Me$_2$SO·H$_2$O	**2**
Formula	$C_{30}H_{37}Cl_2O_3PRuS$	$C_{37}H_{35}Cl_2O_4PRu$
Fw	680.59	746.59
T, K	100(2)	293(2)
λ, Å	0.71073	0.71073
Crystal system	Triclinic	Triclinic
Space group	*P*1	$P\bar{1}$
a, Å	8.1267(3)	10.9850(3)
b, Å	9.0933(3)	12.0865(4)
c, Å	11.0788(7)	13.9883(4)
α, °	102.780(2)	114.0750(10)
β, °	97.314(2)	92.914(2)
γ, °	107.4730(10)	97.381(2)
Cell Volume, Å^3	744.89(6)	1670.65(9)
Z	1	2
D_c, g cm^{-3}	1.517	1.484
μ, mm^{-1}	0.860	0.716
F(000)	350	764
Crystal size, mm	0.18×0.15×0.11	0.16×0.13×0.12
θ limits, °	1.827–26.999	1.605–25.498
Reflections collected	12584	25440
Independent reflections	6398 [R_{int} = 0.0300]	6194 [R_{int} = 0.0587]
Data / restraints /parameters	6398 / 6 / 352	6194 / 0 /406
Goodness on fit on F^2	1.049	1.042
R_1 (I> 2σ(I))	0.0250	0.0443
wR_2 (all data)	0.0640	0.1134
Largest diff. peak and hole, e Å^{-3}	1.146 / -0.506	0.770 / -0.351

Stability studies.

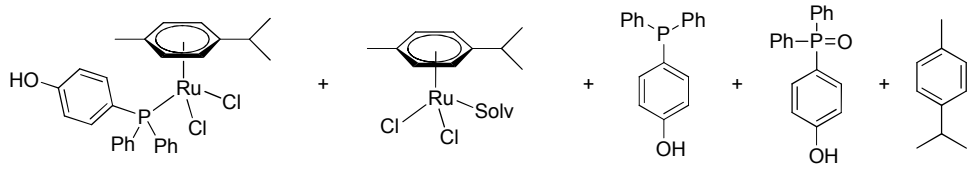
General procedure. Complexes **1**−7 were dissolved in DMSO-d_6/D_2O 9:1 *v*/*v* (1.0 mL; [Ru] = $2\cdot10^{-2}$ mol·L^{-1}). An aliquot of the resulting solution (0.40 mL) was transferred into a NMR tube, maintained at 37°C for 72 hours and analyzed by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy as a function of time. The remaining solution was diluted up to 4.0 mL with DMSO/H_2O 9:1 *v*/*v* (final [Ru] = $3\cdot10^{-3}$ mol·L^{-1}), maintained at 37 °C for 72 hours and its conductivity was measured as a function of time. Parallel NMR analyses were carried out on DMSO-d_6/D_2O solutions prepared by the same procedure described above, and with the addition of NaCl (0.1 mol·L^{-1}). Values of molar conductivity (Λ_m) were calculated with respect to the starting material. Percent values of compounds in solution are based on ^1H NMR spectroscopy and refer to identified compounds only. NMR signals in braces {} indicate superimpositions with other species.

Reference data. NMR spectra of the following compounds were recorded in DMSO-d_6/D_2O 9:1 *v*/*v* and used for comparison for NMR assignments. ***p*-cymene**. ^1H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.12–7.03 (m, 4H), 2.80 (hept, $^3J_{HH}$ = 6.9 Hz, 1H), 2.23 (s, 3H), 1.15 (d, $^3J_{HH}$ = 6.9 Hz, 6H). **ASP-CO_2H**. ^1H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.91 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.62 (td, *J* = 7.8, 1.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 2.22 (s, 3H). **IBU-CO_2H**. ^1H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.17 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 3.61 (q, *J* = 7.1 Hz, 1H), 2.39 (d, *J* = 7.1 Hz, 2H), 1.78 (non, *J* = 6.7 Hz, 1H), 1.32 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 6H). **EA-CO_2H**. ^1H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.24 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 7.02 (d, $^3J_{HH}$ = 8.7 Hz, 1H), 6.03 (s, 1H), 5.52 (s, 1H), 4.83 (s, 2H), 2.30 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 1.01 (t, $^3J_{HH}$ = 7.4 Hz, 3H). **IM-CO_2H**. ^1H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.64 (pseudo-q, *J* = 8.7 Hz, 4H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 6.70 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.74* (s), 3.64 (s, 2H), 2.19 (s, 3H). *partially overlapped with DHO signal. **DF-CO_2H**. ^1H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.49 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.19 (d, $^3J_{HH}$ = 7.3 Hz, 1H), 7.17 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 7.06 (t, $^3J_{HH}$ = 7.7 Hz, 1H), 6.87 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 6.27 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 3.67

(s, 2H). **VP-CO_2H**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 2.26–2.16 (m, 1H), 1.50–1.38 (m, 2H), 1.38–1.27 (m, 2H), 1.21 (sex, $^3J_{HH}$ = 6.8 Hz, 4H), 0.82 (t, $^3J_{HH}$ = 7.1 Hz, 6H).

*Compound **1***. Data are compiled in Table S3 while NMR detected species are shown in Scheme SI1. **1.** ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.74–7.64 (m, 4H), 7.58–7.52 (m, 2H), 7.44–7.32 (m, 6H), 6.77 (d, *J* = 7.3 Hz, 2H), 5.26 (d, *J* = 6.1 Hz, 2H), 5.18 (d, *J* = 5.8 Hz, 2H), 1.73 (s, 3H), 0.94 (d, *J* = 6.9 Hz, 6H). ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 23.0. **S**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 5.79 (d, *J* = 6.1 Hz, 1H), 5.74 (d, *J* = 6.7 Hz, 1H), 2.07 (s, 3H), 1.18 (d, *J* = 7.0 Hz, 6H). **L1**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.61–7.54 (m), {7.43–7.34 (m)}, 7.21–7.14 (m, 4H), 6.80 (d, *J* = 8.2 Hz, 2H). ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = -8.5 ppm. **O=L1**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 6.91 (dd, 2H). ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 27.2. Minor P-containing species: ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 36.6 (72 h).

Scheme S1 and **Table S3**. Molar conductivity and NMR detected species as a function of time for DMSO/water 9:1 *v*/*v* solution of **1** at 37°C. Data for analogous experiment with 0.1 M NaCl are given in parentheses.

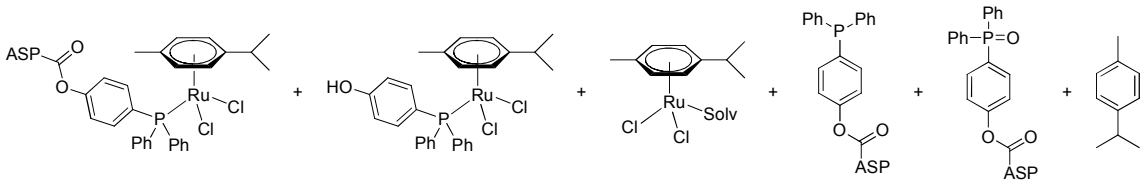


1 **S** **L1** **O=L1**

time / hours		0.5	24	48	72
Λ_m / S·cm^2·mol^{-1}		5.9	7.9	10	13
% NMR (NaCl experiment)	**1**	82 (91)	67 (65)	47 (45)	33 (33)
	S	3 (2)	1 (0)	0 (0)	0 (0)
	L1	0 (1)	6 (11)	17 (21)	24 (27)
	O=L1	8 (1)	10 (3)	10 (5)	10 (6)
	***p*-cymene**	7 (5)	16 (21)	26 (29)	33 (34)

*Compound **2***. Data are compiled in Table S4 while NMR detected species are shown in Scheme SI2. **2**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 8.13 (d, *J* = 6.5 Hz, 1H), 7.83 (t, *J* = 9.2 Hz, 2H), 7.79–7.73 (m, 4H), 7.72–7.64 (m, 1H), 7.52–7.38 (m, 7H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 2H), 5.29 (d, *J* = 6.3 Hz, 2H), 5.26 (d, *J* = 5.6 Hz, 2H), 2.22 (s, 3H), 1.76 (s, 3H), 0.93 (d, *J* = 6.9 Hz, 6H). ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 23.8. **L2**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = {8.13}, {7.79–7-73}, {7.72–7.64}, 7.62–7.54 (m), {7.52–7.38}, 7.34 (d, *J* = 8.5 Hz), 7.29-7.24 (m), {2.21 (s)}. ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = -7.8. **O=L2**. ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 26.6. All ^{1}H signals of **O=L2** are superimposed to those belonging to **L2**. Therefore, only the percent value for the total ^{1}H integral (**L2** + **O=L2**) is given.

Scheme S2 and **Table S4**. Molar conductivity and NMR detected species as a function of time for DMSO/water 9:1 *v*/*v* solution of **2** at 37°C. Data for analogous experiment with 0.1 M NaCl are given in parentheses.

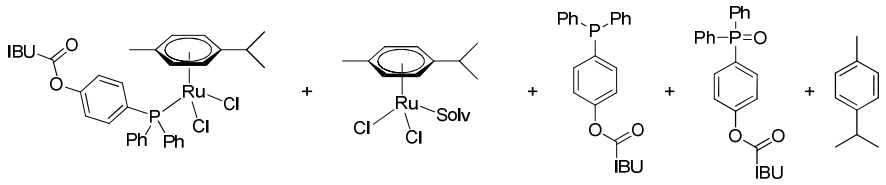


2 **1** **S** **L2** **O=L2**

time / hours		0	6	24	48	72
Λ_m / S·cm^2·mol^{-1}		7.7	11	12	12	14
% NMR (NaCl experiment)	**2**	71 (72)	63 (61)	52 (57)	40 (45)	30 (35)
	1	10 (15)	12 (13)	11 (12)	9 (11)	7 (8)
	S	5 (5)	4 (5)	1 (3)	0 (1)	0 (0)
	L2 + O=L2	11 (4)	13 (13)	19 (13)	27 (18)	32 (28)
	***p*-cymene**	3 (4)	8 (8)	17 (15)	24 (25)	31 (29)

*Compound **3***. Data are compiled in Table S5 while NMR detected species are shown in Scheme SI3. **3.** ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.78–7.66 (m, 6H), 7.47–7.35 (m, 6H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 5.27 (d, *J* = 5.0 Hz, 2H), 5.22 (d, *J* = 5.5 Hz, 2H), 4.01 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.40 (d, *J* = 6.9 Hz, 2H), 1.81–1.75 (m, 1H), 1.73 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 6H), 0.82 (d, *J* = 6.3 Hz, 6H). ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 23.7. **L3**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.67–7.52 (m, 6H), {7.47–7.35 (m, 4H)}, {7.29–7.23 (m, 4H)}, 7.23–7.18 (m, 2H), {7.16–7.12 (m, 2H)}, {4.08–3.99 (m, 1H)}, {2.40 (d, 2H)}, {1.81–1.75 (m, 1H)}, {1.49–1.44 (m, 3H)}, {0.82 (d, 6H)}. ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = -7.8. **O=L3**. ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 26.5. All ^{1}H signals of **O=L3** are superimposed to those belonging to **L3**. Therefore, only the percent value for the total ^{1}H integral (**L3** + **O=L3**) is given. Minor P-containing species: ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 38.1 (48 h).

Scheme S3 and **Table S5**. Molar conductivity and NMR detected species as a function of time for DMSO/water 9:1 *v*/*v* solution of **3** at 37°C. Data for analogous experiment with 0.1 M NaCl are given in parentheses.

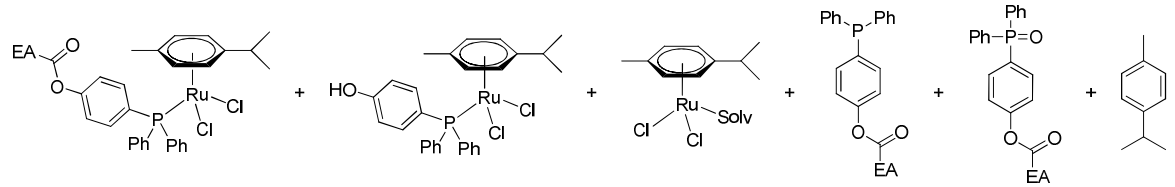


3 **S** **L3** **O=L3**

time / hours		0.5	24	48	72
Λ_m / S·cm^2·mol^{-1}		7.9	10	14	-
% NMR (NaCl experiment)	**3**	85 (84)	64 (74)	44 (50)	34 (42)
	S	5 (4)	1 (1)	0 (0)	0 (0)
	L3 + O=L3	8 (10)	22 (12)	33 (29)	38 (34)
	***p*-cymene**	2 (2)	13 (13)	23 (21)	28 (24)

*Compound **4***. Data are compiled in Table S6 while NMR detected species are shown in Scheme SI4. **4**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.79 (t, *J* = 9.1 Hz, 2H), 7.76–7.69 (m, 4H), 7.49–7.37 (m, 6H), 7.30 (pseudo-q, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.06 (s, 1H), 5.54 (s, 1H), 5.30 (s, 2H), 5.28 (d, *J* = 6.8 Hz, 2H), 5.24 (d, *J* = 5.8 Hz, 2H), 2.34 (q, *J* = 7.2 Hz, 2H), 2.50–2.43* (m, *J* = 6.9 Hz), 1.74 (s, 3H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 6H). *partially overlapped with DMSO signal. $^{31}P\{^{1}H\}$ NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 23.8. **L4**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.69-7.52 (m), {7.33-7.28 (m)}, {6.06 (s)}, {5.54 (s)}, 5.33 (s), {2.34 (q)}, {1.05 (t)}. $^{31}P\{^{1}H\}$ NMR (DMSO-d_6:D_2O 9:1): δ/ppm = -7.5. **O=L4**. $^{31}P\{^{1}H\}$ NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 26.5. All ^{1}H signals of **O=L4** are superimposed to those belonging to **L4**. Therefore, only the percent value for the total ^{1}H integral (**L4**+ **O=L4**) is given. Minor P-containing species: $^{31}P\{^{1}H\}$ NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 27.2 (48 h), 22.4 (48-72 h).

Scheme S4 and **Table S6**. Molar conductivity and NMR detected species as a function of time for DMSO/water 9:1 *v/v* solution of **4** at 37°C. Data for analogous experiment with 0.1 M NaCl are given in parentheses.

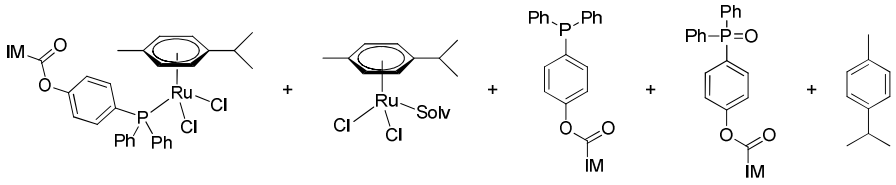


4 **1** **S** **L4** **O=L4**

time / hours		0.5	24	48	72
Λ_m / S·cm^2·mol^{-1}		11	13	15	-
% NMR (NaCl experiment)	**4**	84 (88)	67 (80)	59 (65)	53 (60)
	1	5 (5)	6 (9)	7 (10)	8 (11)
	S	9 (6)	7 (4)	4 (2)	2 (1)
	L4 + O=L4	0 (0)	12 (2)	17 (13)	20 (14)
	***p*-cymene**	2 (1)	8 (5)	13 (10)	17 (14)

*Compound **5***. Data are compiled in Table S7 while NMR detected species are shown in Scheme SI5. **5**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.80–7.68 (m, 6H), 7.64 (pseudo-q, *J* = 8.4 Hz, 4H), 7.48–7.36 (m, 6H), 7.15–7.10 (m, 3H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.71 (dd, *J* = 8.7, 1.7 Hz, 1H), 5.27 (d, *J* = 6.0 Hz, 2H), 5.22 (d, *J* = 5.7 Hz, 2H), 4.05 (s, 2H), 3.74 (s, 3H), 2.49–2.43* (m, *J* = 7.2 Hz), 2.24 (s, 3H), 1.73 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 6H). *partially overlapped with DMSO signal. ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 23.7. **L5**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = {7.64 (pseudo-q)}, {7.48-7.36 (m)}, {6.94 (d)}, {6.71 (dd)}, {4.05 (s)}, {3.74 (s)}, 2.25 (s, 3H). ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = -7.7. **O=L5**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 4.08 (s, 2H), 2.23 (s, 3H). ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 26.5. Minor P-containing species: ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 38.3 (72 h).

Scheme S5 and **Table S7**. Molar conductivity and NMR detected species as a function of time for DMSO/water 9:1 *v*/*v* solution of **5** at 37°C. Data for analogous experiment with 0.1 M NaCl are given in parentheses.

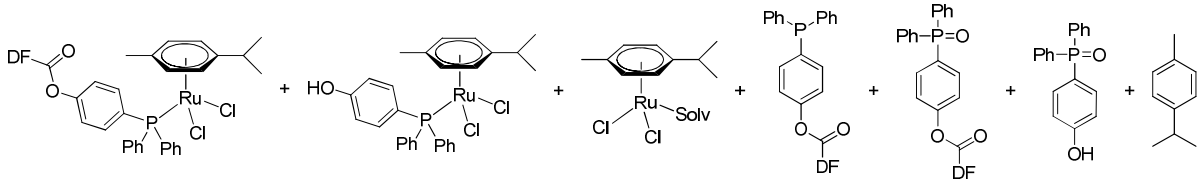


5 **S** **L5** **O=L5**

time / hours		0.5	24	48	72
Λ_m / S·cm^2·mol^{-1}		24	26	28	-
% NMR (NaCl experiment)	**5**	74 (78)	63 (67)	50 (60)	40 (53)
	S	7 (7)	3 (4)	0 (1)	0 (1)
	L5	6 (1)	7 (5)	11 (6)	16 (8)
	O=L5	10 (11)	15 (16)	21 (16)	22 (17)
	***p*-cymene**	3 (3)	12 (8)	18 (17)	22 (21)

Compound ***6***. Data are compiled in Table S8 while NMR detected species are shown in Scheme SI6. **6**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.81–7.69 (m, 6H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.48–7.38 (m, 6H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 2H), 7.10–7.04 (m, 1H), 6.86 (t, *J* = 7.0 Hz, 1H), 6.22 (d, *J* = 8.0 Hz, 1H), 5.27 (d, *J* = 6.2 Hz, 2H), 5.23 (d, *J* = 5.8 Hz, 2H), 4.07 (s, 2H), 2.50–2.42* (m, *J* = 7.0 Hz), 1.74 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 6H). *partially overlapped with DMSO signal. ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 23.6. **L6**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.69-7.52 (m), {7.33-7.28 (m)}, {6.06 (s)}, {5.54 (s)}, 5.33 (s), {2.34 (q)}, {1.05 (t)}. ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = -7.9. **O=L6**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 4.11 (s, 2H). ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 26.5.

Scheme S6 and **Table S8**. Molar conductivity and NMR detected species as a function of time for DMSO/water 9:1 *v*/*v* solution of **6** at 37°C. Data for analogous experiment with 0.1 M NaCl are given in parentheses.

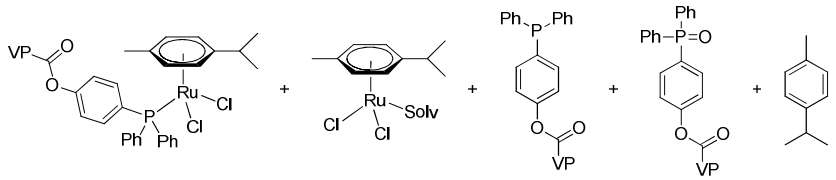


6 **1** **S** **L6** **O=L6** **O=L1**

time / hours		0.5	24	48	72
Λ_m / S·cm^2·mol^{-1}		7.4	12	15	17
% NMR (NaCl experiment)	**6**	77 (86)	67 (52)	48 (37)	38 (29)
	1	0 (2)	2 (11)	2 (12)	2 (10)
	S	4 (5)	2 (5)	0 (4)	0 (4)
	L6	4 (0)	9 (0)	20 (0)	23 (0)
	O=L6	7 (6)	9 (13)	8 (16)	8 (17)
	O=L1	0 (0)	0 (7)	0 (11)	0 (13)
	***p*-cymene**	8 (2)	11 (12)	22 (20)	29 (27)

Compound 7. Data are compiled in Table S9 while NMR detected species are shown in Scheme SI7. **7**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.76 (t, *J* = 9.2 Hz, 2H), 7.73–7.67 (m, 4H), 7.48–7.38 (m, 6H), 7.06 (d, *J* = 7.7 Hz, 2H), 5.27 (d, *J* = 6.1 Hz, 2H), 5.22 (d, *J* = 5.9 Hz, 2H), 2.61–2.54* (m), 2.49–2.42* (m, *J* = 6.8 Hz), 1.74 (s, 3H), 1.64–1.54 (m, 2H), 1.54–1.44 (m, 2H), 1.32 (hex, *J* = 7.1 Hz, 4H), 0.91 (d, *J* = 6.9 Hz, 6H), 0.87 (t, *J* = 7.3 Hz, 6H). *superimposed to DMSO signal. ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 23.8. **L7**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.66–7.51 (m), {7.48–7.37 (m)}, 7.31–7.26 (m, 4H), 7.25–7.19 (m, 4H), {2.60–2.55 (m)}, {1.64–1.54 (m)}, {1.54–1.44 (m)}, {1.37–1.28 (m)}, {0.88 (t, *J* = 7.3 Hz)}. ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = -7.8. **O=L7**. ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 27.2. All ^{1}H signals of **O=L7** are superimposed to those belonging to **L7**. Therefore, only the percent value for the total ^{1}H integral (**L7** + **O=L7**) is given. Minor P-containing species: ^{31}P{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 38.2 (72 h).

Scheme S7 and **Table S9**. Molar conductivity and NMR detected species as a function of time for DMSO/water 9:1 *v*/*v* solution of **7** at 37°C. Data for analogous experiment with 0.1 M NaCl are given in parentheses.



7 **S** **L7** **O=L7**

time / hours		0	6	24	48	72
Λ_m / S·cm^2·mol^{-1}		9.1	10	11	11	12
% NMR (NaCl experiment)	**7**	74 (77)	68 (72)	57 (71)	51 (51)	35 (39)
	S	5 (6)	4 (5)	2 (2)	0 (0)	0 (0)
	L7 + O=L7	19 (15)	23 (16)	31 (16)	30 (31)	38 (33)
	***p*-cymene**	2 (2)	5 (7)	10 (11)	19 (18)	27 (28)

Cell culture and cytotoxicity studies

Human ovarian carcinoma (A2780 and A2780cisR) cell lines were obtained from the European Collection of Cell Cultures (ECACC, UK). The non-tumoral human embryonic kidney (HEK-293) cell line was obtained from ATCC (Sigma, Switzerland). RPMI-1640 GlutaMAX and DMEM GlutaMAX media were obtained from Life Technologies (Switzerland), fetal bovine serum (FBS) was obtained from Sigma, penicillin streptomycin solution was obtained from Life Technologies and cisplatin was obtained from TCI.

The cells were routinely cultured in RPMI-1640 GlutaMAX (A2780 and A2780cisR) and DMEM GlutaMAX (HEK-293) medium containing 10% heat-inactivated FBS and 1% penicillin/streptomyc in solution at 37 °C and CO_2 (5%). The A2780cisR cell line was routinely treated with cisplatin (2 μM) in the medium. The cytotoxicity of compounds was measured using the MTT assay (MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide).[1] Cells were seeded in flat-bottom 96-well plates as a suspension in medium containing 10% heat-inactivated FBS and 1% penicillin/streptomycin solution (100 μL and approximately 4300 cells per well) and incubated for 24 h. Stock solutions of compounds were prepared in DMSO and were rapidly diluted in medium. The solutions were sequentially diluted (final DMSO concentration of 0.5%) to give a compound concentration range (0 μM to 500 μM). Cisplatin was tested as a positive control (0 to 100 μM). The compounds were added to the pre-incubated 96-well plates in 100 μL aliquots and the plates were incubated for 72 h. MTT (20μL, 5 mg/mL in Dulbecco's Phosphate Buffered Saline, DPBS) was added to the cells and the plates were incubated for further 4 h. The culture medium was aspirated, and the purple formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved in DMSO (100 μL per well). The absorbance of the resulting solutions, directly proportional to the number of surviving cells, was quantified at 590 nm using a SpectroMax M5e multi-mode microplate reader and SoftMax Pro software (version 6.2.2). The percentage of surviving cells was calculated from the absorbance of wells

corresponding to the untreated control cells. The reported IC_{50} values (Table 1) are based on means from two independent experiments, each comprising four testings per concentration level.

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