SUPPORTING INFORMATION

Ruthenium-catalyzed Redox Isomerizations inside Living Cells

Cristian Vidal,[1] María Tomás-Gamasa,[1] Alejandro Gutiérrez-González,[1] and José L. Mascareñas[1]*

[1] Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782, Santiago de Compostela, Spain.

Corresponding Author

joseluismascarenas@usc.es

Table of Contents

S1.- GENERAL INFORMATION

Procedures for the synthesis of precursors were performed under an atmosphere of dry nitrogen using vacuum-line and standard Schlenk techniques. Dry solvents were directly purchased from *Sigma Aldrich* and used without further purification. Water used in the catalytic reactions was purchased from *Sigma Aldrich* (LC-MS chromasol) with a pH between 7.4 – 7.6.

Chemicals were purchased from *Sigma Aldrich*, *Alfa Aesar* and *Fluka* and used without further purification.

Compounds **1b-d, f; 2b-d, f; 3a-c; 1a-*d*1 and 4a-b** are known compounds and were synthesized according to the literature. Their ^{1}H and ^{13}C NMR data were in complete agreement with the reported values.

[**Ru**] and [**Ir**] are known complexes, and were synthesized from the corresponding ligands following reported procedures. Their ^{1}H data and ^{13}C NMR were in complete agreement with the reported values.

All catalytic reactions were carried out with degassed solvents unless otherwise stated. Reaction mixtures were stirred using Teflon-coated magnetic stir bars. The abbreviation "r.t." refers to reactions carried out approximately at 23 °C. Temperature was maintained using Thermowatch-controlled heating blocks. Thin-layer chromatography (TLC) was performed on silica gel plates and components were visualized by observation under UV light and / or by treating the plates with $KMnO_4$ or *p*-anisaldehyde followed by heating. Flash chromatography was carried out on silica gel. Dryings were performed with anhydrous $MgSO_4$.

Concentration refers to the removal of volatile solvents via distillation using a rotary evaporator *Büchi R-210* equipped with a thermostated bath *B-491*, a vacuum regulator *V-850*, followed by residual solvent removal under high vacuum.

^{1}H NMR (300 MHz) spectra were recorded at room temperature on a *Varian Mercury* 300 MHz spectrometer. ^{13}C NMR (126 MHz) were recorded on a *Bruker DRX-500* spectrometer. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, bs = broad singlet, dd = doublet doublets, dt = doublet triplets, dq = doublet quartets, td = triplet doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, dddd = doublet of doublet of doublet of doublets), coupling

constants in Hertz (Hz). The chemical shifts for protons (δ) are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ δ = 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ δ = 77.0). NMR spectra were analyzed using *MestreNova© NMR* data processing software (www.mestrelab.com).

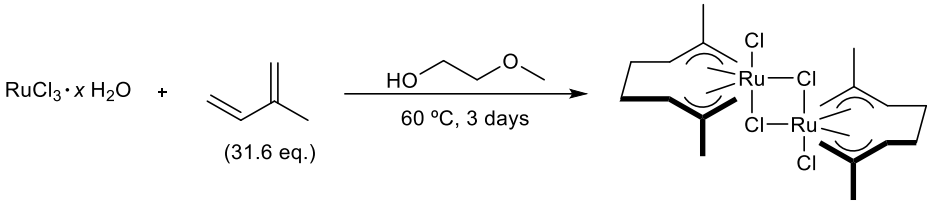
High resolution mass spectra (HRMS) were acquired using electrospray (ESI) and were recorded at the CACTUS facility of the University of Santiago de Compostela.

Measurements of fluorescence were performed using a *Varian Cary Eclipse* fluorimeter thermostated cell compartment at 20 ± 0.5 °C using 1 cm quartz cells. The measurements were made with the following settings: increment 1.0 nm, averaging time 0.1 s, excitation slit width 5.0 nm, emission slit width 5.0 nm, PMT voltage 620 V.

Measurements of UV were performed using a *Jasco V-670* spectrometer.

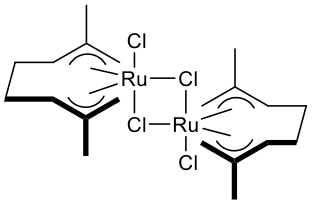
S2.- SYNTHESIS OF COMPLEXES [Ru] and [Ir]

2.1.- Synthesis of [Ru(η^3 : η^3-$C_{10}H_{16}$)Cl(μ^2-*O,O*-O_2CMe)] ([Ru])

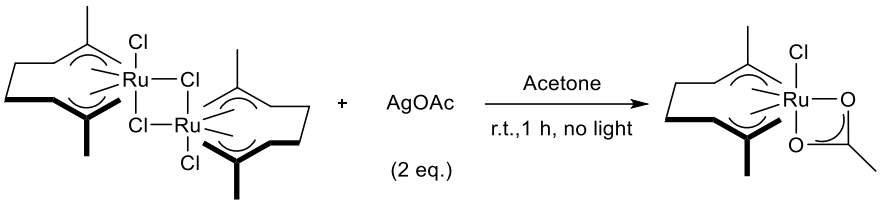


Procedure adapted from Toeriend *et al*.[1]

$RuCl_3$·x H_2O (4.4 mmol, 1.00 g, 1.0 eq.) was added to a heat gun dried pressure Schlenk tube and then 2-methoxyethanol (13.0 mL, 0.34 M) and isoprene (139.9 mmol, 14.0 mL, 31.6 eq.) were added under nitrogen. The solution became dark and was stirred for 3 days at 60 °C. After this time, the reaction was cooled at r.t. and the solid was collected by filtration. The pink solid was washed with Et_2O (3 x 15.0 mL) and dried in vacuum. The ruthenium complex [{Ru(η^3 : η^3-$C_{10}H_{16}$)Cl(μ-Cl)}$_2$] was isolated as a pink solid and stored under nitrogen.



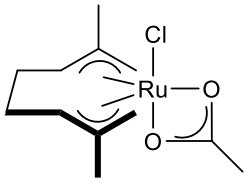
[{Ru(η^3 : η^3-$C_{10}H_{16}$)Cl(μ-Cl)}$_2$]. Pink solid. **Yield** = 38%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.09 (s, 1H), 5.72 (s, 1H), 5.40 (s, 1H), 5.22 (s, 1H), 5.07 (s, 1H), 4.87 (s, 1H), 4.74 (s, 1H), 4.73 (m, 1H), 4.65 (m, 1H), 4.49 (s, 1H), 4.48 (m, 1H), 4.45 (m, 1H), 2.7 - 2.4 (m, 2H), 2.47 (s, 3H), 2.38 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H). Resonances not specifically assigned to different diastereoisomers.



([**Ru**])

Procedure from Tocher *et al*.[2]

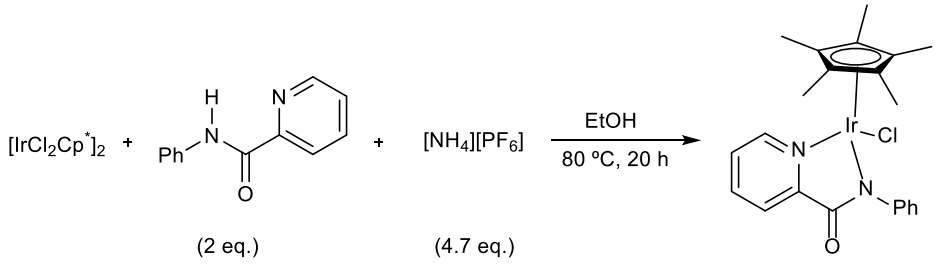
The ruthenium complex [{Ru(η^3 : η^3-$C_{10}H_{16}$)Cl(μ-Cl)}$_2$] (0.3 mmol, 200.0 mg, 1.0 eq.) was suspended in acetone (25.0 mL, 0.01 M) in a heat gun dried Schlenk equipped with a stir bar. Then, AgOAc was added (0.7 mmol, 108.3 mg, 2.0 eq.) and the mixture was stirred at room temperature for 1 h in the absence of light. The resulting orange-red solution was then filtered over Kieselguhr to remove the precipitate of AgCl and the solvent was removed in vacuum to give a pale brown solid. The ruthenium complex [**Ru**] was isolated as a pale brown solid and stored under nitrogen.



([**Ru**])

[Ru(η^3 : η^3-$C_{10}H_{16}$)Cl(μ^2-*O,O*-O_2CMe)] ([**Ru**]). Pale brown solid. **Yield** = 60%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.51 (s, 1H), 4.65 (s, 1H), 4.63 (s, 1H), 4.20 (s, 1H), 3.56 (s, 1H), 3.49 (m, 1H), 2.53 (m, 4H), 2.29 (s, 3H), 2.12 (s, 3H), 1.85 (s, 3H).

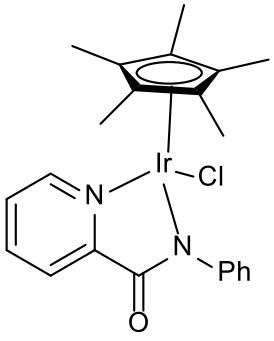
2.2.- Synthesis of [IrCp*(*N*-phenyl-2-pyridinecarbomidate)Cl] ([Ir])



([**Ir**])

Procedure from McGowan *et al*.[3]

Pyridine-2-carboxylic acid phenylamide (75.0 µmol, 14.9 mg, 2.0 eq.) was added to a stirred suspension of $[IrCl_2Cp^*]_2$ (38 µmol, 30.0 mg, 1.0 eq) in EtOH (9.4 mL, 4.0 µM) in a heat gun dried Schlenk equipped with a stir bar. The reaction mixture was stirred at 80 °C. After 15 min, $[NH_4][PF_6]$ (0.2 mmol, 28.8 mg, 4.7 eq.) was added and the mixture was stirred at 80 °C for 20 h. After that, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (30.0 mL), washed with water (2 x 10.0 mL), brine (10.0 mL), dried over $MgSO_4$ and evaporated to form an orange solid. The crude product was recrystallized by vapor diffusion using CH_2Cl_2 / pentane. The iridium complex ([**Ir**]) was isolated as orange crystals and stored under nitrogen.

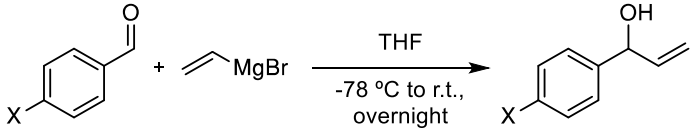


([**Ir**])

[IrCp*(*N*-phenyl-2-pyridinecarbomidate)Cl] ([**Ir**]). Orange crystals. **Yield** = 57%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.57 (br d, *J* = 5.4 Hz, 1H), 8.17 (br d, *J* = 8.0 Hz, 1H), 7.92 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 1H), 7.65 (br dd, *J* = 8.3, 1.1 Hz, 2H), 7.49 (ddd, *J* = 7.5, 5.6, 1.4 Hz, 1H), 7.32 (m, 2H), 7.09 (t, *J* = 7.1 Hz, 1H), 1.41 (s, 15H).

S3.- SYNTHESIS OF SUBSTRATES (1b-d, f-g; 3a-c and 1a-*d*1)

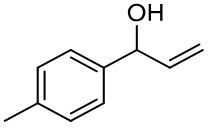
3.1.- General procedure for the preparation of aryl allylic alcohols (1b-d, f)



(**1b-d, f**)

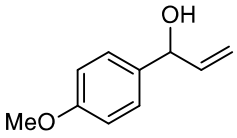
Procedure from Doyle *et al*.[4]

In a heat gun dried round bottom flask, a 1.0 M solution of vinylmagnesium bromide in THF (11.0 mL, 11.0 mmol, 1.1 eq.) was added via syringe to a solution of aryl aldehyde (10.0 mmol) in dry THF (0.3 M) at -78 °C over 30 min. Upon complete addition, the reaction was allowed to reach room temperature and stirred overnight. Then, the reaction was quenched with saturated aqueous NH_4Cl (20.0 mL), stirred for 20 min, and extracted with EtOAc (3 x 25.0 mL). The combined organic phases were washed with brine (20.0 mL), dried, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane / EtOAc (90:10 to 70:30) as eluent.



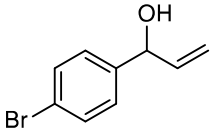
(**1b**)

1-(*p*-tolyl)prop-2-en-1-ol (**1b**). Colorless liquid. $\mathbf{R_f}$ = 0.6 (Hexane / EtOAc 80:20). **Yield** = 72%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.07 (dddd, *J* = 17.1, 10.3, 5.9, 0.4 Hz, 1H), 5.35 (dtd, *J* = 17.1, 1.4, 0.4 Hz, 1H), 5.21 (dtd, *J* = 10.3, 2.0, 0.8 Hz, 1H), 5.14 (d, *J* = 5.9 Hz, 1H), 2.40 (s, 3H).



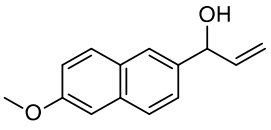
(**1c**)

1-(4-methoxyphenyl)prop-2-en-1-ol (**1c**). Colorless liquid. $\mathbf{R_f}$ = 0.6 (Hexane / EtOAc 80:20). **Yield** = 87%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.0 Hz, 2H) 6.89 (d, *J* = 8.0, 2H), 6.08 - 5.98 (m, 1H), 5.32 (d, *J* = 18.4 Hz, 1H), 5.18 (d, *J* = 10.3, 1H), 5.13 (br s, 1H), 3.78 (s, 3H).



(**1d**)

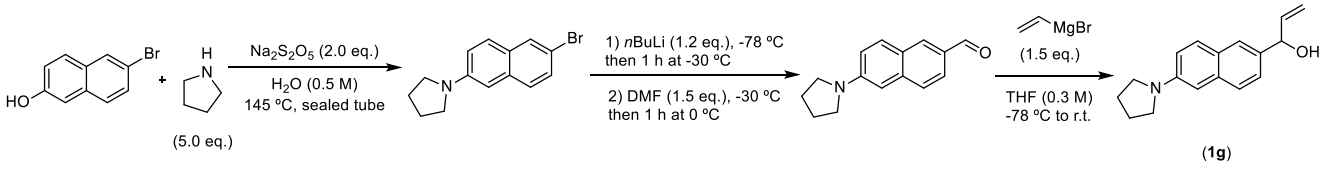
1-(4-bromophenyl)prop-2-en-1-ol (**1d**). Colorless liquid. $\mathbf{R_f}$ = 0.6 (Hexane / EtOAc 80:20). **Yield** = 55%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 8.5, 3.0 Hz, 2H), 7.25 (dd, *J* = 8.5, 3.0 Hz, 2H), 6.04 - 5.97 (m, 1H), 5.34 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.23 - 5.21 (m, 1H), 5.17 (br s, 1H), 2.01 (bs, 1H).



(**1f**)

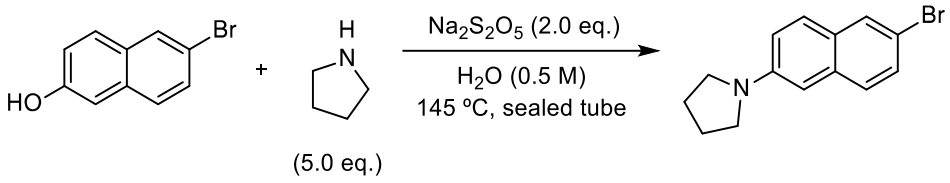
1-(6-methoxynaphthalen)prop-2-en-1-ol (**1f**).[5] White solid. $\mathbf{R_f}$ = 0.17 (Hexane / EtOAc 90:10). **Yield** = 76%. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 - 7.66 (m, 3H), 7.44 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.16 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.12 (d, *J* = 2.5 Hz, 1H), 6.12 (ddd, *J* = 17.1, 10.3, 5.9 Hz, 1H), 5.39 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.29 (d, *J* = 5.9 Hz, 1H), 5.22 (dt, *J* = 10.3, 1.4 Hz, 1H), 3.90 (s, 3H).

3.2.- Synthesis of 1-(6-(pyrrolidin-1-yl)naphthalen-2-yl)prop-2-en-1-ol (1g)



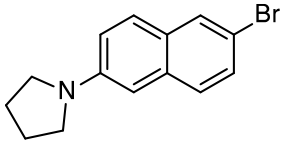
(**1g**)

3.2.1.- Synthesis of 1-(6-bromonaphthalen-2-yl)pyrrolidine



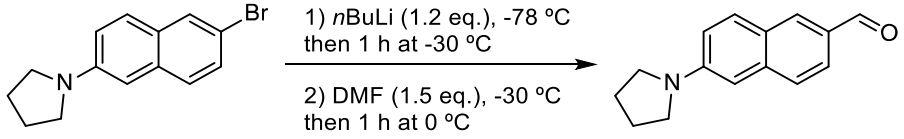
Procedure adapted from Ahn *et al*.[6]

A mixture of pyrrolidine (43.5 mmol, 3.6 mL, 5.0 eq.), 6-bromo-2-naphtol (8.7 mmol, 2.0 g), $Na_2S_2O_5$ (17.4 mmol, 3.3 g, 2.0 eq.) and water (19.3 mL, 0.5 M) in a sealed tube was stirred at 145 °C for 48 h. After being cooled to r.t., the reaction mixture was diluted with 20.0 mL of water and the product was extracted with CH_2Cl_2 (2 x 30.0 mL). The organic phases were dried and concentrated in vacuum. The residue was purified by silica gel column chromatography using hexane / EtOAc (90:10 to 60:40) as eluent. The compound was obtained as a white solid.



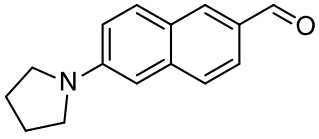
1-(6-bromonaphthalen-2-yl)pyrrolidine. White solid. $\mathbf{R_f}$ = 0.65 (Hexane / EtOAc 90:10). **Yield** = 95%. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.81 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 9.1 Hz, 1H), 7.39 (dd, *J* = 9.1, 2.1, 1H), 7.01 (m, 1H), 6.77 (bs, 1H), 3.41 (m, 4H), 2.07 (m, 4H).

3.2.2.- Synthesis of 6-(pyrrolidin-1-yl)-2-naphthaldehyde



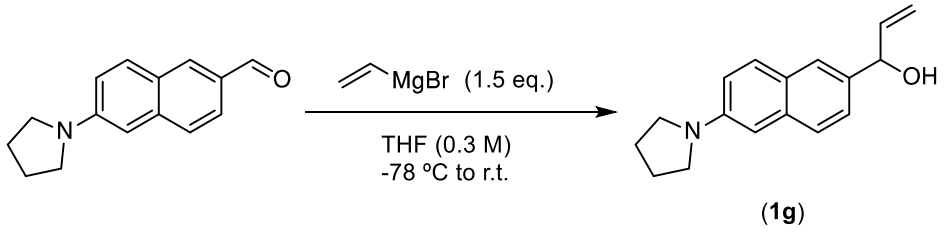
Procedure adapted from Ahn *et al*.[6]

1-(6-bromonaphthalen-2-yl)pyrrolidine (3.0 mmol, 828.5 mg) was dissolved in anhydrous THF (7.5 mL, 0.4 M) in a heat gun dried round bottom flask, and the solution was cooled to -78 °C under nitrogen. Then, 2.5 M *n*BuLi in hexane (4.5 mmol, 1.4 mL, 1.2 eq.) was added. The reaction was stirred at -30 °C for 1 h and then treated with anhydrous DMF (4.5 mmol, 0.4 mL, 1.5 eq.). It was allowed to attain 0 °C and after being stirred at that temperature for 1 h, the reaction mixture was quenched with sat. NH_4Cl (5.0 mL). The product was extracted with CH_2Cl_2 (2 x 30.0 mL). The organic phases were dried and concentrated in vacuum. The residue was purified by silica gel column chromatography using hexane / EtOAc (95:5 to 80:20) as eluent. The compound was obtained as a yellow solid.

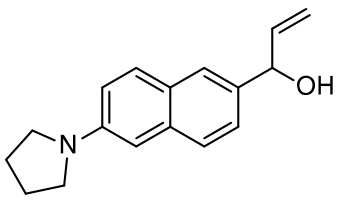


6-(pyrrolidin-1-yl)-2-naphthaldehyde. Yellow solid. $\mathbf{R_f}$ = 0.16 (Hexane / EtOAc 95:5). **Yield** = 86%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.13 (s, 1H), 7.90 (d, *J* = 9.6 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.00 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 3.43 (t, *J* = 6.6 Hz, 4H), 2.11 − 2.06 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 192.0, 148.4, 139.1, 135.3, 131.1, 130.3, 126.6, 124.9, 123.7, 116.5, 104.8, 47.9, 25.

3.2.3.- Synthesis of 1-(6-(pyrrolidin-1-yl)naphthalen-2-yl)prop-2-en-1-ol (1g)



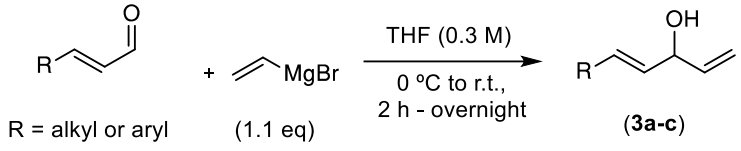
6-(pyrrolidin-1-yl)-2-naphthaldehyde (1.1 mmol, 250.0 mg) was dissolved in anhydrous THF (3.7 mL, 0.3 M) in a heat gun dried round bottom flask. The reaction was cooled to -78 °C and the 1.0 M vinyl magnesium bromide in hexane (1.7 mmol, 1.7 mL, 1.5 eq.) was added via syringe slowly. After that, the reaction was warmed to r.t. and followed by TLC (hexane / EtOAc 80:20). After 3 h, the reaction was quenched with sat. NH_4Cl (5.0 mL). The product was extracted with CH_2Cl_2 (2 x 30.0 mL). The organic phases were dried and concentrated in vacuum. The residue was purified by silica gel column chromatography using hexane / EtOAc (95:5 to 80:20). The product **1g** was obtained as a yellow solid.



(**1g**)

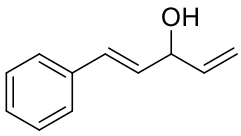
1-(6-(pyrrolidin-1-yl)naphthalen-2-yl)prop-2-en-1-ol (1g). Yellow solid. $\mathbf{R_f}$ = 0.1 (Hexane / EtOAc 90:10). **Yield** = 71%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.70 – 7.62 (m, 3H), 7.35 (dd, *J* = 8.5, 1.3 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.74 (d, *J* = 1.8 Hz, 1H), 6.14 (ddd, *J* = 16.7, 10.3, 5.7 Hz, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.30 (t, *J* = 4.4 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 3.40 (t, *J* = 6.5 Hz, 4H), 2.10 - 2.00 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 146.1 (C *ipso*), 140.4 (CH), 135.2 (C *ipso*), 134.9 (C *ipso*), 128.9 (CH), 126.3 (CH), 125.9 (C *ipso*), 125.0 (CH), 124.9 (CH), 115.9 (CH), 114.7 (CH_2), 104.7 (CH), 75.5 (CH), 47.8(CH_2), 25.5 (CH_2). **LRMS** (*m/z,* ESI): 254.2 $[M-H]^+$. **HRMS-ESI** Calculated for $C_{17}H_{20}NO$: 254.1539, found 254.1537.

3.3.- General procedure for the preparation of (*E*)-1,4-dien-3-ols (3a-c)



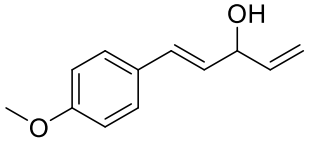
Procedure from Krishna *et al*.[7]

In a heat gun dried round bottom flask, a 1.0 M solution of vinylmagnesium bromide in THF (11.0 mL, 11.0 mmol, 1.1 eq.) was added via syringe to a solution of the corresponding aldehyde (10.0 mmol) in dry THF (0.3 M) at 0 °C over 10 min. Upon complete addition, the reaction was warmed at room temperature and follows by TLC using hexane / EtOAc (80:20) as eluents. Then the reaction was quenched with saturated aqueous NH_4Cl (20.0 mL), stirred for 20 min, and extracted with EtOAc (3 x 25.0 mL). The combined organic layer was washed with brine (20.0 mL), dried, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane / EtOAc (90:10 to 70:30) as eluent.



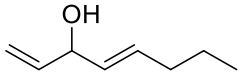
(**3a**)

(*E*)-1-phenylpenta-1,4-dien-3-ol (**3a**). Colorless liquid. $\mathbf{R_f}$ = 0.43 (Hexane / EtOAc 80:20). **Yield** = 84%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.39 (dt, *J* = 2.8, 2.0 Hz, 2H), 7.36 - 7.29 (m, 2H), 7.29 - 7.21 (m, 1H), 6.64 (d, *J* = 16.1 Hz, 1H), 6.30 (d, *J* = 16.1 Hz, 1H), 6.06 (dd, *J* = 17.3, 10.6 Hz, 2H), 5.37 (dd, *J* = 17.3, 1.1 Hz, 2H), 5.23 (dd, *J* = 10.6, 1.1 Hz, 2H), 1.82 (d, *J* = 2.5 Hz, 1H).



(**3b**)

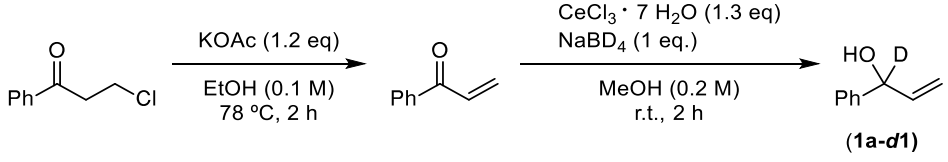
(*E*)-1-(4-methoxyphenyl)penta-1,4-dien-3-ol (**3b**). Yellow syrup. $\mathbf{R_f}$ = 0.41 (Hexane / EtOAc 70:30). **Yield** = 67%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.43 - 7.30 (m, 2H), 6.96 - 6.82 (m, 2H), 6.66 - 6.51 (m, 1H), 6.12 (dd, *J* = 15.9, 6.6 Hz, 1H), 6.00 (ddd, *J* = 17.1, 10.3, 5.8 Hz, 1H), 5.35 (dt, *J* = 17.4, 1.4 Hz, 1H), 5.21 (dt, *J* = 10.4, 1.2 Hz, 1H), 4.81 (q, *J* = 5.5 Hz, 1H), 3.83 (s, 3H).



(**3c**)

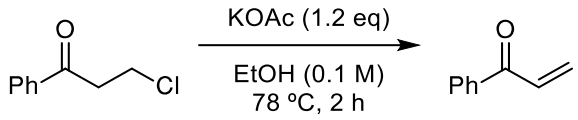
(*E*)-octa-1,4-dien-3-ol (**3c**). Colorless liquid. $\mathbf{R_f}$ = 0.13 (Hexane / EtOAc 95:5). **Yield** = 50%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.02 - 5.82 (m, 1H), 5.78 - 5.63 (m, 1H), 5.58 - 5.44 (m, 1H), 5.25 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.12 (dq, *J* = 10.4, 1.6 Hz, 1H), 4.69 - 4.46 (t, *J* = 5.8 Hz, 1H), 2.12 - 1.93 (m, 2H), 1.48 - 1.31 (m, 2H), 0.90 (td, *J* = 7.4, 1.4 Hz, 3H).

3.4.- Synthesis of 1-phenylprop-2-en-1-*d*-1-ol (1a-*d*1).



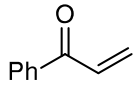
(**1a-*d*1**)

3.4.1.- Synthesis of 1-phenyl-2-en-1-one



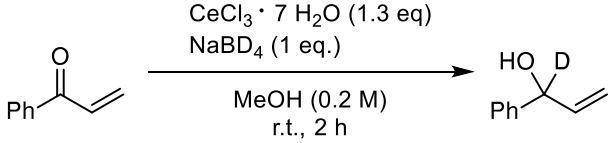
Procedure adapted from Matute *et al*.[8]

A mixture of 3-chloro-1-phenyl-1-propanone (1.0 g, 5.8 mmol) and KOAc (684.0 mg, 6.9 mmol, 1.2 eq.) in EtOH (50.0 mL, 0.1 M) was stirred under reflux for 2.5 h. After cooling to r.t., the solvent was evaporated and the resiude was dissolved in EtOAc (50.0 mL) and washed with H_2O (3 x 50.0 mL). The organic phases were dried, filtered and concentrated. The residue was purified by silica gel column chromatography using hexane / EtOAc (100:0 to 95:5). The product 1-phenyl-2-en-1-one was obtained as a colorless oil.



1-phenyl-2-en-1-one. Colorless oil. $\mathbf{R_f}$ = 0.29 (Hexane / EtOAc 95:5). **Yield** = 50%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.97 - 7.93 (m, 2H), 7.58 (td, *J* = 7.5, 2.0 Hz, 1H), 7.51 - 7.45 (m, 2H), 7.16 (dd, *J* = 17.3, 10.6 Hz, 1H), 6.44 (dd, *J* = 17.3, 1.7 Hz, 1H), 5.94 (dd, *J* = 10.6, 1.7 Hz, 1H).

3.4.1.- Synthesis of *1-phenylprop-2-en-1-d-1-ol* (1a-*d*1)

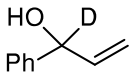


(**1a-*d*1**)

Procedure adapted from Matute *et al*.[8]

$NaBD_4$ (110.9 mg, 2.6 mmol, 1.0 eq.), was added to a mixture of 1-phenylprop-2-en-1-one (350.0 mg, 2.6 mmol) and $CeCl_3$·7 H_2O (1.3 g, 3.4 mmol, 1.3 eq.) in MeOH (14.0 mL, 0.2 M) over a period of 30 min. After 2 h, the solvent was evaporated and the residue was dissolved in Et_2O (30.0 mL) and washed with

H_2O (3 x 25.0 mL). The organic phase was dried, filtered and concentrated. The residue was purified by silica gel column chromatography using hexane / EtOAc (90:10). The product **1a-*d*1** was obtained as a colorless oil.

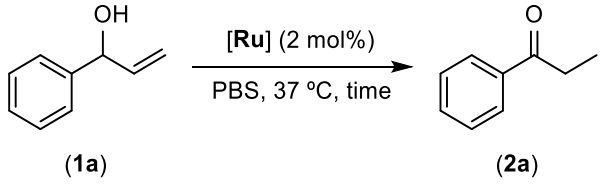


(**1a-*d*1**)

1-phenylprop-2-en-1-d-1-ol (1a-*d*1). Colorless oil. $\mathbf{R_f}$ = 0.15 (Hexane / EtOAc 90:10). **Yield** = 93%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40 - 7.25 (m, 5H), 6.06 (dd, *J* = 17.1, 10.4 Hz, 1H), 5.36 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.21 (dd, *J* = 10.4, 1.2 Hz, 1H). **^{2}H NMR** (300 MHz, $CHCl_3$): δ 5.23 (s).

S4.- RUTHENIUM CATALYZED ISOMERIZATION IN DIFFERENT BIOLOGICAL MEDIA.

4.1.- Representative general procedure for the catalytic isomerization of allylic alcohols (1a-g) in different biological media (exemplified for the substrate 1a using [Ru] as catalyst and PBS as solvent)



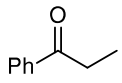
[**Ru**] (4 µmol, 1.3 mg, 2.0 mol%) was added to a Schlenk tube containing a stir bar and PBS (phosphate buffer saline solution, 1.0 mL, 0.2 M), followed by the addition of substrate **1a** (0.2 mmol, 27 µL). The reaction mixture was stirred at 400 rpm and the Thermowatch-controlled heating block was fixed at 37 °C. The reaction was followed by TLC. After 2 h, the reaction mixture was extracted with CH_2Cl_2 (3 x 10.0 mL) and the combined organic fractions were dried, filtered and concentrated and analyzed by ^{1}H-NMR. The obtained yields for the different substrates using different biological media where those reported in the main manuscript, as well as the catalyst loading (**Table 1**).

Table S1. Yields of the isomerization of **1a** using different complexes in different solvents.[a]

Entry	Complex	Solvent	Time (h)	Yield[c]
1	$[RuCl_2(p\text{-cymene})]_2$ (1 mol%)	PBS	2	0%
2	$[RuCl_2(p\text{-cymene})]_2$ (5 mol%)	Lysates[b]	24	36%
3	$[RuCp^*(MeCN)_3][PF_6]$ (2 mol%)	PBS	2	62%
4	$[RuCp^*(MeCN)_3][PF_6]$ (10 mol%)	Lysates[b]	24	56%
5	$[RuCp^*Cl(COD)]$ (10 mol%)	PBS	2	7%
6	$[RuCp^*Cl(COD)]$ (2 mol%)	Lysates[b]	24	40%
7	[**Ir**] (2 mol%)	*t*-BuOH : PBS (2:8)	16	0%
8	[**Ir**] (2 mol%)	PBS	16	0%
9	$[IrCp^*Cl_2]_2$	DMEM	16	8%
10	$[IrCp^*Cl_2]_2$	Lysates[b]	16	3%

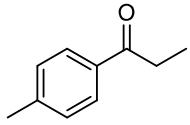
[a] Performed using **1a** (0.2 mmol), solvent (1.0 mL) and the corresponding complex. [b] Cells lysates 7 mg/mL. [c] Yields determined by ^{1}H-NMR using CH_2Br_2 as internal standard.

4.2.- Characterization of the obtained products (2a-2g)



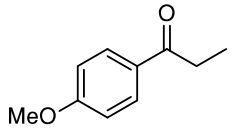
(**2a**)

Propiophenone (**2a**).[9a] Colorless oil. $\mathbf{R_f}$ = 0.42 (Hexane / EtOAc 80:20). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.99 - 7.96 (m, 2H), 7.58 - 7.53 (m, 1H), 7.49 - 7.43 (m, 2H), 3.02 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).



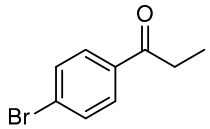
(**2b**)

1-(p-tolyl)propan-1-one (**2b**).[9b] Colorless oil. $\mathbf{R_f}$ = 0.45 (Hexane / EtOAc 80:20). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 2.99 (q, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 1.22 (t, *J* = 7.3 Hz, 3H).



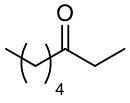
(**2c**)

1-(4-methoxyphenyl)propan-1-one (**2c**).[9c] Colorless oil. $\mathbf{R_f}$ = 0.45 (Hexane / EtOAc 80:20). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H), 2.96 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H).



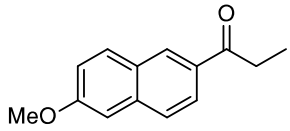
(**2d**)

1-(4-bromophenyl)propan-1-one (**2d**).[9d] Colorless oil. R_f = 0.45 (Hexane / EtOAc 80:20). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 2.96 (q, *J* = 7.2 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H).



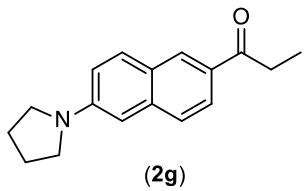
(**2e**)

Octen-3-one (**2e**).[9e] Colorless oil. $\mathbf{R_f}$ = 0.60 (Hexane / EtOAc 80:10). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.39 (t, *J* = 6.8 Hz, 2H), 2.36 (q, *J* = 6.9 Hz, 2H), 1.60 - 1.68 (m, 2H), 1.20 - 1.45 (m, 4H), 1.05 (t, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H).



(**2f**)

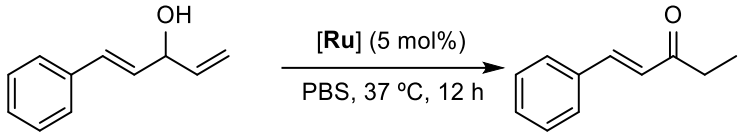
1-(6-methoxynaphthalen-2-yl)propan-1-one (**2f**).[9f] White solid. $\mathbf{R_f}$ = 0.57 (Hexane / EtOAc 80:20). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.35 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.18 (d, *J* = 8.9 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.57 - 7.41 (m, 2H), 4.28 (s, 3H), 3.44 (q, *J* = 7.3 Hz, 2H), 1.62 (t, *J* = 7.3 Hz, 3H).



(**2g**)

1-(6-(pyrrolidin-1-yl)naphthalen-2-yl)propan-1-one (**2g**). Yellow solid. $\mathbf{R_f}$ = 0.60 (Hexane / EtOAc 80:20). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.32 (d, *J* = 1.8 Hz, 1H), 7.92 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.02 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 3.49 - 3.39 (m, 4H), 3.08 (q, *J* = 7.3 Hz, 2H), 2.15 - 2.02 (m, 4H), 1.27 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 200.7 (C *ipso*), 148.0 (C *ipso*), 138.2 (C *ipso*), 131.2 (CH), 130.3 (CH), 130.4 (C *ipso*), 126.1 (CH), 125.1 (C *ipso*), 125.0 (CH), 116.6 (CH), 104.7 (CH), 48.1 (CH_2), 31.8 (CH_2), 25.9 (CH_2), 9.1 (CH_3). **LRMS** (*m/z,* ESI): 254.1 $[M-H]^+$. **HRMS-ESI** Calculated for $C_{17}H_{20}NO$: 254.1539, found 254.1539.

4.3.- Representative general procedure for the catalytic isomerization of 1,4-dien-3-ols (3a-c) in different biological media (exemplified for the substrate 3a using [Ru] as catalyst and PBS as solvent).

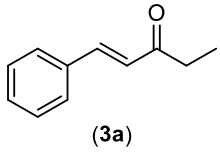


(**3a**) (**4a**)

[**Ru**] (0.01 mmol, 3.3 mg, 5.0 mol%) was added to a Schlenk tube containing a stir bar and PBS (phosphate buffer saline solution, 1.0 mL, 0.2 M), followed by the addition of substrate **3a** (0.2 mmol, 33 mg). The reaction mixture was stirred at 400 rpm and the Thermowatch-controlled heating block was fixed at 37 °C. After 12 h, the reaction mixture was extracted with CH_2Cl_2 (3 x 10.0 mL) and the combined organic fractions were dried, filtered and concentrated and analyzed by ^{1}H-NMR.

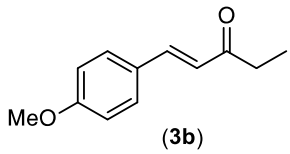
The obtained yields for the different substrates using different biological media where those reported in the main manuscript (**Figure 4a**).

4.4.- Characterization of the obtained products (3a-3c).



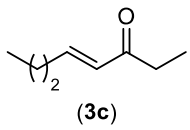
(**3a**)

(*E*)-1-phenylpent-1-en-3-one (**3a**).[10a] White solid. $\mathbf{R_f}$ = 0.42 (Hexane / EtOAc 80:20). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.61 - 7.51 (m, 3H), 7.42 - 7.35 (m, 3H), 6.75 (d, *J* = 16.3 Hz, 1H), 2.70 (q, *J* = 7.5 Hz, 2H), 1.17 (t, *J* = 7.3 Hz, 3H).



(**3b**)

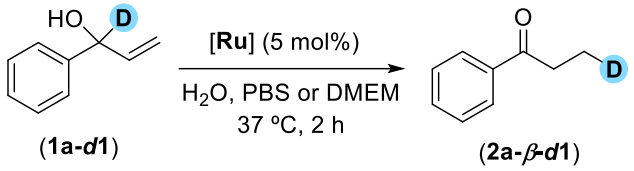
(*E*)-1-(4-methoxyphenyl)pent-1-en-3-one (**3b**).[10a] Yellow solid. $\mathbf{R_f}$ = 0.43 (Hexane / EtOAc 90:10). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.58 - 7.45 (m, 3H), 6.95 - 6.84 (m, 2H), 6.63 (d, *J* = 16.1 Hz, 1H), 3.84 (s, 3H), 2.67 (q, *J* = 7.3 Hz, 2H), 1.16 (t, *J* = 7.3 Hz, 3H).



(**3c**)

(*E*)-oct-4-en-3-one (**3c**).[10b] Colorless oil. $\mathbf{R_f}$ = 0.64 (Hexane / EtOAc 80:20). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.87 (dd, *J* = 15.0, 6.2 Hz, 1H), 6.10 (dt, *J* = 15.2, 0.9 Hz, 1H), 2.51 (q, *J* = 8.0, 2H), 2.27 - 2.20 (m), 1.57 - 1.45 (m, 2H), 1.08 (t, *J* = 7.2, 3H), 0.90 (t, *J* = 7.4, 3H).

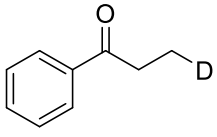
S5.- MECHANISTICS EXPERIMENTS



Only deuteration at beta–position

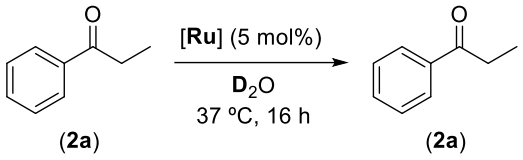
[**Ru**] (0.01 mmol, 3.3 mg, 5.0 mol%) was added to a Schlenk tube containing a stir bar and H_2O or PBS (1.0 mL, 0.2 M), followed by the addition of substrate **1a-*d*1** (0.2 mmol, 27 mg). The reaction mixture was stirred at 400 rpm and the Thermowatch-controlled heating block was fixed at 37 °C. The reaction was followed by TLC using hexane / EtOAc (80:20). After 3 h, the reaction mixture was extracted with CH_2Cl_2 (3 x 10.0 mL) and the combined organic fractions were dried, filtered and concentrated and analyzed by ^{1}H-NMR and ^{2}H-NMR.

As observed by ^{1}H-NMR and ^{2}H-NMR, the isomerization of the substrate **1a-*d*1** furnishes the expected ketone with full deuterium incorporation in the *beta* position. Importantly, the deuterium migration also occurs if the reaction is achieved in biological media (DMEM), which confirms that the ruthenium-hydride intermediate survives these stringent conditions.



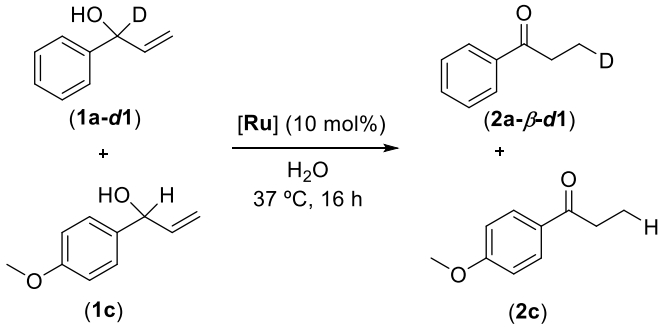
(**2a-β-*d*1**)

2a-β-*d*1. White solid. $\mathbf{R_f}$ = 0.74 (Hexane / EtOAc 80:20). **Yield** = 85% (in PBS), 81% (in DMEM). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.99 - 7.95 (m, 2H), 7.58 - 7.52 (m, 1H), 7.49 - 7.43 (m, 2H), 3.00 (tt, *J* = 7.2, 0.9 Hz, 2H), 1.22 (tt, *J* = 7.2, 3.5 Hz, 2H). **^{2}H NMR** (300 MHz, $CHCl_3$): δ 1.17 (s).



0% of deuterium incorporation

[**Ru**] (0.01 mmol, 3.3 mg, 5.0 mol%) was added to a Schlenk tube containing a stir bar and D_2O (1.0 mL, 0.2 M), followed by the addition of substrate **2a** (0.2 mmol, 27 µL). The reaction mixture was stirred at 400 rpm and the Thermowatch-controlled heating block was fixed at 37 °C. The reaction was followed by TLC using hexane / EtOAc (80:20). After 16 h, the reaction mixture was extracted with CH_2Cl_2 (3 x 10.0 mL) and the combined organic fractions were dried, filtered and concentrated and analyzed by ^{1}H-NMR and ^{2}H-NMR.



No scrambling in crossover experiments

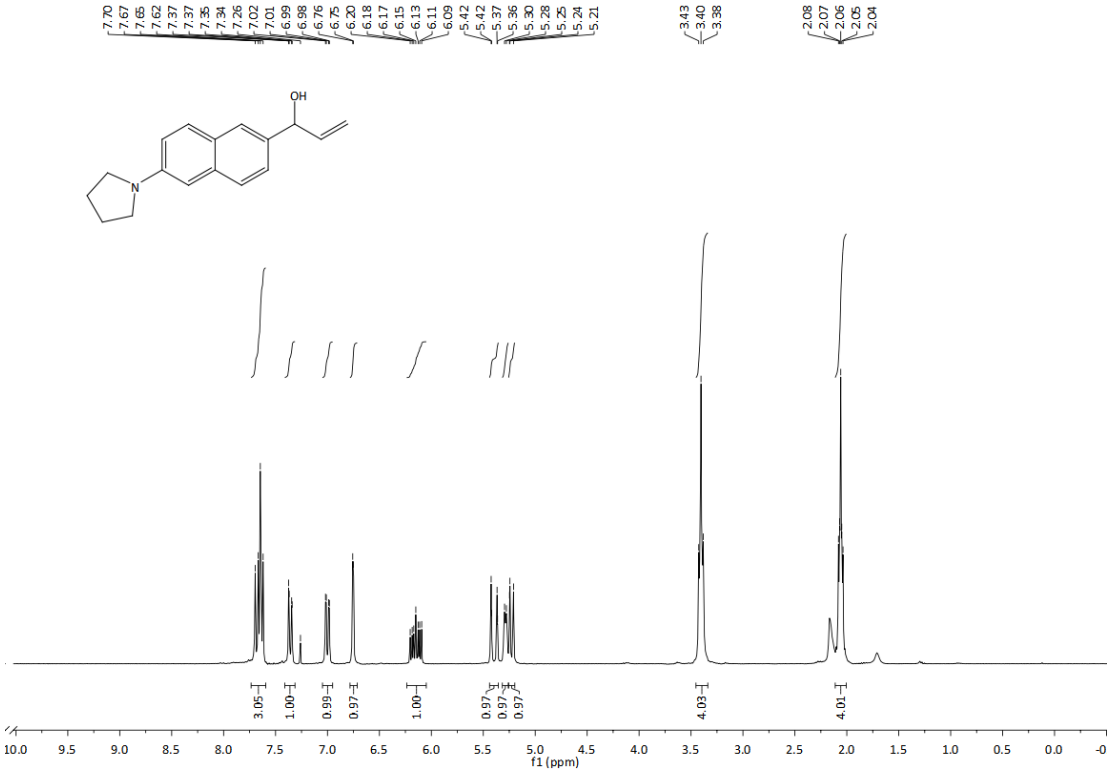
[**Ru**] (0.02 mmol, 6.6 mg, 10 mol%) was added to a Schlenk tube containing a stir bar and H_2O (1.0 mL, 0.2 M), followed by the addition of substrate **2a** (0.2 mmol, 27 µL). The reaction mixture was stirred at 400 rpm and the Thermowatch-controlled heating block was fixed at 37 °C. The reaction was followed by TLC using hexane / EtOAc (80:20). After 16 h, the reaction mixture was extracted with CH_2Cl_2 (3 x 10.0 mL) and the combined organic fractions were dried, filtered and concentrated and analyzed by ^{1}H-NMR and ^{2}H-NMR.

These experiments showed no scrambling in the crossover experiment which is in agreement with an intramolecular hydride transfer.

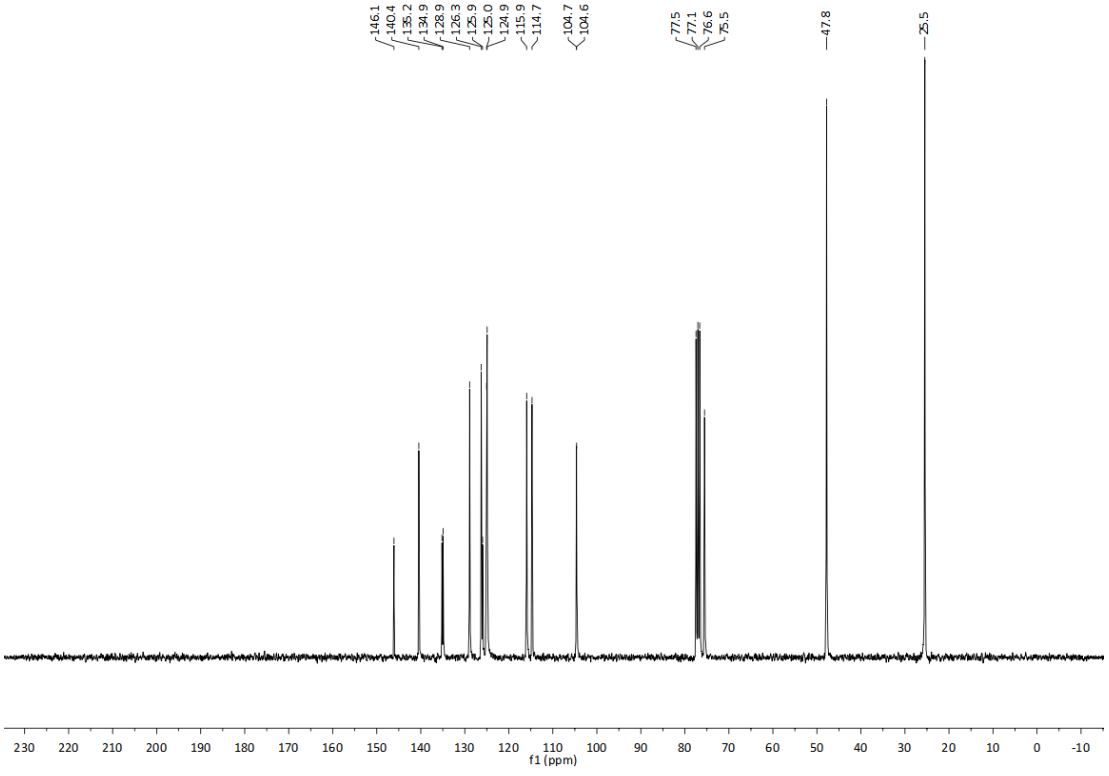
S6.- CHARACTERIZATION OF THE NEW COMPOUNDS (1g and 2g)

6.1.- NMR Spectra of 1-(6-(pyrrolidin-1-yl)naphthalen-2-yl)prop-2-en-1-ol (1g)

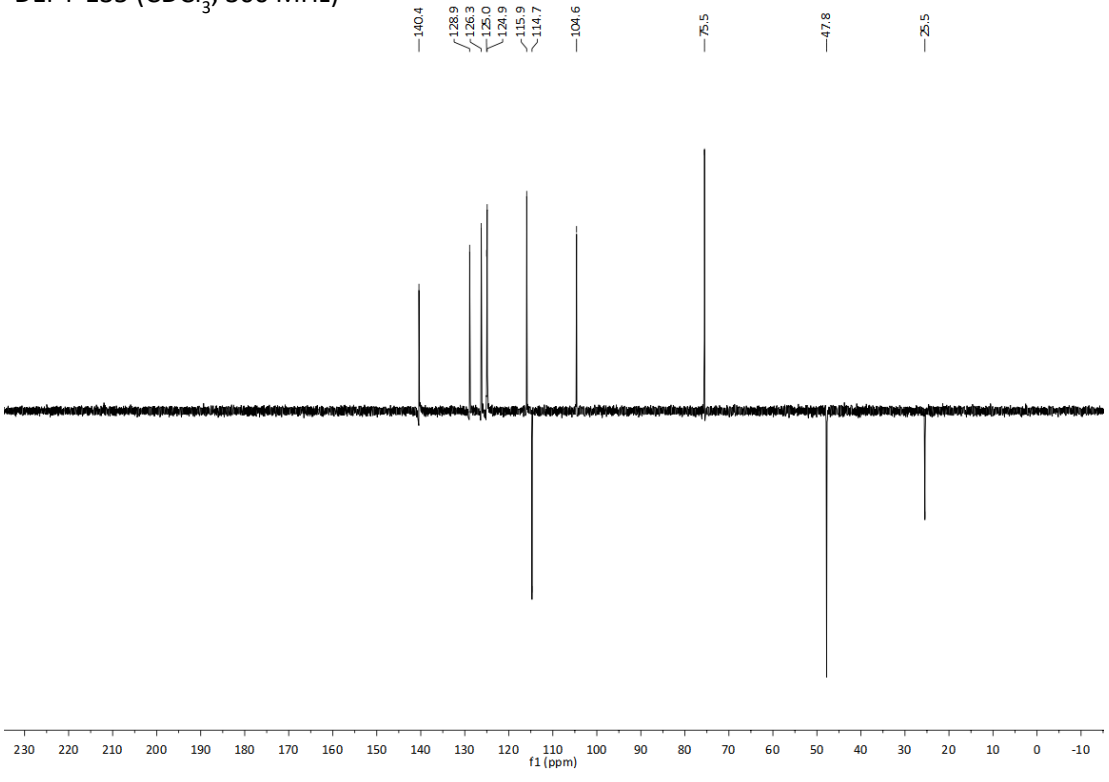
^{1}H ($CDCl_3$, 300 MHz)



^{13}C ($CDCl_3$, 300 MHz)

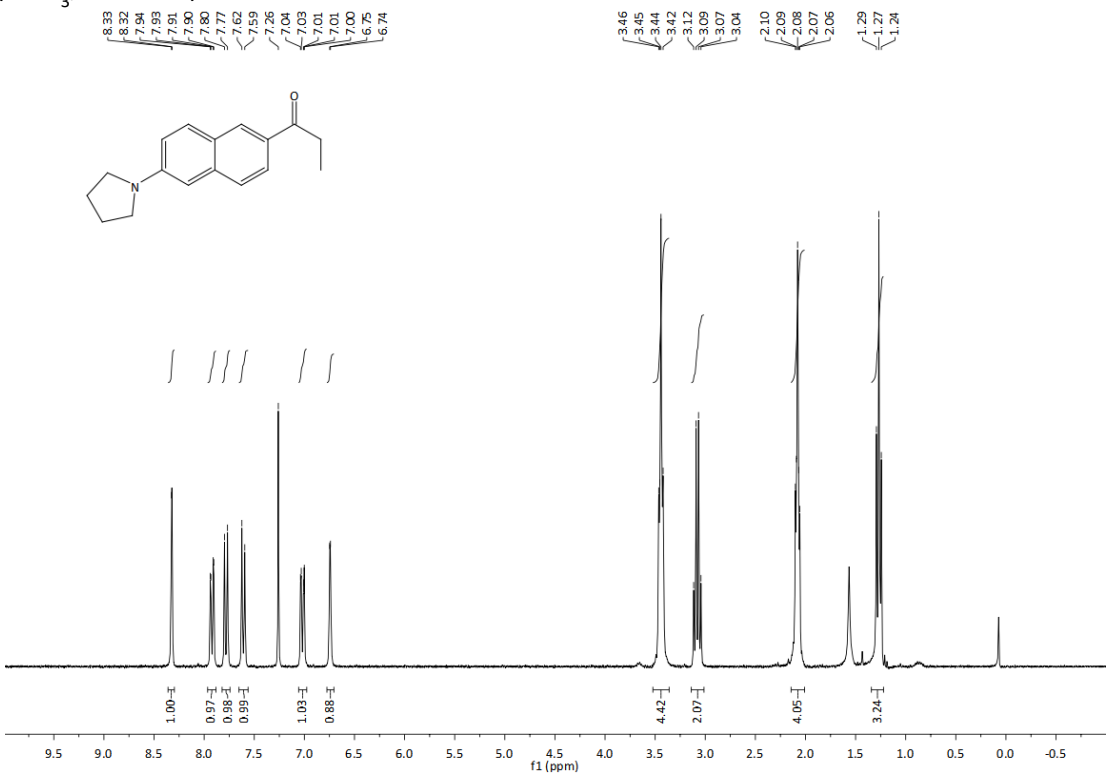


DEPT-135 ($CDCl_3$, 300 MHz)

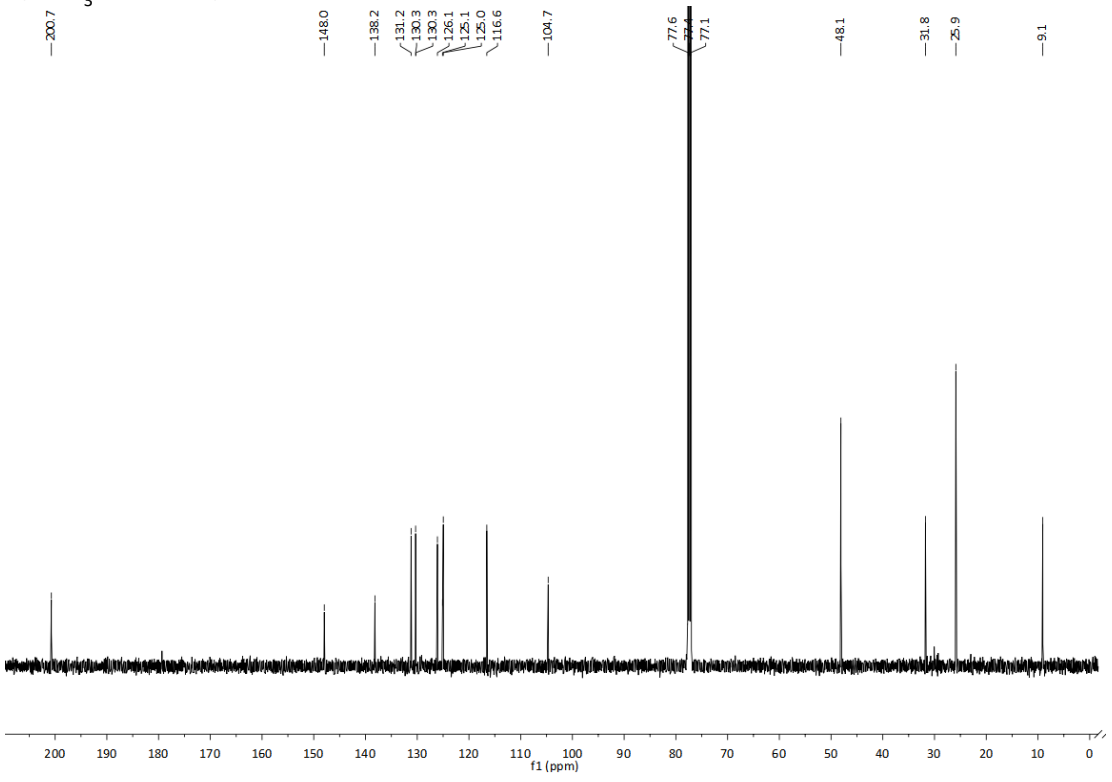


6.2.- NMR Spectra of 1-(6-(pyrrolidin-1-yl)naphthalen-2-yl)propan-1-one (2g).

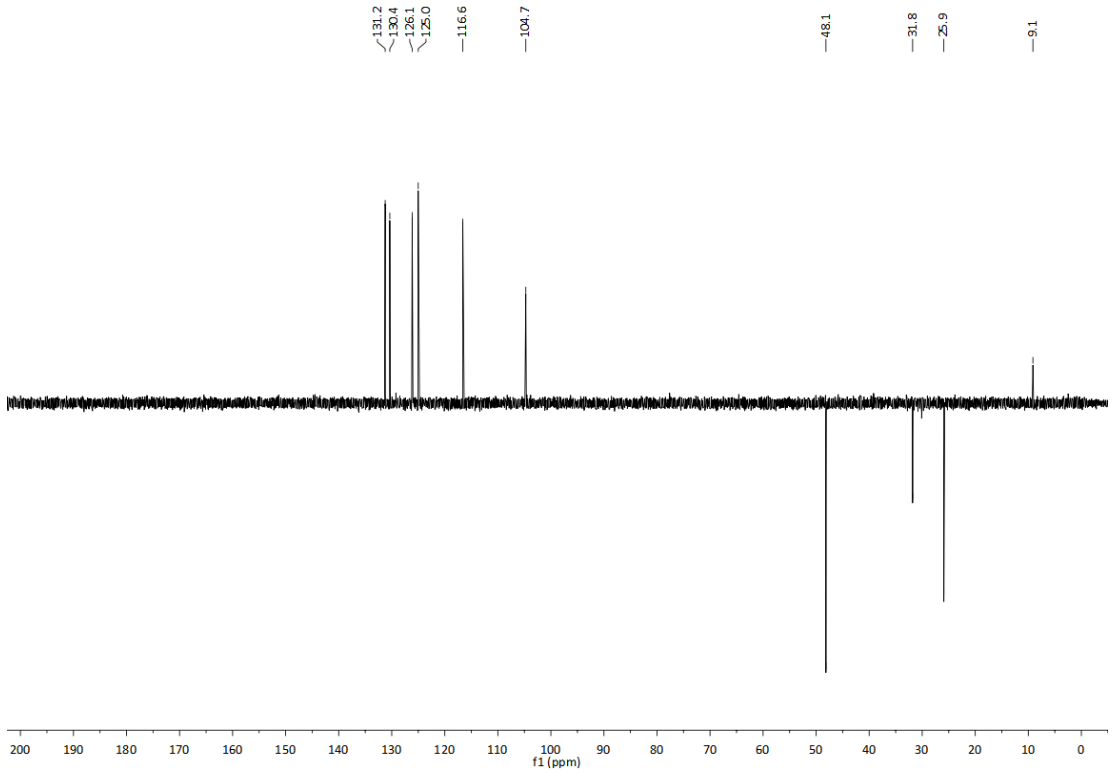
^{1}H ($CDCl_3$, 300 MHz)



^{13}C ($CDCl_3$, 126 MHz)



DEPT-135 ($CDCl_3$, 126 MHz)



6.3.- UV and fluorescence of compounds 1g and 2g

Stock solutions of **1g** and **2g** were prepared in DMSO and the samples used for spectroscopic measurements contained ≈ 0.1% of the stock solvent.

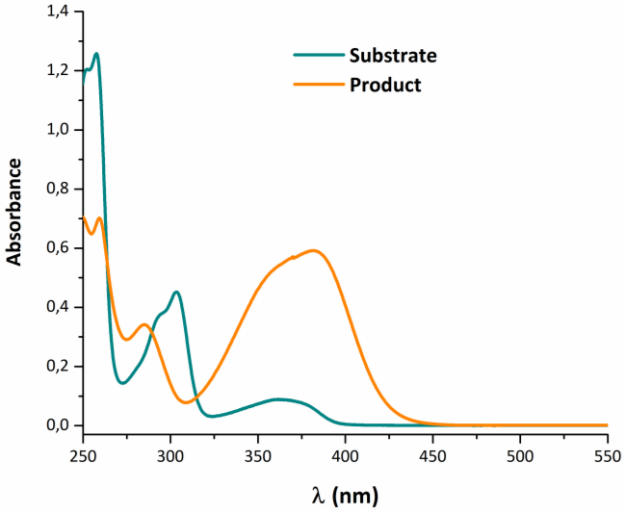


Figure S1. Comparison of UV/Vis absorption spectra of **1g** (20 µM, grey, λ_{abs} = 303 nm) and **2g** (20 µM, orange, λ_{abs} = 381 nm) in MeOH (1.0 mL).

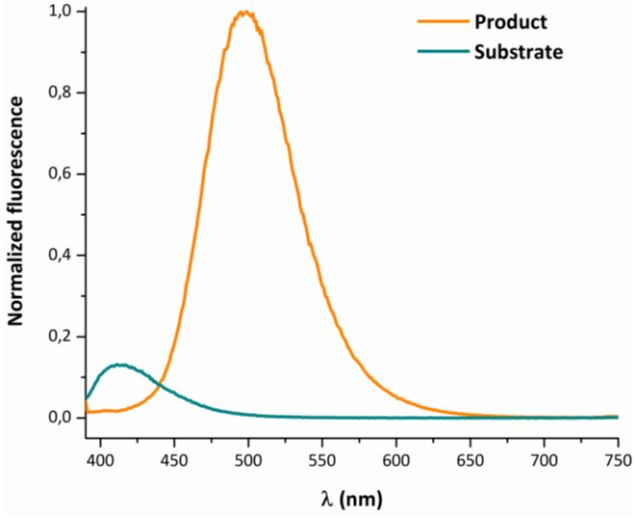


Figure S2. Comparison of normalized fluorescence spectra of **1g** (1 µM, grey, λ_{em} = 411 nm) and **2g** (1 µM, orange, λ_{em} = 498 nm) in MeOH (1.0 mL) with λ_{exc} = 385 nm.

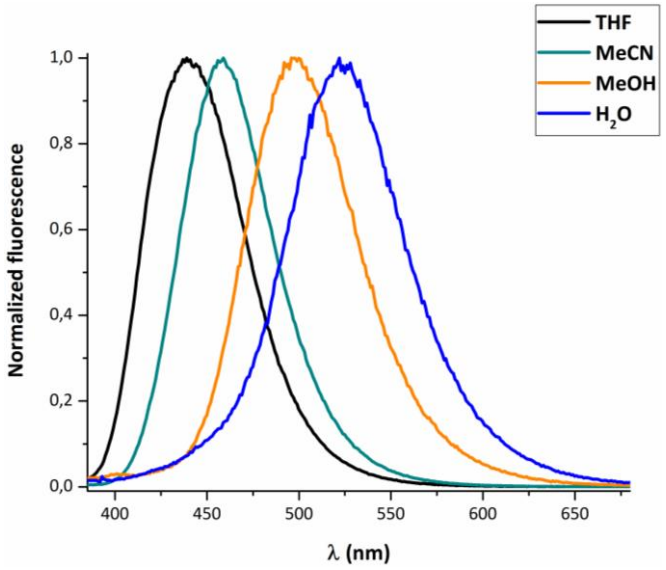


Figure S3. Comparison of normalized fluorescence spectra in different solvents of **2g** (1 µM, λ_{exc} = 350 nm): THF (ε_T = 37.4) λ_{em} = 438 nm; MeCN (ε_T = 45.6) λ_{em} = 458 nm; MeOH (ε_T = 55.4) λ_{em} = 495nm; H_2O (ε_T = 63.1) λ_{em} = 521 nm). ε_T is the polarity index.[11]

S7.- GENERAL INFORMATION FOR THE BIOLOGICAL EXPERIMENTS

All steps were performed on a sterile clean bench *Tesltar AV-100* at room temperature. Solutions stored in a fridge were warmed beforehand in a water bath (37 °C). Unless otherwise specified, all incubations were performed in DMEM.

Cell Culture: All cell lines were cultured in DMEM (Dulbecco´s modified Eagle´s medium), 5 mM glutamine, penicillin (100 units/mL) and streptomycin (100 units/mL) (all from *Invitrogen*). Proliferating cultures were maintained in a 5% CO_2 humidified incubator at 37 °C.

For all the experiments, cells were seeded in the corresponding well at the indicated concentration two days before treatment.

Protein quantification: For protein concentration measurements the Bio-Rad *DC* Protein Assay Kit was used (*Bio-Rad* 500-0114).

GSH detection: For glutathione concentration measurements the GSH/GSSG Ratio Detection Assay Kit from *Abcam* (ab138881) was used.

Fluorescence microscopy: All images were obtained with an *Andor Zyla* mounted on a *Nikon TiE*. Confocal images were acquired in an Andor Dragonfly High Speed Confocal Platform. Images were further processed with *Image J* or NIS software (Nikon).

Microscopy settings: The filter sets for the observation of the fluorescence of the products were as follows:

Widefield: LED λ excitation: 385 nm. Filter cube DAPI-1160B-000 (Semrock): BP 387/11-25 nm, LP 447/60-25 nm and DM 409 nm. Confocal: Laser excitation: 405 nm. LP 450/50 and DM 418 nm.

Widefield: LED λ excitation: 385 nm. Filter cube: BP 375/28x nm, LP 515lp nm and DM 415 nm. Confocal: Laser excitation: 405 nm. LP 525/50 and DM 501 nm.

Widefield: LED λ excitation: 470 nm. Filter cube FITC-3540C-000 (Semrock): BP 482/35 nm, LP 536/40 nm and DM 506 nm. Confocal: Laser excitation: 488 nm. LP 525/50 and DM 501 nm.

TMRE (tetramethylrhodamine, ethyl ester) LED λ excitation: 550 nm. Filter cube TRITC-B-000 (Semrock): BP 543/22-25 nm, LP 593/40-25 nm and DM 562 nm. Confocal: Laser excitation: 561 nm. LP 620/60 and DM 567 nm.

S8.- VIABILITY ASSAYS

8.1.- Toxicity of [Ru], substrates 1g and 3b and their respective ketones 2g and 4b:

The toxicity was tested by using MTT[12] assays in HeLa cell line. A comparison study of the different compounds was carried out.

MTT assay: 15000 cells per well were seeded in 96-well plates two days before treatment with different concentrations of [**Ru**] (2.5-150 μM), allylic alcohols **1g**, **2g** and ketones **3b**, **4b** (5-100 μM). After 6 or 24 h of incubation, HEPES containing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) was added to a final concentration of 0.5 mg/mL. Cells were then incubated for 4 h to allow the formation of formazan precipitates by metabolically active cells. A detergent solution of 10% SDS and 0.01 M HCl was then added and the plate was incubated overnight at 37 °C to allow the solubilization of the precipitates. The quantity of formazan in each well (directly proportional to the number of viable cells) was measured by recording changes in absorbance at 570 nm in a microtiter plate reading spectrophotometer (*Tecan Infinite 200 PRO*).

8.2.- Toxicity observed after the ruthenium-promoted intracellular reaction:

MTT assay of cells treated with [**Ru**] and substrates: 15000 cells per well were seeded in 96-well plates two days before treatment with different concentrations of the ruthenium complex (2.5-50 μM) in DMEM. After 30 min of incubation, 2 washing steps with DMEM were carried out, followed by treatment with different concentrations of the substrates for 6 or 24 h. Cells were then treated following the same protocol described in section 8.1.

Representative figures of MTT studies:

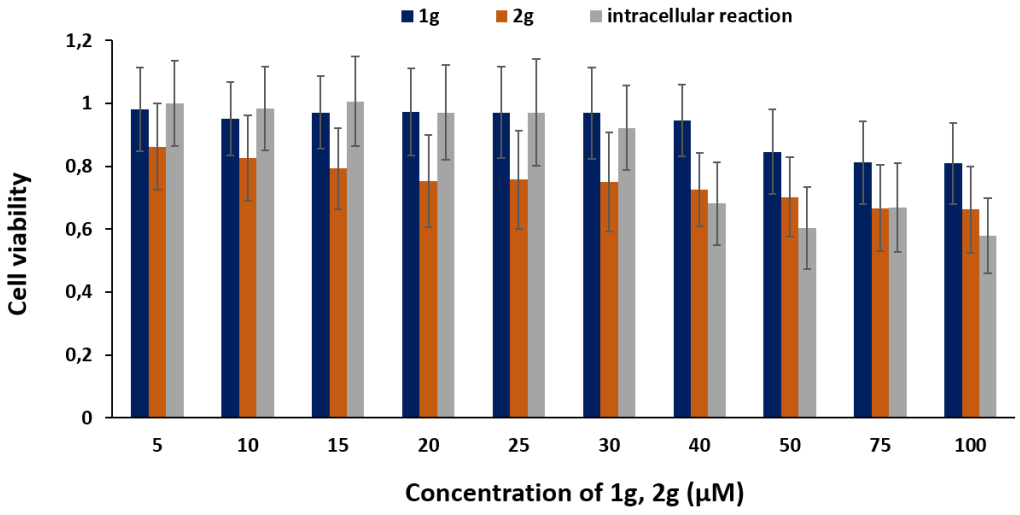


Figure S4. Bars representation of the viability of cells treated with substrate **1g** (5-100 μM), product **2g** (5-100 μM) or after treatment with [**Ru**] (2.5-50 μM) and **1g** (5-100 μM) for 24 h. The viability is expressed as the fold change of the fluorescence/absorbance value with respect to untreated cells (value 1.0). The error bars represent the standard deviation of three different samples.

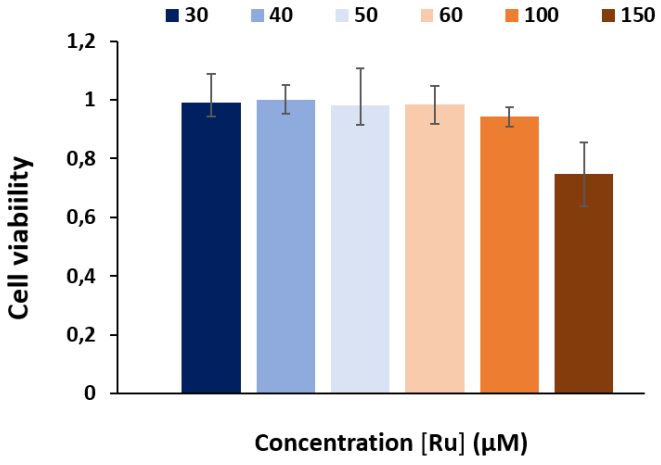


Figure S5. Bars representation of the viability of cells treated with different concentrations of [**Ru**]. The viability is expressed as the fold change of the fluorescence/absorbance value with respect to untreated cells (value 1.0). The error bars represent the standard deviation of three different samples.

S9.- CATALYTIC EXPERIMENTS IN LIVING CELLS

A549, HeLa or Vero cells were seeded on glass coverslips two days before treatment. Then, they were incubated with catalyst [**Ru**] (10 to 50 µM) for 30 min. Cells were then washed twice with DMEM and incubated with substrate **1g** (100 µM) for 30 min (HeLa cells) or 2 h (A549 and Vero cells). Prior to observation by fluorescence microscopy, the samples were washed twice with fresh DMEM. The coverslips were observed *in vivo* in a fluorescence microscope equipped with adequate filters. Digital pictures of the different samples were taken under identical conditions of gain and exposure.

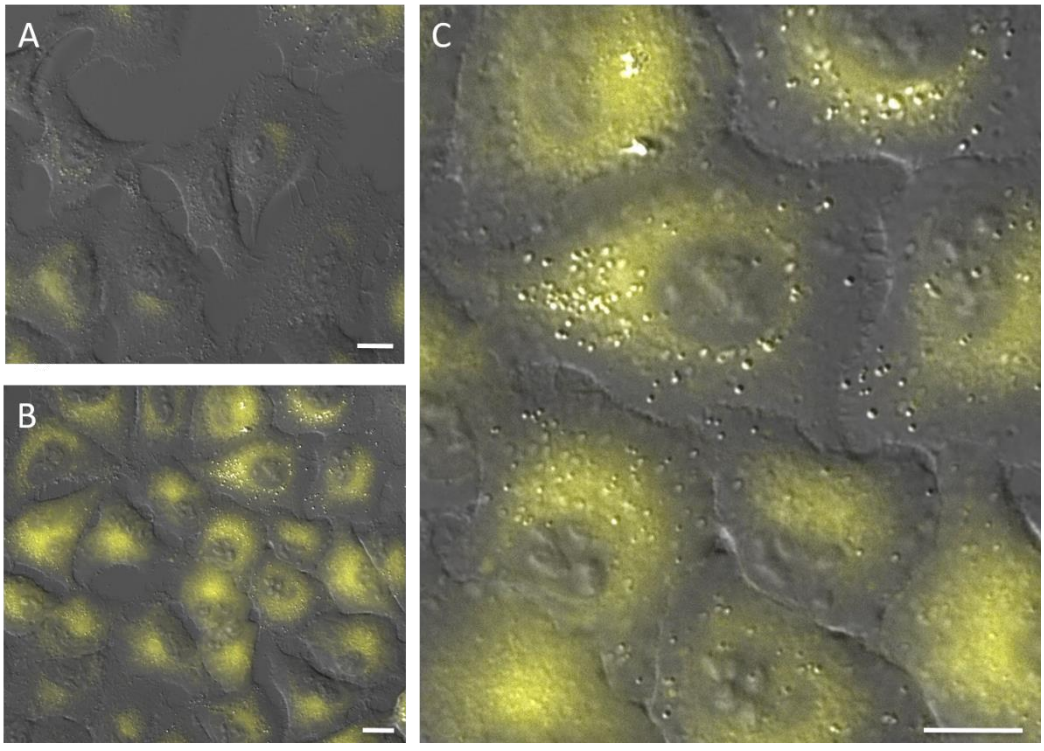


Figure S6. Fluorescence micrographies corresponding to intracellular transformations in A549 cells. (A) Cells incubated with substrate **1g** (Brightfield and green channel); (B) Cells incubated with [**Ru**], washed and treated with substrate **1g** (Brightfield and green channel); (C) Zoom of panel B. Reaction conditions: Cells were incubated with [**Ru**] (50 µM) for 30 min, followed by two washings with DMEM and treatment with substrate **1g** (100 µM) for 2 h. λ_{ex} = 385 nm, λ_{em} = 520-700 nm. Scale bar: 12.5 µm.

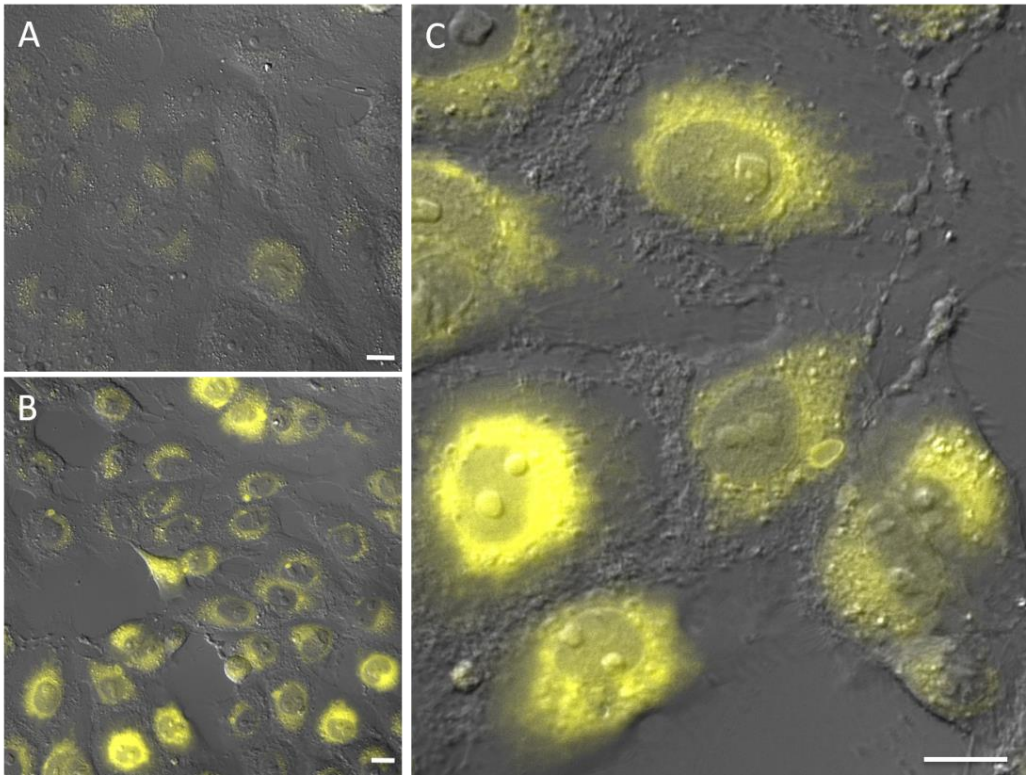


Figure S7. Fluorescence micrographies corresponding to intracellular transformations in Vero cells. (A) Cells incubated with substrate **1g** (Brightfield and green channel); (B) Cells incubated with [**Ru**], washed and treated with substrate **1g** (Brightfield and green channel); (C) Zoom of panel B. Reaction conditions: Cells were incubated with [**Ru**] (50 µM) for 30 min, followed by two washings with DMEM and treatment with substrate **1g** (100 µM) for 2 h. λ_{ex} = 385 nm, λ_{em} = 520-700 nm. Scale bar: 12.5 µm.

S10.- GSH DETECTION

The experiments were performed in 6 well plates as follows: 100000 cells per well were seeded in 6 well plates two days before treatment.

For the ruthenium catalyzed isomerization of **3b** into **4b**, a total of 10^6 HeLa cells growing in 6 well plates were incubated with catalyst [**Ru**] (50 µM) for 30 minutes followed by two washing steps with DMEM. Then, cells were incubated with substrate **3b** (100 µM) for 6 or 24 h. Afterwards, cells were washed with cold PBS. Finally, a commercial kit (GSH/GSSG Ratio Detection Assay Kit-Abcam) was used for the measurement of the glutathione in each well.

Untreated cells and cells incubated either with substrate **3b** or product **4b** (100 µM) for 6 or 24 h were subjected to the same protocol for the GSH detection.

The GSH levels of the samples were measured in a 96-well plate by recording changes in fluorescence at $E_x/_{Em}$ 490/520 nm in a microtiter plate reading spectrophotometer (*Tecan Infinite 200 PRO*).

The changes in fluorescence intensity with GSH concentration can be described as a linear regression:

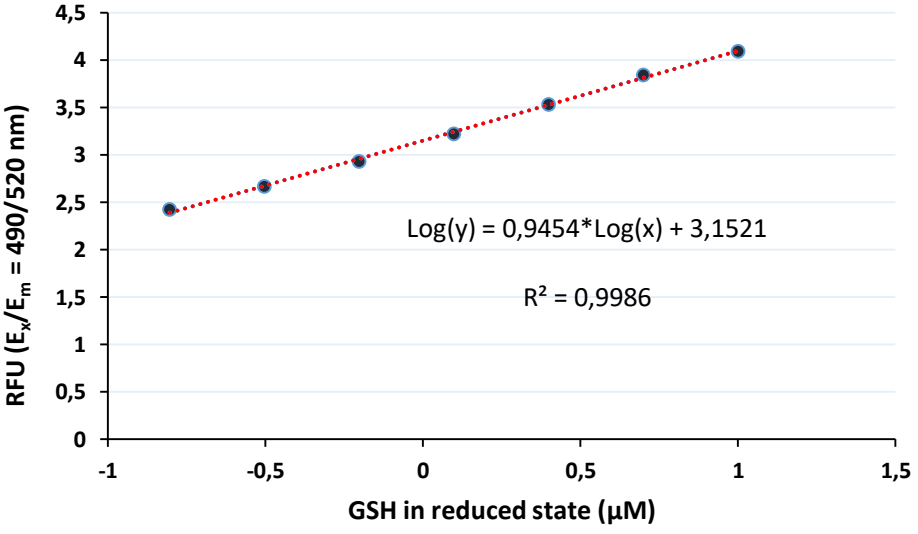


Figure S8. Reduced GSH standard calibration curve.

The results were normalized with respect to the amount of protein in each sample. The protein concentration was measured using the BIO-RAD *DC* Protein Assay.

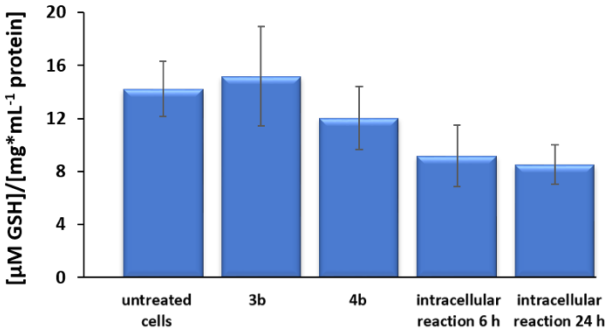


Figure S9. Reduced GSH levels in cell lysates.

S11.- ICP ANALYSIS

The experiments were performed in 6 well plates as follows: 100000 cells per well were seeded in 6 well plates two days before treatment.

For the ICP measurements, a total of 3 x 10^6 HeLa cells growing in 6 well plates were treated with different concentrations of [**Ru**] and [RuCp*Cl(COD)] in DMEM for 1 h. Prior to digestion, the samples were washed with fresh DMEM and then twice with PBS. The obtained fractions were digested in duplicate in HNO_3/H_2O_2 by microwave heating and analyzed.

Representative figures of ICP analysis:

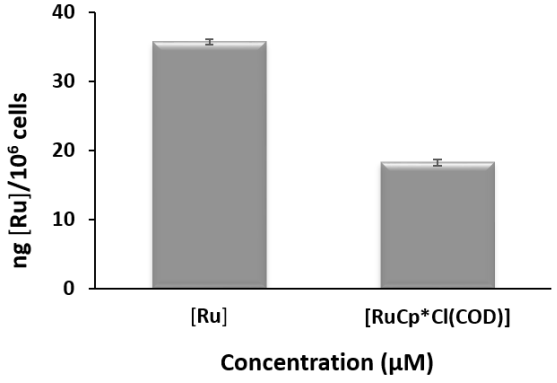


Figure S10. ICP-MS measurements of ruthenium content in HeLa cells incubated with 50 µM of either [**Ru**] or [RuCp*Cl(COD)] complexes, after washing and nitric treatment. The analysis reflects all ruthenium accumulated in the cell. Error bars represent the standard error of three independent experiments. ICP values: [**Ru**] (50 µM, 1 h) = 35.76 ng/10^6 cells; [RuCp*Cl(COD)] (50 µM, 1 h) = 18.2 ng/10^6 cells.

S12.- QUANTIFICATION STUDIES USING LC/MS

For the quantification of the ruthenium catalyzed isomerization of **1g** into **2g** in HeLa cells, a total of 16 x 10^6 HeLa cells growing in 8 plates of 100 mm were used.

The experiments were performed in plates of 100 mm as follows: 100000 cells per well were seeded in 100 mm plated two days before treatment. For each measurement, eight plates were used. Cells were incubated with catalyst [**Ru**] (10-25 µM) for 50 minutes followed by two washing steps with DMEM. Then, cells were incubated with substrate **1g** (100 µM) for 30 min or 6 h. Afterwards, the reaction media was collected for analysis in a 50 mL Falcon. Prior to extraction, cells were washed with 3 mL of DMEM, followed by 3 mL of PBS and the washings were also collected separately in two 50 mL Falcons. Then the cell monolayer was treated with 500 µL of MeOH. After 5 min and pipetting up this solution was transferred to a 15 mL Falcon. Finally, we obtained 4 mL of methanolic extracts from the eight plates employed. All the samples were lyophilized for 3 days and dissolved in MeCN until reach a theoretical concentration of 250 µM.

Figure S11. Schematic representation of the protocol for the quantification of the Ruthenium catalyzed intracellular reaction.

For the quantification of the product, the obtained samples (250 µM in MeCN) were centrifuged at 13500 rpm for 15 minutes and the supernatant was collected. In the case of the methanolic extract, it was diluted 1:4 using MeCN/H_2O 6:4. However, in the case of the samples of the reaction media, first and second washing, no dilution was required.

Each sample was injected in a *Bruker Elute* coupled with *timsTOF* using a column Zorba eclipse BXD-C18 2.1 x 10 mm 1.8 µm and a flow rate of 0.4 mL/min at room temperature. For the solvent system, initial conditions H_2O/MeCN (40:60) were used for 1 min and followed by a gradual change over 4 min to MeCN (100), maintained during 1 min and followed by a gradual change over 20 secs to H_2O/MeCN (40:60) and maintained for 1 min 40 secs.

It's important to mention that in all the cases we have detected significant amounts of substrate **1g**.

12.1.- Results obtained after 30 min of reaction in HeLa cells using 10 µM of [Ru]

A 10 mM standard solution in MeCN of product **2g** was prepared for the calibration curve. The following dilutions were prepared using a mixture of MeCN/H_2O 6:4. For the calibration curve, we represented the intensity obtained in the MS spectra vs the concentration using an internal standard.

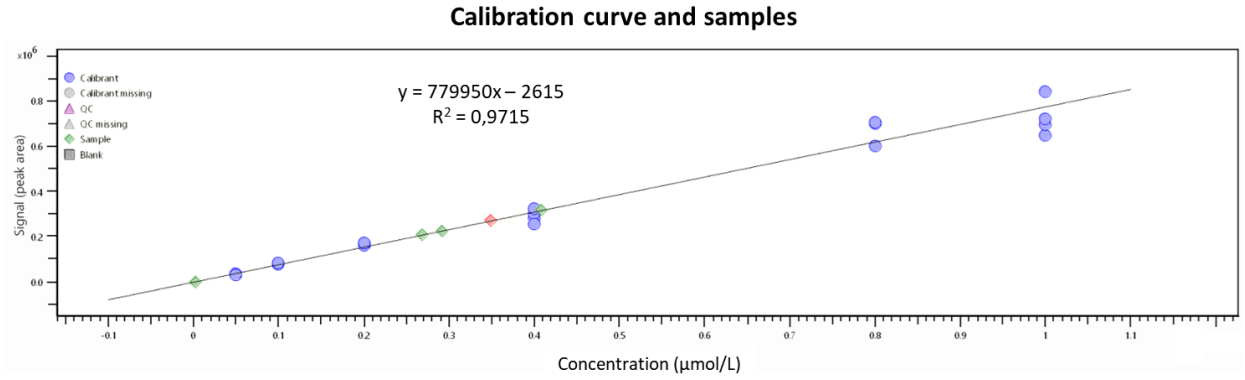


Figure S12. Calibration curve of the product **2g**. Circle: point for calibration; diamond: injected samples.

The table S2 shows the values of the product content detected in the methanolic extracts after 30 min of reaction in HeLa cells. Important, we didn't observe the formation of product in the reaction media and in the two washings steps.

Table S2.

Sample	Concentration (µM)	Original concentration (µM) (dilution factor of 4)
Methanolic extraction	0.292	
Methanolic extraction	0.349	
Methanolic extraction	0.408	
Methanolic extraction	0.268	
Average	0.329 ± 0.062	**1.316 ± 0.250**

Taking into account the number of cells used in these experiments (16 x 10^6 cells), we obtained a 0.082 ± 0.016 µM 10^6 $cells^{-1}$ of product.

ICP value: 3.54 ± 1.29 ng of Ru 10^6 $cells^{-1}$ which means 0.009 ± 0.003 µM of Ru 10^6 $cells^{-1}$

***Estimated TON* = mol product / mol Ru = 0.082 ± 0.016 / 0.009 ± 0.003 = 9.1 ± 4.8**

12.2.- Results obtained after 6 h of reaction in HeLa cells using 10 µM of [Ru].

A 10 mM standard solution in MeCN of product **2g** was prepared for the calibration curve. The following dilutions were prepared using a mixture of MeCN/H_2O 6:4. For the calibration curve, we represented the intensity obtained in the MS spectra vs the concentration using an internal standard.

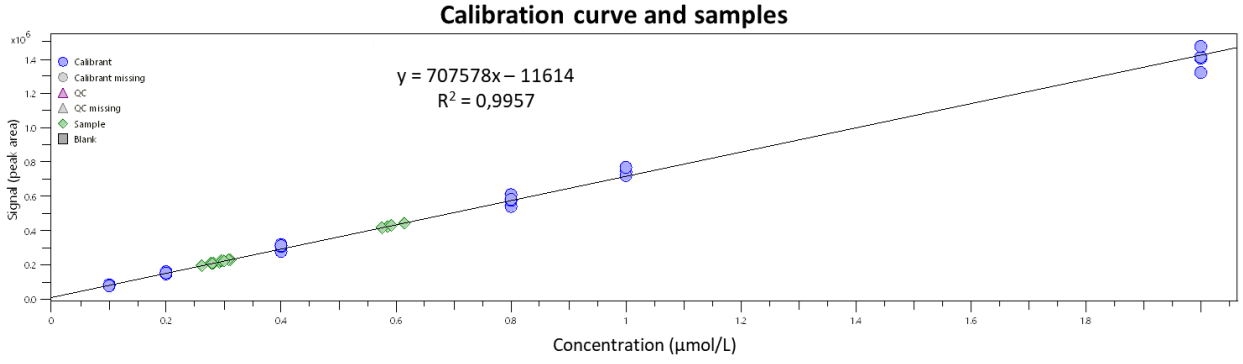


Figure S13. Calibration curve of the product **2g**. Circle: point for calibration; diamond: injected samples.

The table S3 shows the values of the product content detected in the methanolic extracts, the reaction media and the washings steps.

Table S3.

Sample	Value	Original concentration (μM) (dilution factor of 4)
Methanolic extraction	0.586	
Methanolic extraction	0.592	
Methanolic extraction	0.576	
Methanolic extraction	0.614	
Average	0.592 ± 0.016	**2.368 ± 0.064**
Reaction media	0.281	
Reaction media	0.310	
Reaction media	0.293	
Reaction media	0.282	
Average	0.292 ± 0.013	**0.292 ± 0.013**
First washing	0.310	
First washing	0.292	
First washing	0.295	
First washing	0.301	
Average	0.299 ± 0.007	**0.299 ± 0.007**
Second washing	0.294	
Second washing	0.278	
Second washing	0.260	
Second washing	0.280	
Average	0.278 ± 0.014	**0.278 ± 0.014**
Total Value		**3.237 ± 0.098**

Taking into account that all the amount of the product detected in all the fractions analyzed was generated inside the cells, we used the value 3.237 ± 0.098 μM as total concentration of intracellular generated product.

Taking into account the number of cells used in these experiments (16 x 10^6 cells), we obtained a 0.202 ± 0.006 μM 10^6 $cells^{-1}$ of product.

ICP value: 3.54 ± 1.29 ng of Ru 10^6 $cells^{-1}$ which means 0.009 ± 0.003 µM of Ru 10^6 $cells^{-1}$

Estimated TON **= mol product / mol Ru = 0.202 ± 0.006/ 0.009 ± 0.003 = 22.4 ± 8.1**

12.3.- Results obtained after 6 h of reaction in HeLa cells using 25 µM of [Ru].

A 10 mM standard solution in MeCN of product **2g** was prepared for the calibration curve. The following dilutions were prepared using a mixture of MeCN/H_2O 6:4. For the calibration curve, we represented the intensity obtained in the MS spectra vs the concentration using an internal standard.

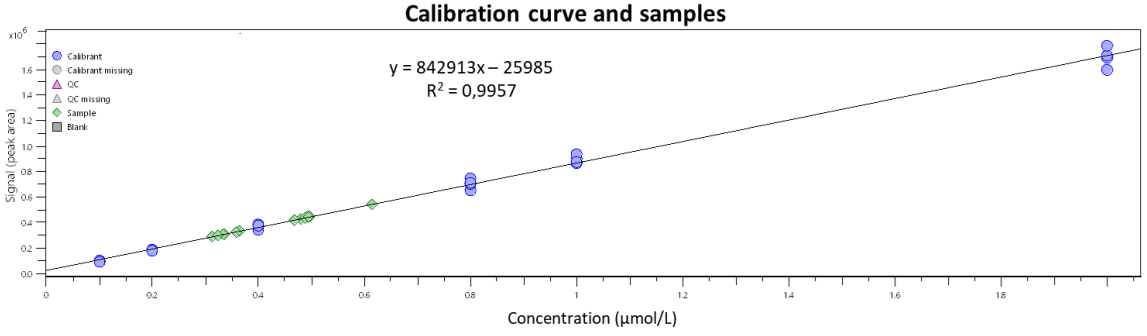


Figure S14. Calibration curve of the product **2g**. Circle: point for calibration; diamond: injected samples.

The table S4 shows the values of the product content detected in the methanolic extracts, the reaction media and the washings steps.

Table S4.

Sample	Value	Original concentration (µM) (dilution factor of 4)
Methanolic extraction	0.477	
Methanolic extraction	0.493	
Methanolic extraction	0.488	
Methanolic extraction	0.603	
Average	0.515 ± 0.059	**2.061 ± 0.236**
Reaction media	0.510	
Reaction media	0.509	
Reaction media	0.494	
Reaction media	0.482	
Average	0.358 ± 0.014	**0.358 ± 0.014**
First washing	0.351	
First washing	0.378	
First washing	0.353	
First washing	0.349	
Average	0.499 ± 0.013	**0.499 ± 0.013**
Second washing	0.329	
Second washing	0.326	
Second washing	0.338	
Second washing	0.379	
Average	0.343 ± 0.025	**0.343 ± 0.025**
Total Value		**3.261 ± 0.287**

Taking into account that the amount of product detected in all the fractions analyzed was generated inside the cells, we used the value 3.261 ± 0.287 µM as total concentration of intracellular generated product.

Taking into account the number of cells used in these experiments (16 x 10^6 cells), we obtained a 0.204 ± 0.018 µM 10^6 $cells^{-1}$ of product.

ICP value: 11.1 ± 1.3 ng of Ru 10^6 cells^{-1} which means 0.028 ± 0.003 µM of Ru 10^6 cells^{-1}

***Estimated TON* = mol product / mol Ru = 0.204 ± 0.017 / 0.028 ± 0.003 = 7.34 ± 1.5**

[1] J. G. Toerien, P.H. van Rooyen, *J. Chem. Soc. Dalton. Trans.* **1991**, 1563.
[2] B. Kavanagh, J. W. Steed, D. A. Tocher, *J. Chem. Soc. Dalton. Trans,* **1993**, 327.
[3] Z. Almodares, S. J. Lucas, B. D. Crossley, A. M. Basri, C. M. Pask, A. J. Hebden, R. M. Phillips, P. C. McGowan, *Inorg. Chem.* **2014**, *53*, 727.
[4] P. Truong, C. S. Shanahan, M. P. Doyle, *Org. Lett.* **2012**, *14*, 3608.
[5] Y. Liu, Y. L. Tan, X. Zhang, G. Bhabha, D. C. Ekiert, J. C. Genereux, Y. Cho, Y. Kipnis, S. Bjelic, D. Baker, J. W. Kelly, *PNAS* **2014**, *111*, 4449.
[6] S. Singha, Y. W. Jun, J. Bae, K. H. Ahn, *Anal. Chem.* **2017**, *89*, 3724.
[7] P. R. Krishna, D. V. Ramana, *J. Org. Chem.* **2012**, *77*, 674.
[8] A. Bartoszewicz, M. Livendahl, B. Martín-Matute, *Chem. Eur. J.* **2008**, *14*, 10547.
[9] a) B. Zhao, X. Lu, *tetrahedron Letters*, **2006**, *47*, 6765; b) Z. Zhang, M. G. Lindale, L. S. Liebeskind, *J. Am. Chem. Soc.* **2011**, *133*, 6403; c) M. L. N. Rao, V. Venkatesh, D. Banerjee, *Tetrahedron* **2007**, *63*, 12917; d) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943; e) P. N. Liu, K. D. Ju, C. P. Lau, *Adv. Synth. Catal,* **2011**, *353*, 275; f) T. Scheidt, H. Land, M. Anderson, Y. Chen, P. Berglund, D. Yi, W.-D. Fessner, *Adv. Synth. Catal.* **2015**, *357*, 1721.
[10] a) M. McConville, O. Saidi, J. Blacker, J. Xiao, *J. Org. Chem*, **2009**, *74*, 2692; b) L.-Y. Wang, Z.-B. Hu, Z. Shi, *Chinese J. Chem,* **2002**, *20*, 514.
[11] C. Reichardt, *Chem. Rev.* **1994**, *94*, 2319.
[12] M. V. Berridge, P. M. Herst, A. S. Tan, *Biotechnol. Annu. Rev.* **2005**, *11*, 127.