Supporting Information

4-Methyltetrahydropyran as Convenient Alternative Solvent for Olefin Metathesis Reaction. Model Studies and Medicinal Chemistry Applications

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Materials and Methods

General

All metathesis reactions were performed under argon using Schlenk technique. Syntheses of starting materials: dienes and other compounds were performed under argon atmosphere unless otherwise stated. All glassware was dried overnight in an oven (135 °C).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness, Merck) with a fluorescent indicator. Visualization of TLC plates was performed by KMnO$_4$ aqueous solution and anisaldehyde/H$_2$SO$_4$ stain. The flash column chromatography was performed using Merck silica gel 60 (230–400 mesh) with n-hexane/ethyl acetate eluent system, unless otherwise stated.

GC analyses were performed by means of PerkinElmer Clarus 580 chromatograph with FID detector and GL Sciences InertCap 5MS/Sil Capillary Column (Inner Diameter 0.25 mm, Length 30 m, df 0.50 μm). GC-MS analyses were performed by means of PerkinElmer Clarus 680 chromatograph with Mass Spectrometer Clarus SQ 8C detector and GL Sciences InertCap 5MS/Sil Capillary Column (Inner Diameter 0.25 mm, Length 30 m, df 0.50 μm).

NMR spectra were recorded on Agilent 400-MR DD2 400 MHz spectrometer. NMR chemical shifts are reported in ppm with solvent residual peak as a reference (7.26 and 77.16 ppm for $^1$H and $^{13}$C in CDCl$_3$). Deuterated chloroform was purchased from Eurisotop, stored over molecular sieves and used without further purification.

The following abbreviations are used in reporting NMR data: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sep (septet), m (multiplet), br (broad). $^1$H NMR signals are given followed by multiplicity, coupling constants $J$ in Hertz, and integration in parentheses.

Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer with diamond ATR accessory, wave numbers are in cm$^{-1}$.

Elemental Analyses (EA) were provided by the EA analytical laboratory at the Institute of Organic Chemistry, Polish Academy of Sciences (PAS).

High Resolution Mass Spectra (HRMS) were provided by the Faculty of Chemistry University of Warsaw or analytical laboratory at the Institute of Organic Chemistry, PAS.

Preparation of anhydrous 4-MeTHP

4-Methyltetrahydropyran (4-MeTHP) was dried by distillation from sodium benzophenone ketyl: sodium wire and benzophenone was added to 4-MeTHP, and the mixture was heated at reflux (105 °C) under argon for 12 hours. After that time the solvents was distilled to an oven-dried ampoule and stored over 3A molecular sieves. The level of water in such prepared 4-MeTHP was 2 ppm as measured by Karl Fischer titrator.

Characterization of solvents

Solvents used for the RCM model reaction of 1 were commercially available, used without any purification either drying or degassing. The water content in each solvent was measured. All solvents were used soon after the bottle was opened unless otherwise stated.
Table S1. Water content in solvents used for the RCM model reaction of 1.

| Solvent  | Producer                        | Purity   | Water content |
|----------|---------------------------------|----------|---------------|
| 1        | 4-MeTHP* CARLO ERBA Reagents    | ≥99.0 %  | 65 ppm        |
| 2        | EtOAc Sigma-Aldrich             | ≥99.7 %  | 185 ppm       |
| 3        | Toluene Sigma-Aldrich           | ≥99.9 %  | 91 ppm        |
| 4        | Anisole Sigma-Aldrich           | 99.7 %   | 759 ppm       |
| 5        | MTBE Sigma-Aldrich              | ≥99.8 %  | 203 ppm       |
| 6        | THF1 Honeywell                  | ≥99.9 %  | 152 ppm       |
| 7        | THF2* Sigma-Aldrich             | ≥99.8 %  | 879 ppm       |

* From opened bottle, stored ≥ 1 year.

Next, peroxides content in two batches of THF was checked. Potassium iodide starch papers were dipped in a standard hydrogen peroxide solution (containing from 0 to 470 mg H₂O₂/kg) in water and left to dry out, to create the color-scale (Figure S1). Using this scale peroxides concentration in THF2 can be roughly estimated to be much higher than the one in THF1.

![Figure S1](image)

Figure S1. Peroxide color-scale (top) and THF1 and THF2 test results (bottom).

Model RCM reaction of diethyl diallylmalonate (Figure 3) in different solvents

A GC vial was charged with 1.3 mg (2 μmol, 1 equiv.) of Ru3d catalyst followed by 1 mL of 1 (0.1 M solution 0.1 mmol, 100 equiv.) in an appropriate HPLC grade, non-deoxygenated solvent. The vial was closed and mixed with shaking it for a few seconds. Next, the solution was quickly transferred to an NMR tube containing inside a sealed capillary with C₆D₆ solvent needed to lock and shim the sample. The tube was closed and transferred to an NMR apparatus to record spectra at 50 °C.
RCM/Isomerization of \(N,N\)-diallyltosylamide (Figure 4)

4 mL vial closed with a screw cap was charged with appropriate ruthenium catalyst (2 μmol) followed by addition of 2.0 mL of the substrate (0.1 M solution, 0.2 mmol, 100 equiv.). The reaction mixture was stirred at 80 °C or 105 °C (boiling 4-MeTHP) for 1 h and next the ruthenium scavenger, SnatchCat, CAS: 51641-96-4 (2.3 mg, 10.2 mmol, 4.4 equiv.) was added to stop metathesis/isomerization reactions, and the solution was stirred for additional 30 minutes. The content of the vial was transferred to 10 mL flasks, the solvent was evaporated under the reduced pressure, and the residue was analyzed by \(^1\)H NMR.

Figure S2. Example of a \(^1\)H NMR spectrum of a crude reaction mixture.

General procedure for ring-closing metathesis reactions

Under argon atmosphere a preheated Schlenk-flask equipped with a Teflon-coated magnetic stirring bar and septum was charged with a 4-MeTHP solution of a diene. The desired amount of catalyst was added in a 4-MeTHP solution and the reaction mixture was stirred for a given time at 70 °C. The reaction progress was monitored by TLC. When full conversion was reached, SnatchCat solution (10 mg in 1 mL 4-MeTHP, 4 equiv. with respect to the catalyst) was added to stop the reaction. Volatiles were removed in vacuum and the crude product was purified by column chromatography.

1-[(4-Methylphenyl)sulfonyl]-2,5-dihydro-1H-pyrrole (2)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.73 - 7.69 (m, 2H), 7.33 - 7.29 (m, 2H), 5.66 - 5.62 (m, 2H), 4.14 - 4.08 (m, 4H), 2.41 (s, 3H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 143.4, 134.2, 129.7, 127.4, 125.4, 54.8, 21.5.\)
The spectra correspond to those described in the literature.¹

**Diethylcyclopent-3-ene-1,1-dicarboxylate (4)**

\[
\text{Et}_2\text{COC}_2\text{Et}
\]

**\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 5.62 - 5.58\) (m, 2H), 4.19 (q, \(J = 7.1\) Hz, 4H), 3.01 (s, 4H), 1.25 (t, \(J = 7.1\) Hz, 6H).**

**\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)) \(\delta = 172.2, 127.8, 61.5, 58.8, 40.8, 14.0\).**

The spectra correspond to those described in the literature.²

**Diethylcyclohex-3-ene-1,1-dicarboxylate (6)**

\[
\text{Et}_2\text{COC}_2\text{Et}
\]

**\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 5.70 - 5.61\) (m, 2H), 4.18 (qd, \(J = 7.1, 1.3\) Hz, 4H), 2.60 – 2.45 (m, 2H), 2.18 – 2.06 (m, 4H), 1.24 (t, \(J = 7.1\) Hz, 6H).**

**\(^{13}\text{C-NMR}\) (101 MHz, CDCl\(_3\)) \(\delta = 171.8, 126.2, 124.1, 61.4, 53.1, 30.6, 27.5, 22.5, 14.2\).**

The spectra correspond to those described in the literature.³

**3-Methyl-cyclopent-3-ene-1,1-dicarboxylic acid diethyl ester (8)**

\[
\text{Et}_2\text{COC}_2\text{Et}
\]

**\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 5.21 - 5.16\) (m, 1H), 4.18 (q, \(J = 7.1\) Hz, 4H), 2.98 – 2.94 (m, 2H), 2.92 – 2.87 (m, 2H), 1.74 – 1.68 (m, 3H), 1.24 (t, \(J = 7.1\) Hz, 6H).**

**\(^{13}\text{C-NMR}\) (101 MHz, CDCl\(_3\)) \(\delta = 172.4, 137.4, 121.2, 61.4, 59.3, 44.6, 40.5, 16.0, 14.0\).**

The spectra correspond to those described in the literature.⁴

**3,4-Dimethyl-1-[(4-methylphenyl)sulfonyl]-2,5-dihydro-1H-pyrrole (10)**

\[
\text{TsNO}
\]

**\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 7.70\) (d, \(J = 8.2\) Hz, 2H), 7.30 (d, \(J = 8.0\) Hz, 2H), 3.96 (s, 4H), 2.41 (s, 3H), 1.53 (s, 6H).**

**\(^{13}\text{C-NMR}\) (101 MHz, CDCl\(_3\)) \(\delta = 143.2, 134.2, 129.6, 127.4, 126.1, 126.1, 58.7, 21.4, 11.0\).**

The spectra correspond to those described in the literature.⁵

**Spiro[cyclopent-3-ene-1,2'-inden]-1'(3'H)-one (12)**

\[
\text{O}
\]

**\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 7.79\) (ddd, \(J = 7.8, 1.3, 0.7\) Hz, 1H), 7.60 (td, \(J = 7.5, 1.2\) Hz, 1H), 7.44 (dp, \(J = 7.7, 0.9\) Hz, 1H), 7.39 (tq, \(J = 7.6, 0.9\) Hz, 1H), 5.76 – 5.70 (m, 2H), 3.18 (s, 2H), 2.94 – 2.86 (m, 2H), 2.39 – 2.31 (m, 2H).**

**\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)) \(\delta = 210.6, 152.9, 136.4, 134.9, 128.9, 127.6, 126.6, 124.4, 55.6, 45.6\).**

The spectra correspond to those described in the literature.⁴

**Spiro[cyclopent-3-ene-1,2'-indene]-1',3'-dione (14)**

\[
\text{O}
\]

**\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 8.03 - 7.96\) (m, 2H), 7.88 – 7.81 (m, 2H), 5.77 – 5.69 (m, 2H), 2.78 – 2.74 (m, 4H).**

**\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)) \(\delta = 203.5, 141.7, 135.7, 128.3, 123.5, 77.0, 57.7, 41.7\).**

The spectra correspond to those described in the literature.⁴

**7,9-Dimethyl-7,9-diaza-spiro[4.5]dec-2-ene-6,8,10-trione (16)**

\[
\text{O}
\]

**\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 5.68 - 5.65\) (m, 2H), 3.31 (s, 7H), 3.02 – 3.00 (m, 4H).**

**\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)) \(\delta = 172.5, 151.4, 127.3, 54.6, 45.5, 29.0\).**

The spectra correspond to those described in the literature.⁴
(2,5-Dihydro-1H-pyrrol-1-yl)(1-tosylpyrrolidin-2-yl)methanone (18)

\[ {^1}H-\text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 7.76 \ (d, J = 8.3 \text{ Hz, 2H}), 7.28 \ (d, J = 7.9 \text{ Hz, 2H}), 5.88 - 5.75 \ (m, 2H), 4.65 - 4.53 \ (m, 2H), 4.34 - 4.24 \ (m, 1H), 4.24 - 4.11 \ (m, 2H), 3.50 - 3.37 \ (m, 2H), 2.41 \ (s, 3H), 2.19 - 1.92 \ (m, 3H), 1.84 - 1.74 \ (m, 1H).

\[ {^{13}}C-\text{NMR} \ (100 \text{ MHz, CDCl}_3) \delta = 169.7, 143.5, 135.8, 129.6, 127.6, 126.0, 125.1, 59.2, 53.5, 53.2, 48.4, 30.4, 25.0, 21.6.

The spectra correspond to those described in the literature.\(^3\)

(6R,7S)-7-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-1-azabicyclo[4.2.0]oct-3-en-8-one (33)

\[ {^1}H-\text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 5.87 - 5.64 \ (m, 2H), 4.20 - 4.12 \ (m, 1H), 4.05 \ (dd, J = 3.0, 18.2, 1H), 3.52 - 3.41 \ (m, 2H), 2.73 \ (dd, J = 1.4, 15.4 \text{ Hz, 1H}), 2.46 - 2.35 \ (m, 1H), 2.20 - 2.07 \ (m, 1H), 1.23 \ (d, J = 6.2, 3H), 0.86 \ (s, 9H), 0.06 \ (s, 6H).

\[ {^{13}}C-\text{NMR} \ (100 \text{ MHz, CDCl}_3) \delta = 167.1, 123.9, 122.4, 66.9, 65.7, 45.9, 38.1, 28.1, 25.6, 22.8, 17.9, -4.2, -5.1.

The spectra correspond to those described in the literature.\(^6\)

(6R,7S)-7-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-3-methyl-1-azabicyclo[4.2.0]oct-3-en-8-one (34)

\[ {^1}H-\text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 5.50 \ (dd, J = 4.9, 2.0 \text{ Hz, 1H}), 4.20 - 4.13 \ (m, 1H), 3.93 \ (d, J = 17.7 \text{ Hz, 1H}), 3.44 - 3.36 \ (m, 1H), 3.36 - 3.27 \ (m, 1H), 2.71 \ (dd, J = 5.5, 1.6 \text{ Hz, 1H}), 2.42 - 2.31 \ (m, 1H), 2.16 - 2.05 \ (m, 1H), 1.69 \ (s, 3H), 1.24 \ (d, J = 6.2 \text{ Hz, 3H}), 0.87 \ (s, 9H), 0.07 \ (s, 6H).

\[ {^{13}}C-\text{NMR} \ (101 \text{ MHz, CDCl}_3) \delta = 167.0, 129.7, 118.4, 66.2, 45.7, 41.6, 28.2, 25.7, 22.8, 20.8, 17.9, -4.2, -5.0.

2-(Benzhydrylthio)-1-(2,5-dihydro-1H-pyrrol-1-yl)ethanone (36)

\[ {^1}H-\text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 7.49 - 7.43 \ (m, 4H), 7.33 - 7.27 \ (m, 4H), 7.25 - 7.20 \ (m, 2H), 5.82 \ (dt, J = 6.5, 2.2 \text{ Hz, 1H}), 5.71 \ (dt, J = 6.4, 2.1 \text{ Hz, 1H}), 5.47 \ (s, 1H), 4.22 - 4.12 \ (m, 4H), 3.11 \ (s, 2H).

\[ {^{13}}C-\text{NMR} \ (100 \text{ MHz, CDCl}_3) \delta = 167.2, 140.7, 128.6, 128.5, 127.3, 126.1, 124.9, 53.5, 53.4, 53.2, 33.9.

The spectra correspond to those described in the literature.\(^7\)

1-(2,5-Dihydro-1H-pyrrol-1-yl)-2-(3-(2,2,3,3-tetramethylcyclopropane-1-carbonyl)-1H-indol-1-yl)ethan-1-one (38)

\[ {^1}H-\text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 8.55 - 8.30 \ (m, 1H), 7.73 \ (s, 1H), 7.31 - 7.11 \ (m, 3H), 5.99 - 5.69 \ (m, 2H), 4.81 \ (s, 2H), 4.36 - 4.19 \ (m, 4H), 1.96 \ (s, 1H), 1.35 \ (s, 6H), 1.28 \ (s, 6H).

\[ {^{13}}C-\text{NMR} \ (101 \text{ MHz, CDCl}_3) \delta = 194.9, 164.7, 137.2, 134.5, 126.3, 126.5, 124.6, 123.4, 123.0, 122.4, 120.7, 109.2, 53.8, 52.9, 48.6, 41.7.

The spectra correspond to those described in the literature.\(^3\)
1-(2-(2,5-dihydro-1H-pyrole-1-carbonyl)pyrrolidin-1-yl)-4-phenylbutan-1-one (40)

\[ {^1}H-NMR \] (400 MHz, CDCl₃) \( \delta = 7.30 - 7.23 \) (m, 2H), 7.22 - 7.11 (m, 3H), 5.90 - 5.74 (m, 2H), 4.75 - 4.56 (m, 2H), 4.41 - 4.09 (m, 3H), 3.69 - 3.59 (m, 1H), 3.48 - 3.38 (m, 1H), 2.68 (t, \( J = 7.5 \) Hz, 2H), 2.41 - 2.19 (m, 3H), 2.16 - 1.90 (m, 5H).

\[ {^{13}}C-NMR \] (101 MHz, CDCl₃) \( \delta = 171.7, 170.6, 141.9, 128.6, 126.2, 125.1, 125.0, 57.6, 53.3, 47.4, 35.3, 33.5, 28.9, 26.1, 25.0.

The spectra correspond to those described in the literature.⁸

**General procedure for cross-metathesis reactions**

Under argon atmosphere a preheated Schlenk-flask equipped with a Teflon-coated magnetic stirring bar and septum was charged with corresponding substrate (1 equiv.) and cross partner (3 equiv.) dissolved in 4-MeTHP. The desired amount of catalyst was added and the mixture was stirred at 70 °C. When no reaction progress was observed another portion of catalyst was added to the reaction mixture. The reaction was stopped by addition of SnatchCat solution (10 mg in 1 mL S-MeTHP, 4 equiv. with respect to the catalyst). All volatiles were removed in vacuum and the crude product was purified by column chromatography.

4-(4-Methoxyphenyl)but-2-en-1-yl acetate, \((E)/(Z)\) mixture (21)

\[ {^1}H-NMR \] (400 MHz, CDCl₃) \( \delta = 7.13 - 7.06 \) (m, 2H), 6.87 - 6.81 (m, 2H), 5.90 (dtt, \( J = 15.3, 6.7, 1.3 \) Hz, 0.8H, E isomer), 5.83-5.76 (m, 0.2H, Z isomer), 5.68-5.56 (m, 1H, E and Z mixture), 4.47-4.71 (m, 0.4H, Z isomer), 4.54 (dq, \( J = 6.4, 1.1 \) Hz, 1.6H, E isomer), 3.79 (s, 2.4H, E isomer), 3.78 (s, 0.6H, Z isomer), 3.41 (d, \( J = 7.6 \) Hz, 0.4H, Z isomer), 3.34 (d, \( J = 6.8 \) Hz, 1.6H, E isomer), 2.08 (s, 0.6H, Z isomer), 2.06 (s, 2.4H, E isomer). ¹³C-NMR (101 MHz, CDCl₃) \( \delta = 170.9, 158.1, 135.0, 131.6, 129.5, 124.9, 113.9, 64.9, 55.3, 37.7, 21.0.

The spectra correspond to those described in the literature.⁹

9-Chloro-2-methylnon-4-ene, \((E)/(Z)\) mixture (24)

\[ {^1}H-NMR \] (400 MHz, CDCl₃) \( \delta = 5.49 - 5.29 \) (m, 2H), 3.54 (td, \( J = 6.7, 1.1 \) Hz, 2H), 2.09 – 1.99 (m, 2H), 1.93– 1.83 (m, 2H), 1.83 – 1.72 (m, 2H), 1.64 – 1.45 (m, 3H), 0.89 (d, \( J = 6.4 \) Hz, 1.5H, Z isomer), 0.87 (d, \( J = 6.4 \) Hz, 4.5H, E isomer).

¹³C-NMR (101 MHz, CDCl₃) \( \delta = 130.7, 130.0, 45.2, 42.1, 36.5, 32.2, 31.9, 28.6, 26.9, 22.4.

HRMS (EI): \( m/z \) calculated for C₁₀H₁₉Cl: \([M]^+\) 174.1175, found 174.1169.

IR (solid film from evaporated CH₂Cl₂ solution): \( \nu = 2955, 2869, 1463, 1383, 1366, 1308, 1168, 1053, 969, 827, 728, 654.

**Anal. Calcd.** for C₁₀H₁₉Cl: C, 68.75; H, 10.96; Cl, 20.29. Found: C, 68.90; H, 10.99; Cl, 20.15.

Dec-6-enoic acid, \((E)/(Z)\) mixture (27)

\[ {^1}H-NMR \] (400 MHz, CDCl₃) \( \delta = 5.48 - 5.28 \) (m, 2H), 2.40 – 2.31 (m, 2H), 2.09 – 1.90 (m, 4H), 1.74 – 1.54 (m, 2H), 1.46 – 1.22 (m, 4H), 0.94 – 0.83 (m, 3H).
$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta = 179.9$, 131.0 ($E$ isomer), 130 ($Z$ isomer), 129.8 ($E$ isomer), 129.2 ($Z$ isomer), 34.8, 34.0, 32.3, 29.1, 24.3, 22.8, 13.8.

The spectra correspond to those described in the literature.$^{10}$

8-Phenyl-oct-5-enal, ($E$)($Z$) mixture (30)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta = 9.76$ (t, $J = 1.8$ Hz, 1H), 7.31 – 7.27 (m, 2H), 7.22 – 7.16 (m, 3H), 5.66 – 5.42 (m, 2H), 3.40 (d, $J = 7.5$ Hz, 0.4H, $Z$ isomer), 3.33 (d, $J = 6.5$ Hz, 1.6H, $E$ isomer), 2.43 (td, $J = 7.3$, 1.8 Hz, 2H), 2.18 (q, $J = 7.2$ Hz, 0.4H, $Z$ isomer), 2.11 – 1.99 (m, 1.6H, $E$ isomer), 1.72 – 1.60 (m, 2H), 1.49 – 1.37 (m, 2H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta = 202.9$, 170.9, 131.3, 128.6, 128.5, 126.1, 60.1, 43.9, 39.2, 32.3, 29.0, 21.7.

Large scale experiment—synthesis of 5-[5-(2,5-dihydro-1H-pyrrol-1-ylsulfonyl)-2-ethoxyphenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (42)

To a solution of 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N,N-di(prop-2-en-1-yl)benzene-sulfonamide (33 g, 70 mmol) in prior distilled 4-MeTHP (720 mL) the catalyst (463 mg, 0.72 mmol, 1 mol%) was added under protective atmosphere of argon. The reaction mixture was stirred at 70 °C for 2 hours, until TLC monitoring showed complete conversion. The reaction mixture was cooled to 0-10 °C and stirred for 60 minutes. The precipitated product was filtered and dried in a vacuum drier. 5-[5-(2,5-dihydro-1H-pyrrol-1-ylsulfonyl)-2-ethoxyphenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one was obtained as a cream colored solid (27.17 g, 61.3 mmol, 88%).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta = 10.88$ (s, 1H), 8.80 (d, $J = 2.4$ Hz, 1H), 7.85 (dd, $J = 8.7$, 2.4 Hz, 1H), 7.12 (d, $J = 8.8$ Hz, 1H), 5.66 (s, 2H), 4.33 (q, $J = 7.0$ Hz, 2H), 4.22 (s, 3H), 4.14 (s, 4H), 2.89 (dd, $J = 8.0$, 7.1 Hz, 2H), 1.89 – 1.76 (m, 2H), 1.59 (t, $J = 7.0$ Hz, 3H), 0.99 (t, $J = 7.4$ Hz, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta = 159.2$, 153.6, 146.9, 146.6, 138.3, 131.3, 130.7, 130.5, 125.5, 124.4, 121.1, 113.2, 77.3, 66.0, 55.0, 38.2, 27.7, 22.3, 14.5, 14.0.

HRMS (ESI): m/z calculated for C$_{21}$H$_{26}$N$_5$O$_4$S ([M]+H)$^+$ 444.1706, found 444.1702.

IR (solid film from evaporated CH$_2$Cl$_2$ solution): $\nu = 3311$, 3108, 2959, 2871, 1690, 1599, 1580, 1558, 1532, 1489, 1466, 1393, 1345, 1278, 1247, 1168, 1129, 1110, 1077, 1029, 928, 819, 738, 697, 675, 654, 618, 585, 560.

Anal. Calcd. for C$_{21}$H$_{25}$N$_5$O$_4$S: C, 56.87; H, 5.68; N, 15.79. Found: C, 56.80; H, 5.70; N, 16.10.
Graphical representation of synthesis of 42 in 33 g scale

**Figure S3.** Weighting (left) the substrate and charging (right) the reactor (on air).

**Figure S4.** Charging of the reactor with 4-MeTHP (on air).
Figure S5. Heating the reactor content.

Figure S6. Weighting (left) and charging (right) of Ru3d catalyst (1 mol%) on air.
Figure S7. Conducting the reaction (2 h).

Figure S8. Cooling down the content of the reactor.
Figure S9. Filtration set-up.
Figure S10. Filtration.

Figure S11. Drying and weighting the product.
HPLC data

Sildenafil pharmacopeal method of analysis:

Column:
- size: \( l = 0.25 \text{ m}, \Omega = 4.6 \text{ mm}; \)
- stationary phase: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase:
- mobile phase A: acetonitrile for chromatography R, buffer solution (20:80 V/V);
- mobile phase B: buffer solution, methanol R1, acetonitrile for chromatography R (20:20:60 V/V/V).

Table S2. Details of the method used.

| Time (min) | Mobile phase A (per cent V/V) | Mobile phase B (per cent V/V) |
|------------|-------------------------------|-------------------------------|
| 0 - 3      | 75                            | 25                            |
| 3 - 26     | 75 \( \rightarrow \) 30       | 25 \( \rightarrow \) 70       |
| 26 - 38    | 30                            | 70                            |

Flow rate: 1.5 mL/min.
Detection: spectrophotometer at 230 nm.
Injection: 10 µL of test solution

4-Ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N,N-di(prop-2-en-1-yl)benzenesulfonamide (41)

HPLC purity: 99.22%.
5-[5-(2,5-dihydro-1H-pyrrol-1-ylsulfonyl)-2-ethoxyphenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (42).

HPLC purity: 99.45%.
ICP-MS measurements

125 mg of 42 was placed in preweighted polytetrafluoroethylene (PTFE) vessel and the weight of the filled vessel was recorded. A mixture of acids (7 mL of nitric acid and 1 mL of hydrochloric acid) and deionized distilled water (3 mL) was added to the vessel. The vessel was capped, stirred for 5 minutes, placed in a microwave reactor, and digested at few steps from 120 °C to 250 °C under a pressure of 20-60 bar (1 bar=1×105 Pa) for 50 min. After digestion, the vessel was cooled to room temperature and placed in ultrasonic bath to degas sample. Content of the vessel was quantitatively transferred without filtration to graduated flask and diluted to a final volume of 50 mL with high-purity deionized distilled water. Ruthenium concentration was determined by ICP-MS, calibrated by using commercially available standards. The concentration obtained from ICP-MS was multiplied by the dilution volume (50 mL) and divided by the calculated sample weight.

ICP-MS method analysis was developed and validated for Sildenafil in accordance with the ICH Q3D guidelines, The United States Pharmacopoeia (USP, chapters: 232 and 233) and the European Pharmacopoeia (EP, chapters 5.20 and 2.4.20).

Calculation of the amount of Ru in reaction mixture for 33 g scale:

\[ m_{\text{cat}} = 463 \text{ mg (mass of Ru3d used in the reaction)} \]
\[ m_{\text{Ru}} = 72.4 \text{ mg} \]
\[ m_{\text{prod}} = 31.05 \text{ g (mass of product obtained if the conversion is 100%)} \]

maximal amount of Ru in product = \[ \frac{m_{\text{Ru}}}{m_{\text{prod}}+m_{\text{cat}}} = \frac{72.4}{31050+463} = 2297 \text{ ppm} \]

Calculation of the amount of Ru in reaction mixture for 10 g scale:

\[ m_{\text{cat}} = 140 \text{ mg (mass of Ru3d used in the reaction)} \]
\[ m_{\text{Ru}} = 21.9 \text{ mg} \]
\[ m_{\text{prod}} = 9.4 \text{ g (mass of product obtained if the conversion is 100%)} \]

maximal amount of Ru in product = \[ \frac{m_{\text{Ru}}}{m_{\text{prod}}+m_{\text{cat}}} = \frac{21.9}{9400+140} = 2295 \text{ ppm} \]
Green chemistry metrics calculations

In order to highlight the user-friendliness and advantages of performing olefin metathesis in 4-MeTHP, green chemistry metrics have been calculated for the ring-closing metathesis of 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N,N-di(prop-2-en-1-yl)benzene-sulfonamide (41) in DCE and 4-MeTHP.

Scheme S1: The influence of solvent on efficiency in RCM reaction of 41.

To a solution of 41 (10 g, 70 mmol) in DCE (200 mL) the catalyst (0.14 g, 1 mol%) was added under protective atmosphere of argon. The reaction mixture was stirred at 70 °C for 2 hours, until TLC monitoring showed complete conversion. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in 10% aqueous solution of NaOH (12 g/120 mL) at 80 °C, purified with activated charcoal (3 g), and precipitated by dropwise addition of concentrated HCl (30 mL). The reaction mixture was cooled down and the precipitated product was filtered and dried in vacuum drier. Product 42 was obtained as a cream solid (7.43 g, 79%).

A) Reaction mass efficiency

Reaction Mass Efficiency (RME) is the percentage of actual mass of the desire product to the mass of all reactants used.

\[
RME = \frac{\text{mass of product}}{\text{mass of substrate(s)}} \times 100
\]

For RCM reaction performed in 4-MeTHP:

RME = 27.17 g × 100 / 33 g = 82.3%

For RCM reaction performed in DCE:

RME = 7.43 g × 100 / 10 g = 74.3%

The reaction mass efficiency is higher in the case of process performed in 4-MeTHP which makes it a more “green” approach.
B) Environmental factor (E)

The calculation of E is defined by the ratio of the mass of waste per mass of product.

\[ E = \frac{\text{mass of total waste}}{\text{mass of product}} \]

In our case:

\[ E = \frac{\sum(\text{mass of reagents}) + \sum(\text{mass of solvent}) - \sum(\text{mass of product})}{\sum(\text{mass of product})} \]

As the amount of catalyst used for RCM reaction was roughly the same (1 mol%), and in the case of the classical reaction in the solution, this values cancel each other out.

For RCM reaction performed in 4-MeTHP:

E = (33 g + 0.463 g + 617 g - 27.17 g) / 27.17 g = 22.94

(where 33 g is mas of 41, 0.463 g is mas of Ru3d, and 617 g is mas of DCE)

For RCM reaction performed in DCE:

E = (10 g + 0.14 g + 250 g + 165 g - 7.43 g) / 7.43 g = 56.22

(where 10 g is mas of 41, 0.14 g is mas of Ru3d, 250 g is mas of DCE, and 165 g is the sum of masses of solutions of NaOH and HCl)

The environmental factor is lower for reaction performed in 4-MeTHP which makes it “green” approach.
C) EcoScale score

The EcoScale\textsuperscript{20} allows the evaluation of the effectiveness of a reaction. It gives a score from 0 to 100, not only for yield, but also includes other parameters such as cost, safety, technical set-up, energy and purification aspects.

\[ \text{EcoScale} = 100 - \text{sum of penalty points} \]

**Table S3.** Calculation of EcoScale score.

| Parameter | DCE | 4-MeTHP |
|-----------|-----|---------|
| 1. Yield (%) | 10 (79\%) | 8 (84\%) |
| 2. Price of reaction components* | | |
| Substrate 41 | 5 (>50$)**| 5 (>50$)** |
| Catalyst Ru3d | 5 (82$) | 5 (82$) |
| Solvent | 0 (4.3$) | 0 (7$) |
| Hydrochloric acid | 0 (0.8$) | - |
| Sodium hydroxide | 0 (0.5$) | - |
| 3. Safety | | |
| Catalyst Ru3d (T) | 5 | 5 |
| DCE (T,F) | 10 | - |
| Substrate 41 (T) | 5 | 5 |
| 4. Technical Setup | | |
| Common setup | 0 | 0 |
| (Inert) gas atmosphere | 1 | 1 |
| Instruments for controlled addition of chemicals | 1 | - |
| 5. Temperature/time | | |
| Heating >1 h | 3 | 3 |
| 6. Workup and purification | | |
| Crystallization and filtration | 1 | 1 |
| Distillation | 3 | - |
| **Summary of penalty points** | 49 | 33 |

\textbf{EcoScale score} 51 67

* Price calculated for 10 mmol reaction scale, prices obtained from Sigma Aldrich, TCI, and Combi Blocks (07.09.2020). ** As 41 is not commercially available its price was calculated based on cost of its preparation. Exact value is trade secret of Polpharma Pharmaceutical Works.
Figure S12. $^1$H NMR of 4-(4-methoxyphenyl)but-2-en-1-yl acetate (21).

Figure S13: $^{13}$C NMR of 4-(4-methoxyphenyl)but-2-en-1-yl acetate (21).
Figure S14. $^1$H NMR of 9-chloro-2-methylnon-4-ene (24).

Figure S15. $^{13}$C NMR of 9-chloro-2-methylnon-4-ene (24).
**Figure S16.** $^1$H NMR of dec-6-enoic acid (27).

Solvent: cdcl3, Scans: 8, Relaxation: 1.0000

**Figure S17.** $^{13}$C NMR of dec-6-enoic acid (27).

Solvent: cdcl3, Scans: 256, Relaxation: 1.0000
**Figure S18.** $^1$H NMR of 8-phenyl-oct-5-enal (30).

**Figure S19.** $^{13}$C NMR of 8-phenyl-oct-5-enal (30).
Figure S20. $^1$H NMR of (6R,7S)-7-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-3-methyl-1-azabicyclo[4.2.0]oct-3-en-8-one (34).

Figure S21. $^{13}$C NMR of (6R,7S)-7-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-3-methyl-1-azabicyclo[4.2.0]oct-3-en-8-one (34).
Figure S22. $^1$H NMR of 2-(benzhydrylthio)-1-(2,5-dihydro-1H-pyrrol-1-yl)ethanone (36).

Figure S23. $^1$H NMR of 1-(2,5-dihydro-1H-pyrrol-1-yl)-2-(3-(2,2,3,3-tetramethylcyclopropane-1-carbonyl)-1H-indol-1-yl)ethan-1-one (38).
Figure S24. $^{13}$C NMR of 1-(2,5-dihydro-1$H$-pyrrole-1-yl)-2-(3-(2,2,3,3-tetramethylcyclopropane-1-carbonyl)-1$H$-indol-1-yl)ethan-1-one (38).

Figure S25. $^1$H NMR of 1-(2-(2,5-dihydro-1$H$-pyrrole-1-carbonyl)pyrrolidin-1-yl)-4-phenylbutan-1-one (40).
**Figure S26.** $^{13}\text{C}$ NMR of -(2-(2,5-dihydro-1H-pyrrole-1-carbonyl)pyrrolidin-1-yl)-4-phenylbutan-1-one (40).

**Figure S27.** $^{1}\text{H}$ NMR of 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N,N-di(prop-2-en-1-yl)benzene-sulfonamide (41).
Figure S28. $^{13}$C NMR of 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N,N-di(prop-2-en-1-yl)benzene-sulfonamide (41).

Figure S29. $^1$H NMR of 5-[5-(2,5-dihydro-1H-pyrrol-1-ylsulfonyl)-2-ethoxyphenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimi-din-7-one (42).
Figure S30. $^{13}$C NMR of 5-[(2,5-dihydro-1H-pyrrol-1-ylsulfonyl)-2-ethoxyphenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (42).
References

1. Smoleń, M.; Kędzioerek, M.; Grela, K., 2-Methyltetrahydrofuran: Sustainable solvent for ruthenium-catalyzed olefin metathesis. Catal. Commun. 2014, 44, 80-84.
2. Guidone, S.; Blondiaux, E.; Samojłowicz, C.; Gułajski, Ł.; Kędzioerek, M.; Malińska, M.; Pazio, A.; Woźniak, K.; Grela, K.; Doppiu, A.; Cazin, C. S. J., Catalytic and Structural Studies of Hoveyda–Grubbs Type Pre-Catalysts Bearing Modified Ether Ligands. Adv. Synth. Catal. 2012, 354 (14-15), 2734-2742.
3. Chołuj, A.; Krzesiński, P.; Ruszczyńska, A.; Bulska, E.; Kajetanowicz, A.; Grela, K., Noncovalent Immobilization of Cationic Ruthenium Complex in a Metal–Organic Framework by Ion Exchange Leading to a Heterogeneous Olefin Metathesis Catalyst for Use in Green Solvents. Organometallics 2019, 38 (18), 3397-3405.
4. Szczepaniak, G.; Ruszczyńska, A.; Kosiński, K.; Bulska, E.; Grela, K., Highly efficient and time economical purification of olefin metathesis products from metal residues using an isocyanide scavenger. Green Chem. 2018, 20 (6), 1280-1289.
5. Gawin, R.; Kozakiewicz, A.; Guńka, P. A.; Dąbrowski, P.; Skowerski, K., Bis(Cyclic Alkyl Amino Carbene) Ruthenium Complexes: A Versatile, Highly Efficient Tool for Olefin Metathesis. Angew. Chem. Internat. Ed. 2017, 56 (4), 981-986.
6. Wdowik, T.; Samojłowicz, C.; Jawiczuk, M.; Malinska, M.; Wozniak, K.; Grela, K., Ruthenium nitronate complexes as tunable catalysts for olefin metathesis and other transformations. Chem. Commun. 2013, 49 (7), 674-676.
7. Szczepaniak, G.; Nogaś, W.; Piątkowski, J.; Ruszczyńska, A.; Bulska, E.; Grela, K., Semiheterogeneous Purification Protocol for the Removal of Ruthenium Impurities from Olefin Metathesis Reaction Products Using an Isocyanide Scavenger. Org. Process Res. Dev. 2019, 23 (5), 836-844.
8. Arai, H.; Nishioka, H.; Niwa, S.; Yamanaka, T.; Tanaka, Y.; Yoshinaga, K.; Kobayashi, N.; Miura, N.; Ikeda, Y., Synthesis of Prolyl Endopeptidase Inhibitors and Evaluation of Their Structure-Activity Relationships: In Vitro Inhibition of Prolyl Endopeptidase from Canine Brain. Chem. Pharm. Bull. 1993, 41 (9), 1583-1588.
9. Heck, R. F., The addition of alkyl- and arylpalladium chlorides to conjugated dienes. J. Am. Chem. Soc. 1968, 90 (20), 5542-5546.
10. Gorodetsky, A.; Zeltser, I.; Shani, A., Retardation effect of jojoba chain length on the chemical reactivity of the liquid wax. J. Am. Oil Chem. Soc. 2005, 82 (5), 373-379.