Access to Substituted Cyclobutenes by Tandem [3,3]-Sigmatropic Rearrangement/[2+2] Cycloaddition of Dipropargylphosphonates under Ag/Co Relay Catalysis

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Table of Content

1. General information ........................................................................................................2
2. General procedure for the preparation of 2 or 4.................................................................3
3. Screening of silver salts for optimization of 2a formation..............................................3
4. Attempted enantioselective desymmetrization of 1a .....................................................4
5. Procedure for the preparation of phosphinate 8 .................................................................4
6. Further derivatization of 4a ..........................................................................................5
7. Mechanism studies .........................................................................................................6
8. Analytical data of the products .......................................................................................10
9. X-ray crystallographic analysis .......................................................................................19
10. NMR spectra ................................................................................................................27
11. Bioscreening data ............................................................................................................75
12. Reference .........................................................................................................................76
1. General information

The products were purified by column chromatography on Merck silica gel 60, particle size 0.040-0.063 mm (230-240 mesh, flash). For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates (silica gel 60 GF254) were used. Visualization of the developed TLC plates was performed with ultraviolet irradiation (254 nm) or staining potassium permanganate solution followed by heating using a heat gun. Mass spectra were acquired on a Finnigan LCQ (ESI) spectrometer and high resolution mass spectra (HRMS) on a Finnigan/MAT 95XLT spectrometer. Enantiomeric excesses (ee) were determined by HPLC analysis on Agilent HPLC units. $^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded on AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26 or DCM δ 5.32), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz).

All reactions were carried out under nitrogen atmosphere. All solvents were purified and dried according to standard methods prior to use. The dipropargylphosphonates were prepared via the reaction of phosphonic dichloride with propargyl alcohol according to the reported procedure.\(^1\)
2. General procedure for the preparation of 2 or 4

To a solution of AgBF₄ (0.05 mmol) and Co(OAc)₂ (0.05 mmol) in toluene (1.0 mL) in a vial in the glovebox was added dipropargylphosphonate (0.1 mmol). The mixture was sealed and taken out of the glovebox. The reaction was heated to 100 °C and allowed to stir for 16 h. The crude mixture was cooled to ambient temperature and directly purified by flash column chromatography using hexanes/ethyl acetate (5:1) as eluent to afford the desired product 2 or 4 in pure form.

3. Screening of silver salts for optimization of 2a formation

Table S1.

| Entry | [Ag]            | Conv. (%) | Yield (%) |
|-------|-----------------|-----------|-----------|
| 1     | AgSbF₆          | 100       | trace     |
| 2     | AgPF₆           | 100       | 60        |
| 3     | AgOMs           | N.R.      | -         |
| 4     | AgBF₄           | 100       | 62        |
| 5     | AgOAc           | N.R.      | -         |
| 6     | AgOTf           | 100       | 7         |
| 7     | AgOTs           | N.R.      | -         |
| 8     | AgClO₄          | 100       | 27        |
| 9     | Silver(II) picolinate | N.R. | -        |
4. Attempted enantioselective desymmetrization of 1a

Table S2.

![Chemical structures and conversions]

| Procedure for the preparation of phosphinate 8. |
|------------------------------------------------|
| ![Chemical structures and conversions] |

5. Procedure for the preparation of phosphinate 8.

A solution of dichlorophenylphosphine (10.0 mmol), 1-(4-Methylphenyl)-1-propyne-3-ol (15.0 mmol) in diethyl ether (25 mL) was stirred at room temperature for 2 h. The solvent was removed under vacuum and the residue was purified by flash column chromatography to afford phosphinate. Phosphinate (5.0 mmol) and thionylchloride (7.5 mmol) was dissolved in toluene under Ar atmosphere at room temperature overnight. After removing thionylchloride and toluene by vacuum, the residue was dissolved in dry DCM. Then propargylic alcohol (5.0 mmol) was slowly added followed by trimethylamine at 0 ℃. The reaction mixture was then warmed up to room temperature and was stirred at room temperature overnight. The solution was quenched with H₂O, extracted with CH₂Cl₂ and concentrated in vacuum, and the residue was purified by flash column chromatography to afford products 8.
6. Further derivatization of 4a

a) Procedure for the synthesis of 12
To a solution of 4a (0.1 mmol) in dry DCM (5 mL) was added m-CPBA (0.11 mmol) at 0 °C. The mixture was warmed up to room temperature and allowed to stir for 6 h. The reaction was quenched with sat. Na₂SO₃ and extracted with DCM (3×10 ml). The combined organic phase was washed with brine, dried over Na₂SO₄ and concentrated by rotor vapor. The residue was purified by flash column chromatography on silica gel with hexanes/ethyl acetate (5:1 v/v) as the eluent.

b) Procedure for the synthesis of 13
To the conc. HCl was added 4a (0.1 mmol). The mixture was allowed to stir at 80 °C for 2 h, and then diluted with H₂O. After extraction with DCM for three times, the combined organic phase was washed with sat. NaHCO₃ and brine. Concentration of the dried organic phase gave the crude product, which was subsequently purified by flash column chromatography on silica gel with hexanes/ethyl acetate (20:1 v/v) as the eluent.

c) Procedure for the synthesis of 14
To a solution of 4a (0.1 mmol) in MeOH (10 mL) was added Raney Ni (0.1 equiv.). After stirring under H₂ (balloon) at room temperature for 12 h, the reaction mixture was filtered through Celite® pad and concentrated by vacuo. The residue was purified by flash column chromatography on silica gel with a mixture of hexanes and ethyl acetate (5:1 v/v) to give desired product.

d) Procedure for the synthesis of 15
To a solution of 4a (0.1 mmol) in MeOH (10 mL) was added 10% Pd/C (0.1 equiv.). After stirring under H₂ (balloon) at room temperature for 12 h, the reaction mixture was filtered through Celite® pad and concentrated by vacuo. The residue was purified by flash column chromatography on silica gel with a mixture of hexanes and ethyl acetate (20:1 v/v) to give desired product.
7. Mechanism studies

a) To the NMR tube was added 1a, 10 mol% catalyst and toluene-\(d_8\) in the glovebox. The mixture was taken outside and heated at 100 °C for 1 h before cooling to room temperature for \(^{31}\text{P}\) NMR.

b) To a solution of 1a in toluene-\(d_8\) was added AgBF\(_4\) (10 mol%) in a vial in the glovebox. After the designated time, an aliquot of 0.55 mL was taken via syringe and diluted for crude \(^1\text{H}\) NMR.

c) 2D NMR for the crude mixture are as shown:
8. Analytical data of the products

2,6-Dimethyl-4-phenyl-3,5-dioxo-4-phospabicyclo[5.2.0]nona-1,6-diene 4-oxide (2a)

Colorless oil, 99% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.92 – 7.83 (m, 2H), 7.61 (dt, $J = 7.2$, 1.8 Hz, 1H), 7.55 – 7.44 (m, 2H), 2.73 – 2.48 (m, 4H), 1.85 (d, $J = 4.2$ Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 139.42 (d, $J_{CP} = 9.5$ Hz), 133.00, 131.45 (d, $J_{CP} = 10.4$ Hz), 128.50 (d, $J_{CP} = 16.1$ Hz), 126.42 (d, $J_{CP} = 198.4$ Hz), 119.67 (d, $J_{CP} = 2.9$ Hz), 22.99, 16.54 (d, $J_{CP} = 6.6$ Hz).

$^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ = 7.76.

HRMS (ESI) $m/z$ Calcd for C$_{14}$H$_{15}$O$_3$P, [M+Na]$^+$ : 285.0651; Found: 285.0659.

2,6-Diethyl-4-phenyl-3,5-dioxo-4-phospabicyclo[5.2.0]nona-1,6-diene 4-oxide (2b)

Colorless oil, 97% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.91 – 7.82 (m, 2H), 7.62 – 7.55 (m, 1H), 7.52 – 7.45 (m, 2H), 2.70 – 2.52 (m, 4H), 2.14 (q, $J = 7.5$ Hz, 4H), 1.07 (t, $J = 7.5$ Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 144.08 (d, $J_{CP} = 10.1$ Hz), 132.89 (d, $J_{CP} = 3.4$ Hz), 131.48 (d, $J_{CP} = 10.2$ Hz), 128.45 (d, $J_{CP} = 16.1$ Hz), 126.67 (d, $J_{CP} = 198.9$ Hz), 118.89 (d, $J_{CP} = 2.9$ Hz), 24.09 (d, $J_{CP} = 6.1$ Hz), 23.20, 10.92.

$^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ = 7.77.

HRMS (ESI) $m/z$ Calcd for C$_{16}$H$_{15}$O$_3$P, [M+Na]$^+$ : 313.0964; Found: 313.0960.

4-Phenyl-2,6-dipropyl-3,5-dioxo-4-phospabicyclo[5.2.0]nona-1,6-diene 4-oxide (2c)

Colorless oil, 88% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.92 – 7.82 (m, 2H), 7.63 – 7.54 (m, 1H), 7.53 – 7.43 (m, 2H), 2.70 – 2.51 (m, 4H), 2.09 (t, $J = 7.3$ Hz, 4H), 1.60 – 1.45 (m, 4H), 0.92 (t, $J = 7.4$ Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 142.90 (d, $J_{CP} = 9.9$ Hz), 132.84 (d, $J_{CP} = 3.2$ Hz), 131.47 (d, $J_{CP} = 10.3$ Hz), 128.42 (d, $J_{CP} = 15.9$ Hz), 126.76 (d, $J_{CP} = 198.8$ Hz), 119.61 (d, $J_{CP} = 2.9$ Hz), 32.60 (d, $J_{CP} = 5.9$ Hz), 23.19, 19.63, 13.55.

$^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ = 7.66.

HRMS (ESI) $m/z$ Calcd for C$_{18}$H$_{23}$O$_5$P, [M+Na]$^+$ : 341.1277; Found: 341.1280.

2,6-Dibutyl-4-phenyl-3,5-dioxo-4-phospabicyclo[5.2.0]nona-1,6-diene 4-oxide (2d)

Colorless oil, 92% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.93 – 7.84 (m, 2H), 7.65 – 7.56 (m, 1H), 7.56 – 7.43 (m, 2H), 2.76 – 2.48 (m, 4H), 2.13 (t, $J = 7.4$ Hz, 4H), 1.60 – 1.44 (m, 4H), 1.42 – 1.30 (m, 4H), 0.90 (t, $J = 7.3$ Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 143.06 (d, $J_{CP} = 9.9$ Hz), 132.85 (d, $J_{CP} = 3.3$ Hz), 131.46 (d, $J_{CP} = 10.4$ Hz), 128.44 (d, $J_{CP} = 15.9$ Hz), 126.78 (d, $J_{CP} = 199.1$ Hz), 119.41 (d, $J_{CP} = 2.8$ Hz), 30.34 (d, $J_{CP} = 6.2$ Hz), 28.34, 23.20, 22.13, 13.82.

$^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ = 7.66.

HRMS (ESI) $m/z$ Calcd for C$_{20}$H$_{27}$O$_5$P, [M+Na]$^+$ : 369.1590; Found: 369.1588.
2,6-Dipentyl-4-phenyl-3,5-dioxo-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2e)

Colorless oil, 78% yield.

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.85 (dd, \(J = 14.2, 7.6\) Hz, 2H), 7.58 (dd, \(J = 7.5, 1.1\) Hz), 7.48 (td, \(J = 7.6, 4.5\) Hz, 2H), 2.69 – 2.49 (m, 4H), 2.10 (t, \(J = 7.4\) Hz, 4H), 1.56 – 1.41 (m, 4H), 1.33 – 1.25 (m, 8H), 0.86 (dd, \(J = 8.8, 4.8\) Hz, 6H).

\(^13\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 143.04 (d, \(J_{CP} = 10.1\) Hz), 132.82, 131.42 (d, \(J_{CP} = 10.2\) Hz), 128.40 (d, \(J_{CP} = 16.0\) Hz), 119.35 (d, \(J_{CP} = 2.8\) Hz), 31.18, 30.57 (d, \(J_{CP} = 6.2\) Hz), 25.89, 23.17, 22.35, 13.94.

\(^{31}\)P NMR (202 MHz, CDCl\textsubscript{3}) \(\delta\) 7.55.

HRMS (ESI) m/z Calcd for C\textsubscript{2}H\textsubscript{13}O\textsubscript{5}P, [M+Na]\textsuperscript{+} : 397.1903; Found: 397.1901.

2,6-Diphenethyl-4-phenyl-3,5-dioxo-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2f)

Colorless oil, 82% yield.

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.93 – 7.86 (m, 2H), 7.69 (td, \(J = 7.5, 1.3\) Hz, 1H), 7.58 (td, \(J = 7.7, 4.7\) Hz, 2H), 7.32 (dd, \(J = 10.3, 4.5\) Hz, 4H), 7.28 – 7.21 (m, 6H), 2.90 – 2.79 (m, 4H), 2.51 – 2.40 (m, 4H), 2.40 – 2.30 (m, 4H).

\(^13\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 142.10 (d, \(J_{CP} = 10.0\) Hz), 141.16, 132.99 (d, \(J_{CP} = 3.1\) Hz), 131.40 (d, \(J_{CP} = 10.3\) Hz), 128.62, 128.48, 128.25, 125.96, 120.16 (d, \(J_{CP} = 2.8\) Hz), 32.74 (d, \(J_{CP} = 6.1\) Hz), 32.52, 22.88.

\(^{31}\)P NMR (202 MHz, CDCl\textsubscript{3}) \(\delta\) 7.53.

HRMS (ESI) m/z Calcd for C\textsubscript{26}H\textsubscript{29}O\textsubscript{5}P, [M+Na]\textsuperscript{+} : 465.1590; Found: 465.1586.

2,6-Bis(methoxymethyl)-4-phenyl-3,5-dioxo-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2g)

Yellowish oil, 71% yield.

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.95 – 7.86 (m, 2H), 7.59 (dd, \(J = 7.3, 1.5\) Hz, 1H), 7.48 (td, \(J = 7.6, 4.7\) Hz, 2H), 3.98 – 3.89 (m, 4H), 3.36 (d, \(J = 0.7\) Hz, 6H), 2.83 – 2.69 (m, 4H).

\(^13\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 139.70 (d, \(J_{CP} = 10.1\) Hz), 133.31, 131.80 (d, \(J_{CP} = 10.7\) Hz), 128.54 (d, \(J_{CP} = 16.2\) Hz), 125.39 (d, \(J_{CP} = 198.5\) Hz), 123.81 (d, \(J_{CP} = 3.0\) Hz), 68.76 (d, \(J_{CP} = 6.5\) Hz), 58.19, 23.69.

\(^{31}\)P NMR (202 MHz, CDCl\textsubscript{3}) \(\delta\) 8.30.

HRMS (ESI) m/z Calcd for C\textsubscript{16}H\textsubscript{19}O\textsubscript{5}P, [M+Na]\textsuperscript{+} : 345.0862; Found: 345.0856.

2,6-Bis(phenoxymethyl)-4-phenyl-3,5-dioxo-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2h)

Yellowish oil, 56% yield.

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.95 – 7.86 (m, 2H), 7.62 (td, \(J = 7.5, 1.3\) Hz, 1H), 7.49 (td, \(J = 7.8, 4.9\) Hz, 2H), 7.31 – 7.26 (m, 4H), 6.98 (t, \(J = 7.4\) Hz, 2H), 6.93 – 6.89 (m, 4H), 4.55 (s, 4H), 2.82 – 2.67 (m, 4H).

\(^13\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 158.25, 138.48 (d, \(J_{CP} = 9.9\) Hz), 133.44 (d, \(J_{CP} = 3.1\) Hz), 131.76 (d, \(J_{CP} = 10.6\) Hz), 129.55, 128.62 (d, \(J_{CP} = 16.4\) Hz), 125.20 (d, \(J_{CP} = 197.5\) Hz), 123.89 (d, \(J_{CP} = 3.2\) Hz), 121.48, 114.82, 65.27 (d, \(J_{CP} = 7.5\) Hz), 24.04.

\(^{31}\)P NMR (202 MHz, CDCl\textsubscript{3}) \(\delta\) 8.09.

HRMS (ESI) m/z Calcd for C\textsubscript{20}H\textsubscript{26}O\textsubscript{5}P, [M+Na]\textsuperscript{+} : 469.1175; Found: 469.1171.
2,6-Bis((benzyloxy)methyl)-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2i)

Yellowish oil, 99% yield.

\(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.00 – 7.83 (m, 2H), 7.60 (td, \(J = 7.4, 1.3\) Hz, 1H), 7.47 (td, \(J = 7.7, 4.8\) Hz, 2H), 7.39 – 7.27 (m, 10H), 4.57 (dd, \(J = 34.4, 11.8\) Hz, 4H), 4.05 (d, \(J = 1.6\) Hz, 4H), 2.80 – 2.58 (m, 4H).

\(^1^C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 139.78 (d, \(J_{CP} = 10.1\) Hz), 137.76, 133.29 (d, \(J_{CP} = 3.3\) Hz), 131.78 (d, \(J_{CP} = 10.7\) Hz), 128.55 (d, \(J_{CP} = 16.2\) Hz), 128.39, 127.83, 127.75, 125.49 (d, \(J_{CP} = 198.6\) Hz), 72.12, 66.29 (d, \(J_{CP} = 6.6\) Hz), 23.74.

\(^{31}\)P NMR (202 MHz, CDCl\(_3\)) \(\delta\) 8.25.

HRMS (ESI) \(m/z\) Calcd for C\(_{28}\)H\(_{27}\)O\(_5\)P, [M+Na]\(^+\): 497.1488; Found: 497.1489.

2,6-Dicyclopropyl-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2j)

Colorless oil, 30% yield.

\(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.77 (ddd, \(J = 14.2, 8.2, 1.4\) Hz, 2H), 7.58 (dd, \(J = 7.6, 1.6\) Hz, 1H), 7.47 (td, \(J = 7.6, 4.6\) Hz, 2H), 2.78 – 2.64 (m, 4H), 1.50 – 1.41 (m, 2H), 0.83 – 0.61 (m, 8H).

\(^1^C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 141.84 (d, \(J_{CP} = 9.2\) Hz), 132.91 (d, \(J_{CP} = 3.4\) Hz), 131.29 (d, \(J_{CP} = 10.4\) Hz), 128.49 (d, \(J_{CP} = 16.0\) Hz), 126.44 (d, \(J_{CP} = 198.5\) Hz), 118.72 (d, \(J_{CP} = 2.9\) Hz), 23.33, 11.18 (d, \(J_{CP} = 7.1\) Hz), 4.89, 4.24.

\(^{31}\)P NMR (202 MHz, CDCl\(_3\)) \(\delta\) 8.04.

HRMS (ESI) \(m/z\) Calcd for C\(_{18}\)H\(_{19}\)O\(_3\)P, [M+Na]\(^+\): 337.0964; Found: 337.0971.

4-Phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2k)

White solid, 63% yield.

\(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.89 – 7.81 (m, 2H), 7.61 (td, \(J = 7.7, 1.3\) Hz, 1H), 7.49 (td, \(J = 7.8, 4.8\) Hz, 2H), 6.14 (d, \(J = 20.0\) Hz, 2H), 2.82 – 2.63 (m, 4H).

\(^1^C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 133.27 (d, \(J_{CP} = 3.2\) Hz), 131.71 (d, \(J_{CP} = 10.5\) Hz), 131.45 (d, \(J_{CP} = 10.6\) Hz), 128.59 (d, \(J_{CP} = 16.4\) Hz), 125.77 (d, \(J_{CP} = 3.6\) Hz), 125.71 (d, \(J_{CP} = 198.3\) Hz), 22.98.

\(^{31}\)P NMR (202 MHz, CDCl\(_3\)) \(\delta\) 8.97.

HRMS (ESI) \(m/z\) Calcd for C\(_{12}\)H\(_{11}\)O\(_3\)P, [M+Na]\(^+\): 257.0338; Found: 257.0334.

4-Ethyl-2,6-dimethyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2l)

Colorless oil, 81% yield.

\(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 2.67 – 2.50 (m, 4H), 1.92 (dq, \(J = 18.6, 7.7\) Hz, 2H), 1.81 (s, 6H), 1.31 – 1.21 (m, 3H).

\(^1^C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 138.71 (d, \(J_{CP} = 9.9\) Hz), 119.19 (d, \(J_{CP} = 3.0\) Hz), 22.96 (s), 17.52 (d, \(J_{CP} = 141.5\) Hz), 16.44 (d, \(J_{CP} = 6.4\) Hz), 6.18 (d, \(J_{CP} = 7.2\) Hz).

\(^{31}\)P NMR (202 MHz, CDCl\(_3\)) \(\delta\) 22.88.

HRMS (ESI) \(m/z\) Calcd for C\(_{10}\)H\(_{15}\)O\(_3\)P, [M+Na]\(^+\): 237.0651; Found: 237.0649.
4-Benzyl-2,6-dimethyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2m)

White solid, 83% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.41 – 7.17 (m, 5H), 3.33 (d, $J = 21.7$ Hz, 2H), 2.57 (dd, $J = 17.0, 12.4, 9.2$ Hz, 4H), 1.70 (s, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 138.64 (d, $J_{CP} = 9.9$ Hz), 130.25 (d, $J_{CP} = 9.2$ Hz), 129.89 (d, $J_{CP} = 7.1$ Hz), 128.59 (d, $J_{CP} = 3.0$ Hz), 127.21 (d, $J_{CP} = 3.7$ Hz), 119.03, 31.72 (d, $J_{CP} = 134.5$ Hz), 23.08, 16.27 (d, $J_{CP} = 7.1$ Hz).

$^{31}$P NMR (202 MHz, CDCl$_3$) δ 15.01.

HRMS (ESI) m/z Calcd for C$_{15}$H$_{17}$O$_3$P, [M+Na]$^+$ : 299.0821; Found: 299.0824.

2,6-Diethyl-4-phenoxy-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,6-diene 4-oxide (2n)

Yellowish oil, 75% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.34 (t, $J = 7.9$ Hz, 2H), 7.25 (d, $J = 8.7$ Hz, 2H), 7.19 (t, $J = 7.3$ Hz, 1H), 2.63 (s, 4H), 2.15 – 1.93 (m, 4H), 0.99 (t, $J = 7.5$ Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 150.08 (d, $J_{CP} = 7.1$ Hz), 142.58 (d, $J_{CP} = 9.8$ Hz), 129.66 (s), 125.42, 120.08 (d, $J_{CP} = 5.1$ Hz), 118.15, 23.65 (d, $J_{CP} = 8.6$ Hz), 23.47 (s), 10.72.

$^{31}$P NMR (202 MHz, CDCl$_3$) δ -21.16.

HRMS (ESI) m/z Calcd for C$_{16}$H$_{19}$O$_3$P, [M+Na]$^+$ : 329.0909; Found: 329.0913.

2,4,8-Triphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4a)

White solid, 73% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.04 – 7.97 (m, 2H), 7.65 – 7.49 (m, 5H), 7.40 (dd, $J = 10.4, 4.7$ Hz, 2H), 7.34 – 7.22 (m, 6H), 5.45 (dd, $J = 15.3, 7.8, 4.3$ Hz, 1H), 5.19 – 5.05 (m, 1H), 3.72 – 3.46 (m, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 140.75, 137.54, 133.93 (d, $J_{CP} = 7.9$ Hz), 133.67 (d, $J_{CP} = 10.2$ Hz), 133.33, 133.11 (d, $J_{CP} = 3.1$ Hz), 131.59 (d, $J_{CP} = 10.2$ Hz), 128.87, 128.60, 128.49 (d, $J_{CP} = 5.2$ Hz), 128.34, 127.98, 126.68 (d, $J_{CP} = 200.6$ Hz), 126.48, 125.50, 121.70 (d, $J_{CP} = 3.2$ Hz), 63.13 (d, $J_{CP} = 7.4$ Hz), 34.60.

$^{31}$P NMR (202 MHz, CDCl$_3$) δ 20.61.

HRMS (ESI) m/z Calcd for C$_{24}$H$_{20}$O$_3$P, [M+Na]$^+$ : 409.0964; Found: 409.0965.

4-Phenyl-2,8-di-p-tolyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4b)

Yellowish solid, 39% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.04 – 7.96 (m, 2H), 7.65 – 7.59 (m, 1H), 7.52 (dd, $J = 7.6, 4.7$ Hz, 2H), 7.46 (d, $J = 8.2$ Hz, 2H), 7.21 (d, $J = 8.1$ Hz, 2H), 7.13 (dd, $J = 8.0, 3.5$ Hz, 4H), 5.47 – 5.38 (m, 1H), 5.10 (dd, $J = 25.0, 15.4$ Hz, 1H), 3.63 – 3.48 (m, 2H), 2.36 (d, $J = 18.7$ Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 140.42, 138.67, 137.85, 136.47, 133.52 (d, $J_{CP} = 10.2$ Hz), 133.04 (d, $J_{CP} = 3.1$ Hz), 131.62 (d, $J_{CP} = 10.1$ Hz), 131.24 (d, $J_{CP} = 8.0$ Hz), 130.78, 129.61, 129.07, 128.53 (d, $J_{CP} = 15.8$ Hz), 126.88 (d, $J_{CP} = 200.4$ Hz), 126.43, 125.40, 121.14 (d, $J_{CP} = 3.2$ Hz), 63.19 (d, $J_{CP} = 7.4$ Hz), 34.58, 21.48, 21.25.
$^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ 20.52.

HRMS (ESI) m/z Calcd for C$_{26}$H$_{23}$O$_3$P, [M+Na]$^+$ : 437.1277; Found: 437.1288.

2,8-Bis(4-fluorophenyl)-4-phenyl-3,5-dioxo-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4c)

Yellowish oil, 68% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.04 – 7.95 (m, 2H), 7.68 – 7.60 (m, 1H), 7.56 – 7.49 (m, 4H), 7.24 – 7.16 (m, 2H), 7.10 (dd, $J$ = 12.0, 5.3 Hz, 2H), 7.05 – 6.97 (m, 2H), 5.42 (ddd, $J$ = 15.3, 7.8, 4.0 Hz, 1H), 5.08 (dd, $J$ = 25.2, 15.4 Hz, 1H), 3.57 (dt, $J$ = 13.1, 3.1 Hz, 1H), 3.50 (ddd, $J$ = 13.1, 4.1, 2.0 Hz, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 162.62 (d, $J$$_{CF}$ = 250.7 Hz), 162.43 (d, $J$$_{CF}$ = 248.8 Hz), 139.48, 136.89, 133.22 (d, $J$$_{CP}$ = 3.1 Hz), 131.56 (d, $J$$_{CP}$ = 10.2 Hz), 130.07 (d, $J$$_{CF}$ = 8.1 Hz), 129.04 (d, $J$$_{CF}$ = 8.0 Hz), 129.69 (d, $J$$_{CP}$ = 3.4 Hz), 128.58 (d, $J$$_{CP}$ = 15.9 Hz), 128.21 (d, $J$$_{CF}$ = 8.2 Hz), 127.30 (d, $J$$_{CF}$ = 8.0 Hz), 126.47 (d, $J$$_{CP}$ = 199.2 Hz), 120.95, 116.14 (d, $J$$_{CF}$ = 22.1 Hz), 115.42 (d, $J$$_{CF}$ = 21.8 Hz), 63.02 (d, $J$$_{CP}$ = 7.4 Hz), 34.54.

$^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ 20.73.

HRMS (ESI) m/z Calcd for C$_{24}$H$_{17}$F$_2$O$_3$P, [M+Na]$^+$ : 445.0776; Found: 445.0778.

Dimethyl 4,4’-(4-oxido-4-phenyl-3,5-dioxo-4-phosphabicyclo[5.2.0]nona-1,7-diene-2,8-diylo) dibenzoate (4d)

White solid, 56% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J$ = 8.3 Hz, 2H), 8.03 (ddd, $J$ = 7.8, 8.5, 5.3 Hz, 4H), 7.74 – 7.64 (m, 3H), 7.58 (td, $J$ = 7.7, 4.8 Hz, 2H), 7.32 (d, $J$ = 8.3 Hz, 2H), 5.50 (ddd, $J$ = 15.6, 7.3, 3.9 Hz, 1H), 5.18 (dd, $J$ = 25.4, 15.7 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.71 (dt, $J$ = 13.1, 3.0 Hz, 1H), 3.65 (ddd, $J$ = 13.2, 4.1, 2.0 Hz, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 166.58, 166.40, 140.49, 140.34, 138.01 (d, $J$$_{CP}$ = 7.9 Hz), 136.97, 133.93 (d, $J$$_{CP}$ = 10.1 Hz), 133.42 (d, $J$$_{CP}$ = 3.1 Hz), 131.61 (d, $J$$_{CF}$ = 10.3 Hz), 130.20, 129.82, 129.70, 129.52, 128.68 (d, $J$$_{CF}$ = 16.0 Hz), 126.40, 126.16 (d, $J$$_{CF}$ = 200.8 Hz), 125.33, 63.06 (d, $J$$_{CF}$ = 7.4 Hz), 123.55 (d, $J$$_{CF}$ = 3.2 Hz), 52.28, 52.17, 34.85.

$^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ 20.93.

HRMS (ESI) m/z Calcd for C$_{28}$H$_{23}$O$_7$P, [M+Na]$^+$ : 503.1254; Found: 503.1267.

2,8-Bis(3-methoxyphenyl)-4-phenyl-3,5-dioxo-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4e)

Yellow oil, 92% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.00 (dd, $J$ = 14.0, 8.2 Hz, 2H), 7.62 (dd, $J$ = 10.8, 4.2 Hz, 1H), 7.52 (dd, $J$ = 12.2, 7.5 Hz, 2H), 7.32 (t, $J$ = 7.9 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.19 – 7.15 (m, 1H), 7.11 (s, 1H), 6.86 (dd, $J$ = 8.2, 1.9 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.74 (s, 1H), 5.48 – 5.39 (m, 1H), 5.11 (dd, $J$ = 25.1, 15.4 Hz, 1H), 3.83 (s, 3H), 3.78 (d, $J$ = 0.8 Hz, 3H), 3.64 – 3.51 (m, 2H).
13C NMR (126 MHz, CDCl3) δ 159.86, 159.48, 140.70, 137.80, 135.24 (d, JCP = 8.1 Hz), 134.55, 133.58 (d, JCP = 10.3 Hz), 133.09 (d, JCP = 3.1 Hz), 131.54 (d, JCP = 10.1 Hz), 129.88, 129.33, 128.52 (d, JCP = 16.0 Hz), 126.60 (d, JCP = 200.4 Hz), 121.88 (d, JCP = 3.2 Hz), 119.15, 118.15, 114.05, 113.29, 111.89, 111.42, 63.03 (d, JCP = 7.3 Hz), 55.25, 55.21, 34.70.

31P NMR (202 MHz, CDCl3) δ 20.57.

HRMS (ESI) m/z Calcd for C26H25O3P, [M+Na]+: 469.1175; Found: 469.1184.

2,8-Bis(3,5-dimethylphenyl)-4-phenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4f)

Yellowish oil, 60% yield.

1H NMR (500 MHz, CDCl3) δ 8.06 – 7.96 (m, 2H), 7.63 (td, J = 7.6, 1.2 Hz, 1H), 7.52 (td, J = 7.7, 4.6 Hz, 2H), 7.19 (s, 2H), 6.93 (d, J = 24.9 Hz, 2H), 6.87 (s, 2H), 5.43 (dt, J = 15.1, 6.2 Hz, 1H), 5.10 (dd, J = 24.6, 15.3 Hz, 1H), 3.60 (dt, J = 13.3, 3.0 Hz, 1H), 3.51 (dddd, J = 13.2, 4.0, 2.0 Hz, 1H), 2.34 (s, 6H), 2.30 (s, 6H).

13C NMR (126 MHz, CDCl3) δ 140.93, 138.38, 137.79, 137.11, 133.91 (d, JCP = 7.9 Hz), 133.80 (d, JCP = 10.3 Hz), 133.39, 132.99, 131.65 (d, JCP = 10.1 Hz), 130.39, 129.77, 128.52 (d, JCP = 15.8 Hz), 126.94 (d, JCP = 199.8 Hz), 124.37, 123.44, 121.67, 63.17 (d, JCP = 7.4 Hz), 34.79, 21.45, 21.33.

31P NMR (202 MHz, CDCl3) δ 20.44.

HRMS (ESI) m/z Calcd for C26H25O3P, [M+Na]+: 465.1590; Found: 465.1602.

4-Ethyl-2,8-diphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4g)

Yellowish oil, 80% yield.

1H NMR (500 MHz, CDCl3) δ 7.59 (d, J = 7.8 Hz, 2H), 7.42 – 7.33 (m, 4H), 7.29 (q, J = 7.3 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 5.34 (dddd, J = 15.3, 7.5, 3.9 Hz, 1H), 5.09 – 4.97 (m, 1H), 3.63 – 3.42 (m, 2H), 2.07 (dd, J = 18.9, 7.7 Hz, 2H), 1.35 (dt, J = 20.8, 7.7 Hz, 3H).

13C NMR (126 MHz, CDCl3) δ 140.42, 137.79, 134.14 (d, JCP = 7.6 Hz), 133.42, 133.32, 128.86, 128.42, 128.37, 127.98, 126.44, 125.50, 121.47 (d, JCP = 3.6 Hz), 62.84 (d, JCP = 7.9 Hz), 34.49, 18.78 (d, JCP = 145.1 Hz), 6.55 (d, JCP = 7.0 Hz).

31P NMR (202 MHz, CDCl3) δ 36.27.

HRMS (ESI) m/z Calcd for C26H25O3P, [M+Na]+: 361.0964; Found: 361.0965.

4-Benzyl-2,8-diphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1,7-diene 4-oxide (4h)

White solid, 83% yield.

1H NMR (500 MHz, CDCl3) δ 7.49 (dd, J = 5.3, 3.4 Hz, 2H), 7.45 – 7.27 (m, 11H), 7.24 – 7.19 (m, 2H), 5.32 (dddd, J = 15.3, 7.9, 4.3 Hz, 1H), 5.02 (ddt, J = 24.6, 15.4, 2.6 Hz, 1H), 3.60 – 3.43 (m, 4H).

13C NMR (126 MHz, CDCl3) δ 140.54, 137.57, 133.96 (d, JCP = 7.4 Hz), 133.34, 130.54 (d, JCP = 9.8 Hz), 129.98 (d, JCP = 6.8 Hz), 128.86, 128.70 (d, JCP = 3.1 Hz), 128.48, 128.32, 127.94, 127.25 (d, JCP = 3.8 Hz), 126.45, 125.42, 121.66, 63.15 (d, JCP = 8.0 Hz), 34.47, 33.25 (d, JCP = 141.2 Hz).

31P NMR (202 MHz, CDCl3) δ 28.60.

HRMS (ESI) m/z Calcd for C25H25O3P, [M+Na]+: 423.1121; Found: 423.1119.
2,8-Dimethyl-4,6,9-triphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]nona-1(9),6-diene 4-oxide (4i)

Colorless oil, 50% yield

$^1$H NMR (500 MHz, CD$_2$Cl$_2$) δ 8.02 – 7.94 (m, 2H), 7.68 – 7.61 (m, 1H), 7.54 (ddd, $J = 9.7, 6.0, 3.0$ Hz, 4H), 7.46 – 7.30 (m, 8H), 5.84 – 5.77 (m, 1H), 4.09 (qd, $J = 6.7, 2.2$ Hz, 1H), 1.62 (dd, $J = 6.6, 1.0$ Hz, 3H), 1.10 (d, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) δ 146.46, 141.22, 133.98 (d, $J_{CP} = 7.9$ Hz), 133.34 (d, $J_{CP} = 9.6$ Hz), 132.91, 132.89, 132.06, 131.46 (d, $J_{CP} = 10.0$ Hz), 128.74, 128.52, 128.45, 128.40, 128.21, 128.13, 127.61, 127.60 (d, $J_{CP} = 215.2$ Hz), 126.87, 71.94 (d, $J_{CP} = 7.6$ Hz), 41.23, 19.35 (d, $J_{CP} = 10.5$ Hz), 14.74.

$^{31}$P NMR (202 MHz, CD$_2$Cl$_2$) δ 17.76.

HRMS (ESI) m/z Calcd for C$_{36}$H$_{32}$O$_2$P, [M+Na]$^+$: 437.1277; Found: 437.1284.

4,6,9-Triphenyl-3-oxa-5-thia-4-phosphabicyclo[5.2.0]nona-1(9),6-diene 4-oxide (6)

Yellowish oil, 38% yield.

$^1$H NMR (500 MHz, CD$_2$Cl$_2$) δ 7.85 (ddd, $J = 13.8, 8.0, 1.0$ Hz, 2H), 7.58 – 7.53 (m, 1H), 7.50 – 7.39 (m, 7H), 7.28 – 7.19 (m, 5H), 5.68 – 5.60 (m, 1H), 5.27 (dd, $J = 23.2, 13.4$ Hz, 1H), 3.52 (dd, $J = 14.3, 2.6$ Hz, 1H), 3.41 (d, $J = 14.3$ Hz, 1H).

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) δ 148.58, 142.18, 137.45, 136.62, 132.96, 132.88 (d, $J_{CP} = 3.2$ Hz), 132.82, 131.75, 131.20 (d, $J_{CP} = 10.9$ Hz), 129.70, 128.93, 128.49 (d, $J_{CP} = 15.1$ Hz), 128.27, 127.65, 127.52, 127.32, 61.54 (d, $J_{CP} = 8.2$ Hz), 37.52.

$^{31}$P NMR (202 MHz, CD$_2$Cl$_2$) δ 45.15.

HRMS (ESI) m/z Calcd for C$_{34}$H$_{30}$O$_2$PS, [M+Na]$^+$: 425.0736; Found: 425.0731.

O-but-2-yn-1-yl S-buta-2,3-dien-2-yl phenylphosphonothioate (7)

Colorless oil, 65% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.96 – 7.86 (m, 2H), 7.58 (dd, $J = 8.0, 6.8$ Hz, 1H), 7.54 – 7.47 (m, 2H), 4.87 – 4.80 (m, 2H), 4.51 (dddd, $J = 7.3, 6.6, 3.3, 0.8$ Hz, 2H), 1.90 (dddd, $J = 4.2, 2.6, 0.9$ Hz, 3H), 1.88 (td, $J = 2.3, 0.8$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.02 (d, $J_{CP} = 7.7$ Hz), 132.67 (d, $J_{CP} = 3.2$ Hz), 131.71 (d, $J_{CP} = 10.9$ Hz), 131.31 (d, $J_{CP} = 149.5$ Hz), 128.35 (d, $J_{CP} = 15.0$ Hz), 88.21 (d, $J_{CP} = 7.0$ Hz), 74.84 (d, $J_{CP} = 4.2$ Hz), 73.31 (d, $J_{CP} = 10.0$ Hz), 54.21 (d, $J_{CP} = 5.4$ Hz), 22.35, 3.72.

$^{31}$P NMR (202 MHz, CDCl$_3$) δ 44.68.

HRMS (ESI) m/z Calcd for C$_{13}$H$_{15}$O$_2$PS, [M+Na]$^+$: 301.0423; Found: 301.0428.

2-Ethyl-4-phenyl-5-(p-tolyl)-3-oxa-4-phosphabicyclo[4.2.0]octa-1,5-diene 4-oxide (9)

White solid, 57% yield.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.78 (ddd, $J = 13.5, 8.3, 1.5$ Hz, 2H), 7.46 (dd, $J = 7.3, 1.7$ Hz, 1H), 7.39 (ddd, $J = 8.5, 6.6, 3.7$ Hz, 2H), 7.34 (d, $J = 7.9$ Hz, 2H), 7.02 (d, $J = 7.9$ Hz, 2H), 3.51 – 3.24 (m, 1H), 3.17 – 2.91 (m, 3H), 2.36 (d, $J = 7.6$ Hz, 2H), 2.24 (s, 3H), 1.15 (t, $J = 7.6$ Hz, 3H).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 152.03 (d, $J_{CP} = 4.4$ Hz), 147.80 (d, $J_{CP} = 14.0$ Hz), 136.95, 132.56, 132.20 (d, $J_{CP} = 2.9$ Hz), 131.88 (d, $J_{CP} = 11.4$ Hz), 131.11, 130.65 (d, $J_{CP} = 13.2$ Hz), 129.31, 128.29 (d, $J_{CP} = 13.9$ Hz), 127.39 (d, $J_{CP} = 8.5$ Hz), 118.15 (d, $J_{CP} = 22.3$ Hz), 116.53, 115.33, 31.11 (d, $J_{CP} = 13.7$ Hz), 24.63 (d, $J_{CP} = 4.3$ Hz), 21.15, 10.05.

$^{31}$P NMR (160 MHz, CDCl$_3$) δ 25.93.

HRMS (ESI) m/z Calcd for C$_{21}$H$_{25}$O$_3$P, [M+H]$^+$ : 337.1352; Found: 337.1347.

4-phenyl-5-((p-toly]-8-(trimethylsilyl)-3-oxa-4-phosphabicyclo[4.2.0]octa-1(8),5-diene-4-oxide (10)

White solid, 63% yield.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.81 (ddd, $J = 13.1$, 7.6, 1.6 Hz, 2H), 7.45 (dd, $J = 7.4$, 1.6 Hz, 1H), 7.37 (dd, $J = 10.4$, 5.8 Hz, 4H), 7.00 (d, $J = 7.9$ Hz, 2H), 5.27 – 5.14 (m, 1H), 4.81 (tdd, $J = 15.8$, 3.4, 1.9 Hz, 1H), 3.55 (dd, $J = 14.1$, 2.7 Hz, 1H), 3.36 – 3.14 (m, 1H), 2.23 (s, 3H), 0.16 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 152.45 (d, $J_{CP} = 3.1$ Hz), 152.00, 151.80, 149.35 (d, $J_{CP} = 3.8$ Hz), 137.31, 132.23 (d, $J_{CP} = 3.0$ Hz), 131.64 (d, $J_{CP} = 10.8$ Hz), 131.41. 130.46 (d, $J_{CP} = 12.0$ Hz), 130.00, 129.31, 128.43 (d, $J_{CP} = 13.7$ Hz), 127.53 (d, $J_{CP} = 7.5$ Hz), 116.73, 115.57, 63.46 (d, $J_{CP} = 8.4$ Hz), 39.43 (d, $J_{CP} = 13.8$ Hz), 21.16, -2.04.

$^{31}$P NMR (160 MHz, CDCl$_3$) δ 21.71.

HRMS (ESI) m/z Calcd for C$_{22}$H$_{23}$O$_2$PSi, [M+H]$^+$ : 381.1434; Found: 381.1428.

But-2-yn-1-yl buta-2,3-dien-2-yl phenylphosphonate (11)

Colorless oil, 73% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.93 – 7.83 (m, 2H), 7.62 – 7.54 (m, 1H), 7.47 (tdd, $J = 6.8$, 4.5, 1.3 Hz, 2H), 6.15 (ddd, $J = 17.0$, 10.8, 2.2 Hz, 1H), 5.58 (dd, $J = 16.9$, 1.2 Hz, 1H), 5.18 (dq, $J = 10.8$, 1.1 Hz, 1H), 5.09 (q, $J = 2.0$ Hz, 1H), 4.76 (ddq, $J = 10.0$, 5.0, 2.5 Hz, 2H), 4.71 (t, $J = 2.3$ Hz, 1H), 1.79 (t, $J = 2.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 151.01 (d, $J = 8.2$ Hz), 132.82 (d, $J = 3.2$ Hz), 131.98 (d, $J = 10.3$ Hz), 131.52 (d, $J = 5.5$ Hz), 128.41 (d, $J = 15.6$ Hz), 127.41 (d, $J = 191.8$ Hz), 116.25, 102.12 (d, $J = 4.2$ Hz), 84.54, 73.34 (d, $J = 8.1$ Hz), 54.88 (d, $J = 4.8$ Hz), 3.59.

$^{31}$P NMR (202 MHz, CDCl$_3$) δ 16.65.

HRMS (ESI) m/z Calcd for C$_{25}$H$_{19}$O$_2$PS, [M+H]$^+$ : 263.0832; Found: 263.0829.

2,4,7-Triphenyl-3,5-dioxo-4-phosphabicyclo[5.2.0]non-1-en-8-one 4-oxide (12)

Colorless oil, 75% yield.

$^1$H NMR (500 MHz, Acetone-$d_6$) δ 8.05 – 7.97 (m, 3H), 7.69 – 7.65 (m, 1H), 7.57 – 7.48 (m, 9H), 7.37 – 7.30 (m, 2H), 5.59 – 5.39 (m, 2H), 3.59 (ddd, $J = 13.2$, 3.0, 1.9 Hz, 1H), 3.47 (ddd, $J = 13.1$, 3.1, 1.1 Hz, 1H).

$^{13}$C NMR (126 MHz, Acetone-$d_6$) δ 196.04 (d, $J = 2.0$ Hz), 144.13, 135.27, 134.24 (d, $J = 3.1$ Hz), 133.67, 133.06 (d, $J = 10.5$ Hz), 131.79, 131.34, 130.90, 130.35, 130.18, 129.87, 129.75, 129.413 (d, $J = 151.3$ Hz) 128.87, 82.32 (d, $J = 6.4$ Hz), 66.18 (d, $J = 7.8$ Hz), 43.53 (d, $J = 2.5$ Hz).

$^{31}$P NMR (202 MHz, Acetone-$d_6$) δ 14.49.

HRMS (ESI) m/z Calcd for C$_{28}$H$_{19}$O$_5$P, [M+Na]$^+$ : 425.0913; Found: 425.0916.
(2-(Chloromethyl)-3-phenylcyclobut-2-en-1-yl)(phenyl)methanone (13)

Yellowish oil, 44% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.07 – 8.00 (m, 2H), 7.63 – 7.59 (m, 1H), 7.51 (t, $J = 7.7$ Hz, 2H), 7.43 – 7.33 (m, 5H), 4.69 (dd, $J = 5.3$, 2.0 Hz, 1H), 4.59 (d, $J = 12.2$ Hz, 1H), 4.40 (d, $J = 12.2$ Hz, 1H), 3.16 (dd, $J = 13.3$, 5.0 Hz, 1H), 2.97 (dt, $J = 12.8$, 1.8 Hz, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.18, 143.58, 136.22, 134.77, 133.50, 133.37, 128.78, 128.66, 128.59, 128.20, 126.66, 44.90, 39.26, 32.05.

HRMS (APCI) m/z Calcd for C$_{18}$H$_{15}$ClO, [M+H]$^+$: 283.0884; Found: 283.0886.

(2,4,8-Triphenyl-3,5-dioxa-4-phosphabicyclo[5.2.0]non-1-ene 4-oxide (14)

Colorless oil, 69% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.02 – 7.89 (m, 2H), 7.59 (d, $J = 7.6$ Hz, 1H), 7.56 – 7.45 (m, 4H), 7.35 (qt, $J = 14.5$, 7.5 Hz, 7H), 7.25 – 7.21 (m, 1H), 4.29 (td, $J = 11.0$, 6.4 Hz, 1H), 4.21 – 4.11 (m, 1H), 3.95 (td, $J = 9.7$, 5.6 Hz, 1H), 3.76 – 3.57 (m, 2H), 3.38 (dt, $J = 12.2$, 5.6 Hz, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 140.85, 138.97, 133.74, 132.94, 131.64 (d, $J_{CP} = 9.9$ Hz), 128.63, 128.38 (d, $J_{CP} = 2.0$ Hz), 128.34 (d, $J_{CP} = 154.0$ Hz), 127.73, 127.09, 126.15, 124.19, 65.47 (d, $J_{CP} = 6.6$ Hz), 46.48, 37.14, 32.82.

$^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ 16.92.

HRMS (ESI) m/z Calcd for C$_{24}$H$_{21}$O$_3$P, [M+Na]$^+$: 411.1121; Found: 411.1122.

(3-Benzyl-2-methylcyclobutyl)benzene (15)

Colorless oil, 78% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33 – 7.27 (m, 4H), 7.22-7.12 (m, 6H), 3.68 – 3.55 (m, 1H), 2.86 (qd, $J = 13.7$, 7.5 Hz, 2H), 2.79 – 2.59 (m, 1H), 2.53 – 2.39 (m, 1H), 2.33 – 2.02 (m, 2H), 0.76 (d, $J = 7.3$ Hz, 1H, minor), 0.59 (d, $J = 7.1$ Hz, 2H, major).

$^{13}$C NMR (126 MHz, CDCl$_3$, major diastereomer) $\delta$ 142.23, 141.18, 128.69, 128.25, 128.05, 127.94, 125.76, 125.58, 41.88, 41.68, 39.60, 39.50, 28.72, 16.27; minor diastereomer $\delta$ 141.54, 141.40, 128.43, 128.28, 127.90, 127.64, 125.63, 125.52, 39.34, 37.14, 36.71, 35.43, 29.30, 10.48.

HRMS (APCI) m/z Calcd for C$_{18}$H$_{20}$, [M+H]$^+$: 237.1638; Found: 237.1633.
9. X-ray crystallographic analysis

a) The structure of 2k was assigned by X-ray crystallographic analysis:

Table S3. Sample and crystal data for g546.

| Identification code | g546       |
|---------------------|------------|
| Chemical formula    | C₁₂H₁₁O₃P  |
| Formula weight      | 234.18 g/mol |
| Temperature         | 100(2) K   |
| Wavelength          | 0.71073 Å  |
| Crystal size        | (0.080 x 0.160 x 0.350) mm³ |
| Crystal system      | monoclinic |
| Space group         | P 1 2(1)/c 1 |
| Unit cell dimensions| a = 8.145(3) Å, α = 90° |
|                     | b = 13.268(4) Å, β = 108.850(10)° |
|                     | c = 10.374(3) Å, γ = 90° |
| Volume              | 1061.0(6) Å³ |
Z

Density (calculated) 1.466 g/cm³
Absorption coefficient 0.246 mm⁻¹
F(000) 488

Table S4. Data collection and structure refinement for g546.

Theta range for data collection 2.58 to 30.55°
Index ranges -11<=h<=10, -16<=k<=18, -14<=l<=14
Reflections collected 11289
Independent reflections 3235 [R(int) = 0.0337]
Coverage of independent reflections 99.4%
Absorption correction multi-scan
Max. and min. transmission 0.9810 and 0.9190
Refinement method Full-matrix least-squares on F²
Refinement program SHELXL-2014/7 (Sheldrick, 2014)
Function minimized Σ w(Fo² - Fc²)²
Data / restraints / parameters 3235 / 0 / 145
Goodness-of-fit on F² 1.031
Final R indices 2751 data; I>2σ(I) R1 = 0.0344, wR2 = 0.0836
all data R1 = 0.0442, wR2 = 0.0886
w=1/[σ²(Fo²)+(0.0386P)²+0.5991P]
Weighting scheme where P=(Fo²+2Fc²)/3
Largest diff. peak and hole 0.422 and -0.366 eÅ⁻³
R.M.S. deviation from mean 0.060 eÅ⁻³
b) The structure of **4a** was assigned by X-ray crystallographic analysis

![Molecule's view of 4a:](image)

**Table S5. Sample and crystal data for g511.**

| Identification code  | g511          |
|----------------------|---------------|
| Chemical formula     | C_{24}H_{19}O_3P |
| Formula weight       | 386.36 g/mol   |
| Temperature          | 100(2) K      |
| Wavelength           | 0.71073 Å      |
| Crystal size         | (0.174 x 0.271 x 0.567) mm³ |
| Crystal system       | monoclinic    |
| Space group          | P 1 2(1)c 1   |
| Unit cell dimensions | a = 14.464(6) Å, α = 90°  
|                      | b = 13.000(5) Å, β = 97.227(10)°  
|                      | c = 10.236(4) Å, γ = 90°  |
| Volume               | 1909.4(13) Å³ |
| Z                    | 4             |
Density (calculated) 1.344 g/cm$^3$
Absorption coefficient 0.167 mm$^{-1}$
F(000) 808

**Table S6. Data collection and structure refinement for g511.**

- **Theta range for data collection**: 2.54 to 29.36°
- **Index ranges**: $-19 \leq h \leq 19$, $-17 \leq k \leq 17$, $-14 \leq l \leq 14$
- **Reflections collected**: 31186
- **Independent reflections**: 5211 [R(int) = 0.1016]
- **Coverage of independent reflections**: 99.3%
- **Absorption correction**: multi-scan
- **Max. and min. transmission**: 0.9720 and 0.9110
- **Refinement method**: Full-matrix least-squares on $F^2$
- **Refinement program**: SHELXL-2014/7 (Sheldrick, 2014)
- **Function minimized**: $\Sigma w(F_o^2 - F_c^2)^2$
- **Data / restraints / parameters**: 5211 / 0 / 253
- **Goodness-of-fit on $F^2$**: 1.037
- **$\Delta/\sigma_{max}$**: 0.001
- **Final R indices**: 3840 data; I>2$\sigma$(I) R1 = 0.0548, wR2 = 0.1326
- **Final R indices**: all data R1 = 0.0818, wR2 = 0.1457
- **Weighting scheme**: $w=1/[\sigma^2(F_o^2)+(0.0742P)^2+0.7139P]$
  where $P=(F_o^2+2F_c^2)/3$
- **Largest diff. peak and hole**: 0.499 and -0.574 eÅ$^{-3}$
- **R.M.S. deviation from mean**: 0.083 eÅ$^{-3}$
c) The structure of 4i was assigned by X-ray crystallographic analysis:

![Molecule's view of 4i](image)

**Table S7. Sample and crystal data for g766.**

| Characteristic                | Value                        |
|-------------------------------|------------------------------|
| Identification code           | g766                         |
| Chemical formula              | C_{26}H_{23}O_{3}P            |
| Formula weight                | 414.41 g/mol                 |
| Temperature                   | 100(2) K                     |
| Wavelength                    | 0.71073 Å                    |
| Crystal size                  | (0.112 x 0.233 x 0.344) mm$^3$|
| Crystal system                | monoclinic                   |
| Space group                   | P 1 2(1)/c 1                 |
| Unit cell dimensions          | a = 14.668(5) Å, α = 90°     |
|                              | b = 13.512(4) Å, β = 92.316(9)° |
|                              | c = 10.815(3) Å, γ = 90°     |
| Volume                        | 2141.7(11) Å$^3$            |
| Z                             | 4                            |
| Density (calculated)          | 1.285 g/cm$^3$               |
| Absorption coefficient        | 0.153 mm$^{-1}$              |
| F(000)                        | 872                          |
Table S8. Data collection and structure refinement for g766.

Theta range for data collection 2.41 to 30.18°

Index ranges  
-20≤h≤20, -19≤k≤18, -15≤l≤15

Reflections collected 31655

Independent reflections 6290 [R(int) = 0.0655]

Coverage of independent reflections 99.0%

Absorption correction Multi-Scan

Max. and min. transmission 0.9830 and 0.9490

Refinement method Full-matrix least-squares on F²

Refinement program SHELXL-2014/7 (Sheldrick, 2014)

Function minimized Σ w(F₀² - Fc²)²

Data / restraints / parameters 6290 / 0 / 273

Goodness-of-fit on F² 1.021

Δ/σₘₐₓ 0.001

Final R indices 4671 data; R1 = 0.0456, wR2 =

I>2σ(I) 0.0968

R1 = 0.0753, wR2 =

all data 0.1073

Weighting scheme w=1/[(σ²(F₀²) + (0.0446P)²+0.9664P)]

where P=(F₀²+2Fc²)/3

Largest diff. peak and hole 0.324 and -0.431 eÅ⁻³

R.M.S. deviation from mean 0.065 eÅ⁻³
d) The structure of 14 was assigned by X-ray crystallographic analysis:

![Molecule's view of 14]

Table S9. Sample and crystal data for g807.

| Identification code | g807        |
|---------------------|-------------|
| Chemical formula    | C₆H₁₇O₃P    |
| Formula weight      | 388.38 g/mol|
| Temperature         | 100(2) K    |
| Wavelength          | 0.71073 Å   |
| Crystal size        | (0.134 x 0.237 x 0.304) mm³ |
| Crystal system      | monoclinic  |
| Space group         | P 1 c 1     |
| Unit cell dimensions| a = 6.2565(10) Å, α = 90°  
b = 9.4325(10) Å, β = 96.178(4)°  
c = 16.395(2) Å, γ = 90°  |
| Volume              | 961.9(2) Å³  |
| Z                   | 2           |
| Density (calculated)| 1.341 g/cm³ |
| Absorption coefficient | 0.166 mm⁻¹ |
Table S10. Data collection and structure refinement for g807.

Theta range for data collection  2.50 to 30.59°
Index ranges   -8<=h<=8, -13<=k<=13, -23<=l<=23
Reflections collected  33800
Independent reflections  5781 [R(int) = 0.0258]
Coverage of independent reflections  99.7%
Absorption correction  Multi-Scan
Max. and min. transmission  0.9780 and 0.9510
Structure solution technique  direct methods
Structure solution program  SHELXT, Acta Cryst., Sect. A 2015, A71, 3-8.
Refinement method  Full-matrix least-squares on F²
Refinement program  SHELXL-2014/7 (Sheldrick, 2014)
Function minimized  \( \Sigma w(F_o^2 - F_c^2)^2 \)
Data / restraints / parameters  5781 / 2 / 254
Goodness-of-fit on F²  1.025
Final R indices  5652 data; I>2σ(I)  R1 = 0.0252, wR2 = 0.0678
                   all data  R1 = 0.0263, wR2 = 0.0685
Weighting scheme  
                   \( w=1/[σ^2(F_o^2)+0.0475P]^2+0.1011P] \)
                   where P=(F_o^2+2F_c^2)/3
Absolute structure parameter  -0.013(12)*
Extinction coefficient  0.0180(40)
Largest diff. peak and hole  0.272 and -0.219 eÅ⁻³
R.M.S. deviation from mean  0.044 eÅ⁻³

* Flack x determined using 2671 quotients [(I+)-(I-)]/[(I+)+(I-)]
  (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
10. NMR spectra

$^{1}H$ NMR of 2a

$^{13}C$ NMR of 2a
$^3$P NMR of 2a

![31P NMR spectrum of 2a](image)

$^1$H NMR of 2b

![1H NMR spectrum of 2b](image)
$^{13}$C NMR of 2b

![C NMR spectrum of 2b](image)

$^{31}$P NMR of 2b

![P NMR spectrum of 2b](image)
$^1$H NMR of $2c$

$^{13}$C NMR of $2c$
$^3$P NMR of 2c

$^1$H NMR of 2d
$^{13}$C NMR of 2d

$^{31}$P NMR of 2d
$^1$H NMR of 2e

$^{13}$C NMR of 2e
$^{31}$P NMR of 2e

$^1$H NMR of 2f
$^3$C NMR of 2f

$^3$P NMR of 2f
$^1$H NMR of 2g

$^{13}$C NMR of 2g
$^{31}$P NMR of $2g$

$^1$H NMR of $2h$
$^{13}$C NMR of 2h

$^{31}$P NMR of 2h
$^1$H NMR of 2i

$^{13}$C NMR of 2i
$^{13}$C NMR of $2j$

$^{31}$P NMR of $2j$
$^1$H NMR of 2k

$^{13}$C NMR of 2k
$^{31}$P NMR of 2k

$^1$H NMR of 2l
$^{13}$C NMR of 21

$^{31}$P NMR of 21
$^1$H NMR of $2m$

$^{13}$C NMR of $2m$
$^{31}$P NMR of $2m$

$^1$H NMR of $2n$
$^{13}$C NMR of 2n

$^{31}$P NMR of 2n
\textbf{H NMR of 4a}

\textbf{\textsuperscript{13}C NMR of 4a}
$^{31}$P NMR of 4a

$^1$H NMR of 4b
$^{13}$C NMR of 4b

$^{31}$P NMR of 4b
$^1$H NMR of 4c

$^{13}$C NMR of 4c
$^3$P NMR of 4c

$^1$H NMR of 4d
$^{13}$C NMR of 4d

$^{31}$P NMR of 4d
$^1$H NMR of 4e

$^{13}$C NMR of 4e
$^{31}$P NMR of 4e

![31P NMR spectrum of 4e](image)

$^1$H NMR of 4f

![1H NMR spectrum of 4f](image)
$^{13}$C NMR of $4f$

$^{31}$P NMR of $4f$
$^1$H NMR of 4g

$^{13}$C NMR of 4g
31P NMR of 4g

31P NMR of 4h

1H NMR of 4h
$^{13}$C NMR of 4h

$^{31}$P NMR of 4h
\( ^1H \) NMR of 4i

\( ^13C \) NMR of 4i
$^{31}$P NMR of 4i

$^1$H NMR of 6
$^{13}$C NMR of 6

![C NMR spectrum of 6]

$^{31}$P NMR of 6

![P NMR spectrum of 6]
$^1$H NMR of 7

[Chemical structure and spectrum image]

$^{13}$C NMR of 7

[Chemical structure and spectrum image]
$^{31}\text{P NMR of 7}$

$^{1}\text{H NMR of 9}$
$^{13}$C NMR of $9$

$^{31}$P NMR of $9$
$^1$H NMR of 10

![NMR spectrum of 10](image)

$^{13}$C NMR of 10

![NMR spectrum of 10](image)
$^{31}$P NMR of 10

$^1$H NMR of 11
$^1$C NMR of 11

$^{31}$P NMR of 11
$^1$H NMR of 12

$^{13}$C NMR of 12
$^{31}$P NMR of 12

$^1$H NMR of 13
$^{13}$C NMR of 13

$^1$H NMR of 14
$^{13}$C NMR of 14

$^{31}$P NMR of 14
$^1$H NMR of 15

$^{13}$C NMR of 15
NOESY of 15
11. Bioscreening data

Material and methods

Cell cultures
Human derived colorectal cancer cell line, DLD1 was obtained from American Type Culture Collection (ATCC) and was maintained in DMEM medium supplemented with 10% fetal calf serum and 100U/ml penicillin-streptomycin (Sigma-Aldrich) in humidified 37oC incubator with 5% CO2. Cells were passaged and harvested with 0.25% trypsin for use in subsequent in vitro experiments. For all experiments, equal number of DLD1 cells were seeded for all conditions within the same experimental setup.

Cellular proliferation and IC50 determination
End point cellular proliferation was assessed using standard MTT assay. Briefly, 0.5mg/ml of (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) reagent was added to DLD1 cell culture that were treated with either the medium ring compounds at various concentrations or DMSO for 48 hours and incubated in a humidified 37oC incubator with 5% CO2 for two hours. The resultant purple formazan salt crystals were solubilised with DMSO before measurement at test wavelength of 570 nm (reference wavelength at 630 nm). Level of cellular proliferation was expressed as percentage relative to DMSO control. IC50 of the respective medium ring compound was subsequently determined using the variable slope model which incorporated the proliferation rate of DLD1 after treatment with the different medium ring compounds at dosage between 0.15mg/ml to 0.005 mg/ml for 48 hours.

On the other hand, real-time assessment of cellular proliferation and viability were assessed using xCELLigence real-time cell analysis (RTCA) assay (ACEA Bioscience, Inc. USA). DLD1 cells were seeded and rested overnight before addition of the respective compounds or DMSO as control. Impedance-based time-dependent cell response profiles (TCRPs) were recorded for 48 hours post treatment. The TCRPs showed changes in impedance which reflect the changes in cell density due to variation in cellular proliferation capacity, viability and apoptotic rate. Two or more independent experiments were carried out for all proliferation assays with 4-8 replicates per group.

Cellular apoptosis
Levels of cellular apoptosis in DLD1 cells treated with the respective compounds or DMSO for 48 hours were determined using FITC Annexin V apoptosis detection kit with 7-AAD (Biolegend, USA). Relative fluorescence were analysed using flow cytometer, BD Fortessa (BD Biosciences, USA) and data were tabulated using FlowJo™ v10.6 software (FlowJo, USA). Two independent experiments were carried out with at least two replicates for each condition tested.

Statistical analysis
All statistical analysis and graphing were done using GraphPad Prism (Graphpad Software, USA). Non-parametric, One-way ANOVA with Dunn’s multiple comparison test were carried out for all multiple comparisons.
12. Reference

1. a) N. P. Kenny, K. V. Rajendran and D. G. Gilheany, Chem. Commun., 2015, 51, 16561-16564; b) D. A. Erzunov, G. V. Latyshev, A. D. Averin, I. P. Beletskaya, N. V. Lukashev, Eur. J. Org. Chem. 2015, 2015, 6289-6297.

2. T. Mosmann, J. Immunol. Methods 1983, 65, 55-63.