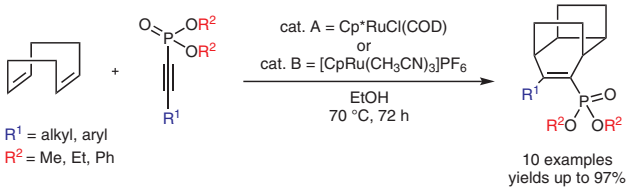
Synthesis D. Petko et al. Paper

Ruthenium-Catalyzed [2+2+2] Bis-Homo-Diels–Alder Cycloadditions of 1,5-Cyclooctadiene with Alkynyl Phosphonates

Dina Petko
Austin Pounder
William Tam*

Guelph-Waterloo Centre for Graduate Work in Chemistry and Biochemistry, Department of Chemistry, University of Guelph, Guelph, Ontario, N1G 2W1, Canada
wtam@uoguelph.ca



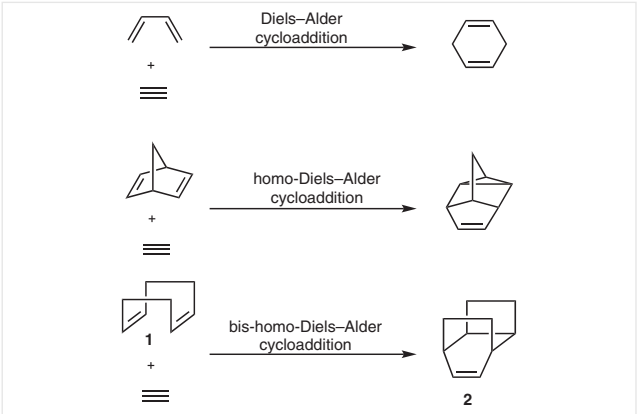
Received: 16.07.2019
Accepted after revision: 31.07.2019
Published online: 21.08.2019
DOI: 10.1055/s-0039-1690612; Art ID: ss-2019-m0399-op

Abstract The ruthenium-catalyzed [2+2+2] bis-homo-Diels–Alder cycloaddition between 1,5-cyclooctadiene and alkynyl phosphonates was investigated. Various alkynyl phosphonate moieties were found to be compatible with the cycloaddition to give the tricyclo[4.2.2.0^{2,5}]dec-7-ene tricyclic compounds in yields of 46–97%.

Key words 1,5-cyclooctadiene, bis-homo-Diels–Alder reaction, cycloaddition, ruthenium-catalyzed, alkynyl phosphonate

Cycloadditions are amongst the most powerful in the repertoire of ring-forming reactions producing multiple carbon–carbon bonds in a single step. Cycloadditions are achieved under photochemical or thermal conditions or promoted by Lewis acids. Transition-metal catalysts expanded the scope of the cycloaddition and have been used for construction of a wide array of four- to eight-membered rings.[1] Transition-metal-catalyzed [2+2],[2] [3+2],[3] Diels–Alder [4+2],[4] and homo-Diels–Alder [2+2+2][5] are all well described in literature; however, very few examples of the bis-homo-Diels–Alder [2+2+2][6–8] cycloaddition exist. The bis-homo-Diels–Alder (BHDA) reaction was first reported by Trost et al. in 1993 as a cycloaddition between 1,5-cyclooctadiene (COD, **1**) and an alkyne resulting in the formation of the tricyclo[4.2.2.0^{2,5}]dec-7-ene bicyclic framework **2** (Scheme 1).[7] Unlike the Diels–Alder and homo-Diels–Alder cycloadditions, which can both occur thermally or by transition metal catalysts such as Ni, Co, Rh, and Pd,[1] the BHDA cycloaddition has only been achieved using a Ru catalyst[6–8] (Scheme 1).

The BHDA cycloaddition provides a facile method of synthesis of the tricyclo[4.2.2.0^{2,5}]dec-7-ene bicyclic frameworks, which can be found in several biologically active



Scheme 1 Diels–Alder, homo-Diels–Alder, and bis-homo-Diels–Alder cycloadditions

compounds such as mitindomide[9] and kingianin C[10] (Figure 1). Both mitindomide and kingianin C have been shown to have anticancer activity. For instance, mitindomide is

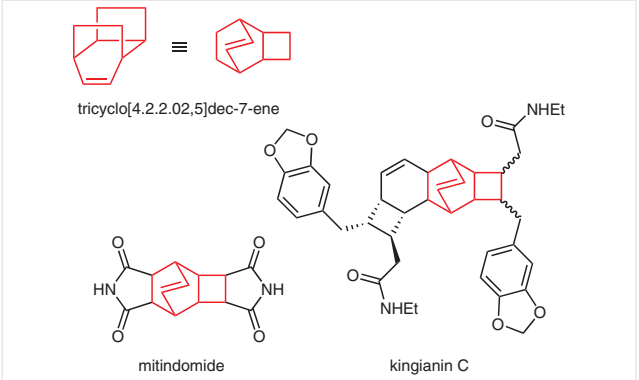
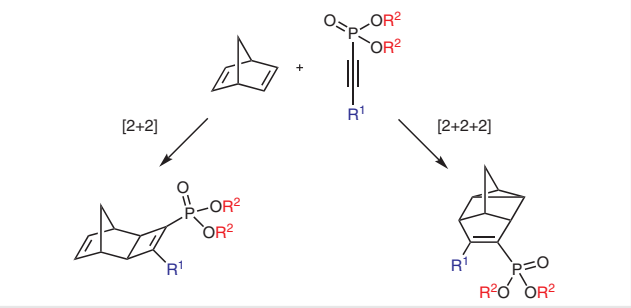


Figure 1 Two biologically active compounds containing the tricyclo-[4.2.2.0^{2,5}]dec-7-ene framework

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

known to be an inhibitor of DNA topoisomerase II, which is needed for DNA replication and cell proliferation.[9] Additionally, kingianin C has been shown to have inhibitory effects on anti-apoptotic protein Bcl-xL, which is commonly found in cancer cells, particularly those that are resistant to conventional chemotherapies.[10]

In the past, our research group has investigated ruthenium-catalyzed [2+2][11] and homo-Diels–Alder [2+2+2] cycloadditions[12] between bicyclic alkenes and alkynyl phosphonates to generate cyclobutene and deltacyclanes adducts, respectively (Scheme 2).



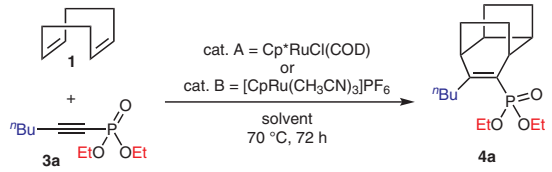
Scheme 2 [2+2] and homo-Diels–Alder [2+2+2] reactions of bicyclo-[2.2.1]hepta-2,5-diene and alkynyl phosphonates

To date, the development of new biologically active compounds depends heavily on organic synthetic chemistry. Thus, the introduction of new functional groups into these attractive polycyclic frameworks would offer more opportunities to discover new intriguing, and possibly pharmaceutically relevant molecules.

Vinyl phosphonates have been found to be important biomolecules in metabolic processes, as anticancer and antiviral drugs, and as antibacterial and antifungal compounds.[13–18] The vinyl phosphonate group can be further modified by established procedures. The alkene can undergo cyclopropanation,[19] ozonolysis,[20] or Diels–Alder cycloadditions[21] while the phosphonate can be converted to a variety of other phosphorus groups including phosphines.[22] To the best of our knowledge, there are no examples of the BHDA cycloaddition involving alkynes directly attached to a heteroatom. The formation of the BHDA cycloadduct containing a vinyl phosphonate is thus desirable, and investigations into the Ru-catalyzed BHDA cycloaddition were further pursued.

Initial studies began screening a series of solvents for the BHDA cycloaddition of COD with diethyl 1-hexynylphosphonate (**3a**) using two commercially available Ru-catalysts: Cp*RuCl(COD) (cat. A) and $[CpRu(CH_3CN)_3]PF_6$ (cat. B). Several polar protic, polar aprotic, and nonpolar solvents were investigated. Using NMP, 1,4-dioxane, THF, or DCE as a solvent (Table 1, entries 2, 8, 10, 14) or running the reaction neat (entry 1) produced the desired cycloadduct in a 48–85% yield but only using cat. B. Next, we turned to additives to see if the introduction of silver salts would facilitate the activation of Cp*RuCl(COD) in aprotic solvents. Pleasingly, the addition of silver salts promoted the cycloaddition using cat. A in the previously noneffective aprotic solvents although only in a 72–80% yield (entries 5–7, 9, 11, 13). The yield of **4a** was improved with the use of polar protic solvents (entries 3 and 4) as high as 93%. EtOH was found to be the optimal solvent to promote the formation of the BHDA cycloadduct for both Ru catalysts in high yields.

Table 1 Optimization of Solvent for the Ru-Catalyzed BHDA [2+2+2] Cycloaddition of COD **1** with 1-Hexynylphosphonate **3a**



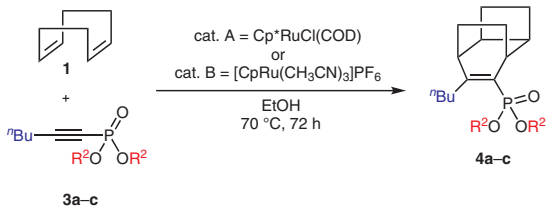
Entry	Solvent	Silver salt[a]	Yield (%)[b]	
			Cat. A	Cat. B
1	neat	–	0 (51)[c]	48
2	NMP	–	0 (93)[c]	85
3	EtOH	–	91	93
4	MeOH	–	91	89
5	1,4-dioxane	$AgSbF_6$	80	–
6	1,4-dioxane	$AgBF_4$	78	–
7	1,4-dioxane	AgOTf	79	–
8	1,4-dioxane	–	0 (90)[c]	83
9	THF	$AgSbF_6$	77	–
10	THF	–	0	60
11	toluene	$AgSbF_6$	72	–
12	toluene	–	0	0 (79)[c]
13	DCE	$AgSbF_6$	77	–
14	DCE	–	0	85

[a] Silver salts were only added to reactions containing cat. A Cp*RuCl(COD).
[b] Isolated yield.
[c] Percentage of starting material recovered.

After establishing the above optimized condition, the scope of the Ru-catalyzed BHDA cycloaddition of COD and alkynyl phosphonates was investigated. First, the effects of the substituent on the phosphonate moiety were explored (Table 2). Alkynyl phosphonates **3a–c** were synthesized using known literature procedures[11,23–25] and subjected to optimized BHDA conditions to produce cycloadducts **4a–c** in yields up to 97%. The reaction was found to be amenable to the size of the phosphonate moiety with yields decreasing as substituent size was increased. The effect of increasing steric bulk and replacing an aliphatic group with an aromatic functionality on the phosphonate is demonstrated by **4c** (R = Ph, Table 2, entry 3). Because the OMe moiety (entry 1) produced the cycloadduct **4b** in the greatest yield for

both catalysts, it was chosen as the model phosphonate moiety for further exploration into the scope of the BHDA cycloaddition.

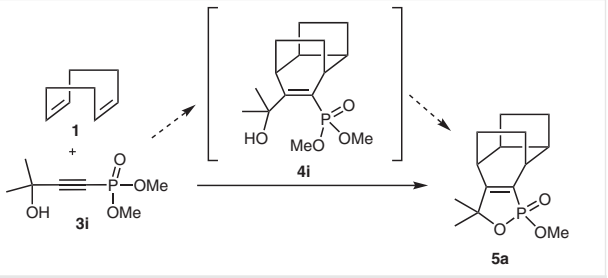
Table 2 Ru-Catalyzed BHDA [2+2+2] Cycloadditions of COD **1** with Alkynyl Phosphonates **3a–c**



Entry	R^2	Cycloadduct	Yield (%)[a]	
			Cat. A	Cat. B
1	Me	**4b**	95	97
2	Et	**4a**	91	93
3	Ph	**4c**	78	86

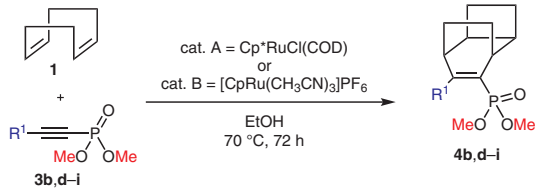
[a] Isolated yield.

The effects of alkyne substitution were examined with several examples of primary, secondary, and tertiary alkyl and aryl substituents (Table 3). The reaction was found to be susceptible to the steric bulk of the alkyne substituent with yields decreasing with increased steric hindrance. This effect was particularly significant with cat. A with no reaction proceeding when substituents lacked a methylene group (entries 2, 3, 4, and 7). When using cat. B, the BHDA cycloaddition showed compatibility with various functional groups including phenyls, benzyls, and protected alcohols (Table 3, entries 4–6). Unfortunately, the reaction did not proceed with either catalysts when the alkyne was substituted with a tertiary carbon (entry 3). Interestingly, when an unprotected alcohol (entry 7) underwent the BHDA cycloaddition, an unexpected cycloadduct was formed (Scheme 3). It is believed that cycloadduct **4i** is formed initially and undergoes an intramolecular cyclization to form the unpredicted tetracyclic cycloadduct **5a**. We have previously shown that propargylic alcohols and homopropargylic alcohols usually gave higher yields and react faster in the Ru-catalyzed BHDA cycloadditions.[6] It is likely that the ruthenium may bind to the hydroxyl group and enhance the reactivity of the alkynyl phosphonate **3i** in the Ru-catalyzed BHDA cycloaddition, which outweighs the steric hindrance of the tertiary propargylic alcohol group.



Scheme 3 Formation of unexpected cycloadduct **5a** via intramolecular cyclization

Table 3 Ru-Catalyzed BHDA [2+2+2] Cycloadditions of COD **1** with Alkynyl Phosphonates 3b and 3d–i

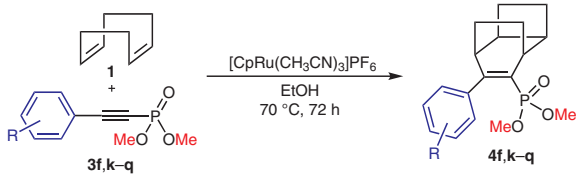


Entry	R^1	Cycloadduct	Yield (%)[a]	
			Cat. A	Cat. B
1	*n*-Bu	**4b**	95	97
2	Cy	**4d**	0 (35)[b]	80
3	*t*-Bu	**4e**	0 (78)[b]	0 (69)[b]
4	Ph	**4f**	0 (35)[b]	46
5	$BnOCH_2$	**4g**	58	66
6	$BnOCH_2CH_2$	**4h**	66	68
7	$Me_2C(OH)$	**4i**	0	43[c]

[a] Isolated yield after chromatography.
[b] Percentage of starting material recovered.
[c] Unexpected cycloadduct **5a** formed (see Scheme 3).

Examining the effects of the aromatic substituents, a series of *ortho*-, *meta*-, and *para*-substituted dimethyl 1-phenylethynyl phosphonates were synthesized using known literatures procedures.[23–25] Since Cp*RuCl(COD) originally failed the catalyze the BHDA cycloaddition with Ph as an alkyne substituent (Table 3, entry 4), only [Cp$Ru(CH_3CN)_3]PF_6$ was used for further trials. The reaction was found to be affected by the electronic density of the aromatic substituent. When electron-withdrawing substituents were placed at the *meta*- or *para*-position (Table 4, entries 2, 3, 5) yields were increased from 46% (Table 4, entry 1) to as high as 79%. Unsurprisingly, the BHDA cycloaddition did not proceed when substituents were placed at the *ortho*-position, most likely due to the steric hindrance (entries 4, 6, 8). Continuing with this trend, electron-donating substituents failed to undergo the BHDA cycloaddition with neither product nor starting material being recovered (entries 7 and 8). Interestingly, a similar observation was noted in our groups previous investigations of the homo-Diels–Alder cycloaddition of alkynyl phosphonates with bicyclo-[2.2.1]hepta-2,2-diene where electron-donating aryl substituents promoted thermal decomposition of the final cycloadduct.[11]

Table 4 Ru-Catalyzed BHDA [2+2+2] Cycloadditions of COD **1** with Alkynyl Phosphonates 3f and 3k–q



Entry	R	Cycloadduct	Yield (%)[a]
1	H	**4f**	46
2	*p*-CF_3	**4k**	79
3	*m*-CF_3	**4l**	79
4	*o*-CF_3	**4m**	0 (72)[b]
5	*m*-Cl	**4n**	74
6	*o*-Cl	**4o**	0 (78)[b]
7	*p*-OMe	**4p**	0
8	*o*-OMe	**4q**	0 (91)[b]

[a] Isolated yield.
[b] Percentage of starting material recovered.

In conclusion, we have demonstrated the first examples of Ru-catalyzed BHDA [2+2+2] cycloaddition between 1,5-cyclooctadiene and heteroatom-substituted alkynes. The desired cycloadducts were obtained in yields ranging from 46 to 97%. The reaction was found to be amenable to the steric bulk of both the phosphonate and alkynyl moieties. Further, we demonstrated the compatibility for both aliphatic and aromatic substituents, as well as a range of functional groups in poor to excellent yields. Finally, exploration of the intramolecular variant of this reaction, or the modification of the vinyl phosphonate could further expand the scope and applicability of this reaction.

All commercial reagents were used without further purification. Solvent was obtained from an LC-SPS solvent purification system supplied with dry packed columns containing 3Å molecular sieves. Standard column chromatography was performed on 230–400 mesh silica gel using flash column chromatography techniques. Analytical TLC was performed on pre-coated silica gel 60 F254 plates. All reactions carried out in an atmosphere of dry argon. ^{1}H NMR spectra were recorded on 600 or 400 MHz in $CDCl_3$, ^{13}C{H} NMR spectra were recorded on 150 or 100 MHz in $CDCl_3$. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) with the solvent resonance as the internal standard ($CHCl_3$: δ = 7.26). Chemical shifts for ^{13}C {H}NMR spectra are reported in parts per million with the solvent as the internal standard ($CHCl_3$: δ = 77.16). Standard abbreviations are used to denote signal multiplicities. IR spectra were obtained on thin films on NaCl disks using a Bomem MB-100 FTIR or Nicolet-380 FTIR spectrophotometer. HRMS samples were ionized by chemical ionization (CI), electron impact (EI), or electrospray ionization (ESI) as specified, and detection of the ions was performed by time of flight (TOF). Alkynyl phosphonates **3a**, **3d**, **3f**, and **3p** are known compounds and were prepared using known literature procedures.[11,12,23–25]

Alkynyl Phosphonates 3c and 3e; General Procedure

i-Pr_2NH (reaction scale 0.50–4.0 mmol, 1.5 equiv) was dissolved in THF (§0.8 M) at 0 °C in a flame dried round-bottomed flask (RBF). A 1.35 M solution of *n*-BuLi (1 equiv) in hexanes was added and the solution stirred at r.t. for 1 h. The mixture was then added via cannula to a second RBF containing the terminal alkyne (1 equiv) in THF (§0.6 M) at –78 °C, which was then stirred while warming to r.t. for 2 h. In a third RBF, the chlorophosphate (2 equiv) was dissolved in THF (§0.6 M) and cooled to –78 °C. The deprotonated alkyne was then added dropwise via cannula to the electrophile. The reaction mixture was then stirred at –78 °C for 1 h, 0 °C for 1 h, and r.t. for 4 h or until complete; the reaction progress was followed by TLC. When the reaction was complete the solution was quenched with sat. aq NH_4Cl. The aqueous layer was separated and extracted with Et_2O (3 ×). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The resulting product was then purified by flash column chromatography on 230–400 mesh silica gel with hexanes/EtOAc mixture as the mobile phase.

Diphenyl Hex-1-yn-1-ylphosphonate (3c)

The crude product was purified by column chromatography (1:3 EtOAc/hexanes) to provide the alkyne **3c** as a clear oil; yield: 106.5 mg (0.338 mmol, 68%); R_f = 0.31 (1:3, EtOAc/hexanes).

IR (neat): 3491 (s), 3070 (w), 2960 (w), 2934 (w), 2873 (w), 2206 (m), 1590 (m), 1489 (s), 1284 (s), 1212 (s), 1188 (s), 1162 (s), 949 (s), 774 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36–7.31 (m, 4 H), 7.27–7.22 (m, 4 H), 7,21–7.17 (m, 2 H), 2.27 (td, *J* = 7.0, 4.6 Hz, 2 H), 1.46–1.43 (m, 2 H), 1.31–1.25 (m, 2 H), 0.84 (t, *J* = 7.3 Hz, 3 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 150.0 (d, *J* = 7.5 Hz), 129.7, 125.5 (d, *J* = 1.2 Hz), 120.7 (d, *J* = 4.7 Hz), 106.6 (d, *J* = 55.5 Hz), 69.5 (d, *J* = 322.2 Hz), 29.0 (d, *J* = 2.2 Hz), 21.6, 18.9 (d, *J* = 4.8 Hz), 13.3.

^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz): δ = –16.69.

HRMS: *m*/*z* [M^+] calcd for $C_{18}H_{19}O_3P$: 314.1072; found: 314.1078.

Dimethyl (3,3-Dimethylbut-1-yn-1-yl)phosphonate (3e)

The crude product was purified by column chromatography (EtOAc) to provide the alkyne **3e** as a clear oil; yield: 291.3 mg (1.53 mmol, 38%); R_f = 0.46 (EtOAc).

IR (neat): 3489 (s), 2973 (m), 2907 (w), 2872 (w), 2853 (w), 2220 (w), 2182 (m), 1269 (s), 1033 (s), 839 (m), 798 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.70 (d, *J* = 12.2 Hz, 6 H), 1.22 (s, 9 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 111.3 (d, *J* = 51.2 Hz), 67.1 (d, *J* = 305.1 Hz), 53.1 (d, *J* = 5.4 Hz), 29.8 (d, *J* = 1.8 Hz), 28.0 (d, *J* = 3.8 Hz).

^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz): δ = –4.52.

HRMS: *m*/*z* [M + H^+] calcd for $C_8H_{15}O_3P$: 191.0837; found: 191.0840.

Alkynyl Phosphonates 3b, 3d, and 3f–q; General Procedure

H-Phosphonate (reaction scale 0.080–1.6 mmol), terminal alkyne (1 equiv), CuCl or $Cu(OAc)_2$ (10 mol%), and Et_3N (0.2 equiv) were dissolved in DMSO (0.5 M) in a flame-dried round-bottomed flask and stirred for 24 h at 70 °C under an inert atmosphere. The resulting mixture was extracted using EtOAc (3 ×). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The resulting product was then purified by flash column chromatography on 230–400 mesh silica gel with hexanes/EtOAc mixture as the mobile phase.

Dimethyl Hex-1-yn-1-ylphosphonate (3b)

The crude product was purified by column chromatography (EtOAc) to provide the alkyne **3b** as a yellow oil; yield: 42.0 mg (0.221 mmol, 65%); R_f = 0.42 (EtOAc).

IR (neat): 3494 (s), 2957 (m), 2874 (w), 2205 (m), 1274 (s), 1034 (s), 838 (m), 784 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.72 (d, J = 12.3 Hz, 6 H), 2.31 (td, J = 7.1, 4.5 Hz, 2 H), 1.54–1.49 (m, 2 H), 1.41–1.36 (m, 2 H), 0.87 (t, J = 7.3 Hz, 3 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 104.1 (d, J = 53.5 Hz), 69.0 (d, J = 305.8 Hz), 53.1 (d, J = 5.6), 29.3 (d, J = 2.1 Hz), 21.8, 18.8 (d, J = 4.5 Hz), 13.4.

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = –2.5.

HRMS: m/z [M + H^+] calcd for $C_8H_{15}O_3P$: 191.0837; found: 191.0841.

Dimethyl [3-(Benzyloxy)prop-1-yn-1-yl]phosphonate (3g)

The crude product was purified by column chromatography (EtOAc) to provide the alkyne **3g** as a clear oil; yield: 91.8 mg (0.408 mmol, 48%); R_f = 0.45 (EtOAc).

IR (neat): 3031 (w), 2954 (w), 2853 (w), 2204 (w), 1266 (m), 1022 (s), 837 (m), 784 (m), 739 (m), 698 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.34–7.27 (m, 5 H), 4.57 (s, 2 H), 4.24 (d, J = 3.8 Hz, 2 H), 3.76 (d, J = 12.3 Hz, 6 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 136.5, 128.5, 128.2, 128.1, 97.2 (d, J = 50.0 Hz), 75.1 (d, J = 296.8 Hz), 72.2, 57.0 (d, J = 4.4 Hz), 53.49 (d, J = 5.5 Hz).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = –3.9.

HRMS: m/z [M + H^+] calcd for $C_{12}H_{15}O_4P$: 225.0786; found: 255.0778.

Dimethyl [4-(Benzyloxy)but-1-yn-1-yl]phosphonate (3h)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **3h** as a yellow oil; yield: 150.5 mg (0.559 mmol, 46%); R_f = 0.1 (1:1 EtOAc/hexanes).

IR (neat): 3029 (w), 2953 (w), 2853 (w), 2207 (m), 1265 (m), 1023 (s), 835 (m), 779 (m), 734 (m), 699 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.23 (m, 5 H), 4.50 (s, 2 H), 3.72 (d, J = 12.3 Hz, 6 H), 3.60 (t, J = 6.7 Hz, 2 H), 2.62 (td, J = 6.8, 4.4 Hz, 2 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 137.6, 128.4, 127.8, 127.6, 100.7 (d, J = 53.2 Hz), 73.1, 70.1 (d, J = 303.5 Hz), 66.8 (d, J = 2.6 Hz), 53.2 (d, J = 5.4 Hz), 20.7 (d, J = 4.5 Hz).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = –2.9.

HRMS: m/z [M + H^+] calcd for $C_{13}H_{17}O_4P$: 269.0943; found: 269.0932.

Dimethyl (3-Hydroxy-3-methylbut-1-yn-1-yl)phosphonate (3i)

The crude product was purified by column chromatography (EtOAc) to provide the alkyne **3j** as an orange oil; yield: 30.9 mg (0.160 mmol, 57%); R_f = 0.28 (EtOAc).

IR (neat): 3360 (s), 2986 (w), 2957 (w), 2854 (w), 2202 (w), 1253 (m), 1220 (m), 1027 (s), 922 (s), 841 (s), 820 (s), 729 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.72 (d, J = 12.3 Hz, 6 H), 1.49 (s, 6 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 106.9 (d, J = 49.3 Hz), 69.4 (d, J = 300.9 Hz), 64.6 (d, J = 4.1 Hz), 53.5 (d, J = 5.7 Hz), 30.4 (d, J = 1.2 Hz).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = –2.8.

HRMS: m/z [M + H^+] calcd for $C_7H_{13}O_4P$: 193.0630; found: 193.0624.

Dimethyl {[4-(Trifluoromethyl)phenyl]ethynyl}phosphonate (3k)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **3k** as a yellow oil; yield: 140.3 mg (0.626 mmol, 39%); R_f = 0.17 (1:1 EtOAc/hexanes).

IR (neat): 3488 (s), 2958 (w), 2856 (w), 2193 (m), 1325 (s), 1277 (m), 1172 (m), 1130 (s), 1067 (s), 1037 (s), 865 (m), 843 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.68–7.61 (m, 4 H), 3.84 (d, J = 12.2 Hz, 6 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 133.0 (d, J = 2.3 Hz), 132.4 (d, J = 33.0 Hz), 125.6 (q, J = 3.8 Hz), 123.4 (d, J = 272.9 Hz), 123.1 (d, J = 7.6 Hz), 97.5 (d, J = 52.6 Hz), 79.3 (d, J = 299.8 Hz), 53.6 (d, J = 5.4 Hz).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = –3.2.

HRMS: m/z [M^+] calcd for $C_{11}H_{10}F_3O_3P$: 278.0320; found: 278.0318.

Dimethyl {[3-(Trifluoromethyl)phenyl]ethynyl}phosphonate (3l)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **3l** as a yellow oil; yield: 164.7 mg (0.592 mmol, 43%); R_f = 0.11 (1:1 EtOAc/hexanes).

IR (neat): 3477 (s), 2958 (w), 2855 (w), 2192 (m), 1332 (s), 1280 (s), 1219 (s), 1171 (s), 1037 (s), 908 (m), 755 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.72–7.67 (m, 2 H), 7.57–7.53 (m, 2 H), 3.83 (d, J = 12.4 Hz, 6 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 135.1 (d, J = 2.7 Hz), 132.8 (d, J = 31.5 Hz), 131.8, 130.6, 127.1, 126.2 (q, J = 4.9), 123.0 (d, J = 271.5 Hz), 94.9 (d, J = 52.1 Hz), 82.3 (d, J = 295.8 Hz), 53.6 (d, J = 5.6 Hz).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ = –3.5.

HRMS: m/z [M + H^+] calcd for $C_{11}H_{10}F_3O_3P$: 279.0398; found: 279.0399.

Dimethyl {[2-(Trifluoromethyl)phenyl]ethynyl}phosphonate (3m)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **3m** as a yellow oil; yield: 130.1 mg (0.466 mmol, 65%); R_f = 0.24 (1:1 EtOAc/hexanes).

IR (neat): 3485 (s), 2958 (w), 2856 (w), 2194 (m), 1320 (s), 1271 (s), 1178 (s), 1132 (s), 1035 (s), 869 (m), 785 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.79 (s, 1 H), 7.70 (dd, J = 15.9, 7.8 Hz, 2 H), 7.50 (t, J = 7.9 Hz, 1 H), 3.83 (d, J = 12.3 Hz, 6 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 135.7, 131.4 (q, J = 33.2 Hz), 129.5 (sext, J = 2.8 Hz), 129.3, 127.4 (q, J = 3.5 Hz), 123.3 (d, J = 272.67 Hz), 120.4 (d, J = 5.8 Hz), 97.5 (d, J = 52.7 Hz), 78.6 (d, J = 299.6 Hz), 53.6 (d, J = 5.4 Hz).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = –3.2.

HRMS: m/z [M + H^+] calcd for $C_{11}H_{10}F_3O_3P$: 279.0398; found: 279.0399.

Dimethyl [(3-Chlorophenyl)ethynyl]phosphonate (3n)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **3n** as a yellow oil; yield: 86.9 mg (0.355 mmol, 44%); R_f = 0.22 (1:1 EtOAc/hexanes).

IR (neat): 3493 (s), 3063 (w), 2999 (w), 2955 (w), 2852 (w), 2194 (m), 1276 (s), 1035 (s), 902 (s), 841 (s), 788 cm^{-1} (s).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.53–7.52 (m, 1 H), 7.44–7.40 (m, 2 H), 7.29 (t, J = 7.9 Hz, 1 H), 3.83 (d, J = 12.2 Hz, 6 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 134.5, 132.4 (d, *J* = 2.6 Hz), 131.2, 130.8 (d, *J* = 2.5 Hz), 129.9, 121.0 (d, *J* = 5.6 Hz), 97.8 (d, *J* = 52.8 Hz), 78.1 (d, *J* = 300.3), 53.5 (d, *J* = 5.7 Hz).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = –2.9.

HRMS: *m*/*z* [M + H^+] calcd for $C_{10}H_{10}ClO_3P$: 245.0134; found: 245.0135.

Dimethyl [(2-Chlorophenyl)ethynyl]phosphonate (3o)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **3o** as an orange oil: yield: 7.4 mg (0.030 mmol, 35%); R_f = 0.18 (1:1 EtOAc/hexanes).

IR (neat): 3454 (s), 3056 (w), 2955 (w), 2853 (w), 2193 (m), 1267 (s), 1038 (s), 869 (m), 737 cm^{-1} (s).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.58 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.43 (dd, *J* = 4.1, 1.0 Hz, 1 H), 7.38 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.27 (td, *J* = 7.6, 1.4 Hz, 1 H), 3.87 (d, *J* = 12.4 Hz, 6 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 137.1, 134.4 (d, *J* = 2.3 Hz), 131.8, 129.6, 126.7, 119.7 (d, *J* = 5.1 Hz), 96.1 (d, *J* = 52.7 Hz), 81.7 (d, *J* = 298.3 Hz), 53.6 (d, *J* = 5.5 Hz).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = –2.9.

HRMS: *m*/*z* [M^+] calcd for $C_{10}H_{10}ClO_3P$: 244.0056; found: 244.0048.

Dimethyl [(2-Methoxyphenyl)ethynyl]phosphonate (3q)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **3q** as a clear oil; yield: 100.9 mg (0.419 mmol, 56%); R_f = 0.14 (1:1 EtOAc/hexanes).

IR (neat): 3490 (s), 3004 (w), 2954 (w), 2851 (w), 2181 (w), 1289 (m), 1038 (s), 840 (m), 802 cm^{-1} (s).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.24 (t, *J* = 8.0 Hz, 1 H), 7.12 (d, *J* = 7.6 Hz, 1 H), 7.03 (t, *J* = 2.0 Hz, 1 H), 6.96 (qd, *J* = 8.4, 2.4, 0.9 Hz, 1 H), 3.83–3.76 (m, 9 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 159.3, 129.6, 125.2 (d, *J* = 2.4 Hz), 120.2, (d, *J* = 5.6 Hz), 117.7, 117.2 (d, *J* = 2.2), 99.9 (d, *J* = 53.4 Hz), 76.6 (d, *J* = 302.6 Hz), 55.4, 53.5 (d, *J* = 5.4 Hz).

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = –2.3.

HRMS: *m*/*z* [M + H^+] calcd for $C_{11}H_{13}O_4P$: 241.0630; found: 241.0633.

Cationic Ru-Catalyzed Cycloaddition; General Procedure

The alkynyl phosphonate (reaction scale 0.10–0.18 mmol) and 1,5-cyclooctadiene (1.1–1.3 equiv) were weighed into oven-dried screw cap vials, purged with argon and imported into a glovebox. Within the glovebox the alkynyl phosphonate, 1,5-cyclooctadiene, ruthenium catalyst (0.04–0.06 equiv), and anhydrous solvent (2 mL) were combined and mixed in a two-dram screw cap vial equipped with a small stir bar. The vials were then sealed and exported out of the glove box and allowed to react for 72 h at 70 °C. Products were purified using flash column chromatography on 230–400 mesh silica gel with hexanes/EtOAc mixture as the mobile phase.

Diethyl (8-Butyltricyclo[4.2.2.$0^{2,5}$]dec-7-en-7-yl)phosphonate (4a) (Table 2, entry 2)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **4a** as a yellow-brown oil; yield: 41.8 mg (0.128 mmol, 93%); R_f = 0.46 (1:1 EtOAc/hexanes).

IR (neat): 3472 (s), 2950 (m), 2927 (m), 2871 (w), 1725 (w), 1243 (m), 1094 (s), 1052 (s), 950 (s), 785 (m), 565 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 4.06–3.93 (m, 4 H), 2.75 (dd, *J* = 11.9, 3.4 Hz, 1 H), 2.62–2.57 (m, 2 H), 2.44 (br s, 1 H), 2.17–2.08 (m, 4 H), 2.02–1.85 (m, 4 H), 1.42–1.33 (m, 4 H), 1.28 (td, *J* = 7.0, 1.8 Hz, 6 H), 1.14–1.10 (m, 2 H), 0.89 (t, *J* = 7.0 Hz, 3 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 165.2 (d, *J* = 10.2 Hz), 125.2 (d, *J* = 184.3 Hz), 60.9 (d, *J* = 5.0 Hz), 39.4 (d, *J* = 14.2 Hz), 35.6 (d, *J* = 9.7 Hz), 35.2 (d, *J* = 2.9 Hz), 34.0 (d, *J* = 3.2 Hz), 33.4 (d, *J* = 5.4 Hz), 30.6 (d, *J* = 2.5 Hz), 22.9, 20.4 (d, *J* = 3.1 Hz), 19.8 (d, *J* = 3.1 Hz), 18.2, 17.63, 16.4, 14.0.

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 19.0.

HRMS: *m*/*z* [M^+] calcd for $C_{18}H_{31}O_3P$: 326.2011; found: 326.2012.

Dimethyl (8-Butyltricyclo[4.2.2.$0^{2,5}$]dec-7-en-7-yl)phosphonate (4b) (Table 2, entry 1)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **4b** as a yellow oil; yield: 58.5 mg (0.196 mmol, 97%); R_f = 0.17 (1:1 EtOAc/hexanes).

IR (neat): 3475 (s), 2951 (s), 2929 (s), 2872 (m), 2855 (m), 1609 (w), 1458 (w), 1248 (s), 1053 (s), 1029 (s), 821 (m), 780 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.60 (dd, *J* = 11.1, 4.7 Hz, 6 H), 2.70–2.66 (m, 1 H), 2.57–2.53 (m, 2 H), 2.43–2.41 (m, 1 H), 2.13–2.04 (m, 4 H), 1.98–1.79 (m, 4 H), 1.40–1.26 (m, 4 H), 1.11–1.07 (m, 2 H), 0.85 (t, *J* = 7.1 Hz, 3 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 166.6 (d, *J* = 10.6 Hz), 123.9 (d, *J* = 184.8 Hz), 51.7 (dd, *J* = 5.1, 1.4 Hz), 39.4 (d, *J* = 14.4 Hz), 35.6 (d, *J* = 9.7 Hz), 35.1 (d, *J* = 2.9 Hz), 33.9 (d, *J* = 3.0 Hz), 33.4 (d, *J* = 5.5 Hz), 30.6 (d, *J* = 2.9 Hz), 22.8, 20.3 (d, *J* = 3.2 Hz), 19.8 (d, *J* = 3.0 Hz), 18.2 (d, *J* = 1.1 Hz), 17.5, 13.9.

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 21.8.

HRMS: *m*/*z* [M + H^+] calcd for $C_{16}H_{27}O_3P$: 299.1776; found: 299.1770.

Diphenyl (8-Butyltricyclo[4.2.2.$0^{2,5}$]dec-7-en-7-yl)phosphonate (4c) (Table 2, entry 3)

The crude product was purified by column chromatography (1:3 EtOAc/hexanes) to provide the alkyne **4c** as a yellow oil; yield: 32.8 mg (0.078 mmol, 86%); R_f = 0.51 (1:3 EtOAc/hexanes).

IR (neat): 2953 (m), 2929 (m), 2871 (w), 1593 (m), 1490 (s), 1262 (m), 1216 (m), 1193 (s), 921 (s), 770 (m), 732 (m), 690 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.27 (t, *J* = 7.8 Hz, 4 H), 7.20–7.16 (m, 4 H), 7.11 (t, *J* = 7.3 Hz, 2 H), 2.96 (d, *J* = 12.2 Hz, 1 H), 2.73–2.68 (m, 2 H), 2.48 (br s, 1 H), 2.13–2.04 (m, 4 H), 2.01–1.85 (m, 4 H), 1.37–1.23 (m, 4 H), 1.05 (d, *J* = 8.8 Hz, 2 H), 0.85 (t, *J* = 7.0 Hz, 3 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 168.9 (d, *J* = 11.2 Hz), 150.7 (d, *J* = 7.2 Hz), 129.5, 124.6, 124.0 (d, *J* = 186.1 Hz), 120.5 (d, *J* = 4.7 Hz), 39.8 (d, *J* = 15.2 Hz), 35.9 (d, *J* = 9.5 Hz), 35.0 (d, *J* = 3.0 Hz), 33.9 (d, *J* = 3.1 Hz), 33.6 (d, *J* = 5.4 Hz), 30.4 (d, *J* = 2.3 Hz), 22.9, 20.2 (d, *J* = 3.5 Hz), 19.7 (d, *J* = 3.0 Hz), 18.2, 17.6, 14.0.

$^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ = 9.0.

HRMS: *m*/*z* [M^+] calcd for $C_{26}H_{31}O_3P$: 422.2011; found: 422.2008.

Dimethyl (8-Cyclohexyltricyclo[4.2.2.$0^{2,5}$]dec-7-en-7-yl)phosphonate (4d) (Table 3, entry 2)

The crude product was purified by column chromatography (EtOAc) to provide the alkyne **4d** as a yellow oil; yield: 36.2 mg (0.112 mmol, 80%); R_f = 0.14 (EtOAc).

IR (neat): 3484 (s), 2928 (s), 2851 (m), 1600 (w), 1449 (m), 1246 (s), 1071 (s), 1028 (s), 820 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.64 (dd, *J* = 11.12, 3.4 Hz, 6 H), 3.34–3.27 (m, 1 H), 2.78–2.72 (m, 1 H), 2.69–2.67 (m, 1 H), 2.15–2.02 (m, 4 H), 2.01–1.81 (m, 4 H), 1.70–1.64 (m, 3 H), 1.57–1.45 (m, 2 H), 1.37–1.24 (m, 4 H), 1.15–1.08 (m, 2 H), 1.06–0.99 (m, 1 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 170.3 (d, *J* = 10.8 Hz), 122.7 (d, *J* = 182.7 Hz), 83.0, 51.7 (d, *J* = 5.1 Hz), 41.8 (d, *J* = 5.4 Hz), 35.6 (d, *J* = 9.8 Hz), 35.0 (d, *J* = 14.4 Hz), 34.8 (d, *J* = 2.9 Hz), 34.2 (d, *J* = 3.0 Hz), 30.8 (d, *J* = 2.0 Hz), 30.5 (d, *J* = 1.9 Hz), 26.1, 25.9 (d, *J* = 5.2 Hz), 20.2, 20.1 (d, *J* = 3.4 Hz), 18.1, 17.5.

^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz): δ = 22.2.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{18}H_{29}O_3P$: 325.1932; found: 325.1934.

Dimethyl (8-Phenyltricyclo[4.2.2.0^{2,5}]dec-7-en-7-yl)phosphonate (4f) (Table 3, entry 4)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **4f** as a yellow oil; yield: 2.3 mg (0.070 mmol, 46%); R_f = 0.14 (1:1 EtOAc/hexanes).

IR (neat): 3462 (s), 2947 (m), 2848 (w), 1236 (m), 1020 (s), 819 (s), 781 (s), 768 (s), 698 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.31–7.25 (m, 5 H), 3.42 (dd, *J* = 11.1, 1.1 Hz, 6 H), 3.02–2.98 (m, 1 H), 2.76–2.75 (m, 1 H), 2.39–3.33 (m, 2 H), 2.21–2.18 (m, 2 H), 2.07–1.91 (m, 4 H), 1.39–1.27 (m, 2 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 161.2 (d, *J* = 7.2 Hz), 140.4 (d, *J* = 6.7 Hz), 127.8, 127.7, 127.6 (d, *J* = 186.1 Hz), 127.6 (d, *J* = 1.6 Hz), 51.8 (d, *J* = 6.5 Hz), 42.7 (d, *J* = 13.1 Hz), 36.5 (d, *J* = 9.4 Hz), 34.7 (d, *J* = 3.0 Hz), 34.2 (d, *J* = 3.0 Hz), 19.9, 19.9, 18.1, 17.6.

^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz): δ = 20.0.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{18}H_{23}O_3P$: 319.1463; found: 319.1465.

Dimethyl {8-[(Benzyloxy)methyl]tricyclo[4.2.2.0^{2,5}]dec-7-en-7-yl}phosphonate (4g) (Table 3, entry 5)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **4g** as a yellow oil; yield: 24.5 mg (0.068 mmol, 66%); R_f = 0.17 (1:1 EtOAc/hexanes).

IR (neat): 3462 (s), 2948 (m), 2872 (w), 2849 (w), 1454 (s), 1244 (s), 1047 (s), 1017 (m), 819 (m), 780 (m), 736 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.31–7.24 (m, 5 H), 4.59–4.51 (m, 2 H), 4.49 (s, 2 H), 3.65 (dd, *J* = 11.1, 6.1 Hz, 6 H), 2.87 (br s, 1 H), 2.77 (d, *J* = 11.7 Hz, 1 H), 2.18–2.12 (m, 4 H), 2.04–1.87 (m, 4 H), 1.23–1.12 (m, 2 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 161.6 (d, *J* = 9.3 Hz), 138.5, 128.3, 128.2 (d, *J* = 183.5 Hz), 127.6, 127.5, 72.4, 68.4 (d, *J* = 5.4), 52.0 (d, *J* = 3.7 Hz), 36.5 (d, *J* = 13.4 Hz), 35.9 (d, *J* = 8.7 Hz), 34.8 (d, *J* = 2.7 Hz), 33.9 (d, *J* = 3.1 Hz), 20.2 (d, *J* = 3.3 Hz), 19.6 (d, *J* = 2.9 Hz), 18.0, 17.5.

^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz): δ = 20.0.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{20}H_{27}O_4P$: 363.1725; found: 363.1716.

Dimethyl {8-[2-(Benzyloxy)ethyl]tricyclo[4.2.2.0^{2,5}]dec-7-en-7-yl}phosphonate (4h) (Table 3, entry 6)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **4h** as a yellow oil; yield: 30.6 mg (0.0813 mmol, 68%); R_f = 0.17 (1:1 EtOAc/hexanes).

IR (neat): 3408 (s), 2947 (m), 2851 (w), 1496 (m), 1242 (m), 1020 (s), 818 (m), 729 (s), 697 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.23 (m, 5 H), 4.48 (s, 2 H), 3.61–3.58 (m, 8 H), 3.03–2.91 (m, 2 H), 2.71 (d, *J* = 11.8 Hz, 1 H), 2.52 (br s, 1 H), 2.12–2.07 (m, 4 H), 2.01–1.83 (m, 4 H), 1.18–1.08 (m, 2 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 163.3 (d, *J* = 9.6 Hz), 138.5, 128.3, 127.6, 127.4, 126.4 (d, *J* = 183.4 Hz), 72.7, 69.0 (d, *J* = 2.7 Hz), 51.8 (d, *J* = 5.1 Hz), 39.7 (d, *J* = 14.1 Hz), 35.7 (d, *J* = 9.3 Hz), 34.9 (d, *J* = 2.9 Hz), 33.7 (d, *J* = 5.5 Hz), 33.6 (d, *J* = 3.0 Hz), 20.2 (d, *J* = 2.9 Hz), 19.5 (d, *J* = 3.2 Hz), 18.1, 17.5.

^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz): δ = 21.3.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{21}H_{29}O_4P$: 377.1881; found: 377.1883.

Dimethyl {8-[4-(Trifluoromethyl)phenyl]tricyclo[4.2.2.0^{2,5}]dec-7-en-7-yl}phosphonate (4k) (Table 4, entry 2)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **4k** as a yellow oil; yield: 38.4 mg (0.099 mmol, 79%); R_f = 0.19 (1:1 EtOAc/hexanes).

IR (neat): 3455 (s), 2952 (m), 2852 (w), 1326 (s), 1251 (s), 1166 (s), 1124 (s), 1065 (s), 1031 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.55 (d, *J* = 8.1 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 3.47 (dd, *J* = 11.1, 2.4 Hz, 6 H), 3.04–2.99 (m, 1 H), 2.73–2.70 (m, 1 H), 2.38–2.33 (m, 2 H), 2.24–2.18 (m, 2 H), 2.10–1.92 (m, 4 H), 1.38–1.31 (m, 2 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 159.9 (d, *J* = 6.9 Hz), 143.9 (d, *J* = 6.8 Hz), 129.8, 128.5, 127.9 (d, *J* = 1.6 Hz), 124.6 (q, *J* = 3.7 Hz), 124.1 (d, *J* = 272.1 Hz), 51.9, 42.7 (d, *J* = 12.8 Hz), 36.5 (d, *J* = 9.0 Hz), 34.5 (d, *J* = 3.0 Hz), 34.1 (d, *J* = 3.0 Hz), 19.9 (d, *J* = 3.2 Hz), 19.8 (d, *J* = 3.5 Hz), 17.9, 17.5.

^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz): δ = 19.3.

HRMS: *m*/z [M + H$^+$] calcd for $C_{19}H_{22}F_3O_3P$: 387.1336; found: 387.1342.

Dimethyl {8-[3-(Trifluoromethyl)phenyl]tricyclo[4.2.2.0^{2,5}]dec-7-en-7-yl}phosphonate (4l) (Table 4, entry 3)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **4l** as a yellow oil; yield: 40.4 mg (0.105 mmol, 79%); R_f = 0.14 (1:1 EtOAc/hexanes).

IR (neat): 3454 (s), 2952 (s), 2875 (w), 2851 (w), 1321 (s), 1249 (s), 1165 (s), 1072 (s), 1030 (s), 824 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.48 (m, 3 H), 7.43–7.39 (m, 1 H), 3.46 (dd, *J* = 11.1, 1.5 Hz, 6 H), 3.05–3.01 (m, 1 H), 2.74–2.72 (m, 1 H), 2.41–2.30 (m, 2 H), 2.27–2.17 (m, 2 H), 2.11–1.91 (m, 4 H), 1.38–1.32 (m, 2 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 159.6 (d, *J* = 6.6 Hz), 141.0 (d, *J* = 6.8 Hz), 131.1, 130.2, 128.6, 128.1, 124.4, 124.4, 124.1 (d, *J* = 272.4 Hz), 51.9 (d, *J* = 10.4 Hz), 42.6 (d, *J* = 12.6 Hz), 36.5 (d, *J* = 9.3 Hz), 34.6 (d, *J* = 3.0 Hz), 34.2 (d, *J* = 3.0 Hz), 19.9 (d, *J* = 3.2 Hz), 19.8 (d, *J* = 3.4 Hz), 18.0, 17.5.

^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz): δ = 19.4.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{19}H_{22}F_3O_3P$: 387.1336; found: 387.1349.

Dimethyl [8-(3-Chlorophenyl)tricyclo[4.2.2.0^{2,5}]dec-7-en-7-yl]phosphonate (4n) (Table 4, entry 5)

The crude product was purified by column chromatography (1:1 EtOAc/hexanes) to provide the alkyne **4n** as a yellow oil; yield: 28.3 mg (0.080 mmol, 74%); R_f = 0.08 (1:1 EtOAc/hexanes).

IR (neat): 3442 (s), 2950 (s), 1249 (w), 1071 (s), 1053 (s), 1029 (s), 824 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.28–7.19 (m, 4 H), 3.48 (d, *J* = 11.1 Hz, 6 H), 3.04–3.00 (m, 1 H), 2.73–2.72 (m, 1 H), 2.37–2.32 (m, 2 H), 2.23–2.19 (m, 2 H), 2.08–1.91 (m, 4 H), 1.35–1.31 (m, 2 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 159.7 (d, *J* = 6.7 Hz), 142.1 (d, *J* = 6.7 Hz), 133.5, 129.0 (d, *J* = 186.3 Hz), 128.9, 127.8, 127.5 (d, *J* = 1.8 Hz), 126.0 (d, *J* = 1.6 Hz), 51.9, 42.6 (d, *J* = 12.7 Hz), 36.5 (d, *J* = 9.3 Hz), 34.6 (d, *J* = 3.0 Hz), 34.1 (d, *J* = 3.0 Hz), 19.9 (d, *J* = 3.6 Hz), 19.8, 18.0 (d, *J* = 1.0 Hz), 17.6.

^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz): δ = 19.6.

HRMS: *m*/*z* [M$^+$] calcd for $C_{18}H_{22}ClO_3P$: 352.0995; found: 352.0990.

1-Methoxy-3,3-dimethyl-1,3,4,4a,5,6,6a,7-octahydro-4,7-ethanocyclobuta[4,5]benzo[1,2-*c*][1,2]oxaphosphole 1-Oxide (5a) (Table 3, entry 7; Scheme 3)

The crude product was purified by column chromatography (EtOAc) to provide the alkyne **5a** as a clear oil; yield: 21.4 mg (0.079 mmol, 43%); R_f = 0.34 (EtOAc).

IR (neat): 3457 (s), 2977 (m), 2951 (m), 2932 (m), 2229 (w), 1615 (w), 1267 (s), 1252 (s), 1048 (s), 959 (s), 901 (s), 795 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.71–3.64 (m, 3 H), 2.94–2.90 (m, 1 H), 2.65–2.63 (m, 1 H), 2.32–2.09 (m, 4 H), 2.06–1.97 (m, 4 H), 1.45 (t, *J* = 22.2 Hz, 6 H), 1.31–1.05 (m, 2 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 171.62 (dd, *J* = 18.9, 5.8 Hz), 126.1 (dd, *J* = 168.4, 4.7 Hz), 85.8 (dd, *J* = 7.1, 2.3 Hz), 52.9 (d, *J* = 6.5 Hz), 35.4 (d, *J* = 2.7 Hz), 35.0 (dd, *J* = 5.5, 2.7 Hz), 33.6 (dd, *J* = 12.5, 2.4 Hz), 32.1 (dd, *J* = 9.5, 1.0 Hz), 27.1 (dd, *J* = 22.3, 2.1 Hz), 26.0 (dd, *J* = 22.1, 1.7 Hz), 20.3 (dd, *J* = 3.2, 2.3 Hz), 20.2 (d, *J* = 3.6 Hz), 17.5 (dd, *J* = 4.2, 1.8 Hz), 17.1 (d, *J* = 13.4 Hz).

^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz): δ = 35.9, 35.9.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{14}H_{21}O_3P$: 269.1306; found: 269.1301.

Funding Information

This work was supported by the Natural Sciences and Engineering Council of Canada (NSERC).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690612.

References

(1) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.
(2) (a) Allen, A.; Villeneuve, K.; Cockburn, N.; Fatila, E.; Riddell, N.; Tam, W. *Eur. J. Org. Chem.* **2008**, 4178. (b) Villeneuve, K.; Riddell, N.; Tam, W. *Tetrahedron* **2006**, *62*, 3823. (c) Shibata, T.; Takami, K.; Kawachi, A. *Org. Lett.* **2006**, *8*, 1343. (d) Villeneuve, K.; Tam, W. *Organometallics* **2006**, *25*, 843. (e) Villeneuve, K.; Tam, W. *Angew. Chem. Int. Ed.* **2004**, *43*, 610. (f) Jordan, R. W.; Tam, W. *Org. Lett.* **2001**, *3*, 2367. (g) Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem. Int. Ed.* **1994**, *33*, 580. (h) Mitsudo, T.; Hori, Y.; Watanabe, Y. *J. Organomet. Chem.* **1987**, *334*, 157. (i) Schrauzer, G. N.; Glockner, P. *Chem. Ber.* **1964**, *97*, 2451.
(3) (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. (b) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429. (c) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2326.
(4) (a) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624. (b) Hilt, G.; Smolko, K. I. *Angew. Chem. Int. Ed.* **2003**, *42*, 2795. (c) Carmona, D.; Lamata, M. P.; Oro, L. A. *Coord. Chem. Rev.* **2000**, *200*, 717. (d) Murakami, M.; Ubukata, M.; Itami, K.; Ito, Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 2248. (e) O'Mahoney, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, 443. (f) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. (g) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432.
(5) (a) Tenaglia, A.; Gaillard, S. *Org. Lett.* **2007**, *9*, 3607. (b) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863. (c) Lautens, M.; Edwards, L. G.; Tam, W.; Lough, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 10276. (d) Lautens, M.; Tam, W.; Sood, C. *J. Org. Chem.* **1993**, *58*, 4513. (e) Lautens, M.; Lautens, J. C.; Smith, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 5627. (f) Lautens, M.; Crudden, C. M. *Organometallics* **1989**, *8*, 2733. (g) Lyons, J. E.; Myers, H. K.; Schneider, A. *J. Chem. Soc., Chem. Commun.* **1978**, 636.
(6) Petko, D.; Stratton, M.; Tam, W. *Can. J. Chem.* **2018**, *96*, 1115.
(7) Trost, B. M.; Imi, K.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 8831.
(8) Alvarez, P.; Gimeno, J.; Lastra, E.; García-Granda, S.; Van der Maelen, J. F.; Bassetti, M. *Organometallics* **2001**, *20*, 3762.
(9) Hasinoff, B. B.; Creighton, A. M.; Kozlowska, H.; Thampatty, P.; Allan, W. P.; Yalowich, J. C. *Mol. Pharmacol.* **1997**, *52*, 839.
(10) Leverrier, A.; Awang, K.; Guéritte, F.; Litaudon, M. *Phytochemistry* **2011**, *72*, 1443.
(11) Cockburn, N.; Karimi, E.; Tam, W. *J. Org. Chem.* **2009**, *74*, 5762.
(12) Kettles, T. J.; Cockburn, N.; Tam, W. *J. Org. Chem.* **2011**, *76*, 6951.
(13) Chrobak, E.; Bebenek, E.; Kadela-Tomanek, M.; Latocha, M.; Jelsch, C.; Wenger, E.; Boryczka, S. *Molecules* **2016**, *21*, 1123.
(14) Smith, P. W.; Chamiec, A. J.; Chung, G.; Cobley, K. N.; Duncan, K.; Howes, P. D.; Whittington, A. R.; Wood, M. R. *J. Antibiot. (Tokyo)* **1995**, *48*, 73.
(15) Holstein, S. A.; Cermak, D. M.; Wiemer, D. F.; Lewis, K.; Hohl, R. J. *Bioorg. Med. Chem.* **1998**, *6*, 687.
(16) Ouahrouch, A.; Taourirte, M.; Schols, D.; Snoeck, R.; Andrei, G.; Engels, J. W.; Lazrek, H. B. *Arch. Pharm. (Weinheim)* **2016**, *349*, 30.
(17) East, J. E.; Carter, K. M.; Kennedy, P. C.; Schulte, N. A.; Toews, M. L.; Lynch, K. R.; Macdonald, T. L. *Med. Chem. Commun.* **2011**, *2*, 325.
(18) Prakash, T. P.; Lima, W. F.; Murray, H. M.; Li, W.; Kinberger, G. A.; Chappell, E.; Gaus, H.; Seth, P. P.; Bhat, B.; Crooke, S. T.; Swayze, E. *Nucleic Acid Res.* **2015**, *43*, 2993.
(19) Chemagin, A. V.; Yashin, N. V.; Grishin, Y. K.; Kuznetsova, T. S.; Zefirova, N. S. *Synthesis* **2010**, 259.
(20) Mollat du Jourdin, X.; Noshi, M.; Fuchs, P. L. *Org. Lett.* **2009**, *11*, 543.
(21) Benmeddah, A.; Villemin, D.; Mostefa-Kara, B.; Bar, N.; Legay, R. *Can. J. Chem.* **2017**, *95*, 871.
(22) Hiney, R. M.; Higham, L. J.; Mueller-Bunz, H.; Gilheany, D. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7248.
(23) Moglie, Y.; Mascaro, E.; Gutierrez, V.; Alonso, F.; Radivoy, G. *J. Org. Chem.* **2016**, *81*, 1813.
(24) Qu, Z.; Chen, X.; Yuan, J.; Qu, L.; Li, X.; Wang, F.; Ding, X.; Zhao, Y. *Can. J. Chem.* **2012**, *90*, 747.
(25) Gao, Y.; Wang, G.; Chen, L.; Xu, P.; Zhao, Y.; Zhou, Y.; Ha, L.-B. *J. Am. Chem. Soc.* **2009**, *131*, 7956.