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The Virtue of Methylenecyclopropane Terminators in Intramolecular Pauson-Khand Reactions[1]

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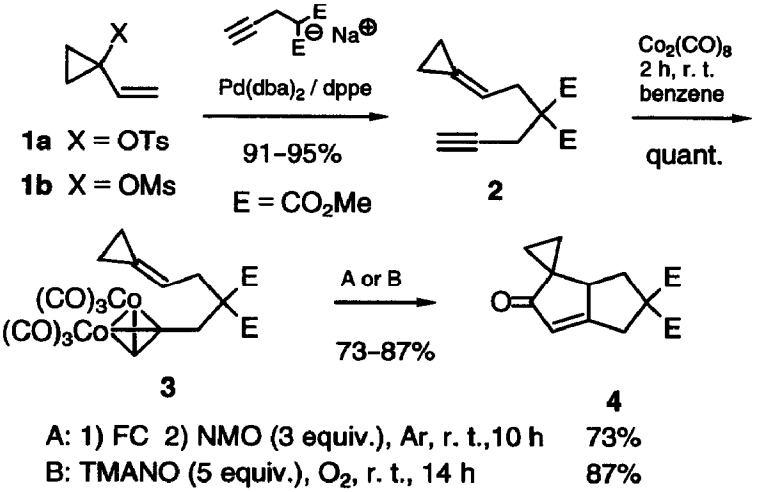
Keywords: Pauson-Khand reaction, intramolecular; methylenecyclopropanes, double bond activation in; bicyclo[3.3.0]oct-1-en-3-ones; spirocyclopropane derivatives.

Abstract: 6-Cyclopropylidene-1-hexynes like **2**, e. g. prepared via palladium(0)-catalyzed substitution of 1-ethenyl cyclopropyl sulfonates **1**, undergo an intramolecular Pauson-Khand reaction both efficiently and regioselectively.

Among the known methods for the construction of five-membered carbocyclic ring systems the Pauson-Khand reaction (PKR), i. e. the cobalt mediated cycloaddition of an alkyne to an alkene with carbonyl insertion yielding a cyclopentenone, has attracted particular interest.[2] Several new variants of this method have been put forward in attempts to achieve greater selectivity under milder conditions.[3] Since methylenecyclopropanes have successfully been employed in intermolecular Pauson-Khand reactions,[4] we envisaged to combine our recently developed Pd(0)-catalyzed alkylation of a propargyl substituted malonate with a 1-ethenylcyclopropyl derivative giving cyclopropylideneethyl derivatives,[5] with an intramolecular Pauson-Khand reaction, as this would lead to a facile construction of potential precursors to naturally occurring oligoquinane systems.

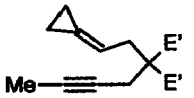
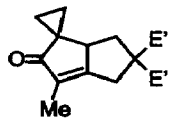
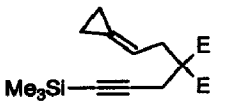
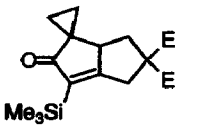
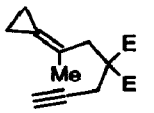
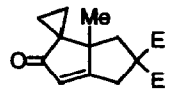
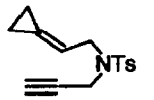
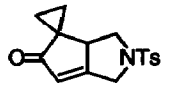
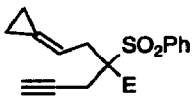
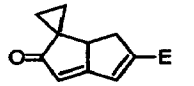
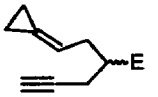
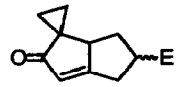
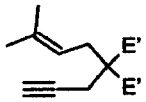
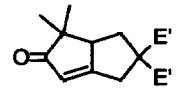
Scheme 1



The alkynecobalt complex **3** was prepared under standard conditions from (2-cyclopropylidene-ethyl)propargylmalonate **2**[5] and octacarbonyldicobalt. Treatment of **3** either with *N*-methylmorpholine *N*-oxide (NMO) under an argon atmosphere (method A) or with trimethylamine *N*-oxide (TMANO) under oxygen

(method B) gave the bicyclo[3.3.0]octenone **4**.[6] Best results were obtained by stirring the reaction mixture at room temperature in anhydrous dichloromethane for 14 h after 5 equiv. of anhydrous TMANO had been added at –78 °C to the preformed alkynecobalt complex without isolation. The spirocompound **4** was thus obtained as a colourless solid, m. p. 70–71 °C, in 87% yield after flash chromatography (FC). In contrast, the isopropylidene analogue **18** (Table 1, last entry) did not cyclize under identical conditions. This is in accord with reports about trisubstituted alkenes to give only poor yields in intramolecular PKR.[7]

Table 1. Products and Yields of Pd(0)-Catalyzed Allylic Alkylations of 1-Ethenylcyclopropyl Sulfonates and Intramolecular Pauson-Khand Reactions of 6-Cyclopropylidene-1-hexynes[6]

Cyclopropyl sulfonate	Cyclopropylidene-alkyne[a]		Yield[b] (%)	PKR Product		Method[c]	Yield[b] (%)
1a		**5**	82		**6**	B	75
1b		**7**	55		**8**	A	35[d]
 **9**		**10**	81		**11**	A	64
1a		**12**	85		**13**	B	80
1a		**14**	92		**15**	B	15
1a		**16**	59[e]		**17**	B	73[f]
–		**18**	–		**19**	A	0

[a] E = CO_2CH_3, E' = CO_2Et. – [b] Yield of isolated products after flash chromatography. – [c] See text. – [d] Yield of isolated alkyne cobalt complex of **7** 61%, yield of PKR 57%. – [e] Yield corresponds to substitution reaction followed by dealkoxycarbonylation. – [f] *endo*/exo** = 1:1.7 (according to ^1H NMR).

The reaction sequence was applied to a variety of differently substituted 6-cyclopropylidene-1-hexynes to give the corresponding spiro{cyclopropane-1,4'-bicyclo[3.3.0]oct-1-en-3-ones} in good to very good yields except for one case (see Table 1). The cyclopropylidenealkynes **5**, **7**, **10**, **12** and **14** were prepared by reacting each of the corresponding 1-ethenylcyclopropyl sulfonates **1a,b** or **9** with the appropriate nucleophile (sodiopropargylmalonate, sodiopropargylsulfonylacetate or sodiopropargyltosylamide, 1-3 equiv.) under $Pd(dba)_2$/

dppe catalysis (2 mol%) at room temperature (5 min to 14 h).[5] Compound **2** was converted to the monoester **16** by dealkoxycarbonylation (1.5 equiv. NaCN, DMSO, 120 °C, 4h)[8] in 62 % yield.

It is noteworthy that even enyne **10** with a tetrasubstituted double bond gave the bicyclooctenone with an angular methyl substituent in 64 % yield.[9] The methylenecyclopropane end group as a trisubstituted olefin also facilitates the cycloaddition to a terminally substituted triple bond as in **5** and **7**. No PKR type cyclization had been observed for the corresponding isopropylidene compound.[7] In addition, disubstitution at C-4 of the enynes, which usually is believed to enhance the yields in the Pauson-Khand reaction due to the Thorpe-Ingold effect, is not necessary. The monosubstituted enynes **12** and **16** are cyclized in high yield, albeit with poor diastereoselection[10] for the latter case. Unfortunately the sulfonyl substitution at C-4 was not tolerated under these reaction conditions, compound **14** thus gave only the elimination product **15** in low yield.

Typical procedure

Diethyl 2'-Methyl-3'-oxospiro[cyclopropane-1,4'-bicyclo[3.3.0]oct-1'-en]-7,7-dicarboxylate (**6**): Diethyl (2'-cyclopropylideneethyl)-(but-2"-yn-1"-yl)malonate (**5**) (60 mg, 0.21 mmol) and octacarbonyldicobalt (81 mg, 0.23 mmol) in dichloromethane (2 ml) were kept in the dark until no starting material was detectable by thin layer chromatography. The reaction mixture was cooled to –78 °C, and dry trimethylamine N-oxide (TMANO) (94.5 mg, 1.46 mmol) was added. The mixture was then stirred at room temperature for 14 h while kept under an oxygen atmosphere with a balloon. The reaction mixture was filtered through a layer (1 cm) of silica gel, the silica gel was washed with dichloromethane (80 ml), and the crude product was purified by flash chromatography to give 48 mg (75 %) of **6** as a colourless solid, m. p. 78–79 °C.

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6. All new compounds (except **15**) were fully characterized by spectroscopic techniques (^{1}H NMR, ^{13}C NMR, IR, MS) and their molecular formulas established by elemental analysis and/or HRMS. Physical data for relevant compounds: **5**: IR (neat) 3050, 2990, 1740 (C=O), 1440, 1280, 1200, 990, 825 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90–1.10 (bs, 4 H), 1.32 (t, 6 H), 1.76 (t, 3 H), 2.52 (q, 2 H), 2.94, (d, 2 H), 4.18 (q, 4 H), 5.50–5.68 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 1.85, 2.91, 3.48, 14.05, 22.92, 34.56, 57.27, 61.36, 76.15, 78.44, 111.61, 126.79, 170.33. – **6**: M. p. 78–79 °C; IR (neat) 2990, 1730 (C=O),

1690 (C=O), 1670 (C=O), 1260, 1240, 1180, 1070, 1050, 960, 750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.80–1.09 (m, 3 H), 1.18–1.44 (m, 7 H), 1.65 (t, 1 H), 1.85 (s, 3 H), 2.49 (dd, 1 H), 3.04 (dd, 1 H), 3.18 (d, 1 H), 3.31 (d, 1 H,), 4.18 (q, 2 H), 4.25 (q, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 8.96, 13.70, 14.00, 14.29, 32.68 , 34.18, 36.95, 49.13, 60.99, 61.92, 62.03 , 132.99, 170.95, 171.64, 175.63, 208.55. – **7**: IR (neat) 2985, 2190, 1740 (C=O), 1440, 1290, 1250, 1210, 1040, 850, 760 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.14 (s, 9 H), 0.98–1.12 (m, 4 H), 2.80 (s, 2 H,), 2.95 (d, 2 H), 3.68 (s, 6 H), 5.50–5.60 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ –0.10, 1.90, 2.98, 23.96, 34.67, 52.62, 57.36, 87.91, 101.60, 111.33, 127.38, 170.39. – **8**: M. p. 77–78 °C; IR (neat) 2960, 1730 (C=O), 1685 (C=O), 1610, 1280, 1260, 1240, 1160, 1070, 860, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.23 (s, 9 H), 0.84–0.98 (m, 3 H), 1.20–1.43 (m, 1 H), 1.64 (t, 1 H), 2.50 (dd, 1 H), 3.11 (dd, 1 H), 3.30 (d, 1 H), 3.41 (d, 1 H), 3.71 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 0.98, 13.11, 14.11, 33.31, 36.51, 36.70, 52.52, 53.00, 53.15, 60.87, 136.84, 171.40, 172.00, 189.81, 211.57. – **10**: IR (neat) 3295 (C≡C), 2970, 2940, 2900, 2830, 1725 (C=O), 1430, 1200, 910, 730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95–1.10 (m, 4 H), 1.72 (m, 3 H), 2.00 (t, 1 H), 2.58 (d, 2 H), 2.99 (s, 2 H), 3.75 (s, 6 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 2.67, 3.91, 21.36, 22.87, 38.92, 52.61, 56.94, 71.17, 76.62, 117.58, 122.41, 170.79. – **11**: M. p. 72 °C; IR (neat) 2980, 1740 (C=O), 1700 (C=O), 1640, 1440, 1420, 1270, 1260, 1110, 1070, 860 cm^{-1}; ^1H NMR δ 0.80–0.93 (m, 1 H), 0.95–1.06 (m, 5 H), 1.20–1.35 (m, 1 H), 2.07 (d, 1 H), 2.30 (d, 1 H), 3.28 (d, 1 H), 3.55 (d, 1 H), 3.71 (s, 3 H), 3.78 (s, 3 H), 5.97 (d, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.66, 15.85, 24.38, 34.87, 40.78, 42.66, 52.01, 53.18, 53.87, 60.14, 124.44, 171.63, 172.12, 186.67, 208.52. – **12**: M. p. 86–88 °C; IR (neat) 3290 (C≡C), 3058, 2980, 2929, 2860, 1500, 1245, 1160, 1090, 652 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.00–1.18 (m, 4 H), 1.97 (t, 1 H), 2.44 (s, 3 H), 3.98 (d, 2 H), 4.09 (d, 2 H), 5.65–5.74 (m, 1 H), 7.30 (d, 2 H), 7.86 (d, 2 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 1.94, 2.61, 21.54, 35.63, 47.76, 73.26, 76.80, 111.83, 127.73, 128.66, 129.41, 136.50, 143.35. – **13**: IR (neat) 3050, 2870, 1710 (C=O), 1650, 1300, 1265, 1165, 1115, 990, 730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88–1.05 (m, 3 H), 1.28–1.42 (m, 1 H), 2.42 (s, 3 H), 2.56 (dd, 1 H), 3.21 (dddd, 1 H), 3.78 (t, 1 H), 4.05 (d, 1 H), 4.40 (ddd, 1 H), 6.08–6.12 (m, 1 H), 7.33 (d, 2 H), 7.82 (d, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.78, 14.89, 21.57, 31.47, 48.17, 50.01, 50.72, 126.54 , 127.42, 130.02, 133.51, 144.19, 176.65, 207.15. – **14**: IR (neat) 3300, 3040, 2960, 2910, 1730 (C=O), 1675, 1440, 1260, 995, 840, 730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 1.05–1.10 (m, 4 H), 2.00 (t, 1 H), 2.96 (d, 2 H), 3.04–3.24 (m, 2 H), 3.64 (s, 3 H), 5.72–5.83 (m, 1 H), 7.52–7.60 (m, 2 H), 7.64–7.73 (m, 1 H), 7.82–7.89 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 2.93, 3.10, 21.30, 33.06, 53.01, 71.75, 78.09, 110.59, 128.43, 128 80, 130.29, 134.29, 137.19, 167.29. – **15**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.86–1.10 (m, 2 H), 1.12–1.34 (m, 1 H), 1.37–1.51 (m, 1 H), 2.38 (ddd, 1 H), 2.75 (ddd, 1 H), 3.52–3.62 (m, 1 H), 3.83 (s, 3 H), 6.18 (d, 1 H), 7.38 (bs, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.24, 17.89, 33.59, 34.21, 52.11, 53.05, 124.00, 134.69, 148.50, 164.57, 182.82, 211.03. – **16**: IR (neat) 3300, 2980, 2960, 1740 (C=O), 1440, 1200, 1168 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95–1.10 (m, 4 H), 2.00 (t, 1 H), 2.38–2.65 (m, 4 H), 2.68–2.80 (m, 1 H), 3.70 (s, 3 H), 5.63–5.75 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 1.93, 2.60, 20.63, 33.24, 44.30, 51.79, 66.77, 81.53, 113.87, 124.89, 174.47. – **17** (endo): M. p. 68–70 °C; IR (neat) 2980, 2930, 1730 (C=O), 1710 (C=O), 1270, 1200, 1180, 1130, 735 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80–1.05 (m, 3 H), 1.25–1.38 (m, 1 H), 1.47 (ddd, 1 H), 2.20 (dd, 1 H), 2.93 (dd, 1 H), 3.02–3.18 (m, 2 H), 3.25 (ddd,, 1 H), 3.70 (s, 3 H), 6.01–6.05 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.65, 14.32, 30.76, 31.98, 33.35, 43.46, 50.45, 52.28, 125.08, 175.85, 186.00, 207.56. – **17** (exo): IR (neat) 3000, 1740 (C=O), 1710 (C=O), 1635, 1440, 1270, 1240, 1220, 1200, 1130, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90–1.05 (m, 3 H), 1.30–1.45 (m, 2 H), 2.10–2.23 (m, 1 H), 2.90–3.13 (m, 3 H), 3.23–3.40 (m, 1 H), 3.23 (s, 3 H), 6.05 (s, 1 H).

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