Pergamon

Tetrahedron 56 (2000) 2305–2311

TETRAHEDRON

Studies on Chromium(0)-Mediated Three Component Cycloaddition Reactions

James H. Rigby,* Charles R. Heap and Namal C. Warshakoon

Department of Chemistry, Wayne State University, Detroit, MI, 48202-3489, USA

Accepted 7 December 1999

Abstract—A novel chromium(0)-promoted three-component alkyne–triene higher-order cycloaddition process is presented. The transformation features tethered alkynes participating in a tandem [6π+2π], [6π+2π] cycloaddition event with cyclic trienes serving as the third reactant. Isomerically homogeneous products possessing five rings and six stereogenic centers are isolated from this reaction in good to excellent yield. © 2000 Elsevier Science Ltd. All rights reserved.

Metal mediation of the cycloaddition process has resulted in numerous advances in which ring constructions not normally accessible via conventional metal-free conditions have become almost routine.[1] So-called higher-order cycloaddition reactions[2] have been principal beneficiaries of metal intervention. These somewhat obscure pericyclic processes are potentially quite valuable for the rapid preparation of a range of medium-sized ring systems, and significant recent progress in this arena includes: Ni(0)-promoted [4π+4π] cycloadditions,[3] Mn-based [5+4] additions,[4] Rh(I)-mediated [5+2] combinations,[5] as well as numerous cobalt-mediated higher-order cycloaddition processes (Fig 1).[6]

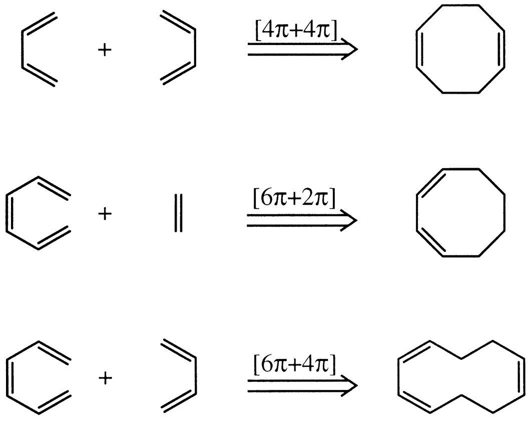
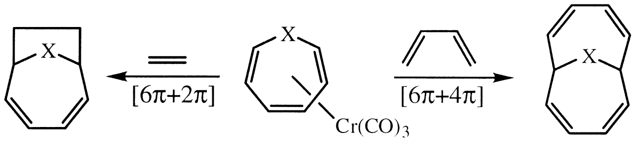


Figure 1. Typical higher-order cycloaddition reactions.

Chromium(0)-promoted [6π+4π] and [6π+2π] cycloadditions have also received considerable attention in recent years,[7] and these processes when applied to *cyclic* 6π partners nicely illustrate many of the advantages that accrue from metal mediation of the cycloaddition event (Scheme 1). While allowed thermally, the corresponding metal-free [6+4] cycloaddition process is frequently ineffective at delivering higher-order adducts due, primarily, to periselectivity issues, which are often known to limit the synthetic utility of higher-order cycloaddition reactions.[8] In stark contrast, Cr(0)-mediated versions of these transformations afford bicyclo[4.4.1]undecane adducts in excellent yields with accompanying high levels of stereocontrol.[7] The corresponding [6+2] reactions have also been rendered more synthetically useful through metal-participation in the ring forming event.[9,10]

An intriguing and potentially significant extension of this concept of metal-mediated ring assembly has been realized with the recent discovery of a novel and efficient three-component, one-pot cycloaddition process. This new reaction pathway is characterized by the Cr(0)-mediated combination of two equivalents of an alkyne with a cyclic triene to afford the unusual tetracyclo[8.1.0.0.^{3,7}0^{4,11}]undeca-5,8-diene ring system.[11,12] While of considerable mechanistic interest, the remarkably rapid increase in molecular complexity is the most striking feature of this process from a synthetic perspective. Fully five carbon–carbon bonds, three new rings, and six stereogenic centers are

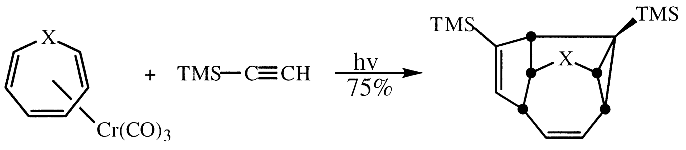


Scheme 1.

Keywords: chromium and compounds; cycloadditions; cycloheptatrienes; diynes.

* Corresponding author. Fax: +1-313-577-1377; e-mail: jhr@chem.wayne.edu

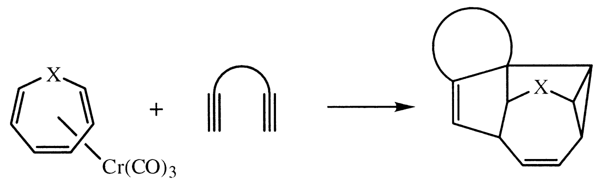
PII: S0040-4020(99)01113-8



Scheme 2.

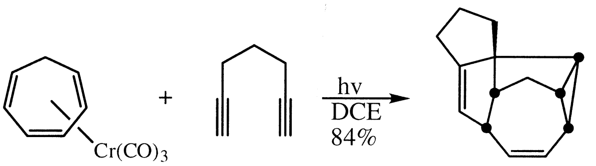
efficiently created in one operation (Scheme 2). Furthermore, the products emerging from this process are generated as *single* regio- and stereoisomers in every case examined to date.

A potentially quite powerful variant of this transformation can be envisaged in which the two alkyne reaction partners are tethered to each other by spacers of various lengths and compositions. If successful, this version of the three-component reaction would be capable of delivering up to four new rings and six stereocenters in a one-pot operation. This notion has now been brought to practice and the reaction appears to be quite general in nature (Scheme 3).



Scheme 3.

A typical example of this transformation is illustrated by the photocycloaddition between (η^6-cycloheptatriene)tricarbonylchromium(0) and the commercially available diyne, 1,6-heptadiyne, that affords the novel pentacyclic adduct **1** in 84% yield (Eq. (1)).[13] The reaction can be conducted on gram scales by immersion well irradiation (Pyrex filter) of the Cr(0)-triene complex in dichloroethane (DCE) with slow addition of the diyne to the reaction mixture at 0°C.

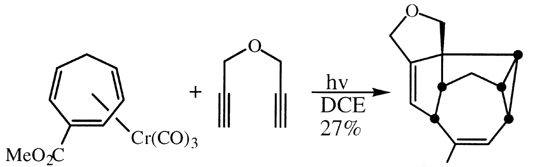


(1)

1

The versatility and generality of this tandem [6π+2π], [6π+2π] process for the assembly of polycyclic systems can be seen in the examples compiled in Table 1. A range of spacer lengths between the alkynes can be accommodated as can a variety of non-carbon and non-hydrogen substituents at various locations in the reaction partners. In addition, heterocyclic trienes are useful participants as evidenced by Entries 7–9. The stereochemical homogeneity of the adducts is a consequence of initial bond formation on the metal-bearing face of the triene and is enforced by the spatial constraints imposed on the subsequent cyclizations by the first-formed bicyclo[4.2.1]nonatriene system. The apparent facility of these ensuing events is also a likely consequence of the relative rigidity of this bicyclic array.

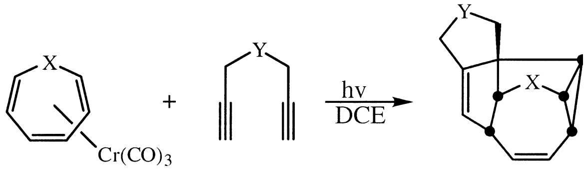
Regioselectivity is an issue of particular importance for cycloadditions of this intricacy when unsymmetrically substituted diynes or triene complexes are employed. Several examples of this type of reaction have been explored to address these questions, and in each case examined only a *single* regioisomer was obtained. These results are noteworthy in that regiocontrol has often been found to be sporadic in a number of the other Cr(0)-mediated higher-order cycloadditions studied in our laboratory.[14] Several examples are depicted in the following equations. Only the so-called '*syn*' regioisomer[16] was obtained in cycloadditions in which an electron deficient substituent (CO_2R) was positioned at C3 in the triene partner (Eqs. (2) and (3)).



2 **3**

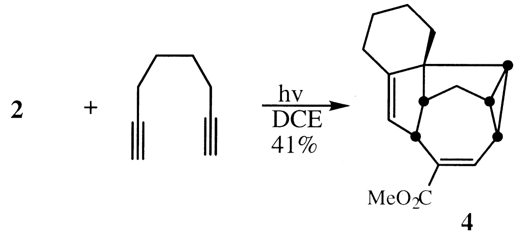
(2)

Table 1. The tandem [6π+2π], [6π+2π] cycloadduct addition reaction



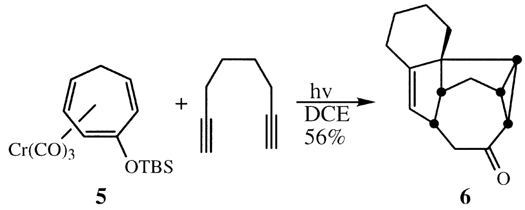
Entry	X	Y	Run time (h)	Yield (%)[a]
1	CH_2	$(CH_2)_2$[b]	1.5	76
2	CH_2	$(CH_2)_3$[b]	2	69
3	CH_2	O[b]	1.5	47
4	CH_2	$C(CO_2Et)_2$[c]	1.5	77
5	CH_2	$C(CH_3)_2$[d]	1	36
6	CH_2	$C(Ph)CO_2Et$[e]	1.5	53
7	$N(CO_2Et)$[f]	CH_2	0.5	40
8	SO_2[g]	CH_2	2	57
9	SO_2[g]	$(CH_2)_2$	2	32

[a] Yields are for isolated, purified products.
[b] Commercially available.
[c] Prepared by bis-alkylation of diethyl malonate with propargyl bromide.
[d] Prepared from ethyl 2-methyl-propionate and propargyl bromide.
[e] Prepared by bis-alkylation of methyl phenylacetate.
[f] Ref. 14.
[g] Ref. 15.

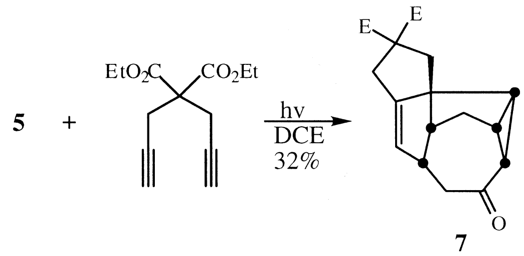


(3)

Interestingly, only the corresponding '*anti*' adducts[16] are obtained when related cycloadditions are performed with trienes that are substituted with an electron donor (OTBS) at C3 (Eqs. (4) and (5)).[17] The regiocomplementarity of these processes is strongly suggestive that an electronic effect is dictating the course of reaction, and that this influence is manifested in the first alkyne–triene [6π+2π] cycloaddition step that initiates the overall transformation.[18] No comparable regiocontrol has been observed previously in Cr(0)-mediated [6π+2π] reactions in which the 2π components are alkenes.[19]

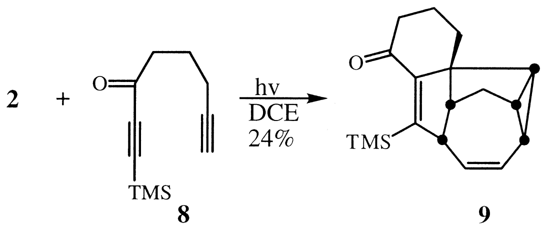


(4)



(5)

When differentially substituted diynes are added to a cyclic triene partner, two isomeric adducts are capable of being formed depending upon which alkyne adds to the triene partner first. We have briefly examined this issue, however only a few cycloadditions involving unsymmetrically substituted diynes have been successfully executed at this point in time. In each case only one adduct was obtained, albeit in modest yields. A typical example is shown in Eq. (6). In this instance, it seems clear that the more sterically accessible, terminal alkyne would undergo initial reaction, and that the modest yield obtained for the overall event can be attributed to the relative reluctance of non-terminal alkynes to participate in the second '*homo*' [6π+2π] cycloaddition. This latter observation is consistent with previous results from our laboratory in which only relatively simple and modestly hindered internal alkynes underwent clean cycloaddition.[20]



(6)

The mechanistic details of these reactions remain obscure at this point, and with little data currently available to support the presence of one pathway over another it is difficult to make substantive comments in this regard. However, it is tempting to rationalize these transformations by invoking a tandem Cr(0)-promoted [6π+2π] cycloaddition between the alkyne and triene followed by a second homo-[6π+2π] process on the Cr(0) complex of the adduct resulting from the first event. In support of this notion, it is well known from our previous work in this area that cycloadduct–metal complexes are usually the first isolable products emerging from these reactions,[14] and it is not all that unreasonable to find that these complexes can themselves undergo further metal-mediated transformations under appropriate circumstances.

In summary, the reaction of tethered alkynes with cyclic trienes under Cr(0)-mediated photocycloaddition conditions affords a range of structurally elaborate and stereochemically rich products with good efficiencies. Studies on a number of synthetically productive post-cycloaddition manipulations of these adducts is currently underway in our laboratory and will be reported in due time.

Experimental[21]

General cycloaddition procedure

The cycloaddition reactions were run in a photochemical reactor vessel utilizing a medium-pressure mercury light source and a water-cooled, Pyrex filter. In some cases, it was beneficial to immerse the entire apparatus in an ice bath to slow chromium decomplexation—these examples are indicated as employing external cooling. The photochemical reactor was charged with 0.9 mmol of triene–(tricarbonyl)chromium(0) complex and 175 mL of dichloroethane (DCE). The system was purged of oxygen by bubbling argon through the solvent for 30 min. While continuing the argon purge, the light source was turned on and slow addition of the diyne (1.5 equiv., dissolved in 3–5 mL of dichloroethane) was initiated. Slow addition of the diyne over 1–4 h resulted in complete reaction of the chromium complex as indicated by the reaction changing from a clear red to an opaque green color. The reaction mixture was concentrated to dryness and filtered through a pad of Celite with ethyl acetate to remove the chromium(III) species. Purification of the resultant oil by flash column chromatography gave the desired [6+2+2] cycloadducts.

Pentacyclo[6.6.0.0.^{2,6}0.^{2,12}0^{11,13}]tetradeca-6,9-diene (1). 1.0 g (4.4 mmol) of (η^6-cycloheptatriene) tricarbonyl chromium(0) and 300 mL of DCE were added to the photochemical reaction and the apparatus was immersed in a bucket of ice water. Slow addition of 1,6-heptadiyne (0.60 mL, 5.3 mmol) over 2 h provided 0.675 g (84%) of a clear, colorless oil after chromatography (hexanes): IR (CDCl$_3$) ν 3018, 2903, 2855, 1652, 1443, 1338 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.78 (dd, J=10.2, 7.2 Hz, 1H), 5.67 (dd, J=10.7, 7.1 Hz, 1H), 5.35 (s, 1H), 2.93 (br s, 1H), 2.59 (t, J=8.1 Hz, 1H), 2.27–2.31 (m, 1H), 2.20 (q, J=7.5 Hz, 1H), 2.15 (m, 1H), 1.98–2.03 (m, 2H), 1.84–1.89 (m, 1H), 1.74 (qd, J=5.2, 2.3 Hz, 1H), 1.57 (d, J=13.4 Hz, 1H), 1.51 (q, J=10.8 Hz, 1H), 1.41 (t, J=6.1 Hz, 1H), 1.34 (q, J=7.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 155.1 (C), 131.6 (CH), 124.6 (CH), 124.0 (CH), 68.4 (C), 57.1 (CH), 52.5 (CH), 36.5 (CH$_2$), 29.9 (CH), 27.9 (CH), 27.8 (CH$_2$), 26.7 (CH$_2$), 24.3 (CH$_2$), 22.2 (CH); HRMS (EI) *m/z* (M)=184.1252 (calcd for C$_{14}$H$_{16}$), *m/z* (M)=184.1257.

Pentacyclo[7.6.0.0.^{2,7}0.^{2,13}0^{2,14}]pentadeca-7,10-diene (Table 1, Entry 1). The reactor was charged with 200 mg (0.88 mmol) of (η^6-cycloheptatriene)tricarbonylchromium(0) and 175 mL DCE. Slow addition of 1,7-octadiyne (0.18 mL, 1.3 mmol) over 1.5 h resulted in 132 mg (76%) of a clear, colorless oil after chromatography (hexanes): IR (CDCl$_3$) ν 3019, 2932, 2830, 1645, 1432, 1326, 1247, 1010 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.75 (dd, J=10.9, 6.6 Hz, 1H), 5.71 (dd, J=10.9, 7.3 Hz, 1H), 5.23 (t, J=2.5 Hz, 1H), 2.64 (br t, J=6.8 Hz, 1H), 2.43 (dt, J=14.3, 2.0 Hz, 1H), 2.35 (t, J=8.5 Hz, 1H), 1.98–2.09 (m, 3H), 1.82 (do, J=12.7, 2.0 Hz, 1H), 1.75 (do, J=13.4, 1.8 Hz, 1H), 1.56–1.60 (m, 3H), 1.53 (qt, J=13.4, 3.3 Hz, 1H), 1.24–1.29 (m, 2H), 1.19 (qt, J=13.2, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.3 (C), 131.3 (CH), 125.2 (CH), 58.3 (C), 56.4 (CH), 46.2 (CH), 38.6 (CH$_2$), 28.7 (CH$_2$), 27.7 (CH), 26.9 (CH$_2$), 25.5 (CH$_2$), 25.1 (CH), 24.0 (CH$_2$), 21.9 (CH); HRMS (EI) *m/z* (M)=198.1409 (calcd for C$_{15}$H$_{18}$), *m/z* (M)=198.1413.

Pentacyclo[8.6.0.0.^{2,8}0.^{2,14}0^{13,15}]hexadeca-8,11-diene (Table 1, Entry 2). The reactor was charged with 200 mg (0.88 mmol) of (η^6-cycloheptatriene)tricarbonylchromium(0) and 175 mL DCE. Slow addition of 1,8-nonadiyne (0.14 mL, 1.3 mmol) over 2.0 h provided 128 mg (69%) of a clear, colorless oil after chromatography (hexanes); IR (CDCl$_3$) ν 3016, 2938, 2857, 1647, 1443 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.89 (ddd, J=10.9, 6.8, 0.6 Hz, 1H), 5.78 (dd, J=10.8, 7.1 Hz, 1H), 5.43 (d, J=2.6 Hz, 1H), 2.74 (td, J=8.9, 2.8 Hz, 1H), 2.53–2.60 (m, 2H), 1.94–2.10 (m, 5H), 1.71–1.78 (m, 2H), 1.86 (d, J=13.4 Hz, 2H), 1.31–1.43 (m, 4H), 1.24 (qt, J=12.4, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 150.0 (C), 132.5 (CH), 130.6 (CH), 125.7 (CH), 63.3 (C), 52.2 (CH), 47.0 (CH), 38.6 (CH$_2$), 33.4 (CH$_2$), 33.3 (CH$_2$), 33.0 (CH), 31.1 (CH$_2$), 26.7 (CH$_2$), 26.7 (CH), 25.2 (CH$_2$), 23.3 (CH); HRMS (EI) *m/z* (M)=212.1565 (calcd for C$_{16}$H$_{20}$), *m/z* (M)=212.1567.

Oxapentacyclo[6.6.0.0.^{2,6}0.^{2,12}0^{11,13}]tetradeca-6,9-diene (Table 1, Entry 3). (200 mg, 0.88 mmol) (η^6-cycloheptatriene)tricarbonylchromium(0) complex and 200 mL of DCE were added to the photochemical reactor. Slow addition of propargyl ether (0.14 mL, 1.3 mmol) over 1.5 h provided 77 mg (47%) of a clear, colorless oil after chromatography: IR (CDCl$_3$) ν 3022, 2960, 2923, 2859, 1645, 1443, 1346, 1072, 1013 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.87 (ddt, J=11.0, 6.4, 1.0 Hz, 1H), 5.67 (dd, J=11.0, 7.2 Hz, 1H), 5.50 (s, 1H), 4.27 (ABq, J_{AB}=12.9 Hz, $\Delta\nu$=55.5 Hz, 2H), 3.74 (ABq, J_{AB}=7.9 Hz, $\Delta\nu$=227 Hz, 2H), 3.07 (qd, J=6.6, 3.0 Hz, 1H), 2.73 (t, 8.2 Hz, 1H), 1.93 (ddd, J=13.7, 8.9, 4.9 Hz, 1H), 1.78 (dt, J=8.6, 5.3 Hz, 1H), 1.66 (ddd, J=7.6, 5.8, 1.5 Hz, 1H), 1.56 (d, J=13.4 Hz, 1H), 1.39 (q, J=7.8 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 150.0 (C), 130.6 (CH), 125.2 (CH), 125.0 (CH), 77.4 (CH$_2$), 70.0 (C) 64.8 (CH$_2$), 54.1 (CH), 53.8 (CH), 28.5 (CH), 28.2 (CH$_2$), 26.6 (CH), 21.8 (CH); HRMS (EI) *m/z* (M)=186.1045 (calcd for C$_{13}$H$_{14}$O$_1$), *m/z* (M)=186.1043.

Ethyl 4-(ethoxycarbonyl)-pentacyclo[6.6.0.0.^{2,6}0.^{2,12}0^{12,13}]-tetradeca-6,9-diene-4-carboxylate (Table 1, Entry 4). The reactor was charged with (η^6-cycloheptatriene)tricarbonylchromium(0) (200 mg, 0.88 mmol) and 175 mL of dichloroethane. Slow addition of 307 mg (1.30 mmol) of 3-(dicarboethoxy)-1,6-heptadiyne over 1.5 h yielded 221 mg (77%) of a clear, colorless oil after chromatography (1:1 CH$_2$Cl$_2$/hexanes): IR (CDCl$_3$) ν 3308, 3019, 2969, 2916, 2853, 1731, 1716, 1367, 1264, 1058.4 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.69 (dd, J=10.9, 6.6 Hz, 1H), 5.60 (dd, J=10.9, 7.2 Hz, 1H), 5.39 (t, J=2.5 Hz, 1H), 4.13–4.24 (m, 4H), 2.98 (d, J=2.8 Hz, 1H), 2.83–2.86 (m, 2H), 2.67 (t, J=8.2 Hz, 1H), 2.38 (s, 2H), 1.97 (ddd, J=13.4, 8.6, 4.8 Hz, 2H), 1.77 (dt, J=8.4, 5.3 Hz, 1H), 1.52 (d, J=13.4 Hz, 1H), 1.41 (ddd, J=7.6, 6.1, 1.4 Hz, 1H), 1.20–1.27 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$)(δ 173.4 (C), 173.2 (C), 150.3 (C), 132.2 (CH), 127.4 (CH), 125.9 (CH), 72.8 (C), 68.3 (C), 62.7 (CH$_2$), 62.6 (CH$_2$), 59.6 (CH), 52.6 (CH), 44.8 (CH$_2$), 35.6 (CH$_2$), 31.1 (CH), 29.7 (CH), 27.7 (CH$_2$), 23.3 (CH), 15.2 (CH$_3$), 15.1 (CH$_3$); HRMS (EI) *m/z* (M)=328.1675 (calcd for C$_{20}$H$_{24}$O$_4$), *m/z* (M)= 328.1678.

4,4-Dimethylpentacyclo[6.6.0.0.^{2,6}0.^{2,12}0^{11,13}]tetradeca-6,9-diene (Table 1, Entry 5). The photochemical reactor was charged with 150 mg (0.66 mmol) of (η^6-cycloheptatriene)tricarbonylchromium(0) and 175 mL of dichloroethane. Slow addition of 4,4-dimethylhepta-1,6-diyne (110 mg, 0.92 mmol) over 1 h gave, after the usual workup, 50.4 mg (36%) of a clear, colorless oil after chromatography (hexanes): IR (CDCl$_3$) ν 3019, 2953, 2926, 2854, 1434, 1364.0 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.61 (dd, J=10.9, 7.3 Hz, 1H), 5.51 (d, J=11.4 Hz, 1H), 5.37 (s, 1H), 2.81 (td, J=8.0, 3.2 Hz, 1H), 2.56 (t, J=8.4 Hz, 1H), 2.16 (m, 1H), 2.06 (ABq, $\Delta\nu$=90.7 Hz, J_{AB}=13.8 Hz, 2H), 1.75 (dt, J=8.1, 5.5 Hz, 1H), 1.58 (ABq ($\Delta\nu$=75.8 Hz, J_{AB}=13.4 Hz, 2H), 1.52 (m, 1H), 1.40 (dd, J=7.1, 6.3 Hz, 1H), 1.27 (q, J=7.7 Hz, 1H), 1.18 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.8 (C), 131.7 (CH), 125.2 (CH), 124.5 (CH), 59.6 (CH), 51.4 (CH$_2$), 50.5 (CH), 46.2 (C), 42.5 (CH$_2$), 41.8 (C), 32.0 (CH), 31.3 (CH$_3$), 30.6 (CH$_3$), 28.5 (CH$_2$), 22.4 (CH); HRMS (EI) *m/z* (M)=212.1565 (calcd for C$_{16}$H$_{20}$), *m/z* (M)=212.1565.

Methyl-4-phenylpentacyclo[6.6.0.0.^{2,6}0.^{2,12}0^{11,13}]tetradeca-6,9-diene-4-carboxylate (Table 1, Entry 6). The photochemical reactor was charged with 250 mg (1.09 mmol) (η^6-3-(carbomethoxy)-cycloheptatriene) tricarbonylchromium(0) complex and 200 mL dichloroethane.

Slow addition of ethyl 2-phenyl-2-prop-2-ynylpent-4-ynoate (280 mg, 1.31 mmol) over 1.5 h followed by the usual workup gave the cycloadduct (185 mg (53%)) as an inseparable mixture of diastereomers at the carbon 4 position after chromatography (1:1 CH_2Cl_2/hexanes): ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.42 (m, 5H), 5.62–5.75 (m, 2H), 5.54 (s, 0.5H), 5.38 (s, 0.5H), 3.58 (s, 1.5H), 3.59 (s, 1.5H), 3.62 (A of ABq, 0.5 H), 3.27 (ABq, 2H), 3.08 (B of ABq, 0.5H), 2.80 (br, 1H), 2.70 (dd, 0.5H), 2.65 (t, 0.5 H), 1.98–2.13 (m, 2H), 1.81 (m, 1H), 1.56 (m, 1H), 1.25–1.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0 (C), 175.8 (C), 150.4 (C), 149.8 (C), 145.3 (C), 141.9 (C), 131.3 (CH), 131.1 (CH), 128.5 (CH), 128.3 (CH), 128.3 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH), 126.6 (CH), 126.3 (CH), 125.4 (CH), 124.8 (CH), 127.8 (CH), 124.7 (CH), 67.7 (C), 65.0 (C), 61.9 (C), 60.3 (C), 58.5 (CH), 52.6 (CH_3), 52.4 (CH_3), 51.8 (CH), 49.7 (CH), 47.3 (CH_2), 45.9 (CH_2), 37.5 (CH_2), 36.2 (CH_2), 32.3 (CH), 29.0 (CH), 29.0 (CH), 28.5 (CH), 26.7 (CH_2), 26.5 (CH_2), 22.4 (CH), 22.2 (CH); HRMS (EI) *m/z* (M)=318.1620 (calcd for $C_{22}H_{22}O_2$), *m/z* (M)=318.1620.

Ethyl-14-azapentacyclo[6.6.0.0.^{2,6}0.^{2,12}0^{11,13}]tetradeca-6,9-diene-14-carboxylate (Table 1, Entry 7). The photochemical reactor was charged with 250 mg (0.83 mmol) of (η6-(*N*-carboethoxy)-azepin) tricarbonylchromium(0) 0.14 mL (1.25 mmol) of 1,6-heptadiyne, and 300 mL of dichloroethane. Irradiation for 30 min gave 85 mg (40%) of a clear oil after chromatography (1:19, Et_2O/CH_2Cl_2) (*note:* some doubling of peaks due to the presence of rotamers, occurred in the ^1H and ^{13}C, NMR spectra): IR ($CDCl_3$) ν 3028, 2953, 2982, 1985, 1906, 1697, 1674, 1425, 1311, 1122, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65–5.70 (m, 2H), 5.35–5.37 (m, 1H), 4.54 (d, *J*=7.3 Hz, 0.5H), 4.41 (d, *J*=7.3 Hz, 0.5 H), 4.09–4.21 (m, 2H), 3.94 (dd, *J*=6.7, 5.8 Hz, 0.5H), 3.84 (dd, *J*=6.1, 5.8 Hz, 0.5H), 3.41 (br, 0.5H), 3.27 (br, 0.5H), 1.88–2.38 (m, 5H), 1.60–1.68 (m, 3H), 1.24–1.32 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2 (C), 132.8 (CH), 132.0 (CH), 125.2 (CH), 124.3 (CH), 75.0 (CH), 74.7 (CH), 66.6 (C), 61.7 (CH_2), 53.6 (CH), 52.9 (CH), 47.6 (CH), 47.6 (CH), 46.6 (CH), 36.9 (CH), 36.9 (CH_2), 36.8 (CH_2), 28.2 (CH), 28.0 (CH), 24.9 (CH), 24.6 (CH), 24.5 (CH_2), 15.5 (CH_3), 15.4 (CH_3); HRMS (EI) *m/z* (M)=257.1416 (calcd for $C_{16}H_{19}O_2N$), *m/z* (M)=257.1413.

14-Thiapentacyclo[6.6.0.0.^{2,6}0.^{2,12}0^{11,13}]tetradeca-6,9-diene-14,14-dione (Table 1, Entry 8). The photochemical reactor was charged with 240 mg (0.86 mmol) of (η^6-thiepin-1,1-dioxide) tricarbonyl chromium(0) and 200 mL of dichloroethane. Slow addition of 0.30 mL (2.59 mmol) of 1,6-heptadiyne over 2 h produced 115 mg (57%) of a clear, colorless oil after chromatography (1:9 Et_2O/CH_2Cl_2): IR ($CDCl_3$) ν 3038, 2939, 2860, 1448, 1405, 1302, 1256, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (ddd, *J*=11.4, 6.9, 1.2 Hz, 1H), 5.88 (dd, *J*=11.1, 7.1 Hz, 1H), 5.46 (m, 1H), 3.76 (dd, *J*=7.5, 1.4 Hz, 1H), 3.57 (td, *J*=7.0, 3.0 Hz, 1H), 3.22 (ddd, *J*=8.9, 6.9, 1.8 Hz, 1H), 1.80–2.20 (m, 7H), 1.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2 (C), 135.2 (CH), 124.8 (CH), 123.8 (CH), 76.0 (CH), 64.0 (C), 51.7 (CH), 46.4 (CH), 36.6 (CH_2), 30.2 (CH), 28.3 (CH_2), 24.6 (CH_2), 22.3 (CH); HRMS (EI) *m/z* (M)=234.0174 (calcd for $C_{13}H_{14}O_2S$), *m/z* (M)=234.0712.

15-Thiapentacyclo[7.6.0.0.^{2,7}0.^{2,13}0^{12,14}]tetradeca-7,10-diene-15,15-dione (Table 1, Entry 9). The photochemical reactor was charged with 240 mg (0.86 mmol) of (η^6-thiepin-1,1-dioxide) tricarbonyl chromium(0) and 175 mL of dichloroethane. Slow addition of 0.17 mL (1.3 mmol) of 1,6-octadiyne over 2 h produced 68.1 mg (32%) of a clear, colorless oil after chromatography (3:1:3 hexanes/Et_2O/CH_2Cl_2); IR ($CDCl_3$) ν 3038, 2939, 2861, 1448, 1405, 1302, 1256, 1127 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (dd, *J*=10.9, 6.8 Hz, 1H), 5.75 (dd, *J*=11.1, 7.6 Hz, 1H), 5.37 (br s, 1H), 3.60 (d, *J*=7.6, 1H), 3.27 (q, *J*=7.6 Hz, 1H), 3.12 (t, *J*=7.1 Hz, 1H), 2.60 (br d, *J*=9.6 Hz, 1H), 2.44 (br d, *J*=14.4 Hz, 1 H), 2.27 (t, *J*=7.6 Hz, 1H), 2.06 (t, *J*=14.7 Hz, 1H), 1.99 (q, *J*=8.4 Hz, 1H), 1.84 (m, 1H), 1.47–1.59 (m, 3H), 1.21–1.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0 (C), 125.0 (CH), 123.0 (CH), 122.1 (CH), 76.1 (CH), 54.1 (C), 44.1 (CH), 43.8 (CH), 37.2 (CH_2), 27.6 (CH_2), 26.8 (CH), 125.7 (CH_2), 22.5 (CH_2), 120.8 (CH); HRMS (EI) *m/z* (M)=248.0871 (calcd for $C_{14}H_{16}O_2S$), *m/z* (M)=248.0870.

Methyl 4-oxapentacyclo[6.6.0.0.^{2,6}0.^{2,12}0^{11,13}]tetradeca-6,9-diene-9-carboxylate (3). The photo-chemical reactor was charged with 280 mg (0.98 mmol) of η$^{(}$(3-(carbomethoxy)-cycloheptatriene tricarbonyl chromium(0) and 175 mL of DCE. Slow addition of propargyl ether (0.15 mL, 1.5 mmol) over 2.5 h yielded 66 mg (27%) of a clear, colorless oil after chromatography (6:1:6 hexanes/Et_2O/CH_2Cl_2): IR ($CDCl_3$) ν 3007, 2953, 1705, 1415, 1362, 1223, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J*=7.3 Hz, 1H), 5.51 (br s, 1H), 4.27 (ABq, J_{AB}=12.9 Hz, $\Delta\nu$=45.0 Hz, 2H), 3.95 (d, *J*=8.4 Hz, 1H), 3.74 (s, 1H), 3.73 (s, 3H), 3.53 (d, *J*=7.9 Hz, 1H), 2.84 (t, *J*=8.1 Hz, 1H), 1.92–2.04 (m, 3H), 1.53–1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3 (C), 150.3 (C), 140.8 (CH), 134.1 (C), 125.8 (CH), 70.2 (C), 69.3 (CH_2), 65.4 (CH_2), 53.8 (CH), 53.4 (CH), 52.5 (CH_3), 32.8 (CH), 32.5 (CH), 27.4 (CH_2), 23.6(CH); HRMS (EI) *m/z* (M)=244.1099 (calcd for $C_{15}H_{16}O_3$), *m/z* (M)=244.1096.

Methyl-pentacyclo[7.6.0.0.^{2,7}0.^{2,13}0^{2,14}]pentadeca-7,10-diene-10-carboxylate (4). The photochemical reactor was charged with 150 mg (0.52 mmol) of η^6-3-(carbomethoxy)-cycloheptatriene tricarbonyl chromium(0) and 175 mL of dichloroethane. Slow addition of 1,7-octadiyne (0.15 mL, 1.10 mmol) over 1.5 h gave 55 mg (41%) of a clear, colorless oil after chromatography (1:1 CH_2Cl_2/hexanes): IR ($CDCl_3$) ν 3035, 2937, 2858, 1700, 1635, 1436, 1244 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, *J*=7.9 Hz, 1H), 5.25 (br s, 1H), 3.71 (s, 3H), 3.33 (d, *J*=7.6 Hz, 1H), 2.40–2.47 (m, 2H), 1.99–2.07 (m, 3H), 1.86 (d, *J*=7.8 Hz, 2H), 1.84 (m, 1H), 1.79 (dd, *J*=31.2, 13.1 Hz, 1H), 1.56 (d, *J*=13.7 Hz, 1H), 1.51 (qt, *J*=13.4, 3.1 Hz, 1H), 1.42 (q, *J*=7.9 Hz, 1H), 1.29 (td, *J*=13.2, 3.6 Hz, 1H), 1.20 (qt, *J*=13.2, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8 (C), 146.1 (C), 140.5 (CH), 134.4 (C), 126.3 (CH), 59.0 (C), 55.8 (CH), 52.4 (CH_3), 46.0 (CH), 39.0 (CH_2), 32.2 (CH), 29.7 (CH), 29.2 (CH_2) 27.4 (CH_2), 26.3 (CH_2), 24.6 (CH_2), 23.2 (CH); HRMS (EI) *m/z* (M)=256.1463 (calcd for $C_{17}H_{20}O_2$), *m/z* (M)=256.1463.

Pentacyclo[7.6.0.0.^{2,7}0.^{2,13}0^{2,14}]pentadeca-7-en-11-one (6). The photochemical reactor was charged with η^6-(3-(*t*-

butyldimethylsiloxy)-cycloheptatriene) tricarbonyl chromium(0) complex (320 mg, 0.89 mmol) and 200 mL of DCE. Slow addition of 1,7-octadiyne (0.18 mL, 1.3 mmol) over 1.5 h provided 107 mg (56%) of a clear, colorless oil after chromatography (3:1 CH_2Cl_2/hexanes): IR ($CDCl_3$) ν 3036, 2927, 2858, 1663, 1447, 1260, 1133, 988, 937 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)(δ(5.05 (s, 1H), 2.54 (br s, 1H), 2.51 (d, *J*=4.3 Hz, 2H), 2.47 (t, *J*=8.4 Hz, 1H), 2.34–2.39 (m, 3H), 2.25 (ddd, *J*=12.9, 8.1, 4.6, 2H), 2.11 (d, *J*=14.1 Hz, 1H), 2.00 (d, *J*=13.2 Hz, 1H), 1.94 (dd, *J*=9.0, 5.9 Hz, 1H), 1.87 (q, *J*=6.3 Hz, 1H), 1.80–1.83 (m, 1H), 1.74 (t, *J*=8.5 Hz, 2H), 1.53 (qt, *J*=13.4, 3.1 Hz, 1H), 1.32 (td, *J*=13.4, 3.8 Hz, 1H), 1.21 (qt, *J*=13.2, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8 (C), 147.5 (C), 123.1 (CH), 59.4 (C), 53.8 (CH), 47.5 (CH_2), 41.2 (CH), 39.1 (CH_2), 35.6 (CH), 33.3 (CH), 30.5 (CH), 28.4 (CH_2), 27.3 (CH_2), 27.3 (CH_2), 24.0 (CH_2); HRMS (EI) *m/z* (M)=214.1358 (calcd for $C_{15}H_{18}O_1$), *m/z* (M)=214.1356.

Ethyl-4-(ethoxycarbonyl)-pentacyclo[6.6.0.0.^{2,6}0.^{2,12}0^{11,13}]-tetradeca-6-en-10-one-4-carboxylate (7). The photochemical reactor was charged with 270 mg (0.75 mmol) of η^6-3-(*t*-butyldimethylsiloxy)-cycloheptatriene tricarbonyl chromium(0) complex and 175 mL of dichloroethane. Slow addition of 3,3-(dicarboethoxy)-1,6-heptadiyne (230 mg, 0.98 mmol) over 1.5 h gave 81 mg (32%) of a clear, colorless oil after chromatography (6:1:6 hexanes/Et_2O:CH_2Cl_2): IR ($CDCl_3$) ν 2985, 2938, 1725, 1667, 1256, 1062 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (br s, 1H), 4.16–4.23 (m, 5H), 2.93 (d, *J*=5.3 Hz, 1H), 2.86 (dd, *J*=7.9, 3.9 Hz, 1H), 2.76 (t, *J*=8.2, 1H), 2.57 (dd, *J*=15.1, 4.3 Hz, 1H), 2.53 (d, *J*=13.9 Hz, 1H), 2.48 (dd, *J*=15.1, 3.1 Hz, 1H), 2.26 (ddd, *J*=13.4, 7.8, 4.6 Hz, 1H), 2.20 (ABq, J_{AB}=14.1 Hz, $\Delta\nu$=104 Hz, 2H), 2.02 (q, *J*=5.8 Hz, 1H), 1.78–1.85 (m, 2H), 1.26 (t, *J*=7.1 Hz, 3H), 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6 (C), 173.2 (C), 173.0 (C), 151.5 (C), 123.3 (CH), 68.5 (C), 63.8 (CH_2) 62.9 (CH_2), 62.8 (CH_2), 55.8 (CH), 48.0 (CH), 47.8 (CH), 44.8 (CH_2), 36.7 (CH), 34.9 (CH_2), 34.6 (CH), 33.0 (CH), 29.0 (CH_2), 15.2 (CH_3), 15.2 (CH_3); HRMS (EI) *m/z* (M)=344.1624 (calcd for $C_{20}H_{24}O_5$), *m/z* (M)=344.1624.

8-(1,1-Dimethyl-1-silaethyl)pentacyclo[7.6.0.0.^{2,7}0.^{2,13}0^{2,14}]-pentadeca-7,10-dien-6-one (9). The photochemical reactor was charged with 200 mg (0.88 mmol) (η^6-cycloheptatriene) tricarbonyl chromium(0) and 170 mL of dichloroethane. Slow addition of 203 mg (1.06 mmol) of 2,2-dimethyl-2-siladeca-3,9-diyne-5-one over 4 h gave 52.1 mg (24%) of a white film after chromatography (1:3 CH_2Cl_2/hexanes): IR ($CDCl_3$) ν 3024, 2933, 2856, 1670, 1572, 1246, 1166, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56–5.64 (m, 2H), 2.99 (dd, *J*=8.4, 6.6 Hz, 1H), 2.60 (t, *J*=8.6 Hz, 1H), 2.50–2.56 (m, 1H), 2.19–2.26 (m, 1H), 2.09–2.13 (m, 1H), 1.98–2.08 (m, 3H), 1.59–1.68 (m, 3H), 1.54 (ddd, *J*=7.6, 6.0, 1.6 Hz, 1H), 1.31 (q, *J*=7.8, 1H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0 (C), 160.0 (C), 151.3 (C), 128.6 (CH), 127.6 (CH), 64.2 (C), 58.2 (CH), 53.2 (CH), 42.0 (CH_2), 36.9 (CH_2), 29.8 (CH), 26.8 (CH), 26.5 (CH), 23.0 (CH), −0.2 (CH_3); HRMS (EI) *m/z* (M)=284.1596 (calcd for $C_{18}H_{24}O_1$), *m/z* (M)=284.1595.

Acknowledgements

The authors wish to thank the National Institute of Health (GM-30771) for their generous support of this research.

References

1. For an excellent overview of metal-mediated cycloaddition, see: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

2. For reviews of higher-order cycloaddition reactions, see: (a) Rigby, J. H. *Org. Reactions* **1997**, *49*, 331. (b) Rigby, J. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., Pergamon: Oxford, 1991; Vol. 5, pp 617–643. (c) Wender, P. A.; Siggel, L.; Nuss, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 645–673.

3. (a) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (b) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (c) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904.

4. (a) Kreiter, C. G.; Lehr, K.; Leyendecker, M.; Sheldrick, W. S.; Exner, R. *Chem. Ber.* **1991**, *124*, 3. (b) Kreiter, C. G.; Lehr, K. *J. Organomet. Chem.* **1991**, *406*, 159.

5. (a) Wender, P. A.; Husfield, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940. (b) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720.

6. (a) Lautens, M.; Tam, W.; Sood, C. *J. Org. Chem.* **1993**, *58*, 4513. (b) Lautens, M.; Tam, W.; Edwards, L. G. *J. Org. Chem.* **1992**, *57*, 8. (c) Lautens, M.; Edwards, L. G. *J. Org. Chem.* **1991**, *56*, 3761. (d) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863.

7. (a) Rigby, J. H. *Tetrahedron* **1999**, *55*, 4521. (b) Rigby, J. H. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed., JAI Press, 1995; Vol. 4, pp 89–127. (c) Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579.

8. (a) Houk, K. N.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4143. (b) Rigby, J. H.; Cuisiat, S. V. *J. Org. Chem.* **1993**, *58*, 6286.

9. (a) Ward, J. S.; Pettit, R. *J. Am. Chem. Soc.* **1971**, *93*, 262. (b) Mach, K.; Antropiusova, H.; Sedmera, P.; Hanus, V.; Turecek, F. *J. Chem. Soc., Chem. Commun.* **1983**, 805. (c) Rigby, J. H.; Henshilwood, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 5122. (d) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Henshilwood, J. A.; Short, K. M.; Sugathapala, P. A. *Tetrahedron* **1993**, *49*, 5495. (e) Fischler, I.; Grevels, F.-W.; Leitich, J.; Özkar, S. *Chem. Ber.* **1991**, *124*, 2857. (f) Chaffee, K.; Sheridan, J. B.; Aistars, A. *Organometallics* **1992**, *11*, 18.

10. For a useful photochemical, metal-free [6+2] cycloaddition, see: (a) Feldman, K. S.; Come, J. H.; Freyer, A. J.; Kosmider, B. J.; Smith, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 1327. (b) Feldman, K. S.; Wu, M.-J.; Rotella, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 8490.

11. Rigby, J. H.; Warshakoon, N. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6094.

12. For related multicomponent processes, see: (a) Chen, W.; Chaffee, K.; Chung, H.-J.; Sheridan, J. B. *J. Am. Chem. Soc.* **1996**, *118*, 9980; (b) Etkin, N.; Dzwiniel, T. L.; Schweibert, K. E.; Stryker, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 9702.

13. The structure of the basic pentacyclic system has been

established by single crystal X-ray analysis and will be reported in due time.

14. Rigby, J. H.; Ateeq, H. J.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382.

15. Rigby, J. H.; Ateeq, H. J.; Krueger, A. C. *Tetrahedron Lett.* **1992**, *33*, 5873.

16. The *syn* and *anti* designations in these cases refer to the relative ring positioning of the triene substituent and the ring from the diyne tether.

17. Surprisingly, the TBS group was lost during the cycloaddition event, which is unprecedented in our experience.

18. While it is possible that the other regioisomer was selectively destroyed in these examples, no evidence of substantial decomposition was noted in these reactions.

19. Rigby, J. H.; Sugathapala, P.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 8851.

20. Several simple internal alkyne reaction partners have undergone the tandem [6π+2π], [6π+2π] cycloaddition, however, a variety of products were isolated.

21 For general experimental procedures and details, see: Ref. 14.