JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

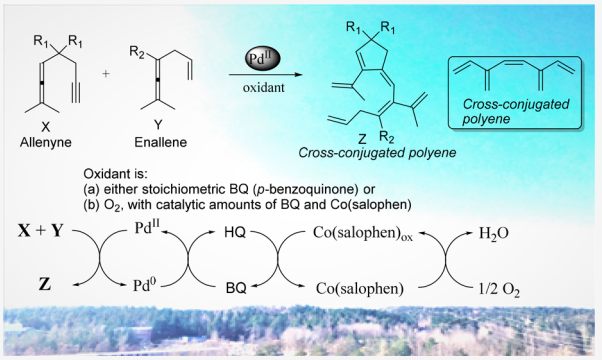
Synthesis of Cross-Conjugated Polyenes via Palladium-Catalyzed Oxidative C−C Bond Forming Cascade Reactions of Allenes

Veluru Ramesh Naidu* and Jan-E. Bäckvall*

Cite This: J. Org. Chem. 2020, 85, 5428−5437 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An efficient palladium-catalyzed oxidative C−C bond forming cascade reaction of allenes involving a coupling between an enallene and an allenyne followed by a carbocyclization of the generated Pd-intermediate was developed. This cascade reaction afforded functionalized cross-conjugated polyenes. The enallene is initially activated by palladium and reacts with the allenyne to give the cross-conjugated polyenes.

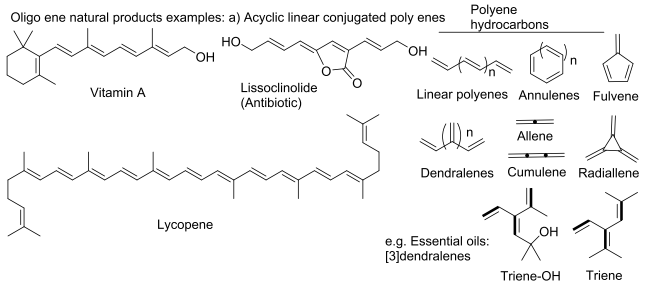


INTRODUCTION

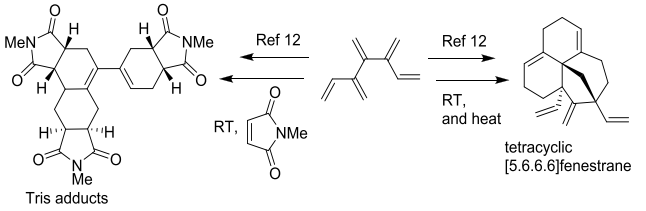
Stereo- or regiocontrolled selective construction of unsaturated molecular scaffolds through sequential multiple carbon−carbon (C−C) bond formation remains one of the major challenges in organic chemistry. In particular, in cascade reactions, transition-metal-catalyzed cyclizations of allenes provide efficient and atom-economical routes to polyunsaturated molecules.[1] Polyenes and oligoenes occur as structural elements in pharmaceutically active compounds and important natural products such as Vitamin A, Lycopene, β-carotene, Lutein, lissoclinolide, naturally occurring [3]dendralenes, etc. (Scheme 1).[2] The synthesis of such nonaromatic cross-conjugated [3]dendralenes have recently attracted considerable interest.[3,4]

In recent years, acyclic cross-conjugated polyenes (dendralenes) have been used in diene transmissive Diels−Alder (DTDA) sequences for rapid generation of complex scaffolds bearing multiple stereogenic centers (Scheme 2).[5] Due to regioselective functionalization of the multiple olefinic sites,

Scheme 1. Examples of Polyene Compounds



Scheme 2. Examples of Cross-Conjugated Polyenes Applications



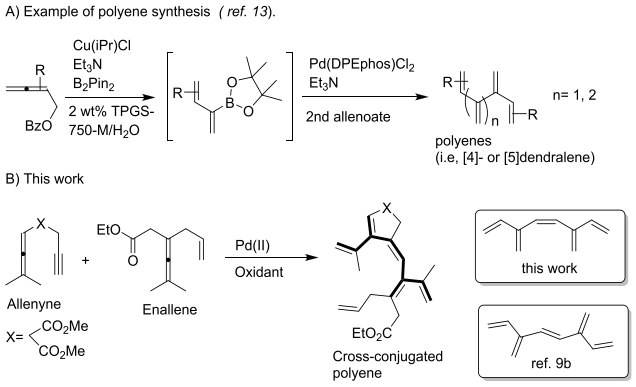
other applications of dendralenes are found in the synthesis of ivyane family compounds,[6] vinylogous Nazarov reactions,[7] organocatalytic domino cyclizations,[8] oxidative reactions,[9a] and metathesis of [3]dendralene−$Fe(CO)_3$ complexes.[9b] However, synthetic methods for the preparation of higher cross-conjugated polyenes are quite limited as one-step reactions. In this respect, Hopf, Sherburn, Shimizu and their co-workers reported on acyclic cross conjugated polyenes.[3b,10−12] Recently, the Lipshutz group reported a tandem borylation/Suzuki−Miyaura reaction for the synthesis of cross-conjugated polyenes such as [4]- and [5]dendralene (Scheme 3A).[13]

In the past decade, our research group has focused on Pd(II)-catalyzed oxidative carbocyclization reactions of allenes[1h] and

Received: January 23, 2020
Published: March 24, 2020

https://dx.doi.org/10.1021/acs.joc.0c00186
J. Org. Chem. 2020, 85, 5428−5437

Scheme 3. Example of Polyene Synthesis and Proposal for this Work



we reported the synthesis of various types of [3]dendralenes via C−C bond formation.[3d] Compared to intramolecular reactions of allenes, intermolecular couplings of allenes are more challenging and would provide an array of novel conjugated structures. To the best of our knowledge, intermolecular cascade reactions between allenes with C−C bond formation for the synthesis of cross-conjugated polyenes have not yet been reported in a one-pot reaction. We therefore decided to study palladium(II)-catalyzed oxidative coupling and carbocyclization reactions of enallenes with allenynes for the synthesis of polyenes (Scheme 3 B). These cross-conjugated polyenes will have the (*Z*)-configuration at the middle double bond. The synthesis of the unsubstituted (*E*)-isomer of the corresponding polyene has been reported by Paddon-Row and Sherburn (lower box, Scheme 3B).[9b]

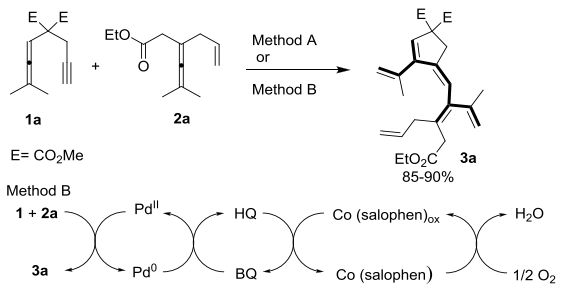
In this report, palladium-catalyzed intermolecular carbocyclization cascade reactions provide a wide variety of interesting polyene products in high yield and with excellent regio- and stereoselectivity (Scheme 3, B).

RESULTS AND DISCUSSION

In our initial investigation, allenyne **1a** and enallene **2a** were chosen as the substrates for this challenging transformation (Scheme 4).

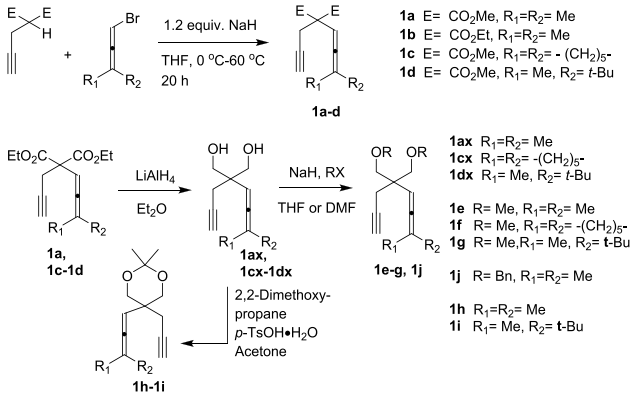
Preparation of Starting Materials. All allenynes **1** were prepared from propargyl malonate and the corresponding bromoallenes (Scheme 5 and Experimental Section). The eneallenes **2** were synthesized from propargyl alcohol derivatives

Scheme 4. Cascade Reaction[a]



[a]**Method A**: **2a** (2 equiv), $Pd(OAc)_2$ (5 mol %), BQ (2 equiv), Na_2CO_3 (20 mol %), CH_3CN, 80 °C, 24 h. **Method B**: $Pd(OAc)_2$ (5 mol %), BQ (20 mol %), Co(salophen) (5 mol %), Na_2CO_3 (20 mol %), CH_3CN, 80 °C, O_2 balloon, 24 h.

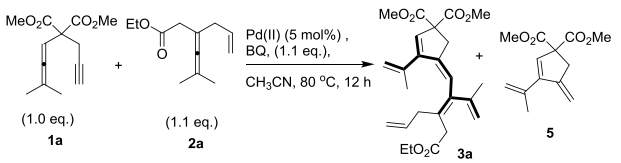
Scheme 5. Preparation of Allenynes



and subsequent 1,3-rearrangement or iron-catalyzed S_N2' Grignard reaction (see Supporting Information).

In preliminary experiments, we observed that treatment of **1a** and 1.1 equiv of **2a** with 5 mol % of $Pd(OAc)_2$ and 1.1 equiv of benzoquinone (BQ) in DCE at 80 °C gave a 64% NMR yield of the regio- and stereodefined dendralene derivative **3a** together with 6% of cycloisomerization product **5** (Table 1, entry 1).[14] With these inspiring results in hand, we set out to determine the

Table 1. Optimizatiion of the Reaction[a]



Entry	Cat. (Pd)	Solvent	Yield (%)[b] 3a	Yield (%)[b] 5	Recovery of **1a**/**2a** (%)[b]
1	$Pd(OAc)_2$	DCE	64	6	–
2	$Pd(OAc)_2$	Dioxane	51	6	–
3	$Pd(OAc)_2$	DMSO	55	–	–
4[c]	$Pd(OAc)_2$	THF	43	–	–
5[c]	$Pd(OAc)_2$	MeOH	50	4	–
6[c]	$Pd(OAc)_2$	Acetone	33	–	–
7	$Pd(OAc)_2$	Toluene	65	7	–
8	$Pd(OAc)_2$	MeCN	75	–	–
9	$Pd(TFA)_2$	MeCN	–	–	94/91
10	$Pd(PPh_3)_2Cl_2$	MeCN	–	–	70/71
11	$Pd(MeCN)_2Cl_2$	MeCN	–	–	71/47
12	$Pd(acac)_2$	MeCN	60	6	–
13[g]	$Pd(OAc)_2$	MeCN	80	–	–
14[d,f]	$Pd(OAc)_2$	MeCN	83	–	–
15[d,e]	$Pd(OAc)_2$	MeCN	88	–	–
16[d,e,h]	$Pd(OAc)_2$	MeCN	94	–	–
17[d,h,i]	$Pd(OAc)_2$	MeCN	91	–	–
18[d,h,j]	$Pd(OAc)_2$	MeCN	90	–	–

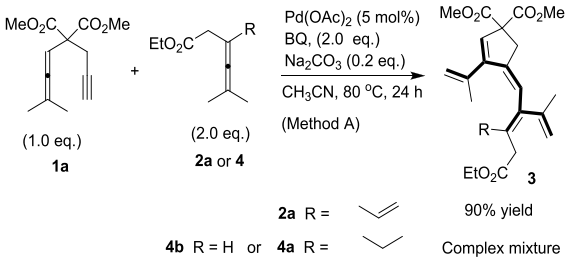
[a]The reaction was conducted in the indicated solvent (1 mL) at 80 °C using **1a** (0.1 mmol), allene-ene **2a** (0.11 mmol), and BQ (1.1 equiv) in the presence of palladium catalyst (5 mol %). [b]Yield determined by ^1H NMR analysis using anisole as the internal standard. [c]The reaction was run at 60 °C. [d]**2a** (2.0 equiv) and 2.0 equiv of BQ was used. [e]0.2 equiv of Na_2CO_3 was used. [f]1 mol % $Pd(OAc)_2$ was used. [g]**2a** (1.5 equiv) and 1.5 equiv of BQ was used. [h]Reaction time 24 h. [i]Et_3N (20 mol %). [j]AcOH (20 mol %).

https://dx.doi.org/10.1021/acs.joc.0c00186
J. Org. Chem. 2020, 85, 5428−5437

role of the solvent and the Pd(II) catalyst. In a screening of various solvents in the presence of $Pd(OAc)_2$ catalyst (Table 1, entries 1−8), CH_3CN was found to be the best solvent, which delivered the product **3a** in 75% yield without formation of side product **5** (entry 8). Furthermore, palladium catalyst screening showed that $Pd(TFA)_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(PhCN)_2Cl_2$ were not suitable for the reaction and in these cases the allenyne **1a** and enallene **2a** were recovered (Table 1, entries 9−11). However, $Pd(acac)_2$ catalyzed the reaction efficiently to give the product **3a** in 60% yield. (Table 1, entry 12). In further optimizations, treatment of **1a** and 1.5 equiv of **2a** with 5 mol % of $Pd(OAc)_2$, and 1.5 equiv of BQ afforded **3a** in 80% yield (Table 1, entry 13). Increasing **1a** and BQ to 2.0 equiv each with 1 mol % of $Pd(OAc)_2$ improved the yield of **3a** to 83% (Table 1, entry 14). The yield of **3a** further increased with the addition 0.2 equiv of Na_2CO_3 (Table 1, entry 15). With an increased reaction time, we found that treatment of **1a** and 2.0 equiv of **2a** with 5 mol % of $Pd(OAc)_2$, and 2.0 equiv of BQ in CH_3CN at 80 °C for 24 h afforded **3a** in 94% yield (Method A) (Table 1, entry 16). Additives such as Et_3N or AcOH did not improve the yield of **3a** (Table 1, entries 17−18).

To demonstrate the necessity of the olefin group in the enallene **2a**,[15] comparative experiments with allenes lacking the pending olefin were carried out. Without the pending olefin, these reactions failed to give any cross-conjugated polyene product **3** with Method A in CH_3CN (Scheme 6). Thus, when

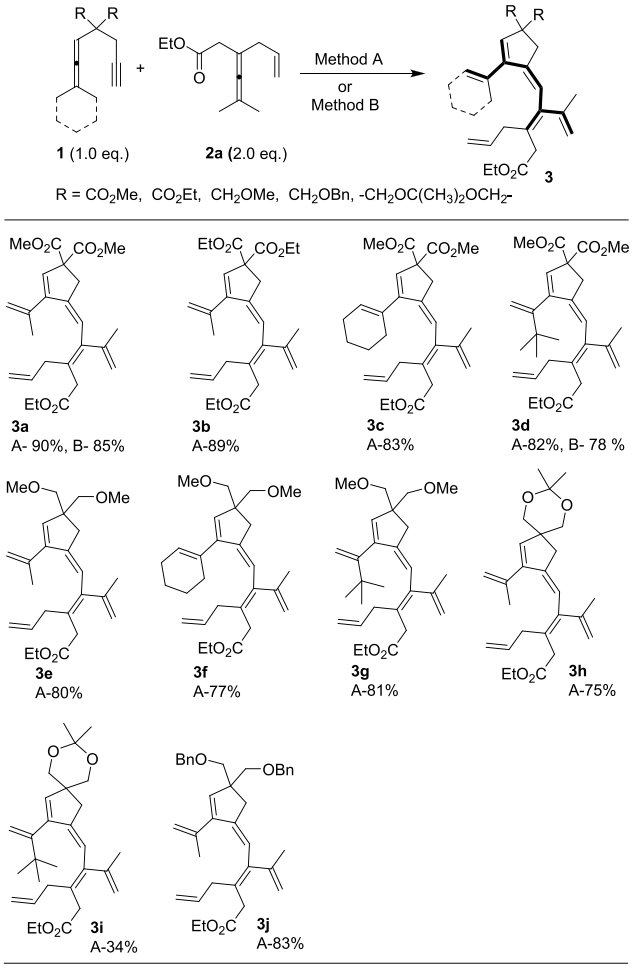
Scheme 6. Comparative Experiment



4a and **4b** were allowed to react with **1a**, no detectable amounts of **3** were formed. These results are in accordance with previous results that the olefin group of **2a** is an indispensable assisting/directing group for activation of the allene.[15]

In further studies, we investigated Pd(II)-catalyzed aerobic oxidative coupling−carbocyclization reactions between allenyne **1a** and enallene **2a** for the synthesis of **3a** (Scheme 4, Method B). We have previously developed various biomimetic methods for palladium-catalyzed aerobic oxidation of unsaturated substrates.[16] The employment of an aerobic biomimetic oxidation system is an environmentally benign process associated with high atom economy.[17] A key feature of Scheme 4, Method B is the multistep electron transfer occurring, which enables a mild aerobic oxidation. This multistep electron transfer system involves three redox pairs: Pd^{II}/Pd^0, (BQ)/HQ, and Co(salophen)^{ox}/Co(salophen). The BQ and Co(salophen) are used as electron transfer mediators (ETMs), and molecular oxygen is applied as the oxidant. We found that reaction of **1a** with **2a** in the presence of catalytic amounts of $Pd(OAc)_2$ (5 mol %), BQ (20 mol %), and Co(salophen) (5 mol %) in CH_3CN at 80 °C under molecular oxygen (1 atm) for 24 h afforded **3a** in 85% yield (Method B). Under optimized reaction conditions Methods A and B, we investigated the scope of the reaction by using different allenyne substrates (Table 2, **1a−1j**).

Table 2. Scope of Substrate 1[a]



[a]Isolated yield after column chromatography **Method A**: **2a** (2 equiv), $Pd(OAc)_2$ (5 mol %), BQ (2 equiv), Na_2CO_3 (20 mol %), CH_3CN, 80 °C, 24 h. **Method B**: $Pd(OAc)_2$ (5 mol %), BQ (20 mol %), Co(salophen) (5 mol %), Na_2CO_3 (20 mol %), CH_3CN, 80 °C, O_2 balloon, 24 h.

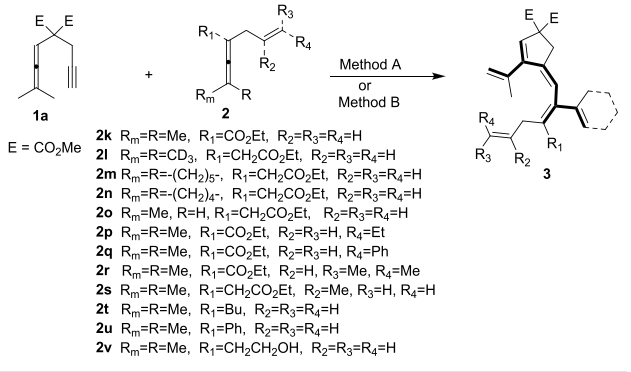
Under standard nonaerobic conditions (Method A), with methyl groups at the terminal position of the allene moiety of the allenenyne or when these methyl groups were changed to cyclohexylidene or one of them to *t*-Bu, the reaction with **2a** gave the corresponding cross-conjugated polyene (Table 2, **3a−3d**) in good yields (82−90%). The use of either stoichiometric amounts of BQ (Method A) or catalytic amounts of BQ under aerobic conditions (Method B) afforded similar results, as shown in Table 2 from the examples **3a** and **3d.** It is worth noting that the reaction of allenyne substrates **1e−1j** (Table 2) having two methyl ethers, a 1,3 dioxane, or two benzyl ethers in place of the two carboalkoxy groups, along with cyclohexylidene or tertiary butyl on the allene moiety, afforded the corresponding polyene derivatives (Table 2, **3e−3j**) selectively in good yields (70−83%), except for **1i**, which afforded **3i** in 34% yield. These results show that the malonate group of the tether is not necessary for a successful transformation.

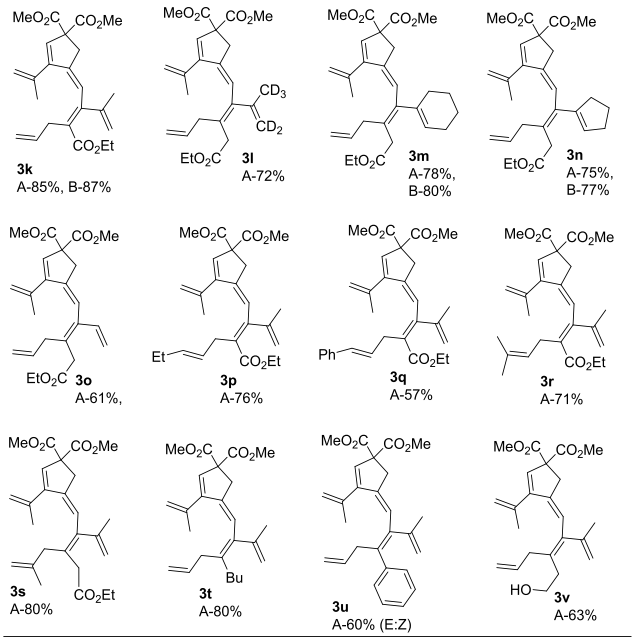
To expand the scope of the method, we tested differently substituted enallenes **2** for the coupling−carbocyclization cascade reaction using allenyne **1a** as the cosubstrate. Under standard conditions (Method A), a number of functionalized enallenes **2** served as excellent candidates for formation of cross-

https://dx.doi.org/10.1021/acs.joc.0c00186
J. Org. Chem. 2020, 85, 5428−5437

conjugated polyenes in good yields. When allyl-substituted 2,3-dienoate (**2k**) was employed, the reaction gave the desired product **3k** in 85% yield. Variation of the methyl groups on the allene moiety of **2**, e.g. deuterated methyls (**2l**), cyclohexylidene group (**2m**), cyclopentylidene group (**2n**), or one methyl presence (**2o**), in the reaction with **1a** provided the corresponding cross-conjugated polyenes in good yields (Table 3, **3l**–**3o**). Moreover, substrates **2p**–**2s** with methyl,

Table 3. Scope of Enallene Substrates 2[a]

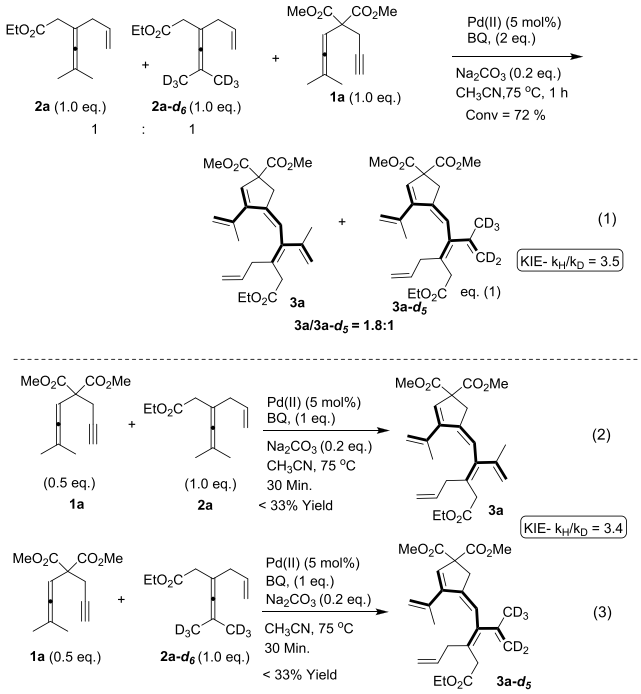




[a]Isolated yield after column chromatography. **Method A**: **2a** (2 equiv), $Pd(OAc)_2$ (5 mol %), BQ (2 equiv), Na_2CO_3 (20 mol %), CH_3CN, 80 °C, 24 h. **Method B**: $Pd(OAc)_2$ (5 mol %), BQ (20 mol %), Co(salophen) (5 mol %), Na_2CO_3 (20 mol %), CH_3CN, 80 °C, O_2 balloon, 24 h.

ethyl, or phenyl substitution on the olefin moiety afforded **3p**–**3s** (Table 3) in moderate to good yields (57–80%). Reaction of substituted enallenes **2t**–**2v** with **1a** afforded the desired products **3t**–**3v** in 60–80% yield (Table 3). As shown in Table 3, the reaction also works under aerobic conditions with catalytic amounts of BQ together with Co(salophen) in catalytic amounts (Method B). Thus, reaction of enallenes **2k, 2m**–**2n** with **1a** using molecular oxygen as the oxidant afforded products **3k**, **3m**–**3n** in 77–85% yield (Table 3).

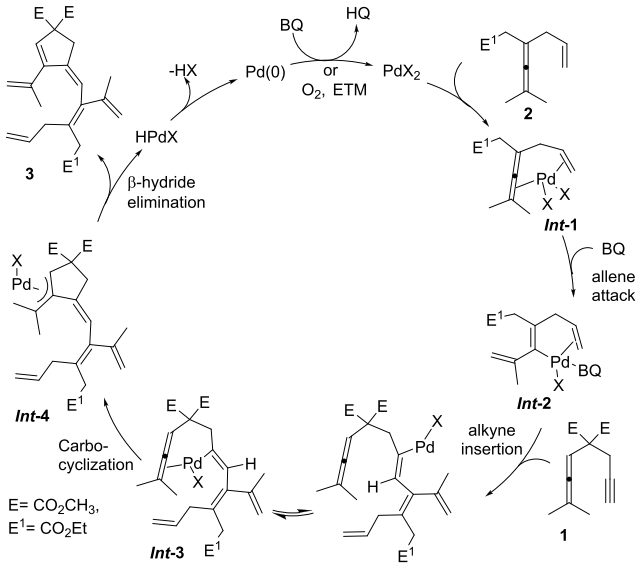
To gain further insight into the reaction mechanism, the deuterium kinetic isotope effects (KIE) were studied (eqs 1–3).



An intermolecular competition experiment was conducted at 75 °C using a 1:1 mixture of **2a** and **2a**-d_6 (eq 1). The products ratio **3a** and **3a**-d_5 was measured as 1.8:1, from which the competitive KIE was determined to be k_H/k_D = 3.5 (see Supporting Information). Furthermore, parallel kinetic experiments afforded a KIE (k_H/k_D from initial rate) value of 3.4 (eqs 2 and 3) which indicates the initial allenylic C(sp^3)–H bond cleavage is involved in the rate-determining step in the reaction. The large competitive KIE (k_H/k_D = 3.5) in C–H bond cleavage requires that this step is the first irreversible step.

Based on the mechanistic studies including the KIE measurements (eqs 1–3) and our previous work,[18] we propose the mechanism as shown in Scheme 7. The large deuterium isotope effect found for the C–H bond cleavage of the enallene **2a** indicates that the enallene is the compound first activated and

Scheme 7. Proposed Mechanism for the Formation of 3



https://dx.doi.org/10.1021/acs.joc.0c00186
J. Org. Chem. 2020, 85, 5428–5437

not the allenyne.[19] Initial reaction of $Pd(OAc)_2$ with enallene **2** would give dienyl−Pd^{II} complex *Int*-**2** via allenic C−H bond cleavage of chelated π-complex *Int*-**1** (Scheme 7). This activation of the allene is triggered by the coordination of the assisting olefin.[15] Vinylpalladium intermediate *Int*-**2** would then undergo an insertion of the vinylpalladium bond into the alkyne of allenyne **1**, which leads to *Int*-**3**. Subsequent intramolecular insertion of the vinylpalladium bond of *Int*-**3** into the allene would lead to (π-allyl)-palladium intermediate *Int*-**4**. Subsequent β-hydride elimination via $C(sp^3)$−H bond cleavage would provide the cross-conjugated polyene **3** and release Pd^0 for the next cycle.

CONCLUSION

We have developed an efficient one-pot Pd^{II}-catalyzed oxidative coupling−carbocyclization cascade reaction for the synthesis of cross-conjugated polyene via intermolecular C−C bond formation and subsequent carbocyclization. This transformation allows highly regio- and stereoselective formation of cross-conjugated polyenes using enallene and allenyne under aerobic conditions with environmentally friendly O_2 as the terminal oxidant. These important cross-conjugated polyenes, which are readily obtained in a one-pot cascade reaction in the present work, are difficult to prepare by other methods. Further studies on the scope of natural product synthesis and other synthetic application of this new cascade reaction are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. For the synthesis of complex molecules, unless otherwise noted, all reagents were used as received from the commercial suppliers. $Pd(OAc)_2$ was obtained from Pressure Chemicals and used without further purification. Alkynes were commercially available from Sigma-Aldrich or Acros. The palladium-catalyzed cascade reactions could be performed without any efforts to exclude moisture. DCE was distilled using CaH_2, Dry THF and toluene, were obtained froma VAC Solvent Purifier. The other dry solvents were purchased from Sigma-Aldrich. Reactions were monitored using thin-layer chromatography (TLC) (SiO_2). TLC plates were visualized with UV light (254 nm) or $KMnO_4$ stain. Flash chromatography was carried out with 60 Å (particle size 35−70 μm) normal flash silica gel. NMR spectra were recorded at 400 MHz (^1H) or 500 MHz (^1H) and at 100 MHz (^{13}C) or 125 MHz (^{13}C), respectively. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H = 7.26 and C = 77.0 ppm) as the internal standard, and coupling constants (J) are given in Hz. HRMS data were recorded using ESI-TOF techniques.

Allenynes **1a**[20] and **1c**[21] were prepared as described in literature. Allenynes **1b** and **1d** were prepared from propargylmalonate and the corresponding bromoallene in a similar manner.[20] All allene derivatives **2a**, **2k**−**2v**, and **4a**−**4b** were prepared according to a previously described procedures.[3d,15,18c,22]

Representative Procedure for the Synthesis of 1b and 1d: Synthesis of 1b. To a suspension of NaH (60% in mineral oil, 0.456 g, 11.4 mmol) in anhydrous THF (60 mL) was added a solution of diethyl propargylmalonate (2.0 g, 8.83 mmol) in anhydrous THF (5 mL) at 0 °C. After the addition, the mixture was stirred for another 20 min at room temperature Then a solution of bromoallene (2.6 g, 17.6 mmol) in anhydrous THF (5 mL) was added at room temperature and the resulting mixture was refluxed for 20 h. After the reaction was complete as monitored by TLC, it was cooled to room temperature. Most of the solvent was removed under vacuum, and then the reaction mixture was diluted with 50 mL of Et_2O and quenched with 10 mL of water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over Na_2SO_4. Evaporation and column chromatography on silica gel (pentane/ethyl acetate = 30/1) afforded **1b** (0.71 g, 31%).

Characterization of Allenynes 1b and 1d. *Diethyl-2-(3-methyl-2λ^5-buta-1,2-dien-1-yl)-2-(prop-2-yn-1-yl)malonate (**1b**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 4.94 (sept, J = 2.9 Hz, 1H), 4.25−4.15 (m, 4H), 2.86 (d, J = 2.7 Hz, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.71 (d, J = 2.9 Hz, 6H), 1.25 (t, J = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 201.7, 169.2, 100.5, 87.7, 79.6, 70.4, 61.7, 57.5, 24.3, 19.9, 13.9; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{20}O_4Na$, 287.1254; found, 287.1263. Isolated yield: 31% (0.71 g), as a liquid. Column chromatography on silica gel (pentane/ethyl acetate = 30/1).

In the same manner **1d** was obtained from 1-bromo-3,4,4-trimethyl-1,2-pentadiene.

*Dimethyl-2-(prop-2-yn-1-yl)-2-(3,4,4-trimethyl-2λ^5-penta-1,2-dien-1-yl)malonate (**1d**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 5.64 (q, J = 2.9 Hz, 1H), 3.74 (d, J = 9.5 Hz, 6H), 2.87 (d, J = 2.7 Hz, 2H), 1.97 (t, J = 2.7 Hz, 1H), 1.71 (d, J = 2.8 Hz, 3H), 1.02 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 200.0, 169.6, 114.2, 89.2, 79.5, 70.7, 57.7, 52.8, 52.7, 33.7, 28.8, 24.6, 14.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{22}O_4Na$, 301.1410; found, 301.1421. Isolated yield: 32% (0.79 g), as a liquid. Column chromatography on silica gel (pentane/ethyl acetate = 30/1).

Representative Procedure for the Synthesis of 1ax, 1cx, and 1dx: Synthesis of 1ax. To a suspension of $LiAlH_4$ (171 mg, 4.5 mmol) in anhydrous Et_2O (15 mL) was added a solution of **1a** (0.34 g, 1.5 mmol) in anhydrous Et_2O (10 mL) at 0 °C. After the addition, the mixture was stirred for another 2 h at rt and carefully quenched with H_2O (5 mL). The resulting mixture was extracted with diethyl ether (2 × 30 mL). The combined organic layers were washed with H_2O (20 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane/ethyl acetate = 1:3) to yield **1ax** (203 mg, 79% yield) as a white solid.

Compounds **1cx** and **1dx** were prepared from **1c** and **1d**, respectively, in the same manner.

Characterization of Products 1ax, 1cx, and 1dx. *2-(3-Methyl-2λ^5-buta-1,2-dien-1-yl)-2-(prop-2-yn-1-yl)propane-1,3-diol (**1ax**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 4.94 (sept, J = 2.9 Hz, 1H), 3.69 (s, 4H), 2.40 (d, J = 2.7 Hz, 2H), 2.04 (bs, 2H), 2.02 (d, J = 2.7 Hz, 1H), 1.71 (d, J = 3.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 201.7, 98.3, 90.0, 81.1, 70.6, 67.4, 44.5, 22.9, 20.6; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{11}H_{16}O_2Na$, 203.1043; found, 203.1049. Isolated yield: 79% (203 mg), as a semi-solid. Column chromatography (silica gel, pentane/ethyl acetate = 1:3).

*2-(2-Cyclohexylidene-2λ^5-vinyl)-2-(prop-2-yn-1-yl)propane-1,3-diol (**1cx**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 4.94 (quint, J = 2.9 Hz, 1H), 3.67 (d, J = 1.0 Hz, 4H), 2.39 (d, J = 2.7 Hz, 2H), 2.39 (bs, 2H), 2.16−2.06 (m, 4H), 2.00 (t, J = 2.7 Hz, 1H), 1.42−1.68 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 198.3, 105.5, 89.8, 81.1, 70.6, 67.2, 44.4, 31.6, 27.3, 25.9, 22.9; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{20}O_2Na$, 243.1356; found, 243.1362. Isolated yield: 81% (268 mg), as a semi-solid. Column chromatography (silica gel, pentane/ethyl acetate = 1:2.5).

*2-(Prop-2-yn-1-yl)-2-(3,4,4-trimethyl-2λ^5-penta-1,2-dien-1-yl)-propane-1,3-diol (**1dx**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 5.01 (q, J = 2.9 Hz, 1H), 3.70 (s, 4H), 2.41 (d, J = 2.7 Hz, 2H), 2.17 (bs, 2H), 2.02 (t, J = 2.7 Hz, 1H), 1.71 (d, J = 2.9 Hz, 3H), 1.05 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 200.0, 111.6, 91.7, 81.2, 70.7, 67.5, 67.4, 44.3, 33.1, 29.0, 29.6, 22.8, 15.4; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{22}O_2Na$, 245.1512; found, 245.1521. Isolated yield: 97% (323 mg), as a semi-solid. Column chromatography (silica gel, pentane/ethyl acetate = 1:3).

Representative Procedure for the Synthesis of 1e, 1f, and 1g: Synthesis of 1e. To a suspension of **1ax** (160 mg, 0.89 mmol) in THF (10 mL) was added NaH (60% in mineral oil (142 mg, 3.6 mmol)) at 0 °C. The reaction mixture was subsequently stirred for 30 min at the same temperature, and then MeI (0.45 mL, 7.1 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched by addition of water and extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by flash column

https://dx.doi.org/10.1021/acs.joc.0c00186
J. Org. Chem. 2020, 85, 5428−5437

chromatography (silica gel, pentane/ethyl acetate = 98:2) to afford **1e** (150 mg, 81% yield) as a colorless oil.

In the same manner, **1f** and **1g** were obtained from **1cx** and **1dx**, respectively.

Characterization of Products 1e, 1f, and 1g. *4,4-Bis(methoxymethyl)-7-methyl-6λ⁵-octa-5,6-dien-1-yne (**1e**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.00 (sept, J = 2.9 Hz, 1H), 3.36−3.31 (m, 10H), 2.32 (d, J = 2.5 Hz, 2H), 1.94 (t, J = 2.5 Hz, 1H), 1.68 (d, J = 2.7 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 201.5, 97.4, 90.7, 81.6, 75.4, 69.7, 59.3, 43.4, 23.4, 20.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{13}H_{20}O_2Na$, 231.1356; found, 231.1367. Isolated yield: 81% (150 mg), as a colorless oil. Flash column chromatography (silica gel, pentane/ethyl acetate = 98:2).

*(3,3-Bis(methoxymethyl)-1λ⁵-hex-1-en-5-yn-1-ylidene)cyclohexane (**1f**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.00 (quint, J = 2.1 Hz, 1H), 3.34 (d, J = 2.9 Hz, 4H), 3.33 (s, 6H), 2.34 (d, J = 2.7 Hz, 2H), 2.19−2.05 (m, 4H), 1.94 (t, J = 2.7 Hz, 1H), 1.42−1.67 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 198.0, 104.7, 90.5, 81.5, 75.5, 69.8, 59.4, 43.2, 31.5, 27.3, 26.1, 23.4; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{24}O_2Na$, 271.1669; found, 271.1670. Isolated yield: 95% (209 mg), as a colorless oil. Flash column chromatography (silica gel, pentane/ethyl acetate = 98:2).

*4,4-Bis(methoxymethyl)-7,8,8-trimethyl-6λ⁵-nona-5,6-dien-1-yne (**1g**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.08 (q, J = 2.9 Hz, 1H), 3.36−3.29 (m, 10H), 2.32 (d, J = 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.68 (d, J = 2.7 Hz, 3H) 1.04 (s, 9H); ^{113}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 199.7, 110.7, 92.5, 81.7, 75.5, 69.9, 59.3, 43.3, 33.1, 29.0, 23.3, 15.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{26}O_2Na$, 273.1825; found, 273.1829. Isolated yield: 85% (189 mg), as a colerless oil. Flash column chromatography (silica gel, pentane/ethyl acetate = 98:2).

Representative Procedure for the Synthesis of 1h and 1i: Synthesis of 1h. To a suspension of **1ax** (108 mg, 0.60 mmol) in acetone (5 mL) was added 2,2-dimethoxypropane (72 mg, 0.69 mmol) and p-TsOH·H_2O (5.7 mg, 0.03 mmol). The reaction mixture was stirred at room temperature for 3 h and quenched with sat. $NaHCO_3$ (aq.). Acetone was evaporated, and the residue was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane/ethyl acetate = 97:3) to yield **1h** (111 mg, 84% yield) as a colorless oil.

In the same manner, **1i** was obtained from **1dx**.

Characterization of Products 1h and 1i. *2,2-Dimethyl-5-(3-methyl-2λ⁵-buta-1,2-dien-1-yl)-5-(prop-2-yn-1-yl)-1,3-dioxane (**1h**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.88 (sept, J = 2.9 Hz, 1H), 3.70 (qt, J = 14.5 Hz, J = 11.6 Hz, 4H), 2.53 (d, J = 2.6 Hz, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.40 (d, J = 3.0 Hz, 6H), 1.39 (d, J = 8.1 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 201.7, 98.2, 97.9, 89.9, 81.4, 70.4, 66.9, 36.9, 27.6, 23.8, 20.5, 19.8; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{20}NaO_2$, 243.1356; found, 243.1364. Isolated yield: 84% (111 mg), as a colorless oil. Flash column chromatography (silica gel, pentane/ethyl acetate = 97:3).

*2,2-Dimethyl-5-(prop-2-yn-1-yl)-5-(3,4,4-trimethyl-2λ⁵-penta-1,2-dien-1-yl)-1,3-dioxane (**1i**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.98 (q, J = 2.9 Hz, 1H), 3.77−3.61 (m, 4H), 2.54 (qd, J = 13.0 Hz, 2.6 Hz, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.70 (d, J = 3.0 Hz, 3H), 1.40 (d, J = 6.5 Hz, 6H), 1.04 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 199.9, 111.6, 97.9, 91.5, 81.5, 70.6, 66.9, 66.8, 36.8, 33.0, 29.0, 27.9, 24.0, 19.5, 15.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{26}O_2Na$, 285.1825; found, 285.1822. Isolated yield: 81% (128 mg), as a colorless oil. Flash column chromatography (silica gel, pentane/ethyl acetate = 97:3).

Synthesis and Characterization of 1j. *(((2-(3-Methyl-2λ⁵-buta-1,2-dien-1-yl)-2-(prop-2-yn-1-yl)propane-1,3-diyl)bis(oxy))bis(methylene))dibenzene (**1j**).* To a suspension of NaH (60% in mineral oil, 124 mg, 3.1 mmol) in anhydrous DMF (3 mL) was added a solution of **1ax** (140 mg, 0.78 mmol) in anhydrous DMF (2 mL) at 0 °C. After the addition, the mixture was stirred for another 1 h at 0 °C. Then BnBr (170 μL, 1.4 mmol) was added at 0 °C, and the resulting mixture was stirred at rt overnight. Then the reaction mixture was diluted with 20 mL of Et_2O and quenched with 5 mL of water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with H_2O (10 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane/diethyl ether = 100:1) to yield **1j** (221 mg, 79% yield) as a liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.26 (m, 10H), 5.12 (sept, J = 2.9 Hz, 1H), 4.54 (s, 4H), 3.53 (s, 4H), 2.45 (d, J = 2.7 Hz, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.70 (d, J = 2.9 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 201.5, 138.7, 128.2, 127.3, 97.4, 90.9, 81.7, 73.3, 73.1, 69.8, 43.8, 23.5, 20.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{25}H_{28}O_2Na$, 383.1982; found, 383.1987.

*Method A: Nonaerobic Oxidative Coupling-Carbocyclization for Preparation of **3**. Representative Procedure: Synthesis of **3a**.* In a sealable microwave tube were placed **1a** (47.2 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), 1,4-benzoquinone (BQ) (43.2 mg, 0.4 mmol), anhydrous Na_2CO_3 (4.2 mg, 0.04 mmol), and **2a** (77 mg, 0.4 mmol). To this mixture, 2.0 mL of anhydrous CH_3CN solvent were added and the tube was sealed with the cap. The reaction was stirred at 80 °C in an oil bath for 24 h. After full consumption of starting material **1a** as monitored by TLC, the reaction mixture was concentrated in vacuo and purified via short column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95) affording 77 mg (90%) of **3a** as a liquid. The reaction was also run on a 1.3 mmol scale using **1a** (0.307 g, 1,3 mmol), which afforded 0.45g (81%) of **3a** after short column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Method B: Aerobic Oxidative Coupling-Carbocyclization for Preparation of **3**. Representative Procedure: Synthesis of **3a**.* In a sealable microwave tube were placed **1a** (47.2 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Cobalt(salophen) (3.7 mg, 0.01 mmol), 20 mol % of 1,4-benzoquinone (BQ) (4.4 mg, 0.04 mmol), anhydrous Na_2CO_3(4.2 mg, 0.04 mmol) and **2a** (77 mg, 0.4 mmol). The tube was sealed with the cap. To this mixture was added 2.0 mL of anhydrous CH_3CN via syringe. Then the reaction was stirred at 80 °C in an oil bath under an oxygen atmosphere using molecular oxygen balloon connected via a needle for 24 h. After full consumption of starting material **1a** as monitored by TLC, the reaction mixture was concentrated in vacuo and purified via short column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95) afforded 73 mg (85%) of **3a** as a liquid.

Characterization of Products 3. *Dimethyl-(Z)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-2-(prop-1-en-2-yl)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.24 (s, 1H), 5.94 (s, 1H), 5.76−5.66 (m, 1H), 5.15 (s, 1H), 5.10 (s, 1H), 5.06 (s, 1H), 5.02 (d, J = 4.9 Hz, 1H), 4.98 (s, 1H), 4.85 (d, J = 1.2 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.71 (s, 6H), 3.19 (d, J = 4.0 Hz, 4H), 2.93 (d, J = 6.4 Hz, 2H), 1.92 (s, 3H), 1.81 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 171.9, 170.9, 151.1, 144.2, 142.3, 139.9, 138.0, 135.0, 128.8, 119.5, 116.3, 116.0, 115.9, 63.8, 60.4, 52.7, 38.1, 36.9, 36.7, 23.2, 23.0, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{25}H_{32}O_6Na$, 451.2091; found, 451.2069. Isolated yield: Method A, 90% (77 mg); Method B, 85% (73 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Diethyl-(Z)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-2-(prop-1-en-2-yl)-hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.24 (s, 1H), 5.95 (s, 1H), 5.76−5.66 (m, 1H), 5.15 (s, 1H), 5.10 (s, 1H), 5.06 (s, 1H), 5.02 (d, J = 6.6 Hz, 1H), 4.98 (s, 1H), 4.86 (s, 1H), 4.22−4.04 (m, 6H), 3.19 (s, 4H), 2.94 (d, J = 6.1 Hz, 2H), 1.93 (s, 3H), 1.82 (s, 3H), 1.23 (t, J = 7.1 Hz, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 171.9, 170.5, 151.1, 144.3, 142.6, 140.0, 138.1, 135.0, 129.2, 128.7, 119.4, 116.1, 115.9, 115.8, 64.0, 61.5, 60.4, 38.2, 36.8, 36.7, 23.2, 23.1, 14.1, 13.9; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{27}H_{36}O_6Na$, 479.2404; found, 479.2382. Isolated yield: Method A, 89% (82 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Dimethyl-(Z)-3-(cyclohex-1-en-1-yl)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-2-(prop-1-en-2-yl)hexa-2,5-dien-1-ylidene)cyclopent-2-ene-1,1-dicarboxylate (**3c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.21 (s, 1H), 5.86 (s, 1H), 5.82−5.80 (m, 1H), 5.78−5.68 (m, 1H), 5.11−5.09 (m, 1H), 5.04−5.02 (m, 1H), 4.99 (s, 1H), 4.85 (d, J = 1.2 Hz, 1H), 4.09 (q, J =

https://dx.doi.org/10.1021/acs.joc.0c00186
J. Org. Chem. 2020, 85, 5428−5437

7.1 Hz, 2H), 3.71 (s, 6H), 3.20 (s, 2H), 3.18 (d, J = 2.2 Hz, 2H), 2.94 (d, J = 6.4 Hz, 2H), 2.14−2.10 (m, 4H), 1.82 (s, 3H), 1.72−1.56 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.0, 171.2, 152.0, 144.2, 142.8, 140.2, 135.0, 131.4, 128.5, 128.1, 127.5, 119.2, 115.9, 115.8, 63.8, 60.4, 52.7, 38.2, 36.9, 36.8, 28.6, 25.3, 23.3, 22.7, 22.0, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{36}O_6Na$, 491.2404; found, 491.2392. Isolated yield: Method A, 83% (77 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Dimethyl-(Z)-3-(3,3-dimethylbut-1-en-2-yl)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-2-(prop-1-en-2-yl)hexa-2,5-dien-1-ylidene)cyclopent-2-ene-1,1-dicarboxylate (**3d**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 6.07 (s, 1H), 5.80 (s, 1H), 5.76−5.63 (m, 1H), 5.25 (d, J = 1.4 Hz, 1H), 5.11 (s, 1H), 5.02−4.97 (m, 2H), 4.87−4.86 (m, 1H), 4.74 (d, J = 1.4 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.73 (s, 6H), 3.19 (s, 2H), 3.17 (d, J = 2.2 Hz, 2H), 2.91 (d, J = 6.4 Hz, 2H), 1.79 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.0, 171.2, 152.0, 144.3, 142.8, 140.1, 135.0, 131.4, 128.5, 128.1, 127.5, 119.2, 115.9, 115.8, 63.8, 60.4, 52.7, 38.2, 36.9, 36.8, 28.7, 25.3, 23.3, 22.7, 22.0, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{38}O_6Na$, 493.2561; found, 493.2573. Isolated yield: Method A, 82% (78 mg); Method B, 78% (74 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Ethyl-(Z)-3-allyl-4-((Z)-(4,4-bis(methoxymethyl)-2-(prop-1-en-2-yl)cyclopent-2-en-1-ylidene)methyl)-5-methylhexa-3,5-dienoate (**3e**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 6.18 (s, 1H), 5.85 (s, 1H), 5.78−5.66 (m, 1H), 5.09 (s, 1H), 5.05−4.98 (m, 4H), 4.82 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.31 (s, 6H), 3.26 (s, 4H), 3.19 (s, 2H), 2.94 (d, J = 6.4 Hz, 2H), 2.43 (d, J = 2.1 Hz, 2H), 1.91 (s, 3H), 1.79 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.2, 148.8, 145.0, 144.6, 140.6, 138.9, 136.1, 135.3, 127.2, 118.1, 115.8, 115.3, 115.0, 60.3, 59.3, 52.2, 38.0, 36.9, 36.4, 23.3, 23.2, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{25}H_{36}O_4Na$, 423.2506; found, 423.2494. Isolated yield: Method A, 80% (64 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 4:96).

*Ethyl-(Z)-3-allyl-4-((Z)-(2-(cyclohex-1-en-1-yl)-4,4-bis(methoxymethyl)cyclopent-2-en-1-ylidene)methyl)-5-methylhexa-3,5-dienoate (**3f**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 6.14 (s, 1H), 5.83−5.68 (m, 3H), 5.06−4.98 (m, 3H), 4.81 (dd, J = 2.4 Hz, 0.9 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.31 (s, 6H), 3.26 (s, 4H), 3.19 (s, 2H), 2.94 (d, J = 6.4 Hz, 2H), 2.40 (d, J = 2.1 Hz, 2H), 2.16−2.07 (m, 4H), 1.79 (s, 3H), 1.71−1.57 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.2, 149.8, 145.5, 144.7, 140.8, 135.3, 134.5, 132.1, 126.9, 126.9, 117.7, 115.8, 115.2, 60.3, 59.3, 52.1, 38.1, 36.9, 36.4, 28.7, 25.3, 23.2, 22.9, 22.2, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{40}O_4Na$: 463.2819; found, 463.2825. Isolated yield: Method A, 77% (68 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Ethyl-(Z)-3-allyl-4-((Z)-(2-(3,3-dimethylbut-1-en-2-yl)-4,4-bis(methoxymethyl)cyclopent-2-en-1-ylidene)methyl)-5-methylhexa-3,5-dienoate (**3g**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 5.97 (s, 1H), 5.76−5.68 (m, 1H), 5.66 (s, 1H), 5.20 (d, J = 1.7 Hz, 1H), 5.07−4.97 (m, 3H), 4.82 (dd, J = 2.4 Hz, 0.9 Hz, 1H), 4.69 (d, J = 1.7 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.32 (s, 6H), 3.28 (s, 4H), 3.18 (s, 2H), 2.91 (d, J = 6.4 Hz, 2H), 2.39 (d, J = 2.3 Hz, 2H), 1.76 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.3, 152.7, 148.7, 148.5, 144.4, 140.7, 136.5, 135.2, 127.1, 117.8, 115.6, 115.5, 112.2, 60.3, 59.3, 52.8, 38.1, 36.8, 35.8, 35.2, 29.5, 23.3, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{42}O_4Na$, 465.2975; found, 465.2985. Isolated yield: Method A, 81% (71 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 4:96).

*Ethyl-(Z)-3-allyl-4-((Z)-(8,8-dimethyl-3-(prop-1-en-2-yl)-7,9-dioxaspiro[4.5]dec-3-en-2-ylidene)methyl)-5-methylhexa-3,5-dienoate (**3h**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 6.21 (s, 1H), 5.96 (s, 1H), 5.77−5.66 (m, 1H), 5.11 (s, 1H), 5.07 (s, 1H), 5.04−4.99 (m, 3H), 4.84 (d, J = 1.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.69 (d, J = 11.3 Hz, 2H), 3.59 (d, J = 11.3 Hz, 2H), 3.20 (s, 2H), 2.93 (d, J = 6.4 Hz, 2H), 2.49 (d, J = 2.2 Hz, 2H), 1.92 (s, 3H), 1.79 (s, 3H), 1.43 (d, J = 5.8 Hz, 6H), 1.24 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.1, 149.1, 144.5, 144.1, 140.4, 138.8, 135.2, 135.1, 127.8, 118.6, 115.9, 115.6, 115.2, 97.5, 68.4, 60.4, 46.5, 38.1, 37.5, 36.8, 24.0, 23.5, 23.3, 23.3, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{26}H_{36}O_4Na$, 435.2506; found, 435.2497. Isolated yield: Method A, 75% (62 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Ethyl-(Z)-3-allyl-4-((Z)-(3-(3,3-dimethylbut-1-en-2-yl)-8,8-dimethyl-7,9-dioxaspiro[4.5]dec-3-en-2-ylidene)methyl)-5-methylhexa-3,5-dienoate (**3i**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 6.00 (s, 1H), 5.77 (s, 1H), 5.77−5.66 (m, 1H), 5.21 (s, 1H), 5.09 (s, 1H), 5.02 (d, J = 6.8 Hz, 1H), 4.97 (s, 1H), 4.85 (s, 1H), 4.69 (d, J = 1.5 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.72 (d, J = 11.3 Hz, 2H), 3.60 (d, J = 11.3 Hz, 2H), 3.19 (s, 2H), 2.91 (d, J = 6.4 Hz, 2H), 2.48 (d, J = 2.2 Hz, 2H), 1.77 (s, 3H), 1.43 (d, J = 4.3 Hz, 6H), 1.25 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.3, 152.5, 149.1, 147.4, 144.4, 140.5, 135.5, 135.0, 127.7, 118.7, 115.8, 115.7, 112.5, 97.5, 68.6, 60.4, 47.1, 38.2, 36.8, 36.6, 35.7, 29.6, 24.3, 23.4, 23.3, 14.2;; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{29}H_{42}O_4Na$, 477.2975; found, 477.2977. Isolated yield: Method A, 34% (31 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Ethyl(Z)-3-allyl-4-((Z)-(4,4-bis((benzyloxy)methyl)-2-(prop-1-en-2-yl)cyclopent-2-en-1-ylidene)methyl)-5-methylhexa-3,5-dienoate (**3j**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 7.34−7.23 (m, 10H), 6.19 (s, 1H), 5.93 (s, 1H), 5.80−5.68 (m, 1H), 5.11−4.99 (m, 5H), 4.84 (s, 1H), 4.51 (s, 4H), 4.10 (q, J = 7.1 Hz, 2H), 3.43 (s, 4H), 3.21 (s, 2H), 2.95 (d, J = 6.4 Hz, 2H), 2.50 (d, J = 2.1 Hz, 2H), 1.93 (s, 3H), 1.79 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.2, 148.9, 145.2, 144.7, 140.7, 139.0, 138.8, 136.4, 135.3, 128.2, 127.3, 127.3, 127.2, 117.9, 115.8, 115.3, 115.0, 73.5, 73.2, 60.4, 52.4, 38.0, 36.9, 36.6, 23.4, 23.3, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{37}H_{44}O_4Na$, 575.3132; found, 575.3125. Isolated yield: Method A, 83% (91 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 3:97).

*Dimethyl-(Z)-4-((Z)-3-(ethoxycarbonyl)-2-(prop-1-en-2-yl)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3k**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 6.19 (t, J = 2.2 Hz, 1H), 6.03 (s, 1H), 5.82−5.72 (m, 1H), 5.19 (s, 1H), 5.07−4.99 (m, 3H), 4.95 (s, 1H), 4.87 (d, J = 0.8 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.73 (s, 6H), 3.22 (d, J = 2.2 Hz, 2H), 3.07 (d, J = 6.1 Hz, 2H), 1.93 (d, J = 4.0 Hz, 6H), 1.23 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.7, 169.9, 150.9, 145.8, 145.6, 144.7, 137.6, 134.2, 130.5, 129.8, 118.3, 116.6, 116.0, 115.2, 63.9, 60.3, 52.9, 37.0, 34.4, 23.0, 22.7, 13.8; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{24}H_{30}O_6Na$, 437.1940; found, 437.1950. Isolated yield: Method A, 85% (70 mg); Method B, 87% (72 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Dimethyl-(Z)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-2-(prop-1-en-2-yl-d5)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3l**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 6.26 (s, 1H), 5.95 (s, 1H), 5.73−5.69 (m, 1H), 5.16 (s, 1H), 5.07−4.99 (m, 3H), 4.11 (q, J = 7.0 Hz, 2H), 3.72 (s, 6H), 3.20 (s, 4H), 2.95 (d, J = 5.7 Hz, 2H), 1.94 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.0, 171.0, 151.2, 144.0, 142.3, 139.9, 138.0, 135.0, 128.9, 128.8, 119.6, 116.3, 116.0, 63.9, 60.4, 52.8, 38.2, 36.9, 36.8, 23.1, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{25}H_{27}D_5O_6Na$, 456.2410; found, 456.2393. Isolated yield: Method A, 72% (62 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Dimethyl-(Z)-4-((Z)-2-(cyclohex-1-en-1-yl)-3-(2-ethoxy-2-oxoethyl)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3m**).* ^1H NMR (400 MHz, $CDCl_3$) δ = 6.27 (t, J = 2.2 Hz, 1H), 5.92 (s, 1H), 5.77−5.67 (m, 1H), 5.55 (sept, J = 2.2 Hz, 1H), 5.16−5.15 (m, 1H), 5.06−4.98 (m, 3H), 4.11 (q, J = 7.1 Hz, 2H), 3.73 (s, 6H), 3.22 (d, J = 2.2 Hz, 2H), 3.17 (s, 2H), 2.94 (d, J = 6.1 Hz, 2H), 2.11−2.09 (m, 2H), 1.98−1.93 (m, 5H), 1.60−1.70 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 172.2, 171.1, 151.4, 141.9, 140.5, 138.1, 137.1, 135.2, 129.1, 128.5, 126.9, 120.1, 116.2, 115.8, 63.9, 60.4, 52.8, 38.3, 37.0, 36.8, 28.9, 25.3, 23.1, 22.7, 21.9, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{36}O_6Na$, 491.2404; found, 491.2421. Isolated yield: Method A, 78% (74 mg); Method B, 80% (76 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

https://dx.doi.org/10.1021/acs.joc.0c00186
J. Org. Chem. 2020, 85, 5428−5437

*Dimethyl-(Z)-4-((Z)-2-(cyclopent-1-en-1-yl)-3-(2-ethoxy-2-oxoethyl)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3n**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.27 (s, 1H), 5.93 (s, 1H), 5.77−5.67 (m, 1H), 5.58 (s, 1H), 5.15 (s, 1H), 5.07 (s, 1H), 5.03−4.98 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.72 (s, 6H), 3.17 (s, 2H), 3.09 (d, J = 2.2 Hz, 2H), 2.94 (d, J = 6.1 Hz, 2H), 2.36 (dt, J = 40.2 Hz, 7.1 Hz, 4H), 1.94−1.88 (m, 5H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 172.0, 171.0, 150.8, 142.3, 142.1, 137.9, 135.2, 135.0, 130.0, 129.4, 128.7, 120.2, 116.2, 116.0, 63.7, 60.4, 52.8, 38.3, 37.2, 36.7, 36.2, 32.9, 23.4, 23.0, 14.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{27}H_{34}O_6Na$, 477.2248; found, 477.2249. Isolated yield: Method A, 75% (69 mg); Method B, 77% (71 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Dimethyl-(Z)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-2-vinylhexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3o**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.64 (dd, J = 17.1 Hz, 10.5 Hz, 1H), 6.13 (s, 1H), 6.02 (s, 1H), 5.74−5.63 (m, 1H), 5.20−5.13 (m, 4H), 5.03 (d, J = 6.1 Hz, 1H), 5.00 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.71 (s, 6H), 3.25 (s, 2H), 2.98−2.96 (m, 4H), 1.98 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 171.2, 170.9, 149.1, 144.0, 137.6, 135.2, 134.9, 132.3, 130.4, 129.6, 119.3, 116.8, 116.6, 116.4, 63.3, 60.7, 52.8, 39.3, 37.1, 36.5, 22.9, 14.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{30}O_6Na$, 437.1940; found, 437.1931. Isolated yield: Method A, 61% (50 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Dimethyl-(Z)-4-((2Z,5E)-3-(ethoxycarbonyl)-2-(prop-1-en-2-yl)-octa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3p**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.21 (t, J = 7.1 Hz, 2H), 6.03 (s, 1H), 5.52−5.45 (m, 1H), 5.37−5.30 (m, 1H), 5.19 (pent, J = 1.4 Hz, 1H), 5.07 (s, 1H), 4.95 (pent, J = 1.6 Hz, 1H), 4.87 (dd, J = 1.0 Hz, 1.9 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.73 (s, 6H), 3.22 (d, J = 2.2 Hz, 2H), 3.01 (d, J = 6.1 Hz, 2H), 1.95−1.93 (m, 8H), 1.23 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.7, 170.1, 151.0, 145.7, 145.5, 143.7, 137.7, 134.0, 130.9, 130.3, 124.4, 118.5, 116.6, 115.2, 64.0, 60.3, 52.9, 37.0, 33.4, 25.5, 23.0, 22.7, 13.9, 13.7; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{26}H_{34}O_6Na$, 465.2248; found, 465.2239. Isolated yield: Method A, 76% (67 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 7:93).

*Dimethyl-(Z)-4-((2Z,5E)-3-(ethoxycarbonyl)-6-phenyl-2-(prop-1-en-2-yl)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3q**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33−7.18 (m, 5H), 6.40 (d, J = 15.8 Hz, 1H), 6.27 (s, 1H), 6.18−6.10 (m, 1H), 6.05 (s, 1H), 5.22−5.20 (m, 1H), 5.09 (s, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.72 (s, 6H), 3.26−3.23 (m, 4H), 1.96 (s, 6H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.7, 169.9, 150.9, 146.0, 145.6, 144.9, 137.7, 137.4, 131.3, 130.6, 129.8, 128.4, 127.0, 126.2, 126.1, 118.4, 116.7, 115.2, 64.0, 60.4, 52.9, 37.1, 33.8, 23.1, 22.7, 13.8; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{30}H_{34}O_6Na$, 513.2253; found, 513.2260. Isolated yield: Method A, 57% (56 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Dimethyl-(Z)-4-((Z)-3-(ethoxycarbonyl)-6-methyl-2-(prop-1-en-2-yl)hepta-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3r**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.20 (t, J = 2.2 Hz, 1H), 6.02 (s, 1H), 5.19−5.17 (m, 1H), 5.07−5.04 (m, 2H), 4.93 (s, 1H), 4.86 (s, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.73 (s, 6H), 3.21 (d, J = 2.2 Hz, 2H), 3.01 (d, J = 6.9 Hz, 2H), 1.92 (d, J = 12.5 Hz, 6H), 1.66 (s, 3H), 1.60 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.7, 170.2, 150.9, 145.7, 145.3, 142.9, 137.7, 133.1, 131.6, 130.2, 120.2, 118.5, 116.6, 115.2, 63.9, 60.2, 52.9, 37.0, 29.4, 25.6, 23.0, 22.6, 17.8, 13.8; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{26}H_{34}O_6Na$, 465.2253; found, 465.2238. Isolated yield: Method A, 71% (63 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Dimethyl-(Z)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-5-methyl-2-(prop-1-en-2-yl)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3s**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.26 (s, 1H), 5.94 (s, 1H), 5.16−5.12 (m, 2H), 5.06 (s, 1H), 4.87 (s, 1H), 4.76 (s, 1H), 4.66 (s, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.72 (s, 6H), 3.21 (d, J = 2.1 Hz, 2H), 3.19 (s, 2H), 2.90 (s, 2H), 1.93 (s, 3H), 1.84 (s, 3H), 1.65 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 172.0, 171.0, 151.2, 144.4, 142.7, 142.2, 140.6, 138.0, 129.0, 128.7, 119.8, 116.2, 115.9, 111.7, 63.9, 60.4, 52.8, 40.4, 38.0, 36.9, 23.3, 23.1, 22.3, 14.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{26}H_{34}O_6Na$, 465.2248; found, 465.2240. Isolated yield: Method A, 80% (71 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

*Dimethyl-(Z)-4-((E)-3-allyl-2-(prop-1-en-2-yl)hept-2-en-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3t**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.26 (s, 1H), 5.89 (s, 1H), 5.77−5.67 (m, 1H), 5.15 (s, 1H), 5.08 (s, 1H), 5.06 (s, 1H), 5.03−4.96 (m, 2H), 4.80 (s, 1H), 3.72 (s, 6H), 3.21 (d, J = 2.1 Hz, 2H), 2.86 (d, J = 6.1 Hz, 2H), 2.13−2.09 (m, 2H), 1.93 (s, 3H), 1.84 (s, 3H), 1.36−1.27 (m, 5H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 171.2, 151.7, 144.7, 140.3, 138.2, 137.5, 136.5, 136.1, 127.7, 120.5, 116.2, 115.1, 63.9, 52.8, 36.9, 36.0, 32.9, 31.5, 23.9, 23.2, 23.0, 13.9; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{34}O_4Na$, 421.2349; found, 421.2353. Isolated yield: Method A, 80% (64 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 3:97).

*Dimethyl-(Z)-4-((Z)-3-phenyl-2-(prop-1-en-2-yl)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3u**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27−7.15 (m, 10H), 6.42 (t, J = 2.2 Hz, 1H), 5.98 (s, 1H), 5.91 (t, J = 2.2 Hz, 1H), 5.83 (s, 1H), 5.74−5.65 (m, 2H), 5.21 (s, 2H), 5.15 (s, 2H), 4.90−4.85 (m, 6H), 4.73 (s, 1H), 4.70 (s, 1H), 3.73 (d, J = 4.8 Hz, 12H), 3.27−3.20 (m, 8H), 1.98 (d, J = 14.8 Hz, 6H), 1.65 (d, J = 17.4 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 171.1, 171.0, 152.0, 151.2, 144.4, 143.9, 143.1, 142.5, 141.6, 140.3, 139.0, 138.4, 138.0, 137.8, 137.5, 136.7, 135.0, 129.4, 128.7, 128.6, 127.8, 127.6, 127.5, 126.6, 126.3, 121.9, 121.2, 117.9, 116.3, 116.0, 115.9, 115.5, 115.4, 63.9, 63.9, 52.8, 52.8, 39.7, 39.4, 37.1, 36.8, 23.8, 23.5, 23.1, 22.8; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{27}H_{30}O_4Na$, 441.2036; found, 441.2034. Isolated yield: Method A, 60% (50 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 3:97).

*Dimethy-(Z)-4-((Z)-3-(2-hydroxyethyl)-2-(prop-1-en-2-yl)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**3v**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.27 (s, 1H), 5.93 (s, 1H), 5.81−5.71 (m, 1H), 5.17 (s, 1H), 5.13 (s, 1H), 5.06−5.01 (m, 3H), 4.84 (s, 1H), 4.45 (s, 1H), 3.73 (s, 6H), 3.67 (q, J = 7.1 Hz, 2H), 3.22 (d, J = 2.1 Hz, 2H), 2.91 (d, J = 6.1 Hz, 2H), 2.46 (t, J = 7.1 Hz, 2H), 1.94 (s, 3H), 1.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 171.1, 151.6, 149.4, 144.5, 141.3, 139.4, 138.1, 135.8, 132.6, 128.4, 119.9, 116.3, 116.1, 115.8, 115.6, 63.9, 61.8, 52.9, 36.9, 36.6, 36.2, 24.0, 23.2; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{23}H_{30}O_5Na$, 409.1985; found, 409.1986. Isolated yield: Method A, 63% (49 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 10:90).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00186.

General preparation of starting materials, mechanistic study, kinetic isotope effect (KIE) experiments, and ^{1}H/^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Veluru Ramesh Naidu − *Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden; Department of Natural Sciences, Mid Sweden University, SE-851 79 Sundsvall, Sweden;* Email: rnchem@gmail.com

Jan-E. Bäckvall − *Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden; Department of Natural Sciences, Mid Sweden University,*

https://dx.doi.org/10.1021/acs.joc.0c00186
J. Org. Chem. 2020, 85, 5428−5437

SE-851 79 Sundsvall, Sweden; orcid.org/0000-0001-8462-4176; Email: jeb@organ.su.se

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c00186

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Swedish Research Council (2016-03897), the European Union, and the Olle Engqvist Foundation is gratefully acknowledged.

■ REFERENCES

(1) For reviews on allene reactions, see: (a) Lechel, T.; Pfrengle, F.; Reissig, H.-U.; Zimmer, R. Three Carbons for Complexity! Recent Developments of Palladium-Catalyzed Reactions of Allenes. *ChemCatChem* **2013**, *5*, 2100−2130. (b) Yu, S.; Ma, S. Allenes in catalytic asymmetric synthesis and natural product syntheses. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074−3112. (c) Krause, N.; Winter, C. Gold-Catalyzed Nucleophilic Cyclization of Functionalized Allenes: A Powerful Access to Carbo- and Heterocycles. *Chem. Rev.* **2011**, *111*, 1994−2001. (d) Ye, J. T.; Ma, S. Palladium-Catalyzed Cyclization Reactions of Allenes in the Presence of Unsaturated Carbon-Carbon Bonds. *Acc. Chem. Res.* **2014**, *47*, 989−1000. (e) Lledo, A.; Pla-Quintana, A.; Roglans, A. Allenes, versatile unsaturated motifs in transition-metal-catalysed [2 + 2+2] cycloaddition reactions. *Chem. Soc. Rev.* **2016**, *45*, 2010−2023. (f) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocarnola, S. C-C, C-O, C-N Bond Formation on sp^2 Carbon by Pd(II)-Catalyzed Reactions Involving Oxidant Agents. *Chem. Rev.* **2007**, *107*, 5318−5365. (g) Hong, X.; Stevens, M. C.; Liu, P.; Wender, P. A.; Houk, K. N. Reactivity and Chemoselectivity of Allenes in Rh(I)-Catalyzed Intermolecular (5 + 2) Cycloadditions with Vinylcyclopropanes: Allene-Mediated Rhodacycle Formation Can Poison Rh(I)- Catalyzed Cycloadditions. *J. Am. Chem. Soc.* **2014**, *136*, 17273−17283. (h) Yang, B.; Qiu, Y.; Bäckvall, J.-E. Control of Selectivity in Palladium(II)-Catalyzed Oxidative Transformations of Allenes. *Acc. Chem. Res.* **2018**, *51*, 1520−1531.

(2) For polyenes, see: (a) Woerly, E. M.; Roy, J.; Burke, M. D. Synthesis of most polyene natural product motifs using just 12 building blocks and one coupling reaction. *Nat. Chem.* **2014**, *6*, 484−491. (b) Goodman, G. E.; Thornquist, M. D.; Balmes, J.; Cullen, M. R.; Meyskens, F. L.; Omenn, G. S.; Valanis, B.; Williams, J. H. The Beta-Carotene and Retinol Efficacy Trial: Incidence of Lung Cancer and Cardiovascular Disease Mortality During 6-Year Follow-up After Stopping *β*-Carotene and Retinol Supplements. *J. Natl. Cancer Inst.* **2004**, *96*, 1743−1750.

(3) (a) Hopf, H. Forgotten hydrocarbons prepared. *Nature* **2009**, *460*, 183−184. (b) Hopf, H.; Sherburn, M. S. Dendralenes Branch Out: Cross-Conjugated Oligoenes Allow the Rapid Generation of Molecular Complexity. *Angew. Chem., Int. Ed.* **2012**, *51*, 2298−2338. (c) Wang, H.; Beiring, B.; Yu, D.; Collins, K. D.; Glorius, F. [3]Dendralene Synthesis: Rhodium(III)- Catalyzed Alkenyl C-H Activation and Coupling Reaction with Allenyl Carbinol Carbonate. *Angew. Chem., Int. Ed.* **2013**, *52*, 12430−12434. (d) Qiu, Y.-A.; Posevins, D.; Bäckvall, J.-E. Selective Palladium-Catalyzed Allenic C-H Bond Oxidation for the Synthesis of [3]Dendralenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 13112−13116. (e) George, J.; Ward, J. S.; Sherburn, M. S. A General Synthesis of Dendralenes. *Chem. Sci.* **2019**, *10*, 9969−9973. (f) Horvath, K. L.; Newton, C. G.; Roper, K. A.; Ward, J. S.; Sherburn, M. S. A Broad-Spectrum Synthesis of Tetravinylethylenes. *Chem. - Eur. J.* **2019**, *25*, 4072−4076.

(4) Sherburn, M. S. Preparation and Synthetic Value of *π*-Bond-Rich Branched Hydrocarbons. *Acc. Chem. Res.* **2015**, *48*, 1961−1967.

(5) (a) Lindeboom, E. J.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. Tetravinylethylene. *Angew. Chem., Int. Ed.* **2014**, *53*, 5440−5443. (b) Saglam, M. F.; Alborzi, A. R.; Payne, A. D.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. Synthesis and Diels-Alder Reactivity of Substituted [4]Dendralenes. *J. Org. Chem.* **2016**, *81*, 1461−1475. (c) Naidu, G. S.; Singh, R.; Kumar, M.; Ghosh, S. K. Tuning the Stability and the Reactivity of Substituted [3]Dendralenes for Quick Access to Diverse Copiously Functionalized Fused Polycycles with Step and Atom Economy. *J. Org. Chem.* **2017**, *82*, 3648−3658.

(6) Bojase, G.; Nguyen, T. V.; Payne, A. D.; Willis, A. C.; Sherburn, M. S. Synthesis and properties of the ivyanes: the parent 1,1-oligocyclopropanes. *Chem. Sci.* **2011**, *2*, 229−232.

(7) Rieder, C. J.; Winberg, K. J.; West, F. G. Cyclization of Cross-Conjugated Trienes: The Vinylogous Nazarov Reaction. *J. Am. Chem. Soc.* **2009**, *131*, 7504−7505.

(8) Green, N. J.; Lawrence, A. L.; Bojase, G.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. Domino cycloaddition organocascades of dendralenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 8333−8336.

(9) (a) Mao, M.; Zhang, L.; Chen, Y.-Z.; Zhu, J.; Wu, L. Palladium-Catalyzed Coupling of Allenylphosphine Oxides with N-Tosylhydrazones toward Phosphinyl [3]Dendralenes. *ACS Catal.* **2017**, *7*, 181−185. (b) Toombs-Ruane, H.; Osinski, N.; Fallon, T.; Wills, C.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. Synthesis and Applications of Tricarbonyliron Complexes of Dendralenes. *Chem. - Asian J.* **2011**, *6*, 3243−3250.

(10) Fielder, S.; Rowan, D. D.; Sherburn, M. S. First Synthesis of the Dendralene Family of Fundamental Hydrocarbons. *Angew. Chem., Int. Ed.* **2000**, *39*, 4331−4333.

(11) Shimizu, M.; Kurahashi, T.; Shimono, K.; Tanaka, K.; Nagao, I.; Kiyomoto, S.-I.; Hiyama, T. Facile Synthesis and Palladium-Catalyzed Cross-Coupling Reactions of 2,3- Bis(pinacolatoboryl)-1,3-butadiene. *Chem. - Asian J.* **2007**, *2*, 1400−1408.

(12) Bojase, G.; Payne, A. D.; Willis, A. C.; Sherburn, M. S. One-step synthesis and exploratory chemistry of [5]dendralene. *Angew. Chem., Int. Ed.* **2008**, *47*, 910−912.

(13) Lippincott, D. J.; Linstadt, R. T. H.; Maser, M. R.; Lipshutz, B. H. Synthesis of Functionalized [3]-, [4]-, [5]-, and [6]Dendralenes through Palladium-Catalyzed Cross-Couplings of Substituted Allenoates. *Angew. Chem., Int. Ed.* **2017**, *56*, 847−850.

(14) For a similar gold-catalyzed reaction, see: Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. Gold-Catalyzed Cycloisomerization of 1,5-Allenynes via Dual Activation of an Ene Reaction. *J. Am. Chem. Soc.* **2008**, *130*, 4517−4526.

(15) Zhu, C.; Yang, B.; Jiang, T.; Bäckvall, J.-E. Olefin-Directed Palladium-Catalyzed Regio- and Stereoselective Oxidative Arylation of Allenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 9066−9069.

(16) For aerobic biomimetic palladium-catalyzed oxidations, see: (a) Piera, J.; Bäckvall, J.-E. Catalytic Oxidation of Organic Substrates by Molecular Oxygen and Hydrogen Peroxide by Multistep Electron Transfer-A Biomimetic Approach. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506−3523. (b) Bäckvall, J.-E.; Hopkins, R. B.; Grennberg, H.; Mader, M.; Awasthi, A. K. Multistep electron transfer in palladium-catalyzed aerobic oxidations via a metal macrocycle quinone system. *J. Am. Chem. Soc.* **1990**, *112*, 5160−5166. (c) Piera, J.; Närhi, K.; Bäckvall, J.-E. Pd(II)- Catalyzed Aerobic Allylic Oxidative Carbocyclization of Allene-Substituted Olefins: Immobilization of an Oxygen- Activating Catalyst. *Angew. Chem., Int. Ed.* **2006**, *45*, 6914−6917. (d) Johnston, E. V.; Karlsson, E. A.; Lindberg, S. A.; Åkermark, B.; Bäckvall, J.-E. Efficient Reoxidation of Palladium by a Hybrid Catalyst in Aerobic Palladium-Catalyzed Carbocyclization of Enallenes. *Chem. - Eur. J.* **2009**, *15*, 6799−6801. (e) Naidu, V. R.; Posevins, D.; Volla, C. M. R.; Bäckvall, J.-E. Selective Cascade Reaction of Bisallenes via Palladium-Catalyzed Aerobic Oxidative Carbocyclization-Borylation and Aldehyde Trapping. *Angew. Chem., Int. Ed.* **2017**, *56*, 1590−1594.

(17) For direct reoxidation of Pd(0) by O_2, in palladium-catalyzed oxidations, see: (a) Stahl, S. S. Palladium oxidase catalysis: selective oxidation of organic chemicals by direct dioxygen-coupled turnover. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. Oxidative Cyclizations in a Nonpolar Solvent Using Molecular Oxygen and Studies on the Stereochemistry of Oxypalladation. *J. Am. Chem. Soc.* **2005**, *127*, 17778−17788. (c) Zhang,

Y. H.; Yu, J. Q. Pd(II)-Catalyzed Hydroxylation of Arenes with 1 atm of O2 or Air. *J. Am. Chem. Soc.* **2009**, *131*, 14654−14655.
(18) For allenyne and enallene, see: (a) Deng, Y.; Bäckvall, J.-E. Palladium-Catalyzed Oxidative Acyloxylation/Carbocyclization of Allenynes. *Angew. Chem., Int. Ed.* **2013**, *52*, 3217−3221. (b) Bartholomeyzik, T.; Pendrill, R.; Lihammar, R.; Jiang, T.; Widmalm, G.; Bäckvall, J.-E. Kinetics and Mechanism of the Palladium-Catalyzed Oxidative Arylating Carbocyclization of Allenynes. *J. Am. Chem. Soc.* **2018**, *140*, 298−309. (c) Qiu, Y.; Yang, B.; Zhu, C.; Bäckvall, J.-E. Palladium-Catalyzed Oxidative Carbocyclization-Borylation of Enallenes to Cyclobutenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 6520−6524.
(19) In experiment where an enallene and an allenyne in a 1:1 ratio were allowed to compete with one another in the activation by palladium(II) it was shown that the enallene reacts faster than the allenyne. These studies involved Pd-catalyzed coupling of the competing substrates with B_2pin_2 or $PhB(OH)_2$ (see Supporting Information).
(20) Deng, Y.; Bartholomeyzik, T.; Persson, A. K. Å.; Sun, J.; Bäckvall, J.-E. Palladium-Catalyzed Oxidative Arylating Carbocyclization of Allenynes. *Angew. Chem., Int. Ed.* **2012**, *51*, 2703−2707.
(21) Pardo-Rodríguez, V.; Marco-Martínez, J.; Buñuel, E.; Cárdenas, D. J. Pd-Catalyzed Borylative Cyclization of Allenynes and Enallenes. *Org. Lett.* **2009**, *11*, 4548−4551.
(22) (a) Zhu, C.; Yang, B.; Bäckvall, J.-E. Highly Selective Cascade C-C Bond Formation via Palladium-Catalyzed Oxidative Carbonylation-Carbocyclization-Carbonylation-Alkynylation of Enallenes. *J. Am. Chem. Soc.* **2015**, *137*, 11868−11871. (b) Zhang, H.; Fu, X.; Chen, J.; Wang, E.; Liu, Y.; Li, Y. Generation of Allenic/Propargylic Zirconium Complexes and Subsequent Cross-Coupling Reactions: A Facile Synthesis of Multisubstituted Allenes. *J. Org. Chem.* **2009**, *74*, 9351−9358. (c) Kessler, S. N.; Bäckvall, J.-E. Iron-catalyzed Cross-Coupling of Propargyl Carboxylates and Grignard Reagents: Synthesis of Substituted Allenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 3734−3738.

https://dx.doi.org/10.1021/acs.joc.0c00186
J. Org. Chem. 2020, 85, 5428−5437