Synthesis of Phthalides and 3,4-Dihydroisocoumarins Using the Palladium-Catalyzed Intramolecular Benzannulation Strategy

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A novel method for the synthesis of phthalides and 3,4-dihydroisocoumarins via the palladium-catalyzed *intramolecular* benzannulation of bis-enyne and enyne−diyne systems is described. Various kinds of substituted phthalides **9** and **17** and 3,4-dihydroisocoumarins **19** were synthesized from **8**, **16**, and **18**, respectively, in moderate to excellent yields. The benzannulation reaction proceeded chemoselectively to give the corresponding fused ring compounds **A** without the formation of the regioisomeric products **B** (eq 6). Furthermore, this methodology was applied to the synthesis of biologically active 3-*n*-butylphthalide **23**.

Introduction

Phthalides and 3,4-dihydroisocoumarins are a class of naturally occurring substances exhibiting biological activities.[1,2] They are also attractive intermediates for the synthesis of more complex heterocyclic[3] and carbocyclic[4] compounds, various drugs,[5] and naturally occurring compounds.[6] Although various methods have been developed for the synthesis of phthalides and dihydroisocoumarins, only a limited number of papers are known for the construction of phthalide and dihydroisocoumarin skeletons from acyclic, acetylenic compounds in a one-step procedure.[7−10] For example, the Alder−Rickert reaction,[7] nickel-catalyzed[8] or mediated[9] [2 + 2 + 2] cocyclization of alkyne moieties, and rhodium-catalyzed carbocyclization reaction of diazocarbonyl with tethered alkynes[10] are known as a one-step synthetic procedure. Recently, we reported an efficient method for the construction of benzene rings using palladium-catalyzed *intermolecular homo*-benzannulation reaction of 2-substituted conjugated enynes (eq 1).[11] This reaction was extended to the *intermolecular* enyne−diyne [4 + 2] *cross*-benzannulation for the synthesis of polysubstituted benzenes.[12] We also found that, in the palladium-catalyzed benzannulation, electron-deficient enynes bearing an electron-withdrawing group at the C1 or C2 position exhibit higher reactivity than electron-rich enynes bearing an alkyl or aryl group at the C1 or C2 position, and by applying this finding we were successful in preparing polysubstituted benzenes easily from 1-substituted enynes as well as 1,2- and 2,4-disubstituted enynes.[13] Moreover, we reported the synthesis of carbon-tethered[14] exomethylene paracyclophanes and crown-ether-like cyclophanes[15] via an *intramolecular* palladium-catalyzed *homo*-benzannulation of bis-enynes (eq 2). Synthesis of ortho-, meta-, and paracyclophanes was also achieved via an *intermolecular* palladium-catalyzed enyne-diyne *cross*-benzannulation approach.[16] The palladium-catalyzed benzannulation methodology was applied further to the synthesis of many functionalized benzenes

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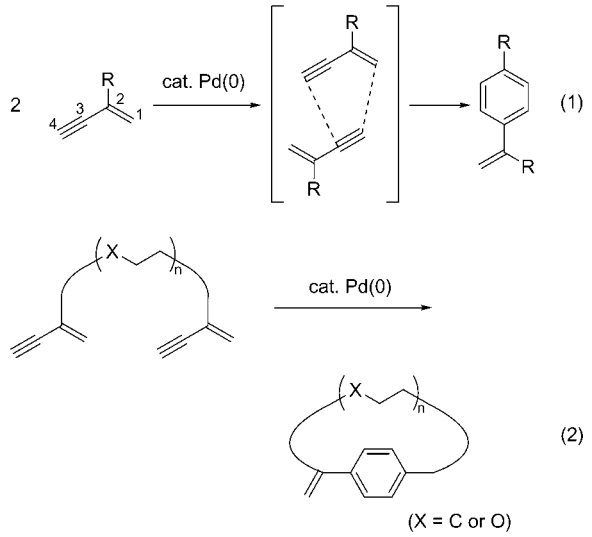
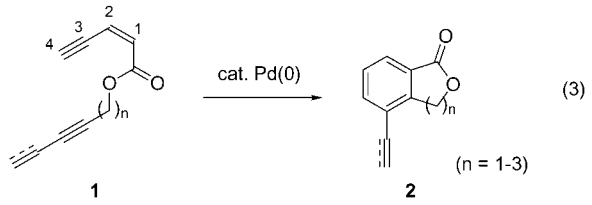
such as phenols[17] and polysubstituted alkoxycarbonyl- or cyanostyrenes.[18] A not only synthetically important but also mechanistically interesting aspect of the [4 + 2] benzannulation reaction lies in the high regio- and chemoselectivity for the annulation.[19]



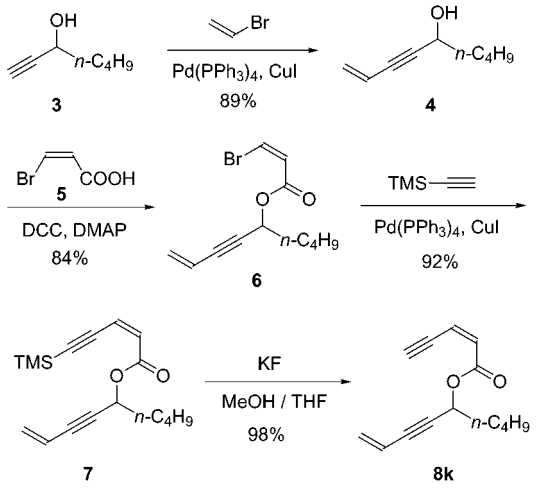
As a further development of these benzannulation reactions, we attempted to synthesize fused rings using the *intramolecular* benzannulation strategy. In this paper, we report a new route for the synthesis of fused rings **2**, such as phthalides and dihydroisocoumarins, via the palladium-catalyzed one-step benzannulation reaction of enyne esters **1**, in which ester group is attached at the C1 position of enyne functionality (eq 3).



Results and Discussion

Preparation of Bis-enynes and Enyne−Diynes. The bis-enyne **8k** was prepared in four steps from commercially available 1-heptyn-3-ol **3** (Scheme 1). The enyne **4** was synthesized by the Sonogashira coupling of **3** with vinyl bromide.[20] Treatment of **4** with (*Z*)-3-bromo-2-propenoic acid **5**[21] in the presence of DCC−DMAP gave the ester **6** in 84% yield. The Sonogashira coupling of this ester with (trimethylsilyl)acetylene gave the protected bis-enyne **7**. Deprotection with KF−MeOH/THF produced the bis-enyne **8k**. Other bis-enynes **8a**−**j**, **18a**−**d**, and **20** and enyne−diynes **16a**,**b** were prepared by a method similar to that shown in Scheme 1, and detailed procedures are mentioned in the Supporting Information.

Scheme 1. Representative Procedure for the Synthesis of Bis-enyne Esters



Synthesis of Phthalides. The unsubstituted bis-enyne **8a** reacted in the presence of a catalytic amount of $Pd(PPh_3)_4$ (40 mol %) and DPPF (80 mol %) to give 4-vinylphthalide **9a** in a moderate yield (Table 1, entry 1). The reaction proceeded smoothly, and no trace amount of regioisomeric fused ring was detected in the reaction mixture. However, a trace amount of 4-phenylfuran-2(5*H*)-one **10a** was obtained as a byproduct.[22] When the reaction of **8a** was carried out under more concentrated conditions (toluene, 30 mM), the *intermolecular* dimerization was accompanied by the desired *intramolecular* annulation. As mentioned above, usually high catalyst loading (40 mol %) was employed to obtain a higher yield of **9a**. When 5 mol % or 10 mol % of $Pd(PPh_3)_4$ was used, **9a** was obtained in 14% or 43% yield, respectively. To obtain the phthalide **9a** efficiently, it was necessary to carry out the reaction of the bis-enyne **8a** under a highly diluted condition (toluene, 2.5 mM), and the bis-enyne should be added slowly (over a period of 3 h) to a toluene solution containing palladium catalyst. The reaction of the alkyl- and aryl-substituted bis-enynes **8b** and **8c** gave the corresponding phthalides **9b** and **9c**, respectively, in high to acceptable yields, though a higher temperature (100 °C) was needed in the reaction of the phenyl-substituted bis-enyne **8c** (Table 1, entries 2 and 3). The bis-enyne **8d** with propargyl alcohol moiety underwent the benzannulation reaction in a manner similar to give the hydroxy-substituted phthalide **9d** in 49% yield (Table 1, entry 4). The bis-enynes **8e** and **8f**, substituted with a methyl group at the R^2 position, reacted smoothly (Table 1, entries 5 and 6). Since electron-deficient enynes are more reactive than alkyl-substituted enynes in the [4 + 2] benzannulation,[13] we also carried out the reaction of the bis-enynes substituted by an electron-withdrawing group (Table 1, entries 7−9). The bis-enynes **8g** and **8h** substituted by (*Z*)-ester at the R^3 position gave the phthalides **9g** and **9h**, respectively, irrespective of the presence or absence of propyl group at R^1 position (Table 1, entries 7 and 8). The bis-enyne **8i** substituted by (*E*)-C_6F_{13} group at the R^4 position also gave the corresponding

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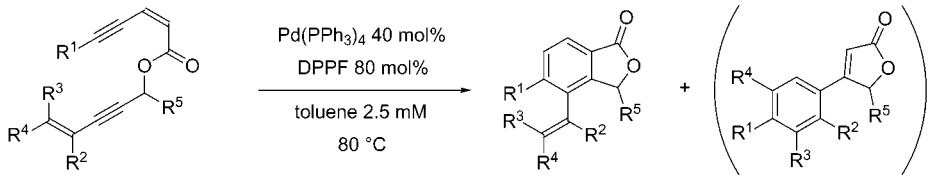
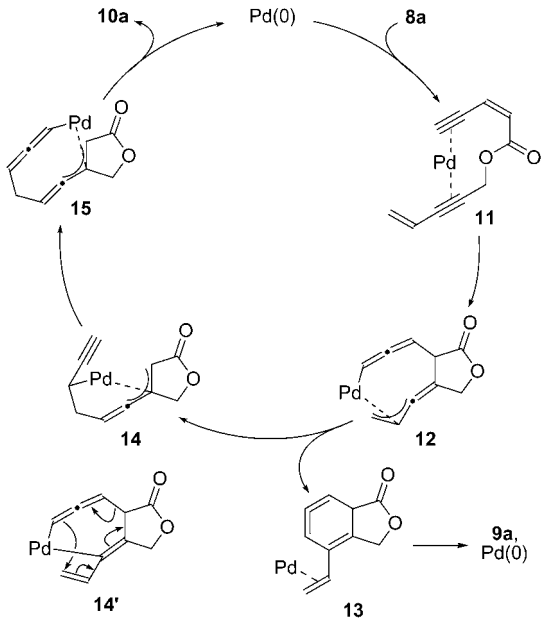
Table 1. Synthesis of Phthalides



entry	enyne	R^1	R^2	R^3	R^4	R^5	reaction time[a] (h)	product	yield[b] (%)
1[c]	**8a**	H	H	H	H	H	0.5	**9a**	53
2	**8b**	*n*-C_6H_{13}	H	H	H	H	1.0	**9b**	81
3[d]	**8c**	Ph	H	H	H	H	18	**9c**	38
4	**8d**	CH_2OH	H	H	H	H	0.5	**9d**	49
5	**8e**	H	CH_3	H	H	H	0.5	**9e**	67
6	**8f**	*n*-C_3H_7	CH_3	H	H	H	7	**9f**	43
7[c]	**8g**	H	H	CO_2CH_3	H	H	0.5	**9g**	57
8	**8h**	*n*-C_3H_7	H	CO_2CH_3	H	H	0.5	**9h**	79
9[e]	**8i**	*n*-C_3H_7	H	H	*n*-C_6F_{13}	H	1.5	**9i**	46
10[c]	**8j**	H	H	H	H	Ph	0.5	**9j**	47
11[c]	**8k**	H	H	H	H	*n*-C_4H_9	0.5	**9k**	54

[a] Bis-enynes **8** were added to a toluene solution containing palladium catalyst over a period of 3 h, and then the mixture was stirred at 80 °C for the indicated time. [b] Isolated yields. [c] A trace amount of the rearranged product **10** was obtained. [d] The bis-enyne **8c** was added to a toluene solution of palladium catalyst over a period of 1 h. [e] The bis-enyne **8i** was added over a period of 1 h, and the reaction was carried out at 100 °C.

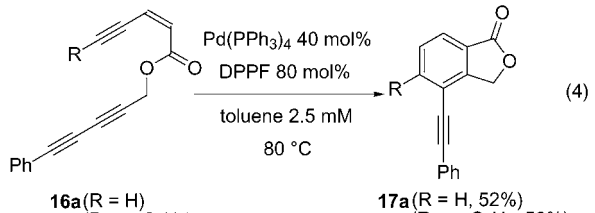
Scheme 2. Proposed Mechanism for the Formation of 10



phthalide **9i** in 46% yield, though a rather higher temperature (100 °C) was needed (Table 1, entry 9). This observation is in agreement with the previous finding that (*Z*)-substituted enynes are in general more reactive than (*E*)-isomers in the palladium-catalyzed benzannulation of enynes.[13] 3-Phenyl- and *n*-butyl-substituted phthalides **9j** and **9k** were prepared from the bis-enynes **8j** and **8k**, respectively, in a similar manner (Table 1, entries 10 and 11). It should be noted that, in entries 1, 7, 10, and 11, trace amounts of the rearranged products **10a**,**g**,**j**,**k** were observed, although in entries 7 and 10 the structural identification of **10g** and **10j** was not unambiguous due to very trace amounts of formation of those products.

Although the rearranged products **10** were obtained only in trace amounts, a mechanistic consideration on the formation of this interesting product seems to be worth mentioning. A proposed mechanism is shown in Scheme 2. The coordination of Pd(0) to alkyne moiety of the bis-enyne **8a** would give the palladacycle **12** through **11**.[12] The reductive elimination of Pd(0) from this complex, as usually observed in the previous benzannulation reactions,[19] must give the phthalide **9a**. Actually, this was observed as apparent from the results of Table 1. On the other hand, the propargylpalladium complex **14** would be formed through the bond reorganization from **12**. To better understand this process, arrows for bond migration are shown in **14′**. Further migration from **14** would lead the formation of the allenylpalladium complex **15**, which would give 4-phenylfuran-2(5*H*)-one **10a** upon reductive elimination of Pd(0).

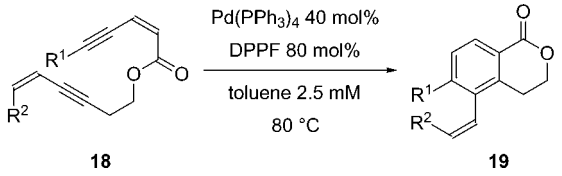
To extend this *intramolecular* benzannulation protocol for the synthesis of fused rings, we investigated the reaction of the enyne−diyne system as shown in eq 4. The reaction of **16a** and **16b** proceeded smoothly under the similar conditions as above to give the corresponding phthalides **17a** and **17b**, respectively, in moderate yields.



(4)

Synthesis of 3,4-Dihydroisocoumarins. The synthesis of 3,4-dihydroisocoumarins **19** was accomplished by the use of **18** as a starting substrate (Table 2). 5-Hexen-3-ynyl (*Z*)-2-buten-4-ynoate **18a** was transformed into 5-vinyl-3,4-dihydroisocoumarin **19a**; a small amount of dimeric aromatic product, which was formed via the *intermolecular* benzannulation reaction, was also obtained (Table 2, entry 1). Here also, the benzannulation reaction proceeded chemoselectively as observed in the formation of phthalides. *n*-Propyl- and phenyl-substituted bis-enynes at R^1 position **18b** and **18c** gave the corre-

Table 2. Synthesis of 3,4-Dihydroisocoumarins

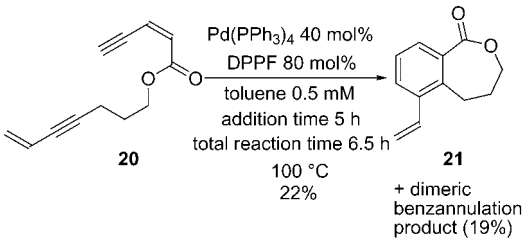


entry	bis-enyne	R^1	R^2	reaction time[a] (h)	product	yield[b] (%)
1[c]	**18a**	H	H	0.5	**19a**	65
2	**18b**	*n*-C_3H_7	H	17	**19b**	83
3[d]	**18c**	Ph	H	4.0	**19c**	90
4	**18d**	H	CO_2CH_3	0.5	**19d**	46

[a] Bis-enynes **18** were added to a toluene solution containing palladium catalyst over a period of 3 h, and then the mixture was stirred at 80 °C for the indicated time. [b] Isolated yields. [c] A trace amount of dimeric product was obtained. [d] The bis-enyne **18c** was added to a toluene solution of palladium catalyst over a period of 1 h, and the reaction was carried out at 100 °C.

sponding 3,4-dihydroisocoumarins **19b** and **19c**, respectively, in good yields (Table 2, entries 2 and 3). The ester-substituted bis-enyne **18d** also reacted smoothly under similar reaction conditions to give **19d** in 46% yield (Table 2, entry 4).

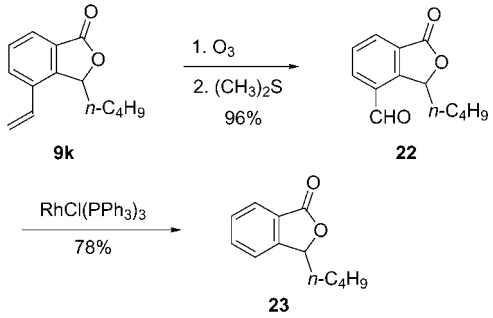
Synthesis of Seven-Membered Ring Skeleton. Since we were successful in synthesizing five- and six-membered ring skeletons, we next attempted to synthesize a seven-membered fused ring. The reaction of 6-hepten-4-ynyl (*Z*)-2-buten-4-ynoate **20** with $Pd(PPh_3)_4$ catalyst was carried out under similar conditions, Pd-$(PPh_3)_4$ (40 mol %) and DPPF (80 mol %) in toluene (2.5 mM). However, only a trace amount of the desired seven-membered ring product **21** was obtained, and the dimeric benzannulation adduct was obtained as a major product. After many optimizations, we could synthesize the seven-membered ring product **21** in 22% yield under highly diluted conditions (0.5 mM) at 100 °C (eq 5). However, even under these conditions, the dimeric product was obtained in 19% yield.



(5)

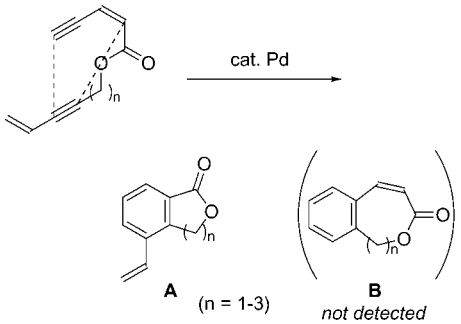
Application to the Synthesis of Biologically Active 3-*n*-Butylphthalide. Phthalides possess a wide range of biological activity. For instance, 3-*n*-butylphthalide, which is a constituent of celery seed oil,[23] is used for seasoning and flavoring purposes, shows anticonvulsant action,[24] increases the duration of anesthesia,[25] and exhibits cerebral antiischemic action.[26] Since both chiral and racemic 3-*n*-butylphthalide have many kinds of biological activity, we became interested in the synthesis of this compound via the palladium-catalyzed benzannulation reaction. As mentioned in Table 1, entry 11, 3-butyl-4-vinylphthalide **9k** was obtained in a moderate yield. Starting from 3-butyl-4-vinylphthalide **9k**, 3-*n*-butylphthalide **23** could be synthesized in two steps (Scheme 3). The ozonolysis of **9k** followed by the decarbonylation of the product **22** with $RhCl(PPh_3)_3$ gave **23** in 75% yield in two steps.

Scheme 3. Synthesis of 3-*n*-Butylphthalide 23



Conclusions

We have accomplished a new synthetic route for the construction of fused rings such as phthalides and 3,4-dihydroisocoumarins via the palladium-catalyzed benzannulation of bis-enyne and enyne−diyne systems. It should be noted that the fused ring formation proceeds in completely chemoselective manner. That is, the enyne attached to the ester-carbonyl group reacted as a four-carbon unit and the enyne (or diyne) attached to ester-oxygen group reacted as a two carbon unit in the [4 + 2] benzannulation reaction, and in all cases the type **A** fused ring was obtained (eq 6). No trace amount of the type **B** fused ring, arising from the reaction between the alkyne moiety attached to ester-carbonyl group as a two-carbon unit and the enyne moiety attached to ester-oxygen group as a four-carbon unit, was detected (eq 6).



(6)

Experimental Section

Palladium-Catalyzed Benzannulation of Bis-Enynes 8. A Representative Procedure. A mixture of $Pd(PPh_3)_4$ (230 mg, 0.20 mmol) and DPPF (220 mg, 0.40 mmol) in dry toluene (195 mL) in a 300 mL flask was kept at 80 °C. To this mixture was slowly added a toluene (5 mL) solution of **8a** (80 mg, 0.50 mmol) for 3 h with a syringe pump. After the mixture was stirred for an additional 30 min, toluene was evaporated and the resulting mixture was passed through a short silica gel column chromatography (hexane and Et_2O). The residue was further purified by silica gel column chromatography (hexane/AcOEt = 10:1) to give **9a** (42 mg, 53%).

4-Vinylphthalide (9a): yellow solid; mp 54.3−55.4 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.51 (dd, J = 7.6, 7.6 Hz, 1H), 6.69 (dd, J =

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(26) Wang, X. W. *Drugs Future* **2000**, *25*, 16−23.

17.7, 11.3 Hz, 1H), 5.66 (d, J = 17.8 Hz, 1H), 5.50 (d, J = 11.4 Hz, 1H), 5.38 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 143.7, 132.6, 132.5, 131.7, 129.5, 126.1, 124.9, 118.3, 69.5; IR (KBr) 3090, 2976, 2957, 2926, 1753, 1655, 1630, 1483, 1364, 1315, 1254, 1061, 1016 cm^{-1}; HRMS calcd for $C_{10}H_8O_2$ 160.0524, found 160.0511.

5-Hexyl-4-vinylphthalide (9b): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 6.89 (dd, J = 17.8, 11.6 Hz, 1H), 5.59 (d, J = 11.5 Hz, 1H), 5.39 (d, J = 18.1 Hz, 1H), 5.34 (s, 2H), 2.74 (dd, J = 7.9, 7.9 Hz, 2H), 1.61−1.50 (m, 2H), 1.37−1.24 (m, 6H), 0.87 (dd, J = 6.8, 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 147.7, 144.9, 131.9, 131.6, 130.9, 124.4, 124.0, 119.7, 70.0, 33.7, 31.6, 30.8, 29.2, 22.5, 14.0; IR (neat) 3096, 3018, 2955, 2930, 2856, 1771, 1676, 1630, 1595, 1468, 1433, 1358, 1321, 1267, 1238, 1084, 1055, 1016 cm^{-1}; HRMS calcd for $C_{16}H_{20}O_2$ 244.1462, found 244.1454.

5-Phenyl-4-vinylphthalide (9c): yellow solid; mp 83.8−84.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.45−7.40 (m, 3H), 7.36−7.33 (m, 2H), 6.61 (dd, J = 18.0, 11.8 Hz, 1H), 5.49−5.45 (m, 3H), 5.38 (d, J = 18.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 147.0, 144.9, 139.4, 133.5, 131.6, 131.0, 129.7, 128.4, 128.1, 125.2, 124.4, 119.0, 70.3; IR (neat) 3105, 3061, 3020, 2957, 2928, 2856, 1763, 1655, 1626, 1593, 1460, 1448, 1425, 1362, 1267, 1072, 1045, 1011 cm^{-1}; HRMS calcd for $C_{16}H_{12}O_2$ 236.0837, found 236.0812.

5-Hydroxymethyl-4-vinylphthalide (9d): brown solid; mp 139.5−141.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 7.9 Hz, 1H), 6.90 (dd, J = 18.0, 11.6 Hz, 1H), 5.65 (d, J = 11.7 Hz, 1H), 5.47 (d, J = 17.9 Hz, 1H), 5.37 (s, 2H), 4.86 (d, J = 5.8 Hz, 2H), 1.80 (dd, J = 5.7, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 144.7, 144.4, 131.4, 130.8, 129.0, 125.4, 124.7, 120.9, 69.9, 62.7; IR (KBr) 3433, 3076, 3018, 2943, 2924, 2878, 2812, 1742, 1597, 1452, 1435, 1364, 1265, 1084, 1059, 1007 cm^{-1}; HRMS calcd for $C_{11}H_{10}O_3$ 190.0630, found 190.0621.

4-(1-Methylvinyl)phthalide (9e): brown solid; mp 52.1−52.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 7.3 Hz, 1H), 7.61 (dd, J = 7.6, 0.9 Hz, 1H), 7.51 (dd, J = 7.6, 7.6 Hz, 1H), 5.37 (s, 2H), 5.33 (m, 1H), 5.10 (s, 1H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 143.5, 141.1, 137.5, 132.0, 129.3, 126.1, 124.5, 116.4, 70.1, 22.8; IR (KBr) 3123, 3080, 3065, 2986, 2953, 2926, 1771, 1655, 1624, 1578, 1541, 1522, 1487, 1447, 1431, 1377, 1356, 1317, 1288, 1258, 1207, 1175, 1144, 1061, 1022 cm^{-1}; HRMS calcd for $C_{11}H_{10}O_2$ 174.0680, found 174.0662.

4-(1-Methylvinyl)-5-propylphthalide (9f): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.73 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 5.34 (dd, J = 1.5, 1.5 Hz, 1H), 5.16 (s, 2H), 4.89 (s, 1H), 2.66−2.61 (m, 2H), 1.68−1.58 (m, 2H), 1.55 (s, 3H), 0.95 (dd, J = 7.4, 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.5, 146.4, 145.0, 141.0, 137.8, 130.3, 124.0, 123.3, 116.9, 69.1, 34.8, 24.9, 23.6, 14.1; IR (neat) 3080, 3028, 2963, 2934, 2872, 1771, 1682, 1643, 1599, 1456, 1377, 1356, 1304, 1258, 1240, 1167, 1142, 1086, 1055, 1018 cm^{-1}; HRMS calcd for $C_{14}H_{16}O_2$ 216.1149, found 216.1156.

4-((*Z*)-2-Methoxycarbonyl-1-vinyl)phthalide (9g): white solid; mp 107.5−108.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.53 (dd, J = 7.6, 7.6 H, 1H), 6.95 (d, J = 12.1 Hz, 1H), 6.17 (d, J = 12.3 Hz, 1H), 5.25 (s, 2H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 165.4, 145.3, 138.0, 133.9, 130.3, 128.9, 125.7, 125.5, 123.2, 69.1, 51.7; IR (KBr) 3258, 3009, 2955, 2924, 2851, 1771, 1753, 1724, 1645, 1458, 1431, 1416, 1265, 1232, 1194, 1165, 1067, 1015 cm^{-1}. Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.95; H, 4.64.

4-((*Z*)-2-Methoxycarbonyl-1-vinyl)-5-propylphthalide (9h): red solid; mp 62.3−63.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.7 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.09 (d, J = 11.9 Hz, 1H), 6.23 (d, J = 11.9 Hz, 1H), 5.10 (s, 2H), 3.60 (s, 3H), 2.61 (dd, J = 7.8, 7.8 Hz, 2H), 1.64−1.51 (m, 2H), 0.92 (dd, J = 7.4, 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 165.1, 146.4, 145.4, 139.6, 130.1, 124.8, 124.2, 123.1, 69.3, 51.6, 35.6, 23.4, 13.8; IR (neat) 3067, 3030, 2961, 2874, 1771, 1728, 1639, 1601, 1456, 1439, 1396, 1358, 1294, 1265, 1221, 1205, 1175, 1090, 1059, 1022 cm^{-1}; HRMS calcd for $C_{15}H_{16}O_4$ 260.1048, found 260.1056.

4-((*E*)-3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-2-octenyl)-5-propylphthalide (9i): brown solid; mp 27.8−28.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.39 (ddd, J = 16.5, 2.3, 2.3 Hz, 1H), 5.90 (ddd, J = 16.3, 11.4, 11.4 Hz, 1H), 5.33 (s, 2H), 2.76 (dd, J = 7.8, 7.8 Hz, 2H), 1.62 (ddddd, J = 7.6, 7.6, 7.6, 7.6, 7.6 Hz, 2H), 0.97 (dd, J = 7.4, 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 148.8, 145.2 (dd, J_{C-F} = 1.2, 1.2 Hz), 134.9 (dd, J_{C-F} = 9.7, 9.7 Hz), 131.5, 127.6, 126.5, 124.6, 122.8−106.6 (m), 120.2 (dd, J_{C-F} = 23.4, 23.4 Hz), 69.3, 35.7, 24.2, 13.7; IR (KBr) 2968, 2941, 2880, 1759, 1366, 1321, 1302, 1271, 1238, 1200, 1144, 1111, 1067, 1026 cm^{-1}; HRMS calcd for $C_{19}H_{13}F_{13}O_2$ 520.0707, found 520.0734.

3-Phenyl-4-vinylphthalide (9j): white solid; mp 83.7−84.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.57 (dd, J = 7.7, 7.7 Hz, 1H), 7.36−7.31 (m, 3H), 7.19−7.16 (m, 2H), 6.43 (s, 1H), 6.37 (dd, J = 17.5, 11.1 Hz, 1H), 5.68 (d, J = 17.5 Hz, 1H), 5.22 (d, J = 10.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 145.7, 135.5, 133.4, 131.0, 130.5, 130.0, 129.6, 129.0, 128.2, 126.8, 124.7, 117.9, 83.0; IR (KBr) 3099, 3088, 3059, 3032, 1753, 1634, 1479, 1456, 1410, 1296, 1271, 1261, 1250, 1082 cm^{-1}. Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.32; H, 5.23.

3-Butyl-4-vinylphthalide (9k): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.48 (dd, J = 7.7, 7.7 Hz, 1H), 6.75 (dd, J = 17.4, 11.0 Hz, 1h), 5.79 (d, J = 17.5 Hz, 1H), 5.62 (dd, J = 8.0, 2.7 Hz, 1H), 5.47 (d, J = 11.1 Hz, 1H), 2.22−2.13 (m, 1H), 1.73−1.52 (m, 1H), 1.46−1.19 (m, 4H), 0.86 (dd, J = 7.0, 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 146.8, 132.7, 131.5, 130.5, 129.3, 126.5, 124.7, 118.0, 81.2, 33.5, 26.7, 22.2, 13.7; IR (neat) 3088, 3017, 2957, 2930, 2872, 1767, 1483, 1354, 1300, 1252, 1078 cm^{-1}; HRMS calcd for $C_{14}H_{16}O_2$ 216.1149, found 216.1152.

5-Butyl-4-phenylfuran-2(5*H*)-one (10k): pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.43 (m, 5H), 6.25 (d, J = 1.4 Hz, 1H), 5.48 (ddd, J = 7.7, 2.9, 1.5 Hz, 1H), 2.04−1.93 (m, 1H), 1.63−1.16 (m, 5H), 0.83 (dd, J = 7.2, 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 167.8, 131.2, 130.2, 129.2, 127.1, 114.3, 82.2, 33.2, 26.5, 22.3, 13.8; IR (neat) 3099, 3065, 3030, 2957, 2930, 2860, 1747, 1622, 1456, 1448, 1171 cm^{-1}; HRMS calcd for $C_{14}H_{16}O_2$ 216.1149, found 216.1149.

Palladium-Catalyzed Benzannulation of Enyne−Diynes 16. Representative Procedure. A mixture of Pd(PPh$_3$)$_4$ (58 mg, 0.05 mmol) and DPPF (55 mg, 0.10 mmol) in dry toluene (45 mL) in a 100 mL flask was kept at 80 °C. To this mixture was slowly added a toluene (5 mL) solution of **16a** (29 mg, 0.13 mmol) for 3 h via a syringe pump. After the mixture was stirred for an additional 30 min, toluene was evaporated, and the resulting mixture was passed through a short silica gel column (hexane and Et$_2$O). The residue was further purified by silica gel column chromatography (hexane/AcOEt = 10:1) to give **17a** (15 mg, 52%).

4-(2-Phenylacetylenyl)phthalide (17a): yellow solid; mp 124.7−126.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.7 Hz, 1H), 7.79 (dd, J = 7.7, 0.8 Hz, 1H), 7.56−7.51 (m, 3H), 7.39−7.35 (m, 3H), 5.40 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 148.4, 136.4, 131.7, 129.3, 129.2, 128.5, 126.2, 125.3, 122.0, 118.5, 95.5, 83.8, 69.5; IR (KBr) 3071, 3047, 2922, 2208, 1759, 1686, 1659, 1611, 1597, 1572, 1541, 1522, 1510, 1497, 1475, 1443, 1397, 1364, 1308, 1261, 1177, 1151, 1061, 1013 cm^{-1}; HRMS calcd for $C_{16}H_{10}O_2$ 234.0680, found 234.0684.

4-(2-Phenylacetylenyl)-5-propylphthalide (17b): white solid; mp 101.7−102.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.9 Hz, 1H), 7.53−7.49 (m, 2H), 7.41−7.36 (m, 4H), 5.37 (s, 2H), 2.93 (dd, J = 7.7, 7.7 Hz, 2H), 1.76 (ddddd, J = 7.5, 7.5, 7.5, 7.5, 7.5 Hz, 2H), 1.00 (dd, J = 7.4, 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 151.3, 149.3, 131.6, 130.1, 129.1, 128.6, 124.9, 123.8, 122.3, 117.5, 98.7, 82.7, 69.5, 36.7, 23.8, 13.9; IR (KBr) 3059, 3020, 2951, 2926, 2866, 1753, 1593, 1493, 1450, 1362, 1315, 1055, 1009 cm^{-1}; HRMS calcd for $C_{19}H_{16}O_2$ 276.1149, found 276.1143.

Palladium-Catalyzed Benzannulation of Bis-enynes 18. Representative Procedure. A mixture of $Pd(PPh_3)_4$ (230 mg, 0.20 mmol) and DPPF (220 mg, 0.40 mmol) in dry toluene (195 mL) in a 300 mL flask was kept at 80 °C. To this mixture was slowly added a toluene (5 mL) solution of **18a** (87 mg, 0.50 mmol) for 3 h via a syringe pump. After the mixture was stirred for an additional 30 min, toluene was evaporated, and the resulting mixture was passed through a short silica gel column (hexane and Et_2O). The residue was further purified by silica gel column chromatography (hexane/AcOEt = 10:1) to give **19a** (57 mg, 65%).

5-Vinyl-3,4-dihydroisocoumarin (19a): white solid; mp 78.0−79.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.37 (dd, J = 7.8, 7.8 Hz, 1H), 6.85 (dd, J = 17.4, 11.0 Hz, 1H), 5.69 (d, J = 17.3 Hz, 1H), 5.43 (d, J = 10.9 Hz, 1H), 4.51 (dd, J = 6.0, 6.0 Hz, 2H), 3.06 (dd, J = 6.0, 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 136.8, 135.6, 132.5, 130.8, 129.9, 127.3, 125.6, 118.0, 66.6, 24.8; IR (KBr) 3069, 2982, 2955, 2914, 1717, 1628, 1591, 1472, 1412, 1396, 1300, 1277, 1256, 1240, 1119, 1088, 1067, 1038 cm^{-1}; HRMS calcd for $C_{11}H_{10}O_2$ 174.0680, found 174.0709. Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.54; H, 6.05.

6-Propyl-5-vinyl-3,4-dihydroisocoumarin (19b): white solid; mp 95.5−96.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 8.1 Hz, 1H), 6.70 (dd, J = 18.0, 11.6 Hz, 1H), 5.63 (dd, J = 11.4, 1.7 Hz, 1H), 5.24 (dd, J = 17.9, 1.8 Hz, 1H), 4.43 (dd, J = 6.0, 6.0 Hz, 2H), 3.05 (dd, J = 5.9, 5.9 Hz, 2H), 2.66−2.60 (m, 2H), 1.64−1.52 (m, 2H), 0.94 (dd, J = 7.3, 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 147.0, 137.4, 136.0, 132.8, 129.1, 128.1, 123.3, 121.5, 67.0, 36.0, 26.7, 23.5, 14.0; IR (KBr) 3090, 2999, 2963, 2928, 2905, 2868, 1713, 1587, 1460, 1391, 1288, 1277, 1246, 1123, 1057, 1040 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.61; H, 7.59.

6-Phenyl-5-vinyl-3,4-dihydroisocoumarin (19c): white oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.1 Hz, 1H), 7.43−7.30 (m, 6H), 6.48 (dd, J = 18.0, 11.6 Hz, 1H), 5.50 (dd, J = 11.5, 1.4 Hz, 1H), 5.20 (dd, J = 17.9, 1.4 Hz, 1H), 4.48 (dd, J = 5.9, 5.9 Hz, 2H), 3.17 (dd, J = 5.8, 5.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 146.4, 140.3, 137.7, 135.0, 133.5, 129.6, 129.2, 129.1, 128.1, 127.6, 124.7, 121.7, 67.1, 26.9; IR (neat) 3084, 3059, 3030, 2984, 2955, 2899, 1717, 1653, 1628, 1587, 1566, 1522, 1497, 1472, 1447, 1394, 1337, 1285, 1259, 1205, 1180, 1157, 1126, 1074, 1057, 1040, 1024 cm^{-1}; HRMS calcd for $C_{17}H_{14}O_2$ 250.0993, found 250.1014.

5-((*Z*)-2-Methoxycarbonyl-1-vinyl)-3,4-dihydroisocoumarin (19d): white solid; mp 88.5−89.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.37 (dd, J = 7.8, 7.8 Hz, 1H), 7.06 (d, J = 12.1 Hz, 1H), 6.16 (d, J = 12.1 Hz, 1H), 4.50 (dd, J = 6.0, 6.0 Hz, 2H), 3.63 (s, 3H), 2.95 (dd, J = 6.0, 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 164.9, 140.8, 137.4, 133.7, 133.6, 130.4, 126.7, 125.2, 123.0, 66.7, 51.5, 25.4; IR (KBr) 3049, 2993, 2955, 2924, 1719, 1638, 1437, 1400, 1296, 1271, 1232, 1190, 1115, 1036 cm^{-1}; HRMS calcd for $C_{13}H_{12}O_4$ 232.0735, found 232.0738.

Supporting Information Available: Details for the preparation and spectroscopic data for compounds **4**−**8**, **16**, **18**, and **20**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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