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Selective Synthesis of Benzene Derivatives via Palladium-Catalyzed Cascade Carbometallation of Alkynes†

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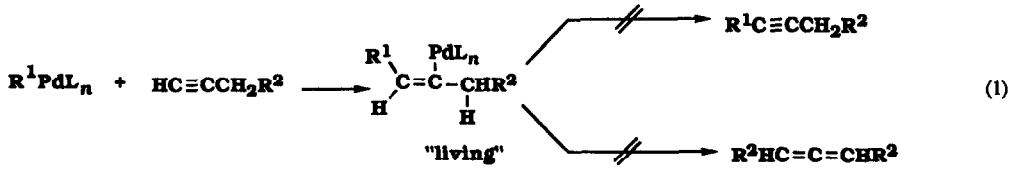
Abstract: A Pd-catalyzed partially intermolecular cascade cyclic carbometallation of haloenynes with monoynes provides a "pair"-selective and regioselective route to benzene derivatives.

INTRODUCTION

Various transition metal complexes have catalyzed cyclotrimerization of alkynes to give benzene derivatives.[1] Early studies on these reactions mostly dealt with the totally intermolecular homo-cyclotrimerization of monoynes. With unsymmetrically substituted alkynes including terminal alkynes, mixtures of at least two regio-isomers were usually obtained. In addition, "pair"-selectivity presents a major problem in the cross-cyclotrimerization of two or three different alkynes. More recent studies, most notably those with Co by Vollhardt,[2] have dealt with this problem, and considerable success has been attained mainly through the use of (i) diynes and (ii) monoynes of appropriate relative reactivity often used in large excess. Even so, the key requirement that a catalyst must alternatingly react with two alkynes of different reactivities imposes a severe restriction.

The ability of organopalladium compounds to add to alkenes and alkynes (carbopalladation) has long been recognized.[3] In cases where the addition product is an alkylpalladium species containing one or more hydrogen atoms β and *syn* to Pd, a facile dehydropalladation reaction follows the addition process, leading to net substitution of an alkene hydrogen with a carbon group (the Heck reaction).[4] On the other hand, alkenylpalladium derivatives obtained by *syn* addition of organopalladium species to alkynes do not readily undergo dehydropalladation even in the presence of a β-hydrogen atom, as in Eq. 1, thereby rendering the addition process "living", i.e., capable of reacting further. This feature is also shared by alkylpalladium derivatives lacking β-hydrogen atoms.[5]

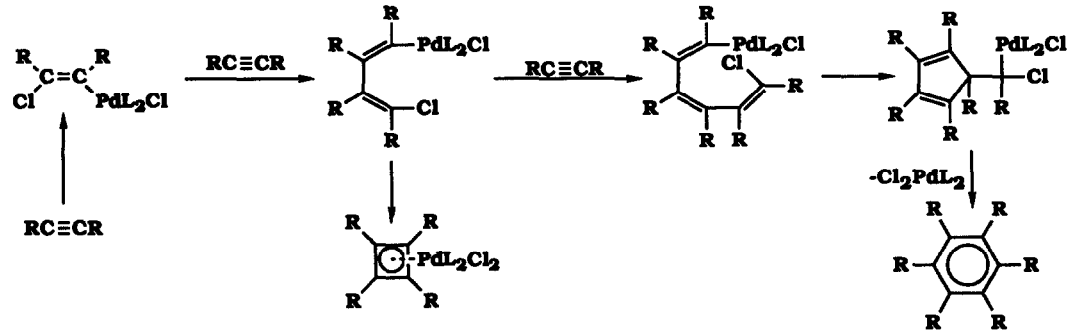


(1)

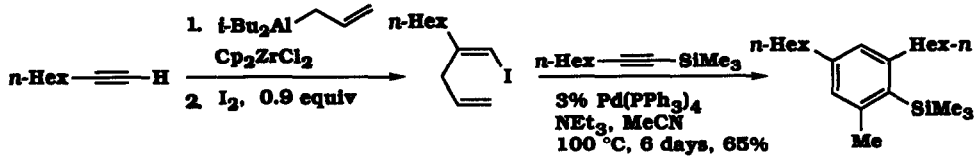
The "living" nature of carbopalladation was recognized earlier in the Pd-catalyzed cyclotrimerization of alkynes to give benzene derivatives, which was shown to proceed by a series of three carbopalladation processes[6,7] (Scheme 1). As such, however, the synthetic utility of the reaction was very limited in that (i) the stoichiometric formation of cyclobutadiene-palladiums was competitive, (ii) the reaction generally lacked regioselectivity, and (iii) the reported intermolecular version was not well suited for "pair"-selective cross-cyclotrimerization of two or three different alkynes.

†Dedicated to Prof. G. P. Chiusoli in recognition of his pioneering contributions to organopalladium chemistry.

Scheme 1

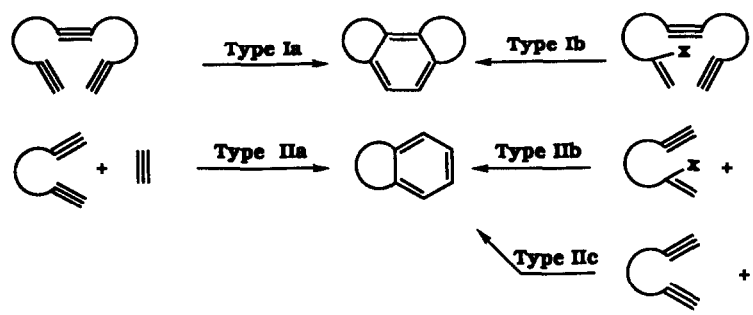


We recently reported a potentially regio- and "pair"-selective synthesis of unsymmetrically substituted benzenes involving Pd-catalyzed cyclization of alkynes, which appeared to be the first such example[8] (Eq. 2).



(2)

Pursuing along this line, we sought selective carbopalladation routes to benzene derivatives with varying degrees of intramolecularity (Scheme 2). The currently available data obtained by us[9] and others[10] indicate that the totally intramolecular Type Ia and Type Ib reactions provide favorable results in a predictable manner, provided that the reactions involve formation of five- and/or six-membered rings.

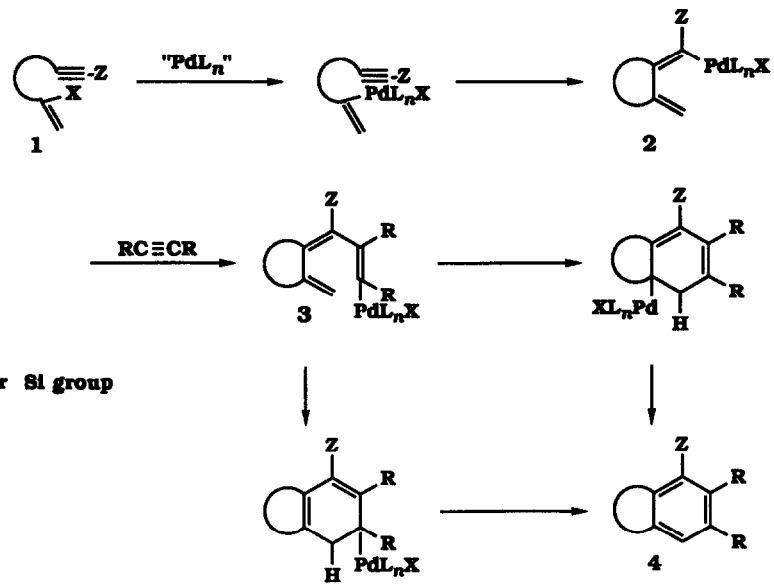


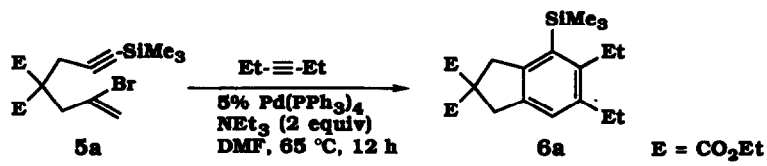
Scheme 2

Turning our attention to partially intramolecular carbopalladation routes to benzenes, i.e., Types IIa-IIc reactions catalyzed by Pd complexes, we found the Type IIa reaction to be difficult to control in general,[9] despite the fact that considerable success has been attained by other workers mainly through the use of Co catalysts.[2] We reasoned that at least with Pd the crucial requirement for a Pd catalyst to alternatingly react with a diyne and a monoyne of different reactivities may not be readily satisfied. Our brief study[9] indicates that the Type IIc reaction leads to the formation of fulvenes. We therefore decided to focus our attention on the Type IIb and related reactions. In the Type IIb reaction, the expected initial step should be oxidative addition of a Pd(0) complex to haloenynes **1**. The resultant alkenylpalladium species should preferentially undergo intramoleuclar carbopalladation to give monocyclic alkenylpalladium species **2**.

If the monoyne used is more reactive than the haloenyne, 2 should preferentially react with the monoenyne to give 3, which could be converted to benzene derivatives 4, either via carbopalladation-dehydropalladtion or via an electrocyclic process followed by dehydropalladation. The course of the reaction should be predictable as outlined in Scheme 3, and the key requirement is that the monoyne be more reactive than the haloenyne, unless the use of a large excess of a monoyne is permitted. Indeed, we have successfully converted 5a and 3-hexyne to 6a in 58% yield[9] (Eq. 3).

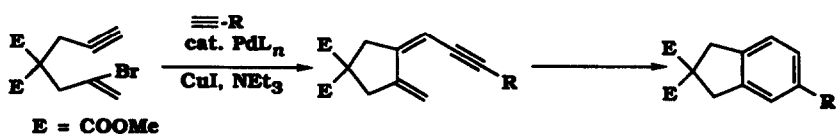
Scheme 3





(3)

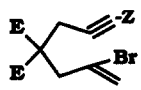
Our interest was further aroused by learning about a closely related reaction of bromoenynes with terminal alkynes,[11] which was thought to proceed via dienyne formation (e.g., Eq. 4). Since the reaction shown in Eq. 3 cannot proceed via a dienyne, it is either that the two reactions proceed via different mechanisms or that some modification of the proposed mechanism may be required. With these synthetic and mechanistic considerations in mind, we have investigated the Pd-catalyzed cyclization reaction of a few bromoenynes 5 with various types of alkynes.



(4)

RESULTS AND DISCUSSION

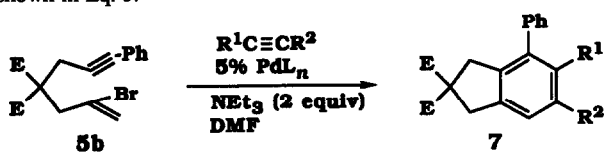
As discussed above, one critical assumption for observing favorable conversion of haloenynes **1** into benzene derivatives **4** was that the monoyne should be more reactive towards organopalladium species than **1**. Although clear-cut data on the relative reactivities of alkynes towards organopalladiums were rather scarce, terminal alkynes appeared to be generally more reactive than internal ones. On this basis, we chose haloenynes containing internal alkynes, i.e., **5a-5c**, along with the parent compound **5d** as the test substrates. These compounds were prepared in good yields by successive alkylations of diethyl malonate first with 2,3-dibromopropene and then with the corresponding propargyl mesylates using NaH as a base. As monoynes, 1-octyne, phenylethyne, 1-(trimethylsilyl)-1-octyne, 2-(trimethylsilyl)-1-phenylethyne, 4-octyne, and diphenylethyne were initially chosen.



a: Z = $SiMe_3$ **c:** Z = Me
b: Z = Ph **d:** Z = H
E = COOEt

5

Their cyclization reactions were initially run using 5 equiv of monoynes to maximize the yields of the desired products in the presence of 2 equiv of NEt_3 and a catalyst generated *in situ* from 5 mol % of $Cl_2Pd(PPh_3)_2$ and 10 mol % of *n*-BuLi. Although MeCN was initially used as a solvent, we soon found that the use of DMF and high reaction temperatures (100-125 °C) were desirable in many cases. Under these conditions **5b** was indeed converted to **7a-7f** in the isolated yields shown in Eq. 5.

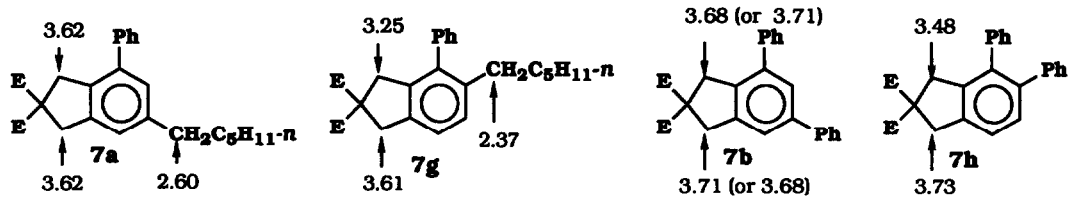


5b **7** (5)

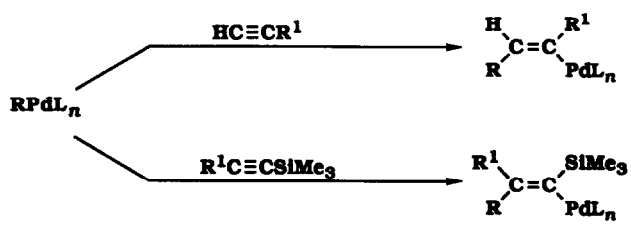
Entry	R^1	R^2	Temp (°C)	Time (h)	Yield (%)	Regioselectivity (%)
7a	H	*n*-Hex	100	1	67	≥93
7b	H	Ph	100	1	73	≥92
7c	*n*-Hex	$SiMe_3$	125	3	63	≥98
7d	Ph	$SiMe_3$	125	3	62	≥98
7e	*n*-Pr	*n*-Pr	125	3	83	-
7f	Ph	Ph	125	3	62	-

The products **7a-7f** have been identified by ^1H and ^{13}C NMR, IR, and high resolution mass spectrometries. The ^1H NMR signals for the two CH_2 groups other than those of the EtO group in **5b** at δ 3.36 and 3.15 ppm shifted to δ 3.61-3.76 and 3.19-3.68 ppm upon conversion to **7a-7f**, while the corresponding ^{13}C NMR signals shifted from δ 22.81 and 42.75 ppm for **5b** to δ 39.75-40.71 ppm for **7a-7f**. The signal for the two carbethoxy-bearing quaternary carbon atom shifted from δ 56.09 ppm to δ 59.85-61.69 ppm upon cyclization. More subtle was the determination of the regiochemistry of the products derived from unsymmetrical monoynes, i.e., **7a-7d**. Significantly, all of these reactions were ≥92% regioselective, and those involving 1-(trimethylsilyl)-1-alkynes were ≥98% regioselective, as judged by ^1H and ^{13}C NMR spectroscopic analysis of the crudely isolated products. Furthermore, protolytic desilylation of **7c** and **7d** with CF_3COOH cleanly produced **7g** and **7h**, respectively, as ≥98% regioisomerically pure species. Comparison of the ^1H and ^{13}C NMR as well as IR spectra of **7a** and **7b** with those of **7g** and **7h**, respectively, permitted the indicated

regiochemical assignments. The shielding effect of the Ph substituent on the ^{1}H NMR chemical shifts of one of the ring CH_2 and the benzylic CH_2 of the *n*-Hex group in **7g** was seen in their shifts from δ 3.62 to 3.25 ppm and from δ 2.60 to 2.37 ppm, respectively. Similarly, the ^{1}H NMR ring CH_2 signal shift from δ 3.68 to 3.48 ppm was seen in going from **7b** to **7h**. In the cases of **7a** and **7g** the regiochemical assignment presented above has been further reinforced by ^{1}H 2D NOESY NMR spectroscopy. Specifically, the Ph group and the α-CH_2 group of *n*-Hex of **7g** show an NOE which is absent in the case of **7a**.



As detailed later, we have concluded that, under the conditions used above, terminal alkynes undergo preferentially carbopalladation, as shown in Scheme 3, rather than cross coupling, as shown in Eq. 4. Consequently, the regiochemical results obtained in the above experiments indicate the following regiochemical preference in carbopalladation of alkynes[9,12] (Eq. 6).



(6)

Table 1. The Pd-Catalyzed Cyclization Reaction of **5b** with a 1:1 Mixture of Two Different Monoynes to Give **7**[a]

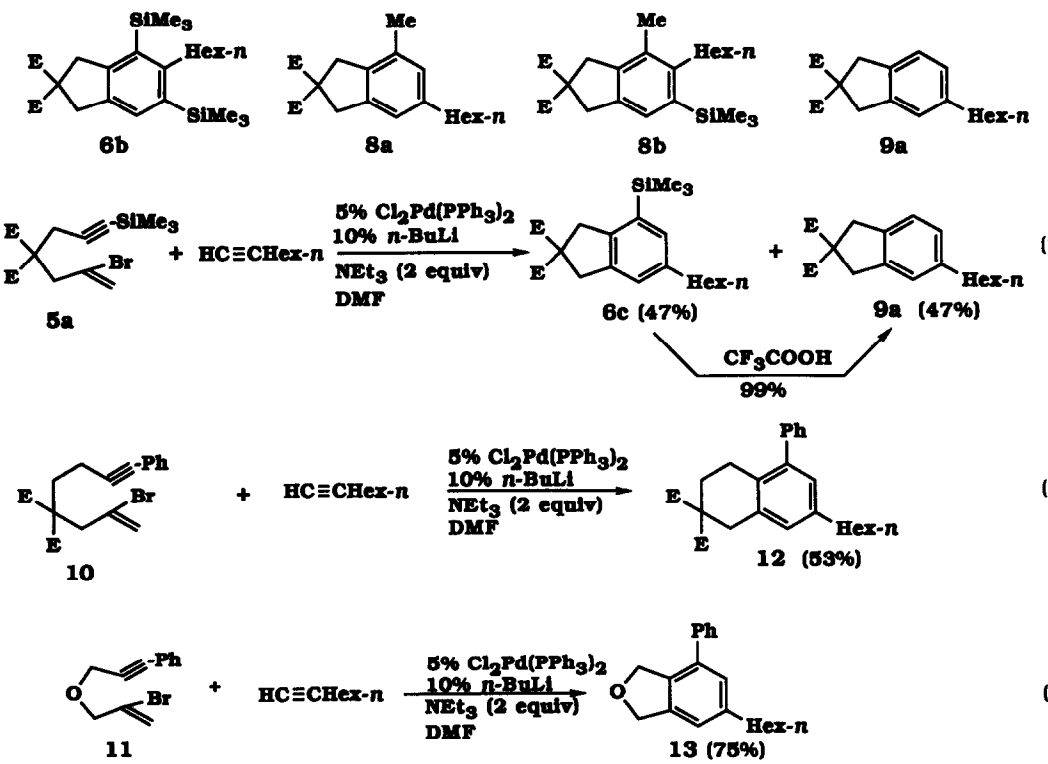
Entry	Monoyne I	Monoyne II	Temp, °C	Time, h	Products (Yield,[b] %)	
1	HC≡CHex-*n*	HC≡CPh	100	1	**7a** (52)	**7b** (43)
2	HC≡CHex-*n*	Me_3SiC≡CHex-*n*	125	3	**7a** (83)	**7c** (17)
3	HC≡CHex-*n*	*n*-PrC≡CPr-*n*	100	16	**7a** (74)	**7e** (<5)
4	Me_3SiC≡CHex-*n*	Me_3SiC≡CPh	125	3	**7c** (53)	**7d** (11)
5	Me_3SiC≡CHex-*n*	*n*-PrC≡CPr-*n*	125	3	**7c** (17)	**7e** (47)
6	*n*-PrC≡CPr-*n*	PhC≡CPh	125	5	**7e** (77)	**7f** (10)

[a]All reactions were run in the presence of a catalyst generated *in situ* by treatment of 5 mol % of $Cl_2Pd(PPh_3)_2$ with 10 mol % of *n*-BuLi and NEt_3 (2 equiv) in DMF. [b] By ^{1}H NMR.

In order to evaluate the effect of alkyne substituents on the product yields, those six reactions shown in Eq. 5 were run using one equiv each of the starting compounds under otherwise the same conditions. The NMR yields of **7a-7f** were as follows: **7a** (76%), **7b** (55%), **7c** (67%), **7d** (45%), **7e** (67%), and **7f** (21%). These results were roughly consistent with the assumption presented earlier, but they did not appear to permit evaluation of the relative reactivities of the monoynes. We therefore considered the reaction of **5b** with a 1:1 mixture of 2 monoynes and ran 6 such

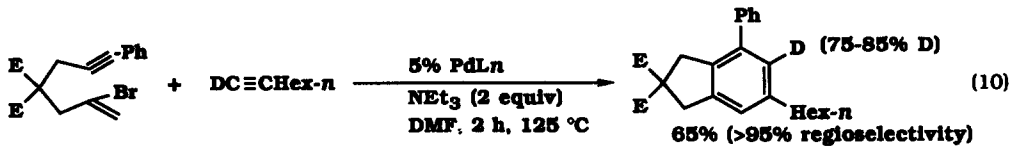
competitive reactions using 6 out of the 15 possible 1:1 mixtures of the 6 monoynes. The results summarized in Table 1 indicate the following. First, terminal alkynes are generally more reactive than internal alkynes (Entries 2 and 3). Secondly, *n*-alkyl groups, such as *n*-Pr and *n*-Hex are more reactive than Ph (Entries 1, 4, and 6). Although very tentative, Me_3Si appears to be less reactive than *n*-alkyl groups (Entry 5).

The reaction of **5a** and **5c** with 1-(trimethylsilyl)-1-octyne under the same conditions as above at 125 °C gave within several hours **6b** (58%, ≥98% regioselective) and **8b** (62%, ≥98% regioselective), respectively. Similarly, the conversion of **5c** and 1-octyne into **8a** was achieved in 89% yield (≥91% regioselective). On the other hand, the reaction of the parent bromoenyne **5d** with 1-octyne gave **9a** in only 50% yield. Interestingly, the reaction of **5a** with 1-octyne led to a 1:1 mixture of **6c** and **9a** in 94% combined yield. Since **6c** was readily converted to **9a** in 99% yield, this provides an indirect but higher yielding alternative to the preparation of **9a** (Eq. 7). Successful conversion of **10** and **11** into **12** (53%, ≥90% regioselective) and **13** (75%, ≥94% regioselective), respectively, indicates that the reaction can accommodate both six-membered rings fused to the benzene ring and some heterocycles (Eqs. 8 and 9).



In an attempt to choose between the two mechanistic alternatives for the reaction of terminal alkynes shown in Scheme 3 and Eq. 4, the reaction of 1-deuterio-1-octyne (>98% D) with **5b** in a 1:1 ratio was carried out in the presence of 5 mol % of $Cl_2Pd(PPh_3)_2$ treated *in situ* with 10 mol % of *n*-BuLi and NEt_3 (2 equiv) in DMF. The reaction provided after 2 h at 125 °C the 5-deuterio derivative of **7a** (75-85% D incorporation) in 65% yield (Eq. 10). The extent of D incorporation was essentially unaffected even when the reaction was carried out in the presence of 5 equiv of Et_3NHBr.

We conclude that, under these conditions, the reaction predominantly follows the carbopalladation path shown in Scheme 3. We also carried out the reaction under the conditions described by S. Torii, et al.[11] using 5 mol % of $Pd(OAc)_2$, PPh_3 (20 mol %), CuI (5 mol %), NEt_3 (1.5 equiv), and DMF. After 2 h at 100 °C the same product was obtained in 60% yield. However, the extent of D incorporation in this case was only 40-50%, and the regioselectivity was 80%. Both the formation of the regioisomer to the extent of 20% and D incorporation to the extent of 40-50% suggest that, even under these conditions, the carbopalladation path appears to be competitive. To develop the organometallic variants the reactions of **5b** with 1-octynylzinc chloride generated *in situ* by treating 1-octynllithium with $ZnCl_2$ (1 equiv) and 1-trimethylstannyl-1-octyne were carried out in the presence of 5 mol % of $Cl_2Pd(PPh_3)_2$ in DMF at 100 °C. The yields of **7a** were 53 and 29%, respectively. In summary, the use of terminal alkynes unassociated with Cu, Sn, or Zn appears to give the most favorable results.



(10)

EXPERIMENTAL

General Procedures. All reactions were conducted under a dry N_2 or Ar atmosphere. Alkyllithiums were titrated with either menthol–2,5'-bipyridiyl or 2-butanol–1,10-phenanthroline. All commercially available reagents were used without further purification unless otherwise noted. THF was distilled from sodium benzophenone ketyl; DMF was distilled from CaH_2 prior to use. Toluene, pentane and Et_3N were dried over molecular sieves 3A.

Preparations of the Cyclization Precursors (5a-5d).

(a) Diethyl (2-Bromo-2-propenyl)-(3-phenyl-2-propynyl)malonate (5b). Representative procedure. In a dry flask (500 mL) equipped with a stirring bar was placed 1.12 g (28 mmol) of NaH (60% in mineral oil). The mineral oil was removed by washing several times with pentane. To this were added sequentially 100 mL of THF and 6.98 g (25 mmol) of diethyl (2-bromo-2-propenyl)malonate and 5.88 g (28 mmol) of 3-phenyl-2-propynyl methanesulfonate. The mixture was stirred overnight, quenched with aqueous NH_4Cl, extracted with Et_2O, washed with brine, and dried over $MgSO_4$. Filtration, evaporation and purification by flash chromatography on SiO_2 (230-400 mesh) with pentane:Et_2O (20:1) provided 8.75 g (89%) of >95% pure **5b**: IR (neat) 1732 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.27 (t, J = 7 Hz, 6 H), 3.15 (s, 2 H), 3.36 (s, 2 H), 4.15-4.3 (m, 4 H), 5.64 (d, J = 1.5 Hz, 1 H), 5.86 (d, J = 1.5 Hz, 1 H), 7.2-7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.69, 22.81, 42.75, 56.09, 61.83, 84.02, 84.06, 122.64, 123.07, 126.60, 128.13, 128.29, 131.62, 169.35. **(b) Diethyl (2-Bromo-2-propenyl)-(3-(trimethylsilyl)-2-propynyl)malonate (5a).** This compound was prepared similarly from diethyl (2-bromo-2-propenyl)malonate and 3-(trimethylsilyl)-2-propynyl mesylate in 91% yield (>95% pure): ^1H NMR ($CDCl_3$) δ 0.08 (s, 9 H), 1.22 (t, J = 7.0 Hz, 6 H), 2.87 (s, 2 H), 3.23 (s, 2 H), 4.1-4.25 (m, 4 H), 5.56 (d, J = 1.3 Hz, 1 H), 5.76 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ -0.43, 13.67, 23.18, 42.58, 55 84, 61.78, 88.75, 101.23, 122.54, 126.59, 169.19. **(c) Diethyl (2-Bromo-2-propenyl)-(2-butynyl)malonate (5c)**: 97% yield (>95% pure): ^1H NMR ($CDCl_3$, Me_4Si) δ 1.22 (t, J = 7 Hz, 6 H), 1.71 (t, J = 2.5 Hz, 3 H), 2.80 (q, J = 2.5 Hz, 2 H), 3.21 (s, 2 H), 4.1-4.25 (m, 4 H), 5.56 (d, J = 1.4 Hz, 1 H), 5.76 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 3.29, 13.81, 22.31, 42.62, 56.01, 61.67, 73.12, 79.21, 122.25, 126.51, 169.22. **(d) Diethyl (2-Bromo-2-propenyl)-(2-propynyl)malonate (5d).** The reaction

of 2.79 g (10 mmol) of diethyl (2-bromo-2-propenyl)malonate with 3-bromopropyne (80% in toluene) as in the representative procedure gave 2.85 g (90%) of **5d** (>95% pure): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.24 (t, J = 7 Hz, 6 H), 2.02 (t, J = 2.7 Hz, 1 H), 2.89 (d, J = 2.7 Hz, 2 H), 3.26 (s, 2 H), 4.1-4.25 (m, 4 H), 5.59 (d, J = 1.5 Hz, 1 H), 5.80 (d, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.68, 21.90, 42.51, 55.72, 61.91, 71.96, 78.68, 122.79, 126.44, 169.24.

Palladium-Catalyzed Reactions of Diethyl (2-Bromo-2-propenyl)-(3-phenyl-2-propynyl)malonate (5b) with Monoynes in a 1:5 Molar Ratio to Produce Diethyl 4-Phenyl-5- and/or -6-substituted-2,2-indanedicarboxylates.

(a) Diethyl 4-Phenyl-6-(*n*-hexyl)-2,2-indanedicarboxylate (7a). Representative Procedure. Into a 25 mL flask equipped with a magnetic stirring bar, a septum inlet and a reflux condenser with a mercury bubbler were introduced 31.5 mg (0.05 mmol) of $Cl_2Pd(PPh_3)_2$ and 0.5 mL of THF. After cooling to -78 °C, *n*-BuLi (2.5 M in hexane, 40 μL, 0.10 mmol) was added. To this were added successively 0.55 g (0.77 mL, 5 mmol) of 1-octyne, 1.0 mL of DMF, 0.202 g (0.28 mL, 2.0 mmol) of Et_3N and 0.393 g (1.0 mmol) of **5b** in 1.0 mL of DMF. The resulting reaction mixture was heated to 100 °C. After stirring for 1 h at 100 °C, the reaction mixture was quenched with aqueous NH_4Cl, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (pentene:Et_2O = 20:1) on SiO_2 (230-400 mesh) afforded 0.28 g (67%) of **7a**: IR (neat) 1733 (s), 1244 (s), 1186 (s), 1074 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.88 (t, J = 6.5 Hz, 3 H), 1.18-1.42 (t + m, J = 7 Hz, 6 H + 6 H), 1.55-1.6 (m, 2 H), 2.60 (t, J = 7.5 Hz, 2 H), 3.62 (s, 4 H), 4.18 (q, J = 7 Hz, 4 H), 7.02 (s, 2 H), 7.25-7.45 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 13.76, 13.87, 22.39, 28.92, 31.47, 31.56, 35.68, 39.75, 40.38, 60.37, 61.53, 123.29, 127.04, 127.85, 128.41, 128.57, 135.06, 138.14, 140.91, 141.09, 142.59, 171.90. High Resolution MS for $C_{27}H_{34}O_4$: calcd, 422.2457; found, 422.2455.

(b) Diethyl 4,6-Diphenyl-2,2-indanedicarboxylate (7b). The reaction of **5b** with phenylethyne on a 0.5 mmol scale was carried out as in the representative procedure to give 0.15 g (73%) of **7b**: IR (neat) 1735 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.24 (t, J = 7 Hz, 6 H), 3.68 (s, 2 H), 3.71 (s, 2 H), 4.21 (q, J = 7 Hz, 4 H), 7.15-7.65 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 13.81, 39.84, 40.50, 60.41, 61.69, 122.07, 126.90, 127.31, 128.58, 128.65, 128.86, 137.08, 138.81, 140.82, 141.12, 141.27, 141.63, 171.84. High Resolution MS for $C_{27}H_{26}O_4$: calcd, 414.1831; found, 414.1827.

(c) Diethyl 4-Phenyl-5-(*n*-hexyl)-6-(trimethylsilyl)-2,2-indanedicarboxylate (7c). The reaction of **5b** with 1-(trimethylsilyl)-1-octyne, which was prepared by treating 1-octyne with *n*-BuLi (1 equiv) and Me_3SiCl (1.3 equiv) at -78 °C in THF, on a 1.0 mmol scale gave 0.31 g (63%) of **7c**: IR (neat) 1734 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.33 (s, 9 H), 0.75 (t, J = 7 Hz, 3 H), 0.9-1.4 (m with t at 1.20 (J = 7 Hz, 6H), 14 H), 2.51-2.61 (m, 2 H), 3.23 (s, 2 H), 3.64 (s, 2 H), 4.16 (q, J = 7 Hz, 4 H), 7.2-7.45 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 0.66, 13.74, 22.01, 29.21, 30.87, 31.36, 33.42, 40.39, 40.59, 59.85, 61.45, 126.78, 128.31, 129.26, 129.75, 136.61, 137.48, 138.62, 140.33, 140.94, 145.24, 171.97. High Resolution MS for $C_{30}H_{42}O_4Si$: calcd, 494.2852, found, 494.2847.

(d) Diethyl 4,5-Diphenyl-6-(trimethylsilyl)-2,2-indanedicarboxylate (7d). The reaction of **5b** with 2-(trimethylsilyl)-1-phenylethyne, on a 1.0 mmol scale gave 0.30 g (62%) of **7d**: IR (neat) 1732 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ -0.04 (s, 9 H), 1.25 (t, J = 7 Hz, 6 H), 3.40 (s, 2 H), 3.76 (s, 2 H), 4.21 (q, J = 7 Hz, 4 H), 7.0-7.2 (m, 10 H), 7.50 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.35, 13.77, 40.51, 40.71, 59.91, 61.55, 126.17, 126.46, 127.00, 127.62, 129.28, 129.74, 131.15, 137.95, 138.41, 139.83, 140.12, 142.05, 146.26, 171.94. High Resolution MS for $C_{30}H_{34}O_4Si$: calcd, 486.2226; found, 486.2216.

(e) Diethyl 4-Phenyl-5,6-di-(*n*-propyl)-2,2-indanedicarboxylate (7e). The reaction of **5b** with 4-octyne on a 1.0 mmol scale gave 0.35 g (83%) of **7e**: IR (neat) 1736 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.72 (t, J = 7 Hz, 3 H),

1.01 (t, J = 7 Hz, 3 H), 1.19 (t, J = 7 Hz, 6 H), 1.2-1.4 (m, 2 H), 1.6-1.7 (m, 2 H), 2.3-2.4 (m, 2 H), 2.59 (q, J = 8 Hz, 2 H), 3.19 (s, 2 H), 3.61 (s, 2 H), 4.17 (q, J = 7 Hz, 4 H), 7.03 (s, 1 H), 7.15-7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.67, 14.16, 14.25, 24.27, 24.56, 31.52, 35.07, 40.12, 40.48, 60.90, 61.32, 124.03, 126.66, 128.20, 129.02, 136.75, 136.84, 138.61, 139.94, 140.79, 171.94. High Resolution MS for $C_{27}H_{34}O_4$: calcd, 422.2457; found, 422.2453.

(f) Diethyl 4,5,6-Triphenyl-2,2-indanedicarboxylate (7f). The reaction of **5b** with diphenylethyne on a 1.0 mmol scale gave 0.26 g (62%) of **7f**: IR (neat) 1718 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$), Me_4Si) δ 1.23 (t, J = 7 Hz, 6 H), 3.46 (s, 2 H), 3.75 (s, 2 H), 4.20 (q, J = 7 Hz, 4 H), 6.75-7.2 (m, 15 H), 7.28 (s, 1 H), ^{13}C NMR ($CDCl_3$) δ 13.78, 40.41, 40.60, 60.04, 61.61, 125.25, 125.64, 126.09, 126.32, 127.00, 127.56, 127.74, 129.91, 129.98, 131.71, 138.30, 138.54, 139.22, 139.70, 139.91, 141.21, 142.29, 171.90. High Resolution MS for $C_{33}H_{30}O_4$: calcd, 490.2144; found, 490.2133.

Diethyl 4-Phenyl-5-(*n*-hexyl)-2,2-indanedicarboxylate (7g). Desilylation[8] of diethyl 4-phenyl-5-(*n*-hexyl)-6-(trimethylsilyl)-2,2-indanedicarboxylate (**7c**) (0.12 g, 0.24 mmol) with CF_3COOH (25 °C, 16 h) gave 0.09 g (88%) (regioisomeric purity ≥98%) of **7g**. IR (neat) 1734 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.79 (t, J = 7 Hz, 3 H), 1.1-1.4 (m with t at 1.20 (J = 7 Hz, 6 H), 14 H), 2.37 (t, J = 7.5 Hz, 2 H), 3.25 (s, 2 H), 3.61 (s, 2 H), 4.15 (q, J = 7 Hz, 4 H), 7.11 (s, 2 H), 7.1-7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.78, 22.26, 28.90, 31.29, 32.66, 40.10, 40.45, 60.14, 61.51, 123.11, 126.90, 128.18, 128.36, 129.14, 137.16, 138.18, 139.18, 139.44, 139.92, 171.99. MS for $C_{27}H_{34}O_4$, M^+ = 422, base peak = 348 (M - HCO_2Et).

Diethyl 4,5-Diphenyl-2,2-indanedicarboxylate (7h). Desilylation[8] of diethyl 4,5-diphenyl-6-(trimethylsilyl)-2,2-indanedicarboxylate (**7d**) with 0.17 g (0.35 mmol) CF_3COOH provided 0.13 g (88%) (regioisomeric purity ≥98%) of **7h**: IR (neat) 1728 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.25 (t, J = 7 Hz, 6 H), 3.48 (s, 2 H), 3.73 (s, 2 H), 4.21 (q, J = 7 Hz, 4 H), 7.05-7.35 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 13.75, 40.28, 40.49, 60.18, 61.57, 123.28, 126.19, 126.58, 127.66, 127.98, 129.59, 129.97, 130.03, 137.09, 139.45, 139.54, 139.89, 141.49, 171.83. MS for $C_{27}H_{26}O_4$: M^+ = 414, base peak = 340 (M - HCO_2Et).

Palladium-Catalyzed Reactions of 5b with Monoynes in a 1:1 Molar Ratio to Produce 7a-7f. All reactions were conducted as in the representative procedure using 1 equiv of monoyne. The NMR yields and regioisomeric purities of the products are as follows: **7a** (82%, ≥93% regioselective), **7b** (55%, ≥97% regioselective), **7c** (67%, ≥98% regioselective), **7d** (45%, ≥96% regioselective), **7e** (67%), and **7f** (21%).

Palladium-Catalyzed Competitive Reactions of 5b with a 1:1 Mixture of Two Different Monoynes in a 1:1:1 Molar Ratio to Produce Diethyl 4-Phenyl-5 and/or 6-substituted-2,2-indanedicarboxylates (7a - 7f). All reactions were carried out under the same conditions as in the representative procedure using one equiv each of two different monoynes on a 0.5 mmol scale and analyzed by ^{1}H and ^{13}C NMR spectroscopy. The results are summarized in Table 1.

Palladium-Catalyzed Reactions of Diethyl (2-Bromo-2-propenyl)-(3-(trimethylsilyl)-2-propynyl)malonate (5a) with Monoynes in a 1:1 Molar Ratio to Produce Diethyl 4-(Trimethylsilyl)-5- and/or -6-substituted-2,2-indanedicarboxylates (6b and 6c).

(a) Diethyl 4,6-Bis(trimethylsilyl)-5-(*n*-hexyl)-2,2-indanedicarboxylate (6b). The reaction was carried out using 1 equiv each of **5a** and 1-(trimethylsilyl)-1-octyne as in the representative procedure for 12 h at 125 °C on a 1.0 mmol scale to give 0.29 g (59%) of **6b**: IR (neat) 1736 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.33 (s, 9 H), 0.43 (s, 9 H), 0.91 (t, J = 6.5 Hz, 3 H), 1.2-1.4 (m with t at 1.27 (J = 7 Hz, 6 H) 14 H), 2.80 (bs, 2 H), 3.53 (s, 2 H), 3.68 (s, 2 H), 4 22 (q, J = 7 Hz, 4 H), 7.35 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.97, 2.75, 14.01, 22.54, 29.59, 32.06, 35.80, 37.19, 39.55, 42.80,

60.48, 61.59, 131.70, 133.87, 136.12, 136.78, 147.60, 154.01, 171.68. High Resolution MS for $C_{27}H_{46}O_4Si_2$: calcd, 490.2935; found, 490.2905.

(b) Diethyl 4-(Trimethylsilyl)-6-(*n*-hexyl)-2,2-indanedicarboxylate (6c). The reaction was carried out using 1 equiv each of **5a** and 1-octyne as in the representative procedure for 4 h at 125 °C on a 1.0 mmol scale to give a 47% NMR yield each of **6c** and **9a**, from which 0.18 g (43%) of **6c** was isolated: IR (neat) 1736 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.34 (s, 9 H), 0.92 (t, *J* = 6.5 Hz, 3 H), 1.24-1.66 (m (+t, 1.28, *J* = 7 Hz, 6 H), 14 H), 2.56 (t, *J* = 7.5 Hz, 2 H), 3.58 (s, 2 H), 3.63 (s, 2 H), 4.24 (q, *J* = 7 Hz, 4 H), 7.06 (s, 1 H), 7.13 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ -0.87, 13.97, 14.04, 22.57, 29.12, 31.68, 35.89, 39.90, 41.03, 60.65, 61.55, 124.97, 132.63, 134.88, 139.28, 140.87, 142.38, 171.67. High Resolution MS for $C_{24}H_{38}O_4Si$: calcd, 418.2539; found, 418.2535.

Diethyl 5-(*n*-Hexyl)-2,2-indanedicarboxylate (9a). Desilylation of **6c** with CF_3COOH gave **9a** in 99% yield: IR (neat) 1736 (s), 1250 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, *J* = 6.5 Hz, 3 H), 1.2-1.65 (m with t at 1.27 (*J* = 7 Hz, 6 H), 14 H), 2.57 (t, *J* = 7.5 Hz, 2 H), 3.58 (s, 4 H), 4.22 (q, *J* = 7 Hz, 4 H), 6.95-7.15 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 13.97, 14.05, 22.56, 29.00, 31.65, 31.69, 35.78, 40.11, 40.38, 60.42, 61.56, 123.80, 124.09, 127.07, 137.10, 139.98, 141.71, 171.70. MS for $C_{21}H_{30}O_4$: M^+ = 364, base peak = 274 ($M-HCO_2Et$). The reaction of **5d** with 1-octyne according to the representative procedure at 125 °C for 2 h gave **9a** in 50% NMR yield.

Palladium-Catalyzed Reactions of Diethyl (2-Bromo-2-propenyl)-(2-butynyl)malonate (5c) with Monoynes in a 1:1 Molar Ratio to Produce Diethyl 4-Methyl-5- and/or -6-substituted-2,2-indanedicarboxylates (8a & 8b).

(a) Diethyl 4-Methyl-6-(*n*-hexyl)-2,2-indanedicarboxylate (8a). The reaction of **5c** with 1-octyne as in the representative procedure at 125 °C for 1 h on a 1.0 mmol scale gave 0.30 g (83 %) of **8a** (≥91% regioselective): IR (neat) 1736 (s), cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.93 (t, *J* = 6 Hz, 3 H), 1.2-1.65 (m with t at 1.30 (*J* = 7 Hz, 6 H), 14 H), 2.27 (s, 3 H), 2.57 (t, *J* = 7.5 Hz, 2 H), 3.54 (s, 2 H), 3.63 (s, 2 H), 4.25 (q, *J* = 7 Hz, 4 H), 6.84 (s, 1 H), 6.89 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.84, 13.93, 18.77, 22.45, 28.94, 31.61, 35.64, 38.88, 40.45, 59.78, 61.39, 121.27, 127.86, 133.06, 135.93, 139.60, 141.89, 171.64. High Resolution MS for $C_{22}H_{32}O_4$: calcd, 360.2301; found, 360.2294.

(b) Diethyl 4-Methyl-5-(*n*-hexyl)-6-(trimethylsilyl)-2,2-indanedicarboxylate (8b). The reaction of **5c** with 1-(trimethylsilyl)-1-octyne as in the representative procedure at 125 °C for 16 h gave 0.27 g (62%) of **8b** (≥ 98% regioselective): IR (neat) 1735 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.31 (s, 9 H), 0.92 (t, *J* = 6.5 Hz, 3 H), 1.21-1.45 (m with t at 1.27 (*J* = 7 Hz, 6 H), 14 H), 2.23 (s, 3 H), 2.55- 2.75 (m, 2 H), 3.56 (s, 2 H), 3.61 (s, 2 H), 4.22 (q, *J* = 7 Hz, 4 H), 7.18 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.60, 13.81, 15.36, 22.48, 29.79, 31.04, 31.55, 33.94, 40.14, 40.59, 59.62, 61.56, 127.91, 131.88, 136.70, 137.22, 141.28, 145.62, 172.18. High Resolution MS for $C_{25}H_{40}O_4Si$: calcd, 432.2696; found, 432.2678.

Diethyl 4-Methyl-5-(*n*-hexyl)-2,2-indanedicarboxylate (8c). Desilylation[8] of 0.20 g (0.45 mmol) of **8b** with CF_3COOH gave 0.16 g (93%) of **8c** (regioisomeric purity ≥97%): IR (neat) 1734 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, *J* = 6.5 Hz, 3 H), 1.20-1.61 (m with t at 1.27 (*J* = 7 Hz, 6 H) 14 H), 2.21 (s, 3 H), 2.57 (t, *J* = 7 Hz, 2 H), 3.55 (s, 2 H), 3.59 (s, 2 H), 4.22 (q, *J* = 7 Hz, 4 H), 6.97 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.76, 13.84, 15.09, 22.41, 29.18, 30.52, 31.56, 33.04, 39.70, 40.38, 59.81, 61.50, 121.18, 128.12, 131.58, 137.12, 139.41, 139.65, 172.10. High Resolution MS for $C_{22}H_{32}O_4$: calcd, 360.2301; found, 360.2297.

Diethyl (2-Bromo-2-propenyl)-(4-phenyl-3-butynyl)malonate (10). This compound was prepared from diethyl (2-bromo-2-propenyl)malonate and 4-iodo-1-phenyl-1-butyne in 70% yield: IR (neat) 1736 (s) cm^{-1}; ^1H NMR ($CDCl_3$,

Me_4Si) δ 1.25 (t, J = 7.1 Hz, 6 H), 2.3-2.5 (m, 4 H), 3.22 (s, 2 H), 4.20 (q, J = 7.1 Hz, 4 H), 5.60 (s, 1 H), 5.71 (s, 1 H), 7.2-7.3 (m, 3 H), 7.3-7.4 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.87, 14.86, 30.65, 43.06, 56.37, 61.65, 81.00, 88.40, 121.93, 123.50, 126.94, 127.63, 128.10, 131.41, 169.97.

2-Bromo-2-propenyl 3-Phenyl-2-propynyl Ether (11). Sodium hydride (60% in mineral oil, 3.19 mg, 7.89 mmol) was washed with pentane. To this were added sequentially 1.00 g (7.59 mmol) of 3-phenyl-2-propyn-1-ol in 10 mL of THF (0-25 °C), and 0.86 mL (8.30 mmol) of 2,3-dibromopropene (0 °C, 2 h). The usual extractive workup and column chromatography provided 1.70 g (89%) of **11**: IR (neat) 2240 (w), 1084 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 4.26 (d, J = 0.8 Hz, 2 H), 4.42 (s, 2 H), 5.66 (d, J = 0.8 Hz, 1 H), 5.95-6.0 (m, 1 H), 7.3-7.4 (m, 3 H), 7.4-7.5 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 57.84, 73.30, 84.15, 86.82, 118.47, 122.29, 128.24, 128.51, 128.57, 131.68.

Diethyl 7-(*n*-Hexyl)-5-phenyl-1,2,3,4-tetrahydronaphthalene-2,2-dicarboxylate (12). The reaction of one equivalent each of **10** with 1-octyne at 125 °C for 2 h provided a 53% NMR yield of **12**, a purified sample of which yielded the following spectral data: IR (neat) 1732 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.88 (t, J = 6.6 Hz, 3 H),1.1-1.5 (m, 12 H), 2.22 (t, J = 6.5 Hz, 2 H), 2.5-2.7 (m, 4 H), 3.32 (s, 2 H), 4.19 (q, J = 7.1 Hz, 4 H), 6.88 (s, 1 H), 6.96 (s, 1 H), 7.2-7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.99, 14.03, 22.54, 24.41, 28.43, 29.06, 31.34, 31.67, 35.07, 35.44, 53.45, 61.30, 126.65, 127.85, 127.90, 127.94, 129.08, 129.62, 133.75, 140.27, 141.40, 141.74, 171.43. High Resolution MS for $C_{28}H_{36}O_4$: calcd, 436.2615; found, 436.2610.

1*H*,3*H*-6-(*n*-Hexyl)-4-phenyldihydroisobenzofuran (13). The Pd-catalyzed reaction of 126 mg (0.50 mmol) of **11** with 74 μL (0.50 mmol) of 1-octyne as in the representative procedure at 125 °C for 1.5 h produced **13** (regioselectivity ≥94%) in 75% NMR yield: IR (neat) 1052 (s), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.89 (t, J = 6.6 Hz, 3 H), 1.2-1.4 (m, 6 H), 1.55-1.7 (m, 2 H), 2.6-2.7 (m, 2 H), 5.13 (s, 2 H), 5.17 (s, 2 H), 7.04 (s, 1 H), 7.14 (s, 1 H), 7.3-7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.57, 29.00, 31.70 (2 C's), 35.80, 73.32, 73.58, 119.72, 127.28, 127.63, 127.76, 128.55, 134.41, 135.68, 140.14, 140.29, 143.04. High Resolution MS for $C_{20}H_{24}O$: calcd, 280.1828; found, 280.1830.

Palladium-Catalyzed Reaction of 5b with 1-Deuterio-1-octyne in a 1:1 Molecular Ratio. (a) In the Absence of CuI. To 18 mg (25 μmol) of $Cl_2Pd(PPh_3)_2$ and 0.5 mL of THF was added at -78 °C 21 μL (50 μmol) of *n*-BuLi (2.35 M in hexane. After 20 min at -78 °C 181 mg (0.50 mmol) of diethyl (2-bromo-2-propenyl)-(3-phenyl-2-propynyl)malonate in 2.0 mL of DMF, 56 mg (0.50 mmol) of 1-deuterio-1-octyne (≥98% D), prepared by treatment of 1-lithio-1-octyne, with D_2O and 0.14 mL (1.00 mmol) of Et_3N were added successively. The reaction mixture was then heated at 125 °C for 2 h. After the standard workup examination of the crude product by ^1H NMR spectroscopy indicated the formation of ≥95% regioisomerically pure **7a** in 65% NMR yield with 75-85% D incorporation.

(b) In the Presence of CuI. The following reaction coditions were patterned after those reported by S. Torii, et al.[11] A mixture of 181 mg (0.50 mmol) of diethyl (2-bromo-2-propenyl)-(3-phenyl-2-propynyl)malonate, 56 mg (0.50 mmol) of 1-deuterio-1-octyne (≥98% D), 5.6 mg (25 μmol) of $Pd(OAc)_2$, 4.8 mg (25 μmol) of CuI, 26.3 mg (0.10 mmol) of PPh_3, and 0.14 mL (1.00 mmol) of Et_3N in 2.0 mL of DMF was stirred at 100 °C for 2 h. After the standard workup examination of the crude product (165 mg) by ^1H NMR spectroscopy indicated the formation of an 80:20 mixture of **7a** and its regioisomer in 60% combined NMR yield. The extend of D incorporation in **7a** was 40-50%.

Palladium-Catalyzed Reaction of 5b with 1-Alkynylmetals in a 1:1 Molecular Ratio. (a) With 1-octynylzinc chloride. To 18 mg (25 μmol) of $Cl_2Pd(PPh_3)_2$ and 0.5 mL of THF was added at -78 °C 21 μL (50 μmol) of *n*-BuLi (2.35 M in hexane). After 20 min at -78 °C, 181 mg (0.50 mmol) of diethyl (2-bromo-2-propenyl)-(3-phenyl-2-propynyl)malonate in 2.0 mL of DMF and 1-octynylzinc chloride, generated *in situ* by treating 1 equiv of 1-octynyllithium with 68 mg (0.50 mmol) of dry $ZnCl_2$ at 0 °C, were added. The reaction mixture was then heated at 100 °C for 2 h. After the standard workup examination of the crude product by ^1H NMR spectroscopy indicated the formation of ≥90% regioisomerically pure **7a** in 53% NMR yield.

(b) With 1-(trimethylstanyl)-1-octyne. A mixture of 181 mg (0.50 mmol) of diethyl (2-bromo-2-propenyl)-(3-phenyl-2-propynyl)malonate, 137 mg (0.50 mmol) of 1-trimethylstanyl-1-octyne, and 18 mg (25 μmol) of $Cl_2Pd(PPh_3)_2$ in 3.0 mL of DMF was stirred at 100 °C for 3 h. After the standard workup examination of the crude product by ^1H NMR spectroscopy indicated the formation of **7a** and **7g** in 29 and 12% yields, respectively.

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