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Palladium-Catalyzed Three-Component 1:2:1 Coupling of Aryl Iodides, Alkynes, and Alkenes to Produce 1,3,5-Hexatriene Derivatives

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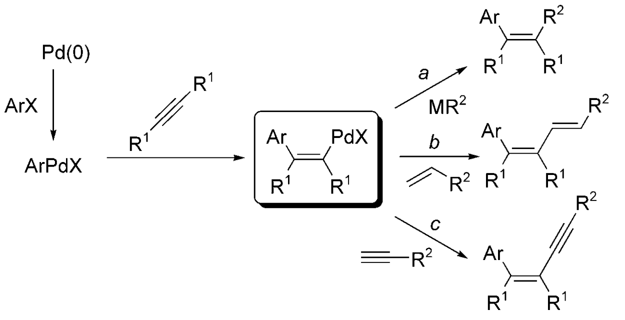
Abstract: The intermolecular three-component coupling of aryl iodides, diarylacetylenes, and alkenes effectively proceeds in the presence of palladium acetylacetonate and silver acetate as catalyst and base, respectively, to give the corresponding 1:2:1 coupling products, 1,3,5-hexatriene derivatives. A further homologation of the oligoene chain of the three-component coupling products by a simple procedure is also presented.

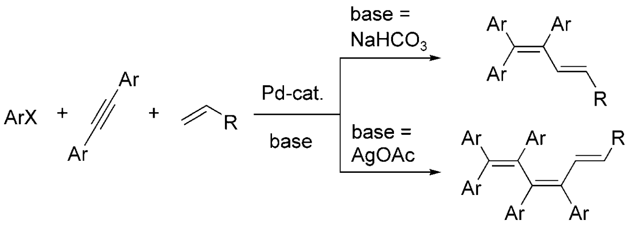
Keywords: C–C coupling; Heck reaction; multicomponent reactions; oligoenes; palladium

The palladium-catalyzed arylation of internal alkynes with aryl halides or their synthetic equivalents *via* carbometalation is a powerful tool for the construction of π-conjugated molecules.[1] Such reactions are often carried out with the addition of various terminators including organometallic reagents, alkenes, and terminal alkynes to give rise to three-component coupling products (Scheme 1). While the reactions *via* intramolecular cyclization with alkynyl(halo)arenes followed by intermolecular termination or the reverse with substrates such as alkenylhaloarenes and alkynes have been studied extensively,[1,2] the fully intermolecular version to afford π-conjugated acyclic compounds have been less explored.[3–6] As one of the rare but efficient examples, Larock and co-workers reported the 1:1:1 coupling of aryl iodides, internal alkynes, and organoboron reagents (route *a* in Scheme 1).[3b–d] We have also demonstrated that two molecules of alkynes can be inserted between aryl halides and arylboronic acids to produce the corresponding 1:2:1 coupling products, 1,4-diaryl-1,3-butadienes.[5] In this unique four-molecule coupling, the use of a silver(I) salt as base was essential to achieve the double alkyne insertion effectively.



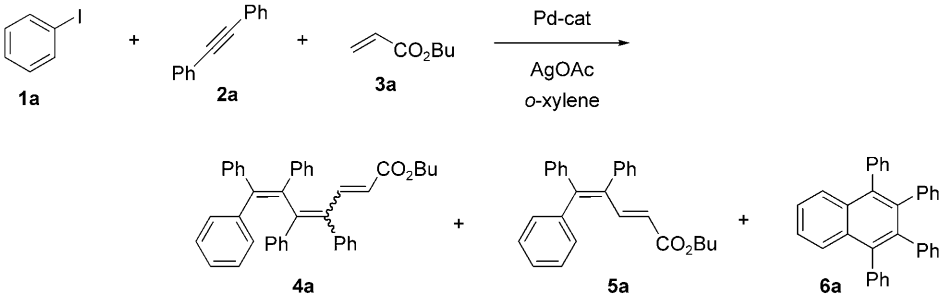
Scheme 1. Palladium-catalyzed three-component 1:1:1 coupling of aryl halides, alkynes, and terminators.

As an example of route *b* in Scheme 1, on the other hand, we have developed a 1:1:1 coupling of aryl halides, alkynes, and alkenes to produce 1,3-butadiene derivatives.[6] During the course of a further study of this reaction, we observed that the double alkyne insertion can also take place smoothly between aryl halides and alkenes by employing the Pd/Ag catalyst system (Scheme 2).[5,7] The scope of the straightforward synthesis of oligoene derivatives, which are of interest for their photo- and electrochemical and biological properties,[8] is described herein.



Scheme 2. Palladium-catalyzed three-component coupling of aryl halides, alkynes, and alkenes.

Table 1. Reaction of iodobenzene (**1a**) with diphenylacetylene (**2a**) and butyl acrylate (**3a**).[a]



Entry	Pd cat.	Temp [°C]	Time [h]	Yield [%][b]		
				4a	5a	6a
1	$Pd(OAc)_2$	140	3	29	10	6
2	$Pd(acac)_2$	140	3	72 (65)[c]	16	3
3[d]	$Pd(acac)_2$	140	1	55	14	8
4[e]	$Pd(acac)_2$	140	1	69	14	9
5	$Pd(acac)_2$	120	1	56	17	3
6	$Pd(acac)_2$	160	1	60	13	4
7[f]	$Pd(acac)_2$	140	1	67	10	10

[a] *Reaction conditions:* [**1a**]:[**2a**]:[**3a**]:[Pd-cat.]:[AgOAc] = 1:4:1:0.05:2 (in mmol), in *o*-xylene (5 mL) under N_2.

[b] GC yield based on the amount of **1a** used. Value in parenthesis indicates yield after purification.

[c] (2*E*,4*E*):(2*E*,4*Z*) = 10:1.

[d] With AgOAc (1 mmol).

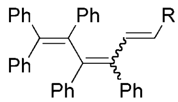
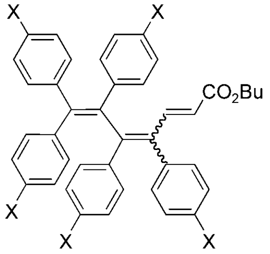
[e] With AgOAc (3 mmol).

[f] **2a** (6 mmol) was used.

When iodobenzene (**1a**) was treated with diphenylacetylene (**2a**) (4 equiv.) and butyl acrylate (**3a**) (1 equiv.) in the presence of $Pd(OAc)_2$ (5 mol%) and AgOAc (2 equiv.) in *o*-xylene at 140 °C for 3 h, the 1:2:1 coupling proceeded predominantly to afford butyl 4,5,6,7,7-pentaphenyl-2,4,6-heptatrienoate (**4a**) in 29% yield, along with minor amounts of 1:1:1 and 1:2:0 coupling products, **5a**[6a,b] and **6a**,[7] respectively (entry 1 in Table 1). Fortunately, the use of $Pd(acac)_2$ in place of $Pd(OAc)_2$ as catalyst dramatically improved the yield of **4a** up to 72% (entry 2, acac = acetylacetonate). The NMR spectra of isolated **4a** indicated that it contained a minor amount of its geometrical isomer [(2*E*,4*E*):(2*E*,4*Z*) = *ca.* 10:1]. Both decreasing and increasing the amount of AgOAc (entries 3 and 4) and the reaction temperature (entries 5 and 6) somewhat decreased the product yield. The use of a further excess amount of **2a** (6 equiv.) did not improve the yield (entry 7).

Table 2 summarizes the results for the reactions of various aryl iodides, diarylacetylenes, and alkenes. The alkenes with an electron-withdrawing group such as ethyl, isobutyl, and cyclohexyl acrylates and *N*,*N*-dimethylacrylamide smoothly reacted with **1a** and **2a** to produce the corresponding trienes **4b–e** (entries 1–4). Although these trienes were obtained as mixtures of geometrical isomers, each major (2*E*,4*E*)-isomer was found to be separable by recrystallization. The structure of (2*E*,4*E*)-**4e** was confirmed by X-ray crystal structure analysis (see Supporting Information).[9] 4-Methoxystyrene also underwent the three-component coupling with **1a** and **2a** to afford 6-(4-methoxyphenyl)-1,1,2,3,4-pentaphenyl-1,3,5-hexatriene (**4f**), albeit in a moderate yield (entry 5). The reactions of 4-iodotoluene with **2a** and **3** gave a complex mixture of at least three geometrical isomers of the expected triene in 59% yield. Therefore, the reactions using the substrate combinations of aryl iodides and diarylacetylenes, in which same aryl groups are contained, with **3a** were examined. Thus, from 4-methyl- and 4-chloro-substituted iodobenzenes and diphenylacetylenes, the corresponding trienes **4g** and **4h** were ob-

Table 2. Reaction of aryl iodides **1** with diarylacetylenes **2** and alkenes **3**.[a]

Entry	Time [h]	Product, Yield [%][b]	4*E*/4*Z*
			
1[c]	9	**4b**: R = CO_2Et, 64 (57)	76/24
2	3	**4c**: R = CO_2Bu-*i*, 66 (62)	63/37
3	1	**4d**: R = CO_2Cy, 65 (62)	79/21
4	1	**4e**: R = $CONMe_2$, 48 (31)	90/10
5	1	**4f**: R = 4-$MeOC_6H_4$, 40 (28)	80/20[d]
			
6	3	**4g**: X = Me, 66 (60)	88/12
7[e]	1	**4h**: X = Cl, (35)	78/22

[a] *Reaction conditions:* [**1**]:[**2**]:[**3**]:[$Pd(acac)_2$]:[AgOAc] = 1:4:1:0.05:2 (in mmol), in *o*-xylene (5 mL) at 140 °C under N_2.

[b] GC yield based on the amount of **1** used. Value in parenthesis indicates yield after purification.

[c] At 100 °C.

[d] (3*E*,5*E*):(3*Z*,5*E*) = 80:20.

[e] A significant amount of 1:1:1 coupling product, butyl (2*E*)-4,5,5-tris(4-chlorophenyl)-2,4-pentadienoate (**5b**) was also isolated (35%).

tained (entries 6 and 7). In contrast to the 1:1:1 coupling we previously reported,[6b] the 1:2:1 coupling of 2-iodothiophene, bis(2-thienyl)acetylene, and **3a** did not take place at all.

A plausible mechanism for the reaction of aryl iodides **1**, diarylacetylenes **2**, and alkenes **3** is illustrated in Scheme 3. The formation of an arylpalladium intermediate **A** *via* oxidative addition of **1** toward Pd(0) species generated *in situ* followed by successive insertion of two alkyne molecules forms a dienylpalladium intermediate **B**. Then, insertion of **3**, β-hydrogen elimination, and release of HX to regenerate Pd(0) may occur to allow the catalytic production of trienes **4**. The results in Table 1 and Table 2 imply that *E*/*Z* isomerization takes place in the intermediate **B**.[10] The use of AgOAc as base, in contrast to $NaHCO_3$ which brought about 1:1:1 coupling, seems to promote the alkyne insertion steps by eliminating the iodide ligand on **A**.[5,7] The lack of triple insertion[5a,11] of **2** suggests that the reaction of **B** with **3** is significantly faster than that with **2** even in the presence of AgOAc, while the reason is not clear at the present stage.

We next examined the synthesis of higher oligoenes by the present three-component coupling. Treatment of β-bromostyrene (**7**) [(*E*):(*Z*) = 6.5:1] with **2a** (4 equiv.) and **3a** (1 equiv.) in the presence of $Pd(acac)_2$ (0.05 mmol) and AgOAc (2 mmol) in *o*-xylene at 140 °C for 1 h gave 1,2,3,4,6-pentaphenylfulvene (**8**) in 55% yield as a 1:2:0 coupling product,[6b] in place of expected acyclic tetraene derivatives (Scheme 4). The intramolecular insertion of the alkenyl moiety of a trienylpalladium intermediate **D**, formed by double alkyne insertion on a styrylpalladium species **C**, may occur in preference to the insertion of **3a**.

Under similar conditions, 1-bromo-1,2,2-triphenylethene (**9**) underwent not the desired 1:2:1 but rather 1:1:1 coupling to afford triene **4a** in 66% yield as a single major product (Scheme 5). This reaction appears to involve a dienylpalladium intermediate **F** formed by single alkyne insertion on an ethenylpalladium species **E. F** may react with **3a** rather than **2a** in a similar manner to that of **B** in Scheme 3.

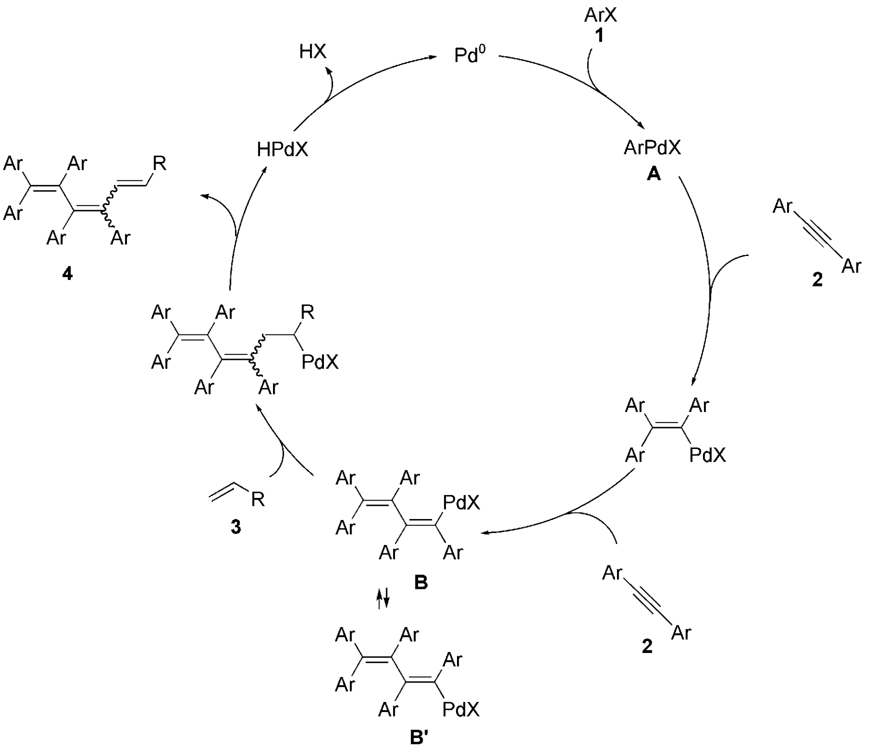
Finally, the synthesis of a pentaene derivative was achieved *via* the homologation of the oligoene chain of the three-component coupling product.[6b] Thus, as depicted in Scheme 6, trienyl bromide **10** was prepared *via* hydrolysis and decarboxylative bromination of (2*E*,4*E*)-**4b**.[12] As expected, **10** underwent the second three-component coupling with **2a** and **3a** under previously reported conditions suitable for 1:1:1 coupling using $NaHCO_3$[6b] to give butyl (2*E*,4*E*,6*E*,8*E*)-4,5,8,9,10,11,11-heptaphenyl-2,4,6,8,10-undecapentaenoate (**11**) in 51% yield. As a whole, the 1:3:2 coupling of **1a**, **2a**, and **3a** was achieved forming five C–C bonds.

Experimental Section

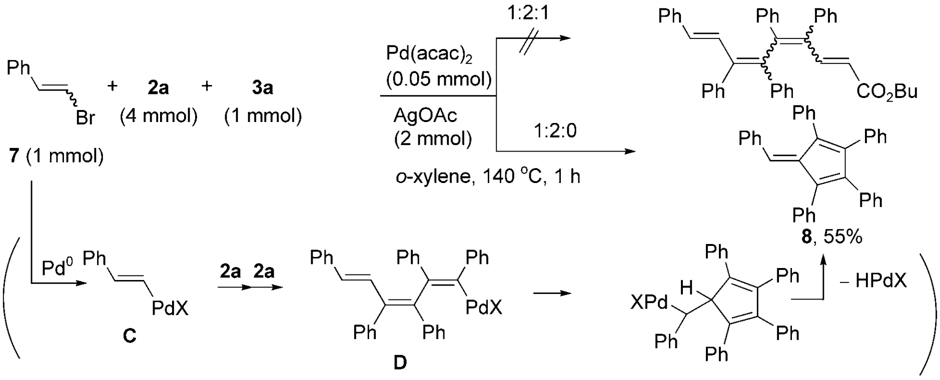
General Remarks

^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, for $CDCl_3$ solutions. MS data were obtained by EI. GC analysis was carried out using a silicon OV-17 column (i.d. 2.6 mm × 1.5 m) or a CBP-1 capillary column (i.d. 0.5 mm × 25 m). GC-MS analysis was carried out using a CBP-1 capillary column (i.d. 0.25 mm × 25 m). The structures of all products were unambiguously determined by ^1H and ^{13}C NMR with the aid of NOE, COSY, HMQC, and HMBC experiments and X-ray crystal structure analysis.

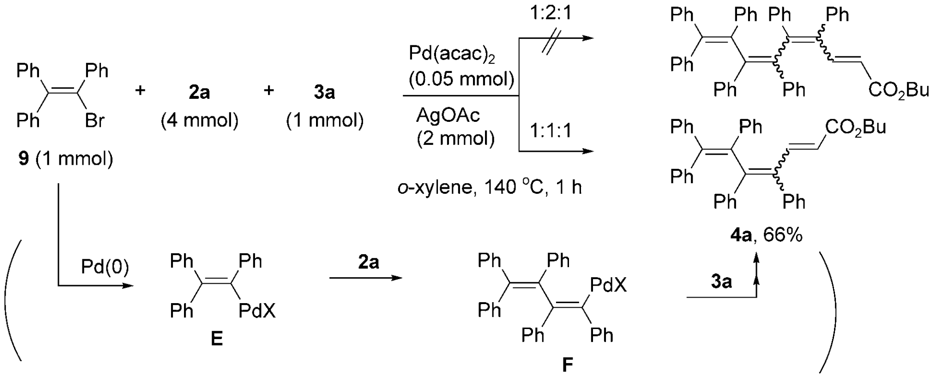
Bis(4-methylphenyl)acetylene, bis(4-chlorophenyl)acetylene, and bis(2-thienyl)acetylene were prepared according to published procedures.[13] Other starting materials were commercially available. Characterization data of all products are reported in the Supporting Information. The following experimental procedures may be regarded as typical in methodology and scale.



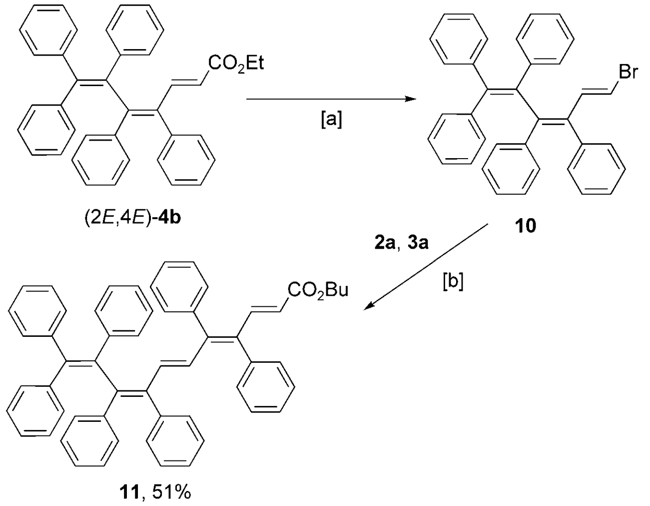
Scheme 3. A plausible mechanism for the reaction of **1** with **2** and **3**.



Scheme 4. Palladium-catalyzed coupling of β-bromostyrene (**7**) with **2a** and **3a**.



Scheme 5. Palladium-catalyzed coupling of 1-bromo-1,2,2-triphenylethene (**9**) with **2a** and **3a**.



Scheme 6. Synthesis of pentaene **11** from **4b**. *Reaction conditions:* [a] i) KOH (4 equiv.), EtOH, 80 °C, 5 hours; ii) NBS (1.2 equiv.), NEt_3 (20 mol%), CH_2Cl_2, room temperature, 5 minutes. [b] [**10**]:[**2a**]:[**3a**]:[$Pd(OAc)_2$]:[PPh_3]:[LiCl]:[$NaHCO_3$] = 0.5:2:0.5:0.025:0.05:0.35:1 (in mmol), DMSO/H_2O (9:1, 2.5 mL) at 120 °C under N_2 for 2 hours.

Pd-Catalyzed Reaction of Iodobenzene (1a), Diphenylacetylene (2a), and Butyl Acrylate (3a) (entry 2 in Table 1)

A mixture of iodobenzene (**1a**) (1 mmol, 204 mg), diphenylacetylene (**2a**) (4 mmol, 712 mg), butyl acrylate (**3a**) (1 mmol, 128 mg), $Pd(acac)_2$ (0.05 mmol, 15 mg), AgOAc (2 mmol, 334 mg), and 1-methylnaphthalene (*ca.* 50 mg) as internal standard was stirred in *o*-xylene (5 mL) under nitrogen at 140 °C. After 3 h, the reaction mixture was cooled to room temperature, Et_2O (100 mL) and water (100 mL) were added, and insoluble materials were removed by filtration through filter paper. Then the organic layer was washed by water (100 mL, three times) and dried over sodium sulfate. GC and GC-MS analyses confirmed the formation of **4a**, **5a**, and **6a** in 72, 16, and 3% yields, respectively. The product **4a** (363 mg, 65%) [(2*E*,4*E*):(2*E*,4*Z*) = 10:1] was isolated by column chromatography on silica gel using hexane-ethyl acetate (99.7:0.3, v/v) as eluant.

Compound 4a [(2*E*,4*E*):(2*E*,4*Z*) = 10:1]: oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.3$ Hz, 3 H), 1.28–1.39 (m, 2 H), 1.52–1.61 (m, 2 H), 4.08 (t, $J = 6.6$ Hz, 2 H), 5.22 (d, $J = 15.8$ Hz, 1 H), 6.91–6.94 (m, 5 H), 6.96–7.03 (m, 3 H), 7.08–7.18 (m, 15 H), 7.31–7.33 (m, 2 H), 8.23 (d, $J = 15.8$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.7$, 19.2, 30.8, 64.0, 122.1, 126.6, 126.9 (overlapped), 127.1, 127.20, 127.24, 127.6, 127.7, 127.8, 128.1, 129.4, 130.5 (overlapped), 131.1, 131.4, 137.3, 138.99, 139.04, 139.3, 140.7, 142.8, 143.4, 146.5, 146.6, 148.1, 167.5; HR-MS (EI): $m/z = 560.2711$, (calcd. for $C_{41}H_{36}O_2$: 560.2715).

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