Palladium-Catalyzed [4+2] *Cross*-Benzannulation Reaction of Conjugated Enynes with Diynes and Triynes

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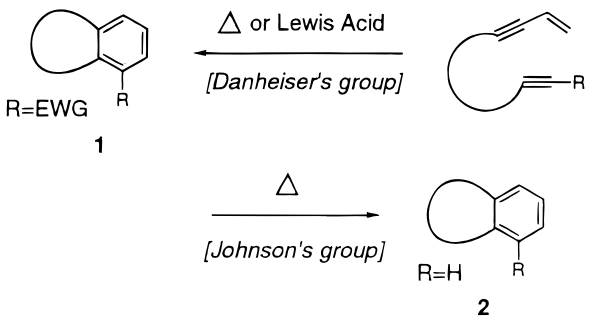
Abstract: The enyne−diyne [4+2] *cross*-benzannulation proceeded smoothly in the presence of Pd(0) catalyst to give 1,2,4-trisubstituted benzenes **8a**−**j**, 1,2,3-trisubstituted benzenes **9a**−**i**, 1,2,3,5-tetrasubstituted benzenes **11a**−**k**, 1,2,3,4-tetrasubstituted benzenes **11l**,**m**, and 1,2,3,4,5-pentasubstituted benzenes **11n**−**p** in moderate to quantitative yields. In all cases the reaction was found to be *regiospecific* with regard to substitution at the benzene ring. The palladium-catalyzed [4+2] cycloaddition of monosubstituted conjugated enynes **3a**−**c** and **5a** with unsymmetrical diynes **13a**−**j** and triynes **16a**−**g** also proceeded with perfect regiochemistry with regard to substitution at the benzene ring. However, since two differently substituted triple bonds are present in the enynophiles **13** and **16**, the enyne preference toward either triple bond in the enynophiles became an issue, and in most cases, two regioisomeric products were obtained. The detailed deuterium-labeling studies were performed, and the mechanism of this regiospecific [4+2] cycloaddition between enynes and diynes was proposed.

Introduction

It is hard to overstate the importance of aromatic compounds in most areas of synthetic organic chemistry and material science. Additionally, these ubiquitous structural units are found in a wide variety of naturally occurring compounds. Accordingly, much attention has been paid toward the synthesis of these classes of compounds by synthetic chemists. Although most of the approaches to date involve various types of modifications of aromatic precursors,[1] certain success has been achieved in the selective construction of the aromatic frameworks from different acyclic units.[2] Among several cycloaddition methodologies, perhaps the Dötz metal carbene−alkyne coupling[3] and alkyne [2+2+2] cyclotrimerizations[4] are the most general approaches toward benzene rings. While the last protocol has proven to be a simple, powerful, and very selective methodology for *intramolecular* alkyne trimerizations,[5] it still suffers from the severe drawback of providing low degrees of regio- and chemoselectivity for the *intramolecular* [2+2+2] alkyne cycloaddition.[6] Furthermore, there are several reports on successful synthesis of benzene derivatives **1** and **2** through thermal[7,8] or Lewis acid-mediated[7] enyne-yne [4+2] cycloaddition reaction (eq 1). However, these cycloaddition methodologies are strictly



(1)

limited to the *intramolecular* version of this reaction.[7,8] We have recently reported a complementary *regiospecific intermolecular* method for the construction of the benzene skeleton *via homodimerization* of conjugated enynes under palladium catalysis.[9] Thus, α,4-disubstituted styrenes **4** and 2,6-disubstituted

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(1) For reviews, see: (a) Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, 1990. (b) Zoltewicz, J. A. *Top. Curr. Chem.* **1975**, *59*, 33. (c) Kobrina, L. S. *Russ. Chem. Rev.* **1977**, *46*, 348. (d) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327. (e) Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957.

(2) For reviews, see: (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(3) For a review, see: Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587.

(4) For a review, see: (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. For the most recent mechanistic study, see: (b) Diercks, R.; Eaton, B. E.; Gürtzgen, S.; Jalisatgi, S.; Matzger, A. J.; Radde, R. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1998**, *120*, 8247.

(5) Lecker, S. H.; Nguen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 856. (b) Negishi, E.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253. See also ref 4 and references therein.

(6) See, for example: (a) Colman, J. P.; Kang, J. W.; Little, W. F.; Sullivan, M. F. *Inorg. Chem.* **1968**, *7*, 1298. (b) Ferreri, R. A.; Wolf, A. P. *J. Phys. Chem.* **1984**, *88*, 2256. (c) Borrini, A.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Serra, G. *J. Mol. Catal.* **1985**, *30*, 181.

(7) (a) Danheiser, R. L.; Gould, A. E.; Fernandez, de la Predilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514. For an oxa-version of this [4+2] cycloaddition reaction, see: (b) Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378.

(8) (a) Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218. For dehydro version of this reaction, see: (b) Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917.

(9) (a) Saito, S.; Salter, M. M.; Gevorgyan, V.; Tsuboya, N.; Tando, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3970. (b) Gevorgyan, V.; Tando, K.; Uchiyama, N.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 7022. For intramolecular version of this reaction, see: (c) Saito, S.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 5042. (d) Weibel, D.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1217.

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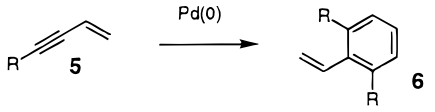
styrenes **6** could be now effectively synthesized in one step from conjugated enynes **3** (eq 2)[9a] and **5** (eq 3)[9b] respectively.

(2)

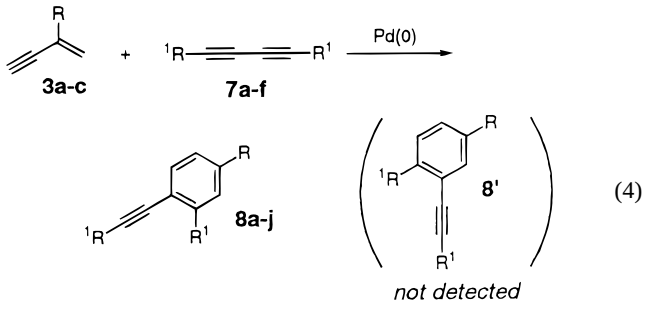


(3)

As a further development of this methodology, we also recently communicated the preparation of multisubstituted benzenes via the palladium-catalyzed *intermolecular* enyne−diyne [4+2] *cross-benzannulation* protocol.[10] In this paper we report a full account on this palladium-catalyzed enyne-yne [4+2] *cross-benzannulation* reaction, involving reactions of conjugated enynes with unsymmetrical diynes and triynes, as well as mechanistic studies of this reaction.

Results and Discussion

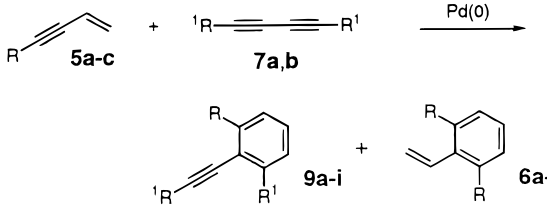
Synthesis of 1,2,4-Trisubstituted Benzenes 8. After trying a number of alkynes in a role of enyne partner in the [4+2] cycloaddition, we discovered that conjugated diynes **7** underwent regiospecific *cross*-cycloaddition with **3** (eq 4). The reaction



(4)

of 2-methyl-1-buten-3-yne **3a** with dodeca-5,7-diyne **7a** in the presence of 5 mol % $Pd(PPh_3)_4$ in THF at 65 °C gave **8a**[11] in 89% yield (entry 1, Table 1). No traces of **8′** were detected by NMR and capillary GLC analyses of crude reaction mixtures. The enyne−diyne *cross*-annulation reaction of enynes **3b**,**c** appeared to be much faster than the corresponding enyne−enyne *homo*- dimerization;[9a] thus an equimolar amount of hexyl-(**3b**) and benzyl- (**3c**) enyne reacted with diynes **7a**,**b**,**d**,**e**,**f** not only in *regio*-, but also in *chemo*-selective manner affording the *cross*-annulation products **8d**−**f**,**h**−**j** exclusively (entries 4−6, 8−10). In contrast, 2−5-fold excess of volatile and less reactive **3a** (toward diynes **7**) were needed to drive the reaction until complete conversion of **7** (entries 1−3).[12] Bulky diyne **7c** reacted with enynes more slowly in comparison with **7a**,**b**,**d**−**f**; thus the slow addition of the enynes **3a**,**c** was employed in order to avoid its dimerization (entries 3, 7).

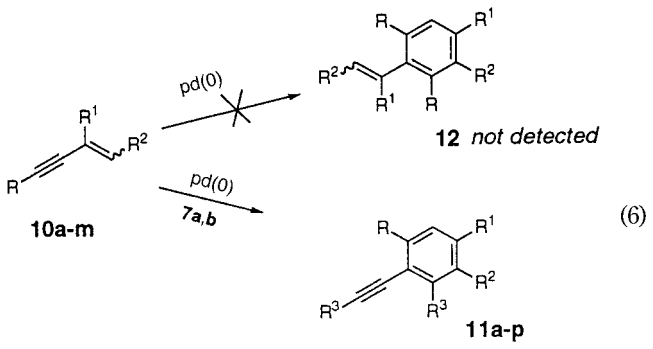
Synthesis of 1,2,3-Trisubstituted Benzenes 9. Encouraged by successful preparation of 1,2,4-trisubstituted benzenes **8** via the palladium-catalyzed *cross*-benzannulation of 2-substituted enynes **3** with diynes **7**, we attempted to perform a similar [4+2] *cross*-cycloaddition reaction employing 4-susbstituted conjugated enyne **5**. Overnight stirring of hexyl-substituted enyne **5a** with dodecadiyne **7a** in the presence of 5 mol % $Pd(PPh_3)_4$ in THF at 65 °C (the best conditions found for the *cross*-benzannulation of 2-substituted enynes **3**) gave *cross*-benzannulation product, benzene **9a**, in 52% yield, accompanied with 7% of *homo*-dimerization product **6a** (eq 5). After certain



(5)

optimization work, it was found that stirring the mixture of the same reactants in toluene at 80 °C afforded **9a** in 66% isolated yield together with 12% of homodimer **6a** (Table 2, entry 1). Other 4-substituted enynes, possessing aryl- (**5b**), keto- (**5c**), chloro- (**5d**), and hydroxy- (**5e**) groups in a side chain underwent smooth cycloaddition reaction with **7a** and diphenyldiyne **7b** to produce 1,2,3-trisubstituted benzenes **9b**−**i** in moderate to good isolated yields (eq 5, Table 2). Although in all cases the enyne−diyne *cross*-benzannulation reaction was absolutely regiospecific, the chemoselectivity of this reaction was not perfect, since in all cases the formation of trace to detectable amounts of enyne *homodimers* **6** was detected (eq 5, Table 2).

Synthesis of 1,2,3,5-Tetrasubstituted Benzenes 11a−k, 1,2,3,4-Tetrasubstituted Benzenes 11l,m, and 1,2,3,4,5-Pentasubstituted Benzenes 11n−p. To test our palladium-catalyzed enyne−diyne [4+2] *cross*-cycloaddition methodology for the preparation of tetra- and pentasubstituted benzenes, we prepared 2,4-disubstituted enynes **10a**−**f**, 1,4-disubstituted enynes **10g**,**h**, and 1,2,4-trisubstituted enynes **10i**−**m**. Control experiments indicated that neither disubstituted enynes **10a**−**h** nor trisubstituted enynes **10i**−**m** were able to undergo the *homo*-dimerization reaction in the presence of $Pd(PPh_3)_4$ even under prolonged heating at 120 °C; no traces of *homodimerized* products **12** were detected by GC-MS analyses of the crude reaction mixtures (eq 6). Encouraged by this fact we examined



(6)

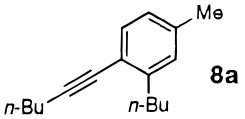
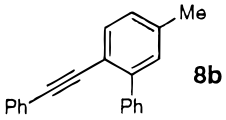
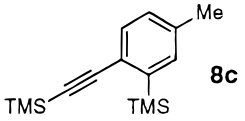
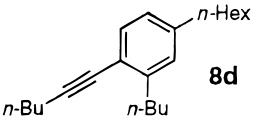
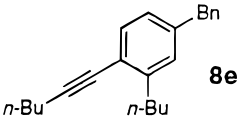
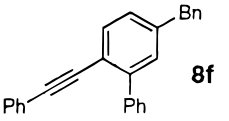
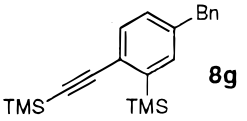
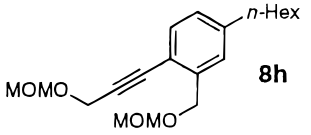
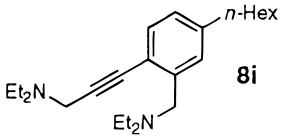
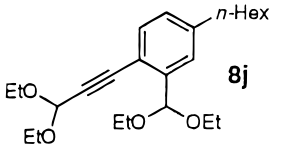
2,4-disubstituted enynes **10a**−**f** in the [4+2] *cross*-cycloaddition reaction with diynes **7a**,**b** (eq 6, Table 3). We found that dialkyl-substituted enyne **10a**, alkylalkenyl-substituted enyne **10b**, and alkylphenyl-substituted enyne **10c** in the presence of 5 mol % of $Pd(PPh_3)_4$ at 80 °C in toluene did not react with **7a**,**b** at all but underwent rather slow reaction (4−5 days) at 100 °C

(10) (a) Gevorgyan, V.; Takeda, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11313. (b) Gevorgyan, V.; Sadayori, N.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 8603.

(11) The structure of *para*-oriented **8d** was unambiguously confirmed by 500 MHz NOE- and COLOC NMR analyses. See Supporting Information (S28−S32).

(12) Excess enyne **3a** underwent *homo*-dimerization, affording **4a**, see also footnote c, Table 1.

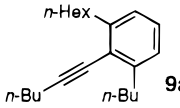
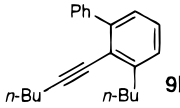
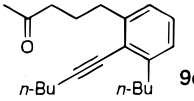
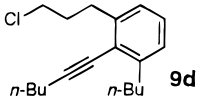
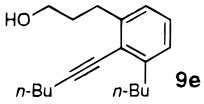
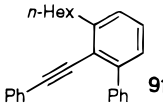
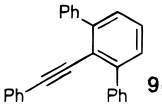
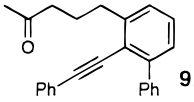
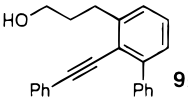
Table 1. Palladium-Catalyzed *Cross*-Benzannulation of 2-Substituted Enynes **3** with Symmetrical Diynes **7**

entry	R	R^1	Product **8**	Yield (%)[a]
1	Me (**3a**)[b,c]	*n*-Bu (**7a**)	 **8a**	89 (10)[d]
2	(**3a**)[b,c]	Ph (**7b**)	 **8b**	>99
3	(**3a**)[c,e,f]	TMS (**7c**)	 **8c**	92
4	*n*-Hex (**3b**)	(**7a**)	 **8d**	60[g] (36)[d]
5	Bn (**3c**)[h]	(**7a**)	 **8e**	89
6	(**3c**)	(**7b**)	 **8f**	86
7	(**3c**)[i]	(**7c**)	 **8g**	80
8	(**3b**)	CH_2OMOM (**7d**)	 **8h**	74
9	(**3b**)	CH_2NEt_2 (**7e**)	 **8i**	88
10	(**3b**)	$CH(OEt)_2$ (**7f**)	 **8j**	88

[a] Isolated yields based on diyne **7**, except for where otherwise indicated. [b] Two equivalents of **3a** were utilized. [c] Excess **3a** underwent homodimerization affording the by-product **4a** (R=Me).[9] [d] Recovery of **7** (%). [e] Five equivalents of **3a** was utilized. [f] **3** was added in 5 portions. [g] NMR yield. [h] One and half equivalents of **3c** was added in 10 portions. [i] Two and half equivalents of **3c** was added during 14 hours using syringe pump.

(Method **A**), affording 1,2,3,5-tetrasubstituted benzenes **11a**−**f** in moderate to high chemical yields (eq 6, Table 3, entries 1−6). Being unsatisfied by the drastic reaction conditions for the benzannulation of **10a**−**c**, we performed a substantial optimization work of the catalyst system. We found that the use of the catalyst system $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %) − P(*o*-tol)$_3$ (40 mol %) in toluene (Method **B**), instead of $Pd(PPh_3)_4$, allowed us to decrease the temperature of the benzannulation reaction from 100 to 50 °C. However the yields of **11a**−**f** in the cases of employment of the Method **B** were 10−15% lower than those for Method **A**. 2,4-Diaryl-substituted enynes **10d**−**f**, in contrast to **10a**−**f**, enabled the benzannulation reaction to go very smoothly. Thus, 2,4-diphenylenyne **10d**, 2,4-di(*p*-tolyl)-enyne **10e**, and 2,4-di(*p*-methoxyphenyl)enyne **10f** reacted with **7a**,**b**

Table 2. Palladium-Catalyzed *Cross*-Benzannulation of 4-Substituted Enynes **5** with Symmetrical Diynes **7**

entry	enyne R	diyne R^1	Time (Days)	products, yields, %[a] **9**		**6**	
1	n-Hex (**5a**)	n-Bu (**7a**)	0.33	 **9a**	66	**6a**	12
2	Ph (**5b**)	(**7a**)	2	 **9b**	40	**6b**	14
3	$CH_3CO(CH_2)_3$ (**5c**)	(**7a**)	0.1	 **9c**	50	**6c**	24
4	$Cl(CH_2)_3$ (**5d**)	(**7a**)	3	 **9d**	36	**6d**	2
5	$HO(CH_2)_3$ (**5e**)	(**7a**)	1	 **9e**	50	**6e**	8
6	n-Hex (**5a**)	Ph (**7b**)	2	 **9f**	61	**6f**	8
7	(**5b**)	(**7b**)	4	 **9g**	58	**6g**	9
8	(**5c**)	(**7b**)	1	 **9h**	62	**6h**	9
9	(**5e**)	(**7b**)	2	 **9i**	52	**6i**	trace

[a] Isolated yields.

under conditions of the Method **B** *even at room temperature*, affording the corresponding tetrasubstituted benzenes **11g**−**k** (Table 3, entries 7−11) in good to *virtually quantitative isolated yields!*

Again, the reactions of the alkyl group-containing *Z*-1,4-disubstituted enynes **10g**,**h** with diynes **7a**,**b** even under very high temperature (120 °C) were rather sluggish and afforded the desired aromatic products with trace to unsatisfactory low yields. The main reason of last would be the low stability of the palladium catalyst under the prolonged heating. This problem was solved by the addition of excess amounts of phosphine ligand to the reaction mixture.[13] Thus, employment of 20 mol % of tris(2,6-dimethoxyphenyl)phosphine − 5 mol % of Pd-$(PPh_3)_4$ combination (Method **C**) allowed us to obtain 1,2,3,4-tetrasubstituted benzenes **11l**,**m** in 40% and 70% yields, respectively (Table 3, entries 12, 13). It was interesting to find that *E*-isomers of **10g**,**h** practically did not undergo the benzannulation reaction under similar conditions at all (Table 3, note b).

(13) During our study on palladium-catalyzed enyne−enyne *homodimerization* reactions[9b] we found that Pd(0) complexes, bulky phosphine ligands combinations (4−10-fold excess of phosphine ligands with respect to Pd content), were rather more thermally stable than Pd(0) complexes alone.

Z-1,2,4-Trisubstituted enyne **10i** was able to react slowly with **7a** under the conditions of Method **C**, affording pentasubstituted benzene **11n** in 47% yield (entry 14). Remarkably, the replacement of the methyl group in the enyne **10i** with electron-withdrawing substituents, such as ester (**10j**) or cyano (**10l**) groups, exerted a dramatic acceleration effect on the *cross*-benzannulation reaction. Thus, *Z*-1,2,4-trisubstituted enynes **10j**,**l**, in contrast to **10i**, smoothly reacted with **7a** even under the conditions of milder Method **A** (in 6 and 48 h at 100 °C for **10j** and **10l**, respectively, versus 5 days at 120 °C for **10i**) to give the multisubstituted benzoate **11o** and cyanobenzene **11p** in high yields (72% and 81%, respectively, entries 15, 17). Again surprisingly, in the case of enynes, possessing electron-withdrawing substituents at the C-1 position, not only *Z*-isomers (**10j**,**l**) but also the corresponding *E*-isomers **10k**,**m** were able to undergo the cycloaddition with **7a** to give the pentasubstituted benzenes **11o**,**p**, although with somewhat lower yields (eq 6, Table 3, entries 16, 18).

Cycloaddition of 2-Substituted Enynes 3 with Unsymmetrical Diynes 13. In all of the above cases the palladium-catalyzed [4+2] *cross-benzannulation* reaction between enynes and diynes was found to be perfectly *regiospecific* with regard

Table 3. Palladium-Catalyzed *Cross*-Benzannulation of Multisubstituted Enynes **10** with Symmetrical Diynes **7**

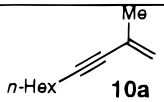
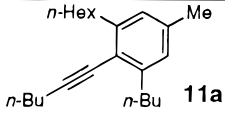
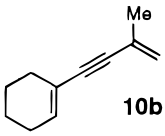
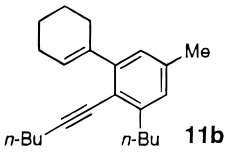
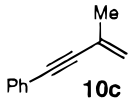
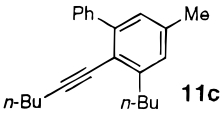
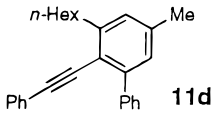
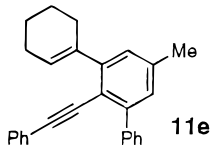
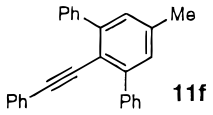
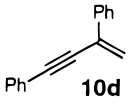
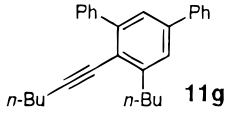
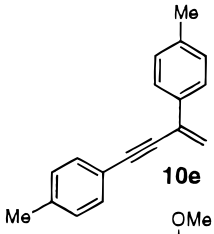
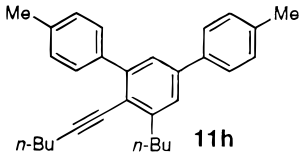
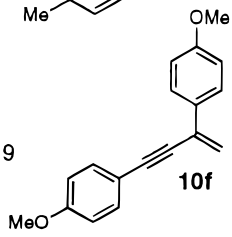
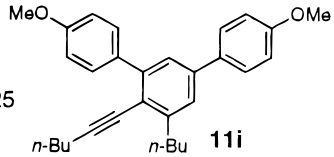
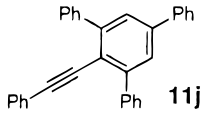
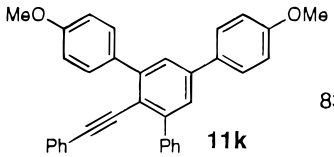
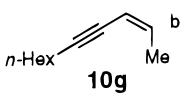
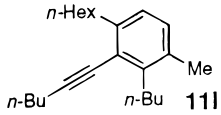
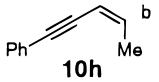
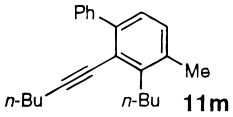
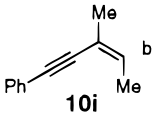
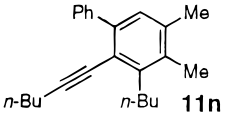
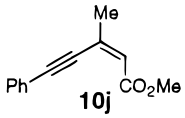
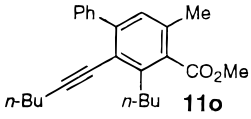
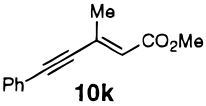
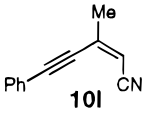
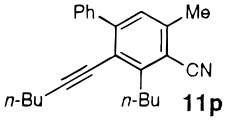
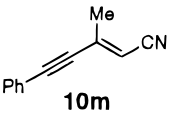
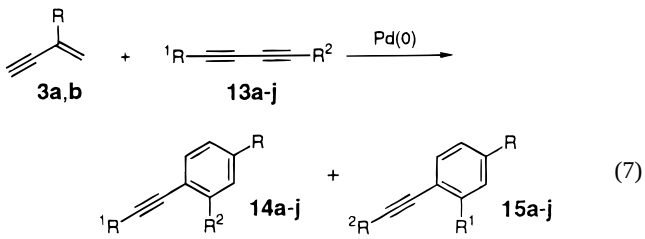
entry	enyne	diyne R^3	method	Time/Temp (days/°C)	product **11**	yields, %[a]
1	 **10a**	*n*-Bu (**7a**)	**A**	5/100	 **11a**	69
2	 **10b**	(**7a**)	**A**	5/100	 **11b**	71
3	 **10c**	(**7a**)	**A**	4/100	 **11c**	90
4	**10a**	Ph (**7b**)	**A**	5/100	 **11d**	63
5	**10b**	(**7b**)	**A**	4/100	 **11e**	41
6	**10c**	(**7b**)	**A**	5/100	 **11f**	87
7	 **10d**	*n*-Bu (**7a**)	**B**	7/25	 **11g**	98
8	 **10e**	(**7a**)	**B**	6/25	 **11h**	82
9	 **10f**	(**7a**)	**B**	6/25	 **11i**	83
10	**10d**	Ph (**7b**)	**B**	2/25 0.2/50	 **11j**	55
11	**10f**	(**7b**)	**B**	6/25	 **11k**	83

Table 3 (Continued)

entry	enyne	diyne R^3	method	Time/Temp (days/°C)	product **11**	yields, %[a]
12	 **10g**	*n*-Bu (**7a**)	**C**	5/120	 **11l**	40
13	 **10h**	(**7a**)	**C**	14/120	 **11m**	77
14	 **10i**	(**7a**)	**C**	5/120	 **11n**	47
15	 **10j**	(**7a**)	**A**	0.25/100	 **11o**	(72)
16	 **10k**	(**7a**)	**C**	7/120	**11o**	55
17	 **10l**	(**7a**)	**A**	2/100	 **11p**	81
18	 **10m**	(**7a**)	**A**	3/100	**11p**	65

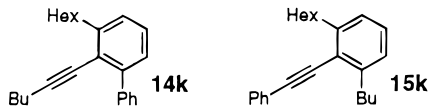
[a] Isolated yields. [b] Reactions employing *E*-isomers of these enynes produced trace amounts of aromatic products.

to the orientation of the unreacted triple bond in the enynophile (diyne), since symmetrically substituted diynes were used. However, in the case if unsymmetrical diynes are employed, two differently substituted triple bonds would be able to undergo the cycloaddition reaction. Consequently, in these cases an additional regiochemistry issue should be considered. To examine above-mentioned topic, we studied the benzannulation of monosubstituted enynes **3a**,**b** with unsymmetrical diynes **13a**−**j** (eq 7, Table 4). The experiment demonstrated that in



(7)

several cases only one triple bond of unsymmetrical diyne was reactive toward the cycloaddition with enyne. Thus, terminal diynes, possessing bulky substituents such as *t*-Bu- (**13b**) and MOMOC(Me)$_2$- (**13d**), reacted with **3a** selectively to produce the single reaction products, phenylacetylenes **14b** and **14d**, in 52 and 80 isolated yields, respectively (eq 7, Table 4, entries 2 and 4). In both products, the bulky groups were attached to the aromatic ring. Two selective reactions were also observed in the case of internal diynes; the only triple bond, attached to the TMS group of unsymmetrical **13f**, and that attached to (HO)C-(CH$_3$)$_2$ group of **13i** underwent the benzannulation reaction to give **14f** and **14i** as sole reaction products in 78% and 54% yields, respectively (entries 6, 9). In all other cases tested, both triple bonds of unsymmetrical diynes (**13a**,**c**,**e**,**g**,**h**,**j**) were reactive in the palladium-catalyzed benzannulation reaction with enynes **3a**,**b** to give both isomeric products **14** + **15a**,**c**,**e**,**g**,**h**,**j** in moderate to good combined yields (eq 7, Table 4, entries 1,3,5,7,8,10).[14] It seems that the reactivity issue of two differ-

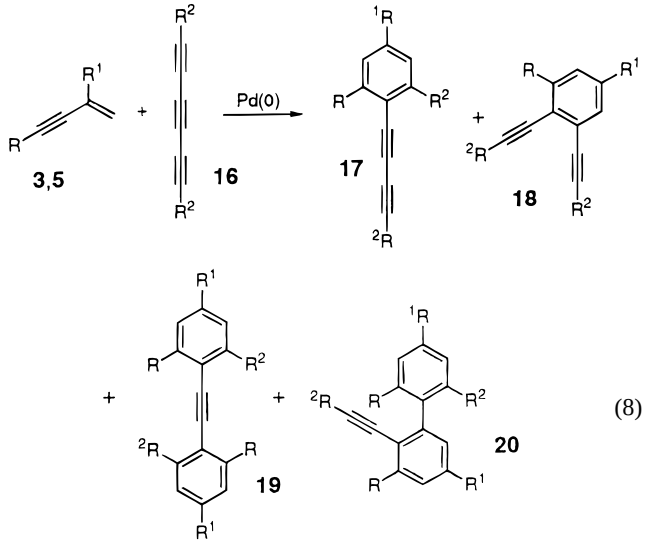


ently substituted triple bonds of unsymmetrical diynes **13a**−**j** could not be explained by the steric factors only. At this stage we have a feeling that electronic factors could play some role in this diverse regioselectivity, as well.[15]

(14) Both triple bonds of **13e** exhibited rather similar reactivities toward 4-substituted enyne **5a**, as well. Accordingly, trisubstituted benzenes **14k** and **15k** were obtained in 36% and 39%, respectively.

(15) Preliminary low level ab initio computations revealed that the triple bond, attached to the TMS group, of unsymmetrical diyne **13f** and of triyne **16g** is more electron-rich than the others.

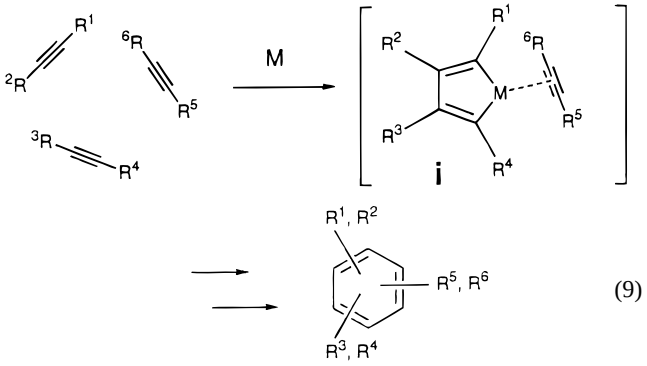
Cycloaddition of Monosubstituted Enynes 3,5 with Triynes 16. Next, we examined the palladium-catalyzed benzannulation of enynes **3a**−**c** and **5a** with conjugated triynes **16a**−**g** (eq 8,



(8)

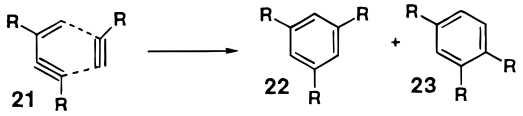
Table 5). Again, the triynes, possessing bulky (**16d**−**h**) and TMS (**16g**) substituents,[15] reacted with enynes **3a**−**c** regioselectively to afford the aromatic conjugated diynes **17d**−**h** as a single reaction product in high isolated yields (Table 5, entries 5−9). In contrast, both different triple bonds of triyne **16b** were similarly reactive to afford an almost statistical distribution of **17b** and **18b** (44% and 28%, respectively, entry 2). Similarly, low regioselectivities were observed in the reactions of triynes **16a**,**c** (entries 1,3). In these cases, the formation of notable amounts of double-benzannulation products **19a**, **20a**, and **20b** were observed (entries 1, 3). Furthermore, the employment of 2.2 equiv of **3b** completely converted initially formed **17c** into a mixture of **19b** and **20b**, while the amount of **18c** remained virtually unchanged (entry 4). The 4-susbstituted enyne **5a**, as expected, reacted with triynes much more slowly. The reaction of **5a** with **16b** produced a mixture of **17i** and **18d** in 36% and 9% yields, respectively (entry 10), whereas the benzannulation with **16d** was even more sluggish, although selective, to give the conjugated diyne **17j** only in 29% yield (entry 11).

Mechanistic Study. Analyzing the problems to control the *regioselectivity* of *intramolecular* trimerization of alkynes proceeding via the traditional metallocycle **i** (eq 9),[4] we realized



(9)

that if a conjugated enyne **21** (as a regiodefined equivalent of dimerized alkyne) would react with an alkyne in a [4+2] cycloaddition manner, this reaction could be more regioselective than [2+2+2] mode of cycloaddition since only the regioselectivity of two bond formation remains questionable (eq 10).



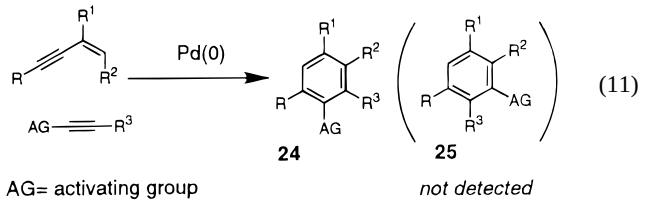
(10)

However, as we have previously mentioned (eqs 4−8, Tables 1−5), in all of the cases of palladium-catalyzed *cross*- [4+2] cycloadditions, only one regioisomer **24** (with regard to relative orientation of enyne and enynophile) was formed, and no traces of regioisomeric **25** were ever detected in the crude reaction mixtures (eq 11, AG = alkyne for enyne-diyne *cross*-benzannulation, and AG = alkene for enyne−enyne *homo*-dimerization[9]).

This fact of remarkable *regiospecificity* completely eliminates involvement of the traditional transition metal-assisted mechanism of alkynes trimerization (eq 9). Indeed, if the mentioned mechanism is operative, the formation of two regioisomers **22** and **23** (eq 10) is unavoidable. Consequently, the observed palladium-catalyzed *regiospecific* [4+2] enyne-yne cycloaddition must proceed through an entirely different mechanism.

It is obvious that at a certain stage of this novel palladium-catalyzed enyne−diyne benzannulation process there should be the migration of one of the hydrogen atoms of conjugated enyne to its internal *sp* carbon (marked as "•", Figure 1). To figure out which hydrogen migrates, we performed comprehensive deuterium-labeling studies. We synthesized the conjugated enynes **26**−**30** with a deuterium atom incorporated into all of the possible positions of them and subjected those deuterated enynes to the benzannulation reaction with diyne **7a** (Figure 1). Thus, the monodeuterated enynes **26** and **27**, possessing a deuterium atom at the C-4 and C-2 positions, afforded the benzenes **31** and **32**, respectively, indicating no migration of D atom (Figure 1). As expected, the cycloaddition of bis-deuterated enyne **28** afforded the bis-deuterated benzene **33**, indicating a deuterium migration to the internal *sp* carbon of enyne. To clarify which particular D migrates, we examined the cycloaddition of *Z*- (**29**) and *E*-deuterated enyne **30**. The benzannulation of **29** revealed no deuterium migration, whereas the reaction of *E*-deuterated enyne **30** produced deuterated benzene **35**, thus unambiguously indicating that the deuterium atom at *E*-position of C-1 migrates to the C-3 of **30**.

The results on deuterium-labeling experiments, taken together with the fact of *regiospecific* formation of *single* regioisomer **24** (eq 11), encouraged us to propose the following mechanistic



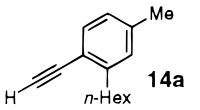
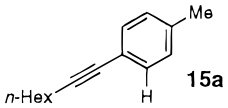
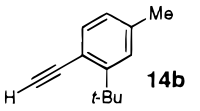
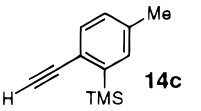
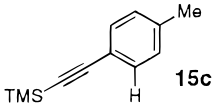
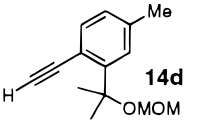
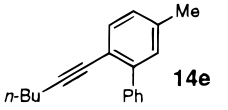
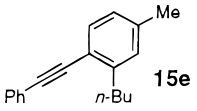
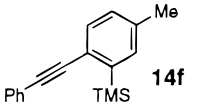
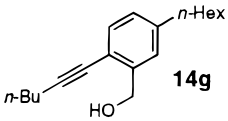
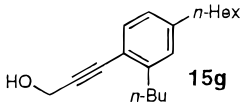
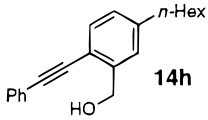
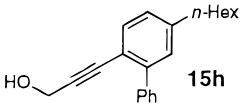
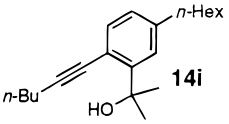
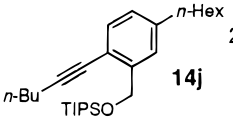
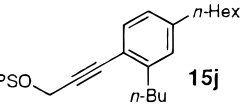
(11)

rationale for this reaction (Scheme 1). The coordination of palladium with enyne and diyne (**36**) would produce palladacycle **37**,[16] stabilized by the coordination of Pd atom with neighboring η^3-propargyl moiety.[17] Then **37** either undergoes sigmatropic shift to form another metallocycle **38**, which via

(16) π-Propargyl palladium complexes have been recently isolated and fully characterized. See: (a) Ogoshi, S.; Tsutsumi, K.; Kurosawa, H. *J. Organomet. Chem.* **1995**, *493*, C19. (b) Ogoshi, S.; Tsutsumi, K.; Ooi, M.; Kurosawa, H. *J. Am. Chem. Soc.* **1995**, *117*, 10415.

(17) The coordination of palladium to propargyl group in the intermediate **37** is supported not only by the exclusive formation of a sole regioisomer **24** but also by the fact that simple alkynes, such as acetylene and its alkyl-, aryl-, halo-, and cyanoderivatives which do not possess such an additional

Table 4. Palladium-Catalyzed *Cross*-Benzannulation of 2-Substituted Enynes **3** with Unsymmetrical Diynes **13**

entry	enyne R	diyne R^1	diyne R^2	Time (h/65°C)	products, yields, %[a] **14**		**15**	
1	Me (**3a**)	H	*n*-Hex (**13a**)	3	 **14a**	50	 **15a**	28
2	(**3a**)	H	*t*-Bu (**13b**)	2	 **14b**	52	**15b**	trace
3	(**3a**)	H	TMS (**13c**)	4	 **14c**	23	 **15c**	18
4	(**3a**)	H	$MOMOC(CH_3)_2$ (**13d**)	2	 **14d**	80	**15d**	none
5	(**3a**)	*n*-Bu	Ph (**13e**)	12	 **14e**	46	 **15e**	54
6	(**3a**)	Ph	TMS (**13f**)	12	 **14f**	78	**15f**	none
7	*n*-Hex (**3b**)	*n*-Bu	$HOCH_2$ (**13g**)	12	 **14g**	38	 **15g**	42
8	(**3b**)	Ph	$HOCH_2$ (**13h**)	12	 **14h**	36	 **15h**	44
9	(**3b**)	*n*-Bu	$HOC(CH_3)_2$ (**13i**)	12	 **14i**	54	**15i**	trace
10	(**3b**)	*n*-Bu	$TIPSOCH_2$ (**13j**)	12	 **14j**	26	 **15j**	50

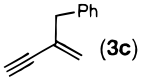
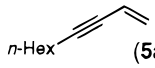
[a] Isolated yields.

reductive coupling affords the benzene **40** and regenerates a Pd(0) catalyst, or forms a strained cyclic cumulene **39** via consecutive reductive elimination of palladium,[18] which is transformed into the aromatic product **40** via sigmatropic rearrangement. Although the reasons for observed hydrogen migration exclusively from *E*-position of conjugated enynes are not clearly understood, this fact is in perfect agreement with the relative reactivities of *Z*- and *E*-isomers of enynes **10g,m** in the benzannulation reaction (Table 3). Thus, as it was mentioned above, the alkyl-substituted *Z*-enynes **10g**−**i**, which possess a hydrogen atom in *E*-position, underwent smooth cycloaddition, whereas their *E*-counterparts (with hydrogen atom in *Z*-position) did not exhibit any notable reactivity under the similar reaction conditions (Table 3, note b). In contrast to above cases, the reactivities of *E*- and *Z*-isomers of activated enynes **10j**−**m** are not so different. As a working hypothesis, we assume that partial E → Z isomerization of activated *E*-enynes **10k** and **10m** into their more reactive *Z*-analogues **10j** and **10l**, under

alkynyl group, do not act as enynophiles in the mentioned reaction at all. Accordingly, an alternative explanation for remarkably high reactivity of diynes in terms of steric effects is discounted by the observation that acetylene itself did not act as an enynophile in that reaction.

(18) This type of six-membered strained cyclic cumulene has been proposed as an intermediate in the dehydro Diels−Alder cycloadditions. (a) For review see: Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111. (b) See also ref 8.

Table 5. Palladium-Catalyzed *Cross*-Benzannulation of Monosubstituted Enynes **3** and **5** with Triynes **16**

entry	enyne	triyne R^2	Time/Temp (h/°C)	products, yields, %[a] 17	18	19	20
1	 (**3a**)	*n*-Bu (**16a**)	22/100	(**17a**) 24	(**18a**) 22	(**19a**) 10	(**20a**) 10
2	 (**3b**)	Ph (**16b**)	2/60	(**17b**) 44	(**18b**) 28	-	-
3	(**3b**)	$MOMOCH_2$ (**16c**)	2/65	(**17c**) 22	(**18c**) 50	-	(**20b**) 6
4	(**3b**)[b]	(**16c**)	15/65	-	(**18c**) 48	(**19b**) 12	(**20b**) 22
5	(**3a**)	$MOMOC(CH_3)_2$ (**16d**)	1/60	(**17d**) 86	-	-	-
6	(**3b**)	(**16d**)	2/60	(**17e**) 84	-	-	-
7	(**3b**)	$HOC(CH_3)_2$ (**16e**)	2/65	(**17f**) 80	-	-	-
8	(**3b**)	$TIPSOC(CH_3)_2$ (**16f**)	2/65	(**17g**) 78	-	-	-
9	 (**3c**)	TMS (**16g**)	2/60	(**17h**) 86	-	-	-
10	 (**5a**)	(**16b**)	24/80	(**17i**) 36	(**18d**) 9	-	-
11	(**5a**)	(**16d**)	72/80	(**17j**) 29	-	-	-

[a] Isolated yields. [b] In this case, 2.2 equiv of **3b** was used. In all the other cases, one equivalent of **3** was used.

the reaction conditions, could be responsible for the surprisingly low reactivities of *E*-enynes **10k** and **10m** (Table 3, entries 16, 18).

Concluding Remarks. As a brief concluding outlook on palladium-catalyzed [4+2] cycloaddition reactions of conjugated enynes to date, we arranged the mono- and multisubstituted enynes in the order of the decrease of their reactivities (Figure 2). The monosubstituted enynes **3** and **5**, as the most reactive substrates, easily react in both *homo*- and *cross*-cycloaddition manner to afford the enyne−enyne *homodimerization* products **4**[9a] and **6**[9b] and enyne−diyne *cross-benzannulation* products **8** and **9**, respectively (Figure 2). In contrast to the above cases, the di- and trisubstituted enynes **10** did not undergo the *homo*-dimerization process; however they reacted with diynes in the *cross*-cycloaddition manner, although in most cases their reactions were slower than that for monosubstituted enynes **3** and **5**, affording multisubstituted benzenes **11** not only in highly *regio*- but also in highly *chemoselective* manner (Figure 2).

Although further investigation to settle a precise reaction mechanism is needed, the present procedure provides a new regiospecific and synthetically useful route to multisubstituted arylacetylenes possessing alkyl-, alkynyl-, aryl-, silyl-, cyano-, and ester functionalities attached to the benzene unit.

Experimental Section

Instrumentation. NMR spectra were recorded on a JEOL JNM LA-300 (300 MHz) and JEOL JNM α-500 (500 MHz) instruments. IR spectra were recorded on a Shimadzu FTIR-8200A spectrometer. High-resolution mass spectra were recorded on a Hitachi M-2500S spectrometer. GC-MS analyses were performed on a Hewlett-Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (30 m × 0.25 mm capillary column, HP-5MS). Capillary GLC analysis was performed on SHIMADZU GC-18A (30 m × 0.25 mm capillary column, DB-5). Column chromatography was carried out employing Merck silica gel (Kieselgel 70−230 mesh), and analytical thin-layer chromatography (TLC) was performed on 0.2 mm precoated silica gel plates (Kieselgel 60 F_{254}).

Chemicals. Anhydrous solvents were purchased from Kanto Chemicals. All other compounds used were commercially available and purchased from Aldrich.

Synthesis of Substrates. Enynes **3b**,[19] **3c**,[20] **5a**−**e**, **10a**−**c**,**g**−**i**,[21] **10d**−**f**,[22] **10j**−**m**,[23] **26**,[24] **27**,[25] **28**,[26] **29**−**30**,[27] diynes **7d**,[28] **7e**,**f**,[21] **13a**,**b**,[29]

(19) Klusener, P. A. A.; Kulik, W.; Brandsma, L. *J. Org. Chem.* **1987**, *52*, 5261.

(20) Benzyl-substituted enyne **3c** was prepared via the following consecutive transformations: acylation of bis-TMS-acetylene with phenylacetyl chloride,[20a] Peterson olefination,[20b] followed by desilylation step.[20c] See: (a) Schwab, J. M.; Lin, D. C. T. *J. Am. Chem. Soc.* **1985**, *107*, 6046.[20a] (b) For a review on Peterson olefination, see for example: Ager, D. J. *Synthesis* **1984**, 384. (c) Corey, E. J.; Ruden, R. A. *Tetrahedron Lett.* **1973**, 1495.

(21) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, The Netherlands, 1988.

(22) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698.

(23) Ester- **10j**,**k**, and cyano-containing enynes **10l**,**m** were synthesized from the corresponding alkynyl ketones via Horner-Wadsworth-Emmons procedure, see: Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624.

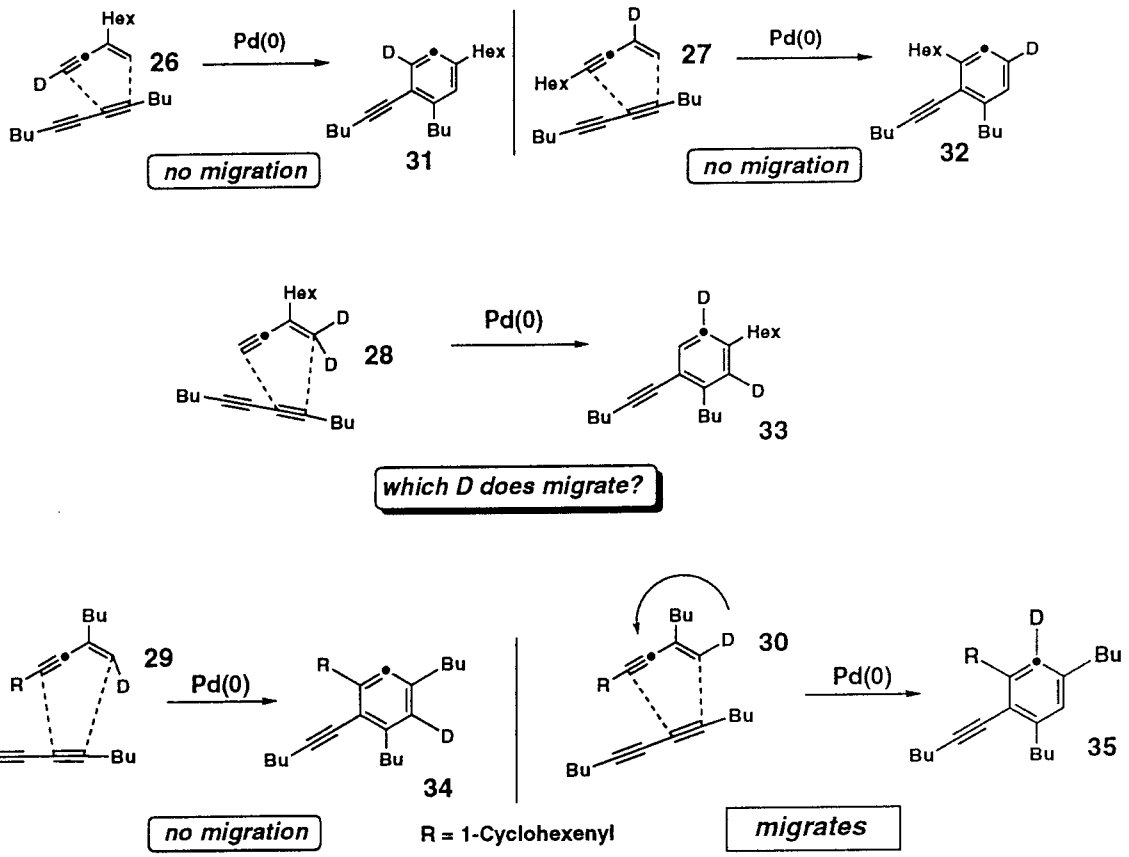


Figure 1. Deuterium-labeling studies.

13c,[21] **13e**−**i**,**j**,[30] and **13f**[31] and triynes **16a**−**d**[30] and **16g**[32] were prepared according to the standard procedures. Enyne **3a** and diynes **7a**−**c** were commercially available and purchased from Aldrich. All manipulations were conducted in oven dried Wheaton microreactors under an argon atmosphere.

Palladium-Catalyzed Enyne−**Diyne (Triyne) [4+2] *Cross*-Benzannulatuion (General Procedure).** A mixtute of enyne (1.0 mmol),[33] diyne (or triyne) (1.0 mmol), and $Pd(PPh_3)_4$ (5 mol %), unless otherwise specified, in THF (2 mL) was stirred under the conditions indicated in the Tables 1−5. The reaction course was monitored by capillary GLC analysis. After completion of the reaction (see Tables 1−5 for details), the mixture was filtered through a short column (silica gel) and concentrated. Benzannulation products were purified by column chromatography (silica gel, eluent-hexane).

Synthesis of 8a (Table 1, Entry 1). To a THF (2 mL) solution of $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) under Ar atmosphere were added **3a** (66.1 mg, 1.0 mmol) and **7a** (81.1 mg, 0.5 mmol), and the resulting mixture was stirred overnight at 65 °C. GLC analysis revealed completion of the reaction. The reaction mixture was filtered through a short florisil column, and the product was purified by a silica gel column chromatography using hexane as an eluent. **8a** was obtained in 89% yield (101.6 mg).

8a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 0H, J = 7.7 Hz), 6.96 (s, 1H), 6.90 (d, 1H, J = 7.7 Hz), 2.71 (t, 2H, J = 7.8 Hz), 2.43 (t, 2H, J = 6.7 Hz), 2.30 (s, 3H), 1.65−1.32 (m, 8H), 0.944 (t, 3H, J = 7.0 Hz), 0.938 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 137.3, 131.9, 129.4, 126.2, 120.3, 92.8, 79.3, 34.4, 32.9, 31.0, 22.7, 22.0, 21.4, 19.2, 14.0, 13.6; IR (neat) 2957, 2930, 2860, 1611, 1497, 1456, 1379, 1329, 1105, 818 cm^{-1}; HRMS calcd for $C_{17}H_{24}$ 228.1877, found 228.1883.

8b. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−6.64 (m, 2H), 7.54 (d, 1H, J = 7.9 Hz), 7.48−7.23 (m, 9H), 7.14 (dd, 1H, J = 7.9, 0.7 Hz), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 140.6, 138.6, 132.7, 131.2 (×2), 130.2, 129.3 (×2), 128.2 (×2), 127.9 (×2), 127.8 (×2), 127.4, 123.6, 118.6, 91.5, 89.5, 21.5; IR (KBr) 3059, 3030, 2920, 1597, 1493, 1443, 908, 820, 770, 756, 733, 698, 691, 665 cm^{-1}; HRMS calcd for $C_{21}H_{16}$ 263.1252, found 268.1230. Anal. calcd for $C_{21}H_{16}$: C, 93.99; H, 6.01. Found: C, 93.77; H, 6.32.

Synthesis of 9a (Table 2, Entry 1). To a toluene (0.5 mL) solution of $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol) and $(o\text{-tol})_3P$ (30.4 mg, 0.1 mmol) under Ar atmosphere were added **5a** (68.1 mg, 0.5 mmol) and **7a** (81.1 mg, 0.5 mmol), and the resulting mixture was stirred for 8 h at 80 °C. GLC analysis indicated completion of the reaction. The mixture was filtered through a short alumina column, and the product was purified as described above. **9a** was obtained in 66% yield (98 mg).

9a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (dd, 1H, J = 8.6, 6.6 Hz), 6.99 (d, 2H, J = 7.5 Hz), 2.76 (t, 2H, J = 8.3 Hz), 2.75 (t, 2H, J = 8.3

(24) Deuterium-containing enyne **26** was synthesized from **3b**[19] by means of deprotonation with *n*-BuLi, followed by quenching with D_2O.

(25) Deuterated enyne **27** was prepared from diyne **13a**[29] via Pd-catalyzed hydrostannation−deuteriodestannation (with DCl_{aq}) sequence. For Pd-catalyzed hydrostannation of diynes, see: Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(26) Bis-deuterated enyne **28** was synthesized by consecutive acylation of bis-TMS-acetylene with heptanoyl chloride,[20a] Wittig olefination with CD_3Ph_3PI, followed by desilylation step.[20c]

(27) *E*-**29**, and *Z*-deuterated enyne **30** were prepared via consequtive haloboration−deuterio (protio) deboration of hexyne-1 (1-deuterio-hexyne-1),[27a] followed by Sonogashira coupling 1-ethynylcyclohexene.[27b] (a) Hara, S.; Dojo, H.; Takunami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731. (b) Matsumoto, Y.; Naito, M.; Hayashi, T. *Organometallics* **1992**, *11*, 2732.

(28) Diyne **7d** was synthesized by oxidative coupling[21] of propargyl alcohol, followed by MOM protection. For MOM protection, see: Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.

(29) Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, *53*, 2655.

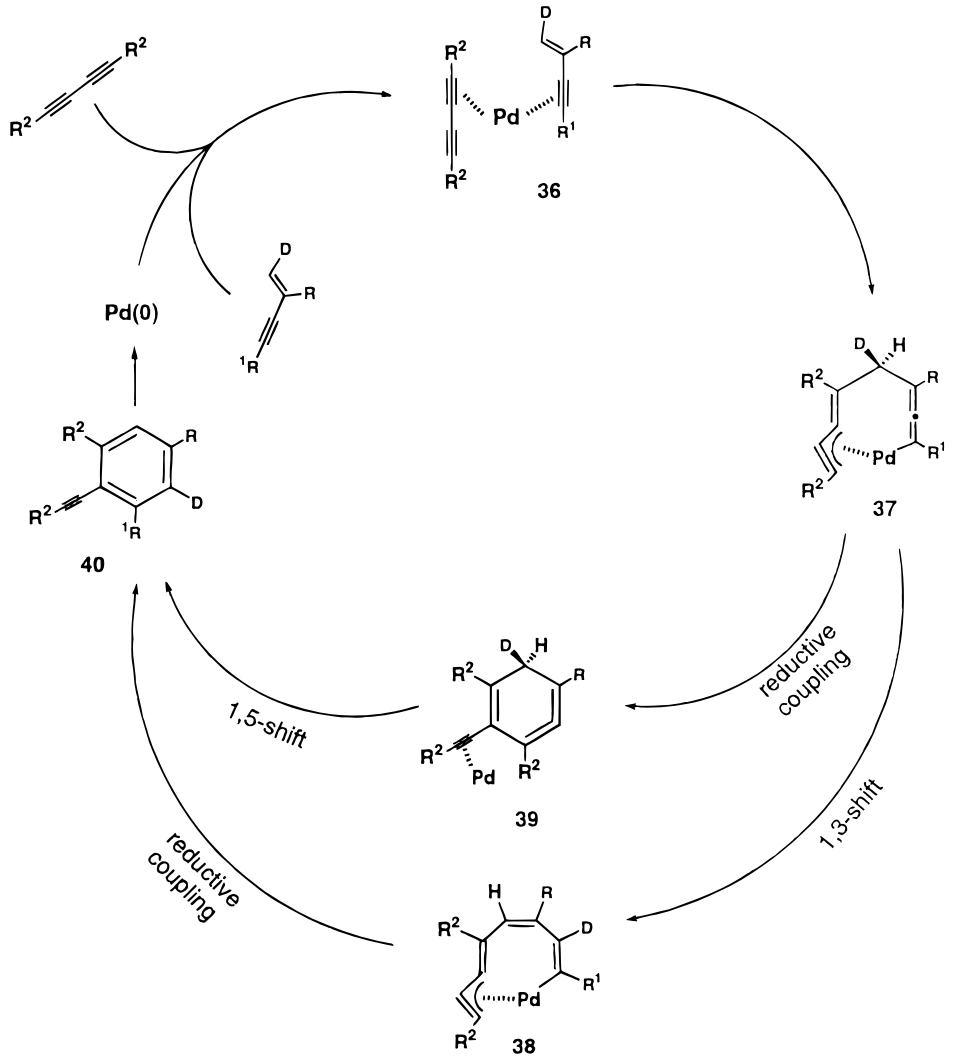
(30) Blanco, L.; Helson, H. E.; Hirthammer, M.; Mestdagh, H.; Spyroudis, S.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1246.

(31) Miller, J. A.; Zweifel, G. *Synthesis* **1983**, 128.

(32) Bis-TMS-triyne **16g** was synthesized from propargyl alcohol *via* oxidative coupling,[21] tosylation,[32a] and silylation[32b] sequence. See: (a) Patel, G. N. *J. Polym. Sci. Pol. Phys. Ed.* **1979**, *17*, 1591. (b) Alberts, A. H. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 242.

(33) The good scalability of this reaction was demonstrated with an essentially quantitative preparation of **8b** (homogeneous by ^{1}H NMR and GLC analyses, isolated yield) in a 5 mmol scale under the mentioned reaction conditions.

Scheme 1. Proposed Mechanism for Palladium-Catalyzed Enyne−Diyne *Cross*-Benzannulation



Hz), 2.49 (t, 2H, J = 6.5 Hz), 1.66−1.31 (m, 16H), 0.95 (t, 3H, J = 6.1 Hz), 0.94 (t, 3H, J = 7.5 Hz), 0.89 (t, 3H, J = 7.1 Hz);^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 145.0, 126.9, 125.9, 122.8, 97.5, 77.7, 35.1, 34.8, 32.9, 31.8, 31.1, 30.7, 29.4, 22.7, 22. 7, 22.0, 19.4, 14.1, 14.0, 13.6; IR (neat) 3061, 2957, 2928, 2858, 2361, 1576, 1466, 1456, 1379, 1327, 1105, 752, 669 cm^{-1}. Anal. calcd for $C_{22}H_{34}$: C, 88.52; H, 11.48. Found: C, 88.53; H, 11.84.

Synthesis of 11a (Table 3, Entry 1). To a toluene (1.0 mL) solution of $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) under Ar atmosphere were added **10a** (75.1 mg, 0.5 mmol) and **7a** (81.1 mg, 0.5 mmol), and the resulting mixture was stirred at 100 °C for 5 days. The same procedure as above was used, giving **11a** in 69% yield (107 mg).

11a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 2H), 2.72 (t, 2H, J = 7.8 Hz), 2.71 (t, 2H, J = 8.0 Hz), 2.47 (t, 2H, J = 6.6 Hz), 2.27 (s, 3H), 1.65−1.31 (m, 16H), 0.95 (t, 3H, J = 7.2 Hz), 0.94 (t, 3H, J = 7.2 Hz), 0.89 (t, 3H, J = 6.6 Hz);^{13}C NMR (75 MHz, $CDCl_3$) δ 144.93, 144.86, 136.6, 126.8, 126.7, 119.8, 96.6, 77.7, 35.1, 34.7, 33.0, 31.1, 30.8, 29.4, 22.8, 22.7, 22.0, 21.4, 19.4, 14.1, 14.0, 13.6; IR (neat) 2957, 2930, 2858, 2731, 2667, 2361, 2343, 1609, 1566, 1466, 1377, 1364, 1329, 1300, 1105, 854, 727, 665 cm^{-1}. Anal. calcd for $C_{23}H_{36}$: C, 88.39; H, 11.61. Found: C, 88.50; H, 11.66.

Synthesis of 14f **(Table 4, Entry 6).** To a THF (2 mL) solution of $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) under Ar atmosphere were added **3a** (66.1 mg, 1.0 mmol) and **13f** (99.2 mg, 0.5 mmol), and the resulting mixture was stirred at 65 °C overnight. Completion of the reaction was confirmed by GLC analysis, and the mixture was filtered through a short florisil column. Purification of the product with a silica gel column chromatography using hexane as an eluent gave **14f** in 78% yield (102.5 mg).

14f. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2H), 7.46 (d, 1H, J = 7.7 Hz), 7.38−7.32 (m, 4H), 7.15 (dd, 1H, J = 7.8, 1.2 Hz), 2.36 (s, 3H), 0.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 137.2, 134.7, 132.5, 131.1 (×2), 129.6, 128.4 (×2), 128.0, 125.3, 123.7, 91.32, 91.29, 21.6, −1.0 (×3); IR (neat) 3018, 2955, 2214, 1597, 1493, 1468, 1443, 1246, 1140, 1070, 889, 841, 754, 689 cm^{-1}; HRMS calcd for $C_{18}H_{20}Si$ 264.1333, found 264.1336.

Synthesis of 17h (Table 5, Entry 9). To a THF (2 mL) solution of $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) under Ar atmosphere were added **3c** (71.1 mg, 0.5 mmol) and **16g** (109.2 mg, 0.5 mmol), and the resulting mixture was stirred at 65 °C for 2 h. The same procedure as above gave **17h** in 86% yield (148.7 mg).

17h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, 1H, J = 7.9 Hz), 7.35−7.15 (m, 6H), 7.08 (d, 1H, J = 7.7 Hz), 3.97 (s, 2H), 0.35 (s, 9H), 0.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 141.4, 140.3, 134.6, 134.2, 129.3, 128.9, 128.5, 126.3, 124.1, 90.8, 88.0, 79.1, 76.7, 42.0, −0.3 (×3), −1.1 (×3); IR (neat) 3028, 2959, 2899, 2201, 2098, 1587, 1495, 1452,1250, 1015, 883, 841, 760, 700, 633 cm^{-1}; HRMS calcd for $C_{23}H_{28}Si_2$ 360.1728, found 360.1721.

Deuterium-Labeling Studies. The reaction of **26** (97% D-content) with **7a** was carried out in a manner similar to that described for the synthesis of **8a**; **31** (97% D-content) was obtained in 64% yield. The reaction of **27** (95% D-content) with **7a** was carried out in a manner similar to that described for the synthesis of **9a**; **32** (95% D-content) was obtained in 41% yield. The reaction of **28** (82% D-content for both deuteriums at C-1 positions) with **7a** was carried out as described above, and **33** was obtained in 61% yield in which D-content at C-3

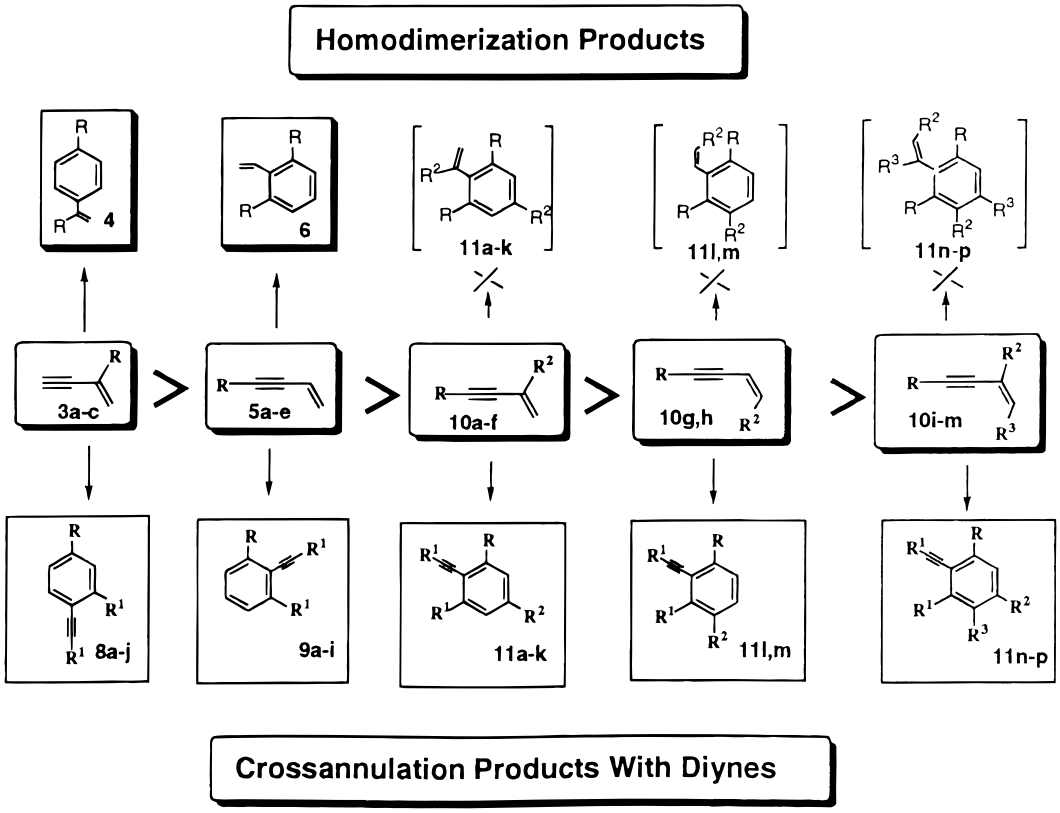


Figure 2. Summary on palladium-catalyzed [4+2] benzannulation of conjugated enynes.

was 84% and that at C-5 was 71%. The reaction of **29** and **30** was carried out as described in Table 3 entry 2, giving the [4+2] adducts **34** and **35**, respectively, in ~70% yield.

Supporting Information Available: Analytical and spectroscopic data of **8**, **9**, **11**, **14**, **15**, **17**, **18**, **19**, **20**, **26**, **27**, **28**, **31**, **32**, and **33** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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