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Review

Palladium-catalyzed enyne–yne [4 + 2] benzannulation as a new and general approach to polysubstituted benzenes☆

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Abstract

Monosubstituted conjugated enynes smoothly underwent [4 + 2] homodimerization in the presence of palladium catalyst to give 4, α- and 2,6-disubstituted styrenes. Analogous cross-cycloaddition of conjugated enynes and diynes afforded a variety of polysubstituted benzenes, including phenol and aniline derivatives. Alkynes and diynes in the presence of a palladium catalyst underwent novel formal [2 + 2 + 2] sequential cyclotrimerization to afford multifunctional benzenes in one step with high degrees of regio- and chemoselectivities. Mechanisms of these novel transformations are discussed.

Keywords: Enynes; Diynes; Alkynes; Palladium; Cycloaddition; Benzene

1. Introduction

It was in early 1866 that Berthelot first reported the thermal cyclotrimerization of acetylene. The reaction conditions were rather drastic (400°C), and benzene was formed as a minor product, accompanied with higher oligomeric materials [1]. Remarkably, it took more than 80 years for chemists to find an essentially more effective methodology for acetylene cyclotrimerization! In fact, significant success in this field was achieved in 1948 when Reppe demonstrated the first transition metal-catalyzed version of this reaction [2]. This discovery initiated an immense interest among organic, organometallic, and inorganic chemists and soon this area became crowded. As a result, a large number of transition metal catalysts, as well as Ziegler-type catalysts [3], were proven to give rise to this reaction [4]. Despite the 50 year history of this method, it still has a severe drawback: the low degrees of regio- and chemoselectivity for the intermolecular version of this process [5] seriously narrows the scope of this intriguing reaction. Indeed, a mixture of two regioisomers, 1,2,4- and 1,3,5-trisubstituted benzenes, is usually obtained in the homotrimerization of terminal alkynes, whereas in the case of heterotrimerization of three different acetylenes the number of possible regio- and chemoisomers rises up to 38 (Eq. (1)) [5]. Vollhardt succeeded in solving these problems for several types of intramolecular (Eq. (2)) [6] or partially intramolecular (Eq. (3)) [7] modes of cyclotrimerization: three new bonds were formed under the cobalt catalysis affording cyclophane-type aromatic products in chemo- and regioselective manner (Eqs (2) and (3)) [6,7].

☆ Dedicated to Professors Jiro Tsuji and Richard F. Heck, in recognition of their pioneering and outstanding contributions to organic chemistry of palladium.

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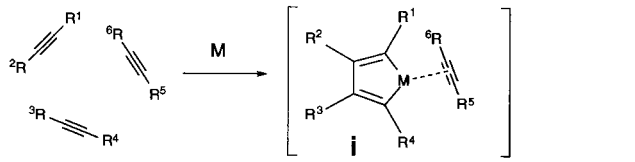

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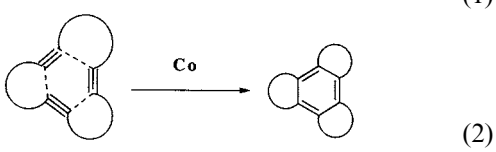

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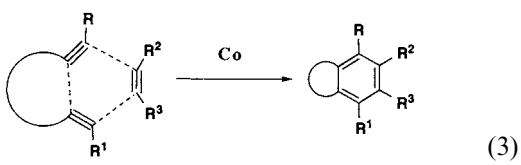

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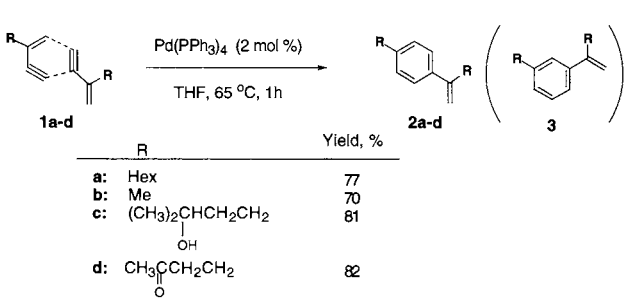
It is generally accepted that a variety of regio- and chemoisomeric products of transition metal catalyzed intermolecular trimerizations of alkynes arise from a variety of different modes of orientation of alkynes in assembling metallocyclopentadiene intermediate ***i*** (Eq. (1)) [5]. In spite of enormous attempts to control regio- and chemoselectivity of formation of ***i***, not much success was achieved for the intermolecular [2 + 2 + 2] cycloaddition reaction. Consequently, alternative approaches toward regio- and chemoselective construction of the benzene skeleton from three different alkynes are greatly desired.

We entered into the area of benzannulation reactions in 1995, motivated by our serendipitous discovery of palladium catalyzed non-traditional regiospecific [4 + 2] homodimerization of conjugated enynes, that lead to the 1,4-disubstituted benzenes [8]. At this stage we assumed that we had found a palladium-catalyzed version of dehydro Diels–Alder transformation. The more we investigated this reaction, the more we realised that we were dealing with the event proceeding via an entirely different mechanism. Encouraged by this intriguing finding [8], and motivated by the challenging goal of regioselective construction of benzene skeleton from acyclic units in general, we started our journey into the fascinating benzannulation land. In this review we will describe our results on the highly chemo- and regioselective formation of polysubstituted benzenes via non-classical [4 + 2] and formal [2 + 2 + 2] cycloadditions reactions, and we will discuss the plausible mechanisms of these novel approaches.



Scheme 1. Homodimerization of 2-substituted enynes **1**.

2. Homodimerization reactions of enynes

In this chapter the inter- and intramolecular palladium-catalyzed [4 + 2] homocycloaddition reactions of conjugated enynes and bis-enynes will be described.

2.1. Synthesis of 4, α-disubstituted styrenes via homodimerization of 2-substituted enynes

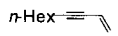
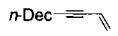
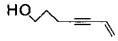
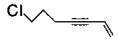
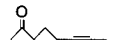
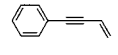
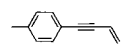
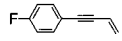
We found that 2-substituted conjugated enynes **1** in the presence of $Pd(PPh_3)_4$ (2 mol%) smoothly underwent [4 + 2] homocycloaddition reaction to afford 1,4-disubstituted benzenes **2** in good yields (Scheme 1) [8]. It should be pointed out that in all cases the reactions proceeded with perfect regiocontrol and no traces of the isomeric 1,3-disubstituted benzenes **3** were detected by NMR analyses of the crude reaction mixtures. Although such funtionalities as hydroxy- (**1c**) and keto-groups (**1d**) in the side chain of enynes were tolerated (81 and 82% yields of **2c** and **2d**, correspondingly, Scheme 1), the enynes possessing TMS (**1e**) and *t*-butyl (**1f**) groups did not dimerize under the mentioned reaction conditions, perhaps due to the steric reasons [8].

2.2. Synthesis of 2,6-disubstituted styrenes via homodimerization of 4-substituted enynes

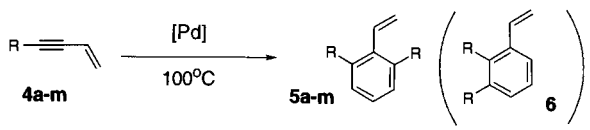
Styrene derivatives are of great importance in the polymeric industry [9] and for synthetic organic chemistry [10]. Despite obvious potential significance of 2,6-disubstituted styrenes as monomers [11] and as substrates for various types of organic transformations [12], only 2,6-dimethyl-, and 2,6-dimethoxystyrene have been reported to date [13]. Furthermore, the methods for their preparation are lengthy, cumbersome and not general in character [13]. Accordingly, an efficient and general method for the preparation of 2,6-disubstituted styrenes is intensely welcomed [14].

During our study on dimerization of the 2-substituted enyne **1** [8] we found that even prolonged heating of the 4-substituted enyne **4a** at 60°C in the presence of 2 mol% of $Pd(PPh_3)_4$ (the best conditions which were found for dimerization of **1**) did not cause any notable transformation of the starting material. However, we found that at 100°C in the presence of 5 mol% of $Pd(PPh_3)_4$ (Method **A**) hexylsubstituted **4a** smoothly

Table 1
Preparation of 2,6-disubstituted styrenes **5** via cyclodimerization of 4-substituted enynes **4**

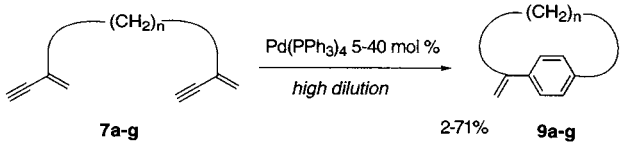
entry	enyne **4**	catalyst system[a]	time (h)	styrene **5**	yield (%)[b]
1	 **4a**	C	24	**5a**	86
2	 **4b**	C	10	**5b**	92
3	 **4c**	B	66	**5c**	81
4	 **4d**	C	22	**5d**	30
5	 **4e**	A	72	**5e**	51
6	**4f**	B	24	**5f**	100
7	 **4g**	B	24	**5g**	100
8	**4h**	A	48	**5h**	71
9	 **4i**	C	84	**5i**	71
10	 **4j**	B	96	**5j**	40
11	**4k**	B	48	**5k**	80[c]
12	**4l**	B	24	**5l**	69
13	 **4m**	B	48	**5m**	81

underwent the [4 + 2] cyclodimerization reaction affording the desired 2,6-dihexylstyrene **5a** in an 87% NMR yield (Eq. (4)) [15].



(4)

Optimization of the catalyst system allowed a decrease in the amount of palladium catalyst from 5 to 1 mol% by adding another 10 mol% of ligand ((*o*-Tol)$_3$P and COD, Methods **B** and **C**, respectively, Table 1). Thus, among alkyl chain substituted enynes the hexyl- (**4a**), decyl- (**4b**), hydroxypropyl- (**4c**), methoxymethyl- (**4f**), and diethylaminomethyl (**4g**) substituted enynes reacted smoothly producing the corresponding 2,6-dialkylsubstituted styrenes **5a**,**b**,**c**,**f** and **g**, respectively, in excellent to quantitative yields (Table 1, entries 1–3, 6, 7) [15]. Exceptionally low yields in the cases of enynes, bearing chloro- (**4d**) and keto- (**4e**) functionalities in the side



7	n	Yield,%
a	7	2
b	8	18
c	9	36
d	10	47
e	11	61
f	12	71
g	14	71

Scheme 2. Synthesis of the *exo*-methylene paracyclophanes **9**.

chain are accounted for by possible strong coordination of the palladium catalyst to the halogen of **4d**, or to the CO group of **4e**, thus diminishing the overall cycloaddition process. Among aryl- and heteroaryl substituted enynes (**4h**–**m**) only the *p*-methoxyphenyl derivative (**4j**) gave a low yield of the corresponding styrene **5j** (entry 10). In all other cases the reaction proceeded well to give phenyl- (**5h**), *p*-tolyl- (**5i**), *p*-fluorophenyl- (**5k**), 2-furyl- (**5l**), and 2-thienylsubstituted (**5m**) styrenes in good yields (Table 1, entries 8, 9, 11–13). It should be mentioned that enynes bearing bulky substituents, such as *t*-butyl- (**4n**), TMS- (**4o**), and naphthyl- (**4p**), did not undergo the cyclodimerization reaction at all, perhaps due to steric reasons. In all cases reactions proceeded with excellent regioselectivity and no traces of isomeric **6** were detected in the crude reaction mixtures [15].

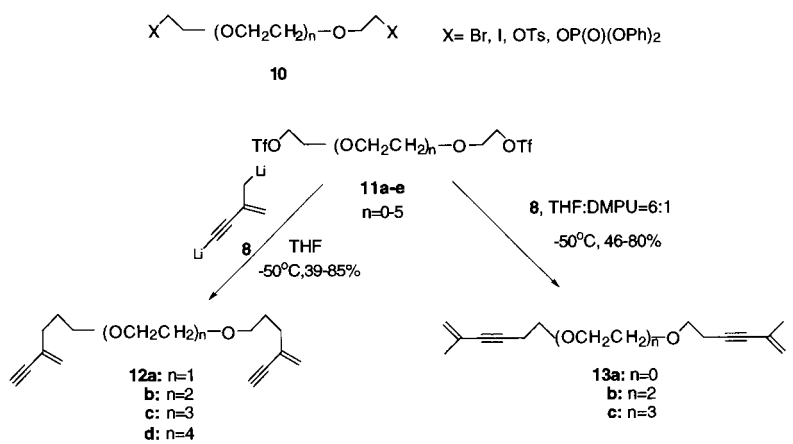
2.3. Synthesis of exo-methylene paracyclophanes via intramolecular dimerization of bis-enynes

Next we examined an intramolecular mode of the homodimerization of 2-substituted enynes [16]. The starting bis-enynes **7a**–**g** ($n = 7$–14) were readily prepared from the corresponding dibromides and dilithiated 2-methyl-1-buten-3-yne **8** using Brandsma's alkylation methodology [17]. All the starting bis-enynes **7** were tested in the intramolecular homodimerization reaction in the presence of Pd(PPh$_3$)$_4$ using the high dilution technique (Scheme 2) [16]. As it was expected, even under highly diluted conditions [18], the yields of the cyclophanes **9** were strongly dependent upon the length of the methylene bridge. Thus, the bis-enynes **7e**–**f**, bearing a relatively long tether chain, gave the cyclophanes **9e**–**f** in good yields (61–71%), whereas **7b** and **7a**, having a methylene chain equal to **8** and **7**, produced the highly strained cyclophanes **9b** and **9a** in 18 and 2% only, respectively (Scheme 2) [16].

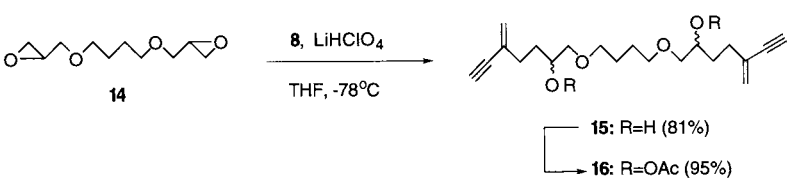
2.4. Synthesis of polyether exomethylene cyclophanes via intramolecular dimerization of bis-enynes

In contrast to alkylation of the dibromides mentioned above [16], alkylation of the polyethylene glycol

derivatives **10**, bearing an alkoxy group β to the leaving group, proved extremely difficult [19]. Thus, halides (Br and I), phosphate and tosyloxy derivatives **10** failed to undergo alkylation with **8** under the previously mentioned reaction conditions [16]. After considerable investigation, only triflate was found to be an acceptable leaving group for this displacement reaction, which led to concerns regarding the instability of bis-triflate intermediates [20]. Bis-triflates **11a–e** were consequently prepared according to the standard procedures and immediately submitted to alkylation with **8** (Scheme 3). Polyether bis-triflates **11a–e** selectively reacted with the ambident nucleophile **8** under the typical reaction conditions [16] to afford the polyether bis-enynes **12a–d** in moderate to good chemical yields (Scheme 3) [21]. It worth noting that the addition of DMPU to the reaction mixture as a co-solvent, prior to the addition of the nucleophile, dramatically changed the mode of alkylation (Scheme 3). Although it is known that DMPU enhances the nucleophilicity of acetylides [22], we were surprised to find that it could cause a complete reversal of reactivity between sp^3- and sp-anions in the ambident nucleophile **8**, in favor of the acetylide moiety. Thus, only bis-enyne **13** was produced in the presence of DMPU, and no traces of **12** were detected under these reaction conditions by GLC and NMR analysis of the crude



Scheme 3. Alkylation of the polyethylene glycol derivatives **11**.



Scheme 4. Alkylation of the diglycidyl ether **14**.

Table 2
Benzannulation of the polyether bis-enynes **12**

Bis-enyne		$Pd(PPh_3)_4$ (mol%)	Ligand (mol%)	Concentration (mM)	Product (yield, %)
12a	$n=1$	4	PPh_3 (50)	20	**17a** (34)
12b	$n=2$	5	PPh_3 (40)	15	**17b** (100)
12c	$n=3$	4	P(*o*-Tol)$_3$ (12)	7	**17c** (>95) NMR
12d	$n=4$	10	P(*o*-Tol)$_3$ (30)	5	**17d** (50) NMR

reaction mixtures (Scheme 3) [21]. In contrast to unreactive **10**, diglycidyl ether **14**, which also formally possesses an alkoxy moiety to a leaving group, reacted with **8** in a regioselective manner [23] affording the diastereomeric diol **15** in good chemical yields (Scheme 4). Consequent acylation of **15** using the standard procedures afforded the diacetoxy bis-enyne **16** in high yields (Scheme 4).

We next examined the benzannulation of the polyether bis-enynes **12a–d** (Table 2). Unsatisfied with the reaction conditions requiring high dilutions and excessively large amounts of palladium catalyst for the benzannulation of **7** (Scheme 2) [16], we initiated an investigation for a more synthetically useful procedure. After brief experimental optimizations, we found that the bis-enynes **12a–d** in DMSO (5–20 mM) at 100°C in the presence of a combined catalyst system, $Pd(PPh_3)_4$ (4–10 mol%) additional phosphine ligand (12–50 mol%), smoothly underwent intramolecular benzannulation to afford the exomethylene paracyclophanes **17a–d** in satisfactory to quantitative yields (Table 2). Although the reasons for the moderate yield of **17a** are not clearly understood, cyclophanes **17b** and **17c** bearing three and four oxygen atoms, respectively, at the polyether chain were obtained in quantitative yields (Table 3). The largest cyclophane synthesized, **17d**, containing a total of 20 atoms in the bridging chain (excluding exocyclic olefin) was obtained in a 50% yield.

The remarkably high yield of **17b** and **17c** deserves special note. Fully optimized conditions for cyclization of the closest carbon analogues **7f,g** ($n = 12$, 14) [16] required 40 mol% of the Pd catalyst and high dilution (2.5 mM) to afford exomethylene paracyclophanes **9** in a 71% yield (Scheme 2) [16]. Such high dilution conditions were absolutely necessary to avoid formation of dimers and oligomers [16]. In contrast, polyether bis-enynes **12b,c** cyclize in the presence of 4–5 mol% (10 to 8-fold decrease) of the Pd catalyst and under relatively concentrated conditions (15–7 vs. 2.5 mM for **7** [16]), producing the corresponding polyether cyclophanes **17b,c** quantitatively (Table 3) [21]. It is worth noting that no traces of dimers or higher oligomers were detected in these cases suggesting perfect intramolecular control. Taken together, the above observation may be explained by the following proposal: a host/guest relationship between palladium and **12b**, and **12c** [24] bearing three and four oxygen atoms, respectively, could be responsible for the observed perfect intramolecular control of cyclization (Fig. 1) [21].

Scheme 5. Benzannulation of the bis-enynes **15**, **16**.

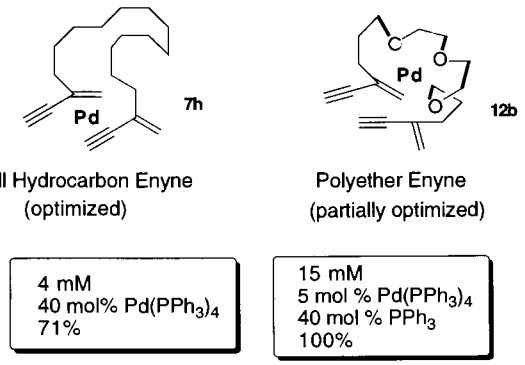


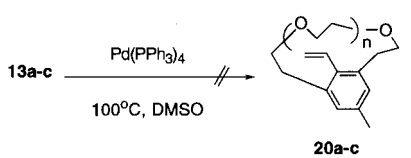
Fig. 1.

Benzannulation of the unprotected diol **15** appeared to be reasonably unfacile. All attempts to perform this reaction with small amounts of the Pd catalyst failed, perhaps due to a strong affinity of Pd to the hydroxy groups of **15**. Subsequently, the cyclic diol **18** was obtained in a 44% yield by employing 40 mol% of the palladium catalyst (Scheme 5). In contrast to **15**, the acetoxy protected bis-enyne **16** smoothly underwent benzannulation in the presence of 10 mol% of $Pd(PPh_3)_4$, affording **19** in nearly quantitative yield (Scheme 5) [21]. Conversely, the bis-enynes **13**, possessing 2,4-disubstituted enyne units [25], remained unreacted under all reaction conditions examined, with no trace of *meta*-cyclophane **20** being detected by GC–MS analysis of reaction mixtures (Scheme 6) [21].

3. [4 + 2] Cross-benzannulation of enynes with diynes

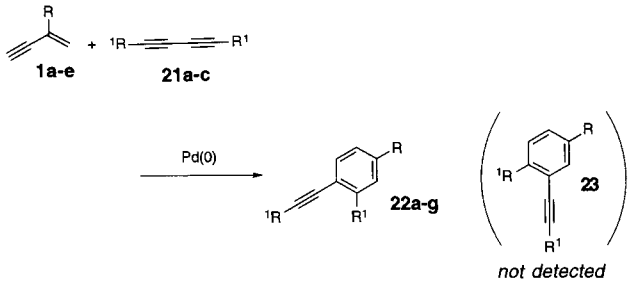
3.1. Synthesis of alkyl-, aryl-, and silylsubstituted benzenes via enyne–diyne cross-cycloaddition pathway

Inspired by successful inter- [8,15], and intramolecular [16,21] versions of palladium-catalyzed [4 + 2] homodimerization of conjugated enynes, we attempted to develop a cross-benzannulation version of this reaction, which is essentially more attractive from a synthetic point of view [26]. After trying a number of alkynes in a role of enyne partner in the [4 + 2] cycloaddition, we discovered that the conjugated diynes **21** underwent regiospecific cross-cycloaddition with **1**. The reaction of 2-methyl-1-buten-3-yne **1b** with dodeca-5,7-diyne **21a** in the presence of 5 mol% $Pd(PPh_3)_4$ in THF gave **22a** [27]



Scheme 6. Attempts on benzannulation of the polyether bis-enynes **13**.

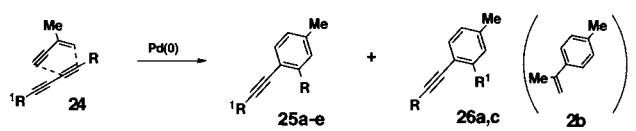
in a 89% yield (Eq. (5), Table 3, entry 1) [28]. No traces of **23** were detected by NMR and capillary GLC analyses of crude reaction mixtures. The enyne–diyne cross-annulation reaction of the enynes **1a**,**e** appeared to be much faster than the corresponding enyne–enyne homo-dimerization [8], thus an equimolar amount of the hexyl- (**1a**) and benzyl- (**1e**) enyne reacted with **21a**,**b** not only in regio-, but also in chemo-selective manner exclusively affording the cross-annulation products **22d**–**f**, (entries 4–6).



(5)

In contrast, a 2 to 5-fold excess of volatile and less reactive **1b** (towards diynes **21**) was needed to drive the reaction until complete conversion of **21** (entries 1–3) [29]. The bulky diyne **21c** reacted with enynes rather slower than **21a**,**b**, thus the slow addition of the enynes **1b**, **d**.

Although the enyne–diyne cycloaddition proceeded with absolute regiocontrol with respect to the *para*-orientation of the triple bond toward the R group in the aromatic product **22** (the isomeric **23** with *meta*-orientation has never been detected), it was not clear whether any kind of selectivity could be achieved in the case if unsymmetric diynes were employed. Accordingly, we investigated the enyne–diyne [4 + 2] cycloaddition of the enynes **1b**,**e** with the unsymmetric diynes **24** and triynes **27** (selected examples are illustrated in Schemes 7 and 8, respectively) [30]. It was proven that

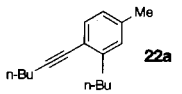
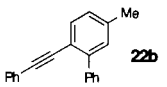
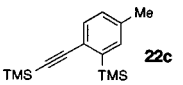
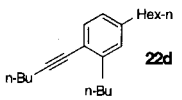
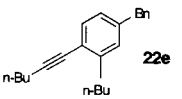
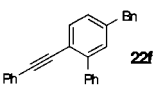
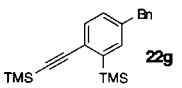


Yield, %

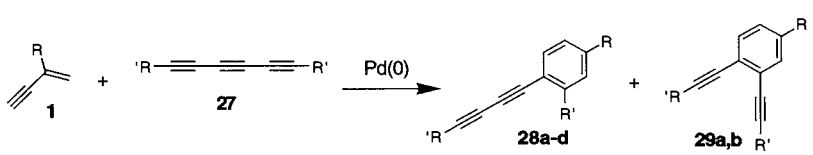
24	R	R^1	25	26
a	Bu	Ph	54	46
b	TMS	Ph	78	-
c	Hex	H	50	28
d	tBu	H	52	-
e	$C(Me)_2OMOM$	H	80	-

Scheme 7. Cross-benzannulation of **1b** with the unsymmetric diynes **24**.

Table 3
Palladium catalyzed enyne–diyne cross-benzannulation

entry	R	R^1	Product **22**	Yield (%)[a]
1	Me (**1b**)[b,c]	n-Bu (**21a**)	 **22a**	89 (10)[d]
2	Me (**1b**)[b,c]	Ph (**21b**)	 **22b**	>99
3	Me (**1b**)[c,e,f]	TMS (**21c**)	 **22c**	92
4	n-Hex (**1a**)	n-Bu (**21a**)	 **22d**	60[g] (36)[d]
5	Bn (**1e**)[h]	n-Bu (**21a**)	 **22e**	89
6	Bn (**1e**)	Ph (**21b**)	 **22f**	86
7	Bn (**1e**)[i]	TMS (**21c**)	 **22g**	80

[a]Isolated yields based on diyne **21**, except for where otherwise indicated. [b]Two equivalents of **1b** were utilized. [c]Excess of **1b** underwent homodimerization affording the by-product **2** [8]. [d]Recovery of **21** (%). [e]Five equivalents of **1b** were utilized. [f]**1** was added in 5 portions. [g]NMR yield. [h]One-half equivalents of **1e** were added in 10 portions. [i]Two and a half equivalents of **1e** were added during 14 hours with syringe pump. was employed in order to avoid its dimerization (entries 3,7) [28].



Yield, %

1, R	27, R'	28	29
Me	Bu (**a**)	44	22
Hex	Ph (**b**)	44	28
Bn	TMS (**c**)	82	-
Hex	$C(CH_3)_2OMOM$ (**d**)	84	-

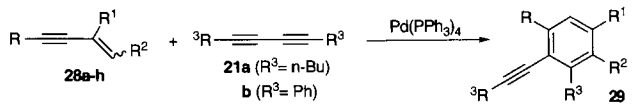
Scheme 8. Cross-benzannulation of **1b**,**e** with the triynes **27**.

regiochemistry of cycloaddition in these cases is not so simple. Thus, perfect regiocontrol was observed for the unsymmetric diynes **24b**,**d**,**e** and for the triynes **27c**,**d**, whereas in other cases the products distribution was more or less statistical (Schemes 7 and 8) [30]. The fact that in most cases the products **25** and **28**, in which the most bulky substituents were attached to the aromatic rings, were formed as single or major reaction products (Schemes 7 and 8) diminished the importance of steric factors in the regiochemistry of this cycloaddition. It occurred to us that not steric but electronic factors might affect the regiochemistry of this reaction. Consequently, we performed an ab initio calculation of selected unsymmetrical diynes and triynes and compared the character of the electron density distribution in these molecules with the experimental results on the regiochemistry of their cycloaddition reaction [30]. Some selected examples are depicted in the Schemes 9–11. The comparison of the electron densities of the unsymmetrical diyne **24b** and triynes **27a,c** with the experimental results on *cross*-cycloaddition reactions with enynes **1** brought some insight into our attempts to understand the major factors influencing the regiochemistry of this reaction. It became rather clear that enynes prefer the more electron rich triple bonds of enynophiles. Indeed, **1** selectively reacted with more electron rich triple bonds in diyne **24b** (Scheme 9) and triyne **27c** (Scheme 10), affording the single regioisomeric reaction products **25b** and **28c**, correspondingly. In contrast to the above cases, the triyne **27a**, in which an electron cloud covers homogeneously all the triple bonds (Scheme 11), showed no selectivity and gave perfectly statistical distribution of cycloaddition products **28a** and **29a** (Schemes 8 and 9) [30].

3.2. Chemoselective enyne–diyne [4 + 2] cycloaddition reactions

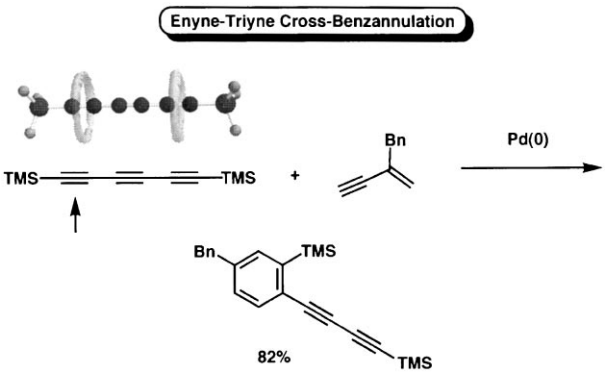
We next attempted to use multiply-substituted enynes in the cycloaddition reaction. The control experiments showed that neither di- nor trisubstituted enynes underwent the homodimerization reaction even under prolong heating at 120°C [31]!

Encouraged by this fact, we submitted the differently substituted enynes **28a**–**h** to the cross-benzannulation reaction with the diynes **21a**,**b** (Eq. (6), Table 5) [31]. We found that in all cases the benzannulation reaction proceeded with perfect regiocontrol (no other regioisomers of **29** were detected by GC–MS analysis of the crude reaction mixtures) and perfect chemocontrol (no traces of the homo-dimers **2** [8] were formed).

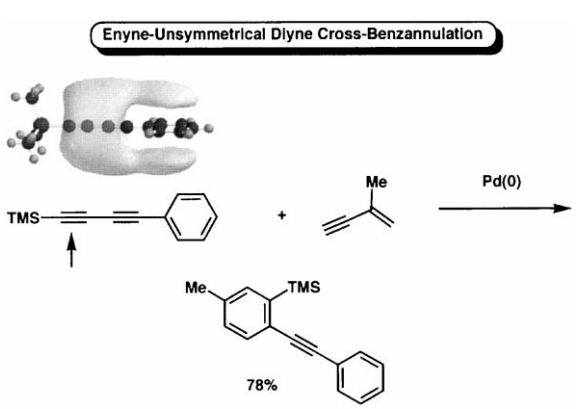


(6)

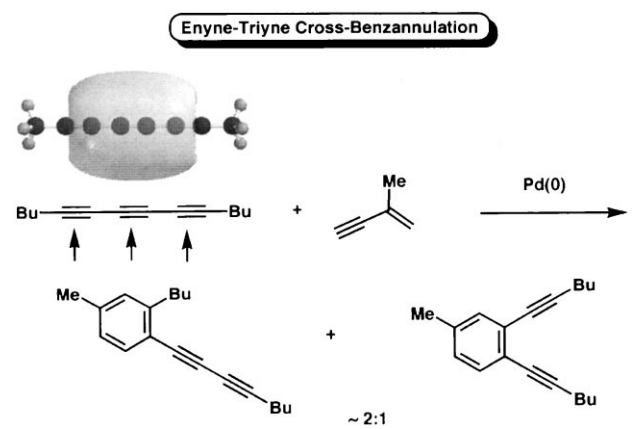
The 2,4-disubstituted enynes **28a**–**c** were found to be the most reactive towards the diynes **21** among the all enynes tested. Accordingly, the tetrasubstituted benzenes **29a**–**f** were obtained in high to excellent chemical yields (entries 1–6). In contrast, the reaction of the 1,4-disubstituted enynes **28d**,**e** with the diyne **21a** even under more elevated temperatures (120°C) was rather sluggish and afforded the desired aromatic products



Scheme 10. Electrostatic potential density and cycloaddition reaction of **27c**.



Scheme 9. Electrostatic potential density and cycloaddition reaction of **24b**.



Scheme 11. Electrostatic potential density and cycloaddition reaction of **27a**.

with trace to unsatisfactory low yields. The main reason for the last observation would be low stability of the palladium catalyst under the prolong heating. This problem was solved by addition of tris(2,6-dimethoxyphenyl)phosphine (TDMPP) to the reaction mixture (four equivalents vs. Pd). Accordingly, tetrasubstituted benzenes **29g** and **29h** were obtained in 45 and $>95\%$ yields, respectively (entries 7 and 8, Table 4). Benzannulation of the trisubstituted **28f** gave the pentasubstituted benzene **29i** in a rather moderate yield (entry 9), whereas reaction of its carbomethoxy analogue **28g** produced the polysubstituted benzoate **29j** in an 88% yield (entry 10). It was surprising for us that the ester-containing *E*-enyne **28h**, in contrast to its alkyl- and phenyl analogues (entries 7–9, note d), enabled benzannulation reaction to go ahead, even though the yield of **29j** in this case was moderate (entry 11) [31].

Table 4
Palladium-catalyzed cross-benzannulation of multisubstituted enynes **28** with diynes **21** [29]

Entry		R	R^1	R^2	Diyne	Reaction conditions		Product (yield, %)[a]
						Time (days)	Temperature (°C)	
1	**28a**	*n*-Hex	Me	H	**21a**	3	100	**29a** (95)
2	**28a**	*n*-Hex	Me	H	**21b**	3	100	**29b** (84)
3	**28b**	Ph	Me	H	**21a**	3	100	**29c** (79)
4	**28b**	Ph	Me	H	**21b**	3	100	**29d** (80)
5	**28c**	*c*-Hexenyl	Me	H	**21a**	3	100	**29e** (89)
6	**28c**	*c*-Hexenyl	Me	H	**21b**	3	100	**29f** (68)
7	**28d**	(*Z*)[b]*n*-Hex	H	Me	**21a**	5	120	**29g** (45)[c]
8	**28e**	(*Z*)[b]Ph	H	Me	**21a**	5	120	**29h** (>95)[c]
9	**28f**	(*Z*)[b]Ph	Me	Me	**21a**	5	120	**29i** (43)[c]
10	**28g**	(*Z*)Ph	Me	CO_2Me	**21a**	2	120	**29j** (88)
11	**28h**	(*E*)Ph	Me	CO_2Me	**21a**	2	120	**29j** (42)

[a] NMR yield.
[b] Reactions employing *E*-enynes produced trace amounts of aromatic products.
[c] (TDMPP, 20 mol%) was used as an additive.

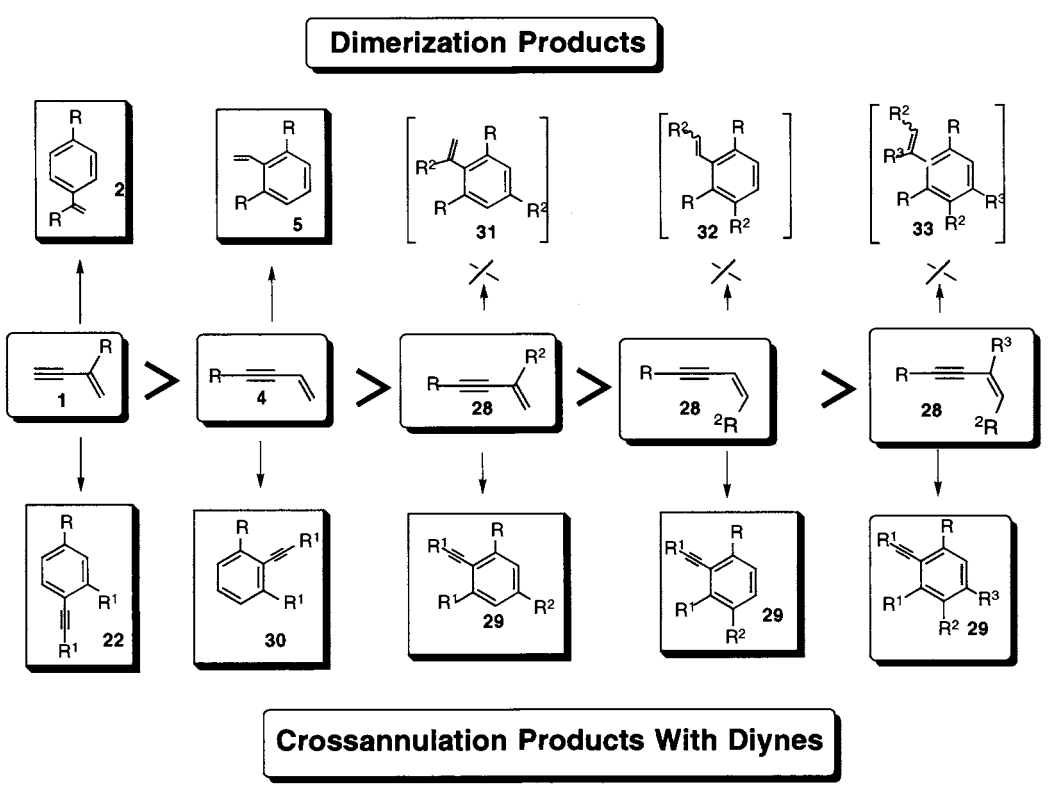


Fig. 2. Homo- and cross-cycloaddition of conjugated enynes: a general outlook.

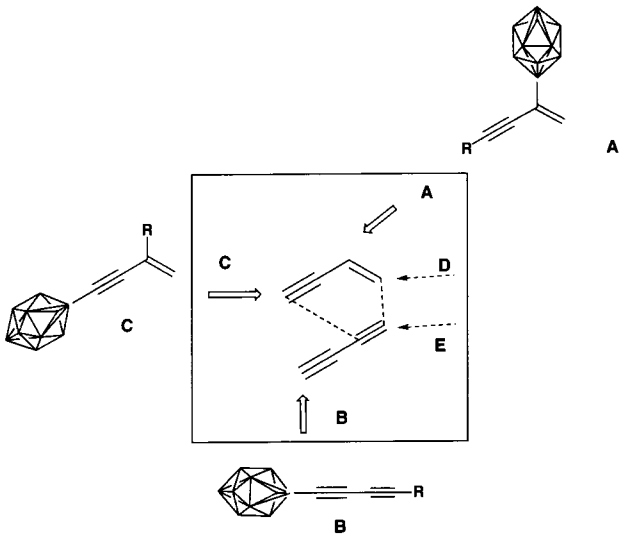
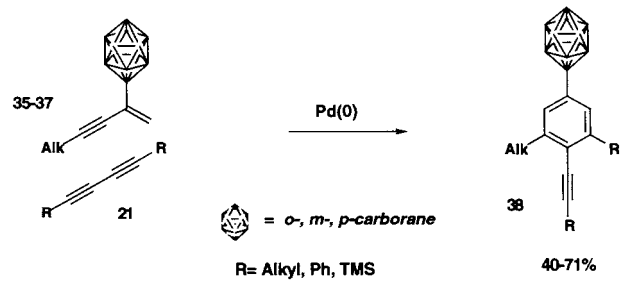


Fig. 3. Approaches toward carborane-containing enynes and diynes.

As a brief concluding outlook on homo- and cross-cycloaddition reactions of conjugated enynes, we arranged the mono- and multisusbstituted enynes in decreasing order of their reactivities (Fig. 2) [30]. The monosubstituted enynes **1** and **4**, as the most reactive substrates, easily react in both a homo- and cross-cycloaddition manner to afford the homodimerization products **2** [8] and **5** [15], respectively, and cross-cycloaddition products **22** [28] and **30** [30] for **1** and **4**, correspondingly (Fig. 2). In contrast to the above cases, the di- and trisubstituted enynes **28** did not undergo the homo-dimerization process, however they reacted with diynes in the cross-cycloaddition manner (although rather slower than monosubstituted **1** and **4**) affording multisubstituted benzenes **29** in a chemo- and regioselective manner (Fig. 2) [30,31].

3.3. Synthesis of carboranyl benzenes

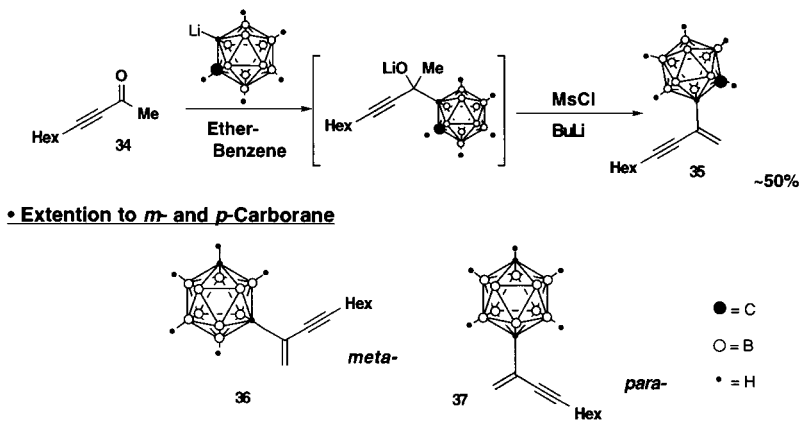
Carboranes containing aromatic compounds are of potential interest for material science and for BNCT



Scheme 13. Preparation of carboranyl-containing benzenes **38**.

connected projects. Several research groups recently reported syntheses of liner [32], cyclic [33] and attempted grid-type [34] conjugated systems, containing both aromatic rings and carborane clusters. Motivated by this, we attempted to develop an alternative approach towards these types of compounds via our novel [4 + 2] cycloaddition methodology. In order to achieve this goal, we analyzed possible ways for incorporating the carborane cage into either molecules of enyne or diyne (Fig. 3) [35]. Based on our experience with the palladium-catalyzed enyne–diyne cross-cycloaddition reactions (Fig. 2) [28,30,31], we considered three main approaches **A**, **B**, and **C**, as the most promising ways towards the synthesis of carborane-containing substrates. The approaches **D** and **E** were not seriously counted [30]. We prepared the carborane-containing enyne **C** and diyne **B** via the conventional methods, however they did not exhibit satisfactory reactivity in the palladium-catalyzed [4 + 2] cycloaddition reaction [35]. The most promising 2-substituted *o*- (**35**), *meta*- (**36**), and *para*- (**37**) carboranyl enynes of type **A** were prepared in a one pot procedure from commercially available acetylenic ketone **34** (Scheme 12) [35].

As was expected, the enynes of type **A** (**35**–**37**), in contrast to the carborane-containing enyne **C** and diyne **B**, smoothly underwent the palladium-catalyzed [4 + 2] cycloaddition reaction with the diynes **21** to



Scheme 12. One-pot preparation of carboranyl enynes of type **A**.

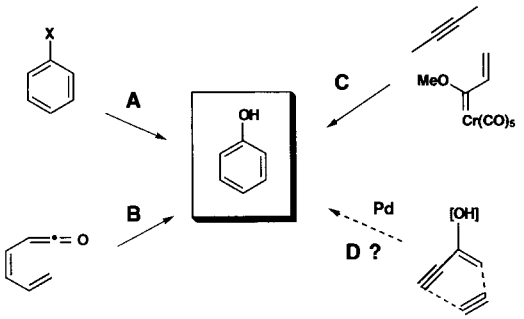


Fig. 4. Approaches toward phenol.

afford the benzenes **38**, possessing both an alkyne moiety and *para*-oriented *o*-, *meta*-, or *para*-carboranyl unit (Scheme 13) [35].

3.4. Synthesis of polysubstituted phenols, aryl ethers, and benzofuranones

Phenol derivatives are usually prepared via various kinds of modification of aromatic precursors (approach **A**, Fig. 4) [36], through ring closure of dienylketenes (approach **B**), or by means of cycloaddition of Fisher carbenes with alkynes (approach **C**) [37]. To the best of our knowledge, there is no precedent for the preparation of phenol derivatives through a [4 + 2] benzannulation pathway. Accordingly, we were intrigued whether one can assemble a phenol through the novel palladium-catalyzed [4 + 2] enyne–diyne cycloaddition methodology (approach **D**, Fig. 4). The obvious impossibility of introducing an unprotected hydroxy group into either partners (enynes or diynes) of the [4 + 2] cycloaddition reaction prompted us to search for more suitable precursors for phenol synthesis, bearing a hydroxy group equivalent. After certain work on design of reactants we found that readily available and easily handled 2-siloxysubstituted enynes **39** could perfectly serve for this purpose (Scheme 14) [38]. We found that a variety of polysubstituted phenols **41** could be easily prepared by this means in good yields either via the stepwise way or through a one-pot benzannulation–deprotection sequence (Scheme 14) [38].

In addition, the aryl ethers **43** were similarly prepared from methoxyenyne **42** [38], however in this case the cycloaddition reactions were not perfectly chemoselective. Thus, notable amounts of the homodimer **44** ([8], Fig. 2) were formed together with the major cross-benzannulation products **43** [38] (Scheme 15).

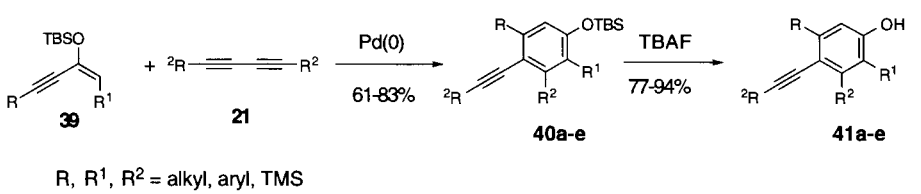
The dialkoxy-substituted benzene **45** was analogously synthesized from the corresponding dialkoxy diyne, which were converted into the benzofuranone **46** under acidic conditions (Scheme 16) [39]. It should be pointed out that **46** could be even more effectively prepared in one-pot sequence (overall yields for two steps > 80%, Scheme 16) [39]. Analogously, the benzofuranone **47** could be made, however in a rather moderate yield (Scheme 16) [39].

3.5. Synthesis of anilines

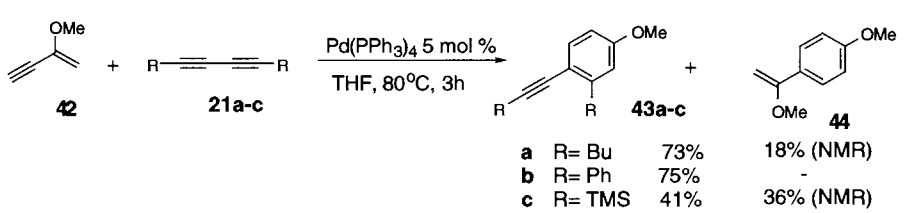
An exhaustive search for suitable precursors for preparation of anilines via the [4 + 2] cycloaddition motif pointed to nitrogen-containing enynes **48** [40]. We found that **48** reacted with diynes **21** to give the polysubstituted anilines **49** in reasonable yields. The deprotection work of **49** is now underway in our laboratories (Scheme 17).

3.6. Synthesis of cyclophanes via intermolecular cycloaddition of cyclic enynes and diynes

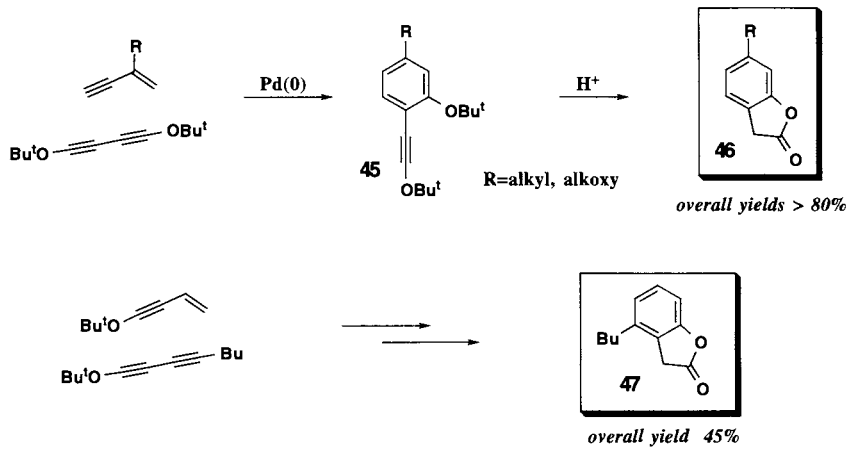
As we have previously mentioned [16], the methodology for the synthesis of carbocyclophanes via intramolecular protocol required both high dilution conditions and large amounts of the palladium catalyst.



Scheme 14. Synthesis of polysubstituted phenols **41**.

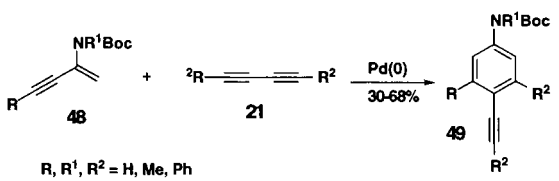


Scheme 15. Synthesis of aryl ethers **43**.

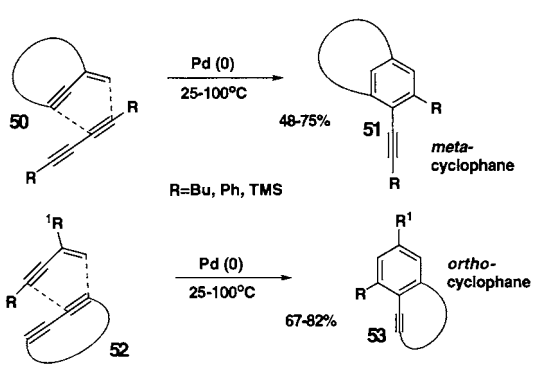


Scheme 16. Synthesis of benzofuranones.

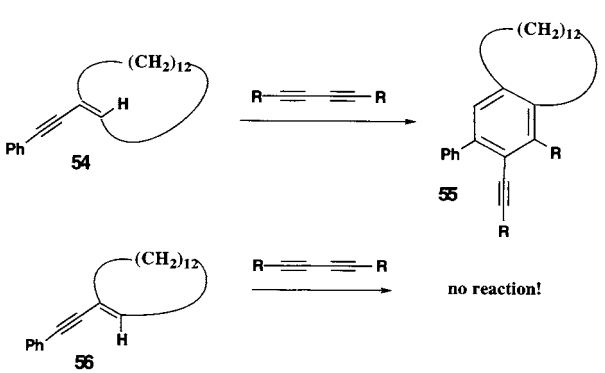
It occurred to us that we could partially dissolve these severe synthetic problems via an intermolecular reaction mode employing cyclic substrates. Indeed, the cyclic enyne **50** and diyne **52** smoothly underwent the intermolecular cycloaddition to give the *meta*- (**51**) and *ortho*- (**53**) cyclophanes in good yields (Scheme 18) [41]. It was interesting to find that the 1,4-disubstituted (*Z*) cyclic enyne **54**, as in the case of its acyclic analogues [31], underwent the cycloaddition reaction affording an *ortho*-cyclophane **55**, whereas its (*E*) counterpart **56** gave no trace of **55** (Scheme 19) [41]. Furthermore, the cyclophane **57** of an unusual type was easily prepared from **50** and **52** (Eq. (7)) [41].



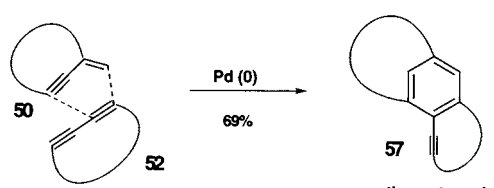
Scheme 17. Synthesis of anilines **49**.



Scheme 18. Synthesis of cyclophanes from cyclic enynes and diynes.



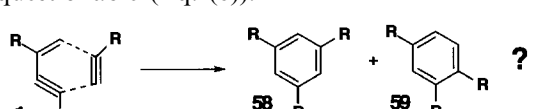
Scheme 19. Cycloaddition of (*Z*) versus (*E*) cyclic enynes.



(7)

4. Mechanistic study

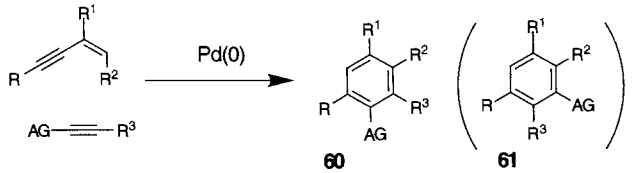
Analyzing the problems in controlling the regioselectivity of intramolecular trimerization of alkynes proceeding via the traditional metallocycle **i** (Eq. (1), [5]), it occurred to us that in the case if a conjugated enyne **1** (as a regiodefined equivalent of dimerized alkyne) would react with an alkyne in a [4 + 2] cycloaddition manner [26], this reaction could be more regioselective than the [2 + 2 + 2] mode of cycloaddition since only the regioselectivity of two bond formation remains questionable (Eq. (8)).



(8)

However, as we have previously mentioned (chapters **2** and **3**), in the all cases of palladium-catalyzed homo- [8,15,16] and cross- [28,30,31,35,38,39,41] [4 + 2] cycloadditions, only the one regioisomer, **60** (with regard

to relative orientation of enyne and enynophile) was formed, and no traces of regioisomeric **61** were ever detected in the crude reaction mixtures (Eq. (9))!



(9)

This fact of remarkable regiospecificity completely eliminated involvement of the traditional transition metal-assisted mechanism of alkynes trimerization (Eqs (1) and (9)). Indeed, if the mentioned mechanism is operative the formation of two regioisomers **60** and **61** (Eq. (10)) is unavoidable. Consequently, we realized that the observed palladium-catalyzed regiospecific [4 + 2] enyne–yne cycloaddition proceeded through an entirely different mechanism. As part of the mechanistic study of this reaction, we performed a comprehensive deuterium-labeling experiment (Fig. 5) [30]. Thus, the monodeuteriated enynes **62** and **64**, possessing a deuterium atom at the C-4 and C-2 positions afforded the benzenes **63** and **65** respectively, indicating no migration of the D atom (Fig. 5). However, the enyne **66**, having two deuterium atoms at the C-1 position, gave the bis-deuteriated benzene **67** in which one of the D-atoms obviously migrated. In order to understand the stereochemistry of D-migration, we prepared (*E*)-(**68**) and (*Z*)- (**70**) deuterio enynes and submitted them to the cross-benzannulation reaction with diynes. It was

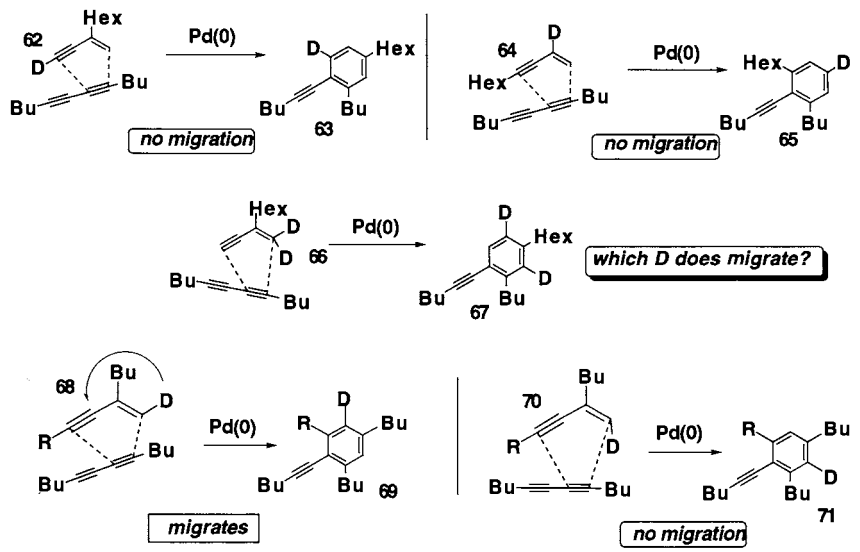


Fig. 5. Deuterium-labeling study.

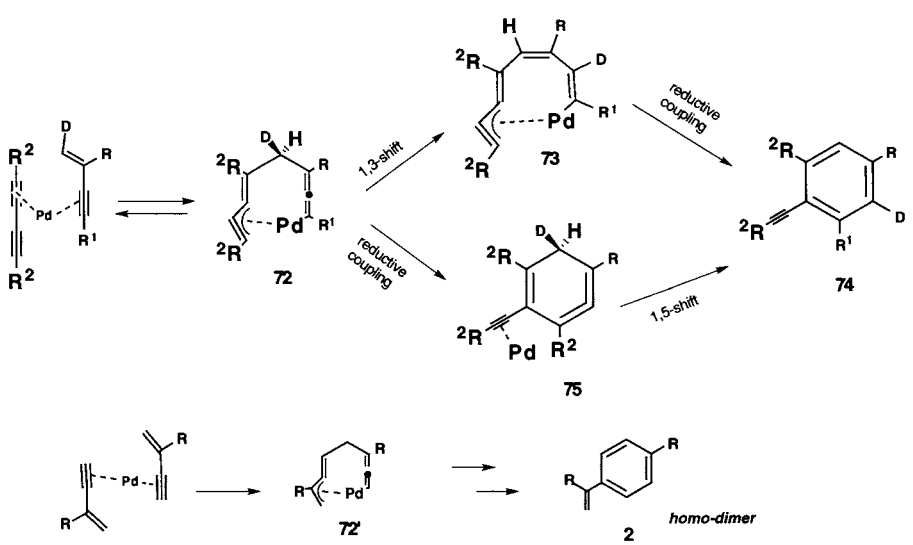
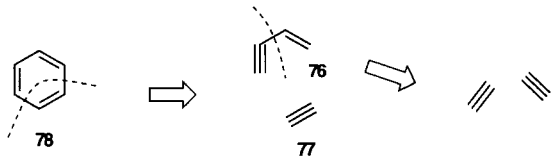


Fig. 6. Proposed mechanism for palladium-catalysed [4 + 2] enyne–yne cycloaddition.



Scheme 20. The concept of formal [2 + 2 + 2] sequential trimerization of alkynes.

discovered that only the (*E*) deuteriated enyne **68** produced benzene **69** with selective deuterium migration, whereas reaction of (*Z*) deuteriated **70** gave the aromatic product **71** in which deuterium did not move (Fig. 5) [30].

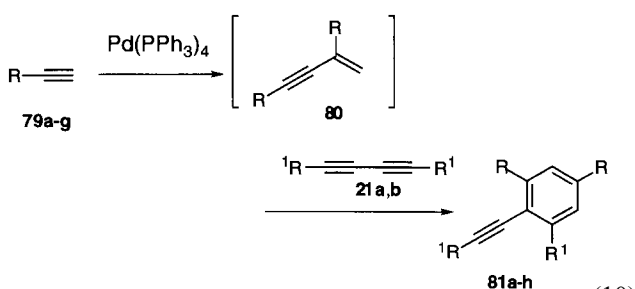
The results of the deuterium labeling experiments, taken together with the fact of regiospecific formation of single regioisomer **60** (Eq. (10)), encouraged us to propose the following mechanistic rationale for this reaction (Fig. 6). The reversible coordination of palladium with enyne and diyne would produce palladacycle **72** [42], stabilized by coordination of the Pd atom with the neighboring η^3-propargyl moiety [43]. Then **72** either undergoes a sigmatropic shift to form another metallocycle **73**, which via reductive coupling affords the benzene **74**, or via consecutive reductive elimination of palladium which forms a strained cyclic cumulene **75** [44], which is transformed into the cross-annulation product **74** via sigmatropic rearrangement. A similar mechanism could be operative for the homo-dimerization of enynes (the bottom line, Fig. 6).

5. Highly chemo- and regioselective formal [2 + 2 + 2] sequential trimerization of alkynes

5.1. Synthesis of tetrasubstituted benzenes via alkyne dimerization/cycloaddition sequence

Encouraged by the success of regiospecific formation of benzenes from conjugated enynes and activated alkynes (chapters **2**, **3**) and motivated by the challenging goal of regiospecific intermolecular trimerization of alkynes (chapter **1**, Eq. (1)), we attempted to apply our new [4 + 2] benzannulation methodology for the trimerization process on a sequential basis. Indeed, a simple retrosynthetic analysis of benzene **78** lead to a possible nonclassical assembling shown in Scheme 20 [26]. The proposed new concept of formal [2 + 2 + 2] alkyne trimerization sequence presumes consecutive dimerization of two alkynes to form a conjugated enyne **76**, followed by its [4 + 2] benzannulation with an enynophile **77** under the same reaction conditions to give benzene **78** (Scheme 20) [45]. Since we already have a technology for assembling a benzene ring from **76** and **77** [28,30,31], to complete the sequence (Scheme 20), the only selective formation of conjugated enyne **76** from two alkynes under the conditions of the [4 + 2] benzannulation reaction remained questionable [46].

In order to investigate the possibility of accomplishing the above mentioned sequence in the presence of $Pd(PPh_3)_4$ [47], the following experiment was performed. A mixture of phenylacetylene (**79a**, 2.4 mmol), 5,7-dodecadiyne (**21a**, 1 mmol) and $Pd(PPh_3)_4$ (5 mol%) was heated in THF (1 ml) for 12 h at 100°C (Method **A**). The result surpassed all expectations mentioned above: the tetrasubstituted benzene **81a** was obtained as a sole reaction product in an 89% NMR yield (Eq. (10), Table 5, entry 1).



(10)

Table 5
Synthesis of tetrasubstituted benzenes **81a–h** via sequential homodimerization of terminal alkynes **79**/[4+2] benzannulation with diynes **24**

Entry	Alkyne **79**, R	R^3 (Diyne)	Product	Method	Yield (%)[a]
1	Ph (**a**)	^{n}Bu (**24a**)	**81a**	**A**	89[b]
2	Ph (**a**)	^{n}Bu (**24a**)	**81a**	**B**[c]	82
3	$Ph(CH_2)_2$ (**b**)	^{n}Bu (**24a**)	**81b**	**B**	56
4	^{n}Bu (**c**)	^{n}Bu (**24a**)	**81c**	**B**	59
5	Ph (**a**)	Ph (**24b**)	**81d**	**B**	65
6	$MeOCH_2$ (**d**)	^{n}Bu (**24a**)	**81e**	**A**	56
7	$MeOCH_2$ (**d**)	Ph (**24b**)	**81f**	**A**	48
8	$MOMO(CH_2)_2$ (**e**)	^{n}Bu (**24a**)	**81g**	**B**	54
9	$Cl(CH_2)_3$ (**f**)	^{n}Bu (**24a**)	**81h**	**B**	64

[a] Isolated yield.
[b] NMR yield.
[c] Terminal alkyne **79** (2.5 equivalents), diyne **24** (one equivalent), $Pd_2dba_3 \cdot CHCl_3$ (5 mol%), and $(o\text{-Tol})_3P$ (40 mol%) were stirred in THF (0.5 M) at 25–60°C for 12–72 h (Method **B**).

Table 6
Synthesis of pentasubstituted benzenes **84i–p** via sequential cross-coupling of terminal alkynes **79** with internal alkynes **82**/[4+2] benzannulation with 5,7-dodecadiyne **21a**

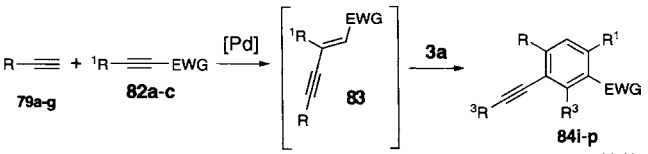
Entry	**79**, R	R^1	EWG	Product	Method[a]	Yield (%)[b]
1	^{n}Oct (**h**)	Me	CO_2Et (**82a**)	**84i**	**C**	60[c]
2	^{n}Oct (**h**)	Ph	CO_2Et (**82b**)	**84j**	**E**	61
3	Ph (**a**)	Me	CO_2Et (**82a**)	**84k**	**D**	54
4	Ph (**a**)	Ph	CO_2Et (**82b**)	**84l**	**D**	55
5	Et_2NCH_2 (**g**)	Ph	COMe (**82c**)	**84m**	**E**	50
6	Et_2NCH_2 (**g**)	Me	CO_2Et (**82a**)	**84n**	**C**	50
7	Et_2NCH_2 (**g**)	Ph	CO_2Et (**82b**)	**84o**	**E**	53
8	 (**i**)	Ph	CO_2Et (**82b**)	**84p**	**E**	52

[a] A mixture of terminal alkyne **79** (one equivalent), internal alkyne **82** (1.5 equivalents), diyne **21** (1.5 equivalents), and $Pd(PPh_3)_4$ (5 mol%) in toluene (1 M) was stirred for 3–6 days at 100°C (Method **C**); the same mixture was stirred first for 1 day at 50°C, then for 3–6 days at 100°C (Method **D**); $Pd(OAc)_2$ (5 mol%) and TDMPP (15 mol%) were added to the same mixture as above and the mixture was stirred for 1 day at 25°C, followed by stirring for 3–6 days at 100°C (Method **E**).
[b] Isolated yield.
[c] NMR yield.

Thus, it is obvious that two molecules of phenylacetylene (**79a**) combined together in the presence of $Pd(PPh_3)_4$ exclusively in the head-to-tail fashion producing 2,4-diphenylbut-1-ene-3-yne (**80a**), which then underwent the [4+2] cycloaddition with diyne **21a** to give the tetrasubstituted benzene **81a** as a single chemo- and regioisomer. Furthermore, the formation of the enyne **80** was confirmed by GC–MS analysis of the reaction mixture at the early stage, thus unambiguously proving the sequential mode of the observed transformation. Encouraged by the successful sequential trimerization of **79a** with **21a**, we attempted to generalize this methodology with other terminal alkynes and diynes. Thus, methyl propargyl ether (**79d**) enabled to undergo selective trimerization with dibutyl- **21a** and diphenyldiyne **21b** affording the aromatic products **81e** and **81f**, respectively, in moderate yields (entries 6 and 7). In contrast to the above cases, the chemoselectivity of the analogous reaction with other terminal alkynes under conditions **A** appeared to be not perfect. Thus, **79b**,**c**,**e**,**f**, at the first stage of sequence, produced not only homodimers **80**, but also trace to notable amounts of adducts with diyne **21**, which then underwent the second step of the sequence to give 5–7% of the corresponding chemoisomers together with the major product **81**, hence decreasing an overall chemoselectivity of the sequential process. It was thought that this low selectivity of alkyne dimerization was due to the rather drastic conditions of method **A**. Consequently the search for a milder catalyst system for the dimerization/benzannulation sequence was performed. After significant optimization work, it was discovered that the $Pd_2(dba)_3 \cdot CHCl_3$-(*o*-Tol)$_3$P combination enabled us effectively catalyze both steps of the sequence in the temperature range of 25–60°C (Method **B**). Reactions with all the terminal alkynes tested under these conditions proceeded in an absolute regio- and chemoselective manner to afford the desired benzenes **81** in moderate to good chemical yields (entries 2–5, 8, 9) [45]. It should be pointed out that in all cases no traces of any other regio- or chemoisomers of **81** were detected by GC–MS and NMR analyses of the crude reaction mixtures.

5.2. Synthesis of pentasubstituted benzenes through alkyne–alkyne cross-coupling/cycloaddition sequence

Inspired by successful preparation of tetrasubstituted benzenes **81** via the sequential homodimerization/benzannulation motif, we intended to combine two different alkynes in the first step of the sequential process [45]. If regio- and chemoselectivity of alkyne cross-coupling could be controlled, this reaction mode would allow us to obtain polysubstituted benzene from three different acetylenic units. The literature search indicated that selective cross-coupling of alkynes is possible. Trost demonstrated that 1,2,4-trisubstituted enynes could be effectively prepared via selective *syn*-addition of a terminal alkyne (donor alkyne) to an internal alkyne, possessing an electron-withdrawing group (acceptor alkyne), in the presence of $Pd(OAc)_2$–TDMPP (tris(2,6-dimethoxyphenyl)phosphine) catalyst system (see [46], for more details see also the review by Trost in this issue). Accordingly, we applied this donor/acceptor alkyne cross-coupling concept for the first step of our sequential strategy (Eq. (11), Table 6).



(11)

We found that in the presence of $Pd(PPh_3)_4$ (Method **C**) 1-decyne (**79h**) and 1,1-diethylpropargylamine (**79g**) (donor alkynes) selectively coupled with ethylbutynoate (**82a**) (acceptor alkyne) to form trisubstituted enynes **83**, which then reacted with the diyne **21a** to give the pentasubstituted alkylbenzene **84i** and benzylamine derivative **84n**, respectively (entries 1, 6). The slightly modified method **D** was used for sequential trimerization of **79a** with **82a**,**b** and **24a** to afford bis-aryls **84k**,**l** (entries 3 and 4). Furthermore, the combined method **E** gave the best chemoselectivities in the formation of the pentasubstituted benzenes **84j**,**m**,**o**,**p** (entries 2, 5, 7, 8). In all cases the pentasubstituted benzenes **84i**–**p** were obtained as a single reaction product, although in moderate isolated yields [45].

6. Conclusions

We are now in a position to effectively prepare various types of di-, tri-, tetra-, and pentasubstituted benzenes in an absolutely chemo- and regioselective manner via novel palladium-catalyzed [4 + 2] homo- and cross-cycloaddition of conjugated enynes. The wide synthetic applicability of this reaction was demonstrated by the synthesis of carborane derivatives, polysubstituted phenols, aryl ethers, anilines and carbo- and polyether type cyclophanes. The development of highly chemo- and regioseclective formal [2 + 2 + 2] sequential trimerization of alkynes partially resolved the long standing challenging problem of selective intermolecular trimerization of alkynes.

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References

[1] M.C. Berthelot, R. Acad. Sci. 62 (1866) 905.
[2] W. Reppe, O. Schlichting, K. Klager, T. Toepel, Justus Liebigs Ann. Chem. 560 (1948) 1.
[3] (a) L.S. Meriwether, E.C. Clothup, G.W. Kennerly, R.N. Reusch, J. Org. Chem. 26 (1961) 5155. (b) V.O. Reikhstel'd, K.L. Makovetskii, Russ. Chem. Rev. 35 (1966) 510.
[4] For recent reviews, see: (a) K.P.C. Vollhardt, Angew. Chem. Int. Ed. Engl. 23 (1984) 539. (b) N.E. Schore, Chem. Rev. 88 (1988) 1081. (c) B.M. Trost, Science 254 (1991) 1471. (d) M. Lautens, W. Klute, W. Tam, Chem. Rev. 96 (1996) 49.
[5] See, for example: (a) J.P. Colman, J.W. Kang, W.F. Little, M.F. Sullivan, Inorg. Chem. 7 (1968) 1298. (b) R.A. Ferreri, A.P. Wolf, J. Phys. Chem. 88 (1984) 2256. (c) A. Borrini, P. Diversi, G. Ingrosso, A. Lucherini, G. Serra, J. Mol. Catal. 30 (1985) 181. (d) H. Yasuda, A. Nakamura, Rev. Chem. Intermed. 6 (1986) 365.
[6] (a) S.H. Lecker, N.H. Nguen, K.P.C. Vollhardt, J. Am. Chem. Soc. 108 (1986) 856. (b) E. Negishi, L.S. Harring, Z. Owczarczyk, M.M. Mohamud, M. Ay, Tetrahedron Lett. 33 (1992) 3253. (c) For earlier works see also [4a] and references therein.
[7] See for example: (a) R.L. Halterman, N.H. Nguyen, K.P.C. Vollhardt, J. Am. Chem. Soc. 107 (1985) 1379. (b) B.C. Berris, G.H. Hovakeemian, Y.-H. Lai, H. Mestdagh, K.P.C. Vollhardt, J. Am. Chem. Soc. 107 (1985) 5670. (c) H.E. Helson, K.P.C. Vollhardt, Z.-Y. Yang, Angew. Chem. Int. Ed. Engl. 24 (1985) 114. (d) R. Grigg, R. Scott, P. Stevenson, Tetrahedron Lett. 23 (1982) 2691.
[8] S. Saito, M.M. Salter, V. Gevorgyan, N. Tsuboya, K. Tando, Y. Yamamoto, J. Am. Chem. Soc. 118 (1996) 3970.
[9] For review, see: (a) E.R. Moore (Ed.), Styrene Polymers in Encyclopedia of Polymer Science and Engineering, 2nd ed. Vol. 16, Wiley Interscience, New york, 1989; and references therein. See also (b) K. Matyajaszewski (Ed.), Cationic Polymerizations: Mechanisms, Synthesis, and Applications, Marcel Dekker, New York, 1996. For an earlier review see: (c) R.H. Boundy, R.F. Boyer, Styrene, Its Polymers, Copolymers, and Derivatives, Reinhold, New York, 1952. For example of recent work, see: (d) B.R. Stranix, J.P. Gao, R. Barghi, J. Salha, J. Org. Chem. 62 (1997) 8987, and references therein.
[10] See for example: (a) N. Nomura, J. Jin, H. Park, T.V. RajanBabu, J. Am. Chem. Soc. 120 (1998) 459. (b) S.P. Kolis, M.D. Chordia, R. Liu, M.E. Kopach, W.D. Harman, J. Am. Chem. Soc. 120 (1998) 2218. (c) S.K. Deb, T.M. Maddux, L. Yu, J. Am. Chem. Soc. 119 (1997) 9079. (d) A. Nzeru, J.R. Ebdon, S. Rimmer, J. Am. Chem. Soc. 119 (1997) 8928. (e) E. Galardon, S. Roue, P. Maux, G. Simonneaux, Tetrahedron Lett. 39 (1998) 2333. (f) R. Bruckner, R. Huisgen, J. Schmid, Tetrahedron Lett. 31 (1990) 7129.
[11] For a review see: (a) R.F. Boyer, in: H.F. Mark, N.G. Gaylord, N.M. Bikales (Eds.), Encyclopedia of Polymer Science and Technology. Vol. 13, Wiley Interscience, New York, 1970. (b) A. Ravve, Principles of Polymer Chemistry, Plenum Press, New York, 1995, and references therein. For earlier examples, see: (c) W.Y. Lau, C.M. Burns, Can. J. Chem. 47 (1969) 2057. (d) H. Hopf, F. Lochner, Macromol. Chem. 84 (1965) 261. (e) V.V. Korshak, N.G. Matveeva, Bull. Acad. Sci. USSR Div. Chem. Sci. Engl. Transl. (1953) 547.
[12] (a) S.A. Hardinger, C. Bayne, E. Kantorowski, R. McClellan, L. Larres, M.-A. Nuesse, J. Org. Chem. 60 (1995) 1104. (b) T.J. Kwok, D.J. Wink, Organometallics 12 (1993) 1954. (c) K. Srinivasan, P. Michaud, J.K. Kochi, J. Am. Chem. Soc. 108 (1986) 2309. (d) M.H. Chisholm, C.E. Hammond, D. Ho, J.C. Huffman, J. Am. Chem. Soc. 108 (1986) 7860. (e) J.P. Collman, P.D. Hampton, J.I. Brauman, J. Am. Chem. Soc. 112 (1990) 2986. (f) R.H. Crabtree, M.F. Mellea, J.M. Quirk, J. Am. Chem. Soc. 106 (1984) 2913. (g) A.L. Lyons, N. Turro, J. Am. Chem. Soc. 100 (1978) 3177. (h) H. Coutelle, R. Huttel, J. Organomet. Chem. 153 (1978) 359.
[13] (a) J.M. Saa, G. Martorell, A. Garsia-Raso, J. Org. Chem. 57 (1992) 678. (b) G. Martorell, A. Garsia-Raso, J.M. Saa, Tetrahedron Lett. 31 (1990) 2357. (c) L.H. Schwartzman, B.B. Corson, J. Am. Chem. Soc. 76 (1954) 781. (d) See also ref [4f].

[14] Very recently an elegant method for the preparation of 2,6-disubstituted styrenes was reported, however this method was restricted to the preparation of styrenes which neccessarily possess an additional substituent at the β-position. M. Catelani, F. Frignani, A. Rangoni, Angew. Chem. Int. Ed. Engl. 36 (1997) 119.
[15] V. Gevorgyan, K. Tando, N. Uchiyama, Y. Yamamoto, J. Org. Chem. 63 (1998) 7022.
[16] S. Saito, N. Tsuboya, Y. Yamamoto, J. Org. Chem. 62 (1997) 5042.
[17] P.A.A. Klusener, W. Kulik, L. Brandsma, J. Org. Chem. 52 (1987) 5261.
[18] For recent reviews on synthesis of cyclophanes, see: (a) Top. Curr. Chem. 172; E. Weber (Ed.), Springer-Verlag, Berlin, 1994. (b) F. Vögtle (Ed.), Cyclophane Chemistry, Willey, Chichester, 1993. (c) F. Diederich, Cyclophanes, Royal Society of Chemistry, Cambridge, 1991.
[19] It is generally accepted that alkylation of substrates bearing a β-alkoxy functionality is difficult due to the electron-withdrawing nature of the β-oxygen. For a review see: A. Streitwieser, Solvolytic Displacement Reactions, McGraw-Hill, New York, 1962, pp. 16–18.
[20] Direct nucleophilic alkylation at the carbon center of triflates bearing a β-oxygen atom has been reported. For a review on alkylations with organocuprate reagents see for example: (a) B.H. Lipshutz, Synthesis (1987) 325. For alkylations with Grignard reagents see: (b) H. Kotsuki, I. Kadota, M. Ochi, Tetrahedron Lett. 30 (1989) 1281.
[21] D. Weibel, V. Gevorgyan, Y. Yamamoto, J. Org. Chem. 63 (1998) 1217.
[22] H. Kotsuki, I. Kadota, M. Ochi, Tetrahedron Lett. 31 (1990) 4609.
[23] For regioselective epoxide ring openings with acetylides in the presence of metal salts, see: M. Chini, P. Crotti, L. Favero, F. Macchia, Tetrahedron Lett. 32 (1991) 6617.
[24] A template-directed effect of alkali metal salts in the rutheniumcatalyzed ring-closure metathesis has been recently demonstrated see: M.J. Marsella, H.D. Maynard, R.H. Grubbs, Angew. Chem. Int. Ed. Engl. 36 (1997) 1101.
[25] It was also found that 2,4-disubstituted enynes do not undergo intermolecular homo-benzannulation under the mentioned reaction conditions, see Ref. [29].
[26] Although scattered data on related processes such as thermal (a, b) or Lewis acid mediated (a) intramolecular enyne–yne [4 + 2] cycloaddition reaction were recently reported, the more synthetically useful intermolecular enyne–yne cross-benzannulation still remained unemployed. (a) R.L. Danheiser, A.E. Gould, R. Fernandez de la Predilla, A.L. Helgason, J. Org. Chem. 59 (1994) 5514. (b) R.C. Burrell, K.J. Daoust, A.Z. Bradley, K.J. DiRico, R.P. Johnson, J. Am. Chem. Soc. 118 (1996) 4218.
[27] The structure of *para*-oriented **22** was unambiguously confirmed by 500 MHz NOE- and COLOC NMR analyses.
[28] V. Gevorgyan, A. Takeda, Y. Yamamoto, J. Am. Chem. Soc. 119 (1997) 11313.
[29] The excess of enyne **1a** underwent homo-dimerization, affording **2**, see also footnote c, Table 4.
[30] V. Gevorgyan, A. Takeda, M. Honma, N. Sadayori, Y. Yamamoto (manuscript in preparation).
[31] V. Gevorgyan, N. Sadayori, Y. Yamamoto, Tetrahedron Lett. 38 (1997) 8603.
[32] (a) X. Yang, W. Jiang, C.B. Knobler, M.F. Hawthorne, J. Am. Chem. Soc. 114 (1992) 9719. (b) J. Müller, K. Base, T.F. Magnera, J. Michl, J. Am. Chem. Soc. 114 (1992) 9721.
[33] W. Clegg, W.R. Gill, J.A.H. MacBride, Angew. Chem. Int. Ed. Engl. 32 (1993) 1328.
[34] U. Schöberl, T.F. Magnera, R.M. Harrison, F. Fleicher, J.L. Pflug, P.F.H. Schwab, X. Meng, D. Lopiak, B.C. Noll, V.S. Allured, T. Rudalevige, S. Lee, J. Michl, J. Am. Chem. Soc. 119 (1997) 3907.
[35] V. Gevorgyan, Y.-H. Kim. N. Sadayori, Y. Yamamoto (manuscript in preparation).
[36] For a general review, see: (a) D.A. Whiting, in: J.F. Stoddart (Ed.), Comprehensive Organic Chemistry. Vol. 1, Pergamon Press, Oxford, 1979, Ch. 4.2. For a review on aryl C–O bond-forming reactions, see: (b) C.K.-F. Chiu, in: A.R. Katritzky, O. Meth-Cohn, C.W. Rees (Eds.), Comprehensive Organic Functional Group Transformations. Vol. 2, Pergamon Press, New York, 1995, Ch. 2.13.
[37] For reviews, see: (a) W.D. Wulff, in: B.M. Trost, I. Fleming (Eds.), Comprehensive Organic Synthesis. Vol. 5, Pergamon Press, New York, 1991, p. 1065. (b) N.E. Schore, Chem. Rev. 88 (1988) 1081. See also: (c) C.A. Merlic, D. Xu, J. Am. Chem. Soc. 113 (1991) 7418. (d) P. Turnbull, M.J. Heilman, H.W. Moore, J. Org. Chem. 61 (1996) 2584. (e) S.H. Koo, L.S. Liebeskind, J. Am. Chem. Soc. 117 (1995) 3389. (f) A. Covarrubias-Zúñiga, E. Ríos-Barrios, J. Org. Chem. 62 (1997) 5688. (g) D. Collomb, A. Doutheau, Tetrahedron Lett. 38 (1997) 1397. (h) J. Barluenga, A. Refnández-Acebes, A.A. Trabanco, J. Flórez, J. Am. Chem. Soc. 119 (1997) 7591.
[38] V. Gevorgyan, L.G. Quan, Y. Yamamoto, J. Org. Chem. 63 (1998) 1244.
[39] V. Gevorgyan, L.G. Quan, Y. Yamamoto (manuscript in preparation).
[40] G. Reginato, A. Mordini, A. Degl'Innocenti, M. Caracciolo, Tetyrahedron Lett. 36 (1995) 8275.
[41] V. Gevorgyan, N. Tsuboya, Y. Yamamoto (manuscript in preparation).
[42] π-Propargyl palladium complexes have been recently isolated and fully characterized. See: (a) S. Ogoshi, K. Tsutsumi, H. Kurosawa, J. Organomet. Chem. 493 (1995) C19. (b) S. Ogoshi, K. Tsutsumi, M. Ooi, H. Kurosawa, J. Am. Chem. Soc. 117 (1995) 10415.
[43] The coordination of palladium to the propargyl group in the intermediate **72** is supported not only by the exclusive formation of a sole regioisomer **74** 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 alkynyl group, do not act as enynophiles in the mentioned reaction. Accordingly, an alternative explanation of remarkable reactivity of diynes in terms of steric effects was discounted by the observation that acetylene itself did not act as an enynophile in that reaction.
[44] This type of 6-membered strained cyclic cumulene has been recently proposed as an intermediate in the dehydro Diels–Alder cycloadditions. (a) For review see: R.P. Johnson, Chem. Rev. 89 (1989) 1111. (b) See also reference [26b].
[45] V. Gevorgyan, U. Radhakrishnan, A. Takeda, Y. Yamamoto (manuscript in preparation).
[46] Although various transition metals including Pd(II) are known to catalyze selective dimerization of alkynes, to the best of our knowledge, there are no reports in the literature concerning the use of $Pd(PPh_3)_4$ in this reaction. For selective alkyne coupling in the presence of $Pd(OAc)_2$, see: B.M. Trost, M.T. Sorum, C. Chan, A.E. Harms, G. Rühter, J. Am. Chem. Soc. 119 (1997) 698. For other transition metal-catalyzed alkyne dimerizations, see references therein.
[47] The control experiments demonstrated that in the presence of $Pd(OAc)_2$–TDMPP catalyst system [46] no [4 + 2] benzannulation took place, although the dimerization of alkynes proceeded smoothly.