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In Situ Generation of Vinyl Allenes and Its Applications to One-Pot Assembly of Cyclohexene, Cyclooctadiene, 3,7-Nonadienone, and Bicyclo[6.4.0]dodecene Derivatives with Palladium-Catalyzed Multicomponent Reactions

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Abstract: A novel tandem Pd-catalyzed cross-coupling and [4 + 4] cycloaddition sequence allows the rapid synthesis of eight-membered carbocycles starting from α-bromovinyl arenes and propargyl bromides in one reaction vessel. It is noteworthy that four components are assembled into one molecule via this procedure. In contrast to α-bromovinyl arenes, α-bromovinyl alkanes afforded tandem cross-coupling and homo [4 + 2] cycloaddition products. Subjecting an equimolar mixture of α-bromostyrene and 2-bromo-1-octene to propargyl bromides furnished the tandem Pd-catalyzed cross-coupling and hetero [4 + 2] cycloaddition product. Exposure of equimolar mixtures of α-bromovinyl arenes to allenylindium resulted in tandem a Pd-catalyzed cross-coupling and hetero [4 + 4] cycloaddition products. Synthesis of vinylallene from the reaction of vinyl triflate with allenylindium followed by Pd-catalyzed carbon monoxide insertion reaction gave the corresponding 3,7-nonadienone product via tandem Pd-catalyzed cross-coupling and [4 + 4 + 1] annulation. Tandem Pd-catalyzed cross-coupling, [4 + 4] cycloaddition, and [4 + 2] cycloaddition provided the rapid synthesis of bicyclo[6.4.0]dodecene derivatives starting from α-bromovinyl arenes, propargyl bromides, and dienophiles in one operation, in which five components were integrated into one molecule.

Introduction

Transition metal-catalyzed multicomponent reactions (MCR) have attracted considerable attention due to the fact that complex organic molecules and drugs can be easily prepared from simple compounds in one reaction sequence.[1] Although a range of strategies involving the sequential generation of radical and anionic species has been used for such transformations,[2] relatively few transition metal-catalyzed MCRs have been reported for the synthesis of complex cyclic compounds.[3] Thus, development of new multicomponent reactions that allow assembly of polysubstituted carbocycles in a regioselective manner is in high demand. In particular, the construction of eight-membered carbocycles via MCR remains a significant synthetic challenge because they constitute common structural cores of a large number of biologically important natural and unnatural products.[4,5]

Recently, we discovered an efficient method for the synthesis of substituted allenes, polyallenes, and unsymmetrical bis(allenes) from the reactions of a variety of electrophilic coupling partners with allenylindiums generated in situ.[6] Thus, α-bromostyrene reacted with 1-bromo-2-butyne (**2d**) bearing a methyl substituent at the γ-position to give 3-methyl-4-phenyl-1,2,4-pentatriene (**3**) in 85% yield via cross-coupling reaction. *trans*-4-Phenyl-1,2,4-hexatriene (**5**) was obtained in 92% yield from *cis*-1-bromo-2-methyl-1-phenylethene (**4**) and propargyl bromide (**2a**). However, treatment of α-bromostyrene with allenylindium produced unexpectedly 3,4-dimethylene-1,6-diphenyl-1,5-cyclooctadiene (**6b**) in 94% yield (Scheme 1).

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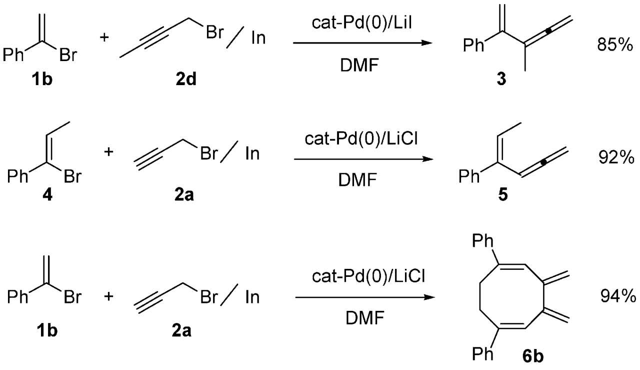
10.1021/ja054144v CCC: $33.50

Scheme 1

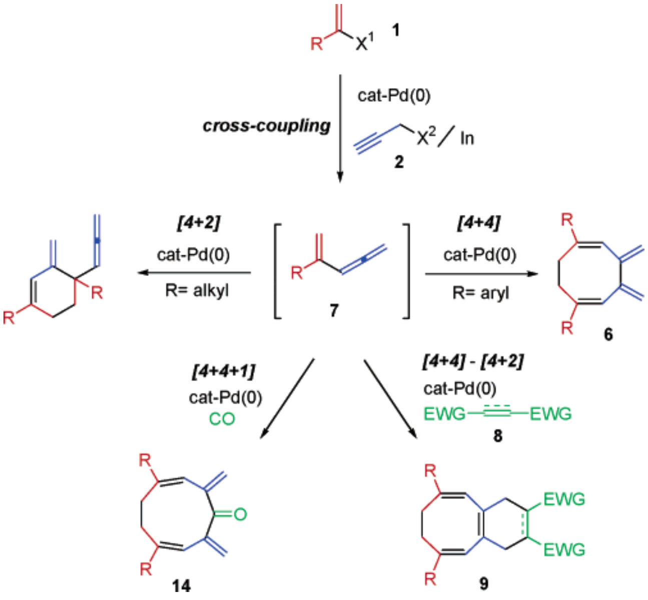


Stimulated by these results, we reported the highly efficient synthesis of bicyclo[6.4.0]dodecene derivatives by tandem five-component reactions of two molecules of α-bromostyrene, two molecules of propargyl bromide, and a dienophile.[7] As part of a project aimed at finding new MCRs that would be useful in organic synthesis, we report herein in full the novel intermolecular tandem Pd-catalyzed cross-coupling reactions, Pd-catalyzed [4 + 4] cycloaddition reactions, and [4 + 2] cycloaddition reactions and Pd-catalyzed cross-coupling reactions followed by [4 + 4 + 1] annulation or [4 + 2] cycloaddition reactions to give cyclooctadiene, bicyclo[6.4.0]-dodecene, 3,7-nonadiene, and cyclohexene derivatives in one-pot multicomponent assembly (Scheme 2).

Results and Discussions

Pd-Catalyzed Cross-Coupling Reactions and Pd-Catalyzed [4 + 4] Cycloadditions. Four-component assembly by Pd-catalyzed cross-coupling and Pd-catalyzed [4 + 4] cycloaddition was first examined by using α-bromostyrene and propargyl bromide. The organoindium reagent obtained from 1 equiv of indium and 1.5 equiv of propargyl bromide was added to a solution of 1 equiv of α-bromostyrene in the presence of 4 mol % of $Pd(PPh_3)_4$ and 3 equiv of LiCl,[6,8] and the solution was stirred at 50 °C for 2 h. In the ^{1}H NMR spectrum of the crude product mixture, 3,4-dimethylene-1,6-diphenyl-1,5-cyclooctadiene (**6b**) was observed as the major compound, indicative of a tandem Pd-catalyzed cross-coupling−Pd-catalyzed [4 + 4] cycloaddition taking place, yielding **6b** in 94% isolated yield.

Scheme 2



Reaction of the enol triflate of 3-bromoacetophenone with allenylindium produced 4-(3-bromophenyl)-1,2,4-pentatriene (**10**) in 70% yield (DMF, 50 °C, 1 h) via Pd-catalyzed cross-coupling. Prolonged reaction time (2 h) gave **6m** in 79% yield (Scheme 3).[5n,9] This result implies that **6m** is produced via Pd-catalyzed [4 + 4] cycloaddition reaction of **10**.

For the vinyl bromides as electrophilic coupling partners, electronic variation on the aromatic substituents did not diminish the efficiency and selectivity (entries 8−19, Table 1). It is noteworthy that protection of hydroxyl and amino groups on substrates is not necessary, as demonstrated by the reaction of 3-hydroxy-α-bromostyrene (entry 11) and 3-amino-α-bromostyrene (entries 12 and 13). The reaction worked equally well with α-bromovinyl arenes having halides such as Cl and Br (entries 14 and 17). 4-Bromo-α-bromostyrene selectively afforded the desired cyclooctadiene **6p** in 84% yield under the present conditions (entry 17). This result implies that vinyl bromide is more reactive than aryl bromide in coupling reactions with allenylindium. 2-Deutero-1-bromo-1-phenylethene (cis:trans = 1:1.7) gave cyclooctadiene **6c** in 87% yield in which deuterium was inserted at the 7- and/or 8-positions (Scheme 4).

Reaction of α-bromostyrene with 3-bromo-1-butyne and indium provided the product **6d** in 90% yield consisting of three stereoisomers (1.3:1.0:1.3) with respect to the orientation of the two methyl groups of the exocyclic double bonds (entry 5). Vinyl triflates can also be used in tandem cross-coupling/cycloaddition catalyzed by Pd(0) (entries 7 and 16). For propargyl halides as nucleophilic cross-coupling partners, the

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(5) For [2 + 2 + 2 + 2] cycloaddition, see: (a) Salem, B.; Suffert, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2826. (b) Boussie, T. R.; Streitwieser, A. *J. Org. Chem.* **1993**, *58*, 2377. (c) Walther, D.; Braun, D.; Schulz, W.; Rosenthal, U. *Z. Anorg. Allg. Chem.* **1989**, *577*, 270. (d) Lawrie, C. J.; Gable, K. P.; Carpenter, B. K. *Organometallics* **1989**, *8*, 2274. (e) Colborn, R. E.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 5470. For [4 + 2 + 2] cycloaddition, see: (f) Baik, M.-H.; Baum, E. W.; Burland, M. C.; Evans, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 1602. (g) Evans, P. A.; Baum, E. W. *J. Am. Chem. Soc.* **2004**, *126*, 11150. (h) Varela, J. A.; Castedo, L.; Saa, C. *Org. Lett.* **2003**, *5*, 2841. (i) Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8782. (j) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784. (k) Chen, Y.; Snyder, J. K. *J. Org. Chem.* **1998**, *63*, 2060. (l) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863 and references therein. For [5 + 2 + 1] cycloaddition, see: (m) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876. For [4 + 4] cycloaddition, see: (n) Murakami, M.; Itami, K.; Ito, Y. *Synlett* **1999**, 951. (o) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suarez-Sobrino, A.; Vagberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908 and references therein. (p) Itoh, K.; Masuda, K.; Fukahori, T.; Nakano, K.; Aoki, K.; Nagashima, H. *Organometallics* **1994**, *13*, 1020. (q) Schneider, R.; Siegel, H.; Hopf, H. *Liebigs Ann. Chem.* **1981**, 1812. For [6 + 2] cycloaddition, see: (r) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. J. *J. Am. Chem. Soc.* **2000**, *122*, 7815 and references therein. (s) Rigby, J. H. *Tetrahedron* **1999**, *55*, 4521. (t) Chafee, K.; Huo, P.; Sheridan, J. B.; Barbieri, A.; Aistars, A.; Lalancette, R. A.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 1900.

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(9) Although reaction of the enol triflate of 3-bromoacetophenone with allenylindium produced **6m** in 79% yield (DMF, 50 °C, 2 h) via Pd-catalyzed cross-coupling reaction and [4 + 4] cycloaddition, 4-(3-bromophenyl)-1,2,4-pentatriene (**10**) via Pd-catalyzed cross-coupling reaction was obtained in 70% yield using DMF at 50 °C for 1 h. The fact that **6m** is not formed in any amount under these conditions is a confusing observation.

Scheme 3

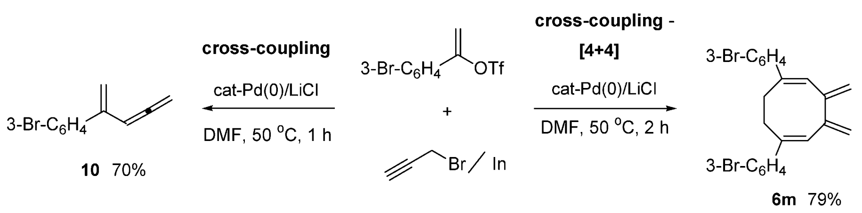
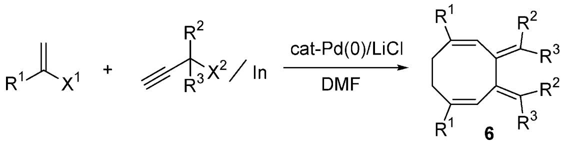


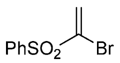
Table 1. Tandem Cross-Coupling−[4 + 4] Cycloaddition[a]

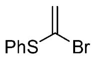


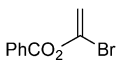
entry	R^1	R^2	R^3	X^1	X^2	compd	yield^b (%)
1	TMS	H	H	Br	Br	**6a**	71
2	Ph	H	H	Br	Br	**6b**	94
3	Ph	H	H	Br	Br	**6c**	87^c
4	Ph	H	H	OTf	Br	**6b**	71
5	Ph	Me	H	Br	Br	**6d**	90^d
6	Ph	Me	Me	Br	Cl	**6e**	91^e
7	Ph	Me	Me	OTf	Cl	**6e**	72^e
8	4-Me-C$_6$H$_4$	H	H	Br	Br	**6f**	87
9	4-MeO-C$_6$H$_4$	H	H	Br	Br	**6g**	87
10	4-MeO-C$_6$H$_4$	Me	Me	Br	Cl	**6h**	79^e
11	3-HO-C$_6$H$_4$	H	H	Br	Br	**6i**	81
12	3-H$_2$N-C$_6$H$_4$	H	H	Br	Br	**6j**	71
13	3-H$_2$N-C$_6$H$_4$	Me	Me	Br	Cl	**6k**	63^e
14	2-Cl-C$_6$H$_4$	H	H	Br	Br	**6l**	83
15	3-Br-C$_6$H$_4$	H	H	OTf	Br	**6m**	79
16	3-Br-C$_6$H$_4$	Me	Me	OTf	Cl	**6n**	65^e
17	4-Br-C$_6$H$_4$	H	H	Br	Br	**6p**	84
18	4-F$_3$C-C$_6$H$_4$	H	H	Br	Br	**6q**	91
19	4-F$_3$C-C$_6$H$_4$	Me	Me	Br	Cl	**6r**	71^e

[a] Reaction performed in the presence of 4 mol % of Pd(Ph$_3$P)$_4$, 1 equiv of In, and 1.5 equiv of propargyl halide in DMF for 2 h at 50 °C. [b] Isolated yields. [c] 87% *d*-incoporated 2-deutero-1-bromo-1-phenylethene (cis:trans = 1:1.7) was used. [d] The product consisted of three stereoisomers (1.3:1.0: 1.3) with respect to the orientation of the two methyl groups of the exocyclic double bonds. [e] 2 equiv of In, 3 equiv of 3-chloro-3-methyl-1-butyne, and 5 equiv of LiBr were used.

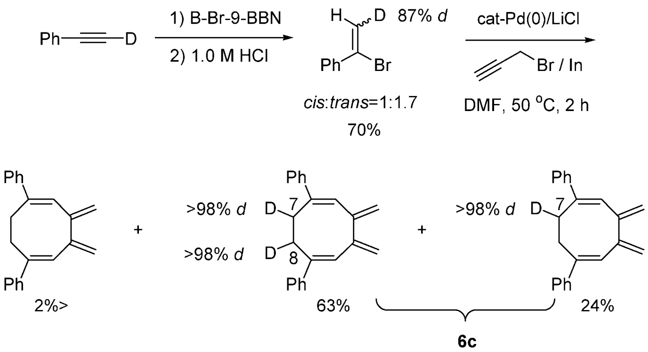
presence of two methyl substituents at the α-position exhibited little effect on both the reaction rate and product yield. In the case of 3-chloro-3-methyl-1-butyne, products **6e**,**h**,**k**,**n**,**r** having four methyl groups on terminal olefins were obtained in 63−91% yields under the optimum conditions (entries 6, 7, 10, 13, 16, and 19). (α-Bromovinyl)trimethylsilane reacted with propargyl bromide and indium to produce **6a** in 71% yield (entry 1). However, α-bromovinyl phenyl sulfone, α-bromovinyl phenyl sulfide, and α-bromovinyl benzoate failed to deliver the desired compounds due to their thermal instability.



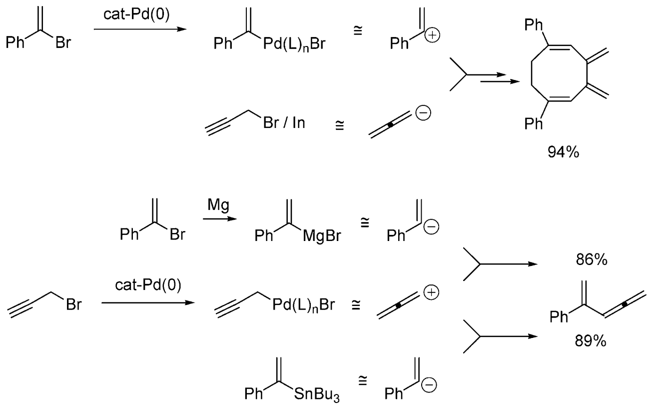




Scheme 4



Scheme 5



Pd-catalyzed [4 + 4] cycloaddition reactions using the vinylallene as a starting material were recently reported.[5n] In the reported reaction, the vinylallene was obtained from (1-phenylvinyl)magnesium bromide and propargyl bromide in the presence of Pd(0) catalyst.[10] However, in situ preparation of vinylallenes using inversion of the charge polarization of the reaction components (α-bromostyrene and propargyl bromide) was applied using the present method (Scheme 5). Although we tried to prepare cyclooctadiene from α-bromostyrene under the Murakami conditions in one-pot operation, vinylallenes were produced exclusively in 86% yield and no [4 + 4] cycloaddition product of the vinylallene was formed. (1-Phenylvinyl)tributyltin was prepared in 90% yield from Grignard reagent obtained from α-bromostyrene and Mg with tributyltin chloride. Treatment of (1-phenylvinyl)tributyltin with propargyl bromide in the presence of Pd(0) catalyst gave vinylallene in 89% yield, and the longer reaction time (24 h) resulted in decomposition of vinylallene.[10]

Pd-Catalyzed Cross-Coupling and Homo [4 + 2], Hetero [4 + 2], or Hetero [4 + 4] Cycloaddition Reactions. To demonstrate the efficiency and scope of the present method, we applied this MCR to 2-halo-1-alkenes. Although α-halovinyl arenes produced 3,4-dimethylene-1,6-diphenyl-1,5-cyclooctadiene derivatives in good to excellent yields via tandem cross-coupling and [4 + 4] cycloaddition reactions catalyzed by Pd(0), treatment of 2-halo-1-alkenes with propargyl bromide and indium under the optimized conditions afforded cyclohexene derivatives via the tandem cross-coupling and [4 + 2] cycloaddition sequence. Reaction of 2-bromo-1-octene or 2-iodo-1-octene with the allenylindium reagent gave rise to 1,4-dihexyl-3-methylene-4-propadienyl-1-cyclohexene (**11**) in 71% and 43% yields, respectively (Scheme 6).[5n]

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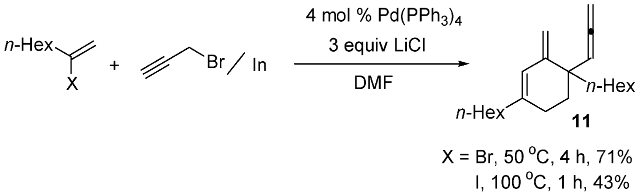
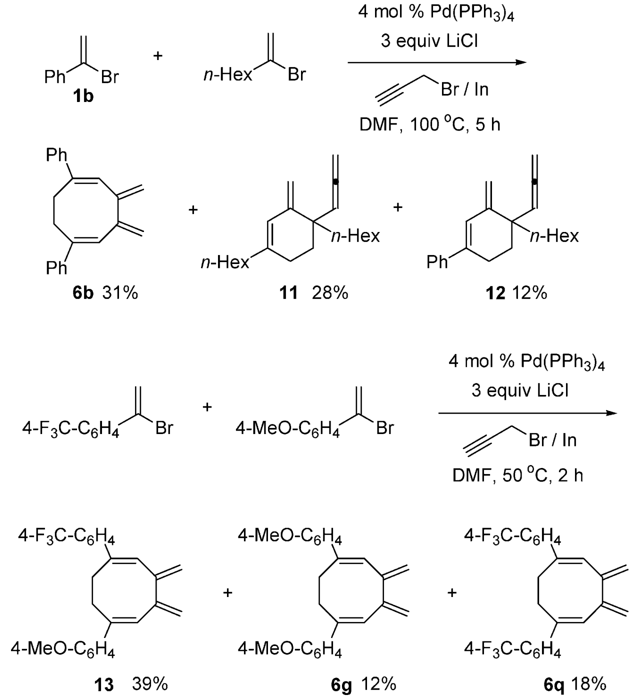
Scheme 6. Tandem Cross-Coupling−Homo [4 + 2] Cycloaddition from 2-Halo-1-alkenes



Scheme 7. Tandem Cross-Coupling−Homo or Hetero [4 + 2] Cycloaddition and Cross-Coupling−Hetero [4 + 4] Cycloaddition



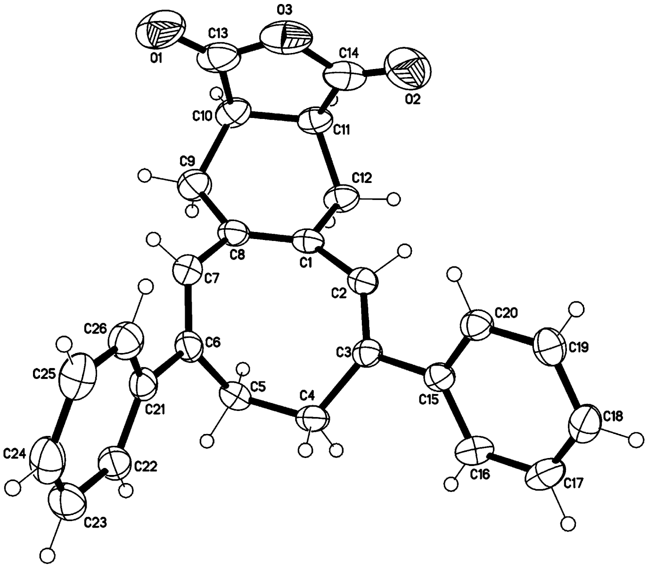
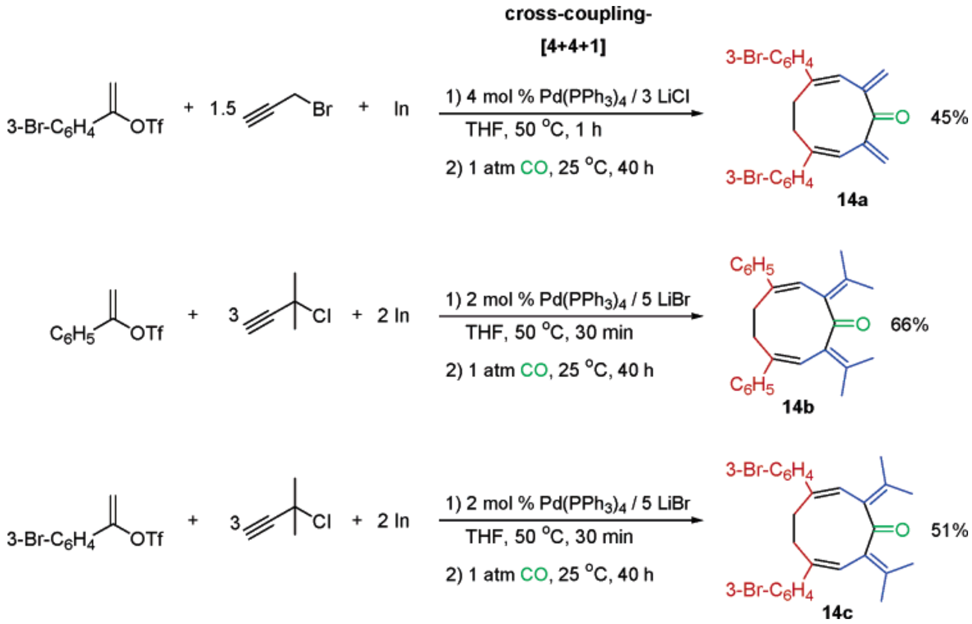


Figure 1. Molecular structure of **9i** along with the atom-numbering schemes. Displacement ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) and angles (deg): C1−C2 1.478(2), C2−C3 1.346(2), C3−C4 1.516(2), C4−C5 1.520(2), C1−C8 1.351(2), C1−C12 1.521(2), C10−C11 1.524(2), C11−C12 1.532(2); C1−C2−C3 134.29-(14), C1−C12−C11, 111.06(13), C2−C3−C4 127.84(14), C3−C4−C5 116.39(13), C8−C1−C2 128.16, C8−C1−C12 116.45(14).

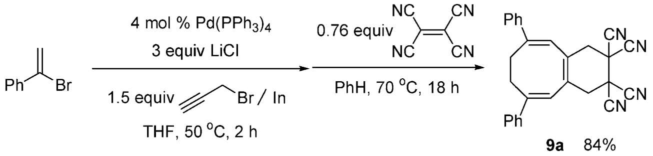
We also examined the tandem Pd-catalyzed cross-coupling/cycloaddition sequence with the mixture of a α-bromovinyl arene and 2-halo-1-alkenes. Reaction of equimolar mixture of α-bromostyrene and 2-bromo-1-octene with 2 equiv of propargyl bromide under the optimum conditions produced tandem cross-coupling−homo [4 + 4] cycloaddition products **6b** and cross-coupling−homo [4 + 2] cycloaddition products **11** in 31% and 28% yield, respectively, and tandem cross-coupling−hetero [4 + 2] cycloaddition product **12** in 12% yield. Subjecting a mixture of 4-(trifluoromethyl)-α-bromostyrene and 4-(methoxyphenyl)-α-bromostyrene to 1.5 equiv of propargyl bromide and 1 equiv of indium gave the tandem cross-coupling−hetero [4 + 4] cycloaddition product **13** in 39% yield and cross-coupling−homo [4 + 4] cycloaddition products **6g**,**q** in 12% and 18% yield, respectively (Scheme 7).

After the Pd-catalyzed cross-coupling of the enol triflate of 3-bromoacetophenone with allenylindium, exposure of the crude

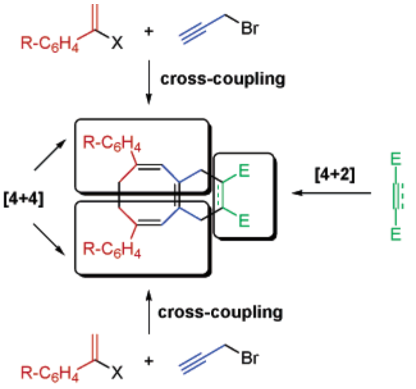
Scheme 8

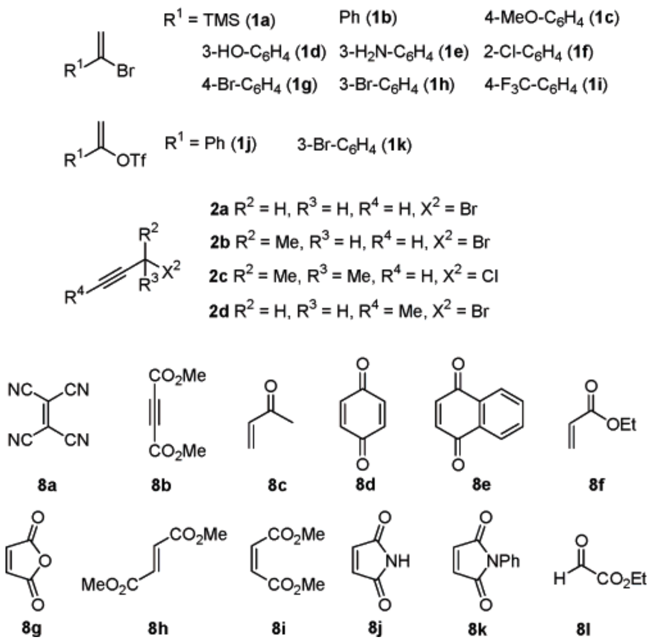


Scheme 9. Tandem Cross-Coupling−Homo [4 + 4] Cycloaddition−[4 + 2] Cycloaddition



Scheme 10. Assembly of 5 Components via Tandem Cross-Coupling−[4 + 4] Cycloaddition−[4 + 2] Cycloaddition





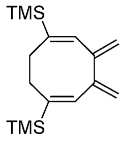
product to carbon monoxide atmosphere under balloon pressure resulted in 3,7-nonadienone **14a** in 45% yield, which was produced via a tandem Pd-catalyzed five-component reaction by cross-coupling and [4 + 4 + 1] annulation (Scheme 8).[11] Treatment of enol triflates with indium reagents in situ generated from 3-chloro-3-methyl-1-butyne and indium followed by carbon monoxide afforded **14b**,**c** in 66% and 51% yields, respectively, in one-pot.

Pd-Catalyzed Cross-Coupling Reactions: [4 + 4] and [4 + 2] Cycloadditions. Because **6b** was a 1,3-diene, we investigated the following tandem [4 + 2] cycloaddition of crude 1,3-diene **6b**. Thus, **6b** was treated with 1.5 equiv of tetracyanoethylene (70 °C, benzene, 18 h) to afford **9a** in 84% yield (Scheme 9). The structure of **9a** was determined by spectroscopy. In addition, the compound **9i** as a representative was characterized structurally using X-ray crystallography (Figure 1).[12]

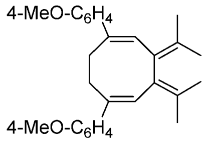
This transformation shows that five-components were assembled via intermolecular tandem cross-coupling−[4 + 4] and [4 + 2] cycloaddition (Scheme 10).

We next focused on the scope and functional group tolerance of the above MCR reaction. The results of several five-component MCRs are summarized in Table 2. With a variety of dienophiles (**8a**−**d** and **8f**−**l**), intermediate **6b** gave rise to bicyclo[6.4.0]dodecene derivatives in good yields (entries 1−11). Similarly, α-bromostyrene reacted with maleimide (**8j**) to produce **9g** in 79% yield (entry 7). For a vast number of α-bromovinyl arenes as organic electrophiles, the presence of various substituents such as 4-methoxy, 2-chloro, 3-bromo, and 4-trifluoromethyl on the aromatic ring did not affect the efficiency of the tandem reactions (entries 12 and 13 and 16−18). The reaction performed equally well with α-bromovinyl arenes having unprotected hydroxyl and amino groups (entries 14 and 15). Treatment of 4-trifluoromethyl-α-bromostyrene (**1i**) with 2 equiv of propargyl bromide and indium followed by 1 equiv of naphthoquinone (**8e**) afforded **9s** in 64% yield (entry 18). Reaction of **1d** with allenylindium followed by glyoxylic acid ethyl ester produced **9n** in 69% yield (entry 14). The enol triflate of 3-bromoacetophenone underwent the tandem reaction to afford **9r** in 66% yield under the present conditions (entry 17).

Unfortunately, the desired bicyclo[6.4.0]dodecene derivatives from (α-bromovinyl)trimethylsilane and propargyl bromide or 4-methoxy-α-bromostyrene and 3-chloro-3-methyl-1-butyne under the present conditions were not obtained, due to the instability of **6a** under the conditions of the [4 + 2] cycloaddition reaction and the development of severe nonbonded interactions in the case of **6h**.

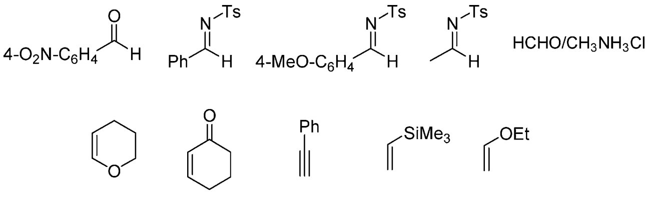


6a



6h

Although a variety of dienophiles could be used in MCRs, the following dienophiles did not partake in tandem [4 + 2] cycloadditions:



Mechanistic Insights. Although the mechanism to describe the formation of the six-, eight-, and nine-membered rings has not been established, a possible reaction pathway is described in Scheme 11. Oxidative addition of a Pd(0) catalyst to the vinyl bromide, subsequent transmetalation with organoindium re-

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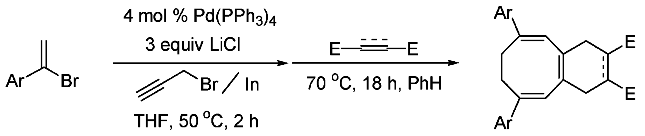
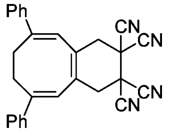
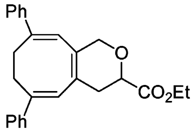
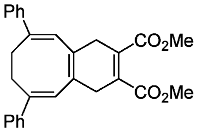
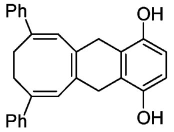
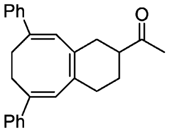
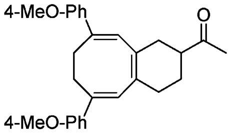
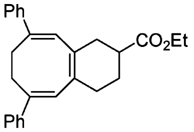
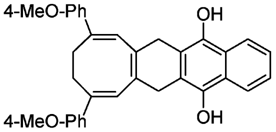
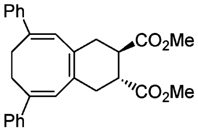
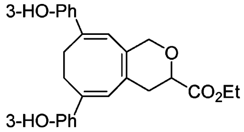
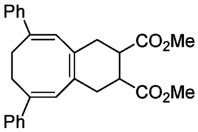
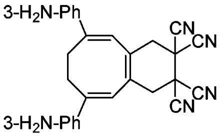
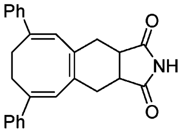
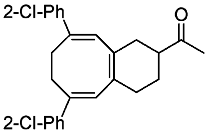
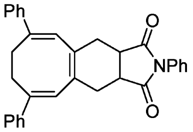
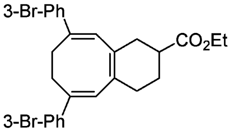
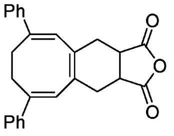
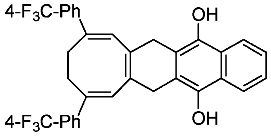
(11) Murakami, M.; Itami, K.; Ito, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 3418.

(12) *SHELXTL NT Crystal Structure Analysis Package*, version 5.14; Bruker AXS, Analytical X-ray System: Madison, WI, 1999.

Table 2. Tandem Cross-Coupling−[4 + 4] Cycloaddition and [4 + 2] Cycloaddition[a]



entry	reactants	product (yield / %)	entry	reactants	product (yield / %)
1	**1b/2a/8a**	 **9a**(84)[b]	10	**1b/2a/8l**	 **9j**(67)
2	**1b/2a/8b**	 **9b**(76)	11	**1b/2a/8d**	 **9k**(72)
3	**1b/2a/8c**	 **9c**(72)[c]	12	**1c/2a/8c**	 **9l**(79)[c]
4	**1b/2a/8f**	 **9d**(71)	13	**1c/2a/8e**	 **9m**(71)
5	**1b/2a/8h**	 **9e**(74)[d]	14	**1d/2a/8l**	 **9n**(69)
6	**1b/2a/8i**	 **9f**(66)[e]	15	**1e/2a/8a**	 **9p**(65)
7	**1b/2a/8j**	 **9g**(79)	16	**1f/2a/8c**	 **9q**(72)[c]
8	**1b/2a/8k**	 **9h**(79)	17	**1k/2a/8f**	 **9r**(66)[f]
9	**1b/2a/8g**	 **9i**(77)	18	**1i/2a/8e**	 **9s**(64)[g]

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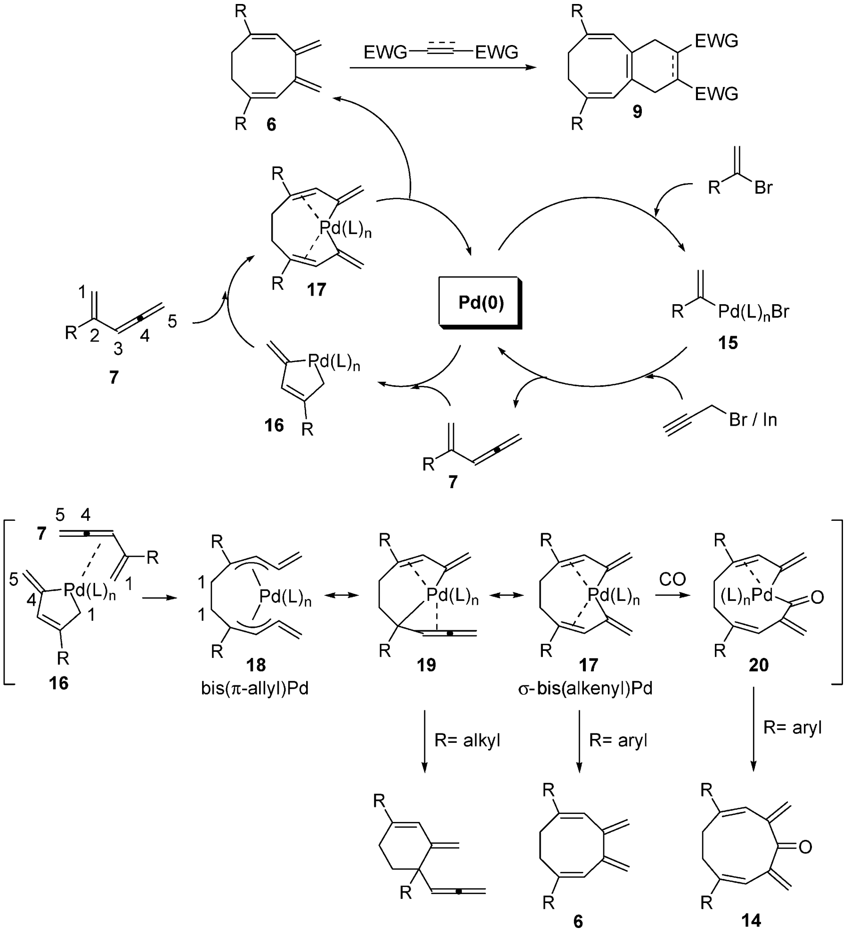
[a] Cross-coupling and [4 + 4] cycloaddition: in THF (2 mL), **1** (0.5 mmol), **2** (0.75 mmol), and indium (0.5 mmol) were reacted in the presence of 4 mol % Pd(PPh$_3$)$_4$ and LiCl (1.5 mmol) under N$_2$ at 50 °C for 2 h. [4 + 2] cycloaddition: crude **6** was reacted with **8** (0.38 mmol) in benzene (2 mL) at 70 °C for 18 h. [b] [4 + 2] cycloaddition proceeded in benzene at 80 °C for 2 h. [c] 2.5 equiv of methyl vinyl ketone was used. [d] Dimethyl fumarate was used. [e] Dimethyl maleate was used. Isomeric ratio of product: 1:1.2 = cis:trans. [f] Enol triflate of 3-bromoacetophenone was used as starting material.

agent[13] in situ generated from propargyl bromide and indium, and reductive elimination affords the vinylallene **7**. Insertion of Pd(0) to the vinylallene produces a five-membered palladacycle **16**, which subsequently reacts with another molecule of **7** at the internal double bond of the allene. The C−C bond formed from connection of the 1-position of the allenes gives

Scheme 11



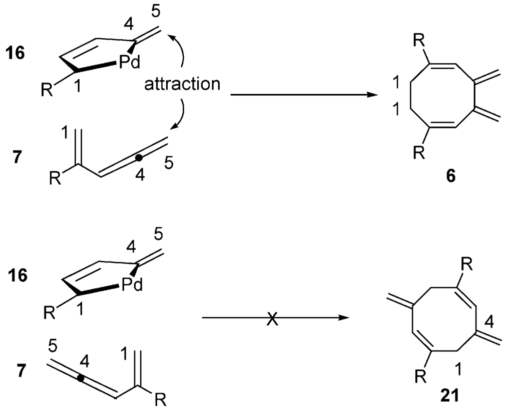
a bis(π-allyl)palladium intermediate **18**. If R is an aromatic group, the σ-bis(alkenyl)palladium intermediate **17**, which is one of resonance contributors of **18**, would be more significant as it is stabilized by the extended conjugation from the aromatic R substituent to the endocyclic C−C double bond. Subsequent reductive elimination of **17** would then give eight-membered carbocycle **6**. Finally, [4 + 2] cycloaddition of the 1,3-diene **6** with a variety of dienophiles produces the observed bicyclo-[6.4.0]dodecene derivatives **9**. Alternatively, insertion of carbon monoxide to σ-bis(alkenyl)palladium intermediate **17** followed by reductive elimination affords a nine-membered ring **14**.

In sharp contrast with substrates in which R is an aromatic ring, if R is an alkyl group, six-membered carbocycles were produced selectively. In this case, the σ-bis(alkenyl)palladium intermediate **17** is expected to be a minor contributor due to the lack of stabilization by conjugation, and reductive elimination of the other contributor 19 produces six-membered ring preferentially.

In case of Scheme 7, the rate of formation of **6b** is higher than that of **11** and **12**, which could be confirmed by both GC and TLC. Therefore, **1b** is consumed more rapidly than 2-bromo-1-octene under the optimum conditions. Although **12** might be more stabilized due to the increased congujation, **11** (28%) might be produced to a larger extent than **12** (12%) due to lack of α-bromostyrene (**1b**).

No eight-membered product **21** obtained from [4 + 4] cycloaddition reactions by head to tail connection was ever observed. Exclusive formation of **6** from Pd-catalyzed [4 + 4] cycloaddition of vinylallene by head to head connection might be due to an attractive secondary orbital interaction between the π system of C_4−C_5 of the five-membered palladacycle **16** and that of the double bond at C_4−C_5 of the vinylallene (Scheme 12).

Scheme 12



Conclusions

In conclusion, this study has led to the development of a novel tandem Pd-catalyzed cross-coupling/[4 + 4] cycloaddition reaction that allows the rapid synthesis of eight-membered carbocycles starting from α-bromovinyl arenes and propargyl bromides in one reaction vessel. It is noteworthy that four

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(13) Miao, W.; Chung, L. W.; Wu, Y.-D.; Chan, T, H. *J. Am. Chem. Soc.* **2004**, *126*, 13326.

components are assembled into one product via this procedure. In contrast to α-bromovinyl arenes, treatment of 2-halo-1-alkenes and propargyl bromides under the optimum conditions afforded tandem cross-coupling and homo [4 + 2] cycloaddition products. Subjecting mixtures of α-bromostyrene and 2-bromo-1-octene to propargyl bromides furnished tandem Pd-catalyzed cross-coupling reaction−hetero [4 + 2] cycloaddition products. Exposure of equimolar mixtures of a series of α-bromovinyl arenes to in situ generated allenylindium reagents resulted in tandem Pd-catalyzed cross-coupling and hetero [4 + 4] cycloaddition product together with tandem Pd-catalyzed cross-coupling/[4 + 4] cycloaddition products. After formation of vinylallene from the reaction of a vinyl triflate with an allenylindium reagent, exposure to carbon monoxide gave the 3,7-nonadienone product. Also, tandem Pd-catalyzed cross-coupling/[4 + 4] cycloaddition and [4 + 2] cycloaddition led to the rapid assembly of bicyclo[6.4.0]dodecane derivatives starting from α-bromovinyl arenes, propargyl bromides, and dienophiles. In addition, the present process is one of the comparatively few examples in which a Pd(0) complex is simultaneously involved in two catalytic cycles.[14] The present method provides highly efficient syntheses of eight-membered carbocycles, bicyclo[6.4.0]dodecenes, 3,7-nonadienones, and cyclohexene derivatives in good to excellent yields in one-pot operation and therefore complements existing synthetic methods.

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Supporting Information Available: Experimental procedures and characterization of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA054144V

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(14) (a) Ho, T.-L. *Tactics of Organic Synthesis*; Wiley-Interscience: New York, 1994; p 79. (b) Ho, T.-L. *Tandem Organic Reactions*; Wiley-Interscience: New York, 1992.