

Palladium-Catalyzed Benzannulation from Alkynes and Allylic Compounds

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Various alkynes reacted with allyl tosylates in the presence of palladium catalysts, giving polysubstituted benzenes with good to high regioselectivity. Pentasubstituted and trisubstituted benzenes were readily prepared by reaction of internal alkynes and terminal alkynes, respectively. The combination of allyl alcohols and *p*-toluenesulfonic anhydride could be utilized in place of isolated allyl tosylates. The cyclization of diynes with allyl tosylate afforded bicyclic compounds containing an aromatic ring.

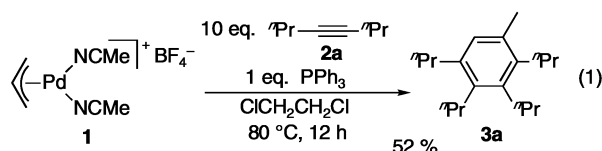
Introduction

Because allylmetal compounds possess a wide range of reactivity toward various organic molecules, they have been extensively utilized in organic syntheses. The reaction of allylmetals containing main group metals with alkynes normally gives 1,4-pentadienyl compounds (allylmetalation).¹ Allyl-transition metals show a unique reactivity toward alkynes; for example, five-, six-, and seven-membered rings are formed by incorporation of one or two molecules of alkyne.² In contrast to the stoichiometric reactions of the allyl/alkyne addition reactions described above, a fair number of reports have been published involving catalysis that includes reactions of allylmetals with alkynes as a key step.^{3–6} Several palladium- and nickel-catalyzed intramolecular reactions of allylic compounds and alkynes were reported by Oppolzer et al. In some cases, these reactions were followed by carbonylation to give cyclopentenones.⁴ Nickel-catalyzed

three-component coupling reactions of allyl chlorides, alkynes, and alkynylstannanes afford 1,4-pentadienyl compounds.⁵ The reactions of allyl chlorides and benzyne, which is a type of activated alkyne, are catalyzed by palladium complexes to give phenanthrenes.⁶ During an investigation of π -allylpalladium complexes, we recently found that a cationic π -allyl complex reacted with a simple alkyne to afford a substituted benzene. On the basis of this finding, we have developed a novel palladium-catalyzed benzannulation from allylic compounds and alkynes.⁷ Herein we report the details of the inter- and intramolecular versions of this benzannulation.

Results and Discussion

Stoichiometric Reaction. In the course of our investigation into the reactivity of π -allylpalladium complexes, we found that treatment of the cationic complex [$(\eta^3\text{-C}_3\text{H}_5)\text{Pd}(\text{CH}_3\text{CN})_2](\text{BF}_4^-)$ (**1**) with an excess of 4-octyne (**2a**) at 80 °C in the presence of 1 equiv of triphenylphosphine per palladium resulted in the formation of 1-methyl-2,3,4,5-tetrapropylbenzene (**3a**) in 52% yield (eq 1). In



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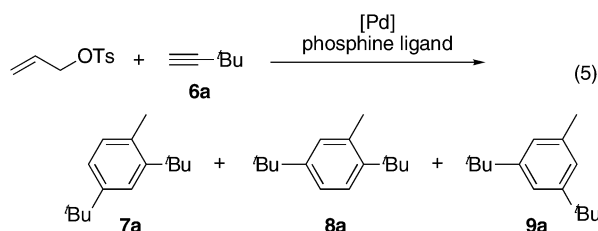
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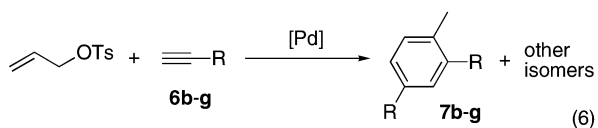
TABLE 2. Benzannulation Using Allyl Tosylate and 3,3-Dimethyl-1-butyne (6a)^a

entry	ligand	cone angle (deg)	total yield ^b (%)	ratio ^b		
				7a	8a	9a
1			12	90	5	5
2	P(<i>o</i> -Tol) ₃	194	59	34	32	34
3	P(C ₆ F ₅) ₃	184	17	71	29	0
4	PPh ₃	145	41	56	34	10
5	P(<i>o</i> -Tol) ₃	141	32	81	18	1
6	P(OPh) ₃	128	47	>99	0	0
7	P(OEt) ₃	109	30	93	7	0

^a Reaction conditions: allyl tosylate (0.5 mmol), **6a** (2.0 mmol), [Pd₂(dba)₃]·CHCl₃ (0.025 mmol), a phosphine ligand (0.05 mmol), 1,2-dichloroethane (3 mL) at 80 °C for 12 h. ^b Yields and ratios are determined by ¹H NMR with diphenylmethane as an internal standard.

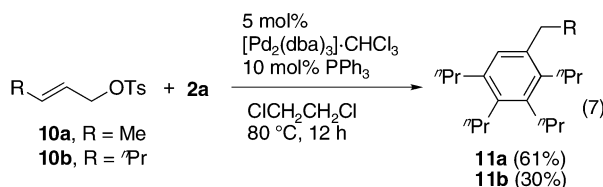


yields of the desired products, no selectivity was observed (entry 2). All triarylphosphines exhibited unsatisfactory regioselectivity (entries 2–4). In contrast, higher regioselectivity was obtained in the reactions using phosphite ligands (entries 5–7), finally yielding **7a** as the sole product by using triphenyl phosphite (entry 6). The reactions of other terminal alkynes were also investigated (eq 6), and the results summarized in Table 3. Phenyl-



acetylene (**6b**) reacted with allyl tosylate to afford **7b** with high regioselectivity (entry 1). Selectivity was modest in the reactions of alkynes **6c–g** bearing less bulky substituents; nevertheless, the yields were higher than those produced by the reactions of **6a** and **6b**, and **7c–g** were obtained as the major products (entries 2–6). A nitrile triple bond is compatible with the described benzannulation (entry 6).¹⁰

The reactions of several substituted allyl tosylates also were investigated. Crotyl and (*E*)-2-hexenyl tosylates (**10a** and **10b**) participated in the reaction to produce the corresponding pentasubstituted benzenes **11a** and **11b** in 61% and 30% yield, respectively, upon reaction with **2a** (eq 7). No product was obtained in the reaction of



methallyl tosylate and **2a**. Other allyl tosylates, especially those bearing substituents at their allylic position,

TABLE 3. Benzannulation Using Allyl Tosylate and Various Terminal Alkynes^a

entry	alkyne	total yield ^b (%)	major product	ratio ^c	
				major	others
1	6b , R = Ph	31	7b	>99	<1
2	6c , R = Bn	42	7c	70	30
3	6d , R = <i>i</i> -Bu	51	7d	80	20
4	6e , R = <i>n</i> -Bu	81 ^d	7e	73	27
5	6f , R = <i>n</i> -Hex	66 ^d	7f	73	27
6	6g , R = (CH ₂) ₃ CN	47 ^d	7g	73	27

^a Reaction conditions: allyl tosylate (0.5 mmol), **6** (2.0 mmol), [Pd₂(dba)₃]·CHCl₃ (0.025 mmol), P(OPh)₃ (0.05 mmol), 1,2-dichloroethane (3 mL) at 80 °C for 12 h. ^b Determined by ¹H NMR with diphenylmethane as an internal standard. ^c Determined by GC and GC-MS analysis. ^d Isolated yields of a mixture of regioisomers.

TABLE 4. Benzannulation Using Allyl Alcohol and 4-Octyne (2a)^a

entry	mmol of Ts ₂ O	base (mmol)	yield of 3a ^b (%)
1			0
2	0.5		47
3	1.0		55
4	2.0		34
5	0.5	pyridine (0.5)	32
6	0.5	<i>i</i> -Pr ₂ NEt (0.5)	69
7	0.5	Et ₃ N (0.5)	76
8	0.5	Et ₃ N (1.0)	tr

^a Reaction conditions: allyl alcohol (0.5 mmol), **2a** (2.0 mmol), [Pd₂(dba)₃]·CHCl₃ (0.025 mmol), PPh₃ (0.05 mmol), 1,2-dichloroethane (3 mL) at 80 °C for 12 h. ^b Determined by GC analysis.

TABLE 5. Benzannulation Using Various Allylic Alcohols and 4-Octyne (2a)^a

entry	alcohol	R ¹	R ²	product	yield ^b (%)
1	12a	Me	H	11a	42
2	12b	<i>n</i> -Pr	H	11b	44
3	12c	Ph	H	11c	30 ^c
4	12d	Me	Me	11d	27
5	13a	Me	H	11a	53
6	13b	<i>n</i> -Pr	H	11b	49
7	13c	Ph	H	11c	38 ^c
8	13d	Me	Me	11d	35

^a Reaction conditions: **12** or **13** (0.5 mmol), **2a** (2.0 mmol), Ts₂O (0.5 mmol), [Pd₂(dba)₃]·CHCl₃ (0.025 mmol), PPh₃ (0.05 mmol), 1,2-dichloroethane (3 mL) at 80 °C for 12 h. ^b Isolated yields. ^c Determined by ¹H NMR with diphenylmethane as an internal standard.

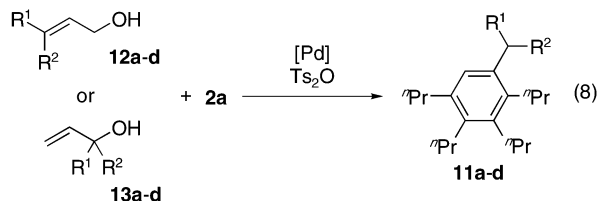
cannot be used in the benzannulation because they are not thermally stable enough for isolation at room temperature.

Benzannulation Using Allylic Alcohols in the Presence of Ts₂O. Since substituted allyl tosylates other than **10a** and **10b** could not be prepared, in situ generation of the tosylates from allylic alcohols and *p*-toluenesulfonic anhydride (Ts₂O) was investigated. First, the reaction of allyl alcohol with **2a** was optimized; the results summarized in Table 4. The reaction of allyl alcohol and **2a** in the presence of Ts₂O yielded **3a** in moderate yield (entries 2 and 3), whereas no product was obtained in the reaction without Ts₂O (entry 1). An excess amount of Ts₂O was not effective (entry 4). To neutralize the *p*-toluenesulfonic acid formed by reaction of allyl

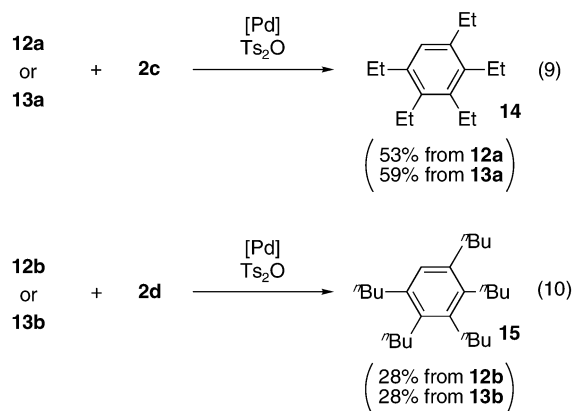
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alcohol and Ts_2O , various organic and inorganic bases were added, and trialkylamines were found to improve the yield of **3a** (entries 6–8). Using 1 equiv of triethylamine per Ts_2O , **3a** was obtained in 76% yield (entry 7). Unexpectedly, 2 equiv of triethylamine hindered formation of **3a** (entry 8).

This method was applied to the reactions of substituted allyl alcohols **12** and **13** (eq 8, Table 5); however, all



reactions were conducted without the addition of triethylamine, because the addition decreased the yield of **11**. Crotyl alcohol (**12a**) and (*E*)-2-hexenyl alcohol (**12b**), as well as the corresponding tosylates **10a** and **10b**, reacted with **2a** in the presence of Ts_2O to give **11a** and **11b** as sole products in 42% and 44% yield, respectively (entries 1 and 2). The reaction of cinnamyl alcohol (**12c**) also selectively afforded the pentasubstituted benzene **11c** in 30% yield (entry 3). Alcohol **12d** bearing two methyl groups on the terminal carbon was utilized for the benzannulation to yield **11d** (entry 4). The reactions of secondary and tertiary allylic alcohols **13a–d** resulted in the formation of the same benzene derivatives **11a–d** with the corresponding primary alcohols **12a–d** bearing the same substituents as **13a–d** on the terminal carbon, respectively (entries 5–8). None of the reactions yielded a hexasubstituted benzene isomer, indicating that the benzannulation reactions from **12** and **13** proceed via a common intermediate. A pentasubstituted benzene bearing the same five substituents can be obtained by selection of the appropriate allylic alcohol and an alkyne. For example, pentaethylbenzene (**14**) and pentabutylbenzene (**15**) are easily prepared by reaction of **12a** (or **13a**) with **2c**, and **12b** (or **13b**) with **2d**, respectively (eqs 9 and 10).



Benzannulation Using Allyl tosylate And diynes.

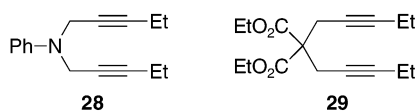
Bicyclic compounds were formed by reaction of allyl tosylate with diynes. Table 6 summarizes the results of the syntheses of the bicyclic systems. Reaction of 1,6-diyne **16a–e** selectively yielded indan derivatives **17a–e** (entries 1–5). The reaction of diynes **16b** and **16c**, which

TABLE 6. Benzannulation Using Allyl Tosylate and Diynes^a

entry	diyne	product	yield ^b /%
1	16a , R = Me	17a	37
2	16b , R = Et	17b	63
3	16c , R = Pr	17c	67
4	16d , R = Ph	17d	29
5	16e , R = CO ₂ Me	17e	40
6	18a , R = H	19a	36
7	18b , R = Me	19b	43
8	18c , R = Et	19c	50
9	18d , R = Ph	19d	21
10	20	21	24
11	22	23	57
12	24	25	47
11	26	27	16

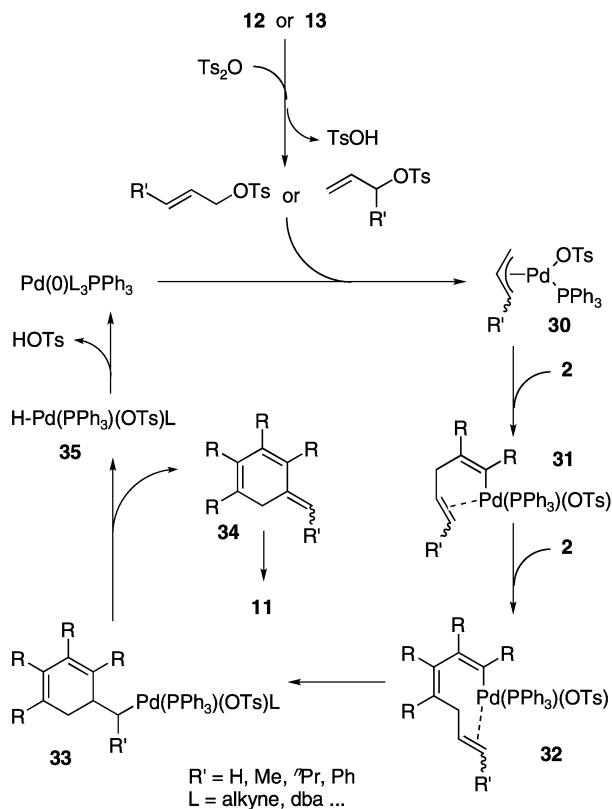
^a Reaction conditions: allyl tosylate (0.5 mmol), diyne (1 mmol), $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (0.025 mmol), $\text{P}(\text{OPh})_3$ (0.05 mmol), 1,2-dichloroethane (3 mL) at 80 °C, 12 h. ^b Isolated yields.

contained less hindered alkyl substituents on the terminal carbons, afforded products **17b** and **17c**, respectively, in satisfactory yields (entries 2 and 3). Bulky substituents on **16d** and **16e** decreased the yields of **17d** and **17e** (entries 4 and 5). The cyclization of 1,7-diyne **18a–d** with allyl tosylate gave the tetrahydronaphthalene derivatives **19a–d**. Bicyclic compound **21**, which contains a seven-membered ring, also was obtained from reaction of 1,8-diyne **20**, although the yield was low. The benzannulation from unsymmetrical diyne **22** proceeded regioselectively, giving only one indan derivative **23** in 57% yield. Diyne **24** having an ester group also selectively reacted with allyl tosylate to afford **25**. The regioselectivity is due to the difference between the reactivity of the two alkyne groups in **22** and **24**. Heteroatom-tethered diyne **26** slowly decomposed under the present reaction conditions, giving phthalan derivative **27** in low yield. No product was formed from reaction of diyne **28**, which possesses a nitrogen tether. Unexpectedly, the malonate derivative **29** did not react with allyl tosylate and was recovered in almost quantitative yield, whereas the ester groups in **16e** and **24** did not hinder cyclization.

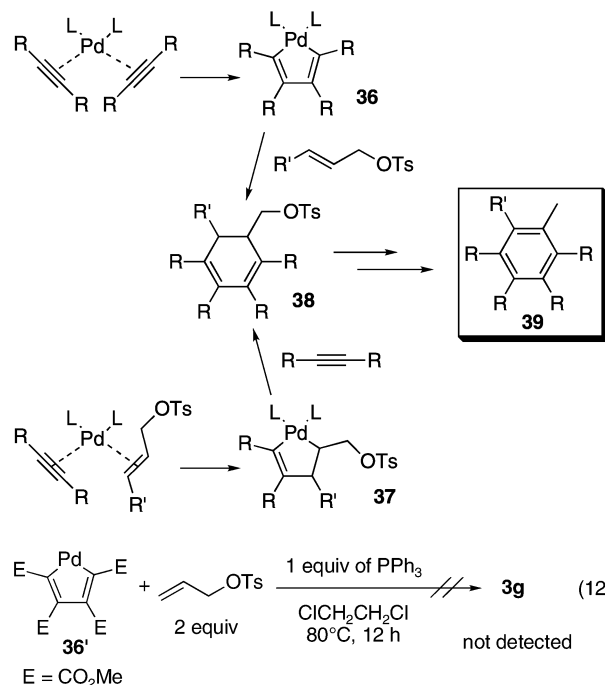


Mechanism. A plausible mechanism for reaction of **12** or **13** with **2** (Scheme 1) can apply to the benzannulation of other allylic compounds and alkynes. Oxidative addition of a substituted allyl tosylate, generated from **12** or **13** and Ts_2O , yields the π -allylpalladium complex **30**. The common intermediate **30** accounts for reactions of **12** and **13** giving the same products in similar yields. Displacement of the tosylate ligand on **30** with an alkyne and insertion of the alkyne to the Pd-allyl bond of **30** would afford **31**. Ligand-displacement would be less active in the case of acetate or bromide coordinated to palladium instead of tosylate.¹¹ Negishi reported that the palladium-catalyzed reactions of 1-halo-1,4-pentadienes with alkynes afforded polysubstituted benzenes, which might proceed via an intermediate similar to **31**.¹² The consecutive insertion of the second alkyne and intramolecular olefin would generate **33**. The β -hydrogen elimination from **33** would afford the palladium hydride complex **35** and the cyclized product **34**, which immediately isomerizes to the benzene derivative **11**. The elimination of HOTs from **35** would regenerate Pd(0).¹³ Another possible mechanism is [2 + 2 + 2] cycloaddition via the palladacycles **36** or **37** (Scheme 2).^{14,15} If the present benzannulation proceeds through **36** or **37**, hexasubstituted benzene **39** should be obtained in the reaction involving **10** (or **12**). The actual reaction, however, did not afford any **39**. Moreover, a control experiment showed that the treatment of **36'** with allyl tosylate in the presence of PPh_3 did not give any cycloadduct (eq 12). These data and the above-mentioned

SCHEME 1



SCHEME 2



NMR experiment indicate that π -allylpalladium **30** is more reasonable as the reaction intermediate than is **36** or **37**, although other mechanisms¹⁶ cannot be ruled out completely.

A mechanism involving reaction of π -allylnickels with alkynes has been proposed for the Chiusoli reaction.^{3b-c,17} After studying the reaction widely and systematically,¹⁸

(11) Sulfonates such as tosylate and triflate exhibit weaker coordination ability than carboxylates and are often used as counteranions for cationic complexes. Although the tosylate-coordinated complex **30** was observed in CDCl_3 (see ref 7), the tosylate is predicted to be partially replaced with alkynes under the reaction conditions. (a) Carina, R. F.; Williams, A. F. *Inorg. Chem.* **2001**, *40*, 1826. (b) Milani, B.; Anzilutti, A.; Vicentini, L.; o Santi, A. S.; Zangrando, E.; Geremia, S.; Mestroni, G. *Organometallics* **1997**, *16*, 5064. (c) Gusev, O. V.; Kalsin, A. M.; Peterleitner, M. G.; Petrovskii, P. V.; Lyssenko, K. A.; Akhmedov, N.; Bianchini, C.; Meli, A.; Oberhauser, W. *Organometallics* **2002**, *21*, 3637.

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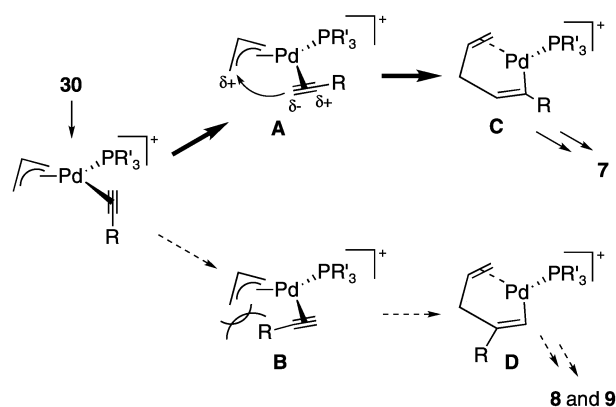
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SCHEME 3



Moretó et al. reported that the regioselectivity depends on alkyne triple-bond polarization if steric effects are not very demanding.¹⁹ The regioselectivity of the present palladium-catalyzed benzannulation using terminal alkynes can be similarly explained (Scheme 3). The electrophilic allyl moiety of the π -allylpalladium intermediate **A** adds to the more electron-rich carbon atom of the alkyne, leading to the preferred formation of **7** via intermediate **C**. Because alkynes bearing bulky substituents exhibit higher regioselectivity than other alkynes, steric effects must also be considered. The bulky R groups can interrupt approach of the alkyne to the allylic moiety in intermediate **B**. Thus, formation of the regioisomers **8** and **9** is unfavorable as a result of electronic and steric effects.

Both steric and electronic factors of phosphine ligands affect regioselectivity. The results summarized in Table 2 show that triaryl and trialkyl phosphites, having smaller cone angles,²⁰ exhibit regioselectivities higher than those of triarylphosphines. The reversals of P(OPh)₃ and P(OEt)₃, or PPh₃ and P(C₆F₅)₃, are due to their electronic factors. In conclusion, the less hindered phosphorus ligand having a lower basicity showed higher regioselectivity in the reactions of terminal alkynes. The low basicity might increase the electrophilicity of the π -allyl terminal carbon at the trans position in **A**, and the small cone angles might decrease steric repulsion between PR'₃ and R in **A**.

High regioselectivities also were observed in the reactions involving unsymmetrical diynes **22** and **24**. The cyclization of **22** begins with reaction of the π -allylpalladium intermediate **30** with the less hindered ethyl-substituted alkyne rather than the phenyl-substituted one, leading to formation of **23**. In the case of **24**, the polarized alkyne is more reactive than the normal alkyne to afford **25** selectively.

Conclusion

In summary, we have developed a palladium-catalyzed regioselective synthesis of polysubstituted benzenes from one molecule of allyl tosylate and two molecules of alkyne. Pentasubstituted and trisubstituted benzenes were easily prepared by reaction of internal alkynes and terminal alkynes, respectively. Triphenyl phosphite, having a small cone angle and low basicity, showed the highest regioselectivity with terminal alkynes. Although a substituted allyl tosylate cannot be prepared because of its low stability, the combination of the corresponding allylic

alcohol and *p*-toluenesulfonic anhydride makes the reaction possible. The cyclization of diynes with allyl tosylate affords bicyclic compounds containing an aromatic ring. All of the reaction results described in this study can be rationalized by a mechanism involving a π -allylpalladium intermediate.

Experimental Section

Materials. Commercially available chemicals were used as received except for the solvents, which were distilled by the usual method. Palladium complexes **1**²¹ and **36**^{14a} were synthesized according to literature procedures. Tosylates **10a,b**²² were prepared by reaction of the corresponding allylic alcohols with excess tosyl chloride and potassium hydroxide in THF and were used without purification. Dienes **16a–c**, **18a–c**, and **20** were prepared by alkylation of commercially available terminal alkynes according to the published method.²³ Dienes **16d**,²⁴ **16e**,²⁵ **18d**,²⁴ and **26**²⁶ were prepared according to literature procedures. Dienes **22** and **24** were obtained by Sonogashira coupling²⁴ and carbonylation,²⁵ respectively, of 1,6-nonadiyne.²⁷

General Procedure for Benzannulation from Alkynes and Allyl Tosylate. To a solution of Pd₂(dba)₃·CHCl₃ (26 mg, 0.025 mmol) and a phosphorus ligand (0.05 mmol) in 1,2-dichloroethane (3 mL) was added allyl tosylate (0.5 mmol) under nitrogen atmosphere in a pressure vial. After 0.5 h of stirring at room temperature, an alkyne (2.0 mmol) or diyne (1.0 mmol) was added to the solution. After heating at 80 °C for 12 h, the mixture was filtered through a short silica gel column using ether as an eluent. Solvents and excess alkyne were removed under reduced pressure, and the benzene derivative was purified by silica gel column chromatography.

General Procedure for Benzannulation from Alkynes and Allylic Alcohols in the Presence of Ts₂O. To a solution of Pd₂(dba)₃·CHCl₃ (26 mg, 0.025 mmol), PPh₃ (13 mg, 0.05 mmol), and Ts₂O (163 mg, 0.5 mmol) in 1,2-dichloroethane (3 mL) was added an allylic alcohol (0.5 mmol) under nitrogen atmosphere in a pressure vial. After 1 h of stirring at room temperature, an alkyne (2.0 mmol) was added to the solution. After heating at 80 °C for 12 h, the mixture was filtered through a short silica gel column using ether as an eluent. Solvents and excess alkyne were removed under reduced pressure, and the benzene derivative was purified by silica gel column chromatography.

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Supporting Information Available: Characterization data for benzene derivatives **3**, **5**, **7**, **11**, **14**, **15**, **17**, **19**, **21**, **23**, **25**, and **27**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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