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Benzannulation from Alkynes and Allyl Tosylates via a π-Allylpalladium Intermediate

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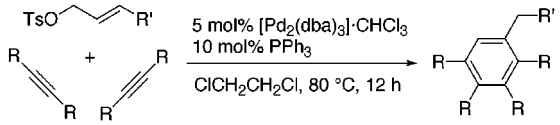
ABSTRACT



Allyl tosylate is a good allyl source for a novel palladium-catalyzed benzannulation that affords polysubstituted benzenes from 1 mol of an allyl compound and 2 mol of internal alkynes. Using triphenyl phosphite as a ligand, the reaction with terminal alkynes gave trisubstituted benzenes regioselectively.

Remarkable progress has been made in the application of π-allylpalladium chemistry to catalytic organic synthesis. A π-allylpalladium intermediate reacts with varied reactants including soft and hard nucleophiles, aldehydes, carbon monoxide, and organometallics to give various allylated organic compounds normally.[1] However, insertion of an alkyne, which is one of the simplest organic molecules, to a π-allylpalladium species has not been reported except for a dimerization−allylation reaction of terminal alkynes[2] and several intramolecular reactions followed by carbonylation.[3] On the other hand, typical allyl metals are known to undergo allylmetalation to alkynes to give 1,4-pentadienyl compounds.[4,5] Furthermore, allyl transition metal complexes show a wider range of reactivities toward alkynes.[6] For example, five-membered[6b,c] or six- and seven-membered[6d−f] ring systems are obtained by incorporation of 1 or 2 mol of alkynes, respectively. However, a stoichiometric amount of allylmetals is needed in these reactions, except for the reaction of π-allylnickel, which is an intermediate on the allylation of alkynes catalyzed by Ni(0).[7,8] Herein we wish to report a palladium-catalyzed synthesis of pentasubstituted benzenes from 1 mol of allyl tosylates and 2 mol of alkynes

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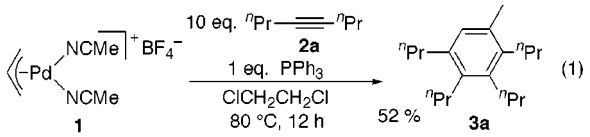
that proceeds via insertion of alkyne to a π-allylpalladium intermediate.

During the investigation into the reactivity of cationic π-allylpalladium complexes toward organic compounds, we found that the acetonitrile-coordinated complex **1** reacted with excess 4-octyne **2a** at 80 °C in the presence of 1 equiv of triphenylphosphine per palladium to afford 1-methyl-2,3,4,5-tetrapropylbenzene **3a** in 52% yield (eq 1).[9] In contrast, without addition of triphenylphosphine, only a trace amount of **3a** was obtained, and the reaction using 2 equiv of triphenylphosphine or 1 equiv of bidentate phosphine ligand like dppe did not yield **3a** at all. (π-Allyl)chloro(triphenylphosphine)palladium **4** also gave no products under the same conditions. These results imply that the present benzannulation need the presence of 1 equiv of triphenylphosphine and at least one weakly coodinating ligand on palladium.[10] More than two phosphorus atoms per palladium or a firmly coodinating choride ligand would disturb the benzannulation. On the basis of these findings in the stoichiometric reactions, the catalytic benzannulation reaction was then explored.



$[Pd_2(dba)_3]\cdot CHCl_3$ combined with 1 equiv of triphenylphosphine to palladium was used as a catalyst since oxidative addition of an allyl ester or halide to Pd(0) can generate a π-allylpalladium complex in situ. At first, the reaction of **2a** with a typical allylating agent, allyl bromide or allyl acetate, was examined (eq 2). However, **3a** was not afforded at all. This result may be ascribed to the formation of an inactive π-allyl complex bearing bromide or acetate ligand, which coordinates to the palladium center firmly. Therefore, we intended to incorporate a weakly ligating anion. The reaction with allyl trifluoroacetate gave **3a**, although the yield was low. Allyl mesylate was more reactive, giving **3a** in 80% yield. Finally, we discovered that allyl tosylate was a good allyl source for this benzannulation to afford **3a** in 91% yield.

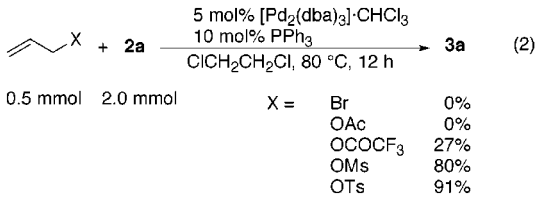
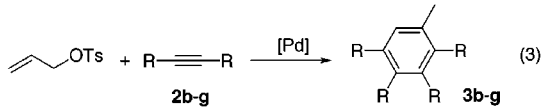


Table 1 summarizes the results of the benzannulation using allyl tosylate and various internal symmetric alkynes. In all cases, the cyclotrimerization of excess alkynes to hexasubstituted benzenes was sufficiently suppressed (yield <6%), although some polymerization of the alkynes took place. Dialkylethynes **2b**−**d** provided the corresponding pentasubstituted benzenes **3b**−**d** in good to high yields (entries 1−3).

Table 1. Palladium-Catalyzed Benzannulation[a]



entry	alkyne	R	product	yield[b]/%
1	**2b**	Me	**3b**	41 (63)
2	**2c**	Et	**3c**	93
3	**2d**	*n*-Bu	**3d**	82
4	**2e**	Ph	**3e**	(28)
5	**2f**	CH_2OMe	**3f**	32
6	**2g**	CO_2Me	**3g**	41

[a] Reaction conditions: allyl tosylate (0.5 mmol), **2** (2.0 mmol), $Pd_2(dba)\cdot CHCl_3$ (0.025 mmol), PPh_3 (0.05 mmol), 1,2-dichloroethane (3 mL) at 80 °C for 12 h. [b] Isolated yields (NMR yield in parentheses).

Diphenylacetylene **2e** also afforded the sterically crowded product **3e** in 28% yield (entry 4). In this reaction, allyl tosylate was completely consumed, while unreacted **2e** was recovered. Ether group-containing alkyne **2f** reacted with allyl tosylate to give **3f** in low yield (entry 5). Alkyne **2g** bearing electron-withdrawing groups exhibited decreased reactivity to give the benzene derivative **3g** in 41% yield (entry 6).[11]

The reactions of several allyl tosylates were also investigated. Crotyl and (*E*)-2-hexenyl tosylates (**5a** and **5b**) took part in the reaction to produce the corresponding pentasubstituted benzenes **6a** and **6b** in 61% and 30% yield, respectively, upon reaction with **2a** (eq 4). Besides internal alkynes, terminal alkynes **2h** and **2i** reacted as well (eq 5). Although when $[Pd_2(dba)_3]\cdot CHCl_3-PPh_3$ was used as catalyst the regioselectivity was not amenable to affording a mixture of isomers of di-*tert*-butyl(or diphenyl)methylbenzene, $[Pd_2(dba)_3]\cdot CHCl_3-P(OPh)_3$ showed high regioselec-

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(9) Without addition of PPh_3, only a trace amount of **3a** was obtained.

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(11) A conjugate addition product of *p*-toluenesulfonic acid to **2g** was obtained as a byproduct, whereas unreacted **2g** was also recovered.

(12) See the Supporting Information.

(13) It is not clear at the present time how the insertion of alkynes to the palladium−allyl bond occur. However, it is known that insertion reaction of an intramolecular alkene to a π-allylpalladium proceeds via a cationic π-allyl complex coordinated with the alkene: Gómez-Bengoa, E.; Cuerva, J. M.; Echavarren, A. M.; Matrorell, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 767. See also; Meching, S.; Keim, W. *Organometallics* **1996**, *15*, 2650.

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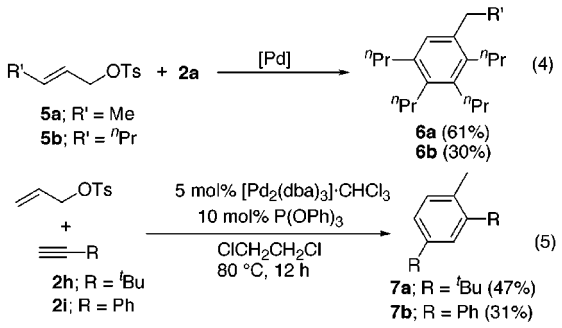
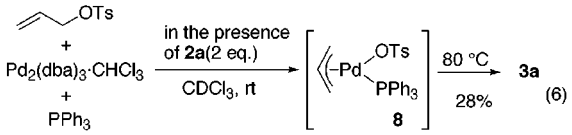
tivity to give only one isomer, 1,3-di-*tert*-butyl-5-methylbenzene (**7a**) or 1,3-diphenyl-5-methylbenzene (**7b**), in 47% and 31% yield, respectively.

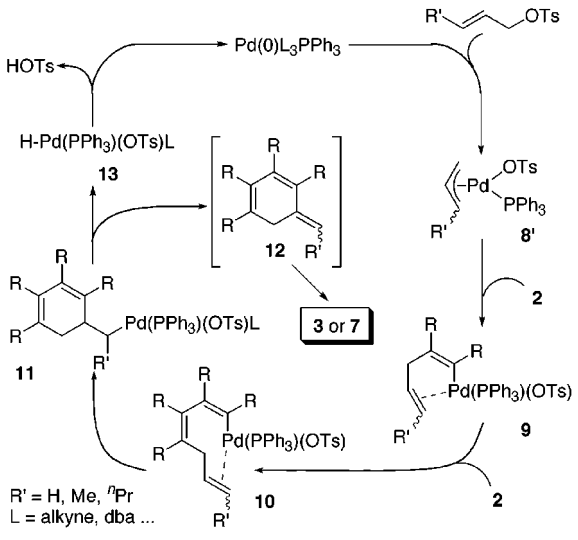


To ascertain whether a π-allylpalladium complex is an intermediate in the catalytic benzannulation as well as the stoichiometric one, an NMR experiment was carried out (eq 6). Oxidative addition of allyl tosylate to Pd(0) proceeded smoothly in $CDCl_3$ at room temperature even in the presence of **2a**. The π-allyl complex **8** was observed in the ^{1}H NMR spectrum of the reaction mixture, without any indication of other complex formation.[12] Further, this reaction mixture gave **3a** on heating at 80 °C.



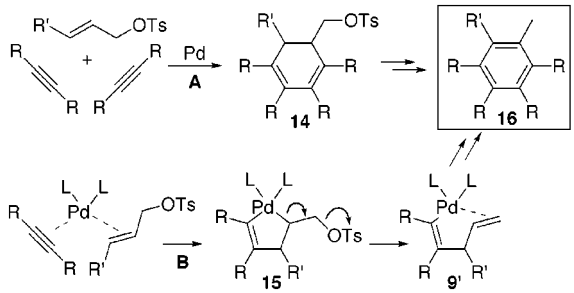
The following is a plausible mechanism of the reaction (Scheme 1). Oxidative addition of allyl tosylate to Pd(0)

Scheme 1



generates the π-allylpalladium complex **8′**. Insertion of an alkyne to the Pd−allyl bond of **8′** would afford **9**.[13] Negishi briefly reported that the palladium-catalyzed reactions of 1-halo-1,4-pentadienes with alkynes afforded polysubstituted benzenes, which might proceed via a similar intermediate to **9**.[14] The consecutive insertion of the second alkyne and the intramolecular carbon−carbon double bond would generate **11**. The β-hydrogen elimination from **11** would give the palladium hydride complex **13** and the cyclized product **12**, which isomerizes immediately to the benzene derivative **3** or **7**. The elimination of HOTs from **13** would regenerate Pd(0).[15] Other possibilities are a [2 + 2 + 2] cycloaddition[16] via **14** (Scheme 2, route A) and a similar mechanism to

Scheme 2



Scheme 1 through **9′**, which could be generated from **15**[17] by β-elimination of tosylate (route B). If the present benzannulation proceeds through **14** or **9′**, benzene derivatives **16** should be produced. The reaction of **5a** or **5b** with **2a**, however, does not produce **16** only the isomers **6a** or **6b**, respectively. These and the above-mentioned NMR experiment indicate that the π-allylpalladium **8′** is more reasonable as the reaction intermediate than **14** and **15**, although other mechanisms cannot be ruled out completely.

The transition metal mediated synthesis of aromatic rings is mainly accomplished by cyclotrimerization of alkynes. However, when two or three different alkynes were used to prepare a penta- and a trisubstituted benzene, a mixture of several benzene derivatives was obtained in most cases.[18,19] The reaction reported here further develops the chemistry of π-allylpalladium and is a convenient route to polysubstituted benzenes.

Supporting Information Available: Experimental procedures and analytical and spectroscopic data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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