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Highly Efficient Route to *o*-Allylbiaryls via Palladium-Catalyzed Three-Component Coupling of Benzynes, Allylic Halides, and Aryl Organometallic Reagents

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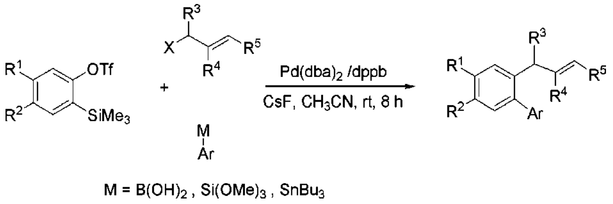
ABSTRACT



***o*-Allylbiaryl derivatives have been prepared in good to excellent yields by the palladium-catalyzed three-component reaction of allyl halides, benzynes, and aryl organometallic reagents.**

Palladium-catalyzed three-component coupling reactions based on an oxidative addition, insertion of the resulting organopalladium species into multiple bonds (carbopalladation), and followed by transmetalation have fundamentally revolutionized synthetic concepts for the formation of carbon−carbon and carbon−heteroatom bonds.[1] Among these reactions, those that involve carbopalladation of alkynes,[2] alkenes,[3] and allenes[4] have proven to be extraordinarily versatile. A similar reaction sequence based on carbopalladation of benzynes would be highly useful and interesting, considering that benzynes are generally very reactive species and that the reaction would lead to the formation of two different C−C bonds at the ortho positions of a benzene ring.

The development of new methods for the generation of benzynes under mild conditions[5] has led several groups to explore the possibility of using arynes as partners for metal-catalyzed reactions. In this context, palladium-catalyzed [2 + 2 + 2] cyclotrimerization of benzynes[6] and cocyclotrimerization of benzynes with alkynes and allylic halides have been reported.[7] Recently, also, we showed that benzynes readily underwent [2 + 2 + 2] cocyclotrimerization with

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bicyclic alkenes, allenes, and diynes.[8] Further, we found that a benzyne carbopalladated by a π-allylpalladium intermediate can be terminated efficiently with alkynyltin reagents to yield 1-allyl-2-alkynylbenzene derivatives.[9] Given the importance of substituted biaryl compounds in drugs,[10] natural products,[11] and material science,[12] we envisaged that termination of a carbopalladation sequence involving benzyne with an aryl nucleophile would lead to *o*-substituted biaryl derivatives. Herein, we report a highly efficient route for the synthesis of *o*-allyl-substituted biaryl derivatives from allyl chlorides, benzynes, and areneboronic acids catalyzed by palladium complexes under mild conditions. It is noteworthy that *o*-allyl biphenyl derivatives were found in clusiparalicolines, isolated from the roots of *Clusia paralicola*, and used as DNA strand-scission active compounds.[13]

Treatment of 2-(trimethylsilyl)phenyl triflate (**1a**) with allyl chloride (**2a**) and phenylboronic acid (**3a**), in the presence of Pd(dba)$_2$/dppb (5 mol %) and CsF in acetonitrile at ambient temperature for 8 h, afforded 2-allylbiphenyl (**4a**) in 88% isolated yield (Table 1). Product **4a** was thoroughly characterized by its ^{1}H NMR, ^{13}C NMR, and mass data. Control experiments revealed that in the absence of either palladium catalyst or CsF, no **4a** was obtained.

The phosphine ligand was crucial for the success of the foregoing catalytic reaction. Phosphine-free palladium complexes Pd(dba)$_2$, Pd(OAc)$_2$, and PdCl$_2$(CH$_3$CN)$_2$ in acetonitrile were totally ineffective for mediating the reaction. Monodentate phosphine complexes such as Pd(PPh$_3$)$_4$, PdCl$_2$(PPh$_3$)$_2$, and PdCl$_2$(PCy$_3$)$_2$ were active but gave **4a** in low yields (31−38%). It appears that a proper bidendate phosphine ligand is required for the reaction to proceed with high yield. Pd(dba)$_2$ with an equivalent of dppb afforded **4a** in excellent yield. Other bidendate phosphine ligands such as dppm, dppe, dppp, dpppentane, dpphexane, and dppf are less effective, giving **4a** in only 22−55% yields. On the basis of these optimization studies, we chose Pd(dba)$_2$/dppb as the catalyst for this palladium-catalyzed three-component reaction.

The presence of 4 equiv of CsF relative to benzyne precursor **1a** was necessary to ensure a high product yield. When only 2 equiv of CsF was employed, the reaction gave product **4a** in 46% yield with 41% benzyne precursor **1a** unreacted. In the reaction, CsF is used to react with trimethylsilyl group in **1a** for the generation of benzyne and also for the activation of phenylboronic acid (**3a**). The method for the benzyne generation is also important for the success of the present catalytic three-component coupling reaction. Product **4a** was not obtained when KF/18-crown-6 in THF was used instead of CsF in acetonitrile as in Table 1. Other methods of generating benzyne, including 1,2-dibromobenzene with *n*-BuLi, and *o*-aminobenzoic acid with isoamylnitrite are not compatible with the present catalytic reaction.

Under the optimized reaction conditions, substituted allylic chlorides underwent the three-component reaction with **1** and **3a** to afford the corresponding 2-allylbiphenyl derivatives in good yields (Table 1). Thus, methallyl chloride (**2b**) afforded **4b** in 76% yield (entry 2), while both 1-chloro-but-2-ene (**2c**) and 3-chloro-but-1-ene (**2d**) on treatment with **1b** and **3a** gave regioisomeric products **4c**,**d** in 75 and 74% combined yields, respectively (entries 3 and 4). The regioisomeric ratios in both cases were approximately 85:15, favoring the linear product **4c**.

The reaction of 3-chlorocyclohexene (**2e**) with **1a** and **3a** under the optimized reaction conditions proceeded smoothly to give the corresponding product **4e** in 77% yield (entry 5). In a similar manner, cinnamyl chloride (**2f**) reacted with **3c** and **1b** to provide **4f** in 66% yield (entry 6). It is noteworthy that the allylation of benzyne by **2f** is highly regioselective, giving exclusively the cinnamyl-substituted product (entry 6).

In addition to **1a**, various benzyne precursors were successfully used for the three-component reaction with **2a** and **3a**. Thus, **1b** with two methyl groups on the phenyl ring furnished product **4g** in 87% yield (entry 7), and indene derivative **1c** afforded **4h** in 85% yield (entry 8). 4-Methyl-substituted benzyne precursor **1d** gave a mixture of regioisomers (entry 9) as expected for a reaction using 4-methylbenzyne as a substrate.

The scope and generality of the present catalytic reaction can be further extended to various arylboronic acids. Under the standard conditions, the reaction of **1a** and **2a** with 3-methoxybenzeneboronic acid (**3b**), 4-fluorobenzeneboronic acid (**3c**), 4-bromobenzeneboronic acid (**3d**), and 3-nitrobenzeneboronic acid (**3e**) gave the corresponding *o*-allylbiphenyl derivatives **4k**−**n** in 81−87% yields (entries 10−13). The presence of a formyl group (**3f**) and a vinyl group (**3g**) at the 4-position of benzeneboronic acid was compatible with the present catalytic reaction, yielding products **4o** and **4p** in 78 and 81% yields, respectively (entries 14 and 15). 1-Naphthaleneboronic acid also successfully underwent the three-component reaction with **1b** and **2a** to give **4q** in 71% yield (entry 16). The present protocol can also be applied to heterocyclic reagents; 2-thiopheneboronic acid (**3i**) and 2-benzo[*b*]furanboronic acid (**3j**) gave the desired product **4r** and **4s** in 85% and 68% yields, respectively, (entries 17 and 18).

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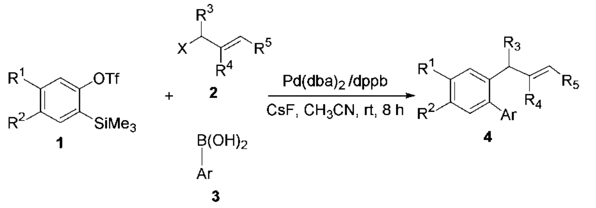
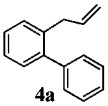
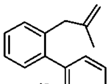
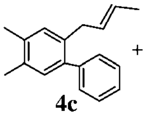
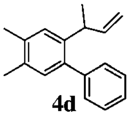
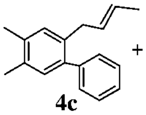
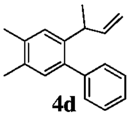
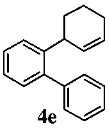
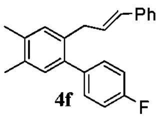
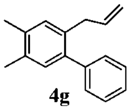
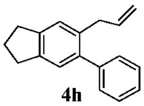
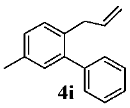
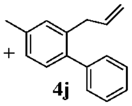
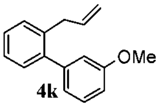
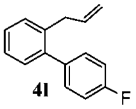
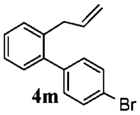
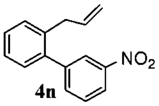
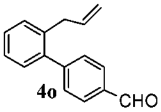
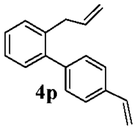
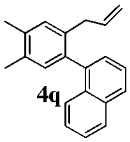
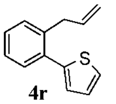
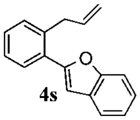
Table 1. Results of Palladium-Catalyzed Three-Component Reaction of Benzyne Precursors **1**, Allylic Chlorides **2**, and Arylboronic Acids **3**[a]



1a : $R^1 = R^2 = H$
1b : $R^1 = R^2 = CH_3$
1c : $R^1 = R^2 = \text{-}(CH_2)_3\text{-}$
1d : $R^1 = H$, $R^2 = CH_3$

2a : $R^3 = R^4 = R^5 = H$
2b : $R^3 = R^5 = H$, $R^4 = CH_3$
2c : $R^3 = R^4 = H$, $R^5 = CH_3$
2d : $R^4 = R^5 = H$, $R^3 = CH_3$
2e : 3-chlorocyclohexene
2f : $R^3 = R^4 = H$, $R^5 = Ph$

3a : Ar = C_6H_5
3b : Ar = m-C_6H_4OMe
3c : Ar = p-C_6H_4F
3d : Ar = p-C_6H_4Br
3e : Ar = m-$C_6H_4NO_2$
3f : Ar = p-C_6H_4CHO
3g : Ar = p-$C_6H_4CHCH_2$
3h : Ar = 2-naphthalene
3i : Ar = 2-thiophene
3j : Ar = 2-benzo[b]furan

entry	1	2	3	Product	Yield (%)[b]
1	**1a**	**2a**	**3a**	 **4a**	88(90)
2	**1a**	**2b**	**3a**	 **4b**	76
3	**1b**	**2c**	**3a**	 **4c** +  **4d**	76 (85:15)
4	**1b**	**2d**	**3a**	 **4c** +  **4d**	74 (84:16)
5	**1a**	**2e**	**3a**	 **4e**	77
6	**1b**	**2f**	**3c**	 **4f**	66
7	**1b**	**2a**	**3a**	 **4g**	87
8	**1c**	**2a**	**3a**	 **4h**	85
9	**1d**	**2a**	**3a**	 **4i** +  **4j**	85
10	**1a**	**2a**	**3b**	 **4k**	87
11	**1a**	**2a**	**3c**	 **4l**	82
12	**1a**	**2a**	**3d**	 **4m**	81
13	**1a**	**2a**	**3e**	 **4n**	84
14	**1a**	**2a**	**3f**	 **4o**	78
15	**1a**	**2a**	**3g**	 **4p**	81
16	**1b**	**2a**	**3h**	 **4q**	71
17	**1a**	**2a**	**3i**	 **4r**	85
18	**1a**	**2a**	**3j**	 **4s**	68

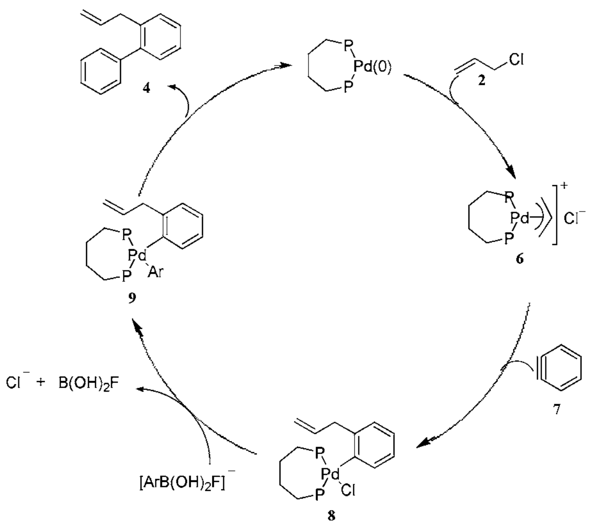
[a] Reaction conditions: 0.50 mmol of benzyne precursor **1**, 0.60 mmol of allyl chloride **2**, 0.50 mmol of arylboronic acid **3**, 0.025 mmol of $Pd(dba)_2$ and dppb, and 2.0 mmol of CsF under nitrogen in 3.0 mL of CH_3CN at room temperature for 6 h. [b] Isolated yields; yields in parentheses were determined by the ^1H NMR integration method with mesitylene as an internal standard.

Allyl acetates and allyl carbonates, commonly used as allylic electrophiles in industrial and organic synthesis, also reacted with **1a** and **3a** under the present conditions to yield **4a** in 72% and 61% yields, respectively. While allyl bromide gave the corresponding product **4a** in good yield (81%), allyl iodide underwent the reaction only in 44% yield. It should be noted that in these reactions, the conditions were not optimized and the same reaction conditions as shown in Table 1 were employed.

We further found that the three-component assembly reaction could also be extended to other common aryl organometallic reagents. Thus, when phenyltributyltin was treated with **1a** and **2a** under the present conditions, **4a** was obtained in 67% yield. Similarly, when phenyltrimethoxysilane was treated with **1a** and **2a** in the presence of Pd(dba)$_2$/dppb (5 mol %) and CsF in acetonitrile at 80 °C for 8 h, **4a** was obtained in 41% yield.

On the basis of the known palladium-catalyzed domino reactions,[2−8] a mechanism is proposed to account for the present catalytic reaction (Scheme 1). The first step involves oxidative addition of allyl chloride to Pd(0) to give the π-allyl palladium complex **6**. Benzyne **7** generated from **1** in the presence of CsF then inserts into **6** to afford aryl palladium intermediate **8**. Transmetalation of the arylboronic acid **3** with **8** gives intermediate **9** and B(OH)$_2$F. Subsequent reductive elimination of **9** affords the final product and regenerates the Pd(0) catalyst.

Scheme 1



Strong support for the involvement of benzyne in the reaction is the formation of two regioisomers, **4i** and **4j**, in a ca. 50:50 ratio (entry 9, Table 1). The lack of regioselectivity of the reaction is consistent with insertion of unsymmetrical benzyne into a palladium−carbon bond. The insertion of benzyne into Pd(II)−allyl intermediate **8** is proposed in the literature.[6c,d]

One other possible pathway is the oxidative addition of allyl chloride to Pd(0) to give π-allylpalladium complex **6**, followed by transmetalation of arylboronic acid **3** with **6** to give an aryl π-allyl palladium intermediate. Subsequent transfer of the aryl and allyl groups to the benzyne moiety affords the final product **4** and regenerates the Pd(0) catalyst.[14] This pathway cannot be completely ruled out.

A third possible pathway involves the addition of arylboronic acid to benzyne forming 2-biphenylboronic acid followed by coupling with allyl electrophile. However, the stoichiometric reaction of benzyne, generated from precursor **1a** in the presence of CsF, with benzeneboronic acid **3a** in acetonitrile and Pd(dba)$_2$/dppb at ambient temperature for 6 h did not afford the corresponding 2-biphenylboronic acid. The observation rules out the possibility of this pathway.

In conclusion, we have described a carbopalladation of highly reactive benzynes in a catalytic manner employing a variety of allyl electrophiles and aryl nucleophiles, thereby preparing various *o*-allylbiaryls in good yields. Further studies on the use of other carbopalladation partners, mechanistic details as well as potential synthetic applications of the present methodology are underway.

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Supporting Information Available: General experimental procedures, spectral data for all compounds, and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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