Palladium-catalyzed three-component coupling of arynes with allylic acetates or halides and terminal alkynes promoted by cuprous iodide†

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Benzynes react with allylic acetates or halides and terminal alkynes in the presence of $Pd(PPh_3)_4$, CuI and CsF in CH_3CN at 50 °C for 5 h to give 1-allyl-2-alkynylbenzene derivatives in good to excellent yields.

Palladium-catalyzed three-component assembling of an electrophile and a nucleophile to a π-component is an efficient method for constructing complex organic molecules.[1] The π-components used in these reactions mostly are alkynes,[2] alkenes[3] and allenes.[4] Recently, benzynes as the π-components also has attracted attention[5–11] due to the fact that it can construct two different C–C bonds at the *ortho* positions of an aromatic ring in one pot.

In 1983, Kobayashi and his coworkers observed the *in situ* generation of benzyne from *ortho*-silyl aryltriflates in the presence of fluoride source under mild reaction conditions.[5] Since that, many reports using benzynes as π-components for the metal-catalyzed organic reactions including [2 + 2 + 2] cycloaddition reactions,[6] carbocyclization reactions,[7] metal–metal bond addition reactions[8] and coupling reactions[9,10] have appeared. Yamamoto and his coworkers observed an intermolecular carbopalladation of allylic halides with two benzynes and also bisallylation of benzynes.[6c,d] We reported three-component coupling of benzynes with allylic halides and organometallic reagents such as alkynyl stannanes, allenyl stannanes and organoboronic acids.[10] We demonstrated an intermolecular carbocyclization of aryl iodides with two arynes and also arynes with aryl iodides and bicyclic alkenes.[7b,c] Larock and his coworkers revealed a partially intermolecular carbocyclization of 2-halobiaryls with benzynes and also an intermolecular carbocyclization of benzynes with aromatic halides and alkynes.[7a,d] Recently, Greaney *et al*. reported Heck-type three-component reaction of benzynes with benzyl or aromatic halides and acrylates,[11] while we found a nickel-catalyzed three-component coupling of benzynes with activated alkenes and organoboronic acids.[9]

Our continuous interest in metal-catalyzed three-component assembling reaction[12] and recent attention in benzyne chemistry[10] prompted us to explore the possibility of using benzynes as the π-component in three-component coupling reaction. Herein, we wish to report a palladium-catalyzed three-component coupling of benzyne with allylic acetates or halides and terminal alkynes promoted by CuI affording 1-allyl-2-alkynylbenzene derivatives in good to excellent yields under mild reaction conditions.

When 2-trimethylsilylphenyl triflate (**1a**) was treated with allyl acetate (**2a**) and 1-heptyne (**3a**) in the presence of $Pd(PPh_3)_4$ (3 mol%), and CsF (3.0 equiv.) at 50 °C for 5 h, a three-component assembling product 1-allyl-2-(hept-1-ynyl)-benzene (**4a**) was observed in 67% yield.

To optimize the present reaction, various additives, phosphine palladium complexes, and allylating reagents were tested for the reaction of **1a** with **2a** and **3a** at 50 °C for 5 h in CH_3CN (see ESI†). The addition of CuI (3.0 mol%) to the reaction using $Pd(PPh_3)_4$ (3.0 mol%), the yield of product **4a** was increased into 95%. The addition of other copper(I) halides CuBr and CuCl gave **4a** in 70 and 79% yields, respectively. In the absence of palladium complex, CuI alone does not catalyze the reaction to give **4a**.

On the basis of these optimization studies (see ESI†), we chose $Pd(PPh_3)_4$ or $Pd(dba)_2$/dppe as the catalyst, CuI as promoter and CH_3CN as solvent for this palladium-catalyzed three-component coupling reaction.

The present catalytic reaction is successfully extended to various substituted allylic halides and acetates **2**. Thus, 2-methallyl acetate (**2b**) reacted with **1a** and **3a** under the optimized reaction conditions to give **4b** in 87% yield (entry 2). As expected, both 3-chloro-1-butene (**2c**) and crotyl bromide (**2d**) reacted with **1b** and **2b** to afford two regioisomers **4c** and **4d** in 79 and 82% combined yields (entries 3 and 4). The regioisomeric ratios of **4c** : **4d** for 3-chloro-1-butene (**2c**) is approximately 85 : 15 and for crotyl bromide (**2d**) is approximately 65:35, both favoring the linear addition product **4c**. The reaction of cinnamyl acetate (**2e**) with **1a** and **3a** provided product **4e** in 74% yield. Similarly, cinnamyl chloride (**2f**) reacted with **1a** and **3b** to give **4f** in 69% yield. The allylation of benzyne with **2e** and **2f** were highly regioselective, giving exclusively the cinnamyl-substituted product in both cases.

A wide range of functional groups on the alkynes are compatible with the present allylalkynylation reaction (Table 1). Phenyl acetylene (**3b**) reacted with **1a** and **2a** providing **4g** in 92% yield (entry 7). Heterocyclic alkyne, 2-ethynyl pyridine (**3c**) afforded **4h** in 85% yield (entry 8). Methyl propargyl ether (**3d**) and methyl hex-5-ynoate (**3e**) gave products **4i** and **4j** in 82 and 87% yields, respectively (entries

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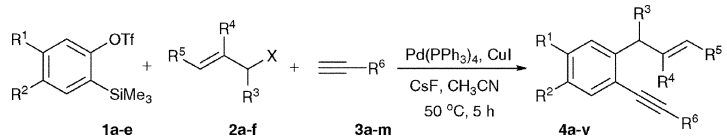
† Electronic supplementary information (ESI) available: Optimization studies, general experimental procedure, spectral data (^1H, ^{13}C NMR and HRMS) and copy of ^1H and ^{13}C NMR spectra of all compounds. See DOI: 10.1039/b800118a

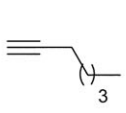
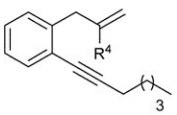
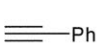
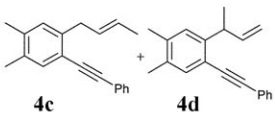
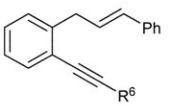
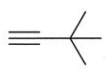
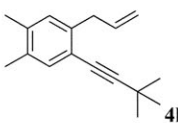
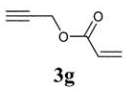
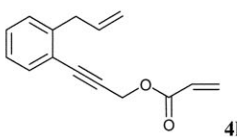
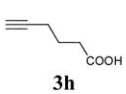
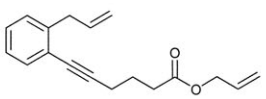
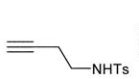
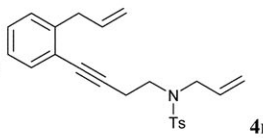
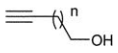
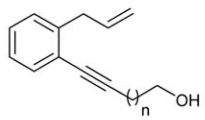
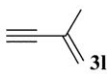
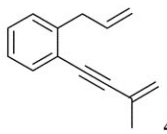
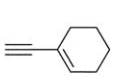
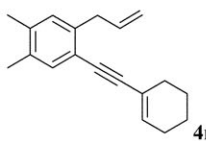
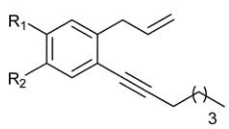
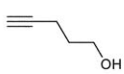
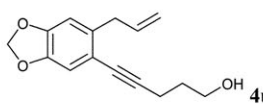
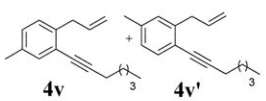
Table 1 Results of the coupling of arynes **1**, allylic acetates or halides **2** and terminal alkynes **3**[a]



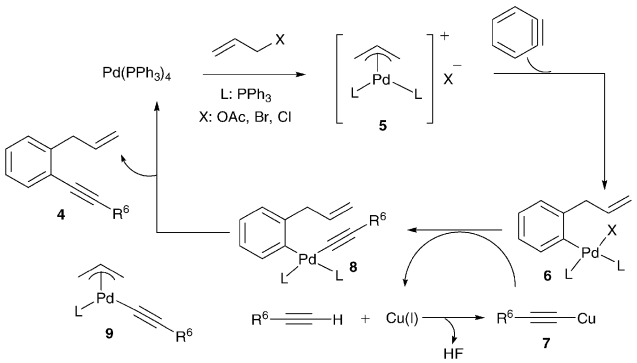
1a-e **2a-f** **3a-m** **4a-v**

1a: $R^1 = R^2 = H$
1b: $R^1 = R^2 = CH_3$
1c: $R^1+R^2 = -(CH_2)_3-$
1d: $R^1+R^2 = -OCH_2O-$
1e: $R^1 = H$, $R^2 = CH_3$

2a: $R^3 = R^4 = R^5 = H$, X = OAc
2b: $R^3 = R^5 = H$, $R^4 = CH_3$, X = OAc
2c: $R^3 = CH_3$, $R^4 = R^5 = H$, X = Cl
2d: $R^3 = R^4 = H$, $R^5 = CH_3$, X = Br
2e: $R^3 = R^4 = H$, $R^5 = Ph$, X = OAC
2f: $R^3 = R^4 = H$, $R^5 = Ph$, X = Cl

Entry	1	2	3	Product 4	Yield (%)[b]
1	**1a**	**2a**	 **3a**	 **4a**: $R^4 = H$ **4b**: $R^4 = CH_3$	89 (95)
2	**1a**	**2b**			87
3	**1b**	**2c**	 **3b**	 **4c** **4d**	79[c]
4	**1b**	**2d**			82[c]
5	**1a**	**2e**	**3a**	 **4e**: R^6 = *n*-pentyl **4f**: R^6 = Ph	74
6	**1a**	**2f**	**3b**		69
7	**1a**	**2a**	**3b**: R^6 = Ph	**4g**: R^6 = Ph	92[d]
8	**1a**	**2a**	**3c**: R^6 = 2-pyridinyl	**4h**: R^6 = 2-pyridinyl	85[d]
9	**1a**	**2a**	**3d**: R^6 = -CH_2OMe	**4i**: R^6 = -CH_2OMe	82
10	**1a**	**2a**	**3e**: R^6= -$(CH_2)_3CO_2$Me	**4j**:R^6= -$(CH_2)_3CO_2$Me	87
11	**1b**	**2a**	 **3f**	 **4k**	85
12	**1a**	**2a**	 **3g**	 **4l**	77[d]
13	**1a**	**2a**	 **3h**	 **4m**	81[e]
14	**1a**	**2a**	 **3i**	 **4n**	79[e]
15	**1a**	**2a**	 **3j**: n = 1 **3k**: n = 2	 **4o**: n = 1 **4p**: n= 2	77
16	**1a**	**2a**			75
17	**1a**	**2a**	 **3l**	 **4q**	87
18	**1b**	**2a**	 **3m**	 **4r**	83
19	**1b**	**2a**	**3a**	 **4s**: $R^1 = R^2 = CH_3$ **4t**: $R^1+R^2 = -(CH_2)_3-$	85
20	**1c**	**2a**			82
21	**1d**	**2a**	 **3k**	 **4u**	72
22	**1e**	**2a**	**3a**	 **4v** **4v'**	89 (1:1)

[a] All reactions were carried out using benzyne precursor **1** (1.0 mmol), allylic acetates or halides **2** (for **2a–d** 1.3 mmol and **2e–f** 1.0 mmol), terminal alkynes **3** (1.1 mmol), $Pd(PPh_3)_4$ (3 mol%), CuI (3 mol%), CsF (3.0 mmol) and CH_3CN (3.0 mL) at 50 °C for 5 h. [b]Isolated yields; yield in the parenthesis was determined by ^1H NMR method using mesitylene as an internal standard. [c]The regioisomeric ratio of **4c** : **4d** for **2c** is 85 : 15 and **2d** is 65 : 35. [d]1 : 1 ratio of CH_3CN + THF (1.5 + 1.5 mL) was added. [e]2.5 mmol of **2a** was used.



Scheme 1

9–10). *tert*-Butyl acetylene (**3f**) and propargyl acrylate (**3g**) provided **4k** and **4l** in 85 and 77% yields, respectively (entries 11–12). 5-Alkynoic acid **3h** and *N*-but-3-ynyl sulfonamide **3i** also efficiently participated in the reaction affording product **4m** and **4n** in 81 and 79% yields, respectively (entries 13 and 14). However, in these reactions, allylation of the COOH and N–H groups on the alkyne substrates also occurred.[1] Under similar reaction conditions, alkynyl alcohols **3j** and **3k** provided **4o** and **4p** in 77 and 75% yields, respectively (entries 14 and 15). In these two cases, no allylation was observed on the OH group of the alkynyl alcohols. The present catalytic reaction was also successfully applied to enynes. Thus, acyclic and cyclic 1,3-enynes, **3l** and 1-ethynylcyclohex-1-ene (**3m**) efficiently reacted with **1a** or **1b** and **2a** to give the corresponding allylalkynylation products **4q** and **4r** in 87 and 83% yields, respectively (entries 17 and 18).

To understand the effect of substituents on the benzyne moiety in the present reaction, various substituted benzyne precursors **1b–e** were tested (Table 1). 3,4-Dimethylbenzyne precursor **1b** reacted smoothly with **1a** and **2a** affording **4s** in 85% yield (entry 19). Likewise, electron-rich benzyne precursors **1c** and **1d** afforded **4t** and **4u** in 82 and 72% yields, respectively (entries 20 and 21). As expected, the reaction of 4-methylbenzyne precursor **1e** with **2a** and **3a** gave a mixture of regioisomeric products **4v** and **4v′** with *ca.* a 50 : 50 ratio in 89% combined yield (entry 22).

A possible catalytic reaction mechanism for the present allylalkynylation reaction is shown in Scheme 1. The catalytic reaction is likely initiated by the oxidative addition of allyl acetate or halide with Pd(0) species giving π-allylpalladium(II) complex **5**. Carbopalladation of benzyne, generated *in situ* from **1** and CsF, with π-allylpalladium(II) intermediate **5** gives allyl palladium intermediate **6**. Transmetallation of copper acetylide **7** with intermediate **6** affords intermediate **8** and Cu(I). Subsequent reductive elimination of **8** gives product **4** and regenerates the Pd(0) catalysts. In addition, copper acetylide can be regenerated from terminal alkyne and Cu(I) in the presence of CsF. The latter acts as a base to remove the proton from the terminal alkyne (Scheme 1) in addition to be a promoter for the generation of benzyne.

An alternative mechanism involving **9** as a key intermediate cannot be totally ruled out. Oxidative addition of allyl acetate or halide with Pd(0) to give π-allylpalladium complex **5** (Scheme 1), is followed by transmetalation of copper acetylide **7** with **5** to afford σ-alkynyl π-allyl palladium intermediate **9**. Subsequent transfer of alkynyl and allyl groups to the benzyne moiety affords the final product **4** and regenerates the Pd(0) catalyst.

In comparison with the previous palladium-catalyzed allylalkynalation of benzyne using alkynylstannane as the nucleophile,[10a] there are three advantages of the present reaction. First, the present catalytic reaction requires a catalytic amount of CuI and a stoichiometric amount of terminal alkyne for the alkynylation, while the previous one used a stoichiometric amount of alkynylstannane and gave $Sn(Bu)_3Cl$ as a product.[10a] Both tin species are known to be toxic. Second, various allylating agents such as allylic acetates and halides can be used in the present reaction. But in our previous report, allylic chlorides was more suitable than other allylating agents. Third, the present catalytic reaction is compatible with various functional groups such as ether, ester, acrylate, hydroxyl and amide groups on the alkynes. However, the corresponding alkynylstannane reagents required in the previous reactions are difficult to prepare.

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