

# Copper-catalyzed three-component coupling of arynes, terminal alkynes and activated alkenes†

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**The three-component coupling of benzyne with terminal alkynes and activated alkenes in the presence of CuI, PCy<sub>3</sub> and CsF in a 1 : 1 mixture of CH<sub>3</sub>CN and THF at 50 °C for 5 h gave 1-alkyl-2-alkynylbenzenes in good to moderate yields.**

Transition metal-catalyzed aryne-involving three-component coupling reaction to form two different carbon–carbon bonds at the two adjacent aryne carbons has drawn substantial attention recently in organic synthesis.<sup>1–9</sup> In 2000, Yamamoto's group reported a palladium-catalyzed carbocyclization of arynes with alkynes and allylic halides and also a bisallylation of arynes with allyl chloride and allyl stannane.<sup>1</sup> Chatani *et al.* reported a palladium-catalyzed carbocyclization of arynes with allylic halides and CO.<sup>2</sup> We reported a palladium-catalyzed three-component coupling of benzyne with allylic halides or acetates and organometallic reagents<sup>3</sup> and also a carbocyclization of arynes with aromatic iodides and bicyclic alkenes.<sup>4</sup> Larock's group described a palladium catalyzed carbocyclization of arynes with aromatic iodides and alkynes.<sup>5</sup> Greaney and co-workers showed three-component Heck type coupling of arynes with organic halides and alkenes.<sup>6</sup> Very recently, Zhang and co-workers observed a copper-catalyzed three-component coupling of benzyne with terminal alkynes and allylic halides.<sup>7</sup>

Recently, we demonstrated a nickel-catalyzed three-component coupling of arynes with activated alkenes and organoboronic acids.<sup>8</sup> In the reaction, alkenyl and aromatic boronic acids worked very well, but alkynylmetal reagents such as alkynyltin was not active as an organometallic reagent for the nickel-catalyzed three-component coupling reaction. In the effort to develop an efficient method for three-component coupling of arynes with activated alkenes and alkylation reagents, we tested the reaction with various alkynylmetal reagents. In the presence of catalytic amounts of CuI, Ni(COD)<sub>2</sub> and PCy<sub>3</sub> (tricyclohexylphosphine), 3,4-dimethylbenzyne precursor **1a**, CsF, terminal alkyne **2a** and ethyl vinyl ketone (**3a**) underwent a three-component coupling reaction to give **4a** in good yield. However, during optimization studies we were surprised that in the absence of nickel catalyst, copper(I) in the presence of a phosphine ligand can serve as a catalyst in

the three-component coupling of benzyne with terminal alkynes and alkenes. Herein, we wish to report this new copper-catalyzed reaction.

The reaction of (2-(trimethylsilyl)-3,4-dimethylphenyl triflate) **1a** with 1-hexyne (**2a**) and ethyl vinyl ketone (**3a**) in the presence of CuI (10 mol%), PCy<sub>3</sub> (2 mol%) and CsF (3.0 equiv.) in a 1 : 1 (v/v) ratio of THF and CH<sub>3</sub>CN at 50 °C for 5 h gave three-component coupling product **4a** in 82% isolated yield (Table 1, entry 1). No three-component coupling reaction occurs in the absence of either CuI or ligand. The product formation of **4a** can be explained by alkynylcupration of benzyne with cuprous acetylide to give 2-alkynylphenyl-cuprous reagent followed by 1,4-addition to activated alkenes (*vide infra*).

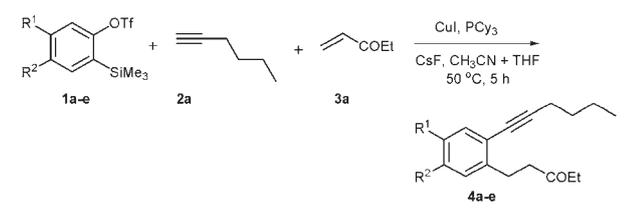
The phosphine ligand used is crucial for the success of the present reaction. Various phosphine ligands (10 mol%) such as PPh<sub>3</sub>, PCy<sub>3</sub>, P(*n*-Bu)<sub>3</sub>, P(*o*-tolyl)<sub>3</sub>, P(*o*-anisyl)<sub>3</sub>, P(*p*-anisyl)<sub>3</sub>, P(2-furyl)<sub>3</sub>, dppe and dppb were examined for the reaction of **1a** with **2a** and **3a** in the presence of CuI (5 mol%) in a 1 : 1 ratio of THF and CH<sub>3</sub>CN at 50 °C for 5 h. Among them, highly electron-rich and sterically hindered PCy<sub>3</sub> gave **4a** in 75% yield. Other phosphine ligands were less effective for the reaction providing **4a** in only 10–35% yields. In all these reactions, a side product 4-(hex-1-ynyl)-1,2-dimethylbenzene (**5a**) from addition of 1-hexyne to 3,4-dimethylbenzyne was observed in various amounts. In order to suppress the formation of this side product, different ratios of PCy<sub>3</sub> and CuI, 2 : 1, 3 : 1, 2 : 5 and 1 : 5 were tested. No side product was observed when the ratio is 1 : 5 (PCy<sub>3</sub>, 2 mol%; CuI, 10 mol%) and the expected product **4a** was formed in 89% yield.

The use of binary solvent system improved the product yield of the present reaction. If the catalytic reaction was carried out in CH<sub>3</sub>CN alone, product **4a** was produced in 55% yield along with side product **5a** in 45% yield. In the 1 : 1 binary solvent systems of CH<sub>3</sub>CN with THF, CH<sub>2</sub>Cl<sub>2</sub>, toluene or DME, the CH<sub>3</sub>CN–THF and CH<sub>3</sub>CN–CH<sub>2</sub>Cl<sub>2</sub> mixtures gave **4a** in 89 and 87% yields, respectively. The other binary systems afforded **4a** in 35 and 20% yields, respectively. The catalytic activity of various cuprous halides, CuI, CuBr, CuCl and CuCN were examined. CuI appears to have the highest activity giving **4a** in 89% yield. The others afforded **4a** in 75, 69 and 55% yields, respectively. Based on these optimization studies, we chose CuI (10 mol%), PCy<sub>3</sub> (2 mol%) in a mixture of CH<sub>3</sub>CN and THF (1 : 1) as the standard catalytic conditions for the studies shown in Table 1.

Under the standard reaction conditions, other benzyne precursors **1b–e** also reacted smoothly with **2a** and **3a**

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† Electronic supplementary information (ESI) available: General experimental procedure, spectral data (<sup>1</sup>H, <sup>13</sup>C NMR and HRMS) and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of all compounds. See DOI: 10.1039/b809409h

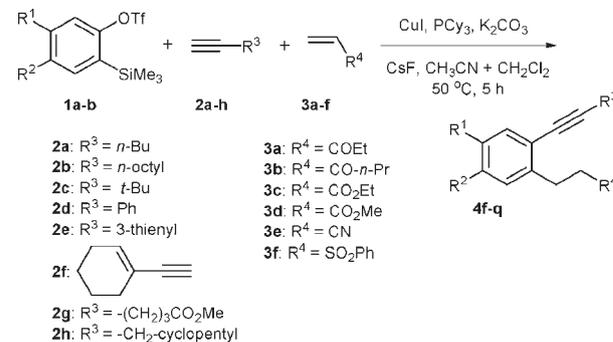
**Table 1** Results of the three-component coupling of arynes **1a–e**, 1-hexyne **2a** and ethyl vinyl ketone **3a**<sup>a</sup>

Entry	<b>1</b>	Product <b>4</b>	Yield (%) <sup>b</sup>
1			82 (89)
2			65 80 (87) <sup>c</sup>
3			81
4			75
5			79 <sup>d</sup>
		<b>4e</b> : R <sup>1</sup> = H, R <sup>2</sup> = Me <b>4e'</b> : R <sup>1</sup> = Me, R <sup>2</sup> = H	

<sup>a</sup> Unless otherwise mentioned, all reactions were carried out using benzyne precursor **1** (1.0 mmol), 1-hexyne **2** (1.0 mmol), ethyl vinyl ketone **3** (2.0 mmol), CuI (10 mol%), PCy<sub>3</sub> (2 mol%), CsF (3.0 mmol) and CH<sub>3</sub>CN–THF (1 : 1) at 50 °C for 5 h. <sup>b</sup> Isolated yields; yield in the parenthesis was determined by <sup>1</sup>H NMR using mesitylene as an internal standard. <sup>c</sup> Reaction was carried out using CuI (5 mol%), PCy<sub>3</sub> (10 mol%) and K<sub>2</sub>CO<sub>3</sub> (1.5 mmol). <sup>d</sup> The regioisomeric ratio **4e** : **4e'** is 1 : 1.

(Table 1). Thus, benzyne precursor **1b** gave **4b** in 65% isolated yield (entry 2). In addition, a side product hex-1-ynylbenzene (**5b**) from addition of 1-hexyne to benzyne was observed in 25% isolated yield. Electron-rich benzyne precursors **1c** and **1d** afforded the corresponding products **4c** and **4d** in 81 and 75% yields, respectively (entries 3 and 4). As expected, the reaction of 4-methylbenzyne precursor **1e** gave a mixture of regioisomeric products **4e** and **4e'** in *ca.* a 1 : 1 ratio in 79% combined yields (entry 5). It should be noted that no direct addition of alkyne with benzyne was observed in the reactions of electron-rich benzyne precursors (entries 1, 3–5) with **2a** and **3a** and the product yields are higher than that using unsubstituted benzyne as the substrate (entry 2). In order to suppress the side reaction of unsubstituted benzyne with 1-hexyne, the reaction of **1b** with **2a** and **3a** was examined in the presence of

CuI (5 mol%), PCy<sub>3</sub> (10 mol%) and various inorganic bases such as Li<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub> and Cs<sub>2</sub>CO<sub>3</sub> in a 1 : 1 ratio of CH<sub>2</sub>Cl<sub>2</sub> and CH<sub>3</sub>CN at 50 °C for 5 h. Among them, K<sub>2</sub>CO<sub>3</sub>

**Table 2** Results of the three-component coupling of arynes **1a–b** with various terminal alkynes **2** and activated alkenes **3**<sup>a</sup>

Entry	<b>1</b>	<b>2</b>	<b>3</b>	Product <b>4</b>	Yield (%) <sup>b</sup>
1	<b>1b</b>	<b>2b</b>	<b>3a</b>		<b>4f</b> : R <sup>3</sup> = <i>n</i> -octyl 77 (85)
2	<b>1b</b>	<b>2c</b>	<b>3a</b>		<b>4g</b> : R <sup>3</sup> = <i>t</i> -Bu 75 (83)
3	<b>1b</b>	<b>2d</b>	<b>3a</b>		<b>4h</b> : R <sup>3</sup> = Ph 59 <sup>c</sup>
4	<b>1b</b>	<b>2e</b>	<b>3a</b>		<b>4i</b> : R <sup>3</sup> = 3-thienyl 56 <sup>c</sup>
5	<b>1b</b>	<b>2f</b>	<b>3a</b>		<b>4j</b> 79 (85)
6	<b>1a</b>	<b>2g</b>	<b>3a</b>		<b>4k</b> : R <sup>3</sup> = CO <sub>2</sub> Me 76 <sup>d</sup>
7	<b>1a</b>	<b>2h</b>	<b>3a</b>		<b>4l</b> 72
8	<b>1b</b>	<b>2a</b>	<b>3b</b>		<b>4m</b> 79
9	<b>1b</b>	<b>2a</b>	<b>3c</b>		<b>4n</b> : R <sup>4</sup> = CO <sub>2</sub> Et 65 <sup>c</sup>
10	<b>1b</b>	<b>2a</b>	<b>3d</b>		<b>4o</b> : R <sup>4</sup> = CO <sub>2</sub> Me 67 <sup>c</sup>
11	<b>1b</b>	<b>2a</b>	<b>3e</b>		<b>4p</b> : R <sup>4</sup> = CN 39 <sup>c</sup>
12	<b>1b</b>	<b>2a</b>	<b>3f</b>		<b>4q</b> : R <sup>4</sup> = SO <sub>2</sub> Ph 32 <sup>c</sup>

<sup>a</sup> Unless otherwise mentioned, all reactions were carried out using benzyne precursor **1** (1.0 mmol), terminal alkyne **2** (1.0 mmol), activated alkene **3** (2.0 mmol), CuI (5 mol%), PCy<sub>3</sub> (10 mol%), CsF (2.5 mmol), K<sub>2</sub>CO<sub>3</sub> (1.5 mmol) and CH<sub>3</sub>CN–CH<sub>2</sub>Cl<sub>2</sub> (1 : 1) at 50 °C for 5 h. <sup>b</sup> Isolated yields; yields in parenthesis were determined by <sup>1</sup>H NMR using mesitylene as an internal standard. <sup>c</sup> The direct addition of terminal alkyne to benzyne was observed. In these reactions, 3.0 mmol of activated alkene and 2.5 mmol of K<sub>2</sub>CO<sub>3</sub> were used. For entries 11 and 12, the catalytic reaction was carried out at 70 °C for 5 h. <sup>d</sup> The catalytic reaction was carried out at 50 °C for 12 h.

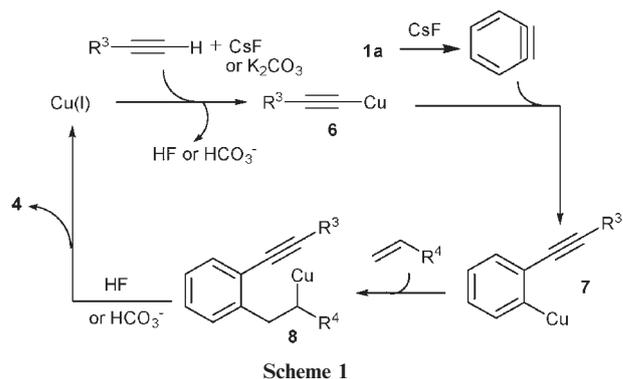
gave **4b** in 87% yield without the formation of side product hex-1-ynylbenzene (**5b**).<sup>7</sup> Others afforded **4b** in 75, 60 and 55% yields, respectively, along with a side product **5b** in various amounts.  $K_2CO_3$  is probably used as a base to neutralize the proton released during the alkynylcupration of benzyne.<sup>10</sup> The reaction conditions were also effective for electron-rich benzyne precursors **1a** and **1c–e**. In the reaction, the corresponding three-component coupling products **4a**, **4c–e** were observed in 82, 79, 77 and 80% yields, respectively. The reaction conditions were employed also for the studies shown in Table 2.

The present three-component coupling reaction was successfully extended to various terminal alkynes (Table 2). Thus, 1-decyne (**2b**) and *tert*-butylacetylene (**2c**) reacted with **1b** and **3a** providing **4f** and **4g** in 77 and 75% yields, respectively (entries 1 and 2). Phenyl acetylene (**2d**) and 3-ethynylthiophene (**2e**) furnished **4h** and **4i** in 59 and 56% yields, respectively (entries 3 and 4). In addition to **4h** and **4i**, side products diphenyl acetylene (**5c**) and 3-(phenylethynyl)thiophene (**5d**) were observed in 31 and 34% isolated yields, respectively. 1-Ethynylcyclohex-1-ene (**2f**) afforded **4j** in 79% yield (entry 5). Under similar reaction conditions, methyl hex-5-ynoate (**2g**) and prop-2-ynylcyclopentane (**2h**) also reacted efficiently with **1a** and **3a** to afford three-component coupling products **4k** and **4l** in 76 and 72% yields, respectively (entries 6 and 7).

In addition to ethyl vinyl ketone (**3a**), *n*-propyl vinyl ketone (**3b**) also underwent coupling reaction effectively with **1b** and **2a** to give **4m** in 79% yield (entry 8). Other activated alkenes such as ethyl acrylate (**3c**), methyl acrylate (**3d**), acrylonitrile (**3e**) and vinylsulfonylbenzene (**3f**) also efficiently participated in the coupling reaction with **1b** and **2a** to give coupling products **4n–q** in 65, 67, 39 and 32% yields, respectively (entries 9–12). In these reactions, a side product hex-1-ynylbenzene (**5b**) was observed in 24, 21, 49 and 52% isolated yields, respectively.

A possible reaction mechanism for the present three-component coupling reaction is shown in Scheme 1. Reaction of terminal alkyne with Cu(I) species in the presence of CsF (or  $K_2CO_3$ ) gives copper acetylide **6**. Alkynylcupration of benzyne<sup>11</sup> with cuprous acetylide **6** affords arylcuprous intermediate **7**. Conjugate addition of **7** to activated alkene **3** gives intermediate **8**. Protonation of intermediate **8** gives product **4** with regeneration of the catalyst. The observation of a side product 1-aryl-1-alkyne can be explained by the protonation of intermediate **7** in the presence of HF or  $HCO_3^-$ .

In conclusion, we have developed a copper(I)-catalyzed three-component coupling of arynes with terminal alkynes and activated alkenes providing 1-alkyl-2-alkynylbenzenes. In most of the three-component coupling reactions, only palladium and nickel complexes were generally employed. This new copper-catalyzed reaction highlights the potential of using copper as an inexpensive and efficient catalyst for the three-component coupling reactions. Further extension of this coupling reaction



with other  $\pi$ -components and organometallic reagents and detailed mechanistic investigation are in progress.

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