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A Cooperative Copper- and Palladium-Catalyzed Three-Component Coupling of Benzynes, Allylic Epoxides, and Terminal Alkynes**

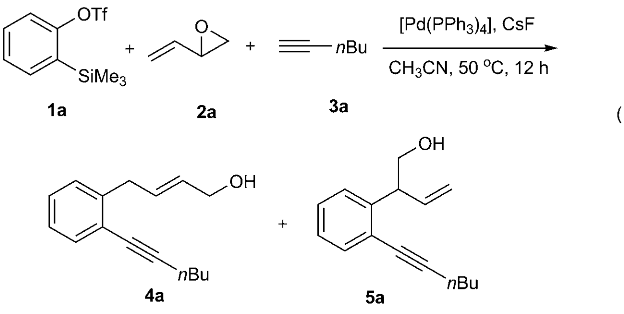
*Masilamani Jeganmohan, Sivakolundu Bhuvaneswari, and Chien-Hong Cheng**

The transition-metal-catalyzed three-component sequential coupling of electrophiles and nucleophiles to carbon–carbon π-components, such as alkynes, alkenes, and allenes, is an ideal method in organic synthesis for constructing two different consecutive carbon–carbon bonds from simple starting materials in one pot.[1] Over the past decade, the use of benzyne as a carbon–carbon π-component has attracted considerable attention, owing to its capability of efficiently constructing two different C–C bonds *ortho* to each other on a benzene ring in one pot.[2–4]

Whereas several allylic electrophiles, such as allylic acetates, carbonates and halides, are successfully used in three-component sequential coupling reactions, to our knowledge, no such reaction using an allylic epoxide as an electrophile has to date been reported, most likely as a result of complicated selectivity problems, which arise from the four potential reactive carbon centers of allylic epoxides.[5]

In recent years, dual-metal-catalyzed reactions have gained much attention in organic transformations, owing to their ability in enhancing selectivity and reactivity in reactions.[6] Herein, we wish to report for the first time a cooperative palladium- and copper-catalyzed highly regio- and chemoselective atom-economical three-component coupling of benzynes with allylic epoxides and terminal alkynes. This reaction provides an efficient strategy for the synthesis of *ortho*-disubstituted arenes containing alkynyl and 4-hydroxy-2-butenyl groups. This type of compound is useful as a synthetic intermediate in various organic reactions.[7]

The reaction of benzyne precursor **1a** with 2-vinyloxirane (**2a**) and 1-hexyne (**3a**) in the presence of $[Pd(PPh_3)_4]$ (5.0 mol%) and CsF (3.0 equiv) in a 1:1 mixture of CH_3CN and toluene at 50°C for 12 h gave two regioisomeric three-component coupling products, **4a** and **5a**, in a 62:38 ratio in 79% combined yield [Eq. (1)]. No three-component coupling reaction occurred in the absence of palladium catalyst.



(1)

To understand the nature of the present coupling reaction and improve its regioselectivity, the activities of various palladium phosphine complexes were examined (for detailed studies, see the Supporting Information). A substantial change in the regioselectivity occurred when the bidentate phosphine complex system $[Pd(dba)_2]$/dppp was used (dba = dibenzylideneacetone, dppp = 1,3-bis(diphenylphosphanyl)-propane). Products **4a** and **5a** were formed in an 80:20 ratio in 69% combined yield. The addition of CuI to the reaction mixture led to further improvement of the regioselectivity, producing **4a** exclusively in 81% isolated yield. The catalytic reaction is also highly stereoselective, giving only the *E* stereoisomer. In the absence of palladium complex, CuI, alone with phosphine ligand, gave only the hydroalkynylation product PhC≡C–*n*Bu (**6a**). Based on these studies, we used, as the standard catalytic conditions, $[Pd(dba)_2]$ (5 mol%), dppp (5 mol%), and CuI (5 mol%), in a 1:1 mixture of CH_3CN and toluene.

To explore the scope of present reaction, the reactions of substituted benzyne precursors **1b–f** with **2a** and **3a** were examined (Table 1). Electron-rich 3,4-dimethyl-substituted **1b** provided **4b** in 87% yield (Table 1, entry 1). Other electron-rich precursors **1c** and **1d** afforded **4c** and **4d** in 84% and 77% yields, respectively (Table 1, entries 2 and 3). Electron-deficient 3,4-diflurobenzyne precursor **1e** gave **4e** in moderate 63% yield (Table 1, entry 4). As expected, an approximately 50:50 mixture of regioisomeric products **4f** and **4f'** in 85% combined yield was detected for the 4-methyl-substituted precursor **1f** (Table 1, entry 5).

We next examined the effect on the reaction of various substituted allylic epoxides **2b–e** with **1a** and **2a** (Table 1). All of these reactions were completely regioselective, although stereoselectivity varied with the epoxides used. For 2-methyl-2-vinyloxirane **2b**, the reaction gave **4g** in 57% yield in addition to hydroalkynylation product PhC≡C-*n*Bu_3 (**6a**, 35% yield). In order to suppress hydroalkynylation, the reaction was carried out in the absence of CuI. In this case no hydroalkynylation product was detected and the yield of the three-component coupling product **4g** was increased to 79% with an 85:15 *E*/*Z* stereoisomeric ratio (Table 1, entry 6). Similarly, 2-phenyl-2-vinyloxirane (**2c**) provided **4h** in 75% yield with an 80:20 *E*/*Z* stereoisomeric ratio (Table 1, entry 7). Under the optimized reaction conditions, isoprene

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[*] Dr. M. Jeganmohan, S. Bhuvaneswari, Prof. Dr. C.-H. Cheng
Department of Chemistry, National Tsing Hua University
Hsinchu 30013 (Taiwan)
Fax: (+886) 3572-4698
E-mail: chcheng@mx.nthu.edu.tw

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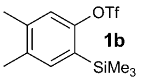
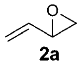
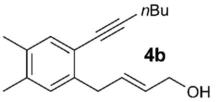
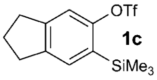
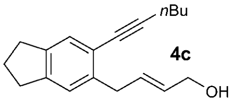
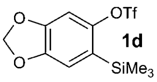
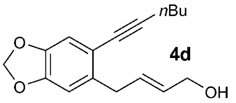
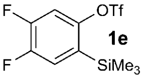
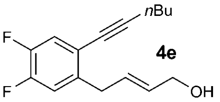
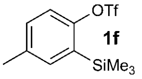
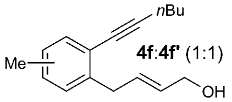
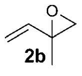
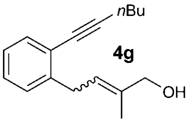
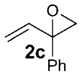
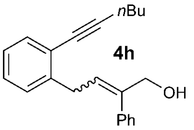
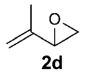
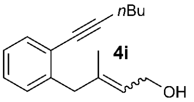
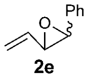
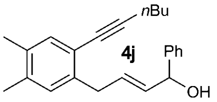
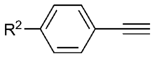
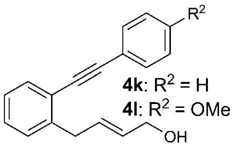
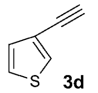
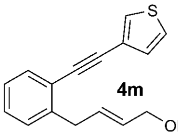
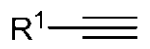
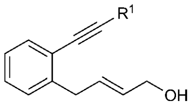
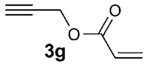
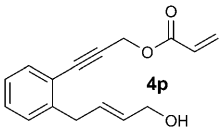
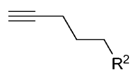
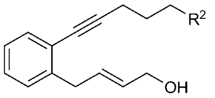
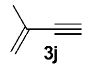
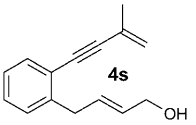
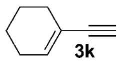
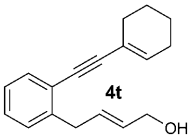
Table 1: Results of the three component coupling of benzynes with allylic epoxides and 1-hexyne (**3a**).[a]

Entry	1	2	4	Yield [%][b]
1	 **1b**	 **2a**	 **4b**	87
2	 **1c**	**2a**	 **4c**	84
3	 **1d**	**2a**	 **4d**	77
4	 **1e**	**2a**	 **4e**	63
5	 **1f**	**2a**	 **4f**:**4f'** (1:1)	85
6	**1a**	 **2b**	 **4g**	79[c,d]
7	**1a**	 **2c**	 **4h**	75[c,d]
8	**1a**	 **2d**	 **4i**	69[d]
9	**1b**	 **2e**	 **4j**	74

[a] Unless otherwise stated, all reactions were carried out using benzyne **1** (1.1 mmol), allylic epoxide **2** (1.2 mmol), 1-hexyne **3** (1.0 mmol), [Pd(dba)$_2$] (5 mol%), dppp (5 mol%), CuI (5 mol%), CsF (3.0 mmol) in CH$_3$CN/toluene (8.0 mL, 1:1 mixture) at 50°C for 12 h. dba = dibenzylideneacetone; dppp = 1,3-bis(diphenylphosphanyl)propane. [b] Yields of isolated product. [c] The catalytic reaction was carried out with a catalytic system of [Pd(dba)$_2$] (5 mol%) and tri-2-furylphosphine (20 mol%) in CH$_3$CN (6 mL). [d] E/Z stereoisomeric ratio: **4g** 85:15, **4h** 80:20, **4i** 82:18.

Table 2: Results of the three component coupling of benzyne **1a**, 2-vinyloxirane **2a**, and terminal alkynes **3b–k**.[a]

Entry	3	4	Yield [%][b]
1 2	 **3b**: R^2 = H **3c**: R^2 = OMe	 **4k**: R^2 = H **4l**: R^2 = OMe	87 92
3	 **3d**	 **4m**	72
4 5	 **3e**: R^1 = *t*Bu **3f**: R^1 = CH$_2$OMe	 **4n**: R^1 = *t*Bu **4o**: R^1 = CH$_2$OMe	83 79[c]
6	 **3g**	 **4p**	77
7 8	 **3h**: R^2 = CO$_2$Me **3i**: R^2 = OH	 **4q**: R^2 = CO$_2$Me **4r**: R^2 = OH	76 59[c]
9	 **3j**	 **4s**	82
10	 **3k**	 **4t**	80

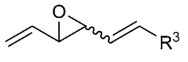
[a] Unless otherwise stated, all reactions were carried out using benzyne **1** (1.1 mmol), allylic epoxide **2** (1.2 mmol), 1-hexyne **3** (1.0 mmol), [Pd(dba)$_2$] (5 mol%), dppp (5 mol%), CuI (5 mol%), CsF (3.0 mmol) in CH$_3$CN/toluene (8.0 mL, 1:1 mixture) at 50°C for 12 h. [b] Yields of isolated product. [c] The reaction was carried out at 70°C.

epoxide (**2d**) afforded a three-component coupling product **4i** in 69% yield with an 82:18 *E*/*Z* stereoisomeric ratio (Table 1, entry 8). In the reaction, the hydroalkynylation product PhC≡C-*n*Bu (**6a**) was detected in 22% yield. Interestingly, the reaction of a *cis*/*trans* mixture (45:55) of 2-phenyl-3-vinyloxirane **2e**[8] with **1b** and **3a** gave only the *E* isomer **4j** in 74% yield (Table 1, entry 9).

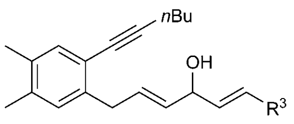
The scope of this method was further examined with various terminal alkynes (Table 2). Phenyl acetylene (**3b**) and 4-methoxy phenyl acetylene (**3c**) reacted with **1a** and **2a** providing **4k** and **4l** in 87 and 92% yields, respectively (Table 2, entries 1 and 2). The heterocyclic alkyne, 3-ethynyl thiophene (**3d**) afforded **4m** in 72% yield (Table 2, entry 3). Other terminal acetylenes, including *tert*-butyl acetylene (**3e**), methyl propargyl ether (**3f**), propargyl acrylate (**3g**), methyl hex-5-ynoate (**3h**), and pent-4-yn-1-ol (**3i**), afforded **4n–r** in 83, 79, 77, 76, and 59% yields, respectively (Table 2, entries 4–8). The catalytic reaction conditions are tolerant to the presence of functional groups OMe, CO$_2$Me, S, and OH on the terminal alkynes **3**. In addition, 1,3-enynes, **3j** and **3k**, also efficiently participated in the reaction, giving products **4s** and **4t** in 82 and 80% yields, respectively (Table 2, entries 9 and 10).

For further understanding of regioselectivity in the present catalytic reaction, the reaction of substituted 2,3-divinyloxiranes **2f** and **g** with **1b** and **3a** was investigated in the presence of [Pd(dba)$_2$]/dppp (see below). In this case, a 29:71 *cis*/*trans* mixture of **2f** (R^3 = Ph)[8] afforded only the

E isomer **4u** in 75% yield, in a highly regio-, stereo- and chemoselective manner. Similarly, a 25:75 *cis/trans* mixture of 2-(but-1-enyl)-3-vinyloxirane (**2g**)[8] provided the *E* isomer **4v** in 73% yield. In this reaction, there were four possible reaction sites, but reaction only occurred at the less-hindered unsubstituted alkene carbon of **2f** and **g**.

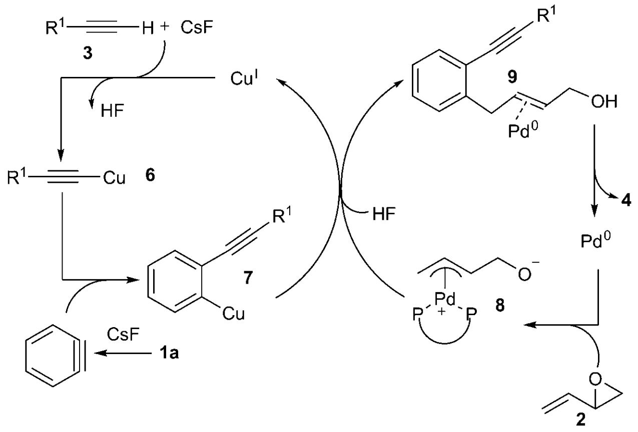


2f: R^3 = Ph
2g: R^3 = Et



4u: R^3 = Ph, 75%
4v: R^3 = Et, 73%

A proposed mechanism for the cooperatively palladium- and copper-catalyzed three-component coupling (Scheme 1) incorporates two catalytic cycles, operating in tandem. In the copper catalytic cycle, the reaction is initiated by the formation of cuprous acetylide **6** from terminal alkyne **3** and Cu$^{\mathrm{I}}$ in the presence of CsF. Alkynylcupration of benzyne[9] with cuprous acetylide **6** affords arylcuprous intermediate **7**.[10] Attack of **7** at the less hindered unsubstituted carbon of the π-allyl group or at the palladium center of π-allylpalladium intermediate **8** affords the Pd^0 intermediate **9** and regenerates the Cu$^{\mathrm{I}}$ species. Dissociation of product **4** from **9** regenerates the Pd^0 active catalyst, which then undergoes oxidative addition with allylic epoxide **2** to form intermediate **8** for further reaction with **7**.

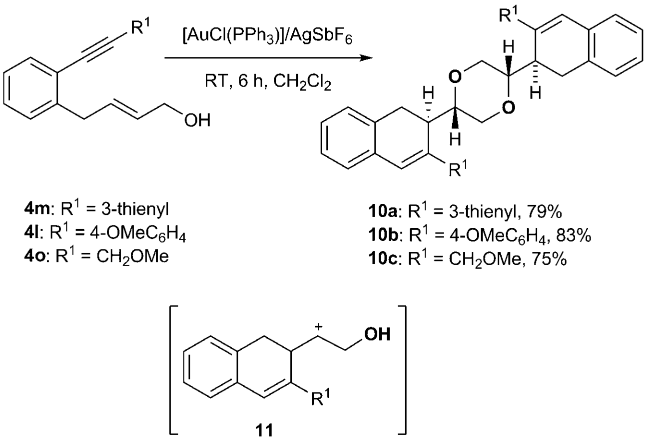


Scheme 1. Proposed mechanism of palladium- and copper-catalyzed three-component coupling reaction.

The proposed alkynylcupration of benzyne with cuprous acetylide **6** in the present dual-metal-catalyzed reaction is supported by: a) the formation of hydroalkynylation products as side products in the catalytic reactions; b) the facile hydroalkynylation of benzynes by terminal alkynes, catalyzed by the CuI/dppp or dppe system; c) the recently reported Cu$^{\mathrm{I}}$-catalyzed three-component coupling reaction involving arynes and terminal alkynes;[10] d) the known nucleophilic addition of copper reagents or organometallic reagents to palladium π-allyl complexes.[5,11]

For the three-component coupling reaction catalyzed by palladium complex alone, the mechanism is likely similar to that proposed for the reaction of benzynes, allyl chlorides and alkynylstannanes.[2d]

In the presence of [AuCl(PPh$_3$)] (2 mol%) and AgSbF$_6$ (6 mol%), in CH$_2$Cl$_2$ at room temperature for 6 h, product **4m** underwent cyclization to give substituted 1,4-dioxane derivative **10a** in 79% yield in a highly regioselective manner (Scheme 2). The reaction occurs by the intramolecular 6-*endo*-dig cyclization of the enyne group in **4m**, to provide intermediate **11**, followed by dimerization of **11**.[7a,12] The structure of **10a** was confirmed by X-ray crystallographic studies. Under similar reaction conditions, **4l** and **4o** also underwent cyclization in a highly regioselective manner to give products **10b** and **c** in 83 and 75% yields, respectively. To our knowledge this cyclization is to date unprecedented in literature.[7a,12]



Scheme 2. Gold-catalyzed cyclization of **4**.

In summary, we have demonstrated a cooperative palladium- and copper-catalyzed atom-economical three-component coupling of benzynes with allylic epoxides and terminal alkynes. Although, the three-component reaction also proceeds in the presence of the palladium complex alone without Cu$^{\mathrm{I}}$, the dual-metal catalyst system greatly enhances the regioselectivity of the reaction. Extension of this three-component reaction to other carbon–carbon π-components and detailed mechanistic studies of the catalytic reaction are in progress.

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Keywords: arynes · copper · cross-coupling · cyclization · palladium

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