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

Sivakolundu Bhuvaneswari, Masilamani Jeganmohan and Chien-Hong Cheng*

Received (in Cambridge, UK) 3rd June 2008, Accepted 10th July 2008 First published as an Advance Article on the web 1st September 2008 DOI: 10.1039/b809409h

The three-component coupling of benzynes with terminal alkynes and activated alkenes in the presence of CuI, PCy₃ and CsF in a 1 : 1 mixture of CH₃CN 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.¹⁻⁹ 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.¹ Chatani et al. reported a palladium-catalyzed carbocyclization of arynes with allylic halides and CO.² We reported a palladium-catalyzed three-component coupling of benzynes with allylic halides or acetates and organometallic reagents³ and also a carbocyclization of arynes with aromatic iodides and bicyclic alkenes.⁴ Larock's group described a palladium catalyzed carbocyclization of arynes with aromatic iodides and alkynes.⁵ Greaney and co-workers showed three-component Heck type coupling of arynes with organic halides and alkenes.⁶ Very recently, Zhang and co-workers observed a copper-catalyzed three-component coupling of benzynes with terminal alkynes and allylic halides.⁷

Recently, we demonstrated a nickel-catalyzed threecomponent coupling of arynes with activated alkenes and organoboronic acids.⁸ In the reaction, alkenyl and aromatic boronic acids worked very well, but alkynylmetal reagents such as alkynyltin was not active as an organometallic regent 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 alkynylation reagents, we tested the reaction with various alkynylmetal reagents. In the presence of catalytic amounts of CuI, Ni(COD)₂ and PCy₃ (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 benzynes 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%), PCy₃ (2 mol%) and CsF (3.0 equiv.) in a 1 : 1 (v/v) ratio of THF and CH₃CN 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-alkynylphenylcuprous 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 PPh₃, PCy₃, P(n-Bu₃), P(o-tolyl)₃, P(o-anisyl)₃, P(p-anisyl)₃, P(2-furyl)₃, 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 CH₃CN at 50 °C for 5 h. Among them, highly electron-rich and sterically hindered PCy3 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 PCy₃ and CuI, 2:1, 3:1,2:5 and 1:5 were tested. No side product was observed when the ratio is 1 : 5 (PCy₃, 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 CH₃CN alone, product **4a** was produced in 55% yield along with side product **5a** in 45% yield. In the 1 : 1 binary solvent systems of CH₃CN with THF, CH₂Cl₂, toluene or DME, the CH₃CN–THF and CH₃CN–CH₂Cl₂ 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%), PCy₃ (2 mol%) in a mixture of CH₃CN 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

Department of Chemistry, National Tsing Hua University, Hsinchu, 30013, Taiwan. E-mail: chcheng@mx.nthu.edu.tw; Fax: 886-3-5724698; Tel: 886-3-5721454

 $[\]dagger$ Electronic supplementary information (ESI) available: General experimental procedure, spectral data (¹H, ¹³C NMR and HRMS) and copies of ¹H and ¹³C NMR spectra of all compounds. See DOI: 10.1039/b809409h





^{*a*} 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%), PCy₃ (2 mol%), CsF (3.0 mmol) and CH₃CN–THF (1 : 1) at 50 °C for 5 h. ^{*b*}Isolated yields; yield in the parenthesis was determined by ¹H NMR using mesitylene as an internal standard. ^{*c*}Reaction was carried out using CuI (5 mol%), PCy₃ (10 mol%) and K₂CO₃ (1.5 mmol). ^{*d*}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 regio-isomeric 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 **1b** with **2a** and **3a** was examined in the presence of

CuI 5 mol%), PCy₃ (10 mol%) and various inorganic bases such as Li₂CO₃, Na₂CO₃, K₂CO₃ and Cs₂CO₃ in a 1 : 1 ratio of CH₂Cl₂ and CH₃CN at 50 °C for 5 h. Among them, K₂CO₃

Table 2Results of the three-component coupling of arynes 1a-b with
various terminal alkynes 2 and activated alkenes 3^a



^{*a*} 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%), PCy₃ (10 mol%), CsF (2.5 mmol), K₂CO₃ (1.5 mmol) and CH₃CN–CH₂Cl₂ (1 : 1) at 50 °C for 5 h. ^{*b*} Isolated yields; yields in parenthesis were determined by ¹H NMR using mesitylene as an internal standard. ^{*c*} The direct addition of terminal alkyne to benzyne was observed. In these reactions, 3.0 mmol of activated alkene and 2.5 mmol of K₂CO₃ were used. For entries 11 and 12, the catalytic reaction was carried out at 70 °C for 5 h. ^{*d*} 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**).⁷ 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.¹⁰ 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-decayne (**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(1) species in the presence of CsF (or K₂CO₃) gives copper acetylide **6**. Alkynylcupration of benzyne¹¹ 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 HCO₃⁻.

In conclusion, we have developed a copper(1)-catalyzed threecomponent 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 coppercatalyzed 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 π -components and organometallic reagents and detailed mechanistic investigation are in progress.

We thank the National Science Council of Republic of China (NSC-96-2113-M-007-020-MY3) for support of this research.

Notes and references

- (a) E. Yoshikawa, K. V. Radhakrishnan and Y. Yamamoto, J. Am. Chem. Soc., 2000, 122, 7280; (b) E. Yoshikawa, K. V. Radhakrishnan and Y. Yamamoto, *Tetrahedron Lett.*, 2000, 41, 729.
- 2 N. Chatani, A. Kamitani, M. Oshita, Y. Fukumoto and S. Murai, J. Am. Chem. Soc., 2001, 123, 12686.
- 3 (a) M. Jeganmohan and C.-H. Cheng, Org. Lett., 2004, 6, 2821; (b)
 M. Jeganmohan and C.-H. Cheng, Synthesis, 2005, 5, 1693; (c) T.
 T. Jayanth, M. Jeganmohan and C.-H. Cheng, Org. Lett., 2005, 7, 2921; (d) S. Bhuvaneswari, M. Jeganmohan and C.-H. Cheng, Chem. Commun., 2008, 2158.
- 4 S. Bhuvaneswari, M. Jeganmohan and C.-H. Cheng, *Org. Lett.*, 2006, 8, 5581.
- 5 Z. Liu and R. C. Larock, Angew. Chem., Int. Ed., 2007, 46, 2535.
- 6 (a) J. L. Henderson, A. S. Edwards and M. F. Greaney, J. Am. Chem. Soc., 2006, **128**, 7426; (b) J. L. Henderson, A. S. Edwards and M. F. Greaney, Org. Lett., 2007, **9**, 5589.
- 7 While preparing the manuscript, a report of copper-catalyzed three-component coupling of benzynes with terminal alkynes and allylic halides was appeared in the literature. In the reaction, K₂CO₃ was used to suppress the direct addition of terminal alkyne to benzyne. See: C. Xie, L. Liu, Y. Zhang and P. Xu, *Org. Lett.*, 2008, **10**, 2393.
- 8 T. T. Jayanth and C.-H. Cheng, Angew. Chem., Int. Ed., 2007, 46, 5927.
- 9 Selected literature references for transition metal-catalyzed aryne-involving reactions: [2+2+2] Co-cylotrimerization reactions: (a) E. Guitian, D. Perez and D. Pena, *Top. Organomet. Chem.*, 2005, **14**, 109; (b) T. T. Jayanth, M. Jeganmohan and C.-H. Cheng, J. Org. Chem., 2004, **69**, 8445; (c) J.-C. Hsieh, D. K. Rayabarapu and C.-H. Cheng, Chem. Commun., 2004, 532; (d) J.-C. Hsieh and C.-H. Cheng, Chem. Commun., 2005, 2459. Bismetallation of arynes: (e) H. Yoshida, J. Ikadai, M. Shudo, J. Ohshita and A. Kunai, J. Am. Chem. Soc., 2003, **125**, 6638; (f) H. Yoshida, K. Tanino, J. Ohshita and A. Kunai, Angew. Chem., Int. Ed., 2004, **43**, 5052. Carbocyclization reaction: (g) T. T. Jayanth and C.-H. Cheng, Chem. Commun., 2006, 894.
- 10 A. B. Dounay and L. E. Overman, Chem. Rev., 2003, 103, 2945.
- 11 Benzyne generation: Y. Himeshima, T. Sonoda and H. Kobayashi, *Chem. Lett.*, 1983, 1211.