

Copper-Catalyzed 2:1 Coupling Reaction of Arynes with Alkynes

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ABSTRACT



A formal insertion reaction of two molar amounts of arynes into a C–H bond of terminal alkynes is efficaciously catalyzed by copper(I) chloride, giving 2-alkynylbiaryls in one step.

Transition-metal-catalyzed transformations of arynes have recently received much attention as an efficient method for constructing benzo-annulated structures or multisubstituted arenes that are otherwise difficult to be synthesized.¹ Since the pioneering work on the transformations, that is, palladium-catalyzed trimerization of arynes, was disclosed by Peña,² most of the effort has been hitherto devoted to developing catalysis of palladium or nickel complexes.³ During our ongoing studies on element–element σ -bond addition reactions^{4,5} and three-component coupling⁶ utilizing highly electrophilic character of arynes, we envisaged that copper acetylides of sufficient nucleophilicity, being readily producible from terminal alkynes and a catalytic amount of

copper(I) salts, should be suitable reagents for capturing arynes, which leads to new catalytic transformations for constructing aromatic compounds and opens up copper catalysis in aryne chemistry.^{7,8} We report herein that arynes can be coupled with alkynes by the use of a copper(I) salt in a totally different manner from those observed in the palladium- or nickel-catalyzed reactions,⁹ giving diverse

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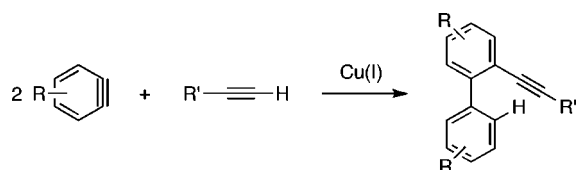
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(7) Copper-catalyzed reactions of arynes have recently been reported. (a) Xie, C.; Liu, L.; Zhang, Y.; Xu, P. *Org. Lett.* **2008**, 10, 2393. (b) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2008**, 5013.

(8) Palladium-catalyzed three-component coupling of arynes, alkynes, and allylic electrophiles using cuprous iodide has recently been reported: Bhuvaneswari, S.; Jeganmohan, M.; Yang, M.-C.; Cheng, C.-H. *Chem. Commun.* **2008**, 2158.

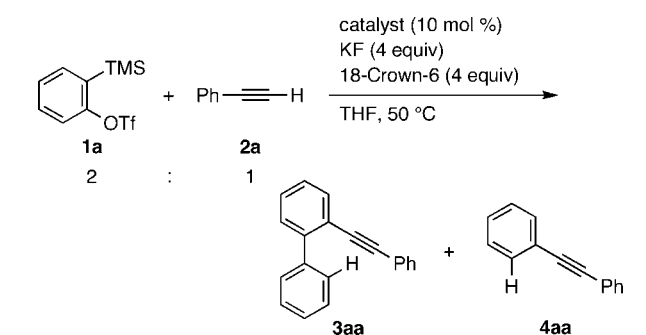
Scheme 1. Copper-Catalyzed 2:1 Coupling of Arynes with Alkynes



2-alkynylbiaryls straightforwardly (Scheme 1). Recently, a similar coupling reaction promoted by a Au(I)–Cu(I) co-catalytic system has been reported.¹⁰

Initially, a reaction of benzyne, generated in situ from **1a**¹¹ and a fluoride ion, with phenylacetylene (**2a**) was examined with various copper catalysts (Table 1). By use of copper(I) chloride, two molar amounts of benzyne were found to be formally inserted into a C(sp)–H bond of **2a** to afford a 64% yield of 2-(phenylethynyl)biphenyl (**3aa**) containing a small portion of diphenylacetylene **4aa** (entry 1). Increasing the amount of **1a** improved the selectivity for the formation of

Table 1. Reaction of Benzyne with Phenylacetylene^a

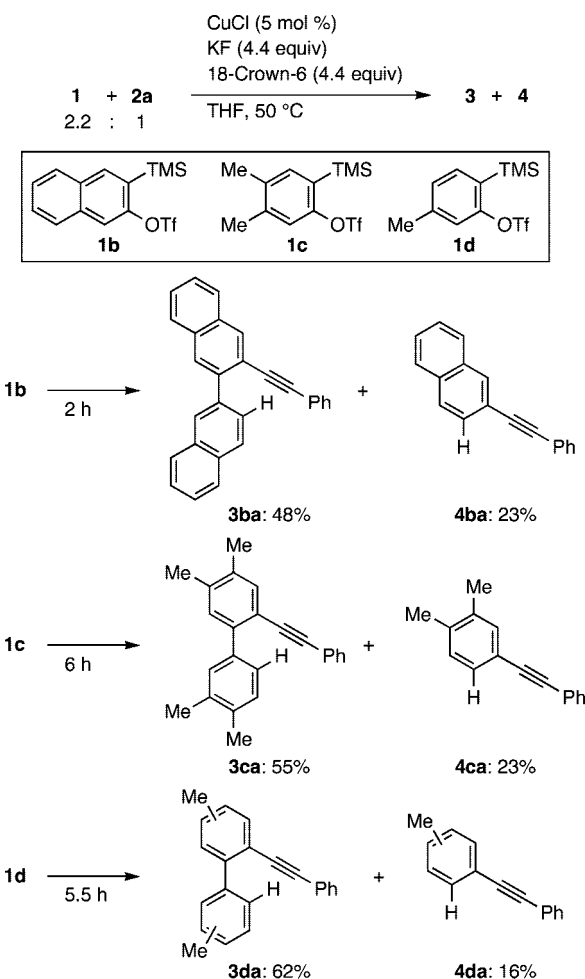


entry	catalyst	time (h)	3aa (%) ^b	4aa (%) ^b
1	CuCl	4	64	4
2 ^c	CuCl	4	77	trace
3	CuBr	1	37	20
4	CuI	1	24	54
5	(Ph ₃ P) ₃ CuCl	1	34	28
6	Cu(OAc) ₂	3	24	14
7	none	5	—	—
8	AgCl	15	—	—
9	NiCl ₂	27	—	—

^a The reaction was carried out in THF (0.5 mL) at 50 °C using **1a** (0.20 mmol), **2a** (0.10 mmol), KF (0.40 mmol), and 18-crown-6 (0.40 mmol) in the presence of a catalyst (0.01 mmol). ^b Isolated yield based on **2a**. ^c **1a** = 0.44 mmol, **2a** = 0.20 mmol, KF = 0.88 mmol, 18-crown-6 = 0.88 mmol, CuCl = 0.01 mmol, THF = 2 mL.

3aa (77% yield), and only a trace of **4aa** was detected (entry 2). Other copper salts including CuBr, CuI, (Ph₃P)₃CuCl, and Cu(OAc)₂ also exhibited catalysis toward the present aryne–alkyne coupling, albeit at the cost of product selectivity (entries 3–6). In marked contrast, none of the coupling products were produced in the absence of a copper catalyst

Scheme 2. Copper-Catalyzed 2:1 Coupling of Substituted Arynes



(entry 7), and the reaction using AgCl or NiCl₂ resulted in the formation of a complex mixture (entries 8 and 9), which demonstrates the vital role of the copper catalysis in the 2:1 coupling reaction.

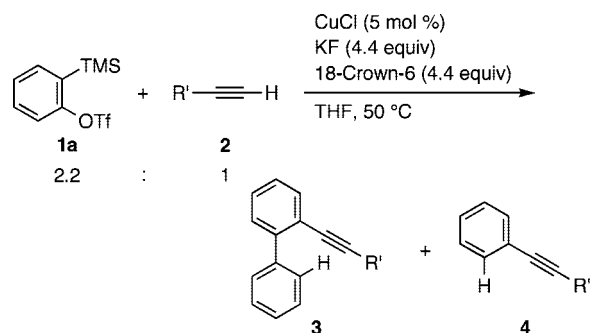
We next conducted the reaction of various alkynes using CuCl as a catalyst (Table 2). Aryl alkynes bearing a *n*-butyl (**2b**), fluoro (**2c**), or methyl (**2d**) substituent smoothly reacted with benzyne in a manner similar to **2a**, producing the respective 2-alkynylbiphenyls (**3ab**–**3ad**) in 68%, 54%, or 53% yield (entries 1–4). Preferential formation of 2:1 coupling products was also observed with 1-naphthylacetylene (**2e**), 2-naphthylacetylene (**2f**), or dimethoxypheny-

(9) Cocyclization of arynes with alkynes generally occurs by use of a palladium or nickel catalyst. For examples, see: (a) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827. (b) Radhakrishnan, K. V.; Yoshikawa, E.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 7533. (c) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *Synlett* **2000**, 1061. (d) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **2000**, *65*, 6944. (e) Hsieh, J.-C.; Cheng, C.-H. *Chem. Commun.* **2005**, 2459. (f) Caeiro, J.; Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Adv. Synth. Catal.* **2006**, *348*, 2466. (g) Sato, Y.; Tamura, T.; Kinbara, A.; Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 647. (h) Hsieh, J.-C.; Cheng, C.-H. *Chem. Commun.* **2008**, 2992.

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Table 2. Copper-Catalyzed 2:1 Coupling of Benzyne with Alkynes^a



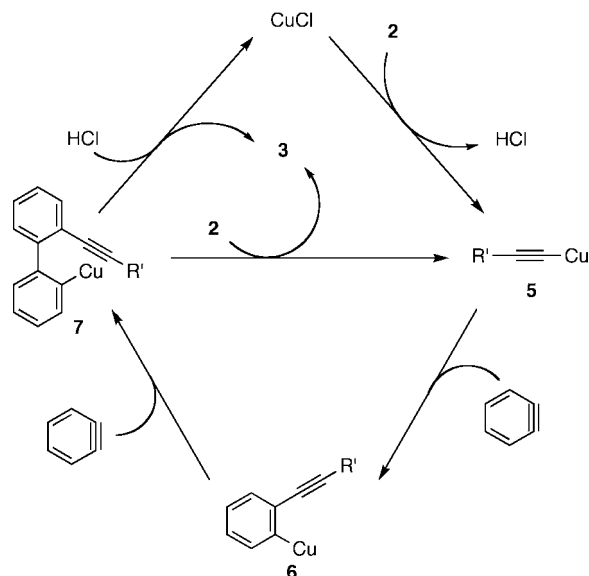
entry	R'	time (h)	3 (%) ^b	4 (%) ^b
1	Ph	2a	4	77
2		2b	2.5	68
3		2c	5	54
4		2d	4	53
5		2e	2	60
6		2f	3	52
7		2g	2.5	57
8		2h	2.5	63
9	<i>n</i> -Hex	2i	2	55
10	<i>t</i> -Bu	2j	2	32
11	MeOCH ₂	2k	5	40

^a The reaction was carried out in THF (2 mL) at 50 °C using **1a** (0.44 mmol), **2** (0.20 mmol), KF (0.88 mmol), and 18-crown-6 (0.88 mmol) in the presence of CuCl (0.01 mmol). ^b Isolated yield based on **2**.

lacetylene (**2g**), and moreover, a 63% yield of **3ah** was generated in the reaction of enyne **2h** (entries 5–8). In addition, aliphatic alkynes (**2i** or **2j**) or methyl propargyl ether (**2k**) were found to be convertible into 2:1 coupling products **3ai–3ak** as well (entries 9–11).

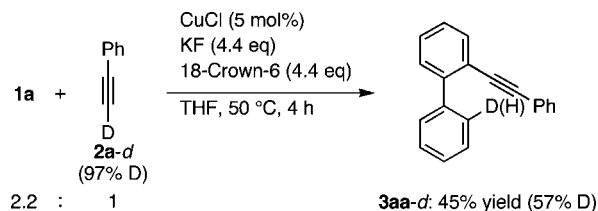
Multisubstituted biaryl frameworks could be constructed by the reaction of substituted arynes as shown in Scheme 2. Thus, 2,3-naphthalene (from **1b**) or 4,5-dimethylbenzyne (from **1c**) underwent the reaction with **2a** to provide 2,2'-binaphthyl **3ba** or tetramethylbiphenyl **3ca** in 48% or 55% yield, respectively. The reaction of an unsymmetrical aryne such as 4-methylbenzyne (from **1d**) also took place smoothly, giving a mixture of four regioisomers in an almost equal

Scheme 3. Plausible Catalytic Cycle



ratio, which confirms that the present reaction proceeds through an aryne intermediate.

Scheme 4. Reaction Using Phenylacetylene-*d*



A plausible catalytic cycle for the present 2:1 coupling reaction is depicted in Scheme 3. First a copper acetylide (**5**), generated from a terminal alkyne and CuCl, attacks an aryne to give an aryl copper species (**6**).¹² Subsequent nucleophilic attack of **6** to a second aryne produces biaryl copper **7**, which then reacts with an alkyne (or HCl) to furnish product **3** with regeneration of **5** (or CuCl). In all cases, neither 3:1 coupling products nor higher oligomers were produced. At present, the reason why the 2:1 coupling products form preferentially is unclear.

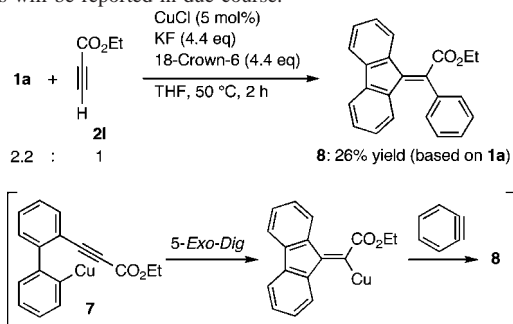
To gain insight into a catalytic cycle, we also performed the reaction using a labeled alkyne (**2a-d**) (Scheme 4) and observed that deuterium-incorporated biphenyl (**3aa-d**) was produced in 45% yield (deuterium incorporation ratio = 57%), which supports a hydrogen-transfer process between an alkyne and biaryl copper **7** (see Scheme 3).¹³ The

(12) Nucleophilic attack of organocuprates to arynes has been disclosed. See: Meyers, A. I.; Pansegrau, P. D. *J. Chem. Soc., Chem. Commun.* **1985**, 690.

moderate incorporation ratio may be ascribable to fluoride ion-induced D–H exchange between **2a-d** and contaminated water.

In conclusion, we have demonstrated that a copper(I) salt exhibits the characteristic catalysis on a coupling reaction

(13) A preliminary experiment revealed that the reaction using ethyl propiolate (**2l**) gave ethyl 2-(9*H*-fluoren-9-ylidene)-2-phenylacetate (**8**) as the major product, which should arise from 5-*Exo-Dig* cyclization of intermediate **7**. This result strongly supports the intermediacy of **7** in the present 2:1 coupling and demonstrates that the intramolecular cyclization of **7** takes place with an electron-deficient alkyne. Thus, it would be reasonable to assume that protonation of **7** is much faster than the intramolecular cyclization in the cases of the reactions using electron-rich alkynes (**2a–2k**). Detailed results of the reaction using electron-deficient alkynes will be reported in due course.



of arynes with alkynes, which is completely distinct from that of nickel or palladium complexes. Upon the basis of the present 2:1 coupling reaction, diverse 2-alkynylbiaryls of great synthetic usefulness¹⁴ are synthesized straightforwardly via formal insertion of two molar amounts of arynes into a C(sp)–H bond of alkynes. Further studies on copper-catalyzed transformations of arynes as well as on the detailed catalytic cycle are in progress in our laboratory.

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Supporting Information Available: Experimental procedure and characterization of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) Various carbocyclic compounds can be readily synthesized by intramolecular cyclizations of 2-alkynylbiaryls. For example, see: (a) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 4578. (b) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Org. Chem.* **1998**, *63*, 1676. (c) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264. (d) Fürstner, A.; Mamane, V. *Chem. Commun.* **2003**, 2112. (e) Mamane, V.; Hannen, P.; Fürstner, A. *Chem.–Eur. J.* **2004**, *10*, 4556. (f) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677. (g) Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511. (h) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636.