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

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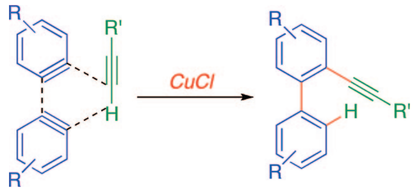
ABSTRACT



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 coupling[6] 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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[1] For reviews, see: (a) Pellissier, H.; Santelli, M. *Tetrahedon* **2003**, *59*, 701. (b) Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 4093.

[2] Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2659.

[3] For recent examples, see: (a) Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 15716. (b) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426. (c) Quintana, I.; Boersma, A. J.; Peña, D.; Pérez, D.; Guitián, E. *Org. Lett.* **2006**, *8*, 3347. (d) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5581. (e) Jayanth, T. T.; Cheng, C.-H. *Chem. Commun.* **2006**, 894. (f) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 223. (g) Liu, Z.; Larock, R. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2535. (h) Jayanth, T. T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5921. (i) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 5589.

[4] For a review, see: Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579.

[5] (a) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247. (b) Yoshida, H.; Terayama, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2004**, 1980. (c) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292. (d) Yoshida, H.; Minabe, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3454. (e) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729. (f) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Lett.* **2005**, *34*, 1538. (g) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 1505. (h) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405.

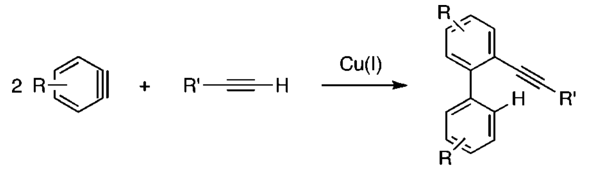
[6] (a) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3935. (b) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2004**, *45*, 8659. (c) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040. (d) Yoshida, H.; Fukushima, H.; Morishita, T.; Ohshita, J.; Kunai, A. *Tetrahedron* **2007**, *63*, 4793. (e) Yoshida, H.; Morishita, T.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2007**, *9*, 3367. (f) Morishita, T.; Fukushima, H.; Yoshida, H.; Ohshita, J.; Kunai, A. *J. Org. Chem.* **2008**, *73*, 5452.

[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.

10.1021/ol802609j CCC: $40.75

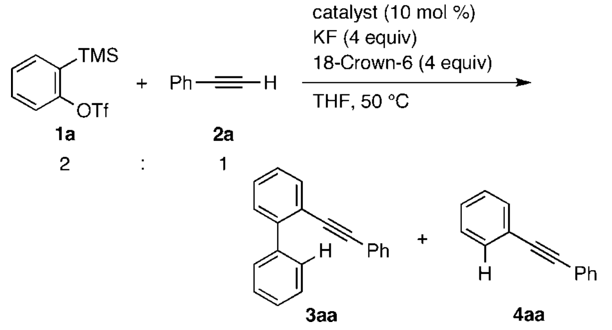
Scheme 1. Copper-Catalyzed 2:1 Coupling of Arynes with Alkynes



2-alkynylbiaryls straightforwardly (Scheme 1). Recently, a similar coupling reaction promoted by a Au(I)−Cu(I) cocatalytic 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 **3aa** (77% yield), and only a trace of **4aa** was detected (entry 2). Other copper salts including CuBr, CuI, $(Ph_3P)_3CuCl$, 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 (entry 7), and the reaction using AgCl or $NiCl_2$ 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.

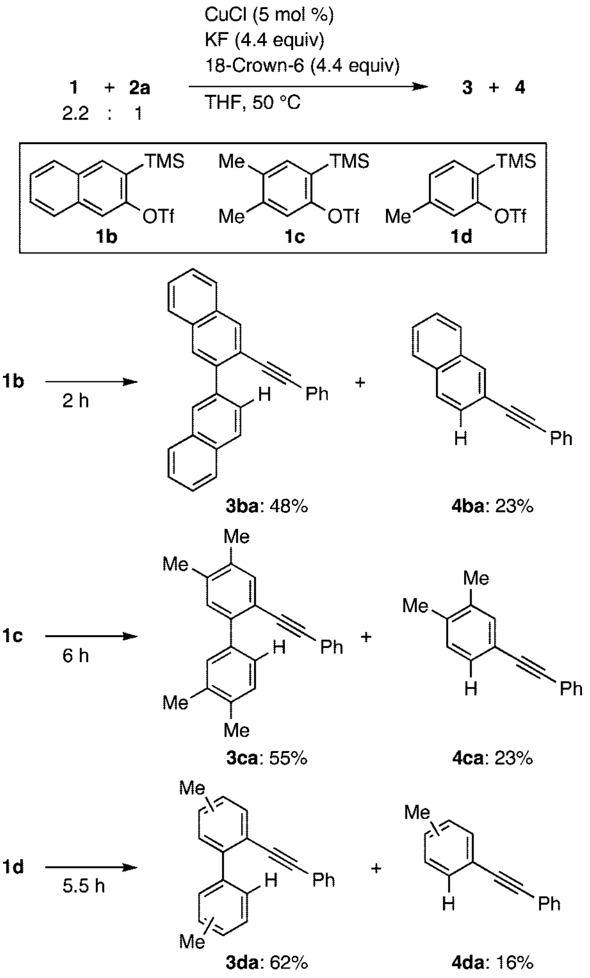
Table 1. Reaction of Benzyne with Phenylacetylene[a]



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	$(Ph_3P)_3CuCl$	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.

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



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-

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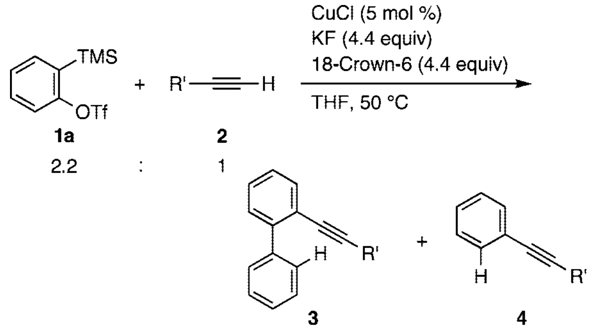
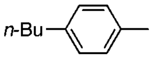
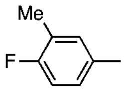
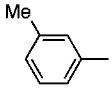
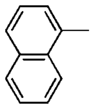
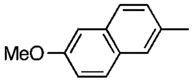
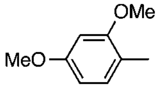
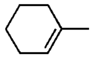
(9) Cocyclization of arynes with alkynes generally occurs by use of a palladium or nickel catalyst. For examples, see: (a) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827. (b) Radhakrishnan, K. V.; Yoshikawa, E.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 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.

(10) Xie, C.; Zhang, Y.; Yang, Y. *Chem. Commun.* **2008**, 4810.

(11) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

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



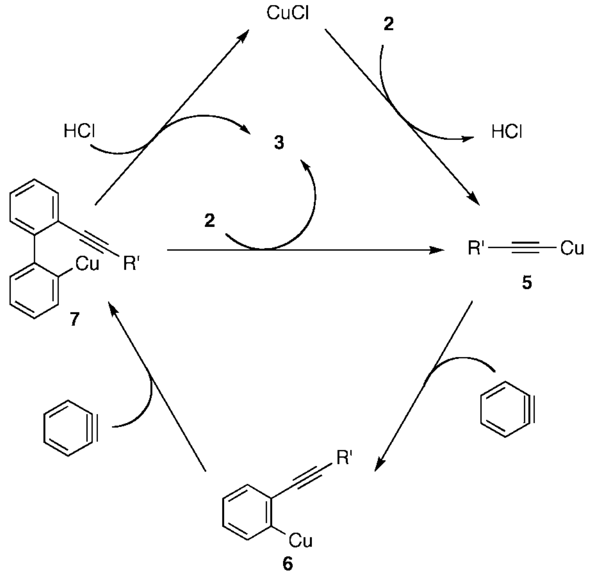
entry	R'		time (h)	**3** (%)[b]		**4** (%)[b]
1	Ph	**2a**	4	77	**3aa**	trace
2		**2b**	2.5	68	**3ab**	11
3		**2c**	5	54	**3ac**	–
4		**2d**	4	53	**3ad**	–
5		**2e**	2	60	**3ae**	13
6		**2f**	3	52	**3af**	7
7		**2g**	2.5	57	**3ag**	15
8		**2h**	2.5	63	**3ah**	10
9	*n*-Hex	**2i**	2	55	**3ai**	38
10	*t*-Bu	**2j**	2	32	**3aj**	–
11	$MeOCH_2$	**2k**	5	40	**3ak**	–

[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**.

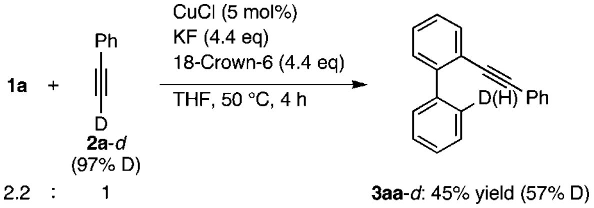
lacetylene (**2g**), and moreover, a 63% yield of **3ah** was generated in the reaction of enyne **2h** (entries 5−8). In addition, aliphatic alkynes (**2i** or **2j**) or methyl propargyl ether (**2k**) were found to be convertible into 2:1 coupling products **3ai**−**3ak** as well (entries 9−11).

Multisubstituted biaryl frameworks could be constructed by the reaction of substituted arynes as shown in Scheme 2. Thus, 2,3-naphthalyne (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 ratio, which confirms that the present reaction proceeds through an aryne intermediate.

Scheme 3. Plausible Catalytic Cycle



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

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(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 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 usefulness[14] 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.

Acknowledgment. We thank Central Glass Co Ltd. for a generous gift of trifluoromethanesulfonic anhydride.

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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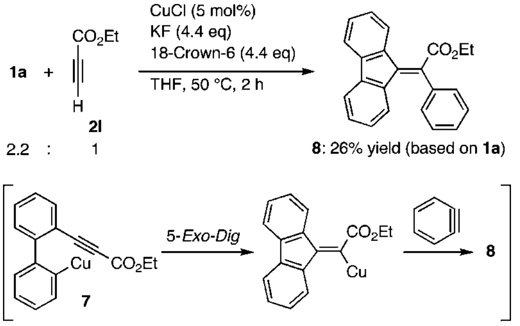
(13) A preliminary experiment revealed that the reaction using ethyl propiolate (**2l**) gave ethyl 2-(9*H*-fluoren-9-ylidene)-2-phenylacetate (**8**) as the major product, which should arise from 5-*Exo-Dig* cyclization of intermediate **7**. This result strongly supports the intermediacy of **7** in 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.



(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.