Paper in Celebration for the 2010 Nobel Prize in Chemistry

doi:10.1246/cl.2011.972

Copper-catalyzed Sila-Sonogashira–Hagihara Cross-coupling Reactions of Alkynylsilanes with Aryl Iodides under Palladium-free Conditions

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An efficient and inexpensive catalytic system using a readily available CuCl/PPh_3 combination for the catalytic cross-coupling reactions of alkynylsilanes with a variety of aryl iodides affords unsymmetrical diarylethynes in good to excellent yields.

Aryl alkynes and related conjugated enynes are important intermediates in pharmaceutical chemistry, natural products, and materials science.[1] These compounds can conveniently be synthesized from terminal alkynes and aryl or vinyl halides or triflates by the Sonogashira–Hagihara cross-coupling reaction between sp^2 and sp carbon centers, employing palladium catalysts in conjunction with a copper(I) salt.[2,3] A decade before the discovery of the Sonogashira–Hagihara cross-coupling, Stephens and Castro reported stoichiometric couplings between aryl iodides and copper acetylides, in the absence of palladium, in refluxing pyridine under a nitrogen atmosphere.[4] Although application of the Stephens–Castro reaction became far less common with the advent of the usually more efficient Pd/Cu-catalyzed Sonogashira–Hagihara coupling, recently the palladium-free Sonogashira–Hagihara coupling (copper-catalyzed Stephens–Castro coupling; eq 1) of alkynes with aryl halides has gained increasing attention due to the expense of palladium.[5]

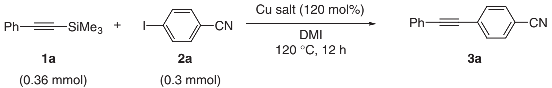
$$\mathrm{R^1{-}{\equiv}{-}H} \; + \; \mathrm{X{-}R^2} \xrightarrow[\substack{\text{or} \\ \text{catalytic Stephens-Castro coupling: [Cu}^{\text{I}}]}]{\text{Sonogashira-Hagihara coupling: [Pd}^0/\text{Cu}^{\text{I}}]} \mathrm{R^1{-}{\equiv}{-}R^2} \qquad (1)$$

Developments in catalytic Stephens–Castro coupling reactions have involved copper complexes with various ligands[6–16] (for example, a recently reported bis(μ-iodo)bis[(−)-sparteine]-dicopper(I) complex[17]) as well as microwave-assisted[18] and copper nanoparticle-catalyzed variants.[19]

The terminal acetylene component of Sonogashira–Hagihara cross-coupling is often ultimately derived from trimethylsilylethyne, and thus silyl-group deprotection to afford the terminal alkyne coupling partner often precedes the cross-coupling step. Methods which allow a direct coupling of the alkynylsilanes are thus desirable as they enhance the overall efficiency of the process. In continuation of our studies on a direct activation of a carbon–silicon bond in alkynylsilanes by a copper(I) salt,[20] we herein report copper-catalyzed cross-coupling reaction of alkynylsilanes with aryl iodides in DMI (*N*,*N*′-dimethylimidazolidinone) under palladium-free conditions.

Initially, the coupling reaction between trimethyl(phenylethynyl)silane (**1a**) and 4-iodobenzonitrile (**2a**) was chosen as a model reaction for the discovery of copper species which promote stoichiometric Stephens–Castro-type reaction. As summarized in Table 1, copper(I) halides, such as CuCl, CuBr, and CuI gave the cross-coupled product **3a** in up to 22% yield (Entries 1–3). Copper(I) oxide and copper(I) or copper(II) acetate were found to afford the undesired homocoupled product, 1,4-diphenyl-1,3-butadiyne (**4**) (Table 1, Entries 4–6). Gratifyingly, when the copper salt was changed to copper(I) thiophene-2-carboxylate (CuTC),[21] **3a** was obtained quantitatively, albeit contaminated with **4** (Table 1, Entry 7). In contrast, the alternate carboxylates, copper(I) pyridine-2-carboxylate (CuPC) and copper(I) furan-2-carboxylate (CuFC), did not promote coupling (Table 1, Entries 8 and 9).

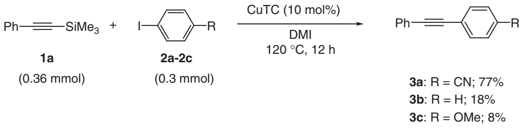
Table 1. A stoichiometric reaction of trimethyl(phenylethynyl)silane (**1a**) with 4-iodobenzonitrile (**2a**)[a]



Entry	Cu salt	Yield/%[b] **3a** (cross)	Yield/%[c] **4** (homo)
1	CuCl	0	0
2	CuBr	22	0
3	CuI	8	0
4	Cu_2O	5	5
5	CuOAc	18	16
6	$Cu(OAc)_2$	20	38
7	**CuTC**	**>99**	**8**
8	CuPC	4	0
9	CuFC	0	0

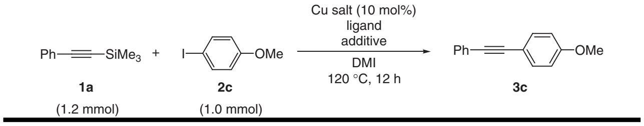
[a] The reactions were carried out with **1a** (0.36 mmol) and **2a** (0.30 mmol), a copper compound (120 mol %) in 0.15 mL (2.0 M) of DMI at 120 °C for 12 h. [b] GC yield based on an aryl iodide **2a**. [c] GC yield based on an alkynylsilane **1a**.

In order to investigate catalytic use of CuTC in this coupling, various aryl iodides **2a**–**2c** were subjected to the reaction conditions of Table 1, Entry 7. Although the desired cross-coupling was ultimately achieved with 10 mol % of CuTC for **2a** which bears an electron-withdrawing group, neutral or electron-donating substituents on the benzene ring retarded the reaction (eq 2).



We next screened conditions for the reaction of **1a** with less reactive 4-iodoanisole (**2c**) in the presence of 10 mol % of a copper salt in DMI at 120 °C for 12 h. As shown in Table 2, Entry 2, the yield of **3c** with a combination of CuCl with NaTC, which presumably generates CuTC in situ, gave a comparable result to that with stoichiometric CuTC. We thus employed CuCl as a copper catalyst hereafter owing to its low cost and ease of

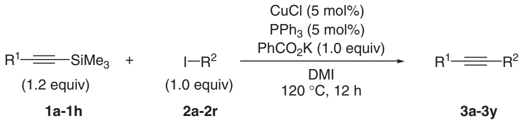
Table 2. Catalytic reaction of trimethyl(phenylethynyl)silane (**1a**) with 4-iodoanisole (**2c**)[a]



Entry	Cu salt	Ligand	Additive	Yield/%[b]
1	CuTC	none	none	8
2	CuCl	none	NaTC	8
3		P*n*-Bu$_3$ (10 mol %)		29
4		PCy$_3$ (10 mol %)		5
5		P*t*-Bu$_3$ (10 mol %)		<1
6		PPh$_3$ (10 mol %)		64
7		PPh$_3$ (20 mol %)		21
8		PPh$_3$ (30 mol %)		6
9		PPh$_3$ (10 mol %)	AcONa	84
10			AcOK	>98
11[c]			AcOK	63
12			PhCO$_2$K	95
13[c]			**PhCO$_2$K**	**>98 (89)**
14			PhCO$_2$Na	67
15			PhCO$_2$Li	32

[a] The reactions were carried out with **1a** (1.2 mmol) and **2c** (1.0 mmol), a copper salt (10 mol %), additive (1.0 mmol) in 0.5 mL (2.0 M) of DMI at 120 °C, unless otherwise stated. [b] GC yield based on an aryl iodide **2c**. An isolated yield is shown in parenthesis. [c] 5 mol % of CuCl and PPh$_3$ was used.

Table 3. Cu-catalyzed cross-coupling reaction of alkynylsilanes **1** with aryl iodides **2**[a]



Entry	Alkynylsilane **1**, R^1 =	Aryl Halide **2**, R^2 =	Product, **3**	Yield /%[b]
1	C$_6$H$_5$- (**1a**)	4-NC-C$_6$H$_4$ (**2a**)	**3a**	88
2[c]	**1a**	C$_6$H$_5$ (**2b**)	**3b**	91
3	**1a**	4-MeO-C$_6$H$_4$ (**2c**)	**3c**	89
4	**1a**	4-Me-C$_6$H$_4$ (**2d**)	**3d**	97
5	**1a**	4-MeCO-C$_6$H$_4$ (**2e**)	**3e**	85
6	**1a**	4-O$_2$N-C$_6$H$_4$ (**2f**)	**3f**	76
7	**1a**	4-Cl-C$_6$H$_4$ (**2g**)	**3g**	79
8	**1a**	4-EtO$_2$C-C$_6$H$_4$ (**2h**)	**3h**	78
9[c]	**1a**	4-H$_2$N-C$_6$H$_4$ (**2i**)	**3i**	87
10	**1a**	4-Br-C$_6$H$_4$ (**2j**)	**3j**	91
11	**1a**	2-Br-C$_6$H$_4$ (**2k**)	**3k**	63
12[c]	**1a**	2-MeO-C$_6$H$_4$ (**2l**)	**3l**	64
13[c]	**1a**	2-Me-C$_6$H$_4$ (**2m**)	**3m**	69
14	**1a**	2-MeCO-C$_6$H$_4$ (**2n**)	**3n**	55
15[c]	**1a**	2,4,6-Me$_3$-C$_6$H$_2$ (**2o**)	**3o**	51
16	**1a**	2-H$_2$N-C$_6$H$_4$ (**2p**)	**3p**	44
17	**1a**	1-naphthyl (**2q**)	**3q**	92
18[d]	**1a**	2-pyridyl (**2r**)	**3r**	94
19	4-MeO-C$_6$H$_4$- (**1b**)	**2a**	**3s**	93
20	**1b**	**2d**	**3t**	80
21	**1b**	**2e**	**3u**	83
22	4-NC-C$_6$H$_4$ (**1c**)	**2c**	**3s**	97
23	4-MeCO-C$_6$H$_4$ (**1d**)	**2c**	**3u**	63
24	4-O$_2$N-C$_6$H$_4$ (**1e**)	**2c**	**3v**	80
25	4-CF$_3$-C$_6$H$_4$ (**1f**)	**2c**	**3w**	93
26	2-thienyl (**1g**)	**2a**	**3x**	80
27[c]	*n*-C$_6$H$_{13}$ (**1h**)	**2a**	**3y**	62

[a] Conditions: **1** (1.2 mmol), **2** (1.0 mmol), CuCl (5 mol %), PPh$_3$ (5 mol %), PhCO$_2$K (1.0 mmol), DMI (0.5 mL) unless otherwise stated. [b] Isolated yields based on aryl iodides **2**. [c] CuCl (10 mol %), PPh$_3$ (10 mol %), 24 h. [d] CuCl (10 mol %), PPh$_3$ (10 mol %).

handling. When 10 mol % of P*n*-Bu$_3$ was added to CuCl (Cu/P = 1/1), the cross-coupled product **3c** was obtained in 29% yield (Table 2, Entry 3). Although other phosphane ligands PCy$_3$ and P*t*-Bu$_3$ were examined as ligands, none of them were superior to PPh$_3$, which gave **3c** in 64% yield (Table 2, Entries 4 and 5 vs. Entry 6). The reaction was found to be very sensitive to the amount of the PPh$_3$ ligand added; a lower product yield was obtained when the PPh$_3$/Cu ratio was more than 2 (Table 2, Entries 6–8). After screening various carboxylate additives, it was discovered that PhCO$_2$K afforded a quantitative yield of **3c**, even when just 5 mol % of CuCl/PPh$_3$ was used as a catalyst (Table 2, Entries 9–15).[22] No reaction occurred in the absence of a copper catalyst.

Furthermore, analysis of the reaction mixture by ^{1}H NMR and GC-MS revealed no trace of homocoupled product **4**. Compared to the copper-mediated versions, the present copper-catalyzed protocols have significant advantages. First, because the formed alkynylcopper species can undergo oxidative homocoupling (Glaser coupling)[23] leading to lower yields of the desired cross-coupling products and in turn, complicating their purification, a gradually generated alkynylcopper species in the reaction mixture can be selectively transformed to the cross-coupled products.

Next, we were able to apply this new method to a broad range of targets, including aryl-, heteroaryl-, and alkyl-substituted alkynylsilanes **1a**–**1h** and various aryl iodides **2a**–**2r** substituted by electron-withdrawing and electron-donating groups, using 5 mol % of CuCl/PPh$_3$. The results obtained are presented in Table 3. This protocol is rather general in scope for reaction of 4-substituted aryl iodides with trimethyl(phenylethynyl)silane (**1a**), good to excellent yields of the cross-coupled products **3a**–**3i** (Entries 1–9) were obtained for systems featuring either electron-donating or electron-withdrawing groups at C-4. In a sharp contrast, aryl bromides did not react at all under these reaction conditions. Therefore, 4- and 2-bromoiodobenzenes reacted with **1a** to afford **3j** and **3k**, respectively, in which the bromides remain intact (Entries 10 and 11). Bulkier aryl iodides like 2-iodoanisole, 2-iodotoluene, 2-iodoacetophenone, and, 2,4,6-trimethyliodobenzene required longer reaction times and increased catalyst loadings to afford the cross-coupled products **3l**–**3o** in moderate yields (Entries 12–15). When 2-iodoaniline (**2p**) was reacted with **1a**, 2-(phenylethynyl)aniline (**3p**) was obtained in 44% yield rather than 2-phenylindole (<1%) (Entry 16). As demonstrated in Table 3, Entries 17–26, the present catalytic systems proved to accelerate the cross-coupling reactions to generate the desired products **3q**–**3x** in moderate to excellent yields. The reactions of aliphatic alkynylsilane **1h** proceeded slowly to afford the desired product **3y** albeit in 62% yield (Entry 27).

Concerning the mechanism, we can only present a working hypothesis for the palladium-free cross-coupling reactions. On the basis of our previous studies,[20g] it seems reasonable to propose copper chloride(I) as a catalytic species, with a triphenylphosphane ligand coordinating to copper giving a more soluble and/or active species. In the first step, transmetalation of alkynylsilanes **1** could generate an alkynylcopper species, which would react, by oxidative addition, with aryl iodides **2** to form -a four-coordinated copper(III) complex from which reductive elimination expels the cross-coupled product **3** to give copper iodide. We have already found that copper iodide is less effective for transmetalation of alkynylsilanes **1** than CuCl and CuOTf.[20d] The additive, potassium benzoate, might play dual roles: transforming relatively inactive CuI into more active CuOCOPh, while also trapping Me_3SiCl which would otherwise retard transmetalation from silicon to copper to generate the requisite organocopper species. However, it can be ruled out that the terminal alkynes were formed in the presence of potassium benzoate, because we confirmed that desilylation of **1** never occurred (<5%) in the presence of potassium benzoate and that the desilylated compound of **1a**, phenylethyne gave only a trace amount of cross-coupled product under the optimized conditions.

In summary, we have discovered conditions for the cross-coupling reactions of alkynylsilanes with aryl iodides using $CuCl/PPh_3$ as a catalyst. Since this novel catalytic system is tolerant, versatile, and significantly less expensive than "traditional" Pd/Cu-cocatalyzed Sonogashira–Hagihara cross-couplings, practical use should be found for the synthesis of unsymmetrical diarylethynes.[24] Efforts to clarify the reaction mechanism, to modify the reaction conditions, and to apply the reaction to the less reactive aryl bromides and chlorides are in progress.

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan. Y. N. is grateful to Chisso Petrochemical Corporation for generous donation of trimethylsilylacetylene to prepare **1**.

This paper is in celebration of the 2010 Nobel Prize awarded to Professors Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi.

References and Notes

1 a) L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133. b) J. Liu, J. W. Y. Lam, B. Z. Tang, *Chem. Rev.* **2009**, *109*, 5799.

2 a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467. b) Y. Tohda, K. Sonogashira, N. Hagihara, *Synthesis* **1977**, 777. c) K. Sonogashira, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. by E. Negishi, A. de Meijere, Wiley-Interscience, New York, **2002**, pp. 493–529.

3 For reviews on the Sonogashira–Hagihara reaction: a) E.-i. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979. b) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874. c) H. Doucet, J.-C. Hierso, *Angew. Chem., Int. Ed.* **2007**, *46*, 834.

4 a) C. E. Castro, R. D. Stephens, *J. Org. Chem.* **1963**, *28*, 2163. b) R. D. Stephens, C. E. Castro, *J. Org. Chem.* **1963**, *28*, 3313. c) C. E. Castro, E. J. Gaughan, D. C. Owsley, *J. Org. Chem.* **1966**, *31*, 4071.

5 For recent reviews for the Cu-catalyzed Sonogashira–Hagihara coupling: see, H. Plenio, *Angew. Chem., Int. Ed.* **2008**, *47*, 6954.

6 a) K. Okuro, M. Furuune, M. Enna, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 4716. b) J. T. Guan, G.-A. Yu, L. Chen, T. Q. Weng, J. J. Yuan, S. H. Liu, *Appl. Organomet. Chem.* **2009**, *23*, 75.

7 P. Saejueng, C. G. Bates, D. Venkataraman, *Synthesis* **2005**, 1706.

8 D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450.

9 J.-H. Li, J.-L. Li, D.-P. Wang, S.-F. Pi, Y.-X. Xie, M.-B. Zhang, X.-C. Hu, *J. Org. Chem.* **2007**, *72*, 2053.

10 J. Mao, J. Guo, S.-J. Ji, *J. Mol. Catal. A: Chem.* **2008**, *284*, 85.

11 F. Monnier, F. Turtaut, L. Duroure, M. Taillefer, *Org. Lett.* **2008**, *10*, 3203.

12 M. Wu, J. Mao, J. Guo, S. Ji, *Eur. J. Org. Chem.* **2008**, 4050.

13 K. G. Thakur, E. A. Jaseer, A. B. Naidu, G. Sekar, *Tetrahedron Lett.* **2009**, *50*, 2865.

14 H.-J. Chen, Z.-Y. Lin, M.-Y. Li, R.-J. Lian, Q.-W. Xue, J.-L. Chung, S.-C. Chen, Y.-J. Chen, *Tetrahedron* **2010**, *66*, 7755.

15 E. Zuidema, C. Bolm, *Chem.—Eur. J.* **2010**, *16*, 4181.

16 C.-H. Lin, Y.-J. Wang, C.-F. Lee, *Eur. J. Org. Chem.* **2010**, 4368.

17 S. Priyadarshini, P. J. A. Joseph, P. Srinivas, H. Maheswaran, M. L. Kantam, S. Bhargava, *Tetrahedron Lett.* **2011**, *52*, 1615.

18 a) H. He, Y.-J. Wu, *Tetrahedron Lett.* **2004**, *45*, 3237. b) E. Colacino, L. Daïch, J. Martinez, F. Lamaty, *Synlett* **2007**, 1279.

19 B.-X. Tang, F. Wang, J.-H. Li, Y.-X. Xie, M.-B. Zhang, *J. Org. Chem.* **2007**, *72*, 6294.

20 a) K. Ikegashira, Y. Nishihara, K. Hirabayashi, A. Mori, T. Hiyama, *Chem. Commun.* **1997**, 1039. b) Y. Nishihara, K. Ikegashira, A. Mori, T. Hiyama, *Chem. Lett.* **1997**, 1233. c) A. Mori, A. Fujita, Y. Nishihara, T. Hiyama, *Chem. Commun.* **1997**, 2159. d) Y. Nishihara, K. Ikegashira, A. Mori, T. Hiyama, *Tetrahedron Lett.* **1998**, *39*, 4075. e) Y. Nishihara, K. Ikegashira, K. Hirabayashi, J.-i. Ando, A. Mori, T. Hiyama, *J. Org. Chem.* **2000**, *65*, 1780. f) Y. Nishihara, J.-i. Ando, T. Kato, A. Mori, T. Hiyama, *Macromolecules* **2000**, *33*, 2779. g) Y. Nishihara, K. Ikegashira, F. Toriyama, A. Mori, T. Hiyama, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 985. h) Y. Nishihara, M. Takemura, A. Mori, K. Osakada, *J. Organomet. Chem.* **2001**, *620*, 282. i) Y. Nishihara, T. Kato, J.-i. Ando, A. Mori, T. Hiyama, *Chem. Lett.* **2001**, 950. j) Y. Nishihara, E. Inoue, Y. Okada, K. Takagi, *Synlett* **2008**, 3041. k) Y. Nishihara, E. Inoue, D. Ogawa, Y. Okada, S. Noyori, K. Takagi, *Tetrahedron Lett.* **2009**, *50*, 4643.

21 Y. Nishihara, Y. Inoue, M. Fujisawa, K. Takagi, *Synlett* **2005**, 2309.

22 Typical procedure is as follows. To a solution of CuCl (5 mg, 0.05 mmol, 5 mol %), PPh_3 (13.1 mg, 0.05 mmol, 5 mol %), and potassium benzoate (160 mg, 1.0 mmol) in DMI (0.5 mL) were added **1a** (236 µL, 1.2 mmol), and **2c** (234 mg, 1.0 mmol) at room temperature. The reaction mixture was stirred for 12 h at 120 °C, quenched with 3 M HCl, and extracted with diethyl ether (25 mL × 2). The combined ethereal layer was washed with aq $NaHCO_3$ solution and brine and dried over $MgSO_4$. Filtration and evaporation provided a brown oil (GC yield >98%). Purification by column chromatography (SiO_2, hexane:diethyl ether = 9:1; $R_f = 0.49$) gave **3c** (185 mg, 89% yield) as white solid.

23 For a review, see: P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.

24 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.