

Non-Sonogashira-Type Palladium-Catalyzed Coupling Reactions of Terminal Alkynes Assisted by Silver(I) Oxide or Tetrabutylammonium Fluoride

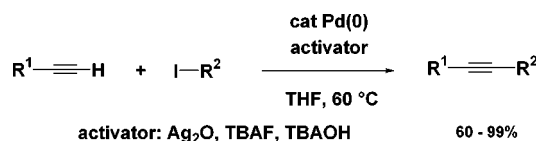
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ABSTRACT



Palladium-catalyzed reaction of aryl and alkenyl halides with terminal alkynes in the presence of silver(I) oxide as an activator furnishes various arylated or alkenylated alkynes in good to excellent yields. The similar coupling reaction is also found to proceed using tetrabutylammonium fluoride (TBAF) or tetrabutylammonium hydroxide (TBAOH) as an activator.

Much effort has been paid to the construction of organic frameworks bearing alkynyl moieties since these are found in a wide range of natural and unnatural organic materials. The carbon–carbon bond-forming reaction with terminal alkynes and a variety of carbon electrophiles such as carbonyl, imine, organohalogen compounds, etc. attracts much attention.¹ Among these, the reaction with a halide or a related compound of an sp² carbon is of particular importance as a transition metal-catalyzed cross-coupling reaction. The development of efficient and practical synthetic methodology for the alkyne coupling, therefore, is of considerable importance.²

The Sonogashira coupling, a reaction of terminal alkynes catalyzed by Pd(0)/CuI with excess amounts of an amine as

a (co)solvent, has widely been used as a practical tool for such synthetic strategies. However, an alternative coupling reaction of alkynes with a much simpler system but higher efficiency has been a part of our continuing interest.³

We recently reported the palladium-catalyzed cross coupling of silanols, silanediols, and silanetriols with silver(I) oxide as an activator.^{4,5} The reaction proceeded using silicon reagents bearing an aryl or alkenyl group with an aryl iodide to furnish the corresponding coupling products. In addition,

(3) (a) Campbell, I. B. In *Organocopper Reagents. A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; Chapter 10, pp 217–236. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds; Wiley: Weinheim, 1997; Chapter 5, pp 203–229.

(4) (a) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299. (b) Hirabayashi, K.; Kondo, T.; Toriyama, F.; Nishihara, Y.; Mori, A. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 985. (c) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* In press.

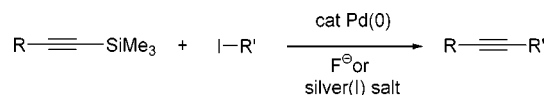
(5) See also: (a) Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 7893. (b) Mateo, C.; Fernández-Rivas, C.; Echavarren, A. M.; Cárdenas, D. J. *Organometallics* **1997**, *16*, 1997. (c) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565.

(1) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245. (b) Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463.

(2) (a) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* **1997**, 1233. (b) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780. (c) Nishihara, Y.; Ando, J.; Kato, T.; Mori, A.; Hiyama, T. *Macromolecules* **2000**, *33*, 2779.

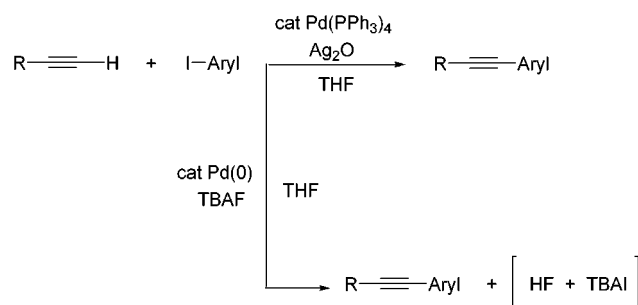
coupling with Ag₂O was revealed to be effective with *trimethylsilylated* (bearing no heteroatom substituent on silicon) substrate when the organic counterpart was an alkynyl group as anticipated from the results by Hatanaka and Hiyama⁶ on the coupling of *trimethylsilylalkynes* using a fluoride ion as an activator^{7,8} (Scheme 1)

Scheme 1



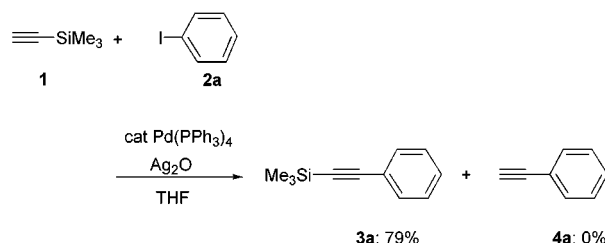
During the course of our further studies on these couplings, we unexpectedly learned that Ag₂O-assisted coupling also proceeds with *terminal alkynes* as substrates. Furthermore, the coupling of terminal alkynes was found to occur by activation with tetrabutylammonium fluoride (TBAF); the results are much more surprising since the progress of the reaction may be explained by the formation of hydrogen fluoride (Scheme 2). Herein we describe the coupling of alkynes with the above two activators.

Scheme 2



The new findings were revealed in the reaction of trimethylsilylthyne (**1**) with iodobenzene (**2a**) in the presence of a catalytic amount of Pd(PPh₃)₄ and a 1 mol amount of Ag₂O to afford phenyl(trimethylsilyl)thyne (**3a**) in 79% yield, while phenylethyne (**4a**) was not obtained at all. As shown in Scheme 3, the coupling occurred at the terminal of **1**.

Scheme 3



The reactions of **1** with iodobenzene (**2a**), 4-methoxyiodobenzene (**2b**), and 4-iodoacetophenone (**2c**) under similar

conditions proceeded to give the coupling products in 79%, 60%, and >99% yields, respectively, demonstrating that the reaction is applicable to a wide range of aryl iodides with both electron-withdrawing and electron-donating substituents.

We then considered that the coupling reaction might also be possible with various terminal alkynes. The reaction of 1-octyne (**5a**) with **2a** proceeded at 60 °C for 8 h in 90% yield. The reaction of phenylethyne (**5b**) with **2a** afforded the coupling product in 60% yield under similar conditions. On the other hand, no reaction occurred in the coupling reaction with an aryl bromide and a triflate. These results are similar to those for the coupling reactions of silanols using Ag₂O.⁴ However, it was found that reaction with alkenyl bromide **6** proceeded under similar conditions to give the corresponding enyne in 79% yield. The reaction of *tert*-butylethyne (**5c**) or **5d**, an alkyne bearing a hydroxy group, also afforded the corresponding coupling products in good to excellent yields. The results of these experiments are summarized in Table 1.

Table 1. Cross-Coupling of 1-Alkynes^a

$\text{R}^1-\text{C}\equiv\text{C}-\text{H} + \text{X}-\text{R}^2 \xrightarrow[\text{THF, 60 } ^\circ\text{C}]{\text{cat Pd(PPh}_3)_4, \text{Ag}_2\text{O}} \text{R}^1-\text{C}\equiv\text{C}-\text{R}^2$			
R ¹	X-R ²	time/h	yield/%
(CH ₃) ₃ Si- (1)	I-C ₆ H ₅ (2a)	3	79
1	4-I-C ₆ H ₄ -OCH ₃ (2b)	3	60
		8	72
1	4-I-C ₆ H ₄ -COCH ₃ (2c)	3	>99
		8	90
<i>n</i> -C ₆ H ₁₃ - (5a)	2a	8	60
C ₆ H ₅ - (5b)	2a	8	60
5b	4-Br-C ₆ H ₄ -OCH ₃	6	0
5b	4-TfO-C ₆ H ₄ -OCH ₃	6	0
5b	(<i>E</i>)-Br-CH=CH-C ₆ H ₅ (6)	6	79
<i>t</i> -Bu- (5c)	2c	6	87
HO(CH ₂) ₂ C- (5d)	2a	6	73 ^b

^a Reaction conditions: solvent (2 mL), **1** or **5** (0.22 mmol), **2** (0.2 mmol), Pd(PPh₃)₄ (5 mol %), Ag₂O (0.2 mmol) unless noted. ^b Five molar amounts (1.0 mmol) of **5d** and Ag₂O were used.

We were surprised to learn that the coupling of terminal alkynes occurs in the presence of tetrabutylammonium fluoride (TBAF) as an activator. After screening the reaction conditions,⁹ the coupling reaction was found to proceed using a smaller amount of palladium catalyst (0.5 mol % of

(6) (a) Hatanaka, Y.; Matsui, K.; Hiyama, T. *Tetrahedron Lett.* **1989**, 30, 2403. (b) For a review: Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P., Eds; Wiley: Weinheim, 1997; Chapter 10, pp 421–453.

(7) Hirabayashi, K.; Kawashima, J.; Mori, A. Unpublished results. The reaction of phenyltrimethylsilane with 4-methoxyiodobenzene in the presence of Pd(0) (0.05 mol amount) and Ag₂O (1 mol amount) afforded the coupling product in 98% yield.

(8) Coupling of alkynylsilane with Ag₂CO₃ was recently reported independently: Koseki, Y.; Omino, K.; Anzai, S.; Nagasaka, T. *Tetrahedron Lett.* **2000**, 41, 2377.

(9) See Supporting Information.

Table 2. Cross-Coupling of 1-Alkynes by the Activation of TBAF^a

$$\text{R}^1\text{—}\text{C}\equiv\text{C}\text{—}\text{H} + \text{X—R}^2 \xrightarrow[\text{THF, 60 }^\circ\text{C}]{\text{Pd}_2(\text{dba})_3 (0.5 \text{ mol}\%), \text{PPh}_3 (2 \text{ mol}\%), \text{TBAF}} \text{R}^1\text{—}\text{C}\equiv\text{C}\text{—}\text{R}^2$$

R ¹	X-R ²	time/h	yield/%
C ₆ H ₅ - (5b)	4-I-C ₆ H ₄ -OCH ₃ (2b)	6	83
5b	I-C ₆ H ₄ -CN	5	86
5b	2b	6	76
5b	4-Br-C ₆ H ₄ -COCH ₃	48	54
<i>n</i> -C ₆ H ₁₃ - (5a)	4-Br-C ₆ H ₄ -COCH ₃	24	75
5a	2b	24	81
5a	I-C ₆ H ₅ (2a)	6	59
HOCH ₂ - (5e)	4-I-C ₆ H ₄ -COCH ₃ (2c)	24	59
HO(CH ₂) ₂ - (5f)	2a	5	64
HO(CH ₃) ₂ C- (5d)	2a	24	64

^a Reactions were carried out at 60 °C under the following reaction conditions: THF (2 mL), alkyne (0.6 mmol), aryl halide (0.5 mmol), Pd₂(dba)₃ (0.5 mol %)-PPh₃ (2 mol %), TBAF (0.55–0.6 mmol).

Pd₂(dba)₃CHCl₃ and 2 mol % of PPh₃). Although the reaction using a catalytic amount of TBAF was attempted, the coupling product was obtained in a yield corresponding to the employed amount of TBAF.⁹

As summarized in Table 2, aryl iodides with an electron-donating or electron-withdrawing substituent similarly underwent the reactions in good yields. In contrast to the results using Ag₂O, the reaction with an aryl bromide proceeded, although relatively longer reaction periods than those of iodides were necessary.¹⁰ In addition to 1-octyne (**5a**) and phenylethyne (**5b**), terminal alkynes bearing a hydroxy functional group (**5d–5f**) could effect the coupling reactions in good yields.

TBAF has been recognized to be an effective desilylating agent for a variety of organosilicon compound to convert a X–Si bond to a X–H bond (X = O, N, C, etc.).¹¹ In addition, TBAF has been utilized as an activating reagent of organosilanes for carbon–carbon bond-forming reactions such as Sakurai–Hosomi reaction¹² and palladium-catalyzed cross-coupling reactions with various organic electrophiles.⁶ In a sharp contrast with numerous examples of such smooth coupling of alkynyltrimethylsilane with aryl or alkenyl halides, the coupling of terminal alkynes using TBAF as an activator has not been reported so far to the best of our knowledge.¹³

(10) Attempted reaction with a triflate under similar conditions gave unidentified products.

(11) For a review on the use of fluoride ion, see: Clark, J. H. *Chem. Rev.* **1980**, 429.

(12) (a) Pilcher, A. S.; DeShong, P. J. *Org. Chem.* **1996**, 61, 6901. (b) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043.

Other fluoride ions and inorganic bases such as KF (0%), CsF (0%), AgF (11%), and K₂CO₃ (0%) were used in the coupling reaction of alkynes; however, such additives showed little or no effect as a competent activator. The use of tetrabutylammonium hydroxide (TBAOH; as a 40% aqueous solution), in contrast, was also found to promote the coupling under similar conditions, giving a >99% yield in the reaction of **5b** and **2a**.

Although the coupling reactions using Ag₂O or TBAF were found to proceed smoothly, these reactivities seem slightly inferior to that of the Sonogashira reaction under similar conditions.^{3,14} However, worthy of note is the procedural simplicity of the reactions despite stoichiometric use of Ag₂O or TBAF. The Sonogashira reactions generally use excess amounts of amine as a solvent or cosolvent, which might cause difficulties in procedures for removal of a high-boiling solvent and of the thus formed ammonium salts. In contrast, the workup procedure of the reaction using Ag₂O in THF could be carried out by easy filtration of the solid residue followed by purification of the concentrated crude material by simple column chromatography, distillation, and/or recrystallization. The workup in the reaction with TBAF was also similar. Thus, we consider that the present reactions can be a viable alternative to the Sonogashira coupling with a wide variety of organic electrophiles.

In conclusion, the coupling reactions of terminal alkynes with organic halides proceeded highly efficiently. Since isolation and purification in these reactions can be performed much more easily, the reactions could be used as an alternative to the Sonogashira coupling. Further studies on the optimization of reaction conditions to find highly reactive catalyst systems are now in progress.

Acknowledgment. The authors thank Asahi Glass Foundation for financial support.

Supporting Information Available: Experimental procedures for typical palladium-catalyzed coupling reactions using Ag₂O and TBAF as activators and additional results concerning optimization of the reaction conditions shown in Table 2. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) Although several coupling reactions of terminal alkynes have been shown to proceed without Cu(I), the use of highly reactive organic electrophiles and/or excess amounts of amine as a (co)solvent are necessary. For example: (a) Austin W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, 46, 2280. (b) Alami, M.; Ferri, F.; Linstumelle, G. *Tetrahedron Lett.* **1993**, 34, 6403. (c) Schaus, J.; Panek, J. S. *Org. Lett.* **2000**, 2, 469. See also the use of AgI instead of CuI: (d) Bertus, P.; Pale P. *Tetrahedron Lett.* **1996**, 37, 2019.

(14) The reaction of 1-octyne and iodobenzene with 5 mol % of Pd catalyst was compared using Ag₂O (90%: 60 °C, 8 h), TBAF (82%: 60 °C, 3 h), and typical Sonogashira conditions (see ref 3b) (91%: rt, 1 h).