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Silver-Catalyzed Intramolecular Chloroamination of Allenes: Easy Access to Functionalized 3-Pyrroline and Pyrrole Derivatives

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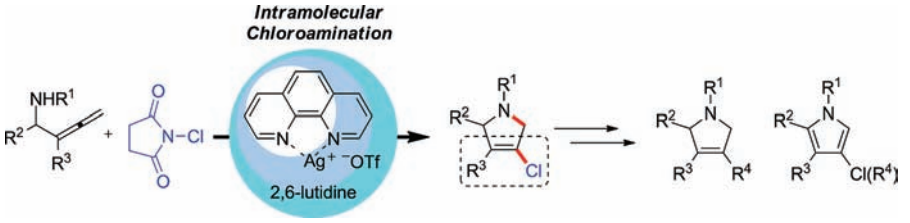
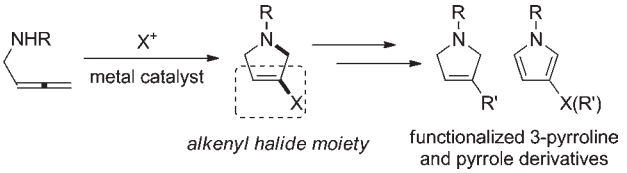
ABSTRACT



A 1,10-phenanthroline-ligated cationic silver complex allows the intramolecular chloroamination of allenes with *N*-chlorosuccinimide using 2,6-lutidine as a base. This process proceeds under mild conditions and can tolerate a variety of functional groups. The chloroamination products are useful synthetic intermediates and can be easily transformed into functionalized 3-pyrroline and pyrrole derivatives.

The intramolecular haloamination of alkenes has emerged as a powerful tool for the construction of azacycles carrying halogen atoms at the β-position of the nitrogen.[1] These reactions have been performed using a halogen cation equivalent (X^+) with/without transition-metal catalysts.[2,3] However, reactions with alkynes[3d] or allenes[4] instead of alkenes have hardly been investigated thus far. When the haloamination of 1-amino-2,3-butadiene proceeds in a 5-*endo* manner, it yields a pyrroline derivative with a halogen on sp^2-carbon (Scheme 1). The alkenyl halide moiety can be utilized for further transformations such as cross-coupling reactions. Furthermore, pyrrolines are readily converted to synthetically useful pyrrole derivatives. In this manner, the intramolecular haloamination of allenes are extremely important.

Scheme 1. Intramolecular Haloamination of Allenes



To realize the proposed reaction, we initially focused on silver catalysts since they have already been demonstrated

(1) (a) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 469−513. (b) Qiu, J.; Silverman, R. B. *J. Med. Chem.* **2000**, *43*, 706.

(2) For examples of noncatalytic intramolecular haloamination of alkenes, see: (a) Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491. (b) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 1063. For a review, see:(c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

(3) For examples of transition-metal-catalyzed intramolecular haloamination of alkenes, see: (a) Michael, F. E.; Sibbald, P. A.; Cochran, B. M. *Org. Lett.* **2008**, *10*, 793. (b) Lei, A.; Lu, X.; Liu, G. *Tetrahedron Lett.* **2004**, *45*, 1785. (c) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618. (d) Danielec, H.; Klügge, J.; Schlummer, B.; Bach, T. *Synthesis* **2006**, 551. (e) Sjöholm, Å.; Hemmerling, M.; Pradeille, N.; Somfai, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 891.

(4) During the preparation of this manuscript, silver-catalyzed aminofluorination of activated allenes was reported: Xu, T.; Mu, X.; Peng, H.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, DOI:10.1002/anie.201103225.

(5) For a review, see: Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174.

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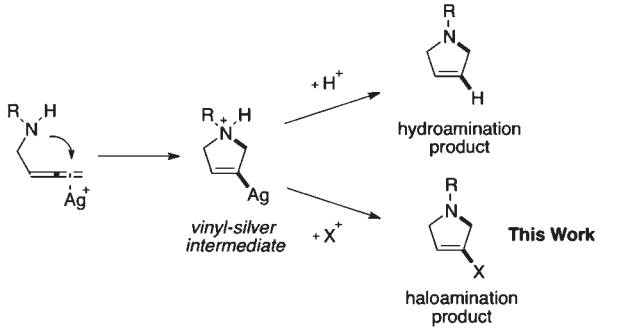
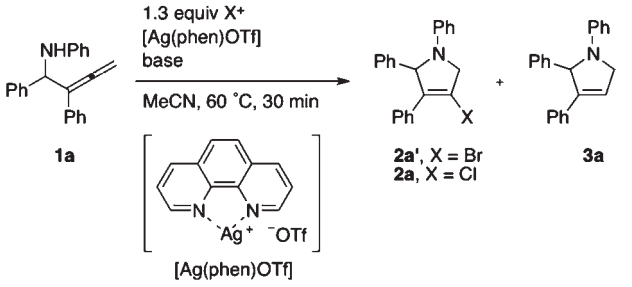
to be effective in activating C−C multiple bonds toward the addition of various functional groups.[5] In particular, the silver-catalyzed 5-*endo*-*trig* cyclization of α-aminoallenes has been well established.[5,6] In this transformation, as outlined in Scheme 2, the vinyl-silver intermediate is considered to be generated by the intramolecular addition of the amine to the activated π-bond. Subsequently, the resulting C(sp^2)−Ag bond is rapidly quenched by a proton to afford the intramolecular hydroamination product. However, this mechanism suggests that the intermediate can be trapped by an electrophile other than a proton.[7,8] Therefore, if a halogen cation equivalent (X^+) can intercept the intermediate prior to protonation, a facile and efficient method for the synthesis of 3-pyrrolines[9] bearing a C(sp^2)−X bond can be achieved.

Scheme 2. Competition between Protonation and Halogenation of the Vinyl-Silver Intermediate



The most important issue is to control the competition between the protonation and halogenation of the vinyl-silver intermediate. Thus, initial investigations into intramolecular haloamination were performed using *N*-bromosuccinimide (NBS) as an electrophilic halogen source. To our delight, treatment of α-aminoallene **1a**[10] with NBS in the presence of a catalytic amount of [Ag(phen)OTf][11] indeed provided the desired bromoamination product **2a′**. However, a substantial amount of the hydroamination byproduct **3a** was also formed (Table 1, entries 1 and 2). Our attempts to improve the reaction by increasing the amount of the catalyst or NBS were unsuccessful (Table 1, entries 3 and 4). Hence, to suppress the undesired formation of **3a**, we replaced NBS with *N*-chlorosuccinimide (NCS). The use of NCS efficiently suppressed the competitive side reaction, and the chloroamination product **2a**[12] was obtained in a fairly good yield (Table 1, entry 5).[13]

Table 1. Optimization of Reaction Conditions[a]



entry	X^+/base (mol %)	[Ag] (mol %)	yield (%)[b] **2**	**3a**
1	NBS/–	20	**2a′**, 14	52
2[c]	NBS/–	20	**2a′**, 32	68
3[c]	NBS/–	100	**2a′**, 32	67
4[d]	NBS/–	20	**2a′**, 0	0
5	NCS/–	20	**2a**, 91	11
6	NCS/DBU (150)	20	**2a**, 0	2
7	NCS/Et_3N (150)	20	**2a**, 0	6
8	NCS/*N*-methylimidazole (150)	20	**2a**, 16	0
9	NCS/pyridine (150)	20	**2a**, 70	21
10	NCS/2,6-di-*tert*-butylpyridine (150)	20	**2a**, 91	9
11	NCS/2,6-lutidine (150)	20	**2a**, 98	1
12	NCS/K_2CO_3 (150)	20	**2a**, 49	0
13	NCS/NaO*t*Bu (150)	20	**2a**, 3	43
14[c]	NCS/2,6-lutidine (40)	10	**2a**, 99 (83)[e]	1
15	chloramine-T/–	20	**2a**, 33	49
16[c]	*N*-chlorophthalimide/2,6-lutidine (40)	10	**2a**, 83	1

[a] Reaction conditions: α-aminoallene **1a** (0.50 mmol), X^+ (0.65 mmol), [Ag(phen)OTf], base, MeCN (4.0 mL), 60 °C, 30 min. [b] Determined by ^1H NMR spectroscopy. [c] At 80 °C. [d] With NBS (2.0 equiv). [e] Isolated yield.

We further hypothesized that an appropriate base could temper the reaction acidity and retard the protonation of the presumed vinyl-silver imtermediate. Therefore, our next step was to test the effects of base additives.

(6) Other transition metals such as Au, Pd, and Cu were also known to catalyze the cyclization of α-aminoallenes. Au: (a) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121. Pd:(b) Ma, S.; Yu, F.; Gao, W. *J. Org. Chem.* **2003**, *68*, 5943. (c) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855. (d) Karstens, W. F. J.; Klomp, D.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron* **2001**, *57*, 5123. (e) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992. (f) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4257. Cu: see ref 10.

(7) On the basis of the similar concept, the gold-catalyzed iodoalkoxylation of allene has already been reported, see: Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957.

(8) For examples of the catalytic reaction of *N*-iodosuccinimide (NIS) with in situ generated vinyl-gold intermediates, see: (a) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *11*, 2147. (b) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2310. (c) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515. (d) Buzas, A.; Gagosz, F. *Synlett* **2006**, 2727.

(9) 3-Pyrroline units are prominent structural motifs in natural products, see: (a) Smith, T. A.; Croker, S. J.; Loeffler, R. S. T. *Phytochemistry* **1986**, *2*, 683. (b) Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1987**, *30*, 2144.

(10) α-Aminoallenes can be readily prepared by the NHC-Cu-catalyzed selective allenylation of imines, see: Sai, M.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3294. We slightly modified this procedure for the preparation of α-aminoallene substrates **1**. See the Supporting Information for details.

(11) Carney, J. M.; Donoghue, P. J.; Wuest, W. M.; Wiest, O.; Helquist, P. *Org. Lett.* **2008**, *10*, 3903.

(12) The structure of **2a** was unambiguously identified by spectroscopic and X-ray crystallographic analyses. See the Supporting Information for details.

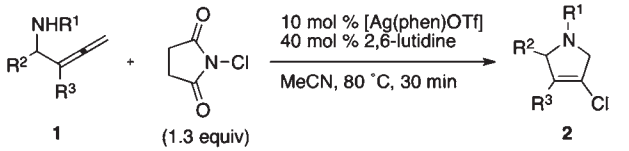
(13) It should be noted that the use of more electrophilic silver salts such as AgOTf and $AgNO_3$ led to a mixture of products, in which **2a** was detected in only 20 and 14% NMR yield, respectively.

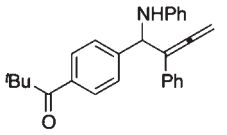
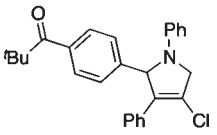
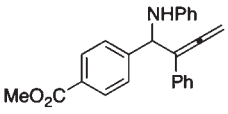
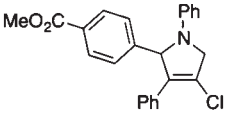
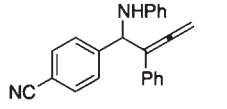
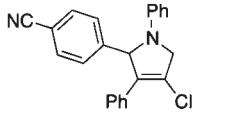
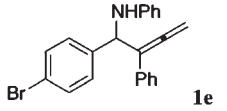
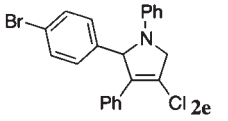
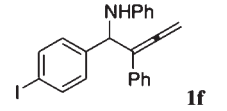
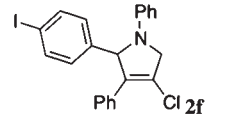
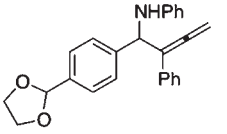
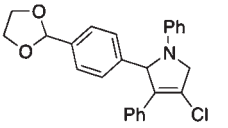
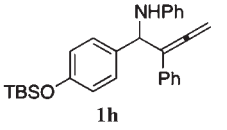
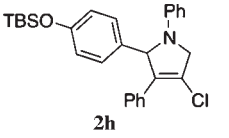
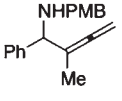
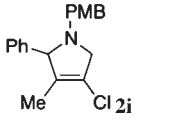
Consequently, we found that the reaction outcomes were closely related to the pK_b values of the employed bases.[14] The addition of strong bases such as DBU, triethylamine (pK_b = 9.00), and *N*-methylimidazole seriously inhibited the cyclization step probably due to the coordination to the metal center (Table 1, entries 6−8). The use of weak bases such as pyridine (pK_b = 3.4) and 2,6-di-*tert*-butylpyridine (pK_b = 0.90) did not have beneficial effects on this reaction (Table 1, entries 9 and 10). We eventually found that the addition of a mild base 2,6-lutidine (pK_b = 4.46) significantly prevented the formation of **3a**, leading to the improved yield of **2a** (Table 1, entry 11). Inorganic bases gave poor results (Table 1, entries 12 and 13). It should be noted that **2a** was not formed in the absence of silver catalysts. Further optimization of the reaction conditions revealed that the catalyst and base amounts could be reduced without any loss in the yield of **2a** (Table 1, entry 14). The product **2a** underwent partial decomposition during silica gel column chromatography even under basic conditions. Thus, the crude product was recrystallized from acetonitrile to yield **2a** as a white solid in 83% isolated yield. We also investigated the performances of other electrophiles such as chloramine-T and *N*-chlorophthalimide, but they proved to be less effective than NCS (Table 1, entries 15 and 16).

Having established the optimal conditions, we explored the scope of the reaction. Various α-aminoallene substrates **1** successfully underwent the silver-catalyzed intramolecular chloroamination to yield the corresponding products in good to excellent yields.[15] Moreover, the reaction tolerates an array of functional groups such as keto, ester, and cyano (Table 2, entries 1−3). Carbon−halogen bonds also survive the reaction and are useful for further reactions using the products (Table 2, entries 4 and 5). The reaction occurs under mild conditions, and as a result, even acid-labile functional groups such as acetal and silyl ether are completely tolerated (Table 2, entries 6 and 7). The high functional group tolerance highlights the utility of the cationic silver complexes as an extremely soft and thus carbophilic Lewis acid. *N*-protected substrate **1i** bearing a methyl substituted allene moiety is also a suitable substrate (Table 2, entry 8). In this case, a 4% yield of *N*-chloroamine and unidentified products were also detected. Unfortunately, **2i** is relatively unstable and gradually decomposes.

To gain insight into the mechanism, we conducted the following experiments (Scheme 3). Based on the fact that a small amount of *N*-chloroamine **4a** was observed in the reaction of **1i**, we considered that the chloroamination reaction could proceed through a pathway starting from in situ generated **4a**.[16] In fact, the reaction of **1i** with NCS in the absence of the silver catalyst gave **4a** in 92% NMR yield. However, when **4a** was heated with the silver catalyst, the chloroamination product **2i** was hardly obtained. Next, we suspected that **4a** might act as the actual chlorinating

Table 2. Scope of the Substrate[a]



entry	substrate	product	yield /%[b]
1	 **1b**	 **2b**	91 (96)
2	 **1c**	 **2c**	82 (99)
3	 **1d**	 **2d**	91 (98)
4	 **1e**	 **2e**	76 (98)
5	 **1f**	 **2f**	77 (99)
6	 **1g**	 **2g**	94 (94)
7	 **1h**	 **2h**	89 (94)
8[c]	 **1i**	 **2i**	30 (77)[d]

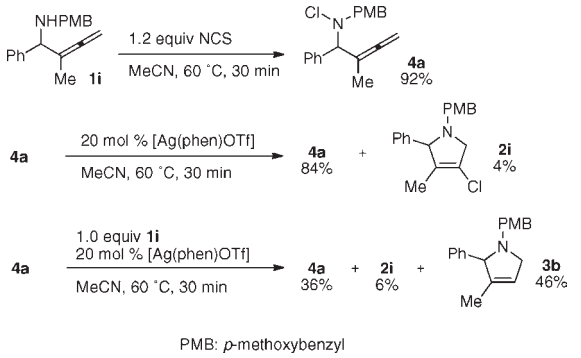
[a] Reaction conditions: α-aminoallene (0.50 mmol), NCS (0.65 mmol), [Ag(phen)OTf] (10 mol %), 2,6-lutidine (40 mol %), MeCN (4.0 mL), 80 °C, 30 min. [b] Yield is of isolated product. Yields determined by ^{1}H NMR spectroscopy are given in parentheses. [c] In the absence of 2,6-lutidine. [d] Four percent of *N*-chloroamine and unidentified products were detected. PMB = *para*-methoxybenzyl.

(14) (a) Ripin, D. H.; Evans, D. A. "pKa's of Nitrogen Acids", http://evans.harvard.edu/pdf/evans_pKa_table.pdf, April, 5, 2011 updated. (b) Reich, H. J. "Bordwell pKa Table", http://www.chem.wisc.edu/areas/reich/pkatable/, February, 23, 2011 updated.

(15) The reactions of monosubstituted allenes were sluggish likely due to the poor ability to stabilize the generating allyl cation.

(16) Cyclization of *N*-chloroalkenylamines to vicinally chlorinated azacycles has been reported. For reviews, see: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Stella, L. *Angew. Chem., Int. Ed.* **1983**, *22*, 337. (c) Mackiewicz, P.; Furstoss, R. *Tetrahedron* **1978**, *34*, 3241. (d) Minisci, F. *Acc. Chem. Res.* **1975**, *8*, 165. (e) Kovacic, P.; Lowery, M. K.; Field, K. W. *Chem. Rev.* **1970**, *70*, 639.

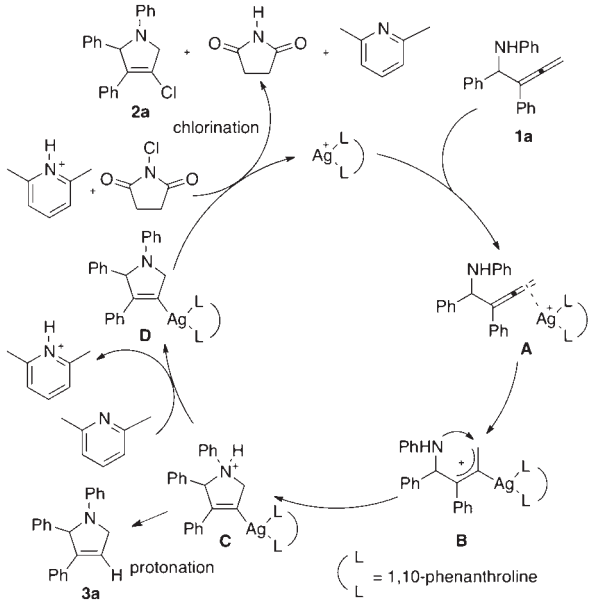
Scheme 3. Mechanistic Investigations



PMB: *p*-methoxybenzyl

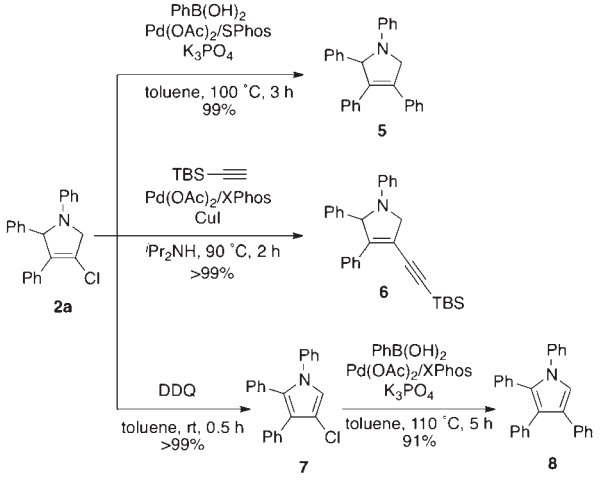
agent instead of NCS. To confirm this hypothesis, **4a** was reacted with **1i** under silver catalysis, which afforded **2i** in only 6% yield. These results suggest that *N*-chloroamine **4a** is not involved in the reaction either as a starting material or as a chlorinating reagent.

Scheme 4. Proposed Mechanism



Although mechanistic details require further studies, our proposed catalytic cycle is shown in Scheme 4. The reaction is initiated by the coordination of the cationic silver complex to the allenic π-bond of **1a** to give the π-complex **A**. Subsequently, intramolecular nucleophilic attack of the nitrogen atom on the terminal carbon of **B** occurs to form the vinyl-silver intermediate **C**. 2,6-Lutidine that will be more basic than **3a** reacts with **C** to form **D**, which significantly retards the protonation pathway.[17] Then, **D** reacts with NCS to produce the chloroamination product **2a** and regenerate the cationic silver catalyst.

Scheme 5. Transformation of **2a**



The chloroamination products are versatile synthetic intermediates that can be easily transformed into other azacycles (Scheme 5). For example, treatment of **2a** with phenylboronic acid under palladium catalysis affords tetrasubstituted 3-pyrroline **5** almost completely.[18] **2a** also underwent the Sonogashira cross-coupling reaction[19] to furnish enyne **6**. Moreover, oxidation of **2a** mediated by DDQ and subsequent Suzuki–Miyaura cross-coupling yielded tetrasubstituted pyrrole **8**.

In conclusion, we have developed a silver-catalyzed intramolecular chloroamination of allenes. This process proceeds under mild conditions and can tolerate a variety of functional groups such as keto, ester, cyano, halogen, acetal, and silyl ether. The high functional group tolerance highlights the utility of the silver catalyst as an extremely soft and carbophilic Lewis acid. The chloroamination products are versatile synthetic intermediates and can be easily transformed into functionalized 3-pyrroline and pyrrole derivatives.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research and GCOE Research from JSPS. M.S. acknowledges JSPS for financial support.

Supporting Information Available. Experimental procedures, spectroscopic and analytical data of new compounds, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) 2,6-Lutidine (pK_b = 4.46) is considered to be more basic than *N*-phenyl-3-pyrroline derivatives, because the pK_b value of structurally related *N*,*N*-dimethylaniline is 2.50.

(18) For a review, see: Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

(19) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.