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Palladium-Catalyzed Addition of Silyl-Substituted Chloroalkynes to Terminal Alkynes

Tatsuya Wada,[a] Masayuki Iwasaki,[a, b] Azusa Kondoh,[a] Hideki Yorimitsu,*[a, b] and Koichiro Oshima*[a]

The transition-metal-catalyzed addition of a carbon–halogen σ-bond to an alkyne is a very useful and attractive reaction in organic synthesis because both a carbon–carbon bond and a carbon–halogen bond are formed simultaneously and atom-economically. The transformation can provide structurally complex haloalkenes that can be further modified by carbon–carbon bond-forming reactions including cross-coupling reactions. In spite of their usefulness, such carbohalogenation reactions were mainly limited to the additions of acid chlorides[1] and allyl halides.[2,3] Very recently, Jiang and co-workers reported the first example of the addition of a carbon–halogen σ-bond of a haloalkyne to an unactivated alkyne.[4,5] They disclosed the palladium-catalyzed addition of bromoalkynes to internal alkynes. Although a variety of internal alkynes can participate in the reaction, terminal alkynes are unsuitable. Moreover, addition of the carbon–chlorine σ-bond of chloroalkynes has not been reported. Herein, we report the addition reaction of silyl-substituted chloroalkynes to terminal alkynes under palladium catalysis to afford (*Z*)-1-chloro-1,3-enynes with perfect regio- and stereoselectivity, which are useful building blocks for the synthesis of highly functionalized enynes.[6]

Treatment of phenylacetylene (**1a**) with 4 equivalents of (chloroethynyl)triisopropylsilane (**2a**) in the presence of catalytic amounts of $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) and triphenylphosphane in decalin at 130 °C for 6 h afforded the corresponding (*Z*)-1-chloro-1,3-enyne[7] **3aa** in 46% yield as determined by NMR spectroscopy. Nonpolar solvents, such as decalin, cyclooctane, and xylene, were the solvent of choice, and decalin gave the best result. Ethereal solvents, such as di-*n*-butyl ether, and aprotic polar solvents, such as DMF, decreased the yield. With respect to the catalyst precursor, palladium (II) complexes, such as $Pd(OAc)_2$ and $[PdCl_2(MeCN)_2]$ with triphenylphosphane (2 equiv relative to Pd), also showed catalytic activity and gave results similar to those with $[Pd_2(dba)_3]$. Interestingly, the method for the addition of phenylacetylene dramatically affected the yield of **3aa**. First, phenylacetylene was divided into two portions, and the reaction was performed for 6 h, with addition of one portion at the beginning and the second portion after 3 h, to provide **3aa** in 62% yield (as determined by NMR spectroscopy) and 60% yield of the isolated product (Table 1, entry 1).[8] Second, slow addition of phenylacetylene over 3 h followed by heating for an additional 3 h was also effective and gave **3aa** in 55% yield by NMR spectroscopy.[9] Further optimization including the screening of phosphane ligands, concentration, and additives, did not improve the yield.[10]

Other haloalkynes were tested under the optimized reaction conditions (Table 1, entries 1–4). In this reaction, the silyl substituent on the haloalkynes was crucial. The reactions of chloroalkynes that have a silyl group, such as the reactions of triisopropylsilyl-, triethylsilyl-, and *tert*-butyldimethylsilyl-substituted chloroalkynes **2a**–**2c** with phenylacetylene, proceeded smoothly to afford the corresponding products in good yields (Table 1, entries 1–3). Whereas the reactions of chloroalkynes derived from phenylacetylene or 1-octyne provided complex mixtures with only trace amounts of the corresponding adducts (<10%). A silyl-substituted bromoalkyne **2d** also underwent the addition reaction to yield bromoalkene **3ad** in moderate yield. However, the use of an iodoalkyne did not result in any formation of the desired adduct.

[a] T. Wada, M. Iwasaki, Dr. A. Kondoh, Prof. Dr. H. Yorimitsu, Prof. Dr. K. Oshima
Department of Material Chemistry
Graduate School of Engineering, Kyoto University
Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510
Fax: (+81) 75-383-2438
E-mail: oshima@orgrxn.mbox.media.kyoto-u.ac.jp

[b] M. Iwasaki, Prof. Dr. H. Yorimitsu
Present address
Department of Chemistry
Graduate School of Science, Kyoto University
Sakyo-ku, Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-3970
E-mail: yori@kuchem.kyoto-u.ac.jp

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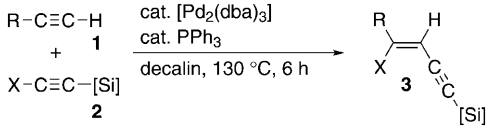
Table 1. Palladium-catalyzed addition of silyl-substituted haloalkynes to terminal alkynes.[a]

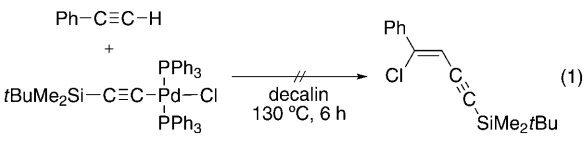


Entry	1	R	2	[Si]	X	3	Yield [%][b]
1	**1a**	Ph	**2a**	iPr$_3$	Cl	**3aa**	60
2	**1a**	Ph	**2b**	tBuMe$_2$Si	Cl	**3ab**	71
3	**1a**	Ph	**2c**	Et$_3$Si	Cl	**3ac**	74
4	**1a**	Ph	**2d**	Et$_3$Si	Br	**3ad**	38
5	**1b**	p-MeO-C$_6$H$_4$	**2c**	Et$_3$Si	Cl	**3bc**	69
6	**1c**	p-CF$_3$-C$_6$H$_4$	**2c**	Et$_3$Si	Cl	**3cc**	63
7	**1d**	p-Cl-C$_6$H$_4$	**2c**	Et$_3$Si	Cl	**3dc**	66
8	**1e**	o-Me-C$_6$H$_4$	**2c**	Et$_3$Si	Cl	**3ec**	34
9	**1f**	nC$_{10}$H$_{21}$	**2c**	Et$_3$Si	Cl	**3fc**	65
10	**1g**	cC$_6$H$_{11}$	**2c**	Et$_3$Si	Cl	**3gc**	56
11	**1h**	AcO(CH$_2$)$_9$	**2c**	Et$_3$Si	Cl	**3hc**	64
12	**1i**	Ac(CH$_2$)$_8$	**2c**	Et$_3$Si	Cl	**3ic**	59
13	**1j**	HO(CH$_2$)$_9$	**2c**	Et$_3$Si	Cl	**3jc**	62

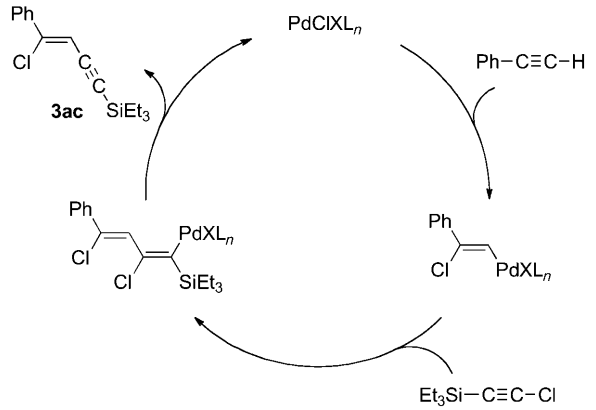
[a] Conditions: **1** (0.25 mmol×2), **2** (2.0 mmol), [Pd$_2$(dba)$_3$] (0.0063 mmol), PPh$_3$ (0.013 mmol), decalin (4.0 mL). [b] Yield of the isolated product.

Next, the scope of terminal alkynes was investigated (Table 1, entries 5–13). Electron-rich and electron-deficient arylacetylenes underwent the reaction to yield the products in good yields (Table 1, entries 5–7). The steric hindrance of **1e** decreased the yield (Table 1, entry 8). Aliphatic alkynes also participated in this reaction. The reactions of primary and secondary alkyl-substituted alkynes occurred to provide the corresponding products in good yields (Table 1, entries 9 and 10). However, *tert*-butylacetylene was converted into the product in very low yield due to its bulkiness. A variety of functional groups including ester, keto, and hydroxy groups, were tolerated under the reaction conditions (Table 1, entries 11–13). Even a chloro group on the benzene ring of terminal alkynes remained intact (Table 1, entry 7). Attempted reactions of internal alkynes, instead of terminal alkynes, resulted in no conversion.

The reaction mechanism of this haloalkynylation is not clear at this stage. One of the possible pathways is a Pd^0/Pd^{II} mechanism initiated by oxidative addition of a haloalkyne to Pd^0, which is related to the transition-metal-catalyzed addition of acid chlorides to alkynes.[1] The oxidative addition affords (alkynyl)chloropalladium(II). *Syn*-chloropalladation[2] or alkynylpalladation[11] of a terminal alkyne followed by reductive elimination provides the product and regenerates the initial Pd^0 complex. However, the stoichiometric reaction of phenylacetylene with (*tert*-butyldimethylsilylethynyl)chlorobis(triphenylphosphine)palladium[12] afforded a complex mixture containing the trimer of phenylacetylene, 1,3,5- and 1,2,4-triphenylbenzene [Eq. (1)]. The Pd^0/Pd^{II} mechanism is thus unlikely.

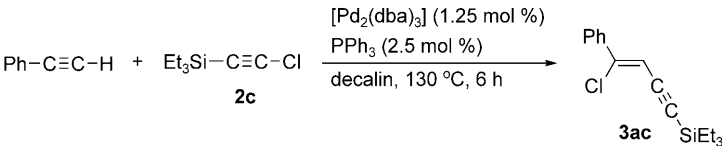


A more plausible mechanism would be a Pd^{II}-based mechanism (Scheme 1), which is similar to the mechanism of haloallylation of alkynes.[2] In this mechanism, an active chloropalladium(II) complex participates in *syn*-chloropalladation of a terminal alkyne to provide a 2-chloro-1-alkenylpalladium species. Insertion of a haloalkyne followed by *anti*-β-chloride elimination[13] affords the adduct and regenerates the initial palladium(II) complex.



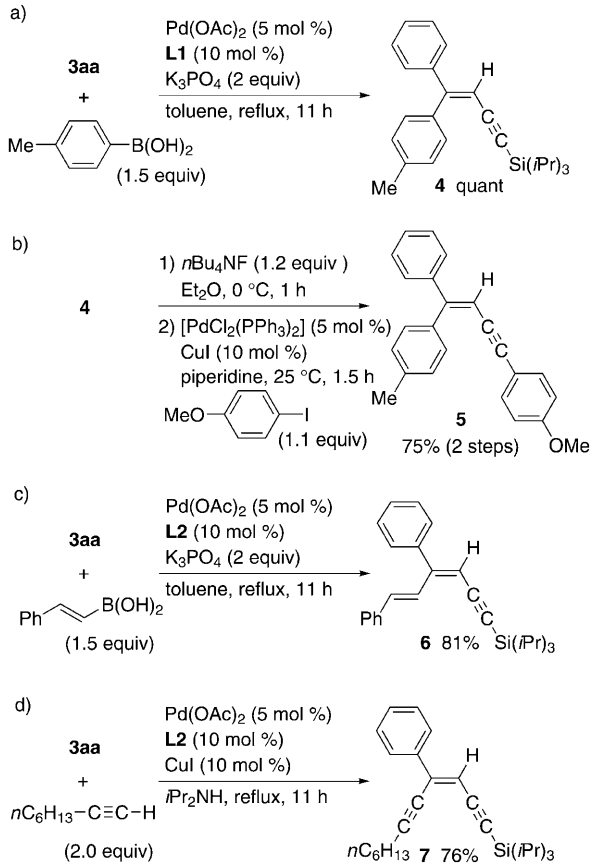
Scheme 1. A plausible mechanism.

As shown in Scheme 2, the amount of chloroalkyne is quite important. As the amount of **2c** increases, the yield of **3ac** was improved. In all the reactions, phenylacetylene was completely consumed and the trimers of phenylacetylene were observed. These results imply that the insertion of the chloroalkyne (Scheme 1) would compete with that of phenylacetylene. Further investigation is required to evaluate these and other hypotheses including a Pd^{II}/Pd^{IV} mechanism.[4]

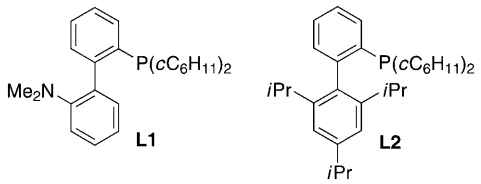


Scheme 2. The effect of varying the amount of chloroalkyne: **2c** (1 equiv)→**3ac** (30%) (with 0.21 equiv of **2c** recovered); **2c** (2 equiv)→**3ac** (48%) (with 0.32 equiv of **2c** recovered); **2c** (3 equiv)→**3ac** (58%) (with 0.42 equiv of **2c** recovered); **2c** (4 equiv)→**3ac** (74%).

Finally, the utility of the chloroalkynylation products was demonstrated by an array of palladium-catalyzed cross-coupling reactions (Scheme 3). The choice of phosphane ligand was quite important for the transformations (Scheme 4). Suzuki–Miyaura coupling of **3aa** with arylboronic acid[14] proceeded by using **L1**[15] as the ligand to yield **4** quantitatively (Scheme 3a). Product **4** is amenable to further transformations. For instance, desilylation under mild conditions followed by Sonogashira coupling[16] afforded **5** in good yield (Scheme 3b). The adduct **3aa** also underwent Suzuki–



Scheme 3. Transformations of **3aa**.



Scheme 4. Useful ligands in the transformation of **3aa**.

Miyaura coupling with alkenylboronic acid and Sonogashira coupling with 1-octyne by using **L2**[17] as the ligand to provide 1,3-dien-5-yne **6** and 3-en-1,5-diyne **7**, respectively, in high yields (Scheme 3c and d).

In conclusion, we have developed the addition reaction of the carbon–chlorine σ-bond of chloroalkynes to terminal alkynes under palladium catalysis. The products, 1-chloro-1,3-enynes, are demonstrated to be useful building blocks for the synthesis of polysubstituted 1,3-enynes. Studies on the reaction mechanism, as well as the application of this reaction to the synthesis of complex molecules are under investigation.

Experimental Section

Typical procedure: $[Pd_2(dba)_3]$ (5.7 mg, 0.0063 mmol) and triphenylphosphane (3.3 mg, 0.013 mmol) were placed in a 20 mL reaction flask under argon. Decalin (1.0 mL) was added, and the mixture was stirred for 15 min. Phenylacetylene (**1a**, 0.026 g, 0.25 mmol), (chloroethynyl)triethylsilane (**2c**, 0.35 g, 2.0 mmol), and decalin (2.0 mL) were sequentially added, and the resulting mixture was heated at 130 °C for 3 h. After which time the mixture was cooled to ambient temperature and a solution of phenylacetylene (0.026 g, 0.25 mmol) in decalin (1.0 mL) was added. The reaction mixture was then stirred at 130 °C for an additional 3 h. After which the mixture was cooled to room temperature and the reaction was quenched with water. The product was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification on silica gel (eluted with hexane) provided **3aa** (0.10 g, 0.37 mmol) in 74 % yield as a yellow oil.

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Keywords: addition reactions · alkynes · enynes · palladium · synthetic methods

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[7] The regiochemistry was determined by radical reduction of a bromoalkynylation product. The *Z* stereochemistry was assigned by NOE analysis. See the Supporting Information.

[8] See the Experimental Section for the detailed experimental procedure.

[9] When **1a** was added in two portions or slowly, the amount of unidentified byproduct derived from **1a** was reduced, which would lead to the increase of yield of **3aa**.

[10] For the screening of phosphane ligands, see the Supporting Information.

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