ELSEVIER

Journal of Organometallic Chemistry 653 (2002) 141–149

Journal of Organometallic Chemistry

www.elsevier.com/locate/jorganchem

# Studies on stereoselective Sonogashira coupling of 1,1-dibromo-1-alkene

Jun'ichi Uenishi *, Katsuaki Matsui, Hirohisa Ohmiya

*Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan*

Received 31 August 2001; received in revised form 22 November 2001; accepted 23 November 2001

**Abstract**

The stereoselective Sonogashira coupling of 1,1-dibromo-1-alkene was described. The use of $PdCl_2$(dppf) as a catalyst with trialkylsilylacetylene in benzene selectively gave the (*Z*)-bromoenyne (**2a**) along with small amounts of the enediyne (**3a**). Based on the experimental results, a mechanism of the selectivity was proposed. The bromoenyne was coupled with some electrophiles to give the substituted (*Z*)-bromoenynes after deprotection of the terminal silyl group. © 2002 Elsevier Science B.V. All rights reserved.

*Keywords:* Sonogashira coupling; Bromoenyne; 1,1-Dibromo-1-alkene; Stereoselective reaction

## 1. Introduction

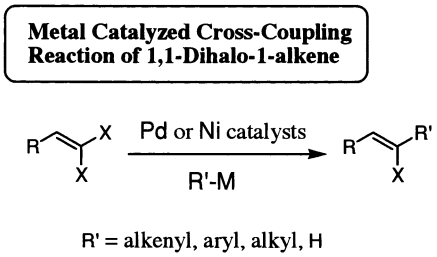
Enynes and enediynes have recently received considerable attention as functional units of biologically active compounds, natural products, and new functional materials [1]. Sonogashira coupling is a reliable and convenient reaction for constructing enyne and enediyne units, and has often been used for the preparation of such compounds [2]. In this paper, we report the stereoselective preparation of bromoenyne by the Sonogashira coupling of 1,1-dibromo-1-alkene with a terminal alkyne. In the early stage of the chemistry of 1,1-dihalo-1-alkene, a differentiation of the geminal carbon–bromine bonds was thought to be difficult [3]. Minato et al. first achieved the differentiation of the two carbon–bromine bonds in the Ni and Pd catalyzed cross-coupling reactions of 1,1-dichloro-1-alkene with Grignard and organo zinc reagents [4]. Since then, several stereoselective replacements of the *trans* carbon–bromine bond of the 1,1-dibromo-1-alkene, including Suzuki coupling [5], Stille coupling [6], and hydrogenolysis [7], have been reported. In all of these cases, the metal catalyzed reactions of the 1,1-halo-1-alkene first takes place at the *trans* carbon–halogen bond, not at the *cis* carbon–halogen bond, meaning that the first oxidative addition always occurs at the less-hindered side of the carbon–halogen bonds. This selectivity was explained by the large different rates of oxidative addition of Pd to the *cis* and *trans* carbon–halogen bonds due to steric reasons. For the same reason, the second cross-coupling to the resultant trisubstituted haloalkene hardly occurred under the same reaction conditions [8] (Scheme 1).

However, the Sonogashira coupling of the 1,1-dibromo-1-alkene is somewhat different [9], and there have been few reports on this subject [10]. In fact, the reaction of 1,1-dibromo-1-alkene under typical Sonogashira conditions [11] gave a mixture of bromoenyne, enediyne, and recovery of the starting dibromoalkene [9], indicating that no chemo-selective reaction had occurred. The use of alkynylmagnesium [10a,10c] and alkynylzinc [10b] reagents instead of the terminal alkyne for the cross-coupling improved the yield of the bromoenyne, which was still unsatisfactory (28–66%). The use of the free terminal alkyne is thought to have some advantages; there is no necessity to prepare alkynyl metal reagents, and protection of the fragile functional group against organometallic reagents is not needed. Therefore, this prompted us to study the Sonogashira coupling of 1,1-dibromo-1-alkene using a terminal alkyne.

* Corresponding author. Tel.: +81-75-595-4665; fax: +81-75-595-4763.

*E-mail address:* juenishi@mb.kyoto-phu.ac.jp (J. Uenishi).

0022-328X/02/$ - see front matter 
PII: S0022-328X(02)01262-7



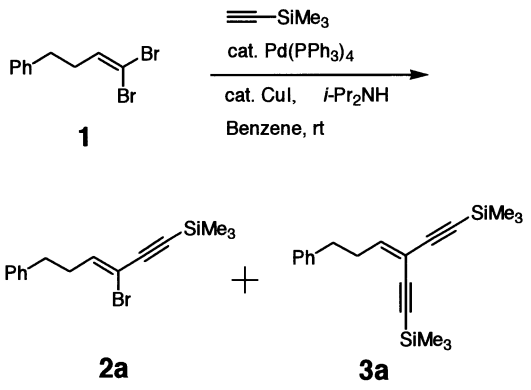

Scheme 1.

## 2. Results and discussion

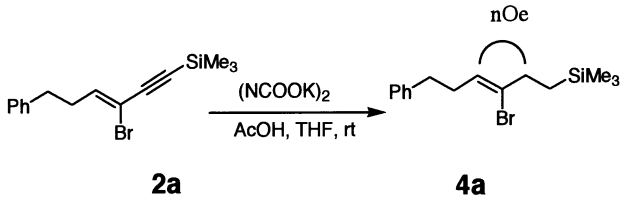
We first tried the Sonogashira coupling using 1,1-dibromo-3-phenyl-1-butene (**1**) with trimethylsilylacetylene. The reaction was carried out under standard Sonogashira conditions, i.e. with trimethylsilylacetylene (1.5 equivalents), in the presence of diisopropylamine (three equivalents), a catalytic amount of $Pd(PPh_3)_4$ (5 mol%), and CuI (4 mol%) in benzene. The reaction seemed to stop after 2 h. The products were separated by HPLC to give the bromoenyne (**2a**) in 20% yield, the enediyne (**3a**) in 22% yield and the recovery of **1** in 41% yield. A volatile dimer of trimethylsilylacetylene was also obtained (Scheme 2).

The structures of **2a** and **3a** were confirmed by a mass spectrum and NMR spectra including the H–H and C–H COSY experiments, and the stereochemistry of **2a** was determined by the following experiments. The treatment of **2a** with the diimide generated from dipotassium diazodicarboxylate with acetic acid [12] selectively reduced the alkynyl bond to give the trisubstituted bromoalkene (**4**), in which no isomerization of the alkenyl bond should take place. In an *n*Oe experiment of **4**, positive enhancement was clearly observed between the alkenyl (C*H*) proton appearing at 5.70 ppm and the methylene ($CH_2$–$CH_2$–$SiMe_3$) protons appearing at 2.41 ppm (Scheme 3).

It has been reported that the oxidative addition of Pd to 1,1-dibromo-1-alkenes selectively occurs at the *trans* position and that the rate for the second oxidative




Scheme 2.




Scheme 3.

addition to the resultant first coupling product is far slower than that of the first addition [4–7]. However, the above result of **1** with trimethylsilylacetylene using $Pd(PPh_3)_4$ was poorly selective. We examined other Pd catalysts, and these results are shown in Table 1. The use of $PdCl_2(PPh_3)_2$ gave similar results to those of $Pd(PPh_3)_4$. On the other hand, $PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$, and $Pd(dppe)_2$ were poorly reactive, and **1** was recovered in these reactions. Eventually, $PdCl_2$(dppf) was found to be exceptionally selective (entry 6). The reaction was completed within 15 min to afford **2a** in 68% yield and **3a** in 13% yield after HPLC purification, and no starting material remained [13]. We also examined other conditions, and these results are listed in Table 2. When the reaction was prolonged overnight, **2a** and **3a** were obtained in 65 and 15% yields, respectively, (entry 2). The reaction was completed in 10 min at 40 °C and in 2 min at the refluxing temperature (entries 3 and 4). Although heating the reaction accelerated the reaction rate, it had little effect on the production ratio of **2a** and **3a**. Furthermore, when two to four equivalents of trimethylsilylacetylene were treated, the yields of **2a** and **3a** were not significantly changed. When THF was used as a solvent, the reaction gave a mixture of **2a** in 40%, **3a** in 20%, and the recovery of **1** in 20% [14].

We were interested in these observations, particularly the slow transformation rate from **2a** to **3a**. This must be a principal reason for the selectivity. Therefore, compound **2a** was subjected to the second Sonogashira reaction under the same reaction conditions. These results are shown in Table 3. Compound **3a** was obtained in only 3% yield after 15 min, and in 18% after 3 h (entries 1 and 2). When the reaction was conducted under refluxing conditions, the formation of **3a** was not increased (entry 3). Obviously, the second coupling of **2a** was considerably slower than the first coupling. The reaction using $Pd(PPh_3)_4$ become much slower with the yield of **3a** being only 4% after 3 h (entry 4). Although $Pd(PPh_3)_4$ was more effective for the formation of **3a** from **1** than was $PdCl_2$(dppf), (entries 1 and 6 in Table 1), it was less effective for the formation of **3a** from **2a** than was $PdCl_2$(dppf).

A plausible mechanism for these unique reactivities of 1,1-dibromo-1-alkene and bromoenyne in the $PdCl_2$(dppf) catalyzed cross coupling reactions with trimethylsilylacetylene is described in Fig. 1. During

Table 1
Pd Catalysts for the formation of **2** and **3**

| Entry | Pd catalysts [a] | Time (min) | Yield (%) [b] | | |
|---|---|---|---|---|---|
| | | | **2** | **3** | **1** (recovery) |
| 1 | $Pd(PPh_3)_4$ | 120 | 20 | 22 | 41 |
| 2 | $PdCl_2(PPh_3)_2$ | 50 | 14 | 37 | 26 |
| 3 | $PdCl_2(CH_3CN)_2$ | 120 | 0 | 0 | 77 |
| 4 | $PdCl_2(PhCN)_2$ | 120 | 0 | 0 | 82 |
| 5 | Pd $(dppe)_2$ | 120 | 5 | 6 | 61 |
| 6 | $PdCl_2$(dppf) | 15 | 68 | 13 | 0 |

[a] Pd catalysts (5 mol%) and trimethylsilylacetylene (1.5 equivalents) were used in the presence of CuI (4 mol%) and diisopropylamine (three equivalents). All the reactions were carried out in benzene at room temperature.
[b] Yields are shown after purification by HPLC.

the first step, the oxidative addition of Pd to 1,1-dibromo-1-alkene occurs at the *trans* carbon–bromine bond, giving an alkenylpalladium bromide intermediate, and successive transmetallation with copper trimethylsilylacetylide produces the intermediate **I**. The reductive elimination of Pd then affords the bromoenyne **3a** as the major reaction course. During the minor course of the reaction, Pd stays with the enyne after the reductive elimination forming the Pd intermediate **II** with a tight or loose coordination. The transformation of **II** then occurs fast to give the intermediate **III**, which is exactly the product by the oxidative addition product of Pd to **2a**. Transmetallation with trimethylsilylacetylene followed by the second reductive elimination furnishes the formation of **3a**.

After the formation of the intermediate **I**, the reaction step was separated from **I** by two pathways leading to **2a** or the intermediate **II**. Since the facts that the reaction rate to **3a** from **2a** was slow (Scheme 4) and the production ratio of **2a** and **3a** was consistent and not influenced by the reaction conditions (Table 2), the formation of **2a** and **3a** would be determined by this step. Pd and its ligand may play a key role in this step. When $PdCl_2$(dppf) is employed, **2a** is preferentially formed from **I**. The coordinate intermediate **II** derived from **I** is thought to be unfavorable because the steric interaction is present with a bulky trialkylsilyl group bearing alkyne. The slow oxidative addition of **2a** is also anticipated for this reason, and this will be discussed later in cases with other alkynes. Therefore, we examined other terminal alkynes for the coupling. Table 4 shows these results (Scheme 5).

Triethylsilylacetylene also reacted with **1** under the same conditions within 10 min at room temperature, and the reaction of *tert*-butylacetylene proceeded well within 60 min at room temperature. Both reactions gave the bromoenyne in good yields with good selectivities (entries 2 and 3). However, the reaction of phenylacetylene gave a mixture of the bromoenyne (**2d**) and enediyne (**3d**) in 41 and 31% yield, respectively, and **1** was recovered in 34% yield (entry 4). The reaction for a longer period of time did not improve the result (entry 5). The reactivity of 1-hexyne was found to be poor, and the reaction at room temperature for 60 min gave a mixture of **2e**, **3e**, and **1** in 15, 20 and 49% yields, respectively, (entry 6). However, a prolonged reaction

Table 2
Sonogashira coupling reaction of **1**

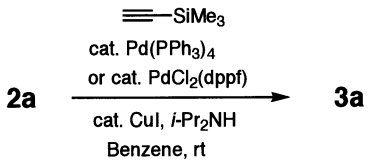
| Entry | TMS acetylene (equivalent) [a] | Solvent | Temperature | Time (min) | Yield (%) [b] | |
|---|---|---|---|---|---|---|
| | | | | | **2a** | **3a** |
| 1 | 1.5 | benzene | r.t. | 15 | 68 | 13 |
| 2 | 1.5 | benzene | r.t. | over night | 65 | 15 |
| 3 | 1.5 | benzene | 40 °C | 10 | 77 | 10 |
| 4 | 1.5 | benzene | reflux | 2 | 72 | 14 |
| 5 | 2.0 | benzene | r.t. | 15 | 64 | 14 |
| 6 | 3.0 | benzene | r.t. | 15 | 68 | 17 |
| 7 | 4.0 | benzene | r.t. | 15 | 69 | 9 |
| 8 | 1.5 | THF | r.t. | 120 | 40 | 20 [c] |

[a] Pd catalysts (5 mol%) and trimethylsilylacetylene (1.5 equivalents) were used in the presence of CuI (4 mol%) and diisopropylamine (three equivalents).
[b] Yields were shown after purification by HPLC.
[c] Starting material **1** was recovered in 20% yield.

Table 3
Sonogashira coupling of **2a**

| Entry | TMS acetylene (equivalent) [a] | Catalyst | Temperature | Time (min) | Yield (%) [b] | |
|---|---|---|---|---|---|---|
| 1 | 1.5 | $PdCl_2$(dppf) | r.t. | 15 | 87 | 3 |
| 2 | 1.5 | $PdCl_2$(dppf) | r.t. | 180 | 65 | 18 |
| 3 | 1.5 | $PdCl_2$(dppf) | reflux | 60 | 45 | 24 |
| 4 | 1.5 | $Pd(PPh_3)_4$ | r.t. | 180 | 89 | 4 |

[a] Pd catalysts (5 mol %) and trimethylsilylacetylene (1.5 equivalents) were used in the presence of CuI (4 mol %) and diisopropylamine (three equivalents). All the reactions were carried out in benzene.
[b] Yields are shown after purification by HPLC.




Scheme 4.

eventually transformed all of the starting dibromoalkene and a considerable part of the bromoenyne into the enediyne (entry 7).

These results indicated that the reaction rate of the alkynes bearing bulky groups such as trialkylsily or *tert*-butyl substituted acetylenes is higher than that of alkynes bearing small groups such as butyl or phenyl substituted acetylenes for the formation of **2**. On the other hand, a bulky substituted group at the terminal position of the acetylene has a negative effect on the reaction rate during the second coupling, because the formation of the intermediate **II** is unfavorable**.** This idea was also supported by the second coupling reaction of **2** affording **3**. The reaction of **2d** gave **3d** in 76% yield, and that of **2e** gave **3e** in 78% yield. These yields are much higher than that (18%) in the reaction of **2a** to **3a** shown in Table 3 under the same reaction conditions. This observation implies that the corresponding intermediate **III** would be formed from **2** through the alkyne coordinated Pd complex (the corresponding intermediate **II**). It is interesting that a substituent group located far from the carbon–bromine bond influenced the rate of the oxidative addition (Scheme 6).

As is described above, $PdCl_2$(dppf) shows a unique property, which can control the course of the reaction for the Sonogashira coupling of the 1,1-dibromo-1-alkene with the terminal acetylene bearing a bulky substituted group in benzene. The reaction of the more functional 1,1-dibromo-1-alkene (**5**) with trimethylsilylacetylene under the same conditions gave **6** in 81% yield along with the enediyne in 17% yield. It was found that this catalyst is also effective for the reaction with alkynylmagnesium bromide, producing similar results. The reaction of **5** with trimethylsilylethynylmagnesium

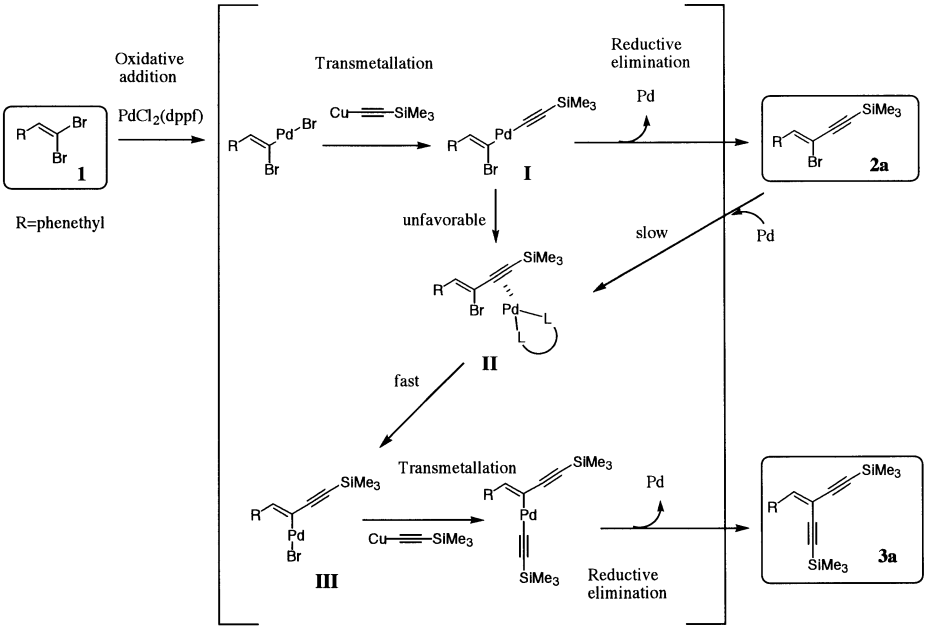
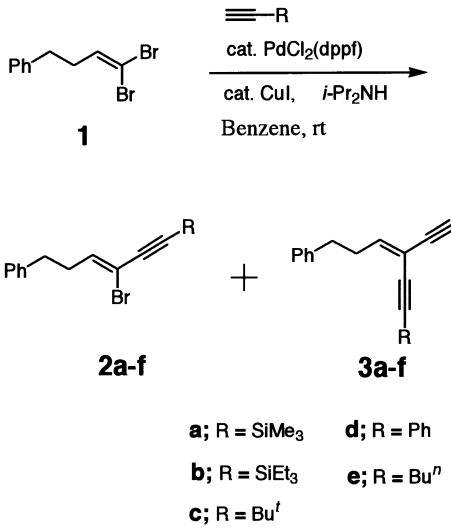



Fig. 1. A plausible mechanism for the formation of **2a** and **3a.**

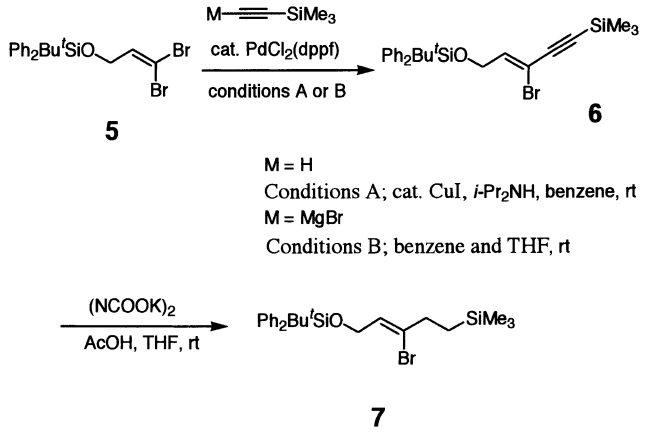
Table 4
Sonogashira coupling of **1** with Terminal alkynes

| Entry | Alkyne, R [a] | Time (min) | Yield (%) [b] | | |
|---|---|---|---|---|---|
| | | | **2a–f** | **3a–f** | **1** (recovery) |
| 1 | $SiMe_3$ | 15 | 68 | 13 | 0 |
| 2 | $SiEt_3$ | 10 | 61 | 13 | 0 |
| 3 | $Bu^t$ | 60 | 56 | 11 | 0 |
| 4 | Ph | 60 | 41 | 31 | 34 |
| 5 | Ph | Over night | 24 | 42 | 24 |
| 6 | $Bu^n$ | 60 | 15 | 20 | 49 |
| 7 | $Bu^n$ | Over night | 17 | 61 | 0 |

[a] Alkyne (1.5 equivalents) and Pd catalyst (5 mol %) were used in the presence of CuI (4 mol %), and diisopropylamine (three equivalents). All the reactions were carried out in benzene at room temperature.
[b] Yields are shown after purification by HPLC.




Scheme 5.



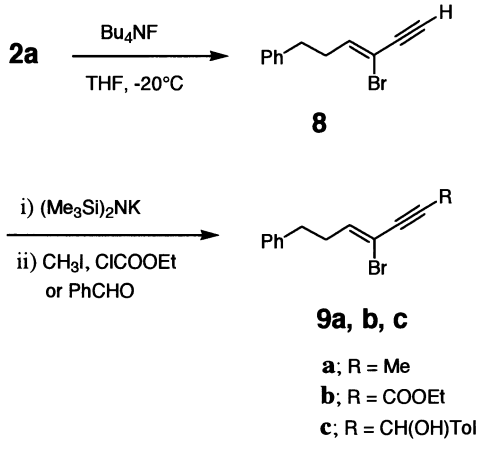

Scheme 6.

bromide in the presence of $PdCl_2$(dppf) gave **6** in 82% yield along with the enediyne in 15% yield [15]. The structure, including geometry, of **6** was determined by the same procedure as that used for **2a**. The reduction of the alkynyl bond selectively gave the partially saturated compound **7** in 68% yield. Since compound **6** possesses a silyl protecting allyl alcohol and terminal trialkylsilylethynyl groups, carbon elongation will be possible in both carbon terminals, some of which are shown in Scheme 7.

For synthetic purposes, the synthesis of **2** with satisfied selectivity is limited to terminal acetylenes bearing a bulky substituent. However, the extension of the carbon chain from the terminal trialkylsilylkyne is possible. Deprotection of the silyl group in **2a** or **2b** with tetrabutylammonium fluoride gave **8** in 95% yield. The deprotonation of **8** with potassium hexamethylsilazide in THF and the reaction with iodomethane gave the methylated bromoenyne (**9a**) in 97% yield. This anion also reacted with ethyl chloroformate to give **9b** in 80% yield, and with *p*-tolualdehyde to give **9c** in 88% yield.

## 3. Conclusion

Selective Sonogashira coupling of 1,1-dibromo-1-alkene with trialkylsilylacetylene was performed without




Scheme 7.

using alkynylmagnesium or zinc reagents. $PdCl_2$(dppf) was found to be an excellent catalyst for the coupling reaction. The substituent group of acetylene plays a key role in the selectivity. Although effective coupling is limited to the trialkylsilyacetylenes (**2a**,**b**), the resultant silyl substituted bromoenyne (**3a**,**b**) can be easily desilylated and coupled with electrophiles to give substituted bromoenynes (**9**).

## 4. Experimental

### 4.1. General procedures

All air- and moisture-sensitive reactions were carried out in flame-dried glassware under an Ar atmosphere. Solvents were distilled freshly over sodium–benzophenone ketyl for benzene, and THF under nitrogen atmosphere. Thin layer chromatography (TLC) was performed with Merck $60F_{254}$ precoated silica gel plates. JAIGEL-1H and 2H columns (size $20 \times 500$ mm) were used for HPLC and chloroform was used as an eluent.

### 4.2. Typical Sonogashira coupling reaction

To a mixture of 1,1-dibromo-3-phenyl-1-butene (1 mmol), alkyne (1.5 mmol), in benzene (10 ml) were added Pd catalyst (5 mol%), CuI (4 mol%), and diisopropylamine (3 mmol) successively at room temperature (r.t.). The mixture was stirred under the conditions (time and temperature) shown in Tables. After the reaction completed, the mixture was diluted with hexane, and washed with water and brine. The organic layer was dried over $MgSO_4$, and condensed in vacuo. The crude mixture was roughly purified by silica gel column chromatography. At this stage, separation of **2** and **3** was possible by column-chromatographic purification. However, in order to identify accurate yields and ratios for the products, separations of **2** and **3** were performed by HPLC. In the case of **2a** and **3a**, retention times were 35 min for **2a**, and 38 min for **3a**.

#### 4.2.1. (2)–3-Bromo-6-phenyl-1-trimethylsilyl-3-hexen-1-yne (*2a*)

Oil; $Rf = 0.39$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.35–7.15 (5H, m), 6.36 (1H, t, $J = 7.0$ Hz), 2.75 (2H, t, $J = 7.5$ Hz), 2.59–2.49 (2H, m), 0.21 (9H, s); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 140.8, 139.9 (CH), 128.5, 128.4, 126.2, 103.1, 120.2, 95.2, 33.9, 33.6, −0.3; MS (EI) $m/z$ (relative intensity) 308 and 306 [$M^+$, 0.2 and 0.2]. HRMS $m/z$ Calc. for $C_{15}H_{19}SiBr$: [$M^+$], 308.0419 and 306.0439. Found: $m/z$ 308.0423 and 306.0446.

#### 4.2.2. 6-Phenyl-1-trimethylsilyl-3-(trimethylsilylethynyl)hexen-1-yne (*3a*)

Oil; $Rf = 0.23$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.35–7.15 (5H, m), 6.44 (1H, t, $J = 7.2$ Hz), 2.82–2.60 (4H, m), 0.23 (9H, s), 0.21 (9H, s); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 150.2 (CH), 141.1, 128.4, 128.3, 126.1, 106.6, 102.4, 99.6, 98.9, 91.9, 34.5, 32.5, −0.09, −0.12; MS (EI) $m/z$ (relative intensity) 324 [$M^+$, 2]. HRMS Calc. for $C_{20}H_{28}Si_2$: [$M^+$], 324.1730. Found: $m/z$ 324.1722.

#### 4.2.3. (Z)-3-Bromo-1-triethylsilyl-6-phenyl-3-hexen-1-yne (*2b*)

Oil; $Rf = 0.55$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.33–7.15 (5H, m), 6.34 (1H, t, $J = 7.2$ Hz), 2.74 (2H, t, $J = 7.7$ Hz), 2.58–2.47 (2H, m), 1.00 (9H, t, $J = 7.7$ Hz), 0.63 (6H, q, $J = 7.7$ Hz); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 140.8, 139.6 (CH), 128.5, 128.4, 126.2, 103.6, 103.2, 93.1, 33.9, 33.7, 7.4, 4.3; MS (EI) $m/z$ (relative intensity) 350 and 348 [$M^+$, 1 and 1]. HRMS $m/z$ Calc. for $C_{18}H_{25}SiBr$: [$M^+$], 350.0889 and 348.0909. Found: $m/z$ 350.0901 and 348.0895.

#### 4.2.4. Triethylsilyl-3-(triethylsilylethynyl)-6-phenyl-3-hexen-1-yne (*3b*)

Oil; $Rf = 0.40$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.32–7.15 (5H, m), 6.39 (1H, t, $J = 7.3$ Hz), 2.78–2.62 (4H, m), 1.01 (9H, t, $J = 7.9$ Hz), 1.00 (9H, t, $J = 7.9$ Hz), 0.68–0.56 (12H, m); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 149.2 (CH), 141.2, 128.4, 128.3, 126.0, 106.9, 104.0, 101.1, 96.3, 89.5, 34.6, 32.6, 7.4, 4.4; MS (EI) $m/z$ (relative intensity) 408 [$M^+$, 13]. HRMS Calc. for $C_{26}H_{40}Si_2$: [$M^+$], 408.2669. Found: $m/z$ 408.2674.

#### 4.2.5. (Z)-3-Bromo-1, 1-dimethyl-6-phenyl-3-hepten-1-yne (*2c*)

Oil; $Rf = 0.42$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.33–7.16 (5H, m), 6.16 (1H, t, $J = 7.0$ Hz), 2.73 (2H, t, $J = 7.8$ Hz), 2.57–2.46 (2H, m), 1.24 (9H, s); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 141.0, 137.1 (CH), 128.5, 128.4, 126.1, 103.9, 99.0, 78.1, 34.0, 33.6, 30.6, 27.9; MS (EI) $m/z$ (relative intensity) 292 and 290 [$M^+$, 3 and 3]. HRMS $m/z$ Calc. for $C_{16}H_{19}Br$: [$M^+$], 292.0650 and 290.0670. Found: $m/z$ 292.0642 and 290.0674.

#### 4.2.6. 1,1-Dimehyl-3-(3,3-dimethylbutynyl)-6-phenyl-3-hepten-1-yne (*3c*)

Oil; $Rf = 0.23$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.32–7.15 (5H, m), 6.15 (1H, t, $J = 7.3$ Hz), 2.75–2.65 (2H, m), 2.65–2.54 (2H, m), 1.27 (9H, s), 1.24 (9H, s); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 144.9 (CH), 141.6, 128.4, 125.9, 106.7, 101.8, 95.1, 77.7, 75.2, 34.8, 32.2, 31.0, 30.9, 28.1, 27.7; MS (EI) $m/z$ (relative intensity) 292 [$M^+$, 9]. HRMS Calc. for $C_{22}H_{28}$: [$M^+$], 292.2191. Found: $m/z$ 292.2193.

*4.2.7. (Z)-3-Bromo-1, 6-diphenyl-3-hexen-1-yne (**2d**)*

Oil; $Rf = 0.37$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.47–7.42 (2H, m), 7.34–7.28 (5H, m), 7.24–7.20 (3H, m), 6.37 (1H, t, $J = 7.0$), 2.78 (2H, t, $J = 7.7$), 2.65–2.55 (2H, m); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 140.8, 139.2 (CH), 131.7, 128.8, 128.5, 128.4, 128.3, 126.2, 103.1, 89.3, 87.6, 34.0, 33.7; MS (EI) *m/z* (relative intensity) 312 and 310 [$M^+$, 8 and 8]. HRMS *m/z* Calc. for $C_{18}H_{15}Br$: [$M^+$], 312.0337 and 310.0357. Found: *m/z* 312.0323 and 310.0353.

*4.2.8. 1, 6-Diphenyl-3-(2-phenylethynyl)-3-hexen-1-yne (**3d**)*

Oil; $Rf = 0.17$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.52–7.45 (4H, m), 7.36–7.17 (11H, m), 6.47 (1H, m), 2.86–2.78 (4H, m); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 147.9 (CH), 141.1, 131.7, 128.5, 128.5, 128.4, 128.3, 128.3, 128.3, 126.1, 123.0, 122.9, 106.4, 93.2, 87.3, 86.9, 34.8, 32.6; MS (EI) *m/z* (relative intensity) 332 [$M^+$, 5]. HRMS Calc. for $C_{26}H_{20}$: [$M^+$], 332.1565. Found: *m/z* 332.1563.

*4.2.9. (Z)-4-Bromo-1-phenyl-3-decen-5-yne (**2e**)*

Oil; $Rf = 0.44$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.33–7.15 (5H, m), 6.18 (1H, t, $J = 7.0$ Hz), 2.73 (2H, t, $J = 7.6$ Hz), 2.57–2.47 (2H, m), 2.36 (2H, t, $J = 6.9$ Hz), 1.58–1.35 (4H, m), 0.92 (3H, t, $J = 7.2$ Hz); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 141.0, 137.2 (CH), 128.5, 128.4, 126.1, 103.9, 91.5, 79.4, 34.0, 33.5, 30.4, 22.0, 19.0, 13.6; MS (EI) *m/z* 292 and 290 [$M^+$, 0.8 and 0.8]. HRMS *m/z* Calc. for $C_{16}H_{19}Br$: [$M^+$], 292.0650 and 290.0670. Found: *m/z* 292.0653 and 290.0654.

*4.2.10. 4-Hexynyl-1-phenyl-3-decen-5-yne (**3e**)*

Oil; $Rf = 0.24$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.32–7.16 (5H, m), 6.16 (1H, t, $J = 7.2$ Hz), 2.75–2.58 (4H, m), 2.35 (2H, t, $J = 6.9$ Hz), 2.28 (2H, t, $J = 7.0$ Hz), 1.58–1.36 (8H, m), 0.91 (3H, t, $J = 7.3$ Hz), 0.91 (3H, t, $J = 7.2$ Hz); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 145.1 (CH), 141.5, 128.3, 125.9, 106.6, 94.0, 87.3, 79.1, 34.8, 32.2, 30.8, 30.7, 22.0, 19.2, 19.0, 13.6; MS (EI) *m/z* (relative intensity) 292 [$M^+$, 1]. HRMS Calc. for $C_{22}H_{28}$: [$M^+$], 292.2191. Found: *m/z* 292.2190.

*4.3. Hydrogenation of trimethylsilylethynyl group with diimide*

To a mixture of **2a** (65 mg, 0.212 mmol) and dipotassium azodicarboxylate (412 mg, 2.12 mmol) in THF (2 ml) was added a solution of acetic acid (255 mg, 4.24 mmol) in THF (1 ml) at r.t. over a period of 2 h. The reaction mixture was stirred for 18 h at the same temperature, and then it was diluted with hexane (5 ml), washed with water (3 ml) and brine (3 ml). The organic layer was dried over $MgSO_4$, and condensed in vacuo. The crude mixture was purified by silica gel column chromatography eluted with hexane to **4** (40 mg) in 61% yield. (*Z*)-3-Bromo-1-trimethylsilyl-6-phenyl-3-hexene (**4**); Oil; $Rf = 0.56$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.35–7.16 (5H, m), 5.70 (1H, t, $J = 6.6$ Hz), 2.71 (2H, t, $J = 7.7$ Hz), 2.53–2.36 (4H, m), 0.83–0.75 (2H, m), 0.01 (9H, s); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 141.6, 132.4 (CH), 128.4, 128.4, 125.9, 125.7, 36.4, 34.7, 33.0, 16.1, −1.7; MS (EI) *m/z* (relative intensity) 312 and 310 [$M^+$, 1.2 and 1.3]. HRMS *m/z* Calc. for $C_{15}H_{23}SiBr$: [$M^+$], 312.0732 and 310.0752. Found: *m/z* 312.0737 and 310.0747.

*4.4. Preparation of 3-bromo-1-(tert-butyldiphenylsilyl)oxy-5-trimethylsilyl-2-penten-4-yne (**6**)*

The same reaction procedure described in the typical Sonogashira coupling was used. Compound **5** was yielded in 81%. Oil; $Rf = 0.34$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.64–7.68 (4H, m), 7.37–7.47 (6H, m), 6.55 (1H, t, $J = 5.3$ Hz), 4.33 (2H, d, $J = 5.3$ Hz), 1.05 (9H, s), 0.22 (9H, s); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 140.4, 135.5, 133.1 (CH), 129.8, 127.8, 101.6, 100.7, 96.1, 64.2, 26.7, 19.2, −0.4; MS (FAB) *m/z* 495 and 493 [M + Na]$^+$. HRMS Calc. for $C_{24}H_{31}BrOSi_2Na$: [M + Na]$^+$, 495.0978 and 493.0995. Found: *m/z* 495.0095 and 493.1008.

*4.5. 3-Bromo-1-(tert-butyldiphenylsilyl)oxy-5-trimethylsilyl-2-pentene (7)*

The same hydrogenation procedure described for the preparation of **4** was used. The reaction of **6** gave **7** in 68% yield. Oil; $Rf = 0.26$ (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.72–7.65 (4H, m), 7.47–7.35 (6H, m), 5.92 (1H, double t, $J = 5.5$, 1.1 Hz), 4.35 (2H, dt, $J = 5.5$, 1.1 Hz), 2.45–2.34 (2H, m), 1.07 (9H, s), 0.80–0.71 (2H, m), 0.02 (9H, s); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$ 135.6, 133.7 (CH), 130.6, 129.7, 127.7, 126.9, 64.3, 36.3, 26.9, 19.2, 15.8, −1.7; MS (EI) *m/z* (relative intensity) 476 and 474 [$M^0$, 0.4 and 0.4]. HRMS *m/z* Calc. for $C_{24}H_{35}Si_2Br$: [$M^+$], 476.1389 and 474.1409. Found: *m/z* 476.1392 and 474.1401.

*4.6. Preparation of 3-bromo-6-phenyl-3-hexen-1-yne (**8**)*

To a mixture of **2a** (126 mg, 0.4 mmol) in THF (3 ml) was added a THF solution of *n*-$Bu_4NF$ (0.4 ml, 0.4 mmol, 1.0 M in THF) at r.t. The mixture was stirred for 15 min, diluted with hexane (5 ml), washed with water (2 ml) and brine (2 ml). The organic layer was dried over $MgSO_4$, and condensed in vacuo. The crude mixture was purified by silica gel column chromatography eluted with hexane to give **8** (91 mg) in 95% yield. Oil; $Rf =$ 0.44 (hexane); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ 7.35–7.27 (2H, m), 7.25–7.17 (3H, m), 6.42 (1H, t, $J = 7.0$ Hz), 3.09 (1H, s), 2.76 (2H, t, $J = 7.7$ Hz), 2.56 (2H, td, $J =$

7.7, 7.0 Hz); $^{13}$C-NMR (75 MHz, $CDCl_3$) δ 140.9, 140.6 (CH), 128.5, 128.4, 126.3, 102.1, 81.7, 77.5, 33.8, 33.5; MS (EI) *m/z* (relative intensity) 236 and 234 [$M^+$, 0.8 and 0.8]. HRMS Calc. for $C_{12}H_{11}Br$: [$M^+$], 236.0024 and 234.0044. Found: *m/z* 236.0018 and 234.0042.

#### 4.6.1. Preparation of (Z)-4-bromo-7-phenyl-4-hepten-2-yne (**9a**)

To a mixture of **8** (30 mg, 0.13 mmol) and iodomethane (77 mg, 0.64 mmol) in THF (0.2 ml) was added a solution of lithium bis(trimethylsilyl)amide (0.52 ml, 0.52 mmol, 1.0 M in THF) at −20 °C and the mixture was stirred for 20 min at the same temperature. Then, it allowed to warm up to 0 °C during 10 min. The mixture was diluted with ether, and washed with water and brine. The ethereal solution was dried over $MgSO_4$ and condensed. The residual oil was purified by column chromatography on silica gel eluted with hexane. **9a** (28 mg) was obtained in 97% yield. Oil; *Rf* = 0.43 (2% EtOAc in hexane); $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.35–7.17 (5H, m), 6.18 (1H, t, *J* = 7.0 Hz), 2.73 (2H, t, *J* = 7.7 Hz), 2.53 (2H, td, *J* = 7.7, 7.0 Hz) 2.01 (3H, s); $^{13}$C-NMR (75 MHz, $CDCl_3$) δ 140.9, 137.4 (CH), 128.5, 128.4, 126.1, 103.8, 86.9, 78.6, 34.0, 33.5 4.3; MS (EI) *m/z* (relative intensity) 250 and 248 [$M^+$, 1.5 and 1.5]. HRMS Calc. for $C_{13}H_{13}Br$: [$M^+$], 250.0180 and 248.0200. Found: *m/z* 250.0166 and 248.0208.

#### 4.6.2. Preparation of ethyl 4-bromo-7-phenyl-4-hepten-2-ynoate (**9b**)

The same procedure as described for **9a** was employed except the use of ethyl chloroformate instead of iodomethane. Compound **9b** was obtained in 80% yield. Oil; *Rf* = 0.35 (5% EtOAc in hexane); $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.35–7.16 (5H, m), 6.66 (1H, t, *J* = 7.0 Hz), 4.26 (2H, q, *J* = 7.2 Hz), 2.77 (2H, t, *J* = 7.3 Hz), 2.66–2.57 (2H, m) 1.32 (3H, t, *J* = 7.2 Hz); $^{13}$C-NMR (75 MHz, $CDCl_3$) δ 153.3, 146.2, 140.2, 128.6, 128.4, 126.4, 100.3, 83.0, 79.8, 62.3, 33.9, 33.6 14.0; MS (EI) *m/z* (relative intensity) 306 and 308 [$M^+$, 7.2 and 6.8]. HRMS Calc. for $C_{15}H_{15}BrO_2$: [$M^+$], 308.0235 and 306.0255. Found: *m/z* 308.0249 and 306.0266.

#### 4.6.3. Preparation of 4-bromo-7-phenyl-1-(p-tolyl)-4-hepten-2-yn-1-ol (**9c**)

The same procedure as described for **9a** was employed except the use *p*-tolualdehyde instead of iodomethane, and the addition temperature at −60 °C instead of −20 °C. A 3:2 mixture of hexane and ether was used as an eluent for silica gel column chromatography. Compound **9c** was obtained in 88% yield. Oil; *Rf* = 0.38 (20% EtOAc in hexane); $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.1 Hz), 7.33–7.16 (7H, m), 6.35 (1H, t, *J* = 7.3 Hz), 5.56 (1H, d, *J* = 5.5 Hz), 2.74 (2H, t, *J* = 7.7 Hz), 2.55 (2H, td, *J* = 7.7, 7.3 Hz), 2.36 (3H, s) 2.19 (1H, d, *J* = 5.5 Hz); $^{13}$C-NMR (75 MHz, $CDCl_3$) δ 140.7, 140.1, 138.5, 137.2, 129.4, 128.5, 128.4, 126.7, 126.2, 102.4, 89.0, 84.7 64.7, 33.9, 33.6, 21.2; MS (EI) *m/z* (relative intensity) 356 and 354 [$M^+$, 8 and 8]. HRMS Calc. for $C_{20}H_{19}BrO$: [$M^+$], 356.0599 and 354.0619. Found: *m/z* 356.0594 and 354.0620.

## Acknowledgements

The authors are grateful to Professor Y. Ito for his encouragement and valuable discussions. This work was financially supported by the Grant-in-Aid for Scientific Research on Priority Areas (A) from the Ministry of Education, Science, Sports and Culture, Japan, and a Special Grant for Cooperative Research administered by the Japan Private School Promotion Foundation.

## References

[1] (a) M.E. Maier Synlett (1995) 13;
(b) J.W. Grissom, G.U. Gunawardena, D. Klingberg, D. Huang, Tetrahedron 52 (1996) 6453;
(c) K.C. Nicolaou, A.L. Smith, Acc. Chem. Res. 25 (1992) 497;
(d) D. Kuhnt, T. Anke, H. Besl, M. Bross, R. Herrmann, U. Mocek, B. Steffan, W. Steglich, J. Antibiot 43 (1990) 1413;
(e) T. Kusumi, I. Ohtani, K. Nishiyama, H. Kakisawa, Tetrahedron Lett. 28 (1987) 3981;
(f) T. Ohta, K. Uwai, R. Kikuchi, S. Nozoe, Y. Oshima, K. Sasaki, F. Yoshizaki, Tetrahedron 55 (1999) 12087;
(g) W. Trowitsch-Kienast, E. Forche, V. Wray, H. Riechenbach, G. Hunsmann, G. Höfle, Liebigs Ann. Chem. (1992) 659;
(h) A.M. Boldi, J. Anthony, V. Gramlich, C. Knobler, C. Boudon, J. –P. Gisselbrecht, M. Gross, F. Diederich, Helv. Chim. Acta 78 (1995) 779;
(i) G. Hynd, G.B. Jones, G.W. Plourde, II, J.M. Wright, Tetrahedron Lett. 40 (1999) 4481;
(j) S. Shimada, A. Masaki, K. Hayamizu, H. Matsuda, S. Okada, H. Nakanishi, Chem. Lett. (2000) 1128;
(k) S.C. Ciulei, R.R. Tykwinski, Organic Lett. 2 (2000) 3607.
[2] (a) K. Sonogashira, in: B.M. Trost, I. Fleming (Eds.), Comprehensive Organic Synthesis, vol. 3, Pergamon Press, New York, 1991, p. 521;
(b) K. Sonogashira, in: F. Diederich, P.J. Stang (Eds.), Metal-Catalyzed Cross-coupling Reactions, Wiley–VCH, Weinheim, 1998, p. 203.
[3] For example, hydrogenolysis of 1,1-dihalo-1-alkene; (a) T. Hirao, T. Masunaga, Y. Ohshiro, T. Agawa, J. Org. Chem. 46 (1981) 3745.
(b) K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, K. Utimoto, K. Bull. Chem. Soc. Jpn. 62 (1989) 143.
[4] A. Minato, K. Suzuki, K. Tamao, J. Am. Chem. Soc. 109 (1987) 1257.
[5] (a) W.R. Roush, K.J. Moriarty, B.B. Brown, Tetrahedron Lett. 31 (1990) 6509;
(b) W.R. Roush, K. Koyama, M.L. Curtin, K.J. Moriarty, J. Am. Chem. Soc. 118 (1996) 7502.
[6] W. Shen, L. Wang, J. Org. Chem. 64 (1999) 8873.
[7] (a) J. Uenishi, R. Kawahama, O. Yonemitsu, J. Tsuji, J. Org. Chem. 61 (1996) 5716;
(b) J. Uenishi, R. Kawahama, Y. Shiga, O. Yonemitsu, J. Tsuji, Tetrahedron Lett. 37 (1996) 6759.

[8] Harsh conditions or the use of a large excess of coupling reagent for a longer period of time gave enediyne and/or complicated products.
[9] J. Uenishi, R. Kawahama, O. Yonemitsu, J. Tsuji, J. Org. Chem. 63 (1998) 8965.
[10] (a) A. Bryant-Friedrich, R. Neidlein, Synthesis (1995) 1506;
(b) M. Ogasawara, H. Ikeda, K. Ohtsuki, T. Hayashi, Chem. Lett. (2000) 776;
(c) M. Braun, J. Rahematpura, C. Bühne, T.C. Paulitz, Synlett (2000) 1070.
[11] K. Sonogashira, Y. Tohda, N. Hagiwaha, Tetrahedron Lett. 1975, 4756.
[12] D.J. Pasto, R.T. Taylor, Org. Reaction 40 (1991) 91.
[13] For quantitative analyses, 30–50 mg of **1** was used for each reaction, and the products were purified by HPLC. Therefore, all of the yields listed in Tables were comparable numbers. In the productive scale (0.3–1.0 g), the yield of **2a** increased up to 75–87%.
[14] Only a trace amount of **2a** was yielded in other solvents such as acetonitrile, methylene chloride, and DMSO.
[15] The result using $Pd(PPh_3)_4$ gave poor yield.