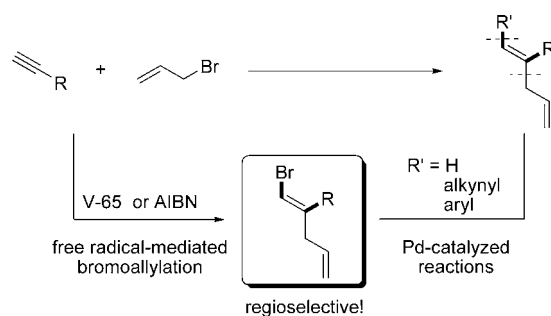# Regioselective Synthesis of 1-Bromo-1,4-dienes by Free-Radical-Mediated Bromoallylation of Activated Acetylenes

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ABSTRACT

The free-radical-mediated bromoallylation of acetylenes proceeded efficiently in the presence of V-65 (2,2-azobis(2,4-dimethylvaleronitrile)) as the radical initiator. The regioselective reaction, which yields 1-bromo-2-substituted 1,4-dienes, is complementary to the Pd-catalyzed bromoallylation reaction previously reported by Kaneda. The products of the free-radical-mediated bromoallylation of acetylenes could be converted into a variety of substituted dienes by subsequent Pd-catalyzed reactions.

Bromoallylation of acetylenes, one of the most basic transformations, can lead to bromo-substituted 1,4-dienes, which are versatile synthetic building blocks. In principle the bromoallylation of terminal acetylenes can give type **A** and **B** of 1,4-dienes (eq 1). Therefore, control of the regiochemistry is essential for the bromoallylation reaction to be synthetically useful.
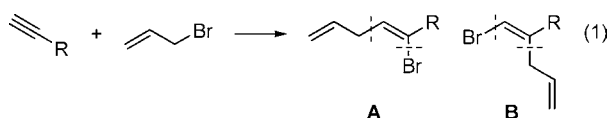
In 1974, Kaneda and co-workers reported that bis(benzonitrile)palladium dibromide catalyzed bromo-allylation of terminal acetylenes to selectively yield type **A** 4-bromo-1.4-dienes.[1] Subsequently, other research groups studied the use of zinc chloride[2a] and other palladium complexes[2b,c] as catalysts and observed that the **A** dienes were favored in these reactions. In the reactions that used supported Pd complexes, such as Pd on diphenylbenzylphosphine-functionalized polymer[3] or Pd on Al$_2$O$_3$,[4] a mixture of type **A** and **B** 1,4-dienes formed, in which the **A** dienes were the major products (>75%). However, the regioselective bromoallylation of acetylenes to give type **B** bromo-dienes has yet to be achieved. Herein, we report that the free-radical-mediated bromoallylation of acetylenes with allylbromide proceeded regioselectivity to give type **B** 1-bromo-2-substituted 1,4-dienes in good yields (Scheme 1).[5]

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(2) (a) Miller, A.; Moore, M. *Tetrahedron Lett.* **1980**, 577. (b) Bäckvall, J.-E.; Nilsson, Y. I. M.; Gatti, R. G. P. *Organometallics* **1995**, *14*, 4242. (c) For Pd-catalyzed chloroallylation reaction starting from allyl alcohol, see: Huang, J.; Zhou, L.; Jiang, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 1945.
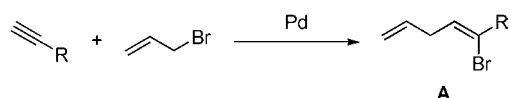
(3) Kaneda, K.; Uchiyama, T.; Terasawa, M.; Imanaka, T.; Teranishi, S. *Chem. Lett.* **1976**, 449.

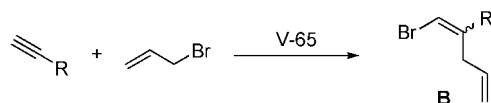(4) Fukuyama, T.; Kippo, T.; Ryu, I. *Res. Chem. Intermed.* **2009**, *35*, 1053.

(5) For the free-radical-mediated iodoallylation of alkynes to give type **A** of iodo-1,4-dienes, see: Liu, S. Q.; Wang, S. W.; Qing, F. L. *J. Fluorine Chem.* **2005**, *126*, 771.

**Scheme 1.** Bromoallylation of Acetylenes

Previous Work

This Work

We examined the reaction of phenylacetylene (**1a**) and allylbromide (**2a**) as a model system under a variety of radical reaction conditions. The results are summarized in Table 1.

Table 1. Free-Radical-Mediated Bromoallylation Reaction of Phenylacetylene (**1a**) and Allylbromide (**2a**) in the Presence of Radical Initiator
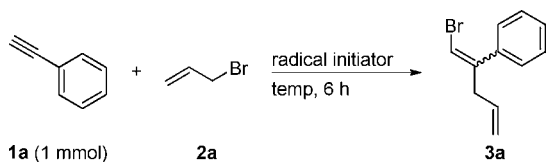
entry	2a (mL)	initiator (mol %)	temp (°C)	yield[a] (%)	E/Z[b]
1	1	V-65 (30)	60	37[c]	9/91
2	3	V-65 (30)	60	62	19/81
3	5	V-65 (30)	60	80	13/87
4	**5**	**V-65 (20)**	**60**	**80**	**23/77**
5	5	V-65 (10)	60	60	13/87
6	5	AIBN (20)	80	78	15/85
7[d]	5	AIBN (20)	rt	79	19/81

[a] Isolated yield based on **1**. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by ^{1}H NMR using anisole as internal standard. [d] Under photo irradiation (xenon lamp 300 W, Pyrex).

When a mixture of **1a** (1 mmol), **2a** (1 mL, 11.5 mmol), and 30 mol % V-65 (2,2-azobis(2,4-dimethyl-valeronitrile); half-life = 2 h at 60 °C) was stirred at 60 °C under an argon atmosphere, the bromoallylated product **3a** was obtained in 37% yield (entry 1). Although the yields were rather low, we were pleased that the reaction was regioselective for the type **B** diene, as the regioisomer was not present in the crude reaction mixture. When the amount of **2a** was increased to 5 mL, the yield of **3a** was increased to 80% (entry 3). Reducing the amount of the radical initiator to 20 mol % did not affect the yield of **3a** (entry 4), whereas when 10 mol % of V-65 was used, a significant amount of **1a** remained unreacted (entry 5). The reaction using AIBN (2,2-azobisisobutyronitrile; half-life = 2 h at 80 °C) as the radical initiator at 80 °C and photoirradiation conditions at room temperature gave results similar to that obtained with V-65 (entry 6 and 7).

After we identified the optimal reaction conditions, we investigated the generality of the free-radical-mediated bromoallylation, the results of which are shown in Table 2.

Table 2. Synthesis of Bromo-1,4-dienes by Free-Radical-Mediated Bromoallylation of Acetylenes[a]

| entry	1	2	3	yield[b] (%)	E/Z[c]
1	**1a** (R = Ph)	2a	R = Ph	3a (80)	23/77
2	**1b** (R = Me)	2a		3b (80)	16/84
3	**1c** (R = OMe)			3c (70)	23/77
4	**1d** (R = CO$_2$Et)			3d (93)	35/65
5	**1e** (R = Ac)			3e (94)	27/73
6	**1f** (o-Cl)	2a		3f (97)	6/94
7	**1g** (m-Cl)			3g (85)	14/86
8	**1h** (p-Cl)			3h (81)	18/82
9	**1i**	2a		3i (90)	6/94
10	**1j**	2a		3j (83)	99/1
11	**1k**	2a		3k (87)	26/74
12	**1l**	2a		3l (77)	58/42
13	**1m**	2a		3m (86)	26/74
14	**1n**	2a		3n (49)	34/66
15	**1a**	**2b**		3o (95)	10/90

[a] Conditions: acetylenes **1** (1.0 mmol), allylbromides **2** (5 mL, 58.0 mmol), V-65 (0.2 mmol), 60 °C, 6 h under an argon atmosphere. [b] Isolated yield by silica gel chromatography based on **1**. [c] Determined by ^{1}H NMR of the crude reaction mixture.

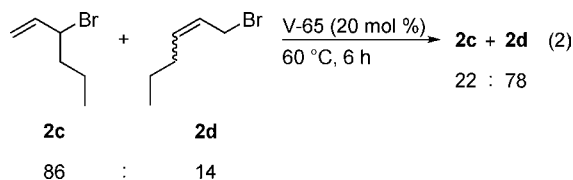**Scheme 2.** Proposed Reaction Mechanism

Initiation Step
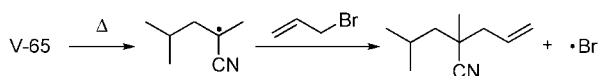

Chain Propagation Step


major   *minor*
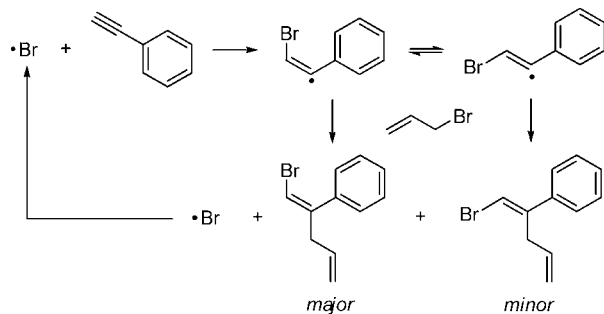
Irrespective of whether the substituents of the aryl acetylenes were electron-donating or electron-withdrawing, the bromoallylation reaction proceeded well to give the corresponding 1,4-dienes in good yield. (entries 2−5). The reactions with the Cl-phenyl-substituted terminal alkynes proceeded smoothly regardless of the position of the Cl on the ring of the phenyl group (entries 6−8). The reaction of 2,5-dimethoxyphenyl acetylene (**1i**) with **2a** gave 1-bromo-2-(2,5-dimethoxyphenyl)-1,4-pentadiene (**3i**) in 90% yield (entry 9). The reactions of the 1- and 2-naphtyl-substituted acetylenes, **1j** and **1k** also proceeded well (entries 10 and 11). Interestingly, the reaction of **1j** with **2a** gave the *E* isomer almost exclusively, unlike the other reaction shown in Table 2 (vide infra).

The reaction also worked well for acetylenes with a heteroaromatic substituent, such as **1l** (entry 12). The reaction with ethyl propiolate (**1m**) and with DMAD (dimethyl acetylenedicarboxylate, **1n**) gave the corresponding 1,4-dienes in 86% and 49% yield, respectively (entries 13 and 14). Aliphatic acetylenes, such as 1-hexyne, gave only traces of the bromoallylated product (2%). We also examined several substituted allylic bromides. The reaction using β-methallyl bromide (**2b**) proceeded smoothly to give 1-bromo-1,4-diene **3o** in 95% yield (entry 15). In contrast, no reaction took place with crotyl bromide or prenyl bromide, presumably due to the steric hindrance caused by the substitution at the 3-position. Surprisingly, the reaction of **1a** with 3-bromo-1-hexene (**2c**) was unsuccessful. The reaction did not proceed because of radical-mediated isomerization of **2c** to the unreactive crotyl like **2d** during the reaction. This isomerization behavior was confirmed by a separate experiment (eq 2).

2c   **2d**

86   :   14

Scheme 3. Three-Component Processes with the Subsequent Pd-Catalyzed Reactions

4 (80%)

5a (70%, R = Ph)
5b (80%, R = 1-naphthyl)

**6** (77%, *E/Z* = 17/83)

7 (75%, *E/Z* = 13/87)
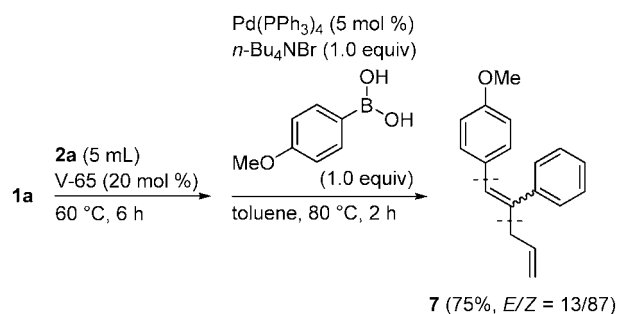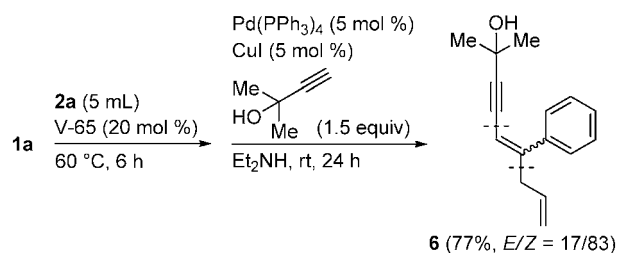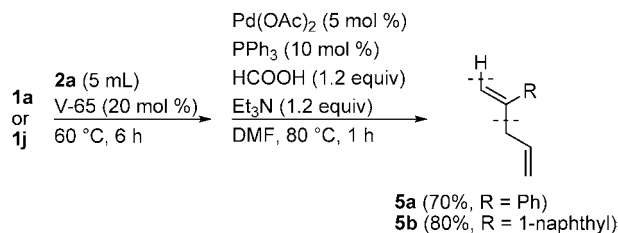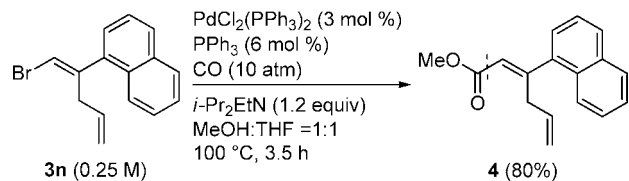
A reaction mechanism for the free-radical-mediated bromoallylation of acetylenes is outlined in Scheme 2, which employs the reaction of **1a** with **2a** as an example. Tanko and co-workers recently reported that bromine radicals act as chain propagators,[6] and this mechanism might be operative even in our system. Thus, thermal decomposition of V-65 generates the initiating radicals, which add to allylbromide to generate bromo radicals. The bromo radicals then selectively attack the acetylene terminus to form vinyl radicals. The resulting vinyl radicals react with allylbromide in an S_H2' manner, which gives 1-bromo-2-phenyl-1,4-diene and regenerates bromo radicals, thus creating a radical chain.[7] In general, *Z*-forms are preferred because the site of attack by allylbromide is less hindered.

(6) (a) Tanko, J. M.; Sadeghipour, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 159. (b) Struss, J. A.; Sadeghipour, M.; Tanko, J. M. *Tetrahedron Lett.* **2009**, *50*, 2119.
(7) A similar mechanism was proposed in radical addition of allylic sulfones to phenylacetylene; see: Harvey, I. W.; Philips, E. D.; Whitham, G. H. *Tetrahedron* **1997**, *53*, 6493.

For the exception **1j**, the *E*-vinyl radical was preferred due to the steric hindrance caused by bromine and peri-hydrogen (eq 3).

$$E\text{-}\mathbf{3j} \quad (3)$$
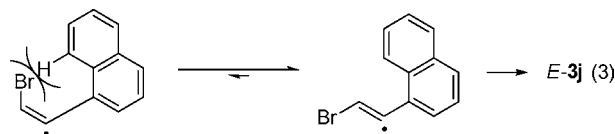
The products **3** that resulted from the present radical reaction involved terminal vinyl bromide substructures, which readily undergo Pd-catalyzed reactions (Scheme 3).[8,9] Indeed, the carbonylation[10] of **3n** proceeded smoothly under 10 atm of carbon monoxide to yield the corresponding α,β-unsaturated ester **4** in 80% yield. One-pot syntheses of 2-aryl-1,4-pentadiene (**5a**, **5b**), 2-methyl-6-phenyl-5,8-nonadiene-3-yn-2-ol (**6**), and 1-(4-methoxy-phenyl)-2-phenyl-1,4-pentadiene (**7**) were successfully achieved via a palladium-catalyzed, formic acid reduction,[11] the Sonogashira reaction,[12] and the Suzuki−Miyaura coupling reaction,[13] respectively.

In conclusion, the free-radical-mediated bromo-allylation reactions of acetylenes with allylbromides gave regioselective 1-bromo-2-substituted-1,4-dienes. The observed regioselectivity was complementary to that previously reported for palladium-catalyzed reactions. The bromoallylation procedure was successfully combined with carbonylation, a Pd-catalyzed reduction, the Sonogashira reaction, or the Suzuki−Miyaura coupling reaction to provide a variety of substituted 1,4-dienes, in a two-step process.

Supporting Information Available: Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For related one-pot methods, see: (a) Bazin, M.-A.; Jouanne, M.; El-Kashef, H.; Rault, S. *Synlett* **2009**, 2789. (b) Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Tetrahedron* **2005**, *61*, 4043. (c) Kutsumura, N.; Niwa, K.; Saito, T. *Org. Lett.* **2010**, *12*, 3316.

(10) Silveira, P. B.; Monteiro, A. L. *J. Mol. Catal.* **2006**, *247*, 1.

(11) Clasby, M. C.; Chackalamannil, S.; Czarniecki, M.; Doller, D.; Eagen, K.; Greenlee, W. J.; Lin, Y.; Tagat, J. R.; Tsai, H.; Xia, Y.; Ahn, H.; Agans-Fantuzzi, J.; Boykow, G.; Chintala, M.; Hsieh, Y.; McPhail, A. T. *Tetrahedron* **2007**, *17*, 3647.

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