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Silver-Catalyzed Difunctionalization of Terminal Alkynes: Highly Regio- and Stereoselective Synthesis of (*Z*)-*β*-Haloenol Acetates

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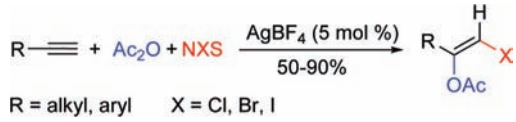
ABSTRACT



A new silver-catalyzed highly regio- and stereoselective difunctionalization reaction of simple terminal alkynes was reported in which the (*Z*)-*β*-haloenol acetate derivatives were formed efficiently. The resulting products were versatile intermediates in organic synthesis.

Transition-metal-catalyzed reactions are versatile tools for carbon−carbon and carbon−heteroatom bond formation and, hence, are the focus of intense synthetic attention.[1] In particular, recent advances in the transition-metal-catalyzed functionalization of alkynes have provided rapid and concise access to complex chemical frameworks.[2] Terminal alkynes are readily accessible starting materials, and remarkable progress has been made in the transition-metal-catalyzed difunctionalization of terminal alkynes in the past decades.[3] The *β*-haloenol acetate molecular skeletons are important intermediates in organic synthesis, as the vinyl halide moiety is often employed for transition-metal-catalyzed cross-coupling reactions and halogen−metal exchange reactions,[4] and enol acetates are frequently used as intermediates in organic synthesis and pharmaceutical chemistry.[5,6] However, there are very few catalytic methods for forming the OC═CX bond (X = Cl, Br, I) in one step from simple terminal alkynes.[7] For example, Barluenga[7b] described an elegant electrophilic addition reaction that gave anti addition (*E*)-products from the terminal alkynes. On the other hand, over

(1) (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (c) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (d) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840.

(2) (a) Li, Y.; Liu, X.; Jiang, H.; Feng, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 3338. (b) Minami, Y.; Kuniyasu, H.; Miyafuji, K.; Kambe, N. *Chem. Commun.* **2009**, 3080. (c) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (e) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725.

(3) For recent selected examples of difunctionalization of terminal alkyne, see :(a) Goossen, L. J.; Rodríguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9592. (b) Mizuno, A.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 8318. (c) Sha, F.; Huang, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 3458. (d) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. (e) Dutta, B.; Gilboa, N.; Marek, I. *J. Am. Chem. Soc.* **2010**, *132*, 5588. (f) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (g) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786.

(4) For recent selected examples, see: (a) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (b) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435. (c) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314. (d) Bettinger, H. F.; Filthaus, M. *J. Org. Chem.* **2007**, *72*, 9750. (e) Uchiyama, M.; Furuyama, T.; Kobayashi, M.; Matsumoto, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 8404. (f) Boukouvalas, J.; Loach, R. P. *J. Org. Chem.* **2008**, *73*, 8109.

(5) For selected examples, see: (a) Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1997**, 507. (b) Goossen, L. J.; Paetzold, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1095. (c) Zhang, D.; Ready, J. M. *Org. Lett.* **2005**, *7*, 5681. (d) DeBergh, J. R.; Spivey, K. M.; Ready, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7828. (e) Tang, W.; Liu, D.; Zhang, X. *Org. Lett.* **2003**, *5*, 205.

(6) *β*-Haloenol acetates are known to be effective precursors of α-keto dianions; see: (a) Kowalski, C. J.; Haque, M. S. *J. Org. Chem.* **1985**, *50*, 5140. (b) Kowalski, C. J.; O'Dowd, M. L.; Burke, M. C.; Fields, K. W. *J. Am. Chem. Soc.* **1980**, *102*, 5411. (c) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429.

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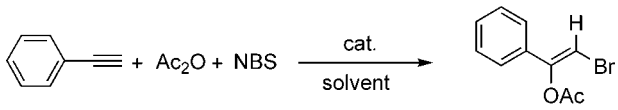
the past decades, the use of silver catalysts in synthetic organic chemistry has become well-established as a result of the ability of silver salt to selectively activate particular functional groups under mild reaction conditions.[8] Recently, our group has reported a series of silver-catalyzed functionalization of different alkynes.[9] As part of this continuing project, we would like to present the first example of a silver-catalyzed highly regio- and stereoselective difunctionalization reaction using simple terminal alkynes, which are easily available from commercial vendors, to afford the (*Z*)-*β*-haloenol acetate derivatives efficiently.

The reaction of phenylacetylene (**1a**) with acetic anhydride was chosen as the model reaction. First, four different commonly used metal salts were used as the catalyst to conduct this reaction. To our delight, we found that $AgBF_4$ could afford the corresponding product in 90% yield (Table 1, entry 4). The reaction did not proceed without silver salt (Table 1, entry 5); only trace product was detected using HBF_4 as the catalyst instead (Table 1, entry 6). Then $AgBF_4$ was used as the catalyst of choice. Except acetic anhydride, DMF and 1,4-dioxane could afford the products as well, albeit in lower yield (Table 1, entries 7−11). The lower temperature disfavored the reaction, and the reaction gave 74% yield after 6 h (Table 1, entries 12−14). Furthermore, microwave radiation can also provide satisfied reaction results (Table 1, entry 15).

Table 1. Optimization of Reaction Conditions for the Difunctionalization of Phenylacetylene[a]



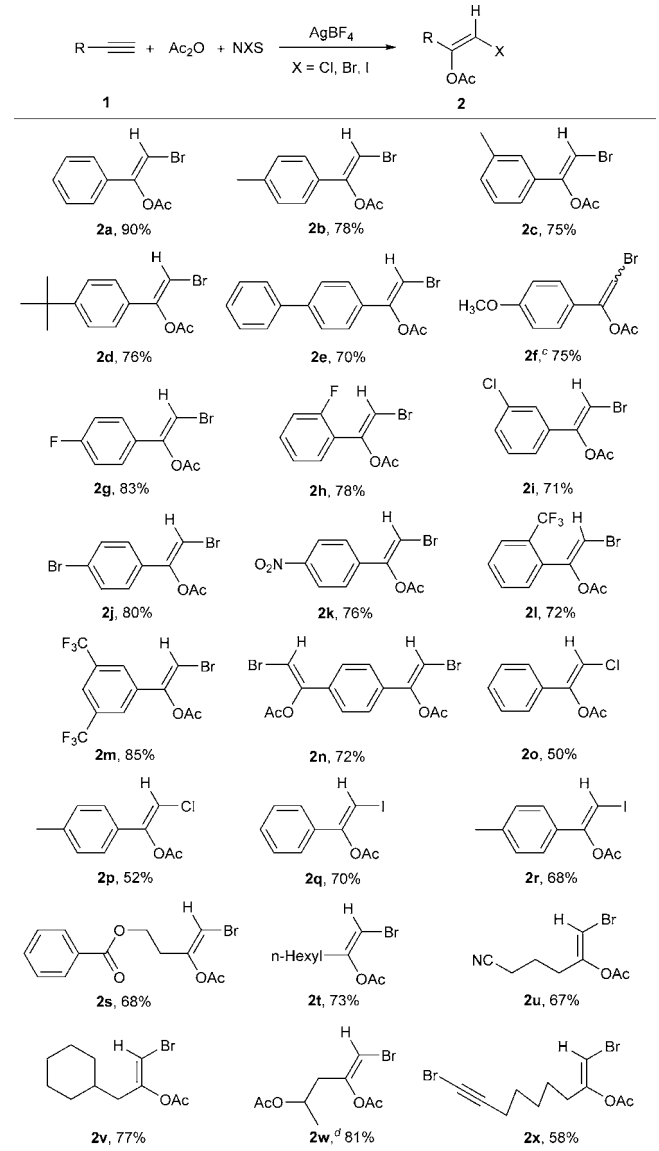
1a **2a**

entry	catalyst	solvent	yield[b] (%)
1	$Pd(OAc)_2$	Ac_2O	n.p.
2	CuI	Ac_2O	n.p.
3	$FeCl_3$	Ac_2O	n.p.
4	**$AgBF_4$**	**Ac_2O**	**90**
5[c]		Ac_2O	n.p.
6[d]	HBF_4	Ac_2O	trace
7	$AgBF_4$	water	trace
8[e]	$AgBF_4$	HOAc	n.p.
9	$AgBF_4$	DMF	73
10	$AgBF_4$	1,4-dioxane	60
11	$AgBF_4$	DMSO	trace
12[f]	$AgBF_4$	Ac_2O	20
13[g]	$AgBF_4$	Ac_2O	53
14[h]	$AgBF_4$	Ac_2O	74
15[i]	$AgBF_4$	Ac_2O	67

[a] Reaction conditions: phenylacetylene (1.0 mmol), NBS (1.2 mmol), acetic anhydride (5 mmol), solvent (2.0 mL), and catalyst (5 mol %) at 120 °C for 12 h. [b] Isolated yield. [c] Without catalyst. [d] 20 mol % of HBF_4. [e] The products were acetophenone and 2-bromo-1-phenylethanone. [f] Room temperature. [g] At 60 °C. [h] 6 h. [i] Reacted at 120 °C for 0.5 h under microwave conditions.

With the optimized conditions in hand (Table 1, entry 4), we next turned our attention to the scope of the difunctionalization reaction from the terminal alkynes. As shown in Scheme 1, aromatic terminal alkynes with either electron-donating or electron-withdrawing groups attached to the benzene rings were able to undergo a difunctionalization reaction smoothly and generated the corresponding *β*-haloenol acetates in moderate to excellent yields (**2a**−**r**) except the 4-methoxyphenylacetylene substrate, in which the mixture of *E*- and *Z*- isomers were obtained (**2f**). The treatment of alkyl- or aryl-substituted substrates afforded the corresponding products in good yields (**2b**−**e**).

Scheme 1. Silver-Catalyzed Synthesis of (*Z*)-*β*-Haloenol Acetates[a,b]



[a] Reaction conditions: terminal alkyne (1.0 mmol), NBS (1.2 mmol), acetic anhydride (2 mL), and $AgBF_4$ (5 mol %) at 120 °C for 12 h. [b] Isolated yield. [c] 5:4 *Z*/*E* mixture as determined by ^1H NMR spectra. [d] The substrate was pent-4-yn-2-ol.

Meanwhile, good yields were achieved when electron-withdrawing substituted substrates were used (**2g**−**m**).

Interestingly, dienol diacetate formation was performed when diyne was used (**2n**). NCS and NIS could afford the corresponding β-haloenol acetates in moderate to good yields as well (**2o**−**r**). As the challenging substrates, aliphatic alyknes can also react with NBS and acetic anhydride giving the (*Z*)-β-haloenol acetates in moderate to good yields (**2s**−**x**). It was discovered that the alkynol afforded the 2,4-diacetoxy product (**2w**). Moreover, the substrate nona-1,8-diyne formed the mono difunctionalization product in moderate yield (**2x**).

The regio- and stereochemistry of β-haloenol acetates were determined based on X-ray diffraction and related literature.[10] For example, the X-ray crystallographic analyses of **2e** clearly indicated the position of the groups (Figure 1)

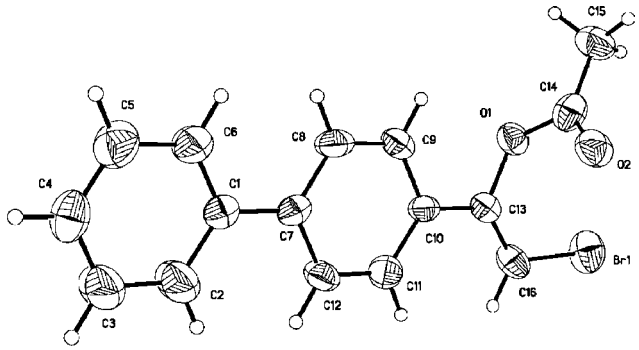
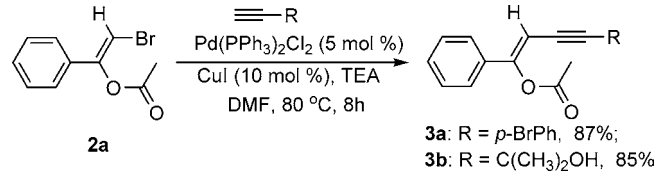


Figure 1. X-ray structure of **2e**.

The resulting product haloenol acetates appeared highly attractive as intermediates for the preparation of more highly functionalized enol acetates. Take **2a** as an example to increase molecular complexity via palladium- and copper-catalyzed reactions (Schemes 2). Compound **2a** underwent a Sonogashira reaction with terminal alkynes affording the corresponding **3a** and **3b** in 87 and 85% yield, respectively. Moreover, the bromo group of **3a** could be utilized for further transformation through a transition-metal-catalyzed reaction, and **3b** was easily transformed to the functionalized terminal alkyne.[11]

To elucidate the mechanism, controlled experiments were conducted (Scheme 3). Compound **2a** was obtained regio- and stereospecifically from **4a** with acetic anhydride as the solvent in excellent yield (Scheme 3, eq 1). Compound **5a**

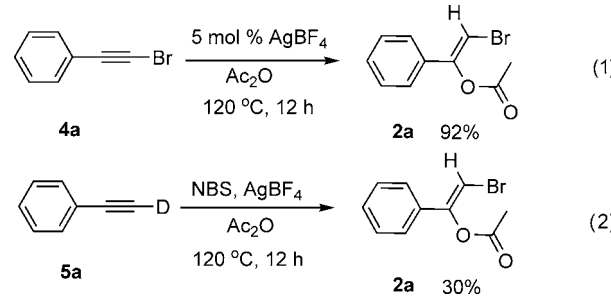
Scheme 2. Sonogashira Reaction of the (*Z*)-β-Haloenol Acetates



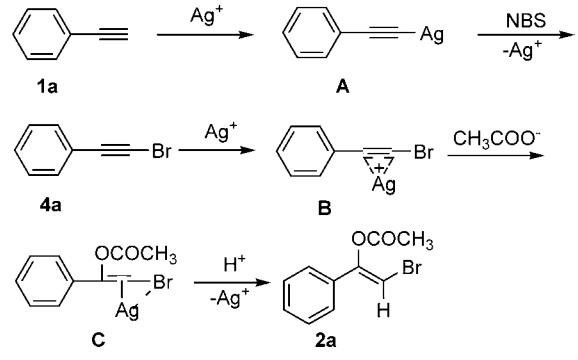
could transform to **2a** as well; although the yield was low, there was no D-labeled **2a** product (Scheme 3, eq 2). The controlled experiments suggested that the difunctionalization reaction may undergo a **4a** intermediate and the vinyl hydrogen atom of **2a** resulted from the water in the solvent or air.

Consequently, the possible mechanisms were proposed (Scheme 4) on the basis of the previous work mechanism and our reaction results.[12,13] In the first step, the silver phenylacetylide intermediate **A** is formed, which is transformed to **4a**. Then the silver cation attacks the triple bond of **4a** and formed a π-complex **B**, which is then subsequently converted to the corresponding σ-complex **C** by nucleophilic attack of the acetic anion. Perhaps the halo atom has some stabilization action to the silver, as the silver complex **C** decomposed to a β-haloenol acetate by substitution of the silver atom with a proton in a certain direction, and the product has high regio- and stereoselectivity.

Scheme 3. Controlled Experiments



Scheme 4. Possible Reaction Mechanisms



(7) (a) Pincock, J. A.; Yates, K. *Can. J. Chem.* **1970**, *48*, 3332. (b) Barluenga, J.; Rodríguez, M. A.; Campos, P. J. *J. Org. Chem.* **1990**, *55*, 3104.

(8) (a) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132. (b) Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3199. (c) Ding, Q.; Wu, J. *J. Comb. Chem.* **2008**, *10*, 541. (d) Yoshida, S.; Fukui, K.; Kikuchi, S.; Yamada, T. *J. Am. Chem. Soc.* **2010**, *132*, 4072. (e) Oh, C. H.; Karmakar, S.; Park, H.; Ahn, Y.; Kim, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 1792. (f) Luo, Y.; Li, Z.; Li, C.-J. *Org. Lett.* **2005**, *7*, 2675.

(9) (a) Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2010**, *12*, 312. (b) Cao, H.; Jiang, H.; Mai, R.; Zhu, S.; Qi, C. *Adv. Synth. Catal.* **2010**, *352*, 143. (c) Jiang, H.-F.; Zhao, J.-W. *Tetrahedron Lett.* **2009**, *50*, 60.

(10) (a) Kowalski, C. J.; Haque, M. S. *J. Org. Chem.* **1985**, *50*, 5140. (b) Kowalski, C. J.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 7194.

(11) (a) Zhu, N.; Hu, W.; Han, S.; Wang, Q.; Zhao, D. *Org. Lett.* **2008**, *10*, 4283.

In summary, we have developed a convenient and expedient method for the synthesis of β-haloenol acetates using silver tetrafluoroborate as the catalyst. In most cases, the (*Z*)-β-haloenol acetates were obtained regio- and stereospecifically in moderate to excellent yields. The results also indicated that the silver-catalyzed difunctionalization reaction tolerated a variety of functional groups. The useful intermediates were briefly transformed to the conjugated enyne acetates in good yields. Further synthetic applications and studies of the mechanism of the difunctionalization reaction are underway.

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Supporting Information Available: Typical experimental procedure and characterization for all products and X-ray data of **2e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For representative preparation bromoalkynes from terminal alkynes with silver as the catalyst, see: (a) Mu, Z.; Shu, L.; Fuchs, H.; Mayor, M.; Chi, L. *J. Am. Chem. Soc*. **2008**, *130*, 10840. (b) Nie, X.; Wang, G. *J. Org. Chem.* **2006**, *71*, 4734**.**

(13) (a) Ishino, Y.; Nishiguchi, I.; Nakao, S.; Hirashima, T. *Chem. Lett.* **1981**, 641. (b) Lewandos, G. S.; Maki, J. W.; Ginnebaugh, J. P. *Organometallics* **1982**, *1*, 1700**.**