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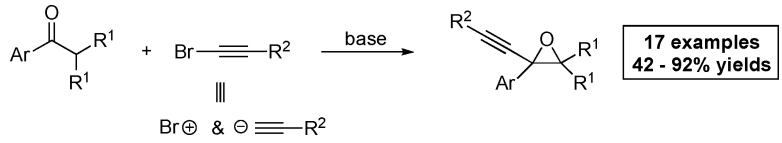

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Dual Role of Alkynyl Halides in One-Step Synthesis of Alkynyl Epoxides

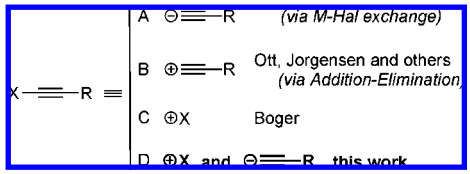
Alexander Trofimov, Natalia Chernyak, and Vladimir Gevorgyan*

Depatment of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

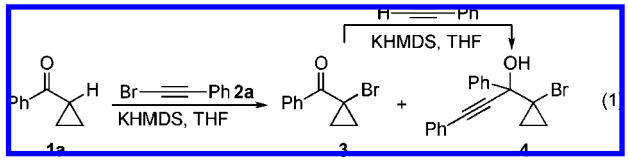
Received August 6, 2008; E-mail: vlad@uic.edu

Haloalkynes are highly versatile synthons for synthetic organic chemistry.[1] Traditionally, they are employed as a source of acetylides via metal−halogen exchange (Scheme 1A).[2] As first shown by Ott,[3a] and later in an enantiocatalytic version by Jorgensen,[3g] haloalkynes can also be used as equivalents of an electrophilic acetylenic unit upon reaction with nucleophiles via an addition−elimination protocol (B).[3,4] On the other hand, Boger demonstrated that phenylalkynylbromide and -iodide can serve as effective sources of the corresponding X^+ ion when reacted with aryl lithium species (C).[5] Herein, we wish to report that alkynylhalides can serve as a source of both X^+ and acetylide ions in the same transformation (Scheme 1D).

Scheme 1

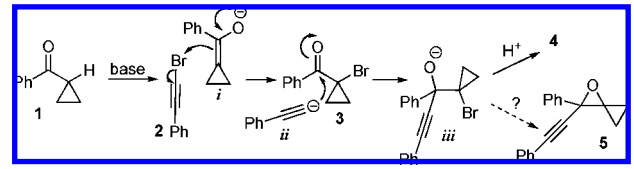


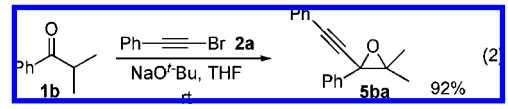
During our ongoing studies on alkynylation of sp^2-carbons with alkynyl halides,[4c] we found an interesting transformation: cyclopropylphenyl ketone **1a**, in the presence of KHMDS, reacted with phenylethynyl bromide **2a** to afford a mixture of brominated cyclopropylphenyl ketone **3** and propargyl alcohol **4** (eq 1). Moreover, ketone **3**, upon reaction with phenyl acetylide, was converted to propargyl alcohol **4**, thus supporting



the intermediacy of **3** in the formation of **4**. We found this result quite interesting, as generally reactions of enolates with alkynyl halides result in the α-alkynylation of the carbonyl compound (Scheme 1B).[3] Apparently, the reaction proceeded via the following pathway (Scheme 2). Base-induced enolization of cyclopropylphenone **1** produced enolate ***i***, which by the aid of alkynylbromide **2**, got brominated at the α-position to form **3**.[5] The carbonyl group of the latter undergwent a nucleophilic attack by the produced phenylacetylide ***ii*** to give alkoxide ***iii***, which, upon protonation, furnished alcohol **4**. α-Bromoalkoxide ***iii*** neither under the reaction conditions nor when generated from **4** underwent known cyclization[6] into spiro cyclopropyl oxirane **5**.[6c] Gratifyingly, it was found that employment of less-strained isobutyrophenone **1b** under similar reaction conditions *led to exclusive formation of alkynyl epoxide* **5ba** in 92% yield (eq 2)!

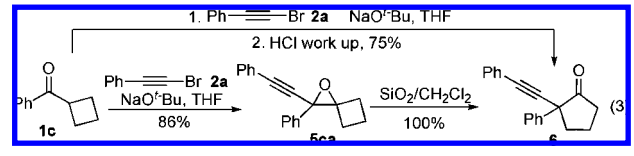
Scheme 2





Next, the scope of this cascade transformation was explored. First, the nature of halogen at the alkynyl halide was examined. It was found that alkynylbromide is superior over the iodide in that reaction (Table 1, entry 1). On the other hand, employment of phenylalkynyl chloride led to the formation of the α-alkynylated ketone[7] apparently via the alternative aforementioned path B (Scheme 1).[3] The cascade epoxidation reaction appeared to be quite general with respect to the carbonyl component as a variety of α,α-disubstituted aryl ketones[8] **1** were easily converted into the corresponding epoxides (entries 1−9). Thus, isopropyl-, cyclobutyl-, and cyclohexylphenylketones **1b**−**d** (entries 1−3), as well as electronically different aryl- and heteroaryl ketones **1e**−**j** (entries 4−9), smoothly reacted with **2a** to produce epoxides **5** in good to excellent yields. Ketones possessing different β-substituents readily reacted with **2a** producing the corresponding epoxides in high yields albeit with low degrees of diastereoselectivity.[9] Cascade cyclization of different aryl-, heteroaryl-, and alkylalkynyl bromides with isobutyrophenones proceeded uneventfully, providing the corresponding alkynyl epoxides in good yields (entries 10−15). Remarkably, silyl bromoalkynes **2f** and **2g** were also efficiently employed in this reaction to give epoxides **5bf** and **5bg** in 42% and 82% yields, respectively (entries 16−17). The latter, upon treatment with TBAF, was easily desilylated into the corresponding terminal alkynyl epoxide, a useful synthon for organic chemistry[10a] (entry 17).

Of note, it was found that **5ca**, obtained from **1c** (entry 2), upon silica gel chromatography with 10% dichloromethane in hexane, quantitatively rearranged[11] into the α-alkynylcyclopentanone **6** (eq 3). Alternatively, **6** can be directly obtained from **1c** upon acidic workup in 75% yield (eq 3).



In summary, we have demonstrated that bromo- and iodoalkynes can serve as efficient sources of both halogen$^+$ and acetylide[12]

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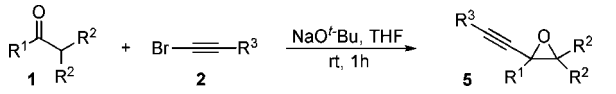
Table 1. Synthesis of Alkynyl Epoxides



#	R^1	R^2		R^3			Yield %[a]
1	Ph	Me	**1b**	Ph	**2a**	**5ba**	92 (76)[b]
2		-$(CH_2)_5$-	**1c**			**5ca**	79
3		-$(CH_2)_5$-	**1d**			**5da**	81
4	3-Py	Me	**1e**			**5ea**	80
5	*p*-$F_3CC_6H_4$		**1f**			**5fa**	81
6	2-Np		**1g**			**5ga**	87
7	1-Np		**1h**			**5ha**	51
8	*p*-$MeOC_6H_4$		**1i**			**5ia**	70
9	*m*-BrC_6H_4		**1j**			**5ja**	86
10				1-Np	**2b**	**5jb**	64
11	2-Np		**1g**			**5gb**	69
12	*p*-$F_3CC_6H_4$		**1f**	*p*-$O_2NC_6H_4$	**2c**	**5fc**	50[c,d]
13	Ph	Me	**1b**	3-Py	**2d**	**5bd**	89
14				Bu	**2e**	**5ae**	73[e]
15		-$(CH_2)_5$-	**1d**			**5de**	73[e]
16		Me	**1b**	$SiEt_3$	**2f**	**5bf**	42[e]
17			**1b**	$SiMe_2Ph$	**2g**	**5bg**	82[e] (81)[e]

[a] Isolated yields. [b] Iodoalkynylbenzene was used. [c] KHMDS was used as a base. [d] The reaction was performed at 0 °C. [e] Yield of the desilylated product. See Supporting Information for details.

species in the same cascade transformation. This allowed for development of a novel and efficient one-step synthesis of alkynylepoxides, highly valuable organic synthons,[10] from easily available enolizable ketones.

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Supporting Information Available: Preparative procedures, analytical and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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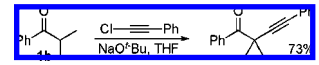
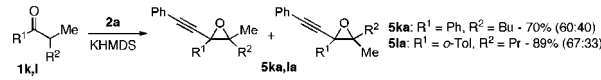
(7) Reaction of **1b** with phenylalkynyl chloride under standard reaction conditions led to α-alkynylated product, exclusively.



(8) Employment of primary and secondary enolizable ketones, as well as nonaromatic ketones, led to complex mixtures of products.

(9) Cyclizations of **1k,l** with **2a** produced unseparable mixtures of diastereomers **5ka, 5la**. See Supporting Information for details.



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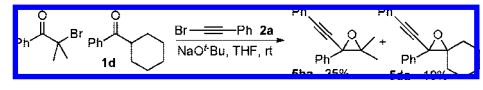
(12) The involvement of free acetylide species in this transformation was additionally supported by the results of the following cross-over experiment. See Supporting Information for details.



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