Organic LETTERS

Letter

pubs.acs.org/OrgLett

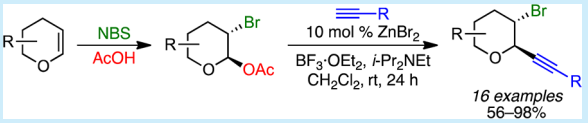
Diastereoselective, Zinc-Catalyzed Alkynylation of α-Bromo Oxocarbenium Ions

Tatsiana Haidzinskaya,[†,§] Hilary A. Kerchner,[‡,§] Jixin Liu,[§] and Mary P. Watson*

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, United States

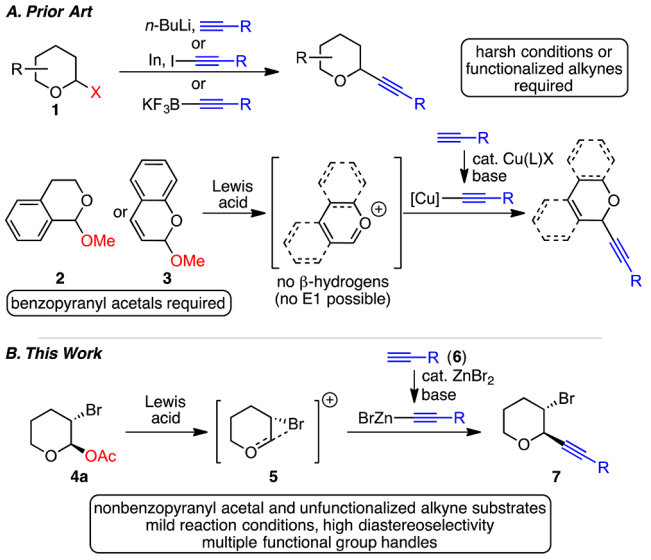
Supporting Information

ABSTRACT: We have developed a bromination/alkynylation sequence that enables efficient transformation of simple cyclic enol ethers to difunctionalized products. The success of this strategy relies on a highly diastereselective, zinc-catalyzed addition of terminal alkynes to α-bromo oxocarbenium ions, formed in situ via ionization of acetal precursors. Using this method, *trans*-α-alkynyl-β-halo pyran and furan derivatives can be prepared with high diastereoselectivity and excellent functional group tolerance.



α-Substituted oxygen heterocycles represent a privileged scaffold in both natural products and bioactive molecules.[1] A powerful approach to deliver α-carbon substituents to these oxygen heterocycles is the alkynylation of an acetal substrate. The alkyne can then be elaborated to a range of α-carbon substituents. However, known methods for the addition of alkynes to acetals often require either a strong base or a functionalized alkyne, thereby limiting functional group tolerance or convenience (Scheme 1A).[2,3] Previously, we reported the addition of unfunctionalized terminal alkynes to cyclic oxocarbenium ions using either a zinc or copper catalyst.[4] We envisioned that this approach may offer a general, functional-group-tolerant and convenient strategy for the addition of alkynes to acetals. However, to date, this method has been limited to oxocarbenium ions that lack β-hydrogens and therefore cannot undergo decomposition via E1 elimination (Scheme 1A). We now report a zinc-catalyzed alkynylation of α-halo tetrahydropyranyl and tetrahydrofuranyl acetals to deliver *trans*-3-halo-2-alkynyl oxygen heterocycles in high yields and excellent levels of diastereoselectivity (Scheme 1B). When combined with the efficient preparation of the 3-halo-2-acetoxy substrates via halogenation of cyclic enol ethers,[5] this method enables a difunctionalization of cyclic enol ethers. The halide substituent not only promotes higher yields in the alkynylation but also provides the *trans*-3-bromo-2-alkyl oxygen heterocycle motif present in a number of marine natural products,[1a−c,6] as well as a handle for further elaboration.[2a]

Scheme 1. Alkynylations of Acetals



We began our investigation with the addition of phenyl acetylene to 2-acetoxytetrahydropyran, which can be easily prepared from dihydropyran.[7] Although CuI and $ZnBr_2$ were both effective catalysts in the alkynylation of benzopyranyl acetals **2** and **3**,[4b] the use of a copper(I) catalyst in the alkynylation of acetal **8** provided only trace product (20 mol % CuI, $BF_3{\cdot}OEt_2$, NEt_3, Et_2O, rt, 24 h, 4% yield by ^1H NMR analysis). However, desired product **9** was observed when $ZnBr_2$ was used as catalyst (Table 1, entry 1). The yield of **9** was increased to 50% by using dioxane as solvent (entries 2 and 3), but further attempts to optimize the reaction failed. We assume that competitive E1 elimination of the oxocarbenium ion and subsequent polymerization of the resulting dihydropyran prevents higher yields.[8]

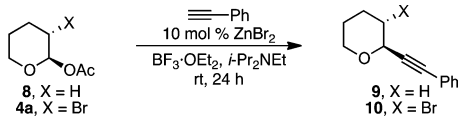
We envisioned that the use of an α-bromo substituent might electronically disfavor E1 elimination, as well as control diastereoselectivity and provide a second functional group handle in the product. *trans*-3-Bromo-2-acetoxy pyran **4a** was readily prepared in 85% yield and 7:1 dr via bromination of dihydropyran in acetic acid.[5] Alkynylation of acetal **4a** resulted in only 38% yield when dioxane was used as solvent (entry 4). Use of CH_2Cl_2 as solvent resulted in an increased yield of 75% (entry 5). By increasing the equivalents of $BF_3{\cdot}OEt_2$, an 85% yield of **10** was observed. Under all conditions, a single

Received: June 25, 2015

 © XXXX American Chemical Society

DOI: 10.1021/acs.orglett.5b01838
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Reaction Optimization[a]



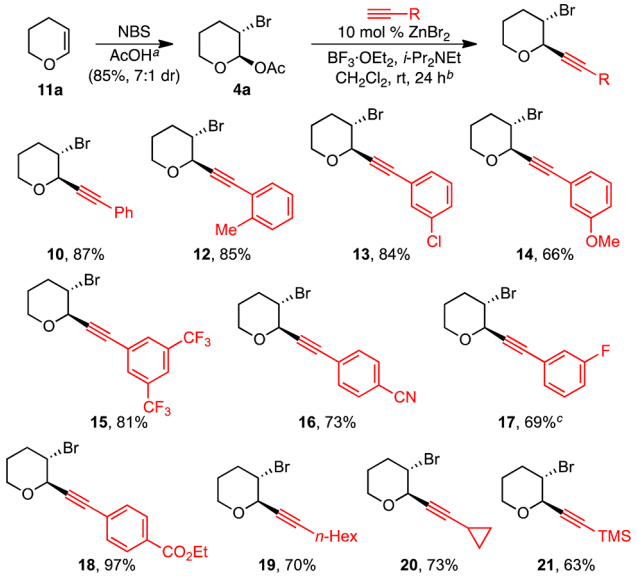
entry	acetal	solvent	equiv $BF_3{\cdot}OEt_2$	yield (%)[b]
1	**8**	Et_2O	1.3	19
2	**8**	dioxane	1.3	50
3	**8**	CH_2Cl_2	1.3	28
4	**4a**	dioxane	2.0	38
5	**4a**	CH_2Cl_2	2.0	75
6	**4a**	CH_2Cl_2	3.0	85

[a]Conditions: acetal (0.10 mmol, 1.0 equiv), $ZnBr_2$ (0.010 mmol, 10 mol %), alkyne (0.13 mmol, 1.3 equiv), $BF_3{\cdot}OEt_2$ (0.15 mmol, 1.5 equiv), *i*-Pr_2NEt (0.15 mmol, 1.5 equiv), solvent (0.20 M). [b]Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

diastereomer of **10** was formed. A promising, albeit not synthetically useful, yield was observed when the bromination/alkynylation was performed in one pot; a 15% yield of alkyne **10** was obtained when dihydropyran **11a** was treated with NBS, followed by $ZnBr_2$, phenyl acetylene, *i*-Pr_2NEt, and $BF_3{\cdot}OEt_2$.

Under the optimized conditions, a wide variety of terminal alkynes undergo reaction with α-bromoacetal **4a** (Scheme 2).

Scheme 2. Scope of Alkynes



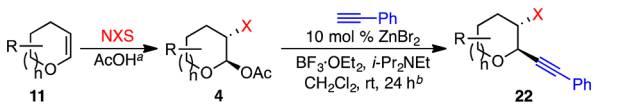
[a]Conditions: **11a** (11.5 mmol, 1.0 equiv), NBS (1.3 equiv), AcOH (10.0 equiv), 0 °C to rt. [b]Acetal **4a** (0.50 mmol, 1.0 equiv), $ZnBr_2$ (0.050 mmol, 10 mol %), alkyne (0.65 mmol, 1.3 equiv), $BF_3{\cdot}OEt_2$ (1.5 mmol, 3.0 equiv), *i*-Pr_2NEt (0.75 mmol, 1.5 equiv), CH_2Cl_2 (0.18 M), rt, 24 h. Average isolated yields of duplicate experiments (±6%), unless otherwise noted. [c]Result of a single experiment.

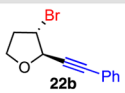
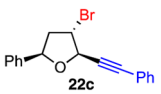
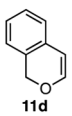
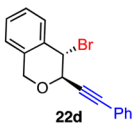
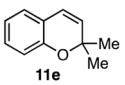
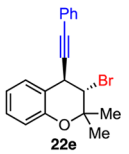
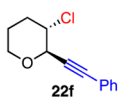
With aryl-substituted alkynes, substituents are well tolerated at the *ortho*, *meta*, and *para* positions. Alkynes with both electron-rich (**12**) and electron-poor (**13**–**18**) aryl groups can be utilized. In addition, a range of functional groups are tolerated, including chloride (**13**), ether (**14**), trifluoromethyl (**15**), nitrile (**16**), fluoride (**17**), and ester (**18**). Alkynes with aliphatic substitution are also successful in this alkynylation (**19** and **20**).

Addition of trimethylsilylacetylene was also effective, allowing access to terminal alkynes via deprotection of the TMS group (see below). In every case in Scheme 2, a single diastereomer of product was observed, consistent with our hypothesis that the α-bromide may stabilize the oxocarbenium ion via a bromonium-like structure (see **5** in Scheme 1B). The *trans* configuration of product **16** was confirmed by X-ray crystallography.[9] The configurations of other products were assigned by analogy.

This halogenation/alkynylation sequence was also successful in the preparation of other *trans*-3-halo-2-alkynyl cyclic ethers (Table 2). As for dihydropyran **11a**, this sequence resulted in a

Table 2. Scope of Halogens and Enol Ethers



entry	enol ether	alkyne prod	yield of **4** (%)	yield of **22** (%)
1	 **11b**	 **22b**	71[c]	75
2[d]	 **11c**	 **22c**	64	98
3[d]	 **11d**	 **22d**	68	91
4[d]	 **11e**	 **22e**	60	85
5[e]	 **11a**	 **22f**	44[f]	53[g]

[a]Conditions: **11** (1.0 equiv), NBS (1.3 equiv), AcOH (10.0 equiv), 0 °C to rt. Yields of single experiments. [b]Acetal **4** (0.50 mmol, 1.0 equiv), $ZnBr_2$ (0.050 mmol, 10 mol %), phenyl acetylene (0.65 mmol, 1.3 equiv), $BF_3{\cdot}OEt_2$ (1.5 mmol, 3.0 equiv), *i*-Pr_2NEt (0.75 mmol, 1.5 equiv), CH_2Cl_2 (0.18 M), rt, 24 h. Average isolated yields of duplicate experiments (±4%). [c]17:1 dr. [d]Bromination conditions: **11** (1.0 equiv), NBS (1.3 equiv), AcOH (10.0 equiv), CH_2Cl_2 (3.0 mL), 0 °C. [e]NBS was replaced by NCS. [f]2.9:1 dr. [g]17:1 dr.

single diastereomer for each 3-bromo-2-alkynyl heterocycle shown in Table 2 (entries 1–4). The bromination and alkynylation of dihydrofuran **11b** proceeded in 71% (17:1 dr) and 75% yields, respectively, demonstrating that this strategy is not limited to pyrans (entry 1). Importantly, the bromination of substituted dihydrofuran **11c** proceeded in high diastereoselectivity, ultimately giving a single diastereomer of 3-bromo-2-alkynyl furan **22c** (entry 2). The relative configuration of **22c** was assigned by analogy to the configuration of its acetal precursor (**4c**), which was determined by X-ray crystallography.[9] Isochromene **11d** and vinylogous enol ether **11e** also underwent the bromination/alkynylation in high yields (entries 3 and 4). For these latter substrates (**11c**–**11e**), the

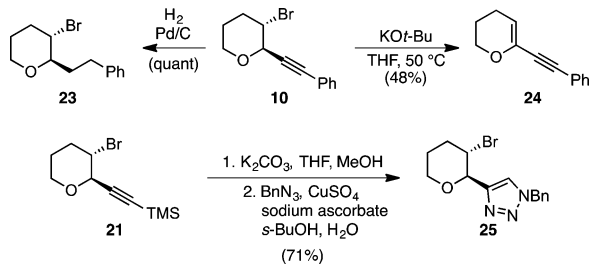
DOI: 10.1021/acs.orglett.5b01838
Org. Lett. XXXX, XXX, XXX–XXX

bromination reactions were performed in $AcOH/CH_2Cl_2$ instead of neat AcOH to avoid decomposition of the bromo acetal intermediates.

In addition to bromination, chlorination of dihydropyran **11a** can be performed, albeit in lower yield and diastereoselectivity than the analogous bromination (Table 2, entry 5). Subsequent alkynylation of the α-chloro acetal delivered **22f** in moderate yield, but excellent diastereoselectivity (17:1 dr). The analogous iodination was not successful.

Elaboration of the alkyne products can be accomplished in high yields to give single diastereomers of products (Scheme 3). For example, hydrogenation of alkyne **10** resulted in

Scheme 3. Elaboration of Products



quantitative formation of tetrahydropyran **23**. After deprotection of the trimethylsilyl group of alkyne **21**, a copper-catalyzed Click reaction delivers triazole in 71% yield.[10] The bromide also provides a handle for functionalization; elimination delivers enyne **24** in moderate yield.

In summary, we have developed mild reaction conditions for the addition of unfunctionalized, terminal alkynes to α-halo oxocarbenium ions, formed in situ from acetal precursors. When coupled with halogenation, this method enables the preparation of difunctionalized oxygen heterocycles from simple enol ether precursors in excellent diastereoselectivities. Ongoing efforts are directed toward the application of this method to additional enol ether substrates, as well as glycals, to enable efficient preparation of multisubstituted oxygen heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray crystal structure, characterization data, and spectra of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01838.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mpwatson@udel.edu.

Present Addresses

[†]The Chemours Company FC, LLC, Experimental Station 402/4331, 200 Powder Mill Rd., Wilmington, DE 19803, Tatsiana.Haidzinskaya@chemours.com.

[‡]University of Michigan, Department of Chemistry, 930 N. University Ave., Ann Arbor, MI 48109, hkerch@umich.edu.

Author Contributions

[§]T.H., H.A.K., and J.L. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Acknowledgement is gratefully made to the National Science Foundation (CAREER CHE 1151364) for support of this research. H.A.K. thanks the American Chemical Society Division of Organic Chemistry and GlaxoSmithKline for summer undergraduate research fellowships. NMR and other data were acquired at UD on instruments obtained with the assistance of NSF and NIH funding (NSF CHE 0421224, CHE 1229234, and CHE 0840401; NIH P20 GM103541 and S10 RR02682).

■ REFERENCES

(1) (a) Kennedy, D. J.; Selby, I. A.; Cowe, H. J.; Cox, P. J.; Thomson, R. H. *J. Chem. Soc., Chem. Commun.* **1984**, 153. (b) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, *6*, 1091. (c) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193. (d) Cai, X.; Chorghade, M. S.; Fura, A.; Grewal, G. S.; Jauregui, K. A.; Lounsbury, H. A.; Scannell, R. T.; Yeh, C. G.; Young, M. A.; Yu, S.; Guo, L.; Moriarty, R. M.; Penmasta, R.; Rao, M. S.; Singhal, R. K.; Song, Z.; Staszewski, J. P.; Tuladhar, S. M.; Yang, S. *Org. Process Res. Dev.* **1999**, *3*, 73. (e) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1643. (f) Kool, E. *Acc. Chem. Res.* **2002**, *35*, 936. (g) Hocek, M.; Stambasky, J.; Kocovsky, P. *Chem. Rev.* **2009**, *109*, 6729.

(2) (a) Karadogan, B.; Edwards, N.; Parsons, P. J. *Tetrahedron Lett.* **1999**, *40*, 5931. (b) Lubin-Germain, N.; Baltaze, J.-P.; Coste, A.; Hallonet, A.; Laureano, H.; Legrave, G.; Uziel, J.; Auge, J. *Org. Lett.* **2008**, *10*, 725. (c) Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 42.

(3) For addition of alkynes to glycals via allylic substitution, see: (a) Kusunuru, A. K.; Tatina, M.; Yousuf, S. K.; Mukherjee, D. *Chem. Commun.* **2013**, *49*, 10154. (b) Tatina, M. B.; Kusunuru, A. K.; Yousuf, S. K.; Mukherjee, D. *Org. Biomol. Chem.* **2014**, *12*, 7900.

(4) (a) Maity, P.; Srinivas, H. D.; Watson, M. P. *J. Am. Chem. Soc.* **2011**, *133*, 17142. (b) Srinivas, H. D.; Maity, P.; Yap, G. P. A.; Watson, M. P. *J. Org. Chem.* **2015**, *80*, 4003.

(5) (a) Shelton, J. R.; Cialdella, C. *J. Org. Chem.* **1958**, *23*, 1128. (b) Bateman, G.; Brown, B. R.; Campbell, J. B.; Cotton, C. A.; Johnson, P.; Mulqueen, P.; O'Neill, D.; Shaw, M. R.; Smith, R. A.; Troke, J. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2903.

(6) For syntheses of these classes of natural products, see: (a) Park, J.; Kim, B.; Kim, H.; Kim, S.; Kim, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4726. (b) Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127. (c) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483. (d) Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499. (e) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029. (f) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, *7*, 75.

(7) Iwanami, K.; Aoyagi, M.; Oriyama, T. *Tetrahedron Lett.* **2006**, *47*, 4741.

(8) Kamio, V. K.; Meyersen, K.; Schulz, R. C.; Kern, W. *Makromol. Chem.* **1966**, *90*, 187.

(9) CCDC 973169 (**16**) and 1404542 (**4c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(10) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

DOI: 10.1021/acs.orglett.5b01838
Org. Lett. XXXX, XXX, XXX−XXX