Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

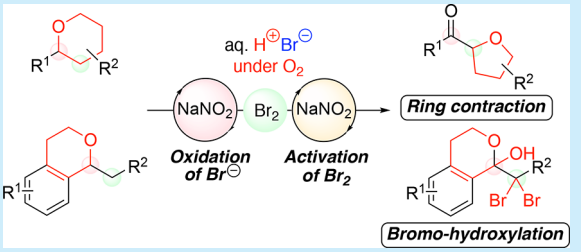
Ring-Contraction Reaction of Substituted Tetrahydropyrans via Dehydrogenative Dual Functionalization by Nitrite-Catalyzed Double Activation of Bromine

Kazuhiro Watanabe, Tsukasa Hamada, and Katsuhiko Moriyama*

Department of Chemistry, Graduate School of Science, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan
Molecular Chirality Research Center, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Supporting Information

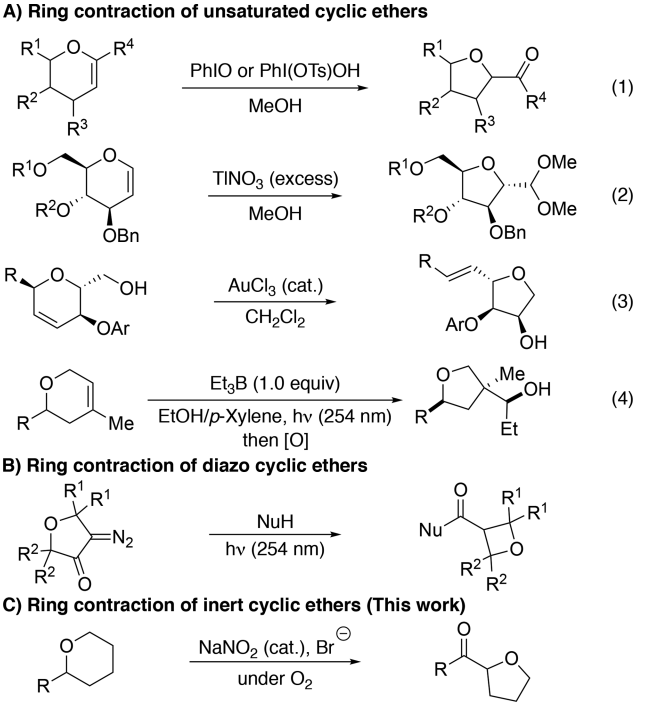
ABSTRACT: A nitrite-catalyzed ring contraction reaction of substituted tetrahydrofurans by oxidation of bromide under aerobic conditions as a dehydrogenative dual functionalization was developed to provide 2-acyltetrahydrofurans in good yields. On the other hand, the oxidation reaction of 1-substituted isochromans occurred via the bromohydroxylation to give 1-(dibromoalkyl)-1-hydroxyisochromans in high yields.



In fine organic synthesis, the ring contraction reaction of organic molecules is one of the elegant transformations that proceeds with high atom economy.[1] This reaction occurs via the rearrangement of some covalent bonds, representative examples of which include the Favorskii rearrangement, the Demjanov rearrangement, the Wolff rearrangement, and the pinacol rearrangement. In particular, the use of oxygen-containing heterocyclic compounds in this reaction is an ingenious methodology to construct substituted cyclic ethers in spite of the availability of various synthetic methods for substituted cyclic ethers[2] found in biologically active compounds and pharmaceuticals.[3] In regard to the formation of ring-contracted cyclic ethers via the ring contraction of cyclic ethers, the transformation of dihydropyrans into 2-carbonyl tetrahydrofurans using hypervalent iodine compounds, such as PhIO or PhI(OTs)OH, was reported as a ring-contraction reaction of unsaturated cyclic ethers (Scheme 1A, eq 1).[4] Likewise, the reaction of protected glycals with an excess amount of thallium(III) nitrate was developed to obtain tetrahydrofuran dimethyl acetals (Scheme 1A, eq 2).[5] The synthesis of 2-vinyltetrahydrofurans by the Au(III)-catalyzed ring contraction of aryl ether *C*-glycosides was also demonstrated (Scheme 1A, eq 3).[6] Recently, Larionov et al. reported a photoinduced carboborative ring contraction of unsaturated cyclic ethers (Scheme 1A, eq 4).[7] Tetrasubstituted diazofuranones have also been employed in the photochemical ring contraction (Scheme 1B).[8] All of the above-mentioned studies required cyclic ethers containing reactive groups, such as alkene and diazo groups, for the ring contraction to proceed.

On the other hand, we have been working on the dual functionalization of organic molecules, especially, the retained dual functionalization[9] and the dehydrogenative dual functionalization, using halogen reagents.[10] Through the development of our dual functionalization chemistry, an activated bromine generated via umpolung of bromide by a nitrite-catalyzed aerobic oxidation efficiently promoted the transformation of inert ethers.[10] Therefore, we envisioned that bromine activated by a nitrite catalyst would promote the ring contraction of

Scheme 1. Ring Contraction of Cyclic Ethers



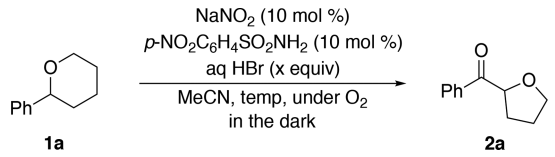
Received: August 3, 2018

DOI: 10.1021/acs.orglett.8b02488
Org. Lett. XXXX, XXX, XXX−XXX

saturated tetrahydropyrans to furnish 2-acyltetrahydrofurans by a formal multistep transformation through various oxidation manners (Scheme 1C). We report herein the ring contraction of substituted tetrahydropyrans by nitrite-catalyzed double activation of bromine as a dehydrogenative dual functionalization of inert organic molecules.

First, we chose the transformation of 2-phenyltetrahydropyran (**1a**) into 2-benzoyltetrahydrofuran (**2a**) as an example of the ring contraction and screened for the amount of HBr, the temperature, and the reaction time on the basis of the previously reported reaction conditions[10] (Table 1). Treatment of **1a** with aq HBr (5.0 equiv) in the presence of co-catalysts of $NaNO_2$ (10 mol %) and *p*-$NO_2C_6H_4SO_2NH_2$ (10 mol %) in MeCN at 60 °C increased the yield of **2a** by shortening the reaction time (entries 1−3). By adjusting the reaction temperature, we found that the reaction at 50 °C is the most suitable to yield the desired product (entries 4−6). The use of air and HBr in AcOH solution instead of O_2 and aq HBr and the absence of $NaNO_2$ in the reaction failed to yield the desired product (entries 7−9), whereas the reaction without *p*-$NO_2C_6H_4SO_2NH_2$ slightly decreased the yield of **2a** (entry 10). Use of 4.0 equiv of aq HBr did not affect the efficiency of the ring contraction, whereas decreasing the amount of aq HBr decreased the yield of **2a** (entries 11−13). Therefore, we found that the optimum conditions were **1a**, aq HBr (4.0 equiv), $NaNO_2$ (10 mol %), and *p*-$NO_2C_6H_4SO_2NH_2$ (10 mol %) in MeCN at 60 °C under O_2 by interrupting light (entry 11).

Table 1. Screening for Ring Contraction of 1a

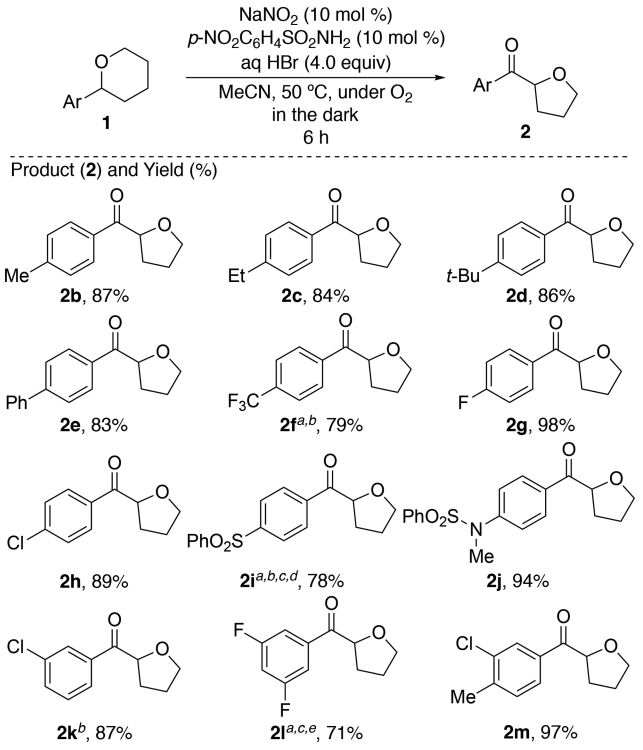


entry	*x*	temp (°C)	time (h)	conv (%)	yield (%)
1[a]	5.0	60	24	>99	0
2[a]	5.0	60	12	>99	75
3[a]	5.0	60	6	>99	69
4	5.0	60	6	>99	72
5	5.0	50	6	>99	92
6	5.0	40	6	>99	72
7[b]	5.0	50	6	13	0
8[c]	5.0	50	6	>99	0
9[d]	5.0	50	6	0	0
10[e]	5.0	50	6	>99	88
11	4.0	50	6	>99	91
12	3.0	50	6	>99	88
13	1.0	50	6	>99	80

[a]Under daylight conditions. [b]In air. [c]HBr in AcOH solution was used. [d]Absence of $NaNO_2$. [e]Absence of *p*-$NO_2C_6H_4SO_2NH_2$.

To explore the substrate scope of the ring contraction, 2-aryltetrahydropyrans (**1**) were examined under the optimum reaction conditions (Scheme 2). When *para*-substituted phenyltetrahydropyrans bearing hydrocarbon (**1b−e**), halogen (**1g** and **1h**), and heterofunctional groups (**1f**, **1i**, and **1j**) were used in the reaction, the corresponding products (**2b−j**) were obtained in high yields (78−98%). *Meta*-substituted and disubstituted phenyltetrahydropyrans (**1k−m**) also gave the desired products (**2k−m**) in high yields.

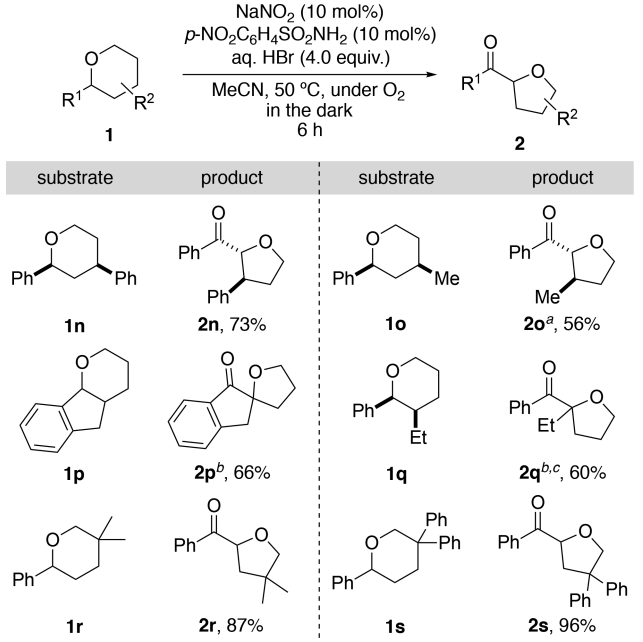
Scheme 2. Ring Contraction of 2-Aryltetrahydropyrans (1)



[a]Aqueous HBr (5.0 equiv). [b]At 60 °C. [c]$NaNO_2$ (20 mol %). [d]For 8 h. [e]At 70 °C.

Moreover, the ring contraction of di- and trisubstituted tetrahydropyrans was also examined via the nitrite-catalyzed aerobic oxidation of bromide (Scheme 3). 2,4-Substituted tetrahydropyrans (**1n** and **1o**) furnished 2-acyl-3-substituted tetrahydrofurans (**2n** and **2o**) as a single diastereomer in good

Scheme 3. Ring Contraction of Multisubstituted Tetrahydropyrans (1)



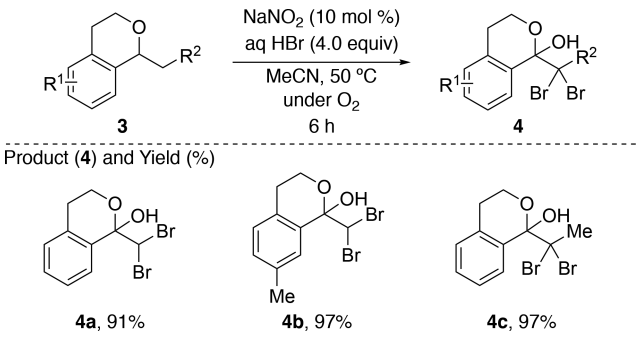
[a]$NaNO_2$ (20 mol %). [b]At 60 °C. [c]For 24 h.

DOI: 10.1021/acs.orglett.8b02488
Org. Lett. XXXX, XXX, XXX−XXX

yields. The reaction of 2,3-substituted (**1p** and **1q**) and 2,4,4′-substituted (**1r** and **1s**) tetrahydropyrans also gave tetrahydrofurans with a quaternary carbon center (**2p** and **2q**) and 2-acyl-4,4′-disubstituted tetrahydrofurans (**2r** and **2s**) in good yields. Fortunately, we succeeded in determining the structure of **2s** by X-ray crystal structure analysis.[11]

Next, we tried to accomplish the dual functionalization of 1-substituted isochromans (**3**) as tetrahydropyran derivatives using this reaction (Scheme 4). Unexpectedly, the reaction of

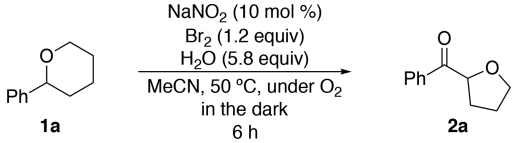
Scheme 4. Dual Functionalization of 1-Alkylisochromans (3)



1-methylisochroman (**3a**), 1,7-dimethylisochroman (**3b**), and 1-ethylisochroman (**3c**) occurred via bromohydroxylation and not ring expansion to give 1-(dibromoalkyl)-1-hydroxyisochromans (**4a**–**c**) in high yields, respectively.

To elucidate the reaction mechanism in the ring contraction of substituted tetrahydropyrans (**1**) via the nitrite-catalyzed aerobic oxidation of bromide, we investigated some mechanistic studies in this reaction. For the ring contraction of **1a** with molecular bromine (Br_2), which is considered to be produced by the aerobic oxidation of bromide, the required reagents for this reaction were explored (Table 2). When

Table 2. Reagents for Ring Contraction of 1a with Br_2



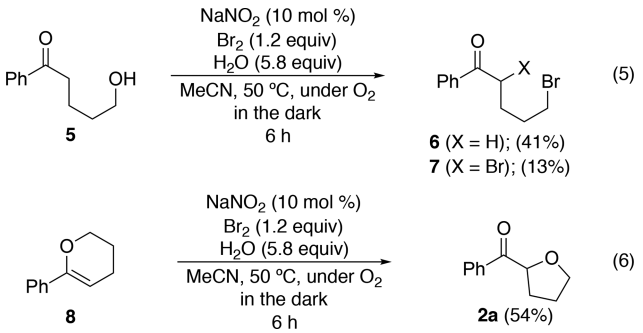
entry	$NaNO_2$	Br_2	H_2O	O_2	yield (%)
1	○	○	○	○	74
2	×	○	○	○	0 (86)[a]
3	○	×	○	○	0 (100)[a]
4	○	○	×	○	36 (8)[a]
5[b]	○	○	○	×	0 (75)[a]

[a]Number in parentheses indicates the recovery of **1a**. [b]The reaction was carried under Ar.

$NaNO_2$ (10 mol %), Br_2 (1.2 equiv), and H_2O (5.8 equiv) were used under O_2 atmosphere in this reaction of **1a**, the ring contraction smoothly occurred to give **2a** in 74% yield (entry 1). The reaction in the absence of Br_2 or O_2 did not produce **2a** at all, and **1a** was recovered in a large amount, whereas the absence of H_2O produced **2a** in low yield (entries 2–5). Together, the results indicate that all the reagents are essential for the late catalytic cycle, that is, the activation of Br_2, to promote the ring contraction.

In addition, the reactions of 5-hydroxy-1-phenylpentan-1-one (**5**) and 2-phenyldihydropyran (**8**) with Br_2 were performed under aerobic conditions to clarify the possible intermediates of the ring contraction (Scheme 5). The reaction

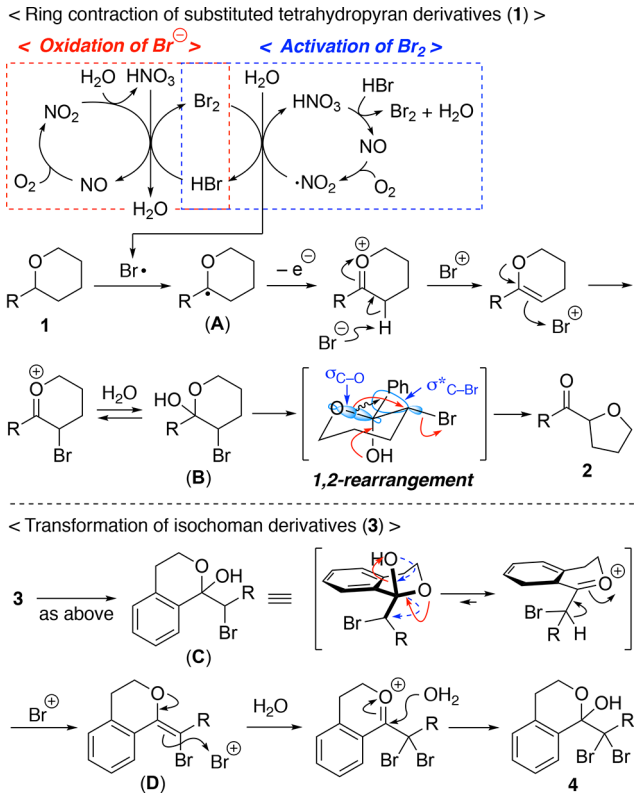
Scheme 5. Possible Intermediates in Ring Contraction



of 2-phenyldihydropyran (**8**) with $NaNO_2$ (10 mol %), Br_2 (1.2 equiv), and H_2O (5.8 equiv) provided **2a** in 54% yield (Scheme 5, eq 6), whereas that of 5-hydroxy-1-phenylpentan-1-one (**5**) gave not a ring contraction product but brominated products **6** (41% yield) and **7** (13% yield) (Scheme 5, eq 5). We suggest that the ring contraction takes place with **8** and not **5** via the ring-opening reaction with bromine or acid[12] as intermediate, as observed in the transformation of **1a** by bromine.

We propose a reaction mechanism in Scheme 6 on the basis of the above experiments in the reaction mechanism study and our previous research of the dual functionalization of ethers.[10] The aerobic oxidation of bromide with $NaNO_2$ and O_2 occurs to generate of Br_2, which is the inert source for the present

Scheme 6. Plausible Reaction Mechanism

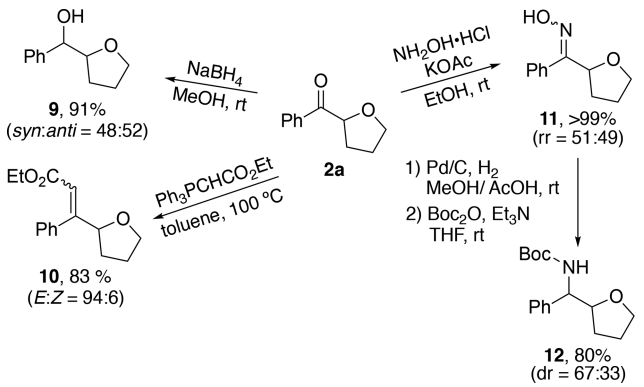


DOI: 10.1021/acs.orglett.8b02488
Org. Lett. XXXX, XXX, XXX–XXX

reaction. On the contrary, the $NaNO_2$ catalyst activates Br_2 under aerobic conditions to generate a bromo radical by single-electron transfer (SET) on a nitrite radical, which is generated via the reoxidation of NO with O_2.[13] The bromo radical reacts with **1** to obtain α-radical intermediate (**A**) via abstraction of the H atom at the α-position of the ether group, and **A** is converted into β-bromo hemiacetal (**B**) via one-electron oxidation, the bromination of dihydropyran, and the addition of H_2O. The bromination of dihydropyran with the bromonium ion species is slightly accelerated by the *p*-$NO_2C_6H_4SO_2NH_2$ catalyst. In the case of 3-bromo-2-hydroxytetrahydropyran, the 1,2-rearrangement rapidly proceeds through the overlap of an antibonding orbital on the C−Br bond (σ^*_{C-Br}) and a bonding orbital on C−O of the ether group (σ_{C-O}) to obtain ring contraction product (**2**). In contrast, the reaction of 1-substituted isochromans (**3**) proceeds through the dibromination of 2-bromo hemiacetal (**C**), which favors the generation of 2-bromovinyl ether (**D**) via the formation of the oxonium cation intermediate, followed by the formation of vinyl ether (red arrow) rather than the 1,2-rearrangement (blue dashed arrow) of 1-hydroxyisochromans as the 7-membered ring expansion is extremely slow. Therefore, the reaction of isochromans (**3**) via nitrite-catalyzed dual functionalization provides 1-(dibromoalkyl)-1-hydroxyisochromans (**4**). It is noteworthy that the $NaNO_2$ catalyst functions as a double-activation catalyst in the ring contraction, namely, the oxidation of bromide and the activation of Br_2, under aerobic conditions to promote the inert C−H activation of tetrahydropyrans.

To demonstrate the synthetic utility of the ring-contraction products, 2-benzoyltetrahydrofuran (**2a**) was used to derive various tetrahydrofuranyl compounds (Scheme 7). The

Scheme 7. Derivatization of 2-Benzoyltetrahydrofuran (2a)



transformation into tetrahydrofuranyl alcohol (**9**) by reduction with $NaBH_4$ and α,β-unsaturated tetrahydrofuranyl ester (**10**) through C−C bond formation by the Wittig reaction[14] was successful. In regard to the synthesis of amino-containing tetrahydrofuranyl compounds, the nucleophilic addition of hydroxylamine converted **2a** into corresponding oxime (**11**) in quantitative yield. This was followed by hydrogenative reduction with palladium catalyst and protection with Boc_2O to furnish protected amine (**12**) in 80% yield with a diastereomeric ratio of 67:33.

In conclusion, we have developed a nitrite-catalyzed ring-contraction reaction of tetrahydropyrans via dehydrogenative dual functionalization by the double activation of bromine, that is, the oxidation of bromide followed by the activation of molecular bromine, to obtain 2-acyltetrahydrofurans in good yields. In addition, the reaction of 1-alkylated isochromans proceeded via bromohydroxylation and not a ring-expansion reaction to give 2,2′-dibromo-1-hydroxyisochroman derivatives in high yields. Work on the nitrite-catalyzed direct transformation by activation of an inert C−H bond on hetero compounds is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02488.

Experimental procedures, spectral data, crystallographic data, and detailed experimental results (PDF)

Accession Codes

CCDC 1857675 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: moriyama@faculty.chiba-u.jp.

ORCID

Katsuhiko Moriyama: 0000-0001-8443-3599

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support in the form of a Grant-in-Aid for Scientific Research (No.G15K17819) from the Ministry of Education, Culture, Sports, Science and Technology in Japan is gratefully acknowledged.

■ REFERENCES

(1) For reviews on the ring contraction, see: (a) Silva, L. F., Jr. *Tetrahedron* **2002**, *58*, 9137−9161. (b) Silva, L. F., Jr. *Molecules* **2006**, *11*, 421−434. (c) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523−7526 For [2,3] Wittig ring contraction of macrocyclic allylic propargylic ethers, see:. (d) Marshall, J. A.; Lebreton, J. *Tetrahedron Lett.* **1987**, *28*, 3323−3326. (e) Marshall, J. A.; Robinson, E. D.; Lebreton, J. *Tetrahedron Lett.* **1988**, *29*, 3547−3550. (f) Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925−2931. (g) Marshall, J. A.; Yu, B. *J. Org. Chem.* **1994**, *59*, 324−331.

(2) For reviews on synthesis of substituted cyclic ethers, see: (a) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261−290. (b) Jalce, G.; Franck, X.; Figadère, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2537−2581.

(3) For reviews on oxygen heterocycles, see: (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407−2473. (c) Elliott, M. C. *J. Chem. Soc., Perkins Trans.* **2000**, *1*, 1291−1318. (d) Elliott, M. C.; Williams, E. *J. Chem. Soc., Perkins Trans.* **2001**, *1*, 2303−2340. (e) Elliott, M. C. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 2301−2323. (f) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348−4378. (g) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. *Chem. Rev.* **2013**, *113*, 4567−4610.

(4) (a) Zefirov, N. S.; Caple, R.; Palyulin, V. A.; Berglund, B.; Tykvinskii, R.; Zhdankin, V. V.; Koz'min, A. S. *Bull. Acad. Sci. USSR,*

DOI: 10.1021/acs.orglett.8b02488
Org. Lett. XXXX, XXX, XXX−XXX

Div. Chem. Sci. **1988**, *37*, 1289−1289. (b) Kirschning, A. *Liebigs Ann.* **1995**, *1995*, 2053−2056. (c) Moriarty, R. M.; Prakash, O.; Duncan, M. P.; Vaid, R. K.; Rani, N. *J. Chem. Res., Synop.* **1996**, 432−433. (d) Harders, J.; Garming, A.; Jung, A.; Kaiser, V.; Monenschein, H.; Ries, M.; Rose, L.; Schoning, K. U.; Weber, T.; Kirschning, A. *Liebigs Ann-Recueil* **1997**, *1997*, 2125−2132. (e) Kirschning, A. *Eur. J. Org. Chem.* **1998**, *1998*, 2267−2274.

(5) (a) McKillop, A.; Hunt, J. D.; Kienzle, F.; Bigham, E.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3635−3640. (b) Kaye, A.; Neidle, S.; Reese, C. B. *Tetrahedron Lett.* **1988**, *29*, 1841−1844. (c) Kaye, A.; Neidle, S.; Reese, C. B. *Tetrahedron Lett.* **1988**, *29*, 2711−2714. (d) Bettelli, E.; D'Andrea, P.; Mascanzoni, S.; Passacantilli, P.; Piancatelli, G. *Carbohydr. Res.* **1998**, *306*, 221−230.

(6) Yeager, A. R.; Min, G. K.; Porco, J. A., Jr.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 5065−5068.

(7) Jin, S.; Nguyen, V. T.; Dang, H. T.; Nguyen, D. P.; Arman, H. D.; Larionov, O. V. *J. Am. Chem. Soc.* **2017**, *139*, 11365−11368.

(8) (a) Rodina, L. L.; Mishchenko, V. L.; Malashikhin, S. A.; Platz, M.; Nikolaev, V. A. *Russ. J. Org. Chem.* **2003**, *39*, 1530−1532. (b) Rodina, L. L.; Malashikhin, S. A.; Galkina, O. S.; Nikolaev, V. A. *Helv. Chim. Acta* **2009**, *92*, 1990−1998. (c) Nikolaev, V. A.; Galkina, O. S.; Sieler, J.; Rodina, L. L. *Tetrahedron Lett.* **2010**, *51*, 2713−2716.

(9) (a) Moriyama, K.; Ishida, K.; Togo, H. *Org. Lett.* **2012**, *14*, 946−949. (b) Moriyama, K.; Ishida, K.; Togo, H. *Chem. Commun.* **2012**, *48*, 8574−8576. (c) Moriyama, K.; Ishida, K.; Togo, H. *Chem. Commun.* **2015**, *51*, 2273−2276. (d) Moriyama, K.; Hamada, T.; Ishida, K.; Togo, H. *Chem. Commun.* **2018**, *54*, 4258−4261.

(10) Moriyama, K.; Hamada, T.; Nakamura, Y.; Togo, H. *Chem. Commun.* **2017**, *53*, 6565−6568.

(11) For a detail of the X-ray crystal-structure analysis of **2s**, see the Supporting Information.

(12) The reaction of **1a** in the presence of HBr did not produce any ring-opening products (see Table 1, entry 9).

(13) Goldstein, S.; Lind, J.; Merényi, G. *Chem. Rev.* **2005**, *105*, 2457−2470.

(14) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318−1330.

DOI: 10.1021/acs.orglett.8b02488
Org. Lett. XXXX, XXX, XXX−XXX