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Chemoselective Oxygen-Centered Radical Cyclizations onto Silyl Enol Ethers

Maria Zlotorzynska, Huimin Zhai, and Glenn M. Sammis*

Department of Chemistry, 2036 Main Mall, University of British Columbia, Vancouver, British Columbia V6T 1Z1, Canada

gsammis@chem.ubc.ca

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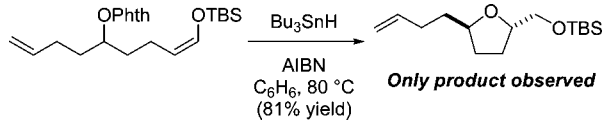
ABSTRACT



A new oxygen-centered radical cyclization onto silyl enol ethers has been developed and utilized for the synthesis of versatile siloxy-substituted tetrahydrofurans. The reactions display excellent chemoselectivity for cyclization onto the electron-rich silyl enol ether when competing terminal alkene cyclization, 1,5-hydrogen abstraction, and β-fragmentation pathways are present. The increased chemoselectivity also allows for the synthesis of tetrahydropyrans, a challenging substrate class to access using oxygen-centered radical alkene cyclizations due to competing 1,5-hydrogen abstractions.

Oxygen-containing heterocycles are common motifs in natural products and pharmaceuticals, and the synthesis of these compounds remains an important challenge in total synthesis. A direct method for their synthesis is the cyclization of an oxygen-centered radical onto an olefin as alkoxy radicals add rapidly and irreversibly to alkenes (R = H, alkyl, aryl).[1] Advances in oxygen-centered radical cyclizations have enabled the formation of a wide range of tetrahydrofurans including several simple tetrahydrofuran-containing natural products.[1,2] Despite progress in the field, alkoxy-radical cyclizations are still not as highly utilized in natural product synthesis compared to carbon-centered cyclization analogues[3,4] as methods based on oxygen-centered radicals are not sufficiently developed for the synthesis of complex substrates. The synthetic utility of the cyclization product can be increased by trapping carbon radical **2** with functional groups such as halogen[1b,c,5] or sulfur[6] but it is difficult to access α-hydroxylated rings, a motif common in bioactive tetrahydrofuran- and tetrahydropyran-containing natural products.[7] Furthermore, it is difficult to control the high reactivity of the oxygen-centered radicals as they readily undergo 1,5-hydrogen abstraction[8] and β-fragmentation pathways[9] (Scheme 1).

(1) For the first example of oxygen-centered radical cyclizations, see: (a) Surzur, J. M.; Bertrand, M. P.; Nougier, R. *Tetrahedron Lett.* **1969**, *48*, 4197–4200. For recent reviews, see: (b) Hartung, J. *Eur. J. Org. Chem.* **2001**, 619–632. (c) Hartung, J.; Gottwald, T.; Špehar, K. *Synthesis* **2002**, 1469–1498, and references therein.

(2) For a representative example of the use of oxygen-centered radicals for the formation of natural products, see: Hartung, J.; Kneuer, R. *Tetrahedron: Asymmetry* **2003**, *14*, 3019–3031.

(3) For reviews on carbon−radical cyclizations, see: (a) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541–3676. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4,Chapter 4.1, pp 715−777. (c) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc., New York, 1996; Vol. 48,Chapter 2, pp 303−856. (d) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771–2788, and references therein.

(4) For reviews, see: (a) Curran, D. P. *Synthesis* **1988**, 417–439. (b) Curran, D. P. *Synthesis* **1988**, 440–513. (c) Jasperse, C. P.; Curran, D.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286, and references therein.

(5) For representative examples, see: (a) Hartung, J.; Kneuer, R. *Eur. J. Org. Chem.* **2000**, 1677–1683. (b) Hartung, J.; Kopf, T. M.; Kneuer, R.; Schmidt, P. C. R. *Acad. Sci. Paris, Chem./Chem.* **2001**, 649–666.

(6) Hartung, J.; Gallou, F. *J. Org. Chem.* **1995**, *60*, 6706–6716.

(7) For representative examples of bioactive tetrahydrofuran and tetrahydropyran-containing natural products with oxygenation alpha to the ring, see: Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303.

(8) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1961**, *83*, 4076–4083.

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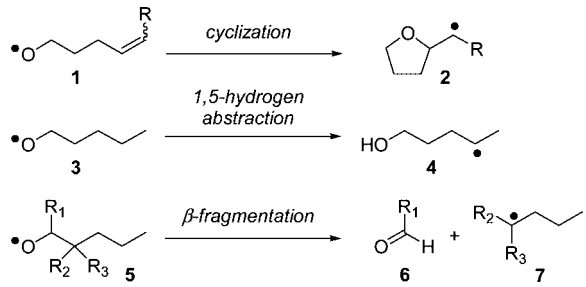
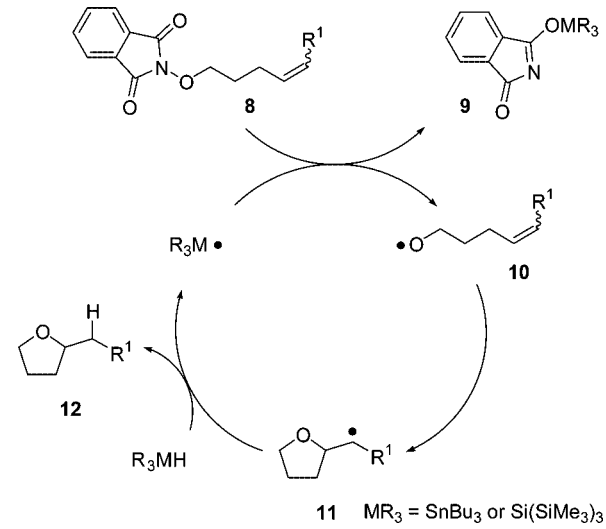
Scheme 1. Oxygen-Centered Radical Reaction Pathways



Scheme 2. Alkoxy Radical Generation via Deprotection of *N*-Alkoxyphthalimides



We were interested in investigating a substituent on the alkene that could provide a versatile synthetic handle for further functionalization as well as lead to increased rates of cyclization. Introduction of an oxygen substituent (R = OTBS) addresses both of these issues. The oxygen-radical cyclization would provide oxacycles with a modular protected primary alcohol substituent. Furthermore, the increased electron density of the olefinic acceptor should increase cyclization rates because alkoxy-radicals are electron deficient[10] and have been shown to cyclize more rapidly onto alkenes with increasing alkyl substitution.[11] Herein, we report the successful application of this approach for chemoselective oxygen-centered radical cyclizations onto electron-rich silyl enol ether acceptors.[12] This provides a general method for the preparation of siloxy-functionalized tetrahydrofurans as well as a route to tetrahydropyrans, a challenging class of substrates to access using oxygen-centered radical cyclizations due to rapid 1,5-hydrogen abstraction pathways.

A common strategy for the generation of oxygen-centered radicals is the cleavage of weak oxygen−heteroatom bonds in protecting groups such as *N*-alkoxyphthalmide (PhthOR),[13] *N*-alkoxypyridinethione,[14] and *N*-alkoxythiazolethione.[15] We began our investigations with alkoxy-radical generation via cleavage of *N*-alkoxyphthalimides as these groups can be readily incorporated into a compound and are stable under a wide range of reaction conditions. *N*-alkoxyphthalimides, such as **8**, can be converted to an oxygen-centered radical through the reaction with stannyl or silyl radicals (Scheme 2).[13a] This should result in homolytic cleavage of the oxygen−nitrogen bond to afford oxygen-centered radical **10**, which should then add to the π-system. Hydrogen atom abstraction by the resulting carbon radical in **11** propagates the radical and should provide tetrahydrofuran **12**. Indeed, treatment of silyl enol ether **8a** with either tributyltin hydride or tris(trimethylsilyl)silane[16] and azobisisobutyronitrile (AIBN) resulted in the desired 5-*exo* cyclization in quantitative conversion by ^{1}H NMR spectroscopy (Scheme 3).

Photochemically induced cleavage of *N*-alkoxypyridinethione **13**also leads to cyclization onto the silyl enol ether (Scheme 4). In the absence of a source of hydrogen atom the initial carbon-centered radical cyclized product is quenched with pyridinethione[17,18] to afford tetrahydrofuran **14**. This route provides both an alternative to using reductive stannyl and silyl hydrides as well as a direct route to protected aldehydes.

With the basic reactivity established, we next focused on examining the chemo- and diastereoselectivities in oxygen-centered radical cyclizations onto silyl enol ethers for a wide range of substitution patterns (Table 1).[19] Simple unsubsti-

(9) For representative examples, see: (a) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1593–1597. (b) Boto, A.; Hernádez, D.; Suárez, *Eur. J. Org. Chem.* **2003**, *68*, 5310–5319.

(10) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.2.5, pp 811−814.

(11) For kinetic experiments demonstrating increased rates with increased alkyl substitution, see: (a) Hartung, J.; Hiller, M.; Schmidt, P. *Liebigs Ann.* **1996**, 1425–1436. (b) Hartung, J.; Kneuer, R.; Rummey, C.; Bringmann, G. *J. Am. Chem. Soc.* **2004**, *126*, 12121–12129.

(12) To the best of our knowledge, there is only one example of the use of a silyl enol ether as an acceptor for an oxygen-centered radical cyclization. In the course of a study on β-fragmentations, there is one example of an oxygen-centered radical addition to a silyl enol ether in which the system is directed to cyclize onto the carbon α to the siloxy substituent. Kim, S.; Kim, K. H.; Cho, J. R. *Tetrahedron Lett.* **1997**, *38*, 3915–3918.

(13) (a) Kim, S.; Lee, T. A.; Song, Y. *Synlett* **1998**, 471–472. (b) Okada, K.; Okamoto, K.; Oda, M. *J. Am. Chem. Soc.* **1998**, *110*, 8736–8738. (c) Barton, D. H. R.; Blundell, P.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1989**, *30*, 2341–2344.

(14) (a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1988**, *110*, 4415–4416. (b) Hay, B. P.; Beckwith, A. L. J. *J. Org. Chem.* **1989**, *54*, 4330–4334.

(15) Hartung, J.; Kneuer, R.; Schwarz, M.; Svoboda, I.; Fueb, H. *Eur. J. Org. Chem.* **1999**, 97–106.

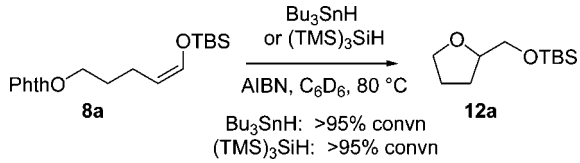
(16) For the development of tris(trimethylsilyl)silane as a radical reducing agent, see: (a) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641–3642. (b) Chatgilialoglu, C. *Chem.—Eur. J.* **2008**, *14*, 2310–2320. For the use of tris(trimethylsilyl)silane in the generation of oxygen-centered radicals, see ref 13a.

(17) For a review on the use of thiohydroxamic esters in carbon-radical cyclizations with concomitant sulfur trapping, see: Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675–684.

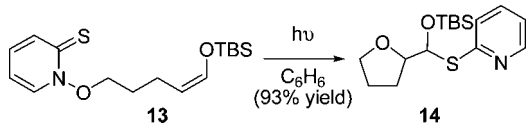
(18) For a representative example of the use of *N*-alkoxypyridinethiones in oxygen-centered radical cyclizations with concomitant sulfur trapping, see: Hartung, J.; Gallou, F. *J. Org. Chem.* **1995**, *60*, 6706–6716.

(19) Substrates **8a**−**h** are *Z*-enriched. See the Supporting Information for *E*/*Z* ratios.

Scheme 3. Tin- or Silyl-Mediated Oxygen-Centered Radical Cyclization onto a Silyl Enol Ether from an *N*-Alkoxyphthalimide



Scheme 4. Photolysis of an *N*-Alkoxypyridinethione Derivative



tuted silyl enol ethers derived from aldehydes (entry 1) and ketones (entry 2) cyclized to the corresponding tetrahydrofurans in good yield. Cyclization of secondary oxygen-centered radicals (entries 4 and 5) also proceeded in good yields. These cyclizations displayed comparable diastereoselectivity to what was observed with oxygen-centered radical cyclizations onto terminal alkenes.[1,6,20]

Substrates **8d**−**g** (entries 4−7) were used to examine the effects siloxy-substitution on the alkene has on the rates of possible β-fragmentation and 1,5-hydrogen transfer pathways. Fragmentation was not observed in substrates that could undergo β-scission to secondary carbon radicals (entries 4 and 5).[21] Both **8d** and **8e** chemoselectively cyclized to the tetrahydrofurans **12d** and **12e** in excellent yield. Even substrate **8f**, which can fragment to a benzyl radical, afforded tetrahydrofuran **12f** as the dominant product (84:16 cyclization/fragmentation).

Substrates **8e** and **8g** reacted to give tetrahydrofurans **12e** and **12g** exclusively in high yields (entries 5 and 7). Consistent with increased alkyl substitution,[11] this suggests that the activation provided by the siloxy substitutent to the olefinic acceptor results in a rate of cyclization that is faster than the rate of a possible 1,5-hydrogen abstraction pathway. Furthermore, the cyclization of **8g** occurred in high diastereoselectivity.[22] Increasing the steric bulk of the substituent from a methyl (**8g**) to a phenyl group (**8h**) led to comparable yields, but with even higher diastereoselectivity (entry 8).

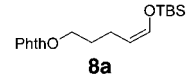
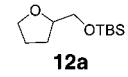
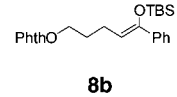
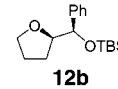
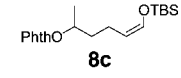
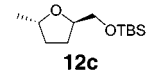
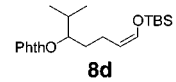
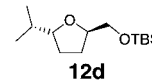
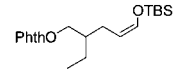
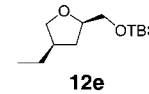
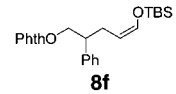
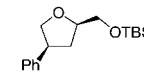
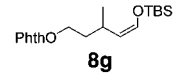
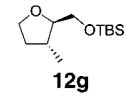
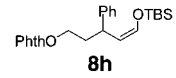
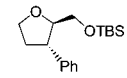
For this cyclization methodology to be a valuable synthetic tool, it must be highly chemoselective in the presence of

(20) For representative diastereoselectivity studies, see: (a) Hartung, J.; Hiller, M.; Schmidt, P. *Chem.—Eur. J.* **1996**, *2*, 1014–1023. (b) Hartung, J.; Kneuer, R.; Laug, S.; Schmidt, P.; Špehar, K.; Svoboda, I.; Fuess, H. *Eur. J. Org. Chem.* **2003**, 4033–4052. (c) Hartung, J.; Stowasser, R.; Vin, D.; Bringmann, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2820–2823.

(21) Unless mentioned in the text, no products resulting from 1,5-hydrogen abstraction or β-fragmentation pathways were observed in crude ^{1}H NMR mixtures. Therefore, it is still possible that they are present in <5% overall yield.

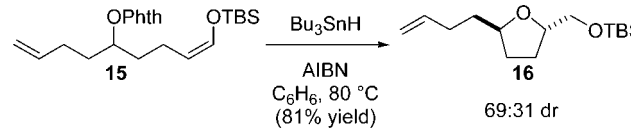
(22) The diastereoselectivity dropped to 88:12 when *E*-enriched silyl enol ether **8g** was used.

Table 1. Oxygen-Centered Radical Cyclization To Form Substituted Tetrahydrofurans

entry	substrate[a]	product[b]	isolated yield[c] (%)	*dr*[d]
1	 **8a**	 **12a**	51[e]	-
2	 **8b**	 **12b**	69	67:33
3	 **8c**	 **12c**	81	67:33
4	 **8d**	 **12d**	73	66:34
5	 **8e**	 **12e**	86	58:42
6	 **8f**	 **12f**	82	72:28
7	 **8g**	 **12g**	71	92:8
8	 **8h**	 **12h**	68	>95:5[f]

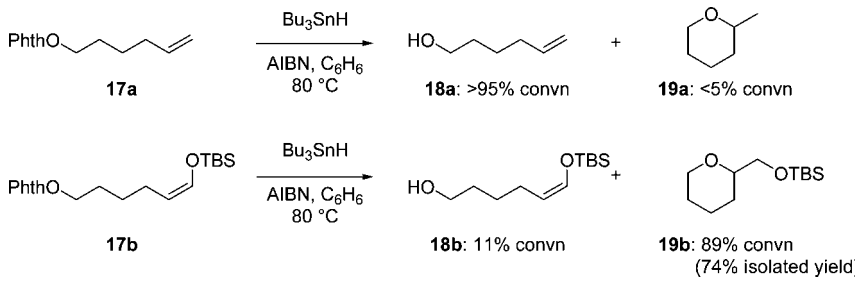
[a] Reactions were carried out on a >0.25 mmol scale. [b] The relative stereochemistry was determined by conversion of **12b**, **12c**, **12f**, and **12h** to the known alcohols. See the Supporting Information for experimental details. [c] Isolated yields of the mixture of diastereomers after flash chromatography. [d] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [e] The product was obtained in >95% conversion by ^{1}H NMR spectroscopy with no other side products. [f] None of the minor isomers could be detected by ^{1}H NMR.

Scheme 5. Competition Experiment To Examine the Relative Rate of Cyclization onto a Silyl Enol Ether versus a Terminal Olefin



reactive functional groups. Therefore, we next investigated the degree of chemoselectivity of cyclization onto a silyl enol ether relative to a simple alkene. This was accomplished using a competition experiment in which the oxygen-centered radical could undergo a 5-*exo* cyclization with either a silyl

Scheme 6. Synthesis of Substituted Tetrahydropyrans



enol ether or a terminal olefin (Scheme 5). The oxygen-centered radical generated from **15** displayed complete chemoselectivity for addition to the silyl enol ether. Thus, cyclization exclusively formed product **16**.

A traditional limitation of oxygen-centered radical cyclizations onto alkenes is the formation of six-membered ring systems because the high reactivity of the oxygen-centered radical often leads to a 1,5-hydrogen abstraction of the allylic hydrogen.[23,24] Consistent with previous attempts, cyclization of *N*-alkoxyphthalimide **17a** resulted in exclusive formation of 1,5-hydrogen abstraction product 5-hexen-1-ol (Scheme 6). Previous studies have demonstrated that the rate of cyclization can be increased via gem-dialkyl substituents[23c] or alkyl substitution[23a] on the alkene receptor, but the tetrahydropyrans can only be formed in a maximum of 39% yield.[23a] Complete mass balance experiments indicate that the major product results from a 1,5-hydrogen abstraction pathway.[23] We hypothesized that the silyl enol ether may be sufficiently electron-rich to increase the rate of cyclization to allow for a synthetically useful method for the formation of substituted tetrahydropyrans. Gratifyingly, our experiments demonstrate that we can successfully cyclize silyl enol ether **17b** to substituted tetrahydropyran **19b** in a 74% isolated yield with an 8:1 preference for cyclization versus 1,5-hydrogen abstraction.

In summary, we have found that oxygen-centered radicals chemoselectively cyclize onto silyl enol ethers with fewer side reactions than with alkenes to provide a synthetically general method for the formation of both tetrahydrofurans and tetrahydropyrans. This high selectivity for heteroatom-centered radicals has the potential to provide a reliable and predictable new reaction for use in total synthesis. Efforts to explore the newly uncovered reactivity in the context of natural product synthesis are currently underway.

Acknowledgment. This work was supported by the University of British Columbia, Merck-Frosst, the Natural Sciences and Engineering Research Council of Canada (NSERC), and a doctoral fellowship from NSERC to M.Z.

Supporting Information Available: Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) For representative examples of attempts to form tetrahydropyrans using 6-*exo* oxygen-centered radical cyclizations, see: (a) Hartung, J.; Gottwald, T. *Tetrahedron Lett.* **2004**, *45*, 5619–5621. (b) Johns, A.; Murphy, J. A. *Tetrahedron Lett.* **1988**, *29*, 837–840. (c) Bertrand, M. P.; Surzur, J. M.; Boyer, M.; Milhailović, M. L. *Tetrahedron* **1979**, *35*, 1365–1372.

(24) Tetrahydropyrans can be formed in high yield from oxygen-centered radical 6-*exo* cyclizations when the allylic position is fully substituted and there are no allylic hydrogen atoms available for abstraction. For representative examples, see refs 10 and 23b