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# Alkoxy Radical Cyclizations onto Silyl Enol Ethers Relative to Alkene Cyclization, Hydrogen Atom Transfer, and Fragmentation Reactions

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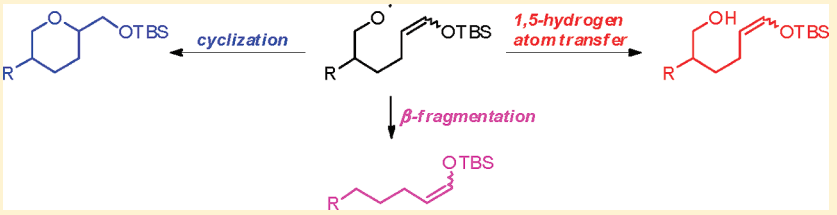
Supporting Information

**ABSTRACT:**




This study examines the chemoselectivity of alkoxy radical cyclizations onto silyl enol ethers compared to competing cyclizations, 1,5-hydrogen atom transfers (1,5-HATs), and $\beta$-fragmentations. Cyclization onto silyl enol ethers in a 5-*exo* mode is greatly preferred over cyclization onto a terminal alkene. The selectivity decreases when any alkyl substitution is present on the competing alkene radical acceptor. Alkoxy radical 5-*exo* cyclizations displayed excellent chemoselectivity over competing $\beta$-fragmentations. Alkoxy radical 5-*exo* cyclizations onto silyl enol ether also outcompeted 1,5-HATs, even for activated benzylic hydrogen atoms. In tetrahydropyran synthesis, where 1,5-HAT has plagued alkoxy radical cyclization methodologies, 6-*exo* cyclizations were the dominant mode of reactivity. $\beta$-Fragmentation still remains a challenge for tetrahydropyran synthesis when an aryl group is present in the $\beta$ position.

## INTRODUCTION

Radical cyclizations are powerful methods for the construction of complex molecular architectures.[1] Alkyl radical cyclizations are widely used both for the construction of building blocks and for late-stage cascade annulations[2] because much is known about the rates of cyclization relative to competing radical reactions.[3] In contrast, alkoxy radical cyclizations are rarely utilized in synthesis because it is often difficult to control the high reactivity of oxygen-centered radicals.[4] Alkoxy radicals primarily undergo three reactions: cyclization (Figure 1, eq 1),[5] 1,5-hydrogen atom transfer (1,5-HAT; eq 2),[6] and $\beta$-fragmentation (eq 3).[7] It is challenging to achieve cyclization chemoselectivity as all three are fast processes, with rates measured to be between $10^8$ and $10^9$ $s^{-1}$ at 80 °C.[8−10] Despite the potential versatility of alkoxy radical cyclizations, their seemingly uncontrollable nature has limited their use in natural product synthesis.[11]

The challenges of achieving high chemoselectivity in alkoxy radical cyclizations are particularly evident in literature case studies investigating the syntheses of tetrahydropyrans.[12] An alkoxy radical can undergo the desired 6-*exo* cyclization or a 1,5-HAT of the allylic hydrogen atom (Figure 2). When there is no substitution on the alkene (R = H), the alkoxy radical chemoselectively undergoes a 1,5-HAT and no cyclization is observed.[13] Even when an $\alpha,\beta$-enoate, a good radical acceptor, was incorporated, low yields of tetrahydropyran were reported (Scheme 1, eq 4).[12b] Cyclization has been promoted through the use of *gem*-dialkyl effects[12a] (eq 5) or increasing the substitution of the alkene

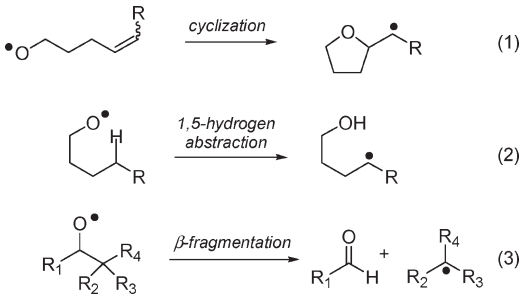



**Figure 1.** Alkoxy radical reactions.

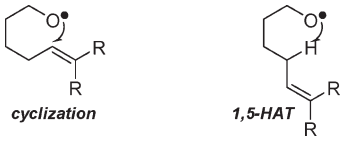



**Figure 2.** Competing reactions in alkoxy radical cyclizations to form tetrahydropyrans.

through incorporation of aryl or alkyl groups (eq 6).[12c,d] These studies constitute an important advance in tetrahydropyran

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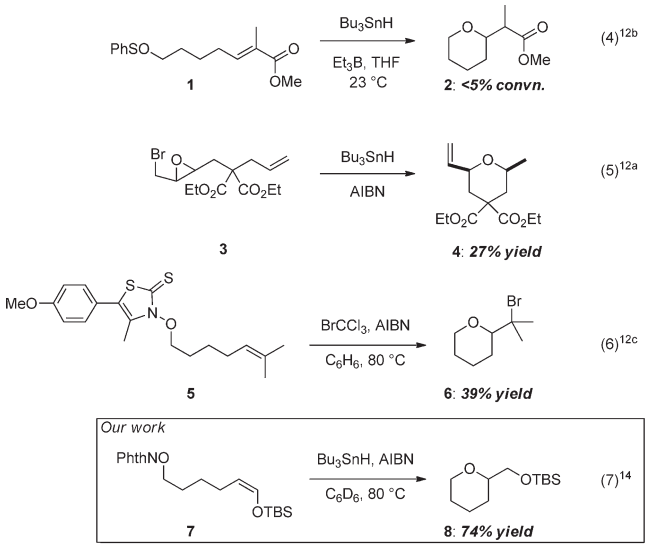
**Scheme 1. Alkoxy Radical Cyclizations To Form Tetrahydropyrans**




formation using alkoxy radicals. Unfortunately, radical 1,5-HAT is still the dominant mode of reactivity during attempted 6-*exo* cyclization processes.

We recently reported the first use of silyl enol ethers as acceptors for alkoxy radical cyclizations.[14] Silyl enol ethers are excellent acceptors for alkoxy radicals in 5-*exo* cyclizations, providing substituted tetrahydrofurans in good to excellent yields and diastereoselectivities. More importantly, silyl enol ethers enable the syntheses of tetrahydropyrans with high chemoselectivity (eq 7). While products resulting from an alkoxy radical 1,5-HAT are still observed, the 6-*exo* cyclization is the dominant mode of reactivity. Cyclizations onto silyl enol ethers have the additional benefit of providing versatile silyl ethers that enable postcyclization functionalization.

The high chemoselectivity for 6-*exo* cyclization onto silyl enol ethers compared to a competing 1,5-HAT clearly indicates the synthetic potential of this methodology in complex molecular settings. However, little is known about the chemoselectivity of 5- and 6-*exo* cyclizations onto heteroatom-substituted alkenes compared to other alkoxy radical reactions (Figure 1). An extensive knowledge of this relative chemoselectivity is vital for alkoxy radical cyclizations to be more predictable and thus more commonly utilized in natural product synthesis. This study examines the reactivity of alkoxy radical cyclizations onto silyl enol ethers relative to competing alkene cyclization, 1,5-HAT, and $\beta$-fragmentation utilizing a series of competition substrates. The information obtained from these competition substrates details the scope and potential utility of these cyclizations in a complex molecular target.

## RESULTS AND DISCUSSION

**Substrate Design and Synthesis.** Five different types of competition substrates were used to probe the relative reactivity of cyclization onto a silyl enol ether versus competing alkene cyclization (Figure 3, type A), 1,5-HAT (types B and C), $\beta$-fragmentation (type D), or multiple pathways (type E). Types B and C substrates were used to explore the relative reactivity of cyclization compared to 1,5-HAT in both 6-*exo* and 5-*exo*

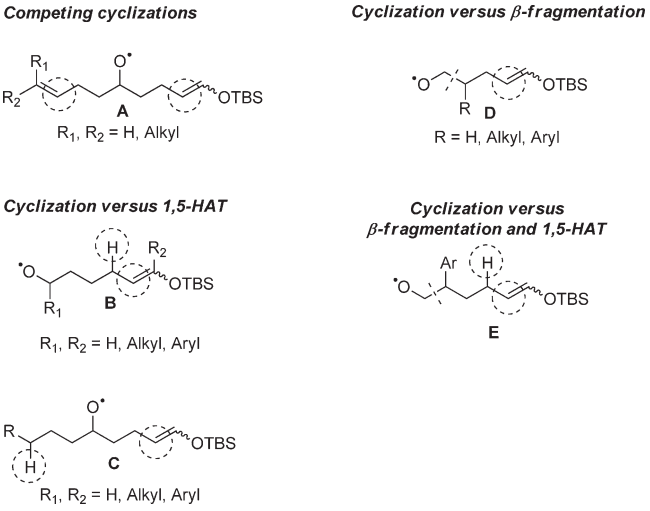



**Figure 3.** Cyclization competition substrates.

cyclizations. The relative rate of $\beta$-fragmentation compared to cyclization was explored in type D substrates. The final substrate, type E, was used to explore the relative rate of alkoxy radical 6-*exo* cyclization versus both competing 1,5-HAT and $\beta$-fragmentation.

The synthetic routes to the competition substrates outlined in Figure 3 intercepted common intermediate **9** (Scheme 2). Depending on the substrate class, alcohol **9** was prepared using standard methods that include either Grignard reagent-mediated epoxide opening or addition of a Grignard reagent to an aldehyde. The final four steps in the synthesis for each of the competition substrates were similar. Mitsunobu installation of the *N*-alkoxyphthalimide[15] followed by silyl deprotection[16] afforded primary alcohol **11**. A subsequent Ley oxidation[17] followed by formation of a *Z*-enriched silyl enol ether afforded the desired cyclization substrate (**12**). Alternatively, the *E*-enriched silyl enol ether could be synthesized using (TBS)Cl and DBU.

**Competition between Alkoxy Radical Cyclization onto a Silyl Enol Ether and Cyclization onto a Substituted Alkene (Type A Substrates).** Investigations began with competition studies between alkoxy radical cyclizations onto silyl enol ethers and cyclizations onto simple alkenes (Figure 4). Achieving chemoselectivity between two competing alkoxy radical cyclizations was anticipated to be challenging because these cyclizations are irreversible and very fast, with rates on the order of $10^9$ $s^{-1}$.[8] Once generated, alkoxy radical A will either cyclize onto the alkene to provide tetrahydrofuran **13** or cyclize onto the silyl enol ether to afford tetrahydrofuran **14**. The resulting radical is too far from the remaining $\pi$-radical acceptor to cyclize again, so the only pathway left is a simple hydrogen transfer to provide the corresponding tetrahydrofurans **15** and **16**. Since alkoxy radical cyclizations are not reversible,[8c,12d] the relative rates of cyclization between the two radical acceptors can be determined from the ratio of the two tetrahydrofuran products (**15** and **16**).

*Part 1. Validation of the Competition Substrate Strategy.* For these intramolecular competition experiments to be self-consistent and generalizable, the electronics of the acceptor needs to be the overriding factor that governs cyclization chemoselectivity. In an effort to validate this competition substrate strategy, we began our investigations with an alkoxy radical cyclization competition between a terminal alkene and a *trans*-disubstituted alkene (Scheme 3, **17**) because the individual rates of a secondary alkoxy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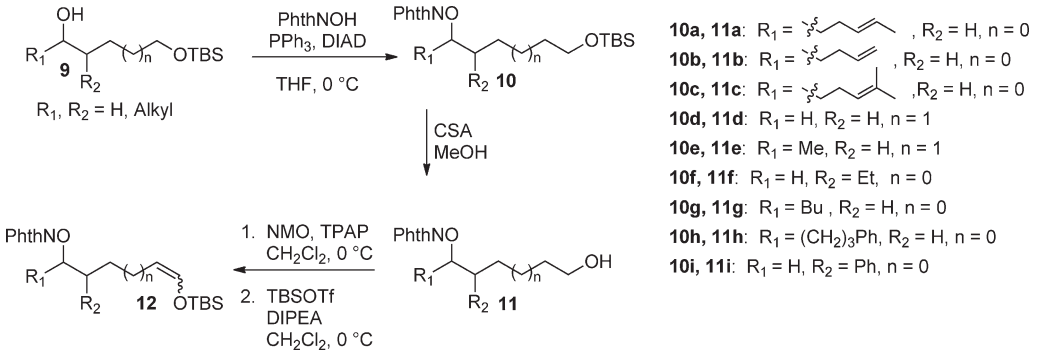
**Scheme 2. Synthetic Route for the Preparation of the Competition Substrates**



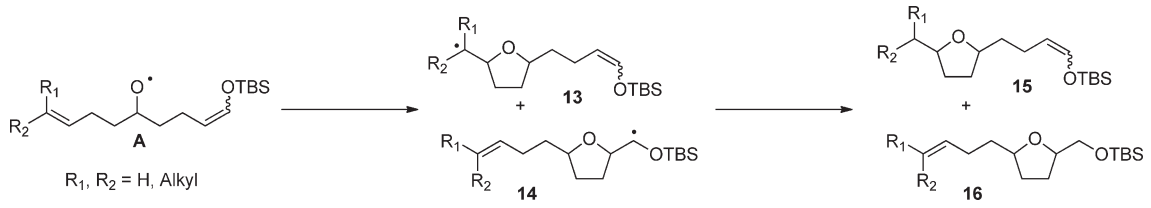
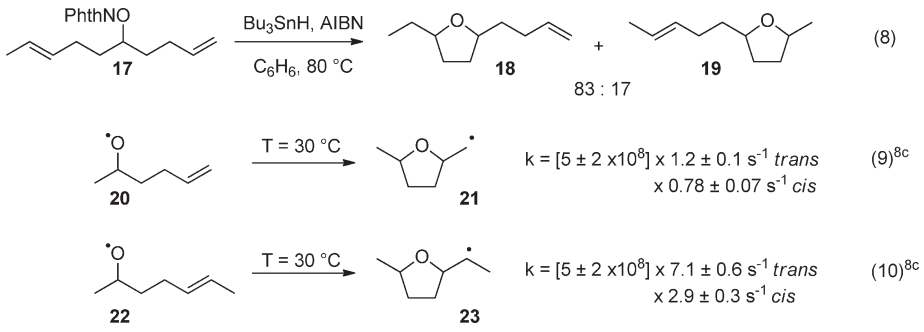




**Figure 4.** Intramolecular cyclization competition studies.

**Scheme 3. Comparison of Competing Cyclization Substrate with Literature Cyclization Rates**




radical cyclization onto a terminal alkene (eq 9) and a secondary alkoxy radical cyclization onto a disubstituted alkene (eq 10) have been reported by Hartung and Gallou.[8c] If the increased sterics of the competition substrate do not significantly affect the rate of cyclization, then the relative ratios of the two tetrahydrofurans (**18** and **19**) should match the ratios of the known cyclization rates.

Cyclization of **17** provided tetrahydrofurans **18** and **19** (Scheme 3, eq 8) in an 83:17 ratio,[18] which matches well with the known rates (Scheme 3, eqs 9 and 10).[19,20] As the competition compares an averaged rate of cyclization onto either alkene, this comparison is rigorous if both cyclization acceptors, the terminal alkene and the *trans*-disubstituted alkene, provide the same diastereomeric ratio (dr). Cyclization studies confirm that alkoxy radical cyclization onto each acceptor occurs with the same diastereoselectivity.[8c] For type A competition substrates, it is assumed that siloxy substitution does not significantly alter cyclization diastereoselectivity. Previous rate studies validate this assumption as substitution on the alkene acceptor does not modify cyclization dr[21] and increases in temperature merely degrade the dr toward nonselectivity.[8c]

*Part 2. Cyclization of Type A Substrates:*[22] With successful validation of the experimental method, we next examined a series of competition substrates between silyl enol ethers and substituted alkenes (type A substrates). Cyclization of competition substrate **24**, which features the competition of an alkoxy radical cyclization between a *trans*-disubstituted alkene and a silyl enol ether (Scheme 4, eq 11), provides a 67:33 ratio of cyclization products **26** and **25**. In addition to providing useful cyclization comparisons, the data from substrates **24** and **17** (Scheme 3, eq 8) can be used to further examine the predictability and self-consistency of these cyclization experiments. Given that competition between a terminal alkene and a *trans*-disubstituted alkene favored cyclization onto the latter in a ratio of 83:17 (Scheme 3, **17**, eq 8) and that competition of a *trans*-disubstituted alkene and a silyl enol ether favored cyclization onto the silyl enol ether in a ratio of 67:33 (Scheme 4, eq 11), competition between a silyl enol ether and a terminal alkene (Scheme 4, substrate **27**) should favor the silyl enol ether in a ratio of 91:9. However, in a previous cyclization competition experiment between a terminal alkene and a silyl enol ether, the only product isolated was believed to be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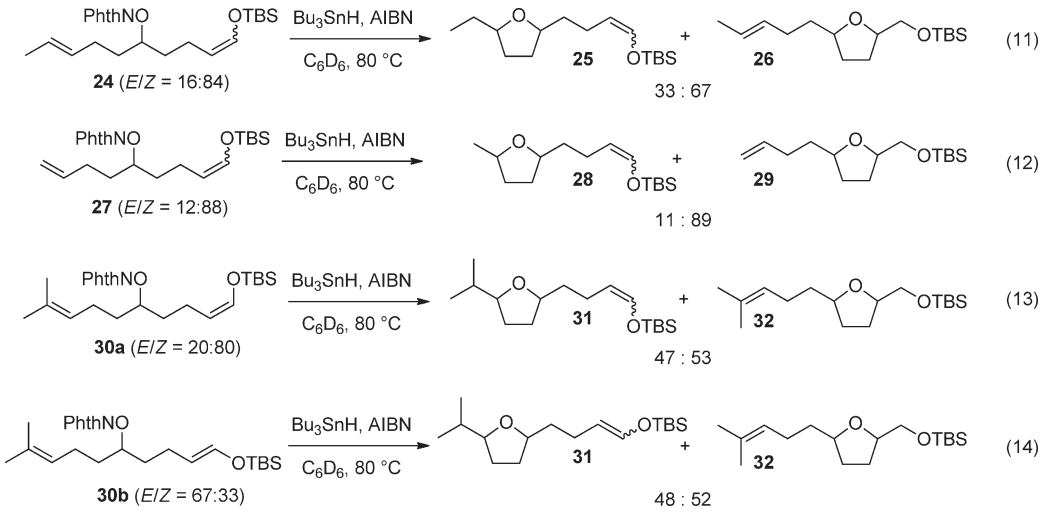
**Scheme 4. Cyclization of Alkoxy Radicals onto Silyl Enol Ethers vs Cyclization onto Substituted Alkenes**



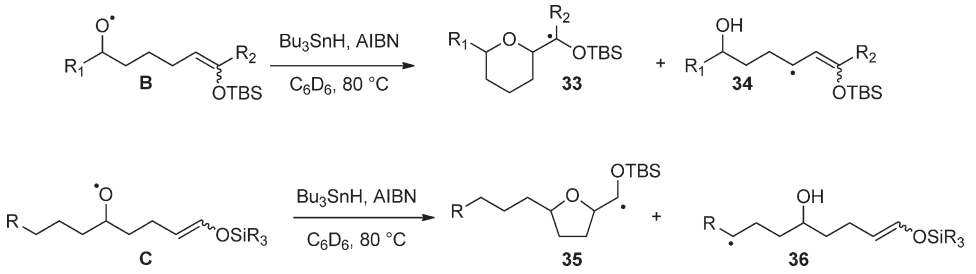




**Figure 5.** Competing cyclization versus 1,5-HAT substrates.

the silyl enol ether cyclized product (**29**) and small amounts of uncyclized competition substrate **27**.[14] Re-examination of **29** indicated minute amounts of tetrahydrofuran **28** that were masked by the uncyclized product. As it is possible that more substantial amounts of alkene cyclized product **28** were present but decomposed upon isolation, cyclization of substrate **27** was repeated in deuterated benzene and the crude reaction mixture was analyzed prior to any workup.[23] $^1$H NMR analysis indicated that the cyclization reaction still strongly favors cyclization onto the silyl enol ether in an 89:11 ratio (eq 12).[24]

We next examined the cyclization competition between a trialkyl-substituted alkene and a silyl enol ether (eq 13, **30**). Despite observed increases in the relative rates between 6-*exo* cyclization and 1,5-HAT between silyl enol ethers and trialkyl-substituted alkenes (Scheme 1, eqs 6 and 7), there was no noteworthy difference in the ratios of 5-*exo* cyclization between the two radical acceptors (Scheme 4, eq 13). Changing the silyl enol ether geometry from *Z*-enriched (eq 13 **30a**) to *E*-enriched (eq 14, **30b**) did not have a significant effect on the ratio of tetrahydrofurans **31** and **32**. One possible explanation for why the two acceptors provided identical relative cyclization rates in 5-*exo* cyclizations despite an increase in the electron density of the acceptor is there is an upper threshold to which these competition substrates can measure differences. The cyclization rates of all these alkoxy radicals are extremely fast, so subtle differences in cyclization rate may be impossible to observe using these competition substrates. However, notable differences were observed in tetrahydropyran synthesis (Scheme 1, eqs 6 and 7). This may be due to slower rates of 6-*exo* cyclization, so the differences in electron density are manifested to a greater degree.

**Competition between Alkoxy Radical Cyclization onto a Silyl Enol Ether and 1,5-HAT (Type B and C Competition Substrates).** Two substrate designs were used to probe competing alkoxy radical cyclizations onto silyl enol ethers and 1,5-HATs (Figure 5). The first substrate design (type B) compares the relative rate of a 6-*exo* cyclization onto a silyl enol ether compared to a 1,5-HAT of an allylic hydrogen atom. The substrate design facilitates testing differences in reactivity between primary and secondary alkoxy radicals (type B, $R_1$ = H, alkyl). The second substrate design (type C) is analogous to the substrates used to probe competing cyclizations and can be used to examine the rates of 5-*exo* cyclizations relative to a 1,5-HAT.

Achieving high cyclization chemoselectivity compared to a competing 1,5-HAT has far-reaching consequences, particularly in the context of challenging tetrahydropyran syntheses. We have previously shown that primary alkoxy radicals preferentially cyclize onto silyl enol ethers in an 89:11 ratio over products resulting from a 1,5-HAT (Scheme 1, eq 7).[13] Primary alkoxy radical precursor **7** was first re-examined using our new, and more accurate, analysis methods.[20] The 90:10 ratio of tetrahydrofuran **8** to linear alcohol **37** (Scheme 5, eq 15) closely matched our previously reported ratio.

We next examined how substitution along the backbone would affect the relative rate of 6-*exo* cyclization. Secondary alkoxy radical precursor **38** (Scheme 5, eq 16) was subjected to the same radical cyclization conditions. The secondary alkoxy radical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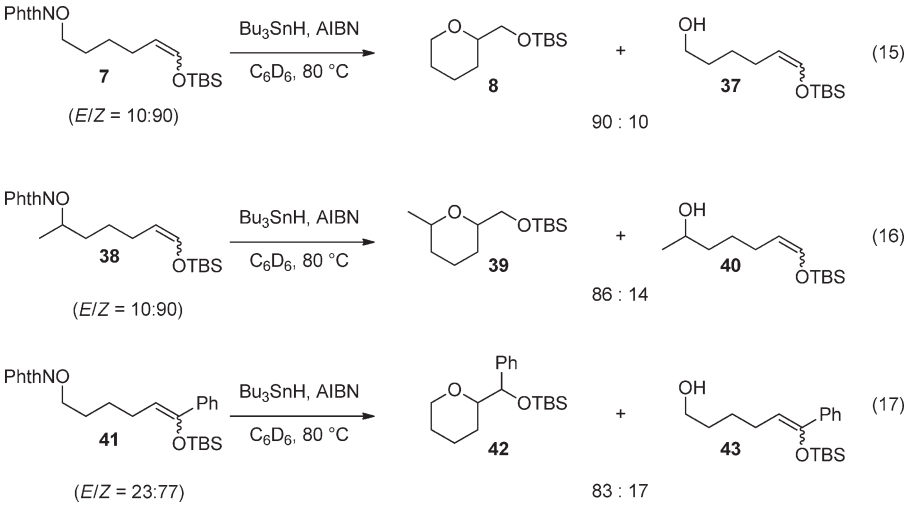
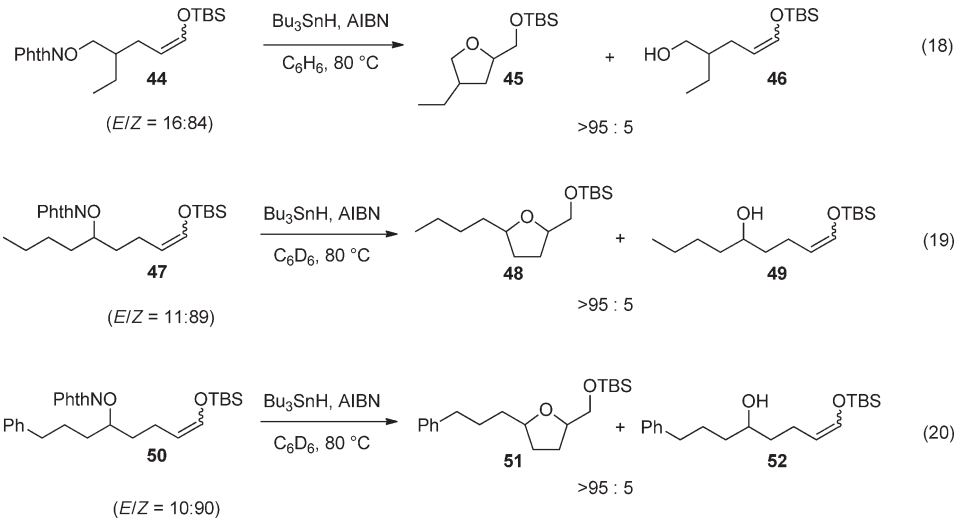
**Scheme 5. Competition of an Alkoxy Radical 6-*exo* Cyclization onto Silyl Enol Ethers vs 1,5-HAT**




**Scheme 6. Competition of an Alkoxy Radical 5-*exo* Cyclization onto Silyl Enol Ethers vs 1,5-HAT**




favored tetrahydropyran formation over 1,5-HAT, albeit in a slightly decreased ratio of 86:14.[25] Cyclization of alkoxy radical precursor **41**,[26] possessing a phenyl substitution on the silyl enol ether, provided an 83:17 ratio of tetrahydropyran **42** to linear alcohol **43**. While the phenyl group provided an increase in the relative rate of 1,5-HAT compared to cyclization, the tetrahydropyran is still the primary product observed.

The next series of substrates examined competitions between alkoxy radical 5-*exo* cyclizations and 1,5-HAT (Figure 5, type C). We have previously demonstrated that the alkoxy radical generated from substrate **44** does not undergo a 1,5-HAT of the terminal carbon−hydrogen bond and cyclizes exclusively to provide tetrahydrofuran **45** (Scheme 6, eq 18).[14] We next examined cyclizations relative to weaker carbon−hydrogen bonds (eqs 19 and 20). Competition substrate **47** explored the competition between 5-*exo* cyclization and 1,5-HAT from a secondary hydrogen. Similar to competition substrate **44**, the reaction displayed excellent cyclization chemoselectivity[27] and the 1,5-HAT product (**49**) could not be detected by $^1$H NMR spectroscopic analysis.

With perfect chemoselectivity for all substrates attempted thus far, we next examined a more challenging competition, substrate **50**, which compares alkoxy radical cyclization and 1,5-HAT of a benzylic hydrogen. A benzylic hydrogen was selected in this competition as they are particularly susceptible to radical abstraction. Gratifyingly, competition substrate **50** exclusively cyclized to provide tetrahydrofuran **51**.[28] It is clear from these studies that 1,5-HAT pathways do not compete with 5-*exo* cyclizations onto silyl enol ethers.

**Competition between Alkoxy Radical Cyclization onto a Silyl Enol Ether and *β*-Fragmentation (Type D Competition Substrate).** The next class of competing reactions we examined were competitions between alkoxy radical cyclization and *β*-fragmentation reactions (Figure 6, type D). Alkoxy radicals can be induced to efficiently undergo *β*-fragmentation in a strained cyclic system or through the positioning of a radical-stabilizing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group $\beta$ to the alkoxy radical. Alkoxy radical cyclization substrates with substitution at $C_2$ (Figure 6, R = alkyl, phenyl) can be used to examine the competition between alkoxy radical cyclization and $\beta$-fragmentation.

In our previous study investigating the cyclization of alkoxy radicals onto silyl enol ethers, two of the substrates had the potential for $\beta$-fragmentation relative to cyclization onto a silyl enol ether.[14] Simple alkyl substitution $\beta$ to the alkoxy radical (Scheme 7, eq 21) does not induce fragmentation, and only cyclized product was detected.[29] However, the presence of a good radical-stabilizing group, such as a phenyl substituent $\beta$ to the alkoxy radical, facilitates $\beta$-fragmentation. The reaction of radical precursor **57** produced both cyclization product **58**[30] and fragmentation product **59** in a ratio of 84:16, favoring cyclization.

**Cyclization versus $\beta$-Fragmentation and 1,5-HAT (Type E Competition Substrate).** The last substrate to conclude our study was the combined triple competition of cyclization onto a silyl enol ether, 1,5-HAT, and $\beta$-fragmentation (Scheme 8, type E). Competition substrate **60**[22] contains the elements for all three possible radical pathways and might mimic the level of complexity found in late-stage total synthesis. Treatment of phthalimide **60** with the standard radical reaction conditions produced a mixture of products. $^1$H NMR spectroscopic analysis of the reaction mixture indicated a 41% conversion to 6-*exo* cyclization product **61**.[31] We were unable to cleanly identify the other reaction products, but on the basis of literature precedent[12d] and the products obtained from competition substrates **7** (Scheme 1) and **57** (Scheme 7), the remainder of the mass balance likely consists of both fragmentation product **62** and 1,5-HAT product **63**.

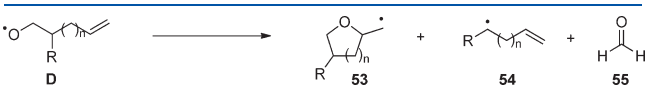



**Figure 6.** Competing cyclization versus $\beta$-fragmentation.

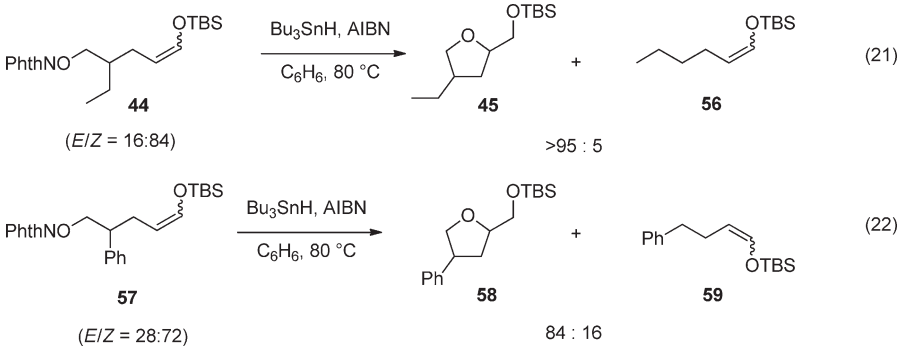
## CONCLUSION

Despite the high reactivity inherent in an oxygen-centered radical, these studies indicate that the cyclization of an alkoxy radical onto a silyl enol ether generally outcompetes common radical pathways, such as cyclizations onto alkenes, 1,5-HATs, and $\beta$-fragmentations (Table 1). These results are noteworthy given the high rates of all the competing radical processes. The greatest degree of chemoselectivity, and thus reaction control, was observed in competitions between 5-*exo* cyclization and 1,5-HAT, where cyclization was the only product observed in all substrates attempted (Table 1, type C competition substrate). Even in tetrahydropyran synthesis, where 1,5-HAT has plagued alkoxy radical cyclization methodologies, 6-*exo* cyclizations were the dominant mode of reactivity (Table 1, competition substrate B). Cyclization onto silyl enol ethers in a 5-*exo* mode is greatly preferred over cyclization onto a terminal alkene (Table 1, type A competition substrate). The selectivity decreases when alkyl substitution is present on the competing alkene radical acceptor. Alkoxy radical 5-*exo* cyclization also outcompeted $\beta$-fragmentation, even when radical-stabilizing groups were introduced $\beta$ to the oxygen-centered radical (Table 1, type D competition substrate). $\beta$-Fragmentation still remains a challenge for tetrahydropyran synthesis when an aryl group is present in the $\beta$ position. However, cyclization still occurs in appreciable conversion (Table 1, type E competition substrate). We believe the demonstrated high chemoselectivity exhibited by silyl enol ethers as radical acceptors expands the scope of alkoxy radical cyclizations and makes these reactions suitable candidates for complex total synthesis.

## EXPERIMENTAL SECTION

**General Methods.** All reactions were performed under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran, diethyl ether, and dichloromethane were purified by a solvent purification system. All other solvents were used without further purification. Silica gel used in column chromatography was stirred with triethylamine prior to packing.

**Scheme 7. 5-*exo* Cyclization of Alkoxy Radicals onto Silyl Enol Ethers vs Fragmentation**




**Scheme 8. Competition among 6-*exo* Cyclization into a Silyl Enol Ether, 1,5-HAT, and $\beta$-Fragmentation**

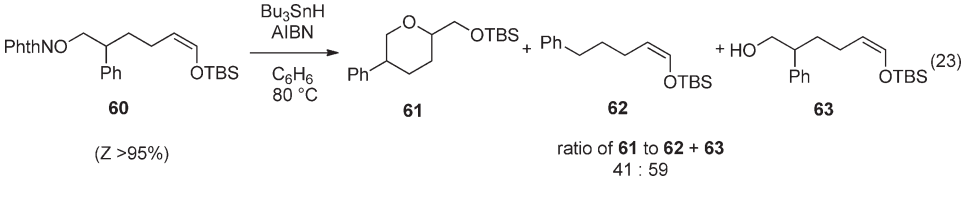




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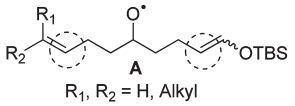
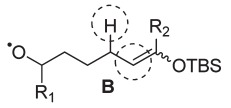
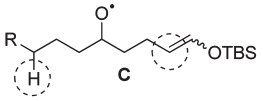
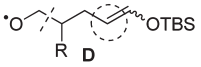
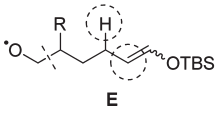
**Table 1. Summary of Competition Experiments**

| Type of Competition Substrate | Substitution | Selectivity for silyl enol ether cyclization |
|---|---|---|
| *Competing Cyclization* | | |
|  A; $R_1$, $R_2$ = H, Alkyl | $R_1$, $R_2$ = H<br>$R_1$ = H, $R_2$ = alkyl<br>$R_1$, $R_2$ = alkyl | Good (89:11)<br>Moderate (67:37)<br>Not selective (48:52) |
| *Cyclization versus 1,5-HAT* | | |
|  B | $R_1$, $R_2$ = H<br>$R_1$ = $CH_3$, $R_2$ = H<br>$R_1$ = H, $R_2$ = Ph | Good to excellent<br>(all >83:17) |
|  C | R = $CH_3$, Ph | Excellent (>95:5) |
| *Cyclization versus β-fragmentation* | | |
|  D | R = $CH_3$, Ph | Good to Excellent<br>(84:16 to >95:5) |
| *Cyclization versus β-fragmentation and 1,5-HAT* | | |
|  E | R = Ph | Moderate<br>(41% cyclization) |

All chemicals were purchased from commercial sources and used as received.

**General Mitsunobu Reaction Procedure.** To a 0.1 M solution of alcohol **9** (1.0 equiv) in dry THF at 0 °C were added *N*-hydroxyphthalimide (1.5 equiv) and triphenylphosphine (1.5 equiv), each in one portion. The resulting solution was stirred for 10 min, and then diisopropyl azodicarboxylate (1.8 equiv) was added slowly over 30 min. The resulting red solution was stirred for 18 h at ambient temperature. The reaction mixture was diluted with $Et_2O$ and washed with saturated $NaHCO_{3(aq)}$ until the aqueous layer was colorless. The combined organics were washed with brine, dried over $Na_2SO_4$, and filtered, and the solvent was removed by rotary evaporation. Flash chromatography purification (95:5 hexanes/AcOEt) yielded the *N*-alkoxyphthalimide **10**.[32]

*(E)-2-((1-((Triethylsilyl)oxy)dec-8-en-5-yl)oxy)isoindoline-1,3-dione (**10a**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.82 (dd, $J$ = 5.3, 3.1 Hz, 2H), 7.73 (dd, $J$ = 5.3, 3.2 Hz, 2H), 5.50−5.38 (m, 2H), 4.23 (q, $J$ = 6.0 Hz, 1H), 3.61 (d, $J$ = 5.7 Hz, 2H), 2.20 (ddt, $J$ = 37.6, 14.8, 7.6 Hz, 2H), 1.75−1.67 (m, 4H), 1.62 (d, $J$ = 5.6 Hz, 3H), 1.55 (t, $J$ = 6.3 Hz, 4H), 0.94 (t, $J$ = 7.9 Hz, 9H), 0.58 (q, $J$ = 7.9 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 164.5, 134.5, 130.6, 125.7, 123.5, 87.9, 62.8, 33.0, 32.53, 32.41, 28.2, 22.6, 21.4, 18.1, 6.9, 4.6. IR ($CDCl_3$): 2951.57, 2875.16, 179.86, 1737.19, 1731.47, 1700.06, 975.80, 701.44 cm$^{-1}$. HRMS-ESI ($m/z$): $[M + Na]^+$ calcd for $C_{24}H_{37}NO_4NaSi$ 454.2390, found 454.2397.

*2-((1-((tert-Butyldimethylsilyl)oxy)-9-methyldec-8-en-5-yl)oxy)-isoindoline-1,3-dione (**10c**).* $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.81−7.91 (m, 2H), 7.70−7.81 (m, 2H), 5.14 (t, 1H, $J$ = 7.1 Hz), 4.19−4.34 (m, 2H), 3.55−3.74 (m, 2H), 2.10−2.33 (m, 2H), 1.47−1.82 (m, 14H), 0.91 (s, 9H), 0.07 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 164.6, 134.6, 129.2, 123.58, 123.53, 88.0, 77.5, 77.2, 76.8, 63.2, 62.7, 33.0, 32.8, 32.2, 26.1, 25.8, 23.90, 23.80, 20.9, 17.9, −5.1. IR ($CDCl_3$): 2916.55, 2879.55, 1789.55, 1732.98, 1374.89, 1187.59, 976.36, 877.88, 702.05 cm$^{-1}$. HRMS-ESI ($m/z$): $[M + Na]^+$ calcd for $C_{25}H_{39}NO_4NaSi$ 468.2546, found 468.2537.

*2-((7-((tert-Butyldimethylsilyl)oxy)heptan-2-yl)oxy)isoindoline-1,3-dione (**10e**).* $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.82 (dd, $J$ = 5.5, 3.1 Hz, 2H), 7.73 (dd, $J$ = 5.5, 3.1 Hz, 2H), 4.36 (d, $J$ = 6.2 Hz, 1H), 3.60 (t, $J$ = 6.4 Hz, 2H), 1.86−1.36 (m, 8H), 1.32 (d, $J$ = 6.2 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.5, 134.5, 129.1, 123.5, 84.6, 63.3, 35.0, 32.9, 26.10, 25.96, 25.2, 18.9, 18.5, −5.1. IR ($CDCl_3$): 2931.29, 2857.32, 1790.49, 1737.02, 1467.69, 1375.30, 1255.03, 1097.58, 976.12, 835.84, 701.73 cm$^{-1}$. HRMS−EI ($m/z$): $[M]^+$ calcd for $C_{21}H_{23}NO_4NaSi$ 414.2077, found 414.2087.

*2-((1-((tert-Butyldimethylsilyl)oxy)nonan-5-yl)oxy)isoindoline-1,3-dione (**10g**).* Polar impurities were removed using a silica plug, and the semicrude mixture was used without further purification.

*2-((8-((tert-Butyldimethylsilyl)oxy)-1-phenyloctan-4-yl)oxy)isoindoline-1,3-dione (**10h**).* Polar impurities were removed using a silica plug, and the semicrude mixture was used without further purification.

**General Deprotection Procedure.** To a 0.1 M solution of *N*-alkoxyphthalimide **10** in MeOH was added camphorsulfonic acid (0.1 equiv) in one portion. The resulting solution was stirred at ambient temperature for 1.5 h. The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (gradient 4:1 to 7:3 hexanes/AcOEt) to yield alcohol **11**.[32]

*(E)-2-((1-Hydroxydec-8-en-5-yl)oxy)isoindoline-1,3-dione (**11a**).* This compound was not isolated, and the semicrude mixture was used without further purification.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*2-((1-Hydroxy-9-methyldec-8-en-5-yl)oxy)isoindoline-1,3-dione (**11c**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.82 (dt, $J$ = 5.9, 3.1 Hz, 2H), 7.75 (dt, $J$ = 5.9, 3.1 Hz, 2H), 5.11 (ddd, $J$ = 7.1, 5.8, 1.3 Hz, 1H), 4.25 (dd, $J$ = 7.1, 4.1 Hz, 1H), 3.68 (t, $J$ = 6.0 Hz, 2H), 2.18 (t, $J$ = 7.6 Hz, 2H), 1.72−1.62 (m, 16H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 164.6, 134.5, 132.3, 129.2, 123.75, 123.57, 88.0, 77.5, 77.1, 76.8, 62.7, 32.8, 32.2, 25.8, 23.9, 20.9, 17.9. IR ($CDCl_3$): 2936.72, 1789.29, 1782.94, 1374.85, 1187.71, 1123.03, 1081.48, 1015.08, 976.59, 877.99, 702.07 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcd for $C_{19}H_{25}NO_4NaSi$ 354.1681, found 354.1674.

*2-((7-Hydroxyheptan-2-yl)oxy)isoindoline-1,3-dione (**11e**).* $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.83 (dd, $J$ = 5.5, 3.1 Hz, 2H), 7.74 (dd, $J$ = 5.5, 3.1 Hz, 2H), 4.38 (sextet, $J$ = 6.0 Hz, 1H), 3.67 (d, $J$ = 3.7 Hz, 2H), 1.87−1.40 (m, 9H), 1.33 (d, $J$ = 6.3 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.5, 134.6, 129.1, 123.6, 84.4, 62.9, 35.0, 32.7, 25.7, 25.0, 19.1. IR ($CDCl_3$): 3390.48, 2936.41, 2861.78, 1789.09, 1731.80, 1466.93, 1377.34, 1187.83, 1123.92, 1081.99, 1016.02, 976l45, 878.51, 702.07 cm$^{-1}$. HRMS-EI ($m/z$): [M]$^+$ calcd for $C_{15}H_{19}NO_4$ 277.13141, found 277.13115.

*2-((1-Hydroxynonan-5-yl)oxy)isoindoline-1,3-dione (**11g**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.83 (dd, $J$ = 5.4, 3.1 Hz, 2H), 7.74 (dd, $J$ = 5.4, 3.1 Hz, 2H), 4.23 (t, $J$ = 5.5 Hz, 1H), 3.68 (s, 2H), 1.70−1.35 (m, 14H), 0.91 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 164.6, 134.6, 129.2, 123.6, 88.3, 62.7, 32.8, 32.27, 32.17, 27.3, 22.9, 20.9, 14.2. IR (neat): 3408.94, 2937.80, 2868.87, 1789.81, 1728.20, 1467.82, 1374.75, 1187.73, 1122.80, 1081.81, 1015.84, 976.65, 878.71, 701.56 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcd for $C_{17}H_{23}NO_4NaSi$ 328.1525, found 328.1532.

*2-((8-Hydroxy-1-phenyloctan-4-yl)oxy)isoindoline-1,3-dione (**11h**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.89 (dd, $J$ = 5.4, 3.1 Hz, 2H), 7.80 (dd, $J$ = 5.5, 3.1 Hz, 2H), 7.33−7.21 (m, 5H), 4.32 (t, $J$ = 5.6 Hz, 1H), 3.71 (t, $J$ = 5.9 Hz, 2H), 2.79−2.66 (m, 2H), 1.97−1.59 (m, 11H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 164.6, 142.3, 134.6, 129.1, 128.58, 128.42, 125.9, 123.6, 88.0, 62.7, 35.9, 32.7, 32.16, 32.05, 26.9, 20.9. IR (neat): 3415.94, 2939.82, 2862.88, 1788.78, 1726.18, 1466.82, 1454.83, 1373.71, 1187.65, 1123.75, 1081.71, 975.53, 877.60, 699.31. HRMS-ESI ($m/z$): [M + Na]$^+$ calcd for $C_{22}H_{25}NO_4Na$ 390.1681, found 390.1685.

**General Ley Oxidation[17] Followed by an Enolization Procedure.** To a 0.1 M solution of alcohol **11** (1 equiv) in dichloromethane at 0 °C were added 4 Å molecular sieves followed by *N*-methylmorpholine *N*-oxide (2.0 equiv). The reaction was then stirred for 15 min. Tetrapropylammonium perruthenate (5 mol %) was added in one portion. The resulting black suspension was stirred for 1 h at 0 °C and 1 h at ambient temperature and then filtered through a bed of silica. The filtrate was washed with $Et_2O$. The organics were combined, and the solvent was removed via rotary evaporation to yield the desired aldehyde. The crude material was used without further purification. To a 0.1 M solution of aldehyde **11** in dry dichloromethane at 0 °C was added diisopropylethylamine (2.0 equiv) in one portion, and the resulting solution was stirred at 0 °C for 15 min. *tert*-Butyldimethylsilyl trifluoromethanesulfonate was then added in one portion and the resulting solution stirred at 0 °C for 30 min and then at ambient temperature for 1.5 h. The reaction mixture was quenched with saturated $NaHCO_{3(aq)}$ and extracted with dichloromethane. The combined organics were washed with brine, dried over $Na_2SO_4$, and filtered, and the solvent was removed by rotary evaporation. Purification using flash chromatography (95:5 hexanes/AcOEt) provided silyl enol ether **12**.[32]

*2-(((8*E*)-1-((tert-Butyldimethylsilyl)oxy)deca-1,8-dien-5-yl)oxy)-isoindoline-1,3-dione (**24**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.88−7.79 (m, 2H), 7.79−7.70 (m, 2H), 6.33 (d, $J$ = 11.9 Hz, 1H (0.16 *trans*)), 6.18 (d, $J$ = 5.8 Hz, 1H (0.84 *cis*)), 5.57−5.35 (m, 2H), 4.51−4.46 (m, 1H), 4.31−4.23 (m, 1H), 2.38−2.13 (m, 4H), 1.86−1.70 (m, 5H), 1.64 (d, $J$ = 5.1 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 18.07, 19.54, 21.49, 25.79, 28.14, 32.44, 32.50, 48.49, 87.75, 123.53, 125.56, 129.29, 130.71, 134.46, 139.21, 164.49, −5.2. IR ($CDCl_3$): 2928.27, 2855.68, 1736.68, 1255.87, 1119.82, 976.41, 837.97, 701.73 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcd for $C_{24}H_{35}NO_4NaSi$ 452.2233, found 452.2225.

*2-((1-((tert-Butyldimethylsilyl)oxy)-9-methyldeca-1,8-dien-5-yl)oxy)-isoindoline-1,3-dione (**30a**).* $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.80−7.88 (m, 2H), 7.68−7.79 (m, 2H), 6.33 (d, 0.2H, $J$ = 11.8 Hz, *trans*), 6.18 (d, 0.8H, $J$ = 5.7 Hz, *cis*), 5.13 (t, 1H, $J$ = 7.0), 4.49 (q, 1H, $J$ = 7.0 Hz), 4.19−4.34 (m, 1H), 2.14−2.37 (m, 4H), 1.70−1.84 (m, 4H), 1.68 (s, 3H), 0.91 (s, 9H), 0.11 (s, 5H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 164.5, 139.2, 134.4, 129.3, 123.5, 109.9, 109.5, 88.0, 35.2, 32.67, 32.54, 25.87, 25.79, 23.8, 19.6, −5.2. IR (neat): 2928.66, 2856.76, 1790.68, 1735.35, 1655.08, 1467.2, 13, 1362.84, 1255.55, 1187.55, 1120.57, 976.79, 837.76, 701.62 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcd for $C_{25}H_{37}NO_4NaSi$ 466.2390, found 466.2393.

*2-((1-((tert-Butyldimethylsilyl)oxy)-9-methyldeca-1,8-dien-5-yl)oxy)-isoindoline-1,3-dione (**30b**).*[33] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.83 (dd, $J$ = 5.4, 3.1 Hz, 2H), 7.74 (dd, $J$ = 5.6, 2.9 Hz, 2H), 6.32 (d, $J$ = 11.8 Hz, 0.67H, *trans*), 6.17 (d, $J$ = 5.8 Hz, 0.33H, *cis*), 5.12−5.10 (m, 1H), 4.99 (dt, $J$ = 11.9, 7.5 Hz, 1H), 4.48 (dd, $J$ = 13.2, 7.0 Hz, 1H), 4.27−4.20 (m, 1H), 2.23−2.14 (m, 4H), 1.75−1.62 (m, 9H), 0.90 (d, $J$ = 3.8 Hz, 9H), 0.11 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 164.5, 139.2, 134.4, 129.3, 123.5, 109.9, 109.5, 88.0, 35.2, 32.67, 32.54, 25.87, 25.79, 23.8, 19.6, −5.2. IR (neat): 2928.66, 2856.76, 1790.68, 1735.35, 1655.08, 1467.2, 13, 1362.84, 1255.55, 1187.55, 1120.57, 976.79, 837.76, 701.62 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcd for $C_{25}H_{37}NO_4NaSi$ 466.2390, found 466.2393.

*(Z)-2-((7-((tert-Butyldimethylsilyl)oxy)hept-6-en-2-yl)oxy)isoindoline-1,3-dione (**38**).* $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.30 (dd, $J$ = 5.4, 3.1 Hz, 2H), 6.79 (dd, $J$ = 5.4, 3.1 Hz, 2H), 6.35 (d, $J$ = 11.9 Hz), 6.20 (d, $J$ = 5.9 Hz, 1H), 5.16 (dt, $J$ = 11.8, 7.5 Hz), 4.57−4.50 (m, 1H), 4.40−4.31 (m, 1H), 2.35−2.28 (m, 2H), 1.89−1.61 (m, 5H), 1.23 (d, $J$ = 6.2 Hz, 3H), 0.94 (s, 9H), 0.05 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 164.5, 139.0, 134.5, 129.2, 123.5, 110.1, 84.6, 34.6, 25.8, 25.5, 23.6, 19.0, 18.3, −5.2. IR ($CDCl_3$): 2928.97, 2856.45, 1790.07, 1732.63, 1652.70, 1465.77, 1373.58, 1255.34, 1186.97, 1080.26, 974.80, 877.57, 836.03, 700.50 cm$^{-1}$. HRMS-TOF ES+ ($m/z$): [M]$^+$ calcd for $C_{21}H_{32}NO_4Si$ 390.2101, found 390.2091.

*(Z)-2-(6-(tert-Butyldimethylsilyloxy)-6-phenylhex-5-enyloxy)isoindoline-1,3-dione (**41**).* This cyclization precursor was not accessed through the general procedure. See the Supporting Information for more synthetic details. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.81−7.87 (m, 2H), 7.72−7.77 (m, 2H), 7.20−7.45 (m, 5H), 5.11 (t, $J$ = 7.04 Hz, 1H), 4.24 (t, $J$ = 6.65 Hz, 2H), 2.28 (q, $J$ = 7.44 Hz, 2H), 1.86 (quintet, $J$ = 6.65 Hz, 2H), 1.54−1.70 (m, 3H), 0.98 (s, 7H), 0.91 (s, 2H), 0.03 (s, 1H), −0.05 (s, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.7, 150.8, 140.7, 135.4, 130.0, 129.4, 128.9, 128.8, 126.9, 124.5, 112.2, 79.5, 28.9, 26.9, 26.7, −3.0, −3.5. IR (neat): 2954, 2930, 2887, 2857, 1790, 1732, 1650, 1468 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcd for $C_{26}H_{33}NO_4SiNa$ 474.2077, found 474.2073.

*2-((1-((tert-Butyldimethylsilyl)oxy)non-1-en-5-yl)oxy)isoindoline-1,3-dione (**47**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.82 (dd, $J$ = 5.5, 3.1 Hz, 2H), 7.74 (dt, $J$ = 5.8, 3.1 Hz, 2H), 6.32 (d, $J$ = 11.9 Hz, 0.11), 6.16 (d, $J$ = 5.8 Hz, 0.89 H), 4.98 (dt, $J$ = 11.9, 7.5 Hz), 4.48 (q, $J$ = 6.6 Hz, 1H), 4.25 (quintet, $J$ = 6.0 Hz, 1H), 2.29−2.18 (m, 2H), 1.78−1.68 (m, 4H), 1.57−1.32 (m, 5H), 0.89 (s, 9H), 0.10 (d, $J$ = 1.5 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 164.5, 139.2, 134.4, 129.3, 123.5, 109.5, 88.2, 32.5, 32.1, 27.1, 25.8, 22.9, 19.6, 18.4, 14.2, −5.2. IR (neat): 3032.97, 2955.78, 2930.77, 2858.83, 1790.82, 1731.19, 1655.75, 1467.76, 1362.74, 1254.63, 1187.65, 1121.59, 1101.65, 1082.59, 975.49, 877.58, 835.32, 779.42, 699.25 cm$^{-1}$. HRMS-ESI ($m/z$): [M + Na]$^+$ calcd for $C_{23}H_{35}NO_4NaSi$ 440.2233, found 440.2240.

*2-((8-((tert-Butyldimethylsilyl)oxy)-1-phenyloct-7-en-4-yl)oxy)-isoindoline-1,3-dione (**50**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.30 (dd, $J$ = 5.4, 3.1 Hz, 2H), 7.19−7.05 (m, 21H), 6.79 (dd, $J$ = 5.4, 3.1 Hz, 2H), 6.51 (d, $J$ = 11.9 Hz, 0.1 H), 6.16 (d, $J$ = 5.8 Hz, 0.9 H), 5.19 (dt, $J$ = 11.9,

7.5 Hz), 4.60 (q, $J$ = 6.6 Hz, 1H), 4.40 (quintet, $J$ = 5.8 Hz, 1H), 2.70−2.45 (m, 4H), 2.09−1.72 (m, 6H), 0.92 (s, 9H), 0.03 (s, 5H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 164.1, 142.6, 139.2, 133.6, 129.5, 128.8, 128.5, 122.9, 109.9, 100.1, 87.8, 36.1, 32.9, 32.3, 26.9, 25.7, 20.0, 18.4, −5.4. IR (neat): 3028.94, 2950.83, 2929.81, 2857.85, 1790.82, 1730.20, 1654.75, 1467.79, 1362.75, 1254.65, 1187.66, 1119.56, 1081.60, 975.50, 877.59, 835.35, 779.45, 747.60, 697.19 cm$^{-1}$. HRMS-ESI ($m/z$): $[M + Na]^+$ calcd for $C_{28}H_{37}NO_4NaSi$ 502.2390, found 502.2379.

*(Z)-2-(6-(tert-Butyldimethylsilyloxy)-2-phenylhex-5-enyloxy)isoindoline-1,3-dione (**60**).* This cyclization precursor was not accessed through the general procedure. See the Supporting Information for more synthetic details. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.67−7.83 (m, 4H), 7.14−7.33 (m, 5H), 6.18 (d, $J$ = 5.71 Hz, 1H), 4.38−4.54 (m, 2H), 4.24−4.38 (m, 1H), 3.09−3.26 (m, 1H), 1.94−2.16 (m, 4H), 1.58−1.84 (m, 1H), 0.93 (s, 5H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.5, 141.3, 139.1, 134.5, 129.0, 128.6, 128.1, 126.8, 123.5, 109.9, 82.0, 60.6, 44.6, 32.9, 25.9, 25.8, 21.4, 21.2, 18.4, 18.2, 14.4, −3.4, −5.2. IR (neat): 3030, 2954, 2930, 2886, 2857, 1790, 1732, 1656, 1469 cm$^{-1}$. HRMS-ESI ($m/z$): $[M + Na]^+$ calcd for $C_{26}H_{33}NO_4SiNa$ 474.2077, found 474.2080.

**Synthesis of (*E*)-2-(Deca-1,8-dien-5-yloxy)isoindoline-1,3-dione (17).** To magnesium turnings (0.48 g, 20 mmol, 4.0 equiv) and a small iodine crystal was added dropwise a solution of crotyl chloride (0.98 mL, 10 mmol, 2.0 equiv) in THF (10 mL), maintaining a gentle reflux. The resulting suspension was heated to reflux for 1 h. THF (10 mL) was then added, and the reaction was removed from the heat source for 5 min. To a separate flask containing copper(I) iodide (95 mg, 0.5 mmol, 0.1 equiv) and 1,2-epoxy-5-hexene (0.56 mL, 5 mmol, 1.0 equiv) was added THF (5 mL), and the resulting solution was cooled to 0 °C. To the suspension was added the Grignard solution over 15 min. The reaction was stirred for 18 h and allowed to warm to ambient temperature. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (10 mL) and poured into $Et_2O$ (100 mL). The organics were washed with water (25 mL), 1.0 M $HCl_{(aq)}$ (2 × 25 mL), and brine (25 mL), dried over $Na_2SO_4$, and filtered. Removal of the solvent by rotary evaporation provided the crude alcohol as a yellow oil. To this oil were added *N*-hydroxypthalimide (1.2 g, 7.5 mmol, 1.5 equiv), triphenylphosphine (1.96 g, 7.5 mmol, 1.5 equiv), and THF (50 mL). The solution was cooled to 0 °C, and diisopropyl azodicarboxylate (1.8 mL, 9.0 mmol, 1.8 equiv) was added dropwise over 20 min. The reaction was stirred for 18 h and allowed to warm to ambient temperature. The reaction was quenched with saturated $NaHCO_{3(aq)}$ (50 mL) and poured into $Et_2O$ (100 mL). The organics were washed with saturated $NaHCO_{3(aq)}$ (2 × 50 mL) and brine (25 mL), dried over $Na_2SO_4$, and filtered. Rotary evaporation and flash chromatography purification (3:1 hexanes/$Et_2O$) yielded 315 mg (21%) of *N*-alkoxypthalimide **17** as a clear colorless oil. $^1$H NMR (400 MHz, $C_6D_6$): $\delta$ 7.28 (dd, $J$ = 3.0, 5.2 Hz, 2H), 6.78 (dd, $J$ = 3.0, 5.2 Hz, 2H), 5.74−5.91 (m, $J$ = 6.7, 6.7, 10.1, 17.0 Hz, 1H), 5.38−5.57 (m, 2H), 5.13 (d, $J$ = 17.1 Hz, 1H), 5.00 (d, $J$ = 10.1 Hz, 1H), 4.29 (quin, $J$ = 5.6 Hz, 1H), 2.33−2.52 (m, 2H), 2.11−2.33 (m, 2H), 1.73−1.87 (m, 2H), 1.68 (qd, $J$ = 5.2, 9.7 Hz, 2H), 1.54−1.63 (m, 3H). $^{13}$C NMR (101 MHz, $C_6D_6$): $\delta$ 164.5, 138.8, 134.1, 131.4, 129.8, 126.0, 123.4, 115.5, 87.8, 87.6, 33.2, 33.1, 32.5, 29.9, 29.8, 28.7, 23.1, 18.5. IR ($CHCl_3$): 2922.74, 2854.08, 1772.00, 1730.23, 1700.30, 1638.83, 1652.87, 1187.69, 976.12, 701,18 cm$^{-1}$. HRMS-ESI ($m/z$): $[M + Na]^+$ calcd for $C_{18}H_{21}NO_3Na$: 322.1419, found 322.1409.

**General Cyclization Procedure.** A solution of tributyltin hydride (40 $\mu$L, 0.15 mmol, 1.5 equiv) and azobisisobutyronitrile (3.3 mg, 0.02 mmol, 0.2 equiv) in 2 mL of $d_6$-benzene was added at a rate of 1.0 mL/h to a refluxing solution of *N*-alkoxypthalimide (0.1 mmol, 1.0 equiv) in $d_6$-benzene (5 mL, 0.02 M). The reaction mixture was refluxed at 80 °C for 4 h before being cooled to ambient temperature. An aliquot was taken directly from the reaction vessel for NMR analysis with an inverse spectrometer (20 scans, 4 s overall pulse sequence). See the Supporting Information for analysis of the cyclization products.

## ■ ASSOCIATED CONTENT

**Supporting Information.** 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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(18) Ratio obtained from the average of two runs. All cyclizations reported in this paper went to complete conversion, and no other products were observed other than those reported. NMR yields of the products closely matched yields based solely on reported product ratios. See the Supporting Information for details.
(19) On the basis of the reported rate constants from Hartung and Gallou,[8c] the predicted ratio of products is 84:16 at 30 °C. We observed an 83:17 ratio of products at 80 °C. Because these reactions are very fast, it is possible that a difference in 50 K does not significantly influence the relative cyclization rates.
(20) All of the cyclization experiments utilized $Bu_3SnH$. While $(Me_3Si)_3SiH$ also provided cyclized products, the reactions frequently did not go to completion. No other metal hydride reagents were examined.
(21) When a large steric substituent, such as a 2,6-disubstituted phenyl group, is adjacent to the alkoxy radical, substitution on the alkene moderately affects the diastereomeric ratio. Substrates from this competition study do not possess steric bulk of that magnitude; see: Hartung, J; Hiller, M.; Schmidt, P. *Liebigs Ann.* **1996**, 1425–1436.
(22) The cyclization diastereoselectivity was not determined for substrates **26**, **29**, and **32**. However, substrates with identical substitution patterns and comparable sterics (**48** and **51**) cyclized in a 67:33 ratio of *trans* to *cis* isomers.
(23) For a full description of this new analysis method, see the Supporting Information.
(24) The silyl enol ether started as an 18:82 mixture of *E*/*Z* isomers. This ratio did not change after cyclization was complete, suggesting that there was no preference for cyclization of either geometric isomer.
(25) The tetrahydropyran was formed in a 53:47 ratio of *cis*/*trans* isomers.
(26) Synthesis of substrates **41** and **60** did not follow the general route outlined in Scheme 2. See the Supporting Information for details.
(27) The tetrahydrofuran was formed in a 67:33 ratio of *trans*/*cis* isomers.
(28) The tetrahydrofuran was formed in a 67:33 ratio of *trans*/*cis* isomers.
(29) The tetrahydrofuran was formed in a 58:42 ratio of *cis*/*trans* isomers.
(30) The tetrahydrofuran was formed in a 72:28 ratio of *cis*/*trans* isomers.
(31) The tetrahydropyran was formed in a 69:31 ratio of *trans*/*cis* isomers.
(32) The syntheses of compounds **7**, **10b, 10d, 10f, 10i, 11b, 11d, 11f, 11i**, **27**, **44**, and **57** can be found in the Supporting Information of ref 13.
(33) Different enolization conditions were used for the synthesis of **30b**. See the Supporting Information for details.