extension of this chemistry to more complex substrates is currently under investigation, along with the development of alternative methods to generate the starting tertiary alkoxyl radicals.[18]

Experimental Section

6b: 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU; 1.08 mL, 7.24 mmol) was added to a solution of allylic alcohol **1b** (1.00 g, 7.24 mmol) in dry CH_2Cl_2 (123 mL) at room temperature. NIS (5.32 g, 21.7 mmol) was added in portions over 3 h at −40 °C. The reaction was stirred overnight at room temperature and then water was added. After extraction with CH_2Cl_2, the organic phases were washed with aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated. Flash column chromatography (Et_2O/hexane 1:12) of the crude product afforded **6b** (1.4 g, 73 %) as a white solid. M.p.: 74–76 °C; IR (KBr): $\tilde{\nu}$ = 3009, 2930, 2361, 1633, 1408, 1147, 1049, 964, 927 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ = 5.87 (dd, J = 17.7, 10.9 Hz, 1H; C*H*=CH_2), 5.31 (dd, J = 17.2, 0.9 Hz, 1H; CH=C*H*H), 5.23 (m, CH=CH*H*, 2H; 1-H), 5.06 (d, J = 5.0 Hz, 1H; 6-H), 4.90 (dd, J = 3.2, 1.4 Hz, 1H; 3-H), 4.29 (s, 1H; I-CH), 2.26 (d, J = 12.7 Hz, 1H; *endo* 8-H), 1.93 ppm (dd, J = 12.9, 4.5 Hz, 1H; *exo* 8-H); ^{13}C NMR (90.5 MHz, $CDCl_3$): δ = 135.1 (d), 116.4 (t), 92.7 (s), 85.9 (d), 83.8 (d), 82.1 (d), 43.4 (d), 28.2 ppm (t). MS (CI): m/z (%): 265 (26) $[M^+ + 1]$, 137 (72) $[M\text{-}I]^+$, 109 (100), 95 (95), 83 (50), 55 (51); elemental analysis: calcd for $C_8H_9IO_2$ (264.06): C 36.39, H 3.44; found: C 36.44, H 3.39.

7: A solution of Bu_3SnH (0.3 mL, 1.14 mmol) and AIBN (6 mg, 0.04 mmol) in benzene (3 mL) was added over 15 h (syringe pump) to the iodide **6b** (200 mg, 0.76 mmol) in refluxing *t*BuOH (74 mL). Heating was stopped at the end of the addition process and CH_2Cl_2 (30 mL) was added. The mixture was cooled at −20 °C and NBS[17] (137 mg, 0.77 mmol) was added in portions over 15 min. After 2 h at −20 °C, the organic layer was washed with water, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (EtOAc/hexane 1:9) gave the stable iodoacetal **7** (143 mg, 60 %) as a colorless oil. IR (film): $\tilde{\nu}$ = 2974, 2936, 1722, 1368, 1003 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ = 5.51 (d, J = 3.2 Hz, 1H; OCHO), 4.57 (td, J = 6.4, 6.4 Hz, 1H; 7a-H), 3.88 (dd, J = 3.9, 4.1 Hz, 1H; ICH), 2.6–2.82 (m, 3H, 2 × 7-H, 3a-H), 2.43–2.54 (m, 1H; 5-H), 1.95–2.26 (m, 3H; 2 × 4-H, 5-H), 1.23 ppm (s, 9H; *t*Bu); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 209.6 (s), 106.5 (d), 75.7 (d), 75.6 (s), 47.2 (d), 44.3 (t), 36.8 (t), 31.0 (d), 28.6 (q), 24.5 ppm (t); MS (CI): m/z (%):339 (1) $[M^+]$, 265 (100) $[M^+ - O$*t*$Bu]$, 137 (29); HRMS (CI, isobutane) for $C_{12}H_{19}O_3I$ ($[M^+$-O*t*Bu]): calcd 264.97199; found 264.97194.

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[17] Both NIS and NBS furnished iodide **7b**; we assume that NBS reacts rapidly with Bu_3SnI to give Bu_3SnBr and NIS.
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Allyl Sulfoxides as Precursors for Radical Two-Carbon Ring Expansion of Cyclobutanones**

Rachel Chuard, Anne Giraud, and Philippe Renaud*

Ring-expansion reactions are extremely useful processes that take advantage of existing ring structures for the construction of larger cyclic systems. Various ion-based methods have been developed for selective ring-expansion reactions.[1] More recently, following the tremendous development of preparative radical chemistry, ring expansion of ketones by using alkoxyl radicals (Dowd–Beckwith reaction) has been reported.[2–5] This approach proved to be quite efficient for one-, three-, and four-carbon ring expansions. However, enlargement by two carbon atoms is not possible.[3] For this purpose, Galatsis et al. developed a three-step method based on the rearrangement of 1-vinylcycloalkoxyl radicals.[6–8] The low yields and lack of regioselectivity make this procedure unsatisfactory for preparative purposes.[6] Therefore, an efficient two-step procedure for the ring expansion of cycloalkanones would be useful.[9,10] The strategy that we developed is based on an unusual cascade reaction, which consists of a [2,3]-sigmatropic rearrangement (Mislow–Braverman–Evans rearrangement)[11–13] of an allylic sulfoxide followed by a radical fragmentation–cyclization process (Scheme 1). The experimental reaction sequence involves the one-pot preparation of an allylic sulfoxide from the ketone according to the procedure of Evans et al.,[14] followed by treatment of the sulfoxide with tributyltin hydride in refluxing benzene. The challenge of this approach is to develop a chain process with a radical precursor that is available from an equilibrium reaction. The efficacy of the reaction will depend on the ability of the intermediate sulfenate, present only in small amounts, to sustain a chain reaction.

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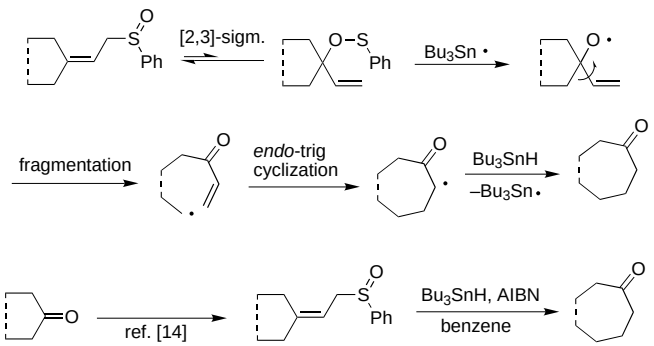
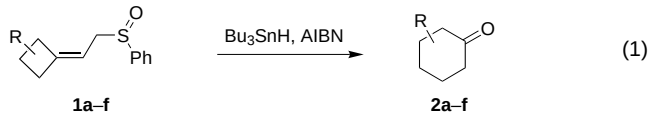


Scheme 1. General strategy for the two-carbon ring expansion.

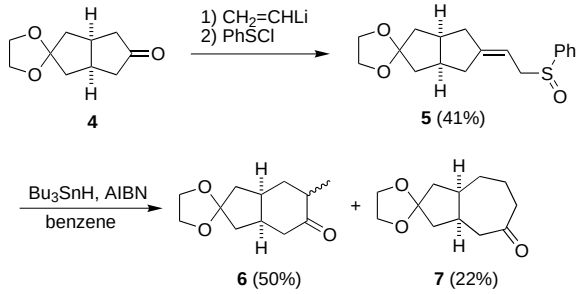
Allylic sulfoxides are easily prepared from cyclobutanones by treatment with vinyllithium followed by phenylsulfenyl chloride.[14] Yields for this transformation lie between 40 and 75%, depending on the freshness of phenylsulfenyl chloride (see Experimental Section for a typical example). The radical rearrangement [Eq. (1)] was examined and optimized with



(1)

the sulfoxide **1a**, which was prepared from 3-phenylcyclobutanone. The best results are obtained by adding 1.5 equivalents of Bu_3SnH over 12 hours to a 0.01M solution of the sulfoxide in refluxing benzene. Under these conditions, the expected product of the two-carbon ring expansion, **2a**, was isolated in 66% yield (Table 1, entry 1). As a side product, 2-methyl-4-phenylcyclopentanone **3a**, which results from a final 5-*exo* cyclization, was isolated in 19% yield.[15] Bicyclic sulfoxides were also investigated. Sulfoxides **1b** and **1c** give the desired products of ring expansion **2b** and **2c** in 43% and 67% yield, respectively (Table 1, entries 2 and 3). In these two examples, the final product results from the regioselective ring opening of the cyclobutyloxyl radical followed by a 6-*endo* cyclization. Sulfoxide **1d** gives **2d** and **2d′** in 64% and 10% yields, respectively (Table 1, entry 4). In this case, the ring opening of the cyclobutane is not completely regioselective, and the major product results from the fragmentation, which leads to a secondary alkyl radical followed by a 6-*endo* cyclization. The precursor **1e** affords the fused cyclohexanone **2e** in 66% yield (Table 1, entry 5). The regioselectivity is explained by the formation of the more stable 1-oxysubstituted radical. The limitation of the regioselectivity control of the ring-opening process is demonstrated by the reaction of sulfoxide **1f** (Table 1, entry 6). In this case, a 1:1 mixture of two secondary alkyl radicals is generated and their cyclization furnishes **2f** (36%) and **2f′** (36%).

The ring expansion of a cyclopentanone derivative was examined next (Scheme 2). Galatsis et al.[6] and Walton and co-workers[7] have shown that the ring expansion of cyclopentanones provides mainly 2-methylcyclohexanone through a 6-*exo* cyclization. Our result confirms this observation, as

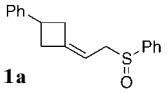
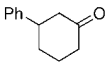
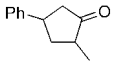
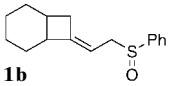
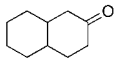
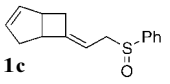
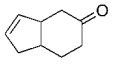
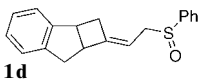
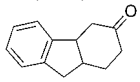
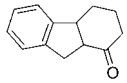
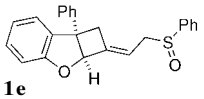
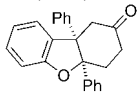
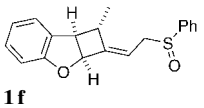
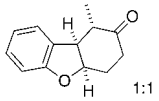
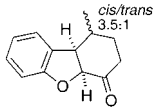


Scheme 2. Ring expansion of cyclopentanone.

sulfoxide **5** obtained from the ketone **4** gives the bicyclo[4.3.0] ketone **6** as the major product (50% yield) together with the bicyclo[5.3.0] ketone **7** (22% yield). Interestingly, the yield of this transformation (72%) is much higher than that obtained by the procedure of Galatsis et al. (29% yield).[16]

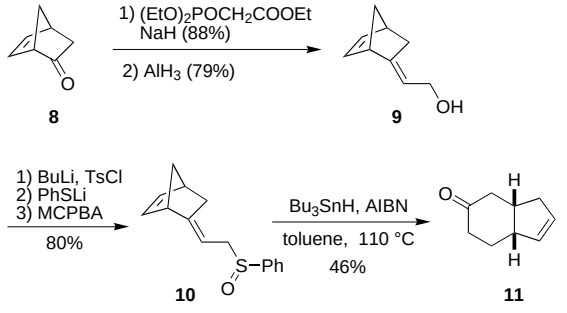
Finally, we have tested our novel method for the generation of the allyloxyl radical in a different reaction cascade, that is,

Table 1. Ring expansion of cyclobutanones according to Equation (1).

Entry	Substrate	Ring-expansion products[a]	
1	 **1a**	 **2a** (66%)	 **3a** (19%)
2	 **1b**	 **2b** (43%)	
3	 **1c**	 **2c** (67%)	
4	 **1d**	 **2d** (64%)	 **2d′** (10%)
5	 **1e**	 **2e** (66%)	
6	 **1f**	 1:1 **2f** (36%)	 cis/trans 3.5:1 **2f′** (36%) 1:1

[a] Bu_3SnH (1.5 equiv) was added over 12 h to a solution of the sulfoxide **1** (0.01M) in refluxing benzene.

the radical oxy-Cope rearrangement.[17] For this purpose, the sulfoxide **10** was prepared from norbornenone **8** via the allylic alcohol **9** (the direct synthesis with the procedure of Evans et al. does not work in this particular case). By treating the sulfoxide **10** with Bu_3SnH and azobisisobutyronitrile (AIBN) in refluxing toluene, the desired rearranged compound **11** is obtained in an unoptimized 46% yield (Scheme 3). This reaction consists of a sequence of a [2,3]-sigmatropic rearrangement followed by generation of an allyloxyl radical, regioselective fragmentation to an allyl radical, and finally a 6-*endo* cyclization.[17]



Scheme 3. Radical oxy-Cope rearrangement.[17] MCPBA = *meta*-chloroperbenzoic acid.

In conclusion, we have demonstrated that allylsulfoxides, which are easily available from ketones, are suitable precursors for allyloxyl radicals. An unique method for the two-carbon ring expansion of cyclobutanones has been developed based on a sequential radical-chain reaction. To the best of our knowledge, this is the first cascade process in which the radical precursor is continuously generated in an equilibrium reaction as a minor component of the reaction mixture. The stability of the sulfoxide radical precursors and the mild reaction conditions of the ring expansion renders this reaction attractive for preparative purposes. The control of the regioselectivity of the process requires a proper design of the system. Extension of this reaction to other ring sizes and more complexed systems is currently under investigation.

Experimental Section

General procedure for the radical ring expansion: A solution of Bu_3SnH (0.49 mL, 1.84 mmol) and AIBN (10 mg, 0.06 mmol) in C_6H_6 (3 mL) was added over 12 h with a syringe pump to a refluxing solution of the allylic sulfoxide (1.23 mmol) in C_6H_6 (123 mL, 0.01M). (For sulfoxide **1e**, better results were obtained when irradiation with a 300-W sunlamp was performed during the reaction.) The solvent was removed under reduced pressure and the crude product was purified by flash chromatography.

2c: From **1c** (300 mg, 1.23 mmol), flash-column chromatography (EtOAc/hexane) afforded **2c** (112 mg, 67%) as a colorless oil. IR (film): $\tilde{\nu} = 3050$, 2930, 2360, 1720, 1450, 1410, 1230 cm^{-1}, ^1H NMR (360 MHz, $CDCl_3$): $\delta =$ 5.72 (m, 1H; C*H* = CH), 5.54 (m, 1H; CH = C*H*), 3.15 (m, 1H; 3a-H), 2.66–2.79 (m, 1H; 1-H), 2.49–2.65 (m, 2H; 7a-H, 4-H), 2.1–2.36 (m, 4H; 2 × 6-H, 1-H, 4-H), 1.93–2.03 (m, 1H; 7-H), 1.65–1.76 ppm (m, 1H; 7-H); ^{13}C NMR (90.5 MHz, $CDCl_3$): $\delta = 213.7$ (s), 133.3 (d), 130.2 (d), 43.2 (d), 42.4 (t), 39.6 (t), 37.5 (t), 33.6 (d), 27.1 (t). MS (EI): *m/z* (%): 136 (53) [M^+], 79 (100); HRMS (EI-MS) for $C_9H_{12}O$ ([M^+]): calcd 136.08826; found 136.08836.

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[14] D. A. Evans, C. L. Sims, G. C. Andrews, *J. Am. Chem. Soc.* **1977**, *99*, 5453.
[15] Experiments with tributyltin deuteride have demonstrated that the cyclohexanone **2a** results mainly from a 6-*endo* cyclization (deuteration at C2) and that a 5-*exo*-cyclization process followed by a Beckwith–Dowd-type rearrangement (deuteration at C3) only contributes marginally to the formation of **2a**.
[16] A deuterium-labeling experiment with Bu_3SnD proved that the cycloheptanone derivative **7** results from a 7-*endo* cyclization and not from a 6-*exo* cyclization followed by ring expansion.
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Low-Temperature Stopped-Flow Studies on the Reactions of Copper(II) Complexes and H_2O_2: The First Detection of a Mononuclear Copper(II)–Peroxo Intermediate**

Takao Osako, Shigenori Nagatomo, Yoshimitsu Tachi, Teizo Kitagawa, and Shinobu Itoh*

Mononuclear copper-active oxygen complexes are key reactive intermediates in many biological and catalytic oxidation processes.[1–4] Aliphatic hydroxylation by O_2 is accomplished at the mononuclear copper-active sites in dopamine β-hydroxylase (DβH) and peptidylglycine α-amidating monooxygenase (PAM), and the oxidative modifications of tyrosine to 2,4,5-trihydroxyphenylalanine quinone (TPQ) and lysine tyrosylquinone (LTQ) cofactors are per-

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