Stereoselective Construction of the Tetrahydrofuran Nucleus by Alkoxyl Radical Cyclizations

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Dedicated to Professor Dr. Bernd Giese on the occasion of his 60th birthday

Keywords: Cyclizations / Oxygen / Radicals / Asymmetric synthesis / Heterocycles

Whereas carbon radical cyclizations have been applied for many years in the stereoselective synthesis of carbocyclic compounds, intramolecular C–O bond formations using alkoxyl radical reactions are less well understood. Since the discovery of *N*-alkoxypyridine-2(1*H*)-thiones **8** as efficient sources of oxygen-centered radicals, and the marked progress in the synthesis of these and related compounds which has been made in the last five years, however, a systematic study of *O*-radical cyclizations under neutral conditions has become available. Kinetic experiments using the radical clock technique found that the parent 4-penten-1-oxyl radical **1** undergoes an extremely fast 5-*exo*-trig ring-closure [$(4 \pm 2) \times 10^8$ s^{-1} (30 °C)] which, after hydrogen trapping, selectively affords 2-methyltetrahydrofuran (**50**). Tetrahydropyran (**56**), which originates from the slower 6-*endo*-trig cyclization, was observed in minor amounts. This observation pointed to a more diverse regioselectivity of *O*-radicals in intramolecular addition reactions to olefinic double bonds than had been predicted from earlier experiments. A mechanistic study of ring-closure reactions of the substituted 4-penten-1-oxyl radicals **51** led to two major conclusions. Firstly, 1-, 2-, 3-, and 5-substituted radicals cyclize stereoselectively *and* 5-*exo*-trig-regioselectively. The degree of stereoselectivity is governed by steric effects. To date, the only exceptions to this rule remain cyclizations of the *para*-substituted 1-aryl-4-penten-1-oxyl radicals **51e**–**m**. These intermediates cyclize regioselectively, *but not* stereoselectively. Secondly, substituents at position 4 of the 4-penten-1-oxyl radical are the key for controlling regioselectivities in *O*-radical ring-closure reactions. Thus, the 4-phenyl-4-penten-1-oxyl radical **51u** cyclizes 6-*endo*-trig-selectively to afford, after hydrogen trapping, 2-phenyltetrahydropyran (**59u**) as the major product (5-*exo*:6-*endo* = 5:95). Results from mechanistic and theoretical studies have been combined in order to derive a general model for predicting alkoxyl radical selectivities in ring closure reactions. The utility of this predictive device has recently been confirmed in the course of a new stereoselective synthesis of the central ring in muscarine alkaloid **72**.

1. Introduction

This year brings the centenary of a discovery that heralded the chemistry of organic free radicals. In 1900, Moses Gomberg reported on the generation and reactivity of the trityl radical.[1] In the following decades, little progress in synthetic free radical chemistry was made. Research interests were primarily guided by kinetic, mechanistic, or industrial aspects of radical reactivities and selectivities. Although these issues were important for the field of applied industrial chemistry, they were often far removed from studies directed towards the application of free radicals in fine chemical synthesis.[2] However, this research laid three cornerstones of modern radical chemistry: (i) the design and application of efficient radical chain reactions, (ii) the

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Jens Hartung was born in Offenbach am Main (1961) and studied chemistry at the Technische Universität Darmstadt. During his Diploma work he was supervised by Professor Dr. Klaus Hafner (1987), and investigated [3.3]sigmatropic rearrangements of dihydroazulenes and reactivities of lithium organic compounds. Afterwards, he joined the group of Professor Dr. Bernd Giese and explored photochemical reactions of organocobalt and organorhodium compounds. In 1990, the author received his Ph. D. and moved as a postdoctoral fellow to the Massachusetts Institute of Technology. There, he worked in the research group of Professor Dr. K. Barry Sharpless and discovered the class of phthalazine- and pyrazine-bridged cinchona alkaloids, which today are widely in use as auxiliaries for the enantioselective osmium tetroxide-catalyzed dihydroxylation of olefins. Back in Germany, the author in 1992 joined an interdisciplinary research team in the cardiovascular division of Hoechst AG, in order to search for a cardioselective K_{ATP}channel inhibitor that has recently been forwarded into phase II clinical trials. In 1994, the author moved to the Universität Würzburg in order to pursue the chemistry of oxygen-centered radicals, heterocyclic chemistry, and transition metal-catalyzed oxidations. He finished his Habilitation in 1998 and has since then held the position of a Privatdozent.

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prediction of radical reactivities, stereoselectivities, and regioselectivities, and (iii) the making available of a large diversity of carbon-centered free radicals from a variety of structurally different stable organic compounds, under mild and neutral conditions.[3−8] The significant progress in intra- and intermolecular stereoselective radical reactions that has been achieved in the last few years will contribute even further to the acceptance of this method for the synthesis of complex target molecules.[9] In view of these considerations, it is surprising to note that the chemistry of heteroatom-centered radicals, especially of alkoxyl radicals, has not attained the same degree of importance as that of their carbon analogues, although remote functionalization (such as the Barton reaction),[10−11] selective β-C−C bond cleavage,[12] phenolic coupling,[13] and a number of important biochemical conversions[14] all profit from the reactivity and selectivity of these intermediates. One major obstacle to a continuous development of *O*-radical chemistry was certainly the restricted number of easily accessible, efficient, and reliable sources of oxygen-centered radicals. Furthermore, data on *O*-radical reactivities and selectivities largely refer to hydrogen abstractions and β-C−C fissions,[15] but not to synthetically probably more useful C−O bond-forming reactions (Figure 1).[16,17]

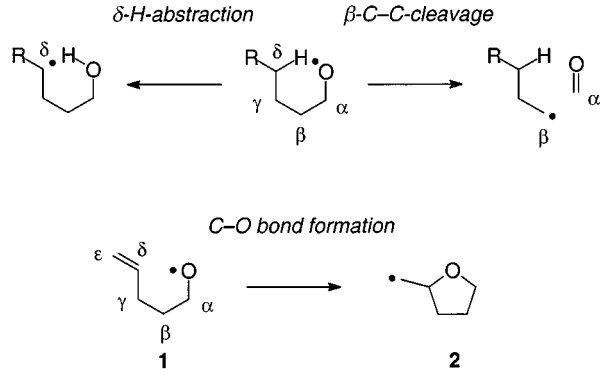


Figure 1. Fundamental reactions of alkoxyl radicals

It was Beckwith and Hay′s discovery of *N*-alkoxypyridine-2(1*H*)-thiones[16] as efficient sources of alkoxyl radicals under mild and neutral conditions that opened a new era in alkoxyl radical chemistry.[18−21] For those who doubted the utility of oxygen-centered radicals in synthesis, it must have come as a surprise that *O*-radicals have recently been successfully applied in the key step of a new stereoselective synthesis of a muscarine alkaloid.[22] Therefore, it is the aim of this review to give a short introduction to the chemistry of *O*-radical precursors. Subsequently, results from pioneering work in alkoxyl radical 5-*exo*-trig ring-closures are provided, and a state-of-the-art description of stereoselective tetrahydrofuran synthesis using alkenoxyl radical cyclizations is given.

2. Generation of Oxygen-Centered Radicals

2.1. Classification of Major Types of *O*-Radical Precursors

Alkoxyl radicals are moderately electrophilic,[23] highly reactive intermediates, which are formed by homolysis of a weak oxygen-heteroatom bond.[24] The existing *O*-radical precursors can be subdivided into four different types. They differ in the origin of the oxygen atom finally converted into the radical center, in whether or not *O*-radicals originate from sources which are only accessible in situ, or in whether *O*-radicals are generated through rearrangements of oxygen-containing carbon radicals. In type-I precursors, the oxygen atom of interest is part of a hydroxyl group that is converted, by esterification, say, into the functionality containing, for instance, a weak oxygen-nitrogen,[25,26] -sulfur,[16,27] or -chlorine bond[28] (synthesis of compounds **3**−**7**). In principle, *O*-radicals with any organic residue R (i.e. *prim*-, *sec*-, *tert*-alkyl, or allyl, aryl) are available from the sequence outlined in Figure 2.

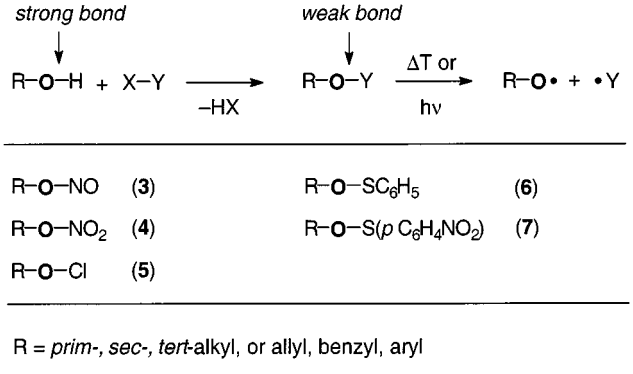


Figure 2. Conversion of alcohols into type-I *O*-radical precursors

The major disadvantage of type-I *O*-radical precursors is the chemical instability of most given examples. The only exceptions to this rule seem to be the alkyl *p*-nitrophenylsulfenates **7**.[27,29,30] However, experimental difficulties have been observed in some instances upon photochemical generation of alkoxyl radicals from these compounds in synthetic reactions.[30] In type-II *O*-radical precursors (Figure 3), the radical oxygen atom is introduced into the alkyl residue by a separate nucleophilic substitution process (compounds **8**−**13**),[31−35] or by insertion of an O_2 molecule (e.g. autoxidation; precursors **14** and **15**).[36−38] In principle, a *prim*-, *sec*-, *tert*-alkyl, or allyl, benzyl, or aryl group should be applicable as substituent R.

Other *O*-radical precursors of interest in, for instance, the field of natural product synthesis (e.g., phenolic couplings) are in many cases not stable, but have to be generated in situ from the combination of an alcohol (or a phenol) and a strong oxidant such as $Pb(OAc)_4$,[39] $Ag_2S_2O_8$,[40] $(NH_4)_2[Ce(NO_3)_6]$,[41] or I_2/PhIO/hν.[42] These *O*-radical sources are grouped as type-III precursors (Figure 4).

The epoxymethylene radicals **16**, which are available from a number of different carbon radical precursors, rearrange efficiently to afford *prim*-, *sec*-, or *tert*-allyloxyl radicals **17** (Type-IV precursors, Figure 5).[43]

The final question that still remains is that of which *O*-radical precursor should be chosen for a mechanistic study of *O*-radical selectivities in ring-closure reactions. The major criteria for guiding this decision are the purity and the synthetic ease by which the material is available, combined

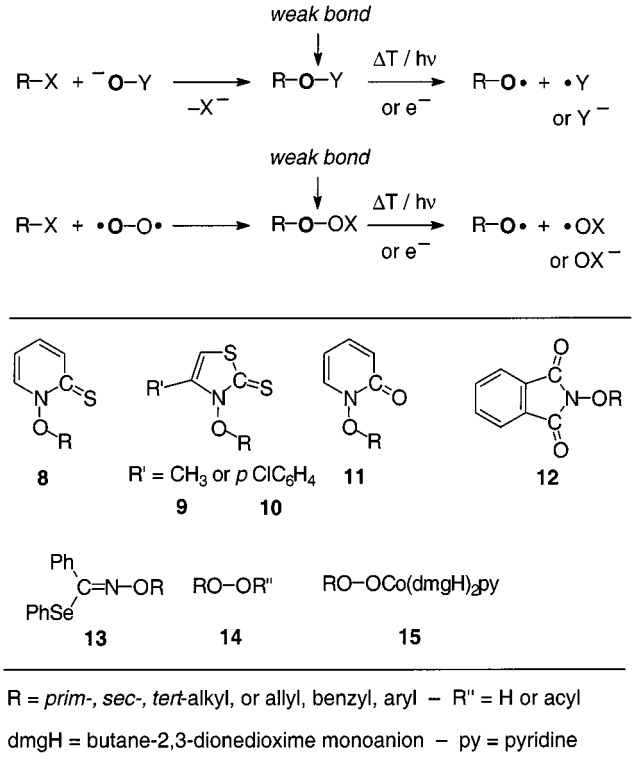


Figure 3. Transformation of R–X by nucleophilic substitution (top) or by oxygen insertion (bottom) into type-II *O*-radical precursors

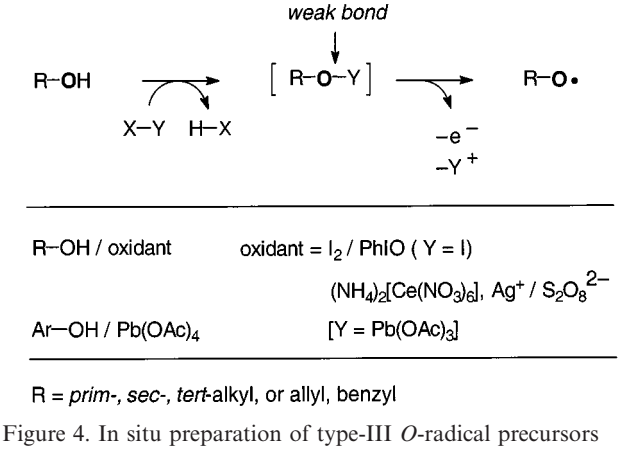


Figure 4. In situ preparation of type-III *O*-radical precursors

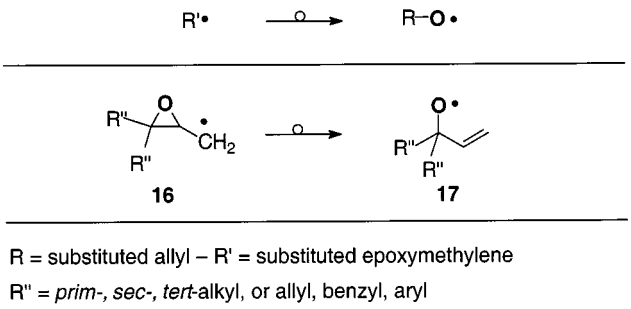
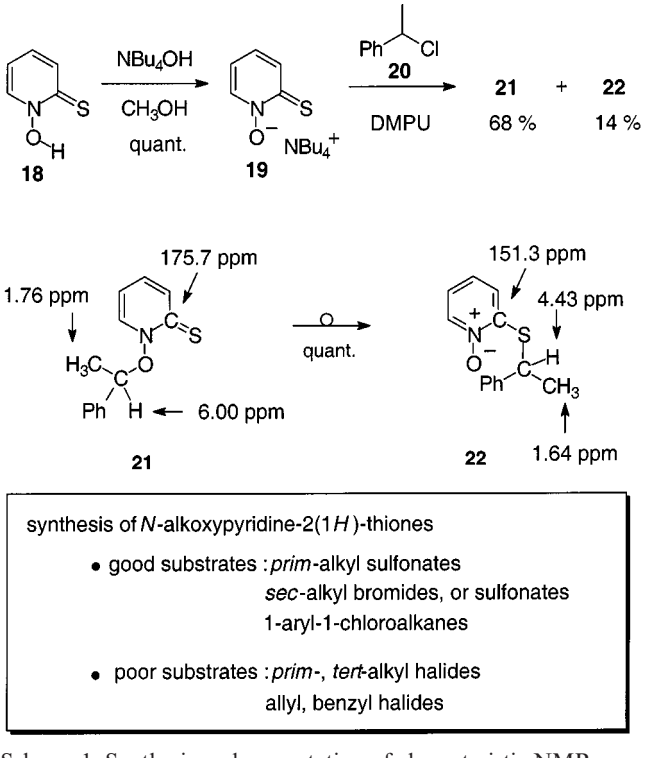


Figure 5. Rearrangement of a carbon radical to an alkoxyl radical (type-IV *O*-radical precursors)

with its efficiency in liberating alkoxyl radicals in, if possible, non-tin-mediated chain reactions.[4,44] For practical reasons, long shelf life and convenient handling of the compounds are desirable for good radical precursors. On the basis of these criteria, almost all the studies summarized in sections 3.2 and 3.4 were carried out with cyclic thiohydroxamic acid-*O*-esters,[45] such as **8**–**10** (Figure 3). The next section of this review therefore deals with the chemical and physical properties of *N*-alkoxypyridinethiones **8** and corresponding thiazolethiones **9** and **10**.

2.2. Preparation and Properties of Thiohydroxamate-Derived *O*-Radical Precursors

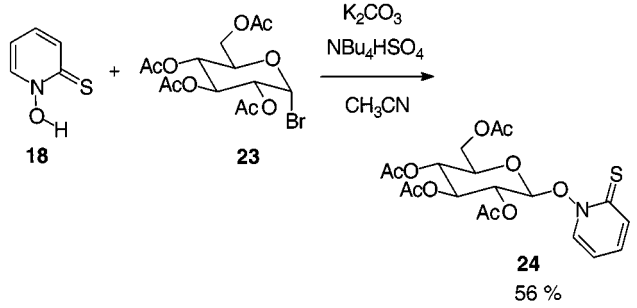
The discovery in 1988 of *N*-alkoxypyridine-2(1*H*)-thiones **8** as clean sources of alkoxyl radicals in efficient chain reactions opened up new perspectives in *O*-radical chemistry.[16] Thus, the study of *O*-radicals structurally different from those generated from type-IV compounds became possible under neutral reaction conditions. Our own experience with *N*-alkoxypyridinethiones **8** was superb in terms of the efficiency of the radical reaction. It soon became obvious, however, that their original, tedious, synthesis had to be improved for a broader application in synthesis. The use of the tetrabutylammonium salt **19** instead of its tetraethylammonium derivative, and DMPU as solvent instead of DMF, are some minor improvements.[31] Still, alkylation of the ambident nucleophile in **19** affords, besides 50–75% of the desired *N*-alkoxypyridinethione such as **21**, up to 50% (in some cases) of 2-alkylsulfanylpyridine *N*-oxides (e.g., **22**, Scheme 1).[19,20,46,47]



Scheme 1. Synthesis and presentation of characteristic NMR spectroscopic data of *N*-alkoxypyridinethione **21** and its isomer **22**, see ref.[20]

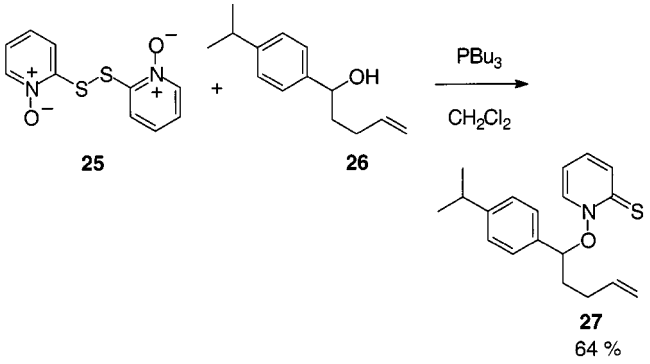
In order to circumvent the additional effort involved in preparing and storing highly hygroscopic *N*-hydroxypyrid-

ine-2(1*H*)-thione tetraalkylammonium salts (e.g. **19**), two new strategies for pyridinethione-derived *O*-radical precursors were established. The first method starts with the acid **18**, which is alkylated with, for instance, acetobromoglucose **23** under phase transfer conditions.[31] CH_3CN is required as solvent, K_2CO_3 as base, and NBu_4HSO_4 as catalyst (Scheme 2). Using this method, carbohydrate-derived pyridinethione **24** was obtained in 56% yield. Another useful route to, for example, pyridinethione **27** is by treatment of the readily accessible 2,2-dithiopyridine 1,1-dioxide (**25**),[48] with an alkenol, such as **26**, in the presence of tributylphosphane (Scheme 3).[49]



- good substrates : *prim*-alkyl sulfonates
  sec-alkyl chlorides, bromides, or sulfonates
  1-aryl-1-chloroalkanes
- poor substrates : *prim*-, *tert*-alkyl halides
  allyl, benzyl halides

Scheme 2. Alkylation of *N*-hydroxypyridinethione **18** using phase-transfer conditions, see ref.[31]



- good substrates : *sec*-alcohols
  1-aryl-1-alkanols
- poor substrates : *prim*-alcohols
  allylic alcohols, benzyl alcohol

Scheme 3. Preparation of *N*-alkoxypyridinethione **27** from disulfide **25** and alkenol **26**, see ref.[49]

N-Alkoxypyridinethiones **8** are light-sensitive, yellow, and frequently oily compounds. Upon heating neat samples of *N*-alkoxypyridinethiones **8**, exothermic decomposition is recorded in the temperature range of 70−120 °C [differential thermal analyses (DTA)].[50] Subsequent product analyses of samples from DTA studies indicate that the compounds that are formed must have originated from an N−O fission as the primary decomposition step.[20] The absorption of longest wavelength in *N*-alkoxypyridinethiones **8** is observed at λ_{max} = 360 nm. The signals in the ^1H and ^{13}C NMR spectra of, for example, thione **21** (Scheme 1) and its heteroaromatic isomer **22** differ significantly, and are therefore reliable tools to distinguish products of *O*-alkylation from those of *S*-alkylation. The chemical shifts in **21**, for example, point to a significant magnetic anisotropy of the thiocarbonyl group.[50,51] X-ray crystallography of the *trans*-4-*tert*-butylcyclohexyloxy-substituted pyridinethione **34** (Figure 6) shows a C−S distance of 1.668(4) Å, which is in the typical range for the thioamide functionality.[50] The N−O bond length in **34** is 1.384(4) Å. These values compare with a C−S bond length of 1.684(2) Å and an N−O distance of 1.377(3) Å for the parent acid **18**.[52]

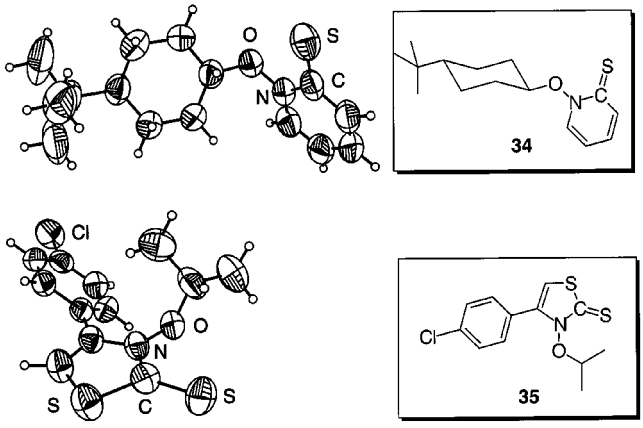
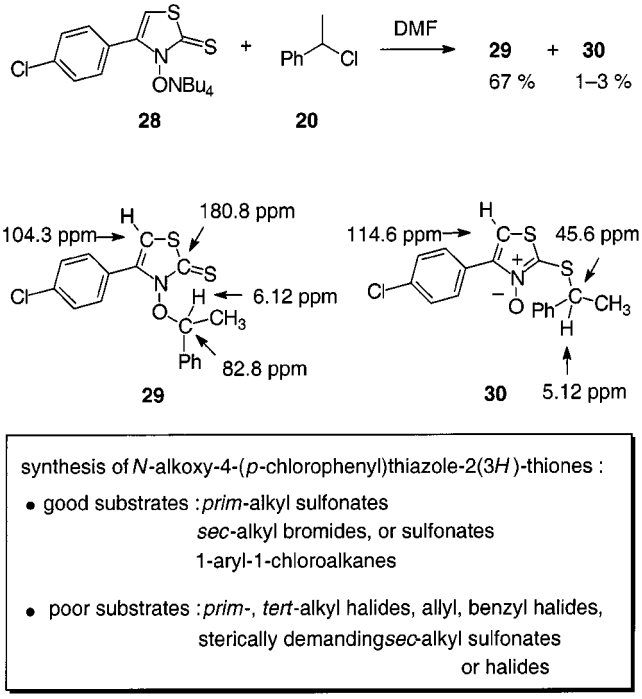


Figure 6. Ellipsoid graphics of single-crystal structure analyses of pyridinethione **34** and thiazolethione **35**; ellipsoids are drawn at the 50% level, hydrogen atoms are depicted as circles of arbitrary radius, see ref.[21,50]

Although the progress summarized in Schemes 2 and 3 helped to further study *O*-radical reactions, the instability of a number of thiones was unsatisfactory.[20] Compound **21**, for example, when stored in a refrigerator, affords the heteroaromatic isomer **22** in quantitative yield within a few days. Furthermore, to avoid their fast decomposition, thiones **8** had to be handled in the dark, soon after being synthesized. Thus, to permit further fast and thorough development of alkoxyl radical chemistry, new *O*-radical precursors with improved characteristics were needed. For conceptual reasons, which are given in Section 2.1, we considered staying with thiohydroxamates as the key functionality. However, the new compounds were intended to show two major improvements: (i) they should not, in the absence of additional radical traps, decompose either by N−O or by C−O fission, and (ii) the next generation of *O*-radical precursors should be crystalline materials, to improve handling and purification methods. On the basis of these prerequis-

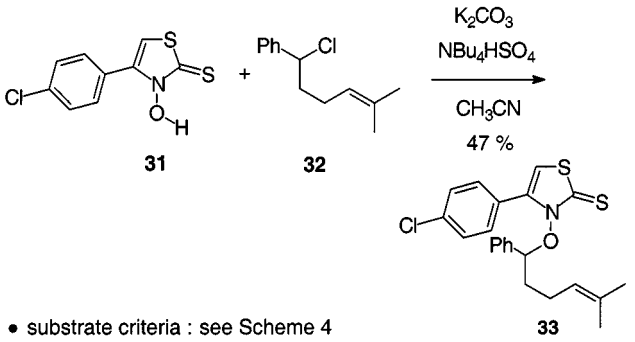
ites and of the fundamental work done by Barton and coworkers,[53] we discovered in a structure/reactivity study that *N*-alkoxy derivatives of 4-(*p*-chlorophenyl)thiazole-2(3*H*)-thiones almost perfectly fulfil these requirements (Scheme 4).[21,54] A large-scale synthesis was developed, making the acid **31** readily available.[55] Furthermore, alkylation of the tetrabutylammonium salt **28** with an extensive variety of alkyl sulfonic acid esters, bromides or chlorides proceeded highly *O*-selectively. For instance, treatment of salt **28** with α-phenylethyl chloride **20** afforded the crystalline, tan colored *N*-alkoxy derivative **29** in good yields, while the unwanted isomer **30** was obtained only in minor amounts.[56] A comparison of the NMR spectroscopic data obtained in the pyridinethione series quickly allowed structure elucidation, thus showing which of the colorless to tan products resulted from *O*-alkylation, and which from *S*-alkylation.



Scheme 4. Synthesis and presentation of characteristic NMR spectroscopic data of *N*-alkoxy-(*p*-chlorophenyl)thiazole **29** and its isomer **30**, see ref.[21,56]

Subsequent experiments indicated that the phase-transfer alkylation methodology could easily be adapted from the synthesis of *N*-alkoxypyridinethiones **8** to that of *N*-alkoxythiazolethiones, such as compound **33** (Scheme 5).[31] This fact opened ready access to a large number of structurally diverse *O*-radical precursors with excellent shelf lives.

The absorption of longest wavelength in *N*-alkoxy-*p*-chlorophenylthiazolethiones — heterocycle **33**, for example — is shifted to a shorter wavelength (λ_{max} = 320 nm) than in the pyridinethiones **8** (λ_{max} = 360 nm).[21] The reactivity of both types of heterocycles in *O*-radical reactions, however, is comparable. Likewise, X-ray crystallographic data obtained from the analysis of *N*-(isopropoxy)thiazolethione **(35)** verified that bond lengths in the central thiohydroxamate functionality of thiazolethione **35** [C−S = 1.658(3) Å, N−O = 1.369(3) Å] are similar to those observed in pyridinethione **34** (Figure 6).[21,50]

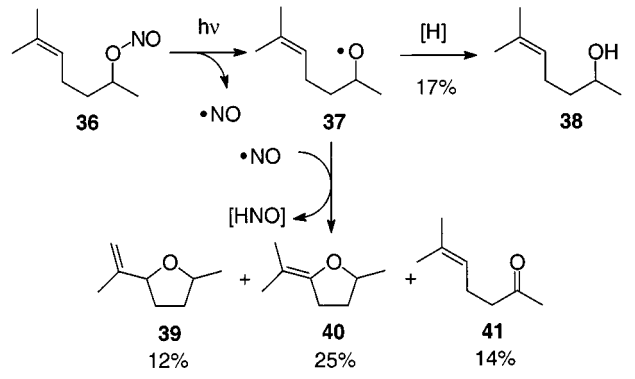


Scheme 5. Alkylation of *N*-hydroxy-(*p*-chlorophenyl)thiazolethione **31** using phase-transfer conditions, see ref.[31]

3. The Synthesis of Substituted Tetrahydrofurans from 4-Penten-1-oxyl Radical Ring-Closure Reactions

3.1 Early Works

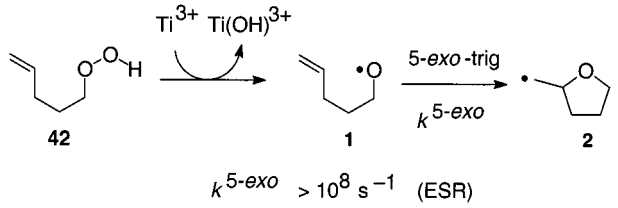
Early investigators into the 4-penten-1-oxyl radical ring-closure used types of precursors other than thiohydroxamic acid *O*-esters, and therefore faced a number of problems not encountered with the latter compounds. In 1969, Surzur, Bertrand, and Nougier reported the photochemical synthesis of tetrahydrofurans from alkenyl nitrites, such as **36** (Scheme 6).[57] These compounds are known to afford *O*-radicals on UV-excitation.[10] Light absorption is followed by homolysis of the weaker N−O bond to afford, in the given example, the 6-methyl-5-hepten-2-oxyl radical **37**. Intermediate **37** adds intramolecularly to the olefinic double bond in a 5-*exo*-trig manner. The observed yields of substituted cyclic ethers **39** and **40** were small. Since the weakly oxidizing intermediate NO is the major reactive radical trap in this mixture, cyclized radicals presumably afford the cyclic ethers **39** and **40** upon oxidation and deprotonation. Reaction of the NO radical with **37** prior to cyclization may account for the formation of ketone **41**, whereas parent alcohol **38** is likely to originate from direct hydrogen trapping by **37** from a solvent molecule.



Scheme 6. Products derived from photochemical conversion of alkenyl nitrite **36** (type-I radical precursor), see ref.[57]

A few years later, Rieke and Moore resumed photochemical investigations on alkenyl nitrites.[58] Unfortunately, no significant advances on Surzur's, Bertrand's and Nougier's results were made. Both reports faced difficulties in deriving clear-cut radical reactivities and selectivities. Since neither Surzur's nor Rieke's group identified reaction products that might have pointed to a competitive 6-*endo* cyclization mode, the 4-penten-1-oxyl radical ring-closure was for many years assumed to proceed 5-*exo*-specifically — in contrast to 5-hexen-1-yl radical cyclizations.[59]

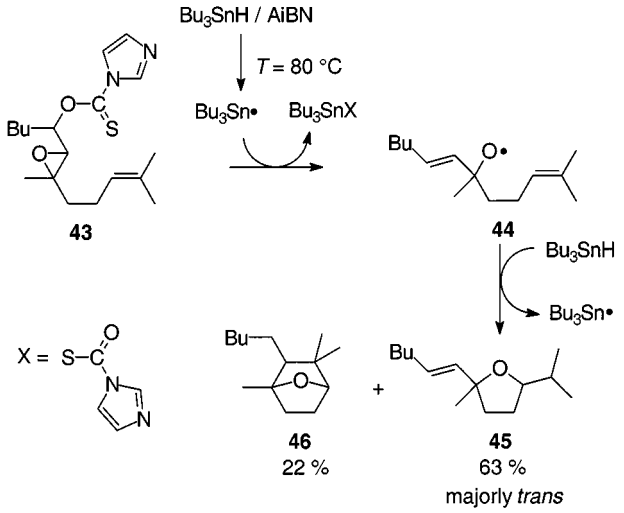
Almost a decade later, Gilbert and co-workers subjected 4-pentenyl 1-hydroperoxide (**42**) to a selective titanium(III)-mediated reduction to afford the 4-penten-1-oxyl radical (**1**) in the cavity of an EPR-spectrometer.[60] The authors set up a flow system and tried to calculate the rate constant of the 5-*exo*-trig cyclization **1** → **2** from the speed of flow and the signal intensities of radicals **1** and **2**. Since the tetrahydrofurylmethyl radical **2** was the only organic radical detected, the authors estimated that $k^{5\text{-}exo}$ must exceed $10^8 s^{-1}$ (Scheme 7).



Scheme 7. Generation of *O*-radical **1** by titanium(III)-mediated reduction of alkenylhydroperoxide **42** (type-II radical precursor), see ref.[60]

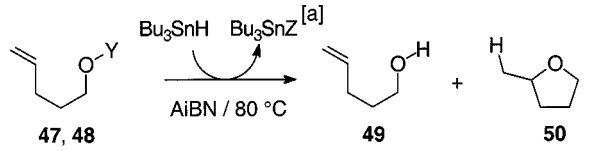
In 1988, Murphy and Johns achieved a major result on the path to an explanation of 4-penten-1-oxyl radical ring-closures.[61] They subjected thiocarbonylimidazole **43** to a thermal reduction with Bu_3SnH and AIBN, and obtained a mixture of diastereomeric tetrahydrofurans **45**, as well as bicyclic product **46** (originating from a *cis*-5-*exo*-trig *O*-radical cyclization as the initial step) (Scheme 8). This result showed that alkoxyl radical reactions could be conducted under neutral conditions. According to NOE studies, *trans*-**45** was the major product in the monocyclic tetrahydrofuran fraction. Unfortunately, the *cis:trans* ratio of **45** was not reported in the original paper, which makes it impossible to judge whether or not the first diastereoselective *O*-radical cyclization was discovered in the course of these experiments.

In the same year, Beckwith and Hay were able to estimate the rate constant of the 5-*exo*-trig cyclization of the 4-penten-1-oxyl radical **1** more precisely (Table 1).[16] The authors subjected pyridinethione **48** to a reduction, with Bu_3SnH [$c_o(Bu_3SnH)$ = 0.030 M] as hydrogen donor and AIBN as initiator, at T = 80 °C (Table 1). Since only 2-methyltetrahydrofuran (**50**), and no 4-penten-1-ol (**49**) (≤ 1%), was detected in the reaction mixture, a value of $k^{5\text{-}exo} \geq 6 \times 10^8 s^{-1}$ (80 °C) was derived. In a following report, Beckwith, Hay, and Williams published a more accurate $k^{5\text{-}exo}$ value from the reduction of sulfenate **47** in a thermally initiated radical chain reaction under *pseudo*-first order conditions [$c_o(Bu_3SnH)$ = 0.300 M]. This reaction afforded a mixture of alcohol **49** and 2-methyltetrahydrofuran (**50**). On the basis of a number of well justified assumptions, the authors calculated $k^{5\text{-}exo} = 5.2 \times 10^8 s^{-1}$ (80 °C).



Scheme 8. Formation of *O*-radical **44** and derived cyclization products **45** and **46** in the presence of Bu_3SnH; see ref.[61]

Table 1. Determination of rate constant $k^{5\text{-}exo}$ from competition experiments using 4-pentenoxysulfenate **47** and pyridinethione **48** (radical clock technique; see also Scheme 9), see ref.[16,17]



Y	47, 48	c_o (Bu_3SnH) [mol l^{-1}]	$k^{5\text{-}exo}$ [s^{-1}]	yields [%] 49	50
SC_6H_5	**47**	0.300	$5.2 \times 10^8 s^{-1}$	26	73
	**48**	0.030	$\geq 6 \times 10^8 s^{-1}$	≤ 1	80

[a] Z = SPh (**47** as precursor) or Z = 2-pyridylsulfanyl (**48** as precursor).

3.2. Mechanistic Studies — Cyclizations of Substituted 4-Penten-1-oxyl Radicals

Results from the studies mentioned in Section 3.1 left behind the impression that the 4-penten-1-oxyl radical cyclization must be distinctively different from its carbon analogue in terms of reactivity and selectivity.[62–66] The major issue to be addressed, if the full scope of alkenoxyl radical cyclizations in tetrahydrofuran synthesis was to be clearly rationalized, involved the investigation of whether or not intramolecular additions of the *O*-radical would proceed stereoselectively, in spite of the high rate constants which were expected on the basis of the $k^{5\text{-}exo}$-value of the parent cyclization process **1** → **2**. In order to be able to extract the most important facts from the following

schemes, tables, and figures, the underlying radical chain reaction for the synthesis of tetrahydrofurans from cyclic thiohydroxamic acid *O*-esters **8**−**10** is outlined briefly at the beginning of this section (Figure 7). Thermal or photochemical activation of thiones **8**−**10** leads to homolysis of the central N−O bond. The alkoxyl radical **51** is formed in this initial step. Intermediate **51** cyclizes to the carbon-centered radical **52**, which is trapped by A−B to afford a cyclic ether **53**, as well as radical A·. This latter intermediate A· must add to the thiocarbonyl group of a starting thione **8**−**10** in order to afford a 2-substituted heterocycle and yet another free radical, **51**. The role of A· in performing an efficient tetrahydrofuran synthesis becomes increasingly important as the initiation process becomes less efficient.[21]

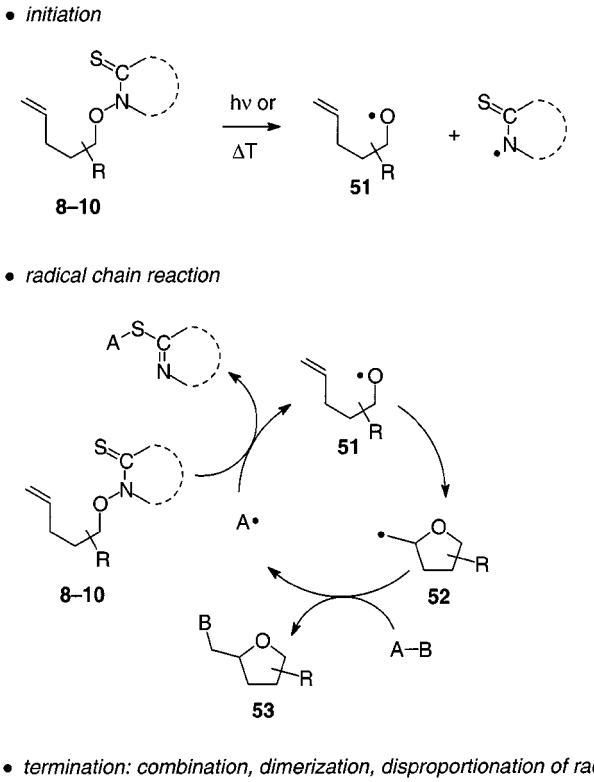
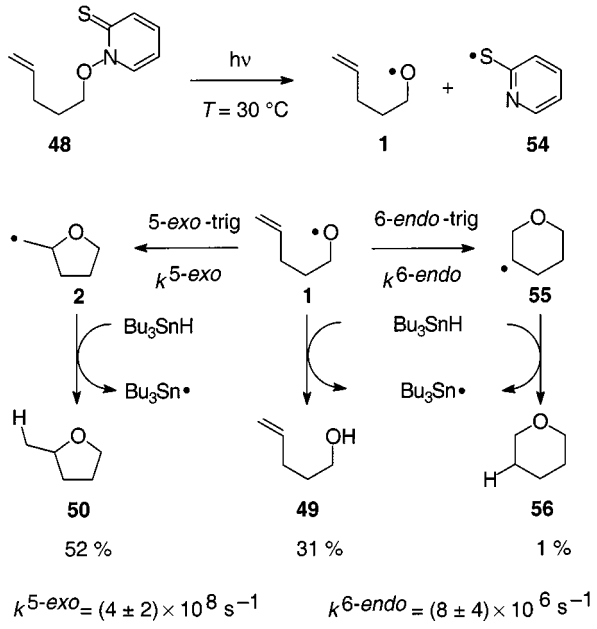


Figure 7. Fundamentals of formation of *O*-radicals **51** from cyclic thiohydroxamic acid *O*-esters **8**−**10** and transformation of **51** into tetrahydrofurans **53** by a radical chain reaction, see ref.[21]

Although the value for the rate constant $k^{5\text{-}exo}$ had already been reported in the literature, its magnitude was redetermined using the radical clock technique and a larger set of competition experiments, since it represents an important reference value in alkenoxyl radical chemistry.[18] Thus, pyridinethione **48** was treated at $T = 30$ °C with Bu_3SnH under *pseudo*-first order conditions to afford mixtures of 4-pentenol **49** and 2-methyltetrahydrofuran (**50**). The ratios of **49**:**50** were dependent on the concentration of the radical trap Bu_3SnH (Scheme 9). Since the intercept of a plot of [**49**]:[**50**] vs. [Bu_3SnH] was zero within the experimental error, it was assumed that the 5-*exo*-trig reaction of radical **1** is irreversible. This issue was further addressed in a separate study which confirmed the irreversibility of the 5-*exo*-trig *O*-radical ring-closure under those reaction conditions.[18,20] In other words, the 4-pentenoxyl radical cyclizations which are described in this section and in section 3.4 proceed under kinetic control. A rate constant for the rearrangement **1** → **2** of $k^{5\text{-}exo} = (4 \pm 2) \times 10^8\ s^{-1}$ (30 °C) was derived from competition kinetics (Scheme 9). This value is somewhat smaller than the number given by Beckwith, Hay, and Williams [$k^{5\text{-}exo} = 5.2 \times 10^8\ s^{-1}$ (80 °C)]. For comparison, unimolecular rate constants of the 5-hexen-1-yl radical cyclization,[67,68] its nitrogen analogues,[9c] and *O*-radical **1**[16,18] are ranked in Figure 8. This graphic clearly shows that the ring closure **1** → **2** is the fastest in this series.



Scheme 9. Photoreaction of 4-pentenoxypyridinethione **48** with Bu_3SnH: product analysis and competition kinetic studies (radical clock technique), see ref.[18]; reported yields refer to $c_o(Bu_3SnH) = 0.44$ M

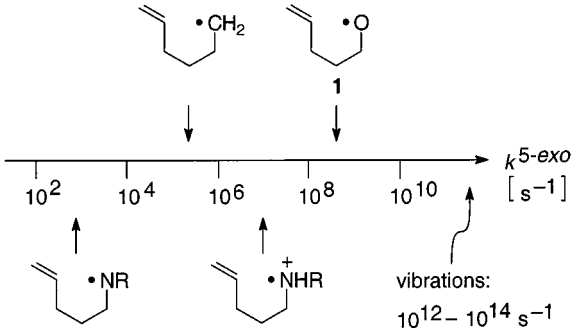


Figure 8. Comparison of ranges of rate constants for 5-*exo*-trig cyclizations of the 5-hexen-1-yl radical (see ref.[68]) an aminyl radical, an aminyl radical cation (see ref.[9c]) and the 4-penten-1-oxyl radical (**1**), see ref.[16,18]

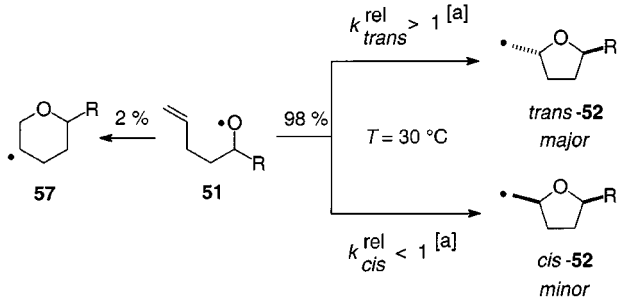
Further analysis of the photoproducts originating from the reduction of 4-pentenoxypyridinethione **48** with Bu_3SnH showed that tetrahydropyran (**56**) was formed in minor amounts. Thus, the 4-pentenoxyl radical cyclization

is not 5-*exo*-specific, but 5-*exo*-selective. However, formation of tetrahydrofuran **50** is appreciably favored in this reaction (**50:56** = 98:2).

Subsequently, the 1-substituted pentenoxyl radicals **51a**−**d** were generated from the respective pyridinethiones in the presence of Bu_3SnH, and their ring-closure reactions were studied (Figure 9).[18] The technique which was applied corresponded to that used for the study of the parent radical **1** (product analysis, competition kinetics). The yields of products related to radicals **51a**−**d** (tetrahydrofurans, tetrahydropyrans, and alcohols) ranged from 79−99%. The relative rate constants for reactions **51a**−**d** → **52a**−**d**, relative to the $k^{5\text{-}exo}$ value of the reaction **1** → **2** (see Figure 1) as reference (i.e. $k^{ref} \equiv 1.00$), indicated that the processes listed in Figure 9 are of the same order of magnitude as the reference value for the conversion of **1** → **2**. Furthermore, two products derived from 5-*exo*-trig cyclizations of the *O*-radicals **51a**−**d** were discovered in each of the reaction mixtures. Results from competition kinetics show that the *trans* cyclization **51a**−**d** → *trans*-**52a**−**d** is faster than k^{ref} ($k^{rel}_{trans} > 1$), while the *cis* reaction **51a**−**d** → *cis*-**52a**−**d** is slower ($k^{rel}_{cis} < 1$). The moderate stereoselectivities that were observed for cyclization of the 2-methyl- and 2-ethyl-substituted *O*-radicals **51a** and **51b** match with values from corresponding halogen-based cyclizations[69,70] and are almost identical to the data obtained from related 5-hexenyl radical cyclizations![62,66] An increase in the steric demand of the alkyl group in position 1 of radical **51** improves the stereoselectivity from *cis*:*trans* = 36:64 (**51a**, R = CH_3) to *cis*:*trans* = 15:85 [**51d**, R = $C(CH_3)_3$]. If the observed stereoselectivities are expressed in $\Delta\Delta G^{\ddagger}$ values (T = 30 °C), a correlation with Taft's steric parameters E_s [71] is observed (Figure 9; R2 = 0.998). Stereoselectivities in *O*-radical cyclizations **51a**−**d** → *trans*-**52a**−**d** should therefore originate from steric substituent effects.

As a matter of fact, the formation of minor amounts of tetrahydropyrans **59** (6-*endo*-trig cyclization) from *O*-radicals **51** is generally observed (5-*exo*:6-*endo* ≈ 98:2; but see also Table 4).

The 1-*para*-aryl-substituted 4-pentenoxyl radicals **51e**−**m** undergo *non*stereoselective 5-*exo*-trig cyclization.[19,20] The source of this observed behavior might be a coplanar arrangement of a rectangle defined by the oxygen radical center, the adjacent carbon atom, and the *ipso* and the *ortho* carbons of the aromatic substituent. This rather tight arrangement, which has been exploited in structurally related *para*-substituted cumyloxyl radicals as a basis for an analysis of their absorptions of longest wavelength,[72] should lead to torsional strain. Steric interactions between *ortho*-hydrogens and hydrogen atoms in the pentenoxyl radical chain should then reduce the rate constants of *trans* ring-closures of, say, the 1-phenyl-substituted *O*-radical **51h**, whereas similar effects in cyclizations of, for instance, 1-cyclohexyl- or 1-benzyl-substituted 4-penten-1-oxyl radicals (not shown in Table 2) are absent.[20] Experimental evidence for this model is derived from competition kinetic experiments, which indicated that k^{rel}_{trans} **51h** → *trans*-**52h** is smaller than k^{ref}.[19,20] If *ortho*-methyl groups are present in the aryl



R	51, 52, 57	52 *cis* : *trans*	$\Delta\Delta G^{\ddagger}_{trans-cis}$ [kJ mol^{-1}]
CH_3	**a** [b]	36 : 64	−1.45
C_2H_5	**b** [b]	35 : 65	−1.56
$CH(CH_3)_2$	**c** [b,c]	30 : 70	−2.14
$C(CH_3)_3$	**d** [c]	15 : 85	−4.39

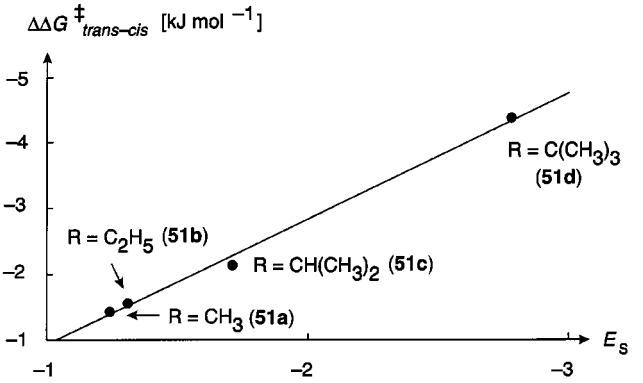
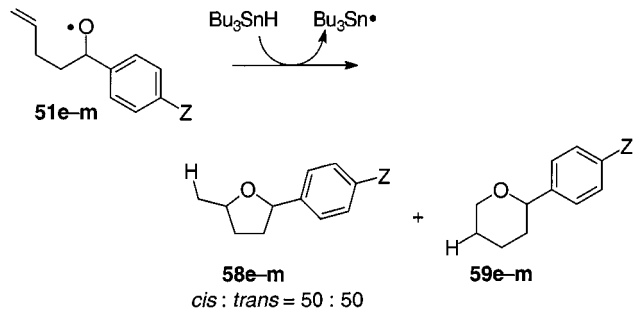


Figure 9. Stereoselectivity and regioselectivity of ring-closure reactions of *O*-radicals **51a**−**d** and correlation of observed stereoselectivities of radicals **51a**−**d** in 5-*exo*-trig cyclizations (see ref.[18]) with Taft's steric parameters E_s (ref.[71])
[a] Relative rate constants refer to the reference reaction **1** → **2** ($k^{ref} \equiv 1.00$). − [b] The alkoxy radical **51** was generated from the corresponding *N*-alkoxypyridinethione. − [c] The alkoxyl radical **51d** was generated from the corresponding benzene *O*-sulfenate.

nucleus, even more torsional strain seems to be imposed on the radical (e.g. **51n**), leading then to *trans*-selective 5-*exo*-trig cyclization, since the rate constant of the *cis* cyclization is reduced more than the corresponding value for the *trans* ring-closure (Table 3).[19,20]

Puzzling, but synthetically useful, is the fact that methyl groups in position 5 of a 1-phenyl-substituted radical, such as **51o**, permit stereoselective tetrahydrofuran syntheses by the corresponding *O*-radical cyclization (Table 3). Thus, a *trans*-selective 5-*exo*-trig cyclization is observed for intermediate **51o**, which after hydrogen trapping affords 5-ethyl-2-phenyltetrahydrofuran **58o** − a compound that possesses an interesting mushroom-like scent. Competition kinetics revealed that a single CH_3 group in position 5 increases the relative rate constant of the *trans*-5-*exo*-trig reaction by a factor of 6.5, compared to that of the 1-phenyl-4-penten-1-oxyl radical (**51h**). A second CH_3 group at position 5 (i.e. the 5-methyl-1-phenyl-4-hexen-1-oxyl radical, not shown in Table 3) results in a further increase in the relative rate constant of tetrahydrofuran formation and causes a 15.6-fold

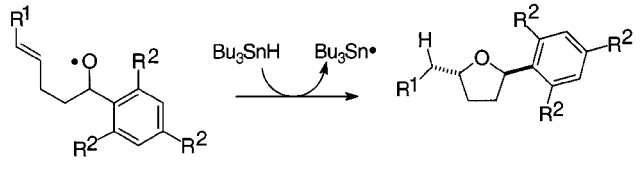
Table 2. Ring-closure reactions of 1-aryl-substituted 4-penten-1-oxyl radicals **51e−m**, [a] see ref.[19,20,73]



Z	58, 59	yield of 58 [%][b]	Z	58, 59	yield of 58 [%][b]
OCH_3[c]	e	76 (7)	Cl [c]	i	85 (5)
$CH(CH_3)_2$[d]	f	61 (14)	CN [d]	j	49 (20)
CH_3 [c]	g	82 (6)	CF_3[d]	k	73 (9)
H [c]	h	75 (10)	OCF_3[d]	m	76 (20)

[a] $c_o(Bu_3SnH)$ = 0.18 M. − [b] Numbers in brackets denote yields of 1-aryl-4-penten-1-ol. − [c] **58**:**59** = 98:2. − [d] Amount of **59f**, **59j**, **59k**, **59m** was not determined.

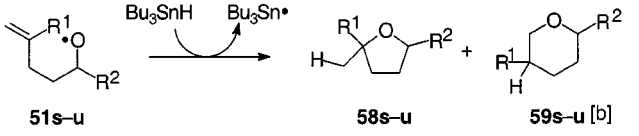
Table 3. Stereoselective 5-*exo*-trig cyclizations of 1-mesityl-substituted pentenoxyl radical **51n** and of 1-phenyl-1-hexen-4-yl radical **51o**, [a] see ref.[19]



51	R^1	R^2	58	Yield [%]	cis : trans [b]
n	H	CH_3	n	26	7 : 93 [c]
o	CH_3	H	o	90	30 : 70 [d]

[a] $c_o(Bu_3SnH)$ = 0.18 M. − [b] Regioselectivity for cyclization of **51n−o**: **51n**: 5-*exo*:6-*endo* = 96:4; **51o**: 5-*exo*:6-*endo* = 96:4. − [c] Yield of 1-mesityl-4-penten-1-ol: 70%. − [d] Yield of 1-phenyl-4-hexen-1-ol: 7%.

Table 4. Formation of tetrahydropyrans **59s−u** from 6-*endo*-trig cyclization of 4-substituted radicals **51s−u**,[a] see ref.[73]



51	R^1	R^2	58 : 59	Yields [%] [c]	
				58 (cis : trans)	59 (cis : trans)
s	CH_3	CH_3	82 : 18	73 (−)	16 (8 : 92)
t	$C(CH_3)_3$	CH_3	37 : 63	18 (50 : 50)	16 (17 : 83)
u	C_6H_5	H	5 : 95	5 (−)	89 (−)

[a] $c_o(Bu_3SnH)$ = 0.18 M, T = 30 °C. − [b] The tetrahydropyrans **58u** and **59q** (Figure 11) are structurally identical. − [c] Yields of alkenols: 5-methyl-5-hexen-2-ol: 8%, 5-*tert*-butyl-5-hexen-2-ol: 11%, 4-phenyl-4-penten-1-ol: 5%.

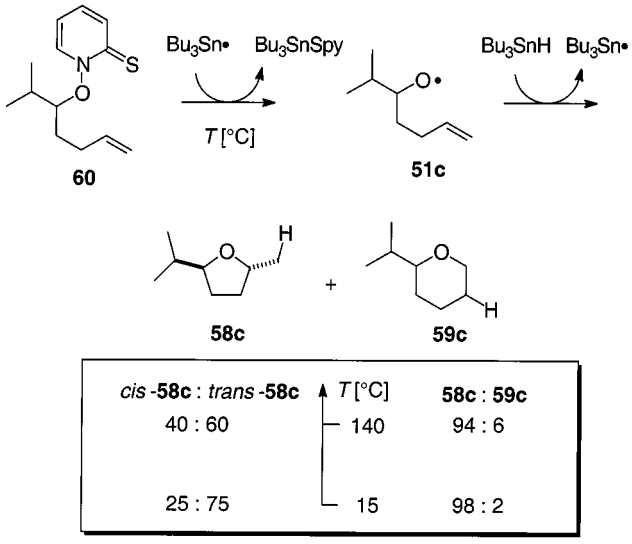


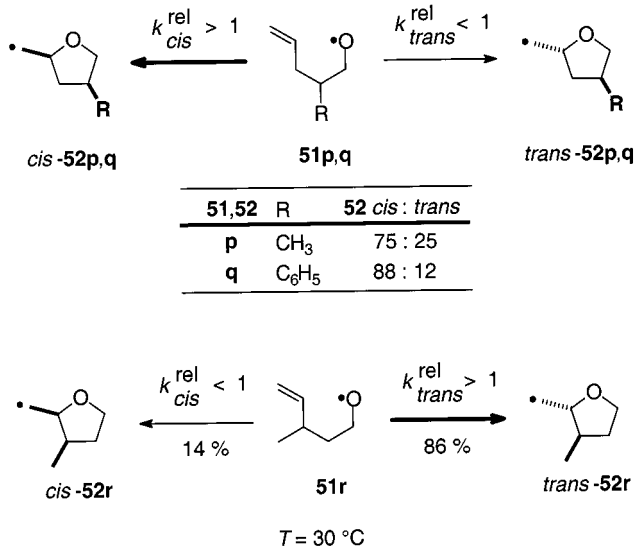
Figure 10. Temperature effects on regioselectivities and stereoselectivities in photochemical syntheses of cyclic ethers **58c** and **59c** from pyridinethione **60** and Bu_3SnH, see ref.[18]

enhancement of $k_{trans}^{5\text{-}exo}$ compared with the corresponding reaction of 1-phenylpenten-1-oxyl radical **51h**.[19] These findings point to the electrophilic nature of *O*-radicals in 5-*exo*-trig ring closure reactions.

The stereoselectivities and regioselectivities of alkoxyl radical cyclizations are temperature-dependent (Figure 10). For example, the reaction of pyridinethione **60** and Bu_3SnH leads to a drop in *exo*/*endo* selectivity from **58c**:**59c** = 98:2 at T = 15 °C to 94:6 at T = 140 °C, whereas the stereoselectivity of **58c** changes from *cis*:*trans* = 25:75 to 40:60 over the same temperature range.[18]

If the 2-substituted 4-pentenoxyl radicals **51p** and **51q** are subjected to competition kinetics, an increase of k_{cis}^{rel} is observed, while k_{trans}^{rel} becomes smaller than the reference reaction for radical **1** → **2**. These findings imply that 2-substituted pentenoxyl radicals cyclize *cis*-selectively (Scheme 10).[18,20] The reverse situation is encountered in the 5-*exo*-trig cyclization of the 3-methyl-4-penten-1-oxyl radical (**51r**): a slower *cis* cyclization cannot compete with a faster *trans* reaction, hence giving rise to a *trans*-selective ring closure of **51r** (*cis*:*trans* = 14:86) (Scheme 10).[18]

2-Phenyl-4-penten-1-oxyl radical cyclizations have been used as mechanistic probes in order to explore solvent effects in the synthesis of 4-phenyl-2-methyltetrahydrofuran (**58q**) (Figure 11).[73,74] Photoreaction of *N*-(2-phenylpentenoxy)pyridinethione **61**[20] and Bu_3SnH in different solvents provided two distinct results: (i) although the yields of cyclic ethers **58q** and **59q** increased on changing the solvent from, for example, bromobenzene to *tert*-butylbenzene, neither the relative rate constants $k_{cis}^{5\text{-}exo}$ or $k_{trans}^{5\text{-}exo}$, nor the



Scheme 10. Stereoselectivities and relative rate constants of 5-*exo*-trig cyclizations of the 2-substituted 4-pentenoxyl radicals **51p** and **51q** (top) and the 3-methyl-4-penten-1-oxyl radical (**51r**) (bottom, see ref.[18,20]); relative rate constants refer to the reference reaction **1** → **2** ($k^{ref} \equiv 1.00$)

ratios of **58q**:**59q** differed significantly for any of the solvents given in Figure 11, and (ii) if the concentration of hydrogen donor is decreased [down to $c_o(Bu_3SnH) = 0.07$ M], ratios of alcohol **62** to tetrahydrofuran **58q** decrease linearly. This means that Bu_3SnH is, in all cases, the major source of reactive hydrogens for conversion of the 2-phenyl-4-pentenoxyl radical **51q** to alkenol **62**. Thus, the solvent

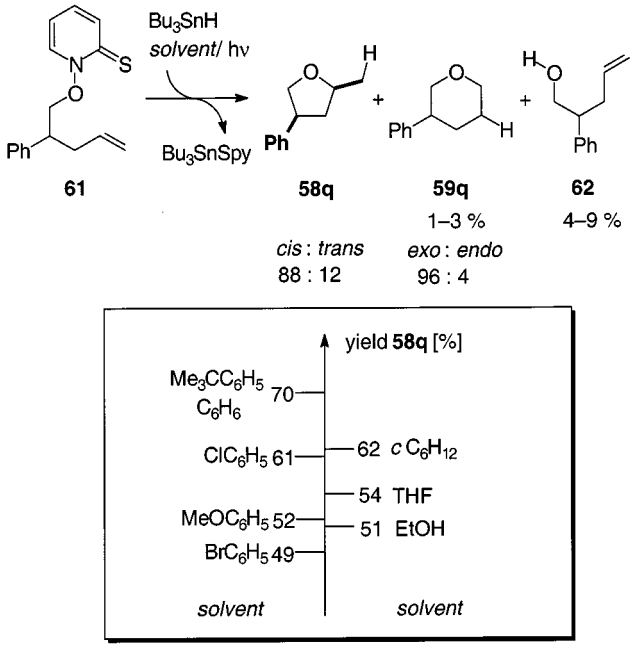


Figure 11. Study of solvent effects in photoreactions of pyridinethione **61** and Bu_3SnH, see ref.[73]

effect on *O*-radical cyclizations themselves should be negligible (no change in reactivity and selectivity), although the efficiency of the photochemical synthesis of cyclic ethers from **61** and Bu_3SnH is dependent on the reaction medium (yields of heterocycles **58q** and **59q**, and of alcohol **62**).

Substituents at position 4 of the 4-pentenoxyl chain opened up perspectives for increasing the efficiency of tetrahydropyran formation by *O*-radical cyclization.[18,20] The ratio of 6-*endo*- to 5-*exo*-cyclized products increases in the 4-substituent series R = H < CH_3 < $C(CH_3)_3$ < C_6H_5 (Scheme 9, Table 4).[73] The origin of the underlying effects that favor the formation of the six-membered ring, however, may be different for alkyl substituents than for a phenyl group. A methyl group in position 4 (of radical **51s**, say) causes a minor increase in k^{rel} of the 5-*exo*-trig cyclization, presumably because of polar effects. Thus, the increase in tetrahydropyran formation relative to ring-closure reactions of the respective pentenoxyl radicals **51a** or even **1** should originate from steric shielding of the sp^2-hybridized carbon atom at position 4 along the trajectory of the radical addition. This model should also be applicable for explaining the formation of significant amounts of 6-*endo*-cyclized product from the reaction of the 4-*tert*-butyl-1-methyl-substituted pentenoxyl radical **51t** (**58t**:**59t** = 37:63). Trapping of cyclized tetrahydropyranyl radicals by Bu_3SnH proceeds stereoselectively and affords, for instance, the *trans*-tetrahydropyrans **59s** and **59t** as major products (Table 4).[18,20,73] This selectivity can be explained by a combination of conformational (the methyl substituent at C1 is preferentially situated in the *pseudo*-equatorial position) and torsional effects (Bu_3SnH preferentially delivers its hydrogen from the axial face to a radical center in a saturated six-membered ring unless unfavorable steric blocking by vicinal substituents occurs).[75]

The 4-phenyl-substituted alkoxyl radical **51u** affords, after hydrogen trapping, 2-phenyltetrahydropyran **59u** as the major product (5-*exo*:6-*endo* = 5:95).[20] Comparison of k^{rel} values for both ring-closure reactions of **51u** ($k_{rel}^{6\text{-}endo}$ = 8.0 ± 0.7, $k_{rel}^{5\text{-}exo}$ = 0.48 ± 0.04) indicates that, in this case, a favorable rate constant for the 6-*endo* ring-closure is the driving force for tetrahydropyran formation from intermediate **51u**.

Substituent effects that have so far been observed in 4-penten-1-oxyl radical cyclizations can be summarized as follows:

(i) 1- or 3-Substituted 4-pentenoxyl radicals **51**, with the exception of 1-aryl-substituted penten-1-oxyl radicals lacking an *ortho*-methyl group (e.g. **51e**−**m**, Table 2), preferentially cyclize in a 5-*exo*-trig-*trans*-selective manner. The stereoselectivity is guided by steric substituent effects.

(ii) 2-Substituted pentenoxyl radicals **51** preferentially afford *cis*-disubstituted oxolanes (*cis*-**52**) upon cyclization.

(iii) Substituents at position 4 increase the ratio of 6-*endo*-trig cyclized product.

(iv) Alkyl- or aryl-groups at position 5 increase the reactivity (expressed in the relative rate constants) and selectivity (regioselectivity and stereoselectivity) of 5-*exo*-trig cyc-

lizations, regardless of their relative configuration (*E* or *Z*) at the olefinic double bond.[19]

3.3. Theoretical Considerations — Transition Structures of 5-*exo*- and 6-*endo*-Cyclization

The data that have so far been collected for 4-penten-1-oxyl radical cyclizations have to be unified into a stereochemical model in order to rationalize the observed product distributions and to predict new selectivities for an application of *O*-radical reactions in synthesis. In 1987, Houk and Spellmeyer developed a modified MM2 force-field for the prediction of stereoselectivities and regioselectivities of 5-hexenyl radical cyclizations.[76] The method was an alternative approach to the Beckwith-Schiesser procedure that had been published two years earlier.[66] Although both models had been established in order to investigate the origin of selectivities in carbon radical cyclizations, Houk also included the 4-penten-1-oxyl radical (**1**) in his studies, and correctly predicted a ratio of 5-*exo*- versus 6-*endo*-cyclized radicals of **2**:**55** = 98:2 from intermediate **1**! Almost a decade later, the 4-pentenoxyl radical cyclization was reinvestigated using higher-order ab initio methods.[77,78] Furthermore, density functional methods and post-Hartree−Fock corrections (UQCISD-calculations) were applied for deriving the enthalpies of activation from theoretical methods. The computational studies indicated that at least two low energy transition structures exist for addition of the radical center to the olefinic double bond. The lowest energy transition structure corresponds to the intermediate of the 5-*exo*-trig attack (TS-5-*exo*-**1**), and the higher energy transition structure to its 6-*endo* counterpart (TS-6-*endo*-**1**). With the assumption of $\Delta\Delta S^{\ddagger}_{exo-endo} \approx 0$ J K^{-1} mol^{-1}, calculated differences in the enthalpies of formation of the transition structures (e.g. UHF/6−31G*: $\Delta\Delta H^{\ddagger}_{exo-endo} = -9.70$ kJ mol^{-1}) are in good agreement with the experimental $\Delta\Delta G^{\ddagger}_{exo-endo}$ (T = 298 K) of −9.50 kJ mol^{-1}. The UHF/6−31G*-calculated geometry of TS-5-*exo*-**1** indicates that the distance between the radical center and C4 is still 1.907 Å, which points to a transition state early on the reaction coordinate. The computed angle of attack of the radical center at C4 is 104.6° (Figure 12). The overall geometry of TS-5-*exo*-**1** is reminiscent of a tetrahydrofuran flattened envelope conformer. Substituents larger than hydrogen should therefore be located in *pseudo*-equatorial positions (shaded balls) and give rise to the observed major products of *O*-radical cyclizations. The small increase in $k^{5\text{-}exo}$ values for such intermediates may have statistical origins, since steric repulsion between the substituent and the reactive sites of pentenoxyl radicals should increase their frequency of encounter. On the other hand, substituents in *pseudo*-axial positions give rise to torsional strain (1,3-*pseudo*-diaxial interactions), which in turn is considered to be the origin of the deceleration in *O*-radical ring closures leading to the minor tetrahydrofuran stereoisomers. All in all, this model for the description of stereoselectivities in cyclizations of substituted 4-penten-1-oxyl radicals is reminiscent of the Beckwith−Houk model, which, however, was elucidated in order to rationalize selectivities in 5-hexen-1-yl radical cyclizations.[66,76]

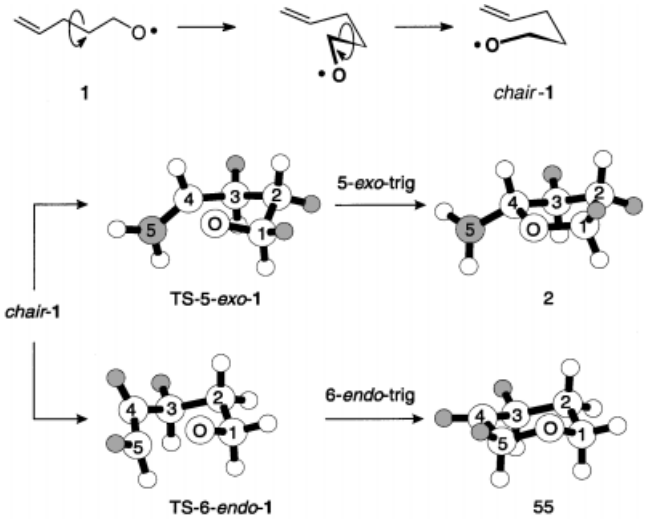


Figure 12. Ball-and-stick presentation of calculated (UHF/6−31G*) transition structures and products from the 5-*exo*-trig cyclization (TS-5-*exo*-**1** → **2**) and the 6-*endo*-trig ring-closure (TS-6-*endo*-**1** → **55**) of the 4-penten-1-oxyl radical (**1**), see ref.[78]

The TS-6-*endo*-**1** transition structure differs significantly from the TS-5-*exo*-**1** one. In the course of the attack of O1 at the C−C double bond (UHF/6−31G* geometry: d_{O-C5} = 1.925 Å), hydrogen 4-H, which in the early stage of the addition process has moved towards the oxygen atom, passes in between the shaded hydrogens at C3 and C5 to afford the tetrahydropyranyl radical **55**. Thus, a 6-*endo* reaction is accompanied by torsional strain that is absent in a 5-*exo*-trig addition.

3.4. Application in Synthesis — Towards a Synthesis of *allo*-Muscarine

The structural model for stereoselective 4-penten-1-oxyl radical ring closures (Figure 12) poses the challenge to design further experiments in order to examine its predictive power. A reliable stereochemical model for *O*-radical cyclizations in turn should be of notable utility, since stereoselectivities using this method, in natural product synthesis, for example, might then become predictable. If two substituents in a pentenoxyl radical were located in *pseudo*-equatorial positions (Figure 13, left), significant stereoselectivities should be observed. In the corresponding diastereomer (Figure 13, right), however, at least one substituent has to be situated in a *pseudo*-axial arrangement. If the overall chair geometry is retained, this arrangement should lead to low stereoselectivities.

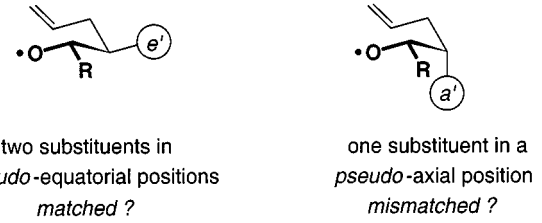
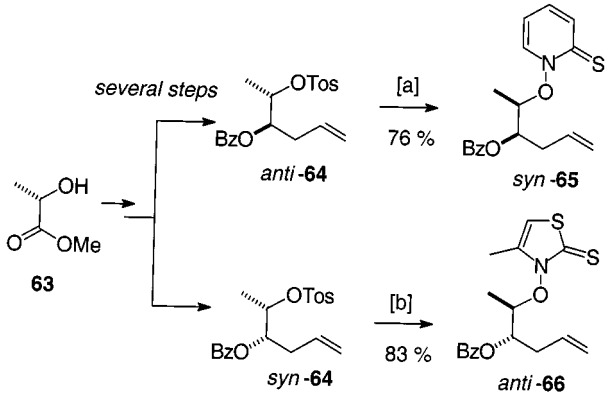


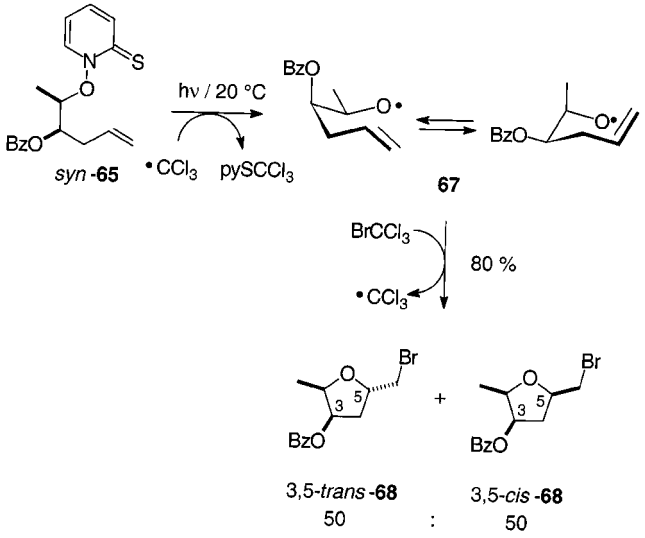
Figure 13. Working hypothesis: favorable *matched* arrangements should increase stereoselectivities in *O*-radical cyclizations, while disfavored *mismatched* transpositions of substituents should decrease them.

In order to probe this concept, a new synthesis of muscarine alkaloids[79,80] was devised. In this synthetic approach, a radical cyclization was used for the first time for constructing the central tetrahydrofuran nucleus of this class of physiologically active compounds.[81] Thus, methyl (2*S*)-lactate (**63**) was converted into the 2,3-*anti*-configured tosylate *anti*-**64**. Treatment of *anti*-**64** with *N*-hydroxypyridine-2(1*H*)-thione tetrabutylammonium salt (**19**) afforded pyridinethione *syn*-**65** (Scheme 11). In the same manner, the 2,3-*anti*-configured thiazolethione *anti*-**66** was obtained in very good yield from tosylate *syn*-**64**.

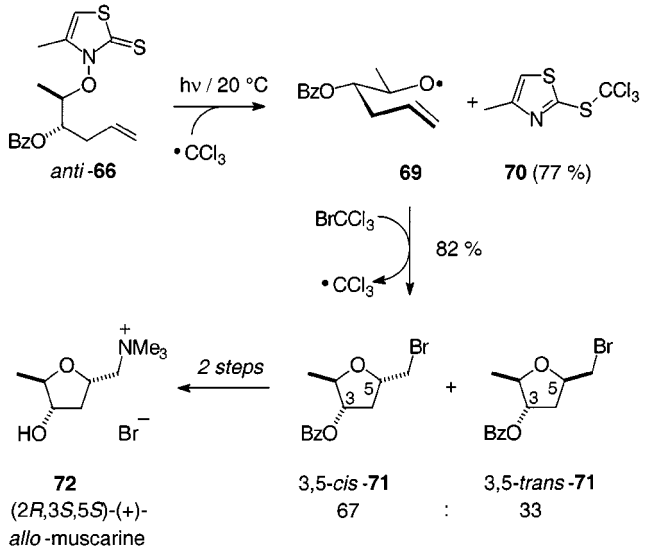


Scheme 11. Stereoselective synthesis of *O*-radical precursors *syn*-**65** (see Scheme 12) and *anti*-**66** (see Scheme 13) for the construction of the tetrahydrofuran core in muscarine alkaloids, see ref.[22] [a] *N*-Hydroxypyridine-2(1*H*)-thione tetrabutylammonium salt (**19**), DMF. – [b] *N*-Hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt, DMF.

Photoreaction of pyridinethione *syn*-**65** and $BrCCl_3$ afforded the two stereoisomeric bromomethyl-substituted tetrahydrofurans 3,5-*trans*-**68** and 3,5-*cis*-**68**, in a total yield of 80% (Scheme 12). The 5-*exo*-trig cyclization of intermediate **67** shows no selectivity. Thus, competition of the methyl and the benzoyloxy substituent for a more favorable *pseudo*-equatorial position in radical **67** obviously does not lead to a significant preference of either conformer. In terms of a stereoselective ring closure, the situation is much more favorable in *anti*-**66**, and therefore in the 2,3-*anti*-configured radical **69**, since both substituents may now be arranged *pseudo*-equatorially in a chair-like transition state (Scheme 13). Cyclization of intermediate **69** and the trapping of intermediate carbon-centered radicals by $BrCCl_3$ led to a moderate selectivity of 3,5-*cis*-**71**:3,5-*trans*-**71** = 67:33 (T = 20 °C). As well as these, trichloromethylsulfanylthiazole **70** was isolated. Its yield nearly matched the combined yield of bromides **71**. The major product, 3,5-*cis*-**71**, was converted in two subsequent steps into (+)-*allo*-muscarine (**72**).[81,82]



Scheme 12 Photoreaction of pyridinethione *syn*-**65** and $BrCCl_3$, see ref.[22]



Scheme 13. Photoreaction of *N*-alkoxy-4-(methyl)thiazolethione *anti*-**66** and $BrCCl_3$, and completion of the synthesis of (+)-*allo*-muscarine (**72**), see ref.[22]

4. Conclusion and Future Perspectives

The development of new radical precursors to allow the study of alkoxyl radical reactivities and selectivities under neutral conditions, without competing oxidation or reduction processes, has opened new perspectives for the chemistry of oxygen-centered radicals. This has led to significant progress in the field of stereoselective *O*-radical cyclizations. Thanks to the mild and neutral reaction conditions, unique

radical selectivities, and enormous 5-*exo*-trig cyclization rate constants, which are generally reflected in highly efficient tetrahydrofuran syntheses, the radical pathway may now be considered as an alternative to ionic methods.[69,70] As outlined in this review, the fundamental exploration of this novel method for the stereoselective synthesis of tetrahydrofurans was basically concerned with mechanistic aspects.[18−21] The new synthesis of (+)-*allo* muscarine (**72**), however, illustrates, that *O*-radical cyclizations are now on the verge of entering the field of synthetic application.[22] Certainly, more examples will follow in the near future. Major issues to be addressed in forthcoming studies will probably be related to the discovery of new cyclization modes, or even to the search for guidelines for conducting intermolecular alkoxyl radical reactions under neutral conditions. Also, a more fundamental study of the interactions between *O*-radicals and metal ions in aqueous systems, which play important roles in biochemistry[83] − for instance, in the active sites of several enzymes[84] − will challenge scientists from different disciplines to increase our knowledge of oxygen-centered radicals in the broadest sense.

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