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Tertiary alkoxyl radicals from 3-alkoxythiazole-2(3*H*)-thiones

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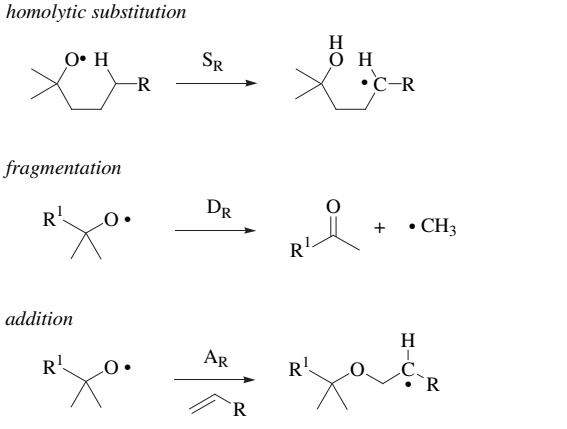
ABSTRACT

This study deals with the synthesis of *tert*-*O*-alkyl thiohydroxamates and their use as *tert*-alkoxyl radical precursors. *tert*-Alkoxyl radicals were applied in mechanistic studies to determine rate constants of (i) *p*-chlorocumyloxyl radical addition to bicyclo[2.2.1]heptene ($k=1\times10^7$ M^{-1} s^{-1}), (ii) 2-phenylhex-5-en-2-oxyl radical 5-*exo*-*trig*-cyclization ($k^{cis}=3\times10^9$ s^{-1}, $k^{trans}=1\times10^9$ s^{-1}), and (iii) 2-methyl-5-phenylpent-2-oxyl to 2-hydroxy-2-methyl-5-phenylpent-5-yl radical isomerization (1,5-H-atom shift; $k=0.4–1.5\times10^8$ s^{-1}). The reactions pose key steps in synthesis of 2,2,5-substituted tetrahydrofurans and 2-bromo-3-alkoxybicyclo[2.2.1]heptanes. Stereoselectivity in 5-*exo*-*trig* cyclization (2,5-cis) and intermolecular addition (*exo*/*endo*>99:1), originates from torsional strain in transition structures of alkoxyl radical reactions.

1. Introduction

In a given chemical environment, *tert*-alkoxyl radicals undergo fast unimolecular and bimolecular reactions, to leave diagnostic product mixtures. Chemical changes thereby follow distinct patterns of homolytic substitution (S_R), β-C,C-homolysis (D_R), and π-bond addition (A_R), to mention the most important elementary reactions (Scheme 1).[1–4] It is this combination of reactivity and selectivity that explains the significance, *tert*-alkoxyl radicals have gained for elucidating reaction mechanisms in physical organic chemistry,[5–7] atmospheric science,[8] biochemistry,[9–11] and macromolecular chemistry.[12,13] With the advent of more selective progenitors, this interest, however, has partly shifted from mechanistic to more synthetically oriented studies. The desire to apply alkoxyl radicals in synthesis thereby comes from electrophilic properties of the radical oxygen, for example, in additions or homolytic substitutions. Alkoxyl radicals therefore add a component to organic synthesis that is not available from other intermediates.[14–16]

In an earlier study, we had shown that 3-alkoxy-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thiones (e.g., **1**) almost quantitatively liberate alkoxyl radicals, if thermally or photochemically activated in the presence of a mediator.[17] Primary and secondary 3-alkoxy-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thiones are synthetically available in yields between 70 and 90%.[17] Attempts to prepare tertiary derivatives thereof from



Scheme 1. Alkoxyl radical elementary reactions relevant for the present study [for R^1 see Fig. 1; R=alkyl or phenyl (vide infra); nomenclature: A=associative step, S=substitution, D=dissociative step, R=radical-based transformation].

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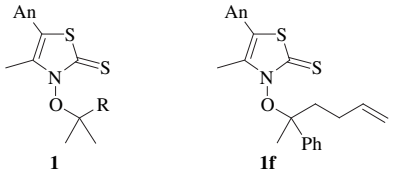
alcohols or haloalkanes under solvolysis conditions, on the other hand, were not successful.[18,19,24] Strategies to apply Lewis-acids for more effective carbon electrophile-activation resulted in precipitation of thiohydroxamate complexes.[20–22] None of these complexes were receptive for O-alkylation.[23]

Since *tert*-alkoxyl radicals for synthetic applications remained difficult to generate,[24] we chose to develop a practical method for synthesis of 3-(*tert*-alkoxy)-thiazole-2(3*H*)-thiones **1a**–**f** (Fig. 1). To validate the performance of these compounds, we devised a project on synthesis of 2,2,5-substituted tetrahydrofurans and 2-bromo-3-alkoxybicyclo[2.2.1]heptanes from intra- and intermolecular alkoxyl radical reactions. The compounds (vide infra) are derivatives of mono- and bicyclic secondary metabolites, pharmaceuticals, and pesticides, which sometimes are difficult to prepare in ionic reactions.[25–27] The most important results from the study show that synthesis of tertiary *O*-alkyl thiohydroxamates **1a**–**f** using a newly developed procedure is feasible in up to 64% yield. If activated, the molecules liberate *tert*-alkoxyl radicals, suitable for application in mechanistic and synthetic studies.



1 **1f**

1	R
a	CH_3
b	C_2H_5
c	$(CH_2)_3C_6H_5$
d	C_6H_5
e	4-ClC_6H_4

An = 4-$(H_3CO)C_6H_4$

Fig. 1. Structure formulas and indexing of tertiary 3-alkoxythiazole-2(3*H*)-thiones **1a**–**f**.

2. Results and interpretation

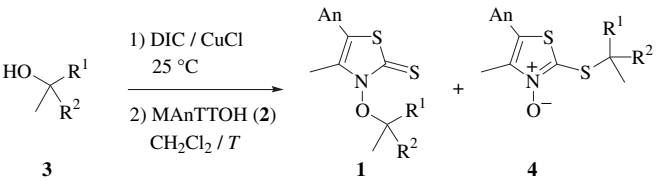
2.1. Tertiary 3-alkoxy-4-methylthiazole-2(3*H*)-thiones

The general strategy for *O*-alkylthiohydroxamate synthesis from thiohydroxamic acids requires selective alkylation at oxygen. The thiohydroxamic acid we chose in this study, 3-hydroxy-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (MAnTTOH; **2**), has a remarkable affinitity for substitution at oxygen instead of sulfur, if treated with an appropriate carbon electrophile.[17] To develop a synthetic method (**1a**, **1b**; Section 2.1), investigate thermal stability (**1d**; Section 2.2), perform intramolecular reactions (**1c**, **1f**; Section 2.3 And 2.4), and explore intermolecular alkoxyl radical additions (**1a**, **1d**–**e**; Section 2.5), we selected *tert*-alcohols **3a**–**f** as substrates to in situ generate carbon electrophiles.

In previous studies[28,29] we had discovered that *O*-*tert*-butyl-*N*,*N*-diisopropyl isourea[30,31] is a suitable reagent to use for developing a more efficient and general method for *tert*-O-alkylation of acid **2**. The isourea is available from *tert*-butanol **3a**, diisopropyl carbodiimide (DIC), and catalytic amounts of CuCl. We now report that slow addition of 5.5 equiv of the alkylation reagent to a CH_2Cl_2-solution of thiohydroxamic acid at 24 °C furnishes O-*tert*-butyl ester **1a** in 58–64% yield, besides *S*-*tert*-butyl derivative **4a** (25%).[17,19,32]

A change in solvent to DMF, fewer *O*-*tert*-butyl isourea equivalents, or lower reaction temperature (≤0 °C) reduces the yield of *tert*-butyl ester **1a**. Higher rates of *O*-*tert*-butyl isourea addition lead to formation of 1,2-bis-[5-(4-methoxyphenyl)-4-methylthiaz-3-yl]-disulfane (**5**)[33] as additional product in up to 13% yield, whereas the yield of product **1a** decreases. Substitution of dicyclohexyl carbodiimide (DCC) for DIC (cf. Table 1, entry 1) was not successful in our hands (22% of **1a** under conditions used in Table 1, entry 1).

Table 1
Products of 3-hydroxy-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione alkylation and selected characteristics of target products **1a**–**f**



3 **1** **4**

Entry	**1**/**3**/**4**	R^1	R^2	*T*/°C	**1**/%	Mp **1**/°C	**4**/%
1	**a**	CH_3	CH_3	24	58–64[a]	112	25[c]
2	**b**	CH_3	C_2H_5	0	45–47[b]	72	33[c]
3	**c**	CH_3	$(CH_2)_3C_6H_5$	0	44	64	11[c]
4	**d**	CH_3	C_6H_5	−30	15	108	38
5	**e**	CH_3	*p*-ClC_6H_4	−30	13	95	33
6	**f**	$(CH_2)_2CH{=}CH_2$	C_6H_5	−30	18	110	27[b]

[a] Mean value from five experiments.
[b] Mean value from three experiments.
[c] Determined via ^1H and ^{13}C NMR.

We furthermore used the in situ method to convert *tert*-amyl alcohol **3b**, 2-methyl-5-phenylpentan-2-ol (**3c**) (44–47%; Table 1, entries 2 and 3), and 2-arylalcohols **3d**–**f** (13–18%; Table 1, entries 4–6) into *O*-esters **1b**–**f**. Alkylsulfanylthiazole *N*-oxides **4b**–**f**, but also alkenes, such as a 52/48-mixture of 2-methyl-5-phenylpent-1-ene and 2-methyl-5-phenylpent-2-ene (63–76% from **3c**), α-methylstyrene (**6**) (39% from **3d**), *p*-chloro-α-methylstyrene (48% from **3e**), and a 63/37-mixture of 2-phenylhexa-1,5-diene and 5-phenylhexa-1,4-diene (24–38% from **3f**), were found as by-products. Since we had no head space equipment available, elimination products formed from **3a** and **3b** escaped analysis.

3-Alkoxythiazolethiones were obtained as colorless (**1c**–**f**) to pale yellow (**1a**,**b**) crystalline compounds that melted between 64 °C (**1c**) and 112 °C (**1a**). Electronic spectra of the thiazolethiones in solutions of EtOH showed a band located at λ=336–338 nm (ε ~3.20–3.28 m^2 mol^{-1}). This absorption is relevant for photochemical alkoxyl radical generation from **1** (vide infra). The only NMR-spectroscopic aspect that deserves attention was a systematic absence of ^{13}C resonances from methyl groups attached to tertiary C-atoms, in the room temperature NMR spectra (except of **1a** and **1b**). Resonances of protons bound to such *unseen* carbons were broad. The reason behind this observation is a slow topomerization of substituents by N,O-rotation, as clarified via low temperature NMR-spectroscopy. For example, on cooling a solution of *p*-chlorocumyl ester **1e**, proton resonances of diastereotopic CH_3-groups coalesce at −3 °C (referenced versus the MeOH NMR thermometer).[34,35] At −62 °C two base line separated signals at δ_H 1.89 and 2.11 are found, which correlate with sharp resonances at δ_C 22.0 and 31.9 ppm (HMQC). The barrier to N,O-rotation ($\Delta G^{\ddagger}_{270}$=53 kJ mol^{-1}) that was calculated from the spectral information (Supplementary data) is, in view of an estimated precision of ±10%, close to the value of 44 kJ mol^{-1} reported for ester **1d** (coalescence temperature: 276 K).[18]

In the crystal structure of **1e**, the *p*-chlorocumyl substituent is almost orthogonally offset from the heterocyclic plane [C2–N3–O1–C14=96.8(2)°] (Fig. 2). The N3–O1–C14 angle [116.0 (1)°] is widened and correlates with the value of ~116° that was predicted for *tert*-*O*-esters of **2** on the basis of a Taft–Dubois-relationship.[18] Distances N3–O1 [1.383(2) Å] and C2–S2 [1.659(3) Å] fit into a N–O/C=S-correlation derived from crystallographic data of ten MAnTTORs (Supplementary data). N,O-bond lengthening in this

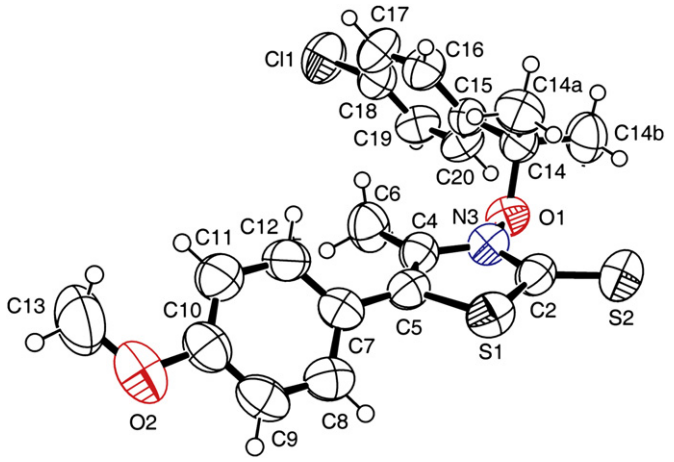
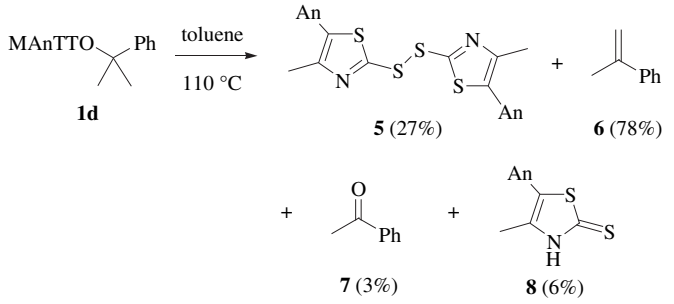


Fig. 2. Ellipsoid graphic (50% probability) of 3-[2-(*p*-chlorophenyl)-2-propoxy]-thiazolethione **1e** in the solid state [293 K; H-atoms were drawn as circles of an arbitrary radius; the (*M*)-enantiomer was selected from the racemate in the unit cell; C2/*c*, *Z*=8].

product class, by introducing a sterically demanding substituent at oxygen, causes a shortening of the associated C=S bond. This structural responsivity is stronger than for any other type of investigated thiohydroxamic acid, and explains why heterocycle **2** handles strain at oxygen so well.[18]

2.2. Thermal stability

N-Cumyloxythiazolethione **1d** (mp 108 °C) decomposes within 60 min, if heated in boiling toluene (Scheme 2). The reaction provides disulfide **5**, α-methylstyrene **6**, acetophenone **7**, and thiolactam **8**.[36] The product spectrum suggests a Tschugaeff-type fragmentation, which should have also afforded MAnTTOH (**2**). To detect the latter, a color test was performed using Fe(II)-stained TLC-sheets. A green color thereby denotes Fe(II)/(bis)thiohydroxamate formation, and thus a positive analytical response. During thermal decomposition of **1d**, while continuously being checked with the spotting test, a transient positive analytical response (green spot) is found, however, only within a quite narrow time frame. Intensity and time-line of the photometric response correlate with results from a control, starting from thiohydroxamic acid **2** in boiling toluene. We stopped the reaction as no further acid **2** was detectable. Analysis of this solution (^{1}H NMR, TLC) shows disulfide **5** as major product.



Scheme 2. Products of thermal 3-cumyloxythiazolethione decomposition.

2.3. Homolytic substitution

3-Alkoxy-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thiones liberate alkoxyl radicals, if photochemically excited (λ=350 nm, 25 °C) or heated in the presence of initiator AIBN. For both modes of activation C_6H_6 or $C_6H_5CF_3$ are useful solvents, and $BrCCl_3$ the preferred mediator for conducting synthetic and mechanistic investigations.[17]

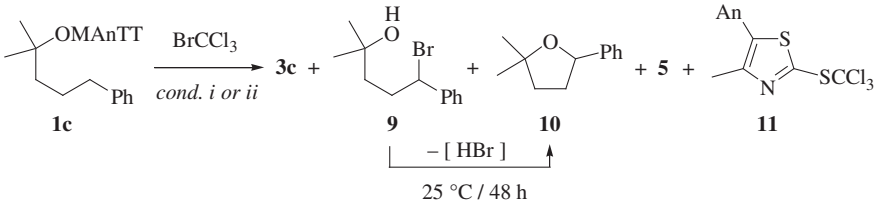
Photolysis of 3-(2-methyl-5-phenylpent-2-oxy)-thiazolethione **1c** and $BrCCl_3$ (c_0=1.70 M) in a solution of C_6D_6 furnishes alcohol **3c** (36%), δ-bromohydrin **9** (41%), tetrahydrofuran **10** (22%), disulfide **5** (20%), and 5-(4-methoxyphenyl)-4-methyl-2-trichloromethylsulfanyl thiazole (**11**) (10%). Acetone (**12**) is obtained in 3–5% yield. A triplet at δ=2.91 (*J*=6.5 Hz) points to 3-bromo-1-phenylpropane formation. Signal overlap (^{1}H NMR/GC) precluded quantitative analysis of this product. As the solution is allowed to rest for 48 h at 25 °C, bromoalcohol **9** is converted into additional 2,2-dimethyl-5-phenyltetrahydrofuran (**10**).[37] The latter compound was isolated from additional photochemical and thermally-induced experiments that used the same reactant concentrations, leading to similar yields of **10** (Table 2, entries 2 and 3).

From product analysis we conclude that the 2-methyl-5-phenylpent-2-oxyl radical (**Ic**) is formed in photochemical and thermally-induced reactions starting from *N*-alkoxythiazolethione **1c** and $BrCCl_3$ (Scheme 3). A 1,5-H-atom shift transforms alkoxyl radical **Ic** into stabilized benzylic radical **II**. The latter abstracts a Br-atom from $BrCCl_3$ to give δ-bromohydrin **9** and $^{\bullet}CCl_3$. Bromoalcohol **9** cyclizes upon standing to furnish tetrahydrofuran **10**. The total amount of 1,5-H-shifted intermediate **II** therefore relates to the combined yield of products **9** and **10** (63%). Since acetone (**12**) and 3-bromo-1-phenylpropane are formed as by-products, radical **Ic** not only undergoes 1,5-H-atom shift **Ic**→**II** but also β-C,C-homolysis **Ic**→**III**+**12**. On the assumption that both reactions follow kinetic control, and Br-atom trapping by **II** is quantitative,[17] the ratio (**9**+**10**)/**12**=12.6–21.0 reflects relative reactivity of 1,5-H-atom shift versus β-C,C homolysis, that is, $k^{S_{R_{Ic}}}/k^{D_{R_{Ic}}}$. The rate constant for the β-fragmentation thereby can be approximated with the value for acetone liberation from *tert*-butoxyl radical fragmentation ($k^{D_{R_{Ia}}}$ =2.0×10^4 s^{-1}, for 25 °C in C_6H_6).[38] Since the ethyl radical forms by a factor of 150–350 faster from alkoxyl radical β-C,C-fragmentation than the methyl radical,[7,39] a value of 3.0×10^6 s^{-1} was used as lower and 7.0×10^6 s^{-1} as upper limit for unknown $k^{D_{R_{Ic}}}$. The range obtained for $k^{S_{R_{Ic}}}$ (0.4–1.5×10^8 s^{-1}) indicates that the 1,5-H-shift in *tert*-alkoxyl radical **Ic**, in spite of its steric encroachment near oxygen, is not slower than 1,5-H-shift in the 1-pentoxyl radical (k^{S_R} =2.7×10^7 s^{-1} at 20 °C).[40,41]

Yields of alcohol **3c** between 23 and 36% show that an effective H-atom donor exists in reaction mixtures used for mechanistic experiments starting from **1c** (Table 2). Since benzylic radicals, for example, **II**, abstract a Br-atom from $BrCCl_3$ much faster than an H-atom from any known reductant, the issue of radical reduction is restricted to alkoxyl radical **Ic**. Although this chemistry does not interfere with the kinetic analysis outlined above and in the following sections, clarifying the nature of the reductant could also mean finding ways to inhibit unwanted alkoxyl radical consumption. A control performed by photolyzing *tert*-butoxythiazolethione **1a** in solutions of C_6D_6 or CCl_4, provided *t*-BuOH, disulfide **5**, and at least one additional thiazole-derived product. Attempts, to separate the additional thiazole derivative failed. On the basis of signal integration it seems that a methyl group attached to thiazole probably is the unknown H-atom donor. Support for this interpretation comes from mass-balancing: the yield of alcohol **3c**, and of other alcohols obtained from 3-alkoxythiazolethiones, for example, **1c**–**f** (Sections 2.4 and 2.5), never exceeded the amount of thiazole-derived products that remained unidentified.

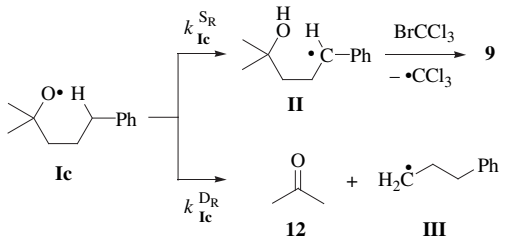
In previous work, we had explained formation of thiazole **11** via $^{\bullet}CCl_3$-addition to the thiocarbonyl group of a 3-alkoxy-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione. This step is crucial for the mechanistic model, because it explains how $^{\bullet}CCl_3$ is able to propagate the chain reaction.[17] The major thiazole-derived product from **1c**, however, was disulfide **5**. Controls performed by photolyzing CCl_3-adduct **11** and $BrCCl_3$ in a solution of C_6D_6 (for 45 min, λ=350 nm, 25 °C) provided 58% of unspent material **11** and

Table 2
Products formed from 3-(5-phenyl-2-methylpentoxy)-thiazolethione **1c** and $BrCCl_3$



Entry	Conditions	Solvent	**3c**/%	**9**/%	**10**/%
1	(i) hν (350 nm)/25 °C[a]	C_6D_6	36	41	22
2	(i) hν (350 nm)/25 °C[b]	$C_6H_5CF_3$	23	—[c]	58
3	(ii) AIBN 80 °C	C_6H_6	—[c]	—[c]	(84) 61[d]

[a] In situ-analysis (^{1}H NMR) after 2 h; additional products: 20% of **5**, 10% of **11**, and 3–5% of acetone (**12**).
[b] Product composition after work up; additional products: 17% of **5**, 27% of **11**.
[c] Not determined.
[d] Number in parentheses refer to yield prior to work up (^{1}H NMR); yield of thiazole-derived products **5** and **11** not determined.



Scheme 3. Proposed scheme for mechanistic discussion of 2-methyl-5-phenylpent-2-oxyl radical reactivity in the presence of $BrCCl_3$ (roman numbers refer to transients).

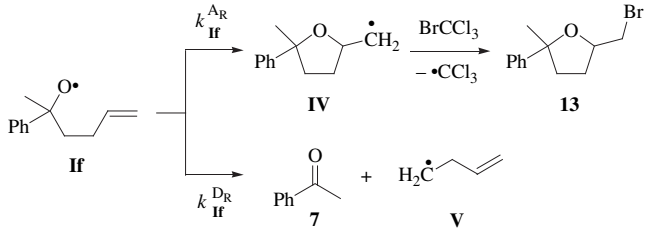
21% of disulfide **5**. Subjecting disulfide **5** and $BrCCl_3$ to the same conditions did not give **11**. This information shows that **11** cannot be precursor of the entire amount of **5**. In view of the strain imposed by *tert*-*O*-alkyl substitution (cf. Section 2.1),[18] it moreover seems that fragmentation of excited **1c** occurs in competition to the chain process, leading directly to O-radical **Ic** and a thiyl radical, that is the monomer of disulfide **5**.

2.4. Intramolecular addition

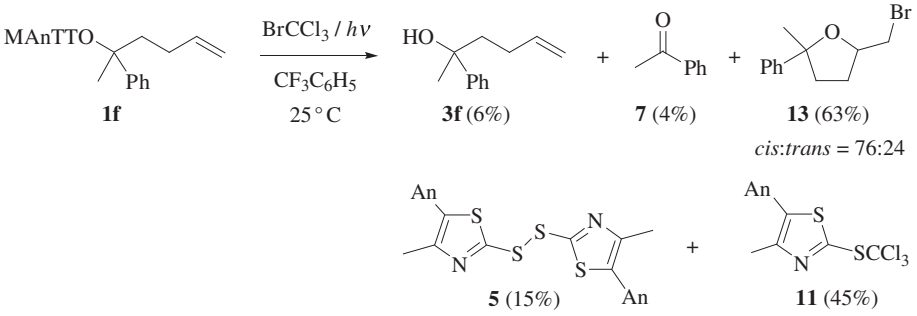
Photolysis of a solution of *N*-(2-phenylhex-5-en-2-oxy)-thiazolethione **1f** and $BrCCl_3$ (c_0=0.83 M) provides 2-methyl-2-phenyl-5-bromomethyltetrahydrofuran (**13**),[42] acetophenone **7**, alkenol **3f**, disulfide **5**, and trichloromethylsulfanyl thiazole **11** (Scheme 4). 1-Phenylpent-4-en-1-one, a product of interest for the mechanistic discussion outlined below, was not detected using authentic reference (^{1}H and ^{13}C NMR, GC). A modification of the reaction conducted in boiling C_6H_6 using AIBN as initiator provided 63% of bromomethyltetrahydrofuran **13** (*cis*/*trans*=73:27), 8% of ketone **7**, and 21% of alkenol **3f**.

NOESY-spectra show a strong cross signal 5-H↔CH_3 for major bromocyclization product, which led to assignment of cis-configuration (i.e., *cis*-**13**). A 5-H↔C_6H_5 correlation and the absence of a 5-H↔CH_3 cross peak was taken as evidence for trans-configuration of the minor component (i.e., *trans*-**13**).

The chemical nature of products obtained leads us to the conclusion that radical **If** is liberated from *N*-alkenoxythiazolethione **1f** and $BrCCl_3$. Alkenoxyl radical **If** cyclizes stereoselectively (major: **If**→*cis*-**IV**), fragments (**If**→**7**+**V**), or abstracts a hydrogen atom (**If**→**3f**; vide supra). Since 5-*exo*-*trig* alkenoxyl radical addition to a terminal π-bond is irreversible and Br-atom abstraction by nucleophilic C-radicals from $BrCCl_3$ is virtually quantitative,[17] product ratios of 12 (for *cis*-**13**/**7**) and 3.8 (for *trans*-**13**/**7**; Scheme 4) reflect relative reactivity of cyclization versus β-C,C-homolysis for **If**, as expressed by $k^{A_R cis}_{If}/k^{D_R}_{If}$ and $k^{A_R trans}_{If}/k^{D_R}_{If}$ (Scheme 5). Approximation of the unknown value for $k^{D_R}_{If}$ with the rate constant of 2-(4-methylphenyl)-but-2-oxyl radical fragmentation into *p*-tolylacetophenone and $•C_2H_5$ (k^{D_R} =2.5×10^8 s^{-1} in CH_3CN at 22 °C),[7] provides $k^{A_R cis}_{If}$ =3×10^9 s^{-1} and $k^{A_R trans}_{If}$ =1×10^9 s^{-1}. Both values are slightly larger than references from 5-*exo*-*trig* cyclizations of structurally related secondary alkoxyl radicals to double bonds of the same substitution pattern.[43,44]



Scheme 5. Reaction scheme for kinetic analysis of 2-phenylhex-5-en-2-oxyl radical reactions.



Scheme 4. Products formed from 3-(2-phenylhex-5-en-2-oxy)-thiazolethione **1f** and $BrCCl_3$.

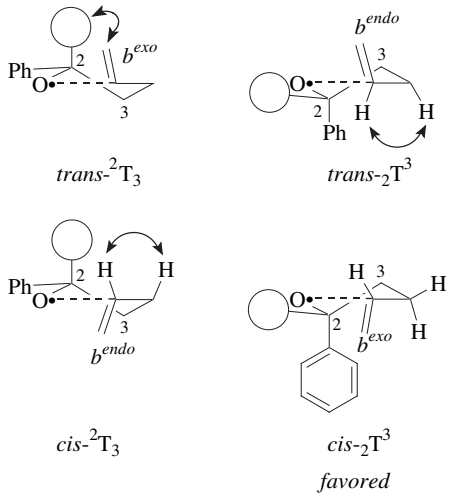


Fig. 3. Transition structure model on the origin of 2,5-cis-stereoselectivity in cyclization **If**→**IV** (CIP hierarchy for assignment of relative configurations: Ph>CH_3; the CH_3 substituent was drawn as a circle of an arbitrary radius for tutorial reasons; one enantiomer of the radical was arbitrarily chosen for presentation; arrows represent origin and effector of steric repulsion).

The observed 2,5-cis-stereoselectivity **If**→*cis*-**IV** for alkenoxyl radical cyclization is new: 1-alkyl-4-penten-1-oxyl radical cyclize 2,5-trans-selectivity, whereas 1-aryl-4-penten-1-oxyl radicals furnish a ~50/50-mixture of stereoisomers.[43,44] To explain stereoselectivity in this chemistry, a mnemonic device exists. It is applicable to kinetically controlled reactions and considers steric effects in transition structures.[45] Low in energy and thus significantly populated transition structures thereby derive from $_2T^3$- *and* $^2T_3$ conformers of tetrahydrofuran. One of the C,O-bonds is at equilibrium distance of 1.47 Å and the second, that is, the newly formed bond, stretched to ~2.05 Å (Fig. 3).[45] This geometry takes stereoelectronic prerequisites for the O-radical addition to the π-bond and minimization of torsional strain, that is, a twist rather than an envelope conformer, into account. Since the inner carbon of the vinyl group is part of the three atom unit defining the twist plane, two bisectional (*b*) arrangements for the $=CH_2$-segment exist. The conformer having the vinyl terminus and the second next neighbor, that is, C3 on opposite sides is referred to as *exo*-bisectional (b^{exo}). The opposite orientation is called *endo*-bisectional (b^{endo}). In the *exo*-bisectional form, which is the favored arrangement, H-atoms at positions 4 and 5 exhibit synclinal orientation. The *endo*-bisectional arrangement, on the other hand, leads to an eclipsing of hydrogens at the two carbons thus increasing torsional strain of the conformers (Fig. 3). Since the phenyl group in benzyloxyl radicals favors co-planar alignment of aromatic plane and radical oxygen,[46] axial phenyl, and *exo*-bisectional vinyl group orientation lead to no significant steric repulsion (Fig. 3, bottom right). In the *trans*-$^2T_3$-configured transition structure, 1,3-interactions between vinyl and methyl groups arise that increase free energy of this conformer.[45] For a rapidly equilibrating system, selectivity of a reaction, according to transition state theory and the Curtin-Hammett-principle is given by a Boltzmann-distribution covering all relevant intermediates. For our simplified model this means that the lowest in energy conformer out of the ensemble of four intermediates displayed in Fig. 3, that is, transition structure *cis*-$_2T^3$, is relevant for describing stereoselectivity of the 5-exo-ring closure of alkenoxyl radical **If**.

2.5. Intermolecular addition

2.5.1. Synthetic and kinetic aspects. Photochemical reactions of 3-alkoxythiazolethiones **1a**, **1d**, and **1e** in $C_6H_5CF_3$-solutions containing an excess of bicyclo[2.2.1]heptene (**14**) (c_0=2.76 M) and $BrCCl_3$ (c_0=278 mM) furnish 3-alkoxy-2-bromobicyclo[2.2.1]heptanes **16a**, **16d**, and **16e**. Yields of β-bromohydrin ethers grow along the series of transferred radicals *tert*-butoxyl (20%), *p*-chlorocumyloxyl (44%), and cumyloxyl (46%) (Table 4, entries 1–3). 1-Bromo-2-trichloromethylbicyclo[2.2.1]heptane **17**[47,48] and 2-chloro-1-thiazylsulfanylbicyclo[2.2.1]heptane **18** are formed as co-products. Trichloromethylsulfanyl thiazole **11** was surprisingly not found. Controls indicate that compound **11** is converted into adduct **18**, if photolyzed in an excess of olefin **14**. The mechanism of this reaction is under current investigations.

As the norbornene concentration is lowered from 0.21 M to 0.05 M, the fraction of addition product **16e** deminishes, whereas the amount of *p*-chloroacetophenone **15** grows (Table 5, entries 4–6). *p*-Chlorophenyl-2-propanol (**3e**) is obtained as additional product, presumably for reasons outlined in Section 2.3. Its yield supplemented the percentage of *p*-chlorocumyloxyl radical-derived products to 73–89%. A plot of ratios **16e**:**15** versus norbornene concentration was linear ([**16e**]/[**15**]=(9.33 M^{-1})[**14**]; R^2=0.9997). The slope, according to a kinetic model that takes irreversible *p*-chlorocumyloxyl radical fragmentation into ketone **15** and $^{\bullet}CH_3$, and a kinetically controlled addition of *p*-chlorocumyloxyl radical **Ie** to olefin **14** into account, corresponds to the ratio of $k^{A_{R_{Ie}}}/k^{D_{R_{Ie}}}$ (Scheme 6 and Supplementary data). Approximation of $k^{D_{R_{Ie}}}$ for the reaction **Ie**→**15** in $C_6H_5CF_3$ with the value determined in CH_3CN ($k^{D_{R_{Ie}}}=1\times10^6$ s^{-1} for 22 °C)[6,49] provides the rate constant $k^{A_{R_{Ie}}}=1\times10^7$ M^{-1} s^{-1}. This value is one order of magnitude higher than an EPR-spectroscopically determined reference for *tert*-butoxyl radical addition to olefin **14** ($k^{A_{R_{Ia}}}=1.1\times10^6$ s^{-1} for 27 °C).[50]

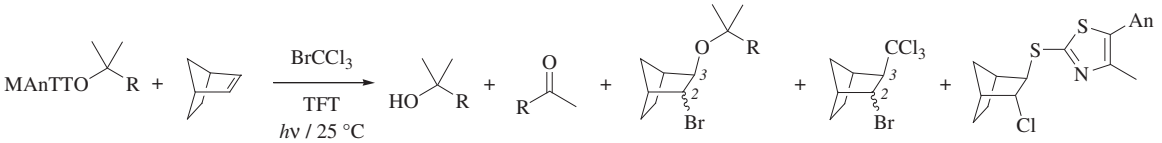
2.5.2. Stereochemical aspects. NOESY-cross signals 2-H↔7-H and 3-H↔6-H correlate with 3-*exo*-2-*endo*-configuration of major isomers of alkoxyl radical addition products **16a**, **16d**, and **16e** (Table 3, entries 1–3). For the minor isomers, 3-H↔2-H, 2-H↔6-H, and 3-H↔5-H NOESY-cross signals were found pointing to 3-*exo*-2-*exo*-configuration. Alkoxyl radical addition to norbornene **14** therefore had appeared almost exclusively from the *exo*-side. Products of Br-atom trapping, i.e., **16a**, **16d**, and **16e**, show typical 2-exo/2-endo-ratios imposed by steric shielding of the exo-face of adduct radical **VI** by a sterically demanding substituent.[47]

Since the origin of the *exo*-stereoselectivity of alkoxyl radical additions was not evident from the literature,[47,51] it was pursued using electronic structure methods.[52,53] To investigate the role of steric effects, the methoxyl radical (**Ig**) was included into the study. Experimental stereoselectivities for addition of **Ig** and the *tert*-butoxyl radical (**Ia**) to olefin **14** are identical.[15] Based on method assessment for reproducing relative energies of radicals and transition structures from our own studies,[45,54] and from work of other groups,[55,56] we chose Becke's three parameter hybrid functional (B3LYP)[57,58] and Becke's half and half functional (BHandHLYP)[59] in combination with the 6-31+G** basis set for conducting the computational analysis. The selected basis set includes diffuse and polarization wave functions, which are needed to adequately reproduce selectivities in radical additions. For exploring basis set dependence, the results were supplemented by BHandHLYP/6-311G**-calculations.[56]

Equilibrium structures of reactands **Ia**/**g** and **14**, conformationally flexible products **VIa**/**g**, and transition structures *exo*/*endo*-**VIIa**/**g** were located on respective potential energy surfaces according to an established procedure.[45] Calculation of second derivatives (Hessian matrix) that lacked in negative eigenvalues or imaginary frequency by diagonalization, characterized computed structures of alkoxyl radicals **Ia**/**g**, olefin **14**, and bicyclic carbon radicals *exo*/*endo*-**VIa**/**g** as minima. Exactly one imaginary frequency *i* associated with an O,C2-stretching vibration shows that computed structures *exo*-**VIIa**/**g** and *endo*-**VIIa**/**g** are transition

structures with respect to C,O-bond formation (Table 4). Geometrical parameters of transition structures **VIIa**/**g** relevant for explaining the origin of *exo*-selectivity are listed in Table 4, zero-point energy-corrected electronic energies (*E* for 0 K), Gibbs free energies (*G* for 298.15 K), and expectation values of the spin operator (for radicals) in the Supplementary data.

Table 3
Products of 3-alkoxythiazolethione photoreactions with norbornene **14** and $BrCCl_3$

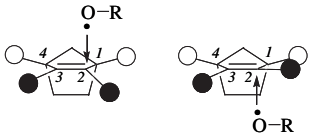


1 **14** **3** **7 / 12 / 15** (±)-**16** (±)-**17** (±)-**18** [a]

Entry	**1**	R	c_0^{14}/M	**3**/%	**7**/**12**/**15**/%	**16**/%(2-*exo*/2-*endo*)[b]	**17**/%(2-*exo*/2-*endo*)[b,c]
1	**1a**	CH_3	2.76	—[e]	**12**: —[d]	**16a**: 20 (20:80)	90 (7:93)
2	**1d**	C_6H_5	2.76	—[e]	**7**: —[d]	**16d**: 46 (28:72)	92 (5:95)
3	**1e**	*p*-ClC_6H_4	2.76	—[e]	**15**: —[d]	**16e**: 44 (28:72)	93 (7:93)
4	**1e**	*p*-ClC_6H_4	0.21	27	**15**: 19	**16e**: 36 (30:70)	82 —[e]
5	**1e**	*p*-ClC_6H_4	0.11	30	**15**: 30	**16e**: 29 (24:76)	89 —[e]
6	**1e**	*p*-ClC_6H_4	0.05	38	**15**: 26	**16e**: 12 (22:78)	73 —[e]

[a]Not quantified.
[b] 3-*exo*-configuration (GC, ^1H NMR).
[c] Yield referenced versus $BrCCl_3$.
[d] Not detected (GC).
[e] Not determined.

Table 4
Selected geometrical parameters of transition structures *exo*/*endo*-**VIIa**/**g**[a]



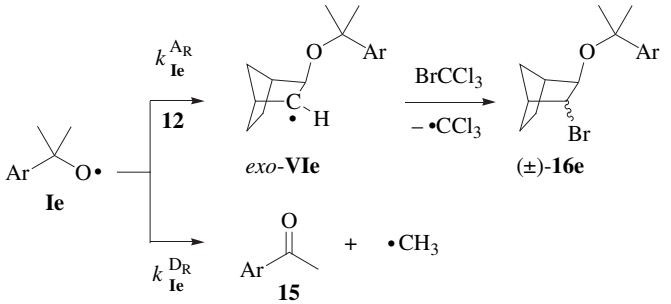
exo-**VII** *endo*-**VII**

VII/R	*i*[b]/cm^{-1}	O–C2/Å	O–C2–C3/°	H1–C1–C2–H2/°	H4–C4–C3–H3/°
exo-**VIIa**/*t*-Bu	−227	2.105	112.0	41.5	−28.8
	(−390)	(2.039)	(111.6)	(43.7)	(−29.5)
	[−407]	[2.024]	[109.3]	[−43.7]	[−29.7]
exo-**VIIg**/CH_3	−157	2.211	102.9	36.0	−26.4
	(−357)	(2.082)	(106.4)	(46.0)	(−28.4)
	[−389]	[2.056]	[105.8]	[40.8]	[−27.7]
endo-**VIIa**/*t*-Bu	−290	2.104	101.3	−0.3	−20.7
	(−443)	(2.054)	(103.1)	(−2.0)	(−20.3)
	[−453]	[2.043]	[102.5]	[−2.0]	[−20.0]
endo-**VIIg**/CH_3	−277	2.124	98.0	−3.6	−22.7
	(−430)	(2.062)	(101.0)	(0.9)	(−21.1)
	[−454]	[2.043]	[100.8]	[0.8]	[−20.7]

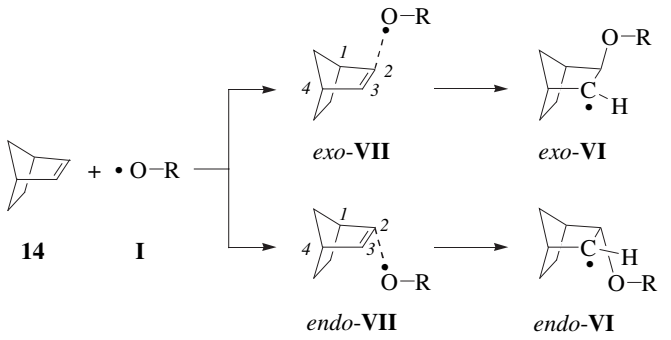
[a] Figures B3LYP/6-31+G** structures, numbers in parentheses to BHandHLYP/6-31+G** structures, and values in brackets to BHandHLYP/6-311G** structures (○ and ● symbolize key H-atoms relevant for explaining stereoselectivity).
[b] *i*=Imaginary mode of vibration.

Table 5
Zero-point vibrational energy-corrected activation energies ($\Delta E^{\ddagger}$), reaction energies ($\Delta_R E$), intrinsic energy barriers ($\Delta E_i^{\ddagger}$), thermodynamic contribution $\Delta E_{TD}^{\ddagger}$ to $\Delta E^{\ddagger}$, free energy differences ($\Delta G_{298.15}=G_{298.15}^{exo}-G_{298.15}^{endo}$), and estimated transition structure positioning $x^{\ddagger}$ for alkoxyl radical additions to norbornene **14** (Scheme 7, Eqs. 1–3)

Reaction	Method	$\Delta E^{\ddagger}$/kJ mol^{-1}	$\Delta_R E$/kJ mol^{-1}	ΔE_i/kJ mol^{-1}	$\Delta E_{TD}^{\ddagger}$/kJ mol^{-1}	$x^{\ddagger}$	$\Delta G_{298.15}$/kJ mol^{-1}
Ia+**14**→***exo*-VIa**	B3LYP/6-31+G**	14.8	−66.6	41.4	−26.6	0.0	≡0.0
(R=*t*-Bu)	BHandHLYP/6-31+G**	32.0	−74.9	64.0	−32.0	0.2	≡0.0
	BHandHLYP/6-311G**	28.2	−76.6	60.4	−32.2	0.2	≡0.0
Ia+**14**→***endo*-VIa**	B3LYP/6-31+G**	30.4	−67.0	59.2	−28.8	0.2	15.9
(R=*t*-Bu)	BHandHLYP/6-31+G**	50.3	−75.3	81.7	−33.4	0.3	18.4
	BHandHLYP/6-311G**	46.0	−77.6	80.1	−34.1	0.3	18.1
Ig+**14**→***exo*-VIg**	B3LYP/6-31+G**	7.7	−80.5	37.0	−29.3	(−0.8)	≡ 0.0
(R=CH_3)	BHandHLYP/6-31+G**	24.6	−87.9	60.6	−36.0	0.1	≡ 0.0
	BHandHLYP/6-311G**	21.8	−88.5	57.3	−35.7	0.0	≡ 0.0
Ig+**14**→***endo*-VIg**	B3LYP/6-31+G**	20.3	−78.8	52.3	−32.0	0.0	12.6
(R=CH_3)	BHandHLYP/6-31+G**	39.9	−86.6	77.0	−37.1	0.2	15.3
	BHandHLYP/6-311G**	37.3	−87.4	74.7	−37.4	0.2	15.6



Scheme 6. Elementary reactions for kinetic analysis of intermolecular alkoxyl radical addition to norbornene **14** via the *p*-chlorocumyloxyl-'radical clock' (Ar=*p*-ClC_6H_4).



Scheme 7. Structure formulas and indexing of reactands for modeling alkoxyl radical addition to norbornene **14** [R=$C(CH_3)_3$ for **Ia**, **VIa**, and **VIIa**; R=CH_3 for **Ig**, **VIg**, and **VIIg**; see also Table 4 and the Supplementary data].

Computed zero-point vibrational energy-corrected electronic barriers ($\Delta E^{\ddagger}$) were split into an intrinsic term ($\Delta E_i^{\ddagger}$) and a thermodynamic component ($\Delta E_{TD}^{\ddagger}$), according to Marcus-theory (Eqs. 1–3).[60–62] The intrinsic part reflects steric contributions in a thermoneutral, i.e., degenerated reaction having a barrier of $\Delta E_i^{\ddagger}$ located at $x^{\ddagger}$=0.5 on the reaction coordinate (Fig. 4). The thermodynamic part refers to energy terms originating from bond formation and bond breaking.

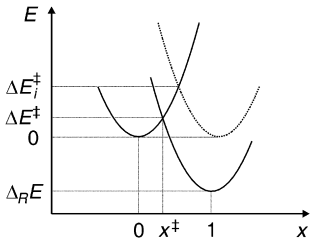


Fig. 4. Positioning of activation ($\Delta E^{\ddagger}$) and intrinsic barrier ($\Delta E_i^{\ddagger}$) according to Marcus-theory in $E(x)$ profiles using harmonic potentials of equal curvature for initial (x=0) and final state (x=1).[60,61]

$$\Delta E_i^{\ddagger} = \frac{\Delta E^{\ddagger} - \frac{\Delta_R E}{2} + \sqrt{\left(\Delta E^{\ddagger}\right)^2 - (\Delta_R E)\left(\Delta E^{\ddagger}\right)}}{2} \quad (1)$$

$$X^{\ddagger} = \frac{1}{2}\left(1 + \frac{\Delta_R E}{4\Delta E^{\ddagger}}\right) \quad (2)$$

$$\Delta E^{\ddagger} = \Delta E_i^{\ddagger} + \Delta E_{TD}^{\ddagger} \quad (3)$$

Calculated atomic distances, angles, and energy differences change gradually but not fundamentally, as the applied theoretical methods were varied (Tables 4 and 5). Independent from the method, theory predicts strongly exothermic reactions and thus a high barrier for the reverse reaction, which means kinetic reaction control. Reaction energies for *exo*- and *endo*-additions of the radicals **Ia** and **Ig** are surprisingly similar. If compared to methoxyl radical additions, the *tert*-butoxyl radical additions, however, are consistently less exothermic. Location of the B3LYP-calculated transition structure *exo*-**VIIg** at $x^{\ddagger}$=−0.8 shows that values obtained with this method should be treated with more care than the BHandHLYP data.[56] Calculated O···C2-distances of 2.0–2.2 Å and values for the $x^{\ddagger}$ parameter between 0 and 0.3 (for exception vide supra) correlate with early transition structures on the reaction coordinates. Computed Gibbs free energies at 298.15 K favor transition structures *exo*-**VIIa**/**g** by 15–18 kJ over structures *endo*-**VIIa**/**g**, which leads to theoretical *exo*/*endo*-ratios of >99:1. These numbers agree in an excellent manner with the experimental findings.

The origin of the *exo*-selectivity in alkoxyl radical additions to norbornene **14** in this model arises from subtle geometrical changes that occur in an early phase of the reaction. As the radical approaches the π-bond, the hydrogen at the attacked olefinic carbon moves backward. The vicinal olefinic hydrogen, on the other hand, shifts toward the incoming radical (cf. angles H1–C1–C2–H1 and H3–C3–C4–H4 in Table 4).[63] In transition structures *endo*-**VIIa**/**g** these changes lead to an eclipsing of hydrogens at the attacked carbon and the proximal bridgehead position. In the approach from the opposite side, that is, via intermediate *exo*-**VIIa**/**g**, the same hydrogens show synclinal orientation leading to less torsional strain (Table 4). These strain effects are furthermore evident from lower intrinsic barriers $\Delta E_i^{\ddagger}$ for *exo*-additions, while thermodynamic contribution $\Delta E_{TD}^{\ddagger}$ to the activation barrier remain for *exo*/*endo*-transition structures approximately similar.

In terms of steric effects, it becomes apparent from the computed numbers that *tert*-butoxyl radical additions were throughout the study associated with higher intrinsic barriers than methoxyl radical additions. These trends were attributed to a small but systematic size effect on alkoxyl radical reactivity.

3. Concluding remarks

The strong affinity of 3-hydroxy-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**2**) for alkylation at oxygen, in combination with the driving force of *O*-alkyl isoureas to transfer *tert*-alkyl groups to nucleophiles paved the road to synthesis of a new class of *tert*-alkoxyl radical progenitors.[18,64] Although the chosen compounds (i.e., **1a**–**f**) pose a selection from our laboratory, we think that the method offers a general solution for converting trialkyl-substituted alcohols into *tert*-alkoxyl radical precursors. Synthetic problems arose in esterifications of tert-2-arylalkan-2-ols (e.g. 3**d**), due to extensive elimination. Fortunately, an upscaling in such cases was feasible. This approach may be helpful in selected instances, to prepare sufficient material for conducting more specialized investigations using the thiohydroxamate method for *tert*-alkoxyl radical generation.

Using *O*-alkyl thiohydroxamates **1a** and **1c**–**f**, we were for the first time able to prepare 2,2,5-substituted tetrahydrofurans (i.e., **10**, **13**) and 2-bromo-3-alkoxynorbornans (i.e., **16a**, **16d**–**e**) via an alkoxyl radical pathway, which operates under mild and neutral conditions. The rate constants from the mechanistic part of the study show that *tert*-alkyl substitution near oxygen does not reduce alkoxyl radical reactivity, at least in the investigated cases. However, we believe that true value of these data lies in the possibility they offer for more precisely setting up the selectivity requirement for new syntheses based on *tert*-alkoxyl radical chemistry.

Bicyclo[2.2.1]heptene (**14**) was a rewarding alkene to explore intermolecular alkoxyl radical additions. Its strained double bond and comparatively strong C,H-bonds offer favorable characteristics for the addition. Still we conclude from the kinetic data that intermolecular

alkoxyl radical additions have the potential to become more and more important, as the knowledge about this reaction increases.

As a final remark, we wish to address the aspect of stereoselectivity in *tert*-alkoxyl radical additions. It is well understood that stereoselectivity in cyclization is attainable via substrate control.[45] However, it seems worth to emphasize that stereoelectronic effects and geometrical changes within the π-bond, as a system approaches its transition structure, add another important component to this picture. With the wisdom of hindsight, it could have been anticipated that similar means for stereocontrol in intermolecular additions must exist, because the underlying reaction is the same. As we continue to seek for new stereoselective radical additions, the seemingly insignificant geometrical change in the early phase of the alkoxyl radical addition may be the most valuable hint, where to look.

4. Experimental

4.1. General

For general laboratory practice and instrumentation see Ref. 17 and the Supplementary data.

4.2. 3-(Alkoxy)-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thiones

*4.2.1. General method for esterification of alcohols **3a**–**c**.* CuCl (2 mol %) was added to a stirred solution of alcohol **3** (5.5 mmol) and DIC (5.5 mmol). Stirring was continued for 22–24 h at 20 °C. The resulting product was transferred into a syringe and was added over a period of 90 min in a dropwise manner at 24 °C (for **3a**) or at 0 °C (for **3b**,**c**) to a solution of 3-hydroxy-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (MAnTTOH; **2**) (1 mmol) in CH_2Cl_2 (2 mL). After complete addition, solids were removed by filtration to afford a clear solution, which was concentrated under reduced pressure. The remaining oil was purified by column chromatography (SiO_2) using the eluent gradient (EG) specified below.

*4.2.2. General method for esterification of 2-arylalcohols **3d**–**f**.* CuCl (2 mol %), alcohol **3** (2 mmol), and DIC (2 mmol) were stirred for 24–26 h at 20 °C as described in general method 4.2.1. The solution was added at −30 °C to a solution of 3-hydroxy-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**2**) (1 mmol) and CH_2Cl_2 (2 mL). The resulting mixture was worked up as specified in Section 4.2.1.

*4.2.3. Esterification of 2-methylpropan-2-ol (**3a**).* *tert*-Butanol **3a** (408 mg, 5.5 mmol) was treated as described in general method 4.2.1. EG: *tert*-butyl methyl ether/pentane=1:1 (v/v)→acetone/pentane=1:1 (v/v). 3-(2-*Methylprop*-2-*oxy*)-5-(4-*methoxyphenyl*)-4-*methylthiazole*-2(3*H*)-*thione* (**1a**).[28] Yield: 198 mg (64%), pale yellow solid, mp 114–115 °C. R_f=0.45 for *tert*-butyl methyl ether/pentane=1:1 (v/v). UV (EtOH) λ_{max} (log ε/m^2 mol^{-1})=337 nm (3.25), 260 (2.89), 228 (3.13). Anal. Calcd for $C_{15}H_{19}NO_2S_2$ (309.44): C, 58.22; H, 6.19; N, 4.53. Found: C, 58.21; H, 6.02; N, 4.36. 2-(2-*Methylpropyl*-2-*sulfanyl*)-5-(4-*methoxyphenyl*)-4-*methylthiazole N-oxide* (**4a**). Yield: 78.3 mg (25%) yellow oil. R_f=0.30 for acetone/pentane=1:1 (v/v). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H), 2.45 (s, 3H), 3.85 (s, 3H), 6.98 (d, 2H, *J*=8.6 Hz), 7.36 (d, 2H, *J*=8.3 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.9, 31.4, 52.5, 55.4, 114.6, 122.9, 129.8, 131.9, 133.5, 141.6, 160.4.

*4.2.4. Esterification of 2-methylbutan-2-ol (**3b**).* *tert*-Amylalcohol **3b** (485 mg, 5.5 mmol) was treated as described in general method 4.2.1. EG: *tert*-butyl methyl ether/pentane=1:1 (v/v)→acetone/pentane=1:1 (v/v). 3-(2-*Methylbut*-2-*oxy*)-5-(4-*methoxyphenyl*)-4-*methylthiazole*-2(3*H*)-*thione* (**1b**). Yield: 152 mg (47%) pale yellow solid, mp 72–73 °C. R_f=0.52 for *tert*-butyl methyl ether:-pentane=1:1 (v/v). UV (EtOH) λ_{max} (log ε/m^2 mol^{-1})=338 nm (3.26), 227 (3.17). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (t, 3H, *J*=7.5 Hz), 1.56 (br s, 6H), 1.98–2.08 (m, 2H), 2.30 (s, 3H), 3.83 (s, 3H), 6.94 (d, 2H, *J*=8.8 Hz), 7.24 (d, 2H, *J*=8.9 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 8.97, 14.1, 25.7, 35.0, 55.4, 94.6, 114.4, 119.3, 122.8, 129.8, 134.4, 159.7, 182.4. Anal. Calcd for $C_{16}H_{21}NO_2S_2$ (323.47): C, 59.41; H, 6.54; N, 4.33. Found: C, 59.37; H, 6.53; N, 4.26. 2-(2-*Methylbutyl*-2-*sulfanyl*)-5-(4-*methoxyphenyl*)-4-*methylthiazole N-oxide* (**4b**) Yield: 106 mg (33%), yellowish oil. R_f=0.33 for acetone/pentane=1:1 (v/v). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.98 (t, 3H, *J*=7.4 Hz), 1.35 (s, 6H), 1.68 (q, 2H, *J*=7.4 Hz) 2.39 (s, 3H), 3.79 (s, 3H), 6.93 (d, 2H, *J*=8.7 Hz), 7.30 (d, 2H, *J*=8.5 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 9.2, 12.8, 28.3, 35.6, 55.2, 56.5, 114.4, 122.5, 129.6, 131.9, 133.8, 141.2, 160.3.

*4.2.5. Esterification of 2-methyl-5-phenylpentan-2-ol (**3c**).* Alcohol **3c** (980 mg, 5.5 mmol) was treated as described in general method 4.2.1. EG: *tert*-butyl methyl ether/pentane=1:5 (v/v)→*tert*-butyl methyl ether/pentane=1:1 (v/v)→acetone:pentane=1:1 (v/v). 3-(2-*Methyl*-5-*phenylpent*-2-*oxy*)-5-(4-*methoxyphenyl*)-4-*methythiazole*-2(3*H*)-*thione* (**1c**). Yield: 182 mg (44%), colorless solid, mp 64 °C. R_f=0.59 for *tert*-butyl methyl ether/pentane=1:1 (v/v). UV (EtOH) λ_{max} (log ε/m^2 mol^{-1})=337 nm (3.21), 260 (2.87). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54 (s, 6H), 1.80–1.93 (m, 2H), 1.95–2.10 (m, 2H), 2.22 (s, 3H), 2.67 (t, 2H, *J*=7.3 Hz), 3.84 (s, 3H), 6.94 (d, 2H, *J*=8.8 Hz), 7.16–7.30 (m, 7H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.1, 26.2, 26.3, 26.9, 36.1, 42.0, 55.4, 94.0, 114.4, 119.3, 122.9, 125.8, 128.3, 128.5, 129.8, 134.4, 142.1, 159.8, 182.4. MS (EI) *m/z* 270 (5), 238 (15), 152 (100), 104 (68). Anal. Calcd for $C_{23}H_{27}NO_2S_2$ (413.59): C, 66.79; H; 6.58; N, 3.39. Found: C; 66.88; H; 6.58; N, 3.05. 2-(2-*Methyl*-5-*phenylpentyl*-2-*sulfanyl*)-5-(4-*methoxyphenyl*)-4-*methylthiazole N-oxide* (**4c**). Yield: 43.7 mg (11%), yellowish oil. R_f=0.38 for acetone/pentane=1:1 (v/v). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 6H), 1.70–1.73 (m, 2H), 1.81–1.89 (m, 2H), 2.45 (s, 3H), 2.64 (t, 2H, *J*=7.2 Hz), 3.87 (s, 3H), 7.00 (d, 2H, *J*=8.6 Hz), 7.12–7.20 (m, 3H),7.24–7.27 (m, 2H), 7.35 (d, 2H, *J*=8.6 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.9, 26.8, 27.0, 29.1, 36.0, 42.6, 55.4, 56.1, 114.6, 122.9, 125.6, 128.3, 128.5, 128.9, 131.9, 141.5, 142.1, 160.5, 160.6.

*4.2.6. Esterification of 2-phenylpropan-2-ol (**3d**).* Cumylalcohol **3d** (2.05 g, 15.0 mmol) and MAnTTOH (**2**) (1.91 g, 7.5 mmol) were treated as described in general method 4.2.2. 3-(2-*Phenylprop*-2-*oxy*)-5-(4-*methoxyphenyl*)-4-*methylthiazole*-2(3*H*)-*thione* (**1d**).[18] Eluent used for chromatographic purification: *tert*-butyl methyl ether/pentane=1:2 (v/v). Yield: 421 mg (15%), colorless crystals, mp 108 °C. R_f=0.36 for pentane/Et_2O=2:1 (v/v). 2-(2-*Phenylpropyl*-2-*sulfanyl*)-5-(4-*methoxyphenyl*)-4-*methylthiazole N-oxide* (**4d**). Cumylalcohol **3d** (1.36 g, 10.0 mmol) and MAnTTOH (**2**) (1.26 g, 5.0 mmol) were treated as described in general method in Section 2.2. Eluent for chromatographic purification: acetone/pentane=1:1 (v/v). Yield: 713 mg (38%), colorless solid, mp 72–73 °C. R_f=0.24 for acetone/pentane=1:1 (v/v). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90 (s, 6H), 2.39 (s, 3H), 3.82 (s, 3H), 6.93 (d, 2H, *J*=8.5 Hz), 7.19–7.24 (m, 3H), 7.30–7.34 (m, 2H), 7.56 (d, 2H, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.6, 30.3, 55.4, 56.7, 114.5, 122.9, 126.7, 127.4, 128.3, 129.7, 131.6, 135.0, 140.7, 144.7, 160.3. Anal. Calcd. For $C_{20}H_{21}NO_2S_2$ (371.51): C, 64.66; H, 5.70; N, 3.77. Found: C, 64.46; H, 5.95; N, 3.85.

*4.2.7. Esterification of 2-(4-chlorophenyl)-propan-2-ol (**3e**).* *p*-Chlorocumyl alcohol **3e** (1.71 g, 10.0 mmol) and MAnTTOH (**3**) (1.27 g, 5.0 mmol) were treated as described in general method 4.2.2. EG: *tert*-butyl methyl ether/pentane=1:2 (v/v)→*tert*-butyl methyl ether/pentane=1:1 (v/v)→acetone/pentane=1:1 (v/v). 3-[2-(4-*Chlorophenyl*)-*prop*-2-*oxy*]-5-(4-*methoxyphenyl*)-4-*methylthiazole*-2(3*H*)-*thione* (**1e**). Yield: 264 mg (13%), colorless crystals, mp 110 °C. R_f=0.44 for pentane/Et_2O=1:1 (v/v). UV (MeOH) λ_{max} (log ε/m^2 mol^{-1}) 337 nm (3.01), 223 (3.19). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, 3H), 1.99 (s, 6H), 3.81 (s, 3H), 6.89 (d, 2H, *J*=8.5 Hz), 7.13 (d, 2H, *J*=8.6 Hz), 7.36 (d, 2H, *J*=8.5 Hz), 7.53 (d, 2H, *J*=8.6 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz, 20 °C) δ 13.8, 27.9, 55.4, 91.9, 114.5, 119.0, 122.8, 127.1, 128.5, 129.8, 134.2, 134.3, 143.5, 159.9, 182.5. MS (EI) *m*/*z* 253 (67), 236 (35), 205 (25), 177 (27), 155 (86), 152 (100), 137 (68), 117 (85), 102 (56). Anal. Calcd. For $C_{20}H_{20}ClNO_2S_2$ (405.96): C, 59.17; H, 4.97; N, 3.45. Found: C, 59.22; H, 4.99; N, 3.29. Crystals suitable for X-ray diffraction were grown from a saturated solution in pentane/Et_2O=1:1 (v/v). T=293(2) K, λ=0.71073 Å, monoclinic, C2/*c*, a=17.561(4) Å, b=8.8759(18) Å, c=26.777(5) Å, β=106.73(3)°, Z=8, μ=0.414 mm^{-1}, completeness to 2θ=95.1%, goodness-of-fit on F^2=0.747, final R indices [$I>2\sigma(I)$]: $R1$=0.0312, $wR2$=0.0612. 2-[2-(4-*Chlorophenyl*)-*propyl*-2-*sulfanyl*]-5-(4-*methoxyphenyl*)-4-*methylthiazole N-oxide* (**4e**). Yield: 658 mg (33%), colorless solid, mp 102 °C. R_f=0.29 for acetone/pentane=1:1 (v/v). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.89 (s, 6H), 2.42 (s, 3H), 3.85 (s, 3H), 6.97 (d, 2H, J=8.9 Hz), 7.25–7.31 (m, 4H), 7.50–7.52 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.7, 30.3, 55.4, 56.3, 114.5, 122.8, 128.2, 128.4, 129.8, 132.0, 133.2, 134.1, 141.0, 143.4, 160.4. Anal. Calcd. For $C_{20}H_{20}ClNO_2S_2$ (405.97): C, 59.17; H, 4.97; N, 3.45. Found: C, 58.83; H, 4.71; N, 3.44.

*4.2.8. Esterification of 2-phenylhex-5-en-2-ol (**3f**).* Alkenol **3f** (7.05 g, 40 mmol) and MAnTTOH (**2**) (5.06 g, 20 mmol) were treated as described in general method 4.2.2. EG: pentane/Et_2O/CH_2Cl_2=5:1:1 (v/v/v)→acetone/pentane=1:2 (v/v). 3-(1-*Methyl*-1-*phenylpent*-4-*en*-1-*oxy*)-5-(4-*methoxyphenyl*)-4-*methylthiazole*-2(3*H*)-*thione* (**1f**). Yield 1.48 g (18%), colorless solid, mp 94–95 °C. R_f=0.30 for pentane/Et_2O/CH_2Cl_2=5:1:1 (v/v/v). UV (EtOH) λ_{max} (log ε/m^2 mol^{-1}) 338 nm (3.28). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (s, 3H), 1.72–1.80 (m, 1H), 1.88 (s, 3H), 1.91–2.00 (m, 1H), 2.62 (dt, 1H, J_d=12.8 Hz, J_t=4.6 Hz), 2.89 (dt, 1H, J_d=12.6 Hz, J_t=5.0 Hz), 3.79 (s, 3H), 4.91 (dd, 1H, J=10.2, 1.5 Hz), 4.95 (dd, 1H, J=17.2, 1.6 Hz), 5.75 (ddt, 1H, J_d=16.8, 10.2 Hz, J_t=6.4 Hz), 6.87 (d, 2H, J=8.5 Hz), 7.10 (d, 2H, J=8.2 Hz), 7.34–7.41 (m, 3H), 7.53 (d, 2H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 13.6, 20.2, 29.4, 42.4, 55.3, 95.1, 114.3, 114.7, 118.7, 122.7, 126.2, 128.3, 128.6, 129.1, 129.7, 134.6, 137.7, 159.7, 182.1. Anal. Calcd. For $C_{23}H_{25}NO_2S_2$ (411.58): C, 67.12; H, 6.12; N, 3.40. Found: C, 67.22; H, 6.05; N, 3.68. 2-(1-*Methyl*-1-*phenylpent*-4-*enyl*-2-*sulfanyl*)-5-(4-*methoxyphenyl*)-4-*methylthiazole N-oxide* (**4f**). Yield 2.19 g (27%), yellowish oil. R_f=0.35 for acetone/pentane=1:1 (v/v). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82–1.92 (m, 1H),1.92 (s, 3H), 2.07–2.23 (m, 2H), 2.34–2.41 (m, 1H), 2.39 (s, 3H), 3.83 (s, 3H), 4.93 (dd, 1H, J=10.2, 1.5 Hz), 4.98 (dd, 1H, J=16.2, 1.2 Hz), 5.75 (ddt, 1H, J=16.9, 10.4 , 6.3 Hz), 6.93 (d, 2H, J=8.6 Hz), 7.22–7.24 (m, 3H), 7.31–7.34 (m, 2H), 7.53 (d, 2H, J=7.4 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 12.6, 26.2, 29.1, 42.1, 55.4, 60.2, 114.5, 114.9, 123.0, 127.3, 127.4, 128.4, 129.8, 131.6, 134.7, 137.7, 140.7, 142.9, 160.3.

4.3. Alkoxyl radical reactions

*4.3.1. Reaction of 3-(tert-butoxy)-thiazolethione **1a** with norbornene **14**.* An oxygen-free solution of norbornene (**14**) (4.80 g, 51.0 mmol), *tert*-butoxythiazolethione **1a** (158 mg, 510 μmol), and $BrCCl_3$ (1.01 g, 5.10 mmol) in dry $C_6H_5CF_3$ (18.5 mL, c_0^{14}=2.76 M) was photolyzed for 40 min at 25 °C in a Rayonet® chamber reactor equipped with 12 light bulbs (λ=350 nm). The resulting mixture was concentrated under reduced pressure (100→20 mbar, 40 °C) to furnish a residue, which was purified by column chromatography (SiO_2) using pentane/Et_2O=20:1 (v/v) as eluent. 2-*endo*-3-*exo*-2-*Bromo*-3-*trichloromethylbicyclo*[2.2.1]*heptane* 2-*endo*-3-*exo*-(**17**).[47] Yield: 1.24 g (84%), colorless oil. R_f=0.68 for pentane/Et_2O=20:1 (v/v). 2-*exo*-3-*exo*-2-*Bromo*-3-*trichloromethylbicyclo*[2.2.1]*heptane* 2-*exo*-3-*exo*-(**17**).[47] Yield: 93.1 mg (6%), colorless oil, R_f=0.60 for pentane/Et_2O=20:1 (v/v). 2-*Bromo*-3-(2-*methylprop*-2-*oxy*)-*bicyclo*[2.2.1]*heptane* (**16a**). Yield: 25.3 mg (20%), colorless oil, 20/80-mixture of 2-*exo*-3-*exo*/2-*endo*-3-*exo*-isomers. R_f=0.40 for pentane/Et_2O=20:1 (v/v). Anal. Calcd. For $C_{11}H_{19}OBr$ (247.17): C, 53.45; H, 7.75. Found: C, 53.22; H, 7.69. 2-*endo*-3-*exo*-2-*Bromo*-3-(2-*methylprop*-2-*oxy*)-*bicyclo*[2.2.1]*heptane* 2-*endo*-3-*exo*-(**16a**). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.16–1.22 (m, 1H), 1.20 (s, 9H), 1.31 (dq, 1H, J_d=10.4 Hz, J_q=1.8 Hz), 1.41–1.46 (m, 1H), 1.50–1.58 (m, 1H), 1.71–1.76 (m, 1H), 1.85 (ddt, 1H, J_d=12.4, 9.3 Hz, J_t=2.9 Hz) 2.01 (d, 1H, J=5.0 Hz), 2.35–2.40 (m, 1H), 3.43 (t, 1H, J=2.3 Hz), 3.90–3.91 (m, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 23.8, 25.0, 28.8, 34.5, 42.8, 44.6, 63.6, 73.6, 83.4. MS (EI) *m*/*z* 248 (2), 246 (2), 233 (3), 191 (16), 175 (5), 110 (11), 93 (15), 57 (100). 2-*exo*-3-*exo*-3-*Bromo*-3-(2-*methylprop*-2-*yl*)-*bicyclo*[2.2.1]-*heptane* 2-*exo*-3-*exo*-(**16a**). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.10–1.19 (m, 3H), 1.21 (s, 9H), 1.43–1.51 (m, 1H), 1.51–1.57 (m, 1H), 1.97 (dquint, 1H, J_d=10.3 Hz, J_{quint}=1.9 Hz), 2.05–2.06 (m, 1H), 2.48–2.49 (m, 1H), 3.37–3.39 (m, 1H), 4.00 (dd, 1H, J=6.1, 2.0 Hz). ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.4, 27.5, 28.1, 33.4, 44.8, 46.6, 62.0, 74.2, 74.9. MS (EI) *m*/*z* 248 (1) 246, 233 (3), 191 (17), 175 (3), 110 (11), 93 (14), 57 (100).

*4.3.2. Conversion of 3-(2-methyl-5-phenylpent-2-oxy)-thiazolethione **1c**.* $BrCCl_3$ 310 mg (750 μmol) and 1.50 g (7.50 mmol, 0.75 mL) in C_6H_6 (9.0 mL) according to procedure in Section 4.3.1. Eluent used for chromatographic purification: pentane/*tert*-butyl methyl ether=10:1 (v/v)→pentane/*tert*-butyl methyl ether=2:1 (v/v). 2,2-*Dimethyl*-5-*phenyltetrahydrofuran* (**10**):[37] Yield: 76.6 mg (58%), yellow liquid, R_f=0.65 for *tert*-butyl methyl ether/pentane=1:2 (v/v). 5-(4-*Methoxyphenyl*)-4-*methyl*-2-(*trichlormethylsufanyl*)-*thiazole* **11**.[17] Yield: 71.9 mg (27%), yellowish crystals. R_f=0.43 for *tert*-butyl methyl ether/pentane=1:2 (v/v). 1,2-*Bis*-[5-(4-*methoxyphenyl*)-4-*methylthiaz*-2-*yl*]-*disulfane* (**5**).[33] Yield: 59.0 mg (33%), yellowish oil. R_f=0.19 for *tert*-butyl methyl ether/pentane=1:2 (v/v). 2-Methyl-5-phenylpentan-2-ol (**3c**). Yield: 30.5 mg (23%), yellowish oil. R_f=0.18 for *tert*-butyl methyl ether/pentane=1:2 (v/v).

*4.3.3. Conversion of 3-(1-methyl-1-phenylpent-4-enyloxy)-thiazolethione **1f**.* Alkenoxythiazolethione **1f** (308 mg, 748 μmol) and $BrCCl_3$ (1.49 g, 7.50 mmol) in C_6H_6 (9 mL) are treated according to procedure 4.3.1 (35 min reaction time). GC/MS analysis of the reaction mixture using *n*-decane as internal standard: *phenyl methyl ketone* (**7**) (3.3 mg, 4%). The reaction mixture was worked up as described in procedure 4.3.1. 5-*Bromomethyl*-2-*methyl*-2-*phenyltetrahydrofuran* (**13**).[42] Yield: 120 mg (63%), yellowish oil, 74/26-mixture of cis/trans-isomers. R_f=0.42 (*trans*) and 0.36 (*cis*) for pentane/Et_2O=10:1 (v/v). Anal. Calcd. For $C_{12}H_{15}OBr$ (255.15): C, 56.49; H, 5.93. Found: C, 56.14; H, 6.03. *trans*-5-*Bromomethyl*-2-*methyl*-2-*phenyltetrahydrofuran trans*-(**13**). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.56 (s, 3H), 1.87–1.97 (m, 2H), 2.09–2.16 (m, 1H), 2.22–2.29 (m, 1H), 3.45 (dd, 1H, J=10.0, 6.6 Hz), 3.54 (dd, 1H, J=10.0, 4.5 Hz), 4.26–4.30 (m, 1H), 7.21–7.24 (m, 1H), 7.31–7.34 (m, 2H), 7.37–7.38 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 30.1, 30.4, 36.2, 38.8, 77.8, 86.0, 124.5, 126.5, 128.2, 147.5. MS (EI) *m*/*z* 241 (56), 239 (56), 179 (1), 177 (1), 161 (6), 143 (7), 128 (7), 117 (13), 115 (13), 105 (100). *cis*-5-*Bromomethyl*-2-*methyl*-2-*phenyltetrahydrofuran cis*-(**13**). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.52 (s, 3H), 1.72–1.76 (m, 1H), 2.09–2.16 (m, 1H), 2.21–2.29 (m, 2H), 3.29 (dd, 1H, J=10.0, 7.5 Hz), 3.54 (dd, 1H, J=10.0, 5.4 Hz), 4.41–4.45 (m, 1H), 7.21–7.24 (m, 1H), 7.31–7.34 (m, 2H), 7.43–7.45 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 29.8, 30.7, 35.7, 39.2, 78.6, 85.7, 124.6, 126.5, 128.1, 148.1. MS (EI) *m*/*z* 241 (50), 239 (50), 161 (4), 143 (7), 128 (9), 117 (16), 115 (16), 105 (100). 5-(4-*Methoxyphenyl*)-4-*methyl*-2-(*trichlormethylsufanyl*)-*thiazole* **10**.[17] Yield: 119 mg (45%), yellowish crystals. R_f=0.14 for pentane/Et_2O=10:1 (v/v). 2-*Phenyl*-5-*hexen*-2-*ol*.[17] Yield: 119 mg (45%), yellowish crystals. R_f=0.14 for pentane/Et_2O=10:1 (v/v). 2-*Phenyl*-5-*hexene*-2-*ol*[65] (**3f**). Yield: 7.9 mg (6%), yellowish oil. R_f=0.07 for pentane/Et_2O=10:1 (v/v). 1,2-*Bis*-[5-(4-*methoxyphenyl*)-4-*methylthiaz*-2-*yl*]-*disulfane* (**5**).[33] Yield: 55.0 mg (15%), yellow oil.

Crystallographic data (excluding structure factors) for the structure of 3-(4-chlorocumyloxy)-alkoxythiazolethione **1e** in this paper have been deposited with the Cambridge Crystallographic

Data Centre as supplementary publication (CCDC 791992). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Supplementary data

Instrumentation, reagent specification, 3-alkoxythiazole-2(3*H*)-thione transformations, kinetic analyses, variable temperature NMR, N–O/C=S-bond length correlation, computational details and data. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.12.071.

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