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Self-Terminating Radical Cyclizations: How Are Thiyl Radicals Performing?

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Dedicated to Professor Bernd Giese on the occasion of his 70th birthday

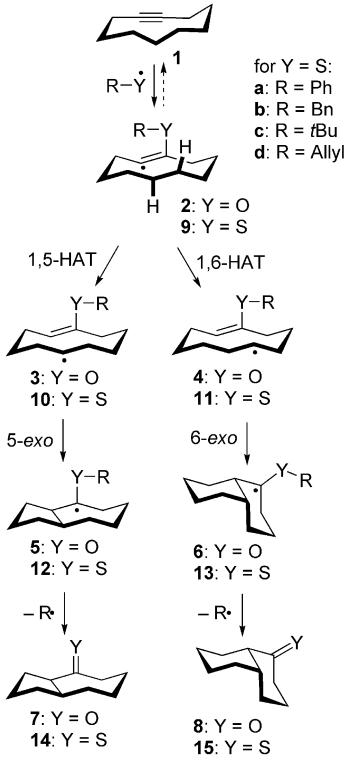
Keywords: Radicals / Radical cyclizations / Thiyl radicals / Alkynes / Computational chemistry / Reaction mechanisms

The performance of thiyl radicals RS$^{\cdot}$ in "self-terminating radical cyclisations" was explored. Using the medium-sized cyclodecyne (**1**) as model system, the reaction of PhS$^{\cdot}$ generated by photolysis of $(PhS)_2$ was used to study the intermolecular *S*-radical addition and subsequent intramolecular radical translocations. This reaction resulted in the formation of three stereoisomeric sulfides **17a** in very good yield, which all possess the bicyclo[4.4.0]decane framework with either *cis* and *trans* ring fusion. The isomeric bicyclo[5.3.0]decane framework was not formed. Product identification was performed using a combination of techniques, e.g. synthesis of authentic samples, X-ray analysis and computational studies of the potential energy surface, which also revealed valuable insight into the mechanism of this radical cyclisation cascade. The $(PhS)_2$/PhS$^{\cdot}$ system provides an efficient source for in situ generated thiols, which mediate reduction of the α-thio radical, e.g., **13a**→**17a**. The radical cascade initiated by the addition of BnS$^{\cdot}$, *t*BuS$^{\cdot}$ or AllylS$^{\cdot}$, respectively, to cycloalkyne **1** was typically terminated also by reduction, even in the absence of an apparent H-donor, and resulted in formation of various bicyclic and monocyclic thioethers. The desired "self-termination", e.g., β-fragmentation of the S–R bond in radical intermediate **12**/**13** and release of a stabilized radical R$^{\cdot}$, was only observed as minor reaction pathway in one particular instance where *t*BuS$^{\cdot}$ was generated by autoxidation of *t*BuSH. Computional studies showed that the different stereochemical outcome of the radical cyclizations involving *S*-radicals, compared to *O*- or *N*-centred radicals, could be attributed to the reversibility of the initial intermolecular *S*-radical addition to the C≡C triple bond in cycloalkyne **1**.

Introduction

Compared with intermolecular radical additions to alkenes, radical reactions initiated by addition of *C*- or heteroatom-centred radicals to alkynes have been much less explored. Self-terminating radical cyclisations are a recent concept in radical chemistry developed by our group, by which alkynes can be oxidized to carbonyl compounds under mild conditions in a radical cyclisation cascade initiated by the addition of *O*-centered radicals to C≡C triple bonds.[1] The suggested mechanism of this sequence, which is based both on experimental and computational studies,[1,2] is shown in Scheme 1 (with Y = O) for the generalized reaction of *O*-radicals RO$^{\cdot}$ using the medium-sized cycloalkyne **1** as example.

The initial radical addition is strongly exothermic and leads to the *Z*-configured vinyl radical **2**, which undergoes



Scheme 1.

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a transannularly favourable 1,5- or 1,6-hydrogen atom transfer (HAT), **2**→**3/4**, followed by *cis* selective 5-*exo* and 6-*exo* radical cyclizations, **3/4**→**5/6**, respectively. The sequence is terminated through β-fragmentation of the O–R bond in **5/6** by which the carbonyl group in the ketones *cis*-**7/8** is formed, with release of R˙.

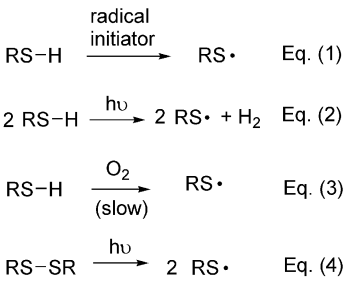
We have shown that this radical cyclization cascade can be performed with every major class of inorganic and organic *O*-centred radicals, such as, amongst others, nitrate, NO_3˙, or acyloxyl radicals, R′C(O)O˙, respectively.[1] Since the released R˙ has, so far, not been observed to propagate a radical-chain process, in these reactions RO˙ can be considered as synthon for *O* atoms in solution. We have recently found that self-terminating radical cyclizations can principally also be performed with *N*-centred aminium and amidyl radicals, where termination of the sequence occurs through a pathway involving a redox process.[3]

In our ongoing quest to extend the concept of self-terminating radical cyclizations to other heteroatom-centred radicals, we decided to systematically study the reaction sequence shown in Scheme 1 using *S*-centered thiyl radicals, RS˙, which are known to undergo (reversible) addition to π systems in alkenes or alkynes.[1d,4] Thus, if the substituent R in RS˙ would form a stabilized radical in the terminating β-fragmentation step, this sequence would represent a mild access to thioketones (for example **14/15** in the reaction involving **1**), which could be an interesting and mild alternative to the existing synthetic procedures that require harsh reaction conditions.[5]

In this work, we wish to report the results of our study on the performance of *S*-radicals in self-terminating radical cyclizations, namely phenylthiyl (PhS˙), benzylthiyl (BnS˙), *tert*-butylthiyl (*t*BuS˙) and allylthiyl radicals (AllylS˙), using the reaction with the well-explored cyclodecyne (**1**) as model system (Scheme 1).[1,3] In addition to experimental studies, extensive computational studies were performed to obtain detailed insight into the potential energy surface of these radical cyclizations and the reaction mechanism.

Results and Discussion

In this work, the *S*-radicals were generated in the presence of cycloalkyne **1**, as shown in Scheme 2, from the respective thiols through reaction with a radical initiator, Eq. (1), by photolysis, Eq. (2), or by autoxidation in the presence of excess oxygen, Eq. (3), and also through photochemical cleavage of disulfides, Eq. (4).



Scheme 2.

1. Reaction of Cyclodecyne (1) with PhS˙

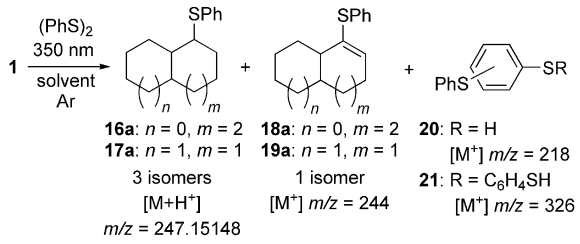
1.1 Optimization of the Reaction Conditions

Because of the fast enolization of C=S groups in thioketones, resulting in formation of an activated alkene moiety,[6] which could be attacked by radicals in an unwanted secondary reaction, we decided to study first the reaction of PhS˙ with **1** in order to explore whether the first three steps of the cyclization cascade, e.g. initial radical addition and the subsequent two transannular radical translocation steps (HAT and *exo* cyclization) are principally possible.[7] Because of the poor stability of Ph˙, the terminating homolytic S–Ph bond cleavage **12a/13a**→**14/15** (Scheme 1) was not expected to occur (and no enolization of the thiocarbonyl moiety), so that insight into the stereoselectivity of the radical cyclization could be obtained. The experiments were performed on analytical scale, where PhS˙ was generated through photolysis of diphenyl disulfide $(PhS)_2$ at λ = 350 nm according to procedures established for self-terminating radical cyclizations with photochemically generated *O*- and *N*-centred radicals.[1b,1d,3] Careful exclusion of residual oxygen was essential to avoid trapping of the *S*-radicals by O_2 prior to their addition to the alkyne.[4b,8] The reaction mixtures were directly analyzed by GC–MS and quantitative GC, using *n*-hexadecane as internal standard (for details see Exp. Sect. and Supporting Information).

In this reaction three isomeric compounds were formed as main products with approximately equal GC signal intensities. High Resolution Mass Spectrometry (HRMS) of the mixture revealed the protonated molecular ion, [M + H^+] at *m*/*z* = 247.15148 for all three compounds, which is in excellent agreement with the calculated value of *m*/*z* = 247.15150 for $C_{16}H_{22}S$ and suggests formal addition of PhSH to cycloalkyne **1**. Unfortunately, purification of the products obtained from a reaction performed on preparative scale only led to separation of two of the three sulfides, with both fractions being contaminated with the third product, which suggests that these compounds must be structurally very similar. Although DEPT-^{13}C NMR analysis of both fractions clearly revealed that all products possess a bicyclic carbon-framework,[9] it was not possible to determine from these mixtures the ring size and stereochemistry at the bridging carbons in the various compounds. In fact, product identification turned out to be unexpectedly challenging and was only possible using a combination of different experimental and computational techniques, which will be described in section 1.2.

Thus, in order to simplify the following discussion, the products were tentatively assigned as isomers of the bicyclic sulfides **16a/17a** (Scheme 3), which could be formed through reduction of the α-thio radical intermediates **12a/13a** through a yet unknown H atom donor. Evidence supporting the structures in Scheme 3 will be presented below.

Table 1 compiles the experimental conditions and combined yields of the products **16a/17a**, determined by quantitative GC.



Scheme 3.

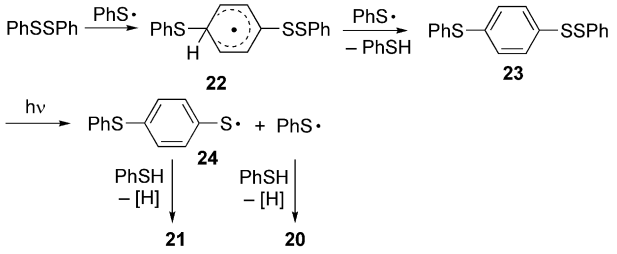
Table 1. Experimental conditions and results for the reaction of photochemically generated PhS· with cyclodecyne (**1**).[a]

Entry	[**1**] /mM	[$(PhS)_2$] /mM	Solvent[b]	Irradiation time /h	% Yield[c] **16a** + **17a**
1	10[d]	50	Me_2CO	6.5	70
2	10[d]	50	MeCN	6	41
3	10[d]	50	C_6H_6	6	50
4	10[d]	50	*c*-C_6H_{12}	6.5	48
5	20[d]	50	C_6H_6	17.75	57
6	10[d]	25	C_6H_6	17.75	67
7	10	5[d]	C_6H_6	6	34

[a] Irradition at λ = 350 nm. [b] In 5 mL. [c] Combined quantitative GC yield with respect to alkyne **1**, using *n*-hexadecane as internal standard (see text). [d] Complete reactant consumption.

Assuming quantitative conversion of the disulfide according to $(PhS)_2 \rightarrow 2$ PhS·, initial experiments were performed using a ten-fold excess of PhS· {e.g., [$(PhS)_2$]/[**1**] = 5} in order to ensure complete consumption of alkyne **1**. Under these conditions, after 6–6.5 hours of irradiation in different solvents, combined yields of 41–70% were obtained (entries 1–4), with the highest yield being found in acetone (entry 1), whereas the reaction in acetonitrile performed poorest (entry 2). The reaction in benzene was selected to study the influence of irradiation time, reactant ratio and concentration on the reaction outcome. Using [PhS·]/[**1**] = 5, a drastically elongated irradiation led to a slight improvement of the yield (entry 5), but, most importantly, this experiment also showed that the sulfides **16a/17a** were photochemically stable under these conditions. Interestingly, when the total reactant concentration was halved, the yield of sulfides **16a/17a** rose to 67% (entry 6). This observation is consistent with earlier findings where related photo-initiated radical reactions were found to perform better in not too concentrated solutions.[1b] With [PhS·]:[**1**] = 1 consumption of **1** was incomplete whereas the disulfide was fully consumed (entry 7), which can be taken as indication for side reactions of PhS· (see below).

In addition to the bicyclic saturated sulfides **16a/17a**, the reaction of PhS· with **1** led also to formation of a very minor by-product possessing a [M^+] at *m/z* = 244. Although this could be tentatively assigned as unsaturated bicyclic sulfide of type **18a/19a** (Scheme 3), which could result from disproportionation of the α-thio radicals **12a/13a**, no attempts were made to further consolidate its structure. In addition to this, a number of aromatic thiols were also formed, such as PhSH and di- and trisulfides of type **20/21**. These products were assigned by GC/MS through their respective [M^+] signals (in the case of PhSH also through comparison with reference EI-mass spectra[10]), and characteristic fragment ions (see Supporting Information). PhSH, **20** and **21** are formed through light-induced coupling of $(PhS)_2$, as was verified by an independent experiment, where a solution of $(PhS)_2$ in benzene was irradiated in the absence of cycloalkyne **1**.[11] The suggested mechanism for formation of these thiols is outlined in Scheme 4.



Scheme 4.

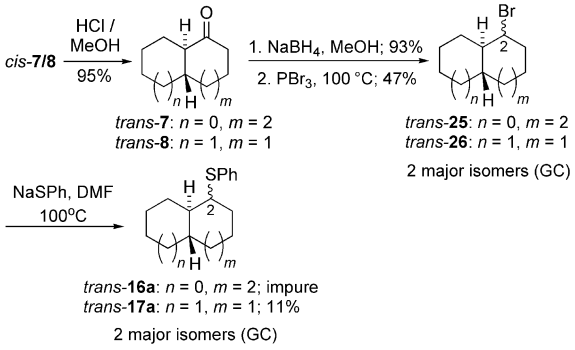
Radical addition of PhS· at $(PhS)_2$ (exemplary shown for *para* attack) leads to the intermediate radical adduct **22**, which is re-aromatized through HAT by PhS·. The resulting trisulfide **23** likely undergoes photochemical cleavage of the disulfide bond, leading to *S*-radicals **24** and PhS·. Their subsequent trapping through addition to PhSH, followed by re-aromatization yields sulfides **20** and **21**. We suggest that this light-induced formation of thiols PhSH, **20** and **21** provides an in situ source for H atoms, which mediate efficient reduction of the α-thio radicals **12a/13a** to sulfides **16a/17a**. We will discuss stereochemical aspects of this process in detail below. This unexpected side reaction of PhS· with $(PhS)_2$ explains, why an excess of $(PhS)_2$ was required to drive consumption of cycloalkyne **1** to completion.

1.2 Identification of the Bicyclic Sulfides 16a/17a

Because isolation of the isomeric sulfides **16a/17a** and their identification by spectroscopic methods was not possible, their structures were determined using a combination of techniques, such as independent synthesis of authentic samples, chemical modification for X-ray structural analysis and computational studies.

a) Identification using authentic samples: In principle, the bicyclic framework in **16a/17a** could be either *cis* or *trans* fused. Our synthetic route to the *trans* sulfides *trans*-**16a/17a** is outlined in Scheme 5.

The self-terminating radical cyclization of cycloalkyne **1** with electrogenerated NO_3· was used to access the required [4.4.0]- and [5.3.0]-bicyclic framework, and the ketones were obtained with a GC ratio of *cis*-**7**:*cis*-**8** = 2.3 (see Scheme 1).[1a] This mixture was isomerized to the respective *trans* configured bicyclic ketones *trans*-**7/8** through treatment with hydrochloric acid in methanol. Reduction of the carbonyl group in *trans*-**7/8** with sodium borohydride oc-



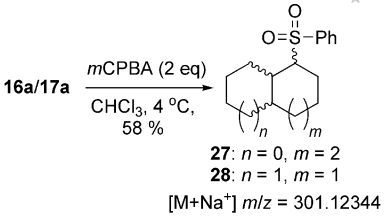
Scheme 5.

curred in a non-diastereoselective fashion, and was followed by bromination of the resulting mixture of four isomeric alcohols (not shown). The latter reaction proceeded with a moderate combined yield of 47% and gave only two isomeric bromides (suggesting that the other two isomers obviously underwent decomposition), which were not separated. Since GC analysis revealed a peak area ratio of 2.2 for these two bromides, which is similar to the ratio of ketones **7/8** in the first step of this reaction sequence, it was concluded that the product mixture contained both the [4.4.0] and the [5.3.0]-bicyclic framework. In the final step, the mixture of these two bromides, *trans*-**25/26**, was converted into a mixture of the respective thioethers *trans*-**16a/17a** by treatment with thiophenolate, which was confirmed by their respective GC–MS signals showing an $[M^+]$ at m/z = 246. The minor isomer *trans*-**17a**, which possessed the [4.4.0]-bicyclic framework, could be isolated by column chromatography in 11% yield, but the stereochemistry at C-2 could not be assigned. In contrast to this, the major isomer possessing the [5.3.0]-bicyclic framework, *trans*-**16a**, could not be obtained in pure form, but the quality of the sample was satisfactory for the subsequent analytical experiments.

GC co-injection of these two independently synthesized sulfides *trans*-**16a** and *trans*-**17a**, respectively, with the sulfide mixture **16a/17a** isolated from the reaction of PhS$^{\cdot}$ with cycloalkyne **1** revealed unequivocally that *trans*-**17a** is a product of this reaction. On the other hand, the isomeric sulfide *trans*-**16a** possessing the *trans*-configured [5.3.0]-bicyclic framework was not formed.

Unfortunately, synthesis of the respective *cis*-fused thioethers *cis*-**16a/17a** through a reaction sequence similar to that shown in Scheme 5 (without the *cis*/*trans* isomerization of *cis*-**7/8**) was not possible, which illustrates the difficulty to access complex *cis* fused bicyclic frameworks using conventional ionic methods, compared to radical cyclizations.

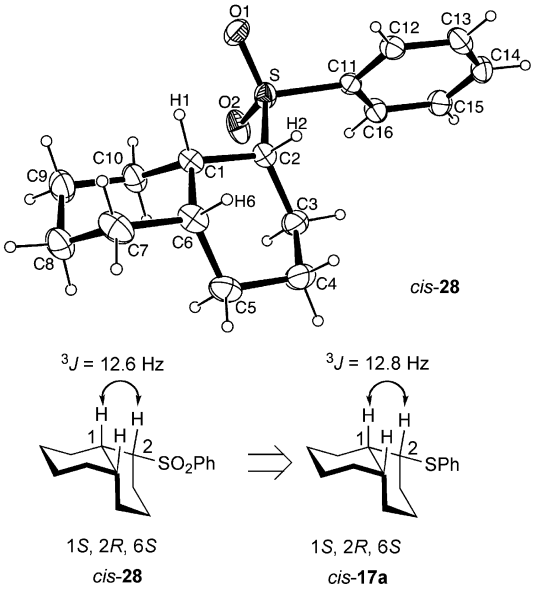
b) Identification using X-ray diffraction analysis: Because of the limited synthetic availabiltiy of authentic samples, product identification was also pursued using single-crystal X-ray diffraction analysis. For this, a mixture of sulfides **16a/17a**, which could be enriched in one isomer (relative GC peak area = 75%) by chromatography, was oxidized with *meta*-chloroperoxybenzoic acid (*m*CPBA) to give the sulfone mixture **27/28** (Scheme 6).[12]



Scheme 6.

HRMS of this mixture, which contained, as expected, one major product (relative GC peak area = 85%), revealed the sodiated molecular ion, $[M + Na^+]$, at m/z = 301.12344, which was in good agreement with the calculated value of m/z = 301.12327 for $C_{16}H_{22}O_2S$.

The major compound could be separated by crystallization and analysed by X-ray diffraction analysis. This revealed a *cis*-bicyclo[4.4.0]decane framework with the sulfone group at C2 in equatorial position and *trans* to the proton H1 (*cis*-**28**, Scheme 7). ^{1}H NMR was used to confirm that the oxidation shown in Scheme 6 did not change the absolute configuration at C2. Thus, the signal of H2 in *cis*-**28** at δ = 2.94 ppm revealed a coupling constant of ^3J = 12.6 Hz associated with the doublet component, which is characteristic for axial-axial interactions.[9] In the sulfide mixture **16a/17a**, which was used to synthesize *cis*-**28**, the H2 signal of the major isomer at δ = 3.26 ppm showed a practically identical coupling constant of ^3J = 12.8 Hz associated with the doublet component (Scheme 7). It can therefore be concluded that *cis*-**17a**, which possesses a 1*S*,2*R*,6*S* configuration at the various stereocentres, was also formed as product in the reaction of PhS$^{\cdot}$ with **1**.



Scheme 7.

c) Computational modeling: Because experimental methods only revealed the structure of two of the sulfides formed in the reaction of PhS$^{\cdot}$ with **1**, of which one showed a so far unprecedented (with regard to self-terminating radical

cyclizations) *trans* fused bicyclic framework,[13] we used computational methods to calculate the potential energy surface of the reaction of PhS· with cycloalkyne **1**, in order to obtain insight into the reaction mechanism and, based on these data, to predict the so far unassigned product. The calculations were carried out with the hybrid density functional BHandHLYP[14] in combination with the 6-311G** or cc-pVTZ basis set, respectively. These methods have been shown in our previous work on related systems to give reliable energy data.[3] Energy values are reported in kJ mol^{-1}, with zero-point vibrational energy correction (ZPC) included. Further details are given in the Experimental Section and Supporting Information.

We first explored the initial radical addition, transannular HAT and *exo* cyclization step (according to Scheme 1, with Y = S and R = Ph). The calculated activation barriers ($E^{\ddagger}$) and reaction energies (ΔE) are compiled in Table 2.

Table 2. Calculated activation barriers $E^{\ddagger}$ and reaction energies ΔE for the reaction of PhS· with cycloalkyne **1** (BHandHLYP/6-311G**).[a]

Entry	Reaction	$E^{\ddagger}$	ΔE
I. Formation of *cis*-fused bicyclic framework			
1	Addition: [PhS· + **1**][b] → **9a**	50.7	16.8
2	1,5-HAT: **9a** → **10a**	41.6	–52.3
3	5-*exo*: **10a** → *cis*-**12a**	22.6	–74.1
4	1,6-HAT: **9a** → **11a**	27.6	–41.3
5	6-*exo*: **11a** → *cis*-**13a**	20.6	–118.7
II. Formation of *trans*-fused bicyclic framework[c]			
6	Addition: [PhS· + **1**][b] → **9a***	50.7	19.6
7	1,5-HAT: **9a*** → **10a***	46.6	–44.5
8	5-*exo*: **10a*** → *trans*-**12a**	78.0	–95.1
9	1,6-HAT: **9a*** → **11a***	46.1	–32.1
10	6-*exo*: **11a*** → *trans*-**13a**	29.0	–128.9

[a] Energies in kJ mol^{-1}, including ZPC. [b] Via association complex of PhS· and **1**. [c] Cyclization cascade proceeds through conformational isomers of radical intermediates **9a**–**11a**, e.g. **9a***, **10a*** and **11a*** (see text).

Addition of PhS· to **1** proceeds via an association complex of both reactants and leads to the *Z* configured vinyl radical **9a** in a reversible and endothermic reaction (entry 1). Because of transannular ring strain formation of an *E* configured vinyl radical is energetically unfavourable (not shown). The reverse fragmentation of **9a** is associated with $E^{\ddagger}$ = 33.9 kJ mol^{-1} and ΔE = –16.8 kJ mol^{-1}. However, this fragmentation is competing with the 1,5- or 1,6-HAT processes, respectively, which both are strongly exothermic and associated with moderate to low activation barriers (entries 2 and 4). The subsequent 5-*exo* or 6-*exo* cyclisations, respectively, proceed in a *cis* selective fashion and are both fast and highly exothermic (entries 3 and 5), which could be explained with mesomeric and hyperconjugation stabilization effects[15] of the unpaired electron by the adjacent sulfur atom in *cis*-**12a/13a**. According to the computational predictions, the pathway leading to the α-thio radical *cis*-**13a** possessing the [4.4.0]-framework is both kinetically and thermodynamically significantly more preferable, than formation of the [5.3.0] framework in *cis*-**12a**. This supports our experimental finding of sulfide *cis*-**17a** as a product in the reaction of PhS· with cycloalkyne **1**, which results from reduction of α-thio radical *cis*-**13a**.

Because of the flexibility of the ten-membered ring system, the various radical intermediates possess a number of different low-energy conformations. Indeed, calculations of the potential energy surface leading to the *trans* configured α-thio radical intermediates *trans*-**12a/13a**, revealed conformational isomers of the vinyl radical, e.g. **9a***, and the secondary radicals, e.g. **10a*/11a*** (see Supporting Information). These conformers could principally arise from ring-flips in **9a** and/or **10a/11a**, respectively. However, computations showed also that such ring-flips are associated with high activation barriers of some 80 kJ mol^{-1} for **9a** → **9a*** and ca. 91 and 98 kJ mol^{-1} for **10a** → **10a*** and **11a** → **11a***, respectively, which are caused by strain in the medium-sized ring. Thus, these slow ring-inversions cannot compete with the reverse fragmentation or transannular HAT in vinyl radical **9a**, or the respective *exo* cyclisations **10a** → *cis*-**12a** and **11a** → *cis*-**13a** (entries 3 and 5). We therefore believe that the experimentally observed formation of a *trans*-fused ring system is due to the reversibility of the PhS· addition to the C≡C triple bond in **1**, which could lead directly to **9a*** (entry 6).

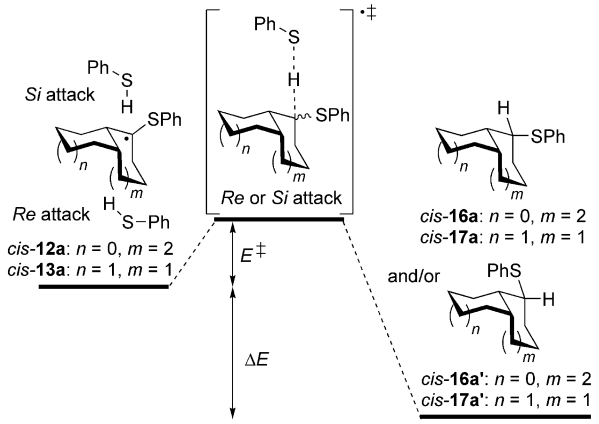
The computed $E^{\ddagger}$ and ΔE data for the reaction steps leading to *trans*-**12a/13a** (see Table 2) show that the transannular radical translocation in **9a*** is associated with a slightly (1,5-HAT), or significantly (1,6-HAT) higher activation barrier, respectively, compared to the analog processes in the conformational isomer **9a**. Interestingly, the 5-*exo* cyclization **10a*** → *trans*-**12a** requires a considerable activation energy of 78 kJ mol^{-1} (entry 8). Thus, although this pathway is exothermic (ΔE = –95.1 kJ mol^{-1}), it is kinetically unfavourable. This is experimentally supported by the fact that the *trans* configured [5.3.0]-bicyclic framework, e.g. *trans*-**16a**, was not formed in the reaction of PhS· with cycloalkyne **1**. On the other hand, the 6-*exo* cyclization leading to *trans*-**13a** is associated with a low activation barrier of 29 kJ mol^{-1} and is exothermic (entry 11). Thus, according to the computational data, of the possible *trans* bicyclic frameworks, only formation of the [4.4.0]-bicyclic system is both kinetically and thermodynamically favourable. This is in excellent agreement with the experimental finding of sulfide *trans*-**17a** as reaction product.

It is worth to note that the kinetic preference for formation of the bicyclo[4.4.0]-framework in the reaction of *S*-radicals with cycloalkyne **1** differs from self-terminating radical cyclizations initiated by addition of *O*- or *N*-centred radicals to **1**. Both experimental and computational studies have clearly shown that the latter are much less regioselective and always lead to formation of both isomeric bicyclic frameworks. This clearly indicates that the nature of the radical initiating the radical cyclization cascade has a strong influence on the reaction pathway.[1–3]

In order to assign the structure of the third sulfide formed in the reaction of PhS· with cycloalkyne **1**, we next performed calculations to explore the stereoselectivity of the reduction of the α-thio radical intermediates *cis*-**12a/**

13a → *cis*-**16a/17a** using PhSH as model H donor. Reduction of the isomeric *trans*-**12a/13a** was not explored, since (i) the computations predicted, in agreement with experimental findings, that formation of *trans*-**12a** is kinetically not favourable, and (ii) the sulfide *trans*-**17a**, resulting from reduction of *trans*-**13a**, was already identified as reaction product (albeit with a non-defined stereochemistry at C2).

The α-thio radical intermediates *cis*-**12a/13a** exhibit a nearly planar geometry at the carbon atom bearing the unpaired electron, and reduction could principally occur from both faces. This would lead to the diastereomeric [5.3.0]-bicyclic sulfides *cis*-**16a** (after *Si* attack) and *cis*-**16a′** (after *Re* attack) and/or the [4.4.0]-bicyclic sulfides *cis*-**17a** (after *Si* attack) and *cis*-**17a′** (after *Re* attack), respectively (Scheme 8). The calculated activation barriers ($E^{\ddagger}$) and reaction energies (ΔE) are given in Table 3.



Scheme 8.

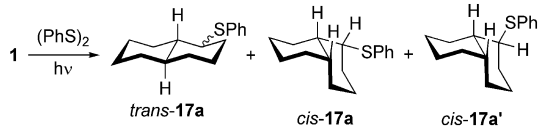
Table 3. Calculated activation barriers $E^{\ddagger}$ and reaction energies ΔE for the reduction of *cis*-**12a/13a** by PhSH (BHandHLYP/6-311G**).[a]

Entry	Reaction[b]	$E^{\ddagger}$	ΔE
1	*Si* attack: *cis*-**12a** → *cis*-**16a**	37.2	–50.4
2	*Re* attack: *cis*-**12a** → *cis*-**16a′**	31.1	–38.1
3	*Si* attack: *cis*-**13a** → *cis*-**17a**	21.8	–60.9
4	*Re* attack: *cis*-**13a** → *cis*-**17a′**	26.6	–57.9

[a] Energies in kJ mol^{-1}, including ZPC. [b] Via association complexes of *cis*-**12a/13a** and PhSH, and *cis*-**16a**$^{(\prime)}$/**17a**$^{(\prime)}$ and PhS$^{\cdot}$.

In general, the proposed HAT is energetically highly feasible. As expected, products possessing the SPh substituent in equatorial position, which are formed through reduction from the *Si* face, are thermodynamically more favourable, although the energy difference is very small for the diastereomeric sulfides *cis*-**17a/17a′**. Reduction of the α-thio radicals *cis*-**12a** is associated with a slightly higher $E^{\ddagger}$ by 5 (*Re*-face attack) to 15 (*Si*-face attack) kJ mol^{-1}, compared to *cis*-**13a**. This could be explained by an increase in strain in the seven-membered ring of the former associated with the transition from an sp^2 hybridized radical centre to the sp^3 carbon in the closed-shell product. *Si*-face reduction of *cis*-**12a** requires a 6.1 kJ mol^{-1} higher activation energy than reduction from the *Re* face. Interestingly, the opposite is the case for the reduction of the isomeric *cis*-**13a**, where attack from the *Re* face requires an activation energy, which is ca. 5 kJ mol^{-1} higher than the *Si* face attack.

When these results are now combined with the data shown in Table 2, where radical intermediate *cis*-**12a** is thermodynamically less stable by more than 44 kJ mol^{-1} compared to *cis*-**13a** (entry 3 vs. 5), formation of sulfide *cis*-**17a** possessing the [4.4.0]-bicyclic framework through *Si*-face reduction of *cis*-**13a** should be the kinetically and thermodynamically most favourable pathway. This is in excellent agreement with the experimental finding of this compound as reaction product. In addition to this, the agreement between experiment and computational prediction that *trans*-**17a** should is formed, but not its [5.3.0]-bicyclic isomer *trans*-**16a**, justifies our conclusion that the computational data are reliable and can be used to predict the nature of the third product. Based on this, we conclude that the *cis* configured sulfide *cis*-**17a′** possessing a [4.4.0] framework and an axial SPh substituent at C2, which results from reduction of *cis*-**13a** from the *Re* face, must also be formed in the reaction of PhS$^{\cdot}$ with cycloalkyne **1**. All identified bicyclic sulfides in this reaction are shown in Scheme 9.



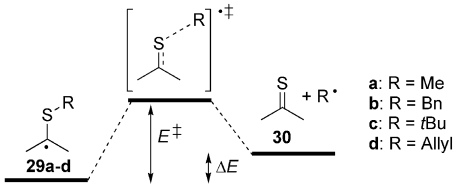
Scheme 9.

2. Reaction of Cyclodecyne (1) with BnS$^{\cdot}$, *t*BuS$^{\cdot}$ and AllylS$^{\cdot}$

In the previous section, we have shown that *S*-radical addition to the C≡C triple bond and the subsequent transannular HAT and cyclisation steps do readily occur. We next explored, whether the entire self-terminating radical cyclisation cascade can be performed with *S*-radicals possessing a substituent R, which could be released as R$^{\cdot}$ through homolytic β-fragmentation of the S–R bond in the α-thio radical intermediates **12/13** (Scheme 1).

2.1 Computational Studies on the β-Scission of the S–R Bond

In order to gain theoretical insight into the energetics of the β-fragmentation step in dependence on the nature of R, computations of the potential energy surface were performed using α-thio radicals **29a–d** as simplified model systems (Scheme 10). The calculated activation barriers ($E^{\ddagger}$) and reaction energies (ΔE) are given in Table 4.



Scheme 10.

Table 4. Calculated activation barriers $E^{\ddagger}$ and reaction energies ΔE for the β-fragmentation in **29a–d** (BHandHLYP/cc-pVTZ).[a]

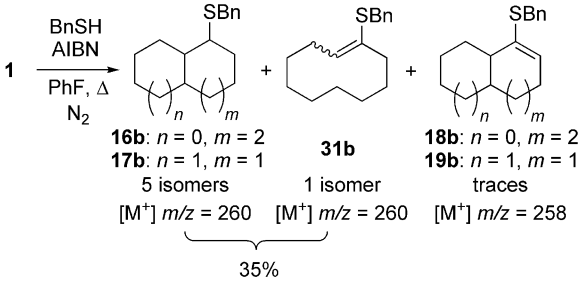
Entry	Reaction[b]	$E^{\ddagger}$	ΔE
1	**29a** → **30** + Me$^{\cdot}$	100.0	84.5
2	**29b** → **30** + Bn$^{\cdot}$	54.8	21.3
3	**29c** → **30** + *t*Bu$^{\cdot}$	56.0	46.0
4	**29d** → **30** + Allyl$^{\cdot}$	53.6	11.5

[a] Energies in kJ mol^{-1}, including ZPC. [b] Via association complex of **30** and R$^{\cdot}$.

According to the computations, β-fragmentation in **29a–d** is endothermic in all cases. As expected, release of the unstabilized Me$^{\cdot}$ (entry 1) is both kinetically and thermodynamically highly unlikely, compared to release of Bn$^{\cdot}$, *t*Bu$^{\cdot}$ and Allyl$^{\cdot}$, respectively. For the latter three, the computed $E^{\ddagger}$ values are very similar and around 55 kJ mol^{-1}, but the reaction energies vary. Quite obviously, resonance stabilization in the released R$^{\cdot}$ renders β-fragmentation thermodynamically more favourable than inductive stabilization (entries 2 and 4 vs. 3). With regards to self-terminating radical cyclizations, we envisaged that, although as an isolated step the homolytic S–R bond cleavage is endothermic, the high overall exothermicity associated with formation of the α-thio radical intermediates **12/13** through the radical cyclization cascade (see Table 2), should outweigh the energy required for the final radical fragmentation, when R$^{\cdot}$ = Bn$^{\cdot}$, *t*Bu$^{\cdot}$ or Allyl$^{\cdot}$, respectively.

2.2 Reaction of Cyclodecyne with BnS$^{\cdot}$

BnS$^{\cdot}$ was generated, in analogy to literature procedures,[16] from BnSH in refluxing fluorobenzene in the presence of excess cycloalkyne **1** using 2,2-azobisisobutyronitrile (AIBN) as initiator (Scheme 11).



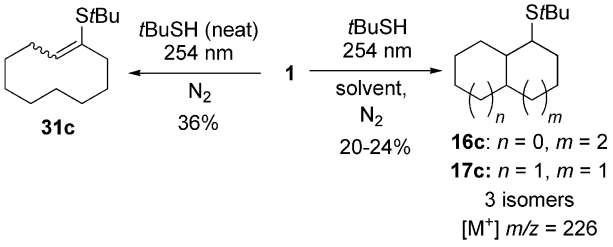
Scheme 11.

To our surprise, GC/MS analysis of the reaction mixture revealed no formation of the expected thioketones **14/15**. Instead, apart from traces of $(BnS)_2$, which was identified by co-injection with an authentic sample and results from dimerisation of BnS$^{\cdot}$, six products with [M^{+}] at *m*/*z* = 260 (corresponding to a molecular formula $C_{17}H_{24}S$) were found in 35% combined GC yield. Since five of these showed EI-MS fragmentation pattern analog to that of the bicyclic sulfides **16a/17a** formed in the reaction of PhS$^{\cdot}$ with **1**, it is suggested that these compounds could be stereoisomeric bicyclic sulfides **16b/17b**. The EI-MS fragmentation spectrum of the remaining isomer suggests a more stable connection between the benzylthio moiety and the cycloalkyl ring, which could be taken as indication for formation of the ten-membered thioenol ether **31b**, in analogy to the reaction of **1** with *t*BuS$^{\cdot}$, which will be described in section 2.3.

Although we did not further pursue identification of the reaction products, it appears that under the experimental conditions the radical cyclisation cascade was terminated by reduction of various radical intermediates, with BnSH being the likely source of H. Whereas formation of the bicyclic sulfides **16b/17b** results from reduction of the α-thio radical intermediates **12b/13b**, the cyclodecene derivative **31b** could be formed through trapping of the initially formed vinyl radical **9b** and/or the secondary radicals **10b/11b** (see Scheme 1). It should be noted that in this reaction also trace amounts of a product with [M^{+}] at *m*/*z* = 258 were formed, which can be taken as indication for an unsaturated bicyclic sulfide **18b/19b** that could result from disproportionation of radical intermediates **12b/13b**.

2.3 Reaction of Cyclodecyne with *t*BuS$^{\cdot}$

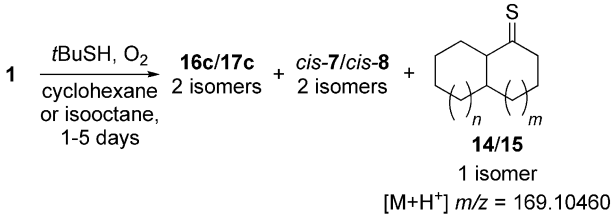
*t*BuS$^{\cdot}$ was generated in the presence of **1** by photolysis of neat *t*BuSH at λ = 254 nm, Equation (*2*).[17] Under these conditions, however, only formation of the unsaturated sulfide **31c** in 36% isolated yield (Scheme 12) occurred, which was confirmed by standard characterization techniques. Thioketones **14/15** were not found.



Scheme 12.

Since vinyl sulfide **31c** obviously results from rapid reductive trapping of the respective vinyl radical **9c** and/or the secondary radicals **10c/11c** by excess *t*BuSH, the reactions were also performed in either acetonitrile or cyclohexane as solvent, respectively, with [*t*BuSH]:[**1**] = 10. Under these conditions, however, trapping of radical intermediates by HAT could also not be avoided, but was at least delayed to the stage of the thermodynamically most stable radical intermediates, e.g. the α-thio radicals **12c/13c**. Three isomeric products were formed in 20–24% GC yield, which were tentatively assigned as sulfides **16c/17c** based on their respective molecular ions [M^{+}] at *m*/*z* = 226 (corresponding to $C_{14}H_{26}S$), and their EI-MS fragmentation pattern, which showed strong analogies with the fragmentation pattern of sulfides **16b/17a**,**b** formed in the reaction of PhS$^{\cdot}$ or BnS$^{\cdot}$, respectively, with **1**. Formation of thioketones **14/15** did not occur. The comparably low yield of **16c/17c** may be due to partial loss of the volatile *t*BuSH as a result of the nitrogen gas stream, which was required to ensure absence of O_2.

We also explored the reaction of **1** with *t*BuS˙ generated by slow autoxidation of *t*BuSH (Scheme 3).[18] Using [*t*BuSH]:[**1**] = 4 under an atmosphere of O_2 in O_2-saturated solvent, GC–MS analysis after a reaction time of 5 days revealed, besides formation of small amounts of $(tBuS)_2$ (identified by co-injection with an authentic sample), sulfides **16c/17c** as major products and trace amounts of the ketones *cis*-**7/8**, which were identified by co-injection with an authentic sample (Scheme 13).

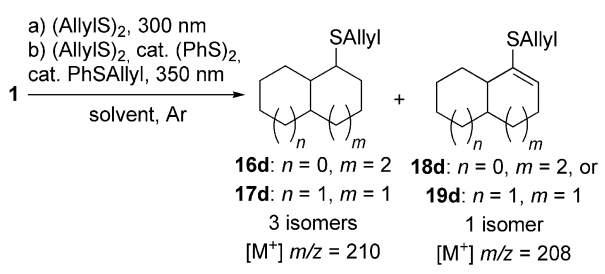


Scheme 13.

In addition to this, small amounts of a new compound were formed, which showed the protonated molecular ion [M + H$^+$] at *m*/*z* = 169.10460 in the ESI-HRMS, which corresponds to $C_{10}H_{16}S$ (calcd. 169.10455).[19] Also, a fragmentation pattern similar to that of the bicyclic ketones *cis*-**7/8** was observed in the EI-mass spectrum of this compound, which suggests a similar molecular structure. We therefore believe that this compound is the desired thioketone **14/15** (and/or its tautomeric thioenol). Unfortunately, we were not able to isolate and characterize this product. Also, all attempts to synthesise an authentic sample through an independent pathway were unsuccessful.[20]

2.4 Reaction of Cyclodecyne with AllylS˙

In order to avoid the unwanted reduction of the α-thio radical intermediates **12/13**, the reaction of AllylS˙ with excess cycloalkyne **1** was explored using direct photolysis of $(AllylS)_2$ or photolysis of $(AllylS)_2$ in the presence of catalytic amounts (5%) of $(PhS)_2$ and phenyl allyl sulfide, respectively,[20] to generate AllylS˙. However, independent of the radical source, it turned out that neither variation of reaction time (3.5–18.5 h), solvent (benzene, acetonitrile, cyclohexane), batch or syringe addition of the *S*-radical precursor(s), and reactant ratios did have a significant influence on the outcome, and formation of desired thioketones **14/15** was never observed (Scheme 14). Instead, GC–MS analysis of the reaction mixture indicates formation of three isomeric bicyclic sulfides **16d/17d** in very moderate combined GC yields of around 10%, in addition to small amounts of one unsaturated bicyclic alkene (all assignments are based on the EI-MS fragmentation pattern and comparison with the products of the other reactions in this study).



Scheme 14.

Thus, although no obvious hydrogen donor (e.g., a thiol) was present in these reactions, it appeared that, still, reduction of the intermediate α-thio radical **12d/13d** occurred at a faster rate than homolytic S–Allyl bond fragmentation. Although we have not further explored the nature of the reducing agent in this reaction, it may be suggested that the allylic hydrogen atoms in the precursor for AllylS˙ could be abstracted by **12d/13d**. In addition to this, to a minor extent disproportionation according to **12d/13d** → **16d/17d** + **18d/19d** could also occur.

Conclusions

In this work, we have explored whether self-terminating radical cyclizations can be performed with *S*-radicals RS˙. Using photo-generated PhS˙ as a model system for *S*-radicals, for which the terminating homolytic S–Ph bond fragmentation in the intermediate α-thio radicals **12a/13a** should not be possible, we were able to show that thiyl radicals readily undergo addition to the C≡C triple bond in cycloalkyne **1**, followed by transannular HAT and *exo* cyclization. Although the initial radical addition is reversible and endothermic, computational studies revealed that the subsequent radical translocation steps are very fast and exothermic, thus forcing the reaction to proceed. This radical cyclization resulted in exclusive formation of stereoisomeric α-thio radicals **13a** possessing a [4.4.0]-bicyclic framework, which were reductively trapped to give three stereoisomeric sulfides *cis*/*trans*-**17a**. The latter were identified using a combination of experimental and computational methods. Interestingly, reduction of the radical intermediates **13a** appeared to be a highly efficient process, although the reaction was performed in the absence of an apparent H atom donor. It turned out that the $(PhS)_2$/PhS˙ system provides an efficient source for in situ generated thiols, which mediate reduction of **13a**.

Our studies on the reactions of cycloalkyne **1** with thiyl radicals BnS˙, *t*BuS˙ and AllylS˙, which were all possessing stablized radical leaving groups R˙, e.g. Bn˙, *t*Bu˙ and Allyl˙, respectively, have shown that a terminating homolytic fragmentation of the S–R bond in the α-thio radicals **12b–d/13b–d** can obviously not compete with direct reduction of the latter through *inter*molecular HAT. Even when the reactions were performed in the absence of a specific H donor, the "tug of war" in **12b–d/13b–d** between the slightly (R = Bn, Allyl) or considerably (R = *t*Bu) endothermic unimolecular S–R bond fragmentation on the one hand and the bimolecular HAT to give **16b–d/17b–d** on the other hand was always decided in favour of the latter. In the reaction of cycloalkyne **1** with *t*BuS˙ performed by irradiation in neat *t*BuSH, reductive trapping occurred already at the stage of the vinyl radical **9c** and/or the secondary radicals **10c/11c**,

respectively, to give the cyclodecene derivative **31c**, whereas **16c/17c** were not formed. Thus, it appears that thiols are excellent compounds for studying the kinetics of the transannular radical translocation steps in self-terminating radical cyclizations, and we will explore this in detail in our future work.

Based on these findings, we have to conclude that self-terminating radical cyclizations in the "original" sense cannot be performed with *S*-radicals. However, the sequence consisting of intermolecular *S*-radical addition to alkynes, followed by transannular radical translocation and termination through reduction is energetically highly favourable and offers exciting opportunities for the synthesis of complex bicyclic frameworks possessing a thioether moiety in a regioselective fashion in only few steps. Of the various *S*-radicals studied in this work, the reaction of cycloalkyne **1** with BnS$^{\cdot}$, *t*BuS$^{\cdot}$ and AllylS$^{\cdot}$, respectively, was considerably slower, and the cyclization cascade apparently less efficient, than with PhS$^{\cdot}$.

Our experimental and computational studies revealed some remarkable differences between reactions of *S*-centred radicals compared to *O*- and *N*-centred radicals, respectively. Thus, in contrast to self-terminating radical cyclizations involving *O*- and *N*-centred radicals, where only products with *cis*-fused bicyclic frameworks were obtained,[1–3] the reactions involving *S*-centred radicals leads also to *trans*-configured bicyclic products, which is highly unusual for intramolecular radical cyclizations resulting in formation six-membered ring systems.[21] According to our calculations, this is caused by the reversibility of the initial *S*-radical addition to the C≡C triple bond in cycloalkyne **1**. This leads to different conformational isomers of vinyl radical **9**, which can either undergo a *cis* or a *trans* selective radical translocation/cyclization, respectively.

Another remarkable difference is the apparent regioselectivity of the transannular radical translocation steps following initial addition of the *S*-radical to the C≡C triple bond in cycloalkyne **1**. Whereas the reactions involving *O*- and *N*-centred radicals always give a mixture of products possessing either a [4.4.0]- or [5.3.0]-bicyclic framework (due to similar rates of the 1,5- and 1,6-HAT),[1–3] in the reactions with *S*-centred radicals (or at least in the case of PhS$^{\cdot}$, where unequivocal identification of the major products was possible), the transannular radical cascade leads exclusively to the [4.4.0]-bicyclic framework. Although we have currently no clear explanation for the unexpected preference of the 1,6-HAT compared to the alternative 1,5-HAT in the radical cyclizations initiated by *S*-radicals, it may be suggested that these different regioselectivites are caused by differences in the electron density at the C=C double bond in the respective vinyl radicals. Computational studies are currently underway in our group to explore this hypothesis further.

Experimental Section

Computational Methods: Geometry optimizations were performed with the Gaussian 03 software package[22] at the BHandHLYP/6-311G** and BHandHLYP/cc-pVTZ levels of theory, using restricted and unrestricted methods for closed- and open-shell systems, respectively. The optimized structures were verified by vibrational frequency analysis at the same levels of theory, and all identified transition states showed only one imaginary frequency. Vibrational frequencies also provided zero-point vibrational energy corrections (ZPC), which were applied to all energies. For each of the optimized geometries, the spin expectation value, $\langle s^2 \rangle$, was very close to 0.75 after spin annihilation ($\langle s^2 \rangle_A$) for doublet radicals (except for the transition state for the reaction **29b**→**30**, where $\langle s^2 \rangle_A = 0.762$). The archive entries of the Gaussian output files for all optimized ground and transition state structures are available in the Supporting Information

Experimental Methods: $(PhS)_2$, BnSH, *t*BuSH and $(AllylS)_2$ were commercially available and directly used. Cyclodecyne (**1**) was synthesized according to ref.[1a] The flame ionization detector of the GC was calibrated for quantitative analysis against *n*-hexadecane as an internal standard using an authentic sample of the sulfide mixture *cis*/*trans*-**17a**. The obtained peak area correction factor, f_{GC}, for these compounds was compared with correction values, f_{ECN}, obtained for the same compounds using the incremental ECN method,[23] to give the correlation factor f_c, where $f_c = f_{GC}/f_{ECN}$. Using the f_c value, the peak area correction factors for the sulfide mixtures obtained in the individual experiments, $f_{GC(calc)}$, were then determined according to $f_{GC(calc)} = f_c \times f_{ECNx}$, where f_{ECNx} is the f_{ECN} for each of the corresponding sulfides **x**. Details on all reactions performed in this study, including analytical and spectroscopic data, are given in the Supporting Information

General Procedure for Photochemical Generation of Thiyl Radicals: The solution level of a solution of alkyne **1** and radical precursor (in benzene, acetone, acetonitrile or cyclohexane) in a pyrex (or quartz for irradiation at $\lambda = 254$ nm) test-tube was marked. A further 1–2 mL of solvent was added, and the solution was thoroughly degassed by sonicating under a constant stream of nitrogen for at least 15 min, where the solution level returned to the marked level. The solutions were irradiated $\lambda = 254$, 300 or 350 nm in a Rayonet photoreactor, under an argon atmosphere for the required reaction time at room temperature. After the reaction, the solvent level was restored, a known amount of standard solution (*n*-hexadecane in ethyl acetate) was added to the reaction solution, and the reaction mixture was analysed by GC.

Supporting Information (see also the footnote on the first page of this article): Experimental conditions and spectroscopic data for all reactions, Gaussian archive entries for all ground and transition states.

CCDC-779074 (for *cis*-**28**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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