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PAPER

Treasures from the *Free Radical Renaissance Period* – Miscellaneous hexenyl radical kinetic data†‡

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Rate constant data and Arrhenius parameters have been determined for a series of substituted hexenyl radicals of differing electronic and steric demand. Electron-withdrawing groups (CF_3, CO_2Et) directly attached to the radical centre slighly accelerate 5-*exo* ring-closure ($k_{cis} + k_{trans} \sim 2.1 \times 10^5$ s^{-1} at 25°) relative to donating groups (OMe; 1.6×10^5 s^{-1} at 25°). Sterically demanding groups (*tert*-Bu), as expected, slow the cyclization process (1×10^5 s^{-1}). These observations are consistent with subtle changes in activation energy for 5-*exo* ring-closure. Interestingly, the nature of the solvent would appear to have a significant influence on this chemistry with the *cis*/*trans* stereoselectivity sometimes improved as the solvent polarity is increased. Except for the system containing the CF_3 (electron-withdrawing) group which displays an increase in the cyclization/capture rate constant (k_c/k_H), a general decrease in the k_c/k_H ratio as solvent polarity is increased is noted; these changes have been speculated to arise mainly from changes in k_H in the various solvents employed.

Introduction

There was a time when free radicals were scorned by organic chemists and when "practically every organic text book written" contained a statement that free radicals were "incapable of an independent existence".[1] Except for polymer chemistry, these reactive species were mostly regarded as poorly-understood curiosities, often scape-goats for unwanted outcomes during synthesis, or when the practitioner required that elusive explanation for his or her unwanted observation. Those were the *Dark Ages* of free radical chemistry, the lengthy period between the "discovery" of organic free radicals by Gomberg in 1900 and their resurgence some seventy or so years later.[2,3]

Many of us appreciate that there was a brief period of enlightenment before the *Dark Ages*; Marcellin Berthelot devotes a section to *radicaux* in his *La Synthèse Chimique*, published in 1887,[4] and Wurtz was generating alkyl radicals as early as 1855.[5]

The *Dark Ages*, of course, were interspersed with significant contributions by Hey and Waters,[6] Kharash,[7] Walling[8] and others,[9] but free radicals remained largely inaccessible to synthetic chemists until their *Renaissance* during the period 1970–1990 in which the factors that control the reactivity, regiochemistry and stereochemistry of radical reactions began to be teased out. Ingold,[10] Julia,[11] Barton,[12] Surzur,[13] Davies,[14] Fischer,[15] Giese,[16] Curran,[17] Newcomb[18] and one of us[19] (as well as others) were all significant contributors to the dramatic rise in our understanding of free radical chemistry during this period, and to their general acceptance in the wider chemistry community.[20]

A plethora of vital rate constant data became available, and molecular modeling provided for the first time an explanation for the *exo*/*endo* paradox associated with the ring-closure of the 5-hexenyl radical.[21,22] Who would have thought that transition state ring-strain is the primary driver for most alkenyl radical ring-closures? As the implications of the Beckwith–Houk model became more widely appreciated, so did the more-general use of free radicals in synthesis.[20]

It is during this *Renaissance Period* that we asked key questions in relation to the factors controlling ω-alkenyl radical ring closures. How important are steric factors during cyclization? Is the geometry of the alkene important? What about electronic demand on the radical centre – do electon-donating and electron-withdrawing groups play important roles? What about solvent effects?

While some of our investigations toward answering these questions have been published,[23] some required key kinetic data to become available in the *post-Renaissance* period for meaningful conclusions to be drawn. We now report miscellaneous kinetic data that contribute to our further understanding of radical

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† In memory of Athel Beckwith who contributed significantly to enlightenment during the Free Radical Renaissance period.

‡ Electronic supplementary information (ESI) available: Procedures for the preparation of **1b-H**, **2b-H**, **3b-H**, **3c-H**, **4a-H**, **4b-H**, **7-H**, **8-H**, **25-H** and **27**; derivation of eqn (6) kinetic data for the cyclization of **1a**, **1b**, **1c**, **6** and **24** under various reaction conditions. See DOI: 10.1039/c0ob00708k

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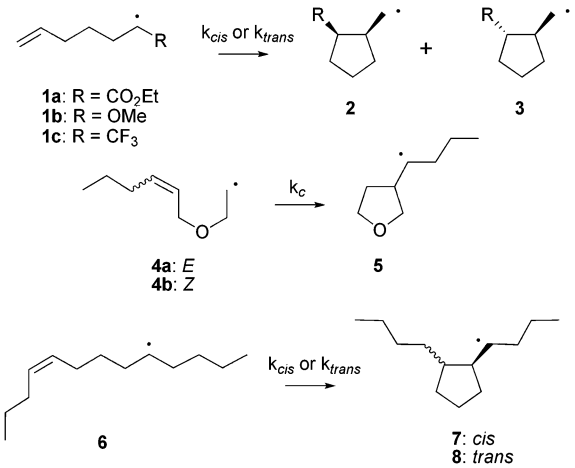
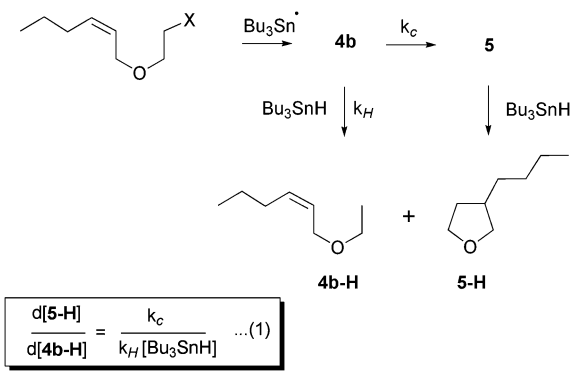
ring-closure chemistry and go some way to answering the questions presented above.

Results

Some of the issues raised above could be addressed through the determination of kinetic parameters of appropriately substituted hexenyl radicals. Accordingly, we chose to explore the ring-closure chemistry of radicals **1**, **4** and **6** as depicted Scheme 1. Rate constants for cyclization (k_{cis}, k_{trans}, k_c; Scheme 1) were determined through the use of standard free radical competition kinetics as decribed previously by us,[24] as well as others and is illustrated in Scheme 2 using radical **4b** as an example. We appreciate that kinetic data for radicals **1a** and **1b** have been published by Newcomb,[25] however, the work presented in this paper predates those reports and provides solvent effect data not previously made available; it is therefore instructive to compare our results with those other seminal contributions to the field.



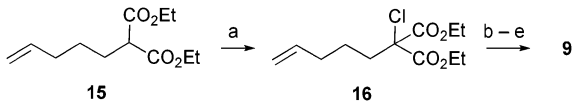
Scheme 1



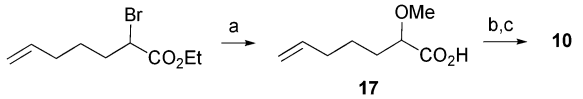
Scheme 2

Preparation of Radical Precursors

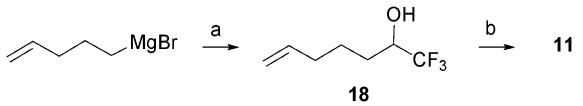
In order to facilitate this study, precursors to the radicals of interest were required, and these were prepared as described below. To that end chloride (**9**), thiohydroxamic ester (**10**), thionocarbonates (**11**, **12**) and bromides (**13**, **14**) were prepared following the procedures outlined in Schemes 3–7.



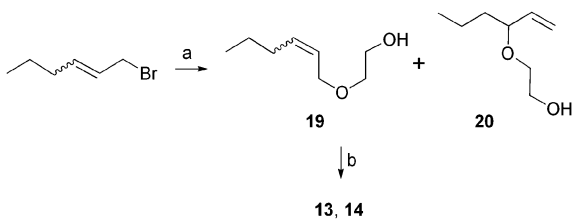
Scheme 3 *Reagents and conditions*: (a) NaH, NCS, DMF, 81%; (b) NaOH, EtOH, reflux; (c) △, neat; (d) $SOCl_2$ (e) EtOH. 69% over four steps.



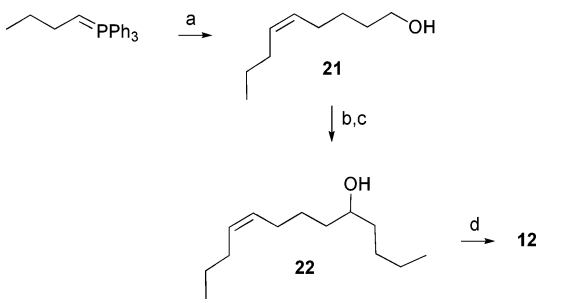
Scheme 4 *Reagents and conditions*: (a) NaOMe, 91%; (b) $SOCl_2$ (c) 1-hydroxy-5-methyl-(1*H*)-thiazolin-2-thinone. 24% over two steps.



Scheme 5 *Reagents and conditions*: (a) CF_3CO_2Et, 56%; (b) PhOC(S)Cl, pyridine, 67%.



Scheme 6 *Reagents and conditions*: (a) ethylene glycol, NaH, 75%; (b) PBr_3, 38%.



Scheme 7 *Reagents and conditions*: (a) 2-hydroxytetrahydropyran; 47%; (b) PDC; (c) n-butylmagnesium bromide, 40% over two steps; (d) PhOC(S)Cl, pyridine, 74%.

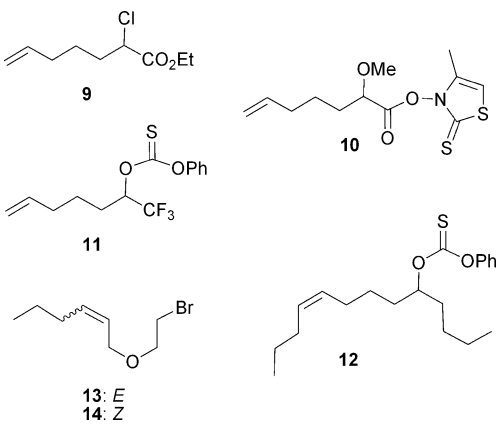


Table 1 Rate data and Arrhenius functions for the 5-*exo* cyclizations of substituted 5-hexenyl radicals

Entry	Radical	Solvent	k_{cis}[a]	f_{cis}[b]	k_{trans}[a]	f_{trans}[b]
1	**1a**	benzene	1.0×10^5	$(8.6 \pm 0.6)–(4.9 \pm 0.6)/\theta$	1.1×10^5	$(8.5 \pm 0.6)–(4.7 \pm 0.6)/\theta$
2	**1a**[c]	benzene	7.1×10^4	$11.7–8.7/\theta$[d]	1.3×10^5	
3	**1b**	benzene	8.1×10^4	$(9.9 \pm 0.6)–(6.8 \pm 0.9)/\theta$	7.7×10^4	$(10.1 \pm 0.6)–(7.1 \pm 0.9)/\theta$
4	**1b**[c]	THF	8.9×10^4	$10.8–7.5/\theta$[d]	1.1×10^5	
5	**1c**	hexane	1.2×10^5	$(9.4 \pm 0.4)–(5.9 \pm 0.5)/\theta$	9.4×10^4	$(9.6 \pm 0.4)–(6.3 \pm 0.5)/\theta$
6	**4a**[e]	hexane	4×10^6	n.d.[f]		
7	**4b**[d]	hexane	4×10^6	n.d.[f]		
8	**6**	hexane	7.8×10^4	$(10.2 \pm 0.4)–(7.3 \pm 0.5)/\theta$	1.4×10^5	$(10.0 \pm 0.4)–(6.6 \pm 0.5)/\theta$
9	**23**[g]	hexane	7.3×10^4	$(8.9 \pm 0.4)–(5.5 \pm 0.5)/\theta$	2.6×10^4	$(10.8 \pm 0.4)–(8.7 \pm 0.5)/\theta$
10	**24**[e,h]	cyclopropane	7.3×10^4	$(9.3 \pm 0.3)–(5.6 \pm 0.5)/\theta$		
11	**24**[e]	benzene	4×10^4	$(9 \pm 1)–(6 \pm 1.5)/\theta$		

[a] Rate constants (s^{-1}) at 25° calculated from Arrhenius function. [b] Arrhenius function in kcal mol^{-1}; $\theta = 2.3RT$; Errors expressed to 2σ. [c] Ref. 25 [d] Combined Arrhenius function for $k_{cis} + k_{trans}$. [e] Cyclization data (k_c) only; no stereochemistry for this radical. [f] Not determined, see text; Rate constants determined from experiment performed at 25°. [g] Ref. 23; note that the *cis* and *trans* products (**2**, **3**) were originally incorrectly assigned (see ref. 23). [h] Ref. 31.

Diethyl hex-5-en-1,1-dicarboxylate (**15**)[26] was treated with sodium hydride, followed by *N*-chlorosuccinimide to afford the corresponding chloride (**16**) in 81% yield. Saponification followed by decarboxylation and subsequent re-esterification afforded the required precursor (**9**) to radical **1a** (Scheme 3).

Ethyl 2-bromohept-6-enoate, prepared in identical fashion to **9** from **15** and *N*-bromosuccinimide, was reacted with excess sodium methoxide to afford the acid (**17**) after acidic workup. Further treatment with thionyl chloride followed by 3-hydroxy-4-methyl-(3*H*)-thiazole-2-thione afforded **10** in low yield (Scheme 4).

Thionocarbonate **11** was prepared according to Scheme 5 in which ethyl trifluoroacetate was reacted with 4-pentenylmagnesium bromide to afford the alcohol **18**. This transformation requires two-equivalents of the Grignard reagent; the first equivalent adds to the ester to afford the trifluoromethylketone which is then further reduced with the second equivalent of reagent. The reduction of trifluoromethyl ketones by Grignard reagents is well documented.[27] Further treatment with phenylchlorothionocarbonate afforded the required precursor **11** in moderate yield.

Bromides **13** and **14** were prepared by reacting ethylene glycol with sodium hydride followed by either (*Z*)- or (*E*)-1-bromo-2-hexene (Scheme 6). Alcohols **19** were obtained in 75% yield after separation from byproduct **20** by MPLC; presumably **20** arises by an S_N2' process. While the *E* isomer was isolated in excellent purity, the *Z* isomer was contaminated with approximately 20% of the *E* isomer, however this did not present a problem during the kinetic study.¶ Further treatment of **19** with phosphorus tribromide under standard conditions afforded the required bromides (**13**, **14**) in low yield after flash chromatography.

The final precursor (**12**) was prepared from 2-hydroxy-tetrahydropyran following treatment with n-butyltriphenylphosphorane under Wittig conditions to give (*Z*)-5-nonen-1-ol (**21**). Oxidation to the corresponding aldehyde followed by treatment with n-butylmagnesium bromide afforded the alcohol **22** in moderate yield. Conversion to the corresponding thionocarbonate was achieved in analogous fashion to the preparation of **11** (Scheme 7).

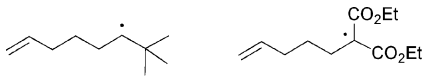
Kinetic Experiments

With the required radical precursors in hand, we next turned our attention to their ring-closure chemistry. Approximately 10 mol% of the required precursor was added to a pre-prepared (standard) solution of Bu_3SnH in hexane or benzene in a pyrex tube. A crystal of AIBN was added. After de-gassing through freeze-thaw cycles, the tube was sealed and the sample emersed in an oil-bath at the required temperature. For temperatures below 50°, reactions were initiated by irradiation with a 200 W mercury lamp. Product analyses were performed by gas chromatography and products were identified by comparison with authentic standards prepared as described below, or by direct isolation from the reaction mixture using preparative GC. All kinetic experiments were performed in triplicate. Under these conditions, eqn (1) (Scheme 2) reduces to:

$$\frac{[\mathbf{5 - H}]}{[\mathbf{4b - H}]} = \frac{k_c}{k_H[Bu_3SnH]} \quad (2)$$

Similar equations apply for each cyclization reaction in this study.

Application of eqn (2) to the data collected from the experiments described above, together with known values for k_H,[28–30] afforded the rate and associated Arrhenius data listed in Table 1.‖

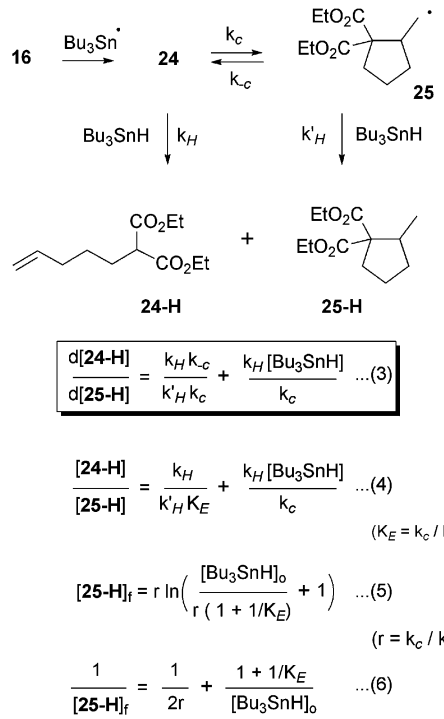


23 **24**

As radical **24** is known to undergo reversible cyclization,[32] ring-closure of **1a** was also expected to be reversible; indeed this was confirmed by dilution experiments which showed increased formation of the thermodynamically more stable *trans* product **3a** at lower Bu_3SnH concentrations. Therefore, for the ring-closure of **1a**, we chose to examine the application of rate eqn (3) for reversible ring closure as illustrated for **24** in Scheme 8. Eqn (3) integrates to eqn (4) under pseudo first-order and to eqn (5) under second-order conditions.‡ Assuming that the first two terms in the Taylor series expansion dominate, eqn (5) can be expanded to eqn (6), which together with eqn (4) is capable of providing cyclization (k_c) as well as hydrogen transfer (k_H) rate constants through application

¶ Product ratios for **14** obtained from reactions using the 80 : 20 ratio of **14** : **13** were corrected using the data obtained using pure **13**.

‖ Previously published data for **1a** and **1b**, the *tert*-butyl substituted system **23**,[23] and the diester **24**[31] are included for completeness.



$$\frac{d[\mathbf{24\text{-}H}]}{d[\mathbf{25\text{-}H}]} = \frac{k_H k_{-c}}{k'_H k_c} + \frac{k_H [Bu_3SnH]}{k_c} \quad ...(3)$$

$$\frac{[\mathbf{24\text{-}H}]}{[\mathbf{25\text{-}H}]} = \frac{k_H}{k'_H K_E} + \frac{k_H [Bu_3SnH]}{k_c} \quad ...(4)$$

$$(K_E = k_c / k_{-c})$$

$$[\mathbf{25\text{-}H}]_f = r \ln\left(\frac{[Bu_3SnH]_o}{r\,(1 + 1/K_E)} + 1\right) \quad ...(5)$$

$$(r = k_c / k_H)$$

$$\frac{1}{[\mathbf{25\text{-}H}]_f} = \frac{1}{2r} + \frac{1 + 1/K_E}{[Bu_3SnH]_o} \quad ...(6)$$

Scheme 8

of known values for k'_H; k_H values for ester-substituted radicals were unknown at the time this work was carried out.

In order to validate our assumptions, we chose to first apply eqns 4 and 6 to the diethyl 1,1-dicarboxy-5-hexenyl radical **24**. To that end, chloride **16** was reacted under the (pseudo first-order) reaction conditions described above, as well as under second order conditions.‡ The cyclization data obtained in this manner are included in Table 1 and, gratifyingly, are in good agreement with those obtained by Roberts several years later using kinetic EPR techniques.[31] These experiments also provided approximate k_H data for the trapping of **24** by Bu_3SnH; $k_H \sim 9 \times 10^5$ $M^{-1}s^{-1}$ at 25° in benzene.** To the best or our knowledge, k_H data for **24** have not been reported previously.

Our data for **24** have greater uncertainties than those reported by Roberts mainly because application of eqn (5) requires extrapolation of the data to the intercept of eqn (4) where $[Bu_3SnH]$ vanishes.

It is interesting to note that the 6-*endo* product, diethyl cyclohexanedicarboxylate was only observed (~ 5%) at stannane concentrations of 0.01 M or below, consistent with reversible 5-*exo* ring-closure.[32]

When these techniques were applied to radical **1a**, and the k_c/k_H data obtained were combined with hydrogen transfer rate constants (k_H) reported by Newcomb[30] some ten years after this work was carried out, the kinetic data provided in Table 1 (entry 1) were obtained.

Interestingly, radical **1b** proved to ring-close in an irreversible fashion under our reaction conditions; once again application of k_H values provided by Newcomb[29] afforded the data in entry 3 of Table 1. While our data are very similar to those reported by Newcomb for **1b** (entry 4),[25] it is notable that different solvents were employed in each of these studies (benzene *vs.* THF) and this may account for the observed discrepancies, in particular in the observed **2a**/**2b** ratios.

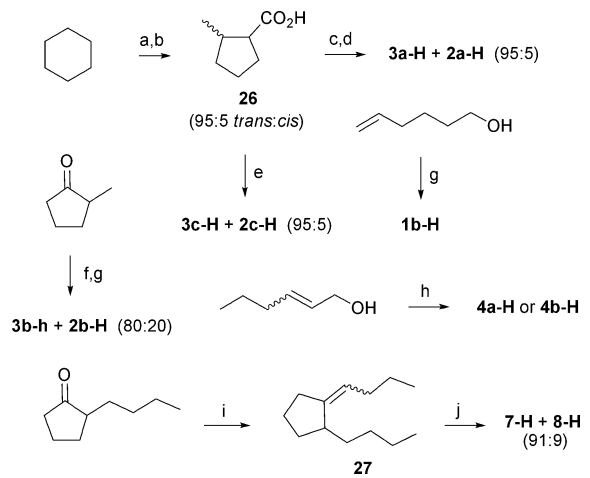
In the case of **1a**, differences are once again noted; the most significant being in the Arrhenius functions. We speculate that, perhaps, the experiments leading to entry 2 were affected by trace amount of benzeneselenol, possibly through minor decomposition of the phenylseleno precursor used in that study;[28] benzeneselenol contaminants are known to interfere with radical kinetics.[33]

It was not possible to produce reliable Arrhenius data for radicals **4** as the bromides **13**, **14** appeared to initiate before the reaction solution had reached the desired temperature; this was partially overcome by addition of the precursor to a preheated solution of Bu_3SnH in hexane, however, scatter in the data at higher temperatures nevertheless meant that the room temperature data were the most robust.

Identification of Products

As mentioned above, products resulting from kinetic experiments were identified either by GC comparison with synthesized authentic standards, or through direct isolation from reaction mixtures using preparative GC. Indeed, **5-H**, and **25-H**[32] were isolated reaction products.

The remaining product standards were prepared according to Scheme 9. Ester **1a-H** was prepared by the treatment of diester **15** with sodium chloride in DMSO at elevated temperatures as described by Schmidt and Ingold,[34] while a 95 : 5 mixture of **3a-H** : **2a-H** was prepared from cyclohexane following literature precident.[35]



Scheme 9 *Reagents and conditions*: (a) Acetyl chloride, AlCl3, 23%; (b) NaOBr, 86%; (c) $SOCl_2$ (d) EtOH. 36% over two steps; (e) SF_4; (f) $LiAlH_4$, 97%; (g) NaH, MeI; (h) NaH, EtI, 23%; (i) n-Butyltriphenylphosphonium bromide, NaH, DMSO, 29% (j) H_2, Pd-C; 98%.

Ether **1b-H** was prepared from commercially available 5-hexen-1-ol, while an 80 : 20 mixture of **3b-H** : was obtained from 2-methylcyclohexanone by reduction with lithium aluminium hydride followed by Williamson etherification.[36]

A 95 : 5 mixture of trifluoromethylcyclopentanes **3c-H** : **2c-H** was prepared from the 95 : 5 mixture of acids **26** by treatment with sulfur tetrafluoride, while the remaining peak in the gas chromatogram obtained after the reaction of **1c** was assigned to

** $\log k_H \sim 7.4–2.0/\theta$

Table 2 Relative rate data for the 5-*exo* cyclizations of some substituted 5-hexenyl radicals in different solvents

		[*cis*/*trans*]		
Entry	Radical	benzene or hexane	DME[a]	1-propanol
1	**1b**	0.95	0.93	0.94
2	**1c**	1.13	1.86	1.70
3	**6**	0.57	0.57	0.57
4	**23**[c]	3.1	4.4	5.9
		k_c/k_H[b]		
		benzene or hexane	DME[a]	1-propanol
5	**1b**	0.398	0.347	0.278
6	**1c**	0.160	0.216	0.293
7	**6**	0.136	0.112	0.094
8	**23**[c]	0.078	0.062	0.039

[a] 1,2-Dimethoxyethane. [b] $k_c = k_{cis} + k_{trans}$. [c] Ref. 23.

be **1c-H** after it was removed from the reaction mixture by the addition of excess bromine.

Alkenes **4a-H** and **4b-H** were prepared from commercially available (*Z*)- or (*E*)-2-hexen-1-ol after treatment with sodium hydride followed by iodoethane.

Hydrocarbon **6-H** was prepared by the reaction of nonanal with n-butylenetriphenylphorphorane, while an 91 : 9 mixture of *cis*- and *trans*-1,2-dibutylcyclopentane was prepared from 2-butylcyclohexanone[37] by the action of n-butylenetriphenylphorphorane and subsequent hydrogenation (H_2/Pd-C) of the resultant alkene **27**.

Solvent Effect Studies

We were interested in what effect, if any, solvent plays in the cyclization chemistry of substituted hexenyl radicals. As a consequence, we published solvent-effect data for **23** showing that the stereoselectivity of the cyclized product was sensitive to solvent polarity.[23] We now report solvent effect data for other radicals in this study. Table 2 lists the *cis*/*trans* ratios observed for radicals **1b**, **1c**, **6** and **23** at 25° in non-polar (benzene or hexane), intermediate polarity (DME) and polar (1-propanol) solvents, together with relative rate constant data (k_c/k_H).

Discussion

The data listed in Table 1 provide interesting insight into the effect of substitution on the rate constants for hexenyl radical ring-closures. Firstly, electron-withdrawing groups (entries 1, 2, 5) appear to increase the rate of cyclization relative to the methoxy-substituted system; $k_{cis} + k_{trans}$ values of 2×10^5 s^{-1} are observed for the cyclization **1a** and **1c**, while **1b** (entries 3, 4) ring-closes with a (combined) rate constant of 1.6×10^4 s^{-1} at 25°. These values are to be compared with reported data for the 5-hexenyl radical (2.3×10^5 s^{-1} at 25°)[21,24] and the "1-methyl-5-hexenyl radical" (**1**, R = Me) (1.5×10^4 s^{-1} at 25°).[21,38] Arrhenius data suggest that these rate constants are mosly affected by changes in activation energy for ring-closure, and that the effects are observed for both modes (*cis*/*trans*) of cyclization.

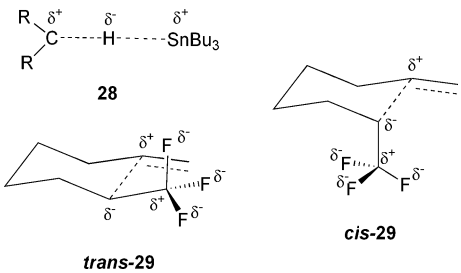
The alkyl-substituted systems (entries 8, 9) ring-close with rate constants lower than the "parent", consistent with possible steric factors, while entries 10 and 11 demonstrate that excessive stabilization of the radical also retards ring-closure.

Values of 4×10^6 s^{-1} for k_c each of the (*E*)- and (*Z*)-3-oxa-5-nonenyl radicals **4** are to be compared with data for the parent 3-oxahexen-1-yl radical which ring-closes with a rate constant of 9.3×10^6 s^{-1} at 25° in cyclopropane.[21,39] The data also suggest that the geometry of the double bond has little effect on ring-closure rate constants for hexenyl-type radicals.

Inspection of Table 2 reveals interesting trends associated with the effect of solvent polarity on ring-closure. In two of the four systems investigated, the *cis*/*trans* ratio is generally observed to increase as the solvent polarity is increased, however two systems show no difference in this ratio as the solvent is changed. While these results are intriguing, we are not in a position to provide an explanation for these observations at present.

Table 2 also reveals interesting trends in k_c/k_H as solvent polarity is changed. Entries 5, 7 and 8 show that for radicals with electron donating or alkyl groups, k_c/k_H generally decreases as the solvent polarity is increased, while the (withdrawing) trifluoromethyl-substituted system (entry 6) shows a clear opposite trend. Indeed k_c/k_H approximately doubles for radical **1c** in moving from hydrocarbon to propanol, while it halves for **23**. These observations are very likely to be the result of a delicate interplay between energy and entropy terms operating in both hydrogen-transfer as well as cyclization reactions.

For example, if we consider alkyl radicals to be nucleophilic, then the transition state for hydrogen transfer from tin to carbon is likely to be polarized as depicted in **28**. Polar solvents will stabilize **28** over non-polar solvents leading to an increase in k_H and, consquently, a decrease in k_c/k_H.



On the other hand, in the case of **1c**, the trifluoromethyl substituent is likely to destabilize transition state **28**; the consqeuence of this would be a reduced dependence of k_H on solvent polarity. Assuming Beckwith–Houk transition states for the cyclization of **1c**,[21,22] the CF_3 group will lead to polarized transition states **29** for cyclization leading to an increase in k_c as well as the *cis*/*trans* ratio, as ***cis*-29** is likely to have a greater dipole moment than ***trans*-29**.

It is clear that further examples of solvent-dependent values of k_c/k_H are needed before a definitive conclusion can be drawn, however, our data urge the use of caution when combining Arrhenius or kinetic data that have been determined in different solvents.

Conclusions

Rate constant data and Arrhenius parameters have been determined for a series of substituted hexenyl radicals of differing

electronic and steric demand. Electron-withdrawing groups directly attached to the radical centre slightly accelerate 5-*exo* ring-closure, while donating groups would appear to retard the rate of cyclization. Steric factors, es expected, slow the cyclization process, which also appears to be largely unaffected by the geometry (*E*/*Z*) of the alkene.

Interestingly, the nature of the solvent would appear to have a significant influence on this chemistry with the *cis*/*trans* stereoselectivity sometimes improved as the solvent polarity is increased. Except for the system containing the CF_3 (electron-withdrawing group) which displays an increase in k_c/k_H, a general decrease in the k_c/k_H ratio as solvent polarity is noted; for most systems these changes have been speculated to arise mainly from changes in k_H in the various solvents employed.

Experimental

Unless otherwise stated, all starting materials and reagents were purchased from Aldrich and were used without further purification. Bu_3SnH was prepared as previously described[40] and distilled before use.

Medium performance liquid chromatography (MPLC) was performed using a Merck LiChroprep Si 60 (40–63 μm) column fitted with a Waters R-403 differential refractometer detector. Analytical GC experiments were performed on various capillary columns purchased from SGE as detailed in the ESI‡ using a Varian 6000 or Hewlett-Packard 3390A gas chromatograph fitted with an HP 3390A integrator. Preparative GC was performed using either a 20% SE-30 on Chromosorb W (80–100 mesh) or 3% OV-17 on GC-Q (80–100 mesh) column.

Remaining instrumentation and general experimental methods (*etc.*) are provided in full in previous publications.[41]

Experimental details for the preparation or isolation of product standards are provided as part of the ESI.‡

Diethyl 1-chlorohex-5-en-1,1-dicarboxylate (16). Diethyl hex-5-en-1,1-dicarboxylate[26] (**15**) (3.0 g, 13.2 mmol) was added to a suspension of sodium hydride (360 mg, 15.0 mmol) in DMF (50 mL) and the mixture stirred under nitrogen until the evolution of hydrogen has ceased (~20 min). *N*-Chlorosuccinimide (1.73 g, 12.9 mmol) was added and the mixture stirred for 45 min, after which it was poured into water (250 mL), extracted with ether (3×), the combined extracts dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown oil. Excess DMF was removed by filtration through a short silica column, eluted with dichloromethane. The solvent was removed *in vacuo* and the residue distilled (Kügelrohr) to give the title ester as a colourless oil (2.8 g, 81%). Bp ~100 °C/0.1 mmHg; ^{1}H NMR δ 5.4–6.1 (m, 1H), 4.7–5.3 (m, 2H), 4.23 (q, J = 8 Hz, 2H), 1.0–2.5 (m, 6H), 1.30 (t, J = 8 Hz, 6H); IR (neat): 1765, 1745, 1640 cm^{-1}; MS (CI) *m*/*z* (relative intensity) 263/265 (74), 39 (100). (Found: C, 54.9; H, 7.3. $C_{12}H_{19}ClO_4$ requires C, 54.9; H, 7.3%).

Diethyl 1-bromohex-5-en-1,1-dicarboxylate was prepared in identical fashion to **16** using diethyl hex-5-en-1,1-dicarboxylate[26] (**15**) (3.0 g, 13.2 mmol) and *N*-bromosuccinimide (2.30 g, 12.9 mmol). The title compound was isolated as a colourless oil after distillation. Bp ~100 °C/0.1 mmHg; ^{1}H NMR δ 5.4–6.1 (m, 1H), 4.7–5.3 (m, 2H), 4.23 (q, J = 8 Hz, 2H), 1.0–2.5 (m, 6H), 1.30 (t, J = 8 Hz, 6H); IR (neat): 1765, 1740, 1640 cm^{-1}; (Found: C, 47.0; H, 6.5. $C_{12}H_{19}BrO_4$ requires C, 46.9; H, 6.3%).

Ethyl 2-chlorohept-6-enoate (9). Diethyl 1-chlorohex-5-en-1,1-dicarboxylate (**16**) (2.5 g, 9.52 mmol) was added to a stirred solution of sodium hydroxide (2.0 g, 50 mmol) in ethanol (60 mL) and the mixture heated under reflux for 4 h, then cooled. The precipitate was collected and dissolved in aqueous sodium bicarbonate (20 mL) and the solution washed with ether (4×), the combined extracts dried ($MgSO_4$) and the solvent removed to yield the crude diacid which was heated neat at 130–140 °C until the evolution of carbon dioxide had ceased. The residue was dissolved in thionyl chloride (30 mL) and the mixture heated under reflux until the evolution of gas had ceased (~1 h). The excess thionyl chloride was removed *in vacuo*, ethanol (40 mL) added and solution heated to reflux for 10 min. After cooling the solvent was removed *in vacuo* to give a brown oil that was distilled (Kügelrohr) to give the title ester as a colourless oil (1.26 g, 69%). Bp ~100 °C/0.2 mmHg; ^{1}H NMR δ 5.4–6.1 (m, 1H), 4.7–5.2 (m, 2H), 3.9–4.4 (m, 3H), 1.0–2.4 (m, 6H), 1.25 (t, J = 7 Hz, 3H); IR (neat): 1745, 1640 cm^{-1}. (Found: C, 56.8; H, 8.1. $C_9H_{15}ClO_4$ requires C, 56.6; H, 7.9%).

Ethyl 2-bromohept-6-enoate was prepared in identical fashion to **9** using diethyl 1-bromohex-5-en-1,1-dicarboxylate and isolated as a colourless oil after distillation (350 mg, 16%).%). Bp ~90 °C/1.0 mmHg; ^{1}H NMR δ 5.6–6.1 (m, 1H), 4.9 –5.2 (m, 2H), 4.1–4.4 (m, 3H), 1.0–2.3 (m, 6H), 1.29 (t, J = 7 Hz, 3H); IR (neat): 1740, 1640 cm^{-1}; MS (CI) *m*/*z* (relative intensity) 166/168 (35), 155 (25). HRMS calcd. for $C_9H_{15}BrO_2$ [M − Br]$^+$ 155.1072, found 155.1072.

2-Methoxyhept-6-enoic acid (17). Ethyl 2-bromohept-6-enoate (300 mg, 1.28 mmol) was added to a solution of sodium methoxide in methanol (prepared by adding dry methanol (10 mL) to sodium hydroxide (180 mg, 7.5 mmol) with vigorous stirring) and the mixture heated under reflux for 20 h. After cooling, the resultant solution was poured into 10% hydrochloric acid (50 mL) and the mixture extracted with ether (3×). The combined extracts were washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was distilled (Kügelrohr) to give the title acid as a colourless oil (185 mg, 91%). Bp ~80 °C/0.4 mmHg; ^{1}H NMR δ 10.3 (s, br, 1H), 5.7 –5.9 (m, 1H), 4.9–5.1 (m, 2H), 3.7–3.8 (m, 1H), 3.43 (2, 3H), 2.0–2.1 (m, 2H), 1.7–1.8 (m, 2H), 1.5–1.6 (m, 2H); ^{13}C NMR δ 178.1, 138.0, 114.9, 80.0, 58.2, 33.2, 31.9, 24.2; IR (neat): 3080 (br), 1720, 1640 cm^{-1}. (Found: C, 60.7; H, 9.0. $C_9H_{15}ClO_4$ requires C, 60.7; H, 8.9%).

3-(2-Methoxyhept-6-enoyl)-4-methyl-(3*H*)-thiazole-2-thione (10). 3-Hydroxy-4-methyl-(3*H*)-thiazole-2-thione (140 mg, 950 μmol), 2-methoxyhept-6-enoyl chloride (prepared from 2-methoxyhept-6-enoic acid (**17**) (140 mg, 886 μmol) and thionyl chloride (3 mL)), pyridine (100 μL) and 4-dimethylaminopyridine (4 mg) were stirred in ether (5 mL) for 20 min. The precipitate was filtered off and the solvent removed *in vacuo*. The residual green oil was separated by flash chromatography (dichloromethane) to afford the title thiohydroxamic ester as a pale oil (60 mg, 24%). ^{1}H NMR δ 6.28 (s, 1H), 5.7–5.9 (m, 1H), 4.9–5.1 (m, 2H), 4.1–4.3 (m, 1H), 3.55 (d, J = 4 Hz, 3H), 2.17 (s, 2H), 1.9–2.2 (m, 4H), 1.6–1.8 (m, 2H); ^{13}C NMR δ 168.3, 137.8, 136.6, 115.1, 106.7, 79.1, 58.9, 33.1, 32.3, 24.3, 13.3; MS *m*/*z* (relative intensity) 288

(1), 261 (48), 214 (10), 132 (100). HRMS calcd. for $C_{12}H_{17}NO_3S_2$ $[M + H]^+$ 288.0728, found 288.0728.

1,1,1-Trifluorohept-6-en-2-ol (18). Ethyl trifluoroacetate (2.0 g, 14.1 mmol) in dry ether (5 mL) was added dropwise to an ice-cooled, stirred solution of 4-pentenylmagnesium bromide (prepared from magnesium (800 mg, 33 mmol), 5-bromopent-1-ene (4.47 g, 30 mmol) in dry ether (10 mL)). The mixture was heated at reflux for 1 h, then poured into 10% hydrochloric acid (100 mL) and extracted with ether (3×). The combined extracts were washed with water (2×), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was distilled to give the title alcohol as a colourless oil (1.3 g, 56%). Bp = 145–147 °C; ^{1}H NMR δ 5.4–6.2 (m, 1H), 4.7–5.2 (m, 2H), 3.6–4.2 (m, 1H), 2.36 (s, br, 1H), 1.3–2.3 (m, 6H); MS *m/z* (relative intensity) 168 (0.2), 150 (31), 54 (100). HRMS calcd. for $C_7H_{11}F_3O$ $[M]^+$ 168.0762, found 168.0761.

***O*-Phenyl-*O*-(1,1,1-trifluorohept-6-en-2-yl)thionocarbonate (11).** 1,1,1-Trifluorohept-6-en-2-ol (**18**) (500 mg, 2.98 mmol) was dissolved in dichloromethane (15 mL) and pyridine (940 mg) added. The reaction vessel was flushed with argon, phenylchlorothionocarbonate (570 mg, 3.30 mmol) added, and the mixture stirred at r.t. under argon overnight. The mixture was poured into water (100 mL) and extracted with ethyl acetate (2×). The combined extracts were washed with 10% hydrochloric acid (4×), satd. sodium bicarbonate, brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was separated by MPLC (40% ethyl acetate: hexane) to give the title compound as a yellow oil (610 mg, 67%). ^{1}H NMR δ 6.9–7.6 (m, 5H), 5.4–6.2 (m, 2H), 4.8–5.2 (m, 2H), 1.2–2.4 (m, 6H); ^{13}C NMR δ 194.7, 153.6, 137.4, 126.9, 129.7, 121.7, 115.7, 123.6 (q, J_{CF} = 183 Hz), 78.9 (q, J_{CF} = 32 Hz), 33.3, 27.3, 23.6; MS *m/z* (relative intensity) 305 (100), 223 (9), 211 (8), 195 (8), 110 (38), 94 (95). HRMS calcd. for $C_{14}H_{15}F_3O_2S$ $[M + H]^+$ 305.0823, found 305.0822.

(*E*)-2-(2-Hexen-1-oxy)ethanol (*E*-19). Dry ethane-1,2,-diol (16 mL) was added to sodium hydride (454 mg, 19 mmol) with vigorous stirring with the reaction vessel cooled in an ice bath. When the evolution of hydrogen had ceased, (*E*)-1-bromo-2-hexene (3.0 g, 18.0 mmol) was added and the solution stirred at 100 °C overnight. After cooling, the residual ethane-1,2-diol was removed by filtration through a short silica column eluted with ethyl acetate. Removal of the solvent *in vacuo* afforded a brown oil that was separated by MPLC (1 : 1 ethyl acetate–dichloromethane). The third fraction proved to contain the title compound which was further distilled to afford the product as a colourless oil (2.0 g, 75%). Bp ~ 130 °C/40 mmHg (Kügelrohr); ^{1}H NMR δ 5.48–5.78 (m, 2H), 3.97 (d, *J* = 5.9 Hz, 2H), 3.69–3.74 (m, 2H), 3.52 (t, *J* = 7.5 Hz, 2H), 3.21 (s, br, 1H), 1.97–2.08 (m, 2H), 1.32–1.46 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 134.9, 126.2, 71.9, 71.2, 61.6, 34.4, 22.3, 13.7; IR (neat): 3420 (br), 1670 cm^{-1}. (Found: C, 66.5; H, 11.0. $C_8H_{16}O_2$ requires C, 66.6; H, 11.2%).

(*Z*)-2-(2-Hexen-1-oxy)ethanol (*Z*-19) was prepared in identical fashion to ***E*-19** and isolated as a colourless oil (2.0 g, 75%) containing 20% of the (*E*)-isomer (***E*-19**) by ^{13}C NMR spectroscopy. Bp ~ 130 °C/40 mmHg (Kügelrohr); ^{1}H NMR δ 5.45–5.80 (m, 2H), 4.05–4.10 (m, 1.6H), 3.95–4.00 (m, 0.4H), 3.65–3.80 (m, 2H), 3.45–3.60 (m, 2H), 3.05 (s, br, 1H), 1.95–2.10 (m, 2H), 1.30–1.50 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 133.7 (*Z*), 134.9 (*E*), 126.0 (*Z*), 126.2 (*E*), 71.4 (*Z*), 71.9 (*E*), 66.7 (*Z*), 71.2 (*E*), 61.6, 29.6 (*Z*), 34.4 (*E*), 22.6 (*Z*), 22.3 (*E*), 13.7; IR (neat): 3420 (br), 1660 cm^{-1}.

(*E*)-1-Bromo-2-(2-hexen-1-oxy)ethane (13). Phosphorus tribromide (220 mg, 820 μmol) was added to a solution of (*E*)-2-(2-hexen-1-oxy)ethanol (***E*-19**) (300 mg, 2.08 mmol) in ether (10 mL). Pyridine (160 μL) was added and the mixture stirred at r.t. overnight. The mixture was poured into 10% hydrochloric acid (20 mL), extracted with pentane (2×), the combined extracts washed with satd. sodium bicarbonate, brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The brown residue was separated by flash chromatography (40% pentane in dichloromethane) to give the title compound as a colourless oil (65 mg, 38%). ^{1}H NMR δ 5.49–5.72 (m, 2H), 3.79–4.01 (m, 2H), 3.70–3.76 (m, 2H), 3.43–3.49 (m, 2H), 1.97–2.10 (m, 2H), 1.34–1.49 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 135.5, 125.9, 71.9, 69.6, 34.3, 30.4, 22.2, 13.7; IR (neat): 1660 cm^{-1}; MS *m/z* (relative intensity) 206/208 (2), 163/165 (63), 107/109 (100). HRMS calcd. for $C_8H_{15}{}^{79}BrO$ $[M]^+$ 206.0306, found 206.0299.

(*Z*)-1-Bromo-2-(2-hexen-1-oxy)ethane (**14**) was prepared in identical fashion to **13** using (*Z*)-2-(2-hexen-1-oxy)ethanol (***Z*-19**) and isolated as a colourless oil (64 mg, 37%). ^{1}H NMR δ 5.49–5.71 (m, 2H), 4.09–4.12 (m, 1.6H), 3.79–4.01 (m, 0.4H), 3.68–3.77 (m, 2H), 3.44–3.49 (m, 2H), 1.95–2.13 (m, 2H), 1.32–1.50 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 134.1 (*Z*), 135.3 (*E*), 125.6 (*Z*), 125.9 (*E*), 69.8 (*Z*), 71.9 (*E*), 66.6 (*Z*), 69.6 (*E*), 29.6 (*Z*), 34.3 (*E*), 22.6 (*Z*), 22.2 (*E*), 13.7. HRMS calcd. for $C_8H_{15}{}^{79}BrO$ $[M]^+$ 206.0306, found 206.0295.

(*Z*)-9-Tridecen-5-ol (22). (*Z*)-5-Nonen-1-ol[42] (500 mg, 3.51 mmol), pyridinium dichromate (2.71 g, 7.2 mmol) and finely divided 4 Å molecular sieves (2.4 g) were stirred in dichloromethane (18 mL) for 3 h. The solution was filtered through a short silica column eluted with dichloromethane. The filtrate was collected and the solvent removed *in vacuo* to give *crude* (*Z*)-5-nonenal. The crude aldehyde was added dropwise to an ice-cooled solution of n-butylmagnesium bromide (prepared from magnesium (80 mg, 3.23 mmol) and 1-bromobutane (390 mg, 2.85 mmol) in dry ether (5 mL)). The resultant solution was heated under reflux for 1 h, then poured into 10% hydrochloric acid (50 mL) and extracted with ether (3×). The combined extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was separated by MPLC (20% ethyl acetate in dichloromethane) and further purified by Kügelrohr distillation to give the title alcohol as a colourless oil (260 mg, 92%). Bp ~ 120 °C/1.5 mmHg; ^{1}H NMR δ 5.33–5.39 (m, 2H), 3.48–3.62 (m, 1H), 1.94–2.10 (m, 4H), 1.84 (s, br, 1H), 1.31–1.54 (m, 12H), 0.86–0.93 (m, 6H); ^{13}C NMR δ 130.1, 129.7, 71.9, 37.3, 37.1, 29.4, 27.9, 27.3, 25.8, 22.9, 22.8, 14.1, 13.8; IR (neat): 3340 (br), 1650 cm^{-1}. HRMS calcd. for $C_{20}H_{30}O_2S$ $[M+H]^+$ 335.2045, found 335.2046.

(*Z*)-*O*-Phenyl-*O*-(9-tridecen-5-yl)thionocarbonate (**12**) was prepared in identical fashion to **11** using (Z)-9-tridecen-5-ol (**22**) (120 mg, 610 μmol) and phenylchlorothionocarbonate (123 mg, 710 μmol) and was isolated as a pale oil after flash chromatography (20% dichloromethane in hexane) (150 mg, 74%). ^{1}H NMR δ 7.06–7.42 (m, 5H), 5.28–5.49 (m, 3H), 1.99–2.14 (m, 4H), 1.31–1.80 (m, 12H), 0.86–0.94 (m, 6H); ^{13}C NMR δ 194.9, 153.5, 130.4, 129.2, 129.4, 126.3, 122.1, 85.5, 33.2, 33.1, 29.4, 27.3, 27.0, 25.2, 22.9,

22.6, 14.0, 13.8; MS (CI) *m/z* (relative intensity) 355 (5), 248 (2), 231 (100), 198 (58). (Found: C, 78.7; H, 13.3. $C_8H_{16}O_2$ requires C, 78.7; H, 13.2%).

Kinetic experiments. The sample, prepared as described below, was thermolysed ($T > 50$ °C) or photolysed ($T < 50$ °C) at constant temperature for times indicated in the ESI.‡ Thermolysis was achieved by immersing the sample in a constant temperature oil bath, while photolysis was achieved by irradiating the sample with a 250 W mercury lamp at a distance of 20 cm while immersed in a constant temperature water bath (or liquid ammonia bath for temperatures of –33 °C). The sample mixtures were directly analysed by gas chromatography (GC) using capillary columns as detailed in the ESI.‡ Product identification was achieved by direct GC comparison with standards prepared or isolated as described in the ESI.‡ Suitable hydrocarbon internal standards were incorporated into some reactions for the purpose of determining product concentrations.

Standard Method A. Standard solutions of Bu_3SnH in the required solvent were prepared to concentrations detailed in the ESI.‡ A pyrex tube was charged with the required solution (100 μL), the required radical precursor **9–14**, **16** (~ 10 mol%) and a crystal of AIBN added. The solution was frozen in liquid nitrogen and the tube sealed under vacuum. After the solution had thawed, the tube was heated or irradiated at the required temperature and then analysed as described.

Standard Method B. Standard solutions were prepared as described in Method A. A vial fitted with a septum inlet was charged with the required solution (100 μL) and a crystal of AIBN added. Deoxygenation was achieved by passing a slow stream of nitrogen through the solution for 1–2 min. The vial was immersed in the required constant temperature bath for 5 min. The required radical precursor **13** or **14** was injected. After 5–10 min. the sample was removed and analysed as described.

Standard Method C. Bu_3SnH (1.0 equiv.) and the required radical precursor 9 or 16 (1.05 equiv) were dissolved in benzene and made up to concentrations as described in the ESI.‡ A pyrex tube was charged with the required solution (200 μL) and a few crystals of AIBN added. The solution was frozen in liquid nitrogen under vacuum, thawed and then refrozen. The tube was sealed under vacuum, thawed, heated or irradiated and then analysed as described.

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