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Picosecond Radical Kinetics. Alkoxycarbonyl Accelerated Cyclopropylcarbinyl Radical Ring Openings

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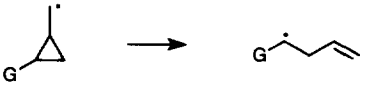
Abstract: Rate constants and Arrhenius functions for ring openings of the (*trans*-2-ethoxycarbonylcyclopropyl)methyl radical and the (*trans*-2-*tert*-butoxycarbonylcyclopropyl)methyl radical were determined by the PTOC-thiol method with PhSeH trapping. At 25 °C, these radicals rearrange with rate constants of 7 and 12 x 10^{10} s^{-1}, respectively.

Mechanistic probes have often been employed in studies of reactions that might involve radical intermediates. For such a purpose, one employs a substrate that can give a radical that will react in a characteristic manner, most often an isomerization or structural rearrangement. When the rate constant for the radical reaction is known, the substrate becomes a "radical clock"[1] which can be used to "time" the competing processes, and a variety of unimolecular radical rearrangements have been calibrated for clock purposes.[1,2]

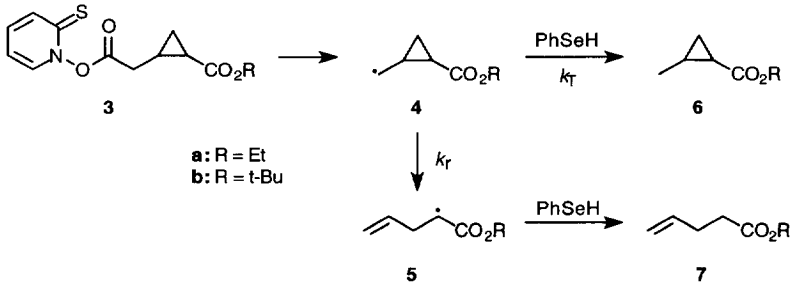
The cyclopropylcarbinyl (CPC) radical ring opening to the 3-butenyl radical (**1** → **2**, G = H) is the archetypal fast radical reaction with a rate constant at 25 °C of 1 × 10^8 s^{-1}.[3,4] The addition of radical stabilizing groups to the incipient radical center (G in **1**) or the incorporation of a cyclopropylcarbinyl radical into a more highly strained system results in rate accelerations over that of the parent that can amount to several orders of magnitude. Thus, at 25 °C, polymethyl-substituted CPC radicals[5] rearrange with rate constants of up to 4 × 10^9 s^{-1}, the bicyclo[2.1.0]pent-2-yl radical[5,6] ring opens with a rate constant of 1.5 × 10^9 s^{-1}, phenyl-substituted CPC radicals[7] ring open with rate constants of 3-5 × 10^{11} s^{-1}, and a spiro-fluorenyl CPC radical[8] ring opens with a rate constant of 6 × 10^{12} s^{-1}.



1 **2**

In 1989, Beckwith and Bowry reported that the ethoxycarbonyl group accelerated the CPC ring opening to a rate constant > 6 × 10^{10} s^{-1} at 60 °C.[9,10] One can estimate the entropic term for a CPC radical ring opening (see below), and, from this, one calculates that **1** (G = CO_2Et) would rearrange at 25 °C with a rate constant > 3 × 10^{10} s^{-1}. Because of our interest in "probing" and "timing" enzyme catalyzed oxidation processes which requires exceptionally fast radical rearrangements, we have calibrated ring openings of two alkoxycarbonyl substituted CPC radicals.[11]

Scheme 1

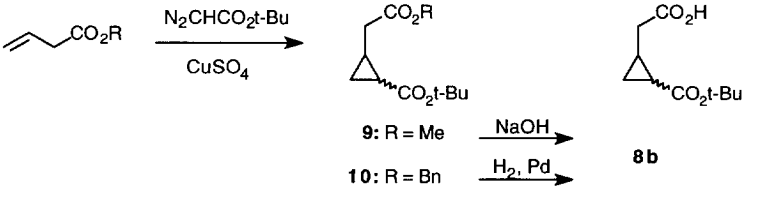


METHOD AND PRODUCT IDENTIFICATIONS

Kinetics were determined by the PTOC-thiol method[2b,3d] with PhSeH trapping[12] (Scheme 1). In this method, a PTOC ester[13] (**3**) serves as the radical precursor. Reaction of **3** in a radical chain step gives an acyloxyl radical that rapidly decarboxylates to the radical of interest (**4**). Radical **4** is trapped by PhSeH to give cyclopropane **6** or rearranges to ring opened radical **5** which is subsequently trapped by the selenol to give ring opened product **7**. The ratios of rearranged and trapped products were determined by GC analyses permitting measurements of ratios exceeding 100:1. Because PhSeH was employed in large excess, its concentration was effectively constant throughout the reaction, and the ratio of the rate constant for rearrangement (k_r) to that for trapping (k_T) can be calculated from equation 1 where (**7/6**) is the observed ratio of rearranged and unrearranged products and $[PhSeH]_m$ is the average concentration of selenol during the reaction. With an assumption that PhSeH trapping of the substituted CPC radical occurs with the same rate constants as does trapping of the parent CPC radical, one can use the ratio from equation 1 to calculate the rate constant for rearrangement.

$$k_r/k_T = (\mathbf{7/6})\ [PhSeH]_m \qquad (1)$$

PTOC precursors **3** were prepared from the corresponding cyclopropylacetic acids. Beckwith and Bowry reported the preparation of (2-ethoxycarbonylcyclopropyl)acetic acid (**8a**) as a ca. 2:1 mixture of *trans* and *cis* isomers;[9] in our hands, a similar mixture of acids **8a** was obtained. Acid **8b** was available from two routes. Reaction of *tert*-butyl diazoacetate with methyl 3-butenoate gave the diester **9** which was partially saponified to give acid **8b** as a ca. 2:1 mixture of *trans* and *cis* isomers. Alternatively, reaction of *tert*-butyl diazoacetate with benzyl 3-butenoate gave the diester **10** which could be converted to **8b** by hydrogenolysis of the benzyl ester; this procedure also gave a 2:1 mixture of *trans* and *cis* isomers.



Acids **8** were converted to the PTOC precursors **3** by a conventional sequence[13] involving reaction of the acid with oxalyl chloride to give the corresponding acid chloride and reaction of this with the sodium salt of *N*-hydroxypyridine-2-thione. PTOC ester **3a** was obtained as a 2:1 mixture of *trans* and *cis* isomers as determined by NMR spectroscopy reflecting the original composition of the acid employed. In the case of PTOC ester **3b**, however, we obtained the *trans* isomer after chromatography with very little (<5%) of the *cis* isomer present as determined by NMR spectroscopy. The stereochemistry of *trans*-**3b** was established by characterizing both isomers of acid **8b** by n.O.e. experiments and hydrolyzing a portion of **3b** to give *trans*-**8b**. We presume that the *cis*-**3b** was formed in the PTOC preparation but hydrolyzed upon silica gel chromatography.

Authentic samples of the ester products **6** and **7** formed in the radical chain reactions were prepared, and the products of the reactions of PTOC esters **3**, analyzed by GC-mass spectrometry, were found to be identical to the authentic samples. In the case of reactions of the mixture of isomers of **3a**, we observed formation of a small amount of *trans*-**6a** but none of the *cis* isomer. However, the peaks from authentic *trans*- and *cis*-**6a** were incompletely resolved in our GC analyses, and it is possible that a small amount of *cis*-**6a** (i.e. 10% or less of the amount of *trans*-**6a**) could have been present.

KINETIC STUDIES

Reactions of PTOC esters **3** in THF in the presence of varying amounts of PhSeH were conducted between temperatures of -42 and 37 °C, and product ratios were determined by GC. The results are given in Tables 1 and 2. As expected for the fast ring openings of radicals **4**, only a small amount of trapping occurred. For PTOC ester **3a**, reactions were conducted with the 2:1 mixture of isomers, but the only trapped product observed was *trans*-**6a**. Therefore, in order to estimate the **7/6** ratio for the *trans* isomer, we have used a value of 0.67 × (% yield of **7a**) in the calculation of this ratio. The assumption is that the two isomers of PTOC ester **3a** were converted to radicals **4a** with equal efficiency, but we note that it is possible that this is not the case.[14] Fortunately, because *cis*-**3a** was the minor isomer, unequal efficiencies in the production of radicals from the isomeric PTOC esters would have introduced only a small error in the calculated rate constants for ring opening of *trans*-**4a**. Because *trans*-**3b** was >95% of the PTOC sample, we have treated the data as if none of the *cis* isomer was present.

The relative Arrhenius functions for rearrangement and trapping of radicals **4** are given in equations 2 and 3 (errors at 2σ in the final significant figure are given in parentheses) and are shown graphically in Figure 1. Benzeneselenol was calibrated[12] against the cyclopropylcarbinyl radical ring opening, and we make the common assumption that PhSeH trapping of the substituted and parent CPC radicals occurs with the same rate constants. Therefore, addition of the relative Arrhenius functions for rearrangement and trapping in equations 2 and 3 to the Arrhenius function for PhSeH trapping[15] gives the Arrhenius functions for rearrangement of *trans*-**4a** and *trans*-**4b** in equations 4 and 5. The error values in the latter equations reflect precision relative to cyclopropylcarbinyl radical ring opening kinetics. The calculated rate constants for ring openings of these two radicals at 25 °C are 7×10^{10} s^{-1} (**4a**) and 12×10^{10} s^{-1} (**4b**), about three orders of magnitude faster than rearrangement of the unsubstituted parent system. As one would expect, the Arrhenius functions and rate constants for ring opening of the two radicals are quite similar. We note that the *cis*-**4a** must have rearranged faster than *trans*-**4a** because we did not observe the cyclic product *cis*-**6a**.

Table 1. Products from reactions of the (*trans*-2-ethoxycarbonylcyclopropyl)methyl radical (**4a**).[a]

Temp	$[PhSeH]_m$	Yield	**7a/6a**	k_r/k_T
25	0.52	82	64.3	33.4
	0.70	75	57.2	40.0
	0.98	83	25.8	25.3
	1.09	88	36.0	39.2
	1.66	84	20.3	33.7
-23	0.70	83	26.9	18.8
	1.16	85	16.1	18.7
-42	0.164	87	90.8	14.9
	0.44	79	40.1	17.6
	0.71	81	20.2	14.3
	0.89	81	16.4	14.6
	1.44	78	9.3	13.2

Table 2. Products from reactions of the (*trans*-2-*tert*-butoxycarbonylcycloropyl)methyl radical (**4b**).[a]

Temp	$[PhSeH]_m$	Yield	**7b/6b**	k_r/k_T
37	0.62	83	115	71.3
	0.90	100	76.5	68.9
	1.28	72	42.7	54.7
	1.71	64	33.8	57.8
0	0.44	62	130	57.2
	0.72	73	67.9	48.9
	0.98	74	33.1	32.4
	1.44	93	22.1	31.8
-42	0.34	65	58.9	20.0
	0.54	89	39.2	21.2
	0.80	63	20.2	16.2
	1.25	65	16.4	20.5

[a]Temperatures in °C are believed to be accurate to ± 2 °C. The yield columns give total % yields of **6** and **7** determined against an internal standard.

(for *trans*-**4a**) $\log ((k_r/k_T)/M) = 2.8(3) - 1.7(3)/2.3RT$ (2)

(for *trans*-**4b**) $\log ((k_r/k_T)/M) = 3.3(4) - 2.1(5)/2.3RT$ (3)

(for *trans*-**4a**) $\log ((k_r)\cdot s) = 13.8(3) - 4.0(3)/2.3RT$ (4)

(for *trans*-**4b**) $\log ((k_r)\cdot s) = 14.3(4) - 4.4(5)/2.3RT$ (5)

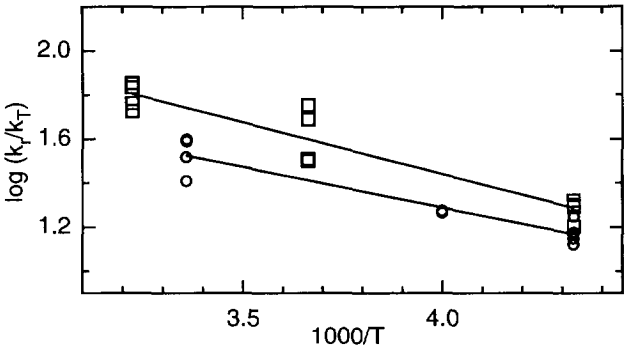


Figure 1. Relative Arrhenius functions for ring openings of radicals **4a** (circles) and **4b** (squares).

DISCUSSION

One method for evaluating our data involves consideration of the entropic terms in the Arrhenius functions for openings of radicals **4**. As noted by Ingold,[3a] the cyclopropylcarbinyl radical is relatively rigid with only one rotor, the methylene group, which must be isolated in the transition state for ring opening. Therefore, one can calculate the $\Delta S^{\ddagger}$ term which gives a log A value very close to the experimentally observed value of 13.15 for the cyclopropylcarbinyl radical (which has two modes of ring opening) or 12.85 for cleavage of one bond in this radical.[3,16] Radicals **4** are similarly rigid, and the log A terms in equations 4 and 5 should be close to 12.85; they clearly are greater than expected. Log A values in the vicinity of 14 also were obtained for other very fast ring openings of substituted CPC radicals[7,8] calibrated by PhSeH trapping with large concentrations of trapping agent, and these results might reflect a systematic error in the method.[17] Despite any systematic errors, however, the relative rate constants for ring openings of aryl and alkoxycarbonyl substituted CPC radicals should be reasonably reliable because high concentrations of PhSeH were employed in all of these studies.[7,8]

The kinetic acceleration in the rate constants for ring openings of radicals **4** of about three orders of magnitude over that of the unsubstituted parent system is consistent with values one might have predicted. For example, rate enhancements of approximately three orders of magnitude in comparison to reactions of unsubstituted analogs have been reported for 5-*exo* cyclizations of the 6-cyano-5-hexenyl radicals,[12b,18] for 3-*exo* cyclizations of 4-(*tert*-butoxycarbonyl)-3-butenyl radicals,[19] and for intermolecular reactions of alkyl radicals with acrylate esters and acrylonitriles.[20] The primary difference between the examples listed above and the ring openings studied in this work is that π-bonds in α,β-unsaturated systems were consumed in the former reactions as opposed to the cyclopropyl ring bond in the openings of radicals **4**. Apparently, any polarization of the extended π-systems that favors the transition states for alkyl radical additions to α,β-unsaturated esters is matched by similar polarizations of the "α,β-cyclopropa" groups in radicals **4**.

One can analyze the rate constants for openings of **4** from a different perspective. Previously, our group used a Marcus theory analysis of the ring opening reactions of aryl-substituted cyclopropylcarbinyl radicals.[7,8] In brief, we first used the Marcus equation (6) to calculate an intrinsic free energy term ($\Delta G^{\ddagger}_{int}$) at 25 °C for a cyclopropylcarbinyl radical ring opening from the known values for the kinetics of ring opening and free energy change in ring opening of the cyclopropylcarbinyl radical. Then, the differences in the C-H bond dissociation energies (BDE) of simple primary alkyl centers and aryl substituted positions were used to estimate the ΔG^0 values for aryl substituted CPC ring openings. From these, an expected value of $\Delta G^{\ddagger}$ for each substituted system was calculated via equation 6. The calculated $\Delta G^{\ddagger}$ values for aryl substituted CPC radical ring openings were in reasonable agreement with the experimental values.[7,8] Recent preliminary results on the kinetic effect of an alkoxy group on the CPC radical ring opening[21] suggest that this acceleration also will be predicted adequately by the Marcus theory approach.

However, when one applies the same type of Marcus theory analysis to the ring opening reactions of radicals **4**, the calculated rate constants are significantly smaller than those observed. A carbonyl group adja-

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{int} + 1/2\ \Delta G^0 + ((\Delta G^0)^2/16\Delta G^{\ddagger}_{int}) \qquad (6)$$

cent to a C-H bond leads to about a 3 kcal/mol reduction in BDE,[22,23] and the "secondary" radical center in ring opened radicals **5** contributes another 2-3 kcal/mol reduction in BDE.[23a] From combustion results, the total strain energy of methyl cyclopropanecarboxylate is somewhat less than 1 kcal/mol greater than that in cyclopropane.[24] Therefore, the expected ΔG^0 term for ring openings of radicals **4** would be about 6 to 7 kcal/mol more exothermic than that of the parent system which corresponds to predicted rate constants at 25 °C of 2-4 $\times$ 10^9 s^{-1}.[7] The 20-40 fold difference in the observed versus the predicted rate constants, amounting to about a 2 kcal/mol reduction in the observed versus the expected $\Delta G^{\ddagger}$, shows that the free energy approximation of the Marcus approach is not appropriate for the ester substituted radicals **4**. Again, one might speculate that the reduction in $\Delta G^{\ddagger}$ for openings of radicals **4** arises from favorable polarization in the transition states.

In conclusion, ester substituted cyclopropylcarbinyl radical ring openings are now calibrated; the rearrangements were found to be about three orders of magnitude faster than that of the parent, unsubstituted system. This kinetic acceleration is similar to that observed in a number of radical reactions of α,β-unsaturated esters and nitriles, and it is likely that the transition states for these reactions enjoy some degree of favorable polarization. With radical lifetimes at room temperature of about 10 ps, precursors to ester substituted cyclopropylcarbinyl radicals such as **4** fit our definition of hypersensitive radical probes that can be employed in mechanistic tests against even the fastest possible competing reactions.

EXPERIMENTAL SECTION

General. NMR spectra were obtained at 300 MHz (^{1}H) or 75 MHz (^{13}C) on $CDCl_3$ solutions containing TMS. GC-MS analyses were performed on a Hewlett Packard 5890 GC interfaced to an HP 5791A mass selective detector (EI, 70 eV). PhSeH was prepared and handled as previously described;[6,12b] typically, samples of PhSeH were contaminated with <5% of Ph_2Se_2.

(2-Ethoxycarbonylcyclopropyl)acetic acid (8a) was prepared by the method of Beckwith and Bowry.[9] The acid was obtained as a 2:1 (*trans:cis*) mixture of isomers as reported.[9]

(2-*tert*-Butoxycarbonylcyclopropyl)acetic acid (8b). A solution of *tert*-butyl diazoacetate[25] (9.6 g, 0.067 mol) in 30 mL of methylcyclohexane was added dropwise over 3.5 h to a stirring suspension of 2.0 g of $CuSO_4$ and 20 g (0.2 mol) of methyl 2-butenoate in 20 mL of methylcyclohexane at 95 °C under N_2. The reaction was allowed to proceed at 95 °C for 2 h. The cooled reaction mixture was passed through a short pad of neutral alumina. The resulting oily residue was distilled to give 5.7 g (0.027 mol, 40%) of methyl (2-*tert*-butoxycarbonylcyclopropyl)acetate (**9**) (bp 72-73 °C, 0.1 Torr) as a 2:1 (*trans:cis*) mixture of isomers.

A mixture of diester **9** (1.7 g, 7.9 mmol) and 1 equiv. of NaOH in 23 mL of MeOH and 2 mL of water was heated at a gentle reflux for 3 h. The mixture was cooled, 10 mL of water was added, and the resulting mixture was extracted with ether. The aqueous solution was acidified to pH 2-3 and extracted with ether. The latter ethereal phase was dried ($MgSO_4$) and concentrated to give 0.9 g (4.5 mmol, 57%) of acid **8b** as an oil that was a 2:1 mixture of *trans* and *cis* isomers. HRMS (of the mixture): calcd for $C_{10}H_{16}O_4$ $(M-C_4H_8)^+$, 144.0422; found, 144.0426. For *trans*-**8b**. ^{1}H NMR: δ 2.46-2.22 (m, 2 H), 1.64-1.60 (m, 1 H), 1.44 (s, 9 H), 1.41-1.38 (m, 1 H), 1.22-1.16 (m, 1 H), 0.77-0.72 (m, 1 H). ^{13}C NMR: δ 172.0, 80.5, 37.4, 28.1, 21.0, 16.9, 14.4. For *cis*-**8b**. ^{1}H NMR: δ 2.78-2.61 (m, 2 H), 1.76-1.72 (m, 1 H), 1.49-1.43 (m, 1 H), 1.44 (s, 9 H), 1.09-1.04 (m, 1 H), 0.94-0.88 (m 1 H) (OH signal not observed). ^{13}C NMR: δ 172.7, 80.7, 32.0, 28.1, 18.7, 15.9, 12.8 (carboxylic acid carbons not observed). The structures of acids **8b** were deduced from ^{1}H NMR decoupling and n.O.e. experiments performed at 500 MHz.

1-[[(2-(Ethoxycarbonyl)cyclopropyl)methyl)carbonyl]oxy]-2(1*H*)-pyridinethione (3a). A mixture of acid **8a** (2.1 g, 12.2 mmol) and oxalyl chloride (1.9 g, 15 mmol) in 10 mL of dry CH_2Cl_2

was stirred for 10 h. Excess oxalyl chloride and solvent were removed under vacuum. The residue was dissolved in 10 mL of dry benzene, and the resulting solution was added dropwise to a stirred suspension of the sodium salt of *N*-hydroxypyridine-2-thione (2.18 g, 14.6 mmol) and DMAP (0.14 g) in 10 mL of benzene in a 0 °C bath in a vessel shielded from light. After 12 h at room temperature, the reaction mixture was extracted with 10% aqueous $NaHSO_4$ soln, 5% aqueous $NaHCO_3$ soln and satd aqueous NaCl soln. The organic layer was dried ($MgSO_4$) and concentrated to give a residue that was purified by chromatography (silica gel, hexanes/ethyl acetate, 9:1, v:v) to yield 2.0 g (7.1 mmol, 58%) of **3a**. ^{1}H NMR spectroscopy showed that the product was a 2:1 mixture of *trans* and *cis* isomers. ^{1}H NMR: δ 7.68 (overlapping doublets, 1 H, J = 8.6 Hz), 7.60 (overlapping doublets, 1 H, J = 6.9 Hz), 7.22 (overlapping triplets, 1 H, J = 8.4 Hz), 6.65 (overlapping triplets, 1 H, J = 6.8 Hz), 4.21-4.07 (overlapping quartets, 2 H, J = 7.1 Hz), 3.22-3.01 (m, 0.7 H), 2.83-2.68 (m, 1.3 H), 1.91-1.80 (m, 1.3 H), 1.68-1.62 (m, 0.7 H), 1.39-1.33 (m, 1 H), 1.30-1.24 (overlapping triplets, 3 H, J = 7.1 Hz), 1.05-0.93 (m, 1 H).

1-[[((*trans*-2-(*tert*-Butoxycarbonyl)cyclopropyl)methyl)carbonyl]oxy]-2(1*H*)-pyridinethione (*trans*-**3b**) was prepared from a 2:1 (*trans:cis*) mixture of acid **8b** by a procedure similar to that used above for the preparation of **3a**. Silica gel chromatography (hexanes/ethyl acetate, 9:1, v:v) gave *trans*-**3b** in 40% yield. ^{1}H NMR: δ 7.68 (dd, 1 H, J = 8.8, 1.8 Hz), 7.59 (dd, 1 H, J = 6.8, 1.8 Hz), 7.21 (dt, 1 H, J = 8.7, 1.6 Hz), 6.64 (dt, 1 H, J = 6.8, 1.7 Hz), 2.83-2.63 (m, 2 H), 1.82-1.73 (m, 1 H), 1.57-1.51 (m, 1 H), 1.44 (s, 9 H), 1.30-1.24 (m, 1 H), 0.91-0.84 (m, 1 H).

Ethyl *trans*-2-methylcyclopropanecarboxylate (*trans*-**6a**) and ***tert*-butyl *trans*-2-methylcyclopropanecarboxylate** (*trans*-**6b**) were prepared by cyclopropanation of ethyl and *tert*-butyl *trans*-crotonate, respectively, with the reagent prepared from trimethylsulfoxonium iodide and NaH in DMF by the reported method.[26]

For *trans*-**6a**. ^{1}H NMR: δ 4.15 (q, 2 H, J = 7.2 Hz), 1.36-1.32 (m, 1H), 1.30-1.26 (m, 1 H), 1.22 (t, 3 H, J = 7.1 Hz), 1.14-1.10 (m, 1 H), 1.07 (d, 3 H, J = 5.9 Hz), 0.64-0.60 (m, 1 H). ^{13}C NMR: δ 174.4, 60.2, 21.2, 17.7, 16.9, 16.6, 14.2. MS: *m/z* (rel. int.), 101 (18), 100 (77), 83 (84), 82 (18), 69 (17), 55 (100), 54 (19), 53 (15). HRMS: calcd for $C_7H_{12}O_2$, 128.0837; found, 128.0837.

For *trans*-**6b**. ^{1}H NMR: δ 1.42 (s, 9 H), 1.31-1.26 (m, 1 H), 1.24-1.20 (m, 1 H), 1.08 (d, 3 H, J = 5.8 Hz), 1.07-1.04 (m, 1 H), 0.68-0.65 (m, 1 H). ^{13}C NMR: δ 173.8, 79.9, 28.1, 22.3, 17.8, 16.6, 16.4. MS: *m/z* (rel int.), 101 (42), 100 (40), 83 (62), 57 (100), 56 (23), 55 (25). HRMS: calcd for $C_9H_{16}O_2$ (M-C_4H_8)$^+$, 100.0524; found, 100.0529.

A mixture of *cis*- and *trans*-**6a** (ca. 1:4) was prepared for GC and GC-mass spectral analyses by reaction of ethyl acrylate with CH_3CHI_2 and Et_2Zn.[27]

Ethyl 4-pentenoate (**7a**) and ***tert*-butyl 4-pentenoate** (**7b**) were prepared by esterification of commercial 4-pentenoic acid via the acid chloride (oxalyl chloride).

Kinetic Method. The method employed was the same as that previously described.[7,12] Solutions of PTOC esters **3a** and **3b** (ca. 0.04 mmol), a hydrocarbon internal standard and PhSeH in 1 mL of THF were prepared in shielded reaction vessels. After equilibration in a temperature regulated bath for several minutes, the shields were removed, and the reaction mixtures were irradiated with a 150 W tungsten-filament bulb at a distance of 0.5 m for 30 min. The product mixtures were analyzed by GC-mass spectrometry (25 m × 0.25 mm, Carbowax column) to identify the products. Yields were determined by GC (15 m × 0.5 mm, Carbowax column) on an FID equipped instrument. Tables 1 and 2 contain the results.

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