Kinetics of Cyclopropylcarbinyl Radical Ring Openings Measured Directly by Laser Flash Photolysis

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Abstract: The kinetics of ring openings of cyclopropylcarbinyl radicals containing reporter groups were measured directly by laser flash photolysis (LFP) methods. The reporter groups are aryl-substituted cyclopropanes at the position of the radical center in the incipient product, and the initial ring-opening reaction gives an aryl-substituted cyclopropylcarbinyl radical that opens "instantly" on the nanosecond time scale to give benzylic and diphenylalkyl radical products that are detected by UV spectroscopy. Three reporter group designs have been studied. The most useful design is that in substituted (*trans*-2-(2,2-diphenylcyclopropyl)-cyclopropyl)methyl radicals (**7**). The important synthetic intermediate for production of this series is *N*-methoxy-*N*-methyl-*trans*-2-(2,2-diphenyl-1*R**-cyclopropyl)-1*S**,2*R**-cyclopropanecarboxamide (**15a**) which has been prepared diastereomerically pure. The syntheses of **15a** and a series of PTOC ester radical precursors derived from **15a** are described. Laser photolysis (355 nm) of PTOC esters gave acyloxyl radicals that decarboxylated to give cyclopropylcarbinyl radicals that were studied. The substitutions at the cyclopropylcarbinyl position of radicals **7** were H, H (**7a**); H, Me (**7b**); Me, Me (**7c**); H, CO_2Et (**7d**); Me, CO_2Et (**7e**); and H, Ph (**7f**). The kinetics of ring openings of radicals **7** were measured in THF and in four cases in CH_3CN in the temperature range −41 to +50 °C. Alkyl radicals **7a** and **7b** displayed no kinetic solvent effect, whereas ester-substituted radicals **7d** and **7e** did. The ester-substituted radicals react about as fast as the alkyl-substituted radicals due to favorable polarization in the transition states for ring opening. The phenyl-substituted radical **7e** ring-opens about 3 orders of magnitude less rapidly than the parent radical **7a**. The structures and energies of the ground states, rotational transition states, and ring-opening transition states for a series of substituted cyclopropylcarbinyl radicals corresponding to **7a**−**e** were computed by the hybrid density functional theory B3LYP/6-31G*, and the ring-opening kinetics were compared to those predicted from the computational barriers. The precision in the Arrhenius functions for ring openings of radicals **7** permits meaningful comparisons of the log *A* terms to those predicted from thermochemical considerations.

Knowledge of the rate constants of radical reactions is necessary both for mechanistic work and for planning of radical-based conversions in synthesis. For alkyl radicals, the linchpin kinetic values are the rate constants for simple unimolecular rearrangements, often referred to as "radical clocks",[1] such as the cyclization of the 5-hexenyl radical and ring opening of the cyclopropylcarbinyl radical. From numerous competition kinetic studies, the rate constants of these reactions have been incorporated into rate constants of other radical reactions such that an extensive, interrelated scale of alkyl radical kinetics exists.[2]

The cyclopropylcarbinyl radicals, with rate constants for ring opening on the order of 10^8 s^{-1} at ambient temperature, are important for a number of reasons. Simple cyclopropylcarbinyl radicals are the best calibrated of the "fast-reacting" radical clocks, and their rate constants provide the foundation for the kinetics of radicals that react faster. In addition, they provide excellent platforms for the study of steric and electronic effects of substituents due to the rigidity of the systems, and they are among the more tractable from a computational perspective due to the small number of atoms and the inflexible ring. It is somewhat unusual, therefore, that virtually none of the rate constants for cyclopropylcarbinyl ring-opening reactions have been measured directly. ESR spectroscopic measurements of the rates of ring opening of the cyclopropylcarbinyl radical were conducted at low temperatures,[3] and the muon-containing analogues of 1-methyl- and 1,1-dimethylcyclopropylcarbinyl radical were studied by muon spin-rotation spectroscopic methods.[4] However, the Arrhenius functions obtained in these studies are unreasonable, and the results cannot be extrapolated to ambient temperature with confidence. Laser flash photolysis (LFP) kinetic units have adequate temporal resolution for direct measurements of cyclopropylcarbinyl radical reactions at ambient temperature, but the lack of a prominent chromophore in most of these radicals and their ring-opened products precludes UV detection. Thus, the kinetics of ring openings of most cyclopropylcarbinyl radicals are available indirectly from competition trapping studies with calibrated trapping agents.[2]

We recently introduced the use of "reporter groups" for direct LFP kinetic studies of radicals that do not otherwise contain useful chromophores.[5] The reaction of interest produces an aryl-substituted cyclopropylcarbinyl radical that ring-opens "instantly" to give a benzylic or diphenylalkyl radical that can be observed in the UV. Examples of the application of the method for measuring cyclopropylcarbinyl radical ring openings were

(1) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317−323.
(2) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.
(3) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024−7026.
(4) Burkhard, P.; Roduner, E.; Hochmann, J.; Fischer, H. *J. Phys. Chem.* **1984**, *88*, 773−777.
(5) Newcomb, M.; Tanaka, N.; Bouvier, A.; Tronche, C.; Horner, J. H.; Musa, O. M.; Martinez, F. N. *J. Am. Chem. Soc.* **1996**, *118*, 8505−8506.

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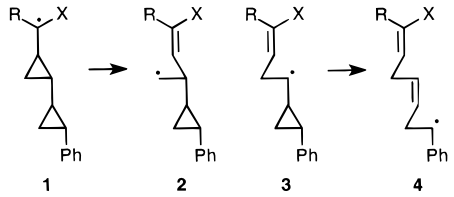
Scheme 1



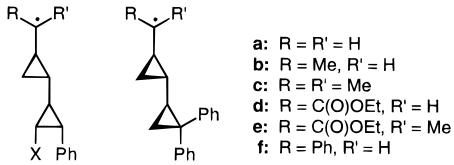
reported in the original communication[5] and more recently.[6] In this work we report the syntheses of a diastereomerically pure intermediate and several precursors to substituted cyclopropylcarbinyl radicals, detailed LFP kinetic studies of cyclopropylcarbinyl radical ring openings, and analyses of the kinetics via computational studies of the parent radicals.

Results

Design of Reporter Groups. The reporter group approach as applied to cyclopropylcarbinyl radical ring openings is exemplified in Scheme 1. The radical of interest (**1**) is produced by laser irradiation. The ring opening of **1** will give both **2** and **3**. Radical **3** is a 2-arylcyclopropylcarbinyl radical which rapidly ring-opens to give a UV-detectable benzylic radical (**4**) in this example. Because the rearrangements of aryl-substituted cyclopropylcarbinyl radicals are extremely fast, $k > 1 \times 10^{11}$ s^{-1} at ambient temperature,[7] the kinetics of the reporting reaction are not convoluted with those of the reaction of interest. That is, the observed kinetics are for the initial radical ring-opening reactions. One should note that the sums of the rate constants for reaction by both channels (i.e., **1** → **2** + **3**) are measured even though the observed products are from only one of the reaction channels.

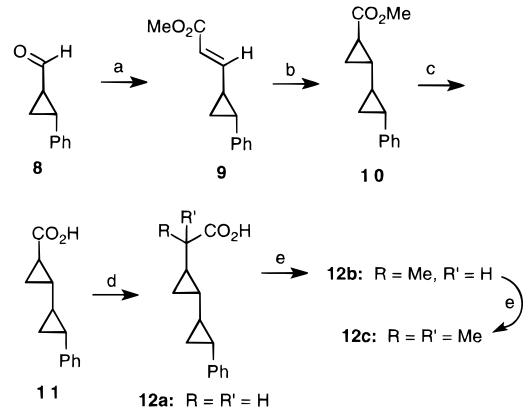
In principle, several designs for the reporting group moiety are possible; the only requirement is that the final product is detectable by UV spectroscopy. In practice, the molar absorptivity of the reporter radical and the difficulty in synthesis of diastereomerically pure compounds can place limits on the practicality of a given design. The second point is especially important for studies of cyclopropylcarbinyl radicals with reporter groups because several asymmetric centers are present in the initial radicals and it is likely that diastereomers will react with different rate constants, thus precluding detailed analysis of the kinetic effects of substituents.

We have studied three different reporter designs (shown in radicals **5**−**7**), each of which performed as expected. The



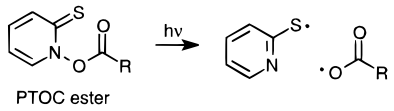
precursors to radicals **5** are prepared from commercially available *trans*-2-phenylcyclopropanecarboxylic acid, but the syntheses of the precursors for radicals **6** and **7** require additional steps. An advantage of the precursors to radicals **6** is that the symmetry of the reporting group reduces the number of diastereomers produced in the syntheses. The reporter moiety in radicals **7** offers the advantage that the products of the reporting reaction are diphenylalkyl radicals which have larger molar extinction coefficients than benzylic radicals,[8] thus permitting more precise kinetic measurements. An early intermediate in the synthesis of the precursors to radicals **7** could be crystallized to diastereomeric purity, and most of the studies described here involve this series.

Scheme 2[a]



[a] Key: (a) $Na^+(EtO)_2P(o)C(^-)HCO_2Me$; (b) (*N*,*N*-dimethylamino)(methyl)(phenyl)sulfoxonium tetrafluoroborate; (c) KOH, H_2O; (d) (i) $(COCl)_2$, (ii) CH_2N_2, (iii) AgO; (e) LDA, CH_3I.

For studies of the relatively fast ring openings of cyclopropylcarbinyl radicals, another limitation on the design of the radical precursors exists. The target radicals must either be produced directly from laser irradiation or result from very fast unimolecular processes such as the decarboxylations of acyloxyl radicals which occur with rate constants exceeding 1×10^9 s^{-1} at ambient temperature.[9,10] The latter choice is desired for the systems studied here because the immediate radical precursors can be prepared from cyclopropylacetic acid derivatives that are stable. Several peroxy acid and related derivatives afford acyloxyl radicals upon irradiation. We employed Barton's PTOC ester derivatives,[11,12] which are known to be excellent sources of acyloxyl radicals when irradiated with 355 nm light from a Nd:YAG laser.[13−15] PTOC esters are prepared from the



corresponding carboxylic acids which were our synthetic targets.

Syntheses of Precursors. The synthesis of the requisite carboxylic acids for PTOC ester precursors to the series of primary, secondary, and tertiary radicals **5** (Scheme 2) was previously reported.[5] Thus, Horner−Emmons olefination of aldehyde **8** gave acrylate **9** which was cyclopropanated to give **10**. Following saponification, acid **11** was homologated by a

(6) Newcomb, M.; Horner, J. H.; Emanuel, C. J. *J. Am. Chem. Soc.* **1997**, *119*, 7147−7148.

(7) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915−10921.

(8) Chatgilialoglu, C. In *Handbook of Organic Photochemistry*; Scaiano, J. C., Ed.; CRC Press: Boca Raton, FL, 1989; Vol. 2, pp 3−11.

(9) Falvey, D. E.; Schuster, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 7419−7420.

(10) Bockman, T. M.; Hubig, S. M.; Kochi, J. K. *J. Org. Chem.* **1997**, *62*, 2210−2221.

(11) The acronym PTOC derives from pyridinethioneoxycarbonyl. PTOC esters are actually anhydrides of a carboxylic acid and the thiohydroxamic acid *N*-hydroxypyridine-2-thione.

(12) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−3924.

(13) Bohne, C.; Boch, R.; Scaiano, J. C. *J. Org. Chem.* **1990**, *55*, 5414−5418.

(14) Ha, C.; Horner, J. H.; Newcomb, M.; Varick, T. R.; Arnold, B. R.; Lusztyk, J. *J. Org. Chem.* **1993**, *58*, 1194−1198.

(15) Aveline, B. M.; Kochevar, I. E.; Redmond, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 9699−9708.

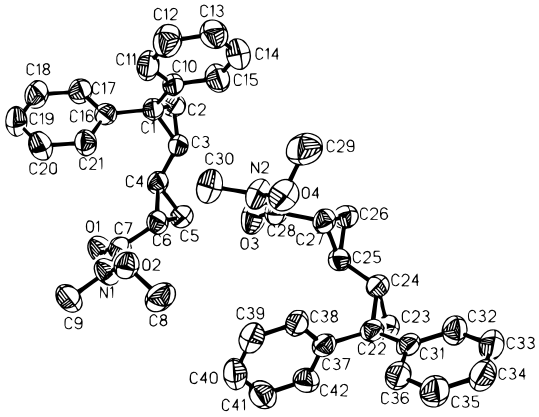
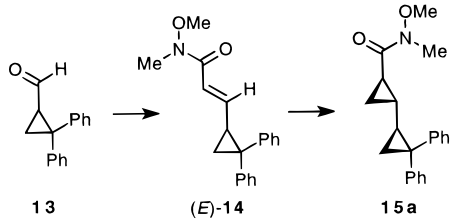


Figure 1. ORTEP drawing of **15a**. The unit cell contains two molecules.

Wolff rearrangement to give acid **12a** that was sequentially methylated to **12b** and **12c**. The reactions in Scheme 2 proceeded in good-to-excellent yield, but ester **10** was formed as a 1:1 mixture of diastereomers that was not separated. Therefore, acids **12** were diastereomeric mixtures, and acid **12b** was a mixture of up to four diastereomers. Each of the diastereomeric mixtures of acids **12** was converted to the corresponding mixture of PTOC esters for LFP studies.[5] A mixture of diastereomers of 2-(*trans*,*trans*-2,3-diphenylcyclopropyl)cyclopropylacetic acid was prepared from *trans*,*trans*-2,3-diphenylcyclopropanecarboxaldehyde by a similar sequence of reactions.[16]

In initial syntheses of the precursors for radicals **7**, a diastereomer problem similar to that arising in the preparation of acids **12** was apparent. 2,2-Diphenylcyclopropancarboxaldehyde (**13**) was converted to the corresponding α,β-unsaturated methyl ester, but a sluggish cyclopropanation reaction led to an approximately 1:1 mixture of diastereomers.[5] Therefore,



we examined the use of Weinreb amides for the syntheses of the series of acids necessary for precursors to radicals **7**. Aldehyde **13** was converted to a 5:1 mixture of diastereomers of the corresponding Weinreb amides from which amide (*E*-**14**), the major diastereomer, was obtained by chromatography. Cyclopropanation of (*E*-**14**) gave amide **15a** and its diastereomer **15b** as a 5.5:1 mixture. Diastereomerically pure **15a**, obtained by crystallization, was characterized by an X-ray crystal structure determination (Figure 1).

Compound **15a** was the starting point for the syntheses of all of the precursors for radicals **7** (Scheme 3). The reduction of **15a** and reactions with methyl and phenyl Grignard reagents gave aldehyde **16a** and ketones **16b** and **16f**, respectively. The carbonyl compounds were converted to enol ethers **17** by Wittig reactions, and the enol ethers were hydrolyzed to give the homologated aldehydes **18**. The hydrolysis reaction of enol ether **17f** proceeded in poor yield, and several variations of the reaction sequence were attempted with even poorer results. Oxidation of aldehydes **18** gave the corresponding carboxylic

(16) Tanaka, N.; Newcomb, M. Unpublished results.

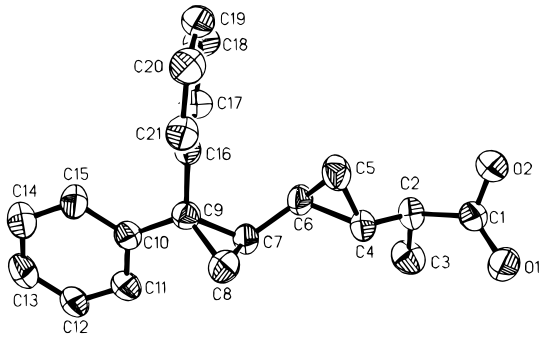


Figure 2. ORTEP drawing of diastereomer 1 of acid **19b**.

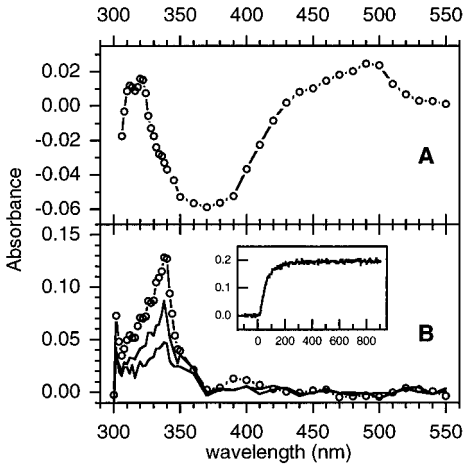
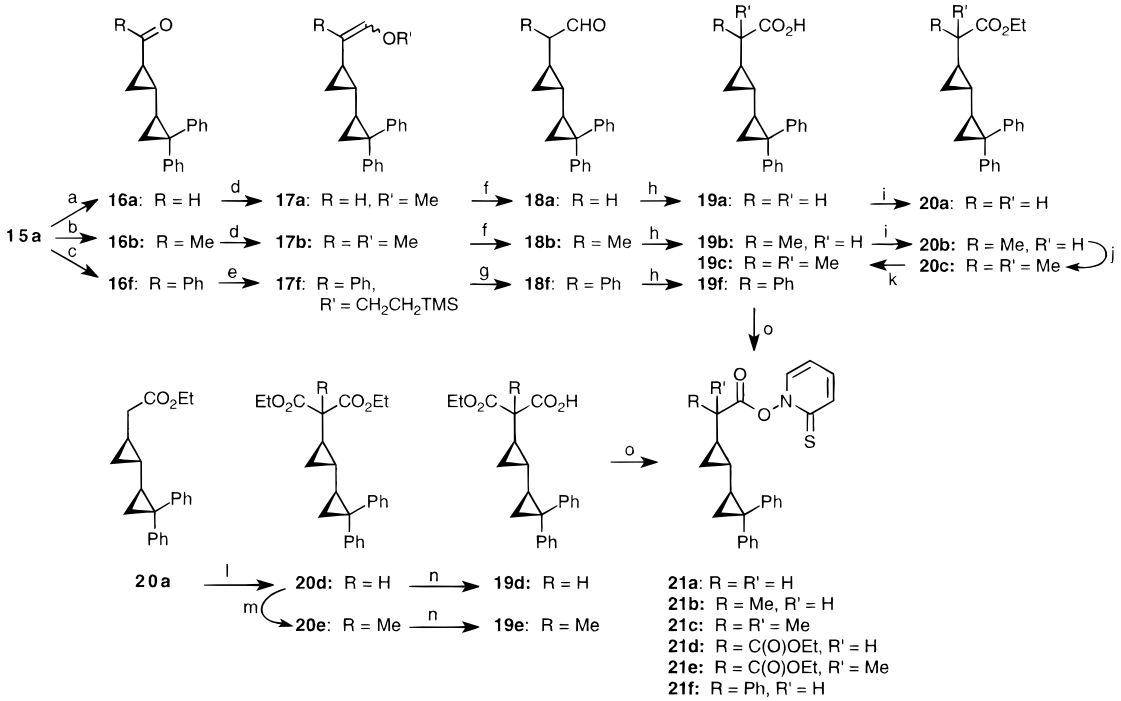


Figure 3. (A) Observed spectrum 34 ns after laser irradiation of the PTOC precursor to radical **5a** at ambient temperature. The benzylic radical product (**22a**) has λ_{max} at ca. 320 nm, and the pyridine-2-thiyl radical has λ_{max} at 490 nm. The strong bleaching is due to destruction of the PTOC precursor which has λ_{max} at ca. 360 nm. (B) Time-resolved spectra from laser irradiation of precursor **21e** at 20 °C. The spectra are for 52, 72, and 160 (-O-) ns after irradiation; the data at 32 ns have been subtracted to give a baseline. Product radical **23e** with λ_{max} at 335 nm is forming with time; decay of the pyridine-2-thiyl radical is insignificant on the time scale of these measurements. The inset shows a kinetic trace at 338 nm where the *x* axis is time in nanoseconds.

acids **19a**, **19b**, and **19f**. Esterification of acid **19b** to the ethyl ester (**20b**) followed by methylation of the lithium enolate gave ester **20c**, which was hydrolyzed to give acid **19c**. Acid **19a** was esterified to ethyl ester **20a**, which was converted to the diethyl malonate **20d** by ethoxycarboxylation of the lithium enolate, and methylation of the enolate of **20d** gave diethyl malonate **20e**. Partial hydrolysis of malonates **20d** and **20e** gave the monoesters **19d** and **19e**. The PTOC ester precursors **21** were prepared from the corresponding acids **19** by reaction of the corresponding acyl chlorides with *N*-hydroxypyridine-2-thione sodium salt.

In the synthetic sequence for PTOC esters **21**, only acids **19a** and **19c** were produced as single diastereomers; each of the other acids was obtained as a mixture of diastereomers. However, the center of asymmetry that results in diastereomeric mixtures for acids **19b** and **19d**−**f** is at the incipient radical position in radicals **7**, and the mixtures of diastereomers of PTOC esters **21** will give a single radical in each case and result in no complications in the kinetic studies. This was explicitly demonstrated in the case of PTOC ester **21b**. The two diastereomers of acid **19b** were separated by column chromatography, and one of these diastereomers was characterized by X-ray crystallography (Figure 2). When the two diastereomerically pure PTOC esters **21b** were prepared from the diastere-

Scheme 3[a]



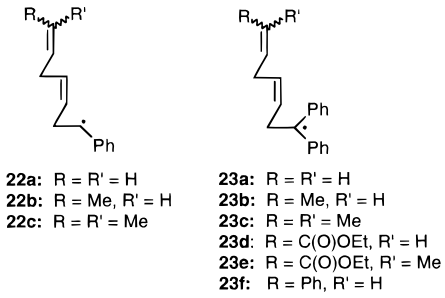
[a] Key: (a) $LiAlH_4$; (b) MeMgBr; (c) PhMgBr; (d) LiHMDS, $Ph_3P^+CH_2OCH_3Cl^-$; (e) LiHMDS, $Ph_3P^+CH_2OCH_2CH_2Si(CH_3)_3Cl^-$; (f) HCl, H_2O, heat; (g) CF_3CO_2H; (h) CrO_3, H_2SO_4, acetone; (i) EtOH, TsOH, benzene, heat; (j) LDA, CH_3I; (k) KOH, H_2O; (l) LDA, $NCCO_2Et$; (m) NaH, CH_3I; (n) LiOH (1 equiv), EtOH; (o) (i) $(COCl)_2$, benzene, DMF (catalyst), (ii) *N*-hydroxypyridine-2-thione sodium salt

omers of acid **19b** and studied independently by LFP, the results were indistinguishable (see below).

Spectroscopy. Members of the PTOC family of radical precursors have a strong, long wavelength absorbance centered at approximately 360 nm, and irradiation with the third harmonic of a Nd:YAG laser (355 nm) cleaves these compounds with high efficiency.[15] These two features require that LFP studies are conducted with dilute, flowing solutions. To measure kinetics at variable temperatures, solutions of the precursor were thermally equilibrated in a jacketed addition funnel. Temperatures were controlled with a $MeOH/H_2O$ solution from a temperature-regulated bath that was circulated through the jacket of the addition funnel. After thermal equilibration and sparging with helium, the PTOC ester solutions were allowed to flow through a quartz flow cell. Temperatures were measured with a thermocouple placed in the flowing stream about 1 cm above the irradiation zone.

Low-temperature LFP studies with flowing solutions present an additional problem in that condensation on the cell faces must be avoided. For studies conducted below 0 °C, a flow cell in an argon gas-filled, fabricated housing that contained quartz windows was employed. The practical lower temperature limit with our unit is −40 °C, at which temperature we observed variations of about ±0.25 °C during the course of a series of runs.

The ultimate detectable products from radicals **5** are benzylic radicals **22** which were expected to have long wavelength λ_{max} at about 315−320 nm, and those from radicals **7** are diphenylalkyl radicals **23** which should have λ_{max} at about 330−335 nm.[8] The PTOC esters absorb modestly in the region 300−340 nm, so the initial photochemical reaction results in a decrease in signal intensity, a bleaching, in the region where the products absorb except for the special case of radical **7f**, which is discussed below. Following the initial bleaching, benzylic or diphenylalkyl radical signals grew in at the expected wavelengths. Figure 3 shows some typical spectra observed following production of radicals **5a** and **7e** from the corresponding PTOC esters. The spectrum from **5a** shows the absorbance of the benzylic radical product **22a** with λ_{max} at about 320 nm, a strong bleaching centered at 370 nm from destruction of the PTOC ester, and a long wavelength absorbance due to the byproduct radical, pyridine-2-thiyl, with λ_{max} at 490 nm.[14,17] The time-resolved spectrum of **23e** was obtained by subtracting the signals observed at short reaction time from those observed later, with the result that growing signals evolve in a positive direction from the baseline and decaying signals evolve negatively; virtually no decay of the pyridine-2-thiyl radical signal at 490 nm occurs in the short time frame of the cyclopropylcarbinyl radical ring openings.



The benzylic radical **7f** is a special case. The first observable transient, radical **7f**, absorbs with λ_{max} at about 315 nm, but the initial UV spectrum contained a maximum absorbance close to 310 nm due to the combined effect of the superimposition of the spectrum of **7f** with the bleaching spectrum from destruction of the PTOC precursor **21f**. With time, the spectrum of the benzylic radical **7f** evolved smoothly into the spectrum of the diphenylalkyl radical **23f** (Figure 4). Because the extinction coefficient of the diphenylalkyl radical is larger than that of

(17) Alam, M. M.; Watanabe, A.; Ito, O. *J. Org. Chem.* **1995**, *60*, 3440−3444.

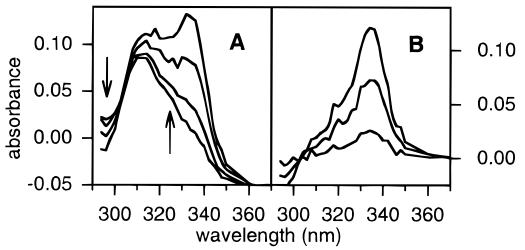


Figure 4. Time-resolved spectra obtained upon irradiation of **21f**. (A) Data collected 0.20, 1.00, 1.80, and 5.80 μs after irradiation; the arrows show the direction of signal evolution with time. (B) Data from 1.00, 1.80, and 5.80 μs; the data at 0.20 μs have been subtracted to give a baseline.

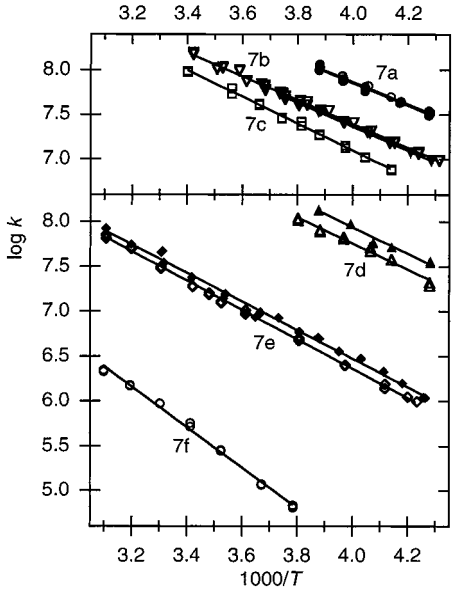


Figure 5. Observed rate constants (s^{-1}) for fragmentations of radicals **7a**−**f**. The hollow symbols are measurements in THF, and the solid symbols are measurements in acetonitrile. The lines are the Arrhenius functions in Table 1.

the benzylic radical, the initially observed absorbance at λ_{max} for **7f** never decreased, but an isosbestic point was observed at 304 nm. Figure 4A shows the observed time-resolved spectra with no corrections, and Figure 4B shows the same spectra with the data at 200 ns subtracted from data obtained later. The subtraction procedure removes negative signals from the bleaching of precursor **21f** and positive signals from the spectrum of the initially formed radical **7f**. The spectrum in Figure 4B is mainly that of the diphenylalkyl radical product **23f** because the extinction coefficients of benzylic radicals are only about 25% as great as those of diphenylalkyl radicals at the respective λ_{max} values and benzylic radicals have no appreciable absorbance above 330 nm.[8]

Kinetics. The ring-opening reactions of cyclopropylcarbinyl radicals have rate constants in the range of 10^8 s^{-1} at ambient temperature, and the reporter groups impart a small kinetic acceleration to these reactions as discussed below. Thus, we performed studies with several systems at temperatures within the range of −40 to +50 °C. The minimum represents the lower limit of our apparatus. An upper temperature limit exists due to the thermal instability of the PTOC esters, but there is also a maximum kinetic limit due to the response time of the electronics of the system. The measured response of our apparatus to an "instantaneous" signal was 2.5×10^8 s^{-1}. This instrumental response will be convoluted into all kinetic measurements, but the error introduced in reactions with rate constants smaller than 4×10^7 s^{-1} is insignificant (<3%) in comparison to observed temperature variations of ±0.25 °C.

For reactions faster than 4×10^7 s^{-1}, the instrumental response rate was deconvoluted from the observed kinetic traces by standard Fourier transform (FT) methods using eq 1 where

$$K_{deconvol} = FT^{-1}[FT(K_{exp})/FT(K_{inst})] \quad (1)$$

$K_{deconvol}$ is the deconvoluted kinetic trace, K_{exp} is the experimentally measured kinetic trace with rate constant k_{exp}, and K_{inst} is the impulse response function of the system. In this case, K_{inst} was taken to be a "noiseless" exponential function decaying with a rate of 2.5×10^8 s^{-1} in order to avoid the introduction of additional random error. The actual errors in values for k_{exp} were small in all cases (about 1% for reactions of radicals **7**), but the magnitude of the error after deconvolution increases in an exponential fashion as the rate constant approaches the instrumental limit. Thus, for example, the error in $k_{exp} = (8.93 \pm 0.08) \times 10^7$ s^{-1} increased upon deconvolution to give $k = (9.89 \pm 0.35) \times 10^7$ s^{-1}. The fastest reaction studied in this work had $k_{exp} = 1.3 \times 10^8$ s^{-1} which gave $k = 1.6 \times 10^8$ s^{-1} when deconvoluted.

Radicals **5a**−**c** and **6a** were investigated in preliminary demonstrations of feasibility before the kinetic unit was equipped for operation below 0 °C, and a mixture of diastereomers of the precursors was used in each case. For the primary radicals **5a** and **6a** in THF, rapid signal growth was observed at 315 nm even at 0 °C; the rate constants for these reactions were greater than 1×10^8 s^{-1}. Radicals **5b** and **5c** in THF displayed measurable rate constants of 5.6×10^7 s^{-1} at 11 °C for **5b** and 3.0×10^7 s^{-1} at 10.5 °C for **5c**. The observed reduction in rate constants with increasing substitutions was consistent with expectations suggesting that the method was useful, but the rate constants were clearly greater than those for the analogous parent radicals that lacked the reporter groups, indicating that the reporter groups imparted a small kinetic acceleration. Because of the relatively weak signal growth from the ultimate benzylic radical products, which reduced precision in the kinetic measurements, and the fact that diastereomeric radicals were present, we did not attempt variable-temperature studies with these systems.

The kinetics of ring openings of radicals **7a**−**f** were measured in THF and, with the exceptions of **7c** and **7f**, in acetonitrile. Each measurement is a sum of ca. 15 experimental runs. A total of between 10 and 33 independent determinations for each radical was obtained within the temperature range −41 to +50 °C. Standard errors in k_{exp} were about 1%, and in duplicate determinations made at a given temperature, the differences in k were typically 1−3% although differences as small as 0.1% were obtained in some cases. Two pairs of duplicate measurements made in the −35 to −40 °C range at nominally the same temperatures differed by 10−12%, suggesting that temperature control and measurement were becoming significant problems.

Complete listings of observed rate constants for radicals **7** are given in the Supporting Information. Table 1 lists the Arrhenius functions for the ring-opening reactions and values of the rate constant at 20 °C calculated from these Arrhenius functions, and Figure 5 shows the kinetics for **7a**−**f** in graphical form. The notable features of the kinetics are the following. High precision was obtained in the Arrhenius functions for most of the radicals **7**, but radicals **7a** and **7d** reacted so fast that only a limited range of temperatures could be studied. No solvent effect was observed for the "alkyl" series of radicals **7a**−**c**, but the polar radicals containing the α-ethoxycarbonyl group (**7d** and **7e**) displayed obvious solvent effects on

Table 1. Arrhenius Parameters and Rate Constants for the Ring Openings of Radicals **7**[a]

radical	solvent	temp range (°C)	points[b]	log *A*	E_a (kcal/mol)	$k_{(20)}$[c] (s^{-1})
7a	THF	−39 to −15	18	12.89 ± 0.38	5.75 ± 0.34	3.9×10^8
	CH_3CN	−39 to −15	10	12.94 ± 0.30	5.81 ± 0.34	4.0×10^8
7b[d]	THF	−31 to 20	18	12.81 ± 0.15	6.18 ± 0.18	1.57×10^8
7b[e]	THF	−41 to 12	30	12.66 ± 0.16	6.03 ± 0.19	1.43×10^8
7b[f]	THF			12.74 ± 0.11	6.11 ± 0.13	1.50×10^8
7b[e]	CH_3CN	−40 to −5	16	12.72 ± 0.16	6.12 ± 0.15	1.41×10^8
7c	THF	−31 to 21	18	13.10 ± 0.16	6.86 ± 0.19	0.95×10^8
7d	THF	−39 to −10	12	13.18 ± 0.58	6.22 ± 0.65	3.4×10^8
	CH_3CN	−40 to −15	10	13.84 ± 0.70	6.76 ± 0.79	6.2×10^8
7e	THF	−37 to 49	22	12.88 ± 0.10	7.46 ± 0.13	2.04×10^7
	CH_3CN	−38 to 49	33	12.79 ± 0.17	7.23 ± 0.21	2.46×10^7
7f	THF	−9 to 50	14	13.39 ± 0.32	10.32 ± 0.43	4.81×10^5

[a] Errors are at 2σ. [b] Number of independent determinations. [c] Rate constant at 20 °C. [d] Diastereomer 1. [e] Diastereomer 2. [f] Weighted average of both diastereomers.

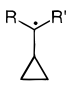
Table 2. Relative Energies (kcal/mol) for Radicals **24**[a]

radical	anti[b]	syn[b]	rot TS[c]	anti-TS[d]	syn-TS[d]	PMP2[e]
24a	0		3.0	8.4		8.31
24b	0	0.7	2.5	8.6	9.5	7.47
24c	0	(1.2)[f]	(1.5)[g]	9.0		
24d	0	1.2	5.4	10.2	11.6	
24e	0	0.8	4.1	11.6	13.0	
24v	0					12.81

[a] Results at the B3LYP/6-31G*//B3LYP/6-31G* level. See Figure 6 for structures. [b] Energies for the bisected minima. [c] Transition state for rotation. [d] Transition states for ring opening. [e] PMP2/6-31G* barriers for the anti-TS for ring opening from ref 19. [f] Energy of the perpendicular minimum. [g] Barrier for rotation between the bisected and perpendicular minima.

proceeding from THF to acetonitrile. Despite intuitive notions regarding radical stabilities, the ester-substituted secondary radical **7d** opened more rapidly than the methyl-substituted secondary radical **7b**. The benzylic radical **7f** reacted nearly 3 orders of magnitude less rapidly than the unsubstituted parent radical **7a**, as one would expect. The observed rate constants for **7f** are listed, but this special system requires analysis in terms of a prior equilibration (see Discussion).

Computational Studies. The LFP kinetic results for radicals **7** were quite precise, and it was of interest to compare them with computational results. Affordable computational results closely track with the experimental rate constants for reactions of simple cyclopropylcarbinyl radicals,[18,19] and the B3LYP[20] hybrid density functional theory (DFT) method is known to be quite accurate for radicals.[21] We studied the simple cyclopropylcarbinyl radicals **24** with B3LYP at the 6-31G* level.



24a: R = R' = H
24b: R = Me, R' = H
24c: R = R' = Me
24d: R = C(O)OMe, R' = H
24e: R = C(O)OMe, R' = Me
24v: R = $CHCH_2$, R' = H

Table 2 lists relative energy values for radicals **24**. Our objective was to compare the results for different substitution patterns, and the barriers are not corrected with zero point energies. More powerful computers than the PC we employed would permit more accurate calculations in terms of absolute values, and the barriers for the ring-opening reactions would be slightly reduced by incorporation of thermal corrections due to bond relaxations in the transition states. For example, the barrier for the ring opening of the cyclopropylcarbinyl radical (**24a**) computed at the G2 level was 7.89 kcal/mol,[18,19] and PMP2/6-31G* calculations with thermal corrections for the barriers for the ring opening of **24a** and **24b** were 8.31 and 7.47 kcal/mol, respectively.[18]

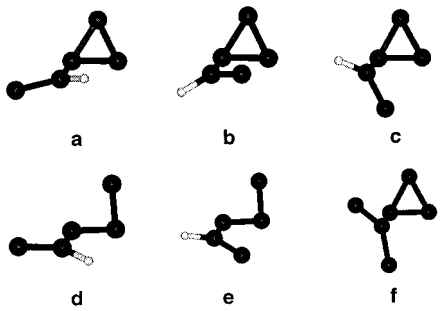


Figure 6. Representative computed minima and transition structures for radicals **24**: (a) anti-bisected minimum for **24b**, (b) syn-bisected minimum for **24b**, (c) TS for rotation of **24b**, (d) anti-TS for the ring opening of **24b**, (e) syn-TS for the ring opening of **24b**, (f) perpendicular (local) minimum for **24c**.

The minimum-energy conformations of radicals **24** are "bisected" structures with the substituents on the radical center perpendicular to the C2−C3 bond of the cyclopropyl ring. Two minima exist for the unsymmetrically substituted radicals **24b**, **24d**, and **24e**, anti and syn with respect to the ring (Figure 6). Low barriers for rotation through "perpendicular" transition states were found. The dimethyl-substituted radical **24c** is a special case where the bisected conformer is the global minimum and the perpendicular structure is a local minimum (Figure 6); this unusual situation has the unpleasant result that the computed global minimum-energy structure of **24c** changes depending on the level of theory employed. The low-energy rotational barriers for the cyclopropylcarbinyl radicals permit production of an equilibrium population of conformers before ring opening. Thus, any differences in populations arising from the initial photochemical generation of radicals from different diastereomers of a precursor will not be important, as was specifically demonstrated for the ring opening of radical **7b**.

All of the transition structures for the ring openings of radicals **24** were similar; Figure 6 shows examples. The breaking bond of the cyclopropyl ring (C1−C2) is offset slightly from collinear with the p orbital of the radical center. This results in an eclipsing interaction between C3 of the cyclopropyl ring and one of the groups at the nearly sp^2-hybridized radical center. For the radicals that are not symmetrically substituted at the radical center (**24b**, **24d**, and **24e**), the eclipsing interaction resulted in differences in energies for the two possible transition states for ring opening that amounted to 1−1.5 kcal/mol. From

(18) Martinez, F. N.; Schlegel, H. B.; Newcomb, M. *J. Org. Chem.* **1996**, *61*, 8547−8550.
(19) Martinez, F. M.; Schlegel, H. B.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 3618−3623.
(20) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(21) Fox, T.; Kollman, P. A. *J. Phys. Chem.* **1996**, *100*, 2950−2956.

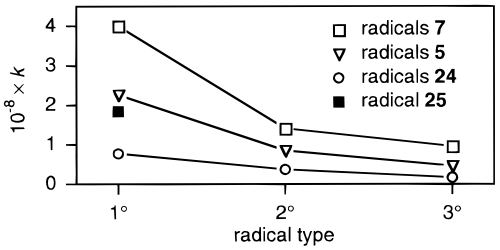


Figure 7. Rate constants for radical ring openings at 20 °C.

the energies of the transition states, one can calculate the reactivity through each channel. For example, at ambient temperature, the reaction through the high-energy channel in the methyl-substituted radical **24b** (the methyl-eclipsing C3 of the ring) will be 0.2 times as fast as the reaction through the low-energy channel. The result will be that the log *A* term in the Arrhenius function for the ring opening of **24b** should be slightly smaller (by about 0.1) than those for symmetrically substituted radicals that have degenerate pathways for ring opening.

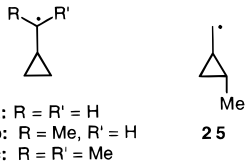
A phenyl-substituted cyclopropylcarbinyl radical was too large to calculate with the resources available, but the vinyl-substituted radical **24v** is a reasonable model for the a phenyl-substituted cyclopropylcarbinyl radical that has been addressed computationally.[19] The low-energy transition-state barrier for the ring opening of **24v** was 4.5 kcal/mol larger than the barrier for the opening of **24a** at the PMP2/6-31G* level, and the increased barrier for **24v** was due mainly to a loss of resonance energy of the allylic radical in the transition state.[19]

Discussion

Alkyl-substituted Cyclopropylcarbinyl Radicals. One can compare the rates of ring openings of radicals **7a**−**c** with those of other cyclopropylcarbinyl radical reactions in order to evaluate the kinetic effects of the reporter groups. A brief comment on the Arrhenius log *A* terms for cyclopropylcarbinyl radical fragmentations is given below, but we note here that the values of log *A* can be predicted for cyclopropylcarbinyl radicals due to the rigidity of the systems. This expediency was previously employed by Bowry, Lusztyk, and Ingold.[22]

The rate constants at 20 °C for ring-opening reactions of 1°, 2°, and 3° cyclopropylcarbinyl radicals are shown in Figure 7. The results for the reporter group-containing radicals **5** and **7** were measured by LFP in this work. The rate constant for radical **24a** is from the known Arrhenius function.[23] The rate constants for radicals **24b**,[22] **24c**,[24] and **25**[22] are obtained from Arrhenius functions calculated with the appropriate log *A* values using a rate constant measured near room temperature. The Arrhenius functions for ring openings of the muon-containing analogues of radicals **24b** and **24c** do not appear to be reasonable,[4] and the kinetics obtained by this method were not used. There is a regular increase in rate constants for ring openings due to the reporter groups with the phenylcyclopropyl group in radicals **5** giving about a 2.5-fold increase in rate, about the same amount of acceleration as imparted by the methyl group in **25**. The diphenylcyclopropyl group in radicals **7** results in a 4−5-fold acceleration.

That the kinetic effects of the reporter groups are relatively benign is indicated by the consistency of the *relative* rate



24a: R = R' = H
24b: R = Me, R' = H
24c: R = R' = Me
25

constants for the ring openings of radicals **5**, **7**, **24**. Relative rate constants at 20 °C are given in eqs 2−5 where *R* is the

$$(\mathbf{24}, \text{experimental})\ R = 1.00{:}0.47{:}0.22 \quad (2)$$

$$(\mathbf{5})\ R = 1.00{:}0.38{:}0.20 \quad (3)$$

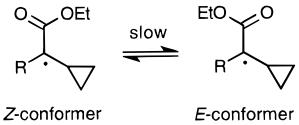
$$(\mathbf{7})\ R = 1.00{:}0.37{:}0.24 \quad (4)$$

$$(\mathbf{24}, \text{computed})\ R = 1.00{:}0.44{:}0.37 \quad (5)$$

ratio of rate constants for the 1°, 2°, and 3° radicals in the indicated series. One should note that the relative errors in the indirectly measured rate constants for radicals **24** are likely to be significantly greater than the errors in the directly measured rate constants for the reporter group series because the methods for measuring the kinetics of radicals **24** differed. Equation 5 gives the relative rate constants for radicals **24** that one calculates from the computational barriers to ring opening listed in Table 2 with the assumption that the entropy terms for all fragmentation channels are the same; the relative rate constants calculated from the inexpensive computations are clearly useful at the predictive level.

The absence of a solvent effect on the kinetics of ring openings of radicals **7a** and **7b** is noteworthy (see Table 1 and Figure 5A). It is commonly assumed that simple radical reactions will not have polarized transition states and, thus, will not display solvent effects. This is a reasonable assumption when the radical centers in reactants and products do not have functional groups, and it was previously demonstrated to hold by indirect kinetic studies of cyclopropylcarbinyl ring openings in competition with nitroxyl radical trapping reactions.[25] The demonstration of the absence of a solvent effect for **7a** and **7b** at the level of precision available from the direct studies clearly supports the premise that gas-phase kinetic values or computed activation energies can be used to predict the kinetics of simple radical reactions in solution.[18,19] However, obvious solvent effects on the ring-opening reactions of the ester-substituted radicals **7d** and **7e** show that functional-group substitution at a radical center can result in polarized transition states for seemingly simple reactions.

Ester-Substituted Cyclopropylcarbinyl Radicals. Rotations about the C−C bond between the cyclopropylcarbinyl carbon and the cyclopropane ring are faster than ring openings for cyclopropylcarbinyl radicals, as shown by the barriers listed in Table 2. For the ester-substituted radicals **7d** and **7e**, however, two distinct conformers can exist on the time scale of the ring-opening reactions. Rotation about the bond between the radical center and the carbonyl carbon that interconverts the *E*- and *Z*-conformers of the ester-substituted radicals is definitely slower than that of the ring-opening reaction of **7d** and most likely also is slower than the ring opening of **7e**.



Studies from Fischer's laboratory gave rate constants of (1−2)

(22) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687−5698.
(23) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275−277.
(24) Engel, P. S.; He, S. L.; Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1997**, *62*, 1210−1214.

$\times$ 10^6 s^{-1} at 20 °C for this rotation in ester-substituted radicals,[26,27] and 5-exo cyclizations of ester-substituted radicals with rate constants of $(2-5) \times 10^7$ s^{-1} were shown to be faster than conformational interconversion.[28] Therefore, it is possible that two reactive forms of **7d** and **7e** were present in the LFP experiments. Nevertheless, the kinetic data was well-fit by single-exponential solutions; that is, double-exponential solutions of the data gave the same values for the one rate constant, obtained in single-exponential solutions and small values for the second rate constant. This requires either that **7d** and **7e** were produced primarily in one conformation or that both conformations reacted with the same rate constants.

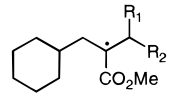
An ethoxycarbonyl group is considered to be a radical stabilizing group, although a consensus on the extent of stabilization is not apparent. Bordwell's estimate[29] that the C−H bond-dissociation energy (BDE) of ethyl acetate is about 7.5 kcal/mol less than that of methane appears to be reasonable and can be compared to the 4.2 kcal/mol reduction in BDE for ethane relative to methane.[30] An intuitive conclusion from the radical stabilizing effect of the ester group might be that the ester-substituted radicals **7d** and **7e** should ring-open less rapidly than their alkyl-substituted counterparts **7b** and **7c**. This conclusion is supported by the computational results at the B3LYP/6-31G* level which give estimated ring-opening rate constants at 20 °C for the secondary and tertiary methoxycarbonyl-substituted radicals **24d** and **24e** that are only 0.03 and 0.003 times as fast, respectively, as that for the parent radical **24a**.

Nevertheless, the secondary ester-substituted radical **7d** reacts faster than the secondary alkyl radical **7b**, and in acetonitrile, the activation free energy for the fragmentation of **7d** is nearly 1 kcal/mol less than that for the ring opening of **7b**. The seemingly counterintuitive kinetic results for **7d** must arise from a polarized transition state for the reaction and are consistent with previous results. Specifically, thermodynamic cycles for the additions of an alkyl radical to an alkene and to an acrylate (the reverse of the fragmentation reactions of **7d** and **7e**) indicate that the additions to acrylates are more exothermic by about 2 kcal/mol.[31] This value is smaller than the differences in BDE between alkyl- and ester-substituted radicals because the ester group also stabilizes the double bond in the acrylate. From kinetic studies of the additions of alkyl radicals to alkenes and acrylates, one finds that the $\Delta G^{\ddagger}$ for additions to acrylates is about 4 kcal/mol smaller than that for additions to alkenes.[32] The increased stabilization in the transition states for the additions to acrylates is due to favorable polarization, and the same polarization will be present in the reverse reaction, the fragmentation of an ester-substituted radical.

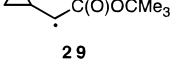
One effect of polarized transition states is that, unlike the case of the alkyl-substituted radicals, the rates of the ring opening of the ester-substituted radicals **7d** and **7e** displayed solvent effects with accelerated rearrangements proceeding from THF to the more polar solvent acetonitrile. Another obvious effect is that the gas-phase calculated barriers for ring openings of the ester-substituted radicals are clearly inconsistent with those for the alkyl radicals.

The tertiary ester-substituted radical **7e** fragments less rapidly than the tertiary alkyl radical **7c** by about a factor of 4 at 20 °C, but this appears to be the result of steric effects and not electronic effects. In the computed transition structures for the fragmentation reactions of radicals **24**, an eclipsing interaction is produced between one of the substituents at the radical center and the C3 of the cyclopropyl ring (Figure 6). This eclipsing interaction can be relieved by distorting the planar radical center which will produce a minor energy penalty for an alkyl radical but a more significant penalty for the conjugated ester-substituted radical. The net result is that the computed energy barrier for the tertiary alkyl radical **24c** is only 0.4 kcal/mol greater than the *lower* energy barrier for the ring opening of the secondary radical **24b**; whereas, both energy barriers for the ring opening of the tertiary ester-substituted radical **24e** are 1.4 kcal/mol greater than the corresponding barriers for the secondary ester-substituted radical **24d**.

Polarized transition states for α-ester radical fragmentations were previously implicated. Metzger and co-workers studied high-temperature fragmentation reactions of α-methoxycarbonyl radicals in competition with hydrogen atom transfer trapping reactions. They found that radical **26** eliminates an ethyl radical more readily than it eliminates a methyl radical[33] and that the stabilized (methoxycarbonyl)methyl radical cleaves from radical **27** less rapidly than the 2-propyl radical cleaves from **28**.[34] In



26: R_1 = Me, R_2 = Et
27: R_1 = CO_2Me, R_2 = H
28: R_1 = *i*-Pr, R_2 = H



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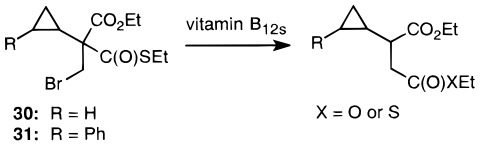
both cases, the less thermodynamically favored fragmentation is faster because loss of the more nucleophilic radical is favored by transition-state polarization effects.

The kinetics of ring opening of another ester-substituted cyclopropylcarbinyl radical, the *tert*-butoxycarbonyl-substituted radical **29**, was previously studied by Beckwith and Bowry.[35] They reported rate constants for the the ring opening of **29** from competition kinetic studies with nitroxyl radical trapping. Their rate constants were about 2 orders of magnitude smaller than those we find for **7d**. For example, from the Arrhenius function for ring opening of **7d** in THF, one calculates a rate constant at 80 °C of 2×10^9 s^{-1}, but the reported rate constant for the ring opening of **29** at this temperature is 1.4×10^7 s^{-1}.[35] Two factors that should result in a larger rate constant for the ring opening of **7d** are (1) the reporter group in radicals **7a**−**c** resulted in a 4−5-fold acceleration in the rate constants for ring opening in comparison to those of radicals **24**, and a similar acceleration would be expected for **7d** in comparison to **29**, and (2) Beckwith and Bowry's kinetic studies with **29** were performed in cyclohexane, a nonpolar solvent that would be expected to reduce the rate constant for the fragmentation relative to that observed in THF.

(25) Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983−4992.
(26) Lung-Min, W.; Fischer, H. *Helv. Chim. Acta* **1983**, *66*, 138−147.
(27) Strub, W.; Roduner, E.; Fischer, H. *J. Phys. Chem.* **1987**, *91*, 4379−4383.
(28) Newcomb, M.; Horner, J. H.; Filipkowski, M. A.; Ha, C.; Park, S. U. *J. Am. Chem. Soc.* **1995**, *117*, 3674−3684.
(29) Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1994**, *116*, 8885−8889.
(30) Griller, D.; Kanabus-Kaminska, J. M.; Maccoll, A. *THEOCHEM* **1988**, *40*, 125−131.
(31) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976.
(32) Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* **1996**, *118*, 437−439. Walbiner, M.; Wu, J. Q.; Fischer, H. *Helv. Chim. Acta* **1995**, *78*, 910−924.
(33) Klenke, K.; Metzger, J. O.; Lübben, S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1168−1170.
(34) Metzger, J. O.; Klenke, K. *Chem. Ber.* **1990**, *123*, 875−879.
(35) Beckwith, A. L. J.; Bowry, V. W. *J. Am. Chem. Soc.* **1994**, *116*, 2710−2716.

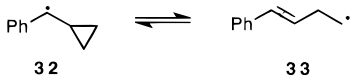
Nevertheless, it seems unlikely that the combination of the solvent effect and the reporter group effect could amount to more than an order of magnitude difference in the rate constants for the ring openings of **7d** and **29**. Another factor that might be involved in the large apparent difference in the two sets of results is the fact that the rate constants for the nitroxyl radical coupling reaction with the ester-substituted radical **29**, the competing reaction in the Beckwith and Bowry study, were not available and were estimated to be about 0.25 times as large as those for reaction of the nitroxyl radical with a secondary alkyl radical. It is conceivable that the rate constants for nitroxyl trapping of **29** are as great as those for reaction with an alkyl radical given that the enthalpies of nitroxyl radical coupling reactions do not appear to have a large effect on the kinetics.[36] It is also possible that the products of nitroxyl radical trapping were not stable and equilibrated partially by homolysis, radical rearrangement, and coupling.

The ramifications of the kinetic results with the ester-substituted radicals **7d** and **7e** should be emphasized. Cyclopropylcarbinyl radical ring openings have often been employed as mechanistic probes for reactions in which putative radical intermediates might exist, and He and Dowd have used an ester-substituted cyclopropane probe (**30**) and an ester-substituted 2-phenylcyclopropane probe (**31**) in attempts to determine whether radicals are involved in model studies of the vitamin B_{12}-catalyzed methylmalonyl-CoA to succinyl-CoA rearrangement.[37] They found that the rearrangements occurred with no



detectable amount of radical ring opening. Because the ester substitution has a minimal effect on the kinetics of the ring openings of cyclopropylcarbinyl radicals and given that the (*trans*-2-phenylcyclopropyl)methyl radical is known to ring-open with a rate constant of 3×10^{11} s^{-1}, the absence of ring-opened products in their studies with probe **31** requires that the maximum lifetime of a radical intermediate in the rearrangement was <5 ps even with conservative estimates of detection limits,[37,38] a value within an order of magnitude of the "lifetime" of a transition state and much too short for any diffusively free intermediate.

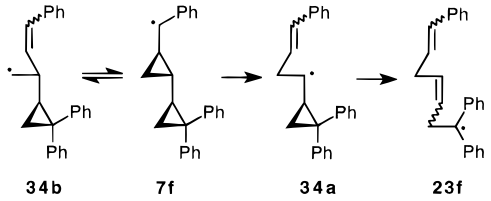
Phenyl-Substituted Cyclopropylcarbinyl Radicals. The equilibrium between the phenyl-substituted cyclopropylcarbinyl radical **32** and its ring-opened product **33** is known to lie on the side of cyclic radical **32**. This was demonstrated by Ingold's



group in a 1990 paper that disproved claims to the contrary and showed that the use of phenyl-substituted cyclopropanes in mechanistic studies could be complicated.[39] The Ingold group established a rate constant of 1.2×10^7 s^{-1} at 42 °C for the cyclization of **33** to **32** via isotopic scrambling in **33** in competition with Bu_3SnH trapping.[39] Beckwith and Bowry later reported rate constants for cyclization of **33** to **32** determined via nitroxyl radical trapping reactions;[35] their values for the cyclization ($k = 0.8 \times 10^7$ s^{-1} at 42 °C) are in reasonable agreement with the rate constant determined by Ingold's group. In unpublished work, our group has studied rate constants for cyclization of **33** by direct LFP methods; the rate constant at 42 °C from direct measurements is virtually identical to that found by Ingold's group (1.1×10^7 s^{-1}).[40]

Because **32** is favored at equilibrium, one cannot directly measure the rate constants for the ring opening of this radical in a conventional LFP experiment. Indirect kinetic studies involving competing trapping reactions are possible,[2] and Beckwith and Bowry[35] reported rate constants for ring opening of **32** determined via nitroxyl radical trapping. In addition, rate constants for the ring opening of a bicyclic version of radical **32**, determined by competitive trapping by *t*-BuSH, were reported by Venkatesan and Greenberg.[41] In these indirect studies, however, the rate constants for the competition trapping reactions were not known and had to be estimated.

The reporter group approach provides a way to circumvent the equilibrium problem, thus permitting direct LFP kinetic studies of the ring opening of a benzyl-substituted cyclopropylcarbinyl radical. Product **34a** from the ring opening of radical **7f** fragments to **23f** with a rate constant in excess of 1×10^{11} s^{-1},[7] several orders of magnitude larger than the rate constant for the back reaction of **34a** to **7f**. Nevertheless, the



measured rate constants for formation of **23f** are not equal to those for fragmentation of radical **32** and, in fact, are not necessarily equal to those for fragmentation of **7f**. A small accelerating effect of the reporter group is expected on the basis of the results with the simple cyclopropylcarbinyl radicals **7a**−**c**, and **7f** should react faster than **32**. In addition, a small decelerating effect will result from the production of radical **34b** in the initial fragmentation of **7f**. Because the cyclization of radical **34b** must be on the order of 5×10^6 s^{-1} at ambient temperature, about an order of magnitude faster than fragmentation of **7f**, an "equilibrium" between **7f** and **34b** will be established, and any **34b** present serves as an unreactive reservoir of **7f** with regard to the ultimate production of the detectable radical **23f**.

One can estimate the kinetic effect of production of **34b** in the following manner. The (*trans*-2-methylcyclopropyl)methyl radical (**25**) is known to fragment about equally to the two possible ring-opened products,[22] a result mainly due to approximately equal amounts of relief of steric compression in the two possible transition states.[18] Therefore, one might assume that the accelerating effect of the reporter group is also due mainly to steric effects and that **7f** partitions approximately equally to **34a** and **34b**. Through the use of this assumption and the use of the rate constants for cyclization of radical **33** discussed above and that measured for reactions of **7f**, the

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(38) Reference 37b places the limit at 50 ps, but this appears to be a typographical error.

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equilibrium constant for **34b** and **7f** is found to be about 10 (favoring **7f**). Because of the (assumed) equal partitioning of **7f** to **34a** and **34b**, the measured rate constants for production of **23f** would be about 5% smaller than the rate constants for fragmentation of **7f**, about 4.6×10^5 s^{-1} at 20 °C.[42]

In regard to the specific case of radicals **32** and **33**, one might estimate that the reporter group effect in all radicals **7** is due to sterics. In this case, the same 4−5-fold acceleration in ring-opening kinetics at 20 °C would be present in **7f** in comparison with **32**. Therefore, the estimated rate constant for the ring opening of **32** at 20 °C is 1×10^5 s^{-1}. This value can be compared with a rate constant for the opening of **32** of 4×10^4 s^{-1} at 20 °C extrapolated from the nitroxyl radical trapping studies[35] and to a total rate constant for two (nondegenerate) ring openings of a bicyclic version of **32** of 5×10^6 s^{-1} at 25 °C from *t*-BuSH trapping studies.[41] It is likely that the estimates for the trapping rate constants in both of the indirect studies introduced errors, and it would appear that the error in the estimate of the *t*-BuSH trapping rate constant is considerable, although the rigid bicyclic structure of the radical studied might have had a kinetic effect. Combination of the rate constant for the ring opening of **32** estimated from our results with the directly measured rate constant for cyclization of **33** at 20 °C ($k = 5.6 \times 10^6$ s^{-1})[40] gives an equilibrium constant of $K \approx 60$ favoring **32**; the benzyl-substituted cyclopropylcarbinyl radical **32** is clearly favored, as demonstrated by Ingold's group.[39]

Entropic Terms. One of the attractions of studying cyclopropyl systems is that the rigidity of the compounds precludes much of the conformational freedom one would have in an acyclic compound and the transition states for its reactions. In the case of the ring opening of the cyclopropylcarbinyl radical (**24a**), Ingold has previously noted that the entropy of activation ($\Delta S^{\ddagger}$) could be predicted with confidence.[3] To obtain the transition state, the rotation of the methylene group must be "frozen", which results in an entropic penalty. However, the cyclopropylcarbinyl radical has four equivalent reaction channels available for ring opening (two by virtue of the symmetrical substitution at the radical center and two from the different bonds in the cyclopropyl ring that can break), and this increases log *A*. At ambient temperature, these two effects cancel such that $\Delta S^{\ddagger} = 0$ and log $A = 13.15$ at ambient temperature.[3]

The calibration of the cyclopropylcarbinyl radical ring opening using rate data obtained from kinetic ESR, nitroxyl trapping, and PhSH trapping results that span a total of about 250 °C gives exactly the above value, log $A = 13.15$.[23] The agreement of the experimental result with the result predicted thermochemically leads to the reasonable expectation that one can compute an accurate Arrhenius function for a cyclopropylcarbinyl radical ring opening from one precisely determined rate constant and the assumption that log *A* must be 12.85 for each bond that can break; this expedient has been employed previously.[22]

(42) We note in passing that the kinetic effect due to the initial partitioning of **7f** is a result of the fact that the back cyclization of **37b** to **7f** is faster than fragmentation of **7f**. Similar effects are not possible for the other reporter group radicals studied in this work because the back reactions are slower than the initial fragmentations. The 3-butenyl radical has a rate constant for cyclization on the order of 10^4 s^{-1} at ambient temperature,[2] and that for the 4-(*tert*-butoxycarbonyl)-3-butenyl radical is about 1×10^7 s^{-1}.[35] The effects of back reactions for these cases would be the superimposition of a slow reaction (the back cyclization reaction) with the fast reaction fragmentation with a net effect of double-exponential kinetic behavior if the transients **23** were persistent and data were acquired for an extended period. For all cases except **7f**, the measured kinetics are the sum of the rate constants for fragmentation to both possible products.

The symmetry-breaking features of radicals **7** will have only minor effects on the entropy terms.[43] Increasing moments of inertia for radicals **7** containing substituents at the radical center will reduce log *A* slightly, but increasing barriers to rotation will mitigate that effect somewhat.[31] The net result is that log *A* should be in the range of about 12.6−13.0 for **7b**−**f**. This was generally found for the cases in Table 1 where the precision in log *A* was good. It is apparent that one can accurately estimate an Arrhenius function for a cyclopropylcarbinyl radical ring opening from one precisely measured kinetic value and an estimated log *A* term, but estimating log *A* will require some computational or experimental results. In the absence of those results, log $A = 12.8 \pm 0.2$ is a good approximation for any substituted cyclopropylcarbinyl radical.

Conclusion

The reporter group approach permits highly precise direct measurements of the kinetics of cyclopropylcarbinyl radical ring openings, a group of reactions for which most of the previously available kinetic data were obtained by indirect kinetic methods. The precision in both the kinetic measurements and the derived Arrhenius functions for the radicals studied here provides highly reliable radical clocks that might be employed in competition kinetic and mechanistic studies of radicals or putative radical intermediates. The power of the approach was shown in the measurement of the rate constants for the ring openings of ester- and phenyl-substituted radicals which were studied previously by competition methods for which the rate constants of the competing basis reactions were not available. The ester-substituted radical **7d** reacted at least an order of magnitude faster than one would have predicted on the basis of an earlier report, and solvent effects on the ring openings of ester-substituted radicals **7d** and **7e** were readily demonstrated. The synthetic route presented gives a diastereomerically pure intermediate (**15a**) that can be converted to a wide range of radical precursors.

Experimental Section

General Methods. Commercially available reagents were purchased from either the Sigma or the Aldrich chemical companies and were used as received. Tetrahydrofuran (THF) and diethyl ether were distilled under a nitrogen atmosphere from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from phosphorus pentoxide. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were distilled under reduced pressure from calcium hydride. The sodium salt of *N*-hydroxypyridine-2-thione was purified as described previously.[44] 2,2-Diphenylcyclopropanecarboxaldehyde was prepared by PCC oxidation of (2,2-diphenylcyclopropyl)methanol.[45] ^{1}H NMR spectra (300 or 500 MHz) and ^{13}C NMR spectra (75 or 125 MHz) were obtained on Varian Gemini 300 and Unity 500 spectrometers. Melting points were obtained on a Thomas-Hoover capillary melting

(43) Two symmetry-breaking features are possible for radicals **7**, the reporter group and the substituents at the radical center. On the basis of (1) the observation that the C1−C2 and C1−C3 bond breaking in *trans*-2-methylcyclopropylcarbinyl radical (**25**) are nearly equal,[22] (2) the computational results that suggest that the effect of the methyl group in **25** is almost entirely due to sterics,[18] and (3) the observation by NMR spectroscopy that reactions of **5a**, **6a**, and **7a** in the presence of PhSH gave products containing some intact cyclopropyl groups, we assume that the C1−C2 and C1−C3 bond breakings in radicals **7** occur with equal rates. The maximum possible effect of the substituent at the radical center in radicals **7b** and **7d**−**f** would be to preclude one reaction channel which would reduce log *A* by 0.3. From the computational results in Table 2, the minimum effect of the substituent would be for radical **24b** where log *A* would be reduced by 0.1.

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point apparatus and are uncorrected. High-resolution mass spectral analyses and X-ray structural determinations were performed by the Central Instrumentation Facility at Wayne State University.

The syntheses of amides **14** and 2-(2,2-diphenylcyclopropyl)-cyclopropanes **15**, the starting point for all precursors to radicals **7**, are given here. Synthetic details for preparation of PTOC esters **21** are in Supporting Information.

(*E*)-*N*-Methoxy-*N*-methyl-3-(2,2-diphenylcyclopropyl)propenamide ((*E*)-14) and (*Z*)-*N*-Methoxy-*N*-methyl-3-(2,2-diphenylcyclopropyl)propenamide ((*Z*)-14). 2,2-Diphenylcyclopropanecarboxaldehyde (13.75 g, 0.061 mol) and *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (24.5 g, 0.067 mol) were dissolved in methylene chloride and stirred at room temperature overnight. The solvent was removed under reduced pressure to give a brown semisolid mass. Addition of hexanes/EtOAc (3/1, 1 L) caused a tan precipitate to form. After filtration through a bed of silica to remove the precipitate, the filtrate was concentrated under reduced pressure to give a yellow oil. The crude product was chromatographed on silica (3/1 hexanes/EtOAc) to give, in order of elution, (*Z*)-**14** (2.62 g, 14%) as an oil and (*E*)-**14** (14.35 g, 76%) as a white solid. Mp: 78−81 °C. ^{1}H NMR of (*E*)-**14** (300 MHz): δ 1.73 (t, J = 5.3 Hz, 1 H), 1.80 (dd, J = 8.5, 4.9 Hz, 1 H), 2.45 (ddd, J = 10.1, 8.5, 5.8 Hz, 1 H), 3.19 (s, 3 H), 3.67 (s, 3 H), 6.33 (dd, J = 15.5, 10.1 Hz, 1 H), 6.53 (d, J = 15.5 Hz, 1 H), 7.1−7.3 (m, 10 H). ^{13}C NMR of (*E*)-**14** (75 MHz): δ 23.4, 30.7, 32.3, 39.6, 61.6, 117.6, 126.2, 127.0, 127.2, 128.4, 128.6, 130.7, 140.5, 145.8, 148.3, 166.5. MS of (*E*)-**14** *m*/*z* (rel int): 307 (4), 277 (10), 276 (35), 219 (55), 217 (21), 204 (18), 203 (15), 202 (16), 191 (14), 178 (16), 165 (30), 141 (33), 127 (100), 115 (33), 97 (17), 95 (35), 91 (97). HRMS of (*E*)-**14**, $C_{20}H_{21}NO_2$: calcd, 307.1572; found, 307.1568. ^{1}H NMR of (*Z*)-**14** (300 MHz): δ 1.65 (t, J = 5.2 Hz, 1 H), 1.72 (dd, J = 8.5, 4.9 Hz, 1 H), 3.27 (s, 3 H), 3.67 (s, 3 H), 3.92 (ddd, J = 10.6, 8.5, 5.8 Hz, 1 H), 5.30 (t, J = 11.1 Hz, 1 H), 6.22 (d, J = 11.6 Hz, 1 H), 7.1−7.3 (m, 10 H). ^{13}C NMR of (*Z*)-**14** (75 MHz): δ 23.9, 26.1, 32.3 (br), 39.8, 61.5, 126.1, 126.6, 127.9, 128.3, 128.4, 130.5, 141.5, 145.9, 148.9, 167.9. MS of (*Z*)-**14** *m*/*z* (rel int): 276 (6), 219 (13), 178 (11), 141 (12), 127 (100), 115 (14), 105 (16), 96 (35), 91 (34), 77 (11). HRMS of (*Z*)-**14**, $C_{19}H_{18}NO$ ($M^+ - OCH_3$): calcd, 276.1388; found, 276.1383.

***N*-Methoxy-*N*-methyl-*trans*-2-(2,2-diphenyl-1*R**-cyclopropyl)-1*S**,2*R**-cyclopropanecarboxamide (15a) and *N*-Methyl-*N*-methoxy-*trans*-2-(2,2-diphenyl-1*R**-cyclopropyl)-1*R**,2*R**-cyclopropanecarboxamide (15b).** Trimethylsulfoxonium iodide (26.5 g, 0.12 mol) was added slowly over 2 h via a solids addition funnel to a stirred suspension of NaH (2.90 g, 0.12 mol) in DMSO (70 mL). After this mixture was stirred for an additional 0.5 h, a solution of (*E*)-**14** (11.5 g, 0.037 mol) in DMSO (70 mL) was added, and the reaction mixture was stirred for 30 h at room temperature. The reaction mixture was poured into brine (300 mL) and extracted with ether/methylene chloride (1/1). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the resulting crude product was chromatographed on silica gel (3/1 hexanes/EtOAc) to give a white solid (7.1 g) as a 5.5/1 mixture of diastereomers (**15a** and **15b**). The major isomer (**15a**) was obtained by recrystallization from hexanes/EtOAc (5.8 g, 60%). Mp: 83−84 °C. Slow concentration of the mother liquors gave **15b** (0.21 g, 2%). Mp: 91−92 °C. ^{1}H NMR of **15a**: δ 0.65 (ddd, J = 8.0, 6.0, 3.9 Hz, 1 H), 0.90−1.2 (m, 2 H), 1.22−1.38 (m, 2 H), 1.58 (dt, J = 8.5, 6.1 Hz, 1 H), 2.10 (br m, 1 H), 3.19 (s, 3 H), 3.78 (s, 3 H), 7.1−7.5 (m, 10 H). ^{13}C NMR of **15a**: δ 14.4, 17.6, 19.3, 23.2, 28.8, 32.7, 35.4, 61.6, 125.6, 126.5, 127.2, 128.2, 130.7, 141.3, 146.9, 174.0. MS of **15a** *m*/*z* (rel int); 321 (7.6), 290 (15), 261 (6), 233 (14), 217 (26), 206 (40), 205 (17), 193 (16), 192 (11), 191 (33), 178 (16), 167 (62), 165 (30), 155 (16), 154 (31), 141 (11), 129 (16), 115 (27), 105 (14), 91 (100), 77 (11), 55 (29). HRMS of **15a**, $C_{21}H_{23}NO_2$: calcd, 321.1729; found, 321.1725. ^{1}H NMR of **15b** (500 MHz): δ 0.95 (m, 2 H), 1.22 (m, 1 H), 1.34 (m, 3 H), 2.06 (br m, 1 H), 3.11 (s, 3 H), 3.66 (s, 3 H), 7.13 (m, 3 H), 7.21 (m, 3 H), 7.30 (t, J = 7.4 Hz, 2 H), 7.42 (d, J = 7.3 Hz, 2 H). ^{13}C NMR of **15b** (125 MHz): δ 15.1, 17.4, 20.2, 23.2, 29.8, 32.5 (br), 35.5, 61.4, 125.6, 126.5, 127.2, 128.2, 128.4, 130.8, 141.4, 146.9, 173.6 (br). MS of **15b** *m*/*z* (rel int): 321 (11), 290 (15), 261 (5), 233 (15), 217 (27), 206 (37), 205 (17), 193 (16), 192 (11), 191 (32), 178 (19), 167 (56), 165 (31), 155 (16), 154 (29), 141 (12), 129 (16), 115 (26), 105 (13), 91 (100), 77 (12), 55 (34). HRMS of **15b**, $C_{21}H_{23}NO_2$: calcd, 321.1729; found, 321.1723.

X-ray Crystallography. Crystallographic data were collected at room temperature on a S/N/S automated R3 diffractometer with monochromated Cu radiation. The structures were solved using the programs in SHELXL-93.[46]

Structure of Compound 15a. Crystals of **15a** suitable for X-ray crystallography were grown by slow (1 week) crystallization from diethyl ether/hexanes. Compound **15a** consisted of colorless, striated, flat rods. Compound **15a** belongs to the triclinic space group P(−1) with a = 11.1311(12) Å, b = 12.983(2) Å, c = 14.162(2) Å, α = 67.597(12)0, β = 88.428(11)0, γ = 70.483(10)°, Z = 4, and D = 1.205 g/cm^3. Absorption corrections were applied on the basis of ψ scans. The asymmetric unit contains two crystallographically independent molecules. R = 0.0470, and R_{w2} = 0.1328 for 3348 reflections with $I > 2\sigma(I)$. [R = 0.0615 for all data.] GOF = 1.074. Other experimental parameters along with positional and anisotropic thermal parameters are given in Supporting Information.

Structure of Compound 19b (Diastereomer 1). Crystals of **19b** (diastereomer 1) suitable for X-ray crystallography were grown by slow (1 week) crystallization from hexanes/EtOAc. Diastereomer 1 of **19b** belongs to the monoclinic space group $P2_1/c$ with a = 10.2756(14) Å, b = 23.384(4) Å, c = 7.6671(8) Å, β = 111.831(9)°, Z = 4, and D = 1.190 g/cm^3. R = 0.0372, and R_{w2} = 0.0957 for 2113 reflections with $I > 2\sigma(I)$. [R = 0.0442 for all data.] GOF = 1.029. Other experimental parameters along with positional and anisotropic thermal parameters are given in Supporting Information.

Kinetic Measurements and Data Analysis. All kinetic measurements were carried out with an Applied Photophysics LK-50 laser kinetic spectrometer using the third harmonic (355 nm) of a Nd:YAG laser (7 ns pulse duration, 40 mJ/pulse). The flow system for low-temperature measurements consisted of a jacketed funnel attached directly to a UV cuvette. A Neslab ULT-80 circulating bath was used to circulate chilled fluid through the jacket of the funnel. For measurements below 0 °C, the entire funnel and cuvette assembly was enclosed in a box made of black Delrin. The box was equipped with four optical windows which allowed the laser and analyzing beams to pass through the sample cuvette. The interior of the box was flushed with argon to prevent water condensation. Sample temperatures were measured by means of a copper−constantan thermocouple wire inserted into the interior of the cuvette through the sample outflow opening. Data were digitized using a Hewlett-Packard 54522 oscilloscope with a maximum time resolution of 0.5 ns. Each kinetic trace contained 512 data points. Typically, two sets of data, each containing 14 kinetic traces, were collected at one temperature. Each set was summed to improve the signal/noise ratio. For kinetic traces with rates greater than 4×10^7 s^{-1}, the observed kinetic trace is the convolution of the impulse response of the instrument with the real kinetic trace. To carry out deconvolution, the traces were zero-filled to 512 points and Fourier transformed. This Fourier transformed trace was then divided by the "noiseless" Fourier transform calculated to match the instrument impulse response function. The resulting function was inverse Fourier transformed to generate the deconvoluted kinetic trace.

Instrument Response Time. When the (2,2-diphenylcyclopropyl)-carbinyl radical was generated by flash photolysis from the corresponding PTOC ester, a kinetic trace corresponding to a growth of 2.5×10^8 s^{-1} was observed. Because this radical was previously found by indirect methods to open with a rate constant of 6×10^{11} s^{-1} at 20

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°C,[7] the rate observed in the kinetic traces must correspond to the electronic response of the detection system. The impulse response of the system for use in deconvolution was therefore taken as a decaying exponential with a rate of 2.5×10^8 s^{-1}.

Computational Methods. Ab initio molecular orbital calculations were performed using the Gaussian 94 series of programs[47] on a PC. Reactants and transition structures were optimized with the B3LYP[20] hybrid density functional theory using the 6-31G*[48] basis set.

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Supporting Information Available: Tables of kinetic data for radicals **7**; tables of crystallographic data, atomic coordinates, and anisotropic displacement parameters for **15a** and **19b** (diastereomer 1); and synthetic procedures for preparation of all compounds in Scheme 3 (34 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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