Benzylic Stabilization as a Mechanistic Tool for Studying Radical Rearrangements†

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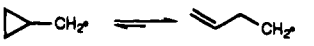
The kinetic parameters for the rearrangement of, and the relative energies of radicals involved in the equilibria of, a bicyclic cyclopropylmethyl/homoallyl system were determined. Benzylic stabilization of the cyclopropylmethyl radical facilitates characterization of all four ring opening and closing processes. Kinetically disfavored endocyclic ring opening produces the thermodynamically favored homoallyl radical (**10**). Cyclohexenyl radical **10** is approximately 1.7 kcal/mol lower in energy than **9**. The regioselectivity of ring opening of **8** is independent of any assumptions involving trapping rate constants of radicals. The regioselectivity for ring opening of **8** (k_1/k_2 = 30.2 at 298 K) is similar to that of bicyclo[3.1.0]hexan-1-yl (**1**). These experiments suggest that benzylic stabilization does not significantly perturb the position of the transition state for ring opening. Therefore, phenyl substitution of a bicyclic cyclopropylmethyl radical should be a useful tool for analyzing the effects of substituents elsewhere in the system.

There is a synergistic relationship between organic synthesis and mechanistic organic chemistry. This synergism is readily apparent in the chemistry of free radicals.[1] For example, the 5-hexenyl radical cyclization has proven to be a venerable reaction in organic synthesis.[1c-e] The contribution of mechanistic studies to the development of this methodology is not overlooked by its creative practitioners. The cyclopropylmethyl to homoallyl radical rearrangement has also found its place amongst the tools of organic synthesis (eq 1).[2,3] When



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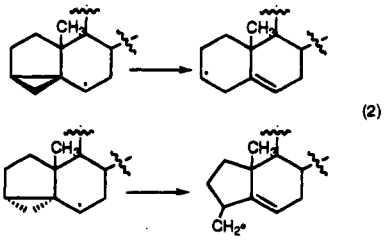
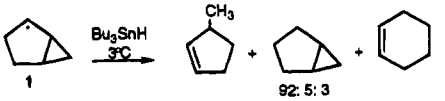


(2)

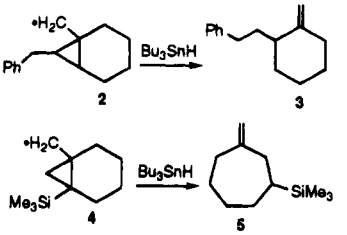
placed within the framework of a conformationally constrained system, the cyclopropylmethyl radical ring opening exhibits exquisite regioselectivity, reflective of stereoelectronic control (eq 2).[4] We wish to report the results of experiments on a bicyclic cyclopropylmethyl radical system which enables one to evaluate the rate constants for ring opening and closing, as well as the relative energies of the radicals.[5]

The strong preference for exocyclic ring scission in nonstabilized, unsubstituted bicyclic cyclopropylmethyl radicals produces what is assumed to be the thermodynamically less stable of the two possible homoallyl radicals (eq 3).[6] The effectively irreversible nature of



(3)

these rearrangements precludes determination of the relative energies of the radicals on the reaction surface, as well as the respective rate constants for rearrangement. Not surprisingly, efforts have been put forth that are aimed at controlling the regioselectivity of the cyclopropylmethyl radical ring opening. In a system where the radical center was free to rotate, cyclopropyl substituents were shown to have a remarkable effect on the regioselectivity of cyclopropylmethyl radical ring opening. The authors attributed the differences in regioselectivity of **2** and **4** to the kinetic reversibility of the rearrangement in **4**, whereas ring scission of **2** is irreversible under the reaction conditions.[3a] Kinetic analysis of product



formation was not provided to corroborate this proposal. An alternative explanation for the experimental observations asserts that the products are formed under kinetic conditions in both systems. The differing regioselectivity is a manifestation of the freedom of the radical center to adopt whatever conformation is necessary to yield the

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(1) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States;* Academic Press: New York, 1980; Vol 1. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Curran, D. P. *Synthesis* **1988**, 417. (e) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986.

(2) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275.

(3) (a) Destabel, C.; Kilburn, J. D.; Knight, J. *Tetrahedron* **1994**, *38*, 11267. (b) Weng, W.-W.; Luh, T.-Y. *J. Org. Chem.* **1993**, *58*, 5574.

(4) Beckwith, A. L. J.; Phillipou, G. *Aust. J. Chem.* **1976**, *29*, 123.

(5) A preliminary account of this work has appeared: Venkatesan, H.; Greenberg, M. M. *J. Org. Chem.* **1994**, *59*, 3514.

(6) (a) Roberts, C.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1983**, 879. (b) Friedrich, E. C.; Holmstead, R. L. *J. Org. Chem.* **1972**, *37*, 2550.

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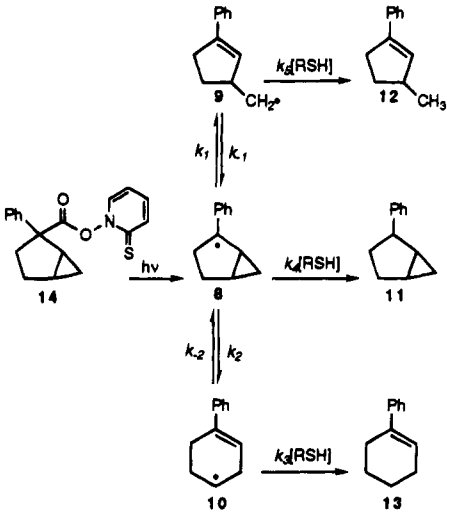
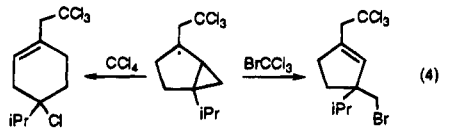
Scheme 1



thermodynamically favored homoallyl radical, which faces the correspondingly lower barrier to ring opening. This rationale was employed recently to explain the chemoselectivity of a series of tandem radical processes.[3b]

Selective trapping of thermodynamic or kinetic homoallyl radicals was achieved by utilizing radical traps that differ in their rate constants by 4 orders of magnitude (eq 4).[7,8] Selective formation of the substituted



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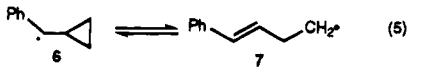


(5)

cyclohexene in the presence of CCl_4 is consistent with trapping of the thermodynamically preferred radical under conditions where ring opening is reversible. In this system, the equilibria are probably affected both by stabilization of the cyclopropylmethyl radical and the endocyclic ring opening product due to their being tertiary radicals. Stabilization of the cyclopropylmethyl radical is a potentially useful tool for overcoming the kinetic preference of exocyclic ring scission. Benzylic stabilization has long been known to perturb the equilibrium of the cyclopropylmethyl homoallyl radical equilibrium.[9] More recently, kinetic studies have shown that the ring closed system is the thermodynamically preferred species (eq 5).[10] In order to gain a handle on the energetics of isomeric homoallyl radicals, and the relative barriers to their formation, we took advantage of the modulation of the cyclopropylmethyl homoallyl radical rearrangement imparted by phenyl substitution (Scheme 1). Equations describing the dependence of product ratios on trap concentration are obtained by making the

$$\frac{[11]}{[12]} = \frac{k_4[8][RSH]}{k_5[9][RSH]} = \frac{k_{-1}k_4}{k_1k_5} + \frac{k_4}{k_1}[RSH] \quad (6)$$

$$\frac{[11]}{[13]} = \frac{k_4[8][RSH]}{k_3[10][RSH]} = \frac{k_{-2}k_4}{k_2k_3} + \frac{k_4}{k_2}[RSH] \quad (7)$$

$$\frac{[12]}{[13]} = \frac{k_5[9][RSH]}{k_3[10][RSH]} = \left(\frac{k_1}{k_2}\right)\left[\frac{(k_{-2}/k_3) + [RSH]}{(k_{-1}/k_5) + [RSH]}\right] \quad (8)$$

steady state assumption for each homoallyl radical in Scheme 1 (eqs 6–8). These equations reveal several important features of the system:

1. The regioselectivity (k_1/k_2) of the process is independent of any assumptions regarding the magnitude of k_4. It is common practice to extrapolate known absolute rate constant measurements for hydrogen atom abstraction to structurally similar radicals. However, absolute rate constant measurements for benzylic radicals are relatively scarce, and one could propose that application of the reactivity selectivity principle will result in substituents inducing larger rate effects than in nonconjugated alkyl radicals. Hence, assuming that **8** is trapped (k_4) with the same rate constant as benzyl radical may not be legitimate, because **8** is benzylic and tertiary.[8]

2. Provided that the respective y-intercepts obtained by plots of eqs 6 and 7 are large enough to be measured accurately, $\Delta\Delta G°$ of the two cyclopropylmethyl homoallyl radical equilibria are determinable from the ratio of these two measurements. This requires that we assume a value for the ratio of k_3:k_5, which is a more conservative assumption than assuming a value for k_4, because neither **9** or **10** is expected to deviate from the reactivity of typical primary or secondary radicals, respectively.

3. Evidence for reversibility is obtained from any of the three product ratio dependencies on hydrogen atom donor concentration (eqs 6–8). The qualitative dependence of the ratio of **12**:**13** on trap concentration will enable us to determine whether both rearrangements are reversible under the reaction conditions (nonlinear) or if only one of the processes (and which one) is reversible (linear). If only K_{exo} (k_1/k_{-1}) is reversible under the reaction conditions (k_{-2} is negligible), then **13**:**12** will vary linearly with respect to the reciprocal of the trap concentration. Likewise, **12**:**13** will vary linearly with respect to the reciprocal of the trap concentration if k_{-1} is negligible. If neither process is reversible, the ratio of **12**:**13** will be independent of trap concentration.

Results

Synthesis. Radical **8** was generated via a photolabile, thermally stable Barton PTOC ester ([(2-thioxopyridinyl)-*N*-oxy]carbonyl, **14**). The general strategy for the synthesis of the requisite Barton PTOC ester and products was summarized in a preliminary communication.[5]

Olefin **18** was a necessary intermediate enroute to **14** (Scheme 2). Elimination from **16** or its respective mesylate (**17**) proved to be more difficult than expected. No reaction of **16** was observed using Martin's sulfurane dehydrating agent.[11] Similarly, elimination from **16** could not be effected using Burgess' reagent.[12] Mesylate **17** was impervious to treatment with potassium acetate

(7) Batey, R. A.; Grice, P.; Harling, J. D.; Motherwell, W. B.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1992**, 942.

(8) For an overview of absolute rate constants of calibrated bimolecular radical reactions see: Newcomb, M. *Tetrahedron* **1993**, *49*, 1151 and references therein.

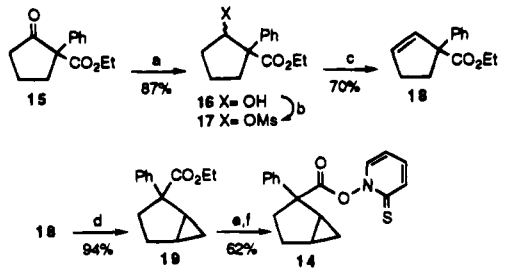
(9) Halgren, T. A.; Howden, M. E. H.; Medof, M. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1967**, *89*, 3051.

(10) (a) Beckwith, A. L. J.; Bowry, V. W. *J. Am. Chem. Soc.* **1994**, *116*, 2710. (b) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Chem. Soc., Chem. Commun.* **1990**, 923.

(11) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.

(12) Burgess, E. M.; Penton Jr., H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

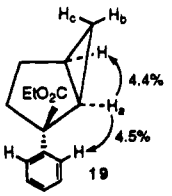
Scheme 2[a]



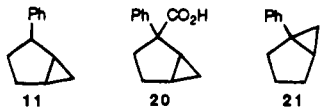
[a] Key: (a) $NaBH_4$, EtOH, 0 °C; (b) CH_3SO_2Cl, pyridine, 0 °C; (c) DBU, DMAP (cat.), toluene, reflux; (d) Et_2Zn, CH_2I_2, hexanes, −78 to 25 °C; (e) 0.2 N KOH, dioxane/H_2O, 90 °C; (f) 2-mercaptopyridine, *N*-oxide, DCC, DMAP, CH_2Cl_2, 25 °C.

in HMPT at 100 °C, or potassium *tert*-butoxide in DMSO. Treatment of **17** with DBU and catalytic DMAP in CH_2Cl_2 also failed to yield **18**. Elimination was finally achieved using the same pair of bases in refluxing toluene in 70% overall yield from **16**.

Cyclopropanation of **18** was facile at room temperature, yielding a single diastereomer of **19**. We expected the carbethoxy group to direct the cyclopropanating agent via coordination to the zinc. The relative stereochemistry of the cyclopropane ring with respect to the phenyl substituent was established via NOE experiments. Irradiation of H_a gave rise to an enhancement of the other cyclopropane bridgehead hydrogen, one of the cyclopropane methylene protons, and the two aromatic protons that are *ortho* to linkage between the phenyl ring and the bicyclic skeleton. Irradiation of either cyclopropane methylene proton (H_b, H_c) has no effect on the aromatic protons. These effects are consistent with the assigned stereochemistry in **19**.

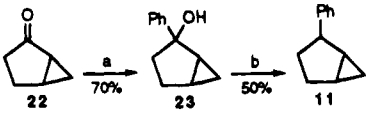


The remainder of the synthesis of **14** was straightforward, involving saponification and activation of **20** via DCC coupling. Carboxylic acid **20** was stable to long term storage and was transformed into **14** as needed for kinetic experiments.



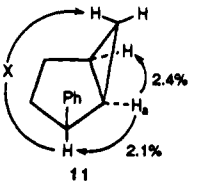
Synthesis of 1-phenylbicyclo[3.1.0]hexane (**11**) via cyclopropanation of 3-phenylcyclopent-1-ene was ineffective. The alkene substrate, prepared via Heck coupling, was unreactive in the presence of diazomethane. Cyclopropanation was readily effected via carbenoid generation from CH_2I_2 using either Zn/Cu couple or diethylzinc. However, an inseparable mixture of **11** and **21** were obtained, due to migration of the double bond in competition with cyclopropanation. Instead, **11** was obtained as a single diastereomer via reduction of **23** (Scheme 3).[13]

Scheme 3[a]

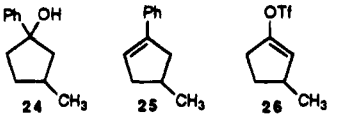


[a] Key: (a) PhLi, THF, −78 °C; (b) $BF_3{\cdot}Et_2O$, BH_3, THF, 0 °C.

The tertiary alcohol was obtained via exclusive nucleophilic addition to the carbonyl face of **22** which is *trans* to the cyclopropyl moiety. The stereochemical relationship between the phenyl and cyclopropane ring in **11** was established via NOE and HETCOR experiments. Irradiation of H_a gives rise to enhancements at two of the other cyclopropane protons and the benzylic proton. Irradiation of the benzylic proton results in enhancement of the bridgehead hydrogen signal (H_a), and at least one of the adjacent methylene hydrogens, but does not show any enhancement at either of the cyclopropane methylene hydrogens. These observations support the assignment of a *syn* relationship between the phenyl substituent and the cyclopropane ring.



1-Phenylcyclohexene (**13**) was readily prepared via acid-catalyzed elimination of the respective tertiary alcohol. As expected, similar treatment of **24**, which was obtained via phenyllithium reduction of 3-methylcyclopentanone, gave a 1:1 mixture of **25** and **12**. Unfortunately, these regioisomers were inseparable by GC or column chromatography using $AgNO_3$ impregnated supports. Preparation of the exocyclic ring opened product (**12**) was finally achieved by reacting the vinyl triflate **26** with phenyl cuprate.[14]



Kinetic Studies. Kinetic runs were carried out in benzene, under pseudo-first-order conditions, using *t*-BuSH as radical trap. Thiol concentration ranged from 0.5 to 2.0 M, whereas the activated ester (**14**) concentration was maintained at 25 mM. Due to coelution of **11** and **12**, product analyses were carried out using GC/MS. The response factors for both **11** and **12** versus hexadecane were measured at the m/z ratios that corresponded to the base peak for each product. Cyclopropylmethyl radical trapping product (**11**) exhibited a base peak corresponding to styrene and a very weak molecular ion. In comparison, the methyl cyclopentene product (**12**) had a strong molecular ion and only a very weak styrene fragment. The concentrations of each product were determined by solving the two simultaneous equations that account for the contribution to the intensity of m/z = 158 and 104 by each product. Similarly, the response factor for 1-phenylcyclohexene (**13**) relative to hexade-

(13) He, G.-X.; Almarsson, O.; Bruice, T. C. *Tetrahedron* **1992**, *48*, 3275.

(14) (a) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313. (b) Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335.

Table 1. Rate Constant Ratios Derived From Product Ratio Dependencies On Trap Concentration For Individual Kinetic Runs[a]

T (K)	k_4/k_1 ($\times 10^3$, M^{-1})	$(k_{-1}k_4)/(k_1k_5)$ ($\times 10^3$)	k_4/k_2 ($\times 10^3$, M^{-1})	$(k_{-2}k_4)/(k_2k_3)$ ($\times 10^3$)
273	5.80 ± 0.2	10.4 ± 0.3	199 ± 6.4	−28.7 ± 8.1
	4.34 ± 0.4	12.1 ± 0.5	155 ± 14.0	7.00 ± 18.0
	6.14 ± 0.4	12.0 ± 0.5	228 ± 6.1	−29.0 ± 7.7
	4.62 ± 0.2	10.0 ± 0.3	156 ± 24.0	46.5 ± 33.0
298	3.27 ± 0.7	9.86 ± 1.0	111 ± 3.2	1.28 ± 4.4
	3.63 ± 0.7	10.9 ± 0.9	101 ± 7.4	−0.20 ± 9.4
	4.03 ± 0.6	12.1 ± 0.8	117 ± 5.0	0.85 ± 6.7
313	2.34 ± 0.5	9.60 ± 0.6	64.3 ± 7.4	5.85 ± 9.3
	2.69 ± 0.3	9.45 ± 0.4	63.7 ± 5.7	10.7 ± 7.2
	3.14 ± 0.3	7.75 ± 0.4	59.9 ± 7.6	2.25 ± 9.6

[a] Standard deviation refer to the deviation in the respective slopes and y-intercepts of the plots from which the rate constant ratios are obtained.

cane, which was separable from products **11** and **12** by capillary GC, was determined using its parent ion.

Analysis of **11** by selected ion mass spectrometry raises an important issue regarding the stereochemistry of this product that is formed via radical trapping. It is common to assume that diastereomers exhibit the same response factor upon gas chromatography analysis using flame ionization detection. However, the relative intensities of the molecular ion (m/z= 158) and base peak (m/z = 104) need not be the same in the two diastereomers of **11** in which the phenyl and cyclopropane rings are *syn* and *anti*, respectively. Since we were unable to synthesize the *anti* diastereomer of **11**, we examined the product mixture formed by ^{1}H NMR. The cyclopropyl methylene group in **11** is separated from any other protons by more than 0.6 ppm. Analysis of the crude photolysate by ^{1}H NMR showed no cyclopropyl methylene group, other than that attributable to **11** in which the cyclopropane group is *syn* to the phenyl group. This diastereomer of **11** is the expected kinetic product from **8** and was independently synthesized (see above).

Stability of the radical trapping products (**11-13**) to the reaction conditions was established via a three-pronged approach. In tube 1, irradiation of a known amount of one of the respective products in the presence of internal standard and hydrogen atom donor showed no product degradation. Evidence that the products were stable in the presence of alkyl radicals was obtained by comparing the amount of product in the above experiment to the amount of the same product present in two tubes in which equal amounts of activated ester **14** was present. Tube 2 contained **14**, trap, and internal standard. In addition to these three species, one of the three trapping products was added to tube 3 in an amount equal to that present in tube 1. The total amount of product in tube 3 was compared to the summation of product observed in tubes 1 and 2. Analysis of the stability of each product (**11**−**13**) separately indicated less than 10% possible product degradation.

Analyses were carried out at three different temperatures, ranging from 273 to 313 K. Mass balances, as determined by selected ion GC/MS, were between 55% and 85%. 3-Methyl-1-phenylcyclopentene was the major product, accounting for as much as 93% of the product mixture. Standard deviations for individually determined kinetic parameters were obtained from the least square analysis of the product ratios with respect to trap concentration (Table 1). For k_4/k_1, $(k_{-1}k_4)/(k_1k_5)$, and k_4/k_2 the deviations were with but few exceptions, on the order of 5−10%. The error associated with the measurement of $(k_{-2}k_4)/(k_2k_3)$ is typically much larger and implies that our data do not allow us to statistically distinguish

Table 2. Average Values of Rate Constant Ratios from Multiple Kinetic Runs[a]

T (K)	273	298	313
k_4/k_1 (M^{-1})	5.23 (0.8) × 10^{-3}	3.64 (0.3) × 10^{-3}	2.72 (0.3) × 10^{-3}
$(k_4k_{-1})/(k_1k_5)$	1.11 (0.09) × 10^{-2}	1.10 (0.09) × 10^{-2}	0.89 (0.08) × 10^{-2}
k_{-1}/k_5 (M)	2.12	3.02	3.27
k_4/k_2 (M^{-1})	1.85 (0.31) × 10^{-1}	1.10 (0.07) × 10^{-1}	0.63 (0.02) × 10^{-1}
$(k_4k_{-2})/(k_2k_3)$	1.05 (31.1) × 10^{-3}	0.64 (0.62) × 10^{-3}	6.27 (3.50) × 10^{-3}
k_{-2}/k_3 (M)	5.68 × 10^{-3}	5.82 × 10^{-3}	99.5 × 10^{-3}
k_1/k_2	35.4	30.2	23.2

[a] Standard deviations refer to the variation of the individual rate constant ratios determined from individual kinetic runs (Table 1).

the magnitude of this ratio of rate constants from zero. In fact, it is only at the highest temperature at which product analysis was conducted (313 K) that the measured value of $(k_{-2}k_4)/(k_2k_3)$ was consistently greater than zero. Nonetheless, the average value determined for $(k_{-2}k_4)/(k_2k_3)$ was greater than zero at all temperatures (Table 2). It is not surprising that the error in $(k_{-2}k_4)/(k_2k_3)$ is significantly greater than that of k_4/k_1, despite the fact that the magnitudes of these two ratios are similar. The ratio of the bimolecular rate constant for trapping of **8** (k_4) to exocyclic ring opening (k_1) of this radical is determined from the dependence of the ratio of the major product (**12**) versus a minor product (**11**) on trap concentration, whereas $(k_{-2}k_4)/(k_2k_3)$ is determined from a similar dependence of two minor products (**11** and **13**). We attribute the greater error in $(k_{-2}k_4)/(k_2k_3)$ to the correspondingly larger error in measuring the concentration of two minor products than that of one major and one minor product. The error in $(k_{-2}k_4)/(k_2k_3)$ is carried through to the determination of k_{-2}/k_3, which is obtained by dividing the value of the y-intercept of eq 7 by the slope of this line.

The observation that **12**:**13** behaves nonlinearly with respect to varying thiol concentration is gratifying and confirms that both equilibria involving **8** are reversible over the entire temperature for which the system was studied (Figure 1). More specifically, with respect to the above discussion, this result shows that k_{-2} is indeed nonzero. Nonlinear regression analysis was carried out by using the experimentally determined ratio of **12**:**13** as a function of thiol concentration, as well as the calculated ratio of k_1/k_2 and k_{-1}/k_5 to determine k_{-2}/k_3. It is pertinent to point out that determination of k_{-2}/k_3 via nonlinear regression analysis is not completely independent of the dependence of **11**:**13** on trap concentration, because the nonlinear regression analysis relies upon the value determined for k_4/k_2. However, as reflected in the standard deviation of individual values of k_4/k_2, the confidence in this rate constant ratio is as high as any involving **11**:**12**. The values of k_{-2}/k_3 determined for

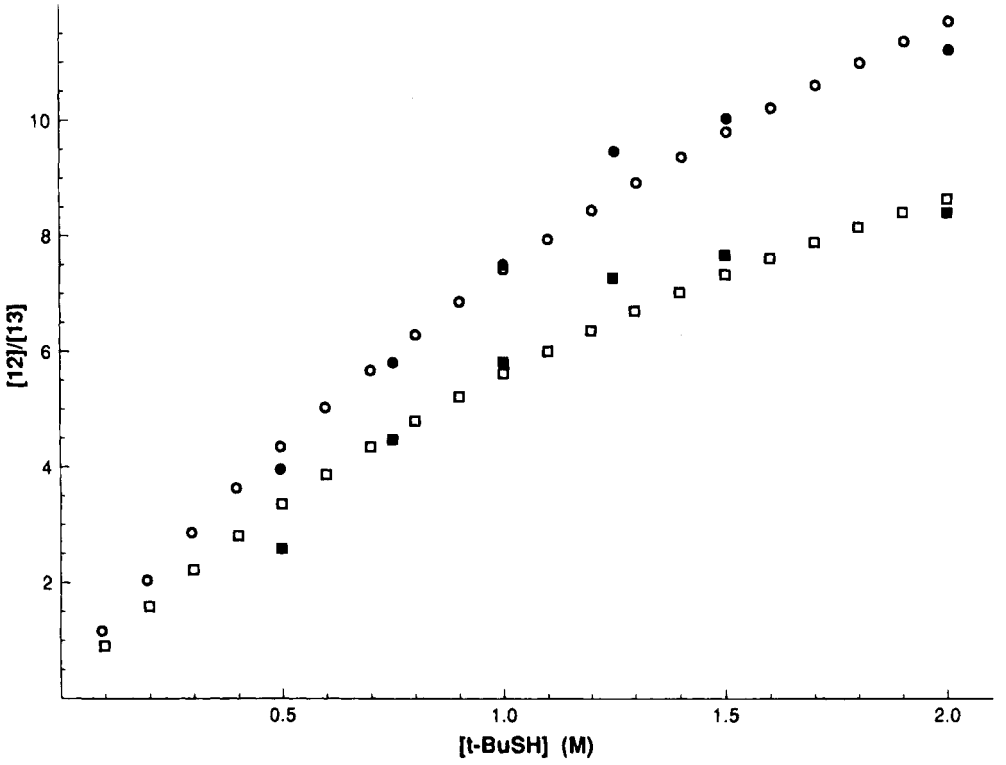


Figure 1. Ratio of **12**:**13** as a function of trap concentration. Experimental measurements, filled symbols; calculated product ratios, open symbols; T = 273 K, circles; T = 313 K, squares.

individual kinetic runs obtained via this method of analysis yields very similar values as those obtained from nonlinear regression analysis of **12**:**13** versus thiol concentration. The ratio of k_{-2}/k_3 displays the greatest temperature dependence (Table 2), consistent with **10** facing the largest barrier to rearrangement. Similarly, k_4/k_1 and $(k_4k_{-1})/(k_1k_5)$ show the least temperature dependence, consistent with the respective ring opening and closing processes facing smaller barriers than k_{-2}.

As pointed out earlier, the ratio of rate constants for ring opening in **8** does not require any assumption of the magnitude of k_4 (Table 2). It is interesting to note that the kinetic preference measured for exocyclic ring opening in **8** at 273 K (35.4) is very close to the number extrapolable (~31:1) from trapping of the parent bicyclo[3.1.0]hexan-1-yl (**1**) in neat Bu_3SnH at 276 K (eq 1). This suggests that while the phenyl substituent imparts enough benzylic stabilization on the cyclopropylmethyl radical system so as to make the equilibrium readily reversible, it does not significantly shift the position of the transition state for ring opening relative to the parent system. The relative activation parameters for the two respective ring opening processes are obtainable from the dependencies of **8**:**9** and **8**:**10** on trap concentration as a function of temperature (Table 2). An Arrhenius plot of this data (Figure 2) indicates that exocyclic ring opening of **8** is kinetically favored in comparison to endocyclic ring opening for both enthalpic ($\Delta\Delta H^{\ddagger} = -1.70$ kcal/mol) and entropic ($\Delta\Delta S^{\ddagger} = 0.47$ eu) reasons. At 298 K, this translates into $\Delta\Delta G^{\ddagger} = -1.84$ kcal/mol for exocyclic ring scission.

The specific values of $\Delta G^{\ddagger}$ for each radical rearrangement process, as well as the relative energetics of the three radicals involved in this study, can be obtained by assuming values for k_3, k_4, and k_5. Homoallyl radicals **9** and **10** are not unusually hindered and are expected to react with t-BuSH at rates similar to those for other primary and secondary radicals, respectively.[8] Although specific data for t-BuSH are not as abundant as for Bu_3SnH, the reactivity of hydrogen atom donors such as Bu_3SnH and PhSH with primary, secondary, and tertiary radicals vary by less than 25%. Hence, in calculating the relative energies of the radicals in this system, it is assumed that $k_3 \sim k_5 = 8.0 \times 10^6$ M^{-1} s^{-1} at 298 K. Estimation of trapping of **8** by t-BuSH is more involved.[8] To our knowledge, there is no direct determination of the rate constant for trapping of a benzyl radical by t-BuSH. We estimated the magnitude of k_4 by extrapolating the rate constants for trapping benzyl radical and primary alkyl radicals by PhSH, relative to the trapping of primary alkyl radicals by t-BuSH. From this linear extrapolation, we estimate k_4 to be 1.8×10^4 M^{-1} s^{-1} at 298 K.[8] The calculated rate constants for ring opening and closing, as well as the respective equilibria, using these values for bimolecular trapping rate constants are

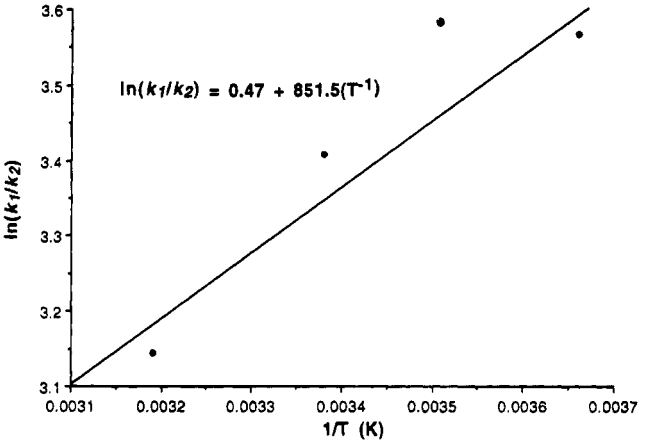


Figure 2. Arrhenius plot of k_1/k_2.

Table 3. Individual Rate Constants and Equilibrium Constants at 298 K

k_1 (s^{-1})	4.95×10^6	k_{-2} (s^{-1})	4.65×10^4
k_{-1} (s^{-1})	2.4×10^7	K_{exo}[a]	0.21
k_2 (s^{-1})	1.6×10^5	K_{endo}[b]	3.44

[a] $K_{exo} = k_1/k_{-1}$. [b] $K_{endo} = k_2/k_{-2}$.

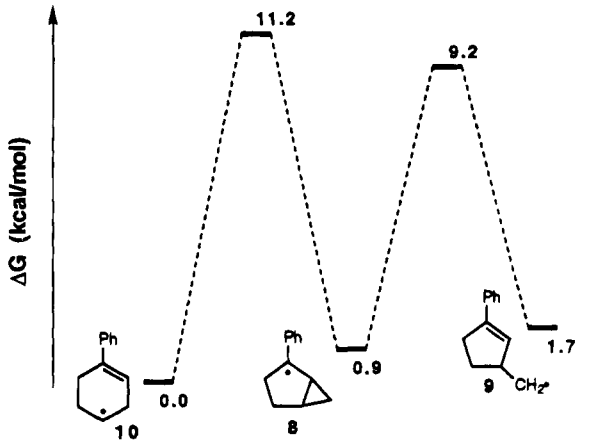


Figure 3. Relative energies of cyclopropylmethyl and homoallyl radicals and respective transition states for rearrangement.

listed in Table 3. These data confirm the presumption that endocyclic ring scission results in formation of the thermodynamic radical (**10**) and enable one to approximate the relative energies of **8**-**10** and respective transition state energies for the rearrangement of **8** (Figure 3). Determination of the $\Delta\Delta G^{\ddagger}$ for the ring opening processes in **8** via this methods yields a value of 2.0 kcal/mol, which is very close to the 1.84 kcal/mol determined directly from the temperature dependance of k_1/k_2 (Figure 2).

The equilibria involving **8** both favor the homoallyl radical significantly more than the respective species in the parent system. In fact, the cyclohexenyl radical (**10**) is approximately 0.9 kcal/mol more stable than **8**. One possible explanation for these results is that **8** is destabilized relative to the α-cyclopropylbenzyl radical, due to increased strain in the bicyclo[3.1.0]hexane framework. Alternatively, **8** could exist in a conformation in which the phenyl ring is forced to rotate to such an extent that the radical center effectively does not enjoy benzylic stabilization. This latter explanation seems unlikely to us, because if **8** did not enjoy appreciable stabilization by the phenyl substituent, then the exocyclic ring closure process would not be nearly as competitive with trapping of **9** as it is ($k_{-1}/k_5 = 3.02$ at 298 K).

Conclusions. Benzylic stabilization of a bicyclic cyclopropylmethyl radical facilitates characterization of the reaction surface involving the ring closed isomer and its rearrangement products by conventional kinetic methods involving product analysis. Comparison of the observed regioselectivity for **8** to that extracted from the unsubstituted bicyclo[3.1.0]hexan-1-yl (**1**) suggests that the phenyl substituent does not perturb the position of the transition state for ring opening. This suggests that benzylic stabilization will be a useful tool for determining structural effects (such as cyclopropyl bridgehead substituents) on the kinetics of radical rearrangements which would be inaccessible otherwise. Systematic analysis of such substituent effects should be useful in the rational application of cyclopropylmethyl (and related) radical rearrangements to organic synthesis.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 300, 270, or 200 MHz. IR spectra were obtained on a Perkin Elmer 1600 Series FT-IR. GC/MS analysis was carried out on an HP 5970 Series MSD equipped with an HP 5890 GC. Selected ion monitoring was done using a 80 ms dwell time. Response factors for **11**–**13** versus *n*-hexadecane were determined separately for ions $m/z = 104$ and 158. The C_6H_{13} fragment ($m/z = 85$) was used for *n*-hexadecane. Response factors were determined for each product in the same concentration range as they were formed in kinetic experiments. Internal standard was maintained at 5.12 mM. Individual response factors were determined from the general relationship shown below:

$$\frac{[\text{Prod}]}{[\text{Std}]} = (\text{resp.factor}_{\text{prod;ion x}})\frac{A_{\text{prod;ion x}}}{A_{\text{Std; 85}}} \qquad (9)$$

response factor: ion (m/z)

product	104	158
11	0.73	2.88
12	177.3	2.73
13	9.98	1.88

The concentrations of products **11** and **12**, which coelute, were obtained by solving the two independent equations below. The [Std] is known *a priori*. The areas are measured.

$$A_{\mathbf{11+12};\,104} = \frac{(A_{\text{Std; 85}})[\mathbf{11}]}{(\text{resp.factor}_{\mathbf{11};\,104})[\text{Std}]} + \frac{(A_{\text{Std; 85}})[\mathbf{12}]}{(\text{resp.factor}_{\mathbf{12};\,104})[\text{Std}]} \qquad (10)$$

$$A_{\mathbf{11+12};\,158} = \frac{(A_{\text{Std; 85}})[\mathbf{11}]}{(\text{resp.factor}_{\mathbf{11};\,158})[\text{Std}]} + \frac{(A_{\text{Std;85}})[\mathbf{12}]}{(\text{resp.factor}_{\mathbf{12};\,158})[\text{Std}]} \qquad (11)$$

All reactions were run under nitrogen atmosphere in oven-dried glassware, unless specified otherwise. Pyridine, benzene, and $BF_3{\cdot}Et_2O$ were freshly distilled from CaH_2. DMF was freshly distilled under aspirator pressure from CaH_2. *t*-BuSH was freshly distilled from CaO. THF and diethyl ether were distilled from Na/benzophenone ketyl.

Kinetic runs were carried out in a temperature-controlled Pyrex Dewar, using a 275 W tungsten bulb. Samples were freeze-pump-thaw degassed three times. Pyrex tubes were oven dried. Samples were stored at 77 K until analyzed. Samples were analyzed in duplicate. The concentration of **14** was 25 mM in all kinetic runs.

Alcohol 16. $NaBH_4$ (490 mg, 12.9 mmol) was added to **15**[15] (1 g, 4.3 mmol) in EtOH (50 mL) at 0 °C. The reaction was stirred and allowed to warm to room temperature over 3 h. The reaction was quenched with H_2O (5 mL) and the solvents removed in vacuo. The residue was taken up in H_2O (5 mL) and extracted with Et_2O (3 × 20 mL). The organic layers were washed with brine and dried over $MgSO_4$. The alcohol (mixture of diastereomers) was obtained as a colorless liquid in 87% yield, following flash chromatography (EtOAc:hexanes 1:5): ^{1}H NMR ($CDCl_3$) δ 7.44–7.24 (m, 5H), 4.87–4.86 (m, 1H),

(15) Barton, D. H. R.; Blazejewski, J. C.; Charpiot, B.; Firet, J. P.; Motherwell, W. B.; Papoula, M. T. B.; Stanforth, S. P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2667.

4.15–4.00 (m, 2H), 2.58–2.51 (m, 1H), 2.30–2.20 (m, 1H), 2.02–1.66 (m, 4H), 1.15–1.1 (t, 3H, $J = 7$ Hz), 1.31 (s, 1H); IR (thin film) 3503, 2977, 1721, 1446, 1235, 1082 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.00; H, 7.75.

Cylopentene 18. Freshly distilled methanesulfonyl chloride (514 mg, 4.48 mmol) was added to the above alcohol (750 mg, 3.21 mmol) in freshly distilled pyridine (16 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 8 h. The reaction was quenched with H_2O (15 mL) and extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Following removal of the organics, the crude mesylate was taken up in toluene (6 mL) and refluxed for 3 days in the presence of DBU (3.513 g, 23 mmol) and catalytic DMAP (20 mg). The reaction was poured into H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 0.1 N HCl (15 mL) and then again with H_2O (2 × 20 mL). The organics were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (Et_2O:hexanes 1:11) yielded 480 mg (70%) of **18** as a colorless liquid: ^1H NMR ($CDCl_3$) δ 7.35–7.23 (m, 5H), 6.10–6.02 (m, 2H), 4.18–4.11 (m, 2H), 2.99–2.90 (m, 1H), 2.53–2.41 (m, 2H), 2.18–1.98 (m, 1H), 1.22–1.17 (t, 3H, $J = 7$ Hz); IR (thin film) 2980, 1728, 1447, 1241, 1056, 698 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.26. Found: C, 77.61; H, 7.26.

Cyclopropanation product 19. Diethylzinc (13.35 mL; 1 M) in hexanes was added slowly to **18** (480 mg, 2.20 mmol) in hexanes (1 mL) at −78 °C. Diiodomethane (7.14 g, 26.6 mmol) was then slowly added with vigorous stirring. The mixture was allowed to warm to room temperature and stirred for 3 days. The reaction was quenched by pouring into a saturated solution of NH_4Cl (25 mL) and extracted with Et_2O (3 × 50 mL). The combined organics were washed with a 1% solution of $Na_2S_2O_3$ (25 mL) and then brine (25 mL) and dried over $MgSO_4$. Flash chromatography (Et_2O:hexanes 1:11) yielded 480 mg (94%) of **19** as a colorless liquid: ^1H NMR ($CDCl_3$) δ 7.36–7.22 (m, 5H), 4.19–4.12 (m, 2H), 2.08–2.03 (m, 1H), 1.79–1.62 (m, 5H), 1.20–1.15 (t, 3H, $J = 7$ Hz), 0.5–0.42 (m, 2H); IR (thin film) 2977, 1727, 1447, 1239, 1052 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.19; H, 7.84.

Carboxylic Acid 20. Ester **19** (395 mg, 1.72 mmol) was refluxed in a mixture of dioxane (10 mL) and 0.2 M KOH (42 mL) for 48 h. Additional water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The aqueous layer was acidified to pH 2 and extracted again with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (25 mL) and dried over $MgSO_4$. The crude product was recrystallized from MeOH/H_2O to yield 305 mg (88%) of **20**: mp 194–196 °C; ^1H NMR ($CDCl_3$) δ 7.44–7.24 (m, 5H), 2.03–1.56 (m, 6H), 0.57–0.53 (m, 2H); IR (thin film) 2975, 1688 1492, 733 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.27; H, 6.67.

PTOC Ester 14. *N*-Hydroxypyridine-2-thione (69.3 mg, 0.54 mmol) was added to **20** (100 mg, 0.495 mmol) and DMAP (50 mg, 0.41 mmol) in CH_2Cl_2 (2 mL) at room temperature. DCC (112 mg, 0.54 mmol) in CH_2Cl_2 (2 mL) was then added, and the mixture was stirred for 12 h in a vessel shielded from light. The CH_2Cl_2 was removed in vacuo. The residue was taken up in EtOAc (20 mL) and washed sequentially with 1 M $KHSO_4$ (5 mL), H_2O (10 mL), 5% $NaHCO_3$ (5 mL), and H_2O (10 mL), and dried over anhydrous $MgSO_4$. Flash chromatography (EtOAc:hexanes 1:6) yielded (104 mg) 68% of **14**; ^1H NMR ($CDCl_3$) δ 7.67–7.12 (m, 8H), 6.57–6.52 (m, 1H), 2.37–2.32 (m, 1H), 2.03–1.62 (m, 5H), 0.81–0.73 (m, 2H); IR (thin film) 3024, 2932, 1791, 1526, 1493, 1281 cm^{-1}.

Bicyclic Benzyl Alcohol (23). Phenyllithium was freshly prepared by treatment of Li (24 mg, 3.44 mmol) in Et_2O (1.3 mL) with bromobenzene (270 mg, 1.72 mmol). The phenyllithium was added via syringe to **22**[16] (150 mg, 1.56 mmol) in THF (8 mL) at −78 °C. The solution was stirred for 1 h and quenched with saturated NH_4Cl (2 mL) and H_2O (10 mL). The aqueous mixture was extracted with Et_2O (3 × 30 mL), washed with brine (20 mL), and dried over $MgSO_4$. Flash chromatography (EtOAc:hexanes 1:5) yielded 190 mg (70%) of **23** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.57 (d, 2H, $J = 7$ Hz), 7.38 (t, 2H, $J = 7$ Hz), 7.28 (m, 1H), 1.57–1.83 (m, 7H), 0.75 (m, 1H), 0.61 (m, 1H); IR (thin film) 3372, 3060, 2962, 1601, 1491, 1446, 1202, 1095, 1035, 762 cm^{-1}.

1-Phenylbicyclo[3.1.0]hexane (11). $BF_3{\cdot}Et_2O$ (0.82 mmol, 6.66 mmol) was added to $NaBH_4$ (190 mg, 5 mmol) in THF (1 mL) at 0 °C. The reaction was stirred and warmed to room temperature over 1.5 h, at which time **23** (75 mg, 0.431 mmol) in THF (3 mL) was added. The reaction was quenched with H_2O (1 mL) after 8 h. H_2O_2 (30%, 3 mL) was added, followed by 3 N NaOH (2 mL), and the mixture was stirred for 15 min. The aqueous layer was extracted with ether (3 × 15 mL), washed with brine (10 mL), and dried over $MgSO_4$. Flash chromatography (hexanes) yielded 34 mg (50%) of **11**; ^1H NMR ($CDCl_3$) δ 7.45–7.15 (m, 5H), 3.41–3.33 (m, 1H), 1.95–1.81 (m, 3H), 1.54–1.19 (m, 3H), 0.53–0.39 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 146.0, 128.5, 128.0, 126.0, 45.0, 28.5, 21.5, 18.0, 5.0; IR (thin film) 3026, 2861, 1602, 1494, 1027, 740 cm^{-1}; HRMS calcd 158.1095 (M^+), found 158.1096.

3-Methyl-1-phenylcyclopent-1-ene (12). Freshly prepared PhLi (5.2 mL, 1.32 M) in Et_2O was added to a solution of CuBr (0.5 g, 3.5 mmol) in Et_2O (1 mL) at 0 °C. A solution of **26**[14b] (0.4 g, 1.75 mmol) was added at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 8 h. The mixture was poured into a solution of NH_4Cl and NH_4OH (pH 8, 10 mL), and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (25 mL) and dried over $MgSO_4$. Flash chromatography (hexanes) yielded 80 mg (28%) of **12** as a colorless liquid; ^1H NMR ($CDCl_3$) δ 7.43–7.16 (m, 5H), 6.07 (s, 1H), 2.93–2.64 (m, 3H), 2.26–2.20 (m, 1H), 1.57–1.47 (m, 1H), 1.10–1.08 (d, 1H, J= 7 Hz); ^{13}C NMR ($CDCl_3$) δ 141.3, 136.8, 132.1, 128.4, 126.8, 125.5, 40.6, 32.8, 32.3, 20.9; IR (thin film) 2954, 1494, 1448, 1330, 1079, 755 cm^{-1}. HRMS calcd 158.1095 (M^+), found 158.1090.

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(16) de Costa, B. R.; Mattson, M. V.; George, C.; Linders, J. T. M. *J. Med. Chem.* **1992**, *35*, 4704.