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Access to cyclopropyl cations via carbene fragmentation

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Abstract—Photolysis of cyclopropyloxychlorodiazirines affords cyclopropyloxychlorocarbenes whose fragmentations provide access to ion pairs, which feature cyclopropyl cations.

1. Introduction

Cyclopropyl cations are high energy species due to ring strain and geometric restrictions that prevent the attainment of the optimal 120° angle at the cationic carbon atom (angle strain). An isodesmic calculation places the parent cyclopropyl cation ~30 kcal/mol above the 2-propyl cation.[1] Solvolyses of *sec*-cyclopropyl tosylates (**1**) do not afford cyclopropyl products; participation of the ring's distal C–C bond in the solvolytic process leads directly to allylic cation intermediates and then to allylic products.[2]

With *tert*-cyclopropyl tosylates (**2**), however, cyclopropyl cations may participate in solvolysis, leading to significant yields of cyclopropyl products.[3] This is especially evident when R is a decent cation stabilizing group such as cyclopropyl or phenyl.[3] Thus, solvolysis of **2** in aqueous ethanol (containing $CaCO_3$ buffer) affords both cyclopropyl (**3**) and ring-opened allylic (**4**) products. When R = cyclopropyl, the **3**:**4** ratio is 68.5/31.5, whereas it reverses to 32/68 when R = phenyl.[3] These results are interpreted as supporting more effective stabilization of a cyclopropyl cation intermediate by the cyclopropyl as opposed to the phenyl substituent.[3] Kinetics and activation parameters are in accord with this interpretation.[3]

Cyclopropyl cations can also be approached by deaminative reactions.[4,5] Secondary cyclopropyl diazonium ions (e.g., **5**, R=Ph or Me) readily open to allylic acetates and *trans*-3-chloro-1-R-propene in acetic acid; cyclopropyl products are absent.[5]

However, *tert*-cyclopropyl diazonium ions can give cyclopropyl products.[4] Methanolysis of **6**, for example, gives 4–5% of the corresponding cyclopropyl methyl ether, with 95–96% inversion from either diastereomeric precursor.[4] It is unlikely that cyclopropyl cations are intermediates here; the products are mostly derived from ring-opened allylic cations, while the small quantities of cyclopropyl products form with inversion, suggestive of S_N2 processes.[4,5]

Substitution of a more effective cation stabilizing substituent permits greater cyclopropyl cation participation in deaminative solvolyses, leading to substantial yields of cyclopropyl products. Thus **7** (R=cyclopropyl) decomposes in MeOH to yield 81.7% of the cyclopropyl methyl ether analogous to **3**, and 18.3% of the allylic methyl ether corresponding to **4**.[4] There is somewhat more preservation of the reactant cyclopropyl ring from diazonium ion **7** (~82%) than from tosylate **2** (~68%, with R=cyclopropyl). Stereochemical studies with D-labeled **7** indicate the stereorandom formation of the product cyclopropyl methyl ether, consistent with the intermediacy of achiral cyclopropyl cation **8**.[4]

We have found that photolyses (or thermolyses) of alkoxychlorodiazirines (**9**) generate alkoxychlorocarbenes (**10**), which fragment to ion pairs (**11**).[6] This process serves as a nonsolvolytic portal to carbocations (or related ion pairs) of special structural interest; for example, the 2-norbornyl[7] or 1-norbornyl[8] cations. The fragmentation of carbenes **4** with loss of CO is analogous to the decomposition of diazonium ions (RN_2^+) with loss of nitrogen,[9] a correspondence that has

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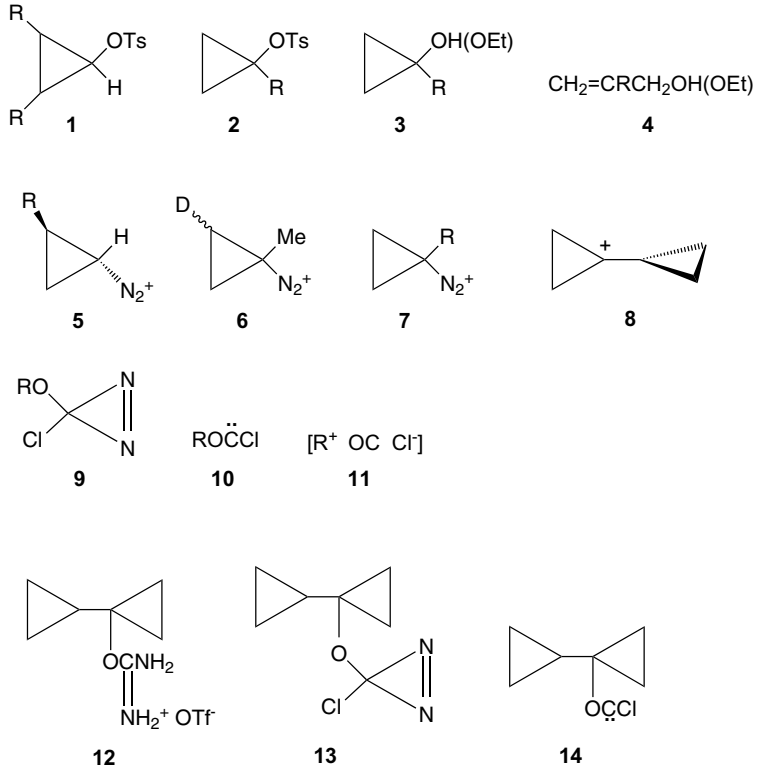


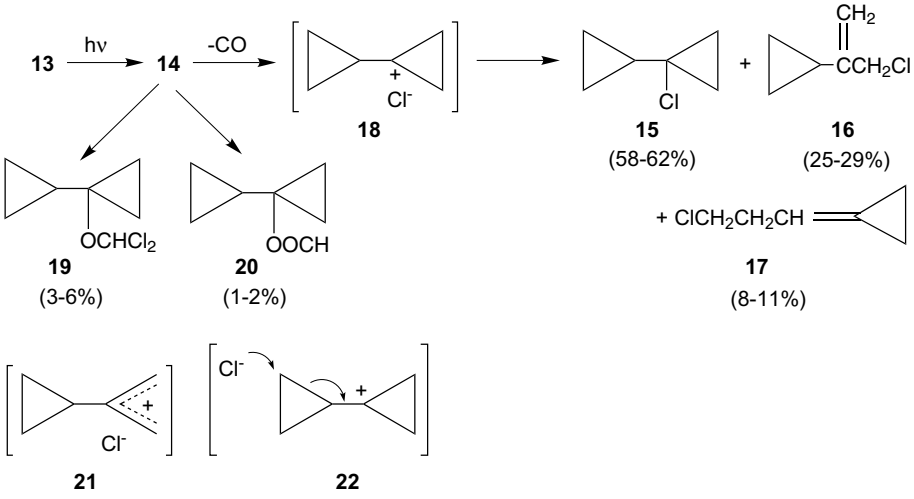
recently been documented in the menthyl and neomenthyl series.[10] Accordingly, we envisioned photochemical access to cyclopropyl cations via fragmentation reactions of **10**, where R=cyclopropyl. Here, we report successful tests of this concept.

2. Bicyclopropyl system

1-Cyclopropyl-1-cyclopropanol[11] was converted to the isouronium triflate **12** with cyanamide and triflic acid in THF (50 °C, 30 h).[12] Oxidation[13] of **12** with 12% aqueous NaOCl (saturated with NaCl) in LiCl–DMSO/pentane then gave diazirine **13**. The diazirine was extracted into the pentane phase as it formed, and was subsequently purified by chromatography on silica gel with pentane elution. The pentane was then evaporated and replaced with 1,2-dichloroethane (DCE) or $CDCl_3$.

Diazirine **13** was characterized by ^1H and ^{13}C NMR, IR (1541 cm^{-1}, N=N), and UV (λ_{max} 348, 360 nm in DCE).

Photolysis of the diazirine ($\lambda > 300$ nm, $A_{352} = 1.0$) afforded chlorides **15**–**17**, derived from the fragmentation of carbene **14**, as well as small quantities of dichloride **19** and formate **20**, formed by capture[14] of the carbene by HCl or H_2O, respectively (Scheme 1). The



Scheme 1.

identities of **15**–**17** were established by ^{1}H NMR, GC–MS, and capillary GC (CP-Sil 5CB, dimethyl polysiloxane, 30 m) comparisons with authentic samples. 1-Chlorobicyclopropyl (**15**) was prepared by reaction of 1-cyclopropyl-1-cyclopropanol with $SOCl_2$ in dry ether (−10 °C, 30 min) in the presence of (diethylaminomethyl)polystyrene.[15] Chloride **15** was isolated in 75% yield after chromatography on silica gel (9:1 hexane–EtOAc), accompanied by 22% of **16** and 3% of **17**. The ^{1}H NMR spectrum of **15** was in accord with the literature description.[16] Similarly, the key ^{1}H NMR resonances of (**16**)[17] and (**17**)[16] could be discerned in the product mixtures from carbene **14** and from (1-cyclopropyl-1-cyclopropanol+$SOCl_2$). Dichloride **19** and formate **20** were identified by their distinctive NMR signals at δ 7.39 (C*H*Cl_2) and 8.07 (OOC*H*), which were augmented when the fragmentations of **14** were carried out with added HCl or H_2O, respectively.

The product distribution ranges shown in Scheme 1 were obtained from four experiments, with analysis by capillary GC and ^{1}H NMR. The formation of chlorides **15**–**17** is most economically rationalized via the intermediacy of ion pair **18**, formed upon fragmentation of carbene **14**: chloride return yields **15**; opening of the cyclopropyl cation to allylic cation **21**, followed by chloride return, gives **16**; and chloride attack on a distal carbon of the substituent cyclopropyl ring of **18**, coupled with opening of that ring, leads to **17** (see **22**).

The formation of **15** and **16** from **18** in a ratio of ~2.2 resembles the ethanolysis of tosylate **2** (R = cyclopropyl), where **3** and **4**, analogues of **15** and **16**, also form in a ratio of 2.2.[3] Deaminative methanolysis of **7** (R = cyclopropyl) affords a higher (4.5) cyclopropyl/allyl product ratio.[4] The formation of chloride **17** from carbene **14** is not precedented in either solvolysis of tosylate **2** or the methanolysis of diazonium ion **7**, but can be accounted for by distal chloride attack on cation **8** (**22**). We note, however, that if the fragmentation of carbene **14** admixes any radical character,[18] opening of a radical pair analogous to **18** would be expected[16] to furnish **17** (as well as **16**).

3. 1-Phenyl-1-cyclopropyl system

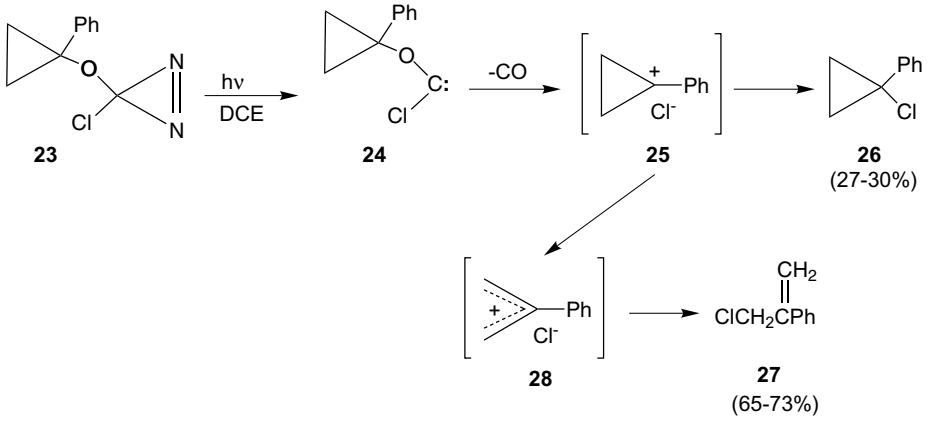
1-Phenyl-1-cyclopropanol[19] was converted[12] to the isouronium triflate and the latter was oxidized[13] to diazirine **23**, as was described above for the preparation of diazirine **13**. Diazirine **23** was characterized by ^{1}H and ^{13}C NMR, and IR (1541 cm^{-1}), and UV spectroscopy (348, 360 nm in DCE). Photolysis of **23** ($\lambda > 300$ nm, $A_{352} = 1.0$) in DCE or $CDCl_3$ gave chlorides **26** and **27**, derived from the fragmentation of carbene **24** (Scheme 2). In $CDCl_3$, ~4% of the dichloride (HCl trapping product of **24**) also formed.

The identities of **26** and **27** follow from GC–MS, ^{1}H and ^{13}C NMR, and capillary GC comparisons with authentic materials: **26** was prepared by the LiCl/$Pb(OAc)_4$ decarboxylation of 1-phenyl-1-cyclopropanecarboxylic acid,[20] whereas the allylic chloride, **27**, was synthesized by Wittig olefination of phenacyl chloride.[21]

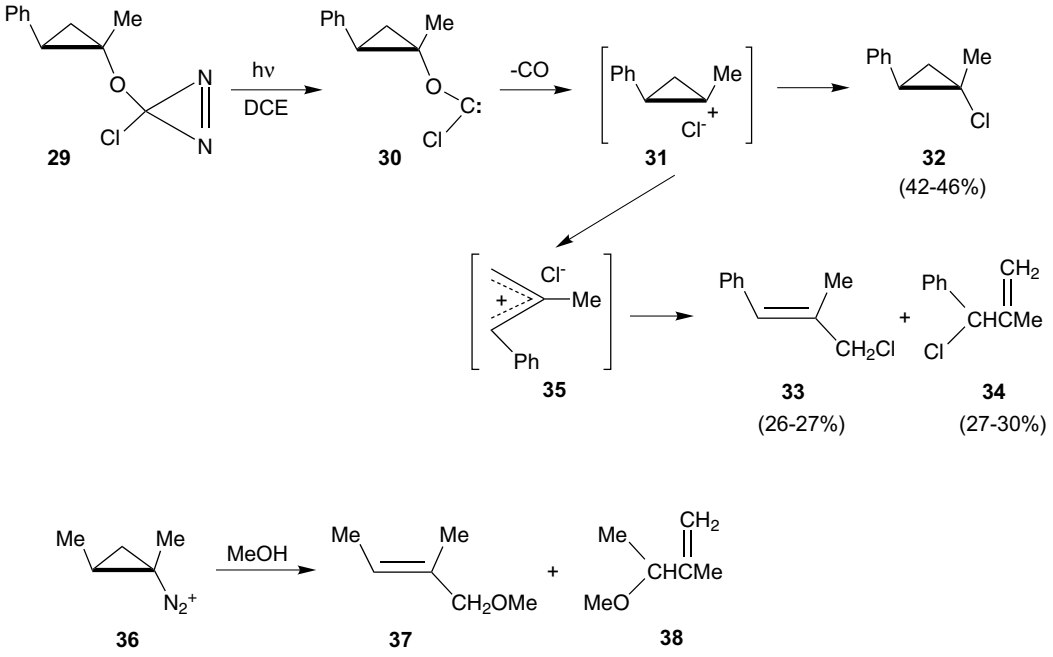
The fragmentation products of carbene **24** can be understood with reference to ion pair **25**. Chloride return provides cyclopropane **26**, while ring opening to ion pair **28**, followed by collapse with chloride, affords 2-phenyl-3-chloropropene (**27**). The product distribution shown in Scheme 2 (**26**/**27** ~ 0.41) is similar to the corresponding cyclopropyl/allyl product ratio (0.47) obtained from the aqueous ethanolysis of tosylate **2** (R=Ph).[3] The greater preservation of the cyclopropyl ring, relative to ring opening, in the fragmentation of carbene **14** (ratio ~ 2.2, Scheme 1) versus carbene **24** (ratio ~ 0.41, Scheme 2) is consistent with the previously noted[3] greater stabilization of a cyclopropyl cation by a 1-cyclopropyl as opposed to a 1-phenyl substituent.

4. 2-Phenyl-1-methylcyclopropyl system

E-2-phenyl-1-methylcyclopropanol[22] was converted[12] to the isouronium triflate, which was oxidized[13] to diazirine **29**. The latter was characterized by ^{1}H and ^{13}C NMR, IR (1542 cm^{-1}) and UV spectroscopy (350, 369 nm in DCE). Photolysis ($\lambda > 300$ nm, $A_{352} = 1.0$) of **29** in DCE or $CDCl_3$ gave chlorides **32**–**34**, derived from the



Scheme 2.



Scheme 3.

fragmentation of carbene **30** (Scheme 3). Carbene capture products (dichloride or formate) were not observed.

Product identities were established by GC–MS, ^{1}H, and ^{13}C NMR comparisons with independently prepared samples. Cyclopropane **32** (and its *Z* stereoisomer) were synthesized by the addition of photogenerated MeCCl[23] to styrene. Structure *E*-**32** was assigned to the fragmentation product of carbene **30** based on its 'high-field' ^{1}H NMR methyl resonance (δ 1.32), relative to the lower-field resonance (δ 1.77) of its *Z* stereoisomer.[24] Vicinal phenyl groups are known to shield *cis* methyl relative to *trans* methyl groups in cyclopropanes.[25] Chloride **33** was obtained by reacting α-methyl-*trans*-cinnamyl alcohol with $SOCl_2$ in dry ether.[26] Similar treatment of 1-phenyl-2-methyl-3-propene-1-ol gave a mixture of chlorides **33** (67%) and **34** (33%).[27]

The fragmentation products of carbene **30** (Scheme 3) can be understood in terms of ion pair **31**. Return of chloride affords cyclopropane **32** with retention of configuration relative to the carbene. The stereochemistry of chloride return is known to be retention in related carbene fragmentation reactions.[28] Disrotatory ring opening of the cyclopropyl cation of **31** to ion pair **35**, followed by chloride return, gives allylic chlorides **33** and **34**; there is no evidence for the *Z* isomer of **33**.

The extent of cyclopropyl ring preservation in the fragmentation of **30** (44% of product **32**) is much greater than the 0.02–0.07% of cyclopropyl methyl ether products observed in the methanolysis of diazonium ion **36**.[4] In this reaction, ring opening products **37** (39.8%) and **38** (60.1%) almost completely account for the fate of **36**. Possibly, the *vic*-phenyl group of **31** helps to stabilize the adjacent developing carbocation and maintain the cyclopropyl ring.

5. Kinetics

The fragmentation kinetics of carbenes **14**, **24**, and **30** were determined by laser flash photolysis (LFP)[14,29] using the pyridine ylide method[30] to visualize the carbenes. Thus, LFP of diazirine **13** at 351 nm (25 °C, DCE) in the presence of pyridine generated a transient at 420 nm, which was assigned to the ylide formed by the addition of carbene **14** to pyridine. A correlation of the apparent rate constants for ylide formation, k_{obs} ($2.0–4.5\times10^{5}\ s^{-1}$) versus pyridine concentration (2.47–6.59 M) was linear (6 points, $r = 0.997$) with a slope of $6.02\times10^{4}\ M^{-1}\ s^{-1}$, taken as the rate constant for ylide formation, k_y. The *Y*-intercept of the correlation is taken as the rate constant for fragmentation[30] of carbene **14**, $k_{frag} = 5.27 \times 10^{4}\ s^{-1}$.[31] Rate constants k_y and k_{frag} for carbenes **14**, **24**, and **30** appear in Table 1.

Despite the high energy of cyclopropyl cations,[1,2] fragmentations of their cyclopropyloxychlorocarbene progenitors are rapid. The fragmentation of **14** in DCE is about 8 orders of magnitude faster than the ethanolysis of tosylate **2** (R=cyclopropyl),[3] with both reactions leading to comparable ion pairs. ROCCl fragmentations are generally rapid,[6] even when the imposition of cationic character on R leads to considerable strain, for example, the fragmentation of 1-norbornyloxychlorocarbene in DCE occurs with $k_{frag} = 3.3 \times 10^{4}\ s^{-1}$.[8]

Table 1. Absolute rate constants for carbene fragmentation[a]

Carbene	k_{frag} (s^{-1})	k_y ($M^{-1}\ s^{-1}$)
14	$(5.22\pm0.05)\times10^{4}$	$(6.23\pm0.21)\times10^{4}$
24	$(2.87\pm0.11)\times10^{5}$	$(3.56\pm0.12)\times10^{5}$
30	$(5.52\pm0.39)\times10^{5}$	$(2.58\pm0.02)\times10^{5}$

[a] Results are mean values (±average deviation from the mean) of two determinations.

An Arrhenius study was carried out for the fragmentation of carbene **14**. A correlation of $\ln(k_{frag})$ versus $1/T$ over the temperature range 253–303 K was linear (6 points, $r = 0.991$) and gave $E_a = 2.3$ kcal/mol, $\log A = 6.6$, $\Delta S^*_{298} = -30$ e.u. The low activation energy for fragmentation is opposed by a sizable unfavorable entropy of activation, suggesting that there might by significant cyclic 'S_Ni' character to the fragmentations of these cyclopropyloxychlorocarbenes.[6,32]

In conclusion, photolysis of cyclopropyloxychlorodiazirines affords cyclopropyloxychlorocarbenes whose fragmentations provide access to ion pairs that feature cyclopropyl cations. When 'stabilized' by electron releasing α substituents, these cations collapse with their chloride counterions yielding significant quantities of ring-preserved cyclopropyl products. Preliminary studies show that the reaction can be extended to secondary cyclopropyloxychlorocarbenes, although with a diminished yield of carbene fragmentation and increasing carbene capture.[33,34]

Acknowledgements

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24. 400 MHz ^{1}H NMR of *E*-**32** (δ, $CDCl_3$): 1.22 (t, $J = 7$ Hz, 1H, ring CH), 1.32 (s, 3H, Me), 1.51 (m, 1H, ring CH), 2.65 (dd, $J = 7.2$, 2.8 Hz, 1H, PhC*H*), 7.1–7.4 (m, 5H, Ph). *Z*-**32**: 1.28 (m, 1H, ring CH), 1.47 (t, $J = 7$ Hz, 1H, ring CH), 1.77 (s, 3H, Me), 2.17 (t, $J = 8$ Hz, PhC*H*), 7.15–7.35 (m, 5H, Ph).
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26. 400 MHz ^{1}H NMR of **33** (δ, $CDCl_3$): 1.93 (s, 3H, CH_3); 4.12 (s, 2H, CH_2Cl), 6.52 (s, 1H, vinyl CH), 7.18–7.30 (m, 5H, Ph).
27. 400 MHz ^{1}H NMR of **34** (δ, $CDCl_3$): 1.74 (s, 3H, CH_3), 5.00 (s, 1H, PhC*H*Cl), 5.17 (s, 1H, vinyl CH), 5.48 (s, 1H, vinyl CH), 7.2–7.3 (m, 5H, Ph).
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31. At [pyridine] = 0, fragmentation of **14** accounts for >90% of the carbene; cf. (Scheme 1).
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33. For example, fragmentation of *trans*-2-phenyl-1-cyclopropyloxychlorocarbene in DCE affords 12% of *trans*-2-phenyl-1-chlorocyclopropane, 9% of *cis*-2-phenyl-1-chlorocyclopropane, 11% of *trans*-1-phenyl-3-chloro-1-propene, 19% of 3-chloro-3-phenylpropene, 41% of the dichloride due to HCl capture of the carbene, and 8% of the formate due to water capture of the carbene.
34. Preparation of compounds **12** and **13**. 1-Cyclopropyl-1-cyclopropylisouronium triflate (**12**). In a 50 mL round bottom flask fitted with a stirring bar and reflux condenser protected with a calcium chloride drying tube, were placed 1.00 g (23.8 mmol) of cyanamide, 4.67 g (47.6 mmol) of 1-cyclopropyl-1-cyclopropanol,[11] and 15 mL of anhydrous THF. Then 3.57 g (23.8 mmol) of trifluoromethanesulfonic acid in 10 mL of THF was slowly added. The mixture was stirred magnetically at 50 °C (oil bath) for 30 h, and then cooled to room temperature. THF was removed on the rotary evaporator to give a yellow oil, which was washed three times with pentane. The oil was characterized as triflate **12** (containing some urea) by NMR, and was used in the next step without further purification. 3-Chloro-3-(1-cyclopropyl-1-cyclopropyloxy)diazirine (**13**). Isouronium salt **12** (4.5 g) and 3.50 g of LiCl were added to a mixture of 25 mL of DMSO and 50 mL of pentane. The mixture was stirred magnetically and cooled to 20 °C. Then 100 mL of commercial 12% aqueous sodium hypochlorite solution (pool chlorine), saturated with NaCl, was slowly added while the temperature was kept below 30 °C. After the addition was complete, stirring was continued for 15 min at 15 °C. The reaction mixture was poured into a separatory funnel containing 150 mL of ice water. The

organic phase was removed and saved, the aqueous phase was washed with pentane (2×30 mL), and then discarded. The pentane washings were back washed with 2×75 mL of ice water. Then the combined organic phases were dried for 1 h over calcium chloride at 0 °C. The pentane/diazirine solution was purified by column chromatography over 200–400 mesh, 60 Å silica gel, eluted with pentane. The pentane solution of product was reduced by rotary evaporation and replaced by DCE or $CDCl_3$. Residual pentane was then removed by rotary evaporation at 0 °C. The yield of **13** was approximately 25%, based on 1-cyclopropyl-1-cyclopropanol.

^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.2–0.9 (m, 8H, ring CH_2), 1.61–1.65 (m, 1H, CH). ^{13}C NMR (δ, $CDCl_3$): 70.35, 65.76, 13.73, 9.82, 4.85. IR (NaCl): 1543 cm^{-1} (diazirine). UV (λ_{max}, DCE): 352, 361 nm.