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Dicationic ring opening reactions of *trans*-2-phenylcyclopropylamine•HCl: electrophilic cleavage of the distal (C₂-C₃) bond of cyclopropanes

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Abstract

Electrophilic ring opening of *trans*-2-phenylcyclopropylamine•HCl occurs at the distal (C₂-C₃) bond. This is consistent with weakening of the distal bond by the σ -withdrawing ammonium group and charge-charge repulsive effects in the transition state.

Cyclopropane ring opening reactions have been the subject of a vast number of synthetic, mechanistic, and biological studies.¹ Among the synthetic reactions, the ring opening reactions of donor-acceptor cyclopropanes have been particularly useful.^{2–7} With ring opening by bond heterolysis, the vicinal bond generally undergoes cleavage to form the zwitterionic species wherein the charge centers are stabilized by the appropriate substituents (eq 1).⁸ This is often followed by reactions with a nucleophile and electrophile. Among recent examples of this chemistry, Mattson and coworkers used a boronate urea Lewis acid to promote ring opening of the nitrocyclopropane (**1**, Scheme 1).⁹ Reaction of the zwitterionic species (**2**) with 4-(trifluoromethoxy)aniline provides the addition product (**3**) in good yield. Further synthetic steps provide a CB-1 receptor inverse agonist drug from intermediate **3**.

(1)

It has long been thought that donor-acceptor cyclopropane ring opening reactions involve electron donation into the π -acceptor groups. Theoretical studies by Cruz-Cabeza, Allen,

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, ¹H and ¹³C NMR spectra, computation procedures and results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Clark and Schleyer have suggested that these processes involve interaction of the $3e'$ orbital of the cyclopropane ring with the low-lying unoccupied orbital of the π -acceptor substituent group(s).¹⁰ This interaction leads to weakening and lengthening of the vicinal (C_1 - C_2) bonds of the cyclopropane and it can lead to bond heterolysis. Interestingly, strong σ -acceptor groups are predicted to interact with the cyclopropane $1e''$ orbital and this leads to lengthening (and weakening) of the distal (C_2 - C_3) bond of the cyclopropane. This theoretical prediction has been confirmed by crystallographic data from cyclopropanes having strong σ -acceptor groups. For example, 1,1-difluorocyclopropane has bond lengths of 1.468 Å and 1.540 Å, for the vicinal and distal C-C bonds, respectively.¹¹ The lengthened - and weakened - distal bond of 1,1-difluorocyclopropane is well known for its tendency to undergo bond homolysis reactions.¹² In the following communication, we describe the ring opening reactions of *trans*-2-(phenyl)cyclopropylamine•HCl in superacid and trapping of the resulting ammonium-carbenium dication with arene nucleophiles. This chemistry is a rare example of distal bond cleavage accompanied by nucleophilic and electrophilic reactions. The observed chemical reactions are in accord with the theoretical predictions made by Clark and Schleyer.^{10a}

Our studies began with the superacidic reaction of cyclopropane **4** (*trans*-2-(phenyl)cyclopropylamine, a clinically useful anti-depressant drug). We reasoned that both the amino group and cyclopropane ring would be protonated in the superacid, leading to the formation of a reactive, dicationic superelectrophile.¹³ When compound **4** is reacted with benzene in the presence of the Bronsted superacid CF_3SO_3H (triflic acid), ring opening occurs to provide the addition product **6** in good yield (Scheme 2). The structure of the product was verified by full characterization including DEPT NMR analysis. This conversion may be explained by protolytic ring opening of **4** to give the 1,3-dication (**5**). Superelectrophile **5** then reacts with benzene to eventually provide compound **6**. The formation of product **6** involves regioselective protonation at the distal (C_2 - C_3) rather than vicinal (C_1 - C_2) bond of the cyclopropane ring. Protolytic cleavage of the vicinal bond would produce a more stable benzylic 1,4-dication (*vide infra*) - leading to product **7** - however this is not observed.

In order to probe the regiochemistry of this cyclopropane ring-opening, theoretical calculations were done (Figure 1). Calculations were done by geometry optimization at the M06/6-31+G(d,p) level using the Jaguar program suite,¹⁴ followed by single point energy calculation at the M06/cc-pvtz(-f) level of theory. Energy values were calculated from the optimized structures using the PBF solvent continuum model (triflic acid solvent sphere) and with a specific triflic acid as the protonating agent. Protonation of the cyclopropane ring can give two isomeric dications, the 1,4-dication (**9**) and 1,3-dication (**12**). It has been previously shown that increasing charge separation tends to stabilize dicationic species.¹⁵ As a result, the 1,4-dication (**9**) is found to be 5.7 kcal/mol more stable than the 1,3-dication (**12**). Nevertheless, reaction in superacid leads to the exclusive formation of the 1,3-dication (i.e., **12**) and subsequently gives product **6** by Friedel-Crafts reaction with benzene (Scheme 3). The reaction course may be understood, however, by considering the energies of the respective transition states (**10** and **11**). The transition state (**10**) leading to protolysis of the C_1 - C_2 bond is found to be 28.7 kcal/mol above the starting monocation **8**, while the transition state (**11**) leading to protolysis of the distal (C_2 - C_3) bond is found to be 22.2

kcal/mol above monocation **8**. Thus, transition state **11** is 6.5 kcal/mol more stable than transition state **10**. With the lower energy barrier leading to dication **12**, this becomes the kinetically preferred reaction path. An examination of the transition state structures **10** and **11** reveals that protolysis of the distal bond provides the structure (**11**) with a larger distance between the ammonium charge and the developing carbocation charge. In structure **11**, the distance between the ammonium nitrogen and the incoming proton (from triflic acid) is found to be 3.6 Å, while in structure **10**, the distance between the ammonium nitrogen and the incoming proton is found to be 2.3 Å.¹⁶ In order to rule out steric effects for the regioselectivity of protonation, calculations were also done without the triflate anion. Even without triflate, distal bond cleavage is preferred by about 5.0 kcal/mol over vicinal bond cleavage.

As expected from previous theoretical calculations,¹⁰ the distal (C₂-C₃) bond is lengthened prior to protonation (relative to the vicinal bonds). For cation **8**, the distal (C₂-C₃) bond is estimated to be 1.510 Å, while the vicinal bonds are (C₁-C₂) 1.502 Å and (C₁-C₃) 1.483 Å. Clark and Schleyer previously noted that the longest cyclopropane bond is generally the bond most easily cleaved.^{10a} To further support this, we also calculated the natural atomic orbital bond orders of **8** which were found to be, 0.817 (C₂-C₃), 0.828 (C₁-C₂), and 0.830 (C₁-C₃). Taken together, this suggests that the observed distal bond cleavage is the result of two effects: lengthening and weakening of the (C₂-C₃) bond by the σ-acceptor properties of the ammonium group and the charge-charge repulsive effects in the transition states leading to ring opening. Ring opening is of course initiated by protonation.

A similar reaction is seen in the ring opening chemistry of an amide derivative of *transylcypromine*. When compound **13** is reacted with benzene in superacid, compound **16** is formed as the exclusive product (Scheme 3). This conversion likely involves formation of ion **14**, followed by protonation at the distal C₂-C₃ bond to give dication **15**. Electrophilic reaction with benzene and deprotonation then gives the final product **16**. In contrast, the isomeric amide (**17**) - derived from 2-phenylcyclopropane carboxylic acid - gives ring opening from cleavage of the vicinal C₁-C₂ bond of the cyclopropane ring (Scheme 4). This reaction also involves protonation of the amide carbonyl bond to give cation (**18**), although diprotonation of the amide may also be possible in the superacidic media.¹³ In either case, the resulting carboxonium ion should possess a low-lying carbonyl LUMO. This triggers an opening of the vicinal C₁-C₂ bond and the resulting dication (**19**) is formed. The reaction with benzene then provides the final addition product **20**. Although amides **13** and **17** are similar in structure, they undergo ring opening reactions by two distinctly different mechanisms.

Like other cyclopropanes having strong π-acceptor groups, the amide group of **17** - and its carboxonium ion (**18**) - interacts with 3e' orbital of the cyclopropane ring and this leads to lengthening and cleavage of the vicinal C₁-C₂ bond. Interestingly, the same reaction with homolog **21** leads to cleavage of the distal C₂-C₃ bond and formation of product **24** (Scheme 5). Thus, the reaction with CF₃SO₃H leads to formation of the carboxonium ion **22**. Because the carboxonium group is no longer in conjugation with the cyclopropane ring, the protonated amide is not a π-acceptor group but rather it is a cationic σ- acceptor group. This leads to interaction with the cyclopropane 1e'' orbital and lengthening of the distal C₂-C₃

bond with electrophilic and nucleophilic reaction at this site. Following protonation of the distal C₂-C₃ bond, the superelectrophile **23** is formed and Friedel-Crafts reaction gives the final product **24**. In a similar respect, the amine and piperazine derivatives (**25** and **27**) exhibit ring opening at the distal C₂-C₃ bond of the cyclopropane ring (eqs 2–3). This leads to the respective Friedel-Crafts products **26** and **28**.

(2)

(3)

In summary, we have found unusual examples of distal bond cleavage in several cyclopropane systems having cationic σ -acceptor group. The results are consistent with earlier observations that σ -acceptor groups lengthen the distal bond of cyclopropane rings. Theoretical calculations also indicate that ring opening is a kinetically controlled process in which charge-charge repulsive effects may be important in the transition state structures.

EXPERIMENTAL SECTION

General

All reactions were performed using oven-dried glassware under an argon atmosphere. Trifluoromethanesulfonic acid was freshly distilled prior to use. All commercially available compounds and solvents were used as received. ^1H NMR and ^{13}C NMR were done using a 300 MHz spectrometer; chemical shifts were made in reference to NMR solvent signals. Low-resolution mass spectra were obtained from a gas chromatography instrument equipped with a mass-selective detector, while high-resolution mass spectra were obtained from a commercial analytical laboratory (electron impact ionization; sector instrument analyzer type).

1-Methyl-2,2-diphenylethylamine (**6**)

In a vented flask or vial (CAUTION: vent is necessary because superacid protonates the chloride - generating HCl gas and modest internal pressure), salt **4** (0.1 g, 0.59 mmol) is suspended in 1 mL of anhydrous benzene, to which is added $\text{CF}_3\text{SO}_3\text{H}$ (1.0 mL, 1.9 mmol). The mixture is stirred at 25°C for 4–6 hours after which the solution is poured over several grams of ice. Chloroform (30 mL) is poured into the mixture and the aqueous phase is made

basic (pH paper) by slow addition of 10 M NaOH. Extraction and separation of the organic phase is followed by a second chloroform extraction (30 mL) of the aqueous phase. The combined chloroform extracts are washed with H₂O and then brine (twice). Following a drying step (Na₂SO₄), filtration, and removal of solvent, compound **6**¹⁷ is isolated (oil, 0.096 g, 0.45 mmol).

***N*-(1,1-Diphenylpropan-2-yl)benzamide (16)**

Compound **4** (0.2 g, 1.18 mmol) is partitioned between dichloromethane (15 mL) and 1.0 M NaOH (15 mL) in a separatory funnel. Extraction of the free amine is followed by drying of the organic solution with Na₂SO₄. The resulting solution is filtered directly into a reaction flask, to which is added triethylamine (0.2 mL, 1.43 mmol) and benzoyl chloride (0.14 mL, 1.18 mmol). The solution is stirred for 2 hrs after which it is washed with 1.0 M HCl, water, and then brine (twice). Further purification with silica gel chromatography (ether:hexanes) provides the known cyclopropyl amide **13**.¹⁸

Amide **13** (0.1 g, 0.42 mmol) is suspended in 1 mL of anhydrous benzene, to which is added CF₃SO₃H (1.0 mL, 1.9 mmol). The mixture is stirred at 25°C for 4–6 hours after which the solution is poured over several grams of ice. Chloroform (30 mL) is poured into the mixture and the aqueous phase is made basic (pH paper) by slow addition of 10 M NaOH. Extraction and separation of the organic phase is followed by a second chloroform extraction (30 mL) of the aqueous phase. The combined chloroform extracts are washed with H₂O and then brine (twice). Following a drying step (Na₂SO₄), filtration, removal of solvent, and silica chromatography (ether:hexanes), compound **16**¹⁹ is isolated (0.114 g, 0.36 mmol) as a light yellow solid, MP 163–164°C. ¹H NMR (CDCl₃, 500 MHz) δ 1.27 (d, *J* = 6.5 Hz, 3H), 4.03 (d, *J* = 9.4 Hz, 1H), 5.07–5.13 (m, 1H), 7.18–7.25 (m, 2H), 7.31–7.39 (m, 8H), 7.45 (tt, *J* = 1.2, 7.4 Hz, 1H), 7.48–7.53 (m, 3H), 7.62 (tt, *J* = 1.8, 7.4 Hz, 1H), 7.83–7.84 (m, 1H). ¹³C NMR (CDCl₃, 125 MHz) δ 20.4, 48.0, 58.1, 126.6, 126.8, 128.3, 128.5, 128.7, 130.1, 131.2, 132.4, 135.0, 137.6, 141.7, 142.1, 166.9. Low resolution mass spectrum, EI: 315 (M⁺), 194, 167, 165, 148, 105. HRMS, EI: calcd for C₂₂H₂₁NO, 315.16232; found, 315.16253.

***N*-(3,3-Diphenylpropyl)benzamide (20)**

trans-2-Phenylcyclopropane-1-carbonyl chloride (0.2 g, 1.1 mmol) is dissolved in anhydrous dichloromethane (10 mL) and the solution is cooled in an ice bath. To this solution, aniline (0.25 mL in 5 mL dichloromethane) is added slowly. The mixture is stirred for 2 hrs after which it is washed with 1.0 M HCl, water, and then brine (twice). Further purification with silica gel chromatography (ether:hexanes) provides the known cyclopropyl amide **17**.²⁰

Amide **17** (0.1 g, 0.42 mmol) is suspended in 1 mL of anhydrous benzene, to which is added CF₃SO₃H (1.0 mL, 1.9 mmol). The mixture is stirred at 25°C for 4–6 hours after which the solution is poured over several grams of ice. Chloroform (30 mL) is poured into the mixture and the aqueous phase is made basic (pH paper) by slow addition of 10 M NaOH. Extraction and separation of the organic phase is followed by a second chloroform extraction (30 mL) of the aqueous phase. The combined chloroform extracts are washed with H₂O and then brine (twice). Following a drying step (Na₂SO₄), filtration, removal of solvent, and silica chromatography (ether:hexanes), compound **20** is isolated (0.13 g, 0.41 mmol) as an oil. ¹H

NMR (CDCl₃, 300 MHz) δ 2.32 (t, J = 7.9 Hz, 2H), 2.48–2.55 (m, 2H), 3.99 (t, J = 7.8 Hz, 1H), 7.18–7.41 (m, 13H), 7.64 (d, J = 7.7 Hz, 2H), 8.27 (s, 1H). ¹³C NMR (CDCl₃, 75 MHz) δ 31.2, 35.9, 50.6, 120.3, 124.3, 126.5, 128.0, 128.7, 129.0, 138.3, 144.3, 171.8. Low resolution mass spectrum, EI: 315 (M⁺), 178, 167, 165, 152, 135, 105, 93, 92. Low resolution mass spectrum, EI: 315 (M⁺), 178, 165, 152, 135, 92. HRMS, EI: calcd for C₂₂H₂₁NO, 315.16232; found, 315.16280.

***N*-phenyl-2-(2-phenylcyclopropyl)acetamide (21)**

(*E*)-4-Phenylbut-3-enoic acid (0.162 g, 1.0 mmol), aniline (0.09 mL, 1 mmol), EDCI (0.23 g, 1.2 mmol), and DMAP (0.05 g, 0.4 mmol) are dissolved in anhydrous dichloromethane (20 mL). The solution is stirred for 12 h at 25 °C, after which it is partitioned between cold water and CHCl₃. The organic layer is separated, washed with H₂O (2×) and brine (2×), and dried over anhydrous sodium sulfate. The crude product is isolated, with further purification done via column chromatography (hexane:ethyl acetate) to give the known amide, (*E*)-*N*,4-diphenylbut-3-enamide.²¹

Based on a published procedure, a stirred solution of (*E*)-*N*,4-Diphenylbut-3-enamide (0.237 g, 1.0 mmol) is prepared with anhydrous dichloromethane (15 mL) and diethyl zinc (1.0 M in hexane, 2.5 mL, 2.5 mmol) is then added at -20 °C under an argon atmosphere. After 10 min, diiodomethane (0.25 mL, 3 mmol) is slowly added to the mixture. Stirring is continued for 10 h. A saturated NH₄Cl solution is added to the mixture and the resulting solution extracted with ethyl acetate. The organic extract is washed with brine, dried over Na₂SO₄, and then concentrated in vacuo. Silica gel column chromatography (2:1, hexanes:ethyl acetate) provides a colorless solid (0.228 g, 91%), MP 80–81 °C. ¹H NMR (CDCl₃, 300 MHz) δ 0.97–1.03 (m, 1H), 1.08–1.14 (m, 1H), 1.44–1.53 (m, 1H), 1.82–1.88 (m, 1H), 2.52 (dd, J = 5.2, 9.7 Hz, 1H), 3.36 (s, 1H), 7.11–7.14 (m, 2H), 7.18 (d, J = 7.3 Hz, 1H), 7.20–7.28 (m, 1H), 7.30–7.38 (m, 4H), 7.66 (d, J = 7.6 Hz, 2H), 8.73 (s, 1H). ¹³C NMR (CDCl₃, 75 MHz) δ 15.8, 19.5, 23.1, 41.9, 120.3, 124.3, 125.8, 125.9, 128.5, 129.0, 138.3, 142.4, 171.1. Low resolution mass spectrum, EI: 251 (M⁺), 193, 160, 117, 93, 91, 77. HRMS, EI: calcd for C₁₇H₁₇NO, 251.13102; found, 251.13120.

3-Methyl-*N*,4,4-triphenylbutanamide (24)

Compound **21** (0.251 g, 1.0 mmol) is dissolved in benzene (3 mL) and CF₃SO₃H (3 mL, 34 mmol) is added slowly with stirring. The reaction mixture stirred overnight at room temperature and then the reaction mixture poured over several grams of ice. Chloroform (ca. 30 mL) is then added and the aqueous layer is made basic with 10 M NaOH. Separation of the organic phase is followed by washings with water, and then twice with saturated brine. The organic solution is dried with Na₂SO₄, and then concentrated in vacuo. Further purification with silica gel column chromatography (2:1 hexanes:ethyl acetate) yields compound **24** as a colorless oil (0.26 g, 79%): ¹H NMR (CDCl₃, 300 MHz) δ 1.02 (d, J = 6.6 Hz, 3H), 2.04 (dd, J = 4.5 Hz, 1H), 2.49 (dd, J = 3, 14.5 Hz, 1H), 3.02–3.13 (m, 1H), 3.58 (d, J = 11.1 Hz, 1H), 7.15–7.40 (m, 13H), 7.62 (d, J = 7.8 Hz, 2H), 8.01 (s, 1H). ¹³C NMR (CDCl₃, 75 MHz) δ 18.9, 34.3, 43.5, 58.8, 120.2, 124.3, 126.3, 126.5, 128.0, 128.6, 128.8, 129.0, 138.2, 143.7, 143.8, 171.5. Low resolution mass spectrum, EI: 329 (M⁺), 194, 167, 165, 135, 115, 92, 77. HRMS, EI: calcd for C₂₃H₂₃NO, 329.17797; found, 329.17821.

***N,N*-Diethyl-2-methyl-3,3-diphenylpropan-1-amine (26)**

Compound **25** was prepared using a published procedure.²² Amine **25** (0.1 g, 0.49 mmol) is suspended in 1 mL of anhydrous benzene, to which is added CF₃SO₃H (1.0 mL, 1.9 mmol). The mixture is stirred at 25°C for 4–6 hours after which the solution is poured over several grams of ice. Chloroform (30 mL) is poured into the mixture and the aqueous phase is made basic (pH paper) by slow addition of 10 M NaOH. Extraction and separation of the organic phase is followed by a second chloroform extraction (30 mL) of the aqueous phase. The combined chloroform extracts are washed with H₂O and then brine (twice). Following a drying step (Na₂SO₄), filtration, removal of solvent, and silica chromatography (ether:hexanes), known compound **26** is isolated (0.090 g, 0.32 mmol) as an oil.²³

1-Methyl-4-((2-phenylcyclopropyl)methyl)piperazine (27)

Compound **27** is prepared using a published synthetic method²³ and it is isolated as an oil, ¹H NMR (CDCl₃, 500 MHz) δ 0.76–0.80 (m, 1H), 0.90–0.94 (m, 1H), 1.19–1.23 (m, 1H), 1.63 (pent, *J* = 4.9 Hz, 1H), 2.24 (s, 3H), 2.31 (q, *J* = 6.6 Hz, 2H), 2.37–2.42 (m, 4H), 2.50 (q, *J* = 6 Hz, 4H), 6.99–7.01 (m, 2H), 7.07–7.11 (m, 1H), 7.20 (t, *J* = 7.6 Hz, 2H). ¹³C NMR (CDCl₃, 125 MHz) δ 15.0, 20.7, 22.7, 46.1, 53.1, 55.1, 63.0, 125.4, 125.6, 128.3, 142.8. Low resolution mass spectrum, EI: 230 (M⁺), 229, 215, 139, 91, 70. HRMS, EI: calcd for C₁₅H₂₂N₂, 230.17830; found, 230.17855.

1-Methyl-4-(2-methyl-3,3-diphenylpropyl)piperazine (28)

Amine **27** (0.102 g, 0.43 mmol) is suspended in 1 mL of anhydrous benzene, to which is added CF₃SO₃H (1.0 mL, 1.9 mmol). The mixture is stirred at 25°C for 4–6 hours after which the solution is poured over several grams of ice. Chloroform (30 mL) is poured into the mixture and the aqueous phase is made basic (pH paper) by slow addition of 10 M NaOH. Extraction and separation of the organic phase is followed by a second chloroform extraction (30 mL) of the aqueous phase. The combined chloroform extracts are washed with H₂O and then brine (twice). Following a drying step (Na₂SO₄), filtration, removal of solvent, and silica chromatography (ether:hexanes), compound **28** was isolated (0.123 g, 0.0004 mmol) as a light brown solid: MP 141–142 °C; ¹H NMR (CDCl₃, 500 MHz), δ 0.95 (d, *J* = 6.5 Hz, 3H), 2.13 (dd, *J* = 3.1, 10.8 Hz, 1H), 2.28 (dd, *J* = 4.4, 12.4 Hz, 1H), 2.40–2.45 (m, 3H), 2.61–2.67 (m, 8H), 3.70 (d, *J* = 9.6 Hz, 1H), 7.18–7.33 (m, 9H). ¹³C NMR (CDCl₃, 125 MHz) δ 17.4, 34.3, 45.4, 52.6, 54.9, 56.8, 63.2, 126.1, 126.1, 128.0, 128.4, 128.5, 143.9, 144.2. Low resolution mass spectrum, EI: 308 (M⁺), 252, 193, 167, 165, 113, 70. HRMS, EI: calcd for C₂₁H₂₈N₂, 308.22525, found 308.22471.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. a. Rappoport, Z., editor. The Chemistry of the Cyclopropyl Group, Vol. 1,2. 1987. b. Boche, G., Walborsky, HM. Cyclopropane Derived Reactive Intermediates. Patai, S., Rappoport, Z., editors. Chichester: Wiley; 1990. c. De Meijere, A. Topics in Current Chemistry. Vol. Volume 207. Berlin: Springer; 2000.
2. Trost BM, Morris PJ, Sprague SJ. J. Am. Chem. Soc. 2012; 134:17823. [PubMed: 23030714]
3. Zhou YY, Wang L-J, Li J, Sun X-L, Tang Y. J. Am. Chem. Soc. 2012; 134:9066. [PubMed: 22578301]
4. Moran J, Smith AG, Carris RM, Johnson JS, Krische MJ. J. Am. Chem. Soc. 2011; 133:18618. [PubMed: 22026505]
5. Campbell MJ, Johnson JS, Parsons AT, Pohlhaus PD, Sanders SD. J. Org. Chem. 2010; 75:6317. [PubMed: 20863142]
6. Lifchits O, Charette AB. Org. Lett. 2008; 10:2809. [PubMed: 18522391] f. Yu M, Pagenkopf BL. Tetrahedron. 2005; 61:321–347.
7. Reissig H-U, Zimmer R. Chem. Rev. 2003; 103:1151. [PubMed: 12683780]
8. Ring opening at the distal bond, however, is well known with methylene cyclopropanes and in transition-metal catalyzed reactions. See, for example: Shi M, Lu JM, Wei Y, Wei LX. Acc. Chem. Res. 2012; 45:641. [PubMed: 22166122] Aïssa C. Synthesis. 2011:3389.
9. So SS, Auviel TJ, Garza VJ, Mattson AE. Org. Lett. 2012; 14:444. [PubMed: 22208166]
10. a. Clark T, Spitznagel GW, Klose R, Schleyer PvR. J. Am. Chem. Soc. 1984; 106:4412. b. Cruz-Cabeza AJ, Allen FH. Acta Cryst. 2011; B67:94.
11. Cruz-Cabeza AJ, Allen FH. Acta Cryst. 2012; B68:182.
12. Dolbier WR Jr, Battiste MA. Chem. Rev. 2003; 103:1071. [PubMed: 12683777]
13. Olah, GA., Klumpp, DA. Superelectrophiles and Their Chemistry. New York: Wiley & Sons; 2008.
14. Jaguar, version 7.9. New York, NY: Schrodinger, LLC; 2011.
15. Klumpp DA. Chem. Eur. J. 2008; 14:2004. [PubMed: 18165954]
16. It should be noted that transition state **11** resembles the corner-protonated cyclopropanes described by DePuy and coworkers. See: DePuy CH, Fünfschilling PC, Andrist AH, Olson JM. J. Am. Chem. Soc. 1977; 99:6297.
17. Klumpp DA, Aguirre SL, Sanchez GV Jr, de Leon SJ. Organic Lett. 2001; 3:2781.
18. Moreau B, Alberico D, Lindsay VNG, Charette AB. Tetrahedron. 2012; 68:3487.
19. Christol H, Laurent A, Solladie G. Bull. de la Soc. Chim. France. 1963; 4:877.
20. Imamoto T, Yokoyama H, Yokoyama M. Tetrahedron Lett. 1981; 22:1803.
21. Zhu M, Zheng N. Synthesis. 2011:2223. [PubMed: 23543799]
22. Teotino UM, Della Bella D, Gandini A, Benelli G. J. Med. Chem. 1967; 10:1091. [PubMed: 6056036]
23. Li A, Kindelin PJ, Klumpp DA. Org. Lett. 2006; 8:1233. [PubMed: 16524311]

Figure 1.
Calculated relative free energies in solution for distal (**8**, **11**, **12**) and vicinal (**8**, **10**, **9**) ring opening reactions involving cyclopropane **8** and transition state structures **10** and **11**.

Scheme 1.
Donor-Acceptor Ring Opening of Cyclopropane **1**.

Scheme 2.
Supracid-promoted Ring Opening of Cyclopropane **4**.

Scheme 3.
Supercid-promoted Ring Opening of Cyclopropane **13**.

Scheme 4.
Supercid-promoted Ring Opening of Cyclopropane **17**.

Scheme 5. Supercid-promoted Ring Opening of Cyclopropane **21**.