

C–C Bond Activation and Demethylenation of Epoxides by Amine Radical Dications

Eric Holt, Nathaniel G. Garrison, Rozhin Rowshanpour, Justin Jeeyoung Kim, Nicolas Henriquez, Winson Lam, Neil Kiame, Jack Williams, Sherrie Zhao, Travis Dudding,* and Thomas Lectka*

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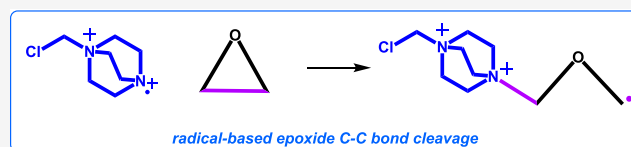


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ABSTRACT: In this note, we explore a unique reactivity pattern that involves a rare radical-based C–C bond scission of epoxides followed by demethylenation. The reaction is accomplished by Selectfluor and its radical dication working in tandem; a mechanism supported by experiment and DFT calculations is proposed that involves the generation and identification of a key reactive intermediate. The reaction seems to be fairly general for 1,1-disubstituted epoxides.



Over the past decades, there has hardly been a functional group more central to the modern practice of synthetic organic chemistry than the epoxy group. Both its formation and ring opening have led to pioneering discoveries and highly useful synthetic methods alike. In terms of ring opening, most documented cases involve scission of the C–O bond (Figure 1), as the attacking reagent is generally nucleophilic in character.⁴ Instances of nucleophilic C–C scission are rare, and limited to epoxides containing electron-withdrawing groups.⁶ It occurred to us that ring opening by certain free radicals may produce a different outcome,⁷ as C–O bond scission becomes somewhat less energetically favorable. On the other hand, typical alkyl free radicals show little propensity to react with epoxides through attack at carbon, although oxygen coordination by metalloradicals followed by C–O bond cleavage is well-known.⁸ In this note, we document how the situation can be transformed by amine radical cations,⁹ which we envisaged to react with epoxides through a three-center, three-electron transition state¹⁰ involving C–C bond cleavage.

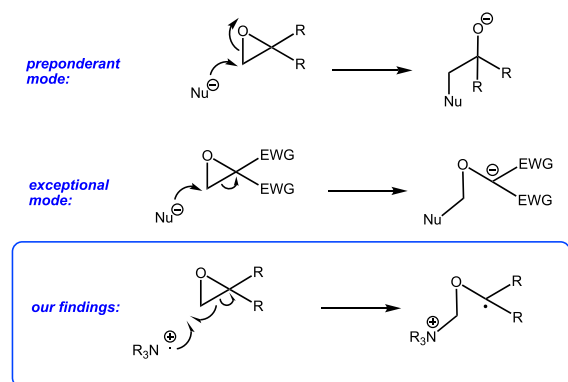


Figure 1. Epoxide ring opening modes.

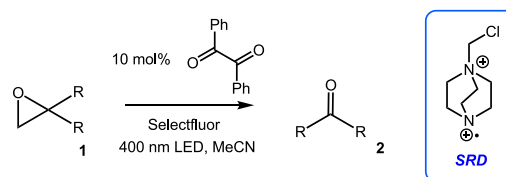


Figure 2. Reaction conditions for epoxide demethylenation.

In this case, the character and polarity of the reaction are quite different from normal cleavage reactions—the attacking agent is both a radical and electrophilic.

In an initial screening, we found that treatment of epoxide 1a with 2 equiv Selectfluor (SF) and 10 mol % benzil under blue light irradiation produces ketone 1b in 80% yield after 2 h (Figure 2). As we have shown in prior work, the Selectfluor-derived radical dication (SRD) is generated by the reaction of triplet state benzil with Selectfluor; no reaction happens in the dark or in the absence of benzil.¹¹ A number of other epoxides were screened in the reaction (Figure 3); success is attainable with 1,1-disubstituted substrates exclusively.

A proposed mechanism is shown in Figure 4. We imagine an amine radical dication initiated attack on the least hindered terminus,^{12,13} with the unpaired spin accumulating on the disubstituted end, delocalized by hyperconjugation. Once the intermediate radical forms, its fluorination by SF is presumed from precedent to be extremely fast.¹⁴ The resultant fluoroacetal is extremely labile and hydrolyzes very rapidly to

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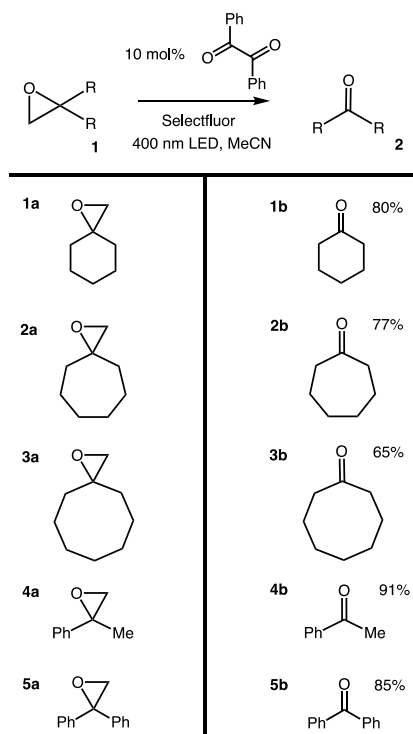


Figure 3. Starting epoxides **1a–5a** and products **1b–5b**.

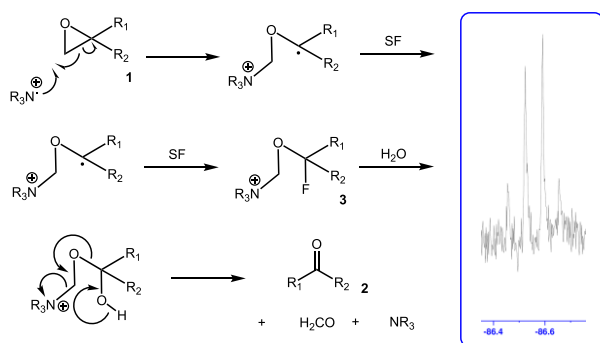


Figure 4. Proposed mechanism of epoxide demethylation (left); ^{19}F NMR of putative intermediate **3** (right).

the hemiacetal, which then fragments to the product ketone, formaldehyde, and amine. In the ^{19}F NMR spectra of the reaction of **4a** (minimization of water maintained throughout) a quartet resonance at -86.6 ppm (vs CF_3COOH) was identified, which we assign to the putative intermediate **3**.¹⁵

The calculated chemical shift of this species ($\text{R}_1 = \text{Me}$, $\text{R}_2 = \text{Ph}$, at B3LYP/6-311++G** as -83.5 ppm)¹⁶ corresponds closely to the observed value. Moreover, the peak disappears rapidly in the presence of water to generate the ketone product.

To gain further insight into this reactivity, we performed density functional theory calculations [SMD = MeCN¹⁷ $\omega\text{B97XD}/6\text{-}31+\text{G}(\text{d,p})$] using the Gaussian 16 software package.¹⁸ To this end, we explored the ring opening of a model epoxide, 1,1-dimethyloxirane (**1f**), with two different radicals, *viz.*, open-shell dicationic radical SRD and the electrophilic trifluoromethyl radical as a point of comparison.¹⁹ The computed reaction of SRD with epoxide **1f** revealed that C–C bond scission is preferred through transition state **TSa** (bond breaking and bond making distances of 1.62 and 2.21

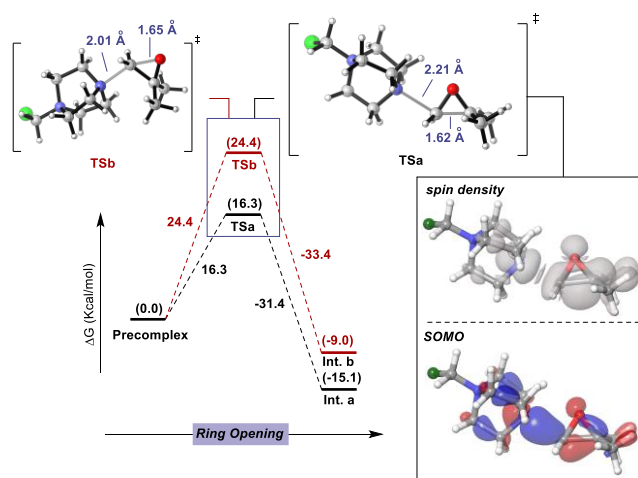


Figure 5. Transition state geometries (**TSa** (favored) vs **TSb**) and relative energies (kcal/mol) for attack of SRD on 1,1-dimethyloxirane (**1f**) computed at the (SMD = MeCN) $\omega\text{B97XD}/6\text{-}31+\text{G}(\text{d,p})$ level of theory.

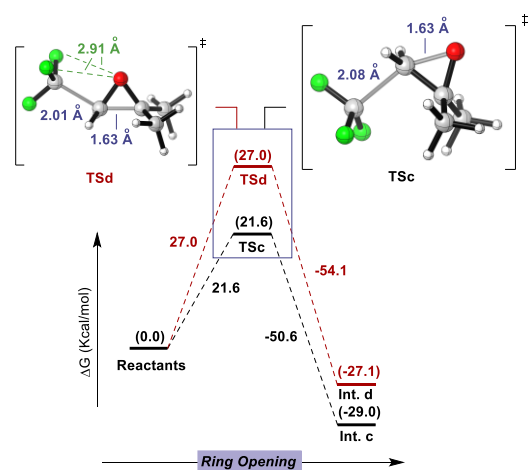


Figure 6. Transition state geometries (**TSc** (favored) vs **TSd**) and relative energies (kcal/mol) for attack of trifluoromethyl radical on 1,1-dimethyloxirane (**1f**) computed at the (SMD = MeCN) $\omega\text{B97XD}/6\text{-}31+\text{G}(\text{d,p})$ level of theory.

Å) with a Gibbs free energy activation barrier ($\Delta G^\ddagger$) of 16.3 kcal/mol (Figure 5). Overall, this addition mode was exergonic ($\Delta G^\circ = -15.1$ kcal/mol relative to reagents) and resulted in the formation of ring-opened intermediate **Int. a**. A view of the SOMO of transition state **TSa** is also informative as it clearly shows orbital interactions between SRD and 1,1-dimethyloxirane that parallel the spin density (Figure 4). Of additional importance were favorable hydrogen bond C–H $\cdots$ O contacts measuring 2.47 and 2.68 Å with natural bond order (NBO) charges ($\text{O} = -0.531$ e, $\text{H} = 0.296$ e, $\text{H} = 0.305$ e) indicative of columbic character. By contrast, backside epoxide ring opening through **TSb** (bond breaking and bond making distances of 1.65 and 2.01 Å) is noncompetitive ($\Delta G^\ddagger = 24.4$ kcal/mol) owing in part to repulsive C–H $\cdots$ H steric contacts (distances = 2.26 and 2.36 Å), the lack of stabilizing H-bonding interactions, and partial oxy-radical character.

In contrast, C–O bond cleavage of **1f** is preferred in the case of electrophilic trifluoromethyl radical attack, which occurs through reoriented backside addition (see structure **TSd**, $\Delta G^\ddagger = 21.6$ kcal/mol) resulting in the exergonic ($\Delta G^\circ = -29.0$

kcal/mol) formation of ring-opened intermediate **Int. c**. The salient bond breaking and bond making distances of **TSc** measure 1.63 and 2.08 Å (Figure 6). Conversely, front-side addition through **TSd** (bond breaking and bond making distances of 1.63 and 2.01 Å) was disfavored, with a larger calculated activation barrier ($\Delta G^\ddagger = 27.0$ kcal/mol). Hindering attack by this addition mode were a pair of repulsive epoxide oxygen and approaching trifluoromethyl radical-based fluorine contacts with equivalent distances of 2.91 Å.

Most notably, the computational results are congruent with our proposed mechanism, and highlight the fundamentally different electronic character of amine radical cations versus neutral free radicals. Further work in this area will concentrate on the development of new synthetic methods derived from C–C epoxide ring openings.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

■ Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.3c00605>.

Experimental procedures, spectra, and computational data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Travis Dudding – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada; orcid.org/0000-0002-2239-0818; Email: tdudding@brocku.ca

Thomas Lectka – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada; orcid.org/0000-0003-3088-6714; Email: lectka@jhu.edu

Authors

Eric Holt – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada; orcid.org/0000-0003-2068-6962

Nathaniel G. Garrison – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada

Rozhin Rowshanpour – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada

Justin Jeeyoung Kim – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada

Nicolas Henriquez – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada

Winson Lam – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada

Neil Kiame – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada

Jack Williams – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada

Sherrie Zhao – Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States; Department of Chemistry, Brock University, St. Catharines, Ontario L2S3A1, Canada

Complete contact information is available at:

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Notes

The authors declare no competing financial interest.

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