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Note

Complementary Tandem Reaction Manifolds and “Switch Mechanisms” in the Reaction of Epoxides with Selectfluor

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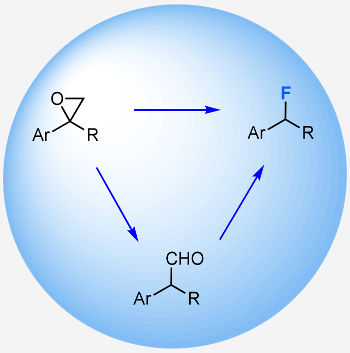
ABSTRACT: Tandem reactions are highly sought after transformations in organic synthesis as they accomplish multiple steps at once and can serve as golden keys unlocking mechanistic complexities. Reactions that operate through different mechanisms depending on the conditions (“switch mechanisms”) are of intense interest to organic chemists as fonts of new reactivity. We report that Selectfluor can catalyze the rearrangement of 1,1-disubstituted epoxides, providing a new approach to benzylic fluorination. These results complement earlier work involving radical-cation-based ring opening of epoxides.

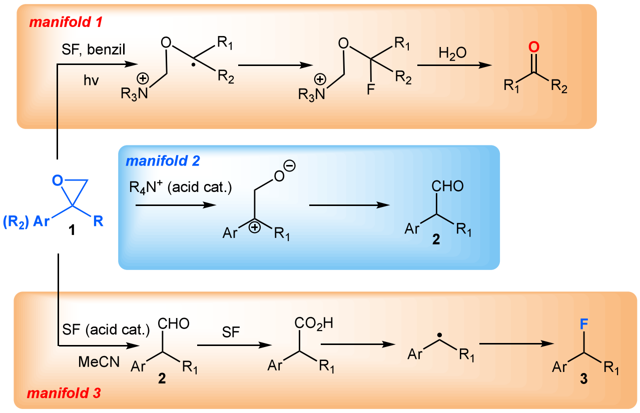


Epoxide groups have profound significance across the fields of both medicinal and synthetic chemistry. From a pharmacological perspective, they represent a bioactive moiety that has facilitated numerous drug discovery efforts, and from a synthetic methodology perspective, they represent a uniquely facile approach to introducing chiral centers as well as a convenient handle for further modification.[1,2] Based on prior work with carbonyl and hydroxyl directing groups, we postulated that it might be possible to exploit their mild Lewis basicity to direct a photocatalyzed hydrogen atom transfer (HAT) reaction with Selectfluor (SF), thereby expanding both the utility of that methodology and the potential for late-stage fluorination of epoxides.[3] This approach led to the serendipitous discovery of a remarkable radical-based C−C bond scission mechanism that culminated in the demethylation of the substrate to afford a ketone (Scheme 1, manifold 1).

In an initial discovery of this study, we found that dabco-derived diammonium salts could catalyze the rearrangement of 1-alkyl-1-aryl epoxides to the corresponding aldehydes in high yield. These highly electrophilic ammonium salts act as hydrogen-bonding-based Brønsted acids through a network of N^+−C−H−O interactions that we documented in prior work.[4] Generally speaking, these so-called Meinwald rearrangements are conducted in the presence of Lewis acids.[5−8] The observed dabco salt-catalyzed rearrangement was rapid, high yielding, and tolerated very mild conditions, showing neither water nor air sensitivity.

This finding prompted us to think that we could combine epoxide rearrangement with oxidation, decarboxylation, and radical fluorination in one. Our premise was that rearrange-

Scheme 1[a]



[a]Manifold 1: Selectfluor (SF) activates the C−C bond through a radical dication mechanism, leading to ring opening of the epoxide and culminating in a demethylative oxidation back to the ketone. Manifold 2: non-fluorinated derivatives of Selectfluor act as Lewis acid catalysts for a Meinwald type rearrangement, generating aldehydes in near-quantitative yield. Manifold 3: with a dark induction period, SF will catalyze the rearrangement and then, when light is applied, perform a photocatalyzed decarboxylative fluorination.

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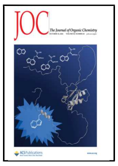

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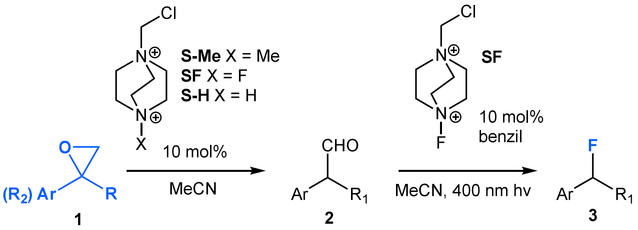
ment could be made faster than the ring opening of epoxides by the Selectfluor radical dication (SRD) through the appendage of a cation-stabilizing aryl group to the substrate.[9] On the other hand, sufficient SRD would be needed to accomplish decarboxylation in its turn.[10] To our satisfaction, we found that epoxide **1d** rearranged rapidly to aldehyde **2d** in the presence of SF (rearrangements with the other dicationic salts **S−Me** and **S−H** resulted in improved yields, likely due to the reduced potential for side-reactions). Employing a back-of-the-hand calculation, we reckoned that this process would be faster than competitive ring opening by SRD, indicating that modified conditions could regulate which of the two products formed. Initial trials reacting epoxide **1d** with SF (10 mol % benzil, 400 nm light in MeCN solvent) produced benzyl fluoride **3d** in 33% yield, and further optimizations, including increasing the equivalents of SF and allowing a photochemical induction period, ultimately improved yields to near-quantitative levels. This approach proved quite robust, and a selection of fluorinated products were produced in high yield (Scheme 5). Suppression of ketone formation could be accomplished by a staged reaction: prearrangement of the epoxide to the aldehyde, followed by reaction with photochemically generated SRD as the oxidant, and finally fluorination of the resulting benzylic radical (Scheme 2).

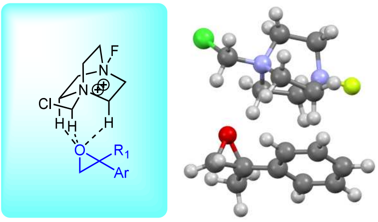
Scheme 2. Staged Experimental Procedure[a]



[a]A brief induction period in the absence of light yields rearrangement; subsequent application of 400 nm light effects fluorination.

The energy barrier to ring opening must be lowered considerably by the coordination of a diammonium salt to the epoxide through nonclassical H-bonding. A computational examination shows that the precomplex of the epoxide with SF consists of a trifurcated array with a pyramid-shaped arrangement of H-bonds composed of two interactions with the bicyclic core and one interaction with the chloromethyl group (Scheme 3). The simple interaction energy of the two fragments was calculated to be −11.22 kcal/mol. Atoms-in-molecules (AIM) analyses indicate bond critical points for each of the three interactions with ρ = 0.0148 and 0.0119 for the core and ρ = 0.0116 for the chloromethyl interaction, indicative of their electrostatic character.

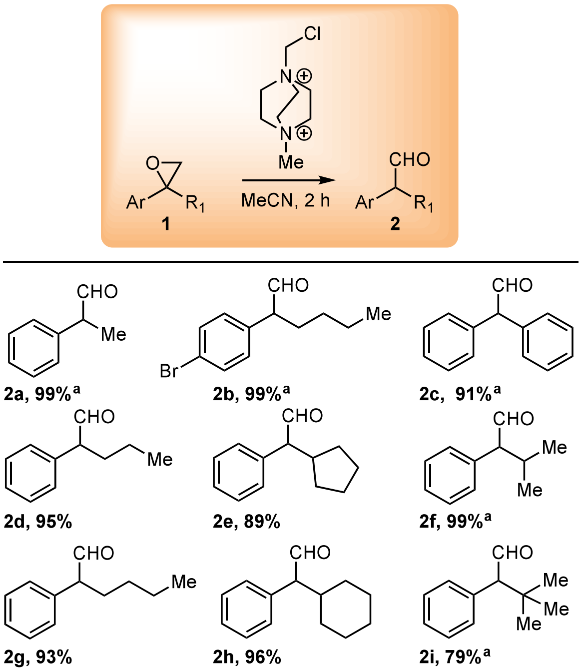
Scheme 3. Putative Complex of SF and a Model Epoxide[a]



[a]The association yields a stabilization of −11.22 kcal/mol (ωb97xd/6-311+G**), likely through an array of three H-bonding interactions between the epoxide oxygen and three relatively acidic methylene protons off the dicationic SF.

We prepared a range of epoxide substrates and investigated the efficiency of combining manifold 2 and decarboxylative fluorination manifold 3 (Scheme 1). While the rearrangement necessitates a benzylic epoxide, both manifolds exhibit reasonable tolerance toward changes in the aromatic system, high steric bulk, and variously substituted α-carbons. Regarding α-carbons, while both the primary acetophenone-derived substrate and the tertiary *t*-butyl substrate necessitated more rigorous conditions to perform the rearrangement (Scheme 4), both the rearranged and fluorinated products were obtained in nearly quantitative yields. The high yields observed with the benzophenone-derived substrate were particularly interesting due to its structural similarity to certain pharmaceuticals such as ketoprofen.

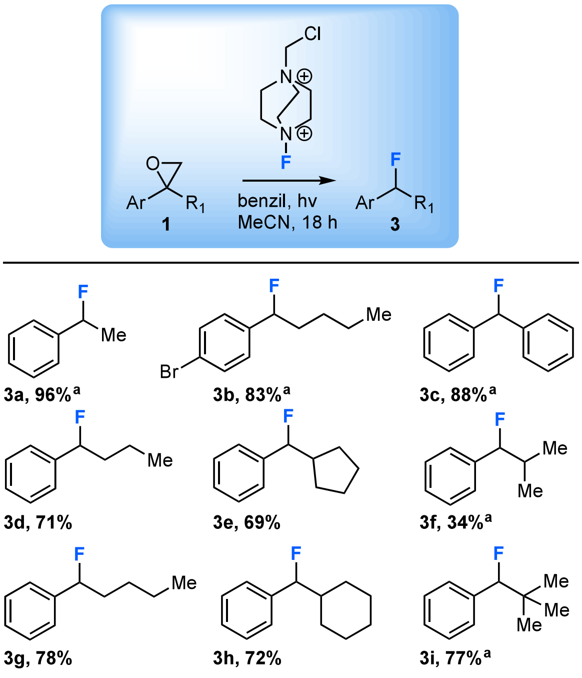
Scheme 4. Rearrangement of Epoxides 2a−i through the Process Described in Manifold 2[b]



[a]Yields determined from NMR conversion. [b]Identical conditions were used for all except **2i**, which required heat and additional reaction time. SF works as well, albeit with a slower rate.

A significant mechanistic insight came from a series of control experiments performed on various components of the reaction scheme. Alternative fluorinating agents proved to be less effective; a trial reaction with *N*-fluorobenzenesulfonamide (NFSI) yielded a mixture of the starting material and undirected fluorination products. A subsequent optimization trial compared two reactions with 2-phenyl-2-propyloxirane using MeCN either from an open bottle or freshly distilled over molecular sieves. Our prior work with directed fluorination indicated the importance of air- and water-free conditions.[11] However, there has been literature precedent for solvent-dependent selectivity switching in a SET fluorination system, so it was perhaps unsurprising that the relatively wet, undistilled MeCN proved more efficient.[12] An unstaged reaction using dry MeCN yielded a 1:2 ratio of fluorinated product to ketone. Using water-contaminated MeCN shifted the ratio to favor the fluorination product over the demethylated ketone by 9:1, which could be further improved by a prearrangement, ultimately resulting in ratios as high as 99:1 and near-quantitative yields.

Scheme 5. Decarboxylative Fluorination of Epoxides 3a−i using the Process Described in Manifold 3



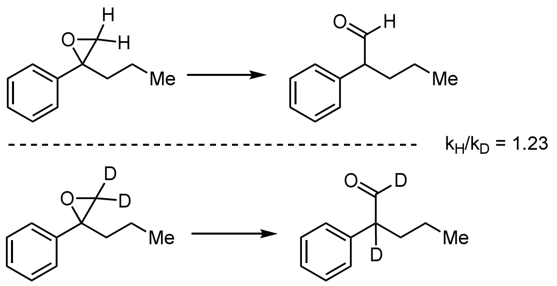
[a]Yields determined from NMR conversion.

Note that water is a necessary reagent in decarboxylative oxidation through a putative hydrate. Despite water's crucial involvement, there appears to be a "Goldilocks's zone" of ideal water content, as reactions performed with excess water all returned unreacted starting material. This is perhaps explained through a proposed solvent caging effect on the dication catalyst, suppressing the preliminary rearrangement at higher water concentrations. However, since quantifying the precise degree of water contamination necessary proved impractical, this conclusion remains speculative.

For further support of the proposed mechanism, we performed a series of kinetic isotope effect (KIE) experiments to explore the dabco salt-catalyzed aldehyde rearrangement (Scheme 6). A series of parallel rate-determining experiments using 2-phenyl-2-propyloxirane-3,3-d_2 as the substrate afforded a secondary KIE of k_H/k_D = 1.23.[13] This result contrasts with prior studies on boron-based Lewis acid-catalyzed Meinwald rearrangements, which yielded putative primary effects.[14,15] The secondary KIE value suggests that the epoxide ring opening represents the rate-determining step rather than the hydride transfer.

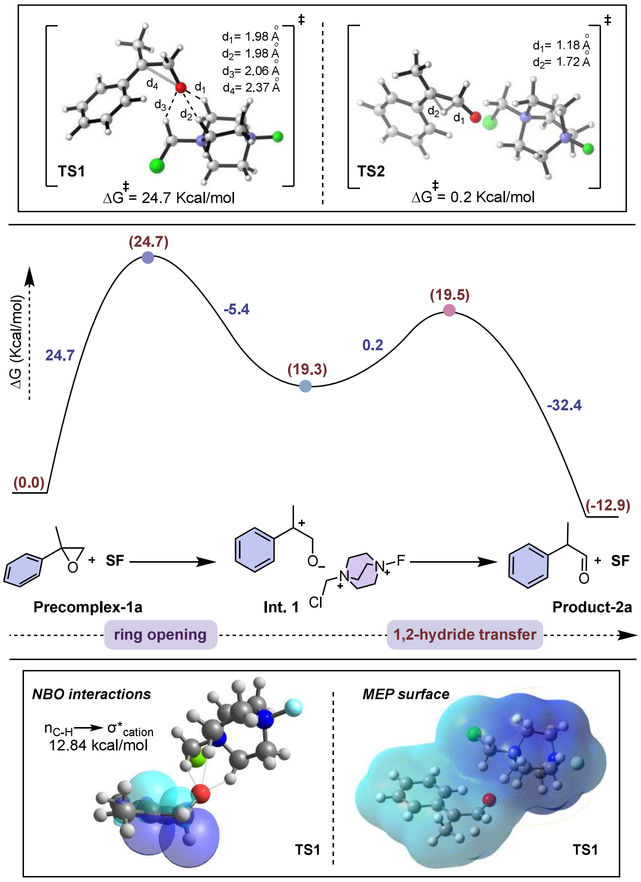
To gain further insight into this result, we performed density functional theory calculations at the (IEFPCM = MeCN) B3LYP-D3(BJ)/6-311++G(2d,2p)//IEPCM$_{(\text{MeCN})}$ B3LYP-D3(BJ)/6-31+G(d,p) level of theory[16] using the Gaussian 16 software package.[17] As expected, the Meinwald-type rearrangement proceeds by initial epoxide ring opening from precomplex-**1a**. The methylphenyloxirane (**1a**) ring opens through transition state **TS1** with an elongated bond breaking distance of 2.37 Å and a rather high $\Delta G^{\ddagger}$ of 24.7 kcal/mol (Scheme 7). In this transition state, the SF catalyst is poised atop the developing oxyanion, providing stabilization through an enzyme-like oxyanion-hole composed of three favorable hydrogen bond C−H···O contacts measuring 1.97, 2.10, and 1.97 Å with natural bond order (NBO) charges (O = −0.531 e, H = 0.296 e, H = 0.305 e, H = 0.305 e) indicative of

Scheme 6[a]



[a]Parallel independent rate-measuring KIE experiments yield k_H/k_D = 1.23, a small secondary effect consistent with ring opening in the rate-determining step.

Scheme 7. DFT Analysis of the Rearrangement of Methylphenyloxirane (1a)[a]



[a]All structures were computed at the IEPCM$_{(\text{MeCN})}$B3LYP-D3(BJ)/6-311++G(2d,2p)//IEPCM$_{(\text{MeCN})}$B3LYP-D3(BJ)/6-31+G(d,p) level of theory. The bottom-left image displays the Natural Bond Orbital (NBO) analysis for **TS1**, while the bottom-right image presents the Molecular Electrostatic Potential (MEP) surface of **TS1**.

Coulombic character. Additionally, the MEP surface suggests further stabilization from the nearby SF dication, shown by a highly diffuse positive charge in **TS1**. Further stabilization comes from hyperconjugation between an adjacent C−H bond and the developing carbocation (NBO $n_{\text{C-H}} \rightarrow \sigma^*_{\text{cation}}$ = 12.84 kcal/mol). The resulting ring-opened species (**Int. 1**) ($\Delta G°$ = 19.3 kcal/mol relative to the precomplex) undergoes facile 1,2-hydride migration to the adjacent carbocation with a computed low barrier of 0.2 kcal/mol (**TS2**). Defining this process are the short C−H bond-breaking and elongated C···H bond-forming distances of 1.18 and 1.72 Å, indicative of an early transition state. The resulting carbonyl product **2a** is formed through a highly favorable exergonic event ($\Delta G°$ = −12.9 kcal/mol relative to reagents). The rate-determining C−O bond-breaking yielded a predicted *β*-secondary KIE of 1.33,[18] in agreement with experimental results. The product determining the 1,2-hydride shift yielded a primary KIE of 1.54. It should be noted that these calculated values exhibit significant method-dependence that should caution against drawing any rock solid conclusions. However, in aggregate, these results are consistent with the proposed mechanism with an epoxide ring opening as the rate-determining step.

In conclusion, tandem reactions have long been a subject of much interest in organic chemistry due to their utility and mechanistic intricacy.[19] This Note presents a system that can generate three different products through simple adjustments in catalytic salt and light application. This branching manifold further expands the synthetic utility of epoxides with potential applications for late-stage fluorination as well as other derivatization experiments.

■ 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.4c01470.

Experimental procedures, spectra, and computational data (PDF)

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Notes

The authors declare no competing financial interest.

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