Catalytic 1,3-Difunctionalization via Oxidative C–C Bond Activation

Catalytic 1,3-Difunctionalization via Oxidative C–C Bond Activation

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Supporting Information Placeholder

ABSTRACT: Electronegative substituents arrayed in 1,3-relationships along saturated carbon frameworks can exert strong influence over molecular conformation due to dipole minimization effects. Simple and general methods for incorporation of such functional group relationships could thus provide a valuable tool for modulating molecular shape. Here, we describe a general strategy for the 1,3-oxidation of cyclopropanes using aryl iodide(I-III) catalysis, with emphasis on 1,3-difluorination reactions. These reactions make use of practical, commercially available reagents and can engage a variety of substituted cyclopropane substrates. Analysis of crystal and solution structures of several of the products reveal the consistent effect of 1,3-difluorides in dictating molecular conformation. The generality of the 1,3-oxidation strategy is demonstrated through the catalytic oxidative ring opening of cyclopropanes for the synthesis of 1,3-fluoroacetoxylated products, 1,3-diols, 1,3-amino alcohols, and 1,3-diamines.

The strategic disposition of substituents in 1,3-relationships is a well-established tool for influencing the conformation of organic molecules. Control elements such as *syn*-pentane and $A_{1,3}$ interactions,[1] which rely on minimization of steric repulsion between 1,3-substituents, are most familiar and are broadly exploited in molecular design. Dipole minimization, although considerably less well developed as a design strategy, can provide biasing effects of similar magnitude in structures possessing electronegative functional groups disposed in a 1,3-manner. For example, acyclic, saturated 1,3-difluoro compounds have been shown to display a strong bias to adopting dipole-minimized conformations (Figure 1a).[2]

In an effort to devise efficient and general routes from simple precursors to products bearing 1,3-oxidation patterns, we undertook an investigation of methods for the direct activation of substituted cyclopropanes. The majority of approaches to cyclopropane ring-opening have relied on vicinal donor-acceptor (DA) substitution on the strained ring,[3] or oxidative addition by a transition metal to form metallacyclobutane intermediates.[4] Strategies for non-DA cyclopropane functionalization have invoked both radical[5] and electrophilic addition,[6] and a catalytic method that achieves 1,3-aminofluorination of arylcyclopropanes through the intermediacy of radical cations has been reported recently.[7] Analyses of electrophilic additions to cyclopropanes have revealed subtle nuances regarding the mechanism of ring-opening,[4a,8] but the development of general and practical synthetic methods that capitalize on these reactivity manifolds has not yet been achieved.

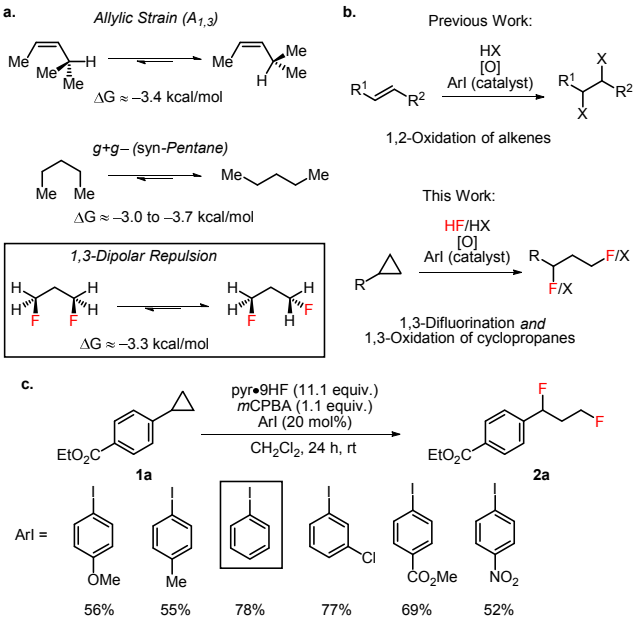

Figure 1. 1,3-Difluorination of cyclopropanes. **a.** Conformational properties of 1,3-difluorides. **b.** Aryl iodide-catalyzed oxidation of alkenes and cyclopropanes. **c.** Catalyst optimization studies.

We and others have developed oxidative 1,2-difunctionalization reactions of alkenes based on aryl iodine(I-III) catalysis,[9] and we hypothesized that the alkene-like π-donating properties of unactivated cyclopropanes could give rise to promotion of 1,3-oxidation reactions by similar mechanisms (Figure 1b). Indeed, Szabó and coworkers demonstrated very recently that 1,1-disubstituted cyclopropanes undergo 1,3-difluorination in the presence of stoichiometric iodine (III) reagents together with stoichio-

metric $AgBF_4$.[10] We describe here the discovery of a catalytic and general method for the ring-opening 1,3-oxidation of substituted cyclopropanes with simple aryl iodide catalysts.

We initiated experimental efforts toward the ring-opening difluorination of substituted cyclopropanes using *m*CPBA as an oxidant, and HF-pyridine as a nucleophilic fluoride source, and commercially available aryl iodides as catalysts. With this reagent protocol, the carboethoxy-substituted arylcyclopropane **1a** was converted to the corresponding 1,3-difluorination product in the presence of a variety of electron rich and electron deficient aryl iodides (Figure 1c). In contrast, cyclopropylbenzene and more electron-rich analogs decomposed to uncharacterized products. Iodobenzene afforded the highest yields in the difluorination of **1a**, and this simplest of potential aryl iodide catalysts was selected for further investigation of the reaction scope.[11]

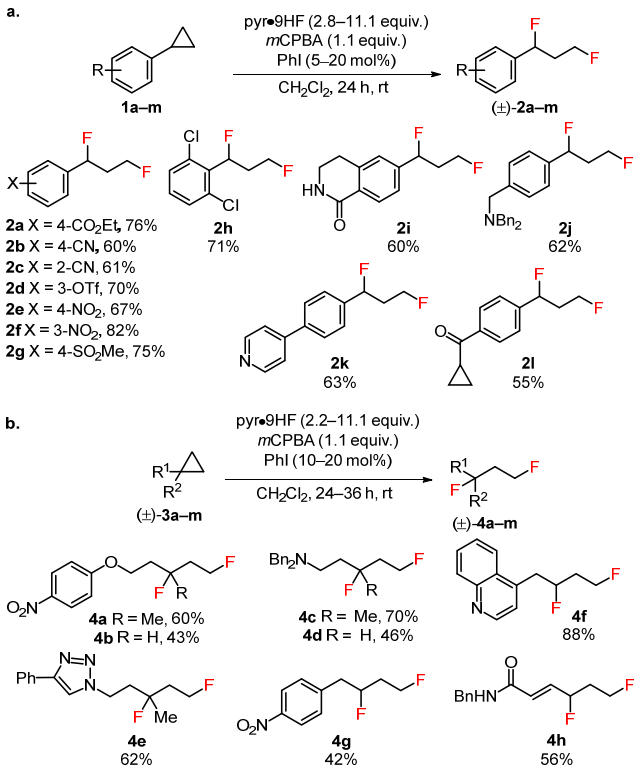

Figure 2. Evaluation of substrate scope for 1,3-difluorination. **a.** Substrate scope evaluation for aryl cyclopropanes. **b.** Substrate scope evaluation for aliphatic and vinyl cyclopropanes. Isolated yields are indicated below each product (**2** and **4**); experimental details are provided in the Supporting Information.

In general, aryl cyclopropanes bearing electron-withdrawing substituents were useful substrates in the catalytic reaction, undergoing regioselective difluorination in moderate-to-good yields (Fig. 2a). Substrates bearing amine substituents (**1j**) and *N*-heterocycles (**1k**) also underwent successful difluorination, by virtue of basic groups undergoing *in situ* protection via protonation by HF. The reaction was chemoselective for the most electron rich cyclopropane in **1l**, providing **2l** as the only detectable 1,3-difluorinated product.

Non-conjugated monosubstituted cyclopropanes also underwent oxidation under the catalytic conditions (Fig. 2b). Increased catalyst loadings (20 mol%) were required for non-conjugated cyclopropane substrates due to competitive hydrofluorination, a known reaction of HF-pyridine and aliphatic cyclopropanes.[12] Substrates containing ether (**4a**, **4b**) and amine (**4c**, **4d**) functionality underwent difluorination in good yields. 1,1-Disubstituted cyclopropanes were converted to the corresponding 1,3-difluorinated products more cleanly in higher yields relative to the monosubstituted analogs (**4a**, **4c** vs. **4b**, **4d**). The compatibility of basic nitrogen functionality with the acidic, oxidizing conditions was demonstrated by the isolation of triazole **4e** and quinoline **4f** in good yields. Subjection of β-cyclopropyl acrylamide **3h** to the reaction conditions resulted ring-opening 1,3-difluorination to afford **4h**, with no detectable difluorination of the alkene.

In contrast to the established effectiveness of chiral aryl iodide catalysts in enantioselective fluorofunctionalizations of alkenes,[9g,9j,13] only very low levels of enantiocontrol were observed in the corresponding 1,3-difluorination of cyclopropanes such as **1a** with a variety of catalysts (see Supporting Information). While the identification of effective chiral catalysts for enantioselective ring-opening difluorination reactions will demand further effort, we found that stereochemically complex 1,3-difluorination products could be accessed effectively with achiral aryl iodide catalysts from readily accessible chiral cyclopropanes. For example, tetrasubstituted substrates **5a**–**e** underwent difluorination stereospecifically in the presence of iodobenzene (>20:1 d.r., diastereomeric ratio, Fig. 3a). Cyclopropane **5f** underwent difluorination to afford a mixture of diastereomers; this substrate required the use of high concentrations of pyr•9HF (5.6 equiv.) to reach complete conversion. The loss of diastereospecificity is ascribable to the highly acidic medium, as similarly diminished diastereoselectivities were obtained in reactions of **5a** and **5b** using >2.2 equivalents of pyr•9HF.

To gain insight into the stereospecificity of both C–F bond-forming steps, cyclopropanes **5g** and **7a-b** were subjected to the catalytic fluorination conditions (Fig. 3b). Whereas **5g** underwent ring-opening to provide **6g** as a 1.3:1 mixture of diastereomers, the less highly substituted substrates **7a-b** underwent stereospecific difluorination to afford diastereomerically pure products. The relative configuration of the two fluoride-bearing stereocenters in **8b** was determined to be syn via X-ray diffraction analysis of a crystalline derivative. The divergent stereochemical behavior observed between **5g** and **7a-b** can be rationalized according to the mechanism outlined in Fig. 3c. The first C–F bond formation is proposed to occur via regioselective invertive ring-opening at the most electrophilic benzylic position to afford fluoroiodinated species $\mathbf{5_{II}}$. In the case of the fully substituted intermediate (R = Et), ionization of the C-I^{III} bond would be facile and yield tertiary carbocation $\mathbf{5_{III}}$, which can be trapped

by fluoride non-stereospecifically in an S_N1 process. In the case of the secondary intermediate (R = H), concerted, invertive fluoride substitution appears be favored, leading to the observed syn product stereospecifically. The relative stereochemistry observed in **8** is consistent with edge activation of cyclopropanes by I^{III} in a manner analogous to the activation of alkenes by I^{III} activation of alkenes. The stereospecificity observed in the difluorination reactions described above represents an important practical feature of this electrophilic catalytic system.

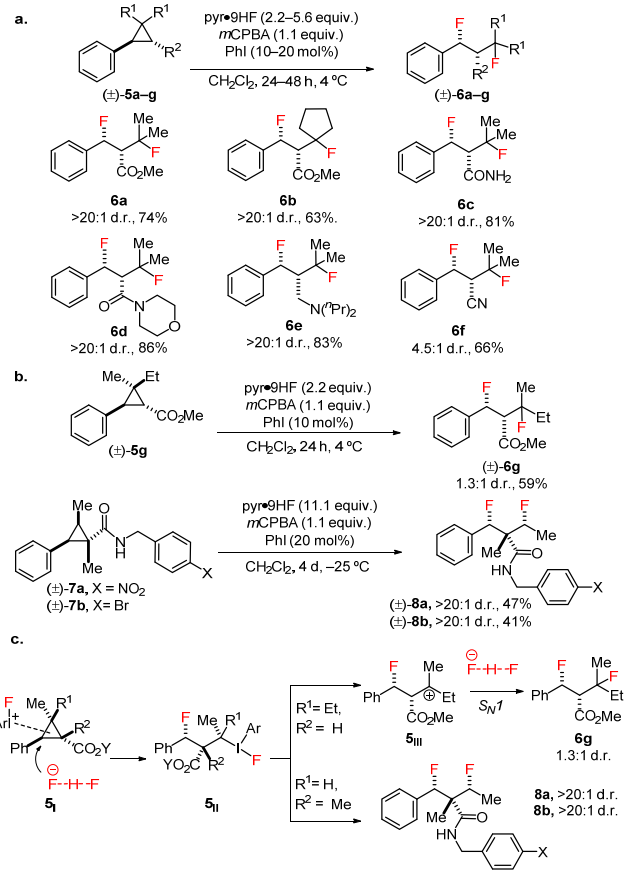

Figure 3. Stereospecificity in the generation of 1,3-difluorination products. **a,** 1,3-Difluorination of chiral highly substituted cyclopropanes. **b.** Evaluation of the stereospecificity of both C–F bond forming steps. **c.** Mechanistic proposals for the divergent stereochemical outcomes observed between substrates **5** and **6**. Isolated yields are indicated for all products (**6**, **8**); experimental details are provided in the Supporting Information.

X-ray crystal structures were obtained for compounds **4a**, **4h**, **6c** and **6d**. In all cases, the molecules adopt solid-state conformations wherein the 1,3-difluoro substituents are oriented in the *gauche-gauche* relationships that minimize dipolar interactions (Fig. 4). Both **6e** and **6f** were found to adopt similar 1,3-dipolar minimized conformations in solution, as determined by vicinal H-F NMR coupling constants ($^3J_{H\text{-}F}$). These findings add to the growing body of crystallographic and solution state data demonstrating that fluorides disposed in a 1,3-relationship impose strong conformational biases to saturated, acyclic carbon frameworks.

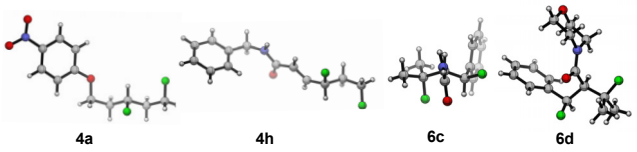

Figure 4. X-ray crystal structures of 1,3-difluorides

The catalytic ring-opening difluorination protocol could be applied successfully to 1,1-difluorocyclopropane substrates, affording products corresponding formally to alkene 1,2-fluorotrifluoromethylation (Fig. 5). Several substituted 1,1-difluoroarylcyclopropanes were transformed to fluorotrifluoromethylated products **10a–f** in good-to-excellent yields. 1,1-Difluorocyclopropanes have been calculated to possess very high ring strain energies (ca. 40 kcal/mol),[14] and this might offset the expected deactivating inductive effect of fluorine substitution on the cyclopropane ring and enable the 1,3-difluorination reaction. However, large excesses of pyr•9HF (5.6-11.1 equiv.) were required to achieve complete substrate conversion. Only modest diastereoselectivity (3:1) was observed in the ring-opening of the substituted cyclopropane **5g** consistent with similar results obtained with **5f** under strongly acidic conditions (see above).

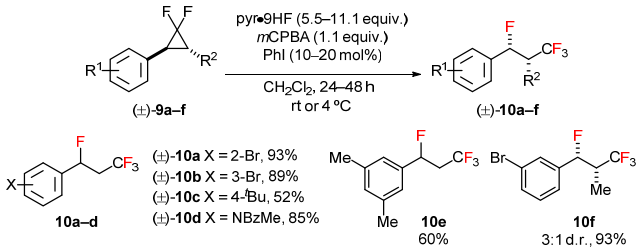

Figure 5. 1,3-Difluorination of 1,1-difluorocyclopropanes.

The protocol for catalytic 1,3-oxidation reactions of cyclopropanes could be adapted in a straightforward manner to allow introduction of electronegative groups other than fluorine. Introduction of excess acetic acid to the 1,3-difluorination conditions led to formation of fluoroacetoxylation products (**11a–c**) in good yields and with complete regioselectivity (Fig. 6a). Net 1,3-dihydroxylation of cyclopropanes was achieved using trifluoroacetic acid as both an acidic promoter and nucleophile (Fig. 6b). The initially formed 1,3-trifluoroacetoxy products were subjected to hydrolysis under mild conditions to provide 1,3-diols (**12a–c**) from cyclopropanes in moderate-to-excellent yields. When the same reactions of cyclopropanes and trifluoroacetic acid were conducted in acetonitrile, 1,3-amino alcohols could be obtained with complete regioselectivity and in good yields (Fig. 6c, **13a–c**). The formation of 1,3-amino alcohol products in this reaction suggests Ritter-type substitution reactions are available to the highly electrophilic species generated under I^{III} catalysis. Catalytic 1,3-cyclopropane oxidation could also be applied to the synthesis of 1,3-diamine products (Fig. 6d). These reactions require BF_3•OEt_2 as a stoichiometric activator with a sulfonamide nitrogen source and proceed in moderate yield (**14a–c**). Taken together, these

1,3-difunctionalization reactions demonstrate the rich variety of 1,3-oxidation patterns that should be accessible from unactivated cyclopropanes using ArI catalysis.

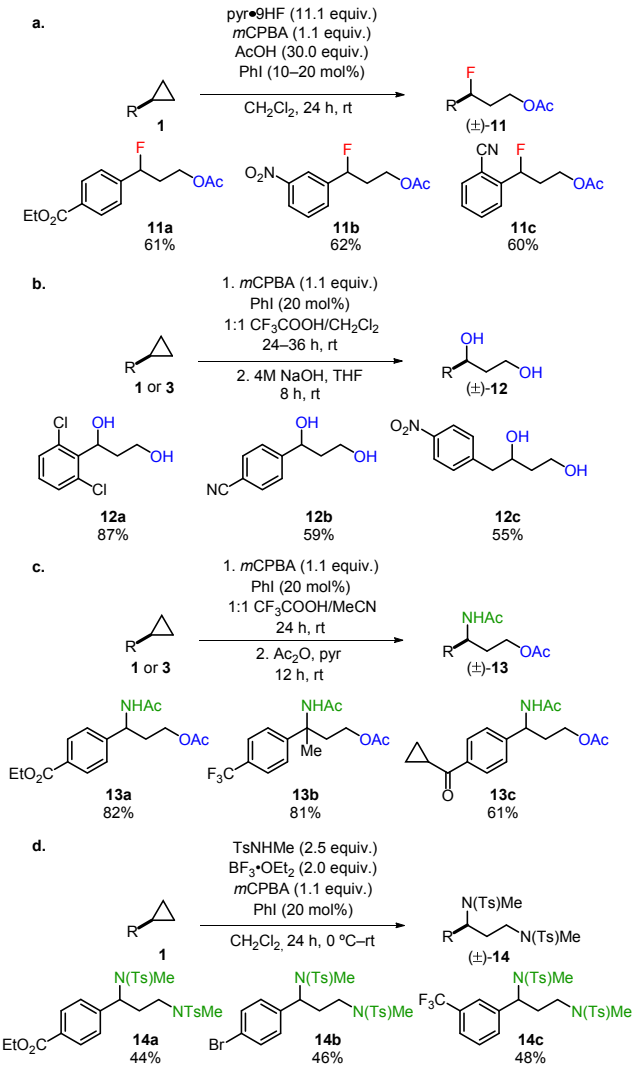

Figure 6. General 1,3-catalytic oxidative difunctionalization of cyclopropanes. **a.** Synthesis of fluoroacetoxylated products using acetic acid as a cosolvent. **b.** Synthesis of 1,3-diols using trifluoroacetic acid as a cosolvent followed by hydrolysis. **c.** Synthesis of 1,3-amino alcohols using trifluoroacetic acid and acetonitrile as cosolvents. **d.** Synthesis of 1,3-diamines using *p*-tolylmethanesulfonamide and BF_3•OEt_2. Isolated yields are indicated below each product (**11**, **12**, **13**, **14**); for experimental details, see the Supporting Information.

The discovery of a direct, catalytic method for the construction of 1,3-difluorinated compounds introduces a new tool for the modulation of molecular conformation. Generalization of this cyclopropane C-C bond activation strategy holds promise for accessing a variety of 1,3-oxidation patterns, as demonstrated here in the synthesis of 1,3-fluoroacetoxy, 1,3-diol, 1,3-amino alcohol, and 1,3-diamine products. Further efforts to exploit catalytic, electrophilic activation for cyclopropane functionalization are currently underway.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures; characterization data (PDF)

Crystallographic data for **4a** (CIF)

Crystallographic data for **4h** (CIF)

Crystallographic data for **6c** (CIF)

Crystallographic data for **6d** (CIF)

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Notes

The authors declare no competing financial interest.

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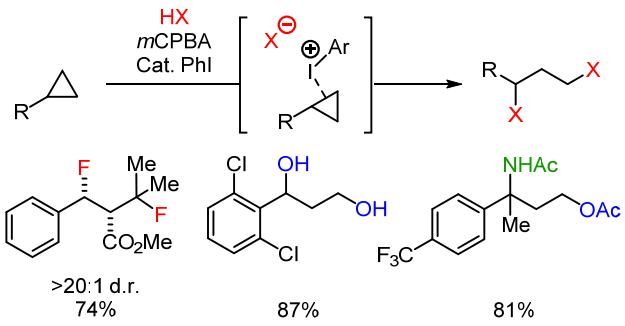

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