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Nucleophilic Ring Opening of Donor−Acceptor Cyclopropanes Catalyzed by a Brønsted Acid in Hexafluoroisopropanol

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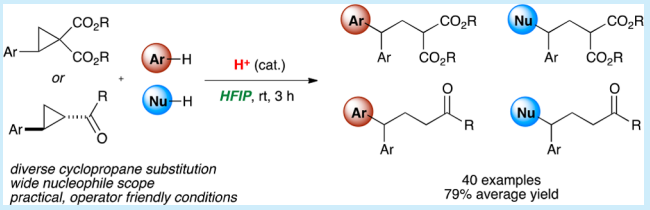
Supporting Information

ABSTRACT: A general, Brønsted acid catalyzed method for the room temperature, nucleophilic ring opening of donor−acceptor cyclopropanes in fluorinated alcohol solvent, HFIP, is described. Salient features of this method include an expanded cyclopropane scope, including those bearing single keto-acceptor groups and those bearing electron-deficient aryl groups. Notably, the catalytic system proved amenable to a wide range of nucleophiles including arenes, indoles, azides, diketones, and alcohols.



Donor−acceptor (DA) cyclopropanes serve as "spring-loaded" synthetic intermediates owing to the inherent C−C bond polarization afforded by the synergistic combination of donor and acceptor substituents.[1] Consequently, they have found widespread application in modern synthetic organic chemistry, and a range of catalytic methodologies have been developed that engage DA-cyclopropanes in cycloaddition,[2] 1,3-difunctionalization,[3] and homoconjugate addition-type reactions[4] with a variety of nucleophiles including amines, alcohols, thiols, carboxylic acids, and azides.[5] Outside of reactions with heteroatomic nucleophiles, a handful of catalytic arylation reactions of DA-cyclopropanes have been developed; however, currently developed systems are typically limited to a single class of nucleophiles such as indole derivatives,[6] anilines,[7] electronically activated anisole derivatives,[8] and 2-naphthols.[9] Typically, all of the aforementioned catalytic systems employ high (10−20 mol %) loadings of Lewis acidic catalysts,[10] namely rare-earth triflates, with the reactions typically operating at elevated temperatures. As these Lewis acidic catalyst systems seek to take advantage of dual coordination to geminal diester-bearing cyclopropanes, a striking limitation in terms of cyclopropane substitution becomes apparent. Likewise, the activation of such DA-cyclopropanes relies on polarization of the C−C bond by the synergistic interaction of the D and A groupings. Consequently, in almost all conjugate addition-type ring openings, the tolerated donor substitution is limited to electron-donating or -neutral aryl substituents (Figure 1, top).

Given our recent investigations into aggregation phenomena in acid catalysis[11] we recognized an opportunity to develop an alternative Brønsted acid catalyzed protocol for the activation of DA-cyclopropanes. We hypothesized that a strong Brønsted acid catalyst system would provide a dual advantage in the activation of DA-cyclopropanes, allowing both a wider nucleophile scope and the employment of a wider range of cyclopropane scaffolds beyond the typical structural limitations.

Herein, we report the successful realization of such a scenario, whereby trifluoromethanesulfonic acid (TfOH) in hexafluoroisopropanol (HFIP)[12,13] acts as a highly active and general catalyst system for the nucleophilic ring opening of DA-cyclopropanes. A wide array of nucleophiles (*C*-, *O*-, *N*-) can be employed in the protocol, and typical limitations of the DA-cyclopropane architecture have also been surpassed, allowing chalcone derived cyclopropanes bearing a single keto-acceptor motif to engage in catalytic nucleophilic ring opening (Figure 1, This work). The developed method is also highly user-friendly providing numerous practical advantages; the reactions operate at ambient temperature, under open-flask conditions with most reactions typically complete within 3 h.

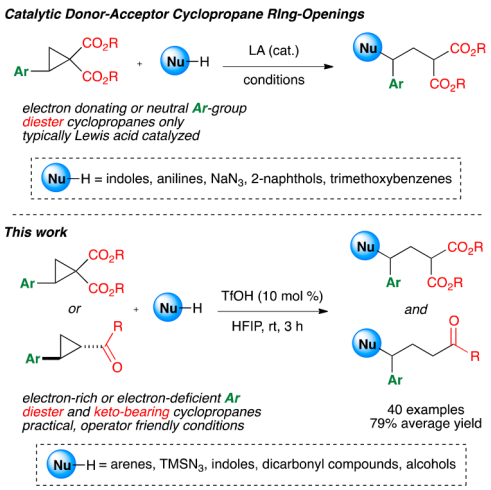


Figure 1. Existing Lewis acid catalyzed methodologies for the nucleophilic ring opening of diester-bearing DA-cyclopropanes. This work: Brønsted acid catalyzed nucleophilic ring opening of a wide range of DA-cyclopropanes.

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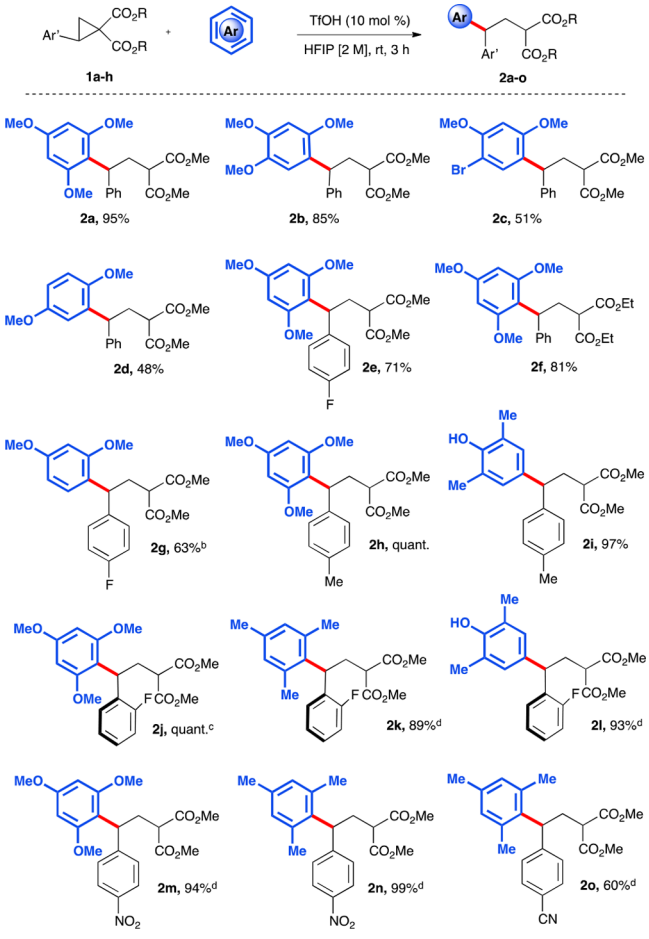
Synthetic investigations began with a benchmark reaction—the arylative ring opening of DA-cyclopropane **1a**[14] in combination with 1,3,5-trimethoxybenzene—a reaction known to proceed at 80 °C in the presence of 20 mol % of $Yb(OTf)_3$.[8c] It was rapidly established that, by slight modification of catalytic conditions already established within the group,[11d] the arylative ring opening of such cyclopropanes could be initiated at rt by TfOH when employing HFIP as solvent. Further slight tweaking established 10 mol % of TfOH in HFIP as a reliable system for this transformation leading to complete conversion in just 3 h and a 95% yield of the desired arylated material **2a** after simple column chromatography (Scheme 1).

Scheme 1. Scope of Brønsted Acid Catalyzed Arylative Ring Opening of DA-Cyclopropanes Bearing a Geminal Diester Motif[a]

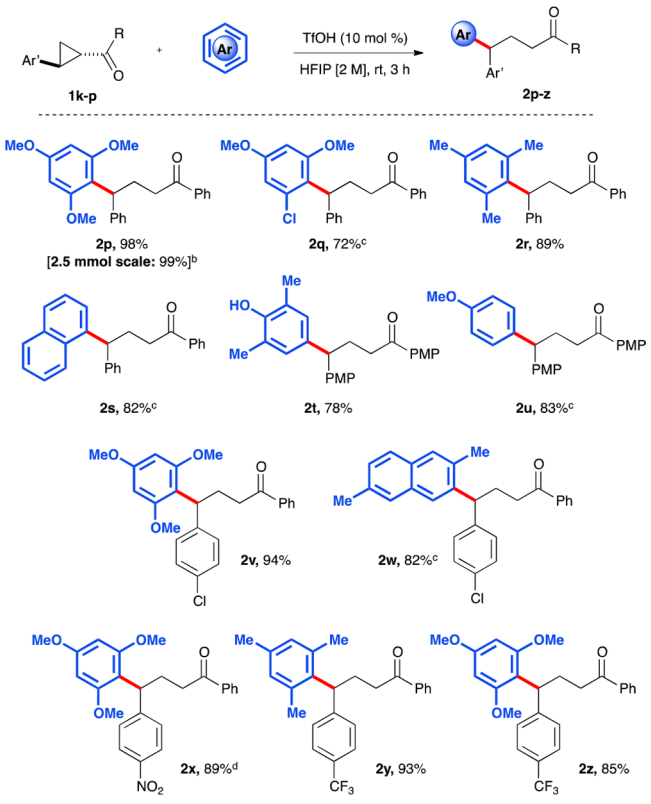


[a]Isolated yields after column chromatography. [b]Isolated as a mixture of regioisomers; see Supporting Information (SI) for further details. [c]Reaction performed at 40 °C for 4 h. [d]Reaction performed at 50 °C for 24 h.

Application of these catalytic reaction conditions across a range of DA-cyclopropane substrates was then undertaken. 1,2,4-Trimethoxybenzene also proved to be an excellent nucleophile furnishing the desired product **2b** in 85% yield. Reaction of various cyclopropane substrates bearing electron-donating or -neutral aryl substituents with a range of di- and trimethoxybenzene derivatives provided the desired arylated products in moderate to good yields (**2c**–**2h**) including arylated diethylester **2f**. 2,6-Dimethylphenol also proved to be an excellent nucleophile in this system generating arylated product **2i** in 97% yield. A DA-cyclopropane bearing a 2-fluorophenyl substituent was also well tolerated in this catalytic system, delivering arylated products **2j**, **2k**, and **2l** with 1,3,5-trimethoxybenzene, mesitylene, and 2,6-dimethylphenol, respectively. As a further demonstration of the generality of the developed catalytic system, DA-cyclopropanes bearing a 4-nitrophenyl group and a 4-benzonitrile aryl substituent were also smoothly engaged in arylation with 1,3,5-trimethoxybenzene and mesitylene (**2m**–**2o**) in good to excellent yields.

Attention next turned to DA-cyclopropanes bearing a single ketone substituent as the "acceptor" motif. To the best of our knowledge, such scaffolds have yet to find widespread uptake as substrates in catalytic cyclopropane methodology development owing to the prior focus on Lewis acid catalyzed methods believed to require a geminal diester cyclopropane substitution pattern. Nevertheless, upon reaction with 1,3,5-trimethoxybenzene, chalcone derived cyclopropane **1k** delivered the desired arylated product **2p** in 98% yield (Scheme 2). Furthermore, this

Scheme 2. Scope of Brønsted Acid catalyzed Arylative Ring Opening of DA-Cyclopropanes Bearing a Keto-Acceptor Group[a]



[a]Isolated yields after column chromatography. [b]Reaction performed with 5 mol % TfOH. [c]Isolated as a mixture of regioisomers; see the SI for further details. [d]Reaction performed at 80 °C.

reaction was successfully scaled up to 2.5 mmol, catalyzed by only 5 mol % TfOH, and duly delivered 0.971 g of the arylated product in 99% yield. Variation of the nucleophilic component in this reaction system proved unproblematic (**2q**–**2s**), as did variation of the chalcone-derived cyclopropane scaffold to include electron-rich aryl groups (**2t** and **2u**) and halogenated aryls (**2v** and **2w**). Notably, mesitylene (**2r**), naphthalene derivatives (**2s** and **2w**), 2,6-dimethylphenol (**2t**), and anisole

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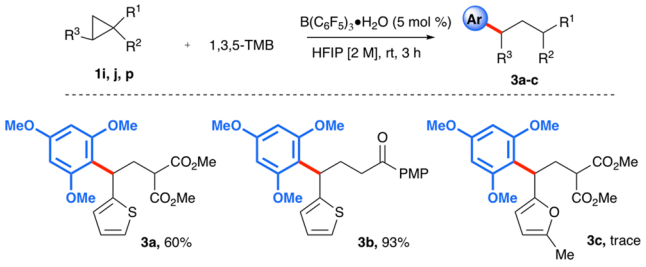
(**2u**) were all tolerated in the reaction system in excellent yield. Once again, DA-cyclopropanes bearing electron-deficient aryl substituents (4-NO_2 and 4-CF_3) were successfully engaged in arylative ring opening (**2x**, **2y**, and **2z**) with only moderate heating required in the case of the reactions employing the 4-nitro substituted starting material. Additionally, cyclopropanes bearing heterocyclic motifs were also successfully engaged in arylative ring opening with 1,3,5-trimethoxybenzene under slightly modified conditions;[15] thiophene-bearing products **3a** and **3b** were isolated in 60% and 93% yield respectively, yet methyl-furan bearing product **3c** proved sensitive to decomposition during purification and was only isolated in trace amounts (Scheme 3).

Scheme 3. Brønsted Acid Catalyzed Arylative Ring Opening of DA-Cyclopropanes Bearing Heterocyclic Donor Groups[a]

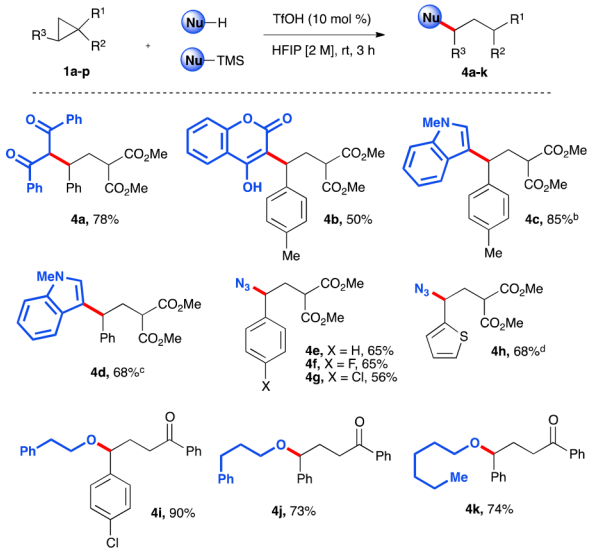


[a]Isolated yields after column chromatography.

Further investigation of this reaction system revealed that the same catalytic conditions were able to promote cyclopropane ring opening with nucleophiles other than activated arenes. Reaction with diketones proceeded smoothly to yield highly functionalized products **4a** and **4b** in 78% and 50% yield, respectively. Investigation of the reactions of DA-cyclopropanes with indoles revealed HFIP to be an inefficient solvent for such reactions, most likely owing to its ability to hydrogen bond to basic groups, thus attenuating the nucleophilicity of these species. Rather, *N*-methylindole proved to be a competent reaction partner with DA-cyclopropanes when employing $B(C_6F_5)_3{\cdot}H_2O$ as a catalyst in nitromethane, a catalytic duo previously investigated in our research group.[11a] Under these conditions, products **4c** and **4d** were delivered in 85% and 68% yield, respectively. Ring opening with TMS-N_3 also proved facile with the developed catalytic protocol, with products **4e**−**4h** isolated in good to excellent yield. Additionally, primary alcohols could be employed as nucleophiles with no change in reaction conditions required and products **4i**−**4k** were delivered as expected in up to 90% yield (Scheme 4).

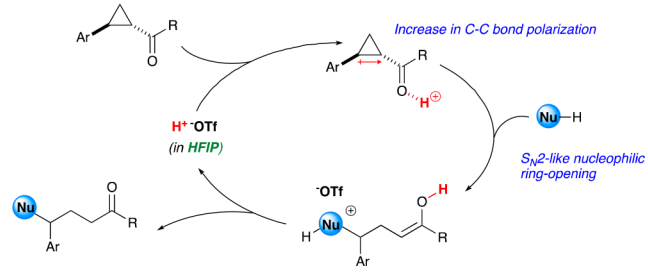
In a system designed to shed light on the mechanistic course of such cyclopropane opening reactions, treatment of enantiopure cyclopropane (*S*)-**1a** with 1,3,5-trimethoxybenzene under standard conditions delivered (*R*)-**2a** in high yield.[16] This observation is in line with prior Lewis acid catalyzed protocols[8c] and suggests that, under Brønsted acid catalyzed conditions, cyclopropane ring opening occurs via a predominantly S_N2-like mechanistic pathway. This allows the following mechanistic rationale to be proposed (Scheme 5). Initial protonation of the cyclopropane "acceptor-motif" by a Brønsted acid catalyst[17] leads to an increase in cyclopropane C−C bond polarization, thus activating the benzylic carbon to nucleophilic attack in a mechanism analogous to an S_N2-like displacement. Subsequent enol-tautomerization or protonation, together with proton abstraction, regenerates the

Scheme 4. Scope of Brønsted Acid Catalyzed Nucleophilic Ring Opening of DA-Cyclopropanes[a]



[a]Isolated yields after column chromatography. [b]Reaction performed with 5 mol % $B(C_6F_5)_3{\cdot}H_2O$ in $MeNO_2$ at 80 °C for 24 h. [c]Reaction performed with 10 mol % $B(C_6F_5)_3{\cdot}H_2O$ at 80 °C for 24 h. [d]Reaction performed with 5 mol % $B(C_6F_5)_3{\cdot}H_2O$.

Scheme 5. A Plausible Mechanistic Scenario



Brønsted acid to enable turnover of the cycle and in the process delivers the desired ring-opened product.

In conclusion, a unified Brønsted acid catalyzed nucelophilic ring opening of DA-cyclopropanes has been developed. The salient features of this system are the operator-friendly reaction procedure and the wide scope with respect to both the cyclopropane scaffold and nucleophile. The combination of TfOH and HFIP provides a simple yet highly active Brønsted acid system allowing novel classes of cyclopropane, including those bearing electron-deficient aryl groups and those derived from chalcones, to engage in nucleophilic ring-opening reactions for the first time. Initial observations suggest that ring opening occurs via an S_N2-like mechanistic pathway; however, comprehensive mechanistic studies into the Brønsted acid catalyzed activation of small-ring cycloalkyl species are currently ongoing within our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03688.

Optimization data, experimental procedures, characterization of new compounds, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(14) See the Supporting Information for full structural details of the cyclopropanes and for details of their preparation.

(15) Using TfOH as a catalyst with heterocyclic substrates led to significant decomposition and lower yields of products. Consequently, $B(C_6F_5)_3{\cdot}H_2O$ was employed as a milder Brønsted acidic catalyst.

(16) See the Supporting Information for further details.

(17) NMR titration of TfOH into a solution of cyclopropane/HFIP indeed reveals a downfield shift of cyclopropane methylene protons by ^{1}H NMR, and a downfield shift of keto-carbonyl by ^{13}C NMR. Taken together, this is highly suggestive of 'acceptor'-protonation occurring facilely under the reaction conditions.

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