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Research Article

Skeletal Ring Contractions via I(I)/I(III) Catalysis: Stereoselective Synthesis of *cis*-α,α-Difluorocyclopropanes

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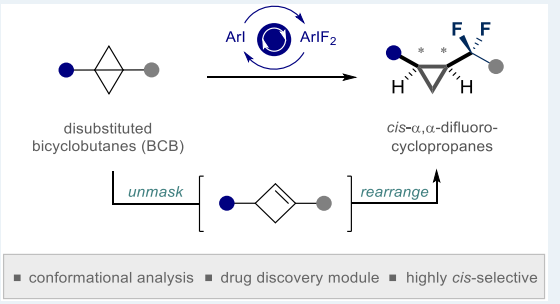
ABSTRACT: The clinical success of α,α-difluorocyclopropanes, combined with limitations in the existing synthesis portfolio, inspired the development of an operationally simple, organocatalysis-based strategy to access *cis*-configured derivatives with high levels of stereoselectivity (up to >20:1 *cis*:*trans*). Leveraging an I(I)/I(III)-catalysis platform in the presence of an inexpensive HF source, it has been possible to exploit disubstituted bicyclobutanes (BCBs) as masked cyclobutene equivalents for this purpose. *In situ* generation of this strained alkene, enabled by Brønsted acid activation, facilitates an unprecedented 4 → 3 fluorinative ring contraction, to furnish *cis*-α,α-difluorinated cyclopropanes in a highly stereoselective manner (up to 88% yield). Mechanistic studies are disclosed together with conformational analysis (X-ray crystallography and NMR) to validate *cis*-α,α-difluorocyclopropanes as isosteres of the 1,4-dicarbonyl moiety. Given the importance of this unit in biology and the foundational $n_o \rightarrow \pi^*$ interactions that manifest themselves in this conformation (e.g., collagen), it is envisaged that the title motif will find application in focused molecular design.



KEYWORDS: *cyclopropanes, fluorination, hypervalent iodine, isosteres, stereoelectronic effects*

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The emergent success of cyclopropanes in advancing lead drug candidates to the clinic is a compelling incentive to further explore this area of chemical space.[1] First validated as a pharmacophore over 50 years ago,[2] the inclusion of this carbocycle in marketed pharmaceuticals continues to follow a steep trajectory.[3] Contracted C(sp^3)−H bonds and deviation from an idealized tetrahedral geometry reveal a structural dichotomy that traverses the saturated/unsaturated functional group continuum, and this ultimately manifests itself in the venerable Walsh bonding description (Scheme 1A).[4,5] The rigidity of the carbocycle mitigates conformational isomerism, ensuring that substrate exit vectors are well-defined for bioisostere design,[6,7] and this provides a unique platform to tailor physicochemistry in the context of focused molecular design.[8] This is exemplified by the "*Janus-face*" (*syn*)-fluorinated cyclopropanes developed by O'Hagan and co-workers to modulate log *P* values[9] and the success of fluorinated cyclopropanes in medicinal chemistry and peptidomimetics in a broader sense.[10] Motivated by the popularity of cyclopropyl isosteres, coupled with the popularity of fluorine in contemporary medicinal chemistry to tailor ADMET properties,[11] attention was directed to an underexplored constitutional isomer series,[12] the α,α-difluorocyclopropanes (Scheme 1A, top). This motif has gained distinction in recent years due to its successful deployment in the development of next-generation antivirals,[13] which include voxilaprevir (Vosevi)[13a] and glecaprivir (Mavyret)[13b] for the treatment of chronic hepatitis C (Scheme 1, top), the newly approved lenacapivir (Sunlenca) for HIV/AIDS,[13c] and Bristol-Myers Squibb's potent inhibitors of Hepatits C NS3 protease.[13d]

Given their highly preorganized topology, relaxation of the internal C−C−C angle[14] and oxidative resilience of the *gem*-difluoromethylene group,[15] a strategy to access the *cis*-configured products was deemed to be particularly appealing: this would generate conformationally restricted isosteres of 1,4-dicarbonyl groups that are ubiquitous in biology (Scheme 1B).[16] Importantly, a structural analysis of the C(sp^2)=O → C(sp^3)F_2 replacement would provide a platform from which to interrogate the foundational $n_o \rightarrow \pi^*$ interaction[17] that underpins collagen structure[18] and manifests itself in maleate to fumarate isomerization.[19]

It was envisaged that the target scaffold might derive from a fluorinative ring contraction of aryl-substituted cyclobutene derivatives under the auspices of I(I)/I(III) catalysis (Scheme 1C). Confidence in this strategy stemmed from a seminal report by Hara and Yoneda describing the synthesis of α,α-

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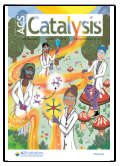

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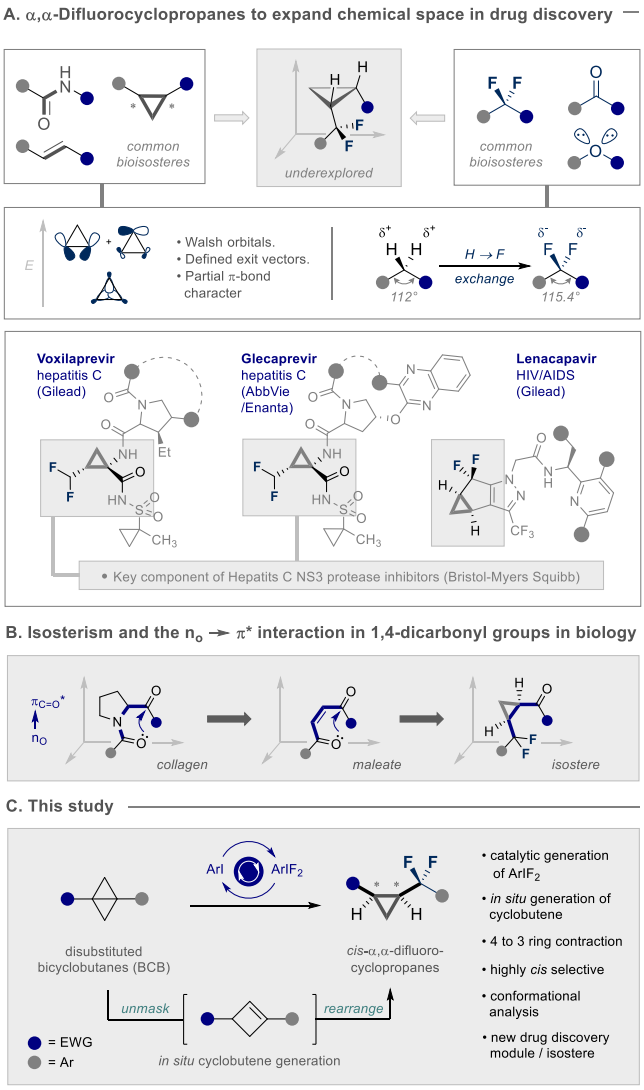
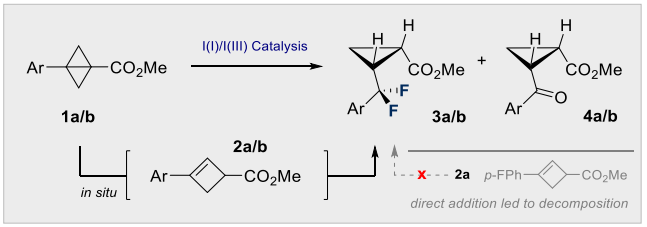
Scheme 1. (A) Evolution of *α,α*-Difluorocyclopropanes as New Drug Discovery Modules; (B) n → *π Interaction in Biology and Isostere Design.; (C) Catalysis-Based Strategy to Enable the Direct Conversion of Bicyclobutanes to *cis*-*α,α*-Difluorocyclopropanes Enabled by I(I)/I(III) Organocatalysis**



difluorocyclopentanes from cyclohexenes upon treatment with stoichiometric $ArIF_2$ species and HF sources.[20] Furthermore, easily accessible disubstituted bicyclobutanes (BCBs)[21] were explored as cyclobutene equivalents that would be unmasked under the Brønsted acidic reaction conditions.[22] If successful, the strategy would expand upon the existing routes[23,24] and introduce direct direct difluorocyclopropane formation to the ever-growing portfolio of transformations enabled by I(I)/I(III) catalysis.[25−28]

To validate the working hypothesis delineated in Scheme 1 (bottom), bicyclobutanes **1a,b** were exposed to oxidative fluorination conditions with *p*-TolI functioning as an inexpensive organocatalyst, Selectfluor as the terminal oxidant, amine·HF complexes as fluoride reservoirs, and DCE as the reaction medium (Table 1). It is pertinent to note that exposing cyclobutene **2a** directly to the reaction conditions led to rapid decomposition, rendering this approach impractical.[29] However, bicyclobutane reagents[30] proved to be compatible

Table 1. Reaction Optimization[a]



Entry[a]	Ar	Amine:HF Ratio (eq.)	Yield **3a/b** (%)[b] (*d.r., cis:trans*)	Yield **4a/b** (%)[b]
1	*p*-F (**1a**)	1:5 (~80)	18 (9.0:1)	19 (18.0:1)
2	*p*-F (**1a**)	1:7 (~80)	34 (2.8:1)	47 (14.7:1)
3	*p*-F (**1a**)	1:9 (~80)	7 (n.d.)	26 (5.5:1)
4	*p*-F (**1a**)	1:7 (~20)	60 (9.0:1)	25 (11.5:1)
5	*p*-F (**1a**)	1:7 (~10)	40 (20.0:1)	16 (15.0:1)
6[c]	*p*-F (**1a**)	1:7 (~20)	<5 (n.d.)	<5 (n.d.)
7[d]	*p*-F (**1a**)	1:7 (~20)	72 (17.0:1) *59 (>20:1)*[e]	18 (17.0:1)
8	*m*-CF_3 (**1b**)	1:7 (~20)	<5 (n.d.)	<5 (n.d.)
9[f]	*m*-CF_3 (**1b**)	1:7 (~80)	51 (13.2:1)	26 (n.d.)
10[f]	*m*-CF_3 (**1b**)	1:7 (~60)	55 (14.0:1)	17 (n.d.)
11[d,f]	*m*-CF_3 (**1b**)	1:7 (~60)	64 (8.1:1) *53 (>20:1)*[e]	19 (n.d.)
12[f]	*p*-F (**1a**)	1:7 (~80)	46 (1:3.6)	28 (4.6:1)

[a]Standard reaction conditions: **1** (0.20 mmol), *p*-TolI (20 mol %), Selectfluor (0.30 mmol), Py·HF (4−16 mmol), Et_3N (0.22−1.50 mmol), DCE (0.50 mL), 24 h, room temperature. [b]Yield and dr determined by ^{19}F NMR with *α,α,α*-trifluorotoluene as an internal standard. [c]*p*-TolI was excluded from the reaction mixture. [d]0.50 mmol scale. [e]Isolated yield. [f]Heated to 50 °C.

with the reaction conditions, and their propensity to rapidly isomerize to the corresponding cyclobutene under acidic conditions[22] rendered them ideally suited as masked reagents. When substrate **1a** (*p*-F-Ph) was exposed to 20 mol % of the catalyst in the presence of an amine·HF complex (ratio 1:5), it was possible to generate the desired product **3a** (dr 9.0:1 *cis:trans*, Table 1, entry 1), albeit with comparable quantities of the 1,4-diketone **4a** (dr 18.0:1 *cis:trans*). Variation in the amine:HF ratio revealed 1:7 to be optimal, and to suppress the competing hydrolysis (entries 1−4), the water content was reduced by lowering the stoichiometry to 20 equiv. (dr 9.0:1, Table 1, entry 4). Further reduction to 10 equiv. improved the dr but at the expense of catalysis efficiency (entry 5). Reactions performed in the absence of *p*-TolI were not productive, thereby supporting the involvement of an I(I)/I(III) cycle (entry 6). Moreover, increasing the scale to 0.5 mmol generated **3a** in 72% yield (dr 17.0:1) (Table 1, entry 7). In the case of the more electron deficient substrate **1b** (*m*-CF_3-Ph), direct translation of these optimized conditions was not productive (entry 8). However, elevated temperatures and amounts of amine·HF (entries 9−11) allowed the target *cis*-*α,α*-difluorocyclopropane to be formed in 64% yield (dr 8.1:1).

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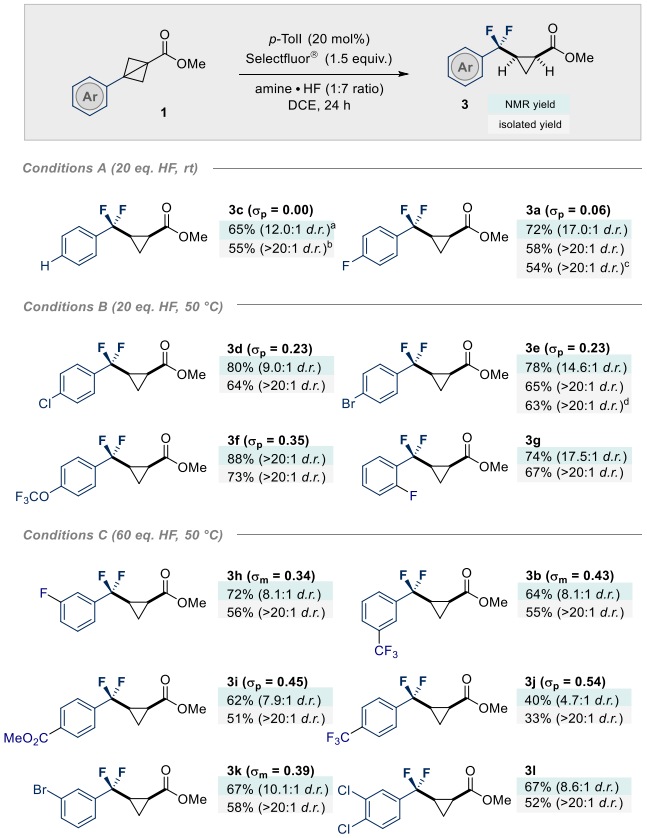
ACS Catal. 2022, 12, 14507−14516

In a reversal of circumstances, exposure of bicyclobutane **1a** (*p*-F-Ph) to these conditions resulted in an inversion of diastereoselectivty to favor the *trans* product (Table 1, entry 12). This comparative optimization process proved valuable in identifying variables that allow the product distribution and diastereoselectivity to be regulated.

To establish the scope and limitations of the transformation, a series of BCBs with electronically modulated aryl rings were investigated (Scheme 2). Guided by the findings summarized in Table 1, three sets of reaction conditions were employed, varying only the temperature and equivalents of amine·HF complex. As a convenient method to categorize this substrate set, the Hammett σ value of the aryl substituent was used. This revealed a clear trend linking the increased HF/temperature with the electronic nature of the ring (*vide infra*).

Scheme 2. Substrate Scope of the Difluorinative Cyclopropanation of BCBs by I(I)/I(III) Catalysis

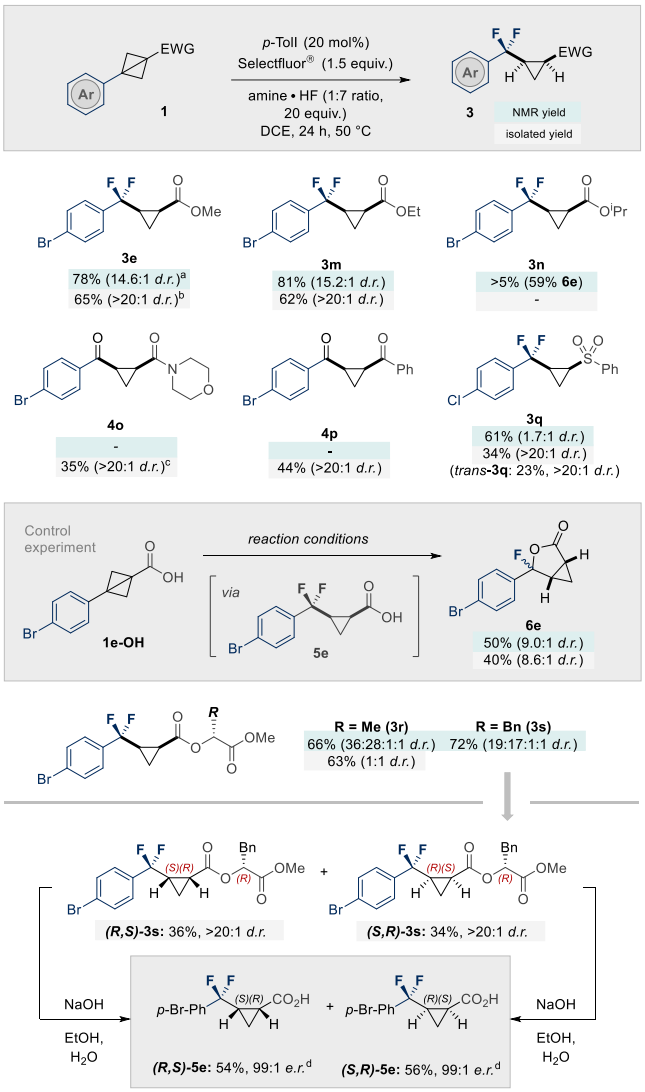


[a]Green box: combined yield of both *cis* and *trans* isomers and dr determined by ^{19}F NMR with α,α,α-trifluorotoluene as an internal standard. [b]Gray box: isolated yield following column chromatography, average of 2 runs, 0.50 mmol scale. [c]Reaction performed on a 4.00 mmol scale. [d]Reaction performed on a 3.75 mmol scale.

Whereas conditions A were sufficient to process the *p*-H and *p*-F substrates to products **3c** and **3a**, respectively, (up to 72%, 17:1 *cis*:*trans*), the conversion of BCBs **1d−g** to α,α-difluorocyclopropanes **3d−g** required an increased reaction temperature of 50 °C (up to 88%, >20:1 *cis*:*trans*). Although challenging, it was possible to induce the fluorinative skeletal rearrangement of highly electron deficient substrates, to generate products **3b**,**h−l** (up to 72%, up to 10.1:1 *cis*:*trans*) by increasing the amounts of HF. In all cases, product isolation proved facile by column chromatography, enabling the target *cis*-α,α-difluorocyclopropanes to be isolated in >20:1 dr.

To further expand the reaction scope, the impact of modifying the pendant methyl ester was investigated (Scheme 3, top). Whereas the methyl and ethyl derivatives were smoothly processed to **3e**,**m** (up to 81%, dr 15.2:1), the ^{i}Pr ester (**1n**) hydrolyzed under the reaction conditions, furnishing the bicyclic lactone **6e** as the major product (59%). As a control experiment, the carboxylic acid **1e-OH** and intermediate **5e** were independently exposed to the reaction conditions and this led to comparable lactone formation (please see the Supporting Information for full details). Intriguingly, replacement of the ester with an amide or a ketone led almost exclusively to 1,4-ketones **4o**,**p** (35% and 44% isolated yields, respectively). In both cases, traces of the

Scheme 3. Investigating the Impact of the Electron Withdrawing Group and the Generation of Optically Active Derivatives



[a]Green box: combined yield of both *cis* and *trans* isomers and dr determined by ^{19}F NMR with α,α,α-trifluorotoluene as an internal standard. [b]Gray box: isolated yield following column chromatography, average of 2 runs, 0.50 mmol scale. [c]0.20 mmol scale. [d]er determined by esterification to form **3e**, followed by analysis by HPLC.

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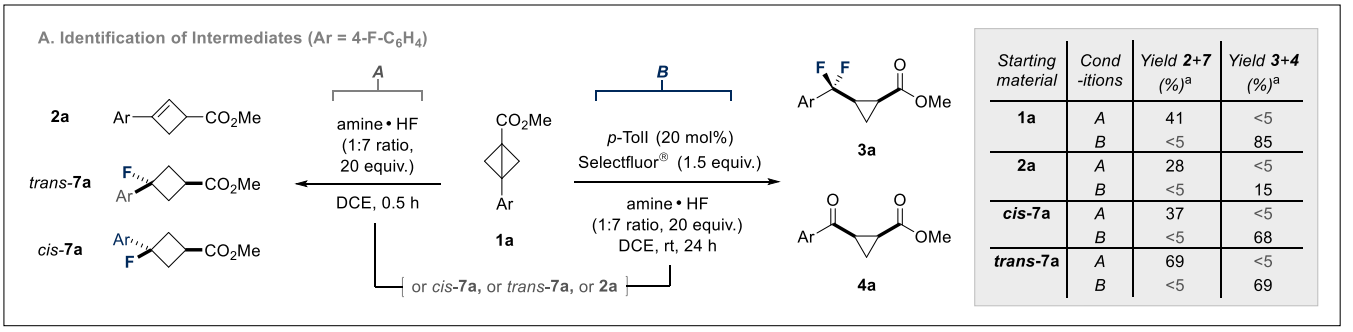
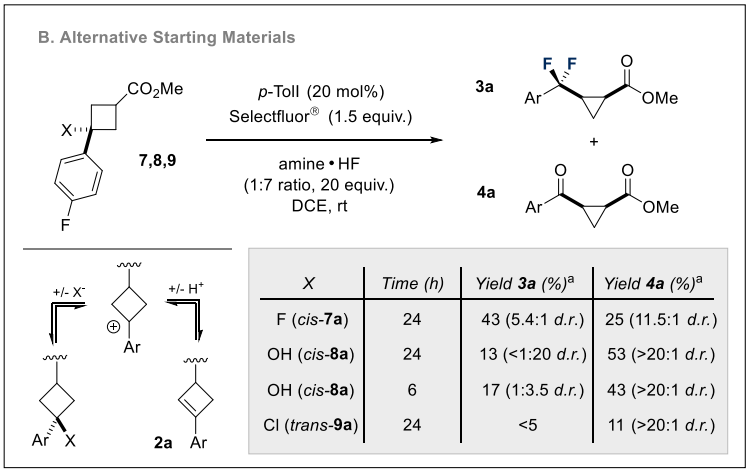
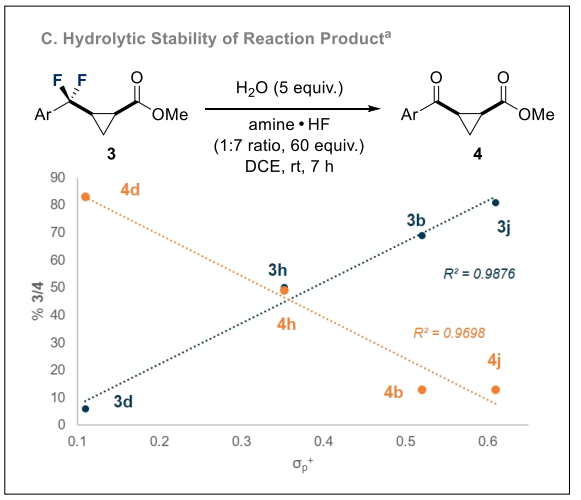
Scheme 4. (A) Identification of Cyclobutene 2 and Fluorinated Cyclobutane 7 as Intermediates within the Reaction Pathway; (B) Validating Alternative Cyclobutene Precursors; (C) Correlating Hydrolytic Stability with Hammett σ_p^+ Parameter; (D) Correlating Aryl Group Electronics with Diastereoselectivity; (E) Proposed Reaction Mechanism

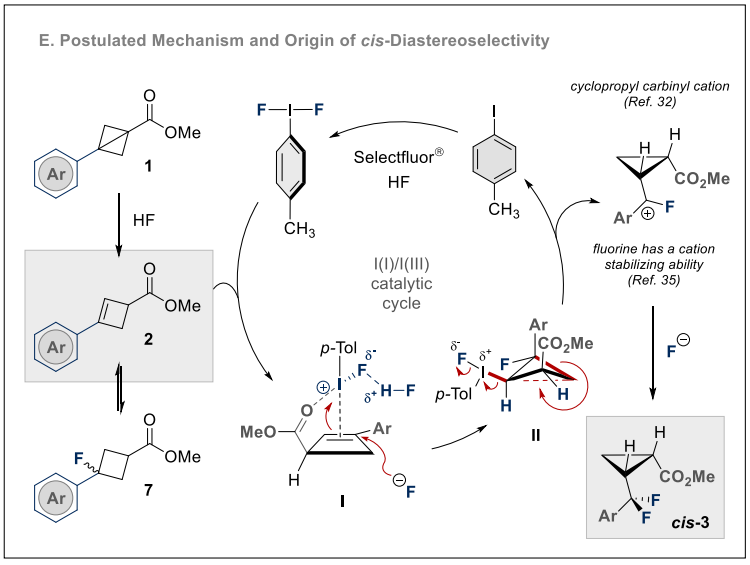


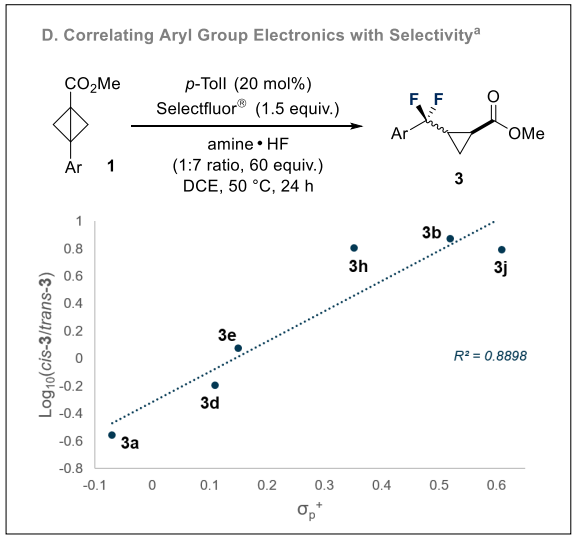
Starting material	Cond -itions	Yield 2+7 (%)[a]	Yield 3+4 (%)[a]
1a	*A*	41	<5
	B	<5	85
2a	*A*	28	<5
	B	<5	15
***cis*-7a**	*A*	37	<5
	B	<5	68
***trans*-7a**	*A*	69	<5
	B	<5	69



X	*Time (h)*	*Yield **3a** (%)*[a]	*Yield **4a** (%)*[a]
F (*cis*-**7a**)	24	43 (5.4:1 *d.r.*)	25 (11.5:1 *d.r.*)
OH (*cis*-**8a**)	24	13 (<1:20 *d.r.*)	53 (>20:1 *d.r.*)
OH (*cis*-**8a**)	6	17 (1:3.5 *d.r.*)	43 (>20:1 *d.r.*)
Cl (*trans*-**9a**)	24	<5	11 (>20:1 *d.r.*)







[a]Yields determined by ^{1}H and ^{19}F NMR analyses.

expected difluorocyclopropane were visible in the ^{19}F NMR spectra, demonstrating postreaction hydrolysis of the *geminal* CF_2 group. Gratifyingly, the process proved to be compatible with sulfones, enabling **3q** to be forged in 61% yield. To access enantiomerically pure materials via this strategy, the bicyclobutanes **1r,s** were prepared in which the methyl ester was replaced by an auxiliary. Both substrates were compatible with the reaction conditions, enabling **3r,s** to be prepared in synthetically useful yields (66% and 72%, respectively). In the case of cyclopropane **3s**, a facile separation/saponification sequence afforded both enantiomers of *cis*-**5e** (er 99:1 for both enantiomers).

To interrogate the mechanism, a series of control experiments were conducted (Scheme 4). As the reaction hinges on the *in situ* generation of cyclobutenes from bicyclobutanes in the presence of HF, this initial process was investigated. Exposure of bicyclobutane **1a** to amine·HF, in the absence of Selectfluor or the organocatalyst, generated cyclobutene **2a** and

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ACS Catal. 2022, 12, 14507−14516

a diastereomeric mixture of cyclobutane **7a** as determined by NMR analyses (Scheme 4A).

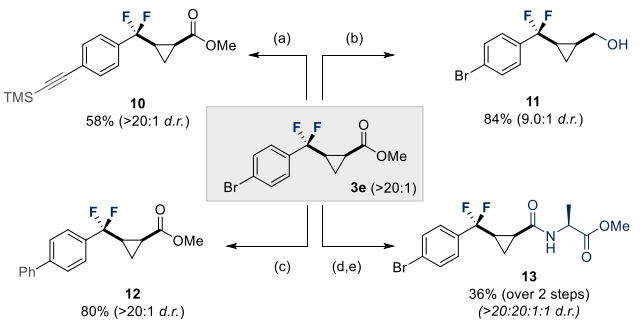
The isolation of these compounds and subsequent exposure to the amine·HF complex afforded similar mixtures, as judged by NMR analysis, which indicates a dynamic equilibrium. The product distribution shifts to the generation of **3a** and **4a** upon addition of the catalyst *p*-TolI and Selectfluor (conditions A versus conditions B; see table in the inset).

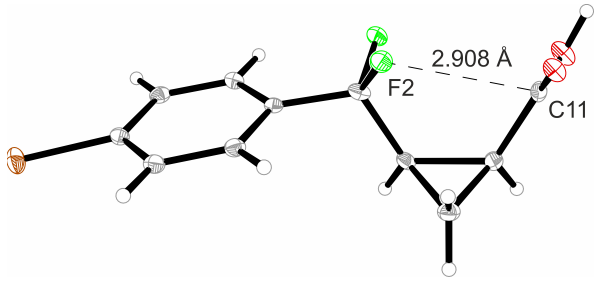
To further support the involvement of cyclobutane **7a**, additional cyclobutane derivatives were validated as cyclobutene sources (Scheme 4B). It is interesting to note that exposure of *cis*-**8a** (X = OH) to the standard reaction conditions did indeed generate the ring-contracted product (**3a**) in 13% yield, but substantial hydrolysis was observed even when employing reduced reaction times. This is likely due to the residual water that is generated upon elimination to generate the cyclobutene **2a**. This observation and the degradation of the chlorinated derivative **9a** under the reaction conditions underscore the value of bicyclobutanes for this transformation. To establish the electronic influence of the aryl substituent on the relative stabilities of the product *cis*-α,α-difluorocyclopropanes, representative examples were exposed to modified conditions in the presence of water (5 equiv) and absence of catalyst. A plot of the starting material and product after 7 h against the Hammett σ_p^+ parameter confirmed a linear dependence (Scheme 4C). This demonstrates that, while diketone **4a** is stable under the reaction conditions (see the Supporting Information for full details), difluorocyclopropanes (**3**) slowly hydrolyze over time. It is pertinent to note that HF has been leveraged to enable the Brønsted acid activation of benzylic fluorides.[31] In this study, the contribution of the cyclopropyl Walsh orbitals cannot be discounted, given their contribution to the stability of the cyclopropinyl carbinyl cation.[4,32] This trend was mirrored in the plot of selectivity ($\log_{10}$[*cis*-**3**/*trans*-**3**]) versus σ_p^+ (Scheme 4D) and demonstrated that an erosion of diastereoselectivity occurred at higher temperatures and HF equivalents.

Collectively, these data allow a mechanistic scenario to be postulated that is contingent on *in situ* generation of **2**; a species that exists in dynamic equilibrium with the HF adduct **7** (Scheme 4E). Simultaneously, *p*-TolI$^{III}F_2$ is generated via Selectfluor-mediated oxidation of *p*-TolI in the presence of HF.[33] The dominant formation of the *cis* isomer suggests that the ester functionality may play a role in coordinating the iodine(III) species to the same face of the alkene. This coordinating role of the ester is well-established in the I(I)/I(III)-catalyzed fluorohydration of alkynes (the fluoro-Kucherov reaction)[34] and supported by the observation that $CO_2Me \rightarrow SO_2Ph$ exchange erodes stereoselectivity (**3q**; Scheme 3). Fluorination to generate the cyclobutane **II** would enable a stereospecific ring contraction to liberate the catalyst and generate a *cis*-configured cyclopropyl carbinyl cation. In addition to being benzylic, this cation is stabilized by the cyclopropyl Walsh orbitals and the proximal fluorine atom.[35] The stereochemical course of this reaction is complementary to a recent study by Aggarwal and co-workers on *trans*-selective cyclopropane formation enabled by treating bicyclo[1.1.0]-butyl pinacol boronic esters with sterically hindered nucleophiles.[30h]

To demonstrate the synthetic utility of the difluorocyclopropyl motif, derivative **3e** was subjected to standard Sonogashira and Suzuki cross-coupling conditions to afford the products **10** and **12**, respectively. Modification of the ester motif was also facile, as was demonstrated by the formation of alcohol **11** and amide **13** (Scheme 5). To facilitate conforma-

Scheme 5. (Top) Derivatization of Substrate 3e; (Bottom) X-ray Crystallographic Analysis of 5k and Preparation of a Fluorinated Analogue of the API, UPF-648[a]





[a]Reaction conditions: (a) TMS-acetylene (1.5 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol %), CuI (20 mol %), $^iPr_2NH$, 80 °C, 3 h; (b) $LiAlH_4$ (2.2 equiv), THF, 0 °C, 1 h; (c) $PhB(OH)_2$ (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), Cs_2CO_3 (2.0 equiv), H_2O, 1,4-dioxane, 80 °C, 3 h; (d) NaOH (6.0 equiv), MeOH, rt, 5 h; (e) H-Ala-OMe·HCl (1.1 equiv), EDC (1.1 equiv), DMAP (5 mol %), DCM, rt, 16 h. Yields and dr values refer to isolated products.

tional analysis of the *cis*-α,α-difluorocyclopropane moiety by single-crystal diffraction, compounds **3k,l** were saponified to generate the acids **5k,l**, respectively (Scheme 5, bottom).[36] Compound **5l** is a novel isostere of UPF-648, which is a widely studied kynurenine 3-monooxygenase (KMO) inhibitor that has a range of clinical applications in translational neurology.[37,38] In the case of **5k**, the X-ray analysis reveals a C−C−C bond angle of 114° and a F−C−F angle of 104°: this further demonstrates the distorting impact of fluorination on an idealized tetrahedral geometry. In addition, the proximity of one fluorine atom to the carbonyl group (2.99 Å) is reminiscent of the preferential conformation adopted by 1,4-carbonyl groups in collagen ($n_O \rightarrow \pi_{C=O}^*$).

To further explore α,α-difluorocyclopropanes as structural mimics, the interatomic distances of crystalline samples of **5e,k** and **3s** were compared[39] with the 1,4-diketone **4e-OH** and two known compounds in which $n_o \rightarrow \pi^*$ interactions are operational (**14** and **15**) (Scheme 6). In the case of **5e,k**

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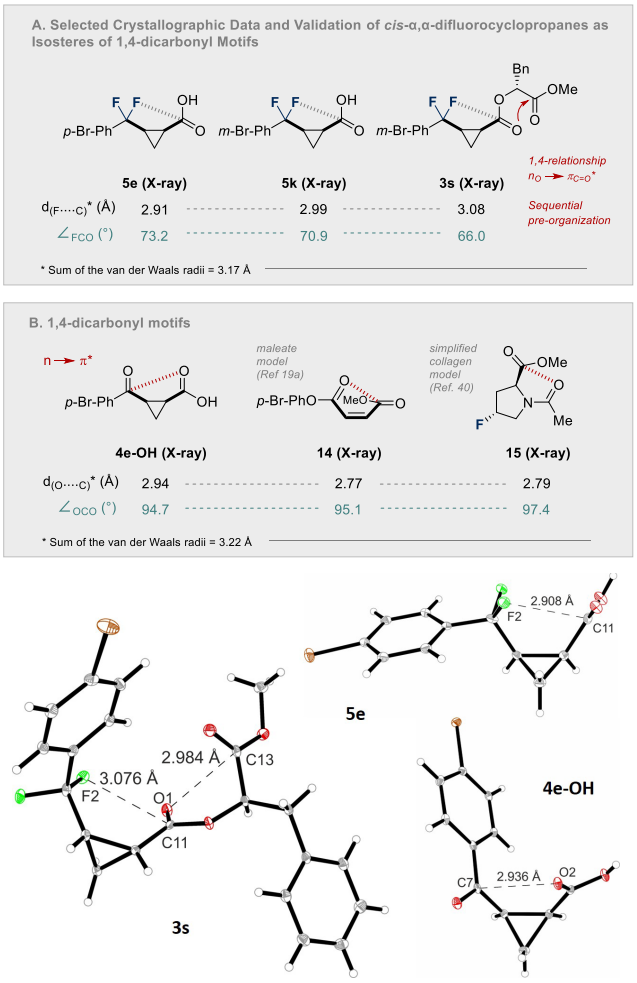
Scheme 6. Selected X-ray Structural Data and Validation of *cis*-α,α-Difluorocyclopropanes 3s and 5s as 1,4-Dicarbonyl Bioisosteres (4e-OH)



and **3s**, the distances between one of the F atoms and the C(sp^2) center were found to be less than the sum of the van der Waals radii. This was also noted for the ketone derived from **5e** (**4e-OH**). These values (2.91−3.08 Å) are in good agreement with the structural analyses of a model maleate (**14**, 2.77 Å)[19a] and Raines' simplified collagen model **15** (2.79 Å).[40] This study contributes to the current interest in C−F···C═O(amide) interactions, as is exemplified by a recent crystallographic and spectroscopic study by Lectka and co-workers.[41]

Clinical success is an effective driver for the conception and development of synthetic methodology. Motivated by the emergence of α,α-difluorocyclopropanes on the drug discovery landscape, and the conspicuous dearth of methods to facilitate their construction, a fluorinated skeletal rearrangement of disubstituted bicyclobutanes (BCBs) has been developed that leverages I(I)/I(III) catalysis. The Brønsted acidity of the HF serves to unmask the BCB and reveal a cyclobutene: this then engages with *in situ* generated *p*-TolIF$_2$. A fluorination/stereospecific ring contraction/fluorination sequence then ensues to liberate the *cis* product with high levels of selectivity. It is postulated that this unprecedented 4 → 3 rearrangement proceeds via a cation in which all three substituents confer a stabilizing effect. The route facilitates access to structural isosteres of 1,4-dicarbonyl compounds, and an X-ray analysis indicates that similar conformational behavior is observed in the solid state. In addition to expanding the pharmacophore discovery arsenal, this transformation enables the generation of fluorinated isosteres and peptidomimetics. It is envisaged that this study will stimulate interest in the activation of strained-ring systems by hypervalent iodine catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c04511.

Experimental procedures, product characterization, X-ray data, and NMR spectra (PDF)

CheckCIF and PLATON report (PDF)

Crystallographic data (CIF)

■ AUTHOR INFORMATION

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■ ABBREVIATIONS

BCBs,bicyclobutanes; HPLC,high-performance liquid chromatography; NMR,nuclear magnetic resonance

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