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Communication

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Enantioselective, Catalytic Fluorolactonization Reactions with a Nucleophilic Fluoride Source

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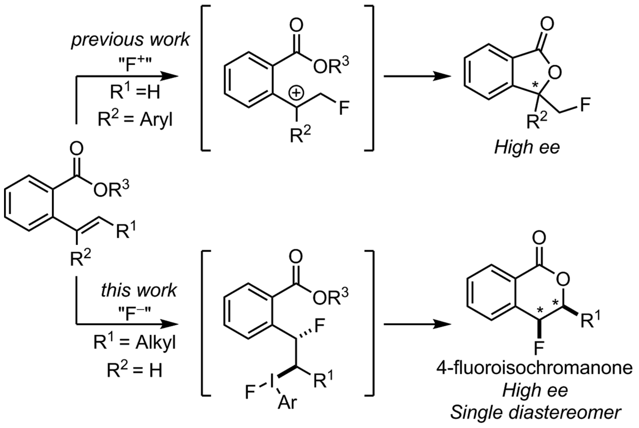
Supporting Information

ABSTRACT: The enantioselective synthesis of 4-fluoroisochromanones via chiral aryl iodide-catalyzed fluorolactonization is reported. This methodology uses HF-pyridine as a nucleophilic fluoride source with a peracid stoichiometric oxidant and provides access to lactones containing fluorine-bearing stereogenic centers in high enantio- and diastereoselectivity. The regioselectivity observed in these lactonization reactions is complementary to that obtained with established asymmetric electrophilic fluorination protocols.

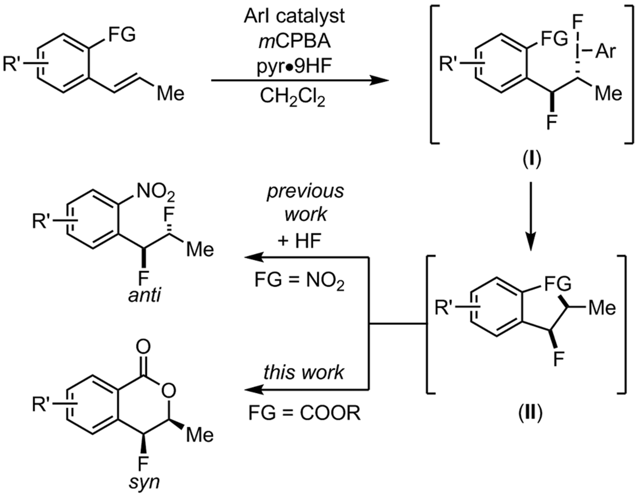
The stereocontrolled construction of C−F bonds represents a frontier endeavor in synthetic chemistry, motivated in large part by the important ways that fluorine incorporation is known to modulate the physical and biological properties of organic molecules.[1] Electrophilic fluorine sources ("F^+") such as Selectfluor, *N*-fluoropyridinium salts, and *N*-fluorobenzenesulfonimide (NFSI) have been used extensively in the enantiocontrolled generation of fluorine-bearing stereogenic centers,[2] most often via the intermediacy of enolate equivalents to produce α-fluorocarbonyl compounds.[2a,3] Fluorofunctionalization of alkenes using F^+ sources is another powerful approach to the enantioselective synthesis of fluorine-containing chiral compounds that allows for the synthesis of highly functionalized products from simple olefin-containing starting materials.[4,5] In reported efforts directed toward enantioselective fluorolactonization reactions, electrophilic fluorinating reagents have been shown to afford γ-butyrolactone products with exocyclic fluoromethyl substituents in moderate-to-high enantioselectivity (Scheme 1, top).[6] We hypothesized that hypervalent iodine catalysis of a nucleophilic fluorination pathway ("F^-") could provide a complementary approach to regioisomeric fluorolactone products containing a C−F stereogenic center (Scheme 1, bottom), in a manner analogous to that observed in recently described enantioselective acetoxylactonization reactions.[7] Herein, we report the development of an enantioselective, catalytic fluorolactonization reaction for the preparation of 4-fluoroisochromanones in high enantio- and diastereoselectivity.

We reported recently a protocol for the aryl iodide-catalyzed diastereoselective 1,2-difluorination of both terminal and internal alkenes[8,9] using HF-pyridine (pyr·9HF) as a nucleophilic fluorine source and *meta*-chloroperbenzoic acid (*m*CPBA) as a stoichiometric oxidant. These conditions were first developed by Shibata and co-workers in the context of catalytic aminofluorination reactions.[10] Alkenes bearing proximal weakly Lewis basic groups were shown to undergo net anti difluorination, while substrates lacking such functionality afforded *syn*-difluoride products. We proposed that properly positioned weakly nucleophilic groups (e.g., the *o*-NO_2 group in Scheme 2) can displace the aryl iodide from intermediate **I** to

Scheme 1. Enantioselective Fluorolactonizations with Electrophilic and Nucleophilic Fluorinating Agents



Scheme 2. Achimeric Assistance in 1,2-Difluorination of Styrenes with ArI-Catalysts and an Analogous Fluorolactonization Pathway



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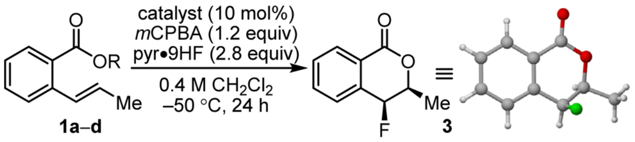
form an unstable bridged intermediate **II**. Invertive displacement of the neighboring group by fluoride led to the *anti*-diastereomeric outcome. The propensity for such anchimeric assistance in these reactions suggested that styrenes containing other nucleophilic neighboring groups such as an *ortho*-carboxylic acid or ester might undergo fluorolactonization reactions.[11] As outlined in the proposed catalytic pathway in Scheme 2, nucleophilic displacement of the aryliodo group in intermediate **I** with a carboxylate equivalent would lead to formation of 4-fluoroisochromanone products. This approach would produce a fluorine-bearing stereogenic center with a *syn* relationship between the two newly formed bonds,[12] a stereochemical outcome distinct from prototypical bromo- and iodolactonizations.[13] Furthermore, as members of the polyketide-derived 4-oxyisochromanone class of natural products are known to possess interesting biological activity,[14] we were motivated by the possibility that an efficient, stereocontrolled route to 4-fluoro analogs may be of interest for biological or pharmacological applications.

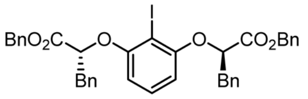
Methyl benzoate derivative **1a** was evaluated as a model substrate for the proposed fluorolactonization reaction. Various classes of chiral aryl iodides were examined as potential catalysts, including chiral resorcinol derivatives such as **2a**–**2d**,[7,15] which have found application previously in a variety of enantioselective alkene oxidation reactions.[16] In the presence of catalysts **2a**–**d**, *m*CPBA as the oxidant, and pyr·9HF as the fluorine source and acid promoter, **1a** was observed to undergo cyclization to fluoroisochromanone **3** as a single observable diastereomer (Table 1).[17] The syn relative configuration was determined via X-ray crystallographic analysis, consistent with the reaction pathway outlined in Scheme 2.[18]

Table 1. Optimization of the Fluorolactonization Reaction[a]

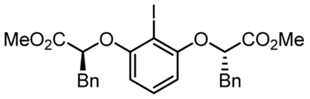


entry	substrate	R	catalyst	ee (%)[b]	yield (%)[c]
1	**1a**	Me	**2a**	87	72
2	**1a**	Me	**2b**	−87	50
3	**1a**	Me	**2c**	−94	68
4	**1a**	**Me**	**2d**	**95**	**86 (68)**[d]
5	**1b**	*i*Pr	**2d**	95	72
6	**1c**	Bn	**2d**	87	42
7	**1d**	H	**2d**	89	95 (70)[d]

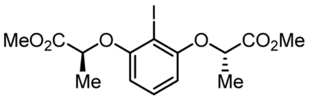
[a] Conditions: substrate (0.10 mmol), catalyst (10 mol %), *m*CPBA (0.12 mmol), pyr·9HF (2.5 mmol HF) in CH_2Cl_2 (0.25 mL) cooled to −50 °C, 24 h. [b] Enantioselectivities were determined by GC or HPLC analysis with commercial chiral columns. [c] Yields were measured by GC and are based on an internal standard. [d] Isolated yield on a 1 mmol scale.



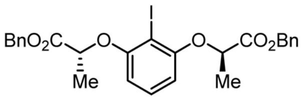
2a



2b



2c



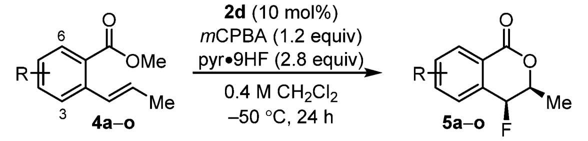
2d

Catalysts **2c** and **2d** were found to impart significantly higher enantioselectivities than the corresponding benzyl-substituted analogs **2a**–**b** (entries 1–4). This observation stands in contrast to results obtained in the migratory geminal difluorination of *β*-substituted styrenes reported recently by our group,[19] where that trend was reversed and the polarizable benzylic groups in para-substituted analogs of **2a**–**b** were shown to play a critical role in enhancing ee. It is evident that subtle yet fundamentally different factors are responsible for enantioinduction in these closely related reactions. Variation of the ester group of the catalyst had very little effect on the enantioselectivity of the fluorolactonization reaction, but measurably improved yields were obtained with benzyl ester catalysts **2a** and **2d** relative to their methyl ester counterparts. On the basis of these results, **2d** was selected as the optimal catalyst for further study.

Variation of the carboxylate equivalent (**1a**–**c**) or use of the free carboxylic acid **1d** resulted in formation of fluorolactonization product **3**, albeit with discernible changes in ee and yield (entries 4–7) and with methyl ester **1a** affording the best results.

The effect of arene substitution in the enantioselective fluorolactonization reaction catalyzed by **2d** is illustrated in Table 2. Alkyl, halide, or trifluoromethoxy substitution at the 6-, 5-, and 4-positions of **1** is generally well tolerated, with the fluorolactone products obtained in 80–96% ee (entries 1–3, 5–10). However, substrates bearing more electron-deficient trifluoromethyl or carbomethoxy groups underwent reaction in reduced yields and enantioselectivities (entries 12–15). In all cases, the fluorolactone product was obtained as a single diastereomer.[20]

Table 2. Fluorolactonization of Aryl-Substituted Substrates[a]

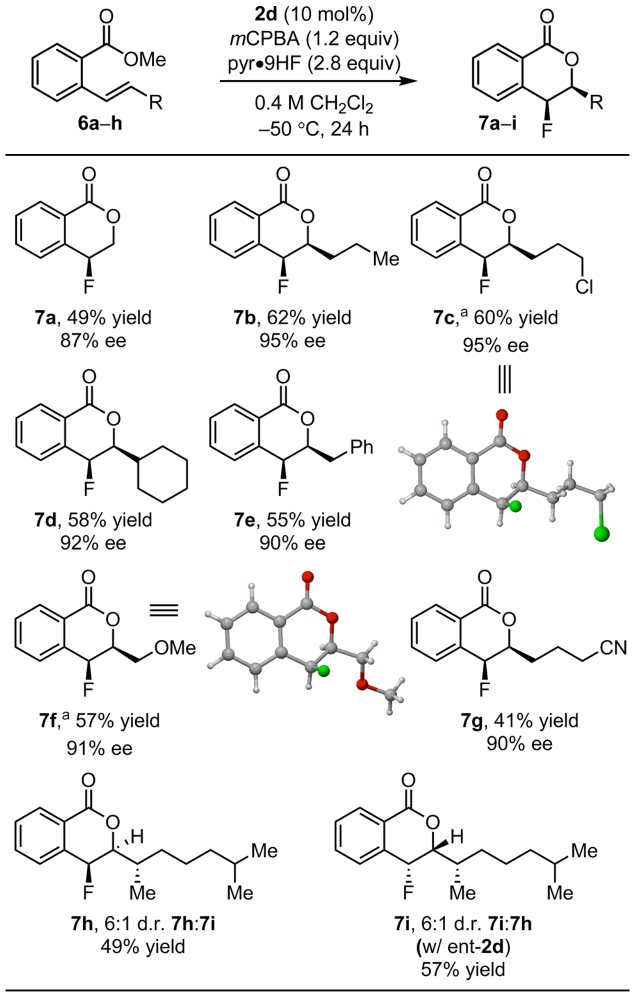


entry	4	R	5	ee (%)[b]	yield (%)[c]
1	**4a**	6-Me	**5a**	96	53
2	**4b**	5-Me	**5b**	93	50
3	**4c**	4-Me	**5c**	94	64
4	**4d**	3-Me	**5d**	66	52
5	**4e**	5-OCF_3	**5e**	89	55
6	**4f**	5-Br	**5f**	86	48
7	**4g**	5-Cl	**5g**	86	60
8	**4h**	6-F	**5h**	83	67
9	**4i**	5-F	**5i**	93	57
10	**4j**	4-F	**5j**	80	61
11	**4k**	3-F	**5k**	30	49
12	**4l**	5-CF_3	**5l**	73	60
13	**4m**	4-CF_3	**5m**	76	44
14	**4n**	5-CO_2Me	**5n**	70	35
15	**4o**	4-CO_2Me	**5o**	58	51

[a] Conditions: substrate (1 mmol), catalyst (10 mol %), *m*CPBA (1.2 mmol), pyr·9HF (25 mmol HF) in CH_2Cl_2 (2.5 mL) cooled to −50 °C, 24 h. [b] Enantioselectivities were determined by HPLC or GC analysis with commercial chiral columns. [c] Isolated yields are reported.

The new fluorolactonization reaction was also extended successfully to a variety of *β*-substituted styrene derivatives (Table 3). In general, substituents of varying size and

Table 3. Fluorolactonization of Substituted Alkene Substrates[a]



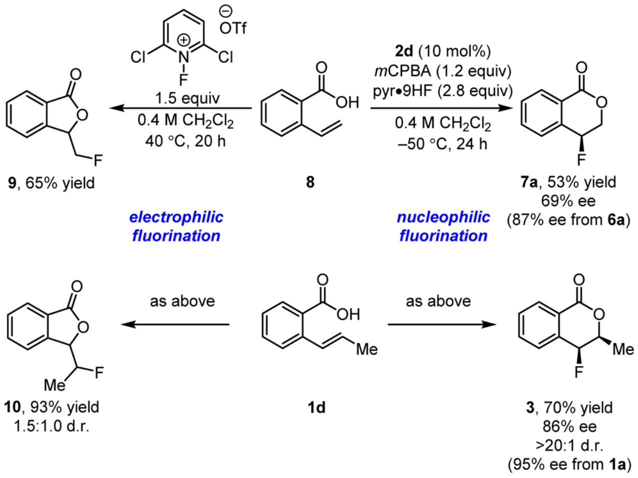
[a]Conditions: substrate (1 mmol), catalyst (10 mol %), mCPBA (1.2 mmol), pyr·9HF (25 mmol HF) in CH_2Cl_2 (2.5 mL) cooled to −50 °C, 24 h. Enantioselectivities were determined by HPLC or GC analysis with commercial chiral columns. Isolated yields are reported. [b]Absolute configuration was determined by X-ray crystallographic analysis; all other products are assigned by analogy.

functionality have little impact on reaction enantioselectivity. The Lewis basic ether and cyano substituents in **7f** and **7g** are observed not to alter the relative stereochemical outcome of the fluorolactonization reaction, despite the propensity toward anchimeric assistance pathways in these reactions as noted above. Catalyst control over stereoselectivity of the reaction was observed with **7h** and **7i**, with complementary diastereoselectivity obtained using **2d** or ent-**2d**.

As illustrated in Scheme 3, the regioselectivity observed in the fluorolactonization reactions with a nucleophilic fluoride source is opposite to that obtained with electrophilic reagents.[21] Furthermore, as demonstrated with **1d**, electrophilic fluorolactonizations of disubstituted styrenes are observed to be poorly diastereoselective. The successful introduction of C−F stereocenters in a highly stereocontrolled manner is thus a significant feature of the new catalytic protocol.

In conclusion, the enantio- and diastereoselective, catalytic synthesis of 4-fluoroisochromanones can be accomplished with HF-pyridine as a nucleophilic fluoride source. Readily accessible chiral aryl iodides catalyze fluorolactonization with generation of C−F stereogenic centers from simple styrene precursors. Ongoing efforts are directed toward exploring the scope of fluorofunctionalization reactions induced by hypervalent iodine(III) catalysis, as well as elucidating the basis of the subtle catalyst structural properties that control the enantioselectivity in these reactions.

Scheme 3. Comparison of the Reactivity of Electrophilic and Nucleophilic Fluorinating Reagents



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09499.

Experimental procedures and characterization data for new compounds (PDF)
Crystallographic data (CIF, CIF, CIF)

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Notes

The authors declare no competing financial interest.

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(17) Reducing the number of equivalents of pyr·9HF resulted in lower yields of **3**, albeit with consistent enantioselectivities (1.1 equiv of pyr·9HF: 93% ee and 28% yield; 5.6 equiv of pyr·9HF: 93% ee and 83% yield). Reactions conducted at −20 °C led to the generation of **3** in 86% ee and 71% yield (yields determined by GC analysis).

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(21) For an additional example of a racemic, regioselective fluorocyclization reaction with hypervalent iodine reagents, see: Geary, G. C.; Hope, E. G.; Stuart, A. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 14911.