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## Catalytic Diastereo- and Enantioselective Fluoroamination of Alkenes

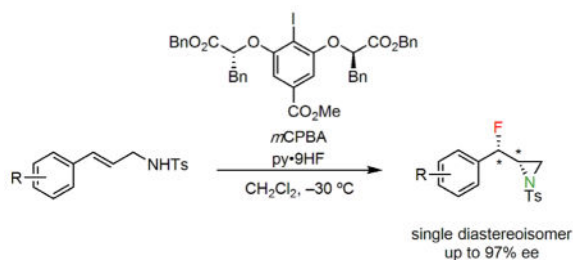
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### Abstract

The stereoselective synthesis of *syn*- $\beta$ -fluoroaziridine building blocks via chiral aryl iodide-catalyzed fluorination of allylic amines is reported. The method employs HF-pyridine as a nucleophilic fluoride source together with *m*CPBA as a stoichiometric oxidant, and affords access to arylolefinamine derivatives featuring fluorine-containing stereocenters in high diastereo- and enantioselectivity. Catalyst-controlled diastereoselectivity in the fluorination of chiral allylic amines enabled the preparation of highly enantioenriched 1,3-difluoro-2-amines bearing three contiguous stereocenters. The enantioselective catalytic method was applied successfully to other classes of multi-functional alkene substrates to afford *anti*- $\beta$ -fluoropyrrolidines, as well as a variety of 1,2-oxyfluorinated products.

### Graphical Abstract



The unique ability of fluorine substituents to modulate the physical and biological properties of organic molecules<sup>1</sup> has inspired widespread efforts to develop methods for the selective construction of C–F bonds.<sup>2</sup> Given the crucial importance of basic nitrogen groups in

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#### Notes

The authors declare no competing financial interest.

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 **3b** (CIF)

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

Crystallographic data for *syn*-**6a** (CIF)

Crystallographic data for *anti*-**6a** (CIF)

Crystallographic data for **8** (CIF)

Crystallographic data for **12** (CIF)

Crystallographic data for **16** (CIF)

bioactive compounds, the stereoselective construction of fluoroamines has emerged as a particularly promising direction in organofluorine chemistry. For example, introduction of a stereodefined  $\beta$ -fluorine in the piperidine ring of MK-0731 was found to attenuate the basicity of the amine while reducing cellular efflux by *P*-glycoprotein and improving metabolic stability (Figure 1a).<sup>3</sup> Strategic incorporation of fluorine-bearing stereocenters into  $\beta$ -peptide structures has been demonstrated to induce powerful and predictable conformational effects (Figure 1b).<sup>4</sup>

As a result of the strong interest in accessing compounds possessing the vicinal fluoroamine substructure, a variety of approaches have been devised for their synthesis. Thanks to the availability of effective organocatalytic methods for  $\alpha$ -fluorination of carbonyl compounds,<sup>5</sup> one-pot  $\alpha$ -fluorination/reductive amination protocols are possible for accessing enantioenriched vicinal fluoroamines.<sup>6</sup> An alternative metal-free approach involves the fluoroamination of alkenes promoted by hypervalent iodine compounds.<sup>7</sup> For example, a method to generate fluorinated piperidines enantioselectively using stoichiometric iodine(III) reagents has been reported by Nevado and coworkers.<sup>7a</sup> Other notable approaches include the use of anionic phase-transfer<sup>8</sup> and Lewis basic<sup>9</sup> catalysts together with Selectfluor in the stereoselective fluorination of enamides and indoles, respectively. Transition-metal catalysis has also been applied to fluoroamination reactions.<sup>10</sup> In a particularly significant advance, an enantio- and regioselective iron(II)-catalyzed intermolecular fluoroamination of alkenes was described recently by Xu *et al.*<sup>10d</sup> These examples highlight the significant progress made toward accessing  $\beta$ -fluoroamines, as well as the continuing need for general catalytic methods for their stereocontrolled synthesis.

We and others have developed a variety of oxidative fluorofunctionalization reactions of alkenes based on aryl iodine(I–III) catalysis.<sup>11</sup> In the presence of even weakly nucleophilic groups proximal to the alkene, the C(sp<sup>3</sup>)–I(III) intermediate that is proposed to be generated after initial fluoride addition (e.g., **A**, Figure 1b) can be intercepted either temporarily or permanently to give rise to a variety of different pathways and products. This principle has been exploited with *C*<sub>2</sub>-symmetric aryl iodide catalysts in the highly enantioselective syntheses of *anti*-1,2-difluorinated cinnamamides,<sup>11g</sup> chiral  $\beta$ ,  $\beta$ -difluoroarylethanes<sup>11m</sup> and 4-fluoroisochromanones.<sup>11j</sup> We hypothesized that enantioenriched *syn*- $\beta$ -fluoroaziridines might be generated in an analogous manner by trapping the key ArI(III) intermediate **A** with appropriately positioned nitrogen nucleophiles (Figure 1b). This methodology would provide access to versatile precursors to  $\beta$ -fluoroamines, as the strained aziridine may be engaged in regioselective ring opening with a wide variety of nucleophiles.<sup>12</sup> We describe here the successful development and application of this principle to the highly stereoselective fluoroaziridination of cinnamyl amine derivatives, and elaboration of the products to a variety of novel fluorinated phenethylamine derivatives.<sup>13</sup>

Cinnamyl tosylamide derivative **2a** was evaluated as a model substrate in the proposed fluoroaziridination reaction. Evaluation of a variety of reagent combinations and experimental protocols led to the identification of optimal conditions similar to those reported in our previously described alkene 1,1-difluorination and fluorolactonization reactions (see Supplementary Information).<sup>11j,m</sup> Thus, in the presence of chiral aryl iodide catalysts, *m*CPBA as a stoichiometric oxidant and HF-pyridine as a nucleophilic fluoride

source and acid promoter, **2a** was observed to undergo selective oxidation to generate the corresponding  $\beta$ -fluoroaziridine product (**3a**) as a single detectable diastereoisomer. Catalyst **1a** proved superior with respect to both yield and enantioselectivity (94% ee) among all chiral aryl iodides that were evaluated (see Supplementary Information). Judicious optimization of HF loading (15 equiv. HF) and temperature ( $-30\text{ }^{\circ}\text{C}$ ) proved crucial for obtaining the desired aziridine product in high yield; at higher HF loadings and/or temperatures, the 1,3-difluoride product resulting from opening of the putative aziridinium ion intermediate was obtained. Sulfonamides proved to be uniquely effective in the fluoroaziridination reaction, as carbonyl-based protecting groups (amides, carbamates) led to the formation of 1,2-oxy-fluorinated products instead. Variation of the sulfonyl protecting group had no effect on the enantioselectivity of the reaction, but the toluenesulfonamides generally afforded the highest yields (see Supplementary Information) and were therefore selected for investigation of substrate scope.

A variety of electron-deficient cinnamyl tosylamides were found to undergo clean conversion to the corresponding  $\beta$ -fluoroaziridine products (**3a–m**) as single diastereoisomers and with high enantioselectivity (Figure 2a). The *syn* relative stereochemistry of the products was established by X-ray crystallographic analysis of **3b**, and is consistent with the intermediacy of a fluoroiodinated adduct (**A**, Figure 1b). Substrates bearing electron-donating substituents were poor substrates for the fluoroaziridination reaction (see below), but it proved possible to generate products bearing *O*-aryl substituents by employing triflate-protected derivatives (**3e** and **3h**). This result bears significance given the prevalence of 3- and 4-hydroxy-substitution patterns in biologically important aryylethylamines. Trisubstituted cinnamyl tosylamides proved less effective as substrates, as reflected by the tertiary fluoride **3n** being isolated in moderate yield and enantioselectivity.

Substrates lacking electron-withdrawing substituents were found to undergo a phenonium ion rearrangement pathway to afford 1,1-difluoromethylated products in competition with the desired fluoroaziridination reaction (Figure 2b).<sup>11m</sup> For example, nearly exclusive formation of the 1,1-difluoromethylated product was observed in the case of the unsubstituted phenyl substrate ( $R = H$ ). Indeed, a good correlation between the electronic properties of the substituents ( $\sigma^+$ ) and the selectivity for the desired product was observed.<sup>14</sup>

The  $\beta$ -fluoroaziridine product **3c** was selected as a model for synthetic elaboration studies. We found that ring opening with different classes of nucleophiles could be effected smoothly to yield a variety of  $\alpha$ -fluoroarylethyl amine products in excellent yields and without compromise of enantiomeric integrity (Figure 3a). Fluoride opening could be accomplished by simply subjecting **3c** to HF-pyridine at room temperature to yield the corresponding 1,3-difluoride (**4a**). Treatment of **3c** with other strong Brønsted acids such as hydrobromic and trifluoroacetic acid also resulted in clean ring opening, affording **4b** and **4c** respectively. In contrast, strongly basic nucleophiles were found to promote elimination pathways predominantly. In accordance with literature precedent, regioselective ring opening of **3c** with trimethylsilyl azide and trimethylsilylcyanide in the presence of catalytic base was observed to yield **4d** and **4e** respectively,<sup>15</sup> while **4f** was obtained in quantitative yield by heating **3c** with thiophenol in dimethyl sulfoxide.<sup>16</sup> While removal of tosyl protecting

groups is generally challenging, preparation, elaboration and deprotection of the analogous nosyl derivatives (e.g. **3o**) proved straightforward (Figure 3b).<sup>17</sup> While the fluoroaziridination reaction was found to be restricted to cinnamyl amine derivatives, the aromatic group in **3h** could be degraded oxidatively to a functional carboxylic acid handle in a simple two-step sequence (Figure 3c).

1,3-Difluorides (**6a–e**) bearing three contiguous stereocenters were generated when the reaction protocol was applied to chiral substrates bearing an aliphatic allylic substituent, as in **5a** (Figure 4a). Higher HF loadings (25–50 equiv. HF) were required to achieve full conversion of the starting material, and under these conditions the fluoride addition products were obtained exclusively. Completely regioselective ring opening of the putative 1,2-disubstituted aziridinium ion intermediate was observed, presumably due to the  $\beta$ -fluorine inductively deactivating ring opening at the homobenzylic position. The degree and sense of diastereoselectivity in the reaction was found to be subject to high levels of catalyst control. In the presence of an achiral catalyst such as iodobenzene, subjection of enantiopure **5a** to the fluoroaziridination protocol resulted in generation of the 1,3-difluoride **6a** in low, 1.7:1 d.r. (*anti/syn*). In contrast, chiral catalyst **1a** promoted formation of either diastereomer of **6a** with high selectivity depending on the enantiomer of catalyst employed. Consistent results were obtained in the catalyst-controlled difluorination of other substituted cinnamyl sulfonamides (**5b–5e**). X-Ray crystal structure analyses of both diastereomers of **6a** revealed that the alkyl chains adopt dramatically different conformations in the solid state to minimize unfavorable dipolar interactions between the 1,3-difluoro substituents. These observations add to the increasing body of evidence that 1,3-difluorides can serve as potentially valuable conformational control elements.

Variation of the spacing between the alkene and the sulfonamide was examined with an interest in generating fluorinated *N*-heterocycles of varying size. Substrates bearing either two or four methylene groups between the alkene and sulfonamide did not form the desired 4- or 6-membered *N*-heterocycles. Instead, low reactivity and conversion of the starting material to multiple uncharacterized fluorinated products were observed. In contrast, the fluoroamination protocol was applied successfully to the formation of 5-membered *N*-heterocycles. For example,  $\beta$ -fluoropyrrolidine **8** was obtained in good yield and in high levels of diastereo- and enantioselectivity (Figure 4b). The enantiomeric purity of **8** was readily upgraded to >99% by recrystallization. While a *syn* relationship is observed in the case of the fluoroaziridine products (**2a–n**), *anti*-fluoroamination of the alkene in **7** was observed.<sup>7a</sup> The fluoroaziridination and fluoropyrrolidination reactions therefore must proceed by fundamentally different mechanisms, yet both pathways can be promoted with high enantioselectivity using the same aryl iodide catalyst **1a**.

For several classes of cinnamyl derivatives, neighboring group participation by *O*-centered functional groups was found to result in stereoselective generation of oxyfluorinated products. Benzyl ether **9** underwent a fluorinative rearrangement reaction to generate the 1,3-difluoride **10**, consistent with formation and fluorinative ring opening of the corresponding oxiranium ion intermediate. As noted above, allylic amine substrates bearing carbonyl-containing nitrogen protecting groups such as carbamates and acetamides were found to undergo cyclization via reaction at the carbonyl oxygen rather than the nitrogen,

resulting in the formation of a variety of novel 1,2-oxyfluorinated products (Figure 5). For example, when the reaction protocol was applied to Cbz-protected cinnamyl amine **11**, formal 1,2-oxyfluorination of the alkene was observed to generate the cyclic carbamate **12** as a single observable diastereoisomer in good yield and in 93% ee. Allylic acetates such as **13** were observed to undergo reaction via an analogous pathway, resulting in the formation of mixtures of hydroxy and acetoxy products that presumably arise from hydrolytic ring opening of an acetoxonium ion intermediate. Treatment of the product mixture with acetic anhydride yielded the corresponding 1-fluoro-2,3-diacetoxy product **14** in good yield and as a single observable diastereoisomer in 94% ee.

The catalytic enantioselective fluorofunctionalization reactions described herein provide access to a variety of new fluorine-containing chiral compounds with potentially unique conformational and functional properties. Efforts to evaluate and exploit the utility of these polyfunctional fluorinated compounds are currently underway.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

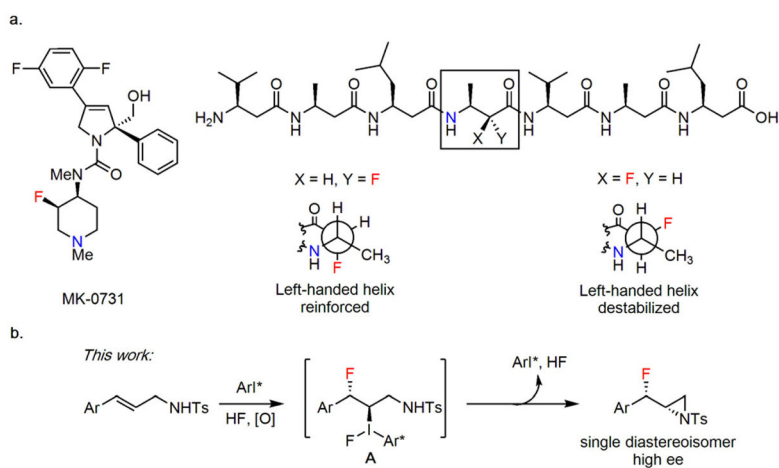
## Acknowledgments

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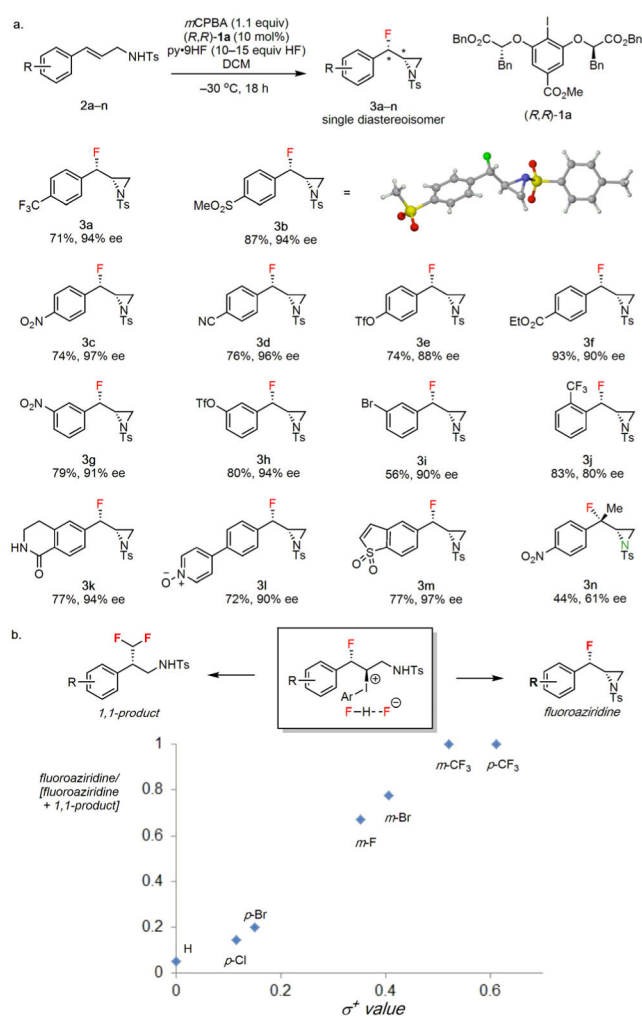
## References

1. For some leading reviews, see: Gillis EP, Eastman KJ, Hill MD, Donnelly DJ, Meanwell NA. *J Med Chem.* 2015; 58:8315. [PubMed: 26200936] Wang J, Sánchez-Roselló M, Aceña JL, del Pozo C, Sorochinsky AE, Fustero S, Soloshonok VA, Liu H. *Chem Rev.* 2014; 114:2432. [PubMed: 24299176] Purser S, Moore PR, Swallow S, Gouverneur V. *Chem Soc Rev.* 2008; 37:320. [PubMed: 18197348] Hagmann WK. *J Med Chem.* 2008; 51:4359. [PubMed: 18570365]
2. For some leading reviews, see: Yang X, Wu T, Phipps RJ, Toste FD. *Chem Rev.* 2015; 115:826. [PubMed: 25337896] Lectard S, Hamashima Y, Sodeoka M. *Adv Synth Catal.* 2011; 352:2708.
3. (a) Morgenthaler M, Schweizer E, Hoffman-Roder F, Benini F, Martin RE, Jaeschke G, Wagner B, Fischer H, Bendels S, Zimmerli D, Schneider J, Hiedrich F, Kansy M, Muller K. *ChemMedChem.* 2007; 2:1100. [PubMed: 17530727] (b) Cox CD, Coleman PJ, Breslin MJ, Whitman DB, Garbaccio RM, Fraley ME, Buser CA, Walsh ES, Hamilton K, Schaber MD, Lobell RB, Tao W, Davide JP, Diehl RE, Abrams MT, South VJ, Huber HE, Torrent M, Prueksaritanont T, Li C, Slaughter DE, Mahan E, Fernandez-Metzler C, Yan Y, Kuo LC, Kohl NE, Hartman GD. *J Med Chem.* 2008; 51:4239. [PubMed: 18578472]
4. (a) Seebach D, Dubost E, Mathad RI, Jaun B, Limbach M, Löweneck M, Flögel O, Gardiner J, Capone S, Beck AK, Widmer H, Langenegger D, Monna D, Hoyer D. *Helv Chim Acta.* 2008; 91:1736. (b) Mathad RI, Gessier F, Seebach D, Jaun B. *Helv Chim Acta.* 2005; 88:266.
5. For seminal examples utilizing organocatalysts, see: Shibata N, Suzuki E, Takeuchi Y. *J Am Chem Soc.* 2000; 122:10728. Cahard D, Audouard C, Plaquevent JC, Roques N. *Org Lett.* 2000; 2:3699. [PubMed: 11073679] Kim DY, Park EJ. *Org Lett.* 2002; 4:545. [PubMed: 11843587] Enders D, Hüttl MR. *Synlett.* 2005; 6:991. Marigo M, Fielenbach D, Braunton A, Kjærsgaard A, Jørgensen KA. *Angew Chem, Int Ed.* 2005; 44:3703. Steiner DD, Mase N, Barbas CF III. *Angew Chem, Int Ed.* 2005; 44:3706. Beeson TD, MacMillan DWC. *J Am Chem Soc.* 2005; 127:8826. [PubMed: 15954790]

6. (a) Fadeyi OO, Lindsley CW. *Org Lett.* 2009; 11:943. [PubMed: 19159275] (b) Schulte ML. *Org Lett.* 2011; 13:5684. [PubMed: 21942742] (c) Appayee C, Brenner-Moyer SE. *Org Lett.* 2010; 12:3356. [PubMed: 20575576]
7. (a) Kong W, Feige P, de Haro T, Nevado C. *Angew Chem Int Ed.* 2013; 52:2469.(b) Chen H, Kaga A, Chiba S. *Org Biomol Chem.* 2016; 14:5481. [PubMed: 26426571]
8. (a) Honjo T, Phipps RJ, Raunivar V, Toste FD. *Angew Chem Int Ed.* 2012; 51:9684.(b) Phipps RJ, Hiramatsu K, Toste FD. *J Am Chem Soc.* 2012; 134:8376. [PubMed: 22574822]
9. Lozano O, Blessley G, Matrinez del Campo T, Thompson AL, Giuffredi GT, Bettati M, Walker M, Borman R, Gouverneur V. *Angew Chem Int Ed.* 2011; 50:8105.
10. (a) Wu T, Yin G, Liu G. *J Am Chem Soc.* 2009; 131:16354. [PubMed: 19856929] (b) Qiu S, Xu T, Zhou J, Guo Y, Liu G. *J Am Chem Soc.* 2010; 132:2856. [PubMed: 20148557] (c) Zhang H, Song Y, Zhao J, Zhang J, Zhang Q. *Angew Chem Int Ed.* 2014; 53:11079.(d) Lu D-F, Zhu C-L, Sears JD, Xu H. *J Am Chem Soc.* 2016; 138:11360. [PubMed: 27529196]
11. (a) Dohi T, Kita Y. *Chem Commun.* 2009:2073.(b) Martín, Romero R., Wöste, TH., Muñiz, K. *Chem Asian J.* 2014:9.(c) Yoshimura A, Zhdankin VV. *Chem Rev.* 2016; 116:3328. [PubMed: 26861673] (d) Suzuki S, Kamo T, Fukushi K, Hiramatsu T, Tokunaga E, Dohi T, Kita Y, Shibata N. *Chem Sci.* 2014; 5:2754.(e) Haubenreisser S, Wöste T, Martínez C, Ishihara K, Muñiz K. *Angew Chem Int Ed.* 2016; 55:413–417.(f) Mizar P, Laverny A, El-Sherbini M, Farid U, Brown M, Malmedy F, Wirth T. *Chem Eur J.* 2014; 20:9910. [PubMed: 25042733] (g) Banik SM, Medley JW, Jacobsen EN. *J Am Chem Soc.* 2016; 138:5000. [PubMed: 27046019] (h) Molnár IG, Gilmour R. *J Am Chem Soc.* 2016; 138:5004. [PubMed: 26978593] (i) Wöste TH, Muñiz K. *Synthesis.* 2016; 48:816.(j) Woerly EM, Banik SM, Jacobsen EN. *J Am Chem Soc.* 2016; 138:13858.(k) Muñiz K, Barreiro L, Romero RM, Martínez C. *J Am Chem Soc.* 2017; 139:4354. [PubMed: 28277652] (l) Gelis C, Dumoulin A, Neuville L, Masson G. *Org Lett.* 2017; 19:278. [PubMed: 28009522] (m) Banik SM, Medley JW, Jacobsen EN. *Science.* 2016; 353:51. [PubMed: 27365443]
12. Yudin, AK. *Aziridines and Epoxides in Organic Synthesis.* Wiley-VCH; Feb. 2006
13. (a) Trachsel D. *Drug Testing and Analysis.* 2012; 4:577. [PubMed: 22374819] (b) Nichols DE. *Journal of Pharmaceutical Sciences.* 1981; 70:839. [PubMed: 7031221]
14. A traditional Hammett plot depicting the log(product ratio) vs  $\sigma+$  has a similar appearance to Figure 2b and is provided in the Supporting Information.
15. Wu J, Hou X-L, Dai L-X. *J Org Chem.* 2000; 65:1344. [PubMed: 10814094]
16. Wu J, Sun X, Sun W. *Org Biomol Chem.* 2006; 4:4231. [PubMed: 17312980]
17. Fukuyama T, Jow C-K, Cheung M. *Tetrahedron Lett.* 1995; 36:6373.

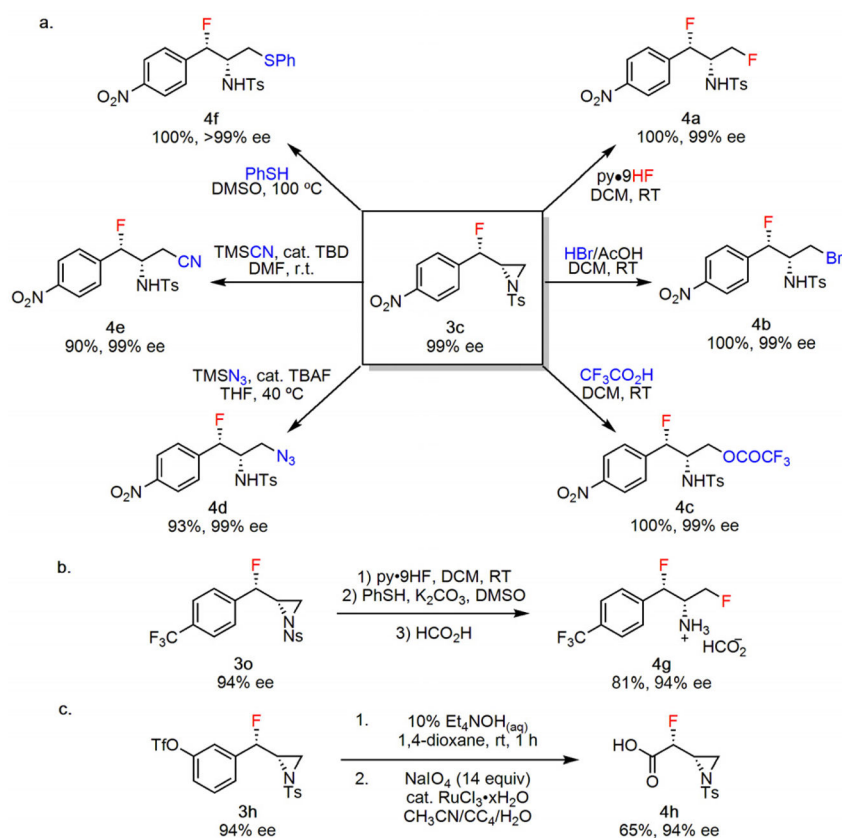


**Figure 1.** Fluoroamination of alkenes. **a**, Examples of compounds where incorporation of a stereodefined C–F bond in a  $\beta$ -relationship to a nitrogen has been shown to impart beneficial properties to the molecule. **b**,  $\beta$ -Fluoroaziridination *via* sulfonamide trapping of a C(sp<sup>3</sup>)–I(III) intermediate.

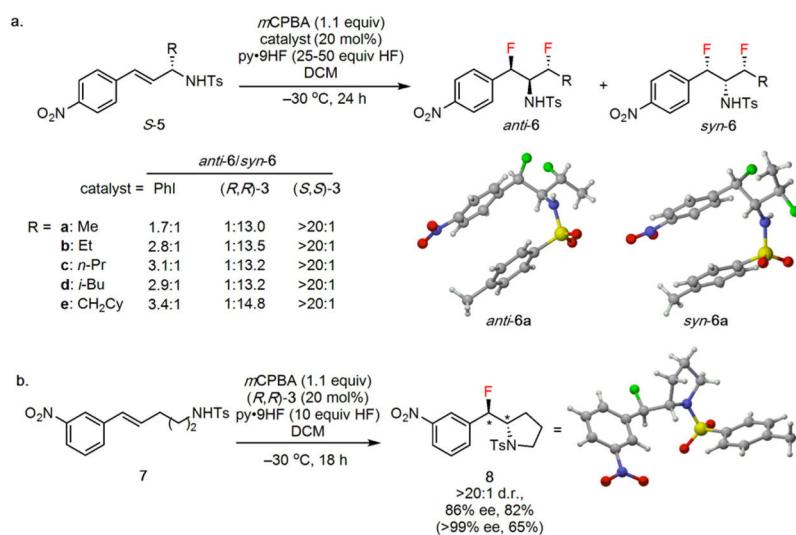


**Figure 2.** Evaluation of substrate scope for *syn*- $\beta$ -fluoroaziridination. **a**, Substrate scope evaluation for electron-deficient cinnamyl tosylamides. Isolated yields are indicated below each product (**3**); conditions: substrate (0.52 mmol), catalyst (10 mol%), *m*CPBA (0.6 mmol),  $py\cdot 9HF$  (7.5 mmol HF) in DCM (3.0 mL) cooled to  $-30\text{ }^\circ\text{C}$ , 18 h. **b**, Product selectivity as a function of substituent. The ratio of fluorooziridine product yield to the sum of fluorooziridine and 1,1-difluoromethylated product was determined by  $^{19}\text{F}$  NMR analysis of the crude mixture.

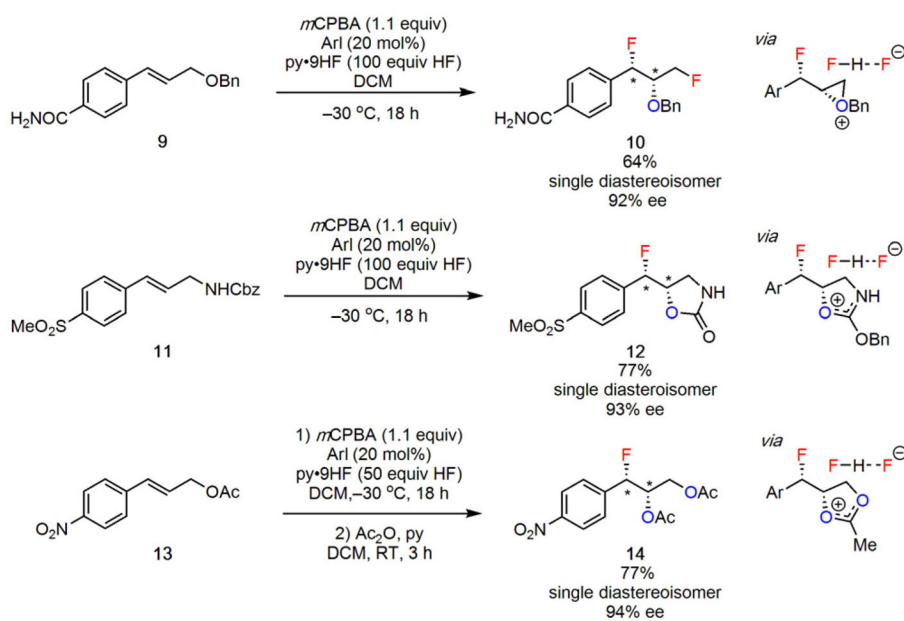




**Figure 3.** Synthetic elaboration studies. **a**, Reactions of fluoroozaziridine **3c** (upgraded from 97 to 99% ee by recrystallization). **b**, Reactions of the nosyl-protected fluoroozaziridine **3o**. **c**, Oxidative degradation of aromatic group in **3h** to a carboxylic acid. Isolated yields are indicated below each product (**4**); experimental details are provided in the Supplementary Information. TBD, triazabicyclodecene; TBAF, tetrabutylammonium fluoride.



**Figure 4.** Extension of the fluoroamination reaction protocol. **a**, Formation of 1,3-difluoro-2-amines bearing three contiguous stereocenters from enantioenriched allylic sulfonamides. **b**, Fluoroamination of bis-homoallylic sulfonamide **7** results in formation of the corresponding *anti*- $\beta$ -fluoropyrrolidine. Isolated yields are indicated below all products; the yield in parentheses corresponds to re-crystallized product. Full experimental details are provided in the Supplementary Information.



**Figure 5.** Catalytic diastereo- and enantioselective 1,2-oxyfluorination reactions. Isolated yields are indicated below each product. Experimental details are provided in the Supplementary Information.