Synthesis of β-Fluoroamines by Lewis Base Catalyzed Hydrofluorination of Aziridines

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ⓢ *Supporting Information*

ABSTRACT: Lewis base catalysis promotes the in situ generation of amine-HF reagents from benzoyl fluoride and a non-nucleophilic alcohol. The hydrofluorination of aziridines to provide β-fluoroamines using this latent HF source is described. This protocol displays a broad scope with respect to aziridine substitution and N-protecting groups. Examples of regio- and diastereoselective ring opening to access medicinally relevant β-fluoroamine building blocks are presented.
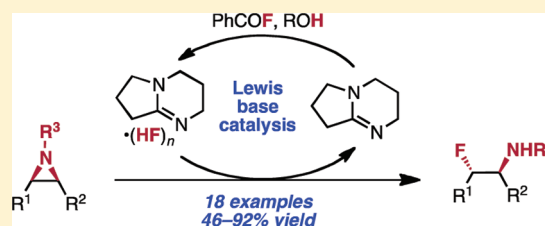
Since the initial report of pyridinium poly(hydrogen fluoride) (PPHF) by Bergstrom et al. in 1963,[1] amine-HF reagents have become commonplace in synthetic organic chemistry as an alternative to anhydrous HF.[2] Although Olah and co-workers developed a wide range of C—F bond-forming reactions using PPHF in the 1970s,[3] in modern laboratories, this reagent and the milder $Et_3N \cdot 3HF$[4] are primarily used for silyl ether deprotections.[5] Given the significant interest in new methods for the preparation of organofluorine compounds, it is surprising that these reagents have not experienced greater development in recent years. Presumably, this is in part due to the limited number of commercially available amine-HF reagents, which are prepared using anhydrous HF, and the requirement for a large excess of HF (>20 equiv) relative to substrate,[3] as well as their corrosiveness and functional group incompatibility.

In the context of developing an asymmetric fluoride ring-opening reaction of epoxides, we anticipated that the solvolysis of an acid fluoride catalyzed by a Lewis base, such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), would generate an amine-HF reagent in situ. We recognized that this strategy could prove of significant practical utility, overcoming many of the traditional challenges associated with this class of reagents. Indeed, the combination of PhCOF and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) serves as a synthetically useful latent source of HF and effects enantioselective ring opening in the presence of a chiral Lewis acid cocatalyst.[6] Detailed mechanistic studies, however, demonstrated that the catalytically relevant nucleophile in these epoxide-opening reactions was a transition-metal fluoride, *not* an amine-HF species.[7] Nevertheless, the catalytic generation of an amine-HF reagent for hydrofluorination remains an intriguing goal. In this note, we demonstrate the successful application of this strategy to a practical and general synthesis of β-fluoroamines by aziridine hydrofluorination.

The β-fluoroamine motif is of great importance in medicinal chemistry,[8] occurring in numerous drug candidates (Figure 1).[9] In addition to the improved metabolic stability and binding
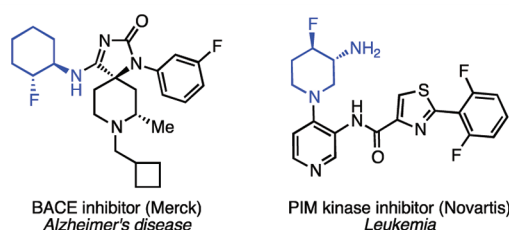

**Figure 1.** β-Fluoroamine-containing bioactive targets.

affinity offered by drugs containing C—F bonds, β-fluoro substitution lowers the pK_a of amines, which in turn improves bioavailability and increases blood-brain barrier penetration.[10]

Because of the utility of β-fluoroamines, the past decade has witnessed the development of many new methods for their synthesis. Many of these strategies rely on the electrophilic fluorination of carbonyl-containing compounds or imines and require further elaboration to provide the desired β-fluoroamine.[11] In contrast, aziridine ring-opening by fluoride offers a direct route to β-fluoroamines. Although methods using metal or tetraalkylammonium fluoride salts have been developed, these reactions are effective only with activated aziridines (e.g., N-tosyl).[12] The seminal studies of Wade[13] and Laurent[14] demonstrated that anhydrous HF and amine-HF reagents effect the hydrofluorination of simple unactivated aziridines. However, the reactions often afford stereoisomeric mixtures of products and suffer from acid-promoted side reactions.

We chose to evaluate our catalytic hydrofluorination conditions for the ring opening of Boc-protected cyclohexene imine 1a, an acid-sensitive substrate that is not stable to PPHF. Gratifyingly, the desired β-fluoroamine 2a was formed in 93% yield within 15 min (Table 1, entry 1). These conditions are mild (50 °C), require only 2 equiv of the fluorinating reagent PhCOF, and are performed at high concentrations (1 M) in a green solvent (*tert*-butyl methyl ether, TBME). A control

Table 1. Reaction Development[a]
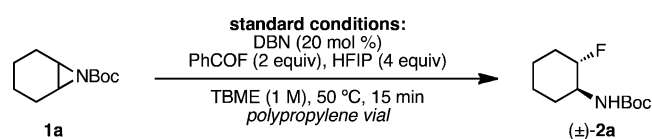
entry	variation from standard conditions	conv.[b] (%)	yield[b] (%)
1	none	100	93
2	without DBN	20	6
3	in glass vial	98	89
4	with TFE instead of HFIP	75	68
5	1.1 equiv of PhCOF, 2.2 equiv of HFIP	81	79
6	at 24 °C	35	30

[a]Reaction conditions: **1a** (0.25 mmol), DBN (0.05 mmol), PhCOF (0.5 mmol), HFIP (1 mmol), and TBME (0.25 mL), 50 °C, sealed polypropylene vial, 15 min. [b]Determined by GC using dodecane as a quantitative internal standard.

reaction demonstrated that the DBN catalyst is required for productive reactivity, although minimal background reaction was observed in its absence (entry 2). While optimal results were observed in a polypropylene reaction vessel, the reaction proceeded nearly as efficiently in glass (entry 3). The more inexpensive proton source 2,2,2-trifluoroethanol (TFE) provided lower reactivity, but the yield of product remained high (entry 4). Lower equivalents of PhCOF may also be employed at the expense of reaction rate (entry 5), and the hydrofluorination was significantly slower when performed at room temperature (entry 6). After a 1 h reaction time, the hydrofluorinations in entries 3 and 4 proceed to full conversion with >90% yield.

Notably, the hydrofluorination of **1a** may be performed on a gram scale in a standard glass round-bottom flask, without exclusion of air or moisture. Quenching the reaction after 1 h with methanolic ammonia, followed by aqueous workup, allowed isolation of the fluoroamine **2a** in 92% yield without column chromatography (Table 2, entry 1).

The scope of the catalytic hydrofluorination with respect to the N-substituent of the aziridine was next investigated. Because the reaction of amine-HF with glass competes with ring opening and the aziridines displayed variable reactivity, the hydrofluorinations were performed in polypropylene reaction vessels to standardize the reaction protocol.[15] Commonly employed protecting groups were tolerated in addition to Boc, including Cbz (Table 2, entry 2) and Bn (entry 3). N-Alkyl aziridines, such as **1c**, are sufficiently basic that hydrofluorination occurs in the absence of DBN. N-Aryl and heteroaryl aziridines are readily synthesized from aryl bromides and N−H aziridines using conditions developed by Yudin[16] and also provided β-fluoroamines in good yield (entries 4 and 5). An aziridine functionalized with caffeine, which contains several potentially problematic Lewis basic sites, required extended reaction times due in part to its minimal solubility in organic solvents, but afforded product **2f** in high yield (entry 6). Acyl aziridines, including those derived from picolinic and 4-thiazolecarboxylic acid, provided β-fluoroamides with minimal production of the oxazoline derived from acid-catalyzed rearrangement[14] (entries 7−10). However, N-tosyl aziridine **1k** reacted sluggishly, highlighting the complementarity of this hydrofluorination method to ring-opening protocols by metal fluorides (entry 11). In all cases, solely the trans-β-fluoroamine product was observed, as determined by comparison of the ¹H

Table 2. Substrate Scope: N-Substitution[a]
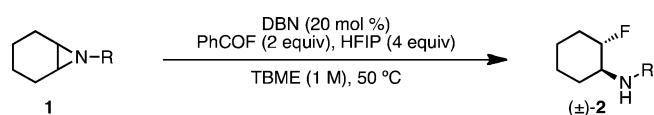
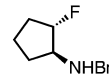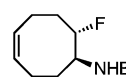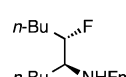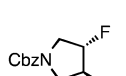| entry	R	aziridine	product	time (h)	yield[b] (%)
1[c]	Boc	**1a**	**2a**	1	92
2	Cbz	**1b**	**2b**	4	82
3	Bn	**1c**	**2c**	18	87
4	(2-pyridyl)	**1d**	**2d**	16	76[d]
5	(2-MeO-phenyl)	**1e**	**2e**	30	74
6[e]	(caffeinyl)	**1f**	**2f**	72	92
7	Bz	**1g**	**2g**	3	64[f]
8	(2-pyridylcarbonyl)	**1h**	**2h**	8	81[d]
9	(4-thiazolylcarbonyl)	**1i**	**2i**	24	77
10	(4-NO₂-benzoyl)	**1j**	**2j**	3	80
11	Ts	**1k**	**2k**	48	46[g]

[a]Reaction conditions: aziridine (1 equiv), DBN (0.2 equiv), PhCOF (2 equiv), and HFIP (4 equiv) in TBME (1 M based on aziridine), 50 °C, sealed polypropylene vial. [b]Isolated yield; average of two experiments on a 0.5−1 mmol scale. [c]Reaction was performed with **1a** (1 g, 5.07 mmol) in a glass round-bottom flask. [d]95% purity (¹H NMR). [e]0.5 M in cyclopentyl methyl ether (CPME). [f]Accompanied by 24% isolated yield of oxazoline byproduct. [g]Accompanied by 48% isolated yield of unreacted **1k**.

and ¹⁹F NMR spectra to known compounds.[12] This is important in a medicinal-chemistry context: the relative configuration of vicinal amine and fluoride substituents is known to influence binding potency and bioavailability.[8,10]

Additionally, the standard reaction conditions effect the hydrofluorination of other cyclic and acyclic meso aziridines in high yield. The fluorination of an unsaturated eight-membered ring fused aziridine (**5**) provided **6** as the only fluorinated product (Table 3, entry 2). An acyclic N-Fmoc aziridine (**7**) underwent hydrofluorination in good yield, despite the sensitivity of this protecting group to basic conditions, and provided the product as a single diastereomer (**8**, entry 3). This protocol enables the synthesis of useful heterocyclic building blocks, such as the β-fluoroamine-substituted pyrrolidine **10** (entry 4). However, a significant limitation remains the laborious synthesis of functionalized aziridines, which are accessed in three or more steps from the corresponding epoxide or alkene.

Next, we chose to evaluate unsymmetrically substituted aziridines. 2-Carboxymethyl N-Boc aziridine **11**, which may be synthesized in enantioenriched form by an organocatalytic

Table 3. Substrate Scope: Backbone Substitution[a]

entry	aziridine	product		time (h)	yield[b] (%)
1	**3**		**4**	24	82
2	**5**		**6**	12	81
3	**7**		**8**	6	92[c]
4	**9**		**10**	24	82

[a]Reaction conditions: see Table 2. [b]Isolated yield; average of two experiments on a 0.5−1 mmol scale. [c]92% purity (LC).

protocol,[17] gave N-Boc-O-Me β-fluoro-α-amino acid **12** under the standard reaction conditions, albeit with an extended reaction time (Scheme 1, eq 1). The hydrofluorination

Scheme 1. Regioselective Hydrofluorination for the Preparation of Medicinally Relevant Building Blocks
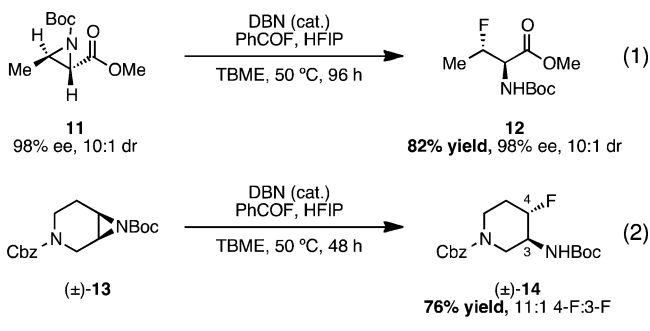
proceeds with excellent diastereoselectivity and no erosion of ee. Consistent with literature precedent,[13,14] the reaction is also regioselective, with fluorination occurring at the carbon that best stabilizes a positive charge. This synthetic sequence provides efficient access to enantioenriched fluorinated amino acids in three steps from readily available α,β-unsaturated aldehydes.[17]

The orthogonally protected piperidine aziridine **13** represents a common intermediate in the synthesis of medicinal chemistry targets.[18] Indeed, hydrofluorination of **13** provides a β-fluoroamine that can be found in several patents (Figure 1); however, existing syntheses suffer from high step count, inconvenient protecting group manipulations, and low yields in the C−F bond-forming reaction.[9b,19] We were pleased to find that under the standard conditions, aziridine **13** delivers 4-fluoro-3-aminopiperidine **14** in 76% isolated yield, as an 11:1 ratio of regioisomers (Scheme 1, eq 2).

Despite significant recent advances in the field of asymmetric fluorination,[20] the synthesis of enantioenriched cyclic *trans*-fluoroamines still relies on chiral chromatography and suffers from poor overall yields (typically <3%).[11d] As expected based on preliminary experiments suggesting that the nucleophilic

species in this catalytic hydrofluorination protocol is a DBN·(HF)$_4$ adduct,[6] **2a** is produced in <15% ee when chiral amine catalysts are used (see the Supporting Information). However, the flexibility of the method with respect to N-substitution offers the opportunity to achieve asymmetric induction with a chiral auxiliary.

We selected aziridine **15**, derived from inexpensive (S)-1-phenylethylamine in two steps, as a model substrate for diastereoselective hydrofluorination (Scheme 2). This aziridine

Scheme 2. Diastereoselective Hydrofluorination of 15[a]
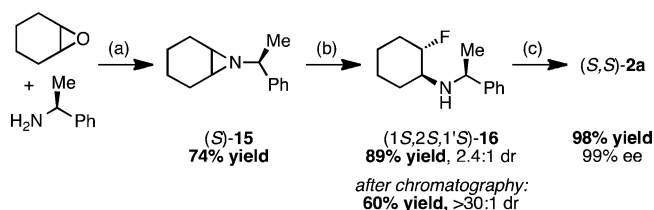
[a]Reagents and conditions: (a) 1. LiClO$_4$, MeCN, reflux, 40 h; 2. MsCl, Et$_3$N-CH$_2$Cl$_2$, 0 °C−rt, 24 h; (b) cat. DBN, PhCOF, HFIP, TBME, 50 °C, 18 h; (c) cat. Pd(OH)$_2$/C, 1 atm H$_2$, Boc$_2$O, EtOH, rt, 8 h.

has been used for the synthesis of chiral ligands and organocatalysts and provides modest diastereoselectivity in ring-opening reactions with a variety of heteroatomic nucleophiles.[21] Under our standard catalytic conditions, the ring opening of **15** proceeded smoothly to provide a mixture of fluoroamine (1S,2S) and (1R,2R) diastereomers with modest selectivity (2.4:1 dr; for additional chiral auxiliaries and reaction conditions, see the Supporting Information). Alternative sources of HF provided poor reactivity in the hydrofluorination of **15**, which is considered an unactivated aziridine.[22]

These diastereomers could be separated by standard column chromatography on SiO$_2$, providing the major diastereomer (1S,2S,1′S)-**16** in 60% isolated yield and >30:1 dr, as judged by ^{19}F NMR.[23] The observed sense of diastereoinduction is consistent with literature precedent.[21] Furthermore, the chiral auxiliary was readily cleaved by hydrogenolysis in the presence of Boc$_2$O to provide (S,S)-**2a** in 98% yield and 99% ee. This procedure provides enantioenriched fluoroamine in 44% overall yield from commercial materials, a significant improvement over previous approaches.

In conclusion, we anticipate that this practical method will provide access to useful quantities of versatile β-fluoroamine building blocks.

■ EXPERIMENTAL SECTION

General Experimental Methods. Hydrofluorinations were performed in 8 mL polypropylene tubes and sealed with caps fitted with rubber O-rings. Column chromatography was performed with silica gel (40−53 μm, 60 Å). 1,5-Diazabicyclo[4.3.0]non-5-ene was distilled from CaH$_2$ and stored over activated 3 Å molecular sieves. Benzoyl fluoride was filtered through SiO$_2$, eluting with pentanes, and solvent was removed in vacuo. It was stored in a plastic vial in a desiccator containing CaSO$_4$.

7-Azabicyclo[4.1.0]heptane,[24] (Z)-9-azabicyclo[6.1.0]non-4-ene,[25] *cis*-2,3-dibutylaziridine,[26] benzyl 3,6-diazabicyclo[3.1.0]hexane-3-carboxylate,[27] 8-bromocaffeine,[28] **1a**,[29] **1b**,[30] **1c**,[31] **1d−1f**,[16] **1g**,[34] **1j**,[32] **1k**,[33] **3**,[34] **11**,[17] **13**,[18] and **15**[35] were prepared according to literature procedures.

General Procedure for Boc Protection. To a 0.67 M solution of N−H aziridine (1 equiv), DMAP (0.05 equiv), and triethylamine (2.5 equiv) in anhydrous CH$_2$Cl$_2$ cooled to 0 °C under N$_2$ was added

Boc$_2$O (2.5 equiv), and the solution was warmed to rt. Upon completion, the reaction was concentrated and purified by column chromatography.

General Procedure for Acylation. To a 0.2 M solution of N−H aziridine (1 equiv) in anhydrous CH$_2$Cl$_2$ at rt under N$_2$ was added 4-dimethylaminopyridine (1.1 equiv), N,N′-dicyclohexylcarbodiimide (1.1 equiv), and the appropriate carboxylic acid (1 equiv). The reaction was stirred for 12−24 h, and upon completion, the suspension was diluted with hexanes, filtered, and concentrated. The crude reaction was purified by column chromatography (5−40% EtOAc-hexanes with 0.5% Et$_3$N).

7-(2-Methoxyphenyl)-7-azabicyclo[4.1.0]heptane (1e):[16] 0.390 g, 96% yield; FTIR (thin film, cm^{-1}) 2993, 2933, 2855, 1593, 1496, 1438, 1410, 1266, 1231, 1117, 1030; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.97−6.74 (m, 4H), 3.86 (s, 3H), 2.23 (s, 2H), 2.14−2.05 (m, 2H), 1.94−1.82 (m, 2H), 1.56−1.44 (m, 2H), 1.37−1.22 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 152.9, 144.11, 122.4, 120.6, 120.3, 110.8, 55.6, 39.4 (2C), 24.4 (2C), 20.6 (2C); HRMS (ESI+) calculated for C$_{13}$H$_{18}$NO ([M + H]$^+$), 204.1383; found, 204.1392.

8-(7-Azabicyclo[4.1.0]heptan-7-yl)-1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (1f):[16] 0.614 g, 85% yield; FTIR (thin film, cm^{-1}) 2938, 2860, 1652, 1698, 1499, 1433; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.85 (s, 3H), 3.49 (s, 3H), 3.38 (s, 3H), 2.87−2.82 (m, 2H), 2.09−2.01 (m, 2H), 1.99−1.91 (m, 2H), 1.57−1.48 (m, 2H), 1.38−1.30 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.0, 154.9, 151.9, 147.0, 105.5, 41.4 (2C), 31.0, 29.8, 27.9, 24.0 (2C), 20.0 (2C); HRMS (ESI+) calculated for C$_{14}$H$_{20}$N$_5$O$_2$ ([M + H]$^+$), 290.1612; found, 290.1609.

7-Azabicyclo[4.1.0]heptan-7-yl(pyridin-2-yl)methanone (1h). Prepared from 7-azabicyclo[4.1.0]heptane and picolinic acid according to the general procedure for aziridine acylation and isolated as a white solid in 72% yield (0.731 g). FTIR (thin film, cm^{-1}) 2935, 1670, 1585, 1440, 1417, 1323, 1137; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.70 (d, J = 4.6 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.81 (t, J = 7.7 Hz, 1H), 7.42 (dd, J = 7.4, 4.8 Hz, 1H), 2.86 (d, J = 2.9 Hz, 2H), 2.29−2.10 (m, 2H), 1.96−1.80 (m, 2H), 1.59−1.49 (m, 2H), 1.40−1.29 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.9, 151.2, 149.6, 136.8, 126.4, 124.1, 37.5 (2C), 23.9 (2C), 20.2 (2C); HRMS (ESI+) calculated for C$_{12}$H$_{15}$N$_2$O ([M + H]$^+$), 203.1179; found, 203.1179.

7-Azabicyclo[4.1.0]heptan-7-yl(thiazol-4-yl)methanone (1i). Prepared from 7-azabicyclo[4.1.0]heptane and 4-thiazolecarboxylic acid according to the general procedure for aziridine acylation and isolated as a white solid in 82% yield (0.683 g). FTIR (thin film, cm^{-1}) 3092, 2930, 2854, 1647, 1489, 1419, 1297; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.82 (d, J = 2.1 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 2.91−2.85 (m, 2H), 2.23−2.10 (m, 2H), 1.92 (td, J = 8.8, 4.3 Hz, 2H), 1.62−1.47 (m, 2H), 1.42−1.27 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.3, 153.0, 152.0, 125.9, 37.6 (2C), 24.0 (2C), 20.2 (2C); HRMS (ESI+) calculated for C$_{10}$H$_{13}$N$_2$OS ([M + H]$^+$), 209.0743; found, 209.0743.

(Z)-tert-Butyl 9-Azabicyclo[6.1.0]non-4-ene-9-carboxylate (5). Prepared from (Z)-9-azabicyclo[6.1.0]non-4-ene according to the general procedure for Boc-protection (1−10% acetone-hexanes) and isolated as a yellow oil in 50% yield (1.00 g). FTIR (thin film, cm^{-1}) 3357, 2978, 2933, 1714, 1441, 1367, 1298, 1244, 1154, 1088; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.61−5.52 (m, 2H), 2.51−2.33 (m, 4H), 2.19−2.08 (m, 2H), 2.06−1.89 (m, 4H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 163.7, 129.3 (2C), 80.9, 42.1 (2C), 28.3 (2C), 28.0 (3C), 24.3 (2C); HRMS (ESI+) calculated for C$_{13}$H$_{22}$NO$_2$ ([M + H]$^+$), 224.1645; found, 224.1649.

cis-(9H-Fluoren-9-yl)methyl 2,3-Dibutylaziridine-1-carboxylate (7). cis-2,3-Dibutylaziridine (0.663 g, 4.27 mmol, >50:1 dr) was dissolved in THF−H$_2$O (1:1, 17 mL). The biphasic solution was cooled to 0 °C, and Na$_2$CO$_3$ (0.679 g, 6.4 mmol) was added, followed by FmocCl (1.33 g, 5.12 mmol). The reaction was stirred, warming to rt, for 22 h; then, the layers were separated and the aqueous layer was extracted with Et$_2$O (2×). The combined organics were washed with brine, dried over MgSO$_4$, filtered, and concentrated. The crude material was purified by column chromatography (5−40% Et$_2$O-hexanes) to obtain the title compound as a viscous pale yellow oil (1.59 g, 99% yield). FTIR (thin film, cm^{-1}) 2955, 2928, 2859, 1717,

1450, 1280, 1222, 1089; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 4.45 (d, J = 6.6 Hz, 2H), 4.23 (t, J = 6.5 Hz, 1H), 2.31 (s, 2H), 1.52−1.33 (m, 12H), 0.92 (t, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 164.2, 143.9 (2C), 141.5 (2C), 127.9 (2C), 127.2 (2C), 125.2 (2C), 120.1 (2C), 67.8, 47.2, 43.0 (2C), 29.8 (2C), 27.5 (2C), 22.6 (2C), 14.2 (2C); HRMS (ESI+) calculated for C$_{25}$H$_{32}$NO$_2$ ([M + H]$^+$), 378.2428; found, 378.2428.

3-Benzyl 6-tert-Butyl-3,6-diazabicyclo[3.1.0]hexane-3,6-dicarboxylate (9). Prepared from benzyl 3,6-diazabicyclo[3.1.0]-hexane-3-carboxylate according to the general procedure for Boc-protection (7−60% EtOAc-hexanes) to provide the title compound as an off-white solid in 94% yield (1.20 g). FTIR (thin film, cm^{-1}) 3977, 2877, 1702, 1421, 1314, 1145, 1115; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37−7.27 (m, 5H), 5.11 (d, J = 12.3 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 4.08 (d, J = 12.0 Hz, 2H), 3.34 (t, J = 11.1 Hz, 2H), 3.07 (d, J = 1.3 Hz, 2H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.4, 154.9, 136.4, 128.6 (2C), 128.2, 128.2 (2C), 81.9, 67.2, 45.4, 44.9, 39.8, 39.6, 27.9 (3C); HRMS (ESI+) calculated for C$_{17}$H$_{22}$N$_2$NaO$_4$ ([M + Na]$^+$), 341.1472; found, 341.1467.

General Procedure for Hydrofluorination on 1 mmol Scale. In an 8 mL polypropylene tube, the aziridine (1 mmol, 1 equiv) was dissolved or suspended in TBME (1 mL). 1,5-Diazabicyclo(4.3.0)non-5-ene (24.7 μL, 0.2 mmol, 0.2 equiv) was charged, followed by HFIP (0.42 mL, 4 mmol, 4 equiv) and PhCOF (0.22 mL, 2 mmol, 2 equiv). The tube was sealed, placed in an aluminum heating block preheated to 50 °C, and stirred for the designated time. Unless otherwise specified, the reaction was quenched with saturated aqueous NaHCO$_3$ and extracted with EtOAc (3×). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated. The crude material was purified by column chromatography (5−40% EtOAc-hexanes).

Hazard Note. *Caution!* HF is generated in these reactions; while less corrosive than PPHF or anhydrous HF, avoid all contact with skin and quench carefully.

tert-Butyl (trans-2-Fluorocyclohexyl)carbamate (2a). The general procedure was performed *in a 50 mL glass round-bottom flask* with **1a** (1 g, 5.07 mmol), and quenched with 25 mL of 7 M methanolic NH$_3$. After 3 h, the reaction mixture was poured into 1 M aqueous NaOH (100 mL) and diluted with 20% Et$_2$O-hexanes (35 mL). The organic layer was washed with 1 M NaOH (2×), and the aqueous layer was extracted with 20% Et$_2$O-hexanes (15 mL). The combined organic extracts were stirred vigorously over MgSO$_4$ and SiO$_2$, filtered, and concentrated. The title product was obtained as a white solid (1.01 g, 4.65 mmol, 92% yield; 1.01 g, 4.65 mmol, 92% yield). FTIR (thin film, cm^{-1}) 3334, 2939, 2866, 1684, 1520, 1365, 1321, 1254, 1164, 1010; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.58 (br s, 1H), 4.20 (dddd, J = 50.3, 9.8, 9.8, 4.5 Hz, 1H), 3.66−3.50 (m, 1H), 2.17−2.01 (m, 2H), 1.81−1.70 (m, 1H), 1.65−1.47 (m, 2H), 1.44 (s, 9H), 1.36−1.11 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 155.7, 93.6 (d, J = 178.5 Hz), 79.6, 53.9 (d, J = 18.1 Hz), 31.3, 31.2 (d, J = 5.5 Hz), 28.5 (3C), 23.9, 23.4 (d, J = 10.1 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) δ −179.1 (d, J = 49.0 Hz); HRMS (ESI+) calculated for C$_{11}$H$_{20}$FNNaO$_2$ ([M + Na]$^+$), 240.1370; found, 240.1377.

Benzyl (trans-2-Fluorocyclohexyl)carbamate (2b): White solid (211 mg, 0.84 mmol, 84% yield; 202 mg, 0.8 mmol, 80% yield); FTIR (thin film, cm^{-1}) 3325, 2941, 2864, 1695, 1533, 1454, 1318, 1257, 1232, 1053, 1021; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36−7.28 (m, 5H), 5.20 (s, 1H), 5.14−5.04 (m, 2H), 4.22 (dm, J$_{HF}$ = 50.3 Hz, 1H), 3.66 (s, 1H), 2.07 (s, 2H), 1.74 (d, J = 10.2 Hz, 1H), 1.64−1.46 (m, 2H), 1.32−1.14 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 156.1, 136.5, 128.4 (2C), 128.1, 128.0 (2C), 93.4 (d, J = 178.6 Hz), 66.6, 54.2 (d, J = 17.6 Hz), 31.1 (d, J = 18.1 Hz), 31.0 (d, J = 3.7 Hz), 23.8, 23.2 (d, J = 10.1 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) δ −178.5 (d, J = 48.7 Hz); HRMS (ESI+) calculated for C$_{14}$H$_{19}$FNO$_2$ ([M + H]$^+$), 252.1400; found, 252.1402.

trans-N-Benzyl-2-fluorocyclohexanamine (2c). Extracted with Et$_2$O; chromatographed 5−60% Et$_2$O-hexanes; clear oil (176 mg, 0.85 mmol, 85% yield; 183 mg, 0.88 mmol, 88% yield). This compound is known.[12b]

N-(*trans*-2-Fluorocyclohexyl)pyridin-2-amine (2d): White solid, 95% purity (148 mg, 0.76 mmol, 76% yield; 148 mg, 0.76 mmol, 76% yield); FTIR (thin film, cm^{-1}) 3261, 2936, 2861, 1611, 1524, 1487, 1419, 1029; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.08−8.06 (m, 1H), 7.42−7.37 (m, 1H), 6.59−6.54 (m, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.36 (dddd, *J* = 50.0, 9.4, 9.4, 4.4 Hz, 1H), 3.82−3.73 (m, 1H), 2.24−2.08 (m, 2H), 1.80 (dd, *J* = 8.7, 3.6 Hz, 1H), 1.71−1.58 (m, 2H), 1.46−1.20 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.5, 148.2, 137.5, 113.2, 107.4 (d, *J* = 1.2 Hz), 94.8 (d, *J* = 177.7 Hz), 54.5 (d, *J* = 18.0 Hz), 31.2, 31.1 (d, *J* = 14.1 Hz), 23.8, 23.3 (d, *J* = 9.8 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) δ −177.9 (d, *J* = 51.0 Hz); HRMS (ESI+) calculated for C$_{11}$H$_{16}$FN$_2$ ([M + H]$^+$), 195.1298; found, 195.1294.

N-(*trans*-2-Fluorocyclohexyl)-2-methoxyaniline (2e). Extracted with DCM; chromatographed 5−75% DCM-hexanes; white solid (164 mg, 0.74 mmol, 74% yield; 0.92 mmol scale: 152 mg, 0.68 mmol, 74% yield). FTIR (thin film, cm^{-1}) 3417, 2938, 2863, 1602, 1514, 1457, 1255, 1222, 1028; ^{1}H NMR (500 MHz, MeOD) δ 6.78−6.72 (m, 2H), 6.68−6.65 (m, 1H), 6.60−6.56 (m, 1H), 4.34 (dddd, *J* = 50.0, 9.3, 9.2, 4.4 Hz, 1H), 3.79 (s, 3H), 3.36−3.28 (m, 1H), 2.12−2.01 (m, 2H), 1.79−1.70 (m, 1H), 1.68−1.50 (m, 2H), 1.41−1.28 (m, 2H), 1.27−1.17 (m, 1H); ^{13}C NMR (125 MHz, MeOD) δ 148.6, 138.8, 122.2, 118.0, 112.3, 110.8, 95.9 (d, *J* = 177.0 Hz), 57.8 (d, *J* = 17.3 Hz), 56.0, 32.4 (d, *J* = 18.4 Hz), 32.0 (d, *J* = 5.2 Hz), 24.9, 24.4 (d, *J* = 10.1 Hz); ^{19}F NMR (282 MHz, MeOD) δ −178.8 (d, *J* = 49.6 Hz); HRMS (ESI+) calculated for C$_{13}$H$_{19}$FNO ([M + H]$^+$), 224.1451; found, 224.1454.

8-((*trans*-2-Fluorocyclohexyl)amino)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (2f). Performed on a 0.5 mmol scale in 1 mL CPME; quenched by diluting with Et$_2$O and filtering; solid residues were chromatographed 1−10% MeOH-CHCl$_3$; white solid (143 mg, 0.46 mmol, 92% yield; 144 mg, 0.47 mmol, 93% yield). FTIR (thin film, cm^{-1}) 3366, 2938, 2861, 1702, 1655, 1614, 1579, 1550, 1483, 1454, 1223, 1033; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.43 (dddd, *J* = 50.7, 9.9, 9.9, 4.5 Hz, 1H), 4.18 (d, *J* = 5.9 Hz, 1H), 3.97−3.86 (m, 1H), 3.68 (s, 3H), 3.52 (s, 3H), 3.37 (s, 3H), 2.43−2.35 (m, 1H), 2.20 (ddd, *J* = 12.6, 8.9, 4.0 Hz, 1H), 1.89−1.81 (m, 1H), 1.76−1.69 (m, 1H), 1.67−1.59 (m, 1H), 1.47−1.22 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.5, 152.8, 151.9, 148.5, 103.3, 94.0 (d, *J* = 178.5 Hz), 56.9 (d, *J* = 17.2 Hz), 31.5, 31.4 (d, *J* = 10.2 Hz), 29.9, 29.7, 27.8, 24.0 (d, *J* = 1.3 Hz), 23.6 (d, *J* = 10.6 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) δ −179.0 (d, *J* = 50.6 Hz) HRMS (ESI+) calculated for C$_{14}$H$_{21}$FN$_5$O$_2$ ([M + H]$^+$), 310.1674; found, 310.1683.

N-(*trans*-2-Fluorocyclohexyl)benzamide (2g): White solid (169 mg, 0.76 mmol, 76% yield; 112 mg, 0.51 mmol, 51% yield). This compound is known.[12b]

N-(*trans*-2-Fluorocyclohexyl)picolinamide (2h): White solid, 95% purity (175 mg, 0.79 mmol, 79% yield; 185 mg, 0.83 mmol, 83% yield); FTIR (thin film, cm^{-1}) 3366, 2940, 2864, 1663, 1519, 1025; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.55 (d, *J* = 4.2 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 6.9 Hz, 1H), 7.85 (ddd, *J* = 7.7, 7.7, 1.6 Hz, 1H), 7.43 (ddd, *J* = 7.5, 4.7, 1.1 Hz, 1H), 4.44 (dddd, *J* = 50.1, 9.8, 9.7, 4.5 Hz, 1H), 4.21−4.09 (m, 1H), 2.22−2.13 (m, 2H), 1.86−1.80 (m, 1H), 1.75−1.58 (m, 2H), 1.47−1.29 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 164.2, 149.9, 148.1, 137.5, 126.3, 122.5, 93.4 (d, *J* = 179.5 Hz), 52.5 (d, *J* = 18.1 Hz), 31.3 (d, *J* = 17.9 Hz), 30.9 (d, *J* = 5.4 Hz), 24.0, 23.4 (d, *J* = 10.3 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) δ −178.5 (d, *J* = 50.4 Hz); HRMS (ESI+) calculated for C$_{12}$H$_{16}$FN$_2$O ([M + H]$^+$), 223.1247; found, 223.1250.

N-(*trans*-2-Fluorocyclohexyl)thiazole-4-carboxamide (2i). Chromatographed 5−40% acetone-hexanes; white solid (175 mg, 0.77 mmol, 77% yield; 0.75 mmol scale: 131 mg, 0.57 mmol, 77% yield). FTIR (thin film, cm^{-1}) 3333, 3116, 2940, 2863, 1638, 1545, 1490, 1027; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.75 (d, *J* = 2.1 Hz, 1H), 8.18 (d, *J* = 2.1 Hz, 1H), 7.40 (br s, 1H), 4.40 (dddd, *J* = 50.1, 9.7, 9.7, 4.5 Hz, 1H), 4.19−4.08 (m, 1H), 2.25−2.11 (m, 2H), 1.86−1.79 (m, 1H), 1.75−1.60 (m, 2H), 1.48−1.28 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 160.8, 152.7, 151.2, 123.5, 93.4 (d, *J* = 179.6 Hz), 52.5 (d, *J* = 19.4 Hz), 31.3 (d, *J* = 18.2 Hz), 31.0 (d, *J* = 4.8 Hz), 24.4, 23.4 (d, *J* = 10.2 Hz); ^{19}F NMR (282 MHz, CDCl3) δ −178.5 (d, *J* = 44.1 Hz);

HRMS (ESI+) calculated for C$_{10}$H$_{14}$FN$_2$OS ([M + H]$^+$), 229.0811; found, 229.0810.

N-(*trans*-2-Fluorocyclohexyl)-4-nitrobenzamide (2j). Chromatographed 5−40% acetone-hexanes; white solid (203 mg, 0.76 mmol, 76% yield; 0.85 mmol scale: 191 mg, 0.72 mmol, 84% yield). FTIR (thin film, cm^{-1}) 3290, 2931, 2864, 1637, 1548, 1520, 1338, 1029, 694; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.29 (d, *J* = 8.7 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H), 6.18 (d, *J* = 6.2 Hz, 1H), 4.40 (dddd, *J* = 24.7, 10.2, 10.2, 4.6 Hz, 1H), 4.17−4.09 (m, 1H), 2.31−2.16 (m, 2H), 1.86 (d, *J* = 12.7 Hz, 1H), 1.73 (d, *J* = 11.4 Hz, 1H), 1.69−1.60 (m, 1H), 1.46−1.29 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.6, 149.7, 140.4, 128.3 (2C), 124.0 (2C), 93.5 (d, *J* = 179.7 Hz), 54.1 (d, *J* = 17.4 Hz), 31.6 (d, *J* = 17.4 Hz), 31.1 (d, *J* = 5.6 Hz), 24.0 (d, *J* = 1.6 Hz), 23.6 (d, *J* = 10.5 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) δ −178.5 (d, *J* = 50.9 Hz); HRMS (ESI+) calculated for C$_{13}$H$_{16}$FN$_2$O$_3$ ([M + H]$^+$), 267.1145; found, 267.1129.

N-(*trans*-2-Fluorocyclohexyl)-4-methylbenzenesulfonamide (2k): White solid (115 mg, 0.42 mmol, 42% yield; 136 mg, 0.5 mmol, 50% yield). This compound is known.[12b]

***trans*-N-Benzyl-2-fluorocyclopentanamine (4):** Clear oil (160 mg, 0.83 mmol, 83% yield; 156 mg, 0.81 mmol, 81% yield); FTIR (thin film, cm^{-1}) 3029, 2958, 2875, 1454, 1357, 1109; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36−7.27 (m, 5H), 4.87 (dddd, *J* = 53.3, 5.5, 2.6, 2.6 Hz, 1H), 3.82 (s, 2H), 3.26 (dddd, *J* = 15.1, 6.5, 6.4, 2.3 Hz, 1H), 2.11−1.71 (m, 5H), 1.43−1.33 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 140.3, 128.6 (2C), 128.3 (2C), 127.2, 100.1 (d, *J* = 175.3 Hz), 64.5 (d, *J* = 23.9 Hz), 52.7, 31.6 (d, *J* = 21.8 Hz), 31.4 (d, *J* = 2.9 Hz), 21.8 (d, *J* = 1.9 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) δ −175.8 (dddd, *J* = 54.0, 30.5, 24.1, 21.1 Hz); HRMS (ESI+) calculated for C$_{12}$H$_{17}$FN ([M + H]$^+$), 194.1345; found, 194.1340.

***tert*-Butyl (*trans*-(*Z*)-8-Fluorocyclooct-4-en-1-yl)carbamate (6).** Extracted with Et$_2$O; chromatographed 3−30% Et$_2$O-hexanes; white solid (196 mg, 0.806 mmol, 81% yield; 195 mg, 0.801 mmol, 80% yield). FTIR (thin film, cm^{-1}) 3345, 2932, 1695, 1518, 1366, 1251, 1171, 1023; ^{1}H NMR (501 MHz, CDCl$_3$) δ 5.72−5.58 (m, 2H), 4.70 (br s, 1H), 4.49 (ddd, *J* = 48.3, 6.5, 6.5 Hz, 1H), 4.02 (br s, 1H), 2.47−2.36 (m, 1H), 2.33−2.23 (m, 1H), 2.23−2.11 (m, 3H), 2.10−1.98 (m, 1H), 1.98−1.86 (m, 1H), 1.52 (ddd, *J* = 14.7, 10.9, 5.7 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.7, 130.1, 128.7, 94.4 (d, *J* = 173.8 Hz), 79.5, 52.5 (d, *J* = 18.5 Hz), 32.0 (d, *J* = 22.7 Hz), 31.6 (d, *J* = 4.1 Hz), 28.5 (3C), 23.0, 22.3 (d, *J* = 9.6 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) δ −178.9 (m); HRMS (ESI+) calculated for C$_{13}$H$_{22}$FNNaO$_2$ ([M + Na]$^+$), 266.1527; found, 266.1533.

(9*H*-Fluoren-9-yl)methyl (*trans*-6-Fluorodecan-5-yl)carbamate (8). Performed on a 0.5 mmol scale; chromatographed without aqueous workup, 2−20% Et$_2$O-hexanes; white solid, 92% purity (189 mg, 95% yield; 176 mg, 89% yield); analytically pure product was obtained by preparatory SFC (162 mg, 0.408 mmol, 81% yield). FTIR (thin film, cm^{-1}) 3305, 2957, 2931, 2859, 1687, 1539, 1253, 1117, 1043; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.41 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.32 (ddd, *J* = 7.3, 7.3, 1.1 Hz, 2H), 4.76 (d, *J* = 10.0 Hz, 1H), 4.47 (dddd, *J* = 47.8, 8.5, 4.4, 1.4 Hz, 1H), 4.44 (d, *J* = 7.0 Hz, 2H), 4.23 (t, *J* = 6.8 Hz, 1H), 3.70 (dddd, *J* = 28.5, 8.3, 8.3, 8.3 Hz, 1H), 1.76−1.13 (m, 12H), 0.90 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 156.6, 144.0 (2C), 141.5 (2C), 127.8 (2C), 127.2 (2C), 125.2 (2C), 120.1 (2C), 95.5 (d, *J* = 171.9 Hz), 66.7, 53.6 (d, *J* = 18.7 Hz), 47.5, 32.5, 31.6 (d, *J* = 20.8 Hz), 28.2, 27.5 (d, *J* = 5.1 Hz), 22.7, 22.6, 14.15, 14.13; ^{19}F NMR (282 MHz, CDCl$_3$) δ −196.6 (ddd, *J* = 76.2, 38.5, 22.4 Hz); HRMS (ESI+) calculated for C$_{25}$H$_{33}$FNO$_2$ ([M + H]$^+$), 398.2490; found, 398.2483.

***trans*-Benzyl 3-((*tert*-Butoxycarbonyl)amino)-4-fluoropyrrolidine-1-carboxylate (10):** Clear oil (281 mg, 0.83 mmol, 83% yield; 274 mg, 0.81 mmol, 81% yield); FTIR (thin film, cm^{-1}) 3310, 2977, 1682, 1524, 1420, 1357, 1166, 1111, 768; ^{1}H NMR (500 MHz, CDCl$_3$, mixture of rotamers) δ 7.40−7.30 (m, 5H), 5.14 (s, 2H), 5.05 (dd, *J* = 50.1, 13.4 Hz, 1H), 4.60−4.50 (m, 1H), 4.31−4.16 (m, 1H), 3.78−3.58 (m, 3H), 3.50 (d, *J* = 12.1 Hz, 0.5H), 3.44 (d, *J* = 11.8 Hz, 0.5H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$, mixture of

rotamers; rotameric peaks indicated by *) δ 154.92, 154.89, 136.4, 128.7 (2C), 128.3 (2C), 128.2, 94.0 (d, J = 182.0 Hz), 93.1* (d, J = 181.6 Hz), 80.7, 67.4, 54.8 (d, J = 28.2 Hz), 54.0* (d, J = 27.0 Hz), 50.4 (d, J = 23.5 Hz), 50.1* (d, J = 23.5 Hz), 49.7, 49.6*, 28.4 (3C); ^{19}F NMR (282 MHz, MeOD) δ −181.5 (ddddd, J = 90.4, 49.8, 34.5, 28.9, 11.4); HRMS (ESI+) calculated for $C_{17}H_{23}FN_2NaO_4$ ([M + Na]$^+$), 361.1534; found, 361.1544.

(2R,3S)-Methyl 2-((tert-Butoxycarbonyl)amino)-3-fluorobutanoate (12). Extracted with Et$_2$O; chromatographed 1−15% acetone-hexanes; pale yellow oil (192 mg, 0.82 mmol, 82% yield, 10:1 dr; after 48 h: 141 mg, 0.60 mmol, 60% yield, 6:1 dr). FTIR (thin film, cm$^{−1}$) 3367, 2984, 2927, 1745, 1718, 1512, 1368, 1166; ^1H NMR (500 MHz, CDCl$_3$) δ 5.38 (d, J = 7.4 Hz, 1H), 4.86 (dm, J_{HF} = 46.9 Hz, 1H), 4.46 (dd, J = 22.7, 6.6 Hz, 1H), 3.80 (s, 3H), 1.47−1.39 (s, 9H + m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.6 (d, J = 5.0 Hz), 155.2, 90.7 (d, J = 175.5 Hz), 80.6, 57.7 (d, J = 22.0 Hz), 52.7, 28.4 (3C), 17.5 (d, J = 22.3 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) δ major: −184.2 (ddq, J = 47.4, 23.7, 23.7 Hz); minor: −185.8 (m); HRMS (ESI+) calculated for $C_{10}H_{18}FNNaO_4$ ([M + Na]$^+$), 258.1112; found, 258.1114; $[\alpha]_D^{21}$ = +15.1 (CHCl$_3$, c = 1.39, 98% ee); GC (β-TBDAc, 1 mL/min, 100 °C, 20 min, 10 °C/min, 130 °C, 15 min): t_R(minor) = 31.2 min, t_R(major) = 33.0 min. The ^1H NMR data for both diastereomers have been reported.[36]

(3S,4S)-Benzyl 3-((tert-Butoxycarbonyl)amino)-4-fluoropiperidine-1-carboxylate (14): Clear viscous oil (258 mg, 0.73 mmol, 73% yield, 11:1 rr; on 0.75 mmol scale: 209 mg, 0.59 mmol, 79% yield, 11:1 rr); FTIR (thin film, cm$^{−1}$) 3330, 2977, 1683, 1523, 1429, 1365, 1229, 1160, 1017, 735; ^1H NMR (500 MHz, MeOD) δ 7.44−7.28 (m, 5H), 5.14 (s, 2H), 4.49 (dd, J = 48.8, 3.7 Hz, 1H), 4.03−3.77 (m, 2H), 3.69−3.57 (m, 1H), 3.27−2.97 (m, 2H), 2.18−2.02 (m, 1H), 1.77−1.63 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, MeOD) δ 157.8, 156.8, 138.0, 129.6 (2C), 129.2, 129.0, 128.8, 91.2 (d, J = 180.0 Hz), 80.5, 68.5, 52.0 (d, J = 21.1 Hz), 46.5 (d, J = 4.4 Hz), 41.7, 30.6 (d, J = 43.3 Hz), 28.7 (3C); ^{19}F NMR (282 MHz, MeOD) δ major: −184.9 (m); minor: −190.5 (m); HRMS (ESI+) calculated for $C_{18}H_{25}FN_2NaO_4$ ([M + Na]$^+$), 375.1696; found, 375.1691.

(1S,2S)-2-Fluoro-N-((S)-1-phenylethyl)cyclohexanamine ((1S,2S,1'S)-16). Extracted with DCM; chromatographed 5−40% EtOAc-hexanes; clear oil (140 mg, 0.63 mmol, 63% yield, >30:1 dr; 126 mg, 0.57 mmol, 57% yield, >30:1 dr). FTIR (thin film, cm$^{−1}$) 3026, 2936, 2863, 1493, 1450, 1130, 1025, 761; ^1H NMR (500 MHz, CDCl$_3$) δ 7.36−7.28 (m, 4H), 7.25−7.19 (m, 1H), 4.29 (dddd, J = 48.9, 10.5, 10.4, 4.7 Hz, 1H), 3.98 (q, J = 6.6 Hz, 1H), 2.57 (qd, J = 9.9, 4.3 Hz, 1H), 2.10−1.99 (m, 1H), 1.72−1.38 (m, 5H), 1.34 (d, J = 6.6 Hz, 3H), 1.28−0.95 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 147.0, 128.5 (2C), 126.8, 126.6 (2C), 97.7 (d, J = 174.2 Hz), 59.3 (d, J = 16.3 Hz), 56.8 (d, J = 1.8 Hz), 31.7 (d, J = 7.5 Hz), 31.3 (d, J = 18.0 Hz), 24.9, 24.1 (d, J = 1.6 Hz), 23.7 (d, J = 11.1 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) δ major: −177.2 (d, J = 52.0 Hz); minor: −180.0 (d, J = 51.0 Hz); HRMS (ESI+) calculated for $C_{14}H_{21}FN$ ([M + H]$^+$), 222.1653; found, 222.1656.

tert-Butyl ((1S,2S)-2-Fluorocyclohexyl)carbamate ((S,S)-2a). A round-bottom flask capped with a rubber septum containing (S,S,1'S)-16 (111 mg, 0.5 mmol) and Boc$_2$O (0.33 g, 1.5 mmol) was evacuated and backfilled with N$_2$ (3×). Pd(OH)$_2$/C (20 wt %, 26 mg) was charged, and the flask was again evacuated and backfilled with N$_2$ (3×). EtOH (6.25 mL) was charged via syringe, and the flask was evacuated and backfilled with H$_2$ (3×). The reaction was stirred under a balloon of H$_2$ for 8 h, until TLC indicated complete consumption of the starting material. Upon completion, the reaction was filtered through Celite, rinsing with EtOAc, and concentrated in vacuo. The crude material was purified by column chromatography (5−40% Et$_2$O-hexanes) to obtain the title product as a white solid (107 mg, 0.49 mmol, 98% yield). Spectral data were consistent with those of the racemate; $[\alpha]_D^{22}$ = +27.5 (CHCl$_3$, c = 1.01, 99% ee). GC (Cyclodex-B, 1 mL/min, 130 °C isotherm): t_R(minor) = 34.9, t_R(major) = 35.5 min.

ASSOCIATED CONTENT

S Supporting Information
^1H and ^{13}C NMR spectra, chiral GC traces, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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REFERENCES

(1) Bergstrom, C. G.; Nicholson, R. T.; Dodson, R. M. *J. Org. Chem.* **1963**, *28*, 2633−2640.
(2) For a review, see: Yoneda, N. *Tetrahedron* **1991**, *47*, 5329−5365.
(3) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872−3881 and references therein.
(4) Haufe, G. *J. Prakt. Chem.* **1996**, *338*, 99−113.
(5) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031−1069.
(6) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268−3269.
(7) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 16001−16012.
(8) For a review, see: Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330.
(9) For two examples directly relevant to this work, see: (a) Coburn, C. A.; Egbertson, M. S.; Graham, S. L.; McGaughey, G. B.; Stauffer, S. R.; Yang, W.; Lu, W.; Fahr, B. PCT International Patent Application US2006/027544, July 14, 2006. (b) Burger, M.; Lan, J.; Lindvall, M.; Nishigughi, G.; Tetalman, M. PCT International Patent Application EP2009/052506, March 3, 2009.
(10) (a) O'Hagan, D. *Chem. Soc. Rev* **2008**, *37*, 308−319. For examples, see: (b) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem* **2007**, *2*, 1100−1115.
(11) For examples, see: (a) Andrews, P. C.; Bhaskar, V.; Bromfield, K. M.; Dodd, A. M.; Duggan, P. J.; Duggan, S. A. M.; McCarthy, T. D. *Synlett* **2004**, 791−794. (b) Malamakal, R. M.; Hess, W. R.; Davis, T. A. *Org. Lett.* **2010**, *12*, 2186−2189. (c) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12*, 3356−3359. (d) Schulte, M. L.; Lindsley, C. W. *Org. Lett.* **2011**, *13*, 5684−5687.
(12) (a) Hu, X. E. *Tetrahedron Lett.* **2002**, *43*, 5315−5318. (b) Fan, R.-H.; Zhou, Y.-G.; Zhang, W.-X.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2004**, *69*, 335−338. (c) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Synlett* **2004**, 2218−2220. (d) van Oosten, E. M.; Gerken, M.; Hazendonk, P.; Shank, R.; Houle, S.; Wilson, A. A.; Vasdev, N. *Tetrahedron Lett.* **2011**, *52*, 4114−4116.
(13) Wade, T. N. *J. Org. Chem.* **1980**, *45*, 5328−5333 and references therein.
(14) Alvernhe, G. M.; Ennakoua, C. M.; Lacombe, S. M.; Laurent, A. J. *J. Org. Chem.* **1981**, *46*, 4938−4948 and references therein.

(15) The hydrofluorinations of aziridines **1b** and **1c** displayed comparable efficiency in glass vials under otherwise identical conditions: **2b** (93% yield), **2c** (84% yield).

(16) Sasaki, M.; Dailili, S.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 2045−2047.

(17) Arai, H.; Sugaya, N.; Sasaki, N.; Makino, K.; Lectard, S.; Hamada, Y. *Tetrahedron Lett.* **2009**, *50*, 3329−3332.

(18) Schramm, H.; Pavlova, M.; Hoenke, C.; Christoffers, J. *Synthesis* **2009**, 1659−1662.

(19) (a) le Huerou, Y.; Blake, J. F.; Gunwardana, I. W.; Mohr, P.; Wallace, E. M.; Wang, B.; Chicarelli, M.; Lyon, M. PCT International Patent Application US2009/043691, May 13, 2009. (b) Ninkovic, S.; Braganza, J. F.; Collins, M. R.; Kath, J. C.; Li, H.; Richter, D. T. PCT International Patent Application IB2009/053389, August 4, 2009.

(20) For a recent review, see: Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708−2732.

(21) For representative examples with O, S, Se, and N nucleophiles, see: (a) Chandrasekhar, M.; Sekar, G.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 10079−10083. (b) Ekegren, J. K.; Roth, P.; Källström, K.; Tarnai, T.; Andersson, P. G. *Org. Biomol. Chem.* **2003**, *1*, 358−366. (c) Kumar, M.; Gandhi, S.; Singh Kalra, S.; Singh, V. K. *Synth. Commun.* **2008**, *38*, 1527−1532. (d) Pérez-Bautista, J. A.; Sosa-Rivadeneyra, M.; Quintero, L.; Höpfl, H.; Tejeda-Dominguez, F. A.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2009**, *50*, 5572−5574.

(22) Et_3N-3HF (20 equiv), DCM, rt, 24 h (ref 14): 27% yield, 3.0:1 dr. $KF \cdot 2H_2O$ (2 equiv), n-Bu_4NHSO_4 (1 equiv), MeCN, 45 °C, 24 h (ref 12b): <5% yield, dr not determined.

(23) The relative stereochemistry of the diastereomers was assigned by X-ray crystallography of the minor diastereomer ($1R,2R,1'S$)-**16**·HCl.

(24) Watson, I. D. G.; Afagh, N.; Yudin, A. K. *Org. Synth.* **2010**, *87*, 161−169.

(25) Sasaki, T.; Kanematsu, K.; Yukimoto, Y. *J. Org. Chem.* **1972**, *37*, 890−894.

(26) Tanner, D.; Birgersson, C.; Gogoll, A. *Tetrahedron* **1994**, *50*, 9797−9824.

(27) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084−12085.

(28) Koppel, H. C.; Springer, R. H.; Robins, R. K.; Schneider, F. H.; Cheng, C. C. *J. Org. Chem.* **1962**, *27*, 2173−2177.

(29) da Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* **1993**, *76*, 2602−2615.

(30) Ekegren, J. K.; Roth, P.; Källström, K.; Tarnal, T.; Andersson, P. G. *Org. Biomol. Chem.* **2003**, *1*, 358−366.

(31) Watson, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 5160−5167.

(32) Hayashi, M.; Ono, K.; Hoshimi, H.; Oguni, N. *Tetrahedron* **1996**, *52*, 7817−7832.

(33) Coburn, C. A.; Egbertson, M. S.; Graham, S. L.; McGaughey, G. B.; Stauffer, S. R.; Yang, W.; Lu, W.; Fahr, B. Patent WO 2007/11810 A1, January 25, 2007.

(34) The procedure in ref 31 was used. Spectral data were consistent with literature values: Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515−4523.

(35) Anaya de Parrodi, C.; Moreno, G. E.; Quintero, L.; Juaristi, E. *Tetrahedron: Asymmetry* **1998**, *9*, 2093−2099.

(36) Vidal-Cros, A.; Bory, S.; Gaudry, M.; Marquet, A. *Tetrahedron Lett.* **1989**, *30*, 1799−1802.