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Communication

Development of a Scalable Synthesis of *trans*-4-Fluorocyclohexylamine via Directed Hydrogenation

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ABSTRACT: Herein, a scalable and practical process to prepare *trans*-4-fluorocyclohexylamine hydrochloride (**1a**) is described. By exploitation of the embedded *gem*-difluoride motif in the commercially available 4,4-difluorocyclohexanecarboxylic acid, a derived orthoester-masked acid underwent dehydrofluorination to provide the requisite vinyl fluoride for a directed hydrogenation event, enabling selective access to the *trans*-configuration of **1a**.

KEYWORDS: *vinyl fluoride, directed hydrogenation, dehydrofluorination, trans-4-fluorocyclohexylamine*

INTRODUCTION

Classical protocols to access fluorinated compounds typically involve the use of costly fluorinating reagents and building blocks accompanied by stoichiometric byproducts, rendering these methods difficult for implementation in large-scale production.[1] Efforts have been devoted to simplify and improve the quality of these C−F bond-forming transformations to accommodate the increasing demand for fluorinated compounds in materials science,[2] agricultural,[3] and pharmaceutical industries.[1,4] In the past decade, both academic and industrial researchers sought to develop more user- and environmental-friendly methods to expand the current toolbox for incorporating fluorine into architecturally complex molecules. Due to the unique chemical properties of fluorinated medicinally relevant compounds in the pharmaceutical industry, synthetic strategies to access these molecules remains an active area of investigation. Stereoselective synthesis of these fluorinated compounds is of particular interest owing to the limited methodologies.[5] From the industrial perspective, rapid access to these chiral fluorinated building blocks selectively is vital in accelerating drug discovery programs to expedite the development of a potential drug candidate. Additionally, reagents involved in the synthesis pose direct impact on process safety and production cost. Recently, a comprehensive review by Caron highlighted the challenges in accessing fluorinated molecules in the pharmaceutical industry, providing insights into the unmet synthetic challenges of incorporating fluorine into active pharmaceutical ingredients (APIs).[1]

As part of a recent drug discovery program, *trans*-4-fluorocyclohexylamine (**1**), featuring a *trans*-configuration between the fluorine and the amino group, was a building block of interest (Figure 1). Although this compound is commercially available, it is extremely costly and materials provided by external vendors are predominantly *cis*/*trans*-isomeric mixtures, which required additional chromatographic purification to remove the major, undesired *cis*-isomer.

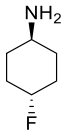

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Figure 1. *trans*-4-fluorocyclohexylamine (**1**).

Following known literature procedures,[6] most methodologies involve inverting the stereogenic center via deoxyfluorination of the corresponding *N*-protected *cis*-alcohol. However, these processes are typically low yielding, require the use of fluorinating reagents that are undesirable for scale-up, and occur with significant amounts of elimination byproduct which can be difficult to separate from the desired product (Scheme 1). Therefore, a practical and scalable synthesis to supply **1** with a high level of *trans*-selectivity needed to be developed.

RESULTS AND DISCUSSION

Our initial investigations to develop a practical and scalable route to **1** focused on establishing the *trans*-configuration by selective reduction of an *N*-sulfinylimine, which could be prepared by condensation with 4-fluorocyclohexanone **7**. Unfortunately, all attempts to access **7** from the corresponding alcohol **8** or from ketal protected derivatives of **8** by S_N2 displacement of derived tosylates or other leaving groups with fluoride or by deoxyfluorination of the alcohol were not successful and resulted almost exclusively in products of elimination (Scheme 2).

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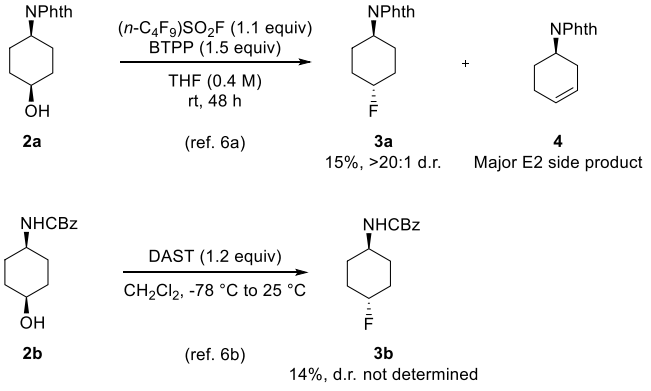
Scheme 1. Literature Reports of Deoxyfluorination[6]



The observed dominant elimination pathway in all attempts to prepare **7** prompted an alternative strategy to exploit readily available fluorinated building blocks. Recently, Glorius and coworkers reported a direct access to all *cis*-(multi)fluorinated cycloalkanes via rhodium−carbene catalyzed hydrogenation of fluoroarenes.[7] As described in the report, TBS-protected phenol **9** could readily undergo hydrogenation to the corresponding *cis*-isomer **10** in >10:1 *cis*/*trans*-selectivity and near quantitative yield on the gram scale (Scheme 3). Theoretically, the corresponding cyclohexanol, upon TBS deprotection, could be displaced with a masked amine equivalent to access the desired *trans*-isomer of **1**. Unfortunately, further evaluation led to the finding that neither the rhodium complex nor the carbene ligand employed in this transformation was commercially available, rendering the strategy impractical for our purposes.

While the fluorophenol hydrogenation approach was not feasible due to the nonavailability of the catalyst and ligand, a new strategy utilizing hydrogenation of a vinyl fluoride emerged. It is known that carboxamide and carboxylate substituents exhibited directing effects when Crabtree's catalyst was employed in the hydrogenation of cyclohexenes.[8] As hypothesized in the report, the amide or ester carbonyl is capable of coordinating to the cationic iridium center, which allows for hydrogen delivery from the same face with respect to the carboxyl moiety, enabling direct access to cyclohexane derivatives with high *trans*-selectivity (Scheme 4).

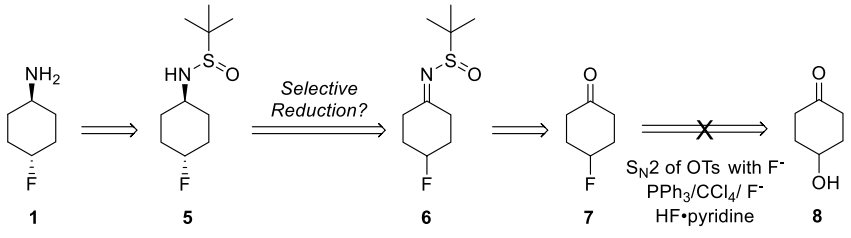
Taking advantage of this concept, we postulated that directed hydrogenation of a vinyl fluoride could allow for a highly diastereoselective synthesis of **1**. While recent advances in methodologies for vinyl fluoride synthesis offer creative approaches to access this moiety,[9] many of these operations are substrate specific and require cryogenic conditions or a transition metal catalyst. To enable quick access to the requisite vinyl fluoride motif to test our hypothesis, we were attracted to a report on the use of XtalFluor-E to convert various cyclohexanones under mild conditions to the corresponding vinyl fluorides (Scheme 5).[10] Our initial attempts focused on exploring amino derivatives as potential directing groups to promote the desired selectivity. With the vinyl fluorides in hand, a variety of amino derivatives were evaluated for their respective directing effects under the reported hydrogenation conditions. Unfortunately, all derivatives offered either no reactivity (R = NHBoc, NHAc) or furnished only the undesired *des*-fluoro product (R = NH_2), suggesting that a carboxylic acid derivative might be required at the 4-position of the cyclohexene.

The observed lack of reactivity prompted the investigation of substrates containing carboxylic acid directing groups. Vinyl fluoride **14** was prepared by the aforementioned deoxyfluorination of the commercially available cyclohexanone **13**. One advantage of having the ester handle in **14** was that simple elaborations gave access to various derivatives, i.e., carboxylic acid **15** and carboxamide **16**, to enable a quick screen of their directing abilities in the hydrogenation event (Scheme 6). Additionally, these functional handles could be readily converted to the required amine via known rearrangement methods.

With the available substrates for our study, we set out to examine the selectivity of the hydrogenation employing the literature conditions. Interestingly, moderate reactivity and stereoselectivity was observed in the case of ester **14**, while acid **15** furnished <5% product (Table 1). In contrast, primary amide **16** provided excellent *trans*/*cis*-selectivity, resulting in predominantly the desired *trans*-isomer (≥95:5 d.r.). Notably, during the hydrogenation screening, olefin migration was not detected by ^{1}H NMR. Guided by this encouraging result, more in-depth process optimization was initiated to supply high-quality **1** for our discovery program.

Development of Practical Vinyl Fluoride Synthesis. Having established the directed hydrogenation of the carboxamide **16**, production of vinyl fluoride **14** was scaled up to over the 100 g scale. Unfortunately, the deoxyfluorination method used to access the vinyl fluoride moiety was accompanied by formation of a *gem*-difluoride byproduct. Formation of this impurity significantly increased with scale up to 30%, and it was not possible to remove the impurity by chromatographic purification of the ester **14**, which was an oil. The acid **15** and the amide **16** were both crystalline solids, but recrystallization of these intermediates also failed to purge the corresponding *gem*-difluoride impurities. In addition, the fluorination reaction itself posed operational and safety challenges due to the highly corrosive nature of the reaction mixture which contained 3 equiv of XtalFluor-E and 2 equiv of $Et_3N{\cdot}3HF$. Any glass-on-glass contacts in the reaction setup would become fused during the course of the reaction. On larger scale in the lab, quenching and workup of the reaction mixture proved to be laborious and volume intense, and the

Scheme 2. Proposed Retrosynthetic Analysis of 1 via Selective Reduction



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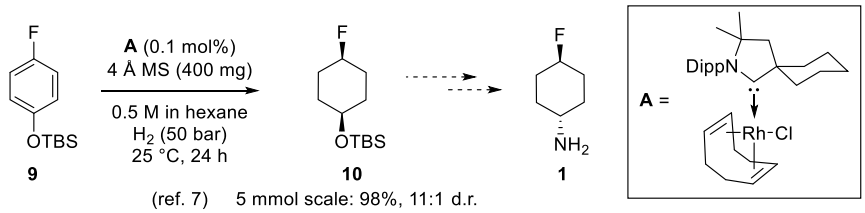
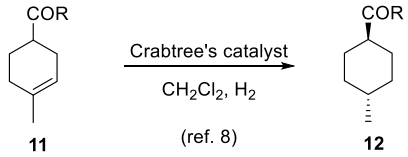
Scheme 3. Proposed Synthetic Approach to 1 Using Rh-Catalyzed Hydrogenation Reported by Glorius[7]



(ref. 7) 5 mmol scale: 98%, 11:1 d.r.

Scheme 4. Iridium-Catalyzed Stereoselective Hydrogenation[8]



R = OMe, **11a**
R = N(CH$_2$)$_4$, **11b**

12a: 87%, 41:1 *trans*:*cis*
12b: 90%, 130:1 *trans*:*cis*

waste generated from this process required special segregation due to the high fluoride content. Further scale-up beyond the lab was not pursued due to these issues.

The challenges in removing the major *gem*-difluoride impurity along with the cost and operational difficulties associated with use of XtalFluor-E necessitated the development of a practical and scalable synthesis of vinyl fluoride **14**. During our investigation on methods to recycle the *gem*-difluoride byproducts from deoxyfluorination, a strategy exploiting the *gem*-difluoride emerged. We proposed that an appropriate base could potentially promote an elimination pathway to access the requisite vinyl fluoride moiety. To test this, elimination of commercially available 4,4-difluorocyclohexanecarboxylic acid **19** was attempted and was unsuccessful. To ensure that the acid moiety was not interfering with the elimination, acid **19** was subsequently masked as Corey's OBO-ester through a rearrangement of ester **20** mediated by $BF_3{\cdot}OEt_2$, setting the stage for investigating the feasibility of the subsequent elimination (Scheme 7).

While preparation of the vinyl fluoride motif by way of dehydrofluorination of *gem*-difluorides is known, conditions are typically harsh or are limited to activated substrates.[11] The initial screen using metal bis(trimethylsilyl)amide bases did not provide any desired product. Of the bases screened for the elimination reaction, alkoxides at elevated temperature afforded the desired vinyl fluoride **22**, albeit in low conversions (Table 2, entries 7−9). Switching to potassium *t*-amylate (KO*t*-Amyl) led to a remarkable increase in conversion to desired product (entries 10 and 11).

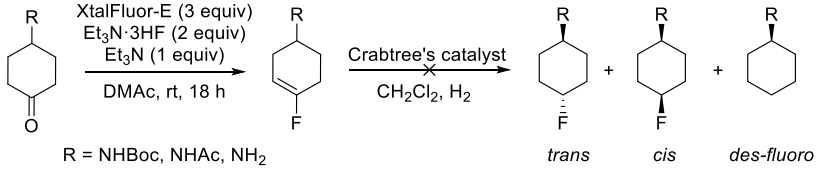
With this encouraging result, further optimization led to complete consumption of the *gem*-difluoride **21** in the presence of 4 equiv of KO*t*-Amyl in xylene at reflux for 24 h (Scheme 8). Surprisingly, when dehydrofluorination was performed on the gram scale, the reaction resulted in a mixture of **22** and a major side product, later confirmed as the *t*-amyl vinyl ether **23**. Presumably, an excess amount of base promoted displacement of the initially formed vinyl fluoride that led to formation of vinyl ether **23**.

Although vinyl ether byproduct **23** could be purged in the subsequent orthoester deprotection step, further evaluation of the reaction conditions was desired to avoid or minimize formation of this byproduct. Reaction parameters were extensively studied. Overall, potassium alkoxide bases were proven crucial for promoting dehydrofluorination. More importantly, reaction concentration and temperature were critical in avoiding vinyl ether formation. Although near complete consumption of *gem*-difluoride **21** could be achieved with excess base, i.e., 3 equiv, a 3:1 mixture of vinyl fluoride/vinyl ether was obtained (Table 3, entry 2). Extended reaction time was required for lower base loading as the reaction appeared to be more sluggish (entry 3).

Fine-tuning of base stoichiometry and reaction time led to the optimal conditions of 2 equiv of KO*t*-Amyl for 96−120 h. It is also worth noting that commercial KO*t*-Amyl is available as a 25% solution in toluene and can be used directly without further dilution with additional solvent. Not only was this process scalable and easy to operate, it provided a safer and more practical alternative to synthesize the vinyl fluoride motif required for the subsequent chemistry. With the dehydrofluorination method in place, vinyl fluoride **22** was readily prepared on an over 100 g scale in excellent yields (Scheme 9). Deprotection of the OBO-ester under mild conditions revealed the carboxylic acid, which was further converted to carboxamide **16** for the directed hydrogenation. Importantly, residual imidazole (as low as 0.07 wt %) from the amidation mediated by CDI could affect the diastereoselectivity of the subsequent hydrogenation step, along with formation of a *des*-fluoro impurity. To our delight, isolated amide could be slurried in a minimal amount (1−1.5 vol) of cold water to ensure complete removal of residual imidazole while minimizing loss of water-soluble **16**.

Directed Hydrogenation of Vinyl Fluoride 16. As previously mentioned, the directed hydrogenation employing Crabtree's catalyst revealed that a primary amide at the 4-position of the cyclohexene was critical in achieving high *trans*-diastereoselectivity. Unfortunately, defluorination was observed on scale, suggesting that a different transition metal

Scheme 5. Ir-Catalyzed Hydrogenation of Vinyl Fluorides Bearing Amino Groups



R = NHBoc, NHAc, NH$_2$ *trans* *cis* *des-fluoro*

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Scheme 6. Synthesis of Vinyl Fluorides with Different Carboxylic Acid Derivatives

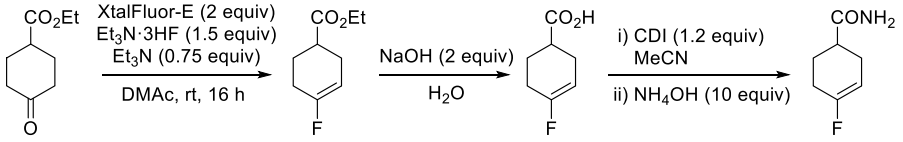
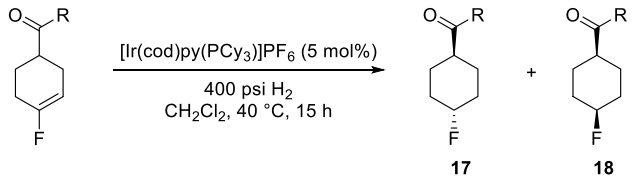


Table 1. Ir-Catalyzed Hydrogenation of Vinyl Fluorides Containing Carboxylic Acid Derivatives



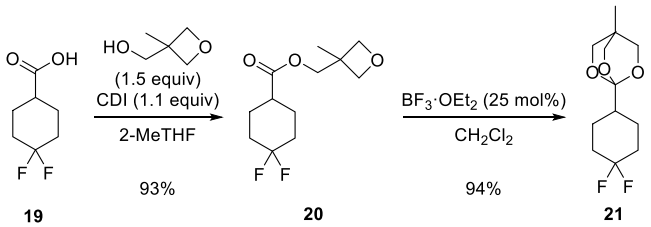
14: R = OEt
15: R = OH
16: R = NH_2

17a, 18a: R = OEt
17b, 18b: R = OH
17c, 18c: R = NH_2

entry	R	% conversion[a]	% yield[a]	17:18[a]
1	OEt (**14**)	77	18	72:28
2	OH (**15**)	22	<5	N/D
3	NH_2 (**16**)[b]	95	69	>95:5

[a]Conversions and yields were determined by ^{1}H NMR. [b]2 mol % [Ir(cod)py(PCy_3)]PF_6 was used.

Scheme 7. Preparation of OBO-Ester 21

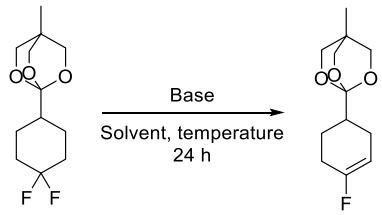


might be required to circumvent this problem. This observation was in agreement with the report by Krska et al.[12] Thus, we turned our attention to cationic rhodium catalysts to minimize the undesired defluorination pathway.

Both chiral and achiral bidentate phosphine ligands delivered moderate to good reactivity and excellent *trans*-selectivity in all cases except for DPPB. Unlike previously reported conditions by Krska et al., use of methanol as solvent led to a significant amount of *des*-**F-17c** (Table 4, entry 6), while <1% *des*-**F-17c** was observed with dichloromethane (entry 3).[12] Due to the urgent request for >100 g of **1** in a short time, the nonproprietary DPDBF ligand was selected for further optimization on the basis of its clean reaction profile and lower cost compared to SL-J002-1 without further screening.

At the 40 g scale, it was found that 1.0 mol % Rh was sufficient to achieve complete conversion of vinyl fluoride to obtain the isolated product in 82−86% yield. However, the process suffered from several drawbacks such as the use of toxic dichloromethane, prolonged reaction time (12−24 h), and the need for a solvent switch from dichloromethane to hexanes to isolate the product (Table 5, entry 1 and 2). Further process optimization studies revealed that the same reaction efficiency could be achieved with lower rhodium loading (0.5%) and in a much shorter time (4 h) when THF

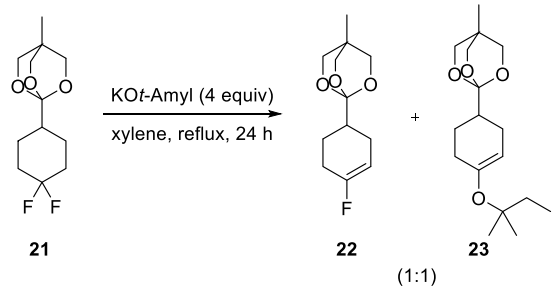
Table 2. Screening of Elimination of *gem*-Difluoride 21[a]



entry	base	solvent	temp (°C)	% conversion[b]
1	LiHMDS	THF	−20 to rt	NR
2	NaHMDS	THF	−20 to rt	NR
3	KHMDS	THF	−20 to rt	NR
4	KHMDS	PhMe	110	NR
5	LDA	THF	−78 to rt	NR
6	*n*-BuLi	THF	−78 to 0	5
7	NaO*t*-Amyl	PhMe	110	3[c]
8	KO*t*-Bu	THF	65	5
9	KO*t*-Bu/*t*-BuOH	PhMe	110	10[c]
10	KO*t*-Amyl	PhMe	110	97.5[c]
11	KO*t*-Amyl	PhMe	120	99.5
12	DBU	NMP	120	5

[a]Reactions were conducted on 100 mg scale. [b]Conversions were obtained by GCMS and were confirmed by ^{19}F-NMR. [c]40 h.

Scheme 8. Byproduct Vinyl Ether Formation



was used as solvent. In addition, the product can be precipitated in >99 wt % purity simply by adding heptane to the crude product mixture. Attempts to reduce the catalyst loading to 0.2% led to incomplete conversion.

Although a reliable and reproducible directed hydrogenation process was demonstrated, the intermittent commercial availability of the DPDBF ligand might pose potential problems if **1** was needed in kilogram quantities. Continued screening identified the more accessible DTBPF as an equally effective replacement for DPDBF. Interestingly, DTBPF delivered complete conversion and consistently >90% yield even at 0.1% rhodium. It is worth mentioning that imidazole present in the vinyl fluoride in trace amount (<0.1% by ^{1}H NMR) diminished reaction efficiency and lowered *trans*-selectivity (Table 6, entry 5), which was most likely a result

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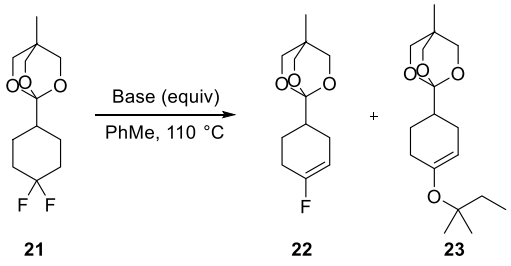
Table 3. Optimization of Base Stoichiometry[a]



entry	base	equiv	% conversion[b]
1	KO*t*-Bu (solid)	1.5	18
2	KO*t*-Amyl	3.0	97.2, 3:1 **21**:**22**
3	KO*t*-Amyl	1.5	92.9[c]

[a]Reactions were conducted on 1 g scale. [b]Conversions were determined by GCMS. [c]72 h.

of competitive binding of imidazole to the cationic rhodium center.

End Game to 1a: Hofmann Rearrangement. With carboxamide **17c** in hand, the conversion to the amine by way of a Hofmann rearrangement was explored. Although many reagents may be employed to effect the Hofmann rearrangement, we were particularly attracted to a report using $PhI(OAc)_2$ due to the simplicity and mild reaction conditions.[13a] Notably, use of $PhI(OAc)_2$ in Hofmann rearrangement has been demonstrated on the kilogram scale production,[13] which further demonstrates the safety and scalability of the reaction. Simply stirring a solution of the carboxamide and $PhI(OAc)_2$ in a mixture of MeCN and water at rt resulted in complete conversion, but a significant amount (15%) of symmetrical urea byproduct **24** was also formed (Scheme 10). To minimize urea formation, HCl and TFA were examined as acid additives in the reaction. Addition of HCl provided little conversion to **1a** and led to formation of other unknown impurities. Pleasingly, in the presence of TFA, a clean reaction profile was obtained with only minor amounts of urea byproduct that could readily be removed upon recrystallization from MTBE/MeCN.

To confirm the established *trans*-geometry of the fluoro and amino groups of **1a**, corresponding 4-bromobenzamide derivative was prepared to obtain a single-crystal X-ray (Figure 2). The crystal structure determined was in agreement with our assigned *trans*-configuration of **1a**.

CONCLUSIONS

In summary, a seven-step synthesis of **1a** was developed starting from the widely available and inexpensive 4,4-difluorocyclohexanecarboxylic acid **19** (Scheme 11). By exploitation of an orthoester to protect the carboxylic acid, access to the vinyl fluoride was made feasible without the use of fluorinating reagents on scale. This route eliminated the concerns for associated *gem*-difluoride byproduct, rendering the approach greener and more efficient. Subsequent implementation of a highly diastereoselective directed hydrogenation allowed for clean delivery of carboxamide **17c** as a single *trans*-isomer. Finally, a mild Hofmann rearrangement converted the amide group in **17c** to the required amino group in **1**. Overall, scalability and practicality of this synthesis was demonstrated by its ease of product isolation and purification by way of recrystallization, enabling production of **1a** of high quality and purity.

EXPERIMENTAL SECTION

General Information. Commercially available reagents and solvents were used without further purification unless stated otherwise. NMR spectra (^1H, ^{13}C, ^{19}F) were recorded on a Bruker DRX-500 using $CDCl_3$ or DMSO-d_6 as solvent unless stated otherwise. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz) and referenced relative to TMS (0 ppm). The following abbreviations are used to indicate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, dq = doublet of quartets, td = triplet of doublets, qd = quartet of doublets, ddt = doublet of doublet of triplets, m = multiplet, app = apparent, and br = broad resonance. Analysis by gas chromatography−mass spectrometry (GC−MS) was performed on an Agilent 6890N GC system equipped with MS (70 eV electron Impact (EI, positive)) with the following conditions: Agilent HP-5MS column (ID 0.25 mm, length 30 m, film thickness 0.25 μm); run time 12 min, temperature hold at 100 °C for 2 min, ramp 25 °C/min to 300 °C, hold at 300 °C for 2 min; inlet split 30:1, inlet temperature 280 °C; carrier gas helium at a constant flow mode at a flow rate 1.0 mL/min. Differential scanning calorimetry was performed on a Mettler Toledo DSC 3^+ featuring sensor FRS 6^+. High-resolution mass spectrometry (HRMS) data were obtained on Thermo LTQ FT Ultra mass spectrometer at 100 000 resolving power using direct analysis in real time (DART) source ionization in the positive ion mode. Analysis by ultraperformance liquid chromatography−mass spectrometry (UPLC−MS) was performed on a Waters UPLC-MS (TQD) equipped with MS (electrospray positive/negative ionization) with the following conditions: Acquity UPLC BEH C18 column (ID 2.1 mm, length 5 cm, particle diameter 1.7 μm); run time 3 min, temperature 30 °C, injection volume 0.5 μL, flow rate 0.6 mL/min and post run 0.5 min; mobile phase A, water with 0.1% formic acid (HPLC grade); mobile phase B, acetonitrile (HPLC grade); gradient starts at 15% B at 0 min, ramps to 95% B over 2.1 min, is held at 95% B from 2.1 to 2.7 min, and ends at 15% B at 3.0 min.

Scheme 9. Preparation of Hydrogenation Precursor 16

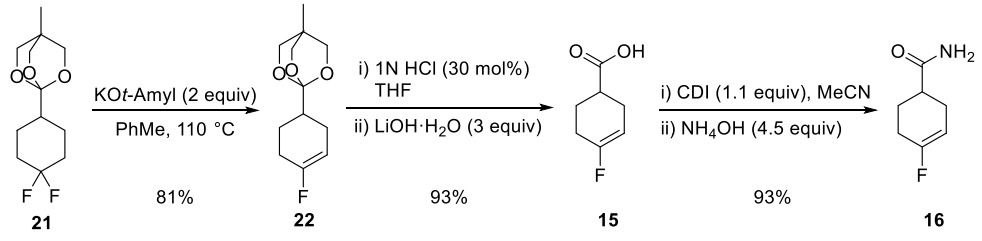


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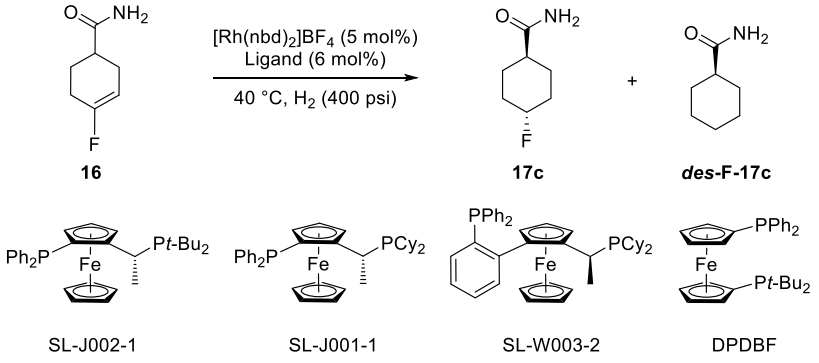
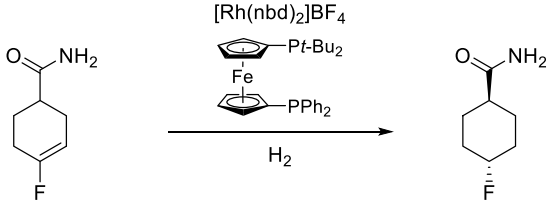
Table 4. Screening of Cationic Rhodium Catalysts with Bidentate Phosphine Ligands[a]



entry	ligand	time (h)	A% **16**	A% **17c**	A% ***des*-F-17c**
1	DPPB	12	100	0	0
2	SL-J002-1	12	14	86	0
3	SL-J001-1	4	29	71	0
4	SL-J001-1[b]	4	18	54	28
5	SL-W003-2	4	11	36	53
6	*rac*-BINAP	12	20	74	6
7	DPDBF	12	14	86	0
8	DPPF	12	19	77	4

[a]A% was determined by UPLC-MS. [b]MeOH as solvent.

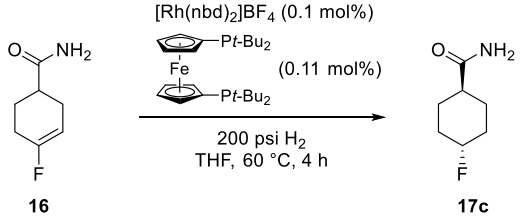
Table 5. Directed Hydrogenation of 16 with DPDBF



entry	% Rh loading	% DPDBF loading	H_2 pressure (psi)	solvent	temp (°C), time (h)	% yield[a]
1	1.0	1.1	400	CH_2Cl_2	40, 24	86
2	1.0	1.1	400	CH_2Cl_2	40, 12	82
3	0.5	0.55	100	THF	60, 4	86

[a]Isolated yields.

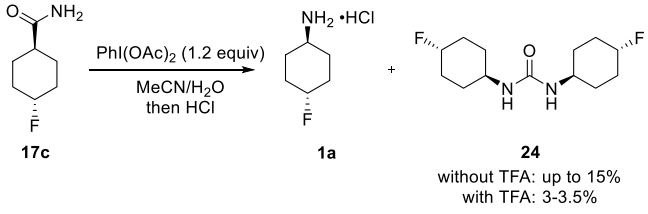
Table 6. Directed Hydrogenation of 16 with DTBPF



entry	scale (g)	% conversion	*trans*:*cis*	% yield[a]
1	55	>95	>98:2	86
2	40	>95	>98:2	96
3	40	>95	>98:2	96
4	40	>95	>98:2	92
5	42	>95	>98:2	94
6[b]	4	71	83:17	N/D

[a]Isolated yields. [b]<0.1 mol % imidazole present in the vinyl fluoride starting material.

Scheme 10. Hofmann Rearrangement of Carboxamide 17c to 1a



(3-Methyloxetan-3-yl)methyl 4,4-difluorocyclohexane-1-carboxylate (20). To a solution of 4,4-difluorocyclohexane-1-carboxylic acid (**19**) (200.0 g, 1.22 mol, 1.0 equiv) in 2-MeTHF (1.6 L, 8 vol) at 0 °C was charged 1,1′-carbonyldiimidazole (CDI) (217.3 g, 1.34 mol, 1.1 equiv) in six portions. (Note: rapid gas evolution was observed.) The resulting solution mixture was warmed to rt and was stirred at rt for 1 h, at which point 3-methyl-3-oxetanemethanol (182.3 mL, 1.83 mol, 1.5 equiv) was charged. The resulting reaction mixture continued to stir at rt overnight. Upon reaction completion, the reaction mixture was quenched with H_2O (1.0 L, 5 vol). The organic layer was washed with water and saturated $NaHCO_3$ (1.0 L, 5 vol) to remove unreacted acid, followed by a wash with 1 N HCl (1.0 L, 5 vol) and a final wash with H_2O (1.0 L, 5 vol) to remove residual CDI. The organic layer was subsequently concentrated under reduced pressure to an oil, at which point PhMe (200.0 mL, 1 vol) was added and the resulting solution was further concentrated under reduced pressure to afford 328.6 g of crude **20** as a yellow oil (92.5% assay yield).

1-(4,4-Difluorocyclohexyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (21). To a solution of crude **20** (328.6 g, 1.13 mol, 1 equiv) in CH_2Cl_2 (1.6 L, 5 vol) at 0 °C was charged $BF_3{\cdot}OEt_2$ (34.9 mL, 0.28 mol, 25 mol %). The resulting reaction mixture was slowly warmed to rt over 30 min and continued to stir at rt for 12−14 h. When **20** was consumed, Et_3N (157.8 mL, 1.13 mol, 1 equiv) was charged.

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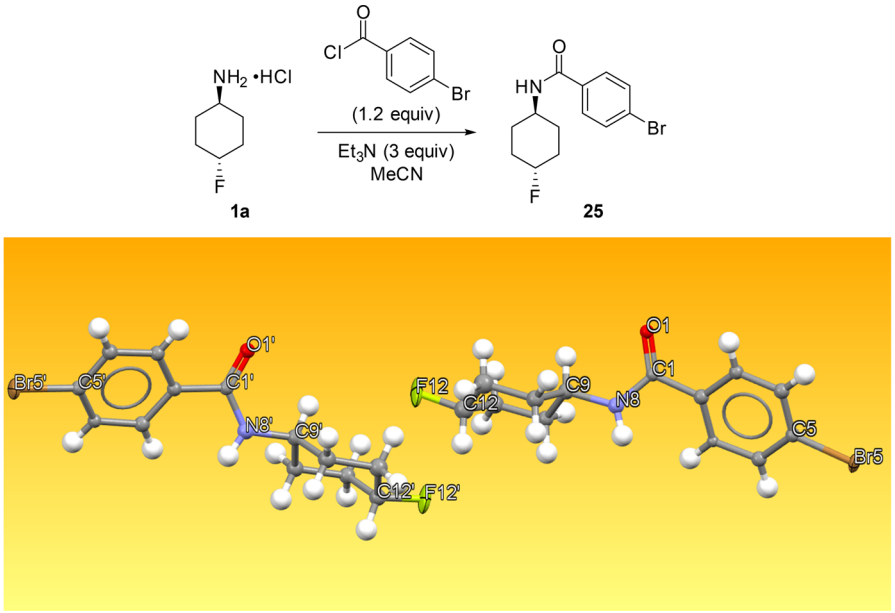
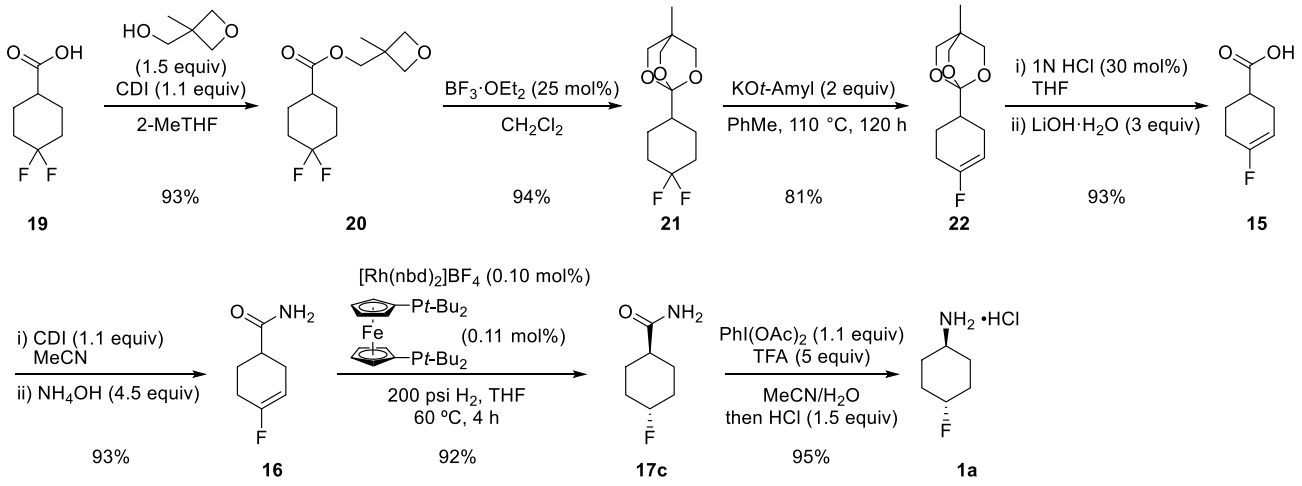


Figure 2. Thermal ellipsoid plot of **25** in the crystal structure.

Scheme 11. Optimized Synthesis of 1a



The reaction mixture continued to stir at the same temperature for 30 min, at which point 1 N NaOH (657.2 mL, 2 vol) was added to quench the reaction mixture. The organic layer was washed with H_2O (657.2 mL, 2 vol) and was concentrated under reduced pressure to afford an oil, to which 2-MeTHF (821.5 mL, 2.5 vol) was charged. The resulting slurry was heated to 60−65 °C to reach homogeneity and was subsequently cooled to rt over 1 h. Heptane (2.5 L, 7.5 vol) was charged slowly. The resulting slurry was stirred for 1 h at rt, further cooled to 0 °C over 30 min, and stirred for an additional hour. Solids were collected by filtration, rinsed with heptane (328.6 mL, 1 vol), and dried at 30 °C under vacuum with a nitrogen bleed for 12 h to afford 205.8 g of **21** as an off-white solid (crop 1). Mother liquor was concentrated under reduced pressure to give crude solids, which were dissolved in 2-MeTHF (1 vol), and the solution was heated to 60−65 °C to obtain a homogeneous solution. The solution was cooled to rt to result in a slurry, to which was charged heptane (3 vol) slowly. The slurry continued to stir at rt for 30 min, was cooled to 0 °C over 30 min, and was stirred for an additional hour. Solids were collected by filtration, rinsed with heptane (1 vol), and dried at 30 °C under vacuum with a nitrogen bleed for 12 h to afford another 58.1 g of **21** as an off-white solid (crop 2), providing a total of 263.9 g of **21** (93.9% yield); mp 133 °C (from DSC). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (s, 6 H), 2.11−2.06 (m, 2 H), 1.91−1.88 (m, 2 H), 1.70−1.47 (m, 5 H), 0.79 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 123.5 (dd, J = 238.4, 1.9 Hz), 109.3 (d, J = 2.2 Hz), 72.6, 42.3 (dd, J = 1.7 Hz), 33.2 (dd, J = 22.3, 2.8 Hz), 30.2, 22.9 (d, J = 9.8 Hz), 14.5. ^{19}F NMR ($CDCl_3$, 470 MHz): δ −96.7 (d, J = 235.7 Hz), −101.9 (d, J = 237.6 Hz). HRMS, m/z: $[M + H]^+$ calcd for ($C_{12}H_{19}F_2O_3^+$), 249.12968; found, 249.12984.

1-(4-Fluorocyclohex-3-en-1-yl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (22). A solution of **21** (166.6 g, 0.67 mol, 1 equiv) in KO*t*-Amyl as a 25% solution in PhMe (753.0 mL, 1.34 mol (2 equiv) was heated to about 110−115 °C and was stirred at this temperature for 120 h. The reaction was cooled to rt, quenched with H_2O (333.2 mL, 2 vol), and then diluted with EtOAc (666.4 mL, 4 vol). The organic layer was washed with H_2O (333.2 mL, 2 vol) and was subsequently

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concentrated to about 2 vol under reduced pressure. Heptane (333.2 mL, 2 vol) was charged and 2 vol of solvent was removed under reduced pressure at 55 °C. This process was repeated twice until a slurry was obtained. The resulting slurry was cooled to rt, filtered, and rinsed with heptane (333.2 mL, 2 vol) to afford 134.4 g of **22** as a white solid (81.3% yield); mp 70 °C (from DSC). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.16−5.11 (m, 1 H), 3.88 (s, 6 H), 2.26−2.12 (m, 3H), 2.07−1.98 (m, 2 H), 1.82−1.76 (m, 1 H), 1.55−1.47 (1 H), 0.80 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.4 (d, J = 251.6 Hz), 109.6, 101.1 (d, J = 15.9 Hz), 72.6, 40.0 (d, J = 2.2 Hz), 30.2, 25.3 (d, J = 23.9 Hz), 23.0 (d, J = 8.2 Hz), 22.7 (d, J = 9.1 Hz), 14.5. ^{19}F NMR ($CDCl_3$, 470 MHz): δ −104.2. HRMS, m/z: $[M + H]^+$ calcd for ($C_{12}H_{18}FO_3^+$), 229.12345; found, 229.12362.

4-Fluorocyclohex-3-ene-1-carboxylic acid (15). To a solution of **22** (134.4 g, 0.589 mmol, 1 equiv) in THF (537.6 mL, 4 vol) was charged 1 N HCl (176.6 mL, 0.177 mmol, 30 mol %). The resulting reaction mixture was stirred at rt. After 30−40 min, **22** was consumed and H_2O (537.6 mL, 4 vol) was charged, followed by addition of $LiOH·H_2O$ (74.1 g, 1.77 mol, 3 equiv). The resulting reaction mixture continued to stir at rt for an additional 1.5−2 h, at which point MTBE (672 mL, 5 vol) was charged. The aqueous layer acidified with 6 N HCl until pH 1−2 was reached and was subsequently extracted with EtOAc (537.6 mL, 4 vol). The organic layer was washed with H_2O (268.8 mL, 2 vol). Three volumes of solvent was distilled at 40 °C under reduced pressure. At this point heptane (268.8 mL, 2 vol) was charged and 2 vol of solvent was distilled at 40 °C under reduced pressure. This process was repeated once; then heptane (537.6 mL, 1 vol) was charged to obtain a slurry. The resulting slurry was cooled to 5−10 °C and was stirred at the same temperature for 30−40 min. Solids were collected by filtration, rinsed with heptane (537.6 mL, 1 vol), and dried at 40 °C under reduced pressure with a nitrogen bleed for 6 h to afford 80.8 g of **15** as a white solid (93.3% yield); mp 59 °C (from DSC). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.26 (s, 1 H), 5.22−5.19 (m, 1 H), 2.48−2.43 (m, 1 H), 2.25−2.14 (m, 4 H), 2.00−1.96 (m, 1 H), 1.76−1.68 (m, 1 H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 176.2 (d, J = 1.9 Hz), 159.3 (d, J = 250.9 Hz), 101.22 (d, J = 15.9 Hz), 38.1 (d, J = 2.2 Hz), 25.0 (dd, J = 8.2, 2.3 Hz), 24.6, 24.4. ^{19}F NMR (DMSO-d_6, 470 MHz): δ −101.6. HRMS, m/z: $[M + H]^+$ calcd for ($C_7H_{10}FO_2^+$), 145.06593; found, 145.06606.

4-Fluorocyclohex-3-ene-1-carboxamide (16). To a solution of **15** (153.0 g, 950.9 mmol, 1 equiv) in MeCN (765.0 mL, 5 vol) was charged 1,1′-carbonyldiimidazole (169.6 g, 162.1 mmol, 1.1 equiv) in six portions at room temperature. (Note: gas evolution was observed.) The resulting mixture was stirred at rt for 1 h, at which point the reaction mixture was cooled to 0−5 °C. To the cooled stirring reaction mixture was charged NH_4OH (595.0 mL, 4.8 mol, 4.5 equiv) at a rate to maintain the internal temperature below 25 °C. The reaction mixture was subsequently warmed to rt and continued to stir at the same temperature for 30−40 min. Five volumes of solvent was distilled at 55 °C under reduced pressure followed by addition of heptane (765.0 mL, 5 vol). This process was repeated to result in a slurry, at which point a solution of 15% NaCl in 3 N HCl (900.0 mL, 6.3 vol) was charged at a rate that maintained the internal temperature below 40 °C. The resulting solution mixture was stirred for 2 h, at which point solids were collected by filtration and rinsed with heptane (306.0 mL, 2 vol). Solids were suspended in cold H_2O (229.5 mL, 1.5 vol). The resulting slurry was cooled to about 10−15 °C and was stirred at the same temperature for 30 min. The slurry was subsequently filtered. Solids were dried on filter for 45−60 min and were further dried at 55 °C under reduced pressure with a nitrogen bleed for 12 h to afford 130.0 g of **16** as a white solid (93.2% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.29 (s, 1 H), 6.79 (s, 1 H), 5.22−5.19 (s, 1 H), 2.31−2.12 (m, 5 H), 1.89−1.86 (m, 1 H), 1.70−1.62 (m, 1 H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 176.5 (d, J = 2.1 Hz), 159.2 (d, J = 250.8 Hz), 101.5 (d, J = 15.6 Hz), 39.3 (d, J = 2.2 Hz), 25.7 (t, J = 9.3 Hz), 25.1, 24.9. ^{19}F NMR (DMSO-d_6, 470 MHz): δ −101.9. HRMS, m/z: $[M + H]^+$ calcd for ($C_7H_{11}FNO^+$), 144.08192; found, 144.08204.

***trans*-4-Fluorocyclohexane-1-carboxamide (17c).** To a 2-dram vial equipped with a stir bar were charged [Rh(nbd)$_2$]BF_4 (102 mg, 0.1 mol %), 1,2′-bis(di-*tert*-butylphosphino)ferrocene (142 mg, 0.11 mol %), and 1 mL CH_2Cl_2. The resulting dark red solution was stirred at rt for 15 min and then transferred by a pipet to a stainless steel reactor containing **16** (40.2 g, 28 mmol, 1 equiv) and anhydrous THF (400 mL, 10 vol). The reaction mixture was purged with nitrogen three times followed by hydrogen three times and then placed under 200 psi hydrogen. The mixture was heated to 60 °C and stirred for 4 h and then cooled to rt. The product mixture was transferred to a RB flask and concentrated to 5 vol. To the slurry was charged hexanes (200 mL, 5 vol). The slurry was stirred at rt for 1 h. The solid was collected on a filtration funnel and washed with 1:1 THF/hexanes (2 × 40 mL, 2 vol). The solid was dried at 50 °C under reduced pressure with a nitrogen bleed for 12 h to afford 36.4 g of **17c** as a white solid (91.9% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.22 (s, 1 H), 6.71 (s, 1 H), 4.49 (d, 1 H, J = 48.9 Hz), 2.15−1.93 (m, 3 H), 1.86−1.68 (m, 2 H), 1.50−1.28 (m, 4 H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 176.9 (d, J = 2.6 Hz), 91.7 (d, J = 170.3 Hz), 42.4 (d, J = 1.5 Hz), 31.9 (d, J = 18.5 Hz), 26.9 (d, J = 11.4 Hz). ^{19}F NMR (DMSO-d_6, 470 MHz): *trans*-isomer, δ −168.0 (d, J = 44.5 Hz); *cis*-isomer, δ −148.3 (d, J = 28.1 Hz). HRMS, m/z: $[M + H]^+$ calcd for ($C_7H_{13}FNO^+$), 146.09757; found, 146.09769.

***trans*-4-Fluorocyclohexan-1-amine Hydrochloride (1a).** To a solution of PhI(OAc)$_2$ (215.5 g, 669.1 mmol, 1.1 equiv) in MeCN (618.1 mL, 7 vol) was charged H_2O (264.9 mL, 3 vol) and TFA (232.9 mL, 3.04 mol, 5 equiv). The resulting reaction mixture was stirred at rt for 15−20 min, at which point **17c** (88.3 g, 608.2 mmol, 1 equiv) was charged in one portion as solids. The resulting reaction mixture continued to stir at rt overnight. Solvent was distilled to minimum stirrable volume under reduced pressure. The mixture was azeotroped with PhMe (883.0 mL, 10 vol) five times at 55 °C under reduced pressure to remove residual water from the mixture. To the mixture was charged MTBE (883.0 mL, 10 vol), and solvent was distilled to a minimum stirrable volume. This process was repeated twice. To the mixture was charged MTBE (883.0 mL, 10 vol), followed by 4 M HCl in dioxane (228.1 mL, 912.3 mmol, 1.5 equiv) at a rate that maintained the internal temperature below 30 °C. The resulting mixture was stirred at rt for 1 h. Solids were collected by filtration and rinsed with MTBE (176.6 mL, 2 vol). Crude solids were suspended in MTBE (176.6 mL, 2 vol) and MeCN (353.2 mL, 4 vol). The resulting mixture was heated to 65 °C and was stirred at the same temperature for 15−20 min, at which point it was cooled to rt and stirred for an additional 15 min. Solids were collected by filtration and rinsed with 1:1 MTBE:MeCN

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(176.6 mL, 2 vol) followed by MTBE (176.6 mL, 2 vol). Filtered solids were dried at 30 °C under reduced pressure with a nitrogen bleed for 12 h to afford 88.4 g of **1a** as an off-white solid (94.6% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.13 (s, 3 H), 4.61−4.46 (m, 1 H), 3.05−3.00 (m, 1 H), 2.06−1.95 (m, 4 H), 1.55−1.38 (m, 4 H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 90.6 (d, J = 169.6 Hz), 48.1 (d, J = 1.4 Hz), 29.8 (d, J = 19.9 Hz), 27.4 (d, J = 11.3s Hz). ^{19}F NMR (DMSO-d_6, 470 MHz): δ −172.1. HRMS, m/z: [M−HCl^{+} H]$^{+}$ calcd for ($C_6H_{13}F^{+}$), 118.10265; found, 118.10275.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00444.

^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

Crystallographic data for **25** (CIF)

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Author Contributions

[#]The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. These authors contributed equally.

Notes

The authors declare no competing financial interest.

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