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Article

Synthesis of BACE1 Inhibitors E2609/E2071 via Oxime−Olefin Cycloaddition Following a Process Risk Mitigation Strategy

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Cite This: https://doi.org/10.1021/acs.oprd.1c00223

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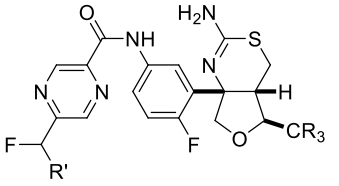
ABSTRACT: Process development of **E2609** from the preclinical stage to the clinical stage following a process risk mitigation strategy is described here. Key features include a turbo Grignard reaction monitored by in-situ IR, [3 + 2] cycloaddition in water, chemoselective amide coupling via in-situ protection, and a Reformatsky/decarboxylation approach to install a difluoromethyl group. Toward safe and scalable manufacture of **E2071**, an analog of **E2609**, a flow-reaction process for trifluoromethylation of aldehydes is presented here.

KEYWORDS: *BACE1 inhibitor, turbo Grignard reaction, [3 + 2] cycloaddition, chemoselective amide coupling, Reformatsky reaction, flow chemistry*

INTRODUCTION

The amyloid hypothesis of Alzheimer's disease (AD) suggests that interfering with the production and accumulation of amyloid beta (Aß) peptides, especially Aß42, could provide a disease-modifying therapy.[1] *β*-Amyloid cleaving enzyme 1 (BACE1) was found to be a key enzyme responsible for the production of Aß peptides and therefore has been a prime therapeutic target.[2] **E2609** and **E2071**, novel potent orally administered BACE1 inhibitors, were developed as Aß peptide-lowering small molecule agents that could serve as disease-modifying therapeutics for AD patients (Figure 1).[3] **E2609** and **E2071** share a common cis-fused 5,6-tetrahydrofuran (THF)−isothiourea scaffold substituted with a 2-fluoro-5-aminophenyl aromatic acylated on the amino moiety with a 2-fluoromethylated-pyrazine-5-carboxylic acid. The oxime−olefin cycloaddition approach initially utilized to discover the cis-fused 5,6-THF-isothiourea scaffold was viewed as a solid strategy that could be developed further provided that efficient chiral resolution and aryl substitution protocols could be implemented. **E2609** and **E2071** differ in the distribution and total number of fluoro substituents on the two methyl groups attached to the THF and pyrazine rings. In particular, incorporation of a difluoromethylpyrazine on **E2609** and a trifluoromethyl group on the THF ring of **E2071** presented practical and safety-related concerns that needed to be addressed prior to scale-up and manufacturing. Herein, are described (1) the development and scale-up of an oxime−olefin cycloaddition approach to directly and diastereoselectively assemble 3 contiguous stereogenic centers on a THF template, (2) development of a practical diastereomeric salt resolution of the amino−alcohols derived from oxime−olefin cycloaddition, (3) a practical decarboxylative Reformatsky approach to efficiently incorporate a difluoromethyl group onto a pyrazine ring, and (4) a safe and practical flow chemistry process for incorporating a trifluoromethyl group into the oxime−olefin cycloaddition substrate required for manufacture of **E2071**.



E2609 R = H, R' = F
E2071 R = F, R' = H

Figure 1. Structures of BACE1 inhibitors **E2609** and **E2071**.

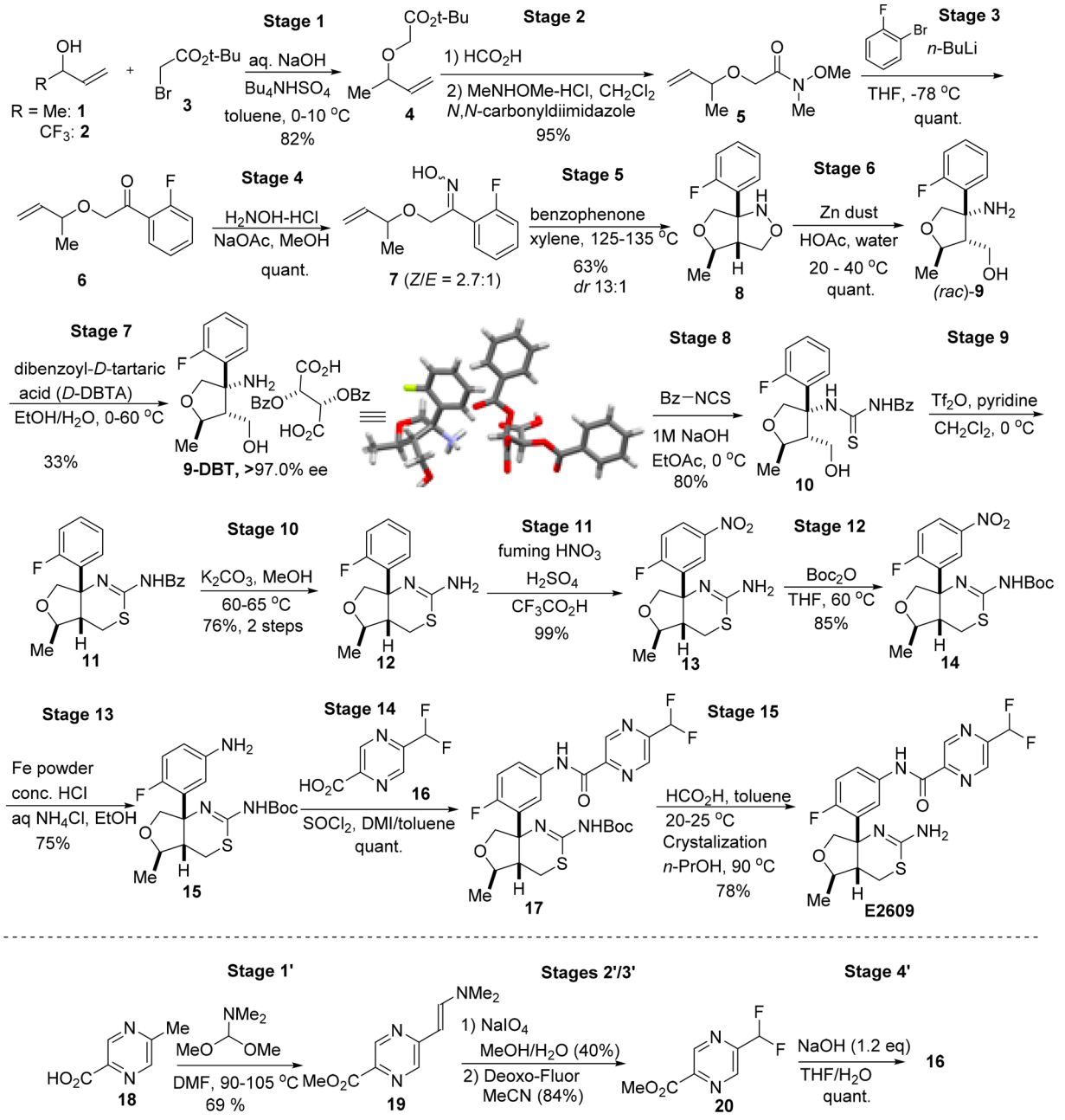
RESULTS AND DISCUSSION

The initial synthetic route used during the discovery phase was adapted and optimized to generate early batches of **E2609** for preclinical studies. The resulting first-generation route outlined

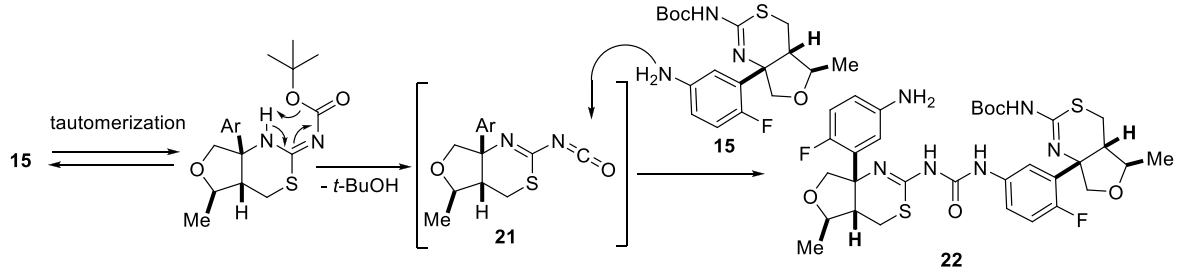
Special Issue: Excellence in Industrial Organic Synthesis 2021

Received: June 12, 2021

Scheme 1. First-Generation Manufacturing Route of E2609



Scheme 2. Generation of Dimer Impurity 22 from 15 and Its Plausible Mechanism



in Scheme 1 consists of 19 synthetic stages and proceeds in 4.8% overall yield. Process highlights of the route include multiple crystalline intermediates in the late stages, a diastereoselective [3 + 2] cycloaddition (dr 13:1)[4] to establish the relative stereochemistry of all three stereogenic centers (Stage 5), and a classical diastereomeric salt resolution utilizing dibenzoyl-D-tartaric acid (D-DBTA) to isolate the desired enantiomer whose configuration was confirmed by X-ray

https://doi.org/10.1021/acs.oprd.1c00223
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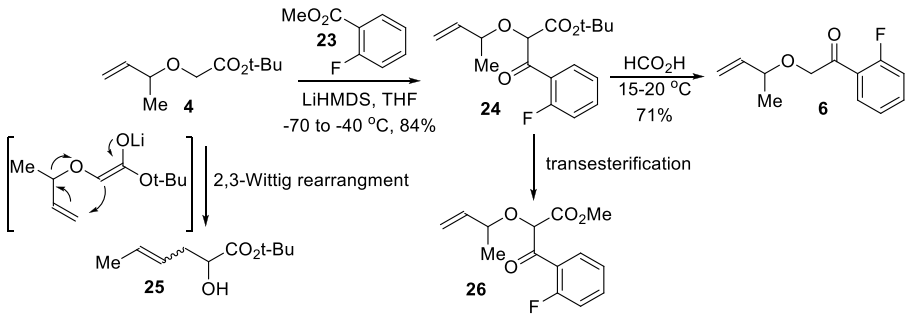
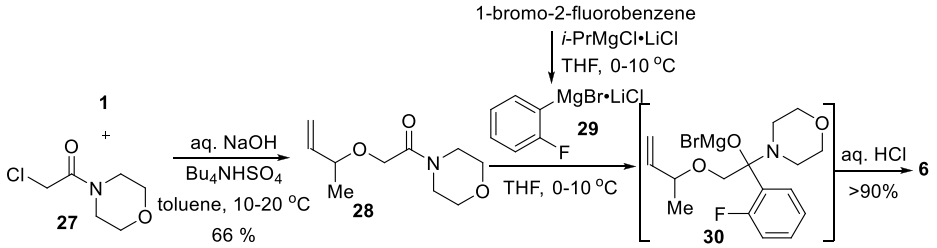
Scheme 3. Crossed Claisen Condensation/Decarboxylation Approach to Ketone 6



Scheme 4. Generation of Ketone 6 via Turbo Grignard Reaction



(Stage 7). Pyrazinoic acid **16** was prepared from acid **18** in 4 steps employing deoxofluorination as the key step. While the majority of the route developed for **E2609** was applicable to **E2071** and is therefore not discussed separately here, the presence of the trifluoromethyl−THF ring in **E2071** necessitated developing a process for manufacture of the corresponding allylic alcohol cycloaddition substrate [1,1,1-trifluoro-2-hydroxy-3-butene (**2**)].

Through our initial research and early manufacturing experiences described above, five main risks associated with this route were identified as follows.

- In Stage 3, the lithiation of 1-bromo-2-fluorobenzene required cryogenic conditions (below −60 °C) to prevent benzyne formation,[5] which was throughput limiting and increased manufacturing cost.
- Two late-stage intermediates, Boc-protected isothioureas **14** and **15**, posed handling challenges due to instability. For example, a significant dimeric urea impurity **22** was generated from **15** in either a solid or solution even at ambient temperature (Scheme 2).
- The Stage 3′ deoxofluorination has a limitation for scale-up due to the high cost of Deoxo-Fluor and the requirement of special facilities for the handling of hazardous reagents.[6]
- The route contains 15 linear synthetic stages with 4.8% overall yield, leading to a long production time.
- Trifluoromethylation of aldehydes with Ruppert−Prakash reagent [trifluoromethyltrimethylsilane (CF_3TMS)], a process for the generation of 1,1,1-trifluoro-2-hydroxy-3-butene (**2**), is an autocatalytic reaction[7] and therefore raised a safety concern of controlling the reaction heat on scale.

Development of an Alternative Approach to the Cryogenic Aryl Lithiation. An approach which would preclude the need for an aryl lithiation was envisioned by utilizing a crossed Claisen condensation as shown in Scheme 3. Treatment of a mixture of *tert*-butyl ester **4** and methyl 2-fluorobenzoate (**23**) with lithium hexamethyldisilazide (LiHMDS) provided *β*-ketoester **24** in 84% yield. Decarboxylation in formic acid then generated ketone **6** in 71% yield. Although the reaction can proceed at noncryogenic temperatures (>−20 °C), considerable amounts of impurities were generated when the reaction temperature was raised above −40 °C: alcohol **25** via 2,3-Wittig rearrangement[8] and methyl ester **26** via transesterification. Therefore, retaining cryogenic conditions was required to minimize these side reactions.

A shorter, noncryogenic route to ketone **6** was developed upon evaluation of commercial chloroacetamide compounds as an alternative starting material. Coupling reaction of *N*-(chloroacetyl)morpholine **27** with alcohol **1** in the presence of aqueous sodium hydroxide and phase transfer catalyst tetrabutylammonium hydrogensulfate (n-Bu_4NHSO_4)[9] proceeded well to give butenyl ether **28** in good yield (66%, Scheme 4). Although the resulting amide (**28**) would undergo the cryogenic aryl lithium addition, a search for noncryogenic conditions led to the evaluation of aryl magnesium complexes.[5] Treatment of 1-bromo-2-fluorobenzene with isopropylmagnesium chloride lithium chloride complex (turbo Grignard reagent)[10] provided aryl magnesium complex **29**, which then reacted with amide **28** to give tetrahedral adduct **30** at noncryogenic temperatures (0 °C). Upon treatment with aqueous hydrochloric acid, ketone **6** was obtained in >90% yield.

Formation of aryl Grignard reagent **29** and tetrahedral adduct **30** could not be directly monitored using conventional in-process control (IPC) methods (e.g., HPLC, GC). Therefore, in-situ IR spectroscopy was employed to monitor these species directly.[11] First, based on IR spectra collected at various reaction time points, the most intense and well-resolved IR absorption bands for each species were selected for reaction monitoring: the peak at 1161 cm^{-1} for aryl Grignard reagent **29**, the peak at 1200 cm^{-1} for adduct **30**, and the peak at 1635 cm^{-1} for amide **28**.[12] Next, the changes in the absorption intensities at these three wavelengths were plotted as a function of time, highlighting how the concentration of

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each component changed with reaction progress (Figure 2). Such data showed that aryl magnesium bromide formation

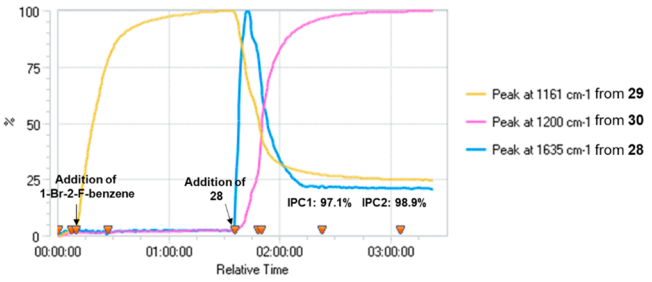


Figure 2. In-line monitoring of the turbo Grignard reaction using in-situ IR spectroscopy: Normalized time-dependent relative concentration trends for amide **28**, aryl Grignard reagent **29**, and tetrahedral adduct **30** based on univariate (one wavelength) analysis of IR.

seems to be complete in 1.5 h after starting the addition of 1-bromo-2-fluorobenzene.[13] In addition, toward the end of the reaction, the conversion rate from **28** to **6** was measured with an HPLC IPC method. At time points marked as IPC1 and IPC2, the conversion rates were found to be 97.1% and 98.9%, respectively. These data correlated well with the calculated transformation obtained from IR data.

[3 + 2]-Cycloaddition in Water. One of the reasons for the moderate yield of the [3 + 2] cycloaddition was attributed to be the modest *Z*/*E* ratio (2.7/1) of oxime **7**. Only the *Z* isomer undergoes the desired [3 + 2] cycloaddition via NH nitrone intermediate **31** formed by tautomerization of the *Z* isomer, while the *E* isomer would give byproducts such as **32** via an azaprotiocyclo transfer reaction (APT) (Scheme 5).[14] The first attempt for the optimization was to increase the *Z*/*E* ratio by changing the reaction solvents and temperature, but the improvement was only marginal. Next, based on literature reports that the *E*/*Z* isomerization of oximes is promoted in water, we decided to explore water as a reaction solvent for the [3 + 2] addition.[15] Given that the oxime formation proceeded well in water, the oxime formation and cycloaddition steps were combined into a single step; the desired product (**8**) was generated via intermediate **7** upon treatment of ketone **6** with hydroxylamine−hydrochloride in water at 100 °C.

The reaction progress was monitored by HPLC (Figure 3). The *Z*/*E* ratio of oxime **7** was 1.9/1 at 0.5 h after 40% conversion of ketone **6** and became 1.2/1 at 4 h, at which point all of ketone **6** was consumed and some of the resulting

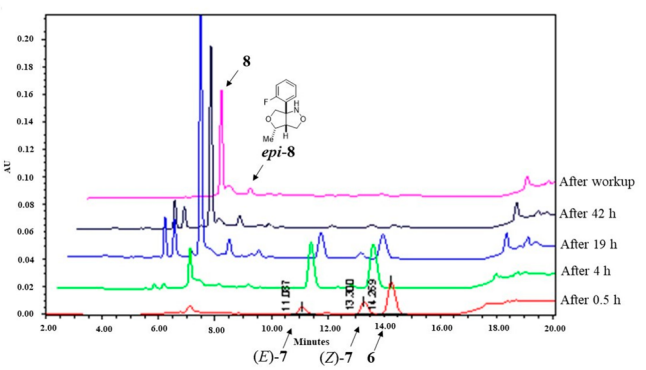


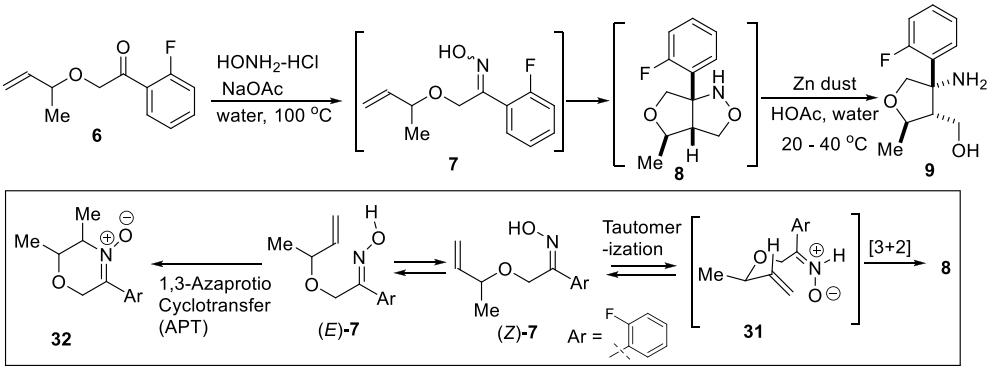
Figure 3. HPLC overlay chromatograms of the oxime formation/[3 + 2] cycloaddition reaction.

oximes underwent the [3 + 2] cycloaddition to give **8**. After 42 h, most of the oximes were consumed (93% conversion), and a 14:1 mixture of the desired product **8** and the methyl epimer (*epi*-**8**) was obtained after workup in 81% yield. In scale-up, without isolation of the resulting product, treatment of the reaction mixture with zinc and acetic acid led to the N−O bond cleavage to give amino alcohol **9** (Scheme 5). This one-pot, three-step process reduced two synthetic stages and increased the overall yield from ca. 50% to ca. 80%.[16]

Development of Chemoselective Coupling of Diamine 34 via In-Situ Protection. To address the stability issue of intermediates **14** and **15**, alternative protecting groups were searched. Serendipitously, a hint for the best protecting group was given during the process impurity fate studies. When compound **15** spiked with 10.75% of compound **13** was subjected to the following stage, it was noticed that the expected byproduct **33** was not detected at all while **13** still remained at a level of 2.66% (Scheme 6) after isolation. These results indicated that protection of the isothiourea moiety of compound **15** might not be needed during the amide coupling.

To our delight, diamine **34**, which was prepared from **13** via nitro reduction with iron powder, underwent a chemoselective coupling with acid chloride **35** to give **E2609** in a quantitative yield along with <0.2% byproduct **36** in the crude product (Scheme 7).[17] We reasoned that 1 equiv of hydrogen chloride (HCl) in-situ generated from the acid chloride formation would selectively protonate the more basic isothiourea amine moiety of **34** to give an in-situ-protected form **34**-HCl. In contrast, the undesired amide (**37**) was selectively generated under the base-mediated 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-

Scheme 5. One-Pot, Three-Step Process to Amino Alcohol 9 and Plausible Mechanism



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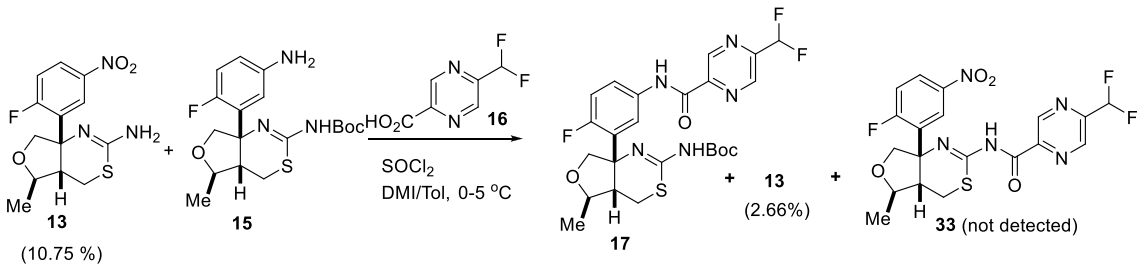
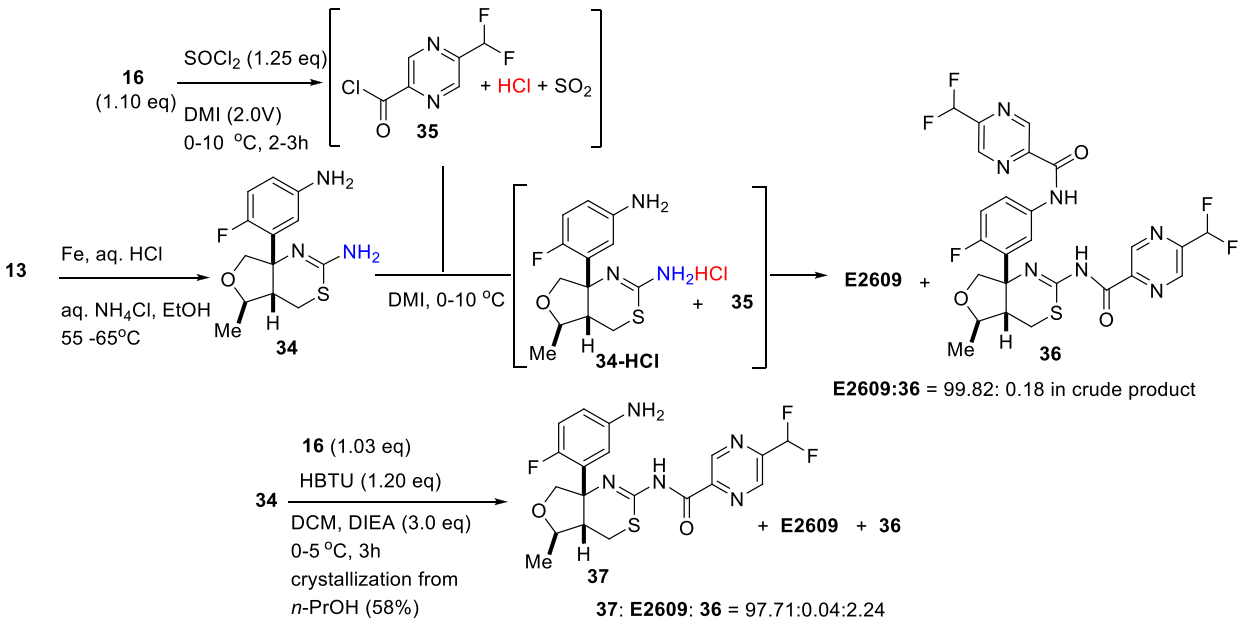
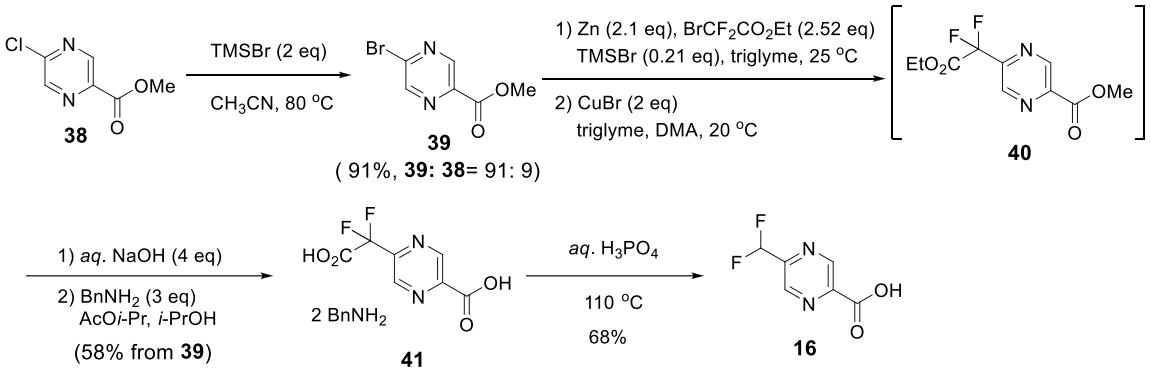
Scheme 6. Fate Study of Process Impurity 13



Scheme 7. Chemoselective Amide Coupling of Diamine 34 with Acid 16



Scheme 8. Second-Generation Manufacturing Route for Difluoromethyl Pyrazinoic Acid 16



tetramethyluronium hexafluorophosphate (HBTU) coupling conditions, underscoring the importance of utilizing the base-free coupling conditions. This chemoselective amide coupling eliminated two unstable intermediates (**14** and **15**) and shortened the overall synthesis by two stages: installation and removal of the isothiourea protecting group.

Development of the Reformatsky/Decarboxylation Approach for Difluoromethyl Pyrazinoic Acid 16. To avoid the hazardous deoxofluorination step (Scheme 1), introduction of the difluoromethyl group by Reformatsky reaction of halo-pyrazinoic ester with 2-bromo-2,2-difluoroethyl acetate followed by decarboxylation reaction was investigated (Scheme 8). Due to the low reactivity of chloride **38** for the Reformatsky coupling reaction, chloride **38** was converted into more reactive bromide **39** by treating with trimethylsilyl bromide (TMSBr) while continuously distilling off byproduct trimethylsilyl chloride (TMSCl).[18] The coupling reaction of **39** with the Reformatsky reagent ($BrZnCF_2CO_2Et$) prepared from $BrCF_2CO_2Et$ with activated Zn[19] proceeded well in the presence of CuBr to give **40**.[20] Hydrolysis followed by salt formation with benzylamine afforded bis(benzylamine) salt **41** in 58% overall yield from **39**. The decarboxylation

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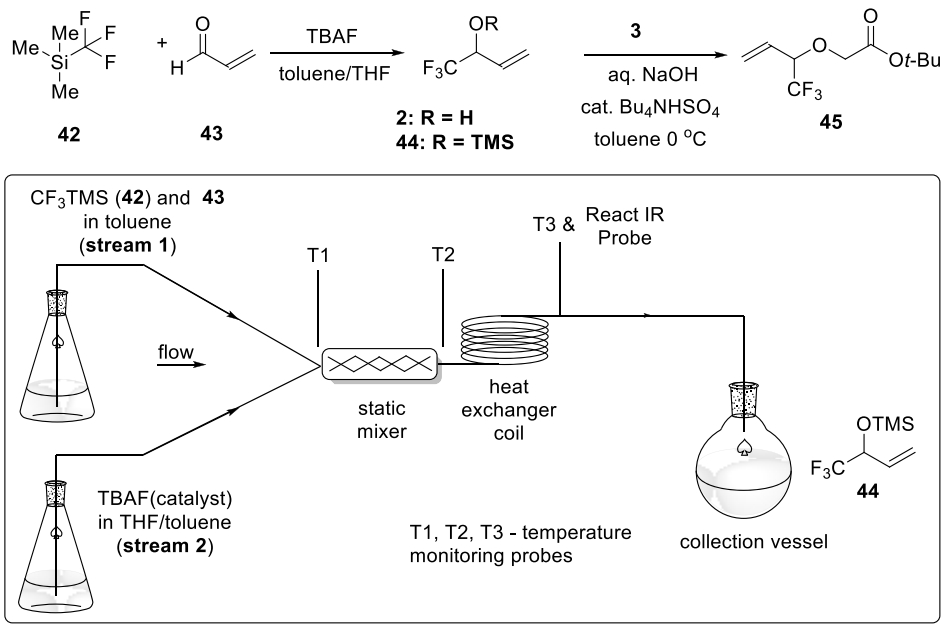
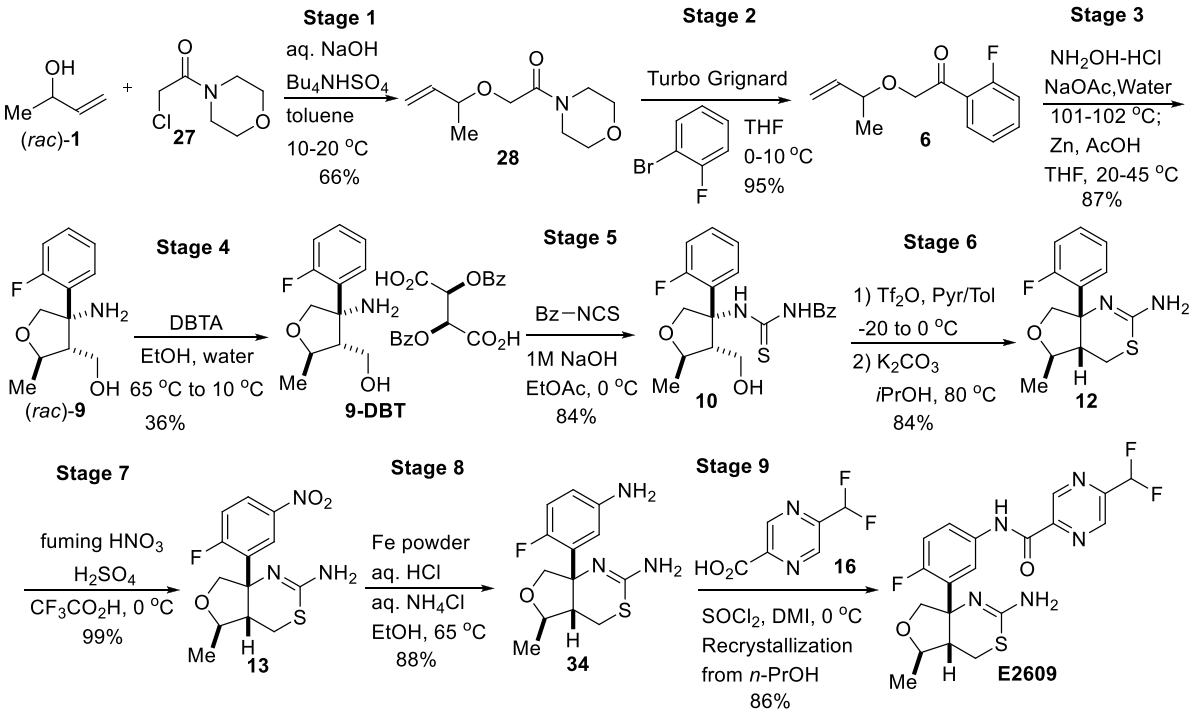
Scheme 9. Synthetic Route to 45, and Schematic Representation of the Flow Reactor



Scheme 10. Second-Generation Manufacturing Route of E2609



reaction[21] of **41** was performed under acidic and thermal conditions, leading to difluoromethylpyrazinoic acid **16** in 68% yield after crystallization. According to this method, any special facilities and use of hazardous fluorinating reagents were not required to make further scale-up manufacturing feasible.

Development of a Flow Chemistry Process for 1,1,1-Trifluorobut-3-en-2-ol (2). In the initial experiment, treatment of a solution of acrolein and Ruppert−Prakash reagent (CF_3TMS)[7] in THF with a catalytic amount of tetrabutylammonium fluoride (TBAF) rapidly generated TMS ether **44** (Scheme 9). Moreover, by performing the reaction in toluene, the crude product could be used directly in a phase-transfer alkylation of **3** to afford desired intermediate **45**. However, the temperature of the reaction mixture changed from ca. 0 to 80 °C almost instantaneously (within seconds) even on a relatively small scale (e.g., 1 g) upon addition of a sufficient amount of TBAF to initiate this autocatalytic process: the fluoride ion from TBAF initiated the reaction which was subsequently self-catalyzed by the resulting alkoxide ion of the product.[7] The autocatalytic trifluoromethylation reaction precluded conduction of a batch process on scale and thus provided a clear and compelling reason to utilize flow

https://doi.org/10.1021/acs.oprd.1c00223
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

chemistry to directly address the safety concerns. Moreover, the kinetics and homogeneity of the process seemed ideal for the adaptation to a flow system.[22] A two-streamflow system with a solution of CF_3TMS and acrolein in toluene as stream 1 and a solution of TBAF (catalyst) in toluene/THF as stream 2 (Scheme 9) was designed. The two streams were mixed by simultaneous flow through a static mixer, and the released heat was cooled by a subsequent temperature-controlled heat-exchange coil. In order to assess the effects of flow rate on the reaction and enable rapid optimization via close temperature control of the process, three temperature probes (T1, streams meeting point before the static mixer; T2, immediately after the static mixer; T3, after the heat exchange cooling loop) were used. A React IR probe was also inserted along with T3, and specific high-intensity IR peaks for key starting materials (1700 cm^{-1} for acrolein, 1050 cm^{-1} for CF_3TMS) and product (**44**, 1100−1200 cm^{-1}) were monitored for real-time assessment of the reaction.[23] The resulting reactor setup provided the possibility of high production rates of up to 6 kg of **44** per hour and was utilized to produce **45** on a 24 kg scale in a single run.

CONCLUSION

In summary, the second-generation manufacturing route of **E2609** in Scheme 10 was developed to address process issues identified in the first manufacturing route for the preclinical stage. A turbo Grignard reaction with in-situ monitoring by IR spectroscopy was employed in Stage 2 to realize noncryogenic arylation. In Stage 3, oxime formation followed by [3 + 2] oxime−olefin cycloaddition and reduction was performed in water to improve the yield and shorten the reaction steps. In Stage 9, the chemoselective amide coupling of diamine **34** was realized via in-situ protection, eliminating two unstable intermediates and shortening two reaction stages. For pyrazinoic acid **16**, a much safer and scalable Reformatsky/decarboxylation protocol to install the difluoromethyl group was established and implemented on scale. These process optimization steps resulted in shortening the linear synthetic stage count from 15 to 9 and improving the overall yield to 10% from 4.8% in the first-generation route. Using this route, 19 kg of **E2609** with clinical trial quality was manufactured successfully. For **E2071**, the flow process for trifluoromethyl ether **44** was developed to control the exothermic autocatalytic process and was successfully implemented on industrial scale.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Varian Inova 500 or 400 MHz or Bruker 600 or 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm). For ^1H NMR spectra [$CDCl_3$, CD_3OD, or $(CD_3)_2SO$], the residual solvent peak was used as the internal reference (7.26 ppm in $CDCl_3$; 3.31 ppm in CD_3OD; 2.50 ppm in $(CD_3)_2SO$), while the central solvent peak was the reference (77.0 ppm in $CDCl_3$; 49.0 ppm in CD_3OD; 39.5 ppm in $(CD_3)_2SO$) for ^{13}C NMR spectra. Water contents were measured by Karl Fischer titration (Metrohm, 831 KF coulometer). All of the positive/negative-ion mode electrospray ionization mass spectra were recorded on an LTQ Orbitrap XL mass spectrometer (Thermo Fisher Scientific).

2-(But-3-en-2-yloxy)-1-morpholinoethanone (28). A reactor was charged with toluene (260 kg), 4-(chloroacetyl)-morpholine (**27**) (100 kg, 611 mol), tetrabutylammonium hydrogen sulfate (9.4 kg, 28 mol, 0.05 equiv), and 3-buten-2-ol (**1**) (53 kg, 735 mol, 1.20 equiv). The resulting mixture was cooled to 0−10 °C. While maintaining the internal temperature below 20 °C, 50 wt % aqueous sodium hydroxide (146 kg, 1834 mol, 3.0 equiv) was added. After the addition, the mixture was stirred between 10 and 20 °C for 1 h and the reaction was monitored for complete consumption of **27** (target >97.0% conversion). After being cooled down to below 5−10 °C, the reaction mixture was treated with deionized water (153 kg) while maintaining an internal temperature below 20 °C. After being stirred for 15 min at 15−23 °C, the layers were allowed to partition. The lower aqueous layer was separated out and extracted with methyl-*tert*-butyl ether (MTBE) (220 kg). The combined organic layers were washed with 1.0 M aqueous hydrochloric acid (50 L, 50 mol, 0.08 equiv) and concentrated under reduced pressure (jacket T < 45 °C) to give **28** (80.9 kg, 96.3 GC area % purity, 406 mol, 66.4% yield) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (ddd, J = 7.6, 10.1, 17.4 Hz, 1H), 5.33−5.10 (m, 2H), 4.19−4.12 (m, 1H), 4.07−3.99 (m, 1H), 3.97−3.83 (m, 1H), 3.68 (br s, 4H), 3.64−3.48 (m, 4H), 1.29 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.19, 138.94, 117.24, 77.65, 67.62, 66.87, 66.78, 45.78, 42.14, 21.13.

2-(But-3-en-2-yloxy)-1-(2-fluorophenyl)ethanone (6). A reactor was charged with a solution of isopropylmagnesium chloride−lithium chloride in THF (14%, 326 kg, 450 mol, 1.1 equiv) and cooled to 0−5 °C. 1-Bromo-2-fluorobenzene (81 kg, 449 mol, 1.1 equiv) was added while maintaining the internal temperature between 0 and 10 °C. Upon complete addition, the mixture was stirred between 0 and 10 °C for 1 h. A solution of amide **28** (80.9 kg, 406 mol) in THF (46 kg) was added while maintaining the internal temperature between 0 and 10 °C. A 1 kg amount of THF was used for rinsing. After stirring the reaction for 3 h, the reaction was monitored for complete consumption of amide **28** (>97.0% conversion). The reaction mixture was transferred into a reactor containing a mixture of MTBE (195 kg) and 2.0 M HCl (470 L, 2.3 equiv) while maintaining the internal temperature below 20 °C. A 5 kg amount of THF was used for rinsing. The mixture was stirred for 15 min, and then the phases were separated. The aqueous layer was extracted with 125 kg of MTBE. The combined organic layers were washed with 5.0 wt % aqueous sodium bicarbonate (169 kg), deionized water (163 kg), and 17 wt % aqueous sodium chloride solution (196 kg). The organic phase was concentrated under reduced pressure (T < 40 °C) to give ketone **6** (80.0 kg, 86.6 GC area % purity, 384 mol, 94.6% yield) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (dt, J = 7.6, 1.8 Hz, 1H), 7.57−7.49 (m, 1H), 7.24 (dt, J = 14.6, 3.8 Hz, 1H), 7.12 (ddd, J = 11.0, 8.3, 0.8 Hz, 1H), 5.77 (ddd, J = 17.3, 10.2, 7.6 Hz, 1H), 5.21 (d, J = 17.6 Hz, 1H), 5.17 (dd, J = 10.3, 0.8 Hz, 1H), 4.69 (dd, J = 18.1, 3.2 Hz, 1H), 4.60 (dd, J = 18.1, 3.4 Hz, 1H), 4.00 (dq, J = 12.9, 6.4 Hz, 1H), 1.36 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.24 (d, J_{CF} = 5.3 Hz), 162.03 (d, J_{CF} = 253.9 Hz), 139.42, 134.86 (d, J_{CF} = 8.9 Hz), 130.64 (d, J_{CF} = 3.4 Hz), 124.67 (d, J_{CF} = 3.2 Hz), 123.57 (d, J_{CF} = 15.3 Hz), 116.89, 116.45 (d, J_{CF} = 23.7 Hz), 77.93, 74.11 (d, J_{CF} = 11.2 Hz), 21.19.

4-Amino-4-(2-fluorophenyl)-2-methyltetrahydrofuran-3-yl)methanol (9). A reactor was charged with ketone **6** (80.0 kg, 384 mol), and deionized water (400 kg), hydroxylamine hydrochloride (28.0 kg, 403 mol, 1.05 equiv), and sodium acetate (34.7 kg, 423 mol, 1.10 equiv) were added. The resulting mixture was diluted with 320 kg of deionized water, heated to 101−102 °C for at least 40 h, and monitored for

https://doi.org/10.1021/acs.oprd.1c00223
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complete conversion to tetrahydrooxazole **8** (>90.0% conversion). The mixture was cooled to below 25 °C, and THF (140 kg) and acetic acid (69.3 kg, 1155 mol, 3.0 equiv) were added. Zinc dust (75.4 kg, 1155 mol, 3.0 equiv) was added while maintaining the internal temperature below 45 °C. The resulting mixture was stirred between 35 and 45 °C for 1 h, and the reaction was monitored for complete conversion to amino alcohol **9** (>98.0% conversion). The mixture was cooled to 15−20 °C, and dichloromethane (205 kg) was added. Aqueous ammonium hydroxide (25%, 107 kg) was added until the pH reached 10−12. The resulting mixture was stirred for 15 min, and 40 kg of Celite was added. After 30 min of stirring, the suspension was filtered in two equal portions by means of a centrifuge. Each portion was washed with 20 kg of dichloromethane. The combined filtrates were transferred to a reactor, and the layers were separated. The upper aqueous layer was extracted twice with dichloromethane (230 kg each). The combined organic layers were washed with 65 kg of deionized water, treated with 7 kg of sodium sulfate, and filtered through a bag filter. The resulting organic layer was concentrated under reduced pressure (jacket T < 35 °C); meanwhile, solvent exchange was performed with 235 kg of absolute ethanol. After solvent exchange, 236.5 kg of concentrate containing amino alcohol **9** (75.2 kg, 80.3 area % purity, 334 mol, 86.9% yield) was obtained. ^{1}H NMR (500 MHz, DMSO) δ 7.63 (td, J = 8.6, 1.7 Hz, 1H), 7.32−7.24 (m, 1H), 7.20−7.08 (m, 2H), 4.43 (s, 1H), 4.07 (dd, J = 8.7, 1.3 Hz, 1H), 4.02 (dq, J = 8.5, 6.1 Hz, 1H), 3.68−3.57 (m, 2H), 3.55−3.46 (m, 1H), 2.23 (dd, J = 14.4, 6.7 Hz, 1H), 1.24 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 160.69 (d, J_{CF} = 244.7 Hz), 133.57 (d, J_{CF} = 11.3 Hz), 128.95 (d, J_{CF} = 8.8 Hz), 128.81 (d, J_{CF} = 4.8 Hz), 124.33 (d, J_{CF} = 3.2 Hz), 116.32 (d, J_{CF} = 23.5 Hz), 79.58 (d, J_{CF} = 4.9 Hz), 78.52, 63.99 (d, J_{CF} = 3.5 Hz), 59.39, 56.91 (d, J_{CF} = 2.2 Hz), 21.37.

((2*R*,3*R*,4*S*)-4-Amino-4-(2-fluorophenyl)-2-methyltetrahydrofuran-3-yl)methanol (2*S*,3*S*)-2,3-Bis(benzoyloxy)succinate (9-DBT). A reactor was charged with 236 kg of an ethanol solution containing amino alcohol **9** (75.2 kg, 334 mol) and ethanol (253 kg). The mixture was heated to an internal temperature of 65−70 °C. To the mixture was added a solution of dibenzoyl-D-tartaric acid (125 kg, 332 mol, 1.0 equiv) in ethanol (148 kg) and deionized water (12.8 kg) in 5−10 min while maintaining the internal temperature above 60 °C. After being stirred for 60 min at 60−70 °C, the mixture was cooled to 50 °C at a rate 3 °C/h, while crystal seeds were added in every hour. After being stirred for 1 h at 50 °C, the mixture was cooled to 10 °C (at 10 °C/h) and stirred for at least 2 h at 5−10 °C. The crystals were then filtered, rinsed with prechilled ethanol (15 kg), and dried under vacuum at 50 °C to a constant weight. A 74.0 kg amount of 9-**DBT** (98.7 area % purity, 95.5 ee %, water 5.6%, 120 mol, 35.9% yield) was obtained as a white powder. ^{1}H NMR (500 MHz, CD_3OD) δ 8.14−8.10 (m, 4H), 7.60 (t, J = 7.4 Hz, 2H), 7.55 (td, J = 8.1, 1.3 Hz, 1H), 7.47 (t, J = 7.8 Hz, 4H), 7.46−7.42 (m, 1H), 7.30−7.19 (m, 2H), 5.90 (s, 2H), 4.39−4.26 (m, 2H), 4.15 (dd, J = 10.4, 2.4 Hz, 1H), 3.93 (dd, J = 11.7, 4.4 Hz, 1H), 3.87 (dd, J = 11.7, 5.4 Hz, 1H), 2.52 (dt, J = 8.4, 5.0 Hz, 1H), 1.31 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 171.37, 167.32, 161.76 (d, J = 245.5 Hz), 134.36, 132.46 (d, J_{CF} = 9.8 Hz), 131.16, 130.98, 129.47, 128.98 (d, J_{CF} = 2.9 Hz), 126.23 (d, J_{CF} = 3.9 Hz), 125.65 (d, J_{CF} = 10.8 Hz), 117.84 (d, J_{CF} = 23.5 Hz), 77.75, 75.73 (d, J_{CF} = 4.9 Hz), 74.91, 67.01 (d, J_{CF} = 2.0 Hz), 58.84, 56.28, 20.40.

Chiral HPLC Parameters. Column: Chiralcel OD-H, 4.6 × 250 mm, 5 μm, mobile phase (isocratic):*n*-heptane/2-propanol/triethylamine = 98/2/0.05, flow rate 1.0 mL/min, injection volume 20 μL, temperature 40 °C, detection 262 nm, total running time 80 min, dilution solvent 2-propanol, relative retention time (RRT) of (*ent*)-**9** = 0.90, RRT of **9** = 1.00

***N*-((3*S*,4*R*,5*R*)-3-(2-Fluorophenyl)-4-(hydroxymethyl)-5-methyltetrahydrofuran-3-ylcarbamothioyl)-benzamide (10).** A reactor was charged with **9-DBT** (30.0 kg, 48.5 mol) and ethyl acetate (81 kg). The mixture was cooled to 0−10 °C. A 1.00 M aqueous NaOH (120 L, 120 mol, 2.47 equiv) solution was added. Benzoyl isothiocyanate (9.42 kg, 56.5 mol, 1.16 equiv) was added with vigorous stirring while maintaining the internal temperature between 0 and 10 °C. After complete addition, stirring was continued at 0−5 °C over 2 h and the reaction was monitored for complete consumption of **9-DBT** (target >98.0% conversion). The reaction mixture was filtered, and the filter cake was rinsed with (1) deionized water (60 kg) and (2) a mixture of heptane (27 kg) and ethyl acetate (36 kg). The solid was dried under reduced pressure (T < 40 °C) to give **10** (17.0 kg, 93.5 wt % purity, 40.9 mol, 84.3% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.78 (s, 1H), 8.88 (s, 1H), 7.88−7.82 (m, 2H), 7.67 (td, J = 8.1, 1.6 Hz, 1H), 7.65−7.59 (m, 1H), 7.50 (dd, J = 10.8, 4.8 Hz, 2H), 7.30−7.23 (m, 1H), 7.15 (td, J = 7.8, 1.2 Hz, 1H), 7.01 (ddd, J = 12.3, 8.2, 1.1 Hz, 1H), 4.73 (d, J = 10.1 Hz, 1H), 4.42 (dd, J = 10.1, 1.7 Hz, 1H), 4.10−4.03 (m, 1H), 4.03−3.91 (m, 2H), 2.80 (t, J = 5.3 Hz, 1H), 2.63−2.52 (m, 1H), 1.35 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.42, 166.60, 160.35 (d, J_{CF} = 247.4 Hz), 133.60, 131.81, 129.27 (d, J_{CF} = 8.9 Hz), 129.20 (d, J_{CF} = 3.7 Hz), 129.15, 127.55, 127.39 (d, J_{CF} = 10.0 Hz), 123.96 (d, J_{CF} = 3.3 Hz), 116.18 (d, J_{CF} = 23.0 Hz), 76.90 (d, J_{CF} = 2.8 Hz), 76.27, 69.26, 59.49, 58.03, 20.04.

(4a*S*,5*R*,7a*S*)-7a-(2-Fluorophenyl)-5-methyl-4a,5,7,7a-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-2-amine (12). A reactor was charged with isothiourea **10** (17.0 kg, 40.8 mol), pyridine (49 kg) and toluene (44 kg). The resulting mixture was cooled to below −15 °C. Trifluoromethanesulfonic anhydride (12.7 kg, 45.0 mol, 1.10 equiv) was added while maintaining the internal temperature below 0 °C. Upon complete addition, stirring between −5−0 °C was continued for 1.5 h and the reaction was monitored for complete conversion of **10** (≥97.0%). Toluene (88 kg) and 20 wt % aqueous ammonium chloride solution (71 kg) were added. The resulting biphasic mixture was warmed to 15−25 °C, stirred for at least 15 min and then allowed to partition. The lower aqueous layer was separated, and the upper organic phase was collected. The aqueous layer was extracted with toluene (44 kg). The combined organic layers were washed with deionized water (34 kg) and concentrated under reduced pressure to give crude **11** as a thick brown oil. 2-propanol (41 kg) and 3.0 M aqueous sodium hydroxide (60 kg, 51 L) were added, and the resulting reaction mixture was heated to 80 °C for 6 h and monitored for complete conversion of **11** (>99.0%). *n*-Heptane (24 kg) and deionized water (17 kg) were added while keeping the internal temperature above 60 °C. The resulting mixture was cooled to 0−5 °C, maintained at this temperature for at least 2 h, and then filtered. The reactor and filter cake were rinsed with a mixture of deionized water (31 kg) and 2-propanol (2.7 kg), and then a mixture of heptane (20 kg) and ethyl acetate (3.1 kg). The solids were dried to give isothiourea **12** (9.45 kg, 96.7 wt % purity, 34.3

https://doi.org/10.1021/acs.oprd.1c00223
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mol, 84.1% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (td, J = 8.2, 1.6 Hz, 1H), 7.28−7.20 (m, 1H), 7.15−7.09 (m, 1H), 7.03 (ddd, J = 12.4, 8.1, 0.7 Hz, 1H), 4.81−4.42 (s, 2H), 4.61 (dd, J = 8.7, 0.5 Hz, 1H), 4.40−4.27 (m, 1H), 3.80 (dd, J = 8.7, 2.2 Hz, 1H), 3.07 (dd, J = 13.3, 3.9 Hz, 1H), 2.70 (dd, J = 13.3, 3.9 Hz, 1H), 2.56−2.47 (m, 1H), 1.34 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.03 (d, J_{CF} = 247.0 Hz), 149.41, 130.73 (d, J_{CF} = 10.0 Hz), 129.80 (d, J_{CF} = 4.1 Hz), 128.83 (d, J_{CF} = 8.7 Hz), 124.02 (d, J_{CF} = 3.4 Hz), 116.38 (d, J_{CF} = 23.5 Hz), 78.54 (d, J_{CF} = 4.8 Hz), 76.43, 66.97 (d, J_{CF} = 4.6 Hz), 44.50 (d, J_{CF} = 3.7 Hz), 23.70, 19.83.

(4a*S*,5*R*,7a*S*)-7a-(2-Fluoro-5-nitrophenyl)-5-methyl-4a,5,7,7a-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-2-amine (13). A reactor (reactor 1) was charged with trifluoroacetic acid (35 kg) and cooled down to 0−5 °C. **12** (9.45 kg, 34.3 mol) was added portionwise with stirring, while maintaining the internal temperature below 20 °C. The holding vessel and reactor were rinsed with trifluoroacetic acid (14.2 kg). The mixture was cooled below 5 °C and then sulfuric acid (12.3 kg) was added while maintaining the internal temperature below 15 °C. The resulting solution was cooled down to 0−5 °C and then fuming nitric acid was added (purity >90%, 3.0 kg, 41 mol, 1.2 equiv) while maintaining the internal temperature below 25 °C. Upon complete addition, stirring was continued with cooling (bath temperature: 0−5 °C) over 0.5 h, and the reaction was monitored for complete consumption of **12** (target >98.0% conversion). Another reactor (reactor 2) was charged with 3.0 M NaOH (246 kg, 217 L) and cooled to 3−7 °C. The reaction mixture was transferred into the second reactor while maintaining the internal temperature below 30 °C. The first reactor was rinsed with deionized water (19 kg). Additional 3 M NaOH to make the pH > 12 was added if necessary. After stirring for 0.5−1 h at 23−27 °C, the mixture was filtered and the reactor and filter cake were rinsed with deionized water (38 kg). The filter cake was dried under reduced pressure (T < 30 °C) overnight to give **13** (12.89 kg, 81.9 wt % purity, 33.9 mol, 98.9% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (dd, J = 6.9, 2.9 Hz, 1H), 8.20−8.14 (m, 1H), 7.21 (dd, J = 10.8, 9.0 Hz, 1H), 4.55 (dd, J = 9.1, 0.9 Hz, 1H), 4.41−4.31 (m, 1H), 3.80 (dd, J = 9.1, 1.8 Hz, 1H), 3.05 (dd, J = 13.5, 3.8 Hz, 1H), 2.74 (dd, J = 13.5, 4.1 Hz, 1H), 2.52−2.42 (m, 1H), 1.37 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.56 (d, J_{CF} = 258.9 Hz), 150.91, 144.23, 133.73 (d, J_{CF} = 12.3 Hz), 126.05 (d, J_{CF} = 6.2 Hz), 124.76 (d, J_{CF} = 10.8 Hz), 117.53 (d, J_{CF} = 26.3 Hz), 78.83 (d, J_{CF} = 4.0 Hz), 76.96, 66.91 (d, J_{CF} = 4.8 Hz), 45.26 (d, J_{CF} = 3.1 Hz), 23.88, 19.63.

(4a*S*,5*R*,7a*S*)-7a-(5-Amino-2-fluorophenyl)-5-methyl-4a,5,7,7a-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-2-amine (34). A reactor (reactor 1) was charged with powder iron (11 kg, 170 mol, 5.0 equiv) and ethanol (67 kg) at 18−25 °C. To the resulting slurry was added concentrated hydrochloric acid (37 wt %, 1.7 kg, 0.50 equiv). The resulting mixture was warmed up to 60−70 °C, stirred for 2 h, and cooled down to 50−55 °C. A saturated aqueous ammonium chloride solution (27 wt %, 42 kg, 6.3 equiv) was added while keeping the internal temperature between 45 and 55 °C. Another reactor (reactor 2) was charged with **13** (12.89 kg, 33.9 mol) and ethanol (38 kg). The resulting mixture was cooled to 10−15 °C and treated with concentrated hydrochloric acid (37 wt %, 3.4 kg, 1.0 equiv) while keeping the internal temperature below 25 °C. The resulting solution was added into the first reactor while keeping the internal temperature below 65 °C; it was rinsed with ethanol (4.1 kg), and the ethanol wash was transferred into the first reactor. The reaction mixture was stirred between 55 and 65 °C until complete consumption of starting material **13** (target ≥99.0% conversion). The reaction mixture was diluted with ethanol (51 kg) and cooled below 20 °C. After being stirred for 1−2 h, the mixture was filtrated through a Celite pad (11 kg), rinsing with ethanol (106 kg). Concentration of the filtrate in vacuo gave an orange solid, which was dissolved in deionized water (84 kg) and stirred at 18−25 °C for at least 15 min. The resulting solution was filtered through a Celite pad (2 kg) to remove the remaining particles, rinsing with deionized water (21 kg). A 3.0 M sodium hydroxide in deionized water solution (35 L) was added over 1 h. The resulting slurry was stirred for 1 h at 18−25 °C while monitoring the pH. If necessary, additional 3 M NaOH was added until pH ≥ 10. After 1−2 h of stirring at 18−25 °C, the mixture was filtered, and the filter cake was rinsed with deionized water three times (21 kg each). Drying in an oven vacuum at 45 °C provided **34** (8.73 kg, 96.4 wt % purity, 29.9 mol, 88.2% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO) δ 6.76 (dd, J = 12.3, 8.6 Hz, 1H), 6.59 (dd, J = 7.1, 2.8 Hz, 1H), 6.45−6.36 (m, 1H), 5.91 (s, 2H), 4.87 (s, 2H), 4.29 (d, J = 8.2 Hz, 1H), 4.20−4.11 (m, 1H), 3.61 (dd, J = 8.0, 2.7 Hz, 1H), 2.93 (dd, J = 13.3, 3.7 Hz, 1H), 2.82 (dd, J = 13.3, 3.7 Hz, 1H), 2.37−2.28 (m, 1H), 1.23 (d, J = 6.1 Hz, 3H); ^{13}C NMR (126 MHz, DMSO) δ 151.44 (d, J_{CF} = 231.8 Hz), 147.68, 144.51, 130.86 (d, J_{CF} = 11.7 Hz), 116.04 (d, J_{CF} = 25.4 Hz), 114.91 (d, J_{CF} = 3.9 Hz), 112.87 (d, J_{CF} = 7.8 Hz), 78.05 (d, J_{CF} = 4.9 Hz), 75.48, 66.03 (d, J_{CF} = 4.9 Hz), 43.22 (d, J_{CF} = 3.9 Hz), 22.44, 19.81.

***N*-(3-((4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5,7,7a-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a-yl)-4-fluorophenyl)-5-(difluoromethyl)pyrazine-2-carboxamide (E2609).** 5-(Difluoromethyl)pyrazine-2-carboxylic acid **16** (9.5 kg, 54.7 mol, 1.1 equiv) was charged into a reactor. DMI (29 kg) was added, and the mixture was cooled down to 0−5 °C. Thionyl chloride (7.39 kg, 62.1 mol, 1.30 equiv) was added while keeping the internal temperature below 10 °C. The resulting solution was stirred at 4−10 °C until the conversion was >95.0% by HPLC. The mixture was cooled down to 0 °C, and a solution of **34** (14.0 kg, 47.8 mol) in DMI (36 kg) was charged while keeping the internal temperature below 5 °C. The vessel was rinsed with DMI (7.3 kg), and the reaction mixture was stirred until the conversion was >99.0%. Deionized water (168 kg) was charged, and the resulting mixture was stirred at 15−20 °C for 0.5 h. EtOAc (168 kg) and then 50% aq. NaOH (21 kg, 253 mol, 5.3 equiv) were added while keeping the internal temperature below 30 °C. The pH was monitored to make sure that it was above 10. The aqueous phase was separated and extracted with EtOAc (63 kg). The organic layers were combined and washed with 30 wt % aqueous sodium chloride (94 kg) and deionized water twice (70 kg). The mixture was filtered through a Celite pad (7.0 kg), rinsing with EtOAc (38 kg). The filtrate was concentrated under reduced pressure at 40−50 °C. 1-Propanol (169 kg) was charged, and the resulting mixture was warmed up to 90−100 °C. Stirring continued until a clear solution was obtained. The mixture was cooled down to 0−5 °C over 2 h. After 1 h of stirring, the mixture was filtered, rinsing with cold 1-propanol twice (28 kg). Drying in vacuo at 45 °C provided the title compound **E2609** (18.5 kg, 97.4 wt % purity, 41.2 mol, 86.2% yield) as an off-white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 9.38 (s, 1H), 9.00 (s, 1H), 7.89−7.77 (m, 2H), 7.14 (dd, J =

https://doi.org/10.1021/acs.oprd.1c00223
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11.9, 8.8 Hz, 1H), 6.94 (t, J = 54.3 Hz, 1H), 4.80 (s, 2H), 4.58 (d, J = 8.9 Hz, 1H), 4.37−4.28 (m, 1H), 3.81 (dd, J = 8.8, 2.4 Hz, 1H), 3.14 (dd, J = 13.5, 4.0 Hz, 1H), 2.88 (dd, J = 13.5, 4.1 Hz, 1H), 2.61−2.54 (m, 1H), 1.33 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 162.59, 158.36 (d, J_{CF} = 244.5 Hz), 156.34, 151.63 (t, J_{CF} = 25.9 Hz), 147.96, 144.72, 141.45 (t, J_{CF} = 3.9 Hz), 135.15 (d, J_{CF} = 2.0 Hz), 132.13 (d, J_{CF} = 11.7 Hz), 123.47 (d, J_{CF} = 3.9 Hz), 122.90 (d, J_{CF} = 8.8 Hz), 117.81 (d, J_{CF} = 24.5 Hz), 114.38 (t, J_{CF} = 239.6 Hz), 78.98 (d, J_{CF} = 4.9 Hz), 78.21, 67.91 (d, J_{CF} = 4.9 Hz), 46.57 (d, J_{CF} = 2.9 Hz), 24.02, 20.00.

Methyl 5-Bromopyrazine-2-carboxylic Acid (39). To a mixture of methyl 5-chloropyrazine-2-carboxylic acid **38** (35.4 kg, 205.1 mol) and acetonitrile (139.2 kg) was added TMSBr (62.7 kg, 409.6 mol, 2.00 equiv), and 35 L of volatile was distilled off at 80 °C under reduced pressure (atmosphere to −25 kPa). After acetonitrile (28.1 kg) was added, 35 L of volatile was distilled off. After cooling to room temperature, EtOAc (159.4 kg) and 6.2 wt % aqueous $NaHCO_3$ (283.5 kg) were added. The aqueous layer was separated and re-extracted with EtOAc (161.7 kg). The combined organic layers were washed with 4.9 wt % aqueous NaCl (93.4 kg). After addition of *N*,*N*-dimethylacetamide (DMA, 166.9 kg), the resulting solution was concentrated to 177 L under reduced pressure at 60 °C. After the solution was azeotroped three times with EtOAc (160 kg × 3) and then two times with an EtOAc/DMA mixture (160 kg/22 kg × 2) under reduced pressure at 60 °C, DMA (199.8 kg) was added to give **39** (397.1 kg, content 40.7 kg, 91% yield, **39**:**38** = 91:9) as a solution. The **39**:**38** ratio was confirmed by HPLC as follows: Sunniest RP-AQUA (3 μm, 4.6 mm × 150 mm), 1.0 mL/min, oven temperature = 45 °C, UV detection at 270 nm, mobile phase A = 990:10:1 v/v/v H_2O/MeCN/CF_3CO_2H, mobile phase B = 100:900:1 v/v/v H_2O/MeCN/CF_3CO_2H, gradient (time (min)/B conc (%)) = 0/0 → 30/30 → 35/100 → 45/100 → 45.01/0 → 55/stop, relative retention time (RRT) of **38** = 0.90, RRT of **39** = 1.00. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.01 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.7, 147.5, 146.3, 144.2, 141.8, 53.0; HRMS (ESI+) calcd for $C_6H_5BrN_2NaO_2^+$ ([M + Na]$^+$) 238.9427, found 238.9417.

Methyl 5-(2-Ethoxy-1,1-difluoro-2-oxoethyl)pyrazine-2-carboxylate (40). To a mixture of zinc (13.0 kg, 198.8 mol, 2.11 equiv) and triglyme (97.6 kg) was added TMSBr (3.1 kg, 20.2 mol, 0.21 equiv). The resulting mixture was stirred at 70 °C for 1.5 h and cooled to rt. $BrCF_2CO_2Et$ (48.0 kg, 236.5 mol, 2.52 equiv) was added for 2 h while keeping the internal temperature around 25 °C. Formation of the Zn reagent was monitored by ^{1}H NMR. After the reaction mixture was quenched with H_2O/CD_3CN to generate the corresponding ethyl difluoroacetate, the proton of the resulted difluoromethyl group (HF_2C−) was quantitated by comparison with those of triglyme, which is one of the reaction solvents.

After cooling to below 10 °C, the zinc reagent mixture was added to a mixture of **39** in DMA (198.6 kg, content 20.4 kg, 94.0 mol) and DMA (101.6 kg) at 0 °C. The resulting mixture was warmed to rt. CuBr (28.4 kg, 198.0 mol. 2.00 equiv) was then added in five portions over 1 h, and the resulting reaction mixture was stirred for 30 min at rt. After cooling to below 5 °C, the reaction mixture was added to a precooled (5 °C) mixture of 6.2 wt % aqueous NaCl (317.1 kg), concentrated HCl (97.2 kg), and toluene (302.1 kg), rinsing with toluene (43.5 kg). The resulting mixture was warmed to rt. The organic layer was separated and washed with aqueous NaCl twice (5.6 wt % solution, 200.4 kg; 2.9 wt % solution, 199.5 kg) to give a solution of **40**. The remaining half of the solution of **39** was processed in the same manner as described above. The product solutions were combined and used in the next step without further purification (assumed 100% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.30 (brs, 1H), 9.28 (brs, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.3, 161.7 (t, J_{CF} = 32 Hz), 148.2 (t, J_{CF} = 28 Hz), 145.5, 145.1, 141.8 (t, J_{CF} = 3 Hz), 111.5 (t, J_{CF} = 252 Hz), 64.1, 53.2, 13.8; HRMS (ESI+) calcd for $C_{10}H_{11}F_2N_2O_4^+$ ([M + H]$^+$) 261.0681, found 261.0684.

Benzylamine Salt of 5-Carboxy(difluoro)-methylpyrazine-2-carboxylic Acid (41). To a solution of **40** (theoretical content 48.9 kg, 187.9 mol) in toluene (117.6 kg) was added 48% aqueous NaOH (62.52 kg, 750.4 mol, 4.0 equiv). The resulting mixture was stirred at rt for 20 h. After cooling to below 15 °C, the reaction mixture was treated with concentrated HCl (20.3 kg) to adjust the pH to 3−4 (actual 4.2) and warmed to rt. The organic layer was separated and re-extracted with water (24.6 kg). To the combined aqueous extracts were added *i*-PrOAc (257.8 kg) and concentrated HCl (68.2 kg). The aqueous layer was separated and re-extracted with *i*-PrOAc (116.1 kg). To the combined organic extracts were added *i*-PrOAc (20.1 kg) and 2-propanol (352.2 kg). The resulting mixture was cooled to 10 °C. Benzylamine (60.3 kg, 562.8 mol, 3.00 equiv) was added while keeping the internal temperature under 25 °C. The precipitated solids were collected and washed with 2-propanol (77.8 kg). The solids were dried under reduced pressure at 50 °C to give **41** (46.8 kg, 108 mol, 58% yield from **39**) as an orange-brown powder. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.99 (d, J = 0.6 Hz, 1H), 8.73 (d, J = 0.7 Hz, 1H), 8.58 (brs, 6H), 7.46−7.33 (m, 10H), 4.02 (s, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.7, 163.8 (t, J_{CF} = 30 Hz), 151.3, 150.4 (t, J_{CF} = 30 Hz), 143.7, 140.7 (t, J_{CF} = 8.0 Hz), 134.9, 128.9, 128.7, 128.4, 113.5 (t, J_{CF} = 255 Hz), 42.5; HRMS (ESI+) calcd for $C_7H_3F_2N_2O_4^-$ ([M - H]$^-$) 217.0066, found 217.0070.

5-(Difluoromethyl)pyrazine-2-carboxylic Acid (16). To a mixture of **41** (44.8 kg, 103.6 mol), water (209.3 kg), and toluene (194.1 kg) was added 48% aqueous NaOH (21.5 kg, 258.1 mol, 2.49 equiv), and the aqueous layer was separated. To the aqueous extract was added 85% aqueous H_3PO_4 (83.6 kg, 725.1 mol, 7.00 equiv), and then it was stirred at 110 °C under a nitrogen atmosphere for 21 h. To the reaction mixture was added 48% aqueous NaOH (77.6 kg, 931.4 mol, 9.0 equiv) to adjust the pH to 6−7 (actual 6.4), and then it was stirred at 110 °C for 17 h. After cooling to rt, *i*-PrOAc (157.9 kg) and concentrated HCl (91.7 kg) were added and polish filtration of the resulting solution was performed, rinsing with *i*-PrOAc (39.4 kg). The aqueous layer was separated and re-extracted with *i*-PrOAc (197.0 kg). After the extracts were combined with *i*-PrOAc (10.5 kg), the mixture was washed with water five times (67.0 kg ×5). The five aqueous layers were combined and then re-extracted with *i*-PrOAc (197.0 kg). After the extracts were combined with *i*-PrOAc (10.8 kg), the resulting solution was concentrated to 300 L under reduced pressure at 50 °C, and then polish filtration was performed, rinsing with *i*-PrOAc (14.7 kg). The filtrate was reconcentrated to 45 L under reduced pressure at 50 °C. The resulting mixture was heated at 60 °C to completely dissolve the solid. The resulting solution was then cooled to rt to induce crystallization. *n*-Heptane (42.9 kg) was added dropwise over 1 h. After aging at 0 °C, the crystals were

https://doi.org/10.1021/acs.oprd.1c00223
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collected and washed with *n*-heptane (15.4 kg). The crystals were dried under reduced pressure at 50 °C to give **16** (12.4 kg, 70.4 mol, 68% yield) as an orange-yellow powder. ^{1}H NMR (600 MHz, CD_3OD) δ 9.32 (s, 1H), 9.00 (s, 1H), 6.92 (t, J = 54.3 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 165.9, 151.8 (t, J_{CF} = 26 Hz), 146.7, 146.5, 142.5 (t, J_{CF} = 4 Hz), 114.3 (t, J_{CF} = 240 Hz); HRMS (ESI+) calcd for $C_6H_3F_2N_2O_2^-$ ([M − H]$^-$) 173.0168, found 173.0164.

Procedure for the Synthesis of *tert*-Butyl 2-(1,1,1-Trifluorobut-3-en-2-yloxy)acetate (45) by Lab-Scale Flow Reaction. In a glass bottle were added acrolein (133 mL, 1.99 mol), CF_3TMS (353 mL, 2.39 mol, 1.20 equiv), and toluene (335 mL), resulting in stream 1 solution. In another glass bottle were added TBAF (34.8 mL, 34.8 mmol of a 1.0 M solution in THF, 0.0175 equiv), THF (56 mL), and toluene (725 mL), resulting in stream 2 solution. Using the lab-scale flow reactor, the two solutions were pumped through the reactor setup with equal flow rates starting with 20 mL/min and gradually increasing to ca. 200 mL/min until the reaction solutions were consumed (the temperature profile of the reaction run in this manner is shown in SI Table 1). Several other options for the streams had been considered. For example, placing the initiator (TBAF) with acrolein was found to promote polymerization, leading to insoluble material which would be detrimental to the flow reactor. Alternatively, a flow system with three separate inputs (acrolein, CF_3TMS, and TBAF) was considered but not explored due to the increased complexity. Therefore, premixing acrolein and CF_3TMS in desired stoichiometry and pumping as a single stream were chosen to ensure initiation of the reaction in the desired stoichiometry upon contact with the TBAF solution.

The static mixer and heat exchange coil were submerged in an ice bath during the reaction. The reaction flow was collected in a 4 L glass container and analyzed by NMR, providing ca. 25 wt % of **44** in toluene, which was used in next step as is. To **44** (244 g total weight, 307 mmol, 1.20 equiv) from the flow-reaction output were added *tert*-butyl bromoacetate (**3**) (50 g, 256 mmol) and nBu$_4$NHSO$_4$ (8.7 g, 26 mmol, 0.10 equiv). The reaction mixture was cooled to 0 °C, and NaOH (205 g of a 50 wt % solution in water, 2.56 mol, and 10 equiv) was added in a controlled manner while keeping the internal temperature below 10 °C. The reaction mixture was warmed to 15−20 °C and analyzed by GC. Upon completion, the reaction mixture was diluted with MTBE (300 mL) and then deionized water (150 mL) while keeping the internal temperature below 30 °C. The organic layer was separated and washed with deionized water (150 mL) and aqueous saturated NaCl (75 mL). The resulting organic solution was concentrated under vacuum to afford **45** as a pale yellow oil (90 g, quantitative yield, contains ca. 30% residual solvents). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86−5.74 (m, 1H), 5.59 (d, J = 17.5 Hz, 1H), 5.56 (d, J = 10.9 Hz, 1H), 4.37−4.30 (m, 1H), 4.11 (d, J = 16.5 Hz, 1H), 4.06 (d, J = 16.4 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.51, 128.49 (d, J_{CF} = 1.7 Hz), 123.86, 123.71 (q, J_{CF} = 281.8 Hz), 82.22, 78.67 (q, J_{CF} = 31.5 Hz), 66.60, 28.02.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00223.

Additional experimental details/spectroscopic data for Schemes 1, 2, 3, 7, and 9 and Figures 2 and 3; copies of ^{1}H and ^{13}C{^{1}H} NMR spectra of compounds **6**, **9-DBT**, **16**, **34**, and **E2609** (PDF)

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https://doi.org/10.1021/acs.oprd.1c00223
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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank our colleagues N. Shibuguchi (Eisai Co., Ltd), I. Kushida (Eisai Co., Ltd), K. Kono (Eisai Co., Ltd), E. Troy (Eisai Inc.), and Dr. M. Alaimo (Eisai Inc.) for data analysis support, M. Vachon (Eisai Inc.) and M. Takahashi (Eisai Co., Ltd) for process validations support, and Dr. H.-w. Choi for valuable feedback and proofreading. We also thank Dr. R. Staples (Crystallographic Resources Inc.) for X-ray crystallographic data of compound **9-DBT**.

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https://doi.org/10.1021/acs.oprd.1c00223
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