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Development of an Efficient Synthesis of Two CRF Antagonists for the Treatment of Neurological Disorders

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Abstract:

BMS-764459 (1) and BMS-763534 (2) are CRF1 antagonists for the treatment of neurological disorders such as depression and anxiety. An efficient synthesis of 1 and 2 is described, which features an efficient palladium-catalyzed cyanation of a 5-chloropyrazinone where zinc acetate suppresses dehalogenation. This synthesis was applied to the preparation of >5 kg of 1 and 2 for clinical studies.

Introduction

Corticotropin-releasing factor (CRF), an important modulator of the hypothalamus−pituitary−adrenal (HPA) axis, helps coordinate the body's response to stress.[1] Hypersecretion of CRF has been linked to a variety of psychiatric disorders, including depression and anxiety, as well as other neurodegenerative and gastrointestinal disorders.[2] A large body of evidence supports the hypothesis that inhibition of the CRF_1 receptor may offer a useful therapy for diseases that result from elevated levels of CRF.[3]

As part of a program directed towards CRF_1 antagonists, two structurally similar compounds, BMS-764459 (**1**) and BMS-763534 (**2**), emerged as potential clinical candidates (Scheme 1).[4] This contribution describes the first kilogram-scale preparation of CRF_1 antagonists **1** and **2** for preclinical and phase I supplies. The key element of our synthetic strategy involved the use of **2** as the final intermediate for the synthesis of **1**. As both active pharmaceutical ingredients (APIs) were required for clinical and preclinical studies, this approach would maximize efficiency. This strategy was realized through the development of an efficient palladium-catalyzed cyanation of a 5-chloropyrazinone.

Results and Discussion

Structurally, compounds **1** and **2** only differ in the substituent at the 5-position of the 2-pyrazinone moiety (Scheme 1). Hence, the synthesis of **1** directly from **2** via a metal-catalyzed cyanation reaction would be an attractive strategy. Compound **2** in turn would result from a displacement of the more reactive chloride at the C-3 position of **4** with pyridylamine **3**. For this strategy to be successful, a number of challenges had to be overcome. First, 5-chloropyrazinones display very low reactivity. Indeed, very few examples of metal-catalyzed carbon−carbon bond-forming processes have been reported using 5-chloropyrazinones.[4a,5] Second, prior work by our Discovery colleagues has shown that unacceptably high catalyst loadings (30 mol %) were required for this transformation.[4a] Finally, control of impurities would need to be tightly maintained as the cyanation step would be the final step of the synthetic sequence to prepare the API for clinical use. However, recent advances in palladium-catalyzed aromatic cyanations gave us encouragement that this key transformation could be accomplished efficiently.[6]

Preparation of Pyridylamine Intermediate 3. Nitropyridinone **8** is a known compound synthesized via a Chichibabin amination reaction of 2,5-lutidine followed by nitration and hydrolysis of the resulting 6-amino-2,5-lutidine.[7] This synthetic sequence was undesirable due to the extremely harsh reaction

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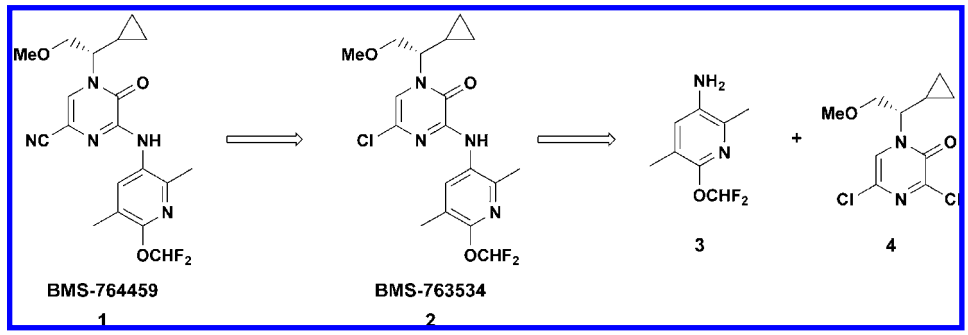
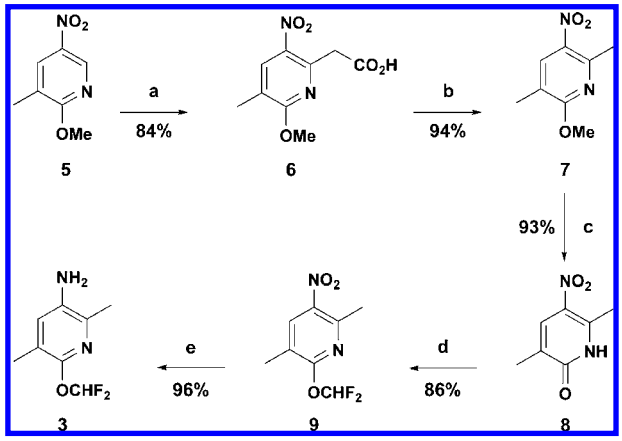
Scheme 1. **Retrosynthesis for CRF_1 antagonists 1 and 2**



Scheme 2. **Synthesis of pyridylamine 3**[a]



[a] Reagents and conditions: (a) i. *tert*-butylchloroacetate, *t*-BuOK, THF, −20 °C, ii. TFA, DCE, 60 °C. (b) K_2CO_3, DMF, 90 °C. (c) 12 N HCl, 110 °C. (d) $FSO_2CF_2CO_2H$, NaH, MeCN, 10 °C. (e) H_2, cat. $Pd(OH)_2$, MeOH, 20 °C.

conditions, low yields, and difficult isolation for the Chichibabin reaction coupled with the potential for the nitration reaction to run away. Hence, a more scalable three-step sequence was developed that starts from the commercially available nitropicoline **5** (Scheme 2).[4a] The installation of the second methyl substituent was accomplished by a vicarious nucleophilic substitution reaction using *tert*-butylchloroacetate, followed by cleavage of the resulting *tert*-butyl ester with TFA to give acid **6**.[8,9] Acid **6** was decarboxylated under basic conditions to provide **7**, which was converted to **8** after demethylation using HCl. Chemoselective difluoromethylation of the resulting carbonyl hydroxyl group with 2-(fluorosulfonyl)acetic acid as the difluorocarbene source afforded difluoromethyl ether **9** in 86% yield.[10,11] Finally, reduction of the nitro group using a palladium-catalyzed hydrogenation resulted in the requisite pyridylamine **3**. Notably, this five-step sequence was accomplished in 58% overall yield with 99.6 HPLC area % purity.

Racemic Preparation of the 3,5-Dichloropyrazinone Intermediate 4. The initial route used to prepare the requisite 3,5-dichloropyrazinone **4** relied on a racemic synthesis followed by separation of enantiomers using simulated moving bed (SMB) chromatography (Scheme 3). The synthesis of **4** started with the reaction of methoxyacetonitrile **10** with cyclopropyl magnesium bromide followed by treatment of the resulting magnesium ketimine with a reducing agent to form amine **rac-11**. Due to the high exothermicity of the Grignard formation leading to the potential of a runaway reaction in case of the accumulation of cyclopropyl bromide, the reaction was run using in-line FT-IR to monitor the levels of the bromide.[12] A variety of reducing agents ($LiAlH_4$, $NaBH_4$, $LiBEt_3H$, H_2, etc.) were explored for both the magnesium and free ketimines. Ultimately, only $LiAlH_4$ provided the desired amine **rac-11** in acceptable yield and purity. Isolation of amine **rac-11** was extremely challenging, due to its high solubility in water as well as difficulty in removing the aluminum salts. This was addressed by an inverse quench into a solution of Rochelle salt, although the filtration of the precipitated aluminum salts was very slow. Multiple extractions using a mixture of Isopropyl acetate (IPAc) and THF followed by in situ HCl formation with TMSCl and MeOH provided **rac-11** as the HCl salt in 52% yield with 97−99 GC area % purity.

Alkylation of amine **rac-11** using bromoacetonitrile provided nitrile **rac-12** cleanly in 75% yield. Upon further conversion to the 3,5-dichloropyrazinone **rac-4**, up to 11% of brominated impurity **13** was observed (Scheme 4). The formation of the 5-bromo-3-chloropyrazinone **13** was traced back to the choice of alkylating agent in the previous step. Nitrile **rac-12** was unexpectedly isolated as a mixture of the HCl and HBr salts, owing to the use of bromoacetonitrile. During the pyrazinone formation, HBr is competitive with HCl in forming the haloimine intermediate **ii**, which after cyclization and further chlorination results in the 5-bromo-3-chloropyrazinone impurity **13**.

By-product **13** was easily avoided by replacing bromoacetonitrile with chloroacetonitrile. While an in situ Finkelstein

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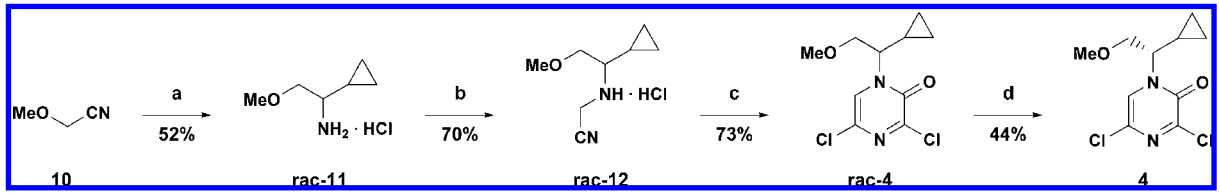
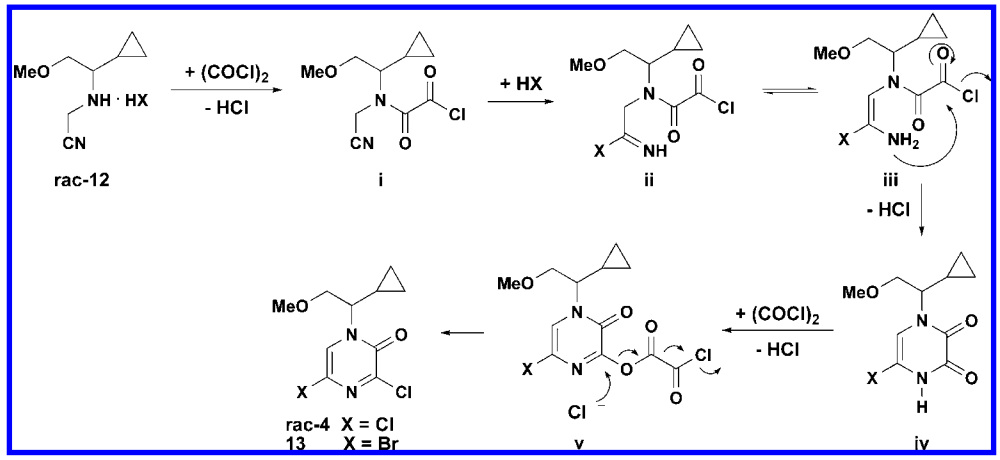
(12) The heat of reaction = −436.9 kJ/mol; *T* adiabatic = +242.6 K.

Scheme 3. **Racemic synthesis of 3,5-dichloropyrazinone 4**[a]

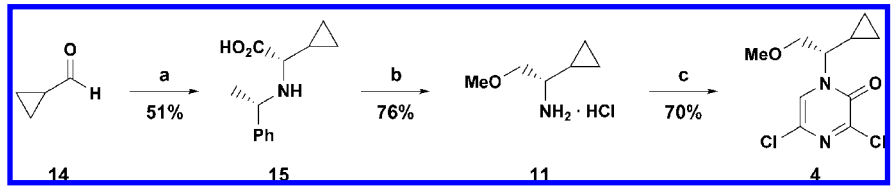


[a] Reagents and conditions: (a) i. cyclopropylmagnesium bromide, THF, 15 °C, then $LiAlH_4$, ii. TMSCl, MeOH, MTBE/THF, 10 °C. (b) i. $ClCH_2CN$, K_2CO_3, KI, MeCN, 50 °C, ii. HCl, IPA, 5 °C. (c) $(COCl)_2$, THF/DCM, RT. (d) Chiral simulated moving bed chromatography.

Scheme 4. **Formation of 5-bromo-3-chloropyrazinone impurity 13**



Scheme 5. **Asymmetric synthesis of 3,5-dichloropyrazinone 4**[a]



[a] Reagents and conditions: (a) i. (*S*)-methylbenzylamine, KCN, AcOH, MeOH, 0 °C, ii. HCl, 85 °C. (b) i. $NaBH_4$, I_2, THF, 0 °C then RT, ii. NaH, MeI, THF, 0 °C, iii. H_2, $Pd(OH)_2$, MeOH, 40 °C, iv. TMSCl, MeOH, 0 °C. (c) i. $ClCH_2CN$, K_2CO_3, KI, MeCN, 50 °C, ii. HCl, IPA, iii. $(COCl)_2$, THF/DCM, RT.

reaction with potassium iodide was required to obtain adequate reactivity using chloroacetonitile, the corresponding 5-iodo-3-chloropyrazinone was not observed in the following reaction. Hence, nitrile **rac-12** was converted to 3,5-dichloropyrazinone **rac-4** under the action of oxalyl chloride in 51% yield over two steps.[13] Separation of the enantiomers using SMB chromatography then provided the homochiral 3,5-dichloropyrazinone **4** in 44% yield and 99.8% ee.

Enantioselective Synthesis of 3,5-Dichloropyrazinone Intermediate 4. The racemic synthesis of **4** suffered from a number of drawbacks. First, since a chromatographic separation was used, the undesired enantiomer was wasted. Furthermore, the separation of enantiomers had to occur at a late stage due to the lack of chromophore in the earlier intermediates, which required carrying along 50% of the mass of intermediates for ultimately no purpose. Finally, the time required to separate the enantiomers on scale was substantial. Five hundred hours of operation was needed to prepare 5.25 kg of **4** due to the limiting flow rates required for adequate separation (23.3 mL/min) using SMB chromatography. With these drawbacks in mind, a more efficient enatioselective route to **4** was desired.

As an alternative enantioselective approach to **4**, a Strecker reaction using a chiral auxiliary could be used to set the key stereochemistry, and then the nitrile could be converted to the methyl ether followed by removal of the auxiliary (Scheme 5).[4a] A telescoped version of the previous sequence would then be used to convert amine **11** to 3,5-dichloropyrazinone **4**. Cyclopropylcarboxaldehyde **14** was treated with (*S*)-methylbenzylamine, potassium cyanide, and acetic acid to form the corresponding Strecker adduct, which was subsequently hydrolyzed to carboxylic acid **15** by heating in HCl.[14] Although the in-process dr was only 2.5:1, it was improved to 49:1 upon crystallization. A single recrystallization upgraded the dr to ≥99 to 1. Amine **11** was subsequently formed via a telescoped reduction, methylation, and hydrogenation sequence, and then was isolated as the HCl salt.[15] Over alkylation on nitrogen was avoided during the methylation step by slow addition of one equivalent of methyl iodide at 0 °C. An improved telescoped procedure to convert amine **11** to 3,5-dichloropyrazinone **4** was also realized, leading to a 27% overall yield for the asymmetric route compared to the 12% overall yield for the racemic route.

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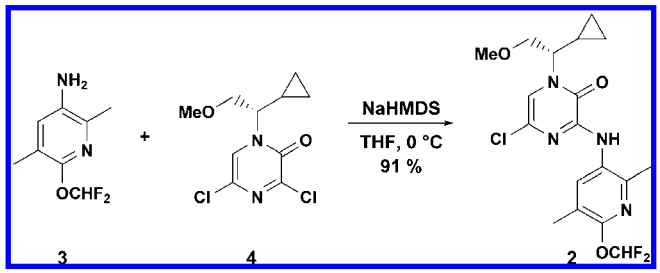
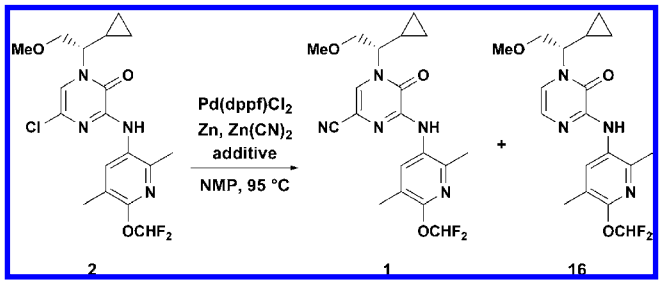
Scheme 6. **Coupling of 3 and 4**



Scheme 7. **Conversion of chloropyrazinone 2 to cyanopyrazinone 1**



Coupling of 3 and 4. The union of pyridylamine **3** with 3,5-dichloropyrazinone **4** was completely regioselective as the 3-chloro atom is part of an imidoyl chloride system while the 5-chloro atom is vinylic and therefore much less reactive.[16] Treatment of a solution of **3** and **4** in THF with NaHMDS effectively provided the CRF antagonist **2** (Scheme 6).

Compound **2** crystallizes in two neat (solvent/water free) polymorphs, N-1 and N-2. N-1 has the morphology of thin rods, and N-2 has the shape of bricks/prisms. The higher solubility of N-1 (~0.126 μg/mL) compared to that of N-2 (~0.082 μg/mL) at room temperature in water indicates N-2 is the more stable form at ambient conditions. However, the lower melting point of N-2 (92 °C vs N-1 104 °C) and its higher heat of fusion (73 J/g vs N-1 55 J/g) suggest N-1 and N-2 are enantiotropically related. Further solubility measurements in a number of solvents pinpointed the crossover temperature of the two polymorphs to be 43 °C, and a limit was set on the crystallization temperature required to obtain the desired N-2 form. Solvent exchange from THF to EtOH at 30−35 °C followed by cooling to room temperature provided N-1 as the kinetic form. The slurry of N-1 was then converted to N-2 through seeding (1−5%) and high-shear mixing by Turrax wet-mill until a pure N-2 slurry was established. The high-shear mixing reduced the time required for the form conversion from 2 h to 30 min. The addition of water as the antisolvent completed the crystallization and limited losses to the mother liquor to 2−5%. Markedly, the chloro API **2** was isolated as the N-2 form in 91% yield and 99.7 HPLC area % purity using this process. With compound **2** in hand, we still needed to convert it to the related cyano API **1** for our strategy to be successful.

Conversion of 2 to 1; Palladium-Catalyzed Cyanation. The key element of our strategy was the conversion of the 5-chloropyrazinone **2** to the 5-cyanopyrazinone **1** (Scheme 7). While significant progress has been made on palladium-catalyzed cyanation reactions of aryl chlorides, the corresponding reactions of 5-halopyrazinones are rare.[4a,6] Although exceptions exist, 5-chloropyrazinones are often not reactive enough to undergo palladium-catalyzed cross-couplings.[4a,5]

Table 1. **Additive effect on dehalogenation to form impurity 16 (Scheme 7)**

entry	additive (20 mol %)	scale	HPLC area % of **16**
1	–	150 mg	0.6
2	–	8 g	2.6
3	$ZnBr_2$	150 mg	3.3
4	$ZnCl_2$	150 mg	2.6
5	$Zn(TFA)_2$·hydrate	150 mg	3.5
6	$Zn(OAc)_2$	150 mg	0.1
7	$Zn(OAc)_2$	2 kg	0.3

Our initial cyanation screen aimed at using the nontoxic $K_4[Fe(CN)_6]$ as the source of cyanide.[6f] These conditions were ineffective, providing only trace amounts of the desired product. Gratifyingly, Jin and Confalone's protocol using zinc cyanide and zinc dust effectively performed this transformation.[6b] Upon optimization, complete conversion could be achieved with only 0.6 HPLC area % of des-chloro impurity **16** (Table 1, entry 1). Attempts to lower the catalyst loading or use the more active $Pd(TFA)_2$/(binapthyl)P(*t*-Bu)$_2$ system were met with increased levels of des-chloro impurity **16**, (up to 5.0 HPLC area %).[6a] Upon moderate scale up of the optimal conditions, a 4-fold increase in the des-chloro impurity **16** was observed (entry 2). The increase of impurity **16** upon scale up was hypothesized to be related to a mass transfer effect. Presumably, agitation was less efficient on scale up effectively starving the reaction for cyanide leading to an increase in the reduced impurity **16**. In order to suppress the undesired dehalogenation a number of additives were examined (Table 1).

It has been previously reported that the addition of $ZnBr_2$ to palladium-catalyzed cyanations can increase the reaction rate by increasing the solubility of cyanide ion.[17] We reasoned that this effect might help to suppress the dehalogenation pathway by preventing the reaction from being starved of cyanide. However, we observed an increase in the formation of the des-chloro impurity **16** when the reaction was carried out in the presence of $ZnBr_2$ (entry 3). Other zinc salts also had a detrimental effect on dehalogention (entries 4−5). The acidity of these salts may explain their poorer performance in terms of dehalogenation. Gratifyingly, addition of the less acidic $Zn(OAc)_2$ did indeed suppress dehalogenation, leading to only 0.1 HPLC area % of impurity **16** (entry 6).[18] There was only a slight increase in formation of **16** when the reaction was scaled up to 2 kg (entry 7). In contrast to $ZnBr_2$, which had been previously reported to increase the rate of palladium-catalyzed cyanations, $Zn(OAc)_2$ was found to reduce the rate of reaction. This intriguing result prompted a detailed kinetic analysis of the reaction.

The cyanation reaction was followed by reaction calorimetry (Omnical, SuperCRC), and the rate of the reaction was determined to be 4-fold slower when using the $Zn(OAc)_2$ additive (Figure 1). The reaction without the additive is between zero and first order in substrate. This is consistent with a change

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(17) Buono, F. G.; Chidambaram, R.; Mueller, R. H.; Waltermire, R. E. *Org. Lett.* **2008**, *10*, 5325–5328.

(18) For an example of zinc acetate improving the conversion of a palladium-catalyzed cyanation see: Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441–1444.

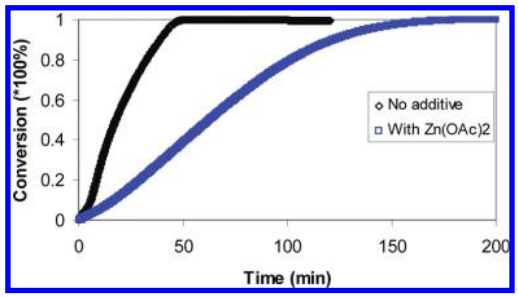

Figure 1. **Conversion vs time for cyanations with and without $Zn(OAc)_2$.**

in the rate-limiting step over the course of the reaction from a mass transfer step (dissolution of $Zn(CN)_2$), to a step on the catalytic cycle. Conversely, the reaction with $Zn(OAc)_2$ is first order in substrate, therefore not mass transfer limited. This implies that the reaction is at no point starved for cyanide ion and thus the dehalogenation is greatly reduced. However, the overall rate when using $Zn(OAc)_2$ is reduced, presumably due to inhibition of the catalyst owing to the increased concentration of dissolved cyanide ions as shown by Grushin.[19,20]

Compound **1** crystallizes in at least five neat polymorphic forms (N-1, N-2, N-3, N-4, and P-3). The thermodynamic behavior of the multiple polymorphs is rather complicated, and the interrelationship can be enantiotropic or monotropic between any two of the five forms. The relative stability at room temperature was found to be N-3 > N-2 > N-4 > N-1, according to a series of slurrying experiments.[21] Application of the optimal cyanation conditions followed by aqueous workup, palladium removal via carbon filtration, and then crystallization from IPAc/heptanes provided compound **1** as the metastable form N-1. The N-1 slurry was converted to the desired N-3 form through seeding. Optionally, the form transformation could be accelerated by at least 3-fold (5 h vs 1.5 h) via high-shear mixing using a Turrax wet-mill. Using this process, the 5-cyanopyrazinone **1** was isolated as the N-3 form in 80% yield and 99.9 HPLC area % purity and <10 ppm of residual palladium.[22] Hence, the development of new palladium-catalyzed cyanation reaction conditions led to the successful implementation of our strategy of using the chloro API **2** as the final intermediate for the related cyano API **1**. Notably, the ability to suppress dehalogentation by using the $Zn(OAc)_2$ additive allowed for excellent control of final quality for API **1**.

Conclusions

An efficient synthesis of two CRF antagonists, BMS-763534 (**2**) and BMS-764459 (**1**) has been described, which enabled the preparation of >5 kg of each for clinical studies. A racemic route to the key 3,5-dichloropyrazinone intermediate was used for rapid entry to initial supplies, but was supplanted by a more efficient enantioselective route based upon an asymmetric Strecker reaction. Development of both APIs could progress in quick succession due to the strategy of using the chloro API **2** as the final intermediate for the related cyano API **1**. This was accomplished using an efficient palladium-catalyzed cyanation of a 5-chloropyrazinone where zinc acetate was found to suppress dehalogenation.

(19) (a) Dobbs, K. D.; Marshall, W. J.; Grushin, V. V. *J. Am. Chem. Soc.* **2007**, *129*, 30–31. (b) Erhardt, S.; Grushin, V. V.; Kilpatrick, A. H.; Macgregor, S. A.; Marshall, W. J.; Roe, D. C. *J. Am. Chem. Soc.* **2008**, *130*, 4828–4845.

(20) For an example of additive effects on cyanide solubility see: Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C.-Y. *Org. Lett.* **2004**, *6*, 3723–3725.

(21) The stability of P-3 relative to that of N-2 and N-4 is unclear because it is a transient polymorph only obtained during the N-1 to N-3 conversion.

(22) The level of residual zinc was <10 ppm, and the level of residual NMP was <0.02 wt %.

Experimental Section

General Methods. HPLC analyses were collected on a Shimadzu LC-10AT liquid chromatograph using a SPD-10AV UV−vis detector, and the results are reported as area percent (area %).

2-(6-Methoxy-5-methyl-3-nitropyridin-2-yl)acetic Acid (6). A mixture of THF (15 L), *tert*-butylchloroacetic acid (985 mL, 6.88 mol), and **5** (925 g, 5.50 mol) was cooled to −18 °C, and potassium *tert*-butoxide (1590 g, 13.74 mol) was charged in portions at ⩽10 °C. The reaction was brought to 20−25 °C and then cooled back to −8 °C and quenched with 2 N HCl (4 L). The organic phase was distilled under vacuum to near dryness. 1,2-Dichloroethane (10 L) was added and concentrated under vacuum to ∼6 L; then trifluoroacetic acid (2.5 kg, 22 mol) was charged, and the reaction was heated at 60 °C for 3 h. NaOH (2.75 N, 10 L) was added at ⩽24 °C, the phases were split, and the organic phase was back extracted with water (6 L). The combined aqueous layers were cooled to 15 °C, and concentrated HCl (800 mL) was charged until pH = 1.7, resulting in a slurry. The slurry was filtered, and the cake was washed with water (2 × 2 L) and then dried in a vacuum oven at 50 °C to afford 1045 g of **6** as a tan solid (99.8% HPLC area purity, 84% isolated yield). Mp 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 8.20 (s, 1H), 4.25 (s, 2H), 4.03 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.59, 163.80, 146.52, 139.16, 135.30, 121.53, 54.86, 42.88, 15.32. Anal. calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.65; H, 4.14; N, 12.30.

2-Methoxy-3,6-dimethyl-5-nitropyridine (7). A mixture of **6** (1,040 g, 4.60 mol), potassium carbonate (335 g, 2.42 mol), and DMF (2 L) was heated to 50−60 °C for 3 h, at which time the bubbling had ceased. The mixture was added to water (13 L), resulting in a slurry. The slurry was filtered, and the cake was washed with water (5 L) and air-dried to provide 785 g of **7** as a tan solid (100.0% HPLC area purity, 94% isolated yield). Mp 85.9−90.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 4.02 (s, 3H), 2.76 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.37, 151.63, 139.44, 135.02, 119.39, 54.45, 24.18, 15.16. Anal. calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.37. Found: C, 52.82; H, 5.28; N, 15.45.

3,6-Dimethyl-5-nitropyridin-2-ol (8). A solution of **7** (775 g, 4.21 mol) in 12 N HCl (8 L) was heated at 80 °C for 2 h. The reaction mixture was cooled to 20−25 °C and added to cold water (8 L), resulting in a slurry. The slurry was aged for 30 min and then filtered, and the cake was washed with water (3 × 2 L) and then dried under vacuum at 50 °C to afford 655 g of **8** as a tan solid (99.8% HPLC area purity, 93% isolated yield). Mp 263 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (br s, 1 H), 8.03 (s, 1 H), 2.61 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.05, 148.73, 132.74, 129.41, 126.14,

19.50, 15.86. Anal. calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.79; N, 16.66. Found: C, 50.01; H, 4.59; N, 16.75.

2-(Difluoromethoxy)-3,6-dimethyl-5-nitropyridine (9). To a suspension of **8** (640 g, 3.77 mol) in MeCN (19.5 L) was added NaH (310 g, 7.75 mol; 60% in mineral oil). After stirring at 20−25 °C for 1.5 h, 2,2-difluoro-2-(fluorosulfonyl)acetic acid (1.0 L, 9.39 mol) was added dropwise over 2 h at ⩽40 °C. After 1 h, the reaction was quenched by the slow addition of water (340 mL). The mixture was filtered through Celite, and then the solvent was switched to heptane and the volume adjusted to 9 L. The mixture was cooled to −14 °C, resulting in a slurry. The slurry was filtered, and then the mother liquor was concentrated and cooled to −14 °C, resulting in a second crop. Both crops were air-dried to provide 703 g of **9** as yellow crystals (99.3% HPLC area purity, 86% yield). Mp 48−49 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.56 (t, J = 72.4 Hz, 1 H), 2.77 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 151.1, 141.9, 137.1, 120.0, 113.8 (t, J = 257.6 Hz), 23.7, 14.8; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −89.8. Anal. calcd for $C_8H_8N_2O_3F_2$: C, 44.04; H, 3.69; N, 12.84. Found: C, 43.78; H, 3.55; N, 12.58.

6-(Difluoromethoxy)-2,5-dimethylpyridin-3-amine (3). To a solution of **9** (400 g, 1.82 mol) in methanol (4 L) was added 10% palladium hydroxide (72 g, 103 mmol), and the resulting suspension was hydrogenated in a 5-L Buchi reactor under 40 psi H_2 at 25 °C for 4 h. The reaction mixture was filtered through a polypropylene 0.5-μm filter cartridge. The solvent was switched to hexane (1.6 L) and the solution cooled to −15 °C, resulting in a slurry which was filtered, and the cake was air-dried to furnish 328 g of **3** (99.8% HPLC area purity, 96% yield). Mp 40−42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 74.0 Hz, 1 H), 6.86 (s, 1 H), 2.27 (s, 3 H), 2.15 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 137.9, 137.5, 127.8, 119.4, 115.3 (t, J = 253.1 Hz), 19.4, 15.0; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −86.9; Anal. calcd for $C_8H_{10}N_2OF_2$: C, 51.12, H, 5.38, N, 14.86. Found: C, 51.17, H, 5.29, N, 14.87.

1-Cyclopropyl-2-methoxyethanamine Hydrochloride (rac-11). A mixture of magnesium turnings (205 g, 8.44 mol) and THF (3.0 L) was cooled to 5 °C, and then a premixed solution of cyclopropyl bromide (1.62 kg, 13.4 mol) in THF (2.5 L) was slowly added. The reaction mixture was cooled to 15 °C, **10** (500 g, 7.03 mol) was charged slowly followed by lithium aluminum hydride (1 M in THF) (3.79 kg, 4.21 mol) at 25 °C. The reaction mixture was then heated to reflux (67 °C) for 12 h and then cooled to 20 °C. The reaction mixture was then added slowly to a solution of Rochelle salt (3.81 kg, 13.5 mol) in water (8.9 L) at 5−10 °C. IPAc (6 L) was added; then the phases were separated, and the rich organic layer was decanted. The aqueous layer was back extracted with 1:1 IPAc/THF (4 × 8 L), and the combined organic layers were concentrated under vacuum and then cooled to 10 °C. Methanol (338 g, 10.6 mol) was slowly added and then trimethylsilyl chloride (765 g, 7.04 mol), resulting in a slurry. The slurry was filtered, and the wet cake was washed with IPAc (3 L) and dried under vacuum at ambient temperature to afford 555 g of **rac-11** (97−99% GC area purity of free base, 52% yield). Mp = 112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 3H), 3.54−3.6 (m, 2H), 3.31 (s, 3H), 2.54−2.44 (m, 1H), 0.95−1.02 (m, 1H), 0.48−0.53 (m, 3H), 0.33−0.37 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 71.66, 58.29, 55.12, 10.92, 3.96, 3.51. HRMS (ES-MS) Calcd for $C_6H_{14}NO$: 116.1075; HRMS found $[M + H]^+$: 116.1069.

2-(1-Cyclopropyl-2-methoxyethylamino)acetonitrile Hydrochloride *(rac*-12). A mixture of **rac-11** (650 g, 4.29 mol), potassium iodide (783 g, 4.72 mol), potasium carbonate (1480 g, 4.87 mol), MeCN (9.8 L), and chloroacetonitrile (275 mL, 4.34 mol) was heated to 50 °C for 3 h, cooled to 25 °C, and diluted with MTBE (8.0 L). The heterogeneous slurry was filtered to remove the inorganic solids, and then the solvent was switched to 2-propanol. The mixture was concentrated to ∼3.25 L under vacuum (115 Torr), then the batch was cooled to ⩽10 °C, and 4−5 M HCl in 2-propanol (2.0 L) was added dropwise at ⩽20 °C. The mixture was concentrated to ∼3.25 L and then cooled to 20−25 °C, resulting in a slurry which was aged for 15 min. MTBE (6.5 L) was then charged, and the slurry was aged for 15 h and filtered, and the cake was washed with MTBE (2.0 L) and dried under vacuum at 50 °C to afford 570 g of **rac-12** as an off-white solid (70% yield). Mp = 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (bs, 2H), 4.44 (d, A of AB, J_{AB} = 16.4 Hz, 1H), 4.37 (d, B of AB, J_{AB} = 16.4 Hz, 1H), 3.97 (dd, A of ABX, J_{AB} = 10.9 Hz, J_{AX} = 7.8 Hz, 1H), 3.82 (dd, B of ABX, J_{AB} = 11.0 Hz, J_{BX} = 3.0 Hz, 1H), 3.44 (s, 3H), 2.80 (ddd, J = 10.5, 8.0, 2.8 Hz, 1H), 1.30−1.21 (m, 1H), 0.93−0.86 (m, 1H), 0.83−0.73 (m, 2H), 0.44−0.38 (m, 1H); ^{13}C NMR (100 MHz $CDCl_3$) δ 112.80, 71.93, 63.59, 59.23, 33.29, 9.18, 5.51, 3.93. HRMS Calcd for $C_8H_{15}N_2O$, 155.1184; HRMS found $[M+]^+$: 155.1179 (for the free base).

3,5-Dichloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1H)-one (rac-4). A solution of **rac-12** (800 g, 4.20 mol), THF (4.0 L), and DCM (4.0 L) was cooled to 0 °C, and oxalyl chloride (1090 mL, 12.6 mol) was added over 30 min at <10 °C. The mixture was warmed to 20 °C and aged for 15 h and then was added slowly to a saturated KH_2PO_4 solution (8.0 L) at 0 °C over 30 min at ⩽20 °C. The mixture was agitated for 1 h, then the product rich lower organic phase was removed. The aqueous phase was extracted with DCM (2.4 L), and the organic phases were combined. The solvent was switched to IPA under reduced pressure, and the volume was adjusted to ∼4.0 L, resulting in a slurry. Water (8.0 L) was added, and then the slurry was aged for 15 h and filtered; then the cake was washed with 4:1 water/IPA solution (2.5 L) and dried under vacuum at 50 °C to provide 810 g of **rac-4** as a beige solid (99.7% HPLC area purity, 73% yield). Mp = 95−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 4.11 (dt, J = 10.0, 3.6 Hz, 1H), 3.74 (dd, A of ABX, J_{AB} = 10.5 Hz, J_{AX} = 4.5 Hz 1H), 3.64 (dd, B of ABX, J_{AB} = 10.4 Hz, J_{BX} = 3.1 Hz 1H), 3.33 (s, 3H), 1.45−1.36 (m, 1H), 0.85−0.77 (m, 1H), 0.67−0.60 (m, 1H), 0.52 (dq, J = 9.9, 4.8 Hz, 1H), 0.30 (dq, J = 10.7, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.80, 146.38, 125.65, 123.57, 72.03, 63.57, 59.27, 11.17, 6.24, 4.00; Anal. calcd for $C_{10}H_{12}N_2O_2Cl_2$: C, 45.64; H, 4.59; N, 10.64; Cl, 26.94. Found: C, 45.78; H, 4.35; N, 10.52; Cl, 26.86; HRMS calcd for $C_{10}H_{13}Cl_2N_2O_2$: 263.0354; HRMS found $[M + H]^+$: 263.0358.

(*S*)-3,5-Dichloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1*H*)-one (4). A mixture of **rac-4** (3.33 kg, 12.7 mol), *n*-heptane (167 L), ethanol (14.7 L), and methanol (14.7 L) was aged with stirring until dissolved. The solution was then aged without agitation at 20 °C for 10 h and passed through a 10-μm filter, a carbon adsorption pad (11% of **rac-4** irreversibly adsorbed), and a 1-μm filter to obtain the feed solution. The feed solution was prepared every 7−12 days of processing to prevent degradation. A total of 11.94 kg (45.5 mol) of **rac-4** was processed. The feed solution was processed at flow rates of 13.6−23.3 mL/min using 85/7.5/7.5 *n*-heptane/ethanol/methanol (vol %) as the eluent through a Licosep simulated moving bed (SMB) unit (Novasep). The SMB unit employed six spring columns (Alltech) packed with Chiralpak AD 20 μm (5 × 10 cm) and 5-μm frits. The configuration of the SMB process across zones 1−4 was 1/2/2/1. The desired enantiomer **4** was obtained in the raffinate with an in-process yield greater than 48.5% and >99.8% ee. The raffinate solution was stored at 5 °C until the SMB processing was complete. The raffinate solution was then concentrated under reduced pressure to a total volume of 25 L, resulting in a slurry. The slurry was filtered, and the cake was washed with *n*-heptane and then dried under vacuum at 40 °C to provide 5.25 kg of **4** as a white crystalline solid (99.8% HPLC area purity, 99.8% ee, 44% yield). Mp = 109−110 °C; $[\alpha]^{25}_{D}$ −36.61° (*c* 1.014, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 4.11 (dt, J = 10.0, 3.6 Hz, 1H), 3.74 (dd, A of ABX, J_{AB} = 10.5 Hz, J_{AX} = 4.5 Hz 1H), 3.64 (dd, B of ABX, J_{AB} = 10.4 Hz, J_{BX} = 3.1 Hz 1H), 3.33 (s, 3H), 1.45−1.36 (m, 1H), 0.85−0.77 (m, 1H), 0.67−0.60 (m, 1H), 0.52 (dq, J = 9.9, 4.8 Hz, 1H), 0.30 (dq, J = 10.7, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.80, 146.38, 125.65, 123.57, 72.03, 63.57, 59.27, 11.17, 6.24, 4.00. Anal. calcd for $C_{10}H_{12}N_2O_2Cl_2$: C, 45.64; H, 4.59; N, 10.64; Cl, 26.94. Found: C, 45.69; H, 4.50; N, 10.58; Cl, 26.69. HRMS calcd for $C_{10}H_{13}Cl_2N_2O_2$, 263.0354; HRMS found [M + H]: 263.0358.

(*S*)-2-Cyclopropyl-2-((*S*)-1-phenylethylamino)acetic Acid (15). To a mixture of (*S*)-methylbenzylamine (1.04 kg, 8.56 mol) and MeOH (3.6 L) was added **14** (0.60 kg, 8.6 mol). Upon cooling to below 0 °C, potassium cyanide (0.61 kg, 9.4 mol) was added at ⩽10 °C. Acetic acid (0.53 kg, 8.9 mol) was added, and the reaction was aged for 16 h at 25 °C; then water (3.0 L) and EtOAc (6.0 L) were added. The layers were separated, the organic layer was concentrated to ∼2.5 L under vacuum (100 Torr), the mixture was cooled to below 0 °C, and 12 N HCl (3.9 L) was added slowly. The mixture was then heated to 100 °C for 16 h and then cooled to 0 °C; water (6 L) followed by 10 N NaOH (2.5 L) was added until the pH was between 1 and 3. The temperature of the slurry was increased to 25 °C, the material was filtered, and the cake was washed with water (2 × 6 L) and acetone (2 × 6 L). The wet cake was dissolved with 3 N NaOH (2.85 L); then the pH was adjusted to 1 with 1 N HCl (9.4 L), and the resulting slurry was filtered. The cake was washed with water (6 L) and acetone (2 × 6 L) and then dried under vacuum at 50 °C to afford 960 g of **15** as a white solid (99.5% HPLC area purity, 51% yield). ^{1}H NMR (500 MHz, pyridine-d_5) δ 7.52 (br d, J = 7.6 Hz, 2 H), 7.35 (br t, J = 7.6 Hz, 2 H), 7.25 (br t, J = 7.3 Hz, 1 H), 4.08 (q, J = 6.7 Hz, 1H), 2.97 (d, J = 7.3 Hz, 1H), 1.39 (d, J = 6.6 Hz, 3H), 1.25 (m, 1H), 0.60 (m, 1H), 0.39−0.52 (m, 3H); ^{13}C NMR (125 MHz, pyridine-d_5) δ 177.3, 146.5, 128.8, 127.5, 127.3, 62.7, 57.1, 25.5, 15.2, 3.5, 2.7. HRMS Calcd [M + H]: 220.1338; HRMS found [M + H]: 220.1332.

(*S*)-1-Cyclopropyl-2-methoxyethanamine (11). A mixture of **15** (960 g, 4.4 mol), THF (11 L), and $NaBH_4$ (398 g, 10.5 mol) was cooled to −10 °C; then a solution of I_2 (1.1 kg, 4.4 equiv) in THF (2.9 L) was added slowly. The resulting solution was refluxed for 75 min and then was cooled to −10 °C; MeOH (1.1 L) was slowly added followed by 20 wt % KOH (14.4 L), and the layers were separated. The organic layer was concentrated under atmospheric pressure with the addition of THF (30 L) until the water content of the solution was below 0.2 wt %. The solution was cooled to 0 °C; NaH (0.37 kg, 9.2 mol) was slowly added, and the temperature was increased to 20 °C for 1 h at which time it was cooled to 0 °C. MeI (0.62 kg, 4.4 mol) was slowly added, and the reaction was aged for 1 h, and then MeOH (1.2 L) was added followed by 1 N HCl (9.6 L) and heptane (9.6 L). The layers were separated, and 10 N NaOH (1.2 L, 12.5 mol) was added to the aqueous layer (pH > 10). EtOAc (9.6 L) was added, the layers were separated, and the organic layer was concentrated to minimal volume under reduced pressure (100 Torr), and the solvent was switched to MeOH (9.6 L). Pd/C (240 g, 5 wt %) was added, and the mixture was heated to 40 °C under 45 psi of H_2 for 6 h. The mixture was cooled to 0 °C, and TMSCl (560 mL, 4.4 mol) was slowly added. The solvent was switched to IPAc (6 L), resulting in a slurry. The slurry was filtered, and the cake washed with IPAc (2 L) and dried under vacuum at 50 °C to afford 504 g of **11** as a white solid (76% yield). $[\alpha]^{25}_{D}$ +9.00° (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br s, 3H), 3.70 (d, J = 4.0 Hz, 2H), 3.42 (s, 3H), 2.66−2.61 (m, 1H), 1.22−1.14 (m, 1H), 0.75−0.61 (m, 3H), 0.35−0.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.95, 59.10, 57.32, 10.56, 4.10, 3.99. HRMS Calcd [M + H]: 116.1070; HRMS found [M + H]: 116.1070.

Telescoped Procedure for (*S*)-3,5-Dichloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1*H*)-one (4). To a mixture of **11** (650 g, 4.29 mol), K_2CO_3 (1480 g, 10.7 mol), potassium iodide (783 g, 4.72 mol), acetonitrile (9.75 L) was added chloroacetonitrile (327 g, 4.29 mol). The reaction was heated to 50 °C for 4 h, then cooled to 20 °C, diluted with MTBE (9.75 L), and then the solvent was switched under vacuum to IPA. The mixture was concentrated under vacuum to 9.75 L, then cooled to 0 °C. HCl in IPA (4 M, 1.93 L) was added dropwise at ⩽37 °C. The resulting solution was concentrated to dryness via a rotovap. The residue was dissolved in DCM (4090 mL) and then diluted with THF (4090 mL). The reaction was cooled to 0 °C, and oxalyl chloride (1120 mL, 12.9 mol) was added at ⩽10 °C. The mixture was warmed to 20 °C, aged for 15 h, and then added to a saturated KH_2PO_4 solution (8.2 L) at 0 °C over 30 min at ⩽30 °C. The mixture was diluted with DCM (2 L) and then agitated for 1 h, and the phases were split. The organic phase was washed with saturated KH_2PO_4 (8.2 L), then the solvent was switched to IPA under reduced pressure, and the volume was adjusted to 4.1 L, resulting in a slurry. Water (8.2 L) was added, and then the slurry was aged for 1 h and filtered; the cake was then washed with 4:1 water/

IPA solution (4 L) and then dried under vacuum at 50 °C to provide 793 g of **4** as a yellow crystalline solid (99.8% HPLC area purity, 70% yield).

(*S*)-5-Chloro-1-(1-cyclopropyl-2-methoxyethyl)-3-(6-(difluoromethoxy)-2,5-dimethylpyridin-3-ylamino)pyrazin-2(1*H*)-one (2). A solution of **4** (224 g, 0.851 mol), **3** (153 g, 0.813 mol) in THF (4.58 L) was cooled to 0 °C, and then sodium bis(trimethylsilyl)amide solution (1 M in THF, 1.46 kg, 1.62 mol) was added slowly at ⩽7.5 °C. The reaction was aged for 30 min between 5−10 °C; then the reaction was quenched at 0 °C with 20% aqueous NH_4Cl solution (763 mL) and then diluted with water (305 mL). The organic phase was concentrated to ∼1.5 L under vacuum (115 Torr) at ⩽50 °C. The solvent was switched to EtOH, and the volume was adjusted to 3.6 L and the mixture cooled to 30 °C over 1 h. A portion of **2** seeds (N-2 form, 15 g, 5%) was added followed by recirculating through a wetmill until PXRD analysis confirmed complete conversion to the N2 form. Water (6.75 L) was charged, and the slurry was aged overnight at 22 °C. The slurry was filtered and the cake washed with 1:2 EtOH/water (1 L) and then water (0.5 L); then it was dried under vacuum at 50 °C for 15 h to provide 306 g of **2** (99.7% HPLC area purity, 91% yield). Mp = 102 °C; $[\alpha]^{25}_D$ −6.12° (*c* 10.3, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.05 (s, 1H), 7.48 (t, J = 73.8 Hz, 1H), 6.99 (s, 1H), 4.18 (ddd, J = 9.7, 5.9, 3.2 Hz, 1H), 3.76 (dd, A of ABX, J_{AB} = 10.4 Hz, J_{AX} = 6.3 Hz 1H), 3.69 (dd, B of ABX, J_{AB} = 10.4 Hz, J_{BX} = 3.4 Hz 1H), 3.36 (s, 3H), 2.46 (s, 3H), 2.28 (s, 3H), 1.36−1.27 (m, 1H), 0.84−0.77 (m, 1H), 0.65−0.59 (m, 1H), 0.53 (dq, J = 9.7, 4.7 Hz, 1H), 0.35 (dq, J = 10.1, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.46, 150.53, 146.77, 143.51, 132.81, 129.51, 125.76, 118.66, 114.48 (t, J = 254.0 Hz), 112.80, 72.84, 62.04, 59.24, 19.73, 15.17, 11.19, 5.88, 3.75; ^{19}F NMR (400 MHz, $CDCl_3$) δ −88.63. Anal. Calcd for $C_{18}H_{21}ClF_2N_4O_3$: C, 52.12; H, 5.10; N, 13.51; Cl, 8.55; F, 9.16. Found: C, 52.22; H, 5.08; N, 13.40; Cl, 8.21; F, 9.13. HRMS calcd for $C_{18}H_{22}ClF_2N_4O_3$ 415.1348; HRMS found $[M + H]^+$: 415.1353.

(*S*)-4-(1-Cyclopropyl-2-methoxyethyl)-6-(6-(difluoromethoxy)-2,5-dimethylpyridin-3-ylamino)-5-oxo-4,5-dihydropyrazine-2-carbonitrile (1). To a reactor was charged **2** (3.124 kg, 7.53 mol) followed by inertion with nitrogen. (1,1′-bis(diphenylphosphino)ferrocene)palladium(II) chloride (0.180 kg, 0.246 mol) zinc flake (0.100 kg, 1.53 mol), zinc cyanide (0.512 kg, 4.36 mol), and zinc acetate (0.138 kg, 0.752 mol) were added, followed by inertion with nitrogen, then NMP (31 L) was charged, followed by inertion with nitrogen. The mixture was heated to 95−100 °C for 16 h under nitrogen, cooled to 0−5 °C, and ammonium hydroxide (5 N; 9.9 L) was added slowly. After aging for 1 h, MTBE (31 L) was charged, and phases were split. The aqueous phase was back extracted with MTBE (31 L), and the organic phases were combined, washed with 10 wt % brine solution (10 L × 2), and passed through a Cuno zetapad. The filtrate was concentrated under vacuum (100 Torr), the solvent was switched to IPAc, and the volume was adjusted to 7.5 L. The mixture was heated to 50 °C to obtain a clear solution and then cooled to 20 °C, and a portion of **1** seeds (N-3 form, 10 g, 0.4 wt %) was added. The resulting slurry was aged overnight at ambient temperature, followed by addition of *n*-heptane (25 L). The slurry was held an additional 16 h at 20 °C and filtered; the cake was washed with *n*-heptane and then dried under vacuum at 20 °C to afford 2.5 kg of **1** as a white crystalline powder (99.9% HPLC area purity, 80% yield). Mp = 155 °C; $[\alpha]^{25}_D$ −38.16° (*c* 3.3, methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.01 (s, 1H), 7.56 (s, 1H), 7.48 (t, J = 73.7 Hz, 1H), 4.16 (ddd, J = 10.3, 5.4, 3.4 Hz, 1H), 3.67 (dd, J = 10.2, 3.4 Hz, 1H), 3.75 (dd, J = 10.3, 5.4 Hz, 1H), 3.36 (s, 3H), 2.45 (s, 3H), 2.29 (s, 3H), 1.38 (m, 1H), 0.84 (m, 1H), 0.66 (m, 1H), 0.55 (dt, J = 9.3, 4.4 Hz, 1H), 0.33 (dt, J = 10.8, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.09, 150.62, 147.01, 147.01, 143.01, 132.57, 128.72, 124.94, 118.45, 116.60, 114.13 (t, J = 252.1 Hz), 107.11, 72.49, 62.51, 59.47, 20.17, 15.63, 11.59, 6.66, 4.51; ^{19}F NMR ($CDCl_3$) δ −88.7. Anal. Calcd for $C_{19}H_{21}N_5O_3F_2$: C, 56.29; H, 5.22; N, 17.27; F, 9.37. Found: C, 56.5; H, 5.33; N, 17.38; F, 9.21. HRMS (TOF-MS) calcd for $C_{19}H_{22}N_5O_3F_2$: 406.1691; HRMS found $[M + H]^+$: 406.1696.

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