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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00202 • Publication Date (Web): 30 Jun 2017

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Early Development Scale-Up of a Structurally-Challenging 5-Lipoxygenase Activating Protein (FLAP) Inhibitor

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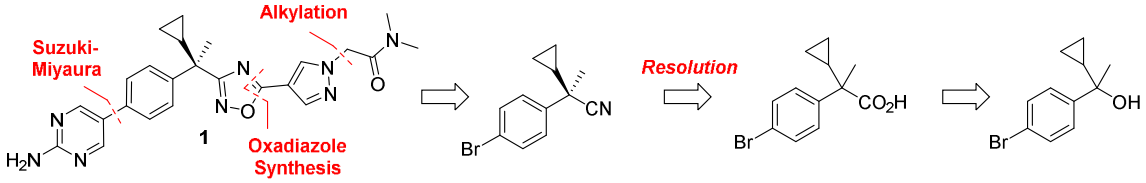


KEY WORDS: quaternary, Suzuki-Miyaura, FLAP, resolution

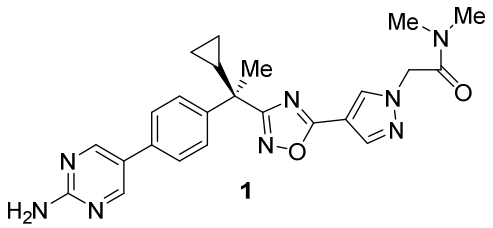
ABSTRACT:

A practical and efficient synthesis of the FLAP inhibitor **1** was developed addressing multiple scale-up and safety concerns posed by the established synthesis and utilized a resolution strategy (replacing supercritical fluid chromatography (SFC) separation) for expedient access to the key structural component of **1**: the challenging chiral quaternary center. Also highlighted are *in situ* IR monitoring, condensation to form the 1,2,4-oxadiazole ring, and an efficient Suzuki-Miyaura coupling.

INTRODUCTION

Cardiovascular disease impacts a large number of patients today and the impact is only expected to grow as the median age in developed countries continues to rise.[1] Therefore the development of effective new treatments for cardiovascular diseases such as atherosclerosis is truly needed. There is evidence that one effective mode of treating such inflammatory-based diseases is by inhibition of the leukotriene (LT) biosynthesis pathway.[2] 5-Lipoxygenase-activating protein (FLAP) inhibitors have been shown to limit plaque growth[3] and to affect biomarkers of atherosclerosis.[4] Compound **1** (Figure 1) is a candidate under development as a FLAP inhibitor.[5]

Process development chemists must always balance the following two key deliverables: expedient delivery of drug substance to support development, and delivery of a scalable process amenable for commercial manufacture. We have previously described several scale-up strategies toward **1**,[6,7,8] as well as a stereoselective total synthesis[9] of **1** via boronate rearrangement - a potential commercial route for **1**. Herein we focus on the early process work that led to the first scalable process of this challenging molecule in our labs which enabled advancement of the molecule through early development by rapidly providing multi-kilogram quantities of drug substance for early toxicological and clinical studies, allowing space for the development of potential commercial routes.



1

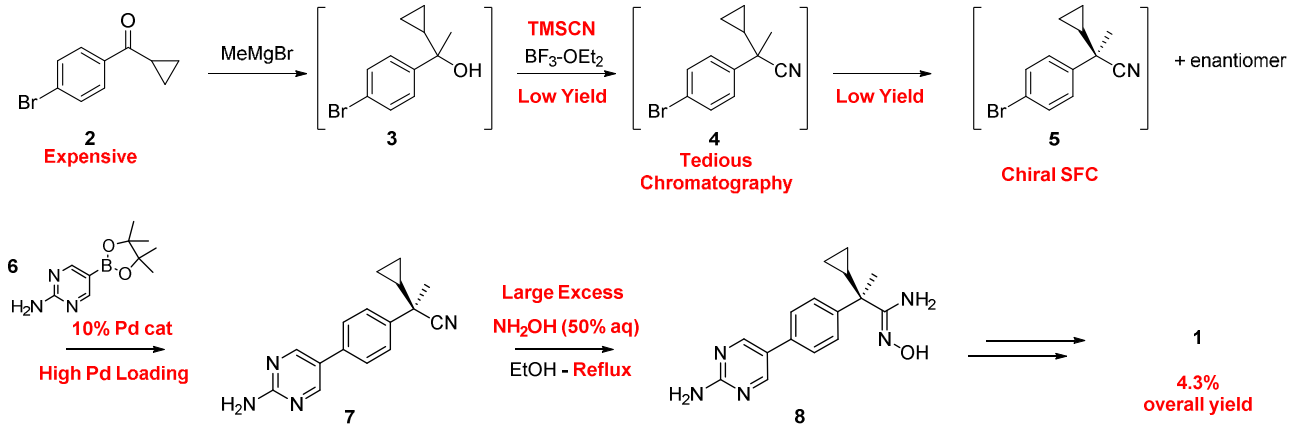
Figure 1. FLAP inhibitor **1**.

RESULTS AND DISCUSSION

Discovery Synthesis of 1.

The strategy developed by the Discovery group[5,10] for the target **1** (Scheme 1) was short and convergent, where the molecule was strategically disconnected via the 1,2,4-oxadiazole ring. The synthesis was well suited for rapidly exploring synthetic space, but for the delivery of kilogram quantities of drug substance for development, several key issues needed to be resolved quickly. The cyanation reaction (**3** to **4**) was not robust and proceeded in low yield which varied between 23 and 47% with the concurrent formation of impurities requiring extensive chromatography to purge. Furthermore, the racemate was subsequently separated using chiral supercritical fluid chromatography (SFC)[11] which is not preferred for large scale synthesis. The conversion of nitrile **7** to amidoxime **8** held additional liabilities. Thermal studies confirmed the reaction conditions[12] using excess NH_2OH in refluxing ethanol were potentially explosive and the reaction produces a high level of amide hydrolysis by-product. In addition, the key Suzuki-Miyaura[13] coupling reaction would require optimization in order to achieve a robust and efficient synthesis of the drug candidate.

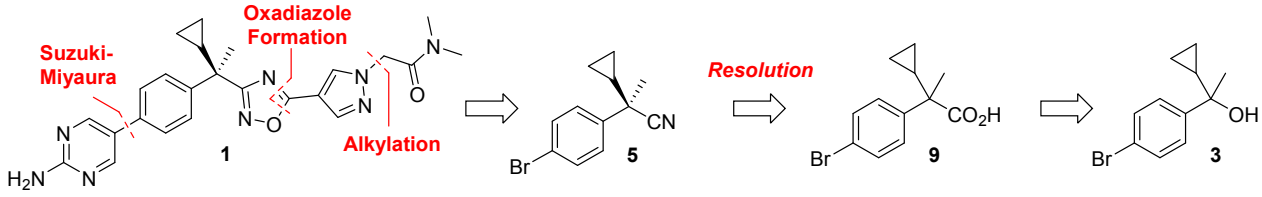
Scheme 1. Discovery Synthesis of 1 and Shortcomings of the Synthesis for Scale-up



A Resolution Strategy.

Our efforts focused primarily on synthesis of nitrile **5**; a resolution strategy to establish the chiral quaternary center avoids the SFC chiral separation and its corresponding throughput bottleneck (Scheme 2). After failed initial attempts to resolve (*R*)- amidoximes **8** or **15** (Scheme 7) from their racemic mixtures, we targeted carboxylic acid **9**, derived from alcohol **3**, as a candidate for diastereomeric salt resolution (Scheme 3).

Scheme 2. Assembly Strategy

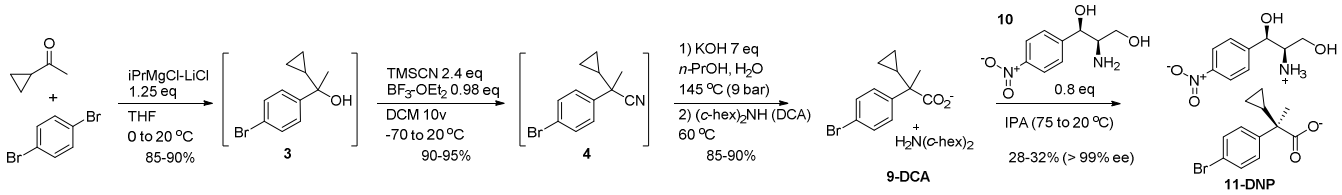


Racemic Acid Synthesis.

Tertiary alcohol **3** was efficiently and cost-effectively produced by reaction of the requisite 4-bromophenyl Grignard[14] reagent, generated *in situ* from 1,4-dibromobenzene using the ^{i}PrMgCl-LiCl complex,[15] with 1-cyclopropylethan-1-one in high yield. Alcohol **3** was used directly in the subsequent cyanation. The low purity observed for nitrile **4** in the Discovery route was likely due to inefficient trapping of the carbocation in the cyanation reaction. Conversely, nearly quantitative yield of **4** could be achieved by premixing the tertiary alcohol **3** with excess TMSCN and slowly adding BF_3-OEt_2[16] to the mixture at low temperature. Since this process was telescoped until isolation of **9-DCA** (the first solid) it was essential that formation of **4** be clean and high yielding.

The hydrolysis of racemic nitrile **4** with potassium hydroxide under pressure (145 °C, 9 bar) provided carboxylic acid **9**.[17] Acid **9** was isolated as its dicyclohexylammonium (DCA) salt since the free acid could not be isolated as a solid.[18] More than 350 kg were produced using this process to provide **9-DCA** in an overall 65% yield (4 steps) from cyclopropyl methyl ketone and 1,4-dibromobenzene.

Scheme 3. Synthesis of Quaternary Acid 11-DNP



Resolution of Racemic Acid 9.

A variety of chiral amines were tested for the resolution, and ultimately a robust process was developed using (*1R,2R*)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-amine (**10**, or DNP) in 2-propanol. The resolved acid was isolated consistently as the DNP salt (**11-DNP**) using temperature cycling to achieve good crystallization control. A total of 46.5 kg of **11-DNP** was produced in a combined yield of 28-32% with >99% ee (after two recrystallization enrichments). Unfortunately, all efforts to resolve racemic carboxylic acid **9** directly after the hydrolysis as the **11-DNP** salt (avoiding the intermediate DCA isolation) led to lower overall recoveries (~20% overall yield), mostly due to higher mother liquor losses.

Amidoxime Formation.

Chiral nitrile **5** was obtained by a telescopic sequence (Scheme 4). The "real-time" IR trace for the transformation from acid **11** to acid chloride **12** to amide **13** is shown in Figure 2. While the nitrile IR signal is difficult to monitor, since it is very week, the final dehydration step could be followed easily by the nearly instantaneous disappearance of the amide IR signal (~1670 cm^{-1}) upon addition of TFAA and pyridine. Concomitant HPLC monitoring of "in process" samples was conducted for this campaign, but with calibration, IR could serve as the sole In Process Testing (IPT) analytical technique for this reaction sequence.

Scheme 4. Formation of Chiral Nitrile 5

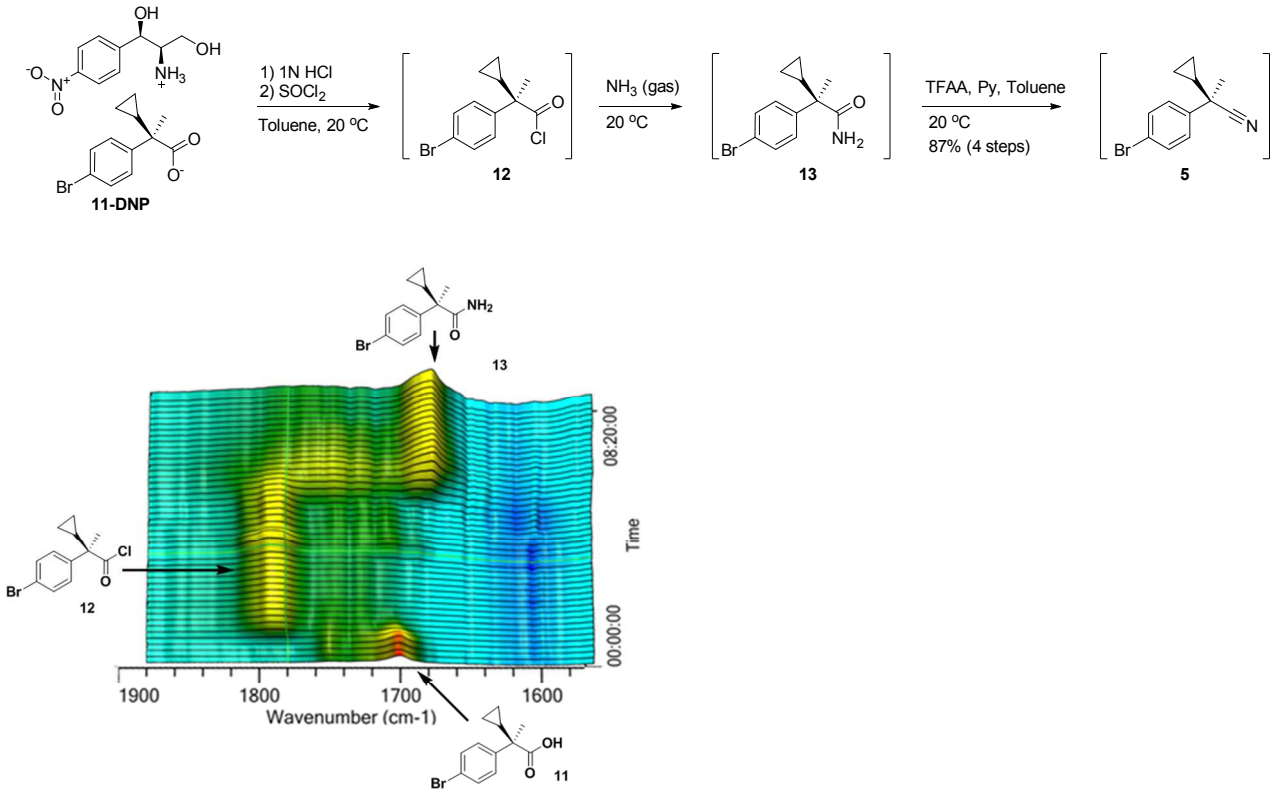
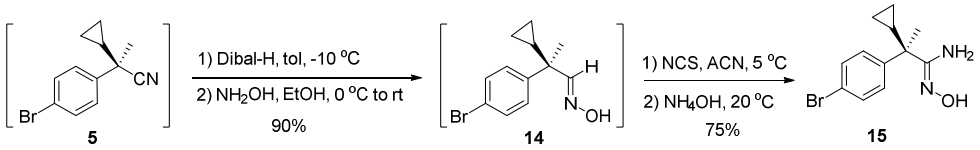


Figure 2. *In situ* IR trace of acid to amide conversion.

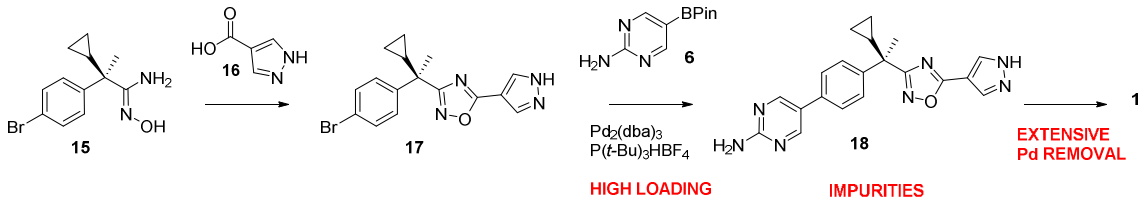
We sought to avoid the unsafe[12] process conditions (excess hydroxylamine in refluxing ethanol) used previously for conversion of the nitrile to amidoxime (**7** to **8** in Scheme 1). So the amidoxime functionality in **15** was installed in a step-wise manner via intermediate oxime **14** (Scheme 5). A Dibal-H reduction of nitrile **5** to the aldehyde was followed by oxime condensation, which could be accomplished safely at 0 °C. Since a rapid exotherm was observed during the HCl quench of Dibal-H, with localized hot spots that led to formation of the amine over-reduction side product; we strongly recommend the reverse quench as a preferred alternative for future scale-up. The amidoxime was then formed from **14** by a safe two-step operation, via chloro-oxime formation using NCS and catalytic acid, followed by ammonia treatment.[9,19] After a subsequent recrystallization from toluene/heptane, 22.9 kg (in 2 batches) of amidoxime **15** was isolated in 75% combined yield (98.9% HPLC purity, 97.3 wt %, 99.4% ee) based on the assay of crude **14**. The overall yield from solid **11-DNP** to solid **15** over 8 operations was 59%.

Scheme 5. Formation of Amidoxime 15



We initially pursued a strategy of oxadiazole formation (**17**) between **15** and pyrazole acid **16**, followed by Suzuki-Miyaura coupling with boronate **6** (Scheme 6); however, this strategy required high palladium loadings (up to 9 mol%) and led to several issues[8] which provided the motivation to change the endgame. We decided to move the coupling one step upstream in the synthetic sequence; providing more opportunities for palladium removal prior to the final API isolation. We also removed dba from the Pd source due to dba-related impurity[8] formation.

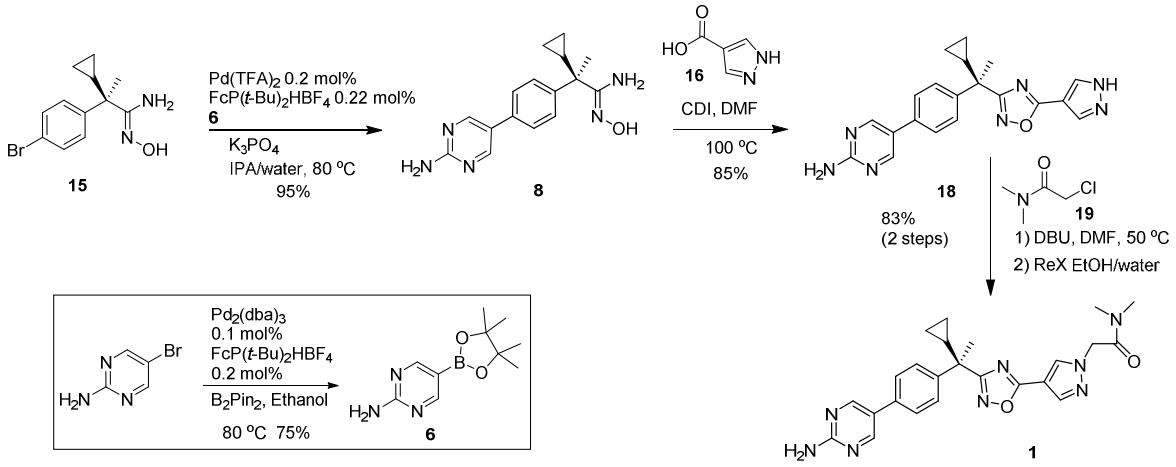
Scheme 6. First Development Strategy Toward Synthesis of 1:



Synthesis Completion.

Fortunately the isolable solid amidoxime **15** proved to be a very competent coupling partner with boronate **6**[9, 20] (Scheme 7). The Suzuki-Miyaura coupling could be run with low catalyst loadings of 0.05 to 0.2 mol% $Pd(TFA)_2$[21] with the patent-free $FcP(t\text{-}Bu)_2\text{-}HBF_4$ ligand, which has been a privileged ligand for Suzuki-Miyaura couplings in our labs. Upon reaction completion, *N*-acetyl cysteine[22] was added to the reaction mixture to reduce the palladium level and the product precipitated from the reaction mixture providing amidoxime **8** (22.7 kg in 2 batches) in 95% yield with >99% HPLC purity.

Scheme 7. Synthesis of 1



Oxadiazole **18** was formed from amidoxime **8** and CDI-activated acid **16** in DMF (Scheme 7). The elimination of an intermediate aminal to form the oxadiazole ring was achieved thermally (without addition of acid), but required high temperature (100 °C). The optimal charges of CDI and **16** were 1.05 and 1.10 equivalents, respectively. A deviation from these ratios was detrimental to the reaction, causing impurity formation. THF functioned exclusively as a carrier solvent for reagent addition; it was then removed by distillation as the reaction temperature was ramped eventually to 100 °C. This strategy permitted only 2.5 volumes of the reaction solvent DMF to be used, which eliminated the need for any back extraction of the aqueous layer during work-up.[23]

Only after several months of project work, were we finally able to obtain oxadiazole **18** in crystalline form from a sample which had spontaneously crystallized. These valuable seeds were used to ultimately facilitate the final crystallization of **18**, providing a valuable additional purification prior to the API step. This seeding strategy was employed on scale-up leading to isolation of 22 kg of oxadiazole **18** in two batches in a combined 86% yield with 99.8% HPLC purity at <10 ppm Pd (obtainable with the combination of carbon treatment and crystallization). A solid form of **18** could not be isolated in the absence of seeds regardless of substrate purity or the solvent system employed.

Alkylation of oxadiazole **18** was achieved by heating a mixture of **18**, chloride **19**,[24] and DBU at 45 °C for 2 h in DMF. These homogenous conditions provided a dramatic rate increase compared with the K_2CO_3/THF conditions employed in the Discovery route. Following an aqueous work-up, crude **1** was

isolated from IPAc. A final recrystallization from ethanol/water provided purified **1** (83% for 2 steps, >99% HPLC purity) with <5 ppm palladium.

CONCLUSION

A practical and efficient resolution-based synthesis of FLAP inhibitor **1** was developed that more than doubled the overall yield of the Discovery synthesis. An optimized synthesis of carboxylic acid **9** was effected from inexpensive cyclopropyl methyl ketone and 1,4-dibromobenzene. Resolution of carboxylic acid **9** as its (*1R,2R*)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-amine (DNP) salt provided expedient and ready access to the challenging chiral quaternary center as an alternative to using SFC chromatography. A safe, step-wise alternative process was implemented for the amidoxime synthesis via a chloro-oxime intermediate to avoid the potentially explosive conditions of excess hydroxylamine in refluxing ethanol. A highly efficient Suzuki-Miyaura coupling of amidoxime **15** and boronate **6** was implemented which reduced palladium loading from ~10 mol% down to $\leq$0.2 mol%. This strategy was an effective fit-for-purpose route which provided drug substance for early development work packages.

EXPERIMENTAL SECTION

1-(4-Bromophenyl)-1-cyclopropylethan-1-ol (3). Turbo Grignard (*i*-PrMgCl·LiCl) solution in THF (443 kg, 14.6 wt %, 629 mol, 1.2 equiv) was added to a solution of 1,4-dibromobenzene (125 kg, 530 mol, 1 equiv) in THF (220 kg) at –4 to 0 °C over 70 min. The solution was warmed to 20 °C and stirred for 22 h, then cooled to 0 °C. Cyclopropylmethylketone (48 kg, 571 mol, 1.08 equiv) was added to the reaction mixture at 0–20 °C. The reaction mixture was stirred for 3 h at 20 °C. The mixture was diluted with heptane (428 kg), cooled to 0 °C, and transferred to a new reactor (50 kg of THF was used as a rinse). An 5% aqueous solution of citric acid (673 kg) was cooled to 0 °C and charged to the Grignard solution over 1.5 h maintaining a temperature of 0–20 °C. At 20 °C the biphasic mixture was stirred for 20 min, the pH was 8–9 so 3 kg additional citric acid was added to bring the pH to 5). The layers were separated and the aqueous layer was removed. The organic layer was washed with 5% aqueous $NaHCO_3$ solution (312 kg) and 5% aqueous NaCl solution (312 kg). The organic layer was concentrated at 35 °C (675–600 torr) and then filtered over Celite (5 kg). The filter cake was rinsed

with heptane (38 kg). The organic layer was further concentrated at 35 °C (150–40 torr) to give carbinol **3** as a pale yellow oil (160 kg, 86% yield, 82.5 wt %, 90 LCAP). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.3-0.45 (m, 3H), 0.45-0.6 (m, 1H), 1.1-1.3 (m, 1H), 1.46 (s, 3H), 7.40 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 8 Hz, 2H). Analytical data consistent with literature.[25]

2-(4-Bromophenyl)-2-cyclopropylpropanenitrile (4). A mixture of carbinol **3** (33.4 kg, 68.9 wt %, 95.4 mol, 1 equiv), TMSCN (23.8 kg, 240 mol, 2.5 equiv), and dichloromethane (288 kg) were cooled to –72 °C and a BF_3•Et_2O (12.2 kg, 86.0 mol, 0.9 equiv) solution in CH_2Cl_2 (10 kg) was added over 20 min maintaining an internal temperature of –75 to –65 °C. The mixture was warmed over 1 h to –20 °C and stirred for 30 min, then warmed over 2 h to 20 °C. Upon completion, the reaction mixture was added to an aqueous 2N NaOH solution (154 kg, 333 mol, 3.5 equiv) maintaining internal temperature of ~20 °C. The biphasic mixture was stirred for 1 h and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 122 kg). The combined 3 organic layers were washed with aqueous 2N NaOH solution (2 × 154 kg) and then with water (2 × 91 kg). The organic layer was concentrated at 40 °C (450–150 torr) and filtered to remove solid bodies. The filter was washed with heptane (5 kg) and the combined organic layers were concentrated at 40 °C (225–40 torr) to yield nitrile **4** as a yellow oil (29.8 kg, 94% yield, 75 wt %, 84.6 LCAP). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45-0.75 (m, 4H), 1.15-1.3 (m, 1H), 1.73 (s, 3H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J*= 8.5 Hz, 2H). Analytical data consistent with literature.[5]

2-(4-Bromophenyl)-2-cyclopropylpropanoic acid (9). A solution of nitrile **4** (50.3 kg, 70 wt %, 140.7 mol, 1 equiv) was solvent switched from heptane to 1-propanol with 3 cycles of the following: 34 L 1-propanol was charged and an equal volume of distillate was collected via distillation at 45 °C (150–30 torr). After the distillation cycles, 42 kg (52 L) of 1-propanol was charged to provide a 37 wt % solution of **4** in 1-propanol. 50 wt % Aqueous KOH (110 kg, 980 mol, 7 equiv) and water (7 kg) were added to the solution. The mixture was stirred for 10–12 h at 145 °C in an autoclave (maximum pressure achieved was 9 bar). The reaction mixture was cooled to 25 °C and diluted with heptane (71 kg) and water (159 kg). Conc. HCl (140 kg) was added at 0 °C until pH ≤ 1. The aqueous layer was

removed. Heptane (63 kg) and 1M aq HCl (132 kg) were added to the organic layer and the aqueous layer was separated. The organic layer was washed with water (105 kg), filtered over Celite® (3 kg), and the filter residue was washed with heptane (18 kg). The organic layer was concentrated to minimum volume at 45 °C (75 torr) to yield acid **9** as a yellow oil (52.4 kg, 94.8% yield, 68.5 wt %, 84.6 LCAP).

Dicyclohexylammonium 2-(4-bromophenyl)-2-cyclopropylpropanoate (9-DCA). A solution of **9** free acid (111 kg, 67 wt %, 279 mol, 1 equiv) was diluted with heptane (514 kg) and heated to 60 °C. Dicyclohexylamine (56 kg) was added over 1 h. The formed suspension was stirred for 1 h at 60 °C, then cooled over 2 h to 20 °C and held for 1 h at this temperature. The suspension was filtered and the filter cake was washed with heptane (96 kg). The product was dried in an oven (45 °C) to yield acid salt **9-DCA** as an off-white solid (117 kg, 92% yield, ~100 wt %, 98.8 LCAP). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30–0.45 (m, 3H), 0.50–0.60 (m, 1H), 1.0-1.30 (m, 10H), 1.16 (s, 3H), 1.40–1.52 (m, 1H), 1.58–1.68 (m, 2H), 1.68–1.76 (m, 4H), 1.82–1.90 (m, 4H), 2.70–2.80 (m, 2H), 7.36 (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.25, 1.92, 18.79, 22.10, 24.82, 25.32, 29.78, 50.67, 52.42, 119.27, 128.90, 130.60, 147.55, 180.25. mp 168.2–170.4 °C.

Resolution

(1*R*,2*R*)-1,3-Dihydroxy-1-(4-nitrophenyl)propan-2-aminium-(*R*)-2-(4-bromophenyl)-2-cyclopropylpropanoate (11-DNP).

Salt Break: To a slurry of **9-DCA** (50.7 kg, 98.9 wt %, 111 mol, 1 equiv) in MTBE (223 kg) was added 2 N aqueous HCl (122 kg, 222 mol, 2 equiv). The mixture was stirred for 1 h and produced a thick slurry. The precipitated dicyclohexylammonium chloride was removed by filtering the reactor contents (both layers). The reactor and filter cake were rinsed with MTBE (74 kg). The filtrates were returned to a clean reactor. The bottom aqueous layer (pH = 1) was removed and the organic layer was washed with 1 N aqueous HCl (113 kg, 111 mol, 1 equiv) then water (117 kg). The assay yield of **9** was determined by HPLC to be 10.8 wt % (32.1 kg of **9** contained). The MTBE was then removed by distillation at 60 °C (760–625 torr). Isopropanol (164 kg) was added to chase residual MTBE at 50–60

°C (760–230 torr) until <0.1 GC wt % MTBE and <1 GC wt % water were achieved. IPA was added (217 kg) to adjust the total isopropanol content to 8 L IPA per 1 kg[I] of **9** (from assay).

11-DNP salt formation: The IPA solution of **9** was heated to 75–80 °C to obtain a clear solution. 1R, 2R-2-Amino-1-(4-nitrophenyl)-propane-1,3-diol (DNP) (18.8 kg, 88.7 mol, 0.8 equiv) was charged as a slurry in IPA (23.4 kg).[I] The mixture was cooled to 50 °C and a seed slurry of **11-DNP** (1.5 kg, >99% ee, 0.05 equiv) in IPA (2.5 kg) was added. The batch was then cooled at a rate of 10 °C/h and a thick slurry developed at 26 °C. Cooling was suspended and a temperature cycle was conducted. The batch was reheated to 55 °C and aged for 2 h, it was then cooled to 20 °C over 5 h. The solid was collected by filtration and the reactor and cake were rinsed with the filtrate to remove held up product. Finally the filter cake was rinsed with IPA (24 kg) and spun in the centrifuge to yield **11-DNP** as a damp, off-white solid (31.72 kg, 67.3 wt %, 67.9% yield, 37.7 mol of the desired isomer based on 82.7% ee). Yield is corrected for the seed load (1.5 kg).

[I] This mass was subtracted from the charge of IPA used above to reach a total isopropanol content of 8 L per 1 kg of acid **9** AFTER addition of the resolving agent slurry.

1st Recrystallization of 11-DNP: Crude **11-DNP** from the previous step and IPA (123.6 kg, 8 L per 1 kg **11-DNP** dry basis) were heated to 75 °C to obtain a clear solution. The solution was then cooled to 60 °C over 30 min and a slurry of **11-DNP** seeds (0.2 kg, 1 wt %; >99% ee) in IPA (1 kg) were charged. The batch was then cooled at a rate of 10 °C/h and a thick slurry developed at 30 °C. Cooling was suspended and a temperature cycle was conducted. The batch was reheated to 55 °C and aged for 2 h, it was then cooled to 20 °C over 5 h. The solid was collected by filtration and the reactor and cake were rinsed with the filtrate to remove held up product. Finally the filter cake was rinsed with IPA (20 kg) and spun in the centrifuge to yield **11-DNP** (23.44 kg, 97.8% ee) as a wet, off-white solid.

2nd Recrystallization of 11-DNP: A slurry of **11-DNP** wet cake from above (23.44 kg, 97.8% ee) and IPA (110 kg) were heated to 78 °C to obtain a clear solution. The solution was then cooled to 60 °C over 30 min. and then a slurry of **11-DNP** seeds (0.2 kg, 1 wt %; >99% ee) in IPA (1 kg) were charged. The batch was then cooled at a rate of 10 °C/h and a thick slurry developed at 23 °C. Cooling was

suspended and a temperature cycle was conducted. The batch was reheated to 55 °C and aged for 2 h, it was then cooled to 20 °C over 5 h and held at 20 °C for 36 h. The solid was collected by filtration and the reactor and cake were rinsed with the filtrate to remove held up product. Finally, the filter cake was rinsed with IPA (20 kg) and spun in the centrifuge and dried at 38 °C (40 torr) to yield **11-DNP** as a white solid (18.8 kg, 31% yield from **9-DCA**, 99 wt %, 99.5% ee). Note: % yield is corrected for the total seed load (1.9 kg) over 3 operations. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.2–0.3 (m, 1H), 0.3–0.38 (m, 1H), 0.38–0.5 (m, 2H), 1.10 (s, 3H), 1.35–1.45 (m, 1H), 2.91 (q, J = 8 Hz, 1H), 3.19 (dd, J = 8, 12 Hz, 1H), 3.40 (dd, J = 4, 12 Hz, 1H), 4.75 (d, J = 8 Hz, 1H), 7.40 (d, J = 12 Hz, 2H), 7.43 (d, J = 12 Hz, 2H), 7.62 (d, J = 8 Hz, 2H), 8.19 (d, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 1.37, 3.71, 18.56, 21.61, 49.62, 58.39, 60.78, 70.76, 118.78, 123.13, 127.89, 128.90, 130.52, 146.58, 146.64, 151.16, 177.90. mp 147.2–151.2 °C.

(*R,Z*)-2-(4-Bromophenyl)-2-cyclopropyl-N'-hydroxypropanimidamide (15). The acid salt **11-DNP** (22.06 kg, 45.8 mol, 1 equiv), toluene (191 kg), and 1 N aqueous HCl (93 kg, 91.7 mol, 2 equiv) were combined at 20 °C. The batch was agitated for 1 h and after settling the aqueous layer was removed. The toluene layer was washed with water (44 kg). Aqueous layers were pH = 1. The batch was distilled to minimal volume at 45–50 °C (80 torr) achieving a KF of 26 ppm. Additional toluene (61 kg) was added to bring the batch to 3 L toluene per 1 kg **11-DNP** (KF 310 ppm). At 22 °C N, DMF (163 g, 2.3 mol, 0.05 equiv) and thionyl chloride (7.54 kg, 59.5 mol, 1.3 equiv) were charged and the batch was heated to 47 °C and held for 1 h. *(Note: The acid chloride is very air / water sensitive, conversion was measured based on the benzyl amide product formed by addition of dry benzylamine to the reaction mixture, which was then diluted with dry ACN for analysis.)* Vacuum was applied (75 torr) to affect removal of ~50 L of distillate. Toluene (57 kg) was added and the batch was cooled to 10 °C. Ammonia gas (1.96 kg, 115 mol, 2.5 equiv) was charged sub-surface over 1.5 h maintaining an internal maximum temperature of 20 °C. After an additional 0.5 h, vacuum was applied at 20 °C for 1 h to remove residual ammonia. The batch was cooled to 0 °C and pyridine (7.24 kg, 91.6 mol, 2 equiv) was charged, followed by TFAA (15.3 kg, 73.3 mol, 1.6 equiv) over 30 min, maintaining a temperature of

10–15 °C. After an additional 30 min at 20 °C the batch was washed sequentially with 10% aqueous Na_2CO_3 (96.8 kg, 91.6 mol, 2 equiv), followed by 1 N aqueous HCl (44 kg, 44 mol, ~1 equiv) and water (44 kg). The batch was distilled to minimal volume at 45–50 °C (275 torr) and cooled to 20 °C to yield a 45 wt % solution of nitrile **5** in toluene (22.1 kg, 40.0 mmol, 91.7 LCAP). Toluene was added (16 kg) (KF <200 ppm). The solution of nitrile **5** was cooled to –15 °C and DIBAL-H (27.3 kg, 25 wt % in toluene, 48 mol, 1.2 equiv) was charged over 1.5 h at <0 °C. The batch was held at –10 °C for 0.5 h, then 4 N aqueous HCl (31.5 kg, 120 mol, 3 equiv) was charged over 1 h at 5–10 °C. The resulting slurry was warmed to 20 °C over 2 h and then held for 8–12 h under vigorous agitation. *(The slurry may thicken initially but should thin within one hour. Extended stirring time is required to break up aluminum-bound species.)* Toluene (26 kg) and 5% aqueous NaCl (10 kg) were charged at 20 °C, mixed with moderate agitation, and allowed to settle. After removal of the bottom aqueous phase, the toluene phase was washed with 5% aqueous NaCl (30 kg) and then distilled to minimal stirrable volume at 45–50 °C (50 torr). Ethanol (19.7 kg) was charged and the batch was cooled to 0 °C. 50 wt % Aqueous hydroxylamine (4 kg, 60 mol, 1.5 equiv) was added over 10 min with a temperature rise to 5 °C. The batch was warmed to 20 °C over 30 min. After addition of IPAc (61 kg) the batch was washed with 5% aqueous NaCl (30 kg x 2) and distilled to minimum volume (~12 L) at 45 °C (40 torr). Acetonitrile (30 kg) was added and the batch was again concentrated at 45 °C (40 torr) to ultimately yield a concentrated solution of oxime **14** in ACN (25.6 kg, 38.6 mmol, 40.5 wt %, 86.5 LCAP). To this solution was charged conc. HCl (1.93 kg, 20 mol, 0.5 equiv) at 10–20 °C. The batch was cooled to 5 °C and a N-chlorosuccinimide (5.23 kg, 40 mol, 1.05 equiv) solution in ACN (18 kg) was charged over 30 min at 0–10 °C. *(Due to stability concerns, the NCS solution should not be prepared more than 2 h before use.)* 28% NH_4OH (10.9 kg, 90 mol, 2.3 equiv) and water (20 kg) were charged to the reactor maintaining the batch temperature 20–25 °C *(NH_4OH addition is very exothermic at the beginning!).* The batch was agitated at 20–25 °C for 1 h. Toluene (70 kg) was charged and the batch was washed with water (20 kg), then twice with 5% aqueous NaCl (40 kg). The batch was distilled down to ~20 L at 45–50 °C (70 torr). Seeds of amidoxime **15** (80 g, >99% ee) were charged as a slurry

in toluene (290 mL), after 1 h at 50–55 °C, heptane (24 kg) was charged slowly over 1 h to the slurry maintaining a temperature of 50–55 °C, the batch was then held at this temperature for 1 h, and cooled to 20–25 °C at a constant rate over 6 h. The solid was collected by filtration, the reactor and cake were rinsed with the filtrate, and finally the collected solids were rinsed with heptane (15 kg). The solid was dried at 20 °C (40 torr) yielding amidoxime **15** as a tan colored solid (5.86 kg, 74% yield, 98 wt %, 99.4% ee, 98.9 LCAP). mp 118.7–120.8 °C. Analytical data consistent with literature.[9]

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (6). 5-Bromopyrimidin-2-amine (15 kg, 86 mol, 1 equiv), bis(pinacolato)diborane (24.2 kg, 95.3 mol, 1.1 equiv), potassium acetate (16.9 kg, 172 mol, 2.0 equiv), $Pd_2(dba)_3$ (80 g, 86 mmol, 0.1 mol %), and di-*tert*-butylphosphinoferrocene tetrafluoroborate [FcP(*t*-Bu)$_2$•HBF$_4$] (72 g, 172 mol, 0.2 mol %) were charged to a reactor which was then purged with nitrogen to O_2 <0.5%. 2-MeTHF (51.5 kg) - degassed with nitrogen – was charged and the mixture was heated to 80 °C for 3–4 h. After verification of reaction completion by HPLC (>99% consumption of 5-Bromopyrimidin-2-amine), 2-MeTHF (200 kg) was charged while adjusting the reaction temperature to 55–60 °C. The mixture was held at this temperature for 2–3 h with stirring. The slurry was filtered through a filter paper at 55–60 °C to remove inorganics, followed by a warm (~50 °C) THF (67 kg) rinse of the reactor and filter cake. After ensuring the reaction vessel was free of solids (rinse with 2-MeTHF if necessary), the filtrate was returned to the reactor and solvent removed at 55 °C (270 torr) to minimum stirrable volume (330 L distillate). Ethanol (59.3 kg) was added and the batch was distilled at 60 °C (280 torr) removing ~75 L of distillate. Additional ethanol (237 kg) was charged and the after full dissolution at 65 °C (1 h) the batch was purified by filtration through a CUNO® (R53SP) activated carbon filter cartridge. The filtrate and the ethanol (24 kg) rinse were collected in a clean reactor for the crystallization. The batch was concentrated at 55–60 °C (270 torr) removing 260 L distillate and then was cooled to 20–22 °C over 2 h, the resulting slurry was aged for 2 h, and then the solid was isolated by filtration. The reactor and cake were rinsed with ethanol (35.5 kg) and then then dried at 45 °C (30–40 torr) for >4 h yielding boronate **6** as off-white needles (14.75 kg, 80% yield, 97.8 wt %, 99.9 LCAP). mp 208.9–211.8 °C. Analytical data consistent with literature.[20]

(*R*,*Z*)-2-(4-(2-Aminopyrimidin-5-yl)phenyl)-2-cyclopropyl-N'-hydroxypropanimidamide (8). Amidoxime **15** (11.32 kg, 99.2 wt %, 39.7 mol, 1 equiv), boronate **6** (11.38 kg, 51.5 mol, 1.3 equiv), $Pd(O_2CCF_3)_2$ (26 g, 78 mmol, 0.20 mol %), and di-*t*-butylphosphinoferrocene tetrafluoroborate [FcP(*t*-Bu)$_2$•HBF_4] (37 g, 88 mmol, 0.22 mol %) were charged to the reactor. The reactor was inerted with three vacuum-Ar purge cycles. A degassed solution of K_3PO_4 (16.9 kg, 79.6 mol, 2 equiv) in water (45 kg) and degassed IPA (44 kg) were charged and the resulting suspension was heated to 80–82 ^oC over 45 min and held for 3–6 h. While maintaining the reaction mixture at 80–82 ^oC, *N*-acetyl cysteine (1.62 kg, 9.9 mol, 0.25 equiv) in water (67.5 kg) was charged over 1 h. The resulting mixture was agitated for 3–8 h at 80–82 ^oC, then allowed to cool down linearly to 20 ^oC over 4 h. The resulting crystalline product was collected by filtration and the cake rinsed with water (34 kg) and IPAc (29 kg) yielding amidoxime **8** as an off-white, crystalline solid (11.32 kg, 94.8% yield, 99.2 wt %, 99.8 LCAP). mp 197.3–200.8 °C. Analytical data consistent with literature.[9]

(*R*)-5-(4-(1-(5-(1H-Pyrazol-4-yl)-1,2,4-oxadiazol-3-yl)-1-cyclopropylethyl)phenyl)pyrimidin-2-amine (18). A solution of pyrazole acid **16** (4.5 kg, 40 mol, 1.3 equiv) in DMF (21.6 kg) was charged over 10 min to a mixture of CDI (6.16 kg, 36.8 mol, 1.2 equiv) and THF (20.3 kg) at 20–22 ^oC. The batch was heated to 50–55 ^oC and held for 0.5 h. A solution of amidoxime **8** (9.2 kg, 99.2 wt %, 30.7 mol, 1 equiv) in THF (57 kg) was added. The batch was heated and THF removed by distillation until the internal temperature stabilized to 105 °C. The batch was maintained at this temperature for 12–20 h and then cooled to 20–22 ^oC. EtOAc (115 kg) and water (64 kg) were charged to the mixture, the layers were separated and the top organic layer was washed with water (64 kg). The organic layer was heated to 45 °C and filtered through a CUNO® (R53SP) activated carbon filter cartridge. The filter was rinsed with EtOAc (74 kg) and the combine filtrates were concentrated at 57 °C (350 torr) removing 330 L of distillate. At 55–60 °C the batch was seeded with **18** (205 g) in IPAc (2 kg), held for 30 min. and IPAc (89 kg) was charged at a constant rate over 1 h maintaining the batch temperature of 55-60 °C. The slurry was concentrated at 57 °C (250 torr) removing 100 L of distillate. Heptane (28 kg) was charged at a constant rate over 1 h at 57 °C. The slurry cooled to 20–22 °C over 4-6 h and held for 1 h. The

solid was collected by filtration, and the cake was rinsed with IPAc (36 kg) then heptane (42 kg). The solid was dried at 60 °C (25 torr) for 12 h, yielding oxadiazole **18** as an off-white solid (9.42 kg, 86% yield, 99.2 wt %, 99.7% ee, 99.8 LCAP). mp 186.4–190.1 °C. Analytical data consistent with literature.[9]

(*R*)-2-(4-(3-(1-(4-(2-Aminopyrimidin-5-yl)phenyl)-1-cyclopropylethyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-N,N-dimethylacetamide (1). **O**xadiazole **18** (11.02 kg, 99.9 wt %, 29.5 mol, 1 equiv), DMF (31.1 kg), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (6.28 kg, 41.25 mol, 1.4 equiv), and 2-chloro-N,N-dimethylacetamide (**19**) (4.65 kg, 38.25 mol, 1.3 equiv). Upon complete addition of **11**, the temperature rose to 37 °C and additional heating was applied to bring the batch to 48–50 °C, where it was held for ≥ 30 min. IPAc (38.4 kg) was charged while maintaining a batch temperature of 45–55 °C. The solution was then seeded with **1** (110 g, 1 wt %) suspended in water (550 mL) at 50–55 °C, and held at this temperature for 30 min. Water (33 kg) was charged over 1 h, then stirred for 30 min at 50–55 °C. A second charge of water (33 kg) was made at 45–55 °C over 1 h, followed by stirring for 1 h. Finally a third charge of water (33 kg) was made at 45–55 °C over 1 h, followed by stirring for 2 h. The batch was cooled to 20 °C over 4 h, then held at 20 °C for 4 h. The crystalline product was collected by filtration, the cake rinsed iteratively with water (33 kg), IPAc (29 kg), and finally heptane (23 kg) and the solid dried at 55 °C (35 torr) for 24 h yielding **1** as an off-white, crystalline solid (13.05 kg, 95.6% yield, 98.6 wt %, 99.7% ee, 99.6 LCAP). Pd content was 160 ppm. Crude **1** was recrystallized from ethanol/water to obtain the desired final form in 95% yield. mp 193.6–196.2 °C. Analytical data consistent with literature.[9]

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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