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# The Evolution of the Synthesis of AMPK Activators for the Treatment of Diabetic Nephropathy: from Three Preclinical Candidates to the Investigational New Drug PF-06409577

*Aaron C. Smith,*[†] Daniel W. Kung,*[†] Andre Shavnya,[†] Thomas A. Brandt,[†] Philip D. Dent,[†] Nathan E. Genung,[†] Shawn Cabral,[†] Jane Panteleev,[†] Michael Herr,[†] Ka Ning Yip,[#] Gary E. Aspnes,[#] Edward L. Conn,[†] Matthew S. Dowling,[†] David J. Edmonds,[#] Ian D. Edmonds,[§] Dilinie P. Fernando,[†] Paul M. Herrinton,[○] Nandell F. Keene,[†] Sophie Y. Lavergne,[†] Qifang Li,[†] Jana Polivkova,[†] Colin R. Rose,[†] Benjamin A. Thuma,[†] Michael G. Vetelino,[†] Guoqiang Wang,[†] John D. Weaver, III,[†] Daniel W. Widlicka,[†] Kristin E. Price Wiglesworth,[†] Jun Xiao,[†] Todd Zahn,[○] Yingxin Zhang[†]*

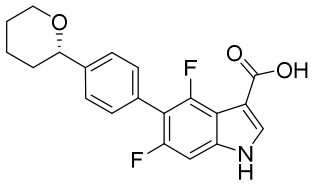
[†]Pfizer Worldwide Research & Development; Eastern Point Road; Groton, Connecticut 06340; United States.

[#]Pfizer Worldwide Research & Development; 610 Main Street; Cambridge, Massachusetts 02139; United States.

[§]Bridge Organics; 311 W. Washington St.; Vicksburg, Michigan 49097; United States

[○]BoroPharm, Inc.; 39555 Orchard Hill Place, Suite 600; Novi, Michigan 48375; United States

**Table of Contents Graphic**

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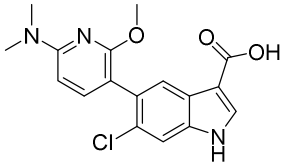


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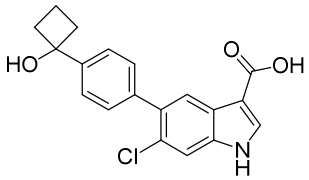



**3**: PF-06409577

## ABSTRACT

Indole acids **1**, **2**, and **3** are potent 5'-adenosine-monophosphate-activated protein kinase (AMPK) activators for the potential treatment of diabetic nephropathy. Compounds **1**–**3** were scaled to supply material for pre-clinical studies, and indole **3** was selected for advancement to first-in-human clinical trials and was scaled to kilogram quantities. The progression of the synthesis strategy for these AMPK activators is described, as routes were selected for efficient SAR generation and then were improved for larger scales. The developed sequences employed practical isolations of intermediates and APIs, reproducible cross-coupling, hydrolysis, and other transformations, and enhanced safety and purity profiles leading to production of 40–50 g of **1** and **2**, and 2.4 kg of **3**. Multiple polymorphs of **3** were observed and conditions for the reproducible formation of crystalline material suitable for clinical development were identified.


Keywords: Suzuki, Negishi, Borylation, Acylation, AMPK, Pinnick

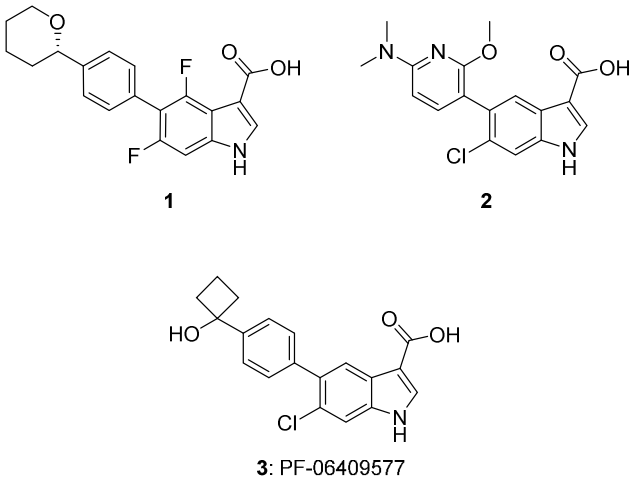
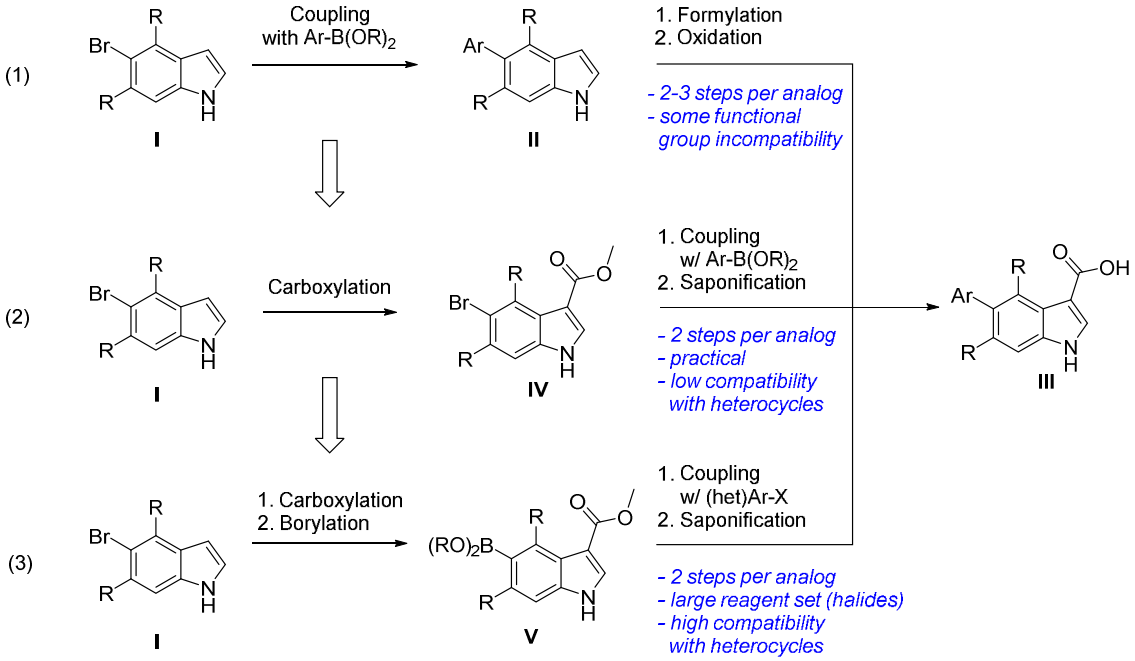



**Figure 1.** Potent Activators of the AMPK α1β1γ1 Isoform

## INTRODUCTION

5'-Adenosine monophosphate-activated protein kinase (AMPK) is a heterotrimeric serine-threonine kinase (consisting of α-, β-, and γ-subunits), which plays a key role in energy homeostasis. Indole acids **1**, **2**, and **3** (Figure 1) were recently identified as potent activators of β1-containing isoforms of AMPK and were evaluated in safety and efficacy studies.[1,2,3] In addition, compound **3** was advanced to first-in-human clinical trials as a potential treatment for diabetic nephropathy. The development of improved synthetic routes for producing multi-gram quantities of **1** and **2**, and kilogram quantities of **3**, is described herein.

**Scheme 1.** General Synthetic Strategies Employed to Study SAR of Lead Series



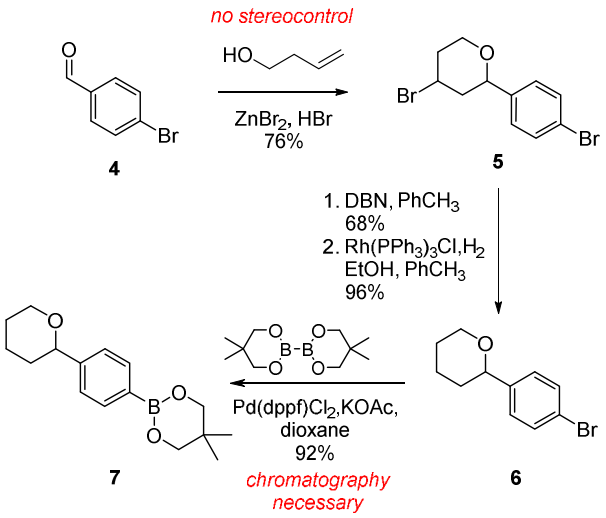

During the discovery phase of the AMPK program, a lead series consisting of a 5-aryl-indole-3-carboxylate was found to activate β1-containing isoforms.[1] Several different synthetic strategies (Scheme 1) were identified to quickly explore SAR of compounds in the lead series. Initial syntheses generally relied upon installation of the 5-aryl moiety through a cross-coupling reaction to a 5-bromo-indole, followed by introduction of the 3-carboxylic acid via formylation and oxidation of the intermediate aldehyde [Eq. (1)]. The order of the reaction steps was also reversed by introduction of the aldehyde first followed by cross-coupling with an aryl boronate. Subsequent routes enabled late-stage diversification of the aryl group through installation of an ester rather than an aldehyde to simplify chemistry downstream of the coupling [Eq. (2)]. A third variation of this sequence was also employed where the reactivity of the Suzuki coupling partners (halide, boronate) was inverted by employing an indole boronate [Eq. (3)], thereby expanding the available reagent set to include aryl and heteroaryl halide coupling partners (rather than the less readily available heteroaryl boronic acids or boronates). These general disconnections and synthetic strategies served as the basis to develop improved syntheses of

indoles **1**, **2**, and **3** on larger scales while also managing reaction concentrations, impurity profiles, reagent costs, and isolation and crystallization of solid intermediates and final products.

## RESULTS AND DISCUSSION

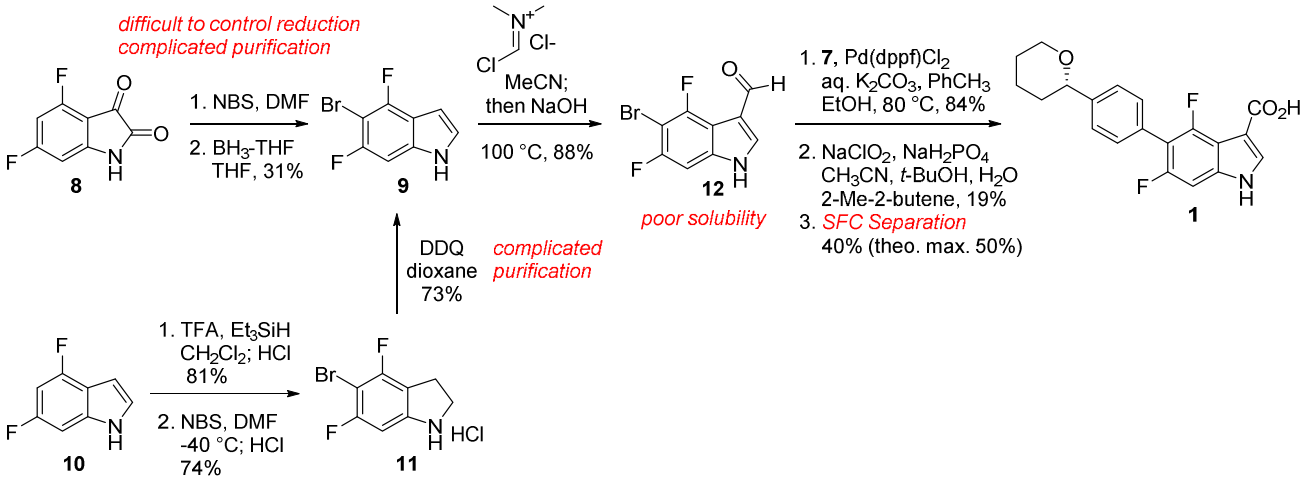
### Discovery Route to Indole 1

**Scheme 2.** Synthesis of THP-Aryl-Boronate **7**




The discovery synthesis of **1** relied upon Suzuki coupling between boronate ester **7** and indole aldehyde **12**. The initial synthesis of boronate **7** started with a Prins cyclization between *p*-bromobenzaldehyde **4** and 3-buten-1-ol to form bromotetrahydropyran **5** (Scheme 2).[4] Elimination to afford the olefin and subsequent hydrogenation provided aryl bromide **6** which was then converted to boronate ester **7**. Although successful, the isolation of **7** was complicated by the presence of excess potassium acetate and chromatography was required to achieve >95% purity.

**Scheme 3.** Discovery Synthesis of **1**

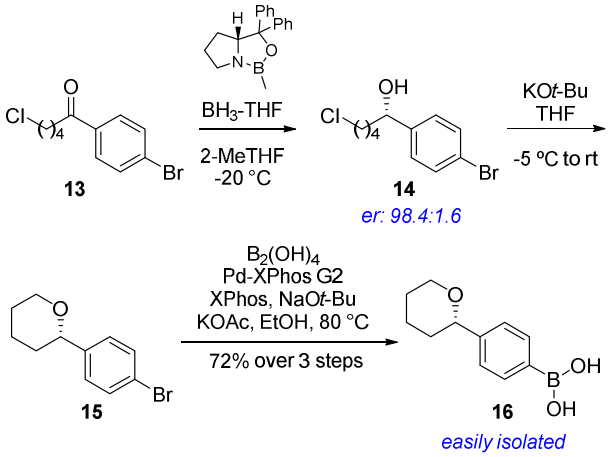



The difluoroindole was initially synthesized from isatin **8** (Scheme 3). A regioselective bromination followed by reduction with borane[5] afforded the indole in low yield (31% over two steps). Difficulty in controlling the reduction (both over- and under-reduced byproducts were identified) and complications in chromatographic separations contributed to the low yield. Higher yields and simplified purification of 5-bromo-4,6-difluoroindole **9** were achieved in an alternative three-step sequence consisting of reduction of commercially available 4,6-difluoroindole **10** to the indoline, regioselective bromination and chromatography-free isolation of bromoindoline **11** as its HCl salt, and oxidation of the indoline to indole with DDQ (44% over three steps). Formylation under Vilsmeier-Haack conditions led to 3-aldehyde **12**. Suzuki coupling between **12** and boronate ester **7** followed by Pinnick oxidation provided the racemic carboxylic acid **1**. Although the coupling was successful, low solubilities of the coupling product led to high dilutions (75 volumes), incomplete conversion of starting material, and difficulties in isolation as HPLC purification was employed on analogue scale. SFC purification on chiral phase was then used to isolate the eutomer, whose absolute configuration was determined by single-crystal X-ray analysis.[6]

Although this route was successful for milligram scale, several problems needed to be addressed to increase practicality for larger scale synthesis: the complex isolation of boronate ester **7** and indole **9**, the low solubility of aldehyde intermediates that led to inconsistent results and complex isolations at the Suzuki coupling and Pinnick oxidation steps, and the use of SFC on chiral phase to isolate the final product.

**Improved Synthesis of 1**

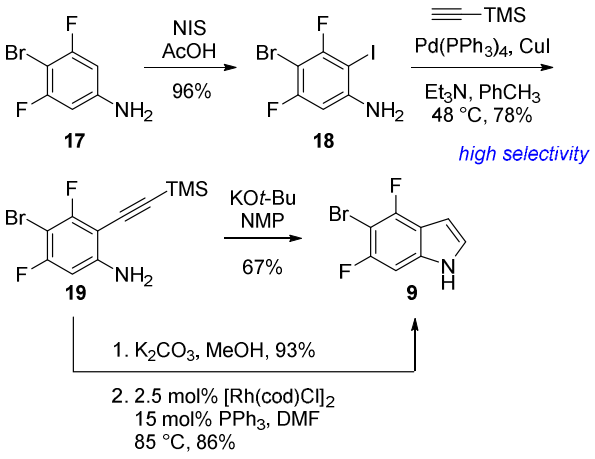
**Scheme 4.** Scalable Synthesis of Boronic Acid **16**




To eliminate the need for chromatographic separation of enantiomers, an enantioselective approach to the tetrahydropyran ring formation was envisioned. Starting from commercially available ketone **13**, several asymmetric reduction methods gave encouraging initial hits, including Noyori hydrogenation (RuCl(p-cymene)[(*S,S*)-Ts-DPEN], 93.5:6.5 er of **15**)[7] and ketoreductase-catalyzed biotransformation (Codex® KRED-P1 B12, 89% conversion, 98.0:2.0 er of **14**).[8] However, CBS reduction[9] (Scheme 4) was selected for further optimization due to the balance of high selectivity, yield, and control over the process. On a 50-g scale, alcohol **14** was obtained as a solid product after aqueous workup (95% yield, 98.4:1.6 er), with temperature control (–20 °C) being a critical variable to ensure high enantioselectivity. Subsequent

cyclization generated tetrahydropyran **15** without the need for chromatography. Synthesis of the corresponding boronic acid **16** (rather than the boronate ester) was proposed to facilitate isolation without chromatography. After utilizing tetrahydroxydiboron[10] in a palladium-catalyzed cross-coupling, the resultant boronic acid was extracted into aqueous basic media, allowing many of the organic impurities to be purged with an MTBE wash. Neutralization and crystallization then produced boronic acid **16** with an isolated yield of 72% (26 g) over the first three steps of the synthesis. Detectable amounts of boroxine were observed by $^{1}$H NMR, but this by-product was not detrimental to downstream chemistry.

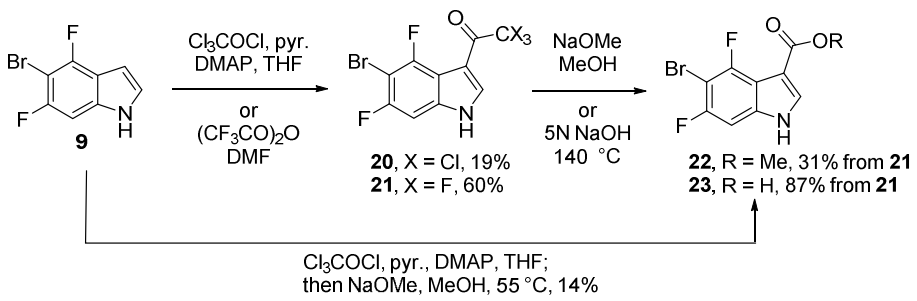
**Scheme 5.** Improved Synthesis of 5-bromo-4,6-difluoro-1*H*-indole **9**




An alternative ring-building strategy was employed to circumvent the challenging redox steps in the synthesis of the difluoroindole coupling partner. Iodination of the symmetrical 4-bromo-3,5-difluoroaniline **17** afforded **18** in high yield by precipitation after the addition of aqueous sodium thiosulfate solution to the reaction mixture (Scheme 5). Sonogashira coupling with TMS-acetylene (charged in two portions to ensure complete conversion of the iodide) proceeded smoothly with 1.6 mol% each of copper and palladium catalysts. Solid **19** was isolated after filtration through Celite and silica, followed by trituration with hexane. Initially, the cyclization

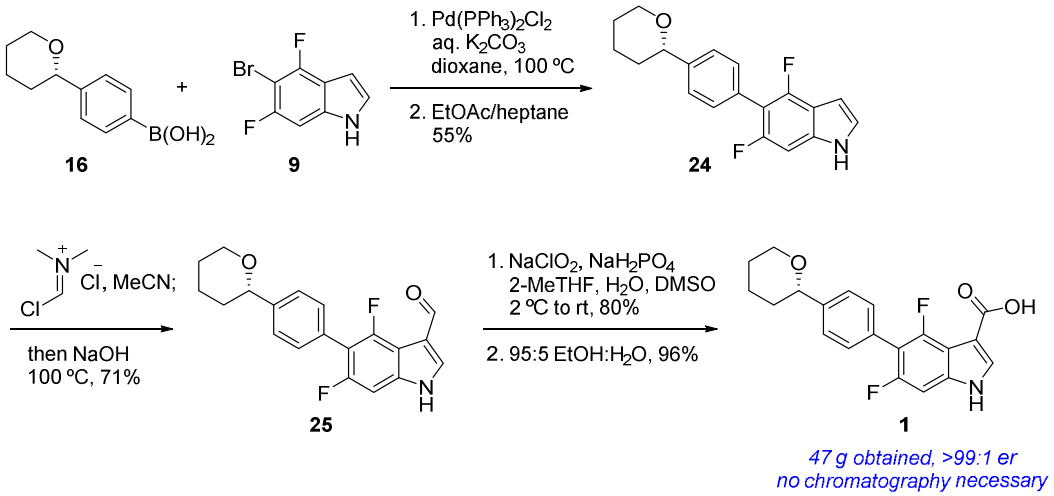
to the indole was effected by the stepwise cleavage of the silyl group followed by rhodium-catalyzed cycloisomerization.[11] Subsequently, the cyclization conditions were simplified by employing potassium *t*-butoxide in NMP to effect both desilylation and cyclization.[12] When this conversion was carried out by addition of **19** in one portion to potassium *t*-butoxide in NMP, the crude indole **9** was obtained in ~85% purity, but this addition was accompanied by a rapid exotherm, from 33 to 87 °C on 100-g scale. Attempts to moderate this exotherm by slow addition of compound **19** resulted in greater formation of impurities (<50% purity of crude product with addition at 20–25 °C over 110 min, or at 58–65 °C over 30 min). With addition in one portion the exotherm was complete within one min, such that the conditions were close to adiabatic and thus were expected to be relatively insensitive to scale. Indeed, on conversion of 1.44 kg of compound **19**, the exotherm (33 to 89 °C) was very close to that observed on the 100-g run. Although this procedure enabled formation of >0.75 kg of pure indole **9**, additional studies are needed to develop a more controlled process before further scale-up and the rhodium-catalyzed method could be a potential alternative. For project expediency, this material was isolated by silica gel chromatography followed by trituration; full optimization of conditions to directly precipitate the product was not completed, although the purified compound **9** was crystalline (m.p. 91–92 °C).

**Scheme 6.** Acylations of Difluoroindole **9**




To mitigate the challenges associated with the low solubility of aldehyde **12**, two complementary strategies were examined. The first approach replaced the aldehyde with an alternative precursor to the carboxylate group, such as a ketone or ester. For many indoles, the two-step esterification at C3 via acylation with trichloroacetyl chloride and subsequent methanolysis[13] was readily achieved; however, for indole **20** the yield was <20% (Scheme 6) due to poor conversion, which we attributed to the electron-withdrawing effect of the two fluoro substituents. Use of trifluoroacetic anhydride as a more reactive acylating agent provided the trifluoromethyl ketone **21** in 60% yield. Unfortunately, the trifluoromethyl ketone proved to be less reactive to methanolysis/hydrolysis than similar trichloromethyl ketones reported in the literature. Methanolysis proceeded in low yield (31%), although hydrolysis at high temperature (140 °C) with sodium hydroxide produced the carboxylic acid in 87% yield. Use of the trifluoromethyl ketone **21** or the acid **23** in the subsequent Suzuki coupling led to low reaction conversion and significant decarboxylation, respectively, and thus this approach was discontinued.

**Scheme 7.** Endgame for Improved Synthesis of **1**

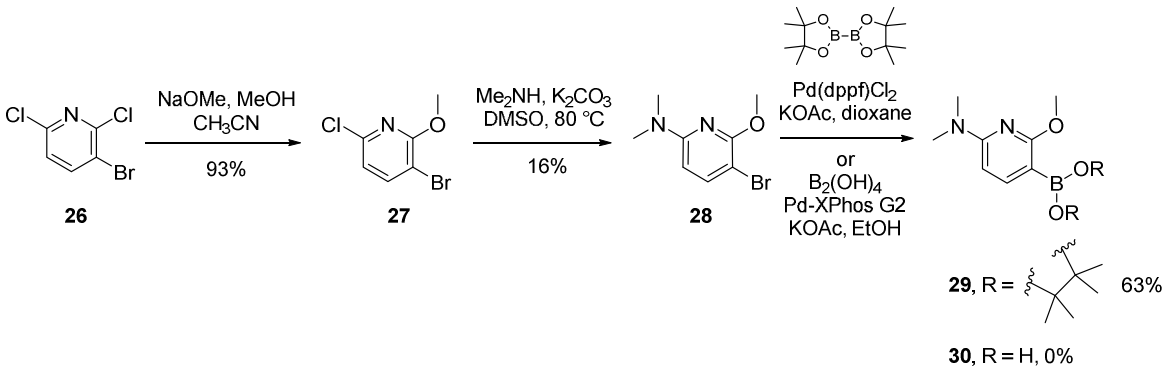



The alternative strategy for addressing the complications caused by the low solubility of aldehyde **12** consisted of re-ordering the synthetic steps in such a way that Suzuki coupling preceded introduction of the aldehyde group (Scheme 7). The Suzuki coupling between boronic acid **16** and bromoindole **9** proceeded under standard conditions and recrystallization of **24** from ethyl acetate–heptane after aqueous workup was employed to provide 55% yield, but a consistent purity profile. One-pot formylation by reaction with the Vilsmeier salt and subsequent hydrolysis with aqueous sodium hydroxide afforded aldehyde **25**, which crystallized directly from the reaction mixture in 71% yield. The solubility of intermediates used in this sequence was appropriate to facilitate material handling and to increase yields on this scale, and all intermediates were isolated by precipitation/crystallization. To increase safety in the Pinnick oxidation, DMSO[14] was employed as a hypochlorite scavenger that was more easily controlled than the volatile 2-methyl-2-butene. Additionally, the solubility of the reaction components was improved by switching to 2-Me-THF/DMSO from acetonitrile (Scheme 3) which led to full conversion of the starting material to greatly facilitate isolation of the final product. After aqueous workup, the product acid **1** was isolated in 80% yield after precipitation from ethyl acetate/2-Me-THF. In a separate step, slurrying in ethanol:water (95:5) led to isolation of

crystalline **1** (47 g, 96% yield, >99:1 er) in 99.5% purity suitable for exploratory toxicology studies.

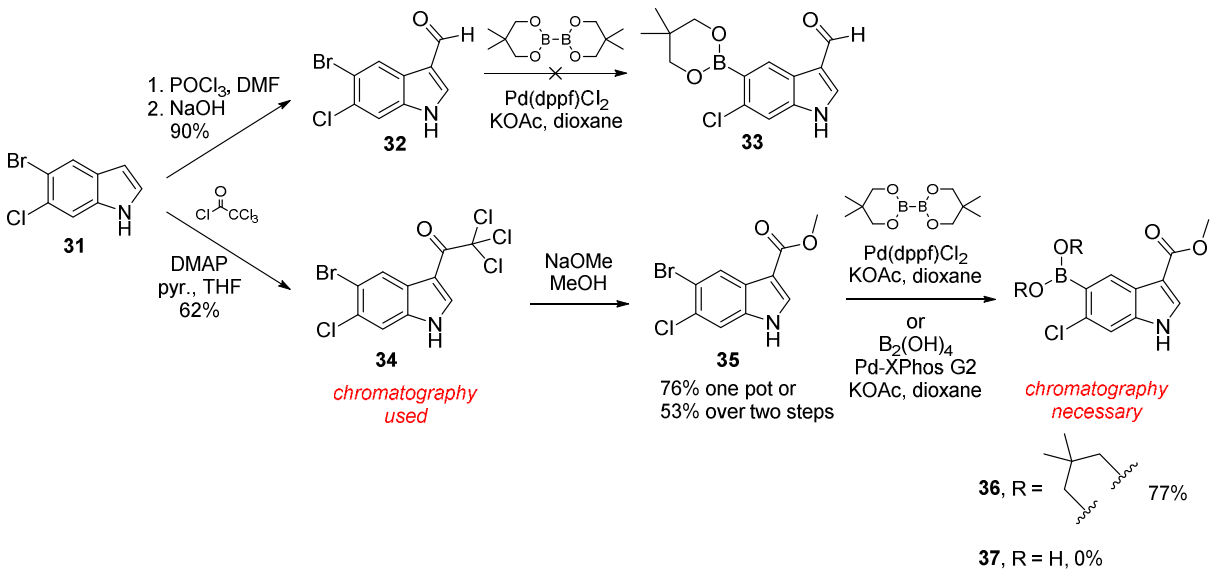
**Discovery Synthesis of 2**

**Scheme 8.** Early Synthesis of Pyridyl Bromide **28** and Boronate **29**




The synthesis of the pyridylindole **2** was initially expected to utilize a similar cross-coupling disconnection as phenylindole **1**. The pyridyl coupling partner was synthesized from dichloropyridine **26** by two successive $S_NAr$ displacements with sodium methoxide and dimethylamine to afford bromopyridine **28** (Scheme 8). The regioselectivity of the methoxide addition was ~5:1 in favor of the desired **27**, leading to low isolated yields of **28** over two steps, primarily due to the difficulty in chromatographic separation of the closely eluting regioisomers. The bromide was then converted to pinacol boronate **29**. However, protodeboronation observed even under mild conditions made isolation problematic and caused concerns about this intermediate's stability. Attempts to synthesize boronic acid **30** were also unsuccessful.

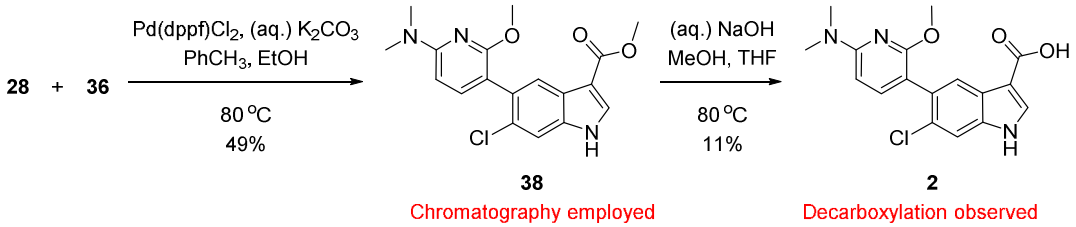
**Scheme 9.** Synthesis of Indole Boronate




Given the complexity of isolating the pyridyl boronate, work began on the synthesis of a 5-borylindole and bromopyridine **28** to invert the roles in the Suzuki coupling. This route modification also supported the discovery project needs for incorporation of varied (hetero)aryl substituents at C5 of the indole by employing the widely available (hetero)aryl halide reagents. Formylation of commercially-available 5-bromo-6-chloroindole **31** under Vilsmeier conditions provided aldehyde **32** (Scheme 9). The corresponding borylated indole **33**, however, could not be successfully isolated, with the product of debromination/deboronation obtained as the major product. However, revisiting the acylation approaches previously examined during the synthesis of difluoroindole **1** showed that the relatively greater nucleophilicity of the chloroindole core allowed the successful use of an alternative route. Acylation of indole **31** with trichloroacetyl chloride provided trichloromethyl ketone **34** in good yield as compared to the less electron-rich difluoroindole **9** (62% vs. 14%, respectively; see also Scheme 6). The trichloromethyl ketone was treated with sodium methoxide in methanol to produce methyl ester **35**. Borylation of this indole was successful and a good yield (77%) of **36** was obtained; however, chromatography was necessary to achieve >95% purity. Attempts to synthesize boronic acid **37** afforded no desired

product due to rapid protodeboronation or dehalogenation; further efforts to access the boronate or to telescope the coupling reaction were not pursued.

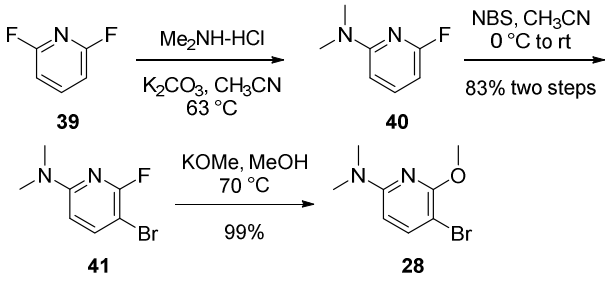
**Scheme 10.** Small Scale Synthesis of **2**




For the initial small-scale synthesis of **2** (Scheme 10), Suzuki coupling between bromopyridine **28** and indoleboronate **36** afforded the ester **38** as a solid product (49% after chromatography). Saponification afforded the desired indole acid, albeit in low isolated yield due to decarboxylation observed under these conditions. While this route successfully delivered milligram quantities of **2** for in vitro characterization, critical disadvantages limited its application on a larger scale. The main problems to be addressed included poor regioselectivity in the preparation and isolation of bromopyridine **28**, isolation and/or stability of 5-borylindole **36**, and decarboxylation of **2**, which in combination resulted in low yields.

**Improved Synthesis of 2 to Support Larger Scale Deliveries**

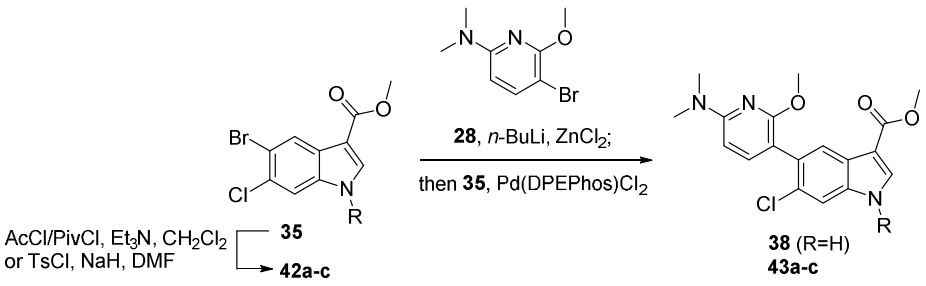
**Scheme 11.** Improved Synthesis of Bromide **28**




To address the concerns with the synthesis of bromopyridine **28** on larger scale, the route was redesigned (Scheme 11). Starting from the less expensive symmetrical 2,6-difluoropyridine **39**, $S_NAr$ reaction with dimethylamine hydrochloride in the presence of $K_2CO_3$ provided pyridine **40**, which was used directly in the next step. Bromination with *N*-bromosuccinimide in acetonitrile was regioselective (>95%) and high-yielding, affording crystalline **41** in 83% yield over two steps after aqueous workup and trituration. The second $S_NAr$ reaction with potassium methoxide in methanol at reflux cleanly displaced the fluoride to provide 1.4 kg of the desired **28** as a crystalline solid in 99% yield after aqueous workup.

Since the initial Suzuki coupling was promising, alternative synthetic conditions were examined to improve formation of boronate ester **36**. Unfortunately, screening and optimization of conditions to improve the synthesis of boronate ester **36** or boronic acid **37** did not lead to the identification of satisfactory conditions, as poor reactivity and debromination/deboronation were recurrent problems.

**Table 1.** Protected Substrates for Negishi Coupling

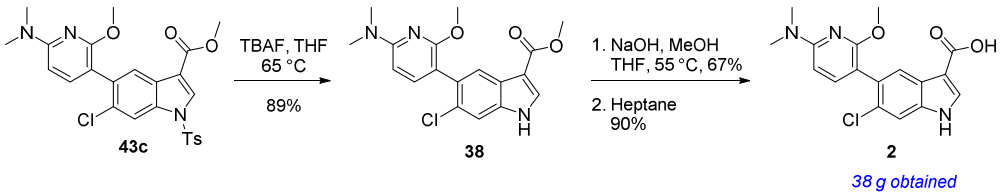



| Bromide | R | Yield of **38/43** |
|---|---|---|
| **35** | H | 0% yield |
| **42a** | Ac | only **35** observed, not isolated |
| **42b** | Piv | mixture of **43b** and **38**, 39% after deprotection/isolation |
| **42c** | Ts | 91% yield of **43c** |

Negishi cross-coupling was considered an attractive alternative because of the stability of the halide substrates and the ability to form the organometallic intermediate in situ. The organozinc was formed from bromopyridine **28** by metal-halogen exchange with *n*-butyllithium followed by treatment with $ZnCl_2$, and then subjected to Pd coupling with indole bromide **35** (Table 1). Although it appeared that the organozinc reagent had successfully formed (observed debromination of the pyridine), no desired product was obtained, which led to the hypothesis that the acidic *NH* of the indole interfered with the cross-coupling. *N*-Protective groups were then employed to test this hypothesis (Table 1). The *N*-acetyl protected **42a** led to formation of *N*-deacylated, uncoupled indole **35** when treated under the coupling conditions. The less labile *N*-pivaloyl protected **42b** provided the desired cross-coupling as a mixture of *N*-pivaloyl protected **43b** and deprotected **38**. After complete deprotection of the mixture in a separate step (1 M NaOH:MeOH, 1:1, 30 min, rt), 39% of **38** was obtained. Finally, use of the more robust *N*-tosyl group led to the most effective coupling without undesirable *N*-deprotection to afford *N*-tosyl indole **43c**. After aqueous workup, the cross-coupling product was purified by crystallization

(MeOH:EtOAc, 20:1) followed by trituration with MeOH (91% yield) to enhance purity to 97.2%.

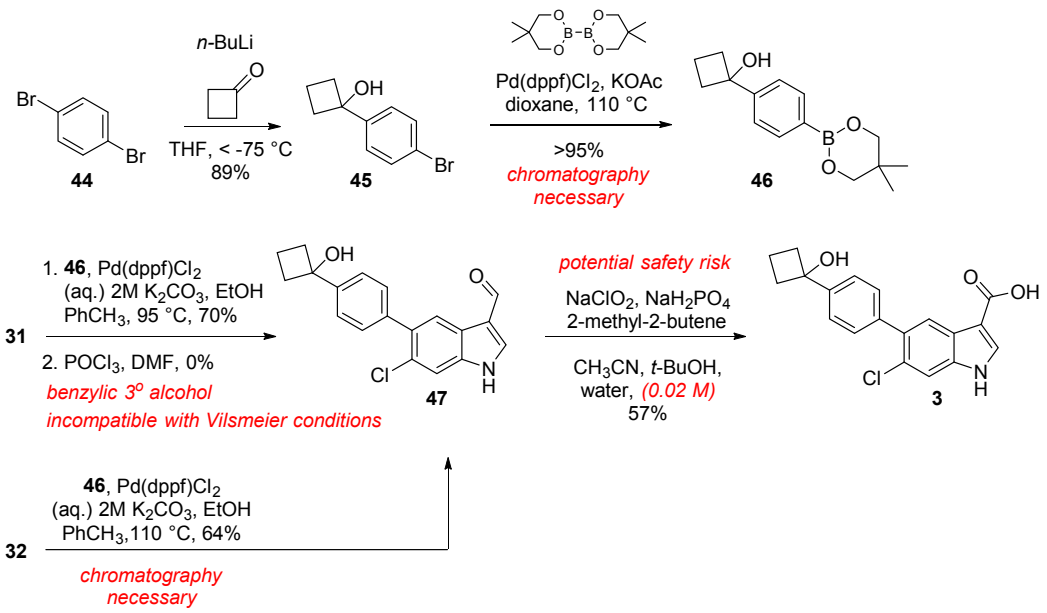
**Scheme 12.** Improved Synthesis of **2**




Removal of both the *N*-tosyl and the ester protecting groups in one pot was attempted under various aqueous NaOH conditions, but incomplete deprotection of the sulfonamide or *N*-methylation of the indole (with MeOH as cosolvent) was observed. Instead, a controlled two-step process was successful, employing tetrabutylammonium fluoride (TBAF) in THF at reflux to cleave the *N*-tosyl group to provide the pyridylindole ester **38** (Scheme 12) in 89% yield after workup and trituration. Subsequent hydrolysis of the ester afforded 38 g of the carboxylic acid which was isolated after workup and recrystallization from heptane. It is important to note that decarboxylation was observed at higher temperatures (3–4% decarboxylation at 60 °C, 20–24 h; >15% at 70 °C, 15 h) or with long reaction times (4% at 50 °C, 110 h); however, decarboxylation by-product formation was reduced (2%) by maintaining the temperature between 50–55 °C and employing a moderate reaction time (36–48 h).

**Discovery Synthesis of 3**

**Scheme 13.** Discovery Route to **3**

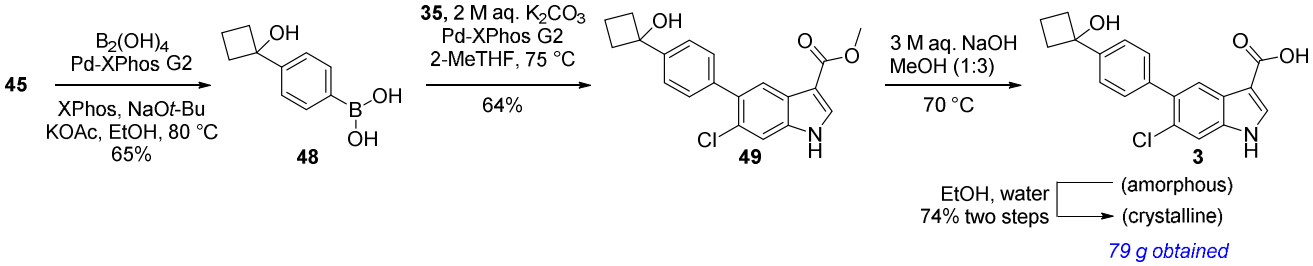



The first synthesis of **3** began with the general strategy utilized for **1** and consisted of Suzuki, formylation, and oxidation steps. Boronate **46** was synthesized starting from 1,4-dibromobenzene **44** through metal-halogen exchange and quenching with cyclobutanone to provide mono-bromide **45**, followed by its conversion to the neopentylglycol boronate **46** in good yields (Scheme 13). Suzuki coupling between boronate **46** and indole **31** installed the 5-aryl group successfully. However, formylation in the presence of the tertiary benzylic alcohol proved problematic and decomposition was observed, presumably due to facile formation of the tertiary benzylic cation. This problem was not mitigated by protecting the hydroxyl group as various ethers. The steps were reordered and aldehyde **32** was employed directly in the Suzuki coupling to provide the desired indole **47** in 64% yield. Pinnick oxidation then provided the desired carboxylic acid analog **3**.

Although this route was successful for delivering milligram quantities of **3**, its use was precluded for accessing larger amounts of material due to issues similar to the other routes, as the isolation of boronate **46** was not feasible without chromatography and the Suzuki coupling and Pinnick oxidation were complicated by the low solubility of aldehydes **32** and **47**.

## Improved Synthesis of 3 for Hundred-Gram Scale

**Scheme 14.** Improved Synthesis of **3**



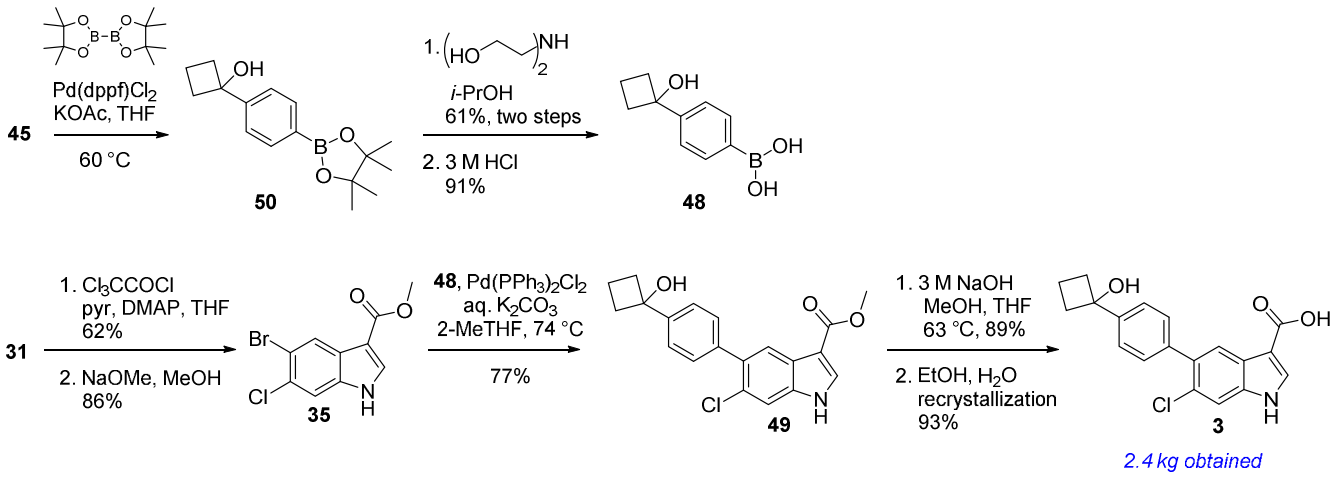

In a strategy similar to the one used for **1**, the boronic acid was targeted as the practical coupling intermediate (Scheme 14) based on the hypothesis that it could be isolated in pure form without chromatography unlike the boronate ester **46**. The borylation of bromide **45** with tetrahydroxydiboron proceeded smoothly on a hundred-gram scale, allowing for isolation of boronic acid **48** through extraction into a basic aqueous phase followed by acidification and crystallization in 65% yield.

The strategy of introducing the aldehyde after Suzuki coupling that was employed for aldehyde **25** (see Scheme 7) was impractical for aldehyde **47**, due to the sensitivity of the tertiary benzylic alcohol to the acidic formylation conditions. Therefore, an alternative sequence of bond constructions was employed. The Suzuki reaction between boronic acid **48** and bromoindole ester **35** proceeded smoothly to provide the desired product in 64% yield. Isolation and purification was achieved through recrystallization from ethyl acetate:heptane (1:1.25) and trituration from methanol and toluene to provide ester **49**. To complete the synthesis, sodium hydroxide and methanol were used to effect saponification of the methyl ester, although this hydrolysis reaction was somewhat challenging. At lower temperature (50 °C, 15 h) incomplete conversion (62%) of the electron rich indole-ester was observed, while at 70 °C or above, significant decarboxylation of the resultant carboxylic acid occurred. Ultimately, for simplicity

of purification, we opted to heat this reaction at 70 °C for 18 h to favor complete conversion at the expense of 17% observed decarboxylation. Indole **3** was isolated by first extracting into basic aqueous media, then washing with MTBE to remove the non-acidic impurities. Neutralization and crystallization from ethanol/water provided the desired product in 74% for the two steps. This method was used to synthesize 79 g of **3** in 99.6% purity, but further process refinements were desirable to provide material suitable for clinical studies.

**Improved Synthesis of 3 for Kilogram Scale**

**Scheme 15.** Synthesis of **3** on Kilogram Scale



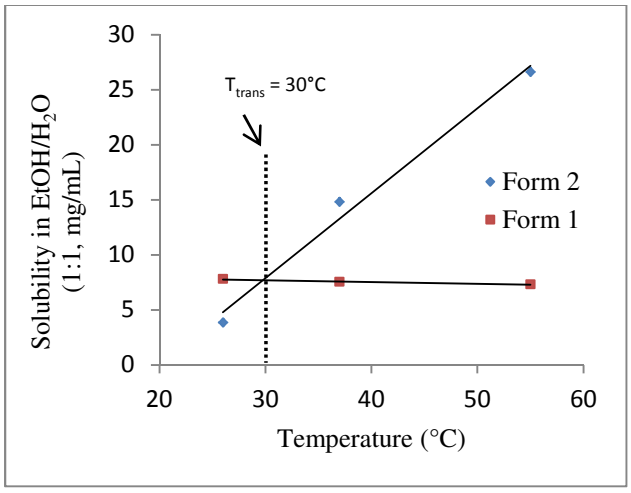

Although the boronic acid **48** offered improved isolation as compared to the boronate ester, the high cost and limited availability of the catalyst (Pd-XPhos G2 precatalyst), as well as concerns about impurities derived from mutagenic tetrahydroxydiboron,[15] made alternative solutions desirable. The synthesis of **48** was modified to a sequential formation of pinacolboronate ester **50** followed by cleavage to the boronic acid (Scheme 15). Borylation of bromide **45** with bis(pinacolato)diboron was achieved with the readily available catalyst Pd(dppf)$Cl_2$. After minimal purification of the boronate ester (simple silica gel plug filtration and crystallization), treatment with diethanolamine released the pinacol to form the diethanolamine-boronate adduct[16]

which was isolated by precipitation from isopropanol-hexane. Hydrolysis with hydrochloric acid and crystallization from the reaction mixture afforded the boronic acid **48** in 55% yield over three steps on >5 kg scale.

To render the synthesis of indole ester **35** more reproducible, a two-step rather than the telescoped sequence was employed (compare to Scheme 9). The intermediate trichloromethyl ketone was isolated in 62% yield via crystallization, and subsequent methanolysis afforded the ester in 86% yield. For the Suzuki coupling of boronic acid **48** and bromide **35**, process optimization focused on the efficiency of the reaction conversion, the Suzuki product isolation, and removal of residual palladium and remaining boronic acid **48** (identified as a weak mutagen).[17] A small reaction screen studying the catalyst, solvent, base, and reaction time identified many suitable catalysts; $Pd(PPh_3)_2Cl_2$ was chosen due to its low cost. The reactants were also significantly more soluble in 2-methyltetrahydrofuran (2-MeTHF), enabling increased reaction concentration. The screen revealed that strong bases such as sodium hydroxide led to increased impurity formation, while potassium carbonate provided complete conversion with no evidence of degradation. In all cases, an excess of boronic acid **48** was required to ensure complete consumption of bromoindole **35**. These improved coupling conditions enabled a decreased reaction time (5 h) on kilogram scale. After aqueous workup, palladium was visually observed both before and after filtration through diatomaceous earth; therefore an additional process was employed to reduce Pd content. After treatment with a silica-supported thiol to scavenge residual Pd, the Suzuki product was isolated in 77% yield by crystallization from 2-MeTHF and acetonitrile. Boronic acid and Pd residues were quantitated at acceptable levels (<30 and 45 ppm, respectively). Conditions for ester saponification were modified as follows: 5 equivalents of aqueous NaOH in 1:1 methanol:THF at reflux for 13–14 h. Use of this mixed

solvent system afforded a balance of minimizing the decarboxylation byproduct (4%) and unreacted ester (2%) impurities. Under the strongly basic conditions, residual Pd from the prior step precipitated as Pd black. An organic wash (MTBE) removed the decarboxylation byproduct and the starting ester. Acidification of the aqueous layer in the presence of ethanol induced crystallization, resulting in an 83% yield (2.4 kg) of compound **3**.

**Figure 2.** Gravimetric Solubility of Crystalline Forms 1 and 2 of Compound **3**




Three crystalline forms of **3** were identified. Forms 1 and 2 were enantiotropically related anhydrous crystalline forms, and Form 3 was a transient hydrate that dehydrated to afford Form 2. Initial syntheses of **3** consistently provided Form 2; however, later syntheses provided Form 1 or mixtures of Forms 1 and 2 from the same binary solvent system (ethanol–water). Further investigation revealed that the later re-crystallizations were performed at 45–50 °C, which predominantly led to Form 1, while earlier experiments were performed at room temperature, leading to Form 2. The gravimetric solubility values shown in Figure 2 were consistent with these observations and ultimately a transition temperature of approximately 30 °C was interpolated. For further development, Form 2 was considered more desirable, as uncontrolled form conversion was unlikely to occur during storage under ambient conditions. In practical

terms, on the largest batch (2.4 kg), Form 1 was converted to a mixture of Forms 2 and 3 by granulation in 50% ethanol–water at 25 °C; subsequent drying under positive nitrogen pressure at 50 °C led to dehydration of Form 3 and complete conversion to Form 2 with monitoring by X-ray powder diffraction (XRD) pattern analysis. Rehydration of Form 2 to Form 3 under ambient conditions was not detected.

## CONCLUSIONS

The evolution of the synthesis of three potent AMPK activators has been described. The challenges associated with the early-stage syntheses including unstable intermediates, difficult isolations, and poor reaction profiles were identified and overcome to deliver material for key in vivo studies. Methods including heteroarene substitutions, borylation, Suzuki and Negishi cross-couplings, and ester hydrolysis were developed with improved reaction reproducibility, enhanced purity and safety profiles, and practical isolation of intermediates and APIs. These improvements ultimately resulted in the successful completion of synthesis campaigns to produce 40–50 g of **1** and **2**, and 2.4 kilograms of clinical candidate **3**[18] for key efficacy and safety studies. Additionally, the challenges in investigating, developing, and controlling the solid form for **3** were overcome to reproducibly prepare a stable crystalline form with properties suitable for further development.

## EXPERIMENTAL SECTION

All chemicals, reagents, and solvents were purchased from commercial sources and were used without further purification. Reactions were carried out at room temperature (~23 °C) unless otherwise indicated. Chemical shifts in NMR analyses were referenced to the residual $^{1}$H solvent signals ($CDCl_3$, δ 7.27; DMSO–$d_6$, δ 2.50; $CD_3OD$, δ 3.31) and solvent $^{13}$C signals ($CDCl_3$, δ 77.0; DMSO–$d_6$, δ 39.51; $CD_3OD$, δ 49.15). Signals are listed as follows: chemical shift in ppm;

multiplicity identified as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz. Purity is reported by relative UV area from HPLC analysis. Water content was determined by Karl Fischer titration. Pd content determined by inductively coupled plasma mass spectrometry (ICP-MS).

*(S)-1-(4-bromophenyl)-5-chloropentan-1-ol* (**14**): A 1 L 3-neck oven-dried round-bottom flask equipped with a digital thermometer and an addition funnel was charged with (*R*)-(+)-2-methyl-CBS-oxazaborolidine (5.25 g, 17.8 mmol), anhydrous 2-MeTHF (60 mL), and borane in THF (1.0 M, 185 mL, 185 mmol) under a $N_2$ atmosphere. The clear colorless solution was cooled to −20 °C using a cryocooler in an acetone bath. **13** (50.0 g, 180 mmol) in anhydrous 2-MeTHF (150 mL, rinsed with 2 x 20 mL) was added dropwise over about 3 h while keeping the internal temperature below −15 °C during addition. The solution was stirred at −20 °C for 1 h. The reaction was monitored by TLC (25% EtOAc/heptane, $KMnO_4$ stain) and GCMS until full conversion of the substrate was observed. MeOH (120 mL) was added dropwise from an addition funnel at a rate targeting an internal temperature of −20 °C. Some effervescence was observed and the temperature rose to −13 °C. The solution was stirred at −10 °C for 1 h until gas evolution ceased. 1 M HCl (150 mL) was added dropwise via addition funnel while stirring at −10 °C. A colorless suspension formed, and the mixture was stirred at 0 °C for 1 h, then stirred at room temperature for 15 h. The cloudy solution was poured into a separatory funnel containing 100 mL of brine. EtOAc (~300 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 400 mL). The organic phases were combined, washed with brine (300 mL), dried over sodium sulfate, filtered, and concentrated to dryness. The resultant oil was dissolved in ~300 mL petroleum ether and stirred at ambient temperature for 20 min. During this time a colorless precipitate formed. The solution was cooled to 0 °C, the

slurry was filtered, and the solids were washed with ~100 mL petroleum ether. The mother liquor was concentrated to dryness to give **14** (53.8 g, quant.), as a colorless oil which was carried forward to the next step without further purification.

An analytical sample was purified via flash column chromatography for characterization. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.2 Hz, 2H), 4.65 (dd, *J*=7.4, 5.9 Hz, 1H), 3.52 (t, *J*=6.6 Hz, 2H), 1.93 (br. s, 1H), 1.85–1.36 (m, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 143.5, 131.6, 127.6, 121.3, 73.7, 44.8, 38.2, 32.3, 23.0. GCMS calc. for $C_{11}H_{13}BrO$ (m/z): 240. Enantiomeric ratio (er): 98.4:1.6 as determined by chiral SFC analysis: (Chiral Tech AD-H, 250mm x 4.6 mm, 5% MeOH/$CO_2$ to 60% MeOH/$CO_2$, 3.0 mL/min, 210 nm, backpressure 120 Bar); $t_R$ = 6.035 min (major), $t_R$ = 7.266 min (minor).

*(S)-2-(4-bromopenyl)tetrahydro-2H-pyran* (**15**): **14** (180 mmol) was transferred to a round bottom flask as a solution in THF (180 mL), and the mixture was cooled to −5 °C (brine/ice bath). Potassium *t*-butoxide solution (250 mL, 250 mmol, 1.0 M in THF) was added slowly to the reaction flask at a rate to maintain internal temperature below 5 °C. The reaction was warmed to room temperature and stirred for 15 h. The reaction mixture was cooled in an ice bath and 1 M HCl (150 mL) was added slowly at a rate to keep the temperature below 8 °C. The reaction mixture was extracted with EtOAc (2 x 300 mL) and washed with brine (150 mL). The combined organic phases were dried over sodium sulfate, filtered, concentrated, and dried under high vacuum to yield **15** (44.2 g, quant.) as an orange-brown oil which solidified upon standing The material was taken forward to the next reaction without further purification.

An analytical sample was purified via flash column chromatography for characterization: GCMS calc. for $C_{11}H_{13}BrO$ (m/z): 240, 242; found: 240, 242. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J*=8.2 Hz, 2H), 7.23 (d, *J*=8.6 Hz, 2H), 4.29 (dd, *J*=11.1, 2.2 Hz, 1H), 4.17–4.10 (m,

*J*=11.2, 2.0, 2.0 Hz, 1H), 3.61 (td, *J*=11.5, 2.7 Hz, 1H), 1.98–1.91 (m, 1H), 1.85–1.77 (m, 1H), 1.73–1.48 (m, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 142.4, 131.3, 127.5, 120.9, 79.3, 68.9, 34.0, 25.8, 23.9. er: 98.11:1.89 as determined by chiral SFC analysis: (Lux Amylose-2, 250mm x 4.6 mm, 5% MeOH/$CO_2$ to 60% MeOH/$CO_2$, 3.0 mL/min, 210 nm, backpressure 120 Bar); $t_R$ = 3.829 min (major), $t_R$ = 4.100 min (minor).

*(S)-(4-(tetrahydro-2H-pyran-2-yl)phenyl)boronic acid* (**16**): A three-necked round bottom flask was equipped with an overhead stirrer, reflux condenser, and a nitrogen line. Sodium *t*-butoxide (251 mg, 2.61 mmol), potassium acetate (41.2 g, 420 mmol, oven dried), chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (Pd-XPhos G2, 734 mg, 0.933 mmol), XPhos (1250 mg, 2.61 mmol), and tetrahydroxydiboron (33.5 g, 373 mmol) were added to the flask, and the flask was purged with $N_2$ for 10 min. EtOH (273 mL) was added to **15** (180 mmol) in a separate flask and the solution was purged with $N_2$ for 10 min. The solution was added to the three-necked reaction flask, washing with more EtOH (100 mL). The yellow suspension was stirred at reflux temperature for 16 h. The reaction mixture turned to a brown suspension. TLC indicated product formation with a small amount of substrate remaining. The reaction was cooled to ambient temperature, MTBE (500 mL) was added and the mixture was filtered through a plug of Celite, washing with an additional 200 mL MTBE. The dark brown solution was concentrated to give a brown foam. MTBE (500 mL) and water (100 mL) were added and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous was extracted with MTBE (100 mL). The organic phases were combined and extracted with 1 M aqueous NaOH (3 x 100 mL, 1 x 50mL). The basic aqueous phases were combined and washed with MTBE (100 mL). The basic aqueous phases were transferred to a round bottom flask fitted with a magnetic stir bar

and cooled in an ice bath. Conc. HCl was added to adjust pH to ~6. During this time oil separated from the solution and the flask was agitated by sonication to induce crystallization, then stirred vigorously for 16 h. Fluffy solids formed and were filtered off to provide **16** as a colorless solid (26.83 g, 72%). m.p. 186–192 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.95 (br. s, 2H), 7.73 (d, *J*=8.2 Hz, 2H), 7.27 (d, *J*=8.2 Hz, 2H), 4.29 (dd, *J*=11.1, 1.8 Hz, 1H), 4.06–3.96 (m, 1H), 3.57–3.47 (m, 1H), 1.90–1.73 (m, 2H), 1.71–1.49 (m, 3H), 1.48–1.34 (m, 1H), (some boroxine formation observed by NMR, ratio of boroxine:boronic acid observed to change with NMR solvent). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 145.3, 133.9, 124.6, 78.9, 67.9, 33.9, 25.5, 23.5, (carbon bonded to B is not observed).

*4-bromo-3,5-difluoro-2-iodoaniline* (**18**): To 4-bromo-3,5-difluoroaniline (1.39 kg, 6.67 mol) in acetic acid (7.5 L) at 20 °C was added *N*-iodosuccinimide (1.53 kg, 6.80 mol). The mixture was stirred at 20 °C for 4 h (initial exotherm to 22 °C was observed) then quenched by the addition of 10% sodium thiosulfate (750 mL) followed by the addition of water (10.5 L) over 1 h (mild initial exotherm to 23 °C was observed). The resulting slurry was stirred at 20 °C for 1 h then the solid was filtered off and washed with water (4 x 1.5 L), air-dried, and then dried under vacuum at 45 °C to afford **18** (2.15 kg, 6.42 mol, 96%) as a white solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 6.58 (d, *J*=11.2 Hz, 1H) 6.03 (br. s, 2H). LCMS: calc. for $C_6H_3BrF_2IN$ (M+H): 333.9; found: 334.0.

*4-bromo-3,5-difluoro-2-((trimethylsilyl)ethynyl)aniline* (**19**): To an inert 20 L reactor was charged **18** (2.19 kg, 6.56 mol), $Pd(PPh_3)_4$ (125 g, 108 mmol), CuI (20 g, 105 mmol) and toluene (9 L). The mixture was deoxygenated using 3 x vacuum / nitrogen cycles and triethylamine (1.25 L, 8.97 mol) was added. The mixture was deoxygenated using 1 x vacuum / nitrogen cycles and TMS-acetylene (1.15 L, 8.30 mol) was added. The mixture was heated to 41 °C for 18 h (TLC

showed 90–95% complete). Additional TMS-acetylene (115 mL, 830 mmol) was added and the mixture was heated to 48 °C for another 3 h. The mixture was cooled to 18 °C and filtered through a short pad of Celite, washing with toluene (3 L). The filtrate was washed with 1 M $NaH_2PO_4$ (3.5 L), dried over $MgSO_4$ and filtered through a 2 kg pad of silica, washing with toluene (4 L). The filtrate was concentrated in vacuo to a solid which was triturated with hexane (3 L) at 50 °C. The slurry was cooled to 10 °C, filtered, and washed with cold hexane (1.5 L) to afford **19** (1.56 kg, 5.11 mol, 78%) as a pale brown solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.31 (dd, *J*=10.0, 1.8 Hz, 1H), 4.50 (br. s, 2H), 0.28 (s, 9 H). LCMS (AP): calc. for $C_{11}H_{12}BrF_2NSi$ (M+H): 304.0, 306.0; found: 304.0, 306.0.

*5-bromo-4,6-difluoro-1H-indole* (**9**): A mixture of potassium *t*-butoxide (587 g, 5.23 mol) and NMP (3.67 kg) was warmed to 33 °C with a 40 °C water bath. The bath was cooled to 25 °C and then a solution of **19** (1.44 kg, 4.72 mol) in NMP (3.22 kg) was added over 60 sec. An exotherm was observed to 89 °C after an additional 60 sec then the reaction temperature slowly decreased to 36 °C over 100 min. The reaction was quenched by pouring onto a mixture of MTBE (9 L), water (5 L), saturated sodium bicarbonate (9 L), and ice (10 kg). The layers were separated and the organic layer was washed sequentially with saturated sodium bicarbonate (6 L), then brine (6 L). The aqueous layers were sequentially extracted with MTBE (2 x 4 L). The organics were dried over magnesium sulfate and filtered through a pad of Celite, washing with MTBE. The filtrate was evaporated and azeotroped with heptane (600 mL) to afford 1.28 kg of crude product. This was combined with a pilot batch obtained from 100 g of **19** and purified by flash column chromatography (20 kg silica, eluent 10–30% EtOAc in hexane). Product fractions were combined, evaporated, and azeotroped with heptane (500 mL). The residue was triturated with hexane (2 L) at 35 °C then cooled to 20 °C, filtered, and washed with hexane (1 L) to afford **9**

(576 g, 49%) as a pale tan solid (HPLC purity 98.7% by area, m.p. 92–93 °C). The filtrate from trituration and mixed fractions from the column were concentrated. The residue was triturated with hexane (1 L) at 35 °C, cooled to 8 °C, filtered, and washed with cold hexane (500 mL) to afford crude (334 g) as a tan solid. This material was pre-adsorbed on 500 g silica and chromatographed (8 kg silica, eluent 50% DCM/hexane). Higher purity fractions were combined and evaporated, then triturated with hexane and filtered to afford a second batch of **9** (200 g, 18%) as a pale tan solid (HPLC purity 96.2%, m.p. 91–92 °C). Total combined yield of both batches: 67%. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.43– 8.15 (br. s, 1H) 7.19 (dd, *J*=3.1, 2.3 Hz, 1H) 7.03 (dt, *J*=8.4, 1.1 Hz, 1H) 6.62 (ddd, *J*=3.2, 2.4, 1.1 Hz, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 153.9 (dd, *J*=235.5, 3.7 Hz), 151.5 (dd, *J*=246.5, 6.6 Hz), 135.8 (t, *J*=13.9 Hz), 127.2 (d, *J*=2.9 Hz), 113.7 (d, *J*=21.3 Hz), 96.8 (br. s), 95.3 (dd, *J*=27.1, 4.4 Hz), 86.3 (dd, *J*=27.1, 23.5 Hz). LCMS (AP): calc. for $C_8H_4BrF_2N$ $(M-H)^-$: 229.9, 231.9; found: 230.2, 232.2.

*(S)-4,6-difluoro-5-(4-(tetrahydro-2H-pyran-2-yl)phenyl)-1H-indole* (**24**): To a 1 L three-necked round bottom flask, fitted with an overhead stirrer, was added **9** (45.0 g, 194 mmol), **16** (48.0 g, 233 mmol), $K_2CO_3$ (80.4 g, 582 mmol), and $Pd(PPh_3)_2Cl_2$ (4.08 g, 5.82 mmol). The flask was purged with $N_2$ for 15 min. Dioxane (300 mL) and water (100 mL) were added, and the flask was purged with $N_2$ for an additional 5 min. The reaction was heated to reflux temperature in a heating block (set at 110 °C) for 18 h. The mixture was filtered through a pad of Celite, then partially concentrated to remove some dioxane. EtOAc (500 mL) was added and the aqueous layer was separated. The organic layer was washed sequentially with saturated aqueous $NH_4Cl$ (100 mL), saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), then dried over $MgSO_4$, filtered, and concentrated to give the crude desired product (~80 g) as a brown solid. This was recrystallized by treatment with EtOAc (160 mL), bringing the mixture to reflux temperature,

adding heptane (50 mL), then cooling slowly by removing the heat and stirring for 15 h. The resultant suspension was filtered, and washed with cold heptane:EtOAc (1:1, 50 mL) to give **24** as an off-white solid (33.23 g, 55%). m.p. 192–194 °C. $^{1}$H NMR (400 MHz, $CD_3OD$) δ 7.46–7.36 (m, 4H), 7.24 (d, *J*=3.5 Hz, 1H), 7.04 (d, *J*=10.2 Hz, 1H), 6.51 (dd, *J*=3.5, 0.8 Hz, 1H), 4.41 (dd, *J*=10.7, 2.2 Hz, 1H), 4.15–4.07 (m, 1H), 3.66 (td, *J*=11.4, 2.5 Hz, 1H), 2.00–1.93 (m, 1H), 1.92–1.85 (m, 1H), 1.80–1.56 (m, 4H). $^{13}$C NMR (101 MHz, $CD_3OD$:$CDCl_3$, 1:1) δ 157.6 (dd, *J* = 237.7, 6.6 Hz), 153.5 (dd, *J*=247.2, 9.5 Hz), 143.3, 137.7 (t, *J* = 14.7 Hz), 131.8 (m), 131.5, 126.7, 126.2 (d, *J*=2.9 Hz), 114.9 (dd, *J*=23.5, 1.5 Hz), 110.0 (dd, *J*=22, 16.9 Hz), 98.6, 94.8 (dd, *J*=27.9, 4.4 Hz), 81.5, 70.0, 35.0, 27.0, 24.9. HRMS (ESI): Calc. for $C_{19}H_{18}F_2NO$ $(M+H)^+$: 314.1351; found: 314.1353.

*(S)-4,6-difluoro-5-(4-(tetrahydro-2H-pyran-2-yl)phenyl)-1H-indole-3-carbaldehyde* (**25**): **24** (56.6 g, 180 mmol) was transferred to a 3-necked 2 L round bottom flask, washing with acetonitrile (260 mL). The flask was fitted with an overhead stirrer and the heterogeneous solution was stirred vigorously as the Vilsmeier reagent (39.3 g, 307 mmol) was added, washing with $CH_3CN$ (100 mL). The suspension quickly became a homogeneous solution, then a pale yellow suspension. The mixture was stirred vigorously for 45 min at ambient temperature. 2 M NaOH (361 mL, 361 mmol), was added dropwise initially then in one portion. Dissolution of solids was observed upon addition and a clear orange solution resulted. The mixture was heated to 100 °C for 30 min and yellow solids formed. The reaction was cooled to ambient temperature, then 0 °C in an ice bath. The mixture was filtered and the pale yellow solid was washed with water (100 mL) and EtOAc/heptane (1:1, 100 mL). The resulting crystalline solid was dried under high vacuum for 15 h to provide **25** as a pale yellow solid (44 g, 71%). m.p. 267–269 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.54 (br. s, 1H), 9.99 (d, *J*=3.1 Hz, 1H), 8.33 (s, 1H), 7.47–

7.39 (m, 4H), 7.33 (d, *J*=9.4 Hz, 1H), 4.39 (dd, *J*=10.9, 2.0 Hz, 1H), 4.05 (d, *J*=10.9 Hz, 1H), 3.61–3.52 (m, 1H), 1.93–1.82 (m, 2H), 1.75–1.42 (m, 4H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 183.4, 156.2 (dd, *J*=239.2, 6.6 Hz), 152.3 (dd, *J*=250.9, 8.8 Hz), 143.2, 137.4, 137.1 (d, *J*=14.7 Hz), 130.2, 128.2, 125.6, 117.3 (d, *J*=5.9 Hz), 111.5 (dd, *J*=22.0, 18.3 Hz), 109.7 (dd, *J*=23.5, 1.5 Hz), 95.7 (dd, *J*=27.9, 4.4 Hz), 78.6, 68.0, 33.8, 25.4, 23.4. LCMS (ES): calc. for $C_{20}H_{17}F_2NO_2$ $(M+H)^+$: 342.1; found: 342.0.

*(S)-4,6-difluoro-5-(4-(tetrahydro-2H-pyran-2-yl)phenyl)-1H-indole-3-carboxylic acid* (**1**): A 4-necked round bottom flask was charged with **25** (21.81 g, 63.89 mmol), DMSO (77 mL, 1.10 mol), and 2-methyltetrahydrofuran (550 mL) and cooled to 0 °C. A solution of sodium chlorite (36.0 g, 319 mmol) and sodium dihydrogenphosphate monohydrate (44.1 g, 320 mmol) in water (320 mL) was added via addition funnel over 30 min at a rate to maintain a temperature < 10 °C. The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 19 h. The reaction mixture was poured in portions over 30 min into a cold (0 °C) solution of sodium thiosulfate pentahydrate (85.3 g, 340 mmol) in water (170 mL) while keeping the temperature < 15°C. The mixture was stirred at 10 °C for 20 min. The reaction was then diluted with EtOAc (250 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 x 250 mL), the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated to ~1/3 of the original volume. The mixture was then cooled to 0 °C and stirred for 30 min. The resultant solid was collected via filtration and dried in vacuo to provide **1** (18.2 g, 80% yield) in high purity (99.7% by HPLC). The reaction was performed on a similar scale and combined for recrystallization. **1** (48.7 g, 136 mmol) was slurried in 95% EtOH (400 mL) and stirred at 50 °C with overhead stirring for 16 h. The mixture was then cooled to 0 °C and

stirred for 30 min. The resultant solid was collected via filtration, washed with 95% EtOH (25 mL) and dried in vacuo to provide **1** (46.8 g, 96% recovery) as a crystalline solid. m.p. 258–260 °C (decomposition). HPLC purity 99.5%. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.13 (br. s, 1H), 11.98 (s, 1H), 8.07 (d, *J*=2.3 Hz, 1H), 7.47–7.36 (m, 4H), 7.25 (d, *J*=9.4 Hz, 1H), 4.37 (dd, *J*=10.9, 1.95 Hz, 1H), 4.08–4.01 (m, 1H), 3.61–3.51 (m, 1H), 1.93–1.81 (m, 2H), 1.73–1.42 (m, 4H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 164.2, 155.8 (dd, *J*=238.4, 5.9 Hz), 151.7 (dd, *J*=253.8, 8.8 Hz), 142.9, 137.2 (dd, *J*=15.4, 13.2 Hz), 134.4 (d, *J*=1.5 Hz), 130.3, 128.7, 125.5, 110.9 (dd, *J*=21.6, 18.7 Hz), 110.5 (dd, *J*=21.3, 1.5 Hz), 107.3 (d, *J*=4.4 Hz), 95.1 (dd, *J*=27.9, 4.4 Hz), 78.7, 68.0, 33.8, 25.5, 23.5. HRMS (ESI): calc. for $C_{20}H_{18}F_2NO_3$ $(M+H)^+$: 358.1249; found: 358.1244. Analytical (%) calc.: C, 67.22; H, 4.80; N, 3.92; found: C, 66.86; H, 4.51; N, 3.84. er: 99.75:0.25 as determined by chiral SFC analysis: (Chiral Tech OJ-H, 250mm x 4.6 mm, 5% MeOH/$CO_2$ to 60% MeOH/$CO_2$, 3.0 mL/min, 210 nm, backpressure 120 Bar); $t_R$ = 6.447 min (major), $t_R$ = 6.813 min (minor).

*methyl 5-bromo-6-chloro-1H-indole-3-carboxylate* (**35**): One-pot procedure: A round bottom flask was charged with 5-bromo-6-chloro-1*H*-indole (30.0 g, 130 mmol), DMAP (1.61 g, 13.0 mmol), pyridine (26.2 mL, 325 mmol), and THF (200 mL) then cooled to 0 °C. Trichloroacetyl chloride (32.1 mL, 286 mmol) was then added dropwise and the obtained mixture was warmed to ambient temperature over 2 h (a precipitate began to form) then stirred for 3 days. The mixture was cooled to 0 °C and methanol (50 mL) was added dropwise at a rate to maintain the temperature < 10 °C. 25% Sodium methoxide in methanol (70 mL) was then added at 0 °C. The mixture was stirred at 55 °C for 2 h. The reaction was then quenched with water (125 mL) and diluted with MTBE (100 mL). The layers were separated and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated to ~25% of the initial volume. MTBE

(200 mL) was added and the mixture was stirred at 70 °C for 2 h then slowly cooled to ambient temperature and stirred for 15 h. The precipitate was collected via filtration, washed with MTBE, and dried in vacuo at 45 °C to obtain **35** (21.3 g, 57%). The mother liquor was concentrated to a heavy slurry. Methanol (70 mL) was added and the mixture was stirred at 65 °C for 2 h, then slowly cooled to ambient temperature and stirred for 15 h. The solids were collected via filtration, washed with methanol, and dried in vacuo at 45 °C to obtain a second crop of **35** (7.43 g, 20%) for a total combined yield of 76% for both batches.

A separate sample was prepared for full characterization: $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.98 (br. s, 1H), 8.25 (s, 1H), 8.17 (s, 1H), 7.73 (s, 1H), 3.81 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 164.1, 136.0, 134.9, 126.4, 126.0, 124.5, 114.0, 113.8, 106.0, 50.9. LCMS (AP): calc. for $C_{10}H_6BrClNO_2$ $(M-H)^-$: 285.9; found: 285.9.

Two step procedure: Step 1: *1-(5-bromo-6-chloro-1H-indol-3-yl)-2,2,2-trichloroethan-1-one* (**34**): To a stirred suspension of 5-bromo-6-chloro-1*H*-indole (250 g, 1.09 mol), pyridine (240 g, 3.04 mol) and DMAP (13.25 g, 108.5 mmol) in THF (2000 mL) was added trichloroacetyl chloride (473.34 g, 2.60 mol) dropwise while maintaining the temperature between 0–10 °C. After addition, the reaction mixture was warmed to 15 °C and stirred for 4 days. MeOH (250 mL) was added followed by water (1500 mL), EtOAc (500 mL) and THF (400 mL). This procedure was repeated a total of 12 times and the reaction mixtures were combined. The layers were separated and the organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The resultant residue was triturated with dichloromethane (18 L) and the solids collected via filtration. The solids were washed with dichloromethane (1.5 L) and dried in vacuo to provide **3** (3.02 kg, 62%) as a yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.74 (br.

s, 1H), 8.69 (s, 1H), 8.48 (s, 1H), 7.85 (s, 1H). LCMS (AP): calc. for $C_{10}H_3BrCl_4NO_2$: 371.8; found: 371.9.

Step 2: *methyl 5-bromo-6-chloro-1H-indole-3-carboxylate* (**35**) A round bottom flask was charged with MeOH (400 mL) and placed under a $N_2$ atmosphere. Sodium (27.89 g, 1.21 mol) was added portion-wise until dissolved to form a ~3 M NaOMe solution. A separate flask was charged with **3** (380 g, 1.01 mol) and MeOH (1120 mL). The freshly-prepared sodium methoxide solution was added dropwise at room temperature and stirred for 1 h. This procedure was repeated in 9 batches and the reaction mixtures were combined and poured onto water (60 L) portion-wise. The resultant precipitate was collected via filtration and washed with water (3 x 2 L) and MTBE (2 L). The crude product was triturated with MeOH:THF (10:1, 13 L) at 60 °C and the mixture was filtered while hot. The collected solids were washed with petroleum ether (3.5 L) and dried in vacuo to provide **35** (2.25 kg, 86%) as a pale yellow solid that matched the analytical data for the one-pot procedure.

*5-bromo-6-fluoro-N,N-dimethylpyridin-2-amine* (**41**):

Step 1: *6-fluoro-N,N-dimethylpyridin-2-amine* (**40**): To 2,6-difluoropyridine (860 g, 7.47 mol) in acetonitrile (8.3 L) was added potassium carbonate (2.05 kg, 14.8 mol) followed by dimethylamine hydrochloride (1.60 kg, 19.6 mol). The mixture was heated to 63 °C for 2.5 h with gas evolution observed upon warming. After NMR analysis indicated complete consumption of starting material, the reaction was cooled to 23 °C and filtered through a pad of Celite which was washed with acetonitrile (8 L). The filtrate was concentrated in vacuo to afford crude **40** (1.16 kg) as a yellow oil that was taken forward without further purification. A sample was purified via flash column chromatography for characterization. $^1$H NMR (600 MHz, $CDCl_3$) δ 7.53–7.45 (m, 1H) 6.28 (dd, *J*=8.2, 2.3 Hz, 1H) 6.09 (dd, *J*=7.6, 2.5 Hz, 1H) 3.07 (s, 6 H). $^{13}$C

NMR (101 MHz, $CDCl_3$,) δ 162.8 (d, *J*=234.8 Hz), 158.4 (d, *J*=16.9 Hz), 141.3 (d, *J*=8.1 Hz), 101.6 (d, *J*=3.7 Hz), 93.9 (d, *J*=37.4 Hz), 37.8. GCMS (EI): calc. for $C_7H_9FN_2$ (m/z): 140.1, found: 140.0.

Step 2: *5-bromo-6-fluoro-N,N-dimethylpyridin-2-amine* (**41**): To crude **40** (1.16 kg, assumed 7.47 mol) in acetonitrile (17 L) at −12 °C was added a solution of *N*-bromosuccinimide (1.33 kg, 7.47 mol) in acetonitrile (10 L) over 45 min at a rate to maintain temperature below 0 °C. The mixture was stirred at 0 °C for 1 h then warmed slowly to room temperature and stirred for 15 h. The mixture was concentrated in vacuo and the oily solid residue was partitioned between a mixture of MTBE (8 L), water (10 L), sodium thiosulfate (100 g) and potassium bicarbonate (800 g). The layers were separated and the organic layer washed with brine (4 L). The aqueous layers were then extracted with MTBE (4 L). The combined organics were dried over magnesium sulfate and filtered through a pad of Magnesol (2 kg), washing with MTBE (10 L). The filtrate was concentrated in vacuo and azeotroped with heptane (1.5 L). The solid residue was triturated with hexane (2.5 L), cooled to 0 °C, filtered, and washed with cold hexane (600 mL) to afford **41** (1.21 kg, 74% over two steps) as a white crystalline solid. The filtrate was concentrated to ~600 mL volume, cooled to 0 °C, filtered and washed with cold hexane to afford a second crop of **41** (150 g, 0.68 mol, 9% over two steps) as a white crystalline solid for a combined yield of 83%. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, *J*=8.8 Hz, 1H), 6.21 (dd, *J*=8.6, 1.6 Hz, 1H), 3.05 (s, 6 H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 158.1 (d, *J*=231.8 Hz), 157.1 (d, *J*=15.4 Hz), 143.8 (d, *J*=2.9 Hz), 103.7 (d, *J*=4.4 Hz), 86.4 (d, *J*=38.9 Hz), 38.1 GCMS (EI) calc. for $C_7H_8BrFN_2$ (m/z): 218.0. found: 218.0.

*5-bromo-6-methoxy-N,N-dimethylpyridin-2-amine* (**28**): A mixture of **41** (1.36 kg, 6.21 mol) and 25% potassium methoxide in MeOH (3.93 kg, 14.0 mol) was heated to 71 °C for 130 min (a

slight exotherm to 75 °C was observed). When TLC analysis indicated complete consumption of starting materal, the mixture was cooled to 35 °C and poured onto to a mixture of EtOAc (10 L), water (10 L), ice (2 kg) and monosodium phosphate (1.4 kg). The layers were separated and the organic layer washed with brine (4 L). The aqueous layers were extracted with EtOAc (4 L). The combined organics were dried over magnesium sulfate and filtered through a pad of Celite, washing with EtOAc (4 L). The filtrate was concentrated in vacuo and azeotroped with heptane (1 L) to afford **28** (1.43 kg, 6.17 mol, 99%) as a white crystalline solid.

m.p. 50–52°C. HPLC: 99.8%. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J*=8.6 Hz, 1H), 5.95 (d, *J*=8.6 Hz, 1H), 3.96 (s, 3H), 3.05 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 158.1, 157.1, 142.3, 98.6, 89.8, 53.7, 38.0. GCMS (ES): calc. for $C_8H_{11}BrN_2O$ (m/z): 230.0, found: 230.0.

*methyl 5-bromo-6-chloro-1-tosyl-1H-indole-3-carboxylate* (**42c**): To a solution of indole **35** (80.0 g, 277 mmol) in DMF (600 mL) at 0 °C was added sodium hydride (60% dispersion in oil, 16.6 g, 416 mmol) portion-wise over 20 min. The reaction was stirred at 0 °C for 60 min followed by the portion-wise addition of 4-methylbenzenesulphonyl chloride (63.4 g, 333 mmol). The reaction was allowed to stir for 2 h at 0 °C, the ice bath was removed and the reaction was allowed to warm to room temperature and stirred overnight. The reaction was poured into water (1.2 L) and stirred for 12 h. The resultant solids were collected via filtration and washed with a further portion of water (700 mL) then heptane (2 x 300 mL). The solids were transferred to a 3 L round bottom flask and dried in vacuo at 40 °C for 15 h to remove residual water. The material was suspended in acetone (600 mL) and heated to reflux temperature for 1 h, removed from heat, cooled to room temperature, and stirred for 1 h. The solids were collected via filtration and washed with acetone (~500 mL) until the filtrate was colorless. The solids were dried to provide **42c** (108.7 g, 89%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.23 (s, 1H),

8.11 (s, 1H), 7.82 (d, *J*=8.6 Hz, 2H), 7.32 (d, *J*=8.2 Hz, 2H), 3.93 (s, 3H), 2.40 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 163.3, 146.4, 134.1, 134.0, 133.2, 131.4, 130.4, 127.6, 127.1, 126.6, 118.7, 114.9, 112.7, 51.8, 21.7. HRMS (ESI): calc. for $C_{17}H_{13}ClNO_4S$ $(M+H)^+$ 443.9488; found: 443.9482.

*methyl 6-chloro-5-(6-(dimethylamino)-2-methoxypyridin-3-yl)-1-tosyl-1H-indole-3-carboxylate* (**43c**): A dried, 1 L, 3-necked round bottom flask under nitrogen was charged with **28** (83.51 g, 361.4 mmol) and THF (400 mL) and cooled to −70 °C. *n*-Butyllithium (2.5 M in hexanes, 140 mL, 350 mmol) was added dropwise via addition funnel over 30 min to maintain the internal temperature below −65 °C. The resultant purple solution was stirred between −65 °C and −70 °C for 20 min. A solution of $ZnCl_2$ in 2-MeTHF (1.9 M, 200 mL, 380 mmol) was then added via cannula at a rate maintaining an internal temperature below −65 °C. The resulting mixture was stirred at −70 °C for 20 min then cooling was removed. The reaction was warmed to room temperature over 1 h, then stirred at room temperature for 2 h. A separate, dried 3 L, 4-necked round bottom flask was charged with **42c** (100.0 g, 225.9 mmol), dichloro[bis(2-(diphenylphosphino)phenyl)ether]palladium(II) (6.45 g, 9.01 mmol), and THF (300 mL). The mixture was degassed with nitrogen/vacuum cycles (x5). The arylzinc solution was then cannulated to the mixture over 15 min (rinsing with 25 mL THF) and the reaction was stirred at ambient temperature for 3 h. During this time, the reaction temperature reached 28 °C before returning to ambient temperature. The reaction was quenched with sat. aq. $NH_4Cl$ (1 L), diluted with EtOAc (1 L), and the layers were separated. The aqueous layer was extracted with EtOAc (250 mL) and the combined organics were washed with brine (500 mL). The mixture was filtered and the collected solids were set aside. The filtrate was concentrated to 1.25 L and additional solids had formed. The mixture was filtered washing with EtOAc until the wash was colorless

and the solids were set aside. The filtrate was concentrated to ~300 mL volume. MeOH (250 mL) was added and solids began to form. A solvent switch with MeOH (3 x 250 mL) was then performed to displace EtOAc. The final volume was adjusted to 500 mL with MeOH to achieve a 20:1 ratio of MeOH:EtOAc. The mixture was slurried for 30 min at 50 °C then cooled to room temperature. The solids were collected via filtration and washed with MeOH (250 mL). The filtered solids from the extraction were combined with the bulk lot, treated with MeOH (500 mL), and triturated at 60 °C for 1 h then room temperature for 15 h. The solids were collected via filtration, washed with MeOH (100 mL), then dried for 15 h to provide **43c** (105.5 g, 91%) as an off-white solid. Purity: 97.2% by UPLC. Pd (173 ppm), Zn (40 ppm). A separate sample was prepared for full characterization:

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.51 (s, 1H), 8.12 (d, *J*=8.6 Hz, 2H), 8.01 (s, 1H), 7.88 (s, 1H), 7.49 (d, *J*=8.2 Hz, 2H), 7.31 (d, *J*=8.2 Hz, 1H), 6.22 (d, *J*=8.2 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.06 (s, 6H), 2.37 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 162.9, 158.7, 157.7, 146.7, 141.0, 133.4, 133.2, 133.1, 133.0, 131.4, 130.7, 127.4, 125.9, 124.3, 113.2, 112.4, 107.3, 96.9, 52.4, 51.8, 37.4, 21.1. HRMS (ESI): calc. for $C_{25}H_{24}ClN_3O_5S$ $(M+H)^+$: 514.1198, found: 514.1196.

*methyl 6-chloro-5-(6-(dimethylamino)-2-methoxypyridin-3-yl)-1H-indole-3-carboxylate* (**38**): To a solution of **43c** (109 g, 212 mmol) in THF (1 L) at room temperature was added tetrabutylammonium fluoride (1.0 M in THF, 400 mL, 400 mmol). The reaction was stirred at reflux for 3 h before cooling to room temperature and diluting with EtOAc (2000 mL). This was washed sequentially with sat. aq. $NaHCO_3$ (2 x 750 mL), sat. aq. $NH_4Cl$ (2 x 750 mL), water (750 mL), and brine (750 mL), and then dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was triturated with MeOH (~500 mL) and filtered. The solids were washed with MeOH (300 mL) and dried on the filter for 15 h to provide **38** (68.2 g, 89%) as a white solid. A

separate sample was prepared for full characterization: $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.99 (s, 1H), 8.13 (s, 1H), 7.82 (s, 1H), 7.58 (s, 1H), 7.32 (d, *J*=8.2 Hz, 1H), 6.21 (d, *J*=8.2 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.07 (s, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 164.4, 159.0, 157.4, 141.2, 135.8, 133.6, 129.8, 128.2, 124.5, 123.2, 112.4, 108.8, 106.3, 96.7, 52.4, 50.7, 37.5. HRMS (ESI): calc. for $C_{18}H_{18}ClN_3O_3$ $(M+H)^+$: 360.1109, found: 360.1110.

*6-chloro-5-(6-(dimethylamino)-2-methoxypyridin-3-yl)-1H-indole-3-carboxylic acid* (**2**): A 4L reactor with a condenser and overhead stirrer was charged with **38** (65.0 g, 181 mmol) in 1:1 THF:MeOH (1.6 L) then heated to 40–50 °C to dissolve the starting material before cooling back to 30–35 °C. Aqueous NaOH (2.0 M, 1.6 L, 3.2 mol) was then added and the reaction heated to 50–55 °C and stirred for 36 h. The reaction was cooled to −5 °C and aqueous HCl (6.0 M, 600 mL, 3.6 mol) was added to adjust to pH 6–7. The reaction was diluted with EtOAc (3.2 L) and the layers separated. The aqueous layer was extracted with EtOAc twice (1.5 L, then 1 L). The combined organic phases were sequentially washed with saturated $NH_4Cl$ (3.2 L), brine (3.2 L), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resultant solids were mixed with acetone (3 L) and heated to 45–50 °C and the volume was reduced to ~1.5 L. The mixture was cooled and stirred at room temperature for 2 h. The resultant solids were collected via filtration to provide **2** (42 g, 67%) with >97% purity by UPLC. The solids were then treated with heptane (1.0 L), heated to 80–90 °C and stirred at that temperature for 48 h to achieve a consistent crystalline form. The mixture was filtered and the collected solids were dried on the filter with a nitrogen bleed for 15 h to provide **2** (37.6 g, 90% recovery) as a white crystalline solid. Purity: 98.4% by UPLC. m.p. 253–254 °C. Analytical (%) calc.: C, 59.05; H, 4.66; N, 12.15; found: C, 59.01; H, 4.64; N, 12.00. A separate sample was prepared for full characterization: $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.03 (br. s, 1H), 11.86 (br. s, 1H), 8.04 (d, *J*=2.7 Hz, 1H), 7.83 (s, 1H),

7.55 (s, 1H), 7.32 (d, *J*=8.2 Hz, 1H), 6.21 (d, *J*=8.2 Hz, 1H), 3.76 (s, 3 H), 3.07 (s, 6 H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 165.7, 159.0, 157.4, 141.2, 135.9, 133.3, 129.4, 127.9, 125.0, 123.3, 112.2, 108.9, 107.5, 96.7, 52.4, 37.5. HRMS (ESI): calc. for $C_{17}H_{16}ClN_3O_3$ $(M+H)^+$: 346.0953; found: 346.0953.

*1-(4-bromophenyl)cyclobutan-1-ol* (**45**): An inert 22 L 4-neck round bottom flask with mechanical stirring, thermocouple, and nitrogen inlet was charged with 1,4-dibromobenzene (1.50 kg, 6.36 mol) and THF (5 L) and the resulting colorless solution was cooled in a −100 °C bath. *n*-Butyllithium (2.5 M in hexane, 2.67 L, 6.68 mol) was added dropwise over 2 h to maintain a reaction temperature less than −75 °C. The reaction was a light yellow/tan color after this addition. A THF solution of cyclobutanone (468 g, 6.68 mol, in 500 mL THF) was added by cannula over 10 min. The temperature rose to −15 °C and the reaction was stirred for 30 min. The reaction was quenched by the addition of 6 N aqueous HCl (1.2 L, 7.2 mol), maintaining the temperature below 20 °C. During the addition the color changed from a clear orange solution to a cloudy orange mixture to a light yellow mixture. The bath was then removed and the mixture stirred for 30 min. The phases were separated and the aqueous was washed with EtOAc (1 L). The organic layers were combined, washed with brine (2 L), filtered through a small pad of silica (450 g), and concentrated to provide an orange oil. The oil was dissolved in hexane (2 L) and filtered through a pad of silica gel (1.5 kg on a 6 L fritted funnel). The cake was washed with hexane (1 x 2 L) then 10% EtOAc/hexane (4 x 2 L). The initial hexane filtrate was discarded. The subsequent hexane wash and first 3 washes from 10% EtOAc were combined and concentrated to provide **45** (1.29 kg, 89%) as a yellow oil. $^1$H NMR (400MHz, DMSO-$d_6$) δ 7.54–7.48 (m, 2H), 7.46–7.41 (m, 2H), 5.58 (s, 1H), 2.40–2.21 (m, 4H), 1.97–1.85 (m, 1H),

1.70–1.57 (m, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 147.2, 130.7, 127.2, 119.4, 74.8, 37.2, 12.6.

*1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobutan-1-ol* (**50**): A 12 L round bottom flask equipped with mechanical stirring, thermocouple, heating mantle, argon/vacuum inlet, and condenser was charged with bis(pinacolato)diboron (671 g, 2.64 mol), potassium acetate (778 g, 7.93 mol), and THF (4.2 L). The flask was flushed with argon with three vacuum/argon cycles. Pd(dppf)$Cl_2$·$CH_2Cl_2$ (32.3 g, 40 mmol) was added as a solid, a final vacuum/argon cycle was performed, and the reaction was heated to 60 °C. In a separate flask, **45** (600 g, 2.64 mol) was dissolved in THF (1.8 L) and nitrogen was bubbled through the solution for 15 min. A solution of **45** (600 g, 2.64 mol in 1.8 L THF) purged with nitrogen for 15 min was then added dropwise via cannula at a rate to maintain a reaction temperature between 55 °C and 65 °C (~25 min). The reaction was then heated to 65 °C for 24 h. Heating was discontinued and the reaction slowly cooled to room temperature with stirring. The resulting slurry was filtered through silica (~1 inch on a 3 L frit) and washed with EtOAc (3 x 600 mL). The filtrate was concentrated in vacuo to a black oil. The oil was dissolved in hexane (1.5 L mL), heated to 65 °C, filtered through silica (~1 inch on a 2 L frit), and washed with hot hexane (500 mL at 65 °C). The filtrate was then cooled in a freezer for 18 h. The resultant crystals were collected by filtration and washed with hexane (3 x 800 mL), and dried to provide **50** (779 g, quant.) that was taken forward without further purification.

*(4-(1-hydroxycyclobutyl)phenyl)boronic acid* (**48**): A 22 L 4-neck round bottom flask equipped with mechanical stirring, thermocouple and nitrogen inlet was charged with diethanolamine (1.38 kg, 13.1 mol) and isopropanol (5 L). Crude **50** (1.80 kg, 6.57 mol) was added with an isopropanol rinse (1 L). The solution was stirred for 10 min, hexane (3 L) was added, and stirring

continued for 18 h. The resulting precipitate was collected via filtration, washed with hexane (3 x 2 L), and dried to provide the intermediate diethanolamine adduct (1.05 kg, 61%). The reaction was repeated on a similar scale and the batches combined (2.0 kg, 7.66 mol). These solids were transferred to a 12 L round bottom flask equipped with mechanical stirring and a nitrogen bubbler. Aqueous 3.0 M HCl (6.0 L, 18 mol) was added and the slurry was stirred for 2 h. The resultant solids were collected via filtration, washed with water (2 x 2 L), hexane (3 x 2 L), and dried to provide **48** (1.34 kg, 91%). The procedure was repeated and batches of **48** (6.6 kg, 34.4 mol) were combined and dissolved in EtOAc (33 L) then filtered to remove a small amount of insoluble material. The solution was concentrated under reduced pressure (50 mm, 40 °C) until the volume was reduced to ~15 L. Heptane (24 L) was added under vacuum and the distillation continued while slowly increasing heat to 50 °C until the volume was reduced to ~12 L. The resulting slurry was cooled and filtered. The solids were washed with cold heptane (2 x 4 L) and then dried under reduced pressure (1-2 mm) at 50 °C until there was no change in weight over at least 2 h to produce crystalline **48** (5.92 kg, 90%) with 85% potency (15% water).

$^1$H NMR (400MHz, DMSO-$d_6$) δ 7.95 (s, 2H), 7.76 (d, $J$=8.2 Hz, 2H), 7.44 (d, $J$=8.2 Hz, 2H), 5.44 (br. s, 1H), 2.42–2.34 (m, 2H), 2.30–2.21 (m, 2H), 1.96–1.86 (m, 1H), 1.69–1.60 (m, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 149.6, 133.9, 131.9, 123.8, 75.2, 37.3, 12.8. LCMS (ES): Calc. for $C_{10}H_{13}BO_3$ $(M+H)^+$: 193.1; found: 175.1 ($M-H_2O+H$).

*methyl 6-chloro-5-(4-(1-hydroxycyclobutyl)phenyl)-1H-indole-3-carboxylate* (**49**): A reactor was charged with 2-MeTHF (48 L), **35** (4.81 kg, 16.7 mol), **48** (5.26 kg, 23.3 mol), $PdCl_2(PPh_3)_2$ (234 g, mmol, added with 1L 2-MeTHF) and the reactor purged with nitrogen. Aqueous $K_2CO_3$ (6.90 kg in 22.08 L water) was then added and the reactor was heated to 74 °C and held for 2 h. The reactor was cooled to 50 °C and the reaction was complete. The reactor was cooled to 30 °C

and held for 15 min. The phases were cut and the aqueous layer removed. Aqueous NaOH (2 kg of 50 wt% solution in 24 L water) was added to the organic layer at 27 °C and the mixture was agitated for 15 min then held for 25 min. The phases were cut and the aqueous layer was removed. The remaining organic layer was filtered through a cartridge filter (500 g diatomaceous earth), rinsing with 2-MeTHF (5 L). The material was transferred to a rinsed reactor, with additional 2-MeTHF (5 L) and purged with nitrogen. Ultrapure Si-Thiol Silica Gel (1.69 kg) was added and the reactor purged with nitrogen. The mixture was agitated for 18 h at 25 °C. The reaction was filtered through a Nutsche Filter (2 kg, diatomaceous earth), rinsing with 2-MeTHF (5 L). The material was transferred to a rinsed reactor with an additional 2-MeTHF (5 L) and concentrated in vacuo to ~26 L and the reaction was held until solids had formed. Acetonitrile (48 L) was then added and the mixture was stirred at 25 °C for 2 h. The resultant solids were then collected via Nutsche filter and dried with a nitrogen stream, then with a tray dryer at 50 °C for 10 h to provide **49** (4.55 kg, 77%) as a tan solid. Pd content: 31 ppm. Note: Since most of the Pd had precipitated as Pd black or was removed with the Si-thiol, standard reactor washing techniques (2-Me-THF, water, acetone) were employed to clean the reactor of any residual metal.

A separate sample was prepared for full characterization: $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.07 (br s, 1H), 8.17 (s, 1H), 7.93 (s, 1H), 7.66 (s, 1H), 7.57 (d, $J$ = 8.3 Hz, 2H), 7.40 (d, $J$ = 8.3 Hz, 2H), 5.53 (s, 1H), 3.80 (s, 3H), 2.48–2.41 (m, 2H), 2.35–2.26 (m, 2H), 2.00–1.91 (m, 1H), 1.75–1.63 (m, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 164.4, 146.7, 138.0, 136.0, 134.1, 133.3, 129.2, 125.9, 124.8, 124.6, 122.5, 113.1, 106.6, 75.1, 50.8, 37.2, 12.8. LCMS (ES): calc. for $C_{20}H_{18}ClNO_3$ $(M-H)^-$: 354.1; found: 354.2.

*6-chloro-5-(4-(1-hydroxycyclobutyl)phenyl)-1H-indole-3-carboxylic acid* (**3**): A reactor was purged with nitrogen and charged with THF (9.15 L), **49** (3.05 kg, 8.57 mol), MeOH (9.15 L), and aqueous NaOH (3.43 kg of 50 wt% solution in 6.34 L water). The reactor was heated to 63 °C for 13.5 h then cooled to 30 °C. The reaction was concentrated in vacuo to ~9 L when solids are observed in the reactor. Water (9.15 L, then 30.5 L) was then added, the reactor cooled to 23 °C, MTBE (33.55 L) was added, and the mixture agitated for 15 min then held for 15 min. The phases were split and the aqueous layer was collected. The organic layer was discarded and the aqueous layer was transferred back to the reactor and agitated with MTBE (33.55 L) for 15 min and held for 25 min. The phases were separated and the aqueous layer collected. The aqueous layer was transferred to a rinsed reactor and cooled to 10 °C. Conc. HCl (4.29 kg, 43.5 mol) was added, maintaining a temperature <10 °C. Ethanol (240 g) was added and the mixture held for 2 h (pH = 2.0). The resultant solids were collected via filtration through a Nutsche filter, rinsing with water (46 L). The solids were transferred to a rinsed reactor. Ethanol (40 L) was added and the mixture held at 27 °C with stirring for 40 min until dissolution had occurred. The mixture was filtered through a 10 micron polypropylene filter into another reactor, rinsing with ethanol (9 L). The mixture was concentrated to ~13 L and heated to 76 °C briefly then held at 60 °C. Water was added (13.3 L) and the reactor was held at 58 °C for 15 min, then cooled to 0 °C over 3 h. The resultant solids were collected via Nutsche filter, rinsed with cold water (6.5 °C, 6.1 L), and dried with a nitrogen stream to provide **3** (2.60 kg, 89%) as a tan solid. To convert to the desired polymorph, a reactor was charged with **3** (2.60 kg, 7.60 mol) and ethanol (7.8 L) under nitrogen and held at 25 °C. Water (7.8 L) was added and the mixture stirred for 7 h. The solids were then collected via Nutsche filter and rinsed with water (5.2 L) and dried with a nitrogen stream for 8 h then with a tray dryer at 50 °C for 15 h to provide **3** (2.42 kg, 93% recovery) as a white

crystalline solid consistent with the PXRD pattern for "Form 2." UPLC purity: 99.20%. Residual **48**: below detection limit (<30 ppm). Pd content: 45 ppm. A separate batch was prepared for full characterization: m.p. 192-194 °C. $^{1}$H NMR (400 MHz, DMSO–$d_6$) δ 12.12 (s, 1H), 11.94 (br. d, *J*=2.2 Hz 1H), 8.08 (d, *J*=2.9 Hz, 1H), 7.95 (s, 1H), 7.64 (s, 1H), 7.57 (d, *J*=8.3 Hz, 2H), 7.40 (d, *J*=8.1 Hz, 2H), 5.52 (s, 1H), 2.48–2.40 (m, 2H), 2.35–2.26 (m, 2H), 2.00–1.89 (m, 1H), 1.74–1.63 (m, 1H). $^{13}$C NMR (101 MHz, DMSO–$d_6$) δ 165.6, 146.6, 138.1, 136.0, 133.8, 133.0, 129.2, 125.6, 125.3, 124.6, 122.8, 112.9, 107.6, 75.1, 37.3, 12.8. MS (ES): calc. for $C_{19}H_{17}ClNO_3$ $(M-H)^-$: 340.1; found: 340.3. Analytical (%) calc.: C, 66.77; H, 4.72; N, 4.10; found: C, 66.59; H, 4.71 N, 3.96.

ASSOCIATED CONTENT

**Supporting Information**. Experimental procedures for additional compounds, NMR spectra of key compounds; crystallographic data for **1**; powder x-ray diffraction patterns, polarized light microscopy, and solubility data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

**Corresponding Author**

*Aaron C. Smith, email: Aaron.Smith2@pfizer.com;

*Daniel W. Kung, email: Daniel.W.Kung@pfizer.com;

Eastern Point Road, Groton, CT 06340.

**Author Contributions**

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ABBREVIATIONS

AMPK, 5'-adenosine monophosphate-activated protein kinase; API, active pharmaceutical ingredient; CBS, (R)-(+)-2-Methyl-CBS-oxazaborolidine or α,α-diphenyl-D-prolinolmethylboronic acid cyclamide ester; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; MTBE, methyl t-butyl ether; NIS, *N*-iodosuccinimide; NMP, *N*-methyl-2-pyrrolidinone; Pd-XPhos G2, chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II); Piv, trimethylacetyl; SAR, structure activity relationship; SFC, supercritical fluid chromatography; TMS, trimethylsilyl.

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