Organic Process Research & Development

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Fit-for-Purpose Development of the Enabling Route to Crizotinib (PF-02341066)

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ABSTRACT: A robust six-step process for the synthesis of crizotinib, a novel c-Met/ALK inhibitor currently in phase III clinical trials, has been developed and used to deliver over 100 kg of API. The process includes a Mitsunobu reaction, a chemoselective reduction of an arylnitro group, and a Suzuki coupling, all of which required optimization to ensure successful scale-up. Conducting the Mitsunobu reaction in toluene and then crystallizing the product from ethanol efficiently purged the reaction byproduct. A chemoselective arylnitro reduction and subsequent bromination reaction afforded the key intermediate **6**. A highly selective Suzuki reaction between **6** and pinacol boronate **8**, followed by Boc deprotection, completed the synthesis of crizotinib **1**.

INTRODUCTION

Crizotinib **1** (PF-02341066) is a potent and selective Mesenchymal epithelial transition factor/Anaplastic lymphoma kinase (c-Met/ALK) inhibitor that is currently in phase III clinical trials.[1] As a result of the positive results observed during initial phase I studies in patients with ALK-positive nonsmall-cell lung cancer (NSCLC),[2] the clinical program was rapidly accelerated resulting in a significant increase in API demand. In order to ensure an uninterrupted supply of **1**, the initial enabling route was used to supply >100 kg while the proposed commercial route was developed. Herein we describe the evolution of the enabling synthetic route from a 'fit-for-purpose' process used to supply 1 kg, through to producing >100 kg of crizotinib **1**.

The initial medicinal chemistry route is shown in Scheme 1, and was designed to facilitate late-stage variation of the (hetero)aryl group attached to the pyridine, which is exemplified for a generic range of pyrazole analogues in Scheme 1.[3] Clearly this route was not ideal for the preparation of crizotinib **1**, and once sufficient data was available, it became evident that the desired biological activity resided in the (*R*)-enantiomeric series. Thus, crizotinib **1** was first prepared by the more convergent route shown in Scheme 2. In this modified process, the chiral center was introduced through resolution of alcohol ***rac*-3**,[4] which was converted to aryl bromide **6** via the sequence illustrated in Scheme 1. The aryl bromide was coupled with pinacol boronate **15**, providing efficient access to the desired product **1**. Given the relatively modest demand when the project was transferred into Process Development (around 1 kg), the decision was taken to use the optimized Medicinal Chemistry process (Scheme 2) to prepare **1**, focusing on removing any safety concerns and streamlining product isolations, where possible. As this route proved to be robust and reliable, when the API demand rapidly increased, this route was used to supply material while a separate team developed the proposed commercial manufacturing route.[5]

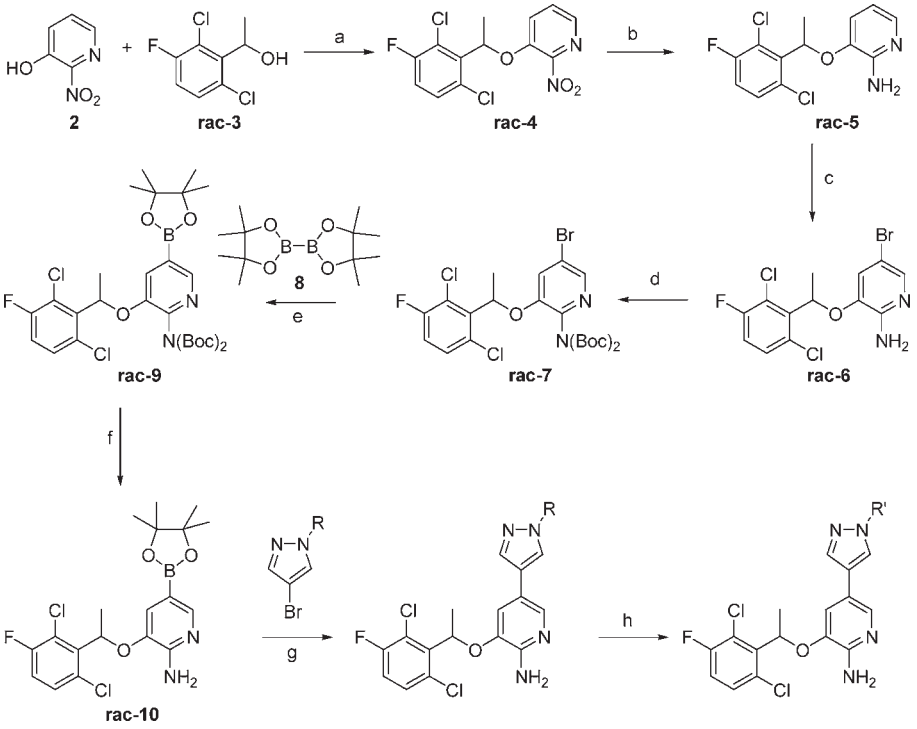
RESULTS AND DISCUSSION

Upon critical examination of the optimized Medicinal Chemistry route (Scheme 2), numerous issues were identified that would need to be addressed prior to scale-up. These will be discussed in more detail, followed by additional modifications that were made as the process was adapted for larger-scale operation.

Synthesis of Boronate 15. The Medicinal Chemistry route used to prepare boronate **15** is shown in Scheme 2 (steps a−c). The first concern was the use of sodium hydride in DMF for the preparation of iodopyrazole **14**. This is a known thermal safety hazard,[6] and so these conditions were deemed unsuitable. Fortunately, alternative conditions were readily identified and implemented—heating a mixture of the mesylate **12**, 4-iodopyrazole **13** and Cs_2CO_3 in NMP at ~80 °C afforded between 85 and 95% conversion after approximately 6 h. Addition of more iodopyrazole **13** and extended reaction times failed to push the reaction

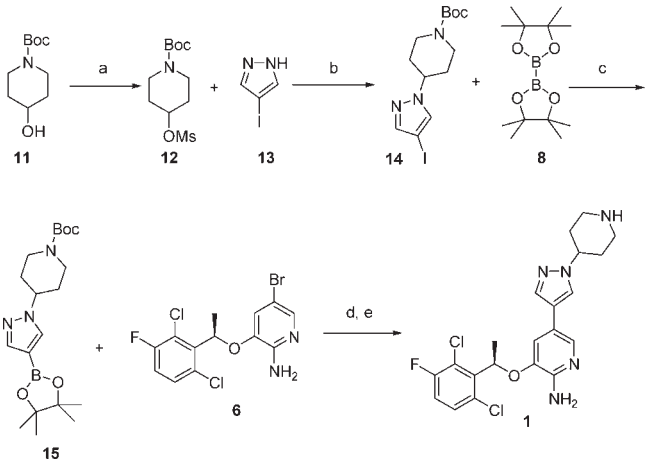
Received: May 17, 2011
Published: June 30, 2011

Scheme 1[a] **Initial medicinal chemistry route to crizotinib analogues**



[a] **Reagents and conditions: (a) Ph_3P, DIAD, THF, 0 °C, 4 h; (b) Fe, AcOH/EtOH, reflux, 1 h; (c) NBS, MeCN, 0 °C, 15 min; (d) $(Boc)_2O$, DMAP, DMF, ambient temperature, 18 h; (e) $Pd(dppf)_2Cl_2$, KOAc, DMSO, 80 °C, 18 h; (f) 4 N HCl, 1,4-dioxane/CH_2Cl_2, 40 °C, 12 h; (g) $Pd(Ph_3P)_2Cl_2$, Na_2CO_3, DME/H_2O, 87 °C, 16 h; (h) deprotection.**

Scheme 2[a] **Optimized medicinal chemistry synthesis of 1**



[a] **Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2; (b) NaH, DMF, 100 °C, 18 h; (c) $Pd(Ph_3P)_2Cl_2$, KOAc, DMSO, 80 °C, 2 h; (d) $Pd(dppf)_2Cl_2$, Cs_2CO_3, DME/H_2O, 90 °C, 3 h; (e) 4 N HCl in 1,4-dioxane, CH_2Cl_2, 0 °C, 4 h.**

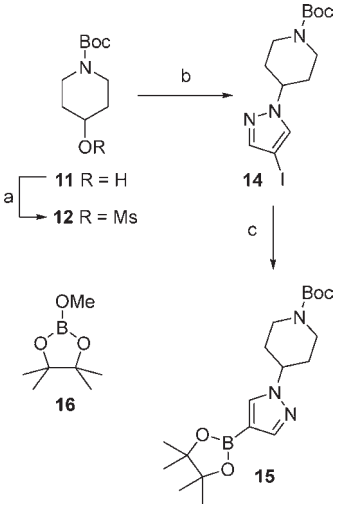
to completion; therefore, the reaction was stopped after 6 h at 80 °C. Addition of water and extraction into MTBE afforded crude product that was crystallized from diisopropyl ether. However, due to safety concerns over the use of diisopropyl ether,[7] this crystallization process was modified to a slow addition of heptane to the MTBE extract. Isolated yields of around 50−60% of **14** were obtained over the two steps . This process was then outsourced to multiple vendors who successfully prepared **14** to support all the manufacturing campaigns described herein.

Palladium-catalyzed boronation of **14** to pinacol boronate **15** suffered from high levels of dimerization upon scale-up. Coupled with the relatively high cost of bis(pinacolato)diboron **8**, it was evident that an alternative process to prepare **15** was required. Fortunately, the Knochel procedure[8] was successful; reaction of iodide **14** with *i*-PrMgCl in THF furnished the expected Grignard reagent, which was quenched with 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **16** yielding **15** in a modest 58% yield after workup, precipitation from heptane and subsequent recrystallization from aqueous ethanol. After the first manufacturing campaign, this step was further optimized. The key modifications were to warm up the initial THF solution to 20 °C to ensure complete consumption of iodide **14**, and direct crystallization of **15** from ethanol−water, thus removing the heptane precipitation. This modified process consistently afforded boronate **15** in 70−80% yield (Scheme 3). Particular care was needed to ensure that sufficient water was added during the crystallization to maximize recovery (a 1:4 mixture of ethanol/water was ideal).

Synthesis of Bromopyridine 6. The medicinal chemistry route to **6** is shown in Scheme 1, and consists of a Mitsunobu[9] reaction of chiral alcohol (*S*)-**3** and 3-hydroxy-2-nitropyridine which proceeded in good yield and with complete inversion of stereochemistry to give the desired ether (*R*)-**4**. Chemoselective reduction of the nitro group with iron and hydrochloric acid (HCl) afforded amine **5**, and regioselective bromination gave the desired product **6**.

dx.doi.org/10.1021/op200131n |*Org. Process Res. Dev.* 2011, 15, 1018–1026

Scheme 3[a] Optimized synthesis of pinacol boronate 15



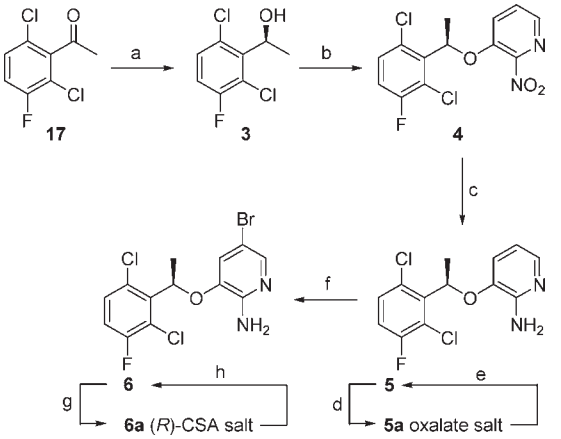
[a] **Reagents and conditions: (a) MsCl, Et_3N, DMAP, MTBE, 0 °C; (b) 13, Cs_2CO_3, NMP, 80 °C; 50−60% (c) (i) 2 M *i*-PrMgCl in THF, 0 °C, then warm to 20 °C; (ii) 16, THF, 20−30 °C, then EtOAc; (iii) EtOH/water cryst, 70−80%.**

For the initial manufacturing campaign, chiral alcohol **3** was prepared via enzymatic hydrolysis of the racemic acetate with pig liver esterase (Scheme 4) as alternative procedures for direct enantioselective reduction of acetophenone **17** afforded little or no selectivity.[4] Recognizing the inherent inefficiency of this resolution approach, significant efforts were invested in developing an alternative process to **3**. These efforts culminated in the successful implementation of a highly selective (>99% ee) and efficient (>99% conversion) ketoreductase process to prepare **3** from **17**.[10] This process was then used to supply chiral alcohol (*S*)-**3** for all subsequent campaigns. One issue is that (*S*)-**3** is a low-melting solid (mp ≈ 38 °C) that required melting in order to charge it from the containers in which it was supplied.

While the Mitsunobu reaction is not ideal for large-scale operations, primarily due to the large quantities of waste generated, alternative displacement processes were hampered by the thermal instability of nitropyridine **2** (safety recommendation is not to heat above 66 °C) and were extremely sluggish and impractical. As a result, the Mitsunobu process was selected for this transformation. The original reaction conditions (Scheme 1) were modified slightly, with the reaction being conducted in toluene rather than in THF. Under these conditions, a significant proportion (80−85%) of the reaction byproduct precipitated from solution as a 1:1 complex of diisopropylhydrazine dicarboxylate and triphenylphosphine oxide[11] and was readily removed by filtration. Despite this, the crude product **4** was still contaminated with a significant waste burden (mainly residual triphenylphosphine oxide and diisopropylhydrazine dicarboxylate).

Due to pressing timelines, the original iron−HCl conditions were used for the first scale-up of the nitro reduction step (Scheme 3, step c), as these were known to be chemoselective and tolerant of the impurities present in crude **4**. After filtration of the byproduct and an aqueous workup, the solvent was exchanged from toluene to ethanol by distillation, and the ethanolic solution of crude **4** was then used directly in the reduction step.

Scheme 4[a] Initial scale-up of the synthesis of 6



[a] **Reagents and conditions: (a) (i) $NaBH_4$, methanol; (ii) Ac_2O, pyridine, 89% (two steps); (iii) pig liver esterase solution, pH 7 phosphate buffer, NaOH; then chromatography, 50%; (iii) LiOH, methanol, 87%. See ref 4 for full details of this process; (b) DIAD, PPh_3, 2, toluene, 0 °C, then EtOH; (c) Fe, HCl, EtOH/water; (d) EtOAc, oxalic acid, then MTBE, reflux; (e) EtOAc, aq NaOH, then heptane, 62%; (f) (i) NBS, MeCN, −5 °C; (ii) $Na_2S_2O_5$, KOH, water; (g) (*R*)-CSA, EtOAc; (h) MTBE, aq KOH, then heptane, 68%.**

Slow addition of 1 M HCl to a mixture of **4** and an excess of iron powder in ethanol, followed by 2 h at reflux afforded complete conversion to aminopyridine **5**; however, the accumulated impurities from both the Mitsunobu and reduction stages meant that aminopyridine **5** was isolated as a dark-brown oil of moderate purity (∼50−60%). A salt screen was conducted, from which the oxalate salt was selected for purification of crude **5**. Treatment of crude **5** with oxalic acid in EtOAc gave the anticipated salt **5a**. This salt was further purified via an MTBE reslurry and was then broken back to **5** with sodium hydroxide and further purified through crystallization from heptane. Using this process, aminopyridine **5** was prepared in 62% overall yield from **3**.

Regioselective bromination of **5** was achieved with *N*-bromosuccinimide (NBS) in acetonitrile at 0 °C. The reaction proceeded rapidly, affording the desired bromopyridine **6**. Accurate control of the reagent stoichiometry was essential as side reactions were observed when a slight excess of NBS was used. The crude product was extracted into ethyl acetate and crystallized as the (*R*)-camphorsulfonic acid (CSA) salt **6a**, to upgrade the ee (from around 98% to >99%) and also remove residual impurities. Pure aminopyridine **6** was then isolated in a moderate 68% yield after salt cleavage (MTBE/KOH) and subsequent crystallization from heptane.

Upon completion of the first manufacturing campaign, a critical assessment of this process indicated several areas that needed improvement prior to further scale-up. These are listed below.

(1) Inadequate purification after the Mitsunobu reaction led to an unacceptable impurity burden resulting in suboptimal conditions being required for the subsequent reduction.

(2) The use of iron/HCl to reduce nitropyridine **4** to aminopyridine **5** would be challenging to operate on scale, and cleaning the iron salts from the reactor was laborious and time-consuming.

(3) Formation of side products during the bromination step resulted in material losses and required purification via salt formation.
(4) Purification of aminopyridines **5** and **6** was accomplished via the formation of salts. While these procedures were required to provide pure **6**, these salt-forming/-breaking steps added significantly to the overall processing time. In addition, material losses occurred at each stage (isolated yields of 62 and 68%, respectively).
(5) Slow phase separations and formation of emulsions during the workup of the bromination reaction were largely due to the water-miscible solvent (acetonitrile) used in this step.

In an attempt to improve the process, the Mitsunobu reaction was investigated in a range of alternative solvents; however, none offered any advantage over toluene. Similarly, alternative phosphines offered no advantage to triphenylphosphine; therefore, the initial reaction conditions were retained. The reaction itself was exothermic and dose-controlled; therefore, a slow addition of DIAD to a mixture of the other components provided clean conversion and a safe process for large-scale operations. No racemization was observed in any of the reactions conducted (from lab to 50-kg scale). The initial workup included an aqueous sodium hydroxide wash to remove excess hydroxypyridine **2**, which generated significant color in the organic phase that proved difficult to remove in later steps. An aqueous hydrochloric acid wash alleviated this color issue, and so was included in the process.

In an attempt to avoid the iron−HCl conditions, catalytic hydrogenation of **4** was examined; however, the residual triphenylphosphine oxide and diisopropylhydrazine dicarboxylate poisoned all the hydrogenation catalysts screened. The key breakthrough occurred when solubility data on nitropyridine **4** showed that it was sparingly soluble in ethanol. Since triphenylphosphine oxide, diisopropylhydrazine dicarboxylate, and their 1:1 complex are all freely soluble in ethanol, this offered a viable process to purify **4** without resorting to chromatography. Upon completion of the Mitsunobu reaction, the toluene solution was filtered to remove the precipitated triphenylphosphine oxide−diisopropylhydrazine dicarboxylate complex. After a series of basic and acidic washes, azeotropic distillation from toluene to ethanol under vacuum (∼50−100 mbar, keeping the temperature below 60 °C) and cooling afforded a thick slurry of **4**, which was isolated in an excellent yield (88%) after filtration and drying. The distillation process took around 24 h on scale-up into the pilot plant.

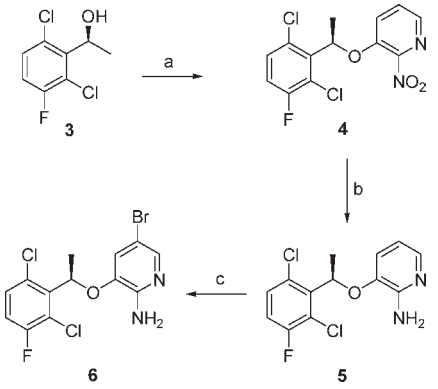
While this was a significant improvement on the previous process and was successfully used for several batches, significant yield losses occurred in the pilot plant as a result of poor phase splits obtained during the aqueous washes. In addition, the multiple aqueous washes were rather slow and somewhat inefficient. With the improved crystallization process in place, the main purpose of the aqueous washes was to remove residual hydroxypyridine **2**. Fortunately, hydroxypyridine **2** is also soluble in ethanol; thus, omitting the aqueous washes had no impact on the purity of isolated product **4** and greatly simplified processing. Therefore, once the reaction was complete, the precipitated byproduct was removed by filtration, the solvent was exchanged to ethanol as before, and the product **4** crystallized in excellent yield and purity. This optimized process was used to prepare significant quantities of **4** (batch sizes of up to 50 kg of **3**) in 80−85% isolated yield. One point to note is that the reaction byproduct (triphenylphosphine oxide−diisopropylhydrazine dicarboxylate complex) does not always crystallize spontaneously during the reaction (a thin haze of diisopropylhydrazine dicarboxylate is always observed). In some cases, seeding was required to ensure that the byproduct complex did indeed crystallize, as this was the most effective method of removing the bulk of the byproduct.

With pure nitropyridine **4** now available, the use of catalytic hydrogenation was re-examined as an alternative to the iron−HCl reduction. Given the potential risk of dehalogenation during hydrogenation of **4**, initial investigations focused on the use of sponge-nickel catalysts, which are much less reactive towards dehalogenation than the corresponding palladium or platinum catalysts.[12] To our delight, hydrogenation of **4** with >5 wt % (preferably 10 wt %) of a sponge-nickel catalyst in methanol was completely chemoselective, and afforded the desired aminopyridine **5**. The reaction proceeded in two distinct stages, consisting of an exothermic reduction of the nitro group to the intermediate hydroxylamine (this is clearly observed by HPLC and ^{1}H NMR analysis of samples isolated at this stage), followed by a much slower reduction of the intermediate hydroxylamine to the aminopyridine **5**. For safety considerations, the initial stage was conducted at ambient temperature, and the heat of reaction was used to warm the reaction mixture to around 30−35 °C. As the observed hydrogen uptake slowed, the mixture was then heated to 50 °C to complete the reduction of the intermediate hydroxylamine to the desired aminopyridine **5**.

In order to develop a suitable isolation and purification process for aminopyridine **5**, preferably as the free base, a range of crystallization options were examined (in addition to a salt screen). From this extensive screen, the optimal process was identified as isolation of the free base **5** from methanol at high concentration and low temperature (the best alternative was addition of heptane to an ethyl acetate solution of **5**). As the hydrogenation reaction was conducted in methanol, this led to a relatively straightforward isolation process. Once the hydrogenation was complete, the spent catalyst was removed by filtration, and the resulting methanol solution of **5** was concentrated to approximately 2 mL/g by distillation. The solution was then cooled to around −10 °C, whereupon the product crystallized and was isolated by filtration. Since aminopyridine **5** has significant solubility in methanol at −10 °C, losses to the mother liquors were relatively high. To minimize these losses, the mother liquors from one batch were added to the posthydrogenation solution of the next batch, prior to concentration and isolation. Using this protocol, a 95% yield was obtained for this reduction and isolation process over four consecutive batches. At this point the impurity burden in the liquors was significant, and they were discarded. This crystallization process removed the need to prepare the oxalate salt **5a** and provided pure **5** in significantly increased yield from chiral alcohol **3** (76−80% vs 62%).

Bromination of aminopyridine **5** proceeded extremely rapidly in acetonitrile, but significant levels of overbromination and other unidentified side products were observed. In addition, severe emulsions occurred during the workup. In order to address these issues, a number of modifications were made to the process. A water-immiscible solvent (dichloromethane, CH_2Cl_2) was introduced to improve the phase separation in the workup. Due to the relatively low solubility of NBS in CH_2Cl_2, and the desire to add NBS as a solution, acetonitrile was retained as a solvent for this reagent.

Scheme 5[a] Optimized synthesis of 6



[a] **Reagents and conditions: (a) (i) DIAD, PPh_3, 2, toluene, 0 °C; (ii) EtOH cryst, 80−85%; (b) (i) H_2, sponge-nickel, MeOH 20−50 °C; (ii) MeOH cryst, 95%; (c) (i) NBS, MeCN/CH_2Cl_2, −15 to −10 °C; (ii) $Na_2S_2O_5$, KOH, CH_2Cl_2/water; (iii) Et_3N, CH_2Cl_2/water; (iv) MeOH cryst, 80−85%.**

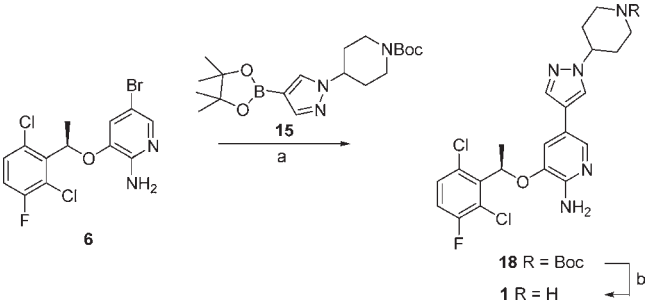
By cooling the reaction down to −15 °C and maintaining it below −10 °C throughout the NBS addition, no overbromination or side reactions were observed. In order to minimize the risk of generating byproduct, careful control of the NBS stoichiometry (1.03 equiv) was required, with all NBS batches being use-tested in the lab prior to scale-up. The reaction itself was rapid, with complete conversion observed immediately following the NBS addition. Using this modified protocol, additional stressing experiments indicated that the bromination reaction was less prone to overbromination and other side reactions. Even with an overcharge of NBS (1.2 equiv) and an increased reaction temperature (up to 0 °C), a clean reaction profile was still obtained. The reason for this improved robustness is not clear and was not investigated further.

In order to minimize the emulsions observed during the workup, the bisulfite quench was reduced, and an additional aqueous triethylamine wash was added to ensure that residual succinimide was purged into the aqueous phase during the workup. A process to crystallize **6** was developed on the basis of the solubility data that showed methanol offered the most favorable properties in this regard (high solubility at elevated temperature and limited solubility at low temperature, plus good purge of impurities). Solvent exchange via distillation from the CH_2Cl_2/acetonitrile mixture post-washing to methanol proceeded smoothly, and the product **6** was isolated from ∼3 mL/g methanol in an excellent 80−85% yield (Scheme 5).

With the introduction of the enzymatic reduction process to prepare chiral alcohol (*S*)-**3** and the improved purity product obtained from the modified process, the chemical and optical purity of **6** was >99%; thus, the purification protocol via the (*R*)-CSA salt was no longer required.

Suzuki−Miyaura Coupling and Deprotection. The conditions used for the Suzuki−Miyaura reaction[13] in the original Medicinal Chemistry process, [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (PdCl_2(dppf)·CH_2Cl_2,) and cesium carbonate in 1,2-DME/water proved acceptable for the first scale-up campaign, with full conversion being achieved within 2.5 h at 50 °C (Schemes 2 and 6). The high loading of catalyst used (3.8 mol %) turned the reaction mixture black. Nevertheless, the separation of the

Scheme 6[a] Optimized synthesis of 1



[a] **Reagents and conditions: (a) (i) PdCl_2(dppf)·CH_2Cl_2, Cs_2CO_3, Bu_4NBr, toluene/water, 70 °C; (ii) cysteine on silica−alumina, toluene, 60 °C; (iii) heptane, 76−80%; (b) (i) HCl, EtOH/EtOAc/CH_2Cl_2; (ii) water; (iii) NaOH, THF; (iv) MeCN/water cryst 75−85%.**

aqueous phase (and washes) postreaction was facile as these were either pale yellow or colorless. Residual palladium was removed by treatment of an ethyl acetate solution of **18** with 10% cysteine on silica−alumina[14] for 16 h at 60 °C. The palladium levels were reduced from ∼5600 ppm to 13 ppm by this process. Pure **18** was then crystallized in 62% isolated yield by solvent exchange to heptane.

While this process worked reasonably well, further scale-up required a few modifications. The main change was to replace the undesirable solvent, 1,2-DME, with toluene in conjunction with a phase-transfer catalyst (Bu_4NBr). This new solvent system enabled a significant reduction in the catalyst loading to be achieved (to 0.8 mol %), and simplified the workup to a straightforward phase separation, as upon reaction completion the product **18** was soluble in toluene. The cysteine on silica−alumina treatment to purge residual palladium was retained; however, the cysteine loading was increased to 15 wt %, and the contact time was extended to ∼25 h. Once this process was complete, the product was crystallized by addition of warm heptane (60 °C) to a warm toluene solution of **18** (60 °C). This modified process consistently afforded pure **18** in around 80% isolated yield.

Initially, deprotection of **18** to **1** was accomplished by treatment with 4 M HCl in 1,4-dioxane/CH_2Cl_2. While the reaction proceeded smoothly, the isolation process was far from ideal, with the main concern being that, after neutralization of an acidic aqueous extract, the product **1** was extracted into THF, and this solution was then concentrated to dryness, whereupon the product spontaneously crystallized as the desired Form A. Since all salt forms investigated were unsuitable, the free base, Form A, was selected for development; therefore, a scaleable process to prepare this form of **1** was required.

Concentrating THF to dryness was not considered a viable option due to the risk of peroxide formation, and in any case variable levels of residual THF were typically retained (1−4%) in the isolated API. A range of alternative crystallization solvents were examined; however, these failed to provide a practical alternative (mostly the product oiled or gummed out of solution upon addition of an antisolvent or when cooled). After some experimentation, a process to precipitate **1** from water was developed and this was used for the first scale-up campaign. The deprotection reaction was conducted with HCl in 1,4-dioxane/CH_2Cl_2, and once complete, water was added and the product **1** was extracted into the aqueous phase. After several

CH_2Cl_2 washes to remove any nonbasic organic impurities, this aqueous HCl solution of **1** was added to a solution of Na_2CO_3 in water, whereupon **1** precipitated from solution, initially as an amorphous gum, but with stirring was converted into a crystalline solid (Form A). After an additional water wash to remove residual inorganic impurities, pure **1** was isolated in 92% yield.

While this process delivered sufficient material to initiate clinical studies, the isolation process was not viable for larger-scale operations; the initial gumming observed presented a risk of damaging the reactor, and the uncontrolled nature of the crystallization of **1** resulted in material with a wide particle size distribution (PSD) that was challenging to formulate. In addition, the use of 1,4-dioxane is severely restricted in our scale-up facilities; therefore, an alternative source of anhydrous HCl was required.

After examining several options, the best source of anhydrous HCl was found to be in situ generation through addition of acetyl chloride to ethanol (making a solution of HCl in a mixture of ethanol and ethyl acetate). Addition of this HCl solution to a solution of **18** in ethyl acetate initially looked promising; however on scale-up, difficulties were encountered as the HCl salt of **1** precipitated from solution as an unstirrable mass. To overcome this, an additional solvent was employed (CH_2Cl_2) to ensure that a mobile slurry of the hydrochloride salt of **1** was formed as the reaction proceeded to completion. Addition of water then gave an acidic aqueous solution of **1**, with efficient removal of nonbasic impurities in the organic phase. Dilution with THF and pH adjustment with sodium hydroxide (to pH > 13) afforded a THF solution of **1** that contained variable levels of water and inorganic impurities.[15] Dilution with ethyl acetate enabled a water wash to be carried out (to remove inorganic salts), and the solvent was then exchanged to acetonitrile by distillation. During this process, **1** crystallized from solution as the desired crystalline form (Form A) in good yield (85−90%) and excellent purity, and this process was used to prepare several batches of **1**. However, with this process the crystallization event was uncontrolled, resulting in a wide PSD. As **1** progressed through development, it became apparent that this product profile would not be suitable for the proposed commercial formulation; therefore, an alternative, controlled crystallization process was required. In addition, some batches were found to contain high levels of inorganic salts, due to inefficient removal during the workup. These batches required a water reslurry to meet residue on ignition specifications.

In order to develop a suitable crystallization process, a series of solubility studies were completed in mixed aqueous/organic solvent systems to identify the best combination for both impurity control and maximum yield. In all of these experiments, only Form A was observed. Solubility measurements in a selection of solvents (acetonitrile, ethanol, isopropanol, and THF) across a range of water content revealed that isopropanol and acetonitrile afforded the best recovery of crystalline **1**. Since the current process had already demonstrated that the solvent exchange into acetonitrile was facile, the decision was made to use aqueous acetonitrile for the crystallization. The solubility curves for **1** in aqueous acetonitrile are shown in Figures 1 and 2.

From the solubility data, it was evident that **1** has maximum solubility at between 20 and 40% aqueous acetonitrile, and at this composition (30%, Figure 2), the solubility has the greatest dependence on temperature. This result suggested that a cooling crystallization was likely to be successful. However, the predicted solubility at ambient and lower temperatures was still significant

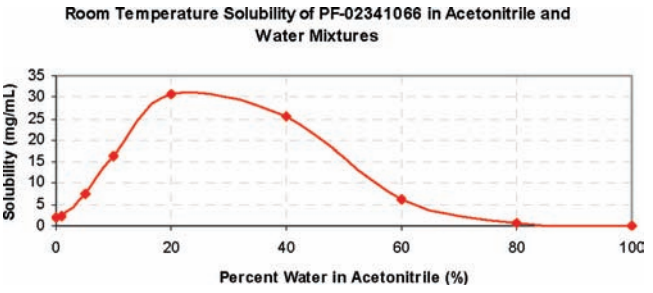


Figure 1. Solubility of **1** in water/acetonitrile mixtures.

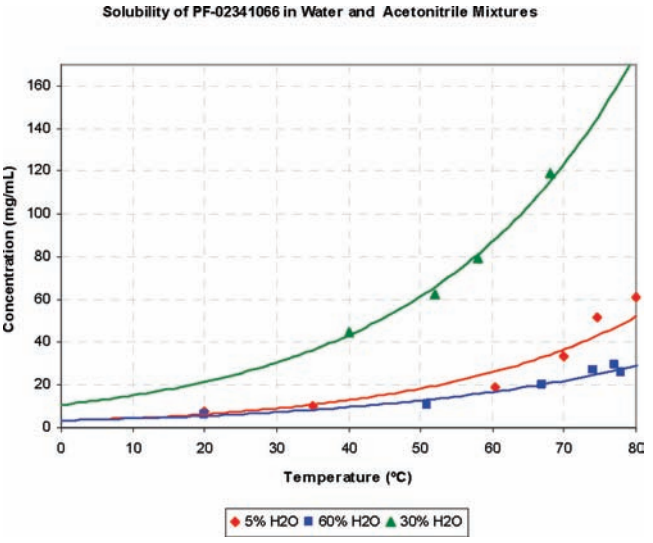


Figure 2. Solubility of **1** in water/acetonitrile mixtures at various temperatures.

(~10 mg/mL at 0 °C); thus, losses to the mother liquors would be significant. Initial lab trials were very promising, with **1** having good solubility in 30% aqueous acetonitrile at reflux and crystallizing in a controlled manner at around 40 °C; however, the recovery was low, and while the PSD was much better defined, the isolated material was unsuitable for formulation as the particles were too large.

Fortunately, both issues were readily overcome. In order to maximize recovery, an initial seed bed of **1** was generated in 30% aqueous acetonitrile at 40 °C, and then the mixture was further diluted to ~70% water content, followed by cooling to 5 °C. This slurry was then subjected to high-shear wet milling to reduce the particle size prior to isolation. Since the isolation solvent contained a relatively high proportion of water, there were no issues with inorganic residues. When utilized on pilot-plant scale, this modified isolation protocol reproducibly generated clinical quality **1** in 75−85% yield.

In conclusion, a robust six-step process for the synthesis of crizotinib **1** has been developed and used to deliver over 100 kg of API in approximately 40% yield from chiral alcohol **3**. The initial 'fit-for-purpose' route used to deliver the first clinical batch was retained; however, extensive modification of the reaction conditions and, in particular, the reaction work-ups and product isolations were made to ensure successful scale-up. Of particular note is the process used for the Mitsunobu reaction, whereby conducting the reaction in toluene, filtering off the precipitated

byproduct, and then crystallizing the product from ethanol efficiently purges the significant quantities of byproduct associated with this reaction, affording the product in high yield and purity.

EXPERIMENTAL SECTION

General Procedures. Intermediates were analysed by reverse phase LC−MS on an Agilent 1100 series instrument, coupled to a Waters Micromass ZQ mass spectrometer according to the following conditions: column SB-C18 3.0 mm × 50 mm i.d., 1.8 μm; eluent A, 0.05% v/v trifluoroacetic acid in purified water; eluent B, acetonitrile; flow rate 1.2 mL/min.; wavelength, diode array (190−400 μm); column temperature, 50 °C; injection volume, 10 μL; at t = 0 min, 5% eluent B; at t = 3.5 min, 100% eluent B; at t = 4.5 min, 100% eluent B; at t = 4.6 min, 5% eluent B. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus spectrometer at 400 and 100.6 MHz, respectively. The quoted melting points for all materials are the onset temperatures observed by DSC.

3-[(1*R*)-1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-2-nitropyridine 4. Containers of chiral alcohol (*S*)-**3** (49 kg, 234.4 mol) were stored in a warming oven at 60 °C for 24 h, during which time the solid melted. The molten **3** was then charged to a reactor containing a solution of 3-hydroxy-2-nitropyridine **2** (33.2 kg, 236.7 mol) in toluene (383.5 L) at 20 °C, and a toluene wash (12.3 L) was used to rinse the containers and charging lines into the reactor. Triphenylphosphine (70.1 kg, 267.2 mol) was added, and the resulting solution was cooled to −15 °C. A solution of diisopropylazodicarboxylate (55 kg, 271.9 mol) in toluene (70.7 L) was then added over 195 min, maintaining a temperature between −20 °C and −10 °C. Toluene (23.6 L) was used as a line wash. The reactor contents were then warmed to 25 °C at a rate of 0.5 °C/min, and the batch was agitated at this temperature for 2 h. Water (4.2 L) was added, and the batch was agitated for 3 h, during which time a dense precipitate formed. The batch was then cooled to −3 °C at a rate of 1 °C/min, then agitated for a further 1 h. The slurry was filtered, and the filter cake was washed with toluene (147 L). The combined filtrate was distilled under vacuum (50−100 mbar) to a residual volume of 196 L, maintaining the internal temperature below 60 °C. Ethanol (196 L) was added, and the resulting solution was distilled under vacuum (50−100 mbar) to a residual volume of 196 L, maintaining an internal temperature below 60 °C. This operation was repeated a further two times using ethanol (2 × 196 L), following which the refractive index of the distillate was NMT 1.38, indicating complete removal of toluene. The temperature was adjusted to 20 °C, and then ethanol (196 L) was added. The resulting slurry was granulated for 1 h; the temperature was then adjusted to 0 °C at a rate of 1 °C/min and the slurry granulated for a further 1 h. The slurry was filtered, the filter cake washed with cold ethanol (49 L; cooled to 0 °C) and then dried to give the *product* **4** (65.4 kg, 84%) as a yellow solid. Mp 98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (dd, J = 4.5, 1.2 Hz, 1H), 7.39 (dd, J = 8.4, 4.5 Hz, 1H), 7.32 (dd, J = 8.8, 4.7 Hz, 1H), 7.23 (dd, J = 8.5, 1.2 Hz, 1H), 7.10 (dd, 8.9, 7.7 Hz, 1H), 6.12 (q, J = 6.7, 1H), 1.86 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 157.5 (d, J = 249.4 Hz), 149.6, 145.1, 139.5, 135.5, 130.2, 128.9 (d, J = 4.3 Hz), 128.2, 123.9, 122.0 (d, J = 19.0 Hz), 117.2 (d, J = 23.7 Hz), 74.6, 18.9. LC−MS: found m/z 330.9, 331.9, 332.9, 334.0, 334.9, 336.0, 336.9 $[M + H]^+$. Anal. Calcd for $C_{13}H_9Cl_2FN_2O_3$: C, 47.15; H, 2.74; N, 8.46. Found: C, 47.31; H, 2.80; N, 8.31.

3-[(1*R*)-1-(2,6-Dichloro-3-fluorophenyl)ethoxy]pyridin-2-amine 5. Sponge nickel (2 kg), methanol (221 L), and nitropyridine **4** (33.4 kg, 101 mol) were charged to a nitrogen-inerted reactor, and the temperature was set to 25 °C. Hydrogen pressure was applied at 1.2 barg until the primary reaction exotherm had subsided; then the temperature was increased to 50 °C at a rate of 0.3 °C/min. The hydrogen pressure was increased gradually to 3.5 barg and the reaction agitated until the hydrogen uptake stopped, signifying reaction completion. The temperature was reduced to 20 °C and the mixture filtered to remove the catalyst, washing with methanol (130 L). The mother liquors from a previous batch were added (∼50 L), and the combined batch was distilled under vacuum (50−100 mbar) to a residual volume of 50 L. The resulting slurry was cooled to −10 °C and granulated for 2 h. The slurry was filtered, and the filter cake was washed with cold methanol (14 L; cooled to −10 °C) and then dried to give the *product* **5** (29.9 kg) as a pale-yellow solid. Mp 109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, J = 4.6 Hz, 1H), 7.29 (dd, J = 8.6, 4.6 Hz, 1H), 7.05 (m, 1H), 6.71 (d, J = 7.9 Hz, 1H), 6.48 (dd, J = 7.7, 5.2 Hz, 1H), 6.02 (q, J = 6.7 Hz, 1H), 4.84 (br s, 2H), 1.83 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 157.4 (d, J = 249.7 Hz), 150.6, 139.8, 139.2, 137.2, 129.9, 128.9 (d, J = 3.7 Hz), 122.0 (d, J = 19.8 Hz), 116.9, 116.5 (d, J = 22.7 Hz), 113.4, 72.5, 18.9. LC−MS: found m/z 300.9, 301.9, 302.9, 303.9, 304.9, 305.9, 307.0. Anal. Calcd for $C_{13}H_{11}Cl_2FN_2O$: C, 51.85; H, 3.68; N, 9.30. Found: C, 51.97; H, 3.68; N, 9.25.

5-Bromo-3-[(1*R*)-1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-pyridin-2-amine 6. A solution of *N*-bromosuccinimide (25.9 kg, 145.3 mol) in acetonitrile (174.2 L) was added to a solution of aminopyridine **5** (42.5 kg, 141.1 mol) in dichloromethane (425 L) at −15 °C over 75 min, maintaining a temperature less than −10 °C, followed by an acetonitrile line wash (29.7 L). The reaction was agitated for 10 min, and then a solution of sodium metabisulfite (13.4 kg, 70.6 mol) and potassium hydroxide (0.264 kg, 4.23 mol) in water (86 L) was added over 10 min; at the same time the reaction temperature was adjusted to 0 °C. A water line wash was then applied (20 L). The reaction mixture was warmed to 20 °C and stirred for 1 h; then the layers were separated. Triethylamine (14.3 kg, 141.1 mol) was added to the lower organic layer, and the solution was agitated for 15 min. Water (59 L) was then added, and following agitation, the layers were separated. The lower organic layer was distilled under atmospheric pressure to a residual volume of 397 L. An atmospheric distill-and-replace operation was performed using methanol (1180 L) added in three portions to achieve <5% acetonitrile in the final distillate and a residual volume of 153 L. The resulting hot solution was cooled to 35 °C at a rate of 0.3 °C/min, and as the temperature reached 50 °C, a seed was added. The slurry was then cooled to −10 °C at a rate of 0.5 °C/min and granulated for 1.5 h. The slurry was filtered, and the filter cake was washed with cold methanol (59.5 L; cooled to −10 °C) and then dried to give bromide **6** (43.1 kg, 80%) as an off-white solid. Mp 103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 1.9 Hz, 1H), 7.34 (dd, J = 8.9, 4.9 Hz, 1H), 7.10 (m, 1H), 6.86 (d, J = 1.9 Hz, 1H), 6.01 (q, J = 6.6 Hz, 1H), 4.84 (br s, 2H), 1.84 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 157.5 (d, J = 249.1 Hz), 149.3, 140.0, 139.5, 136.5, 130.1, 128.9 (d, J = 3.8 Hz), 122.0 (d, J = 19.7 Hz), 120.0, 116.9 (d, J = 23.8 Hz), 106.7, 72.9, 18.8. LC−MS: found m/z 378.8, 379.7, 380.8, 381.8, 382.8, 383.9, 384.8, 385.8. Anal. Calcd for $C_{13}H_{10}BrCl_2FN_2O$: C, 41.08; H, 2.65; N, 7.37. Found: C, 41.05; H, 2.60; N, 6.91.

***tert*-Butyl 4-(4-iodo-1*H*-pyrazol-1-yl)piperidine-1-carboxylate 14.** Triethylamine (250 mL, 1.79 mol) was added to a solution of 4-hydroxypiperidine **11** (153 g, 736 mmol) in MTBE (1.0 L) under nitrogen, keeping the pot temperature below 20 °C. The resulting yellow solution was cooled to −5 to −10 °C, and methanesulfonyl chloride (105 mL, 1.35 mol) was added while keeping the pot temperature below 5 °C. Once the addition was complete, the cooling was removed, and the mixture was warmed to 22 °C and stirred for 1 h. Water (500 mL) was added, the mixture was heated to 40 °C and was phase separated. Heptane (2 L) was slowly added to the retained organic layer, and a white slurry was obtained after a few minutes; this was aged for 1 h. The product was isolated by vacuum filtration and dried under vacuum at 50 °C to afford mesylate **12** (180 g, 88%) as a bright-white solid.

Cesium carbonate (257 g, 790 mmol), 4-iodopyrazole **13** (126 g, 650 mmol) and *N*-methyl-2-pyrrolidinone (NMP, 500 mL) were charged to a 2-L flask equipped with a mechanical stirrer, temperature probe, condenser, addition funnel, and a nitrogen inlet adapter. The resulting slurry was heated to 80 °C, and a solution of **12** (198 g, 708 mol) in NMP (600 mL) was added over 30 min, maintaining a pot temperature of 80 °C. HPLC analysis after 6 h at 80 °C showed ∼16% **13** remaining. Additional **12** (24 g, 86 mmol) was added, and the mixture was stirred at 80 °C for an additional 12 h. The reaction mixture was cooled to 22 °C, at which point HPLC analysis showed ∼10% residual **13**. MTBE (700 mL) and water (700 mL) were added to the cooled mixture, and after a few minutes of vigorous stirring the phases were separated. The retained organic layer was washed with water (4 × 250 mL), heptane (700 mL) was added, and the mixture was seeded. After stirring for 30 min, a slurry had formed, and this was aged for 5 h at 23 °C. The product was isolated by filtration and dried under vacuum at 50 °C, affording *iodide* **14** (141 g, 57%) as a white solid. Mp 97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 (s, 1H), 7.47 (s, 1H), 4.27 (m, 3H), 2.90 (m, 2H), 2.12 (m, 2H), 1.90 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 154.5, 144.0, 131.2, 80.0, 59.8, 55.8, 42.7, 32.3, 28.4. LC−MS: m/z 378 $[M + H]^+$.

***tert*-Butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl]piperidine-1-carboxylate 15.** Isopropylmagnesium chloride (2 M in THF; 108.9 L, 206.5 mol) was added to a solution of iodide **14** (50.3 kg, 133.2 mol) in THF (211.3 L) at −10 °C over 255 min, maintaining a temperature less than 0 °C, followed by a THF line rinse (11.2 L). The temperature was adjusted to 20 °C and the mixture was stirred for 1 h. The resulting solution was transferred to a solution of 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **16** (33.1 kg, 209.2 mol) in THF (222.5 L) over 105 min, maintaining a temperature between 20 and 30 °C throughout the addition. A THF line wash was then applied (20.4 L). The temperature was adjusted to 25 °C and the reaction agitated for 9 h. Ethyl acetate (304 L) was added followed by a solution of water (1.7 L) in THF (41.7 L) over 10 min. A solution of ammonium chloride (77.7 kg, 1451.9 mol) in water (357 L) at 25 °C was then added, maintaining a temperature below 30 °C. The batch was agitated for 30 min then the layers were separated. The lower aqueous layer was removed and the organic layer was distilled under atmospheric pressure to a residual volume of 231 L. An atmospheric distill and replace operation was then performed using ethanol (3 × 337 L), to achieve NMT 1% of either ethyl acetate or THF in the residual solution, and a residual volume of 231 L. The temperature was adjusted to 60 °C, and then warm water (674 L; heated to 60 °C) was added over 5 h, maintaining the temperature between 55 and 65 °C. Following the addition, KF analysis indicated 81.5 wt %/wt water (target = 80 wt %/wt). The batch was stirred for 6.5 h, and then the temperature was ramped down to 20 at 10 °C/h. The resulting slurry was granulated for 9 h and then filtered; the filter cake was washed with water (126 L). The solid was then dried to give *boronate* **15** (40.9 kg, 81%) as a white solid. Mp 95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (s, 1H), 7.75 (s, 1H), 4.27 (m, 3H), 2.90 (m, 2H), 2.14 (m, 2H), 1.91 (m, 2H), 1.49 (s, 9H), 1.33 (s, 12H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 154.6, 145.2, 133.5, 83.3, 79.9, 59.1, 42.8, 32.4, 28.4, 24.8 (signal for C−B not observed). LC−MS: (t_R 3.36 min) m/z 378.1 $[M + H]^+$ boronic ester; (t_R 2.28 min) m/z 296.0 $[M + H]^+$ boronic acid. Anal. Calcd for $C_{19}H_{32}BN_3O_4$: C, 60.49; H, 8.55; N, 11.14. Found: C, 60.39; H, 8.52; N, 11.28.

***tert*-Butyl 4-(4-{6-amino-5-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]pyridin-3-yl}-1*H*-pyrazol-1-yl)piperidine-1-carboxylate 18.** Bromide **6** (49.6 kg, 130.5 mol), pinacol boronate **15** (59.1 kg, 156.6 mol) and tetrabutylammonium bromide (0.38 kg, 1.2 mol) were dissolved in toluene (338.7 L), and the resulting solution was added to a solution of cesium carbonate (140.3 kg, 430.5 mol) in water (301 L) at 22 °C. The resulting biphasic mixture was inerted with nitrogen. [1,1′-Bis-(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (0.96 kg, 1.2 mol) was added to the mixture, and following a second nitrogen inertion, the reaction was heated to 70 °C and agitated for 4.5 h. The mixture was cooled to 25 °C, and the phases were separated. The upper organic layer was diluted with toluene (166 L); then 15% cysteine on silica gel (44.6 kg) was added, and the batch was agitated at 60 °C for 25 h. The slurry was cooled to 22 °C and filtered; the filter cake was washed with toluene (74 L). The filtrate was distilled under vacuum to a residual volume of 318 L. The resulting solution was heated to 60 °C; then warm heptane (662.4 L; heated to 60 °C) was added over 4 h in two roughly equal portions, whilst maintaining a temperature between 55 and 65 °C. The resulting slurry was granulated for 1 h, cooled to 20 °C at a rate of 0.15 °C/min, and then granulated for a further 6 h. The slurry was filtered, the filter cake was washed with heptane (136 L) and then dried to give the *product* **18** (54.4 kg, 75.8%) as a white solid. Mp 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, J = 1.8 Hz, 1H), 7.58 (s, 1H), 7.50 (s, 1H), 7.32 (dd, J = 9.0, 4.9 Hz, 1H), 7.07 (m, 1H), 6.89 (d, J = 1.7 Hz, 1H), 6.09 (q, J = 6.7 Hz, 1H), 4.81 (br s, 2H), 4.27 (m, 3H), 2.92 (m, 2H), 2.16 (m, 2H), 1.94 (m, 2H), 1.88 (d, J = 6.7 Hz, 3H), 1.50 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 157.6 (d, J = 248.3 Hz), 154.6, 148.9, 139.9, 137.0, 135.9, 135.5, 130.0, 129.0 (d, J = 3.6 Hz), 122.6, 122.1 (d, J = 18.9 Hz), 120.0, 119.2, 116.7 (d, J = 22.6 Hz), 115.0, 79.9, 72.5, 59.4, 42.9, 32.4, 28.4, 18.9, LC−MS: found m/z 550.0, 551.0, 552.0, 553.0, 554.0, 555.0, 556.2. Anal. Calcd for $C_{26}H_{30}Cl_2FN_5O_3$: C, 56.73; H, 5.49; N, 12.72. Found: C, 56.97; H, 5.51; N, 12.85.

3-[(1*R*)-1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine 1. Acetyl chloride (67.5 kg, 860.7 mol) was added to anhydrous ethanol (61.2 L, 1048 mol) over 8.5 h, maintaining a temperature between 0 and 5 °C. Following complete addition, the solution was warmed to 20 °C. This acidic solution was promptly added to a solution of **18** (31.4 kg, 57.0 mol) in a mixture of ethanol (31.4 L) and dichloromethane (282.3 L) over 2 h, maintaining a temperature between 0 and 5 °C. Ethyl acetate (14.9 L) was used as a line wash. The reaction was warmed to 25 °C and agitated for 3 h. Water (157 L) was added, maintaining a temperature below

30 °C, and the resulting mixture agitated for 30 min. The layers were separated, and the lower organic layer was re-extracted with water (78 L). The combined upper aqueous layers were extracted with ethyl acetate (157 L). The resulting lower aqueous layer was diluted with tetrahydrofuran (314 L) and cooled to 15 °C; 40% aqueous sodium hydroxide (77.8 L, 1089 mol) was added, maintaining a temperature of 15 °C ± 10 °C, to achieve a final pH >13. Water (19.6 L) was used as a line wash. The phases were separated, and the upper organic layer was diluted with water (62.0 L) and ethyl acetate (157 L). Following agitation the phases were separated, and the upper organic layer was filtered through a 1.0 μm inline filter, using tetrahydrofuran (22.2 L) as a line wash. A distill-and-replace operation was performed using acetonitrile (3 × 314.0 L), to achieve NMT 1% THF and ethyl acetate in the final reactor contents, and a residual volume of 141 L. Following distillation the temperature was adjusted to 72 °C, and water (54.5 L) was added. A KF analysis was conducted to confirm that the water content was in the range 28−32 wt %/wt water (target 30%). The solution was then cooled to 40 °C at a rate of 0.5 °C/min and agitated for 30 min, by which time crystallization had taken place. The resulting slurry was granulated for 1 h. Water (277 L) was then added over 1 h, maintaining a temperature between 35 and 45 °C. KF analysis at this stage indicated the water content was in the range 65−75 wt %/wt water (target 70%). The slurry was cooled to 5 °C at a rate of 0.5 °C/min and then granulated for 3 h. The mixture was then subjected to high shear wet milling using a 2-mm square hole disintegrating head at 4000 rpm until a suitable PSD was achieved (usually 3 h on this scale). The slurry was filtered, and the filter cake was washed with cold acetonitrile (2 × 59.6 L; cooled to 5 °C) and dried to give *crizotinib* **1** (20.7 kg, 80%) as a white solid. Mp 192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, J = 1.8 Hz, 1H), 7.58 (s, 1H), 7.52 (s, 1H), 7.31 (dd, J = 9.0, 4.9 Hz, 1H), 7.06 (m, 1H), 6.89 (d, J = 1.7 Hz, 1H), 6.09 (q, 1H), 4.79 (br s, 2H), 4.21 (m, 1H), 3.26 (m, 2H), 2.78 (m, 2H), 2.17 (m, 2H), 1.90 (m, 2H), 1.87 (d, J = 6.7 Hz, 3H), 1.63 (br s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 157.5 (d, J = 250.7 Hz), 148.9, 139.8, 137.0, 135.7, 135.6, 129.9, 129.0 (d, J = 3.7 Hz), 122.4, 122.1 (d, J = 19.0 Hz), 119.9, 119.3, 116.7 (d, J = 23.3 Hz), 115.0, 72.4, 59.9, 45.7, 34.0, 18.9. LC-MS: found m/z 450.0, 451.0, 452.0, 453.0, 454.0, 455.0. Anal. Calcd for $C_{21}H_{22}Cl_2FN_5O$: C, 56.01; H, 4.92; N, 15.55. Found: C, 56.08; H, 4.94; N, 15.80.

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ACKNOWLEDGMENT

We thank Raymond Chen, Hannah Davies, Craig Donnelly, Jonathan Dunn, David Edwards, Mark Harding, Richard Joyce, Lynne Kalmbach, Nathan Lacher, Nick Pittman, Katie Porter, Mike Rance, Robert Ryan, Stephen Secreast, Ross Wallace, Craig Ward, Xiaobing Xiong, and Adia Zhang for analytical support; Melissa Birch, Dean Brick, Chris Brown, John Draper, Ruth Hardy, Tom Moran, Matthew Morland, and all the pilot-plant operators and analysts are thanked for large-scale support; John Pearce and Clare Crook for Process Safety work; Trevor Newbury and John Deering for hydrogenation support; Jean Cui, Tim Curran, Mark Guinn, Pei Pei Kung, Carlos Martinez, Paul Meenan, Jerry Meng, Lorraine Murtagh, Michael Perry, Paul Richardson, and Bing Shi for useful discussions and support throughout the project.

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