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Development of a Scalable Synthesis of a BTK Inhibitor via C-N and C-C Bond Couplings as an Endgame Strategy

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ABSTRACT. A scalable and convergent synthesis of a BTK (Bruton's Tyrosine Kinase) inhibitor has been developed. Synthetic routes to key intermediates were explored for the scale-up campaign, especially the process for 6-dimethylaminodihydroisoquinolinone, which was prepared *via* a regioselective cyclization of an isocyanate, mediated by $AlCl_3$. Improved routes to key building blocks were demonstrated by expedient multi-kg productions. The target compound was assembled through Pd-catalyzed amidation reaction followed by a Suzuki-Miyaura cross coupling reaction.

KEYWORDS. BTK inhibitor, Dihydroisoquinolinone, Selective cyclization, Friedel-Craft acylation, Pyridone synthesis, Pd-catalyzed amidation, Suzuki-Miyaura cross coupling.

Introduction

Bruton's Tyrosine Kinase (BTK) is a member of the Tec family of tyrosine kinases and an important cell signaling enzyme.[1] Activation of BTK triggers a cascade of signaling events that culminates in the generation of calcium mobilization and fluxes, cytoskeletal rearrangements, and transcriptional regulation involving nuclear factor-κB (NF-κB).[2] Therefore, BTK has been known to be a critical regulator of early B cell development, and mature B cell activation and survival,[3] and it has been clinically validated that B cells play a key role in the pathogenesis of autoimmune and inflammatory diseases.[4] Protein-based therapeutics that deplete B cells showed good efficacy against autoantibody-driven inflammatory diseases such as rheumatoid arthritis.[5] Therefore, inhibition of the protein kinase that is crucial in B cell activation should be a novel approach as useful therapeutics for B cell mediated diseases.[3-5] As good evidence for a role of BTK in autoimmune and inflammation diseases has been already provided by a BTK-deficient mouse model, our Medicinal Chemistry group identified compound **1** shown below as a potent BTK inhibitor (Figure 1), which was selected for further development for the potential treatment of rheumatoid arthritis.[6]

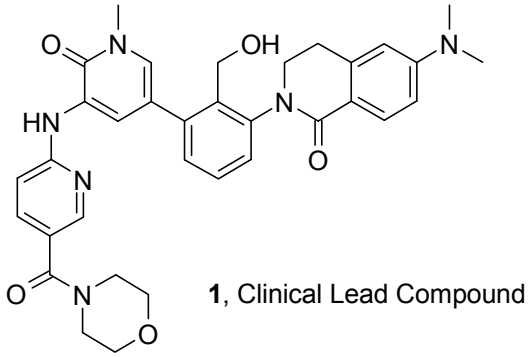


Figure 1. Drug candidate **1**.

The target BTK inhibitor consists of four main key building blocks; selectivity group, linker, core group and front group (Figure 2). Therefore, the synthetic strategy was to develop a process for each component, then assemble them through Pd-catalyzed reactions and S_NAr chemistry. The most

challenging part was the synthesis of the dihydroisoquinolinone derivative, a selectivity group, which was prepared originally by the Medicinal Chemistry group from the corresponding indanone through a Schmidt-type ring expansion,[7] a step deemed unsuitable for direct scale-up due to safety issues and poor selectivity. In an effort to avoid an unsuitable step for scale up, intensive process research activities were undertaken to identify a potential scalable synthetic route. Synthesis of the core group was rather straight forward from a commercially available staring material, but in order to ensure a safe and benign process, the work-up procedure was modified accordingly. In addition, the choice of the linker was very important since it is the pivotal reaction center to construct the whole molecule and also to improve the efficiency of the end game. The selection of 2-bromo-6-chlorobenzaldehyde as a linker provided high selectivity as well as reactivity in the Buchwald C-N bond forming reaction,[8] and the subsequent Suzuki-Miyaura cross coupling[9] was performed to afford the core structure of a BTK inhibitor. Each process and also the crystallization of API will be discussed in detail in this paper.

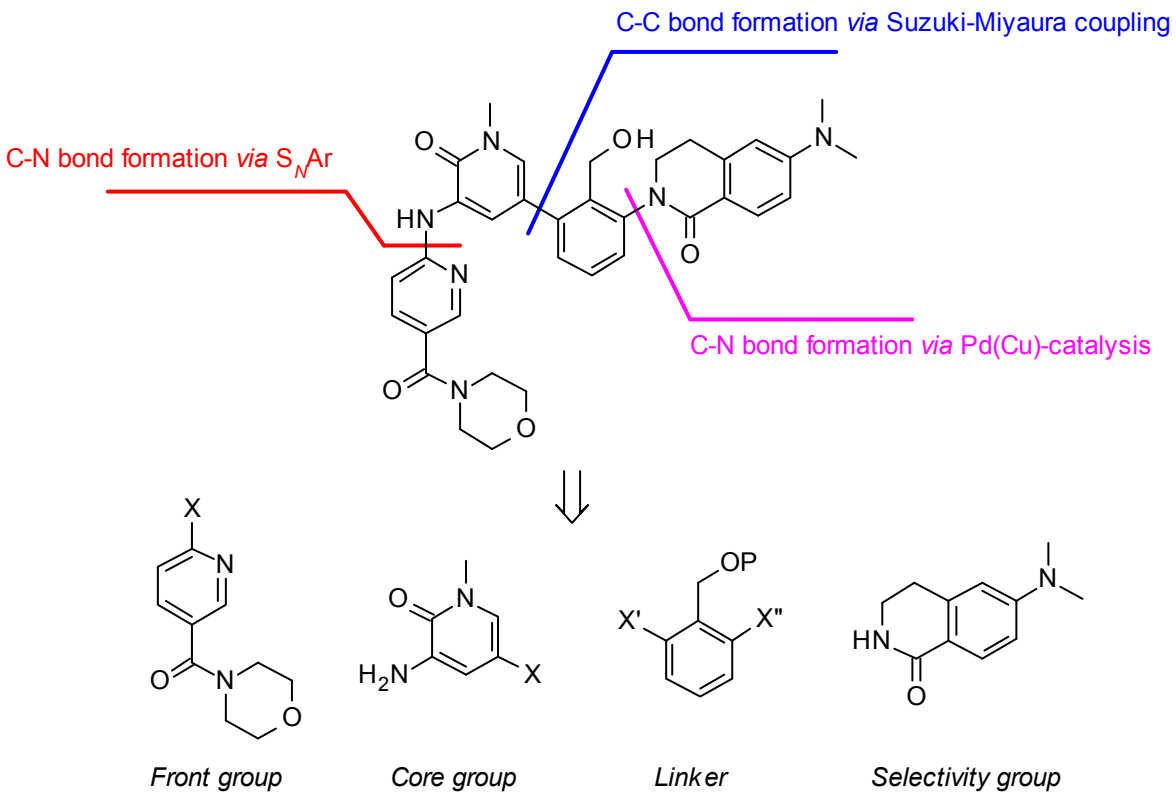
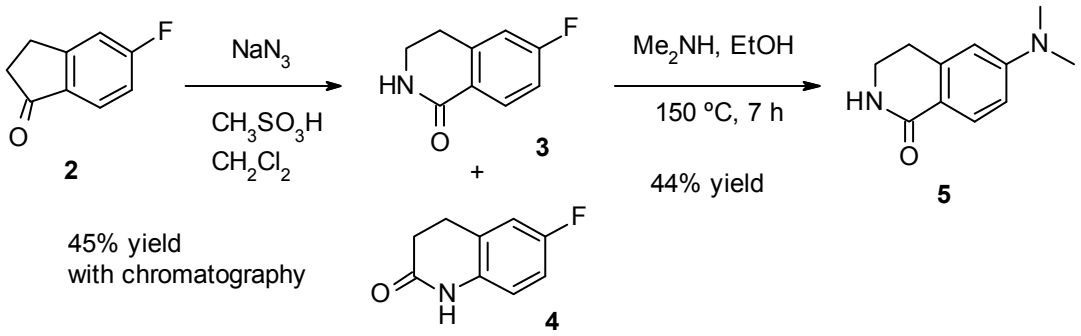


Figure 2. Structural analysis of BTK inhibitor; 4 main subunits.

Results and Discussion

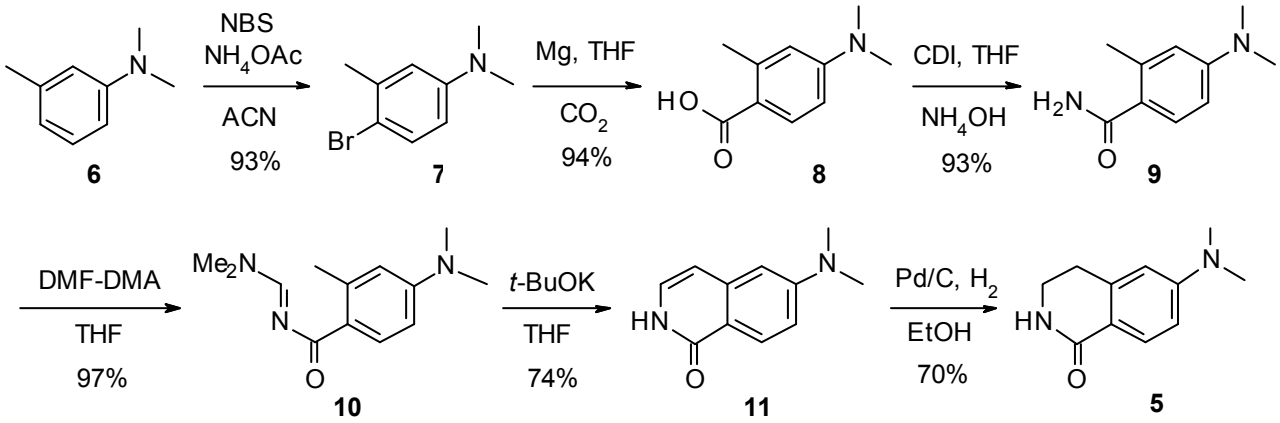
Synthesis of the selectivity group. The original Medicinal Chemistry route for the selectivity group **5** shown in Scheme 1 was not amenable to scale-up due to several issues. First of all, the use of hazardous hydrazoic acid was a significant safety problem. Secondly, lack of selectivity in the Schmidt rearrangement resulted in the generation of a 1:1 isomeric mixture (desired **3** and undesired **4**), that required chromatographic separation, which is not desirable on large scale. Lastly, 4-fluoroindanone (**2**) was a relatively expensive starting material when considering the 27% overall yield of **5**.



Scheme 1. Original Medicinal Chemistry synthesis of *N*,*N*-dimethylaminodihydroisoquinolinone.

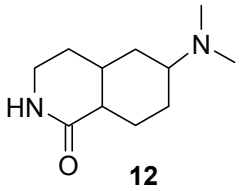
Various alternative syntheses of **5** were pursued. Our first strategy involved the discrete synthesis of the isoquinolinone according to the protocol established by Staab et al.,[10] which utilized cyclization of an acylamidine to build the isoquinolinone scaffold under basic conditions (Scheme 2). Easily accessible dimethyltoluidine **6** was used as the starting material in this first generation approach. Ammonium acetate-catalyzed bromination of **6** in acetonitrile was found to be quite selective and facile. To avoid any significant over-bromination, the reaction was conducted with a slight undercharge of NBS, which resulted in a 93% isolation yield of the desired product. High purity product **7** was precipitated out of the reaction mixture simply by drowning with an adequate amount of water. The halogen–metal exchange reaction of **7** with either *n*-BuLi or *i*-PrMgCl was problematic. However, the corresponding Grignard species was prepared by treatment with Mg in the presence of a catalytic amount of MeMgCl, which was then allowed to react with carbon dioxide by pressurizing the reactor

with carbon dioxide gas at 1-2 psig and maintaining a pot temperature of -15 to 0 °C to yield **8**. The reaction mixture was filtered to remove any unreacted Mg and then treated with a citric acid solution, which caused precipitation of the product in high yield (94%) and high purity (>99%). Benzoic acid **8** was successfully converted to the desired amide **9** *via* sequential treatment with 1 equiv. of CDI at ambient temperature and conc. aqueous NH_4OH in THF. The reaction of amide **9** with a slight excess of DMF-DMA in THF at 60 °C provided the remarkably stable acylamidine **10**, which was isolated by crystallization from heptane after solvent replacement. Cyclization of **10** in the presence of KO*t*Bu in THF proved to be rather sluggish, but could be driven to >96% completion at 60 °C over 24 h. Crystalline **11** was isolated in 74% yield by quenching the crude reaction mixture with 20% citric acid, separating the phases and replacing the organic phase solvent with ethanol. This synthetic sequence was straightforward, and all reactions were successfully demonstrated on a multi-kg scale.



Scheme 2. The first generation process route.

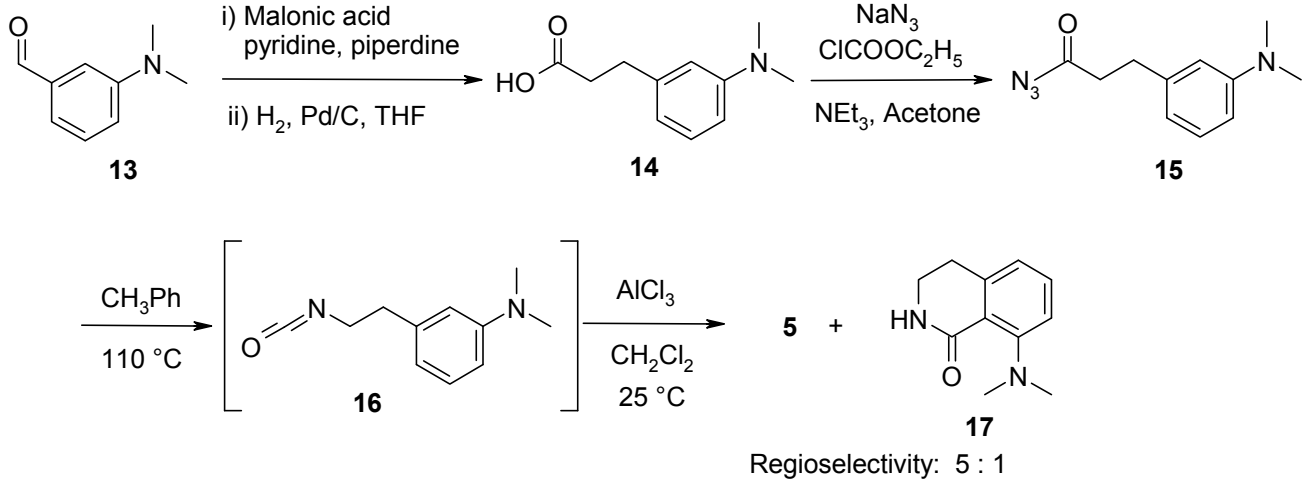
The final hydrogenation turned out to be a little more challenging as it also generated small quantities of the over-hydrogenated byproduct **12** (Figure 3).[11] We also could not afford to carry unreacted **11** into the next reaction since it would cause the Pd-catalyzed amidation to stall. The need of multiple isolations was an additional factor to lead us to seek alternative, more efficient approaches to **5**.



12

Figure 3. Structure of over-hydrogenated byproduct.

An intramolecular Friedel–Crafts cyclization was viewed as a viable way to access the dihydroisoquinolinone scaffold. Acyl azide **15** was prepared from aldehyde **13**, and then a Curtius rearrangement[12] of **15** and subsequent cyclization of isocyanate **16** with $AlCl_3$ in CH_2Cl_2 at ambient temperature produced a mixture of **5** and **17** in only a 5:1 ratio (Scheme 3). Poor selectivity was also observed with a bromo-isocyanate. An isocyanate containing a fluorine substituent was then considered as a potential substrate for this cyclization, given that fluorodihydroisoquinolinone **3** undergoes aminolysis to give the desired product **5** based on the Medicinal Chemistry route. This modification led to improve efficiency in the synthesis of **5** (Scheme 4).



13 **14** **15** **16** **17**

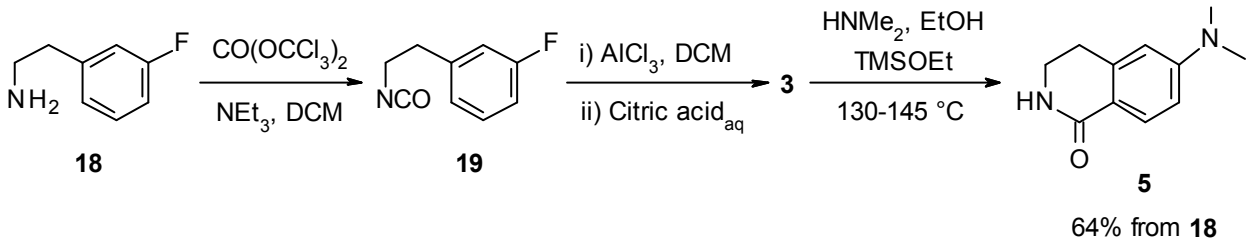
Scheme 3. Exploration of Friedel-Craft cyclization to dihydroisoquinolinone structure.

The precursor of the Friedel–Crafts cyclization, isocyanate **19**, was prepared from commercially available fluorophenethylamine **18**. The formation of isocyanate **19** proceeded smoothly at or below 10 °C employing 0.35 equiv. of bis(trichloromethyl)carbonate and 1.05 equiv. of triethylamine.[13] The

precipitated triethylammonium chloride salts were largely removed by filtration, then a crude solution of **19** (>95% purity by AN GC) could be carried directly into the next step. Alternatively, the DCM solution of **19** could be washed with water and dried over sodium sulfate with minimal hydrolysis. Isocyanate **19** was smoothly converted to **3** *via* addition of the crude DCM filtrate to a slurry of $AlCl_3$ (3 equiv.), followed by stirring at ambient temperature for 12–16 h. After the addition of 4:1 citric acid/water (3 equiv.), the crude product was obtained as a solution in DCM (typically 85–90% pure by AN HPLC). High regioselectivity was achieved in this $AlCl_3$-mediated Friedel–Crafts acylation such that it gave the desired cyclized product **3** exclusively.[14]

Fortunately, the crude DCM solution of **3** again could be carried directly into the amination step, which had already been demonstrated by the Medicinal Chemistry group. However, the conversion of **3** to dihydroisoquinolinone **5** was conducted using a modification of the existing Medicinal Chemistry protocol (**3** + excess 33 wt% dimethylamine in EtOH at 150 °C in a sealed tube) in order to match the capabilities of existing fixed equipment in our pilot plant. On a 20-g scale, the aminolysis reaction was conducted at 130 °C in a stirred Hastelloy C autoclave using 4–5 equiv. of dimethylamine. At pressures ranging from 120 to 160 psig, the reaction was complete within 16 h. However, the fact that one equivalent of fluoride will be released during the aminolysis could lead to etching of the glass-lined autoclave under the rather vigorous conditions employed. The etching test with glass coupons confirmed this possibility as the glass surfaces of the samples were seriously degraded. This observation of significant glass erosion prompted an investigation of alternate means to effect this transformation that would be more compatible with existing equipment. The possibility of a direct S_NAr-type displacement using metal amides was initially explored. In a small scale reaction, a THF solution of **3** was added to a preformed suspension of 3 equiv. of $LiNMe_2$ in THF/hexane at 0–10 °C and the resulting mixture was allowed to warm to ambient temperature. Complete conversion of **3** to the lithium salt of **5** was typically observed within 3 h. However, the extreme reactivity of $LiNMe_2$ as a solid precluded its use on larger scale, necessitating in-situ formation of the reagent from *n*BuLi and

dimethylamine. Also, the presence of fluoride salts interfered with the crystallization of **5** from EtOH or EtOH/water mixtures.

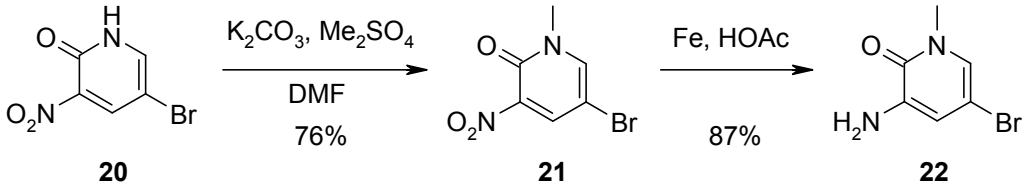


Scheme 4. The second generation synthesis of **5**; a highly selective telescoped process.

Another approach to render the aminolysis of **3** compatible with the glass-lined autoclave would be to scavenge the fluoride ions generated from the reaction mixture as they form. To this end, several experiments incorporating TMSOEt as a component of the reaction mixture were performed in Parr Hastelloy pressure vessels containing samples of the DeDietrich glass liner. On a 10–50-g scale, addition of 1.5–3.0 equiv. of the silane to the standard aminolysis mixture had no adverse effect on the course of the substitution reaction other than a modest reduction in apparent reaction rate. However, the glass liner samples were recovered essentially intact, even upon prolonged heating at 145 °C. Complete conversion of **3** was observed within 24–36 h. In addition, the absence of fluoride salts in the crude reaction mixture rendered isolation of the product *via* concentration much more efficient, providing 60–75% first crop yields of high quality crystalline material (> 99% by AN HPLC). This added benefit provided a compelling rationale for the choice of the protocol to be scaled up. Therefore, aminolysis of the crude fluoroarene **3** produced in the pilot plant was conducted in the 35-L glass-lined autoclave using 1.5 equiv. of TMSOEt and 4 equiv. of dimethylamine at 135–140 °C (maximum internal pressure 130 psig). Due to the limited reactor volume, the reaction was carried out in three portions, with each cycle lasting 36–48 h. No significant corrosion of the reactor liner was detected. The combined solutions were concentrated by distillation at ambient temperature to give 6.1 kg of **5** (64% yield) after

filtration and drying. This whole 3 step process was performed in a telescope manner with only one isolation step (Scheme 4).

Preparation of the core group and front group. The core group, 3-amino-5-bromo-1-methyl-2H-pyridone (**22**), was prepared from the corresponding bromonitropyridone **20** via methylation followed by iron reduction (Scheme 5). A minor modification was made to the Medicinal Chemistry route, which used methyl iodide as the methylating agent and Cs_2CO_3 as the base initially.

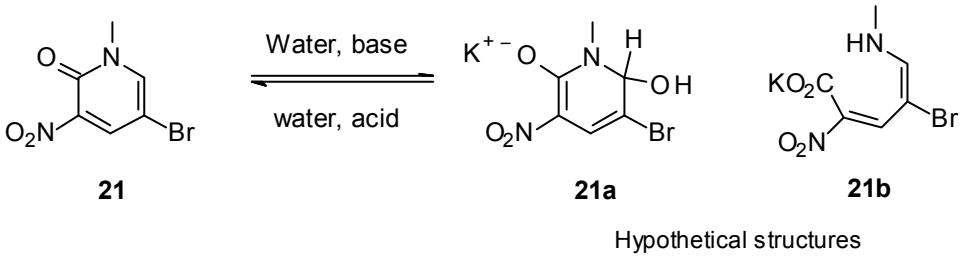


Scheme 5. Synthesis of the core group, 3-amino-5-bromo-1-methyl-2H-pyridone (**22**).

Methylation was carried out by treating **20** with dimethyl sulfate and K_2CO_3 in DMF (Scheme 5). As an initial isolation procedure, the crude product crystallized upon the addition of water, and then it was slurried in EtOAc/*n*-heptane (1/1) to remove 5–10% of the isomeric *O*-methylated product.[15] This simple operation afforded an orange colored solid in 98% purity as judged by AN HPLC. Interestingly, the subsequent iron reduction showed only around 60% yield despite the lack of any significant byproducts. Upon closer examination of **21**, *via* elemental analysis, however it was found that the isolated solid contained about 15 wt% of potassium. Moreover, examination of the UV spectrum revealed completely reversible pH sensitivity, which indicated significant changes in the conjugation of the π–system. In anticipation of scale up, it was standard practice to evaluate concentrated reaction mixtures and isolated intermediates by DSC, which showed the isolated product decomposed exothermically above 100 °C, and that led us to reevaluate the process.

The potassium content, low yield for the subsequent step, and the pH sensitive UV spectrum observations led to the hypothesis that due to excess base in the methylation reaction, hydroxide was

added to the electron-deficient pyridone to give **21a** or, alternatively, a ring-opened product **21b**, which should be in equilibrium with **21** depending upon the pH (Scheme 6).[16]



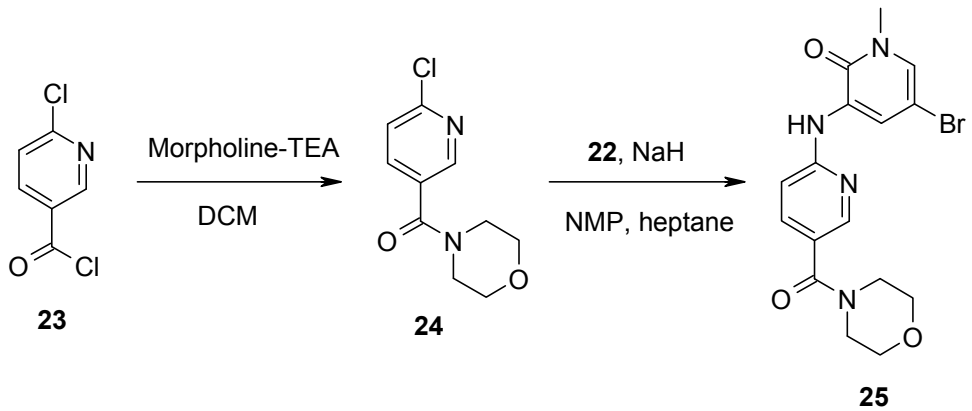
Scheme 6. pH dependent equilibrium of the intermediate **21**.

Working with this hypothesis, the procedure was modified in order to isolate **21** safely. In the new procedure, upon consumption of **20**, the heterogeneous mixture was filtered to remove insoluble salts. A small volume of toluene was then added, followed by concentrated sulfuric acid. Lastly, water was added to precipitate **21** as large crystals. These modifications on work-up procedure allowed for the direct isolation of pure **21**, which had no thermal instability upon heating, and removed up to 10% of the isomeric *O*-methylated byproduct completely.

The reduction of the nitro group was also optimized. Initially, **21a** was subjected to reduction with iron powder in acetic acid at 35 °C, leading to complete reaction within 30 min. However, with pure **21**, the iron reduction stalled. One hypothesis was that some base is required to push the reaction to completion. Therefore, after the iron powder, as slurry in acetic acid, was activated by the addition of a small amount of hydrochloric acid, a small amount of sodium hydroxide was added to generate sodium acetate, which was reliably demonstrated to increase the rate of reaction and to prevent the reaction from stalling near the end. Once the iron activation and NaOH addition was complete, the DCM solution of **21** was added at the rate to maintain the reaction temperature in the range of 30-40 °C. The most important modification was to move away from trying to remove the unwanted iron salts by filtration at the end of the reaction. It was found that the iron salts contaminated **22**, regardless of the volume of solvent used to wash the filter cake. Fortunately, it was discovered that the iron salts could be

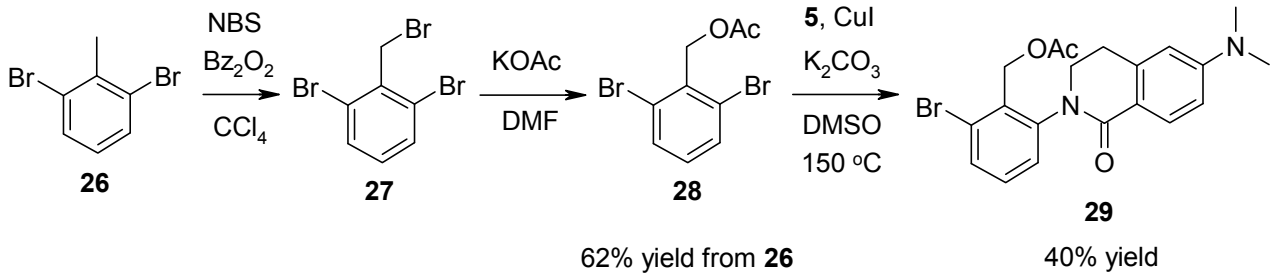
effectively removed by adding 2 M aqueous citric acid to the dichloromethane suspension, which gave an easily separable two-phase mixture. Subsequent wash with water and 2 M sodium citrate gave a tan to brown clear solution of **22** in dichloromethane. The product was then isolated from this solution by concentration and solvent replacement with heptane. Residual iron levels were generally <100 ppm, and the material routinely passed elemental analysis. This two-step protocol was successfully demonstrated at a 20-kg scale and resulted in a 76% yield for the methylation and an 87% yield for the reduction to give 11.7 kg of **22**. Safety was considered as this was an addition controlled process and a flame arrester was incorporated into the reactor train that diluted any hydrogen gas generated with 50-100 volumes of nitrogen.

The preparation of the front piece **24** and coupling with **22** was rather straightforward, starting from acid chloride **23** (Scheme 7). After amide formation with **23** and morpholine in presence of triethylamine, the solution of amide **24** was then combined with amine **22**. The solvent was removed by distillation with concurrent addition of toluene for azeotropic drying. Toluene was subsequently replaced with NMP. The final NMP solution was chilled and added to a slurry of sodium hydride in heptane to afford **25** (90% yield, >99% purity by AN HPLC).[17] Scale up considerations were guided by ARSST testing and the use of a flame arrester in the plant runs to handle the hydrogen generated from NaH.



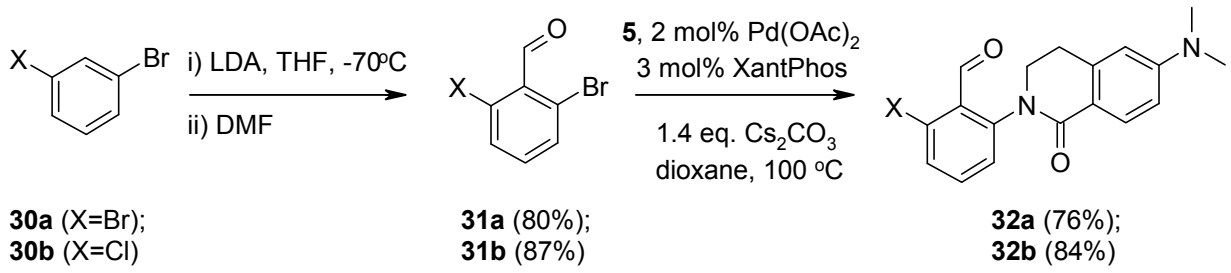
Scheme 7. Synthesis of the front piece **24** and coupling with **22**.

Synthesis of the linker and coupling with the selectivity group. The original Medicinal Chemistry procedure to construct the right side of molecule utilized 2,6-dibromobenzyl acetate (**28**) as the linker, which was prepared from 2,6-dibromotoluene (**26**) through a radical benzylic bromination and subsequent substitution with potassium acetate (Scheme 8). Then, the C-N bond forming reaction with **5** was catalyzed by CuI.[18]



Scheme 8. First generation synthesis of the linker and the C-N bond forming reaction.

The Cu-catalyzed reaction was problematic since it proceeded in only poor yield even with a high catalyst loading (40 mol%) and vigorous heating for several days. Therefore, we sought a more robust palladium catalyzed C-N bond formation, and also explored alternative linkers. Keeping in mind that we needed another metal catalyzed C-C bond formation process and an alcohol functional group at the end, 2,6-dibromobenzaldehyde (**31a**) was considered a better choice for the linker in terms of a facile oxidative addition in the metal catalyzed reactions and a subsequent simple transformation of the aldehyde group to an alcohol. Low-temperature lithiation of 1,3-dihalobenzene **30** produced an aryllithium species that was allowed to react sequentially with DMF and aqueous acid to give **31**. In the initial attempt with **31a**, Buchwald's amidation was directly adopted for the coupling with the selectivity piece, **5**, to afford the desired product (Scheme 9).[8, 19]



Scheme 9. Second generation linker and Pd-catalyzed C-N bond forming reaction.

However, excess of **31a** was required to obtain reasonable selectivity in amidation. Even with 2 molar equivalents of **31a**, significant amount of double-amidation product was detected on HPLC (Table 1, Entry 1). The reaction with 4-5 molar equivalents of **31a** showed acceptable selectivity in Buchwald's amidation (Table 1, Entry 3 and 4). This initial study was implemented in multi-gram scale reaction to demonstrate Pd-catalyzed C-N bond formation, and excess **31a** was easily removed by a single crystallization (Scheme 9).

Table 1. Pd-catalyzed C-N bond forming reaction of dibromobenzaldehyde (**31a**).[a]

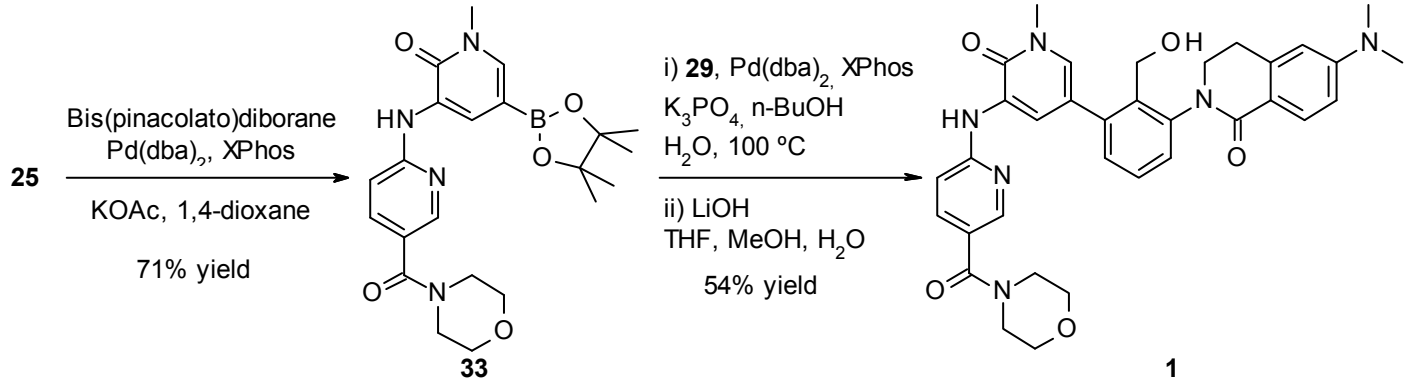
Entry	Molar equivalent of 31a	HPLC yield of 32a (%)	HPLC yield of double-amidation (%)	Isolation yield of 32a (%)[b]
1	2	78	16	Na
2	3	83	12	53
3	4	88	7	79
4	5	90	6	78

[a] reaction conditions; **5** (1.0 mmol), $Pd(OAc)_2$ (0.02 mmol), Xantphos (0.03 mmol), Cs_2CO_3 (1.4 mmol), and 1,4-dioxane (2 mL). 100 °C, 16 hr. [b] isolation by column chromatography (EtOAc/Heptane).

However, further exploration for a more suitable linker found that 2-bromo-6-chlorobenzaldehyde (**31b**) provided much better selectivity in the amidation step, where only around 2-3% of double-amidation product was detected on HPLC and completely removed by crystallization at the end.[20] XantPhos was found to be an effective ligand for the C-N bond formation reaction while X-Phos gave only very poor reactivity. And dppf also showed comparable reactivity but gave a slower reaction rate. Only a slight excess of **31b** (1.2 equiv.) was needed to give full conversion, and Buchwald coupling of

31b with **5** was successfully demonstrated with a 2% catalyst loading to produce multi-hundred grams of **32b**, which was crystallized from the reaction mixture by simple water drowning at 70 °C and isolated in 84% yield and >97% HPLC purity (Scheme 9).

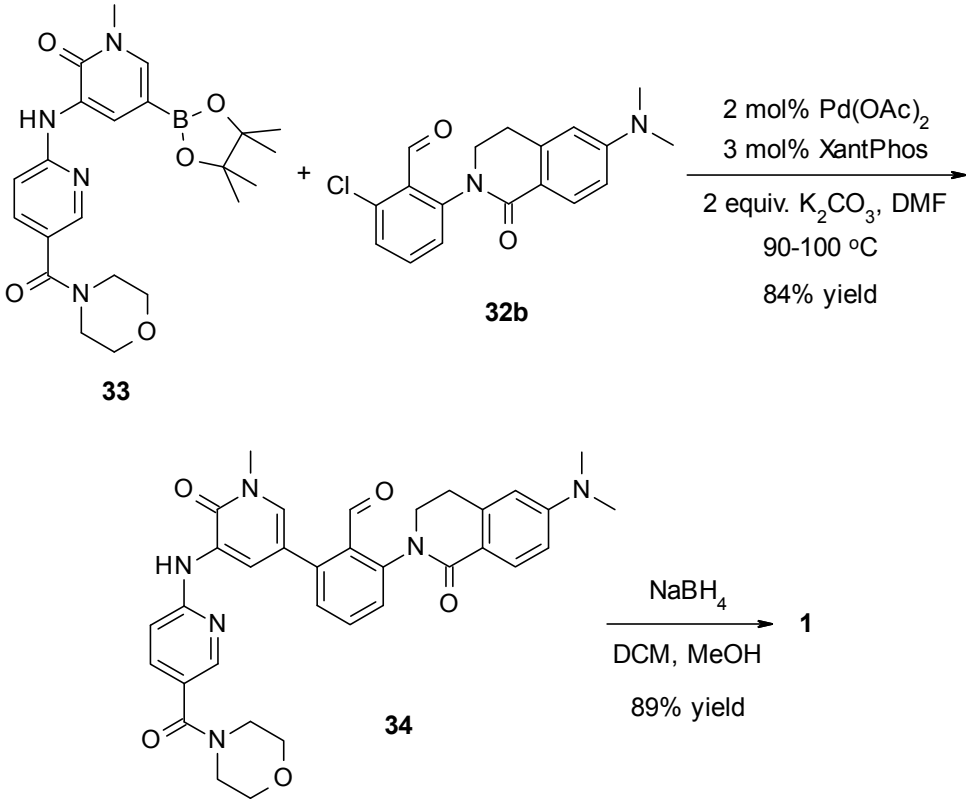
The final assembly: Suzuki-Miyaura cross coupling. As the end game, a Suzuki-Miyaura cross coupling completed the build of the main skeleton of compound **1**.[9, 21] The original coupling reaction was carried out with **29** and the corresponding boronate ester **33**, which was prepared from **25** using standard Miyaura borylation conditions. Final hydrolysis then afforded the target compound in 54% yield over 2 steps (Scheme 10). Even though the yield of the Miyaura borylation was increased to 80% through reaction optimization, the overall yield of the final sequence was too low.



Scheme 10. The original Med. Chem. protocol for the end game.

As an efficient amidation with bromo-chlorobenzaldehyde **31b** had been developed, the final coupling reaction between aryl chloride **32b** and boronate ester **33** was carefully examined. Whether the reaction was run under dry or partially aqueous condition, de-boronation of starting material **33** was a constant problem when 1,4-dioxane was used as the main solvent. Also, a significant volume of 1,4-dioxane was needed to obtain a reasonable conversion, otherwise the coupling reaction stalled. Unlike dioxane, reactions using X-Phos or XantPhos as the ligand in anhydrous DMF gave reliable and clean reaction profiles with little or no de-boronation of **33**. Because XantPhos was used in the Buchwald amidation, it was selected as the preferred ligand over X-Phos in the hope that the Buchwald amidation might

eventually be telescoped to the Suzuki–Miyaura coupling. Therefore, the Suzuki-Miyaura cross coupling was carried out with 2 mol% $Pd(OAc)_2$, 3 mol% XantPhos and 2 equiv. K_2CO_3 in DMF at 90–100 °C for 12 h and, upon completion of reaction, the mixture was cooled, diluted with water and extracted with dichloromethane. The organic extract was diluted with heptane to cause selective precipitation of the homo-coupled byproduct of **33**, which was then removed by filtration. Thereafter the filtrate was diluted with acetone to induce a slow crystallization of **34**. Removal of DCM by distillation led to formation of a slurry of **34** in acetone, which was then cooled and filtered to afford the desired product **34** in >98% HPLC purity and 84% isolated yield (Scheme 11).



Scheme 11. Suzuki-Miyaura coupling reaction with Ar-Cl **32b** and subsequent reduction to the API.

Finally, aldehyde reduction was achieved with $NaBH_4$ as the reducing agent. Since the solubility of crystallized aldehyde **34** was quite low in most organic solvents, except DCM, DMF, DMA, or DMSO, dichloromethane containing a small amount of methanol was selected as the reaction solvent, and

pellets of $NaBH_4$ were used in order to achieve better control of the reaction as the pellets dissolve slowly in the DCM/MeOH mixture. After the reduction was complete, 20% aqueous $NaHSO_3$ solution was added to precipitate the palladium, which was removed by filtration through a short pad of Solka-floc.[22] The desired product **1** was crystallized from IPA or IPA/MIBK in 87% isolated yield on a half-kg scale. This end-game turned out to be quite efficient as compared to the original Medicinal Chemistry route. However, during the reduction step, one unexpected impurity was observed and subsequently identified to be the fused cyclic compound **36**, and the origin of which was traced back to the Suzuki-Miyaura coupling reaction (Figure 4).[23]

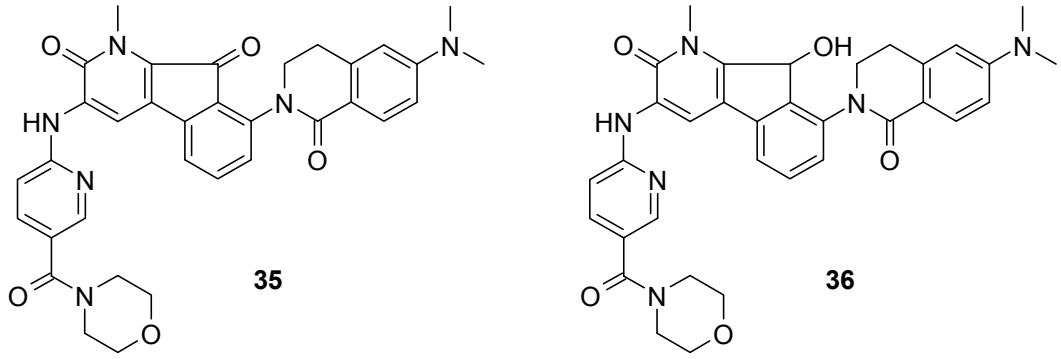
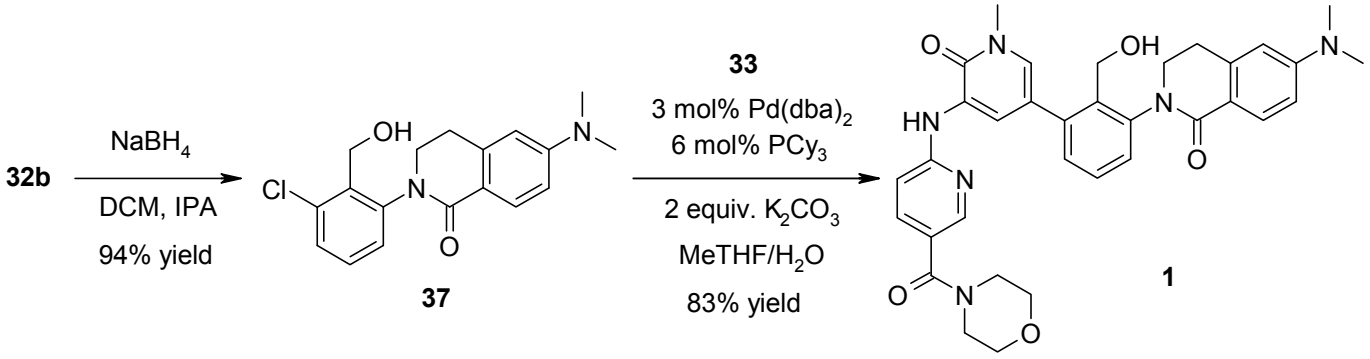


Figure 4. Impurities identified in Suzuki-Miyaura coupling reaction.

Around 3-5% of the byproduct **35** was generated in the coupling step in a multi-hundred gram scale reaction, which was then converted to the corresponding alcohol **36** in the subsequent $NaBH_4$ reduction. Fortunately, in this case it was possible to purge this impurity during the crystallization, but when the coupling reaction was allowed to proceed for another 15 h, the amount of **35** formed increased to 20% by HPLC analysis. Therefore, it was necessary to investigate methods to suppress this side reaction or an alternative end-game approach based on the fact that the reaction time is prone to increase upon further scale up. In a preliminary study, *N*-protection of **33** with a BOC group blocked the undesired cyclization during the Suzuki-Miyaura coupling reaction, but it caused hydrolysis of the morpholine amide during the BOC deprotection. On the other hand, this undesired cyclization could be prevented if the aldehyde functional group was not present, as it seems to be labile in this coupling condition.

Therefore, the reaction order was changed such that the aldehyde group in **32b** was reduced first to give the corresponding benzyl alcohol **37**, which was then coupled with the boronate ester **33** to give the final product (Scheme 12).



Scheme 12. Completion of synthesis of BTK inhibitor **1**.

As one of coupling partners had been modified to incorporate a more electron-rich aromatic ring, a more basic phosphine ligand was needed to achieve a facile oxidative addition. After a quick screen of phosphine ligands, tricyclohexylphosphine and $Pd(dba)_2$ proved to be an quite efficient catalytic system for this coupling reaction.[24] In addition, running the coupling in MeTHF gave a comparable reactivity and a much cleaner reaction profile as compared to DMF.[25] After the reaction was complete, the crude product was isolated by water drowning, followed by treatment with aqueous $NaHSO_3$ solution and activated carbon to remove palladium. Finally, the target API was crystallized from IPA as an IPA solvate in 83% yield and 99% HPLC purity. No byproduct **36** was observed in this final sequence, and all other usual impurities including des-boro and des-chloro compounds were effectively purged during the crystallization.

Initially, it was quite difficult to obtain compound **1** as crystalline material. Even after intensive studies to identify a suitable crystalline form for development, only amorphous material had been isolated. Subsequently, ultra-sonication was suggested as a potential solution to produce crystalline material of **1**.[26] Ultra-sonication in EtOH for 15 min successfully gave a crystalline EtOH solvate

(Figure 5). Seed crystals generated in this manner then led to the development of a more conventional crystallization method for the API.

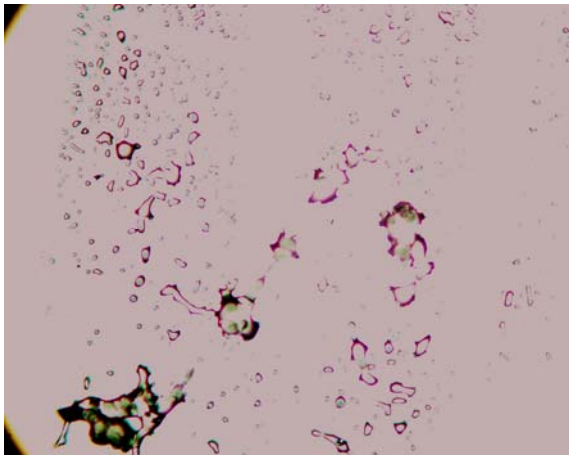
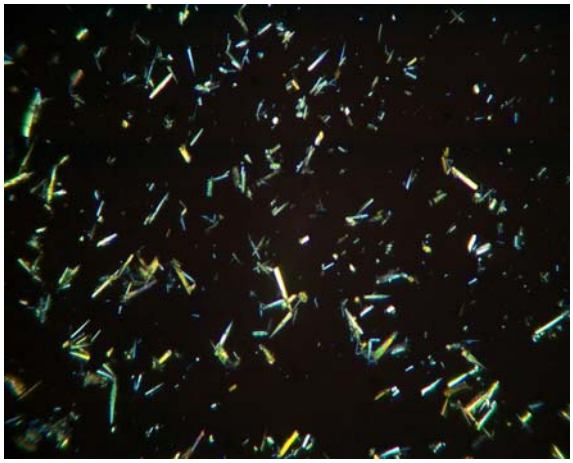
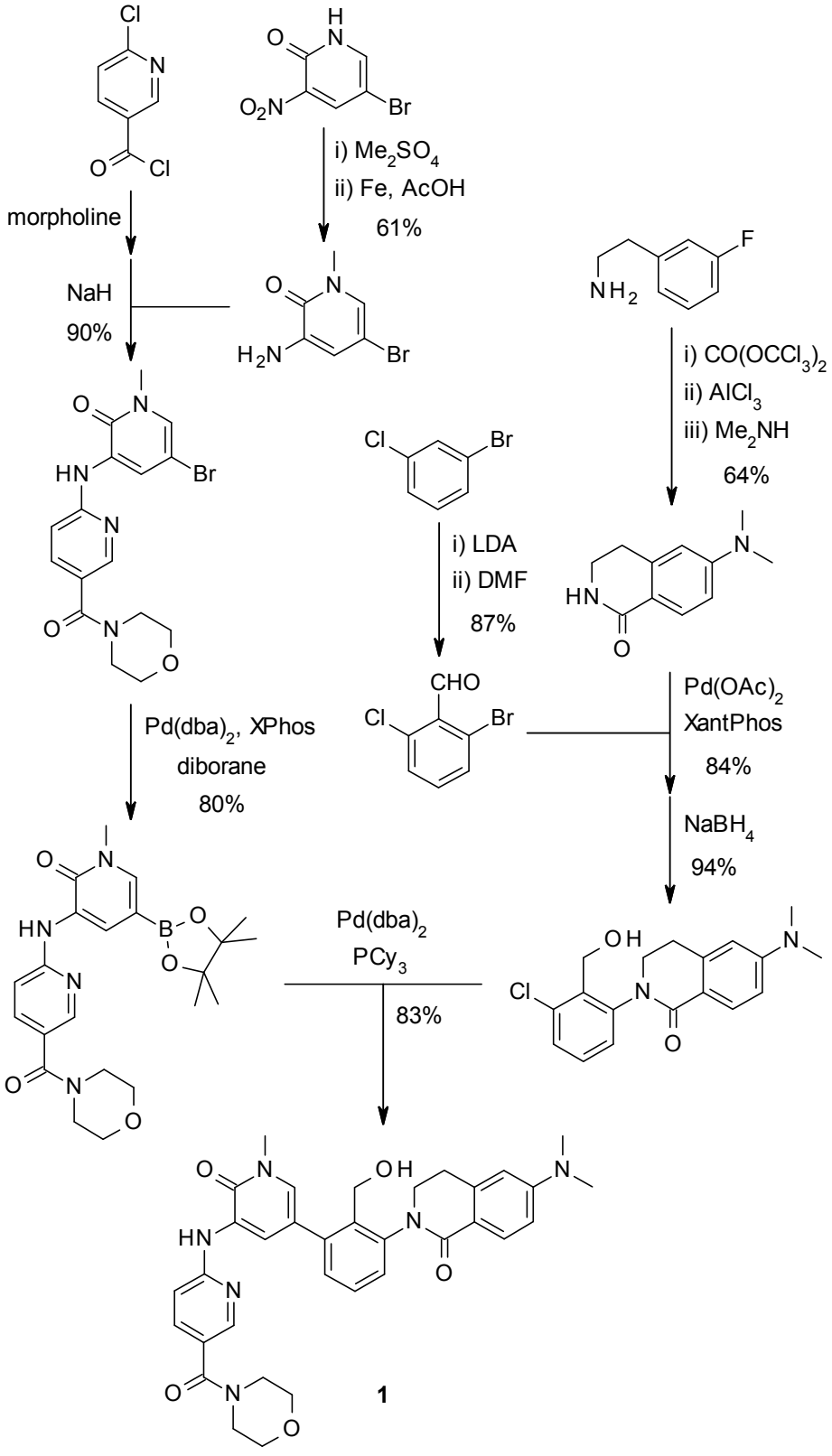
(a)  (b) 

Figure 5. Micro-spectrographs of (a) the amorphous form and (b) the crystalline EtOH solvate.

It turned out that compound **1** had a tendency to form various solvates such that a crystalline IPA solvate was also obtained *via* the ultra-sonication technique. This IPA solvate was subjected to tumbling experiments in diverse solvents and, since the IPA solvate was thermodynamically unstable, it generated new crystalline forms in various solvents. In particular, stirring a suspension of the IPA solvate in MIBK for 6 d gave crystalline non-solvated material, which was determined to be the most stable form (Form A) with a high onset temperature at 265 °C in DSC. Even though ultrasound induced crystallization in MIBK alone did not yield crystalline material, Form A was reproducibly obtained from ultra-sonication in a MIBK/IPA (8/2) mixture. With this initial seed material in hand, a conventional crystallization method was subsequently developed. However, the solubility of Form A was extremely poor in water as well as in bio-relevant media and, moreover, the bioavailability of Form A was too low (dog PK study, F = 2.5%, 20 mg/kg). On the other hand, the crystalline IPA solvate (Form B) showed good kinetic solubility in bio-relevant media and acceptable bioavailability in dog (F = 49%, 20 mg/kg). Therefore, the IPA solvate was selected for the toxicology studies even though it contained 9 wt% of IPA.



Scheme 13. The final process for a BTK inhibitor **1.**

The final process to synthesize a BTK inhibitor **1** was depicted in Scheme 13. We were able to avoid the use of hazardous hydrazoic acid and eliminate column chromatographic separation by developing scalable novel synthesis of key intermediate. And Pd-catalyzed amidation under Buchwald's conditions significantly improved a C-N bond forming step in terms of yield and selectivity with a suitable linker. The end game was refined to minimize impurities in the final API, and crystallization method of API was developed to obtain the desired solid state form. Most of steps were successfully demonstrated with multi-kg scale in the pilot plant campaign. Further fine optimization of reaction conditions and full safety assessment of couples of exothermic steps would be necessary in the next stage of process development.

Conclusion. A modified, scalable, convergent synthesis of BTK inhibitor **1** was developed in order to supply the required API for non-clinical safety studies. An efficient and robust, telescoped process for the preparation of **5** was developed that proceeded *via* a regioselective $AlCl_3$-mediated cyclization. Improvements were made in the synthesis of **25**, and a new linker group showed quite good reactivity in the Pd-catalyzed amidation, as well as the Suzuki-Miyaura cross coupling reaction. As a result of all these process improvements, the target compound was synthesized in 42% overall yield from 3-fluorophenethylamine.

Experimental Section.

General. All HPLC analyses were carried out using a Waters 2690 liquid chromatography system equipped with a Zorbax SB-C8: 3.0 x 100 mm column Component A 0.1% TFA in water; Component B 0.1% TFA in acetonitrile, Gradient 10% to 90% B from 0 to 3 minutes: Hold 90% B for 5 minutes, Flow Rate, 1.2 mL/min. All GC analysis were carried out using an Agilent 6890 system equipped with a DB-5MS column, 15m x 0.25 mm, 0.25 µm. packing (serial # US5326631A), He @ 7 PSI, 60 °C (2 min.) 15 °C/min to 300 °C, hold 2 min. FID, 300 **°C.** LC/MS analyses were carried out using an Agilent 1100MSD system equipped with an electrospray ionization source, nitrogen drying gas = 13 l/min@350 °C, nebulizer @ 60 psi, capillary voltage = 4 kV, fragmentor = 70V.

6-Dimethylamino-3,4-dihydro-2H-isoquinolin-1-one (**5**) A reactor was charged with triphosgene (5.2 kg, 17.5 mol) and dichloromethane (28 L), and the solution was cooled to 0 °C. A dichloromethane (14 L) solution of 3-fluorophenethylamine (**18**, 7.0 kg, 50 mol) and triethylamine (5.3 kg, 52.5 mol) was added at <10 °C. During the addition, precipitation of triethylammonium chloride occurred. Upon reaction completion (conv. >99%), the salts were removed by filtration to provide a crude solution of **19** (>95% purity by GC) in DCM, which was then added to a slurry of $AlCl_3$ (20 kg, 150 mol) in dichloromethane (28 L), followed by stirring at ambient temperature for 12–16 h. After addition of 4:1 citric acid:water (36 kg) and phase separation, the crude **3** was obtained as a solution in DCM (90% pure by HPLC). DCM was then removed by distillation at 40 °C under the slightly reduced pressure while EtOH (30 L) was being added. The resulting EtOH solution was subjected to aminolysis with 33 wt% aqueous dimethylamine (27 kg, 200 mol) in the presence of TMSOEt (8.9 kg, 75 mol) at 135–140 °C. The reaction was carried out in three portions, with each cycle lasting 36–48 h. Upon completion of the aminolysis (conv. >99%), the combined solutions were concentrated by distillation at ambient temperature until onset of crystallization. After further concentration, ramped cooling, filtration and drying, 6.1 kg of **5** (64% yield) was isolated as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) 7.63 (d, J = 8.6 Hz, 1 H), 7.46 (s, 1 H), 6.60 (dd, J = 2.6, 8.7 Hz, 1 H), 6.50 (d, J = 2.5 Hz, 1 H), 3.31 (td, J = 2.8, 6.4 Hz, 2 H), 2.95 (s, 6 H), 2.79 (t, J = 6.4 Hz, 2 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 165.4, 152.3, 140.5, 128.5, 116.8, 109.8, 109.3, 33.9, 28.5; ESI-HRMS calc'd for $C_{11}H_{15}ON_2$ $(M + H)^+$ 191.11789, found 191.11770.

5-Bromo-1-methyl-3-nitro-1H-pyridin-2-one (**21**) A reactor was charged with 5-bromo-3-nitro-1H-pyridin-2-one (**20**, 20 kg, 91.3 mol), K_2CO_3 (18.9 kg, 137 mol) and DMF (80 L), and the resulting slurry was cooled down to –5 °C. Dimethyl sulfate (13.8 kg, 109.6 mol) was added slowly over 1.5 h at <15 °C. Upon completion of the addition, the mixture was warmed to ca. 25 °C, stirred for 12 h and filtered to remove inorganic salts. The filtrate was diluted with toluene (21 L) and acidified with sulfuric acid (5 kg), then water (100 L) was slowly added to crystallize the product. Finally, filtration, followed by washing with water (20 L) and toluene (20 L) afforded the desired product **21** (16.3 kg, 69.9 mol, 76%

yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) 8.58 (dd, J = 2.8, 7.8 Hz, 2 H), 3.57 (s, 3 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 152.9, 147.0, 140.4, 137.9, 92.9, 38.0; ESI-HRMS calc'd for $C_6H_6O_3N_2Br$ $(M + H)^+$ 232.95563, found 232.95560.

3-Amino-5-bromo-1-methyl-1H-pyridin-2-one (**22**) Iron powder (325 mesh, 11.2 kg, 200 mol) and acetic acid (36 kg, 600 mol) were added to a reactor, and to the resulting slurry was added conc. HCl (400 mL) and 50% aqueous NaOH (5 kg) to activate the iron. (**CAUTION**: Hydrogen will be evolved.) A solution of **21** (15.5 kg, 66.5 mol) in dichloromethane (150 L) was then added in a controlled fashion while maintaining a temperature of 35 °C. Upon completion of the reaction (2 h at 35 °C), 2M aqueous citric acid (120 kg) was added to dissolve the majority of the resulting iron salts. The organic layer was separated and washed with water (50 L). The water layer was back-extracted once with a small volume of dichloromethane (40 L). The combined organic layers were then treated with a solution of 2M aqueous citric acid (112 kg) and 50% aqueous NaOH (50 kg), the pH of the mixture was adjusted to 8-10, and the organic layer was separated and filtered. The filtrate was concentrated under vacuum and once crystallization had initiated, heptane (160 L) was added. The resulting slurry was cooled to 0 °C, then filtered and dried to afford **22** (11.7 kg, 57.8 mol, 87% yield) as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) 7.15 (d, J = 2.6 Hz, 1 H), 6.46 (d, J = 2.5 Hz, 1 H), 5.46 (b, 2 H), 3.41 (s, 3 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 156.0, 139.3, 123.9, 111.3, 98.1, 36.6; ESI-HRMS calc'd for $C_6H_8ON_2Br$ $(M + H)^+$ 202.98145, found 202.98140.

5-Bromo-1-methyl-3-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-1H-pyridin-2-one (**25**) A reactor was charged with 6-chloro-nicotinoyl chloride (**23**, 9.8 kg, 55.7 mol) and DCM (75 L) consecutively. After cooling to 5-10 °C, TEA (11.6 kg, 114.7 mol) was added, followed by the addition of morpholine (5.5 kg, 63.1 mol) while keeping the temperature below 30 °C. Upon completion (conv. >99% within 1 h), water (48 L) was added to quench the reaction. After extraction, the organic layer was transferred to another reactor containing solid **22** (10.0 kg, 49.3 mol). The solution was concentrated by distillation at atmospheric pressure while adding toluene (230 L) until the pot volume reached approximately 90 liters to remove residual water. After completion of the distillation, the

solution was cooled to 20 °C, then NMP (82 L) was added and the resulting mixture was re-concentrated under vacuum to a volume of approximately 90 liters. Once the distillation was complete, the concentrated mixture was cooled to 5-10 °C. NaH (60 % dispersion in mineral oil, 3 x 2 kg) was charged to a second, dry reactor. Then, heptane (17 L) was added, and the jacket was cooled to 5 °C. The solution containing **22** and **24** was transferred to the resulting slurry of NaH in heptane. (**CAUTION**: hydrogen will be evolved here and at the quench point). The temperature increased to 62 °C. The reaction mixture was cooled, then stirred overnight at 15-20 °C. Upon completion of the reaction (conv. >99%), a solution of water (3.3 L) and NMP (40 L) was slowly added to the reaction mixture. After all the remaining NaH was quenched, additional water (186 L) was added slowly. After ca. 27 L of water had been added, crystallization occurred. Once the addition of water was complete, the resulting slurry was stirred for 1.5 h and then filtered. The filter cake was washed with water (240 L) and dried under vacuum at 70 °C to give **25** (17.4 kg, 44.2 mol, 90% yield) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) 9.07 (s, 1 H), 8.71 (d, J = 2.6 Hz, 1 H), 8.35 (d, J = 2.5 Hz, 1 H), 7.69 (dd, J = 2.3, 8.7 Hz, 1 H), 7.59 (d, J = 2.5 Hz, 1 H), 7.40 (dd, J = 0.6, 8.7 Hz, 1 H), 3.62 (b, 4 H), 3.53 (s, 3 H), 3.52 (b, 4 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 167.3, 156.1, 155.5, 146.3, 136.7, 131.2, 128.5, 122.7, 119.7, 112.5, 97.3, 66.1, 37.2; ESI-HRMS calc'd for $C_{16}H_{18}O_3N_4Br$ $(M + H)^+$ 393.05568, found 393.05550.

2-Chloro-6-(6-dimethylamino-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-benzaldehyde (**32b**) A reactor was charged with **5** (258 g, 1.36 mol), 2-bromo-6-chloro-benzaldehyde (**31b**, 358 g, 1.63 mol), $Pd(OAc)_2$ (6.1 g, 27.2 mmol), XantPhos (23.6 g, 40.8 mmol), and Cs_2CO_3 (620 g, 1.90 mol). After the reactor was degassed under vacuum and purged with nitrogen 3 times, 1,4-dioxane (3.6 L) and the reaction mixture was heated to reflux for 5.5 h. Once the reaction was complete (conv. >99%), the solution was cooled to 70 °C, and water (2 L) was added slowly while the temperature was maintained at 70 °C to effect crystallization. The resulting slurry was cooled to ambient temperature, filtered, washed with 1:1 water:1,4-dioxane, and dried under vacuum to afford the desired product **32b** (375 g, 1.14 mol, 84% yield) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) 10.02 (s, 1 H), 7.68 (m, 2

H), 7.49 (m, 2 H), 6.66 (dd, *J* = 2.7, 8.8 Hz, 1 H), 6.58 (d, *J* = 2.6 Hz, 1 H), 3.95 (b, 2 H), 3.08 (t, *J* = 6.3 Hz, 2 H), 3.01 (s, 6 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 188.7, 164.1, 152.8, 144.4, 140.7, 133.9, 132.1, 130.2, 129.5, 128.2, 125.0, 115.6, 110.0, 109.0, 49.2, 28.3; ESI-HRMS calc'd for $C_{18}H_{18}O_2N_2Cl$ $(M + H)^+$ 329.10513, found 329.10500.

1-Methyl-3-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-5-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-1H-pyridin-2-one (**33**) Bromopyridone **25** (600 g, 1.53 mol), potassium acetate (granule, 898 g, 9.15 mol), palladium acetate (3.4 g, 15.3 mmol), X-Phos (14.5 g, 30.5 mmol), and bis(pinacolato)diboron (542 g, 2.14 mol) were charged to a suitable vessel, and the atmosphere exchanged with nitrogen. In a separate vessel, 1,4-dioxane (8 L) was degassed by heating to reflux, cooled to near ambient temperature, and then added to the reaction mixture by vacuum transfer. The resulting mixture was heated to 95–100 °C. Once the reaction was complete (conv. >99%), the mixture was filtered hot to remove excess salts. The filtrate was then concentrated by distillation to about half the original volume, and then diluted with heptane (3 L) at 90 °C to induce crystallization. The resulting slurry was cooled to ambient temperature and filtered. Washing with a minimal volume of 50% heptane in 1,4-dioxane, and drying in a vacuum oven afforded the desired product **33** (537 g, 1.22 mol, 80% yield) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) 8.80 (s, 1 H), 8.57 (d, *J* = 1.8 Hz, 1 H), 8.30 (d, *J* = 2.2 Hz, 1 H), 7.63 (dd, *J* = 2.4, 8.7 Hz, 1 H), 7.61 (d, *J* = 2.0 Hz, 1 H), 7.30 (d, *J* = 8.3 Hz, 1 H), 3.62 (b, 4 H), 3.58 (s, 3 H), 3.54 (b, 4 H), 1.29 (s, 12 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 167.4, 158.0, 156.0, 146.5, 137.8, 136.6, 133.5, 129.7, 122.0, 121.1, 111.9, 83.6, 66.3, 66.1, 37.2, 24.6; ESI-HRMS calc'd for $C_{22}H_{30}O_5N_4B$ $(M + H)^+$ 441.23038, found 441.23000.

2-(3-Chloro-2-(hydroxymethyl)phenyl)-6-(dimethylamino)-3,4-dihydroisoquinolin-1(2H)-one (**37**) The benzaldehyde derivative **32b** (100 g, 0.30 mol) was dissolved in DCM (500 ml) in a reactor, then IPA (300 ml) was added. The solution was cooled to 5 °C, then $NaBH_4$ (4.6 g, 1.22 mol) was added portion wise over 1 h. Upon completion of the reduction as indicated by HPLC (conv. >99%), the reaction was quenched with 10% aqueous ammonium chloride solution (300 ml). After the DCM was removed by distillation, the desired product was precipitated from IPA/H_2O. The resulting slurry was

stirred at 80 °C for 2-3 h, then slowly cooled to ambient temperature. Filtration, washing with a minimal volume of 1:1 IPA:H_2O, and drying under vacuum at 80 °C afforded **37** (94.7 g, 0.29 mol, 94% yield) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) 7.71 (d, J = 8.6 Hz, 1 H), 7.45 (dd, J = 1.6, 7.9 Hz, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.30 (dd, J = 1.5, 7.5 Hz, 1 H), 6.67 (dd, J = 2.5, 8.9 Hz, 1 H), 6.59 (d, J = 2.3 Hz, 1 H), 4.86 (dd, J = 4.3, 6.6 Hz, 1 H), 4.51 (dd, J = 4.1, 11.2 Hz, 1 H), 4.41 (dd, J = 6.5, 11.3 Hz, 1 H), 3.92 (td, J = 4.6, 11.2 Hz, 1 H), 3.71 (dt, J = 5.6, 11.7 Hz, 1 H), 3.23-3.12 (m, 1 H), 3.01 (s, 6 H), 3.00-2.93 (m, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 164.4, 152.7, 144.8, 140.6, 136.4, 134.5, 129.7, 129.3, 128.3, 126.6, 116.1, 109.9, 109.1, 57.3, 49.8, 28.3; ESI-HRMS calc'd for $C_{18}H_{19}O_2N_2ClNa$ $(M + Na)^+$ 353.10273, found 353.10240.

6-(dimethylamino)-2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (**1**) To a reactor was added **37** (65 g, 0.196 mol), **33** (112 g, 0.255 mol), $Pd(dba)_2$ (3.4 g, 5.9 mmol), tricyclohexylphosphine (3.3 g, 11.8 mmol), and potassium carbonate (54.3 g, 0.393 mol). The reaction vessel was degassed under vacuum and backfilled with nitrogen, and then MeTHF/H_2O (650 mL, 9/1) was added. The resulting reaction mixture was then heated to reflux overnight. Upon completion (conv. >99%), the reaction was quenched by adding water (330 mL) at 60-70 °C, then the resulting slurry was slowly cooled to room temperature. The crude product was collected by filtration, and washed with water. The filter cake was then dissolved in DCM (1 L), and 20% aqueous solution of $NaHSO_3$ (350 mL) was added. The resulting mixture was heated to 60 °C with vigorous stirring for 4 h. After cooling to ambient temperature, the mixture was diluted with 350 mL of water, and the organic layer was separated. Activated carbon (20 g) was added and the resulting DCM mixture was heated to 40 °C for 4 h. After cooling to room temperature, the mixture was filtered through a short pad of Celite® and the collected solids were washed with a small amount of DCM. The solvent was removed by distillation at atmosphere pressure while gradually adding IPA. When most of the DCM had been removed, seed crystals of the IPA solvate (Form B) were added at 60 and then 80 °C. DCM was completely removed by chasing with IPA, and the resulting IPA slurry (ca. 1 L) was aged at 80 °C for 2-3 h, then slowly

cooled to ambient temperature, and filtered. Washing with a small amount of IPA and drying under vacuum at 80 °C overnight afforded the desired BTK inhibitor **1** (99 g, 163 mmol, 83% yield) as an off-white crystalline solid. ^{1}H NMR (300 MHz, DMSO-d_6) 8.94 (s, 1 H), 8.74 (d, J = 2.2 Hz, 1 H), 8.26 (d, J = 2.3 Hz, 1 H), 7.72 (d, J = 8.8 Hz, 1 H), 7.66 (dd, J = 2.4, 8.7 Hz, 1 H), 7.49-7.44 (m, 2 H), 7.38-7.30 (m, 3 H), 6.67 (dd, J = 2.5, 8.8 Hz, 1 H), 6.59 (d, J = 2.6 Hz, 1 H), 4.83 (t, J = 4.6 Hz, 1 H), 4.35 (d, J = 4.3 Hz, 2 H), 4.34 (1H, IPA), 3.94 (td, J = 4.4, 11.2 Hz, 1 H), 3.82-3.73 (m, 1 H), 3.82-3.73 (m, 1 H, IPA), 3.61 (s, 3 H), 3.58 (br, 4 H), 3.50 (br, 4 H), 3.26-3.16 (m, 1 H), 3.01 (s, 6 H), 2.99-2.94 (m, 1 H), 1.04 (d, J = 6.1 Hz, 6 H, IPA); ^{13}C NMR (75.5 MHz, DMSO-d_6) 167.4, 164.6, 156.6, 155.9, 152.6, 146.6, 144.2, 140.6, 139.9, 136.6, 136.1, 129.5, 129.2, 129.0, 128.7, 128.6, 126.9, 122.0, 120.4, 118.2, 116.4, 111.9, 109.9, 109.1, 66.1, 62.0, 57.4, 50.0, 37.5, 28.4, 25.5; ESI-HRMS calc'd for $C_{34}H_{37}O_5N_6$ $(M + H)^+$ 609.28199, found 609.28250.

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SUPPORTING INFORMATION. ^{1}H and ^{13}C NMR spectra for compound **5**, **21**, **22**, **24**, **25**, **32b**, **33**, **36**, **37** and **1**. This material is available free of charge via the internet at http://pubs.acs.org.

REFERENCES.

1. Vetrie, D.; Vorechovsky, I.; Sideras, P.; Holland, J.; Davies, A.; Flinter, F.; Hammarstrom, L.; Kinnon, C.; Levinsky, R.; Bobrow, M.; Smith, C. I. E.; Bentley, D. R. *Nature* **1993**, *361*, 226-233.

2. (a) Smith, C. I.; Baskin, B.; Humire-Greiff, P.; Zhou, J. N.; Olsson, P. G.; Maniar, H. S.; Kjellen, P.; Lambris, J. D.; Christensson, B.; Hammarstrom, L.; Bentley, D.; Vetrie, D.; Islam, K. B.; Vorechovsky, I.; Sideras, P. *J. Immunol.* **1994**, *152*, 557-565. (b) Conley, M. E.; Dobbs, A. K.; Farmer, D. M.; Kilic, S.; Paris, K.; Grigoriadou, S.; Coustan-Smith, E.; Howard, V.; Campana, D. *Annu. Rev. Immunol*. **2009**, *27*, 199-227.

3. (a) Khan, W. F.; Alt, F. W.; Gerstein, R. M.; Malynn, B. A.; Larsson, I.; Rathbun, G.; Davidson, L.; Müller, S.; Kantor, A. B.; Herzenberg, L. A.; Rosen, F. S.; Sideras, P. *Immunity* **1995**, *3*, 283-299. (b) Ellmeier, W.; Jung, S.; Sunshine, M. J.; Hatam, F.; Xu, Y.; Baltimore, D.; Mano, H.; Littman, D. R. *J. Exp. Med*. **2000**, *192*, 1611-1624.

4. (a) Pan, Z,; Scheerens, H.; Li, S.-J.; Schultz, B. E.; Sprengeler, P. A.; Burrill, L. C.; Mendonca, R. V.; Sweeney, M. D.; Scott, K. C. K.; Grothaus, P. G.; Jeffery, D. A.; Spoerke, J. M.; Honigberg, L. A.; Young, P. R.; Dalrymple, S. A.; Palmer, J. T. *Chem. Med Chem*. **2007**, *2*, 58-61. (b) Jansson, L.; Holmdahl, R. *Clin. Exp. Immunol*. **1993**, *94*, 459-465.

5. Rastetter, W.; Molina, A.; White, C. A. *Annu. Rev. Med*. **2004**, *55*, 477-503.

6. (a) Dewdney, N. J.; Kennedy-Smith, J.; Kondru, R. K.; Loc, B. E.; Lou, Y.; McIntosh, J.; Owens, T. D.; Soth, M.; Sweeney, Z. K.; Taygerly, J. P. G. (Roche Palo Alto LLC, USA). Preparation of pyridinones and pyridazinones as Bruton's tyrosine kinase (Btk) inhibitors. U.S. Pat. Appl. 2009/0306041, 2009. (b) Berthel, S.; Firooznia, F.; Fishlock, D.; Hong, J.-B.; Lou, Y.; Lucas, M.; Owens, T. D.; Sarma, K.; Sweeney, Z. K.; Taygerly, J. P. G. (Roche Palo Alto LLC, USA). Inhibitors of Bruton's Tyrosine Kinase. U.S. Pat. Appl. 2010/0222325, 2010. (c) Dewdney, N. J.; Lou, Y.; Sjogren, E. B.; Soth, M.; Sweeney, Z. K. (F. Hoffmann-La Roche AG, Switz.). Phenylpyrazinones derivatives as kinase inhibitors and their preparation, pharmaceutical compositions and use in the treatment of inflammation and autoimmune diseases. PCT Int. Appl. 2010/000633, 2010. (d) Lou, Y.; Owens, T. D.; Kuglstatter, A.; Kondru, R. K.; Goldstein, D. M. *J. Med. Chem*. **2012**, *55*, 4539-4550.

7. Tangallapally, R. P.; Lee, R. E. B.; Lenaerts, A. J. M.; Lee, R. E. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 2584-2589.

8. (a) Yin, J.; Buchwald, S. L. *Org. Lett*. **2000**, *2*, 1101-1104. For Pd-catalyzed C-N bond formation with aryl halides and amines, see; (b) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem*. **1999**, *64*, 6019-6022. (c) Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett*. **1999**, *40*, 3789-3790.

9. (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res*. **2008**, *41*, 1461-1473. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 9550-9561. (c) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc*. **2007**, *129*, 3358-3366. (d) Achmatowicz, M.; Thiel, O. R.; Wheeler, P.; Bernard, C.; Huang, J.; Larsen, R. D.; Faul, M. M. *J. Org. Chem*. **2009**, *74*, 795-809.

10. Staab, A. J.; Sin, N. (Bristol-Myers Squibb Company). Process for the preparation of substituted heterocycles. U.S. Pat. Appl. 2007/0161670, 2007.

11. Cheng, C.-Y.; Tsai, H.-B.; Lin, M.-S. *J. Heterocyclic Chem*. **1995**, *32*, 73-77.

12. Brookings, D.; Davenport, R. J.; Davis, J.; Galvin, F. C. A.; Lloyd, S.; Mack, S. R.; Owens, R.; Sabin, V.; Wynn, J. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 562-565.

13. (a) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl*. **1987**, *26*, 894-895. (b) Nowick, J. S.; Powell, N. A.; Nguyen, T. M.; Noronha, G. *J. Org. Chem*. **1992**, *57*, 7364-7366.

14. (a) Hanessian, S.; Demont, E.; van Otterlo, W. A. L. *Tetrahedron Lett*. **2000**, *41*, 4999-5003. (b) Wang, X.-J.; Tan, J.; Grozinger, K. *Tetrahedron Lett*. **1998**, *39*, 6609-6612.

15. Ahmad, Y.; Hey, D. H. *J. Chem. Chem*. **1954**, 4516-4523.

16. Bradlow, H. L.; Vanderwerf, C. A. *J. Org. Chem*. **1951**, *16*, 73-83.

17. Considering the unfavorable characteristics of sodium hydride, alternative reagents were evaluated also. The reagents that were tested included K_2CO_3, NaHMDS, KO*t*Bu, *i*PrMgCl, DIEA, tetramethylguanidine, DBU, TEA, and MsOH. But, sodium hydride was found to be superior to all in terms of cleanness of the reaction.

18. (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 7421-7428. (b) Clement, J.-B.; Hayes, J. F.; Sheldrake, H. M.; Sheldrake, P. W.; Wells, A. S. *Synlett* **2001**, 1423-1427. (c) Jones, C. P.; Anderson, K. W. Buchwald, S. L. *J. Org. Chem*. **2007**, *72*, 7968-7973.

19. (a) Manley, P. J.; Bilodeau, M. T. *Org. Lett*. **2004**, *6*, 2433-2435. (b) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett*. **2008**, *10*, 3505-3508. (c) Ligthart, G. B. W. L.; Ohkawa, H.; Sijbesma, R. P.; Meijer, E. W. *J. Org. Chem*. **2006**, *71*, 375-378.

20. Ji, J.; Li, T.; Bunnelle, W. H. *Org. Lett*. **2003**, *5*, 4611-4614.

21. (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457-2483. (b) Doucet, H. *Eur. J. Org. Chem*. **2008**, 2013-2030. (c) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl*. **2007**, *46*, 5359-5363. (d) Payack, J. F.; Vazquez, E.; Matty, L.; Kress, M. H.; McNamara, J. *J. Org. Chem*. **2005**, *70*, 175-178.

22. (a) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal*. **2004**, *346*, 889-900. (b) Konigsberger, K.; Chen, G.-P.; Wu, R. R.; Girgis, M. J.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev*. **2003**, *7*, 733-742.

23. Fox, J. M.; Huang, X.; Chieffi, A. Buchwald, S. L. *J. Am. Chem. Soc*. **2000**, *122*, 1360-1370.

24. (a) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed. Engl*. **2006**, *45*, 1282-1284. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 3387-3388; Cy_3P, XPhos, SPhos, DavePhos, JohnPhos and $t Bu_3P$ were evaluated for Suzuki-Miyaura coupling under the same reaction conditions.

25. See the supporting information for the optimization of reaction conditions.

26. (a) Kaerger, J. S.; Price, R. *Pharm. Res*. **2004**, *21*, 372-381. (b) Amara, N.; Ratsimba, B.; Wilhelm, A. M.; Delmas, H. *Ultrason. Sonochem*. **2001**, *8*, 265-270. (c) Hem. S. L. *Ultrasonics* **1967**, *5*, 202-207.

SYNOPSIS TOC.