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Development of a Practical Synthesis of a Pyrazolopyridinone-Based p38 MAP Kinase Inhibitor

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Abstract:

A practical synthesis of the pyrazolopyridinone-based p38 MAP kinase inhibitor (4) was required for an ongoing program. The synthesis of a key pyrazolopyridinone building block was refined and optimized to provide kilogram quantities of 10 without chromatography or extractive workups. An efficient building-block strategy was employed to give optimal control of the key quality attributes, and *in situ* Raman spectroscopy was used to monitor and understand the complex solid-state properties of 4.

Introduction

p38 Mitogen-activated protein (MAP) kinases are intracellular serine/threonine kinases that positively regulate the production and action of several pro-inflammatory mediators, specifically the release of tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1),[1] and are involved in disease states such as rheumatoid arthritis (RA), Crohn's disease (inflammatory bowel disease), and psoriasis. Biological agents that sequester TNF-α, such as Etanercept, Infliximab, and Adalimumab, show impressive clinical efficacy in the treatment of these diseases. The potential for small-molecule inhibitors of p38 MAP kinase as alternatives for these biological agents has spawned significant activity in the area, resulting in the discovery of a number of selective inhibitors of p38 that have shown great promise in early clinical trials.[2] As part of our ongoing effort in this area, the Medicinal Chemistry team has been pursuing inhibitors of p38 MAP kinase, manifesting in a number of suitable phthalazine-based candidates **1** and **2** (Scheme 1).[3] Most recently, p38 inhibitors based on a pyrazolopyridinone scaffold have been investigated, and compounds **3** and **4** were identified as candidates for further development. While compound **4** was ultimately selected for development, both **3** and **4** were in consideration at the outset of process development.[4] Herein we describe the route scouting and development that led to a suitable synthesis for their large-scale preparation.

The initial route to inhibitors **3** and **4** is shown in Scheme 2. The strategy to assemble the pyrazolopyridinone core **10** entailed fusing a pyridinone ring onto a pyrazoloaminoaldehyde (**7**) using a Knoevenagel-type transformation, with requisite **7** accessed *via* condensation of arylhydrazine **5** with 2-ethoxymethylene malononitrile. Fragment assembly involved coupling of the aryl boronate **11** with **10** under Suzuki coupling conditions. The established chemistry was efficient, robust, and well suited to further development. The end-game, however, was not scalable as Pd-mediated steps present considerable challenges in the form of Pd removal and impurity rejection and are best carried out earlier in the sequence to allow additional isolation points for impurity control.

An effective solution to the problems associated with cross-coupling reactions was the building-block approach shown in Scheme 3.[5] While inclusion of the amidation step as the final chemical transformation decreases the overall convergence, the amidation reaction does not introduce significant process related impurities and its incorporation provides an additional control point to deal with the cross-coupling derived impurities. To deal with the challenging physical properties of **4**, an additional step was included to control the final form of the drug substance. The Suzuki coupling partners **10** and **13** were designated as the key intermediates, leveraging existing technology to access boronic acid **13** on scale.[5a] Although the known synthetic sequence to **10** was lengthy, it was adopted for scale-up as exploratory studies failed to yield a shorter, more convergent route. Along with gaining an in-depth understanding and optimization of each step, some noteworthy challenges presented by the existing route to **10** include the following: the large solvent volumes required for work-ups due to poorly soluble intermediates, an insufficient understanding of chemoselectivity during hydrogenation of nitrile **6**, the use of excess brominating reagent required to access **9**, and the use of sodium hydride combined with an undesirable solvent mixture. The optimized process route to **10** is shown in Scheme 4.

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(1) (a) Chen, Z.; Gibson, T. B.; Robinson, F.; Silvestro, L.; Pearson, G.; Xu, B.; Wright, A.; Vanderbilt, C.; Cobb, M. H. *Chem. Rev.* **2001**, *101*, 2449. (b) Raingeaud, J.; Gupta, S.; Rogers, J. S.; Dickens, M.; Han, J.; Ulevitch, R. J.; Davis, R. J. *J. Biol. Chem.* **1995**, *270*, 7420.

(2) (a) Gaestal, M.; Mengel, A.; Bothe, U.; Asadullah, K. *Curr. Med. Chem.* **2007**, *14*, 2214. (b) Peifer, C.; Wagner, G.; Laufer, S. A. *Curr. Top. Med. Chem.* **2006**, *6*, 113. (c) Margutti, S.; Laufer, S. A. *ChemMedChem* **2007**, *2*, 1116. (d) Schett, G.; Zwerina, J.; Firestein, G. *Ann. Rheum. Dis.* **2008**, *67*, 909.

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(4) Pettus, L. H.; Wurz, R. P.; Xu, S.; Herberich, B.; Henkle, B.; Liu, Q.; McBride, H. J.; Mu, S.; Plant, M. H.; Saris, C. J. M.; Sherman, L.; Wong, L. M.; Chmait, S.; Lee, M. R.; Mohr, C.; Hsieh, F.; Tasker, A. S. *J. Med. Chem.* **2010**, *53*, 2973.

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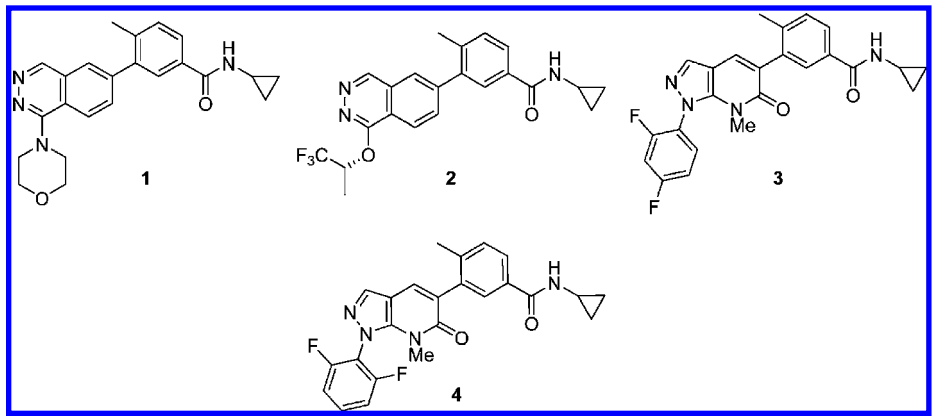
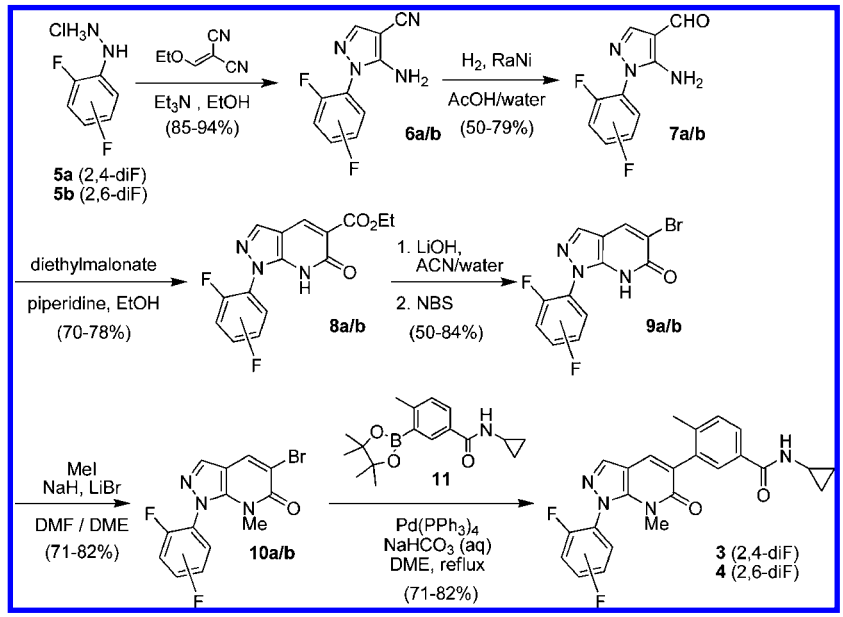
Scheme 1. **Selected p38 MAP kinase inhibitors from Amgen**



Scheme 2. **Initial route to 3 and 4**



Results and Discussion

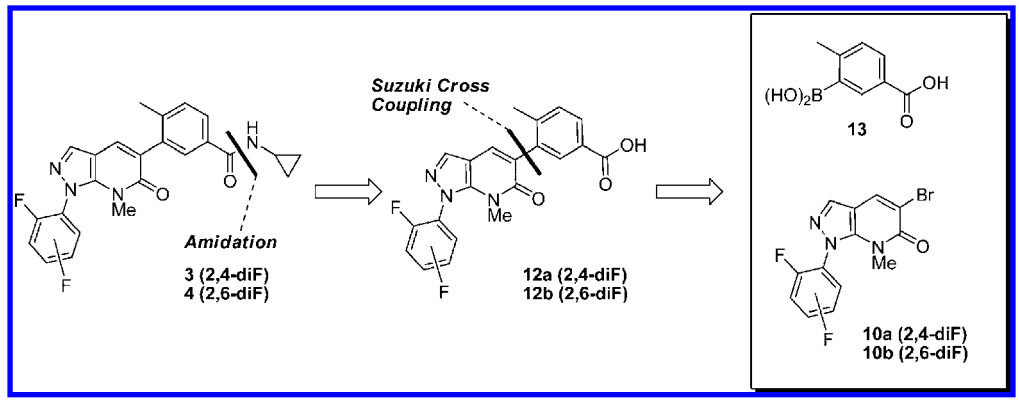
Until intermediate **9**, the development of both regioisomers was pursued. Development was initiated on the 2,4-series, and the resulting conditions were ported to the 2,6-series with further optimization. When **4** was identified as the final candidate, development efforts focused exclusively on the 2,6-difluoro series.

Synthesis of Building Block 10. The first step in the synthesis of **10a** involved condensation of **5a** with 2-ethoxymethylene malononitrile (Scheme 5).[6] The reaction occurs in two stages, a rapid condensation of the hydrazine and 2-ethoxymethylene malononitrile[7] followed by a much slower cyclization of **18** to the aminopyrazole. The initial approach to this reaction involved addition of triethylamine to a suspension of 2-ethoxymethylene malononitrile and **5a** in ethanol. A detailed study of the reaction revealed it to be extremely sensitive to the rate of triethylamine addition, whereas slow triethylamine addition (>30 min) gave a bright-yellow mixture from which **6a** crystallized, rapid triethylamine addition (<1 min) gave a dark-brown slurry from which no product could be isolated, and **19** (Scheme 6) could be observed by LC/MS. A solvent screen showed that the problems associated with the addition rate of triethylamine could be mitigated by performing the reaction in acetic acid. Workup of the reaction was also facilitated by using acetic acid, as neutralization with aqueous sodium hydroxide to pH 6−7 induced crystallization of **6a** as a filterable solid. Application of this protocol on kilogram scale afforded **6a** as a pale yellow solid in 90% yield (96 wt %).

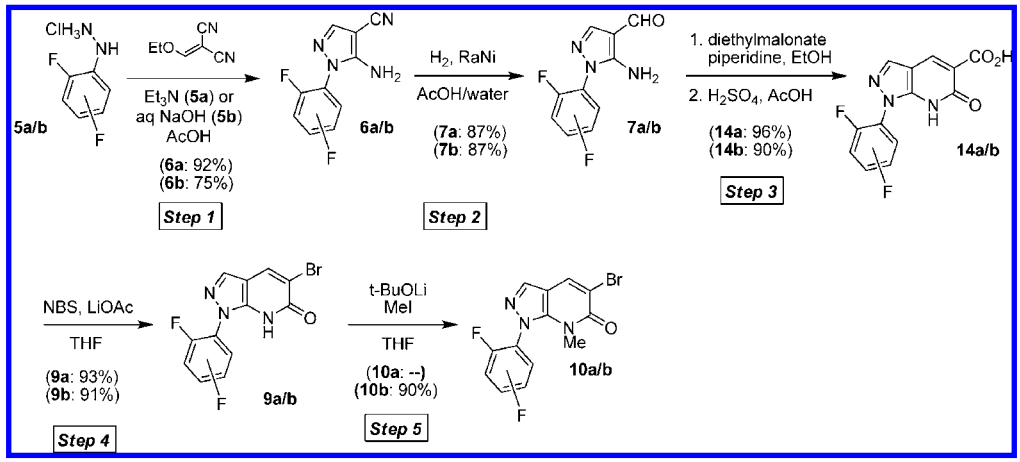
Expectations that development work carried out on the 2,4-difluorophenyl system could be directly applied to the 2,6-difluorophenyl system were quickly proven naive. The first indication of this came during sourcing of **5b**, which was generated via a nonscalable route that lead to long delays in sourcing kilogram quantities. The stability of **5a** and **5b** also contrasted sharply; whereas **5a** was a bench-stable solid over weeks of storage at ambient temperature, **5b** deliquesced and became highly colored within days. An explanation for the differing stabilities of **5a/b** was not investigated further; however, N_2 elimination accompanied by the loss of HF has been reported for related systems (Scheme 7).[8]

(6) Cheng, C.; Robins, R. *J. Org. Chem.* **1956**, *21*, 1240.
(7) **18** may be observed *via* HPLC. Isolated **18** is a crystalline solid that slowly cyclizes to **6a** in the solid state.
(8) (a) Collins, I.; Roberts, S. M.; Suschitzky, H. *J. Chem. Soc. (C)* **1971**, 167. (b) Holland, D. G.; Moore, G. J.; Tamborski, C. *J. Org. Chem.* **1964**, *29*, 3042.

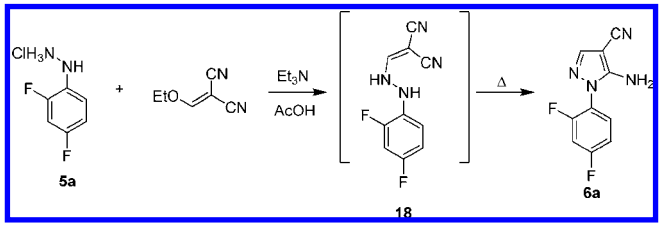
Scheme 3. **End-game strategy to pyrazolopyridinone-based p38 inhibitors**



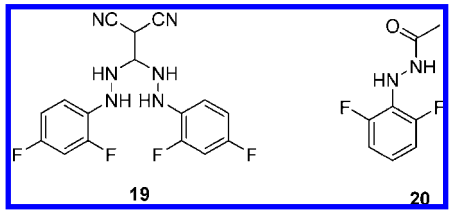
Scheme 4. **Process route to pyrazolopyridinone core**



Scheme 5. **Condensation of 5a with 2-ethoxymethylene malononitrile**

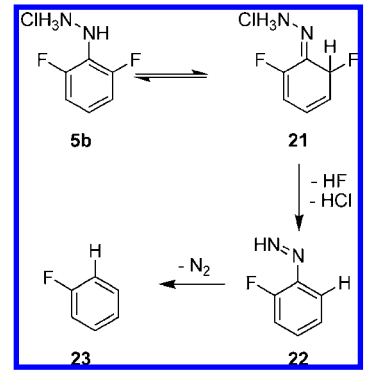


Scheme 6. **Major impurities during formation of aminopyrazoles (6a/b)**



The instability of **5b** also led to its poor performance under the optimized conditions established for the synthesis of **6a**. Significantly, precipitation of the **6b** did not occur upon application of the established workup.[9] Replacing triethylamine with aqueous sodium hydroxide led to a much cleaner reaction, reduced the amount of *N*-acylation, and facilitated isolation via antisolvent induced crystallization. The optimized reaction conditions for the formation of **6b** involved treatment of

Scheme 7. **Potential decomposition pathway of 5b**



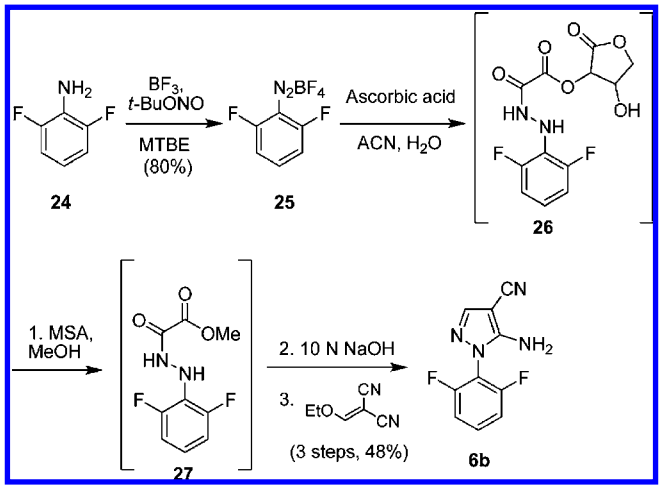
2-ethoxymethylene malononitrile **5b** in acetic acid (5 L/kg) with aqueous sodium hydroxide, affording 5-aminopyazole **6b** in 72% adjusted yield (83 wt %) as a filterable solid upon crystallization induced by the addition of aqueous sodium hydroxide.

As **5b** was not a suitable raw material for future campaigns, an alternate approach to **6b** was required. Cognizant of the stabilization imparted to **5b** upon *N*-acylation, we pursued trapping of the hydrazine as a more stable adduct. Ascorbic acid has been reported as an organic reducing agent that yields the oxalate adduct (i.e., **26**) directly upon reaction with the corresponding diazonium salts (Scheme 8).[10,11] The reduction of **25** with ascorbic acid cleanly afforded **26**, which upon

(9) *N*-Acylation was also observed under the reaction conditions. *N*-Acylation of **5b** imparted significant stabilization.

(10) Weidenhagen, R.; Wegner, H.; Lung, K. H.; Nordstrom, L. *Chem.Ber.* **1939**, *72B*, 2010.

Scheme 8. **Telescoped synthesis of aminopyrazole**



treatment with methanol gave **27** as a nonhygroscopic, bench stable crystalline solid. Treatment of **27** with sodium hydroxide revealed the free hydrazine, which was immediately condensed with 2-ethoxymethylene malononitrile. This approach was demonstrated on gram scale to access **6b** in moderate yield (54%). A telescoped procedure was also developed from the diazonium salt **25**[12] through to the aminopyrazole **6b**. In this case, the solution of **26** was solvent switched into methanol to afford the transesterified product **27**. Without isolation, this mixture was hydrolyzed under basic conditions, and then treated with 2-ethoxymethylene malononitrile to give **6b**. From diazonium **25**, this sequence could be carried out in 48% yield (93 wt %) as demonstrated on 50 g scale.

The second step in the synthesis of building block **10** was the hydrogenation of nitrile **6**. The reaction proceeds through the intermediacy of imine **28** (Scheme 9), which must be hydrolyzed before it has the opportunity to be further reduced to the corresponding aminomethylene compound (**29**). Other possible competing reaction pathways include the reduction of **7** to the corresponding hydroxymethylene (**30**), and the formation of products arising from intermolecular condensation and reduction (i.e., **31**). The established conditions for this transformation used an acetic acid/water mixture (3:1, 15 L/kg of **6a**) under RaNi catalysis (1.15 equiv) and 100 psig of hydrogen.[13] The workup involved removal of the acetic acid *via* distillation, an extractive workup into ethyl acetate and crystallization upon addition of heptane. While this protocol afforded pure material, the yield was highly variable and the low solubility of **7a** in ethyl acetate (56 g/L) made the amount of solvent required for an extractive workup prohibitive.

A closer look at the reaction under the initially reported conditions showed the observed side products to be associated with over-reduction of **28**. Attention was therefore focused on maintaining a low steady state concentration of **28** by decreasing rate of reduction relative to hydrolysis. As expected, a significantly cleaner reaction profile was obtained when the H_2 pressure was reduced to 15 psig.[14] At this H_2 pressure, the established super stoichiometric amounts of catalyst was incrementally decreased to 0.15 equivalents (Table 1), which served to further improve both the purity profile and reaction yield without significantly increasing the reaction time.[15]

Table 1. **Catalyst loading studies**

		yield (%)	
entry	catalyst loading (equiv)	**7a**	**29a**
1	0.6	59	14
2	0.3	71	11
3	0.15	93	2

The originally described isolation conditions involving distillation of acetic acid under reduced pressure at 60−70 °C lead to slow decomposition of **7a** during the solvent removal. To avoid both the distillation and the voluminous extractive workup, a crystallization directly from acetic acid was pursued. This could be achieved upon addition of water to the reaction mixture; however, liquor losses were significant due to the high solubility of **7a** in acetic acid. Use of aqueous sodium hydroxide as the antisolvent remedied this by consuming acetic acid and minimizing the total liquor volume. The optimized procedure for the isolation of **7a** involved removal of the catalyst by filtration, crystallization *via* addition of aqueous sodium to a pH of 4−5, and then isolation *via* vacuum filtration. On kilogram scale (3:1 mixture of acetic acid/water, 6 L/kg of **6a**), **7a** was isolated in 70−79% yield (95 wt %).

Application of this protocol to the reduction of **6b** required only optimization of the reaction and workup volumes. On kilogram scale, using 5 wt % RaNi 2400 (0.15 equiv) in acetic acid/water (3:1, 5 L/kg of **6b**) under 15 psig H_2, **7b** was isolated in 87% yield (100 wt %).

The third step in the synthesis entailed annulation of the pyridinone ring onto aminopyrazole **7**. This was initially achieved *via* condensation of diethylmalonate with **7** under iminium ion catalysis.[16] The product (**8**) was then isolated as a piperidine complex *via* antisolvent (water) induced crystallization. Under the reaction conditions, pyridinone formation was essentially quantitative; however, partial hydrolysis of **8** to the corresponding acid (**14**) significantly impacted the isolated yield of **8**. A telescoped Knoevenagel/hydrolysis protocol was therefore pursued. The low solubility of **8** in aqueous solvent mixtures (Table 2) was the major challenge in the formation of **14**, which was prohibitively slow under both acidic and basic conditions. Mindful of the potential reactivity of the difluorophenyl system to nucleophilic fluoride displacement reactions, hydrolysis under acidic conditions was favored. Attempts to increase the rate of hydrolysis with additives (NaI, I_2, $ZnCl_2$, $MgCl_2$), or cosolvents (DMSO, NMP, THF) were largely ineffective; however, a slight increase in rate was observed using acetic acid which was attributed to the high acetic acid solubilty of **8a**. Instead of adding copious amounts af acetic acid to overcome the low solubility of **8a** in aqueous ethanol, an "anhydrous" hydrolysis protocol in acetic acid/ethanol was

(11) During preparation of this manuscript, Norris *et al.* from Pfizer Process R&D reported a related application of the use of ascorbic acid in the reduction of diazonium salts: Norris, T.; Bezze, C.; Franz, S. Z.; Stivanello, M. *Org. Process Res. Dev.* **2009**, *13*, 354.

(12) Safety studies were carried out and showed **25** to be thermally stable under 160 °C.

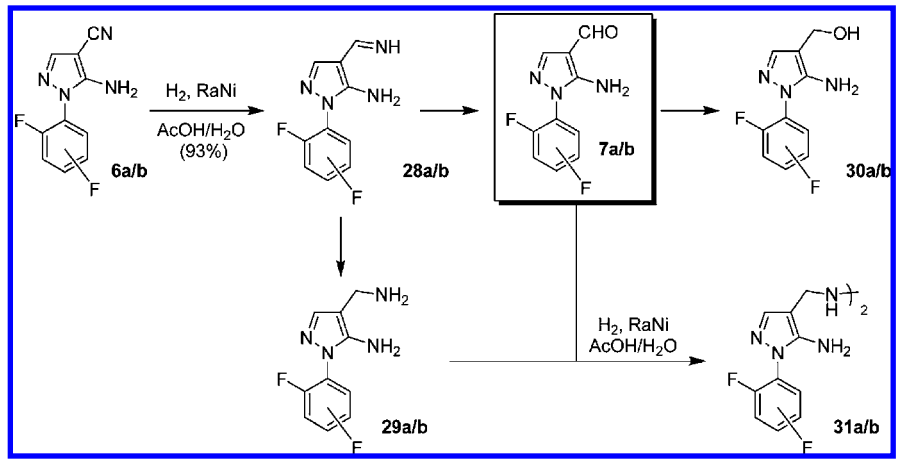
(13) Acevedo, O. L.; Krawczyk, S. H.; Townsend, L. B. *J. Heterocycl. Chem.* **1985**, *22*, 349.

(14) The reaction at 100 psig H_2 afforded 25% of **29a**, 15 psig H_2 afforded 4% of **29a**.

(15) All reactions achieved complete conversion with 19 h.

(16) Ahluwalia, V. K.; Goyal, B. *Synth. Commun.* **1996**, *26*, 1341.

Scheme 9. **Nitrile reduction mediated by Raney nickel**



designed. Carrying out the hydrolysis in acetic acid/ethanol with sulfuric acid maintained the solubility of **8a** while the water required for hydrolysis was slowly generated *via* condensation of ethanol and acetic acid. In the experiment, acetic acid and sulfuric acid were added to the ethanolic mixture of **8a** from the Knoevenagel condensation. The reaction was then heated to reflux, and ethyl acetate was distillatively removed to drive the equilibrium reaction to completion. Under these conditions, hydrolysis of **8a** was complete within 20 h.

On kilogram scale, the piperidine-mediated Knoevenagel reaction between **7a** (2.50 kg) and diethyl malonate was carried out in refluxing ethanol (3 L/kg of **8a**). The reaction reached completion within 20 h, at which time acetic acid (6 L/kg of **8a**) and concentrated sulfuric acid (2 equiv) were added to the cooled reaction mixture. The hydrolysis was then carried out at 80−100 °C with continuous distillation of ethyl acetate to achieve complete conversion within 20 h. The mixture was then cooled, and **14a** was isolated in 96% yield (100 wt %) *via* direct filtration.

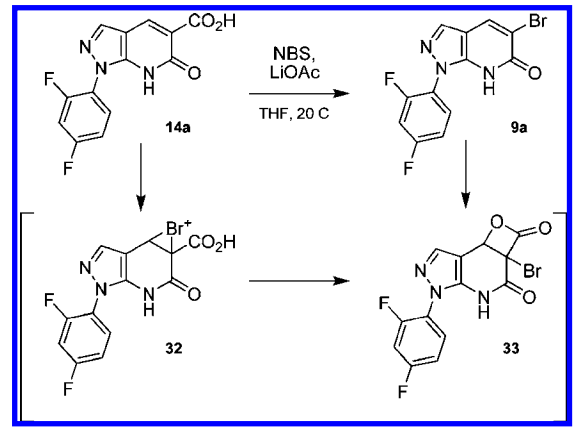
Transfer of this technology to the 2,6-difluoro-phenyl series was straightforward and required only modest optimization of the reaction and isolation volumes. On kilogram scale, **7b** was condensed with diethylmalonate in ethanol (5 L/kg of **7b**) followed by ester hydrolysis and isolation of **14b** in 90% yield (100 wt %).

The next step in the sequence involved a decarboxylative bromination (Hunsdiecker-type)[17] reaction (Scheme 10). In the initial approach this step was telescoped with the hydrolysis of ester **8**. The sequence proceeded under relatively mild conditions; however, the reaction required a significant excess of NBS (2−3 equiv) to achieve full conversion. While the piperidine from the isolated **8-piperidine** complex accounted for some of the required excess of NBS, experiments with pure **14** revealed a background reaction with the solvent (MeCN, DMF, NMP, acetic acid) was also occurring. Use of nonpolar solvents such

Table 2. **Solubility of 8a and 14a in water/ethanol mixtures at 20 °C**

entry	% EtOH in water	**8a** (g/L)	**14a** (g/L)
1	0	6.7	<0.1
2	25	11.6	0.3
3	50	40.8	1.1
4	75	39.8	2.1
5	100	25.6	2.6

Scheme 10. **LiOAc-catalyzed Hunsdiecker reaction of 17a**



as THF eliminated the background reaction; however, very slow reactions and low conversions resulted. Additives such as iodosylbenzene,[18] lithium acetate,[19] and manganese acetate have been shown to be beneficial to the reaction, with lithium acetate standing out for its availability, cost, and safety. This proved to be critical to the reaction, and the bromination of **14** mediated by lithium acetate in a THF/water solvent mixture (6.5 L/kg of **8a**) proceeded to completion with only a slight excess of NBS (1.1 equiv) in the presence of catalytic amounts of lithium acetate. Presumably, the reaction proceeds through β-lactone intermediate **33** as evidenced by an unisolable transient intermediate (Scheme 10).[20] On kilogram scale, NBS was added to the reaction mixture at 25 °C in portions, the mixture was aged until most of the starting material was consumed, and then heated to 50 °C to achieve complete conversion. Upon addition of water, **9a** crystallized and was isolated *via* filtration in 93% yield (99 wt %).

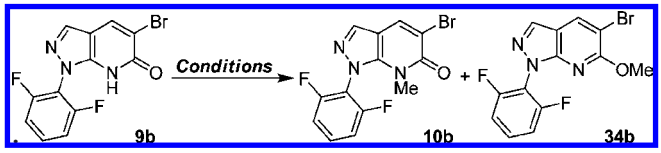
(17) (a) Johnson, R. G.; Ingham, R. K. *Chem. Rev.* **1956**, *56*, 219. (b) Wilson, C. V. *Org. React.* **1972**, *19*, 279. (c) Crich, D. Hunsdiecker and Related Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 717−734.

(18) Graven, A.; Jorgensen, K. A.; Dhal, S.; Stanczak, A. *J. Org. Chem.* **1994**, *59*, 3543.

(19) (a) Chowhury, S.; Roy, S. *J. Org. Chem.* **1997**, *62*, 199. (b) Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Synthesis* **2005**, 1319.

(20) Attempts to observe **33** *via* react-IR failed due to its low concentration. Ionization under standard LC/MS conditions was also not successful. Related intermediates were previously observed by NMR spectroscopy in the decarboxylative bromination of *cis*-cinnamic acid. See ref 19b.

Table 3. **Screen of conditions for pyridine *N*-methylation of 9b**



entry	conditions	**10b**:**34b**	time
1	LiH, LiBr, MeI, 10:1 DME/DMF, rt	28:1	1.5 d
2	LiOtBu, TBAI, MeI, THF, 40 °C	40:1	9 h
3	LiOtBu, TBAI, Me_2SO_4, THF, rt	5.6:1	48 h
4	LiOtBu, LiI, MeI, THF, 40 °C	50:1	9 h
5	LiOtBu, MeI, THF, 40 °C	100:1	9 h
6	LiH, Me_2SO_4, THF, 70 °C	5.6:1	6 h

Up to intermediate **9**, the compounds of the 2,4-difluorophenyl series (**5a**−**8a**) were less soluble than the corresponding 2,6-difluorophenyl series (**5b**−**8b**). Conversely, **9b** is significantly less soluble than **9a** causing its precipitation from the reaction mixture prior to full conversion. Since slurry-to-slurry transformations are difficult to control and often give incomplete conversion,[21] a higher dilution (7.5 L/kg of **8b**) was used to achieve a homogeneous end point. Solubility differences aside, the reactivity and stability of the two series were similar and **9b** was isolated in 91% yield (97 wt %) on kilogram scale.

The remaining development work towards **10** focused exclusively on the 2,6-difluoro-phenyl series (**10b**). The final step in the preparation of the **10b** was *N*-methylation of **9b**. Since pyridinones are ambident nucleophiles, selectivity during their alkylation can be a problem.[22] The initial conditions to effect this transformation involved deprotonation of **9b** with sodium hydride in a 10:1 DME/DMF mixture, followed by treatment with iodomethane in the presence of excess LiBr (10 equiv).[23] These conditions were not considered for scale-up due to the inherent hazards of handling sodium hydride on scale, the undesirable solvent mixture, and the large amounts of LiBr that were required to achieve useful selectivity. Investigation (Table 3) of cation effects showed that *O*-alkylation of the pyridone system to be preferred with a soft counterion (Na, K, Mg), and *N*-alkylation with hard counterions (Li). The leaving group also played an important role, with iodomethane giving much improved *N*-selectivity over dimethylsulfate (entries 2 and 3). Solvent influenced both the rate of reaction and *N*- *vs* *O*-selectivity. Highly polar solvents gave faster reaction rates than nonpolar systems, but had a deleterious effect on selectivity. Fortunately, the selectivity was not temperature dependent, and both a suitable reaction rate and high selectivity could be achieved by running the reaction in nonpolar aprotic solvent at high concentration and at elevated temperature. The optimal reaction conditions consisted of lithium *tert*-butoxide, iodomethane in THF at 40 °C (entry 5). On scale, complete conversion was reached within 18 h with an *N*- *vs* *O*-selectivity of 62:1 (1.5 HPLC A% of **34**). Isolation was carried out *via* water-induced crystallization followed by filtration to give **10b** in 90% yield (99 wt %). Regioisomer (**34b**) levels in the isolated **10b** were further reduced to 0.8 HPLC A%.

Introduction of iodomethane at such a late stage in the sequence required close attention due to its genotoxicity. Historical lots of **10b** consistently contained <500 ppm of residual iodomethane. Spiking studies in the subsequent Suzuki cross-coupling reaction showed it to tolerate up to 5000 ppm iodomethane without impacting catalyst performance or resulting in measurable iodomethane in the resulting **16b** (<76 ppb). The specification for iodomethane content in **10b** was therefore set at 5000 ppm, and no further treatment was necessary for iodomethane control.

To summarize the process development towards building block **10b**, a kilogram-scale route was developed in 48% yield over five steps without extractive workups or chromatography. To achieve this, the isolation points were redesigned to accommodate the reactivity and low solubility of the intermediates, a novel trans-esterification protocol was designed that addressed aqueous solubility problems incurred in the Knoevenagel reaction of **7**, catalytic conditions were applied to the Hunsdiecker reaction of **14** to avoid the use of excess NBS, and simplified alkylation conditions were developed to provide maximal *N*- *vs* *O*-selectivity and reaction rate during the formation of **10**.

Endgame for the Synthesis of 4. With access to both boronic acid **13**[5] and pyrazolopyridinone **10b**, the remainder of the synthesis consisted of a three-step protocol (Scheme 11) that was used for the kilo-scale preparation of related p38 MAP kinase inhibitors **1** and **2**. The order of operations in this sequence was designed to give maximal control of drug substance quality attributes by effecting the cross-coupling reaction first, followed by amidation to give the crude **4**, and then formation of **4-hydrate** as a separate step to accommodate its challenging physicochemical properties.

In developing the cross-coupling reaction, it was desirable to avoid class 2 solvents and bases that could cause off-gassing during the quench, to minimize catalyst loading, and to control the formation of reaction-related impurities. An initial screen of conditions revealed the K_3PO_4[24] in isopropanol/water to be optimal. A range of $Pd(OAc)_2$/ligand combinations along with a number of preformed catalysts were then screened and the three most promising catalyst systems were compared in detail (Table 4).[25] Both $Pd(OAc)_2$/S-Phos[26] (entry 4) and $Pd(A\text{-}Phos)_2Cl_2$[27] (entry 11) gave excellent reaction profiles that minimized the formation of byproducts, with $Pd(A\text{-}Phos)_2Cl_2$ being the ultimate

(21) For poorly soluble products, starting material may become entrained in the product, making it unavailable for reaction.
(22) (a) Kornblum, N.; Smiley, R. A.; Blackwood, P. K.; Iffland, D. C. *J. Am. Chem. Soc.* **1955**, *77*, 6269. (b) Hopkins, G. G.; Jonak, J. P.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040. (c) Chung, N. M.; Tieckelmann, H. *J. Org. Chem.* **1970**, *35*, 2517.
(23) LiBr was critical to improve the *N*- *vs* *O*-selectivity.
(24) K_3PO_4 may be considered a privileged base for large-scale Suzuki couplings of this type as it is applicable to a wide range of substrates and does not present off-gassing issues upon neutralization.
(25) The major byproducts, **36** and **37** derived from **13** *via* deboronation and homocoupling, respectively, and **35** derived from **10b** *via* dehalogenation, were fully characterized and their identities confirmed by synthesis.
(26) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.
(27) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104.

Scheme 11. **Process route to 4-hydrate**

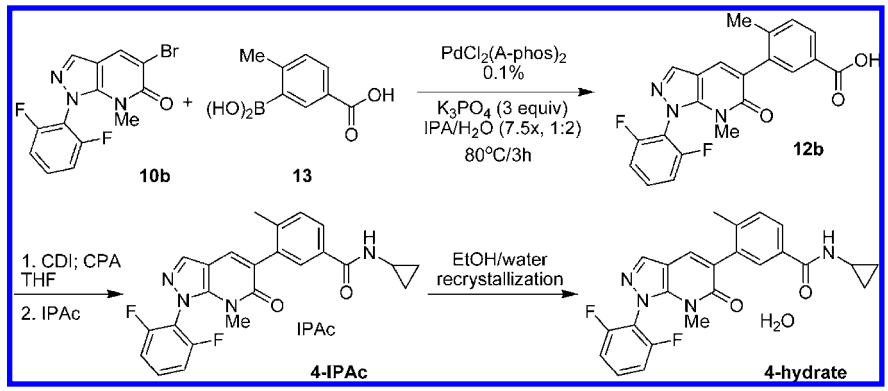
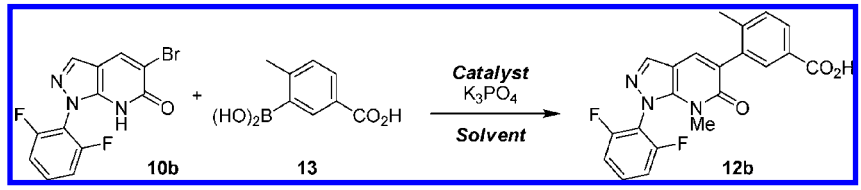
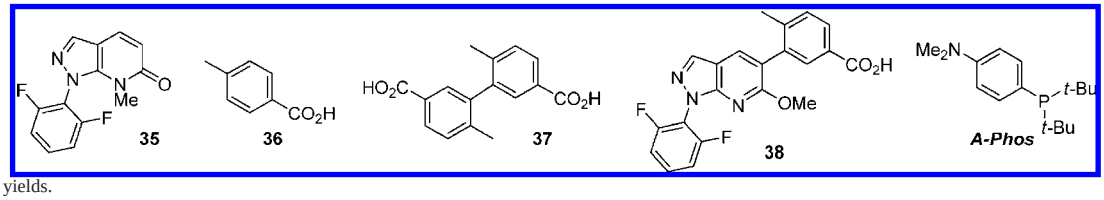


Table 4. **Optimization of cross-coupling conditions**



entry	solvent	catalyst	**12b** (% yld)[a]	**35** (HPLC A%)	**36** (HPLC A%)	**37** (HPLC A%)
1	H_2O	$Pd(PPh_3)Cl_2$	15	–	–	–
2	EtOH	$Pd(PPh_3)Cl_2$	89	–	–	–
3	toluene	$Pd(PPh_3)Cl_2$	46	–	–	–
4	iPrOH	$Pd(PPh_3)Cl_2$	91	2.9	2.5	6
5	iPrOH	$Pd(OAc)_2$/Xantphos	13	–	–	–
6	iPrOH	$Pd(OAc)_2$/X-phos	91	–	–	–
7	iPrOH	$Pd(OAc)_2$/S-phos	96	1.5	5	1.4
8	iPrOH	$Pd(OAc)_2/PCy_3$	87	–	–	–
9	iPrOH	$Pd(OAc)_2$/DPE-phos	83	–	–	–
10	iPrOH	$Pd(OAc)_2$/DPPF	80	–	–	–
11	iPrOH	$Pd(A\text{-}Phos)_2Cl_2$	98	0.6	4.7	1.3



[a] HPLC assay yields.

choice due to its stability and superior turnover number.[28] The optimized reaction conditions were 0.1 mol % $Pd(A\text{-}Phos)_2Cl_2$, K_3PO_4 in IPA/water at 80 °C.

Upon completion of the reaction, the mixture was cooled to 25 °C to give a biphasic system (isopropanol/water)[29] in which the potassium salt of **12b** was contained in the isopropanol layer. Workup of the reaction consisted of separation of the layers, dilution of the isopropanol layer with deionized water, and then washing this with toluene to remove the un-ionized organic impurities (**35** and $Pd(A\text{-}Phos)_2Cl_2$). From the resulting aqueous layer, **12b** was selectively crystallized upon addition of aqueous hydrochloric acid to a pH of 4. Filtration of the product was initially a problem as a nucleation-dominated crystallization caused small particle size (Figure 1). Fortunately, the influence of temperature on the crystal growth was dramatic, and pH adjustment at 70 °C followed by slow cooling to 20 °C resulted in >100-fold increase in particle size. On kilogram scale, the coupling of **10b** and **13** (1.05 equiv) catalyzed by 0.1 mol % $Pd(A\text{-}Phos)_2Cl_2$ in a 1:2 mixture of isopropanol/water (7.5 L/kg **10b**) at 70 °C was complete within 2 h. Isolation was carried out as described above to give **12b** in 93% yield (100 wt %). Pd levels in the isolated **12b** were consistently low (<10 ppm), coupling-related impurities **35**, **36**, and **37** (Table 4) were all below 0.05 HPLC A%, and the major carryover impurity (**38**) was reduced 10-fold. Noteworthy was the efficiency with which palladium was rejected in the workup, which may be attributed to the stability of the catalyst along with its high solubility in toluene.

The amidation of **12b** (Scheme 12) was again based on technology used to deliver kilogram quantities of related cyclopropyl amides **1** and **2** (Scheme 1). During the process development of compound **1**, attempts to activate the acid as its acid chloride were unsuccessful. Conversely, activation using CDI was effective and offered several advantages over use of

(28) Loading studies demonstrating that 0.1 mol % catalyst was sufficient to obtain both full conversion and acceptable reaction kinetics (<4 h).

(29) Isopropanol and water are typically miscible in all proportions; however, aqueous salt solutions are often immiscible with isopropanol.

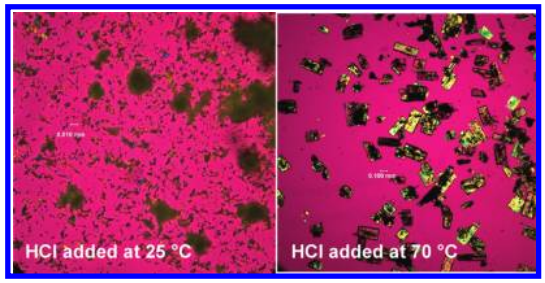


Figure 1. **Microscopy of 16b isolated at 25 and 70 °C.**

Scheme 12. **CDI activation and amidation of 12b with cyclopropylamine (CPA)**

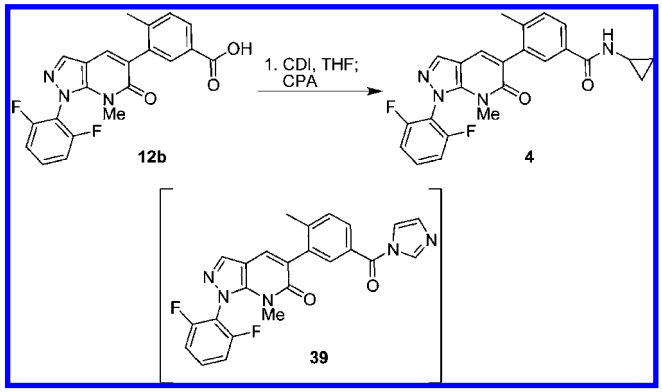


Table 5. **Solubility of 4 in common solvents at 20 °C**

solvent	solubility (mg/mL)	solvent	solubility (mg/mL)
methanol	19.9	IPAc	1.3
ethanol	10.3	acetone	11.9
1-propanol	6.9	toluene	0.7
2-butanol	1.4	THF	7.4
		water	<0.1

the acid chloride including avoidance of HCl gas evolution along with the comparatively facile handling and safety of CDI. The neutral byproducts from CDI-mediated amidations also allow them to be carried out in almost any solvent, THF being particularly well suited for the preparation of **1** and **2**. The protocol developed for these previous campaigns involved treatment of the acid/THF mixture with 1.2 equiv of CDI in portions at 25 °C to give the imidazolide,[30] which was then treated with cyclopropylamine. The primary challenge in the application of this protocol to **12b** (Scheme 12) was the low solubility of **4** (Table 5), which led to cocrystallization of **39** with the product inasmuch as 5−10%.[31] Fortunately, the rapid reaction of **39** with cyclopropylamine, the mild reaction energetics (adiabatic temperature rise of 12 °C) and slow kinetics of crystallization allowed complete conversion to be achieved *via* rapid addition of the cyclopropylamine. Isolation was accomplished *via* solvent switch to isopropyl acetate and then filtration to give **4** as its isopropyl acetate solvate. On kilogram scale, the reaction afforded 94% yield (93.2 wt %, 6 wt % IPAc), the major impurity being the unreacted **12b**.

(30) The imidazolide intermediate was unstable under the HPLC conditions (0.1% TFA in acetonitrile/water); however, it could be quenched with benzylamine and then analyzed as the corresponding benzamide.

(31) The entrained imidazolide remained unreacted in isolated **4**; however, it readily reacted with the solvent upon dissolution in the subsequent step.

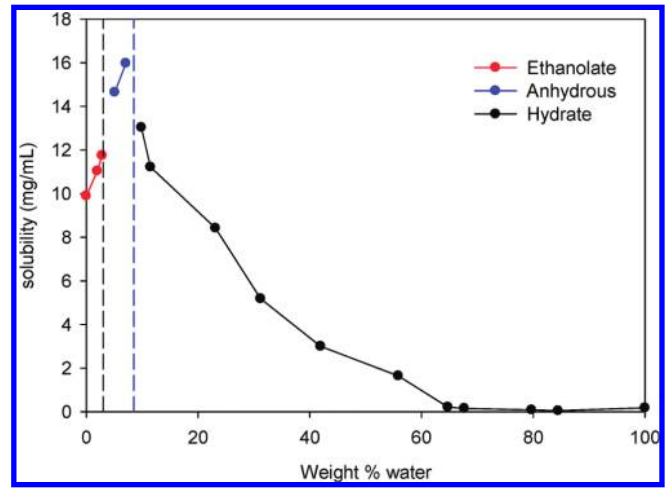


Figure 2. **Solubility of 4 in EtOH/water mixtures.**

Neither the *O*-Me isomer of **4** nor the cross-coupling-derived impurities from **35**, **36**, or **37** could be detected in the isolated product.

The final isolation of **4** was complicated by the availability of a number of distinct solvates, along with a hydrate and an anhydrous form. Solvates are typically undesirable as the final form for a drug substance due to limitations on residual solvents in the active pharmaceutical ingredient (API). Between the hydrate and the anhydrous form, the hydrate was ultimately selected for the final form as it was thermodynamically more stable in aqueous media (preclinical formulations). An ethanol/water system was selected to generate **4-hydrate** on the basis of the solubility and solid-phase data (Figure 2). In order to gain further insight into the pseudo-polymorphic behavior of **4**, Raman spectroscopy was used to monitor the crystallization. Characteristic spectroscopic features were identified for each solvate (ethanol, hydrate) and the anhydrous form (Figure 3), and these were monitored during cooling/turnover experiments in a range of ethanol/water mixtures. In general, rapid cooling afforded the ethanol solvate in most solvent compositions, which turned over to the hydrate upon aging in water/ethanol mixtures greater than 10% water. Slow cooling inconsistently gave either the ethanolate or the hydrate, but seeding with the hydrate afforded the hydrate exclusively. In addition, the ethanol solvate was rapidly converted to the hydrate upon slurrying in 1:1 water/ethanol without seeding.

With the assistance of modeling software[32] and the above data, the following protocol was designed and implemented for the isolation of **4-hydrate**: **4-IPAc** was dissolved in 90:10 ethanol/water (32 L/kg of **4**) at 40 °C, the solution was polish filtered, and the vessel/filter was rinsed with 3 volumes of preheated 90:10 ethanol/water to adjust the concentration to ∼30 mg/mL. Water (1.2 L/kg of **4**) was charged into the reactor,[33] and atmospheric distillation was carried out to remove 25 volumes of distillate and to adjust the concentration to ∼90 mg/mL. The batch was then cooled to 70 °C, and 0.5 wt % of

(32) Modeling of the distillation was carried out using Dynochem modeling software.

(33) This was determined by setting the target after distillation to 10 volumes of solvent composed of 4:1 ethanol/water. To reach this endpoint, Dynochem modeling of the azeotropic system showed a starting volume of 36.2 volumes composed of 6.7:1 ethanol/water to be required.

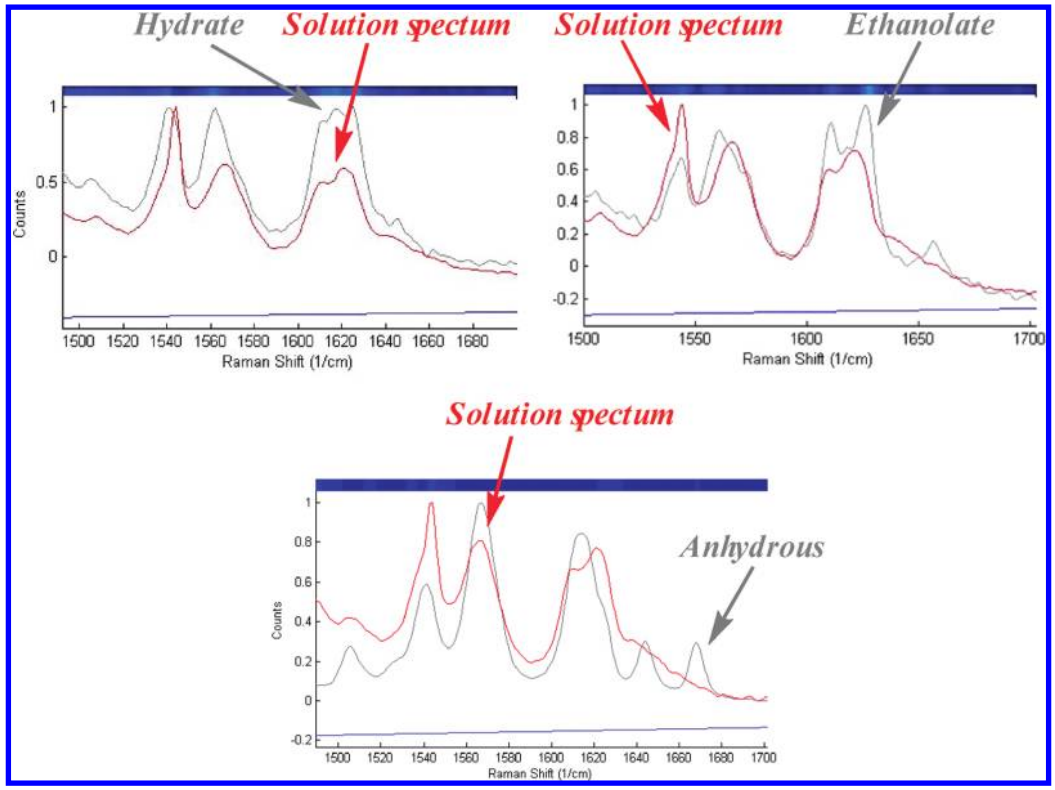


Figure 3. **Raman data for the 4 hydrate, ethanolate, and anhydrous forms. (All spectra are normalized.)**

seed was added. (See Supporting Information for overlay plots of the Raman spectra recorded during the crystallization.) Slow cooling over 4.75 h afforded a solution concentration of 10 mg/mL which was reduced to <1.5 mg/mL upon addition of water (6 L/kg of **4**) and then aged for a further 2 h. The mixture was then filtered, and the cake was washed with water and then dried under a stream of nitrogen to give **4-hydrate** in 96% yield, (96 wt %, 4 wt % water). Using this procedure, kilogram amounts of the drug substance were delivered with the appropriate critical quality attributes, with all impurities and heavy metals controlled and the residual solvent levels well within the ICH guidelines.

Summary and Conclusions

A number of challenges were overcome during the development of a kilogram-scale synthesis of p38 MAP kinase inhibitor **4**. Foremost was the instability and limited availability of the 2,6-difluorophenylhydrazine (**5b**), which was solved *via* development of a telescoped sequence starting from stable, crystalline, and readily available 2,6-difluorobenzenediazonium tetrafluoroborate (**25**). During the synthesis of building block **10b**, a methodical understanding of each step led to highly optimized reaction conditions and designation of more appropriate isolation points. Furthermore, consideration of the isolation during reaction optimization facilitated direct isolation of the intermediates as crystalline solids with minimal manipulation during workup. The endgame strategy of this sequence consisted of a three-step protocol designed to give maximal control of process-related, genotoxic, and heavy-metal impurities. Finally, the complicated physicochemical nature of **4** was navigated with the assistance of process analytics to reliably deliver the prescribed **4-hydrate**. Thus, the drug substance was obtained in eight steps and 38% overall yield for the delivery of kilogram quantities of the highly pure drug substance.

Experimental Section

5-Amino-1-(2,4-difluoro-phenyl)-1*H*-pyrazole-4-carbonitrile (6a). A dry 60-L jacketed reactor equipped with a nitrogen inlet, a temperature probe, a glycol-cooled condenser, and a mechanical stirrer was charged with 2,4-difluororphenylhydrazine hydrochloride (**5a**) (2.0 kg, 10.85 mol) and sodium acetate (445 g, 5.43 mol). Acetic acid (10.0 L) was charged to the reactor, stirring was initiated, and the internal temperature was adjusted to 15 °C. Triethylamine (1.65 kg, 16.28 mol) was charged, while keeping the internal temperature below 30 °C, and then a solution of 2-(ethoxymethylene)malononitrile (1.4 kg, 11.4 mol) in acetic acid (4.0 L) was added to the reaction mixture. The mixture was stirred at 20 °C for 1.5 h (<1 A% **5a** by HPLC), the internal temperature was increased to 60 °C, and the reaction mixture was stirred for 2 h (<1 A% adduct by HPLC). The batch temperature was adjusted to 20 °C, a solution of 5 N aqueous NaOH (10.0 L) was added over 30 min while maintaining the batch temperature below 27 °C, and then the mixture was aged at 20 °C for 8 h. The mixture was then filtered, the cake was washed with water (2 × 4 L) and dried under a stream of nitrogen to give **6a** as a pale-orange solid (2.2 kg, 89.8% yield). The crude **6a** (2.3 kg, 97 wt %) was dissolved in ethyl acetate (23 L) at 75 °C and then cooled to 25 °C over 2 h. Toluene (11.5 L) was charged to the reactor, the batch volume was reduced *in vacuo* (23 L collected), and additional toluene (13 L) was charged to the reactor. The mixture was then filtered, and the cake was washed with toluene

(2 × 4.5 L) and dried under a stream of nitrogen to give **6a** as a pale-beige solid (2.15 kg, 98% yield). Mp 190−191 °C. IR: 3472, 3321, 3234, 3202, 3083, 2230, 1649, 1543, 1511, 1113, 963, 858, 817, 543 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.78 (s, 1H), 7.67−7.49 (m, 2H), 7.25 (t, J = 8.6 Hz, 1H), 6.79 (br s, 2H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ = 167.5 (dd, J = 248.8, 11.3 Hz), 163.0 (dd, J = 281, 13.9 Hz), 158.2, 147.5, 136.4 (d, J = 10.4 Hz), 126.7 (dd, J = 12.1, 3.4 Hz), 120.0, 117.7 (dd, J = 22.5, 3.4 Hz), 110.8 (app t, J = 23.4), 77.2. HRMS *m/e*: Calcd for $C_{10}H_7F_2N_4^+$ (M + H): 221.0633, Found: 221.0639.

5-Amino-1-(2,4-difluoro-phenyl)-1*H*-pyrazole-4-carbaldehyde (7a). A 10-L Buchi autoclave equipped with a mechanical stirrer was charged with 5-amino-1-(2,4-difluoro-phenyl)-1*H*-pyrazole-4-carbonitrile (**6a**) (1.02 kg, 4.63 mol). Acetic acid (4.5 L) and a slurry of Raney nickel 2400 (45.g) in water (0.25 L), followed by a water (1.25 L) rinse were sequentially charged to the autoclave. The autoclave was purged with 15 psig hydrogen, then evacuated (five cycles), and then pressurized to 15 psig hydrogen. Agitation was initiated (800 rpm), and the mixture was stirred for 9 h (<1 A% **6a** by HPLC). The hydrogen was then purged from the reactor with argon, and additional acetic acid (1.5 L) was charged to the reactor. The Raney nickel was then removed *via* filtration (1 and 10 μm bag filter), and the reactor/filter was rinsed with acetic acid (0.5 L). The resulting solution was stable at 0 °C and stored while a second batch of the same scale was carried out. The two batches were charged to a 60-L jacketed reactor followed by an acetic acid (1.0 L) rinse. The batch temperature was adjusted to 6 °C, 5 N aqueous NaOH (6 L) was added over 13 min and the resulting cloudy mixture was aged for 1 h. Aqueous NaOH (5 N, 15 L) was then added over 1.5 h, and the contents of the reactor were aged at 20 °C for 75 min (supernatant concentration of **7a** = 4.5 mg/mL). The resulting slurry was filtered, the cake was washed with water (2 × 4.0 L) and dried under a stream of nitrogen to afford **7a** as yellow powder (1.56 kg, 70.8% yield). Mp 144−146 °C. IR: 3382, 3272, 3124, 2835, 2160, 2030, 1644, 1623, 1531, 1514, 1433, 1412, 1364, 1301, 1272, 1253, 1217, 1198, 1140, 1107, 1102, 1021, 961, 932, 886, 845, 818, 808, 734 cm^{-1}. ^1H NMR (400 MHz, chloroform-*d*) δ 6.95 (s, 2 H) 7.25 (t, J = 8.61 Hz, 1 H) 7.50 − 7.65 (m, 2 H) 7.86 (s, 1 H) 9.61 (s, 1 H). ^{13}C NMR (100.1 MHz, chloroform-*d*) δ 105.6, 112.4, 121.3, 130.9, 150.9, 156.2, 158.6, 161.1, 163.6, 182.6. HRMS *m/e* Calcd for $C_{10}H_8F_2N_3O$ (M + H): 224.0635. Found: 224.0638.

1-(2,4-Difluoro-phenyl)-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid (14a). A 60-L jacketed reactor equipped with a nitrogen inlet, a temperature probe, a glycol-cooled condenser, and a mechanical stirrer was charged was charged with 5-amino-1-(2,4-difluoro-phenyl)-1*H*-pyrazole-4-carbaldehyde (**7a**) (2.5 kg, 11.2 mol), ethanol (7.5 L), followed by dimethyl malonate (2.04 L, 13.44 mol) and piperidine (1.16 L, 11.76 mol). The resulting suspension was heated, becoming homogeneous at 61−62 °C, and stirred for 20 h (<1 A% **7a** by HPLC). The mixture was cooled to 70 °C, ethyl acetate (5.0 L), acetic acid (15 L), and then concentrated sulfuric acid (1.19 L, 22.4 mol) were charged to the reactor. The resulting suspension was heated to reflux (79 °C), and the distillates were collected as the batch temperature gradually climbed to 100−105 °C over 22 h (<1 A% **8a** by HPa LC). The resulting slurry was cooled to 20 °C over 1 h and aged at until ≤5 mg/mL of **14a** remained in solution. The mixture was then filtered, the filter-cake was washed with acetic acid (1 × 3.8 L) followed by water (2 × 5 L), and then the solids were dried under a stream of nitrogen to afford **14a** as a colorless solid (3.142 kg, 96.0% yield). Mp 307−308 °C (acetic acid). IR: 2694, 1742, 1624, 1594, 1565, 1512, 1464, 1434, 1411, 1392, 1309, 1275, 1257, 1197, 1177, 1150, 1112, 1036, 991, 975, 961, 879, 858, 827, 811, 736, 691, 677 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.89−8.84 (m, 1 H), 8.41−8.36 (m, 1 H), 7.78 (td, J = 8.75, 5.97 Hz, 1 H), 7.63 (ddd, J = 10.56, 9.10, 2.84 Hz, 1 H), 7.38−7.31 (m, 1 H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 167.6, 162.3 (J_{CF} = 249, 11 Hz), 157.0 (J_{CF} = 253, 14 Hz), 147.0, 139.0, 138.1, 130.5 (J_{CF} =10 Hz), 121.4 (J_{CF} = 12, 4 Hz), 112.3 (J_{CF} = 24, 4 Hz), 108.9, 108.6, 105.4 (J_{CF} = 27, 23 Hz). HRMS *m/e* Calcd for $C_{13}H_8F_2N_3O_3$ (M + H): 292.0534; Found 292.0523.

5-Bromo-1-(2,4-difluoro-phenyl)-1,7-dihydro-pyrazolo[3,4-*b*]pyridin-6-one (9a). A dry 60-L jacketed reactor equipped with nitrogen inlet, temperature probe, glycol-cooled condenser and mechanical stirrer was charged with **14a** (3.32 kg, 11.39 mol), lithium acetate (75.1 g, 1.14 mol), tetrahydrofuran (20.0 L) and water (1.66 L). Efficient stirring was established, and then *N*-bromosuccinimide (2.23 kg, 12.53 mol, 1.1 equiv) was added at 20 °C in four portions over 3 h during which time the reaction mixture turned from a slurry into a yellow solution that was accompanied by gentle off-gassing. The reaction was stirred at 20 °C for 2 h, heated to 50 °C for 1 h to achieve complete conversion (0.1 PA% **14a** by HPLC) and then cooled to 20 °C. Water (33.16 L) was added over 70 min and then the mixture was aged for 2 h at 20 °C. The resulting slurry was filtered, the reactor/filter cake was washed with water (3 × 6.63 L), and the filter cake was dried under a stream of nitrogen to afford **9a** as a pale-yellow solid (3.30 kg, 89% yield). Mp 223−225 °C. IR: 1638, 1601, 1573, 1530, 1506, 1439, 1296, 1276, 1250, 1190, 1144, 1104, 1063, 1003, 961, 917, 844, 812, 776, 750, 735, 704, 683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.86 (s, 1H), 7.60 − 7.52 (m, 1H), 7.34 − 7.07 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3 (J_{CF} = 252, 11 Hz), 160.2, 157.3 (J_{CF} = 254, 13 Hz), 141.3, 136.5, 135.6, 129.4 (J_{CF} = 10 Hz), 120.6 (J_{CF} = 13 Hz, 3 Hz), 112.5 (J_{CF} = 23, 3 Hz), 109.2, 106.9, 106.2 (J_{CF} = 26, 22 Hz). HRMS *m/e* Calcd for $C_{12}H_7N_3OF_2Br$ (M + H): 325.9735. Found: 325.9732.

5-Amino-1-(2,6-difluoro-phenyl)-1*H*-pyrazole-4-carbonitrile (6b). A 60-L jacketed reactor equipped with a mechanical stirrer, a reflux condenser, and a nitrogen inlet was charged with 2,6-difluorophenylhydrazine hydrochloride (**5b**) (3.2 kg, 17.72 mol), 2-(ethoxymethylene)malononitrile (2.32 kg, 18.61 mol) and acetic acid (16.0 L). The jacket temperature was set to 0 °C, and 10 N aqueous NaOH (2.66 L, 26.58 mol) was added over 9 min. The batch was aged for 1.75 h at 25 °C to achieve complete adduct formation (>1 A% **5b** by HPLC), at which time the mixture was heated to 60 °C for 2.3 h (<0.5 A% of the adduct remained). The mixture was then cooled to 0 °C, the pH was adjusted to 5.25 with 5 N aqueous NaOH (34 L) at such a rate as to maintain the batch temperature <25 °C, and

then aged at 20 °C for 16 h (supernatant concentration of **6b** = 3.2 mg/mL). The mixture was then filtered and washed with water (3 × 6.4 L) followed by toluene (3 × 3.6 L), and then the cake was dried under a nitrogen stream to give **6b** as an orange solid (3.36 kg, 71% yield).

To a dry 2.0-L jacketed reactor equipped with a nitrogen inlet, temperature probe, glycol-cooled condenser, and mechanical stirring, was charged with 2,6-difluorobenzenediazonium tetrafluoroborate (**25**) (65.2 g, 219.4 mmol), *L*-ascorbic acid (39.8 g, 226 mmol), and acetonitrile (250 mL). Water (19.8 g, 1.09 mol) was added to the reaction mixture, stirring was initiated, the jacket was set to 20 °C, and the mixture was stirred until complete consumption of the 2,6-phenyldiazonium tetrafluoroborate (typically 30 min). Methanesulfonic acid (28.5 mL, 438.8 mmol) was added over 15 min followed by methanol (50 mL, 1.23 mol); the internal temperature was then increased to 60 °C and held for >5 h (>95% hydrazine by HPLC). The mixture was then cooled to 20 °C, and 10 N NaOH (83 mL, 830 mmol) was added over 20 min until the pH = 6. 2-Ethoxymethylene malonitrile (26.8 g, 219.4 mmol) was then added to the biphasic mixture, and the temperature was increased to 80 °C and the mixture stirred for >4 h (>95% product by HPLC). The solvent was then switched to isopropyl acetate *via* distillation under vacuum (≤3% by GC, ~5 V IPAc final), and 5 N NaOH (250 mL, 1.25 mol) was added. The resulting mixture was stirred for 30 min and then filtered to remove brown solids. The reactor and wetcake were washed with isopropyl acetate (150 mL, 3.0 V), and the biphasic mixture was charged back into the 2.0-L reactor. The layers were separated, and the organic layer was washed with a 1:1 brine/water (250 mL) mixture. The solvent of the organic layer was switched to 2-BuOH (≤3% IPAC by GC, ~2 V 2-BuOH final) *via* vacuum distillation, the mixture was heated at 50 °C until homogeneous, and then heptane (150 mL, 3 V) was added slowly over 1 h. The solution was then cooled to 30 °C over 1 h, and held at 30 °C for >30 min. A heat cycle was then applied (60 °C for >30 min, cool 20 °C over >1 h) and then held until the mother liquors concentration of **6b** was <25 mg/mL. The resulting slurry was then filtered, and the cake was washed with toluene (1 × 150 mL) and heptane (1 × 150 mL) and dried to constant mass under vacuum/N_2 at room temperature to give **6b** as a tan solid (24.9 g, 48% yield). Mp 130−131 °C. IR: 3324, 3228, 3193, 2225, 1645, 1600, 1568, 1539, 1501, 1476,1246, 1005, 950, 967, 750, 703, 722, 669 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1 H), 7.66 (m, 1 H), 7.35 (t, J = 8.3 Hz, 2 H), 6.95 (s, 2 H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 158.5 (J_{CF} = 253, 3 Hz), 153.7, 142.9, 132.4(J_{CF} = 10 Hz), 114.6, 114.0 (J_{CF} = 16 Hz), 112.8 (J_{CF} = 23, 14 Hz), 71.7. HRMS *m*/*e* Calcd for $C_{10}H_7F_2N_4^+$ (M + H): 221.0633; Found 221.0628.

5-Amino-1-(2,6-difluoro-phenyl)-1*H*-pyrazole-4-carbaldehyde (7b). A 10 L Buchi autoclave equipped with a mechanical stirrer was charged with a solution of 5-amino-1-(2,6-difluorophenyl)-1*H*-pyrazole-4-carbonitrile (**6b**) (1.74 kg 6.4 mol) in acetic acid (5.7 L). Raney nickel 2400 (83.54 g) in water (0.9 L) was then charged followed by a water rinse (1.0 L). The autoclave was purged with 15 psig hydrogen and then evacuated (5 cycles). Hydrogen was charged to the autoclave to a final pressure of 15 psig, agitation initiated (800 rpm) and the mixture was stirred for 6.5 h (<1 A% **6b** by HPLC). The hydrogen was then purged from the autoclave with argon, the Raney nickel was removed *via* filtration (1 and 10 μm bag filter), and the reactor was washed with acetic acid (1.5 L). Aqueous 5 N NaOH was added to the reaction mixture over 2.5 h to adjust the pH to 5.23 (supernatant assay **7b** = 1.8 mg/mL), and the resulting slurry was aged for 1 h at 20 °C. The mixture was filtered, and the cake was washed with water (2 × 10.5 L) and dried under a stream of nitrogen to give **7b** as a yellow solid (1.25 kg, 87.4% yield). Mp 169.7−170.5 °C. IR: 3396.5, 3269, 3120, 1644, 1625, 1597, 1545, 1474, 1405, 1355, 1288.5, 1244.0, 1197.9, 1000, 933, 882, 814, 780, 763.7, 735, 717, 632.2, 593, 531, 498, 456 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1 H) 7.89 (s, 1 H) 7.45 − 7.58 (m, 1H) 7.15 (t, J = 8.03 Hz, 2H) 5.68 (s, 2H). ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 184.0, 158.6 (J_{CF} = 257, 4 Hz), 150.6, 142.9, 131.9 (J_{CF} = 10 Hz), 113.6, 112.9 (J_{CF} = 19, 4 Hz), 106.5. HRMS *m*/*e* Calcd for $C_{10}H_8F_2N_3O$ (M + H): 224.0635. Found: 224.0626.

1-(2,6-Difluoro-phenyl)-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid (14b). To a 60-L jacketed reactor equipped with a nitrogen inlet, a temperature probe, a glycol-cooled condenser and a mechanical stirrer, was charged **7b** (2.37 kg, 10.63 mol) and ethanol (6.0 L). Agitation was initiated, diethylmalonate (1.94 L, 12.76 mol) and piperidine (1.10 L; 11.16 mol) were charged and the reaction mixture was heated at reflux (80 °C) for 7 h (96.7 A% **8b**, and 2.3 A% **18b** by HPLC). The batch was then cooled to 30 °C, acetic acid (18.9 L) was charged to the reaction mixture over 20 min, followed by sulfuric acid (1.11 L). The mixture was heated to reflux (batch temperature = 81 °C), and the distillate was collected until the batch reached a final temperature of 108 °C (<1 A% **8b** by HPLC). The reaction mixture was then cooled to 20 °C and held for 1 h. The solids were isolated by vacuum filtration, washed with a 1:3 acetic acid/water mixture (2 × 7 L), water (1 × 7 L) and dried under a stream of nitrogen to afford **14b** as a pale yellow solid (2.8 kg, 90.1% yield). Mp 304−306 °C. IR: 3030, 2951, 2846, 2688, 1718, 1640, 1615, 1599, 1503, 1478, 1464, 1393, 1291, 1248, 1214, 1196, 1076, 1037, 1001, 876, 788, 780, 750, 693, 635, 583, 572, 549 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ 7.44 (t, J = 8.4 Hz, 2 H) 7.73 (m, 1 H) 8.43 (s, 1 H) 8.87 (s, 1 H), 13 (bs, 1 H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.0, 165.00, 158.1 (J_{CF} = 253.1, 3.2 Hz), 148.39, 138.8, 138.7, 132.5 (J_{CF} = 10 Hz) 114.1 (J_{CF} = 16 Hz) 112.8 (J_{CF} = 19, 3 Hz) 108.9, 108.6. HRMS *m*/*e* Calcd for $C_{13}H_8F_2N_3O_3$ (M + H): 292.0534. Found: 292.05284.

5-Bromo-1-(2,6-difluoro-phenyl)-1,7-dihydro-pyrazolo[3,4-*b*]pyridin-6-one (9b). A dry 60-L jacketed reactor equipped with a nitrogen inlet, a temperature probe, a glycol-cooled condenser, and a mechanical stirrer was charged with **14b** (2.76 kg, 9.48 mol), lithium acetate (63.5 g, 0.95 mol), tetrahydrofuran (19.3 L) and water (1.38 L). Efficient stirring was established, and *N*-bromosuccinimide (1.86 kg, 10.4 mol) was added at 20 °C in four portions over 3 h, during which the reaction mixture turned from a slurry into a yellow solution which was

accompanied by gentle off-gassing. The mixture was stirred at 20 °C for 2 h, and then heated to 50 °C for 1 h (0.1 PA% **18b** remained by HPLC). The reaction mixture was cooled to 20 °C, water (37.3 L) was added over 70 min, and the batch was aged for 2 h at 20 °C. The resulting slurry was then filtered, the cake was washed with a 2:1 mixture of tetrahydrofuran: water (2 × 8.28 L) and dried under a stream of nitrogen to afford **9b** as a pale yellow solid (2.8 kg, 91% yield). Mp 223−225 °C. IR: 1628, 1600, 1572, 1530, 1501, 1484, 1394, 1280, 1250, 1188, 1143, 1103, 1059, 1004, 915, 844, 794, 777, 752, 724, 704 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 8.52 (s, 1H), 8.23 (s, 1H), 7.80−7.64 (m, 1H), 7.48−7.40 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.6, 158.3 (J_{CF} = 253 Hz, 3 Hz), 147.9, 136.9, 136.8, 132.6 (J_{CF} = 10 Hz), 114.8 (J_{CF} = 17 Hz), 112.7 (J_{CF} = 22 Hz), 109.8, 103.4. HRMS *m*/*e* Calcd for $C_{12}H_7N_3OF_2Br$ (M + H): 325.9735. Found: 325.9737.

5-Bromo-1-(2,4-difluoro-phenyl)-7-methyl-1,7-dihydro-pyrazolo[3,4-*b*]pyridin-6-one (10b). A 60-L jacketed reactor equipped with a nitrogen inlet, a temperature probe, a glycol-cooled condenser, and a mechanical stirrer was charged with **9b** (2.78 kg, 8.55 mol) followed by tetrahydrofuran (14 L). Agitation was initiated, and lithium *tert*-butoxide (0.75 kg, 9.4 mol) was added portion-wise, maintaining the internal temperature below 30 °C. The mixture was stirred at 20 °C for 30 min during which time the mixture became homogeneous. Iodomethane (2.43 kg, 17.1 mol) was then added, the jacket was set to 40 °C, and the mixture was stirred for 18 h (>1.5 A% **9b** by HPLC). Water (42 L) was then added over 2 h, and the mixture was aged for an additional 2 h. The slurry was then filtered, and the filter cake was washed with water (2 × 8.5 L) and dried under a stream of nitrogen to afford **10b** of as a colorless solid (2.65 kg, 90% yield). Mp 188−189 °C; IR: 3090, 1645, 1667, 1472, 1002, 988, 773, 744 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.16 (s, 1H), 7.83−7.76 (m, 1H), 7.48 (t, J = 9.0 Hz, 2H), 3.27 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.5 (J_{CF} = 253.2, 2.6 Hz), 157.2, 143.0, 137.5, 134.9, 133.2 (J_{CF} = 10 Hz), 115.9 (J_{CF} = 17 Hz), 112.6 (J_{CF} = 19, 4 Hz), 109.2, 105.4, 30.1. HRMS *m*/*e* Calcd for $C_{13}H_9BrF_2NO_3$ (M + H): 339.9892, Found: 339.9884.

3-[1-(2,6-Difluoro-phenyl)-7-methyl-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-4-methyl-benzoic Acid (12b). A 100-L jacketed reactor equipped with a mechanical stirrer, a condenser, and a nitrogen inlet was charged with 5-bromo-1-(2,6-difluorophenyl)-7-methyl-1*H*-pyrazolo[3,4-b]pyridin-6(7H)-one (**10b**) (2.0 kg, 93.8 wt %, 5.52 mol), 3-borono-4-methylbenzoic acid (**13**) (1.33 kg, 87.2 wt %, 6.45 mol) and isopropanol (5.0 L). Agitation was initiated and a solution of K_3PO_4 (3.52 kg, 16.6 mol) in water (10.0 L) was charged to the reactor followed by a slurry of palladium bis-(4-dimethylaminophenyl-di-*tert*-butylphosphine) dichloride (4.2 g, 6 mmol) in isopropanol (20 mL). The atmosphere was inerted, the jacket temperature was set to 85 °C, and the reaction mixture was stirred for 1 h (<1 A% **10b** by HPLC). The reaction mixture then was cooled to 20 °C, and the layers of the resulting biphasic mixture were separated. The top organic layer was retained, water (1.5 L) was added to this, and the resulting solution was washed with toluene (2.5 L). The lower aqueous layer was polish filtered and then diluted with isopropanol (8.0 L). The colorless solution was then heated to 70 °C, and 2 N aqueous HCl (4 L, 8 mol) was added slowly over 45 min to adjust the pH to 3. The resulting mixture was then cooled to 20 °C over 1 h and aged for a further 12 h (supernatant concentration of **12b** = 1 mg/mL). The mixture was then filtered, washed with a 1:2 isopropanol/water mixture (2 × 6.0 L), and dried under a stream of nitrogen to afford **12b** as a colorless solid (2.05 kg, 93.4% yield). Pd: <0.5. Mp 272−273 °C. IR: 2945, 1701, 1623, 1598, 1552, 1538, 1507, 1475, 1213, 1189, 783, 772, 740, 651 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.20 (s, 1H), 7.91 (s, 1H), 7.87 (dd, J = 2.4, 8.0 Hz, 1H), 7.75−7.82 (m, 2H), 7.49 (t, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 1H), 3.28 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 160.1, 158.2 (J_{CF} = 251 Hz, 2 Hz), 156.9, 143.4, 142.3, 138.3, 137.6, 133.1 ($J_{C\ F}$ = 10 Hz), 132.4. 131.1, 130.0, 128.6, 128.2, 116.3 (J_{CF} = 17 Hz), 112.7 (J_{CF} = 15, 3 Hz), 104.9, 29.0, 19.8.. HRMS *m*/*e* Calcd for $C_{21}H_{16}F_2N_3O_3$ (M + H): 396.1154. Found: 396.1160.

***N*-Cyclopropyl-3-[1-(2,6-difluoro-phenyl)-7-methyl-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-4-methyl-benzamide Hydrate (4-Hydrate).** A dry 60-L jacketed reactor equipped with a nitrogen inlet, a temperature probe, a glycol-cooled condenser, and a mechanical stirrer was charged with **12b** (1.8 kg, 4.56 mol) and tetrahydrofuran (27.4 L). The jacket temperature was set to 20 °C, carbonyldiimidazole (0.96 kg, 5.9 mol) was charged in four equal portions, and the mixture was aged for 1.5 h (<0.1 A% of **16b** by HPLC). The reaction was then heated to 30 °C, and cyclopropylamine (1.120 L, 9.2 mol) was charged over 2 min (max. batch temperature = 42.5 °C). The mixture was aged at 50 °C for 16 h, and then 9.75 L of solvent was removed *in vacuo*. Isopropyl acetate (18.0 L) was charged to the reactor,,,,, and a further 18.0 L of solvent was removed *in vacuo*. Additional isopropyl acetate (7.2 L) was charged, the mixture was cooled to 20 °C and then stirred for 1 h at 20 °C (supernatant concentration of **4** = 3.0 mg/mL). The reaction mixture was then filtered, the cake was washed with isopropyl acetate (2 × 7.2 L) and dried under a stream of nitrogen to afford 4-IPAc as a colorless solid (1.99 kg, 94.2% yield). 4-IPAc (1.95 kg, 4.48 mol) followed by a 9:1 mixture of EtOH:water (62.4 L) was charged to a 100-L jacketed reactor equipped with a nitrogen inlet, a temperature probe, a glycol-cooled condenser and a mechanical stirrer. The mixture was heated to 41 °C, stirred until homogeneous, and then polish filtered into a 100-L jacketed reactor equipped with a nitrogen inlet, a temperature probe, a glycol-cooled condenser, and a mechanical stirrer. The lines, reactor, and filter were washed with warm 9:1 EtOH/water (3 × 1.2 L), and the resulting spec-free solution was distilled at atmospheric pressure to remove 48 L of solvent mixture. The batch temperature was adjusted to 70 °C, seed (9.75 g, 0.5 wt %) was added as a slurry in 1:1 EtOH/water (200 mL), and the mixture was cooled to 20 °C over 4.75 h (supernatant concentration of **4** = 10 mg/mL). Water (11.7 L) was added over 24 min, and the batch was aged for an additional 2 h

(supernatant concentration of **4** = 1.34 mg/mL). The resulting slurry was filtered, the cake was washed with water (2 × 5.9 L) and then dried under nitrogen to give **4-hydrate** as a colorless solid (1.88 kg, 96.4% yield). Mp (hydrate) 240−241 °C. IR: 3520, 3290, 1622, 1608, 1556, 1536, 1530, 1477, 1006, 991, 793, 786, 773, 761, 748, 726 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, J = 3.5 Hz, 1H), 8.20 (s, 1H), 7.89 (s, 1H), 7.85−7.72 (m, 2H), 7.68 (s, 1H), 7.49 (t, J = 8.6 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H), 3.26 (s, 3H), 2.90−2.82 (m, 1H), 2.19 (s, 3H), 0.73−0.65 (m, 2H), 0.59−0.52 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 160.1, 158.2 (J_{CF} = 252, 3 Hz), 143.3, 140.2, 138.2, 137.2, 133.1 (J_{CF} = 10 Hz), 135.3, 131.6, 129.5, 128.9, 126.5, 125.8, 116.3 (J_{CF} = 16 Hz), 112.7 (J_{CF} = 19, 3 Hz), 29.0, 23.0, 19.5, 5.6. HRMS *m*/*e* Calcd for $C_{24}H_{21}F_2N_4O_2$ (M + H): 435.1627. Found: 435.1615.

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Supporting Information Available

Raman spectra from in-situ monitoring of the cooling crystallization and NMR spectra of all intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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