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Development and a Practical Synthesis of the JAK2 Inhibitor LY2784544

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Supporting Information

ABSTRACT: The route selection and process research and development of a practical synthesis for JAK2 inhibitor LY2784544 is described. The first-generation synthesis route, similar to that used in discovery for derivatization of a benzylic amine moiety, was 14 overall steps and possessed several steps that required extensive development for large-scale production. Route selection considerations led to a modified synthesis that utilized a novel vanadium-catalyzed carbon−carbon bond-forming arylation reaction for incorporation of the key benzylic morpholine moiety. A protecting group used to mask an amino pyrazole unit was modified from PMB to *tert*-butyl, resulting in a dramatic reduction in the overall length of the route. These two major changes resulted in an eight-step synthesis, which was six steps shorter than the first-generation synthesis. In the pilot plant, the new synthesis was scaled to produce >100 kg of LY2784544 in high yield and purity under GMP conditions. The overall development including the vanadium-catalyzed C−C bond-forming methodology, a ketone reductive deoxygenation, and a palladium-catalyzed amination is described.

INTRODUCTION

Janus kinase 2 (JAK2) is a human protein tyrosine kinase found in the cytosol that is responsible for nucleotide binding, ATP binding, and transferase activity.[1] The JAK2-V617F mutation occurs when the valine at position 617 of wild-type JAK2 is substituted by phenylalanine, and is the most common molecular abnormality in BCR/ABL-negative myeloid proliferative neoplasms.[2] Myeloproliferative neoplasms such as polycythemia vera (PV), essential thromocytosis (ET), and primary myelofibrosis (PMF) are disorders characterized by abnormal production of blood cells in the bone marrow; these chronic disorders are associated with splenomegaly and the development of leukemia. The JAK2-V617F mutation is present in ∼95% of patients with PV and ∼60% of patients with either ET or PMF. Mutant JAK2 therefore constitutes a potential therapeutic target for myeloproliferative neoplasms, and small-molecule inhibitors of JAK2 have become targeted by the pharmaceutical industry.[3] Examples of JAK2 inhibitors that are undergoing clinical evaluation are presented in Figure 1. LY2784544 (**1**, Scheme 1) has been identified as being highly selective for JAK2-V617F and has advanced into human clinical trials for the treatment of several myeloproliferative disorders.[4] This article describes the ongoing chemical development efforts associated with supply of **1** for the ongoing clinical trials.

The molecular architecture of LY2784544 presents several challenges to the synthetic chemist. As a kinase inhibitor with a dense array of nitrogen atoms, many intermediates can be expected to be sparingly soluble in common organic solvents, which presents challenges to development efforts. At its core, **1** contains a highly functionalized imidazopyridazine, with only one position being unsubstituted. By far the most challenging moiety is the benzylic morpholine at C-8, as the requisite C−C bond is not readily available through commercial starting materials,

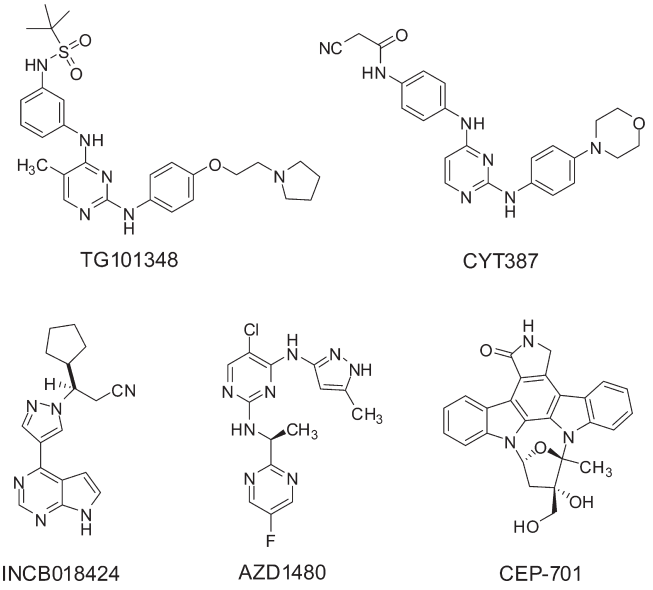

Figure 1. Examples of JAK2 inhibitors.

and must be constructed de novo. The retrosynthesis for **1** is shown in Scheme 1 and relies on a late-stage amination to join an appropriate aminopyrazole (**2**−**4**) with the chloro-imidazopyridizine **5**. Chloride **5** can be constructed from the key building block pyridazine **6** by installation of the benzylic morpholine. Finally, condensation of amidine **7** with α-chloroketone **8** forms

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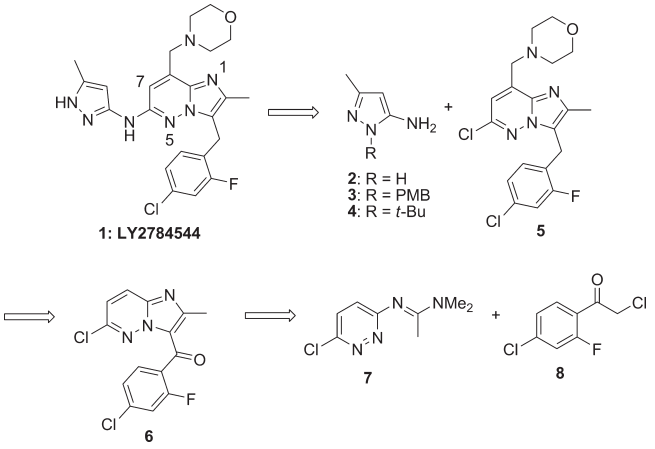
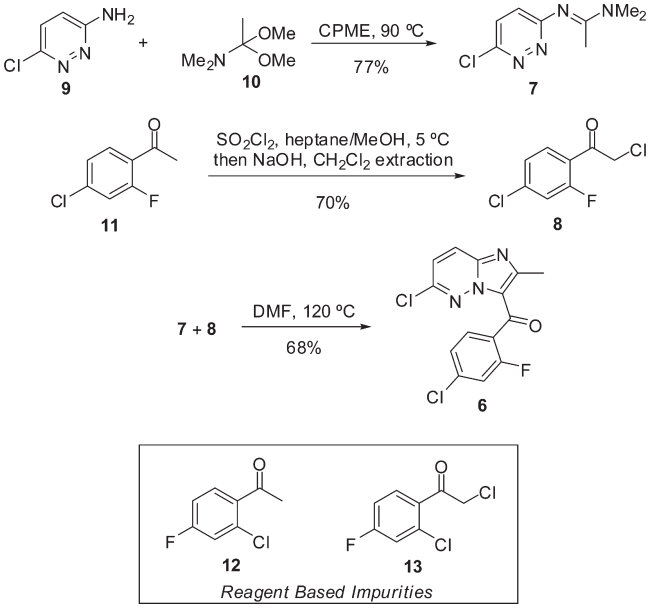
Scheme 1. LY2784544 and retrosynthesis



Scheme 2. First-generation approach to core



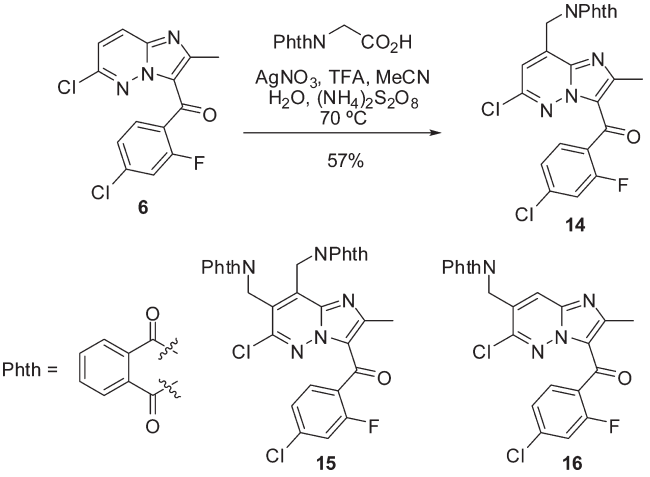
the core imidazopyridazine **6** from readily procured commercial chemicals.

This retrosynthetic plan was utilized for the discovery synthesis and was amenable for the preparation of analogues. Having a need to rapidly prepare API, the retrosynthesis method was also utilized for the first- and second-generation syntheses. As the first-generation synthesis consisted of many limitations, route selection activities resulted in a much more robust second-generation approach. The process development efforts involved with the two approaches are described.

RESULTS AND DISCUSSION

First-Generation Synthesis. The first-generation synthesis utilized readily available 6-chloropyridazin-3-amine (**9**) as starting material (Scheme 2). In three overall steps, a highly functionalized intermediate, imidazopyridazine **6** was rapidly prepared by means of: (i) amidine formation with the dimethylacetal of

Scheme 3. First-generation synthesis free radical alkylation



N,N-dimethylacetamide (**10**) in cyclopentyl methyl ether (CPME) to give amidine **7**,[5] (ii) α-chlorination of acetophenone **11** to give α-chloroketone **8**, and (iii) condensation of **7** and **8** in DMF at elevated temperature to afford **6**.

During the first pilot-plant campaign the presence of isomeric downstream compounds derived from acetophenone isomer **12** was observed. The existence of these impurities was the result of having obtained an impure lot of **11**, which contained 9.6% of isomer **12** by ^{1}H NMR analysis. The fact that **11** was contaminated was not immediately detected, as the certificate of analysis from the supplier claimed high purity, and the preliminary analytical method for detection was not capable of isomer separation; hence, the impure material had been used in production. Due to its volatility (**8** readily sublimes) coupled with lachrymatory properties, efforts were made to minimize handling/exposure, and α-chloroketone **8** was isolated by extraction and utilized in the subsequent step as a solution, which offered no opportunity for isomer rejection. While the impurities were gradually purged to low levels during subsequent isolations, we felt that a control strategy would be needed for future scaleup.

Installation of Morpholine Methyl by Free Radical Alkylation. The strategy to install the benzylic morpholine required three steps. First, Minisci free radical alkylation[6] with *N*-phthaloylglycine introduced the benzylic amine in a protected fashion (Scheme 3). This reaction was complicated by significant competing reactions: *bis*-alkylation at both the C-7 and C-8 positions, and regioisomer alkylation at C-7. Attempts to improve regioselectivity in this step above ~3:1 in favor of **14** were unsuccessful. Furthermore, the introduction of the phthalimide to the imidazopyridizine core yielded products which suffered from extreme insolubility and rapidly precipitated during the course of the reaction, which complicated attempts at reaction optimization, reaction sampling, and isolation/purification. Due to these difficulties, combined with the poor reproducibility of the reaction, the decision was made to scale to only 50-L batch size, and production of 39 kg of **14** was accomplished in a total of 11 batches, which severely limited throughput. While regioisomer **16** was consistently observed to purge to <3% (by HPLC) in the isolated solids, the ranges of extremely insoluble *bis*-adduct **15** varied wildly between 9 and 20% in the isolated product! Fortunately, the *bis*-alkylated products purged well in

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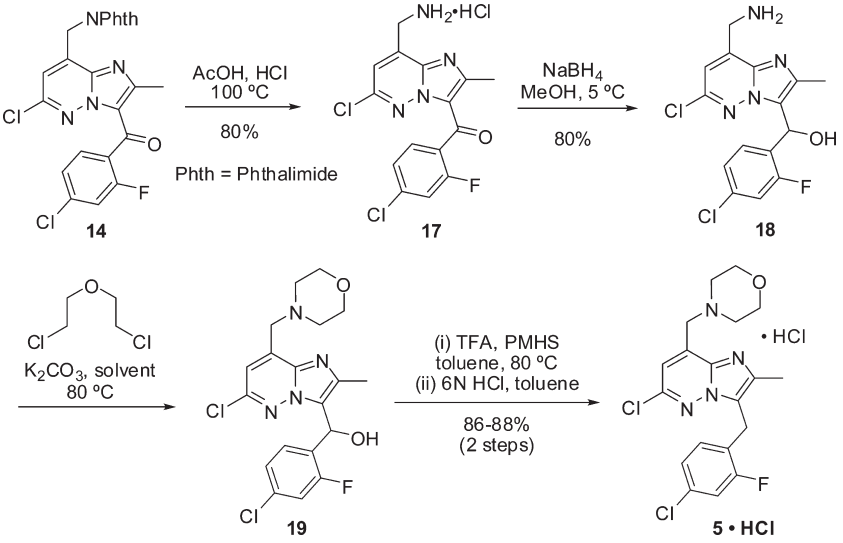
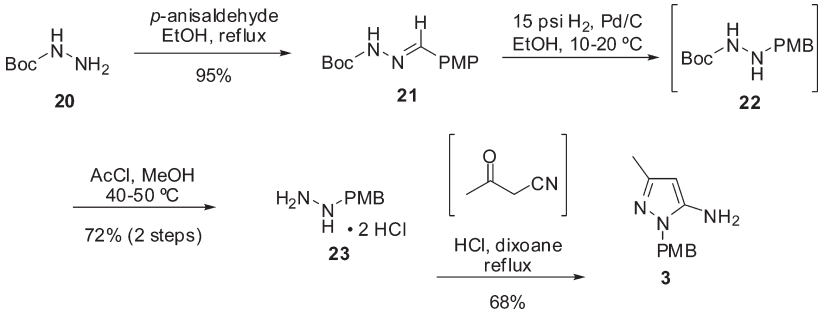
Scheme 4. Completion of first-generation building block synthesis



Scheme 5. First-generation pyrazole preparation



downstream isolations, and this problem was not ultimately impactful on final active pharmaceutical ingredient (API) quality. An additional consideration for the Minisci chemistry was the relatively high levels of silver used in the step, as it was noted to purge at a gradual rate in downstream intermediates. Control of residual silver, should this step be further developed, would need to be addressed. These considerations combined to make replacement of this step our top priority in development of a second-generation route.

Deprotection of the primary amine occurred uneventfully using a mixture of HCl in AcOH, providing hydrochloride **17** (Scheme 4). In order to avoid undesirable potential S_NAr byproducts, the ketone was reduced with $NaBH_4$ to yield alcohol **18**. Morpholine construction was then achieved using *bis*-chloroethyl[7] ether as solvent in the presence of aqueous K_2CO_3. Without isolation of **19**, the crude solution was extracted into toluene and dried azeotropically. TFA and polymethylhydrosiloxane (PMHS) were added, and ketone deoxygenation was then completed under ionic conditions. Previous synthetic efforts had utilized the freebase of **5**, but we found that formation of the hydrochloride salt yielded a significant purity upgrade and greatly facilitated isolation. It appeared that the HCl salt formation was particularly adept at purging polymeric residues left over from use of the PMHS, which greatly compromised the isolation of a downstream intermediate.

Preparation of PMB-Protected Pyrazole 3. A protected amino pyrazole was required because attempts to couple the unprotected amino pyrazole **2** suffered from poor conversion and competing reaction with the pyrazole nitrogens, which resulted in a 3:1 selectivity. PMB-protected pyrazole **3** was prepared using a four-step sequence shown in Scheme 5. *p*-Methoxybenzaldehyde was condensed with Boc-hydrazine to form hydrazone **21**. Reduction of the hydrazone was achieved using hydrogenation conditions to afford 1,2-disubstituted hydrazine **22**. Without isolation of **22**, the Boc group was removed using HCl generated in situ from acetyl chloride and MeOH, and the resulting dihydrochloride salt **23** was isolated in 72% yield over the two steps. Finally, benzyl hydrazine **23** was treated with in situ generated 2-cyanoacetone in order to form pyrazole **3**, the structure of which was confirmed by two-dimensional ^1H NMR analysis and single-crystal X-ray analysis of a subsequent intermediate. Generation of the in situ 2-cyanoacetone was accomplished by reacting methyl acetate with acetonitrile, potassium *tert*-butoxide as base, and THF as solvent at ambient temperature. Although the chemistry utilized to produce **3** was reasonably straightforward, we wondered whether a commercially available or more readily synthesized pyrazole might be available to shorten the synthesis.

The discovery chemistry route has also utilized the same building blocks as we had converged upon for the first-generation

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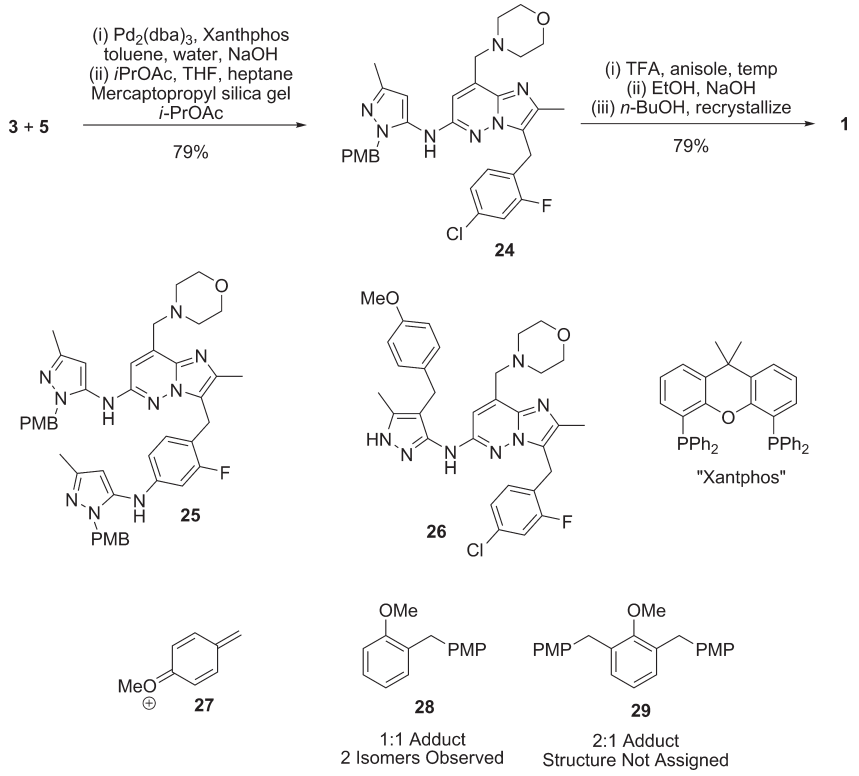
Scheme 6. Completion of the first-generation synthesis of LY2784544



approach (Scheme 6). This sequence was completed by an amination reaction, chromatography of **24** (isolated as a foam), and removal of the PMB protecting group by treatment with neat TFA, which had resulted in the formation of a polymeric residue that complicated isolation of the final API.[8]

Amination Reaction of 3 and 5. A Pd-catalyzed amination reaction[9] was required for the coupling of **3** and **5**. A simple S_NAr reaction was not capable of forming the desired C−N bond (Scheme 6). A brief screen of the required ligands, Pd source, Pd loading, solvents, and base led us to the use of toluene with aqueous NaOH and XantPhos with Pd_2dba_3 as Pd source. Furthermore, significant efforts were invested in identifying a crystalline form of **24**. This intermediate was the last intermediate in the synthesis sequence, and its isolation by crystallization would be an asset in the overall purification strategy of the final API. Crystalline **24** was produced by slow evaporation from MeOH. The crystals that resulted from the methanol evaporation were then utilized as seeds in the development of a robust crystallization process with toluene as solvent. Next, we addressed the concern of residual Pd in the product, and employed a mercaptopropyl silica gel (Silicycle) treatment of the crude product as a THF solution (THF was utilized as solvent to prevent product crystallization during the silica treatment). Finally, removal of THF and concentration in vacuo were accomplished, which resulted in crystallization at scale, and further solvent exchange to *i*-PrOAc resulted in the final product slurry. These conditions worked well at scale, and resulted in a 79% isolated yield of **24**. A byproduct of the amination reaction was *bis*-pyrazole **25**, which was observed to purge very well during the crystallization of **24**.

The PMB protecting group was removed with TFA in the presence of anisole to yield the technical grade API **1** (Scheme 6). The use of anisole deserves comment as it was observed to be a good acceptor of quinone methide **27** generated by PMB cleavage, and was key to elimination of impurities that had been formed during previous efforts in this step. A minor observed impurity generated in this reaction was arylated product **26**, which can be rationalized by attack of the electron-rich and nucleophilic pyrazole nucleus on **27**. After removal of the PMB, the acidic reaction mixture was diluted with aqueous EtOH and washed with heptane to remove anisole, 1:1 byproducts **28** and 2:1 byproducts **29**.[10] Neutralization of the EtOH layer with NaOH resulted in crystallization of the technical grade API. The technical grade API was then taken up in hot *n*-BuOH, polish filtered, and concentrated under vacuum, which resulted in crystallization of the desired final API. The vacuum distillation of *n*-BuOH had the added benefit of azeotropic water removal, as it was determined that the presence of water in the crystallization had the effect of dramatically increasing the solubility of **1**.

The first-generation synthesis delivered 7 kg of final API in 4.3% yield over the longest linear sequence. This campaign was a development of existing routes to **1** and utilized largely existing technology. It afforded time to begin the process of route selection for a long-term manufacturing route. Foremost among the synthetic challenges was installation of the benzylic morpholine unit; the low yield of the radical alkylation and the processing difficulties involved with production of sufficient product for a 7-kg delivery, coupled with the overall three-step installation made investigation of morpholine construction our top development priority. Ketone **6** was viewed as an excellent intermediate because it could be prepared in three steps, and it was also a

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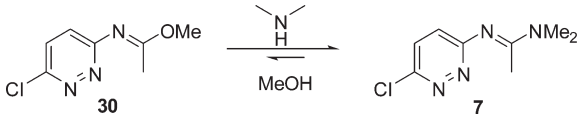


Figure 2. Imidate−amidine equilibrium.

very stable crystalline intermediate with high purity. Therefore, we wanted to utilize **6** in our synthesis route selection designs as a long-term intermediate. Thus, our route selection efforts here would begin with attempts to append the benzylic morpholine unit onto the core, **6**. Our next priority for a second pilot-plant campaign was the replacement of PMB−pyrazole **3** with a commercially available substitute, or one prepared in a more efficient manner. Additionally, we felt that there was a good opportunity to implement a single-step deoxygenation of the ketone directly to the diarylmethane and save a processing step in the route. Finally, there were several conditions we felt could be improved in order to enhance our impurity control strategy. In addition, we wanted to investigate the overall solvent selection, and process mass intensity (PMI).[11]

Second-Generation Synthesis. *Development of Key Building Blocks and Compound* ***5***. The first problem we faced for the preparation of **6** was understanding the reaction that formed imidate **7**. Methyl imidate **30** was a transient intermediate (Figure 2). We observed that once formed, the ether slowly converted to desired amidine **7**, presumably from the presence of dimethylamine in solution.[12] Methyl imidate **30** does not cleanly convert to **6** upon treatment with ketone **8**, and its presence in the isolated **6** was undesired. Prior to these development efforts, the reaction had been run at plant scale under gentle distillation conditions in order to sequester the derived MeOH, which had the added benefit of increasing the boiling temperature of the reaction mixture. We found that methanol removal was not necessary to drive the reaction to high conversion and likely played a detrimental role to the reaction performance by removing volatile dimethylamine from the system.

Previously, **7** had been observed to crystallize directly from CPME upon cooling, but recovery was only 77%, as **7** had high solubility in CPME. With the desire to use toluene for the reaction in mind after a solvent screen had been conducted, we conducted solubility screening on **7** in various toluene/antisolvent mixtures and found an excellent solubility relationship with toluene/heptane mixtures. We chose to target a final solvent composition of toluene−heptane in order to maximize recovery yield. It was determined that even the low levels of MeOH produced in the reaction provided a dramatic increase in the solubility of **7**, and upon reaction completion it was desirable to remove MeOH from the system. In order to achieve this solvent composition, half of the volumes of reaction solvent were removed in vacuo upon completion of the reaction. The solution was cooled to 40 °C, at which time heptane was added. Seed crystals could then be introduced, and the slurry was then gradually cooled to 0−5 °C and filtered. Impurities, including imidate **30**, which were typically present at levels of 1−5% at the end of the reaction purged well under these conditions. A 450-g demonstration of this procedure was performed, and provided a 92% isolated yield of **7**.

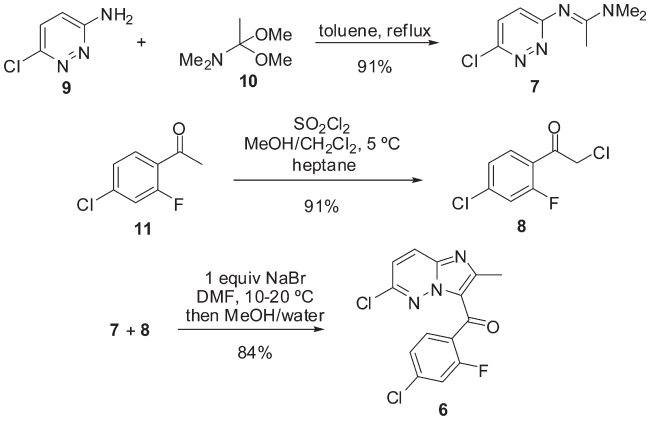
The chlorination of **11** had been performed by slow addition of a solution of sulfuryl chloride in heptane to a chilled mixture of **11** in heptane and methanol. Ketone **11** is a liquid, and it was noted that copious amounts of solid product **8** form during the chlorination reaction. The reaction mixture typically became quite thick, which impeded agitation and made sampling difficult. Upon reaction completion, CH_2Cl_2 was added to completely dissolve the solids and facilitate aqueous washes.

It was during this optimization work that we developed a control strategy for rejection of isomer **13**. We were able to isolate a crystalline sample of ketone **13** and performed solubility comparisons with **8**; these studies clearly showed that **13** possessed higher solubility in a variety of solvent systems. This encouraged us in that it appeared reasonable that **13** could be rejected by crystallization. We modified the workup by addition of EtOAc to the reaction slurry, which dissolved **8** and **13** completely, followed by a wash with aqueous NaOH. Layer separation and a water wash were followed by concentration and solvent exchange back into heptane, which was accompanied by spontaneous nucleation of desired α-chloroketone **8** as a crystalline solid. A 700-g demonstration batch was run under the optimal conditions and afforded product containing 1.1% of isomeric impurity **13** in 73% isolated yield. Although the yield was somewhat low, when it is taken into consideration that 10% of the starting material was the undesired isomer (which was mostly purged in this step), the corrected yield was 81%. Fortunately, future supplies of **11** were virtually devoid of the isomer since a specification on the isomer content was put in place along with appropriate analytical methodology. At scale, the precipitation of the product during the reaction was undesirable, and it was found that the reaction could best be run as a single phase when CH_2Cl_2 was used as solvent. Furthermore, high-quality crystalline product could be isolated after aqueous quenching by concentration of the CH_2Cl_2 solution and partial solvent exchange into heptane.

The existing method for formation of the imidazopyridizine core relied on heating **7** and **8** in DMF at 120 °C for 3−8 h. In the kilo lab, these conditions resulted in 81% isolated yield, but the material produced in this fashion was highly colored. Furthermore, the incorporated extractive workup had rendered the process volume intensive (40 total solvent volumes). During development of this procedure we found that much of the color could be removed by recrystallization from EtOH, but this resulted in a decreased recovery for the overall process. Due to the color, high volumes, recrystallization requirement, and modest recovery, further development was merited.

From a similar system, we knew that Finkelstein reaction conditions were capable of reducing the temperature required for the transformation.[13] We had speculated that the color formation was a result of the high temperatures employed; therefore, this methodology had the potential to eliminate the color. Due to its high solubility in many organic solvents, preliminary efforts employed LiBr in refluxing acetone. With one equivalent of LiBr, 94 area % of **6** was produced, whereas no LiBr afforded only 28 area % **6** over the same time course. The condensation proved to be superior when conducted in DMF, and in DMF it was determined that NaBr was the best bromide source; after 2 h at 60 °C, 60 area % of **6** was formed. We next surmised that the reaction could likely be run at even lower temperatures. Indeed, this was the case as an early 10-g trial containing one equivalent of NaBr resulted in a 92% isolated yield of **6** after stirring for 24 h at ambient temperature. Furthermore, the isolated solids had very little color, and the isolation was operationally simple and involved addition of water to the reaction mixture and filtration. The primary filter cake was observed to be contaminated with residual chloride and bromide, and bromide ion was identified as detrimental to downstream chemistry. Efforts were made to

Scheme 7. Optimized conditions for production of 6

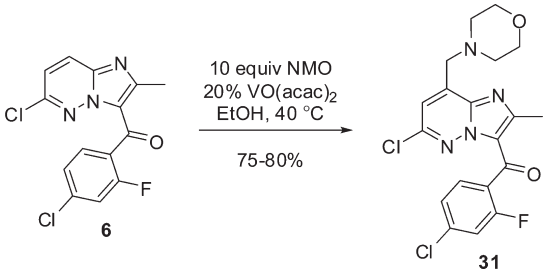


lower the loading of NaBr. Unfortunately, even a 50% loading of NaBr resulted in incomplete reactions and yield reduction. It was necessary to adjust the isolation procedure in order to achieve a high yield, rejection of chloride and bromide, and rejection of residual **8**, which became a problem if too much water was added to precipitate **6** from the reaction mixture. The addition of methanol to the product slurry resulted in good removal of residual **8**, as well as the traces of color that formed in the low-temperature reaction. The final conditions chosen for the reaction are shown in Scheme 7. We were able to lower the solvent volumes for this process to 20, including washes. These conditions were successfully demonstrated at a 500-g scale and resulted in 84% isolated yield.

Development of a $VO(acac)_2$-Catalyzed NMO Addition for the Mannich Product. The installation of the benzylic morpholine was the next subject. One approach we felt that held great potential for a single-step, protecting-group free construction was an electrophilic aromatic substitution involving an iminium ion, such as that derived from morpholine and formaldehyde. Various literature methods for this proposal exists but were unsuccessful when applied for the preparation of **6**.[14] One application we chose to pursue disclosed the $VO(acac)_2$-catalyzed reaction of naphthols and phenols with *N*-methylmorpholine-*N*-oxide (NMO) to provide good yields of the Mannich products.[15]

We began with exposure of compounds **6**, **7**, and **9** to excess NMO with 0.1 equiv of $VO(acac)_2$ in refluxing CH_2Cl_2 for 8 h, and were pleased when **7** provided a 4% conversion to the desired addition product along with >90% unreacted **6**.[16] This result was very encouraging since these conditions had not previously been applied to heterocyclic systems, and the result appeared to be quite regioselective. The challenge for this reaction now became one of trying to push the bulk of **6** to product. Various reaction parameters were investigated in an effort to improve reaction performance and yield. These included reaction temperature, reaction time, solvent, catalyst (loading and catalyst type), Lewis acid, and desiccant additives such as molecular sieves. An early success was recognized with the use of CH_2Cl_2 as solvent. After ~72 h, with 10% $VO(acac)_2$ and a large excess of NMO in the presence of molecular sieves, the reaction progressed to 95% consumption of **7**, and product **31** was isolated in 54% yield. The reaction rate was greatly enhanced in alcoholic solvents and in 2-propanol or ethanol with 15 equiv of NMO and 20% $VO(acac)_2$: complete conversion was observed after 22 h in the

Scheme 8. Vanadium-mediated preparation of 31



absence of molecular sieves. As a proof of concept, the novel reaction was demonstrated using 1 kg of **6** to provide 68% of isolated **31** in >99% purity.

Isolation of **31** from the complex reaction mixture proved to be only a minor challenge. During the reaction with EtOH as solvent, copious amounts of flocculent solids crystallized from solution, and product with good purity (>97 HPLC area %) could be isolated by water addition and filtration. The impurities at the highest levels were residual starting ketone **6** and regioisomer **32**; all other byproducts had sufficiently high solubility in EtOH/water as to have been purged to low levels during isolation. The residual **6** and **32** were rejected to low levels during downstream isolations or other crystallization methods. The spent $VO(acac)_2$ catalyst, and NMO-byproducts remained in the filtrate; the vanadium byproducts appeared to be extremely water-soluble and not readily entrained in the product as simply washing the cake until the washings were observed to be colorless routinely afforded product with vanadium levels of <10 ppm; the deep yellow/orange color of the washings may be indicative of V^{+5}. Because of the successful large-scale demonstration in preparing **31**, this chemistry was incorporated into our selected synthesis route for future development (Scheme 8).

While this transformation accomplished our goal of single-step installation of the benzylic morpholine, a normal HPLC reaction profile contained 15−20 area % of related substances. Several additional products from this unusual reaction were identified and are shown in Figure 3. The regioisomer **32** and *bis*-alkylated byproduct **34** were analogous to those observed in the previous Minisci chemistry. Morpholine **33** ("endo isomer") was noteworthy in that its formation was highly solvent dependent (minimal in EtOH) and indicated the likelihood of two competing reactive species forming from the NMO. Ketone **35** is simply a S_NAr product that can be rationalized by reaction of morpholine (a known byproduct of NMO degradation)[18] and the desired reaction product, **31**. Benzyl alcohol **36** is normally observed at <1% but is an interesting observation; deuterium-labeling studies showed that the newly appended two-carbon side chain originated from the ethanol solvent and not from an NMO decomposition or from acetaldehyde, as a CH_3CHO spiking study produced normal levels of **36**.

The exact chemical mechanism with which this transformation operates is a subject of current investigation in our laboratories. A standard iminium ion mechanism has been proposed that we feel may be operative in the presence of highly nucleophilic substrates.[15] This mechanism does potentially explain the sensitivity of this reaction towards water, as the proposed catalytically active vanadium species possesses a vanadium−oxo bond, that may be in equilibrium with an unreactive hydrated form. In general, it has been observed that exceeding 10 equiv of water

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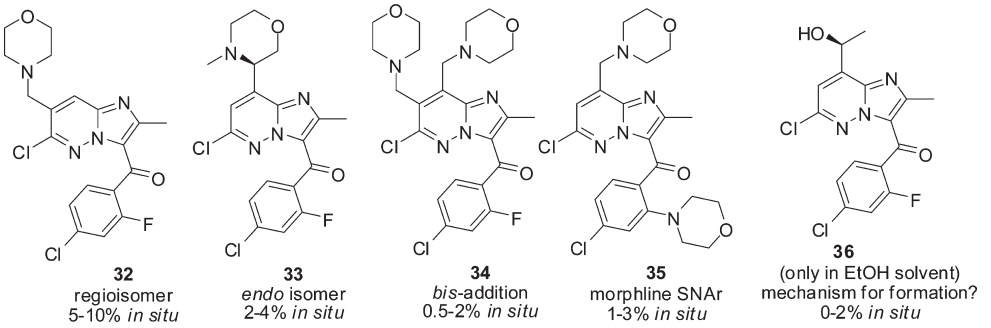


Figure 3. Isolated impurities from vanadium-NMO reaction.

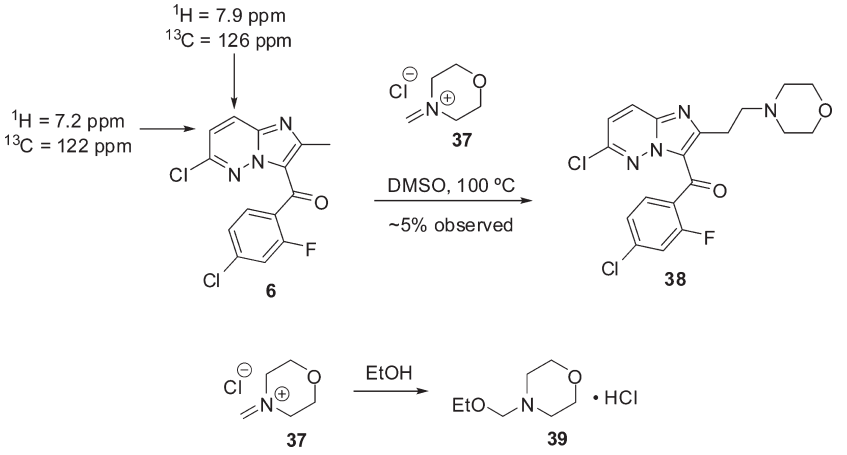
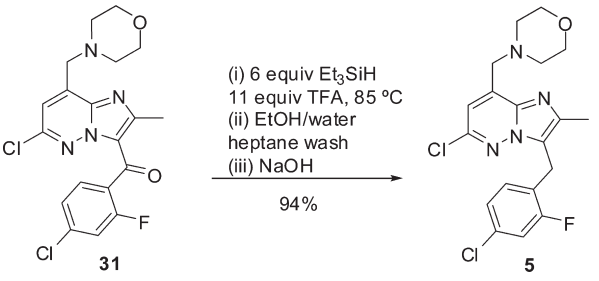


Figure 4. Evidence against iminium mechanism.

(not including any water that may be formed during the reaction) results in incomplete reactions and overall poor performance. Simple NMR analysis (Figure 4) of **6** shows that the C-8 position is unlikely to be the most electron rich and, given the results from the Minisci chemistry, can be thought of as the position most susceptible to *nucleophilic* attack. Furthermore, treatment of **6** with the proposed iminium chloride **37**[17] with or without VO(acac)$_2$ resulted in no reaction whatsoever until forcing conditions were employed (DMSO at 100 °C), at which point reaction occurred at the C-2 methyl group, which is acidified due to its position δ to the carbonyl. It was also observed that iminium **37** reacts instantly with EtOH to afford aminal **39**, thereby decreasing the likelihood that the free iminium species is the true reactive intermediate. Roseneau has studied the transition metal-catalyzed decomposition of NMO, and a wide range of decomposition pathways to possibly reactive intermediate species exist.[18] We feel that there is a reasonable possibility that the reaction is radical in nature, and that the primary radical derived from *N*-methylmorpholine is the reactive species responsible for the productive transformation. A detailed account of our investigations into this highly useful C−C bond forming reaction is forthcoming.

Having a robust strategy in place for production of **31**, we turned our attention to the deoxygenation step. In the preliminary route, the ketone to methylene transformation had utilized a two-step procedure: $NaBH_4$ reduction to the alcohol followed by an ionic silane reduction. We viewed this as an opportunity to potentially develop a single step reduction from ketone to methylene, as this type of transformation is well documented.[19] Indeed, the transformation was feasible by heating a solution of

Scheme 9. Finalized conditions for single-step reduction of 31



31 in the presence of triethylsilane (TES-H) in TFA (Scheme 9). We quickly focused optimization efforts on reaction temperature, minimization of reagents, and isolation of product from the reaction mixture. The boiling point of TFA (85 °C) limited the maximum temperature at which the reaction could be performed without pressurization, and no detrimental effects were noted by simply performing the reaction at reflux. The optimized conditions for deoxygenation of **31** utilized TFA as solvent and TES-H. We were curious as to why the reaction required such an excess of silane, as theoretically only two hydride equivalents are required to achieve the desired reduction. A background reaction between TFA and TES-H at elevated temperatures has been reported, which undoubtedly can account for some silane consumption.[20] Furthermore, the silanol byproducts of the deoxygenation likely react further to afford TES_2O. Finally, since **31** had been isolated from aqueous EtOH, the incoming water content was identified

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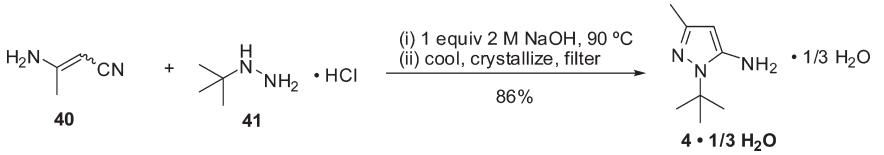
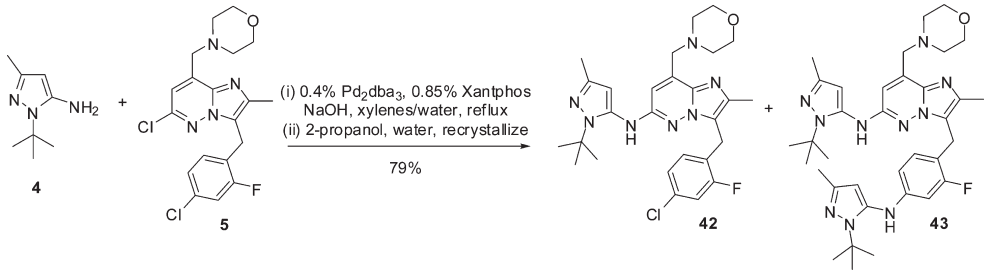
Scheme 10. Aqueous preparation and isolation of 4



Scheme 11. Amination and isolation of 42



as a factor important to a successful reduction, and drying of **31** to KF <0.5% (wt for wt %) was enacted. The isolation procedure for amine **5** involved addition of aqueous ethanol to the reaction mixture, followed by heptane washes to remove the lipophilic silane residues. The pH of the ethanol layer was then adjusted to 11, inducing spontaneous crystallization of **5**, which was then filtered and washed with water to remove the sodium trifluoroacetate to provide **5** in 95% isolated yield after drying. Preparation of the HCl salt of **5** was no longer required as a purification since the crystallization step provided a highly pure intermediate.

Selection of Protected 5-Amino-3-methylpyrazole. Three versions of the required 5-amino-3-methylpyrazole were considered during route selection: (1) unprotected pyrazole **2**, (2) PMB-protected pyrazole **3**, and (3) *tert*-butyl pyrazole **4**. Since pyrazole **3** had required a four-step preparation, the commercially available unprotected form was a very attractive alternative. Additional efforts were made to optimize the conditions to couple the unprotected pyrazole, but still resulted in mixtures of addition products resulting from both amino and pyrazole nitrogen addition. The best outcome was 3:1 selectivity when 1 equivalent of **5** and pyrazole **2** were reacted for 16 h in the presence of $Pd_2(dba)_3$ and Xantphos in refluxing dioxane. Isolation of the API produced under these conditions proved challenging, and we felt that pyrazole protection would offer us greater opportunity for the rejection of related substances as well as residual levels of palladium; this combined with the reaction's poor selectivity caused our attention to turn to other forms of protected pyrazoles. While most attempts at monoprotection of **2** proved futile, the Boc protecting group could be installed successfully to afford the crystalline derivative.[21] However, the carbamate was exceedingly labile, and exposure of the Boc-protected pyrazole to the subsequent amination conditions resulted in loss of the protecting group and a reaction profile similar to that observed for the free pyrazole **2**.

The preparation of pyrazole **3** required three steps to first prepare a monosubstitued hydrazine, followed by a single-step pyrazole formation. Perhaps monosubstituted hydrazines that are commercially available might be useful. A literature report describes the single step formation of pyrazole **4** by reaction of hydrochloride **41** with 3-aminocrotonitrile (**40**) and amine base in ethanol, followed by extractive workup.[22] The use of nitrile **40** is noteworthy in that this is a readily available and highly functionalized four-carbon building block, perfectly suited to aminopyrazole preparation. Furthermore, its use precludes the *in situ* generation of 2-cyanoacetone, as in the previously employed route. Finally, it has been reported that the *tert*-butyl protecting group on the aminopyrazole nucleus could be conveniently removed by formic acid, giving us confidence that we could deprotect the coupled product.[22]

Pyrazole **4** was not available commercially on large scale, so an investigation into its preparation was undertaken. We found that the literature method performed well, but the extraction proved difficult due to the high water solubility of **4** (97 mg/mL at 23 °C). We reasoned that if an inorganic base such as NaOH would prove to be an acceptable substitute for amine base, then an organic solvent may not be required, given the high water solubility of **4**. These thoughts were developed into an efficient procedure in which the substrates were combined in aqueous sodium hydroxide and heated until the reaction was judged complete by HPLC, after which time the reaction was cooled to <60 °C, seeded, and then cooled to ambient temperature (Scheme 10). The isolated crystalline product consisted of large crystals, which were shown to be the 1/3 hydrate by single-crystal X-ray analysis. We were confident that a good recovery of product could be achieved in this fashion. The byproduct of the hydrochloride neutralization, NaCl, had a dramatic effect on the solubility of **4** in water. Neutralization conditions resulted in a 10% brine solution at the end of the reaction, and a solubility experiment showed that **4** was only soluble at 29 mg/mL at that salt concentration. This prediction proved valid in the kilo lab, as a demonstration starting with 1 kg of **17** resulted in 86% isolated yield of product (**4**) in >99% purity. In the pilot plant, similar results were obtained during the preparation of 49 kg of **4**.

Preparation of LY2784544. Compounds **4** and **5** were joined in an amination cross-coupling reaction (Scheme 11) similar to that used in the first-generation synthesis. For the second-generation amination, the Pd catalyst loading, source, ligand, and base were not extensively optimized as the biphasic Pd_2dba_3/Xantphos/NaOH system worked sufficiently well at this stage of project development. Pyrazole **4** appeared to be a less reactive

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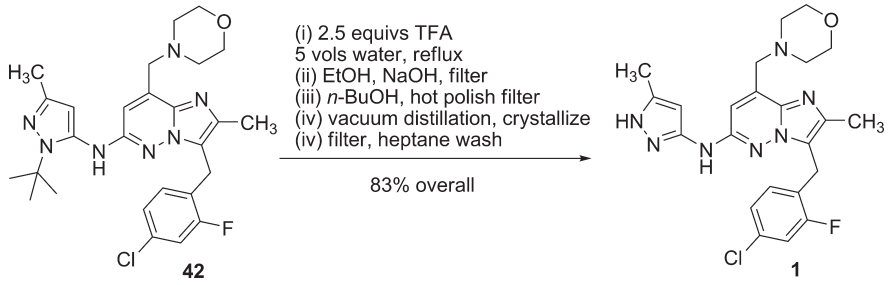
Scheme 12. Deprotection and completion of the synthesis



coupling partner relative to the PMB analogue, and the reaction required higher temperature for reproducibility. The decreased reactivity of **4** is presumably due to the steric bulk of the *t*-Bu group adjacent to the amine. In order to access a higher reflux temperature, xylenes was chosen instead of toluene. Due to the presence of water in the reaction, an azeotropic mixture of organic solvent and water boiled at 99−103 °C. Upon reaction completion, the biphasic system was cooled, and THF was added to solubilize **42**. The mixture was filtered through Celite to remove a solid residue (presumably precipitated palladium black). Layer separation and an additional water wash were followed by a silicycle mercaptopropyl silica gel treatment in order to further reduce residual palladium levels. Vacuum distillation of THF and further distillation/azeotropic drying of the product solution reliably resulted in crystallization of **42**, which was isolated as an off-white granular solid after filtration and heptane cake wash.

At scales larger than 22 L, the reaction began to take longer to reach the desired levels of conversion, and a side reaction, which had been observed at low levels during development became more prominent in the formation of *bis*-coupled pyrazole **43**. Pyrazole **43** is the result of amination at the less-activated aryl-Cl bond, and an analogous product was observed when PMB protected pyrazole **3** had been used (vide supra). It was observed during development that good mixing was associated with successful reactions, and it was theorized that this parameter was crucial to the success of the reaction; this may imply that the organic layer at larger scales with inadequate mixing was starved of base and that the slower coupling at the less activated Ar−Cl position had time to grow in to significant levels. Fortunately, a rework of the isolated product, which was contaminated with percent levels of pyrazole **43**, was rapidly developed. Recrystallization from aqueous 2-propanol was capable of reducing levels of **43** in the isolated solids to <0.5%. Typical isolated yields after the reaction and recrystallization were in the range of 70−79%. We have recognized the liability of the biphasic reaction conditions, and ongoing development efforts are underway in order to provide more robust and scalable amination conditions.

Removal of the *tert*-butyl group in **42** and isolation of LY2784544 was the final challenge in order to implement the second-generation synthesis route. Literature conditions for the *tert*-butyl protecting group removal centered on formic acid as solvent,[22] which worked well when the procedure was applied to our reaction. The large amount of base required to neutralize the formic acid was undesirable. Therefore, we undertook an investigation of alternative acids that could be used in smaller amounts. Acid screening was conducted, with the general conclusion being that most strong acids, for example sulfuric, HCl, HBr, and TFA, will remove the protecting group, but acids weaker than formic (pK_a 3.8), in particular acetic (pK_a 4.8), suffer from slow conversion and byproduct formation becomes dominant. With some acids such as sulfuric, API salt precipitation was observed during the deprotection. In the case of the sulfate salt of **1**, free-basing of the precipitated salt was challenging due to the extreme insolubility of the sulfate, which necessitated a slurry-to-slurry neutralization. Ultimately, we chose to use aqueous TFA. The deprotection reaction was clean and rapid when 2.5 equiv of TFA in water at reflux was utilized. A 110-g demonstration lot performed was successful (88% yield, Scheme 12). Also, TFA was convenient in that the TFA salts of **1** appeared to be highly soluble in water, and undesired precipitation during the deprotection was not observed.

Upon completion of the deprotection, EtOH was added to the reaction mixture, and the pH was adjusted with NaOH, which caused the precipitation of **1**. The solids were isolated by filtration and washed with water to remove sodium salts. Given the experience gained from the first-generation synthesis, we chose to continue the use of *n*-BuOH as final recrystallization solvent since it had afforded good form control, purity, and yield. The technical grade API was again taken into hot *n*-BuOH, polish filtered, concentrated in vacuo, filtered, washed with heptane, and dried to afford the desired crystalline form in 83% overall yield for the deprotection and final crystallization steps.

CONCLUSION

A revised synthesis for JAK2 inhibitor **1** was developed in order to prepare larger quantities of required API on a pilot-plant scale. Improvements were made for the preparation of **6** (common intermediate for both routes), and a novel vanadium-catalyzed addition of NMO to **6** greatly improved efficiency and reduced the overall step count from 14 to 8, which resulted in an overall yield of 35% for the longest linear sequence. Reduction of the V/NMO product, **31**, afforded an intermediate common to both routes, **5**. Since intermediate **5** was common to both routes, the route selection development was able to leverage previous synthesis experiences acquired during processing. Pyrazole **4** was introduced as a replacement for **3**, and was successfully coupled with **5** to afford the penultimate **42**. Removal of the *tert*-butyl protecting group could be accomplished under a wide array of conditions; aqueous TFA was chosen in this case. The versatility in conditions for the protecting group removal will allow an array of choices for future API preparation. Finally, recrystallization from *n*-BuOH as in the previous synthesis afforded the final product in good yield and purity.

EXPERIMENTAL SECTION

Reactions were monitored by reverse phase HPLC (Table 1). Reported yields are corrected for potency. HPLC conditions: Zorbax

Table 1.

time (min)	% A	% B
0	95	5
15	20	80
16	20	80
16.1	95	5
22	95	5

SB C8 column, 4.6 mm × 75 mm, 3.5 μm particle size, 1.0 mL/min flow, 40 °C column temp, detection at 228 nm, solvent A = 1 mL/L TFA in Milli-Q water, solvent B = 1 mL/L TFA in CH_3CN.

(*E*)-*N*′-(6-Chloropyridazin-3-yl)-*N*,*N*-dimethylacetimidamide (7). In a suitable reactor, amine **9** (23.0 kg, 177.5 mol) and acetal **10** (35.6 kg, 86% potency, 229.9 mol) were charged with toluene (202 kg, 233 L) followed by heating to 82 °C for 8 h. After heating, the mixture was concentrated to 80 L at which time heptane (160 kg, 235 L) was added over 7 h. The resulting slurry was then cooled to 5 °C and stirred for 10 h. The solids were isolated by filtration, washed with heptane (2 × 20 kg, 29.4 L), and dried to afford **7** as a solid (32.8 kg, 91% yield); mp = 75.8−76.4 °C; HPLC t_R = 2.80 min; IR(cm^{-1}) 3069, 3020, 2968, 1581, 1558; ^{1}H NMR (400 MHz, DMSO-d_6) 7.57 (d, 1H, J = 8.8 Hz), 7.03 (d, 1H, J = 8.8 Hz), 3.05 (br, 6H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 164.2, 160.2, 148.8, 128.9, 126.0, 37.5 (br, 2C), 15.5; ESI-HRMS calc'd for $C_8H_{12}N_4Cl$ $(M + H)^+$ 199.07450, found 199.07505.

2-Chloro-1-(4-chloro-2-fluorophenyl)ethanone (8). A suitable reactor was charged with CH_2Cl_2 (270 kg, 204.5 L), ketone **11** (138 kg, 799.6 mol), and MeOH (25 kg, 31.25 L, 780 mol), and the solution was cooled to −5−0 °C. Sulfuryl chloride (135.2 kg, 1002 mol) in CH_2Cl_2 (549 kg, 416 L) was added to the ketone solution over 5 h. During the addition, gas evolution was observed, and the gas was scrubbed with aqueous NaOH. The cold solution was stirred an additional 2 h, at which time it was determined that the reaction was complete. A solution of NaOH (13.8% aqueous) was added to the vessel over 5 h, as the pH was adjusted to 6−7. The organic layer was then concentrated (∼300 L) at which point heptane (480 kg, 706 L) was added followed by a second concentration to ∼500 L. Next, the solution was cooled to −5 °C during which time crystallization of the product was observed. The resulting slurry was filtered, washed with heptane (18 kg, 26.5 L), and dried to afford ketone **8** as a crystalline solid (147.0 kg, 91% yield); mp = 77−78 °C; HPLC t_R = 11.02 min; IR(cm^{-1}) 3083, 3072, 3002, 2953, 1689, 1599, 1562; ^{1}H NMR (400 MHz, CDCl3) 7.94 (dd, 1H, J = 7.6, 8.4 Hz), 7.29 (ddd, 1H, J = 0.4, 1.6, 8.4 Hz), 7.23 (dd, 1H, J = 1.6, 10.8 Hz), 4.69 (d, 2H, J = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 188.1 (d, 1C, J(^{13}C,^{19}F) = 4.7 Hz), 161.6 (d, 1C, J(^{13}C,^{19}F) = 256.6 Hz), 141.3 (d, 1C, J(^{13}C,^{19}F) = 10.9 Hz), 132.2 (d, 1C, J(^{13}C,^{19}F) = 3.5 Hz), 125.7 (d, 1C, J(^{13}C,^{19}F) = 3.1 Hz), 121.3 (d, 1C, J(^{13}C,^{19}F) = 14.0 Hz), 117.4 (d, 1C, J(^{13}C,^{19}F) = 27.1 Hz), 49.8 (d, 1C, J(^{13}C,^{19}F) = 11.6 Hz); ESI-HRMS calc'd for $C_8H_6OCl_2F$ $(M + H)^+$ 206.97742, found 206.97783.

(4-Chloro-2-fluorophenyl)(6-chloro-2-methylimidazo-[1,2-*b*]pyridazin-3-yl)methanone (6). A reactor was charged with DMF (150 kg, 158 L), amidine **7** (32.8 kg, 97.6% potency, 161.1 mol), and ketone **8** (35.2 kg, 170.0 mol). The vessel was purged with nitrogen and stirred at 10−25 °C for 15 min, after which time solid NaBr (16.3 kg, 158.4 mol) was added. The mixture was then stirred at 35 °C for 30 h. A mixture of 1:1 MeOH/H_2O (286 kg) was then added to the vessel over 75 min, and the resulting slurry was stirred at 20 °C for 2 h. The solids were isolated by filtration, washed with 1:1 MeOH/H_2O (v:v, 34 kg), slurried in water (478 kg) at 40 °C for 5.5 h, filtered, and dried to afford **6** as a solid (43.95 kg, 84% yield); mp = 163.3−163.9 °C; HPLC t_R = 11.71 min; IR (cm^{-1}) 3106, 3043, 1629, 1607, 1570; ^{1}H NMR (400 MHz, DMSO-d_6) 8.29 (d, 1H, J = 9.2 Hz), 7.67 (t, 1H, J = 8.0 Hz), 7.60 (d, 1H, J = 9.6 Hz), 7.59 (dd, 1H, J = 2.0, 10.4 Hz), 7.47 (ddd, 1H, J = 0.4, 2.4, 8.4 Hz), 2.54 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 179.2, 159.5 (d, 1C, J(^{13}C,^{19}F) = 251.9 Hz), 152.1, 146.3, 138.7, 137.4 (d, 1C, J(^{13}C,^{19}F) = 10.4 Hz), 131.4 (d, 1C, J(^{13}C,^{19}F) = 4.4 Hz), 127.4, 126.4 (d, 1C, J(^{13}C,^{19}F) = 13.9 Hz), 125.2 (d, 1C, J(^{13}C,^{19}F) = 13.1 Hz), 124.3, 122.6, 116.4 (d, 1C, J(^{13}C,^{19}F) = 25.6 Hz), 16.0; ESI-HRMS calc'd for $C_{14}H_9ON_3Cl_2F$ $(M + H)^+$ 324.01012, found 324.01052.

(4-Chloro-2-fluorophenyl)(6-chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-*b*]pyridazin-3-yl)methanone (31). EtOH (269 L) and NMO-monohydrate (188.4 kg, 1394 mol) were added to a reactor to form a solution. A separate reactor was charged with EtOH (362.2 L), ketone **6** (43.5 kg, 134.2 mol), and $VO(acac)_2$ (7.2 kg, 27.15 mol). While the mixture of **6** was stirred and maintained at 30 °C, the NMO in EtOH solution was added over 2.5 h. When the addition was complete, the reactor was heated to 40 °C for 24 h. Water (612 L) was then added to the slurry, while the temperature was maintained at 40 °C and the mixture aged at 40 °C for an additional 2 h, cooled to 10 °C, and stirred for a total of 7 h. The material was filtered, washed with water, and dried to afford **31** as a crystalline solid (44.0 kg, 75% yield); mp = 146−147 °C; HPLC t_R = 8.81 min; IR(cm^{-1}) 3095, 2953, 2923, 2897, 1625, 1607, 1577; ^{1}H NMR (400 MHz, DMSO-d_6) 7.67 (t, 1H, J = 8.0 Hz), 7.59 (dd, 1H, J = 2.0, 10.4 Hz), 7.47 (dd, 1H, J = 2.0, 8.4 Hz), 7.47 (s, 1H), 3.94 (s, 2H), 3.64 (t, 4H, J = 4.4 Hz), 2.55 (s, 3H), 2.52 (brt, 4H, J = 4.8 Hz), ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.3, 159.5 (d, 1C, J(^{13}C,^{19}F) = 252.3 Hz), 151.3, 146.4, 139.1, 138.6, 137.4 (d, 1C, J(^{13}C,^{19}F) = 10.8 Hz), 131.4, 126.5 (d, 1C, J(^{13}C,^{19}F) = 14.4 Hz), 125.2, 124.5, 119.6, 116.4 (d, 1C, J(^{13}C,^{19}F) = 25.5 Hz), 66.1 (2C), 55.2, 53.2 (2C), 16.0; ESI-HRMS calc'd for $C_{19}H_{18}O_2N_4Cl_2F$ $(M + H)^+$ 423.07854, found 423.07897.

4-((6-Chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo-[1,2-*b*]pyridazin-8-yl)methyl)-morpholine (5). A reactor was charged with TFA (131 kg, 88.5 L) and ketone **31** (43.5 kg, 97.2% potency, 99.9 mol), and the mixture was stirred at <25 °C. Triethylsilane (72 kg, 619 mol) was then added over 1 h at <50 °C. The mixture was then heated to 84−88 °C under an atmosphere of nitrogen for 26 h. The mixture was cooled to <45 °C, and water (200 kg) was added over 1 h followed by EtOH (176 kg). This solution was maintained at 30−40 °C and washed with heptane (4 × 60 kg). The pH of the solution was then adjusted with NaOH (140.2 kg of 30% aqueous) while the temperature was maintained at ∼50 °C, to a pH of 10−11; the resultant slurry was cooled to 20 °C and stirred for 10 h. The solids were isolated by filtration and washed with water (∼176 L) and then dried to afford **5** as a solid (39.3 kg, 94% yield).

Mp =143−144 °C; IR(cm^{-1}) 3080, 2957, 2816, 1607, 1543, 1488; ^{1}H NMR (400 MHz, DMSO-d_6) 7.40 (dd, 1H, J = 2.0, 9.6 Hz), 7.20−7.17 (m, 2H), 7.16 (t, 1H, J = 8.4 Hz), 4.29 (s, 2H), 3.89 (s, 2H), 3.62 (t, 4H, J = 4.4 Hz), 2.49 (m, 4H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 160.7 (d, 1C, J(^{13}C,^{19}F) = 247.3 Hz), 145.4, 141.2, 138.0, 136.0, 131.9 (d,

1C, $J(^{13}C,^{19}F)$ = 5.1 Hz), 124.5, 123.5(d, 1C, $J(^{13}C,^{19}F)$ = 15.6 Hz), 122.1, 116.0, 115.8, (d, 1C, $J(^{13}C,^{19}F)$ = 25.6 Hz), 114.8, 66.1 (2C), 55.2 (2C), 53.3, 21.1, 13.5; ESI-HRMS calc'd for C19H20ON4Cl2F $(M + H)^+$ 409.09927, found 409.09972.

1-*tert*-Butyl-3-methyl-1*H*-pyrazol-5-amine (4). To a reaction vessel was charged NaOH (2 M, 4012 mL, 8.02 mol) and solid *tert*-butylhydrazine hydrochloride (1,002 g, 8.04 mol) was added to form a solution. Next, 3-aminobut-2-enenitrile (690 g, 8.0 mol) was added and the resulting reaction mixture heated to 90 °C for 18 h. The reaction mixture was cooled to 5 °C and the resulting precipitate filtered to provide **4** (1.13 kg, 86% yield); mp = 68−70 °C; HPLC t_R = 3.66 min; IR(cm^{-1}) 3440, 3340, 3236, 2983, 2938, 1625, 1555; ^1H NMR (400 MHz, DMSO-d_6) 5.17 (s, 1H), 4.69 (br, 2H), 1.94 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) 146.6, 142.8, 91.3, 56.8, 29.0 (3C), 13.8; ESIHRMS calc'd for $C_8H_{16}N_3$ $(M + H)^+$ 154.13387, found 154.13382.

***N*-(1-*tert*-Butyl-3-methyl-1*H*-pyrazol-5-yl)-3-(4-chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-*b*]pyridazin-6-amine (42).** Chloride **5** (82.6 kg, 98.1% potency, 198.0 mol), pyrazole **4**, (33.1 kg, 96.3% potency, 208.0 mol), xylenes (654 L), NaOH (118.1 kg of 7.4% aqueous, 218.5 mol) were charged to a reactor and the mixturewas inerted with a nitrogen atmosphere. XantPhos (1.00 kg, 1.73 mol) and $Pd_2(dba)_3$ (0.80 kg, 0.87 mol) were then added, and the mixture was heated under reflux for 40 h. The mixture was cooled to <60 °C, and THF (508 L) was added. Cooling to 25−30 °C, filtration of a residue and removal of the water layer was followed by addition of fresh water (269 kg) and stirring at 25−30 °C for ∼1 h. The water layer was removed, and the organic layer was stirred with mercaptopropyl-functionalized silica gel (6.8 kg) at 50−60 °C for 10 h. Removal of the silica was then accomplished by filtration, concentration of the filtrates to 300 L, and the addition of heptane (329 L) at 80 °C in a slurry. The slurry was cooled to 10−15 °C and stirred for 3 h. Filtration of the solids and washing with heptane (60 kg) afforded **42** after drying. (82.4 kg, 79% yield); mp = 188−189 °C; IR(cm^{-1}) 3299, 2950, 2912, 2853, 2819, 1610, 1573, 1484; ^1H NMR (400 MHz, DMSO-d_6) 8.36 (s, 1H), 7.27 (dd, 1H, J = 2.0, 0.8 Hz), 7.00−6.95 (m, 2H), 6.80 (s, 1H), 5.91 (s, 1H), 3.99 (s, 2H), 3.75 (d, 2H, J = 0.8 Hz), 3.61 (t, 4H, J = 4.4 Hz), 2.47 (brt, 4H, J = 4.0 Hz), 2.30 (s, 3H), 2.18 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) 160.1 (d, 1C, $J(^{13}C,^{19}F)$ = 246.9 Hz), 152.5, 143.6, 137.2, 136.9, 135.9, 134.7, 132.4 (d, 1C, $J(^{13}C,^{19}F)$ = 20.0 Hz), 131.4 (d, 1C, $J(^{13}C,^{19}F)$ = 10.4 Hz), 123.9 (m, 2C), 120.8, 115.5 (d, 1C, $J(^{13}C,^{19}F)$ = 25.6 Hz), 106.6, 103.8, 66.1 (2C), 58.6, 55.3, 53.4 (2C), 29.5 (3C), 21.6, 14.0, 13.2; ESI-HRMS calc'd for $C_{27}H_{34}ON_7ClF$ $(M + H)^+$ 526.24919, found 526.24932.

3-(4-Chloro-2-fluorobenzyl)-2-methyl-*N*-(5-methyl-1*H*-pyrazol-3-yl)-8-(morpholinomethyl)-imidazo[1,2-*b*]pyridazin-6-amine (1). A reactor was charged with water (170 L), TFA (22.4 kg, 196.5 mol) and **42** (34 kg, 99.0% potency, 64.0 mol). This mixture was heated to 95−100 °C for 7 h, and then cooled to 50−55 °C, at which time EtOH (139 kg) was added. The pH of the solution was then adjusted to 10−11 using NaOH (11.2 kg in 56 kg water). A slurry formed, and was stirred at 60 °C for 8 h, and then cooled to 15−20 °C. The solids were isolated by filtration and washed with water (51 kg). The solids were dried to afford technical grade **1** as a solid (27.8 kg, 86% yield). **Final Recrystallization:** A vessel was charged with *n*-BuOH (843 kg, 1041 L) and technical grade **1** (105 kg, 89.1% potency, 199.0 mol); the mixture was heated to 95−100 °C to form a solution. Concentration of the solution at 80 °C to 500 L gave a slurry. In order to maximize recovery, the slurry was aged at 2−5 °C for 7.5 h, isolated by filtration, and washed with heptane (210 kg, 309 L). The solids were dried at 75−85 °C to afford **1** as a crystalline solid (89.9 kg, 96% yield); mp = 235.6−237.2 °C; IR(cm^{-1}) 3359, 3262, 2920, 2804, 1588, 1539; ^1H NMR (400 MHz, DMSO-d_6) 11.82 (s, 1H), 9.39 (s, 1H), 7.40 (dd, 1H, J = 2.0, 10.0 Hz), 7.09 (dd, 1H, J = 2.0, 8.4 Hz), 6.99 (t, 1H, J = 8.4 Hz), 6.99 (s, 1H), 6.07 (s, 1H), 4.20 (s, 2H), 3.73 (s, 2H), 3.62 (t, 4H, J = 4.8 Hz), 2.47 (m, 4H), 2.29 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 160.1 (d, 1C, $J(^{13}C,^{19}F)$ = 246.6 Hz), 149.8, 148.5, 137.8, 137.5, 131.4 (d, 1C, $J(^{13}C,^{19}F)$ = 10.1 Hz), 131.1 (d, 1C, $J(^{13}C,^{19}F)$ = 4 Hz), 124.6, 124.5, 120.5, 115.6 (d, 1C, $J(^{13}C,^{19}F)$ = 25.6 Hz), 108.3, 94.8, 66.2 (2C), 55.3, 53.4 (2C), 21.0, 13.3, 10.6; ESI-HRMS calc'd for $C_{23}H_{26}ON_7ClF$ $(M + H)^+$ 470.18659, found 470.18684.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra for compounds **1**, **4**, **5**, **6**, **7**, **8**, **31**, and **42**. This material is available free of charge via the Internet at http://pubs.acs.org.

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