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Article

Development and Scale-Up of an Improved Manufacturing Route to the ATR Inhibitor Ceralasertib

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ABSTRACT: Ceralasertib is currently being evaluated in multiple phase I/II clinical trials for the treatment of cancer. Its structure, comprising a pyrimidine core decorated with a chiral morpholine, a cyclopropyl sulfoximine and an azaindole, makes it a challenging molecule to synthesize on a large scale. Several features of the medicinal chemistry and early development route make it unsuitable for the long-term commercial manufacture of the active pharmaceutical ingredient. We describe the investigation and development of a new and improved route which introduces the cyclopropyl moiety in a novel process from methyl 2,4-dibromobutyrate. Following construction of the pyrimidine ring, large-scale chlorination with phosphoryl chloride was performed with a safe and robust work-up. An S_NAr reaction required an innovative work-up to remove the unwanted regio-isomer, and then a Baeyer–Villiger monooxygenase enzyme was used to enable asymmetric sulfur oxidation to a sulfoxide. A safe and scalable metal-free sulfoximine formation was developed, and then optimization of a Suzuki reaction enabled the manufacture of high-quality ceralasertib with excellent control of impurities and an overall yield of 16%.

KEYWORDS: *ceralasertib, AZD6738, ATR inhibitor, cyclopropanation, phosporyl chloride, S_NAr, BVMO, sulfoximine, Suzuki–Miyaura, Suzuki*

INTRODUCTION

The kinase ataxia telangiectasia mutated and Rad3 related (ATR) is a key regulator of the DNA-damage response of cells, and inhibition of this repair pathway can lead to cell death. Ceralasertib (AZD6738, **1**) was identified by AstraZeneca as a potent and selective inhibitor of ATR[1,2] and is currently being evaluated in multiple phase I/II clinical trials for the treatment of cancer. Its structure, comprising a pyrimidine core decorated with a chiral morpholine, a cyclopropyl sulfoximine and an azaindole, makes it a challenging molecule to synthesize on a large scale. The medicinal chemistry route to ceralasertib was adapted and developed for early clinical active pharmaceutical ingredient (API) manufacturing campaigns (Scheme 1).[3] However, there were several limitations and issues with this synthetic route, and we felt that a new route would be required to provide efficient manufacturing processes suitable for future commercial drug substance.

The early development route was long, with a total step count of 14 steps from the chiral building block D-alaninol when we include the 3 steps that were used to manufacture (*R*)-3-methylmorpholine (**2**) using the route described by Mahajan[4] and the single step used to manufacture boronate ester **14**. There was also an undesirable linear step count of 13. The expensive chiral morpholine **2** was introduced at the start of the route, so it would be preferential from a cost perspective to introduce this at a later stage. The enzymatic S-oxidation to form sulfoxide **8** was not fully optimized and required high process volumes and processing times. We realized that it would be desirable to undergo some directed evolution of the enzyme to improve the efficiency of this process but decided that it would be prudent to establish the commercial route before this undertaking. Rhodium was used in the formation of sulfoximine **9**, and we were concerned about this precious metal from the cost and sustainability perspective. However, the major issue with this route centered around the cyclopropanation of sulfoximine **10**. This cyclopropanation process involves α-deprotonation of the sulfoximine and reaction with 1-bromo-2-chloroethane. This was a low-yielding process because of the propensity of the product to over-react with 1-bromo-2-chloroethane to give the N-alkylated impurity **12** as a byproduct. To minimize this issue, control of reaction time was critical, and a continuous stirred tank process was developed to achieve a moderate yield of 51%. Furthermore, impurity **12**, 1-bromo-2-chloroethane, and other related impurities are potential mutagenic substances which we ideally want to avoid late in the synthetic route. We believed that this was an undesirable process for the potential future commercial manufacture of drug substance.

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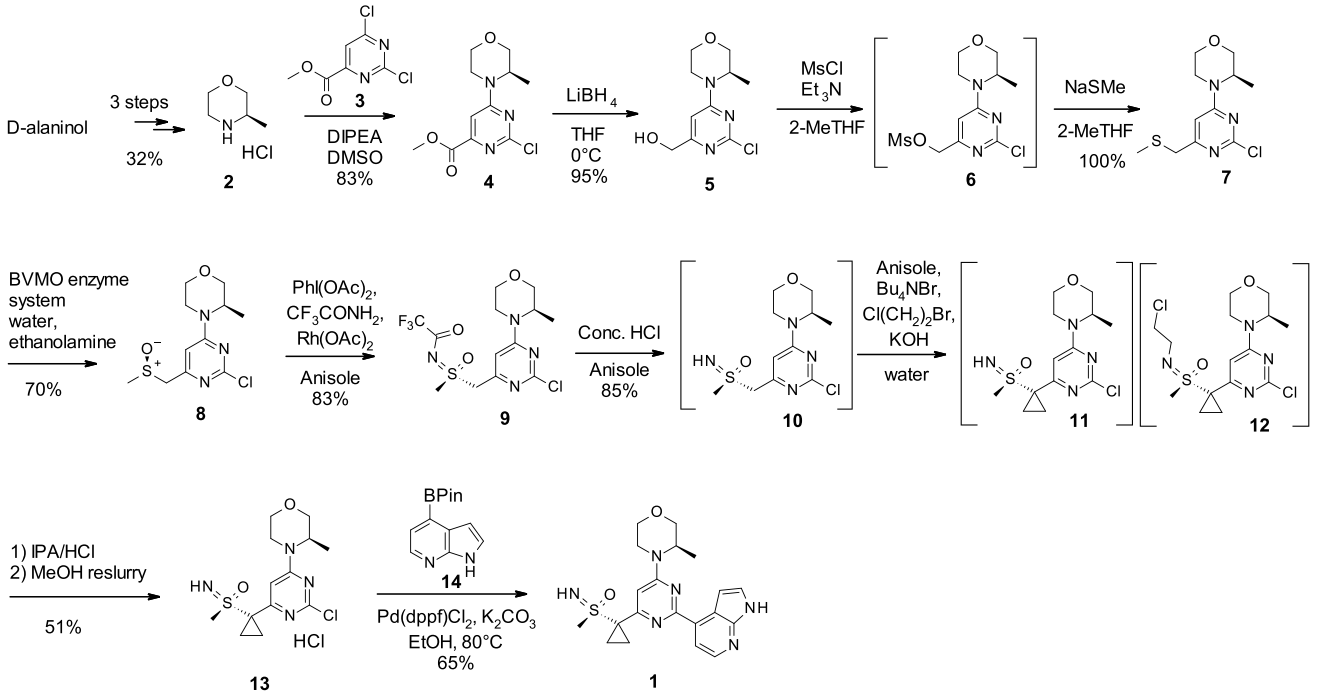
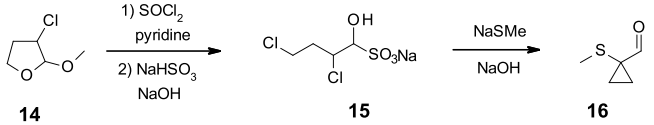
Scheme 1. Early Development Route to Ceralasertib



RESULTS AND DISCUSSION

Initial Route Scouting. As part of a route design exercise, the desire to avoid this unfavorable cyclopropanation process led us to consider alternative options to introduce the cyclopropyl moiety. A thorough literature search confirmed that are no known examples of direct C−C bond forming reactions between a thiocyclopropyl synthon and a pyrimidine ring system. We therefore decided to investigate alternative ways of synthesizing the thiomethylcyclopropyl moiety, and we were interested in building the pyrimidine ring *via* classical condensation chemistry. A literature investigation identified the work of Kanel and Dingwall,[5] which demonstrated the ring opening of 3-chloro-2-methoxytetrahydrofuran (**14**) with thionyl chloride and pyridine to give 2,4-dichlorobutanal, which was isolated as sodium bisulfite adduct **15** (Scheme 2). This was then reacted with sodium thiomethoxide followed by sodium hydroxide to give aldehyde **16** in 80% yield.

Scheme 2. Kanel Synthesis of 1-(Methylsulfanyl)cyclopropanecarbaldehyde



Although this aldehyde was unsuitable for our planned synthetic route, it opened the possibility of synthesizing a related ester or acid which could potentially be useful. Methyl 2,4-dibromobutyrate (**17**)[6] is commercially available in bulk quantities, and we surmised that this could react with sodium thiomethoxide in a similar manner to yield the analogous ester. Gratifyingly, sodium thiomethoxide reacted selectively at C_2 of the ester, and then treatment with 1 equiv of sodium hydroxide resulted in cyclization to form ester **18** (Scheme 3). Further addition of excess sodium hydroxide resulted in ester saponification to yield acid **19** in 86% crude yield following acidic work-up.

We proceeded to develop this process by changing the solvent from tetrahydrofuran (THF) to 2-methyltetrahydrofuran (2-MeTHF). The use of 2-MeTHF as the main solvent enabled us to efficiently telescope the process without the need for an additional solvent such as ethyl acetate for the work-up. The use of methanol as a cosolvent helped to improve the solubility of sodium thiomethoxide and increased the rate of reaction. After an investigation of bases (Table 1), we established that the use of sodium methoxide resulted in more efficient deprotonation and cyclization to the form the cyclopropyl ring. We continued to use aqueous sodium hydroxide for the ester hydrolysis. Following work-up, acid **19** was obtained as a dry 2-MeTHF solution in 93% yield on 118 kg scale (Scheme 4).

To enable the construction of a pyrimidone ring, we needed to convert acid **19** to *β*-keto ester **20**, which could subsequently be

Scheme 3. Initial Investigation into Formation of Acid 19

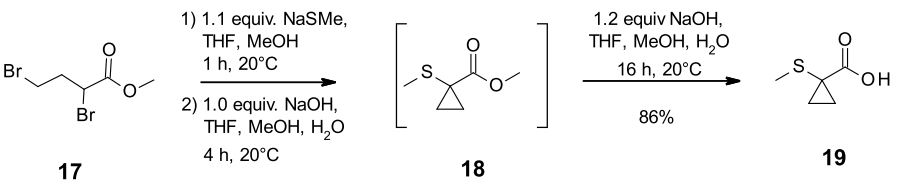


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Table 1. Investigation of Bases for Conversion of 17 to 18[a]

entry	base	time for full conversion to **18**	isolated yield of **19**
1	NaOH	24 h	72%
2	NaOMe	1 h	83%
3	Et_3N	no conversion	0

[a]Reactions performed in 2-MeTHF (4 rel vol) and MeOH (2 rel vol) after the addition of NaSMe (1.1 equiv) at 20 °C.

condensed with an amidine derivative. We applied the well-known methodology for conversion of carboxylic acids to β-keto esters which was reported by Challenger *et al.* on a multikilogram scale.[7] This involved acylation of ethyl potassium malonate with the imidazolide formed by reacting acid **19** with carbonyldiimidazole, followed by decarboxylation under mild conditions in the presence of triethylamine and magnesium chloride. We modified the reported conditions to use 2-MeTHF as the solvent, which enabled us to telescope acid **19** directly into this process as a 2-MeTHF solution (Scheme 4). Our modified process afforded β-keto ester **20** as a 2-MeTHF solution in 90% yield.

Amidine **22** was prepared from 7-azaindole-4-carbonitrile (**21**) by reaction with hydroxylamine, followed by hydrogenation in the presence of acetic anhydride in a process similar to that of Dorsey (Scheme 4).[8] Condensation of amidine **22** with β-keto ester **20** proceeded efficiently in the presence of sodium ethoxide to yield pyrimidone **23**, and then chlorination of the pyrimidone was achieved with phosphoryl chloride. (*R*)-3-Methylmorpholine hydrochloride reacted with chloropyrimidine **24** *via* S_NAr; then, sulfur oxidation was achieved on small scale using Kagan conditions[9] to yield sulfoxide **26** with only moderate stereoselectivity. However, attempts to convert this sulfoxide to sulfoximine **1** (ceralasertib) proved to be unsuccessful. Rhodium-catalyzed conditions that were used in the early development route were initially attempted;[10] then, metal-free sulfoximine formation conditions recently developed by Bull[11,12] also proved to be unsuccessful. This is not only consistent with the general literature but also correlates well with the work of Bull, which showed that spiking reaction mixtures with electron-rich heterocycles shut down the desired sulfoximine formation. It is clear that these reaction conditions do not tolerate the presence of electron-rich heteroaromatic compounds.

Development of the Dichloropyrimidine Route Strategy. We therefore needed to revise our route strategy to an alternative route where the sulfoximine is formed before the introduction of the azaindole ring. We decided that the best way to do this would be to use 2-chloropyrimidine **13** as the final isolated intermediate. This would allow the introduction of the azaindole *via* Suzuki chemistry in a way similar to the early development route. Attempted reaction of β-ketoester **20** with urea resulted in only a trace amount of pyrimidone **31**, so we switched our attention to the more reactive thiourea which formed thiopyrimidone **27**. Initially, sodium ethoxide was evaluated as a base for this reaction based on literature precedent,[13] but we observed a moderate yield of only 60%, mainly due to the formation of unwanted impurities as a result of competing side reactions. The three most significant impurities were tentatively assigned based on liquid chromatography mass spectrometry data as **28** and **29** (formed by reaction of thiourea with 2 molecules of **20**) and **30** (formed as a result of Claisen ester condensation). An investigation of alternative bases and solvents (Table 2) showed that varying these parameters had a significant impact on the ratio of observed products and identified potassium *tert*-butoxide (entry 2) as a superior base for favoring the desired product, while minimizing impurity formation.

The increased steric bulk of *tert*-butoxide compared to ethoxide could decrease the rate of deprotonation of β-ketoester **20**, hence suppressing the formation of the Claisen ester condensation product **30**, but intriguingly, ethanol proved to be a more efficient solvent than *tert*-butanol (entry 8) for this transformation. The use of potassium hydroxide (entry 3) and potassium carbonate (entry 4) led to significant amounts of impurity **28**, and the use of NaOMe resulted in significant amounts of Claisen impurity **30**. The use of potassium *tert*-butoxide (entry 2) was advantageous over sodium *tert*-butoxide (entry 7), so there also appears to be a counterion effect. We were able to develop an efficient process using potassium *tert*-butoxide in ethanol, following a solvent swap from 2-MeTHF. A

Scheme 4. Initial New Route Investigation Using Amidine

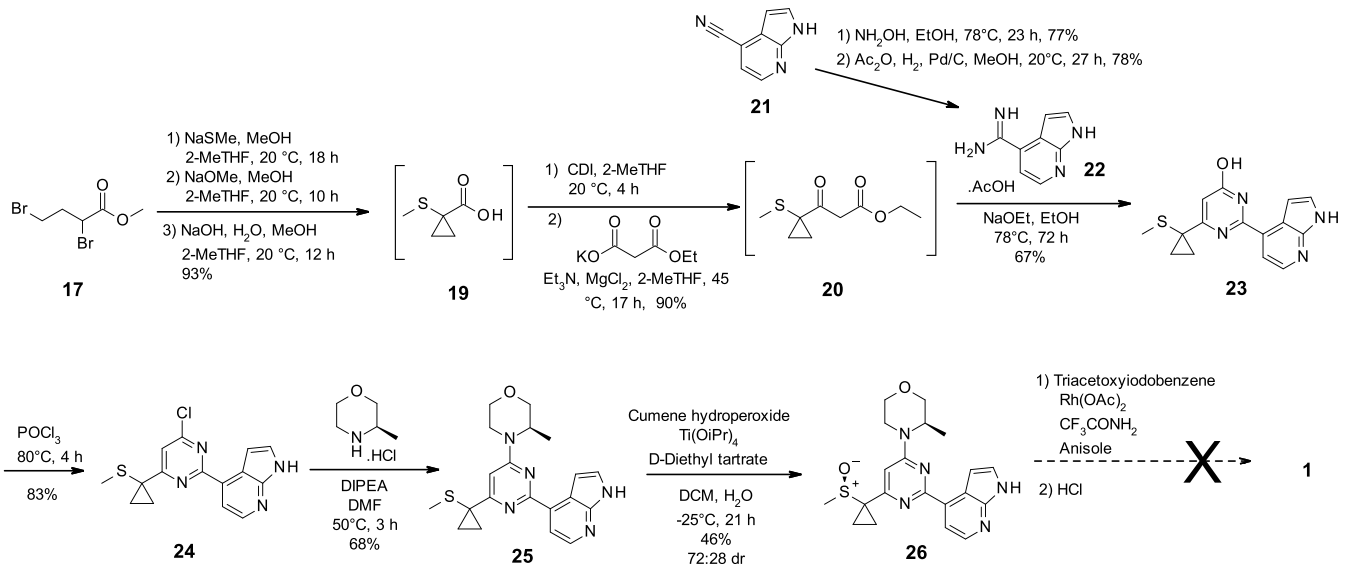

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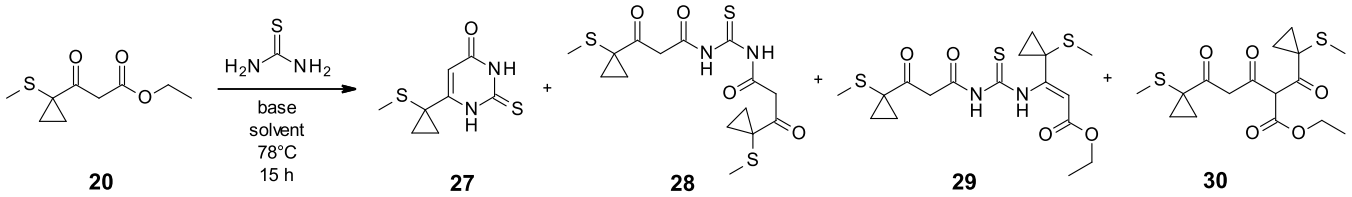
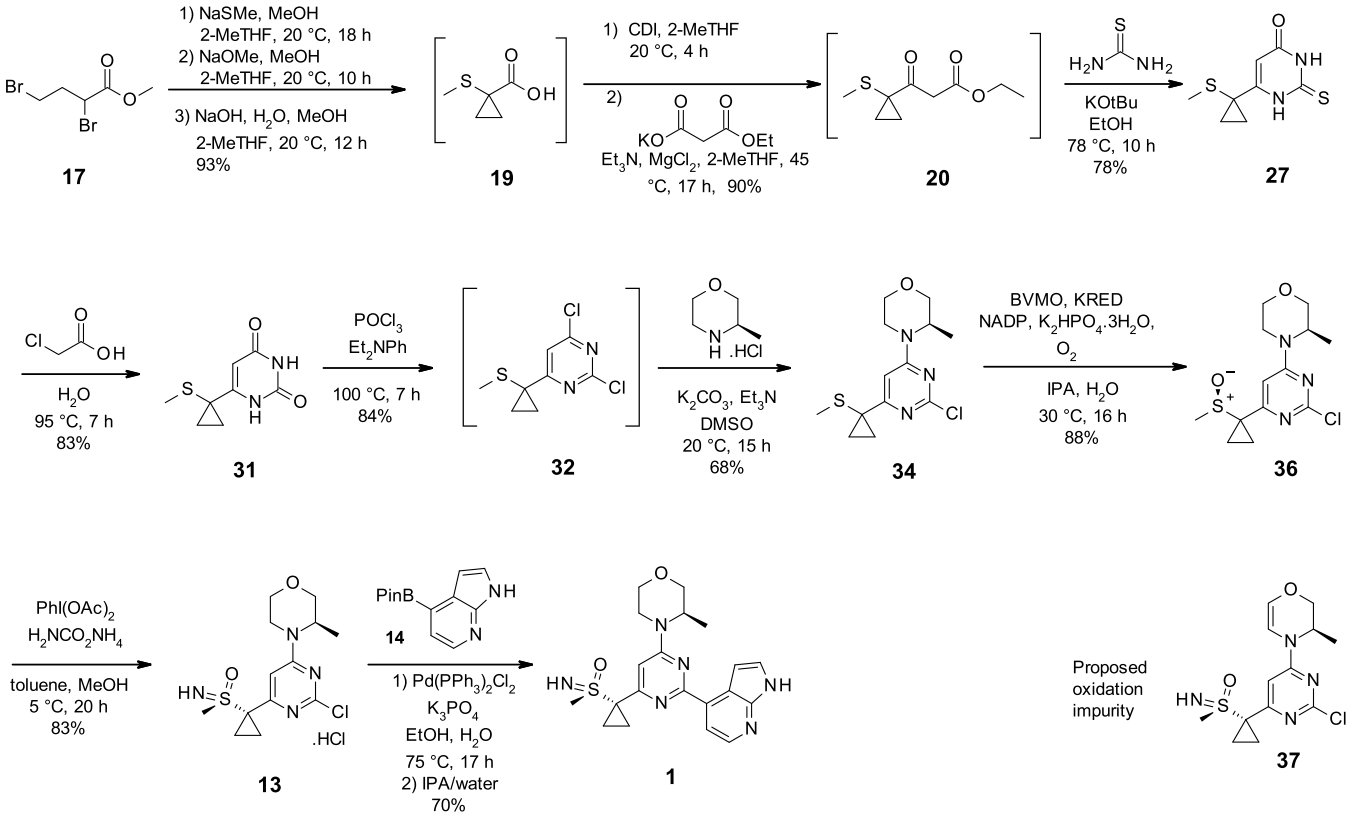
Table 2. Investigation of Bases and Solvents for Formation of Thiopyrimidone 27



			HPLC area %					
entry	base	solvent	product **27**	SM **20**	impurity **28**	impurity **29**	impurity **30**	isolated yield
1	NaOEt	EtOH	81.5	6.1	2.2	3.5	0.3	60
2	KO*t*Bu	EtOH	93.1	1.5	1.5	2.7	0	85
3	KOH	EtOH	16.7	0.7	67	8.4	2.2	NA
4	K_2CO_3	EtOH	22.6	2.5	50.3	18.1	1.5	NA
5	NaOMe	EtOH	26.5	21.2	4.7	4.9	32.0	NA
6	NaOEt	*n*-BuOH	75.9	0.7	2.4	12.8	1.1	NA
7	NaOtBu	EtOH	79.0	0.6	0	8.4	0.5	NA
8	KO*t*Bu	*t*-BuOH	86.0[a]	1.1	NA	NA	NA	58

[a]Reaction time of 24 h.

Scheme 5. Optimized New Route to Ceralasertib



facile work-up was developed involving acidification to pH 1 with hydrochloric acid resulting in the crystallization of thiopyrimidone **27**, affording a yield of 78% upon scale-up to 123 kg on a pilot plant (Scheme 5).

Conversion of thiopyrimidone **27** to pyrimidone **31** was efficiently achieved using a well-known procedure with chloroacetic acid using water as the solvent.[14] Full conversion to product was achieved by heating to 95 °C for 4 h, and then crystallization conveniently occurred upon cooling to 20 °C to afford pyrimidone **31** in 83% yield. This was a remarkably straightforward, green, and highly efficient process which did not require an organic solvent.

Process Development of Chlorination and S_NAr Reaction. To enable the introduction of (*R*)-3-methylmorpholine and azaindole, conversion of pyrimidone **31** to dichloropyrimidine **32** was required. This was achieved using phosphoryl chloride with *N*,*N*-diethylphenylamine, as reported by Frutos.[15] (Scheme 6) Initial investigations using solvents such as toluene and acetonitrile gave a slow rate of reaction resulting in long reaction times and formation of many impurities. A suitable process was developed using a mixture

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Scheme 6. Chlorination of Pyrimidone Followed by Quench

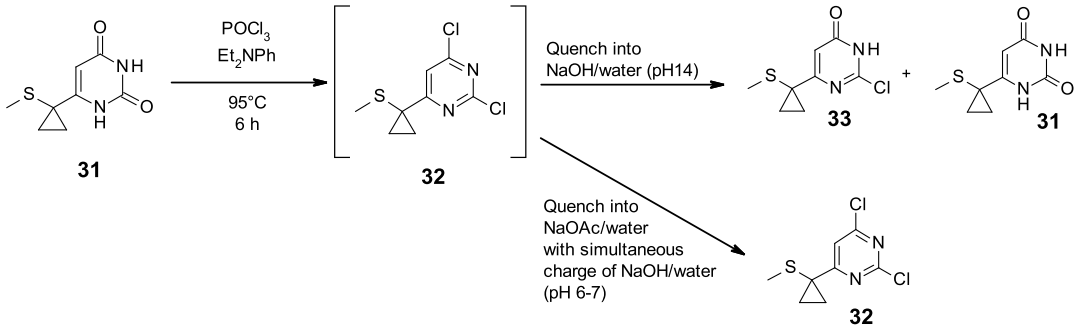
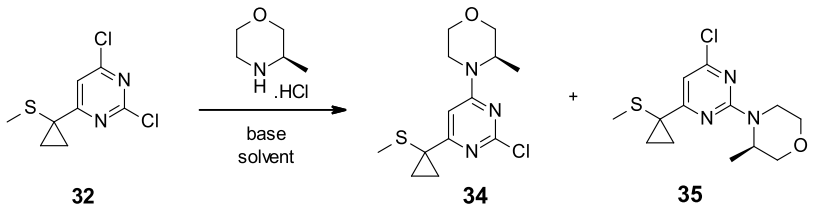


Table 3. Optimization of Parameters for S_NAr Reaction



solvent	base	temp (°C)	**34** (HPLC area %)	**35** (HPLC area %)	reaction time
MeCN	DIPEA	50	77	23	complete in 24 h
MeCN	DIPEA	20	82	18	>3 days
toluene	DIPEA	50	67	33	>3 days
MeOH	DIPEA	20	83	17	complete in 24 h[a]
DMSO	DIPEA	20	80	20	>3 days
DMSO	$Et_3N + K_2CO_3$	20	83	17	complete in 18 h

[a]12% OMe S_NAr product observed.

of phosphoryl chloride and *N*,*N*-diethylphenylamine without additional solvent. Good conversion to dichloropyrimidine **32** was observed over 6 h at 95 °C. However, there were some significant issues encountered with the quench. Quenching directly into water resulted in precipitation of the product. Initially, this looked to be a viable process, but we realized that it was important to perform the quench at temperatures in the region of 20−30 °C in the presence of a base because the formation of metastable partially hydrolyzed intermediates during a cold quench into water could result in significant hazards upon scale-up of the process.[16] A stress test of the quench mixture using 25% NaOH at 50 °C over 15 h resulted in significant hydrolysis back to pyrimidones **33** (51%) and **31** (24%). This issue was overcome by quenching the reaction mixture into a solution of aqueous sodium acetate, with simultaneous addition of aqueous NaOH to maintain the pH in the range of 6−7. Dichloropyrimidine **32** was stable in aqueous conditions at this pH range, and the resulting precipitated solid could be collected by filtration (Scheme 6). This process afforded dichloropyrimidine **32** in a good yield of 79% and high-performance liquid chromatography (HPLC) purity of 95% at 51 kg scale. However, the solid was contaminated with a black tar which was problematic for crystallization in the following stage. This was overcome by extracting the crude product from the quenched mixture into *n*-heptane, followed by treatment with activated carbon. Solvent swap from heptane to dimethyl sulfoxide (DMSO) could then be performed before the next stage. The optimized process afforded **32** as a DMSO solution in 84% yield as measured by NMR assay.

S_NAr chemistry was required to introduce the chiral (*R*)-3-methylmorpholine moiety to the 4-position of pyrimidine **32**. S_NAr reaction under basic conditions clearly favored formation of 4-morpholino isomer **34**, but a significant amount of 2-morpholino isomer **35** also formed. A screen of various solvents, bases, and temperatures demonstrated that the choice of the solvent had a significant impact on the ratio of **34** to **35** (Table 3). We chose to use (*R*)-3-methylmorpholine hydrochloride because of the substance being a solid, which is easy to handle and commercially available in bulk. Our primary objective was improving the selectivity for 4-morpholino isomer **34**, and it was clear that lower temperatures tended to favor increased amounts of **34**. However, the rate of reaction was an issue, particularly at lower temperatures. Methanol as a solvent increased the rate of reaction and gave improved selectivity, but the S_NAr product with MeOH was also observed. DMSO appeared to be a suitable solvent, but the reaction rate was slow when *N*,*N*-diisopropylethylamine (DIPEA) was used alone as a base. However, the combination of both a tertiary amine and potassium carbonate significantly improved the rate of reaction and gave the best observed ratio of 83:17. DIPEA and triethylamine gave similar results, but triethylamine was easier to remove in an aqueous work-up, so we decided to proceed with the combination of triethylamine and potassium carbonate.

For this to become a viable process, removal of the unwanted 2-morpholino isomer **35** was necessary. The crude product as a mixture of isomers was isolated as a gum, and we were unable to develop crystallization as the free base or salt. The problem was solved by considering the difference in pK_a and log *P* between the two isomers. The desired isomer **34** is both more basic than **35** (calculated pK_a of 4.9 compared to 3.8) and more

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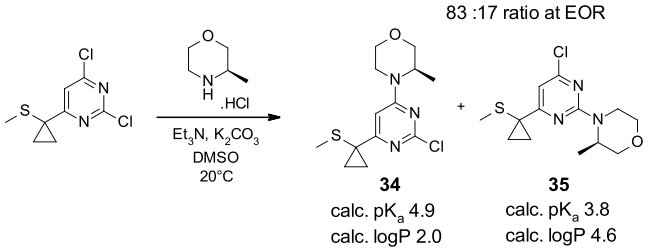
Table 4. Partitioning of Pyrimidine Isomers between MTBE and Aqueous Solutions



	aqueous layer		MTBE layer	
aqueous solution	**34** (HPLC area %)	**35** (HPLC area %)	**34** (HPLC area %)	**35** (HPLC area %)
pH 2.5 buffer	0	0	83	17
2 M HCl solution	100	0	73	27
4 M HCl solution	100	0	40	60
6 M HCl solution	98	2	5	95
12 M HCl solution	89	11	0	100

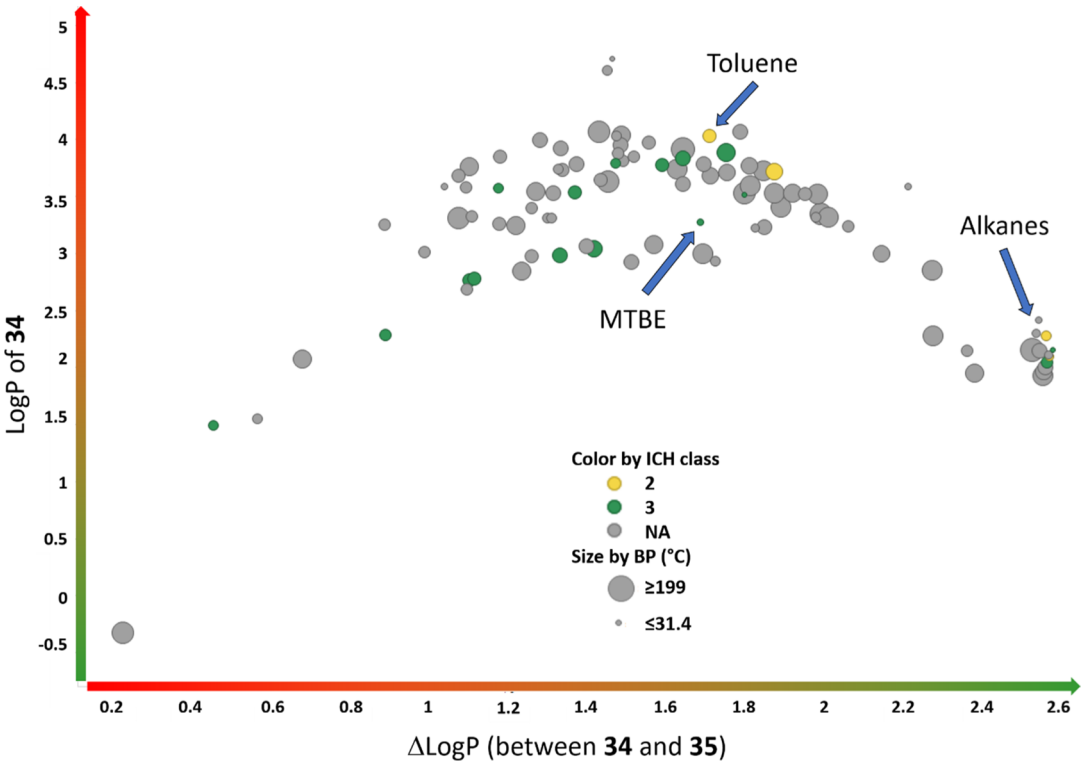


Figure 1. log *P* of **34** *vs* Δlog *P* for a range of organic solvent/water systems using COSMOtherm. Symbol color and size represent ICH class and boiling point, as detailed in the legend.

hydrophilic (calculated log *P* of 2.0 compared to 4.6).[17] We hypothesized that this could work in our favor when performing an extraction into aqueous acid. To investigate this hypothesis, the crude isolated product was dissolved in methyl *tert*-butyl ether (MTBE), and then samples were washed with a range of acidic aqueous solutions to investigate partitioning of the two isomers between the organic and aqueous layers (Table 4). With pH 2.5 buffer solution, both isomers remained fully in the organic layer. However, when the organic solution was washed with 2 M hydrochloric acid, it became apparent that some of 4-morpholino isomer **34** was extracted into the aqueous layer. The use of 4 M hydrochloric acid resulted in most of **34** being extracted into the aqueous layer, but all of 2-morpholino isomer **35** remained in the organic layer. Higher concentrations of hydrochloric acid resulted in all of **34** together with some **35** being extracted into the aqueous layer.

With this encouraging result in hand, we then performed some predictive modelling of partition coefficients to decide on the optimal organic solvent for this extraction. COSMOtherm software[18−21] was used to calculate and plot the log *P* of 4-morpholino isomer **34** against the Δlog *P* between isomers **34** and **35** (Figure 1).

We selected the set of solvents for log *P* predictions from our internal solvent database based on a combination of solvent properties, following an in-house developed approach.[22] We disregarded any ICH class 1 solvents and solvents with boiling points greater than 200 °C. Ideally, we would choose a solvent with a low log *P* and a high Δlog *P* to facilitate extraction of 4-morpholino isomer **34** into the aqueous layer while leaving 2-

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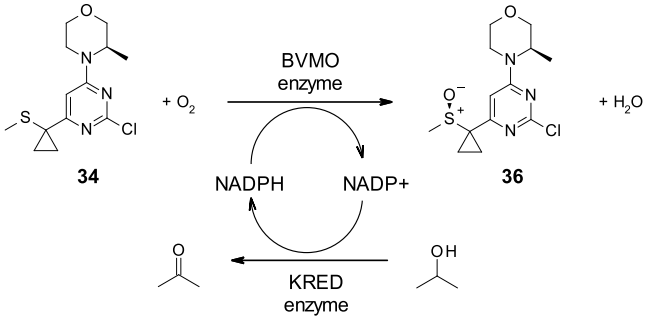
morpholino isomer **35** in the organic layer. MTBE would be a preferable solvent to toluene because **34** has a lower log *P* in this solvent, but Δlog *P* has a similar value. However, the alkane class of solvent provides the best solution, being best for extraction efficiency (low log *P* of **34**) and selectivity (highest Δlog *P* between **34** and **35**). We chose heptane as a process-friendly solvent which provided optimal partitioning for our needs.

n-Heptane also provided the ideal solvent for work-up of the S_NAr reaction in DMSO. At the end of the reaction, water and *n*-heptane were charged to DMSO solution, resulting in a clean partition with both product isomers **34** and **35** in the organic layer. DMSO, excess base, and salts were observed in the aqueous layer with only a trace of the product. A single extraction of the *n*-heptane solution with 4 M aqueous hydrochloric acid resulted in extraction of >98% of 4-morpholino isomer **34** into the aqueous phase, leaving **35** in the organic layer. On scale-up, an additional extraction with 4 M hydrochloric acid was performed to ensure optimal yield. The acidic extracts were then neutralized with NaOH and extracted into MTBE. Distillative solvent swap to propan-2-ol was easily achieved, followed by crystallization to isolate pure **34**. This process enabled the pilot plant production of **34** as a single regioisomer in 99.8% purity on 77 kg scale.

Baeyer–Villiger Monooxygenase-Catalyzed Asymmetric Sulfur Oxidation. For the early development route, biocatalytic sulfur oxidation was performed on a different substrate using a Baeyer–Villiger monooxygenase (BVMO) enzyme to afford the sulfoxide in 79% yield and a chiral purity of >99 de.[10] We were keen to build on this successful development to install the chiral sulfoxide and subsequent sulfoximine for this new route and identified a suitable BVMO enzyme[23] which achieved excellent stereo control to give sulfoxide **36** with >99% de. The enzyme uses oxygen, together with reduced nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor, which is oxidized to $NADP^+$. Recycling of $NADP^+$ to NADPH is achieved with an additional keto-reductase (KRED) enzyme which oxidizes the cosolvent isopropanol to acetone (Scheme 7). The reaction was performed at pH 9 using a

Scheme 7. Asymmetric Sulfur Oxidation with BVMO Enzyme



dipotassium hydrogen phosphate buffer. As was the case for the previous biocatalytic process, the key engineering challenge was the mass transfer of sufficient oxygen, and this was achieved by sparging a mixture of air and nitrogen (1:2) through the reaction mixture at a high rate of stirring. After full conversion to sulfoxide was achieved, the enzyme was denatured using hydrochloric acid and sodium chloride. The solids were removed by filtration, and then the filtrate was extracted with ethyl acetate. The product was crystallized from ethyl acetate using *n*-heptane as an antisolvent to afford sulfoxide **36** in 88% yield and >99% de on 64 kg scale.

Process Development of Metal-Free Sulfoximine Formation. The early development route used a rhodium acetate catalyzed process with diacetoxyiodobenzene as the oxidant and trifluoroacetamide as the nitrogen source, which required subsequent hydrolysis of the acetamide. The cost of rhodium acetate was a concern for a commercial manufacturing process, and we were interested in a recent report by Bull which described metal-free conditions for sulfoximine formation.[11] We initially applied the reported conditions to sulfoxide **36** using diacetoxyiodobenzene (3 equiv) and ammonium carbamate (4 equiv) as a nitrogen source in methanol at 20 °C. Good conversion to product **13** was observed over the course of 1 h at 20 °C, but we were mindful of the potential to generate explosive iodosobenzene in this process, so a moderate reaction temperature and a safe extractive work-up was required which did not involve heating or distillation. Toluene was also investigated as a potential solvent, but the rate of reaction proved to be slower, with only 33% conversion to **13** over 23 h at 20 °C. A mixture of toluene (8 relative volumes) and methanol (2 relative volumes) resulted in a suitable rate of reaction at 20 °C and allowed for an extractive aqueous work-up (Scheme 5). The work-up involved extraction of the product into 30% citric acid solution, followed by basification of the aqueous layer with sodium hydroxide and then extraction into a 3:1 mixture of ethyl acetate and THF. Distillative solvent swap to isopropanol was performed, and then a solution of hydrogen chloride in isopropanol was added to form the hydrochloride salt of **13**, which was isolated following the addition of MTBE as an antisolvent. A small amount of oxidation impurity (up to 3%) was observed, which was tentatively assigned as dihydro-1,4-oxazine **37**, based on MS fragmentation data. The subsequent oxidation impurity in the API could not be efficiently purged by crystallization, so we needed to control its formation at this stage. We developed this process to control the impurity to <0.2% by decreasing the diacetoxyiodobenzene charge from 3.0 to 2.1 equiv, decreasing the reaction temperature to 5 °C, and completing the stage by performing a slurry of the hydrochloride salt of **13** in methanol. The optimized process afforded the hydrochloride salt of sulfoximine **13** in 83% yield on 30 kg scale at >99% purity.

Process Development of Suzuki Reaction. In common with the early development route, the final stage involved a Suzuki coupling between chloropyrimidine **13** and boronate ester **14**. First, we were keen to improve the process which was used to manufacture the boronate ester from the commercially available aryl bromide **38** (Scheme 8). The early development route used a Miyaura borylation process which used B_2Pin_2 with tetrakis(triphenylphosphine)palladium(0) as the catalyst and potassium acetate as the base in 1,4-dioxane. Although conversion to boronate ester **14** proceeded well under these conditions, the work-up was inefficient involving filtration,

Scheme 8. Optimized Miyaura Borylation Reaction

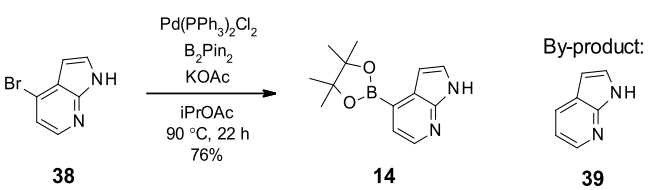


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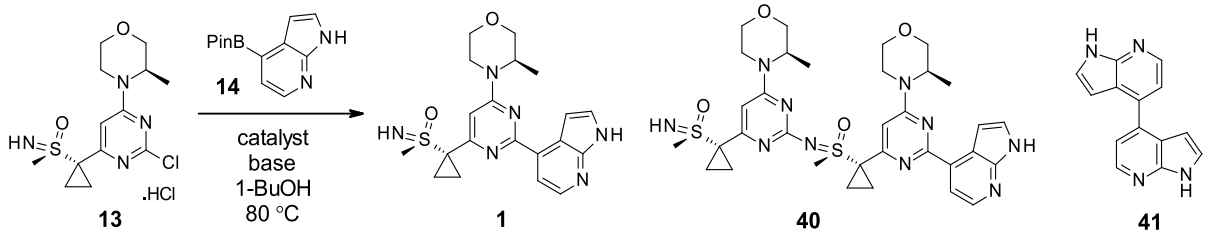
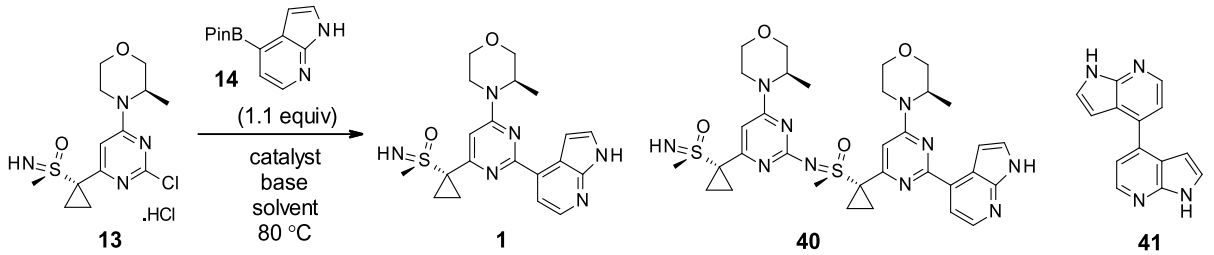
Table 5. Investigation of Catalysts and Bases in 1-BuOH for Suzuki Coupling



				HPLC area % after 23 h		
entry	catalyst	base	equiv of **14**	**1**	**40**	**41**
1	$Pd(dppf)Cl_2$	K_2CO_3	1.1	75.6	16.2	0.6
2	$Pd(dppf)Cl_2$	K_2CO_3	1.3	91.3	3.5	0.4
3	$Pd(dppf)Cl_2$	K_3PO_4	1.1	89.0	6.5	0.1
4	$Pd(dppf)Cl_2$	K_3PO_4	1.3	96.3	0.8	0.4
5	$Pd(PPh_3)_2Cl_2$	K_2CO_3	1.1	92.4	0.9	0.6
6	$Pd(PPh_3)_2Cl_2$	K_2CO_3	1.3	94.9	0.2	0.6
7	$Pd(PPh_3)_2Cl_2$	K_3PO_4	1.1	96.7	0.2	0.4
8	$Pd(PPh_3)_2Cl_2$	K_3PO_4	1.3	94.2	0.7	0.6

Table 6. Investigation of Catalysts, Bases, and Solvents over 2 h for Suzuki Coupling



				HPLC area % after 2 h			
entry	catalyst	base	solvent	**1**	**40**	**41**	other imps >0.2%
1	$Pd(PPh_3)_2Cl_2$	K_2CO_3	2-MeTHF	29.2	0.03	0.32	1
2	$Pd(PPh_3)_2Cl_2$	K_3PO_4	2-MeTHF	30.22	0.13	0.18	1
3	$Pd(PPh_3)_2Cl_2$	K_2CO_3	*i*PrAc	32.4	0.06	0.4	1
4	$Pd(dppf)Cl_2$	K_2CO_3	ethanol	55.24	0.11	0.53	4
5	$Pd(dppf)Cl_2$	K_3PO_4	*i*PrAc	61	0.48	0.2	2
6	$Pd(PPh_3)_2Cl_2$	K_2CO_3	ethanol	62.02	0.13	1.09	2
7	$Pd(dppf)Cl_2$	K_2CO_3	*i*PrAc	71.4	0.24	0.25	4
8	$Pd(PPh_3)_2Cl_2$	K_3PO_4	ethanol	78.54	0.08	0.53	2
9	$Pd(dppf)Cl_2$	K_2CO_3	2-MeTHF	80.9	0.84	0.23	5
10	$Pd(dppf)Cl_2$	K_3PO_4	2-MeTHF	85.69	0.56	0.17	4
11	$Pd(PPh_3)_2Cl_2$	K_3PO_4	ethanol	85.80	0.1	0.36	4

distillation, and then uncontrolled precipitation by addition of water, followed by slurrying with MTBE. We were unsure whether the air-sensitive catalyst tetrakis(triphenylphosphine)-palladium(0) was optimal and were uncomfortable about the use of ICH class 2 solvent 1,4-dioxane in a penultimate stage before the API. A substantial screen was performed using high-throughput experimentation in a 96-well plate format in a glovebox. The main aim of this screen was to find a catalyst, a base, and a solvent system capable of delivering the clean product with the required speed and enabling a smooth time-efficient work-up process. The screen[24] identified several potential catalysts, but there was a clear trend in reaction rates. The reaction rate declined in the order $Pd(PPh_3)_2Cl_2 \approx Pd(OAc)_2/PPh_3 > Pd(dba)_2/PPh_3 > Pd(PPh_3)_4$. A key byproduct that we wanted to avoid was the proto-deboronated compound **39**. The amount of **39** followed the general trend $Pd(dba)_2/PPh_3 \geq Pd(PPh_3)_4 > Pd(OAc)_2/PPh_3 \approx Pd(PPh_3)_2Cl_2$. $Pd(PPh_3)_2Cl_2$ was clearly the preferred catalyst for both the reaction rate and avoidance of **39**, and 2 mol % catalyst worked well for this process. The choice of base clearly impacted the rate of reaction, giving a reaction rate trend of $NMe_4OAc > CsOAc > KOAc$. However, the amount of impurity **39** followed the same trend. We decided that suppression of impurity formation was the most important factor, so decided to use KOAc as the base for this reaction. In terms of solvent, 2-MeTHF and *i*PrOAc offered a good balance of properties for both the reaction and work-up. Boronate ester **14** had a lower solubility in *i*PrOAc, resulting in higher yields from the final crystallization process, so this was chosen as the reaction solvent. Following the reaction, an aqueous work-up was performed to remove potassium salts. Further aqueous washes were necessary to remove boron-related impurities. Treatment with mercaptoalkyl silica was performed to scavenge excess palladium to less than 100 ppm, which ensured that good control of impurities

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was achieved in the subsequent Suzuki stage. The *i*PrOAc solution was azeotropically dried by distillation, and then crystallization was achieved using MTBE as the antisolvent. A yield of 75% was achieved on scale-up to pilot plant using 41 kg of aryl bromide **38** to afford boronate ester **14** with less than 0.1% of the debrominated byproduct **39**.

The final Suzuki coupling between chloropyrimidine **13** and boronate ester **14** had previously been well developed for the early development route. Although this process was high yielding, we were concerned about the complexity and number of unit operations required for the work-up. The previous process used $Pd(dppf)Cl_2$ as the catalyst, potassium carbonate as the base, and ethanol as the reaction solvent. The work-up involved a solvent swap from ethanol to ethyl acetate, followed by aqueous wash and then treatment with a solid-supported silica thiol to scavenge palladium. Finally, another solvent swap to 1-butanol was required, followed by crystallization. We initially evaluated 1-butanol as a single solvent for reaction, work-up, and crystallization (Table 5). Although the reaction proceeded well, we observed the formation of dimeric impurity **40** which was tentatively assigned based on MS data. Dimeric impurity **40** was particularly prevalent when only 1.1 equiv of boronate ester **14** was used in the reaction with $Pd(dppf)Cl_2$ as the catalyst (Table 5, entries 1 and 3). Although the use of $Pd(PPh_3)Cl_2$ as the catalyst appeared to give a cleaner reaction profile (Table 5, entries 5−8), the API was contaminated with residual boronate ester **14** following crystallization. We focused on ethanol as a solvent with a single solvent swap to a suitable solvent, which was immiscible with water for work-up and suitable for crystallization. Although 2-MeTHF gave an unfavorable profile as a reaction solvent, it offered an ideal solvent for aqueous work-up and crystallization. In particular, we were able to purge the homodimer impurity **41** during the crystallization. The use of $Pd(dppf)Cl_2$ carried a higher risk of forming impurity **40** and other unknown impurities (Table 6, entries 4, 5, 7, 9, and 10), which could not be purged by crystallization, so $Pd(PPh_3)_2Cl_2$ (1.3 mol %) was chosen as the catalyst. Potassium phosphate was chosen as the base because it offered a faster rate of reaction than potassium carbonate. At the end of reaction, solvent swap to 2-MeTHF was performed. Overall, this allowed us to improve the work-up, palladium scavenging, and crystallization process.

An investigation of palladium scavenging agents identified L-cysteine as an efficient scavenger which could be used as an aqueous solution to wash the 2-MeTHF solution. Further investigation of additives in combination with scavengers in aqueous solution suggested that fully deprotonated L-cysteine is more effective at scavenging palladium (Table 7, entries 2, 5, and 6). Although DIPEA worked well in combination with L-cysteine, inorganic bases were preferred because of better aqueous solubility. The level of palladium observed in the organic solution decreased from 308 to 2 ppm when washed with the preferred combination of aqueous L-cysteine with potassium phosphate (Table 7, entry 6).

Despite the successful palladium scavenging process, we were mindful of the fact that the final bond-forming stage was a palladium-catalyzed Suzuki process, and there was a risk of palladium contamination in the API. To mitigate this risk and ensure that other impurities were purged to acceptable levels while the API was isolated in the desired crystalline form and particle size distribution, we decided to develop a final recrystallization. We identified isopropanol and water as a binary solvent system, which allowed full dissolution of the API

Table 7. Investigation of Aqueous Solutions for Scavenging Pd from 2-MeTHF Solution

entry	scavenger	molar equiv of scavenger wrt Pd	additive	Pd concentration after aqueous wash (ppm)[a]
1	L-cysteine	50	none	28
2	L-cysteine	50	DIPEA	1
3	L-cysteine ethyl ester	50	DIPEA	28
4	L-cysteine	150	HCl	20
5	L-cysteine	150	NaOH	4
6	L-cysteine	150	K_3PO_4	2
7	trithiocyanuric acid	20	none	30
8	trithiocyanuric acid	20	activated carbon on Celite	65
	Quadrasil-MP	150	none	10

[a]Pd concentration measured as 308 ppm before aqueous wash.

(**1**) in 4 relative volumes of the solvent at 60 °C. However, cooling crystallization and isolation of the API using this binary solvent system resulted in disappointing yields. To achieve an acceptable crystallization recovery of >85%, azeotropic removal of water by reduced pressure distillation was required to ensure that the water content was ≤0.6% w/w by Karl Fischer analysis. We also knew that 1-butanol could be used for crystallization of **1** from the work performed in the early development program,[3] but the isopropanol distillation offered the additional advantage of purging impurity **41**. Our final recrystallization process involved dissolving the crude solid in 2.5 relative volumes of isopropanol and 1.2 relative volumes of water. This solution was filtered to remove particulate impurities, and then azeotropic drying of the solution by reduced pressure distillation with the addition of further isopropanol was performed. When the water content was ≤0.6% by Karl Fischer analysis, seeding and cooling to 5 °C enabled efficient crystallization. This recrystallization was a key part of the overall process, resulting in high-quality API with very good control of key impurities. Purging of the Ames-positive boronate ester **14** was critical, and all isolated batches of API contained <0.01% of **14** or the corresponding boronic acid, as confirmed by residual boron analysis. Residual palladium was also well controlled to less than 3 ppm in all batches. This combined Suzuki reaction and recrystallization process afforded high-quality ceralasertib in 70% yield on a scale of 32 kg.

CONCLUSIONS

In conclusion, we have developed a new and improved route to ceralasertib, which solves many of the scale-up issues faced with the early development route. A low-yielding cyclopropanation which generated mutagenic impurities has been replaced by a novel and high-yielding cyclopropanation from methyl 2,4-dibromobutyrate. Following construction of the pyrimidine ring, large-scale chlorination with phosphoryl chloride has been developed which enables safe quenching of phosphoryl chloride without product decomposition. An innovative work-up of S_NAr reaction has been developed to remove the unwanted regio-isomer, based on differences in pK_a and partition coefficients. High-yielding sulfur oxidation was developed using a BVMO enzyme, and then a safe and scalable metal-free sulfoximine formation was developed, followed by an optimized Suzuki reaction. The chiral morpholine **2** was manufactured in three steps from D-alaninol using the route described by Mahajan[4] in

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an overall yield of 32%. When we consider the manufacture of **2** as part of the longest linear sequence for the early development route,[3] the introduction of this new route has shortened the longest linear sequence from 13 steps to 9 steps and improved the overall yield of this sequence from 4 to 16%. Overall, the introduction of this new route has enabled the manufacture of high-quality ceralasertib with excellent control of impurities, resulting in processes which we believe will be suitable for long-term commercial manufacture.

EXPERIMENTAL SECTION

General Information. All starting materials were commercially available and used without further purification. Large-scale reactions were carried out in stainless steel or glass-lined steel reactors fitted with heat transfer jackets and serviced with appropriate ancillary equipment. NMR spectra were recorded on a Bruker DRX 500 (500 MHz) spectrometer. The central peaks of DMSO-d_6 (δ_H 2.50 ppm) were used as the reference. Sample solutions may also contain an internal standard (2,3,5,6-tetrachloronitrobenzene) for assay determination. Spectral data is reported as a list of chemical shifts (δ, in ppm) with a description of each signal using standard abbreviations (s = singlet, d = doublet, m = multiplet, t = triplet, q = quartet, br = broad, *etc.*).

1-(Methylsulfanyl)cyclopropanecarboxylic acid (19). Methyl 2,4-dibromobutyrate (351 kg, 1350 mol, 1.0 equiv) and 2-methyltetrahydrofuran (1200 kg) were charged to the vessel at 10−15 °C. A solution of sodium thiomethoxide (100.0 kg, 1427 mol, 1.06 equiv) in methanol (551.6 kg) was charged to the vessel at 10−20 °C. The contents of the vessel were stirred at 15−25 °C for 18 h. Sodium methoxide (86.0 kg, 1592 mol, 1.18 equiv) was charged to the vessel at 10−20 °C. The contents of the vessel were stirred at 10−20 °C for 10 h. An aqueous solution of sodium hydroxide (2 M, 801 L, 1.22 equiv) was charged to the vessel at 15−25 °C. The contents of the vessel were stirred at approximately 20 °C for 12 h. The contents of the vessel were concentrated by reduced pressure distillation to a volume of approximately 5 relative volumes. 2-Methyltetrahydrofuran (1200 kg) was charged to the vessel. The mixture was acidified to pH 1−2 with 4 molar aqueous hydrochloric acid solution. The biphasic mixture was stirred for 1 h, and then the batch was allowed to settle. The aqueous layer was removed. The organic solution was washed with brine (2 × 700 kg). The organic solution was charged with 2-methyltetrahydrofuran (2 × 900 kg) to 3 relative volumes by reduced pressure distillation. 2-Methyltetrahydrofuran (920 kg) was charged to the vessel. The organic solution is concentrated under reduced pressure distillation to yield 1-(methylsulfanyl)cyclopropanecarboxylic acid (**19**) as a dry 2-methyltetrahydrofuran solution (987.2 kg, 12.0% w/w, 93% yield). ^{1}H NMR (500 MHz, DMSO, 27 °C): 1.08−1.15 (m, 2H), 1.4−1.46 (m, 2H), 2.15 (s, 3H), 12.55 (s, 1H); ^{13}C NMR (126 MHz, DMSO, 27 °C): 15.49, 18.98, 26.57, 173.74; HRMS (ESI): calcd for $C_5H_7O_2S$ $[M - H]^-$, 131.0172; found, 131.0159.

Ethyl 3-[1-(methylsulfanyl)cyclopropyl]-3-oxopropanoate (20). A solution of 1-(methylsulfanyl)-cyclopropanecarboxylic acid (148.0 kg, 1119.7 mol) in 2-methyltetrahydrofuran (900 kg) was charged to a solution of carbonyldiimidazole (196.0 kg, 1177.3 mol) in 2-methyltetrahydrofuran (764 kg) in vessel 1. The contents of vessel 1 were stirred at approximately 20 °C for 6 h. 2-Methyltetrahydrofuran (1615 kg) was charged to vessel 2, and then stirring was started. Ethyl potassium malonate (285.6 kg, 1678.0 mol) and magnesium chloride (160.0 kg, 1678.4 mol) were charged to vessel 2 at 15−25 °C. Triethylamine (192.4 kg, 1901.4 mol) was charged to vessel 2. The contents of vessel 2 were stirred at approximately 20 °C for 1 h. The contents of vessel 1 were transferred to vessel 2 at 15−25 °C. The resulting mixture was stirred at approximately 40−45 °C for 20 h. The mixture was cooled to approximately 20 °C. Aqueous hydrochloric acid solution (4 M, 1887 kg) was charged, and the mixture was stirred for 1 h. Then, stirring was stopped, and the aqueous layer was removed. Aqueous sodium bicarbonate solution (8% w/w, 799 kg) was charged, and the mixture was stirred for 30 min. Then, agitation was stopped, and the aqueous layer was removed. A solution of sodium chloride (184.6 kg) in water (754 kg) was charged, and the mixture was stirred for 30 min. Then, stirring was stopped, and the aqueous layer was removed. The organic solution was concentrated to 2−3 relative volumes by reduced pressure distillation. Ethanol (236.8 kg) was charged to vessel 2. The organic solution was concentrated to 2−3 relative volumes by reduced pressure distillation. Ethanol (236.8 kg) was charged to vessel 2. The organic solution was concentrated to 3−4 relative volumes by reduced pressure distillation to yield ethyl 3-[1-(methylsulfanyl)cyclopropyl]-3-oxopropanoate (**20**) as an ethanol solution (552.0 kg, 37.0% w/w, 1010.5 mol, 90% yield). ^{1}H NMR (500 MHz, DMSO, 27 °C): 1.19 (t, J = 7.1 Hz, 3H), 1.23−1.31 (m, 2H), 1.50−1.56 (m, 2H), 2.14 (s, 3H), 3.90 (s, 2H), 4.10 (q, J = 7.1 Hz, 2H).

6-[1-(Methylsulfanyl)cyclopropyl]-2-sulfanylidene-2,3-dihydro-4(1*H*)-pyrimidinone (27). Potassium *tert*-butoxide (100.0 kg, 882.4 mol, 1.2 equiv) and thiourea (67.0 kg, 880.2 mol, 1.2 equiv) charged to ethanol (710.0 kg) with stirring at 10−40 °C was charged to the stirred solution, and the resulting mixture was heated to approximately 78 °C. A solution of ethyl 3-[1-(methylsulfanyl)cyclopropyl]-3-oxopropanoate (148.0 kg, 731.7 mol) in ethanol (327.8 kg) was charged to the vessel at 75−80 °C. The contents of the vessel were stirred at approximately 78 °C for 23 h. The mixture was cooled to approximately 20 °C, and then water (590 kg) was charged. Concentrated hydrochloric acid solution (98.8 kg) was added slowly at 15−25 °C. The contents of the vessel were stirred for 2 h. The resulting solid was collected by filtration. The filter cake was washed with a mixture of ethanol (223.2 kg) and water (149.0 kg) and then dried to yield 6-[1-(methylsulfanyl)-cyclopropyl]-2-sulfanylidene-2,3-dihydro-4(1*H*)-pyrimidinone (**27**) as a white solid (123.8 kg, 98.8% w/w, 570.7 mol, 78% yield). ^{1}H NMR (500 MHz, DMSO, 27 °C): 1.02−1.09 (m, 2H), 1.21−1.29 (m, 2H), 2.05 (s, 3H), 5.70 (d, J = 1.6 Hz, 1H), 12.31 (s, 1H), 12.48 (s, 1H); ^{13}C NMR (126 MHz, DMSO, 27 °C): 14.48, 15.70, 26.54, 103.73, 155.33, 161.06, 176.31; HRMS (ESI): calcd for $C_8H_{11}N_2OS_2$ $[M + H]^+$, 215.0307; found, 215.0312.

6-[1-(Ethylsulfanyl)cyclopropyl]-2,4(1*H*,3*H*)-pyrimidinedione (31). 6-[1-(Methylsulfanyl)cyclopropyl]-2-sulfanylidene-2,3-dihydro-4(1*H*)-pyrimidinone (147.5 kg, 679.8 mol) was charged to water (1066 kg) with stirring at 10−30 °C. Chloroacetic acid (316.8 kg, 3352 mol, 4.9 equiv) was charged at 10−30 °C. The contents of the vessel were stirred at approximately 95 °C for 6 h and then cooled to approximately 5 °C. The resulting solid was collected by filtration and then slurried in aqueous hydrochloric acid solution (2 M, 463 kg). The resulting solid was collected by filtration and dried at approximately 40 °C to yield 6-[1-(methylsulfanyl)-cyclopropyl]-2,4(1*H*,3*H*)-pyrimidinedione (**31**) as a white solid (113.9 kg, 97.7% w/w, 561.4 mol, 83% yield). ^{1}H NMR

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(500 MHz, DMSO, 27 °C): 1.03−1.07 (m, 2H), 1.22−1.26 (m, 2H), 2.06 (s, 3H), 5.40 (s, 1H), 10.93 (s, 2H); ^{13}C NMR (126 MHz, DMSO, 27 °C): 14.53, 15.59, 26.69, 98.99, 151.69, 155.34, 164.05; HRMS (ESI): calcd for $C_8H_{11}N_2O_2S$ $[M + H]^+$, 199.0536; found, 199.0540.

2,4-Dichloro-6-[1-(methylsulfanyl)cyclopropyl]-pyrimidine (32). Phosphoryl chloride (594 kg) was charged to vessel 1. 6-[1-(Methylsulfanyl)cyclopropyl]-2-sulfanylidene-2,3-dihydro-4(1*H*)-pyrimidinone (91.7 kg, 452 mol) was charged to the vessel with stirring at 15−20 °C. *N*,*N*-Diethylaniline (164.8 kg, 1128 mol) was charged to the vessel at 15−25 °C. Water (2.70 kg) was slowly charged to the vessel, maintaining the temperature below 50 °C. The contents of the vessel were heated at 90−100 °C for 6 h. The contents of the vessel were cooled to 15−25 °C. A solution of sodium acetate (18.0 kg) in water (540.8 kg) was charged to vessel 2. The contents of vessel 1 and an aqueous solution of sodium hydroxide (25% w/w, 2787 kg) were added to vessel 2 simultaneously, keeping the internal temperature in the range 15−30 °C and pH in the range 5−8. *n*-Heptane (1232.9 kg) was charged to vessel 2, and the mixture was stirred at 35 °C for 2 h. Stirring was stopped, and the aqueous layer was removed. A mixture of activated carbon (9.2 kg) and water (27.2 kg) were charged to vessel 2, and the mixture was stirred for 2 h at 35−40 °C. The mixture was filtered to remove carbon, and then the vessel and filter cake were washed with *n*-heptane (124.3 kg). The aqueous layer was removed. Water (360 kg) and aqueous hydrochloric acid (2 M, 933 kg) were charged, the mixture was stirred at 15−25 °C for 15 min, and then the aqueous layer was removed. The organic solution was washed with water (2 × 270 kg) and then concentrated under reduced pressure to a volume of 180 L. DMSO (300 kg) was charged, and then the mixture was concentrated under reduced pressure to yield 2,4-dichloro-6-[1-(methylsulfanyl)cyclopropyl]pyrimidine (**32**) as a solution in DMSO (394.4 kg, 22.5% w/w, 377 mol, 84% yield). ^{1}H NMR (500 MHz, DMSO, 27 °C): 1.44−1.55 (m, 2H), 1.65−1.76 (m, 2H), 2.14 (s, 3H), 8.02 (s, 1H); ^{13}C NMR (126 MHz, DMSO, 27 °C): 14.94, 23.02, 29.84, 117.66, 159.16, 161.92, 176.54; HRMS (ESI): calcd for $C_8H_9N_2SCl_2$ $[M + H]^+$, 234.9858; found, 234.9863.

(3*R*)-4-{2-Chloro-6-[1-(methylsulfanyl)cyclopropyl]-4-pyrimidinyl}-3-methylmorpholine (34). A solution of 2,4-dichloro-6-[1-(methylsulfanyl)cyclopropyl]pyrimidine (87.5 kg, 372 mol) in DMSO (456.9 kg) was charged to vessel 1. Potassium carbonate (135.0 kg, 967 mol, 2.6 equiv) was charged to vessel 1. (*R*)-3-Methylmorpholine hydrochloride (62.1 kg, 447 mol, 1.2 equiv) was charged to vessel 1. Triethylamine (99.5 kg, 967 mol, 2.6 equiv) was charged to vessel 1. The contents of vessel 1 were stirred at approximately 20 °C for 19 h. Heptane (410.6 kg) and water (450.2 kg) were charged to vessel 1. The contents of vessel 1 were stirred for 30 min, and then a small amount of solid material was removed by filtration. The vessel and the filter cake were washed with water (179 kg) and *n*-heptane (278 kg), and then the layers were separated. The organic layer was charged to vessel 2 and washed with water (353 kg). The aqueous layer was removed. Aqueous hydrochloric acid solution (4 M, 1011 kg) was charged to vessel 2. The contents of vessel 2 were agitated for 30 min, and then the layers were allowed to settle. The aqueous layer was removed and transferred to vessel 3. Aqueous hydrochloric acid solution (4 M, 1011 L) was charged to vessel 2. The contents of vessel 2 were agitated for 30 min, and then the layers were allowed to settle. The aqueous layer was removed and transferred to vessel 3. *tert*-Butyl methyl ether (651 kg) was charged to the stirred contents of vessel 3. Aqueous NaOH solution (50% w/w, 652 kg) was slowly charged to vessel 3 until the contents were adjusted to pH 14. Stirring was stopped, and the layers were allowed to settle. The layers were separated, and then the aqueous layer was recharged to vessel 3. *tert*-Butyl methyl ether (195 kg) was charged to vessel 3. The mixture was stirred for 20 min, then agitation was stopped, and the layers were allowed to settle. The aqueous layer was removed, and then both *tert*-butyl methyl ether solutions were combined in vessel 3. The contents of vessel 3 were concentrated by reduced pressure distillation to a volume of approximately 3 relative volumes. Isopropyl alcohol (278 kg) was charged to vessel 3, and then the contents of vessel 3 were concentrated by distillation to a volume of approximately 3 relative volumes. Isopropyl alcohol (278 kg) was charged to vessel 3, and then the contents of vessel 3 were concentrated by distillation to a volume of approximately 3 relative volumes. The mixture was cooled to 5 °C and stirred for 4 h, and then the solid was collected by filtration and dried to yield (3*R*)-4-{2-chloro-6-[1-(methylsulfanyl)cyclopropyl]-4-pyrimidinyl}-3-methylmorpholine (**34**) as a white solid (77.8 kg, 99.8% w/w, 252 mol, 68% yield). ^{1}H NMR (500 MHz, DMSO, 27 °C): 1.20 (d, J = 6.8 Hz, 3H), 1.23−1.31 (m, 2H), 1.49−1.58 (m, 2H), 2.11 (s, 3H), 3.19 (td, J = 13.0, 3.7 Hz, 1H), 3.44 (td, J = 11.9, 3.1 Hz, 1H), 3.59 (dd, J = 11.6, 3.1 Hz, 1H), 3.71 (d, J = 11.6 Hz, 1H), 3.82−4.09 (m, 2H), 4.33−4.37 (m, 1H), 7.10 (s, 1H); ^{13}C NMR (126 MHz, DMSO, 27 °C): 13.37, 14.90, 20.24, 29.54, 46.73, 65.78, 69.91, 98.37, 159.69, 162.84, 170.76; HRMS (ESI): calcd for $C_{13}H_{19}N_3SOCl$ $[M + H]^+$, 300.0932; found, 300.0939.

(3*R*)-4-(2-Chloro-6-{1-[(*R*)-methylsulfinyl]-cyclopropyl}-4-pyrimidinyl)-3-methylmorpholine (36). Dipotassium hydrogen phosphate trihydrate (49.0 kg) and water (1906 kg) were charged to the vessel. Stirring was started, and then concentrated hydrochloric acid (2.2 kg) was added. A solution of (3*R*)-4-{2-chloro-6-[1-(methylsulfanyl)-cyclopropyl]-4-pyrimidinyl}-3-methylmorpholine (63.3 kg, 211 mol) and isopropyl alcohol (150.7 kg) was charged to the vessel. Nicotinamide adenine dinucleotide phosphate (1.30 kg) was charged to the vessel. Cyclohexanone mono-oxygenase *Rhodococcus ruber* (accession number AAL14233.1, crude cell lysate, 380.4 kg) was charged to the vessel. KRED (Asymchem 6511, 127.2 kg) was charged to the vessel. A mixture of air and nitrogen (1:2) was blown through the reaction mixture using a sparge, and the contents of the vessel were stirred at approximately 30 °C for 16 h. The contents of the vessel were adjusted to pH 3 using 10% aqueous hydrochloric acid solution (52 kg). Sodium chloride (821.1 kg) was charged to the vessel. The resulting mixture was stirred for 2 h. The solid was removed by centrifugation, and the filter cake was washed with ethyl acetate (3 × 570 kg). The combined filtrate was charged to a clean vessel, and then a solution of sodium hydroxide (24.8 kg) in water (101.3 kg) was added at 15−30 °C. The resulting mixture was extracted with ethyl acetate (3 × 1170 kg). The combined organic phases were washed with water (1232 kg). The resulting organic solution was concentrated by reduced pressure distillation to a total volume of approximately 250 L. *n*-Heptane (434 kg) was charged to the vessel, and then the contents of the vessel were concentrated by reduced pressure distillation to a total volume of approximately 150 L. The contents of the vessel were stirred at 80 °C for 2 h and then cooled to approximately 10 °C and stirred for a further 4 h. The solid was collected by filtration. The filter cake was washed with heptane (2 × 170 kg) and dried to yield (3*R*)-4-(2-chloro-6-{1-

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[(*R*)-methylsulfinyl]cyclopropyl}-4-pyrimidinyl)-3-methylmorpholine (**36**) as an off-white solid (64.2 kg, 91.8% w/w, 186.5 mol, 88% yield). ^{1}H NMR (500 MHz, DMSO, 27 °C): 1.19 (d, *J* = 6.8 Hz, 3H), 1.24−1.36 (m, 2H), 1.46 (dddd, *J* = 29.8, 10.5, 7.2, 5.0 Hz, 2H), 2.52 (s, 3H), 3.18 (dt, *J* = 12.3, 6.6 Hz, 1H), 3.42 (td, *J* = 11.9, 2.9 Hz, 1H), 3.56 (dd, *J* = 11.6, 3.0 Hz, 1H), 3.70 (d, *J* = 11.6 Hz, 1H), 3.92 (dd, *J* = 11.5, 3.5 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 1H), 4.28−4.32 (m, 1H), 6.66 (s, 1H); ^{13}C NMR (126 MHz, DMSO, 27 °C): 8.22, 12.91, 13.56, 14.05, 37.03, 42.51, 65.77, 69.87, 99.14, 158.86, 162.51, 166.08; HRMS (ESI): calcd for $C_{13}H_{19}N_3SO_2Cl$ $[M + H]^+$, 316.0881; found, 316.0884.

(3*R*)-4-{2-Chloro-6-[1-(*S*-methylsulfonimidoyl)-cyclopropyl]-4-pyrimidinyl}-3-methylmorpholine hydrochloride (13). Toluene (258 kg) and methanol (47.4 kg) were charged to the vessel. Stirring was started, and the contents were cooled to 0−10 °C. (3*R*)-4-(2-Chloro-6-{1-[(*R*)-methylsulfinyl]cyclopropyl}-4-pyrimidinyl)-3-methylmorpholine (31.7 kg, 94.26 mol) and (diacetoxyiodo)benzene (65.0 kg, 197.9 mol) were charged to the vessel at 0−10 °C. Ammonium carbamate (30 kg, 377.0 mol) was charged to the vessel at 0−10 °C, and then the contents of the vessel were stirred at 0−10 °C for 20 h. Aqueous citric acid solution (30% w/w) was charged to the vessel until the pH was adjusted to 2−3. The mixture was stirred for 30 min. Stirring was stopped, and the aqueous layer was removed. Stirring was restarted, and then aqueous citric acid solution (30% w/w) was charged to the vessel until the pH was adjusted to pH 2. Stirring was stopped, and the layers were partitioned. The aqueous phases were combined, and stirring was started. Aqueous sodium hydroxide solution (30% w/w) was charged until the pH was adjusted to 8−9. Sodium chloride (96 kg) was charged. Ethyl acetate (101 kg) and THF (33 kg) were charged, and the resulting mixture was stirred for 30 min. Stirring was stopped, and the layers were partitioned. The aqueous layer was recharged to the vessel, and stirring was started. Ethyl acetate (89.1 L) and THF (29.7 L) were charged, and the resulting mixture was stirred for 30 min. Stirring was stopped, and the layers were partitioned. The aqueous layer was recharged to the vessel, and stirring was started. Ethyl acetate (101 kg) and THF (33 kg L) were charged, and the resulting mixture was stirred for 30 min. Stirring was stopped, and the layers were partitioned. The organic phases were combined in the vessel and then concentrated to approximately 59 L by distillation. Isopropyl alcohol (48 kg) was charged, and then the solution was concentrated to approximately 59 L by distillation. Isopropyl alcohol (48 kg) was charged, and then the solution was concentrated to approximately 59 L by distillation. The resulting solution was cooled to 0−5 °C, and then a solution of hydrogen chloride in isopropyl alcohol (6 M, 21.7 kg) was charged to the vessel. The resulting mixture was stirred at 0−5 °C for approximately 2 h. MTBE (135 kg) was charged to the vessel, and the contents were stirred for a further 2 h. The solid was collected by filtration and washed with MTBE (45 kg). The solid was recharged to the vessel, and then methanol (54 kg) was added. The slurry was stirred at 35−40 °C for 1 h and then cooled to 20−25 °C. MTBE (103 kg) was charged to the vessel, and the mixture was stirred for 1 h. The solid was collected by filtration, and then the filter cake was washed with MTBE (59 L) and dried to yield (3*R*)-4-{2-chloro-6-[1-(*S*-methylsulfonimidoyl)cyclopropyl]-4-pyrimidinyl}-3-methylmorpholine hydrochloride (**13**) as a white solid (30.2 kg, 78.2 mol, 83% yield). ^{1}H NMR (500 MHz, DMSO, 27 °C): 1.23 (d, *J* = 6.8 Hz, 3H), 1.59−1.77 (m, 1H), 1.92 (d, *J* = 4.6 Hz, 3H), 3.16−3.22 (m, 1H), 3.42 (td, *J* = 11.9, 2.9 Hz, 1H), 3.57 (dd, *J* = 11.6, 3.0 Hz, 1H), 3.72 (d, *J* = 11.6 Hz, 1H), 3.78 (s, 3H), 3.94 (dd, *J* = 11.5, 3.6 Hz, 1H), 4.06−4.16 (m, 1H), 4.38−4.47 (m, 1H), 7.26 (s, 1H); ^{13}C NMR (126 MHz, DMSO, 27 °C): 12.59, 12.72, 13.94, 38.57, 44.94, 65.78, 69.89, 104.70, 158.98, 160.49, 162.72; MS: HRMS (ESI): calcd for $C_{13}H_{20}N_4SO_2Cl$ $[M + H]^+$, 331.0990; found, 331.0991.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (14). Isopropyl acetate (387 kg) was charged to the vessel. The vessel was inerted with nitrogen, and stirring was started. 4-Bromo-7-azaindole (41.5 kg, 211 mol, 1.0 equiv) was charged to the vessel. Potassium acetate (43.1 kg, 430 mol, 2.04 equiv) was charged to the vessel. Bis(pinacolato)-diboron (54.7 kg, 215 mol, 1.02 equiv) was charged to the vessel. Bis(triphenylphosphine)palladium(II) dichloride (2.9 kg, 4.13 mol, 0.02 equiv) was charged to the vessel. The contents of the vessel were heated at 85−90 °C for 22 h. The mixture was cooled to 50 °C and then washed with water (4 × 218 kg). Mercapto silica (27.8 kg) was added to the organic phase, and the mixture was heated at 50 °C for 8 h. The solid was removed by filtration, and the filter cake was washed with isopropyl acetate (98 kg). The combined filtrate was concentrated by reduced pressure distillation to a volume of approximately 240 L. The mixture was cooled to approximately 27 °C, and then MTBE (200 kg) was added. The mixture was cooled to approximately 3 °C and stirred for a further 7 h. The solid was collected by filtration. The filter cake was washed with MTBE (40 kg) and then dried at approximately 40 °C to yield 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (**14**) as an off-white solid (39.7 kg, 98.9% w/w, 161 mol, 76% yield). ^{1}H NMR (500 MHz, DMSO, 27 °C): 1.33 (s, 12H), 6.68 (dd, *J* = 3.4, 1.8 Hz, 1H), 7.30 (d, *J* = 4.6 Hz, 1H), 7.48−7.53 (m, 1H), 8.23 (d, *J* = 4.6 Hz, 1H), 11.65 (s, 1H). ^{13}C NMR (126 MHz, DMSO, 27 °C): 24.69, 83.73, 101.37, 121.00, 123.81, 126.70, 127.56, 141.57, 147.91.

4-{4-[(3*R*)-3-Methyl-4-morpholinyl]-6-[1-(*S*-methylsulfonimidoyl)cyclopropyl]-2-pyrimidinyl}-1*H*-pyrrolo[2,3-*b*]pyridine (1). Anhydrous ethanol (463 kg) was charged to the vessel and then stirring was started. (3*R*)-4-{2-Chloro-6-[1-(*S*-methylsulfonimidoyl)cyclopropyl]-4-pyrimidinyl}-3-methylmorpholine hydrochloride (41.3 kg, 111.9 mol, 1.0 equiv) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (30.1 kg, 122.5 mol, 1.1 equiv) were charged to the vessel. The vessel was inerted with nitrogen. Bis(triphenylphosphine)palladium(II) dichloride (1.0 kg, 1.42 mol, 0.013 equiv) was charged to the vessel. The contents of the vessel were heated to 70 °C. A solution of anhydrous potassium phosphate (71.0 kg, 334.5 mol, 3.0 equiv) in water (199.4 kg) was charged to the vessel. The contents of the vessel were heated to approximately 75 °C for 17 h. The mixture was cooled to 50 °C, and then the mixture was concentrated by reduced pressure distillation to a total volume of approximately 5 relative volumes. 2-MeTHF (354.5 kg), water (82 kg), and L-cysteine (20.5 kg) were charged to the vessel. The mixture was stirred at approximately 60 °C for 4 h. Stirring was stopped, and the aqueous layer was removed. A solution of potassium phosphate (53.1 kg) and L-cysteine (20.8 kg) in water (124 kg) was charged to the vessel. The mixture was stirred at approximately 60 °C for 4 h. Stirring was stopped, and the aqueous layer was removed.

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The organic solution was washed with water (3 × 61 kg). 2-MeTHF (534.9 kg) was charged to the vessel, and then the solution was concentrated by reduced pressure distillation to a volume of approximately 5 relative volumes and then cooled to 3 °C. *n*-Heptane (27.9 kg) was charged, and the mixture was stirred for 2 h. The solid was collected by filtration, and then the cake was washed with 2-MeTHF (70.7 kg) and dried at 45 °C.

The crude solid was charged to the vessel and then dissolved in isopropanol (103.8 kg) and water (49.2 kg) at 60 °C. The mixture was filtered to remove any solid material, and then isopropanol (193 kg) was charged to the solution. The solution was concentrated by reduced pressure distillation to a volume of approximately 6 relative volumes. Isopropanol (193 kg) was charged to the solution. The solution was concentrated by reduced pressure distillation to a volume of approximately 6 relative volumes, until water was measured as ≤0.6%. The mixture was held at 60 °C, and then **1** seed crystal (1.0 kg) was charged. The stirred mixture was cooled to 25 °C and then held at this temperature for 8 h. The stirred mixture was cooled to 5 °C and then held at this temperature for 2 h. The solid was collected by filtration. The filter cake was washed with isopropanol (64.7 kg) and then dried at approximately 40 °C to yield 4-{4-[(3*R*)-3-methyl-4-morpholinyl]-6-[1-(*S*-methylsulfonimidoyl)cyclopropyl]-2-pyrimidinyl}-1*H*-pyrrolo-[2,3-*b*]pyridine (**1**) as a white solid (32.9 kg, 98.0% w/w, 78.1 mol, 70% yield). ^{1}H NMR (500 MHz, DMSO, 27 °C): 1.27 (d, J = 6.8 Hz, 3H), 1.4−1.47 (m, 1H), 1.47−1.6 (m, 2H), 1.76 (ddd, J = 9.7, 7.0, 4.0 Hz, 1H), 3.11 (d, J = 1.1 Hz, 3H), 3.27 (td, J = 12.9, 3.9 Hz, 1H), 3.51 (td, J = 11.8, 3.0 Hz, 1H), 3.66 (dd, J = 11.5, 3.0 Hz, 1H), 3.79 (d, J = 11.4 Hz, 1H), 3.82−3.88 (m, 1H), 4.00 (dd, J = 11.3, 3.5 Hz, 1H), 4.19 (d, J = 10.7 Hz, 1H), 4.55−4.61 (m, 1H), 7.00 (s, 1H), 7.23 (d, J = 2.9 Hz, 1H), 7.59 (dd, J = 3.0, 1.7 Hz, 1H), 7.96 (d, J = 5.0 Hz, 1H), 8.34 (d, J = 5.0 Hz, 1H), 11.80 (s, 1H); ^{13}C NMR (126 MHz, DMSO, 27 °C): 11.28, 12.28, 13.45, 41.14, 46.51, 47.86, 66.04, 70.25, 101.61, 102.90, 114.65, 117.77, 127.33, 136.75, 142.29, 150.18, 161.95, 162.68, 163.28; MS (ESI) for $C_{20}H_{25}N_6O_2S_4$ $[M + H]^+$ 413.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00482.

Details of ^{1}H NMR spectra, ^{13}C NMR spectra, nuclear Overhauser effect NMR spectra, experimental details for initial route investigation, and high-throughput experimental data for the synthesis of **14** (PDF)

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Author Contributions

The manuscript was written by M.A.G. through contributions from all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

API, active pharmaceutical ingredient; ATR, ataxia telangiectasia mutated and Rad3 related; BVMO, Baeyer−Villiger monooxygenase; DCM, dichloromethane; DDR, DNA damage response; DNA, deoxyribonucleic acid; DMSO, dimethyl sulfoxide; DIPEA, *N*,*N*-diisopropylethylamine; EtOH, ethanol; HPLC, high performance liquid chromatography; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; IPA, propan-2-ol; KRED, ketoreductase; LCMS, liquid chromatography mass spectrometry; MeCN, acetonitrile; MeOH, methanol; MTBE, methyl *tert*-butyl ether; MS, mass spectrometry; NADP, nicotinamide adenine dinucleotide phosphate; NMR, nuclear magnetic resonance; 2-MeTHF, 2-methyltetrahydrofuran; S_NAr, nucleophilic aromatic substitution; THF, tetrahydrofuran

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