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Communication

Development of a Nitrene-Type Rearrangement for the Commercial Route of the JAK1 Inhibitor Abrocitinib

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ABSTRACT: The development of a commercial route toward the JAK1 inhibitor abrocitinib is described. The application of a late-stage Lossen rearrangement provided the desired *cis*-diaminocyclobutane, which was subsequently sulfonylated using a novel water-tolerable triazole sulfonylating reagent to provide the active pharmaceutical ingredient.

KEYWORDS: *process chemistry, Curtius rearrangement, Lossen rearrangement, biocatalysis, JAK inhibitor, Pfizer*

INTRODUCTION

The Janus kinase family of intracellular tyrosine kinases consists of four members: JAK1, JAK2, JAK3, and TYK2. JAK inhibitors have demonstrated therapeutic potential for the treatment of autoimmune disorders and hematological malignancies through signaling mediation of various cytokines and growth factors.[1−5] The U.S. Food and Drug Administration (FDA)-approved JAK inhibitors include tofacitinib (Pfizer),[6] baricitinib (Eli Lilly/Incyte),[7] ruxolitinib (Incyte),[8] and upadacitinib (AbbVie).[9] A large number of other JAK inhibitors are currently in various clinical trials. Pfizer's JAK1 inhibitor, abrocitinib (**1**),[10] was granted Breakthrough Therapy designation by the FDA for moderate to severe atopic dermatitis in February 2018. Advancement of **1** to phase 3 clinical trials and preparation for commercial launch has spurred the development of a safe and efficient manufacturing route.

RESULTS AND DISCUSSION

Two strategies were evaluated for **1**, as shown in Figure 1: (A) addition of a diaminocyclobutane to 4-chloropyrrolopyrimidine **2** and (B) addition of a monoaminocyclobutane to **2** with a subsequent amination. Access to the *cis*-1,3-diaminocyclobutane would be a key challenge to either strategy. Current methods to synthesize 1,3-diamino-substituted cyclobutanes remain limited to [2 + 2] cycloaddition,[11] reductive amination,[10,12] amination of halides/sulfonates, and functional-group rearrangements.[10,13] Some challenges to the manufacture of low-molecular-weight diamines include pH-dependent solubility, volatility, and difficult reaction analytics.

While route A offers higher convergence, it requires the synthesis of a fully functionalized diaminocyclobutane. Introduction of the pyrrolopyrimidine core earlier in the synthetic route (route B) may convey better physical properties, such as solubility and/or crystallinity, but requires a post fragment union amination. Both strategies would utilize a high-energy nitrene-type rearrangement to install one or both amine functionalities from a simple carboxylate precursor **3**. Choosing the appropriate rearrangement from a safety and scalability perspective became the primary driver guiding the commercial route selection.

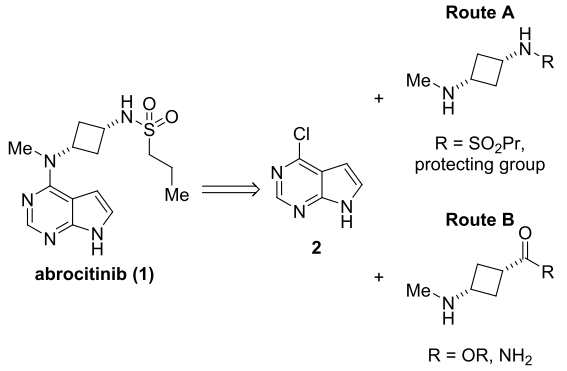

Figure 1. Retrosynthesis of abrocitinib (**1**).

The enabling route utilized a Curtius approach to build diaminocyclobutane **10** (Scheme 1). Readily available cyclobutanone-3-carboxylic acid (**3**) was exposed to diphenylphosphoryl azide (DPPA) in the presence of triethylamine to form acyl azide intermediate **4**. Heating the acyl azide resulted in the nitrene rearrangement to give isocyanate **5**, which was trapped with benzyl alcohol to afford benzyl carbamate **6**.

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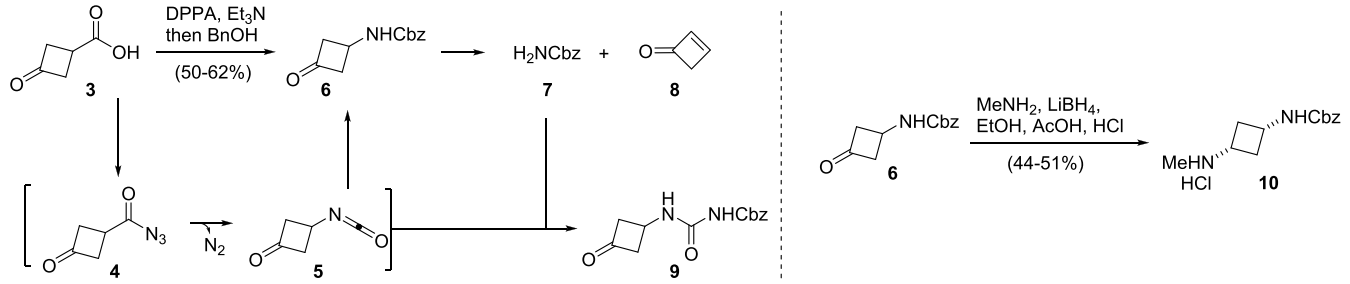
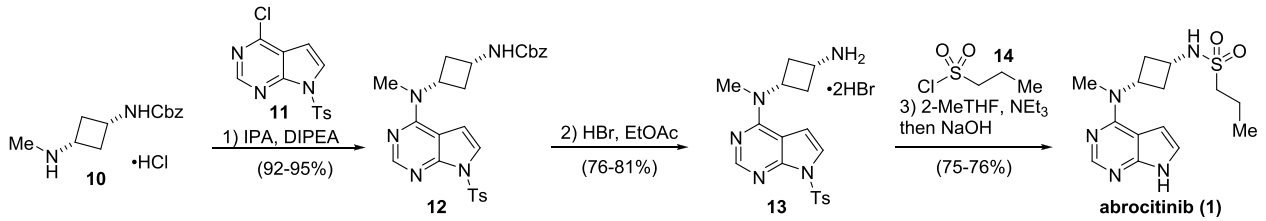
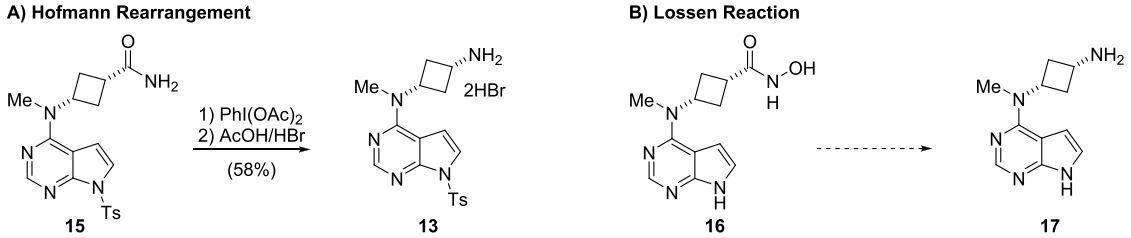
Scheme 1. Curtius Rearrangement to Access *cis*-Diamine 10



Scheme 2. Completion of the Synthesis of API 1



Scheme 3. Alternative Nitrene Rearrangement Approaches



ReactIR studies detected a buildup of **4** prior to heating and rearrangement to form **5**, which occurred when the solution was warmed beyond 50 °C. The most reproducible method for this reaction was to add DPPA to a preheated solution of the acid at 55 °C, which showed little to no buildup of the acyl azide. Yield loss in this process occurred by known degradative pathways,[14] including the formation of carbamate **7** and volatile cyclobutenone **8** from **6** and the subsequent reaction of **7** and **5** to form urea byproduct **9**. Extensive optimization of this reaction, including an evaluation of flow processing, did not improve the yields or achieve better control of byproduct formation. To convert **6** to **10**, a cryogenic reductive amination provided an approximately 4:1 ratio of diastereomers in favor of the desired *cis* isomer **10**. Isolation as the hydrochloride salt and successive recrystallizations improved the diastereomeric ratio to >99:1. Despite these challenges, the Curtius approach (Scheme 1) was scaled successfully to supply >600 kg of **6** for early clinical studies. However, because of the significant safety risk associated with the potential buildup of **4**, the batch size was limited on scale (~60 kg of **3**). The batch size limitation and yield loss due to degradation of highly reactive intermediates called for an alternative method to access the diaminocyclobutane for commercial-scale manufacture.

To complete the active pharmaceutical ingredient (API), the stereoenriched cyclobutyldiamine **10** was reacted with tosyl-protected 4-chloropyrrolopyrimidine **11** in isopropyl alcohol (IPA) with diisopropylethylamine (DIPEA) (Scheme 2). Intermediate **12** was then treated with hydrobromic acid to deprotect the benzyl carbamate and afford the penultimate amine dihydrobromide salt **13** as a solid. Slurrying the dihydrobromide salt of the tosyl core in 2-MeTHF with triethylamine followed by the addition of propane-1-sulfonyl chloride (**14**) provided the tosyl-protected API. Hydrolysis using NaOH followed by pH adjustment crystallized the API. The enabling route was able to produce several hundred kilograms of the API to support early clinical trials for the program while a commercial route was being developed.

As an alternative approach, we chose to evaluate the nitrene chemistry on the cyclobutylamine−pyrrolopyrimidine core structure. The increased molecular size of the heterocyclic core could improve the physical properties and ease of handing of intermediates as well as simplify the reaction analytics.

The Hofmann rearrangement has been used on a multikilogram scale[15−17] and was investigated as an alternative to the Curtius rearrangement (Scheme 3A). Incompatibility of the I^{III} oxidant with the electron-rich pyrrolopyrimidine required prudent selection of reagents, protecting group strategies, and reaction conditions. The aminocyclobutylamide was screened under typical conditions for a Hofmann rearrangement. A blend of $PhI(OAc)_2$ in DMF, THF, and water was found to be effective for the reaction. After treatment with HBr in acetic acid, dihydrobromide salt **13** was isolated in a modest 58% yield. Protection of the pyrrolo nitrogen was found to be critical to the success of the rearrangement, as otherwise rapid oxidative degradation was observed. While this route was viable, we did not pursue this approach because of the increased process mass intensity[18] resulting from the required use of protecting groups.[19]

Compared with the Curtius and Hofmann rearrangements, the Lossen reaction requires less reactive reagents to form the

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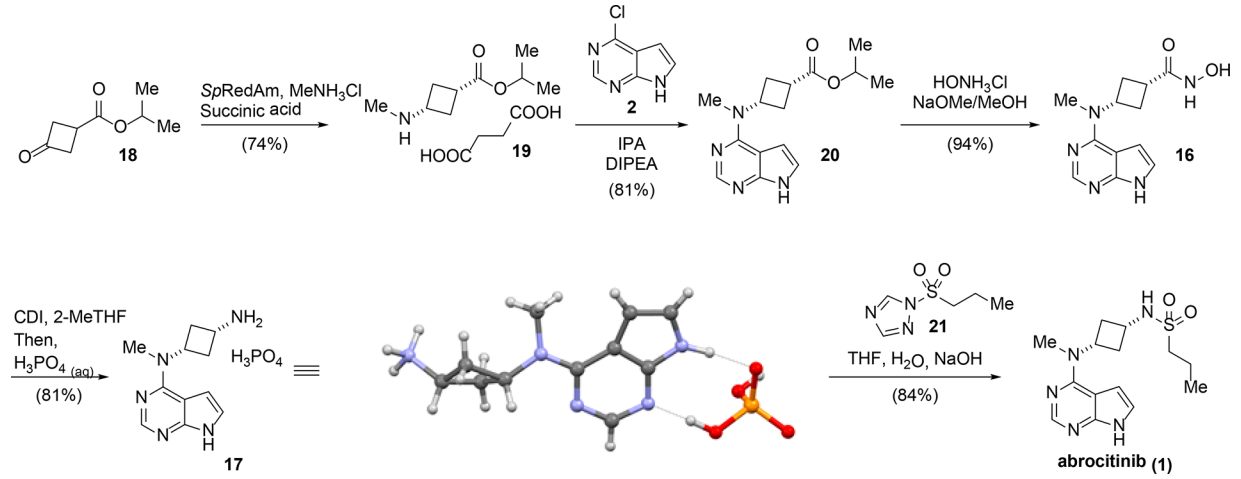
Scheme 4. Commercial Route to Abrocitinib (1)



nitrene-type intermediate because of the "pre-installed" oxidation state of the nitrogen, which is introduced as a hydroxamic acid (**16** in Scheme 3B). The reagents typically employed are dehydrative and would be more compatible with the unprotected pyrrolopyrimidine. We elected to test the Lossen reaction on the advanced intermediate **16**, encouraged by results from Bristol-Myers-Squibb on the reaction of a steroid-derived hydroxamic acid to give a tertiary amine.[20]

Isopropyl ester **18** was identified as the ideal starting material for balancing a facile approach to the hydroxamic acid, stability of the subsequent amino ester during processing, and ease of handling the free-flowing liquid (Scheme 4).[21] Ketone **18** was screened for biocatalytic reductive amination. Several mutant libraries of wild-type *Sp*RedAm from *Streptomyces purpureus* were designed and tested, resulting in a suitable enzyme that provided the desired *cis*-amino ester **19** in 74% yield with a >99:1 diastereomeric ratio after isolation as the succinate salt. The discovery route (Scheme 2) employed tosylated pyrrolopyrimidine **11** to facilitate the S_NAr reaction. While this worked well with amine **19**, the tosyl protecting group was incompatible with the hydroxylamine required to generate the Lossen reaction precursor. During development, it was found that unprotected pyrrolopyrimidine **2** was competent for the S_NAr reaction with an extended reaction time. The fusion of **2** and **19** was optimized to provide **20** in 81% isolated yield. Treatment of ester **20** with hydroxylamine hydrochloride in NaOMe and MeOH afforded hydroxamic acid **16** in 94% yield.

The Lossen rearrangement was then evaluated. Several reagents were tested, and 1,1′-carbonyldiimidazole (CDI) emerged as effective at promoting the rearrangement while minimizing byproduct generation. Acidic hydrolysis was required to avoid urea formation, and a screen revealed that phosphoric acid was much more efficient than other mineral acids. After addition of phosphoric acid and pH adjustment, amine phosphate salt **17** was isolated in 81% yield. An X-ray crystal structure of intermediate **17** was obtained that confirmed the critical *cis* configuration.[22] Analytical tracking of the intermediates, avoidance of haloarenes/phosphoryl azide reagents, and intermediate physical properties rendered the Lossen rearrangement ideal for large-scale manufacturing.

The diaminocyclobutane structure requires sulfonylation to complete the synthesis of **1**. As previously described in the enabling route, the API can be accessed through direct sulfonylation of amine **13** using **14** in organic solvents (Scheme 2). Sulfonylation of amine **17** requires a different approach because of its poor solubility in organic solvents, high solubility in acidic or basic aqueous solutions, reactive heterocyclic core, and reaction hetereogeneity due to complications with residual phosphate salts. The sulfonylation may be conducted in basic aqueous media using **14**, but this also results in sulfonylation of the pyrrolopyridimine nitrogen in addition to competitive degradation of the sulfonyl chloride. This was more successful at low temperature, but the scalability was limited because of the risk of freezing of aqueous media at very low temperatures.

Therefore, a series of alternative sulfonylation reagents were generated and evaluated in organic and aqueous solvent mixtures (Figure 2). These provided less reactive, more stable

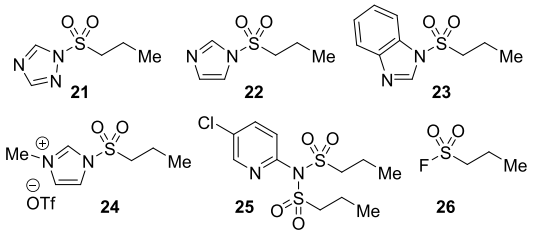


Figure 2. Sulfonyl transfer reagents.

alternatives to **14.** Each reagent was evaluated for safety, stability, relative reactivity, and impurity formation. A combination of safety concerns and undesirable reactivity eliminated **22** and **23.** Imidazolium **24** exhibited excellent reaction kinetics, but an observed methylation impurity was undesirable. Comins' inspired reagent[23] **25** was an attractive option in terms of its physical handling, safety profile, and reaction kinetics, but the cost of purchasing large quantities of the reagent would necessitate developing a method to recover and recycle the reagent. Propane-1-sulfonyl fluoride (**26**) was also evaluated, but the cost of the custom reagent, lack of a chromophore, and concerns about reactor etching with free fluoride were deterrents.

1,2,4-Triazole derivative **21** emerged as the lead sulfonylating agent on the basis of its excellent stability in aqueous systems, fast reaction kinetics, and an acceptable safety profile. This was generated by suspension of 1,2,4-triazole in THF.

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Following aqueous workup, **21** could be generated as a solution in THF or concentrated to an oil. After salt break of **17** in THF with NaOH, **21** could be added as a solution in THF. Addition of water resulted in crystallization of the product **1** in 84% isolated yield.

CONCLUSION

A commercial route to the JAK1 inhibitor abrocitinib was developed, including a biocatalytic reductive amination to afford the *cis*-cyclobutane ring, an S_NAr reaction to incorporate the unprotected pyrrolopyrimidine core, a Lossen rearrangement, and sulfonylation using a novel reagent for sulfonyl transfer. The execution of this new route for clinical and commercial supply is currently underway.[24]

EXPERIMENTAL PROCEDURES

Characterization data for compounds **10**, **11**, **12**, **13**, and **1** have been reported previously.[10]

Synthesis of Abrocitinib (1) from 13. Dihydrobromide salt **13** (10.0 g, 18.8 mmol, 1.0 equiv) and 2-MeTHF (100 mL) were charged to a 250 mL reactor at 25 °C. Triethylamine (15.7 mL, 113 mmol, 6 equiv) was added in a single portion, and the mixture was stirred for 1 h and then cooled to −10 °C. Next, propane-1-sulfonyl chloride (**14**) (3.59 mL, 31.9 mmol, 1.7 equiv) was added dropwise while the temperature was maintained below 0 °C. The reaction mixture was stirred at −10 °C until the reaction was complete and then warmed to 0 °C and quenched by the addition of water (100 mL). The solution was warmed to 25 °C, stirred for 10 min, and then transferred to a separatory funnel. The bottom layer was discarded, and the top layer transferred back to the reaction flask. Darco G60 (1 g) was added, and the mixture was stirred at 25 °C for 1 h and then filtered over a pad of Celite. The Celite cake was rinsed with 2-MeTHF (40 mL), and the filtrate was placed back into the reaction flask. A solution of 10% aqueous NaOH (100 mL) was then charged, and the mixture was heated to 70 °C for 4 h, cooled to room temperature, and transferred to a separatory funnel. The layers were separated, and the organic layer was extracted with 10% aqueous NaOH (50 mL). The extract was combined with the aqueous layer and transferred back to the reaction vessel. The pH was adjusted to 6−7 with 6 N HCl, and the slurry was granulated at ambient temperature for >12 h. The slurry was then filtered, and the solid was rinsed with water (30 mL) and dried in a vacuum oven at 50 °C to afford **1** (5.39 g, 89% yield) as an off-white solid.

(1*S*,3*S*)-3-[Methyl(7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]cyclobutane-1-carboxamide (15). To a 20 mL Schlenk tube, *cis*-3-(methylamino)cyclobutane-1-carboxamide hydrochloride salt (500 mg, 1.0 equiv), isopropyl alcohol (4 mL), 4-chloropyrrolopyrimidine **11** (1.03 g, 1.1 equiv), and DBU (0.97 g, 2.1 equiv) were charged. The mixture was heated to 85 °C and stirred until the reaction was complete by UPLC. The mixture was cooled to 40 °C, and water (20 mL) was added, resulting in a clear solution. Cooling was continued to 20 °C to form a slurry. The solids were filtered and rinsed with water (30 mL). The crude solids (1.18 g) were purified by reversed-phase chromatography (gradient of 2:3 MeOH/H_2O to 100% MeOH, 20 column volumes (CV)). The desired fractions were combined, and the methanol was removed in vacuo, resulting in the precipitation of a white solid. The solid was filtered, rinsed with water (10 mL), and dried in a vacuum oven at 50 °C to afford amide **15** (686 mg, 57% yield). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 4.1 Hz, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.31 (s, 1H), 6.96 (d, J = 4.1 Hz, 1H), 6.82 (s, 1H), 5.07 (p, J = 8.6 Hz, 1H), 3.22 (s, 3H), 2.70 (p, J = 8.6 Hz, 1H), 2.40−2.26 (m, 7H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 175.6, 157.1, 152.8, 151.7, 146.2, 134.9, 130.4, 128.2, 122.0, 106.9, 104.8, 47.3, 32.2, 31.7, 31.0, 21.6; **IR** (cast film, cm^{-1}) 1663, 1567, 1494, 1417, 1371, 1341, 1283, 1260, 1189, 1157, 1089, 1062, 813, 797, 712, 669, 630, 604, 595; **mp** 145−148 °C; **HRMS** (TOF) m/z calcd for $C_{19}H_{21}N_5O_3S^+$ ([M + H]$^+$) 400.1443, found 400.1433.

(1*S*,3*S*)-*N*1-Methyl-*N*1-(7-tosyl-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-yl)cyclobutane-1,3-diamine Dihydrobromide (13). Amide **15** (500 mg, 1.0 equiv) was charged to a vial and dissolved in DMF (5 mL), acetonitrile (5 mL), and water (5 mL). Bis(acetoxy)iodobenzene (492 mg, 1.2 equiv) was then charged, and the reaction mixture was stirred. Once the reaction was deemed to be complete, the solution was transferred dropwise into a KOH (350 μL, 11.5 M)/water (5 mL) quench solution. The amine was then extracted with DCM (15 mL), washed with brine (2 × 10 mL), and dried with $MgSO_4$. The solution was then concentrated, and water was removed via azeotroping with 2-MeTHF (2 × 5 mL). The resulting oil was dissolved in DCM (2 mL), and a 33% solution of HBr in acetic acid was added (0.65 mL, 3.0 equiv). The orange solution was added dropwise into ethyl acetate (10 mL), resulting in immediate precipitation. The solids were filtered and isolated (598 mg), and their spectroscopic data matched those of previously isolated samples. The material could be reslurried in DCM to further improve the purity (384 mg, 58% yield). The spectroscopic data for this material matched that previously reported.

Isopropyl 3-Oxocyclobutane-1-carboxylate (18). Commercially available isopropyl 3-oxocyclobutane-1-carboxylate (**3**) (84.6 g, 1.0 equiv) was dissolved in 2-propanol (500 mL) and *p*-toluenesulfonic acid monohydrate was added (5.56 g, 4 mol %, 0.04 equiv). The solution was heated to 80 °C and stirred for 19 h, at which point the reaction was deemed to be complete by ^{1}H NMR analysis. The reaction mixture was cooled to 40 °C, transferred to a 1 L separatory funnel, diluted with methyl *tert*-butyl ether (MTBE) (200 mL), and washed with saturated sodium bicarbonate (3 × 100 mL), and the layers were separated. The aqueous layer was discarded, and the organic layer was washed with brine (2 × 50 mL). The MTBE layer was dried with sodium sulfate and then concentrated at 40 °C at 25 Torr to afford **18** as a pale-yellow oil (101.6 g, 90.5% yield). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 4.95 (hept, J = 6.3 Hz, 1H), 3.38−3.18 (m, 5H), 1.22 (d, J = 6.3 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6) 203.9, 173.5, 68.7, 51.5, 27.6, 21.7; **IR** (cast film, cm^{-1}) 3126, 3077, 2982, 1790, 1721, 1525, 1401, 1248, 1223, 1170, 1114, 1076, 1088, 1028, 1014, 768, 746, 640; **HRMS** (ESI) m/z calcd for $C_8H_{13}O_3^+$ ([M + H]$^+$) 157.08647, found 157.0857.

Propan-2-yl (1*S*,3*S*)-3-(Methylamino)cyclobutane-1-carboxylate Butanedioic Acid (1:1) (19). To a 100 mL EasyMax reactor was charged potassium phosphate buffer (40 mL, pH 7.2, 100 mM) at 25 °C, followed by methylamine hydrochloride (3.25 g, 1.5 equiv) and glucose monohydrate (7.5 g, 1.3 equiv). The reaction mixture was stirred until homogeneous, and the pH was adjusted to 7 using 20 wt % aqueous sodium hydroxide. Ketone **18** (5.0 g, 1.0 equiv) followed by DMSO (2.5 mL) was charged to the reactor.

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$NADP^+$ (12.5 mg, 0.0005 equiv), GDH (12.5 mg, 0.25 wt % relative to **18**), and the custom enzyme *Sp*RedAm (125 mg) were added. The reaction mixture was held at 25 °C for 72 h, using a pH dosing unit to maintain a constant pH of 7 via titration with 20% aqueous sodium hydroxide solution. When the reaction was complete, the reactor was cooled to 3 °C, and pH was adjusted to 3.3 with aqueous hydrochloric acid (12.2 M). After the mixture was stirred for 30 min, carbon (1.0 g, 2.6 equiv) was charged and the suspension was stirred for an additional 30 min. The carbon was filtered through a layer of Celite and rinsed with water (5 mL). MTBE (100 mL) was charged, and the mixture was cooled to 5 °C, after which aqueous NaOH (20 wt %) was dosed until the pH was 12.3. The phases were split, and the organic layer was collected and concentrated under vacuum (500 mbar) to a final volume of 25 mL. Fresh MTBE (50 mL) was added.

In a separate vessel, MTBE (50 mL) and succinic acid (3.40 g, 0.90 equiv) were charged to a reactor at 20 °C. Seed crystals of **19** (0.05 g, 0.005 equiv) were added, followed by the addition of the MTBE solution of the amine via addition funnel. The resulting slurry was granulated for 1 h at 20 °C. The solids were filtered, rinsed with MTBE (25 mL), and dried in a vacuum oven at 40 °C to afford the desired amine succinate salt **19** (6.86 g, 74% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.66 (br s, 2H), 4.88 (hept, J = 6.2 Hz, 1H), 3.30 (tt, J = 8.8, 7.3 Hz, 1H), 2.82 (tt, J = 9.8, 8.2 Hz, 1H), 2.43−2.34 (m, 2H), 2.31 (d, J = 2.5 Hz, 7H), 2.13−2.00 (m, 2H), 1.18 (d, J = 6.3 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 174.9, 173.1, 67.3, 48.8, 31.1, 30.6, 30.4, 21.5; **IR** (cast film, cm^{-1}) 2987, 2745, 2502, 1720, 1637, 1519, 1377, 1351, 1254, 1191, 1098, 1070, 1017, 875, 801, 755, 669, 585; **mp** 88−89 °C; **HRMS** (TOF) m/z calcd for $C_9H_{17}NO_2^+$ ($[M + H]^+$) 172.1338, found 172.1329.

Propan-2-yl (1*S*,3*S*)-3-[Methyl(7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-yl)amino]cyclobutane-1-carboxylate (20). Succinate salt **19** (75.4 g, 1.0 equiv) and 4-chloropyrrolopyrimidine (**2**) (40.0 g, 1.0 equiv) were combined in a reactor. 2-Propanol (200 mL) was charged, resulting in a slurry. Diisopropylethylamine (114 mL, 2.5 equiv) was charged, resulting in a thin slurry. The reaction mixture was heated to 80 °C, forming a solution, which was held at 80 °C until the reaction was deemed to be complete by UPLC-MS (approximately 48 h). The reaction mixture was cooled to 20 °C and became a slurry. The solids were filtered and washed with two portions of 2-propanol (80 mL each) to afford the desired product (61 g, 81% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 8.12 (s, 1H), 7.16 (dd, J = 3.6, 2.3 Hz, 1H), 6.62 (dd, J = 3.6, 1.7 Hz, 1H), 5.25 (tt, J = 9.4, 7.9 Hz, 1H), 4.92 (hept, J = 6.3 Hz, 1H), 3.26 (s, 3H), 2.88 (tt, J = 9.2, 8.0 Hz, 1H), 2.49−2.36 (m, 4H), 1.21 (d, J = 6.3 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6) 173.6, 156.7, 151.8, 150.5, 121.0, 102.5, 101.3, 67.3, 46.5, 31.3, 30.9, 30.5, 21.6; **IR** (cast film, cm^{-1}) 3090, 2978, 2839, 1719, 1566, 1509, 1489, 1413, 1346, 1336, 1230, 1104, 1124, 1040, 1026, 948, 876, 832, 815, 733, 715, 655, 625; **mp** 177−178 °C; **HRMS** (TOF) m/z calcd for $C_{15}H_{21}N_4O_2^+$ ($[M + H]^+$) 289.1665, found 289.1657.

(1*S*,3*S*)-*N*-Hydroxy-3-[methyl(7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-yl)amino]cyclobutane-1-carboxamide (16). To a reactor were charged methanol (500 mL) and sodium methoxide in methanol (93.7 mL, 25 wt %, 2.4 equiv) under nitrogen. Hydroxylamine hydrochloride (15.1 g, 1.25 equiv) was charged to the room-temperature reaction mixture, resulting in a slight endotherm. Ester **20** (50 g, 1.0 equiv) was then added, resulting in a white slurry. The reaction mixture was warmed to 40 °C and stirred overnight, and the reaction was deemed to be complete by UPLC-MS. To the now-thick slurry was charged hydrochloric acid (1 M, 208 mL) until pH 7.0 was achieved. The slurry was then filtered and rinsed with methanol (100 mL). The material was dried in a vacuum oven overnight to afford **16** (42.7 g, 94% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 10.47 (s, 1H), 8.80 (s, 1H), 8.09 (s, 1H), 7.14 (d, J = 3.6 Hz, 1H), 6.60 (d, J = 3.5 Hz, 1H), 5.21 (p, J = 8.8 Hz, 1H), 3.33 (s, 3H), 2.61 (p, J = 8.4 Hz, 1H), 2.43 (dt, J = 11.5, 9.1 Hz, 2H), 2.32 (qd, J = 8.0, 2.6 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) 170.2, 156.7, 151.7, 150.5, 120.9, 102.4, 101.3, 46.7, 31.4, 30.5, 28.7; **IR** (cast film, cm^{-1}) 3227, 3112, 3044, 2938, 2541, 1580, 1515, 1491, 1453, 1417, 1372, 1340, 1323, 1266, 1111, 1023, 882, 739, 673, 604; **mp**, decomposes above 158 °C; **HRMS** (TOF) m/z calcd for $C_{12}H_{16}N_5O_2^+$ ($[M + H]^+$) 262.1304, found 262.1295.

(1*S*,3*S*)-*N*1-Methyl-*N*1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)cyclobutane-1,3-diamine Phosphoric Acid (1:1) (17). Hydroxamic acid **16** (19.4 g, 1.0 equiv) was charged to a reactor, followed by 2-MeTHF (388 mL), resulting in a white slurry. The slurry was warmed to 30 °C, and 1,1′-carbonyldiimidazole (16.1 g, 1.3 equiv) was added. The reaction mixture was stirred overnight, at which point the reaction was deemed to be complete by UPLC-MS. A solution of phosphoric acid (14.7 M in water, 25.5 mL, 5.0 equiv) was diluted with water (78 mL) and added slowly to the slurry. The slurry dissolved, and the reaction mixture was heated to 60 °C and held for several hours. When the reaction was deemed to be complete, sodium hydroxide (20 wt % in water, 16.4 mL, 1.45 equiv) was added to obtain **17**. The reaction mixture was warmed to 80 °C and then cooled to 25 °C. 2-Propanol (58 mL) was added slowly, and the solid was filtered. The cake was washed with 2-propanol/water (1:1 v/v, 40 mL) and dried in a vacuum oven to afford **17** (19.1 g, 81% yield). Crystals suitable for X-ray analysis were grown by heating a sample (1.34 g) in IPA (27 mL) and adding water with heat cycling (20−75 °C). **^{1}H NMR** (400 MHz, D_2O) δ 7.78 (s, 1H), 6.96 (d, J = 3.6 Hz, 1H), 6.28 (d, J = 3.6 Hz, 1H), 4.52 (s, 1H), 3.60 (s, 1H), 3.00 (s, 3H), 2.67 (dd, J = 9.8, 2.7 Hz, 2H), 2.39 (dd, J = 9.4, 3.1 Hz, 2H); **^{13}C NMR** (101 MHz, D_2O) δ 158.8, 151.6, 151.6, 124.4, 105.3, 104.9, 48.8, 42.0, 35.9, 34.6; **^{31}P NMR** (162 MHz, D_2O) δ 0.31; **IR** (cast film, cm^{-1}) 1582, 1504, 1423, 1387, 1345, 1327, 1244, 1192, 1078, 1032, 948, 913, 879, 762, 728, 696, 635, 620, 607, 564, 538; **mp** >250 °C; **HRMS** (TOF) m/z calcd for $C_{11}H_{16}N_5^+$ ($[M + H]^+$) 218.1406, found 218.1396.

1-(Propylsulfonyl)-1*H*-1,2,4-triazole (21). 1,2,4-Triazole (11.98 g, 2.5 equiv) and THF (40 mL) were charged to an EZ Max reactor equipped with overhead stirring. The suspension was stirred for 10 min, and then propane-1-sulfonyl chloride (7.89 mL, 1.0 equiv) was added at 20 °C. The resulting slurry was stirred at 20 °C until the starting material was consumed as judged by ^{1}H NMR analysis. Once the reaction was complete, the reaction mixture was filtered, and the filtrate was transferred to a separatory funnel, where it was diluted with water (20 mL) and extracted with dichloromethane (50 mL). The layers were separated, and the DCM layer was washed with water (2 × 20 mL) and brine (1 × 20 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to afford sulfonyl triazole **21** (10.66 g, 89% yield) as a

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viscous, clear colorless oil. **^{1}H NMR** (400 MHz, chloroform-*d*) δ 8.67 (s, 1H), 8.13 (s, 1H), 3.55−3.46 (m, 2H), 1.76 (h, J = 7.5 Hz, 2H), 1.03 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, chloroform-*d*) δ 154.4, 145.3, 55.9, 16.9, 12.5; **IR** (cast film, cm^{-1}) 3129, 2975, 1502, 1459, 1371, 1325, 1269, 1168, 1137, 1099, 981, 946, 875, 775, 737, 713, 667, 629, 606, 541; **HRMS** (TOF) m/z calcd for $C_5H_{10}N_3O_2S^+$ ($[M + H]^+$) 176.0494, found 176.0488.

A sample of this material was analyzed via differential scanning calorimetry (DSC) in a sealed high-pressure gold-plated crucible and showed 3 exothermic peaks, the first with an onset of 90 °C and an energy of 32 J/g, the second with an onset of 133 °C and an energy of 495 J/g, and the third with an onset of 198 °C and an energy of 29 J/g. *End users of **21** are strongly advised to conduct internal safety testing and analysis, including DSC and explosivity testing.*

Synthesis of 1 via 21. Water (18 mL) and phosphate salt **17** (3.0 g, 1.0 equiv) were charged to a reactor, followed by sodium hydroxide in water (19 M, 1.5 mL, 3.0 equiv). The reaction exhibited a slight exotherm and was cooled to 25 °C. Propanesulfonyltriazole **21** (4.3 g, 2.5 equiv) was dissolved in THF (12 mL) and added to the hydroxide reaction mixture. Once the reaction was deemed to be complete, water (18 mL) was added, and the material was filtered and dried to afford the product **1** (2.57 g, 84% yield) as a solid.

Abrocitinib (1) via In Situ-Generated 21. The lithium salt of 1,2,4-triazole was prepared using the procedure disclosed in the literature.[23] This lithium salt (1.0 g, 2.1 equiv) and THF (8 mL) were charged to a reactor at 20 °C, followed by **14** (1.47 mL, 2.0 equiv). The slurry was stirred at 20 °C until **14** was consumed, as judged by ^{1}H NMR analysis. In a separate flask, phosphate salt **17** (2.0 g, 1.0 equiv) was dissolved in water (12 mL) at 20 °C, and then 50 wt % aqueous sodium hydroxide (1.0 mL, 3.0 equiv) was added while the temperature was kept below 30 °C. The aqueous solution was cooled to 10 °C, and then the THF solution of the sulfonyltriazole reagent was added while the temperature was maintained below 20 °C. The resulting suspension was stirred until <5% of the amine remained according to UPLC-MS. Then 50 wt % aqueous sodium hydroxide (0.67 mL, 2.0 equiv) was added, and the reaction mixture was heated to 50 °C. Once the sulfonyltriazole reagent was consumed as determined by UPLC-MS, the reaction mixture was cooled to 20 °C, and hydrochloric acid (6 N) was added to achieve pH 5−6. The resulting slurry was cooled to 10 °C, held for 30 min, and filtered. The cake was rinsed with H_2O/THF (75:25 v/v, 10 mL), and the solid was dried at 50 °C in a vacuum oven to afford the desired product as an off-white solid (2.33 g, 114% yield due to inorganic salts). To remove the salts, 1.04 g of the crude solid was suspended in H_2O (8 mL)/THF (2 mL) at 40 °C. After 15 min of stirring, the slurry was filtered, rinsed with H_2O/THF (4:1 v/v, 2 mL), and dried to afford the product **1** (825 mg, 79% recovery) as a solid.

1-(Propylsulfonyl)-1*H*-imidazole (22). A reactor was charged with dichloromethane (203 mL) followed by propane-1-sulfonyl chloride (20 mL, 1.0 equiv) and cooled to 0 °C. Imidazole (2.42 g, 2.0 equiv) was added portionwise over approximately 12 min, and the reaction mixture was held at 0 °C for 30 min. The reaction was deemed to be complete by UPLC-MS, and the reaction mixture was warmed to 20 °C and charged with water. The aqueous layer was discarded, and the dichloromethane solution was dried with brine and $MgSO_4$. The material was concentrated to give **22** (2.48 g, 80% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.29 (s, 1H), 7.18 (s, 1H), 3.30−3.26 (m, 2H), 1.76 (sextet, J = 7.7 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.1, 131.5, 117.8, 57.8, 17.3, 12.6; **IR** (cast film, cm^{-1}) 3126, 2974, 1520, 1458, 1368, 1250, 1166, 1149, 992, 865, 829, 777, 738, 715, 649, 626, 613, 596, 556, 545; **HRMS** (TOF) m/z calcd for $C_6H_{11}N_2O_2S^+$ ($[M + H]^+$) 175.0541, found 175.0534.

A sample of this material was analyzed via DSC in a sealed high-pressure gold-plated crucible and showed three exothermic peaks, the first with an onset of 81 °C and an energy of 18 J/g, the second with an onset of 118 °C and an energy of 662 J/g, and the third with an onset of 317 °C and an energy of 118 J/g. *End users of **22** are strongly advised to conduct internal safety testing and analysis, including DSC and explosivity testing.*

1-(Propylsulfonyl)-1*H*-benzo[*d*]imidazole (23). Benzimidazole (500 mg, 4.23 mmol, 1.0 equiv) was dissolved in DCM (5 mL) and Et_3N (1.47 mL, 2.5 equiv). To this solution was added propane-1-sulfonyl chloride (0.74 mL, 1.5 equiv), and the reaction mixture was stirred at room temperature. When the reaction was complete, water (5 mL) was added. The layers were separated, and the aqueous layer was extracted with DCM (5 mL). The organic layers were combined and concentrated in vacuo, and the crude solid was purified by column chromatography (1 CV heptanes, 9 CV ramp from 100% heptanes to 100% EtOAc, 2 CV EtOAc) to afford the desired product (800 mg, 84% yield) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.90−7.80 (m, 2H), 7.50−7.37 (m, 2H), 3.41−3.31 (m, 2H), 1.83−1.66 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7, 141.6, 131.2, 126.0, 125.3, 121.3, 112.4, 56.7, 17.2, 12.7; **IR** (cast film, cm^{-1}) 3973, 1697, 1608, 1500, 1475, 1369, 1253, 1193, 1157, 1135, 1086, 1066, 1033, 1011, 883, 765, 743, 715, 667, 616, 598, 581, 568, 538; **HRMS** (TOF) m/z calcd for $C_{10}H_{13}N_2O_2S^+$ ($[M + H]^+$) 225.0698, found 225.0690.

A sample of this material was analyzed via DSC in a sealed high-pressure gold-plated crucible and showed two exothermic peaks, the first with an onset of 126 °C and an energy of 543 J/g and the second with an onset of 263 °C and an energy of 87 J/g. *End users of **23** are strongly advised to conduct internal safety testing and analysis, including DSC and explosivity testing.*

3-Methyl-1-(propylsulfonyl)-1*H*-imidazol-3-ium Trifluoromethanesulfonate (24). Sulfonyl imidazole **22** (2.9 g, 1.0 equiv) was dissolved in Et_2O (44 mL) and cooled to 5 °C, and then methyl trifluoromethanesulfonate (1.9 mL, 1.0 equiv) was added dropwise over 10 min. The reaction mixture was stirred at 5 °C for 30 min, during which time a white precipitate formed. The reaction mixture was warmed to 10 °C and then filtered. The solids were rinsed with Et_2O (20 mL) and dried in a vacuum oven at 50 °C to afford **24** (4.8 g, 85% yield) as a white solid. **^{1}H NMR** (400 MHz, acetone-d_6) δ 9.57 (s, 1H), 8.11 (s, 1H), 7.96 (s, 1H), 4.17 (s, 3H), 4.12−3.98 (m, 2H), 1.91 (h, J = 7.4 Hz, 2H), 1.07 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, acetone-d_6) δ 139.6, 126.6, 121.9 (q, J = 321.1 Hz), 121.5, 57.6, 37.7, 17.6, 12.3; **^{19}F NMR** (376 MHz, acetone-d_6) δ −78.98; **IR** (cast film, cm^{-1}) 3126, 3078, 1586, 1525, 1459, 1401, 1339, 1250, 1224, 1168, 1114, 1088, 1076, 1028, 986, 926, 888, 767, 746, 709, 672, 641, 631, 621, 575, 556, 548, 535, 529; **mp** 67−68 °C; **HRMS** (TOF) m/z calcd for $C_7H_{13}N_2O_2S^+$ (M^+) 189.0698, found 189.0691.

A sample of this material was analyzed via DSC in a sealed high-pressure gold-plated crucible and showed two exothermic peaks, the first with an onset of 98 °C and an energy of 474 J/g

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and the second with an onset of 330 °C and an energy of 477 J/g. *End users of* ***24*** *are strongly advised to conduct internal safety testing and analysis, including DSC and explosivity testing.*

***N*-(5-Chloropyridin-2-yl)-*N*-(propylsulfonyl)propane-1-sulfonamide (25).** DCM (50 mL) and Et_3N (43.4 mL, 4.0 equiv) were added to a 250 mL vessel equipped with overhead stirring, followed by 2-amino-5-chloropyridine (10 g, 1.0 equiv). The mixture was cooled to −20 °C, and then DMAP (490 mg, 0.05 equiv) was added. Next, propane-1-sulfonyl chloride (26.3 mL, 3.0 equiv) was added via syringe pump at 5 mL/h while the internal temperature was kept below −10 °C. When the addition was complete, the reaction mixture was stirred for 30 min and then warmed to −10 °C, and water was added (50 mL). The reaction mixture was warmed to room temperature, and the layers were separated. The aqueous layer was extracted with DCM (2 × 50 mL), and the organic layers were combined, washed with water (2 × 50 mL), dried with sodium sulfate, filtered over Celite, and concentrated in vacuo to afford a red oil. Methylcyclohexane (100 mL) was added to the oil, and the mixture was warmed with vigorous stirring until all of the solids had dissolved. The mixture was then cooled slowly to room temperature, and heptane (100 mL) was added, which resulted in precipitation. The slurry was stirred for 30 min, filtered, and rinsed with heptane (100 mL). The solids were dried in a vacuum oven at 50 °C overnight to afford the desired product **25** (24.9 g, 93.9% yield) as a tan solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.68 (d, J = 2.7 Hz, 1H), 8.18 (dd, J = 8.5, 2.7 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 3.78 (dd, J = 8.5, 6.7 Hz, 4H), 1.87 (h, J = 7.8 Hz, 4H), 1.03 (t, J = 7.4 Hz, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 148.1, 146.5, 139.5, 132.7, 127.2, 57.4, 16.4, 12.5; **IR** (cast film, cm^{-1}) 2965, 1547, 1457, 1211, 1370, 1346, 1291, 1257, 1206, 1150, 1125, 1111, 1088, 1017, 982, 954, 926, 913, 834, 779, 750, 737, 708, 641, 614, 579; **mp** 69−70 °C; **HRMS** (TOF) m/z calcd for $C_{11}H_{18}ClN_2O_4S_2^+$ ($[M + H]^+$) 341.0397, found 341.0391.

A sample of this material was analyzed via DSC in a sealed high-pressure gold-plated crucible and showed an exothermic peak with an onset of 204 °C and an energy of 669 J/g. *End users of* ***25*** *are strongly advised to conduct internal safety testing and analysis, including DSC and explosivity testing.*

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00366.

General procedures, preparation of 6 and 9, DSC data for 14 and 27, NMR spectra, NMR spectra, crystallographic data for (PDF)

Crystallographic data for **17** (CIF)

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Author Contributions

All of the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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CCDC 2005131 contains the supplementary crystallographic data for this paper. These data can be obtained via www.ccdc.cam.ac.uk/data_request/cif or data_request@ccdc.cam.ac.uk.

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■ DEDICATION

This paper is dedicated to the memory of Mark Webster.

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