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Development of Flexible and Scalable Routes to Two Phosphatidinylinositol-3-kinase Delta Inhibitors via a Common Intermediate Approach

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ABSTRACT: This paper describes the discovery and development of a flexible route to two candidate drug molecules by a common intermediate approach. Key reactions include Negishi and Suzuki couplings to form biaryl bonds. Conditions for a Miyaura borylation of heteroaryl bromides were also developed. Heteroaryl trifluoroborates and aryl chlorides were used as coupling partners in the Suzuki reaction, thereby minimizing detrimental side reactions such as protodeboronation and oxidative homocoupling. A complementary set of reaction conditions using pinacolboronates with potassium bifluoride as an additive were also developed and used to make 5 kg of drug substance for use in early-phase clinical trials.

Class I phosphatidinylinositol-3-kinases (PI-3-kinases) are a family of enzymes responsible for the production of phosphatidinylinositol-3,4,5-trisphosphate, a cell-membrane-bound phospholipid and important secondary messenger in a range of physiological processes, including cell growth, proliferation, differentiation, and inflammatory response.[1,2] The delta isoform is located primarily in leucocytes, and inhibitors may have therapeutic potential as anti-inflammatories and in autoimmune disease.[3,4] The same pathway has been implicated in potentiating the inflammatory response to allergens in the airways.[5] Dosing of selective PI-3-kinase δ inhibitors to the nose has been shown to reduce lung inflammation and airway hyper-responsiveness in asthma models and to reduce release of mast cells in nasal tissue, and thus, these inhibitors show potential as nonsteroidal anti-inflammatories for the treatment of steroid-insensitive asthmas.[6] Topical administration via a dry-powder inhaler would reduce systemic side effects.

Compounds **1** and **2** were under development as selective inhaled PI-3-kinase δ inhibitors (Figure 1).[7] Synthetic routes to both that could produce multikilogram amounts of drug to fund early-phase clinical trials and safety assessment studies were required. The compounds share an indazole−oxazole core but are differentiated by the oxazole-linked polar amine headgroups and indazole-linked heterocyclic tail groups. Given the high chances of attrition during development, the development of a route via a late-stage common intermediate was particularly attractive since it would allow material to be stockpiled and converted to whichever candidate would be required while reducing the risk of wasted synthetic endeavors. Retrosynthetic analysis revealed bromide **3** as a suitable common intermediate.

Synthetic investigations began with 6-chloro-4-iodoindazole (**4**), which was purchased from a contract research organization. Introduction of orthogonal halides at the 4- and 6-positions would allow construction of the two biaryl bonds in selective and sequential fashion, as oxidative insertion into the C−Cl bond requires a more active catalyst system featuring electon-rich phosphine ligands.[8] The medicinal chemistry route had made the oxazole−indazole bond using a Stille coupling between chlorooxazole **5** and indazole stannane **6**, available from the protected iodoindazole **7** (Scheme 1).[7] Studies showed that the benzenesulfonyl group could be selectively introduced on N_1, was reasonably robust and inert throughout the synthetic sequence, and could then be readily cleaved to reveal the naked indazole. However, it was found that chlorooxazole **5** was susceptible to decomposition at moderate temperatures, and scaling up organotin chemistry with volatile byproducts to multikilogram scale was unattractive.

Alternative protocols such as Suzuki and Negishi reactions were therefore investigated. Suzuki reactions gave low yields and still required use of the unstable chlorooxazole. A Negishi reaction allowed employment of the parent oxazole ester **9**: deprotonation at C_2 followed by transmetalation provided straightforward access to the organozinc species **10**, which coupled efficiently and selectively with iodoindazole **7** upon addition of tetrakis(triphenylphosphine)palladium (Scheme 2).[9]

With a reliable protocol for construction of the first biaryl bond, routes to the oxazole ester were next examined. The ethyl ester **9** was commercially available but not in sufficient quantities to fund a multikilogram plant campaign. A range of solvents and inorganic bases were examined for the reaction between toluenesulfonylmethyl isocyanate (Tosmic, **11**) and ethyl glyoxylate (**12**).[10] Screening ethereal and alcoholic solvents showed that tetrahydrofuran (THF) with an alcoholic cosolvent gave the best conversion, and cesium carbonate was the optimum base. The product oxazole was found to be unstable under the elevated temperatures required for reaction, and thus, processing conditions giving a fast reaction were sought. Methanol gave a much faster reaction than ethanol and was thus selected, despite the fact that partial transesterification was observed. The mixed esters **9** and **13** performed well in the

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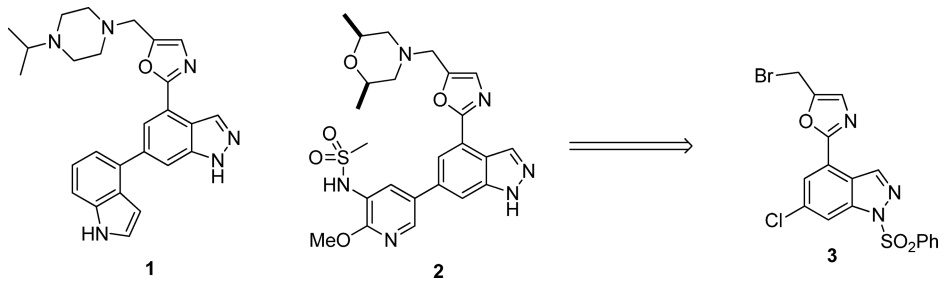
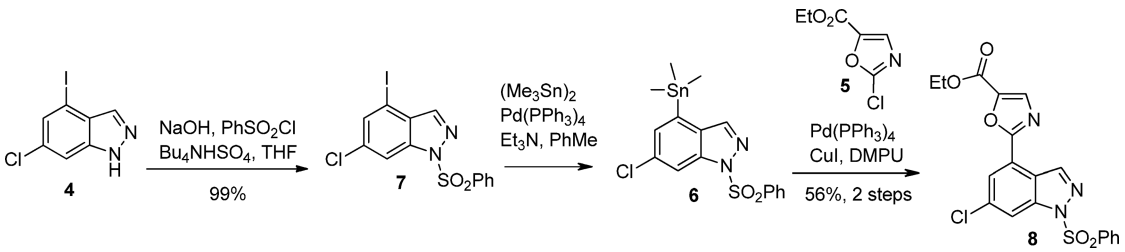
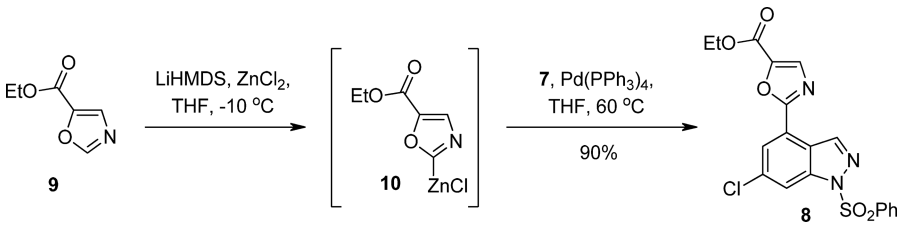


Figure 1. Two drug candidates originate from a common synthetic intermediate.

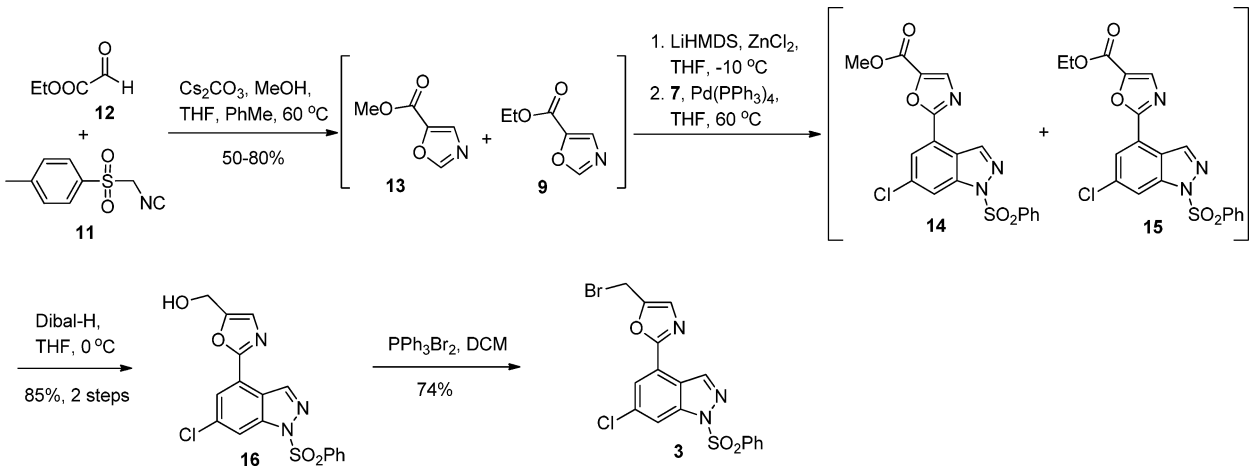
Scheme 1. Construction of the Indazole−Oxazole Biaryl Linkage by Stille Reaction



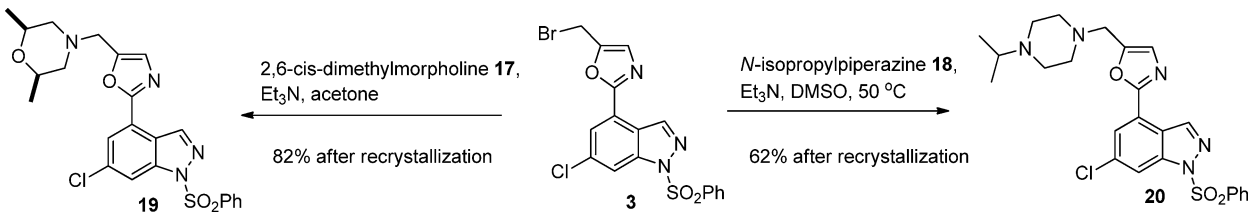
Scheme 2. Construction of the Indazole−Oxazole Biaryl Linkage by Negishi Reaction



Scheme 3. Telescoped Route to Bromide 3



Scheme 4. Conversion of Bromide 3 to Amines 19 and 20



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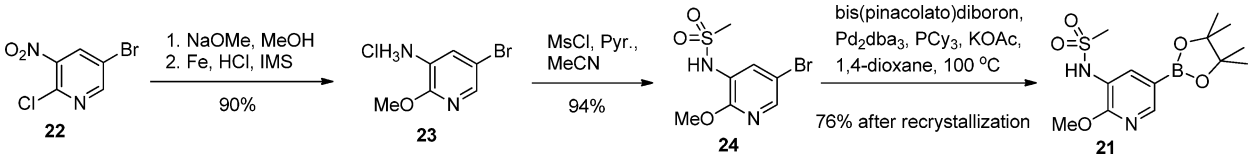
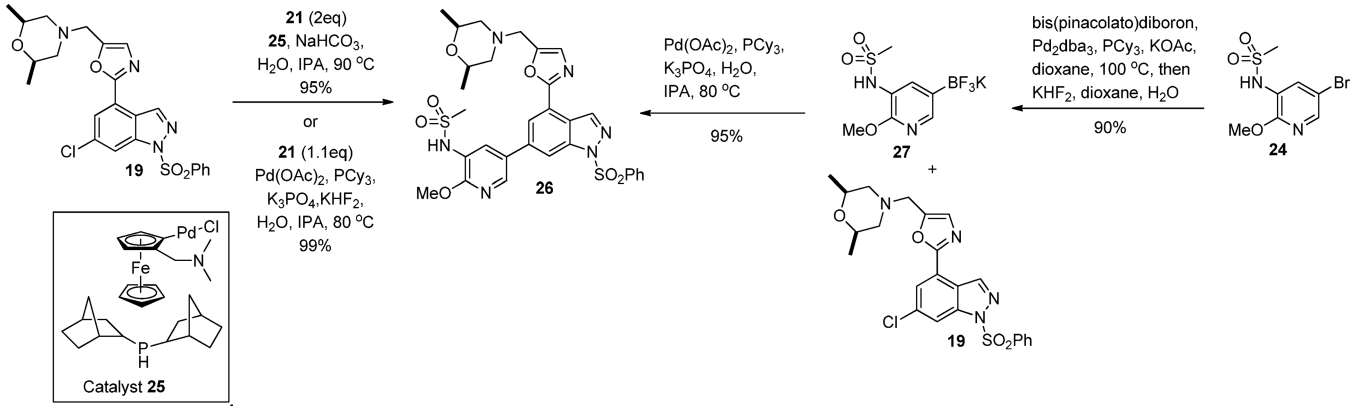
Scheme 5. Synthesis of Pyridineboronate 21



Scheme 6. Synthesis of Trifluoroborate 27 and Subsequent Suzuki Reaction



subsequent Negishi coupling, again affording a mixture of products **14** and **15**. Addition of diisobutylaluminum hydride to the completed Negishi reaction mixture then reduced both esters to afford a single alcohol product, **16**, which was isolated as a solid. Conversion to alkyl bromide **3**, the required common intermediate, was accomplished with triphenylphosphine dibromide (Scheme 3).

At this point, the routes to the two drug substances diverge. Substitution of bromide **3** with the two amines **17** and **18** was next investigated and was achieved in both cases by adding triethylamine to a mixture of the two coupling partners in acetone. Less than 5% quaternization was observed, and the products **19** and **20** were subsequently crystallized by addition of water (Scheme 4). It was later found that the purity of these products was key to a successful Suzuki reaction. Thus, for the reaction of **3** with piperazine **18**, the reaction solvent was switched to dimethyl sulfoxide (DMSO), which significantly improved the isolated purity. An optional recrystallization of both products from DMSO was also introduced, dependent on the outcome of user tests in the downstream chemistry.

With the pair of indazole chlorides in hand, preparation of the required heteroaryl pinacolboronate coupling partners was next investigated. Pyridineboronate **21** was synthesized in four steps from 5-bromo-2-chloro-3-nitropyridine (**22**) (Scheme 5). Treatment with sodium methoxide in methanol followed by reduction of the nitro group afforded aminopyridine **23** as its hydrochloride salt in 90% yield. Mesylation then afforded **24**, also in excellent yield. Finally, Miyaura borylation afforded pinacolboronate **21**. The latter reaction was first carried out under standard conditions using $PdCl_2$(dppf) as the catalyst in *N*,*N*-dimethylformamide (DMF).[11] However, the reaction took upward of 8 h at 100 °C to complete, and 30% protodeboronation was observed under these conditions. The combination of tricyclohexylphosphine and tris-(benzylideneacetone)dipalladium in dioxane proved to be a much more reactive catalyst system, with the reaction taking less than half an hour to complete and the yield of protodeboronated material being reduced to 5%.[12] This latter system was not particularly robust, however, with larger-scale reactions sometimes stalling after precipitation of palladium black. It seemed likely that formation of palladium black would be accelerated by high local concentrations of unligated palladium(0) and that addition of excess ligand should prevent this. However, increasing the Pd:ligand ratio from 1:2 to 1:4 led to much slower reactions. This problem was eventually solved simply by halving the loadings of palladium (from 2 to 1 mol %) and ligand (from 10 to 5 mol %) and diluting from 10 to 20 volumes of dioxane, thus reducing the Pd(0) concentration 4-fold. It is also known that dibenzylideneacetone (DBA) is not an innocent ligand and that tuning its electronics can have an effect on the rate and outcome of palladium-catalyzed processes.[13] Closer analysis of LC−MS spectra recorded during reactions revealed the presence of Michael addition products from tricyclohexylphosphine and DBA. Removal of tricyclohexylphosphine from the reaction system would also lead to unligated palladium(0) and precipitation of palladium black. It was subsequently found that simply adding additional Pd_2dba_3 to a stalled reaction restarted the catalytic cycle and allowed complete consumption of the starting material, albeit with increased protodeboronation due to extended processing times.

The Suzuki reaction between boronate **21** and aryl chloride **19** was next investigated. A screen of catalysts, bases, and solvents revealed that a combination of 5 mol % catalyst **25** (see Scheme 6) and sodium bicarbonate in aqueous 2-propanol gave rapid and complete consumption of aryl chloride **19**. This solvent mixture allowed isolation of the product **26** in excellent yield and purity. However, significant protodeboronation and homodimerization of boronate **21** were observed, and 2 equiv was required to fully consume all of the aryl chloride.[14] Work by the groups of Molander[15] and Lloyd-Jones[16] indicates that the use of trifluoroborates in Suzuki reactions reduces these detrimental processes. Thus, we set about attempting to make trifluoroborate **27** from pinacolboronate **21**.[17] Treatment of boronate ester **21** with potassium bifluoride in aqueous methanol, dioxane, THF, or acetone resulted in trifluoroborate formation, observable by ^{1}H NMR spectroscopy. However, an

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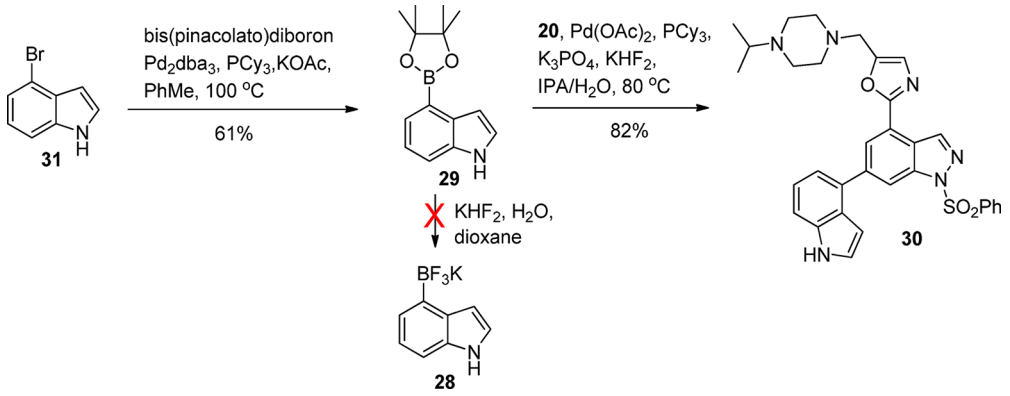
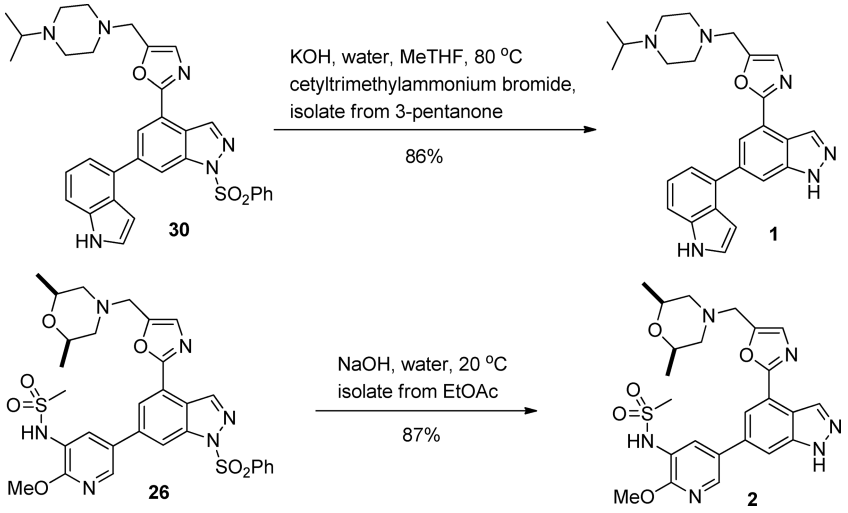
Scheme 7. Optimization of Conditions for the Suzuki Reaction with Indole Pinacolboronate 29



Scheme 8. Deprotection To Afford the Two Drug Substances



equilibrium between pinacolboronate and trifluoroborate exists, and 4 equiv of KHF_2 was required to ensure complete trifluoroborate formation. Under these conditions, crystallization and thus isolation of the trifluoroborate salt was inhibited. Methods to push the equilibrium toward trifluoroborate without using such an excess of fluoride, such as multiple evaporations to dryness to remove pinacol[18a] or addition of sodium periodate to oxidatively cleave pinacol,[18b] were not considered practical on a manufacturing scale.[18c] The trifluoroborate salt was eventually isolated by reducing the water content in aqueous dioxane to 5%, thus allowing an inorganic-rich aqueous layer to separate and be decanted. Azeotropic drying of the resultant solution afforded trifluoroborate **27**, albeit containing 30 wt % inorganic salts, in 90% yield after correction for purity (Scheme 6). This step was readily telescoped with the prior borylation reaction, since they share the same solvent, to deliver a one-pot borylation/fluorination process.

Coupling of trifluoroborate **27** and aryl chloride **19** was next attempted. After screening of a series of electron-rich ligands[19] and bases, a combination of palladium acetate and tricyclohexylphosphine with potassium phosphate as the base in aqueous 2-propanol was selected. Under these conditions, protodeboronation and homodimerization were suppressed, and 1.1 equiv of trifluoroborate was sufficient to consume all of chloride **19**.

In contrast, the formation of indoletrifluoroborate **28** for the synthesis of **1** proved to be much more difficult. The use of 6 equiv of KHF_2 and heating to 60 °C were required to force complete trifluoroborate formation from indole pinacolboronate **29**, but attempts to isolate the salt in analogous fashion to pyridyltrifluoroborate **27** met with failure. Trifluoroborate salt **28** also proved to be susceptible to decomposition, especially at elevated temperature. In Suzuki reactions, potassium trifluoroborates act as sources of the corresponding boronic acids, which are the primary species involved in transmetalation to palladium and subsequent reductive elimination.[16a] For successful implementation of this strategy, however, the hydrolysis to form the boronic acid must happen more slowly or at a rate equivalent to the rate of consumption of the boronic acid via the desired catalytic cycle to prevent its accumulation and participation in detrimental side reactions.[20] We reasoned that adding sufficient potassium bifluoride to a Suzuki reaction of pinacolboronate **29** should have a similar effect and would thus allow clean coupling without significant protodeboronation and homodimerization.[21] We were delighted to find that simply adding 2 equiv of KHF_2 to the reaction mixture did indeed allow complete consumption of aryl chloride **20** with only 1.1 equiv of added pinacolboronate **29**, affording product **30** in 82% yield (Scheme 7). The same conditions also allow coupling of pyridineboronate **21** and aryl chloride **19** in 99% yield (Scheme 6). The effectiveness of potassium and cesium fluoride as bases in Suzuki reactions has also been demonstrated, and they would be preferred as fluoride sources from a process chemistry point of view because of their lower

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toxicity and reduced glass etching, a significant issue with the use of KHF_2.[22,23] However, replacement of KHF_2 with KF under otherwise unaltered reaction conditions led to 20% protodeboronation and incomplete consumption of aryl chloride **20**. While pinacolboronate **29** is commercially available on a small scale, the conditions developed for the synthesis of pyridylboronate **21** also proved to be successful for its preparation starting from 4-bromoindole (**31**). Despite a predilection for polar aprotic solvents in the literature, toluene[24] proved to be a much more effective solvent than dioxane, reducing both the reaction time and the propensity for palladium black precipitation and reaction stalling.

With effective Suzuki coupling methods established, all that remained was to remove the protecting groups and isolate the two drug substances. Indole **30** is sparingly soluble in aqueous media, and thus, elevated temperature and a phase transfer catalyst were required to cleave the sulfonate group. In contrast, the sulfonamide group in **26** is acidic enough to be deprotonated by sodium hydroxide, which allows solubility and deprotection in water at ambient temperature (Scheme 8).

In summary, synthetic routes to two investigational PI-3-kinase δ inhibitors have been developed. The indazole−oxazole core, common to the two compounds, allowed us to access both through a late-stage common intermediate. Conditions for the Miyaura borylation of heteroaryl bromides were developed, and in one case a one-pot conversion to the corresponding potassium trifluoroborate salt was demonstrated. The use of potassium trifluoroborate salts was demonstrated to reduce detrimental side reactions such as protodeboronation and homodimerization in Suzuki coupling reactions. A complementary approach was also demonstrated whereby addition of potassium bifluoride to Suzuki couplings of pinacolboronate esters similarly prevented these side reactions. These optimized conditions allow the amount of the boronate ester required to consume all of the aryl chloride partner to be reduced from 2 to 1.1 equiv. The application of such conditions should find application in Suzuki processes in instances where access to the potassium trifluoroborate salts is not possible.

EXPERIMENTAL SECTION

General Methods. All commercially available chemicals and solvents were used as received without any further purification. ^1H and ^{13}C NMR spectra were acquired on a Bruker spectrometer at frequencies of 400 and 100 MHz, respectively. High-resolution mass spectra were recorded on a linear ion trap combined with a Fourier transform ion cyclotron resonance mass spectrometer using an electrospray ionization source operated in positive ion mode. Observed m/z values and empirical formulas provided refer to $[M + H]^+$. Melting points were recorded using an automated melting point apparatus.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (29). Tris(benzylideneacetone)dipalladium (467 mg, 0.510 mmol) and tricyclohexylphosphine (572 mg, 2.04 mmol) were combined in degassed toluene (20 mL) and aged for 30 min. The resultant purple solution was added via cannula to a suspension of 4-bromoindole (**31**) (20.0 g, 102 mmol), bis(pinacolato)diboron (31.1 g, 122 mmol), and potassium acetate (20.0 g, 204 mmol) in degassed toluene (100 mL) at 100 °C. After 4 h, the mixture was cooled to 60 °C and filtered; the solid was washed with toluene (2 × 40 mL), and the filtrate volume was reduced under vacuum (100 mbar, 50−60 °C) to 80 mL. The mixture was aged at 60 °C for 1 h, then cooled to 20 °C over 2 h, and aged for 1 h, and then heptane (240 mL) was added over 1 h. The slurry was filtered, and the solid was washed with heptane/toluene (4:1, 40 mL) and heptanes (40 mL) and then dried in vacuo at 55 °C to afford 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**29**) (15.1 g, 62.1 mmol, 61%) as a tan solid. δ_H ($CDCl_3$, 400 MHz) 1.42 (12H, s), 7.07−7.10 (1H, m), 7.22 (1H, dd, J = 8.1, 7.1 Hz), 7.25−7.27 (1H, m), 7.50 (1H, dt, J = 8.1, 1.0 Hz), 7.67 (1H, dd, J = 7.1, 0.7 Hz), 8.19 (1H, br, s); δ_C ($CDCl_3$, 100 MHz) 25.0, 83.4, 104.6, 113.9, 121.3, 124.5, 127.9, 132.5, 135.1 (no signal for C−B carbon); HRMS m/z calcd for $C_{14}H_{19}BNO_2$ 244.1503, found 244.1503; mp 172−174 °C.

6-Chloro-4-iodo-1-(phenylsulfonyl)-1*H*-indazole (7). A mixture of 6-chloro-4-iodoindazole (**4**) (17.1 kg, 61.4 mol), sodium hydroxide (5.54 kg, 138 mol), and tetrabutylammonium hydrogen sulfate (1.04 kg, 3.07 mol) was stirred in THF (171 L) at 20 °C for 1 h. The reaction mixture was cooled to 15 °C, and benzenesulfonyl chloride (12.5 kg, 70.8 mol) was added over 30 min, with the reaction temperature maintained at <25 °C. The resulting reaction mixture was stirred at 20 °C for 1 h and then added to hydrochloric acid solution (0.25 M, 350 L) at 0 °C with vigorous stirring, resulting in precipitation of an orange solid. The mixture was aged for 1 h and filtered, and the solid was washed with water (2 × 51 L) and dried in vacuo at 40 °C to afford 6-chloro-4-iodo-1-(phenylsulfonyl)-1*H*-indazole (**7**) (25.2 kg, 60.2 mol, 99%) as an orange solid. δ_H ($(CD_3)_2SO$, 400 MHz) 7.65 (2H, app. t, J = 7.6 Hz), 7.78 (1H, tt, J = 7.6, 1.0 Hz), 7.91 (1H, d, J = 1.5 Hz), 8.02 (2H, dd, J = 7.6, 1.0 Hz), 8.16−8.18 (1H, m), 8.41 (1H, d, J = 0.7 Hz); δ_C ($(CD_3)_2SO$, 100 MHz) 89.0, 112.0, 127.3, 128.8, 130.0, 133.4, 135.1, 135.4, 136.0, 139.2, 144.1; HRMS m/z calcd for $C_{13}H_9ClIN_2O_2S$ 418.9113, found 418.9106; mp 178−182 °C.

(2-(6-Chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)-oxazol-5-yl)methanol (16). To a suspension of cesium carbonate (47.0 kg, 144 mol) in THF (200 L) were added methanol (16.4 kg, 512 mol) and ethyl glyoxylate (**12**) (50 wt % in PhMe, 57.8 kg, 283 mol), and the suspension was heated to 50 °C for at least 30 min. To the suspension was then added *p*-toluenesulfonylmethyl isocyanide (**11**) (25.0 kg, 128 mol), and the suspension was heated to 60 °C for 1 h. The mixture was cooled to 20 °C, and acetic acid (38.5 kg, 641 mol) was added, after which the suspension stirred at 20 °C for 30 min. To the suspension was then added a solution of potassium hydrogen carbonate (57.7 kg, 576 mol) in water (200 L), followed by extraction with diisopropyl ether (4 × 100 L). The combined organic layers were washed with brine (25 L) and distilled down to a volume of 50 L (200 mbar, 35 °C). Diisopropyl ether (125 L) was charged, and then the mixture was distilled down to a volume of 50 L (200 mbar, 35 °C). ***CAUTION**: to avoid peroxide formation, diisopropyl ether distillate should be treated with a stabilizer.* The solution was diluted with THF (110 L) and added to a suspension of zinc chloride (25.7 kg, 189 mol) in THF (110 L) at −10 °C. A solution of lithium hexamethyldisilazide (1.0 M in THF, 94.6 L, 94.6 mol) was added over 45 min, and the solution was aged at −10 °C for 1 h. Then **7** (22.0 kg, 52.6 mol) and tetrakis(triphenylphosphine)palladium (1.80 kg, 1.56 mol) were added, and the mixture was heated to 60 °C for 15 h. The solution was cooled to 0 °C, and diisobutylaluminum hydride (25 wt % in PhMe, 109.8 kg, 193 mol) was added over 1 h. The solution was aged at 0 °C for a further 1 h and then quenched by addition to a solution of citric acid (44 kg, 229 mol) in water (176 L) over 1 h, with the temperature of the contents maintained at <10 °C. The reaction mixture was

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warmed to 20 °C and extracted with EtOAc (198 L). The resultant mixture was stirred at 20 °C for 1 h and filtered, and the organic phase was separated and washed with water (2 × 66 L). The organic layer was distilled at reduced pressure (30 mbar, 40 °C), then diluted with DMSO (242 L), and further distilled at reduced pressure (30 mbar, 40 °C) to remove all low-boiling solvent. The solution was cooled to 20 °C, and water (110 L) was added over 30 min. The resultant suspension was then stirred at 20 °C for 14 h and filtered, and the solid was washed with 1:1 DMSO/water (66 L) (3 vols) followed by water (2 × 66 L) and dried in vacuo at 60 °C to afford (2-(6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)-oxazol-5-yl)methanol (**16**) (17.4 kg, 44.6 mol, 85%) as a tan solid. δ_H ($CDCl_3$, 400 MHz) 4.60 (2H, d, J = 5.9 Hz), 5.55 (1H, t, J = 5.9 Hz), 7.35 (1H, s), 7.64 (2H, app. t, J = 7.6 Hz), 7.76 (1H, dd, J = 7.6, 1.2 Hz), 7.92 (1H, d, J = 1.7 Hz), 8.04 (2H, dd, J = 7.6, 1.2 Hz), 8.26 (1H, dd, J = 1.7, 0.7 Hz), 8.99 (1H, d, J = 0.7 Hz); δ_C ($CDCl_3$, 100 MHz) 53.5, 113.7, 120.6, 121.5, 122.4, 125.9, 127.4, 130.0, 134.9, 135.4, 136.0, 140.7, 141.4, 154.0, 157.1; HRMS m/z calcd for $C_{17}H_{13}ClN_3O_4S$ 390.0310, found 390.0311; mp 170−172 °C.

5-(Bromomethyl)-2-(6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)oxazole (3). A mixture of **16** (24.25 kg, 62.2 mol) and triphenylphosphine dibromide (25.5 kg, 60.4 mol) was stirred in DCM (360 L) at 20 °C for 1 h. To the reaction mixture were then added MeOH (19.5 L) and 8% w/w sodium hydrogen carbonate solution (8 wt %, 243 L) over 15 min. The organic phase was separated, and the aqueous layer was re-extracted with DCM (120 L); the combined organics were washed with water (120 L) and distilled down to 120 L. MeOH (360 L) was added, and the mixture was distilled down to 360 L (260 mbar, 20 °C). The resultant suspension was aged at 20 °C for 9 h and then filtered, washed with MeOH (2 × 25 L), and dried in vacuo at 30 °C to afford 5-(bromomethyl)-2-(6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)oxazole (**3**) (20.9 kg, 46.1 mol, 74%) as a tan solid. δ_H ($CDCl_3$, 400 MHz) 4.95 (2H, s), 7.56 (1H, s), 7.63 (2H, app. t, J = 7.6 Hz), 7.76 (1H, dd, J = 7.6, 1.2 Hz), 7.91 (1H, d, J = 1.7 Hz), 8.04 (2H, dd, J = 7.6, 1.2 Hz), 8.28 (1H, dd, J = 1.7, 0.7 Hz), 8.93 (1H, d, J = 0.7 Hz); δ_C ($CDCl_3$, 100 MHz) 21.2, 114.3, 120.7, 121.0, 122.8, 127.4, 128.3, 130.1, 135.0, 135.5, 136.0, 140.7, 141.3, 149.8, 158.1; HRMS m/z calcd for $C_{17}H_{12}BrClN_3O_3S$ 451.9466, found 451.9463; mp 156−158 °C.

2-(6-Chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole (20). To a solution of *N*-isopropylpiperazine (**18**) (3.5 kg, 27.3 mol) in DMSO (80 L) was added **3** (10.4 kg, 23.0 mol) in four portions over 1 h, and the mixture was aged for a further hour. The mixture was then heated to 50 °C and aged for 1 h, and triethylamine (2.20 kg, 21.7 mol) added over 10 min. The mixture was aged for 40 min, cooled to 20 °C over 1 h, and further aged for 2 h. The resultant slurry was filtered, and the solid was washed with DMSO (31 L) followed by 1:2 acetone/water (3 × 21 L) and dried at 60 °C in vacuo to afford 2-(6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole **20** (8.15 kg, 16.3 mol, 71%). Example of recrystallization: **20** (14.7 kg, 29.4 mol) was dissolved in DMSO (118 L) at 75 °C, and the solution was clarified, cooled to 20 °C over 2 h, aged for 10 h, and filtered. The solid was washed with DMSO (30 L) and then 1:3 acetone/water (59 L then 29 L) and dried in vacuo at 60 °C to afford purified **20** (12.8 kg, 28.3 mol, 87%) as an off-white solid. δ_H ($(CD_3)_2SO$, 400 MHz) 0.91 (6H, d, J = 6.6 Hz), 2.32−2.48 (8H, m), 2.56 (1H, sept., J = 6.6 Hz), 3.68 (2H, s), 7.34 (1H, s), 7.60−7.66 (2H, m), 7.76 (1H, tt, J = 7.5, 1.2 Hz), 7.87 (1H, d, J = 1.7 Hz), 8.01−8.05 (2H, m), 8.23−8.25 (1H, m), 8.92 (1H, d, J = 0.7 Hz); δ_C ($(CD_3)_2SO$, 100 MHz) 18.2, 47.8, 51.3, 52.5, 53.5, 113.7, 120.6, 121.5, 122.4, 127.4, 127.7, 130.1, 134.9, 135.4, 136.0, 140.7, 141.4, 150.8, 157.3; HRMS m/z calcd for $C_{24}H_{27}ClN_5O_3S$ 500.1518, found 500.1513; mp 121−126 °C.

2-(6-(1*H*-Indol-4-yl)-1-(phenylsulfonyl)-1*H*-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole (30). A solution of palladium acetate (58.1 g, 259 mmol) and tricyclohexylphosphine (143 g, 510 mmol) in degassed 2-propanol (32 L) was added to a degassed mixture of **20** (6.40 kg, 12.8 mol), **29** (3.42 kg, 14.1 mol), potassium phosphate (3.26 kg, 15.4 mol), and potassium bifluoride (2.20 kg, 28.2 mol) in 2-propanol (32 L) and water (32 L) at 80 °C. The mixture was aged at 80 °C for 17 h, cooled to 20 °C, aged for a further 1 h, and filtered. The solid was washed sequentially with 1:1 isopropyl alcohol (IPA)/water (2 × 12 L) and water (2 × 13 L) and dried in vacuo at 60 °C to afford 2-(6-(1*H*-indol-4-yl)-1-(phenylsulfonyl)-1*H*-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole (**30**) (6.12 kg, 10.5 mol, 82%) as a tan solid. δ_H ($(CD_3)_2SO$, 400 MHz) 0.89 (6H, d, J = 6.6 Hz), 2.28−2.48 (8H, m), 2.52 (1H, sept, J = 6.6 Hz), 3.69 (2H, s), 6.59−6.63 (1H, m), 7.25−7.35 (3H, m), 7.51−7.57 (2H, m), 7.63 (2H, app. t, J = 7.6 Hz), 7.74 (1H, t, J = 7.6 Hz), 8.00 (2H, d, J = 7.6 Hz), 8.25 (1H, d, J = 1.2 Hz), 8.50 (1H, s), 8.99 (1H, d, J = 0.7 Hz) 11.45 (1H, br s); δ_C ($(CD_3)_2SO$, 100 MHz) 18.1, 47.8, 51.3, 52.5, 53.5, 99.5, 112.2, 112.9, 119.4, 120.5, 120.7, 121.5, 122.9, 125.5, 126.8, 127.2, 127.5, 130.0, 131.0, 135.2, 136.3, 136.5, 141.1, 141.6, 142.9, 150.2, 158.5; HRMS m/z calcd for $C_{32}H_{33}N_6O_3S$ 581.2329, found 581.2316; mp 242−245 °C.

2-(6-(1*H*-Indol-4-yl)-1*H*-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole (1). Potassium hydroxide (5.78 kg, 103 mol) was added to a suspension of **30** (12.0 kg, 20.6 mol) and cetyltrimethylammonium bromide (370 g, 1.02 mol) in 2-methyltetrahydrofuran (120 L), and the mixture was heated to 80 °C for 4 h, cooled to 60 °C, and washed with water (2 × 120 L). 2-Methyltetrahydrofuran (60 L) was added, and the solution was filtered and distilled down to 24 L (150 mbar, 30 °C), followed by two cycles of dilution with 3-pentanone (36 L) and distillation down to 36 L (100 mbar, 30 °C). The resultant slurry was aged for 2 h and then filtered, and the solid was washed with 3-pentanone (12 L) and dried in vacuo at 60 °C to afford 2-(6-(1*H*-indol-4-yl)-1*H*-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole (**1**) (7.78 kg, 17.7 mol, 86%) as an off-white solid. δ_H ($(CD_3)_2SO$, 400 MHz) 0.92 (6H, d, J = 6.6 Hz), 2.38−2.50 (8H, m), 2.57 (1H, sept, J = 6.6 Hz), 3.72 (2H, s), 6.58−6.63 (1H, m), 7.21−7.27 (2H, m), 7.31 (1H, s), 7.45−7.51 (2H, m), 7.90 (1H, s), 8.08 (1H, d, J = 1.2 Hz), 8.59 (1H, d, J = 0.7 Hz), 11.34 (1H, br, s), 13.42 (1H, br, s); δ_C ($(CD_3)_2SO$, 100 MHz) 18.2, 47.9, 51.4, 52.5, 53.5, 99.9, 111.3, 113.0, 118.0, 119.0, 119.1, 119.9, 121.5, 125.7, 126.2, 127.2, 132.3, 133.6, 136.4, 139.0, 141.2, 149.4, 160.0; HRMS m/z calcd for $C_{26}H_{29}N_6O$ 441.2397, found 441.2392; mp 154−157 °C.

5-Bromo-2-methoxypyridin-3-ammonium Chloride (23). To a suspension of 5-bromo-2-chloro-3-nitropyridine (**22**) (20.0 kg, 84.2 mol) in methanol (80 L) was added a solution of sodium methoxide in methanol (25 wt %, 23.6 kg, 109 mol) over 1 h, and the mixture was aged for a further 30 min. Water (100 L) was added over 30 min, with the temperature maintained at <25 °C. The mixture was

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concentrated to 120 L by distillation (100 mbar, 30 °C), and the resulting slurry was filtered, washed with water (2 × 50 L), and dried in vacuo at 35 °C. The resultant solid was taken up in industrial methylated spirit (IMS) (225 L), and iron powder (325 mesh, 16.0 kg, 286 mol) and water (8.7 L) were added, after which the mixture was heated to 40 °C. A solution of HCl (9%, 13.6 kg, 33.5 mol) was added over 2.5 h, and the mixture was aged at 40 °C for a further 4 h. The mixture was cooled to 20 °C and filtered through Celite, and the vessel and cake were washed with IMS (76 L). The combined filtrates were distilled (100 mbar, 30 °C) to 94 L, and toluene (187 L) was added. The mixture was distilled (100 mbar, 30 °C) to 93 L, and toluene (93 L) was added. The solution was cooled to 20 °C, and HCl in IPA (5 M, 17.7 L, 88.5 mol) was added over 30 min. The slurry was aged for 1 h and filtered, and the cake was washed with toluene (77 L) and dried under vacuum at 40 °C to afford 5-bromo-2-methoxypyridin-3-ammonium chloride (**23**) (18.1 kg, 75.6 mol, 90%) as a gray solid. δ_H ($CDCl_3$, 400 MHz) 3.87 (3H, s), 7.48 (1H, d, J = 2.3 Hz), 7.75 (1H, d, J = 2.3 Hz), 8.39 (3H, br s); δ_C ($CDCl_3$, 100 MHz) 53.7, 111.2, 126.0, 127.9, 137.3, 153.0; HRMS m/z calcd for $C_6H_8BrN_2O$ 202.9815, found 202.9814; mp 148−150 °C.

***N*-(5-Bromo-2-methoxypyridin-3-yl)-methanesulfonamide (24).** Compound **23** (18.1 kg, 75.6 mol) was dissolved in a mixture of acetonitrile (40.0 L) and pyridine (18.1 kg, 229 mol), and methanesulfonyl chloride (10.8 kg, 94.3 mol) was added over 20 min. The mixture was aged for 5 h, and then water (159 L) was added over 1 h. The resulting slurry was aged for 2 h and filtered, and the cake was washed with 3:1 water/acetonitrile (18 L) and dried under vacuum at 45 °C to afford *N*-(5-bromo-2-methoxypyridin-3-yl)methanesulfonamide (**24**) (20.0 kg, 71.1 mol, 94%) as a gray solid. δ_H ($CDCl_3$, 400 MHz) 3.05 (3H, s), 4.00 (3H, s), 6.82 (1H, s), 7.89 (1H, d, J = 2.3 Hz), 7.97 (1H, d, J = 2.3 Hz); δ_C ($CDCl_3$, 100 MHz) 40.0, 54.3, 112.0, 122.4, 128.8, 142.1, 152.8; HRMS m/z calcd for $C_7H_{10}BrN_2O_3S$ 280.9590, found 280.9587; mp 136−139 °C.

***N*-(2-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanesulfonamide (21).** Tricyclohexylphosphine (136 g, 485 mmol) and $Pd_2(dba)_3$ (166 g, 181 mmol) were dissolved in degassed toluene (17 L), and the solution was heated to 45 °C for 45 min. The resultant solution was added to a mixture of **24** (17.0 kg, 60.5 mol), bis(pinacolato)diboron (18.4 kg, 72.5 mol), and potassium acetate (11.9 kg, 121 mol) in degassed toluene (170 L) at 90 °C, and the obtained mixture was aged for 20 h. The reaction mixture was cooled to 50 °C and filtered, washing the cake with toluene (34 L). The resultant solution was distilled to 85 L (70 mbar, 40 °C) and cooled to 20 °C. To the resulting slurry was added heptane (85 L) over 30 min, and then the slurry was aged for 13 h, filtered, and washed with 1:1 toluene/heptane (2 × 17 L). The solid was dried under vacuum at 50 °C (21.6 kg, 65.8 mol, quant). A portion of the crude product (1.01 kg) was recrystallized from 2-propanol (4.1 L), dissolving at 75 °C and then cooling to 20 °C over 2 h and aging for 90 min. Filtration, washing with 2-propanol (2 × 1 L), and drying at 50 °C in vacuo afforded *N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanesulfonamide (**21**) (710 g, 2.16 mol, 76% with respect to **24**) as a white crystalline solid. δ_H ($CDCl_3$, 400 MHz) 1.32 (12H, s), 3.01 (3H, s), 4.03 (3H, s), 6.71 (1H, br s), 8.04 (1H, d, J = 1.5 Hz), 8.31 (1H, d, J = 1.5 Hz); δ_C ($CDCl_3$, 100 MHz) 24.8, 39.7, 54.1, 84.0, 120.7, 133.2, 149.4, 156.5 (no signal for C−B carbon); HRMS m/z calcd for $C_{13}H_{22}BN_2O_5S$ 329.1337, found 329.1336; mp 146−148 °C.

Potassium (6-Methoxy-5-(methylsulfonamido)-pyridin-3-yl)trifluoroborate (27). Tris-(dibenzylideneacetone)dipalladium (16.6 g, 18.1 mmol) and tricyclohexylphosphine (25.0 mg, 89.1 mmol) were combined in degassed 1,4-dioxane (2.5 L), and the mixture was aged for 1 h at 20 °C. The resultant orange solution was added to a suspension of **24** (499 g, 1.77 mol), bis(pinacolato)diboron (498 g, 1.96 mol), and potassium acetate (362 g, 3.69 mol) in degassed 1,4-dioxane (8.0 L) at 100 °C, and the mixture was aged for 1 h. The mixture was cooled to 20 °C, aged for 1 h, and filtered, washing with 1,4-dioxane (3 L), and the resultant solution was distilled down to 10 volumes (120 mbar, 50 °C) and then cooled to 20 °C. Water (3 L) was added, followed by potassium bifluoride (555 g, 7.11 mol), and the mixture was stirred for 1 h at 20 °C. The aqueous layer was decanted, and the organic fraction was filtered to remove further inorganics, washing the solids with 9:1 1,4-dioxane/water (2 L). The filtrate was concentrated and azeo-dried by distillation. Put-and-take distillations, charging 1,4-dioxane and then distilling (250 mbar, 60 °C) to 5 L, were repeated until <0.5% w/w water remained (checked by Karl Fischer titration). The mixture was aged at 20 °C for 1 h and then filtered, and the cake was washed with 1,4-dioxane (2 × 1 L) and *tert*-butyl methyl ether (2 × 1 L) and then dried in vacuo at 60 °C to afford potassium (6-methoxy-5-(methylsulfonamido)pyridin-3-yl)trifluoroborate (**27**) (708 g, 69% pure by NMR assay using 1,4-dimethoxybenzene as an internal standard, 1.59 mol, 90% corrected yield). δ_H ($CDCl_3$, 400 MHz) 2.88 (3H, s), 3.82 (3H, s), 7.45 (1H, s), 7.78 (1H, s); δ_C ($CDCl_3$, 100 MHz) 39.9, 52.7, 120.8, 136.4, 144.5, 155.6 (no signal for C−B carbon); HRMS m/z calcd for $C_7H_9BF_3KN_2O_3$ 308.0016, not found; however, the trifluoroborate salt hydrolyzes to the boronic acid on the LC−MS column, HRMS m/z calcd for $C_7H_{12}BN_2O_5S$ 247.0554, found 247.0549; mp 169−171 °C.

4-((2-(6-Chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)-oxazol-5-yl)methyl)-*cis*-2,6-dimethylmorpholine (19). 2,6-*cis*-Dimethylmorpholine (**17**) (178 mL, 1.45 mol) and triethylamine (200 mL, 1.43 mol) were added sequentially to a solution of **3** (587 g, 92% w/w assay, 1.19 mol), in acetone (4.7 L) at 20 °C. After 30 min, water (4.7 L) was added over 10 min, and the resultant slurry was aged for a further 1 h and then filtered. The cake was washed with 2:1 water/acetone (2 × 1.2 L) and dried in vacuo at 45 °C. The dried solid was dissolved in DMSO (5.8 L) at 75−80 °C and after hot filtration was cooled to 20 °C over 3 h, aged at 20 °C for 90 min, and filtered. The cake was washed with DMSO (860 mL) followed by 2:1 water/acetone (2 × 1.2 L) and dried in vacuo at 45 °C to afford 4-((2-(6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)oxazol-5-yl)-methyl)-*cis*-2,6-dimethylmorpholine (**19**) (476 g, 0.977 mol, 82%) as a pale-yellow solid. δ_H ($CDCl_3$, 400 MHz) 1.16 (6H, d, J = 6.3 Hz), 1.86 (2H, app. t, J = 10.6 Hz), 2.76 (2H, dd, J = 10.6, 1.8 Hz), 3.67 (2H, s), 3.70 (2H, dqd, J = 10.6, 6.3, 1.8 Hz), 7.15 (1H, s), 7.50 (2H, app. t, J = 8.1 Hz), 7.61 (1H, tt, J = 8.1, 1.3 Hz), 7.97 (1H, d, J = 1.5 Hz), 8.02 (2H, dd, J = 8.1, 1.3 Hz), 8.32 (1H, s), 8.93 (1H, s); δ_C ($CDCl_3$, 100 MHz) 19.1, 52.4, 59.0, 71.6, 114.5, 121.2, 121.6, 123.2, 127.7, 127.9, 129.4, 134.5, 135.8, 137.2, 141.2, 141.6, 149.6, 158.7; HRMS m/z calcd for $C_{23}H_{24}ClN_4O_4S$ 487.1201, found 487.1192; mp 164−167 °C.

***N*-(5-(4-(5-((*cis*-2,6-Dimethylmorpholino)methyl)-oxazol-2-yl)-1-(phenylsulfonyl)-1*H*-indazol-6-yl)-2-me-**

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thoxypyridin-3-yl)methanesulfonamide (26). Palladium acetate (4.25 g, 18.9 mmol) and tricyclohexylphosphine (10.6 g, 37.8 mmol) were combined in degassed 2-propanol (2.3 L) at 20 °C, and the mixture was stirred for 1 h. The resultant yellow solution was added to a stirred suspension of **19** (460 g, 0.94 mol), **21** (341 g, 1.04 mol), potassium phosphate (241 g, 1.14 mol), and potassium bifluoride (162 g, 2.07 mol) in a mixture of degassed 2-propanol (2.3 L) and water (2.3 L) at 80 °C. The resulting mixture was aged for 2.5 h and then cooled to 30 °C over 1 h, and water (2.3 L) was added. The slurry was aged at 20 °C for 1 h and filtered, and the cake was washed with 1:1 2-propanol/water (2 × 0.92 L) and dried in vacuo at 60 °C to afford *N*-(5-(4-(5-((*cis*-2,6-dimethylmorpholino)methyl)-oxazol-2-yl)-1-(phenylsulfonyl)-1*H*-indazol-6-yl)-2-methoxy-pyridin-3-yl)methanesulfonamide (**26**) (611 g, 0.94 mol, 99%) as an off-white solid. δ_H ($CDCl_3$, 400 MHz) 1.01 (6H, d, J = 6.3 Hz), 1.73 (2H, app. t, J = 10.6 Hz), 2.76 (2H, dd, J = 10.6, 1.8 Hz), 3.14 (3H, s), 3.54 (2H, dqd, J = 10.6, 6.3, 1.8 Hz), 3.70 (2H, s), 4.02 (3H, s), 7.35 (1H, s), 7.61 (2H, app. t, J = 7.6 Hz), 7.74 (1H, tt, J = 7.6, 1.2 Hz), 8.03 (1H, d, J = 2.3 Hz), 8.04 (2H, dd, J = 7.6, 1.2 Hz), 8.10 (1H, d, J = 1.2 Hz), 8.36 (1H, s), 8.46 (1H, d, J = 2.3 Hz), 8.95 (1H, d, J = 1.2 Hz), 9.44 (1H, br s); δ_C ($CDCl_3$, 100 MHz) 18.8, 40.8, 51.2, 53.9, 58.2, 70.9, 111.6, 120.9, 121.0, 121.4, 121.7, 127.3, 127.7, 128.6, 129.9, 130.9, 135.2, 136.1, 138.9, 141.1, 141.2, 141.5, 149.9, 156.8, 158.3; HRMS m/z calcd for $C_{30}H_{33}N_6O_7S_2$ 653.1847, found 653.1832; mp 214−216 °C.

***N*-(5-(4-(5-((*cis*-2,6-Dimethylmorpholino)methyl)-oxazol-2-yl)-1*H*-indazol-6-yl)-2-methoxypyridin-3-yl)-methanesulfonamide (2).** To a suspension of **26** (596 g, 0.913 mol) in water (3.8 L) was added aqueous sodium hydroxide (5 M, 715 mL, 3.58 mol) over 20 min, and the mixture was stirred at 20 °C for 3 h. Propionitrile (2.55 L) was added, and the mixture was allowed to settle, after which the organic fraction was separated and discarded. The aqueous phase was adjusted from pH 10 to 6 with 2 M hydrochloric acid (1.4 L), and 2-methyltetrahydrofuran (4.8 L) was added. The organic phase was collected, and the aqueous phase was re-extracted with 2-methyltetrahydrofuran (4.8 L). The combined organics were washed with water (1.2L) and distilled down to 2.4 L (100 mbar, 25 °C). The solvent was swapped to EtOAc by successive distillations and EtOAc additions, and then the volume was adjusted to 4.8 L by addition of further EtOAc. Crystallization was induced by seeding at 60 °C, aging for 1 h, cooling to 20 °C over 2 h, and aging for a further 16 h. The mixture was filtered, and the cake was washed with EtOAc (2 × 1.2 L) and dried in vacuo at 45 °C to afford *N*-(5-(4-(5-((*cis*-2,6-dimethylmorpholino)methyl)oxazol-2-yl)-1*H*-indazol-6-yl)-2-methoxypyridin-3-yl)methanesulfonamide (**2**) (405 g, 0.790 mol, 87%) as a white solid. δ_H ($CDCl_3$, 400 MHz) 1.03 (6H, d, J = 6.3 Hz), 1.77 (2H, app. t, J = 10.6 Hz), 2.86 (2H, dd, J = 10.6, 2.0 Hz), 3.12 (3H, s), 3.57 (1H, dqd, J = 10.6, 6.3, 2.0 Hz), 3.72 (2H, s), 4.00 (3H, s), 7.34 (1H, s), 7.87 (1H, s), 7.93 (1H, d, J = 1.5 Hz), 8.00 (1H, d, J = 2.3 Hz), 8.41 (1H, d, J = 2.3 Hz), 8.58 (1H, s), 9.37 (1H, br s), 13.47 (1H, br s); δ_C ($CDCl_3$, 100 MHz) 18.9, 40.7, 51.3, 53.8, 58.3, 70.9, 110.0, 117.9, 118.3, 119.6, 121.4, 127.4, 129.5, 130.8, 133.6, 134.8, 140.8, 141.1, 149.1, 152.2, 159.8; HRMS m/z calcd for $C_{24}H_{29}N_6O_5S$ 513.1915, found 513.1906; mp 205−207 °C.

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