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Development of an NH4Cl-Catalyzed Ethoxy Ethyl Deprotection in Flow for the Synthesis of Merestinib

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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.5b00240 • Publication Date (Web): 23 Sep 2015

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Development of an NH_4Cl-Catalyzed Ethoxy Ethyl Deprotection in Flow for the Synthesis of Merestinib

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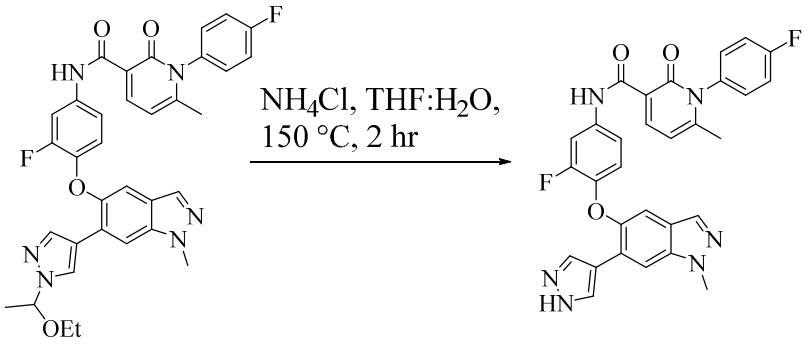


ABSTRACT: An NH_4Cl-catalyzed ethoxy ethyl deprotection was developed for the synthesis of merestinib, a MET inhibitor. Alternative reactor technologies using temperatures above the solvent boiling point are combined with this mild catalyst to promote the deprotection reaction. The reaction is optimized for flow, and has been used to synthesize over 100 kg of the target compound. The generality of the reaction conditions is also demonstrated with other compounds and protecting groups.

KEYWORDS: Merestinib, ethoxy ethyl deprotection, flow chemistry, scale-up, ammonium chloride

INTRODUCTION: MET kinase inhibitors are a class of small molecules that inhibit the enzymatic activity of MET tyrosine kinase and may have therapeutic applications for the treatment of various types of cancers.[1] Merestinib (**1**, Figure 1) is one such molecule and is currently undergoing early-phase clinical studies in cancer patients.[2]

A synthesis of **1** has been previously described which relied on a Boc-protected penultimate compound (**2**).[3] Although successful, lability concerns with the Boc group led us to explore alternative protecting groups. After evaluation of different commercially available protected boronic ester pyrazoles,[4] it was decided that an ethoxy ethyl (EE) protecting group would be explored, as it was believed that it would withstand the desired chemistry, while also being able to be deprotected in high yields.[5,6] Retrosynthetically, merestinib (**1**) can be deconstructed in two ways, the first of which involves breaking the amide bond of **3** to give known carboxylic acid **4**[3] and aniline **5**. The aniline would then be derived from EE-protected pinacol boronic ester **7** and previously described aryl bromide **8**.[3] The second synthetic option would use the same building blocks, but the first retrosynthetic disconnection would break the aryl bond into EE-protected pinacol boronic ester **7** and aryl bromide **9**. Bromide **9** would be split into carboxylic acid **4** and aryl bromide **8**.

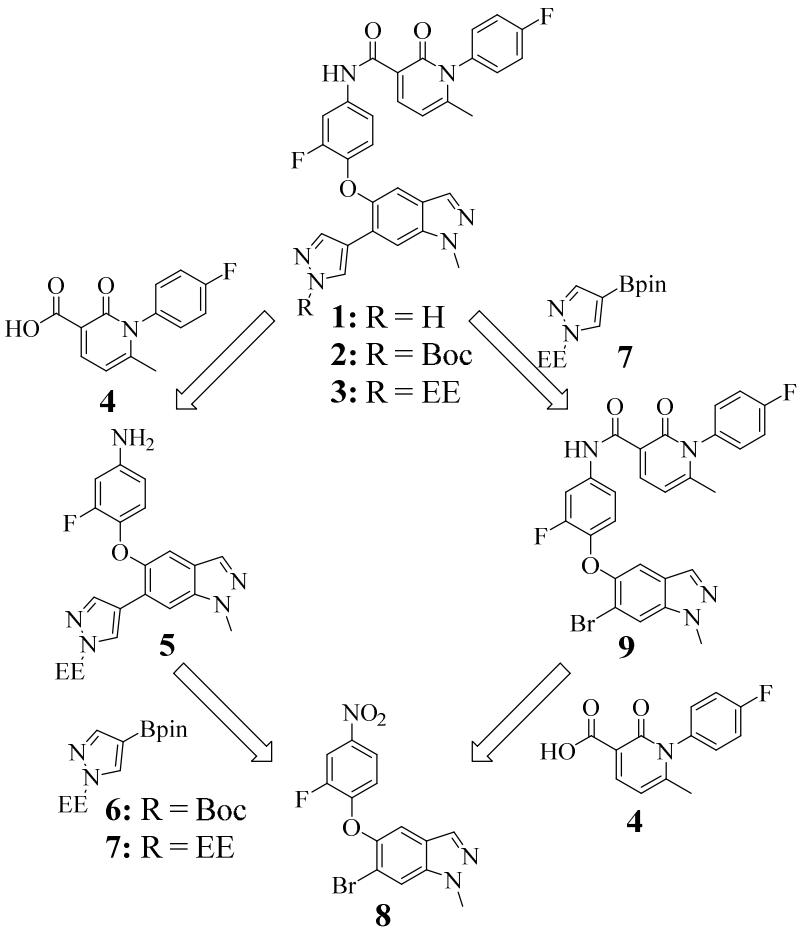
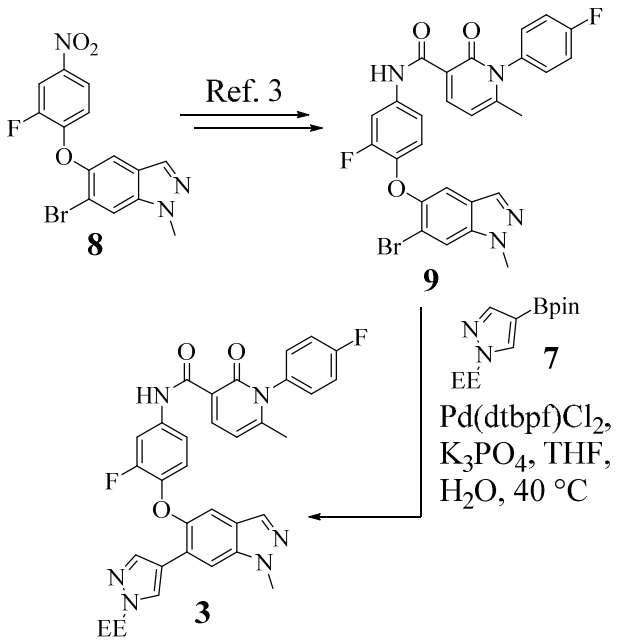


Figure 1. Retrosynthesis of merestinib **1** through two routes starting from common intermediate **8**. pin = pinacol.

RESULTS AND DISCUSSION:

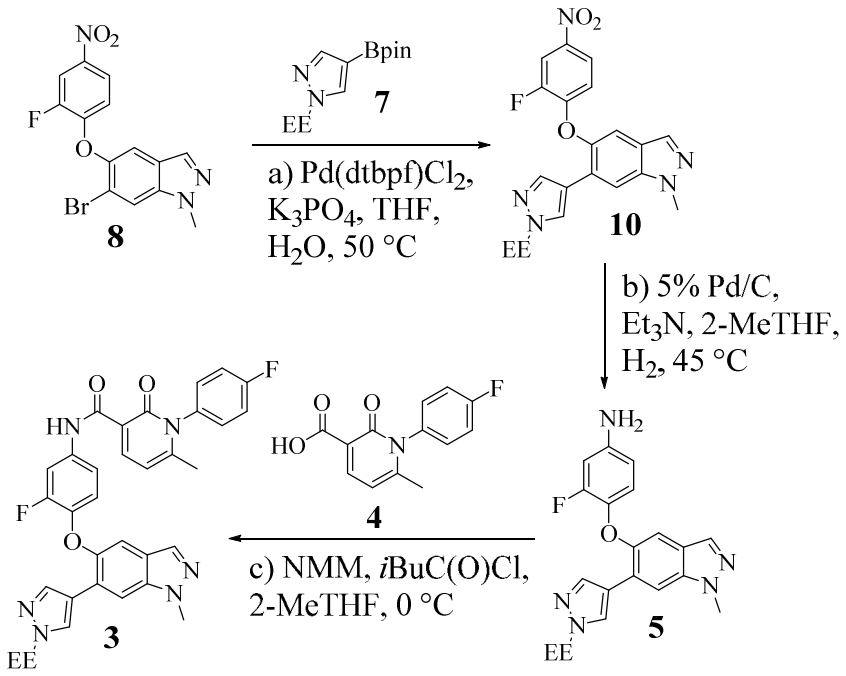
Routes to penultimate compound **3**:

The first route explored mirrored the previously disclosed route,[3] which entailed a nitro reduction of compound **8** followed by amide bond formation to give **9** (Scheme 1). A Suzuki coupling worked very well with EE-protected pyrazole **7** (similar to previously used Boc-protected pyrazole **6**). Using the previously developed conditions [$Pd(dtbpf)Cl_2$, K_3PO_4, THF, H_2O, 40 °C], provided penultimate compound **3** in 96% yield, leaving the deprotection to be explored (*vide-infra*).



Scheme 1. Reagents and Conditions: **7** (1.2 equiv.), K_3PO_4 (2.0 equiv.), $Pd(dtbpf)Cl_2$ (0.012 equiv.), THF, H_2O, 40 °C, 15 hr, 96%. dtbpf = bis(di-*tert*-butylphosphino)ferrocene.

The second route used similar chemistry, but in a different order (Scheme 2). Pinacol boronate **7** was joined with bromide **8** [$Pd(dtbpf)Cl_2$, K_3PO_4, THF, H_2O, 50 °C], to form the biaryl bond of **10** in 87% yield. Performing the Suzuki coupling first was advantageous over the previous route as it removed the risk of debromination during hydrogenation.[7] As a result, simple nitro reduction with 5% Pd/C worked well to afford aniline **5** in 92% yield. Finally, amide bond formation was accomplished by addition of aniline **5** to the freshly prepared mixed anhydride [**4**, *i*BuC(O)Cl], to give penultimate compound **3** in 86% yield.

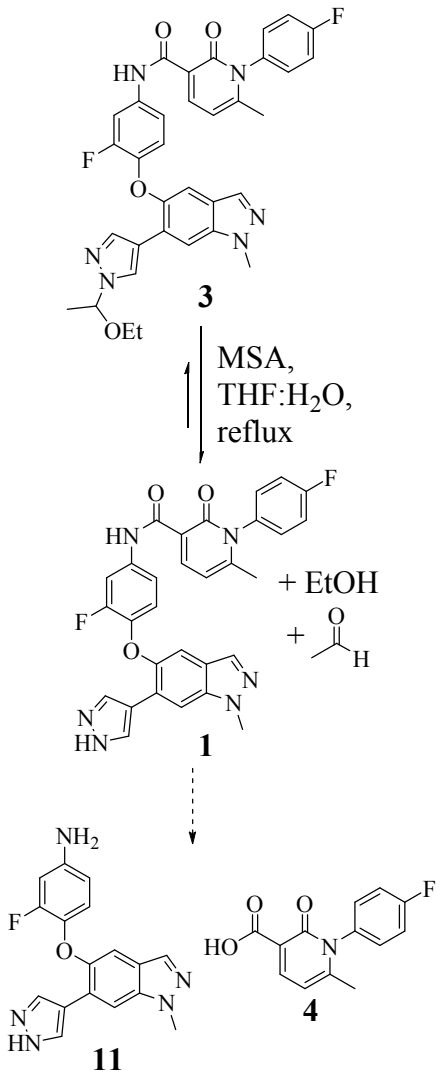


Scheme 2. Reagents and Conditions: a) **7** (1.2 equiv.), K_3PO_4 (2.2 equiv.), Pd(dtbpf)Cl_2 (0.012 equiv.), THF, H_2O, 50 °C, 3.5 hrs, 87%; b) 5% Pd/C (55% H_2O by wt, 0.09 wt%), Et_3N (1.5 equiv.), 2-MeTHF, H_2 (50 psi), 45 °C, 4.5 hr, 92%; c) **4** (1.1 equiv.), NMM (2.5 equiv.), 2-MeTHF, 0 °C, 15 min; *i*BuC(O)Cl (1.3 equiv.), 0 °C, 4 hr; **11** (1.0 equiv.), 0 °C, 3 hr, 86%. NMM = *N*-methylmorpholine.

EE deprotection in batch:

Although the EE-protected compound **3** could be successfully prepared through two similar, but separate routes, a deprotection still needed to be developed. We first explored acid catalyzed removal of the EE group in **3**.[6] A mix of THF:H_2O was used as the solvent for the reaction as they provided the best solubility (maximum solubility for both starting material **3** and product **1** is between 10 and 20 volume% water in THF). Finding an appropriate acid was less straightforward. Weak acids result in very slow reactions, while stronger acids lead to amide bond hydrolysis. Methanesulfonic acid gave the desired balance between rate and stability; however, the reaction would stall with 1–5% of the starting EE-protected compound (**3**) remaining. As starting material **3** is not efficiently removed by crystallization, the purity of target compound **1** was unacceptable. The stalling of the reaction could be overcome by removing acetaldehyde during the reaction through distillation. Unfortunately, the prolonged reaction time would result in further cleavage of the amide bond in **1** affording aniline **11** and

carboxylic acid **4** (Scheme 3). Although the amounts of **11** were low (roughly 1%), aniline **11** is a mutagen that needed to be controlled to below 80 ppm in **1**, and it rejects poorly during crystallization. As a result, another solution was needed for the deprotection.

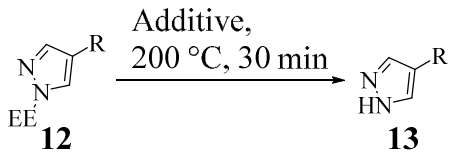


Scheme 3. Reagents and Conditions: MSA (1.0 equiv.), THF, H_2O, reflux, 3 hr, 92% with 1% **11**. MSA = methanesulfonic acid.

EE deprotection in flow:

To avoid the amide bond cleavage, alternative reactor technologies were explored including the possibility of a tubular plug-flow reactor that is capable of heating to higher temperatures, within a shorter period of time.[8] Heating a reaction with various additives (see Table 1) to 200 °C for 30 minutes showed this to be an effective way to synthesize the product.[9] The formation of minimal product for a reaction with no additive (entry 1) clearly demonstrates that the deprotection is not simply thermally

driven.[10] Not surprisingly, protic acids were effective (entries 2–5), but as with reactions at lower temperatures, there was a balance between reaction rate and formation of the undesired aniline. Fortunately, NH_4Cl looked very promising. Interestingly, aprotic additives were also effective in the reaction (entries 6–10).

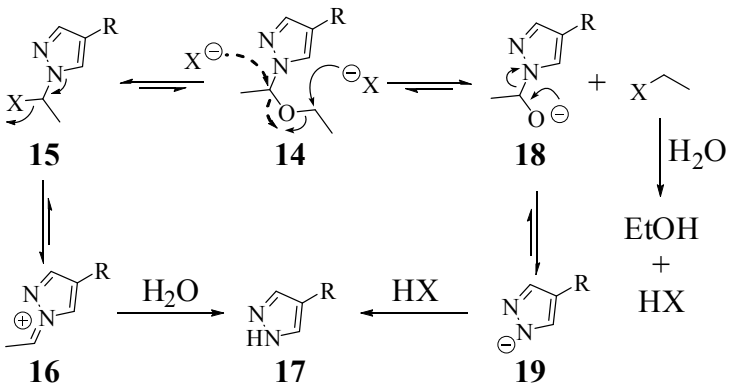


12 **13**

Entry	Additive	Conversion	Aniline (11)
1	None	2	0.00
2	AcOH	21	0.04
3	HCO_2H	92	0.05
4	H_3PO_4	100	0.33
5	NH_4Cl	100	0.00
6	NaCl	80	0.05
7	LiCl	93	0.11
8	LiBr	100	0.03
9	KBr	100	0.00
10	TBAB	100	0.17

Table 1. Reactions run on 0.1 mmol scale with 1 mL high pressure batch reactors in 85:15 THF:H_2O (15 volumes).[9]

Although NH_4Cl was ultimately selected for this reaction, the aprotic additive results led to a better understanding of how the reaction was taking place. Instead of the normally accepted protic acid-mediated mechanism of EE-deprotections, it is believed that this reaction occurs through a Krapcho-type mechanism,[11] which could involve a nucleophilic displacement at two sites on the EE group (Scheme 4). The halogen could displace the ethoxy group affording halo-aminal **15**. The halide would then get pushed out by electrons on the nitrogen pyrazole making the reaction catalytic in the halide and providing the deprotected pyrazole **17** after liberation of acetaldehyde from **16**. Similarly, and perhaps more likely, ethyl halide could be formed along with intermediate **18**. It should be noted that ethyl chloride is not detected during our reaction, but due to the large excess of water and high temperatures, it would be expected to convert to ethanol and HCl very quickly. After expulsion of acetaldehyde from **18**, anion **19** could be quickly protonated to form deprotected **17**.



Scheme 4. Krapcho-type mechanism for the EE deprotection.

For scaling up, a feed solution was created that contained all components: starting material **3**, THF, H_2O, and NH_4Cl. The feeds were pumped through a 12 L coiled tube reactor at 150 °C with 250 psi of back pressure to keep the contents liquid at a flow rate that would provide a two hour residence time.[12] Once the product for one batch was collected, it was worked up in batch.[13] In addition to analysis of the collected final product, on-line HPLC was also in place to monitor the reaction in real-time and be able to respond to any departures from the expected reaction profile (see Experimental Section for more detail about the on-line HPLC). Figure 2 shows the output of the on-line HPLC with area% of starting material (**3**) plotted over time. The results were very consistent across the 90 hours, representing the first of 4 batches.[14] In total, over 100 kg was made in this way with a total yield of 94% and greater than 99.8% purity (Scheme 5).

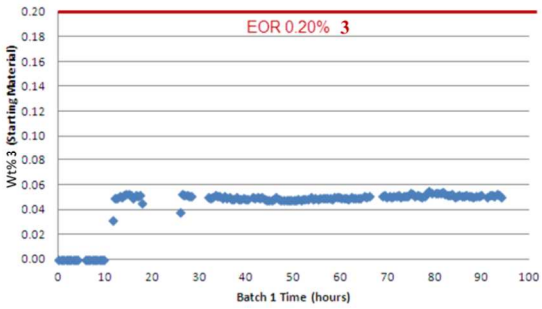
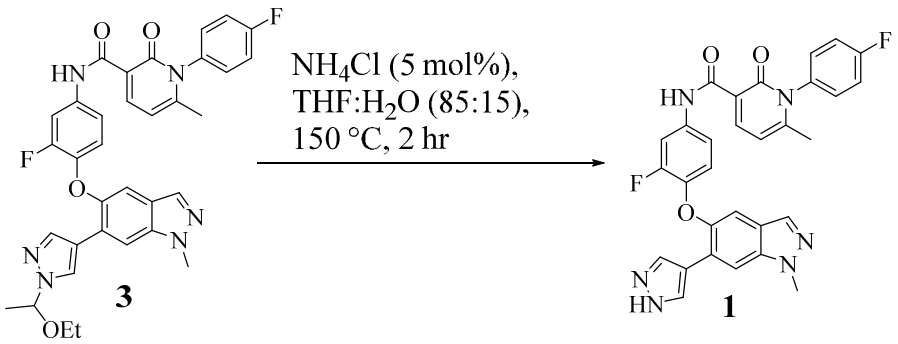


Figure 2. On-line HPLC data of wt% starting material (**3**) remaining over time.



Scheme 5. Reagents and Conditions: NH_4Cl (0.05 equiv.), THF, H_2O, 150 °C, 2 hr, 94%.

Substrate generality:

To further explore the generality of the reaction, a variety of substrates were explored (Table 2). Aliphatic EE-protected alcohols were cleanly deprotected at 150 °C over one hour (entry 1), as well as phenolic (entry 2), primary benzylic (entry 3) and secondary benzylic (entry 4) EE-protected alcohols. Other protecting groups (triethyl silyl, *t*-butyldimethylsilyl, and tetrahydropyranyl) could also be removed with slightly higher temperatures (200 °C) and longer reaction times (2 h), further demonstrating the generality of the reaction.

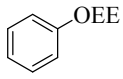
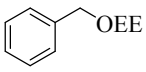
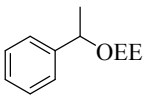
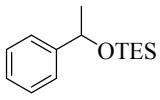
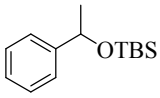
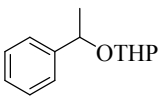
Entry	Substrate	Temp.	Time	Conversion
1	Cholesterol-OEE	150 °C	1 h	100%
2		150 °C	1 h	100%
3		150 °C	1 h	100%
4		150 °C	1 h	100%
5		200 °C	2 h	100%
6		200 °C	2 h	100%
7		200 °C	2 h	100%

Table 2. Reactions on 0.1 to 1.0 mmol scale in 1 mL high pressure batch reactors with NH_4Cl (5 mol%) in 85:15 THF:H_2O (10 volumes) as the solvent composition.

Conclusions: In conclusion, a new deprotection for ethoxy ethyl protecting groups was developed and applied to the synthesis of more than 100 kg of merestinib (**1**). Although high temperatures (150 °C) were required, the conditions (catalytic NH_4Cl) are relatively mild and tolerant of a wide variety of substrates. The methodology was further applied to other protecting groups, demonstrating further generality.

Experimental Section:

On-Line HPLC Description

The automated sampling/dilution system takes a precise volume sample from a continuous process, dilutes it with a precise volume of diluent, mixes the diluted sample, and then parks it at a desired location, for example an injection loop or an overflow Tee 200 feet away.

The dilution factor for this system can be changed from 20 X to 200 X by changing the size of the diluent measure-out zone. There are no automated valves or sample loops in the main process flow path so that this system does not interfere with the flow chemistry process. This system is not designed for slurries; only homogeneous solutions. The process is sampled by using gravity and automated block valves. Sample size is 2 mL. The system operates at ambient temperature. The system uses 15–45 psig N_2 for the mixing and pushing to the LC. The system is electrically classified to reside in the plant module at the reactor outlet tubing, and it pushes the diluted sample to the on-line HPLC in an adjacent laboratory.

The 2 mL sample is taken from an overflow Tee by gravity. The minimum size tubing and fittings are selected so that the sample collection zone is self-venting. Liquid must flow down into the sample zone by gravity only, meaning that the displaced vapor from the sample zone must bubble up. The sample zone is the space between two standard 1/2” block valves. The top valve opens and closes, then the bottom valve opens and closes, which drops a 2 mL sample by gravity into a lower sample chamber. The fittings and tubing below the valve must be at least 1 cm inside diameter, with no smaller internal restrictions, or else the 2 mL sample may not gravity flow down to the lower zone when the valve opens. This depends on the surface tension of the fluid.

The vertical dilution solvent measure out zone fills from bottom up, and empties from top down. This ensures that it gets completely liquid filled with no gas pockets, and that it subsequently completely empties, with only a few surface drops remaining. The dilution solvent measure out zone uses four automated block valves, two at the top and two at the bottom, so that it can overflow back to the solvent vessel while filling, and then push with nitrogen to the mixing vessel after filled.

Pressurized nitrogen pushes the dilution solvent through the lower sample zone, which pushes the sample into the bottom of a mixing chamber. The mixing chamber is typically 5X larger volume than the sum of dilution solvent plus sample. The nitrogen bubbling action into the bottom of the mixing chamber thoroughly mixes the diluted sample. The nitrogen bubbling happens after all of the sample and dilution solvent has been pushed into the mixing chamber, and the nitrogen continues to blow through the valves to pressure up the mixing chamber. This nitrogen pressure in the mixing chamber subsequently serves to push the diluted sample to the on-line HPLC through 200 feet of tubing. There are two automated block valves at the bottom of the mixing chamber, one to allow flow into the chamber from the sample zone, and one to allow flow out of the chamber to the on-line HPLC. The digital control system runs the sequence for all of the automated block valves. It typically takes about 2–10 minutes for this system to go through the entire automated sequence, depending on how far it is pushing the diluted sample to the on-line HPLC, the internal diameter of the tubing, and viscosity and volume of the diluted sample solution. If a PATROL on-line HPLC system (see description below) is used, then it sips the diluted sample from the bottom of an overflow Tee 200 feet away in an adjacent laboratory.

PATROL Description

A PATROL on-line HPLC was coupled to the process via the automated sampling/dilution system described above.[15] The automated sampling/dilution system delivers a sample to the overflow Tee every 30 min for the PATROL to sample. The process sampling valve on the PATROL was connected to the overflow Tee by a 1 meter long segment of 1/16” o.d. x 0.030” i.d. PTFE tubing. The PATROL sips the diluted sample from the bottom of the overflow Tee to ensure only liquid is drawn

into the instrument. When the PATROL run sequence is initiated the PATROL draws 2 mL of sample from the overflow Tee at a flow rate of 4 mL/min. The duration of sampling ensures there is a minimal amount of diluted sample remaining in the overflow Tee between samples being delivered from the automated sampling/dilution system. The 2 mL of sample drawn also flushes the sample fluidic train within the PATROL, ensuring it is flushed with representative material from the process and reducing instrument carryover in the process sample pump. Once this cycle is completed the PATROL performs a secondary dilution on the process sample (5X) by metering the process sample pump in parallel with a diluent pump filled with acetonitrile. The combined effluent from these pumps fills a loop (2 μL) that is injected on column. For this process the PATROL delivered a sample from the overflow tee and performed the analysis every 30 min.

In addition to online sampling, the PATROL has a standard autosampler carousel which enables injection of method calibration samples. Before process start-up a series of method calibration samples were injected to ensure method performance and enable quantitation via external standard method. Over the course of the campaign the method calibration sample was injected at-line daily to demonstrate the method was performing acceptably.

Chemistry Procedures

General Procedure for Table 2, entry 4.

To a 1 mL high pressure batch reactor in a glove box was added 1-(1-ethoxyethoxy)ethylbenzene (50 mg, 0.26 mmol, 1.0 equiv.), THF (0.425 mL, 8.5 volumes), water (0.075 mL, 1.5 volumes) and NH_4Cl (0.69 mg, 0.013 mmol, 0.05 equiv.). The reactor connector was sealed by screwing the lid on tight and then heated in an oven at 150 °C for 1 hour. The reactor connector was then allowed to cool to ambient temperature and was sampled by HPLC for conversion.

***N*-(4-((6-(1-(1-ethoxyethyl)-1H-pyrazol-4-yl)-1-methyl-1H-indazol-5-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (3, Suzuki Coupling).**

To a 1000 gal glass-lined reactor was added **9** (138.8 kg, 238.9 mol, 1.0 equiv.), **7** (76.6 kg, 287.7 mol, 1.2 equiv.), K_3PO_4 (102.0 kg, 480.5 mol, 2.0 equiv.), followed by THF (1044 L, 7.5 volumes) and H_2O

(410 L, 3 volumes). The biphasic mixture was stirred at 25 °C until complete dissolution was observed. To the biphasic mixture was then charged Pd(dtbpf)Cl_2 (1.88 kg, 2.88 mol, 0.012 equiv.) and the solution was heated to 40 °C for 15 hours at which point the reaction was complete by HPLC. The stirring was then stopped and the biphasic mixture was allowed to separate completely over 30 minutes at 40 °C. The aqueous layer was removed and 41 kg of Silica-thiol Pd-scavenging resin[16] was added to the organic layer. The slurry was heated to 60 °C for 6 hours and the resin was removed by filtration. The filtrate was concentrated by vacuum distillation at 30–35 °C to get to a final volume of 870 L (approximately 6 Volumes relative to **3**). To the solution was added seed of **3** (1.62 kg) and the slurry was cooled to 20–25 °C where it was stirred for 10 hours. The slurry was further cooled to 0–5 °C where it was held for another 6 hours. The solid was collected by filtration and the wet cake was dried under vacuum at 55 °C for 60 hours to obtain **3** (136 kg, 208.8 mol, 96% yield) as a yellow solid. **3**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.88 (s, 1 H), 8.43 (d, *J* = 7.6 Hz, 1 H), 8.26 (s, 1 H), 7.99 (s, 2 H), 7.93 (dd, *J* = 13.6, 2.4 Hz, 1 H), 7.89 (s, 1 H), 7.46–7.37 (m, 4 H), 7.27 (s, 1 H), 7.19 (d, *J* = 9.2 Hz, 1 H), 6.80 (t, *J* = 9.2 Hz, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 5.53–5.50 (m, 1 H), 4.05 (s, 3 H), 3.35–3.32 (m, 1 H), 3.08–3.03 (m, 1 H), 2.03 (s, 3 H), 1.55 (d, *J* = 6.0 Hz, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.4, 161.9, 161.2, 153.7, 151.3, 147.7, 144.4, 140.4, 138.5, 137.7, 134.9, 134.8, 134.5, 132.4, 130.5, 127.5, 124.0, 122.4, 120.0, 118.3, 117.4, 117.1, 116.9, 116.4, 109.5, 109.0, 108.9, 108.2, 86.8, 63.4, 36.0, 22.1, 21.7, 15.1 ppm; HR-MS [ESI]: Calcd for $C_{34}H_{31}F_2N_6O_4^+$ [M + H^+]: 625.2369, found 625.2353.

6-(1-(1-ethoxyethyl)-1H-pyrazol-4-yl)-5-(2-fluoro-4-nitrophenoxy)-1-methyl-1H-indazole (10).

To a 250 mL 3N flask was added **8** (5.0 g, 13.6 mmol, 1.0 equiv.), THF (60 mL, 12 volumes), K_3PO_4 (6.56 g, 30.3 mmol, 2.22 equiv.) in 26 mL of water and **7** (4.36 g, 16.4 mmol, 1.2 equiv.). To this mixture was added Pd(dtbpf)Cl_2 (140 mg, 21 μmoles, 0.02 equiv.). The mixture was heated to 50 °C where it became a clear dark brown solution, and then became a slurry. After 3.5 hours, the reaction was complete (HPLC analysis). To the slurry was added THF (10 mL, 2 volumes) and the reaction temperature was raised to 70 °C. The mixture became a dark solution and the aqueous layer was

removed. The organic layer was cooled to 21 °C and stirred for 12 hours at which time product precipitated. The resulting slurry was filtered and rinsed with 30 mL of THF. The wet cake was dried in a vacuum oven at 45 °C to give **10** (5.05 g, 11.8 mmol, 87% yield) as a grey solid. **10**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.27 (dd, *J* = 11.2, 2.4 Hz, 1 H), 8.15 (s, 1 H), 8.04 (s, 1 H), 8.02 (s, 1 H), 7.89 (d, *J* = 11.2 Hz, 1 H), 7.86 (s, 1 H), 7.67 (s, 1 H), 6.74 (t, *J* = 8.8 Hz, 1 H), 5.49–5.45 (m, 1 H), 4.09 (s, 3 H), 3.28–3.23 (m, 1 H), 2.89–2.84 (m, 1 H), 1.51 (d, *J* = 6.0 Hz, 3 H), 0.87 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.2, 151.8, 149.7, 144.8, 141.9, 138.6, 138.3, 132.8, 127.2, 124.6, 122.6, 121.7, 117.8, 116.7, 113.4, 109.8, 86.8, 63.3, 36.1, 21.6, 14.9 ppm; HR-MS [ESI]: Calcd for $C_{21}H_{21}FN_5O_4^+$ [M + H^+]: 426.1565, found 426.1572.

4-((6-(1-(1-ethoxyethyl)-1H-pyrazol-4-yl)-1-methyl-1H-indazol-5-yl)oxy)-3-fluoroaniline (5).

To a 1 L pressure parr reactor was added **10** (40.6 g, 95.4 mmol, 1.0 eq), 5% Pd/C (55% water content, 1.61 g, 0.09% w/w), Et_3N (14.7 g, 146 mmol, 1.53 equiv.) and 2-MeTHF (525 mL, 13 volumes). The reactor was sealed and the reaction mixture was heated to 45 °C under 50 psi of H_2 pressure. The reaction was complete after 4.5 hours (HPLC analysis) and was filtered through Celite (9.4 g), rinsed with 175 mL of 2-MeTHF. The filtrate was heated to 70 °C with 12 g of SiliaMet S Thiol[16] for 7 hours and cooled to 21 °C. The resulting slurry was filtered and rinsed with 100 mL of 2-MeTHF. The filtrate was concentrated to ~400 mL volume and to the solution was added heptane (400 mL) dropwise. After ~55 mL of heptane was added, the reaction solution was seeded with 118 mg of seed and then the remainder of the heptane was added. The light tan slurry was filtered and rinsed with 100 mL of 40% v/v 2-MeTHF/heptane. The wet cake was dried in a vacuum oven at 45 °C to give **5** (35.8 g, 87.8 mmol, 92% yield) as a light tan solid. **5**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 (s, 1 H), 8.06 (s, 1 H), 7.94 (s, 1 H), 7.82 (s, 1 H), 6.94 (s, 1 H), 6.82 (t, *J* = 8.8 Hz, 1 H), 6.49 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.35 (dd, *J* = 8.8, 2.4 Hz, 1 H), 5.59–5.55 (m, 1 H), 5.25 (s, 2 H), 4.02 (s, 3 H), 3.43–3.38 (m, 1 H), 3.21–3.17 (m, 1 H), 1.59 (d, *J* = 6.0 Hz, 3 H), 1.01 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.8, 153.4, 150.6, 147.5, 138.7, 137.0, 132.5, 132.1, 127.6, 123.3, 122.3, 118.7, 110.4, 108.3, 105.3, 102.2,

86.8, 63.4, 35.9, 21.7, 15.2 ppm; HR-MS [ESI]: Calcd for $C_{21}H_{23}FN_5O_2^+$ [M + H^+]: 396.1822, found 396.1830.

***N*-(4-((6-(1-(1-ethoxyethyl)-1H-pyrazol-4-yl)-1-methyl-1H-indazol-5-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (3, Mixed Anhydride Coupling).**

To a 25 mL round-bottom flask was added **4** (0.7 g, 2.78 mmol, 1.1 equiv.), 2-MeTHF (5 mL, 7 volumes) and NMM (0.64 g, 6.3 mmol, 2.5 equiv.). The orange slurry was stirred and cooled to 0–5 °C. Then isobutyl chloroformate (0.45 g, 3.3 mmol, 1.3 equiv.) was added dropwise. After 4 hours of stirring at 0–5 °C, to the reaction was added **5** (1 g, 2.53 mmol, 1.0 equiv.). The thin slurry was stirred at 0–5 °C for 3 hours and then warmed to 21 °C. To the resulting slurry was added 10 mL of water and the resulting biphasic mixture was heated to 50 °C. To the biphasic mixture was added 5 mL of sat. brine and the aqueous layer was removed. To the organic layer was slowly added heptane (10 mL) over 45 min at 21 °C. The resulting slurry was filtered and rinsed with 10 mL of 50% w/w 2-MeTHF/heptane. The wet cake was dried in a vacuum oven at 75 °C to afford **3** (1.35 g, 2.18 mmol, 86% yield) as a light tan solid.

Merestinib (1).

MSA Reaction:

To a 50 mL round-bottom flask equipped with a stir bar, Dean–Stark trap and reflux condenser was charged: **3** (1 g, 1.46 mmol, 1.0 equiv.), THF (13 mL, 13 volumes) and H_2O (2 mL, 2 volumes). The reaction was heated to reflux and to the solution was charged methanesulfonic acid (96 µL, 1.46 mmol, 1.0 equiv.). Five mL of solution was allowed to collect in the Dean–Stark trap at which time the reaction was complete (analysis by HPLC, approximately 3 hours). The solution was allowed to return to ambient temperature by removing the heat source. The reaction solution was quenched by the addition of Et_3N (244 µL, 1.75 mmol, 1.2 equiv.) which resulted in the homogeneous solution separating into two layers. The biphasic mixture was poured into a separatory funnel and the aqueous layer was removed. The organic layer was transferred to a 50 mL round-bottom flask with a distillation head. 10

mL EtOH was added to the solution and then 10 mL of solution was removed by vacuum distillation. 10 mL of EtOH was added a second time and 10 mL more of solution was removed by vacuum distillation. During the second distillation, product started to precipitate. 10 mL of EtOH was added a third time and 10 mL more of solution was removed by vacuum distillation. The solution was allowed to cool to ambient temperature and the product was collected by vacuum filtration and washed with 2 mL of EtOH. The wet cake was dried in a vacuum oven for 16 hours to afford **1** (0.72 g, 1.31 mmol, 90% yield) as a white solid (approximately 1% of aniline **11** present). **1**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.00 (s, 1 H), 11.93 (s, 1 H), 8.45 (d, *J* = 7.5 Hz, 1 H), 8.17 (s, 1 H), 8.05 (s, 1 H), 8.01 (s, 1 H), 7.97 (d, *J* = 2.2 Hz, 1 H), 7.91 (d, *J* = 2.6 Hz, 1 H), 7.50–7.46 (m, 2 H), 7.43–7.40 (m, 2 H), 7.27 (s, 1 H), 7.26–7.25 (m, 1 H), 6.86 (t, *J* = 9.0 Hz, 1 H), 6.67–6.65 (m, 1 H), 4.08 (s, 3 H), 2.03 (s, 3 H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.0, 161.5, 161.0, 153.2, 152.2, 147.5, 144.0, 140.1, 138.0, 137.3, 134.5, 134.1, 132.0, 130.1, 127.4, 124.2, 121.8, 119.8, 117.0, 116.8, 116.6, 116.1, 108.9, 108.6, 108.2, 107.8, 35.5, 21.7 ppm; HR-MS [ESI]: Calcd for $C_{30}H_{23}F_2N_6O_3^+$ [M + H^+]: 553.1794, found 553.1793.

NH_4Cl Reaction:

To a 250 gal stainless steel tank was charged **3** (31 kg, 49.7 mol, 1.0 equiv.), NH_4Cl (132 g, 2.49 mol, 0.05 equiv.), THF (395 L, 12.75 volumes), and H_2O (70 L, 2.25 volumes). The solution was then fed through a 12 L Hastelloy® tube heated to 150 °C at a rate which corresponds to a residence time of 2 hours, with a back pressure of 250 psi. The solution was collected into 50 gal stainless steel tanks on the other side of the tube and combined for work-up in batch.

The combined solution for one batch was transferred to a 250 gal stainless steel tank. The solution was heated to reflux at atmospheric pressure and concentrated from approximately 460 L to a total volume of 260 L (9.5 volumes based on the expected amount of **1**). To the solution was charged 150 L of IPA (5.6 volumes based on expected amount of **1**) and the solution was concentrated through atmospheric distillation to a total volume of 260 L. The solution temperature was lowered to a few degrees below the boiling point (approximately 65 °C) and to the heated solution was charged a slurry of **1** seed (250 g, 1 mol% of expected amount of **1**) in IPA (50 L, 1.9 volumes). To the slurry was charged IPA (100 L, 3.7

volumes) and the slurry was heated to reflux and concentrated to a total volume 260 L (9.5 volumes based on expected amount of **1**), representing the third distillation. To the slurry was charged IPA (100 L, 3.7 volumes) and the slurry was heated to reflux and concentrated to a total volume 260 L (9.5 volumes based on expected amount of **1**), representing the fourth distillation. To the slurry was charged IPA (100 L, 3.7 volumes) and the slurry was heated to reflux and concentrated to a total volume 260 L (9.5 volumes based on expected amount of **1**), representing the fifth distillation. To the slurry was charged IPA (100 L, 3.7 volumes) and the slurry was heated to reflux and concentrated to a total volume 250 L (9 volumes based on expected amount of **1**), representing the sixth and final distillation.[17]

The slurry was cooled to 23 °C, and the solid was collected by filtration. The wet cake was washed with IPA (110 L, 4 volumes based on expected amount of **1**). The wet cake was dried by vacuum at 55 °C for 6 hours to obtain **1** (26.7 kg, 48.2 mol, 94% yield) as a white solid.

ACKNOWLEDGEMENT: The authors thank David Myers and Cynthia Hammill for analytical support.

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[10] The discovery of this reaction was actually quite serendipitous as the reaction worked initially without additives. It was only found after going to subsequent batches of starting materials that trace metals were present in the original batch that helped catalyze the reaction and when they were no longer present, the reaction would not proceed.

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[12] The reaction is heated above the solvents boiling point, so back pressure must be applied to ensure the contents stay a liquid. The equipment used must be able to withstand pressures above those needed, in this case 250 psi.

[13] The reaction was one continuous feed from start to finish, but the product was worked up in 4 batches. In order to keep the reaction continuous, it is necessary that the work-up (solvent swap into

IPA/crystallization, filtration and drying) take less time than the following portion of the solution takes to flow through the tube, which was accomplished in this reaction.

[14] The small gaps are where the on-line HPLC system stopped working and is not indicative of poor quality.

[15] The PATROL system is developed by Waters Corporation (Milford, MA), www.waters.com.

[16] Obtained from Silicycle: www.silicycle.com.

[17] A THF-solvate and monohydrate form of **1** are known. The six distillations assure that only the desired non-solvated form is obtained while also increasing the yield.