ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Full Paper

Kumada-Corriu Heteroaryl Cross-Coupling for Synthesis of a Pharmaceutical Intermediate: Comparison of Batch Versus Continuous Reaction Modes

Xin Linghu, Nicholas Wong, Vera Jost, Serena Fantasia, C. Gregory Sowell, and Francis Gosselin

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00185 • Publication Date (Web): 28 Jun 2017

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Kumada-Corriu Heteroaryl Cross-Coupling for Synthesis of a Pharmaceutical Intermediate: Comparison of Batch Versus Continuous Reaction Modes

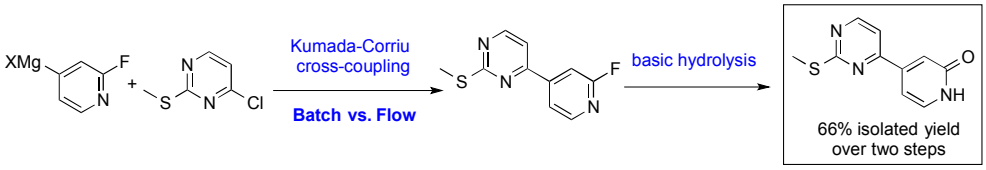
Xin Linghu,*[,†] Nicholas Wong,[†] Vera Jost,[‡] Serena Fantasia,[‡] C. Gregory Sowell,[†] and Francis Gosselin[†]

[†]**Department of** Small Molecule Process Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, United States
[‡]Process Research, F. Hoffmann-La Roche AG, Grenzacherstrasse 124, CH-4070 Basel, Switzerland

Corresponding Author
*E-mail: linghux@gene.com.

ORCID
Xin Linghu: 0000-0002-8095-3244

For Table of Contents Only



ABSTRACT

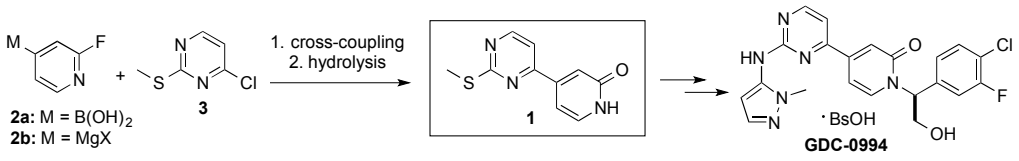
Pyridone **1**, a key intermediate in the preparation of ERK inhibitor GDC-0994, was synthesized via a cross coupling / hydrolysis sequence from commercially available starting materials. C–C bond formation was achieved via an efficient palladium catalyzed Kumada-Corriu cross-coupling reaction. However, the 4-pyridylmagnesium halide reagent generated *in situ* was found to be unstable at the reaction temperature, leading to inconsistent results on scale. In order to address process robustness issues associated with the cross-coupling reaction, we investigated both flow chemistry and a low temperature Kumada-Corriu coupling reaction. Finally, a basic hydrolysis process of 2-fluoropyridine was developed to avoid formation of toxic and corrosive hydrofluoric acid, resulting in a safe and scalable process towards **1**.

Keywords: 4-heteroarylpyridone, Kumada-Corriu cross-coupling, 4-pyridylmagnesium halide, hydrolysis of 2-fluoropyridine.

1. INTRODUCTION

A small molecule inhibitor, GDC-0994, targeting the extracellular-signal-regulated kinases (ERK) was recently discovered as a promising candidate to treat patients with locally advanced or metastatic solid tumors.[1,2] To support preclinical and clinical studies, we developed and reported an efficient asymmetric multi-kilogram scale synthesis of the target molecule (Scheme 1).[3,4] The key intermediate for this transformation was 4-heteroarylpyridone **1**. Herein, we describe the development of an efficient and scalable process towards **1** that relies on an efficient Kumada-Corriu cross coupling reaction.

Scheme 1. Key Transformation Towards GDC-0994



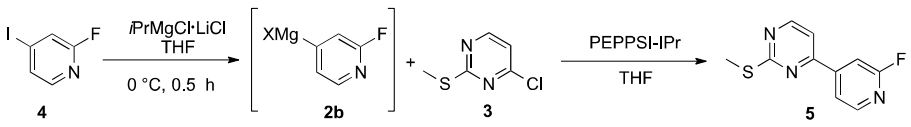
Pyridone **1** was initially synthesized via a cross-coupling / hydrolysis sequence. Aryl-aryl bond formation was achieved via a Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of **2a** and **3**. A lengthy and cumbersome Soxhlet extraction was required to ensure a good purity of **1**, which was found to be essential for a reasonable conversion in the subsequent S_N2 displacement reaction with a benzylic methanesulfonate.[5] When crude pyridone **1** was used directly in the S_N2 reaction, only 10% conversion was observed after refluxing in THF for 30 h. In contrast, pyridone **1**, purified by a 3-day Soxhlet extraction, gave 97% conversion under the same reaction conditions. We speculated that inorganic impurities could coordinate to the pyridone nitrogen and reduce its nucleophilicity, resulting in low conversions.[6] Although the conversion could be improved in high boiling-point solvents at elevated temperatures (>100 °C), we envisioned that an alternative coupling reaction could produce a high

quality intermediate and avoid the tedious purification or harsh reaction conditions. In addition, hydrofluoric acid formed under the acidic hydrolysis of 2-fluoropyridine **5** was disadvantageous for larger scale manufacturing, due to safety concerns and its highly corrosive properties toward glass-lined reactors. Due to those process issues for manufacturing, research efforts were initiated to identify an alternative route.

2. DISCUSSION AND RESULTS

High Temperature Kumada-Corriu Approach. Based on the lack of highly sensitive functional groups in the target molecule, we surmised that a metal catalyzed Kumada-Corriu cross coupling reaction could allow access to **5** (Scheme 2).[7] The 4-pyridylmagnesium halide reagent **2b** was generated through a halogen–metal exchange using iPrMgCl•LiCl in THF.[8] The Kumada-Corriu cross coupling reaction was then performed by introducing **2b** into a mixture of 2-chloropyrimidine **3** and a selected catalyst in THF. A brief catalyst screen indicated that the Pd-catalyzed cross-coupling reactions gave better conversions and cleaner reaction profiles when compared with other transition metal catalysts.[9] The screen revealed PEPPSI-IPr[10,11] as an efficient catalyst for the Kumada-Corriu cross coupling reaction, allowing us to focus on this catalyst system for further process optimization.[12]

Scheme 2. Kumada-Corriu Cross Coupling Reaction



It has been demonstrated that temperature has a significant impact on the reaction rate and yields of PEPPSI-IPr-catalyzed Kumada-Corriu cross coupling reactions.[6c] We therefore embarked on an investigation of temperature effects on this transformation. The

4-pyridylmagnesium halide reagent **2b** was generated at 0 °C and introduced to a mixture of **3** and 1 mol% PEPPSI-IPr in THF at different temperatures. The reaction plateaued at 80% conversion when the entire sequence was conducted at 25 °C (Table 1, entry 1). The conversion was improved and a 65% HPLC assay yield of **5** was obtained when the reaction was warmed to 60 °C over 10 min (entry 2). While assay yields remained modest with **2b** charged and held at lower temperatures (entry 3 and 4), an 81% HPLC assay yield of **5** was obtained when **2b** was charged to a 60 °C mixture of **3** and PEPPSI-IPr catalyst (entry 5). A further increase of the reaction temperature using 2-MeTHF as a solvent resulted in a complex reaction profile and a decreased HPLC assay yield (entry 6).

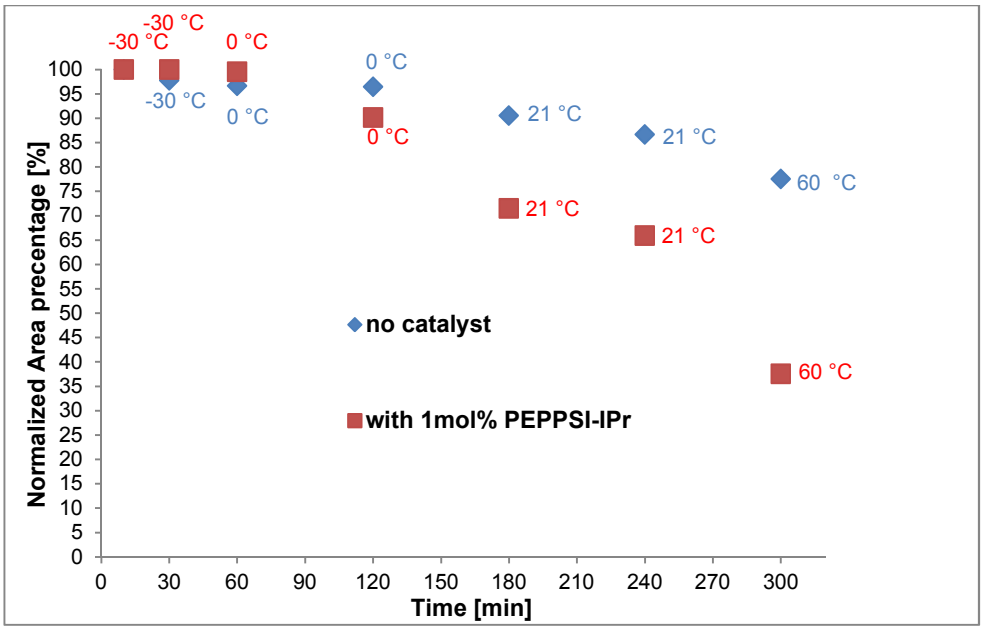
Table 1: Temperature Effect on Kumada-Corriu Cross Coupling[b,c]

entry	temperature (°C)[a]	solvent	% conversion of **3**	% HPLC assay yield of **5**
1	25	THF	80	-
2	25 → 60[d]	THF	95	65
3	40	THF	91	53
4	50	THF	98	64
5	60	THF	100	81
6	70	2-MeTHF	100	70

[a] Temperature of the reaction solution when **2b** was introduced. [b] Reaction conditions: PEPPSI-IPr (0.05 mmol, 1 mol%), **3** (5 mmol, 100 mol%), **4** (6 mmol, 120 mol%), *i*PrMgCl•LiCl (6.3 mmol, 125 mol%, 1.3 M in THF); at the indicated temperature for 8 h. [c] Reaction was monitored by HPLC analysis. [d] **2b** was introduced to the reaction solution at 25 °C and then the temperature was increased to 60 °C in 10 min.

The application of pyridyl organometallic reagents in cross-coupling reactions remains limited due to their unstable nature.[13] We suspected that the temperature dependence of the Kumada-Corriu cross-coupling reaction of **2b** could be attributed to a similar stability issue. To further understand the temperature effect on the reaction yield, a study was performed to evaluate the stability of the 4-pyridylmagnesium halide reagent **2b** over time at different temperatures. As illustrated in Figure 1, **2b** in THF was stable at −30 °C and 0 °C in the absence of catalysts. Approximately 10% decomposition was observed when the solution was warmed to 21 °C. The Grignard reagent further decomposed when the solution was warmed to 60 °C. In the presence of Pd catalyst, **2b** was unstable even at 0 °C and decomposed at an increased rate at 21 °C. Over 50% degradation was observed at 60 °C. Those results seemed contradictory to the data in Table 1. We speculated that reaction kinetics of the desired cross-coupling pathway should be more temperature-dependent than that of the undesired degradation of **2b**. As a result, the degradation data in Figure 1 can be reconciled with the data in Table 1 by considering that the rate of desired reaction was greater than the rate of degradation at higher reaction temperatures.

Figure 1. Stability of 4-Pyridylmagnesium Halide **2b** in THF.[a]



[a] Stability data was obtained by HPLC analysis with 1,3,5-trimethoxybenzene as an internal standard[14]

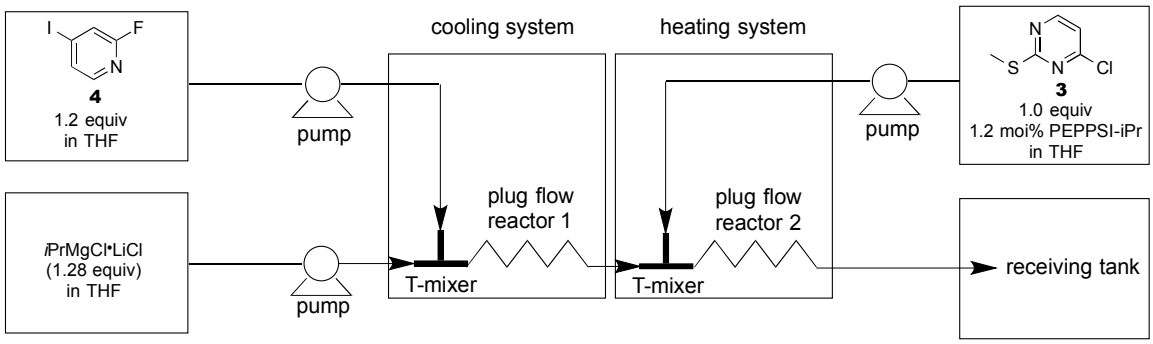
The high temperature Kumada-Corriu cross-coupling process was reproducible on gram scale in the laboratory and consistently gave 75-80% yields of **5**. The same process was performed well during the first scale-up in the kilo-lab, producing 2 kg of **5** in 77% HPLC assay yield and 76A% HPLC purity. However, in the first 30 kg scale demonstration, the reaction failed to reach completion and a 61% HPLC assay yield of **5** was obtained. The reaction efficiency dropped further on 40 kg scale and only a 40% HPLC assay yield of **5** was obtained. We attributed the fluctuations in the reaction performance to the labile nature of the organometallic reagent and the longer processing times on scale that resulted in a significant decomposition of the 4-pyridylmagnesium halide reagent and incomplete reactions.

In order to address scalability issues associated with the Kumada-Corriu cross coupling reaction, we investigated flow chemistry for both halogen–metal exchange and cross coupling steps. Meanwhile, we also conducted an extensive screen of reaction

conditions to identify an efficient catalyst, allowing the Kumada-Corriu cross coupling reaction to be performed consistently in a batch mode.

Development of a Continuous Flow Process. We identified flow chemistry as a first solution to avoid extensive exposure of the sensitive 4-pyridylmagnesium halide reagent at elevated temperatures.[15] A continuous flow process could potentially address the Grignard stability concerns as it allows for the enhanced control of process parameters such as mixing, residence time, and local reaction temperature when compared to batch mode.[16] To improve the manufacturing robustness of the Kumada-Corriu cross coupling reaction we designed and installed a tandem continuous flow process system (Figure 2). For the halogen–metal exchange step, a THF solution of **4** and *i*PrMgCl•LiCl were pre-cooled in a coiled tube. The streams of both solutions merged in the first static mixer and passed through the flow reactor in a cooling flow unit, facilitating the halogen–metal exchange at low temperature. The cross coupling reaction occurred in the subsequent heating flow unit, where a pre-heated THF solution of **3** and the PEPPSI-IPr catalyst was combined with the cooled 4-pyridylmagnesium halide reagent, leading to formation of **5**. Finally, the reaction solution was collected and quenched in a receiving tank.

Figure 2. Continuous Flow Process Diagram of Generation of 4-Pyridylmagnesium Halide and Kumada-Corriu Reaction.



The flow process parameters were optimized based on the batch mode reaction conditions.[17] After screening the reaction temperature and the residence time, it was identified that halogen–metal exchange can be completed in a 12 min residence time at −5 °C. The optimal conditions for the Kumada-Corriu cross-coupling reaction in the heated unit were found to be a 14 min residence time at 60-65 °C. Over the course of evaluating reaction temperature, we observed gas generation in the second reactor, as the reaction temperature was nearly the boiling point of the reaction solvent THF. The bubble formed in the coiled tube would presumably lead to an uncontrolled residence time and inconsistent mixing. In order to suppress off-gassing in the tube reactor, a back-pressure valve (5 psi) was mounted at the collector.

The tandem continuous flow process system was then demonstrated on multiple 40 g scale runs. An average 78% HPLC assay yield of **5** was obtained with a ~80A% crude HPLC purity, similar to the batch mode on 2 kg scale. Finally, the process robustness on larger scale and longer processing time was demonstrated. The tandem flow process was performed on 20 kg scale of **3** continuously for 46 h at an average throughput of 0.49 kg product/h. During this run, a total of 22 kg of the cross-coupling product was generated in 82% HPLC assay yield and 79A% HPLC purity.

Low-temperature Kumada-Corriu Approach. In parallel to the research effort on the design and development of a continuous Kumada-Corriu reaction, we also investigated alternative catalyst systems to address the scalability issue caused by the degradation of **2b**. We aimed for a more efficient catalyst that could facilitate the Kumada-Corriu cross-coupling reaction at a lower temperature, offering greater stability of the 4-pyridylmagnesium halide reagent over the course of the reaction.[18,19]

Based on the aforementioned stability studies, a comprehensive microscale, high-throughput screen of transition metals, readily available ligands and pre-catalysts was performed at ambient temperature. Pd-based catalysts were superior to other transition metal catalysts providing cleaner reaction profiles and higher conversions.[20] A selection of results is summarized in Table 2.[11] Among electron-rich ligands, Xantphos demonstrated a high efficiency and resulted in full conversion but a modest yield (Table 2, entry 4). While Xantphos-Pd-G2 pre-catalyst afforded 80% HPLC assay yield of **5** at 1 mol% catalyst loading (entry 5), we observed diminished performance at lower loadings presumably owing to the catalyst inhibition by the carbazole byproduct formed in the reductive elimination leading to active Pd catalyst (entry 6).[21] This issue was addressed with employing the newer generation of XantPhos-Pd-G4 or the corresponding π-allyl pre-catalysts (entries 7 and 8). The temperature studies indicated the reaction conversion dropped when the Grignard reagent was charged below 10 °C. With the optimal conditions in hand, the low temperature Kumada-Corriu cross coupling reaction was demonstrated on preparative scale with 0.5 mol% Xantphos π-allyl pre-catalyst. The reaction generated the desired product in 82% HPLC assay yield of **5**, 75A% HPLC purity, a similar profile as the continuous flow process.

Table 2: Palladium Catalyst Screen of Kumada-Corriu Cross-Coupling[a,b]

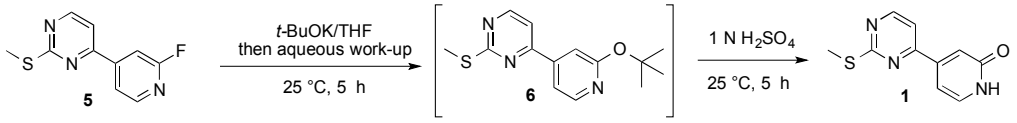
entry	catalyst	catalyst loading (mol%)	reaction time (h)	% conversion of **3**	A% HPLC assay yield of **5**
1	Pd(π -cinnamyl)Cl/ DPEPhos	1.0	20	85	45
2	Pd(π -cinnamyl)Cl/ DavePhos	1.0	20	96	60
3	Pd(π -cinnamyl)Cl/ RuPhos	1.0	20	90	59
4	Pd(π -cinnamyl)Cl/ XantPhos	1.0	20	99	61
5	XantPhos-Pd-G2	1.0	1	>99	80
6	XantPhos-Pd-G2	0.5	1	58	-
7	XantPhos-Pd-G4	0.5	1	98	78
8	XantPhosPd(π -allyl)Cl	0.5	1	>99	82

[a] Reaction conditions: **3** (5 mmol, 100 mol%), **4** (6 mmol, 120 mol%), *i*PrMgCl•LiCl (6.3 mmol, 125 mol%, 1.3 M in THF) at 25 °C for the indicated reaction time. [b]Reaction was monitored by HPLC analysis

Hydrolysis of 2-Fluoropyridine under Basic Conditions. Hydrofluoric acid presumably forms in the hydrolysis of fluoropyridine **5** under acidic conditions.[22] The generation of HF was regarded as a disadvantage for large scale manufacturing, due to safety concerns and its highly corrosive properties toward glass-lined reactors. We investigated other conditions to effect the transformation of 2-fluoropyridine **5** to

pyridone **1**, avoiding a direct acidic media.[23] We found that the S_NAr displacement of 2-fluoropyridine **5** with potassium *t*-butoxide was performed smoothly under mild reaction conditions (Scheme 3). Upon completion of the S_NAr displacement, the reaction was worked up using aqueous $NaHCO_3$ to remove fluoride. Upon treatment with 1N aqueous H_2SO_4, the *t*-butyl ether **6** was hydrolyzed to pyridone **1** in 80-85% yields.[24]

Scheme 3. Two-Step Hydrolysis Through-Process



Pyridone is amphoteric, reacting with acids to form a pyridinium salt or with bases to form a pyridonide salt.[25] Both salt forms of **1** had reasonable solubility in water. The mass recovery of **1** after aqueous work-up was found to be fairly low if the pH was not properly adjusted to account for the amphoteric nature of the molecule. The isoelectric point for **1** in water was determined to be 10.5, which allowed us to maximize isolated yields. To take advantage of the amphoteric feature of **1**, an acidic / basic work-up process was introduced prior to an accurate pH adjustment to purge impurities generated in the cross-coupling and hydrolysis steps. As a result, pyridone **1** was obtained in 66% isolated yield and 96.2A% HPLC purity over two steps. The high quality material produced from this process ensured a consistent and high yielding S_N2 reaction in the downstream chemistry to GDC-0994 API.

3. CONCLUSION

In summary, an efficient and robust synthetic route to the key intermediate pyridone **1** was developed and demonstrated on multiple kilogram-scale batches. An improved synthesis of pyridone **1** was achieved via a practical Pd-catalyzed Kumada-Corriu cross-

coupling reaction followed by hydrolysis of 2-fluoropyridine intermediate **5**. The scalability issue caused by the unstable 4-pyridylmagnesium halide reagent in the cross-coupling reaction was addressed by the development of two complementary solutions. A first solution was based on a continuous flow process for generation of the organomagnesium reagent and the subsequent cross-coupling reaction. Alternatively, a second solution involved the identification of a low-temperature Kumada-Corriu coupling reaction through improved Pd catalysis. Finally, hydrolysis of 2-fluoropyridine intermediate **5** under basic conditions avoided formation of toxic and corrosive hydrofluoric acid and produced pyridone **1** with a high quality. As a result, the robust and efficient access to the key intermediate pyridine **1** ensured a sustainable process to supply GDC-0994 for the clinical studies.

4. EXPERIMENTAL SECTION

General. All commercially available reagents and solvents, including anhydrous solvents, were used without further purification. Assay yields were obtained using analytical standards prepared by recrystallization or preparative chromatography. All isolated yields reflect correction for purity based on HPLC or quantitative NMR assays. The melting points were measured by a Differential Scanning Calorimetry (DSC) and the onset temperatures were reported. ^{1}H and ^{13}C NMR spectra were recorded at room temperature (RT) on a 400 MHz Bruker spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm) relative to the corresponding deuterated solvent peak. HPLC analyses were conducted on an Agilent 1200 series (Agilent Zorbax SB-Phenyl column (150 x 4.6 mm, 3.5 μ m); and mobile-phase gradients consisting of 0.05% TFA in water

and 0.05% TFA in acetonitrile) or (Waters Xbridge Phenyl column (150 x 4.6 mm, 3.5 μ m); and mobile-phase gradients consisting of 0.05% TFA in water and 0.05% TFA in acetonitrile). Analytical characterizations were obtained on materials that were representative or purified for that purpose.

4-(2-Fluoropyridin-4-yl)-2-(methylthio)pyrimidine (5): High Temperature Kumada-Corriu Batch Mode Cross-Coupling Reaction. To a 50 L reactor was charged 2-fluoro-4-iodopyridine **4** (3.60 kg, 16 mol, 1.23 equiv.) and anhydrous THF (9.0 kg). The reaction mixture was stirred for 10 min at 20-30 °C. After the reaction mixture was cooled to −30 °C under N_2, *i*PrMgCl•LiCl (13.2 kg, 16.7 mol, 1.28 equiv., 1.3M in THF) was added dropwise at −10 °C. The reaction was stirred at the same temperature for 2 h. Another 50 L reactor was charged with 4-chloro-2-methylthiopyrimidine **3** (2.0 kg. 13 mol, 1.0 equiv.), anhydrous THF (9.0 kg) and PEPPSI-IPr catalyst (90 g, 0.13 mol, 1.0 mol%). The reactor was degassed 3× with vacuum / N_2 and heated to 50-60 °C. To the mixture was added the Grignard reagent generated in the first reactor over 0.5 h. The resulting reaction solution was stirred at 50-60 °C for 2 h. After the mixture was cooled to 25 °C, the reaction was quenched by water (12.0 kg). The pH of the mixture was adjusted to 8-9 by adding solid citric acid monohydrate (0.5 kg). The organic layer was separated and crude **5** was obtained as a THF solution (32.5 kg, 6.5wt%, 77% HPLC assay yield, 76A% HPLC purity). The THF solution was concentrated and then solvent-switched to iPAc to give 8 total volume of solution at 40-50 °C under a reduced pressure to reach residual THF ≤10wt%. After water (18 kg) was added, the mixture was filtered through a pad of Celite (0.5 kg). The organic layer was separated and used directly to the next step without further purification: mp 98.9 °C; ^{1}H NMR (400MHz, DMSO-d_6): 8.82

(d, 1H J = 5.6 Hz), 8.43 (d, 1H J = 5.2 Hz), 8.07 (m, 1H), 7.93 (d, 1H, J = 5.6 Hz), 7.88 (s, 1H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 172.20, 164.06 (d, J = 234 Hz), 159.46, 149.04 (d, J = 8.4 Hz), 148.79 (d, J = 15.1Hz). 119.38 (d, J = 4.1 Hz), 113.40, 107.16 (d, J = 39.7 Hz), 13.64. HRMS calcd for $C_{10}H_8FN_3S$ [M + H] 222.0501, found 222.0495.

4-(2-Fluoropyridin-4-yl)-2-(methylthio)pyrimidine (5): High Temperature Kumada-Corriu Continuous Flow Cross-Coupling Reaction. To the first reactor was charged 2-fluoro-4-iodopyridine **4** (34.5 kg, 154 mol, 1.24 equiv.) and anhydrous THF (88 kg). The mixture was stirred for 30 min at 20-30 °C to obtain a clear solution. To the second reactor was charged 4-chloro-2-methylthiopyrimidine **3** (20 kg, 124 mol, 1.0 equiv.), PEPPSI-IPr catalyst (1.0 kg, 1.47 mol, 1.19 mol%) and THF (88 kg). Both reactors were degassed 3× with vacuum / N_2. The flow reactor was set up according to Figure 2 and the equipment parameters (Tables 4 and 5 in the Supporting Information). The solution in the first reactor (48 mL/min) and *i*PrMgCl•LiCl solution (119.55 Kg, 149 mol, 1.19 equiv.) (55 mL/min) were pumped into the first reaction tubing at −5 to −10 °C. The solution in the second reactor (50 mL/min) was pumped into the second reaction tubing to mix with the flow coming from the first reaction tubing at 60 to 65 °C. The reaction was quenched with 3.2% citric acid aqueous solution (112.5 Kg) at 25 °C. The organic layer was separated and crude **5** was afforded as a THF solution (294.3 kg, 7.7wt%, 82% HPLC assay yield, 79A% HPLC purity). The THF solution was concentrated and then solvent-switched to iPAc to give 8 total volume of solution at 40-50 °C under a reduced pressure. Residual THF was below 10wt%. After water (180 kg) was added, the mixture

was filtered through a pad of Celite (5 kg). The organic layer was separated and used directly to the next step without further purification.

4-(2-Fluoropyridin-4-yl)-2-(methylthio)pyrimidine (5): Low Temperature Kumada-Corriu Batch Mode Cross-Coupling Reaction. To a 250 mL round bottom flask was charged 2-fluoro-4-iodopyridine **4** (7.22 g, 32.4 mmol, 1.3 equiv.) and anhydrous THF (20 mL). The mixture was degassed 3× with vacuum / N_2. To the resulting solution was added *i*PrMgCl•LiCl (25.5 g, 34.9 mmol, 1.4 equiv., 1.3 M in THF) dropwise over 30 min at −10 to 0 °C. The reaction was stirred at the same temperature for 45 min to result in a complete halogen-metal exchange based on HPLC analysis. To another 250 mL round bottom flask was charged XantPhosPd(π -allyl)Cl (94.8 mg, 0.127 mmol, 0.5 mol%) 4-chloro-2-methylthiopyrimidine **3** (4.0 g, 24.9 mmol, 1.0 equiv.) and anhydrous THF (20 mL). The mixture was degassed 3× with vacuum / N_2. To the resulting solution was charged the 4-pyridylmagnesium halide solution at 10 °C in 30 min. The internal temperature of the reaction was kept < 25 °C. After addition, the reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction was cooled to 15 °C and quenched with water (40 mL). The pH of the mixture was adjusted to 7–8 by adding citric acid monohydrate (360 mg). The organic layer was extracted and washed 2× with brine (40 mL). A crude THF solution was obtained (75A% HPLC purity and 80% HPLC assay yield).

4-(2-(Methylthio)pyrimidin-4-yl)pyridin-2(1*H*)-one (1). The solution of **5** (42.8 kg, 194 mol, 1.0 equiv.) in iPAc was concentrated in vacuo below 50 °C and then solvent-switched to THF (10 total volume). Solid potassium *tert*-butoxide (34.8 kg, 311 mol, 1.6 equiv.) was added in several portions at 15-25 °C. The mixture was warmed to 25 °C for

5 h. Solid $NaHCO_3$ (16.0 kg) was charged at 25 °C. After stirring for 30 min, 5wt% aqueous Na_2SO_4 (353.0 kg) was added to the reaction mixture. After the organic layer was separated, to the resulting THF solution was charged 1N aqueous H_2SO_4 solution (336 kg) at 15-30 °C. The mixture was stirred at 20-30 °C for 4.5 h and then adjusted to pH 7 with addition of 30wt% aqueous NaOH solution (126.0 kg) at 15-30 °C. After MTBE (300 kg) was charged, the reaction solution was adjusted to pH 14 with 30% NaOH aqueous solution (147 kg) at 20-30 °C. The aqueous layer was separated and washed with MTBE (2 × 300 kg). To the aqueous solution were charged 2-MeTHF (472 kg) and THF (475 kg) and adjusted to pH 10.40-10.60 with concentrated HCl (79.6 kg). The organic layer was separated and the aqueous layer was extracted with a mixture of 2-MeTHF (231 kg) and THF (231 kg), while maintaining pH 10.40-10.60 (30wt% aqueous NaOH solution to adjust pH, if necessary). The organic layer was separated and the aqueous layer was extracted again with a mixture of 2-MeTHF (231 kg) and THF (231 kg). The organic solutions were combined and washed with 5wt% aqueous Na_2SO_4 solution (168 kg). The organic solution was concentrated to ~100 L. The batch was solvent-switched to 2-MeTHF (210 kg) and then to MTBE (210 kg), resulting in precipitation of **1**. The crude **1** was filtered and dried in vacuo for 12 h at 50-55 °C. The crude product was then slurried in 2-MeTHF (125 kg) and MTBE (240 kg) at 50-55 °C for 5 h. The slurry was cooled to 0-10 °C over 5 h and stirred at the same temperature for 3 h. The solid was filtered and dried in vacuo at 50-55 °C for 12 h to afford **1** as a brown solid (36.6 kg, 96.2A% HPLC purity, 83% yield): mp 197.9 °C; ^{1}H NMR (400MHz, DMSO-d_6): 8.82 (d, J = 5.6 Hz, 1H), 8.43 (d, J = 5.2 Hz, 1H), 8.07 (m, 1H), 7.93 (d, J = 5.6 Hz, 1H), 7.88 (s, 1H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.85, 162.57,

160.71, 159.09, 147.37, 136.35, 118.26, 113.30, 102.38, 13.61. HRMS calcd for $C_{10}H_9N_3OS$ [M + H] 220.0545, found 220.0538.

ASSOCIATED CONTENT:

Supporting Information:
The Supporting Information is available free of charge on the ACS Publications website: Effect of purity of **1** on S_N2 reactivity; Level of inorganic residues before and after Soxhlet extraction; Structures of catalysts, Initial and extensive catalyst screen of Kumada-Corriu cross coupling; Continuous flow process information; and ^1H and ^{13}C data of compound **1** and **5**.

AUTHOR INFORMATION:

Corresponding Author
*E-mail: linghux@gene.com.
ORCID
Xin Linghu: 0000-0002-8095-3244

ACKNOWLEDGMENTS:

We would like to thank Dr. Shengli Ma, Dr. C.J. Venkatramani, Ms. Tina Nguyen and Ms. Ila Patel for analytical support, and Mr. Colin Masui for high-throughput screening of cross-coupling reactions.

REFERENCE:

(1) Blake, J. F.; Chicarelli, M. J.; Garrey, R. F.; Gaudino, J.; Grina, J.; Moreno, D. A.; Mohr, P. J.; Ren, L.; Schwarz, J.; Chen, H.; Robarge, K.; Zhou, A., **2013**, WO2013130976A1.
(2) Ren, L.; Grina, J.; Moreno, D.; Blake, J. F.; Gaudino, J. J.; Garrey, R.; Metcalf, A. T.; Burkard, M.; Martinson, M.; Rasor, K.; Chen, H.; Dean, B.; Gould, S. E.; Pacheco, P.; Shahidi-Latham, S.; Yin, J.; West, K.; Wang, W.; Moffat, J. G.; Schwarz, J. B. *J Med Chem* **2015**, *58*, 1976.
(3) Linghu, X.; Wong, N.; Iding, H.; Jost, V.; Zhang, H.; Koenig, S. G.; Sowell, C. G.; Gosselin, F. *Org. Process Res. Dev.* **2017**, *21*, 387.
(4) Linghu, X.; Chestakova, A.; Gu, W.; Iding, H.; Li, J.; Lin, J.; Meier, P.; Sha, C.; Stults, J.; Wang, Y.; Zhang, H.; Zhang, J.; Zhang, T., **2017**, US2017/22183.
(5) Results of purity effect of **1** on S_N2 reactivity are summarized in Table S1 in the Supporting Information.
(6) The content of inorganic residues before and after the Soxhlet extraction was examined by the inductively coupled plasma atomic emission spectroscopy (ICP-AES). The results are summarized in Table 2 in the Supporting Information.

(7) For recent reports on Pd, Ni or Fe catalyzed Kumada coupling, see: (a) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162. (b) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844. (c) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem. – Eur. J.* **2007**, *13*, 150. (d) Guo, W.-J.; Wang, Z.-X. *J. Org. Chem.* **2013**, *78*, 1054. (e) Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 9590. (f) Ghosh, R.; Sarkar, A. *J. Org. Chem.* **2010**, *75*, 8283. (g) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844.
(8) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
(9) Results of initial catalyst screen were summarized in Table S3 in the Supporting Information.
(10) PEPPSI = pyridine-enhanced precatalyst preparation, stabilization and initiation; IPr = diisopropyl-phenylimidazolium derivative. For the reference, see *Chem. Eur. J.* **2006**, *12*, 4749.
(11) The structures of catalysts are included in Figure S1 in the Supporting Information.
(12) Kantchev, E.; O'Brien, C.; Organ, M. *ChemFiles*, **2006**, *6*, 1–9; Catalysis: PEPPSITM Catalyst.
(13) (a) Wang, X.-j.; Xu, Y.; Zhang, L.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3141. (b) Lennox, A. J. J.; Lloyd-Jones, G. C. *Isr. J. Chem.* **2010**, *50*, 664. (c) Ackermann, L.; Potukuchi, H. K.; Kapdi, A. R.; Schulzke, C. *Chem. – Eur. J.* **2010**, *16*, 3300. (d) Colombe, J. R.; Bernhardt, S.; Stathakis, C.; Buchwald, S. L.; Knochel, P. *Org. Lett.* **2013**, *15*, 5754. (e) Chen, X.; Zhou, L.; Li, Y.; Xie, T.; Zhou, S. *J. Org. Chem.* **2014**, *79*, 230.
(14) HPLC samples of the magnesium / halogen exchange reaction were prepared by quenching the sample with 0.5wt% aqueous TFA solution. Peaks of internal standard, 1,3,5-trimethoxybenzene and the quenched 4-pyridyl magnesium halide were integrated. The first HPLC sample was collected at 5 min after the magnesium / halogen exchange was completed and its normalized area percentage was set as 100%. Normalized area percentage at different time points was calculated based the following equation: Normalized area percentage = (Area $(FP)_t$)/(Area $(TMB)_t$)×(Area $(TMB)_{t=5\ min}$)/(Area $(FP)_{t=5min}$)×100%, where FP is 2-fluoropyridine; TMB is 1,3,5-trimethoxybenzene.
(15) For a review of cross-coupling in flow mode, see: Noel, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, *40*, 5010.
(16) For recent reviews and applications of flow chemistry, see: (a) Wirth, T. Microreactors in Organic Synthesis and Catalysis, 2nd ed.; Wiley-VCH: Weinheim, **2013**. (b) Darvas, F.; Hessel, V.; Dorman, G. Flow Chemistry; De Gruyter: Berlin, **2014**. (c) Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process Res. Dev.* **2016**, *20*, 2. (d) Laue, S.; Haverkamp, V.; Mleczko, L. *Org. Process Res. Dev.* **2016**, *20*, 480.
(17) Key process parameters of continuous flow proecess were summarized in Table S4 and S5 in the Supporting Information.
(18) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844.
(19) Xi, Z.; Liu, B.; Chen, W. *J. Org. Chem.* **2008**, *73*, 3954.
(20) Results of extensive catalyst screens were summarized in Figure S2 and S3 in the Supporting Information.
(21) DeAngelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J. *J. Org. Chem.* **2015**, *80*, 6794.

(22) Bradlow, H. L.; Vanderwerf, C. A. *J. Org. Chem.* **1949**, *14*, 509.
(23) (a) Gerasyuto, A. I.; Arnold, M. A.; Chen, G.; Karp, G. M.; Qi, H.; Turpoff, A. A.; Wang, J.; Woll, M. G.; Branstrom, A. A.; Narasimhan, J.; Dumble, M. L.; Hedrick, J.; Weetall, M. L., **2016**, WO2016/109706. (b) Clark, J. D.; Davis, J. M.; Favor, D.; Fay, L. K.; Franklin, L.; Henegar, K. E.; Johnson, D. S.; Nichelson, B. J.; Ou, L.; Repine, J. T.; Walters, M. A.; White, A. D.; Zhu, Z., **2005**, US2005/43309.
(24) Direct hydrolysis of **5** under basic aqueous conditions was also attempted. The reaction profile was not as clean as the two-step sequence. In addition, due to its amphoteric nature, pyridone **1** has high solubility in a basic aqueous solution. Fluoride cannot be removed by an acid / basic workup before neutralization and precipitation.
(25) Forlani L.; Cristoni G.; Boga C.; Todesco P. E.; Del Vecchio E.; Selva S.; Monari M. *Arkivoc.* **2002**, XI: 198.