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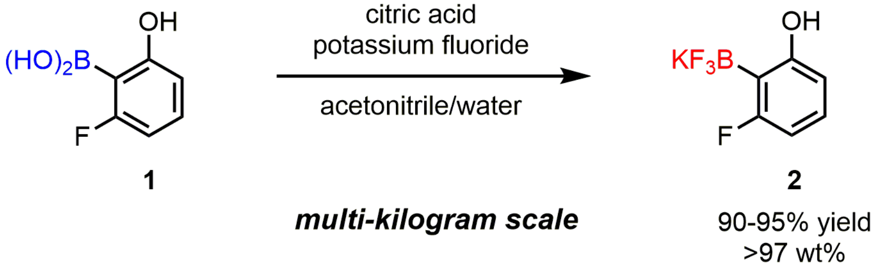
OH
(HO)2B
F
1
citric acid
potassium fluoride
acetonitrile/water
multi-kilogram scale
OH
KF3B
F
2
90-95% yield
>97 wt%

Process Development and Manufacture of Potassium 2-Fluoro-6-hydroxyphenyltrifluoroborate

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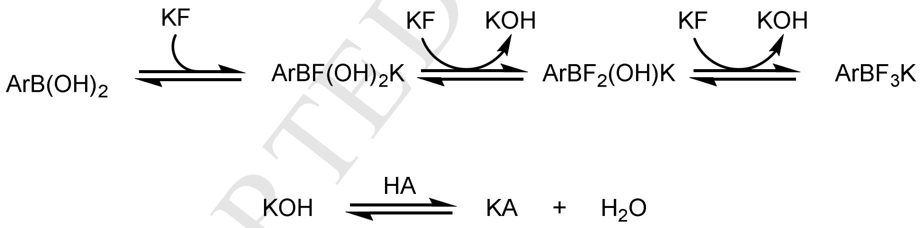
Abstract:

The development of a phase-appropriate manufacturing-scale synthesis of potassium 2-fluoro-6-hydroxyphenyltrifluoroborate was achieved. Investigations into improving the yield and robustness indicated that pH of the reaction medium is a critical process parameter. Additional development resulted in replacing tartaric acid with citric acid, resulting in improved process robustness and enabling scale-up to >10 kg.

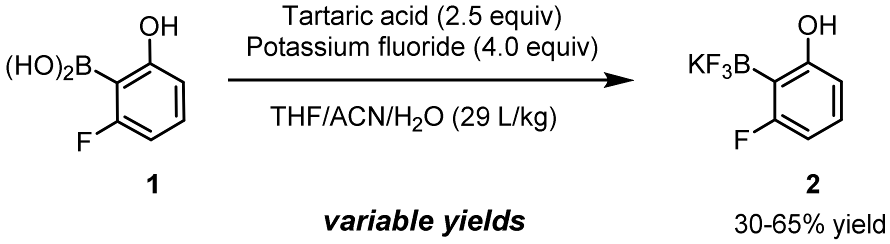
Introduction

Since the discovery of the Suzuki-Miyaura coupling (SMC),[1,2] significant research efforts have focused on designing catalyst systems that improve the efficiency of coupling unstable boronic acids[3] (typically heterocyclic[4] or polyfluorinated[5] arenes). Further improvements to the SMC were realized with the development of stable boron reagents,[6] which are resistant to non-productive decomposition during the reaction[7]. Over the past two decades, potassium organotrifluoroborate (BF_3K) salts have emerged as an attractive alternative to boronic acid/ester reagents due to their improved stability and high performance in the SMC.[8,9] BF_3K salts are typically prepared by the reaction of the corresponding boronic acid or esters with 4-6 equivalents of KHF_2.[1011] One disadvantage of this method is that the reaction conditions are corrosive and can result in reactor etching. Though this method is suitable for lab scale synthesis, to the best of our knowledge there have been no reports of large-scale batch production.[12] Recently, Lennox and Lloyd-Jones[13] reported a protocol for conversion of boronic acids to BF_3K salts using potassium fluoride and acetic/tartaric acid, resulting in improved processability and throughput of potassium organotrifluoroborate salt preparation. Scheme 1 depicts the mechanism of trifluoroborate generation using this protocol (Scheme 1).



Scheme 1: Mechanistic proposal for the preparation of aryl trifluoroborates from boronic acids using KF/acid (adapted from reference)[13]

Herein we report the development and implementation of a modified Lennox/Lloyd-Jones protocol for the manufacture of potassium 2-fluoro-5-hydroxyphenyltrifluoroborate **2**. The present studies involve a discussion of process development activities and investigations aimed towards improving the yield and robustness to enable implementation on multi-kilogram production scale.



Scheme 2: Synthesis of potassium 2-fluoro-5-hydroxyphenyltrifluoroborate (**2**) using tartaric acid

Results and Discussion

The discovery preparation of **2** utilized tartaric acid (2.5 equiv) and potassium fluoride (4.0 equiv) in 39 L/kg of solvent (CH_3CN:THF:H_2O = 50:25:3). Upon reaction completion, the mixture was filtered and concentrated to a minimum volume under vacuum at < 30 °C followed by crystallization from isopropanol. After a 2nd crop crystallization, **2** was isolated in 80% yield and 70% wt/wt assay by quantitative ^{1}H NMR.

Due to the aggressive timeline for this program, the initial multi-kilo delivery implemented a modified discovery process that was optimized to reduce solvent volumes. The overall reaction volume was decreased by reducing the acetonitrile charge from 25 to 15 L/kg (29 overall L/kg **1**). A final reslurry in isopropanol was also implemented to improve product potency. Using this protocol, multiple < 1 kg batches were executed to deliver 4 kg of **2,** with yields ranging between 65-70% and wt/wt potencies of > 90%. Further reduction of solvent quantities resulted in generation of an oily reaction mass instead of the desired free-flowing slurry. Furthermore, attempts to use fewer equivalents of tartaric acid and potassium fluoride resulted in incomplete conversion. With additional material required to support the program, efforts were focused on further development and characterization to improve process robustness for larger scale deliveries. The scale increase also prompted safety and thermal hazard evaluations prior to manufacture on pilot plant scale.[14] For subsequent batches, a Hastelloy reactor was utilized due to etching that occurred during when using glass reactors, suggesting the generation of hydrofluoric acid occurs during the process. Two batches were conducted with 2.0 kg and 2.8 kg input of 2-fluoro-6-hydroxyboronic acid. The first batch yielded 1.88 kg (65%) of **2** with an assay (potency) of 94 wt% by qNMR, which is within the expected range. However, the yield of the second batch (2.8 kg scale) was only 1.5 kg with a potency of 86 wt%. An additional purification (methanol reslurry) was implemented to meet the specifications, resulting in additional liquor loss and a final yield of

1.1 kg (31.5%). Analysis of the mother liquor indicated the presence of 3-fluorophenol, suggesting decomposition of the starting material or product had occurred. Additional optimization resulted in increased lab-scale yield to > 80%, however similar results on > 2.0 kg scale were observed, prompting a more detailed investigation.

Investigations on the low yield batches

To achieve a better understanding of the process and parameters that may be resulting in 3-fluorophenol generation, several different factors were considered:

1. pH and water content: The pH of the reaction mixture was monitored throughout the process during lab and production batches. It was observed that the pH of production batches were more acidic, ranging from 1.5–2.5 while development batches ranged from 4–5.5. It was also observed that water content in the mother liquor from production batches were also higher than the lab batches.
2. Equipment: The reactor used for these batches was 600 L Hastelloy vessel where the occupancy was only 16% during the concentration of the filtrate. Occupancy during development batches was always >70% during this operation.
3. Addition rates: Total time for the tartaric acid addition during production was 3.5 times longer than in lab batches

With the information from the investigation report, downscaling experiments were performed to mimic the exact plant conditions (e.g. longer addition times, lower pH) to identify the root cause for 3-fluorophenol generation observed during the 2.8 kg batch.

Mitigation strategy for the pilot plant-batches

The reaction mixture containing **1** and potassium fluoride is basic, with the reaction only proceeding upon acidification via tartaric acid addition. To better understand the impact of pH on the stability of the reaction mixture, several experiments were carried out at three different pH values (1.9 and 3.6 and 7) and 3-fluorophenol content was monitored (

Table 1). These experiments suggest that high acidity of the reaction mixture can lead to decomposition of the product or starting material into 3-fluorophenol.

Table 1 Stability studies on the filtrate from reaction mixture at various pH

Entry	Process changes	pH	3-Fluorophenol content	
			4 h	7 h
1	pH adjusted by adding additional tartaric acid in THF	1.9	6.5%	25.1%
2	No changes	3.6	3.1%	3.2%
3	pH adjusted by adding additional KF in water	7.3	3.3%	3.2%

Subsequent studies aimed to determine the impact of tartaric acid solution addition rate on the pH of the reaction mixture (Table 2). Two separate small-scale experiments were run with slow (4 mL/min) and fast (12 mL/min) addition rates of tartaric acid solution. It was observed that slow addition resulted in a greater acidity of the reaction mixture (pH = 2.7) compared to fast addition, (pH = 5.9). This is consistent with the high acidity observed during the production runs in which the tartaric acid solution was added at a rate corresponding to 0.85 mL/min. These studies suggest that high acidity of the reaction mixture during production was caused by long tartaric acid addition times, resulting in 3-fluorophenol generation via protodeboronation. While it is unclear why addition rate affects the reaction pH, we postulate that this may be due to different tartrate salt speciation (mono- vs dipotassium tartrate) and their rate of formation.

Table 2. Effect of tartaric acid addition rate on pH

Entry	Addition rate	pH of reaction mixture
1	4 mL/min	2.7
2	12 mL/min	5.9
3[a]	0.85 mL/min	1.5
[a]Production-scale run		

To provide additional control over the process and reduce mother liquor losses during the final crystallization, focused solubility studies were performed on the trifluoroborate product **2** (

Table 3). This data was used to determine an in-process control testing limit to determine an appropriate endpoint for the solvent switch into isopropanol and water content target. While water content had little impact on the solubility in pure isopropanol, the product has high solubility in THF/acetonitrile mixtures (Table 3, entry 5), which nearly doubles in the presence of water (Table 3, entry 6). Based on this data, reduction of THF and acetonitrile content is critical to avoid high liquor losses.

Table 3 Solubility studies of 2-fluoro-5-hydroxyphenyltrifluoroborate (**2**)

Entry	Solvent system	Concentration (mg/mL)
1	THF	30.2
2	IPA	Not detected
3	MeOH	15.8
4	Acetonitrile	204.1
5	THF:CH_3CN (12:15)	176.6
6	THF:CH_3CN:H_2O (12:15:2)	351.3
7	4% water in IPA	3.0
8	8% water in IPA	1.6
9	12% water in IPA	2.6

Based on the above studies, the following process controls were implemented to improve the robustness and yield of **2**:

1. pH of process stream: Maintain a pH of 4 – 6 throughout the process by implementing i) an increased addition rate of tartaric acid; ii) continuous pH monitoring throughout

the process; and iii) Optional KF charge after the tartaric acid addition if the pH is < 4.

2. Crystallization solvent composition: control acetonitrile and THF to < 5% by ^{1}H NMR prior to product isolation

Through implementation of the above improvements, multiple >5 kg batches were executed to consistently provide yields of >85% with >97 wt% potency.

Citric Acid Process

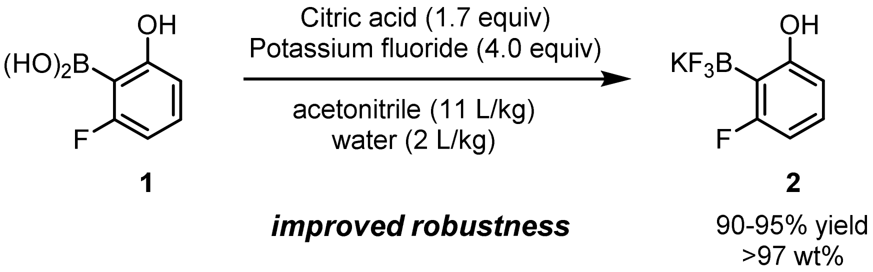
Prior to production of subsequent batches of **2**, additional development activities focused on improving the trifluoroborate conversion process. Due to the pH dependence on the final yield of **2**, we sought to determine if an alternative acid would provide a more robust process. After screening numerous acids, citric acid was identified as a potential replacement for tartaric acid (Scheme 3). Addition rate experiments were performed using citric acid and found no effect on pH was found (Entry 1 and 2, Table 4). Both compounds **1** and **2** were found to be stable in the citric acid solution in acetonitrile during the prolonged stirring for 24 h. Addition of potassium fluoride solution in water to the pre-mixed solution of citric acid and **2** was also found to be within the desired pH range.

Table 4. Effect of addition rate on pH in the citric acid process on lab scale

Entry	Addition details	pH of reaction mixture
1	8 mL/min of citric acid	5.5
2	30 mL/min of citric acid	5.4
3[a]	6.7 mL/min of KF solution in water to a mixture of **1** and citric acid	5.4

[a] Condition followed in the production batches

The use of citric acid provided the following advantages: i) citric acid is soluble in acetonitrile, allowing for the elimination of THF from the process and reduction of reaction volume to 13 L/kg; and ii) the pH of the reaction mixture is not dependent on the addition rate of citric acid solution. The improved citric acid process was executed on multiple 14 kg batches, providing 90-95% yield of **2** with an assay of > 97 wt%.



Scheme 3 Synthesis of potassium 2-fluoro-5-hydroxyphenyltrifluoroborate (**2**) using citric acid

Conclusion

Herein we described the development of a scalable process to produce 2-fluoro-6-hydroxyphenyltrifluoroborate from its corresponding boronic acid using a modified Lennox/Lloyd-Jones protocol. We identified the dependence of pH on tartaric acid addition rate, leading to the implementation of appropriate pH control, resulting in improved yields. Subsequent development resulted in the implementation of citric acid as a replacement for tartaric acid, which provided improved robustness by eliminating the pH-dependence on acid addition rate while simplifying the process. The improved process has been demonstrated on > 10 kg scale, providing high yield and potency of the desired trifluoroborate product **2**.

Acknowledgements

This paper is dedicated to Professors Stephen L. Buchwald and John F. Hartwig to commemorate the 25th anniversary of the Buchwald-Hartwig coupling. We thank Dr. Nilesh Joshi, Krishna Sheena, Rafi Shaik (Syngene Amgen Research Center) and Ramesh Sela (Syngene International Ltd.) for providing technical support during our development. We also thank Dr. Narendra Ambhaikar (Syngene International Ltd) and Dr. Debasis Patra (Amgen, Inc.) for their continued support during this project.

Experimental Section

General Considerations:

The starting material boronic acid **1** was procured from Wuxi AppTech. Tartaric acid was procured from Kaival chemicals. Potassium fluoride was procured from Chempure. Citric acid was procured from Sony Chem. Unless otherwise stated all the chemicals were used without further purification. All reaction solvents employed were of commercial grade. ^{1}H and ^{19}F NMR and ^{11}B NMR spectra were recorded on Bruker AV3-400 (400/376.69/128.51 MHz) spectrometer using the DMSO-d_6 as an internal standard. The values of chemical shifts are reported in parts per million (ppm) with the multiplicities of the spectra reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br), values for coupling constants (J) are assigned in Hz. Residual solvent analysis was recorded using Agilent GC 6890N/7890A series equipped with Head space injection auto sampler. The potassium content was analysed using Agilent (Varian) L720ES instrument. Moisture content was measured using METROHM 907 Titrando (Karl-Fischer titration). Assay purity was measured by quantitative NMR (qNMR) assay using benzyl benzoate as internal standard (procured from Sigma Aldrich).

Tartaric acid procedure:

Lab scale procedure:

To a 4-neck 3 L round-bottom flask (RBF) equipped with thermo pocket and mechanical stirrer was charged (2-fluoro-6-hydroxyphenyl)boronic acid (350.0 g, 2.25 mol) and acetonitrile in (8750 mL, 25 L/kg). To the resulting reaction mixture was added a solution of potassium fluoride in water (522 g, 8.98 mol in 700.0 mL, 2.0 L/kg) at 22-25 °C followed by dropwise addition of (2R,3R)-2,3-dihydroxysuccinic acid (842 g, 5.61 mol) in tetrahydrofuran (4375 mL, 12.5 L/kg) and water (700 mL, 2 L/kg) over a period of 30 min. The reaction mixture was stirred for 16 h at 22-25 °C. After completion of the reaction is indicated by HPLC, the reaction mixture was filtered through celite, washing the bed with THF (5 L/kg). The filtrate was concentrated in vacuo (50 mm Hg) by rotavap (bath temp < 30° C) to approx. 3-4 total volumes (1050-1400 mL). Isopropanol (3500 mL, 10 L/kg) is added and concentrated to approx. 9-10 total volumes (3.0-3.5 L). The resulting slurry was cooled to 0-5 °C and stirred for 2 h. The product was isolated by filtration and washed with isopropanol (2 L/kg). The resulting solid was then dried under vacuum for 4-5 h to afford the product as off-white crystalline solid. Yield: 378.0 g (77%)

Pilot Plant scale procedure consisted of three parts:

Part 1: Tartaric acid solution preparation: To a clean and dry 500 L Hastelloy reactor was charged tetrahydrofuran (72 L, 12 L/kg) and tartaric acid (14.44 kg, 96.2 mol). The resulting mixture was stirred for 10 min at 22-25°C. The temperature was increased to 45-47 °C and aged for 1-2 h. The reaction mass was cooled to 22-28 °C and transferred to a high-density polyethylene (HDPE) container for storage, rinsing the reactor with additional THF (3.0 L, 0.5 L/kg).

Part-2: Preparation of Potassium fluoride solution: To a HDPE (80 L) container potassium fluoride (8.94 kg, 153.93 mol) and water (12.0 L, 2 L/kg) was charged. The resulting mixture was agitated until complete dissolution (10-20 min).

Part-3 Preparation 2-Fluoro-6-hydroxyphenyltrifluoroborate: To a clean and dry 500 L Hastelloy reactor was charged acetonitrile (90 L, 15.0 L/kg) and (2-fluoro-6-hydroxyphenyl) boronic acid (6.0 kg, 38.48 mol). The resulting slurry was stirred for stirred for 5-10 min at 22-28 °C. To this reaction mixture was charged the potassium fluoride solution over 2-5-min. (The reaction mixture initially becomes a solution, but precipitation occurs upon complete addition). The reaction mixture was stirred for 30 min at 25-28 °C and then the tartaric acid solution was added to the reaction mass over a period of 10-12 mins and stirred for an additional 30 min. The progress of the reaction was monitored by TLC. The pH of the reaction mixture was monitored by diluting 2 mL with 2 mL of water. A pH of 2.3 (Limit ≤ 5.5) indicated additional potassium fluoride was required. A potassium fluoride solution (0.24 g was dissolved in 0.32 L water) was charged to adjust the pH between 5.5-6.5. Once the pH was within the desired range, the reaction mass was filtered through celite, washing with THF (12.0 L, 2.0 vol). The combined filtrates were polish filtered through 5.0 µm stainless steel and 0.2 µm polypropylene cartridge into a clean reactor. The solution was concentrated under vacuum (30-50 mm Hg) to approx. 10 total volumes (60 L) at 20-28 °C (< 30 °C). Isopropanol (60 L, 10 L/kg) was added to the reactor and re-distilled to 10 total volumes (60 L). This process was repeated three time until water content reached the desired limit of <12%. The resulting slurry was cooled to 15±5°C and stirred for 1 h. The product was isolated by filtration, washing with isopropanol (2 x 15 L). The product was vacuum dried at < 30 °C to afford the product as off-white crystalline solid. Yield: 7.02 kg (83.6%).

Citric acid procedure:

Procedure: To an 80 L HDPE container was charged water (28 L, 2 L/kg) and potassium fluoride (21 kg, 361.57 mol). The mixture was stirred until a homogenous solution is obtained (approx. 15 min). To a 500 L Hastelloy reactor, acetonitrile (280 L, 10 L/kg), 2-fluoro-6-hydroxyphenyl boronic acid (14 kg, 89.79 mol), and citric acid (29.4 kg, 134.68 mol) was charged. The charging funnel was rinsed with additional acetonitrile (14 L, 1 L/kg) and the resulting reaction mixture was stirred for 15-20 min at 25-28 °C. The premade solution of potassium fluoride was then charged over a period of 60 min, maintaining the batch temperature between 25-30 °C. The reaction mixture is monitored for conversion by TLC. Upon completion (approx. 10 h), the mixture was filtered through celite, rinsing the reactor and filter with acetonitrile (48 L, 3.43 L/kg). The filtrate was charged back into the 500 L Hastelloy reactor. Isopropanol (56 L, 4 L/kg) was added and the mixture was concentrated under vacuum (30-50 mm Hg) at 30-35 °C to 5-8 total volumes (70-112 L). This process was repeated an additional 2-3 times until acetonitrile content was < 5% and water content was < 6%. The resulting product was isolated on a Nutsche filter. The reactor and filter cake were washed with isopropanol (28 L, 2 L/kg). The resulting product was vacuum dried at < 30 °C to obtain the product as off-white crystalline solid. Yield: 18.9 kg (96.5%).

Analytical data

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (q, J = 14.36 Hz, 1H), 6.95 (q, J = 7.92 Hz, 1H), 6.36 (q, J = 8.60 Hz, 2H). (J= H-F coupling constants):^{19}F NMR (376.69 MHz, DMSO--d_6): δ -105.33 (s), -130.0 (q), -148.3 (s) (KHF$_2$ contaminant).^{11}B NMR (128.51 MHz, DMSO-d_6): δ 3.051(br s). Moisture Content (KF titration) = 0.17%, Heavy metal content (ICP-OES: Dilution method) = Other metals (Pd. Hg, As, Pb and Sb) < 5 ppm, potassium content =17.18%

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[14] Process Hazard Identification and Risk Assessment: Basic recommendation for engineering controls such as vacuum and temperature requirement for the distillation were put in place. *DSC studies:* No exothermic decomposition was observed in the analysis of the boronic acid starting material **1**; a moderate exotherm at 191.5°C was observed for the product

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trifluoroborate salt **2**; and low exotherm for the reaction mixture at 166.5°C. These exothermic events were deemed low risk since the operating temperature throughout the process is < 30 °C. *Compatibility test for reactor material of construction (coupon test):* Moderate etching of stainless steel and glass and no etching of the Hastelloy. This suggests hydrofluoric acid is generated during the process. *Filter cake resistance studies:* Moderate specific cake resistance on the order of e10 ft/lb.