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A Continuous Kilogram-Scale Process for the Manufacture of *o*-Difluorobenzene

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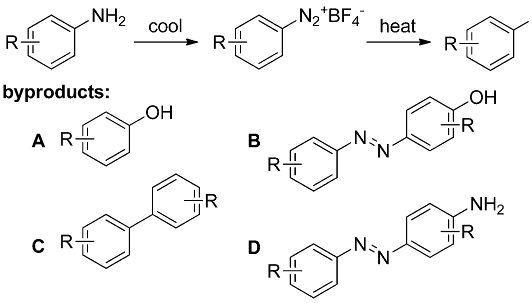
ABSTRACT: An expeditious and multikilogram-scale process for the Balz–Schiemann synthesis of *o*-difluorobenzene from *o*-fluoroaniline via two separate continuous flow reactors in 90.0% yield has been set up. The main steps involved the generation of stable diazonium fluoborate intermediate in situ via continuous diazotization reactor at 20 °C, and the choice of *o*-difluorobenzene as cosolvent to achieve the continuous flow fluorodediazoniation system. Reaction time of both steps could be brought down to within 10 s and 2 min, respectively, by increasing the reaction temperature and thereby taking advantage of improved mass and heat transfer of a continuous flow system.

INTRODUCTION

The Balz–Schiemann reaction is a classical method for replacing the diazonium group by fluorine (fluorodediazoniation) which involves heating $ArN_2^+BF_4^-$ without solvent.[1] Interest in the Balz–Schiemann reaction and its variants has not diminished over time because regiospecific fluorination continuous to be a challenge and demand of aryl fluorides is increasing, although this reaction has disadvantages such as high energy consumption and unstable yields.[2]

Diazotization of aromatic amines is usually exothermic and fast and usually performed on bulk scale in anhydrous conditions at low temperature; however, higher temperature can be achieved with the use of diazonium tetrafluoroborates or certain arenediazonium sulfonates or in the presence of complex anions, e.g. zinc chloride and hexafluorophosphate.[3] Diazotization of aromatic amines in continuous microreactors for iododeamination,[4] chlorodeamination,[5] azo dyes,[6] and chlorosulfonylation[7] has been established, although these contributions were only reported on laboratory-scale. The problems of a large-scale Balz–Schiemann reaction include the following: (i) the thermal instability of the diazonium intermediate, (ii) the difficulty raised by interaction between mixed and unmixed strata in large vessels, and (iii) nonuniform heating or water in the diazonium fluoroborate, leading to an uncontrollable thermal decomposition reaction and more byproduct[8] (see Scheme 1).

Scheme 1. Synthetic route and byproducts of the Balz–Schiemann reaction

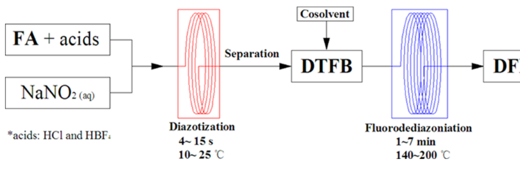


The development of synthetic chemistry utilizing continuous flow synthesis has been of increasing interest in both academia and industry in recent years. Continuous flow reactors offer several advantages over the traditional batch vessels such as the following: (i) mass and heat transfer can be significantly improved by decreasing reactor size and increasing surface-to-volume ratio; (ii) fewer transport limitations can be offered by the feasibility and device flexibility of continuous flow synthesis; (iii) yield and selectivity can be improved due to the precise control of reaction variables such as temperature, pressure, residence time, and stoichiometry; (iv) scale-up of continuous flow synthesis is readily achieved by simply increasing the number of reactors or their sizes.[9]

Motivated by these advantages, our group have been committing to the continuous flow synthesis technology and have reported a continuous kilogram-scale flow reactor for manufacture of 7-ethyltryptophol.[10] We have now applied this technology to the Balz–Schiemann synthesis for *o*-difluorobenzene (**DFB**) including the generation of diazonium tetrafluoroborate (**DTFB**) from *o*-fluoroaniline (**FA**) at moderate temperature and the thermal decomposition reaction (Scheme 2).

Results and Discussions. Continuous Flow Diazotization. The continuous diazotization equipment consists of two

Scheme 2. Synthesis of *o*-difluorobenzene (DFB)



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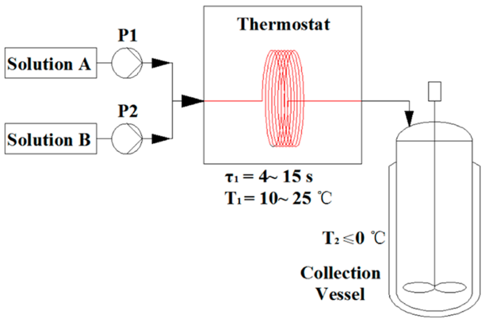
peristaltic pumps (**P1**, **P2**, Boading Longer, China) loaded with silicone tubing connected by a T-joint to a reacting tube (Hastelloy, 8 mm o.d., 6 mm i.d.) which was immersed in a thermostat-controlled oil bath (Scheme 3). Solution A (1.7 M **FA** in acids aqueous) together with solution B (6.0 M sodium nitrite aqueous) were pumped into the tube reactor by **P1** and **P2**, respectively. To reduce the total cost of acids,[11] fluoroboric acid and hydrochloric acid were used together to satisfy the needs of diazotization. After a residence in the reacting tube, mixture flowed through the outlet and accumulated in the collection vessel that was immersed in refrigerant. The intermediate **DTFB** was precipitated from aqueous solution in situ and then filtrated after cooling to about 0 °C. Impurities were washed away by methanol.

Scheme 3. Schematic of the diazotization experimental setup[a]



[a]Solution A is 1.7 M **FA** in HBF_4 and HCl aqueous; solution B is 6.0 M sodium nitrite aqueous. τ_1 represents the residence time in the reacting tube. T_1 represents the temperature of the thermostat, and T_2 represents the temperature of mixture in the collection vessel after cooling.

The optimization of the experimental parameters was systematically investigated by varying the mole ratio of acids, the residence time, and the temperature under convenient continuous flow conditions. The effect of varying the mole ratio of acids to **FA** (with fixed HBF_4/HCl composition) is shown in Figure 1. All experiments were carried out at T_1 = 10 °C and T_2 = 0 °C; the isolated yield of dry **DTFB** powder was seen to increase continuously to a maximum value 75.0% at 10 s. The decrease in yield on increasing the residence time was probably due to some decomposition of the diazonium salt and coupling side reactions. This could be proved by the existence of byproduct **B**. On account of minimizing the cost of acids, the suitable mole ratio of HBF_4:HCl:**FA** was 1.2:1.8:1.

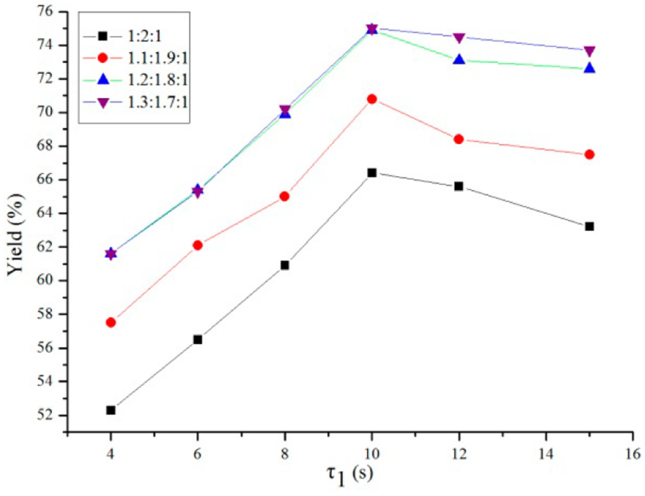


Figure 1. Effect of the mole ratio of HBF_4: HCl: **FA** on the isolated yield of **DTFB**. Legends indicate the mole ratio of HBF_4: HCl: **FA**. Yields were calculated from **FA**.

With the aim of developing a continuous diazotization reactor at moderate temperature, different reaction temperatures were tested systemically. Experiments were run with the HBF_4: HCl: **FA** mole ratio of 1.2: 1.8: 1 and T_2 = 0 °C. As shown in Figure 2, the maximum isolated yield (80.3%) of **DTFB** was achieved at about T_1 = 20 °C. In the experiment, lower temperatures (such as 0 °C or below) resulted in the tube having a tendency to be blocked by the precipitated diazonium salt, whereas higher temperature resulted in an increased likelihood of intermediate decomposition and cross-coupling reactions.[12]

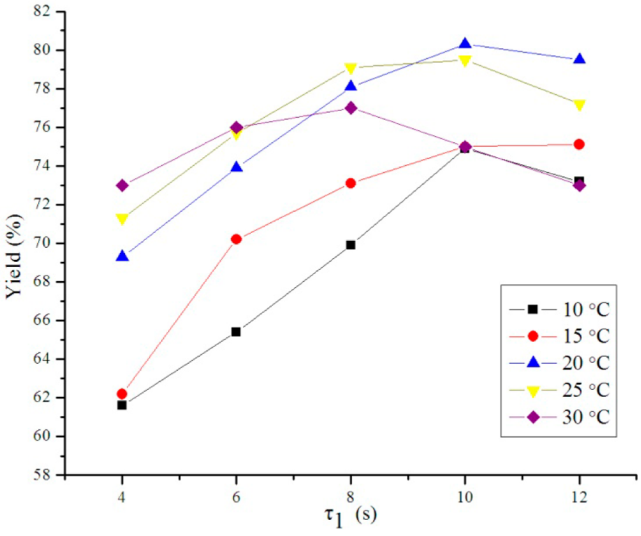


Figure 2. Effect of T_1 on the isolated yield of **DTFB**. Legends indicate T_1. Yields were calculated from **FA**.

With these key observations, the best isolated yield of **DTFB** was only 80.3%. However, the filtrate cake was bright white (HPLC purity >99% before methanol wash), and the filtrate was light-colored, indicating that it contained few coupling byproducts. The most likely reason was that there was still some **DTFB** dissolved in the water. Further experiments were carried out to learn the relationship between the temperature (T_2) and the solubility of **DTFB**. As shown in Table 1, the isolated yield of **DTFB** was increased by lowering the temperature (T_2). The remaining diazonium in water was

Table 1. Effect of T_2 on the isolated yield of DTFB

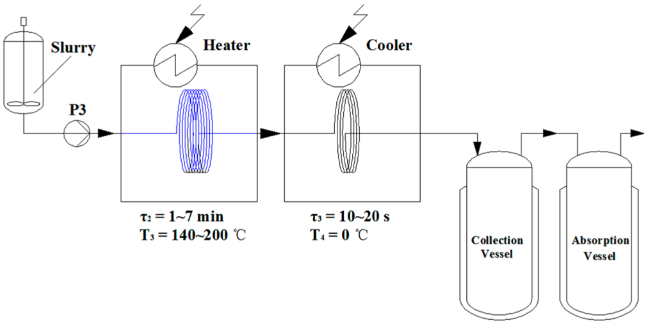
T_2 (°C)	isolated yield (%)[a]
0	80.3
−5	88.6
−10	92.8
−15	93.1
−20	93.2

[a]Yields were calculated from **FA**, and no solidification of the aqueous phase was observed even below −20 °C.

analyzed by quantitative HPLC analysis. The yellowish filtrate collected from the maximum yield group was submitted to HPLC analysis and demonstrated that another 13.6% yield of product was dissolved in water; hence, the actual yield was 93.9%. However, a portion of diazonium still remained in the water even below −20 °C.

Continuous Flow Fluorodediazoniation. The continuous fluorodediazoniation equipment consists of one pump (**P3**) loaded with tubing connected to a reacting tube (Hastelloy, 10 mm o.d., 8 mm i.d.) which was immersed in an oil bath through a fabricated metal connector. Another metallic cooling tube was subsequently connected to the reacting tube through a joint, and the outlet connected to a collection vessel with an exit tube leading to another vessel for absorbing boron fluoride (Scheme 4).

Scheme 4. Schematic of the fluorodediazoniation experimental setup[a]



[a]Slurry is **DTFB** in **DFB** with a ratio of 1/10 (g/mL). τ_2, τ_3 represent the residence time; T_3, T_4 represent the temperature of two thermostats, respectively.

The primary challenge of this continuous process was the feeding of dry **DTFB** powder. Slurry of **DTFB** in a nonreactive cosolvent (such as *o*-dichlorobenzene[11]) was a suitable choice, whereas an additional separation was required. This would probably cause an increase in both cost and operating steps. After unremitting efforts, we got a delightful idea of choosing the target product **DFB** as cosolvent to avoid these problems. The optimization of experimental parameters was greatly facilitated by the continuous flow manner. The ratio of solid to liquid was first tested, and the suitable value was less than 1/8 (g/mL) for continuous feedin of **DTFB**, and 1/10 (g/mL) was chosen in the following experiments. The reaction was supposed to release an equivalent of N_2 and an equivalent of BF_3 with the boiling point of **DFB** of only about 92 °C; however, the reaction temperature was much higher. The stream was a gas mixture. Thus, we prolonged the tube length to control the flow rate, and the pressure drop in the reacting tube could play the role of a back-pressure regulator. The effect of parameters (residence time τ_2 and temperature T_3) is shown in Figure 3. Maximum yield of 96.7% (calculated from **DTFB**) was obtained when τ_2 = 3 min T_3 = 200 °C. The observations indicate that the reaction time could be brought down to within 1 min by increasing the reaction temperature and thereby taking advantage of improved mass and heat transfer. In addition, there were hardly any tar deposits in the reactor (less than 0.1%), and most can be washed out along with **DFB** in this kilogram-scale test.

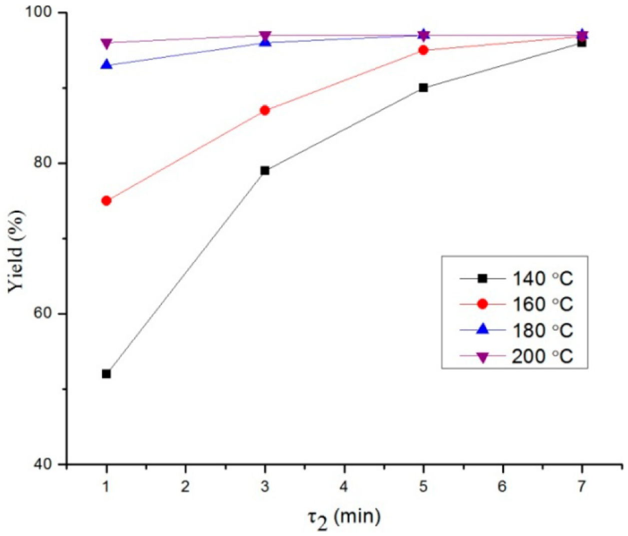


Figure 3. Effect of τ_2 and T_3 on fluorodediazoniation. Yields were calculated from **DTFB**.

Comparative Batch Experiment. For comparison purposes, **DTFB** was prepared in batch manner with the conditions the same as those for the above continuous flow way, and fluorodediazoniation was carried out in batch manner by direct heating without cosolvent.[12] Experimental details can be found in the Experimental Section. The results are shown in Table 2.

Table 2. Comparison of batch process with continuous process

	DTFB	DFB	
operate manner	isolated yield (%)[a]	GC purity (%)	yield (%)[a]
batch process	90.7	98.0	78.6
continuous process	93.1	99.6	90.0

[a]Yields were calculated from **FA**.

CONCLUSION

In summary, an expeditious and high-yielding process for the Balz−Schiemann synthesis of **DFB** from **FA** via two separate continuous flow reactors has been set up. The process is readily adapted for the preparation of analogous compounds and can easily be scaled-up by increasing reactor size or operating several reactors with high throughput in parallel. The larger-scale experiment is still in progress.

EXPERIMENTAL SECTION

All chemicals were purchased from commercial sources and were used without further purification. HPLC analysis for **DTFB** was carried out on an Agilent 1200 system equipped with a XDB-C18 250 mm × 4.6 mm column and detected at 242 nm. Standard method: 95:5 gradient of water/methanol, flow rate 1 mL/min. GC analysis for **DFB** was performed on an Agilent 6890 gas chromatograph. GC conditions: HP-INNOWAX column, 30 m × 0.25 mm × 0.25 μm, carrier gas: helium (1.2 mL/min), injection temp: 250 °C, detector temp: 260 °C, oven: 40 °C (5 min hold) → 220 °C (30 °C/min, 20 min hold).

Batch Experiment. A mixture of 40% aqueous fluoroboric acid (1267 g, 6 mol), 31% aqueous hydrochloric acid (1063 g, 9 mol), **FA** (555 g, 5 mol), and 610 g of water was placed in a 10-L glass jar with a cooling jacket. Another solution of sodium nitrite (363 g, 5.25 mol) in 725 g of water was made ready. When the acid mixture was cooled to 0 °C, sodium nitrite was added to it. Diazotization was begun by the slow addition of the nitrite solution, the temperature being held below 10 °C. The mixture was stirred powerfully for another 30 min when the addition was finished. And after cooling to −15 °C, the solid was filtrated with suction, using Büchner funnels. The yellowish cake was washed by 500 mL of methanol and dried in vacuum. The yield (90.7%) from **FA** was 951 g of **DTFB** as white powder.

A 5-L distilling flask with a wide side arm was used for the decomposition of the **DTFB**. A 1-L distilling flask was fastened directly to the side arm of the decomposition flask and cooled with cold brine. To the side arm of the receiver was connected a rubber tube which was placed over 2 L of water in a 5-L flask. The solid was placed in the decomposition flask and heated gently with an oil bath. When white fumes began to evolve, the oil bath was removed and the decomposition permitted to continue spontaneously. The mixture was heated cautiously from time to time, as necessary to keep the reaction going. Finally vigorous heating was employed until no more fumes of boron fluoride were evolved.[12] The distillate was washed with 1 L of 10% NaOH and 1 kg of water. An amount of 448 g of yellowish crude **DFB** was obtained (78.6% yield from **FA** at 98.0% GC purity).

Continuous Flow Experiment.[13] Solution A of **FA** (1110 g, 10 mol), 40% aqueous fluoroboric acid (2534 g, 12 mol), 31% aqueous hydrochloric acid (2125 g, 18 mol) in 1220 g of water, and solution B of sodium nitrite (725 g, 10.5 mol) in 1450 g of water were pumped into the tube reactor (Hastelloy, 8 mm o.d., 6 mm i.d.) via a T-joint by **P1** and **P2** at flow rates of 740 mL/min and 220 mL/min, respectively; after a residence time of about 10 s at 20 °C, the mixture flowed through the outlet and accumulated in the cooling vessel. Continuous stirring was done vigorously to accelerate heat elimination. After the slurry was cooled to −15 °C or below, the solid was filtrated with suction, using Büchner funnels. The solid was washed by about 1 L of methanol and then dried in vacuum; 1952 g of **DTFB** as white powder was obtained (93.1% yield from **FA**).

Slurry of the above-manufactured **DTFB** in 22,500 g of **DFB** was introduced into the reacting tube (Hastelloy, 10 mm o.d., 8 mm i.d.) continuously by **P3** at a flow rate of 200 mL/min. The mixture was maintained for 2 min at 200 °C and then cooled in the tandem tube. The collected yellowish liquid was washed with 2 L of 10% NaOH and 2 kg of water; 23,526 g of nearly colorless liquid was obtained, and 1026 g of **DFB** was generated actually (90.0% yield from **FA** at 99.6% GC purity). Further purification was on commercial demand.

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Notes

The authors declare no competing financial interest.

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(11) Momota K.; Yonezawa T. (Morita Kagaku Kogyo Co., Ltd., Japan.). JP 199103232828 A, 1991; 2−6 equiv of HCl and 1.3 equiv of HBF_4 to **FA** was used for **DTFB** in this patent.

(12) **SAFETY NOTE**: Heating of diazonium salts in this way is potentially hazardous, depending on the stability of the diazonium salt and can result in corrosive and poisonous off-gases.

(13) No obvious corrosion problems of the reacting tube have been found during our experiment, while the life of silicone tubing was only hundreds of hours.