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Development of a Safer Continuous Flow Process for $B_2(OH)_4$-Mediated Chemoselective Reduction of Nitroarenes to Anilines

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ABSTRACT: Tetrahydroxydiboron $[B_2(OH)_4]$ is a chemoselective reducing reagent for nitro reductions in the presence of other labile functional groups. However, there are significant process safety challenges associated with the application of this reducing reagent, including rapid heat release and thermal instability of $B_2(OH)_4$ in aprotic polar solvents. Herein, we report the development of a safer continuous flow process applying $B_2(OH)_4$-mediated chemoselective nitro reduction conditions. The safety challenges were addressed by employing continuous flow technology along with identifying a suitable protic cosolvent EtOH. Functional group tolerance toward cyano groups, halides, carboxylic acids, olefins, imines, and benzylic alcohols was demonstrated in flow with higher reaction yield compared to that in batch synthesis. The modified reaction conditions provide a potentially scalable approach to widespread applications of this key transformation for the generation of highly functionalized diversified aniline derivatives.

KEYWORDS: *tetrahydroxydiboron, $B_2(OH)_4$, process safety, continuous flow chemistry, nitro reduction, chemoselective reduction*

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1. INTRODUCTION

The reduction of nitro groups to amino groups (anilines) is of paramount importance and allows the generation of aniline intermediates for further functional group interconversions, enabling the introduction of diverse functionalities required for drug molecule efficacy, solubility, and pharmacokinetic properties in the synthesis of pharmaceuticals, agrochemicals, and fine chemicals.[1] Furthermore, chemoselective reduction of nitroarenes in the presence of other reduction labile functional groups is extremely important for the synthetic community as it provides an efficient and step economical protocol for synthesis of key aniline intermediates (Figure 1). There are a number of synthetic methods for nitro reductions such as metal-catalyzed hydrogenation conditions, Fe/NH_4Cl and Zn/NH_4Cl conditions, etc.[2] However, most of the conditions suffer from poor chemoselectivity by affecting other labile functional groups present in the molecules or requiring harsh reaction conditions such as high hydrogen pressure and temperatures. In addition to these limitations, these methods also result in producing toxic metal wastes.[3] Furthermore, other metals such as molybdenum, samarium-mediated and nonmetal benzothiazoline, and B_2Pin_2-mediated chemoselective conditions have also been reported;[4] however, maintaining chemoselectivity might be challenging on scale. We are interested in identifying a general and safer nitro-reduction technology, alternative to hydrogenation conditions. Finding

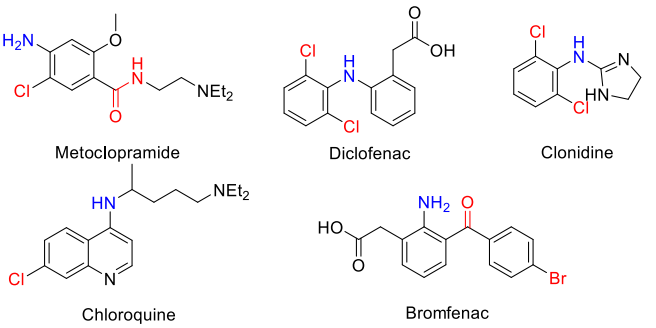

Figure 1. Aniline-containing drug molecules with dense functionalities.

such a technology will provide a highly efficient, economical, and step economy process for these molecules that contain reduction labile functionalities. Recently, tetrahydroxydiboron $[B_2(OH)_4]$ was reported for chemoselective reduction of

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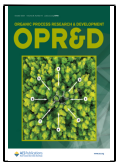

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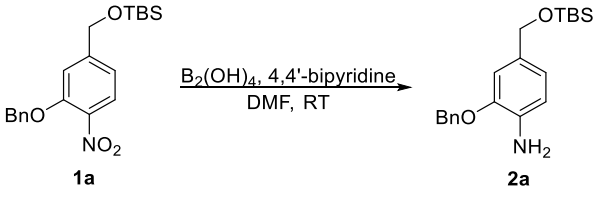
aromatic nitro compounds under metal-free conditions.[5] $B_2(OH)_4$ offers several advantages over other reducing agents, including high chemoselectivity toward nitro groups, commercially available and easy to handle compared to other metal-mediated conditions such as Fe/NH_4Cl or Zn, which may require additional steps for activation or optimization to achieve satisfactory results with extreme safety measures during scale-up. Furthermore, $B_2(OH)_4$ has been well reported as the borylating reagent on scale for Suzuki−Miyaura borylation reactions.[6] In this report, we disclose our findings of applying $B_2(OH)_4$ as a chemoselective nitro-reducing reagent and address its thermal behaviors using appropriate cosolvent and continuous flow technology to generate aniline derivatives in a safer and practical manner. Many labile functional groups are tolerated applying this method including -TBS, -Bn, cyano, halides, carboxylic acids, olefins, allyls, imines, and benzylic alcohols.

2. RESULTS AND DISCUSSION

We started the investigation by applying compound **1a** as a model substrate. We first tested mild hydrogenation conditions using Degussa type 10% Pd/C under 1 atm of H_2 at room temperature in methanol; however, benzyl group deprotection and hydrogenolysis of the silanol group (OTBS elimination) were observed. The Fe/NH_4Cl reduction in ethanol (EtOH) was also attempted, and multiple side products were observed. Similar results were observed with Zn/NH_4Cl-mediated reduction conditions. The challenges were associated with the presence of the labile groups in the molecule which are sensitive toward hydrogenation or other reduction conditions. We then turned our attention to evaluate alternative chemoselective nitro-reduction conditions aiming to develop a potentially scalable synthesis to prepare compound **2a** in the presence of the labile functional groups.

1.1 Batch Evaluation of Nitro Reduction with $B_2(OH)_4$. The reagent $B_2(OH)_4$ in the presence of catalytic 4,4′-bipyridine has been reported recently as a highly chemoselective nitro-reduction reagent in solvent *N*,*N*-dimethylformamide (DMF).[5] First, we started the evaluation of the reported $B_2(OH)_4$-mediated reduction conditions in the batch reaction (Scheme 1).[5a] To a solution of compound **1a** (0.5 g)

Scheme 1. Nitro Reduction of Compound 1a Using Reported Conditions



1a 2a

in DMF (10 V) at room temperature (23 °C), $B_2(OH)_4$ (3.0 equiv) and 4,4′-bipyridine (0.5 mol %) were added sequentially. The initial experiments showed that the reaction rate was very high; complete conversion was observed within a few minutes. We were delighted to find that the desired chemoselective nitro-reduction product was obtained with no over-reduction impurities present. However, there was a rapid temperature rise upon addition of $B_2(OH)_4$[12] and 4,4′-bipyridine. The internal temperature increased to 62 °C from 22 °C even at only a 0.5 g scale. *N*-Boryl-4,4′-bipyridyl radical was believed to be a crucial intermediate in both formation of *N*,*N*′-diboryl-4,4′-bipyridinylidene and the reduction of nitroarene.[9] The color of the reaction mixture changed from purple to pale yellow within a few minutes, indicating completion of the reaction. Higher amounts of 4,4′-bipyridine (5 mol %) also resulted in a similar temperature spike.

We then studied the lower reaction temperature and alternative addition mode to try to mitigate the extreme exotherm. The reaction mass was cooled to 0 °C and the addition of $B_2(OH)_4$ (3.0 equiv) and catalyst (0.05 equiv) was divided into 3 portions. Following this mode of addition, the exotherm was controlled below 20 °C and complete conversion of the starting material was observed after 5 min with a solution yield of 82%. The product **2a** was extracted into the organic layer using isopropyl acetate after slowly quenching with water and taking the organic phase for the next step without further purification. Even though the reaction temperature was controllable at below 5 g scales, a detailed understanding and safety investigation was required before further scaling up.

2.1. Initial Evaluation of Nitro Reduction with $B_2(OH)_4$ under Continuous Flow Mode. We were encouraged that the reduction was fast and the reaction mixture was homogeneous. This reaction would be ideal to be conducted in a continuous flow mode. It was envisioned that flow chemistry could be an effective strategy to mitigate the exotherm and enhance the process safety of this chemoselective reduction. In recent years, the development of flow chemistry has emerged as a powerful strategy to overcome safety concerns and has been applied to nitro reductions as well.[7] The precise control over reaction parameters, including temperature, residence time, and reagent concentration, has allowed for enhanced regio- and chemoselectivity and efficiency outcome. Recently, a continuous-flow chemoselective nitro reduction of nitrochalcone was reported using $B_2(OH)_4$ for the synthesis of chiral tetrahydroquinoline derivatives.[8] In preparation for the flow experiments, we envisioned two streams that were premixed and pumped to the plug flow reactor (PFR) system. Since the reaction proceeds by facile dissociation of $B_2(OH)_4$ in the presence of 4,4′-bipyridine, stream 1 consisted of compound **1a** and 4,4′-bipyridine in DMF and stream 2 consisted of $B_2(OH)_4$ in DMF. To speed up the dissolution process of $B_2(OH)_4$, the solution was prepared at 30−40 °C and cooled to RT (20−25 °C) before use. When 0.085 equiv of 4,4-bipyridine and 3.2 equiv of $B_2(OH)_4$ in DMF solvent were used, the reaction was completed with 8 min of residence time. However, during this preliminary experiment, we observed that when the stock solution of stream 2 stands at room temperature for several hours, formation of a fine stream of gas bubbles, presumably hydrogen gas,[10] was noted. We considered this as an important safety concern, which was not reported previously in the literature where neat DMF[5] or DMSO[8] as a solvent was also used for $B_2(OH)_4$. We immediately evaluated the effect of residual water in the DMF solvent. When dry DMF solvent (KF = 70 ppm) was applied, a similar rate of gas bubble generation was noted compared to $B_2(OH)_4$ in DMF containing 2000 ppm water. We hypothesized that $B_2(OH)_4$ may not be stable in the solvent DMF. At this stage, the emphasis was focused on collecting adequate safety data and identifying safer mixing conditions for extended hours before further development in continuous flow chemistry mode.

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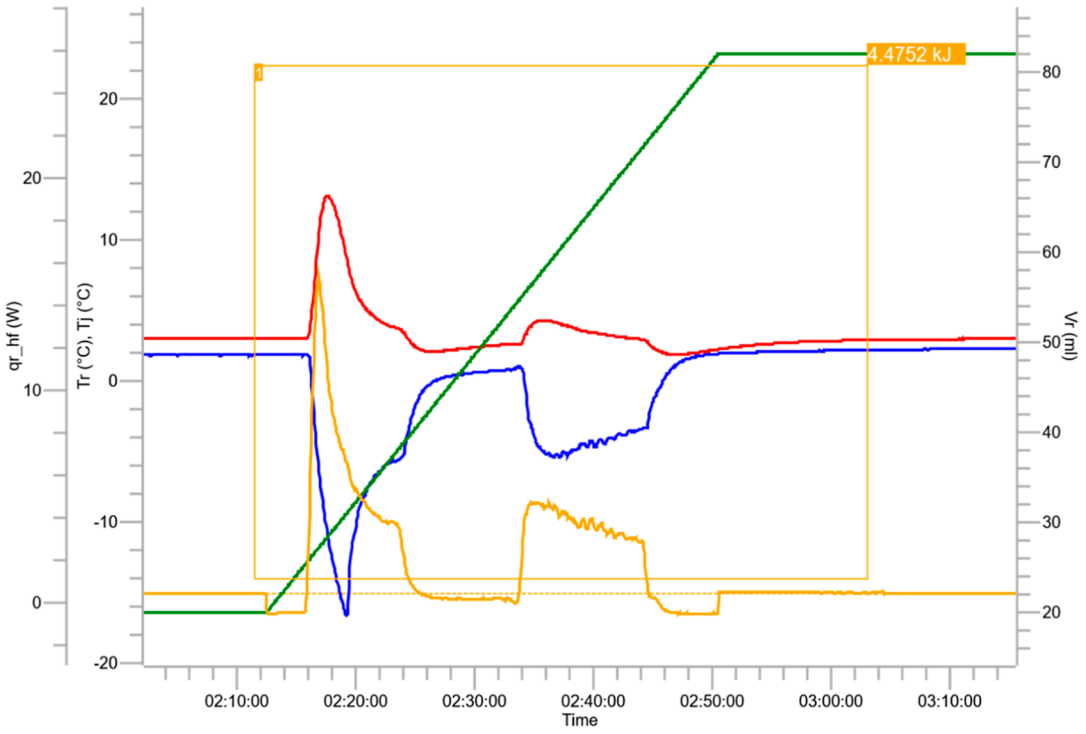

Figure 2. Heat released during addition of $B_2(OH)_4$ [green line: $B_2(OH)_4$ addition, red line: reactor temperature; blue line: jacket temperature; and orange line: heat release].

2.2. Process Safety Evaluation. To understand the temperature spike observed during the addition of $B_2(OH)_4$, an EasyMax reactor equipped with a heat calorimeter was applied to determine the heat of reaction in the absence of the substrate. The reaction was performed in a 100 mL reactor, wherein $B_2(OH)_4$ was added in 3 portions (3.2 equiv) to 4,4′-bipyridine (0.05 equiv) in DMF (50 mL, 10 V). The addition was exothermic, with a rapid temperature rise observed during the initial 25% addition (see Figure 2). No significant temperature rise was noted at the end of addition. The heat of reaction was −563 J/g with an adiabatic temperature rise of 36.8 °C. The heat released during the addition of $B_2(OH)_4$ to 4,4′-bipyridine likely indicates the cleavage of the B−B bond to form the active bipyridinylidene intermediate as reported in the literature[9] that would initiate the nitro reduction.

The thermal stability of $B_2(OH)_4$[12] and 4,4′-bipyridine in DMF was further studied using adiabatic reactive system screening tool (ARSST) where a 10 mL glass test cell was charged with 2 mL DMF and 39 mg 4,4′-bipyridine and the cell was loaded onto ARSST and under ∼300 psig N_2 pressure. A solution of 0.85 g (3.2 equiv) of $B_2(OH)_4$ in 6.2 mL of DMF was transferred slowly to the glass test cell. At the end of the addition, the glass cell contents were heated to 100 °C at a constant heating rate of 2 °C/min. As expected, an initial exotherm was observed and extended into a secondary exothermic event with a sharp increase in the rate of temperature rise starting at ∼80 °C. Upon cooling the contents to room temperature, noncondensable gases were generated. This secondary event indicates the potential incompatibility of $B_2(OH)_4$ and DMF. The above test was repeated to understand interaction between DMF and $B_2(OH)_4$, where 1.2 g $B_2(OH)_4$ was dissolved in 9 mL DMF and loaded into ARSST. The glass cell contents were heated to 150 °C at a constant heating rate of 2 °C/min. Two exothermic events were observed, the first with an onset of ∼64 °C and a second with an onset of 78 °C with the peak rate of temperature rise and pressure rise of >1000 K/min and >1000 psi/min, respectively (Figure 3). Upon cooling down at the end of the experiment, noncondensable gases were generated equivalent to 0.3 L/g of $B_2(OH)_4$.

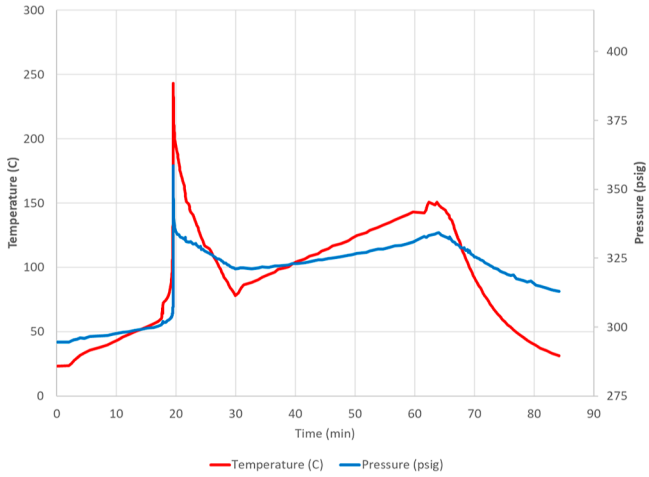

Figure 3. ARSST data for the thermal stability study of a solution of $B_2(OH)_4$ in DMF.

To decipher the above secondary decomposition event and hydrogen gas generation (vide supra), differential scanning calorimetry (DSC) experiments were performed. Initial safety evaluation was performed using a Mettler Toledo DSC where 2−5 mg of $B_2(OH)_4$ in DMF (1.3 M) solution was loaded into a high-pressure gold-plated stainless DSC crucible and heated from 25 to 300 °C at 4 °C/min. Similar to the ARSST data, there was a low onset exotherm event at 98.9 °C and a

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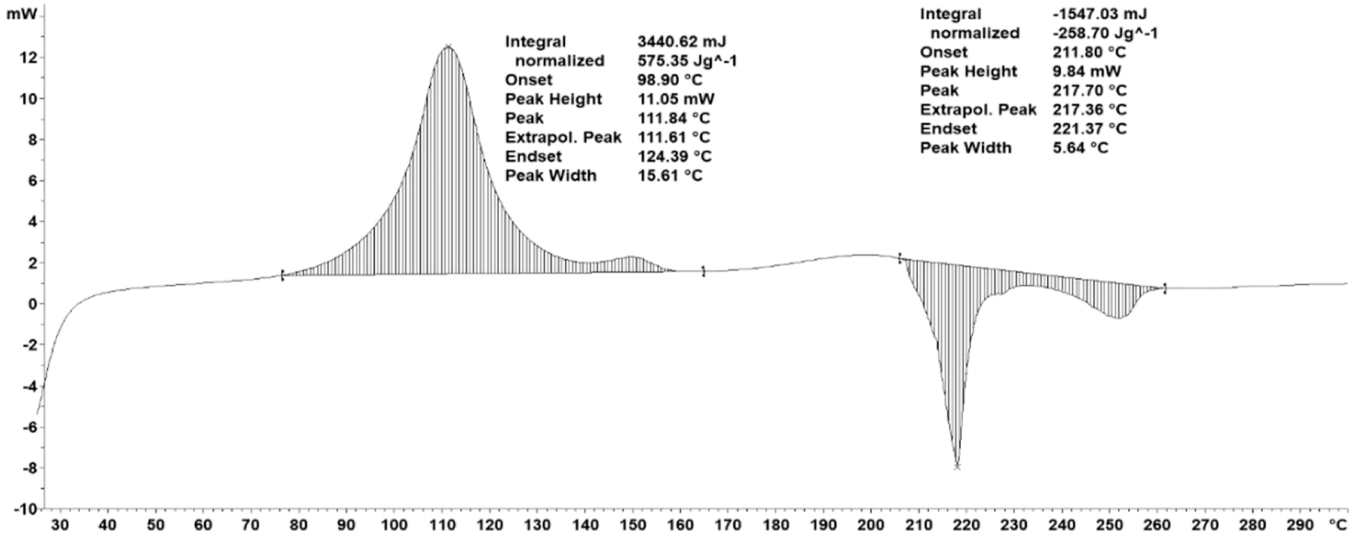

Figure 4. Thermal stability of $B_2(OH)_4$ in neat DMF.

moderate energy release of −575.35 J/g from the DSC thermogram (Figure 4). This indicates that $B_2(OH)_4$ could be incompatible with solvents such as DMF. To investigate this further, dissolution and thermal stability of $B_2(OH)_4$ in other polar aprotic solvents were evaluated including dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylacetamide (DMAc) using the same concentration as in DMF (1.3 M).

It was found that $B_2(OH)_4$ has decreased solubility in the order of DMSO > DMAc > DMF and a steady stream of gas bubble generation was noted with these solvents, too, similar to that in DMF. DSC studies indicated that there were low onset exothermic events observed when $B_2(OH)_4$ was dissolved in DMAc and DMSO, respectively, as summarized in Table 1 and Figures 5 and 6.

Table 1. Summary of Thermal Stability by DSC of $B_2(OH)_4$ in Different Neat Solvent and Cosolvents

solvent system	DMF	DMAc	DMSO	DMF/EtOH 4:1 (v/v)	DMSO/EtOH 3:4 (v/v)
T_{onset} (°C) of the exotherm	98.9	101.4	109.4	109.2	Exo1:76.4 Exo2:146.1
heat released (J/g)	575.4	284.1	255.7	121.5	Exo1:41.7 Exo2:255.6

For the process development in flow, the choice of solvent to ensure the stability of the stock solution of $B_2(OH)_4$ was important. To alleviate the incompatibility of $B_2(OH)_4$ with the solvents studied, dissolution of $B_2(OH)_4$ in other solvents such as methanol, water, and EtOH was studied. When $B_2(OH)_4$ was added to methanol, a quick dissolution accompanied by vigorous gas release was noted as reported in the literature[10] and methanol was not considered for further studies. In contrast, $B_2(OH)_4$ did not completely dissolve in EtOH even at higher volumes (>15 vol) and at higher temperatures with no noticeable gas generation. This was an interesting observation, and we further evaluated the thermal stability of the solution with EtOH as a cosolvent in DMF and DMSO. To our great excitement, a clear solution of $B_2(OH)_4$ with EtOH (up to 60 vol %) was observed, and there was no detectable gas generation even upon standing the solution for 12−16 h. The thermal stability of these solutions by DSC was further studied, as summarized in Table 1 and Figures 7 and 8. The lower intensity of the thermal events accompanied by no visual off-gas release confirms EtOH as a suitable cosolvent that significantly stabilizes $B_2(OH)_4$ in the solvent mixture.

DMSO solvent was applied as the process solvent, considering its higher solubility for $B_2(OH)_4$. Finally, an ARSST study was performed with a stock solution of $B_2(OH)_4$ dissolved in 3:4 (v/v) DMSO/EtOH which indicates that the stock solution is stable within 100 °C of the operating temperature (20−30 °C) (refer to Figure 9). The solvent system DMSO/EtOH was then applied for further evaluation of chemoselective nitro reduction in continuous flow mode.

2.3. Evaluation in Flow. Initial flow experiments were performed using a Vapourtec R-series system with HPLC pumps and 1/16" PFA tubing. Following the observations from the small-scale batch experiments, screening was carried out at low temperatures (0 to 10 °C) using the DMSO/EtOH solvent system.

As captured in the flow scheme (Figure 10), the solution of **1a** with 4,4′-bipyridine was sequentially combined with the solution of $B_2(OH)_4$ in 3:4 (v/v) DMSO/EtOH giving full conversion with a residence time (t_R) of about 7 min (Table 2, entry 1). The yield decreased when DMF was used as a solvent, which was also accompanied by an increased exothermicity (Table 2, entry 2). A reduction in conversion was also observed when using reduced equivalence of 4,4′-bipyridine (4 vs 8 mol %) at both 10 and 22 °C (Table 2, entries 3 and 4). With 6 mol % of 4,4′-bipyridine, complete conversion was observed with a slightly lower yield of **2a** compared to that by applying 8.5 mol % (Table 2, entry 5 vs 1). With 8.5 mol % of 4,4′-bipyridine, the residence time screening was studied (Table 2, entries 6 to 8). Residence times of 3 min were determined to be best, providing a high yield with efficient throughput. Using the best conditions, a 15 g scale synthesis of **2a** was performed using 1/8" O.D. PFR (21.5 mL) gave about 52 g/h throughput (Table 2, entry 9) with an isolated yield of 89%. During all experiments, the temperature of the reaction mixture, monitored by a thermocouple (refer to Figure 10), was usually 1.5 to 3 °C above the set external temperature (refer to Table 2).

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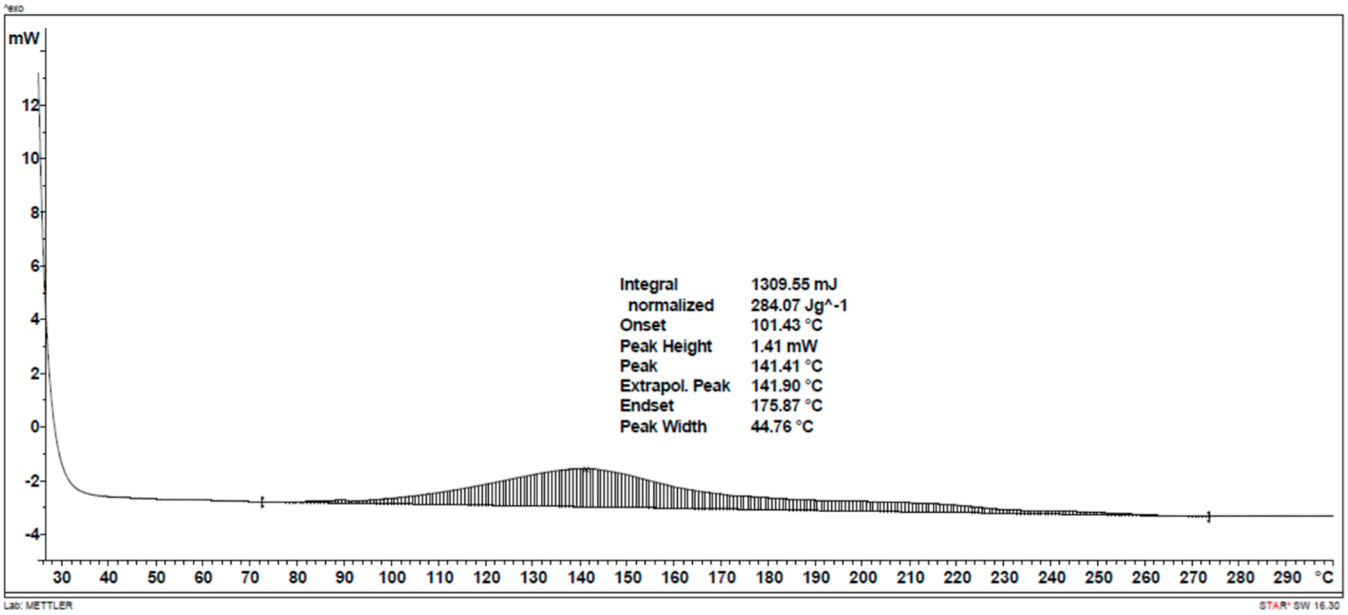

Figure 5. Thermal stability of $B_2(OH)_4$ in neat DMAc.

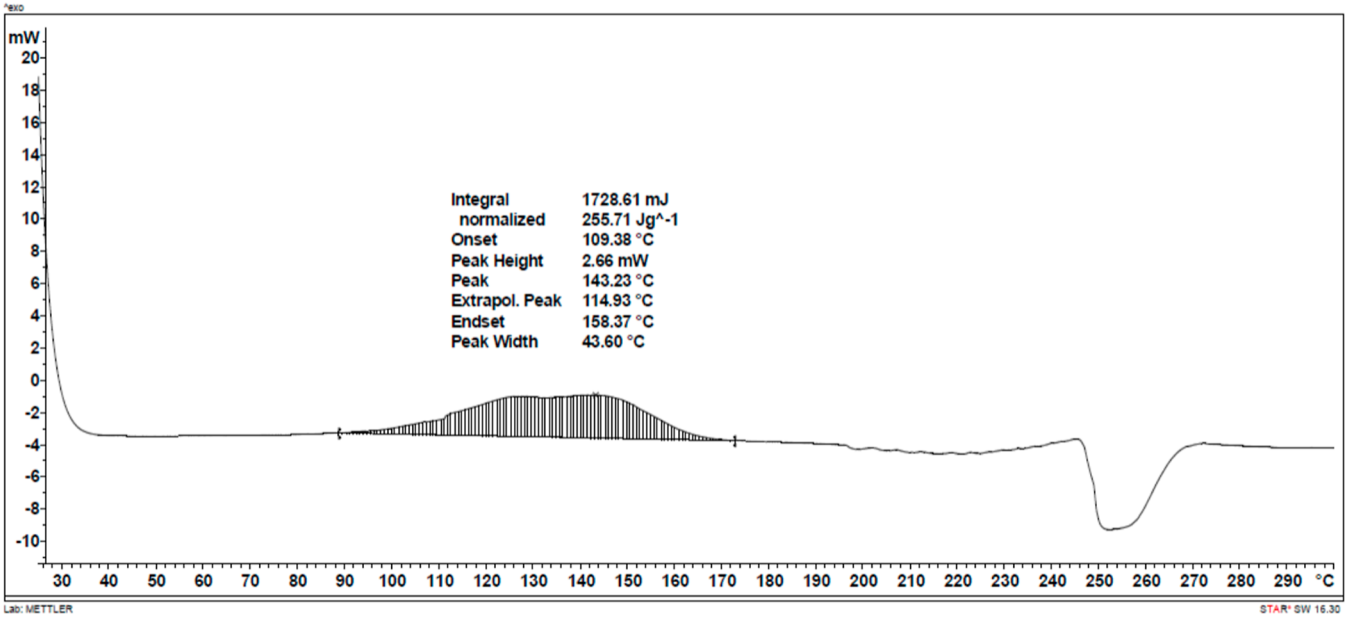

Figure 6. Thermal stability of $B_2(OH)_4$ in neat DMSO.

3. EVALUATION OF THE SUBSTRATE SCOPE IN FLOW MODE

Using optimized conditions, a series of highly functionalized nitro compounds were considered to evaluate reduction efficiency and selectivity (Table 3). A range of functional groups were compatible under the reduction conditions. The corresponding aniline derivatives were isolated in good to excellent yields. Compound **2a** was synthesized on a 15 g scale with an 89% isolated yield. Substrate **2b** containing bromide and nitrile functional groups resulted in an excellent yield without generating any other impurities. Reduction of 2,5-dichloro nitrobenzene **1c** was accomplished with great ease which otherwise requires a nitrogen-doped carbon-encapsulated nickel catalyst system to reduce the nitro group,[11] and the des-Cl impurity would be very challenging to be rejected in the subsequent steps. The compound **2c** is a key component of the drug molecules diclofenac and clonidine. The chemoselective nitro reduction was further applied in the presence of other functional groups such as bromide **2d**, carboxylic acid **2e**, olefin **2f**, and sulfinimine **2g**. In the case of compound **2e**, after the reduction of the nitro group in 2-nitro phenylacetic acid (**1e**), it was cyclized in situ to produce the indolinone, possibly due to the activation by Lewis acidity nature of the boryl reagent. The same product **2e** was reported using SmI_2-promoted reductive intramolecular cyclization of **1e** through a single electron transfer mechanism.[13]

It should be noted that in addition to stabilizing the $B_2(OH)_4$ stock solution, the inclusion of EtOH helps reduce the level of dimer impurities (diazo) during the nitro reduction process (Table 3, entry **2d**). Using the mechanistically required amount of $B_2(OH)_4$ (3.2 equiv vs 5 equiv reported in ref 8)

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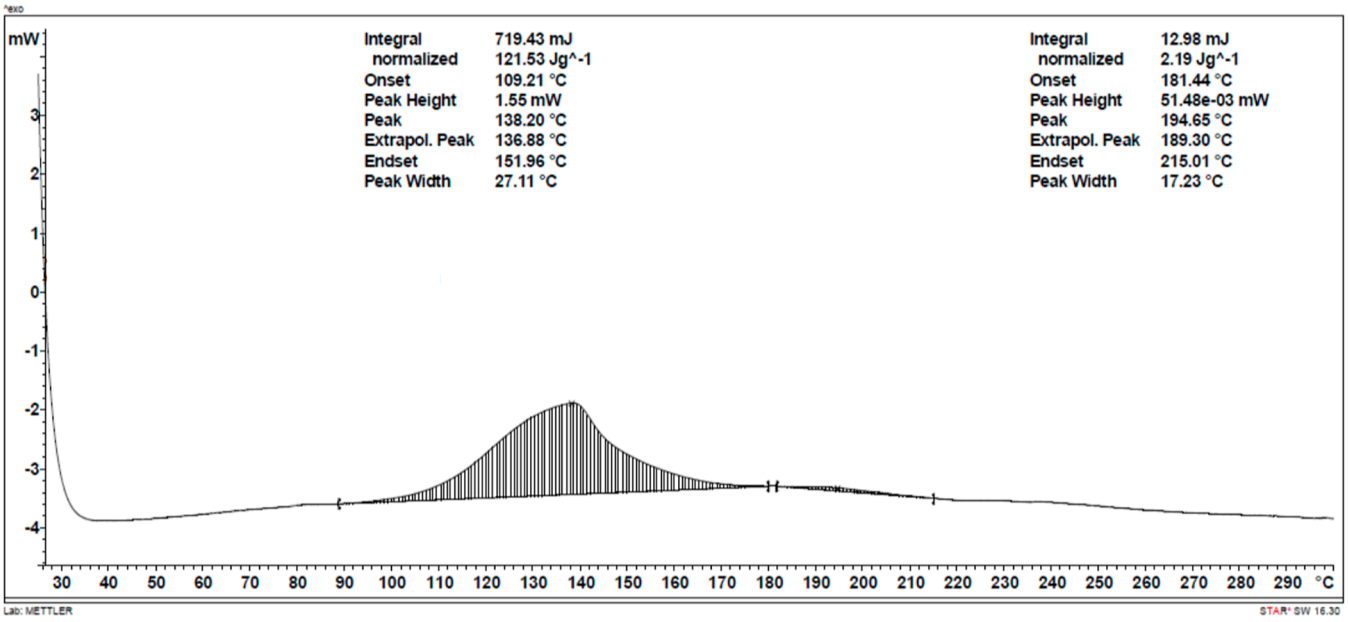

Figure 7. Thermal stability of $B_2(OH)_4$ in 4:1 (v/v) DMF/EtOH.

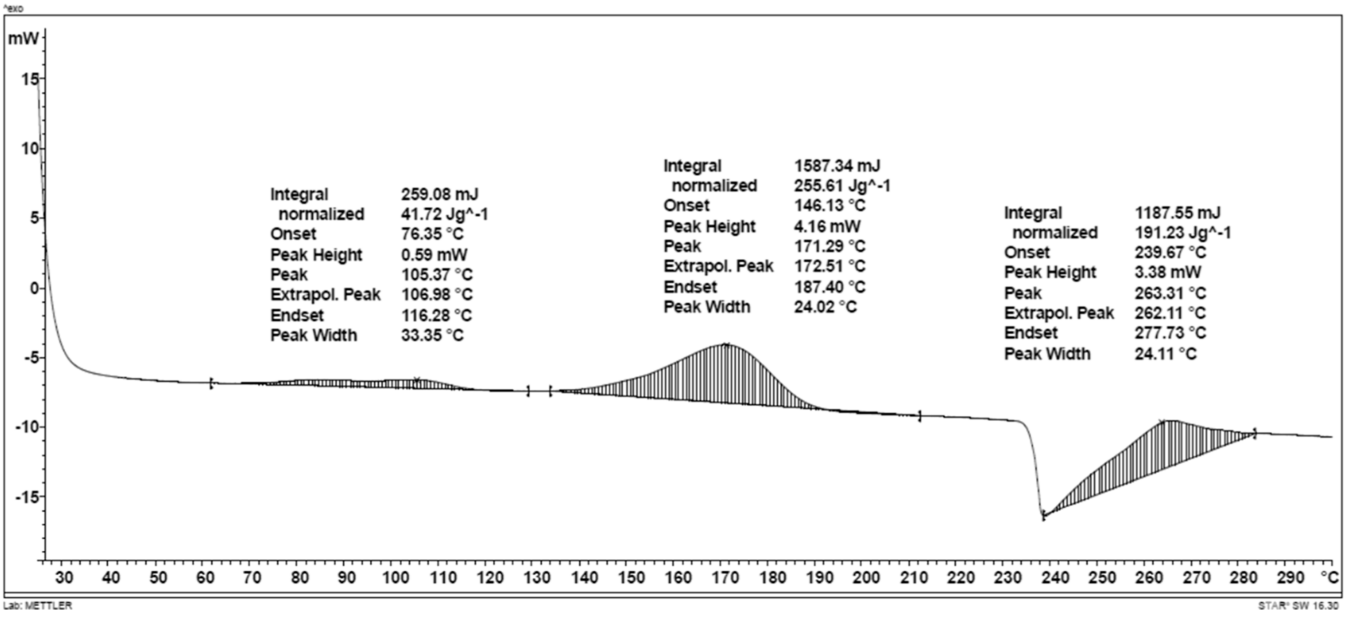

Figure 8. Thermal stability of $B_2(OH)_4$ in 3:4 (v/v) DMSO/EtOH.

positively impacts both chemical efficiency and the economics of the reduction process.

4. CONCLUSIONS

In summary, the integration of EtOH for a $B_2(OH)_4$/4,4′-bipyridine-mediated chemoselective nitro reduction system in continuous flow mode holds great promise for streamlining synthetic transformations in organic synthesis, offering a versatile and alternative approach to accessing various valuable aniline-containing compounds. We identified a safe and continuous flow process by addressing key thermal stability issues associated with the chemoselective nitro-reduction conditions utilizing $B_2(OH)_4$ as a reductant in the presence of catalytic 4,4′-bipyridine. DMSO in EtOH provides much safer scale-up opportunities for this important transformation. The continuous flow process offers the possibility of scaling up these conditions in a practical manner. Many valuable aniline derivatives with diverse labile functional groups were accessed including -TBS and -Bn, cyano, halides, carboxylic acids, olefins, allyls, alkenes, sulfinimines, and benzylic alcohols. Application of this newly developed chemoselective reduction system is being applied for many useful synthetic transformations and will be reported in due course.

5. EXPERIMENTAL SECTION

5.1. General Information. Commercially available solvents (from Oakwood Chemical) and reagents [$B_2(OH)_4$ (ChemScene, ≥98.0%) and 4,4′-bipyridine (ChemScene, ≥98.0%)] were used as received without further purification. All NMR data were recorded using a Bruker 400 MHz instrument. DSC and ARSST were used to collect process safety data. HPLC data were collected on an HPLC instrument

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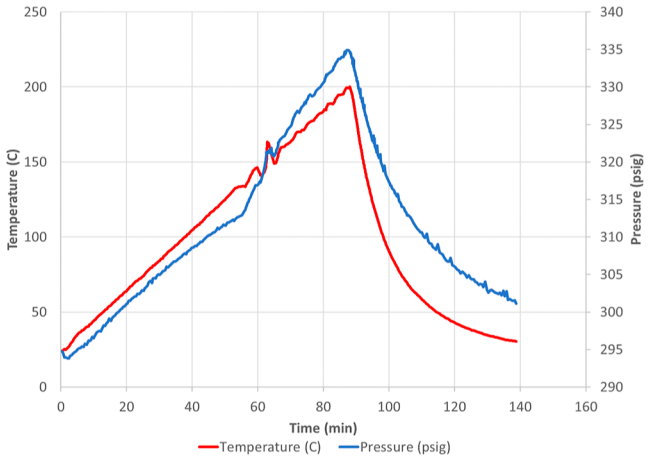

Figure 9. ARSST data for the thermal stability of stock solution of $B_2(OH)_4$ in 3:4 (v/v) DMSO/EtOH.

with UV detection. HPLC conditions were as follows: Poroshell 120 EC-C18, 4.6 × 100 mm, 2.7 μm; 95 to 10% gradient of water (0.1% phosphoric acid): acetonitrile over 9 min, then isocratic 10% water (0.1% phosphoric acid): acetonitrile for 4 min, flow rate 1.0 mL/min; acquisition time 13 min; UV at 225 nm.

5.2. General Procedure for Nitro Reduction in Batch. Dissolve nitro derivative **1** (5 mmol, 1.0 equiv) in DMF (10 V) or DMSO/EtOH (15 V, 1:2) at RT. The solution was cooled to 0 °C and was charged $B_2(OH)_4$ (3 equiv) and 4,4-bipyridine (5 mol %) in 3 equal portions (added both reagents together). Temperature was monitored and controlled at no more than 25 °C during the addition. After completion of the reaction, it was quenched by the addition of water (15 V) dropwise at 10 °C. The obtained solid was filtered and dried to obtain the corresponding aniline product. If the product was not crystallized out from the reaction mixture, it was extracted with IPAc (2 × 10 V). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a crude residue. Solution yield was provided by NMR with an internal standard. The residue was purified by silica gel column chromatography to obtain isolated yield after dryness. The $B_2(OH)_4$–bipyridine complex is expected to be water soluble; as a result, the isolated products have no detectable amount of the side product derived from this complex by the NMR analysis.

5.3. General Procedure for Nitro Reduction in Flow. Reactions were performed at 2.5 g input of the nitro compound using 4,4′-bipyridine (8.5 mol %) and DMSO/EtOH (2:3 v/v) giving about 1.0 M solution (feed stream 1). $B_2(OH)_4$ (3.2 equiv) was dissolved in DMSO/EtOH (3:4 v/v) for about 1.5 M solution (feed stream 2). $B_2(OH)_4$ was dissolved in DMSO/EtOH at 30–40 °C to speed up the dissolution followed by cooling to RT. Feed streams 1 and 2 were supplied using a Vapourtec R-series flow chemistry system using the 1/8 in × 1.5 in PFA static mixer and 1/8″ O.D. PFA tubing housed inside an insulated glass manifold for temperature control. Residence time (about 6 min) was achieved by changing flow rates while maintaining the reaction loop volume constant and temperature at 5 to 15 °C. The temperature in the reactor was recorded by a thermocouple. Only steady-state reaction mixtures were collected and isolated through the addition of water and filtration as for the batch process procedure.

Table 2. Development of Continuous Flow Chemistry Conditions for the Reduction of 1a[a]

entry	4,4-bipyridine	T, °C	t_R, min	**2a**:**1a**, %[b]	**2a**, A %[b]
1[c,d]	0.085 equiv	10.0	7	100:0	96.3
2[e]	0.085 equiv	10.0	7	89:11	81.8
3[d]	0.040 equiv	10.0	10	97:3	91.5
4[d]	0.040 equiv	22.0	7	96:4	91.3
5[d]	0.060 equiv	22.0	7	100:0	95.5
6[d]	0.085 equiv	22.0	5	100:0	95.3
7[d,f]	0.085 equiv	22.0	3	100:0	94.4
8[d]	0.085 equiv	22.0	1.5	86:14	83.2
9[g]	0.085 equiv	22.0	3	100:0	94.4

[a]Reactions were performed at 1.3 g input of **1a** with 3.2 equiv $B_2(OH)_4$ on a Vapourtec R-series flow chemistry system using 1/16″ O.D. PFA tubing with a 1″x 1/8″ static mixer was housed inside an insulated manifold for temperature control. Reaction components were combined according to Figure 10. Residence times were achieved through flow rates varying while maintaining the loop volumes constant. Only steady-state reaction streams were collected to analyze in-process reaction profiles by HPLC. [b]Conversion [relative product (**2a**) to starting material (**1a**) peak area (%) ratios] and product solution purity were determined by HPLC analysis (230 nm) of an aliquot of the quenched reaction mixture. [c]2.5 g scale using 1/8″ O.D. PFA tubing. [d]DMSO (3 V):EtOH (4.2 V) as a solvent. [e]DMF (8 V) as a solvent. [f]Conditions are defined as the best. [g]15 g input using 1/8″ O.D. PFA tubing with the 1″ × 1/8″ O.D. static mixer in 52 g/h throughput.

5.4. Preparation of 2a in Flow. Stock solutions of **1a** (15 g, 1.0 equiv), 4,4′-bipyridine (8.5 mol %) in 2 V DMSO/EtOH (2:3 v/v) (feed stream 1), as well as $B_2(OH)_4$ (3.2 equiv) in 5.2 V DMSO/EtOH (3:4 v/v) (feed stream 2) were prepared in separate feed containers under nitrogen. Feed streams 1 and 2 were pumped by HPLC pumps at flow rates of 2.36 and 4.81 mL/min, respectively, and were combined in a T-mixer. Then, the reaction mixture stream entered a 1/8″ × 1.5″ PFA static mixer followed by a 21.5 mL 1/8″ O.D. reaction loop at room temperature (22 °C) for about 3 min. The temperature of the reaction mixture was monitored by a thermocouple installed

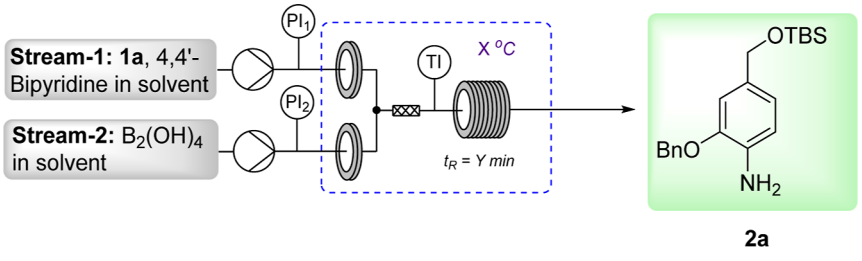

Figure 10. Flow setup scheme for nitro reduction of **1a**.

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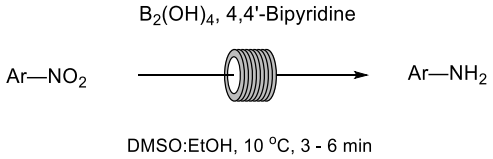
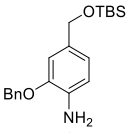
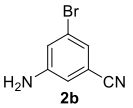
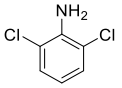
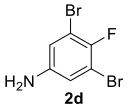
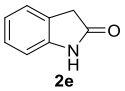
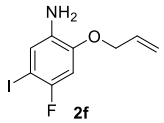
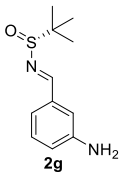
Table 3. Substrate Scope for the Reduction of Nitro Compounds with Labile Functional Groups[a]



Product	Product A% by Flow[e]	Yield[d] Flow	Yield[d] Batch
 **2a**	94[b]	93% (89%)	92% (74%)
 **2b**	98	93% (85%)	85% (78%)
 **2c**	99	95% (90%)	91% (88%)
 **2d**	99	90%	89% (85%)
 **2e**	95[c]	90%	70% (60%)
 **2f**	99	95%	94% (92%)
 **2g**	99	95% (86%)	89% (80%)

[a]Reactions were performed at 2.5 g input of compounds **1a−g** on a Vapourtec R-series flow chemistry system using 1/8″ O.D. PFA tubing equipped with the 1/8″ × 1.5″ PFA static mixer. Reaction components were combined according to Figure 10 using DMSO/EtOH (2:3 v/v) for 1.0 M solution of nitroarene 1 (2.5 g), 4,4′-bipyridine (8.5 mol %), and DMSO/EtOH (3:4 v/v) for 1.5 M solution of $B_2(OH)_4$ (3.2 equiv). Residence time (6 min) was achieved through a change in flow rates while maintaining the reaction loop volume constant at 5 to 15 °C. [b]15 g input with t_R = 3 min at RT (22 °C). [c]Obtained from 2-nitro phenylacetic acid starting material **1e** after isolation (refer to the Supporting Information). [d]Solution yield is provided from the NMR assay and isolated yield is shown in parentheses. [e]Product A % was determined by HPLC analysis (230 nm) of an aliquot of the quenched reaction mixture.

between the static mixer and reactor. Only steady-state reaction streams were used to analyze in-process reaction profiles and subsequent isolation. A sample of the crude reaction mixture was analyzed by HPLC (230 nm) with water and acetonitrile (1:1 v/v) as a diluent. The reaction mixture was diluted with water (10 V) and was extracted with IPAc (2 × 10 V). The IPAc solution was directly applied for the next step of the synthesis. To obtain the analytical data, the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the crude residue which was purified by silica gel column chromatography to give **2a** (12.28 g, 89%) as a colorless oil.

5.5. Synthesis of 2-(Benzyloxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)aniline 2a. Batch: reaction was started with 500 mg of **1a** and 350 mg of compound **2a** was isolated as a colorless oil (92% solution yield, 76% isolated yield). Flow: reaction was started with 15 g of **1a** and isolated 12.3 g of compound **2a** as a colorless oil (93% solution yield, 89% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.24 (m, 5H), 6.82 (s, 1H), 6.67 (d, J = 8.1 Hz, 1H), 6.62 (d, J

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= 7.87 Hz, 1H), 5.02 (s, 2H), 4.55 (s, 2H), 3.71 (br s, 2H), 0.85 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.48, 137.26, 135.39, 131.80, 128.55 (2 × C), 128.23, 127.94, 127.54 (2 × C), 126.23, 119.42, 114.84, 110.72, 70.41, 65.17, 26.00, 18.43, −4.85, −5.13. LCMS: 344.2 [M + H].

5.6. Synthesis of 3-Amino-5-bromobenzonitrile 2b. Batch: reaction was started with 500 mg of **1b** and isolated 340 mg of **2b** as a beige solid (85% solution yield, 78% isolated yield). Flow: reaction was started with 500 mg of **1b** and isolated 370 mg of **2b** as a beige solid (93% solution yield, 85% isolated yield). ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.06−7.03 (m, 2H), 6.85 (d, J = 4.0 Hz, 1H), 5.91 (br s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 151.4, 123.0, 120.7, 120.6, 118.5, 115.7, 113.7.

5.7. Synthesis of 2,6-Dichloroaniline 2c. Batch: reaction was started with 500 mg of **1c** and isolated 370 mg of **2c** as an off-white solid (91% solution yield, 87.6% isolated yield). Flow: reaction was started with 500 mg of **1c** and isolated 382 mg of **2c** as an off-white solid (95% solution yield, 90.4% isolated yield). ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.09 (d, J = 8.0 Hz, 2H), 6.53 (d, J = 8.0 Hz, 1H), 4.36 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 127.8 (2 × C), 119.6 (2 × C), 118.1.

5.8. Synthesis of 3,5-Dibromo-4-fluoroaniline 2d. Batch: reaction was started with 600 mg of **1d** and isolated 458 mg of compound **2d** as an off-white solid (89% solution yield, 85% isolated yield). Flow: reaction was started on 500 mg of **1d**, and the product, **2d**, was assayed with 90% solution yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, J = 5.2 Hz, 2H), 3.61 (br s, 2H); ^{19}F NMR (400 MHz, $CDCl_3$): δ −114.95; ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.51, 148.16, 144.00, 143.97, 118.45, 110.05, and 109.82; LCMS: 269.8 [M + H].

5.9. Synthesis of Indolin-2-one 2e. Batch: reaction was started with 500 mg of 2-nitrophenylacetic acid and isolated 310 mg of compound **2e** as a light-red solid (70% solution yield and 60% isolated yield). Flow: reaction was started with 500 mg scale; product **2e** was assayed with 90% solution yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (br s, 1H), 7.27−7.19 (m, 2H), 7.01 (t, J = 7.82 Hz, 1H), 6.89 (d, J = 8.40 Hz, 1H), 3.54 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.79, 142.52, 127.93, 125.28, 124.61, 122.34, 109.74, 36.48; LCMS: 134.1 [M + H].

5.10. Synthesis of 1-(Allyloxy)-5-fluoro-4-iodo-2-nitrobenzene 1f. A 250 mL RBF was equipped with a magnetic stir bar, septa, and temperature probe. Charged phenol derivative 5-fluoro-4-iodo-2-nitrophenol (6 g, 21.2 mmol), K_2CO_3 (8.79 g, 63.6 mmol), and ACS-grade acetone (10 °C) at rt. Charged allyl bromide (1.96 mL, 23.32 mmol) at rt. The mixture was stirred at 57−59 °C (internal) for 6 h. HPLC shows completion of the reaction, with product **1f** at 96 A %. The reaction mixture was cooled to rt and filtered and the cake was washed with acetone (1 V). The filtrate was concentrated and purified by column chromatography, eluent 2% EtOAc/hexanes to afford 5.5 g of yellow solid **1f** with 80% isolated yield. ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 4 Hz, 1H), 6.80 (d, J = 12 Hz, 1H), 6.04−5.94 (m, 1H), 5.50−5.32 (m, 2H), 4.67−464 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.87, 163.35, 154.25, 154.15, 136.89, 136.17, 136.12, 130.77, 119.06, 103.04, 102.75, 70.59, 68.76, 68.48. LCMS: 324 [M + H].

5.11. Synthesis of 2-(Allyloxy)-4-fluoro-5-iodoaniline 2f. Batch: reaction was started with 500 mg of **1f** and isolated 420 mg of **2f** as an off-white solid (94% solution yield and 92% isolated yield). Flow: reaction was started with 500 mg scale, and the product was assayed with 95% solution yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (d, J = 6.3 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.06−5.97 (m, 1H), 5.41−5.29 (m, 2H), 4.51 (d, J = 5.3 Hz, 2H), 3.67 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.13, 153.79, 147.12, 147.03, 134.14, 134.11, 132.46, 122.85, 122.82, 118.27, 100.76, 100.47, 69.57, 69.14, 68.88; LCMS: 294 [M + H].

5.12. Synthesis of (*R*,*E*)-2-Methyl-N-(3-nitrobenzylidene)propane-2-sulfinamide 1g. (*R*)-*tert*-Butylsulfinamide (3.0 g, 24.79 mmol) was dissolved in THF (15 mL) and 3-nitrobenzaldehyde (4.4 g, 29.75 mmol) was added followed by $Ti(OEt)_4$ (10.4 mL, 49.58 mmol). The reaction mixture was stirred for 5 h at 60 °C. After completion of the sulfinamide, EDTA (17.5 g, 74.32 mmol) was added at 60 °C and stirred for another 1 h. Then, the reaction mixture was cooled to room temperature and stirred with EtOAc to extract the product from the organic layer. The aqueous layer was extracted 2 times with ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness. Purification of the residue by chromatography on SiO_2 (EtOAc/hexane) afforded the desired product **1g** as a white solid (4.0 g, 80% isolated yield, 93 wt %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71−8.69 (m, 1H), 8.66 (s, 1H), 8.36 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 8.14 (dd, J = 5.1, 3.8 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ: 160.62, 148.82, 135.50, 134.94, 130.15, 126.53, 123.54, 58.32, 22.67 (3 × C). LCMS: 254.8 [M + H].

5.13. Synthesis of (*S*,*E*)-N-(3-Aminobenzylidene)-2-methylpropane-2-sulfinamide 2g. Batch: reaction was started with 200 mg of **1g** and isolated 142 mg of **2g** as a white solid (89% solution yield and 80% isolated yield). Flow: reaction was started with 500 mg of **1g** and isolated 380 mg of **2g** as a white solid (95% solution yield and 86% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H), 7.36−7.29 (m, 1H), 7.29−7.24 (m, 2H), 6.90 (ddd, J = 7.8, 2.3, 1.3 Hz, 1H), 3.91 (s, 2H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ: 163.01, 147.00, 135.11, 129.82, 120.40, 119.18, 114.43, 57.71, 22.61 (3 × C). LCMS: 224.9 [M + H].

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.4c00267.

^{1}H NMR and ^{13}C NMR of the products (PDF)

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Notes

The authors declare no competing financial interest.

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