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Continuous Flow Process for Reductive Deoxygenation of ω-Chloroketone in the Synthesis of Vilazodone

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Supporting Information

ABSTRACT: A continuous flow process for the reductive deoxygenation of 3-(4-chlorobutanoyl)-1*H*-indole-5-carbonitrile to 3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile was developed using a continuous stirred tank reactor (CSTR) setup. The opportunity for process optimization as well as scale-up feasibility was investigated at a laboratory scale. Advantages of a continuous process such as increased product yield, minimized impurity formation, enhanced safety, and increased overall purity of the isolated material thereby avoiding a purification step were demonstrated. Both sodium borohydride and a borane·THF complex were explored as reducing agents in conjunction with iron trichloride which produced high purity 3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile not requiring further purification in higher yield than the standard batch process.

KEYWORDS: *Vilazodone, continuous flow, continuous stirred tank reactor (CSTR), reductive deoxygenation*

INTRODUCTION

Vilazodone hydrochloride (**1**, Figure 1) is a 3-alkyl indole drug used for the treatment of major depressive disorder.[1] Several

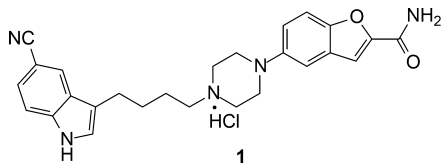

Figure 1. Structure of vilazodone hydrochloride (**1**).

batch-mode processes are known for commercial manufacturing of **1** consisting of *N*-alkylation of compound **4a−c** with compound **3a/b** (Scheme 1).[2] One of the key and most problematic steps of these manufacturing processes is the production of **3a/b**, which is obtained from the reductive deoxygenation of compounds such as **2a/b**. We had previously developed a batch process for the reductive deoxygenation of 3-(4-chlorobutanoyl)-1*H*-indole-5-carbonitrile (**2b**) to 3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile (**3b**) using sodium borohydride and iron trichloride as a reducing agent.[3] To control heat evolution during charging of the reducing agent, the batch process was conducted at low temperature that resulted in accumulation of a difficult to remove impurity (**5**) originated from the competing side reaction (see Scheme 3). Removal of this impurity requires additional batch processing and subsequently reduces the yield of **3b**. Continuous flow processing provides superior control of heat evolution that in turn allows running the reaction at a higher temperature and reducing reaction time resulting in suppression of a side reaction and impurity formation. It was for these reasons we explored the reductive deoxygenation of **2b** in continuous flow mode in the anticipation of suppressing the impurity formation to achieve a higher yield and purity of **3b**.

Flow chemistry processes have become abundant in both the pharmaceutical industry and in academia.[4] This can be attributed to different types of laboratory scale continuous flow chemistry platforms available for research purposes and the acceptance of flow chemistry processes by regulatory agencies.[5] Chemical transformations can benefit from flow processes by reducing impurities, increasing yields/selectivity, and allowing use of hazardous chemicals which would otherwise be dismissed as possible reagents. The difficulty lies with augmenting a chemical reaction to suit the conditions necessary for application to continuous flow, the main concern being avoiding the use of dense solid reagents which can cause issues with pumping and plugging lines of continuous flow equipment such as plug-flow type reactors.

The reductive deoxygenation of **2b** in the batch process involves the portionwise addition of sodium borohydride pellets to a slurry of **2b** and iron trichloride in tetrahydrofuran (Scheme 2). The reaction mixture remains a slurry during the course of the reaction along with the generation of hydrogen gas. Because of the multiphasic nature of the reaction mixture, we decided to use for our studies a continuous stirred tank reactor (CSTR) setup to avoid the above-mentioned mechanical issues. A commercially available agitated cell reactor utilizing the CSTR concept was used for initial experimentations due to its compact design and options to modify the CSTR configuration setting easily.[6] This equipment consists of a reaction block containing 10 cells connected in series by small channels (Figure 2). It is able to accommodate slurries and suspensions due to mechanical agitators in each cell and has a variety of side ports which can be used for reagent additions, thermocouples, and other process analytical techniques (PAT). The internal volume of the reactor block can be altered by changing the size of the agitators used in each cell spanning from 10 to 70 volume % of each cell. This allows for smaller volumes in the initial cells for sufficient mixing and

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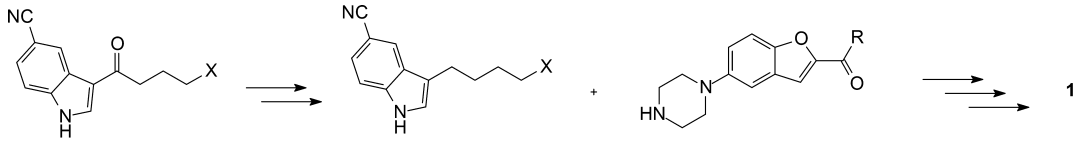
Scheme 1. Synthetic Route Used in Commercial Manufacture of 1



Scheme 2. Batch Process for Synthesis of 3b

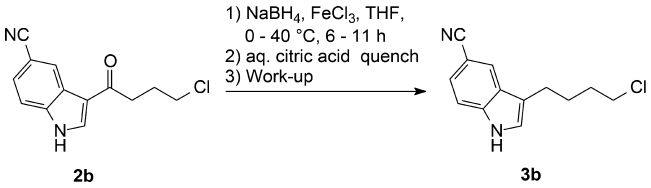


Figure 2. Reaction block from the agitated cell reactor[6] with numbered CSTRs.

heat transfer and larger volumes in later cells for increased residence time.

We focused our efforts on applying continuous flow chemistry to produce the intermediate **3b** in one of the industrial vilazodone manufacture processes (Scheme 2); the reductive deoxygenation of **2b** with sodium borohydride ($NaBH_4$) in the presence of iron trichloride ($FeCl_3$) in tetrahydrofuran leads to **3b**. During the course of the reaction, intermediate **4** is formed which can intercept another molecule of product **3b** to produce impurity **5** (Scheme 3) that is difficult to purge over the remaining manufacturing steps. The reductive deoxygenation step was optimized in the laboratory and scaled up on the 50−70 kg scale. It was observed during the initial scale-up batches that the level of this impurity goes up with increased reaction time (Table 1). The initial process used for production of batch 1 consisted of adding $NaBH_4$ pellets over 1 h in 8 portions to a slurry of **2b** and $FeCl_3$ in THF at 0−5 °C followed by warming to 35−40 °C over 2 h and maintaining the temperature for an additional 3 h for reaction completion. This yielded a low level of impurity **5** but still required purification to remove other dimeric impurities that resulted in an overall product yield of ca. 20%. In batch 2 the temperature was maintained at 0−5 °C for 6 h for reaction completion, where a slightly higher yield of crude material was obtained but a higher level of impurity **5** was observed. During batch 3 the reaction time was extended to 11 h at 0−5 °C for reaction completion which greatly increased both the crude yield and impurity **5** level. Due to the high amount of impurity **5**, multiple purifications were needed to meet the established specification limits and an overall yield of 20% was obtained. From the batch 1 data, we see that higher temperature minimizes the amount of impurity **5**. This may indicate that the intermediate **4** is long-lived at lower temperature allowing it to also react with the product to generate impurity **5**. We envisioned applying continuous flow technology to this process to increase the overall yield and reduce the amount of all impurities by increasing the reaction temperature to 40 °C (compared to below 40 °C in the batch mode) with a much shorter reaction time. In batch mode the reaction cannot be conducted at 40 °C due to safety concerns associated with controlling the exotherm during the sodium borohydride addition.

RESULTS AND DISCUSSION

The reaction mixture generated during the reductive deoxygenation process consists of three physical phases, namely of solid $NaBH_4$ and starting material **2b**, THF as a liquid solvent, and liberated hydrogen gas. An agitated cell reactor CSTR setup is ideal for investigating this type of process, as it allows handling multiphase reaction mixtures, contrary to plug flow reactors which are not suitable for these types of processes. Before studying this process in continuous flow, a few modifications had to be made to the current process at a laboratory scale. First, the reaction temperature was increased to 40 °C at which temperature the reduction reaction was complete within 30 min making it a feasible process for continuous flow. Second, the addition of sodium borohydride into the reaction also had to be addressed. Sodium borohydride is a dense solid in THF which could not be pumped efficiently for use in a continuous flow process. However, sodium borohydride is soluble in diglyme and for

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Scheme 3. Formation of Impurity 5 during the Reductive Deoxygenation Reaction

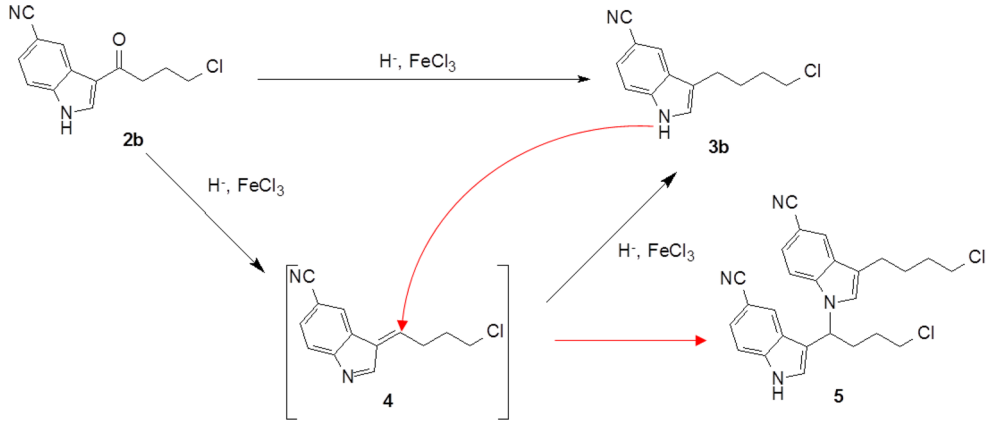

Table 1. Early Scale-up Batch Data (50−70 kg)

batch[a]	$NaBH_4$ addition time (h)/ temp	total reaction time (h)	end temperature	crude **3b** yield (%)/ **5** (a%)	purified **3b** yield (%)[b]
1	1 at 0−5 °C	6	40 °C	41/0.07[a]	20
2	1 at 0−5 °C	6	0−5 °C	49/0.19	30
3	1 at 0−5 °C	11	0−5 °C	66/2.26	20

[a]Due to other dimeric impurities, further purification was required to meet specification. [b]Impurity **5** level meets the specification limit of <0.10%.

our initial work a diglyme solution of sodium borohydride was used in the process. We quickly discovered the solubility of sodium borohydride in diglyme is very sensitive to temperature (Figure 3).[7] When using a saturated solution of sodium

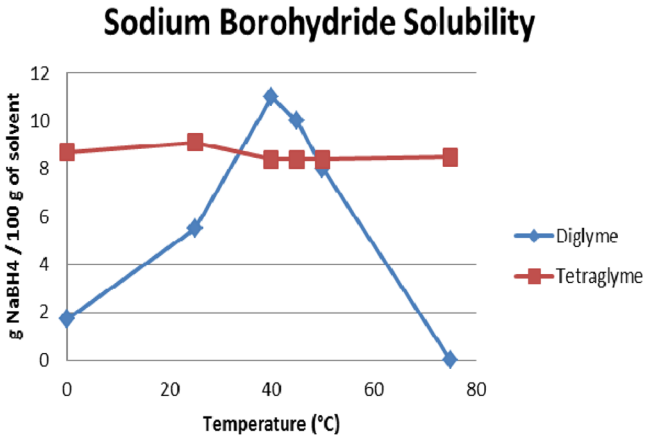

Figure 3. Sodium borohydride solubility in diglyme and tetraglyme at various temperatures.

borohydride, the solution line would plug due to $NaBH_4$ precipitation caused by even small temperature variations. Dilution of the $NaBH_4$ solution was not feasible as we had to minimize the amount of diglyme to allow for sufficient phase separation during the subsequent workup. To overcome this issue the $NaBH_4$ solvent was changed to tetraglyme which provides much more uniform $NaBH_4$ solubility over a wide temperature range and an overall higher solubility at ambient temperatures relative to diglyme.

Our initial experimental conditions were as follows: a solution of 1.1 equiv of iron trichloride in THF pumped into CSTR 1, a slurry of ketone **2b** in THF pumped into CSTR 1, and a solution of 1.2 equiv of $NaBH_4$ in tetraglyme pumped into CSTR 2 at a reaction temperature of 40 °C and a residence time of 30 min (Figure 4). These conditions led to a

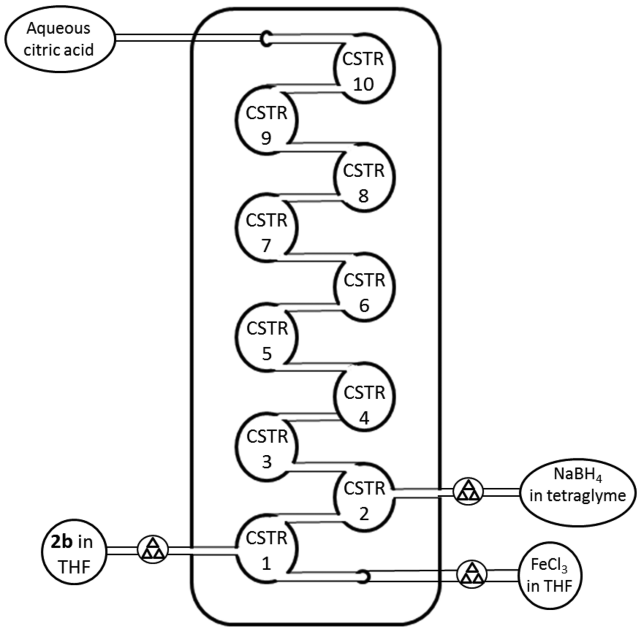

Figure 4. Agitated cell reactor setup.

steady state where the amount of impurity **5** is minimized but about 20% of intermediate **4** remained after the citric acid quench. A sample of this reaction mixture was taken before being quenched and treated with a small amount of $NaBH_4$ in tetraglyme. This led to complete conversion of the intermediate **4** to **3b** (Figure 5).

Since additional $NaBH_4$ was required to completely consume intermediate **4**, a second addition port for $NaBH_4$ was introduced into the agitated cell reactor at CSTR 6 with 0.4 equiv of $NaBH_4$ being charged. The new process setup whereby 1.1 equiv of $NaBH_4$ was added into CSTR 2 and 0.4 equiv was added into CSTR 6 allowed isolation of product **3b** in 34−45% yield with an HPLC purity of 99.5 a% and impurity **5** level of 0.09 a%.

The continuous flow process using the $NaBH_4$ solution in tetraglyme was able to reduce the impurity level and provide high purity **3b**, but the isolated yield was low due to about 23%

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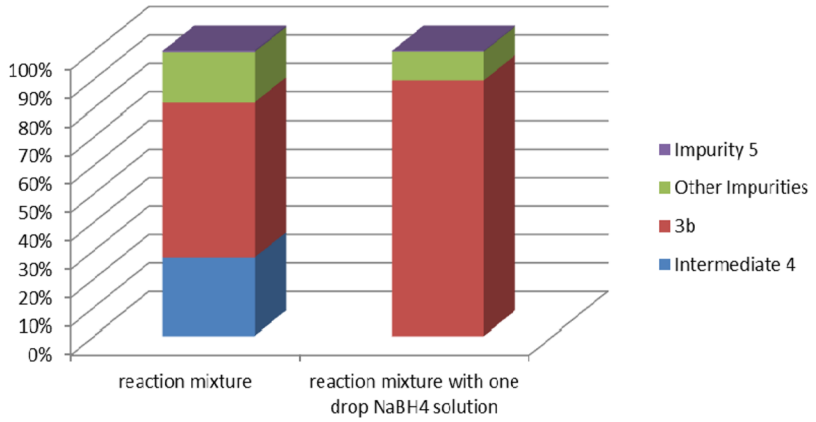

Figure 5. HPLC profile of reaction mixture: Reduction of intermediate **4** via second $NaBH_4$ addition.

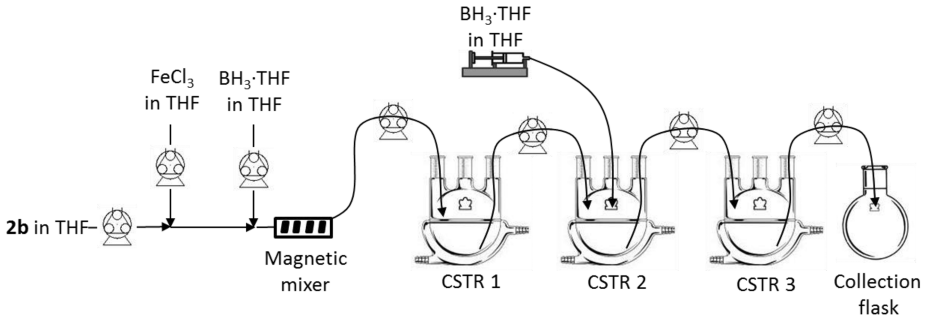

Figure 6. Schematic drawing of the CSTR with three jacketed reactor setup for reductive deoxygenation of **2b**.

of product lost into the mother liquor. To increase the yield, other reducing agents were explored to facilitate a simpler workup and isolation, mainly by eliminating the need for tetraglyme as a cosolvent. The borane tetrahydrofuran (BH_3·THF) complex was found to be an excellent reducing agent in the presence of iron trichloride. After slight optimization we found that charging 1 equiv of iron trichloride to CSTR 1 followed by 1 equiv of BH_3·THF charged into CSTR 2 and 0.2 equiv of BH_3·THF into CSTR 6 at a temperature of 20−25 °C and setting a residence time of 5 min was an ideal set of conditions for efficient reductive deoxygenation of **2b** to **3b**. These conditions led to a 66.5% yield of isolated **3b** with an overall HPLC purity of 99.6 a% and impurity **5** level of 0.09 a %. The 21% increase in yield was due to a combination of an overall higher yielding reaction using BH_3·THF and a reduction in the amount of product lost into the mother liquor during isolation. A batch reaction was conducted at a 5 g scale to compare with the continuous flow process; however, due to the large exotherm observed during BH_3·THF addition, the reaction had to be conducted at 0−5 °C with portionwise addition of BH_3·THF. During each of the six portions of BH_3·THF additions, there was a 5−6 °C increase in internal temperature and the reaction was complete shortly after the last portion was added. After workup and isolation a 64% yield of **3b** was obtained with an HPLC purity of 99.39 a% and impurity **5** level of 0.17 a%. The established specification for **3b** consists of >99.50 a% HPLC purity with <0.10 a% impurity **5**. A purification step would be required to meet these specifications which would reduce the yield by 10−15%. With these data, it is very clear that a batch process using BH_3·THF would be impractical on large scale in terms of safety considerations related to controlling an exothermic reaction as well as product yield and quality considerations.

These results attained using the agitated cell reactor equipment showcased the feasibility of conducting this process in a continuous flow mode. It has to be noted that one of the technical challenges of continuous flow processing associates with accumulation of hydrogen gas generated in agitated cells from the reaction of borane reagent with the acidic proton of the indole ring and during the aqueous citric acid quench of the excess borane reagent. It was found that the hydrogen gas generated in agitated cells effectively flows through the cells along with the reaction mixture into the quench vessel without significant pressure buildup and/or formation of gas pockets in the cells. The combined hydrogen gas is then safely removed via an exit port after diluting with a stream of nitrogen gas. To evaluate the feasibility for a scale out of this process to a kilo or pilot plant setting in light of the above-mentioned possible issue of hydrogen gas accumulation, we investigated the use of the CSTR setup consisting of jacketed reactors for this process.

A CSTR setup with a jacketed reactor was constructed with two 20 mL jacketed reactors and a 150 mL jacketed reactor with a working volume of 30 mL for our experiments. Each CSTR was connected to a nitrogen line to enable the escape of hydrogen gas generated. Our initial setup consisted of the three reagents adding simultaneously into CSTR 1 at 20 °C; however, this led to an internal temperature rise from 20 to 36 °C that would make such a setting unacceptable at a larger scale for safety reasons.

To dissipate the substantial heat generated by the highly exothermic reduction reaction during reagent mixing, a cooling tube maintained at 20 °C with magnetic agitators was introduced as a part of the charging line prior to the CSTR 1 entrance. The three CSTRs were maintained at 20−25 °C using the jacketed cooling system. A second portion of BH_3·THF was added into CSTR 2, and the reaction mixture was

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quenched with aqueous citric acid after exiting CSTR 3 (Figure 6). We were delighted to obtain a 71% yield of isolated **3b** with an overall HPLC purity of 99.6 a% and impurity **5** level of 0.06 a% using this setup.

Comparison of the three different processes—current batch process, $NaBH_4$ continuous flow process, and BH_3·THF continuous flow process—demonstrates the real value of applying continuous flow process to this chemical step. There are several areas which benefit from the batch process to continuous flow process change, namely process safety, number of unit operations, process mass intensity (PMI),[8] and the overall isolated yield (Table 2) to name a few.

Table 2. Comparison of the Three Different Processes

	batch process	$NaBH_4$ CF process	BH_3·THF CF process
yield (%)	25−30	45.6	71
PMI	89.1	73.8	48.6
number of unit operations	18	12	10

Reduction of the unit operation number and PMI value as well as product yield increase in the continuous flow process compared to the batch process using the $NaBH_4$ reducing agent are all due to a much cleaner chemical conversion and, thereby, elimination of the purification step in the CF process. A further increase in yield and decrease in number of unit operations is observed for the BH_3·THF continuous flow process.

CONCLUSIONS

In conclusion, the benefit of a continuous flow process to the synthesis of vilazodone intermediate **3b** is unmistakable. The limitations of controlling the exotherm in a batch reaction are now successfully overcome by conducting the reaction in a continuous flow CSTR settting that is also able to handle heterogeneous mixtures. The continuous flow process reduces the generation of a key dimeric impurity **5** thereby improving the yield of the product **3b**. It was demonstrated that utilizing agitated cell reactor instrumentation for continuous flow process investigation and with slight modifications of the batch process conditions (e.g., using $NaBH_4$ in tetraglyme as the reducing agent) allowed an increase of the yield and purity of the isolated **3b** to a point where a purification process was no longer required. Utilizing BH_3·THF as the reducing agent increased the yield even further and also produced highly pure product which did not require purification. The BH_3·THF process was scaled-out to a CSTR setting using a three-jacketed-reactor system which also yielded a high purity and higher yield of **3b** compared to the current batch process.

EXPERIMENTAL SECTION

Materials and General Considerations. All manipulations of air- and moisture-sensitive substances were carried out using inert conditions with nitrogen gas. Tetraglyme, iron trichloride, sodium borohydride, and borane. THF solution were purchased from Sigma-Aldrich and used as is. THF was obtained from our plant with a KF < 0.5% and used as is. Diglyme was purchased from Sigma-Aldrich and was 99.97% by GC. Compound **2b** was provided by our Apotex Pharmachem Inc. Signa S.A. de C.V., Toluca, Mexico branch. HPLC analysis conducted using a Waters 2695 Separations Module with an X-Bridge C18, 4.6 mm × 150 mm, 3.5 μm column and processed with relative area % values. LC/MS data were obtained using an Agilant Technologies 1200 Series HPLC and Agilant Technologies 6510 Q-TOF LC/MS.

$NaBH_4$ in Tetraglyme Reductive Deoxygenation of 2b. Preparation of a suspension of **2b** in THF: A 100 mL round bottomed flask was charged with **2b** (20 g, 81.09 mmol) and THF (68 mL) and stirred at 20−25 °C gently to avoid splatter on the flask walls. The total suspension volume was 85 mL.

Preparation of $FeCl_3$ solution in THF: A 100 mL two-necked round bottomed flask was charged with THF (56 mL), the headspace was purged with nitrogen gas, and $FeCl_3$ (14.47 g, 89.20 mmol, 1.1 equiv) was added slowly through a solids addition apparatus under nitrogen gas. The addition is exothermic, and the rate was adjusted to maintain a solution temperature of <30 °C. This solution was then transferred via cannula to a conical flask. The total volume of the green solution was 78 mL.

Preparation of $NaBH_4$ solution in tetraglyme: A 100 mL round bottomed flask was charged with $NaBH_4$ (4.60 g, 121.64 mmol, 1.5 equiv) and tetraglyme (60 mL) and stirred at 20−25 °C until a homogeneous solution was obtained (total volume of 65 mL). This solution was split into two portions with a 4:11 ratio to obtain a 17.3 mL (for pumping into CSTR 6) and 47.7 mL (for pumping into CSTR 2) solution respectively. When the solution was split into two portions, they were transferred into conical flasks.

Total reaction volume: The total void volume of the reaction block is 62 mL (10 CSTRs × 10 mL each − 4 × 5 mL agitators − 6 × 3 mL agitators = 62 mL), but from previous experience we calculated that of the 62 mL only 65% of that volume is occupied by liquid while the remainder is occupied by hydrogen gas liberated during the reaction. This provides a total reaction volume of 40.3 mL for which we used to calculated our total flow rate and residence time of 30 min.

Procedure. Once all the feed suspension/solutions were prepared they were connected to the appropriate tubing and placed under a nitrogen atmosphere. The reactor block was heated to 40 °C via circulation of silicon oil from a Julabo heating unit. The four lines were primed with suspension/solutions, and then the suspension of **2b** (20 g, 81.09 mmol, in 68 mL of THF, 5.14 mL/min) and $FeCl_3$ solution (14.47 g, 89.20 mmol, 1.1 equiv, in 56 mL of THF, 0.472 mL/min) were simultaneously pumped into CSTR 1. Once this mixture begins to enter CSTR 2, the main solution of $NaBH_4$ in tetraglyme (3.37 g, 89.20 mmol, 1.1 equiv, in 44 mL of tetraglyme, 0.289 mL/min) was pumped into the reaction block at which point hydrogen gas evolution begins and the suspension becomes an orange/green solution. When this solution starts to enter CSTR 6 the second solution of $NaBH_4$ in tetraglyme (1.23 g, 32.44 mmol, 0.4 equiv, in 16 mL of tetraglyme, 0.105 mL/min) was pumped into the reaction block. The reaction mixture was transferred from the top of the reaction block into a flask containing aqueous citric acid (7.79 g, 40.55 mmol, 0.5 equiv, in 60 mL of water). The hydrogen gas accumulated in this flask was safely diluted with nitrogen gas (below 4 vol.% H_2 in the mixture as per ISO standard) and was released into the atmosphere. When all suspension **2b** was added into the reactor block the flask was rinsed with 10 mL of THF and pumped into the reactor to quantify the transfer of **2b**. At this point all the reagent flasks were changed to flasks containing THF and continue to pump at their original flow

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rates for an additional 30 min while collecting the reaction mixture in the receiving flask. This biphasic solution was concentrated to remove THF and then diluted with *n*-BuOH (60 mL) and water (40 mL), and the phases were separated. The organic phase was washed three times with water (40 mL), diluted with *n*-BuOH (40 mL), and concentrated to 40 mL. The solution was diluted once more with *n*-BuOH (60 mL) and concentrated to 40 mL at which time some solids precipitate. The suspension was charged with 34−37% aqueous HCl (8.19 g, 81.09 mmol, 1 equiv), heated to 65 °C for 3 h, then slowly cooled to 20−25 °C, and maintained at that temperature for 12−16 h. The suspension was filtered at 20−25 °C, washed with 10 mL of cold (−10 to −5 °C) *n*-BuOH and then dried under vacuum to provide 6.80 g (45.6%) of **3b** with an HPLC purity of 99.46 a% (Figure S4) (impurity **5** retention time of 33.482 min). Proton NMR data of **3b**: ^{1}H NMR (DMSO-d6): δ (ppm) 11.41(br s, 1H), 8.09 (s, 1H), 7.52 (d, 1H, J = 8.4 Hz), 7.42 (dd, 1H, J = 1.5 Hz and J = 8.4 Hz), 7.35 (d, 1H, J = 1.7 Hz), 3.68 (m, 2H), 2.75 (m, 2H), 1.77 (m, 4H).

BH_3·THF Reductive Deoxygenation of 2b in Three Jacketed CSTRs. Preparation of a suspension of **2b** in THF: A 100 mL round bottomed flask was charged with **2b** (30 g, 121.61 mmol) and THF (105 mL) and stirred at 20−25 °C gently to avoid splatter on the flask walls. Total suspension volume was 135 mL.

Preparation of $FeCl_3$ solution in THF: A 100 mL two-necked round bottomed flask was charged with THF (103 mL), the headspace was purged with nitrogen gas, and $FeCl_3$ (19.73 g, 121.61 mmol, 1 equiv) was added slowly through a solids addition apparatus under nitrogen gas. The addition is exothermic, and the rate was adjusted to maintain a solution temperature of <30 °C. This solution was then transferred via cannula to a conical flask. Total volume of the green solution was 105 mL.

BH_3·THF was purchased from Sigma-Aldrich as a 1 M solution in THF (item # 176192-800 ML) and used as is. Into the reactor, 1 equiv (121.61 mmol, 121.6 mL) of BH_3·THF was charged from CSTR 2 and 0.2 equiv (24.32 mmol, 24.3 mL) was charged from CSTR 6.

Total reaction volume: CSTR 1 and CSTR 2 reaction volumes were 20 mL and the CSTR 3 reaction volume was 30 mL, with a total reaction volume of 70 mL used to calculate the total flow rate of 14 mL/min for a 5 min residence time. The volume in each CSTR was controlled by turning the subsequent pump on when the CSTR was filled to its desired volume.

Procedure. Once all the solutions were prepared they were connected to the appropriate tubing and placed under a nitrogen atmosphere. The magnetic mixer was maintained at 20 °C by a water bath, and the three CSTRs were maintained at 20 °C by circulation through the jacketed reactors. The three lines and the syringe needle were primed with suspension/solution, and then the suspension of **2b** (30 g, 121.61 mmol) in THF (105 mL) was pumped at 4.898 mL/min and solution of $FeCl_3$ (19.73 g, 121.61 mmol, 1 equiv) in THF (103 mL) was pumped at 3.809 mL/min. Once this mixture reached the second tee the addition of BH_3·THF (121.61 mmol, 121.6 mL, 1 M) solution in THF was pumped at 4.412 mL/min. The mixture is passed through a magnetic mixer which is cooled to maintain an exit temperature of 20 °C (monitored by a thermocouple). The reaction mixture then passes through three CSTRs before being transferred to the collection flask and quenched with an aqueous citric acid solution. Each CSTR is connected to a nitrogen line so that the hydrogen gas generated is safely diluted with nitrogen gas (below 4 vol. % H_2 in the mixture as per ISO standard) and released into the atmosphere. Each flask is marked with a specific volume; when this volume (20 or 30 mL) is reached, a pump is started to begin transfer to the next CSTR. The working volume of each CSTR along with the flow rates of the different reagents accounts for the residence time of the reaction. Supplementary BH_3·THF (24.3 mmol, 24.3 mL, 1 M) solution in THF was pumped at 0.881 mL/min. When all of suspension **2b** was added into the CSTRs the flask was rinsed with 10 mL of THF and pumped into the reactor to quantify the transfer of **2b**. At this point all the reagent flasks were changed to flasks containing THF and continued to pump at their original flow rates for an additional 5 min while collecting the reaction mixture in the collection flask.

Table 3 shows the reaction progression between the three different CSTRs. Most of the conversion occurs in CSTR 1, but the two other CSTRs are required to completely consume **2b** and reduce the amount of intermediate **4**.

Table 3. HPLC Data of the Three CSTR Contents at Steady State

	HPLC a%			
	2b	Intermediate **4**	**3b**	Impurity **5**
CSTR 1	6.59	1.45	90.79	0.18
CSTR 2	0.82	1.48	96.61	0.20
CSTR 3	0	0.26	98.24	0.19

This aqueous phase was separated and discarded, and the organic phase was concentrated to 300 mL. The solution was diluted with *n*-BuOH (60 mL) and water (60 mL), and the phases were separated. The organic phase was washed twice with water (60 mL) and then concentrated to 60 mL at which point a suspension formed. The suspension was heated to 65 °C, charged with 34−37% aqueous HCl (12.45 g, 121.61 mmol, 1 equiv), maintained at 65 °C for 3 h, then slowly cooled to 20−25 °C, and maintained at that temperature for 12−16 h. The suspension was filtered at 20−25 °C, washed with 15 mL of cold (−10 to −5 °C) *n*-BuOH, and then dried under vacuum to provide 20.16 g (71%) of **3b** with an HPLC purity of 99.60 a%. Proton NMR data of **3b**: ^{1}H NMR (DMSO-d6): δ (ppm) 11.41(br s, 1H), 8.09 (s, 1H), 7.52 (d, 1H, J = 8.4 Hz), 7.42 (dd, 1H, J = 1.5 Hz and J = 8.4 Hz), 7.35 (d, 1H, J = 1.7 Hz), 3.68 (m, 2H), 2.75 (m, 2H), 1.77 (m, 4H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00145.

Experimental setup of the two processes including images and diagrams along with detailed procedures and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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