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Continuous flow conditions for high temperature formation of a benzodioxan pharmaceutical intermediate: Rapid scaleup for early phase material delivery

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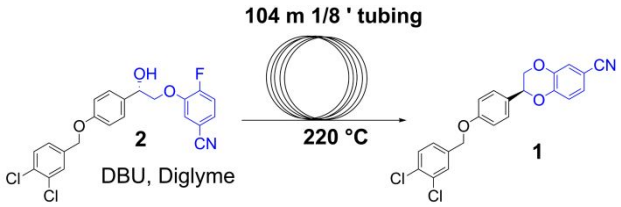

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ABSTRACT

We have developed a continuous flow method to enable rapid scaleup of an enantioenriched benzodioxan intermediate. We propose that the reaction proceeds through an intramolecular S_NAr cyclization. Interestingly, traditional S_NAr conditions resulted in impurity formation. When the starting material **2** was treated with alkali base in polar aprotic solvents an undesired product regioisomer was observed. The formation

of this regioisomer impurity could be suppressed by using less polar solvent, organic base and high temperature. By employing continuous flow technology, these high temperature conditions could be scaled up to produce 540 g of the desired intermediate. The continuous flow reactor allowed for rapid thermal equilibration, which minimized problematic product decomposition by reducing the time that the product was exposed to high temperature.

KEYWORDS

Continuous flow, high temperature, benzodioxan

INTRODUCTION

One of the biggest challenges faced by the pharmaceutical industry is the low rate of clinical success. A recent study analyzed the data of over 21,000 compounds from January 2000 to October 2015.[1] The authors report that only 13.8% of drug programs actually make it from Phase I to approval. Alarmingly, this percentage is significantly lower for small molecule chemical entities than it is for biologics.[2,3]

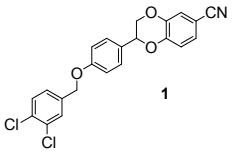
To address this challenge, the pharmaceutical industry needs to implement new strategies to achieve clinical proof of concept. Chemists responsible for delivering molecules in the early Phase portfolio are being tasked with reducing the time and cost of providing material to the clinic. Our goal is to commit minimal investment, while still enabling rapid execution of the key clinical studies required to progress a molecule through development. These studies should provide meaningful data that facilitates the decision to either rapidly terminate or rapidly advance to later Phase development. Advancement from Phase I to Phase II significantly increases the likelihood of achieving

approval (35.1%).[1] One way to deliver a molecule quickly is by utilizing technology that facilitates scaleup of literature routes, avoiding the time and monetary investment required to develop a novel synthetic approach.

We were interested in targeting the enantiopure benzodioxan **1** as an intermediate for the synthesis of an active pharmaceutical ingredient in preclinical development (Equation 1). Several different methods to prepare enantiopure benzodioxan molecules are reported in the literature. Catechol starting materials can be used to dispilace enantiopure electrophiles (Scheme 1, A).[4] In 2016, Tang demonstrated that achiral monoallylated catechols could undergo enantioselective aryloxyarylation of alkenes to furnish enantiopure benzodioxans, albeit with limited substrate scope (Scheme 1, B).[5] In 2001, Buchwald reported that enantiopure alcohols could substitute aryl-bromides via Pd-catalyzed intramolecular C—O etherification (Scheme 1, C).[6] Cai and coworkers expanded on this work, disclosing that the intramolecular C—O etherification can also be employed in the desymmetrization of diols using Pd or Cu in combination with chiral ligands.[7] More recently, Zhang and Senanayake have reported the enantioselective

hydrogenation of substituted benzo[1,4]dioxines using Rh or Ir and chiral phosphine ligands (Scheme 1, D).[8]

Equation 1. Benzodioxan pharmaceutical intermediate



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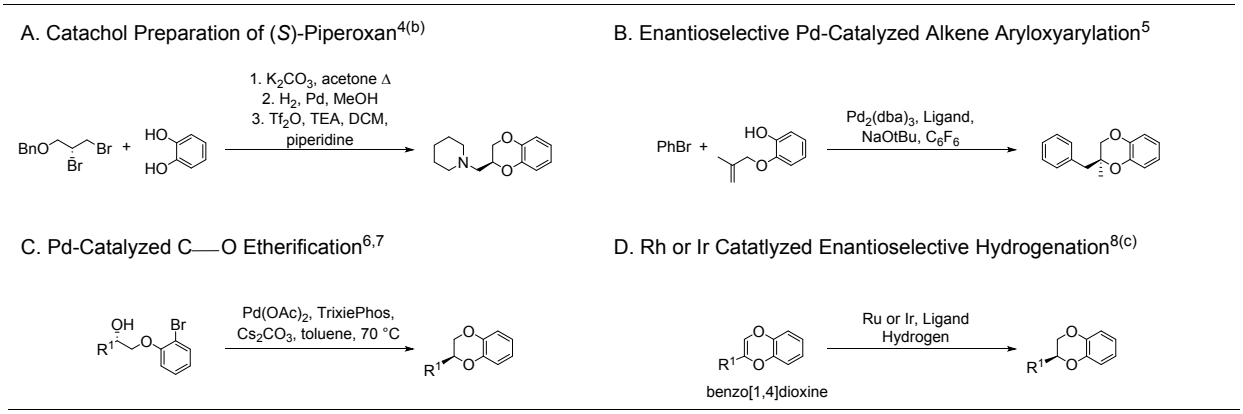
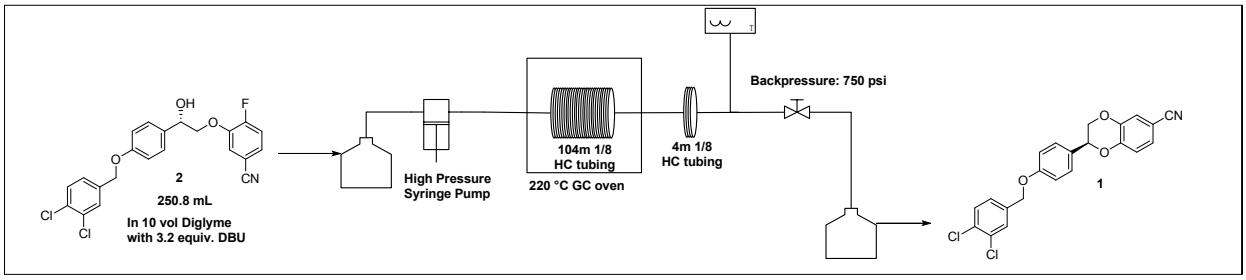
Scheme 1. Methods of preparation of benzodioxans: A) Catechol preparation method.[4] B) Enantioselective allylic aryloxyarylation.[5] C) Intramolecular C—O etherification.[6] D) Enantioselective benzo[1,4]dioxine hydrogenation.[8]



The best method for the preparation of **1** may involve one of these reported methods, or it could involve a completely novel, undisclosed method of preparation. However, due to the potential regioselectivity challenges of a catechol approach,[9,10] in combination with the urgent need for material to fund preclinical toxicology studies, these synthetic approaches were not investigated for this early-phase material delivery. Fortunately, the synthesis of **1** was previously reported in the literature.[11] The reported synthetic method involves the enantiopure alcohol **2** (Scheme 2), which was subjected to high temperature conditions in the presence of NaH for S_NAr cyclization to the benzodioxan **1**. According to the literature report for the preparation of **1**, the S_NAr reaction required immediate cooling. We speculated that the product might not be stable under the reaction conditions over an extended period. In our hands, we observed lower isolated product yields when the reaction was conducted at larger scale in batch mode, presumably due to the extended cooldown time that is required as the reactor volume increased (see below: Table 2, Entries 2 and 3). To address the poor yield associated with product

decomposition, we became interested in applying continuous flow to the production of **1** (Scheme 2).

Scheme 2. This work: Continuous flow S_NAr Cyclization



Continuous reactors have improved the ability of chemists to explore extreme reaction conditions in a safe and controlled manner.[12] The inherent nature of continuous flow processing allows high product throughput using a small reactor size. This small reactor size permits a wide temperature range with rapid heat-up and cooldown time. Many plug flow reactors (PFRs) can withstand high pressure, allowing high temperature reactions to occur in the liquid phase even when operating well above the boiling point of the solvent.

We initially became interested in continuous flow technology for its safety and control aspects.[13,14] Continuous flow can also allow rapid scaleup of literature conditions that might be difficult to achieve in batch mode.[15] This should aid in reducing the lead time and development costs to deliver material for early phase clinical trials.

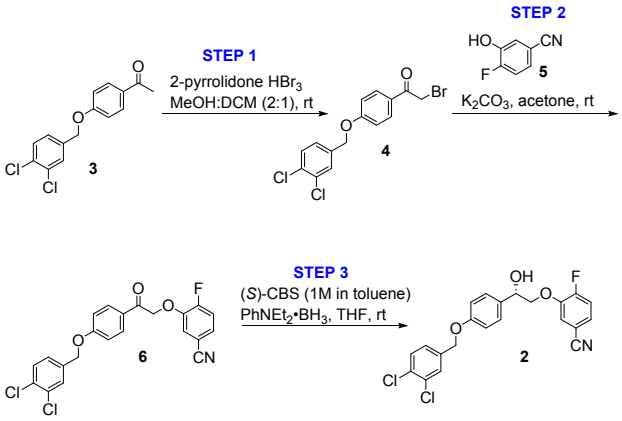
Herein we report the results of continuous flow production of enantioenriched benzodioxin **1** to enable rapid material delivery for preclinical studies (Scheme 2). The reaction can be safely and effectively completed above the boiling point of the solvent. Furthermore, the use of continuous flow technology addresses problematic product decomposition.

RESULTS AND DISCUSSION

To investigate the production of **1** we began by targeting the enantiopure alcohol **2**. The reported method for the preparation of **2** began with acetophenone **3**, which was treated with pyrrolidone hydrogen tribromide to selectively monobrominate the methyl group (Scheme 3).[11] The resulting bromide **4** was next reacted with phenol **5** to afford the ether **6**. The ketone functionality of **6** was reduced under Corey-Bakshi-Shibata (CBS)

reduction conditions with (*S*)-CBS catalyst and the borane diethylaniline complex to produce the alcohol **2**, which was elaborated to more complex enantiopure products.[16]

Scheme 3. Literature Reported Synthesis of Compound **2.**[11]



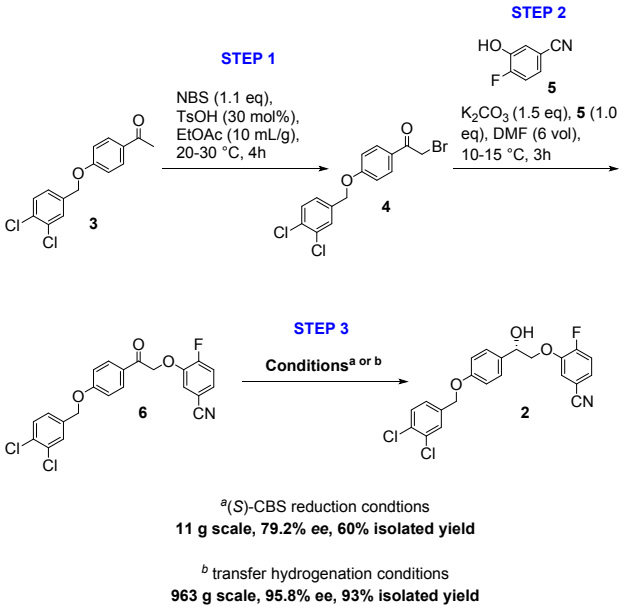
The preparation of ketone **6** was achieved with modifications to the methods reported in the literature (Scheme 4). The bromination reagent in the Step 1 was changed from pyrrolidone hydrogen tribromide to readily available *N*-bromosuccinimide. The modified reaction employed a catalytic amount of toluenesulfonic acid (TsOH) to favor an ionic pathway, affording good conversion of starting material and high selectivity for the

monobromination product. The Step 2 substitution reaction solvent was modified from acetone to DMF. The higher dielectric point of DMF compared to acetone (36.7 vs 20.7) allowed better solubility of the base and permitted a faster rate of reaction. The use of DMF as a solvent also simplified the workup procedure. The product could be directly precipitated and isolated from the reaction mixture by the addition of water and isopropanol.

With ketone **6** in hand we investigated the Step 3 reduction. Unfortunately, in our hands the enantioselectivity of the Step 3 CBS reduction to provide the alcohol **2** was poor (79.1% *ee*, Scheme 4).[16] Alternate reaction conditions for Step 3 were quickly developed and the CBS reduction was modified to a transition metal catalyzed, asymmetric transfer hydrogenation. Ruthenium systems are well established for the enantioselective reduction of aromatic ketones.[17] As such, we investigated several ruthenium catalysts with formic acid: trimethylamine complex as the hydride source (Table 1). Due to the high *ee* of the product and good commercial availability, RuCl[(*R*,*R*)-Tsdpen](*p*-cymene) was selected for further scaleup (Table 1, Entry 1). The use of this ruthenium catalyst resulted in high

quality alcohol **2** with high *ee* on 963 g scale (95.8% *ee*, Scheme 4). The alcohol **2** was isolated by crystallization to investigate the Step 4 S_NAr cyclization.

Scheme 4: Optimization to compound **2**



[a]CBS conditions: *(S)*-CBS catalyst (1M in toluene, 1.05 eq), $PhNEt_2 \bullet BH_3$ (2 eq), THF, -20 °C

[b] Transfer hydrogenation conditions: RuCl[(*R*,*R*)-Tsdpen] (p-cymene) (0.7 mol%), formic acid (4.0 eq), triethylamine (1.6 eq), IPA, 55 °C

Table 1: Transfer Hydrogenation conditions for the formation of **2**

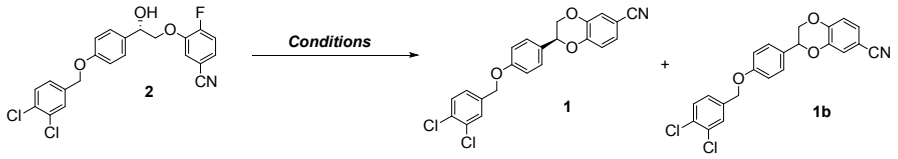
Entry[1]	Catalyst	**2** (area%)	**2** (ee%)
1.	RuCl[(*R*,*R*)-Tsdpen] (p-cymene)	94.4	97.9
2.	RuCl[(*R*,*R*)-Msdenb]	96.2	97.2
3.	RuCl[(*R*,*R*)-Fsdpen] (p-cymene)	96.7	96.1
4.	RuCl[(*R*,*R*)-Tsdeneb]	96.3	97.1
5.[2]	RuCl[(*R*,*R*)-Tsdeneb]	96.6	96.9

[1]All reactions were completed on a 20 mmol scale using 2 mol% Ru catalyst, 2 mL/g formic acid:TEA (5:2) and 10 mL/g toluene at 50 °C for 18 h. [2]MeCN was used in place of toluene as a solvent

With alcohol **2** in hand, we focused our attention on the S_NAr cyclization. The conditions reported in the literature required high temperature (140–150 °C) and utilized sodium hydride as a base. We began by repeating these conditions. When the reaction was performed at 140 ºC with NaH (60% in mineral oil) in diglyme, we were able to obtain 54% isolated product yield (Table 2, Entry 1). In order to avoid the use of NaH, we turned to milder bases. When DBU was used as a base the reaction required 20 h to achieve complete conversion of starting material when completed on a 50 g scale (Table 2, Entry 3). While analysis of a HPLC chromatogram indicated high area% purity, the isolated product yield was only 41%. We suspected that this was due to product decomposition over an extended period at high temperature, resulting in poor mass balance (Table 2, Entry 2 vs Entry 3). To address this product decomposition, we first investigated the use of alternate bases that are known to mediate S_NAr cyclization at lower temperature. When K_2CO_3 was used in place of DBU in diglyme there was no conversion of starting material (Table 2, Entry 4). Stronger bases such as *t*BuOK led to decomposition of starting material, resulting in a significant number of impurities (Table 2, Entry 5). These impurities were not characterized further. We were initially excited to observe complete conversion

of starting material in the presence of K_2CO_3 or Cs_2CO_3 in DMF at 80 °C (Table 2, Entries 6 and 7). Unfortunately, closer inspection of the products by NMR spectroscopy revealed that a mixture of **1** and its regioisomer **1b** had formed in a 3:2 ratio.[18] Presumably, **1b** is generated via substitution of the C—O bond prior to cyclization (see below, Scheme 5). The enantiomeric purity of **1b** was not determined.

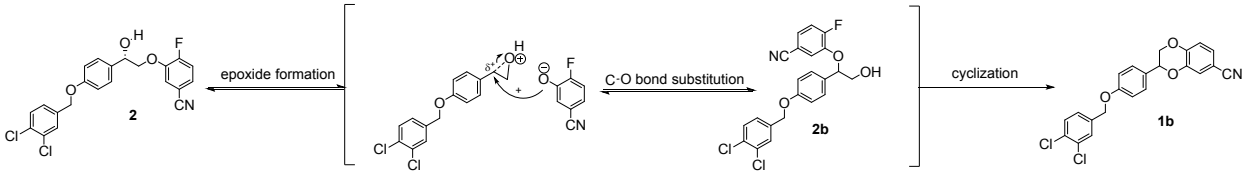
Table 2. Initial reaction exploration for the formation of **1**



Entry	Solvent	Base (eq.)	Temperature	(**2**) area%	(**1**) area% (isolated yield)
1	Diglyme	NaH (1.4)	140 °C (3 h)	0	54
2	Diglyme	DBU (1.2)	140 °C	NA	NA (67%) 10 g scale
3	Diglyme	DBU (1.4)	140 °C (3 h)	33	54
			140 °C (20 h)	0	85 (41%) 50 g scale
4	"	K_2CO_3 (2.0)	100 °C	91	3
5	Toluene	*t*BuOK (2.0)	25 °C	20	0
6	DMF	K_2CO_3 (2.0)	80 °C	0	78 (3:2 mixture of **1** and **1b**)
7	DMF	Cs_2CO_3 (2.0)	80 °C	0	78 (3:2 mixture of **1** and **1b**)

We propose that the formation of regioisomer **1b** begins with epoxide formation to liberate the phenoxide (Scheme 5). This phenoxide can then attack either of the electrophilic carbons of the epoxide to provide **2** and its regioisomer **2b**. The formation of regioisomers as a result of epoxide opening under similar reaction conditions has been reported previously.[19] Cyclization of **2b** would result in formation of the undesired product regioisomer **1b**, cyclization of **2** would lead to the desired product **1**. This pathway is proposed to be operational in the presence of alkali bases and coordinating solvents due to the stabilization of ionic intermediates. A similar pathway involving formation of the epoxide followed by coordination of the Lewis acidic potassium or cesium could also result in the formation of intermediate **2b**.

Scheme 5. Proposed mechanism for the generation of the regioisomer **1b**



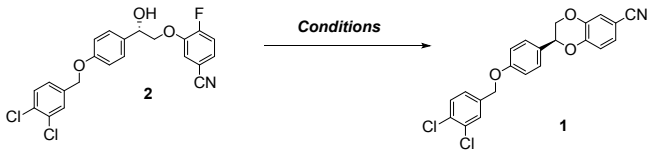
The use of DBU in diglyme at high temperature had resulted in low isolated yield (41%, Table 2, Entry 2). However, we believe that this is due to product decomposition over an extended period at high temperature. To minimize product exposure to the forcing reaction conditions we turned to continuous flow preparation of **1**. Due to its small footprint, continuous flow technology permits rapid thermal equilibration minimizing heat-up and cooldown time. Based on our previous experience with high temperature, high pressure flow reactions,[20] we sought to apply a PFR to the preparation of **1**.[21] When the use of a PFR is suggested, it is useful to conduct small-scale batch screening reactions to rapidly test discrete variables in parallel. These are readily performed in 0.5–1 mL volume pressure reactors constructed of Swagelok or similar steel or Hastelloy parts.[22, 23] Building on our previous results with DBU in diglyme (Table 2), we screened a range of organic bases in diglyme using these small 1 mL pressure vessels (Table 3, Entry 1).

TEA, DIPEA, pyridine, lutidine, *N*-methyl morpholine, and diazabicyclo non-5-ene (DBN) did not provide significant conversion of starting material at 190 °C after 30 m (Table 3, Entries 1a–f). DBU remained our preferred base for this reaction (Table 3, Entry 1g). We next investigated the effect of temperature and base equivalents (Table 3, Entry 2). Increasing the temperature to 240 °C significantly increased the conversion of starting material from 38% to 89 % (Table 3, Entry 1g vs Entry 2a). This was improved further by increasing the equivalents of base to 2.6 eq., giving 99% conversion of starting material and 86 area% of the desired product (Table 3, Entry 2b). The temperature could be lowered to 220 °C with no reduction in product area% (Table 3, entry 2c). Maintaining the equivalents of base between 2.6 and 7.8 provided similar conversion and product area% (Table 3, Entries 2c–e).

We were interested in the effect of solvent on the reaction outcome (Table 3, Entry 3). THF and dioxane did not result in any improvements to the process that utilized diglyme. However, diglyme did provide higher isolated product purity than THF or dioxane and was therefore preferred for early phase material delivery. The polar, aprotic solvent DMAc

initially appeared to provide promising results by HPLC analysis (Table 3, Entry 3b). However, subsequent analysis by chiral chromatography revealed that the product *ee* was low under these conditions (only 50.0 % *ee*). As such, we selected DBU as the base (between 2.6 and 7.8 eq.) in diglyme to investigate in a PFR (Table 3, Entries 2c–e). The undesired impurity **1b** was not observed under these reaction conditions (See Table 2 and Scheme 5 for the structure of **1b**).

Table 3. Small-scale batch reaction to investigate continuous flow conditions



Entry	Base (eq.)	Solvent	Temp[b]	(**2**) area%[c]	(**1**) area%[c] *(in situ* enantiomeric purity)[d]
1a	TEA (1.3)	Diglyme	190 °C	97	2.2
b	DIPEA (1.3)			97	1.8
c	*N*-Me morpholine (1.3)			96	1.6
d	Pyridine (1.3)			97	2.0
e	Lutidine (1.3)			96	2.3
f	DBN (1.3)			35	7.5
g	DBU (1.3)			62	33

2a	DBU (1.3)	Diglyme	240 °C	11	79
b	(2.6)			0.8	86 (94% *ee*)
c	*DBU (2.6)*		*220 °C*	*1.2*	*86*
d	*(5.2)*			*0.3*	*87*
e	*(7.8)*			*0.0*	*86*
3a	DBU (5.2)	THF	220 °C	2.3	85
b		DMAc		0.0	89 (50% *ee*)
c		Dioxane		11	73

[a]All reactions were completed in a 1 mL swagelok port connector. Reactions were carried out on a 0.4 mL scale, with 16 mL/g solvent for 30 min. [b]Reactions were heated in a GC oven fitted with a rotating reactor holder to allow agitation. [c]area% was determined by HPLC analysis using MeCN as an eluant. [d]chiral purity was determined by HPLC analysis using MeOH as an eluant.

A 16.4 m length Hastelloy tubular PFR was selected to test the continuous flow conditions. The reactor contained a 0.125 inch outer diameter and 0.028 inch wall thickness. The reactor was placed in a GC oven to allow for rapid heating. The back-pressure was set to 750 psi using a back-pressure regulator. After the GC oven had reached the desired temperature, a solution of the starting material **2** and DBU in diglyme was pumped into

the reactor using a HPLC pump. The reaction mixture eluted from the GC oven into an additional 1 m of Hastelloy tubing. This allowed cooling of the reaction mixture with the ambient atmosphere prior to product collection. A thermal detector was installed before the back-pressure regulator to ensure that the temperature of the solution had cooled to room temperature prior to collection. The rate of heat transfer of the Hastelloy tubing used in the reactor was tested. We discovered that it can be heated to the desired temperature (220 °C) within 1 minute when placed in the preheated GC oven and can be cooled back to room temperature within 1 min under ambient conditions after eluting from the oven.

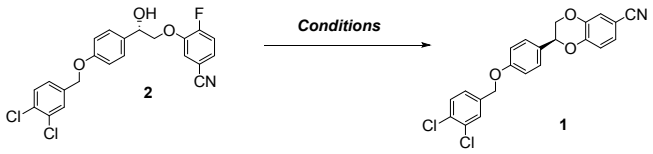
Initial PFR runs were conducted with 15 g of compound **2** to evaluate the chemistry (Table 4). The approximate residence time was calculated by dividing the reactor volume by the flow rate (V/Q). This calculation provides the time necessary to process one volume of reactor fluid at the entrance conditions. It does not account for thermal expansion of the solvent in the high temperature reactor and cannot be assumed to provide the actual mean residence time (t). The residence time distribution can be calculated using tracer techniques that measure the concentration of a tracer moving through the reactor under

the desired conditions.[24] This can provide useful information about the fluid dynamics of a plug-flow system. However, it was not considered necessary for this early phase material delivery. The V/Q was set to 30 min. Each experiment was run for more than 1.5 h before sampling the solution to allow approximately 3 reactor volume turnovers. The starting material **2** that was used for each of these reactions was 95.2% *ee*.

The PFR study began by repeating the conditions identified in batch. The reaction utilized 3.2 eq of DBU, in 15 mL/g of diglyme at 220 °C (Table 4, Entry 1). To test that steady state was achieved after 3 reactor volume turnovers we began sampling the reactor after 1.5 h reaction time. Three aliquots were taken every 5 minutes and analyzed by HPLC. The conversion of starting material and product area% were consistent throughout the reaction progress suggesting that steady state had been achieved. We next investigated the effect of solvent volumes on the reaction outcome. When 10 mL/g of solvent was used in place of 15 mL/g with a V/Q of 30 min. the conversion of starting material improved slightly from 95% to 99% (Table 4, Entries 1 and 2). The in situ chiral purity was 92% *ee* when either 10 or 15 mL/g were used. The isolated yield was also very similar for both

experiments (62 or 63% respectively). However, the purity of the isolated product was superior when 10 mL/g was used in place of 15 mL/g, presumably due to better conversion of starting material (Table 4, Entries 1 and 2). 10 mL/g was preferred due to the improved product purity, and reduced waste that accompanies the use of lower solvent volumes. This did not affect our ability to use a PFR for the S_NAr cyclization as the starting material and product remained soluble under these conditions. Increasing the temperature from 220 °C to 240 °C did not significantly alter the conversion of starting material or area% of product. However, the in situ chiral purity was lower at higher temperature (88% *ee* vs 92% *ee*). This chiral purity remained low when the V/Q was reduced from 30 to 20 minutes at 240 °C. While the chiral purity could be upgraded during product isolation, the lower in situ *ee* resulted in a slight reduction of the isolated yield (58%) (Table 4, Entry 4). We decided to move ahead with the scaleup using 10 mL/g diglyme at 220 °C with a V/Q of 30 min.[25]

Table 4. Continuous flow conditions for the generation of **1**



Entry	Solvent volumes	V/Q	Temperature	(**2**) area%	(**1**) area% (in situ *ee*)
1	15	30 min (1.58 h)	220 °C	4.5	76
		(1.66 h)		4.5	76
		(1.75 h)		4.7	76 (93% *ee*)
Isolated yield, purity and *ee*			62% yield, 97% purity, 95% *ee*		
2	10	30 min (1.58 h)	220 °C	1.0	80
		(1.66 h)		1.0	80
		(1.75 h)		1.0	81 (92% *ee*)
Isolated yield, purity and *ee*			63% yield, 99% purity, 95% *ee*		
3	10	30 min (1.58 h)	240 °C	0.1	79
		(1.66 h)		0.1	80
		(1.75 h)		0.1	79 (88% *ee*)
Isolated yield, purity and *ee*			60% yield, 99% purity, 94% *ee*		
4	10	20 min (1.58 h)	240 °C	0.6	82
		(1.66 h)		0.6	81
		(1.75 h)		0.6	81 (91% *ee*)
Isolated yield, purity and *ee*			58% yield, 98% purity, 97% *ee*		

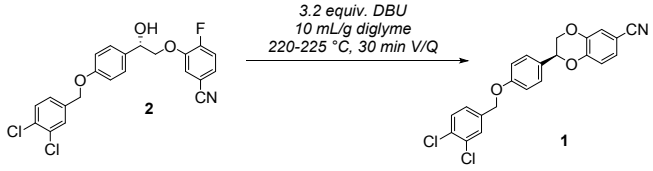
[a]Reactions were completed on a 15 g scale with 3.2 eq. of DBU

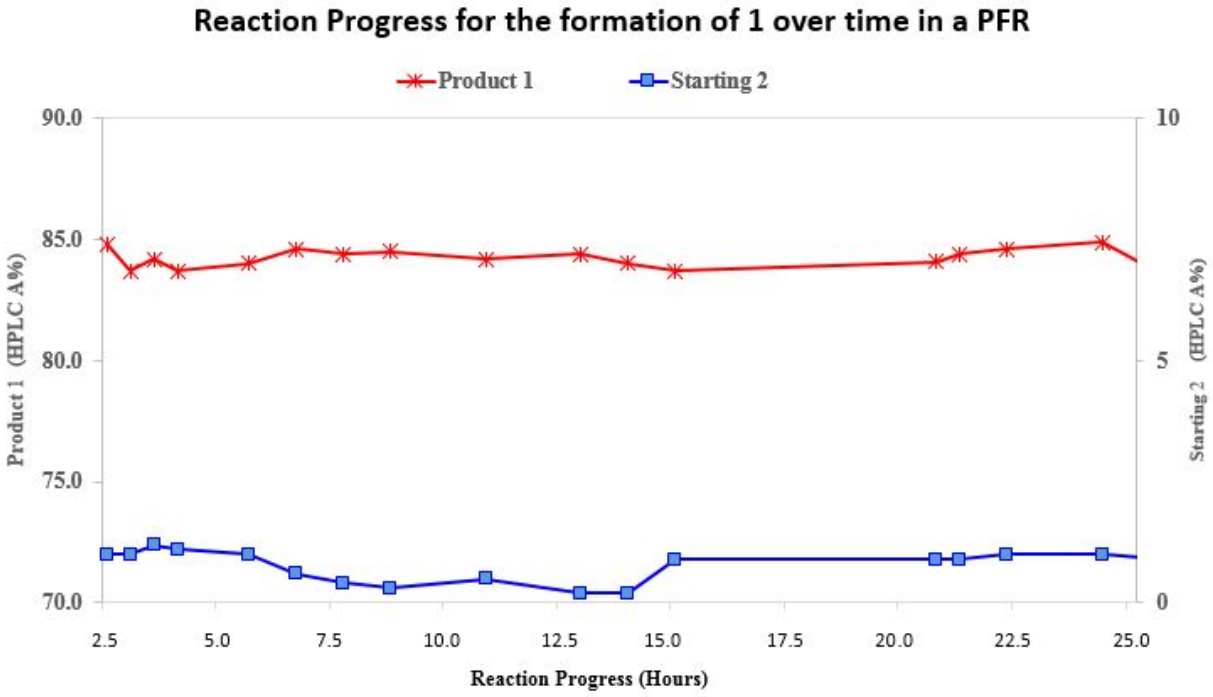
The S_NAr cyclization was completed using 850 g of **2** (after potency correction) in a PFR.

The reaction progress was monitored over time by HPLC (Graph 1). Sample analysis

began after 3 reactor volume turnovers to assure steady state had been achieved . The product area% remained between 80 and 85 area% during the 24 h run. The starting material amount was also consistently between 0 and 2 area% throughout the reaction. The entire reaction solution was collected after the product was pushed out of the reactor with diglyme, and the in situ yield was determined to be 64.4%. After work up the product was isolated in 61.8% yield with 99% purity and 95.1% *ee*. The product loss in the mother liquor was 5%. The mass balance of the isolated product was higher than expected 104%, suggesting a slight error in the analysis of the crude reaction solution.

Graph 1. Reaction progress over time for the generation of **1**





CONCLUSION

In conclusion, we have developed a continuous flow method to permit rapid scaleup of benzodioxan intermediate **1** at high temperature. The use of continuous flow technology allowed the literature conditions to be employed with only minor modification. This avoided the need for a route redesign and route scouting investigations. The starting alcohol **2** was produced with high *ee* in good purity via a ruthenium catalyzed transfer hydrogenation approach. Subjecting **2** to high temperatures with DBU as a base in

diglyme prevented formation of an undesired regioisomer **1b** which was observed under more traditional S_NAr conditions (alkali base in DMF). The desired product **1** was produced in 62% isolated yield, allowing production of 540 g of product with 95 wt% purity (99% area% purity) in 30 h. The reactor was set up employing a back-pressure regulator to achieve high pressures. These high pressures kept the reaction mixture in the liquid phase at high temperature. The V/Q was set to 30 minutes to allow rapid elution of the product and avoid product decomposition that was associated with product instability during prolonged reaction time under the high temperature conditions.

Experimental section

General Experimental

Purchased starting materials and reagents were used without further purification. HPLC analysis (IPC and purity testing) were performed on Shimadzu LC-20A instrument using a Waters Xbridge C18 (75 mm* 4.6 mm, 3.5 μm) column. The analytical method utilized 2 mobile phases; mobile phase A consisted of 0.05% TFA in H_2O (v/v) and mobile phase B consisted of 0.05% TFA in ACN (v/v). The gradient elution method was completed as follows: 0.01 min, 15% of mobile phase B; 15.00 min, 95% of mobile phase B; 18.01 min, 15% of mobile phase B. Eluting material was

detected using a UV detector set at 220 nm. Samples were prepared as follows: for compound **3**, 0.25 mg/mL in ACN; for compound **4**, 0.5 mg/mL in ACN; for compound **5**, 0.4 mg/mL in ACN; for compound **6**, **2** & **1**, 0.25 mg / mL in ACN. HPLC analysis (chiral purity) was performed on a Shimadzu LC-20A Instrument; Analysis method for compound **2**: column, Chiralpak IC (250 mm* 4.6 mm, 5 μm); mobile phase, IPA: Hexane (20 : 80, v/ v); Sample preparation: compound **2** was diluted to 5.0 mg/mL by EtOH; Analysis method for compound **1**: column, Chiralpak IA (250 mm* 4.6 mm, 5 μm); mobile phase, IPA: Hexane (15: 85, v/ v); sample preparation, compound **1** was diluted to 1.0 mg/mL for chiral purity analysis. LCMS analysis was performed on Agilent HPLC 1200 with 6120 Quadrupole LC/MS detector. ^{1}H NMR (400 MHz) and ^{13} C (100 MHz) spectra was recorded on Bruker ultrashield 400, AVANCE II 400.

1-(4-((3,4-dichlorobenzyl)oxy)phenyl)ethan-1-one (3)

To a round bottom flask was added 4-hydroxyacetophenone (100 g, 1.0 eq., 0.73 mol). The flask was charged with DMF (300 mL), then K_2CO_3 (153 g, 1.5 eq., 1.11 mol) and 3,4-dichlorobenzyl chloride (158 g, 1.1 eq., 0.81 mol) were added. The mixture was heated to 60–65 °C and stirred for 18–20 h at this temperature. After complete conversion of 4-hydroxyacetophenone (as monitored by HPLC analysis), the mixture was allowed to cool to 30–35 °C. Then EtOAc (1 L) and water (1.2 L) were added. The biphasic mixture was stirred and then the layers were separated. The organic layer was washed with 0.5 L water. The organic layer was concentrated to 100–200 mL under vacuum. *n*-Heptane (300 mL) was then charged and the mixture was concentrated to 100–200 mL. An additional 100 mL of EtOAc was charged. The obtained solution was heated to 60–65 °C with stirring. *n*-heptane (500 mL) was next added via dropwise addition while

maintaining the temperature between 60 and 65 °C. The resulting suspension was cooled to 20–25 °C over 6 h. The solid was collected by filtration and the filter cake was rinsed with *n*-heptane (100 mL). The solid was dried under vacuum at 50 °C for 8–12 h to provide 195 g of a **3** as a white solid with 99.7%. purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.88 (2H, m); 7.54 (1H, d, J = 2.0 Hz); 7.46 (1H, d, J = 8.4Hz); 7.30–7.24 (1H, m); 7.05–6.95 (2H, m); 5.07 (2H, s); 2.56 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 162.0, 136.5, 132.8, 132.2, 130.9, 130.64, 130.62, 129.2, 126.5, 114.5, 68.6, 26.3; HRMS (ESI) calcd. for $C_{15}H_{12}Cl_2O_2$ $[M + H]^+$ 295.0287, found 295.0309

2-Bromo-1(4-((3,4-dichlorobenzyl)oxy)phenyl)ethan-1-one (4)

To a jacketed round-bottom flask was added **3** (50.0 g, 169.43 mmol, 1.0 eq.). The flask was charged with EtOAc (400 mL), then TsOH•H_2O (9.67 g, 50.84 mmol, 0.3 eq.) and NBS (33.17 g, 186.37 mmol, 1.1 eq.) were added. The reaction mixture was stirred for 4–5 h at 20–30 °C. After complete conversion of **3** (as monitored via HPLC), the reaction was quenched with 300 mL of $NaHCO_3$ (5 wt% aq. solution). Additional EtOAc (450 mL) was added. The biphasic mixture was stirred and then the layers were separated. The organic layer was washed with 300 mL of aq. $NaHSO_3$ to remove excess NBS. The organic layer was next washed with water (150 g), and then concentrated under vacuum. The residue was dissolved in EtOAc (150 mL) by heating to 60–65 °C with stirring. Methylcyclohexane (400 mL) was added over 3 h while maintaining the temperature between 60 and 65 °C. The resulting suspension was stirred for an additional 2 h at

this temperature before cooling to 10–15 °C over 5–6 h. The suspension was stirred for an additional 3–5 h at 10–15 °C. The solid was collected by filtration and washed with methylcyclohexane (100 mL). Finally, the solid was dried under vacuum below 55 °C for 12 h to afford 49.9 g of **4** as white solid with 97.8% purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.86 (2H, m); 7.47 (1H, d, J = 2.0 Hz); 7.40 (1H, d, J = 8.0 Hz); 7.24–7.16 (1H, m); 6.98–6.88 (2H, m); 5.02 (2H, s); 4.33 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 162.7, 136.2, 132.9, 132.4, 131.4, 130.7, 129.2, 127.5, 126.5, 114.8, 68.7, 30.6; HRMS (ESI) calcd. for $C_{15}H_{11}BrCl_2O_2$ $[M + H]^+$ 372.9392, found 397.9413

3-(2-(4-((3,4-dichlorobenzyl)oxy)phenyl-2-oxoethoxy)-4-fluorobenzonitrile (6)

To a round bottom flask was added phenol **5** (37 g, 0.73 mol, 1.0 eq.). The flask was charged with DMF (600 mL) and then K_2CO_3 was added (55 g, 1.5 eq., 0.40 mol). The reaction mixture was cooled to 10–15 °C and stirred at this temperature for 0.5 h. After this time, α-bromoketone **4** (100 g, 1.0 eq., 0.73 mol) was added and the mixture was stirred at 10–15 °C for 20 h. When complete conversion of **4** was observed by HPLC, IPA (200 mL, 2 mL/g) and water (1.8 L, 18 mL/g) were added. The resulting suspension was filtered, and the cake was rinsed with 600 mL of water (6 mL/g) and 200 mL of IPA (2 mL/g). The solid was dried under vacuum oven at 50 °C for 12 h to produce 103.5 g of product **6** as white solid with 95.9% purity. ^{1}H NMR (400 MHz, ppm, $CDCl_3$) δ 8.03–7.96 (2H, m); 7.55 (1H, d, J = 2.0 Hz); 7.48 (1H, d, J = 8.4 Hz); 7.32–7.24 (2H, m); 7.23–7.10 (2H, m); 7.08–6.98 (2H, m); 5.37 (2H, s); 5.08 (2H, s); ^{13}C NMR (100 MHz, DMSO) δ 191.6, 162.3, 154.3 (d, J = 252.3 Hz), 146.7 (d, J = 11.0 Hz), 137.6, 131.2, 130.7, 130.6, 130.2, 129.5,

127.8, 127.5, 126.3(d, J = 8.0 Hz), 118.9(d, J = 2.1 Hz), 118.1, 117.5(d, J = 19.7 Hz), 114.8, 107.6(d, J = 4.3 Hz), 70.7, 67.9; HRMS (ESI) calcd. for $C_{22}H_{14}Cl_2FNO_3$ $[M + H]^+$ 430.0408, found 430.0419.

(*S*)-3-(2-(4-((3,4-dichlorobenzyl)oxy)-2-hydroxyethoxy)-4-fluorobenzonitrile (2)

To a jacketed round-bottom flask was added compound **6** (962.55 g, 2.24 mol, 1.0 eq.). The flask was placed under an atmosphere of nitrogen and 2-propanol (6 L, 6 mL/g), and RuCl [(R, R)-Tsdpen] (*p*-cymene) (10 g, 0.007 eq.) were added. The flask was heated to 50–60 °C and a mixture of HCOOH (428.30 g, 8.92 mol, 4.0 eq.) and TEA (376.09 g, 3.72 mol, 1.7 eq.) in 2-propanol (4 L, 4 mL/g) was slowly added at this temperature (gas was released). The reaction mixture was then stirred for 1–2 h at 50–60 °C. When complete conversion of **6** was observed by HPLC, the reaction mixture was cooled to 20–30 °C over 5–6 h. The suspension was stirred for an additional 3–5 h at 20–30 °C. The solid was collected by filtration and washed with IPA (1.5 L). Finally, the solid was dried under vacuum below 55 °C to afford 896.85 g of **2** as a yellow solid with 98.26% purity and 95.8% *ee*. ^{1}H NMR (400 MHz, DMSO) δ 7.83–7.69 (2H, m), 7.69–7.58 (1H, m), 7.55–7.40 (5H, m), 7.00 (2H, d, J = 8.4 Hz), 5.64 (2H, s), 5.13 (2H, s), 4.91 (1H, s), 4.24–4.07 (2H, m); ^{13}C NMR (100 MHz, ppm, DMSO) δ 157.3, 155.7, 153.1, 147.1 (d, J = 11.7 Hz), 138.4, 134.5, 131.1, 130.6, 130.3, 129.3, 127.7(d, J = 8.0 Hz), 126.1 (d, J = 8.8 Hz), 118.9 (d, J = 3.0 Hz), 118.1, 117.3

(d, J = 19.7 Hz), 114.4, 107.8 (d, J = 3.6 Hz), 74.2, 70.2, 67.6; HRMS (ESI) calcd. for $C_{22}H_{16}Cl_2FNO_3$ $[M + Na]^+$ 454.0384, found 454.0400.

(*S*)-2-(4-((3,4-dichlorobenzyl)oxy)phenyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbonitrile (1)

To a jacketed round bottom flask was charged **2** (893 g, 95.2 wt%, 2.0 mol). Diglyme (8.9 L) and DBU (0.96 Kg, 3.2 eq) were added. The solution was stirred for 1–2 h at room temperature, then filtered through celite to remove any solid particulates. The clear solution was transferred to a pressure bottle to use in the flow reactor. The flow reactor was first prepared by rinsing with diglyme. The back-pressure of the reactor was set to 750 psi and the oven temperature was set to 225 °C. The flow rate was set to 8.3 mL/min. The pump was started. Product collection began after 30 mins reaction time. Small samples were diverted from the flow reactor to allow analysis every 0.5–2 h to monitor the reaction progress. Once the SM solution was consumed, the inlet of line was switched to pure diglyme and continued collected the reaction mixture for an additional 30 minutes, then the outlet of line was switched to a separate collection vessel and the solution was discarded. The product collection vessel was slowly charged with water (4.3 L) over 2.7 h with stirring. The temperature was maintained between 20 and 30 °C during the addition. The resulting suspension was stirred for 20 h. The solid was collected by filtration and rinsed with water. The solid was dried under vacuum below 55 °C for 25 h to provide 540 g of **1** as a white solid with 98.7% purity, 92.7 wt% potency and 95.1% *ee*. ^{1}H NMR (400 MHz, DMSO) δ 7.71 (1H, d, J = 1.5 Hz), 7.65 (1H, d, J = 8.3 Hz), 7.52–7.38 (4H, m), 7.34 (1H, dd, J = 8.5 Hz, J = 2.0 Hz)),

7.18–7.00 (3H, m), 5.29 (1H, dd, *J*= 8.4 Hz, *J* = 2.1 Hz), 5.15 (2H, s), 4.46 (1H, dd, *J* = 11.7 Hz, *J* = 2.4 Hz), 4.17 (1H, *J* = 11.5 Hz, *J* = 8.5 Hz); ^{13}C NMR (100 MHz, DMSO) δ 158.3, 148.0, 143.2, 138.2, 131.1, 130.6, 130.4, 129.4, 128.4, 128.1, 127.7, 126.0, 120.7, 118.7, 118.4, 114.9, 103.4, 74.5, 67.9, 67.7; HRMS (ESI) calcd. for $C_{22}H_{15}Cl_2NO_3$ $[M + H]^+$ 412.0502, found 412.0507.

ASSOCIATED CONTENT

Supporting Information.

NMR spectra, chiral HPLC chromatograms, safety information, and details on small scale Hastelloy port connectors can be found in the supporting information.

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ABBREVIATIONS

CBS, Corey-Bakshi-Shibata; DBA, diazabicyclo non-5-ene; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPEA, diisopropylethylamine; DMAc, dimethylacetamide; DMF, dimethylformamide; eq., equivalents; g, grams; GC, gas chromatography; h, hours; HPLC, high-performance liquid chromatography; m, meters;

min, minutes; mL, milliliters; PFR, plug flow reactor; psi, pounds per square inch; S_NAr, Nucleophilic aromatic substitution; TEA, triethylamine; THF, tetrahydrofuran; TsOH, toluene sulfonic acid; V/Q, volume/flow rate

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