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A Flow Process Built Upon a Batch Foundation – Preparation of a Key Amino-Alcohol Intermediate via Multi-Stage Continuous Synthesis

John Jin Lim[*,†], *Kenneth Arrington*[*†], *Anna L. Dunn*[†], *David C. Leitch*[†‡], *Ian Andrews*[†], *Neil R. Curtis*[ǂ], *Mark J. Hughes*[ǂ], *Daniel R. Tray*[ǂ], *Charles E. Wade*[ǂ], *Matthew P. Whiting*[ǂ], *Charles Goss*[§], *Yangmu Chloe Liu*[§], *Brian M. Roesch*[§]

[†]Chemical Development, API Chemistry, GlaxoSmithKline, Upper Providence, PA, USA.

[‡]Department of Chemistry, University of Victoria, Victoria, BC, V8P 5C2, Canada.

[ǂ]Chemical Development, API Chemistry, GlaxoSmithKline, Stevenage, UK.

[§]Chemical Development, Product and Process Engineering, GlaxoSmithKline, Upper Providence, PA, USA.

Corresponding Authors

* john-jin.x.lim@gsk.com, kenneth.x.arrington@gsk.com

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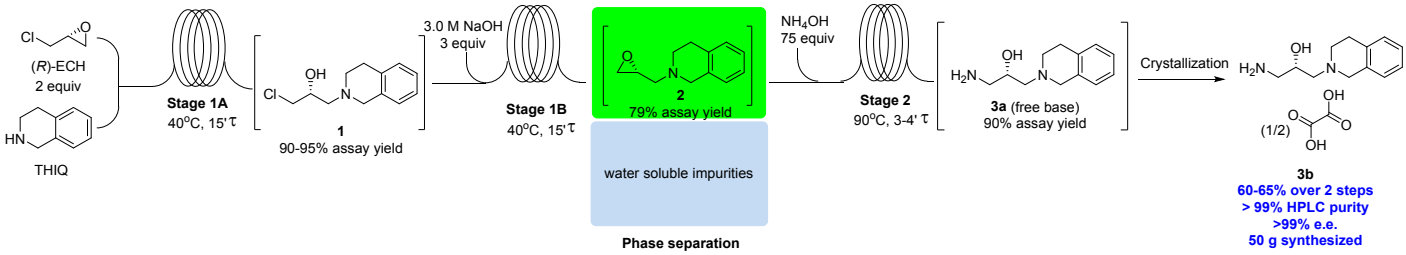


ABSTRACT. This paper describes recent efforts to apply flow technology in the preparation of a key amino-alcohol intermediate (**3b**) so as to address manufacturability issues present in the batch process of a PRMT5 inhibitor. The continuous process, one of the first reported pharmaceutical processes to use aqueous NH_4OH in flow, eliminates an isolation, the use of DCM in the work-up, and improves reaction time >140-fold compared to the batch process to deliver multi-gram quantities of **3b** in 60-65% isolated yield and >99% HPLC area % and >99% *e.e*. While the flow process greatly increases efficiency compared to batch, small scale batch experiments were crucial in gaining reaction understanding to increase kinetics and minimize impurity formation. The holistic process design underscores our belief that large-scale flow processes are built upon the knowledge gained through small scale, well-chosen batch experiments.

Keywords: Continuous processing, batch chemistry, amino-alcohol, ammonium hydroxide, kinetics, PRMT5.

Introduction.

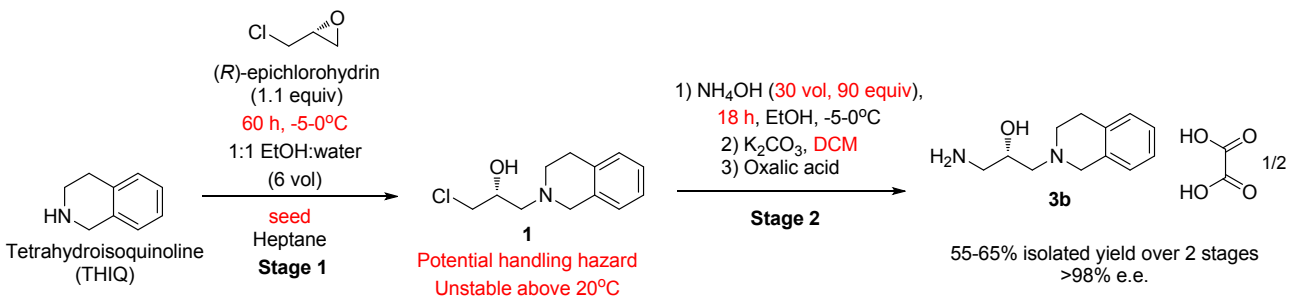
Continuous manufacturing of active pharmaceutical ingredients (APIs) using flow chemistry is a significant and growing aspect of pharmaceutical process development.[1] The benefits of continuous flow reactors as an enabling technology in pharmaceutical research have been well established, with several excellent reviews available.[2-6] It is becoming common for industrial research groups to leverage these benefits by investigating whether their current batch API processes can be converted to continuous flow.[7-13] However, the challenge of transforming a well understood batch process to a continuous process can be daunting.

Through developing multiple continuous processes for clinical candidate APIs,[12,13] our group has found that successful continuous processes are most efficiently built upon reaction understanding gained through traditional batch chemistry. Performing reaction evaluation and optimization experiments in flow can be problematic due to a number of logistical concerns. The more reagents tested, the more feed lines and vessels are required. Testing new chemistry may cause unexpected solid formation, resulting in clogging. Additionally, large amounts of material must be discarded in every experiment

as flow conditions reach steady state. In contrast, traditional batch chemistry presents a much lower barrier to implementation. Screening reactions and time course experiments are often very simple to perform in batch, and provide valuable information regarding reaction conditions and kinetics. The process understanding can then be used to choose the critical process parameters for the flow process, such as residence time and reaction temperature, and helps project teams make crucial equipment choices for scale-up.

As part of synthetic efforts toward protein arginine methyltransferase-5 (PRMT5) inhibitors, a class of promising oncology targets,[14] we required a high-yielding, efficient synthesis of amino alcohol **3b**. The batch synthesis (Scheme 1) required large volumes of ammonium hydroxide (NH_4OH) solution (~30 vol, ~90 equiv) at low temperature and long reaction times, a seeded isolation of unstable and potentially hazardous intermediate **1**, and used the non-preferred solvent dichloromethane (DCM) for the final work-up and isolation of **3b**.

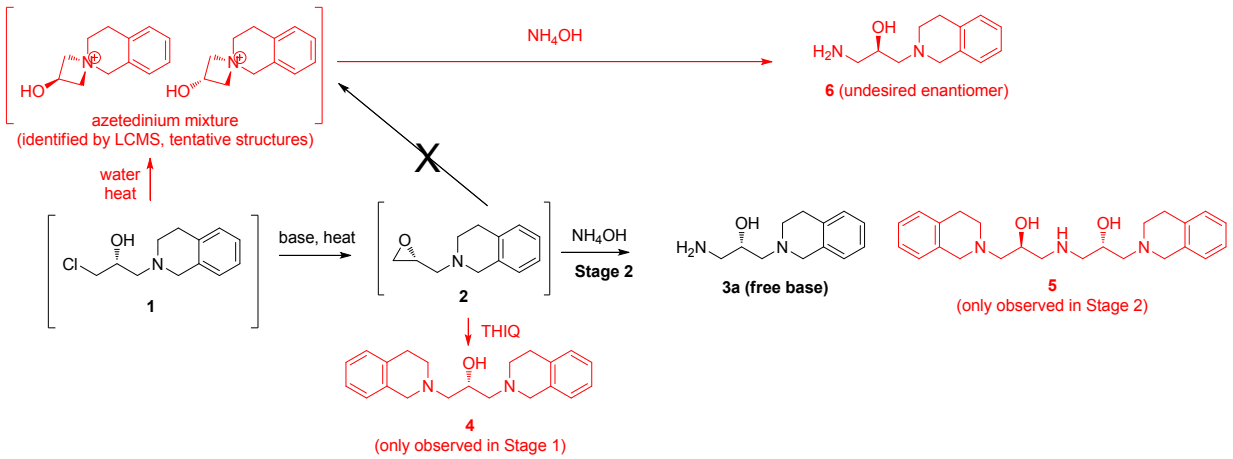
Scheme 1. Batch synthesis of **3b.** Undesirable attributes of this synthesis are labeled in red.



Our group recognized that several challenges to the manufacturability of **3b** could be addressed by utilizing a continuous process. Telescoping the two-step synthesis of **1** to **3b** would eliminate a time consuming isolation of an unstable and possibly hazardous intermediate **1**, which is similar in structure to epichlorohydrin, a suspected carcinogen[15], and thus flagged as a potential handling risk. Furthermore, using a flow reactor at high temperature with sufficient back pressure could remove the need for a high pressure reactor for the ammonium hydroxide reaction while also decreasing reaction time. Modifying our process to telescope two stages into one does remove an isolation step that provides an opportunity to purge impurities; therefore, it is extremely important to assess the impact of this process change to the purity of downstream intermediates and ultimately the target API. Additionally, our laboratory experiments uncovered another

potential risk to address: direct treatment of a solution of chlorohydrin **1** with excess NH_4OH at room temperature in batch results in ~5% racemization of **3a**, presumably through the route shown in Scheme 2.

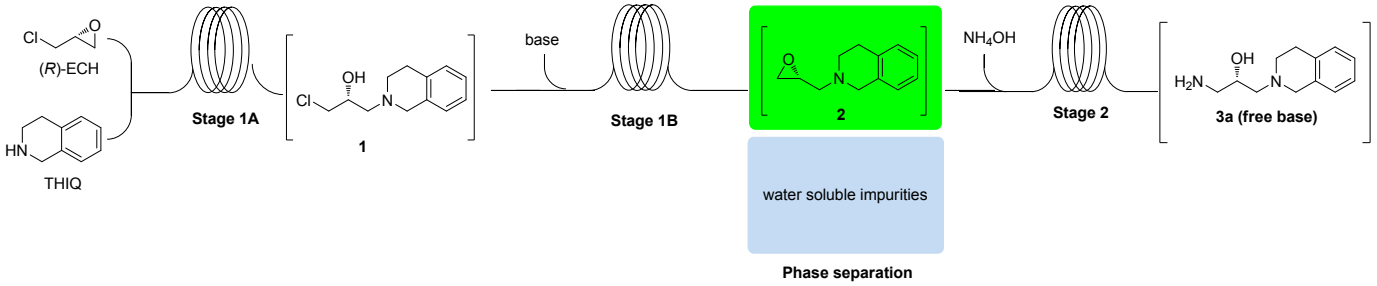
Scheme 2. Impurities (red) formed in Stages 1-2 from **1**.



Although the azetedinium mixture was not isolated or fully characterized, there is abundant literature precedent for its formation from intramolecular cyclization following the reaction of primary and secondary amines and epoxides such as epichlorohydrin (ECH).[16] Because we are using (*R*)-ECH, the intramolecular cyclization results in a 1:1 mixture of non-equivalent azetediniums. Thus, the ammonium hydroxide can react with the mixture to form either **6** or **3a**, resulting in loss of enantiopurity. The **3b** synthesized by the batch process was highly enantiopure; thus, we hypothesize that any undesired

enantiomer **6** that formed in the batch process was either purged during the isolation of **3b**, or the azetedinium mixture that eventually forms **6** was purged during the isolation of **1**. Further study revealed that the azetedinium mixture could not form from epoxide **2**. Thus, our flow strategy (Scheme 3) was to form **1** from THIQ and (*R*)-ECH in Stage 1A then quickly convert it to **2** by the addition of exogenous base in Stage 1B. Next, a liquid-liquid extraction (LLE) is performed to remove water soluble impurities, including the azetediniums which we found partitioned preferentially into the aqueous layer (details in the Supporting Information). Aminolysis of the Stage 1B organic solution containing **2** with NH_4OH in Stage 2 would furnish **3a**. Reaction conditions had to be carefully controlled to minimize the undesired bis-substitution products **4** and **5** that could form in Stage 1 and 2, respectively, since the purging limits of these impurities was unknown. Compound **4** was not observed in large quantities in the batch process due to the milder reaction conditions and the purging of excess THIQ after the Stage 1 isolation.

Scheme 3. Proposed flow scheme Stage 1-2



Stage 1A Development.

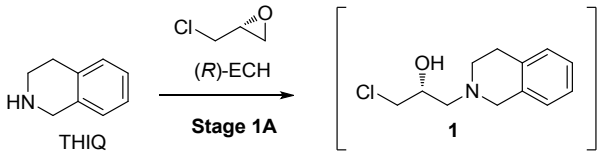
Numerous solvent/base screens were run in batch to evaluate Stage 1 conditions (details in the Supporting Information). Initially *in situ* formation of the epoxide **2** was investigated by adding a base to the reaction with THIQ and (*R*)-ECH. We quickly discovered that addition of base in Stage 1 not only promotes the formation of **2**, but also gives unacceptably high levels of **4**. Alkyl ether side products were observed when employing straight chain alcoholic solvents such as MeOH and EtOH, presumably through a Williamson-type process where the base deprotonates the alcohol to form the alkoxide, which can then displace the chlorine in **1**. Therefore, base is introduced after the formation of **1**. A base screen revealed *t*-AmOH as a suitable solvent, facilitating clean conversion to **1** in the absence of base, albeit at a slower rate than MeOH or EtOH. The hindered nature of *t*-AmOH also renders the solvent less likely to undergo substitution with (*R*)-ECH in the presence of base. To increase the rate of reaction in *t*-AmOH, we investigated

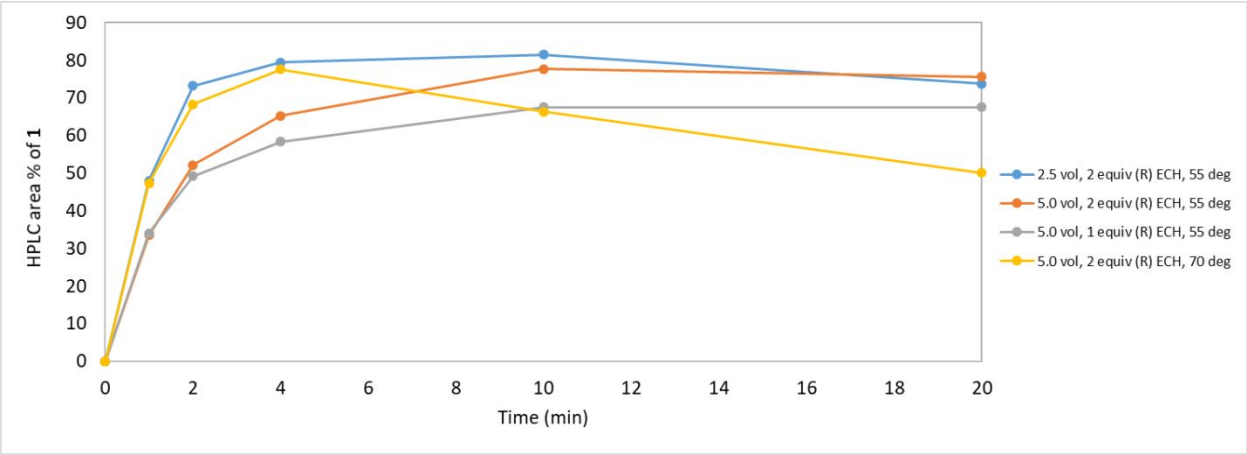
water as a co-solvent. The effect of water on nucleophilic reactions with epoxides have been well studied, with factors ranging from pH, hydrogen bonding interactions, and entropy all relevant for any given reaction.[17-20] We were pleased to see the addition of water not only accelerated the rate of formation of **1**, but likewise suppressed the formation of **4** (details in the Supporting Information). The azetedinium mixture did not increase significantly in the presence of water; we suspect this is due to the relatively mild temperature and that **1** is the more kinetically favored product. Notably, hydrolysis of (*R*)-ECH was not observed. The use of *t*-AmOH also facilitates an LLE after Stage 1B and offered solvent continuity with subsequent stages of chemistry not shown in this paper.

While a full kinetic model for Stage 1A has not yet been determined, several reaction progress experiments were conducted in batch to evaluate reaction conditions using 4:1 *t*-AmOH/water as solvent (Figure 1). It was determined that manipulations of the THIQ concentration and the equivalents of ECH do not significantly impact the **early** rate of reaction but do affect the overall kinetics. Increasing the concentration from 5 to 2.5 volumes increases the overall rate and the use of excess (*R*)-ECH resulted in the

complete consumption of THIQ after 20 min at 55°C, though significantly more azetedinium and **4** were observed. By running Stage 1A more concentrated with an excess of reagent we were able to reduce the temperature, improving the impurity profile. A "same excess" kinetic experiment[21-23] did not implicate (*R*)-ECH decomposition for the slower reaction rate at lower loadings (details in the Supporting Information). While excess (*R*)-ECH loading is not ideal, the reagent is inexpensive and NMR studies indicated that the excess should be at least partially quenched in Stage 1B (details in the Supporting Information). We also felt that any residual (*R*)-ECH or its by-products could be removed by an LLE prior to Stage 2 or during the final isolation of **3b**.

Figure 1. Stage 1A Time Course Data for Compound **1** (batch reactions) demonstrating the effect on the rate of the reaction as a function of reaction concentration, equivalents of (*R*)-ECH, and temperature.





Further kinetic analysis indicated that while the reaction rate to **1** in Stage 1A is not very sensitive to temperature, the rates of impurity formation are strongly temperature dependent (details in the Supporting Information). These insights led to our optimized Stage 1A conditions: THIQ dissolved in 2.5 vol 4:1 *t*-AmOH:water (referred hereafter as Feed 1) treated with 2 equiv of (*R*)-ECH at 40°C and 15 minute residence time (τ). These conditions routinely provide **1** in 90-95% assay yield with ~ 2.1% HPLC area unreacted THIQ and ~2.6% HPLC area azetedinium mixture, with no **4** observed. A flow IR method was developed as an in-line process analytical technique (PAT) to track the formation of **1** for real-time steady state determination of Stage 1A (see Supporting Information)

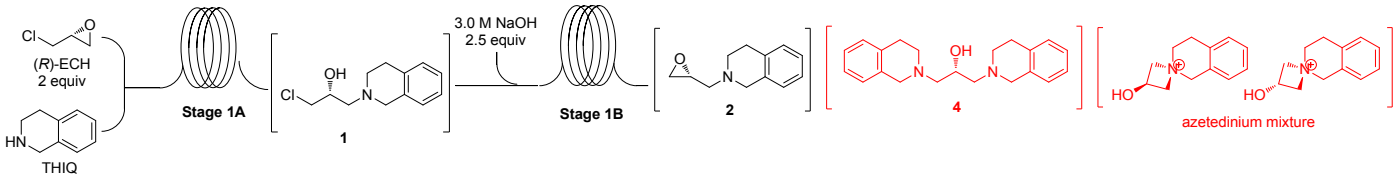
Stage 1B Development.

While direct treatment of the Stage 1A output with NH_4OH is desirable from an operational standpoint, a batch experiment where Stage 1A output produced in flow was treated with excess NH_4OH at room temperature resulted in ~5% loss of enantiopurity for **3a**, presumably through the pathway shown in Scheme 2. Since the (*R*)-ECH from our supplier was >99% enantiopure, we assume the *e.e.* erosion was due to the azetedinium formation. In an effort to ameliorate the *e.e.* erosion, we screened numerous bases in small-scale batch experiments to identify those that favor formation of epoxide **2** over the azetedinium mixture from chorohydrin **1** (details in the Supporting Information). Aqueous 3.0 M NaOH proved to be the most effective in terms of reaction time, side product minimization, and rapid phase separation during the subsequent LLE. Achieving rapid phase separation is critical, as the Stage 1B output stream is not stable over time at room temperature, forming degradation products and **4**.

The use of aqueous base may lead to kinetics being dependent on mass transfer through liquid-liquid mixing. In order to interrogate such effects, we performed several reaction

progress experiments in batch. These experiments clearly indicated the reaction rate is somewhat dependent on mass transfer (details in the Supporting Information). Thus, we studied Stage 1B in flow reactors with varying mixing modes to more clearly elucidate the extent of mass transfer effects (Table 1, see Supporting Information for a picture of the reactor set-up). The Stage 1A conditions were kept constant to maintain a 15 min τ. Because Stage 1A is homogeneous and presumably non-mass transfer limited, we used 10-20 mL perfluoroalkoxy alkane (PFA) reactors (1/16" OD, 0.03" ID) without static mixing elements. Feed 1 (THIQ in 2.5 vol 4:1 *t*-AmOH/water) and Feed 2 (neat (*R*)- ECH) were passed through an MDAT (magnetically driven agitation in a tube)[24] mixer before introduction to the Stage 1A reactor set at 40°C. Stage 1A was monitored by on-line flow IR and off-line HPLC. Assay yields for Stage 1A typically ranged from 90-95% with unreacted THIQ and the azetedinium mixture as the mass balance. The Stage 1A output was premixed with a stream of 3.0 M NaOH (2.5 equiv) in an MDAT prior to introduction to the Stage 1B reactor. An 8 bar back pressure regulator (BPR) was attached at the Stage 1B outlet. The results in Table 1 show the complex interaction of mixing, residence time, and temperature.

Table 1 – Stage 1B Continuous Flow Results Using Tube-Based Reactors.



Condition	Stage 1A reactor volume (mL)	Feed 1 flow rate (mL/min)	(*R*)-ECH flow rate (mL/min)	3.0 M NaOH flow rate (mL/min)	Total flow rate out of Stage 1B (mL/min)	Stage 1B residence time (min)	Stage 1B temp (°C)	HPLC area % of **1**	HPLC area % of **2**	HPLC area % of **4**	HPLC area % of azetedinium mixture	Notes
1	10.0	0.449	0.218	0.983	1.65	7.87	35	44.075	49.824	0.263	1.325	Longer residence time in Stage 1B
2	10.0	0.449	0.218	0.983	1.65	7.87	45	34.079	60.102	0.258	1.484	
3	10.0	0.449	0.218	0.983	1.65	7.87	55	20.587	73.777	0.288	1.872	
4	10.0	0.449	0.218	0.983	1.65	7.87	65	4.344	87.655	0.296	2.223	
5	20.0	0.898	0.436	1.97	3.30	3.94	35	43.042	50.039	0.217	1.087	Better mixing in Stage 1B
6	20.0	0.898	0.436	1.97	3.30	3.94	45	39.336	55.026	0.279	1.283	
7	20.0	0.898	0.436	1.97	3.30	3.94	55	32.384	62.731	0.341	1.288	
8	20.0	0.898	0.436	1.97	3.30	3.94	65	23.884	69.763	0.414	1.741	
9	10.0	0.449	0.218	0.983	1.65	15.1	35	12.761	74.899	n/o*	2.541	no static mixing

Stage 1A: temp = 40°C, τ = 15', conversion = 90-95% for all conditions. *n/o = not observed

Conditions 1-8 used a custom built 13 mL Vapourtec PFA reactor (3/16" OD, 0.13" ID) containing static mixing elements for Stage 1B (details in the Supporting Information). Condition 9 was performed in a 25 mL PFA reactor (1/16" OD, 0.03" ID) without static mixing. For each condition, ~ 5 mL of the Stage 1B output was collected, allowed to phase separate, and the organic layer was sampled for HPLC. Nearly equal conversions were

observed in Condition 5 and Condition 1 despite 50% reduced residence time, demonstrating the effects of better mixing at higher flow rates. Given sufficient residence time, high conversion can be achieved even without active mixing (Condition 9); however, more azetedinium is observed in the organic layer. At shorter residence times (Conditions 5-8), less azetedinium is observed in the organic layer most likely due the increased efficiency of the partitioning at higher flow rates (i.e., better mixing). In effect, the LLE is occurring at the same time as the hydrolysis, so the better mixed conditions show more favorable impurity partitioning. High conversions can be also be achieved by increasing the temperature, though this leads to increased impurity formation (Conditions 4 and 8). Very little of **2** partitioned into the aqueous layer after phase separation, so no back-extraction was necessary.

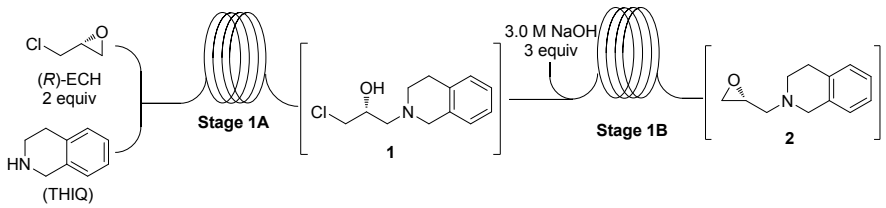
We next examined the mixing effects on Stage 1B with a Corning Low Flow (LF) reactor under several sets of conditions (Table 2). Each plate is comprised of heart-shaped channels which provide intensive mixing even at relatively low flow rates (details in the Supporting Information). Not only does the Corning reactor provide effective mixing, but

lab-scale reactor characterization can be used to predict the behavior of the reaction in plant-scale equipment.[25] The lab-scale reactor is comprised of a number of glass plates, each with an internal volume of 0.40-0.45 mL. At the 2-3 g/min flow rates recommended by the manufacturer, even biphasic reaction mixtures are effectively emulsified.[26] Using these reactors, we collected data on the impact of mixing on the reaction rate and impurity formation by adjusting the flow rates for the telescoped Stage 1A-1B reaction (Diagram of the reactor set-up in the Supporting Information).

The residence time in Stage 1B was controlled by adjusting the flow rates of the three feeds to the process. Due to the number of glass plates available in our labs, the Stage 1A reactors could not be configured to maintain a constant 15 min τ. This constraint on our reactor set-up did not affect the conversion of starting material in Stage 1A (Table 2), but may lead to higher impurity levels than those observed with the optimal 15 min τ; therefore, these studies were used to only investigate conversion to **2**, and not impurity partitioning. We thus quenched the Stage 1B output stream directly into HPLC diluent rather than allowing the Stage 1B output to phase separate and sampling each phase

separately as we had done for the experiments in Table 1. Due to the biphasic nature of the samples, 2-3 samples were taken for each condition. The results are summarized in Table 2 and Figure 2 (a more detailed table showing all flow rates is available in the Supporting Information).

Table 2 – Stage 1B Continuous Flow Results Using a Plate-Based Reactor (Corning LF)

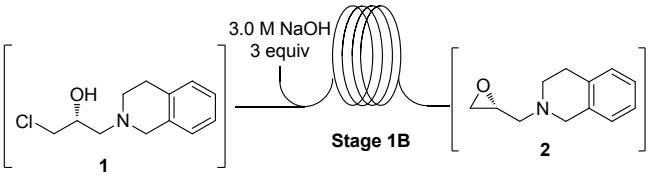


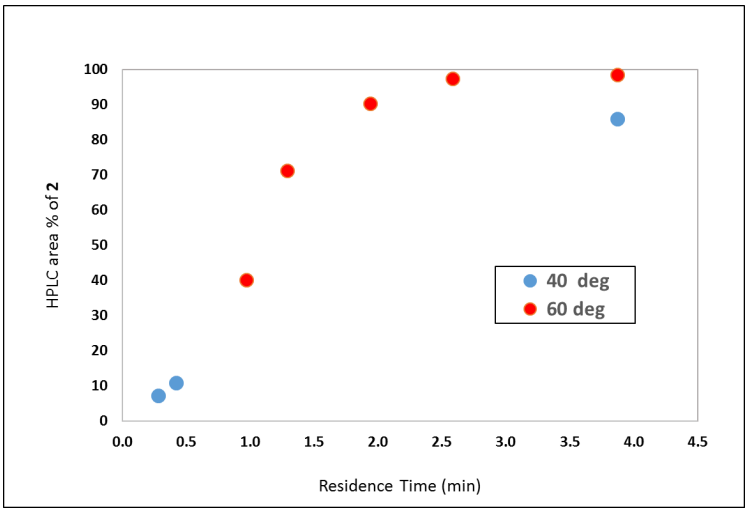
Condition	Stage 1A reactor vol (mL)	Stage 1A conditions	Feed 1 flow rate (g/min)	(*R*)-ECH rate (g/min)	Stage 1A conversion (%)	Stage 1B conditions	3M NaOH flow rate (g/min)	Total Stage 1B flow rate (g/min)	Corning volume (mL)	HPLC area % of **1**	HPLC area % of **2**
1	16	21'τ, 40°C	0.519	0.231	n/a	0.4'τ, 40°C	1.400	2.150	0.85	79.221[a]	9.719[a]
2	16	15'τ, 40°C	0.778	0.347	94	0.3'τ, 40°C	2.101	3.226	0.85	81.402[a]	6.374[a]
3	16	15'τ, 40°C	0.778	0.347	95	1.3'τ, 60°C	2.101	3.226	3.90	27.212[a]	55.084[a]
4	20	14'τ, 40°C	1.038	0.463	93	1.0'τ, 60°C	2.801	4.302	3.90	43.158[a]	45.291[a]
5	16	21'τ, 40°C	0.519	0.231	97	1.9'τ, 60°C	1.400	2.150	3.90	9.040[a]	73.023[a]
6	16	42'τ, 40°C	0.260	0.116	97	3.9'τ, 60°C	0.700	1.075	3.90	1.481[b]	74.064[b]
7	16	42'τ, 40°C	0.260	0.116	96	3.9'τ, 40°C	0.700	1.075	3.90	7.661[b]	77.982[b]
8	16	28'τ, 40°C	0.390	0.173	98	2.6'τ, 60°C	1.050	1.613	3.90	1.789[b]	83.825[b]

[a]Average of 2 HPLC injections. [b]Average of 3 HPLC injections

Density Feed 1 = 0.92 g/mL, Density (*R*)-ECH = 1.18 g/mL, Density 3.0M NaOH = 1.12 g/mL

Figure 2 – Stage 1B Conversion vs Residence Time in Corning LF reactor at 40 and 60°C





As shown in Table 2, poor conversions are observed with short residence times, even with very good mixing (Conditions 1 and 2). As residence time is increased, conversion improves. Even for conditions that deliver sub-optimal mixing (Conditions 6-8, total flow rate < 2 g/min), high conversions can be achieved through a combination of increased temperature and residence time. Encouragingly, even at the higher temperatures, HPLC

quantification of impurity **4** did not exceed 1.1 area %. Due to the material incompatibility of the caustic Stage 1B output with the glass reactor plates, temperatures above 60°C were not examined.

The results from Tables 1 and 2 illustrate that high conversions in Stage 1B are achieved by balancing residence time, mixing, and temperature. It is concluded that the Stage 1B reactions were not completely mass transfer limited because there is a large impact of residence time on conversion, indicating at least a partially kinetically controlled system. Furthermore, reactions run at lower flow rates (and therefore, less mixing) did not result in low conversion which would be the case if the system was strictly mass transfer limited. However, there appears to be a relatively small effect of temperature on conversion between 40 and 60°C (Figure 2). If the system is kinetically limited, one would expect a larger temperature effect; however, we note that this is a relatively small sample size. In addition, our crystallization studies (details in the Supporting Information) do indicate that leftover (*R*)-ECH is present throughout the stages, and its effect on the reaction mechanism for Stage 1B is not currently known. While the exact reaction mechanism for

Stage 1B has yet to be determined, these results demonstrate that the reaction can proceed in high conversions largely independent of reactor type, allowing greater flexibility in reactor choice for Stage 1B. These simple flow experiments revealed an important fact about Stage 1B - given sufficient residence time, good conversions to **2** could be achieved even with sub-optimal mixing. However, more effective partitioning of impurities into the aqueous phase likely occurs when the reaction is better mixed.

Following Stage 1B, the output is collected in an intermediate storage vessel in an ice-water bath. Epoxide **2** partitions exclusively into the organic layer, while the majority of the azetediniums partition into the aqueous (details in the Supporting Information). After phase separation, the organic layer is transferred to a feed vessel, stored cold, and then used as-is for Stage 2.

Stage 2 Development.

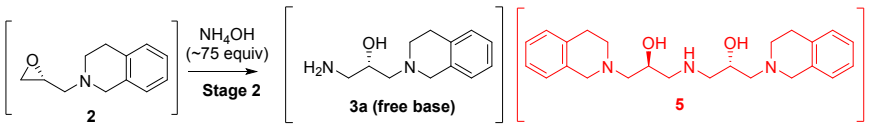
The Stage 2 batch process required large excesses (90 equiv) of NH_4OH at extended reaction times and low temperature (0-5^oC, 18 h) to minimize formation of **5**. As NH_4OH is a poor nucleophile compared to the Stage 2 product **3a**, large excesses are required

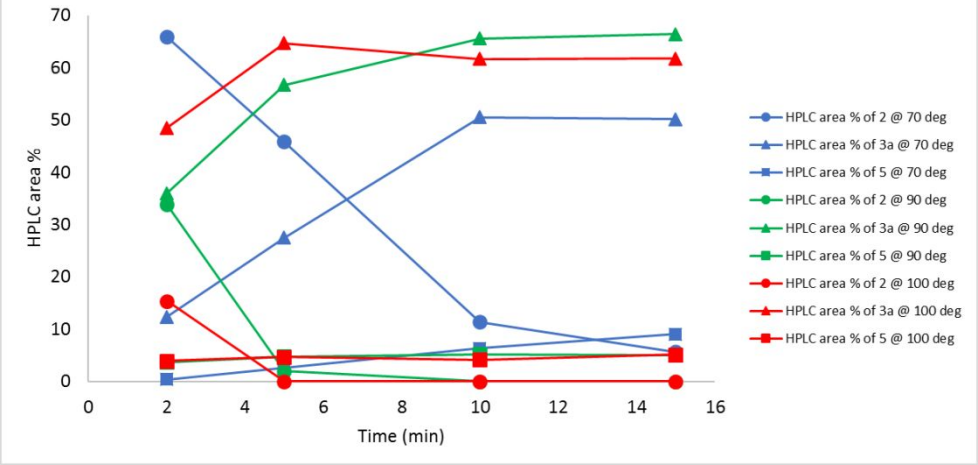
to avoid formation of impurity **5**. Increasing the temperature of the batch reaction would require the use of specialized pressure reactors due to the amount of NH_4OH present, further complicating the process. Thus, we focused our efforts to adapt the batch process to flow utilizing back pressure regulators in standard flow reactors at elevated temperatures. Surprisingly, the use of aqueous NH_4OH in flow organic synthesis has not been frequently reported; we identified only one prior example in the literature.[27] The use of ammonia surrogates was also investigated, but we found these to be unsuitable for flow operation.[28] The use of gaseous ammonia NH_3 in flow was considered but not explored due to development timelines.

Gathering kinetic data for Stage 2 in batch posed a challenge due to the high pressures resulting from using NH_4OH at elevated temperatures. We decided to explore time points at three different temperatures (70°C, 90°C, and 100°C) by dispensing aliquots of Stage 1B organic flow output containing **2** in solution to glass vials equipped for magnetic stirring (Figure 3). Aqueous NH_4OH (24-26% w/w) was added such that very little headspace remained in the vial in an attempt to mimic conditions in a flow reactor (~ 73-75

equivalents based on HPLC assay of **2**). The vials were then placed on a stirring block set at the desired temperature and maximum agitation rate. Vials were removed at designated time points, allowed to cool, and then sampled for HPLC.

Figure 3 – Stage 2 Time Course Data (Batch)



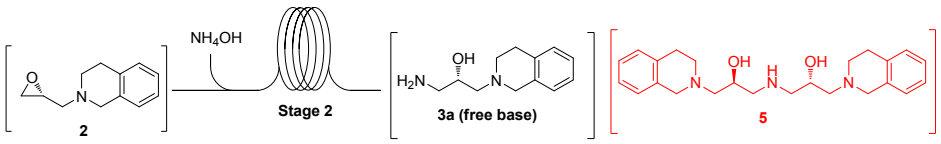


We were pleased that our initial time course data showed Stage 2 was complete in less than 10 min at elevated temperature. Extended reactions times resulted in increased **5**, and temperatures >70°C were required for complete consumption of **2**. It was also noted that the solutions were homogeneous at high temperature, indicating that the kinetics should not be mass transfer limited. Thus, intensive static mixing should not be required for Stage 2.

Following our time course studies in batch, Stage 2 scoping studies were performed in flow (Table 3, see Supporting Information for a picture of the reactor set-up). Stage 2 was performed in a 10 mL PFA reactor (1/16" OD, 0.03" ID). Feed 3 (Stage 1B organic output following phase separation) and Feed 4 (aqueous NH_4OH) were mixed in an MDAT

before introduction to the Stage 2 reactor set at the desired temperature. Feed 3 was kept at ~ 0-5 °C in an ice water bath during the reaction. An 8 bar BPR was attached at the Stage 2 outlet. The system pressure stabilized to 6-7 bar at steady state.

Table 3 - Stage 2 scoping in flow as monitored by offline HPLC.



Condition	NH_4OH (equiv)	Stage 2 residence time (min)	Stage 2 temperature (°C)	HPLC area % of **2**	HPLC area % of **3a**	HPLC area % of **5**	HPLC area % of unknown impurity @ 21 min
1	75	5	75	6.381	54.706	3.010	0.267
2	75	5	80	4.410	58.101	6.155	0.251
3	50	5	85	4.410	46.843	14.091	4.543
4	75	5	85	2.490	55.770	11.279	2.008
5	95	5	85	1.153	58.009	10.335	1.393
6	75	5	90	1.271	58.747	6.850	1.455
7	75	5	95	0.630	48.714	14.412	5.437
8	75	3	90	3.003	55.797	4.534	n/o*
9	75	4	90	1.417	56.974	6.617	0.469
10	75	5	90	1.466	56.682	7.652	0.843
11	75	6	90	1.606	55.917	7.080	1.196

*n/o = not observed

This data gave several important insights into this reaction. Using 50 equiv of NH_4OH is not sufficient for complete conversion for the tested residence times and allows for greater formation of **5** and an unknown non-polar impurity at a 21 min retention time on our HPLC

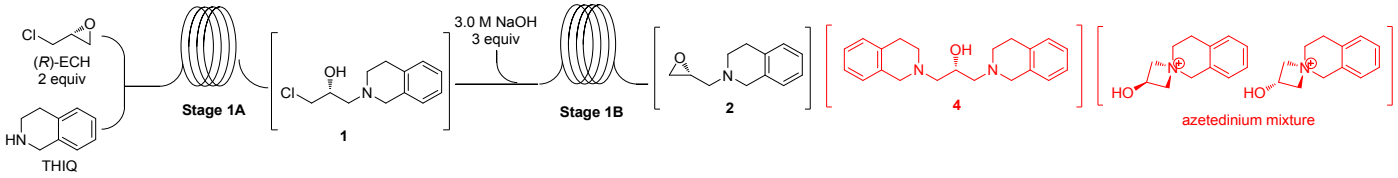
method, possibly a trimeric side product (Condition 3). However, the addition of 95 equiv of NH_4OH does not appear to offer much advantage over 75 equiv (Condition 5). Temperature and residence time also play very important roles, as temperatures < 75°C lead to poor conversion while residence times > 3-4 min lead to greater impurity formation (Conditions 1-7, 10 and 11). The optimal zone appears to be around 90°C and 3-4 minute residence time with 75 equiv of NH_4OH (Conditions 8 and 9). The Stage 2 reaction in flow seems slightly faster than in batch at the same temperature, most likely due to the better heat transfer in the flow reactor.

Stage 1-2 Extended Lab Runs.

Following optimization of Stages 1-2, several extended lab runs were performed (Tables 4 & 5). Although it would be desirable use the Corning reactor for Stage 1B in these extended runs as it is most likely the type of reactor that will be used at pilot and manufacturing scale, we were limited with the number of Corning reactors available. Thus, these extended runs were performed in PFA reactors. The Stage 1A conditions were fixed at 40°C, 2 equiv (*R*)-ECH, 15' τ in a 10 mL PFA reactor. After Stage 1A had

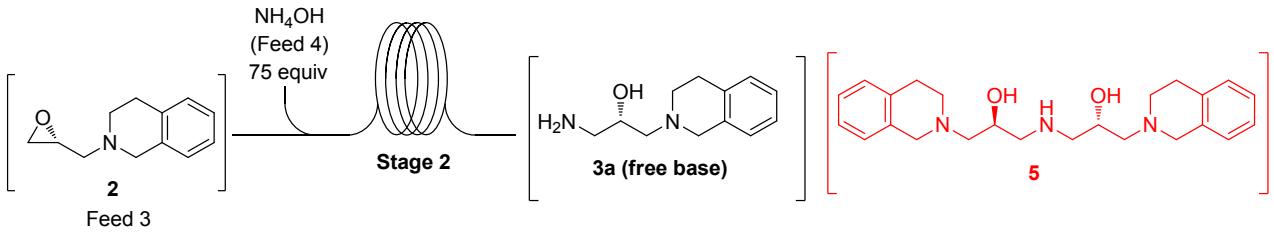
reached steady state by flow IR, Stage 1B conditions were started by commencing flow of 3.0 M NaOH (3 equiv). Stage 1B was performed in either a 25 mL PFA reactor with no static mixing (Runs 1 & 2, Table 4) or a 13 mL PFA reactor with static mixing elements (Run 3, Table 4). After waiting ~ 2 residence times to achieve steady state for Stage 1B, the Stage 1B output was collected into an intermediate storage vessel. After collection, the Stage 1B output was phase separated and the organic layer (~31% of the biphasic output by volume) was assayed by HPLC and then stored cold. The lab equipment was then reconfigured to perform Stage 2 using the same 10 mL PFA reactor in Stage 1A and the Stage 1B organic output (Feed 3) and NH_4OH (Feed 4). Stage 2 conditions were fixed using 75 equiv of NH_4OH, 3'τ, and 90^{o}C. Collection of the Stage 2 output was begun after ~ 2 residence times elapsed.

Table 4 – Stage 1 Extended Lab Runs



Run	Stage 1A conditions	Stage 1B conditions	Stage 1A-1B total flow rate (mL/min)	Stage 1A-1B assay yield of **2** in organic layer (%)	HPLC area % of **4** in organic layer	HPLC area % of azetediniums in the organic layer	Time of Stage 1B collection (h)
1	15'τ, 40°C, 10 mL reactor	14.5'τ, 40°C, 25 mL reactor	1.72	78	0.88	1.36	2.5
2 (repeat of 1)	15'τ, 40°C, 10 mL reactor	14.5'τ, 40°C, 25 mL reactor	1.72	79	0.78	1.41	2.0
3	15'τ, 40°C, 10 mL reactor	7.6'τ, 60°C, 13 mL reactor (static mixing)	1.72	79	2.32	1.62	1.8

Table 5 – Stage 2 Extended Lab Runs



Run	Stage 2 conditions	Feed 3 flow rate (mL/min)	Feed 4 flow rate (mL/min)	Stage 2 total flow rate (mL/min)	Assay concentration of **2** in Feed 3 (mg/g)	Stage 2 assay yield of **3a** (%)	Assay concentration of **3a** in Stage 2 output (mg/g)	HPLC area % of **5**	Time of Stage 2 collection (h)

1	3'τ, 90°C, 10 mL reactor	0.414	2.71	3.10	362.5	90	58.3	5.2	2.0
2 (repeat)	3'τ, 90°C, 10 mL reactor	0.414	2.71	3.10	371.9	n/d	57.1	7.3	2.0

The extended lab runs showed fairly good reproducibility in terms of output quality. For both Stage 1 and 2, no fouling or overpressurizations were observed with these extended run times. The amount of **4** that is observed in the final Stage 1B organic layer (Runs 1-3, Table 4) is slightly higher than the analagous conditions observed in our Stage 1B scoping studies (Table 1), likely due to the reaction of epoxide **2** with unreacted THIQ remaining from Stage 1A during the longer collection times. The increased amount of **4** in Run 3 (Table 4) is probably because the receiving flask was not totally submerged in the ice-water bath and thus the Stage 1B output had an opportunity to warm to ambient temperature. However, **4** can be purged in the final crystallization. Somewhat surprisingly, the amount of azetedinium in the organic layer after Stage 1B was slightly higher for Run 3 (static mixing) than the conditions without static mixing (Runs 1-2, Table 4); however, we attribute this to the fact that the total flow rate for Stage 1A-1B was kept constant for

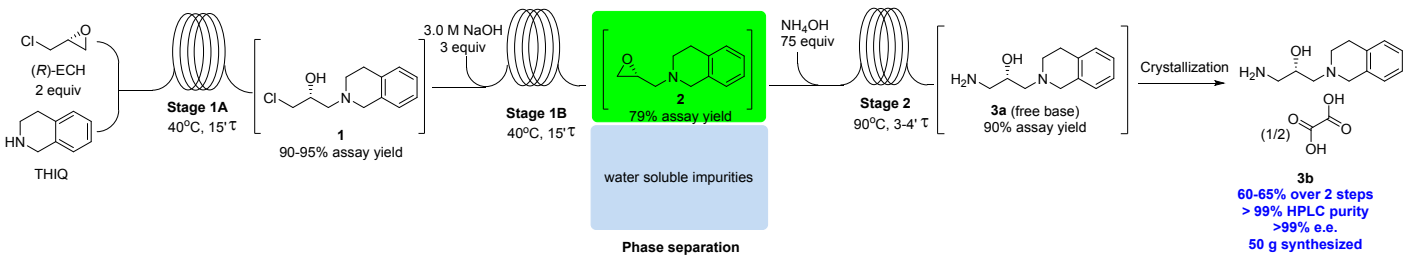
all runs and thus the full benefits of mixing were not realized for Run 3. Analysis of **3a** in the Stage 2 output by chiral HPLC showed >99% e.e, so we presume most of the azetediniums formed during our extended lab runs were purged during the Stage 1B work-up and thus any leftover azetediniums did not produce enough undesired enantiomer **6** in Stage 2 to exceed purging limits. During Stage 2, the amount of **5** that formed seemed consistent with our time course studies in batch (Figure 3) and our scoping studies in flow (Table 3). The throughput of **3a** in solution after Stage 2 with an output flow rate of ~3.1 mL/min is ~ 8.4 g/hour. The entire flow process for Stage 1-2 has been run for ~8-9 h, including start-up/shutdown and reconfiguration of the reactors between Stage 1 and 2.

Stage 2 Preliminary Work-up and Isolation

While the work-up and crystallization from the original the batch process reliably provided pure **3b**, there were manufacturability concerns regarding the number of unit operations and the use of DCM (details in the Supporting Information). We quickly determined that *n*-BuOH was an effective replacement for DCM in extracting **3a** from the predominantly

aqueous Stage 2 output. Following off-gassing of the ammonia, the Stage 2 output was extracted twice with *n*-BuOH to nearly completely remove **3a** from the aqueous layer without the need for a salt such as K_2CO_3 or NaCl. After concentrating the combined organics to 2-3 volumes to make a ~44% wt solution of **3a,** the Stage 2 output was diluted with a 15:1 *n*-BuOH:water which was then heated to 50°C. Oxalic acid dihydrate (0.6 equiv) was charged as a bolus solid. After cooling to ambient temperature and holding overnight, the product was isolated and washed with a 95:5 *n*-BuOH:water mixture and dried under vacuum to afford enantiopure **3b** in 60-65% isolated yield from Stage 1. This procedure can purge up to 22% HPLC area of impurity **5**, as well as any impurity **4** that forms in Stage 1B, and has been used to synthesize up to 50 g of **3b** in >99% HPLC purity and >99% *e.e.* (details in the Supporting Information).

Figure 4 - Final optimized process to produce 50 g of **3b**



Conclusions.

We have successfully developed a simple and effective flow process to generate gram quantities of key amino-alcohol intermediate **3b** in 60-65% yield, >99% HPLC purity, and >99% *e.e.* over 3 steps. Crucial reaction understanding was gained through small scale batch experiments which lead to facile design of the flow process. Flow IR was successfully implemented in Stage 1A as an in-line PAT to track the formation of chlorohydrin intermediate **1** to enable real-time steady state determination. A cumbersome and potentially hazardous isolation was eliminated after Stage 1A, as well as the use of undesirable solvent DCM in the final work-up and isolation. The final aminolysis in Stage 2 still required a large excess of NH_4OH, but the use of a flow reactor at high temperature drastically reduced the reaction time. Chemical reaction times for Stage 1-2 were dramatically improved (78 h combined for Stages 1 and 2 in batch, 20-33 min residence times for Stage 1-2, 142-fold improvement), which project to shorter cycle times on scale.

Experimental Section.

General information:

All solvents and reagents were obtained from commercial sources and used as received. All batch reactions were carried out in oven-dried reaction vessels or glass vials. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer, and are reported as chemical shifts (δ) in parts per million (ppm), and multiplicities are abbreviated as s= singlet, d = doublet, t = triplet, m = multiplet, b = broad, dd = doublet of doublets, ddd = doublet of doublet of doublets. Residual solvent signals were used as reference. HRMS (m/z) was measured using a LTQ Discovery Orbitrap (Thermo) mass spectrometer equipped with a heated electrospray ionization (HESI) ion source. LRMS (m/z) was measured using a Water Acquity SQD mass spectrometer on a Waters CSH column (C18, 30mm x 2.1 mm, 1.7 µm particle size). HPLC achiral analysis was carried out on an Agilent HPLC system equipped with an Atlantis T3-C18 reversed-phase column (250 mm × 4.6 mm, 5 µm). A mobile phase of acetonitrile and water with 0.05% v/v TFA as modifier was used at a flow rate of 1.0 mL/min and a column temperature of 25 °C. The UV detector was set at 210 nm to analyze the column effluent. Unless otherwise noted, HPLC analysis data are reported in area % and not adjusted to weight %. Extended lab

runs were performed using a Vaportec R4 system fitted with PFA reactors as described below and an 8 bar back-pressure regulator. The 3.0 M NaOH feed was pumped using a Syris Asia dual channel syringe pump. IR data was measured using Mettler Toledo ReactIR iC10 (SN RIC-1227), DiComp Probe (6 mm dia, 305 mm long, 1.5m Fiber, SN DSTFP-6-305-1.5-16418). The iCIR v7.0.297 software was run on HP Elitebook 8460p computer with Win7 64bit software. Each data point is an average of 16 scans (8 cm^{-1} resolution) collected over 10 s. See SI for full HPLC & IR details.

Stage 1-2 synthesis of 3a with the continuous flow process (see SI for picture of equipment set-up):

Feed 1 was prepared by dissolving THIQ (100 g) in 4:1 v/v *t*-AmOH:water (2.5 vol, 200 mL *t*-AmOH and 50 mL water). Feed 1 and Feed 2 (*R*-ECH, 138 g) were pumped via a T-joint into an MDAT at 0.495 mL/min and 0.172 mL/min, respectively. This combined stream was then directed into a 10 mL PFA reactor (1/16" OD, 0.03" ID) with reactor temperature set for 40°C and a residence time of 15 min, monitoring by flow-IR. After steady state for Stage 1A has been achieved by IR, a feed of 3.0 M NaOH (743 mL) was

directed into the Stage 1A output stream via a T-joint at 1.05 mL/min to begin Stage 1B. The combined stream was directed into an MDAT and then subsequently into a 25 mL PFA reactor (1/16" OD, 0.03" ID) with reactor temperature set for 40 °C and a residence time of ~15 min, or a 13 mL PFA reactor with static mixing elements (3/16" OD, 0.13" ID) set for 60°C and a residence time of ~7.1 min. The pressure in the reactor was regulated under 8 bar by a BPR. After ~ 2 residence times, the biphasic mixture was collected and allowed to phase separate. Following collection of the Stage 1B output, the aqueous layer was discarded and the organic layer containing **2** (18.9 g, 79% assay yield based on 16.9 g THIQ processed during collection) was collected, stored cold, and used without further processing for Stage 2.

Feed 3, comprised of the organic output of Stage 1B (63 mL, ~18.9 g of **2** by HPLC assay) and Feed 4, 23-26% aqueous NH_4OH (500 mL) were pumped via a T-joint into an MDAT at 0.414 mL/min and 2.71 mL/min, respectively. This stream was then directed into a 10 mL PFA reactor (1/16" OD, 0.03" ID) with reactor temperature set for 90°C and a residence time of 3 min. The pressure in the reactor was regulated under 8 bar by a BPR.

After waiting ~ 2 residence times, the output was collected and then assayed for HPLC upon completion of collection (~345 mL of Stage 2 output containing 14 g of **3a**, >90% assay yield based on 13.5 g of **2** processed during collection).

General procedure for work-up and crystallization of 3b

Following off-gassing of the ammonia, the Stage 2 output was extracted with *n*-BuOH (2 x 12 vol). The combined organics were concentrated under vacuum to 2-3 volumes to make a ~ 44% wt solution of **3a** (102 g of solution containing 45 g of **3a**, 219 mmol). The solution was diluted in a mixture of *n*-BuOH (1374 mL, 30 vol) and water (115 mL, 2.5 vol) at ambient temperature under N_2. The resulting solution was heated to 50°C and stirred for 60 mins. Oxalic acid dihydrate (16.8 g, 133 mmol, 0.6 eq.) was added as a solid in one portion to the pre-heated reaction mixture. The slurry was stirred at 50°C for one hour and then allowed to cool to ambient temperature and stirred overnight. The product was isolated by filtration and the product was washed with 95:5 *n*-BuOH-water (460 mL, 10 vol) followed by industrial methylated spirits (IMS, 460 mL, 10 vol) then dried at 50°C overnight, affording ~50 g of **3b** as a white solid (~64% from Stage 1).

Data for (*S*)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol oxalate (**3b**): ^{1}H NMR (400 MHz, D_2O) δ ppm: 7.22-7.13 (m, 3 H), 7.09 (s, 1 H), 4.16 (m, 1 H), 3.77 (m, 1 H), 3.10 (dd, *J*=13.17, 3.32 Hz, 1 H), 2.84 - 2.97 (m, 5 H), 2.66-2.77 (m, 2 H).

^{13}C NMR (101 MHz, D_2O) δ ppm: 173.4 (s, 1 C), 133.5 (s, 1 C), 132.9 (s, 1 C), 128.7 (s, 1 C), 126.9 (s, 1 C), 126.8 (s, 1 C), 126.2 (s, 1 C), 65.1 (s, 1 C), 60.2 (s, 1 C), 55.2 (s, 1 C), 50.5 (s, 1 C), 43.5 (s, 1 C), 27.0 (s, 1 C).

HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{19}N_2O$: 207.1482; Found 207.1502

ASSOCIATED CONTENT

Supporting Information. Details of IR method, kinetic data, photographs of lab equipment, and characterization data for all isolated compounds. This material is available free of charge via the internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

* john-jin.x.lim@gsk.com, kenneth.x.arrington@gsk.com

Notes

The authors declare no competing financial interests.

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