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Developing a Multistep Continuous Manufacturing Process for (1*R*,2*R*)-2-Amino-1-methylcyclopentan-1-ol

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ABSTRACT: A multistep continuous manufacturing process to synthesize (1*R*,2*R*)-2-amino-1-methylcyclopentan-1-ol (**2**) was developed. The step 1/2 flow process mitigated the safety hazard associated with high exothermicity during epoxidation, the epoxide-opening reaction, and the low onset of the epoxide intermediate. Process improvements included a hybrid plug flow reactor (PFR)/continuous stirred tank reactor (CSTR) reaction and a continuous quench/work-up process in step 1; a continuous reaction, extraction, washing, and thin-film distillation work-up in step 2; and a continuous trickle bed hydrogenation in step 3, which provided the desired product with high purity and high ee. The end-to-end continuous process provided significant advantages of cost-saving, minimization of manufacturing space and utilities, and reduction of the cycle time.

KEYWORDS: *continuous manufacturing, epoxidation, epoxide opening, chiral resolution, trickle bed hydrogenation*

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1. INTRODUCTION

Cyclin-dependent kinases (CDKs) are a class of cellular enzymes that play an important role in cell cycle progression.[1] Many CDK inhibitors have been evaluated as cancer targets in the preclinical and clinical studies since the FDA's approval of palbociclib in 2015.[2] Compound **1** (Figure 1) is a CDK 2/4/6 inhibitor currently being developed by Pfizer as an oncology candidate.[3] One of the key synthetic challenges for this compound is the synthesis of a chiral amino alcohol building block (**2**).

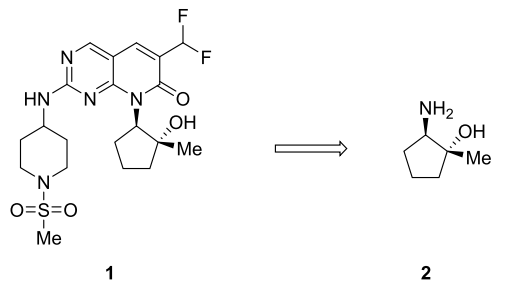

Figure 1. CDK 2/4/6 inhibitor (**1**) and amino alcohol (**2**).

There is limited literature precedence on the synthesis of compound **2**,[4] and several chiral synthetic routes were explored during development with limited success. The initial route[1] for early clinical supply is illustrated in Scheme 1. The synthesis starts from the bromination of methylcyclopentene by 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), followed by base-mediated cyclization of bromohydrin to provide racemic epoxide (**4**). Opening of the epoxide using benzylamine gives the racemic benzylamino alcohol (**5**), with ~5:1 regioselectivity, favoring the desired regioisomer. Chiral resolution by (*S*)-2-(3,5-dinitrobenzamido)-2-phenylacetic acid (DNBPG) gives **7** at 95−97% ee and deprotection by hydrogenation, followed by exposure to p-toluenesulfonic acid provides compound **2** as the tosylate salt.

To support a rapid acceleration for the project, it was determined that the route would be insufficient to provide the required quantity of compound **2** for large-scale API production. While the lack of a commercial source of the resolution reagent is problematic, the biggest limitations of the approach on a larger scale are step 2 epoxide opening and step 1 epoxidation. Although the regioselectivity of the step 2 reaction is consistent (at about 5:1 favoring **5**), the reaction requires using water as the solvent,[5] and a competitive hydrolysis reaction was observed at lower temperatures. Conducting the reaction at elevated temperatures reduces diol (**8**) formation but presents a safety hazard since compound **4** has a very low onset (49 °C even when a base is present) and high thermal event (506 kJ/kg). Furthermore, when the reaction was carried out on a larger scale in an autoclave at 100 °C, a complicated reaction mixture was obtained, which impacted the subsequent chiral resolution. In addition, step 1 epoxidation went through a bromohydrin intermediate, which always gave a mixture with multiple impurities, and the purification of the epoxide intermediate was problematic due to the aforementioned safety hazard.

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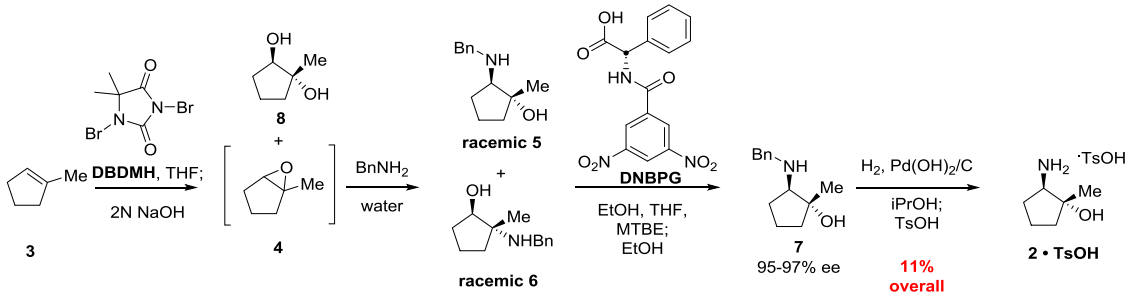
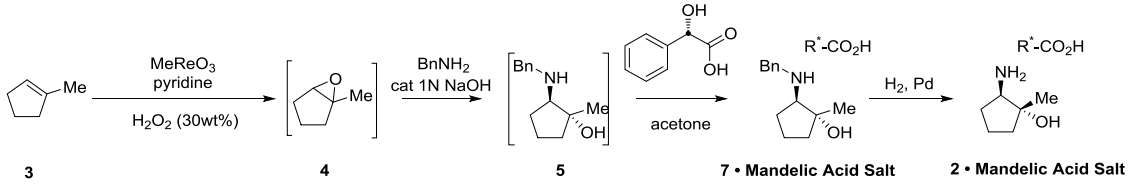
Scheme 1. Initial Route to Tosylate of Compound 2



Scheme 2. New Route to Compound 2



In recent years, continuous manufacturing processes have gained momentum in the pharmaceutical industry due to their many advantages compared to the traditional batch process.[6] One important aspect of a continuous process is the increased safety for thermal hazard reactions by minimizing reaction volumes and maximizing heat-transfer rates. It also allows for wider-temperature operation windows and higher-pressure capabilities. For the problems we encountered in the above synthesis, a continuous manufacturing process could provide the best solution. Herein, we describe a new multistep continuous manufacturing process, which was developed for the preparation of compound **2** on a large scale.

2. RESULTS AND DISCUSSION

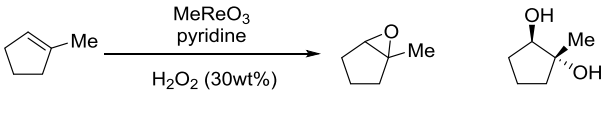
To circumvent the problems identified in the discovery synthesis, a new route was quickly developed and demonstrated at the lab scale (Scheme 2). The synthesis starts from epoxidation of methylcycolpentene using methyltrioxorhenium (MTO) and H_2O_2 as the oxidant, followed by epoxide opening with benzylamine under basic conditions. The chiral resolution is achieved using the more readily available (*S*)-mandelic acid, and the final debenzylation affords compound **2** as a mandelic acid salt. To respond to the urgent clinical need, we quickly developed this route into a process that was capable of producing hundreds of kilograms of amino alcohol **2** using a continuous process. The details of the process development of each step are discussed below.

2.1. Step 1—Epoxidation. Epoxidation of methylcyclopentene through a halohydrin intermediate was effective to a certain extent, but the purity of the product was not satisfactory for direct telescoping to the next step. Isolation and purification of the crude product were proven necessary to ensure an acceptable purity profile for the successful execution of the resolution step. Purification by vacuum distillation was also feasible but presented safety risks on a larger scale.

In an effort to improve the process and avoid the classical resolution, (*R*,*R*)-Jacobsen's catalyst [(*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese-(III)chloride] was explored briefly, but it failed to provide satisfactory stereoselectivity.[7] This was moderately improved using a modified chiral Mn-Salen catalyst, but in these experiments, the reactivity was too low and the approach was abandoned. Enzymatic epoxidation was attempted with chloroperoxidase[8] and lipase (Novozyme 435),[9] but lower purity and yield were often obtained, and the same purification challenge as in the halohydrin route was expected.

The most cost-efficient method identified for the epoxidation is to use catalytic methyltrioxorhenium (MTO) and aqueous H_2O_2 (Scheme 3).[10] MTO is stable, easily accessible,

Scheme 3. Epoxidation of Methylcyclopentene and the Diol Impurity



and the oxidation of the olefin proved to be both highly active and highly selective. The addition of catalytic amounts of pyridine suppresses the ring opening and diol formation, resulting in reaction mixtures of high purity that can be used directly in the subsequent step without additional purification. In the initial laboratory-scale experiments, substoichiometric H_2O_2 (0.95 equiv) was used as neat reactions, resulting in crude reaction mixtures being carried over to the next step without the quench and work-up process.

However, the process safety testing of this reaction indicated that the heat of the reaction was 686 kJ/mol and an adiabatic temperature of 1075 °C was observed. Elongated reaction times and slow addition of H_2O_2 assisted in heat control, but both changes resulted in higher levels of diol and other impurities. Through additional experiments, it was found that the addition of tetrahydrofuran (THF) to the reaction mixture alleviated the heat output, with no detrimental effects on the reaction impurity profile. It was found that the addition of 2 vol of THF to the reaction greatly reduced the exotherm to 218 kJ/mol and the adiabatic temperature increased to 350 °C. While this increased the safety of performing the reaction on a larger scale, the reaction was still limited to volumes of ≤80 L to meet the safety threshold, resulting in a total of 15 smaller batches for a 50 kg delivery.

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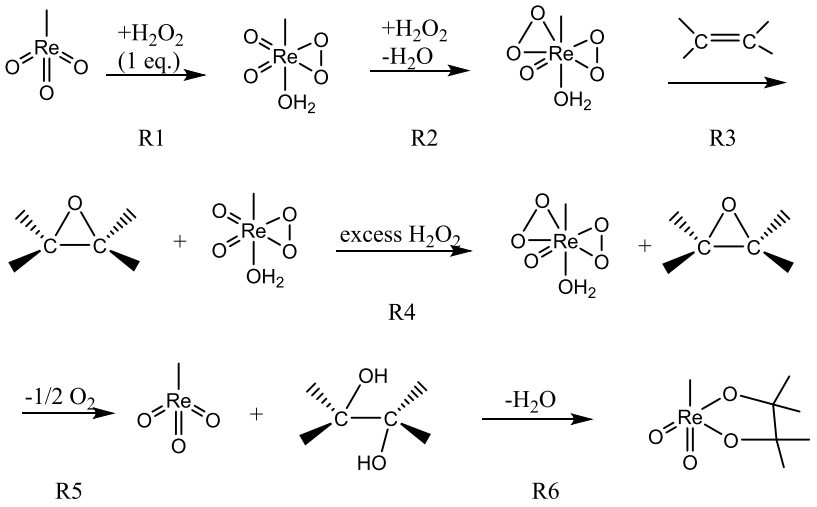
Scheme 4. Epoxidation Mechanism



2.1.1. Flow Epoxidation. To address these limitations, a flow process was studied for possible application and increasing scale-up possibilities for the reaction. An initial assessment of a plug flow reactor (PFR) gave low conversion due to the formation of a biphasic layer and insufficient mixing. While the continuous stirred tank reactor (CSTR) gave similar results to those in the batch reaction, the heat dissipation capacity was not ideal.

To understand the scalability of this reaction, we tried to establish a kinetic model based on the literature mechanism.[11] However, this task was not trivial, as quantification of the reaction product and intermediates proved challenging. Neither NMR nor infrared (IR) was suitable due to the high noise/signal ratio, while GC was abandoned due to epoxide product decomposition during analysis. Finally, we constructed a model (Scheme 4) generated from a multiportion feed experiment in an RC1. The confidence intervals in this model were not in the expected range, but the model was consistent with the empirical data generated in the lab. The empirical model was sufficient for us to model the mixing in scale-up equipment.

The preliminary assessment suggested that better mixing and a longer residence time were beneficial for the reaction conversion and the higher reaction temperature was detrimental. Low conversions were observed with PFR due to poor mixing, but the use of a static mixer (helix-type) helped the conversion only to an extent. Increasing the static mixer length from 10 to 170 cm while keeping the residence time at 9 min failed to improve the conversion further, and the residence time became the critical factor for the further conversion of the reaction.

For the PFR + static mixer system, a high flow rate (~0.106 m/s) was required to achieve the desired mixing. When the system was scaled down (using 1.7 mm OD helical type in a DN3 (0.5 mm wall thickness) tubing), 60 min residence time was needed for full conversion, which translated into an extremely long PFR for scale-up purposes.

While neither PFR nor CSTR gave satisfactory results, a combination of the PFR + CSTR system seemed to provide a better solution. It was envisioned that the PFR coil could be used for managing most of the reactive heat at the initial stage of the reaction as it was more efficient for heat exchange, and the CSTR could be used to drive the reaction to completion since it provided better mixing and a longer residence time. The combination of PFR + CSTR was tested, providing comparable results to the laboratory batch process. In total, 80−85% conversion of the methylcyclopentene and a low assay yield of 80% were consistently obtained with the use of 0.95 equiv of H_2O_2.

2.1.2. Step 1—Quench and Work-up. In our initial hypothesis, the diol impurity (**8**) was formed due to excess H_2O_2 reacting with MTO, which then reacts further with the epoxide. Additional studies suggested that the diol was prone to form under acidic conditions, and in the reaction, the pH became acidic following quenching with sodium bisulfite. Although $NaHSO_3$ is slightly basic, the reaction between $NaHSO_3$ and H_2O_2 resulted in an overall reduction in pH. A typical pH after quenching was measured at 4−5 if 1.2 equiv of H_2O_2 was used. This resulted in up to 50% hydrolysis of the desired product at this pH. When 2.0 equiv of H_2O_2 was used, the pH was further lowered to 2−3 and 100% product was completely hydrolyzed. Switching the quench from $NaHSO_3$ to Na_2SO_3 solved this problem nicely, as we observed a neutral pH (6−7), which greatly minimized the hydrolysis, and less than 8% diol was formed when 1.5 equiv of H_2O_2 was used under these conditions.

The impact of this change is significant. First, excess H_2O_2 can be used instead of substoichiometric amounts, which maximizes the utilization of methylcyclopentene and improves the in situ yield to more than 90%. Second, it also allowed us to reduce the quantity of the MTO catalyst, one of the major cost contributors for the new route. It was found that the catalyst could be reduced to as low as 0.0016 equiv if 1.5 equiv of H_2O_2 was used and the residence time was increased to 80 min (Table 1).

For step 1 quenching, a continuous process using a PFR was selected for efficient heat removal. While perfluoro alkoxy resins like Teflon have a reduced heat-transfer capacity compared to metals, they can allow efficient heat release at localized points while minimizing cost. Therefore, a Teflon coil (4 mm ID) was used and packed with ~1.5 mm glass beads as a static mixer. The residence time was set at 3−4 min, and no temperature increase was observed in the receiving tank during quenching, suggesting adequate heat removal. An assay yield of 88.2% with 4.6% diol impurity was observed post work-up.

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Table 1. Step 1 Catalyst Loading Study

no.	cat. loading (equiv)	equiv of H_2O_2 (equiv)	residence time (min)	conversion (%)	results post quenching
1	0.0064	0.95	5	100	product, 83%; SM, 0; diol, 4.98%
2	0.0032	1.2	30	88	product, 92%; SM, 0.6%; diol, 3.3%
3	0.0016	1.5	80	86.7	product, 82.02%; SM, 7.39%; diol, 4.84%

With the newly developed continuous process, only an 8 L flow reactor (2 L of PFR + 6 L of CSTR) and 1 day were needed for a 100 kg scale production. In comparison, the batch process on the same scale required 10 batches and at least 5 days to deliver. In addition, the continuous work-up process (e.g., quenching, extraction) helped to improve productivity effectively by further reducing the cycle time by about 2−3 days.

For scale-up, we needed to balance the cost-saving from catalyst usage along with the throughput of the process since the minimal catalyst loading (0.0016 equiv) required a longer residence time. In addition, considerable amounts of heat needed to be removed at the lowest catalyst loading using 1.5 equiv of H_2O_2. The decision was ultimately made to choose 0.0032 equiv of MTO and 1.2 equiv of H_2O_2 for the scale-up, which allowed us to manufacture 82 kg per day.

The flow mode configuration is shown in Figure 2. Reaction PFR and a cascading three-stage CSTR were used for step 1, while a combination of a PFR followed by a CSTR was used for quenching. The quenched product was continuously transferred to a series of rotating disk columns (RDC), where the product was phase-separated in the first column followed by a continuous washing of the organic phase with a 14% Na_2SO_3 aqueous solution in the second column. The organic phase after column 2 was collected and directly used in step 2. To our satisfaction, during the scale-up run, there was no starting material (SM) residue and the assay yield was 91.8%, while the diol impurity was controlled to 4.7%.

2.2. Step 2—Epoxide Opening and Chiral Resolution.

Direct aminolysis of the epoxide **4** with ammonia (7 N in methanol) was attempted, as it gave racemic **2** directly without debenzylation. The reaction worked under elevated pressures and temperatures using purified epoxide. However, the intrinsic safety hazard rendered by this approach was deemed unsuitable for scale-up under batch conditions. Flow conditions were considered, but very slow kinetics for the transformation was observed. Thus we focused our effort on epoxide opening using benzylamine (Scheme 5).

2.2.1. Epoxide Opening Reaction Design. A sealed autoclave was initially used to carry out the epoxide opening

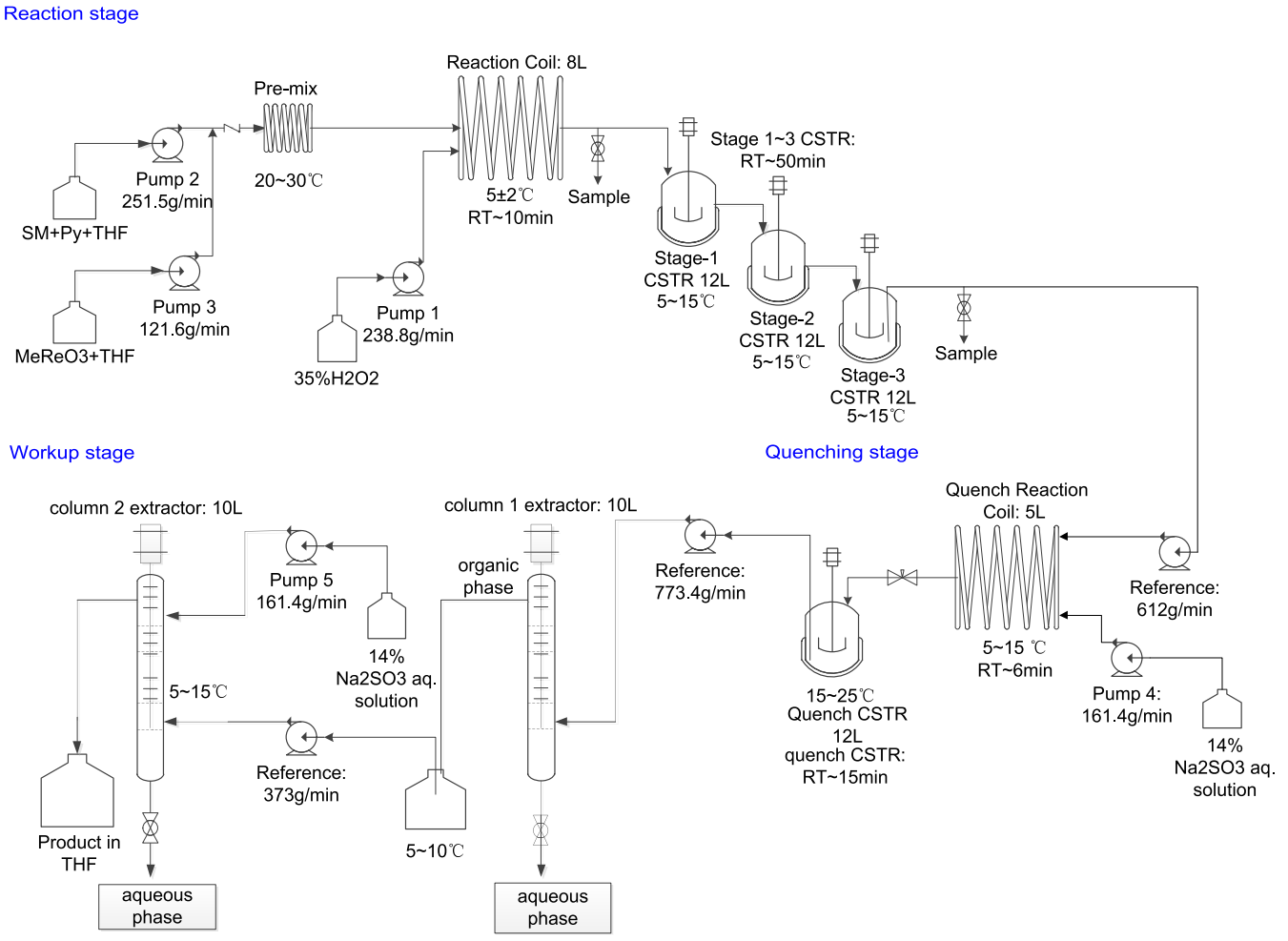

Figure 2. Step 1 scale-up flow process configuration.

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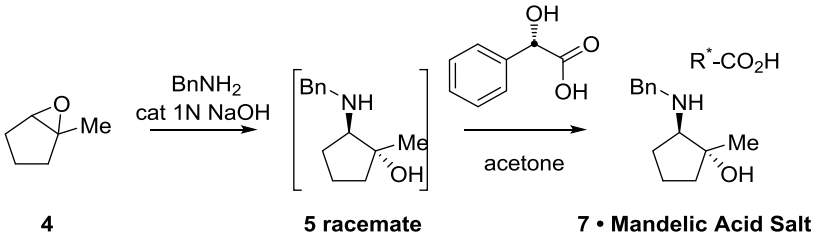
Scheme 5. Epoxide Opening with Benzylamine and Chiral Resolution



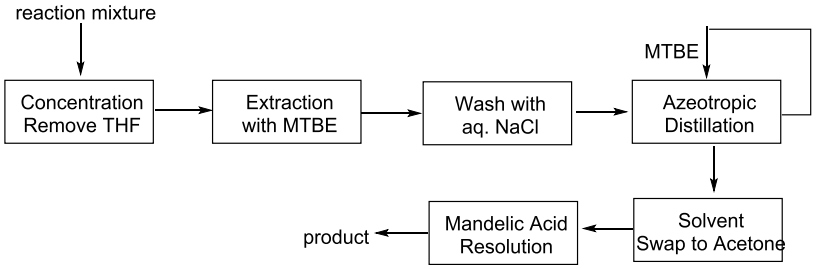


Figure 3. Step 2 work-up unit of operations in the batch process.

reaction and resulted in complete conversion after 18 h at 100 °C. Excess benzylamine was needed to reach reaction completion; however, a competition involving epoxide hydrolysis and polymerization side reactions was significant. In addition, the unreacted benzylamine and formed impurities proved to be a challenge for removal, requiring chromatographic purification of the intermediate prior to the chiral resolution.

A continuous flow process was evaluated and showed promising results.[12] It was found that a solvent of THF/water (4:2 vol) could provide a homogeneous mixture that was suitable for PFR. The reaction mixture was stable up to 24 h in the presence of dilute NaOH; therefore, a single feed stream was suitable. Without the need to consider mixing, the impact of the reaction temperature, pressure, and residence time on conversion/regioselectivity was evaluated. Using a Propel segmented reactor, it was found that the best conversion and selectivity can be achieved at 210−220 °C under 3.8−4.5 MPa with 1 h residence time.

For scale-up, the conditions generated in the lab allowed an easy adaptation on the scale. The reaction temperature range was investigated from 180 to 220 °C, and the best conditions identified were about 200 °C. At lower temperatures (180 °C), higher levels of unreacted start material (more than 5%) were observed, while at higher temperatures (220 °C), the impurity level increased and led to lower in situ yields. The optimum residence time was 60−90 min since lower conversion was obtained at 30 min residence time. With the easy scale-up of the PFR conditions for the step 2 reaction, we turned our focus to the continuous work-up design.

2.2.2. Step 2—Continuous Work-up Design. In the batch process, multiple units of operations were required before chiral resolution (Figure 3).

The extraction/wash/distillation operations relied on a long residence time and high energy consumption, so our initial effort was to simplify the work-up process. A short sequence of extraction, washing, and chiral resolution was ideal. Six different solvents (tetrahydrofuran (THF), acetone, 2-methyltetrahydrofuran (2-MeTHF), isopropylacetate (IPAc), *tert*-butylmethylether (MTBE), and dichloromethane (DCM)) were first screened for the extraction. The THF and acetone were excluded for further investigation based on the solubility of the product in these two solvents, and DCM was not considered due to the insolubility of L-mandelic acid in DCM. Among the other three solvents, when the extract after brine wash was used directly for chiral resolution, no solids were observed in 2-MeTHF and only benzylamine salt was isolated from MTBE and IPAc. Suspecting that residual water in the crude solutions may have been the cause, Karl−Fischer (KF) analysis was performed, which indicated 5.2−5.8% water in these solutions. By distillation of these solutions to NMT 1% H_2O, the desired product was obtained, although benzylamine salt was present in the isolated material.

These experiments indicate that azeotropic distillation is required to control KF before the chiral resolution. Using a conventional batch process, this would require five iterations of distillation to achieve the desired KF and posed a time and throughput challenge to our manufacturing operations on a larger scale. To this end, continuous extraction, continuous washing, followed by a continuous concentration process was developed. RDCs like the ones used in the continuous work-up of step 1 were used to develop the continuous extraction and washing process.

THF and MTBE (3 vol) were evaluated as the solvents for continuous extraction. Both showed <0.1% product loss in the aqueous phase and good recovery of the product in the organic phase. However, there was no differentiation between the product and the residual $BnNH_2$, which was also completely extracted to the organic phase. The KF of the organic phase with MTBE (5.6%) as the solvent was slightly lower than that with THF (6.5%) as the solvent.

Since the KF of the organic phase was to be controlled to NMT 1%, continuous concentration using thin-film evaporation (TFE) was evaluated. In our initial conditions using a flow rate of 33 g/min and a distillation temperature of 40−41 °C, it was found that 5 iterations of distillation were also needed to control the KF to NMT 1% for both THF and MTBE. Further studies showed that when the flow rate was reduced to 27.8 g/min and the temperature increased to 46−47 °C, the dehydration efficiency was greatly improved and required only two iterations of distillation. MTBE was ultimately selected as the solvent for continuous extraction

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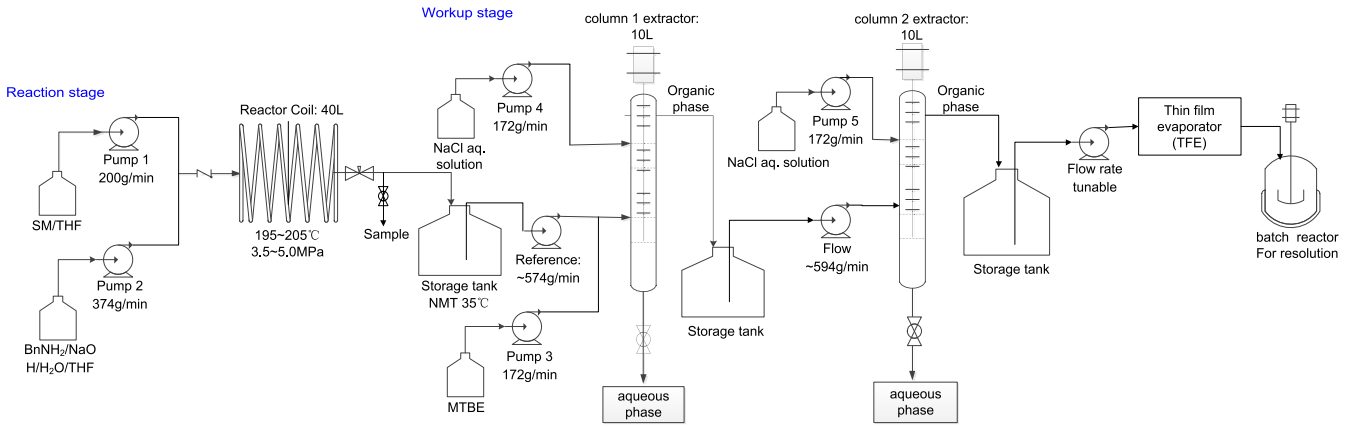

Figure 4. Step 2 reaction and work-up flow process configuration.

and distillation as it contained lower water in the organic phase.

The flow mode configuration for step 2 reaction and work-up is shown in Figure 4. A PFR (coil 1) was used for the reaction, while extraction column 1 was used for continuous extraction with MTBE and washing with a NaCl aqueous solution. Extraction column 2 was used for continuous washing with the NaCl aqueous solution and phase separation. TFE was used for continuous distillation, and the solution after TFE was directly used for chiral resolution.

2.2.3. Step 2—Chiral Resolution. In the early phase of the project, (*S*)-2-(3,5-dinitrobenzamido)-2-phenylacetic acid (DNBPG) was used for the chiral resolution. However, this resolving agent was difficult to obtain on the scale, and a reslurry was required to upgrade the chiral purity to acceptable specifications. A screening study was conducted to find additional resolution reagents, and four chiral acids were identified that gave acceptable er: (1*S*,3*R*)-camphoric acid, *S*-mandelic acid, *R*-Boc-TIC-OH, and *Z*-L-phenylglycine. Based on the commercial availability and cost, *S*-mandelic acid was selected for further optimization. On the laboratory scale, the best results were obtained with 20 vol of acetone and 0.52 equiv of mandelic acid.

Although the mandelic acid resolution process gave the product with high chiral and chemical purity, it was found that the loss of the product in the mother liquor was significant (amount to 18−22%). The typical composition of the mixture after work-up was complicated with ∼74% of racemic **5**, 11% of regioisomer **6**, 6% of benzylamine, and 8% of other impurities. All of these components can form salts with the resolution reagent, which significantly complicated our understanding of the crystallization process. Initial attempts to isolate racemic **5**, either as a free base or a salt, did not provide any benefit, as it added an additional unit of operation and the recovery was poor.

Additional optimization on the chiral resolution conditions was attempted, starting with the use of *R*-mandelic acid to remove the undesired enantiomer before adding *S*-mandelic acid for resolution. While more than 50% of the undesired isomer was successfully removed using *R*-mandelic acid, the resolution of the enriched material did not improve and a substantial loss in the mother liquor was still observed. We next focused on screening the resolution solvent, and it was observed that no solvents were effective in minimizing the mother liquor loss. In many cases, our attempts resulted in the coprecipitation of $BnNH_2$ mandelic acid salt. We then turned our attention to the amount of the resolving agent employed. It was found that a slight increase of mandelic acid to 0.6 equiv helped slightly in the recovery of our product and that increasing the equivalents further (0.7) was not beneficial and could be due to an intrinsic equilibrium among the many components in the mixture. Although the acetone conditions were selected for scale-up, the material loss was deemed unacceptable and the resolution needs to be redesigned to improve the yield of this step.

On a larger scale, we envisioned running the chiral resolution in a CSTR, instead of developing a more technologically complicated continuous crystallization process. The product/acetone solution and mandelic acid/acetone solution were mixed in a CSTR, and the resulting slurry overflowed into an agitated filter dryer (AFD) to complete the filtration and drying. Two parallel AFDs were used in production to maintain continuity of the process by alternating between the vessels.

In summary, a more efficient continuous work-up process was developed for step 2 that included a continuous extraction column for extraction and washing, and thin-film evaporation (TFE) was used in the continuous concentration to reach the desired water content. The continuous work-up process provided a product with a similar yield (15−22%) and ee (99−100%), as well as levels of the $BnNH_2$ residue and product loss compared to the batch process.

Comparing the processes for step 2 (Table 2), it should be noted that approximately 3−4 fewer unit operations are used in the flow process compared to the batch mode, which has a direct impact on the cost of operation. For an 80 kg scale campaign, the cycle time was reduced from 8 to 6 days and benefitted from a significantly reduced manufacturing footprint as well.

Table 2. Comparison of Equipment Use and Cycle Time for Step 2

process	no. of unit operations	equipment	cycle time (days)
batch process	8−9 concentrations; 5−6 extractions; 1 washing; 1 chiral resolution	3000 L glass-lined reactor × 2; 1000 L glass-lined reactor × 1	∼8
flow process	5−6 concentrations; 2−3 extractions; 1 washing; 1 chiral resolution	3000 L glass-lined reactor × 1; continuous extraction column × 2; TFE × 1	∼6

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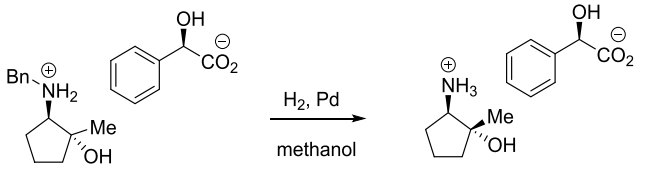
2.3. Step 3—Trickle Bed Hydrogenation. To prepare the desired amino alcohol 2, 7·mandelic acid salt post resolution is hydrogenated using a heterogeneous palladium catalyst (Scheme 6). Under batch conditions, the debenzylation of intermediate 7 reaches complete conversion in 6 h using 5% Pd/$(OH)_2$/C as the catalyst and a loading of 1.5% at 40−50 °C under 4−6 bar hydrogen pressure.

Scheme 6. Hydrogenolysis of 7·Mandelic Acid Salt



7 • Mandelic Acid Salt 2 • Mandelic Acid Salt

Trickle bed hydrogenation has been used in other industries for decades[13,14] and in recent years has been gradually adopted by the pharmaceutical industry.[15−18] Considering the intrinsic process safety hazard associated with the use of H_2 on a large scale and the flammability of Pd$(OH)_2$/C, it is logical to extend continuous processing to the hydrogenation step.

A few Evonic larger particle size catalysts were evaluated following an internal evaluation, and a type of impregnated Pd/C catalyst with 625−675 μm support size was selected because of lower pressure drops across the reactor. The larger particle catalyst was tested with batch processing conditions to understand the reaction rate. >99% conversion was achieved after 16 h at 40−50 °C. When the reaction temperature was increased to 58−62 °C, the reaction went to completion in 10 h, which suggested faster kinetics at higher reaction temperatures. The trickle bed hydrogenation conditions were evaluated with the equipment setup shown in Figure 5. The starting material solution was prepared by dissolving 7·mandelic salt in 10 vol of MeOH.

The flow process was tested initially at 85 °C (entry 1, Table 3). The pressure was set at 0.5−0.6 MPa (5−6 bar). The flow rate of the starting material solution was set at 2.5 g/min. The H_2 flow rate was set at 0.1−0.2 L/min, and the estimated residence time was ∼10 min. At full conversion, a crude purity of 98.67% and ee of 99.96% were observed. Under these conditions, the residence time could be further reduced to 5 min by increasing the flow rate, producing similar conversions (Table 3, entry 2).

The flow rate of the starting material can be further increased for throughput improvement (Table 3, entries 3−5). When the flow rate was increased from 2.5 to 12.5 g/min, the conversion slightly decreased from >99.9 to 99.4%. When the flow rate was maintained at 12.5 g/min, and the pressure was increased from 0.5 MPa (5 bar) to 0.7 MPa (7 bar), the

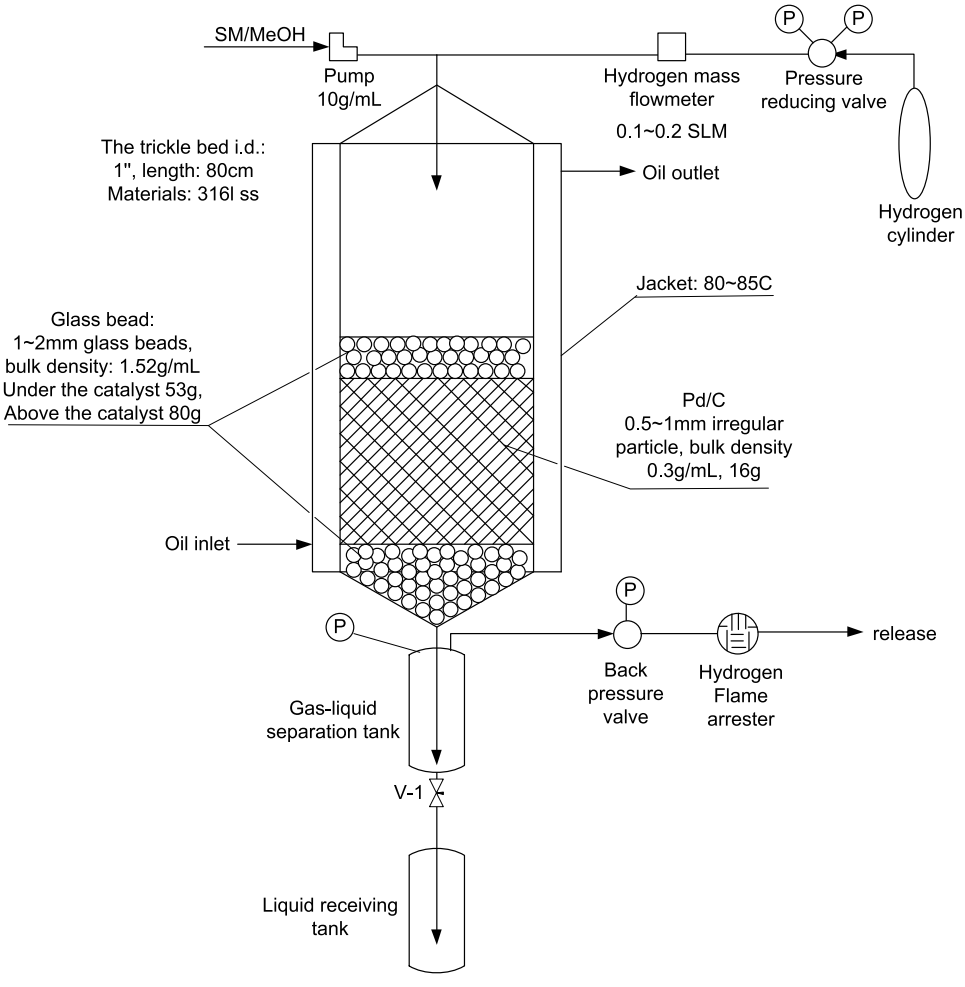


Figure 5. Diagram for step 3 trickle bed hydrogenation.

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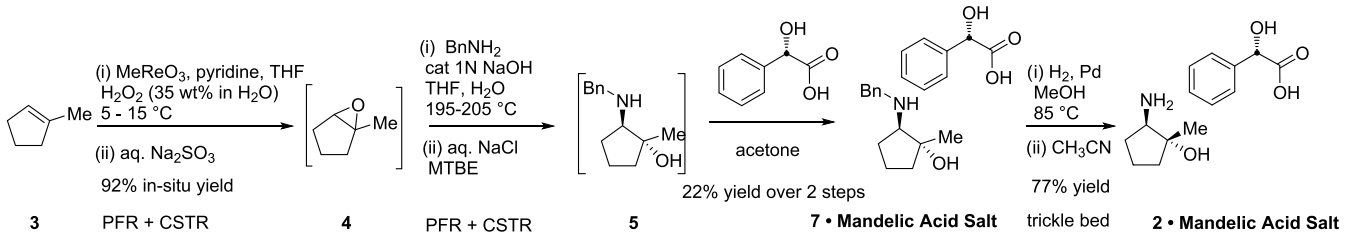
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 3. Trickle Bed Hydrogenation Evaluation

no.	T (°C)	P (MPa)	residence time (min)	SM flow rate (g/min)	H_2 flow rate (L/min)	equiv ratio H_2/ 7	IPC
1	85−88	0.5	10	2.5	0.1−0.2	6.4−12.8	conversion, 100%
2	85−88	0.5	5	5	0.1−0.2	3.2−6.4	conversion, >99.9%
3	85−88	0.5	3.3	7.5	0.1−0.2	2.2−4.4	conversion, 99.9%
4	85−88	0.5	2.5	10	0.1−0.2	1.6−3.2	conversion, 99.8%
5	85−88	0.5	2	12.5	0.2−0.3	2.6−3.6	conversion, 99.4%
6	85−88	0.7	2	12.5	0.2−0.3	3.6−5	conversion, 99.5%
7	65−68	0.5	10	2.5	0.1−0.2	6.4−12.8	conversion, 99.9%

Scheme 7. Improved Continuous Process to 2·Mandelic Acid Salt



conversion returned back to >99.9%. It was also found that the reaction temperature could be reduced from 85−88 °C to 65−68 °C if the flow rate of the starting material was kept at 2.5 g/min; the reaction still gave 99.9% conversion (Table 3, entry 7).

Finally, a mixture with er 80:20 was tested to understand the process tolerance of the enantiomeric impurity. Again, the reaction reached 99.8% conversion within 10 min. Post isolation, UPLC analysis indicated a purity of 96.89% and an improvement in ee (99.2%). This suggested that the excess undesired enantiomer can be purged further in the final isolation due to the presence of mandelic acid, and this provides an opportunity to boost the yield in step 2.

The crystallization of **2** proved straightforward. After the solvent was switched from MeOH to acetonitrile (7−9 vol), the product crystallized upon cooling to 20−30 °C. The MeOH residue was controlled to below 1%, minimizing product loss in the ML. A demonstration batch at a 4.8 kg scale was conducted to have a proof of concept for the trickle bed process. IPC showed the conversion to be >99.9%. After crystallization and isolation, the material was of excellent ee (100%) and good purity (98.7%) in 73.1% isolated yield.

While the flow hydrogenation process only provided a slight benefit in yield compared to the batch process, it delivered the major advantage of a safer process. For the flow process, H_2 is released in smaller amounts continuously and the diminished size of the reactor (1−30 L) greatly minimized the risk brought by handling H_2. The cost was another important factor. As the reactor and conditions remain the same, the cost is solely dependent on the catalyst cost. For one-time use, the catalyst cost for the flow process was 3× higher than the batch process at a 50−100 kg scale. However, our development work has demonstrated that no catalyst deactivation was observed, even after multiple uses. In the longer term, the cost of the catalyst is expected to be significantly lower with an increase in volume and reuse of the catalyst for multiple campaigns.

3. CONCLUSIONS

In summary, an end-to-end continuous process was developed for the manufacturing of compound **2** (Scheme 7). In step 1, a combined PFR + CSTR system was designed to handle the high exothermicity of the reaction and achieved desired conversions. Switching the quench from $NaHSO_3$ to Na_2SO_3 was a key finding that not only minimized the hydrolysis but also allowed the use of excess H_2O_2 to drive the reaction to completion and reduce the catalyst loading. In step 2, a continuous reaction and work-up were designed and demonstrated on the scale. In step 3, a continuous trickle bed hydrogenation was developed for debenzylation, and this process is expected to accrue the cost-saving benefit in the future.

Table 4 summarizes the cycle time for each step and the number of batches needed to deliver 100 kg of the product.

Table 4. Cycle Time Comparison between the Batch Process and the Flow Process

	cycle time			
process	step 1	step 2	step 3	total
batch process	30 batches, 16 days	4 batches, 23 days	1 batch, 8 days	47 days
flow process	1 batch, 4 days	1 batch, 16 days	1 batch, 7 days	27 days

Compared to the batch process, the flow process is capable of delivering the same amount of material in nearly half the time. The average cost-saving per kg of the final product for the continuous process is about 30%. The new process also demonstrates a significant advantage due to the reduced utilization of manufacturing space and equipment while simultaneously reducing the utilities needed to deliver the same amount of material with comparable quality.

4. EXPERIMENTAL SECTION

All reactions were performed under a nitrogen atmosphere unless otherwise stated. All reagents purchased from vendors were used as received.

In step 1, ^{1}H NMR was used to track the ratio of SM/product during the reaction and determine the in situ reaction yield. NMR data was collected using a Bruker AV NEO 400MHz spectrometer with probe Z163739_0076 (PI HR-400-S1-BBF/H/D-5.0-Z SP).

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

In step 2, the reaction and starting material consumption was monitored by GC. GC conditions: Restek RTX-5 Amine; 30 m × 0.32 mm × 1.0 μm; P/N:12354; 250 °C; flow 2.0 mL/min; 1 μL injection volume; carrier gas, helium; detector gas, H_2/Air/N_2 = 40:400:30 (mL/min); gradient 40 °C for 2 min; ramp at 15 °C/min to 260 °C, hold for 5 min; diluent, methanol. The received mixture and final product were analyzed by UPLC. UPLC conditions: Waters HSS T3, 2.1 × 100 mm; 1.8 μm; 25 °C; flow 0.4 mL/min; λ = 210 nm; 1 μL injection volume; A, 0.1% MSA in water; B, acetonitrile; gradient 5% B to 95% B in 7.5 min, re-equilibrate to 5% B in 0.1 min, run time 10 min; diluent, 10:90 acetonitrile/water. The enantiomeric purity of step 2 product was monitored by chiral SFC. Chiral SFC conditions: Chiralpak IC; 4.6 × 250 mm^2; 5.0 μm; 40 °C; flow 2.0 mL/min; λ = 210 nm; 5 μL injection volume; A, CO_2; B, 0.1% MSA and 0.1% IPAm in 50 ACN/50 MeOH (v/v); gradient 20% B held in 0.5 min, ramp to 40% B in 8.5 min, re-equilibrate to 20% B in 0.5 min, run time 15 min; diluent, methanol.

In step 3, the reaction was monitored by reverse-phase UPLC. UPLC conditions: Waters HSS T3; 2.1 × 100 mm^2; 1.8 μm; 25 °C; flow 0.4 mL/min; λ = 210 nm; 1 μL injection volume; A, 0.1% MSA in water; B, acetonitrile; gradient 5% B to 95% B in 7.5 min, re-equilibrate to 5% B in 0.1 min, run time 10 min; diluent, 10:90 acetonitrile/water. The chiral purity of step 3 product was monitored by reverse-phase UPLC after Marfey's derivatization. Derivatization method: dissolve 4.40 mg of Marfey's reagent to 2 mL of ACN; 100 μL of sample solution was placed in a total recovery HPLC vial along with 50 μL of 1:1 water/ACN, 150 μL of Marfey's reagent solution, and 40 μL of 1 M $NaHCO_3$. The solutions were heated at 40 °C for 1 h and then quenched with 40 μL of 1 M HCl and 120 μL of more ACN to help solubilize any solids that precipitated. UPLC conditions: BEH C18; 2.1 × 50 mm; 1.7 μm; 40 °C; flow 0.6 mL/min; λ = 210 nm; 1 μL injection volume; A, 0.1% trifluoroacetic acid in water; B, acetonitrile; gradient 15% B to 45% B in 7.5 min, re-equilibrate to 15% B in 0.5 min, run time 10 min; diluent, 1:1 acetonitrile/water.

4.1. Preparation of Epoxide (4) by the Continuous Process.

1. Prepare the S.M. solution: THF (142.6 kg, 1 V), pyridine (4.7 kg, 59.4 mol, 0.03 equiv), and 1-methylcyclopent-1-ene (166.7 kg, 96 w/w%, 1947.9 mol, 1.0 equiv) were charged into a glass-lined reactor at 20−30 °C and stirred until all materials dissolved. Then, the mixture was discharged into the S.M. solution tank.
2. Prepare the catalyst ($MeReO_3$) solution: THF (142.6 kg, 1 V) was charged into a glass-lined reactor at 20−30 °C and stirred. Methyltrioxorhenium (1.6 kg, 6.4 mol, 0.00328 equiv) was charged into the reactor at 20−30 °C and stirred until all materials dissolved. Then, the mixture was discharged into the catalyst tank.
3. Prepare the 14% sodium sulfite solution: Purified water (480.7 kg) and sodium sulfite (80.1 kg, 635.7 mol, 0.33 equiv) were charged into a glass-lined reactor and stirred at 20−30 °C until all materials dissolved. Then, the mixture was discharged into two Na_2SO_3 aq. tanks.
4. Cooling: The reaction coil jacket temperature was cooled to 5 ± 2 °C and the reaction CSTRs to 5−15 °C. The quench coil jacket temperature was cooled to 5−15 °C and the quench CSTR to 15−25 °C. The continuous extraction column 1 was cooled to 15−25 °C. The continuous extraction column 2 was cooled to 5−15 °C.
5. Run the flow process: Pump 1 was connected with hydrogen peroxide (284.1 kg in total, 35 w/w%, 2924.6 mol, 1.5 equiv) tank, pump 2 was connected with S.M. solution tank of Ins.1, pump 3 was connected with the catalyst solution of Ins. 2, and pumps 4 and 5 were connected with sodium sulfite solution tanks of Ins. 3. The flow rates were set and tuned automated by an automated system. The flow rates and retention time of every stage can be found in Figure 2. Run pumps 1, 2, and 3 simultaneously, first. IPC samples were taken periodically at the outlet of reaction coil and reaction CSTR to track the ratio of SM/product by NMR. When the mixture in reaction CSTR (stage 3 CSTR) reached the overflow volume, the reaction mixture would be transferred into a quenching coil and then into a quenching CSTR. We started pump 4 when the transferring started. The quenched mixture from the quenching CSTR was transferred into the extraction column 1 by a second transfer pump. The organic phase in extraction column 1 overflowed into a transfer tank and then was transferred into the continuous extraction column 2 by a third transfer pump. We started pump 5 at this time. The organic phase in the extraction column 2 overflowed into the product tank. When all of the materials in the tanks were pumped, we connected the pumps into the THF tank to push out and exchange the reaction mixture in the coils and CSTRs. Also, when all of the organic phase was collected, we sampled from the product tank to determine the product assay and the product solution will be used in the next step without further purification. In total, 405 kg of colorless solution was obtained. The assay was 39% analyzed by ^1H NMR.

4.2. Preparation of 7·Mandelic Acid Salt by the Continuous Process.

1. Prepare the benzylamine/catalyst solution: Purified water (316 kg, 2 V), sodium hydroxide (0.7 kg, 17.5 mol, 0.01 equiv), benzylamine (173.1 kg, 1615.5 mol, 1.0 equiv), and THF (281 kg, 2 V) were charged into a glass-lined reactor at 20−30 °C and stirred until all materials dissolved. Then, the mixture was discharged into the $BnNH_2$ solution tank.
2. Prepare the 20% sodium chloride solution: Purified water (621.2 kg) and sodium chloride (161.2 kg) were charged into a glass-lined reactor and stirred at 20−30 °C until all materials dissolved. Then, the mixture was discharged into two NaCl aq. tanks.
3. Heating: We pumped THF into the coil reactor and pressurize the coil to 3.5−5.0 MPa by a backpressure valve. We heated the coil reactor to 195−205 °C. Meanwhile, we maintained the pressure at 3.5−5.0 MPa.
4. Run the flow process: Pump 1 was connected with the compound **4** solution (405 kg in total, 39 w/w%, 1609.9 mol, 1.0 equiv) tank (step 1 product solution from Section 4.1), pump 2 was connected with the $BnNH_2$ solution tank of Ins.1, pump 3 was connected with the MTBE tank, and pumps 4 and 5 were connected with sodium chloride solution tanks of Ins. 2. The flow rates were set and tuned by an automated system. The flow rates and retention time of every stage can be found in

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Figure 4. First, pumps 1 and 2 were run simultaneously. Sampled in a certain interval at the outlet of reaction coil to track the residue of SM and product purity by GC and UPLC. The reaction mixture flowed into the first storage tank then was transferred into the extraction column 1 by a transfer pump. We started pumps 3 and 4 when the transfer pump was started to wash and extract the crude product. The organic phase in the extraction column 1 overflowed into a second storage tank and then was transferred into the continuous extraction column 2 by a second transfer pump. We started pump 5 when the second transfer pump was started. The organic phase in the extraction column 2 overflowed into the third storage tank. The organic phase in the third storage tank would be transferred continuously into the thin-film evaporator (TFE) to remove water azeotropically. When all of the materials in the tanks were pumped, we connected the pumps into the THF tank to push out the reaction mixture in the coil.

5. Resolution: When the water content in the organic phase was qualified, we concentrated and exchanged THF with acetone. The final acetone solution should be 1400−1900 L (9−12 V). The mixture was heated to 40−50 °C. (*S*)-(+)-Mandelic acid (94.3 kg, 620 mol, 0.6 equiv of the racemic product) was added portion-wise to the mixture (20−30 kg in each portion) at the interval of 10−20 min. The mixture was maintained at 40−50 °C for 2−3 h, then cooled to 10−15 °C, and stirred for 10−15 h. Then, the mixture was filtered, and the collected Mandelic acid salt of compound 7 was dried. In total, 87.7 kg of white solid was obtained. The ^{1}H NMR assay was 99.6%. The UPLC purity was 100%, and the ee was 99.2%. The yield was 15.2%.

4.3. Preparation of 2·Mandelic Acid Salt by the Batch Process. A 3000 L autoclave was charged MeOH (692.8 kg, 10 V) and 7·mandelic acid salt (87.1 kg, 243.7 mol, 1.0 equiv) and stirred for 1−2 h. Then, $Pd(OH)_2/C$ (5%, 17.4 kg, 0.2 g/g, wet basis) was added. Oxygen was exchanged with nitrogen eight times and then with hydrogen eight times. The autoclave was pressurized to 0.6 MPa, and then, the mixture was heated to 40−50 °C. The mixture was allowed to react at 40−50 °C, P = 0.4−0.6 MPa. After 6 h, the mixture was sampled for UPLC analysis to assure compound 7 transformed completely. The mixture was cooled to 20−30 °C and then filtered with a 1000 L stainless steel Nutsche filter. Methanol (278 kg, 4 V) was used to rinse the autoclave and the cake. The filtrate and rinsing liquor were combined in a 1000 L glass-lined reactor. The mixture was concentrated under vacuum and exchanged with acetonitrile to remove MeOH. The final acetonitrile solution should be 530−700 L (6−8 V). The acetonitrile solution was cooled to 10−20 °C and stirred for 3−5 h. We filtered, dried, and then collected the white solid (50.7 kg). The final yield was 76.5%. The assay by^{1}H NMR was 98.5%, and the ee was 100%.

4.4. Preparation of 2·Mandelic Acid Salt by the Continuous Process.

1. Prepare 7·mandelic acid salt solution: 4.8 kg of 7·mandelic acid salt (13.428 mol) was dissolved in 48 L of methanol (10 vol).
2. Equipment: A GLFR 1″ ID column with a Julabo chiller unit was used. The reactor is 39 in. long. Pack the column. Bottom pack, charged silica gel (20 g, 8.62 mL, 333 mmol); catalyst, charged palladium; 5% Pd/C Evonic, 600 μm (120 g, 112.8 mmol). The rough measurement is ∼1 g of catalyst/0.25″ column height. Top pack, charged silica gel (top pack) (69.5 g, 30.0 mL, 1160 mmol). The rough measurement is ∼5″ of column height.
3. Pressure test: Start N_2 flow at 1000 cc/min and allow to ramp to the pressure limit; confirm that N_2 flow stops and the N_2 valve closes after reaching the pressure limit; confirm that no leaks are present at any adjusted fitting with soap solution; monitor the system pressure for pressure drop (target <1 psi/min loss).
4. Column inertion: Confirm the backpressure valve is in manual mode and set to −5%; switch on the N_2 flow at 400 cc/min and flow gas for 1 min; confirm proper feed and column output valve positions; switch on the methanol feed at 50 cc/min; confirm that the pump is primed; confirm flow to waste jug and check for leaks; wait for 10 min to the N_2 inert system.
5. Hydrogenation: Bring the system to operating conditions under nitrogen: 725 psi (50 bar), 96 cc/min solvent flow, circulator temperature of 65 °C. Switch the gas feed to H_2; set the flow valve to the auto mode; equilibrate the system under H_2 gas and process solvent conditions for 20 min. Switch the feed to process stream flowing under operating conditions for the duration of the experiment: liquid feed, 90 mL/min; hydrogen feed, 43.65 mL/min; jacket temperature, 65 °C; system pressure, 50 bar. Run the reaction until the feed solution is consumed. Once reaction feed is complete, switch to methanol to flush the column. The product solution is combined for crystallization.
6. Crystallization: Distill the crude product solution under vacuum at 50 °C until ∼6 L. Add acetonitrile (2 × 60 L) and continue to distill to ∼45 L and make sure NMT 1.0% methanol is in the mixture. Heat the batch to 45 °C until all solids are dissolved. Cool the mixture to 20 °C over 6 h. Filter the slurry, wash the filter cake with acetonitrile, and dry the product at 40 °C for 12 h. In total, 2.624 kg of white solids was isolated. Yield, 73.1%; purity, 98.7%; chiral purity, 100%.

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

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Notes

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