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PAPER

The continuous flow Barbier reaction: an improved environmental alternative to the Grignard reaction?

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A key pharmaceutical intermediate (**1**) for production of edivoxetine·HCl was prepared in >99% ee *via* a continuous Barbier reaction, which improves the greenness of the process relative to a traditional Grignard batch process. The Barbier flow process was run optimally by Eli Lilly and Company in a series of continuous stirred tank reactors (CSTR) where residence times, solvent composition, stoichiometry, and operations temperature were optimized to produce 12 g h^{-1} crude ketone **6** with 98% ee and 88% *in situ* yield for 47 hours total flow time. Continuous salt formation and isolation of intermediate **1** from the ketone solution was demonstrated at 89% yield, >99% purity, and 22 g h^{-1} production rates using MSMPRs in series for 18 hours total flow time. Key benefits to this continuous approach include greater than 30% reduced process mass intensity and magnesium usage relative to a traditional batch process. In addition, the flow process imparts significant process safety benefits for Barbier/Grignard processes including >100× less excess magnesium to quench, >100× less diisobutylaluminum hydride to initiate, and in this system, maximum long-term scale is expected to be 50 L which replaces 4000–6000 L batch reactors.

Introduction

At the start of the 20th century organomagnesium chemistry emerged with the discovery of the Barbier and Grignard reactions.[1] Since inception, the Grignard reaction has been extensively studied; it remains one of the most powerful synthetic methodologies and has been widely used in manufacturing within the fine chemicals, agricultural and pharmaceutical industries.[2] The Grignard reaction first involves formation of the organomagnesium reagent by reaction of elemental magnesium with an alkyl or aryl halide. Once formed, the nucleophilic Grignard reagent is then reacted with an electrophile in a separate step to produce an alcohol or ketonic product. To date the Grignard reaction remains the best methodology to produce tertiary alcohols. Most commonly, a Grignard process is commercially practised in a three-vessel setup where the Grignard reagent formation, reaction and quench are segregated and run sequentially in separate vessels.[3] In principle, a Barbier reaction approach is operationally more simple than a conventional Grignard process in that the organohalide and electrophile are combined as a single stream, then added to activated magnesium. However, for this approach to be successful, the key organomagnesium intermediate must be stable at the Grignard formation temperature, which is often a limitation.

Flow technologies have recently received a significant amount of attention in organic synthesis.[4] Established advantages of continuous flow chemistry include the ability to precisely control process variables such as residence time, temperature, pressure, heat transfer, and operation at a different kinetic regime, *e.g.* continuous stirred tank reactor (CSTR) operates at end of reaction conditions. All of these elements can ultimately lead to improved yield and higher chemical purity for the target reaction. In fact, select Grignard reactions with aldehydes and ketones have been shown to be efficient in microreactors using commercially available Grignard reagents.[5] However, in many instances, for practical targets, it is still necessary to prepare the Grignard reagent prior to use due to stability, solubility, or commercial availability issues. Continuous syntheses of select Grignard reagents have been achieved *via* plug flow technology, where a solution of organic halide is continuously passed through a fixed bed or column of magnesium.[6] While there are certain advantages to the plug flow technology, the possibility exists, in certain instances, for hot spots and precipitation of magnesium complexes. CSTRs have been used efficiently for homogeneous processes and recently a CSTR process train has been used to run a heterogeneous hydrogenation process by Pfizer for preparation of an intermediate for a smoking cessation drug.[7] One of key benefits to the CSTR approach is that any solid reagent used in a stirred tank could in principle be used in the CSTR, and batch kinetic data can be directly translated to a CSTR train *via* standard methods. In addition, up to 80% reduction in manufacturing footprint is possible by adoption of the CSTR spproach. Despite these advantages, along with those resulting from steady state

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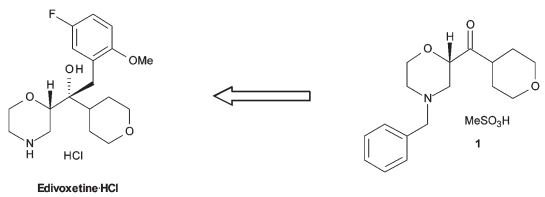
control, very few examples of Grignard reactions run in a CSTR process train exist. In addition, the Barbier reaction has been much less studied than its Grignard counterpart, and to our knowledge a continuous Barbier reaction where chirality is preserved is unprecedented. Recently we disclosed the details for the synthesis of **1**, an important intermediate for the synthesis of edivoxetine·HCl, a highly selective norepinephrine reuptake inhibitor under clinical evaluation for the treatment of depression and ADHD (Scheme 1).[8] Herein we report the development of a continuous flow synthesis of **1** including a novel application of the Barbier reaction which proceeds with preservation of chirality.

Results and discussion

Displacement of morpholine amides with strong nucleophiles is well precedented and the Grignard approach was the most attractive for the production of **1** in that chirality of the *S*-morpholino starting material could be preserved (Scheme 2).[8] However, during the history of this project, several contract manufacturing organizations had difficulty with the Grignard process, and in fact one supplier defaulted on delivery of material. The main issue encountered was a challenging initiation which operated close to the boiling point of the solvent with a potential 100 °C adiabatic heat rise for the process. In addition, there were multiple process sensitivities to racemization, such as addition order, amide feed rate, quench conditions and air/moisture contamination. All of these issues led us to develop a continuous process that operated where kinetic regime (or concentration of reagents with respect to products) and heat evolution were controlled by reactant feed rate and mean residence time at steady state.

Following completion of the most recent pilot plant campaign, proof of concept R&D efforts ensued to transform the batch process to continuous mode. Key objectives were improvements to process safety and material usage reduction, including the 4-chlorotetrahydropyran (4-Cl-THP) reagent, magnesium and both processing and cleaning solvents. The key Grignard reagent was formed continuously in the first tank of a 250 mL CSTR series (CSTR #1) by concomitant feeding of a 4-Cl-THP and THF into a suspension of activated magnesium (Fig. 1). Average hydraulic residence time (τ) in the Grignard formation tank was 1 h. The 4-Cl-THP Grignard reagent, **5**, flowed to the second vessel in the CSTR series through a screen where the output flow rate from the Grignard formation vessel was controlled by an automated pressure swing cylinder which was filled by trapped vacuum from CSTR #1 and pumped liquid forward intermittently at a frequency of about once per minute to CSTR #2 with nitrogen pressure. This transfer zone was designed to prevent clogging by suspended solids, a common problem in continuous flow applications. To keep the transfer zone clear and prevent clogging of solid magnesium on the screen in the exit tube from CSTR #1, after each bolus transfer was complete a reverse-nitrogen purge was applied.

The freshly formed Grignard reagent THF solution flows into a reaction tank (CSTR #2) concurrently with a toluene solution of morpholine amide **3** free base.[9] The hydraulic residence time was 15 min for this second CSTR and the contents of the Grignard reaction tank flowed continuously into a quench tank (CSTR #3) with a concomitant acetic acid/water feed. Initial development of the continuous approach focused on adaptation of parameters developed for the batch process where the temperatures for Grignard formation, reaction, and quench were maintained at 60, 23 and 0 °C, respectively. Unfortunately, when using these conditions, the best conversions achieved for the Grignard reaction were 80–90% and increasing residence time in



Scheme 1 Retrosynthesis of edivoxetine·HCl.

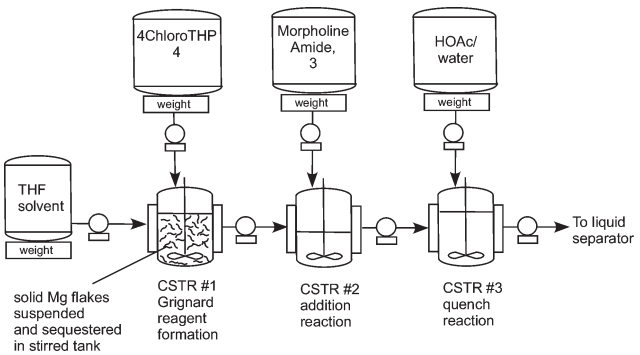
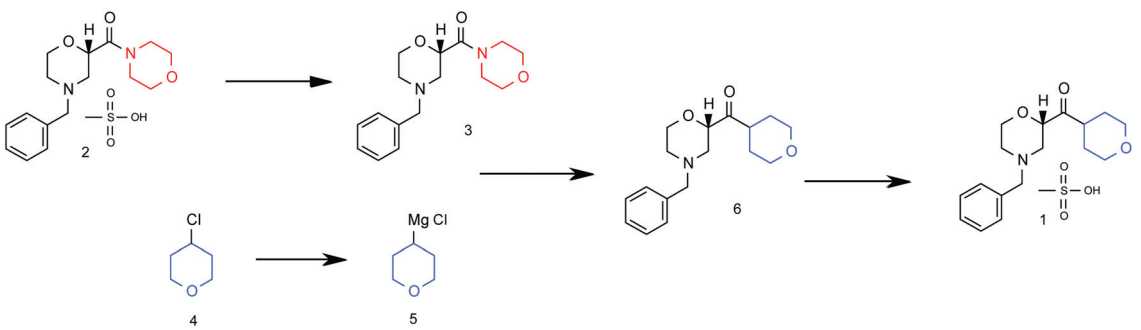


Fig. 1 Three vessel Grignard CSTR process train.

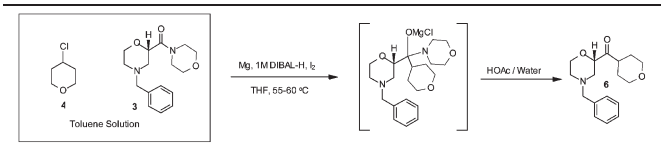


Scheme 2 Grignard synthesis of compound **1**.

the Grignard formation and reaction vessels did not improve conversion. However, a key visual observation was that the appearance within the Grignard formation vessel was changing which led to the hypothesis that the active Grignard complex, intermediate **5**, was precipitating from solution. This was confirmed by the quenching of a Grignard reaction stream sample with a surrogate aldehyde which revealed that the reaction vessel (CSTR #2) was Grignard reagent starved.[10] In order to address the solubility issue of the chloro Grignard reagent, we decided to evaluate the less frequently used Barbier approach. It was surmised that rapid reaction of the Grignard complex as formed, might alleviate the solubility issue. The key consideration for this approach to be successful is that the Grignard reaction and complex formation need to occur at the same temperature, and an essential element in this system is preservation of chirality.

To assess the Barbier chemistry, a dry toluene solution containing 1.5 equiv. of 4-Cl-THP and 1 equiv. of morpholine amide free base **3** was prepared and fed to a THF suspension of activated magnesium over 1 h at 55–60 °C.[11] After completion of the amide **3**/4-Cl-THP stream feed, HPLC analysis revealed 98% conversion with 96% ee. Most importantly, aside from residual magnesium there was no evidence of precipitated magnesium complexes or other salts. With these results in hand, we proceeded rapidly to evaluate the Barbier approach in continuous flow mode. A simple two CSTR process train was used where the Grignard reagent formation and reaction were performed in CSTR #1, then an aqueous acetic acid quench was performed in CSTR #2. A series of 7 experiments were performed over 7 days consisting of 6–8 h continuous runs (Table 1). The run length each day was based upon three volume turnovers of the CSTRs so that the results obtained are near steady state. The average hydraulic residence time for the reaction tank was set at 90 min at 55–60 °C operational temperature and 30 min at 0 °C for the acetic acid/water quench tank. This set of experiments evaluated the impact of 4-Cl-THP and acid quench stoichiometries. Overall, the best results balancing conversion and chiral purity were achieved using 1.25–1.35 equiv. 4-Cl-THP and 3 equiv. of aqueous HOAc for the quench operation. Under these conditions, it was possible to achieve >97% conversion and >95% ee consistently for preparation of crude ketone **6** (Table 1, entries 1–3). In all cases, analysis was performed on the final composite crude solution which reflected closely steady state conversion and ee levels.

Table 1 *In situ* synthesis of **1** *via* CSTR Barbier approach (HPLC area%)



Entry	Conversion (%)	ee (%)	Equiv 4-Cl THP	Equiv acid
1	97.3	96.2	1.25	3.0
2	97.7	95.8	1.25	3.0
3	98.1	95.4	1.35	3.0
4	97.3	94.2	2.0	4.0
5	98.4	91.6	1.5	5.0
6	97.5	94.9	1.5	3.5
7	97.7	92.2	1.5	3.0

Racemization sensitivity analysis

Since chiral control was a critical parameter, and sensitivities were observed in the prior art batch process,[8] we sought to thoroughly investigate racemization sensitivity under Barbier conditions. The first set of experiments involved aging the reaction mixture at 60 °C and monitoring chiral erosion (Fig. 2). The drop in ee of the reaction mixture at 60 °C was shown to be significant with a ~1.5% ee drop per hour. To further understand the system, 0.5 equiv. of both the starting amide **3** and ketone **6** were added to the pre-formed tetrahedral intermediate stirring at 60 °C. As expected, the ketone rapidly racemized upon addition to the tetrahedral intermediate, whereas the starting amide showed reasonable chiral stability with a 1% drop in ee per hour observed at 60 °C. Overall the results from the chiral stability studies indicated that operating at longer than the 90 min residence time at 60 °C in the CSTR system would result in chiral erosion. While it was known that ketone **6** with 90% ee could be upgraded to >98% ee by conversion to its MSA salt **1**, a more robust system was desired. For example, any mechanical malfunctions *e.g.* blockages, pump malfunction *etc.* could cause the reaction mixture to reside in the reaction tank for an extended period of time which would cause ee degradation, perhaps beyond recovery. However, the benefit of CSTR operation is that a small amount of material is at risk in the CSTRs at any one time relative to campaign size.

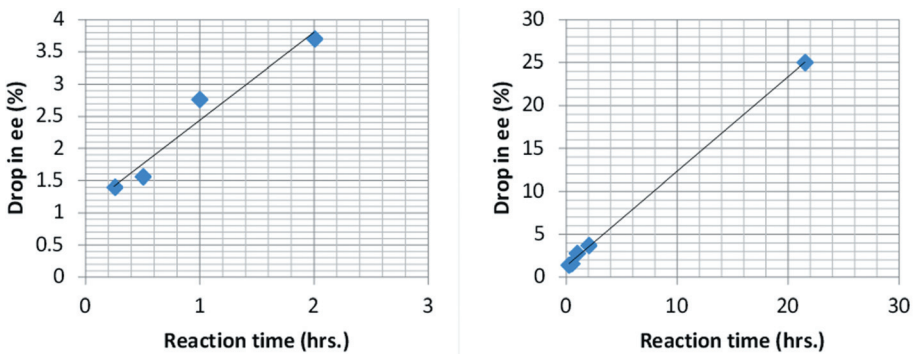


Fig. 2 (a) Drop in ee by HPLC area% as a function of reaction time at 60 °C, (b) drop in ee by HPLC area% aged to longer reaction time at 60 °C.

Reaction temperature and solvent composition optimization

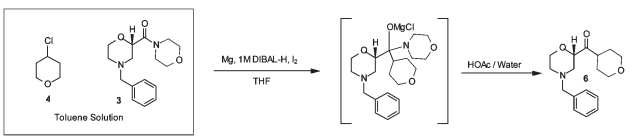
The Barbier reaction temperature was evaluated from 25 to 60 °C and ee degradation monitored under typical process conditions. A key point of failure was observed at temperatures less than 30 °C where productive conversion could not be achieved. However, it was shown that at 40 °C there was minimal chiral degradation with only a 1.3% drop in ee after 5 h. In comparison, for a 5 h age of the system at 60 °C, a ~7.0% drop in ee would be expected (Fig. 2b). In the standard lab model 5 vol of THF was typically used for the Grignard initiation relative to amide **3**, which was fed into the activated magnesium as a 25 wt% solution in toluene. Thus, the amount of THF–toluene present in all lab models at steady state was a fixed ratio at 45 : 55 of THF–toluene. It was found that increasing the ratio of THF to toluene has a significant impact on chirality and the best results were achieved increasing the THF composition to 63 vol% while maintaining the same net reaction volume. Under these conditions, the ee drop was reduced by 50% relative to the toluene rich system, during extended stirs at 40 and 60 °C. Based on these results, an operational temperature of 35–40 °C for the Barbier reaction and a steady state solvent composition of 60–65 vol% THF were established as optimal for future experiments.

Development of CSTR Barbier reaction

A CSTR series was set up evaluating the impact of temperature and solvent composition, the two primary parameters found to impact enantiomeric purity in the batch experiments. The continuous flow Barbier experiments were run on 5 consecutive days with a minimum 4–6 h of steady state observation (Table 2). A 90 min residence time was selected for CSTR #1 (τ = 60 min for CSTR #2) and the stoichiometry of 4-Cl-THP was centered at 1.35 equiv, 10% lower than the traditional batch process. The best conditions at temperature (35–40 °C) and solvent composition (63% vol THF) matched well what was achieved by the optimized batch Barbier process with crude conversion and ee both at 98% or better (Table 2, entries 4 and 5).

For the 35–40 °C experiments the conversion in CSTR #1 was 94% using a 90 min residence time. This left the option to increase the volume in the first CSTR or add a second CSTR to achieve complete conversion. For illustrative purposes only, consider the design equation for an ideal CSTR with irreversible first order reaction and assuming that volumetric flow rate does not change with reaction, where conversion of reagent to product is equal to $1 - 1/(1 + Da)$. *Da* is the dimensionless Damkohler number which is equal to reaction rate constant × mean residence time for a first order reaction ($k\tau$). If the dominating rate limiting step of the Barbier process is *pseudo* first order, at 94% conversion *Da* = 16. However, *Da* = 51 would be needed for 98% conversion, therefore τ (and thus reaction volume) would need to be increased by 3.3× to reach 98% conversion in the single CSTR. Alternatively, if a second CSTR in series operating at the same temperature with 1 h τ is used, then by the same design equation, conversion to greater than 98% will be achieved overall. No doubt, the kinetics of the Barbier Grignard are more complex, but the purpose of the illustration is to explain that, for a positive order reaction, 2 CSTRs in series will have much less combined τ to achieve 98% conversion than a single CSTR. A second CSTR was used with a 1 h residence time at 35–40 °C, which increased conversion to 98%. Since the Barbier reaction went to completion without additional metal added to CSTR #2, this is indicative that Grignard reagent formation at steady state is not rate limiting. The optimal 3 vessel 250 mL CSTR process train for the Barbier process is shown in Fig. 3.

Table 2 CSTR Barbier optimization experiments



Entry	Rxn temp. (°C)	Vol. ratio THF–toluene (%)	Conversion (%)	ee (%)
1	55–60	44	98.2	95.5
2	55–60	63	97.9	97.0
3	35–40	45	96.3	93.7
4	35–40	63	97.9	98.3
5	35–40	63	98.6	98.0
6 (Batch Barbier Model)	35–40	61	98.0	98.7

Initiating the Barbier reaction

One of the key advantages to the continuous flow approach for the Barbier or Grignard reactions is that the possibility exists in principle to activate the metal only once for an entire campaign, which the typical length in the plant is several months. In fact, the metal activation step can often be the most hazardous operation in a Grignard process, so maintaining an always active metal heel is a highly attractive option from a commercial perspective. In principle there are two primary approaches that can be utilized for metal activation which include: (1) use a large excess of magnesium, activate then run for several turnovers before cleaning the residue and starting over; (2) maintain a

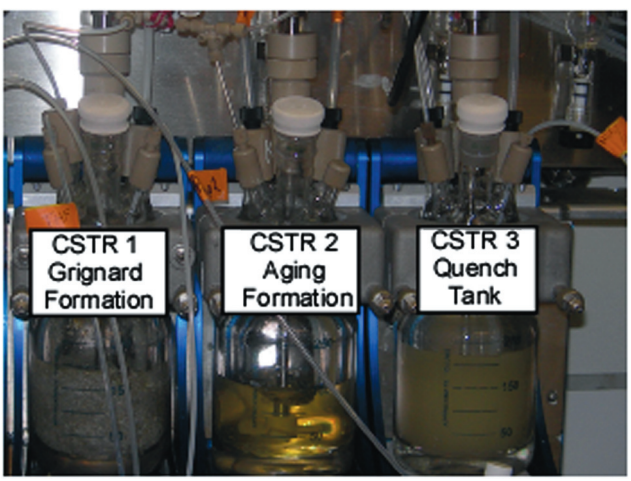


Fig. 3 3-Vessel 250 mL CSTR train for Barbier chemistry.

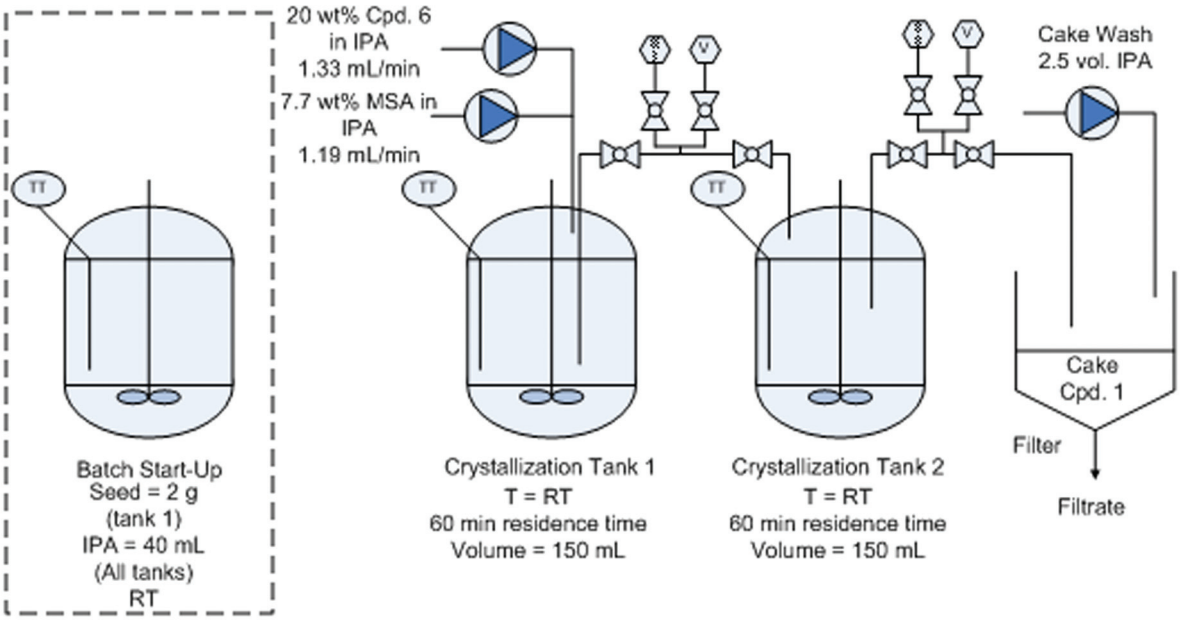


Fig. 4 Continuous crystallization of compound **1**.

pseudo steady state by a periodic re-charge of metal to the system without additional activation. Option 2 was our preferred option, but this necessitated demonstration of effective stopping and restarting the continuous system after metal recharge. To test restart capability, a batch Barbier reaction was run with 3 equiv. magnesium based on an 8 h processing day which delivered 98% crude ee and conversion. After completion of the reaction, the mixture was siphoned from the heel leaving ~5% of the reaction solution on the metal heel (enough reaction material was left so as to completely submerge the magnesium) then diluted with THF under a nitrogen blanket. The next day the mixture was heated to 55 °C, 0.1 equiv. of 4-Cl-THP was added to test if it was still active and the reaction immediately re-initiated without the addition of DIBAL-H and iodine. The temperature was then dropped to 35 °C and a second Barbier was carried out using the same magnesium supply, the material from the second run afforded crude product with 97% ee and 98% conversion.[12]

In continuous flow mode (described in the Experimental section) the same paradigm was tested with several metal recharges accomplished with only temporary mild drop in ee which quickly recovered after the first hour ($<1\tau$). In these cases ~75% of the magnesium sequestered in the CSTR was consumed by reaction before magnesium add back. Unactivated magnesium metal added during recharges is activated by Grignard reagent an existing active metal present in the reactor. In addition, magnesium is physically activated due to the mechanical collisions within the system which keep the fresh metal surface exposed, which is necessary for productive reaction. In principle, a large savings in use of metal is realized by the continuous approach relative to the batch process in that magnesium usage over time theoretically approaches 1.0 equiv. in continuous mode whereas excess magnesium is used for every run in the batch process. This translates to a potential 33% reduction in elemental magnesium usage for the continuous approach, yet there is more magnesium in the Grignard formation tank at any one point in time than batch mode until the very end of the campaign. More importantly, in a production campaign >100× less excess magnesium is used overall, therefore 100× less is disposed of as waste.

Continuous reaction, extraction, and crystallization for isolation of compound 1

Once the optimized Barbier reaction was developed, a two day proof of concept continuous reaction experiment was undertaken. On the basis of preliminary work that had been carried out the flow rates were as follows; THF (0.896 mL min^{-1}) and amide **3**/4-Cl-THP (0.771 mL min^{-1}) which produces a solvent composition at steady state consisting of 1.0 THF to 0.60 toluene. The residence time in CSTR #1 was set at 90 min at 35 °C, the residence times in CSTR #2 (reaction finishing vessel) and CSTR #3 (quench vessel) were set at 60 and 30 min, with 35 and 0 °C operation temperature, respectively. During the course of the day, the conversion and ee of the quench samples were as expected according to the lab model with 98% conversion and >98% ee remained for the whole day. At the end of the first processing day, enough reaction mixture was left in CSTR #1 to cover the magnesium heel which was then diluted with THF and left inerted overnight. The next day the reaction mixture was heated to 55 °C, 0.1 equiv of 4-Cl-THP was added to verify the mixture was still initiated and the temperature lowered to 35 °C prior to commencing the Barbier stream. The flow rates and residence times remained unchanged from the previous day. As with the day before, the conversion and % ee of the quench samples during the course of the day were consistent with expectation. Magnesium re-charge was also demonstrated on the second day, which is essential if the process is going to

be run continuously for any prolonged period of time; no changes in % conversion or % ee were observed after return to steady state conditions. The final organic composite sample showed 98.8% conversion, 98.9% ee of ketone **6** and an overall yield of 88% for both days.

The resulting organic solutions from the two days of continuous reaction experiment were washed in a two-stage continuous cross-flow extraction. Aqueous sodium carbonate was added in stage one to neutralize and the second stage received a water wash to remove residual salts prior to solvent exchange. Solvent exchange was performed to place ketone **6** in a 20 wt% IPA feed stream with precise concentration. This stream was pumped into a continuous crystallization (Fig. 4). The flow rates were designed with the aim to have equi-molar feed streams and a τ of 1 h in each mixed suspension mixed product removal (MSMPR) with a given throughput of material. The 20 wt% ketone **6** IPA solution and a 7.7 wt% methanesulfonic acid IPA solution were pumped into the first MSMPR crystallizer at 23 °C with flow rates of 1.33 and 1.19 mL min^{-1} respectively, which afforded equi-molar addition; the residence time was set for 1 h and the compound **1** slurry was continuously transferred to the second CSTR crystallizer at an average flowrate of 2.52 mL min^{-1}. The hydraulic residence time was 1 h in MSMPR #2. This was designed to allow further desupersaturation of the slurry.

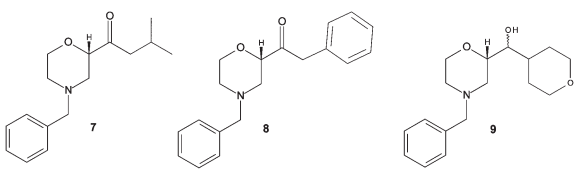
The compound **1** slurry was continuously transferred to a 1 L glass pressure filter using another 4 valve transfer zone pump at a flowrate of 2.52 mL min^{-1}. Liquid was removed from the slurry *via* filtration collecting the mother liquor in a tared filtrate receiver. Once the crystallizers were empty, 2.5 volumes of IPA was added to the first MSMPR crystallizer as a cake rinse. The rinse solution was transferred through the transfer zones as well as the second MSMPR crystallizer, and finally the rinse was transferred to the filter where the cake was rinsed and the filtrate collected in a separate tared filtrate receiver. The wet cake in the filter was transferred to a tared drying dish and dried to a constant weight in a vacuum dryer at 45 °C. The overall yield (potency corrected) over the two days was 89% and the ee of isolated compound **1** was 99.4%.

Impurities

Aside from the *R*-enantiomer, the principle impurity observed in the batch process was isobutyl ketone **7** which was observed at levels as high as 0.5% in MSA salt **1**. The source of this impurity was determined to be from diisobutylaluminum hydride that was used during the Grignard initiation.[8] In addition, minor amounts of alcohol **9** are also observed which is well rejected in the crystallization of MSA salt **1**. For the continuous Barbier chemistry, since it is only necessary to activate the metal once and the system quickly reaches steady state, only trace amounts of impurity **7** which only forms during startup transition are observed in the crude product. However, the Barbier approach does generate impurity **8**, which is observed at minor levels when the standard Grignard reaction is employed (Scheme 3). Benzyl ketone **8** is the primary impurity which results from reaction of benzyl magnesium chloride and morpholine amide **3**.

Continuous flow demo campaign

A 47 h flow campaign using 649g amide **3** was run over four days with a 4 vessel CSTR sequence which included a primary Grignard reagent formation reaction vessel (CSTR #1), reaction



Scheme 3 Barbier process impurities.

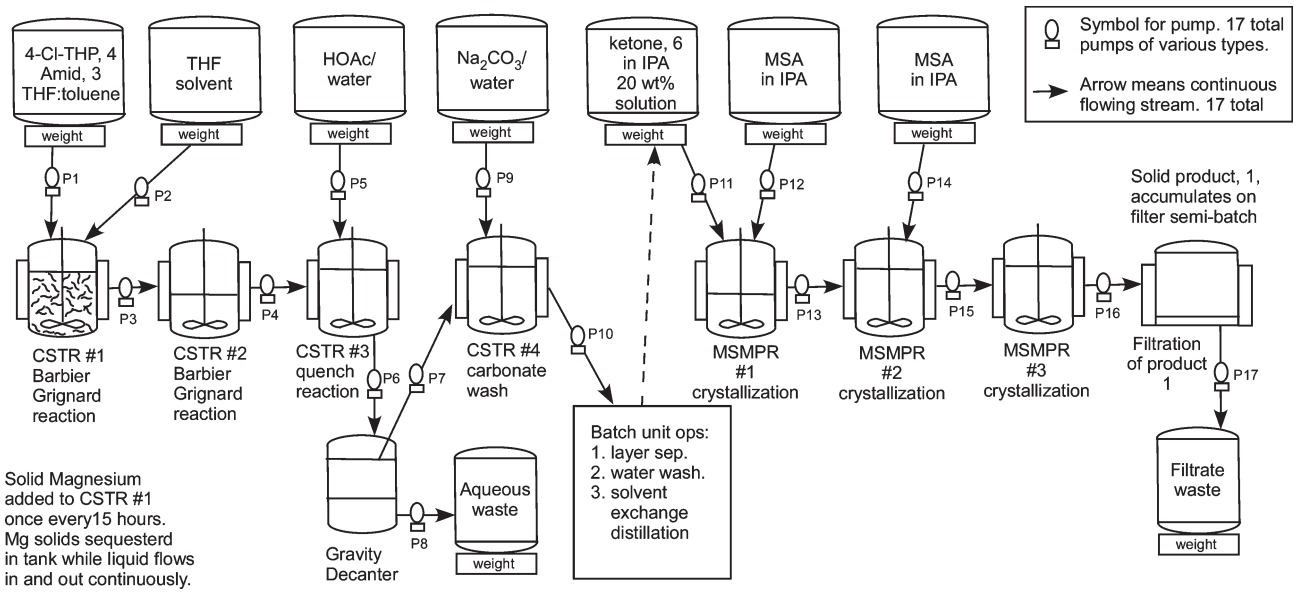


Fig. 5 Flow diagram for the whole continuous process from amide **3** to product **1**.

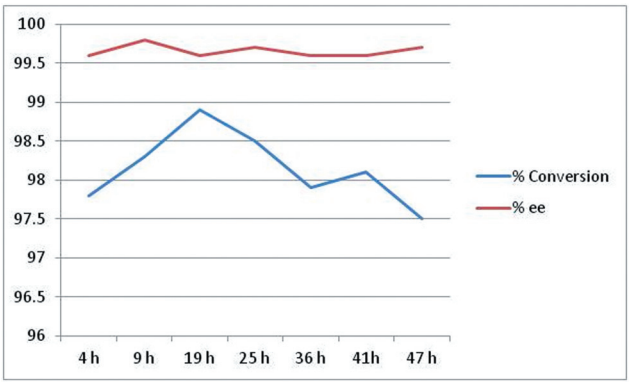
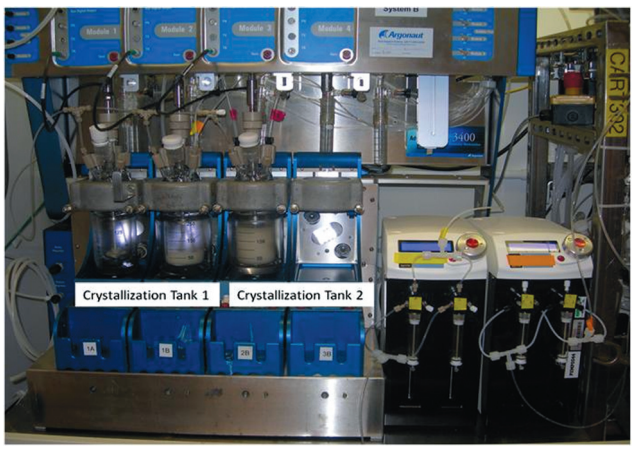


Fig. 6 47 h continuous campaign *in situ* data.

Table 3 Purity data for compound **1** produced by continuous crystallization

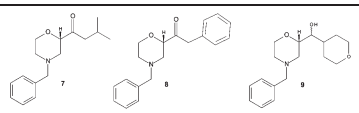


Fraction	Wt (g)	ee (%)	Cpd 2 (%)	Cpd 8[a] (%)	IPA (%)	Toluene (%)
1	48.2	99.7	0.22	0.19	2.89	0.40
2	115.8	99.8	0.17	0.22	2.76	0.36
3	56.8	99.7	0.17	0.27	2.65	0.30
4	40.2	99.8	0.17	0.35	2.63	0.30
5	55.7	99.7	0.20	0.31	2.21	0.30
6	87.8	99.4	0.20	0.28	2.18	0.31
Avg/ total	404.4	99.7	0.19	0.27	2.55	0.33

[a] cpd 8 observed as MSA salt.

finishing vessel (CSTR #2); quench vessel (CSTR #3) and a continuous sodium carbonate extraction (CSTR #4). The flow diagram for the entire continuous process including the continuous crystallization is shown in Fig. 5. For this campaign an adjustment was made to the free base procedure where a silica treatment was added to the organic solution in order to remove a dark coloration present in the amide **3** feedstock. The silica treatment effectively removed the dark coloration from the source amide, but notably had a positive impact on the Barbier reaction chemistry where 98% conversion was observed in the first CSTR vessel at the 35 °C operation temperature. Conversion and ee were monitored hourly through the duration of the campaign (Fig. 6).

Table 4 Continuous/batch crystallization comparison for isolated solid **1**



	Entry 1	Entry 2	Entry 3	Entry 4	Entry 5
Chemistry (batch/CSTR)	Batch Grignard	Batch Barbier	CSTR Barbier	CSTR Barbier	CSTR Barbier
Crystallization (batch/MSMPR)	Batch	Batch	Batch	Batch	MSMPR
ee (%)	99.9	99.9	99.7	99.8	99.7
% 2	0.15	0.18	0.17	0.16	0.19
% 7	0.32	<0.05	<0.05	<0.05	<0.05
% 8	<0.05	<0.05	0.09	0.10	0.27
% 9[a]	<0.05	0.08	0.13	0.07	<0.05
% IPA	5.38	4.39	3.68	3.51	2.53
% Tol	<0.05	<0.05	<0.05	1.05	0.33

[a] Mixture of diastereomers.

Despite the high conversion observed in CSTR #1 the second CSTR reaction finishing vessel was still operated to provide additional conversion. The final datapoint for the continuous demo campaign was collected at 47 h and revealed 97.5% conversion and 99.7% ee. For this campaign a starting charge of 25 g magnesium was used and two 25 g charges of magnesium were accomplished without loss of activation. At the 47 h time point, 2.7 g magnesium remained (96% consumption) and all fractions collected up to this point were acceptable for further processing including the start-up fraction generated during the first hour. Overall 592 g (potency corrected) of compound **1** was isolated. Not all of the material from continuous reaction was isolated, a portion of this campaign was crystallized continuously in the MSMPRs, and a portion was crystallized batch. Isolated compound **1** had about 99.7% ee whether it was isolated by batch or continuous crystallization. Subsequently, two additional continuous Barbier reaction campaigns were run, one using 639 g amide **3** and running for a total of 47 hours flow time, and the other using 1013 g amide **3** and running for 76 hours total flow time. A continuous crystallization demonstration was done to isolate 404 g compound **1** using the ketone **6** solution produced in the second 47 hour continuous Barbier campaign.

The continuous crystallization was improved by adding IPA solutions containing 0.5 equiv. of MSA (1.14 mL min^{-1}) concurrent with 1.0 equiv. of ketone **6** (2.22 mL min^{-1} in MSMPR #1 with a 30 min residence time at 20 °C. The resulting thin slurry containing product **1** continuously flowed to a second crystallization MSMPR where another 0.5 equiv. of 7.8 wt% MSA was added at 1.14 mL min^{-1} with a 30 min residence time, and pumped to MSMPR #3 with 30 min τ. The compound **1** slurry was continuously transferred to a 1 liter glass pressure filter using another 4 valve transfer zone pump at an average overall flow rate of 4.5 mL min^{-1}. Two filters were interchanged throughout the run with each filter cake washed with 3 volumes of isopropanol based on the amount of product entering the system while the filter was online. Six product fractions were collected over 18 h of continuous operation and the resulting

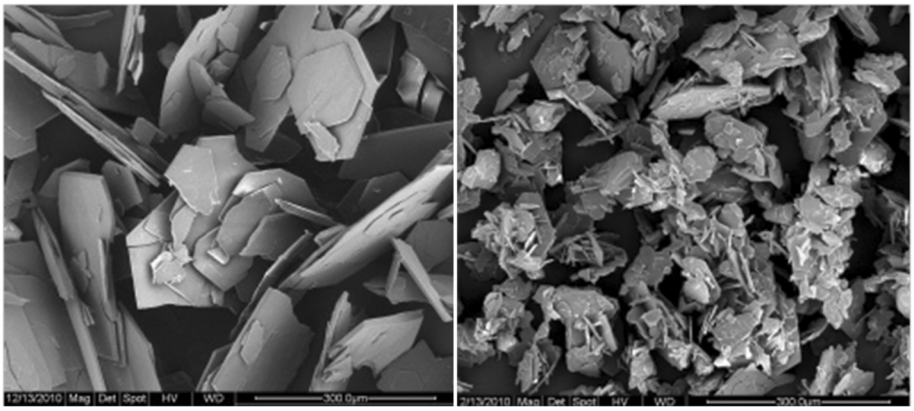


Fig. 7 Microscopy of compound **1** obtained *via* different crystallization processes; (a) batch high temperature crystallization, (b) continuous crystallization at room temperature.

Table 5 Batch/continuous flow comparison for production of 625 kg compound **1** at 125 kg per week throughput

	Single batch	Total 5 batches	Continuous Barbier
THF (L)	884	4400	3480
DIBAL (L)	17	85	0.07
Mg (kg)	16	80	53
Initiated Cl-THP (kg)	79	395	0.084
Total reaction vol. (L)	1400	1400	10.4
Vessel required (L)	2000	2000	15
Total time (h)	168	840	840
Compound **1** kg per week	125	625	625

product wet cakes were dried to constant weight over a minimum of 12 h to produce 404.4 g of compound **1** with exceptional purity (Table 3). The rest of the **6** solution was crystallized batch for comparison.

Continuous/batch crystallization comparison

Compound **1** produced *via* the fully continuous process (Table 4, entry 5) was compared with material made continuously, but crystallized in batch mode (Table 4, entries 3 and 4) along with the batch Barbier process (Table 4, entry 2), as well as material made entirely in batch mode by the Grignard process (Table 4, entry 1).

Overall the impurity compositions, between batch/continuous and Barbier/Grignard approaches were similar except impurity **8** was slightly enriched in the continuous crystallization system (Table 4). For example, entries 4 and 5 in Table 4 directly compare the purity profile of product produced by the batch and continuous crystallizations using the same feedstock from the continuous reaction. One difference between the approaches is that large plate like crystals of **1** are formed when the crystallization is carried out in batch with a slow cooldown from 70 °C. In comparison, much finer crystals of **1** are obtained by the room temperature continuous crystallization and isolation (Fig. 7). Since compound **1** exists as a channel solvate, the finer crystals produced in continuous mode also predictably occluded less residual solvent. However, a significant benefit to the continuous crystallization is that racemization is minimized by operating at 23 °C.

Environmental metrics comparison

A useful comparative metric is to review the amount and type of materials required to produce a given amount of compound **1** produced by both the batch and continuous approaches. A comparison was performed between batch and continuous approaches evaluating production of 625 kg of compound **1** based on traditional batch Grignard process (Table 5).

THF usage was directly reduced by 21% by the continuous approach which is due primarily to elimination of azeotropic drying steps necessary in the batch process. The estimate here is in fact conservative since in practice it may be necessary to use significantly higher quantities of THF to obtain dry reaction vessels (<500 ppm water) suitable for Grignard reagent formation. From a materials usage perspective, not only is 10% less 4-Cl-THP used for the continuous approach, but a single initiation event is required, whereas in batch several metal activations are required. Other hazardous materials such as diisobutylaluminum hydride are also reduced by >99% due to the necessity of only a single metal activation. Another significant upside to the continuous approach is the reaction scale has considerable intrinsic process safety advantages with a maximum operation scale of 15 L whereas, in batch, 2000 L scale reactions would need to be run to achieve the same endpoint of production of 125 kg of **1** in a week. For this project it is expected that ~50 L would be the maximum scale required to produce ~15 MT of compound **1** per year, which would replace 4000–6000 L batch reactors or several 2000 L reactors in series.

Conclusions

A novel Barbier process was run in continuous mode to produce ketone **1**, a useful pharmaceutical intermediate for production of edivoxetine·HCl. Excellent conversion (98%) and enantiomeric purity were achieved (>99% ee) in the crude ketone **6** *via* a four vessel CSTR series for the chemistry and aqueous work-up steps. An efficient continuous reactive crystallization was also developed using a cascade of three 250 mL MSMPRs in series

in which a production rate of 0.4 kg of MSA salt **1** per 18 hours was demonstrated. Overall, the greenness of the process was demonstrated to be significantly improved with reduced process mass intensity and improved intrinsic process safety relative to a traditional batch approach.

Experimental

(*S*)-(4-Benzylmorpholin-2-yl)(morpholino)methanone methanesulfonate, 2 (batch synthesis)

A 25 wt% solution of morpholine amide free base **3** in toluene (preparation, ref. 8) was concentrated to an oil, then the toluene displaced with ethyl acetate by vacuum distillation to produce a 25 wt% solution of **3** (14.7 kg). The 25 wt% solution of amide **3** (14.7 kg, 0.735 kg active) was charged into a 3 necked 22 L RB flask under nitrogen. Methanesulfonic acid (246.5 g; 2.55 moles) was charged slowly, at a temperature between 15–25 °C allowing the product to precipitate slowly. Once addition was complete, the mixture was cooled to 0–15 °C and stirred at this temperature for 1 h. The slurry was filtered and washed with 1.5 L of cold ethyl acetate and dried *in vacuo* at 36 °C overnight to produce 0.92 kg of compound **2** as a white powder in 93.4% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.81 (3H, s), 2.90 (1H, m), 3.20 (1H, m), 3.4–3.7 (10H, m), 4.00 (1H, dd, J = 12.9, 3.0 Hz), 4.25 (2H, m), 4.35 (1H, dt, J = 12.9, 1.6 Hz), 7.44 (3H, m), 7.55 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 39.6 (CH_3), 42.4 (CH_2), 46.2 (CH_2), 50.9 (CH_2), 52.2 (CH_2), 61.7 (CH_2), 63.5 (CH_2), 66.5 (CH_2), 66.7 (CH_2), 69.7 (CH), 127.2 (C), 129.5 (2 × CH), 130.5 (CH), 131.4 (2 × CH), 164.6 (C). HRMS m/z calcd for $C_{16}H_{23}N_20_3$ $(M + H)^+$: 291.1703. Found: m/z = 291.1703 $(M + H)^+$.

(*S*)-(4-Benzylmorpholin-2-yl)(morpholino)methanone, 3 and 4-chlorotetrahydropyran, 4 Barbier solution (batch synthesis)

Sodium carbonate (47.0 g, 439 mmol) was dissolved in water (425 mL) then charged, along with toluene (850 mL), into a 5 L jacketed vessel. Morpholine amide mesylate **2** (150 g, 365 mmol) was slowly added then the mixture stirred for 60 min. The layers were separated and the lower aqueous layer discarded. The organic layer was washed with water (140 mL), then the aqueous layer was removed and discarded. The organic layer was concentrated with a maximum jacket temperature of 60 °C to a volume of 200 mL. Toluene (600 mL) was then charged followed by silica gel (37.5 g). The mixture was stirred for 1 h then filtered. The waste silica cake was rinsed with toluene (150 mL) and the combined filtrates were re-concentrated to a 200 mL volume. Toluene (485 mL) was charged and water content measured by Karl Fischer titration to verify <500 ppm. The wt% of **3** was determined quantitatively using HPLC analysis (20–25 wt% target). Once the precise wt% of **3** was determined, 1.35 equiv. of dry 4-chlorotetrahydropyran, **4** was charged to complete Barbier solution preparation.

(*S*)-(4-Benzylmorpholin-2-yl)(tetrahydro-2*H*-pyran-4-yl)-methanone, 6 (batch synthesis)

Magnesium (17.95 g; 738.5 mmoles) was suspended in THF (100 mL, 3.3 vol) in a 500 mL flask. Diisobutylaluminum hydride 1 M toluene solution (3.0 mL, 3.0 mmol) was added followed by iodine (0.75 g; 2.95 mmol) and the dark suspension was heated to 55 °C. Dry 4-chlorotetrahydropyran (0.10 equiv.) was added. After 10 min of stirring, a 3 °C exotherm was observed. After stirring for an additional 20 min, the mixture was cooled to 35 °C and the toluene Barbier solution (1.0 equiv amide **3** and 1.35 equiv 4-Cl-THP, preparation above) was added dropwise over at least 1 h (Note: during the Barbier solution feed, a steady 2–3 °C temperature rise was observed). After the feed was complete the mixture was stirred for an additional 1 h at 35–40 °C. The reaction was considered complete when <2% starting material remained by HPLC analysis. The supernatant was then cannulated to an inerted addition funnel and the contents were then added dropwise over at least 1 h to a stirred 0 °C inerted 17 wt% acetic acid solution (3 equiv.). The residual magnesium heel was then rinsed with toluene (2 × 30 mL), and the rinses were cannulated into the work-up vessel through an addition funnel (Note: the residual magnesium heel can be reused for subsequent runs provided it is kept inert). After the rinse was complete the mixture was warmed to room temperature and stirred for 30 min, then the layers were separated. The aqueous layer was removed and the organic layer washed with 10 wt% Na_2CO_3 (100 mL) followed by water (100 mL). The organic layer was twice concentrated to an oil, diluted twice with IPA (250 mL), and re-concentrated to an oil. IPA (170 mL) was added to produce a final solution volume of ~190 mL. The crude ketone **6** isopropanol solution was taken directly into the methansulfonic acid salt formation step.

(*S*)-(4-Benzylmorpholin-2-yl)(tetrahydro-2*H*-pyran-4-yl)-methanone methanesulfonate, 1 (batch synthesis)

Compound **6** (21.3 g active; 1.00 equiv.; 73.75 mmol) isopropanol solution (190 mL) from the Barbier reaction was transferred to a 500 mL 3 necked round-bottomed flask and stirred under nitrogen. The solution was heated to 68 °C with mechanical stirring then methanesulfonic acid (4.85 mL; 74.36 mmoles) was added in one portion. The solution was cooled to 60 °C, seeded (1 wt% compound **1** seeds), then stirred for 1 h at 60 °C. The mixture was then cooled to 23 °C, stirred for 1 h and then filtered. The resulting wet cake was washed with IPA (60 mL) and dried overnight at 45 °C to produce 28.4 g of **1** as a white solid in 86% yield.

(*S*)-(4-Benzylmorpholin-2-yl)(tetrahydro-2*H*-pyran-4-yl)-methanone, 6 (flow synthesis). Initiation

Magnesium (25 g, 10 equiv) was suspended in THF (115 mL) in a 250 mL Argonaut flask (CSTR #1) equipped with baffle cage and 0.5 inch outside diameter, 0.376 inch inside diameter draft tube which contained a 0.25 inch outside diameter, 0.125 inch inside diameter, capped transfer line with 1 mm diameter holes drilled in concentric circles on the sides. This transfer line served to pump the product solution out but keep magnesium sequestered in CSTR #1. The resulting slurry was heated to 55 °C. Diisobutylaluminum hydride 1 M toluene solution (1.35 mL; 9.49 mmol) was added followed by a THF solution (5 mL) containing iodine (0.4 g; 1.58 mmol) producing a total volume of

120 mL in CSTR #1. The suspension was stirred at 55 °C for 15 min then 4-Cl-THP (1.62 g; 13.44 mmol; 0.1 equiv.) was added and a mild exotherm to 59 °C was quickly observed. After stirring for 10 min at 55 °C the temperature of the initiated suspension was lowered to 35 °C. Magnesium was charged two more times through the experiment, each time the same amount of magnesium was charged as initially, 25 g each time after >70% metal consumption. Note: The amount of magnesium (75.04 g; 3.08 mol, 1.35 equiv.) used was calculated based on total magnesium needed for a 47 h run in order to generate 1.35 equiv. at all times in CSTR #1 throughout the entire experiment, with the goal of 1 mol of magnesium for 1 mol of 4-Cl-THP. The 1.35 equiv. stoichiometry translates to 2.5 g magnesium consumption per 90 min residence time.

Barbier reaction

After the initiation the reaction mixture was adjusted to 35 °C in CSTR #1, the pumps were started connecting the CSTRs. A 22 wt% solution of *S*-amide **3** in toluene containing 1.35 equiv. of 4-chlorotetrahydropyran (Barbier stream, preparation above) was fed continuously with a flowrate of 1.09 mL min^{-1} to CSTR #1, containing the initiated Grignard, with dual module syringe pumps. Average hydraulic residence time in the CSTR #1 was 90 min governed by the diptube height and mixing in flask, and the total volumetric flow rate. THF was also added continuously *via* a separate syringe pump with a flowrate of 1.35 mL min^{-1} to maintain a 2 : 1 THF–toluene ratio, the pump flow rates were verified by feed cans on balances. During the course of the feed a ΔT ($T_{jacket} - T_{process}$) of 1.5 °C was maintained. Due to the intermittent flow with the use of the transfer zones, the range of $\tau_{CSTR\#1}$ was from 90 to 93 min. The reaction solution was transferred to a second CSTR using a 4 valve transfer zone pump at an average flowrate of 2.44 mL min^{-1}; $\tau_{CSTR\#2}$ was 60 min. The temperature of CSTR #2 was also kept at 35 °C. As with CSTR #1, the intermittent flow kept the $\tau_{CSTR\#1}$ to range from 60 to 63 min.

Quench and aqueous work-up

A 17.3 wt% acetic acid in water solution was prepared and transferred continuously *via* syringe pump at a flowrate of 1.02 mL min^{-1} to the third CSTR, whose jacket temperature was controlled at 5 °C. Simultaneously, the reaction solution in the second CSTR was transferred to the third CSTR using a second 4 valve transfer zone pump at an average flowrate of 2.44 mL min^{-1} and the mixture stirred in the CSTR. $\tau_{CSTR\#3}$ was 30 min. The biphasic solution in the third CSTR was transferred to a settler/separator tank using a third 4 valve transfer zone pump at an average flowrate of 3.46 mL min^{-1} and the layers were allowed to separate continuously. $T_{settler}$ = 30 min. The lower aqueous layer was continuously overflowed to waste using a hydraulic decanter. The upper organic layer from the settler/separator above continuously flowed to a fourth CSTR and a 5 wt% sodium carbonate in water solution was also being continuously added *via* syringe pump at a flowrate of 1.78 mL min^{-1}; $\tau_{CSTR\#4}$ was 30 min. This bi-phasic mixture was transferred *via* a 4 valve transfer zone pump to a collection bottle. Separation of the liquid layers after the carbonate wash was performed batch, for simplicity of this demonstration, however, on scale it would be a continuous gravity decanter similar to the separator following CSTR# 3. The bottom aqueous layer was removed and the upper organic layer was carried on to the final water wash. The organic layer obtained from the carbonate wash was washed as one batch with water in the ratio of half the volume of water to the volume of organic. The bottom aqueous layer was removed and the resulting organic layer was carried into the solvent exchange.

Solvent exchange

Solvent (toluene–THF) in the organic layer was obtained after the final water wash was removed by distillation using reduced pressure in a rotary evaporator (distillation conditions: 100 mm Hg with a water bath of 60 °C). The distillation was continued until an amber oil remained. The oil was assumed to be quantitatively ketone **6** and QS IPA was added to the oil obtained from the vacuum distillation to prepare a 20 wt% solution of ketone **6** in IPA.

Note: This solvent exchange procedure is not intended for traditional plant modules with batch stirred tanks. It is not a vessel ready process for batch, because minimum stir volume prohibits distillation to an oil. However, the parameters have been demonstrated at a 200 L per day scale in-house by running the solvent exchange automated batch in a rotary evaporator distillation system, where the cycle time of the charges is set to match the throughput on the preceding and trailing unit operations. All the intermittent flows and pressure sequences are fully automated and precisely controlled by automated valves DeltaV control system: reaction/extraction product solution in, distillate out, solvent add-back, and dissolved product out. If the workup and isolation must be done in batch due to equipment availability, then the procedure would need to be modified so that it can work in traditional batch distillation tanks. This also could be worse environmentally as there are numerous solvent charge and distillations that would be required to achieve the same consistent crystallization feed stream.

Magnesium re-initiation and re-charge

When the same heel of magnesium was to be used over a week, the solutions in CSTRs #1 and #2 were held overnight when Barbier production was stopped for the day. CSTR #3, the acid quench tank, was emptied nightly to minimize racemization. The quench tank is forward processed through the separator until the sodium carbonate wash. After the quench solution has emptied into the carbonate wash, the process is held overnight in CSTRs #1, #2 and #4 with all the tanks inerted. The next day a residence volume of acetic acid is added to CSTR #3, magnesium is re-charged to CSTR #1 if needed, then the reactors are adjusted to the correct temperatures, and Barbier mixture and THF streams are started at the desired flow rates. Once CSTR #3 reaches the residence volume, the transfer zone pump from CSTR #3 is started up along with the acetic acid flow. Once the separator begins to gravity drain into the carbonate wash tank, the fourth transfer zone and sodium carbonate stream are started up again,

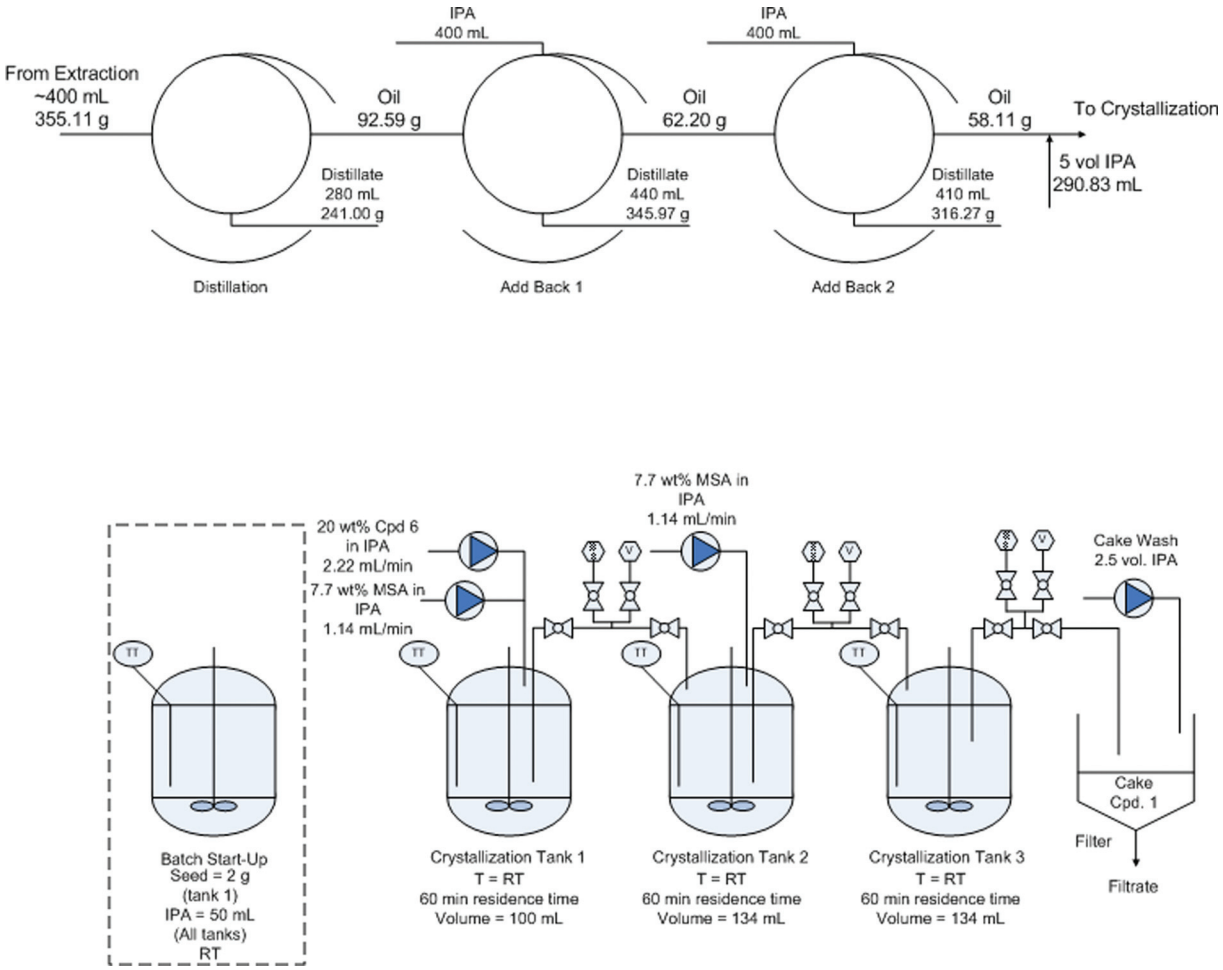


Fig. 8 Distillation and continuous crystallization of compound **1**.

An observed ΔT ($T_{max} - T_{initial}$) of 1.5 °C will return quickly to CSTR #1 once the streams begin and no DIBAL-H or I_2 was required for re-initiation on subsequent days. This ΔT was not adiabatic as the reactor was being controlled with a jacket at 35 °C. It was also demonstrated that fresh untreated magnesium could be charged into the first CSTR during the course of the reaction, with no loss in conversion nor ee of ketone **6**. Also during the re-charge no 4-Cl-THP, DIBAL-H nor I_2 was required, the reaction mixture remained initiated and the exotherm seen as the amide/4-Cl-THP was fed into the first CSTR was maintained throughout the re-charge. The demonstration run went for 47 h, cumulative flow time not including overnight shutdowns, put 2.199 mol into the system and came out with 1.929 mol in the oil, giving us a yield of 88%. The oil was used directly in the continuous MSA salt formation/crystallization process (Fig. 8).

(*S*)-(4-Benzylmorpholin-2-yl)(tetrahydro-2*H*-pyran-4-yl)-methanone methanesulfonate, 1 (flow synthesis)

A seed bed of compound **1** in isopropanol was prepared by charging 2 g of cpd **1** and 50 mL of IPA to the first MSMPR crystallizer and allowed to stir at ambient temperature. A solution of 7.82% w/w methane sulfonic acid in isopropanol was prepared and continuously added *via* syringe pump at a flowrate of 1.14 mL min^{-1}, while simultaneously adding the 22 wt% ketone **6** isopropanol solution using another syringe pump at a flowrate of 2.22 mL min^{-1} to afford 0.5 mol MSA : 1 mol ketone additions, $\tau_{MSMPR\#1}$ = 30 min in the first MSMPR crystallizer. The compound **1** slurry was continuously transferred to the second MSMPR crystallizer using a 4 valve transfer zone pump at an average overall flow rate of 3.36 mL min^{-1}; $\tau_{MSMPR\#2}$ = 30 min. The temperature of the second MSMPR was also kept ambient. Another 0.5 mol of MSA from the 7.82% w/w methanesulfonic acid in isopropanol was added at 1.14 mL min^{-1} into tank 2. The compound **1** slurry was continuously transferred to MSMPR # 3 with τ = 30 minutes, and pumped intermittently to a 1 liter glass pressure filter using another 4 valve transfer zone pump at an average overall flow rate of 4.5 mL min^{-1}. Liquid was removed from the slurry *via* filtration collecting mother liquor in a tared filtrate receiver.

Two filters were interchanged throughout the run with each filter being washed with 3 vol of IPA off line based on the amount of ketone put through the system during the time the filter was online. The continuous crystallization progressed until the supply of 22 wt% ketone **6** IPA solution was exhausted at which point the crystallizers were emptied at the same rate as

they were filled. Once the crystallizers were empty, 2.5 volumes (compound **6** oil basis) of IPA was added to the first MSMPR crystallizer as a cake rinse. The rinse solution was transferred through the transfer zones as well as the second and third MSMPR crystallizer and finally the rinse was transferred to the filter where the cake was rinsed and the filtrate collected in a separate tared filtrate receiver. The wet cake in the filter was transferred to a tared drying dish and dried to a constant weight in a vacuum dryer at 45 °C. The latest run went for 18 h and 1.156 mol of ketone was put into the system, with 1.027 mol of salt collected (corrected for potency), giving a yield of 89%.

(*S*)-1-(4-Benzylmorpholin-2-yl)-2-phenylethanone methane sulfonate, 8

Amide **3** (10 g; 1.00 equiv.; 34.44 mmol) was dissolved in THF (70 mL) then cooled to 0 °C. Benzylmagnesium chloride (16.4 mL; 0.95 equiv.; 32.80 mmol) was then added over 10 min. Once the addition was complete, the cooling was removed and the reaction mixture warmed to 40 °C and stirred for 1 h. The reaction mixture was re-cooled to 0 °C then was quenched by addition of an acetic acid (2 mL, 34.9 mmol) solution in water (20 mL). Toluene (70 mL) was charged and the mixture warmed to room temperature. The layers were separated, then the aqueous layer was extracted with toluene (100 mL). The organic layer was washed with 10 wt% aqueous sodium carbonate (70 mL) then with water (70 mL). The combined organic extracts were concentrated to an oil (17.46 g). The crude oil was purified by silica gel chromatography to produce 6.48 g of purified oil which was dissolved in isopropanol (33 mL) and transferred to a 100 mL, 3-necked round bottom jacketed flask. The solution was heated to 68 °C with mechanical stirring, then methanesulfonic acid (1.45 mL; 22.12 mmol) was added in a single portion, resulting in an exotherm to 80 °C. The solution was cooled to 20 °C to crystallize product **8**. The compound **8** slurry was stirred at room temperature for 1 h, cooled to 0 °C, then stirred for an additional hour. The crystals were filtered, the cake, washed with cold IPA (30 mL). The resulting wet cake was dried *in vacuo* at 45 °C overnight to produce compound **8** as white solid (5.08 g, 46% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.65 (1H, t, J = 11.8 Hz), 2.80 (1H, dd, J = 12.9, 8.4 Hz), 3.39 (1H, d, J = 11.8 Hz), 3.63 (1H, d, J = 12.2 Hz), 3.88 (1H, d, J = 16.2 Hz), 3.94 (1H, d, J = 16.2 Hz), 4.14 (1H, dd, J = 13.2, 3.8 Hz), 4.19 (2H, m), 4.46 (1H, t, J = 12.3 Hz), 4.85 (d, 1H, J = 9.9Hz), 7.15 (2H, d J = 7.0 Hz), 7.27 (1H, m), 7.31 (2H, m), 7.45 (2H, m), 7.48 (1H, m), 7.55 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 45.3 (CH_2), 50.5 (CH_2), 51.4 (CH_2), 61.5 (CH_2), 63.7 (CH_2), 76.0 (CH), 126.8 (C), 127.4 (CH), 128.6 (2 × CH), 129.4 (2 × CH), 129.6 (2 × CH), 130.6 (CH), 131.4 (2 × CH), 132.2 (C), 202.8 (C). Elemental analysis calcd for $C_{19}H_{22}NO_2$. Theory 61.36% C; 6.44% H; 3.54% N; % Found 61.36% C; 6.29% H. 3.54% N. HRMS m/z calcd for $C_{19}H_{22}NO_2$ $(M + H)^+$: 296.1645. Found: m/z = 296.1642 $[M + H]^+$.

(*S*)-4-Benzylmorpholin-2-yl)(tetrahydro-2*H*-pyran-4-yl)-methanol, 9

Sodium tetrahydroborate (0.71 g; 18.77 mmol) was dissolved in ethanol (25 mL; 429.41 mmol) in a 50 mL round-bottom flask and cooled to 0 °C in an ice-bath. To this mixture was added compound **6** (5.17 g; 1.00 equiv.; 17.87 mmol) dissolved in ethanol (15 mL; 257.6 mmol) which was added dropwise at 0 °C over 3 min while keeping the temperature below 3 °C. The mixture was allowed to stir at 0 °C for 15 min before it was warmed to 23 °C then aged for 30 min. The organic layer was concentrated to an oil then dichloromethane (20 mL) was added. The mixture was placed in an ice-bath then 1 N hydrogen chloride (14.3 mL; 14.30 mmol) was added and the mixture stirred for 20 min, then allowed to warm to room temperature. The layers were separated then aqueous Na_2CO_3 was added to the aqueous layer until basic. The aqueous layer was extracted with ethyl acetate (50 mL) then dichloromethane (50 mL). The combined organic layers were concentrated to an oil to produce 4.5 g (88% yield) of compound **9** as a 61 : 39 ratio of diastereomers. Diastereomer #1: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.29 (1H, m), 1.33 (1H, m), 1.45 (1H, m), 1.68 (2H, m), 2.80 (4H, m), 3.09 (1H, dd, J = 6.9, 3.4 Hz), 3.27 (2H, m), 3.67 (5H, m), 3.87 (2H, m), 7.33 (1H, m), 7.36 (2H, m), 7.39 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 29.6 (CH_2), 29.9 (CH_2), 38.2 (CH), 53.6 (CH_2), 55.5 (CH_2), 63.4 (CH_2), 66.9 (CH_2), 68.2 (2 × CH_2), 75.7 (CH), 76.3 (CH), 129.1 (CH), 129.4 (2 × CH), 130.6 (2 × CH). Diastereomer #2: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.33 (1H, m), 1.36 (1H, m), 1.48 (1H, m), 1.55 (1H, m), 1.72 (1H, m), 2.66 (2H, d J = 10.4 Hz), 2.93 (2H. D J = 10.4 Hz), 3.26 (1H, m), 3.29 (1H, m), 3.44 (1H, m), 3.58 (4H, m), 3.80 (2H, m), 3.87 (1H, m), 7.28 (1H, m), 7.33 (2H, m), 7.34 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 27.6 (CH_2), 30.0 (CH_2), 37.3 (CH), 53.6 (CH_2), 55.5 (CH_2), 63.4 (CH_2), 66.9 (CH_2), 68.2 (2 × CH_2), 75.7 (CH), 76.1 (CH), 128.1 (CH), 129.1 (2 × CH), 130.6 (2 × CH). HRMS m/z calcd for $C_{19}H_{22}NO_2$ $[M + H]^+$: 292.1907. Found: m/z = 292.1912 $[M + H]^+$.

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9 (*S*)-Morpholine amide mesylate **2**, was selected as an API starting material for preparation of LY2216684.HCl. The reason for the starting material selection was that the mesylate salt is a stable crystalline solid which is easily campaigned, whereas the freebase form **3** does not have favorable handling properties. The preparation of morpholine amide mesylate**2** is described in the experimental along with an efficient procedure for production of free base **3**.

10 5-Fluoro-2-methoxy benzaldehyde was used as the Grignard reagent derivatization agent.

11 The Grignard initiation was performed with a 0.1 equiv. initiation charge of 4-chloro tetrahydropyran using diisobutylaluminum hydride and iodine as activators, as per ref. 8.

12 It was not necessary to re-initiate the magnesium, addition of 4-Cl-THP resulted in an immediate exotherm indicating productive initiation.

