Grignard Reactions Go Greener with Continuous Processing

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Abstract

Since the start of the 20th century, the Grignard reaction has been applied to the synthesis of numerous intermediates for food additives, industrial chemicals, and pharmaceuticals. Despite these successes, the acute hazards of the Grignard reaction make it one of the more challenging reactions to bring to commercial scale. These hazards include: 1) strongly exothermic activation and reaction steps; 2) heterogeneous reactions with potential problems suspending and mixing the reaction mixture; and 3) extreme operational hazards posed by ethereal solvents such as diethyl ether.

Eli Lilly and Company developed inherently safer Grignard chemistry using a continuous stirred tank reactor (CSTR) approach that allows continuous formation of Grignard reagents with continuous coupling and quenching operations. This strategy minimizes hazards by operating at a small reaction volume, perfoming metal activation only once for each campaign, and using 2-methyltetrahydrofuran (2-MeTHF), as a Grignard reagent and reaction solvent that may be derived from renewable resources. Grignard reactions using 2-MeTHF also result in products with enhanced chemo and stereoselectivity. Relative to batch processing, the continuous approach allows rapid steady state control and overall reductions up to 43% in magnesium usage, 10% in Grignard reagent stoichiometry, and 30% in process mass intensity (PMI). The continuous approach reduces reaction impurities substantially. In addition, small-scale operation at end-of-reaction dilution allows all ambient processing conditions.

Lilly is using its CSTR Grignard approach to produce three pharmaceutical intermediates including the penultimate intermediate of **LY2216684·HCl**, a norepinephrine reuptake inhibitor which is under phase 3 clinical investigation for treatment of depression. In addition, Lilly uses a similar approach to synthesize an intermediate for investigational new drug candidate **LY500307** under clinical evaluation to treat benign prostatic hyperplasia. Lilly anticipates commercial production on 22 liter scales which will replace the 2,000 liter reactors used in batch processes.

Description of Project Milestones

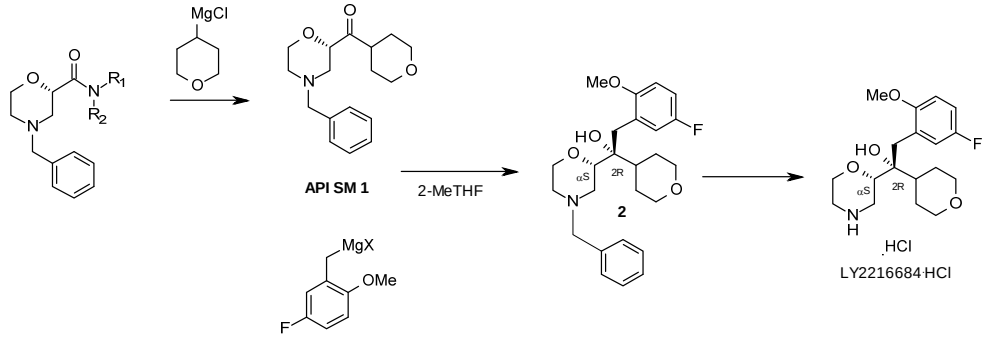
The CSTR methodology for the Grignard reaction was developed at Eli Lilly and Company in 2009 to 2011, with application to the syntheses of intermediates for phase 2 and phase 3 investigational new drug candidates. Proof of concept work was achieved in a 250 mL reactor series which produced 0.5 kg of product per day. Commercial production using these processes will occur on 22 liter scale to produce ~ 50 kg product per day, which replaces 2000-liter reactors used in batch processes. This technology is planned for used in the first production campaign which will eliminate significant waste from the outset of commercialization. The research and development occurred in the Eli Lilly and Company, Indianapolis, IN, Technology Center.

Statement of Focus Areas

This nomination from Eli Lilly and Company is focused on the use of greener reaction conditions and synthetic pathways, and is submitted for consideration in both these award categories. The nominated technology is not eligible for the small business or academic awards.

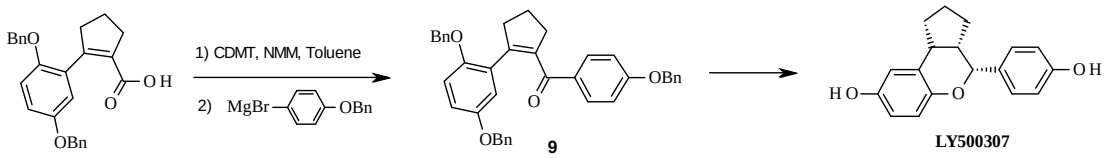
Executive Summary

This nomination illustrates innovative and environmentally improved reaction conditions for the commercial production of investigational new drug candidate **LY2216684·HCl**, a-selective norepinephrine reuptake inhibitor which is under clinical investigation for treatment of depression. The tertiary alcohol intermediate was synthesized by a chelation controlled Grignard reaction which delivers >96 % *in situ* selectivity for the desired (α*S*,2*R*)-isomer and is performed optimally in a CSTR series (Scheme 1).



Scheme 1. LY2216684·HCl synthesis via two consecutive Grignard Reactions.

For the initial pilot plant campaigns, the benzyl Grignard chemistry was run in batch mode which required cryogenic temperatures for the Grignard reagent formation and reaction chemistry due to the large exotherms observed. Under continuous processing conditions, it was optimal to operate the benzyl Grignard reaction at 20 to 25^{o} C. In addition, Eli Lilly has demonstrated the successful production of API starting material **1** via a continuous Barbier reaction which proceeds in > 99 % ee. Furthermore, the CSTR Grignard approach was demonstrated by synthesis of an intermediate to **LY500307**, an investigational new drug candidate at Eli Lilly and Company under evaluation for treatment of benign prostatic hyperplasia (Scheme 2)

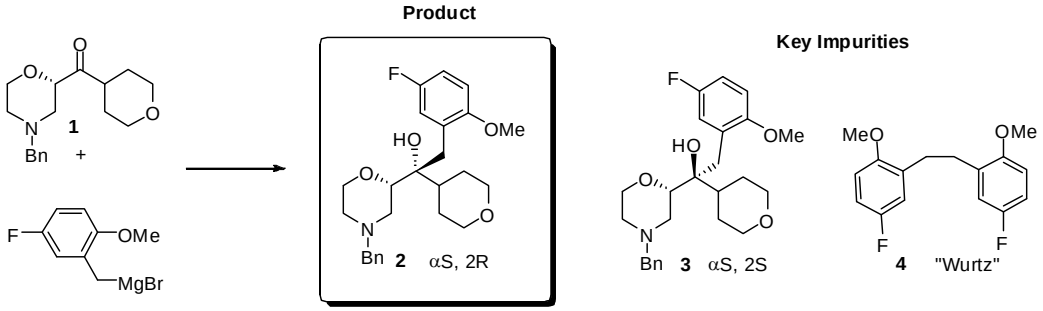


Scheme 2. Synthesis of LY500307 via Grignard Approach.

Lilly believes the technology developed herein for the Grignard and Barbier reactions has broad applicability producing benign environmental by-products. The Grignard strategy is more versatile than zinc based chemistry where removal of hazardous heavy metal zinc by-products from wastewater is costly and energy intensive. Untreated zinc waste can pose a significant health and environmental hazard. In addition, safety improvements are significant relative to usage of highly pyrrophoric organolithium reagents. As exemplified in this nomination, the Grignard reaction is the best method for preparation of complex chiral tertiary alcohols and reduces several steps in a synthesis.

The benzyl Grignard chemistry used to synthesize **LY2216684·HCl** proceeds through a chelation controlled mechanism where the intermediate magnesio-complex delivers the Grignard reagent to the least hindered faceof chiral ketone **1**. The best Grignard reagent formation and

reaction solvent was 2-MeTHF which produced the highest stereoslectivity of all cyclic and acyclic ether solvents that were evaluated (Table 1). In addition, compared with THF, the Wurtz by-product, which is a common impurity in benzylic and allylic Grignard reactions, was suppressed by an order of magnitude using 2-MeTHF (Table 1, entries 1 and 2). The Grignard chemistry using 2-MeTHF affords penultimate intermediate **2** in 87 % yield as a single enantiomer after conversion to a fumarate salt.



Entry	Solvent	Bp (°C)	% 2	% 3	% 4
1	**2-MeTHF**	**80**	**93.9**	**3.2**	**2.9**
2	THF	65	59.0	4.0	37
3	Diethylether	35	80.8	12.7	6.5
4	Cyclopentylmethylether	106	68.4	13.2	18.4
5	Tetrahydropyran	88	78.1	4.0	17.9

Table 1. Benzyl Grignard Reaction *in situ* reaction purity.

Using 2-MeTHF the benzyl Grignard reagent was formed in the first vessel of a 250 mL CSTR series (CSTR #1) by concomitant feeding of a benzyl halide solution and 2-MeTHF into a suspension of activated magnesium (Figure 1). Average hydraulic residence time (tau) in the Grignard formation vessel was 1 hour. The benzyl Grignard reagent flowed to the second vessel in the CSTR series through a fritted filter. The output flow rate from the Grignard formation vessel was controlled by an automated pressure swing cylinder which filled by trapped vacuum from CSTR #1 and pumped liquid forward intermittently 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 filter in the exit tube from CSTR #1, after each bolus transfer was complete, a reverse-nitrogen purge was applied. A large excess of magnesium, 3 equiv. per 8 hour processing day, was charged initially to CSTR #1, and as the reaction progressed magnesium consumption theoretically approached 1 equiv. Magnesium could be recharged, without impacting steady state conversion up to 95% metal consumption. In comparison, the batch process uses 1.75 equiv of magnesium for each lot, and the excess metal has to be quenched and disposed of after every run. Thus, by the continuous approach it is possible to reduce the total magnesium usage up to 43 % relative to the batch process. In addition, Lilly has demonstrated that in continuous mode, only a single activation of the metal is necessary for an entire

campaign; this improves one of the more hazardous aspects of Grignard chemistry as the metal activation typically requires handling of hazardous materials such as diisobutylaluminum hydride or iodine on a per batch basis. As magnesium is consumed during the course of the Grignard reaction, additional metal can be added at any time, which will then be activated either by the Grignard already present and by the mechanical action of the system. Daily recharge of magnesium during continuous operations has been shown to be an effective practice. At the end of the continuous campaign the metal can be fully consumed with electrophile under non-steady sate conditions, which significantly improves process safety.

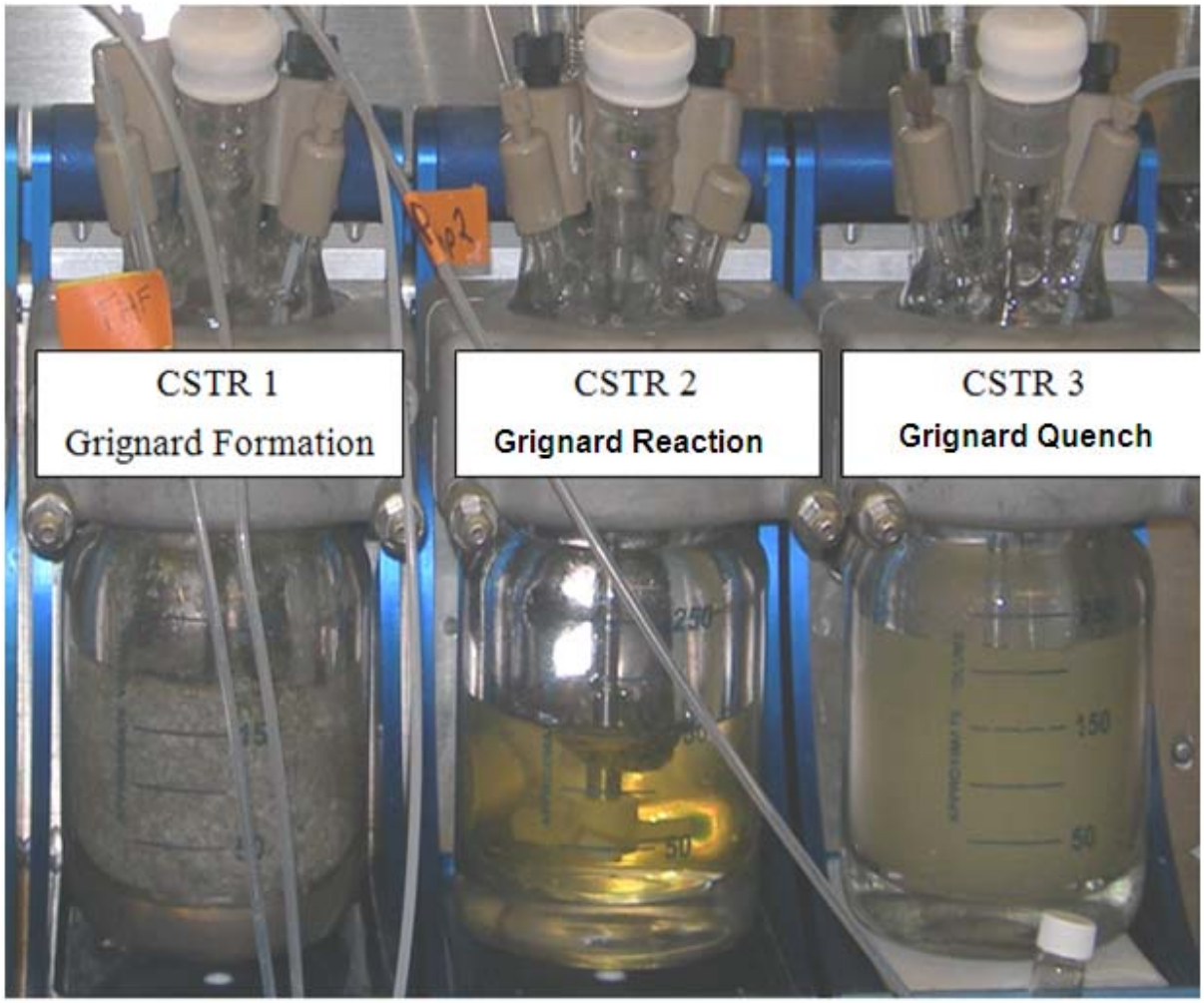
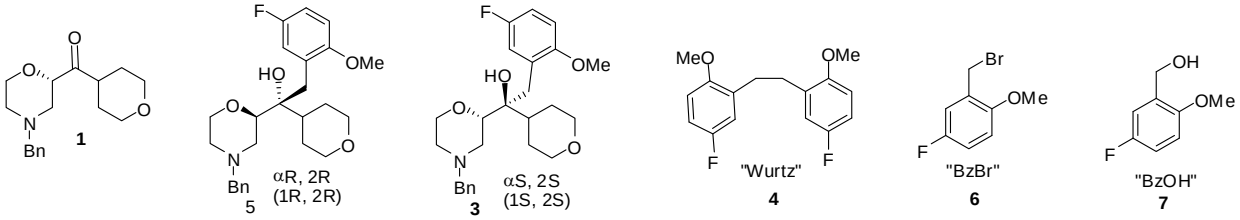


Figure 1. 3- vessel 250mL CSTR Train for Grignard Chemistry.

The contents of the Grignard reaction tank flow continuously into a quench tank (CSTR #3) with a concomitant acetic acid / water feed (Figure 1). Optimal redience times for Grignard reagent formation, reaction and quench were 60 min, 30 min and 60 min, respectively. Each CSTR operated at 20-25^{o} C which was not possible for the batch process due to strong exotherms. Under continuous conditions, a rapid steady state was achieved within an hour and only single CSTR reactors for each operation were needed. Most signifcantly, the *in situ* impurity profile was substantially improved by the continuous approach relative to the batch process with the the key Wurtz byproduct (**4**) reduced from 5% to less than 1% at steady state (Figure 2). In addition, levels of the undesired enantiomer (**3**) and benzyl alcohol (**7**) were also

significantly lower in the continuous approach. In batch processing, scale sensitivity to mixing was observed as evidenced by racemization when substrate feed order was reversed, something not observed in the continuous process because of co-addition of reagents at stoichiometric ratio at steady state. Reaction monitoring by HPLC analysis was performed hourly on each process stream within the reaction and quench tanks. Proof of concept was also achieved monitoring conversion by REACT-IR which is an attractive long-term option for replacement of traditional sampling. The overall improvements in the *in situ* profile in continuous mode allowed us to reduce the stochiometry of the benzyl halide starting material by 10% and achieve the same yield as the best batch process.



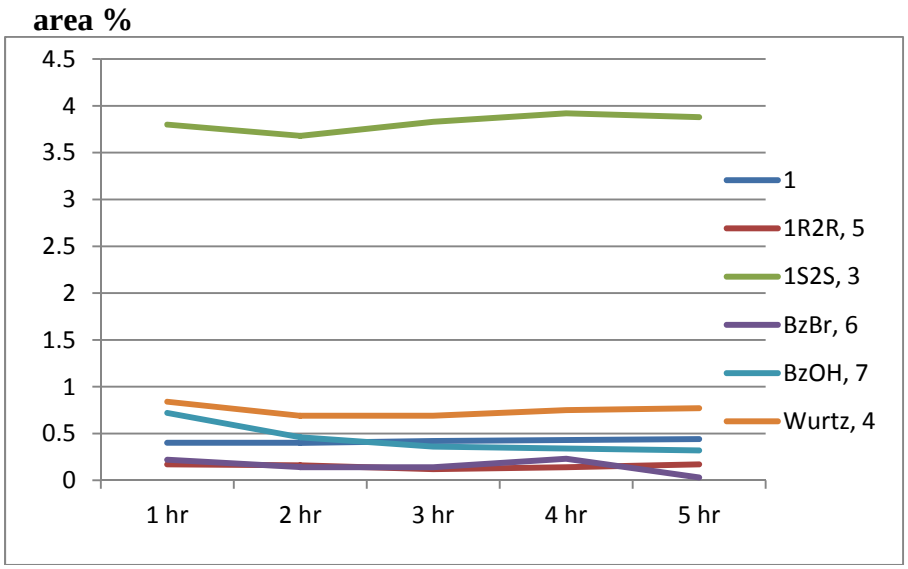
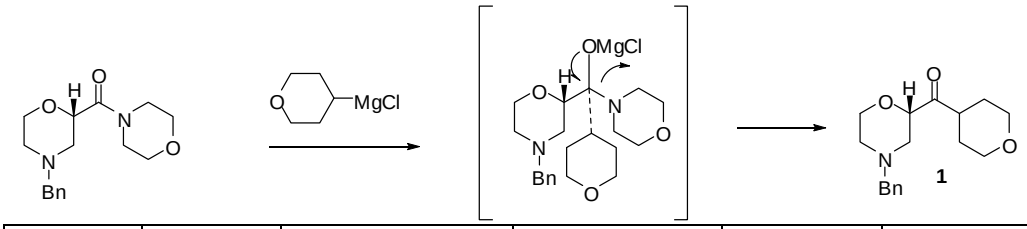


Figure 2. All Ambient Continuous *in situ* Grignard Reaction Purity Profile.

Recently we disclosed details of the synthesis of a starting material (**1**) for API LY2216684·HCl that was prepared in a batch process by a Grignard displacement reaction. During the history of this project, several contract manufacturing organizations had difficulty with the Grignard batch process, and one supplier even defaulted on delivery. The main issue encountered was the very exothermic Grignard initiation (with a potential adiabatic heat rise of 100 °C) that occurred close to the boiling point of the solvent. Also, the initiation time was not always reproducible, sometimes being delayed by several hours. In addition, the starting material, intermediate and product were all sensitive to racemization. Key parameters influencing the level of racemization were addition order, amide feed rate, quench conditions, and air/moisture contamination. All of these issues led us to develop a continuous process where key parameters could be precisely controlled at steady state (Table 2).

In contrast to the chemistry reported for the synthesis of **2**, solubility issues were encountered during formation of the 4-chlorotetrahydropyran (4-Cl-THP) Grignard reagent. The ap-

proach we took to solve this problem was development of a continuous Barbier reaction where Grignard reagent formation and reaction were performed simultaneously. For the Barbier approach, the 4-Cl-THP starting material had a powerful solubilizing effect, and a homogeneous process stream was achieved (aside from suspended magnesium metal). The same basic setup was used as for the preparation of **2**, except a morpholine amide and electrophile solution were fed to activated magnesium as a single stream. In this case, the second CSTR in series was an acetic acid/water quench. A series of experiments was run over 7 days evaluating stoichiometry, temperature, solvent composition and residence time (Table 2). Each days operation consisted of a 6-8 hour run with conversion and enantiomeric excess monitored hourly.



Entry	Temp (°C)	Residence Time (min)	4-Cl-THP (equiv.)	THF (vol %)	Conversion (%)	ee (%)
1	55	60	2.0	45	97	94
2	55	60	1.5	45	98	95
3	55	60	1.35	45	97	96
4	35	60	1.35	45	94	96
5	35	90	1.35	62	98	99
6	35	90	1.35	62	98	99
7	55	30	1.35	62	98	98

Table 2. Continuous Barbier *in situ* results for synthesis of **1**.

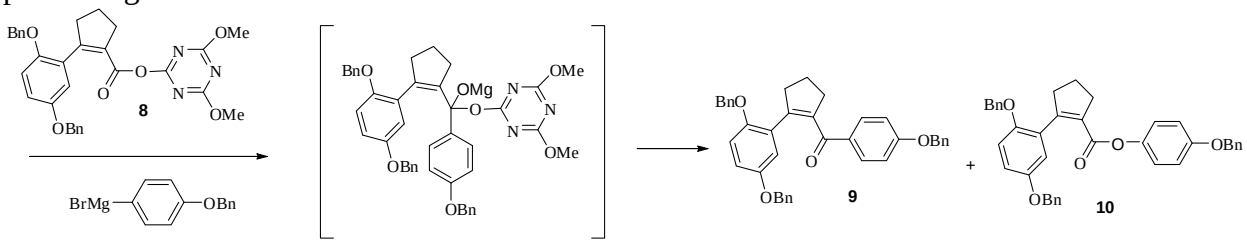
The best results were achieved by reducing both the 4-Cl-THP stoichiometry to 1.35 equiv, and the operation temperature to 35 ^{o}C, while increasing the solvent composition to 62 % THF. Under these conditions, steady state was achieved within an hour with 98 % conversion and 99 % ee. As per the benzyl Grignard chemistry, once initiated, a steady 2 ^{o}C temperature difference between reaction slurry and cooling jacket was observed, and we were able to maintain an “always-on” Grignard reaction without the need for additional chemical activation after magnesium re-charges.

	Single Batch	Total Batch	Continuous
THF (L)	884	4400	2600
DIBAL (L)	17	85	0.07
Mg (kg)	16	80	53
Initiated Cl-THP (kg)	79	395	0.02
Total Rxn Vol (L)	ca. 1400	---	2.6
Vessel Required (L)	2000	---	5
Total Time (hrs)	168	840	672
Compound 1 kg/week	125	125	125

Table 3. Batch / Continuous Flow Camparison for production of 625 kg compound **1**.

A comparison between batch and continuous approaches to produce 625 kg of compound **1** show significant material reduction and process safety advantages for the continuous approach (Table 3). The flow process for the 4-Cl-THP Barbier chemistry uses 33% less magnesium and 41 % less THF. Most notably, only a single charge of diisobutyl aluminum hydride is used only once and total usage of this hazardous material is reduced by >99%. This is due to the necessity to perform only one metal activation per entire continuous flow campaign. Similarly, the amount of initiated 4-Cl THP required is reduced by 99.8% due to the ability to maintain the metal in an always active state in continuous mode. In addition, the maximum continuous scale required is a 5 L CSTR series whereas in batch, 2000 liter scale reactions would need to be run to achieve the same target endpoint of production of 625 kg of **1**.

The final example that demonstrates the benefits of CSTR methodology applied to Grignard syntheses was accomplished by the synthesis of **9** a~~n~~ intermediate to LY500307(Scheme 3). During the batch process, up to 10 % of a problematic benzyl ester impurity **10** was formed from displacement of the CDMT ester intermediate by a benzyl alcohol impurity generated during the Grignard reagent formation. The 3-tank CSTR setup described for the production of **2** was used to produce intermediate **9** with less than 1 % ester by-product at steady state. In this system a 72% yield of intermediate **9** was achieved in continuous mode, a more than 25% improvement from the batch process. The yield improvement is attributed in part to steady state control formation of the unstable tetrahedral intermediate which partially decomposes during batch processing.



Scheme 3. Continuous Grignard reaction with CDMT ester for **LY500307** Synthesis.

Overall, process R&D efforts over the last three ears have led to the discovery of a new approach to the Grignard reaction that improves greeness of this historic transformation. The CSTR methodology was shown to be optimal for preparation of sensitive Grignard reagents and their subsequent reactions. Improved process safety and reduced material usage were achieved, which are central tenants of the 12 principles of green chemistry. Significantly, the reduced environmental footprint and safety improvements will be achieved for the initial commercial production of LY2216684·HCl by implementation of the continuous approach. A key advantage is that the Grignard formation and reaction vessels are always dry, obviating the need for chemically and energetically demanding drying operations between batches. By this approach elimination of between-batch cleaning where re-drying the equipment to < 500 ppm water typically requires 10 L solvent/ kg of product for each Grignard step. For a peak demand of 100 MT of API per year this translates to a 2,000 metric ton reduction in total solvent use per year. In conclusion, the CSTR technology developed for the Grignard reaction has broad applicability for waste reduction and inherently safer manufacture. While this nomination is focused on Grignard chemistry, the technology reported herein may also be extended to other organometallic reactions such as heterogeneous hydrogenations. The work described in this nomination was performed exclusively within the United States at Eli Lilly and Companies Indianapolis, Indiana Technology Center.