Continuous Flow Chemistry for APIs and Intermediates (Part 2 of 2)

A Cambrex webinar overview

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Continuous flow has been an integral part of development and production within the chemical industry for over a century, but has only recently gained traction in pharmaceutical manufacture. The recent interest is due to such factors as the exploration of extreme process conditions to improve throughput and quality, enhancing process safety through improved control and lower cost production of low volume compounds.

Part 1 of this webinar series took place in April 2018 and covered a brief history of continuous flow at Cambrex, the obstacles to be solved and overcome when implementing continuous flow and a brief look at the future. Since the last webinar, we are pleased to report that Cambrex was awarded a high commendation for our continuous flow activities at the CPhI Pharma Awards 2018.

This webinar will:

- Explore relevant examples of continuous flow in the manufacture of APIs and intermediates
- Illustrate examples of available technologies for continuous flow process development, focusing on practical applications and highlighting processing advantages
- Conclude with the use of PAT (Process Analytical Technologies) and integrated control strategies, including their role in commercialization and ultimate release strategies

Cambrex was awarded a high commendation at the CPhI Pharma Awards 2018 for the Continuous Flow Centre of Excellence within the Contract Services and Outsourcing category.

Contributor

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Since joining Cambrex in 2017, Shawn has worked on a number of initiatives including the launch of the Cambrex Center of Excellence for Continuous Flow Process Development. Prior to joining Cambrex, Shawn earned his PhD in Chemical Engineering and subsequently worked for over 15 years in a variety of technical and operations roles, focusing on the development of new technologies and products.

Continuous flow chemistry is a powerful addition to the process toolbox, although its advantages are not yet fully appreciated. Dr Shawn Conway, Director of Engineering, R&D, Cambrex, describes the possibilities that it can unlock.

Continuous flow chemistry has, until recently, largely been a niche problem-solving technology, typically employed when a developed process encounters a hurdle, such as energetic chemistries or issues with capacity that requires an alternative solution. But an institutional reluctance to regard it as anything but a last resort is giving way to an increasing and tangible momentum towards making continuous flow a process of choice as the advantages become more widely understood within the pharmaceutical industry.

A number of pharmaceutical companies have invested in, and are actively investigating the use of continuous flow. Vertex and Johnson & Johnson have the first two FDA-approved continuous flow processes for drug products, meanwhile Lilly, GSK and Novartis, among others, have invested significantly in development and production capabilities, including some key collaborations. Lilly, for example, has built a dedicated, end-to-end GMP continuous flow production facility, while Novartis has been involved for more than a decade in a crucial collaboration with MIT, which is the Center for Continuous Manufacturing, culminating in the opening of a new continuous flow manufacturing facility for Novartis in Basel, Switzerland. It is one of an increasing number of such partnerships and consortia around the world that are focused on developing and testing processes and technologies.

Cambrex, as a global small molecule contract development and manufacturing organization (CDMO), provides solutions for every stage in the API product lifecycle, from early phase research and development through to supporting clinical development, process and product validation, and ultimately to commercial manufacture. The company has shown strong growth in recent years and has invested more than $260 million in its global manufacturing facilities since 2012.

Cambrex has more than 50 years of practical, industrial experience in continuous flow commercial operations, both at its site in Karlskoga, Sweden, and through its continuous flow development group in High Point, North Carolina.

The key advantages

There are five key categories for the advantages of continuous flow. The first of these is cost savings, with several studies showing that operating costs can be reduced by at least 20%, and possibly by as much as 50%, as a result of efficiencies that are gained from yield and quality improvements. Furthermore, a more optimized process can reduce lengthy reaction times and extensive work-ups, drastically lowering occupancy requirements and reducing plant time required for a given process. This not only reduces the cost of a project, but can also free up capacity for additional production and revenue.

A smaller equipment footprint and associated infrastructure can drive capital expenditure down significantly, and energy consumption and solvent use are also reduced as a result of enhanced control.

The second important benefit of continuous flow is its ability to achieve quality improvements. Frequently, a process chemist or engineer is forced to accept a less than ideal synthetic route due to infrastructure constraints, such as achievable pressures, temperatures, addition rates or equipment availability within a plant. These processes can generate impurities that must be removed, and in some situations the majority of an industrial process may be more focused on removing impurities rather than actually making the desired product. In some cases, flow can provide an avenue that avoids these impurities or at least reduces them significantly.

Safety is probably the best-known advantage of a continuous flow process. It reduces the effective volume of a unit operation, enhances control and minimizes exposure and risk so that energetic chemistries or hazardous reagents can be handled safely as a feasible option of a process. Continuous flow does not eliminate safety concerns entirely, but it does reduce the risk factors to levels that are easier to manage and mitigate.

Continuous flow also now makes it possible to use technologies that were not previously feasible on a large scale, such as photochemistry or electrochemistry, with minimal investment. Photochemistry is of great interest throughout the industry, but in a large batch reactor, a light source cannot fully penetrate into the reaction mix with consistency or efficacy. However, with continuous flow this can be achieved very easily, meaning that this technology now can be scaled up and no longer needs to be regarded as a purely academic exercise.

The fifth key advantage is that the overall development phase can be shortened considerably. Depending on the required volumes for a process as it moves through the different clinical phases, the same equipment used for early development can move with that process through later phase batches and possibly even into commercialization. Streamlining this traditional workflow could even eliminate the scale-up phases of the development cycle entirely, saving not only the costs of those batches, but also reducing the time to market by months or even years, enabling development investment costs to be recovered sooner.

Challenges of scale-up

Scaling up can be one of the most difficult aspects of the traditional batch manufacturing process, but continuous flow chemistry can address some of the major challenges and simplify scale-up. Even in the most controlled scenarios, scale-up is inherently non-linear, and this is exacerbated significantly by the variations in equipment design that are often found between facilities or through different phases of process development. Equipment geometry, material quantities and resulting addition rates, agitator design, and heat transfer capability and efficiency all drive scale-up issues associated with the core attributes of a chemical process.

Physical equipment changes can manifest on a molecular level, where the reagents of the mixture have different availability or even different collisions hampering or altering reaction kinetics. Similarly, increased quantities of materials and increased volume of a vessel cause the time to reach the equilibrium to increase at a non-linear rate. Maintaining consistency of flow and mixing profiles within a vessel is critical for efficient thermal transfer and mixing, but as these systems increase in size, it becomes very difficult to predict changes and variations between laminar and turbulent flow on a localized level within a vessel.

Heat loss and gain plays a major role in chemical reactions and controlling temperature is critical to a successful scale-up, and this is particularly true when dealing with exotherms within a reaction. The impact of scale is seen when looking at the ratio of heat transfer surface area – commonly the jacket surface area - to the overall reactor volume. In general, the ratio drops by at least an order of magnitude when a process is scaled up from a laboratory or pilot demonstration batch to a modestly sized production run.

This drop in the ratio hinders the ability to remove the excess heat from the reaction mixture, possibly putting the material at risk as it reaches a temperature limit. It can also lead to localized hot spots within the mixture, which can cause inconsistency and non-homogeneity. The practical solution to avoiding that temperature limit is frequently a reduction in the addition rate of a key reagent. However, this can lead to extended times at reaction conditions that are often not well-understood from process development work, which can in turn result in degradation, side reactions or even potentially runaway conditions.

The reduction in the surface area to volume ratio is still present in the scale-up of a flow process, however that ratio isconsiderably larger for a tube reactor: a 4-inch diameter tube has approximately the same ratio as a typical 0.5 liter laboratory reactor; while more typical tube or pipe reactor diameters will have considerably higher values, ensuring that temperature control and exotherm management can be handled in a straightforward manner.

For a flow process that may utilize stirred vessels or continuous stirred tank reactors (CSTRs) instead of tube reactors, the exotherm impact can be managed by the fact that large-scale reactors are not necessary. Smaller reactors can be put into a continuous regime, leveraging throughput and providing the necessary production while also minimizing the scale-up impact.

Agitation complications

A further scale-up challenge with conventional batch reactors is caused, or at least exacerbated, by issues of agitation. Predicting the difference in mixing profiles between vessels is a complicated process with many variables. Even with constant aspect ratios the characteristic mixing time within a vessel can increase by an order of magnitude with a simple increase in scale from 1 liter to 50 liters.

The design, size, number and location of the agitators all have a role in determining local and overall mixing performance. There are a number of modeling options to help quantify the mixing performance of a system, but assumptions may still need to be made because physical properties are not well characterized during development, and the impact of unknown physical properties, such as viscosity, solution density, particle density and particle size cannot be predicted.

Ultimately the impact of agitation manifests itself by an inability to maintain consistency. Perturbations in concentration can directly affect chemical synthesis as the availability of reagents can limit a desired reaction or potentially cause an undesired reaction. Extending reaction times to ensure full, or at least acceptable, conversion can not only have an adverse effect on product quality but can also extend processing times, thereby decreasing throughput and ultimately increasing the cost.

As with heat transfer, continuous flow is not going to eliminate these agitation issues entirely. With CSTRs, the power comes from leveraging small volume reactors and the throughput to reduce the requirement for larger scale. A telescoped process with a production rate of 500g per hour equates to an entitlement of about 84kg in a week, which is consistent with developmental throughputs using batch processes. These production rates can be achieved with small reaction and processing equipment, making aspect ratios and agitation design parameters easier to control.

Depending on the volume demands of a process as it moves through the phases of the development, volume increases or batch size demands can be achieved by longer run-times as opposed to necessitating an increase in scale: one day to make 10kg, two days to make 20kg, four to make 40kg etc. Scale-up can be effectively eliminated just by utilizing throughput.

The calculation of fluid dynamics and flow profiles in a CSTR is complex. Within a plug flow or tube reactor the profile is much easier to model with dimensionless parameters such as a Reynolds Number. A reasonable approximation of the flow regime for a given system can be kept constant or at least consistent by controlling a few parameters such as the characteristic length or diameter and the linear velocity.

In a turbulent flow regime the fluid undergoes irregular fluctuations and there is an element of randomness. Some applications may be highly sensitive and there may be a need to be more direct in establishing controlled intimate mixing between reagents or process streams. Mixing zones can easily be implemented within the flow path by a number of methods, one of the simplest of which is the inclusion of static mixers, either as pre-mixers or incorporated directly into the reaction zone itself. These come in several different configurations and lengths and can be custom-designed to ensure that the desired mixing profile is achieved. The mixer can increase in scale in conjunction with an increased tube or pipe size to maintain consistency.

Reaction kinetics

While overcoming the challenges of scale-up is a major benefit of continuous flow, an even more powerful advantage is its ability to not just simplify a process but to break through traditional process limitations and constraints.

With regard to reaction kinetics, the rule of thumb is that reaction rate doubles for every increase in 10 degrees of absolute temperature, but at larger scale there are several pitfalls to elevated temperatures. Firstly, as with elevated process pressure, elevated process temperatures often require a much more expensive infrastructure. This issue will be exacerbated by inefficient mixing in large batch reactors, extending reaction times and degrading any process time gains resulting from the accelerated kinetics.

Secondly, after a reaction is completed at elevated conditions the process is typically returned to ambient or near-ambient conditions for quenches, work-ups and subsequent process steps. The large thermal mass in a batch reactor takes a considerable amount of time to adjust, which not only further erodes process time gains but also exposes the reaction mixture to extreme conditions for an extended period of time.

Third, and finally, higher temperatures may have undesired effects on reaction selectivity, while also significantly increasing the risk profile and potential dangers with solvents being raised to or above flash points and reaction mixtures purposely being raised to the point where runaway conditions or over-pressure conditions are a real possibility.

Continuous flow offers a scalable solution to these pitfalls. At its High Point site, Cambrex has installed a small footprint high-pressure reactor skid which couples highly accurate, high pressure pumps with back pressure control to allow for the use of coil or jacketed packed bed reactors, among other configurations. The scale can be easily adjusted by changing the reactor size or a few key components, achieving throughputs of 5kg, 10kg or even more per day.

Impact of temperature

Smaller instantaneous volumes drastically minimize mixing impacts and concentration or temperature gradients, and also bring the amount of material that is in an elevated risk status to a much more palatable level. Furthermore, the reduced thermal mass makes the process of temperature quenching orders of magnitude quicker - if not nearly instantaneous - allowing for a rapid introduction to elevated conditions to drive kinetics, followed by a rapid return to ambient conditions for further processing or to protect the integrity of the products or intermediates that are being formed.

At the other end of the spectrum there are many instances in which temperatures need to be lowered to create cryogenic conditions, often to control stereoselectivity. Low temperatures may also be necessary to protect unstable intermediates. Traditional batch equipment is limited in its ability to achieve and maintain cryogenic temperatures efficiently and consistently across an entire reaction vessel. Additionally, multiple low temperature thermal cycles can have a detrimental impact on the equipment itself and lead to stress cracking and premature equipment failure. A liquid nitrogen injection can often be used to drive cryogenic conditions, but this practice is difficult to control and can become very costly at scale.

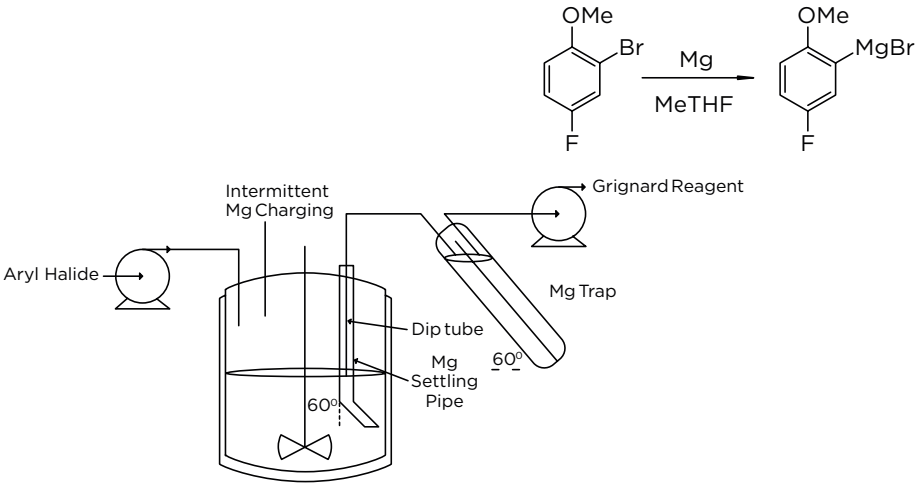
Cryogenic flow reactions are increasingly present in academic and industrial research and throughputs on the scale of 0.5 to 1.0kg/hr have been regularly proven while maintaining aggressive temperature targets. A paper by Grongsaard et al[1] describes collaborative work between Merck and WuXi for the development of a chromatography-free synthesis of an allosteric Akt kinase inhibitor. A key step in that process required deprotonation and a subsequent lithium/halogen exchange and in a side-by-side comparison of batch versus continuous flow for this challenging step, showed a yield of 85% for continuous flow, which was significantly better than the 75% achieved in batch mode. Furthermore, the concentration of a dibrominated side product was lowered from 8% to 4% using continuous methods, and the research team was able to increase the concentration of the flow streams using seven volumes as opposed to ten volumes without encountering any processing issues.

Grignard reactions

While cryogenic conditions are often required for lithiations, an alternative is using Grignard reactions. However, these reactions are challenging in their own right as they are energetic as well as being extremely air and moisture sensitive, and often necessitate the use of pyrophoric reagents. A further complication is that Grignard reagents themselves are best stored in a controlled manner as they lose potency over time leading to potential yield impacts and possible process safety implications.

A publication from Kopach et al[2] from Lilly describes the design, testing and implementation of a CSTR specially designed for a flow Grignard process. A specially designed dip tube/settling pipe combination allows for the removal of the Grignard reagent while efficiently sequestering the solid magnesium particles. Essentially a pure Grignard reagent, as seen in the synthetic scheme, is produced and delivered downstream for further use in the synthesis (Figure 1).

Figure 1: Equipment schematic and synthetic scheme for Grignard process developed by Lilly



The Grignard reactor skid at the Cambrex High Point facility is capable of producing kilograms of product per day for on-demand use, and can easily be scaled up if throughput demands require. Good agitation maintains the suspension of the magnesium within the reactor, while the stainless steel dip tube/settling pipe is behind the agitator shaft and the baffle, which is then used for taking out the reagent. A safe method for just-in-time point-of-use production of Grignard is a powerful addition to process development.

Hydrogenation

Hydrogenation is another widely used synthetic tool; however, its use within standard batch facilities is limited. It is typical to encounter upper limits of 100-150 psi for hydrogenation reactors, requiring alternative pathways that could be less efficient and require additional processing, expensive alternative catalysts, higher loadings or lengthy reaction times.

Flow hydrogenation has become increasingly investigated and accepted technology to solve these issues and strategies and technologies are available allowing for both homogeneous and heterogeneous catalyst processes. Tube reactors and packed bed columns are readily adaptable to much higher processing conditions, easily achieving pressures 10 times that of standard batch reactors. Strategies also exist for replenishing supported catalysts that are consumed over the course of a process, utilizing multiple columns with diverters or automating a semi-batch/semi-continuous process with multiple catalyst charges. By these means, a throughput of several kilograms in a day is readily achievable with a modest equipment footprint.

Work-up and crystallization

Cambrex is also developing continuous flow reactions including crystallizations, which can be incorporated within larger synthetic processes using either batch or continuous equipment. For example, mixed-suspension mixed product removal (MSMPR) is being applied to pharmaceutical processes, either as a single-stage or a cascaded multi-stage process. Tubular crystallizers can also be used if process conditions allow. Developing and implementing these is very similar, if not identical, to doing a traditional batch crystallization with solubility studies, concentration and super-saturation controls, and seed introduction all being studied, defined and implemented.

To incorporate a work-up into a continuous flow process, a standard liquid, liquid extraction can easily be designed and implemented. As an example, at Cambrex a reaction setup uses a CSTR to intimately mix the product solution with any solvent or aqueous wash that may be introduced, and the resulting stream is transferred to a separation zone, where gravity separation can be achieved (as shown in Figure 2). With a simple adjustment of separator size and the back pressure on the outlet, the location of the separation and the overall residence time can easily be adjusted and controlled. For more challenging separations, multiple layers or emulsions or challenging rag layers (an undesirable mixture of dispersed oil, water, and solids) can all be handled, with a flow membrane separator providing a clean separation to carry forward in the process.

Figure 2: Example of a laboratory apparatus utilizing hydrodynamic separation

As well as being run as discrete steps within a larger synthetic process that includes batch process steps, continuous flow steps can be telescoped to ensure that a stable intermediate or product can be achieved. Coupling multiple steps can be used to get a process safely to a stable holding point or to a surge collection point for further processing.

For example, at its High Point site, Cambrex replicated a process published by Kopach et al, involving a Grignard reaction, a formylation coupling, a reduction, quench and finally the addition of a co-solvent (Figure 3). The five reactors were coupled with multiple recirculating temperature controllers, scales and pumps, and the entire process fitted within a double-sided, walk-through hood with a total footprint of about 50 sq. ft. as shown in Figure 4.

Figure 3: Synthetic scheme for telescoped process from publication by Lilly

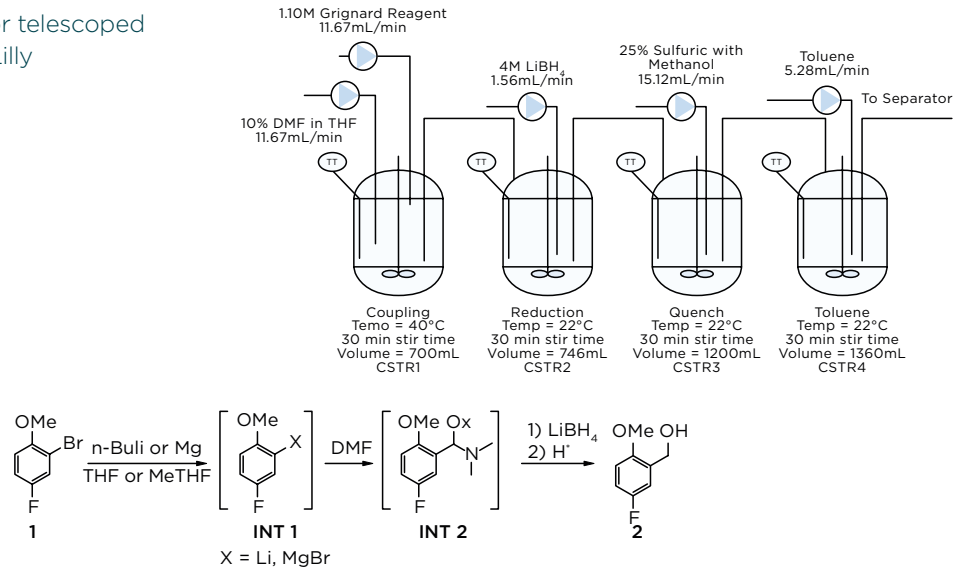


Figure 4: Telescoped process actualized in customer walk-through hood

Control and release

The use of continuous flow technologies has important implications for process control and analytics, including how they relate to release strategies. With most batch processes, critical process parameters are developed and tested throughout the development and validation stages, but quality decisions and material dispositions are often based on offline batch representative testing. Using this approach it is possible an entire production batch can be processed only to fall out of spec and require reprocessing or possibly disposal.

Continuous flow allows for real-time feedback so that measured values are available instantly and potential disruptions can be realized, captured and solved with an appropriate control strategy, avoiding a scenario where an entire batch is put at risk.

Once process parameters have been experimentally established, control strategies need to be evaluated and implemented, which could be as simple as a measurement of the flow rate. The first level of control is an open-loop system. A set point is given to an instrument, which sends a signal to a pump and then delivers the material at that target flow rate. At level two, a secondary sensor, such as a flow meter, pressure indicator, scale or other instrument, can be introduced to monitor the flow rate, providing a check and balance system that sends a feedback signal back to the drive. Constant monitoring of the flow rate means that small changes can be made in real-time to account for fluctuations.

Process analytical technology

Taking this one step further, introducing process analytical technology (PAT) for more sophisticated analysis can provide an extra level of assurance of process performance and product quality. Layering in an additional measurement to track a parameter such as reaction conversion can be utilized to make real-time adjustments to correct raw material variations or drift that may be happening within the process itself.

PAT can take several different forms. In-situ spectroscopic techniques, such as Fourier-transform infrared spectroscopy (FTIR), can be used to map reaction kinetics and then subsequently incorporated into flow streams for real-time monitoring of conversion. Peak depletion or peak growth, depending on the system, can be used during development to define optimal conditions, as well as peak intensity which can be used online during campaigns to monitor for deviations and to develop an online process control response.

Raman spectroscopy

Another technique is Raman spectroscopy. Similar to infrared, tracking wave numbers can be used to monitor reaction conditions, but with Raman, different polymorphs of a substance have unique spectra, enabling its use in a crystallization or precipitation process to ensure that the desired form is produced.

Using these spectroscopic techniques allows for monitoring specific peaks against standard curves. However, chromatographic analysis remains the standard for analytical measurements as it can provide more information and therefore a more complete image of total purity. Equipment has been developed to perform these analyses as close to real-time as possible; when a sample is pulled it is typically representative of the entire flow stream, which by definition is a complete representation of the reaction mixture in that instantaneous moment.

Release strategy

Once this wealth of data is available, developing an appropriate release strategy is critical for transitioning continuous flow processes from an academic laboratory exercise to a GMP commercial manufacturing situation. The PAT data can be used to ensure the process is operating within the window, but having a final formal release is the culmination of all that data. Importantly, it often allows for a process incorporating a single flow step embedded in a larger process to fit nicely within well-established quality systems that exist in most manufacturers.

PAT can manage the elements of process control through analysis and feedback loops, but a process upset caused by a mechanical failure such as a pump seizing, a line plugging or other mechanical malfunction, will completely upset the process flow, halting the entire stream, putting material at risk and requiring another potentially time-consuming period of start-up.

If material stability allows, a solution is implementing surge capacity locations. This can not only provide additional intermediate testing points to alleviate concerns from internal quality or regulatory procedures, but it can also maintain a supply of material for downstream processing, effectively containing any disruption and minimizing its impact.

Conclusions

For continuous flow to achieve successful widespread implementation it must be seen as a technology of choice and not just a niche problem-solving option. The complexity involved in the development and implementation of continuous flow processes requires a dedicated and committed team within an organization that includes all the technical functions while also incorporating quality, regulatory, safety and operations.

Every unit operation associated with traditional batch processing has a flow counterpart, and throughputs achievable with continuous flow can rival batch capacities and often even outperform them for small volume molecules. It is especially powerful when implemented during the development phases. Flow drastically minimizes, if not eliminates, safety and quality complications that arise from inhomogeneity and should therefore be regarded as a truly enabling technology and a powerful development tool.

References

[1] Grongsaard, et.al. Org. Process Res. Dev. 2012, 16, 1069-1081.

[2] Kopach, et.al. Org. Process Res. Dev. 2016, 20, 1581-1592.