Journal of Medicinal Chemistry

Perspective

pubs.acs.org/jmc

Continuous Flow Synthesis. A Pharma Perspective

Laia Malet-Sanz*,[†] and Flavien Susanne[‡]

[†]World-Wide Medicinal Chemistry and [‡]Development API, Pfizer Global Research and Development, Ramsgate Road, Sandwich CT13 9NJ, U.K.

INTRODUCTION

The pharmaceutical industry is going through continuous change, and it is only by adapting to change that it can survive and improve. Enormous pressure to deliver new and successful drugs to the market is impacting the research process. New strategies and innovative solutions on all fronts are needed to improve and speed the journey from early discovery to production.

In the discovery synthetic chemistry arena there has been a change in approach and mentality in the past few years: fewer compounds are being made, and design is more focused, aided by computational techniques and data analysis tools. As a result, synthetic chemists are being asked to deliver target compounds more quickly and at the same time via a synthetic route capable of delivering rapid resynthesis and supporting subsequent scale-up. Besides, they are also being asked to expand the accessible chemical space for designers.

Synthetic chemistry plays a key part in the drug discovery process. It is a vibrant science with significant research being carried out around the world, new reactivity patterns being discovered every day, along with new reactions and applications of established reactions. In terms of actual lab techniques to support these efforts, continuous processing is emerging as one of the techniques that can significantly impact the synthetic process. Several reviews[1−10] have been published highlighting the potential advantages of the technique, namely, high control of the reaction variables, which can translate into higher product quality; increased safety; possibility of reactions at high temperature and pressure (process intensification); possibility of automation; reduced manual handling; easier reproducibility; flexibility of the production volume; possibility of in-line purification techniques and reaction telescoping; increased contact surface between phases for biphasic and triphasic systems; bigger temporary catalyst/substrate ratio in heterogeneously catalyzed reactions, leading also to process intensification and a smaller footprint in a manufacturing plant. Despite its numerous advantages, the large majority of processes in the pharmaceutical industry are still run in batch. Continuous processing is, however, slowly gaining ground.

In this Perspective, we give an overview of this technique from the pharmaceutical industry point of view: how it is currently impacting in each stage of the drug discovery process, what factors are holding it from a more widespread impact, and finally where we see its future. Far from being an exhaustive review, this manuscript intends to provide the reader with a better understanding of the flow technique, its potential, and challenges. We have attempted to capture a large range of reactions where flow has a potential advantage. However, photocatalyzed reactions[11−13] and biotransformations[14] have not been included because of space constraints, despite the important flow potential in these areas.

CONTINUOUS PROCESSING AND THE DRUG DISCOVERY PROCESS AT PFIZER

At Pfizer, once a target has been defined, chemistry starts in the Medicinal Chemistry department. There, design and synthetic efforts are combined to deliver drug candidates. Initial hits are optimized to give compounds that have more druglike properties in terms of target activity, selectivity, metabolism, and pharmacokinetics. The number of series (a structurally similar group of compounds) under investigation is typically narrowed down to 1−3. When the lead discovery (LD) stage is achieved, it has been established that a druglike combination of properties is possible, but a final structure has not yet been fixed. At this stage, few batches larger than that initially required for primary testing (5−10 mg) will have been made, of around 500 mg to 1 g for pharmacokinetic (PK) studies and others. Then the candidate seeking stage (CS) begins. Whereas in the pre-LD stage the design is more speculative, after LD design is more focused and a reduced number of compounds are typically prepared. Libraries of compounds will be relatively small (less than 100 compounds), and key singletons will be prepared, close structural analogues to existing leads. When a particular compound looks interesting after primary testing, 1−2 g of solid material will be immediately required for PK and initial toxicity studies. Synthetic chemists need to be in a position to deliver these quantities quickly. Clearly, the better the synthetic route that is available, the faster this can be delivered. Large scale routes have to be efficient, safe, and reliable. Yields obtained in small scale can often translate poorly on scale, and further optimization is required. If a compound looks interesting, chemists in Medicinal Chemistry will start to liaise with the next department in line: R-API (research active pharmaceutical ingredient). They will allocate some resource to start looking at the route. Then a first exploratory toxicology study (ETS) batch (~5−30 g) will be required for in vivo toxicity studies, which is usually still made within Medicinal Chemistry. If successful, a candidate will be nominated, officially signaled by the candidate alert notice (CAN), and R-API will take over. They will optimize the route for further scale-up and deliver a larger second ETS batch (~30−500 g) for second species toxicity studies. If the compound progresses satisfactorily, it will go to D-API (development active pharmaceutical ingredient) for the development of the commercial route. Optimization of the route will take place

Received: May 16, 2011
Published: January 27, 2012

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098

in each of these stages and kilograms of material will be provided for the clinical studies (Figure 1).

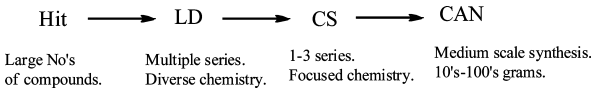


Figure 1. Main drug discovery stages up to candidate nomination.

However, this theoretical scenario can be slightly altered depending on individual project requirements. Time pressures will result in routes being scaled with suboptimal chemistry and bigger batches being prepared at risk while awaiting key experimental data. There is a continuous balance between speed and optimization. This also means that departments are forced to work closely to smooth the transitions. It is in these transitions where flow chemistry can play a key role, and it is only if the technology is embraced in all the departments that the benefit can be maximized.

Continuous processing can provide advantages at each stage of the process, and it should ideally start from Medicinal Chemistry. If a route is carried out in flow within Medicinal Chemistry, material up to the first toxicity batch can be delivered with minimum optimization. Besides, it is more likely that subsequent departments in development will utilize the existing flow route. Manufacturing is another business division within the Pfizer Corporation, and it is the customer for R& D. Since the existing manufacturing equipment is batch equipment and large capital investment is required to implement a flow process in manufacturing, the manufacturing division needs a significant benefit to be able to offset such cost. This can be a common barrier for the flow process uptake in manufacturing. We believe that once that initial barrier is broken, more continuous manufacturing processes will be developed. In the meantime, we must not forget the advantages that it can provide in all the stages of research and development to provide material for animal studies and up to initial clinical trials with greater speed.

Within early research, however, an important consideration is how much time should be invested in optimizing the route of a particular compound. The balance of speed versus optimum chemistry will be shifted to the former for early stage projects and toward the latter in more advanced projects. Another important factor is how general the transformation can be. In other words, a particular step or set of steps in a synthesis can be key not only for one singleton but for many project compounds. In that case, time investment in route development can have a significant project impact. Sometimes route development is required to open up new areas of design: new structural motifs that can potentially be of interest to medicinal chemists but are poorly precedented or not present at all in the literature. Certain compounds are greatly desired, but chemistry is very poor and considerable time and effort are spent to make and test them.

To synthetic chemists the many advantages of flow chemistry are very attractive, but the two major factors that have to be considered are high control of the reaction variables, which can result in an improved reaction profile and safety and the quick scalability with minimum optimization of the reaction conditions up to ~10's to 100's of grams on case by case bases.

■ CHALLENGES AND POSSIBLE SOLUTIONS

Like all the new technologies,[15] continuous processing faces an initial challenge: people are familiar with batch processes. The mind set when designing a new reaction has to be slightly changed. Instead of reaction time, residence time in the reactor needs to be considered, which will depend on the flow rate and the volume of the reactor. Biphasic reactions with a liquid/solid system are usually not tolerated, and changes to homogenize the mixture are required, especially for flow reactors with a small internal diameter. All reagents need to be fed to the reactor with the minimum number of inputs in order to minimize the complexity of the system. Time pressures often prevent people from investigating the possibility of flow, and not everyone is ready to take the challenge or to invest the time to learn it. Continuous processing requires certain engineering skills, including fluid dynamic and kinetic understanding in a discovery arena and a much deeper understanding in the development arena. The availability of increasingly sophisticated commercial systems is making it easier for chemists in research, who usually have limited engineering skills. However, chemists in Development have to work closely with engineers to develop large scale flow routes. Besides, there is also an initial capital investment required for the purchase of flow equipment.

According to a report published by Lonza chemists,[16] half of all reactions would benefit from a continuous approach based upon their reaction kinetics. However, solids are present in more than 60% of these reactions so that less than 40% could be actually transferred to flow without modifications. Sometimes, modifications in the process (solvents, reagents, etc.) can overcome this issue, and with increasing knowledge and experience, our ability to do so will increase. It could be also argued that in cases where dissolution is the limiting rate, if the reactants are in solution, then the reaction could be faster than if they are partially soluble.

A process where the product precipitates out and can be separated by filtration is very desirable in batch chemistry because it aids purification, but it can be a problem in continuous process unless the product is in solution inside the reactor and it precipitates only upon cooling or in contact with a further solution or a solvent. Technical advances that allow handling of solids in continuous processing are still needed. Mesoscale dynamically mixed flow reactors that can handle solids have already come into the market (see "Dynamically Mixed Flow Reactors"). Some large scale tubular continuous reactors and continuous stirred-tank reactors (CSTR) can handle some liquid/solid biphasic systems, but the possibilities are still limited in the laboratory environment.

Some straightforward and clever solutions have been devised in particular cases. Recently Kelly et al.[17] have reported the interception of the flow stream with a suitable organic solvent to fully dissolve the reaction mixture before the back pressure regulator, which is one of the most common points of blockage (Figure 2a). A similar concept was previously reported by Hopkin et al.[18] where a stream of water was added to fully solubilize the NaBr byproduct prior to the back pressure regulator (Figure 2b). Another alternative to effectively dissipate solid aggregates, which is becoming now more popular, is the use of ultrasonic baths (Figure 2c).[19−21] In certain cases, solids can be handled successfully in continuous processing like in the nanoparticle generation[22] or, as demonstrated by Buisson et al.,[23] in a hydrogenation reaction. Finally, handling of solids through microreactor channels is also possible by utilizing disperse-phase droplets as individual reactors, as demonstrated by Poe et al.[24] It is worth highlighting the work carried out by Buchwald, Jensen, and coworkers[25] to understand why solids lead to clogging in Pd catalyzed C−N coupling reactions. They concluded that there are mainly two mechanisms: bridging, which could be eliminated by

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098

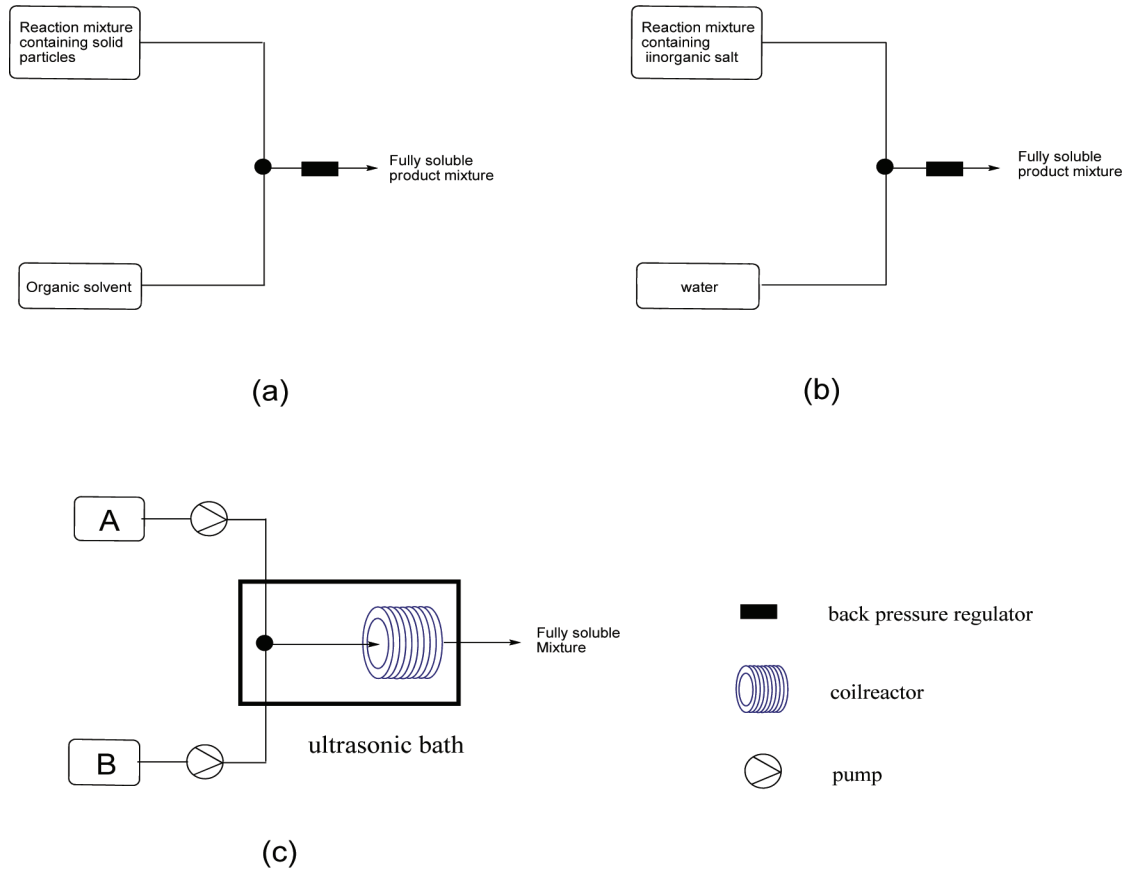


Figure 2. (a) Introduction of an organic solvent stream before the back pressure regulator. (b) Introduction of a water stream before the back pressure regulator. (c) Use of ultrasonic baths.

acoustic radiation, and constriction, which could potentially be managed, at least to a certain extent, by increasing the fluid flow velocity.

Besides the 50% of reactions that can benefit from a flow approach,[16] there are some that are only enabled by continuous flow and their scale-up would be otherwise impractical. This is very difficult to quantify, as chemists tend to avoid such steps and look for alternative routes, which in some cases can be longer or less convenient. Continuous processing can thus open up the available range of reactions and therefore provide more flexibility in route design. This area will now be discussed in greater detail.

OVERVIEW OF THE LABORATORY EQUIPMENT AVAILABLE

Continuous flow reactors can broadly be divided into microscale, mesoscale, and large scale.

Microscale Flow Reactors or Microreactors. The main characteristic is that the channel diameters are small, usually in the micrometer range, and are available in a wide number of materials and shapes. They operate at a laminar flow rate, and the mixing along the channel happens by diffusion. Mixing elements with even smaller channel dimensions may be incorporated where different streams meet.

A microreactor can operate under "plug flow" or "segmented flow" conditions. We refer to "plug flow" when mixing in the direction of the fluid flow is minimized and therefore each "plug" or imaginary cross-section of the channel of a differential length in the microfluidic channel is perfectly mixed in the radial direction and reacts independently of the "plug" ahead or behind it. In plug flow, steady state can be reached where the concentration of reactants at each point in the reactor is constant in time. In "segmented flow", however, steady state is not achieved. We refer to "segmented flow" when the reaction tails at the beginning and at the end of the reaction segment due to dispersion are a significant part of the reaction length.

Reactors can be further classified into three types:

Microchips. The channel geometries are fixed, etched into different materials such as glass, silicone, stainless steel, metals, or polymers. The volumes range from 1 μL to 1 mL and the channel diameters from 50 to 1000 μm depending on the system.[26]

Microscale Coil Reactors. These are commonly made of PTFE but also exist as PFA, PEEK, stainless steel, Hastelloy, and copper.

Microscale Packed Tubular Reactors. These are typically metallic or glass tubes packed with some solid supported reagent, catalyst, or scavenger. Their diameters tend to be larger than those of chip and coil reactors, and they can range from 1 mm to 2 cm.

By combination of HPLC pumps, peristaltic or syringe pumps with a reactor, a fully functional flow system can be created. Alternatively, there are also several integrated commercial platforms, the versatility of which has increased significantly in the past couple of years. Most of them now incorporate software control, fraction collector, and the like.

Examples of fully automated microfluidic platform include the Labtrix-S1 microreactor system,[27] the Africa from Syrris,[28] Future Chemistry,[29] and the Conjure system from Accendo.[30] All these systems are suitable for preparing small amounts of material or for reaction optimization because of the small reactor sizes.

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062–4098

Other common commercial platforms with larger reactor sizes and therefore able to prepare larger amounts of material include the Vapourtec,[31] the Uniqsis,[32] the Asia from Syrris,[33] and the Propel system from Accendo.[34] This second group of reactors represent the most commonly used ones among research laboratories, as they can prepare synthetically useful amounts of material (up to 100's of grams). Although reaction optimization is also routinely carried out, a systematic optimization with a large set of conditions being screened is more efficient and uses less material in the microfluidic platforms formerly mentioned.

Another example is the Alfa Laval ART LabPlate,[35] a stainless steel plate reactor with a volume of 10 mL, which can still be considered as a microreactor because of the small internal diameter.

There are also the more specialized ThalesNano systems,[36] which are designed to carry out reactions at high temperatures and pressures like the X-Cube Flash, hydrogenations like the H-Cube and H-Cube Midi, or ozonolysis like the O-Cube. Another commercial continuous hydrogenation reactor is the FlowCAT reactor from HEL.[37]

Mesoscale Flow Reactors. The channel diameter can range from 1 to 10 mm, and they are designed to produce larger amounts of material, around 10 to 100's of kilograms. Production capabilities will depend on the specific characteristics of the reactor and the process. Manufacturers tend to claim very high production capabilities, but those would only be true for extremely fast reactions and at high concentrations.

There are also the systems that comprise several microreactors in order to increase the total volume and therefore the throughput. They can be classified as mesoreactors despite having a small internal diameter. One of the earliest examples in this group was the CYTOS system from Cellular Process Chemistry Systems GmbH.[38]

IMM[39] provides a whole range of stainless steel microreactors, heat exchangers, and mixers for large scale applications.

Another important example is the Corning's Advanced-Flow glass reactor,[40] which is designed for handling liquid/gas/solid mixtures (slurries with average particle distribution of around 30 μm).[23,41]

Large Scale Flow Reactors. Continuous manufacturing solutions have been applied to other industries like paint, polymers, food, water treatment, chemical, and petrochemical with great success, and only now have they started to break through into the pharmaceutical industry.

Companies such as Alfa Laval provide expertise and appropriate equipment for large scale continuous reactions and alternative workup unit operations.[42] Other companies such as Sulzer (Sulzer Chemtech) provide a large range of continuous reactors and alternative technologies like heat exchangers, static mixers, and plug flow reactors.[43] Another example is Chemineer, which provides reactors and other equipment for large volume producing industries (>100 MT/year).[44]

■ PROCESS INTENSIFICATION

Process intensification (PI), originally developed in the 1970s for the bulk chemical industry, can be defined as the ability to obtain equivalent or better results in terms of purity, selectivity, and yield of the desired product in a reduced period of time and therefore with an enhanced throughput, by increasing parameters such as temperature and pressure. This usually translates into a reduced cost, which has been the main driver behind PI. In this area continuous flow has a significant impact, as reactions at very high temperatures and pressures can be safely carried out, solvents can be heated above their boiling point, and residence time in the reactor can be accurately controlled.

Although process intensification can be very beneficial in the bulk chemical industry, it has not always been beneficial in the pharmaceutical industry. The required product specifications are very strict, and small increases in certain impurities, even if the overall purity level is the same, will not justify the benefits obtained by intensifying the process. As molecular complexity increases, the number of potential byproducts also increases. However, as the value of the process versus the API (active pharmaceutical ingredient) increases, mainly because of the emerging generic market, PI is becoming more relevant. The effects of PI will thus have to be carefully assessed on a case by case basis.

Flash chemistry is a closely related concept defined by Prof. J. Yoshida, which will be discussed later in more detail.[45,46]

V. Hessel goes further and defines the concept of novel process windows.[6] According to him, benefits can be maximized by completely rethinking the process and making use of less conventional process conditions to take full advantage of the technological capabilities of flow chemistry.

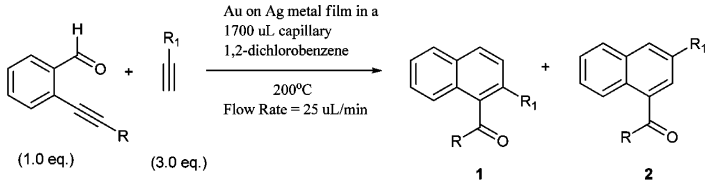
Microwave reactions have become popular in research laboratories, as they can intensify processes significantly by reducing reaction times and even in some cases preventing catalytic cycles from collapse. However, besides the safety concerns of having large pressurized batch vessels at very high temperatures, microwaves have a limited penetration and create temperature gradients within large vessels, which makes the scale-up of batch microwave reactions difficult. Continuous flow is a good way to scale-up batch microwave reactions, either as microwave assisted continuous organic chemistry (MACOS)[47−49] or as thermally heated continuous flow reactors.[50,51] In the same way, small scale microwave batch reactions are sometimes used to optimize reactions (screening), which will be scaled in a continuous flow system.

In some cases with metal catalysts the reaction intensification observed in a microwave can be the result of localized hot spots at significantly higher temperatures than the reaction bulk temperature measured by the IR probe of the microwave. This is believed to be the case in the gold-film-catalyzed benzannulation reaction carried out by Shore et al.[52] These workers coated a microcapillary with a porous gold film on top of a thin silver mirror, which was heated by microwave irradiation (Figure 3). A direct comparison of a reaction was carried out at 190 °C in an oil bath and in a microwave with a significant increase in conversion with the latter (14% vs 68%). The authors observed a degradation of the gold film after 2 h of continuous reaction at 100 °C, which suggests that further improvements are required for long-term stability of the metallic coating.

This hot spots theory was further investigated by Shore et al.[53] in their three-component MACOS facilitated synthesis of propargylamines where Cu and Au coated capillaries were employed. They were able to measure temperatures of 950 °C in the middle of the capillary, which led them to compare this process to flash vacuum thermolysis (FVT) reaction but without any vacuum being required.

Having a significantly enlarged reaction space in terms of temperature and pressure increases the possibilities of finding an optimum reaction zone. It is possible, for example, to reach the

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098



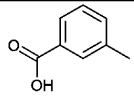
R	R_1	Yield (%)	1:2
		78	75:25
	$(Me)_3Si$-	62	Only **2**
		52	58:42
		62	Only **1**
		60	Only **2**

Figure 3. Examples of benzannulation reactions carried out in a coated microcapillary under microwave irradiation.[52]

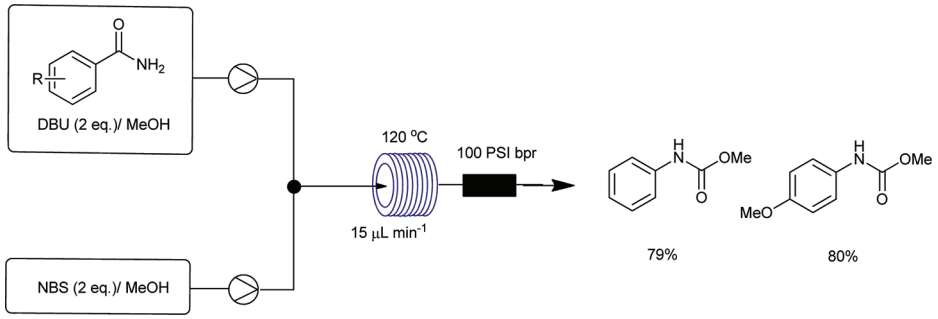


Figure 4. Examples of Hoffman rearrangement of aromatic amides with DBU and NBS.[57]

regions of near-supercritical or supercritical (sc) conditions. Beyond the critical point of pressure and temperature, liquids and gases are indistinguishable fluids, supercritical fluids (scFs), which exhibit very particular physical properties. For example, $scCO_2$ has been used as a very good and environmentally friendly nonpolar solvent, scH_2O has increased dissolving capacity and acidity, and $scCH_3OH$ can be used as solvent and catalyst in esterification reactions because of its elevated acidity.[54]

A very good example of the use of $scCO_2$ is the recent work by Mello et al.[55] in which they were able to tune the selectivity of the oxidation of sulfides to sulfoxides or sulfones in $scCO_2$ by varying the pressure of the system and the hydration of the solid supported catalytic oxidant (hydrated [2-percarboxyethyl]-functionalized silica) (Figure 3).

Process intensification in continuous flow has been demonstrated for a variety of reactions like Diels–Alder, thermal rearrangements, Claisen rearrangements, nucleophilic displacements, etc.[54,56]

An example is the Hofmann rearrangement studied by Palmieri et al.[57] These workers used the previously reported conditions of NBS/DBU; however, their continuous flow method allowed for a much faster reaction than typically reported in batch reactions. They used methanol as a solvent, a temperature of 120 °C, and an effective residence time of 1 min, whereas the reactions in batch typically take 25 min or more in refluxing methanol (Figure 4). For this investigation they used a microfluidic platform[58] initially designed for positron emission tomography (PET) compounds, therefore using very small amounts of material (50–100 μg/reaction). The reactions were readily scaled to 1 g of material with the Uiqsis FlowSyn system.

Several other examples of process intensification like organometallic reactions, metal catalyzed coupling reactions, and others will be discussed in this review.

MORE CONTROL: BETTER RESULTS AND MORE SAFETY

Flow reactors exhibit a high surface/volume ratio, which provides a very accurate temperature control and the possibility to be heated and cooled very quickly. This means that any exotherms generated in the reaction can be dissipated very quickly. This, in some cases, has been associated with a cleaner reaction profile, and several examples are provided below.

The high temperature control coupled with reduced reactor volumes translates into higher safety and control of risk. In the

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062–4098

event of a reactor breakage or explosion, damage is limited. In industry, safety testing of all processes is of imperative importance. In early research, safety testing must be carried out whenever any high energy functionality is involved. This requirement becomes more rigorous, and it is extended to all reactions as scale increases to characterize the temperature accumulation and a potential runaway situation. However, in a flow reactor, despite a higher heat transfer coefficient and larger contact area between process stream and heat transfer fluid, a runaway situation could potentially happen more quickly if the cooling system failed. This is due to the presence of a lower thermo mass to absorb the energy released. In practice, this translates into avoiding certain "dangerous" transformations in nonflow chemistry if at all possible. Continuous flow allows these transformations to be carried out with a limited and understood risk. Besides, more material can be produced by flowing for longer or altering slightly the parameters (e.g., double the flow rate and the reactor volume). Therefore, there might be no need to alter a route if more material is required, for example, for animal testing at short notice. This is very appealing in research, and it has boosted the use of these previously avoided transformations, as in some cases this represents a shorter or more efficient route than trying to avoid the highly reactive functionality transformation.

Some examples of reactions where these advantages are very important are the following:

Nitrations. Nitrations, classical transformations still in common use, are usually highly exothermic, with potentially explosive intermediates and products that are prone to side reactions. This reaction can benefit substantially from continuous flow. However, the highly corrosive nature of the reagents required for many conventional nitration reactions can corrode traditional pumps, and as a result, specialized equipment needs to be used. Commercial suppliers have already launched acid resistant flow systems that can handle H_2SO_4/HNO_3 mixtures. In Pfizer we now carry out nitrations routinely in continuous flow with the acid resistant Vapourtec R2+/R4 module (Figure 5).[59]

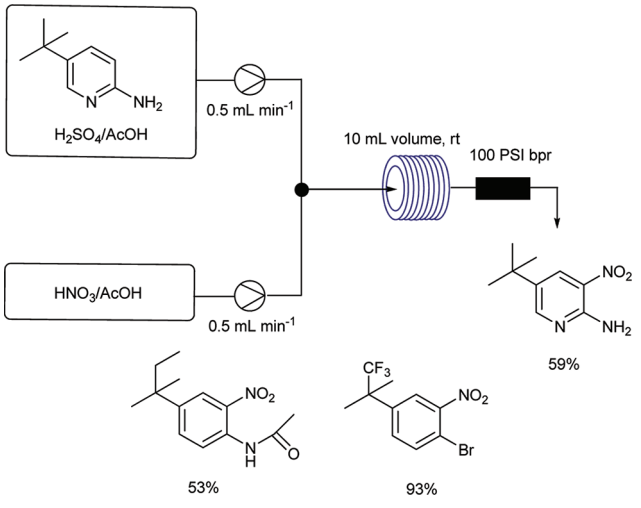


Figure 5. Examples of nitrations carried out at the Sandwich Laboratories, Pfizer.[59]

Kulkarni et al.[60] and others[61−65] reported on the advantages of continuous flow nitration. They were able to improve the selectivity profile of the product versus the corresponding batch reaction. The same authors also reported later another nitration process carried out using syringe pumps.[66] Continuous flow allowed them to perform the reaction at higher temperatures, affording a more favorable ortho/meta ratio of products. The mixing was key to avoiding local concentration gradients, especially at higher temperature where the reaction occurs very quickly and the choice of micromixer was found to affect the reaction.

Chemists at AstraZeneca carried out a large scale nitration of 3-methyl-1*H*-pyrazole (**7**) to 3-methyl-4-nitro-1*H*-pyrazole (**8**) in continuous flow.[67] They were able to carry out the reaction on multigram quantities of material, avoiding by temperature control the formation of a bis nitrated byproduct believed to be 3-methyl-4,5-dinitropyrazole (**9**), which had been classified as a detonating explosive by oxygen balance calculations (Figure 6).

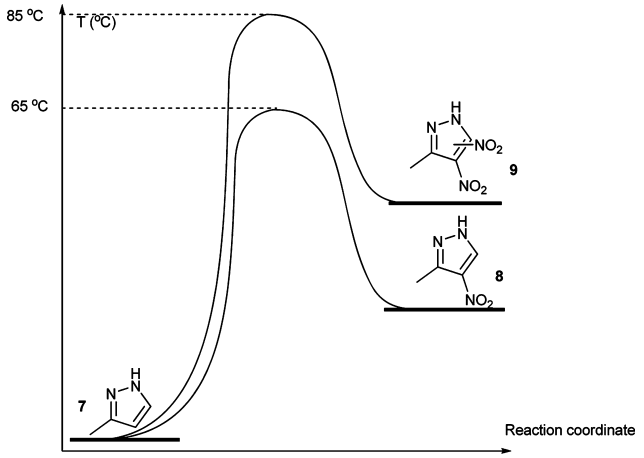


Figure 6. Multigram nitration of 3-methyl-1-*H*-pyrazole.[67]

Fluorinations. Fluorination is another type of reaction that can benefit enormously from the use of continuous flow. The large exotherm associated with electrophilic fluorinations using elemental fluorine as F_2/N_2 mixtures can be better controlled in microreactor devices. Several purpose-made microreactors have been constructed.[68−70] Chambers, Sandford, and co-workers[71] successfully used a microreactor made of nickel and polytrifluorochloroethylene (PTFCE) for the direct fluorination of organic compounds. The reaction conditions were adjusted to achieve "pipe flow". We refer to "pipe flow" when in a biphasic mixture of liquid and gas, the gas forms an internal cylindrical pipe that is surrounded by the liquid within the reactor channels. The cross section would then show concentric circles corresponding to the liquid phase (outer) and the gas phase (inner) to maximize contact between the two phases (Figure 7). With this reactor they selectively fluorinated 1,3-dicarbonyl compounds.

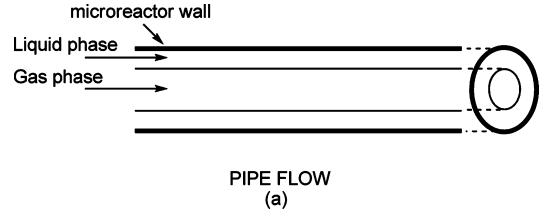


Figure 7. Pipe flow diagram.[71]

The same device was also used by this group to fluorinate deactivated aromatic systems[72] and benzaldehyde derivatives.[73]

Scientists at Syngenta also designed a purpose-made microfluidic reactor for routine fluorinations in their agrochemical

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098

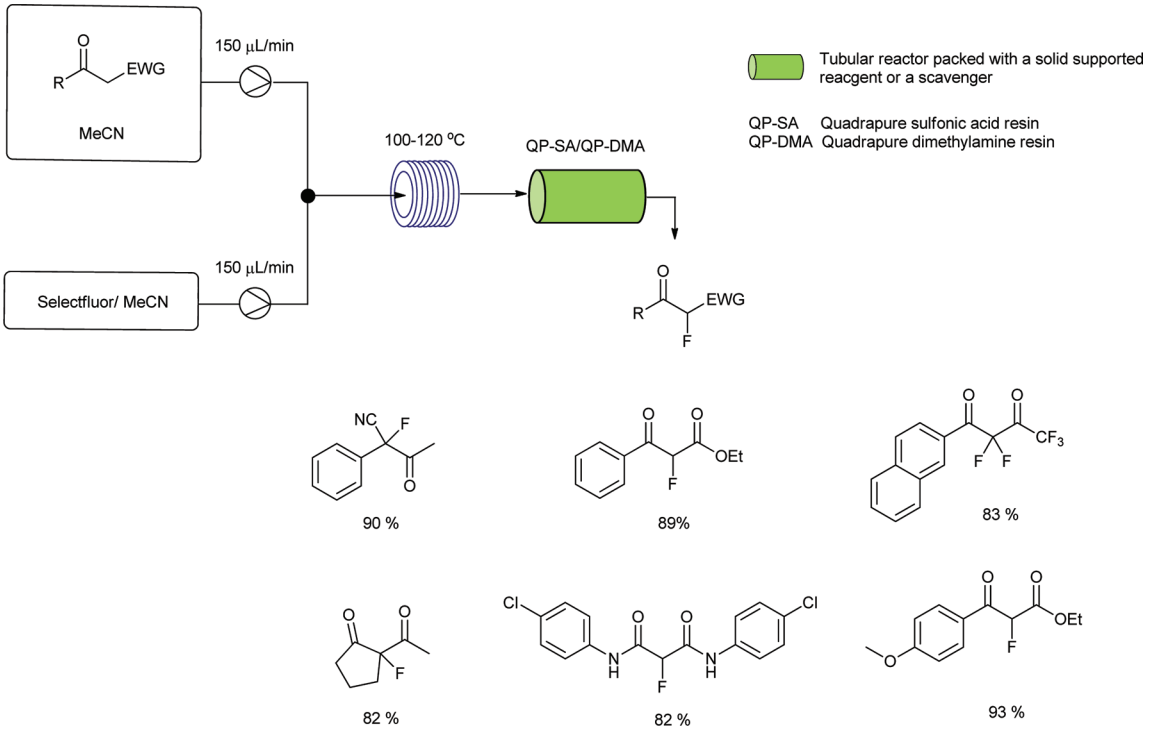


Figure 8. Examples of α-fluorinations of activated carbonyls using Selectfluor.[78]

research department.[74] The handling of F_2 gas has associated hazards, and suitable safety measures have to be in place to avoid exposure. Fluorinations are reactions commonly avoided in medicinal chemistry departments because of the infrastructure required to handle F_2 gas. Instead, alternative fluorinating reagents such as DAST or Selectfluor are used.

However, DAST also has some safety issues to consider. It is known to be unstable to heat and to decompose violently.[75] Therefore, it is recommended that DAST is heated with extreme caution and not above 90 °C.[76] In Medicinal Chemistry at Pfizer, Sandwich, U.K., as a general rule, DAST is not heated above room temperature. Continuous flow reactors, however, offer a safe environment to heat DAST in a controlled manner, providing a closed environment and the possibility of in-line quench of excess reagent.[76] Besides, plastic vessels are recommended, as some of the decomposition products of DAST will readily etch glassware, but PEEK, PFA, or PTFE reactor coils and HPLC fittings are fully compatible with this reagent.

The safe and convenient use of DAST in microreactors has been reported by Gustafsson et al.[77] and Baumann et al.,[76] who subsequently reported the use of Selectfluor[78] with commercial continuous flow devices like the Vapourtec R2+/R4 (Figure 8).

In the Pfizer labs at Sandwich, U.K., fluorination reactions are commonly carried out in continuous flow. An example is the successful fluorination of 3-bromopyridine-2-carbaldehyde (Figure 9).[79]

Reactions with Organometallics. Organometallic species like organolithiums are highly reactive. Therefore, they are usually generated and reacted in situ. Because of their high reactivity, reactions are conducted at very low temperatures (typically below −50 °C) and involve slow addition of reagents to prevent temporary temperature gradients and general temperature increase. This is time-consuming and can lead to

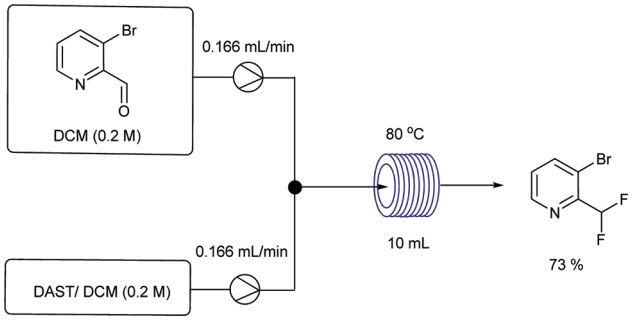


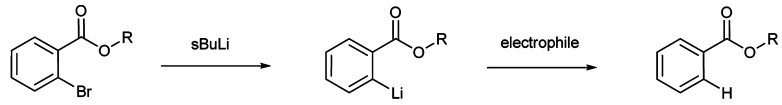
Figure 9. Difluorination of 3-bromopyridine-2-carbaldehyde.[79]

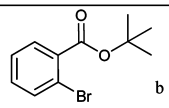
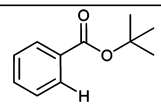
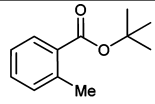
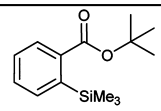
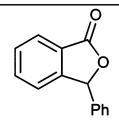
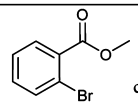
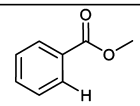
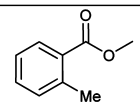
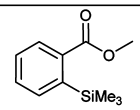
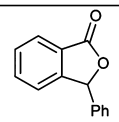
variability. These issues become more significant as scale increases, as does the cost associated with such processes.

Continuous flow is having a big impact in this area. Because of the high temperature and accurate residence time control, it is possible to generate highly reactive organolithium species and react them in situ in a very short time. This allows reactions to be performed at significantly higher temperatures than they would be in batch, increasing the reaction rate and preventing degradation of the organolithium compounds before they can react. Prof. J. Yoshida refers to this approach as flash chemistry. He defines this as an area of chemical synthesis in which extremely fast reactions are conducted in a highly controlled manner to produce desired compounds with high selectivity.[45,46] This would not be possible in a batch reactor, as the lifetime of the reactive intermediate at high temperature would be far lower than the time required to add the substrate without creating a large exotherm.

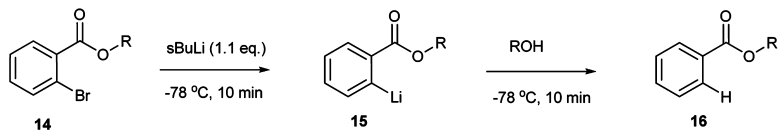
Yoshida and co-workers[80] have described the reaction of organolithium compounds in microreactors in the presence of highly reactive ester functionalities at temperatures from −48 to 0 °C (Figure 10a), some of which did not yield any desired product in batch at −78 °C (Figure 10b).

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098



Ester [a]	Electrophile	Product	Yield (%)
 b	*t*-BuOH		93
	MeI		88
	Me_3SiCl		96
	PhCHO		82
 c	MeOH		74
	MeOTf		95
	Me_3SiOTf		82
	PhCHO		85

(a)

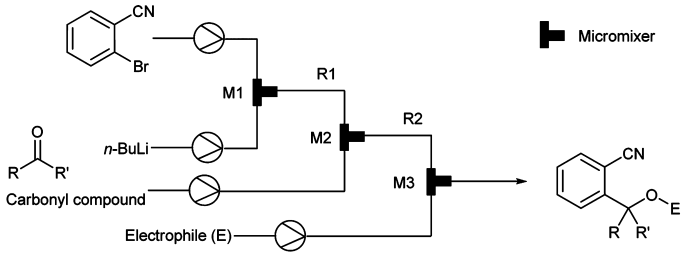


o-Bromobenzoates (14)	Yield of 16 (%)
R = *t*Bu	61
R = *i*Pr	12
R = Et	0
R = Me	0

(b)

Figure 10. (a) Optimized Br/Li exchange reaction of alkyl *o*-bromobenzoates followed by reaction with an electrophile in a flow reactor. Letters in the first column represent the following: a, *o*-bromobenzoates in THF (0.1 M), *s*-BuLi in hexane/cyclohexane (0.42 M), and an electrophile (3.0 equiv) in THF (0.6 M); b, residence time = 0.01 s, 0 °C; c, residence time = 0.02 s, −48 °C. (b) Br/Li exchange of alkyl *o*-bromobenzoates followed by reaction with ROH in a batch reactor.[80]

dx.doi.org/10.1021/jm2006029 | *J. Med. Chem.* 2012, 55, 4062−4098



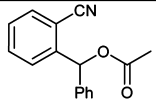
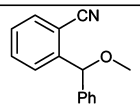
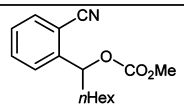
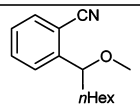
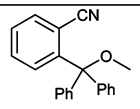
Carbonyl compound [a]	Electrophile	Product	Yield (%)
PhCHO	AcCl		97
	Me_2SO_4		83
n-HexCHO	MeO_2CCl		75
	Me_2SO_4		51
Ph_2CO	Me_2SO_4		66

Figure 11. Reaction of *o*-lithiobenzonitriles with carbonyl compounds followed by reaction with electrophiles.[81]. Superscript letter "a" indicates reactions conducted at 20 °C with residence times R_1 = 0.01 s and R_2 = 2.3 s.

More recently, Yoshida and co-workers[81] have also described the successful reaction of cyano-substituted organolithium species with electrophiles like ketones, which were subsequently trapped with electrophiles (Figure 11).

These results demonstrate substantial differences between batch and flow, and in these cases flow can aid the scale-up process significantly. In a recent review Valera et al.[82] suggested that some organometallic reactions are best carried out in a "semibatch process" by slow addition of the organometallic reactant into the batch vessel. In this case, this approach is clearly not possible, as the metal−halogen exchange needs to be carried out first, before adding the electrophile.

The work above-described by Yoshida was done using syringe pumps, which limit the scale of the process to the syringe volume, being a flow-batch type process, although syringe pumps retain the other advantages of flow processes. In industry a system with HPLC pumps is generally favored, which is fully continuous, and it has the potential for a higher throughput.

However, HPLC pumps with ceramic heads are not compatible with strong lithium bases like *n*-BuLi and LiHMDS. Venturoni et al.[83] devised a clever method to overcome this problem: a dual loop injector, which is continuously being refilled by a liquid handling robot and prevents any contact of the organolithium base with the pump heads. The beauty of this method is that the system is totally automated and controlled by software, and therefore, it can be envisaged as a tool for running several unattended reactions in parallel, either for optimization purposes or for analogue generation as part of a medicinal chemistry program. Using this dual loop injector system, these workers were able to successfully handle *n*-BuLi and LiHMDS (Figure 12).

Since this publication was released, commercial flow systems have improved, and they now offer more resistant pumps that can handle *n*-BuLi as well as strong acids.[31] They also offer cold reactors that can accurately control subzero temperatures.[31,32]

Chemists at Lonza[10] successfully scaled-up a reaction with an organolithium intermediate up to 700 kg of product using a mesoreactor and a static mixer for the lithium exchange and coupling steps (Scheme 1). They stress the homogeneous quality of the product obtained, which facilitated workup operations. They calculated an approximate cost saving of 9% compared to batch production.

Other organometallics like Grignards and organozincs have also been used in continuous flow. The first reported industrial use of Grignard reagents in continuous flow was by scientists at Merck.[84] With five parallel microreactors in the millimeter range they were able to obtain an improved 92% yield, compared to the 88% and 72% obtained in the 0.5 L and 6.3 m^3 batch reactor, respectively.

Rencurosi and co-workers[85] have reported the use of Grignard reagents with a commercial Vapourtec R2+/R4. They reacted alkyl and aryl Grignards with aldehydes and

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098

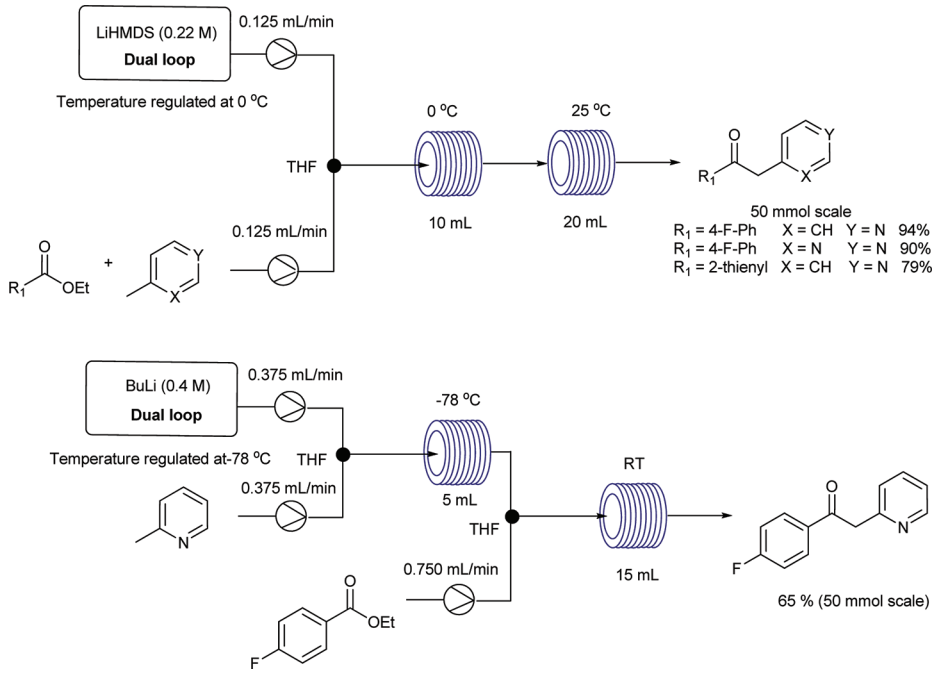
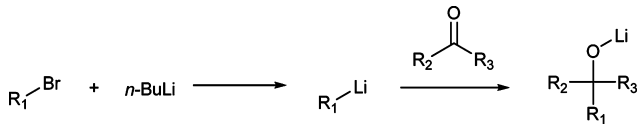


Figure 12. Examples of deprotonation with LiHMDS and *n*-BuLi using the dual loop injection system, followed by reaction with an ester in continuous flow.[83]

Scheme 1. Reaction with an Organolithium Intermediate Carried Out up to 700 kg Scale at Lonza[10]



ketones to form the corresponding alcohols and were able to conduct the reactions at room temperature with excellent yields. In their optimization experiments they noticed that the equivalent batch processes needed a temperature of at least −20 °C to produce similar results. They also observed good chemoselectivity with other electrophiles like cyanides (Figure 13).

Grignards reagents in flow have been also used by Qian et al.[86] in a Vapourtec R2+/R4 as part of a four-step flow synthesis of a δ-opioid receptor agonist (Figure 14).

The use of organozinc reagents was reported by Pericàs and co-workers[87,88] in an enantioselective addition to alcohols catalyzed by a chiral solid supported β-amino alcohol. Reaction times were significantly decreased compared to the corresponding batch processes with the same or better results in terms of conversion and enantioselectivity. This is probably due to the higher temporary catalyst/substrate ratio existing in the flow setup, combined with the fact that the resin beads are not affected by the mechanical stirring, as they are in batch mode (Figure 15).

Reactions with Gas Release and/or Explosive Intermediates. Reactions with gas generation are always a safety concern. They can be performed in a more controlled manner in continuous flow, although they will still have to be carefully assessed before using larger volume continuous reactors, as the damage in the event of an explosion would be greater. For larger scale processes, vented CSTRs or the incorporation of release valves can provide an advantage, as they are able to

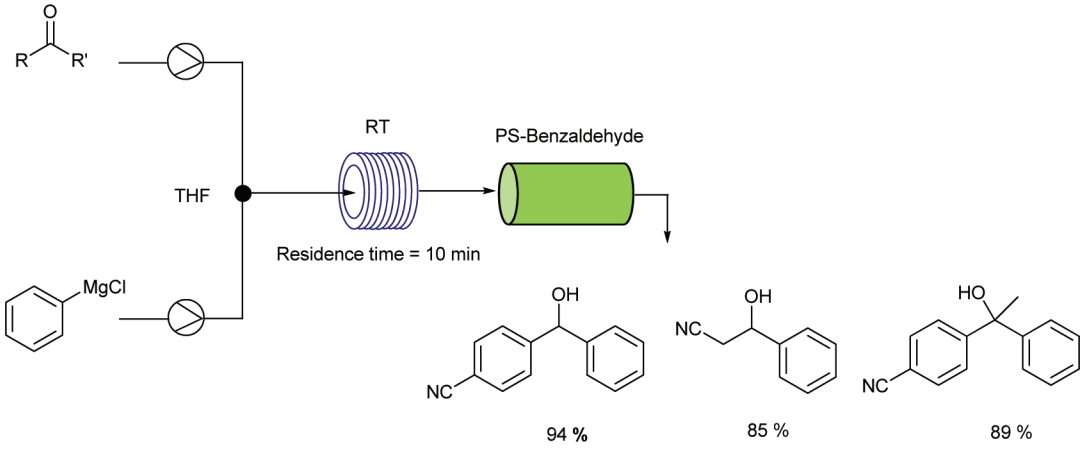


Figure 13. Examples of benzyl magnesium bromide addition to aldehydes and ketones in the presence of nitriles.[85]

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098

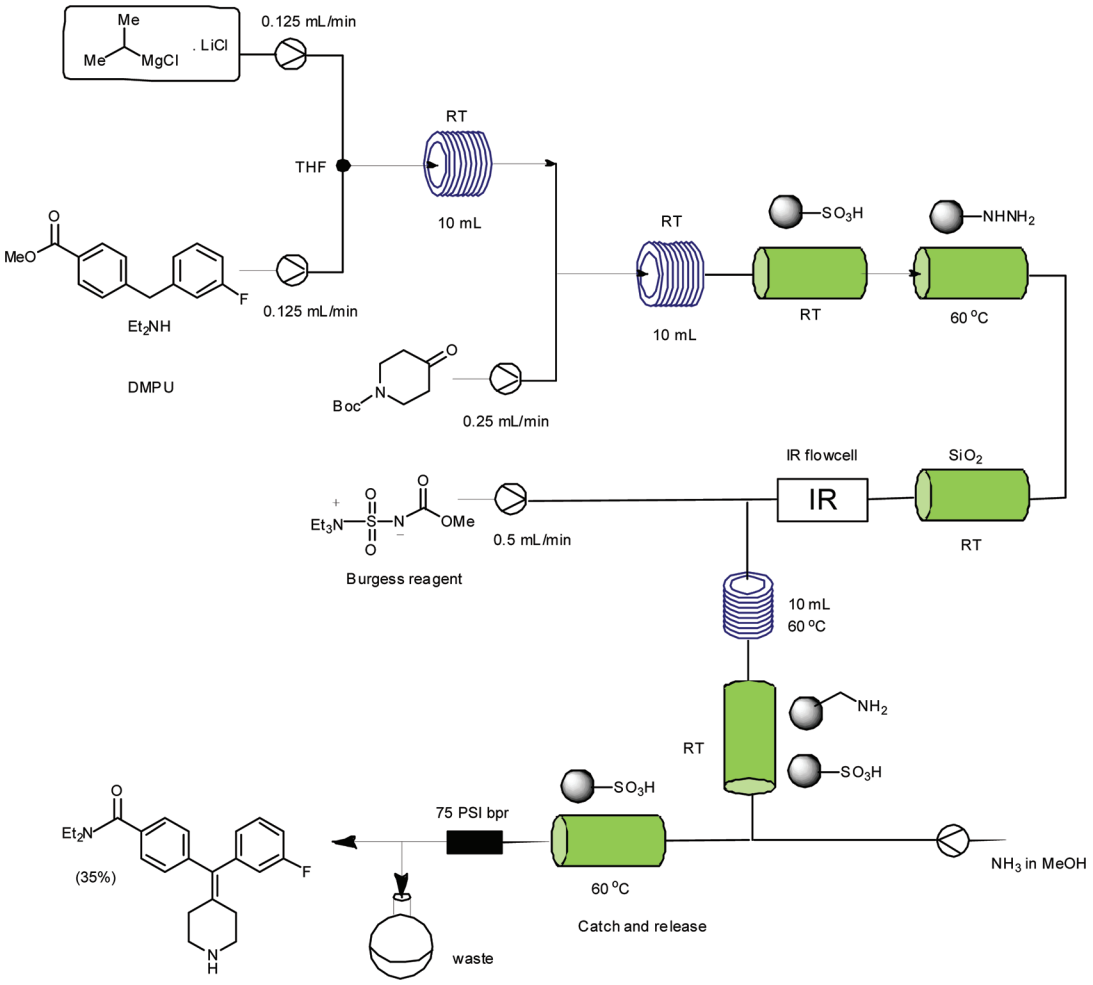


Figure 14. Continuous flow synthesis of *N*,*N*-diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl)-benzamide.[86]

release the gas generated and therefore reduce the pressure on the system. At the same time, potentially explosive, highly toxic or unstable intermediates are continuously generated and reacted in situ, minimizing the accumulation of these species and therefore minimizing associated risks.

In gas releasing reactions, ideally the gas released should remain in solution while pressurized and liquid–gas slugs should be observed only after the back pressure regulator (bpr). In some cases, however, this is difficult and they can be observed before the bpr. This affects the residence time because the total volume increases, and it needs to be taken into account.

A good example is the Curtius rearrangement. This reaction was first reported in continuous flow by Baumann et al.[89] At Pfizer Curtius rearrangements have been successfully carried out in continuous flow. For example, *tert*-butyl 4-(2-bromo-4-fluorophenylcarbamoyloxy)piperidine-1-carboxylate) was prepared from the corresponding benzoic acid in 65% yield. The reaction was initially carried out in 10 mmol scale and subsequently scaled to 100 mmol by flowing it for longer with exactly the same result (Figure 16).[90]

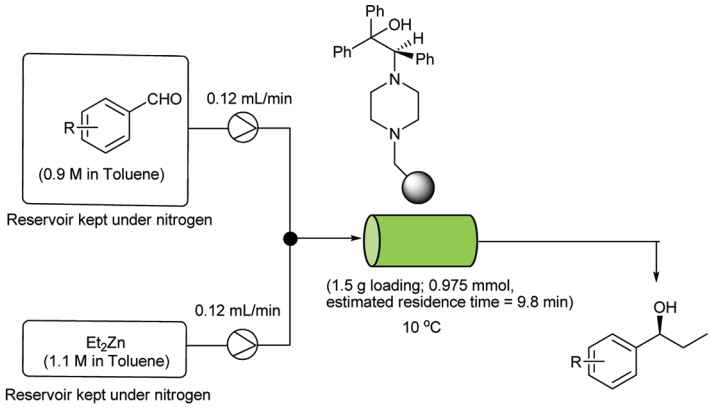
Another approach for the Curtius reaction demonstrated by Baumann et al.[91] is the formation of the acylazide intermediate with solid supported azide. For that, these workers used azide monoliths: azide functionalized polystyrene constituted by a single unit exactly fitting in the cylindrical reactor. They exhibit better properties for continuous flow than conventional polystyrene beads. This approach aids purification, and final compounds were isolated in >95% purity in most of the cases after a simple solvent removal or after a filtration with a small silica plug cartridge prior to solvent removal (Figure 17).

Other examples are Sandmeyer-type reactions. They were first reported in flow by Fortt et al.[92] The authors used *N*,*N*-dimethylformamide (DMF) as a solvent for the $CuCl_2$ catalyzed chlorination. In order to solubilize all components in a reaction, especially in the presence of metal catalysts, very polar and high boiling solvents are often used. However, careful consideration in their choice should be taken. If purification of the final product is hampered by the presence of residual high boiling solvent, which may be difficult to remove, the overall efficiency of the process will be diminished and the advantages of the flow process will have to be balanced against it. Besides, in the case of DMF, additional toxicity issues need to be considered.[93] In this case, the advantages of continuous flow have to be significant to justify the use of DMF as a solvent within a process group.

At Pfizer a metal free iodination procedure has been developed that uses a more benign solvent such as acetonitrile.[94] This was applied to a range of 12 aromatic and heteroaromatic amines with good yields (Figure 18).

Other variations in continuous flow have also been explored in collaboration with S. V. Ley and I. R. Baxendale, such as the sulfonyl chloride formation from anilines.[95] In this work a

dx.doi.org/10.1021/jm2006029 | *J. Med. Chem.* 2012, 55, 4062–4098



Substrate	Conversion (%)	Selectivity (%)	enantioselectivity (%)
benzaldehyde	99 (99)[a]	98 (>99)	93 (93)
2-fluorobenzaldehyde	95 (99)	>99 (99)	87 (91)
4-fluorobenzaldehyde	93 (87)	>99 (98)	93 (92)
2-(trifluoromethyl)benzaldehyde	87 (71)	87 (76)	84 (78)
4-(trifluoromethyl)benzaldehyde	99 (98)	98 (99)	89 (90)
4-cyanobenzaldehyde[b]	>99 (>99)	>99 (>99)	87 (89)

Figure 15. Continuous flow and batch comparison of the catalytic enantioselective ethylation of aldehydes.[88] Superscript letters in the table indicate the following: a, number in parentheses corresponding to the reaction in batch mode; b, total flow rate of 0.72 mL/min (0.36 mL/min for each reagent), estimated residence time of 2.8 min.

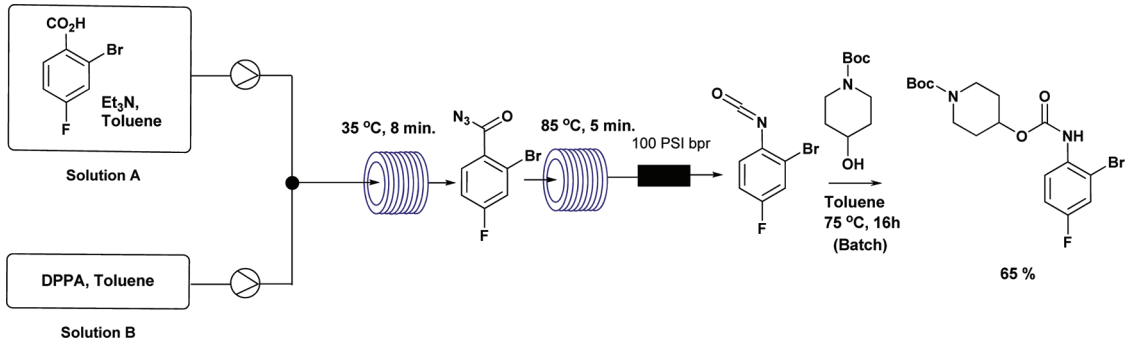


Figure 16. Synthesis of *tert*-butyl 4-(2-bromo-4-fluorophenylcarbamoyloxy)piperidine-1-carboxylate via Curtius rearrangement.[90]

convenient and safe procedure for the conversion of anilines into the corresponding sulfonyl chlorides and subsequently into sulfonamides has been developed. These conditions are significantly milder than the traditional batch procedure and therefore much more convenient for scale-up (Figure 19). In addition, this approach is currently being considered for small scale batch library production.

Another nitrogen releasing reaction is the ring expansion carried out by scientists at Johnson & Johnson[38] in the CYTOS system with ethyl diazoacetate. Because of the thermal profile of the reaction, it would not be advisible to scale up to kilogram scale in batch. However, they were able to safely do it in continuous flow from the initial 70 mg scale to an output of 91 g/h (Scheme 2).

The same reagent was used by Bartrum et al.[96] to make a range of β-ketoesters in continuous flow as precursors to pyrimidines (Figure 20), a very common motif in small drug molecules.

The kinetic study and synthesis of sodium nitrotetrazolate in microreactors by Zaborenko et al.[97] also deserve a mention. The high instability of the reactive intermediates makes typical batch kinetic studies difficult and highly dangerous. It is worth mentioning the use of gas-permeable tubing (Teflon AF) within a vacuum chamber to effectively and safely release the

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062–4098

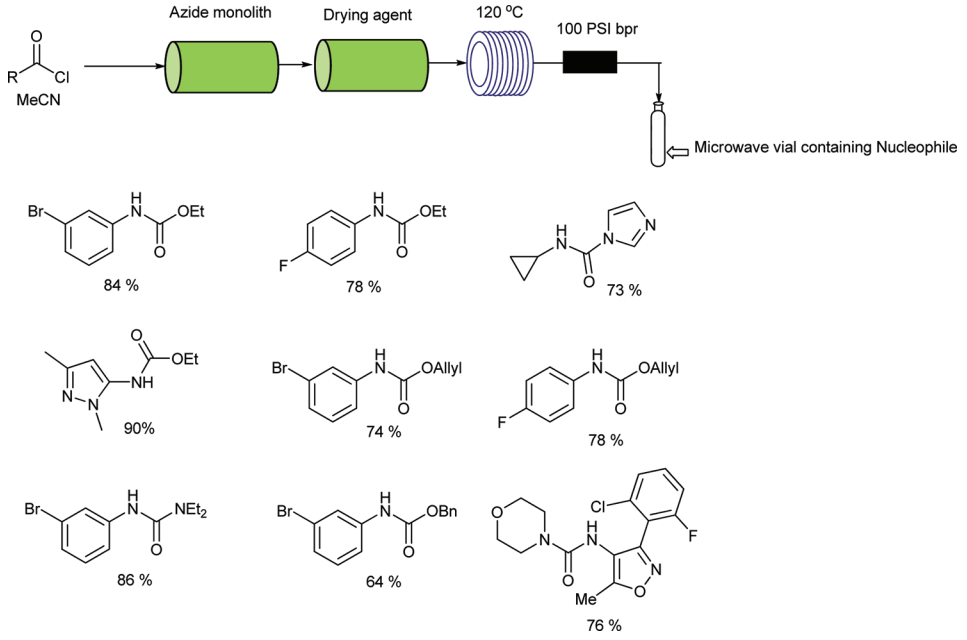


Figure 17. Examples of Curtius rearrangements in continuous flow using an azide monolith.[91]

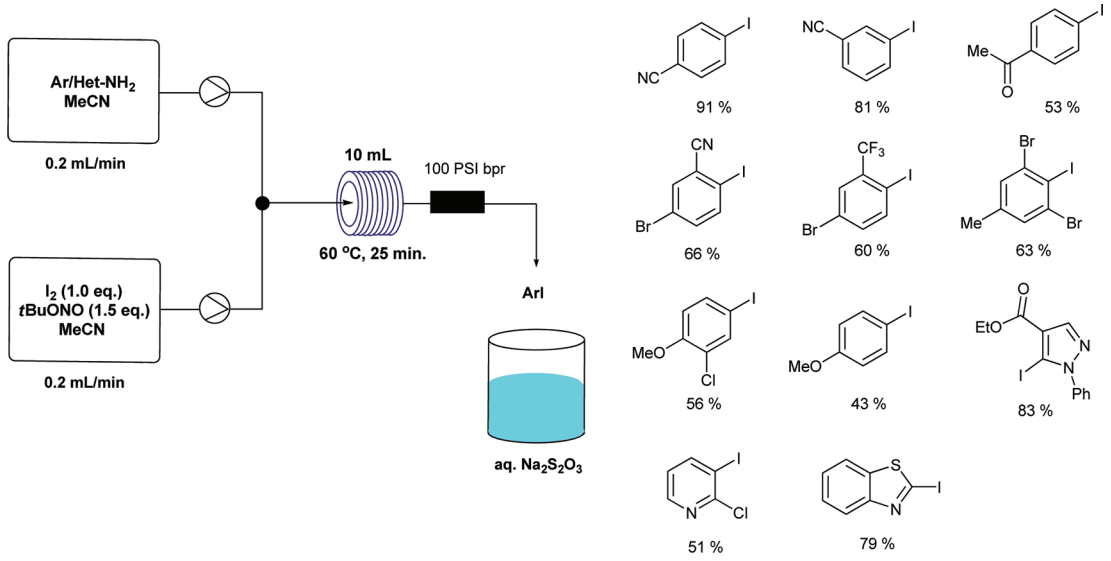


Figure 18. Examples of iododeamination reactions carried out in continuous flow.[94]

nitrogen generated in the reaction. The authors scaled up the reaction to a throughput of 2.8 g/h of sodium nitrotetrazolate, as their flow rate was limited by the syringe pumps used (Figure 21). They suggest that with a suitable system (probably with a higher reactor volume) and HPLC pumps, greater throughputs would easily be achieved.

Another very useful, yet highly toxic and thermally and photochemically labile reagent is diazomethane. Trimethylsilyldiazomethane is a less hazardous and popular substitute, although it is still toxic and needs careful handling. Flow is very useful for handling these kinds of reactions, as demonstrated by Martin et al.[98] These workers generated diazomethyl ketones, another chemically labile species, and used them in situ in a flow reactor for the formation of quinoxalines (Figure 22).

Another species that is used with much caution is hydrazoic acid (HN_3). This is due to its highly toxic nature, combined with its low boiling point (37 °C) and low thermal stability.[99] Safer alternatives commonly used are sodium azide (NaN_3), trimethylsilyl azide, trialkyltin azides, and organoaluminium azides. However, the in situ generation of HN_3 in reaction or workup can still represent a genuine safety issue that has to be adequately assessed, especially on scale.[99] Recently, Roberge, Kappe, and co-workers[100] reported the formation of tetrazoles with the in situ generation of hydrazoic acid in a microreactor without the need of any catalyst or additive. These reactions typically take several hours to days, but they were able to intensify the process using high temperatures and pressures to achieve good yields with only 5−30 min of residence time (Figure 23).

An alternative way to make organic azides without the use of HN_3 is the use of azide ion exchange monoliths.[91] Smith et al.[101] synthesized a range of aliphatic azides utilizing azide ion exchange monoliths and a range of aromatic azides with trimethylsilyl azide.[102] They reacted them in situ with a

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098

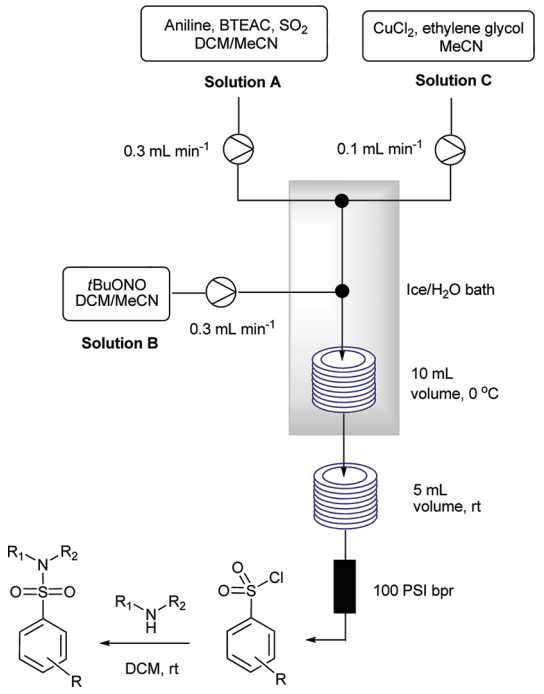


Figure 19. Continuous flow method for the sulfonyl chloride and sulfonamide formation from anilines.[95]

Scheme 2. Ring Expansion with Ethyl Diazoacetate Carried Out in Flow with an Output of Product of 91 g/h [38]

monolithic triphenylphosphine reagent, trapping the aza-Wittig iminophopsphorane intermediates and washing away any contaminants or byproduct. The trapped iminophosphoranes were then reacted with aldehydes to form imines, which were then released or reduced in-line with a borohydrate resin to yield the corresponding secondary amines (Figure 24).

High control of the residence time, combined with the rapid heat exchange that microreactors provide, allowed O'Brien et al.[103] to synthesize several heterocyclic esters via thermolysis of azidodecarboxylates with residence times of seconds (Figure 25).

Oxidations. Moffatt–Swern oxidations are highly exothermic reactions with very reactive intermediates. These are generally carried out at −50 to −78 °C in batch mode, in order to minimize unwanted side reactions like the Pummerer rearrangement, which at the same time, pose a risk of runaway. Microreactors have shown an advantage in this type of reaction, as they allow reactions to be carried out at higher temperatures (−10 to 20 °C) with precise control of the reactive intermediates and, at the same time, avoiding the difficulty of carrying out cryogenic reactions in large batch reactors.[104]

Scientists at Organon[105] developed a continuous flow process for the scale-up of a Moffatt–Swern oxidation at −20 to 0 °C with conversions over 90%. The equivalent batch processes required −45 to −70 °C to achieve these conversions. They were able to run the system for 1.5 h at 0 °C with a consistent throughput over time, obtaining a 95% isolated yield of 4-androstene-3,17-dione (oxidation product from testosterone) and a production rate of 60 g/h. They observed a high reproducibility between experiments, and because of the very fast reaction at this temperature range, they were able to test different conditions in very short periods of time (more than 20 experiments per hour). Interestingly, these workers comment on the negligible effect of using micromixers versus conventional T-pieces and they conclude that the high selectivity observed at high temperatures is only an effect of the short residence time.

This reaction was further studied by Nieuwland et al.[106] who carried out extensive optimization, using a multivariate screening approach, and concluded that for benzyl alcohol substrate the optimal temperature was 70 °C with a residence time of 32 ms, leading to a 96% conversion of the desired benzaldehyde. They agreed with van der Linden[105] that this

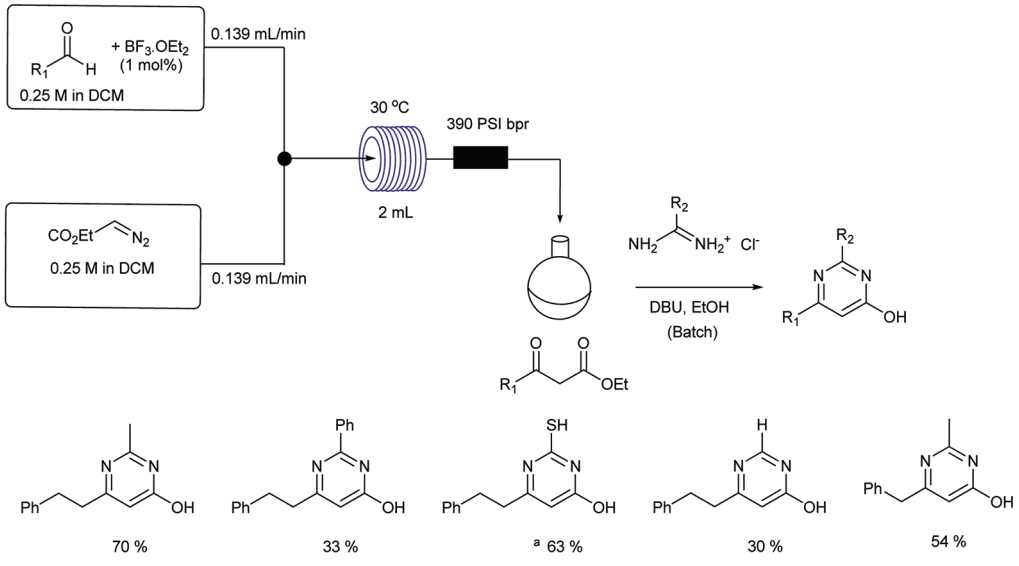


Figure 20. β-Ketoester synthesis with ethyl diazoacetate and subsequent pyrimidine formation.[96] Superscript letter "a" indicates that NaOEt and thiourea were used instead of amidine and DBU.

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062–4098

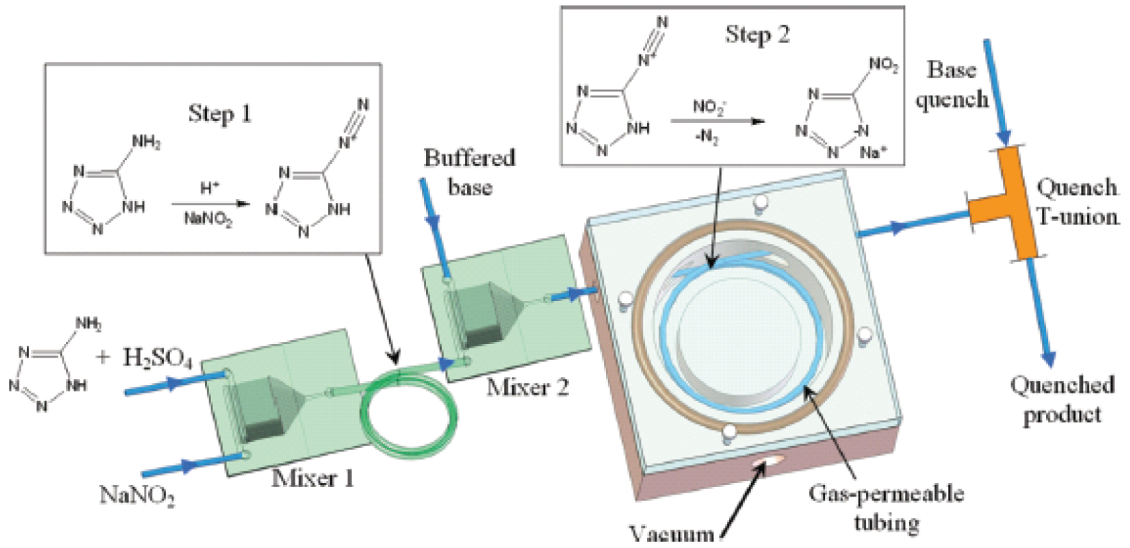


Figure 21. Continuous flow synthesis of sodium nitrotetrazolate using a gas-permeable tubing to vent the nitrogen. Reproduced with permission from *Industrial and Engineering Chemistry Research*.[97] Copyright 2010 American Chemical Society.

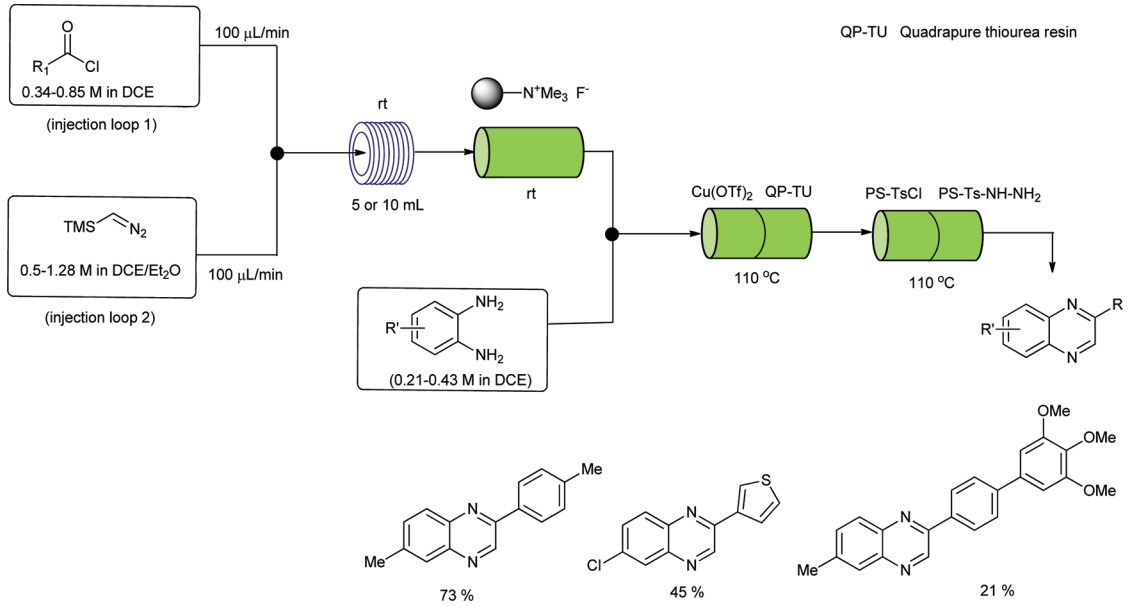


Figure 22. Multistep synthesis of quinoxalines in flow via diazomethyl ketone intermediates.[98] Final products were obtained as mixtures of regioisomers (~1:1).

reaction is not limited by mass transfer for small internal diameters like 125 μm.

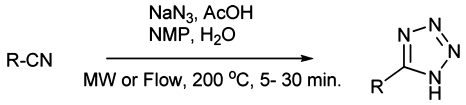
Different oxidation processes have been reported using HOF·MeCN in a microreactor by the group of Chambers-Sandford. The oxidizing mixture is formed in situ with F_2/N_2 and wet MeCN in a purpose made microreactor previously described for fluorination reactions.[71] They successfully reported oxidation of aldehydes, ketones, and Baeyer−Villigers (Scheme 3),[107] as well as epoxidations of alkenes[108] and oxidations of amines to the nitro compounds (Figure 26).[109]

Another oxidation process that can benefit from a continuous flow process is the Nef oxidation. Recently $KMNO_4$-mediated selective oxidation of nitroalkanes to aldehydes, ketones, and carboxylic acids was reported in a continuous flow reactor.[20] This highly exothermic reaction was effectively controlled as a result of the effective heat dissipation and could be carried out at room temperature with very good results. It is worth mentioning the use of an ultrasonic bath to avoid the accumulation of solid MnO_2 particles in the T-junction (Figure 27).

Oxidations of alcohols to carbonyl compounds have also been carried out in flow with different reagents and setups. Kobayashi et al.[110] developed a polymer incarcerated ruthenium catalyst, which is more active than the parent metal source ($RuCl_2(PPh)_3$), and used it, together with NMO as co-oxidant, to catalyze oxidations of alcohols to aldehydes and ketones in continuous flow with excellent results.

Tanaka et al.[111] reported a semicontinuous flow oxidation of alcohols catalyzed by *N*-oxyl-immobilized silica gel in a disperse system with aqueous $NaOCl/NaHCO_3$. The product had to be eluted later from the support, previously filtered, with acetone. The green potential of the method is certainly interesting because of the lack of metals, bromide salts, and organic solvents, but the doability of the process in scale has not been demonstrated.

dx.doi.org/10.1021/jm2006029 | *J. Med. Chem.* 2012, 55, 4062−4098



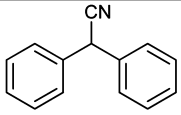
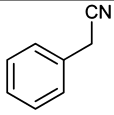
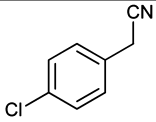
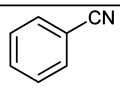
Substrate	Method [a]	t (min.) [b]	Yield (%)
	MW	10	85
	Flow [c]	15	82
	MW	5	94
	Flow	10	94
	MW	5	90
	Flow	10	92
	MW	6	95
	Flow	10	95

Figure 23. Synthesis of 5-substituted 1*H*-tetrazoles with in situ formation of hydrazoic acid.[100] Superscript letters indicate the following: a, MW (microwave) method involving 1.0 mmol of nitrile, 2.0 mmol of NaN_3, 1.0 mL of solvent (NMP/AcOH/H_2O = 7:2:1), 220 °C; flow method involving feed A (1 M solution of nitrile in NMP/AcOH = 5:2) at 0.69 mL/min and feed B (5.2 M NaN_3 in H_2O) at 0.31 mL/min at 220 °C; b, hold times at 220 °C in the case of MW experiments and residence times in the 10 mL heated coil for flow experiments; c, 0.45 mL/min for feed A and 0.21 mL/min for feed B.

In a similar manner, Bogdan et al. later reported on a continuous flow biphasic and metal-free alcohol oxidation catalyzed by solid-supported TEMPO with good results, although they were not able to avoid the use of bromide salts (Figure 28).[112]

Other reported oxidations in continuous flow include the heterogeneous silver oxide catalyzed oxidation of hydroquinones to benzoquinones with hydrogen peroxide[113] and the oxidative cyclization of alkenols with Oxone in *i*-PrOH/H_2O system (Scheme 4).[114]

Oxidation of alcohols and amines to the corresponding aldehydes, ketones, and imines has also been reported in flow using a polystyrene-based monolithic version of *N*-*tert*-butylphenylsulfinimidoyl chloride, which was regenerated in situ with *N*-*tert*-butyl-*N*,*N*-dichloroamine.[115]

Despite the large amount of oxidants that are used in synthetic laboratories, molecular oxygen is the ultimate green oxidant in terms of atom efficiency, minimal waste, and easy product purification. Therefore palladium catalyzed aerobic oxidation processes are highly desirable, but these often require specialized equipment. Large scale batch processes require stirred-tank autoclaves, which are more expensive and less commonly available than the stirred-tank reactors. Another important consideration in this type of reactions is the efficient liquid−gas mass transfer, since poor mixing can lead to irreversible catalyst decomposition. Recently Johnson, Yates, Stahl, and co-workers[116] demonstrated that continuous flow can facilitate these processes. They designed a reactor and optimized the process for the oxidation of a range of alcohols (Scheme 5) and scaled up the process to kilogram scale going from a 400 mL coiled-tube reactor to a 7 L stainless steel coil. They obtained near quantitative yield (99.5%) in the conversion of 1 kg of 1-phenylethanol to acetophenone. The work is currently being implemented at Eli Lilly.

Other Exothermic Reactions. Previously we mentioned the need for careful solvent choice, as homogeneity of the reaction has to be balanced with toxicity and ease of purification. In the following bromination, the process group at AstraZeneca[67] used DMF as a replacement for the even less desirable carbon tertachloride (CCl_4). In this case the authors found DMF to be a good alternative, as all components of the reaction were soluble, and this allowed the successful transfer of a batch bromination process into a continuous flow one. With this, the reaction proceeded at lower temperatures and with a lower reaction time, which could potentially be due to the higher solubility of all the reaction components. Because of the operational safety provided by the continuous flow device, they were able to intensify the process to obtain a throughput of 60 g/h by increasing temperature and decreasing residence time while still maintaining the 70% isolated yield of the orignal batch conditions (Scheme 6).

Another example of exothermic reactions that can benefit from continuous flow is the Ritter reaction,[117] which is usually carried out under highly acidic conditions and in the presence of highly toxic cyanides.

At Pfizer a continuous flow process for the synthesis of pyrrolidines via [3 + 2] dipolar cycloaddition with alkenes and unactivated azomethine ylides has been developed;[118] the products were generated by acid catalysis with TFA. After a few initial optimization experiments on a 2.4 mmol scale, the

dx.doi.org/10.1021/jm2006029 | *J. Med. Chem.* 2012, 55, 4062−4098

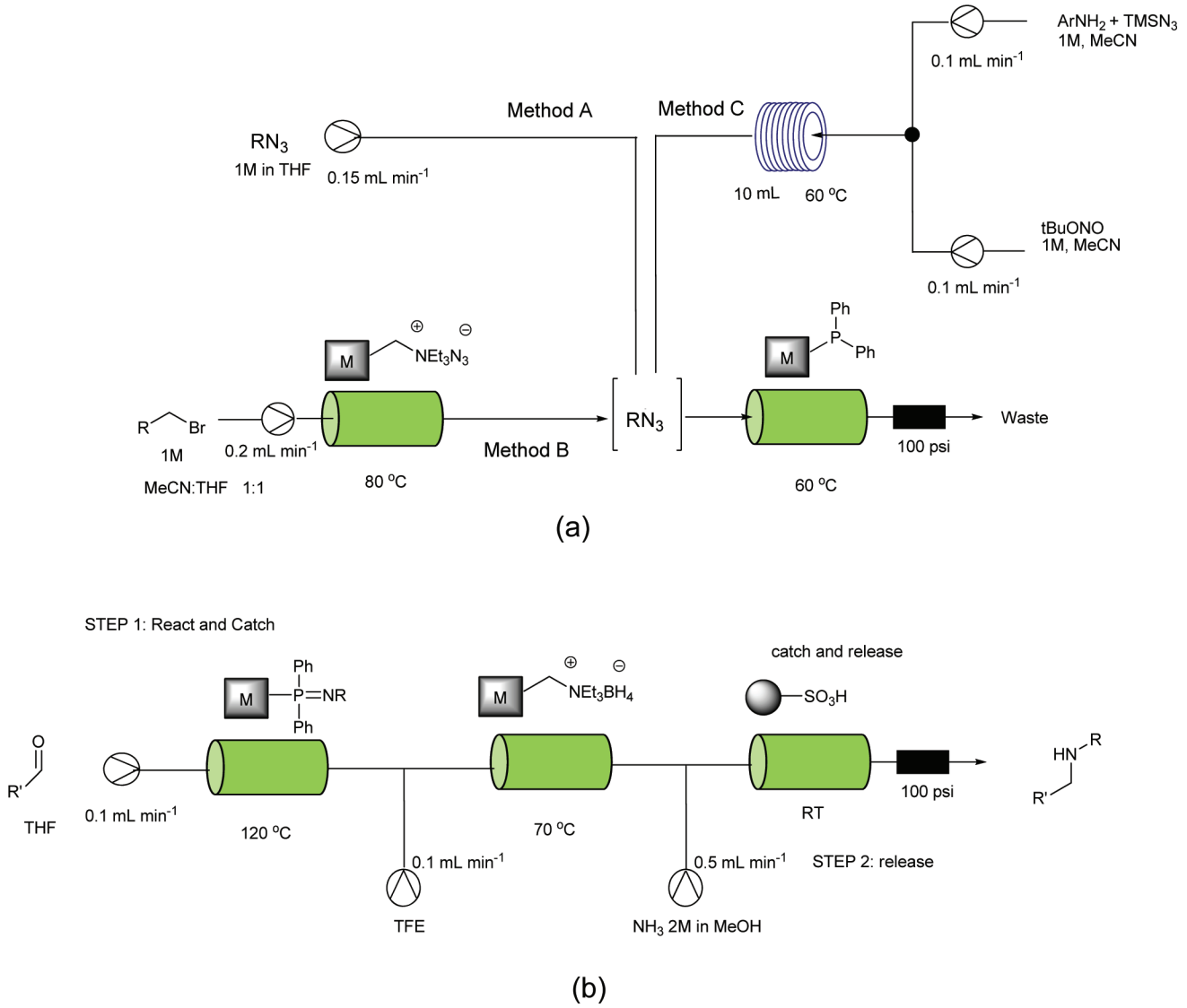


Figure 24. (a) Staudinger reaction in flow: (method A) isolated azides introduced directly; (method B) alkylazides generated from the corresponding alkyl bromides; (method C) arylazides generated from the corresponding anilines. (b) Automated flow process for aza-Wittig reaction, imine reduction, and purification. Figure 24 is from *Organic and Biomolecular Chemistry* (http://dx.doi.org/10.1039/C0OB00813C) (Smith, C. J.; Smith, C. D.; Nikbin, N.; Ley, S. V.; Baxendale, I. R. Flow synthesis of organic azides and the multistep synthesis of imines and amines using a new monolithic triphenylphosphine reagent. *Org. Biomol. Chem.*, **2011**, *9*, 1927−1937);[101] Reproduced by permission of The Royal Society of Chemistry, Copyright 2011.

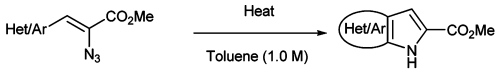
preferred conditions (0.5 M after mixing the reactants in MeCN, 10 min of residence time, 70 °C) were scaled up to 126 mmol (30 g) to yield the desired ethyl 1-benzylpyrrolidine-3-carboxylate in 87% yield after chromatography in only 1 h (Scheme 7). Note that the reactor volume was doubled from 20 to 40 mL and the flow rates were also doubled, increasing the throughput while keeping the same theoretical residence time.

Baumann et al. further developed the reaction in flow by using a fluoride monolith to trigger the azomethine ylide formation and by including in-line scavenging to aid purification.[119] With this setup they were able to diversify the dipolarophiles to obtain sulfonates, phosphonates, and esters (Figure 29).

Radical Reactions. Radical reactions can be highly energetic. They usually have an increased potential for the formation of byproduct and for runaway reactions. The high control of the reaction parameters that flow offers can be of high benefit. This is the case of the Barton−McCombie deoxygenations and dehalogenations carried out by Odedra et al.[120] with tris(trimethylsilyl)silane (TTMSS) and AIBN in microreactors. They were carried out by superheating toluene at 130 °C with a residence time of only 5 min, thus avoiding toxic solvents such as benzene or CCl_4 that are common for these reactions (Figure 30).

■ BIPHASIC REACTIONS

Liquid−liquid and gas−liquid biphasic reactions can potentially be accelerated by conducting them in a microreactor. In a typical laminar flow regime, a contact interface in the form of segmented flow is created. A vortex circulation is generated within each fluid segment, continuously regenerating the interface. It is believed that the large interface generated, coupled with the internal vortex mixing, is responsible for the experimentally observed rate acceleration (Figure 31).[121,122]



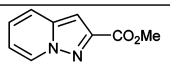
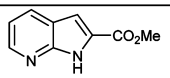
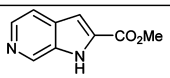
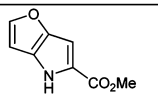
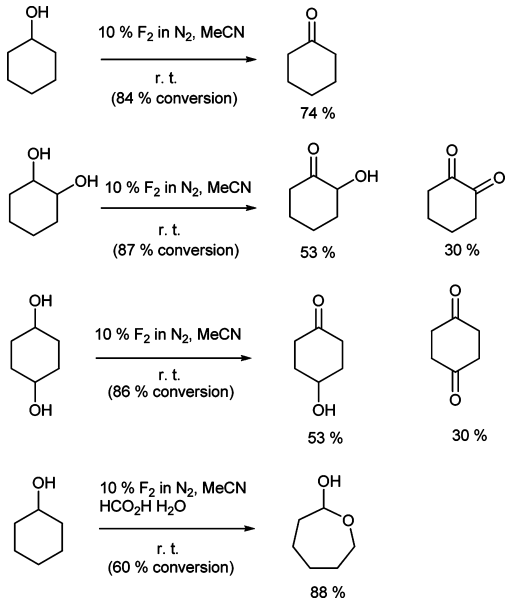
Product	T (°C)	Residence time (s)	Yield (%)
	220	26.5	>99
	220	30.0	57
	160	12.0	0
	180	12.0	>99

Figure 25. Synthesis of heterocycles via thermolysis of azidodecarboxylates.[103]

Scheme 3. Oxidations Using Fluorine Gas in a Microreactor[107]



This phenomenon can also improve mixing in homogeneous reactions. Rate increases have been reported in homogeneous reactions in a segmented flow regime with an inert phase versus the monophasic reaction.[121] For this, a second immiscible phase is incorporated, which does not play an active role other than creating a segmented flow regime and vortex circulations within each segment. Ahmed-Omer et al.[123] investigated this phenomenon applied to Heck couplings. They were able to efficiently generate diazonium salts from the corresponding anilines and react them in situ with styrenes using $Pd(OAc)_2$ as a catalyst to yield the corresponding Heck products. Perfluorodecalin was used to create alternative segments with the reaction mixture, as it is immiscible in DMF even at 120 °C (Figure 32).

Industry has also seen benefits in this area. Merck patented a microfluidic device for carrying out a biphasic phenol alkylation reaction by phase transfer catalysis.[124]

More recently Jovanovic et al.[125] carried out a thorough investigation of a phase transfer catalytic alkylation of phenylacetonitrile **26** (Scheme 8). They were able to show an increase in mass transfer by increasing the aqueous/organic volume ratio (AO) and therefore a decrease in the organic slug size and with that increase the average surface-to-volume ratio. Although an increase in AO showed an increased reaction conversion to the desired alkylated product (**27**), there was also an increase in the amount of bis-alkylated byproduct **29** generated. The optimum value for AO was found to be 2.3, giving 74% conversion and 99% product selectivity, representing a 1.8-fold increase on conversion and 12% on selectivity compared to the stirred tank batch reactors. They were also able to keep the reaction solvent-free while avoiding emulsification of the mixture.

However, a very important consideration in biphasic reactions is the diameter of the channel and the length-to-diameter ratio of the flow reactor, which determines the number of slugs generated and therefore the interfacial area. A narrower channel will also decrease the mixing time by diffusion, which is the mixing limiting factor in a laminar flow regime. Important differences in reaction rates depending on the channel diameter were observed by scientists at Eli Lilly.[100] They observed a significant rate increase in their biphasic azide alkylation reaction when comparing a 20 mL continuous reactor with an internal diameter of 0.6 mm versus a 12 mL one with and internal diameter of 2.2 mm. With the narrower channel reactor, they achieved full conversion at 90 °C in only 20 min, whereas only 64% conversion was achieved in 60 min at the same temperature with the reactor with a wider channel.

When kilogram quantities of material are required, large diameter coil reactors are usually preferred (>1 mm diameter or mesoscale reactors). For biphasic reactions, however, as we have just mentioned, the reaction rate can be significantly affected. Fiber reactors[126] and packed-bed reactors can be a good alternative in these cases.

Packed Bed Reactors. Packed bed reactors are an important variation of the more common coil reactors. Usually a rigid column of glass or stainless steel is packed with microspheres, beads, or other impediments to the flow, which tend to break the laminar flow into a transitional or turbulent flow and improve the mixing.

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062–4098

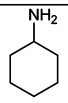
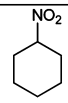
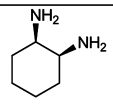
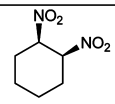
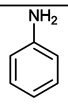
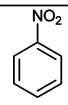
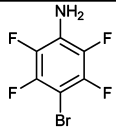
Amine	Nitro compound	Yield (%)
$C_{12}H_{25}NH_2$	$C_{12}H_{25}NO_2$	95
		76
		95
		61
		62

Figure 26. Continuous flow oxidation of amines to nitro compounds using HOF·MeCN.[109]

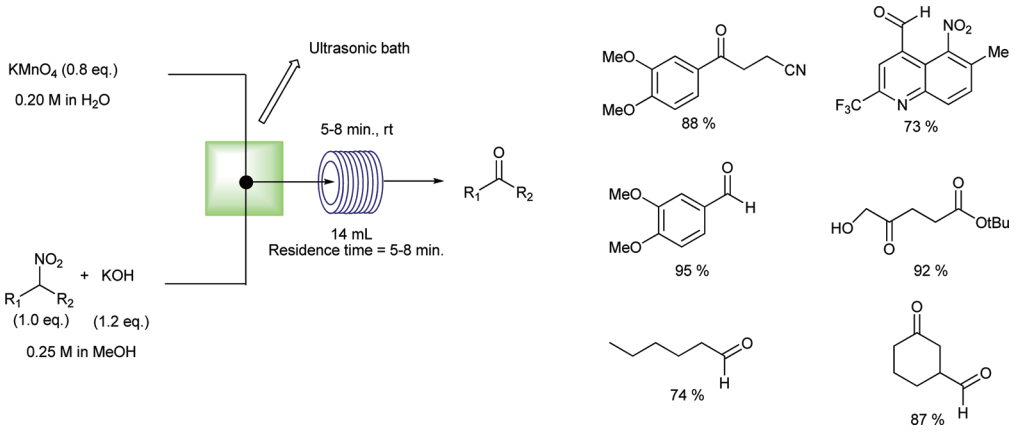


Figure 27. Nef oxidation of nitroalkenes to the corresponding carbonyl.[20]

A process for the safe production of diazoketone **30** (Figure 33), the drug intermediate of (*S*)-1-benzyl-3-diazo-2-oxopropylcarbamic acid *tert*-butyl ester, was developed by Pollet et al. using trimethylsilyldiazomethane as a replacement for diazomethane (Figure 33).[127] They used packed bed reactors (empty HPLC columns: 25 cm × 4.6 mm i.d., packed with 0.5−3 mm glass beds), as they found them to provide an improved mixing versus coil reactors.

A very good example where this concept led to an improved result was recently reported by Naber et al.[128] Since it is indeed difficult to find suitable solvents that are able to solubilize substrate, catalyst, base, ligand, and product in a metal catalyzed coupling reaction, Naber et al. resorted to a biphasic system of toluene and aqueous KOH. The mixing between phases was found to be key to the success, and packed bed reactors were found to provide an improved mixing between phases versus coil reactors where a segmented flow was obtained. The continuous flow process allowed them to use more forcing conditions, significantly reducing the reaction time and allowing the reaction to proceed with a smaller amount of catalyst and a less expensive ligand (Scheme 9).

Furthermore, rather than inert glass beads, packed bed reactors can also contain solid-supported catalysts, benefiting from easy catalyst recovery and improved mixing, without damage of the solid support, which can be a problem with mechanically stirred batch reactors. The already mentioned biphasic alcohol oxidation catalyzed by solid-supported TEMPO (Figure 28) reported by Bogdan et al.[112] is an example of this.

Dynamically Mixed Flow Reactors. In a traditional micro or meso fluidic reactor mixing depends on the reactants, the flow rate, and the reactor dimensions. In a dynamically mixed reactor like the Coflore ACR (agitated cell reactor),[129] the mixing depends on internal agitators (stirrers, agitators, or impellers). This design deserves a special mention because having the advantages of a plug flow system, it is able to handle slurries and certain amount of solids in the reaction mixture, making it a very versatile tool.[130] However, the Coflore ACR, with a minimum volume of 30 mL, is designed for medium to large scale experiments. It is larger than is normally desired in a research laboratory where reactions below 1 g of starting material are routinely carried out.

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098

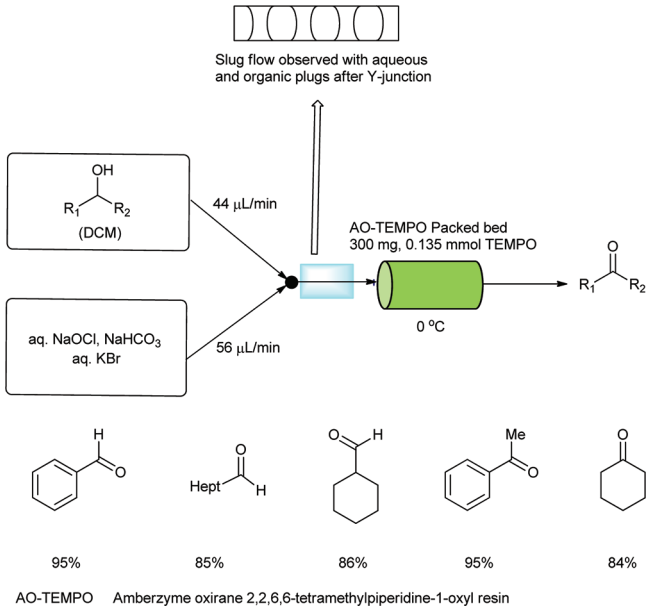


Figure 28. Alcohol oxidation examples using an AO-TEMPO packed bed reactor.[112]

Although there is still a need for a small scale flow reactors able to handle slurries and precipitates, some advances are being made in this direction.

METAL CATALYZED COUPLING REACTIONS

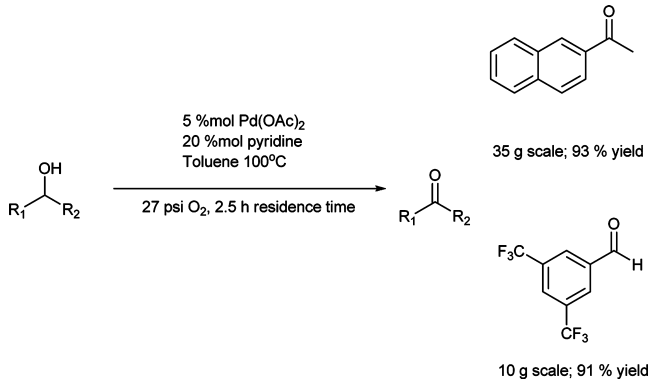
Metal catalyzed coupling reactions can also benefit from continuous flow. Among other advantages, process intensification can have a high impact. The metal catalyst can either be solid supported (heterogeneous catalysis) or dissolved in the reaction (homogeneous catalysis). Each option needs very different practical considerations.[49]

Solid supported catalysts provide advantages in terms of easy recovery and purification, but they can sometimes suffer from reduced activity. Several advances in this area have been reported in recent years.

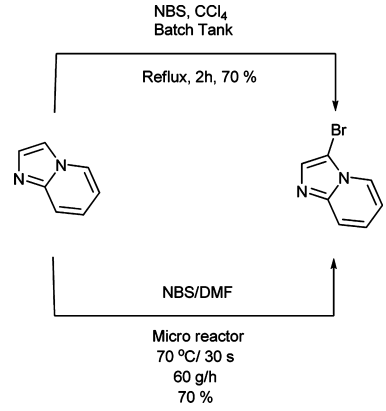
Nikbin et al.[131] reported a monolithic cartridge reactor derivatized with Pd(0) nanoparticles, which was used to effect Heck couplings. They were able to replace DMF, a commonly used solvent for Heck couplings, with the more benign ethanol by superheating it at 130 °C and using a 100 psi back-pressure regulator to keep the solvent in the liquid state, obtaining equivalent results in terms of yield (Scheme 10). They reused the monolith at least 25 times without any loss on activity and efficiently scavenged any leaching with the use of an in-line QuadraPure TU metal scavenger.

Huang et al.[132] developed a heterogeneous Pd-nanoparticle based catalyst, which is significantly superior in the hydroalkoxylation of 2-phenylethynylphenol to other known catalysts like $PdBr_2$ and $Pd(PPh_3)_4$ (Scheme 11). These workers did not

Scheme 5. Aerobic Alcohol Oxidation Results for Reactions Performed in a 400 mL Flow Reactor[116]



Scheme 6. Batch and Continuous Flow Bromination[67]



Scheme 7. Pyrrolidine Formation under Optimized Flow Conditions[118]

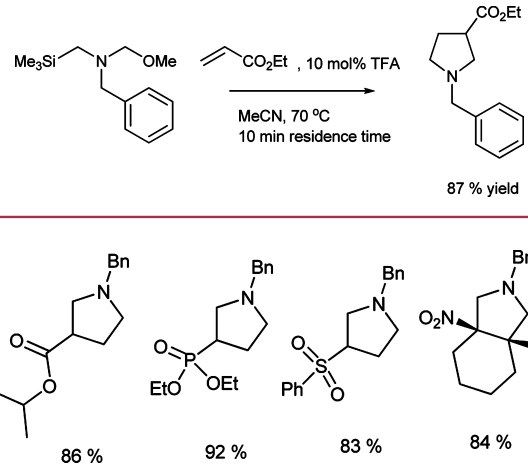
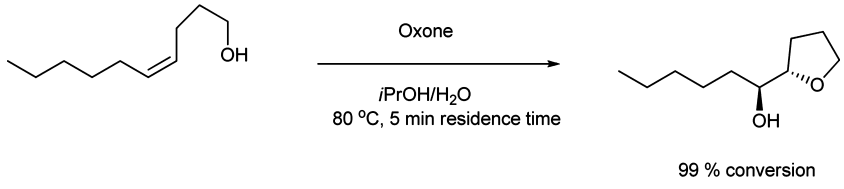


Figure 29. Pyrrolidine formation via [3 + 2] cycloaddition using a fluoride monolith in flow.[119]

Scheme 4. Oxidative Cyclization of Alkenols with Oxone[114]



dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062–4098

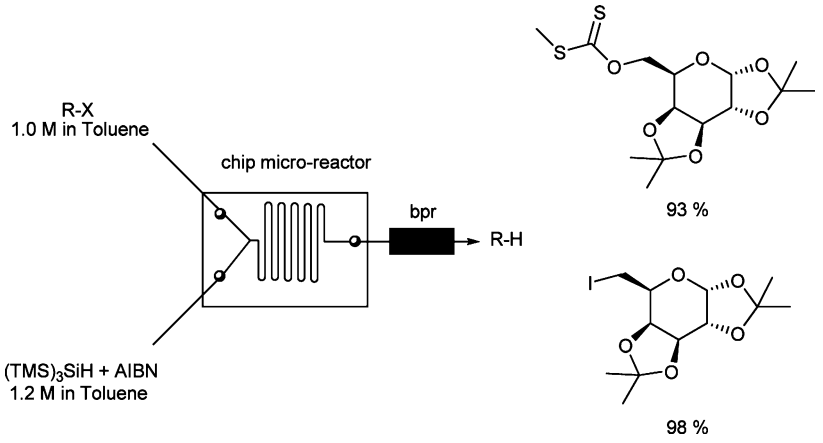


Figure 30. Deoxygenation and dehalogention in continuous flow.[120]

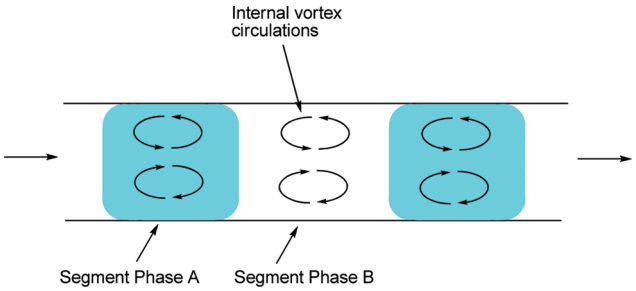


Figure 31. Schematic representation of segmented flow.[121]

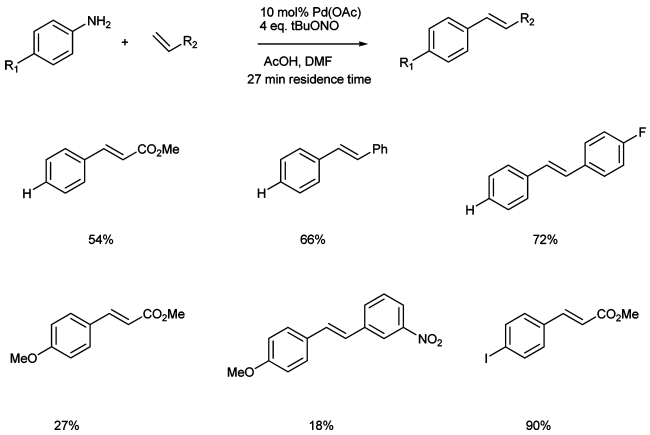


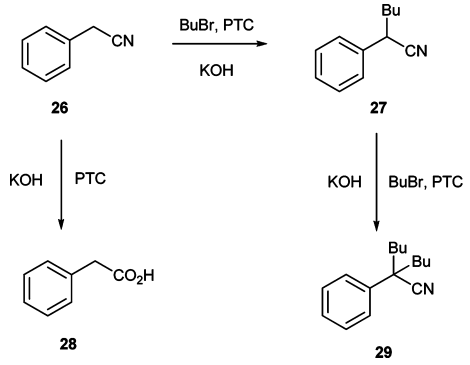
Figure 32. Examples of diazonim Heck couplings of aniline derivatives in segmented flow.[123]

detect any leaching from the support, and the catalyst gave full conversion for 10 h at room temperature when the reaction mixture contained 5 mM $PhICl_2$. In this case process intensification was observed, as the instantaneous ratio of catalyst/substrate is much higher than in batch, and therefore, the reaction proceeds significantly more quickly (98 min of effective residence time in flow versus the 15 h in batch).

In an alternative approach, the catalyst can be immobilized in the reactor walls, as demonstrated by Hornung et al.[133] with their palladium coated microcapillary flow disk reactor (mean diameter of 146 μm), which they successfully used for the transfer hydrogenation of several substrates using triethylsilane.

In some cases, the catalyst can be packed as a solid in a stainless steel column without any solid support. Tagata et al.[134]

Scheme 8. Phase Transfer Catalytic Alkylation of Phenylacetonitrile in Flow[125]



carried out the first CH borylation in continuous flow by packing an iridium catalyst prepared from an iridium precursor: $[IrCl(COD)]_2$ and 2,2′-bipyridine-4,4′-dicarboxylic acid (BPDCA) in a stainless steel column (Scheme 12). With this approach the catalyst could be reused for several runs with minimal leaching.

Homogeneous systems can also benefit from a continuous flow approach as demonstrated by Glasnov et al.[135] These workers were able to intensify a Suzuki–Miyaura cross-coupling, which in batch took between 8 and 18 h at 65–100 °C, to a flow process that took only 15 min at 160 °C. They managed to integrate this homogeneous Pd catalyzed reaction with a subsequent hydrogenation heterogeneously catalyzed by a Pt/C catalyst. The first step was carried out in an X-Cube Flash[36] and the second in an H-Cube (Scheme 13).[36] However, the suitability of this setup for large scale production remains to be proved.

Homogeneous protocols have also been reported for Cu(II) catalyzed N–C and N–O couplings,[136] although problems with the solubility of $Cu(OAc)_2$ in organic solvents limited the authors significantly. N–C couplings were carried out at room temperature with DCM, whereas N–O couplings were carried out in DMF at 130 °C.

Often increased temperatures/pressures allow reactions to proceed with simpler catalyst systems, which can utilize cheaper,[128] ligand-free systems[137] or even zerovalent metal–ligand free systems.

To achieve homogeneous systems that do not clog the reactor for couplings containing several components, including metallic catalysts, bases, and salts (generated as a result of the

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062–4098

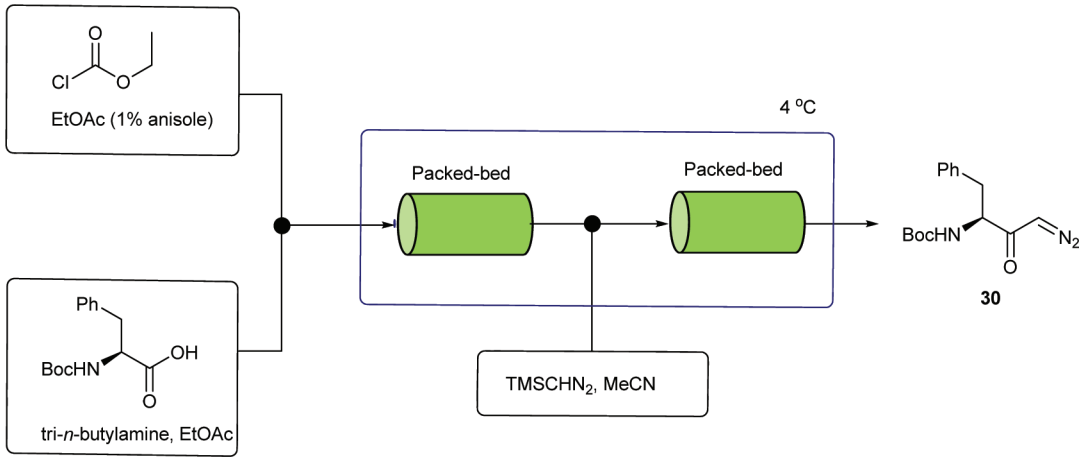
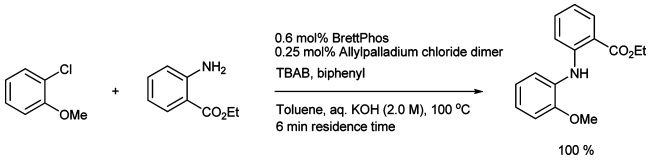


Figure 33. Packed dual reactor system used for the synthesis of diazoketone **30**.[127]

Scheme 9. Example of C−N Cross-Coupling Reaction in Continuous Flow Using a Packed-Bed Reactor[128]



coupling), is not a straightforward task. Some authors have used high boiling and very polar solvents such as DMF or NMP, which, as mentioned before, may not be desirable because of the toxicity of these solvents and/or related difficulties with product isolation. Instead, other authors have resorted to biphasic systems, and some examples have already been described in "Biphasic Reactions". A different approach was taken by Noël et al.[19] in their recent work with a monophasic setup in tetrahydrofuran (THF) or dioxane as solvents (Figure 34). They initially cooled the mixture to prevent reaction and clogging in the T-piece and then warmed the mixture in the coil reactor, which was immersed in an ultrasonic bath to prevent clogging. The mixture was then immediately quenched with water/EtOAc, which fully solubilized it in a larger diameter tubing (2 mm i.d., PFA). With this system, they were able to carry out Pd catalyzed C−N coupling reactions in THF at 60 °C with full conversion after 30−60 s of residence time. They could also carry out the reaction in dioxane at 90 °C with 1−6 min of residence time and a reduced catalyst loading (0.2 mol %).

A different approach was taken by Fukuyama et al.[13] who solubilized metal catalysts with ionic liquids. This approach allowed them to efficiently recover and reuse the palladium catalyst approximately five times in a continuous system running for 11.5 h. The desired butyl (*E*)-cinnamate product was isolated in 80% yield with a throughput of 10 g/h (Figure 35).

In the zerovalent metal−ligand free systems category, copper based coil reactors have proved very useful. An array of 1,4-disubstituted 1,2,3-triazoles was successfully synthesized by Bogdan et al. in a copper coil flow reactor via a Huisgen 1,3-dipolar cycloaddition reaction (Scheme 14).[138] They were able to carry out the reactions with only 5 min of residence time at 150 °C, generating the azides in situ from alkyl halides and sodium azide.

The same approach has also been effectively utilized in macrocycle generation by Bogdan and James,[139] this time with the addition of catalytic amounts of tris[(1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl]amine (TTTA) as a ligand (Figure 36).

More recently, reactions catalyzed by copper tubing in the absence of ligands, such as Ullman, Sonogashira-type, and decarboxylative couplings, have also been reported by Patel and Mainolfi (Figure 37).[140]

Kawanami, Ikushima, and co-workers[137] have developed a continuous reactor with step-by-step rapid mixing and heating in high pressure and high temperature water (HPHT-H_2O) (Figure 38a). They have successfully carried out Cu-free and ligand-free Sonogashira-type reactions with 0.1−4 s of reaction time with a $PdCl_2$ catalyst in a H_2O/NaOH solution at 16 MPa and 250 °C (Figure 38b). Although the substrates are initially insoluble in H_2O, the formation of a homogeneous phase in the HPHT region was demonstrated by IR. It is believed that this was due to the high dielectric constant and the higher diffusibility induced by the turbulent flow (Re ≤ 3600).

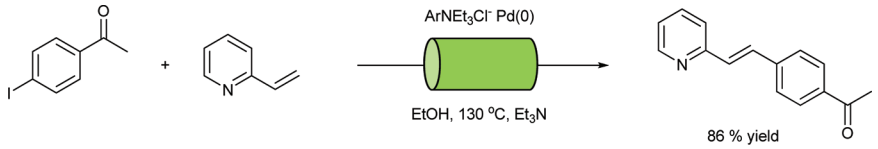
■ REACTIONS WITH A GAS

Hydrogenations. Hydrogenation reactions can benefit from the process intensification and improved safety profile that continuous flow can provide. Heterogeneous hydrogenations are generally exothermic processes that require effective heat removal. In fast reactions mass transfer effects can be limiting over kinetic effects in conventional batch reactors.

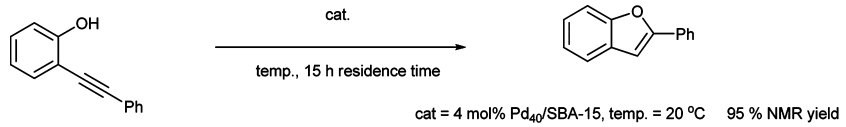
Commercial systems for research scale that are able to carry out these triphasic reactions in continuous flow are available. They have packed-bed reactors that contain the heterogeneous catalyst. H-Cube has become very popular in research laboratories because of its small footprint, coupled with the ability to generate hydrogen from water in an on-demand basis, avoiding the need for hydrogen cylinders in the lab. Prepacked CatCart cartridges (30, 55, 70 mm) containing catalyst are available, which makes the process very user-friendly. However, these cartridges are of a fixed size, and therefore, the possible residence time is limited. Usually the reaction time of hydrogenation reactions can be decreased versus the corresponding batch process by increasing the temperature and/or pressure, besides benefiting from the high catalyst/substrate ratio at each point of the

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098

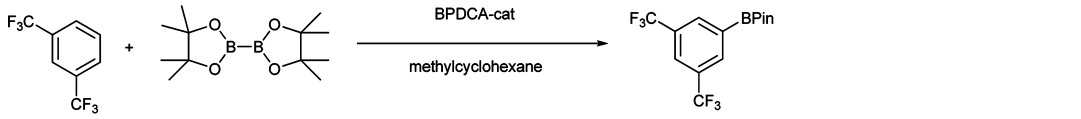
Scheme 10. Example of Heck Cross-Coupling Reaction in Superheated Ethanol[131]



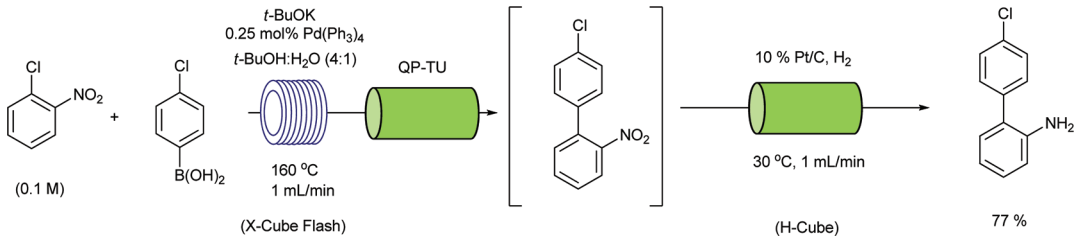
Scheme 11. Palladium Catalyzed Hydroalkoxylation of Phenylethynylphenol[132]



Scheme 12. Example of CH Borylation in Batch and Continuous Flow[134]



Scheme 13. Two-Step Continuous Flow Synthesis of 2-Amino-4-chlorobiphenyl[135]



catalytic bed. Despite this, when reactions are too slow, they have to be carried out using a traditional batch approach. To partially overcome this, together with the possibility of achieving much higher product throughputs, ThalesNano released the H-Cube Midi which has a bigger catalyst bed (90 mm × 9.5 mm).

Knudsen et al.[141] reported the O and N deprotection of amines, amino acids, and dipeptides. They coupled the H-Cube with a robotic liquid handler and a suitable software to efficiently automate the optimization process. One of their observations was a dramatic increase in reactivity of the Pd/C with temperature, being able to achieve full conversion at 80 °C (Figure 39).

The H-Cube reactor was also used by Irfan et al.[142] for the reduction of pyridines. They reduced picolinic acid with a simple Pd/C catalyst at 80 °C with 1 bar of H_2 pressure and only 8.4 s of residence time in the catalytic cartridge (the dead volume of the CatCart cartridges of 30 mm was calculated to be around 140 μL). Furthermore, these workers were able to tune selectivity (Scheme 15) by varying the temperature and pressure of the reactor. Easy deuteration was also achieved by simply replacing the H_2O by D_2O in the electrolytic cell.

Chiral hydrogenations with the H-Cube are also possible. Cserényi et al.[143] have reported the chiral hydrogenation of ketones using Pt on alumina and chiral modifiers like cinchona alkaloids.

Another commercial product is the FlowCAT from HEL, comprising a trickle-bed reactor (TBR) of 3 or 12 mL that can be packed by the user. The FlowCAT needs to be connected to an external hydrogen supply, but it has the flexibility in that the system can be used for other gases such as carbon monoxide. The trickle-bed reactor of the FlowCAT is not limited by hydrogen availability like the H-Cube, and it has been used as starting point for hydrogenation scale-up studies within Pfizer.[144]

Recently, the possibility of carrying out such reactions with the catalyst in a slurry has been investigated by Buisson et al.[23] In their study these workers were able to carry out the same reaction in continuous flow with the same impurity profile at higher temperature and lower residence time, showing potential cost saving advantages in the production process.

Another way of utilizing heterogeneous metal catalyst is by coating it on the walls of a capillary microreactor. Revrov et al.[145] reported the selective hydrogenation of 2-methyl-3-butyne-2-ol (MBY) to 2-methyl-3-buten-2-ol (MBE) using a wall-coated capillary microreactor with bimetallic $Pd_{25}Zn_{75}$ nanoparticles embedded on a mesoporous titania thin film (97% selectivity and 99.9% conversion at 60 °C in the presence of pyridine) (Scheme 16).

Other Gas Reactions. Although hydrogenations are probably the most common gas reactions used in the pharma industry, there are others. In a research laboratory the use of gases always requires some safety precautions, and they are especially important when the gas is toxic or corrosive and exposure has to be avoided. Certain reactions like carbonylation can be very useful, and they are sometimes dismissed

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098

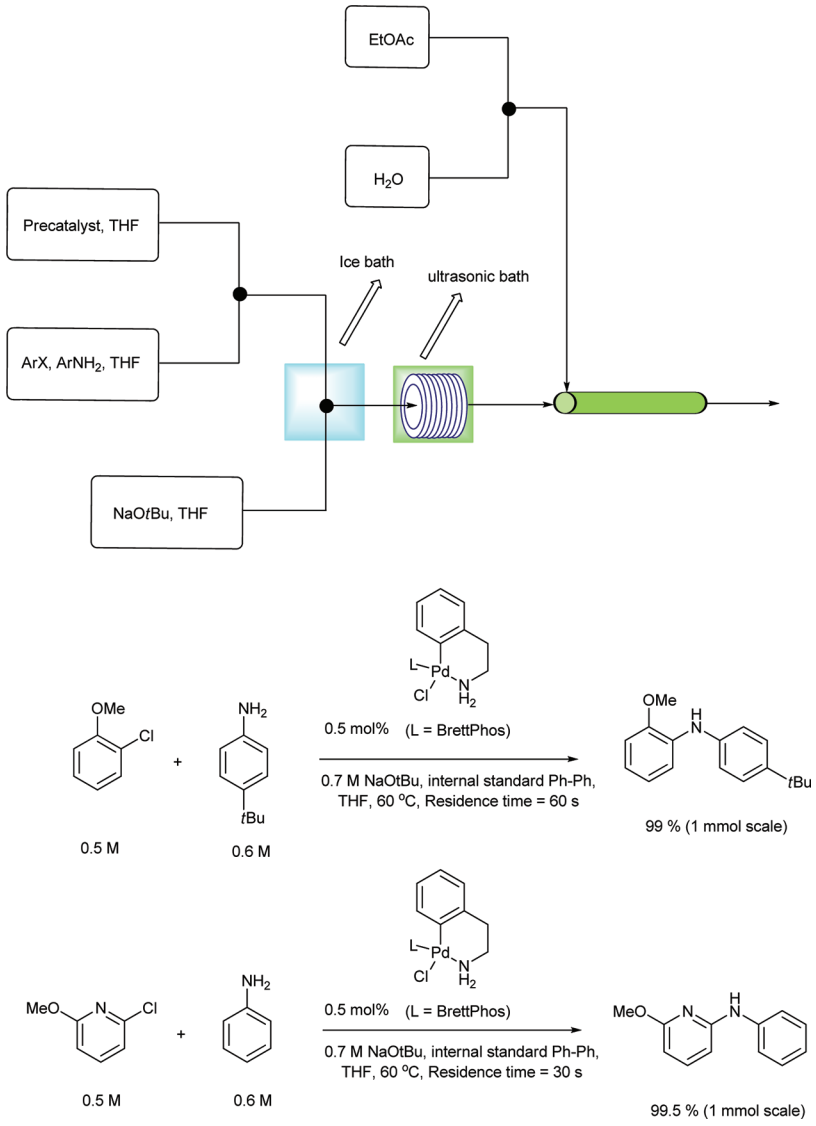


Figure 34. Examples of palladium-catalyzed aminations of aryl chlorides in continuous flow and an experimental setup that can handle the solids formed.[19]

because of the high toxicity of CO gas. These issues are even more important when scale increases. Continuous flow can bring some advantages in this area, as the amount of gas in the reaction can be controlled and minimized, as well as quenched in line. A key factor for the reaction to be successful is good mixing between the liquid and the gas phase. Murphy et al.[146] reported on a Heck aminocarbonylation reaction in a microreactor. They were able to significantly improve the yields and selectivity achieved in batch mode at near atmospheric pressure. Superheating toluene increased the conversion, whereas an increase in pressure resulted in increased selectivity, which is believed to be due to an improvement in mass transfer resulting from segmented gas–liquid flow and higher amounts of CO dissolved in the liquid phase (Figure 40).

An innovative way to deliver the gas into the reactor has been developed by O'Brien et al. using a gas permeable membrane tubing (Teflon AF-2400). Initially these workers reported ozonolysis using Teflon AF-2400 to deliver ozone[147] and more recently carboxylations[148] and carbonylations.[149] Their tube in tube setup allows rapid gas diffusion into the reaction stream in a safe and controlled manner. This approach allowed successful carboxylation of a range of Grignard reagents in good yields (Figure 41).

SOLID-SUPPORTED CATALYSTS

Solid-Supported Asymmetric Catalysts. There has been some efforts into immobilizing asymmetric catalysts[150−153] on solid support and using them in continuous flow systems, although this is an area still in development. Despite the potential for reaction telescoping, easier purification, and low erosion of the solid support due to lack of mechanical stirring, achieving good levels of reactivity, enantioselectivity, and long-term catalyst stability is not trivial. Different types of solid support have been investigated, and their properties are key for success. Different organocatalysts and chiral ligand–metal complexes have been bound to solid supports. This area has been recently reviewed,[150] and it will not be discussed further.

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098

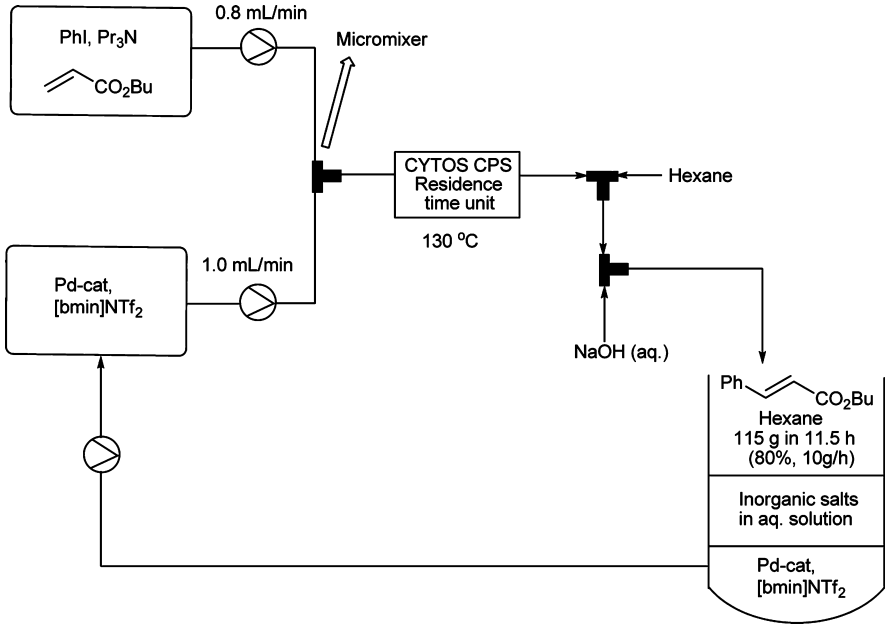
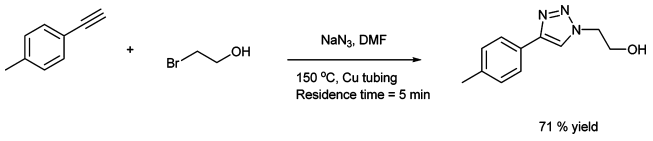
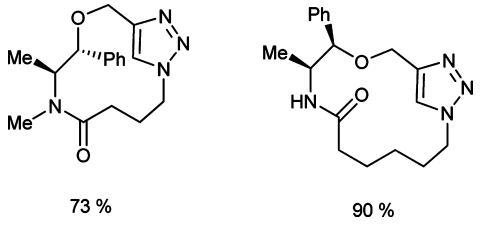


Figure 35. Automated production of butyl cinnamate in continuous flow.[13]

Scheme 14. Example of Optimized One-Pot Huisgen 1,3-Dipolar Cycloaddition Reaction[138]





73 % 90 %

Figure 36. Examples of flow macrocylizations using a Cu tube flow reactor.[139]

Other Solid-Supported Catalysts. Nonasymmetric solid-supported catalysts are slightly more developed than their asymmetric counterparts. Packing these catalysts into fix bed continuous flow reactor makes purification and reaction telescoping easier. Again, the lack of mechanical stirring in the flow reactor can have a favorable impact on the long-term stability of the polymer beads.

An example of solid-supported catalysis is the successful synthesis of amines from alcohols via a hydrogen borrowing approach catalyzed by a solid-supported Ru catalyst, recently reported by Lamb et al.[154] These workers initially immobilized a phosphine based ligand and then complexed a ruthenium metal to form an active catalyst, achieving 98% conversion at 150 °C of their model reaction between benzyl alcohol and morpholine (Scheme 17). Interestingly the calculated TON (turnover number) was 438, comparing favorably with 100 of a typical homogeneous system operating at 1 mol % of catalyst.

Polymer supported $RuCl_3$ was used by Wiles et al.[155] as a Lewis acid to catalyze the Strecker reaction with trimethylsilyl cyanide. This allowed them to isolate the products by simple vacuum distillation in quantitative yield (Figure 42). No Ru leaching was observed by ICP-MS, whereas the corresponding batch process gave the product with 440 ppm of Ru, which was attributed to mechanical degradation of the solid support. The small throughput achieved can be mainly attributed to the long reaction time. A bigger reactor volume would be required to increase it together with an increase in flow rate. Instead, the authors were then able to increase the reaction rate by switching to polymer supported scandium(III) bis-(trifluoromethanesulfonate) [PS-Sc$(OTf)_2$] as a Lewis acid,[156] increasing the throughputs to 30−60 mg/h.

■ REACTION TELESCOPING

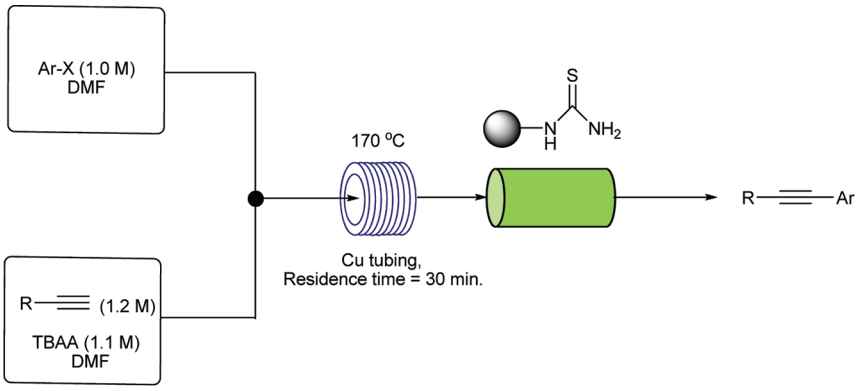
Reaction telescoping is the collapsing of a multistep process into a smaller number of steps or unit operations, and in-line purification and analysis techniques can be vital for that.

In-Line Purification. A chemical process needs to be considered as a whole, considering all the reaction, workup, and purification operations. According to a report from Lonza chemists,[16] in large scale processes the average number of workup unit operations is slightly higher than the number of reaction unit operations (2.7 vs 2.1). Everything is obviously related, and any improvements in process yields can potentially have a positive impact on the downstream operations required.

The Ley group has been particularly active in the area of integrating workup and purification operations into the flow sequence, which has allowed them to telescope reactions and achieve synthesis of pharmaceutically relevant products[18,83,86] and natural products[157] in continuous flow. The formation of triazoles from alkynes generated in situ with the Bestmann−Ohira reagent[158] is a good example, where several solid supported reagents and scavengers are sequentially used (Figure 43).

In this area, it is worth mentioning a recent review by Webb and Jamison on multistep flow synthesis,[159] as well as another by Baumann et al.[160] focused on heterocycle synthesis.

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098



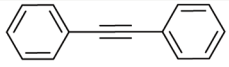
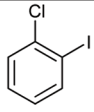
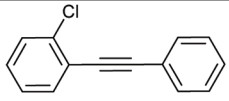
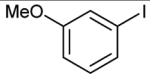
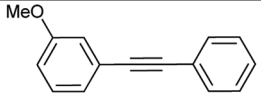
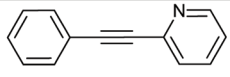
Aryl halides	Product	Yield (%)
		90
		90
		87
		78

Figure 37. Synthesis of arylalkynes in a Cu tube flow reactor.[140]

In some cases, purification steps between chemical steps have successfully been omitted, like in the one-step Hantzsch reaction−ester hydrolysis, where the HBr byproduct generated was used to hydrolyze the *tert*-butyl ester to directly generate pyrrole-3-carboxylic acids.[161] The same workers also reported on the formation of imidazo[1,2-*a*]pyridine-2-carboxamides, including a Mur Ligase inhibitor, without isolation of intermediates.[162] Multistep reaction sequences in flow, telescoped and without purification between chemical steps, have also been reported by workers like Bogdan et al. in their three-step synthesis of ibuprofen.[163]

However, most processes require some kind of purification or cleanup between chemical steps. Certain traditional cleanup operations such as liquid−liquid extraction are already known in continuous flow.[164] Another powerful tool is the use of packed-bed reactors with solid supported reagents, catalysts, or scavengers. They are being used in research laboratories with continuous flow reactors, but examples of their use in large scale are limited. Despite the obvious advantages of using supported reagents and scavengers in small scale synthesis,[165] their suitability for large scale synthesis is still debatable. In a large scale continuous flow operation they would have to be periodically replaced, which makes solid supported reagents and scavengers less attractive. Catalysts, however, have a longer life and are thus more suitable for large scale. The fact that immobilized reagents and scavengers can be expensive may also prevent them from being used on scale, whereas again solid supported catalyst may be more attractive, as the amount of reagent needed is less. However, systems where an automatic switch between packed-bed reactors takes place are conceivable (Figure 44a), although not yet incorporated in most commercial devices. This approach would definitely encourage the use of immobilized reagents, scavengers, and catalysts. In cases where the cost is low and/or they can be easily regenerated (Figure 44b), their use on scale could then be justified. It is worth mentioning that in the petroleum industry solid supported catalysts with continuous regeneration system are commonly used for cracking.[166] It is not a new concept for other industries, and it is an area that remains underdeveloped in the pharmaceutical industry.

A good example of how scavenging columns could be automatically replaced is described by Smith et al.[167] This

dx.doi.org/10.1021/jm2006029 | *J. Med. Chem.* 2012, 55, 4062−4098

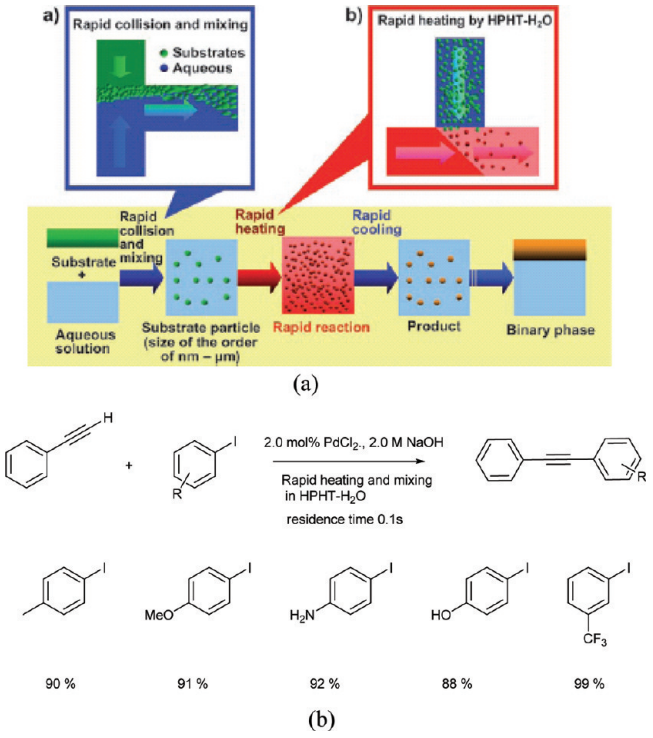


Figure 38. (a) Schematic of a reaction under the conditions of step-by-step rapid mixing and heating in high-pressure, high-temperature water. Reproduced with permission from *Angewandte Chemie International Edition* (Kawanami, H.; Matsushima, K.; Sato, M.; Ikushima, Y. Rapid and highly selective copper-free Sonogashira coupling in high-pressure, high-temperature water in a microfluidic system. *Angew. Chem., Int. Ed.* **2007**, *46*, 5129−5132).[137] Copyright 2007 John Wiley and Sons. (b) Sonogashira couplings of aryl iodides with phenyl acetylene at 250 °C and 16 MPa by the step-by-step rapid mixing and heating method.[137]

group synthesized triazoles from aromatic azides generated in situ from anilines. The acid/base scavenging columns used for in-line purification were switched from run to run by software controlled valves, as depicted in Figure 44a. This work is an early proof of concept that suggests a large potential for automation using solid-supported reagents.

Analytical Tools and In-Line Monitoring. Another important consideration for flow chemistry in general, but particularly for multistep synthesis, is the use of analytical tools. In-line monitoring techniques like UV, IR, or Raman are already being used.[168]

In-line monitoring gives real time information about the process and, in a significant development, can be linked to automatically control pumps in real time using suitable software. Lange et al.[169] were able to demonstrate the accurate control of a third pump to effectively deliver a 1:1 stoichiometry of a third stream to match the dispersion curve, using in-line IR monitoring (Figure 45). Figure 45 shows the IR cell (DiComp) measuring the dispersion curve of ketone **1** after the first reactor, sending the information to a computer, which in turn controls the third pump delivering the nitrobenzene **2** component. The second IR cell (SiComp), placed after the mixing of the third stream, satisfactorily shows a perfect overlap of the two components' dispersion curves, which confirms the successful delivery of the nitrobenzene **2** with a 1:1 stoichiometry with respect to ketone **1**.

In plug flow conditions, the concentrations of all components should be constant at any one point of the flow stream. When reactions are telescoped and, after initial reaction of streams A and B, a third stream C is flowed in, the flow rate at which this has to enter is also constant. However, on a research scale, segmented flow conditions are more common and, in this case, dispersion needs to be considered. As a result, after mixing A and B, the product will not flow out of the reactor with a constant concentration. Therefore, the introduction of a third stream C would have to be with a constantly changing flow rate of the third pump in order to deliver a 1:1 stoichiometry. Until now this was not possible, and reagents were normally added in excess. Software packages like the Flow Commander[31] that are able to predict the dispersion curve are already available, but now the work of Lange et al. has gone one step further.

■ REACTION OPTIMIZATION

Reaction optimization can be performed with microscale systems using a minimal amount of substrate and scaled-up to mesoscale systems, which are more meaningful for large scale production. A common method of initial reaction optimization is to screen different conditions with sequential reaction plugs. Different temperatures may be screened, and flow reactors, because of their large surface to volume ratio, are able to achieve the next set temperature quickly.

A good example is the recent optimization carried out by the group of Jamison and Jensen of epoxide aminolysis.[170] The authors carried out full kinetic modeling and optimization of their model reaction, chosen because of its similarity to the pharmaceutical agent indacaterol, with 35 different experiments carried out in 1 day using less than 5 g of each of the starting materials. They used a 120 μL silicon microreactor and syringe pumps. Optimized conditions used a 12.5 mL stainless steel coil reactor to produce 9 g of the desired amino alcohol (Scheme 18) with 78% yield. The use of one of the automated microfluidic platforms currently available (see "Overview of the Laboratory Equipment Available") should make these processes even more efficient, less labor intensive, and require less starting material.

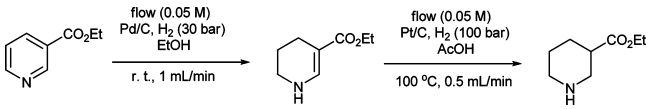
The number of experiments carried out in a reaction optimization can be minimized by incorporating in-line analytical detection and an optimization algorithm. This was demonstrated by McMullen et al.[171] in their multivariable optimization studies with an in-line HPLC system and different software algorithms. They studied a Knoevenagel reaction for temperature and residence time with three different algorithms, all of them arriving at the same optimal reaction conditions. They also carried out a four-dimensional optimization of the oxidation of benzyl alcohol with CrO_3 (Scheme 19). Although this might not be the preferred method for this reaction, the existence of a competing overoxidation reaction to benzoic acid was useful to demonstrate the validity of this method. The optimal conditions after 46 experiments within the range of values considered was T = 88 °C, residence time of 48 s, $[PhCH_2OH]^0$ = 8.2 nM, and 0.65 equiv of CrO_3, yielding 80% of the desired benzaldehyde. These results indicated that the reaction was enhanced at high temperatures and low residence times, although traditionally the reaction is carried out at low temperatures and longer residence times.

dx.doi.org/10.1021/jm2006029 | *J. Med. Chem.* 2012, 55, 4062−4098

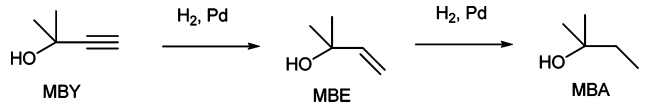
Substrate[1]	Yield (%)
Cbz-Pro-OMe	99[2]
Cbz-Piperazine	80[2]
Cbz-Asp(OMe)-OMe	77
Cbz-(OBn)Tyr-(OMe)	83[3]
Cbz-Ser-Ome	82
Boc-(N-Cbz)-Lys-O(Naph)	86
Cbz-Thr-Tyr(O-*t*-Bu)-O-*t*-Bu	96
Cbz-Pro-tetrazole	99

Figure 39. Deprotection of Cbz compounds using H-Cube at 80 °C.[141] Superscript numbers indicate the following: 1, each reaction performed by automated processing of 3.5 mL of a 0.05 M solution at 1mL/min at 80 °C; 2, product isolated as the HCl salt; 3, both protecting groups removed.

Scheme 15. Tuning the Selectivities between Full and Partial Hydrogenation of Pyridine 3-Carboxylate under Continuous Flow Conditions[142]



Scheme 16. Hydrogenation of 2-Methyl-3-butyne-2-ol to the Corresponding Alkene and Alkane[145]



High throughput of sequential experiments in a fully automated fashion coupled with an appropriate feedback logic algorithm could rapidly provide libraries of data by optimizing a reaction as per the required parameters.

■ IMPACT IN LARGER BATCHES FOR INITIAL CLINICAL STUDIES AND PRODUCTION

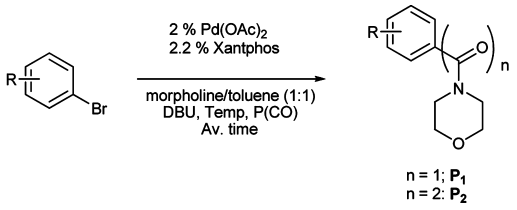
Large scale continuous reactors have been used in bulk chemicals and petroleum industries for decades, and they have enabled process intensification and process cost reduction. Continuous processing is only now, and only slowly, making its way into the collective pharmaceutical-manufacturing mindset, which is still holding onto traditional, yet reliable, processing methods. One of the reasons is that because of the low throughput required, the main value lies in the API rather than in the process. However, the diminution of drug discovery and emergence of generic competitors have pushed pharmaceutical industry to reduce their production cost and investigate continuous processing manufacture.

Within research one of the advantages of flow is the possibility of scale-up with minimum optimization. The system can easily be flowed for a longer time, keeping exactly the same reactor volume and flow rate to obtain more material. In some cases, the throughput can be incremented by increasing the concentration of the reactants or by increasing the reactor volume and the flow rate in the same proportion so that the ratio volume/flow rate or theoretical residence time remains the same. In this case, slight differences may be seen in selectivity and conversion. However, in most cases, similar results may be obtained and the methodology can be suitable for 10's to 100's of grams batches, which is probably enough for the toxicity studies.

For larger batches, a series of microreactors may be used. Usually they are not Lab-on-a-Chip devices but rather reactors with channels of 0.1−1.5 mm of internal diameter, moderate flow rates (10−100 mL/min), and Re of 100−3000, which can be classified as mesoreactors.[10] Metal−lithium exchange reactions among others have been carried out at Lonza with mesoreactors in production scale.[10]

Another method to scale continuous flow reactions is with a scale-out procedure. This concept consists of having several reactors in parallel so that the heat and mass transfer capabilities are the same while having a higher throughput with a relatively small footprint. Some examples are the pressure driven parallel capillary reactor by Styring and Parracho[172] (Figure 46) and the plastic microcapillary flow discs (MFDs) comprising an array of 10 parallel capillaries (150−400 μm diameter) embedded within a polymer film by

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062−4098



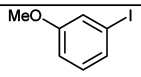
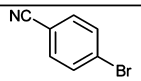
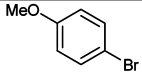
Aryl Bromide	P (bar)	T (°C)	Av. time (min.)	Yield P_1 (%)	Yield P_2 (%)
	7.9	146	3.3	68	28
	7.9	116	4.2	35	65
	2.7	160	7.1	83	0
	14.8	109	6.6	32	57
	2.7	150	12.7	35	0

Figure 40. Maximum yields for various carbonylation reactions.[146]

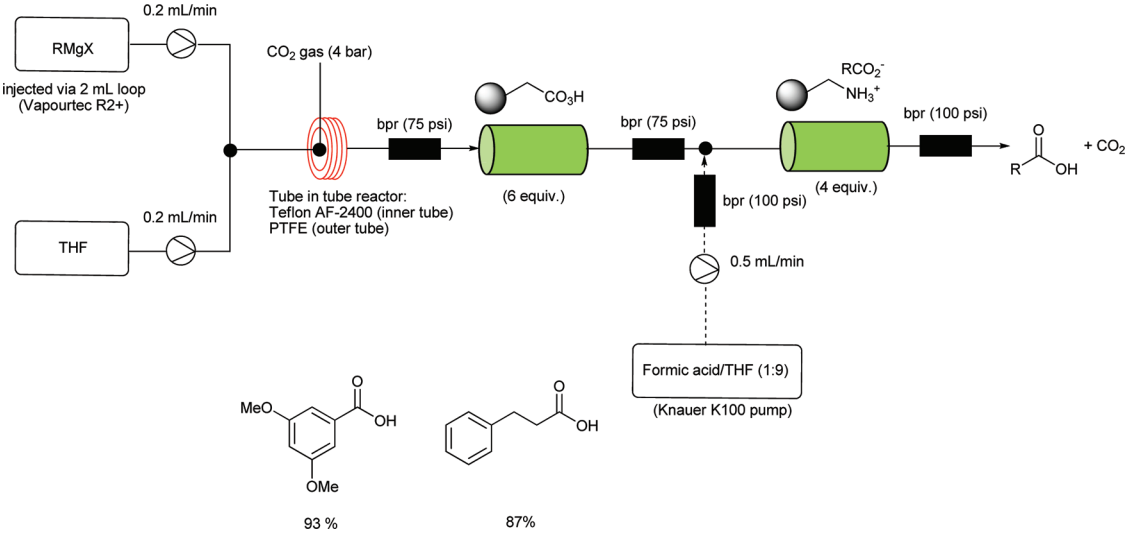
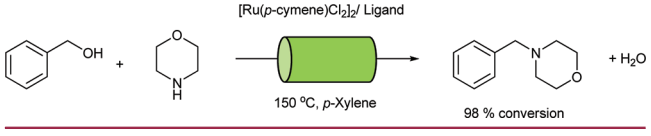


Figure 41. Flow reactor configuration for the carboxylation of Grignard reagents and two examples of carboxylic acid products.[148]

Scheme 17. Synthesis of Tertiary Amines from Alcohols and Secondary Amines Catalyzed by a Solid-Supported Ru Catalyst in Continuous Flow[154]



Hornung et al.[173] (Figure 47). These reactors can be useful for particular applications in a laboratory environment. However, technical difficulties with a scale-out approach such as ensuring exactly the same flow rates and therefore equal distribution of the reaction mixture in all the channels can be envisaged as faster flow rates are employed in faster reactions and/or larger reactors for a higher throughput. The scale-out solution might require a complex engineering setup. The velocity needs to be controlled to enable a similar residence time in each reactor, and any defect may affect the product quality and conversion. Solutions including multiple mass flow meters have been described, but a complex and fully automated rig increases the process cost significantly.

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062–4098

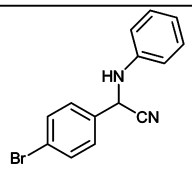
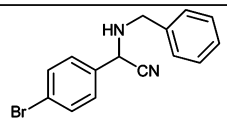
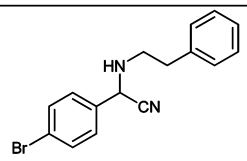
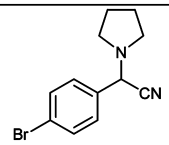
Product	Flow rate[a] (μl/min)	Yield (mg)	Conversion (%)	Throughput (mg/h)[b]
	10	43	100	17.2
	10	45	100	18.1
	10	47	100	18.9
	20	40	100	31.8[c]

Figure 42. Examples of α-aminonitriles synthesized from 4-bromobenzaldehyde in continuous flow using polymer supported $RuCl_3$.[155] Superscript letters indicate the following: a, total flow rate from the three fluidic inputs; b, run time of 2.50 h, unless otherwise stated; c, run time of 1.25 h.

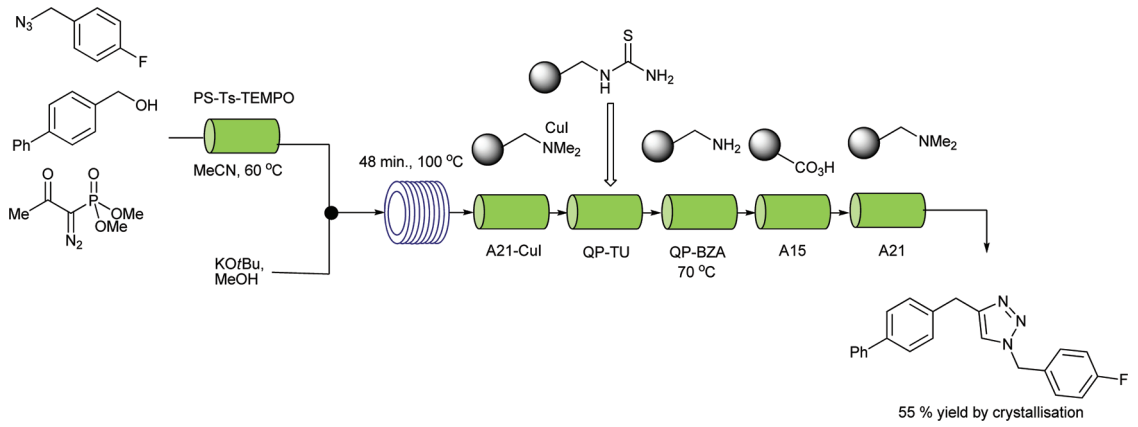


Figure 43. Three-step synthesis of a triazole in continuous flow.[158]

Despite all the developments of continuous processes conducted using micro- and mesoreactors, the solution of choice for manufacturing is the transfer to either a larger volume CSTR or a plug flow reactor, which can be implemented if necessary with a static mixer to reach the turbulent regime and to improve the mixing. Details of a continuous stirred tank reactors, a plug flow reactor, and a fixed bed reactor (right) used in industrial applications are in refs 174, 175, and 174, respectively.

In this case, the scale-up is not as straightforward as it seems or as many claim. The same issues observed for batch process scale-up, which are due to the changes of the physical rates, can be observed in continuous processing too. Similarly, as for batch process scale-up, a proper kinetic

dx.doi.org/10.1021/jm2006029 | J. Med. Chem. 2012, 55, 4062–4098

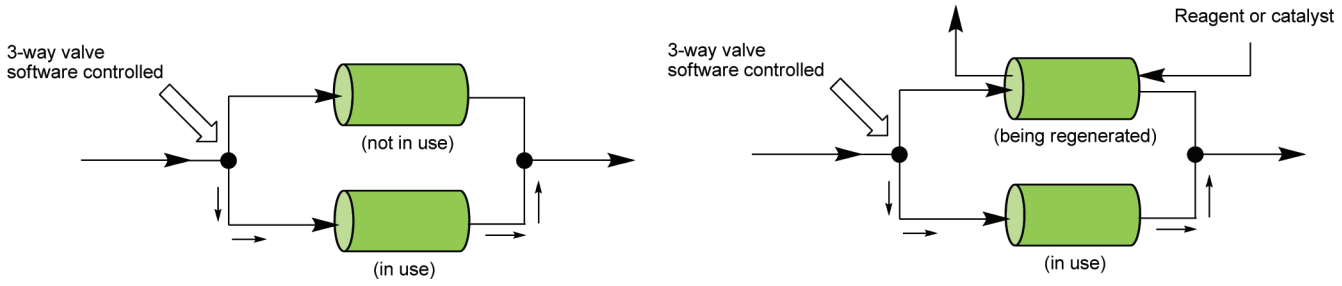


Figure 44. (a, left) Scheme of an automatic switch between packed-bed reactors. (b, right) Scheme of an automatic switch between packed-bed reactors with regeneration.

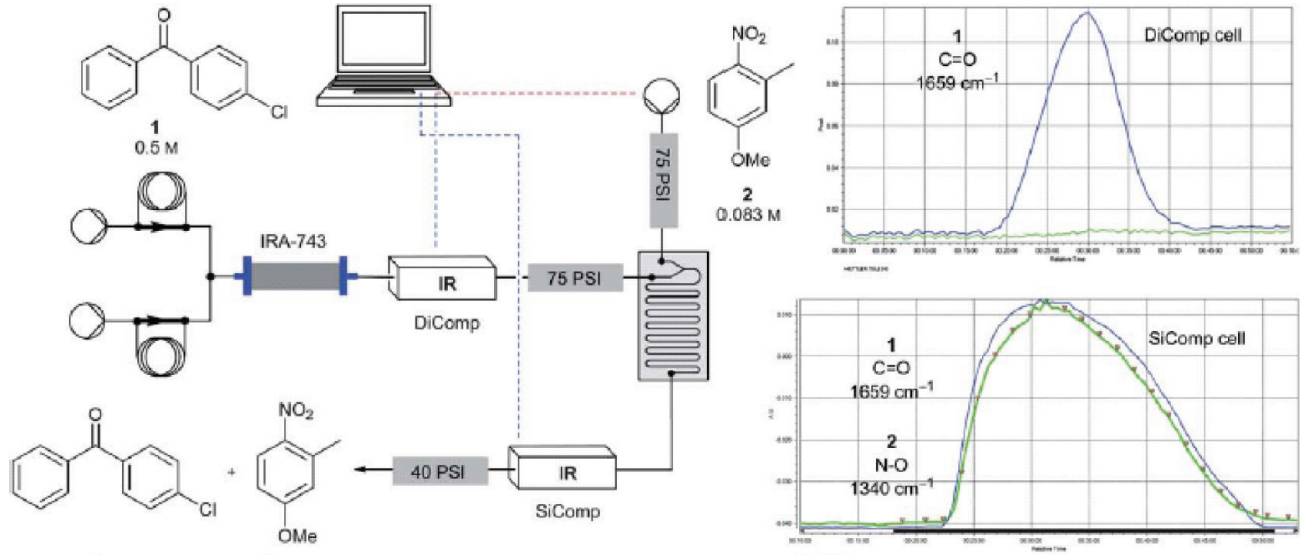
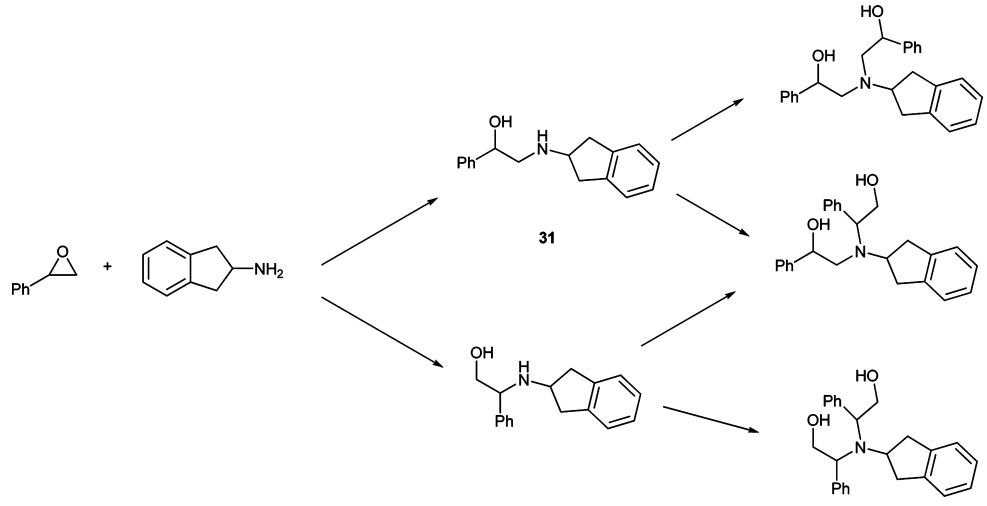


Figure 45. Proof of principle experiment illustrating precise addition of a third stream with 1:1 stoichiometry. From *Chemical Science* (http://dx.doi.org/10.1039/C0SC00603C) (Lange, H.; Carter, C. F.; Hopkin, M. D.; Burke, A.; Goode, J. G.; Baxendale, I. R.; Ley, S. V. A breakthrough method for the accurate addition of reagents in multi-step segmented flow processing. *Chem. Sci.* **2011**, *2*, 765−769);[169] Reproduced by permission of The Royal Society of Chemistry, Copyright 2011.

Scheme 18. Aminolysis Reaction and Possible Side Reactions[170]

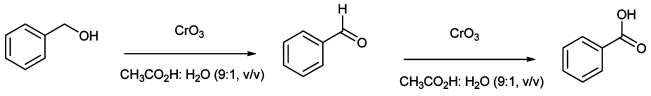


assessment of the reaction is usually recommended to understand the effect of concentration and temperature on the selectivity and conversion. An additional computational fluid dynamic (CFD) modeling of the reactor is usually required to assess potential back mixing, channeling, or dead zone and their impact on the product quality. Another consideration is that a continuous process offers a smaller window of operation than batch processing, and therefore,

greater knowledge of the processes is required. For example, the material usually stays in the reactor for a specific residence time whether or not the reaction is completed, whereas in a batch operation it can be heated for a bit longer if the reaction has not yet gone to completion.

In the pharmaceutical industry multipurpose plants are common because they limit capital investment costs, whereas in the bulk chemical industry dedicated continuous plants are generally the solution of choice.[16] The continuous processing strategy allows a just in time (JIT)[176] production approach and has a reduced footprint.[177,16] A JIT approach produces less waste and reduces costs because, among others, the product accumulation and storage requirements are significantly less. A dedicated continuous plant, commonly used in other industries, is only feasible when large amounts of API are required (~100 T/year), because of the logistics to put it in place.

Scheme 19. Oxidation of Benzyl Alcohol and Benzaldehyde Used To Demonstrate Multiparameter Optimization with the Automated Microfluidic System[171]



CONCLUSION

It is evident that continuous flow chemistry has a lot to offer to the pharmaceutical industry. A wide incorporation of the technique across all departments from early research to development and manufacturing is still a challenge. Although all departments need to work toward that aim, it is in Discovery Chemistry where the initiative should first be incorporated. Synthetic chemists need to change their mindset, and as more experience in the technique is gained, it should become significantly easier. Industry has been investing in flow chemistry, buying expensive pieces of equipment, and setting up collaborations with academic labs to build up knowledge

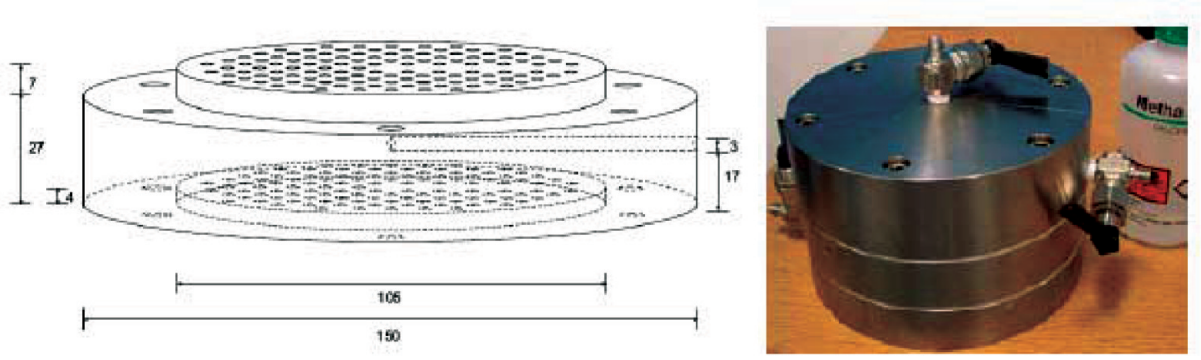


Figure 46. Pressure driven parallel capillary reactor. Reproduced from *Beilstein Journal of Organic Chemistry* (Styring, P.; Parracho, A. I. R. From discovery to production: scale-out of continuous flow meso reactors. *Beilstein J. Org. Chem.* **2009**, *5*, 29; http://www.beilstein-journals.org/bjoc/single/articleFullText.htm?publicId=1860-5397-5-29),[172] under the terms of Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0) and subject to *Beilstein Journal of Organic Chemistry* terms and conditions (http://www.beilstein-journals.org/bjoc). Copyright 2009 Styring and Parracho.

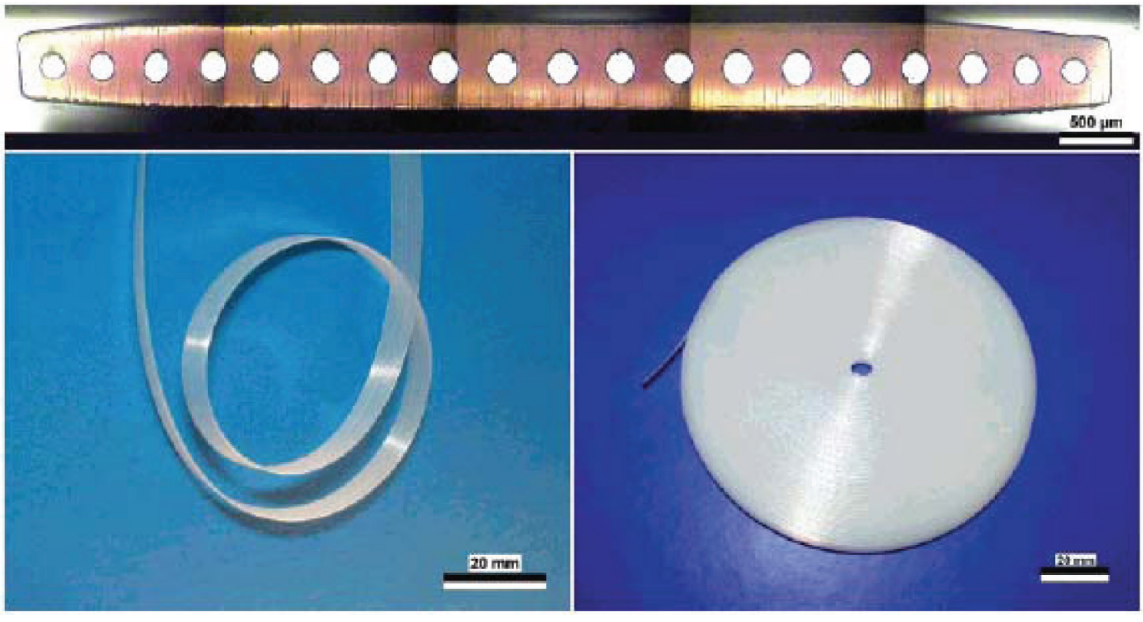


Figure 47. Photographic images of a plastic microcapillary flow disk reactor (MFD). Reproduced with permission from *Organic Process Research and Development*.[173] Copyright 2007 American Chemical Society.

dx.doi.org/10.1021/jm2006029 | *J. Med. Chem.* 2012, 55, 4062–4098

transfer. However, there is still a long way to go to achieve widespread use of this approach. We believe that, as synthetic chemists, we should be versatile. We should be able to decide for each synthesis which method works best. Only a broad knowledge of the possibilities and equipment available and feeling comfortable to use them will allow us to fully capitalize on the advantages of continuous processing.

Continuous processing is an engineering solution alternative to batch processing, which requires kinetic and fluid dynamic expertise, especially in scale-up. These skills have been developed in the bulk chemical, food, and petroleum industry for decades, and the challenge of the pharmaceutical industry, being a world of chemists, is to incorporate such skills.

Within Discovery Chemistry of Pfizer, Sandwich, U.K., flow chemistry was initially used for highly exothermic reactions and/or nitrogen releasing reactions such as Curtius rearrangements[90] or Sandmeyer reactions.[94,95] A dedicated group was then established that would routinely carry out nitrations[79] and fluorinations[59] in flow, as well as investigate a whole range of other reactions that could benefit from this technique. Flow is also evolving in early and late development, as well as in all stages in the Pfizer U.S. laboratories. Among the achievements in this area we can highlight the continuous process for the synthesis of maraviroc (HIV drug), which was successfully designed and carried out in the pilot plant, and the current manufacturing process for pregabalin which incorporates a continuous racemization step.

Although some overstatements may have been made on the advantages of continuous flow, as pointed out by Valera et al.,[82] some of the advantages are also very clear. It is evident that flow chemistry is not going to replace batch completely, but we strongly believe it can end up being utilized for a significant portion of synthesis in the pharmaceutical industry.

A final consideration is how the current trend to outsource a significant portion of the chemical synthesis in Discovery Chemistry and Development is going to affect the use of continuous processing. Our view is that external vendors will also increasingly incorporate this capability for the same reasons that have already been discussed in this manuscript.

AUTHOR INFORMATION

Corresponding Author

*Phone: +44 (0) 1622 299 757. E-mail: laiamalet@hotmail.com.

Biographies

Laia Malet Sanz is a Synthetic Chemist in the Medicinal Chemistry department at Pfizer Global Research and Development's Sandwich Laboratories, U.K. She received her degree in Chemistry from the University of Barcelona, Spain, which was followed by a Masters degree at Queen Mary, University of London, before joining Pfizer in 2003. Since then, she has worked on a wide variety of projects. Her research interests include all aspects of synthetic chemistry together with the use of flow chemistry, for which she was awarded the Pfizer Achievement Award 2009. Recently she completed a flow research project under the supervision of Prof. S. V. Ley and Dr. I. R. Baxendale in the Innovative Technology Center at the University of Cambridge, U.K.

Flavien Susanne is a Chemical Engineer based at Pfizer's Global Research and Development Laboratories in Sandwich, U.K. He received his M.Sc. in Organic Chemistry at the University of Caen, France, and his Chemical Engineering degree at Ecole National Superieur d'Ingenieur from the ENSI of Caen, France. He Joined Pfizer in 2004 as a Chemical Engineer in the Research and Development Department in Sandwich. His research interests include all aspects of process development and process transfer to manufacturing facilities, process modeling, and continuous processing from laboratory to pilot plant scale.

ACKNOWLEDGMENTS

We thank our colleagues and peers A. Brown, M. I. Kemp, A. C. Mansfield, T. Moran, C. J. Pilkington, and T. Underwood for their contributions.

ABBREVIATIONS USED

PK, pharmacokinetics; CSTR, continuous stirred-tank reactor; Bpr, back pressure regulator; PTFE, polytetrafluoroethylene; PFA, perfluoroalkoxy; PEEK, polyether ether ketone; API, active pharmaceutical ingredient; NBS, *N*-bromosuccinamide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DAST, dimethylaminosulfur trifluoride; *n*-BuLi, *n*-butyllithium; AIBN, azobisisobutyronitrile; THF, tetrahydrofuran; TFAA, trifluoroacetic anhydride

REFERENCES

(1) Proctor, L.; Dunn, P. J.; Hawkins, J. M., Wells, A. S.; Williams, M. T. Continuous Processing in the Pharmaceutical Industry. *Green Chemistry in the Pharmaceutical Industry*; Wiley-VCH: Weinheim, Germany, 2010.

(2) Geyer, K.; Gustafsson, T.; Seeberger, P. H. Developing continuous-flow microreactors as tools for synthetic chemists. *Synlett* **2009**, *15*, 2382−2391.

(3) Wiles, C.; Watts, P. Improving chemical synthesis using flow reactors. *Expert Opin. Drug Discovery* **2007**, *2*, 1487−1503.

(4) Wiles, C.; Watts, P. Enhanced chemical synthesis in flow reactors. *Chim. Oggi* **2009**, *27*, 34−36.

(5) Illg, T.; Löb, P.; Hessel, V. Flow chemistry using milli- and microstructured reactors: from conventional to novel process windows. *Bioorg. Med. Chem.* **2010**, *18*, 3707−3719.

(6) Hessel, V. Novel process windows: gate to maximizing process intensification via flow chemistry. *Chem. Eng. Technol.* **2009**, *32*, 1655−1681.

(7) Wiles, C.; Watts, P. The scale-up of organic synthesis using micro reactors. *Chim. Oggi* **2010**, *28*, 3−5.

(8) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. Greener approaches to organic synthesis using microreactor technology. *Chem. Rev.* **2007**, *107*, 2300−2318.

(9) Mills, P. L.; Quiram, D. J.; Ryley, J. F. Microreactor technology and process miniaturization for catalytic reactions: a perspective on recent developments and emerging technologies. *Chem. Eng. Sci.* **2007**, *62*, 6992−7010.

(10) Kockmann, N.; Gottsponer, M.; Zimmermann, B.; Roberge, D. M. Enabling continuous-flow chemistry in microstructured devices for pharmaceutical and fine-chemical production. *Chem.—Eur. J.* **2008**, *14*, 7470−7477.

(11) Horie, T.; Sumino, M.; Tanaka, T.; Matsushita, Y.; Ichimura, T.; Yoshida, J. Photodimerization of maleic anhydride in a microreactor without clogging. *Org. Process Res. Dev.* **2010**, *14*, 405−410.

(12) Shvydkiv, O.; Gallagher, S.; Nolan, K.; Oelgemoller, M. From conventional to microphotochemistry: photodecarboxylation reactions involving phthalimides. *Org. Lett.* **2010**, *12*, 5170−5173.

(13) Fukuyama, T.; Rahman, Md. T.; Sato, M.; Ryu, I. Adventures in inner space: microflow systems for practical organic synthesis. *Synlett* **2008**, *2*, 151−163.

(14) Grogan, G. Biotransformations. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2010**, *106*, 216−242.

(15) Continuous processing is only new in the pharma world, as it has existed in the bulk chemical industry for decades.

(16) Roberge, D. M.; Ducry, L.; Bieler, N.; Cretton, P.; Zimmermann, B. Microreactor technology: a revolution for the fine chemical and pharmaceutical industries? *Chem. Eng. Technol.* **2005**, *28*, 318−323.
(17) Kelly, C. B.; Lee, C. X.; Leadbeater, N. E. An approach for continuous-flow processing of reactions that involve the in situ formation of organic products. *Tetrahedron Lett.* **2011**, *52*, 263−265.
(18) Hopkin, M. D.; Baxendale, I. R.; Ley, S. V. A flow-based synthesis of imatinib: the API of Gleevec. *Chem. Commun.* **2010**, *46*, 2450−2452.
(19) Noël, T.; Naber, J. R.; Hartman, R. L.; McMullen, J. P.; Jensen, K. F.; Buchwald, S. L. Palladium-catalyzed amination reactions in flow: overcoming the challenges of clogging via acoustic irradiation. *Chem. Sci.* **2011**, *2*, 287−290.
(20) Sedelmeier, J.; Ley, S. V.; Baxendale, I. R.; Baumann, M. $KMnO_4$-mediated oxidation as a continuous flow process. *Org. Lett.* **2010**, *12*, 3618−3621.
(21) Horie, T.; Sumino, M.; Tanaka, T.; Matsushita, Y.; Ichimura, T.; Yoshida, J. Photodimerization of maleic anhydride in a microreactor without clogging. *Org. Process Res. Dev.* **2010**, *14*, 405−410.
(22) Zhao, C.; He, L.; Qiao, S. Z.; Middelberg, A. P. J. Nanoparticle synthesis in microreactors. *Chem. Eng. Sci.* **2011**, *66*, 1463−1479.
(23) Buisson, B.; Donegan, S.; Wray, D.; Parracho, A.; Gamble, J.; Caze, P.; Jorda, J.; Guermeur, C. Slurry hydrogenation in a continuous flow reactor for pharmaceutical application. *Chim. Oggi* **2009**, *27* (6), 12−16.
(24) Poe, S. L.; Cummings, M. A.; Haaf, M. P.; McQuade, D. T. Solving the clogging problem: precipitate-forming reactions in flow. *Angew. Chem., Int. Ed.* **2006**, *45*, 1544−1548.
(25) Hartman, R. L.; Naber, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. Overcoming the challenges of solid bridging and constriction during Pd-Catalyzed C−N bond formation in microreactors. *Org. Process Res. Dev.* **2010**, *14*, 1347−1357.
(26) Geyer, K.; Codée, J. D. C.; Seeberger, P. H. Microreactors as tools for synthetic chemists: the chemists' round-bottomed flask of the 21st century? *Chem.—Eur. J.* **2006**, *12*, 8434−8442.
(27) Chemtrix. http://www.chemtrix.com/web/4/1/product.html.
(28) Syrris. Flow Products. http://www.syrris.com/flow-products/africa-flow-chemistry-overview.
(29) Future Chemistry. Flow Chemistry Instruments. http://www.futurechemistry.com/products.html.
(30) http://www.accendocorporation.com/index_files/Conjure2.html.
(31) Vapourtec. The R Series Integrated Flow Chemistry System. http://www.vapourtec.co.uk/products/rseriessystem.
(32) Uniqsis, Accessible Flow Chemistry. http://www.uniqsis.com/.
(33) Syrris. Flow Products. http://www.syrris.com/flow-products/asia-flow-chemistry.
(34) http://www.accendocorporation.com/index_files/Propel2.html.
(35) Alfa Laval. One Flow Reactor—A Lot of Reactionshttp://www.alfalaval.com/campaigns/labplatereactor/Pages/default.aspx.
(36) ThalesNano. http://www.thalesnano.com/.
(37) HEL. http://www.helgroup.com/reactor-systems/hydrogenation-catalysis/flowcat-highpressure-flowchemistry-in-a-compact-unit/.
(38) Zhang, X.; Stefanick, S.; Villani, F. J. Application of microreactor technology in process development. *Org. Process. Res. Dev.* **2004**, *8*, 455−460.
(39) Institut für Mikrotechnik Mainz GmbH. Components/Modules. http://www.imm-mainz.de/index.php?id=components0.
(40) Corning. http://www.corning.com/r_d/emerging_technologies/reactors.aspx.
(41) Lavric, E. D.; Woehl, P. Advanced-flow glass reactors for seamless scale-up. *Chim. Oggi* **2009**, *27*, 45−48.
(42) Alfa Laval. http://www.alfalaval.com/about-us/Pages/About-us.aspx.
(43) Sulzer. Mixing & Reaction Technology. http://www.sulzerchemtech.com/en/DesktopDefault.aspx/tabid-459/.
(44) Chemineer. Kenics Static Mixers. http://www.chemineer.com/kenics_-_static_mixers.php.
(45) Yoshida, J. Flash chemistry using electrochemical method and microsystems. *Chem. Commun.* **2005**, 4509−4516.
(46) Yoshida, J.; Nagaki, A.; Yamada, T. Flash chemistry: fast chemical synthesis by using microreactors. *Chem.—Eur. J.* **2008**, *14*, 7450−7459.
(47) For a good review see Baxendale, I. R.; Hayward, J. J.; Ley, S. V. Microwave reactions under continuous flow conditions. *Comb. Chem. High Throughput Screening* **2007**, *10*, 802−836.
(48) Ullah, F.; Samarakoon, T.; Rolfe, A.; Kurtz, R. D.; Hanson, P. R.; Organ, M. G. Scaling out by microwave-assisted, continuous flow organic synthesis (MACOS): multi-gram synthesis of bromo- and fluoro-benzofused sultams, benzoxathiazepine 1,1-dioxides. *Chem.—Eur. J.* **2010**, *16*, 10959−10962.
(49) Singh, B. K.; Kaval, N.; Tomar, S.; Van der Eycken, E.; Parmar, V. S. Transition metal-catalyzed carbon−carbon bond formation Suzuki, Heck, and Sonogashira reactions using microwave and microtechnology. *Org. Process Res. Dev.* **2008**, *12*, 468−474.
(50) Hodgkinson, J. T.; Galloway, W. R. J. D.; Saraf, S.; Baxendale, I. R.; Ley, S. V.; Ladlow, M.; Welch, M.; Spring, D. R. Microwave and flow syntheses of Pseudomonas quinolone signal (PQS) and analogues. *Org. Biomol. Chem.* **2011**, *9*, 57−61.
(51) Castellano, S.; Tamborini, L.; Viviano, M.; Pinto, A.; Sbardella, G.; Conti, P. Synthesis of 3-aryl/benzyl-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]isoxazole derivatives: a comparison between conventional, microwave-assisted and flow-based methodologies. *J. Org. Chem.* **2010**, *75*, 7439−7442.
(52) Shore, G.; Tsimerman, M.; Organ, M. G. Gold film-catalyzed benzannulation by microwave-assisted, continuous flow organic synthesis (MACOS). *Beilstein J. Org. Chem.* **2009**, *5*, 35.
(53) Shore, G.; Yoo, W.; Li, C.; Organ, M. G. Propargyl amine synthesis catalysed by gold and copper thin films by using microwave-assisted continuous-flow organic synthesis (MACOS). *Chem.—Eur. J.* **2010**, *16*, 126−133.
(54) Darvas, F.; Dormán, G.; Lengyel, L.; Kovács, I.; Jones, R.; Ürge, L. High pressure, high temperature reactions in continuous flow: merging discovery and process chemistry. *Chim. Oggi* **2009**, *27*, 40−43.
(55) Mello, R.; Olmos, A.; Alcalde-Aragonés, A.; Diaz-Rodríguez, A.; González-Núñez, M. E.; Asensio, G. Oxidation of sulfides with a silica-supported peracid in supercritical carbon dioxide under flow conditions: tuning chemoselectivity with pressure. *Eur. J. Org. Chem.* **2010**, 6200−6206.
(56) Razzaq, T.; Glasnov, T. N.; Kappe, C. O. Continuous-flow microreactor chemistry under high-temperature/pressure conditions. *Eur. J. Org. Chem.* **2009**, 1321−1325.
(57) Palmieri, A.; Ley, S. V.; Hammond, K.; Polyzos, A.; Baxendale, I. R. A microfluidic flow chemistry platform for organic synthesis: the Hofmann rearrangement. *Tetrahedron Lett.* **2009**, *50*, 3287−3289.
(58) Advion. NanoTek, a Microfluidic Flow-Chemistry System. http://www.advion.com/biosystems/nanotek/nanotek-positron-emission-tomography.php.
(59) Underwood, T.. Pfizer, Ltd., Sandwich, U.K. Unpublished internal results.
(60) Kulkarni, A. A.; Nivangune, N. T.; Kalyani, V. S.; Joshi, R. A.; Joshi, R. R. Continuous flow nitration of salicylic acid. *Org. Process. Res. Dev.* **2008**, *12*, 995−1000.
(61) Dominique, R.; Laurent, D.; Lonza A. G. Nitration of Activated Aromatics in Microreactors. WO2007087816A1, 2007.
(62) Halder, R.; Lawal, A.; Damavarapu, R. Nitration of toluene in a microreactor. *Catal. Today* **2007**, *125*, 74−80.
(63) Ducry, L.; Roberge, D. M. Controlled autocatalytic nitration of phenol in a microreactor. *Angew. Chem., Int. Ed.* **2005**, *44*, 7972−7975.
(64) Panke, G.; Schwalbe, T.; Stirner, W.; Taghavi-Moghadam, S.; Wille, G. A practical approach of continuous processing to high energetic nitration reactions in microreactors. *Synthesis* **2003**, *18*, 2827−2830.

(65) Burns, J. R.; Ramshaw, C. A microreactor for the nitration of benzene and toluene. *Chem. Eng. Commun.* **2002**, *189*, 1611−1628.
(66) Kulkarni, A. A.; Kalyani, V. S.; Joshi, R. A.; Joshi, R. R. Continuous flow nitration of benzaldehyde. *Org. Process. Res. Dev.* **2009**, *13*, 999−1002.
(67) Pelleter, J.; Renaud, F. Facile, fast and safe process development of nitration and bromination reactions using continuous flow reactors. *Org. Process. Res. Dev.* **2009**, *13*, 698−705.
(68) de Mas, N.; Günther, A.; Schmidt, M. A.; Jensen, K. F. Microfabricated multiphase reactors for the selective direct fluorination of aromatics. *Ind. Eng. Chem. Res.* **2003**, *42*, 698−710.
(69) Jähnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Haverkamp, V.; Löwe, H.; Wille, Ch.; Guber, A. Direct fluorination of toluene using elemental fluorine in gas/liquid microreactors. *J. Fluorine Chem.* **2000**, *105*, 117−128.
(70) Chambers, R. D.; Spink, R. C. H. Microreactors for elemental fluorine. *Chem. Commun.* **1999**, 883−884.
(71) Chambers, R. D.; Holling, D.; Spink, R. C. H.; Sandford, G. Elemental fluorine. Part 13. Gas−liquid thin film microreactors for selective direct fluorination. *Lab Chip* **2001**, *1*, 132−137.
(72) Chambers, R. D.; Fox, M. A.; Sandford, G.; Trmcic, J.; Goeta, A. Elemental fluorine. Part 20. Direct fluorination of deactivated aromatic systems using microreactor techniques. *J. Fluorine Chem.* **2007**, *128*, 29−33.
(73) Chambers, R. D.; Sandford, G.; Trmcic, J.; Okazoe, T. Elemental fluorine. Part 21. Direct fluorination of benzaldehyde derivatives. *Org. Process Res. Dev.* **2008**, *12*, 339−344.
(74) Turnbull, M. D.; Carter, N. B.; Dennison, S.; Deacon, J.; Holley, R. Microfluidics-based reactors for safe fluorinations using elemental fluorine. *Chimia* **2004**, *58*, 159−162.
(75) Messina, P. A.; Mange, K. C.; Middleton, W. J. Aminosulfur trifluorides: relative thermal stability. *J. Fluorine Chem.* **1989**, *42*, 137−143.
(76) Baumann, M.; Baxendale, I. R.; Ley, S. V. The use of diethylaminosulfur trifluoride (DAST) for fluorination in a continuous-flow microreactor. *Synlett* **2008**, *14*, 2111−2114.
(77) Gustafsson, T.; Gilmour, R.; Seeberger, P. H. Fluorination reactions in microreactors. *Chem. Commun.* **2008**, 3022−3024.
(78) Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. Development of fluorination methods using continuous-flow microreactors. *Tetrahedron* **2009**, *65*, 6611−6625.
(79) Mansfield, A. C.; Peach, T. Pfizer, Ltd., Sandwich, U.K. Unpublished internal results.
(80) Nagaki, A.; Kim, H.; Yoshida, J. Aryllithium compounds bearing alkoxycarbonyl groups: generation and reactions using a microflow system. *Angew. Chem., Int. Ed.* **2008**, *47*, 7833−7836.
(81) Nagaki, A.; Kim, H.; Usutani, H.; Matsuo, C.; Yoshida, J. Generation and reaction of cyano-substituted aryllithium compounds using microreactors. *Org. Biomol. Chem.* **2010**, *8*, 1212−1217.
(82) Valera, F. E.; Quaranta, M.; Moran, A; Blacker, J.; Armstrong, A; Cabral, J. T.; Blackmond, D. G. The flow's the thing...or is it? Assessing the merits of homogeneous reactions in flask and flow. *Angew. Chem., Int. Ed.* **2010**, *49*, 2478−2485.
(83) Venturoni, F.; Nikbin, N.; Ley, S. V.; Baxendale, I. R. The application of flow microreactors to the preparation of a family of casein kinase I inhibitors. *Org. Biomol. Chem.* **2010**, *8*, 1798−1806.
(84) Krummradt, H.; Koop, U.; Stoldt, J. Microreactors at Merck, Darmstadt, Germany. *GIT Labor-Fachz.* **1999**, *43* (6), 590−592.
(85) Riva, E.; Gagliardi, S.; Martinelli, M.; Passarella, S.; Vigo, D.; Rencurosi, A. Reaction of Grignard reagents with carbonyl compounds under continuous flow conditions. *Tetrahedron* **2010**, *66*, 3242−3247.
(86) Qian, Z.; Baxendale, I. R.; Ley, S. V. A continuous flow process using a sequence of microreactors with in-line IR analysis for the preparation of *N*,*N*-diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl)benzamide as a potent and highly selective δ-opioid receptor agonist. *Chem.—Eur. J.* **2010**, *16*, 12342−12348.
(87) Rolland, J.; Cambeiro, X. C.; Rodríguez-Escrich, C.; Pericàs, M. A. Continuous flow enantioselective arylation of aldehydes with ArZnEt using triarylboroxins as the ultimate source of aryl groups. *Beilstein J. Org. Chem.* **2009**, *5*, 56.
(88) Pericàs, M. A.; Herrerías, C. I.; Solà, L. L. Fast and enantioselective production of 1-aryl-1-propanols through a single pass, continuous flow process. *Adv. Synth. Catal.* **2008**, *350*, 927−932.
(89) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D.; Tierney, J. P. A modular flow reactor for performing Curtius rearrangements as a continuous flow process. *Org. Biomol. Chem.* **2008**, *6*, 1577−1586.
(90) Bull, D.; Mansfield, A. C. Pfizer, Ltd., Sandwich, U.K. Unpublished internal results.
(91) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D. Azide monoliths as convenient flow reactors for efficient Curtius rearrangement reactions. *Org. Biomol. Chem.* **2008**, *6*, 1587−1593.
(92) Fortt, R.; Wootton, R. C. R.; de Mello, A. J. Continuous-flow generation of anhydrous diazonium species: monolithic microfluidic reactors for the chemistry of unstable intermediates. *Org. Process Res. Dev.* **2003**, *7*, 762−768.
(93) Sigma-Aldrich. Material Safety Data Sheet. http://www.sigmaaldrich.com/catalog/DisplayMSDSContent.do.
(94) Malet-Sanz, L.; Madrzak, J.; Holvey, R. S.; Underwood, T. A safe and reliable procedure for the iododeamination of aromatic and heteroaromatic amines in a continuous flow reactor. *Tetrahedron Lett.* **2009**, *50*, 7263−7267.
(95) Malet-Sanz, L.; Madrzak, J.; Ley, S. V.; Baxendale, I. R. Preparation of arylsulfonyl chlorides by chlorosulfonylation of in situ generated diazonium salts using a continuous flow reactor. *Org. Biomol. Chem.* **2010**, *8*, 5324−5332.
(96) Bartrum, H. E.; Blakemore, D. C.; Moody, C. J.; Hayes, C. J. Synthesis of β-keto esters in-flow and rapid access to substituted pyrimidines. *J. Org. Chem.* **2010**, *75*, 8674−8676.
(97) Zaborenko, N.; Murphy, E. R.; Krlj, J. G.; Jensen, K. F. Synthesis and kinetics of highly energetic intermediates by micromixers: direct multistep synthesis of sodium nitrotetrazolate. *Ind. Eng. Chem. Res.* **2010**, *49*, 4132−4139.
(98) Martin, L. J.; Marzinzik, A. L.; Ley, S. V.; Baxendale, I. R. Safe and reliable synthesis of diazoketones and quinoxalines in a continuous flow reactor. *Org. Lett.* **2011**, *13*, 320−323.
(99) Kopach, M. E.; Murray, M. M.; Braden, T. M.; Kobierski, M. E.; Williams, O. L. Improved synthesis of 1-(azidomethyl)-3,5-bis-(trifluoromethyl)benzene: development of batch and microflow azide processes. *Org. Process Res. Dev.* **2009**, *13*, 152−160.
(100) Gutmann, B.; Roduit, J. P.; Roberge, D.; Kappe, C. O. Synthesis of 5-substituted 1*H*-tetrazoles from nitriles and hydrazoic acid by using a safe and scalable high-temperature microreactor approach. *Angew. Chem., Int. Ed.* **2010**, *49*, 7101−7105.
(101) Smith, C. J.; Smith, C. D.; Nikbin, N.; Ley, S. V.; Baxendale, I. R. Flow synthesis of organic azides and the multistep synthesis of imines and amines using a new monolithic triphenylphosphine reagent. *Org. Biomol. Chem.* **2011**, *9*, 1927−1937.
(102) Stazi, F.; Cancogni, D.; Turco, L.; Westerduin, P.; Bacchi, S. Highly efficient and safe procedure for the synthesis of aryl 1,2,3-triazoles from aromatic amine in a continuous flow reactor. *Tetrahedron Lett.* **2010**, *51*, 5385−5387.
(103) O'Brien, A. G.; Levesque, F.; Seeberger, P. H. Continuous flow thermolysis of azidoacrylates for the synthesis of heterocycles and pharmaceutical intermediates. *Chem. Commun.* **2011**, *47*, 2688−2690.
(104) Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J. Room-temperature Swern oxidations by using a microscale flow system. *Angew. Chem., Int. Ed.* **2005**, *44*, 2413−2416.
(105) van der Linden, J. J. M.; Hilberink, P. W.; Kronenburg, C. M. P.; Kemperman, G. J. Investigation of the Moffatt−Swern oxidation in a continuous flow microreactor system. *Org. Process Res. Dev.* **2008**, *12*, 911−920.
(106) Nieuwland, P. J.; Koch, K.; van Harskamp, N.; Wehrens, R.; van Hest, J. C. M.; Rutjes, F. P. J. T. Flash chemistry extensively optimized: high-temperature Swern−Moffatt oxidation in an automated microreactor platform. *Chem. Asian J.* **2010**, *5*, 799−805.

(107) Chambers, R. D.; Holling, D.; Rees, A. J.; Sandford, G. Microreactors for oxidations using fluorine. *J. Fluorine Chem.* **2003**, *119*, 81−82.
(108) McPake, C. B.; Murray, C. B.; Sandford, G. Epoxidation of alkenes using HOF·MeCN by a continuous flow process. *Tetrahedron Lett.* **2009**, *50*, 1674−1676.
(109) McPake, C. B.; Murray, C. B.; Sandford, G. Continuous flow oxidation processes using HOF·MeCN. *Chim. Oggi* **2010**, *28*, 6−7.
(110) Kobayashi, S.; Miyamura, H.; Akiyama, R.; Ishida, T. Highly active, immobilized ruthenium catalysts for oxidation of alcohols to aldehydes and ketones. Preparation and use in both batch and flow systems. *J. Am. Chem. Soc.* **2005**, *127*, 9251−9254.
(111) Tanaka, H.; Chou, J.; Mine, M.; Kuroboshi, M. The oxidation of alcohols in *N*-oxyl-immobilized silica gel/aqueous NaOCl disperse systems. A prominent access to a column-flow system. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1745−1755.
(112) Bogdan, A.; McQuade, T. A biphasic oxidation of alcohols to aldehydes and ketones using a simplified packed-bed microreactor. *Beilstein J. Org. Chem.* **2009**, *5*, 17.
(113) Derikvand, F.; Bigi, F.; Maggi, R.; Piscopo, C. G.; Sartori, G. Oxidation of hydroquinones to benzoquinones with hydrogen peroxide using catalytic amount of silver oxide under batch and continuous-flow conditions. *J. Catal.* **2010**, *271*, 99−103.
(114) Yamada, Y. M. A.; Torii, K.; Uozumi, Y. Oxidative cyclization of alkenols with Oxone using a miniflow reactor. *Beilstein J. Org. Chem.* **2009**, *5*, 18.
(115) Lange, H.; Capener, M. J.; Jones, A. X.; Smith, C. J.; Nikbin, N.; Baxendale, I. R. Oxidation reactions in segmented and continuous flow chemical processing using an *N*-(*tert*-butyl)phenylsulfinimidoyl chloride monolith. *Synlett* **2011**, *6*, 869−873.
(116) Ye, X.; Johnson, M. D.; Diao, T.; Yates, M. H.; Stahl, S. S. Development of safe and scalable continuous-flow methods for palladium-catalyzed aerobic oxidation reactions. *Green Chem.* **2010**, *12*, 1180−1186.
(117) Brandt, J. C.; Elmore, S. C.; Robinson, R. I.; Wirth, T. Safe and efficient Ritter reactions in flow. *Synlett* **2010**, 3099−3103.
(118) Grafton, M.; Mansfield, A. C.; Fray, M. J. [3 + 2] Dipolar cycloadditions of an unstabilised azomethine ylide under continuous flow conditions. *Tetrahedron Lett.* **2010**, 1026−1029.
(119) Baumann, M.; Baxendale, I. R.; Ley, S. V. Synthesis of 3-nitropyrrolidines via dipolar cycloaddition reactions using a modular flow reactor. *Synlett* **2010**, *5*, 749−752.
(120) Odedra, A.; Geyer, K.; Gustafsson, T.; Gilmour, R.; Seeberger, P. H. Safe, facile radical-based reduction and hydrosilylation reactions in a microreactor using tris(trimethylsilyl)silane. *Chem. Commun.* **2008**, 3025−3027.
(121) Ahmed, B.; Barrow, D.; Wirth, T. Enhancement of reaction rates by segmented fluid flow in capillary scale reactors. *Adv. Synth. Catal.* **2006**, *348*, 1043−1048.
(122) Ueno, M.; Hisamoto, H.; Kitamori, T.; Kobayashi, S. Phase-transfer alkylation reactions using microreactors. *Chem. Commun.* **2003**, *8*, 936−937.
(123) Ahmed-Omer, B.; Barrow, D. A.; Wirth, T. Heck reactions using segmented flow conditions. *Tetrahedron Lett.* **2009**, *50*, 3352−3355.
(124) Wurziger, H.; Pieper, G.; Schmelz, M.; Schwesinger, N. Use of a Microreaction Channel with a Piezo Element. WO0249737A1, 2002-DE10063027, 2002.
(125) Jovanovic, J.; Rebrov, E. V.; Nijhuis, T. A.; Hessel, V.; Schouten, J. C. Phase-transfer catalysis in segmented flow in a microchannel: fluidic control of selectivity and productivity. *Ind. Eng. Chem. Res.* **2010**, *49*, 2681−2687.
(126) Massingill, J. L.; Patel, P. N.; Guntupalli, M.; Garret, C.; Ji, C. High efficiency nondispersive reactor for two-phase reactions. *Org. Process Res. Dev.* **2008**, *12*, 771−777.
(127) Pollet, P.; Cope, E. D.; Kassner, M. K.; Charney, R.; Terett, S. H.; Richman, K. W.; Dubay, W.; Stringer, J.; Eckert, C. A.; Liotta, C. L. Production of (*S*)-1-benzyl-3-diazo-2-oxopropylcarbamic acid *tert*-butyl ester, a diazoketone pharmaceutical intermediate, employing a small scale continuous reactor. *Ind. Eng. Chem. Res.* **2009**, *48*, 7032−7036.
(128) Naber, J. R.; Buchwald, S. L. Packed-bed reactors for continuous-flow C−N cross-coupling. *Angew. Chem., Int. Ed.* **2010**, *49*, 9469−9474.
(129) AM Technology. http://www.amtechuk.com/default.aspx.
(130) Browne, D. L.; Deadman, B. J.; Ashe, R.; Baxendale, I. R.; Ley, S. V. Continuous flow processing of slurries: evaluation of an agitated cell reactor. *Org. Process Res. Dev.* **2011**, *15*, 693−697.
(131) Nikbin, N.; Ladlow, M.; Ley, S. V. Continuous flow ligand-free heck reactions using monolithic Pd[0] nanoparticles. *Org. Process Res. Dev.* **2007**, *11*, 458−462.
(132) Huang, W.; Liu, J. H.; Alayoglu, P.; Li, Y.; Witham, C. A.; Tsung, C.; Toste, F. D.; Somorjai, G. A. Highly active heterogeneous palladium nanoparticle catalysts for homogeneous electrophilic reactions in solution and the utilization of a continuous flow reactor. *J. Am. Chem. Soc.* **2010**, *132*, 16771−16773.
(133) Hornung, C. H.; Hallmark, B.; Mackely, M. R.; Baxendale, I. R.; Ley, S. V. A palladium wall coated microcapillary reactor for use in continuous flow transfer hydrogenation. *Adv. Synth. Catal.* **2010**, *352*, 1736−1745.
(134) Tagata, T.; Nishida, N.; Nishida, A. Continuous-flow C−H borylation of arene derivatives. *Adv. Synth. Catal.* **2011**, *352*, 1662−1666.
(135) Glasnov, T. N.; Kappe, C. O. Toward a continuous-flow synthesis of boscalid. *Adv. Synth. Catal.* **2010**, *352*, 3089−3097.
(136) Singh, B. K.; Stevens, C. V.; Acke, D. R. J.; Parmar, V. S.; Van der Eycken, E. V. Copper-mediated N- and N-arylations with arylboronic acids in a continuous flow microreactor: a new avenue for efficient scalability. *Tetrahedron Lett.* **2009**, *50*, 15−18.
(137) Kawanami, H.; Matsushima, K.; Sato, M.; Ikushima, Y. Rapid and highly selective copper-free Sonogashira coupling in high-pressure, high-temperature water in a microfluidic system. *Angew. Chem., Int. Ed.* **2007**, *46*, 5129−5132.
(138) Bogdan, A. R.; Sach, N. W. The use of copper flow reactor technology for the continuous synthesis of 1,4-disubstituted 1,2,3-triazoles. *Adv. Synth. Catal.* **2009**, *351*, 849−851.
(139) Bogdan, A. R.; James, K. Efficient access to new chemical space through flow-construction of drug-like macrocycles through copper-surface-catalyzed azide−alkyne cycloaddition reactions. *Chem.—Eur. J.* **2010**, *16*, 14506−14512.
(140) Zhang, Y.; Jamison, T. F.; Patel, S.; Mainolfi, N. Continuous flow coupling and decarboxylation reactions promoted by copper tubing. *Org. Lett.* **2011**, *13*, 280−283.
(141) Knudsen, K. R.; Holden, J.; Ley, S. V.; Ladlow, M. Optimisation of conditions for *O*-benzyl and *N*-benzyloxycarbonyl protecting group removal using an automated flow hydrogenator. *Adv. Synth. Catal.* **2007**, *349*, 535−538.
(142) Irfan, M.; Petricci, E.; Glasnov, T. N.; Taddei, M.; Kappe, C. O. Continuous flow hydrogenation of functionalized pyridines. *Eur. J. Org. Chem.* **2009**, 1327−1334.
(143) Cserényi, S.; Szöllösi, G.; Szöri, K.; Fülöp, F.; Bartók, M. Reversal of the ee in enantioselective hydrogenation of activated ketones in continuous-flow fixed-bed reactor system. *Catal. Commun.* **2010**, *12*, 14−19.
(144) Hawkins, J. M. Enantio- and Diastereoselective Hydrogenation of Pharmaceutical Intermediates. Pfizer PharmaTherapeutics: Newport, RI, 2010; http://www.helgroup.com/articles/pdf/c47c98f847ff922d/Hawkins%20Stereochemistry%20GRC%208-4-10.pdf.
(145) Rebrov, E. V.; Klinger, E. A.; Berenguer-Murcia, A.; Sulman, E. M.; Schouten, J. C. Selective hydrogenation of 2-methyl-3-butyne-2-ol in a wall-coated capillary microreactor with a $Pd_{25}Zn_{75}/TiO_2$ catalyst. *Org. Process Res. Dev.* **2009**, *13*, 991−998.
(146) Murphy, E. R.; Martinelli, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. Accelerating reactions with microreactors at elevated temperatures and pressures: profiling aminocarbonylation reactions. *Angew. Chem., Int. Ed.* **2007**, *46*, 1734−1737.

(147) O'Brien, M.; Baxendale, I. R.; Ley, S. V. Flow ozonolysis using a semipermeable Teflon AF-2400 membrane to effect gas−liquid contact. *Org. Lett.* **2010**, *12*, 1596−1598.
(148) Polyzos, A.; O'Brien, M.; Petersen, T. P.; Baxendale, I. R.; Ley, S. V. The continuous-flow synthesis of carboxylic acids using CO_2 in a tube-in-tube gas permeable membrane reactor. *Angew. Chem., Int. Ed.* **2011**, *50*, 1190−1193.
(149) Koos, P.; Polyzos, A.; O'Brien, M.; Baxendale, I. R.; Ley, S. V. Unpublished results.
(150) For a recent review see the following: Mak, X. Y.; Laurino, P.; Seeberger, P. H. Asymmetric reactions in continuous flow. *Beilstein J. Org. Chem.* **2009**, *5*, 19.
(151) Massi, A.; Cavazzini, A.; Del Zoppo, L.; Pandoli, O.; Costa, V.; Pasti, L.; Giovannini, P. P. Toward the optimization of continuous-flow aldol and α-amination reactions by means of proline-functionalized silicon packed-bed microreactors. *Tetrahedron Lett.* **2011**, *52*, 619−622.
(152) Alza, E.; Rodríguez-Escrich, C.; Sayalero, S.; Bastero, A.; Pericàs, M. A. A solid-supported organocatalyst for highly stereoselective, batch, and continuous-flow Mannich reactions. *Chem.—Eur. J.* **2009**, *15*, 10167−10172.
(153) Popa, D.; Marcos, R.; Sayalero, S.; Vidal-Ferran, A.; Pericàs, M. A. Towards continuous flow, highly enantioselective allylic amination: ligand design, optimization and supporting. *Adv. Synth. Catal.* **2009**, *351*, 1539−1556.
(154) Lamb, G. W.; Al Badran, F. A.; Williams, J. M. J.; Kolaczkowski, S. T. Production of pharmaceuticals: amines from alcohols in a continuous flow fixed bed catalytic reactor. *Chem. Eng. Res. Des.* **2010**, *88*, 1533−1540.
(155) Wiles, C.; Watts, P. An integrated microreactor for the multicomponent synthesis of α-aminonitriles. *Org. Process Res. Dev.* **2008**, *12*, 1001−1006.
(156) Wiles, C.; Watts, P. Evaluation of the heterogeneously catalyzed Strecker reaction conducted under continuous flow. *Eur. J. Org. Chem.* **2008**, 5597−5613.
(157) Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. A flow process for the multi-step synthesis of the alkaloid natural product oxomaritidine: a new paradigm for molecular assembly. *Chem. Commun.* **2006**, *24*, 2566−2568.
(158) Baxendale, I. R.; Ley., S. V.; Mansfield, A. C.; Smith, C. D. Multistep synthesis using modular flow reactors: bestmann-ohira reagent for the formation of alkynes and triazoles. *Angew. Chem., Int. Ed.* **2009**, *48*, 4017−4021.
(159) Webb, D.; Jamison, T. F. Continuous flow multi-step organic synthesis. *Chem. Sci.* **2010**, *1*, 675−680.
(160) Baumann, M.; Baxendale, I. R.; Ley, S. V. The flow synthesis of heterocycles for natural product and medicinal chemistry applications. *Mol. Diversity* **2011**, *15*, 613−630.
(161) Herath, A.; Cosford, N. D. P. Fully automated continuous flow synthesis of highly functionalized imidazo[1,2-*a*] heterocycles. *Org. Lett.* **2010**, *12*, 5182−5185.
(162) Herath, A.; Dahl, R.; Cosford, N. D. P. One-step continuous flow synthesis of highly substituted pyrrole-3-carboxylic acid derivatives via in situ hydrolysis of *tert*-butyl esters. *Org. Lett.* **2010**, *12*, 412−415.
(163) Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; Broadwater, S. J.; McQuade, D. T. The continuous-flow synthesis of ibuprofen. *Angew. Chem., Int. Ed.* **2009**, *48*, 8547−8550.
(164) Syrris. FLLEX (Flow Liquid-Liquid Extrator). http://www.syrris.com/flow-products/africa-modules/fllex-flow-liquid-liquid-extrator.
(165) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, I. R.; Taylor, S. J. Multi-step organic synthesis using solid-supported reagents and scavengers: a new paradigm in chemical library generation. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195.
(166) Clark, J. H.; Rhodes, C. N. *Clean Synthesis Using Porous Inorganic Solid Catalysts and Supported Reagents*; Royal Society of Chemistry: Cambridge, U.K., 2000.
(167) Smith, C. J.; Nikbin, N.; Ley, S. V.; Lange, H.; Baxendale, I. R. A fully automated, multistep flow synthesis of 5-amino-4-cyano-1,2,3-triazoles. *Org. Biomol. Chem.* **2011**, *9*, 1938−1947.
(168) Carter, C. F.; Lange, H.; Ley, S. V.; Baxendale, I. R.; Wittkamp, B.; Goode, J. G.; Gaunt, N. L. ReactIR flow cell: a new analytical tool for continuous flow chemical processing. *Org. Process Res. Dev.* **2010**, *14*, 393−404.
(169) Lange, H.; Carter, C. F.; Hopkin, M. D.; Burke, A.; Goode, J. G.; Baxendale, I. R.; Ley, S. V. A breakthrough method for the accurate addition of reagents in multi-step segmented flow processing. *Chem. Sci.* **2011**, *2*, 765−769.
(170) Zaborenko, N.; Bedore, M. W.; Jamison, T. F.; Jensen, K. F. Kinetic and scale-up investigations of epoxide aminolysis in micro-reactors at high temperatures and pressures. *Org. Process. Res. Dev.* **2011**, *15*, 131−139.
(171) McMullen, J. P.; Jensen, K. F. An automated microfluidic system for online optimization in chemical synthesis. *Org. Process. Res. Dev.* **2010**, *14*, 1169−1176.
(172) Styring, P.; Parracho, A. I. R. From discovery to production: scale-out of continuous flow meso reactors. *Beilstein J. Org. Chem.* **2009**, *5*, 29.
(173) Hornung, C. H.; Mackley, M. R.; Baxendale, I. R.; Ley, S. V. A microcapillary flow disc reactor for organic synthesis. *Org. Process Res. Dev.* **2007**, *11*, 399−405.
(174) http://www.engin.umich.edu/~cre/01chap/html/reactors/bp.htm#bp8.
(175) Aqua. Flocculation. http://www.mps-group.nl/en/aqua/system_solutions/primary_treatment/flocculation/.
(176) Lean Manufacturing Concepts. http://www.leanmanufacturingconcepts.com/LeanTool_JIT.htm.
(177) Warman, M. Continuous Processing in Secondary Production. In *Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing*; am Ende, D. J., Ed.; John Wiley & Sons: Hoboken, NJ, 2011; pp 837−851.