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Synthesis of organometallic compounds in Flow

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Dedicated to Prof. Philippe Renaud for his 60th birthday

Microreactor technology has proved to be an important technique in organic synthesis, especially when organometallic compounds are used, because it allows running rapid reactions with reactive and instable intermediates. This review will highlight the preparation of main-group organometallic compounds deriving from Lithium, Magnesium, Zinc and Aluminum and their applications in flow conditions.

Keywords: Microreactor • organolithium • organomagnesium • organozinc • organoaluminum

1. Introduction

The development of microreactor technology has grown more and more in importance in the field of chemical synthesis. This technology offers many advantages like a great heat transfer and better mixing. The small reaction volume used in the reaction allows safe handling of highly exothermic or potentially explosive reactions, reagents or intermediates. Moreover, since the reactions are conducted in a continuous mode, scale-up can be simply obtained by running the reaction for longer time, or by numbering-up the reactors.^[1-3]

Tuan ZHAO received his BSc in Chemical Engineering and Technology at Hefei University of Technology. After obtaining his MSc in Biomedical Engineering (Medicinal Engineering) from Dalian University of Technology in 2016, he joined the group of Dr. L. Micouin at University of Paris Descartes as a PhD student. He is currently working on chemistry of silylated diazoalkynes.



Laurent MICOUIN studied at the Ecole Nationale Supérieure de Chimie de Paris, where he obtained an engineer diploma in 1990. He obtained his PhD under the guidance of Professor J.-C. Quirion in 1995. After a Post-doctoral stay in Marburg (Germany) as a Humboldt Fellow under the direction of Professor Paul Knochel, he got a permanent position in CNRS Paris in 1996 as Chargé de Recherche, and, since October 2005 Directeur de Recherche. His scientific interests include the development of new methods in the field of asymmetric synthesis of nitrogen compounds, organo-aluminum chemistry, as well as the development of new tools in the field of fragment-based approach for the discovery of bioactive compounds



Riccardo PICCARDI obtained his Ph.D in 2005 under the supervision of Prof. P. Renaud at the University of Bern. After two post-doctoral stays, one with Prof. T. Bach at the Technical University of Munich and one with Prof. O. Baudoin at University Claude Bernard Lyon I, he joined the Prof. M.C.Scherrmann as teaching assistant in 2008 at University of Paris Sud. He was then recruited as a CNRS researcher in 2008. In 2014 he joined the team of Dr. L. Micouin where he is developing new methods combining flow and organoaluminum chemistry.



The objective of this review is to show the progresses that have been done in the last 2 decades in the synthesis of organometallic compounds in flow conditions; we will focus on the synthesis of derivatives of lithium, magnesium, zinc and aluminum and their sequential application in flow. An overview on organometallic chemistry in flow conditions has also been published by Noël in 2016.^[4]

2. Lithium derivatives

Organolithium reagents are widespread used to generate new C-C bonds.^[5,6] They can be prepared by reduction, halogen-metal exchange, or by metallation/deprotonation.

2.1 Halogen-metal exchange

Halogen-metal exchange is one of the most used methods to prepare aryllithium derivatives. These reactions are normally very fast and the lithiated species formed are often stable only at very low temperature. As a consequence, their use in very large scale is limited by the need of cryogenic temperatures. This problem can be circumvented performing the reaction in microreactors, since their

heat-transfer characteristics allow an efficient dissipation of reaction's heat. This effect arises from the high ratio between the surface and the volume of the reactor. Moreover, the residence time can be adjusted in function of the volume of the channel and in function of the flow speed. Therefore degradation can be avoided and unstable intermediates, generated with very short residence time, can react in flow with different electrophiles.

Both Villani and Schwalbe reported the first examples of Br-Li exchange in microfluidic systems. The first one was the generation of lithiated species for the synthesis on tramadol.^[7] The second one used a two-stage microreactor for the preparation of 3-methoxybenzaldehyde at a kilogram scale.^[8] However the biggest contribution in this area was made by Yoshida, who developed what he called the *Flash chemistry*, that he defined as "a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce the desired compound with high selectivity".^[9-11]

Monolithiation with *n*-BuLi of *ortho*-dibromobenzene (*o*-DBB) is very challenging because it can easily eliminate LiBr generating benzyne. Yoshida showed that using a two-stage microreactor technology, monolithiated *o*-bromobenzene could be prepared without this side reaction, allowing the functionalization with different electrophiles (Figure 1a).^[12]

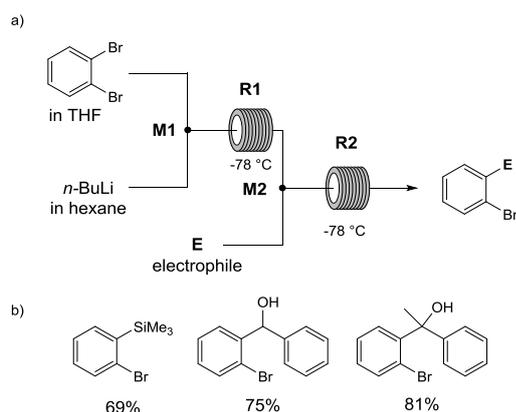


Figure 1. Microreactor system for Br-Li exchange of *o*-DBB and examples.

Residence time was optimized by varying the length of the tube **R1** with a fixed flow rate. Best results were obtained when conducting the reaction at $-78\text{ }^{\circ}\text{C}$ with a residence time of 0.8 s. The use of elevated flow rates combined with a T-mixer, leads to a better mixing that might explain the selective formation of the unstable lithiated species.^[13]

Applying optimized conditions, different electrophiles were then used to prepare different *o*-bromo-substituted benzenes in good yields (Figure 1b). The sequential application of this system to prepare *o*-disubstituted aromatics was then investigated using a multi-stage microreactor where each lithiation was followed by the reaction with an electrophile (Figure 2). It is worth noting that the second lithiation was conducted at $0\text{ }^{\circ}\text{C}$. The authors supposed that the second lithiated species were more stable than *ortho*-bromo phenyllithium, thus cryogenic temperatures were not necessary.

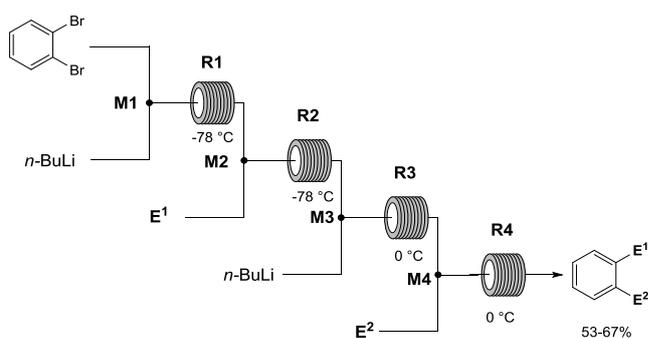


Figure 2. Microreactor system for the sequential Br-Li exchange of *o*-DBB.

This methodology was then generalized to the functionalization of *p*- and *m*-dibromobenzenes,^[14] and bromobenzenes substituted with different reactive groups such as esters,^[15-17] carbamates or carbonates,^[18] cyano^[19] and nitro^[20] or heteroaromatic systems such as dibromopyridines^[21].

Jia and coworkers reported the functionalization of bromo-heterocycles via Br-Li exchange conducted at $10\text{ }^{\circ}\text{C}$ using a similar approach.^[22] In this case, the mixing efficiency was increased by a stainless steel in-line mixer (**IM1**) which is a splitting-and-recombining type micromixer, introduced after the first micromixer (**M1**) (Figure 3).

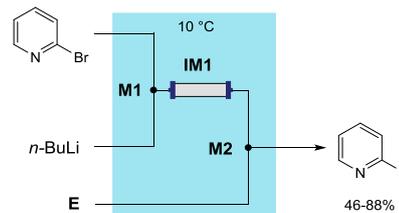
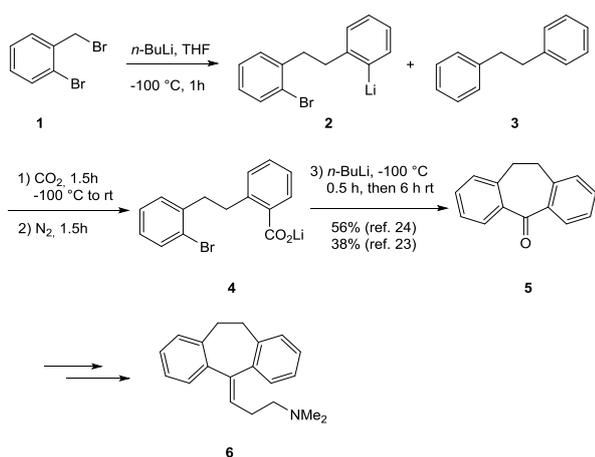


Figure 3. Microreactor system for Br-Li exchange of bromopyridine.

Microreactors are perfectly adapted to handle gas and flow chemistry represents an important alternative to batch processes, especially in carbonylation reactions of lithiated species.

A good example is the synthesis of Amitriptyline **6** reported by Kirschning and Kupracz. The key intermediate of this synthesis is dibenzosuberone **5**, which is prepared by a one-pot Parham cyclization.^[23] The batch synthesis, that was already reported in a previous work,^[24] consists in the formation of the lithiated dimer **2**, which is trapped with CO_2 , affording the carboxylate **4**. Br/Li exchange generates a second lithiated species that attacks the carboxylate forming ketone **5** (Scheme 1). This process however presents different drawbacks: the first Br-Li exchange has to be conducted at very low temperature to avoid the formation of by-product **3**, thus a scale up is very problematic. Moreover the authors reported a lack of reproducibility for the second lithiation-cyclization step.



Scheme 1. Batch synthesis of dibenzosuberone **5**.

For all these reasons they elaborated a new process based on microtechnology that allowed a better handling temperature conditions and gas (Figure 4).

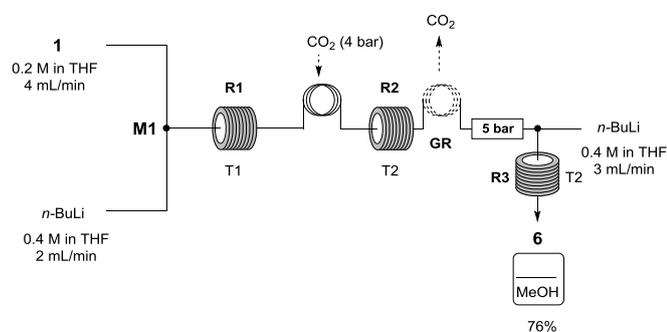


Figure 4. Microreactor system for the preparation of **6**.

The system they developed consisted of a T-shaped micromixer **M1** and a microtube reactor **R1** in which the first step of the reaction took place at $-50\text{ }^{\circ}\text{C}$. A tube-in-tube reactor allowing the introduction of carbon dioxide into the stream of the reactants was introduced directly behind **R1**. The carbonylation occurred at room temperature in a second microtube reactor **R2**. The excess of CO_2 was then eliminated in a gas remover (**GR**) that consisted in a Teflon AF-2400 tube, and a back-pressure regulator. The solution was then mixed in a T-mixer with another equivalent of *n*-BuLi. These Br/Li exchange reaction and cyclisation were carried out at room temperature in **R3**. This set-up allowed the preparation of **6** in 76% yield from **1** with a residence time of 33 s.

Yoshida and coworkers reported another way to handle CO_2 in carbonylation reactions. In particular they were interested in the synthesis of aromatic carboxylic acids or activated aromatic esters.^[25] In their set-up reactions occurred in a series of T-micromixers. The amount of CO_2 introduced in the flow stream was regulated by a flow controller (FC). Before being introduced in the flow stream, CO_2 was pressurized at 3 bar with a gas pressure regulator valve (Figure 5). Once again, the lithiation step occurred at temperatures ranging between 0 and $-60\text{ }^{\circ}\text{C}$ and overall yields of carboxylic acids ranged from 59 to 89 %

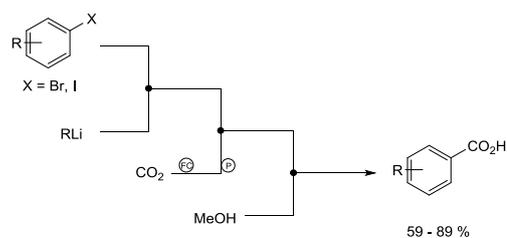
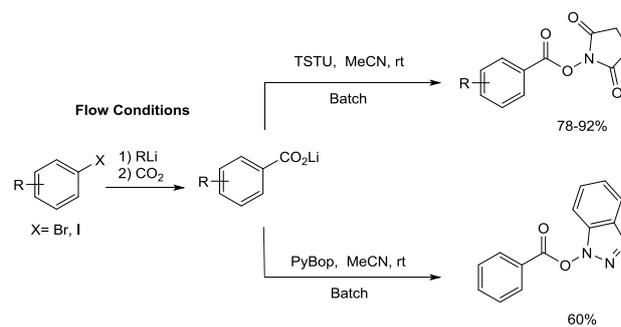


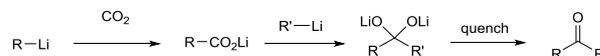
Figure 5. Microreactor system for the preparation of carboxylic acids.

Activated ester could be prepared by trapping the lithiated carboxylic acid with coupling agents like TSTU or PyBop in 60 to 92% overall yields (Scheme 2).



Scheme 2. Preparation of activate esters from lithium carboxylates.

Jamison and coworkers reported the preparation of ketones from carbon dioxide and organolithium or Grignard reagents (Scheme 3).^[26]



Scheme 3. Preparation of ketones from CO_2 and organolithium reagents

In this case the introduction of CO_2 in the reaction stream was performed using a Mass Flow Controller (MFC) that allowed introducing the exact amount of gas (Figure 6).

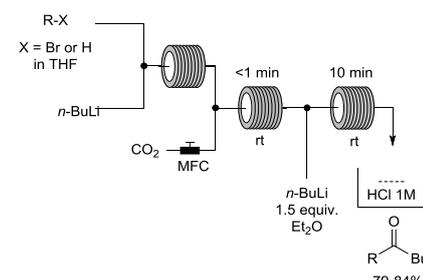
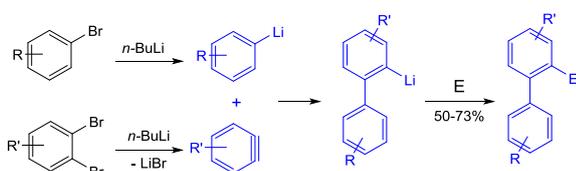


Figure 6. Microreactor system for the preparation of ketones.

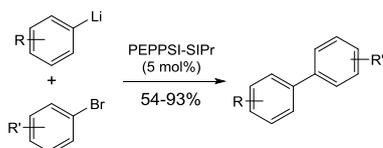
Biaryl derivatives can be prepared by carbolithiation of benzyne. In particular, Yoshida and coworkers showed that, starting from *o*-dibromobenzene it is possible to generate, via Br-Li exchange, benzyne. This one can then react with an aryllithium derivative obtained by halogen-Li exchange. The corresponding biaryllithium can be further functionalized with different electrophiles (Scheme 4a).^[27] This three-component transition metal-free coupling is extremely difficult to conduct in batch. The use of flow chemistry

enables a precise control of the reaction conditions governed by the relative stabilities of the lithiated species.

a) Three component carbolithiation of benzyne in flow conditions



b) Murahashi coupling in flow conditions



Scheme 4. a) Three component carbolithiation of benzyne in flow conditions; b) Murahashi coupling in flow conditions

Organolithium derivatives can also be used in palladium catalyzed cross-coupling reactions, like in the Murahashi reaction. An example of this application in flow conditions was reported by Yoshida and coworkers.^[28] In this case, generated aryllithium was reacted in flow conditions with a mixture of the halide and PEPPSI-SIPr as soluble Pd catalyst (Scheme 4b).

Organolithium derivatives can also be used as precursors for the preparation of boronic acids. Since this class of compounds can be unstable, they can be generated using microreactor technology and directly engaged in Suzuki-Miyaura coupling reactions without isolation.

The first example of preparation of boronic acids in flow conditions was reported by Buchwald and coworkers.^[29] Aryllithium, generated by Br-Li exchange was reacted in a T-mixer with a diluted solution of $B(i\text{-PrO})_3$ (Figure 7). The combined stream was introduced in a tubular reactor that was heated at 60 °C and sonicated to generate the corresponding boronate. The solution of the boronate was then combined with a solution of KOH, and subsequently with a solution of the aryl halide and the precatalyst. These combined streams were then introduced in a tubular reactor that was heated at 60 °C and sonicated for the coupling step. A similar set-up can be used for the Rhodium catalyzed enantioselective 1,4 addition to enones.^[30]

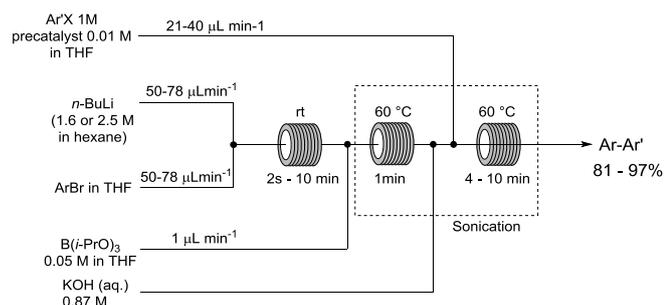


Figure 7. Microreactor system for Suzuki-Miyaura reaction.

Other examples of synthesis of boronic acids or boronic esters were reported by Ley and coworkers;^[31,32] in these cases the reactions were conducted at low temperature (-60 °C) using a Cryo-Flow reactor able to handle cryogenic conditions. Multijet Oscillating Disc (MJOD) reactors can also be used for the synthesis of phenylboronic acids.^[33]

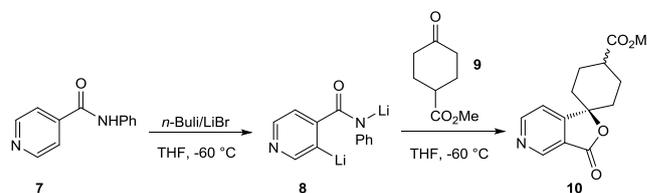
The Miyaura borylation is an important reaction for the preparation of pharmaceutical intermediates. Usutani and Sedelmeier reported a flow process for the kilogram-scale synthesis of a boronic acid starting material for the synthesis of TAK-117, a selective PI3K α inhibitor.^[34]

Trifluoroborates are very often a stable alternative to boronic acids in Suzuki-Miyaura reactions. The synthesis of bromomethyltrifluoroborates in flow conditions has been reported by Broom and coworkers.^[35] It is interesting to mention that the boronate obtained by reacting the lithiated species and $B(i\text{-PrO})_3$ was transformed in the trifluoroboronate using an aqueous solution of HF. This was made possible since in a flow process the handling can be automated, making the operator exposition less of a concern. Furthermore, although the preparation of potassium bromomethyltrifluoroborate was limited to batch sizes of 100 mg, the continuous flow process enabled the production of over 100 kg of this compound in less than one month.

2.2 Metalations

Lithium derivatives of aromatic compounds can be prepared also *via* metalation, especially when there is an *ortho* directing group. This method allows selective lithiation without the need to have a halogenated precursor.

An example of using microreactor technology for *ortho*-metalation was reported by Takasuka and coworkers.^[36] They synthesized spiro lactone **10**, a precursor for the preparation of a neuropeptide Y receptor agonist. The batch synthesis of **10** involved *ortho*-lithiation of **7** at -60 °C to prepare **8**, which was then added to a solution of **9** at the same temperature (Scheme 5).



Scheme 5. Reaction in batch of intermediate spiro lactone **10**.

However, this reaction needs careful control of the mixing and of the temperature to avoid formation of a byproduct coming from a double addition of the lithiated species to ester intermediate. The scale up required an improved process with microreactor technology. The reaction was run in a tubular reactor and the mixing was assured by static mixer. The mixer possessed 27 elements constituted by rectangular plates twisted of 180°. The authors reported that the radial shape of the reactor interior was responsible for an efficient

radial mixing. Moreover, the movement of the fluid from the outer toward the center of the reactor reduced the contact time of the fluid with the high temperatures, thus diminishing the degradation of the product. The system was immersed in a dry/acetone bath to assure the removal of the heating.

Ley and coworkers studied the *ortho*-lithiation of the fluoride **11** for the synthesis of boronic acid **12** (Figure 8).^[37] Metalation was performed at -40 °C using pre-cooled solution of the starting reagents, which were mixed in a Y-piece mixer. In order to improve the mixing at the exiting of the Y-mixer they used a 4 mm tube where they introduced some stirring bars. In proximity of the stirring bars they placed a magnet that was supported on a spinning disk that was moved by a stepped motor. Then the solution enters a 20 mL reactor and the intermediate was then mixed in another Y-piece mixer with B(OMe)₃ at the same temperature, controlled by a thermocouple. The collected boronate was then hydrolyzed into the boronic acids in a batch process. This system ran for 7 hours allowing isolating the desired product in 80% yield with a productivity of 15 g/h.

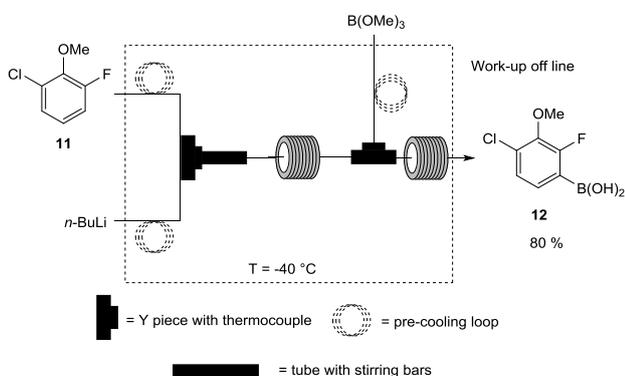
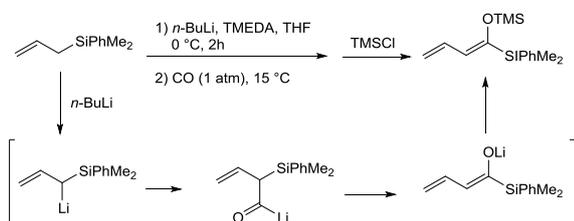


Figure 8. Microreactor system for *ortho*-lithiation.

Another example of how microreactors offer a better solution to a batch process was reported by Ryu Fukuyama and coworkers, who reported the carbonylation of 1-silyl-substituted organolithiums with CO.^[38] They adapted a previously reported batch process for the preparation of lithium enolates via rearrangement of unstable acyllithiums that were produced by carbonylation of 1-silyl-substituted allyllithiums (Scheme 6).^[39,40]



Scheme 6. Carbonylation reaction of lithiated allylsilanes

Starting from the observation that the reaction proceeds faster and cleaner with pressurized CO, they decided to develop a process using microreactor technology. They developed the system depicted in Figure 9 where a solution of *n*-BuLi and a solution of TMEDA and the silane were mixed in a T-shaped mixer (**M1**). The resulting mixture was introduced in a tubular reactor (**R1**) that was maintained

at 25 °C to ensure complete deprotonation. The formed allyllithium was mixed with pressurized CO (4 bar) in a T-mixer (**M2**) with a flow rate that was adjusted with a mass flow controller. The reaction mixture passed then through a tubular reactor (**R2**) that was heated at 80 °C for the carbonylation and rearrangement step. A back pressure regulator was placed behind the reactor to keep the system pressurized. The electrophile was then introduced in the flow stream and mixed in a T-mixer (**M3**). The resulting mixture was introduced in a tubular reactor (**R3**) that was maintained at 25 °C.

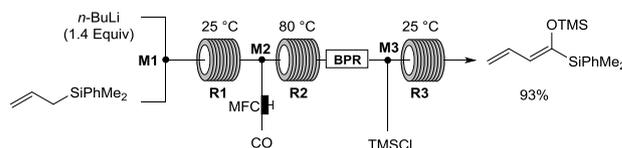
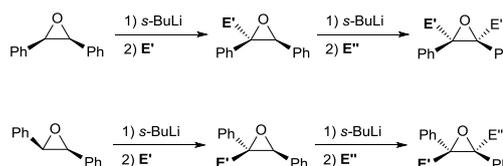


Figure 9. Microreactor system for carbonylation reaction of silyllithiums.

Another interesting application of metalation in flow condition is the formation of oxyanyllithium derivatives. Metalation of epoxides generates an instable species that can be degraded by a second equivalent of lithiating agent. To circumvent this problem, Yoshida and his coworkers reported the use of microreactors for the generation and reaction of oxyanyllithium compounds.^[41] Using a similar approach described in Scheme 1 and 2 they studied the deprotonation of styrene oxide with *s*-BuLi and the subsequent alkylation with MeI and different other electrophiles. They then extended the process to chiral disubstituted epoxides. In this case the challenge is the control of the configurational stability of the organolithium species. However, when the reactions were conducted under flow conditions, epimerization was avoided. This allowed the preparation of tetrasubstituted epoxides by a sequential stereospecific introduction of two electrophiles (Scheme 7).



Scheme 7. Sequential stereospecific introduction of two electrophiles conducted in flow.

Another example in which flow conditions allowed generating stable enantioenriched carbanions was reported by Alezra and coworkers.^[42]

Based on their previous works on Memory of Chirality (MOC)^[43-46] they developed a flow process for the generation of quaternary stereocenters with high selectivity. Chiral enolates, prepared using LDA, reacted with different electrophiles (Figure 10), leading to alkylations with an efficient memory of chirality.

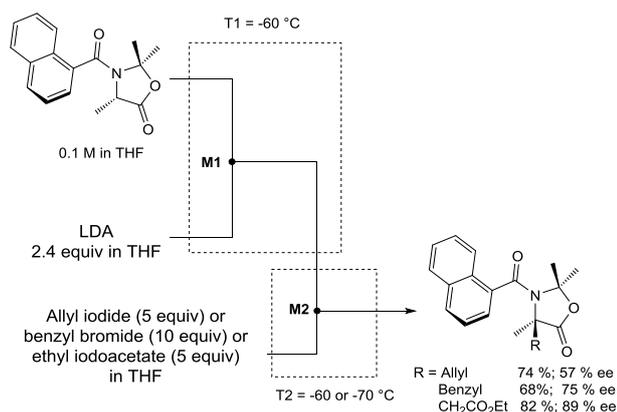


Figure 10. Microreactor system for the generation of quaternary centers.

When the lithium derivatives are too unstable, however, there is the possibility to generate a transient organolithium species in presence of an electrophile (Barbier's conditions) and control the two competitive pathways: degradation versus addition. An example of this approach has been reported by Knochel and coworkers who prepared carbamoyl and thiocarbamoyl lithium derivatives in presence of different carbonyl derivatives (Figure 11).^[47]

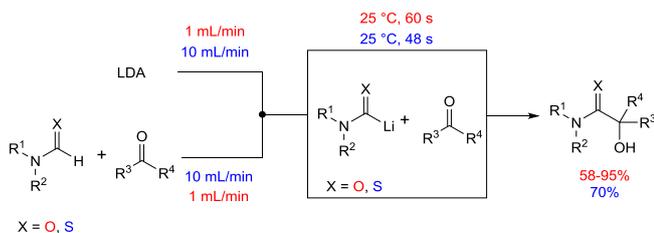


Figure 11. Generation and reaction of carbamoyl and thiocarbamoyl lithiums.

Microreactors allow the manipulation of very unstable compounds, like for instance diazo compounds. Wirth and his collaborators showed that ethyldiazoacetate can be easily lithiated with LDA and reacted *in situ* with ketones.^[48]

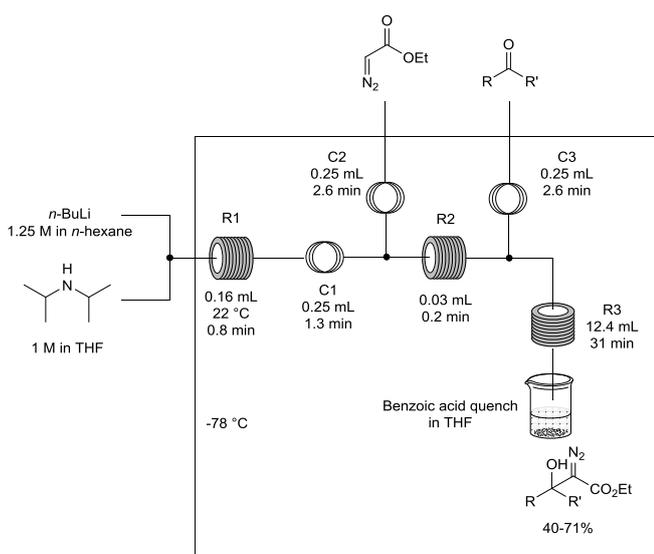
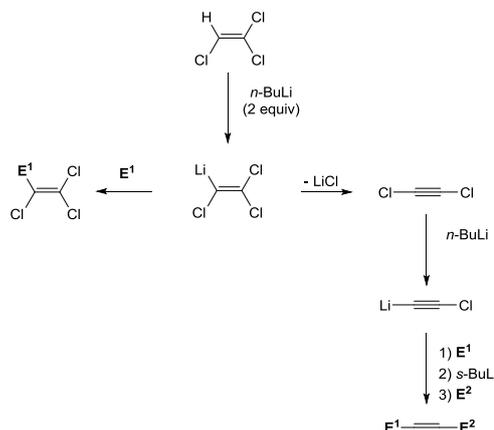


Figure 12. Generation and reaction of ethyl lithium diazoacetate.

The system applied for this synthesis is described in figure 12.

In order to avoid blockage, due to the instability of the lithiates species, all the reactants were pre-cooled at $-78\text{ }^{\circ}\text{C}$ before being mixed together. The collecting vial was also kept at this temperature for the same reason. LDA was prepared in a first reactor with a residence time of 0.8 mL, the flow exiting this coil was cooled down at -78 ° in a 0.25 mL coil before mixed with cooled ethyldiazoacetate. The flow then entered a 0.03 mL reactor to afford the lithiated diazo derivative, which was then combined with a pre-cooled ketone in a T-mixer. The resulting mixture entered a third reactor of 12.4 mL where the addition of diazo onto the ketone occurred. The flow exiting the reactor was then collected and quenched with benzoic acid at $-78\text{ }^{\circ}\text{C}$. Microreactors technics can not only minimize side-products in linear synthesis, but are also excellent tools in divergent syntheses. As an example, Yoshida and coworkers studied the reactivity of trichlorovinyl lithium in flow conditions.^[49] This compound can be trapped with an electrophile, or eliminate LiCl to afford 1,2-dichloroacetylene (Scheme 8). The latter can in turn be functionalized by a sequential Cl-Li exchange and reaction with an electrophile.



Scheme 8. Reactions of trichlorovinyl lithium.

Using similar set-up depicted in Schemes 1 and 3, it is possible to prepare trichlorovinyl-derivatives or unsymmetrical disubstituted alkynes starting from the same precursor using a very fine tuning of the reactions conditions.

3. Magnesium derivatives

Victor Grignard discovered organomagnesium compounds that took his name in 1900.^[50] These compounds are one of the most important reagents for the formations of C-C bonds.^[51-53] They are used in many processes both at laboratory and industrial scale. There are different methods to prepare Grignard reagents, among them the direct insertion of Mg metal into the C-Halogen bond, metalation or halogen-metal exchange. We will give an overview of the method of preparations and of their use.

3.1 Metal insertion

Grignard reported the preparation of MeMgI by treatment of Mg with MeI in diethyl ether. Industrial preparations in a continuous fashion of

these reagents have already been reported long before the appearance of microreactors.^[54,55] However since the reaction is very exothermic, the control of the reaction conditions is very important. High heat release rates can lead to vigorous boiling and result in overpressure and even explosions.^[56]

For production purpose, Continuous Stirred Tank Reactors (CSTR) have been shown to better handle high exothermic reactions in which one or more of the reagents is a solid, as in the synthesis of Grignard reagents.^[57,58]

Other processes are based on the use of thermostated columns containing some rotating blades where granulated magnesium (diam. 1-3 mm) was inserted from the top and the halide pumped from the bottom.^[59,60] The final Grignard reagent was collected from the top in a collecting vessel. However this reactor was used only for the production of alkyl Grignard derivatives.

One interesting feature with flow chemistry is the possibility to perform in-line analyses or quality control. Thus, Duchateau and his group reported the preparation of Grignard reagents in flow condition monitoring the quality of the reagents formed with on-line NMR (Figure 13).^[61] For their set up, they filled a column with Mg particles ranging in size from 100 to 1000 μm . The column was constituted by a stainless steel tube of 1.1 cm of diameter and a total volume of 75 mL and was kept in vertical position to keep the magnesium particles in a fluidized bed. The tube was equipped with a jacket for heating or cooling, and a thermostat for temperature control. The solution of the halide was introduced in the column by an HPLC pump with a flow of 5 mLmin⁻¹. The flow stream at the exit of the reactor was divided in two stream, one of which possessing a flow of 1 mLmin⁻¹ that was connected to a low field bench NMR spectrometer, while the other part of the stream was collected in a flask for further analysis or reactions. The conversion of the reaction was followed by the registering every 10 to 15 s an NMR spectra of the solution flowing through the magnet.

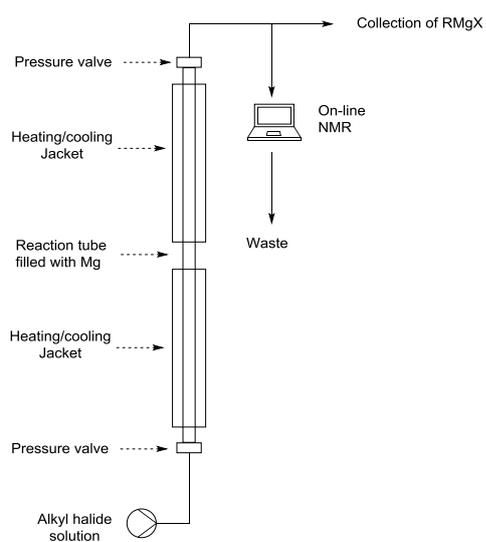


Figure 13. Apparatus for Grignard preparation by metal insertion with In-line NMR monitoring.

A similar approach was reported by Alcázar, de la Hoz and coworkers.^[62] For their process they filled a glass column with

magnesium particles with a size of 20-230 mesh. The size of the particle was chosen with the purpose to avoid an elevated backpressure and at the same time ensuring a high surface area to maximize the contact between the metal and the halide. The solution of the halide was pumped into the column (Figure 14). The activation of the magnesium was done by pumping first a solution of DIBAL-H in toluene and then a solution of TMSCl and 1-bromo-2-chloroethane in a solution of 0.5 M LiCl in THF. Once the column was activated, a 0.5 M solution of the halide in a 1:1 THF/toluene mixture was passed through the column at 50 °C with a residence time of 7.5 min. A 0.38 M solution of the corresponding Grignard was collected under nitrogen. The authors observed that the concentration of the reagent did not drop until ~70 % of the metal was consumed. The remaining metal was not disposed, but the column was refilled and reactivated. The Grignard reagent solution could then be used either in batch or directly by mixing the outcome of the column with different electrophiles. It is worth noting that this method was used to prepare potentially explosive (trifluoromethyl)phenylmagnesium bromides in a safe and reproducible manner.^[63,64]

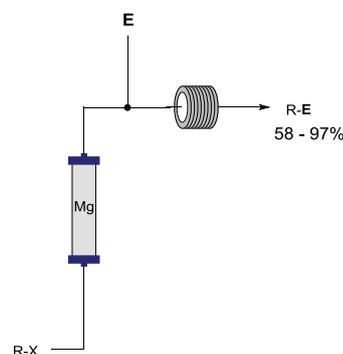


Figure 14. Apparatus for Grignard preparation by metal insertion

3.2 Halogen/metal exchange

A mild method to generate Grignard is the halogen/metal exchange; however this reaction is often very exothermic and in large scale synthesis the control of the temperature can be difficult in batch processes. Yoshida and his group circumvented this problem developing a pilot plant with flow conditions for the preparation of pentafluorophenylmagnesium bromide (PFPMgBr) from bromopentafluorobenzene and ethylmagnesium bromide.^[65] This reaction was initially optimized on a laboratory scale. With the optimized conditions they developed a pilot reactor constituted from a shell tube of 20 cm long and with 17 mm of internal diameter. A heat exchanger constituted of 55 microtubes (i.d. 490 μm , 200 mm long) was introduced into the shell tube. The solutions were mixed in a Toray Hi-mixer, before being introduced in the reactor shell that was kept at a constant temperature of 20 °C. The total residence time was 5s. This system was tested by running for 24 h and enabled a production of pentafluorophenylmagnesium bromide of 92 % yield (GC), corresponding to 14.7 Kg of product.

In the last decades different systems have been developed to monitor the advance of a reaction conducted in flow conditions. Infrared spectroscopy has been used by Ley, Knochel and coworkers for inline monitoring of the metal-halogen exchange reaction with *i*-PrMgBr.^[66] In this case the halide and *i*-PrMgBr were pumped in a tubular reactor that was kept at room temperature. At the exit of reactor an IR probe allowed registering the IR spectrum of the solution in real time (Figure 15). It was possible to follow the generation of the Grignard in real time by integration of the intensities of the typical signal of the reagent. This system was extended to allow the reaction with different electrophiles. A second T-piece was introduced after the IR probe, allowing mixing the Grignard reagent to the electrophile. The IR monitoring enabled to control the time of electrophile addition.

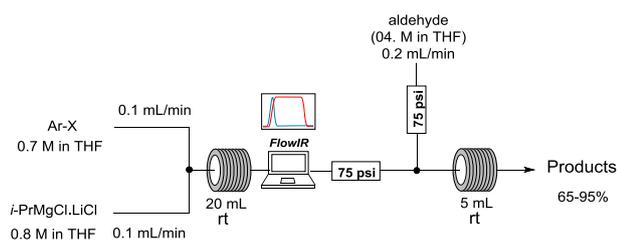


Figure 15. Set-up for the halogen/Mg exchange with IR monitoring.

The halogen/metal exchange between the iodide **13** and *i*-PrMgCl·LiCl (Scheme 16) can also be conducted with chip-based reactors. The corresponding Grignard reacted with different aldehydes and the reaction mixture was then hydrolyzed in flow. The two phases were separated in a flow liquid/liquid extractor. All the systems were fully automated with pumps guided by a computer software program.^[67]

Carboxylic acids can be prepared by reaction of a Grignard reagent and CO₂. The group of Shen and Zhang reported the synthesis of 2,4,5-trifluorobenzoic acid via sequential Br-Mg exchange and carboxylation.^[68]

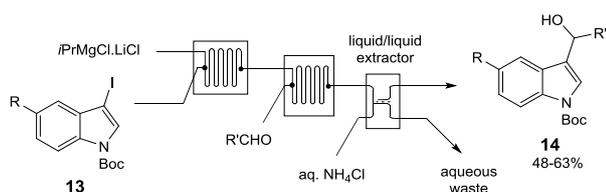


Figure 16. Set-up for the synthesis of **14**.

The reaction of 1-bromo-2,4,5-trifluorobenzene with EtMgBr was conducted in a reactor made of a T-mixer and a delay loop at 30 °C, while the carboxylation reaction occurred at atmospheric pressure in a falling film microreactor (FFMR) (Figure 17). The stream of generated Grignard entered in the top of the FFMR while CO₂ was introduced from the bottom. This reaction was conducted at 5 or 10 °C. In order to get high yields and selectivities, the reaction was performed using a flow rate of 0.4 mLmin⁻¹ for the solutions of EtMgBr and 1-bromo-2,4,5-trifluorobenzene (total flow rate 0.8 mLmin⁻¹) and a flow rate of 30 mLmin⁻¹ for CO₂.

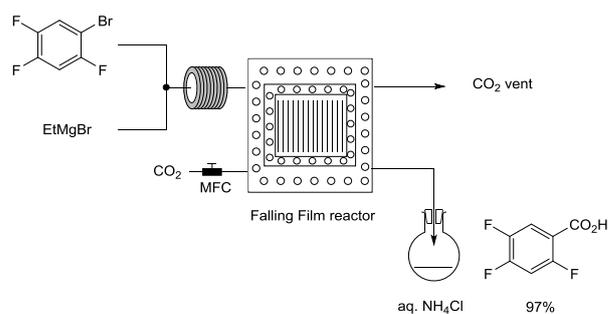


Figure 17. Set up for the carboxylation reaction with a FFMR.

3.3 Metalation

One of the limitations of metalation with lithium amides is the need to use very low temperatures, however this drawback has been circumvented with the use of magnesium amides, and in particular with the development of soluble R₂NMgCl·LiCl.^[69]

Knochel and coworkers reported that TMPMgCl·LiCl can be used to metalate different heterocycles in flow conditions using a chip-based microreactor for the metalation step.^[70] The generated organomagnesium then reacted with different electrophiles in another chip-based reactor followed by a coil reactor (Figure 18). Both steps were realized at 25 °C with very short residence times.

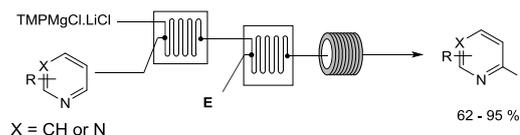


Figure 18. Set-up for heterocycles metalation with TMPMgCl·LiCl

Acrylates are difficult to metalate since they can polymerize and the reaction needs very low temperature. This problem was solved by Knochel and his group using TMPMgCl·LiCl in flow conditions.^[71] The reactions were carried out in a tubular reactor made of PFA or PTFE and at a temperature ranging between room temperature and 50 °C (Figure 19). The metalated species exiting the reactor was

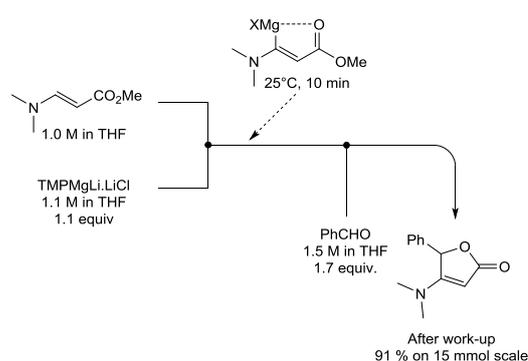


Figure 19. Schematic set-up for the metalation of acrylates.

mixed in flow condition with different electrophiles. This method was used to prepare different butenolides who could in turn be metalated and functionalized with different electrophiles (Figure 20).

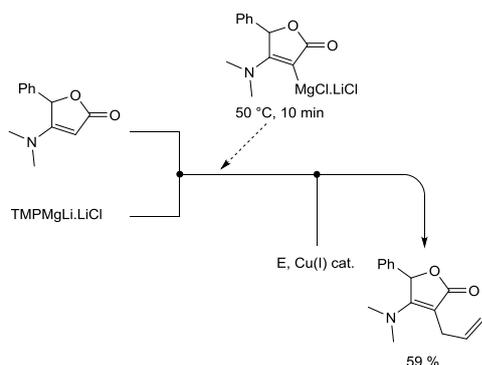


Figure 20. Schematic set-up for the functionalization of butenolides.

3.4 Transmetalation

Organomagnesium compounds can be generated from transmetalation of lithiated species. Interestingly Knochel reported the possibility of *in situ* trapping transmetalation of aromatic or heteroaromatic lithium derivatives prepared by metalation^[72-74] or halogen-lithium exchange.^[75]

They showed that acrylates could be deprotonated by lithium dicyclohexylamide (Cy₂NLi) in presence of MgCl₂ to afford the corresponding magnesium derivative that could then be quenched by different aldehydes (Figure 21).

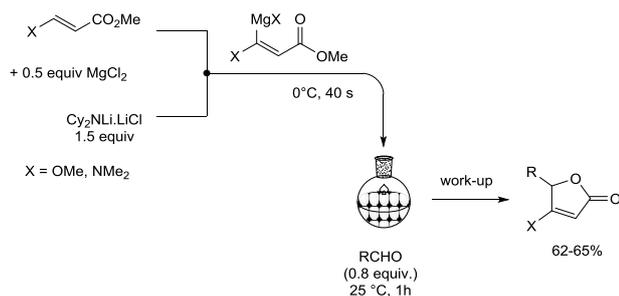


Figure 21. Schematic set-up for the *in-situ* trapping magnesiation of acrylates.

The same approach could be used for the lithiation with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) of aromatic and heteroaromatic compounds (Figure 22).

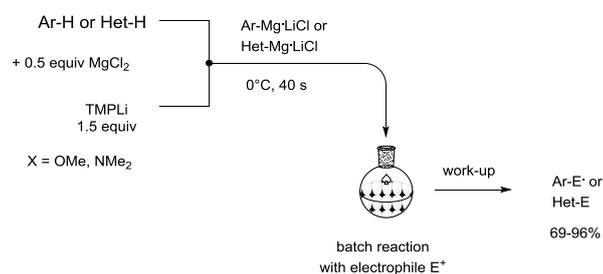


Figure 22. Schematic set-up for the *in-situ* trapping magnesiation of lithium derivatives

In a similar manner lithium-halogen exchange could be used to generate organomagnesium by trapping *in situ* the transient lithiated species with MgCl₂·LiCl (Figure 23).

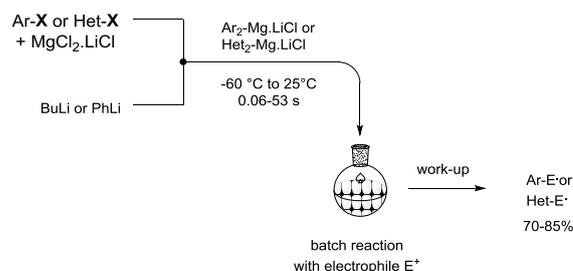


Figure 23. Schematic set-up for the *in-situ* trapping magnesiation of lithium derivatives

4. Zinc derivatives

Since the discovery of diethylzinc in 1849 by Frankland, organozinc derivatives have been used in the formation of new C-C bonds.^[76,77] Organozinc reagents are less reactive than organolithium or organomagnesium reagents. Because of their improved stability, they can tolerate many functional groups and are excellent precursors for transition-metal catalyzed reactions.^[78-82]

In this part we will discuss the different methods of their preparation in flow conditions together with some applications.

4.1 Insertion of zinc metal

Oxidative addition of zinc into organic halides is one of the most general methods to prepare organozinc halides. However this insertion requires activation of the metal, since zinc is prone to passivation. One of the best method of activation is to treat zinc consecutively with 1,2-dibromoethane and chlorotrimethylsilane (TMSCl).^[83] This type of activation was used by Alcázar and McQuade in the first report of direct zinc insertion in flow conditions.^[84] This was done by filling a chromatography-type column (Omnifit® column) with zinc powder with a size of ~30 mesh. Once the zinc was activated and washed with dry THF, a solution of halide was passed through the zinc bed, while the column was heated at temperatures ranging between 30 to 110 °C for alkyl or cycloalkyl halides. Aryl halides didn't lead to the corresponding zinc derivatives, even at 110 °C and higher. This method allowed the preparation of different benzyl or alkyl zinc halides. The flow exiting this column was then mixed with another arylhalide and introduced in another packed column containing SilicaCat DPP-Pd catalyst which allowed a Negishi coupling. This coupling was performed at temperature ranging between 60 and 80 °C (Figure 24).

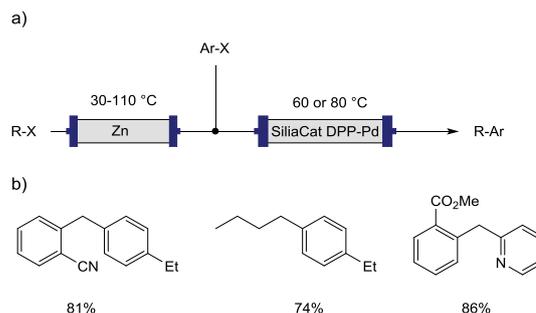


Figure 24. a) Schematic set-up for generation of organozinc halides and subsequent Negishi coupling; b) Examples of product obtained

Using the same system, Tissot and coworkers reported the synthesis of electro-deficient heteroaromatic 1,3-substituted cyclobutyls.^[85] Zinc activation was carried out using 1M aqueous HCl solution. Using a completely automated system, they could create a library of compounds. The comparison between batch and flow synthesis demonstrated the complementarity of the two methods: batch process proved to be better suited for insertion reactions that require long reaction time while flow conditions are more appropriate if the generation of a variety of compounds is needed.

Alcázar and coworkers showed that organozinc halides can be engaged in visible light-induced nickel catalyzed Negishi couplings. In a first example a preformed organozinc halide was mixed in a T-junction with a solution of aryl halide and a nickel catalyst (NiCl₂ glyme + dtbbpy). The resulting stream was injected in a tubular PFA reactor that was irradiated at 450 nm.^[86] In a second work, these authors investigated the scale up of this synthesis. The optimized set up for the 2 reactions sequences (organozinc halide synthesis and Negishi coupling) is depicted in Figure 25.^[87] A first gear pump introduces the halide into the column filled with zinc powder. The flow is controlled by a first mass flow controller (MFC1). The stream exiting the column is introduced in a benchtop NMR allowing monitoring the formation of the organozinc halide. A needle valve is positioned after the NMR to keep the system at 4 bar to avoid potential back flow into the zinc column due to the consumption of the zinc. The pressure is measured at the exit of the column by a pressure sensor. The exact flow entering the photoreactor was measured by a mass flow meter (MFM) that was also able to measure the density of the solution entering the column. Since the density of the halide solution was also measured before entering the zinc column, the comparison of these two values gave an idea of the conversion, and therefore of the zinc consumption. A second gear pump introduces in the photoreactor the solution of the halide and the catalyst. Again the flow was regulated by a second mass flow controller (MFC2). After the photoreactor a back pressure regulator keeps the system at 3.5 bar. The pressure was monitored by a pressure sensor placed before the reactor. In this set up the photoreactor was a CORNING® G1 reactor using a 405 nm LEDs.

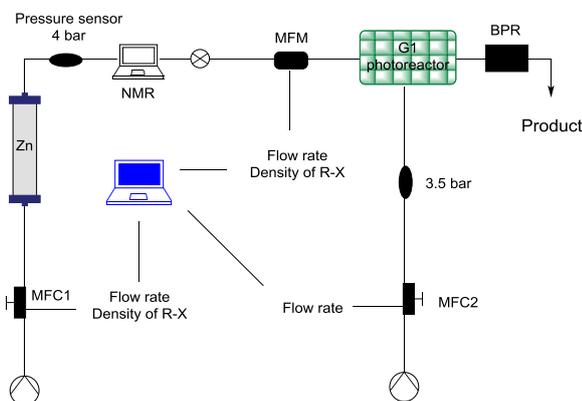


Figure 25. Schematic set-up for scaled up visible light catalyzed Negishi coupling.

With this method, a productivity from 3.4 to 5.6 g/h could be reached with a perfect control of the whole process.

Ley and coworkers reported a Reformatsky like reaction with sulfinylimines under Barbier's conditions.^[88] A mixture of allylic bromide **15** (1.2 equiv), sulfinimine **16** (1.0 equiv) and LiCl (8.0 equiv) in *i*-PrOH was pumped through the zinc reactor, injected in a coil reactor of 10 mL and then passed through a scavenger cartridge filled with QP-SA and QP-TU. In these conditions they were able to obtain the final product **17** in 70 % yield and 99:1 dr (Figure 26).

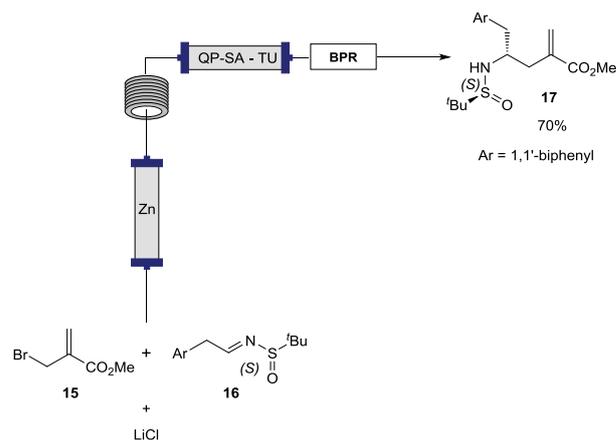


Figure 26. Schematic set-up for Reformatsky reaction with sulfinylimines.

A similar Reformatsky reaction using Barbier's conditions was also reported by Alcázar and coworkers (Figure 27a).^[89]

This system was also applied to the Blaise reaction. In this case, full conversion could not be obtained with conditions developed for the Reformatsky reaction. So a reactor coil of 5 mL heated at 120 °C was inserted after the zinc column. This method allowed, after hydrolysis, the preparation of different β -ketoesters (Figure 27b).

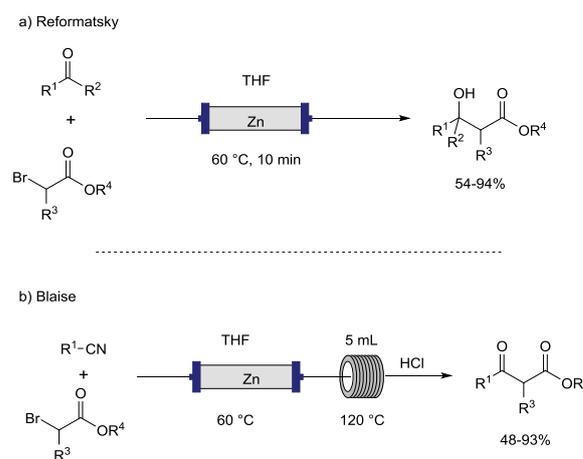


Figure 27. Schematic set-up for a) Reformatsky reaction; b) Blaise reaction

The intermediate enamine generated in flow conditions could be trapped with different electrophiles in a batch reaction (Figure 28)

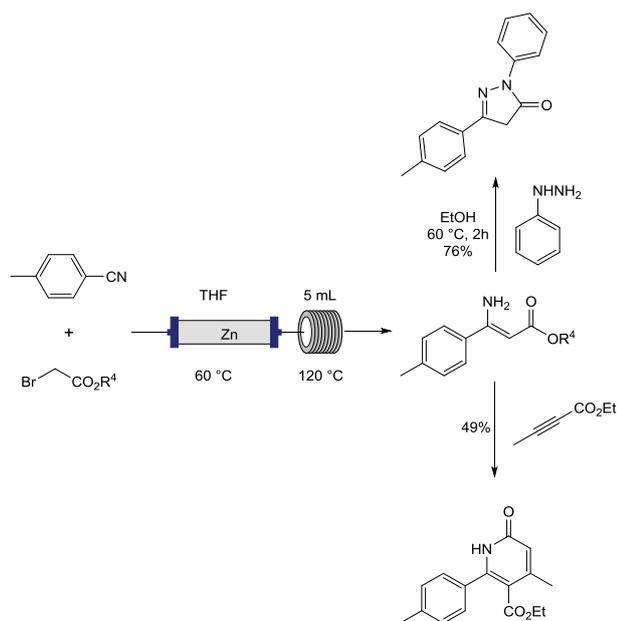


Figure 28. Trapping enamine intermediate with electrophiles

4.2 Metalation

Direct zincation using with zinc amides can be an alternative to lithiation-transmetalation for the preparation of organozinc derivatives. Ganiek et al. reported the direct zincation of acrylonitriles and nitroolefins with TMPZnCl (Figure 29).^[71] The corresponding zinc derivatives were coupled in-line with electrophiles in presence of Pd or copper catalysts.

Zincation of aromatic or heteroaromatic compounds can be also achieved with $(\text{Cy}_2\text{N})_2\text{Zn}\cdot 2\text{LiCl}$, prepared from Cy_2NLi and ZnCl_2 .^[90]

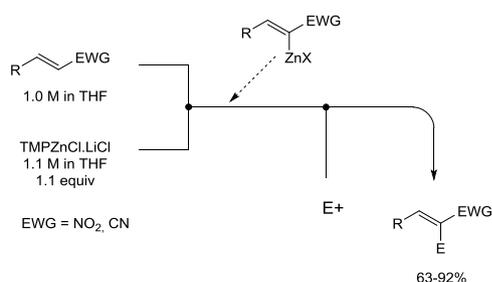


Figure 29. Schematic set-up for zincation of nitroalkenes or cyanoacrylates.

It is worth noting that the regioselectivity of metalation of substituted pyridines can be controlled by switching the metalation agent. $(\text{Cy}_2\text{N})_2\text{Zn}\cdot 2\text{LiCl}$ allowed thermodynamically controlled metalation, while $\text{TMPZn}\cdot 2\text{LiCl}$ afforded the kinetic controlled metalation product (Figure 30).

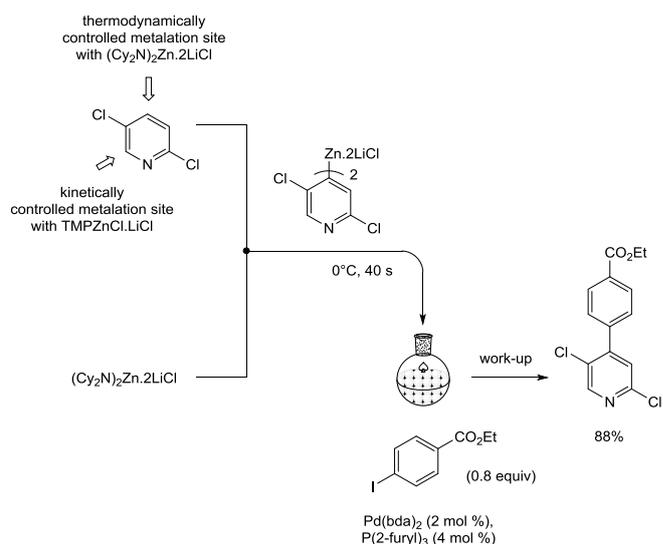


Figure 30. Schematic set-up switching regioselectivity with $(\text{Cy}_2\text{N})_2\text{Zn}\cdot 2\text{LiCl}$.

4.3 Transmetalation

Organozinc halides can be obtained by transmetalation of lithium derivatives in the same manner that has been described for Grignard reagents (Figures 21, 22 and 23).^[72-75]

This methodology was applied efficiently to the zincation of 1,2-dicyanobenzene and other substituted benzonitriles.^[91]

Based on a previous work reported by Knochel,^[92] Loren and his group prepared organozinc halides by transmetalation of transient Grignard reagents that were generated via a LiCl-mediated Mg insertion into the corresponding halide.^[93]

The generation of the Grignard was performed using a column filled with magnesium particles with a size of ~50 mesh, that were activated using the same system described earlier by Alcazar. Better results were obtained by pumping separate solutions of LiCl and ZnCl_2 with a solution of the halide into a T-mixer before passing through the Mg-packed column with a residence time of 5 min. The organozinc compounds can be telescoped downstream to a Negishi or decarboxylative Negishi cross-coupling reaction in glass chips.

5. Aluminum derivatives

Organoaluminum compounds have been discovered by Hallwachs and Schafarik in 1859.^[94] Although aluminum is one of the most abundant metals in the earth's crust and is one of the cheapest metals on the market, the use of organoaluminum reagents in organic transformations is rather limited. The covalent character of the Al-C bond is however expected to be a major advantage for the design of functional organometallic species.^[95] One of the major limitations in the field is the need for a simple method to prepare these compounds without any transmetalation step, and in non-coordinating solvents since the reactivity of organoaluminum compounds is mostly driven by their Lewis acidity.^[96]

We reported a new procedure that allowed the preparation of dimethylalkynylaluminum reagents in non-polar solvents by direct

metalation of terminal alkynes in presence of a catalytic amount of base, thus providing reagents with enhanced reactivity.^[97,98]

This protocol was adapted to a continuous flow process. The catalytic cycle is based on the lower affinity of the base for alkynylalanes than for trimethylaluminum. For this reason we suggested that an amine-supported complex of trimethylaluminum could metalate a terminal alkyne forming an alkynylaluminum complex that could be displaced by trimethylaluminum, regenerating the starting catalytic complex.

For this process a chromatography-type column was filled with methylpiperidine grafted on a polystyrene resin that was chosen as base catalyst. The complex with the base was obtained passing a 1.2 M solution of AlMe₃ through the column. A solution containing the terminal alkyne (1.6 M) and AlMe₃ (1.4 M) in toluene was then passed through the column at a flow rate of 20 μLmin⁻¹ (residence time of 100 min) allowing the formation of the desired alkynylaluminum derivatives (Figure 31). This process enables the preparation of 1.2M to 1.4M toluene solutions of various dimethylalkynylaluminum reagents.^[99]

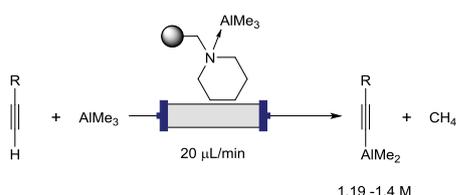


Figure 31. Schematic preparation of dimethylalkynylaluminum reagents

6. Conclusions

The use of microreactor technology is constantly evolving and many synthetic transformations classically conducted in batch have been adapted to flow conditions. As a matter of fact, Roberge and coworkers identified three type of reactions that can be carried out in a microreactor: i) reactions that are very fast (less than 1 s) and that take place in the mixing zone; ii) reactions that are rapid (between 1 s and 10 min) and they are kinetically controlled; iii) slow reactions (more than 10 min) that can benefit of the increased safety deriving from this technology.^[100] However, not all type of reactions can be performed in a microreactor. They showed that only 50 % of the reactions that are carried out at Lonza could benefit from a continuous flow process, with 40 % of them using microreactor technology. The main restriction is the formation of insoluble materials during the process. This solubility problem associated with salt precipitation might be a psychological barrier to explore the preparation of organometallic compounds using microreactor technology.

In this review, we have showed that this technology is on the contrary very well adapted to the preparation and use of organometallic compounds, even on a large scale, and is a remarkable alternative to batch syntheses when cryogenic conditions are required. Moreover instable compounds can be generated and

used in these systems, increasing the safety for the operator. Automations and monitoring of a process are easier, making this technology suitable for both lab-scale and industrial applications.

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Author Contribution Statement

All the authors contributed equally to the redaction of this manuscript

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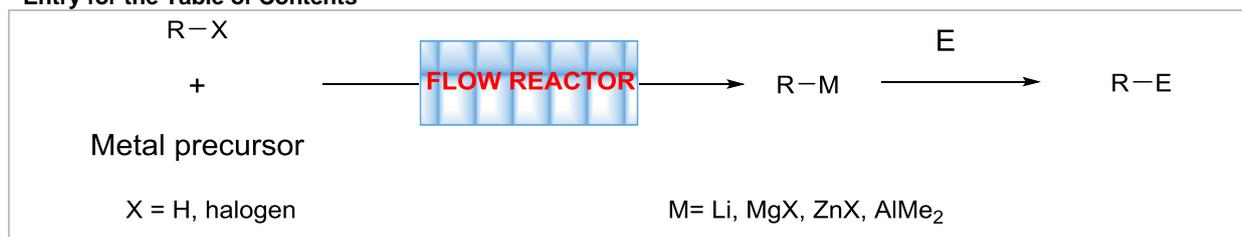
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