Flow Technology for Organometallic-Mediated Synthesis

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In this review recent examples on the use of flow technology for organometallic-mediated synthesis have been collected. The review focused on synthetic relevant processes and on flow techniques developed for handling reactive intermediates, and conduct synthetic steps difficult to perform using traditional "batch" chemistry.

Keywords: flow-chemistry, organometallics, synthesis, catalysis

1. Introduction

Flow technologies and microstructured devices are changing the way to perform organic reactions, moving away from the classical round-bottom flasks and other traditional techniques [1]. Due to high surface-to-volume ratios and enhanced mass and heat transfer, microstructured devices provide fast and better-controlled chemical processes [2]. Thus, in microreactors, chemical transformations often occur with better selectivity, higher reaction rates, and yields compared to batch techniques. In addition, scale-up with microreactors is, in principle, straightforwardly achieved, without further optimization studies, by prolonging the running time of the reactor or by running parallel reactors (numbering up). The recently introduced intelligent microflow systems allow for a self-optimization of reaction parameters, such as mixing, flow rates, and residence time, making implementation in microreactors less time-consuming [3].

The advantages of continuous-flow microreactors are well recognized nowadays, and the number of applications of this technology in modern organic chemistry is increasing constantly [4].

Flow processes are rapidly finding applications in modern synthesis including the preparation of biologically active compounds, materials, natural products, and drugs [5]. As far as organic synthesis is concerned, it might be stated that a huge number of synthetic routes make use of organometallic reagents. However, the development of chemical transformations using organometallics could seldom be problematic because of their high reactivity and intrinsic chemical instability. Nevertheless, organometallic reagents have been successfully handled in flow microreactors, often with better results compared to batch mode. The aim of this review is to provide the reader with an overview about recent advances in the generation and use of organometallic reagents under continuous-flow conditions.

Far to be exhaustive, this review will describe recent achievements in the use of flow technology for the development of synthetic methodologies based on organometallic reagents as organolithiums, organomagnesiums, organozincs, organocuppers, and organopalladiums.

2. Organolithiums-Mediated Flow Synthesis

Organolithium compounds are important organometallic reagents that found widespread use in organic synthesis [6]. Nevertheless, their use requires skills and expertise due to their sensitivity to moisture or oxygen and their extremely high reactivity. In fact, some organolithiums (i.e., *t*-BuLi) are even pyrophoric and usually are employed under cryogenic conditions [7]. Thus, while small-scale reactions involving organolithiums can be easily carried out in batch reactors at laboratory level, a scale-up is quite challenging, causing strong limitations for industrial applications. The very high reactivity has been successfully faced by flow technology. In fact, organolithiums have been found as suitable candidates for continuous-flow processing, and the constantly increasing number of reports appearing in the literature demonstrated how organolithium chemistry would benefit from flow microreactors. Pioneering work by Yoshida demonstrated that the use of flow microreactors allows the generation and use of organolithiums at much higher temperatures than the conventional cryogenic conditions required for batch reactions [8]. Yoshida and coworkers greatly contributed to this field, introducing new concepts such as "flash chemistry," "space integration," and "protecting-group free flow synthesis" [9]. It will be showed, in this section dedicated to lithium compounds, how flow microreactors could represent an enabling technology for performing reactions that are impossible to conduct in batch conditions. A very nice combination of flash synthesis and space integration has recently been reported by Yoshida and coworkers. The 1,3,5-tribromobenzene **1** was used as starting material for the preparation of the ligand for retinoic acid receptors TAC-101 by three sequential lithiation–electrophilic trappings. The integrated microfluidic systems were realized by using six micromixers (M) and six microtube reactors (R), as reported in Scheme 1. Under optimized conditions, highly selective Br–Li exchange reactions could be performed to generate the required aryllithium species [10].

Under optimized conditions, two consecutive silylation reactions followed by reaction with an isocyanate can be executed at 0 °C in 12.2 s. This integrated microfluidic system allows for a productivity of 100–200 mg/min of the target retinoid compounds **2**.

The use of flow microreactor has been found useful in controlling the lithiation of isomeric dibromo benzenes [11]. Compared to batch reactors, the Br–Li permutation on *m*- and *p*-dibromobenzene can be conducted effectively at higher temperature (20 °C vs. −78 °C), and the lithiated intermediate can be trapped with several electrophiles (Scheme 2). The most challenging *o*-dibromobenzene, which could undergo very rapid LiBr elimination, giving the corresponding benzyne intermediate, can be lithiated and trapped at −78 °C in a flow microreactor. It is worth mentioning that this reaction requires temperature as low as −110 °C if performed in a batch reactor [12].

However, Yoshida and coworkers exploited the side reaction leading to benzyne for a very interesting and elegant three-component coupling process [13]. An integrated microfluidic system, consisting in four micromixers and four residence units, working at three different temperatures, has been employed to perform the sequential carbolithiation–electrophilic trapping reported in Scheme 3. Several functionalized biaryls **5** were prepared in this way. 1-Bromo-2-iodobenzene **3** was found as suitable starting material to furnish high yield of *o*-bromophenyllithium **3-Li** in

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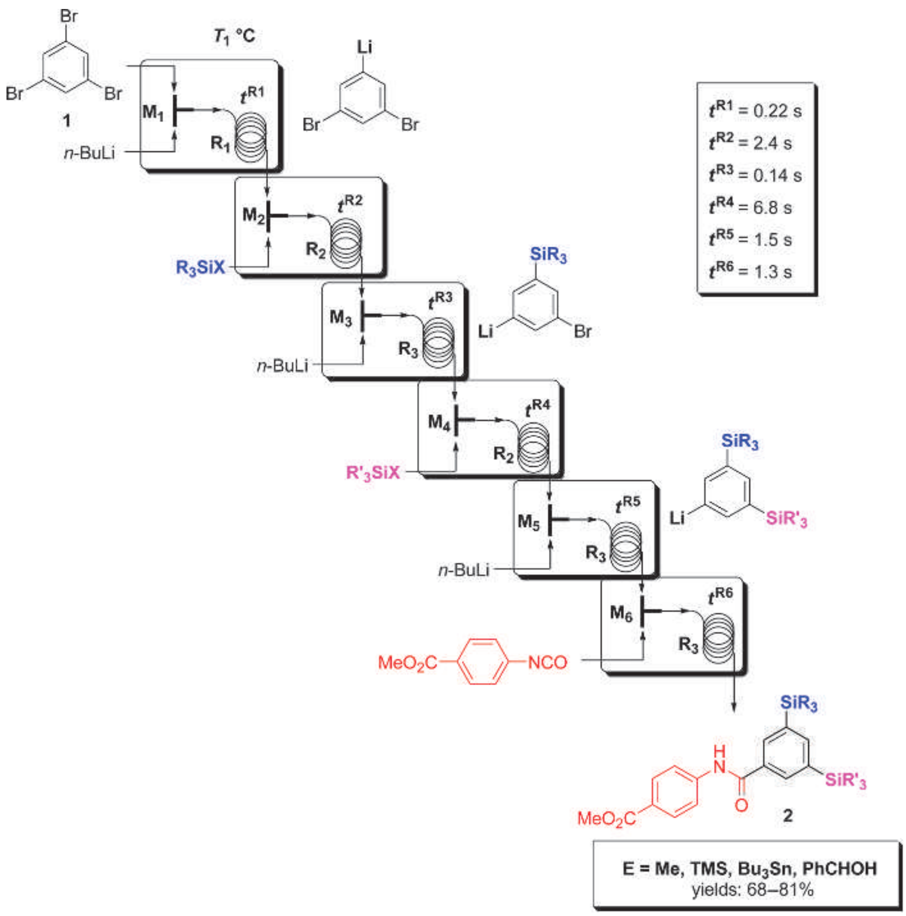
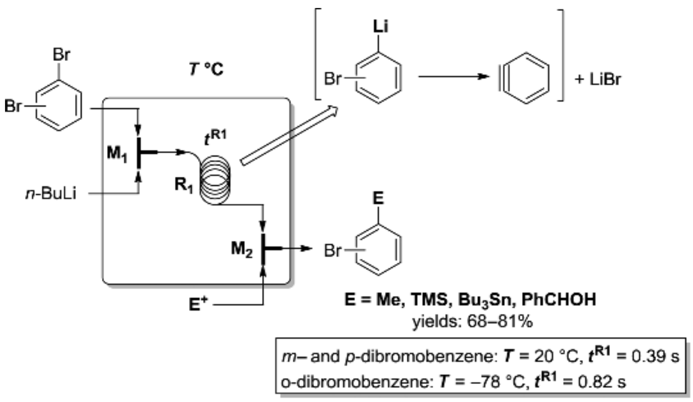
Scheme 1.



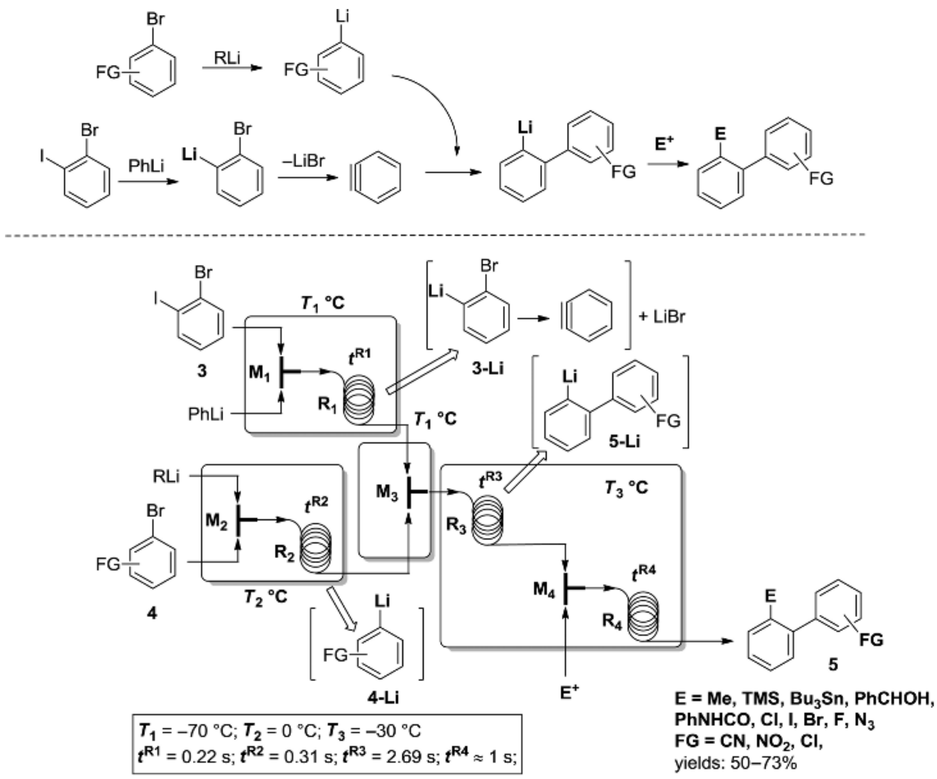
the first micromixer working at −70 °C and with a residence time of 0.22 s. **3-Li** is thermally decomposed to benzyne in R3 at −30 °C in the presence of functionalized aryllithium **4-Li** generated in M2 at 0 °C. Under such conditions, a carbolithiation takes place, as consequence of the addition of aryllithium to benzyne, leading to a functionalized biaryllithium **5-Li** that is reacted with electrophiles in M4. It is worth mentioning that this process is difficult to optimize and conduct in batch mode, and the precise control of the reaction conditions in a flow system is responsible for the success of this process. The reaction is tolerant to functional groups such as nitro and cyano group and allows the use of varied electrophiles. The process has been applied to the synthesis of the fungicide boscalid.

Ley developed a flow platform for the preparation, on a large scale, of aromatic scaffolds. The key intermediates for this transformation were fluorinated ortho-lithiated intermediates amenable of LiF elimination [14]. In the context of protecting-group free synthesis [15], microreactor technology could play an important role because of the precise control on the reaction parameters. Yoshida and coworkers actively contributed to this field demonstrating that highly reactive organometallic species (i.e., organolithiums or organomagnesium) could be generated and used even in the presence of sensitive functionality such as the carbonyl group. It is widely recognized that organolithiums are not compatible with carbonyl derivatives such as esters. Nevertheless, the use of a flow microreactor system consisting of micromixers and microtube reactors allowed to generate and to use aryllithiums bearing an alkoxycarbonyl moiety at positions ortho, meta, and para [16]. Several ortho, meta, and para alkyl lithiobenzoates **6-Li** were generated by a halogen–lithium exchange reaction with PhLi or *sec*-BuLi. PhLi was employed with *p*- and *m*-iodo alkylbenzoates **6** while *sec*-BuLi was used with *o*-bromo alkylbenzoates. A different reactivity was noticed for

Scheme 2.



Scheme 3.

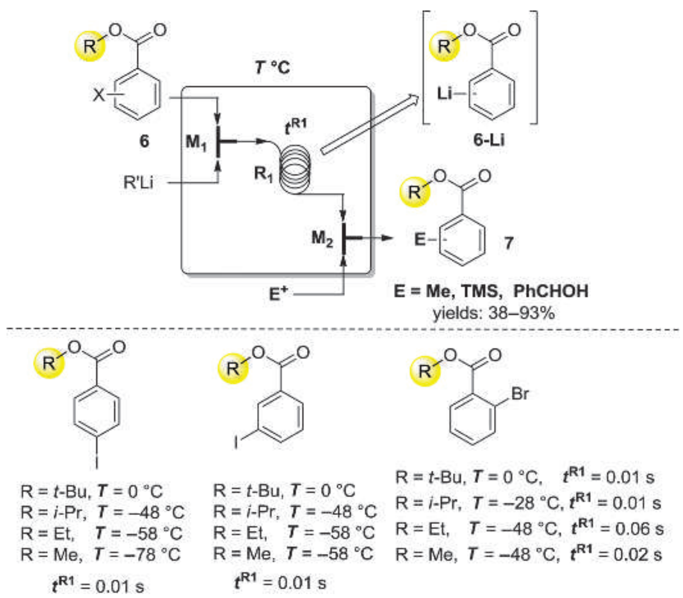


sterically less-demanding ethoxycarbonyl- and methoxycarbonyl-aryllithiums which required lower temperatures for their generation with respect to *iso*-propoxycarbonyl and *tert*-butoxycarbonyl aryllithiums (Scheme 4). However, several *tert*-butoxycarbonyl-substituted aryllithiums could be generated at much higher temperatures (up to 0 °C) than those required under conventional batch conditions. The more unstable isopropoxycarbonyl-, ethoxycarbonyl-, and methoxycarbonyl-substituted aryllithiums, which are practically impossible to generate under conventional batch conditions, were generated under flow conditions by controlling parameters such as residence time and temperature (Scheme 4). Further reactions of the resulting aryllithiums with electrophiles led to substituted alkyl benzoates **7** in good yields without needing to protect the alkoxycarbonyl group.

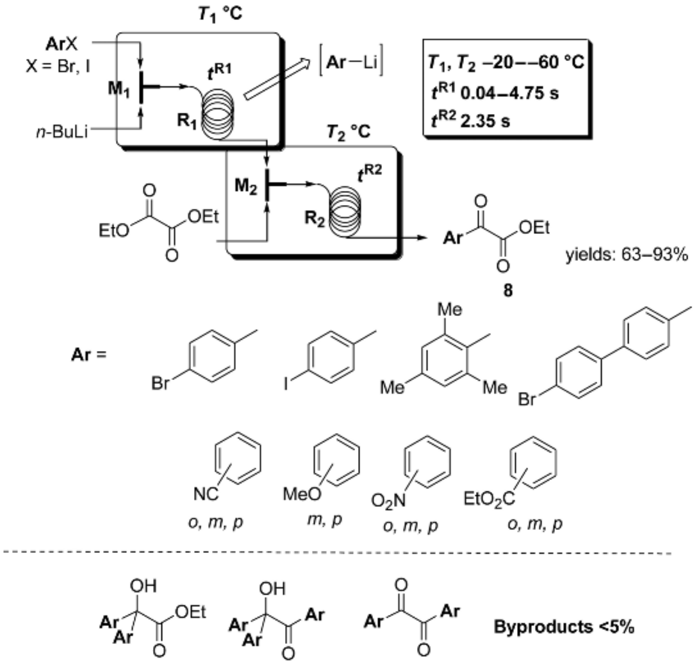
Further, the strategy was extended to aryllithium species deriving from ketones-generated exchange from the corresponding aryl iodides by iodine–lithium exchange reaction with mesityllithium. A very short residence time (0.003 s) was required to avoid side reactions. This method was then applied to the synthesis of natural product Pauciflorol F47 [17].

The compatibility of the carbonyl group with organometallics, under flow conditions, has been further demonstrated by Yoshida, who developed an efficient method for introducing the α-ketoester group into aromatic rings. Several highly reactive functionalized aryllithiums were generated and reacted with diethyloxalate to furnish the corresponding α-ketoesters **8** (Scheme 5) [18]. The amount of byproducts deriving from multiple nucleophilic addition was limited using a microflow system.

Scheme 4.



Scheme 5.

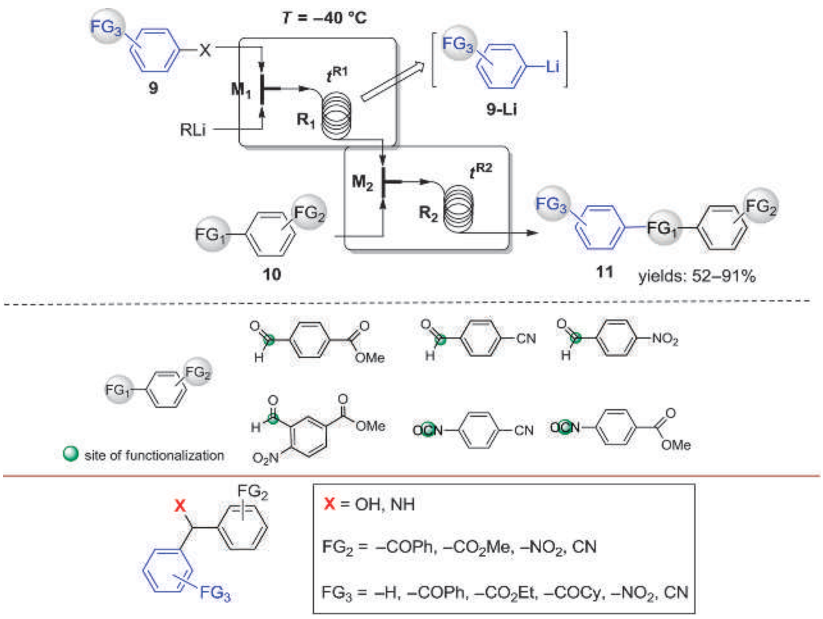


The concept of “functional-group tolerance” and “protecting-group free synthesis” was further harnessed, by Yoshida and coworkers, with the development of a flash method for highly chemoselective reactions of aromatic compounds **10**, having two electrophilic functional groups (FG1 and FG2 in Scheme 6), with aryllithiums **9-Li** bearing an additional functional group (FG3). The use of an integrated microfluidic system allowed for the synthesis of polyfunctional organic molecules **11** hardly obtainable using standard batch operations (Scheme 6) [19].

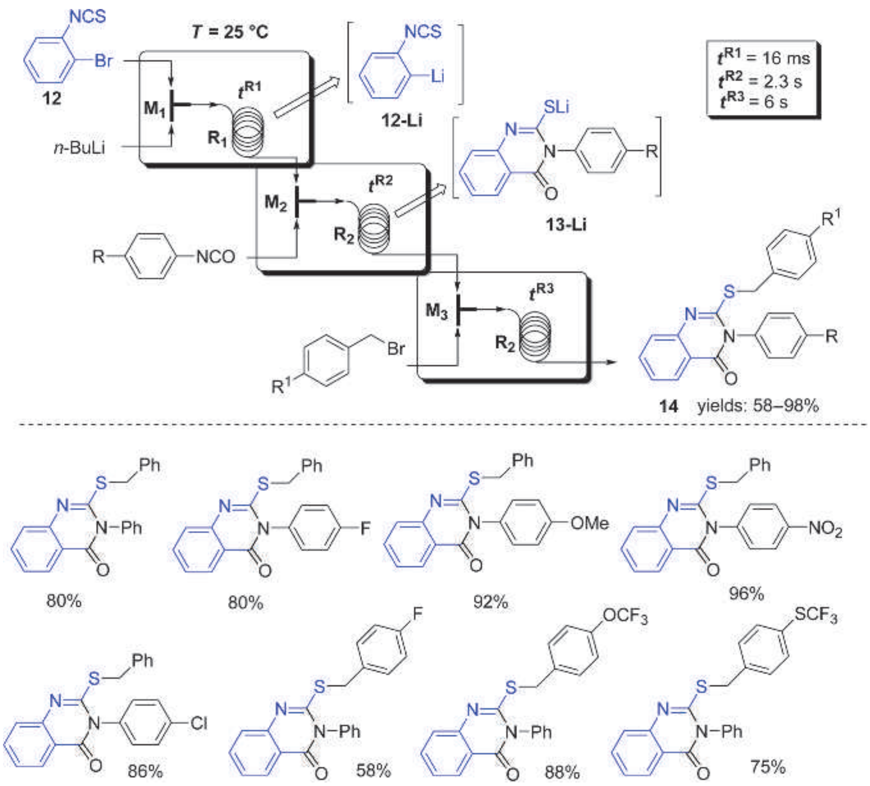
Kim and coworkers reported a nice example of functional-group tolerance in a flow synthesis of a library of biologically active thioquinazolinones. *o*-Lithiophenyl isothiocyanate **12-Li** was generated within a microreactor and reacted with aryl isocyanate to furnish, after quenching with benzylbromides, S-benzyl thioquinazolinone derivatives **14** in high yields (75–98%) at room temperature in only 10 s. The process optimized in the microreactor required 16 ms of residence time for the generation of *o*-lithiophenyl isothiocyanate (t^{R1}) at room temperature and additional 2.3 s for the reaction with aryl isocyanate and intramolecular cyclization, leading to a lithium thiolate **13-Li** intermediate quenched by reacting with a benzyl bromide. A gram-scale synthesis (1.25 g in 5 min) of a multifunctionalized thioquinazolinone has been reported as application of this integrated microfluidic device (Scheme 7) [20].

Halogen–lithium exchange reaction on heterocycle is one of the most efficient methodologies to functionalize heteroaromatics moieties with electrophilic reagents [21], even though conventional batch procedures require cryogenic conditions in order to prevent side reactions and decomposition. For this reason, the generation of heteroaryllithiums has been performed using microreactor technology. Yoshida reported that pyridyllithiums **15-Li** could be generated, under flow conditions, by treatment of the corresponding pyridyl bromides **15** with *n*-BuLi using 55 ms of residence time at 0 °C (Scheme 8) [22].

Scheme 6.



Scheme 7.

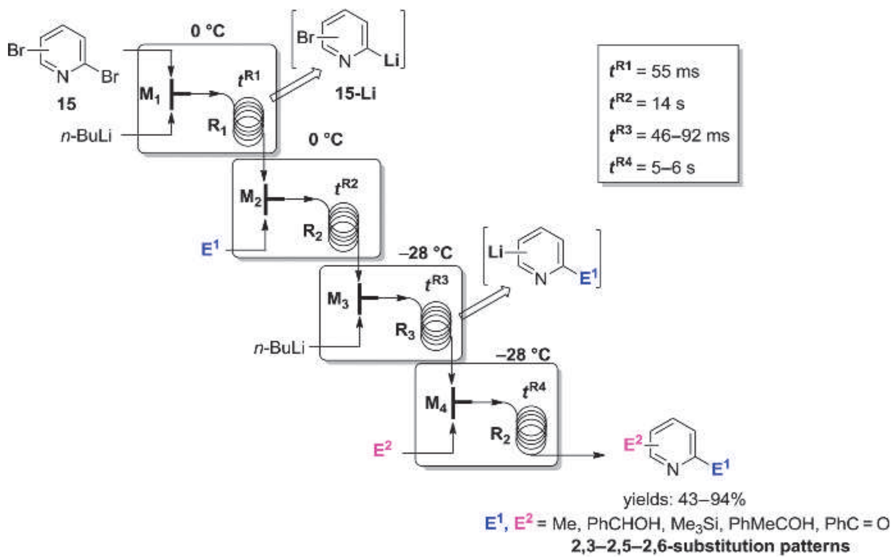


A double lithiation–trapping sequence allowed for introducing two different electrophiles on dibromo pyridines obtaining 2,3-, 2,5-, and 2,6-disubstitution patterns. The reaction proved to be successful with various electrophiles such as iodomethane, TMS-Cl, and benzaldehyde. The reaction required two different temperatures for the bromine–lithium exchange reactions (Scheme 8).

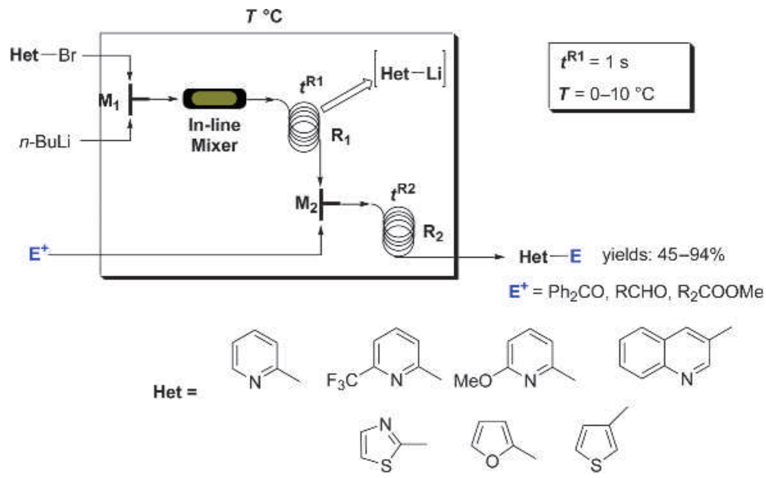
Recently, Jia and coworkers described an extension of Yoshida's work on the flow generation and trapping of lithiated heteroaromatics [23]. The integrated microflow system reported by Jia employs an inline mixer, which was a splitting and recombining micromixer, in order to improve efficiency of the lithiation reaction and yields of the trapping products (Scheme 9).

An interesting application on the use of lithiated heteroaromatics, generated under flow conditions, can be found in the preparation of photochromic diarylethenes recently reported by Yoshida [24]. Photochromic diarylethenes were prepared using an integrated flow microreactor system through the generation of heteroaryllithiums **16-Li** and subsequent reaction with octafluorocyclopentene **17**. A synthesis of symmetrical and unsymmetrical diheteroarylethenes **18** and **21**, bearing thiophene, thiazole, benzothiophene, and benzofuran moieties was accomplished, without needing cryogenic conditions, by accurate control of temperatures and residence times in the halogen–lithium exchange reaction and subsequent reaction with octafluorocyclopentene (Scheme 10, a). Symmetrical diheteroarylethenes **18** could be obtained by controlling temperature and residence time in R2 (t^{R2}), as well as the introduction of a single heteroaryl group could be achieved using one equivalent of lithiated intermediates. The availability of mono-

Scheme 8.



Scheme 9.

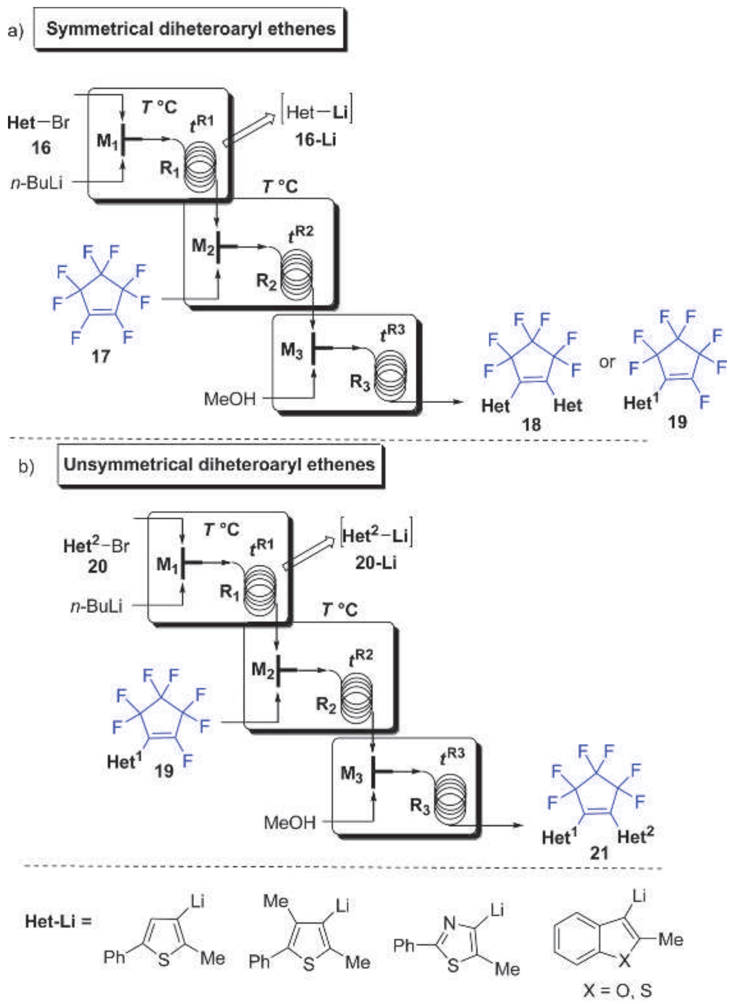


substituted heteroarylethenes **19** allowed the preparation of unsymmetrical diarylethenes **21** by a selective introduction of an additional heteroaryl group (Scheme 10, b). It is worth mentioning that those processes are difficult to perform using conventional batch reactors.

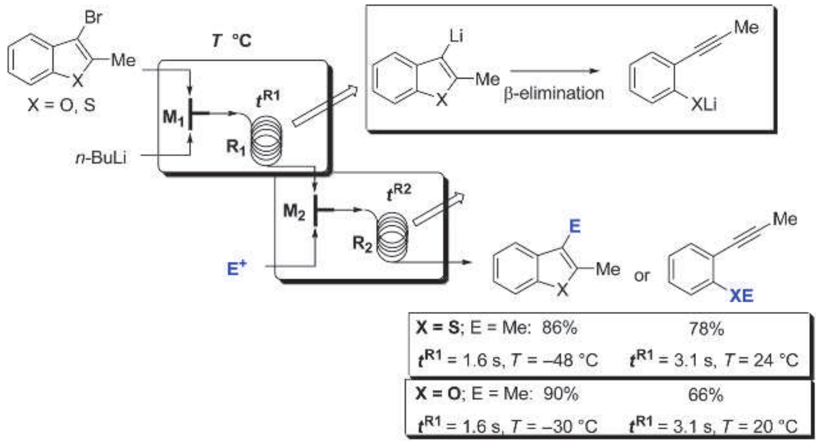
The accurate control of residence time and temperature within a microreactor allows to handle with isomerization processes. In fact, when different reaction pathways can be considered for a lithiated intermediate, a control of the reaction in batch mode can be difficult. For example, 3-lithio benzothiophenes and benzofurans should be generated and used at low temperature in order to avoid the ring opening reaction due to a competing β-elimination process leading to the corresponding arylalkyne (Scheme 11). Performing the lithiation–functionalization sequence using a flow microreactor system allows a selective switch between reaction pathways by simply controlling temperature and residence time [25].

By using lower temperatures and shorter residence time, it is possible to avoid the ring-opening reaction obtaining functionalized benzofurans or benzothiophenes. In striking contrast, running the flow microreactor system at higher temperature and for slightly longer residence times, the β-elimination reaction occurs and O- and S-functionalized arylalkynes can be prepared (Scheme 11).

Scheme 10.



Scheme 11.

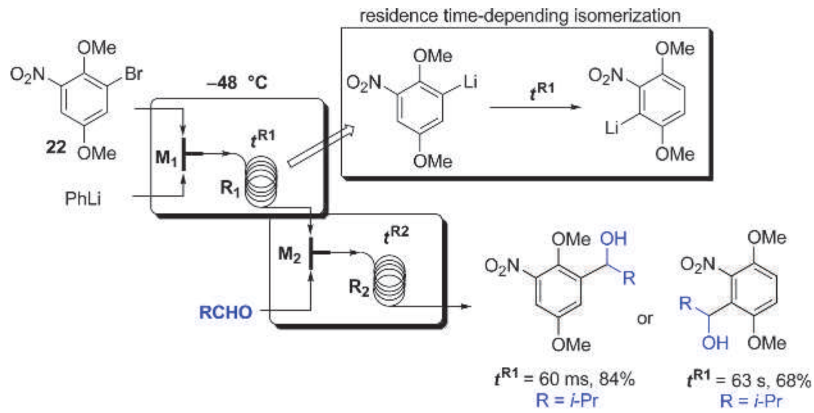


Another example on the use of flow microreactor for switching between kinetic and thermodynamic product can be found in the lithiation of nitroaryl bromides [26]. In fact, using an integrated flow microreactor system (Scheme 12) constitutes of two micromixers (M1 and M2) and two residence units (R1 and R2); the Br–Li exchange of 1-bromo-2,5-dimethoxy-3-nitrobenzene **22** led to a selective formation of the corresponding aryllithium using a residence time of 60 ms at −48 °C. However, increasing the residence time to 63 s, at the same temperature, a lithium migration occurred leading to the isomeric aryllithium species (Scheme 12).

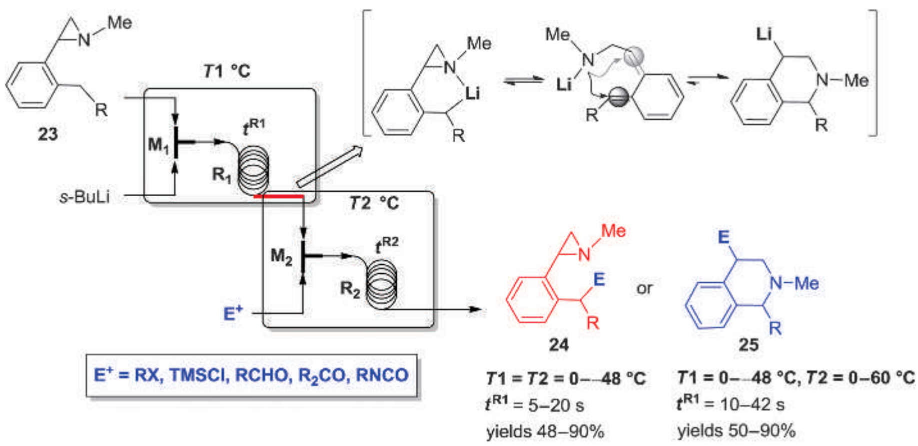
Luisi and Yoshida reported another example of reaction pathways switch exploiting a thermally induced isomerization of laterally lithiated aziridines [27]. In this report, taking advantage of the exquisite temperature control realized in flow microreactors, either functionalized arylaziridines or 1,2,3,4-tetrahydroisoquinolines (THIQs) were synthesized. The most critical parameters were temperature and residence time (Scheme 13). Benzylic lithiation of 1-methyl-2-(ortho-tolyl) aziridine **23** was carried out with *sec*-BuLi at −48 °C (t^{R1} = 20.9 s), and subsequent trapping with electrophiles gave functionalized aziridines **24**. When the laterally lithiated aziridines were introduced in a second tube reactor maintained at 0 °C (t^{R1} = 42 s), isomerization took place, leading to lithiated THIQ that reacted with electrophiles producing the corresponding isoquinoline derivatives **25** (Scheme 13). Such isomerization proved to be difficult to control under batch conditions.

The precise control of the residence time has been useful in controlling the reaction pathway switch for 1,2-dichlorovinyllithium

Scheme 12.



Scheme 13.



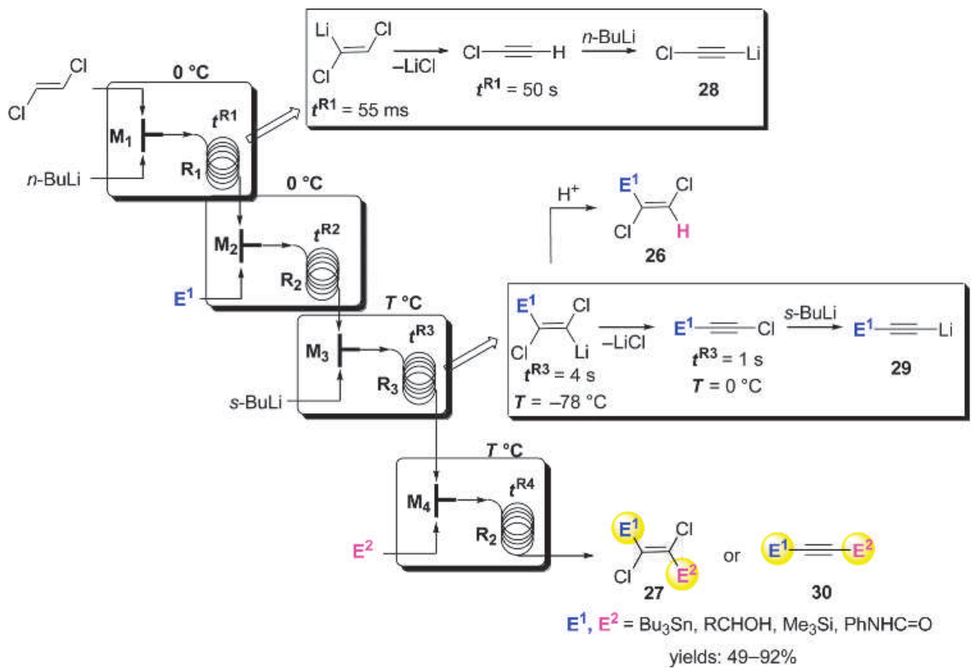
intermediates. Based on this switch, a versatile synthesis of substituted alkenes and alkynes from trans-1,2-dichloroethene has been possible using an integrated flow microreactor system (Scheme 14) [28]. 1,2-Dichlorovinyllithium was generated by deprotonation of 1,2-dichloroethene with *n*-BuLi at 0 °C with 55 ms of residence time in M1 and reacted with electrophiles in M2 to give the corresponding substituted 1,2-dichloroethenes **26**. A second deprotonation with *s*-BuLi, performed at −78 °C, followed by the reaction with a second electrophile led to 1,2-disubstituted 1,2-dichloroethenes **27**. However, prolonging the residence time in M1, it was possible to promote a LiCl elimination furnishing chloroacetylene that undergoes deprotonation in the presence of an excess of *n*-BuLi in R1. The resulting 2-chloroethynyllithium **28** reacted with electrophiles affording substituted chloroacetylenes. Using an integrated flow microreactor system, an additional Cl–Li exchange reaction could be performed on substituted chloroacetylenes in R3 using *s*-BuLi leading to the corresponding 2-substituted ethynyllithium **29** that by reaction with a second electrophile affords 1,2-disubstituted acetylenes **30**. Thus, alkenes and alkynes can be selectively produced on demand from the same starting material.

The control on the elimination pathway in haloalkyllithium intermediates has been extended to fluorinated alkyllithiums which are keen to undergo LiF elimination. Yoshida and coworkers reported that perfluoroalkyllithiums can be generated by halogen–lithium exchange reaction using microreactors operating at −68 °C [29]. Very short residence times are required in order to avoid fast β-elimination and effectively trap the lithiated intermediates with electrophiles (Scheme 15). Several perfluoroalkylated derivatives **31** could be prepared using this strategy.

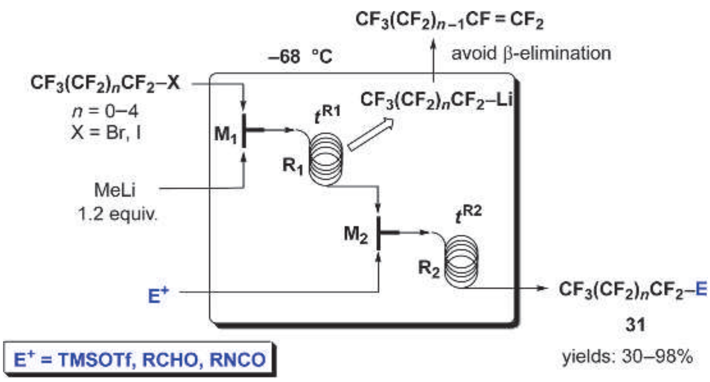
Integrated flow microreactor systems enable also the generation of highly unstable α-(trifluoromethyl)vinyllithium at higher temperatures with respect to batch conditions. Yoshida reported a very interesting continuous-flow three-component synthesis of α-trifluoromethyl amides, which serve as fascinating motifs in peptidomimetics [30]. The intermediate α-(trifluoromethyl)vinyllithium **32-Li** has been generated by bromine–lithium exchange with *s*-BuLi at −78 °C using a residence time (t^{R1}) of 55 ms and trapped with several electrophiles furnishing the corresponding trifluoromethylated alkenes **33** (Scheme 16). When isocyanates were used as electrophiles, the corresponding adducts **34** were further reacted in another microreactor with a suitable nucleophile such as malonates to provide functionalized trifluoromethyl amides **35** in good yields and in a continuous mode (Scheme 16).

Luisi and Degennaro reported the first example of external trapping of the highly reactive chloromethyllithium enabled by a flow microreactor system [31]. This kind of halocarbenoids,

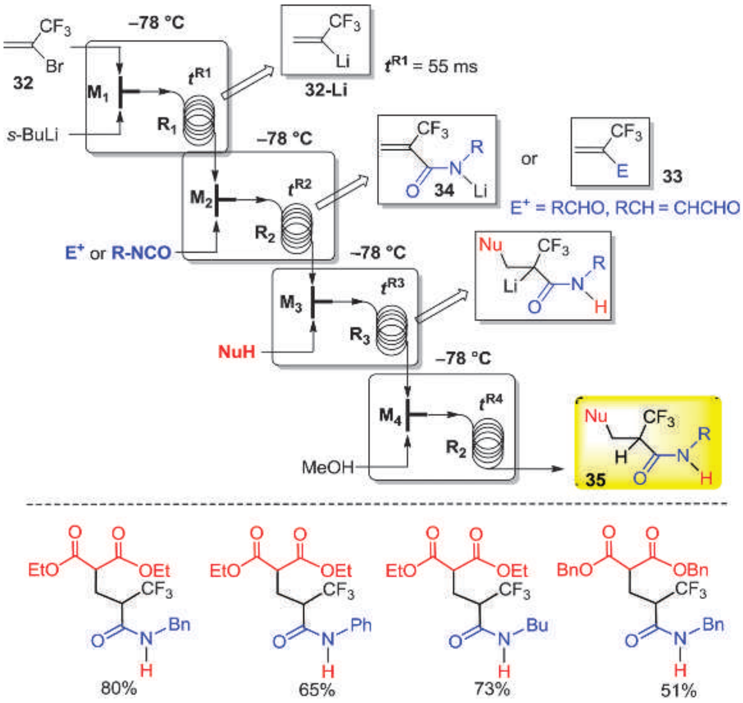
Scheme 14.



Scheme 15.



Scheme 16.



of great synthetic utility for homologation reactions, is used in batch at very low temperatures (i.e., <−78 °C) and under internal quenching conditions. It was found that the carbenoid can be generated, using short residence times (0.18–0.30 s), at much higher temperatures with respect to batch conditions (up to −20 °C) and effectively trapped with electrophile in a second T-shaped micromixer (M2 in Scheme 17). The study evaluated the effect of the temperature, the residence time in M1, and the lithiating agent, showing a better thermal stability of the carbenoid using MeLi LiBr as lithiating agent.

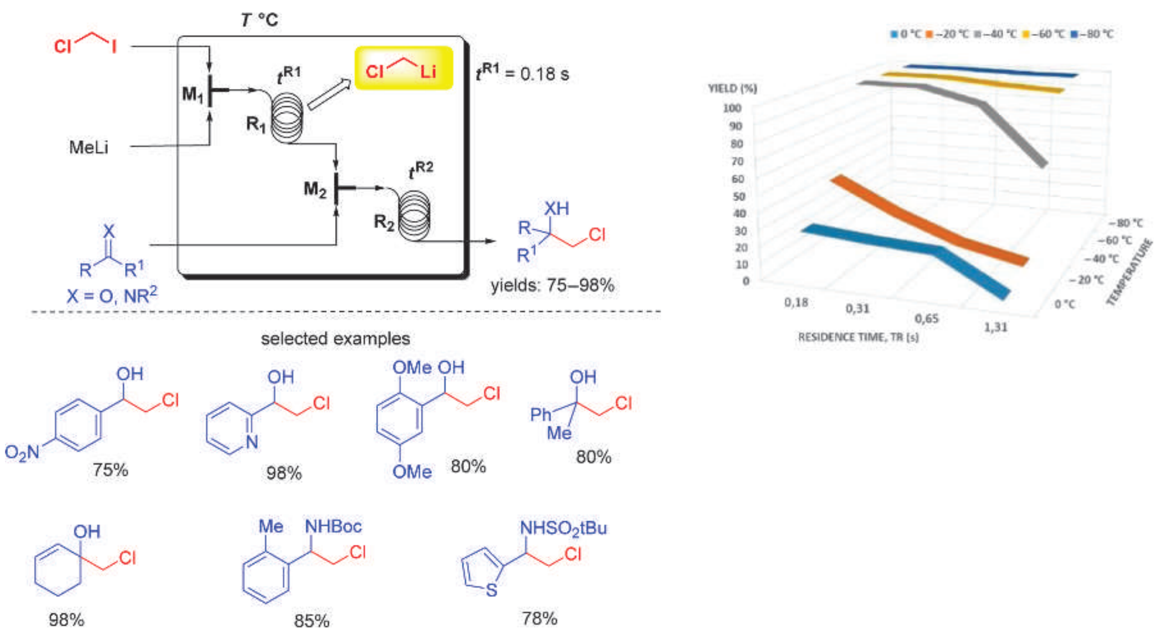
However, using 0.18 s as the residence time at −40 °C, several electrophiles, including aldehydes, ketones, imines, Weinreb amides, and isocyanates, could effectively be trapped, furnishing the corresponding adducts in good to excellent yields.

Further examples on the use of flow technologies for the functionalization of organolithiums come from the use of a gas–liquid system for the effective trapping of CO_2. Three different research groups reported effective strategies for reacting CO_2 with organolithiums. Kappe and coworkers reported a flash-carboxylation method for the direct carboxylation of lithiated terminal alkynes and heterocycles [32]. The methodology provides carboxylic acids at room temperature using a slightly excess of the organometallic base and CO_2 (Scheme 18).

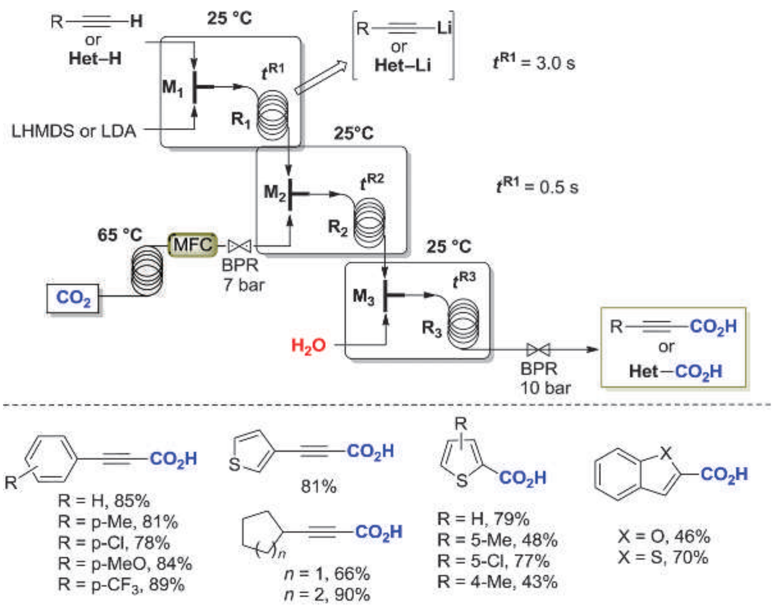
Several functionalized propargylic and heterocyclic carboxylic acids were prepared in continuous-flow mode and at room temperature. The system was designed in a way to allow a controlled feeding of the gas. For the correct introduction of the gas into the flow system, a warmed coil at 65 °C, a back-pressure regulator, and a mass flow controller were employed (Scheme 18).

In a similar way, Yoshida and coworkers reported a flash carboxylation of highly unstable and short-lived organolithiums [33]. Highly reactive organolithiums, bearing electrophilic

Scheme 17.



Scheme 18.



functional groups such as nitro, cyano, and alkoxycarbonyl groups, were effectively trapped with CO_2 to furnish the corresponding carboxylic acids. Temperatures and residence times were critical parameters for the lithiation reactions, while the gas–liquid mass transfer and the reaction with CO_2 were extremely fast (Scheme 19).

Two complementary continuous-flow systems have been developed by Jamison and coworkers for an efficient synthesis of ketones with varied substitution patterns using a double sequence of addition of organolithiums to carbon dioxide [34]. The developed systems, using either stoichiometric or excess of CO_2, avoid the formation of undesired symmetric ketones or tertiary alcohols (Scheme 20). The double sequence uses a surprising solvent effect. In fact, a higher reactivity for organolithium reagents was disclosed in Et_2O with respect to THF. The sequential addition was also extended to Grignard reagents and used for a telescoped one-flow process for preparing ketones from simple precursors.

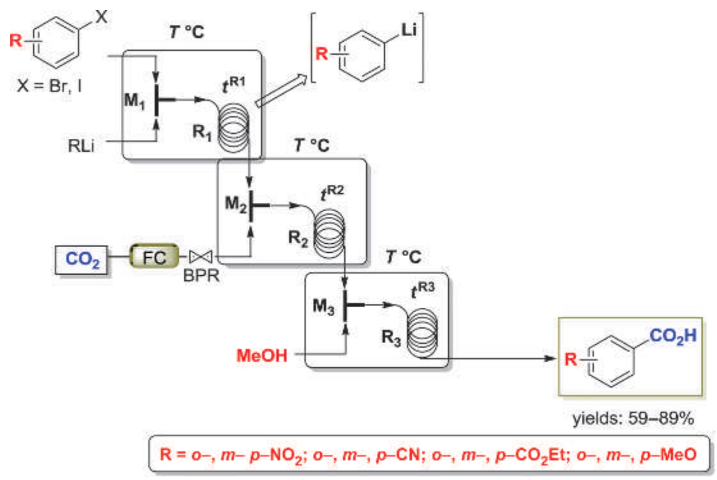
3. Organomagnesium-Mediated Flow Synthesis

Besides their first preparation over a hundred years ago, Grignard reagents are still holding an important role in synthesis. Organomagnesium reagents are commercially available or can be easily prepared by several strategies and have found applications in industrial processes exploiting their excellent reactivities toward electrophiles. Because of their high reactivity, especially towards polarized C═X bonds, reactions involving Grignard reagents often require cryogenic and controlled reactions conditions as seen for the closely related organolithiums. For these reasons, Grignard's chemistry could benefit of microreactor technology.

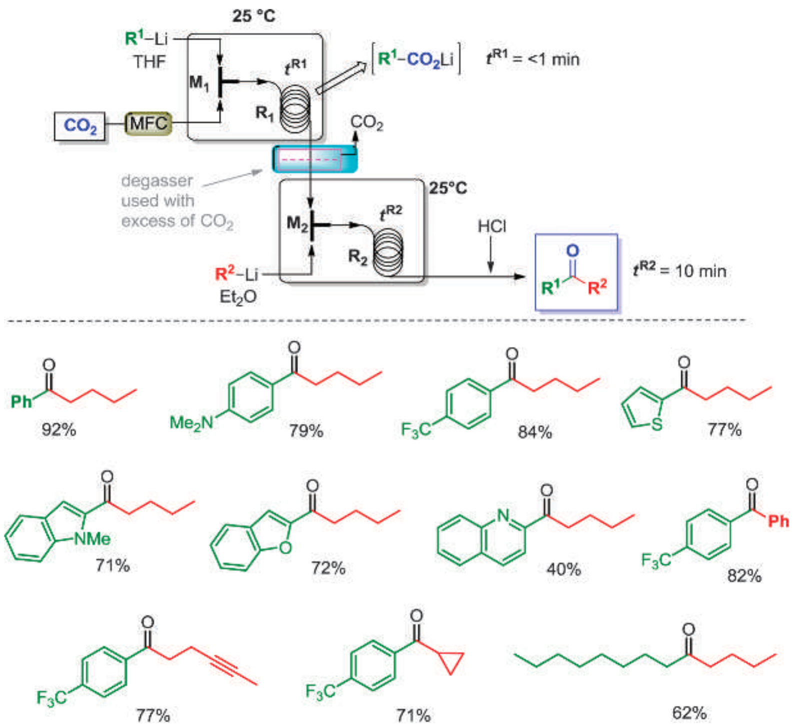
Deng and coworkers reported a continuous-flow protocol for synthesizing the industrial relevant precursor 2,4,5-trifluorobenzoic acid **36**, used in the manufacture of fluoroquinolone antibiotics, via an unstable aryl-Grignard reagent that reacted with gaseous CO_2 [35].

The flow system consists of a T-micromixer, a falling film microreactor, a tube reactor, and a mass flow-controller for delivering of CO_2 (Scheme 21). The use of the falling film microreactor allows for achieving highly efficient gas–liquid reaction with CO_2 under atmospheric pressure. Deng and coworkers investigated many reaction parameters: the effect of temperature, stoichiometry, concentration of EtMgBr, flow rate of CO_2, and the inner diameter of the microreactor. The rated reaction is more efficient at higher temperature. The conversion dramatically increases from 36% to 93%, rising the temperature from 15 °C to 50 °C; even if at 50 °C, the formation of gas led to instability of the system and causes inconvenience in

Scheme 19.



Scheme 20.



stoichiometry. However, in striking contrast, the scaled batch process is costly and inefficient, requiring low-temperature operations and slow controlled addition of one reagent into the other. Brodmann and coworkers reported a continuous-flow process for the preparation of aryl- and heteroaryl Grignard reagents by a halogen–Mg exchange reaction using *i*-PrMgCl–LiCl (Scheme 22) [36].

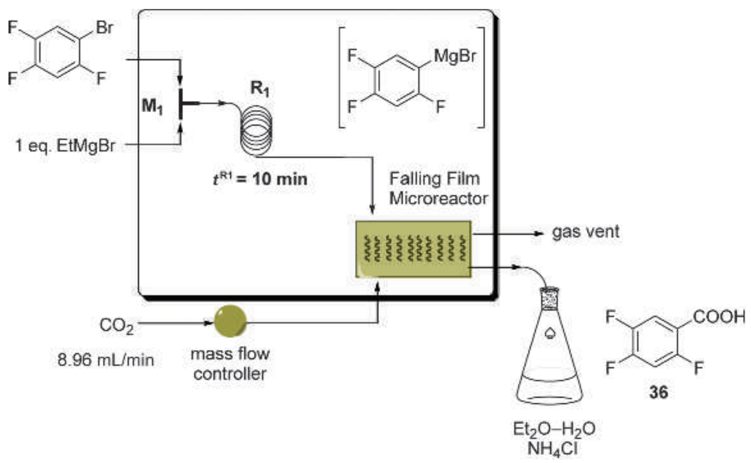
The process was optimized, under continuous-flow conditions, using an in-line Fourier transform infrared (FT-IR) analysis with a React-IR flow cell. The study focuses on the formation of *m*-methylphenylmagnesium chloride (ArMgCl) and on the role of the solvent THF in coordinating to magnesium in the Grignard reagent. IR spectra shows different signals for THF coordinated to ArMgCl and for excess of free THF. According to the study, the in-line IR spectroscopy was successful to ensure the quality of prepared organomagnesium species in solution. Moreover, this tool allows for assessing the concentration of active reagents and the composition of more complex reaction streams for quick reactions' optimization.

Another application on the use of organomagnesium reagents in continuous-flow chemistry is found in the synthesis of 3,3,3-trifluoromethylpropenes reported by Hamlin and coworkers [37]. They developed a Peterson-type olefination reaction by addition of trimethylsilylmethyl magnesium bromide **37** to trifluoromethyl ketones (TFMKs). The addition reaction was conducted in M1 and R1 (Scheme 23) using THF as the solvent which, however, is unsuitable for the eliminative step. A key point in this process is the in-line solvent switch to remove as much THF as possible before the TMSOTf-catalyzed step. The authors proposed an in-line liquid–liquid extraction to remove the water-soluble magnesium salts as well as partitioning the THF between the aqueous phase and the new organic solvent. The PTFE membrane-based liquid–liquid separator showed an excellent chemical compatibility and operated under high pressure (up to 300 psi) with flow rates up to 15 mL/min.

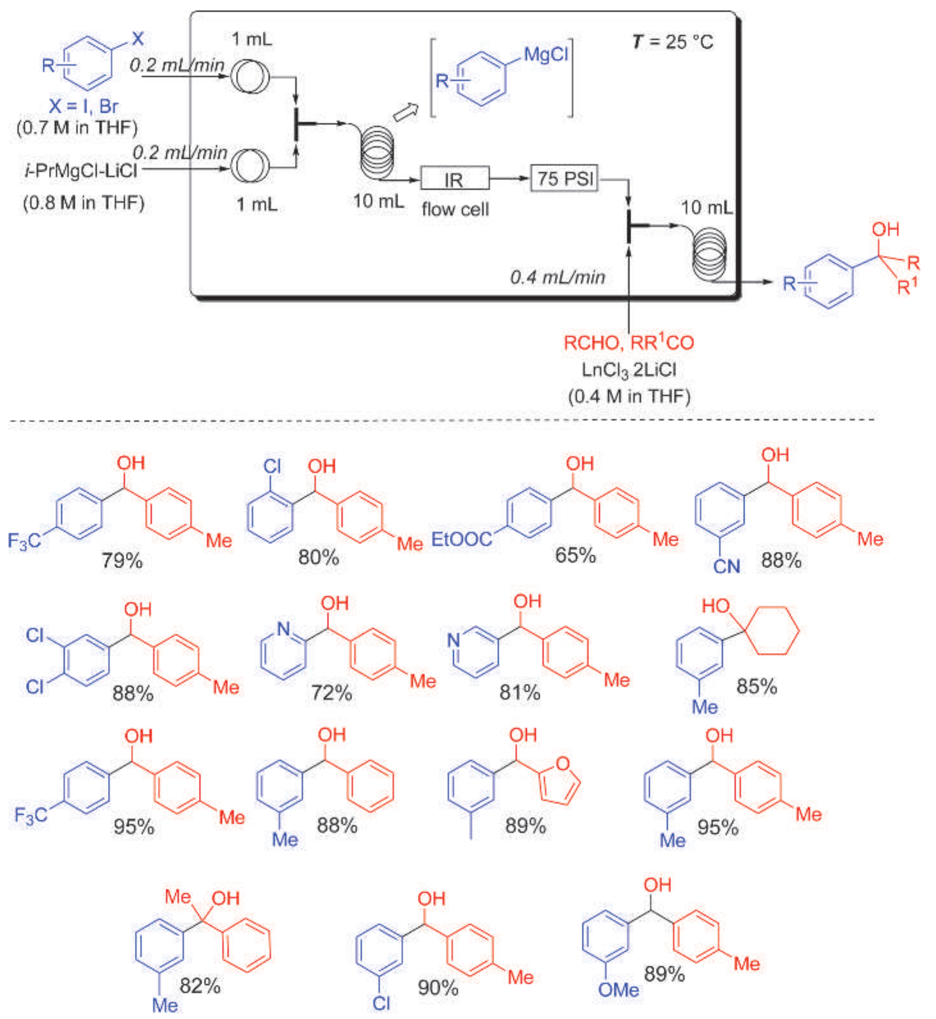
The study probes that the flow process for the synthesis of fluorinated alkenes is faster and higher yielding than the batch approach. In addition, the method allows to produce ~14 g of fluorinated alkene per day.

In another study, Petersen and coworkers explored the use of THF-soluble base TMPMgCl·LiCl to magnesiate a wide range of

Scheme 21.



Scheme 22.

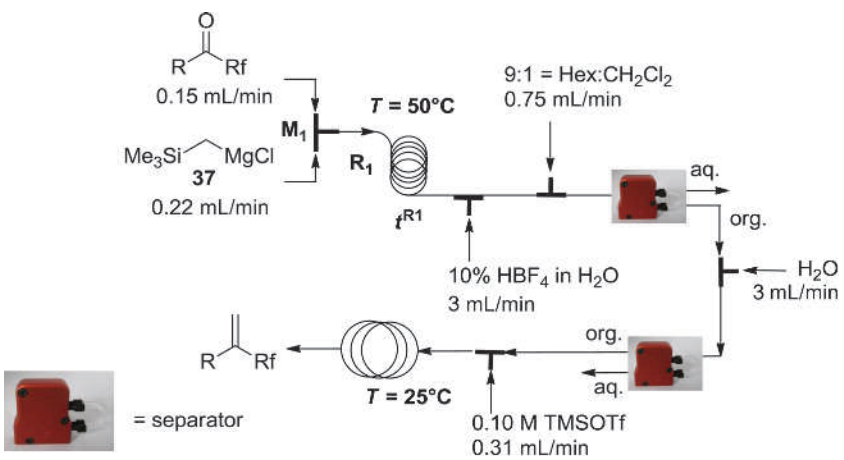


unsaturated polyfunctional heterocycles and acrylates [38]. By using flow technologies, the base TMPMgCl·LiCl was able to magnesiate a wide range of heterocycles at higher temperatures and shorter reaction time, with respect to batch conditions, avoiding side reactions. In the flow system, functionalized Grignard reagents reacted with electrophiles producing the corresponding adducts in good to excellent yields at 25 °C (Scheme 24). Moreover, this synthesis is scalable up to 45 mmol without further optimization maintaining similar yields.

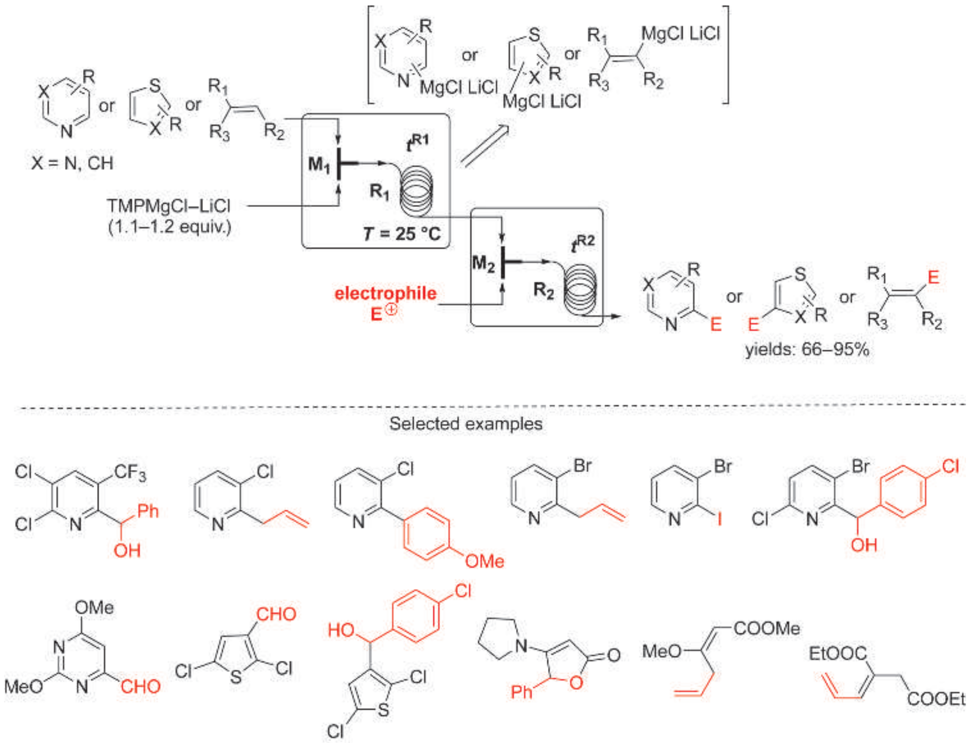
A further application of Grignard reagents for large-scale production has been recently reported by Ley and coworkers who developed a flow platform for the production of library of compounds under continuous-flow conditions [39].

Qian and coworkers developed a continuous-flow synthesis of a selective and potent δ-opioid receptor agonist, using diarylmethyl Grignard reagent **38** as intermediate [40]. An integrated process was developed by using flow microreactors, cartridges packed with solid-supported scavengers, to remove byproducts,

Scheme 23.



Scheme 24.



and an in-line FT-IR monitoring. The Grignard reagents were generated at room temperature in R_1 (Scheme 25), feeding the system with a solution of *i*-PrMgCl·LiCl and a THF solution of diarylmethane, DMPU, and diethylamine (used to avoid precipitation of magnesium salts). The electrophilic addition occurs in M2, and the resulting adduct was telescoped to the next flow steps obtaining the desired pharmaceutical compound with 35% overall yield.

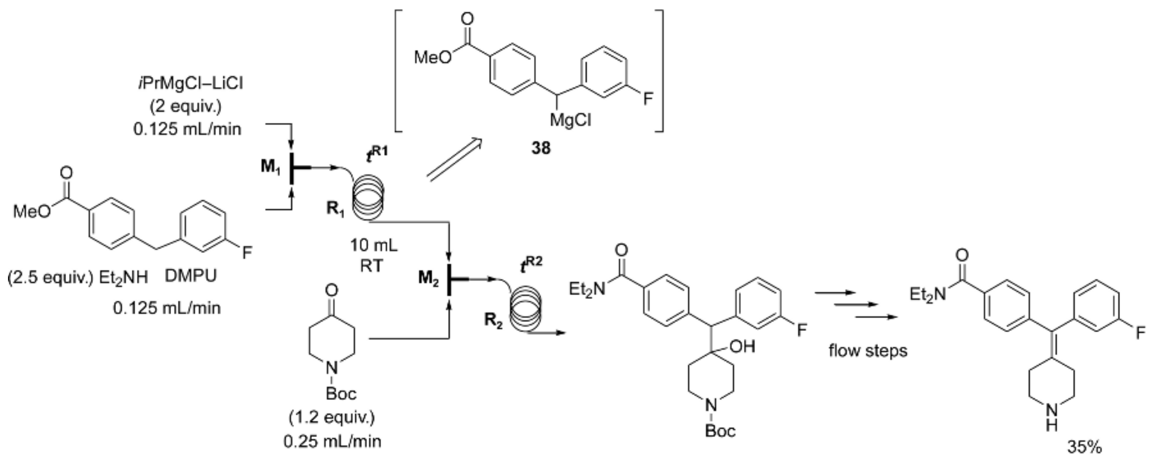
There are few practical examples of scale-out micro- and mesoreactors for large production. An example has been recently reported by Odille and coworkers, who developed a scale-up for a continuous-flow synthesis of ketones from ester by addition of Grignard reagents [41]. They transferred the reaction from a 1-mL volume microreactor to a 13.5-mL volume mesoreactor to achieve a productivity of ca. 0.5 kg. However, as drawback, in mesoreactor, precipitation occurred and cleaning cycles were necessary every 45 min with pressure over 5 bar.

Styring and coworkers developed an efficient system for scaling out a Ni-catalyzed Kumada reaction using first a single channel and then a 120-channel parallel reactor [42]. Each channel was packed with 3% of nickel supported on a Merrifield's resin, and solutions of reactants were pumped through a pneumatically driven calibrated system using a carrier gas (Scheme 26).

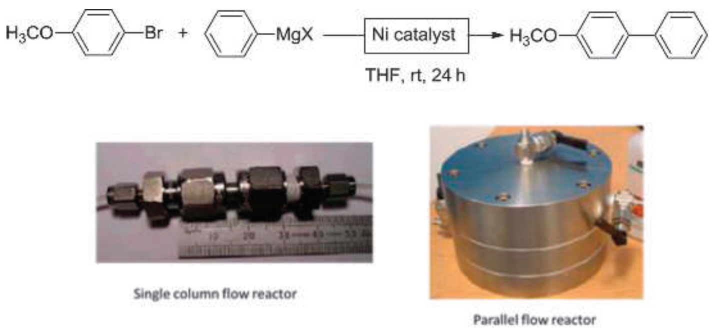
The Kumada reaction yields 137 g of 4-methoxybiphenyl over 24 h. An important aspect was the recyclability of the heterogeneous catalyst; the results of the study show that nickel-packed resin can be reused with a very little decrease in activity.

Seyler and coworkers reported an interesting synthesis of polyalkylthiophenes **40** and **41** emerging semiconducting materials, by using a bench-top continuous-flow reactor which permits to control molecular weight and achieve products with comparable performance to commercial available samples [43]. A Kumada reaction and two different catalysts were used: the notorius Ni(dppp)Cl_2 catalyst, soluble and stable in *o*-dichlorobenzene (*o*-DCB), and a tolyl-functionalized nickel complex, soluble in THF (Scheme 27). The resulting molecular weight was controlled by adjusting the monomer–catalyst ratio and the reactant's concentration in the flow system. The Grignard reagents **39** were prepared in batch conditions using *t*-BuMgCl, while the Ni

Scheme 25.



Scheme 26.



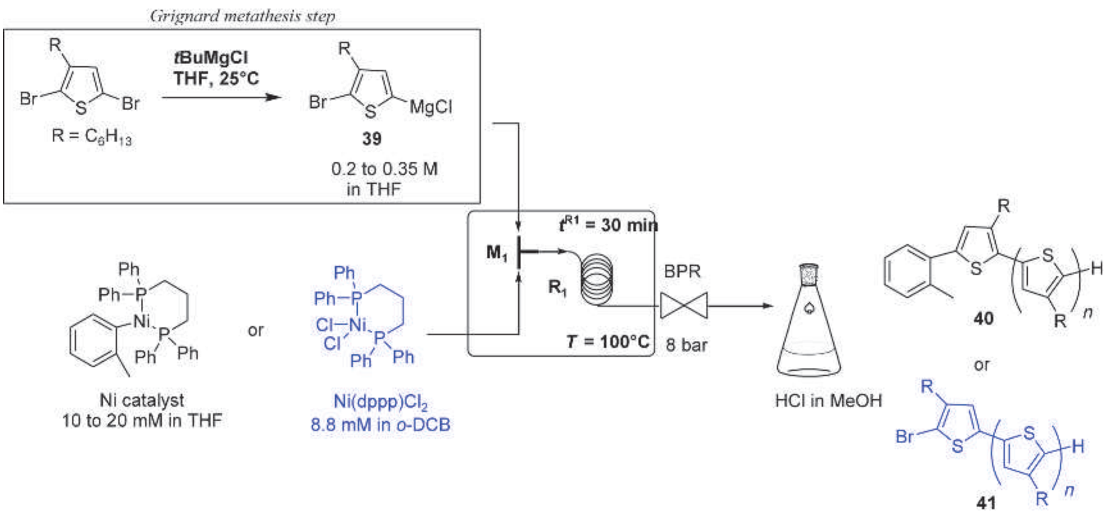
catalyst was loaded via an injection loop, and the polimerization was conducted in a preheated coil reactor (100 °C) over 30 min. Higher degree of polimerization was achieved in PFA (polyfluoroalkoxy) tube reactors while stainless-steel reactors yielded low molecular weight although they have low gas permeability.

An automated flow synthesis of 3-hydroxymethylindoles **42**, based on the use of Grignard's reagents, has been reported by O'Shea and coworkers [44]. Organomagnesium compounds were generated in R1 (Scheme 28) at 0 °C with 12 min of residence time, by *i*-PrMgCl-LiCl-mediated Mg–I exchange reaction on 3-iodoindoles. Trapping with carbonyl electrophiles furnished the corresponding 3-hydroxyalkylated indoles **42** which, in turn, were transferred in other microreactors that performed the nucleophilic substitution step, furnishing the corresponding 3-substituted indoles **43** (Scheme 28). The process was fully automated including also in-line liquid–liquid separator.

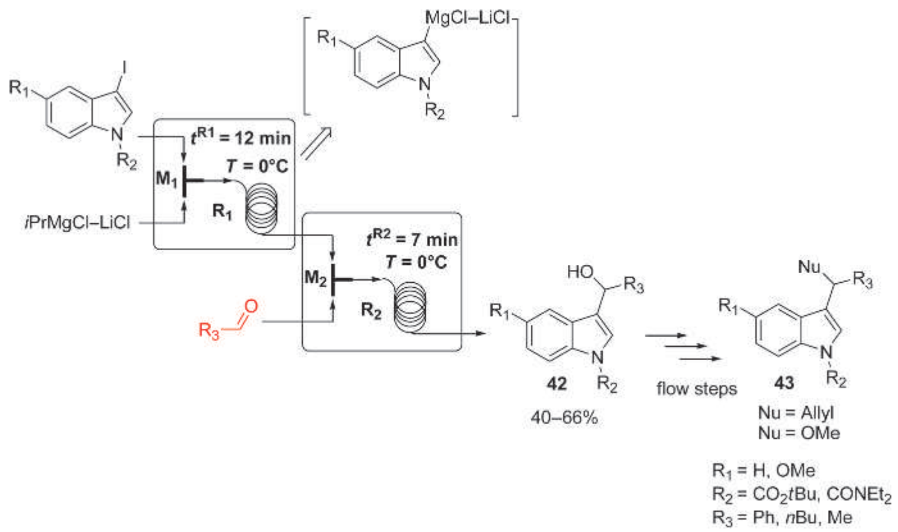
Ley and coworkers developed an efficient, safe, and high-yielding flow process for preparing, even in large scale, 2-aminoadamantane-2-carboxylic acid using a continuous-flow reactor [45].

In particular, the flow process was based on the reaction of ethynylmagnesium bromide (0.5 M solution in THF at 0.2 mL/min), with 2-adamantanone (0.5 M solution in THF

Scheme 27.



Scheme 28.



at 0.18 mL/min), using a 14-mL reactor at 40 °C, leading to 2-ethynyl-2-adamantanol in 80% yield (Scheme 29).

In another recent work, Ley reported an efficient and telescoped continuous-flow synthesis of (*E*/*Z*)-tamoxifen by using a peristaltic pumping system [46].

Organometallic reagents (alkyllithiums, Grignard reagents, DIBAL-H) were pumped into the system, leading to organometallic-mediated transformations (metal–halogen exchanges, additions, additions–eliminations, conjugate additions, and partial reductions) without needing further purification.

In the telescoped process, several steps involving organomagnesium reagents were reported. Interestingly, one of the key steps of the process targeted to the preparation of tamoxifen was the high-yielding continuous-flow synthesis of an intermediate ketone via the addition of phenylmagnesium bromide to a Weinreb amide (Scheme 30). This continuous-flow synthesis allows to produce 40.0 g of ketone in 6 h.

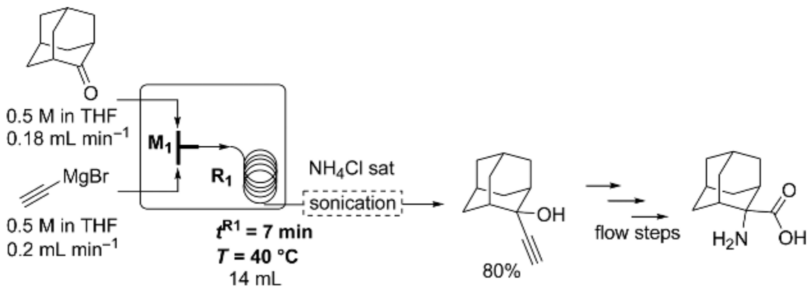
4. Organozinc-Mediated Flow Synthesis

Knochel and coworkers developed a scalable flow process to generate β-substituted acrylates **44** through the metalation of acrylonitriles and nitroolefines, which usually polymerize in presence of bases, at temperature of <90 °C [47]. 3-Ethoxy-acrylonitrile (*E*:*Z* = 2:1) reacted in a flow apparatus with the highly active base TMPZnCl·LiCl at 40 °C with 10 min at residence leading to a vinyl zinc which reacted with allyl bromides, in the presence of 10% CuCN·2LiCl, giving the expected product in good yields (Scheme 31). Interestingly, the α-zincation of nitroolefins, followed by allylation or acylation under continuous flow at 0–25 °C, leads to new α-functionalized nitroolefins difficult to prepare using traditional batch conditions.

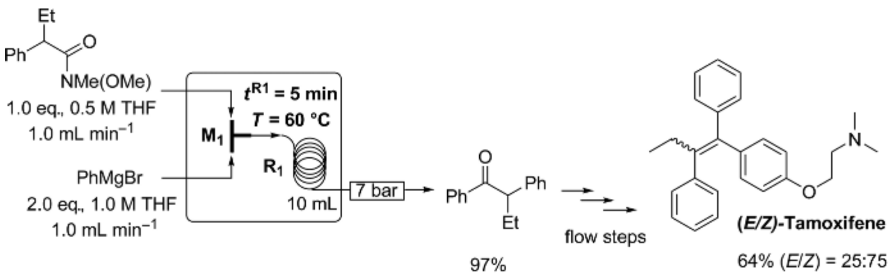
In another work, Knochel and coworkers reported the continuous-flow zincation of functionalized arenes, heteroarenes, and acrylates by LiTMP deprotonation and $ZnCl_2$·2LiCl zincation (40 s, 0 °C) (Scheme 32) [48, 49]. The resulting organozinc intermediates were collected in a batch reactor containing the electrophiles. Nucleophilic addition to aldehydes, ketones, and acyl halides or Pd-catalyzed Negishi-type reaction was performed (Scheme 32).

Ley and coworkers described a Zn-promoted dehalogenation process on α-bromo acyl halides **45** to generate highly reactive ketenes **46** in continuous-flow condition. A flow cell for in-line FT-IR analysis was used for optimization. The so generated

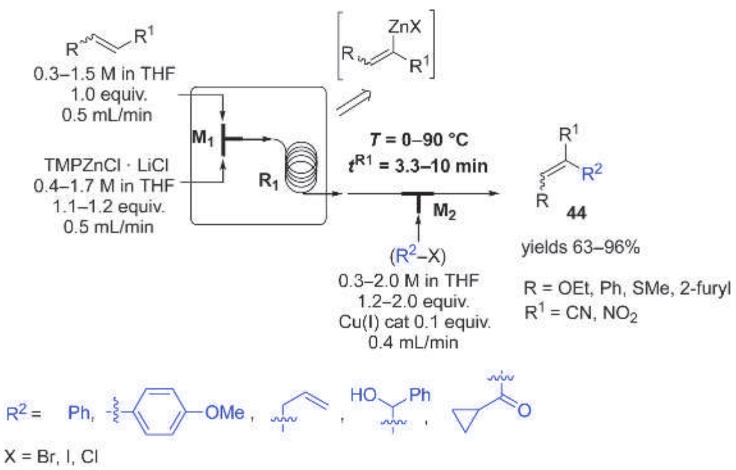
Scheme 29.



Scheme 30.



Scheme 31.



ketenes reacted with imines in R_1 coil reactor through a [2 + 2] cycloaddition, yielding a series of β-lactams **47** at room temperature in less than 10 min (Scheme 33) [50].

The apparatus consisted of a column containing Zn (3.0 equiv.) and glass beads in which a 0.05-M solution of α-bromoacyl halides was pumped through. The highly unstable ketene could not be isolated and was used in batch conditions.

5. Organocopper-Mediated Flow Synthesis

Buchwald and coworkers reported a flow iodination of a variety of aryl and heteroaryl compounds, based on a rapid and efficient copper-catalyzed Br–I–halogen exchange Finkelstein-type reaction [51, 52]. To perform those reactions, a packed-bed reactor filled with NaI (Scheme 34) [51] was employed which provides increased efficiency and reduced safety hazards with respect to batch procedures.

The scope was wide, and several aromatic and heteroaromatic iodides were prepared by simply passing through the reactor a solution containing bromides, a diamine, and CuI.

A two-step copper-catalyzed iodination–amidation of aryl bromides has been realized in continuous flow by using two packed-bed reactors containing $NaCO_3$ and Cs_2CO_3 (Scheme 35). After the Br–I exchange step, the combined solutions were directly pumped into a second Cs_2CO_3 packed-bed reactor at 120 °C, with a residence time of 30 min, without addition of any catalyst or ligand. The resulting mixture was collected and purified, yielding the corresponding amidic products (Scheme 35).

In another work, a synthetic method for the direct introduction of the trifluoromethyl group into aromatic and heteroaromatic compounds, by a copper-mediated cross-coupling, has been developed [52]. This protocol represents the first example of aromatic and heteroaromatic trifluoromethylation conducted in flow using CF_3CO_2K as CF_3 source (Scheme 36).

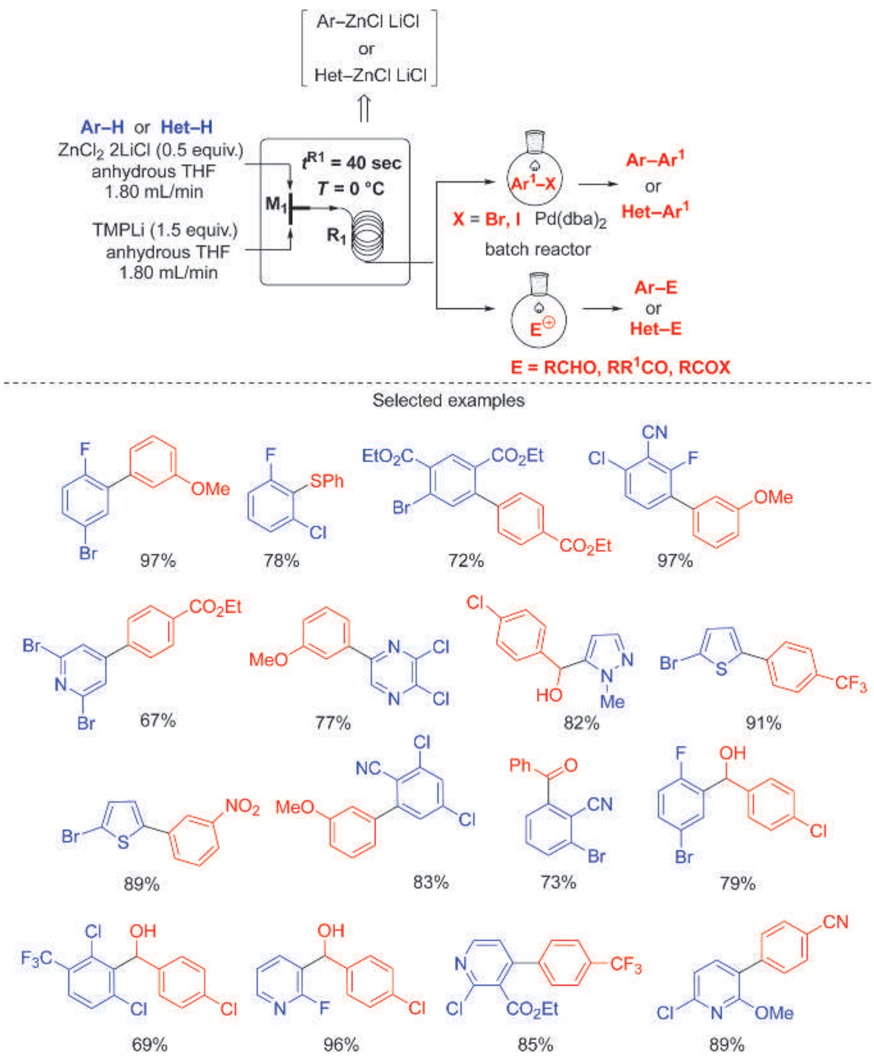
A novel Cu-catalyzed protocol to obtain nonsymmetrical acetal scaffolds was developed by Kappe and coworkers, by a direct coupling between *o*-hydroxy acetophenone and ethers (Scheme 37) [53].

The protocol was firstly optimized in batch using microwave and then translated to a continuous-flow reactor on the basis of the “microwave-to-flow paradigm” [54]. The flow system was fed with a dioxane solution of phenol, ether, and Cu catalyst and a decane solution containing the oxidant TBHP.

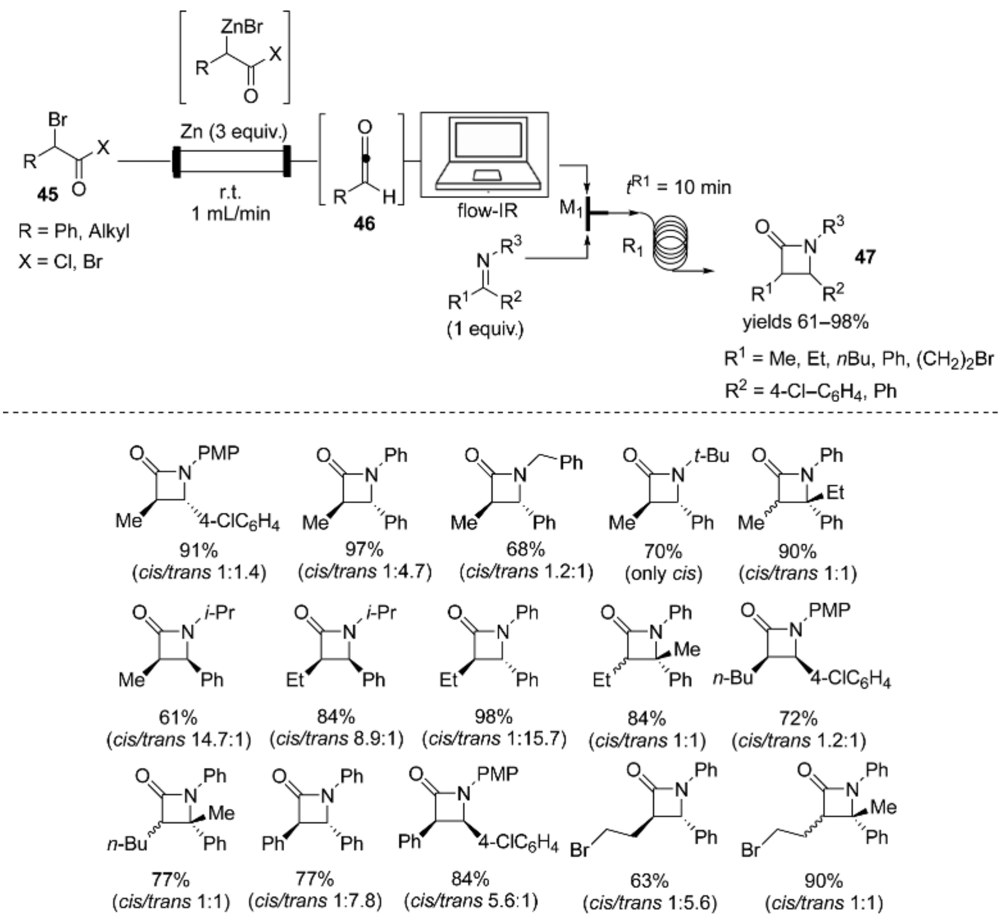
The solution emerging from M_1 was passed in a coil reactor at 130 °C over 20 min of residence time. The corresponding nonsymmetrical acetals **48** were obtained in good yields.

Kappe and coworkers reported some examples of click chemistry in flow [55]. Copper metal and copper-on-charcoal (Cu–C) were suitable sources of “heterogeneous” catalysts for the azide–alkyne cycloaddition (CuAAC). It was demonstrated a “homogeneous” mechanism for this reaction. Such CuAAC reaction, shown in Scheme 38, was optimized at 170 °C, under 20 bar pressure and with a flow rate of 1.5 mL/min. The

Scheme 32.



Scheme 33.



concentration of azide in acetone was 0.25 M, and the resulting triazole derivative **49** was obtained with full conversion and >99% yield.

In another work by Kappe, linear peptoids containing terminal azido and acetylenic functionalities were efficiently synthesized by a continuous multistep protocol by using an Ugi four-component reaction [56].

Intra- and intermolecular cyclization were executed by a copper-catalyzed click reaction under continuous-flow conditions. A Cu coil at 140 °C was employed to catalyze the cycloaddition reaction (Scheme 39).

In a recent work by Ley and coworkers, a series of di- and trisubstituted allenes **50** were obtained through a copper-catalyzed coupling reaction between flow-generated unstable diazo-compounds and terminal alkynes [57]. This was a nice example of integration of flow process with batch procedures. In particular, the protocol in flow allows for generating unstable diazocompounds under controlled conditions, by using a packed-bed reactor, containing MnO_2 fed with a solution of arylhydrazones (Scheme 40).

Jamison and coworkers developed copper-mediated flow reactions, including Ullmann reactions and Sonogashira couplings, using a copper tube flow reactor (CTFR) fed with reactants [58].

The copper tube flow reactor, made of a copper coil with 1.0 mm inner diameter, representing a source of metal itself, can be simply heated at high temperatures, resulting to an easy and more environment friendly protocol (Scheme 41).

Jamison reported, as application of the CTFR flow strategy, the flow synthesis of rufinamide (Scheme 42) [59]. This process is divided in three chemical steps, and flow processing offers several advantages compared to batch protocol: (a) organoazide intermediate was not isolated, reducing the safety hazards, and (b) the unstable propiolamide intermediate was prepared in-line without polymerization. The process was conducted in CTFR at 110 °C, with a residence time of 6.2 min and back pressure regulation at 100 psi. The overall yield of rufinamide was 82% using copper tube reactor. A comparison with PFA and stainless steel tubing revealed the importance of Cu catalysis on both yields and regioselectivity.

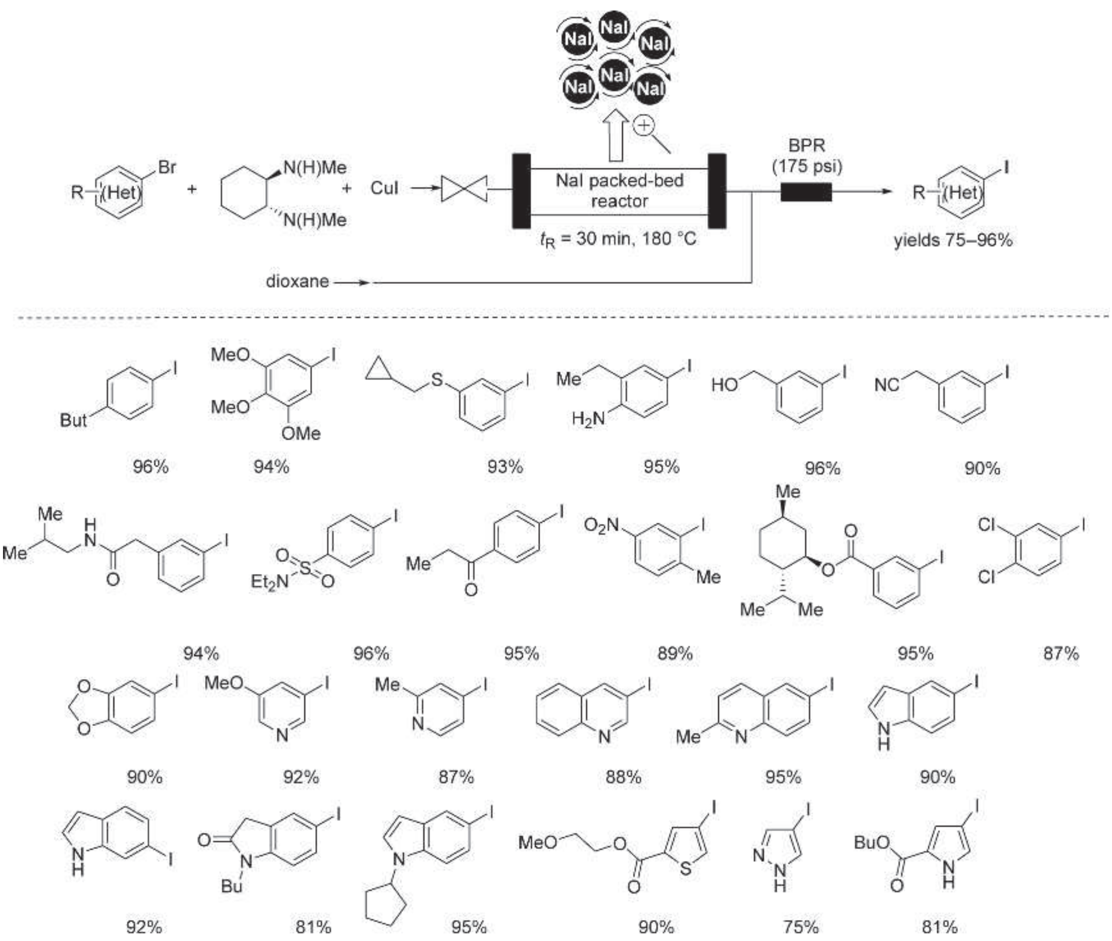
6. Organopalladium-Mediated Flow Synthesis

An important field of application of microfluidic devices is related to Pd-catalyzed synthesis and, in particular, to the development of useful and practical procedures using both homogeneous and heterogeneous palladium catalysts as a more environmentally benign process in terms of time efficiency and productivity. Yoshida has recently reported that highly reactive and unstable aryllithiums, bearing electrophilic functional groups, such as alkoxycarbonyl, cyano, nitro, and ketone carbonyl group, can be rapidly generated in a flow microreactor system and used in a subsequent reaction before decomposing [9, 60].

Such flow strategy, based on flash chemistry, enabled the preparation of arylboronic esters bearing sensitive functional groups. Yoshida reported the integration of borylation of functionalized aryl halides (Ar^1X) and Suzuki–Miyaura cross-coupling in homogeneous conditions, with functionalized aryl halides (Ar^2X) using an integrated flow microreactor system comprising five micromixers and five microtube reactors (Scheme 43) [61].

In another work, Yoshida harnessed the concept of “flash chemistry” in the generation of a reactive short-lived

Scheme 34.

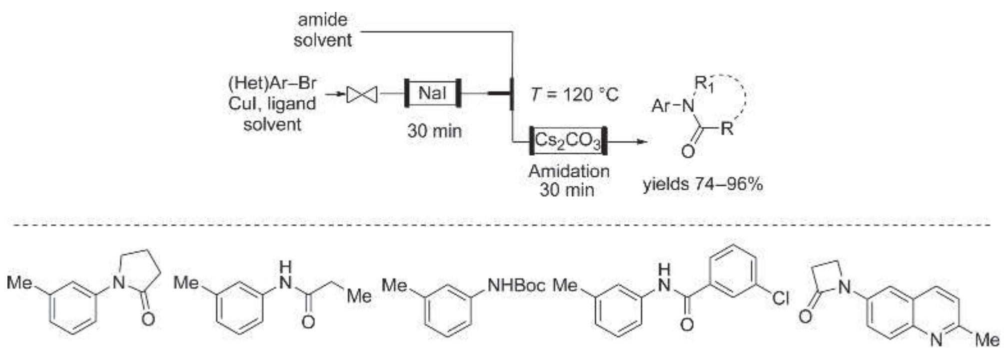


Pd catalyst precursor for Suzuki–Miyaura coupling by a fast 1:1 micromixing of [$Pd(OAc)_2$] and tBu_3P, and the quick transfer of the so generated Pd-catalyst into a batch reactor. Aryl- or heteroarylboronic acids were used as coupling partners, and the reactions could be conducted under mild conditions and were completed within 5 min even at room temperature [62].

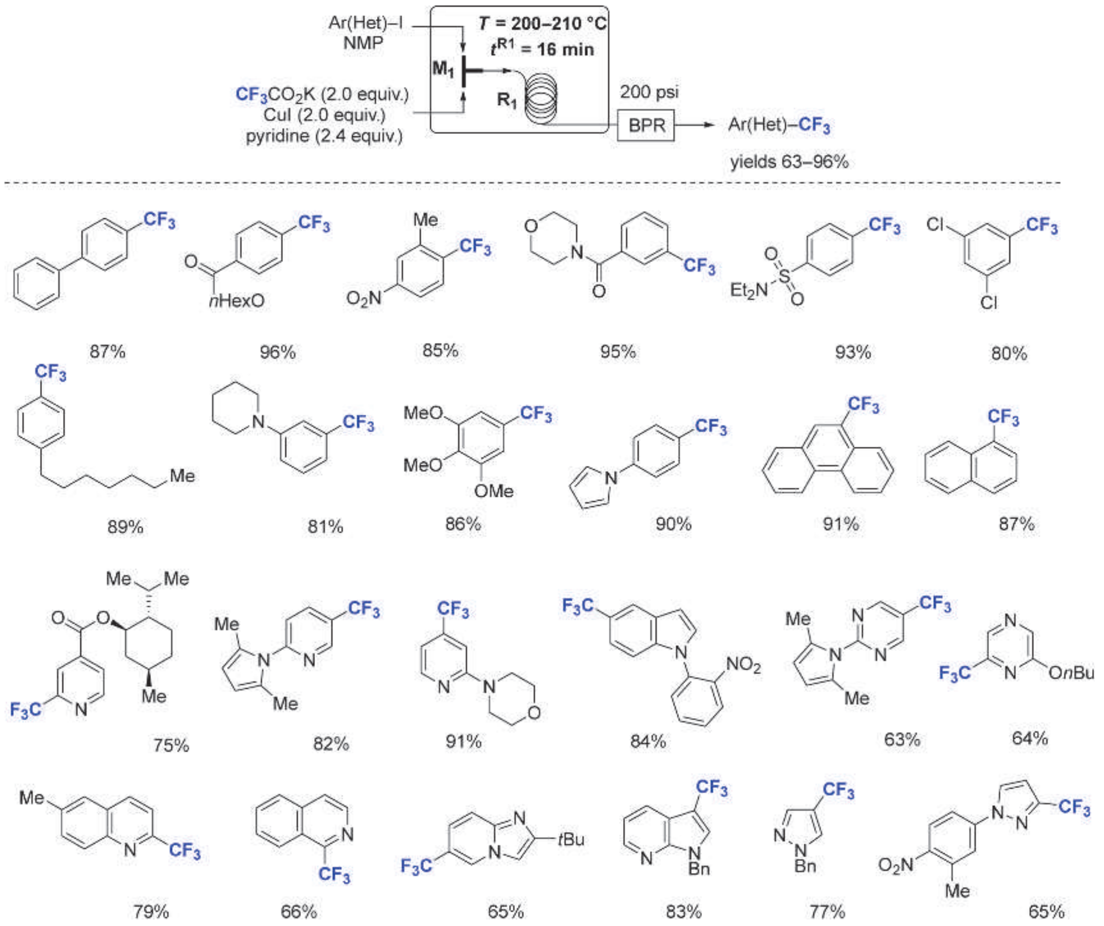
An in-line flow FT-IR spectroscopic analysis was performed to characterize the reactive catalytic species (Scheme 44). The authors proposed that complex **52** was generated by the flash method and that was reduced to Pd(0) species **53**, that is [$Pd(tBu_3P)$], in the reaction vessel just before forming the less reactive palladacycle **51**. Under optimized conditions, Suzuki–Miyaura coupling reactions of several aryl halides with arylboronic acids were performed in a shorter time with respect to batch procedures. It is worth mentioning that this flow method allows the coupling of aryl halides and arylboronic acids easily decomposing under standard conditions.

Several examples of flow technologies using supported palladium catalysts have also been reported and were based on monoliths [63], polyurea-encapsulated $Pd(OAc)_2$(PdEnCat) [64], silica [65], and magnetic nanoparticle supports [66]. Moreover, the use of heterogeneous Pd catalysts could result in a more environmentally benign process because of easy separation and reuse of catalysts. Recently, Yoshida reported a versatile Pd-catalyzed synthesis of polyfunctionalized biaryl compounds based on the preparation of arylboronic esters via aryllithiums and subsequent Suzuki–Miyaura coupling by using a supported palladium catalyst such as monolith integrated in a flow reactor (Scheme 45) [67]. A flow reactor packed with a polymer monolith containing immobilized Pd(0) was used for integration of the borylation of aryl halides (Ar^1X) and

Scheme 35.

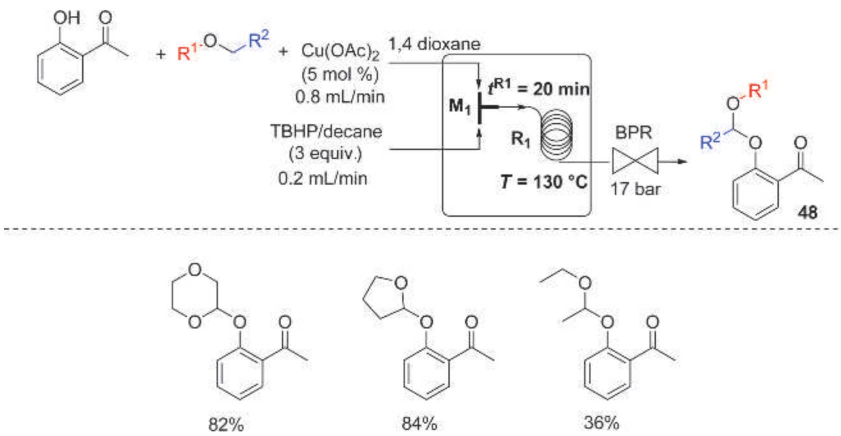


Scheme 36.



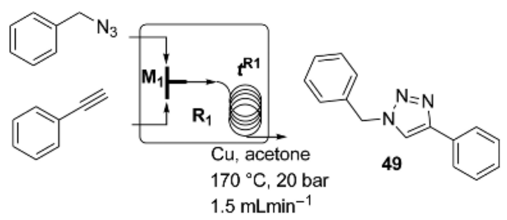
Suzuki–Miyaura coupling with aryl halides (Ar^2X). The reaction was carried out changing residence times (t^R) in the monolith reactor and at several temperatures (T). Interestingly, the Suzuki–Miyaura coupling did not need any additional base. The method was successfully applied to the cross-coupling of various functionalized aryl and heteroaryl iodides as coupling partners. In contrast, the use of aryl bromides resulted in much lower yields. The authors applied the presented method to the synthesis of adapalene, which is used in the treatment of acne, psoriasis, and photoaging. The coupling of lithium [3-(1-adamantyl)-4-methoxyphenyl]trimethoxyborate and methyl 6-iodo-2-naphthoate was carried out in the monolith reactor, and the desired product was obtained in 89% yield [68].

Scheme 37.

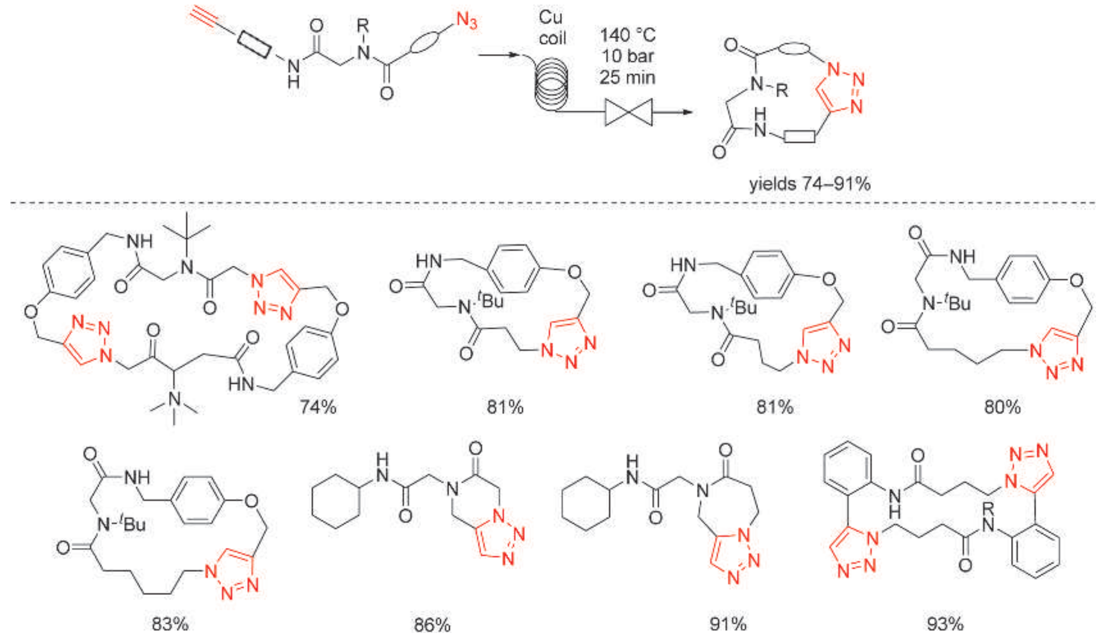


Vaccaro and coworkers proposed in a cyclic flow reactor the Suzuki–Miyaura reaction between phenylboronic acid and

Scheme 38.

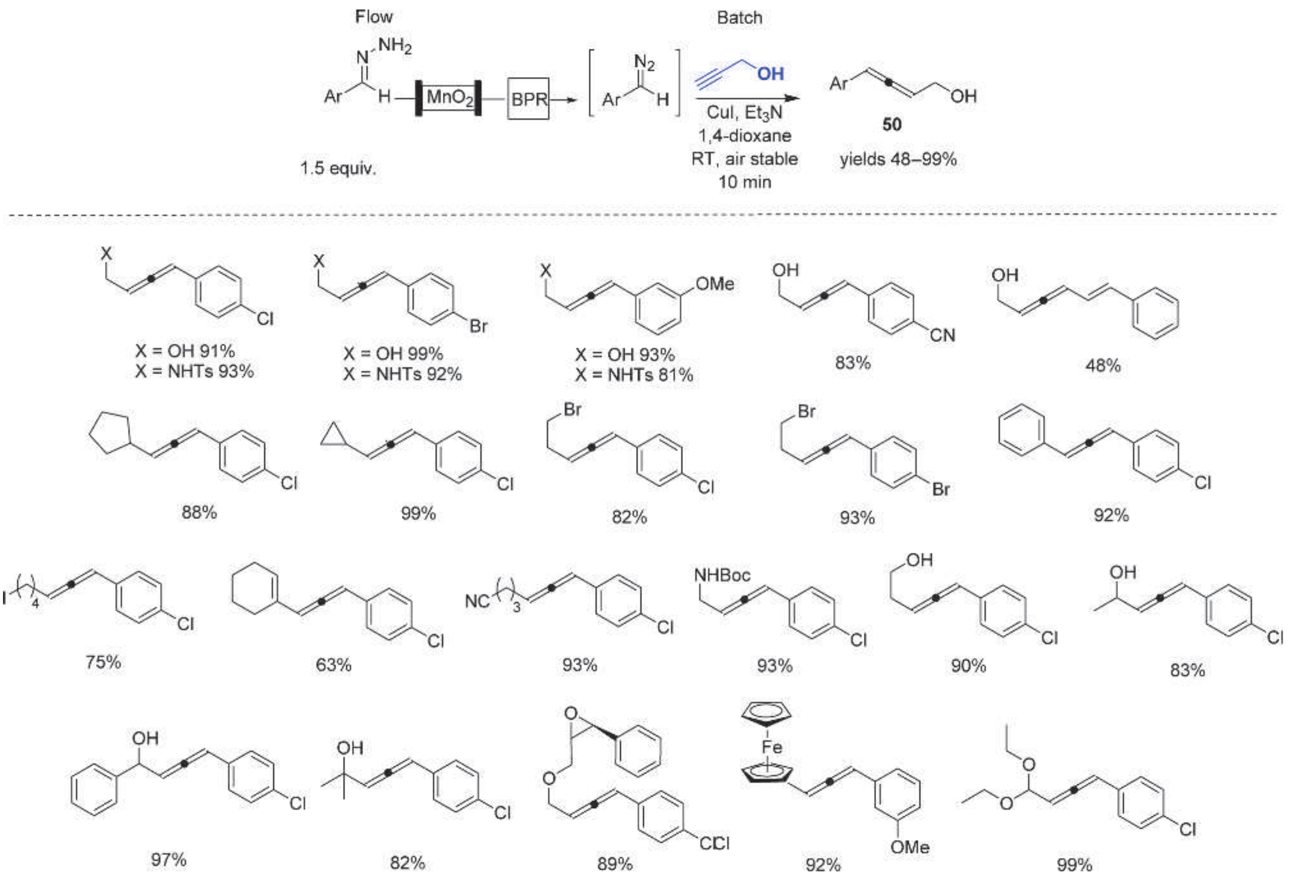


Scheme 39.

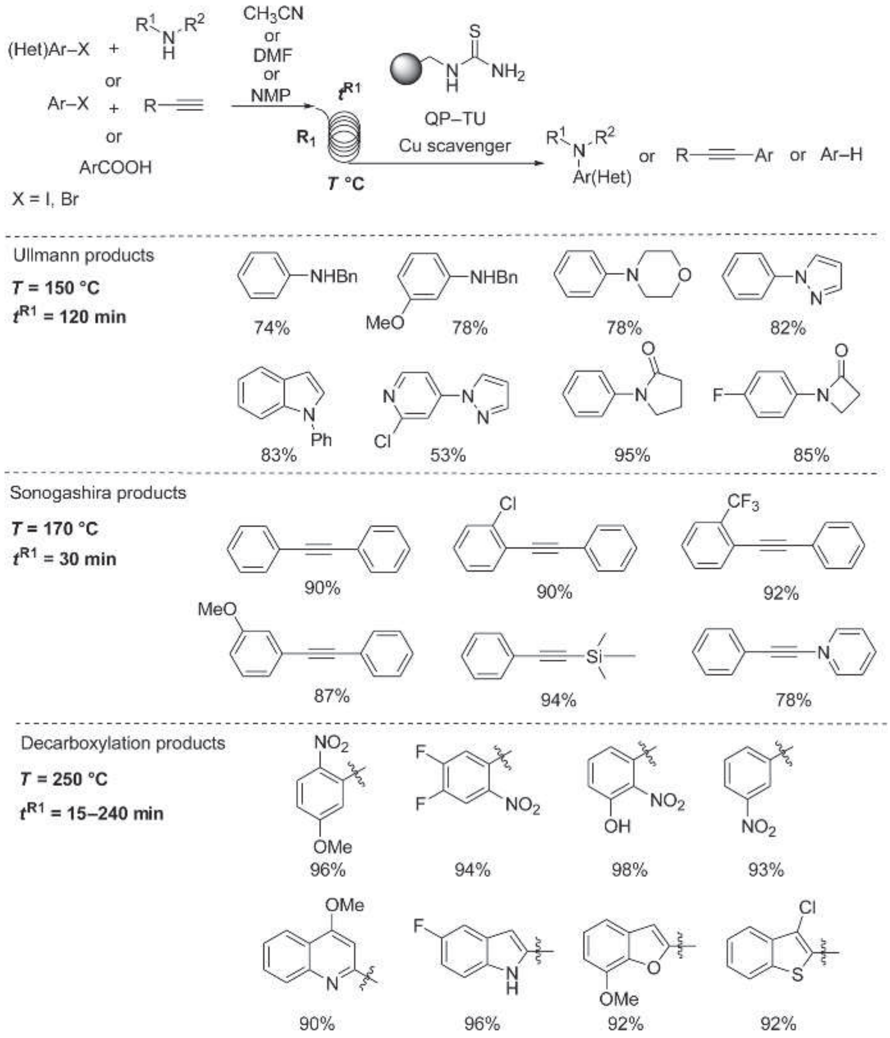


aryl halides catalyzed by a multilayered (or high loaded, up to 10 wt.%) ionic liquid-like material capable of stabilizing a higher amount of catalytically active Pd species. The formation of supported palladium nanoparticles was carried out by immobilization of $PdCl_4^{2-}$ on a highly cross-linked imidazolium network followed by a Pd-reduction step. Starting from an optimized batch protocol, the authors investigated a cyclic flow procedure by a "release and catch" mechanism to optimize the efficiency of the isolation of the pure products and minimize the waste associated to the process (Scheme 46) [69]. To realize the flow protocol the base (K_2CO_3) and the catalyst (0.1 mol%) were separately charged into low-pressure glass columns while the reactants in ethanol 96% were filled into a third column used as a reservoir. The reaction mixture was pumped through the base- and the catalyst-containing columns for 36 h at 50 °C. After this time, the cyclic pumping was set in order to transfer the liquid into the reservoir emptying the other columns. This protocol furnishes a very good proof for the "release and catch" mechanism and

Scheme 40.



Scheme 41.

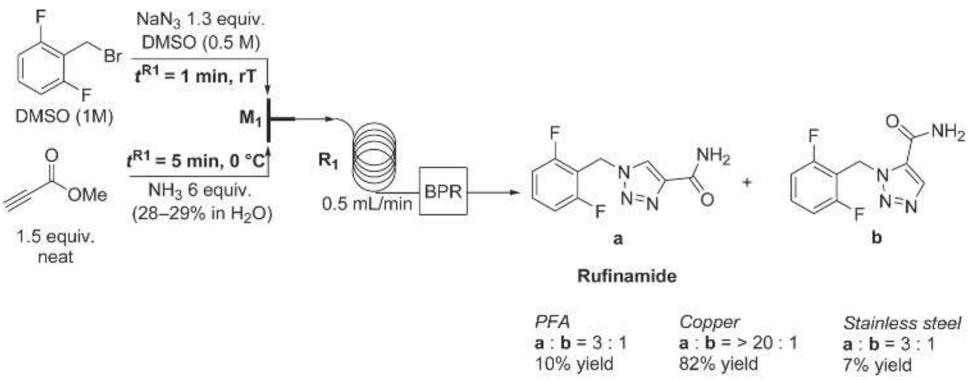


minimization of waste associated to the reaction (E factor reduced by more than 99% with respect to batch conditions).

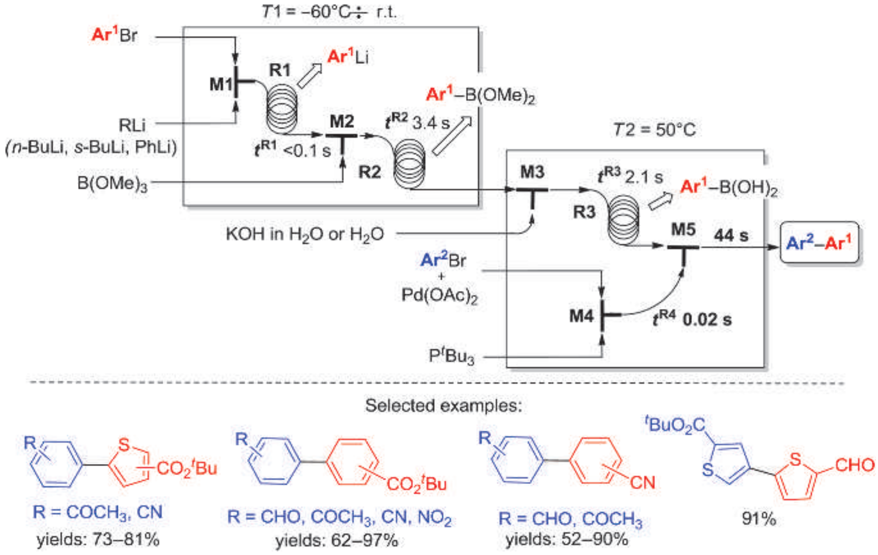
The Suzuki–Miyaura cross-coupling of heteroaryl halides and (hetero)arylboronic acids has been developed in continuous-flow conditions by using a triphasic solvent system (NMP–toluene–H_2O mixture) to ensure good solubility of reagents in a packed-bed reactor, which improves the contact between the immiscible phases. An important key factor in this process consists in the use of second-generation XPhos precatalyst, readily synthesized in a one-pot procedure from commercially available starting materials and easily activated with weak bases at room temperature (Scheme 47) [70]. A wide range of heterobiaryl derivatives **54** could be obtained in good to excellent yields. As shown in Scheme 47, heteroarylhalides, arylboronic acids, and a specific XPhos precatalyst in N-Methyl-2-pyrrolidone (NMP) were combined with aqueous streams of tetrabutylammonium bromide (TBAB) and K_3PO_4. This biphasic mixture was subsequently introduced in a 400-μL packed-bed reactor (stainless steel spheres, 60–125 μm packing), and upon exiting the packed-bed reactor, the reaction mixture was quenched with water and ethyl acetate furnishing the biaryl derivatives in good yields.

For unavailable and unstable aryl triflates, a second flow reactor, equipped with a continuous liquid–liquid extractor device, could be introduced just before M1 (Scheme 47).

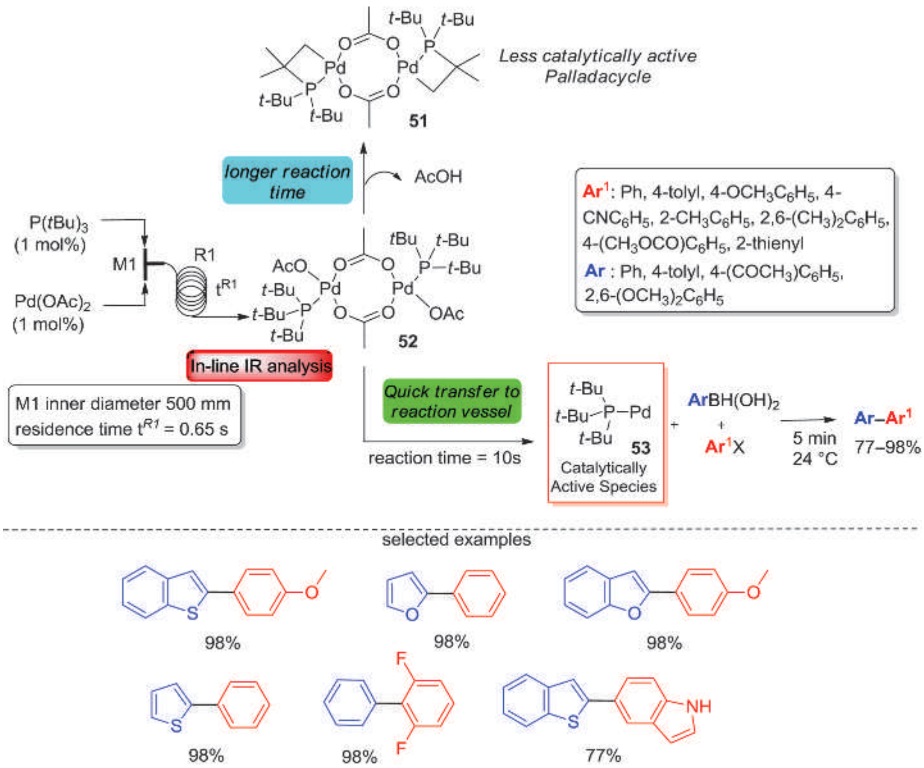
Scheme 42.



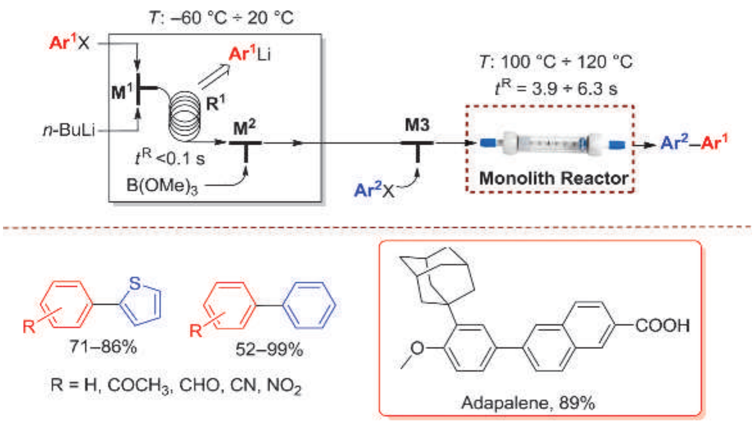
Scheme 43.



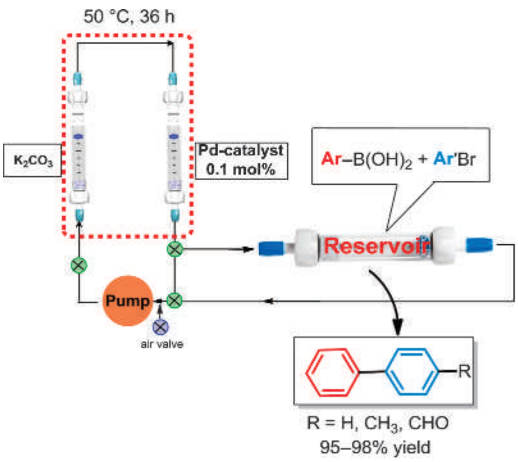
Scheme 44.



Scheme 45.



Scheme 46.

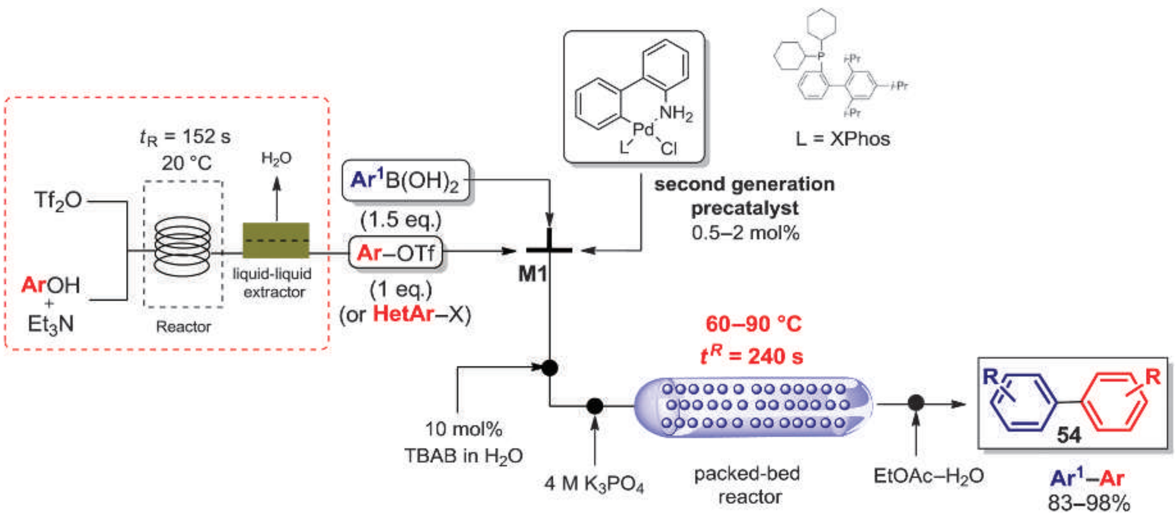


Ley reported a fast, safe, and practical approach for the preparation of functionalized styrenes **55** via a Mizoroki–Heck-type cross-coupling of aryl iodides and ethylene gas (Scheme 48) [71]. The safety concerns, regarding the use of pressurized ethylene gas, were faced by employing the continuous-flow tube-in-tube gas–liquid reactor equipped with a semipermeable membrane to administer the gas in a controlled manner. The amorphous fluoropolymer Teflon® AF-2400, which is highly permeable to a range of gasses but has very low permeability to liquids, accomplished this function very well (Figure 1).

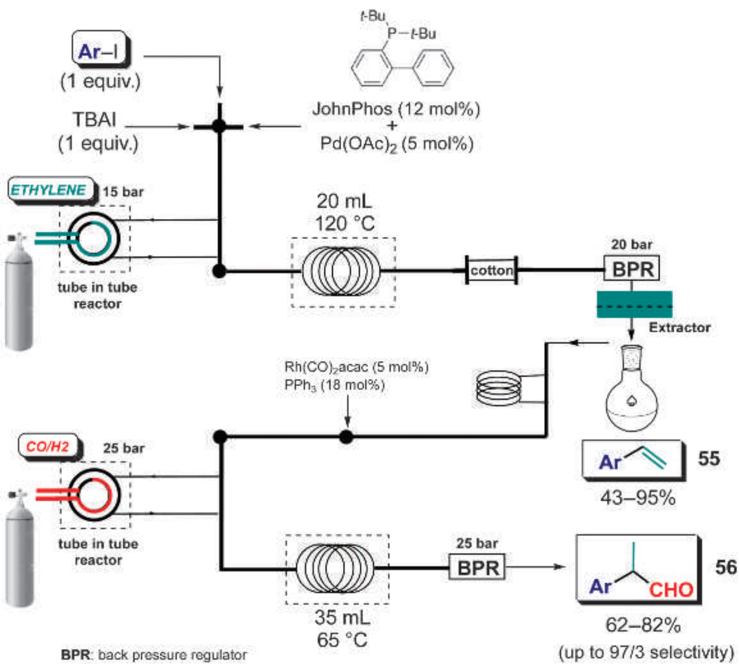
The amount of ethylene gas in the reactants' stream was quantified using in-line IR analysis, allowing for a precise control of ethylene's stoichiometry. Moreover, sequential Heck reactions could be executed, with an effective turnover of the initial catalyst system, leading to unsymmetrical stilbene products (Scheme 48). Alternatively, the Heck process could be integrated with a second, rhodium-catalyzed hydroformylation of styrene derivatives by using tube reactor feeds with CO–H_2 and in-line aqueous wash and liquid–liquid separator, providing branched aldehydes **56** directly from aryl iodides.

Another approach for the oxidative Heck reaction, which uses the tube-in-tube microreactor technology composed of a gas-permeable inner tube (AF2400, DuPont) and gas-imperme-

Scheme 47.



Scheme 48.



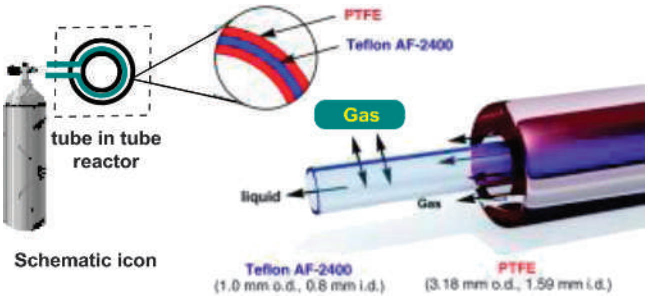
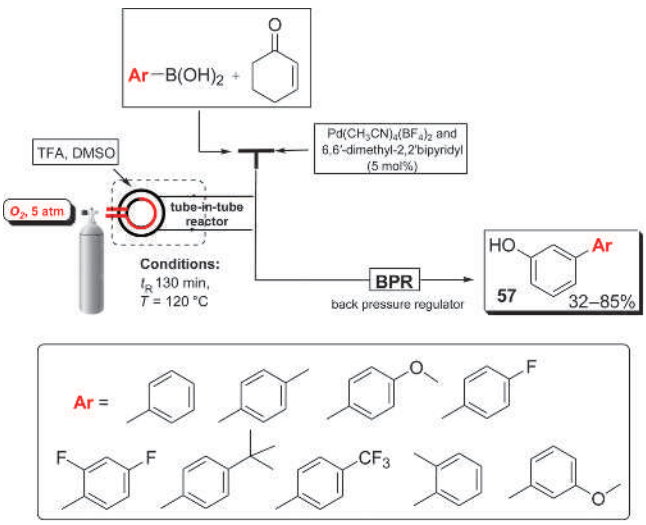


Figure 1. The semipermeable membrane-based tube-in-tube gas reactor

able outer tube, has been proposed by Kim and Park [72]. An NMP solution of phenylboronic acid and cyclohex-2-enone was placed in the first inlet, an NMP solution of a Pd(II) complex and ligand was placed in the second inlet, and oxygen gas at 5 atm was placed in the third inlet. The first and second inlets were connected into a gas-impermeable outer tube, and the third inlet was connected to a gas-permeable inner tube of the tube-in-tube reactor at 120 °C for 130 min (Scheme 49). This flow microreactor system was able to produce meta-substituted phenol derivatives **57** even on gram scale.

Scheme 49.



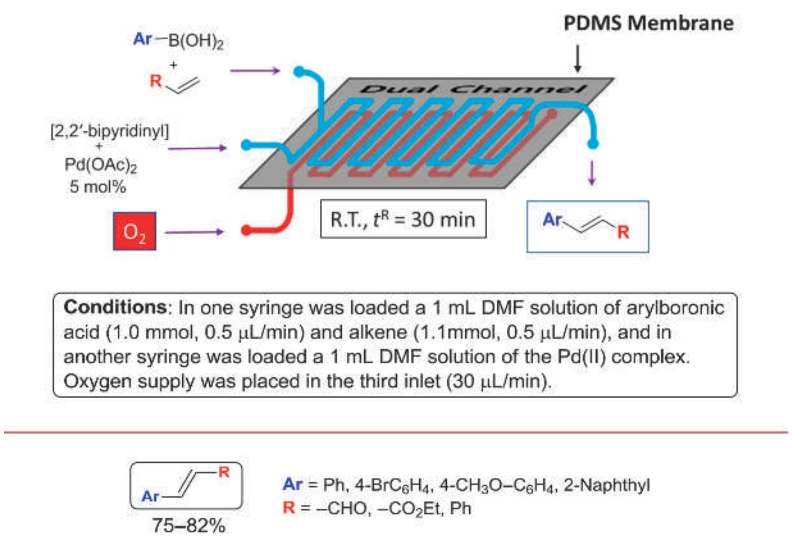
The oxidative Heck reaction could be also carried out in a dual-channel microreactor system, in which the solution duct and the gas channel are in continuous contact through the thin membrane (PDMS), which facilitates permeation of the gas into the liquid, preventing the flow breaking into a segmented flow of gas and liquid (Scheme 50). Relatively large contact area between the two channels would facilitate rapid oxygen diffusion from the gas channel to the solution, and then, oxidative Heck reaction of aryl boronic acids with alkenes could be carried out with better yields and selectivities compared with a small-scale batch system affording to substituted alkenes [73].

The Ley group developed a flow method for Sonogashira and Heck cross-coupling reactions using a low-level palladium perovskite catalyst deposited on cerium oxide [74]. The heterogeneous catalyst for the flow experiments was prepared simply by mixing CeO_2 and $LaFe_{0.95}Pd_{0.05}O_3$ within a shaker, before packing it into an Omnifit glass column. The catalyst was then activated by passing DMF through the column at 130 °C. In the Heck type reaction, the flow system could be applied to a wide range of functionalized substrates, allowing clean and fast delivery of the products within a few minutes (10–30 min), after scavenging the leaching metal with thiourea polymer (QPTU) and sulfonic acid resin (QP-SA). The use of an in-line evaporator–solvent switching device allowed for recovering the solvent and transferring of the products to the next step (Scheme 51). The catalyst could be continuously used for at least 24 h, without any noticeable decrease in catalytic activity.

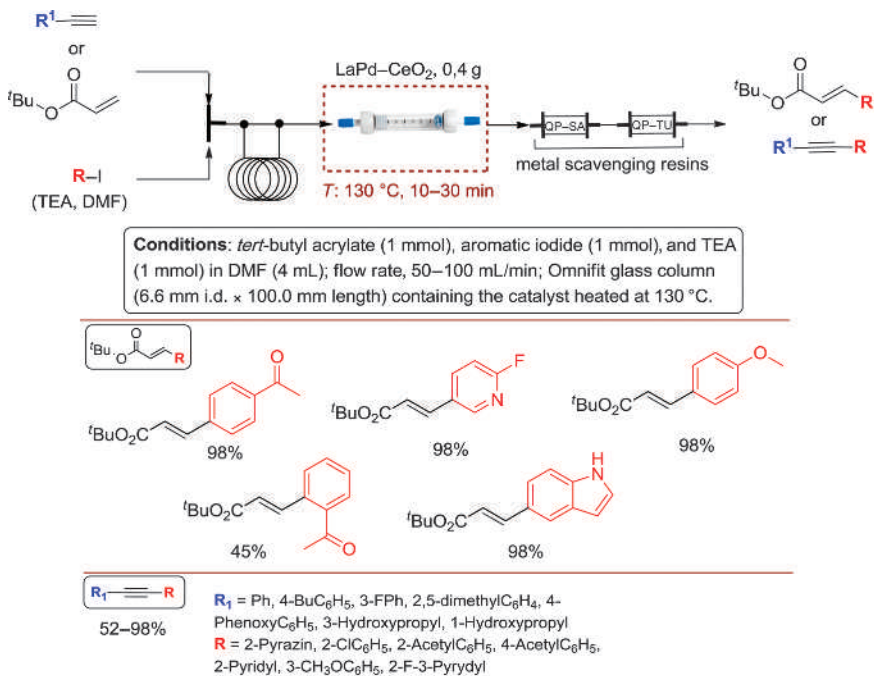
With the same protocol, a variety of alkynes has been prepared starting from commercially available alkyl and arylacetylenes.

Despite the large use of the Suzuki–Miyaura cross-coupling reaction, the direct use of organolithium compounds in cross-coupling reactions has been rather limited, although many aryl–metal species, including aryl–boron compounds, are readily prepared from aryllithium compounds. Since it is noteworthy that X–Li and H–Li exchange of ArX and Ar–H, respectively, and subsequent reactions with electrophiles could be conducted in flow microreactor systems, Murahashi coupling of ArLi with aryl- and vinyl bromides was accomplished by using Pd source as a catalyst in a continuous-flow reactor. In particular, the use of Pd catalysts containing a carbene ligand, such as PEPPSI-SIPr, sped up the Murahashi coupling reactions by enabling its integration with the Br–Li exchange of Ar^1Br with *n*-BuLi [75]. As depicted in Scheme 51, using integrated flow microreactor system consisting of three micromixers (M1, M2, and M3) and three microtube reactors (R1, R2, and R3), at various temperatures (20–70 °C)

Scheme 50.



Scheme 51.



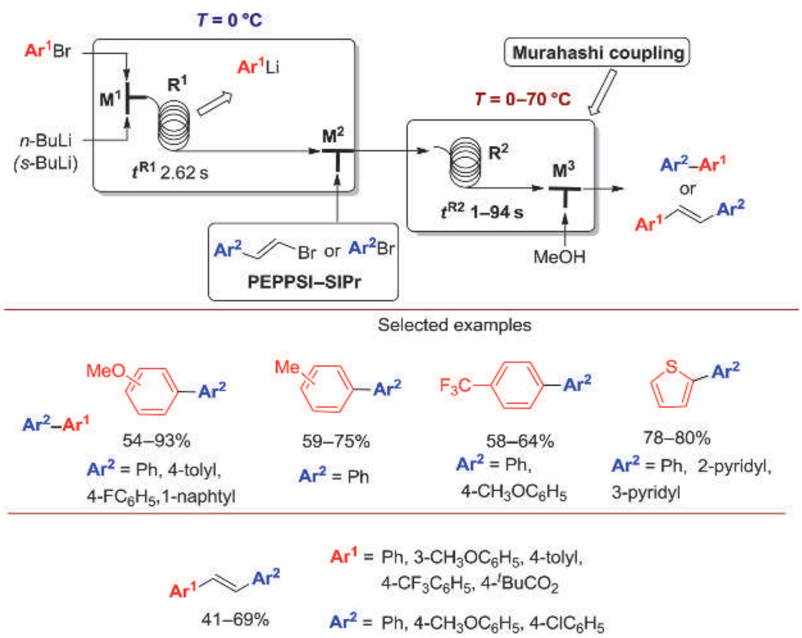
and residence times (1–94 s), the cross-coupling reactions of several aryl bromides yielded the corresponding biaryl products and styrene derivatives in good yields (Scheme 52).

One of the most successful methods to introduce the carbonyl group is by transition-metal-catalyzed reaction of aryl and vinyl halides with carbon monoxide (CO) and a suitable nucleophile. For speeding up the reactions, the gas often has to be pressurized to achieve the concentration required. In order to increase the availability of gas to the liquid reaction phase, various approaches have been developed. Ley's approach was based on a system capable of rapidly and reliably generating homogeneous solutions of gas in a controlled manner.

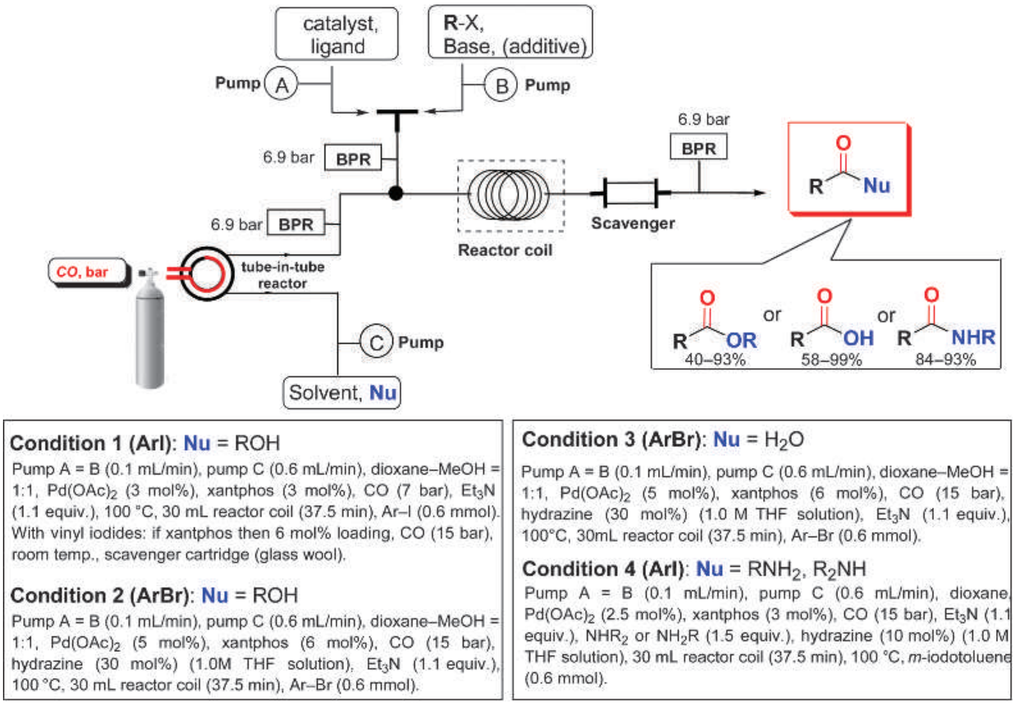
The tube-in-tube gas–liquid flow reactors, set up with an amorphous fluoropolymer (Teflon® AF-2400), enables the generation of homogeneous solutions of CO in continuous flow. The system has been successfully employed in the palladium-catalyzed carbonylation reactions of aryl iodides and bromides, and coupling with a range of hydroxy, alkoxy, and amino nucleophiles to furnish amides, esters, and carboxylic acids [76]. As the volume of pressurized gas within the device is low, the hazards associated with this strategy are greatly reduced with respect to batch processes. While the tube-in-tube device (3.8 m length) still performs the task of enriching the flow stream with CO, it does not come into contact with the substrate and catalyst streams. A back-pressure regulator is needed after the gas–liquid reactor to prevent out-gassing of the dissolved CO (Scheme 53).

Aryl fluorides represent a structural motif of interest in a variety of scientific areas, such as pharmaceuticals and agrochemicals, and in positron emission tomography (PET)

Scheme 52.



Scheme 53.

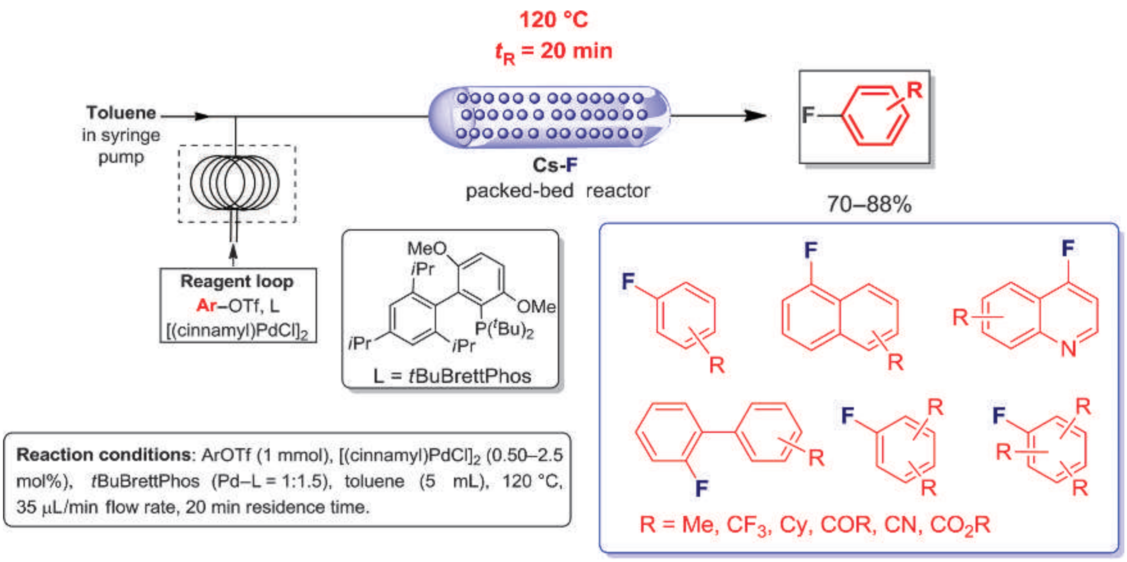


diagnosis. The fluorination reactions that utilized readily available "F⁻" sources as the fluorine atom donors, such as CsF, are required. In batch conditions, the low solubility of anhydrous CsF in nonpolar solvents (e.g., toluene, cyclohexane) is a real drawback, making this heterogeneous fluorination reaction an ideal candidate for microflow technology. Buchwald developed a CsF packed-bed reactor for the Pd-catalyzed conversion of aryl triflates to aryl fluorides in flow conditions [77]. Such flow reactor was filled with finely ground CsF having a particle size distribution of approximately 45–106 mm and used for fluorination of several functionalized aryl and heteroaryl triflates (Scheme 54).

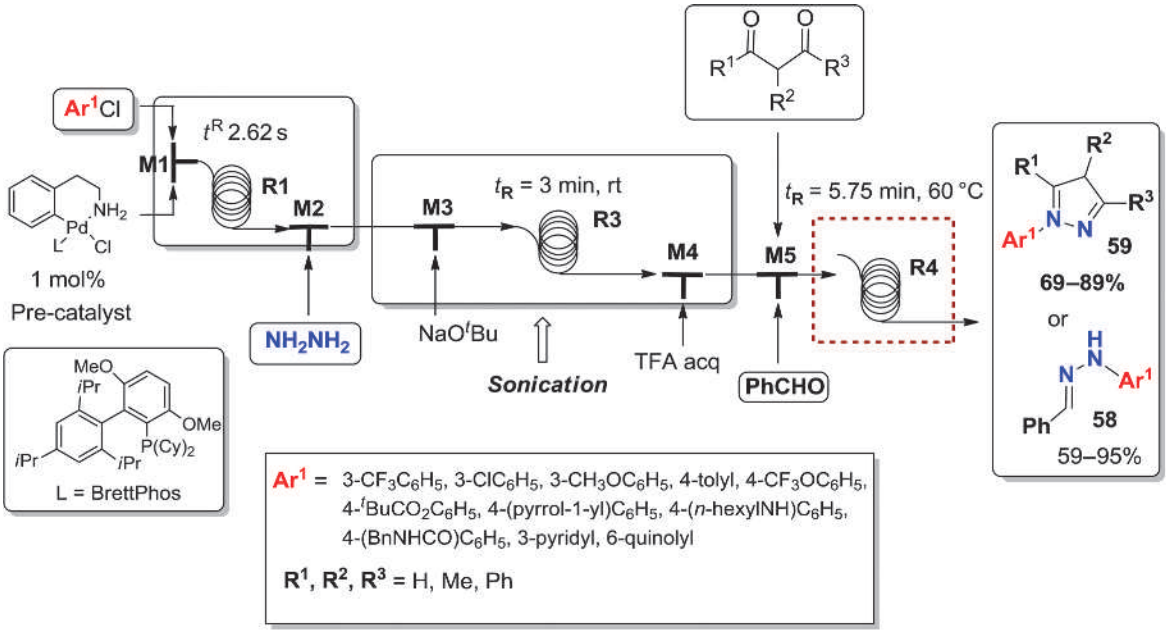
Among the well-known strategies to generate arylhydrazines, such as nucleophilic aromatic substitution or diazotization followed by reduction of the diazonium salt, cross-coupling reactions provide an alternative method for synthesizing aryl hydrazines. However, safety concerns, related to the explosive nature of transition-metal hydrazine complexes, might be taken into consideration in batch processing. Buchwald and coworkers set up a mild and potentially scalable method for the direct cross-coupling of aryl chlorides with hydrazine through the use of continuous-flow technology [78]. Clogging issues, resulting from solids forming with the aryl amination, have been avoided by ultrasonication devices. When THF solutions of precatalyst, ArCl, hydrazine, and NaOtBu were consecutively introduced into R3, the resulting arylhydrazine intermediates were reacted with electrophiles in R4 furnishing either hydrazones **58** or pyrazoles derivatives **59** in good to high yield (Scheme 55).

A similar microfluidic device able to perform the palladium-catalyzed C–N cross-coupling reactions has been assembled as shown in Scheme 56 [79]. The main feature of the apparatus includes an acoustic irradiation system that allows for handling solid byproducts formed in the palladium-catalyzed amination

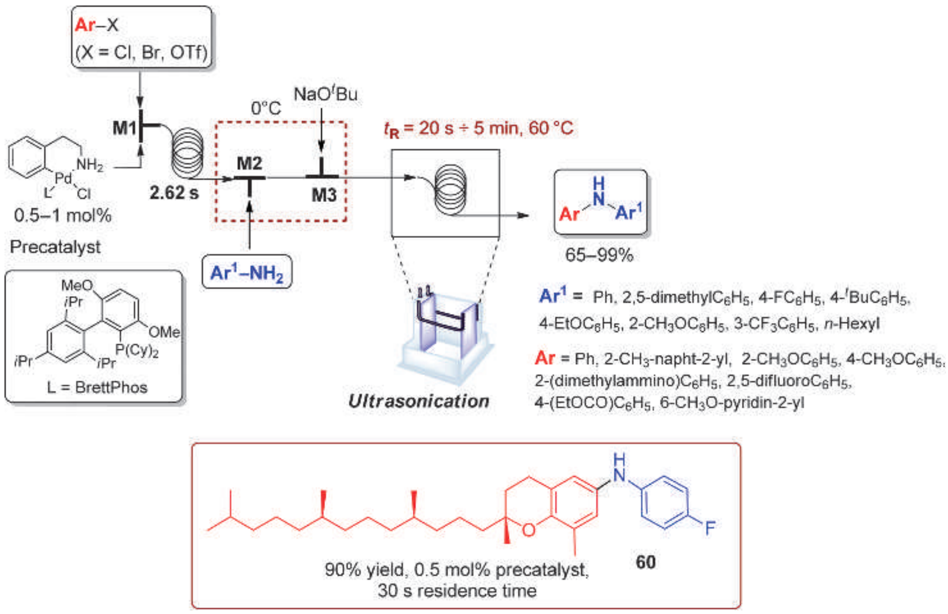
Scheme 54.



Scheme 55.



Scheme 56.

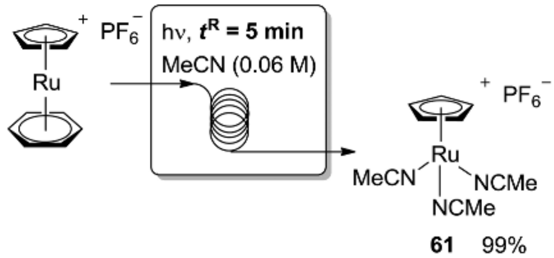


reaction. The authors reported that, inside the channels of the flow system, bridging could be eliminated via acoustic irradiation while constriction could be managed via fluid velocity; both are responsible for clogging. Solutions of the Pd precatalyst, reagents, and NaOtBu in THF were pumped into the microfluidic system via syringe pumps. The catalytically active Pd(0) species was generated, starting from the BrettPhos precatalyst, which is the most active catalyst to date for this type of transformations. The authors were able to couple primary aliphatic and aromatic amines and aryl chlorides, bromides, and triflates in good yield with variable residence times (20 s ÷ 5 min) with 0.5 ÷ 1 mol% of catalyst. Also, biologically active compounds, such as δ-tocopheramines **60**, could be synthesized efficiently in only 30 s.

7. Miscellaneous Cases

Jamison described the preparation of $CpRu(MeCN)_3PF_6$ **61** in excellent yield, without further purification (purity >99%), using a scalable methodology in continuous-flow reactor (Scheme 57) [80]. The optimized conditions for the process required a residence time of 5 min for a complete conversion and a substrate concentration of 0.06 M, compared to a reaction time of 12–36 h and a concentration of 0.02 M for the batch process. A productivity of 1.56 g/h of ruthenium

Scheme 57.



catalyst was obtained in a 5-mL reactor, 10 times higher with respect to the batch process.

Ley explored the direct chemical conversion of cocoa butter triglycerides, a material available as a post-manufacture waste stream from the food industry, to 1-decene by ethenolysis [81]. The conversion of the raw waste material was made possible by use of 1 mol% of the [$RuCl_2$(*i*Bu-phoban)$_2$(3-phenylindenyl)] catalyst. The process has been investigated in both batch and flow conditions, where the latter approach employs a Teflon AF-2400 tube-in-tube gas–liquid membrane contactor to deliver ethylene into the reaction system (Scheme 58).

In another work, Ley described a continuous-flow, rhodium-catalyzed hydroformylation of various styrenes using a tube-in-tube gas–liquid reactor to generate arylaldehydes in good yields [82].

The reaction mixture was pumped into the gas–liquid reactor from a 1-mL PTFE sample loop. Styrene (0.1 mmol) and the Rh$(CO)_2$(acac) (3% mol) were dissolved in methanol–toluene (1 mL), pumped through the gas–liquid reactor pressurized with syngas ($CO–H_2$ = 1:1) and then passed through a back-pressure regulator (BPR) which preserves the homogeneity of the solution and prevents outgassing. Good yields and selectivities for the hydroformylation of a variety of styrene derivatives were obtained (Scheme 59).

Buchwald and coworkers reported the first example of efficient three-step asymmetric catalytic sequence in flow to synthesize enantiopure β-arylated ketones **62**, under sonication conditions [83].

The process required minutes and could be extended to a large scale. The multistep flow process consisted in a safe and efficient lithiation of aryl bromides at room temperature, a subsequent conversion into aryl triisopropylborates, and a final step of rhodium-catalyzed asymmetric 1,4-addition (Scheme 60). An important point of this work is the possibility to handle solids by a sonication step.

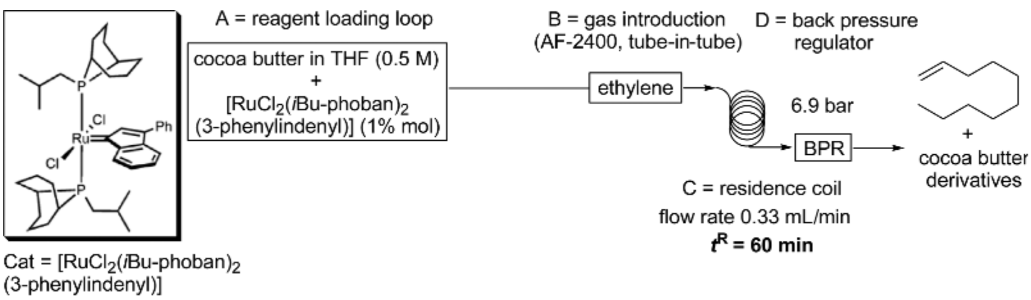
Reiser described an efficient application of a polyisobutylene-tagged Ir(ppy)$_2$(PIB-ppy) photocatalyst in a continuous-flow alkenes isomerization (Scheme 61) [84].

The catalyst showed high catalytic performance and could be easily recycled in batch and in flow conditions, reducing the costs and making this protocol useful for large-scale applications. Alkenes dissolved in heptane–acetonitrile and a solution of Ir(ppy)$_2$(PIB-ppy) in heptane were pumped into a microreactor; the system was heated to 90 °C and irradiated with visible light. Starting from *E*-alkenes **63**, the double bond could be broken through energy transfer from the excited photocatalyst forming a biradical species **65** which generates the corresponding isomerized *Z*-alkenes **64** with constant *Z*/*E* ratio throughout the whole reaction process.

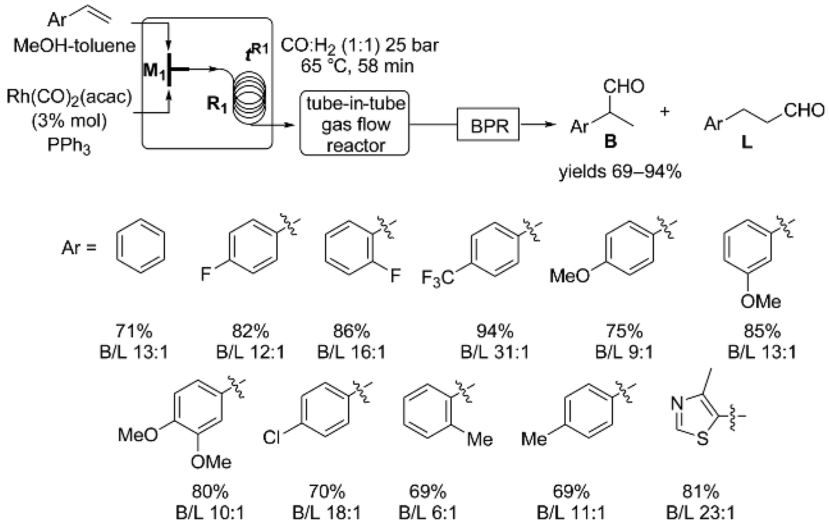
Another organometallic-mediated photochemical process using a flow microreactor system has been developed by Yoshida and coworkers for Pauson–Khand reactions [85].

A solution of dicobalt complex and the corresponding substrate was pumped into the microchannel by a syringe pump. The solution was irradiated and poured into a Schlenk flask. The product solution was collected and then stirred for 5 min at ambient temperature. This methodology provided an activation of alkyne–cobalt complexes, without using additives at room temperature, and can be scaled up by prolonging the operation time. Inter- and intramolecular processes have been developed to obtain derivatives **66** and **67**, respectively (Scheme 62 and Scheme 63).

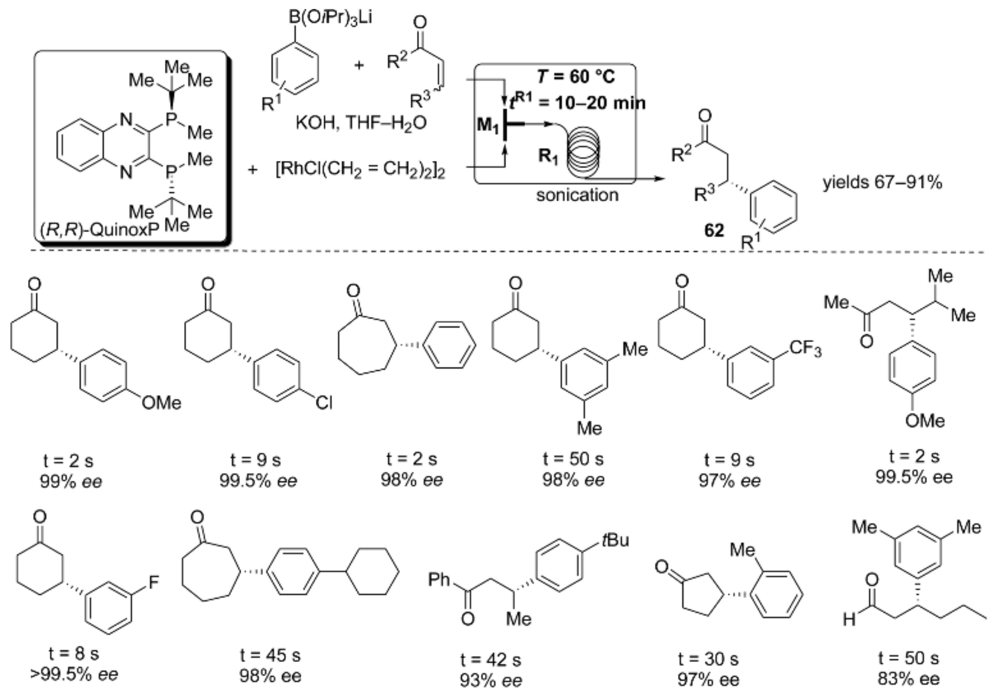
Scheme 58.



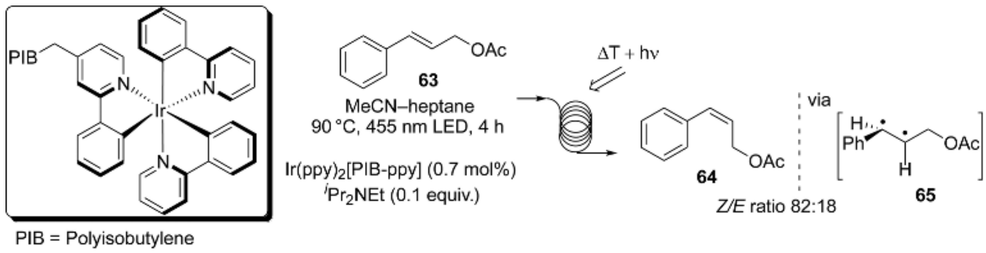
Scheme 59.



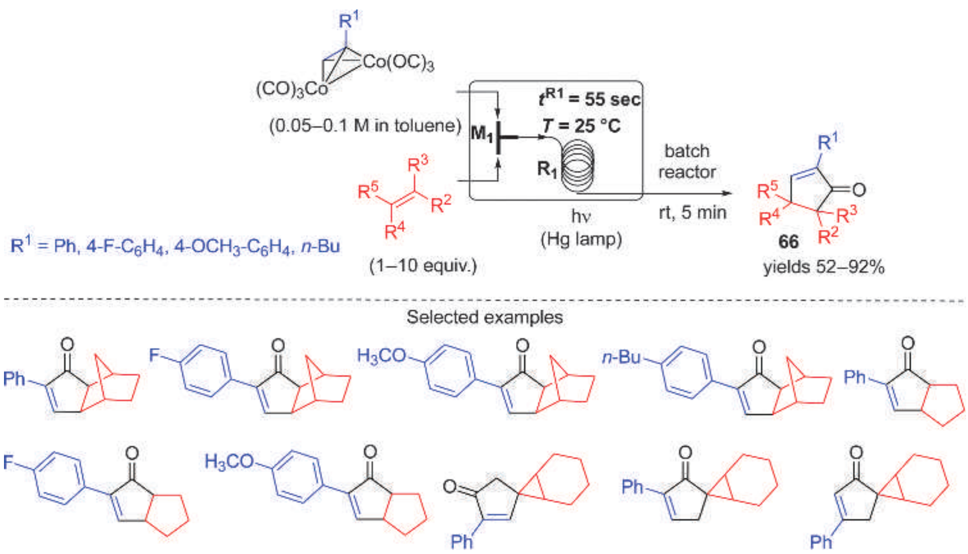
Scheme 60.



Scheme 61.



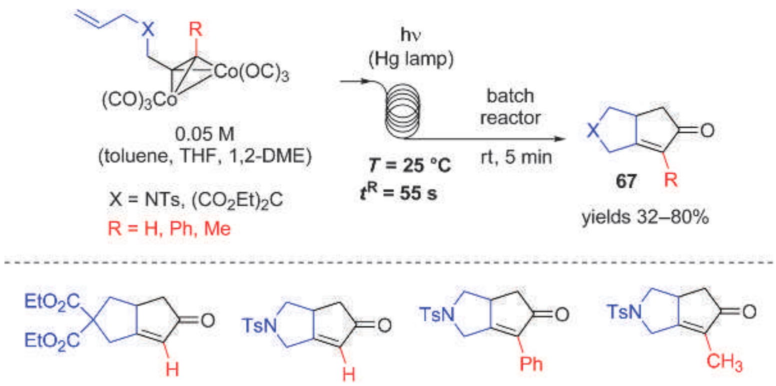
Scheme 62.



8. Conclusions

In conclusion, the flow processes described in this review showed that organometallic-mediated reactions could now be successfully accomplished using flow microreactor technology. The precise control on the reaction parameters (i.e., temperature, stoichiometry, residence time) is responsible for the success of this technology in synthetic plans involving the organometallic species, and "flash chemistry" offers a powerful method for generation of these highly reactive species. Then,

Scheme 63.



organometallic-mediated synthesis using flow microreactor systems enables on-demand and on-site chemical production, leading to less energy consumption for storage and transportation of medical drugs and agrochemicals of short lifetime. Nowadays, some attempts at industrial application have already been made to meet the demands of the pharmaceutical and chemical industries.

The number of applications of flow technology in chemical synthesis is increasing constantly, and it is expected that they will be adopted by the chemical industry in the next future.

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