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RESEARCH ARTICLE

In Continuo Pd-Catalysed Cross Coupling Reactions of Organolithium Reagents with Aryl Bromides Under Aerobic Conditions

Jacopo Brucoli,[a] Davide Gariboldi,[a] Alessandra Puglisi,[a] Sergio Rossi,[a] Vito Capriati[b] and Maurizio Benaglia*[a]

[a] Dr. J. Brucoli, Dr. D. Gariboldi, Prof.ssa A. Puglisi, Prof. S. Rossi, Prof. M. Benaglia*
Dipartimento di Chimica
Università degli Studi di Milano
Via Golgi 19, 20133, Milano, Italy
E-mail: maurizio.benaglia@unimi.it
[b] Prof. V. Capriati
Dipartimento di Farmacia-Scienze del Farmaco
Università degli Studi di Bari "Aldo Moro", Consorzio CINMPIS
Via E. Orabona 4, 70125 Bari, Italy

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Abstract: Transition metal-catalysed C-C couplings are widely used to synthesize organic molecules. In this area, the direct use of readily available and relatively inexpensive organolithium reagents in Pd cross-coupling reactions represents an attractive option, but its large-scale application remains a formidable challenge. The high reactivity of organolithium reagents, along with the need (sometimes) of tailored, expensive catalysts and long reaction times, often prevent these procedures from being applied to industry. However, continuous flow technologies recently emerged as a powerful tool in discovery and process chemistry, and may offer a solution to overcome the above issues. Here, we wish to report fast, efficient, in continuo Pd-catalysed cross coupling reactions of organolithium reagents with aryl bromides, under aerobic conditions, that do not require an inert atmosphere, with a catalyst loading that has been lowered up to 0.5% mol. The methodology has a wide scope and has been successfully applied to the synthesis in flow of a novel class of anti-cancer compounds.

Introduction

In the last fifty years, the discovery of palladium catalysed cross-coupling reactions has started a new era in the C-C bond formation strategies.[1] These transformations have been widely exploited in organic synthesis and their importance has been recognized with the 2010 Nobel Prize in chemistry to R.F. Heck, E. Negishi and A. Suzuki "for palladium-catalysed cross-couplings in organic synthesis".[2]

In this field, a special mention deserves the contribution by Murahashi, who first reported in 1975 the palladium-catalysed cross-coupling reaction between different vinyl bromides and organolithium reagents as nucleophilic coupling partners.[3] After about 40 years, Murahashi cross-coupling has recently been revisited by Feringa and co-workers.[4] Thanks to palladium catalyst activation by oxygen,[5] it was possible to forge the desired products in high yields and in short time: 2 min in the case of alkyllithium or 5 min in the case of aryllithium reagents, also working under neat conditions.[6]

In 2019, an important step forward was taken by Capriati and co-workers: Pd-catalysed cross-coupling reactions between organolithium reagents and (hetero)aryl halides were shown to be successful also working under aerobic and "on-water" conditions.[7] After the preliminary activation of the palladium catalyst, by vigorously stirring the mixture of substrate and catalyst at room temperature in water and under air for 10 min in the presence of NaCl (1 equiv) as an additive, the coupling reaction was complete within 20 s after the addition of the organolithium reagent.

The use of organolithium compounds in cross-coupling reactions has indisputable advantages, being these reagents readily available, cheap and easily generated by lithium-hydrogen or lithium-halogen exchange; furthermore, their direct use cut additional steps related to transmetalation reactions, as many organometallics are usually made from organolithiums, thereby saving time and resources. However, organolithium compounds are known to be highly reactive and to exhibit a low functional group tolerance, are air- and moisture-sensitive with scale-up problems and difficulties on industrial scale. Moreover, having the lithium the lowest electronegativity (0.98) compared to other metals (e.g., zinc: 1.65; tin: 1.96; boron: 2.04) transmetalation reaction remains challenging with organolithium compounds being closely related to the electronegativity of the element,[8] with de-halogenated and homocoupling products usually formed as side products.

Flow chemistry has found widespread application in both academia and industry and can be the solution also to the issues related to the use of organolithium reagents.[9] Flow technologies allow to handle hazardous chemicals in a safer way[10] and may have different advantages compared to in-batch reactions, such as easy scale-up, fast heat and mass transfer, efficient mixing of reagents and the use of small reactor volumes. Reviews/papers dealing with the use of organolithium in flow[11] [10b] [12] even in the presence of unconventional solvents, such as deep eutectic

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solvents,[13] as well as reports about the in-flow scale-up of reactions involving the use of these reagents[14] are available in the literature.

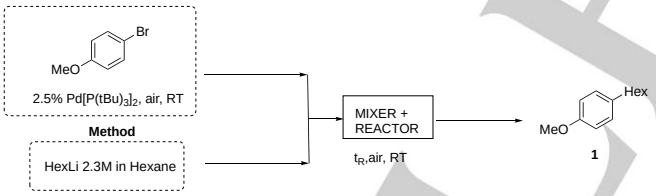
To the best of our knowledge, the only example of Murahashi cross-coupling performed under continuous flow conditions was reported by Yoshida and co-workers in 2010.[15] In this paper, the authors described a two-step in-flow synthesis of biaryl systems from aryl bromides and aryllithium derivatives, the latter being generated in the first reactor from the selected aryl bromide and BuLi by lithium-halogen exchange. A high temperature (50 °C) was used in the second reactor to perform the C-C coupling in good yields.

In the present work, we have reinvestigated the coupling reaction of aryl and alkyl organolithium reagents with (hetero)aryl bromides under continuous flow conditions, screening different conditions, with the aim of developing an optimized, reproducible and highly productive in-flow methodology, while operating under safe experimental conditions.

Results and Discussion

Performing on large scale cross-coupling reactions with organolithium compounds may represent a serious challenge, mainly due to economical and safety concerns.[16] Long reaction times and the need to operate with diluted reagent solutions can increase the cost, while operations with highly concentrated solutions and fast reactions are difficult to handle in batch.

Therefore, we decided to take advantage of the continuous flow technology to overcome the issues of the Murahashi cross-coupling in batch, and, based on the reaction conditions reported in previous works,[4-6] different experimental set ups were investigated in the model reaction of *n*-HexLi with 4-bromoanisole in a coil reactor (Scheme 1).



Scheme 1. In flow model reaction: Pd-catalysed cross coupling of HexLi with 4-bromoanisole. RT = room temperature, t_R = residence time.

Since $Pd[P(tBu)_3]_2$ and PEEPSI-iPr were demonstrated to be the catalysts of choice in promoting cross-coupling reactions when aryllithiums were employed, [4-7] both catalysts were investigated in the present study.

A preliminary screening of the solvents in the reaction between *n*-HexLi and 4-bromoanisole promoted by $Pd[P(tBu)_3]_2$, at a fixed residence time (40 s) and substrate concentration (1 M), allowed to identify toluene as the solvent of choice (Figure 1).[17]

In the standard procedure, typically performed on a 2 mmol scale, a 1M solution of aryl bromide and palladium catalyst ($Pd[PtBu_3]_2$ 2.5 mol%) in toluene was prepared under open flask conditions; the mixture was stirred until the color changed from yellow to red (15-20 seconds). A 1 M solution of this mixture (flow rate= 0.4 mL/min) and a solution of *n*-HexLi (2.3 M in hexanes, 1.1 equiv,

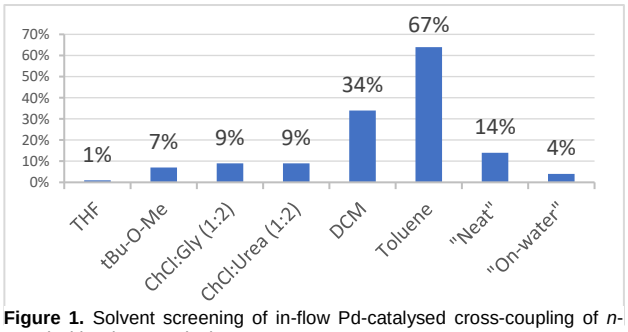


Figure 1. Solvent screening of in-flow Pd-catalysed cross-coupling of *n*-HexLi with 4-bromoanisole.

flow rate = 0.2 mL/min) were fed through a T-mixer into a 20 cm FEP coil reactor (internal volume 0.389 mL), with a residence time of 40 s. Under these conditions, the desired product **1** was isolated in 67% yield (Table 1, entry 1).

Several other parameters like mixer and reactor types, reactants and catalyst concentration, temperature, residence time and organolithium stoichiometry were tested, in order to optimize the reaction conditions (Table 1).

Table 1. Screening of experimental conditions in the in-flow coupling of *n*-HexLi and 4-bromoanisole.[a]

Entry	Catalyst activation	Catalyst loading	Residence time (sec)	ArBr conc.	Yield[b]
1[a]	-	2.5%	40	1M	67%
2[c]	-	2.5%	40	1M	57%
3[d]	-	2.5%	40	1M	56%
4[e]	-	2.5%	40	1M	64%
5[f]	-	2.5%	40	1M	70%
6	O_2 activation	2.5%	40	1M	42%
7	-	2.5%	20	1M	57%
8	-	2.5%	60	1M	69%
9	-	0.5%	40	1M	50%
10	-	5.0%	40	1M	61%
11	-	2.5%	40	0.2M	50%
12	-	2.5%	40	5M	65%
13[g]	-	2.5%	40	1M	70%

[a] Standard conditions: a 1 M solution of aryl bromide (2 mmol) and palladium catalyst ($Pd(PtBu_3)_2$ 2.5 mol%) in toluene (flow rate=0.4 mL/min) and a solution of *n*-HexLi (2.3 M in hexanes, 1.1 equiv., flow rate=0.2 mL/min) were fed through a T-mixer into a 20 cm FEP coil reactor (internal volume 0.389 mL), at RT with a 40 sec residence time. [b] Yield determined via NMR using 1,3,5 trimethoxybenzene as internal standard. [c] QUAD-mixer was used. [d] Reaction was performed in a CSTR (continuous stirred tank reactor). [e] Reaction was performed at 50 °C. [f] 2.2 mol equiv of *n*-HexLi was used. [g] 40 cm coil (0.78 mL) was employed.

The use of other mixers, like QUAD-mixer, or other reactors, such as CSTR (continuous stirred tank reactors), led to lower yields (Table 1, entries 2,3). The reaction at 50 °C did not lead to any

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significant yield improvement when compared to the coupling at RT, as well as the use of 2.2 equiv of *n*-HexLi (Table 1, entries 4,5). With a different protocol, following a literature procedure,[5] oxygen addition led to a lower yield, thus showing that in our standard conditions the catalyst is already activated and it does not require further oxygen addition (entry 6).

Longer residence times led to a marginal improvement (60 s, 69% yield; Table 1, entry 8), while it is worth noting that a residence time of only 20 s afforded **1** in 57% yield (Table 1, entry 7).

A higher catalyst loading was not beneficial (entry 10), while, remarkably, operating with 0.5% equiv of catalyst, the product was obtained in 50% yield, thus clearly demonstrating the possibility to improve the efficiency of the process and to further optimize the reaction with a very low catalyst loading (Table 1, entry 9). The coupling worked well also at a higher concentration of aryl bromide (Table 1, entry 12). However, a 5 M concentration represents a limit over which clogging phenomena more probably occur. These results offer an opportunity to increase the productivity of the process, which can be calculated according to the following eq. 1:

$$output\ (mg/min) = flow\ rate\ (mL/min) * conc.\ (mmol/mL) * MW\ (mg/mmol) * yield\ (\%) \quad \text{eq. 1}$$

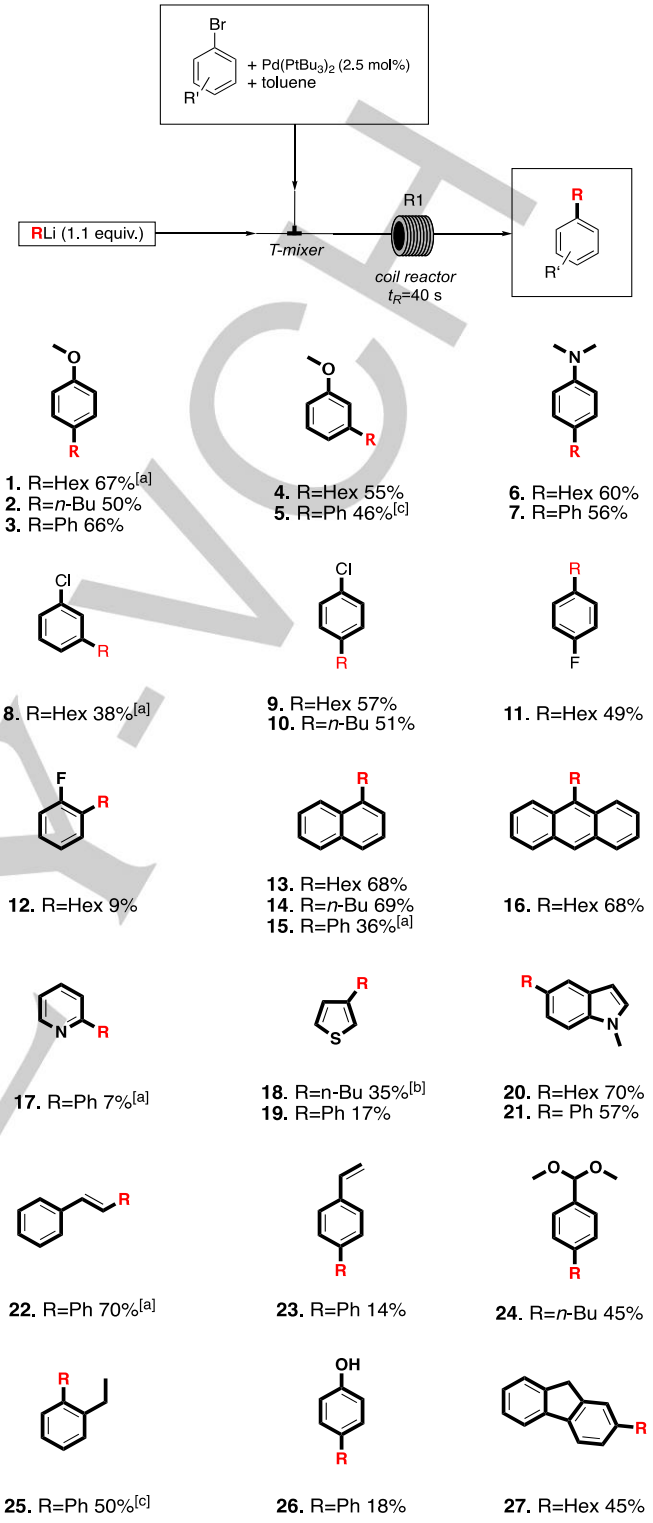
One strategy to improve the productivity is to scale up the volume of the reactor, keeping constant the residence time and increasing the flow rate. In entries 1 and 13 of Table 1, comparable yields were obtained using two different reactor volumes (the diameter of the coil is the same, but the length is different), thus demonstrating the possibility to scale up the reaction without losing the efficiency.

Another approach to reach higher productivities is by operating with more concentrated substrate solutions. For example, with 1 M and 5 M bromoanisole solutions (Table 1, entries 1 and 12), comparable results were found, thus making possible a 5-times improvement of the productivity simply varying the concentration.

Once established the best experimental conditions, the scope of the reaction was explored by investigating the coupling of differently substituted aryl bromides with alkyl and aryllithium reagents (Scheme 2). A 20 cm coil reactor made of FEP (0.389 mL) was used, and a 1 M solution of different aryl bromides and $Pd[P(tBu)_3]_2$ (2.5 mol%) in toluene, jointly with a solution of organolithium reagent (1.1 equiv), were fed in a T mixer with appropriate flow rates to assure a 40 s residence time (conditions of entry 1, Table 1).

The reaction was run on 3-bromoanisole and 4-bromoanisole using *n*-HexLi to evaluate the effect of the methoxy group in meta- and para-position. A better result was achieved with the para-substituted substrate (**1**: 67% yield), but a good yield was realized also with the meta-substituted substrate (**4**: 55% yield).[18]

4-Bromoanisole was also reacted with *n*-BuLi and PhLi to evaluate the effect of different organolithium compounds. Both the products **2** and **3** were obtained in good yields, 50% and 66%, respectively. The reaction between 3-bromoanisole and PhLi afforded product **5** in a 30% yield, that could be improved to 46% when 5% PEPPSI-iPr was alternatively employed as the catalyst. The reaction worked well with the electron-rich 4-bromo-*N*,*N*-dimethylaniline, both with *n*-HexLi and PhLi, to give products **6** and **7** in 60% and 56% yield, respectively.



General procedure. Reaction scale: 2 mmol of aryl bromide. A solution 1 M of (hetero)aryl bromide (RX) and palladium catalyst ($Pd[PtBu_3]_2$ 2.5 mol%) in toluene was prepared under open flask conditions; the mixture was stirred until the color changed from yellow to red (15-20 seconds). The mixture and a solution of organolithium (1.1 equiv) were fed into the coil reactor (internal volume 0.389 mL) to get a residence time of 0.66 min (40 s). Yields determined via NMR using 1,3,5 trimethoxybenzene as internal standard. [a] Isolated yield. [b] A 0.5 M substrate solution was employed. [c] A 5% PEPPSI-iPr was used as the catalyst.

Scheme 2. Scope of the reaction.

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When 1-bromo-4-chlorobenzene was reacted with *n*-HexLi and *n*-BuLi, adducts **9** and **10** were isolated in 57% and 51% yield, respectively, whereas **8** was produced in 38% yield in the reaction of *n*-HexLi with 1-bromo-3-chlorobenzene. The *ortho*-substituted 1-bromo-2-fluorobenzene reacted with *n*-HexLi poorly, to give **12** in 9% yield, while the reaction of 1-bromo-4-fluorobenzene led to **11** in 49% yield.

Polycyclic aromatic compounds were also investigated. The desired products **13** and **14** were isolated in 68-69% yield from the reaction between 1-bromonaphtalene and *n*-HexLi and *n*-BuLi, respectively. On the other hand, PhLi cross-coupled poorly to afford **15** in 36% yield. Cross-coupling between 9-bromo-antracene and *n*-HexLi also took place smoothly to give **16** in 68% yield.

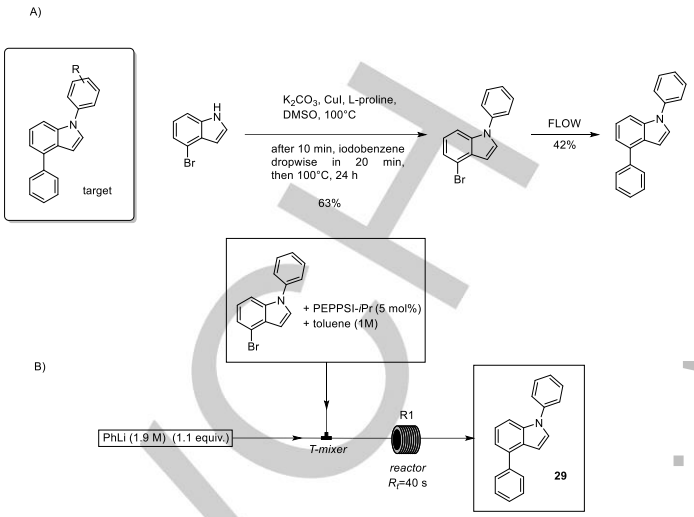
2-Bromopyridine and 3-bromotiophene reacted sluggishly with PhLi to give compounds **17** and **19** in 7–17% yield. 3-Bromotiophene also cross-coupled with *n*-BuLi, although providing **18** in 17% yield. When using a modified version (0.5 M starting material instead of 1 M) the yield of **18** increased up to 35%. 5-Bromo-1-methylindole turned out to be a reactive partner as well, providing compounds **20** and **21** in 57 and 70% yield in the reaction with *n*-HexLi and PhLi, respectively.

Retention of the C=C configuration was observed in the cross-coupling reaction between (*E*)-β bromo-styrene and PhLi, affording (*E*)-stilbene **22** in 70% yield. PhLi was also used as the nucleophilic coupling partner with 4-bromostyrene, providing adduct **23** in 14% yield only. The use of a protected aldehyde, as acetal, led to the formation of **24** in 45% yield. When 2-bromo-ethylbenzene was reacted with PhLi, using 5% PEPPSI-iPr as the catalyst, product **25** was isolated in 50% yield.

In the reaction of substrates with organolithium-sensitive groups, e.g., 4-bromophenol, the desired adduct **26** was isolated in 18% yield in the reaction with PhLi, whereas 2-bromofluorene, featuring a relatively acidic proton at a benzylic-type position, successfully cross-coupled with PhLi to provide **27** in 45% yield.

The methodology was finally applied to the synthesis of a class of lysine and arginine methyltransferase inhibitors used for the treatment of cancer.[19] The disruption of the normal functions of methyltransferases has been implicated in human diseases. Lysine and arginine methylation are covalent histone modifications, that is one of the possible ways to achieve epigenetic control over gene expression. The general scaffold of potential inhibitors is reported in Scheme 3A. Among the possible synthetic strategies, the late stage functionalization of 4-bromo-1*N*-phenyl indole is particularly attractive to generate a wide variety of derivatives of this class of anti-cancer compounds.

To this end, *N*-phenyl-4-bromoindole **28** was first prepared in 63% yield, starting from 4-bromo-1H-Indole.[20] The coupling reaction between **28** and PhLi, using the optimized flow protocol for aryllithium compounds with 5% of PEPPSI-iPr as the catalyst, provided adduct **29** in 42% yield within 40 s, thereby demonstrating the applicability of the methodology also in the field of medicinal chemistry (Scheme 3B).[21]



Scheme 3. A) Synthetic strategy of Lysine and arginine methyltransferase inhibitors; B) In flow coupling reaction.

Conclusion

In the present study, a simple, easy to scale, fast, in continuo methodology for the Pd-mediated cross-coupling reaction of commercially available organolithium reagents with (hetero)aryl bromides has been developed. Noteworthy, the reaction does not require pre-catalyst activation and/or inert atmosphere. The methodology shows quite a wide scope, to generate cross coupling products in moderate-to-good yields, with a high level of productivity. Moreover, the method has been applied to the synthesis of a novel class of anti-cancer active pharmaceutical ingredients, effective for the treatment of methyltransferase associated diseases.

Although the proposed experimental protocol demonstrates that the performance of cross-coupling reactions run under “on water” conditions cannot be easily replicated in flow,[7] however, it offers the possibilities to access, in short time, a large number of products, and thus it may find application in the discovery and generation of focused libraries.

Experimental Section

Material and methods.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-300 spectrometer using $CDCl_3$ as solvent at room temperature. Chemical shifts for protons are reported using residual solvent protons (^{1}H NMR: δ = 7.26 ppm for $CDCl_3$) as internal standard. Carbon spectra were referenced to the shift of the ^{13}C signal of $CDCl_3$ (δ = 77.0 ppm). Accurate mass analysis was performed using Q-ToF Synapt G2-Si HDMS, Acquity UPLC I-Class, Photodiode Optical Detector (PDA) (Waters). Elemental analysis were performed using CHN 2400 (Perkin Elmer).

The reactions were run using a coil reactor (20 cm) made of FEP with an internal volume of 0.389 mL (inner diameter=0.062 inches, outer diameter=1/8’’). The reagents were loaded in two different

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syringes (one for the delivery of the solution containing the starting material and the palladium catalyst in toluene, and the other for the delivery of the organolithium solution), then the two solutions were fed through a T-junction into the coil reactor, at the correct flow rate to reach a residence time of 40 seconds.

General procedure. A solution 1 M of (hetero)aryl bromide (RX) (2 mmol) and palladium catalyst ($Pd[PtBu_3]_2$ 2.5 mol%) in toluene was prepared under open flask conditions and stirred until the color changed from yellow to red (15-20 seconds). The mixture (flow rate=0.4 mL/min) and a solution of organolithium 2.3 M (1.1 equiv) (flow rate=0.2 mL/min) were fed into the coil reactor (internal volume 0.389 mL), to obtain a residence time of 0.66 min (40 s). The output was collected in a collection flask containing water, and at the end of the process the two phases were separated, and the aqueous phase was extracted with Et_2O. The organic phase was filtered using a HPLC filter and 1,3,5-trimethoxybenzene was introduced as external standard. The yields of the products were determined by NMR after concentration of the organic phase under reduced pressure and confirmed as isolated yields after chromatographic purification.

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Keywords: organolithium • flow technologies • cross coupling • Pd catalysis • aryl derivatives

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[17]. Studies have mainly focused on the reactions performed according to the Feringa protocols. A preliminary exploration aimed at transferring in flow the in-batch on water procedure developed by Capriati and coworkers was not successful.

[18]. The reaction with 2-bromoanisole under the present conditions was not successful, probably do to the competitive OR-assisted halogen-lithium exchange.

[19]. Current Patent Assignee: The Rockefeller University - WO2011/82098, 2011, A1 Patent Family Members: WO2011/82098 A1).

[20]. E.C. Elliot, J. L. Maggs, B. K. Park, P. M. O’Neilla, A. V. Stachulski, *Org. Biomol. Chem.*, **2013**, *11*, 8426-8434.

[21]. For details on the experimental set up please see the Supporting Information

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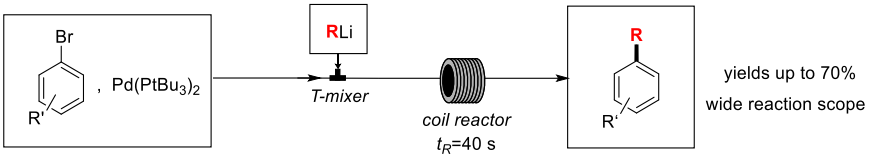

The direct use of readily available and relatively inexpensive organolithium reagents in cross-coupling reactions is grown in recent years. However, the large-scale application of these commodity reagents remains a formidable challenge. Here we report fast, efficient, and in continuo Pd-catalysed cross couplings of organolithium reagents with aryl bromides that proceed in 40 s, allowing the synthesis of a variety of functionalised aryl compounds without pre-catalyst activation and inert atmosphere.

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