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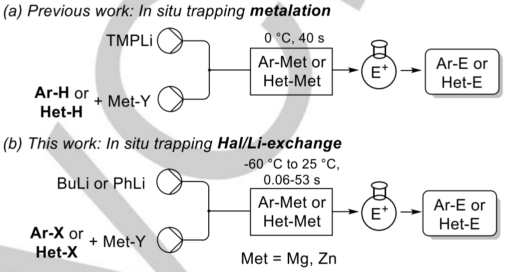
Preparation of Polyfunctional Diorgano-Magnesium and -Zinc Reagents Using In Situ Trapping Halogen-Lithium Exchange of Highly Functionalized (Hetero)aryl Halides in Continuous Flow

Marthe Ketels, Maximilian A. Ganiek, Niels Weidmann and Paul Knochel*

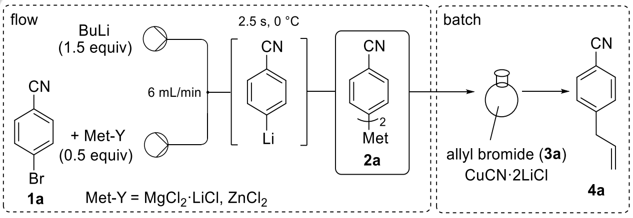
Abstract: *We report a halogen-lithium exchange performed in the presence of various metal salts ($ZnCl_2$, $MgCl_2{\cdot}LiCl$) on a broad range of sensitive bromo- or iodo-(hetero)arenes using BuLi or PhLi as exchange reagent and a commercially available continuous flow setup. The resulting diarylmagnesium or diarylzinc species were trapped with various electrophiles resulting in the formation of polyfunctional (hetero)arenes in high yields. This methodology enabled the functionalization of (hetero)arenes containing highly sensitive groups such as an isothiocyanate, nitro, azide or ester. A straightforward scale-up was possible without further optimization.*

Organolithiums are key organometallic intermediates in organic synthesis.[1] The halogen-lithium exchange reaction is a standard preparation of organolithium compounds[2] and provides access after transmetalation to a broad variety of other useful organometallic species.[3] The scope of halogen-lithium exchange reactions is limited by the presence of sensitive functional groups in these unsaturated substrates,[2,3] precluding the presence of an ester, a nitro, an azide or an isothiocyanato group.[4] These drawbacks were avoided to some extent by the use of cryogenic temperatures[2a], special protecting groups[5] or by fast consecutive transmetalations to less reactive organometallics.[6] Continuous flow setups have emerged as a powerful tool for solving synthetic problems.[6b,7] Thus, Yoshida and others have utilized ultra-fast mixing and precise reaction time control of custom-made flow setups for achieving the generation of lithiated arenes bearing ester, isothiocyanate, cyano or nitro groups.[8] Recently, we have shown that the scope of metalations of arenes (Ar-H) with a strong base like TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl) is dramatically increased by performing these metalations in the presence of metallic salts (Met-Y).[9] The resulting organometallics (Ar-Met) were much more stable than the initially generated lithium reagents and could be broadly functionalized with a variety of electrophiles (E^+). The scope and reaction conditions of this in situ trapping procedure are further improved by switching from a batch to a continuous flow setup (Scheme 1a).[9b-c] Aware of the fast rate of the halogen-lithium exchange,[10] we envisioned an analogous exchange in situ trapping exchange procedure (Scheme 1b). Herein, we wish to report a halogen-lithium exchange performed in the presence of metallic salts for the convenient functionalization of sensitive (hetero)arenes using continuous flow technology (Scheme 1b). This in situ trapping halogen-lithium exchange procedure has the advantage that it provides excellent functional group tolerance including to the best of our knowledge for the first time aryl azides and that it can be conducted using commercially available flow reactors.



Scheme 1. In situ trapping metalation and in situ trapping-exchange using commercially available continuous flow setups.

First, we optimized the reaction conditions of the Br/Li-exchange for 4-bromobenzonitrile (**1a**) using BuLi as exchange reagent. Optimized flow conditions[11] without the addition of a metal salt led after quenching with allyl bromide (2.5 equiv) and $CuCN{\cdot}2LiCl$[12] (10 mol%) to the allylated arene **4a** in 17% GC-yield (Scheme 2). This low yield may be due to the competitive addition of the newly generated aryllithium or BuLi to the cyano group. Addition of the well-soluble $MgCl_2{\cdot}LiCl$ to the aryl bromide **1a** and further optimization of the flow rate, reaction time and temperature increased the GC-yield of **4a** to 85%. Instead of $MgCl_2{\cdot}LiCl$, also $ZnCl_2$ was used as an in situ transmetalating agent leading to **4a** in 82% GC-yield.[13]



Scheme 2. Optimization of the in situ exchange-transmetalation sequence in continuous flow for 4-bromobenzonitrile (**1a**).

The intermediate magnesium species **2a** was used in various quenching reactions such as iodolysis, addition to an aldehyde and acylation resulting in functionalized benzonitriles **4b**-**d** in 70-85% yield (Table 1, entries 1-3). The range of substrates was extended to other bromobenzonitriles which were converted to the corresponding diarylmagnesium species (**2b**-**c**). After batch-quenching with ketones, allyl bromides or acyl chlorides in the presence of $CuCN{\cdot}2LiCl$ the corresponding products **4e**-**g** were obtained in 68-74% yield (entries 4-6). It was also possible to perform an I/Li-exchange on 2-iodo-benzonitrile (**1d**) using similar conditions, providing the diarylzinc species **2d**. Allylation with 3-bromocyclohexene (**3h**) afforded benzonitrile **4h** in 80% yield (entry 7).

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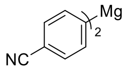
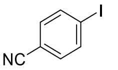
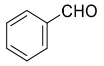
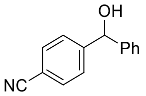
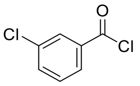
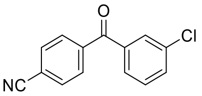
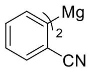
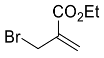
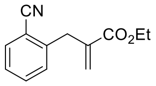
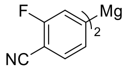
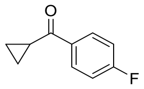
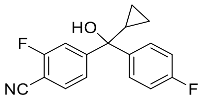
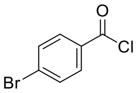
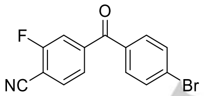
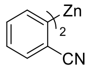
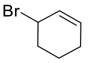
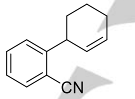
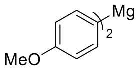
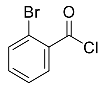
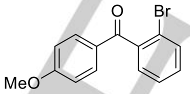
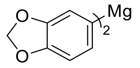
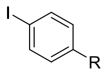
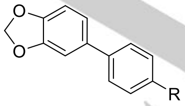
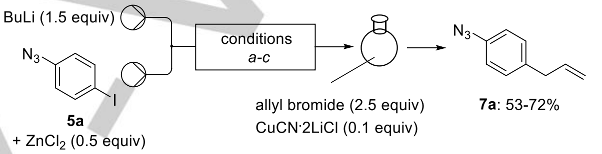
Table 1. In situ exchange-transmetalation for sensitive aryl halides of type **1** leading *via* intermediate diorgano-zincs or -magnesiums of type **2** to polyfunctional arenes of type **4**.

entry	metal species T[°C]; flow rate [mL/min]; t[s]	electrophile	product[a]
1	 **2a**: 0; 6; 2.5[b]	I_2 **3b**[c]	 **4b**: 70%
2	**2a**[b]	 **3c**[d]	 **4c**: 83%
3	**2a**[b]	 **3d**[e],[f]	 **4d**: 85%
4	 **2b**: 0; 9; 1.7[b]	 **3e**[g]	 **4e**: 68%
5	 **2c**: 0; 9; 1.7[b]	 **3f**[d]	 **4f**: 74%
6	**2c**[b]	 **3g**[e],[f]	 **4g**: 74% (76%)[h]
7	 **2d**: 0; 6; 2.5[i]	 **3h**[g]	 **4h**: 80%
8	 **2e**: 0; 12; 25[b]	 **3i**[e],[f]	 **4i**: 68%
9	 **2f**: 0; 6; 2.5[b]	 **3j**: R = NO_2[j]	 **4j**: 85%
10	**2f**[b]	**3k**: R = CO_2Et[j]	**4k**: 70%

[a] Yield of analytically pure isolated product. [b] Metal species prepared from the aryl bromide. [c] 2.0 equiv, 10 min, r.t.. [d] 1.1-1.5 equiv, 1-2 h, 0 °C. [e] 1.1 equiv CuCN·2LiCl was added. [f] 1.5 equiv, 1-2 h, 0 °C. [g] 2.5 equiv, 0.1 equiv CuCN·2LiCl, 30 min, 0 °C. [h] Reaction performed on 10 mmol scale, 3 h, 0 °C. [i] Metal species prepared from the aryl iodide. [j] Negishi cross-coupling was performed in batch, 1.5 equiv, 10 h, 25 °C after transmetalation to $ZnCl_2$.

Remarkably, these exchange reactions proceed at 0 °C in contrast to the standard halogen-lithium exchanges in batch which are performed at -78 °C.[2,6a] Also, electron-rich aryl bromides (**1e**-**f**) were in situ transmetalated in the presence of $MgCl_2·LiCl$ and quenched with acyl chloride **3i** or subjected to a *Negishi* cross-coupling[14] after batch-transmetalation with $ZnCl_2$ using Organ's catalyst PEPPSI-^{i}Pr.[15] The resulting products **4i**-**k** were obtained in 68-85% yield (entries 8-10). While most examples were performed on a 0.5 mmol scale, these in situ trapping exchange reactions can be easily scaled up by simply extending the runtime. Thus, benzophenone **4g** was prepared on a 10 mmol scale in 76% yield (entry 6) without further optimization.[16]

To further demonstrate the broad applicability of in situ trapping exchange reactions in flow, we investigated the compatibility of these exchanges with aryl halides bearing challenging functional groups such as an ester, a ketone, a nitro and heterocumulene groups e.g. an azide or isothiocyanate.[2-6] Notably, only halogen-lithium exchanges of *o*-nitroarenes[2,6] and an alkenyl iodide containing an aliphatic azide[6] at -100 °C under batch conditions are known, as well as several flow protocols for ester-, ketone- and nitro-containing arenes applying ultrafast micromixing and residence times down to 0.0015 s.[8] Again, we found that in the absence of a metal salt 4-iodophenyl azide[17] (**5a**) decomposes completely performing the reaction in flow. However, screening of various in situ trapping exchange conditions, e.g addition of soluble metal salts, flow rate and temperature,[13] led to the desired allylated phenyl azide **7a** in 72% isolated yield (Scheme 3).

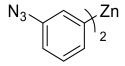
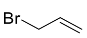
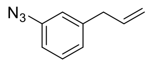
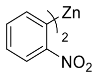
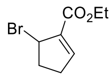
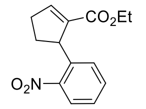
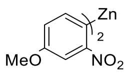
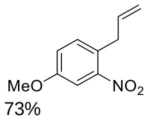


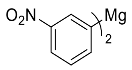
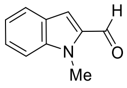
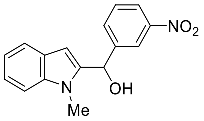
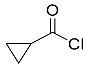
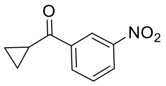
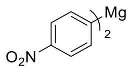
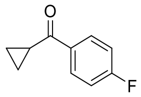
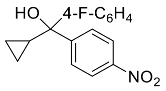
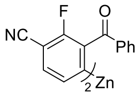
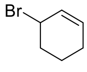
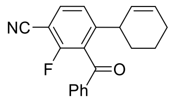
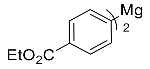
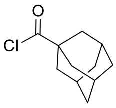
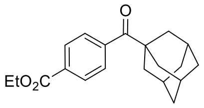
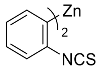
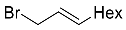
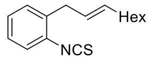
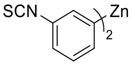
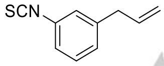
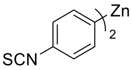
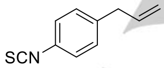
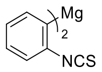
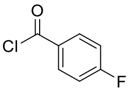
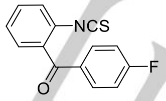
a) In situ exchange, 0 °C, 2.5 s, 6 mL/min: **7a**: 53% yield.
b) 0 °C, 2.5 s; No salt additive: no product and decomposition of reagents.
c) In situ exchange, -40 °C, 1.25 s, 12 mL/min: **7a**: 72% yield (1 mmol); 60% (5 mmol).

Scheme 3. I/Li-exchange in presence of an azide group under various reaction conditions a-c.

Scale-up of this reaction from 1 to 5 mmol provided the aryl azide **7a** in 60% yield. The analogous *m*-allyl azidobenzene (**7b**) was obtained in 83% yield (Table 2, entry 1). Furthermore, nitro-, ketone- and ester-groups were tested because of their pivotal role in organic synthesis and well-known challenges in organometallic chemistry due to competitive electron transfer and nucleophilic addition reactions.[4-5] In order to access aryl organometallics with such functional groups, the best lithiation exchange reagent was found to be PhLi instead of BuLi.

Table 2. In situ exchange-transmetalation for highly sensitive aryl halides of type **5** leading *via* intermediate diorgano-zincs or -magnesiums of type **6** to polyfunctional arenes of type **7**.

entry	metal species T[°C]; flow rate [mL/min]; t[s]	electrophile	product[a]
1	 **6b**: -40; 12; 1.25[b]	 **3a**[c]	 **7b**: 83%
2	 **6c**: -20; 12; 1.25[d]	 **3l**[c]	 **7c**: 78%
3	 **6d**: -20; 12; 0.10[d]	**3a**[c]	 **7d**: 73%

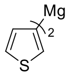
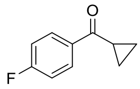
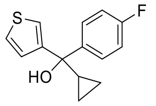
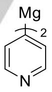
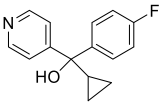
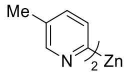
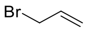
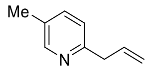
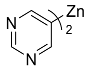
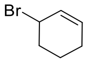
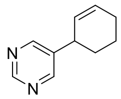
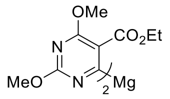
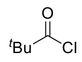
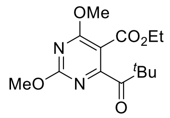
4	 **6e**: -20; 20; 0.06[b]	 **3m**[e]	 **7e**: 60%
5	**6e**[b]	 **3n**[f]	 **7f**: 63%
6	 **6f**: -60; 16; 0.08[b]	 **3f**[e]	 **7g**: 73%
7	 **6g**: -40; 20; 0.06[d]	 **3h**[c]	 **7h**: 78%
8	 **6h**: -40; 16; 0.94[b]	 **3o**[f]	 **7i**: 70%
9	 **6i**: -20; 12; 1.25[d]	 **3p**[c]	 **7j**: 68%
10	 **6j**: -60; 18; 0.07[d]	**3a**[c]	 **7k**: 65%
11	 **6k**: -60; 9; 0.15[d]	**3a**[c]	 **7l**: 67%
12	 **6l**: -20; 16; 0.94[d]	 **3q**[f]	 **7m**: 63%

[a] Yield of analytically pure isolated product. [b] Metal species prepared from the aryl iodide. [c] 2.5 equiv, 0.1 equiv $CuCN\cdot 2LiCl$, 30 min, 0 °C. [d] Metal species prepared from the aryl bromide. [e] 1.1-1.5 equiv, 1-2 h, 0 °C. [f] 1.5 equiv, 1.1 equiv $CuCN\cdot 2LiCl$, 1-2 h, 0 °C., 30 min, 0 °C.

Interestingly, also with PhLi, the exchange is faster than a competitive transmetalation of PhLi therefore allowing an efficient generation of diarylzincs and -magnesiums (**6c**-**h**). Thus, bis-(nitroaryl)zincs **6c**-**f** were generated from the corresponding aryl halides **5c**-**f**. Allylation, acylation and addition to indole aldehyde **3m** or ketone **3f** in batch furnished the desired functionalized nitro arenes **7c-g** in 60-78% yield (entries 2-6). Similarly, the aryl bromide **5g**, containing a ketone was functionalized by in situ trapping exchange reactions at -40 °C in the presence of $ZnCl_2$. Typical quenching conditions led to the allylated product **7h** from the diarylzinc **6g** in 78% yield (entry 7). Furthermore, ethyl 4-iodobenzoate (**5h**) led to **7i** *via* the diarylmagnesium **6h** in 70% (entry 8). It was further possible to perform an Br/Li-exchange on aryl bromides bearing an *p*-, *m*-, and *o*-isothiocyanate moiety without subsequent additions to the electrophilic isothiocyanate.[4d,e] After various copper mediated allylations or acylations,[12] the desired products **7j**-**m** were obtained in 63-68% yield (entries 9-12).

The preparation of polyfunctional heterocyclic organometallics is of key importance for the pharmaceutical and agrochemical industry.[18,19] Thus, sulfur- and nitrogen-containing heterocyclic halides were subjected to in situ trapping exchange reactions. For instance, 3-bromothiophene (**8a**) was converted to the reactive diheteroarylmagnesium species **9a**. Further batch addition to ketone **3h** led to tertiary alcohol **10a** in 77% yield (Table 3, entry 1). To expand the range of substrates, different pyridines and pyrimidines were subjected successfully to the Br/Li-exchange. Thus, pyridine derivatives **8b**-**c** underwent the in situ trapping exchange (entries 2-3). Quenching of the bis-pyridyl-zinc and -magnesium reagents **9b** and **9c** in batch led to the tertiary alcohol **10b** and allylated picoline **10c** in 62-63% yield (entries 2-3). Furthermore, 5-bromopyrimidine (**8d**) and the fully substituted iodopyrimidine **8e** were transmetalated in situ using short reaction times (0.06-1.25 s) at -40-0 °C (entries 4-5). By using PhLi, an ester was tolerated providing the acylated[12] pyrimidine **10e** in 68% yield (entry 5).

Table 3. In situ exchange-transmetalation for highly sensitive heteroaryl halides of type **8** leading *via* intermediate diorgano-zincs or -magnesiums of type **9** to polyfunctional heteroarenes of type **10**.

entry	metal species T[°C]; flow rate [mL/min]; t[s]	electrophile	product[a]
1	 **9a**: 0; 6; 10[b]	 **3f**[d]	 **10a**: 77%
2	 **9b**: 0; 18; 0.83[e]	**3f**[d]	 **10b**: 62%
3	 **9c**: 0; 6; 53[b]	 **3a**[f]	 **10c**: 63%
4	 **9d**: 0; 12; 1.25[b]	 **3h**[f]	 **10d**: 68%
5	 **9e**: -40; 20; 0.06[e]	 **3r**[c]	 **10e**: 68%

[a] Yield of analytically pure isolated product. [b] Metal species prepared from the aryl bromide. [c] 1.5 equiv, 1.1 equiv $CuCN\cdot 2LiCl$, 1-2 h, 0 °C. [d] 1.1 equiv, 1-2 h, 0 °C. [e] Metal species prepared from the aryl iodide. [f] 2.5 equiv, 0.1 equiv $CuCN\cdot 2LiCl$, 30 min, 0 °C.

In conclusion, we report a halogen-lithium exchange in the presence of various metal salts ($ZnCl_2$, $MgCl_2\cdot LiCl$) on a broad range of sensitive bromo- or iodo-(hetero)arenes using BuLi or PhLi as exchange reagent and a commercially available continuous flow setup. The resulting diarylmagnesium or diarylzinc species were trapped with various electrophiles resulting in the formation of polyfunctional (hetero)arenes in high yields. This methodology enabled the functionalization of arenes containing highly sensitive groups such as an isothiocyanate, nitro, azide or ester since the reaction of the functional groups with the lithium species and the transmetalation of BuLi with metal salts are slower than the halogen-lithium exchange.

Acknowledgements

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Keywords: flow chemistry• lithiation• magnesiation• zincation• in situ trapping

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Layout 2:

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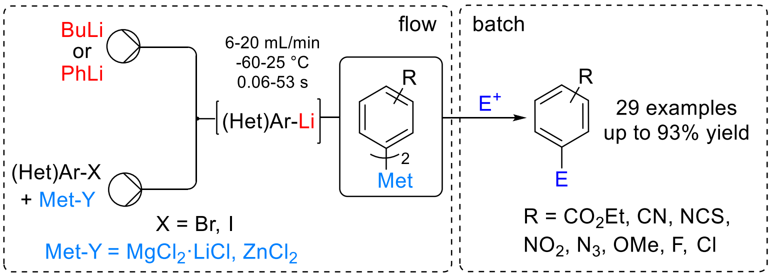

Flow (ex)changes everything: A halogen-lithium exchange using BuLi or PhLi was performed in the presence of various metal salts ($ZnCl_2$, $MgCl_2{\cdot}LiCl$) on a broad range of sensitive bromo- or iodo-hetero(arenes) using a commercially available continuous flow setup. The resulting diarylmagnesium or diarylzinc species were trapped with various electrophiles resulting in the formation of polyfunctional (hetero)arenes in high yields and with excellent chemoselectivity.

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Preparation of Polyfunctional Diorgano-Magnesium and -Zinc Reagents Using In Situ Trapping Halogen-Lithium Exchange of Highly Functionalized (Hetero)aryl Halides in Continuous Flow