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Practical Continuous-Flow Trapping Metalations of Functionalized Arenes and Heteroarenes Using TMPLi in the Presence of Mg, Zn, Cu, or La Halides**

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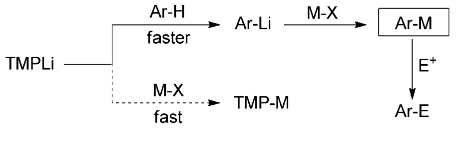
Dedicated to the Technion–Israel Institute of Technology, Haifa

Abstract: *The flow metalation of various arenes and heteroarenes involving an in situ trapping with metal salts ($ZnCl_2$·2 LiCl, $MgCl_2$, CuCN·2 LiCl, $LaCl_3$·2 LiCl) under very convenient conditions (0 °C, 40 s) is reported. The resulting Mg, Zn, Cu, or La organic species are trapped with various electrophiles in high yields. In several cases, unusual kinetically controlled regioselectivities are obtained. All these flow metalations can be scaled up simply by extending the reaction time and without further optimization. The reaction scope of such flow metalations is considerably broader than that of the corresponding batch procedures.*

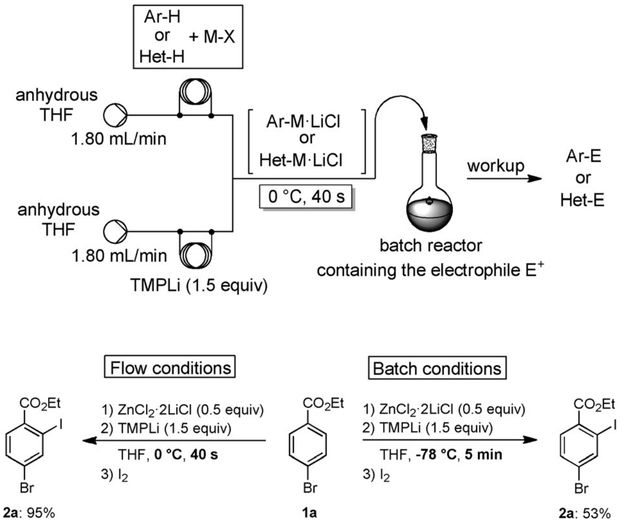
The *ortho*-lithiation of arenes and heteroarenes is a powerful tool for the functionalization of unsaturated molecules.[1] TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl) is an especially efficient base for such lithiations;[2] however, the high ionic character of the carbon–lithium bond in aryllithiums often precludes the presence of sensitive functionalities like esters, nitriles, and nitro groups. The use of highly sterically hindered silylated esters has recently solved this problem.[3] Furthermore, conducting lithiations under continuous-flow conditions has increased the functional-group tolerance as well.[4]

Recently, we have reported that in situ trapping transmetalations can be performed on various aromatic and heterocyclic substrates (Ar-H, Het-H).[5] In this procedure, the unsaturated substrate is mixed at −78 °C with a metal salt (M-X) such as $ZnCl_2$·2 LiCl, $MgCl_2$, or CuCN·2 LiCl and treated with TMPLi. It was found that the lithiation of Ar-H (or Het-H) by TMPLi is faster than the transmetalation of TMPLi with the metal salt (Scheme 1).



Scheme 1. In situ trapping metalation of aromatic substrates.

Although this method can be used to perform a range of new regioselective lithiations, the synthetic scope of such metalations is narrowed since cryogenic temperatures are required. Furthermore, we noticed that the scale-up of these in situ trapping reactions proved to be difficult, requiring much optimization. Herein, we report that these problems can be solved by using continuous-flow conditions[6] allowing the rapid mixing of the reaction components and avoiding the formation of hot spots. Furthermore, the in situ transmetalation with the metal salt present generates a more stable organometallic species. Thus the in situ trapping metalations can now be performed at 0 °C (instead of −78 °C). Moreover, these new reaction conditions considerably increase the reaction scope of this method and permit a straightforward scale-up of such metalations. The use of a continuous-flow setup as described in Scheme 2 makes it possible to "in situ transmetalate" a broad range of unsaturated substrates at 0 °C within 40 s (instead at −78 °C under batch conditions). Thus,



Scheme 2. Continuous-flow setup for in situ trapping metalations using TMPLi in the presence of metal salts ($ZnCl_2$·2 LiCl, $MgCl_2$, CuCN·2 LiCl, $LaCl_3$·2 LiCl) (top) and iodination of ethyl 4-bromobenzoate (**1a**) using flow and batch conditions for the in situ trapping metalation (bottom).

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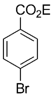
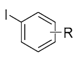
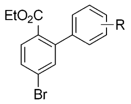
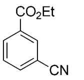
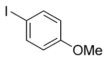
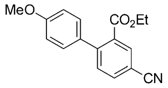
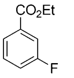
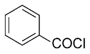
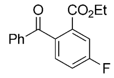
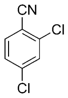
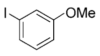
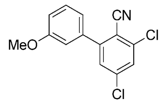
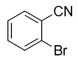
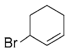
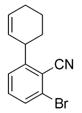
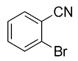
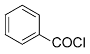
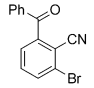
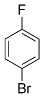
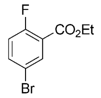
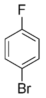
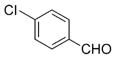
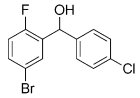
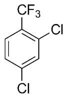
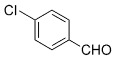
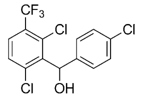
the mixing of a 1:2 mixture of the well-soluble $ZnCl_2{\cdot}2\,LiCl$ and ethyl 4-bromobenzoate (**1a**) in THF with TMPLi (1.5 equiv) in a flow apparatus[7] for 40 s at 0 °C produces after "batch iodolysis" the aryl iodide (**2a**) in 95 % yield.

Table 1: Continuous-flow trapping metalation of arenes **1** followed by reaction with electrophiles leading to products **2**.

Entry	Substrate	Electrophile	Product[a]
			
1	**1a**	R = *m*-OMe	**2b**: 78 %[b,d]
2	**1a**	R = *p*-CO_2Et	**2c**: 77 %[b,d]
			
3	**1b**		**2d**: 73 %[b,d]
			
4	**1c**		**2e**: 70 %[b,e]
			
5	**1d**		**2f**: 83 %[b,d]
			
6	**1e**		**2g**: 88 %[b,f] (87 %)[g]
			
7	**1e**		**2h**: 73 %[b,e]
		NC-CO_2Et	
8	**1f**		**2i**: 84 %[c]
			
9	**1f**		**2j**: 79 %[c]
			
10	**1g**		**2k**: 69 %[c]

[a] Yield of isolated product. [b] $ZnCl_2{\cdot}2\,LiCl$ (0.5 equiv) was used. [c] $MgCl_2$ (0.5 equiv) was used. [d] Obtained using 2 mol % $[Pd(dba)_2]$ and 4 mol % $P(2\text{-furyl})_3$. [e] Obtained by a Cu-mediated acylation. [f] Obtained by a Cu-catalyzed allylation. [g] Yield obtained on a 10 mmol scale.

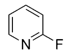
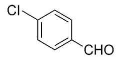
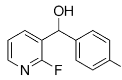
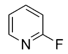
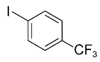
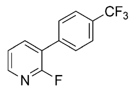
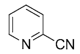
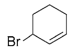
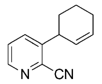
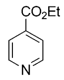
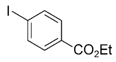
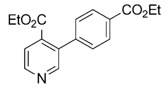
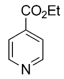
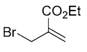
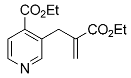
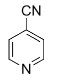
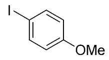
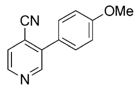
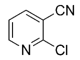
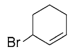
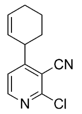
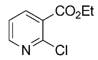
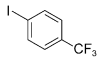
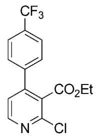
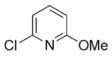
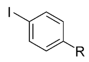
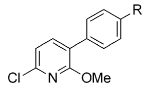
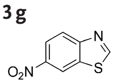
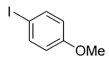
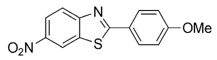
In strong contrast, when this procedure was performed in a standard Schlenk flask (batch conditions) at −78 °C the desired iodide (**2a**) was produced only in 53 % yield despite numerous optimization attempts. It should be noted that $TMP_2Zn{\cdot}2\,LiCl$,[8] which would be produced in the absence of ethyl 4-bromobenzoate (**1a**), does not metalate the aryl bromide (**1a**) under these reaction conditions, showing that the metalating agent of **1a** is TMPLi. After transmetalation with $ZnCl_2{\cdot}2\,LiCl$ the resulting arylzinc reagent is quenched with a range of electrophiles. Thus, a Pd-catalyzed Negishi cross-coupling[9] with aryl iodides having either electron-donating or electron-withdrawing substituents produces the biphenyls (**2b**,**c**) in 77 and 78 % yield, respectively (Table 1, entries 1 and 2).

Remarkable regioselectivities are obtained in such in situ transmetalations. The most acidic hydrogen of the 3-substituted ethyl benzoates (**1b**,**c**) is at position 2. This position is therefore always deprotonated with standard bases such as $TMPMgCl{\cdot}LiCl$ and $(TMP)_2Mn{\cdot}2\,MgCl_2{\cdot}4\,LiCl$.[10] However, under the kinetically controlled reaction conditions described herein, the strong TMPLi base is able to abstract the ring hydrogen at position 6, leading after Negishi cross-coupling or copper-mediated acylation to the trisubstituted arenes (**2d**,**e**) in 70–73 % yield (entries 3 and 4). Such kinetic metalations resulting in unique metalation regioselectivities are not limited to benzoate derivatives. 2,4-Dichlorobenzonitrile (**1d**) is also in situ zincated at position 6, affording the cyano-substituted biphenyl (**2f**) in 83 % yield after Negishi cross-coupling (entry 5). Also 2-bromobenzonitrile (**1e**) undergoes smooth flow metalation with TMPLi in the presence of $ZnCl_2{\cdot}2\,LiCl$ (0 °C, 40 s). Copper-mediated quenching with 3-bromocyclohexene (0.8 equiv) or benzoyl chloride (0.8 equiv) lead to the trisubstituted nitriles (**2g**,**h**) in 73–88 % yield (entries 6 and 7). Most of the examples in Table 1 were performed on a 1.7 mmol scale. However, these metalations can be scaled up by simply extending the reaction time. Thus, the preparation of the trisubstituted nitrile (**2g**) on a 10 mmol scale in 87 % yield is possible without further optimization, demonstrating the striking advantages of continuously processed reactions. Furthermore, the *ortho*-lithiation of haloarenes such as **1f** and **1g**, which are notoriously prone to decompose via benzyne formation,[11] undergo flow metalation with TMPLi in the presence of $MgCl_2$ (0.5 equiv) under standard conditions (0 °C, 40 s). Subsequent reactions with ethyl cyanoformate (1.5 equiv) or *p*-chlorobenzaldehyde (1.5 equiv) lead to the *o*-functionalized haloarenes (**2i**–**k**) in 69–84 % yield (entries 8–10).

These in situ trapping flow metalations are readily extended to a range of highly sensitive, electron-deficient pyridines and benzothiazoles (**3a**–**h**), which are substituted with various electron-withdrawing groups such as a chloride, a fluoride, or a cyano, ester, or nitro group (Table 2). Thus, the 2-substituted pyridines (**3a**,**b**) react under flow conditions in the presence of $MgCl_2$ or $ZnCl_2{\cdot}2\,LiCl$ with TMPLi leading to the corresponding pyridyl-magnesium and -zinc species. These organometallic intermediates undergo various quenching reactions such as an addition to *p*-chlorobenzaldehyde, a Pd-catalyzed Negishi cross-coupling, or a copper-catalyzed allylation providing the corresponding 2,3-disubstituted pyridines (**4a**–**c**) in 80–98 % yield (entries 1–3).

Whereas the metalation of 2-fluoropyridine (**3a**) failed using a standard batch "in situ" trapping protocol (TMPLi, $ZnCl_2{\cdot}2\,LiCl$, −78 °C, 5 min),[5,12] the same metalation performed in a flow mode produces the alcohol (**4a**) on

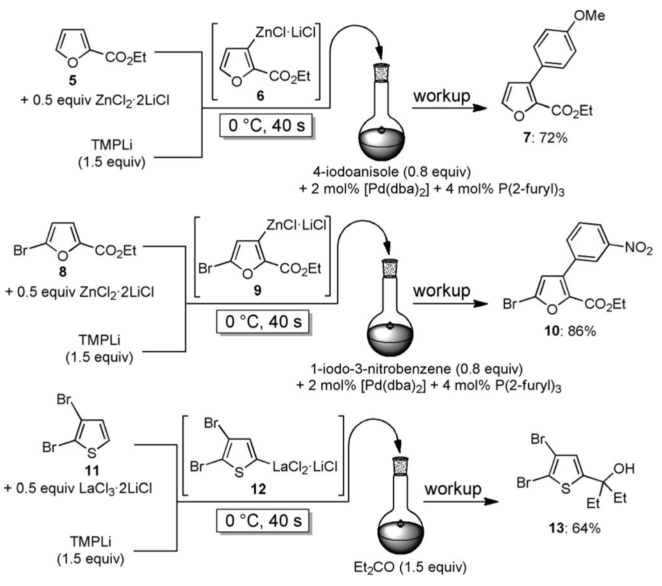
Table 2: Continuous-flow trapping metalation of N-heterocycles **3** followed by reaction with electrophiles leading to products **4**.

Entry	Substrate	Electrophile	Product[a]
1	 **3a**		 **4a**: 96%[c] (84%)[h]
2	 **3a**		 **4b**: 98%[b,e]
3	 **3b**		 **4c**: 80%[b,f]
4	 **3c**		 **4d**: 90%[b,e]
5	 **3c**		 **4e**: 79%[d]
6	 **3d**		 **4f**: 88%[b,e] (83%)[h]
7	 **3e**		 **4g**: 89%[d]
8	 **3f**		 **4h**: 85%[b,e]
9	 **3g**	 R = OMe	 **4i**: 99%[b,e]
10	**3g**	R = CN	**4j**: 89%[b,e] (85%)[h]
11	 **3h**		 **4k**: 63%[b,g]

[a] Yield of isolated product. [b] $\mathrm{ZnCl_2 \cdot 2\,LiCl}$ (0.5–1.1 equiv) was used. [c] $\mathrm{MgCl_2}$ (0.5 equiv) was used. [d] $\mathrm{CuCN \cdot 2\,LiCl}$ (1.1 equiv) was used. [e] Obtained using 2 mol% [Pd(dba)$_2$] and 4 mol% P(2-furyl)$_3$. [f] Obtained by a Cu-catalyzed allylation. [g] Obtained using 5 mol% [Pd(PPh$_3$)$_4$]. [h] Yield obtained on a 8–12 mmol scale.

a 12 mmol scale in 84% yield. Previously known TMPMgCl·LiCl magnesiations of 4-functionalized pyridines such as **3c**,**d** in the presence of $\mathrm{BF_3 \cdot OEt_2}$ lead to a selective metalation at position 3.[13] However, they require low temperatures as well as stoichiometric amounts of the Lewis acid. In contrast, these 4-functionalized pyridines (**3c**,**d**) are smoothly metalated at position 3 under continuous-flow conditions using TMPLi and $\mathrm{ZnCl_2 \cdot 2\,LiCl}$ or $\mathrm{CuCN \cdot 2\,LiCl}$, leading after Negishi cross-couplings or a copper-mediated allylation to the 3,4-disubstituted pyridines (**4d–f**) in 79–90% yield (entries 4–6). Furthermore, the preparation of the nitrile (**4f**) on a 8 mmol scale in flow mode can be realized, affording the desired biaryl (**4f**) in 83% yield. Under our standard conditions, the 2,3-disubstituted pyridines (**3e**,**f**) are smoothly flow-metalated in position 4. Quenching with 3-bromocyclohexene (1.0 equiv) or 4-iodobenzotrifluoride (0.8 equiv) affords the trisubstituted pyridines (**4g**,**h**) in 85–89% yield (entries 7 and 8). Under our flow metalation conditions, 2-chloro-6-methoxypyridine (**3g**) is zincated in position 5 and Negishi cross-couplings with aryl iodides having either electron-donating or electron-withdrawing substituents afford the corresponding biaryls (**4i**,**j**) in 89–99% yield (entries 9 and 10). Interestingly, the metalation of 2-chloro-6-methoxypyridine (**3g**) with TMPLi and $\mathrm{ZnCl_2 \cdot 2\,LiCl}$ failed at −78 °C in a batch reactor, but the flow metalation of **3g** on a 10 mmol scale affords the desired product (**4j**) in 85% yield. Also, the in situ trapping metalation of the sensitive 6-nitrobenzothiazole (**3h**) failed under batch conditions at −78 °C due to side reactions caused by the nitro group. However, the in situ zincation in a flow reactor at 0 °C within 40 s and subsequent Negishi cross-coupling with 4-iodoanisole (0.8 equiv) leads to the 2,6-disubstituted benzothiazole (**4k**) in 63% yield (entry 11).

The metalation of ethyl 2-furoate (**5**) with TMPMgCl·LiCl proceeds at positions 3 and 5 in a 4:1 mixture,[14] but the use of ate bases[15] or in situ trapping[5] in batch provides the 3-metalated furan. The flow conditions lead to a practical metalation (0 °C, 40 s) of **5** in position 3, resulting in the formation of the furylzinc reagent **6** (Scheme 3). Negishi cross-coupling with 4-iodoanisole furnishes the 2,3-disubstituted furan **7** in 72% yield. Similarly, the metalation of ethyl 5-bromo-2-furoate (**8**) is completed under flow conditions in



Scheme 3. In situ trapping zincation or lanthanation of functionalized furans or thiophenes using TMPLi and $\mathrm{ZnCl_2 \cdot 2\,LiCl}$ or $\mathrm{LaCl_3 \cdot 2\,LiCl}$ in flow mode.

40 s at 0 °C leading to the zinc species **9**. Previously, such a metalation required 30 min at −50 °C.[14] Pd-catalyzed cross-coupling of the zincated furan **9** with 1-iodo-3-nitrobenzene furnishes the trisubstituted furan **10** in 86 % yield (Scheme 3).

Although all the previous flow metalations were performed by treating a mixture of the metalating substrate and $MgCl_2$, $ZnCl_2{\cdot}2\,LiCl$, or $CuCN{\cdot}2\,LiCl$ with TMPLi, other valuable salts may be used instead of the above-mentioned Mg, Zn, and Cu halides. Of special interest are lanthanum halides such as $LaCl_3{\cdot}2\,LiCl$[16] since organolanthanums display a higher reactivity towards carbonyl addition compared to Grignard reagents. Thus, we mixed 2,3-dibromothiophene (**11**) with $LaCl_3{\cdot}2\,LiCl$ (0.5 equiv) and submitted it to the flow metalation with TMPLi (0 °C, 40 s). The intermediate lanthanum derivative **12** was obtained in high conversion and reacted with diethyl ketone (1.5 equiv) providing the tertiary alcohol (**13**) in 64 % yield (Scheme 3).

In summary, we have reported that the flow metalation of arenes and heteroarenes involving an in situ trapping with various metal salts ($ZnCl_2{\cdot}2\,LiCl$, $MgCl_2$, $CuCN{\cdot}2\,LiCl$, $LaCl_3{\cdot}2\,LiCl$) proceeds under very convenient conditions (0 °C, 40 s). The resulting Mg, Zn, Cu, or La organic species are trapped with various electrophiles in high yields. In several cases, unusual kinetically controlled regioselectivities are obtained. All these flow metalations are scaled-up simply by extending the reaction time and no special optimization is required. The reaction scope of these flow in situ trapping metalations is considerably broader than that of the batch procedures. Further applications to more complex N-heterocycles and other unsaturated substrates are currently underway.

Keywords: flow chemistry · lithiation · magnesiation · metalation · zincation

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