

Continuous Flow Magnesiation of Functionalized Heterocycles and Acrylates with $\text{TMPMgCl}\cdot\text{LiCl}$ **

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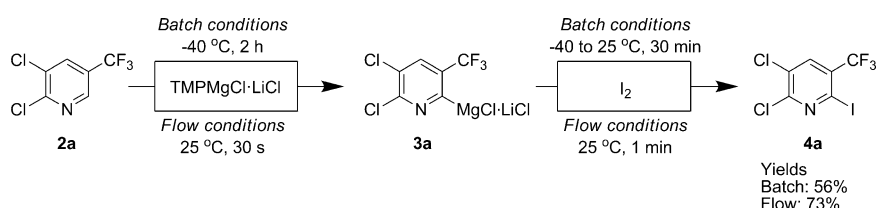
Abstract: A flow procedure for the metalation of functionalized heterocycles (pyridines, pyrimidines, thiophenes, and thiazoles) and various acrylates using the strong, non-nucleophilic base $\text{TMPMgCl}\cdot\text{LiCl}$ is reported. The flow conditions allow the magnesiations to be performed under more convenient conditions than the comparable batch reactions, which often require cryogenic temperatures and long reaction times. Moreover, the flow reactions are directly scalable without further optimization. Metalation under flow conditions also allows magnesiations that did not produce the desired products under batch conditions, such as the magnesiation of sensitive acrylic derivatives. The magnesiated species are subsequently quenched with various electrophiles, thereby introducing a broad range of functionalities.

Whereas most organometallic reactions, including directed metalations,^[1] are conducted under batch conditions in academic laboratories, there has been great interest in the performance of such reactions under flow conditions.^[2] More convenient reaction conditions usually result from flow conditions because of the improved heat transfer and faster mixing of reagents in flow reactors compared to batch reactors; furthermore, this approach may also improve selectivity issues. It has also been shown that the use of continuous flow reactors allows the safe handling of hazardous or explosive reagents.^[3] Pioneering studies by the research groups of Yoshida,^[4] Ley,^[5] Haswell,^[6] and Organ^[7] have already demonstrated that flow conditions may considerably improve the substrate scope of important organometallic reactions such as halogen–lithium exchange^[8] as well as Suzuki^[9] and Murahashi coupling reactions.^[10]

Recently, we reported the use of a highly THF-soluble base $\text{TMPMgCl}\cdot\text{LiCl}$ (**1**, TMP = 2,2,6,6-tetramethylpiperidyl), which is able to magnesiate a wide range of unsaturated polyfunctional substrates.^[11] The metalation of sensitive N-

heterocycles such as pyridines containing electron-withdrawing substituents can be accomplished successfully, although at cryogenic temperatures (as low as -78°C). The low temperatures are required to avoid dimerization through nucleophilic addition reactions to the pyridine ring. Herein, we report that the base **1** enables magnesiation of a range of sensitive N-heterocycles at unprecedentedly high reaction temperatures and short reaction times. The flow technology also allows the metalation of various acrylates that is otherwise not possible.

We first focused our studies on the magnesiation of the very electron-poor 2,3-dichloro-5-trifluoromethylpyridine (**2a**). In batch, full conversion of **2a** into the magnesiated intermediate **3a** was achieved in 2 h at -40°C , thereby furnishing, after iodolysis, the tetrasubstituted pyridine **4a** in 56% yield (Scheme 1). The use of higher reaction temperatures led to extensive decomposition of the pyridylmagnesium reagent through oligomerization. However, by using



Scheme 1. Comparison of batch and flow conditions for the metalation of 2,3-dichloro-5-(trifluoromethyl)pyridine (**2a**) in the presence of $\text{TMPMgCl}\cdot\text{LiCl}$ (**1**) and a subsequent iodolysis.

continuous flow equipment^[12] consisting of three pumps, a glass chip reactor, and a coiled reactor we were able, after some optimization, to prepare the Grignard reagent **3a** at 25°C and with a residence time of 30 s in a glass chip reactor in a yield $> 75\%$. Further quenching with iodine in the chip reactor followed by a coiled reactor (at 25°C with a residence time of 1 min) provided the desired pyridine **4a** in 73% yield.^[13] The magnesiated pyridine also reacted well with benzaldehyde, thereby leading to the functionalized pyridine **4b** in 80% yield (Table 1, entry 1). Interestingly, using acetone, a substrate prone to enolization instead of addition reactions, provided the tertiary alcohol **4c** in 63% yield (Table 1, entry 2). The more-convenient temperature range when using flow techniques is a key advantage.

The metalation of 3-chloropyridine (**2b**) with $\text{TMPMgCl}\cdot\text{LiCl}$ (**1**) under flow conditions was completed in 1 min at 25°C (versus 30 min at 0°C in batch). Quenching the reaction with various electrophiles (DMF, allyl bromide, and iodine) provided the expected pyridines **4d–f** in 66–78% yield (Table 1, entries 3–5). The intermediate 3-chloro-2-pyridyl-

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Table 1: Continuous flow metalation of functionalized pyridines and pyrimidines followed by reaction with electrophiles.

Entry	N-Hetero-cycle [metalation conditions]	Electrophile [quenching conditions]	Product, yield ^[c] [%]
1	 2a [25 °C, 30 s]	benzaldehyde [2.9 equiv, 25 °C, 1.5 min]	 4b : 80
2	2a	acetone [10 equiv, 25 °C, 2.4 min]	 4c : 63
3	 2b [25 °C, 1 min]	DMF [6 equiv, 25 °C, 5 min]	 4d : 78
4	2b	allyl bromide ^[a] [1.2 equiv, 25 °C, 8 s]	 4e : 74
5	2b	I ₂ [1.2 equiv, 25 °C, 2 min]	 4f : 66
6	2b	4-iodotoluene ^[b] [1.5 equiv, 50 °C, 27 min]	 4g : 76
7	2b	4-iodoanisole ^[b] [1.5 equiv, 50 °C, 27 min]	 4h : 95
8	 2c [25 °C, 1 min]	DMF [6 equiv, 25 °C, 2 min]	 4i : 84
9	2c	allyl bromide ^[a] [1.2 equiv, 25 °C, 8 s]	 4j : 78

Table 1: (Continued)

Entry	N-Hetero-cycle [metalation conditions]	Electrophile [quenching conditions]	Product, yield ^[c] [%]
10	2c	I ₂ [1.2 equiv, 25 °C, 2 min]	 4k : 71
11	 2d [25 °C, 1 min]	4-chlorobenzaldehyde [1.7 equiv, 25 °C, 6 s]	 4l : 62
12	 2e [0 °C, 1 min]	DMF [6.1 equiv, 25 °C, 10 s]	 4m : 73
13	 2f [25 °C, 2 min]	4-chlorobenzaldehyde [1.7 equiv, 25 °C, 11 s]	 4n : 66
14	 2g [0 °C, 20 min]	DMF [6.0 equiv, 25 °C, 30 s]	 4o : 78
15	2g	benzaldehyde [2.0 equiv, 25 °C, 2.7 min]	 4p : 87

[a] CuCN·2LiCl (0.03 equiv) was added to the electrophile solution.

[b] [Pd(dba)₂] (0.01 equiv), P(*o*-furyl)₃ (0.02 equiv), and ZnCl₂ (1.1 equiv) were added to the electrophile solution. [c] Yield of isolated product.

magnesium chloride (**3b**) could also be mixed with a stream of THF containing an aryl iodide (1.5 equiv),^[14] ZnCl₂ (1.1 equiv), [Pd(dba)₂] (0.01 equiv), and P(*o*-furyl)₃ (0.02 equiv)^[15] to allow the Negishi cross-coupling, when being pumped through a heated coiled reactor (50 °C, 27 min). The use of 4-iodotoluene or 4-iodoanisole as electrophiles under these conditions resulted in the 2-arylated pyridines **4g** and **4h** being isolated in yields of 76 and 95 %, respectively (Table 1, entries 6 and 7). Alcázar and co-workers recently provided the first example of Negishi cross-coupling reactions under flow conditions using commercially available organozinc reagents.^[16] Complementary to this study, we demonstrate the first *in situ* formation of zinc species by a multistep sequence involving deprotonation, magnesiation, and transmetalation to zinc followed by a Negishi cross-coupling, all in one continuous flow.

Similarly, the magnesiation of the 3-bromopyridine (**2c**) was performed under the same flow conditions (1 min, 25 °C). Subsequent quenching with neat DMF furnished the formylated pyridine **4i** in 84 % yield (Table 1, entry 8). This yield

was obtained on a 1.7 mmol scale; however, it did not require any further optimization to scale-up the reaction to 45 mmol, which provided **4i** in 79 % yield. Under batch conditions, the scale-up of this metalation (> 10 mmol) proved to be complicated, with oligomerization reactions occurring even for this relatively stable pyridine.

Mixing the magnesiated intermediate 3-bromo-2-pyridyl-magnesium chloride (**3c**) with a stream of a solution of allyl bromide (1.2 equiv) in THF in the presence of CuCN·2LiCl (0.03 equiv) instead of DMF furnished the allylated pyridine **4j** in 78 % yield (Table 1, entry 9). Similarly, the iodolysis of **3c** provided the sensitive 2-iodo-3-bromopyridine **4k** in 71 % yield (Table 1, entry 10).

Various dihalopyridines such as **2d–f**, which have previously been metalated by TMPMgCl·LiCl (**1**) in batch at –25 °C or –40 °C, were regioselectively magnesiated under flow conditions within 1 or 2 min at 0 or 25 °C to afford the 6-magnesiated pyridines, which were subsequently treated with DMF or 4-chlorobenzaldehyde to provide the trisubstituted pyridines **4l–n** in 62–73 % yield (Table 1, entries 11–13). 2,4-Dimethoxypyrimidine (**2g**) was regioselectively metalated in position 6 under flow conditions at 0 °C in 20 min to furnish the intermediate magnesium reagent, which was quenched with either DMF or benzaldehyde to provide the formylated product **4o** or the alcohol **4p** in yields of 78 and 87 %, respectively (Table 1, entries 14 and 15).

The extension of our procedure to five-membered heterocycles was readily achieved. Thus, the magnesiation of 2-chlorothiophene (**5a**), which in batch required a reaction time of 1.5 h at 0 °C, was complete under flow conditions in 1 min at 25 °C and proceeded, as expected, at position 5. Quenching the reaction with DMF (25 °C, 10 s) afforded the 2,5-disubstituted thiophene **6a** in 79 % yield (Table 2, entry 1). Treating the magnesiated intermediate with a solution of 4-iodoanisole (1.5 equiv), ZnCl₂ (1.1 equiv), [Pd(dba)₃] (0.01 equiv), and P(*o*-furyl)₃ (0.02 equiv) under flow conditions (50 °C, 27 min) afforded the 5-arylated product **6b** in 87 % yield (Table 2, entry 2).

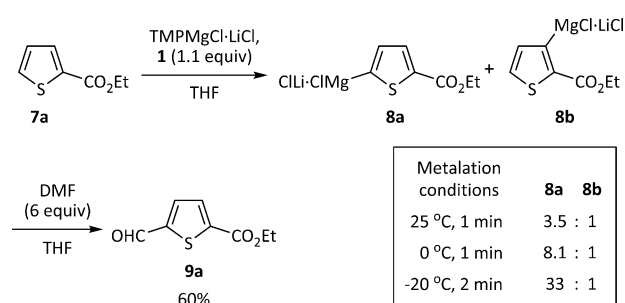
The magnesiation of 2,5-dichlorothiophene **5b** was complete after 30 min at 25 °C in batch, but was achieved under flow conditions at 25 °C in 3 min. Quenching the intermediate with either DMF or 4-chlorobenzaldehyde afforded the products **6c** or **6d** in yields of 72 and 88 %, respectively (Table 2, entries 3 and 4). 2-Bromothiophene (**5c**) was metalated in the 5-position at 25 °C in 1 min under flow conditions (versus 30 min at –40 °C under batch conditions). Quenching with allyl bromide in the presence of a catalytic amount of CuCN·2LiCl led to **6e** in 90 % yield (Table 2, entry 5).

Magnesiating thiophene-2-carboxylic acid ethyl ester (**7a**) under flow conditions at 25 °C for 1 min gave a mixture of two regioisomeric intermediates **8a,b** in a ratio of 3.5:1, with the most acidic C-5 position next to the electron-withdrawing sulfur atom being predominantly deprotonated and favoring the thermodynamically more stable intermediate **8a** (Scheme 2).^[17] Decreasing the temperature to 0 °C improved this ratio to 8.1:1, and further cooling to –20 °C combined with an extension of the reaction time to 2 min to maintain high conversion led to a significantly improved ratio of 33:1. Quenching with DMF gave the formylated product **9a** in 60 %

Table 2: Continuous flow metalation of functionalized five-membered heterocycles followed by reaction with electrophiles.

Entry	Heterocycle [metalation conditions]	Electrophile [quenching conditions]	Product, yield ^[c] [%]
1	 5a [25 °C, 1 min]	DMF [6.1 equiv, 25 °C, 10 s]	 6a : 79
2	5a	4-iodoanisole ^[a] [1.5 equiv, 50 °C, 27 min]	 6b : 87
3	 5b [25 °C, 3 min]	DMF [6 equiv, 25 °C, 13 s]	 6c : 72
4	5b	4-chlorobenzaldehyde [1.7 equiv, 25 °C, 6 s]	 6d : 88
5	 5c [25 °C, 1 min]	allyl bromide ^[b] [1.0 equiv, 25 °C, 8 s]	 6e : 90

[a] [Pd(dba)₃] (0.01 equiv), P(*o*-furyl)₃ (0.02 equiv), and ZnCl₂ (1.1 equiv) were added to the electrophile solution. [b] CuCN·2LiCl (0.03 equiv) was added to the electrophile solution. [c] Yield of isolated product.

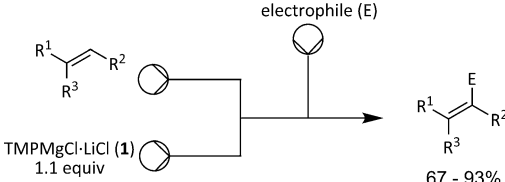
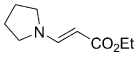
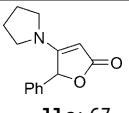
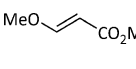
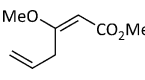
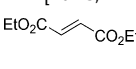
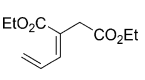


Scheme 2. Temperature-controlled improvement of regioselectivity under flow conditions with TMPMgCl·LiCl (**1**).

yield. This example demonstrates that the fine-tuning of the metalation with TMPMgCl·LiCl (**1**) can dramatically improve the regioselectivity of the magnesiation.

We then turned our attention to the flow metalation of functionalized acrylates, which are notoriously difficult to

Table 3: Continuous flow metalation of functionalized olefins followed by reaction with electrophiles.

			
Entry	Olefin [metalation conditions]	Electrophile [quenching conditions]	Product, yield ^[b] [%]
1	 10a [25 °C, 10 min]	benzaldehyde [2.0 equiv, 25 °C, 4.7 min]	 11a : 67
2	 10b [40 °C, 1 min]	allyl bromide ^[a] [1.2 equiv, 25 °C, 2.7 min]	 11b : 91
3	 10c [−60 °C, 1 min]	allyl bromide ^[a] [1.2 equiv, −60 °C, 1.3 min]	 11c : 93

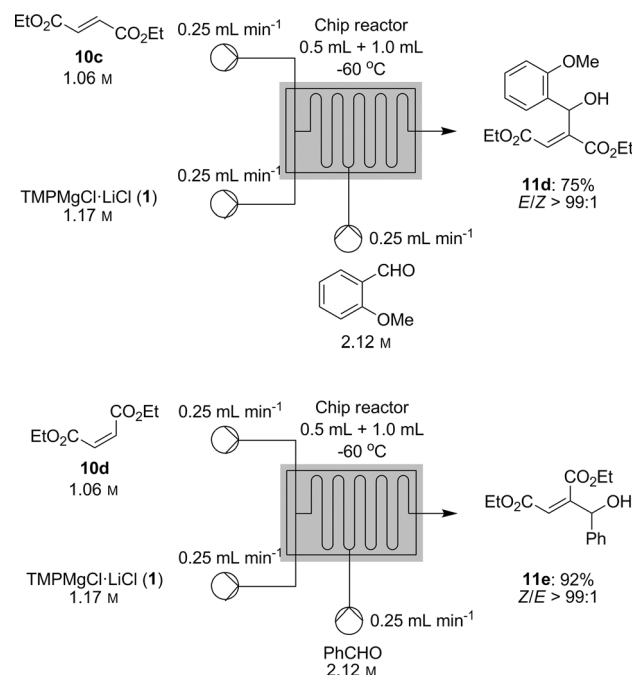
[a] CuCN·2LiCl (0.03 equiv) was added to the electrophile solution.

[b] Yield of isolated product.

metalate because of anionic polymerization. Thus, ethyl (*E*)-3-(pyrrolidin-1-yl)acrylate (**10a**) was magnesiated by TMPMgCl·LiCl (**1**; 1.1 equiv) at the 3-position in 10 min at 25 °C, which led to lactone **11a** in 67 % yield after quenching with benzaldehyde and spontaneous cyclization (Table 3, entry 1). In the case of methyl (*E*)-3-methoxyacrylate (**10b**), the temperature of the metalation could be increased to 40 °C, thereby shortening the reaction time to 1 min. Subsequent allylation furnished the product **11b** in 91 % yield (Table 3, entry 2). Remarkably, no polymerization or oligomerization was detected under these drastic conditions. The magnesiation of diethyl fumarate (**10c**) and diethyl maleate (**10d**) was performed at low temperatures to avoid decomposition of the unstable magnesium intermediate. By cooling a chip reactor to −60 °C, full metalation of **10c** was observed after a residence time of 1 min. The magnesiation of the fumarate **10c** and subsequent allylation led to a selective isomerization that produced the 1,3-dienic diester **11c** as a single stereoisomer (*Z/E* > 99:1) in 93 % yield (Table 3, entry 3).

Interestingly, the metalation of **10c,d** proceeded under our flow conditions with complete retention of configuration, thereby producing, after addition to aromatic aldehydes, the allylic alcohols **11d** and **11e** as single *E* and *Z* isomers in yields of 75 and 92 %, respectively (Scheme 3). Notably, no lactone formation was observed for **11d** because of the low temperature used. Metalation of **10c,d** was also attempted under batch conditions (−60 °C, 1 min), however only polymerization was observed.

In summary, we have shown that the continuous flow metalation of a range of substituted heteroaromatic compounds and highly sensitive functionalized acrylates can be



Scheme 3. Magnesiation of diethyl fumarate (**10c**) and diethyl maleate (**10d**) and subsequent quenching with aromatic aldehydes using TMPMgCl·LiCl (**1**).

readily performed using the commercially available base TMPMgCl·LiCl (**1**). The reactions were performed under more convenient conditions (higher temperatures and shorter reaction times) than comparable batch processes. Very sensitive acrylic derivatives could be stereoselectively metalated and quenched with an aldehyde or an allylic bromide. Furthermore, the flow synthesis was demonstrated to be readily scalable up to 45 mmol without further optimization, with very similar yields obtained. Extensions of this method to more complex systems are currently underway.

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