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High-Temperature Continuous-Flow Zincations of Functionalized Arenes and Heteroarenes Using $(Cy_2N)_2Zn{\cdot}2LiCl$

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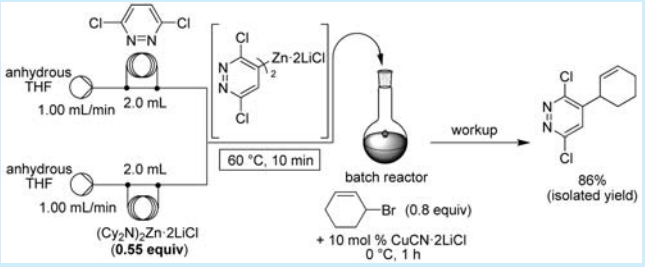
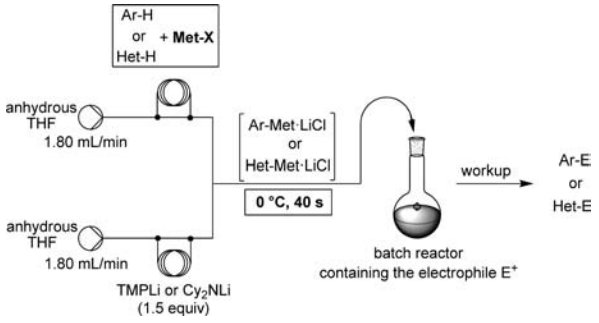
Supporting Information

ABSTRACT: The treatment of sensitive arenes and heteroarenes with the zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ (0.55 equiv), prepared in quantitative yield by the reaction of Cy_2NLi with $ZnCl_2$, leads under flow conditions to a fast zincation within 10 min at temperatures between 25 and 100 °C. The resulting organozinc reagents can be trapped with various organic halides (allylic bromides, aryl iodides) in high yields. Moreover, complementary metalation regioselectivities can be obtained for several substituted pyridines compared to commonly used LiCl-activated TMP-zinc (TMP = 2,2,6,6-tetramethylpiperidyl) and -magnesium bases.

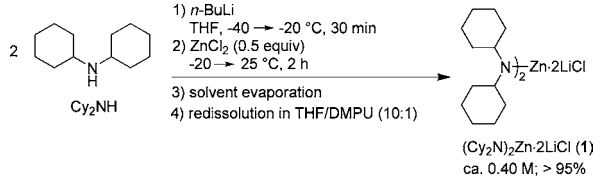


The directed metalation of unsaturated substrates with lithium, magnesium, or zinc bases allows the preparation of polyfunctional aryl- and heteroaryl organometallics, which are key intermediates in organic synthesis.[1,2] Therefore, various ate bases[3] or, more recently, LiCl-activated amides[4] have been developed for their preparation. Furthermore, lithiation[5] in a continuous flow reactor[6] has led to significant improvements and expanded the scope of potential applications. Recently, we have reported the in situ trapping metalation of various aromatic and heteroaromatic substrates (Ar-H, Het-H) in the presence of metal salts (Met-X) such as $ZnCl_2{\cdot}2LiCl$, $MgCl_2$, $CuCN{\cdot}2LiCl$, or $LaCl_3{\cdot}2LiCl$ using either TMPLi or Cy_2NLi.[7] Running the reactions in a continuous flow system allows the completion of these in situ trapping metalations within 40 s at 0 °C due to the fast mixing of the reaction components and the prevention of hot-spot formation (Scheme 1).

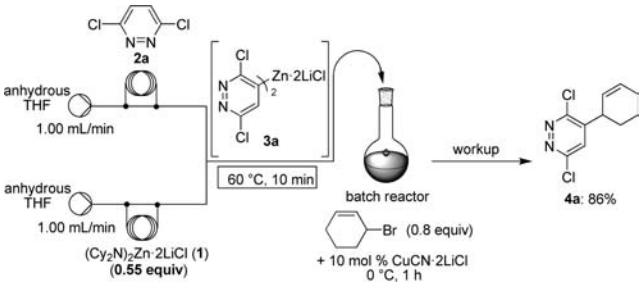
Scheme 1. Continuous Flow Setup for in Situ Trapping Metalations Using TMPLi or Cy_2NLi in the Presence of Metal Salts (Met-X = $ZnCl_2{\cdot}2LiCl$, $MgCl_2$, $CuCN{\cdot}2LiCl$, $LaCl_3{\cdot}2LiCl$) and Subsequent Batch Quenching with Electrophiles (E^+)



Scheme 2. Preparation of the Zinc Bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ (1) in THF/DMPU (10:1)



Scheme 3. Continuous Flow Zincation of 3,6-Dichloropyridazine (2a) Using $(Cy_2N)_2Zn{\cdot}2LiCl$ (1) and Subsequent Cu-Catalyzed Allylation with 3-Bromocyclohexene in a Batch Reactor



Although this method permits the immediate transmetalation to more stable organometallic intermediates, the use of powerful lithium bases still precludes the successful chemo- and regioselective functionalization of a range of sensitive substrates. Attempts to perform metalations of such aromatics with less reactive, readily available, and economic magnesium or zinc

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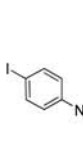
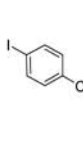
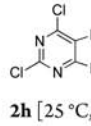
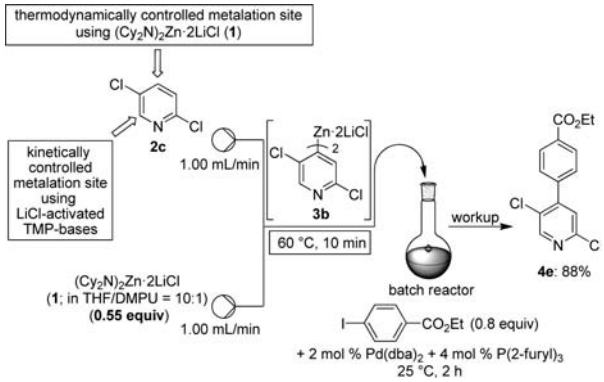
Table 1. Continuous Flow Zincations of Heterocycles 2 Followed by Reaction with Electrophiles Leading to Products of Type 4

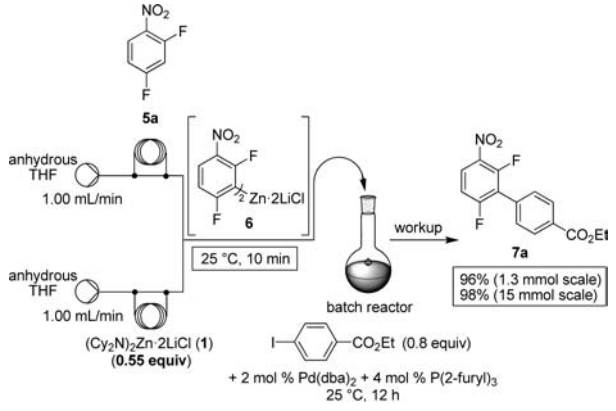
entry	substrate [metalation conditions]	electrophile	product[a]
1	**2a** [60 °C, 10 min]	R = CO_2Et	**4b**: 72%[b]
2	**2a**	R = CF_3	**4c**: 64%[b]
3	**2b** [50 °C, 10 min]		**4d**: 92%[c]
4	**2c** [60 °C, 10 min]		**4f**: 78%[b]
5	**2d** [60 °C, 10 min]		**4g**: 60%[b]
6	**2e** [60 °C, 10 min]		**4h**: 87%[c]
7	**2e**		**4i**: 74%[c]
8	**2f** [60 °C, 10 min]		**4j**: 97%[c]
9	**2f**		**4k**: 64%[c]
10	**2g** [60 °C, 10 min]		**4l**: 66%[b]
11	**2g**	R = *m*-NO_2	**4m**: 62%[b]
12	**2h** [25 °C, 10 min]		**4n**: 78%[c]
13	**2h**	R = *p*-OMe	**4o**: 98%[b]
14	**2h**	R = *p*-NO_2	**4p**: 61%[b]
15	**2i** [80 °C, 10 min]	R = *m*-OMe	**4q**: 70%[b]
16	**2i**	R = *p*-CF_3	**4r**: 64%[b]
17	**2j** [100 °C, 10 min]	R = *p*-CO_2Et	**4s**: 68%[b]
18	**2j**	R = *m*-OMe	**4t**: 64%[b]

[a]Yield of isolated product. [b]Obtained using 2 mol % of [$Pd(dba)_2$] and 4 mol % of P(2-furyl)$_3$. [c]Obtained by a Cu-catalyzed allylation.

Scheme 4. Switching Metalation Regioselectivity for the Continuous Flow Zincation of 2,5-Dichloropyridine (2c) Using $(Cy_2N)_2Zn{\cdot}2LiCl$ (1) and Subsequent Pd-Catalyzed Negishi Cross-Coupling with Ethyl 4-Iodobenzoate in a Batch Reactor



Scheme 5. Continuous Flow Zincation of 2,4-Difluoronitrobenzene (5a) Using $(Cy_2N)_2Zn{\cdot}2LiCl$ (1) and Subsequent Pd-Catalyzed Negishi Cross-Coupling with Ethyl 4-Iodobenzoate on a 1.3 and 15 mmol Scale



amides R_2NMet (R = *i*-Pr, Cy (cyclohexyl), TMS (trimethylsilyl); Met = MgHal, ZnHal) were disappointing either because of insufficient reactivity or extensive side reactions. However, these limitations can be overcome by using the new zinc bis-amide

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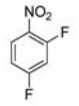
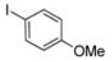
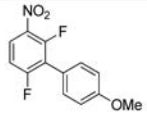
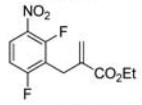
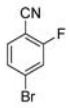
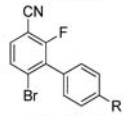
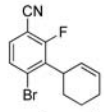
Table 2. Continuous Flow Zincations of Arenes 5 Followed by Reaction with Electrophiles Leading to Products of Type 7

entry	substrate [metalation conditions]	electrophile	product[a]
1	 **5a** [25 °C, 10 min]		 **7b**: 76%[b]
2	**5a**		 **7c**: 71%[d]
3	 **5b** [60 °C, 10 min]	 R = OMe	 **7d**: 85%[c]
4	**5b**	R = CO_2Et	**7e**: 77%[c]
5	 **5b**		 **7f**: 79%[d]

[a]Yield of isolated product. [b]Obtained using 2 mol % of $[Pd(dba)_2]$ and 4 mol % of P(2-furyl)$_3$. [c]Obtained using 5 mol % of $[Pd(PPh_3)_4]$. [d]Obtained by a Cu-catalyzed allylation.

$(Cy_2N)_2Zn{\cdot}2LiCl$ (**1**) made from Cy_2NLi and $ZnCl_2$ in >95% yield (Scheme 2).

Remarkably, by redissolving **1** after solvent evaporation in the binary cosolvent system THF/DMPU (10:1; DMPU = 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one), a higher solubility and an increased reactivity is achieved.[8] Furthermore, this base can be stored for, at least, several weeks at 25 °C without any decomposition under argon. The use of Cy_2NH is particularly desirable, since its price is only ca. 1% of the commonly utilized TMPH (TMPH = 2,2,6,6-tetramethylpiperidine).[9] The zinc bis-amide **1** has, to the best of our knowledge, not yet been used extensively for the metalation of functionalized unsaturated substrates.[10] Herein, we report the selective and highly efficient continuous flow zincation of various functionalized arenes and heteroarenes with $(Cy_2N)_2Zn{\cdot}2LiCl$ (**1**, in THF/DMPU = 10:1), resulting in the preparation of polyfunctional zinc reagents for organic synthesis. In a first experiment, we investigated the flow metalation[11] of 3,6-dichloropyridazine (**2a**), which cannot be performed via an in situ trapping zincation with TMPLi or Cy_2NLi in the presence of $ZnCl_2{\cdot}2LiCl$.[7] However, the zincation of **2a** proceeded smoothly within 10 min at 60 °C using **1** (0.55 equiv). Subsequent batch quenching of the organozinc intermediate **3a** with 3-bromocyclohexene (0.8 equiv), in the presence of 10 mol % of CuCN·2LiCl, afforded the expected product (**4a**) in 86% yield (Scheme 3). Furthermore, Negishi cross-coupling reactions[12] of **3a** with aryl iodides (0.8 equiv) and a standard Pd-catalyst system (2 mol % $Pd(dba)_2$; dba = dibenzylideneacetone and 4 mol % P(2-furyl)$_3$)[13] led to the corresponding biaryls (**4b,c**) in 64−72% yield (Table 1, entries 1 and 2). Similarly, the flow zincation of 2,4,6-trichloropyrimidine (**2b**) occurred in 98% conversion at 50 °C within 10 min. Subsequent quenching with allyl bromide (0.8 equiv) furnished the fully functionalized pyrimidine (**4d**) in 92% yield (entry 3).

Remarkable regioselectivities were obtained when $(Cy_2N)_2Zn{\cdot}2LiCl$ (**1**) was used for such flow zincations. The metalation of substituted pyridines like **2c−f** with LiCl-activated TMP bases such as TMPMgCl·LiCl or TMPZnCl·LiCl preferentially proceeded under kinetic reaction conditions at position 2 or position 6, respectively, due to a distinct substrate−base interaction via a metal−nitrogen coordination.[4,14,15] However, thermodynamically controlled zincations of **2c−f** with $(Cy_2N)_2Zn{\cdot}2LiCl$ (**1**; 0.55 equiv) in a flow reactor (60 °C, 10 min) proceeded regioselectively at position 4 (Scheme 4). Quenching of the corresponding organozinc intermediates with various allylic bromides (0.8 equiv) or aryl iodides (0.8 equiv) furnished the expected pyridines (**4e−k**) in 60−97% yield (entries 4−9). 2,3-Dichloropyridine (**2g**) was also zincated at position 4 within 10 min at 60 °C. Negishi cross-couplings with ethyl 4-iodobenzoate (0.8 equiv) or 3-iodonitrobenzene (0.8 equiv) gave the trisubstituted pyridines (**4l,m**) in 62−66% yield (entries 10 and 11). The MOM-protected (MOM = methoxymethyl) purine (**2h**) was smoothly flow-metalated (25 °C, 10 min) with the zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ (**1**, 0.55 equiv). Subsequent Cu-catalyzed allylation or Pd-catalyzed Negishi cross-coupling reactions led to the fully functionalized purines (**4n−p**) in 61−98% yield (entries 12−14). Moreover, conducting these zincations at elevated temperatures (between 60−100 °C) in a continuous flow apparatus allowed the convenient and safe handling of such unconventional reaction conditions. Thus, 2-furonitrile (**2i**) was metalated with **1** (0.55 equiv) at 80 °C within 10 min at position 5. Negishi cross-couplings with aryl iodides (0.8 equiv) having either electron-withdrawing or electron-donating substituents provided the corresponding 2,5-disubstituted furans (**4q,r**) in 64−70% yield (entries 15 and 16). $(Cy_2N)_2Zn{\cdot}2LiCl$ (**1**) can be used for high-temperature metalations up to 100 °C, and ethyl 2-thiophenecarboxylate (**2j**) was zincated in 90% conversion within 10 min at 100 °C. Quenching with aryl iodides (0.8 equiv) in the presence of a Pd catalyst furnished the expected 2,5-disubstituted thiophenes (**4s,t**) in 64−68% yield (entries 17 and 18). The efficient and economic functionalization of sensitive substrates with the zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ (**1**) is not limited to heteroarenes. In fact, **1** was used for the smooth flow zincation (25 °C, 10 min) of 2,4-difluoronitrobenzene (**5a**), which is notoriously difficult to metalate because of the nitro group (Scheme 5).[16] Batch quenching of the zinc intermediate **6** with ethyl 4-iodobenzoate (0.8 equiv) led to formation of the biphenyl (**7a**) in 96% yield on a 1.3 mmol scale. Furthermore, this reaction was readily scaled up to 15 mmol without further optimization just by running it for a longer time (55 min) to afford **7a** in 98% yield.

Further trapping of **6** with 4-iodoanisole (0.8 equiv) and a Pd catalyst or ethyl 2-(bromomethyl)acrylate (0.8 equiv) in the presence of 10 mol % of CuCN·2LiCl provided the corresponding products (**7b,c**) in 71−76% yield (Table 2, entries 1 and 2). The sensitive nitrile (**5b**) was efficiently zincated by **1** (0.55 equiv) within 10 min at 60 °C. Subsequent quenching via Cu-catalyzed allylation or Pd-catalyzed Negishi cross-coupling afforded the expected bicyclic products (**7d−f**) in 77−85% yield (entries 3−5). Alternative metalations of **5b** using in situ trapping zincations (TMPLi/$ZnCl_2{\cdot}2LiCl$; $Cy_2NLi/ZnCl_2{\cdot}2LiCl$) or a magnesiation with TMPMgCl·LiCl followed by a transmetalation with $ZnCl_2$ led to decomposition.

In summary, we have reported the use of the economic zinc bis-amide $(Cy_2N)_2Zn{\cdot}2LiCl$ (**1**; in THF/DMPU = 10:1) for fast (10 min) and highly efficient (0.55 equiv base) flow zincations of sensitive arenes and heteroarenes. Metalations between 60 and

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100 °C, which are problematic under batch conditions, can be conveniently realized using flow methodology, and a simple scale-up of the zincations without further optimization can be readily achieved. Moreover, complementary metalation regioselectivities were obtained for several substituted pyridines, compared to commonly used LiCl-activated TMP-zinc and -magnesium bases. Further applications and extensions of this method are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00408.

Detailed experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(9) The price of the amine TMPH from Sigma-Aldrich is ca. $630/mol for the largest package. The price of the amine Cy_2NH from Sigma-Aldrich is ca. $6.40/mol for the largest package.

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