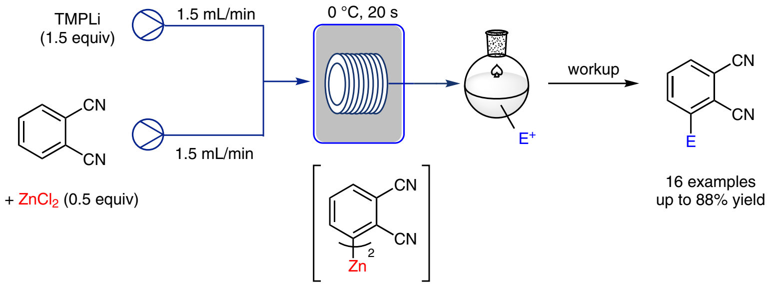
Selective Zincation of 1,2-Dicyanobenzene and Related Benzonitriles in Continuous Flow Using In Situ Trapping Metalations

Marthe Ketels ‡
Dorothée S. Ziegler‡
Paul Knochel *

Department of Chemistry, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, Haus F, 81377 München, Germany
paul.knochel@cup.uni-muenchen.de
‡ These authors contributed equally.

Dedicated to Professor Victor Snieckus on the occasion of his 80th birthday and in recognition of his pioneer contributions in organometallic chemistry



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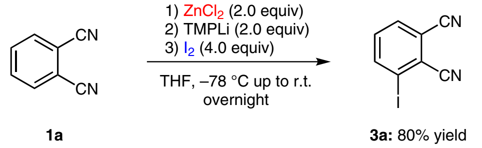
Abstract A mild and general metalation procedure for the functionalization of 1,2-dicyanobenzene and related polyfunctionalized benzonitriles using a commercially available continuous flow setup is reported. The addition of TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl) to a mixture of an aromatic substrate with a metallic salt such as ZnCl$_2$ under appropriate conditions (0 °C, 20 s) leads to fast in situ lithiation of the arene followed by transmetalation with ZnCl$_2$ to afford the corresponding functionalized arylzinc compound that were trapped with various electrophiles in high yields. The reaction scope of these in situ trapping metalations in flow is broader and needs less equivalents of the base and the metal salt than the corresponding batch procedure.

Key words continuous flow, in situ trapping metalation, TMPLi, ZnCl$_2$, 1,2-dicyanobenzene

The metalation of polyfunctionalized aromatics and heterocycles pioneered among others by Victor Snieckus[1] is a key reaction of the expedited functionalization of these unsaturated building blocks for pharmaceutical, agrochemical and material science applications.[2] Of special importance is the functionalization of 1,2-dicyanobenzenes since derivatives of such scaffolds may be used for heterocyclic syntheses and for the elaboration of phthalocyanines with potential applications as solar cells.[3]

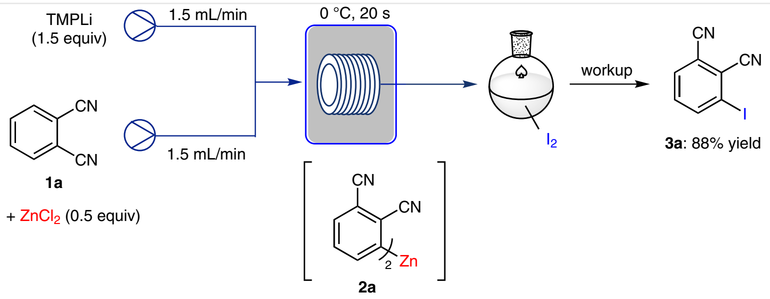
Recently, we have shown that the performance of the so called in situ trapping metalations[4] for polyfunctionalized aromatics can be advantageous since the produced lithium intermediate is immediately trapped with metallic salt such as $MgCl_2\cdot 2LiCl$, $ZnCl_2$, $CuCN\cdot 2LiCl$ or $LaCl_3\cdot 2LiCl$.[5] Preliminary experiments with 1,2-dicyanobenzene (**1a**) have shown that the addition of TMPLi[6] (THF, 1.2 equiv) to a mixture of **1a** with the metal salt ZnCl$_2$ at –78 °C first leads to the lithiation of the arene followed by transmetalation with the metal salt to afford an *ortho*-zincated intermediate and provides after iodolysis the desired 3-iodo derivative (**3a**) in 80% yield. Further experiments showed that the generation of the lithium species and in situ trapping with ZnCl$_2$ requires a temperature of –78 °C in batch and cannot be scaled-up without further optimization (Scheme 1).



Scheme 1 Batch conditions for the functionalization of 1,2-dicyanobenzene (**1a**)

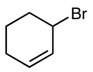
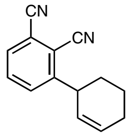
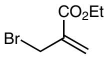
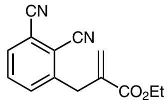
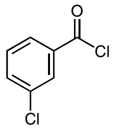
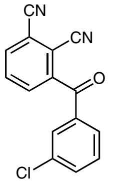
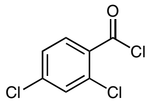
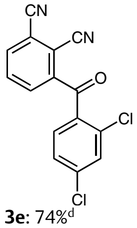
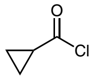
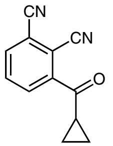
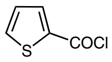
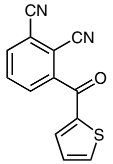
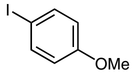
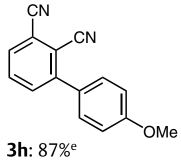
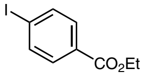
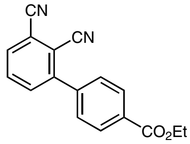
We reported that in situ trapping metalations can be performed at mild conditions using a continuous flow set up.[7] In this procedure, the substrate, here 1,2-dicyanobenzene (**1a**) is mixed with ZnCl$_2$ (0.5 equiv) in THF and this solution is mixed in continuous flow with a THF solution of TMPLi (ca. 0.6 M). Such a mixing is done at 0 °C (and not cryogenic temperatures like for the batch procedure) and requires only 20 seconds reaction time.

Herein, we wish to report the successful use of this setup to prepare a range of functionalized 1,2-dicyanobenzenes of type **3** as well as some related polyfunctionalized benzonitriles of type **4**. Thus, the treatment of a mixture of 1,2-dicyanobenzene (**1a**; 1.0 equiv) and ZnCl$_2$ (0.5 equiv) with TMPLi (1.5 equiv) under flow conditions[8] (1.5 mL/min, 0 °C, 20 s) led to a regioselective lithiation of **1a**, giving after transmetalation with ZnCl$_2$ the corresponding diarylzinc reagent (**2a**), which was quenched with iodine, providing 3-iodo-1,2-dicyanobenzene (**3a**) in 88% yield[9] (Scheme 2).



Scheme 2 Continuous flow setup for in situ trapping metalations of 1,2-dicyanobenzene (**1a**) using TMPLi in the presence of the metal salt $ZnCl_2$

Table 1 Functionalized 1,2-Dicyanobenzenes of Type **3** Obtained via an In Situ Trapping Procedure in Continuous Flow Using $ZnCl_2$ and Subsequent Trapping with an Electrophile (E$^+$) in Batch

Entry	Electrophile (E$^+$)[a]	Product: yield[b]
1		 **3b**: 81%[c]
2		 **3c**: 76%[c]
3		 **3d**: 57%[d]
4		 **3e**: 74%[d]
5		 **3f**: 78%[d]
6		 **3g**: 76%[d]
7		 **3h**: 87%[e]
8		 **3i**: 82%[e]

[a] Amount of E$^+$ used was 1.1 equiv.
[b] Yield of isolated, analytically pure product.
[c] Obtained in the presence of 10 mol% CuCN·2LiCl at 0 °C in 2 h.
[d] Obtained after transmetalation with 1.1 equiv of CuCN·2LiCl at 0 °C in 2 h.
[e] Obtained using 2 mol% of $Pd(OAc)_2$ and 4 mol% of SPhos at r.t., overnight.

This in situ generation of a zincated dicyanobenzene such as **2a** can be used to perform reactions with various classes of organic electrophiles. Thus, collecting the flow stream in a flask containing an allylic bromide such as 2-bromocyclohexene or ethyl 2-(bromomethyl)acrylate and 10 mol% CuCN·2LiCl[10] on a ca. half mmol scale gives the allylated products **3b** and **3c** in 81% and 76% yield, respectively (entries 1 and 2 of Table 1). A scale-up of this procedure is easily possible and is described below.

Similarly, copper-mediated acylations with 3-chlorobenzoyl chloride or 3,5-dichlorobenzoyl chloride afforded the functionalized 1,2-dicyanobenzene derivatives (**3d** and **3e**) in 57% and 74% yield, respectively (Table 1, entries 3 and 4). The ketones (**3f** and **3g**) were obtained in 76–78% yield when the zincated intermediate **2a** was transmetalated to the corresponding copper derivative using CuCN·2LiCl[10] and acylated with cyclopropanecarbonyl chloride or thiophene-2-carbonyl chloride (Table 1, entries 5 and 6). The zinc intermediate **2a** underwent various Negishi cross-couplings[11] with 4-iodoanisole, ethyl 4-iodobenzoate or 4-iodo-1,2-dimethylbenzene using 2 mol% $Pd(OAc)_2$ and 4 mol% SPhos,[12] leading to the desired products **3h** and **3i** in 82 and 87% yield (Table 1, entries 7 and 8).

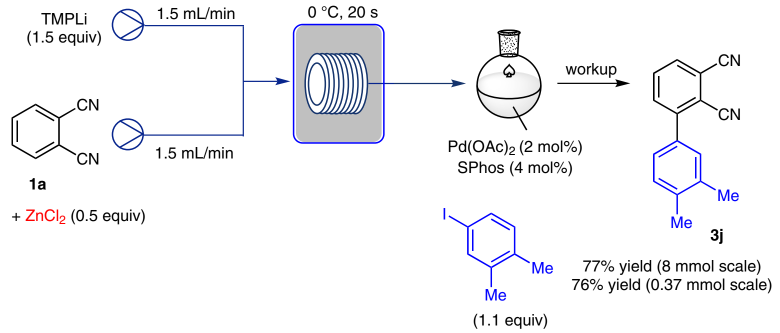
The scale-up of these in situ trapping metalations in flow is readily performed and does not require further optimization. It is realized simply by extending the collection time of the metalated species in batch. Thus, the flow metalation of 1,2-dicyanobenzene (**1a**) was performed on a 8-mmol scale for the Negishi cross-coupling[11] with 2-iodo-1,2-dimethylbenzene (2 mol% $Pd(OAc)_2$, 4 mol% SPhos;[12] Scheme 3) leading to the biphenyl (**3j**) in 77% yield (Scheme 3). In addition a 10-mmol scale-up for the reaction of the zincated 1,2-dicyanobenzene with iodine led to **3a** in 87% yield.

Furthermore, the in situ trapping metalation procedure was extended for the zincation of 1,3-dicyanobenzene (**1b**) and 3-methoxybenzonitrile (**1c**; Table 2). Thus, the treatment of a mixture of 1,3-dicyanobenzene (**1b**; 1.0 equiv) and $ZnCl_2$ (0.5 equiv) with TMPLi (1.5 equiv) under flow conditions (2.5 mL/min, –78 °C, 45 s) led to a regioselective lithiation of **1b** in position 2, giving after transmetalation with $ZnCl_2$ the corresponding diarylzinc reagent (**2b**), which was quenched with iodine, providing the desired product **4a** in 79% yield (entry 1 of Table 2). A copper-catalyzed allylation with 3-bromocyclohex-1-ene provided the 2-allylated 1,3-dicyanobenzene (**4b**) in 88% yield (Table 2, entry 2). Pd-catalyzed Negishi cross-coupling[11] (2 mol% $Pd(OAc)_2$ and 4 mol% SPhos[12]) with 4-iodoanisole furnished the arylated 1,3-dicyanobenzene (**4c**) in 70% yield (Table 2, entry 3).

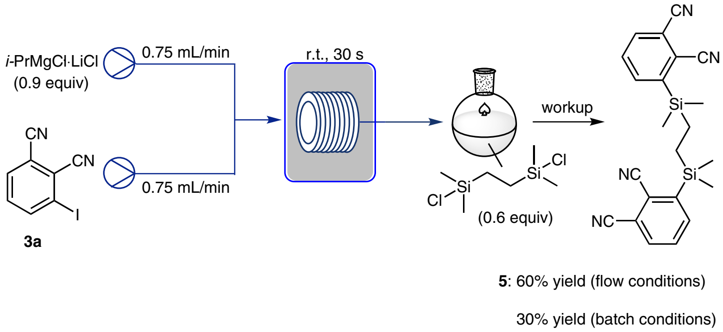
Similiary, 3-methoxybenzonitrile (**1c**) was regioselectively lithiated and transmetalated to the zinc species (**2c**) in continuous flow (2.0 mL/min, 0 °C, 45 s), and iodinated, allylated and cross-coupled, leading to the expected products **4d–f** in 58–82% yield (Table 2, entries 4–6).[13]

The iodinated dicyanobenzene (**3a**) can be further modified to extend the variety of precursors for phthalocyanines. Thus, an iodine–magnesium exchange reaction (Scheme 4) in continuous flow (0.75 mL/min, r.t., 20 s) was realized by the reaction of **3a** with *i*-PrMgCl·LiCl (0.9 equiv).[14] Subsequent quenching with 1,2-bis(chlorodimethylsilyl)ethane (0.6 equiv) produces the desired product **5**, which could act as an interesting precursor for the synthesis of bridged phthalocyanines,[15] in 60% yield while in batch only 30% was isolated (Scheme 4).

In summary, we have developed a general methodology for the functionalization of 1,2-dicyanobenzene and related polyfunctionalized benzonitriles using a commercially available continuous flow setup. The flow metalations of the lithiated substrates involving an in situ trapping with the metallic salt $ZnCl_2$ proceeded under convenient conditions (0 °C, 20 s). The resulting Zn organometallic species

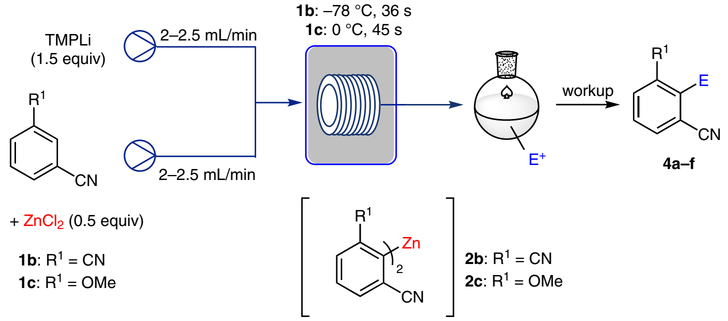


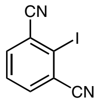
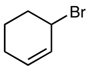
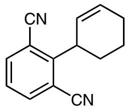
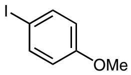
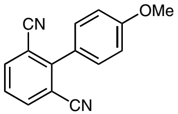
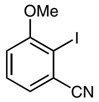
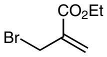
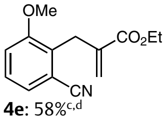
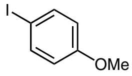
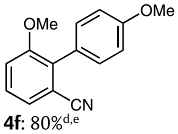
Scheme 3 An 8-mmol scale-up for the in situ trapping metalation of 1,2-dicyanobenzene



Scheme 4 Iodine–magnesium exchange by the reaction of **3a** with *i*-PrMgCl·LiCl.

Table 2 Related Functionalized Benzonitriles of Type **4** Obtained via an In Situ Trapping Procedure in Continuous Flow Using $ZnCl_2$ and Subsequent Trapping with an Electrophile (E^+) in Batch



Entry	Educt	Electrophile (E^+)[a]	Product/Yield[b]
1	**1b**	I_2	 **4a**: 79%
2	**1b**		 **4b**: 88%[c,d]
3	**1b**		 **4c**: 70%[d,e]
4	**1c**	I_2	 **4d**: 82%
5	**1c**		 **4e**: 58%[c,d]
6	**1c**		 **4f**: 80%[d,e]

[a] Amount of E^+ used was 1.1 equiv.
[b] Yield of the isolated, analytically pure product.
[c] Obtained in the presence of 10 mol% CuCN·2LiCl at 0 °C in 2 h.
[d] Amount of E^+ used was 0.8 equiv.
[e] Obtained using 2 mol% of $Pd(OAc)_2$ and 4 mol% of SPhos at r.t., overnight.

were trapped with various classes of electrophiles in high yields. Also a simple scale-up without further optimization of the reaction conditions was possible. The reaction scope of the in situ trapping metalations in flow is broader and needs less equivalents of the base and the metal salt than that of the batch procedures. Further extensions of these in situ trapping metalations are currently underway in our laboratories.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588837.

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(8) Flow reactions were performed with commercially available equipment from Uniqsis Ltd (FlowSyn; http://www.uniqsis.com).

(9) Using the same stoichiometry in a batch reaction leads to a lower conversion and poorer yields are obtained.

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(13) **General Procedure for the In situ Trapping Metalation of 1,2-Dicyanobenzene in Flow followed by the Reaction with an Electrophile in Batch:** The flow system (FlowSyn, Uniqsis) was dried by flushing it with anhyd THF (flow rate of all pumps: 1.00 mL/min, run-time: 30 min). Injection loop A (1.0 mL) was loaded with TMPLi (0.60–0.66 M in anhyd THF; 1.5 equiv) and injection loop B (1.0 mL) was loaded with the reactant solution (0.40–0.43 M in anhyd THF containing 0.5 equiv $ZnCl_2$ additive). The solutions were simultaneously injected into separate THF streams (pump A and B, flow rates: 1.50 mL/min), which passed a pre-cooling loop (1 mL, residence time: 40 s, 0 °C) respectively, before they were mixed in a coiled reactor (1 mL; residence time: 20 s, 0 °C). The combined streams were collected in a flame-dried, argon flushed 25-mL flask equipped with a magnetic stirrer and a septum containing the electrophile (1.1 equiv) dissolved in anhyd THF (1 mL). Then, the reaction mixture was further stirred for the indicated time at the indicated temperature.
4′-Methoxy-[1,1′-biphenyl]-2,3-dicarbonitrile (3h): According to the typical procedure, injection loops A and B were loaded with solutions of 1,2-dicyanobenzene (**1a**; 0.44 M containing 0.5 equiv $ZnCl_2$, 1 mL) and TMPLi (0.66 M, 1 mL), respectively. After injection and in situ trapping metalation the combined streams were collected in a flask containing 4-iodoanisol (113 mg, 0.49 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.0 mg, 2 mol%) and SPhos (7.2 mg, 4 mol%) dissolved in THF (1 mL) at r.t. The reaction mixture was stirred overnight before it was quenched with sat. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3 × 15 mL), the combined organic fractions were dried over anhyd Mg_2SO_4, filtrated and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel; *i*-hexane–EtOAc, 9:1) afforded **3h** as a pale brown solid (89 mg, 0.38 mmol, 87%; mp 200.3–201.5 °C). IR (Diamond-ATR, neat): 2225, 1608, 1580, 1523, 1514, 1460, 1442, 1308, 1298, 1249, 1178, 1117, 1082, 1026, 991, 861, 840, 820, 802, 783, 769, 743, 725, 683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.76 (m, 3 H), 7.49–7.55 (m, 2 H), 7.02–7.06 (m, 2 H), 3.88 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.0, 147.2, 134.1, 133.0, 131.7, 130.2, 128.8, 117.5, 115.9, 115.7, 114.7, 114.2, 55.6. MS (EI, 70 eV): *m/z* (%) = 235 (18), 234 (100), 219 (6), 191 (28), 165 (10), 164 (10), 138 (5), 43 (6). HRMS (EI): *m/z* [M] calcd for $C_{15}H_{10}N_2O$: 234.0793; found: 234.0783.
Ethyl 2-(2,3-Dicyanobenzyl)acrylate (3c): According to the typical procedure, injection loops A and B were loaded with solutions of 1,2-dicyanobenzene (**1a**; 0.42 M containing 0.5 equiv $ZnCl_2$, 1 mL) and TMPLi (0.63 M, 1 mL), respectively. After injection and in situ trapping metalation the combined streams were collected in a flask containing ethyl 2-(bromomethyl)acrylate (89 mg, 0.46 mmol, 1.1 equiv) and CuCN·2LiCl solution (0.04 mL, 10 mol%) dissolved in THF (1 mL) at 0 °C. The reaction mixture was stirred for further 2 h at 0 °C before it was

quenched with sat. NH_4Cl (15 mL). The aq. layer was extracted with EtOAc (3 × 15 mL), the combined organic fractions were dried over anhyd Mg_2SO_4, filtrated and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel; *i*-hexane–EtOAc, 9:1) afforded **3c** as a colorless liquid (77 mg; 0.32 mmol; 76%). IR (Diamond-ATR, neat): 3085, 2984, 2930, 2854, 2362, 2236, 1711, 1632, 1586, 1465, 1447, 1408, 1369, 1329, 1300, 1255, 1200, 1175, 1139, 1096, 1024, 959, 858, 809, 792, 753, 733, 715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.69 (m, 3 H), 6.57 (s, 1 H), 5.72 (s, 1 H), 4.13–4.18 (q, J = 8 Hz, 2 H) 3.9 (s, 2 H), 1.22–1.26 (t, J = 8 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.8, 145.0, 137.0, 134.5, 132.9, 131.7, 128.8, 116.5, 116.1, 115.7, 114.7, 61.3, 37.0, 14.1. MS (EI, 70 eV): m/z (%) = 212 (37), 195 (20), 194 (12), 168 (14), 167 (31), 166 (100), 165 (12), 141 (13), 140 (21). HRMS (EI): m/z [M] calcd for $C_{14}H_{12}N_2O_2$: 240.0899; found: 240.0883.

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