

TMPZnCl·LiCl: A New Active Selective Base for the Directed Zincation of Sensitive Aromatics and Heteroaromatics

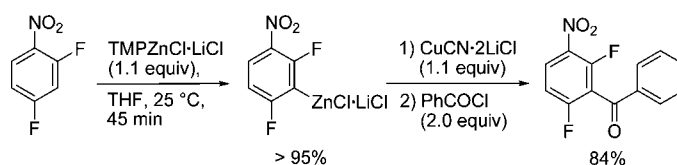
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ABSTRACT



A wide range of polyfunctional aryl and heteroaryl zinc reagents were efficiently prepared in THF via direct zincation using TMPZnCl·LiCl, a new exceptionally mild and efficient base. Activated arenes and heteroarenes are metalated at room temperature. Remarkably, sensitive functions such as an aldehyde as well as a nitro group are tolerated, expanding significantly the scope of directed metalations.

Directed metalation of aromatic and heterocyclic compounds is an important method for the functionalization of these scaffolds. Lithium bases have been extensively used for performing the *ortho*-metalation of various unsaturated systems.¹ The use of magnesium bases, pioneered by Eaton,² has found a renewed interest.³ Recently, lithium magnesiates^{4,5} have found useful synthetic applications. Mixed Mg/Li bases of type R₂NMgCl·LiCl such as 2,2,6,6-tetramethylpiperidine magnesium chloride lithium chloride (TMP-

MgCl·LiCl; Turbo-Hauser base) proved to be an especially effective metalating agent, compatible with functional groups such as an ester, a nitrile, or an aryl ketone.⁶ However, more sensitive functionalities such as an aldehyde or a nitro group are not tolerated. Also sensitive heterocycles may undergo fragmentation.⁷ Therefore a range of zinc amides have been

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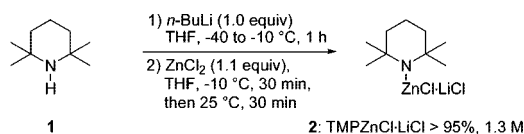
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reported that provide after metalation organozinc reagents compatible with most functionalities. In pioneer work, lithium di-*tert*-butyl-(2,2,6,6-tetra-methylpiperidino)zincate (*t*-Bu₂Zn(TMP)Li) was reported by Kondo to be an excellent base for the zincation of various aromatics.⁸ The use of highly reactive zincates or related ate-bases⁹ is sometimes not compatible with sensitive functions such as an aldehyde or a nitro group. Recently, we have reported the preparation of a highly chemoselective base TMP₂Zn·2MgCl₂·2LiCl for the directed zincation of sensitive aromatics and heteroaromatics.¹⁰ However, with this reagent some electron-poor functionalized arenes and heteroarenes still give unsatisfactory results in terms of yields and reaction selectivity. Moreover, several activated aromatics or heteroaromatics such as nitro derivatives or pyridazines require metalations below −50 °C, which is not convenient for reaction upscaling.^{10a,11} Thus, we have explored the preparation of a more selective zinc base that would allow chemoselective metalations at 25 °C for the directed zincation of sensitive aryl and heteroaryl substrates. The treatment of 2,2,6,6-tetramethylpiperidine (**1**; TMP-H) with *n*-BuLi (1.0 equiv, −40 to −10 °C, 1 h) followed by the addition of ZnCl₂ (1.1 equiv, −10 °C, 30 min) provides a ca. 1.3 M solution of TMPZnCl·LiCl (**2**), stable at room temperature (Scheme 1).¹²

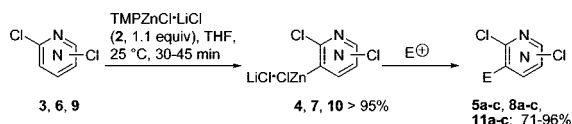
Scheme 1. Preparation of 2,2,6,6-Tetramethylpiperidide Zinc Chloride Lithium Chloride (TMPZnCl·LiCl) (**2**)



In contrast to TMP₂Zn·2MgCl₂·2LiCl, this complex base showed a very good chemoselectivity for the zincation at 25 °C of various sensitive aromatics and heterocycles.

Several sensitive heteroarenes¹⁰ such as pyridazines,¹¹ pyrimidines,¹³ and pyrazines¹⁴ are cleanly zincated at 25 °C using the new base TMPZnCl·LiCl (**2**; Scheme 2 and Table

Scheme 2. Zincation of 3,6-Dichloropyridazine (**3**), 4,6-Dichloropyrimidine (**6**), and 2,6-Dichloropyrazine (**9**) using TMPZnCl·LiCl (**2**; 1.1 equiv; 25 °C) and Trapping with Electrophiles



1). Thus, the treatment of 3,6-dichloropyridazine (**3**) with TMPZnCl·LiCl (**2**; 1.1 equiv, 25 °C, 30 min) leads to the zincated species (**4**), which can be trapped with I₂ or 4-fluorobenzoyl chloride (after transmetalation with CuCN·2LiCl)¹⁵ or undergo a Negishi¹⁶ cross-coupling lead-

Table 1. Products Obtained by Regio- and Chemoselective Zincation of Diazines of Type **3**, **6**, and **9** with TMPZnCl·LiCl (**2**; 1.1 equiv; 25 °C) and Quenching with Electrophiles

entry	substrate of type 3 , 6 and 9	electrophile	product	yield, % ^a
1		I ₂		84
2	3	4-fluorobenzoyl chloride		96 ^b
3	3			83 ^c
4		I ₂		83
5	6	2-furoyl chloride		71 ^b
6	6	allyl bromide		89 ^d
7		I ₂		90
8	9			87 ^c
9	9			72 ^d

^a Isolated, analytically pure product. ^b Transmetalation performed with 1.1 equiv of CuCN·2LiCl. ^c Obtained by palladium-catalyzed cross-coupling using Pd(dba)₂ (3 mol %) and (*o*-furyl)₃P (6 mol %). ^d Transmetalation performed with 5 mol % of CuCN·2LiCl.

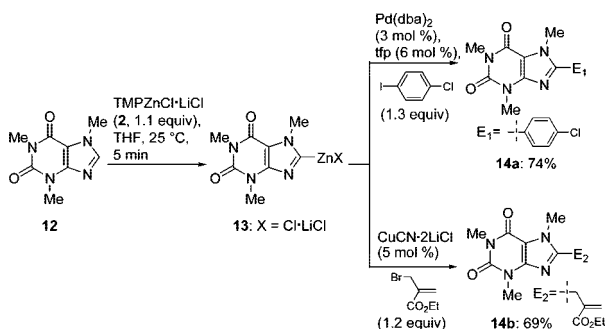
ing to the expected products **5a–c** in 83–96% yield (entries 1–3 of Table 1). Zincations of other sensitive heteroaromatics can be readily achieved by the addition of TMPZnCl·LiCl (**2**). Thus, 4,6-dichloropyrimidine (**6**) is

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converted within 45 min at 25 °C to the 5-zincated species. Trapping with I₂ is furnishing the iodopyrimidine **8a** in 83% yield (entry 4). Reaction with furoyl chloride (after transmetalation with CuCN·2LiCl)¹⁵ provides the 5-ketopyrimidine **8b** in 71% (entry 5). An allylation (after addition of CuCN·2LiCl) leads to the allyled derivative **8c** in 89% (entry 6). Similarly, 2,6-dichloropyrazine (**9**) is zincated quantitatively with TMPZnCl·LiCl (**2**; 1.1 equiv, 25 °C, 30 min) and reacted with iodine or undergoes a Negishi¹⁶ cross-coupling or an allylation with ethyl 2-(bromomethyl)acrylate¹⁷ (after addition of CuCN·2LiCl) affording the expected products **11a–c** in 72–90% yields (entries 7–9).

Other sensitive heterocycles such as purines¹⁸ can be metalated as well under mild conditions (Scheme 3). Thus,

Scheme 3. Zincation of Caffeine (**12**) using TMPZnCl·LiCl (**2**; 1.1 equiv; 25 °C) and Trapping with Electrophiles



caffeine (**12**)¹⁹ undergoes a smooth zincation using TMPZnCl·LiCl (**2**; 1.1 equiv, 25 °C, 5 min) furnishing the zinc species **13**. Negishi¹⁶ cross-coupling or trapping with ethyl 2-(bromomethyl)acrylate¹⁷ (after addition of CuCN·2LiCl)

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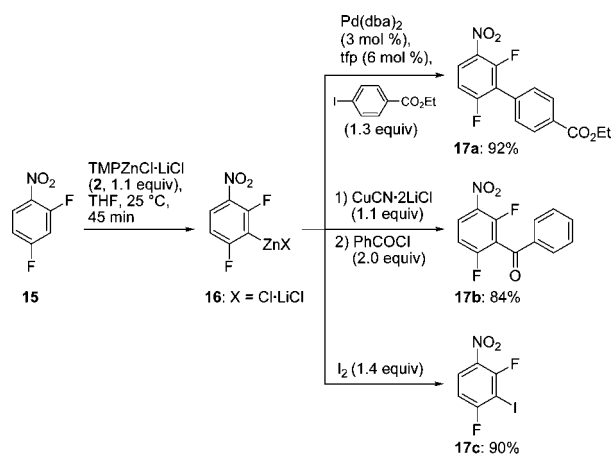
(12) In the absence of LiCl, the zinc base was much less soluble.

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led to the purine derivatives **14a** and **14b**, respectively, in 74% and 69% yields.

A unique advantage of the zinc base **2** is that very sensitive functional groups such as a nitro group can be tolerated at 25 °C.²⁰ Thus, 2,4-difluoronitrobenzene (**15**) was converted to the corresponding zinc reagent **16** by treatment with TMPZnCl·LiCl (**2**; 1.1 equiv, 25 °C, 45 min). A Negishi¹⁶ cross-coupling can be readily performed to furnish the aryl derivative **17a** in 92% yield (Scheme 4). Trapping with benzoyl chloride (after transmetalation with CuCN·2LiCl)¹⁵ provides the ketone **17b** in 84% yield. After trapping with I₂, the iodobenzene derivative **17c** was obtained in 90% yield.

Scheme 4. Zincation of 2,4-Difluoronitrobenzene (**15**) using TMPZnCl·LiCl (**2**; 1.1 equiv; 25 °C) and Trapping with Electrophiles



Other sensitive electron-poor arenes and heteroarenes are metalated as well using the new base **2**. Accordingly, 2-chloro-3-nitropyridine (**18**) undergoes a smooth metalation with TMPZnCl·LiCl (**2**; 1.1 equiv, 25 °C, 45 min) furnishing the zinc species **19**. Trapping with 3-bromocyclohexene (after addition of CuCN·2LiCl) provides the pyridine **20** in 73% yield. Similarly, 4-fluoro-1-methoxy-2-nitrobenzene (**21**) was converted within 6 h at 25 °C to the corresponding zinc reagent **22**. Quenching with ethyl 2-(bromomethyl)acrylate¹⁷ (after addition of CuCN·2LiCl) leads to the allyled derivative **23** in 67% yield. Zincation of methyl 5-nitrofur-2-carboxylate (**24**) can also be readily carried out using **2** (1.1 equiv) and furnishes the zinc species **25** in 30 min at 25 °C. Allylation with 3-bromocyclohexene (after addition of CuCN·2LiCl) gives the furan **26** in 72% yield (Scheme 5).

An aldehyde is also tolerated.²¹ Thus, benzo[*b*]thiophene-3-carbaldehyde (**27**) was converted to the zinc species **28** at

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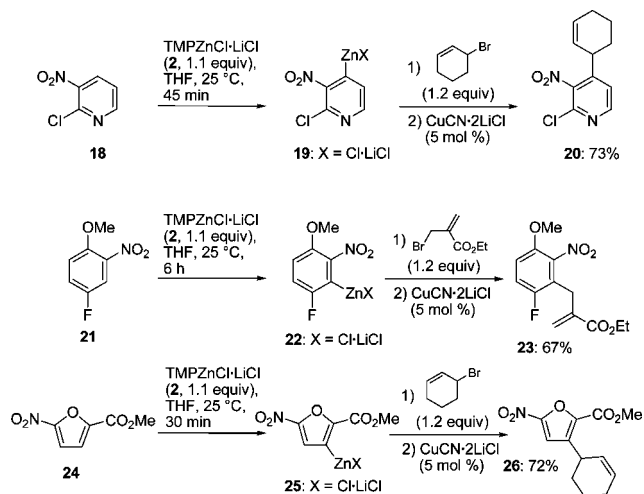
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Scheme 5. Zincation of 2-Chloro-3-nitropyridine (**18**), 4-Fluoro-1-methoxy-2-nitrobenzene (**21**) and Methyl 5-nitrofuran-2-carboxylate (**24**) using TMPZnCl·LiCl (**2**; 1.1 equiv, 25 °C) and Trapping with Electrophiles



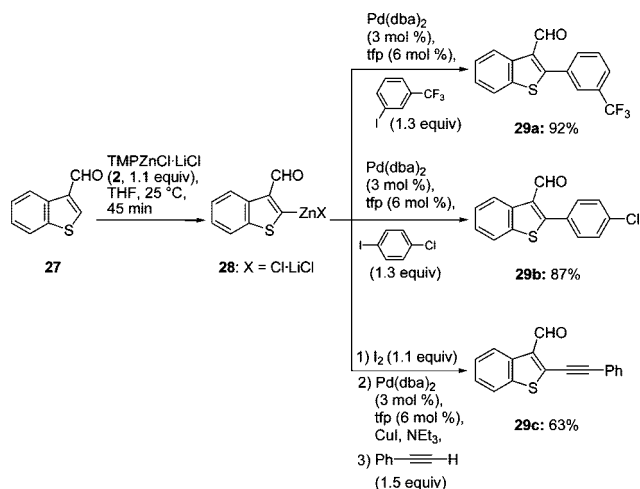
25 °C using TMPZnCl·LiCl (**2**; 1.1 equiv) within 30 min reaction time. The formation of a subsequent carbon–carbon bond is also easily carried out by a Negishi¹⁶ cross-coupling or a Sonogashira²² reaction giving the arylated heterocycles **29a–c** in 63–92% yield.

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(23) **Typical Procedure.** 2,4-Difluoro-1-nitrobenzene **15** (159 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C, and the reaction mixture was then stirred at this temperature for 45 min. CuCN·2LiCl (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was slowly added at –40 °C, and the reaction mixture was stirred at the same temperature for 30 min. Then, benzoyl chloride (281 mg, 2.0 mmol) was added dropwise at –40 °C, and the resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was then quenched with a saturated aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (CH₂Cl₂/pentane, 1:2) furnished compound **17b** (221 mg, 84% yield) as a colorless solid.

Scheme 6. Zincation of Benzo[*b*]thiophene-3-carbaldehyde (**27**) using TMPZnCl·LiCl (**2**; 1.1 equiv; 25 °C) and Trapping with Electrophiles



In summary, we have described a new mild and selective complex base TMPZnCl·LiCl²³ (**2**), which allows chemoselective zincations at room temperature that tolerate sensitive functions such as an aldehyde or a nitro group. Especially, the compatibility with nitro groups opens new avenues in metalations of aromatic and heterocyclic substrates. Further studies on the scope of this base are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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