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Organic Synthesis

Exploiting Coordination Effects for the Regioselective Zincation of Diazines Using TMPZnX·LiX (X = Cl, Br)

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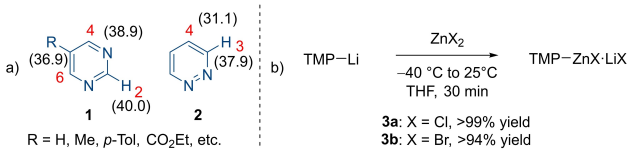
Abstract: A new method for regioselective zincations of challenging *N*-heterocyclic substrates such as pyrimidines and pyridazine was reported using bimetallic bases TMPZnX·LiX (TMP = 2,2,6,6-tetramethylpiperidyl; X = Cl, Br). Reactions occurred under mild conditions (25–70 °C, using 1.75 equivalents of base without additives), furnishing 2-zincated pyrimidines and 3-zincated pyridazine, which were then trapped with a variety of electrophiles. Contrasting with other s-block metalating systems, which lack selectivity in their reactions even when operating at low temperatures, these mixed Li/Zn bases enabled unprecedented regioselectivities that cannot be replicated by either LiTMP nor $Zn(TMP)_2$ on their own. Spectroscopic and structural interrogations of organometallic intermediates involved in these reactions have shed light on the complex constitution of reaction mixtures and the origins of their special reactivities.

Introduction

N-heterocycles are among the most valuable synthetic scaffolds for pharmaceutical and agrochemical research.[1] Their general functionalization has been thoroughly studied[2] and various cross-couplings[3] or metalations of these *N*-heterocycles have been reported for such purpose.[4] A powerful tool for the preparation of *N*-heteroaryl organometallics is the directed C–H metalation using sterically hindered, non-nucleophilic metallic amide bases.[5] Zinc and magnesium derived TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl) have recently emerged as useful reagents for the preparation of highly functionalized *N*-heterocycles.[6] Of special importance for the pharmaceutical industry are diazine building blocks.[7] Thus, the metalation of substituted pyrimidines of type **1** has been studied by using TMPLi and TMPMgCl·LiCl and proceeded with good regioselectivity at the positions 4–6.[8] However, their metalation at the 2-position was poorly investigated and was only achieved in the presence of strong Lewis acid additives.[9] Furthermore, the regioselective functionalization of non-substituted pyrimidine (**1a**) and pyridazine (**2**; Scheme 1a) represents a major challenge since it lacks directing groups generally needed for regioselective control.[10]

The addition of appropriate Lewis acids represents a well-established method for improving regio- and stereoselectivies.[11] BF_3·OEt_2 proved particularly effective allowing high metalation regioselectivities by coordinating to the nitrogen lone pair via the formation of frustrated Lewis-pairs[12] with various metallic amides.[13] However, this approach has several drawbacks such as the formation of mixed boron intermediates of moderate reactivity[14] as well as the need of stoichiometric amounts of this strong and hazardous Lewis acid. Therefore, a mild, practical and regioselective functionalization of *N*-heterocycles of type **1** and **2** is highly desirable.

Since *alpha*-metalated *N*-heterocyclic intermediates are thermally fragile when generated using polar bases such as lithium amides,[7a] we envisioned the use of TMPZnCl·LiCl (**3a**) or TMPZnBr·LiBr (**3b**, Scheme 1b) as possible metalating systems that would allow direct zincation of these sensitive substrates in the presence or absence of additional Lewis acids. Herein, we report the practical and effective



Scheme 1. a) Diazines such as pyrimidines (**1**) and pyridazine (**2**) and their respective pk_a values;[15] b) Preparation of the TMP-bases TMPZnCl·LiCl (**3a**) and TMPZnBr·LiBr (**3b**) starting from TMPLi.

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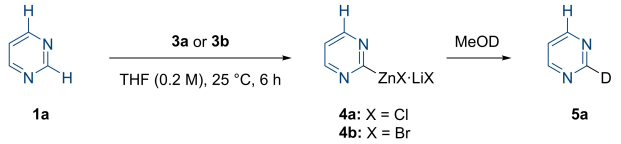
zincation of various functionalized and non-substituted pyrimidines (**1**) and pyridazine (**2**) using TMPZnCl·LiCl (**3a**). Reactions showed an excellent regioselective control enabling the C2 and C3 zincation of pyrimidines and pyridazine respectively. The synthetic potential and versatility of this approach was demonstrated by electrophilic interception furnishing a wide range of newly functionalized pyrimidines and pyridazines. These studies have revealed an interesting effect in the reactivity of these zincated species on the addition of metal salts. Combining NMR reaction monitoring studies with X-ray crystallographic studies, light has been shed on the constitution of organometallic species participating in these transformations and on the possible origins behind the observed special regioselectivities.

Results and Discussion

In preliminary experiments, we have investigated the regioselective zincation of pyrimidine (**1a**) at position 2 with the TMP-zinc bases **3a** or **3b** leading to the zincated pyrimidine **4a** or **4b** (see Table 1). Thus, treatment of a 0.2 M solution of pyrimidine (**1a**) with TMPZnCl·LiCl (**3a**, 1.05 equiv) led to a highly regioselective zincation at 2-position (>99:1) in 34 % ^{1}H NMR yield as determined after deuterolysis (entry 1).[16] This conversion was improved by increasing the amount of base **3a**. Thus, using 1.25 equiv of **3a** provided, after deuterolysis, the deuterated pyrimidine **5a** in 74 % yield with the same excellent regioselectivity (entry 2). Further increase of TMPZnCl·LiCl (**3a**) to 1.50 equiv or 1.75 equiv led to yields of up to 98 % (entries 3 and 4). Using 2.0 equiv of **3a** gave a quantitative conversion, showing that **3a** may complex to **4a** (entry 5). Performing the metalation with the alternative bromide base TMPZnBr·LiBr (**3b**, 2.0 equiv) gave the same result after deuterolysis (entry 6). Despite the excess of base no evidence of dizincation of **1a** was found. The regioselectivity, high yield and mild conditions observed for these reactions contrast with the inefficiency of TMPLi to metalate **1a**, yielding only dimer 6,6′-bipyrimidine even when working under extreme cryogenic temperatures (−100 °C).[10a] Furthermore, these conditions are also superior to that reported using TMPLi in combination with $Ga(CH_2SiMe_3)_3$. By using a trans-metal trapping (*TMT*) approach,[17] C4-gallation was observed in 59 % yield, leaving the C2 position untouched.[18] Interestingly, the same C4-regioselectivity was found by Mongin for zincation of **1a** using an in situ mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv).[10b] Also, when **1a** reacted with TMPMgCl·LiCl[6a] at −20 °C, formation of C4-magnesiated pyrimidine was observed in modest 28 % yield (see Supporting Information), demonstrating the key role of zinc in favoring the C2-metalation.

With these results in hand, we have performed the metalation of pyrimidine (**1a**) with **3a** (1.75 equiv) and have examined the scope of the trapping of resulting 2-pyrimidylzinc chloride (**4a**; Scheme 2). Therefore, quenching **4a** with iodine (1.8 equiv) led to 2-iodopyrimidine (**6a**) in 96 % yield. This useful iodide[19] further reacted with phenylacetylene in a copper-catalyzed Sonogashira cross-coupling providing the alkyne **6b** in 78 % yield. Transmetalation of **4a** with CuCN·2 LiCl (1.0 equiv) followed by addition of allylic bromides such as ethyl 2-(bromomethyl)acrylate or ethyl 6-bromocyclohex-1-ene-1-carboxylate[20] furnished the corresponding enoates **6c–d** in 63–68 % yield. Furthermore, a copper-catalyzed electrophilic amination[21] with morpholino benzoate yielded the tertiary amine **6e** in 55 % yield. Several palladium-catalyzed cross-coupling reactions were performed with 6 mol% of tri(2-furyl)phosphine (tfp)[22] in the presence of 3 mol% $Pd(dba)_2$ (dba = bis(dibenzylidenacetone) affording the arylated products

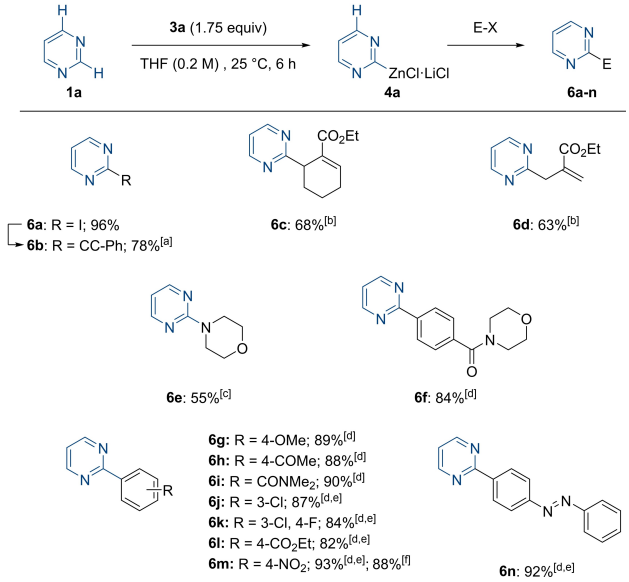
Table 1: Zincation of pyrimidine (**1a**) with TMP-bases **3a** or **3b** furnishing 2-pyrimidylzinc halides (**4a** or **4b**) and subsequent deuterolysis using MeOD leading to the deuterated pyrimidine **5a**.



1a **4a:** X = Cl **4b:** X = Br **5a**

Entry	TMP-base	Equiv	Yield[a]
1	TMPZnCl·LiCl (**3a**)	1.05	34 %
2	**3a**	1.25	74 %
3	**3a**	1.50	90 %
4	**3a**	1.75	98 %
5	**3a**	2.0	99 %
6	TMPZnBr·LiBr (**3b**)	2.0	99 %

[a] Yields are ^{1}H NMR -yields using trichloroethylene as internal standard.



Scheme 2. Zincation of pyrimidine (**1a**) and quenching with various electrophiles. [a] **6a**, phenylacetylene (1.3 equiv), CuI (4 mol%), NEt_3 (1.0 mL), 25 °C, 2 h; [b] CuCN·2 LiCl (1.0 equiv), allyl bromides (1.5 equiv), 0 °C to 25 °C, 14 h; [c] $BzONR_2$ (NR_2 = *N*-morpholino; 0.8 equiv), $CuCl_2$ (5 mol%), 25 °C, 14 h; [d] Aryl iodide (0.8 equiv), $Pd(dba)_2$ (3 mol%), tfp (6 mol%), 25 °C, 14–30 h; [e] Extra 1.0 equiv of $ZnCl_2$ added; [f] Reaction was performed on 5.0 mmol scale.

6f–n in 82–93 % yield. A range of electron-rich and electron-poor aryl iodides containing sensitive functionalities including an ester, an amide and a nitro group were well tolerated in these reactions. Whereas the Negishi cross-coupling was complete within 12–36 h (**6f–i**), we noticed that very long reaction times (up to 96 h) were required for very electron-poor aryl iodides.

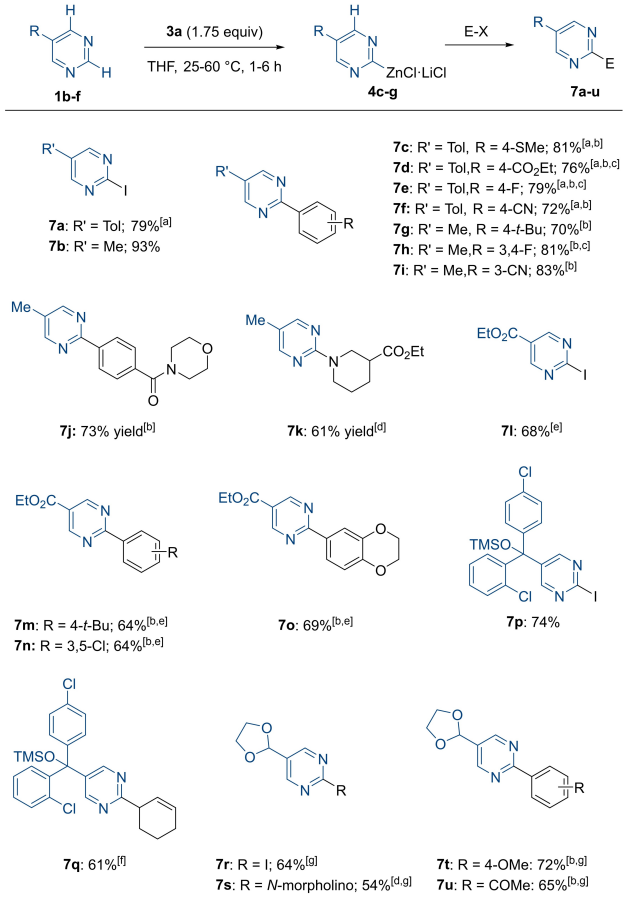
Therefore, we have examined the separate addition of $ZnCl_2$ and $MgBr_2$ salts, after the metalation, in order to modify the constitution of the organometallic intermediate and provide a species more amenable to transmetalation to ArPdX that would enhance the cross-coupling rate.[23] To our delight, the addition of $ZnCl_2$ (1.0 equiv) allowed to reach full conversion within 12 h in the case of these aryl iodides leading to the pyrimidines **6j–n**.

Next, we have extended the scope of this zincation to the functionalized pyrimidines **1b–f** (Scheme 3). Thus, 5-*p*-tolyl-substituted pyrimidine (**1b**)[24] or 5-methylpyrimidine (**1c**) were smoothly zincated under related conditions (1.75 equiv of TMPZnCl·LiCl (**3a**); 50 °C, 3 h in case of **1b** and 1.75 equiv of **3a**; 25 °C, 6 h for **1c**) providing **4c–d** in up to ca. 90 % yield. Quenching with iodine or palladium-catalyzed cross-couplings with functionalized aryl iodides furnished the 2,5-disubstituted pyrimidines **7a–j** in 70–93 % yield. Performing a cobalt-catalyzed electrophilic amination[25] gave the aminated pyrimidine **7k** in 61 % yield. Similarly, ethyl pyrimidine-5-carboxylate (**1c**) was metalated using **3a** (1.75 equiv) for 1 h at 60 °C with a regioselectivity of ca. 96:4. Iodolysis or palladium-catalyzed cross-coupling reactions with aryl iodides provided the desired functionalized pyrimidines **7l–o** in 64–69 % yield, which were isolated as single regioisomers. Using the standard conditions (**3a**, 1.75 equiv, 25 °C, 6 h) developed for pyrimidine (**1a**), we have zincated the silyl-protected fenarimol[26] derivative **1e**.

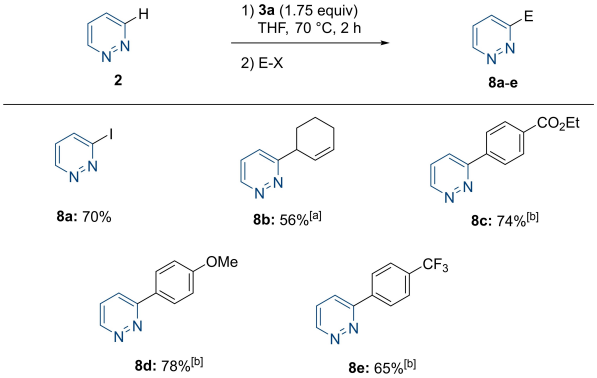
Quenching with iodine or performing a copper-catalyzed allylation gave the corresponding pyrimidines **7p** and **7q** in 61–74 % yield. Also, 5-(1,3-dioxolan-2-yl)pyrimidine (**1f**)[27] was zincated using **3a** (1.75 equiv, 50 °C, 2 h) in ca. 80 % yield and a regioselectivity of 93:7. Iodination, Pd-catalyzed arylations and Co-catalyzed amination provided **7r–u** in up to 72 % yield, which were isolated as single regioisomers.

Next, we focused on the functionalization of pyridazine (**2**, Scheme 4).[1] Its metalation remains a challenging task and could only be achieved in moderate yield or regioselectivity using excess of additives like BF_3·OEt_2 or TMEDA.[10b–c] After several screening experiments,[16] we found that the zincation of **2** in 3-position proceeded at 70 °C within 2 h, providing 3-iodopyridazine (**8a**) with a regioselectivity of 94:6 and 70 % yield after iodolysis. Various quenching reactions such as a copper-catalyzed allylation or palladium-catalyzed arylations were performed providing **8b–e** in 56–78 % yield as single regioisomers after isolation (>99 % purity).

Pleased by these findings, we subsequently took a closer look at the constitution of the zincated intermediates involved in these transformations, using base **3b** and pyrimidine (**1a**) or 5-methylpyrimidine (**1c**) as model substrates. The bimetallic base TMPZnBr·LiBr, prepared in situ in d_8-THF by combining equimolar amounts of TMPLi and $ZnBr_2$, was characterized by multinuclear (^1H, ^{13}C, and



Scheme 3. Zincation of pyrimidines **1b–f** and subsequent quenching with various electrophiles. [a] The metalation was performed at 50 °C for 3 h; [b] Aryl iodide (0.8 equiv), $Pd(dba)_2$ (3 mol%), tfp (6 mol%), 25 °C, 18 h; [c] Extra 1.0 equiv of $ZnCl_2$ was added; [d] *O*-hydroxylamine benzoate (0.8 equiv), $CoCl_2$ (5 mol%), TMEDA (10 mol%), 25 °C, 14 h; [e] Metalation was performed at 60 °C for 1 h; [f] CuCN·2 LiCl (1.0 equiv), 3-bromocyclohex-1-ene (1.5 equiv), 0 °C to 25 °C, 14 h; [g] Metalation was performed at 60 °C for 2 h.



Scheme 4. Zincation of pyridazine (**2**) and quenching with various electrophiles. [a] CuCN·2 LiCl (1.0 equiv), 3-bromocyclohex-1-ene (1.5 equiv), 0 °C to 25 °C, 14 h; [b] Aryl iodide (0.8 equiv), $Pd(dba)_2$ (3 mol%), tfp (6 mol%), 25 °C, 18 h.

^{7}Li) and DOSY NMR spectroscopy (see Supporting Information for details). The results supported formation of a lithium zincate which in solution is most likely to exist as solvent separated ion pair species of formula [{Li(d_8-THF)$_x$}$^+${ZnBr$_2$(TMP)(d_8-THF)}$^-$] (**I**) (see Supporting Information for details). Next, we monitored the reaction of **3b** with **1a** (Figure 1a) under the optimized reaction conditions by ^{1}H NMR (25 °C, d_8-THF, 1.75 equiv of **3b**). While the reaction occured almost instantaneously with full consumption of **1a** and appearance of TMP(H), the aromatic region of the spectrum showed a complex mixture of products (Figure 1b). Its composition did not change significantly over the time but proved to be concentration dependent (Figure 1b, 1c and Supporting Information). Remarkably, when this mixture was quenched with iodine, 2-iodopyrimidine (**6a**) was obtained as single product in 88 % yield consistent with the one obtained carrying out the reaction in situ (Scheme 2).

These findings are consistent with formation of several C2-zincated species present in solution and could be attributed to redistribution of initially formed heteroleptic zincate [{Li(THF)$_x$}$^+${ZnBr$_2$(HetAr)(THF)}$^-$] (**II**) into different species. While the composition of this mixture could not be confidently assigned, the possible formation of different mixed aggregates facilitated by the coordination of the strongly Lewis acidic zinc center to the *N* atoms of a pyrimidyl fragment of a neighboring unit[28] should be considered as a contributing factor to this solution complexity. Interestingly, when assessing the effect of inorganic salts to this complex mixture, we found that introducing stoichiometric amounts of LiBr or MgBr$_2$ did not have any significant effect. However, dosing increasing amounts of ZnBr$_2$ (up to 2 molar equivalents) influenced the constitution of this mixture showing eventual convergence of all species into a single C2-zincated product, displaying a doublet and a triplet at δ 9.20 and δ 7.77 ppm respectively (Figure 1d and Figure S14 in Supporting Information). The ^{13}C NMR spectrum is also consistent with the presence of a single species in solution, displaying a distinct signal at δ 209.5 ppm for the Zn–C2 unit. It should be noted that this species is present in solution in the reaction mixture from the beginning as a major product, especially under dilute reaction conditions (Figures 1b,c). The same behavior in solution was observed for 5-methylpyrimidine (see Supporting Information) and in this case the final product after addition of ZnBr$_2$ was isolated as the crystalline solid **9**, which was structurally authenticated (Figure 2).

Complex **9** is a solvent-separated ion pair. The lithium cation sits in a distorted tetrahedron of THF ligands. More significantly, the anion has a tetranuclear arrangement of zinc centers. Demonstrating that these reactions are genuine zincations, this anion comprises a central Zn center bonded to three C2-metallated 5-methylpyrimidyl fragments (mean Zn–C bond length, 2.029 Å). Three equivalents of ZnBr$_2$ are also incorporated within the structure, each coordinated to two pyrimidyl nitrogen atoms closing three 6-membered {ZnCNZnNC} rings, which are fused by sharing a central Zn vertex (Zn1 in Figure 2). Collectively, this gives an eye-catching motif composed of six fused 6-membered rings. These findings also correlate with the reactivity studies assessing the ability of these systems in cross-coupling processes where significantly shorter reactions times were observed when using an excess of ZnCl$_2$ as an additive (see above). This can be attributed to the formation of a kinetically activated monomeric tris(aryl) zincate similar to **9**.

The notable effect of ZnBr$_2$ on favoring the formation of a single species by blocking the *N*-coordinating sites of the pyrimidyl fragments can also inform on the special regioselective control observed in these metalation processes. Thus, we envisage initial coordination of **1a** to Zn in [{Li(THF)$_x$}$^+$ {ZnBr$_2$(TMP)(THF)}$^-$] (**I**) (Scheme 5) to be key for activating the substrate and also directing the metalation regioselectively towards the C2 position. Furthermore, the fact that full conversion only occurs when an excess of base is employed led us to suspect that perhaps one equivalent of **3b** coordinates to each of the *N*s of **1a**, enhancing even more the acidity of the C2-position compared to the other positions (C4 and C6). These positions should be less acidified since only one adjacent Lewis acid coordinates. A

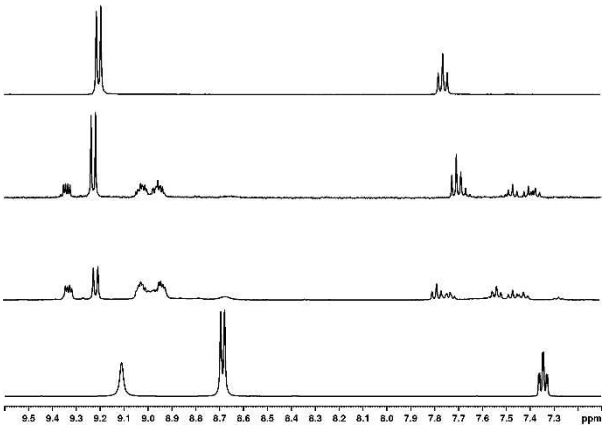


Figure 1. Aromatic region of ^{1}H NMR spectrum in d_8-THF of a) pyrimidine; b) pyrimidine + 1.75 equiv TMPZnBr·LiBr (0.13 M); c) pyrimidine + 1.75 equiv TMPZnBr·LiBr (0.013 M); and d) pyrimidine + 1.75 equiv TMPZnBr·LiBr + 2 equiv ZnBr$_2$.

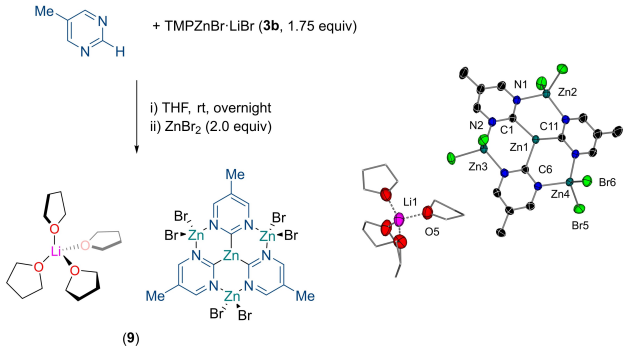
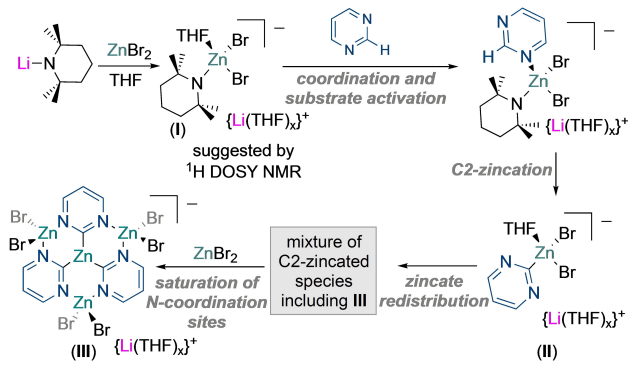
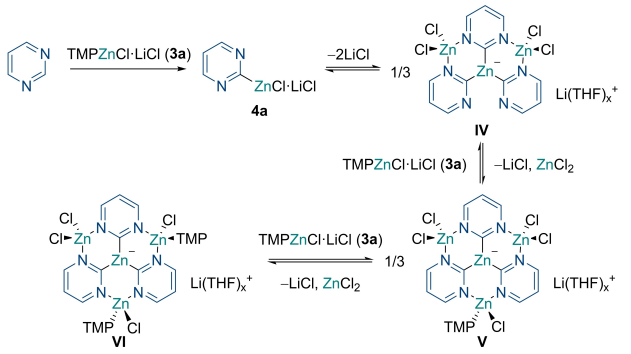


Figure 2. Synthesis of [{Li(THF)$_4$}$^+${Zn(Me-C$_4$H$_2$N$_2$)$_3$(ZnBr$_2$)$_3$}$^-$] (**9**). Molecular structure of **9** with displacement ellipsoids at 30 % probability, all H atoms omitted and C-atoms in THF shown as wires for clarity. One THF molecule present in the unit cell has been removed for clarity.



Scheme 5. Metalation of pyrimidine triggered by substrate coordination to TMPZnBr·LiBr (**3b**).



Scheme 6. Possible involved intermediates in the zincation of pyrimidine (**1a**) using 2 equiv of TMPZnCl·LiCl (**3a**).

proposed metalation intermediate $[\{Li(THF)_x\}^+\{ZnBr_2(C_4H_3N_2)(THF)\}^-]$ (**II**) may form, which in turn undergoes fast redistribution forming an intricate mixture of C2-zincated species including co-complex $[\{Li(THF)_4^+\{Zn(C_4H_3N_2)_3(ZnBr_2)_3\}^-]$ (**III**) (see Figure 1). Adding excess $ZnBr_2$ to these mixtures blocks the *N*-coordination sites on the pyrimidyl rings leading to the selective formation of **III** which was isolated and spectroscopically characterized.

Demonstrating the importance of substrate precoordination to the zinc base, $Zn(TMP)_2$ on its own was found to be incapable of metalating **1a**, which we attributed to the large steric encumbrance (as demonstrated by ^{1}H DOSY NMR studies, see Supporting Information). In contrast, reducing the steric space and increasing the Lewis acidity of the zinc center, we found that TMPZnBr allowed the effective C2 metalation of **1a** affording a white solid which was insoluble in THF (iodolysis of this suspension afforded 2-iodo pyrimidine in 92 % yield). We also investigated the metalation of **1a** by forming first a coordination adduct with $ZnBr_2$ and reacting this complex with LiTMP (Scheme S2 in Supporting Information). Under these conditions, a mixture of 2 and 4-iodopyrimidine was observed (28 % and 37 % respectively) along with some other unidentified products. This illustrates the importance of using a zincating reagent to control the selectivity of the reaction and the stability of the relevant metalated intermediates.

Furthermore, the performance of metalations of pyrimidine (**1a**) with TMPZnCl·LiCl (**3a**) in the presence of bidentate ligands such as 2,2′-bipyridine led to a significant yield decrease of zincated pyrimidine **4a** (see Supporting Information). Therefore, an explanation for the requested excess of base **3a** to achieve complete metalation may be the consumption of one or two equivalents of **3a** in the reaction with complexes such as **IV**, leading to species such as **V** and **VI**. (Scheme 6). Concerning the origin of the regioselectivity of the zinaction of pyridazine (**2**), we propose that the precoordination to the nitrogen is key for a metalation at C3.

Conclusion

In summary, we have reported a convenient zincation of pyrimidines at position C2 and pyridazine at position C3 using TMPZnCl·LiCl (**3a**) and TMPZnBr·LiBr (**3b**). These regioselectivities are rare and unprecedented for non-substituted pyrimidine. Demonstrating the synthetic utility of this approach, a range of functionalized pyrimidines and pyridazines were prepared after various quenching reactions. Combining spectroscopic and crystallographic studies, better understanding has been gained on the constitution of the organometallic intermediates which suggests that the unique regioselective control of these reactions is facilitated by the coordination of the substrate to the organometallic reagent and the formation of thermally stable zincated intermediates.[29]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Diazines · Metalation · Regioselectivity · Salt Effects · Structural Elucidation

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