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TMPZnOPiv•LiCl: A New Base for the Preparation of Air-Stable Solid Zinc Pivalates of Sensitive Aromatics and Heteroaromatics

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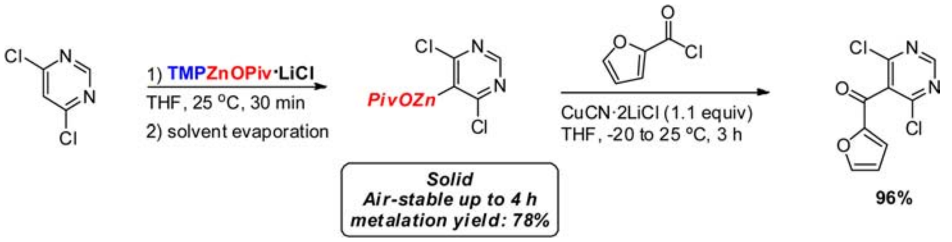
ABSTRACT



A wide range of aryl and heteroaryl zinc pivalates bearing sensitive functionalities were prepared by selective metalation using TMPZnOPiv•LiCl, a new hindered zinc amide base. The new zinc reagents are easy-to-handle solids, which maintain their activity almost entirely (>95%) after 4 h of air exposure and smoothly undergo Negishi cross-couplings and reactions with various electrophiles such as Cu(I)-catalyzed acylations and allylations.

Organozinc reagents hold a special position among other organometallics due to their compatibility with a wide range of sensitive functional groups.[1] In addition, they have proven to be valuable synthetic tools in C–C bond formation reactions, *via* transition-metal catalyzed transformations.[2] A major drawback is their lability when exposed to air and the pyrophoric properties of some of their low molecular weight members. To tackle this problem, we have recently described the preparation of aryl and heteroaryl zinc pivalates which are easy-to-handle solids with exceptional stability when exposed to air.[3] These zinc reagents have been prepared via either Mg insertion in the presence of $Zn(OPiv)_2 \cdot 2LiCl$[3a] or directed metalation using $TMPMgCl \cdot LiCl$ (**1**, TMP = 2,2,6,6-tetramethylpiperidyl) and subsequent transmetalation to $Zn(OPiv)_2$.[3b] However, none of the above methods can be applied efficiently when sensitive functionalities, such as an aldehyde, a nitro group, or other electron-withdrawing groups, are present.

To overcome this limitation, we envisioned the use of a milder zinc amide base. The latter are known to provide zinc reagents which are compatible with most functionalities. In his pioneering work, Kondo introduced lithium di-*tert*-butyl-tetramethylpiperidino zincate (t-$Bu_2Zn(TMP)Li$) as an excellent base for the directed metalation of aromatics.[4] Since then, other zincates and related ate bases have been reported.[5] We have also described the

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(1) (a) Knochel, P.; Almena, J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275. (b) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4115. (c) Knochel, P.; Leuser, H.; Cong, L.-Z.; Perrone, S.; Kneisel, F. F. *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; p 251.

(2) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (c) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (d) Erdik, E. *Tetrahedron* **1992**, *48*, 9577.

(3) (a) Bernhardt, S.; Manolikakes, G.; Kunz, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9205. (b) Stathakis, C. I.; Bernhardt, S.; Quint, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9428.

(4) (a) Kondo, Y.; Shilai, H.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539. (b) Imahori, T.; Uchiyama, M.; Kondo, Y. *Chem. Commun.* **2001**, 2450. (c) Schwab, P. F. H.; Fleischer, F.; Michl, J. *J. Org. Chem.* **2002**, *67*, 443. (d) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otami, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514.

(5) (a) Uchiyama, M.; Matsumoto, Y.; Nobuto, D.; Furuyama, T.; Yamaguchi, K.; Morokuma, K. *J. Am. Chem. Soc.* **2006**, *128*, 8748. (b) Clegg, W.; Dale, S. H.; Drummond, A. M.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *J. Am. Chem. Soc.* **2006**, *128*, 7434. (c) Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *J. Am. Chem. Soc.* **2005**, *127*, 13106. (d) Armstrong, D. R.; Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3775.

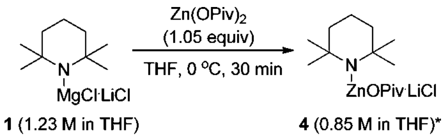
10.1021/ol400242r

preparation of TMP$_2$Zn·2MgCl$_2$·2LiCl (**2**)[6] and TMPZnCl·LiCl (**3**)[7] as two highly chemoselective bases for the metalation of sensitive aromatics and heterocycles.

Herein we wish to report the preparation of a new base tentatively written as TMPZnOPiv·Mg(OPiv)Cl·LiCl (**4**)[8] which is compatible with functionalities such as a nitro group, an aldehyde, or sensitive heteroaromatic rings. In addition, we show that the new base **4** provides a fast and efficient access, after removal of the solvent, to solid zinc pivalates, which exhibit significant tolerance toward hydrolysis or oxidation after air exposure.

TMPZnOPiv·LiCl (**4**, Mg(OPiv)Cl is omitted for clarity) is prepared by the addition of solid Zn(OPiv)$_2$ (1.05 equiv, 0 °C) to a solution of TMPMgCl·LiCl (**1**, 1.23 M in THF) and subsequent dilution with dry THF until a clear solution arises (final concentration: 0.85 M; Scheme 1).

Scheme 1. Preparation of the New Zinc Amide Base TMPZnOPiv·LiCl (**4**) from TMPMgCl·LiCl (**1**)

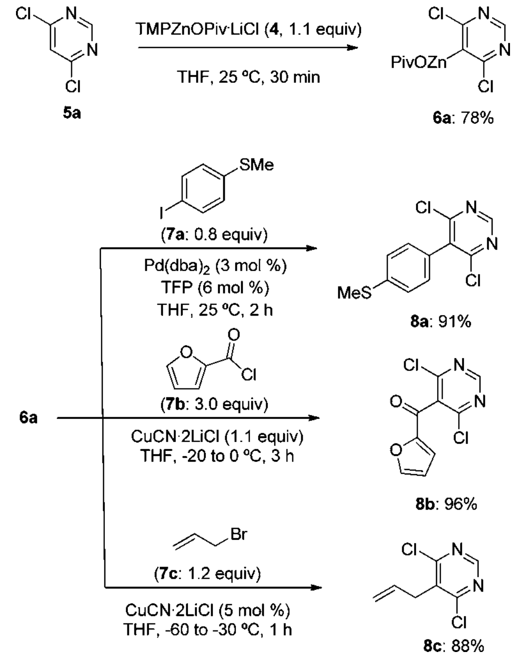


*Mg(OPiv)Cl is omitted for clarity

The new zinc amide base (**4**) was tested for the metalation of a broad range of aromatic and heterocyclic substrates bearing sensitive functionalities and of heteroaromatics prone to fragmentation. In most cases, the metalation proceeded with excellent regio- and chemoselectivity, in short reaction times (< 2 h), using 1.1 to 2.0 equiv of the base at 25 °C or by mild heating at 50 °C. After removal of the solvent under high vacuum (0.1 mmHg, 3 h), a fine powder was obtained which was exposed to air in order to determine the stability of the zinc reagents.[9] The vast majority of the organozinc pivalates tested exhibited exceptional air stability (> 95% activity after 4 h of air exposure), which compared favorably with the stability of the zinc pivalates prepared by metalation with TMPMgCl·LiCl (**1**, > 85% activity after 4 h in air).[3b]

Thus, 4,6-dichloropyrimidine (**5a**) was metalated selectively at position 5 using TMPZnOPiv·LiCl (**4**, 1.1 equiv, THF, 25 °C, 30 min), and the corresponding zinc pivalate (**6a**) was formed in 78% yield (Scheme 2). After evaporation of the solvent under high vacuum, a fine powder was obtained which was left in a vial open to air. The content of the active zinc species was determined after different periods of air exposure, and it was found that after 2 h the entire content was still active (> 99%) while after 4 h this percentage was 96%. A number of other substrates were examined and found to follow the same trend.[9]

Scheme 2. Preparation of 5-(4,6-Dichloropyrimidinyl)zinc Pivalate (**6a**) by Metalation of 4,6-Dichloropyrimidine (**5a**) with TMPZnOPiv·LiCl (**4**) and Reactivity towards Various Electrophiles



Next, the reactivity of the zinc pivalate of 4,6-dichloropyrimidine (**6a**) toward various electrophiles was explored. Therefore, the organozinc pivalate **6a** was subjected to a Negishi cross-coupling[2c,10] with 4-iodothioanisole **7a** using Pd(dba)$_2$/TFP (dba = dibenzylideneacetone, TFP = tri-*o*-furylphosphine)[11] as the catalytic system (Scheme 2). The coupling product **8a** was obtained in 91% isolated yield. When the zinc compound **6a** was transmetalated with CuCN·2LiCl (1.1 equiv, −20 °C) and then reacted with 2-furoyl chloride (**7b**), the acylated pyrimidine **8b** was isolated in 96% yield. Finally, the allylation of **6a** with allyl bromide (**7c**) was readily performed, in the presence of catalytic amounts of CuCN·2LiCl (5 mol %), to furnish the substituted pyrimidine **8c** in 88% yield (Scheme 2). Comparison with

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(6) (a) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685. (b) Wunderlich, S. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 4705. (c) Mosrin, M.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 1468.

(7) (a) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837. (b) Mosrin, M.; Monzon, G.; Bresser, T.; Knochel, P. *Chem. Commun.* **2009**, 5615. (c) Bresser, T.; Mosrin, M.; Monzon, G.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4686. (d) Bresser, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1914. (e) Duez, S.; Steib, A.; Manolikakes, S. M.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7686.

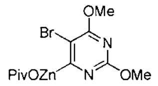
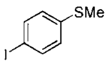
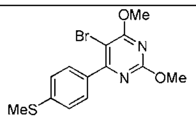
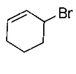
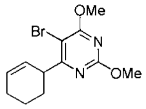
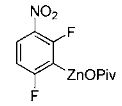
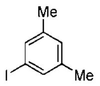
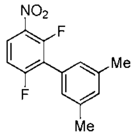
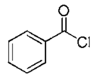
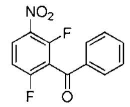
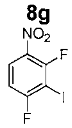
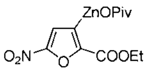
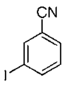
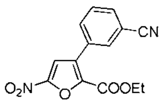
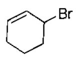
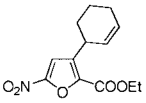
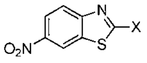
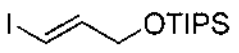
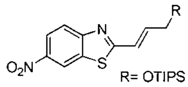
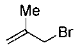
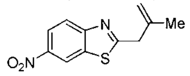
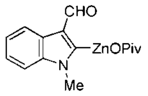
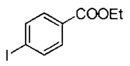
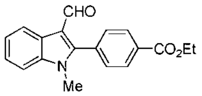
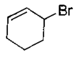
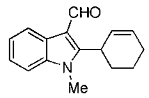
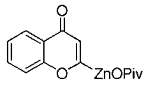
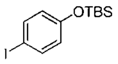
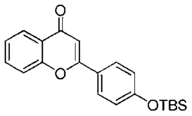
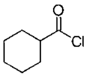
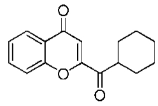
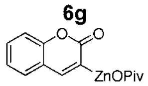
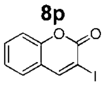
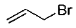
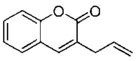
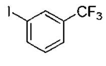
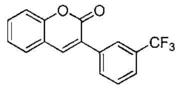
(8) The somewhat lower reactivity of the new base **4** compared to TMPZnCl·LiCl (**3**) led us to prefer the formula TMPZnOPiv·Mg(OPiv)Cl·LiCl rather than TMPZnCl·Mg(OPiv)$_2$·LiCl.

(9) Typical titration via iodolysis was not possible for most of the solid zinc pivalates due to their deep redish or brownish color. In these cases the content of active zinc species was determined by GC analysis and calculation of the iodinated compound derived by iodolysis of a certain amount of zinc pivalate, based on a calibration curve using an external standard. See Supporting Information.

(10) (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Wang, G.; Yin, N.; Negishi, E. *Chem.—Eur. J.* **2011**, *17*, 4118. (d) Negishi, E.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 815.

(11) (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (b) Klement, I.; Rottlander, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.

Table 1. Transition-Metal Catalyzed Reactions of Zinc Pivalates **6b**–**h** with Various Electrophiles

entry	zinc pivalate (temp, time)[a]	electrophile	product	yield (%)[b]
1	 **6b** (25 °C, 3 h)	 **7a**	 **8d**	81
2	**6b**	 **7d**	 **8e**	89
3	 **6c** (25 °C, 45 min)	 **7e**	 **8f**	98
4	**6c**	 **7f**	 **8g**	59
5	**6c**	I_2 **7g**	 **8h**	98
6	 **6d** (-10 °C, 1 h)[c]	 **7h**	 **8i**	66
7	**6d**	 **7d**	 **8j**	70
8	 X = ZnOPiv **6e** (25 °C, 10 min)	 **7i** (> 99% *E*)	 **8k** (> 99% *E*)	95
9	**6e**	 **7j**	 **8l**	88
10	 **6f** (25 °C, 30 min)	 **7k**	 **8m**	91
11	**6f**	 **7d**	 **8n**	98
12	 **6g** (-30 °C, 1 h)	 **7l**	 **8o**	78
13	**6g**	 **7m**	 **8p**	70
14	 **6h** (MWI, 80 °C, 1 h)	I_2 **7g**	 **8q**	92
15	**6h**	 **7c**	 **8r**	98
16	**6h**	 **7n**	 **8s**	96

[a] Temperature and reaction time for the metalation of **5b**–**g** with TMPZnOPiv·LiCl (**4**). Unless otherwise stated the reaction was performed in THF (0.5 M) using 1.1 equiv of the base. [b] Isolated yield. [c] 2.0 equiv of the base were used.

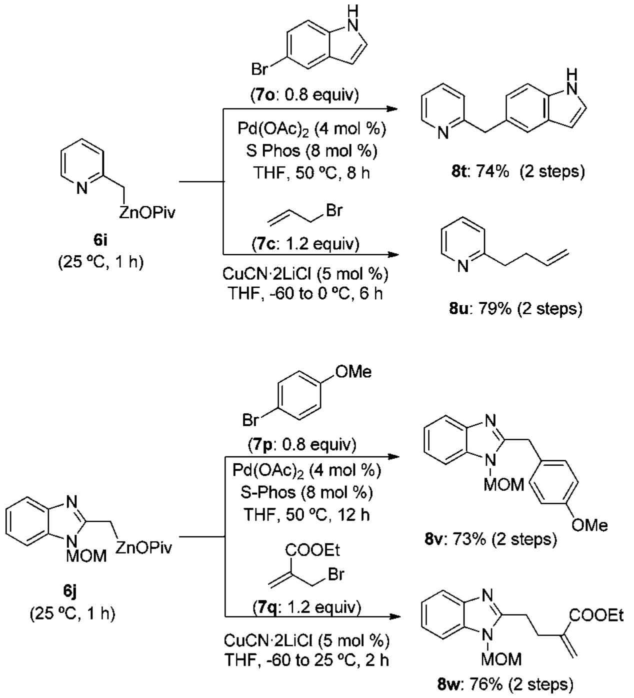
previous preparations of compounds **8b** and **8c** using the corresponding heteroarylzinc chloride (prepared by metalation with TMPZnCl·LiCl, **3**) revealed comparable or even improved yields (in the case of **8b**).[7a]

A broad selection of other zinc pivalates was prepared by metalation with TMPZnOPiv·LiCl (**4**), and their reactivity in transition-metal catalyzed transformations with a range of electrophiles is presented (Table 1).

5-Bromo-2,4-dimethoxypyrimidine (**5b**) was successfully zincated using TMPZnOPiv·LiCl (**4**, 1.1 equiv, THF, 25 °C, 3 h) at the position α to the halogen leaving group providing a stable pyrimidylzinc pivalate (**6b**), which afforded the Negishi cross-coupling product **8d** in 81% yield (entry 1). The allylation of **6b** with 3-bromocyclohexene, after addition of CuCN·2LiCl (10 mol %), was accomplished in 89% yield (entry 2).

Moreover, the new base **4** was applied effectively in the metalation of substrates bearing the sensitive nitro-group. Thus, 2,4-difluoro-1-nitrobenzene (**5c**) was readily zincated with TMPZnOPiv·LiCl (**4**, 1.1 equiv, THF, 25 °C, 45 min) leading to the organozinc pivalate **6c** in 83% yield.[7a] The latter was subjected to cross-coupling with the aryl iodide **7e** or was trapped with either I_2 or benzoyl chloride (after transmetalation with CuCN·2LiCl) to provide the expected products **8f**–**h** in 59–98% yield (entries 3–5). In the same manner, 3-(2-ethoxycarbonyl-5-nitrofuranyl)zinc pivalate (**6d**) was prepared with excellent regioselectivity (> 98:2) using 2.0 equiv of the base **4** (−10 °C, 1 h). The zinc compound **6d** underwent smoothly Negishi cross-coupling with aryl iodide **7h** and allylation with 3-bromocyclohexene (in the presence of 10 mol % CuCN·2LiCl) in 66% and 70% yields, respectively (entries 6 and 7). Metalation with the new base **4** of the sensitive 6-nitrobenzothiazole (**5e**) proceeded in 79% yield under mild conditions (25 °C, 10 min). The resulting zinc reagent **6e** reacted with *E*-alkenyl iodide **7i**[12] to furnish the

Scheme 3. Reactivity of Heterobenzylzinc Pivalates **6i** and **6j** towards Negishi Cross-Coupling and Allylation Reactions with Various Aryl and Allyl Bromides



coupling product **8k** in 95% yield and with complete retention of the double-bond configuration (entry 8). Addition of 2-bromomethylpropene (**7j**) to **6e**, in the presence of 10 mol % CuCN·2LiCl, led to the allylated derivative **8l** in 88% yield (entry 9).

Furthermore, sensitive heterocyclic aldehydes could efficiently be metalated using the new zinc base TMPZnOPiv·LiCl (**4**). Thus, *N*-methyl-3-formylindole (**5f**) was successfully zincated at position 2 (25 °C, 30 min) providing indolylzinc pivalate **6f**.[7c] The reaction of the latter in Negishi cross-coupling with the aryl iodide **7k** and in CuCN·2LiCl catalyzed allylation with 3-bromocyclohexene (**7d**) gave the indoles **8m**–**n** in 91 to 98% yield (entries 10 and 11).

Other sensitive heterocycles which occur in a plethora of natural products with significant biological properties were also functionalized *via* their zinc pivalate precursors. Hence, chromone (**5g**) was metalated with TMPZnOPiv·LiCl (**4**), exclusively at the β-position to the carbonyl group (−30 °C, 1 h), after preactivation with $BF_3\cdot OEt_2$.[13] The zinc reagent **6g** participated effectively in a Negishi cross-coupling with the aryl iodide **7l** and in an acylation reaction with acyl chloride **7m** after transmetalation to CuCN·2LiCl (entries 12 and 13). Moreover, the coumarin derived zinc pivalate **6h** was formed using the new zinc base **4** and microwave irradiation (80 °C, 1 h).[7b] Quenching with I_2 or allyl bromide (after addition of 10 mol % CuCN·2LiCl) and Pd-catalyzed coupling with the aryl iodide **7n** afforded the anticipated products **8q**–**s** in 92–98% yield (entries 14–16).

Finally, TMPZnOPiv·LiCl (**4**) proved to be successful for the metalation at the benzylic position of five- and six-membered heterocycles. More specifically, 2-picoline (**5i**) was zincated smoothly after 1 h at 25 °C to provide the corresponding zinc pivalate **6i**,[7e] while metalation of MOM-protected 2-methylbenzimidazole **5j** (25 °C, 1 h) led to zinc compound **6j** (Scheme 3).[14] Both zinc pivalates underwent Negishi cross-coupling with aryl bromides **7o** and **7p**, respectively (using $Pd(OAc)_2$ and S-Phos[15] as the catalytic system), as well as copper catalyzed allylation with the bromides **7c** and **7q**. The expected heteroaryls **8t**–**w** were obtained in good yields (73–79%, Scheme 3).[16]

In summary, we have reported the preparation of a new selective zinc amide base, TMPZnOPiv·LiCl (**4**).[17] This base provides a fast and efficient access to zinc pivalates of a wide range of aromatic and heteroaromatic substrates with sensitive functionalities such as a nitro group or an aldehyde. The latter are easy-to-handle powders and exhibit excellent air stability. In addition, they smoothly undergo Negishi cross-couplings, as well as CuCN·2LiCl mediated allylations and acylations with various electrophiles. Further investigations on the reactivity of organozinc pivalates are currently in progress in our laboratory.

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

The authors declare no competing financial interest.

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(12) Alkenyl iodide **7i** was prepared in 87% yield according to the procedure described in: Krishnamurthy, V. R.; Dougherty, A.; Haller, C. A.; Chaikof, E. L. *J. Org. Chem.* **2011**, *76*, 5543.

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(16) Due to the unstable nature of the corresponding iodides (resulting from iodolysis of **6i** and **6j**) the yield of the metalation was not possible to be determined; therefore the overall yield is provided.

(17) **Typical procedure:** 4,6-Dichloropyrimidine (**5a**; 298 mg, 2.0 mmol) was dissolved in dry THF (4 mL), and TMPZnOPiv·LiCl (**4**, 2.6 mL, 0.85 M, 2.2 mmol) was added dropwise at 25 °C. Upon completion of the metalation (30 min), the solvent was carefully removed in high vacuum (0.1 mmHg, 3 h) providing solid 5-(4,6-dichloropyrimidyl) zinc pivalate (**6a**) as a fine yellow powder. This crude material was titrated,[9] and the active zinc species concentration was found to be 0.81 mmol/g, which corresponds to a 78% yield. Next, the solid zinc pivalate **6a** (1.2 g, 1.00 mmol) was dissolved in dry THF (2 mL), and the solution was cooled to −20 °C. CuCN·2LiCl (1.1 mL, 1.00 M, 1.1 mmol) was added followed, after 20 min, by 2-furoyl chloride (392 mg, 3.0 mmol). The reaction mixture was warmed slowly to 25 °C and stirred for 3 h. Then, sat. aq. NH_4Cl (10 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (silica gel, *i*hexane/EtOAc = 10:1) afforded the pyridine **6b** (233 mg, 96%) as a brown solid.