ORGANIC
LETTERS

2009
Vol. 11, No. 8
1837−1840

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

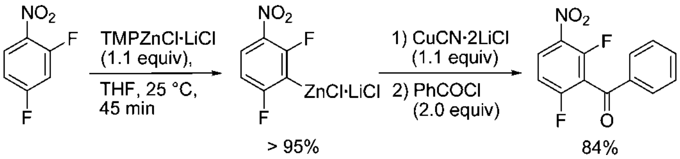
Marc Mosrin and Paul Knochel*

*Department Chemie & Biochemie, Ludwig-Maximilians-Universität,
Butenandtstrasse 5-13, 81377 München, Germany*

paul.knochel@cup.uni-muenchen.de

Received February 16, 2009

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 $R_2NMgCl·LiCl$ such as 2,2,6,6-tetramethylpiperidide 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

---

(1) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Clayden, J.; Stimson, C. C.; Keenan, M. *Chem. Commun.* **2006**, 1393. (c) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376. (d) Henderson, K. W.; Kerr, W. J. *Chem.−Eur. J.* **2001**, 3431. (e) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489. (f) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059. (g) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827. (h) Kauch, M.; Hoppe, D. *Synthesis* **2006**, 1578. (i) Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2371. (j) Hodgson, D. M.; Miles, S. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 93. (k) Yus, M.; Foubelo, F. *Handbook of Functionalized Organometallics*; Knochel, P. Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 1, p 7.

(2) (a) Eaton, P. E.; Martin, R. M. *J. Org. Chem.* **1988**, *53*, 2728. (b) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (c) Eaton, P. E.; Lukin, K. A. *J. Am. Chem. Soc.* **1993**, *115*, 11370. (d) Zhang, M.-X.; Eaton, P. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2169.

(3) (a) Hevia, E.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E.; Sherrington, D. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 68. (b) Andrikopolous, P. C.; Armstrong, D. R.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Mulvey, R. E.; O'Hara, C. T.; Talmard, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 3459. (c) Kondo, Y.; Akihiro, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2331. (d) Shilai, M.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 442. (e) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Bischoff, L.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *J. Org. Chem.* **2005**, *70*, 5190. (f) Eaton, P. E.; Zhang, M.-X.; Komiya, N.; Yang, C.-G.; Steele, I.; Gilardi, R. *Synlett* **2003**, *9*, 1275.

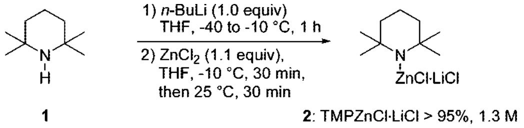
(4) (a) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481. (b) Farkas, J.; Stoudt, S. J.; Hannawalt, E. M.; Pajeski, A. D.; Richey, H. G. *Organometallics* **2004**, *23*, 423. (c) Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *Tetrahedron Lett.* **2004**, *45*, 6697.

(5) (a) Garcia-Alvarez, P.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Weatherstone, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 8079. (b) Mulvey, R. E. *Organometallics* **2006**, *25*, 1060. (c) Mulvey, R. E. *Chem. Commun.* **2001**, 1049. (d) Westerhausen, M. *Dalton Trans.* **2006**, 4755. (e) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802.

10.1021/ol900342a CCC: $40.75

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-$Bu_2Zn(TMP)Li$) 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-bases[9] 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 $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ 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 $ZnCl_2$ (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 constrast to $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, this complex base showed a very good chemoselectivity for the zincation at 25 °C of various sensitive aromatics and heterocycles.

Several sensitive heteroarenes[10] such as pyridazines,[11] pyrimidines,[13] and pyrazines[14] are cleanly zincated at 25 °C using the new base TMPZnCl·LiCl (**2**; Scheme 2 and Table 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 I_2 or 4-fluorobenzoyl chloride (after transmetalation with $CuCN{\cdot}2LiCl$)[15] or undergo a Negishi[16] cross-coupling leading 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

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

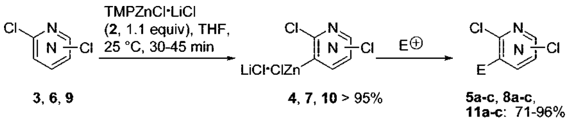
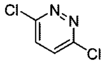
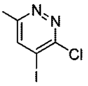
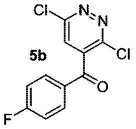
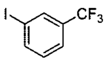
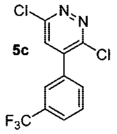
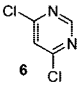
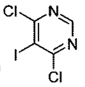
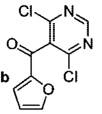
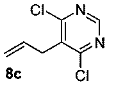
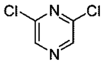
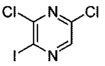
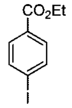
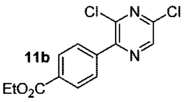
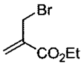
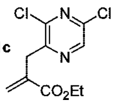


Table 1. Products Obtained by Regio- and Chemoselective Zincation of Diazines of Type **3**, **6**, and **9** with TMPZnCl·LiCl (**2**; 1.1 equiv; 25 °C) and Quenching with Electrophiles

entry	substrate of type **3**, **6** and **9**	electrophile	product	yield, %^{a}
1	 **3**	I_2	**5a** 	84
2	**3**	4-fluorobenzoyl chloride	**5b** 	96^b
3	**3**		**5c** 	83^c
4	 **6**	I_2	**8a** 	83
5	**6**	2-furoyl chloride	**8b** 	71^b
6	**6**	allyl bromide	**8c** 	89^d
7	 **9**	I_2	**11a** 	90
8	**9**		**11b** 	87^c
9	**9**		**11c** 	72^d

[a] Isolated, analytically pure product. [b] Transmetalation performed with 1.1 equiv of $CuCN{\cdot}2LiCl$. [c] Obtained by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (3 mol %) and (o-furyl)$_3$P (6 mol %). [d] Transmetalation performed with 5 mol % of $CuCN{\cdot}2LiCl$.

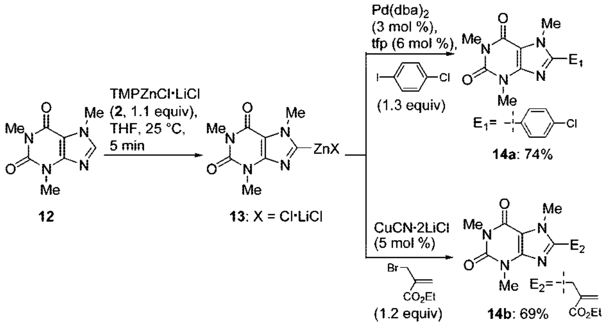
---

(6) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673. (c) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497. (d) Mosrin, M.; Boudet, N.; Knochel, P. *Org. Biomol. Chem.* **2008**, *6*, 3237. (e) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681. (f) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1503.

converted within 45 min at 25 °C to the 5-zincated species. Trapping with I_2 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 Negishi[16] cross-coupling or an allylation with ethyl 2-(bro-momethyl)acrylate[17] (after addition of CuCN•2LiCl) affording the expected products **11a−c** in 72−90% yields (entries 7−9).

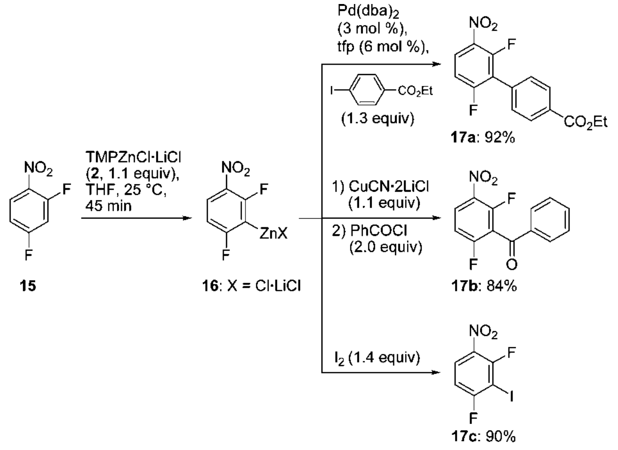
Other sensitive heterocycles such as purines[18] can be metalated as well under mild conditions (Scheme 3). Thus, caffeine (**12**)[19] undergoes a smooth zincation using TMP-ZnCl•LiCl (**2**; 1.1 equiv, 25 °C, 5 min) furnishing the zinc species **13**. Negishi[16] cross-coupling or trapping with ethyl 2-(bromomethyl)acrylate[17] (after addition of CuCN•2LiCl) led to the purine derivatives **14a** and **14b**, respectively, in 74% and 69% yields.

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



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 Negishi[16] 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 I_2, 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)acrylate[17] (after addition of CuCN•2LiCl) leads to the allyled derivative **23** in 67% yield. Zincation of methyl 5-nitrofuran-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

---

(7) (a) Micetich, R. G. *Can. J. Chem.* **1970**, *48*, 2006. (b) Meyers, A. I.; Knaus, G. N. *J. Am. Chem. Soc.* **1974**, *95*, 3408. (c) Knaus, G. N.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 1189. (d) Miller, R. A.; Smith, M. R.; Marcune, B. *J. Org. Chem.* **2005**, *70*, 9074. (e) Hilf, C.; Bosold, F.; Harms, K.; Marsch, M.; Boche, G. *Chem. Ber. Rec.* **1997**, *130*, 1213.

(8) (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.

(9) (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. (e) Clegg, W.; Dale, S. H.; Harrington, R. W.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2374. (f) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatly, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921.

(10) (a) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685. (b) Mosrin, M.; Knochel, P. *Chem.−Eur. J.* **2009**, *15*, 1468. (c) Hlavinka, M. L.; Hagadorn, J. R. *Tetrahedron Lett.* **2006**, *47*, 5049. (d) Seggio, A.; Chevallier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602.

(11) Wunderlich, S. H.; Knochel, P. *Chem. Commun.* **2008**, *47*, 6387.

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

(13) (a) Turck, A.; Plé, N.; Quéguiner, G. *Heterocycles* **1990**, *37*, 2149. (b) Radinov, R.; Chanev, C.; Haimova, M. *J. Org. Chem.* **1991**, *56*, 4793. (c) Imahori, T; Kondo, Y. *J. Am. Chem. Soc.* **2003**, *125*, 8082.

(14) Turck, A.; Trohay, D.; Mojovic, L.; Plé, N.; Quéguiner, G. *J. Organomet. Chem.* **1991**, *412*, 301.

(15) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(16) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

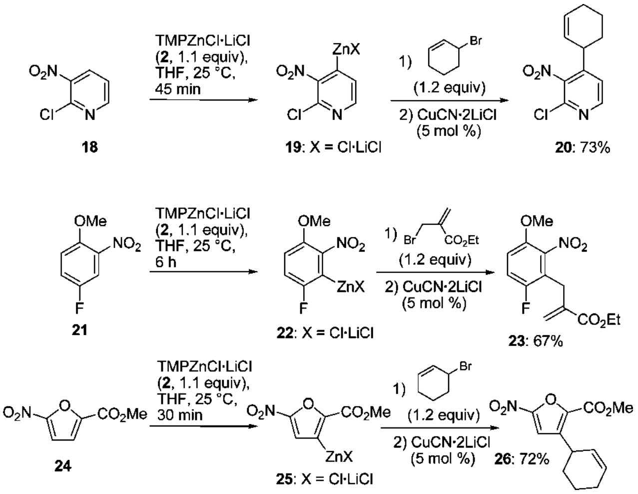
(17) Villiéras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.

(18) (a) Boudet, N; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2007**, *10*, 1715. (b) Tobrman, T.; Dvorak, D. *Org. Lett.* **2006**, *8*, 1291.

(19) Do, H-Q; Kashif-Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.

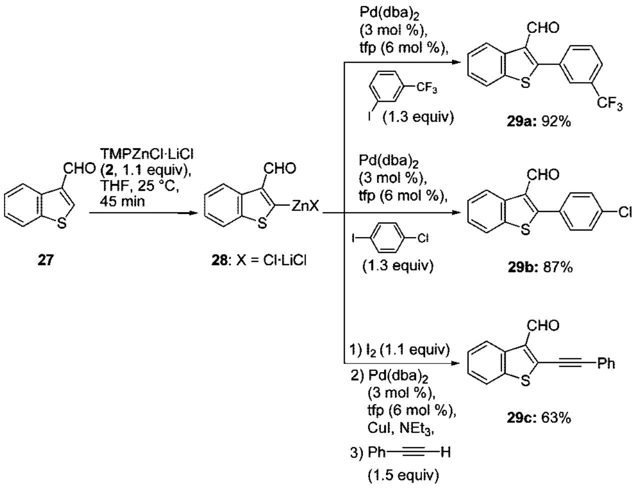
(20) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1610.

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 Negishi[16] cross-coupling or a Sonogashira[22] reaction giving the arylated heterocycles **29a−c** in 63−92% yield.

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•LiCl[23] (**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.

Acknowledgment. We thank the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft (DFG), and the European Research Council (ERC) for financial support. We also thank Evonik GmbH, BASF AG, and Chemetall GmbH for the generous gift of chemicals.

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

OL900342A

---

(21) (a) Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 1017. (b) Gong, L.-Z.; Knochel, P. *Synlett* **2005**, 267.

(22) (a) Benderitter, P.; de Araujo, J. X., Jr.; Schmitt, M.; Bourguignon, J. J. *Tetrahedron* **2007**, *63*, 12465. (b) Kim, J. T.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467. (d) Sonogashira, K. *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol. 3.

(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 quenchend with a saturated aq NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane, 1:2) furnished compound **17b** (221 mg, 84% yield) as a colorless solid.