

High Temperature Metalation of Functionalized Aromatics and Heteroaromatics using $(\text{tmp})_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$ and Microwave Irradiation

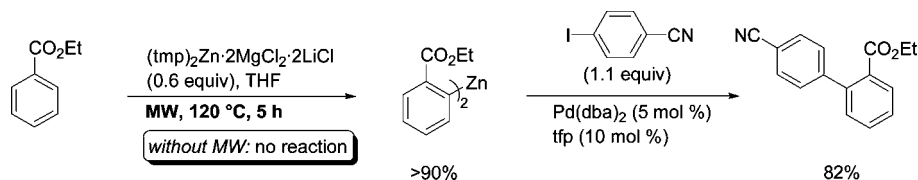
Stefan Wunderlich and Paul Knochel*

Department Chemie and Biochemie, Ludwig-Maximilians-Universität, Butenandtstrasse 5–13, 81377 Munich, Germany

paul.knochel@cup.uni-muenchen.de

Received September 10, 2008

ABSTRACT



A wide range of polyfunctional aryl and heteroaryl zinc reagents were efficiently prepared in THF *via* direct zincation using $(\text{tmp})_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$ and microwave irradiation. Ester and cyano functions as well as ketones are compatible with the high temperatures of the zincation. The resulting *bis*-organo zinc species undergo a number of subsequent reactions leading to highly functionalized aromatics and heteroaromatics in good to excellent yields.

The metalation of aromatic and heteroaromatic rings is of central importance for pharmaceutical, agrochemical, and material research. A number of new selective bases for achieving chemoselective and regioselective metalations have been reported.¹ Especially ate-bases have found useful applications.² Recently, we reported that magnesium bases

such as $\text{tmpMgCl}\cdot\text{LiCl}$ and $(\text{tmp})_2\text{Mg}\cdot 2\text{LiCl}$ (tmp = 2,2,6,6-tetramethylpiperidyl) proved to be highly active and selective magnesium bases.³ Additionally, for the tolerance of very sensitive functionalities like aldehydes or nitro groups, we have prepared the neutral mixed-metal complex base $(\text{tmp})_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$ (**1**).⁴ LiCl leads to a high base solubility,⁵ and MgCl_2 is responsible for the high base reactivity.⁶ The combination of these Lewis-acids⁷ with

(1) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827. (c) Hodgson, D. M.; Miles, S. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 93. (d) Yus, M.; Foubelo, F. *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 1.

(2) (a) Mulvey, R. E. *Organometallics* **2006**, *25*, 1060. (b) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802. (c) Kondo, Y.; Shilai, H.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539. (d) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otami, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514. (e) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatly, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921. (f) Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E.; O'Hara, C. T.; Russo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 731. (g) Usui, S.; Hashimoto, Y.; Morey, J. V.; Wheatley, A. E. H.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, *129*, 15102.

(3) (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) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681. (d) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1503.

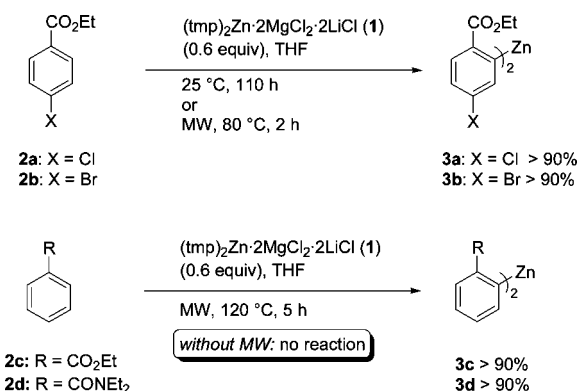
(4) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685.

(5) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 159. (c) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497.

(6) Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 1017.

(tmp)₂Zn⁸ allows highly chemoselective zincations. Over the last decades, microwave irradiation has been used to accelerate numerous organic reactions⁹ including organometallic reactions.¹⁰ Because organozinc reagents of the type RZnX feature a good thermal stability and tolerate functional groups even at elevated temperature,¹¹ we have envisioned to force (tmp)₂Zn-mediated zincations using microwave irradiation. Thus, the direct zincation of ethyl 4-chlorobenzoate or ethyl 4-bromobenzoate with (tmp)₂Zn·2MgCl₂·2LiCl (**1**) at 25 °C requires 110 h for a complete reaction. By applying microwave irradiation, a complete zincation was achieved within 2 h (80 °C) leading to the expected bis-arylzinc species **3a** and **3b** in >90% yield (Scheme 1).

Scheme 1. Zincation of **2a–d** Using **1** With and Without Microwave Irradiation



Additionally, ethyl benzoate (**2c**) or *N,N*-diethyl benzamide, which could not be metalated at 25 °C, reacted with (tmp)₂Zn·2MgCl₂·2LiCl (**1**) under microwave irradiation (120 °C, 5 h) leading to the corresponding zinc reagents **3c–d** in >90% yield (Scheme 1). The microwave irradiation is essential since heating of **2c** or **2d** by using an oil bath at 120 °C provides only 10–20% of the zinc reagents **3c–d**

after 5 h of reaction time. The zincated species **3a–d** could either undergo a copper-mediated acylation¹² or Pd-catalyzed cross-coupling reactions.¹³ The desired biphenyls **4a–d** were isolated in 82–86% yield (Table 1, entries 1–4).

This procedure proved to be quite general (see Table 1). Thus, the zincation of terephthalic acid diethyl ester (**2e**) proceeded after 4 h of (90 °C) and a Pd-catalyzed cross-coupling reaction¹³ afforded the desired biphenyl **4e** in 74% yield (entry 5). In contrast, ethyl 4-cyanobenzoate (**2f**) was regioselectively zincated within only 1 h (80 °C) at 2-position (entry 6).¹⁴ Quenching of the metalated intermediate with ethyl 2-(bromomethyl)acrylate¹⁵ in the presence of CuCN·2LiCl (25 mol %)¹² furnished the allylated product **4f** in 76% yield. Interestingly, ethyl 2-fluorobenzoate (**2g**) and phthalic acid diethyl ester (**2h**) required a longer metalation time (3–4 h at 90–95 °C). After Pd-catalyzed cross-coupling reactions,¹³ the functionalized esters **4g** and **4h** were obtained in 71–74% yield (entries 7 and 8). Also the more sensible benzoic acid methyl ester derivatives like isophthalic acid dimethyl ester (**2i**) and methyl 4-chlorobenzoate (**2j**) underwent a smooth zincations within 2 h and Pd-catalyzed cross-coupling reactions¹³ led to the diesters **4i** and **4j** in 73–79% yield (entries 9 and 10). Furthermore, 2-fluorobenzonitrile (**2k**) and 4-fluorobenzonitrile (**2l**) were reacted with the base **1** leading to the zincated species within 3 h at 80 °C (entries 11 and 12). Pd-catalyzed cross-coupling reactions¹³ gave the biaryls **4k** and **4l** in 88–89% yield. Finally 4-fluorobenzophenone (**2m**) provided a zinc reagent bearing a keto group within 5 h (80 °C). After a Pd-catalyzed cross-coupling reaction¹³ the functionalized benzophenone **4m** was isolated in 70% (entry 13).

We have extended this zincation procedure to heterocyclic systems. Ethyl 2-chloronicotinate (**5a**) could be smoothly zincated within 1 h and a copper-mediated acylation¹² gave the ketone **6a** in 80% yield (entry 14). 4-Cyanopyridine (**5b**) underwent a zincation in 2-position (entry 15). The reaction with ethyl 2-(bromomethyl)acrylate¹⁵ in the presence of CuCN·2LiCl (25 mol %)¹² led to the acrylate derivate **6b** in 68% yield. Substrates such as benzothiophene (**5c**), benzofuran (**5d**) and could hardly be zincated with the base **1** at 25 °C. However, microwave irradiation allowed a smooth zincation at 120 °C. Trapping of the resulting zincated heterocycles with various aryl iodides in the presence of a Pd-catalyst¹³ afforded the heterocycles **6c–d** in 95% yield (entries 16 and 17).

In conclusion, we have reported that in contrast to well-known low temperature lithiations¹ and magnesiations,^{2b,3} a high temperature zincation of various *functionalized aromatics and heteroaromatics* using the complex base (tmp)₂Zn·2MgCl₂·2LiCl (**1**) and microwave irradiation is feasible. This mode of heating proved to be essential since an alternative heating with an oil bath at the same temper-

(7) (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vols. 1 and 2. (b) *Lewis Acid Reagents: A Practical Approach*; Yamamoto, H., Ed.; Oxford University Press: Oxford, 1999. (c) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570.

(8) (a) Hlavinka, M.; Hagadorn, J. *Tetrahedron Lett.* **2006**, *47*, 5049. (b) Hlavinka, M.; Hagadorn, J. *Organometallics* **2007**, *26* (17), 4105. (c) Rees, W.; Just, O.; Schumann, H.; Weimann, R. *Polyhedron* **1998**, *17*, 1001.

(9) (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldiser, L.; Laberge, L.; Rousell, R. *Tetrahedron Lett.* **1986**, *27*, 279. (b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945. (c) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002. (d) *Microwave-Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell Publishing: Oxford, 2005. (e) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006. (f) *Microwave Methods in Organic Synthesis*; Larhed, M., Olofsson, K., Eds.; Springer: Berlin, 2006.

(10) (a) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (c) Tsukamoto, H.; Matsumoto, T.; Kondo, Y. *J. Am. Chem. Soc.* **2008**, *130*, 388. (d) Shore, G.; Morin, S.; Organ, M. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2761. (e) Fustero, S.; Jimenez, D.; Sanchez-Rosello, M.; del Pozo, C. J. *Am. Chem. Soc.* **2007**, *129*, 6700. (f) Constant, S.; Tortoioli, S.; Müller, J.; Linder, D.; Buron, F.; Lacour, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8979.

(11) (a) Walla, P.; Kappe, C. O. *Chem. Commun.* **2004**, 564. (b) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.

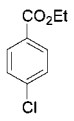
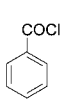
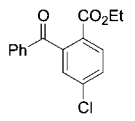
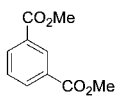
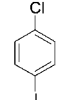
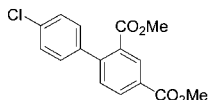
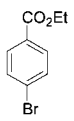
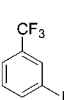
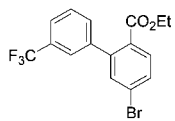
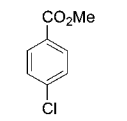
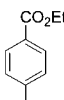
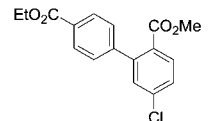


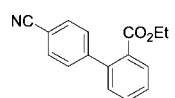
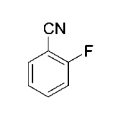
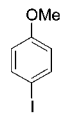
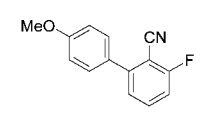


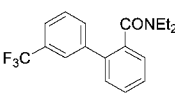
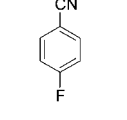
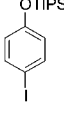
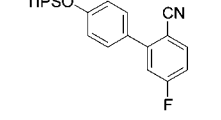
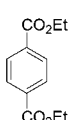
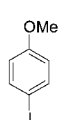
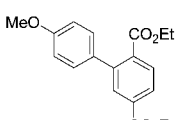
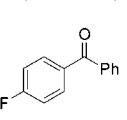
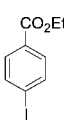
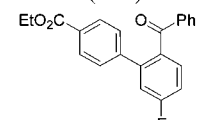
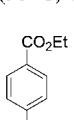
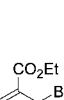
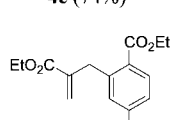
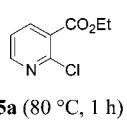
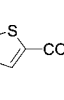
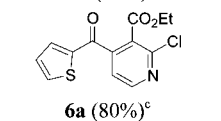
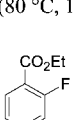
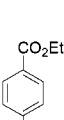
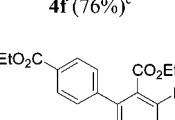
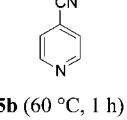

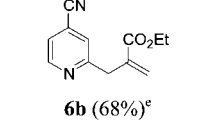
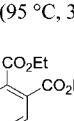
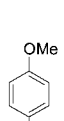
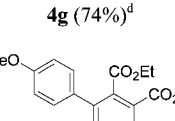
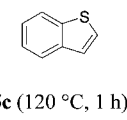
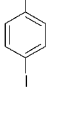
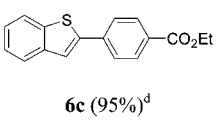
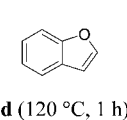
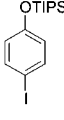
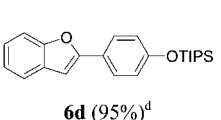
(12) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. J. *Org. Chem.* **1988**, *53*, 2390. (b) Knochel, P.; Rao, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 6146.

(13) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

(14) In contrast, the metalation of ethyl 3-cyano benzoate led to a 3:1 ratio between position 2 and position 6 (80 °C, 1 h).

(15) Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.

Table 1. Products of Type 4 and Type 6 Obtained by Zincation Using (tmp)₂Zn·2MgCl₂·2LiCl (**1**) and Microwave Irradiation and Subsequent Reactions with Electrophiles

entry	substrate ^a	electrophile	product (yield) ^b	entry	substrate ^a	electrophile	product (yield) ^b
1			 4a (86%) ^c	9			 4i (79%) ^d
2			 4b (83%) ^d	10			 4j (73%) ^c
3			 4c (82%) ^d	11			 4k (88%) ^d
4			 4d (85%) ^d	12			 4l (89%) ^d
5			 4e (74%) ^d	13			 4m (70%) ^d
6			 4f (76%) ^c	14			 6a (80%) ^c
7			 4g (74%) ^d	15			 6b (68%) ^c
8			 4h (71%) ^d	16			 6c (95%) ^d
				17			 6d (95%) ^d

^a Numbers in parentheses refer to the metalation conditions. ^b Yields of pure and isolated material. ^c A transmetalation with CuCN·2LiCl (1.1 equiv) was performed. ^d Obtained by palladium-catalyzed cross-coupling using Pd(dba)₂ (5 mol %) and (*o*-furyl)₃P (10 mol %). ^e CuCN·2LiCl (25 mol %) was used.

atures leads only to low metalation rates (see discussion about Scheme 1). Remarkably, functionalities such as an ester, a cyano group or a ketone group are tolerated at these high temperatures (60–120 °C). The scope and further applications of this method are investigated in our laboratories.

Acknowledgment. We thank the Fonds der Chemischen Industrie, the DFG, Merck Research Laboratories (MSD),

Chemetall GmbH (Frankfurt), BASF AG (Ludwigshafen), and W. C. Heraeus GmbH (Hanau) for financial support.

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

OL802118E