Letter

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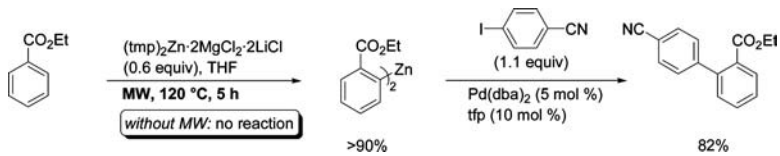

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High Temperature Metalation of Functionalized Aromatics and Heteroaromatics using $(tmp)_2Zn\cdot 2MgCl_2\cdot 2LiCl$ and Microwave Irradiation

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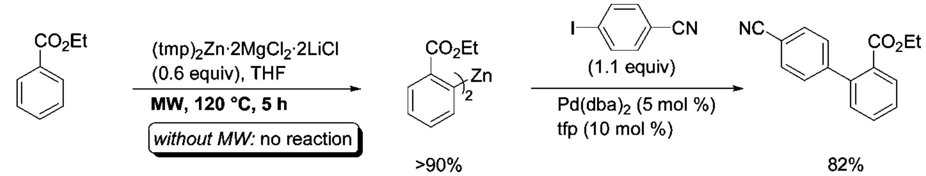
ABSTRACT



A wide range of polyfunctional aryl and heteroaryl zinc reagents were efficiently prepared in THF *via* direct zincation using $(tmp)_2Zn\cdot 2MgCl_2\cdot 2LiCl$ 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 tmpMgCl•LiCl and $(tmp)_2Mg\cdot 2LiCl$ (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 $(tmp)_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**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-acids[7] with

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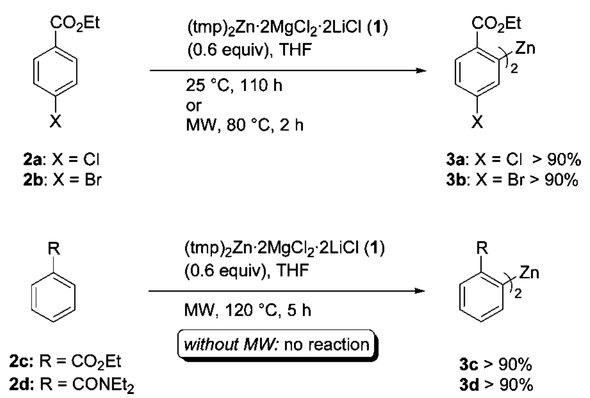
$(tmp)_2Zn$[8] allows highly chemoselective zincations. Over the last decades, microwave irradiation has been used to accelerate numerous organic reactions[9] including organometallic reactions.[10] Because organozinc reagents of the type RZnX feature a good thermal stability and tolerate functional 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 $(tmp)_2Zn•2MgCl_2•2LiCl$ (**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 $(tmp)_2Zn•2MgCl_2•2LiCl$ (**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 acylation[12] 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 reaction[13] 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)acrylate[15] 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 reactions[13] 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 reactions[13] 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 reaction[13] 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 acylation[12] 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)acrylate[15] 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-catalyst[13] 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 lithiations[1] and magnesiations,[2b,3] a high temperature zincation of various *functionalized aromatics and heteroaromatics* using the complex base $(tmp)_2Zn•2MgCl_2•2LiCl$ (**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-

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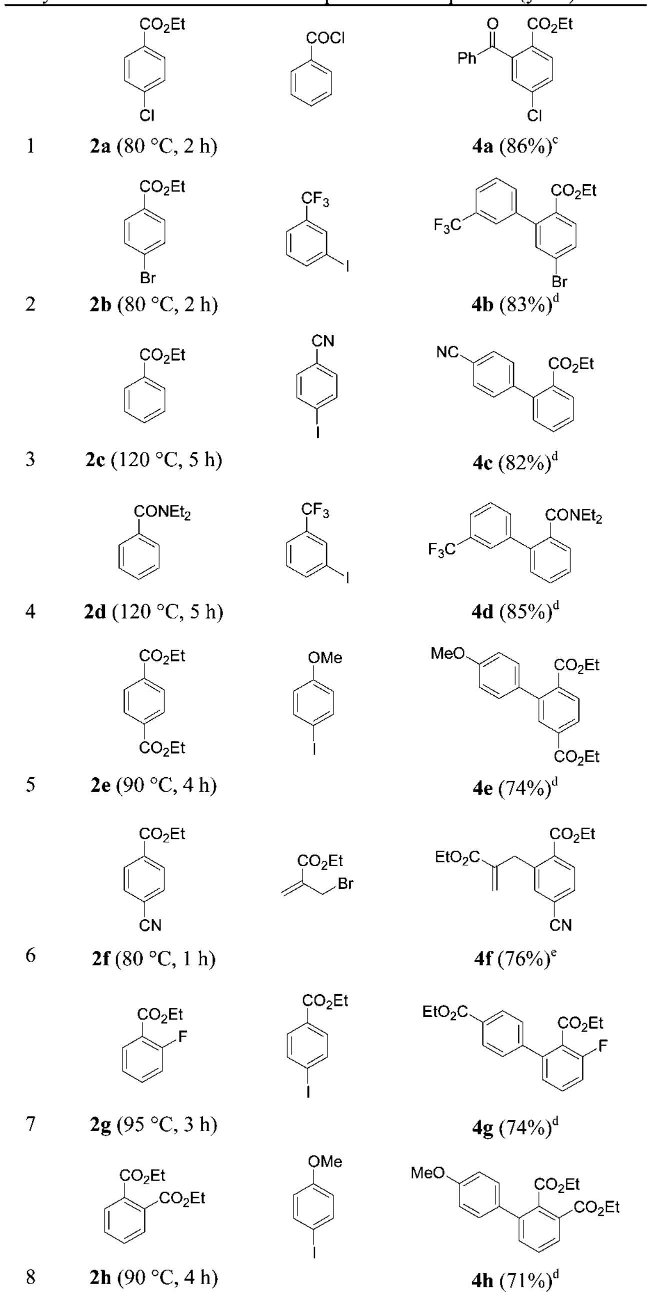
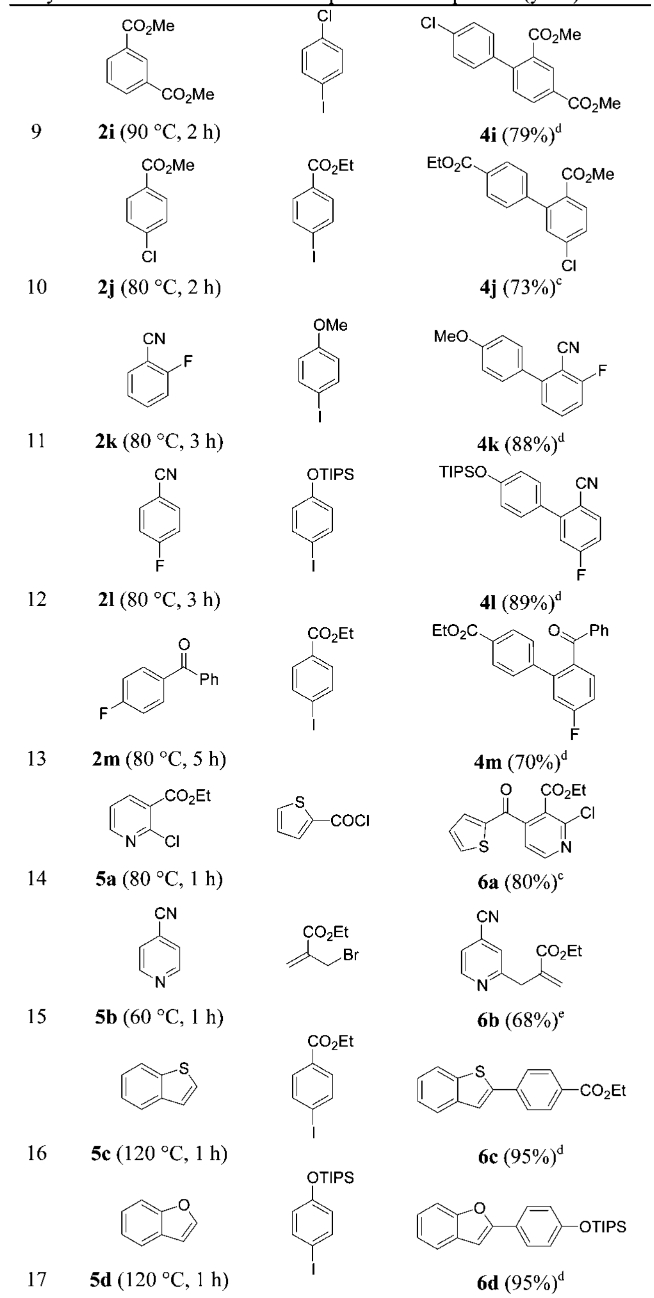
Table 1. Products of Type **4** and Type **6** Obtained by Zincation Using $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**1**) and Microwave Irradiation and Subsequent Reactions with Electrophiles





entry	substrate[a]	electrophile	product (yield)[b]
1	**2a** (80 °C, 2 h)		**4a** (86%)[c]
2	**2b** (80 °C, 2 h)		**4b** (83%)[d]
3	**2c** (120 °C, 5 h)		**4c** (82%)[d]
4	**2d** (120 °C, 5 h)		**4d** (85%)[d]
5	**2e** (90 °C, 4 h)		**4e** (74%)[d]
6	**2f** (80 °C, 1 h)		**4f** (76%)[e]
7	**2g** (95 °C, 3 h)		**4g** (74%)[d]
8	**2h** (90 °C, 4 h)		**4h** (71%)[d]
9	**2i** (90 °C, 2 h)		**4i** (79%)[d]
10	**2j** (80 °C, 2 h)		**4j** (73%)[c]
11	**2k** (80 °C, 3 h)		**4k** (88%)[d]
12	**2l** (80 °C, 3 h)		**4l** (89%)[d]
13	**2m** (80 °C, 5 h)		**4m** (70%)[d]
14	**5a** (80 °C, 1 h)		**6a** (80%)[c]
15	**5b** (60 °C, 1 h)		**6b** (68%)[e]
16	**5c** (120 °C, 1 h)		**6c** (95%)[d]
17	**5d** (120 °C, 1 h)		**6d** (95%)[d]

[a] Numbers in parentheses refer to the metalation conditions. [b] Yields of pure and isolated material. [c] A transmetalation with $CuCN{\cdot}2LiCl$ (1.1 equiv) was performed. [d] Obtained by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol %) and $(o\text{-furyl})_3P$ (10 mol %). [e] $CuCN{\cdot}2LiCl$ (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.

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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.

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