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Synthetic Methods

$(tmp)_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$: A Chemoselective Base for the Directed Zincation of Sensitive Arenes and Heteroarenes**

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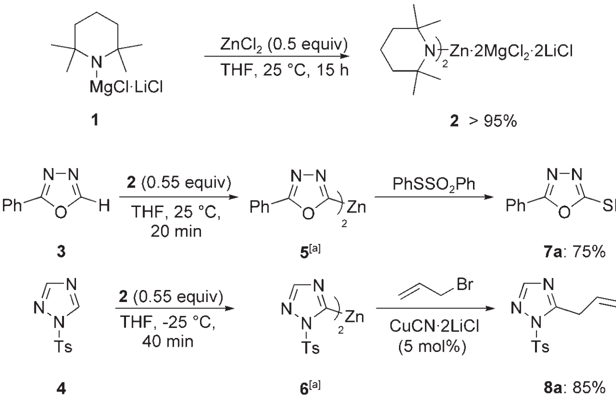
The directed metalation of arenas and heteroarenes is an important method for the functionalization of these scaffolds. Lithium bases have been used extensively to *ortho*-metalate various unsaturated systems.[1] The use of magnesium bases pioneered by Eaton et al.[2] has recently found renewed interest.[3] There are a number of useful synthetic applications of lithium magnesiates[4,5] as well as mixed Mg/Li bases of the type $R_2NMgCl{\cdot}LiCl$. (2,2,6,6-Tetramethylpiperidide)magnesium chloride–lithium chloride, (tmp)MgCl·LiCl (**1**), proved to be especially effective and is compatible with functional groups such as esters, nitriles, and aryl ketones.[6] More sensitive functionalities such as aldehydes and nitro groups are not tolerated. Also some classes of heterocycles, for example 1,3- and 1,2-oxazoles and 1,2,5- and 1,3,4-oxadiazoles, provide unstable lithiated or magnesiated intermediates, which are prone to ring opening.[7] Lithium di-*tert*-butyl-(2,2,6,6-tetramethylpiperidino)zincate, Li[tBu$_2$(tmp)Zn], was reported by Kondo et al. to be an excellent base for the zincation of various arenes.[8] As highly reactive zincates or related ate bases[9] may not be compatible with aldehydes or nitro groups, we have explored the preparation of neutral zinc bases for the directed zincation of arenes and heteroarenes.

We found that treatment of (tmp)MgCl·LiCl (**1**)[6] with $ZnCl_2$ (0.5 equiv, 25 °C, 15 h) provides $(tmp)_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$ (**2**) (Scheme 1). The resulting solution of the complex base has a high activity for the zincation of sensitive heterocycles such as 2-phenyl-1,3,4-oxadiazole (**3**) and *N*-tosyl-1,2,4-triazole (**4**). The lithiated as well as the magnesiated complexes of **3** and **4** are subject to fragmentation.[7,10] However, the reactions of **3** and **4** with **2** (0.55 equiv) provided the zincated heterocycles **5** and **6** after 20 min at 25 °C and 40 min at −25 °C, respectively. When (tmp)MgCl·LiCl was used, the magnesiated species of **3** could be prepared only at temperatures below −70 °C. After quenching with $PhSSO_2Ph$ or allyl bromide in the presence of catalytic amounts of CuCN·2 LiCl[11] (5 mol %), the expected substituted heterocycles **7a** and **8a** were isolated in 75–85 % yield (Scheme 1).



Scheme 1. Preparation of **2** and its reactions with sensitive azole derivatives. [a] $MgCl_2$ and LiCl are omitted for the sake of clarity.

The presence of $MgCl_2$ and LiCl in solutions of $(tmp)_2Zn$[12] was essential for the solubility and high reactivity of the base **2**. In the absence of either $MgCl_2$ or LiCl the metalations of arenes were sluggish and solubility problems were encountered. Additional examples of the zincation of oxadiazole **3**, bromothiazoles **9a**,**b**, and benzothiazole (**10a**) are described in Table 1 (entries 1–7).

The heterocyclic zinc reagents derived from **9** and **10** reacted with various electrophiles such as D_2O (Table 1, entry 2), iodine (Table 1, entries 1 and 4), and Ph_2PCl[13] (Table 1, entry 7). The homocoupling[14] of the organozinc compound derived from **9b** proceeded readily in the presence of chloranil (1.2 equiv, −40 °C to 0 °C, 5 h) to provide the interesting 1,3-thiazole dimer **8e** in 91 % yield (Table 1, entry 5).[15] The mixed base **2** allows the smooth zincation of a range of arenes and heteroarenes bearing various functions (Scheme 2, Scheme 3, and Table 1). Thus, the aromatic diester **11a** bearing three potentially acidic aromatic H atoms was regioselectively zincated in position 6. The resulting diarylzinc species **12a** was readily benzoylated with PhCOCl and CuCN·2 LiCl,[11] leading to the benzophenone **13a** in 83 % yield. The ester-substituted pyridine **11b** was zincated with **2** (0.55 equiv) within 5 h at 25 °C leading to the polyfunctional pyridine derivative **12b** (Scheme 2). Acylation in the presence of CuCN·2 LiCl[11] and tBuCH$_2$COCl provided the pyridine **13b** in 75 % yield.

Interestingly, coumarine (**11c**) underwent a smooth zincation at position 3 (Scheme 2). The resulting zincated coumarine derivate **12c** reacted with ethyl 4-iodobenzoate by a Negishi cross-coupling[16] in the presence of [Pd(dba)$_2$] (5 mol %) and the ligand tri(2-furyl)phosphane (tfp)

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tmp = 2,2,6,6-tetramethylpiperidide.

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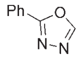
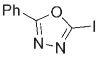
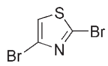
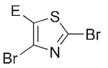
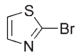
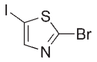
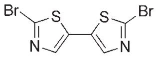
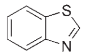
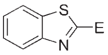
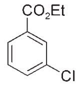
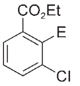
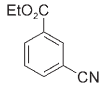
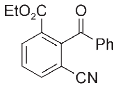
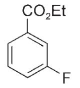
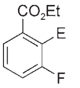
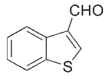
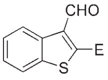
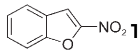
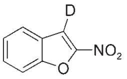
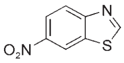
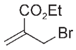
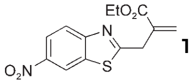
Table 1: Products obtained by the zincation of arenas and heteroarenes with **2** and subsequent reactions with electrophiles.

Entry	Substrate	T [°C], t [h]	E–X	Product	Yield [%][a]
1	 **3**	25, 0.3	I_2	 **7b**	80
2	 **9a**	25, 0.25	D_2O	 **8b**: E = D	91
3		25, 0.25	PhCOCl	**8c**: E = COPh	84[b]
4	 **9b**	25, 0.3	I_2	 **8d**	84
5		25, 0.3	chloranil	 **8e**	91
6	 **10a**	25, 0.5	(allyl)Br	 **8f**: E = allyl	77[c]
7		25, 0.5	Ph_2PCl	**8g**: E = PPh_2	79
8	 **11d**	25, 25	D_2O	 **13d**: E = D	84
9		25, 25	PhCOCl	**13e**: E = COPh	79[b]
10	 **11e**	25, 30	PhCOCl	 **13f**	73[b]
11	 **11f**	25, 12	$tBuCH_2COCl$	 **13g**: E = $COCH_2tBu$	76[b]
12		25, 12	p-C_6H_4CN	**13h**: E = p-C_6H_4CN	69[d]
13	 **14b**	25, 0.25	I_2	 **16b**: E = I	82
14		25, 0.25	p-$C_6H_4CO_2Et$	**16c**: E = p-$C_6H_4CO_2Et$	67[d]
15	 **17a**	−25, 1.5	D_2O	 **19c**	82
16	 **17c**	−50, 0.5		 **19d**	75[c]

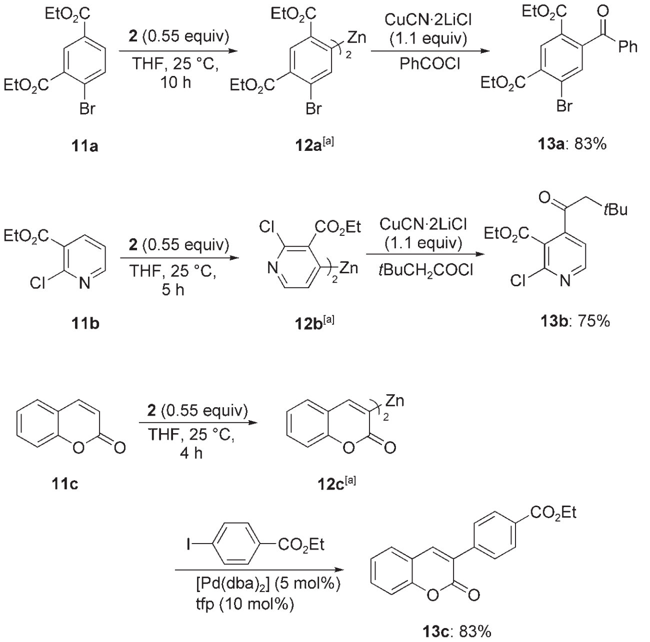
[a] Yield of analytically pure product. [b] Transmetalation with CuCN·2LiCl (1.1 equiv) was performed. [c] Transmetalation with CuCN·2LiCl (5 mol%) was performed. [d] Obtained by palladium-catalyzed cross-coupling.

(10 mol%)[17] to give the 3-arylated coumarine **13c** in 83% yield (Scheme 2).

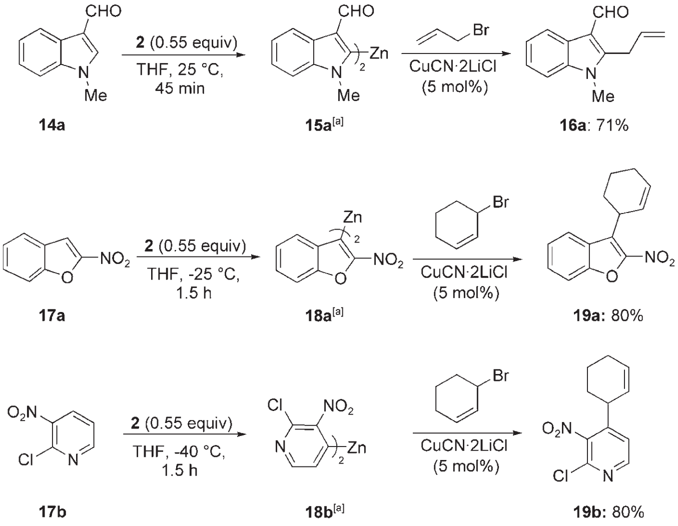
Similarly, the substituted benzoates **11d–f** were smoothly converted to the corresponding diarylzinc compounds. Their reactions with various electrophiles resulted in the expected products **13d–h** in 69–84% yield (Table 1, entries 8–12). A major advantage of the zinc base **2** is that diorganozinc compounds can be prepared that bear very sensitive functional groups such as an aldehyde[18] or a nitro group.[19] Thus, 3-formyl-*N*-methylindole (**14a**) was converted to the corresponding diorganozinc **15a** by treatment with **2** (0.55 equiv; 25°C, 45 min). After allylation with allyl bromide in the presence of CuCN·2LiCl[11] (5 mol%) the desired 2-allylated indole **16a** was obtained in 71% yield (Scheme 3). Related 3-formylbenzothiophene (**14b**) was converted within 15 min at 25°C to the corresponding zinc reagent. After iodolysis or Negishi cross-coupling[16] the expected heterocyclic aldehydes **16b,c** were obtained in yields of 82 and 67%, respectively (Table 1, entries 13 and 14). Finally various nitro-substituted heterocycles were zincated. 2-Nitrobenzofuran (**17a**) reacted with **2** at −25°C (1.5 h) to provide the corresponding zinc reagent **18a**, which was allylated with 3-cyclohexenyl bromide in the presence of catalytic amounts of CuCN·2LiCl[11] (5 mol%) providing the benzofuran derivative **19a** in 80% yield (Scheme 3).

Similarly the nitropyridine **17b** was metalated at −40°C (1.5 h) with $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**2**) leading to the bis(4-pyridyl)zinc derivative **18b**. After allylation with 3-cyclohexenyl bromide, the polyfunctional pyridine **19b** was obtained in 80% yield (Scheme 3). Two additional examples involving a deuteration and an allylation leading to the nitro derivatives **19c** and **19d** are reported in Table 1 (entries 15 and 16).

In summary, we have described the new complex base $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**2**) which does not rely on its "ate" nature for high activity (high kinetic basicity) but rather on the combination with a Lewis acid[20] ($MgCl_2$, LiCl). Remarkably chemoselective zincation can be performed with base **2** and sensitive functions such as aldehydes or a nitro groups are tolerated. Extension of this concept for the development of other new bases is currently underway in our laboratories.



Scheme 2. Preparation of the polyfunctional aryl and heteroaryl diorganozinc compounds **12a–c** bearing an ester or lactone function. [a] $MgCl_2$ and LiCl are omitted for the sake of clarity. dba = dibenzylideneacetone.



Scheme 3. Preparation of diorganozinc compounds bearing an aldehyde or a nitro group. [a] $MgCl_2$ and LiCl are omitted for the sake of clarity.

Experimental Section

2: In an argon-flushed Schlenk flask, $ZnCl_2$ (53.0 mmol, 7.22 g) was dried in vacuo at 140 °C for 4 h. After cooling to room temperature, freshly titrated **1** (100 mmol, 1.00 M, 100 mL) was added dropwise. The resulting mixture was stirred for 15 h at 25 °C. The freshly prepared solution of **2** was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.5 M in THF was obtained.

13a: A dry and argon-flushed 10-mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of the **11a** (0.301 g, 1.0 mmol) in anhydrous THF (1 mL). A solution of **2** (0.50 M in THF, 1.10 mL, 0.55 mmol) was added dropwise, and the reaction mixture was stirred at this temperature for 10 h. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in anhydrous THF. The mixture was then cooled to −20 °C, CuCN·2 LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added, and the reaction mixture stirred for 15 min. Benzoyl chloride (0.353 g, 2.5 mmol) was added dropwise, and the reaction mixture was slowly warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with diethyl ether (3 × 15 mL), and the collected extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation in vacuo. Purification by flash chromatography on silica gel (*n*-pentane/diethyl ether, 3:1) furnished compound **13a** (0.336 g, 83 %) as a colorless solid.

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