Directed Zincation

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tmp_4Zr: An Atom-Economical Base for the Metalation of Functionalized Arenes and Heteroarenes**

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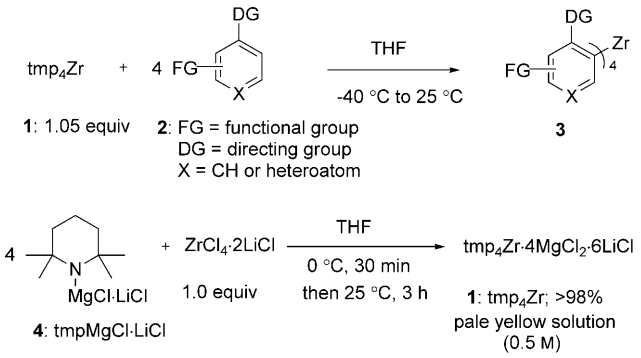
The functionalization of aromatic and heterocyclic ring systems is of central importance in synthetic organic chemistry, beacuse polyfunctional unsaturated units are present in numerous pharmaceuticals and advanced materials.[1] Directed metalation is a convenient method for performing such synthetic tasks. Whereas directed lithiations have been very popular,[2] the recent development of kinetically highly active 2,2,6,6-tetramethylpiperidyl (tmp) bases[3,4] of various transition metals (Mn,[5] Fe,[6] and Ln[7]) that can be solubilized by complexation with lithium chloride allows a unique and simple preparation of polyfunctional Mn, Fe, or La unsaturated organometallic complexes. Early-transition-metal organometallic complexes have a particular reactivity pattern.[8,9] Especially, complexes derived from Ti and Zr are attractive due to their unusual reaction chemistry, the low cost of these metals, and their low toxicity.[9] Herein, we report a new THF-soluble kinetically highly active zirconium base:[10] $tmp_4Zr{\cdot}4\,MgCl_2{\cdot}6\,LiCl$ (abbreviated as tmp_4Zr (**1**)) which for the first time allows a direct zirconation of various functionalized aromatics and heterocycles of type **2** (scheme 1). Remarkably, this base is especially atom economical regarding the amount of transition-metal (0.25 equiv) and the use of tmp groups.[11] All four tmp groups are used effectively in the metalation process allowing the preparation of a range of new, highly functionalized tetraorganozirconium derivatives of type **3** under mild reaction conditions (Scheme 1). Thus, the reaction of ethyl 3-fluorobenzoate (**2a**, 1 equiv) with **1** (0.25 equiv) at 25 °C for 45 min provides the tetraarylzirconium reagent **3a** in over 95 % yield (as indicated by iodolysis or allylation of reaction aliquots). The zirconated reagent **3a** displays a remarkable reactivity. Its allylation with ethyl (2-bromomethyl)acrylate (1.05 equiv, CuCN·2 LiCl (5 mol %), 0 °C, 1 h) furnished the diester **5a**, isolated in 88 % yield (Scheme 2). The addition to benzaldehyde (1.05 equiv, 0 °C, 2 h) led to the lactone **5b** in 86 % yield. A direct palladium-catalyzed cross-coupling without further transmetalation[12a] using $[Pd(PPh_3)_4]$ (3 mol %, 25 °C, 8 h) afforded the biphenyl derivative **5c** in 77 % yield. Styrene oxide was opened by the zirconium reagent **3a** at 50 °C within 1 h providing after workup the annelated lactone **5d** in 65 % yield. Interestingly, the new tetraarylzirconium species (**3a**) reacts smoothly with CO_2 (1 atm, 50 °C, 8 h) furnishing the corresponding acid **5e**, isolated in 84 % yield.[12b,c] Similarly, a range of zirconated aromatic substrates undergo this carboxylation reaction as well leading to the polyfunctional benzoic acids (**5f–j**) in 79–89 % yields (Scheme 2).



Scheme 1. Preparation of **1** and its reaction with aromatics or heterocycles of type **2**.

A range of substituted benzoates were zirconated with **1** (0.25 equiv) at temperatures between −15 °C and 25 °C (see entries 1–10 of Table 1). The resulting zirconated aromatics **2b–j** react with various electrophiles. Thus, a copper(I)-catalyzed acylation[12d] with 2-chlorobenzoyl chloride (1.0 equiv, CuCN·2 LiCl (25 mol %), −20 °C, 1 h) gave the benzophenone **5k** in 82 % yield (entry 1 of Table 1). The addition of **2b** to cyclohexane carbaldehyde (1.0 equiv, 0 °C, 2 h) led to the lactone **5l** in 76 % yield (Table 1, entry 2). A palladium-catalyzed cross-coupling of the zirconated aromatics **2c–e** with various aryl iodides proceeded in each case directly without the need of an additional transmetalation, furnishing the functionalized biphenyls **5m–o** in 78–81 % yields (Table 1, entries 3–5). The stannylation of the tetraarylzirconium reagent derived from **2f** using Me_3SnCl (1.0 equiv, 0 °C, 2 h) gave the arylstannane **5p** in 75 % yield (Table 1, entry 6). Whereas, the zirconation of 3-fluoroanisole (**2g**) with **1** at 25 °C led to a substantial formation of benzyne,[9d] this decomposition pathway can be avoided by performing the zirconation of **2g** at −20 °C (0.25 equiv of **1**, 3 h). Quenching of the resulting tetraarylzirconium compound with thiophene-2-carbonyl chloride (1.0 equiv, CuCN·2 LiCl (25 mol %), −20 °C, 1 h) led to the ketone **5q** in 83 % yield (Table 1, entry 7). The benzonitrile **2h** was metalated by **1** (0.25 equiv, 0 °C, 45 min) in position 2. A cross-coupling

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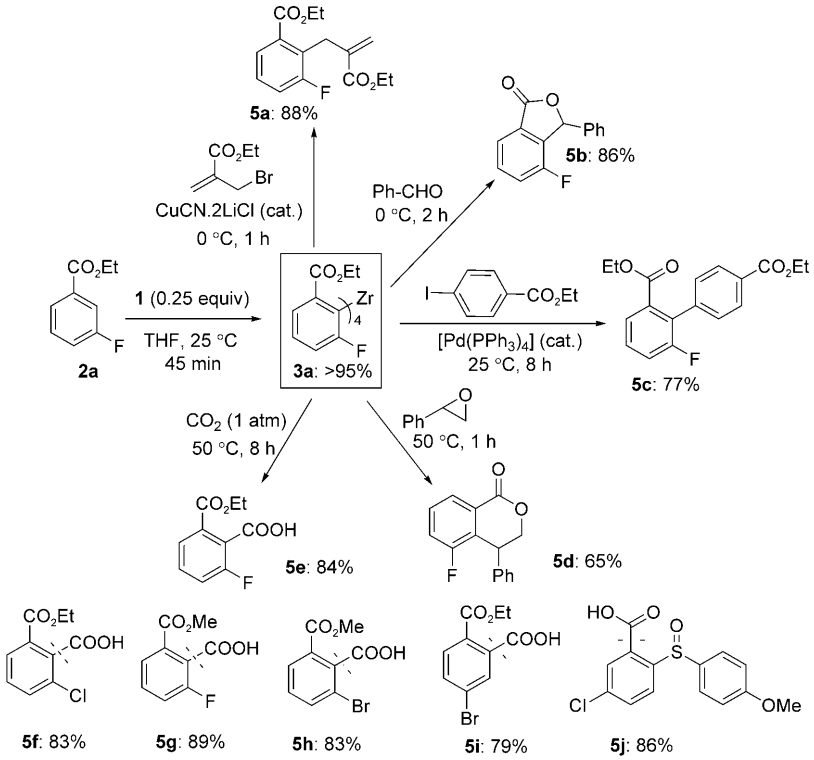
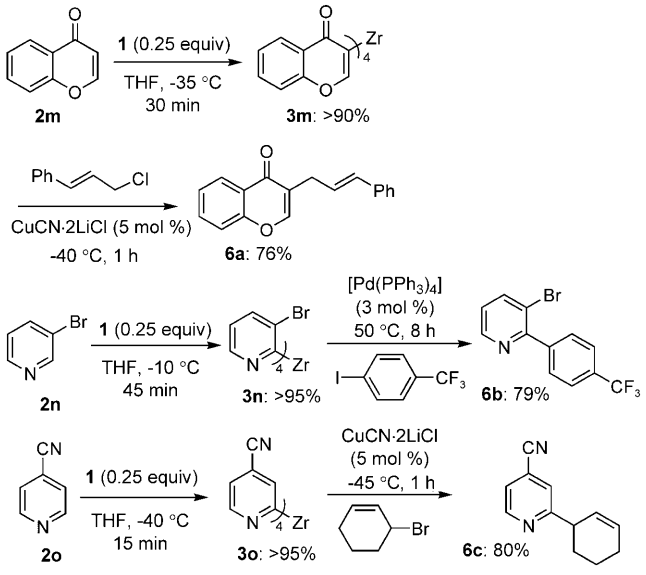


Scheme 2. Preparation of tetraarylzirconium reagent **3a** using **1** and its reactivity with various electrophiles.

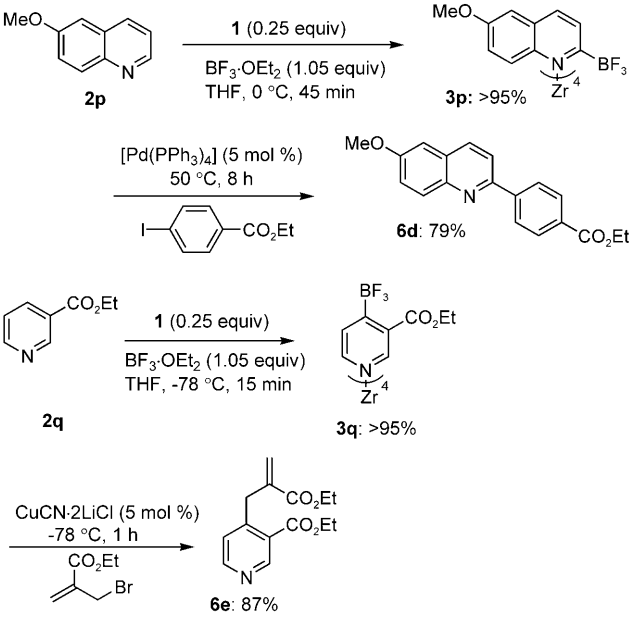
with 4-chloro-1-iodobenzene (0.8 equiv, 25 °C, 8 h) using $[Pd(PPh_3)_4]$ (3 mol %) gave the biphenyl **5r** in 73 % yield (Table 1, entry 8). By treating the ester-substituted aromatic nitrile **2i** with **1** (0.25 equiv) at −15 °C for 1.5 h, a regioselective zirconation at the position *ortho* to the ester function led, after addition of 4-methoxybenzaldehyde, to the lactone **5s** in 79 % yield (Table 1, entry 9). A regioselective metalation with **1** (0.25 equiv, 0 °C, 45 min) was also observed for the bromoester **2j** leading to the biphenyl **5t** in 83 % yield after palladium-catalyzed cross-coupling with 4-trifluoromethyl-1-iodobenzene (0.9 equiv, 25 °C, 8 h; Table 1, entry 10). Sulfamates such as **2k**,**l** are also readily metalated in the position *ortho* to the sulfamate with **1**. After copper-catalyzed acylation with various acid chlorides, the polyfunctional ketones **5u**,**v** were obtained in 79–80 % yields (Table 1, entries 11 and 12).

The functionalization of heterocycles is of key importance for the preparation of novel pharmaceuticals and agrochemicals.[13a] A range of heterocyclic structures could be zirconated using **1**. Thus, chromone (**2m**) reacted smoothly with **1** (0.25 equiv, −35 °C, 30 min) affording the expected zirconium derivative **3m** in approximately 90 % yield. Copper-catalyzed allylation[12d] with cinnamyl chloride (−40 °C, 1 h) provided the S_N2-substitution product **6a** as a single regioisomer in 76 % yield (Scheme 3).

The functionalization of electron-poor pyridines is especially challenging, because of the high tendency of such metalated pyridines to polymerize.[13b,c] Also, the regioselective metalation of substituted pyridines can also be complicated.[13d,e] Treatment of 3-bromopyridine (**2n**) with **1** at −10 °C for 45 min provided a regioselective zirconation in position 2 leading to the tetrapyridylzirconium species **3n**. After a palladium-catalyzed cross-coupling with 4-trifluoromethyl-1-iodobenzene (50 °C, 8 h), the expected pyridine **6b** was obtained in 79 % yield. The sensitive 4-cyanopyridine (**2o**) also reacted smoothly with **1** within 15 min at −40 °C furnish-

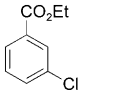
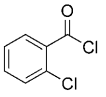
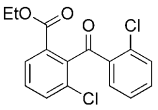
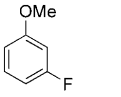
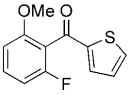
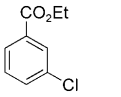
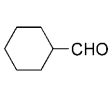
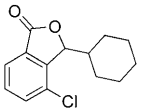
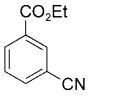
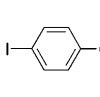
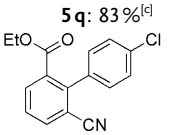
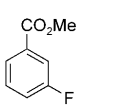
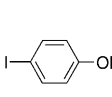
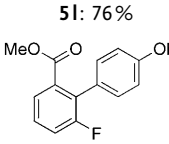
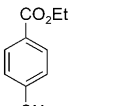
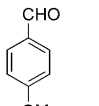
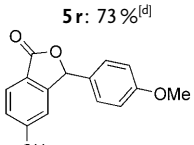
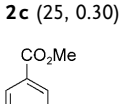
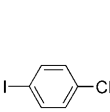
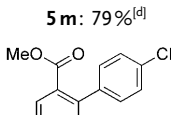
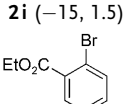
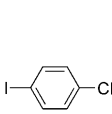
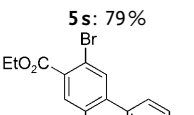
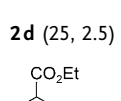
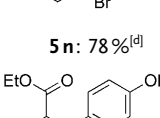
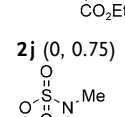
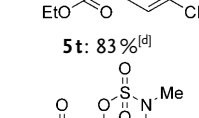
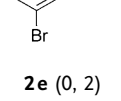
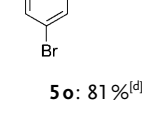
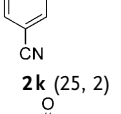
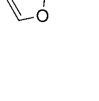
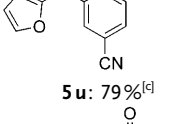


Scheme 3. Direct zirconation of various heterocycles with **1**.



Scheme 4. BF_3-mediated metelation of N-heterocycles using $tmp_4Zr{\cdot}4\,BF_3$.

Table 1: Regioselective zirconation of arenes with **1** and reactions with electrophiles.

Entry	Substrate[a]	Electrophile	Product[b]	Entry	Substrate[a]	Electrophile	Product[b]
1	 **2b** (25, 0.45)		 **5k**: 82%[c]	7	 **2g** (−20, 3)		 **5q**: 83%[c]
2	 **2b** (25, 0.45)		 **5l**: 76%	8	 **2h** (0, 0.75)		 **5r**: 73%[d]
3	 **2c** (25, 0.30)		 **5m**: 79%[d]	9	 **2i** (−15, 1.5)		 **5s**: 79%
4	 **2d** (25, 2.5)		 **5n**: 78%[d]	10	 **2j** (0, 0.75)		 **5t**: 83%[d]
5	 **2e** (0, 2)		 **5o**: 81%[d]	11	 **2k** (25, 2)		 **5u**: 79%[c]
6	 **2f** (0, 2)		 **5p**: 75%	12	 **2l** (25, 4)		 **5v**: 80%[c]

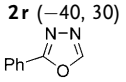
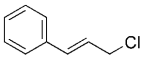
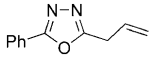
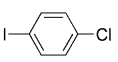
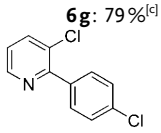
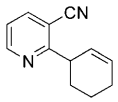
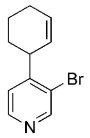
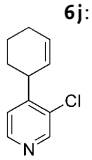
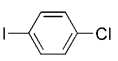
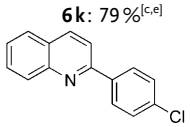
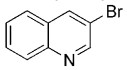
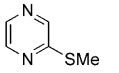
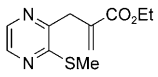
[a] The reaction conditions for the metalation with **1** are given in parentheses (*T* [°C], *t* [h]). [b] Yield of isolated analytically pure product. [c] CuCN·2 LiCl (1.0 M in THF, 0.25 mL, 0.25 mmol) was added. [d] [$Pd(PPh_3)_4$] (3 mol%) was used as catalyst.

ing regioselectivly the tetra(2-pyridyl)zirconium derivative **3o** which, after copper-catalyzed allylation with 3-bromocyclohexene, gave the 2,4-disubstituted pyridine **6c** in 80% yield (Scheme 3).

Recently, we have shown that $BF_3{\cdot}OEt_2$ is compatible with the presence of strong Lewis bases, such as tmpMgCl·LiCl or $tmp_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$.[14] The Lewis pairs formed[15] are reversibly cleaved in the presence of a substrate, such as a pyridine or a quinoline. The new tmp_4Zr base **1** displays a similar behavior. Thus, the reaction of 6-methoxyquinoline (**2p**) with a mixture of **1** (0.25 equiv) and $BF_3{\cdot}OEt_2$ (1.05 equiv, 0 °C, 45 min) provides the mixed Zr–B species **3p** (Scheme 4). The formation of a 2-quinolyltrifluoroborate **3p** was confirmed by ^{13}C-, ^{19}F-, and ^{11}B NMR spectroscopy (see the Supporting Information). Palladium(0)-catalyzed cross-coupling with ethyl 4-iodobenzoate furnished the 2-functionalized quinoline **6d** in 79% yield. Also, the sensitive 3-carbethoxypyridine **2q** was converted at −78 °C (15 min) by the reaction with **1** (0.25 equiv) into the pyridyltrifluoroborate **3q**. After copper-catalyzed allylation, the 3,4-disubstituted pyridine **6e** is obtained in 87% yield (Scheme 4). This direct formation of N-heteroaromatic trifluoroborate complements the well-established preparation of these boron intermediates as described by Molander and Canturk.[16] A number of heterocycles, such as coumarin (**2r**, Table 2, entry 1), 2-phenyl-1,3,4-oxadiazole (**2s**, Table 2, entry 2), electron-deficient 3-substituted pyridines (**2n**, **2t**, **2u**; Table 2, entries 3–6), quinoline (**2v**, Table 2, entry 7), 3-bromoquinoline (**2w**, Table 2, entry 8), and 2-methylthiopyrazine (**2x**, Table 2, entry 9) could be zirconated either directly or in the presence of $BF_3{\cdot}OEt_2$ (Table 2). The corresponding zirconated species efficiently reacted with various electrophiles, such as allylic halides, aryl iodides, or iodine, to give polyfunctional heterocycles in high yields (Table 2, entries 1–9).

In summary, we have developed a directed zirconation of functionalized aromatic and heterocyclic compounds using the new base $tmp_4Zr{\cdot}4\,MgCl_2{\cdot}6\,LiCl$ (**1**). In contrast to most other aryl organometallic complexes, the resulting aryl zirconated species display an excellent reactivity toward

Table 2: Zirconation of functionalized heterocycles with the base **1** and subsequent reactions with electrophiles.

Entry	Substrate[a]	Electrophile	Product[b]
1	**2r** (−40, 30) 		**6f**: 78%[c] 
2	**2s** (0, 20) 		**6g**: 79%[c] 
3	**2t** (0, 30) 		**6h**: 82%[d] 
4	**2u** (−40, 15) 		**6i**: 83%[c] 
5	**2n** (−78, 5) 		**6j**: 77%[c,e] 
6	**2t** (−78, 7) 		**6k**: 79%[c,e] 
7	**2v** (0, 30) 	I_2	**6l**: 83%[c,e] 
8	**2w** (−20, 45) 		**6m**: 85% 
9	**2x** (−35, 20)		**6n**: 81%[c]

[a] The reaction conditions for the metalation with **1** are given in parentheses (*T* [°C], *t* [min]). [b] Yield of isolated analytically pure product. [c] CuCN·2 LiCl (1.0 M in THF, 0.1 mL, 0.1 mmol) was added. [d] $[Pd(PPh_3)_4]$ (3 mol%) was added as catalyst.[e] $BF_3{\cdot}OEt_2$ (1.05 equiv) was added.

electrophiles, such as CO_2 and epoxides. They undergo a smooth palladium-catalyzed cross-couplings (without further transmetalation) leading to a range of new polyfunctional unsaturated compounds. Further extension of the metalation capabilities of **1** are currently under investigation.

Experimental Section

Typical Procedure: Synthesis of **5a**: A dry argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with ethyl 3-fluorobenzoate (**2a**; 336 mg, 2 mmol) in dry THF (2 mL). The $tmp_4Zr{\cdot}4\,MgCl_2{\cdot}6\,LiCl$ (**1**, 0.5 M in THF, 4.2 mL, 2.05 mmol based on tmp) was added dropwise and the mixture was stirred at 25 °C for 45 min. The reaction mixture was cooled to 0 °C, then CuCN·2 LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and ethyl 2-(bromomethyl)acrylate (400 mg, 2.1 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (25 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (silica gel; pentane/diethyl ether, 10:1) to give **5a** (449 mg, 88%) as a colorless oil.

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