Organozinc Reagents

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Improved Air-Stable Solid Aromatic and Heterocyclic Zinc Reagents by Highly Selective Metalations for Negishi Cross-Couplings**

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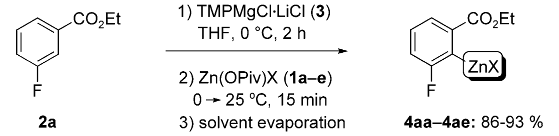
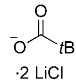
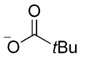
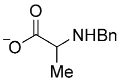
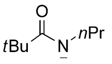
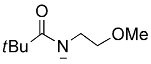
Organozinc reagents constitute a very important class of organometallic compounds,[1] which is mainly due to their efficiency in cross-coupling reactions.[2] However, their broad implementation in industrial laboratories is hampered by their limited stability towards air and moisture. Responding to the demand for more stable and easy-to-handle zinc organometallics, we have recently described the preparation of the first solid salt-stabilized aryl, heteroaryl, and benzylic zinc reagents of the general formula RZnOPiv·Mg(OPiv)X·2 LiCl (X = Cl, Br, I; OPiv = pivalate).[3] These new organozinc species, prepared by magnesium insertion on halogenated precursors and in situ trapping of the Grignard intermediates with $Zn(OPiv)_2$·2 LiCl (**1a**), exhibit excellent reactivity in Negishi cross-coupling reactions and undergo Mg^{II}-promoted additions to carbonyl compounds.[4]

Although the aryl and heteroaryl halides used in the preparation of the solid organozinc pivalates are readily available, we envisioned preparing these organometallics by directed metalation, which allows the use of various arenes and heteroarenes as even more convenient starting materials.[5,6] Furthermore, we were interested in enhancing the stability of the solid zinc species, as currently these can only be handled over a period of few minutes when exposed to air without losing a substantial portion of their reactivity.[3]

Towards this aim, we envisioned that the nature of the counterion could play an important role on the stabilization of the arylzinc compound. Therefore, we have examined the metalation of ethyl 3-fluorobenzoate (**2a**), using TMPMgCl·LiCl (**3**; TMP = 2,2,6,6-tetramethylpiperidide, 1.1 equiv, THF, 0 °C, 2 h)[5] followed by transmetalation with various Zn^{II} salts as the model reaction (Table 1). First, we tested $Zn(OPiv)_2$·2 LiCl (**1a**), and the resulting zinc compound (**4aa**) was found to exhibit increased stability compared to the organozinc pivalates prepared by magnesium insertion (83 % of its initial concentration was maintained after 1 h of air exposure, while this percentage drops to 41 % after 4 h).[7] Several other ligands **1(b–e)** were also tested (Table 1).

Table 1: Air stability of **4aa–4ae**.



	1a	**1b**	**1c**	**1d**	**1e**
X:	 ·2 LiCl				
t[h] in air	Remaining active arylzinc species **4aa–4ae** [%][a]				
0	100	100	100	100	100
1	83	100	92	99	100
2	59	95	83	93	99
4	41	90	70	82	98
24	> 10	24	> 10	20	43

[a] The content of active zinc species was determined by iodometric titration.[7]

Using $Zn(OPiv)_2$ (**1b**) instead of $Zn(OPiv)_2$·2 LiCl (**1a**)[8] for the transmetalation further improved the stability towards hydrolysis and air oxidation. LiCl is known to be highly hydrophilic and has a deleterious effect.[9] Thus, organozinc compound **4ab** was found now to maintain 90 % of its initial concentration after 4 h in air. Next, *N*-benzylalaninate (**1c**) was examined. Despite the additional *N*-coordination, it proved to be an inferior ligand (70 % of the initial concentration of **4ac** remains after 4 h). Comparable with the pivalate **4ab** was also the stability profile of zinc reagent **4ad** obtained by using *n*-propyl pivalamide (**1d**). By increasing the coordination sites on the ligand with an additional methoxy group, as in *N*-(2-methoxyethyl) pivalamide (**1e**), a much more robust compound **4ae** was obtained, which preserved almost all of its activity after 4 h in air, while even after 24 h, a respectful amount of it (43 %) was still active. When tested for their reactivity in Negishi cross-couplings with ethyl 4-iodobenzoate (**5a**), compounds **4aa–4ae** delivered the desired product **6a**[10] in high yields (87–93 %). For the sake of simplicity, in addition to its low cost, we decided to focus our studies on the LiCl-free $Zn(OPiv)_2$ (**1b**), as the ligand of choice.

Herein, we report the synthesis of various functionalized solid aryl and heteroarylzinc pivalates (**4a–m**) by highly regio- and chemoselective metalations of arenes and heteroarenes (**2**) using TMPMgCl·LiCl (**3**),[5] followed by transmetalation with $Zn(OPiv)_2$ (**1b**; Scheme 1 and Table 2). All of them show an excellent stability in air over time. As a general trend, the

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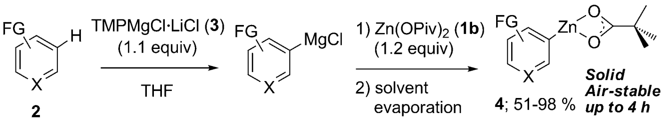
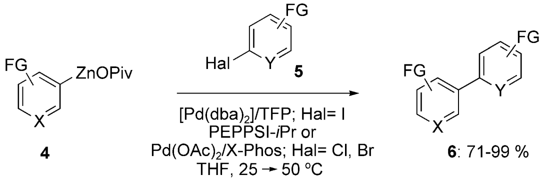


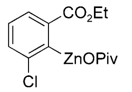
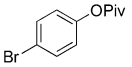
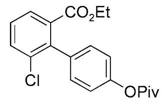
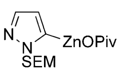
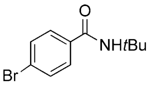
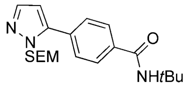
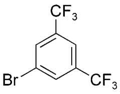
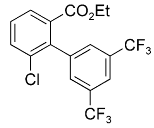
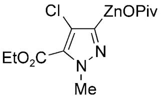
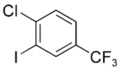
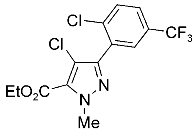
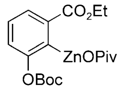
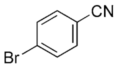
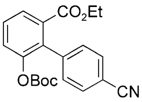
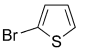
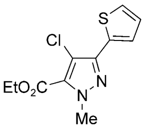
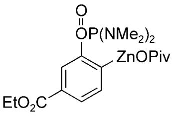
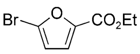
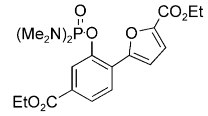
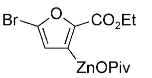
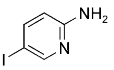
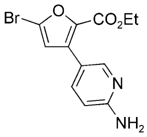
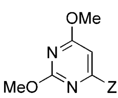
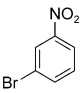
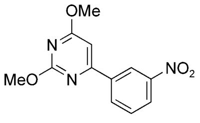
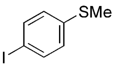
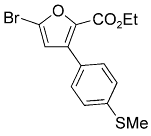
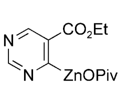
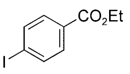
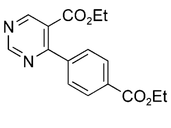
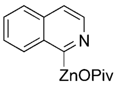
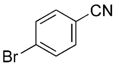
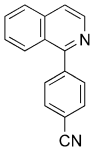
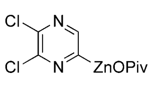
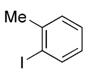
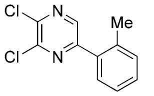
Scheme 1. Preparation of solid air-stable zinc pivalates of type **4** by selective metalation of arenes and heteroarenes **2**. The solid zinc reagents **4** contain also PivOMgCl and LiCl. FG = functional group.

concentration of the new zinc reagents is preserved almost entirely (> 94 %) after 2 h of air exposure, while this percentage remains greater than 85 % even after 4 h in air.[11] The aryl and heteroaryl zinc pivalates of type **4** proved to be excellent nucleophiles in Negishi cross-couplings.

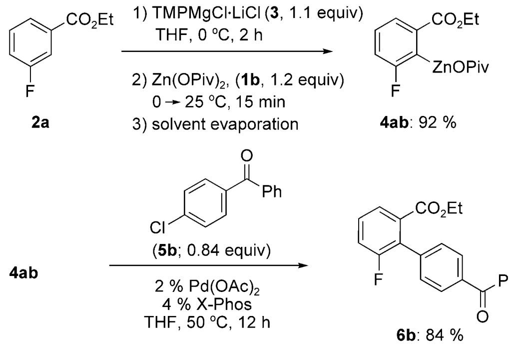
Thus, the zinc pivalate **4ab** was prepared by metalation of ethyl 3-fluorobenzoate (**2a**) with TMPMgCl·LiCl (**3**, 1.1 equiv, THF, 0 °C, 2 h) and subsequent transmetalation with $Zn(OPiv)_2$ (**1b**, 1.2 equiv, 0 to 25 °C, 15 min; Scheme 2). After evaporation of the solvent in high vacuum (0.1 mm Hg,

Table 2: Negishi cross-coupling of various aryl and heteroaryl zinc pivalates **4b–k** with a range of electrophiles.[12]



Entry	Zinc Reagent (T [°C], t)[a]	Electrophile[b]	Product	Yield [%][c]	Entry	Zinc Reagent (T [°C], t)[a]	Electrophile[b]	Product	Yield [%][c]
1	 **4b** (0, 6 h)	 **5c**	 **6c**	76[f]	8	 **4h** (25, 1 h)	 **5i**	 **6j**	78[f]
2	**4b**	 **5d**	 **6d**	71[f]	9	 **4i** (−30, 30 min)	 **5j**	 **6k**	97[d]
3	 **4c** (0, 3 h)	 **5e**	 **6e**	79[e]	10	**4i**	 **5k**	 **6l**	75[e]
4	 **4d** (0, 3 h)	 **5f**	 **6f**	78[f]	11	 **4j** (−25, 45 min)	 **5l**	 **6m**	78[d]
5	 **4e** (25, 15 min)	 **5g**	 **6g**	76[e]	12	**4j**	 **5m**	 **6n**	99[d]
6	 **4f** (−40, 45 min)	 **5a**	 **6h**	90[d]	13	 **4k** (25, 111h)	 **5e**	 **6o**	75[e]
7	 **4g** (−45, 2 h)	 **5h**	 **6i**	89[d]					

[a] Temperature [°C] and time used for the zinc pivalates preparation by metalation with **3**. [b] 0.84 equiv of electrophile were used. [c] Yields refer to analytically pure products. [d] 3 % [Pd(dba)$_2$], 6 % TFP, THF, 25 °C. [e] 2 % PEPPSI-*i*Pr, THF, 50 °C. [f] 2 % Pd(OAc)$_2$, 4 % X-Phos, THF, 50 °C.



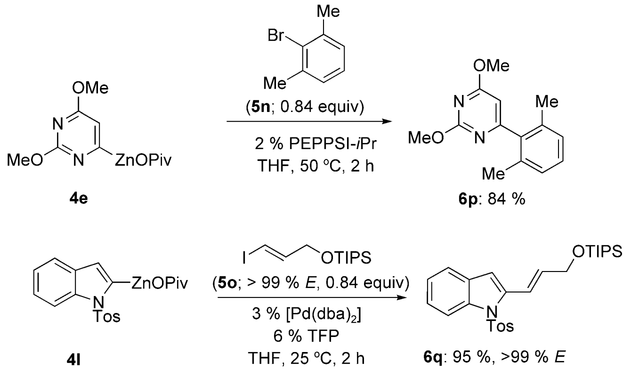
Scheme 2. Preparation of zinc pivalate **4ab** and Negishi cross-coupling with aryl chloride **5b**, using $Pd(OAc)_2$/X-Phos as the catalyst.

3 h), the solid arylzinc pivalate, which contains also PivOMgCl and LiCl, was obtained as a yellow fine powder in 92% yield, as determined by iodometric titration.[7] If this powder is exposed to air for 4 h, 90% of its concentration in active zinc species is preserved. Furthermore, this zinc reagent is stable for, at least, several weeks under argon or nitrogen in a closed vial. Redissolution of the solid zinc compound **4ab** in dry THF (0.5 M), followed by addition of 2% $Pd(OAc)_2$ and 4% X-Phos[13] and subsequently 4-chlorobenzophenone (**5b**, 0.84 equiv), led to biphenyl **6b** in 84% yield (calculated based on the electrophile amount) after heating at 50 °C for 12 h (Scheme 2).

This air stability and cross-coupling behavior was general for a range of aromatic and heteroaromatic substrates (see Table 2). Whereas $Pd(OAc)_2$/X-Phos[13] or either PEPPSI-*i*Pr[14] proved to be excellent catalytic systems for the cross-coupling of unsaturated chlorides and bromides, $[Pd(dba)_2]$/TFP (dba = dibenzylideneacetone, TFP = tri-o-furylphosphine)[15] was found to be the best catalyst when iodides were utilized as the electrophilic component.

The scope and limitations of the solid zinc pivalates (**4b–k**) reactivity in Negishi cross-couplings with various aryl and heteroaryl halides is described in Table 2. Aromatic compounds bearing an ester, a Boc protected phenol,[5b] or a phosphoramidate directing group[5f] were readily magnesiated with TMPMgCl·LiCl (**3**, 1.1 equiv, 0 °C, 2–6 h). After transmetalation with $Zn(OPiv)_2$ (**1b**, 1.2 equiv), Pd-catalyzed cross-coupling with functionalized aryl and heteroaryl bromides (**5c–f**) proceeded in 71–79% yields (entries 1–4). Similarly, pyrimidines were efficiently employed in the directed metalation/cross-coupling sequence. The zinc pivalate of 2,4-dimethoxypyrimidine **4e**,[5e] smoothly reacted with 3-bromonitrobenzene (**5g**) to deliver the coupling product **6g** in 76% yield after heating for 2 h at 50 °C (entry 5). Furthermore, the ester-substituted pyrimidylzinc pivalate **4f** was coupled with iodide **5a** (25 °C, 2 h) in the presence of catalytic amounts of $[Pd(dba)_2]$/TFP[15] to afford the coupling product **6h** in 90% yield (entry 6). The zincated dichloropyrazine **4g**[5g] was arylated under the same conditions with 2-iodotoluene (**5h**) to provide the diazine **6i** in 89% yield (entry 7). Correspondingly, the zinc pivalates of five-membered nitrogen heterocycles such as pyrazoles **4h** and **4i**,[5c] were subjected to coupling with aryl iodides and bromides (entries 8–10). This Negishi cross-coupling is compatible with the use of aryl bromide **5i**, which bears an amidic acidic proton, affording the amide **6j** in 78% yield (entry 8).[16a] In the same vein, the zinc pivalate of ethyl 5-bromofuranoate **4j** was coupled under mild conditions (25 °C, 2 h) with iodide **5l**, which bears a free amine (entry 11).[16b] The isoquinolylzinc pivalate **4k**,[5a] prepared by magnesiation at 25 °C for 1 h and addition of $Zn(OPiv)_2$ (**1b**), efficiently participated in PEPPSI-*i*Pr[14] catalyzed cross-coupling with bromide **5e**, affording compound **6o** in 75% yield (entry 13).

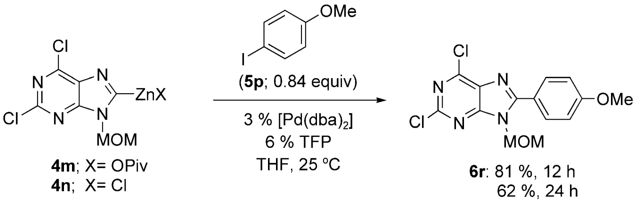
The zinc pivalates were also able to couple with exceptional efficiency with sterically hindered aromatic halides. For instance, 2,4-dimethoxypyrimidine derived zinc pivalate **4e** reacted with 2-bromo-*meta*-xylene (**5n**) in the presence of 2% PEPPSI-*i*Pr as the catalyst to deliver the cross-coupling product **6p** in 84% yield, after heating at 50 °C for 2 h (Scheme 3). Furthermore, an alkenyl iodide, such as the *E*-iodoalcohol derivative **5o**,[17] undergoes a fast coupling with the indolylzinc pivalate (**4l**), prepared by metalation of the corresponding protected indole with TMPMgCl·LiCl (**3**, 25 °C, 45 min) and transmetalation with $Zn(OPiv)_2$ (**1b**), to furnish the *E*-alkenylated indole **6q** in 95% yield and complete retention of the double-bond configuration.



Scheme 3. Negishi cross-coupling of zinc pivalates **4e** and **4l** with the sterically hindered bromide **5n** and alkenyl iodide **5o**. TIPS = triisopropylsilyl, Tos = tosyl.

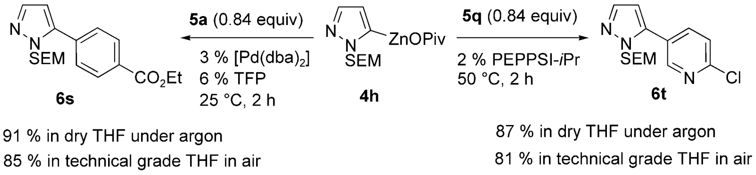
In accordance to our previous observations,[3] zinc pivalates prepared by metalation of arenes and heteroarenes also demonstrate similar or even improved reactivity in Negishi cross-couplings compared to standard zinc reagents RZnX (X = halide). Thus, the Pd-catalyzed cross-coupling of 2,6-dichloropurinylzinc pivalate (**4m**) with 4-iodoanisole (**5p**) was accomplished at 25 °C within 12 h in 81% yield, while the corresponding organozinc chloride **4n** required 24 h for completion and afforded the coupling product **6r** in significantly lower yield (62%; Scheme 4).[18]

Interestingly, the cross-coupling reactions can be performed with comparable efficiency using technical-grade THF in air.[19] Whereas the cross-coupling of pyrazolylzinc pivalate **4h** with iodide **5a** proceeded under argon and dry THF (25 °C, 2 h), affording the product **6s** in 91% yield, the use of technical-grade THF in an open flask led to **6s** with only a minor yield decrement (85%). A similar tendency was noted even when higher reaction temperatures were required,



Scheme 4. Comparison of the reactivity of 2,6-dichloropurinylzinc pivalate **4m** and the corresponding zinc chloride **4n** in Negishi cross-coupling with 4-iodoanisole **5p**. MOM = methoxymethyl.

as in the coupling of **4h** with 5-bromo-2-chloropyridine (**5q**), which was conducted at 50 °C (the yield for **6t** drops only from 87 to 81 %; Scheme 5).



Scheme 5. Negishi cross-coupling of zinc pivalate **4h** in different qualities of THF.

In summary, we have prepared a pool of new solid organozinc pivalates by regio- and chemoselective metalation of various arenes and heterocycles using TMPMgCl·LiCl (**3**), followed by transmetalation with $Zn(OPiv)_2$ (**1b**). The air stability of these new zinc organometallics was substantially superior compared to the zinc pivalates prepared by magnesium insertion previously described in our laboratory. Furthermore, they exhibit excellent reactivity in Negishi cross-coupling reactions with a broad selection of electrophiles. The new, easy-to-handle organozinc pivalates can be regarded as potential building blocks for basic research and industrial applications. Further investigations of their properties and reactivity are currently in progress in our laboratory.

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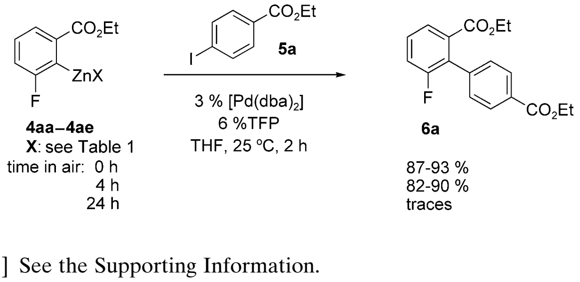
[7] For a titration method of zinc organometallics, see: A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890. As LiCl is already embedded in the organozinc materials, neat THF instead of a 0.5 M solution of LiCl in THF can be used as the titration medium; see the Supporting Information.

[8] LiCl is required for the complete dissolution of $Zn(OPiv)_2$ in THF, which was essential for the preparation of zinc organometallics by Mg insertion into aryl halides in high yields.

[9] Despite its high hydrophilicity, the presence of 1.1 equiv of LiCl in the crude solid organozinc material was unavoidable, as LiCl is essential for the highly kinetic basicity of **3**.

[10] The Negishi cross-coupling of arylzinc species **4aa–ae** with ethyl 4-iodobenzoate (**5a**) was performed at 25 °C using $[Pd(dba)_2]$/TFP as the catalyst (dba = dibenzylideneacetone, TFP = tri-o-furylphosphine):



[11] See the Supporting Information.

[12] For the exact conditions and the yields of preparation of the aryl and heteroaryl zinc pivalates, see the Supporting Information.

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[19] Technical-grade THF was purchased from AppliChem. with a purity of > 98%, while the water content was < 0.5%.