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VIP Organozinc Reagents

Preparation of Solid Salt-Stabilized Functionalized Organozinc Compounds and their Application to Cross-Coupling and Carbonyl Addition Reactions**

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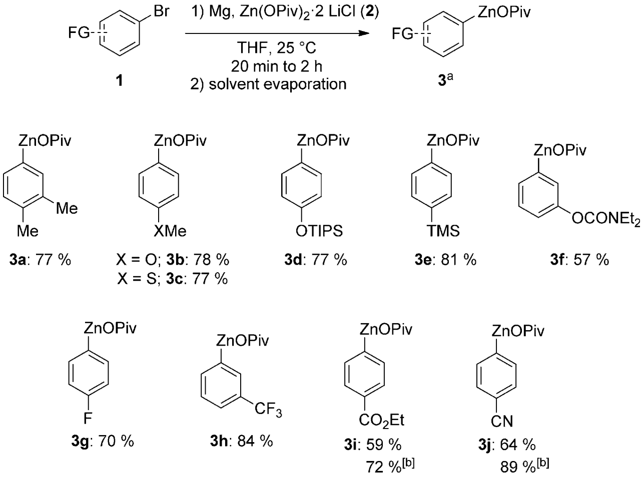
Organozinc reagents have found numerous synthetic applications, especially in the Negishi cross-coupling reaction.[1,2] Various methods for the preparation of organozinc compounds have been reported.[3] However, polyfunctional zinc reagents of type RZnX (X = halide)[4] or R_2Zn are highly sensitive to moisture and air. These properties represent a serious drawback for their practical use in the laboratory and on an industrial scale. Thus, the availability of more easy to handle organozinc compounds is highly desirable. Since their reactivity is strongly influenced by the presence of salts,[5] we anticipated that the presence of appropriate metallic salts may lead to an improved stability towards air and water. Charette et al. have already demonstrated that alkoxides greatly stabilize zinc carbenoids for enantioselective cyclopropanations.[6] Furthermore, Herrmann et al. reported that methylzinc acetate can be efficiently used for the synthesis of methyltrioxorhenium (MTO), even on large scales.[7]

Herein, we report the preparation of solid salt-stabilized functionalized aryl, heteroaryl, and benzylic zinc reagents of the general formula $RZnOPiv{\cdot}Mg(OPiv)(X){\cdot}2\,LiCl$ (X = Cl, Br, or I; OPiv = pivalate; abbreviated RZnOPiv for clarity). These new zinc reagents are readily prepared by a one-pot synthesis in which the organic halide (RX; X = Cl, Br) is treated with magnesium turnings (2.5 equiv)[8] and the THF-soluble salt $Zn(OPiv)_2{\cdot}2\,LiCl$[9] (**2**; 1.5 equiv). Under these conditions, the formation of the zinc reagent is observed at 25 °C within 2 h.[10] The presence of $Zn(OPiv)_2{\cdot}2\,LiCl$ (**2**) not only stabilizes the resulting zinc reagent, but also accelerates its formation dramatically. Whereas 4-bromo-1,2-dimethylbenzene (**1a**) requires 2 h in the presence of Mg/$ZnCl_2{\cdot}2\,LiCl$,[8] the insertion reaction is complete within 20 min when using the combination Mg/$Zn(OPiv)_2{\cdot}2\,LiCl$ (**2**). After evaporation of the solvent, the corresponding solid organozinc pivalate **3a** is obtained in 77% yield.[11] This rate acceleration is essential for tolerating sensitive functional groups. This route is widely applicable and after evaporation of the THF, the resulting solid arylzinc reagents are obtained in 57–84% yield as easy to handle powders (Scheme 1). This is in contrast to regular zinc reagents which produce only highly viscous oils when the solvents are evaporated.



Scheme 1. Preparation of solid functionalized arylzinc pivalates of type **3** from the corresponding aromatic bromides of type **1** by using Mg and $Zn(OPiv)_2{\cdot}2\,LiCl$ (**2**). [a] Complexed Mg(OPiv)X (X = Br, I) and LiCl are omitted for clarity. [b] Prepared by I/Mg or Br/Mg exchange with *i*PrMgCl·LiCl and transmetalation with $Zn(OPiv)_2{\cdot}2\,LiCl$ (**2**). TIPS = triisopropylsilyl, TMS = trimethylsilyl.

By using this method we have prepared a range of arylzinc reagents bearing electron-donating substituents (**3a–f**; FG = Me, OMe, SMe, OTIPS, TMS, $OCONEt_2$; 57–81%) or electron-deficient substituents (**3g–j**; FG = F, CF_3, CO_2Et, CN; 59–84%; Scheme 1). Although the ester- and nitrile-substituted zinc reagents **3i** and **3j** can be prepared in satisfactory yields (59–64%) by direct insertion, an improvement has been achieved by using an I/Mg or Br/Mg exchange with *i*PrMgCl·LiCl followed by transmetalation with $Zn(OPiv)_2{\cdot}2\,LiCl$ (**2**; 72–89%).[12]

Moreover, the solid zinc reagents of type **3** are stable under argon at room temperature for several months without significant loss of activity. Importantly, these zinc compounds can now be weighed in air (95% of the active zinc species **3h** is titrated after 5 min in air). Some decomposition is observed after longer exposure to air (66% of the active zinc species **3h** still remains after 15 min).

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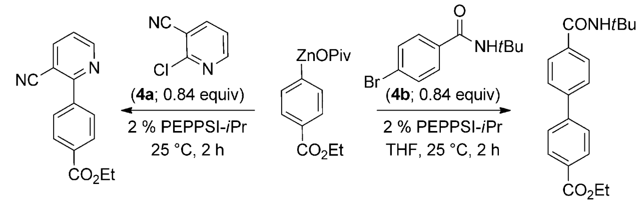
The organozinc compounds of type **3** undergo Negishi cross-coupling reactions under similarly mild conditions as the standard zinc reagents RZnX (X = halide) by using 2% PEPPSI-*i*Pr[13] as the catalyst. Thus, the reaction of a solution of the arylzinc pivalate **3i** in THF with the pyridyl chloride **4a** at 25 °C leads to the desired cross-coupling product **5a** in 84% yield within 2 h.

Interestingly, these cross-coupling reactions can be performed in various solvents. Hence, the coupling of organozinc pivalate **3i** with the chloropyridine **4a** in technical grade ethyl acetate[14] as the solvent provides the biphenyl **5a** in 96% yield. Although aryl bromides bearing relatively acidic protons, such as, for example, on an amide function, are suitable for Negishi cross-coupling reactions, a slow addition of the zinc reagent over 90 min was usually required.[15] However, the use of arylzinc pivalates such as **3i** combined with PEPPSI-*i*Pr[13] as the catalyst allows the bromobenzamide **4b** to be added at once without special precautions, and leads within 2 h at 25 °C to the biphenyl **5b** in 87% yield (Scheme 2).



5a: 84 % in THF
96 % in AcOEt

3i

5b: 87 %

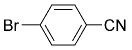
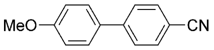
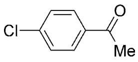
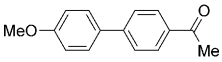
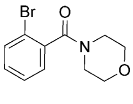
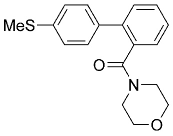
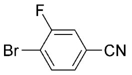
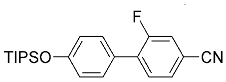
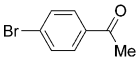
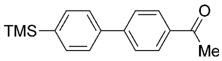
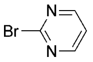
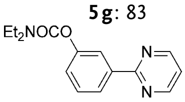
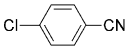
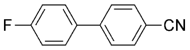
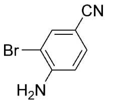
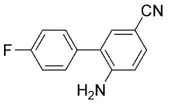
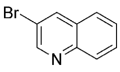
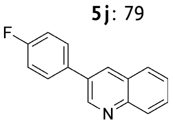
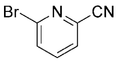
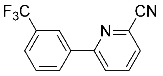
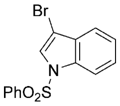
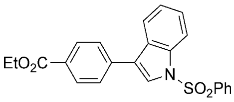
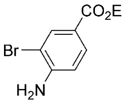
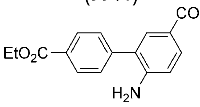
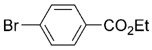
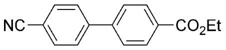
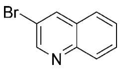
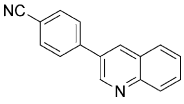
Scheme 2. PEPPSI-*i*Pr-catalyzed one-pot cross-coupling of organozinc reagents of type **3** in THF or AcOEt.

The scope of Negishi cross-coupling reactions with arylzinc pivalates **3b–j** and functionalized aryl bromides or chlorides as well as heteroaryl bromides is very broad (Table 1). The generally fast reactions (2 h) were performed at 25 °C[16] and the expected products were obtained in high yields (67–99%). The presence of an unprotected amine function in the aryl bromides is well tolerated (Table 1, entries 8 and 12). Chloro- and bromoacetophenones **4d** and **4g** also react in satisfactory yields (67–83%; Table 1, entries 2 and 5). No appreciable enolization of the acetyl function could be detected and thus no excess of the organozinc reagents is required.

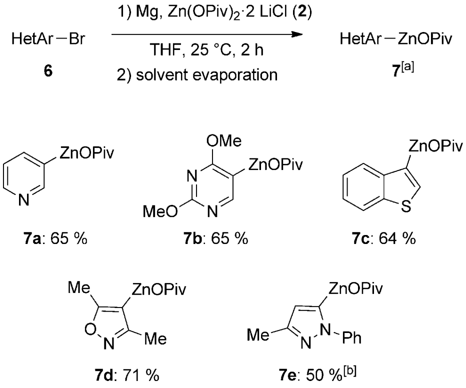
Similarly, we have prepared a range of heteroaromatic zinc pivalates starting from heterocyclic bromides (HetAr–Br) of type **6**. The solid organozinc pivalates **7a–d** were obtained in 64–71% yield under mild conditions (25 °C, 2 h, Scheme 3). The pyrazoylzinc pivalate **7e** was prepared from the corresponding heteroaryl chloride in a moderate yield (50%).

Furthermore, the method was also applicable to the synthesis of various benzylic zinc pivalates of type **9** by using benzylic chlorides of type **8**. The insertion with Mg/Zn-$(OPiv)_2 \cdot 2LiCl$ (**2**) proceeded well at 25 °C within 2 h, and the solid organozinc compounds **9a–e** were obtained in 67–80% yield after evaporation of the solvent (Scheme 4).[17]

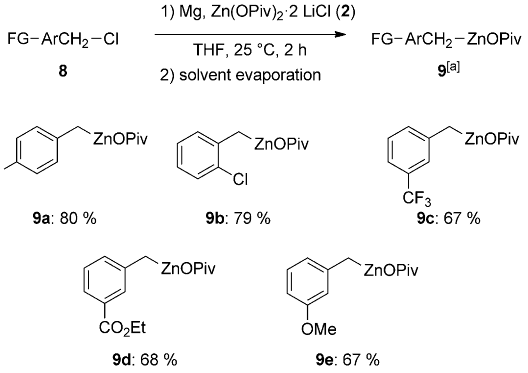
Table 1: PEPPSI-*i*Pr-catalyzed cross-coupling of aromatic organozinc pivalates of type **3** in THF (or AcOEt) within 2 h at 25 °C.

Entry	Arylzinc reagent	Electrophile[a]	Product yield [%][b]
1	**3b**	 **4c**	 **5c**: 86
2	**3b**	 **4d**	 **5d**: 67
3	**3c**	 **4e**	 **5e**: 88
4	**3d**	 **4f**[c]	 **5f**: 89
5	**3e**	 **4g**	 **5g**: 83
6	**3f**	 **4h**	 **5h**: 80
7	**3g**	 **4i**	 **5i**: 80
8	**3g**	 **4j**	 **5j**: 79
9	**3g**	 **4k**	 **5k**: 99
10	**3h**	 **4l**	 **5l**: 78
11	**3i**	 **4m**	 **5m**: 91 (99%)[d]
12	**3i**	 **4n**	 **5n**: 69
13	**3j**	 **4o**	 **5o**: 94[d]
14	**3j**	 **4k**	 **5p**: 88

[a] 0.84 equiv of electrophile was used. [b] Yield of isolated analytically pure product. [c] The cross-coupling was perfomed at 50 °C. [d] The cross-coupling was performed in AcOEt.

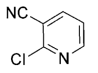
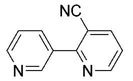
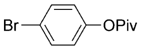
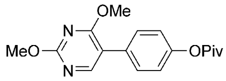
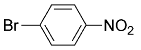
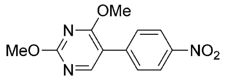
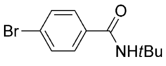
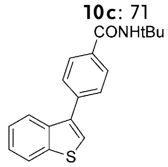
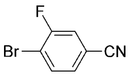
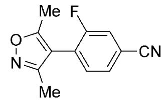
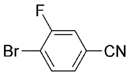
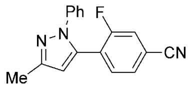
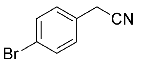
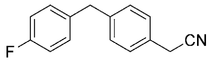
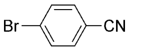
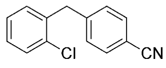
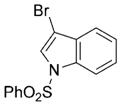
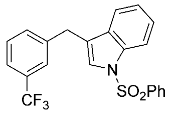
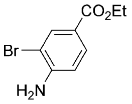
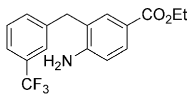
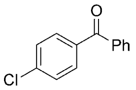
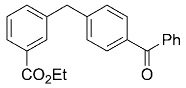


Scheme 3. Preparation of solid functionalized heteroaromatic zinc pivalates of type **7** from the corresponding heteroaromatic bromides **6**. [a] Complexed Mg(OPiv)X (X = Br, Cl) and LiCl are omitted for clarity. [b] Prepared from 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole.



Scheme 4. Preparation of solid functionalized benzylic zinc pivalates of type **9** from the corresponding benzylic chlorides **8**. [a] Complexed Mg(OPiv)Cl and LiCl are omitted for clarity.

Table 2: PEPPSI-*i*Pr-catalyzed cross-coupling of heteroaromatic and benzylic organozinc pivalates of type **7** and **9** in THF in 2 h at 25 °C.

Entry	Zinc reagent	Electrophile[a]	Product Yield [%][b]
1	**7a**	 **4a**	 **10a**: 91
2	**7b**	 **4p**	 **10b**: 80
3	**7b**	 **4q**	 **10c**: 71
4	**7c**	 **4b**	 **10d**: 84
5	**7d**	 **4f**[c]	 **10e**: 99
6	**7e**	 **4f**[c]	 **10f**: 98
7	**9a**	 **4r**	 **11a**: 81
8	**9b**	 **4c**	 **11b**: 70
9	**9c**	 **4m**	 **11c**: 86
10	**9c**	 **4n**	 **11d**: 66
11	**9d**	 **4s**	 **11e**: 85

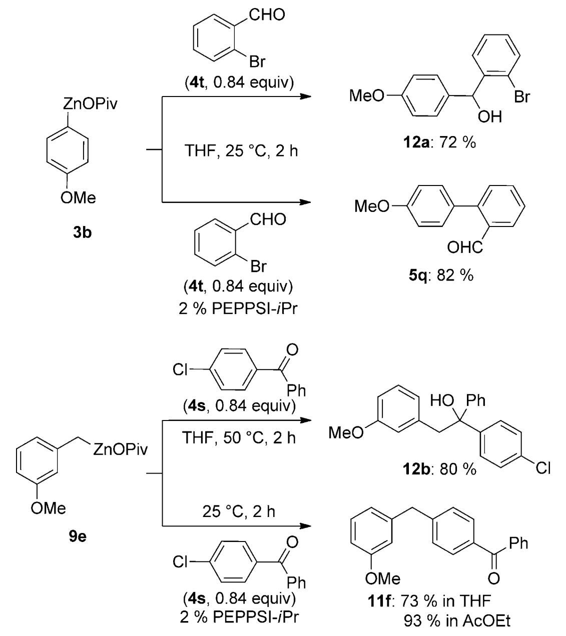
[a] 0.84 equiv of electrophile was used. [b] Yield of isolated analytically pure product. [c] The cross-coupling was performed at 50 °C.

The heteroaromatic zinc pivalates (**7a–c**) and the benzylic zinc pivalates (**9a–d**) also react with various heteroaryl halides and aryl bromides in high yields (66–91 %, Table 2) under mild conditions (25 °C, 2 h) and PEPPSI-*i*Pr catalysis (2 %). The reaction temperature had to be increased to 50 °C for the isoxazolyl- and pyrazolylzinc pivalates **7d** and **7e** to obtain full conversion with the bromobenzonitrile **4f** (Table 2, entries 5 and 6). Electrophiles bearing functionalities with acidic protons such as the amide **4b**, the phenylacetonitrile **4r**, and the benzocaine derivative **4n** were also used in the cross-coupling reactions under our standard conditions (Table 2, entries 4, 7, and 10).

Recently, we have shown that MgCl$_2$ greatly enhances the reactivity of organozinc reagents towards carbonyl derivatives.[5i] In fact both MgCl$_2$ and LiCl[18] increase the intrinsic reactivity of organozinc reagents by boosting their nucleophilicity as well as the electrophilicity of the carbonyl compound (Lewis acid activation).[19]

Such activation is also observed for arylzinc pivalates of type **3**. Thus, the reaction of the arylzinc pivalate **3b** with 2-bromobenzaldehyde (**4t**) produces rapidly the benzhydryl alcohol **12a** in 72 % yield as a consequence of the presence of additional magnesium salts in reagent **3b**. This salt effect can be overcome by the addition of the powerful Pd catalyst PEPPSI-*i*Pr (2 %) which leaves the formyl group of **4t** untouched and provides the Negishi cross-coupling product **5q** in 82 % yield (Scheme 5).

This behavior has some generality and the reaction of a benzylic zinc pivalate such as **9e** with 4-chlorobenzophenone (**4s**) produces, without additional catalyst, the tertiary alcohol **12b** in 80 % yield in THF. However, the addition of 2 %



Scheme 5. Tuneable reactivity of organozinc compounds of type **3** and **9** by the presence or absence of PEPPSI-*i*Pr.

PEPPSI-*i*Pr leads to the cross-coupled benzophenone derivative **11 f** as the sole product in 73% yield in THF. Repeating the reaction in AcOEt led to an improved yield of 93%.

In summary, we have prepared solid salt-stabilized aryl, heteroaryl, and benzylic zinc pivalates from the corresponding aryl- and heterorary bromides as well as benzylic chlorides. These new organozinc pivalates are readily available in a one-pot procedure under mild conditions by using Mg and $Zn(OPiv)_2\cdot 2LiCl$. After evaporation of the solvent, they are obtained as easy to handle powders and even a short manipulation in air is possible. These reagents show an excellent reactivity in Negishi cross-coupling reactions and undergo smooth carbonyl additions. Further applications are currently underway in our laboratory.

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[10] A patent application has been filed.

[11] The content of active zinc species was determined by titration with a 1.0 M solution of iodine in THF.

[12] Ethyl 4-iodobenzoate and 4-bromobenzonitrile were used as starting materials for the halogen–magnesium exchange with *i*PrMgCl·LiCl, see A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

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[16] Only the cross-coupling of 4-TIPSO-phenylzinc pivalate (**3d**) with 4-bromo-3-fluorobenzonitrile (**4f**) had to be performed at 50 °C.

[17] We noticed that the solid benzylic zinc pivalate **9e** displays a slightly lower stability in air compared to the corresponding aryl-

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and heteroarylzinc pivalates (77% of the active zinc species **9e** after 5 min in air; see the Supporting Information).

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