# Preparation of Highly Functionalized Heterocyclic Zinc Organometallics via a Li(acac)-Catalysis of the I/Zn-Exchange Reaction

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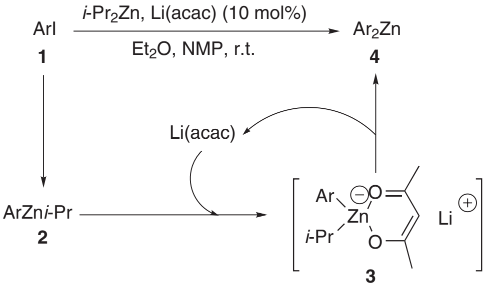
**Abstract:** The reaction of $i$-$Pr_2Zn$ in the presence of catalytic amount of Li(acac) in NMP with various functionalized heterocyclic iodides provides new polyfunctional diheteroarylzincs, which undergo smooth Negishi cross-coupling reactions and CuCN·2LiCl-catalyzed allylation reactions under mild conditions. Remarkably, even an aldehyde function can be present in the diorganozinc reagents.

**Key words:** polyfunctional heterocycles, iodine–zinc exchange reaction, diorganozinc reagent, catalysis, cross-coupling



**Scheme 1** Li(acac)-catalysis of the iodine-zinc exchange

The preparation of polyfunctionalized heterocycles is a major synthetic task since many heterocycles are biologically active compounds.[2] The use of metalated heterocyclic building blocks for the preparation of complex heterocycles has been a very successful approach.[3] Mostly lithiation or magnesiation reactions have been performed, which precludes the presence of sensitive functionalities like a ketone or an aldehyde.[4] Recently, we have found that the addition of catalytic amount of Li(acac) catalyzes the I/Zn-exchange reaction and allows the preparation of diarylzincs bearing various sensitive functionalities including an aldehyde, a ketone or an isothiocyanate.[5] In the absence of Li(acac), the reaction of $i$-$Pr_2Zn$ with an aryl iodide (ArI, **1**) produces only the mixed diorgano zinc species ArZn*i*-Pr (**2**). In the presence of Li(acac), an intermediate zincate **3** is formed allowing the transfer of the second isopropyl rest and leading to the diarylzinc product $Ar_2Zn$ (**4**), see Scheme 1.

Herein, we wish to report that this catalyzed I/Zn-exchange reaction can be successfully applied for the preparation of a broad range of heterocyclic diorganozincs bearing sensitive functional groups including an aldehyde.

We have first examined electron-deficient heterocycles such as 3-iodopyridine (**5a**). Its reaction with $i$-$Pr_2Zn$ (0.55 equiv) in the presence of Li(acac) (10 mol%) in NMP (*N*-methylpyrrolidine) at room temperature (12 h) provides the desired diheteroarylzinc **6a**. Its reaction with various aryl iodides (1.5 equiv) in the presence of $Pd(dba)_2$ (2.5 mol%) and tri(*o*-furyl)phosphine (5 mol%)[6] leads to the cross-coupling products[7] **7a**,**b** in 76–83% yields (entries 1, 2 of Table 1). In the presence of CuCN·2LiCl (20 mol%),[8] it reacts with 3-iodo-cyclohex-2-enone to give **7c** in 60% yield (entry 2). Only a mono-I/Zn-exchange takes place with 3,5-diiodo-4-methoxypyridine (**5b**), leading to the zinc reagent **6b**. Its reaction with ethyl (2-bromomethyl)acrylate[9] in the presence of CuCN·2LiCl[8] leads to the allylated product **7d** in 61% yield (entry 4). The bis-allylated 5-iodouracil (**5c**) provides under our typical conditions the diorganozinc **6c**, which reacts under Pd(0)-catalysis with methyl 4-iodobenzoate giving the arylated uracil **7e** in 58% yield (entry 5). Electron-rich hetereocycles such as indole derivatives react smoothly. Thus, 3-iodo-1-phenylsulfonylindole (**5d**)[10] furnishes the diorganozinc **6d**, which is allylated to furnish the 3-allylindole **7f** in 70% yield (entry 6). A selective mono-I/Zn exchange is also observed with 2,3-diiodo-1-phenylsulfonylindole[11] providing selectively[12] the 2-zincated 3-iodoindole derivative **6e**, which after allylation provides the 3-iodoindole derivative **7g** in 84% yield (entry 7). Similarly, 3-iodoindazoles[13] are readily converted to the corresponding diorganozincs **6f–i** and react with typical electrophiles leading to the products **7h–k** in 69–78% yields (entries 8–11). Of special interest is the Pd-catalyzed cross-coupling of **6f** with methyl 5-bromo-2-furoate leading to the heterocycle **7h** in 78% yield.[14] The $LiBH_4$ reduction of **7h** provides an NO-independent, superoxide-sensitive activator of soluble guanylate cyclax (YC-1).[14]

Interestingly, 5-iodothienyl-2-aldehyde (**8**) and 5-iodo-2-furaldehyde (**11**) are converted under our standard conditions to the zinc reagents **9** and **12** which were respectively allylated with ethyl (2-bromomethyl)acrylate and cross-coupled with methyl 4-iodobenzoate, leading to the functionalized aldehydes **10** and **13**, respectively, in 71% and 70% yields (Scheme 2).

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**Table 1** Preparation of Heterocyclic Diorganozincs of Type **6** and their Reaction with Electrophiles

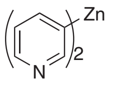
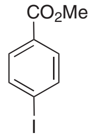
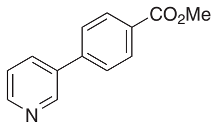
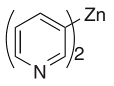
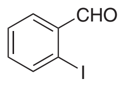
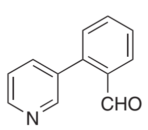
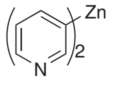
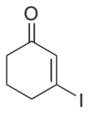
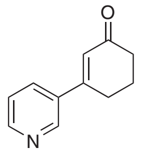
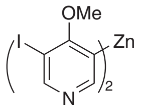
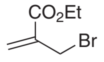
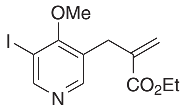
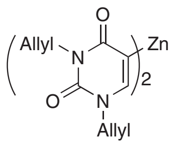
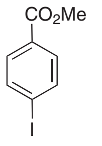
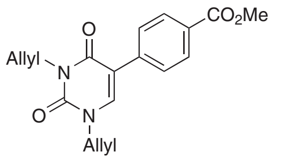
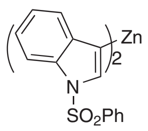
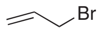
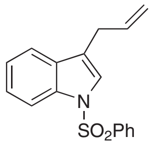
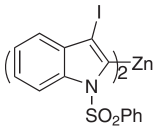
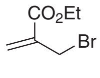
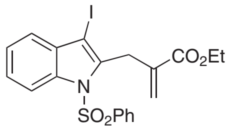
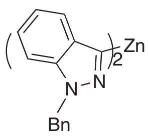
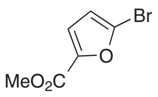
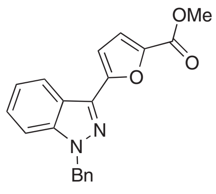
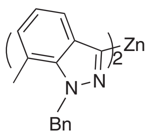
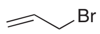
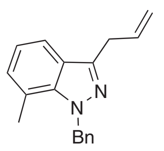
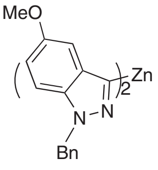
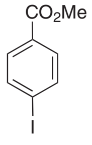
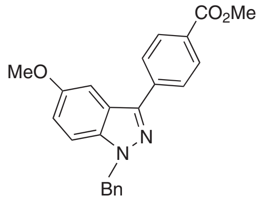
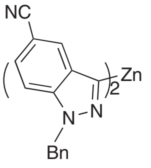
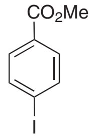
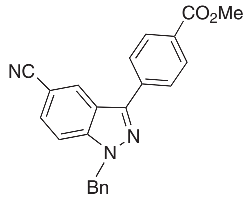
| Entry | Zinc reagent of type **6** | Electrophile | Product of type **7** | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  **6a** |  |  **7a** | 83[b] |
| 2 |  **6a** |  |  **7b** | 76[b] |
| 3 |  **6a** |  |  **7c** | 60[c] |
| 4 |  **6b** |  |  **7d** | 61[c] |
| 5 |  **6c** |  |  **7e** | 58[b] |
| 6 |  **6d** |  |  **7f** | 70[c] |
| 7 |  **6e** |  |  **7g** | 84[c] |
| 8 |  **6f** |  |  **7h** | 78[b] |
| 9 |  **6g** |  |  **7i** | 69[c] |

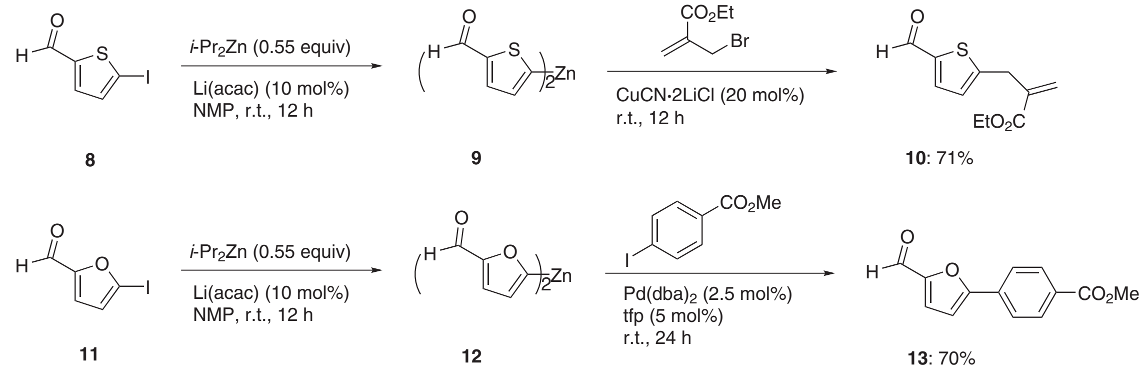
**Table 1** Preparation of Heterocyclic Diorganozincs of Type **6** and their Reaction with Electrophiles (continued)

| Entry | Zinc reagent of type **6** | Electrophile | Product of type **7** | Yield (%)[a] |
|---|---|---|---|---|
| 10 |  **6h** |  |  **7j** | 78[b] |
| 11 |  **6i** |  |  **7k** | 76[b] |

[a] Isolated yield of analytically pure product.

[b] In the presence of 2.5 mol% $Pd(dba)_2$ and 5 mol% tfp.

[c] In the presence of 20 mol% CuCN·2LiCl.



**Scheme 2** Preparation and reactions of heteroarylzincs bearing an aldehyde function

In summary, we have shown that a range of new functionalized hetereocyclic diorganozincs can be prepared by a Li(acac)-catalyzed I/Zn exchange reaction. Extensions of this method are currently underway in our laboratory.[15]

## Acknowledgment

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(15) **Typical Procedure for the Preparation of 4-Pyridin-3-ylbenzoic Acid Methyl Ester (7a)**:
To a solution of 3-iodopyridine **5a** (205 mg, 1.0 mmol) and Li(acac) (11 mg, 0.1 mmol) in anhydrous and degassed NMP (1 mL) was added *i*-$Pr_2Zn$ (5.0 M, 0.11 mL, 0.55 mmol) dropwise at r.t. under argon. The reaction mixture was stirred at r.t. for 12 h. The complete conversion of 3-iodopyridine to the zinc reagent was monitored by GC analysis. The zinc reagent **6a** was treated with a solution of $Pd(bda)_2$ (14 mg, 0.025 mmol), tri(2-furyl)phosphine (12 mg, 0.05 mmol) and methyl 4-iodobenzoate (393 mg, 1.5 mmol) in THF (2 mL). The resulting mixture was stirred at r.t. for 12 h, and was quenched with sat. aq $NH_4Cl$. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried ($Na_2SO_4$). After removal of the solvent, the residue was purified by column chromatography on silica gel (EtOAc–pentane = 1:2) to give the desired product **7a** (176 mg, 83%) as a yellow solid; mp 102.0–102.8 °C. $^1$HMNR (300 MHz, $CDCl_3$): $\delta = 3.93$ (s, 3 H), 7.31–7.42 (m, 1 H), 7.63 (d, $J = 8.4$ Hz, 2 H), 7.90 (td, $J = 7.9, 2.2, 1.8$ Hz, 1 H), 8.12 (d, $J = 8.8$ Hz, 2 H), 8.62 (dd, $J = 1.3, 4.9$ Hz, 1 H), 8.86 (dd, $J = 0.9, 2.2$ Hz, 1 H) ppm. $^{13}$C NMR (75 MHz): $\delta = 52.2$, 123.7, 127.1, 129.8, 130.4, 134.7, 135.7, 142.0, 148.0, 148.9, 166.7. IR (KBr): 2951, 1721, 1608, 1285, 1107, 767 cm$^{-1}$. HRMS (EI): *m/z* calcd for $C_{13}H_{11}NO_2$: 213.0790; found: 213.0795.