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Communication

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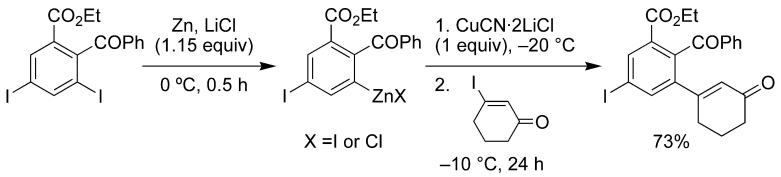

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COMMUNICATIONS

# Directed Ortho Insertion (DoI): A New Approach to Functionalized Aryl and Heteroaryl Zinc Reagents

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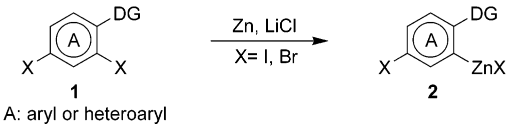
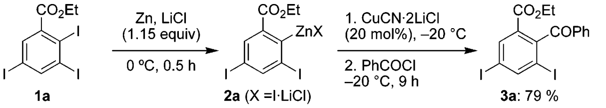
The preparation of polyfunctional organozincs is an important synthetic task since they are versatile organometallic reagents.[1] Recently, we have found that the addition of LiCl to zinc powder considerably facilitates its insertion into various aryl and heteroaryl iodides and bromides.[2] It is well-known that directed metalation groups (DMGs) are essential for the regioselective functionalization of aromatics and heterocycles using Li- or Mg-bases.[3] DMGs have also been used to perform regioselective halogen/metal exchanges[4] and metalations[5] but rarely direct metal insertion.[6] Herein, we wish to report a general directed ortho insertion (DoI) of zinc dust in the presence of LiCl to di- or tri- iodo- or bromo-substituted aromatic and heterocyclic systems of type **1** bearing an DMG or an appropriate heteroatom leading to polyfunctional unsaturated zinc reagents of type **2** showing remarkable regioselectivities (Scheme 1).

***Scheme 1.*** LiCl-Mediated Regioselective Zinc Insertion of Aryl and Heteroaryl Compounds of Type **1**[a]

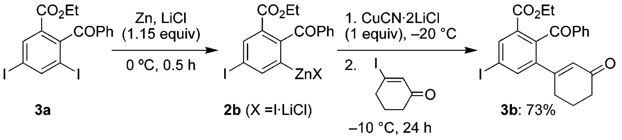


[a] Directing group (DG) = $-CO_2R$, $-COR$, $-OAc$, $-N{=}N-NR_2$, $-OCON(i\text{-}Pr)_2$, $-OSO_2Ar$.

Thus, the triiodobenzoate **1a** reacts readily with zinc dust[7] (1.15 equiv) and LiCl (1.15 equiv) in THF at 0 °C and furnishes after 0.5 h the ortho-zincated intermediate **2a**. After the addition of CuCN·2LiCl (20 mol %),[8] a smooth benzoylation with PhCOCl provides the aromatic ketoester **3a** in 79% yield (eq 1). Interestingly,



(1)



(2)

this diiodide **3a** undergoes a further selective zinc insertion affording the polyfunctional zinc reagent **2b** which after transmetalation with CuCN·2LiCl[8] reacts with 3-iodocyclohexenone[9] furnishing the substitution product **3b** in 73% yield (eq 2). In the absence of LiCl, no zinc insertion is observed, and higher reaction temperature leads to unselective reactions. The ketone group of the diiodide **3a** plays now the role of an ortho-directing group. We have found that other chelating groups such as an aryl sulfonate,[10] an acetate, a carbamate,[11] or a triazene[12] display similar DoI abilities making this approach quite general (Table 1). Thus, the 3,5-diiodobenzonitrile **1c** inserts selectively zinc dust in the presence of LiCl (1.15 equiv) at 0 °C furnishing regioselectively the ortho-zincated product **2c**. After a copper(I)-catalyzed allylation, the aryl iodide **3c** is obtained in 82% yield (entry 1). Similarly, the diiodobenzoate **1d** undergoes a selective zinc insertion providing the arylzinc **2d** which, after a reaction with ethyl (2-bromomethyl)acrylate,[13] leads to the polyfunctional diester **3d** in 85% yield (entry 2). Also various 1,3,5-triodobenzenes such as **1e** and **1f**, in which either a tosylate or an acetate plays the role of a directing group, are converted with a complete regioselectivity to the corresponding zinc organometallics **2e** and **2f**. Quenching with allyl bromide or 3-iodocyclohexenone[9] in the presence of CuCN·2LiCl[8] provides the expected products **3e** and **3f** in 72−82% yield (entries 3 and 4). The dibromoarene **1g** bearing an actate as DoI group is sufficiently reactive toward a zinc insertion and gives the desired zinc reagent **2g** (entry 5; 50 °C, 20 h). In the absence of LiCl, only starting material decomposition is observed. The zinc reagent **2g** undergoes a Pd-catalyzed Negishi cross-coupling reaction[14] with methyl 4-iodobenzoate furnishing the biphenyl **3g** in 73% yield. Remarkably, the mild conditions of the lithium chloride-mediated zinc insertion tolerates also a triazene function which is an important synthetic equivalent of a diazonium functionality.[12,15] Thus, the readily available tribromoaryltriazene **1h**[16] is converted with Zn/LiCl (2 equiv) to the zinc reagent **2h** (50 °C, 20 h) and provides by a Negishi cross-coupling reaction with methyl 2-iodobenzoate the polyfunctional dibromoaryltriazene **3h** in 76% yield (entry 6). This LiCl catalyzed DoI has a broad synthetic potential and can be applied to a wide range of heterocycles (entries 7−13). Various di- or tri- iodo- or bromo-pyridines **1i**−**k** bearing a sulfonate functionality[10] are chemo- and regio-selectively converted to the ortho-zincated pyridyl-sulfonates **2i**−**k**. Their copper(I)-catalyzed allylation or benzoylation affords the polyfunctional pyridines **3i**−**k** in 80−83% yield (entries 7−9). Interestingly, the carbamate group[11] smoothly directs also the zinc insertion with complete regioselectively for the diiodopyridine **1k** leading to the zinc derivative **2k** (entry 9). After allylation, the polyfunctional pyridine **3k** is obtained in 83% yield. Other diiodo-N-heterocyclic compound such as the 4,5-diiodoimidazole[17] **1l** is converted at 50 °C within 2 h to the zinc reagents **2l** (entry 10). In the presence of CuCN·2LiCl,[8] the addition of allyl bromide leads to the corresponding allylated iodoimidazole **3l** in 80% yield. A tosylate is also an excellent DoI group. Thus, the 5,7-diiodoquinoline **1m** inserts selectively Zn dust in the presence of LiCl at 25 °C and leads, after transmetalation with CuCN·2LiCl[8] and quenching with pivaloyl chloride, the polyfunctional quinoline **3m** in 78% yield (entry 11). The mild conditions of the Zn/LiCl insertion allow also a regioselective zinc insertion for heterocycles having well differentiated reactivity sites. Thus, 2,5-dibromothiazole[18] **1n** undergoes a selective zincation at 25 °C and gives the heteroarylzinc bromide **2n** (entry 12). A Pd-catalyzed Negishi cross-coupling with 2-iodobenzaldehyde furnishes

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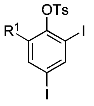
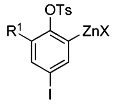
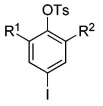
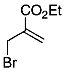
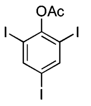
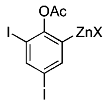
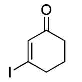
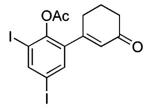
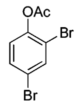
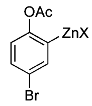
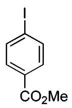
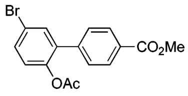
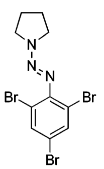
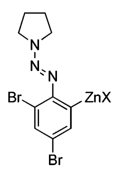
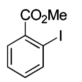
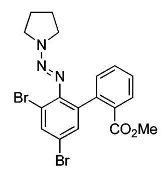
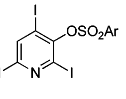
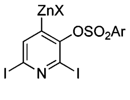
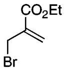
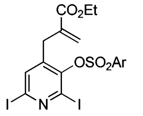
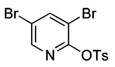
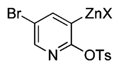
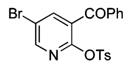
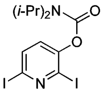
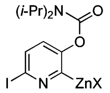
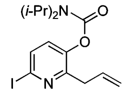
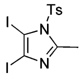
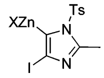
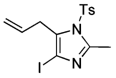
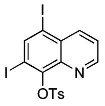
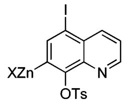
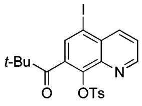
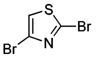
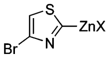
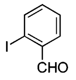
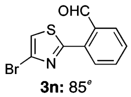
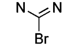
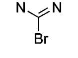
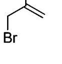
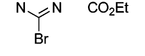
***Table 1.*** Preparations and Reactions of Unsaturated Organozinc Reagents of Type **2** Leading to Products of Type **3**

| Entry | Aryl halide | Zinc reagent[a] (Conditions) | Electrophile | Product, yield (%)[b] |
|---|---|---|---|---|
| 1 | <br>**1c**: $R^1$ = CN | <br>**2c**: $R^1$ = CN<br>(0 °C, 12 h) | $CH_2$=$CHCH_2Br$ | <br>**3c**: $R^1$ = CN, $R^2$ = $C_3H_5$, 82[c] |
| 2 | **1d:** $R^1$ = $CO_2Et$ | **2d:** $R^1$ = $CO_2Et$<br>(0 °C, 12 h) |  | **3d:** $R^1$ = $CO_2Et$,<br>$R^2$ = $CH_2C(CO_2Et)CH_2$, 85[c] |
| 3 | **1e:** $R^1$ = I | **2e:** $R^1$ = I<br>(25 °C, 4 h) | $CH_2$=$CHCH_2Br$ | **3e:** $R^1$ = I,<br>$R^2$ = $CH_2CH$=$CH_2$, 81[c] |
| 4 | <br>**1f** | <br>**2f** (0 °C, 0.5 h) |  | <br>**3f:** 72[d] |
| 5 | <br>**1g** | <br>**2g** (50 °C, 20 h) |  | <br>**3g:** 73[e] |
| 6 | <br>**1h** | <br>**2h** (50 °C, 20 h) |  | <br>**3h:** 76[e] |
| 7[f] | <br>**1i** | <br>**2i** (0 °C, 2.5 h) |  | <br>**3i:** 83[c] |
| 8 | <br>**1j** | <br>**2j** (25 °C, 20 h) | PhCOCl | <br>**3j:** 81[d] |
| 9 | <br>**1k** | <br>**2k** (25 °C, 5 h) | $CH_2$=$CHCH_2Br$ | <br>**3k:** 83[c] |
| 10 | <br>**1l** | <br>**2l** (50 °C, 2 h) | $CH_2$=$CHCH_2Br$ | <br>**3l:** 80[c] |
| 11 | <br>**1m** | <br>**2m** (25 °C, 12 h) | *t*-BuCOCl | <br>**3m:** 78[d] |
| 12 | <br>**1n** | <br>**2n** (25 °C, 0.5 h) |  | <br>**3n:** 85[e] |
| 13 | <br>**1o** | <br>**2o** (0 °C, 12 h) |  | <br>**3o:** 63[c] |

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[a] X = I•LiCl or Br•LiCl. [b] Isolated yield of analytically pure product. [c] Catalytic amount of CuCN•2LiCl was added. [d] A 1 equiv portion of CuCN•2LiCl was added. [e] A 1 mol % portion of $Pd(Ph_3P)_4$ was added. [f] Ar = $4\text{-}ClC_6H_4$.

the corresponding aldehyde **3n** in 85% yield. A selective zinc insertion occurs also with the tribromopyrimidine **1o** at 25 °C within 4 h, leading to the zincated dibromopyrimidine **2o** (entry 13). Addition of ethyl (2-bromomethyl)acrylate in the presence of a catalytic amount of CuCN•2LiCl[8] leads to the substituted dibromopyrimidine **3o** in 63% yield.

In summary, we have shown that the use of Zn dust in the presence of LiCl in THF allows, for the first time, a highly regioselective zinc insertion on poly iodo- and bromo- aryls as well as heteroaryls allowing to prepare polyfunctional zinc reagents otherwise difficult to obtain such as **2b**, **2g**, **2h**, and **2o**. This exceptional regioselectivity is triggered by various DoI groups such as an ester, a ketone, an aryl sulfonate, an acetate, a triazene, or a carbamate, showing the generality of this approach. Further extensions of this work are currently underway in our laboratories.

**Acknowledgment.** We thank the Fonds der Chemischen Industrie, the DFG, Merck Research Laboratories (MSD), Chemetall GmbH (Frankfurt), and BASF AG (Ludwigshafen) for financial support. S.S. thanks the JSPS and P.S. thanks the Humboldt Foundations for financial support.

**Supporting Information Available:** Experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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