Preparation and Reactions of Highly Functionalized Bis-Arylzinc Reagents Using a Li(acac)-Catalyzed Iodine–Zinc Exchange

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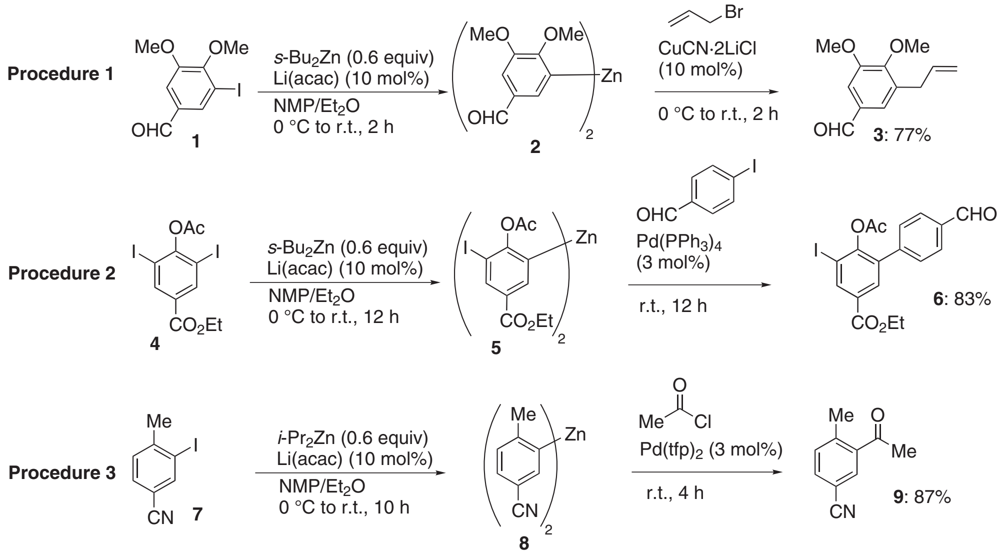
Received 16 June 2005

PSP No 56

Abstract: Polyfunctional bis-arylzinc reagents are accessible via a new lithium acetylacetonate-catalyzed iodine-zinc exchange. This protocol tolerates sensitive functional groups (ketones, aldehydes or isothiocyanates) in the aryl iodides and allows the formation of highly functionalized zinc reagents. These zinc reagents can be used in a variety of catalyzed and uncatalyzed transformations.

Key words: functionalized zinc reagents, halogen–metal exchange, cross-coupling, nucleophilic catalysis



Scheme 1

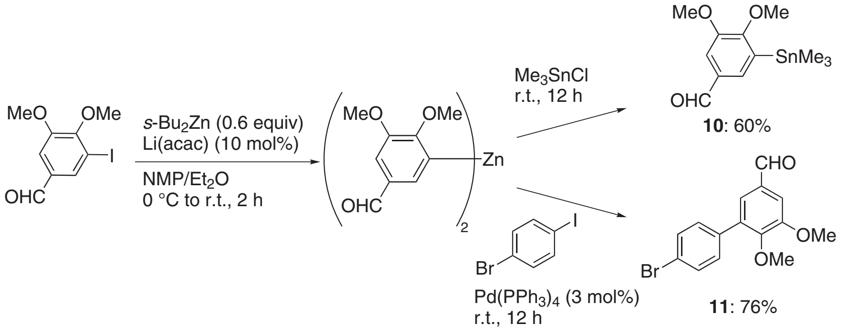
Introduction

The use of polyfunctional organometallic reagents for the synthesis of complex polyfunctional target molecules represents a versatile method for the selective introduction of well-defined and complex building blocks under mild conditions.[1] Various halogen–metal exchange reactions are well established and allow the preparation of functionalized organolithium,[2] organomagnesium[3] and organocopper[4] reagents. Especially organozincs are known to tolerate a wide range of functional groups.[5] Although the preparation of functionalized bis(alkyl)zincs or mixed functionalized arylzinc compounds[6] is well established, a preparation protocol for polyfunctional bis(aryl)zinc reagents was unprecedented.[7] Recently, we have found an iodine–zinc exchange reaction catalyzed by Li(acac) for the preparation of polyfunctional bis(aryl)zinc reagents.[8] Herein, we wish to report three typical practical procedures illustrating this method.

Scope and Limitations

The mild reaction conditions of this procedure for performing an iodine–zinc exchange are compatible with a surprisingly wide variety of functionalities. Thus, the treatment of 3-iodo-4,5-dimethoxybenzaldehyde (**1**) with *s*-Bu_2Zn (0.6 equiv) in the presence of a catalytic amount of Li(acac) (10 mol%) in a *N*-methylpyrrolidinone (NMP)–Et_2O mixture furnished after two hours at room temperature the desired bis(aryl)zinc reagent **2** (Scheme 1).

SYNTHESIS 2005, No. 15, pp 2625–2629
Advanced online publication: 22.07.2005
DOI: 10.1055/s-2005-872097; Art ID: T08305SS



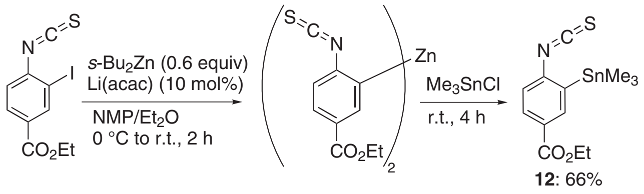
Scheme 2

Allylation of **2** with allyl bromide (1.5 equiv) at room temperature in the presence of CuCN·2LiCl[9] for two hours provided 3-allyl-4,5-dimethoxybenzaldehyde (**3**) in 77% yield (**Procedure 1**). Another application for the arylzinc reagents prepared by this method is a palladium-catalyzed cross-coupling reaction.[10] Bis(aryl)zinc reagent **5**, which was prepared from the aryl iodide **4,** provided ethyl-6-(acetyloxy)-4′-formyl-5-iodobiphenyl-3-carboxylate (**6**) in 83% yield in the presence of $Pd(PPh_3)_4$ (3 mol%) after ten hours at room temperature (**Procedure 2**).

Finally, the reaction of bis(aryl)zinc reagent **8**, which was prepared from the aryl iodide **7** by treatment with i-Pr_2Zn,[11] reacted with acetyl chloride resulting after transmetalation with CuCN·2LiCl in the formation of 3-acetyl-4-methylbenzonitrile (**9**) in 87% yield (**Procedure 3**).

Furthermore, an aryl iodide bearing an aldehyde functionality can be converted into the corresponding bis(aryl)zinc reagent and be directly trapped with Me_3SnCl affording the corresponding formyl-substituted aryltin compound **10**. It can also be used in a Negishi cross-coupling reaction to provide the highly functionalized biphenyl **11** (Scheme 2).[12]

An isothiocyanate functionality is also tolerated in this iodine–zinc exchange reaction. Trapping of an isothiocyanate-substituted zinc compound with Me_3SnCl (4 h, r.t.) provided the aromatic stannane **12** in 66% yield (Scheme 3).[13]

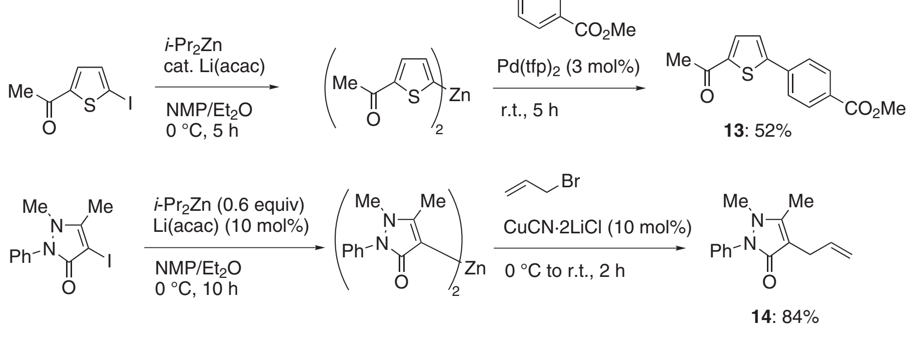


Scheme 3

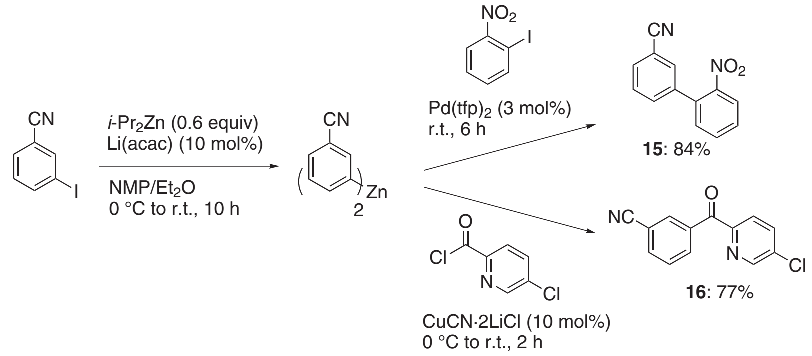
With heterocyclic aromatic iodides, the exchange reaction proceeds also well. The corresponding bis(heteroaryl)zinc species could be applied in a Negishi cross-coupling reaction with methyl p-iodobenzoate resulting in the formation of the expected biaryl **13** in 52% yield. Another reaction pathway for the conversion of heteroaromatic bis(organo)zincs is a copper-catalyzed allylation which yields the expected functionalized heteroarene **14** in 84% yield (Scheme 4).

The bis(aryl)zinc species containing a m-cyano group reacted in a cross-coupling reaction with 2-nitro-iodobenzene and yielded biaryl **15** in 84% yield. Reaction with 4-chloronicotinoyl chloride in the presence of CuCN·2LiCl (10 mol%) furnished the functionalized mixed diaryl ketone **16** with 77% yield (Scheme 5).

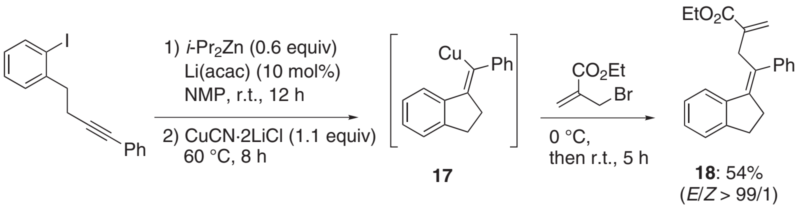
The iodine–zinc exchange was also performed on a readily available alkynyl iodide[14] with i-Pr_2Zn in the presence of Li(acac) (10 mol%) resulting in the bis(aryl)zinc reagent. Subsequently, a smooth intramolecular carbomet-



Scheme 4



Scheme 5

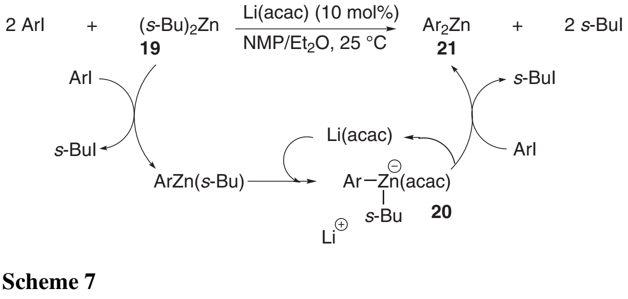


Scheme 6

alation reaction[15] occurred in the presence of CuCN·2LiCl (1.1 equiv) at 60 °C giving the expected copper reagent **17**. Intermediate **17** was trapped with ethyl (2-bromomethyl)acrylate[16] to provide the tetrasubstituted *E*-alkene **18** (*E*/*Z* = >99:1) in 54% overall yield (Scheme 6).

Crucial for the formation of the bis(aryl)zinc species **21** from the bis(alkyl)zinc precursor **19** is the addition of Li(acac) and the use of NMP. The acetylacetonate ligand coordinates to the mixed zinc species resulting in the formation of the zincate **20** which undergoes a rapid exchange reaction with another equivalent of ArI leading to the diarylzinc **21** (Scheme 7).

In summary, the Li(acac)-catalyzed iodine–zinc exchange reaction allows the preparation of a range of new polyfunctional arylzinc reagents which undergo typical reactions with various electrophiles like allylic halides, aromatic iodides, acid chlorides and trialkyltin chloride.



Scheme 7

s-Dibutylzinc (*s*-Bu$_2$Zn)

s-BuLi (100 mmol, 71 mL, 1.4 M in cyclohexane, 1.0 equiv) was purified by filtration through Celite®. The concentration of the alkyllithium reagent was determined thoroughly according to the literature.[17,18] The solution was cooled to 0 °C and the volume was reduced in vacuo to approximately 7 mL. The orange, highly viscous solution was cooled to –78 °C. An ethereal solution of $ZnCl_2$[18] (6.82 g, 50 mmol, 1.0 M, 0.5 equiv) was slowly added. The solution was allowed to warm up slowly to r.t. and stirred overnight under strict light exclusion by protection with aluminum foil. The precipitated LiCl was removed from the solution either by decantation, filtration or centrifugation.[19] The resulting clear solution of *s*-Bu$_2$Zn is light sensitive and is approximately 0.60–0.80 M in concentration (determined by iodometric titration).[20]

3-Allyl-4,5-dimethoxybenzaldehyde (3); Procedure 1

A dry and argon-flushed 10-mL round-bottom flask equipped with a magnetic stirrer was charged with 4,5-dimethoxy-3-iodobenzaldehyde (**1**; 584 mg, 2.0 mmol, 1.0 equiv) and Li(acac) (21 mg, 0.2 mmol, 0.1 equiv) in anhyd NMP (1.5 mL) and cooled to 0 °C. The previously prepared *s*-Bu$_2$Zn solution (1.4 mL of a 0.8 M solution, 1.1 mmol, 0.6 equiv) was added. The reaction mixture was stirred at r.t. for 3 h and the complete formation of the zinc reagent **2** was checked by GC analysis using tetradecane as internal standard. Allyl bromide (363 mg, 3.0 mmol) was added to the zinc reagent **2**, followed by the dropwise addition of CuCN·2LiCl (0.2 mL, 0.2 mmol, 0.1 equiv, 1.0 M in NMP). After 5 h, the conversion was complete. The consumption of the zinc reagent was checked by GC analysis of a reaction aliquot. Aq sat. NH_4Cl solution (5 mL) was added to the mixture. After addition of aq NH_4Cl (30 mL), the aqueous phase was extracted with Et_2O (3 × 80 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated and the product was purified by flash chromatography (SiO_2, pentane–Et_2O, 80:20) to give the aldehyde **3** (317 mg, 77%) as a colorless oil.

IR (film): 3079 (w), 3005 (w), 2978 (m), 2941 (m), 2837 (m), 2739 (w), 1694 (s), 1639 (m), 1586 (s), 1487 (s), 1464 (s), 1427 (s), 1388 (s), 1333 (m), 1299 (s), 1232 (m), 1140 (s), 1074 (m), 1003 (s), 915 (m), 858 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.86 (s, 1 H), 7.32 (d, *J* = 1.5 Hz, 1 H), 7.30 (d, *J* = 2.1 Hz, 1 H), 5.87–6.03 (m, 1 H), 5.01–5.14 (m, 2 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.43–3.47 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.3, 153.3, 152.6, 136.4, 134.4, 132.3, 126.6, 116.4, 109.1, 60.8, 55.9, 34.0.

MS (EI, 70 eV): *m/z* (%) = 206 (M^+, 100), 191 (4), 177 (14), 163 (9), 147 (7), 135 (11), 131 (13), 103 (22), 91 (14).

HRMS: *m/z* calcd for $C_{12}H_{14}O_3$ $[M]^+$: 206.0943; found: 206.0944.

Ethyl 6-(Acetyloxy)-4′-formyl-5-iodobiphenyl-3-carboxylate (6); Procedure 2

Ethyl 4-(acetyloxy)-3,5-diiodobenzoate[21] (**4**; 920 mg, 2.0 mmol, 1.0 equiv) and Li(acac) (21 mg, 0.2 mmol, 0.1 equiv) were dissolved in anhyd NMP (1.5 mL). The iodine–zinc exchange with *s*-Bu_2Zn (1.8 mL, 1.1 mmol, 0.6 M in Et_2O) at 0 °C was complete after 10 h according to GC analysis. $Pd(PPh_3)_4$ (55 mg, 0.05 mmol, 3 mol%) in anhyd THF (2 mL) was stirred with 4-iodobenzaldehyde (371 mg, 1.6 mmol, 0.8 equiv) at r.t. for 5 min, and the freshly prepared solution of bis(aryl)zinc reagent **5** was added at 0 °C. After stirring for 12 h at r.t., aqueous workup with aq NH_4Cl solution (80 mL), extraction with Et_2O (3 × 80 mL) and purification by flash chromatography (SiO_2, pentane–Et_2O, 70:30) yielded aldehyde **6** (583 mg, 83%) as colorless crystals; mp 125–126 °C.

IR (KBr): 3423 (w), 1768 (s), 1721 (s), 1698 (s), 1606 (m), 1367 (m), 1301 (s), 1241 (s), 1171 (s), 1048 (m), 841 (m), 766 cm^{-1} (m).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.07 (s, 1 H), 8.53 (d, *J* = 1.72 Hz, 1 H), 8.05 (d, *J* = 1.72 Hz, 1 H), 7.95 (d, *J* = 8.17 Hz, 2 H), 7.59 (d, *J* = 7.95 Hz, 2 H), 4.40 (q, *J* = 7.09 Hz, 2 H), 2.13 (s, 3 H), 1.40 (t, *J* = 7.09 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 191.7, 167.4, 164.2, 151.9, 142.7, 140.5, 135.9, 135.3, 132.0, 130.3, 129.8 (2 C), 129.5 (2 C), 92.3, 61.7, 21.0, 14.3.

MS (EI, 70 eV): *m/z* (%) = 30 (M^+, <1), 315 (100), 300 (28), 285 (10), 270 (7), 225 (3).

HRMS: *m/z* calcd for $C_{18}H_{15}IO_5$ $[M]^+$: 437.9964; found: 437.9968.

3-Acetyl-4-methylbenzonitrile (9); Procedure 3

3-Iodo-4-methylbenzonitrile (**7**; 486 mg, 2.0 mmol) and Li(acac) (21 mg, 0.2 mmol) were dissolved in anhyd NMP (1.5 mL). The iodine–zinc exchange was performed at r.t. using *i*-Pr_2Zn[11] (0.2 mL, 1.1 mmol, 0.6 equiv). The iodine–zinc exchange was completed after 10 h. To a preformed palladium–phosphine complex, generated by dissolving $Pd(dba)_2$[21] (30 mg, 2.5 mol%) and tfp (tri-2-furylphosphine)[12a] (25 mg, 5.0 mol%) in THF (2 mL), was added AcCl (237 mg, 3.0 mmol) at r.t. and the solution was stirred for 10 min. Subsequently, the freshly prepared solution of the zinc reagent **8** was added dropwise at r.t. The mixture was stirred for 4 h. After addition of aq NH_4Cl (30 mL), the aqueous phase was extracted with Et_2O (3 × 80 mL) and the combined organic layers were dried ($MgSO_4$). Flash chromatographic purification (SiO_2, pentane–Et_2O, 70:30) yielded ketone **9** (277 mg, 87%) as a yellow solid; mp 101–102 °C.

IR (film): 3115 (w), 3080 (w), 3045 (w), 2971 (w), 2931 (w), 2228 (s), 1687 (s), 1557 (m), 1494 (w), 1443 (s), 1379 (s), 1362 (s), 1291 (m), 1250 (s), 1141 (w), 1060 (w), 1034 (w), 972 (m), 960 (w), 918 (w), 897 (m), 827 (s), 656 (m), 615 (m), 545 (m), 516 (m), 446 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.8 Hz, 1 H), 7.51–7.58 (m, 2 H), 2.58 (s, 3 H), 2.51 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.8, 141.6, 139.0, 135.3, 129.6, 129.1, 118.1, 114.8, 29.8, 21.0.

MS (EI, 70 eV): *m/z* (%) = 159 (M^+, 29), 144 (100), 128 (1), 116 (31), 103 (1), 89 (11), 75 (1), 63 (5).

HRMS: *m/z* calcd for $C_{10}H_9NO$ $[M]^+$: 159.0684; found 159.0698.

Acknowledgment

We thank the Fonds der chemischen Industrie and the DFG for financial support. We thank Chemetall GmbH (Frankfurt) and BASF AG (Ludwigshafen) for the generous gift of chemicals.

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(18) The exact determination of all the concentrations of the solutions used (*s*-BuLi, $ZnCl_2$, *s*-Bu_2Zn) is decisive for the success of this procedure. Threefold titration and averaging have been typically done.

(19) The complete absence of LiCl is decisive for the success of the iodine–zinc exchange procedure.

(20) Threefold titration has been performed.

(21) Prepared by acylation of 4-hydroxy-3,5-diiodobenzoate with Ac_2O (1.3 equiv) in pyridine in the presence of DMAP (0.1 equiv).