Synthesis of 1,2-Dimetallic Compounds via Direct Insertion of Zinc Powder in the Presence of InCl₃: Synthesis of *ortho*-Bis-functionalized Aromatics

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Abstract: A variety of functionalized 1,2-dizinc reagents can be prepared by an indium-catalyzed insertion of zinc powder into aromatic 1,2-dibromides or 1-bromo-2-triflates. These 1,2-dimetallics undergo Cu- or Pd-catalyzed acylations, allylations, or cross couplings. **Key words:** zinc, 1,2-dimetallic, insertion, cross-coupling, indium(III) chloride



Scheme 1 Typical procedures for the preparation of 1,2-dizinc reagents via indium(III) chloride catalyzed insertion of zinc powder into aromatic 1,2-dibromides or 1-bromo-2-triflates (Procedure 1) and subsequent functionalization via cross coupling (Procedure 2) or acylation (Procedure 3)

Introduction

Organozinc reagents are important for organic synthesis and the interest in their unique chemical properties has increased during the past two decades.¹ Due to their high functional group tolerance and reactivity in transitionmetal-catalyzed reactions, such as Negishi cross couplings, they have found numerous synthetic applications.^{2,3} Aryl- and benzylzinc reagents are accessible under mild conditions by direct insertion of commercially

SYNTHESIS 2014, 46, 0290–0294 Advanced online publication: 13.11.2013 DOI: 10.1055/s-0033-1340106; Art ID: SS-2013-T0671-PSP © Georg Thieme Verlag Stuttgart · New York available zinc dust (activated with 1,2-dibromoethane and chlorotrimethylsilane) into the corresponding aryl bromides or benzyl chlorides in the presence of lithium chloride.^{4,5} However, this method fails for the preparation of aryl dimetallics. The works of Takai⁶ and others⁷ have shown that activation of the metal surface is important for insertion reactions into different unsaturated aryl halides. It was shown that salts such as indium(III) chloride can activate several metals very effectively for direct insertion reactions,^{7c} and we have envisioned a novel catalyzed insertion of aluminum or zinc into substituted arenes to afford 1,2-dimetallics. We found that the insertion of zinc dust is greatly enhanced by catalytic amounts of indium(III) chloride (7.5 mol%), allowing the generation of

Scope and Limitations

1.2-Dimetallic zinc reagents are accessible under mild conditions starting from 1,2-dibromides or 1-bromo-2-triflates. Thus, the addition of the ester-functionalized triflate 1a to zinc dust (3 equiv) and indium(III) chloride (7.5 mol%) in 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1H)-one (DMPU) furnished the expected dizinc reagent 2a in 75% yield.⁹ The described insertion reaction was performed on a 20 mmol scale and proceeds smoothly in two hours at 50 °C (Scheme 1, procedure 1). The resulting dizinc reagent 2a reacted well with 4-bromobenzaldehyde (3a) in a twofold palladium-catalyzed cross-coupling reaction in the presence of 1.4 mol% [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-iPr),¹⁰ affording the ester 4a in 69% yield on a 2 mmol scale. Upscaling was easily possible leading to a similar yield of 70%, on a larger scale (Scheme 1, procedure 2). The unprotected aldehyde was perfectly compatible with the reaction conditions. Furthermore, the electron-rich aromatic dibromide 1b underwent a smooth insertion, furnishing the 1,2-dizinc reagent 2b in 59% yield. 1,2-Dimetallics bearing electron-donating groups are generally more difficult to obtain than reagents bearing electron-withdrawing substituents. After subsequent palladium-catalyzed acylation with ethyl chloroformate (3b), the diester 4b was obtained in 72% vield on a 2 mmol scale, and in 69% vield on a 16 mmol scale (Scheme 1, procedure 3). Interestingly, only palladium-catalyzed acylations were found to proceed smoothly and attempts to perform acylation reactions in the presence of copper(I) salts resulted in extensive decomposition. Similarly, the dizinc reagent 2a underwent a smooth acylation reaction with 4-chlorobenzoyl chloride (3c) in the presence of 10 mol% tetrakis(triphenylphosphine)palladium(0) (Table 1, entry 1). It should be noted that other palladium-catalysts are not as efficient for performing such acylation reactions. A cross coupling with 4-bromobenzonitrile (3d) led to the corresponding ortho-substituted product 4d in 63-64% yield (entry 2). Even a sensitive methyl ester 1c was tolerated under these reaction conditions, and Negishi cross coupling of the corresponding 1,2-dimetallic reagent 2b with ethyl 3-bromobenzoate (3e) furnished the triester 4e in 61–63% yield (entry 3). Remarkably, using these synthetic procedures, a nitrile functionality (1d) could be tolerated, and the corresponding dimetallic reagent 2c was obtained in 57% yield. After subsequent palladium-catalyzed acylation, the diketone 4f was isolated in 63-68% yield (entry 4).

Table 1 Indium(III) Chloride Catalyzed Zinc Insertion into Substrates 1 and Subsequent Functionalization Leading to Products 4ª



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Entry	Substrate	Yield ^b (%)	Electrophile ^c	Product ^d	Scale (mmol)	Yield (%)
5 ^f	1d		3g	NC	20 2	53 55
6 ^e	Br OTf	60		$\begin{array}{c} 4\mathbf{g} \\ \overbrace{0}^{0} \\ \overbrace{0}^{\mathbf{C}_{6}\mathbf{H}_{4}-4-\mathbf{C}\mathbf{I}} \\ \overbrace{0}^{\mathbf{C}_{6}\mathbf{H}_{4}-4-\mathbf{C}\mathbf{I}} \\ 4\mathbf{h} \end{array}$	20 2	61 62
7 ^f	1e		Br CO ₂ Et	OHC CO ₂ Et	15 2	58 ^g 54 ^g
8 ^f	1e		Br O O	OHC COMe	15 2	59 ^g 60 ^g
9 ^f	EtO ₂ C EtO ₂ C OTf	45	OMe 3i	EtO ₂ C EtO ₂ C OMe	10 2	64 69
10 ^h	Br Br 1g	59	GO ₂ Et Br 3j	4K CO ₂ Et CO ₂ Et 4I	20 2	63 61
11 ^f	MeO Br Br 1b	59	CO ₂ Me	MeO CO ₂ Me	15 2	71 68

Table 1 Indium(III) Chloride Catalyzed Zinc Insertion into Substrates 1 and Subsequent Functionalization Leading to Products 4^a (continued)

 a Reaction temperature: 50 °C; reaction time: 2 h.

^b Yield determined by GC analysis of iodolyzed reaction aliquots.

^c 2.0 equiv of electrophile were used.

^d Yield of isolated analytically pure compounds.

^e 10 mol% [Pd(PPh₃)₄] was used.

f 1.4 mol% PEPPSI-iPr.

^g Yield including a deprotection step.

^h 10 mol% CuCN·2LiCl was added.

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Cross coupling of the organometallic reagent 2c with ethyl 4-iodobenzoate (3g) afforded the desired product 4g in 53–55% yield (entry 5). An aldehyde was not compatible with the insertion reaction conditions; however, after protection as an acetal, the bromo triflate 1e reacted well with zinc powder and led to the 1,2-dizinc reagent 2d in 60% yield. This dimetallic reagent was smoothly acylated with 4-chlorobenzoyl chloride (3c), affording the diketone 4h in 61-62% yield (entry 6). Furthermore, Negishi cross coupling of this dizinc reagent with ethyl 3-bromobenzoate (3e) or the methyl ketone 3h, followed by acetal cleavage, furnished the expected products 4i, j in 54-60% yield (entries 7 and 8). Also, a dimetallic species bearing two ester groups 2e could be generated, and after cross coupling with 4-iodoanisole (3i), the highly functionalized terphenyl 4k was obtained in 64–69% yields (entry 9). Similarly, 1,2-dizinc reagents can be derived from aromatic 1,2-dibromides. Thus, 1,2-dibromobenzene (1g) or the electron-rich 1,2-dibromoanisole (1b) were converted into the corresponding 1,2-dizinc reagents 2e,f both in 59% yield. The hereby obtained reagents were allylated (10 mol% CuCN·2LiCl)¹¹ with ethyl 2-(bromomethyl)acrylate¹² (**3j**) or underwent a Negishi cross coupling with an aryl bromide 3k, providing the bis(acrylate) 4l and the terphenyl **4m** in 61–71% yields (entries 10 and 11).

Conclusion

In summary, a straightforward and efficient insertion of zinc powder promoted by catalytic amounts of indium(III) chloride was demonstrated. The preparation of various functionalized 1,2-dizinc species using commercially available metal powder and aromatic dibromides or readily available 1-bromo-2-triflates under mild reaction conditions was performed. The chemical properties of these organometallic reagents and the topological proximity of the two metals allow a novel approach to a variety of *or*-*tho*-bis-functionalized aromatics. We have extended our previous work and have reported herein readily scalable experimental procedures (12–40 mmol scale) using standard laboratory glassware and usual laboratory techniques. Further synthetic extensions of this method are currently underway in our laboratories.

All reactions were carried out under argon atmosphere in dried glassware. Commercially available starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. THF was continuously refluxed and freshly distilled from Na/benzophenone ketyl under N₂. Yields refer to isolated compounds estimated to be >95% pure as determined by ¹H NMR and capillary GC analyses.

Preparation of a 1 M CuCN·2LiCl Solution in THF

A Schlenk flask was charged with LiCl (16.96 g, 0.40 mol) and CuCN (17.95 g, 0.20 mol) and dried for 6 h at 150 °C under high vacuum ($5\cdot10^{-2}$ mbar; dry stirring). Careful addition of THF (200 mL) and stirring overnight furnished a slightly yellowish to greenish solution that was stored over 4 Å molecular sieves.

Preparation of Aromatic 1,2-Dizinc Reagents from Aromatic 1,2-Dibromides or ortho-Bromo Triflates; Typical Procedure 1 InCl₃ (7.5 mol%) was placed in an argon-flushed Schlenk flask and dried for 5 min by heating with a heat gun (450 °C) under high vacuum. Zinc powder (3 equiv) was added under argon, and the drying process was repeated for a further 5 min. The flask was evacuated and backfilled with argon $(3 \times)$ and then DMPU (1-2 mL/mmol)was added, along with the internal standard (heptadecane). TMSCl (3 mol%) was added, and the mixture was heated with a heat gun until it began to boil. The mixture was cooled to r.t. (20 °C), the triflate or bromide (1 equiv) was added in one portion, and the mixture was stirred at 50 °C. The progress of the insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots quenched with 2 M HCl or sat. aq NH₄Cl solution until a conversion of >95% was reached (usually 2 h). The zinc powder was allowed to settle down, and the remaining solution containing the zinc reagent was used for further reactions.

Ethyl 4,4"-Diformyl-[1,1':2',1"-terphenyl]-4'-carboxylate (4a);⁸ Typical Procedure 2

The zinc reagent **2a** was prepared according to typical procedure 1 from ethyl 3-bromo-4-[(trifluoromethylsulfonyl)oxy]benzoate (**1a**, 7.54 g, 20 mmol), Zn powder (3.92 g, 60 mmol), and InCl₃ (0.33 g, 1.5 mmol). The reaction was carried out in DMPU (20 mL) at 50 °C for 2 h. Iodolysis indicated 75% yield (15.0 mmol) of bimetallic reagent. The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask containing a solution of 4-bromobenzaldehyde (**3a**, 7.40 g, 40 mmol) and PEPPSI-*i*Pr (0.19 g, 0.28 mmol) in THF (20 mL). The mixture was stirred at 50 °C for 12 h and then it was quenched with 2 M HCl (50 mL). Flash column chromatographical purification (silica gel, isohexane–Et₂O, 5:1) afforded **4a** as a white solid (3.76 g, 10.5 mmol, 70%); mp 123–126 °C.

IR (diamond-ATR, neat): 2955, 2926, 2849, 2748, 1716, 1696, 1602, 1574, 1568, 1517, 1473, 1424, 1400, 1387, 1366, 1302, 1286, 1266, 1235, 1211, 1169, 1140, 1106, 1043, 1020, 1010, 1003, 918, 895, 838, 828, 767, 748, 735, 723, 702, 666 cm⁻¹.

¹H NMR (400 MHz, C_6D_6): $\delta = 9.58$ (s, 1 H), 9.58 (s, 1 H), 8.27–8.24 (m, 1 H), 8.18 (dd, J = 8.0, 1.8 Hz, 1 H), 7.38–7.32 (m, 4 H), 7.12 (dd, J = 8.0, 0.4 Hz, 1 H), 6.88–6.84 (m, 4 H), 4.21 (q, J = 7.2 Hz, 2 H), 1.08 (t, J = 7.1 Hz, 3 H).

¹³C NMR (100 MHz, C₆D₆): δ = 190.6, 190.6, 165.7, 146.0, 145.9, 143.7, 140.0, 135.8, 135.6, 132.0, 131.2, 131.0, 130.5, 130.4, 129.6, 129.5, 129.4, 61.3, 14.3.

MS (EI, 70 eV): *m/z* (%) = 359 (20), 358 (100), 313 (40), 285 (10), 229 (40), 228 (33), 227 (11), 226 (11).

HRMS (EI): m/z [M]⁺ calcd for C₂₃H₁₈O₄: 358.1205; found: 358.1196.

Diethyl 4-Methoxyphthalate (4b);⁸ Typical Procedure 3

The zinc reagent **2b** was prepared according to typical procedure 1 from 1,2-dibromo-4-methoxybenzene (**1b**, 4.25 g, 16 mmol), Zn powder (3.14 g, 36 mmol), and InCl₃ (0.2 g, 1.2 mmol). The reaction was carried out in DMPU (16 mL) at 50 °C for 2 h. Iodolysis indicated that the bimetallic reagent was obtained in 59% yield (9.44 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask and cooled to -30 °C. Pd(PPh₃)₄ (1.85 g, 1.6 mmol) was added at -30 °C, followed by subsequent addition of ethyl chloroformate (**3b**, 3.47 g, 32 mmol). The mixture was stirred at -30 °C and slowly warmed to r.t. and was quenched after 14 h with 2 M HCl (16 mL). Flash column chromatographical purification (silica gel, isohexane–EtOAc, 4:1) afforded **4b** as colorless oil (1.64 mg, 6.51 mmol, 69%).

IR (diamond-ATR, neat): 2982, 2939, 1714, 1602, 1573, 1500, 1464, 1446, 1423, 1390, 1366, 1324, 1274, 1229, 1182, 1173, 1115, 1067, 1030, 930, 924, 849, 803, 779, 702, 672 cm⁻¹.

¹H NMR (400 MHz, C₆D₆): δ = 7.76 (d, *J* = 8.6 Hz, 1 H), 7.12 (d, *J* = 2.5 Hz, 1 H), 6.57 (dd, *J* = 8.6, 2.7 Hz, 1 H), 4.26 (q, *J* = 7.0 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 3.05 (s, 3 H), 1.10 (t, *J* = 7.1 Hz, 3 H), 1.03 (t, *J* = 7.1 Hz, 3 H).

 ^{13}C NMR (100 MHz, C₆D₆): δ = 168.1, 166.3, 162.2, 137.0, 131.7, 123.5, 115.7, 113.8, 61.5, 61.0, 54.9, 14.1, 14.1.

MS (EI, 70 eV): m/z (%) = 252 (29), 207 (25), 180 (10), 179 (100).

HRMS (EI): m/z [M]⁺ calcd for C₁₃H₁₆O₅: 252.0998; found: 252.0999.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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