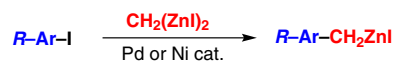


# Preparation of an Arenylmethylzinc Reagent with Functional Groups by Chemoselective Cross-Coupling Reaction of Bis(iodozincio)methane with Iodoarenes

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*R-Ar*: XC<sub>6</sub>H<sub>4</sub>, EtOCOC<sub>6</sub>H<sub>4</sub>, Bpin-C<sub>6</sub>H<sub>4</sub>, etc. >76% (Pd cat., 9 examples)

*R-Ar*: Py, X-Py >30% (Ni cat., 5 examples)

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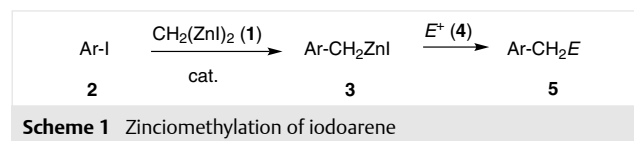
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**Abstract** Palladium-catalyzed cross-coupling reaction of bis(iodozincio)methane with iodoarenes carrying various functionalities such as ester, boryl, cyano, and halo groups proceeded chemoselectively to give the corresponding arenylmethylzinc species efficiently. The moderate reactivity of the *gem*-dizinc reagent imparted functional group tolerance to the process. The transformations from iodoheteroarenes were also performed; in the case of iodopyridine derivatives, the nickel-catalyzed reaction gave the corresponding organozinc species efficiently. The obtained arenylmethylzinc species underwent the copper-mediated coupling reaction with a range of organic halides.

**Keywords** arenylmethylzinc, organozinc, cross-coupling, palladium, nickel

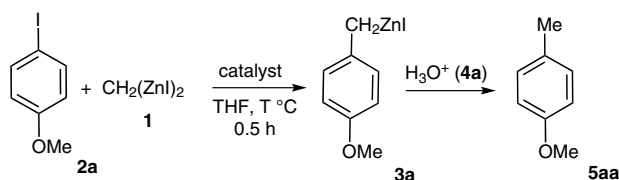
Aromatic components are important structures for pharmaceuticals and materials, and their insertion has been studied intensively in order to synthesize many molecules.<sup>1</sup> Nucleophilic introduction of arene moieties is often performed by using the corresponding arenylmetals. Schlosser developed an approach for the preparation of highly functionalized arenyllithium through the oriented deprotonation method.<sup>2</sup> In addition, the formation of a functionalized arenylmagnesium from the magnesium amide is also an efficient route.<sup>3</sup> Compared with the established route for the preparation of highly functionalized arenylmetals, the homologous arenylmethylmetals with several functional groups have not been well studied, although they can also play a crucial role in the introduction of an aromatic skeleton. Recently, Knochel and co-workers reported an efficient route to heteroarenylmethylzinc reagents from iodoheteroarenes through magnesium-iodine exchange, chloromethylation, and reduction with Zn-LiCl.<sup>4,5</sup> Given that highly functional iodoarenes had been established by the oriented deprotonation method, this homologative method was considered to be an easily accessible and reasonable route. Since we have studied the use of

bis(iodozincio)methane (**1**),<sup>6,7</sup> which can be used to introduce the iodozinciomethyl group directly, we tried to develop a shorter route from aryl iodide **2** to arenylmethylzinc reagent **3**. As shown in Scheme 1, the cross-coupling reaction of **1** with **2** was examined in the presence of a transition-metal catalyst.<sup>8</sup>



To find an appropriate catalyst for the cross-coupling reaction, treatment of iodoanisole (**2a**) with bis(iodozincio)methane (**1**) was examined in the presence of palladium catalyst (5 mol%) with various ligands (Table 1). The obtained arenylmethylzinc species **3a** was quenched with 1 M aqueous HCl and its yield was estimated by the amount of 4-methoxytoluene (**5aa**). A use of the electron-deficient ligand, tris[3,5-bis(trifluoromethyl)phenyl]phosphine, gave good results. As the migrating iodozinciomethyl group can be regarded as an electron-rich moiety, the electron-withdrawing ligand might be necessary for the transmetalation and the reductive elimination.<sup>9</sup> The use of Pd<sub>2</sub>dba<sub>3</sub> as a palladium source resulted in satisfactory yield (entries 5 and 6). Further tuning of the reaction temperature and the ratio of the ligand gave the product in excellent yields (entries 6–10). The further cross-coupling product, bis(4-methoxyphenyl)methane, was not identified in the reaction mixture.<sup>10</sup>

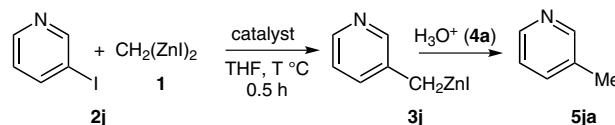
As shown in Scheme 2, the functional group tolerance of this coupling reaction was examined. Halo, cyano, trifluoromethyl, boryl, and ester groups did not disturb the transformation; however, 4-nitro-1-iodobenzene afforded the corresponding zinc reagent in only 12% yield. The zinciomethylation of 3-iodopyridine under the Pd catalyst also gave the corresponding coupling product in low yield.

**Table 1** Optimization of Zinciomethylation of **2a**<sup>a</sup>

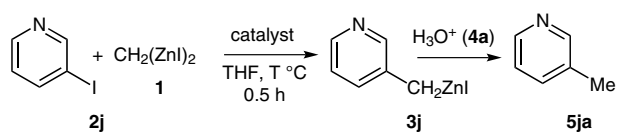
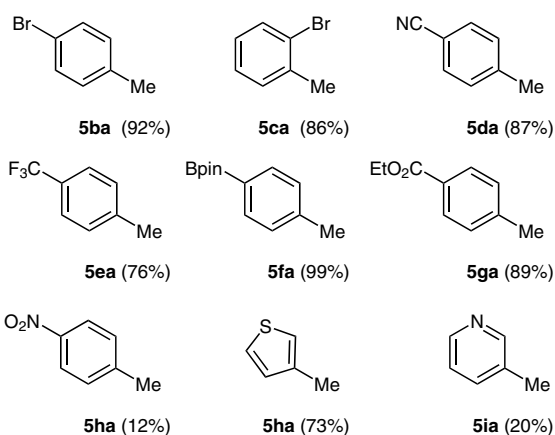
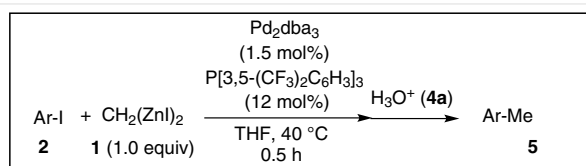
Entry	<b>1</b> (equiv)	Temp (°C)	Metal (mol%)	Ligand (mol%)	<b>5aa</b> <sup>b</sup> (%)
1	1.1	25	PdCl <sub>2</sub> (5)	Ph <sub>3</sub> P (10)	<5
2	1.1	25	PdCl <sub>2</sub> (5)	(EtO) <sub>3</sub> P (10)	<5
3	1.1	25	PdCl <sub>2</sub> (5)	(2-furyl) <sub>3</sub> P (10)	<5
4	1.1	25	PdCl <sub>2</sub> (5)	(3-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> P (10)	19
5	1.1	25	PdCl <sub>2</sub> (5)	[3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ] <sub>3</sub> P (10)	45
6	1.1	25	Pd <sub>2</sub> dba <sub>3</sub> (2.5)	[3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ] <sub>3</sub> P (10)	50
7	1.1	40	Pd <sub>2</sub> dba <sub>3</sub> (2.5)	[3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ] <sub>3</sub> P (10)	22
8	1.1	40	Pd <sub>2</sub> dba <sub>3</sub> (2.5)	[3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ] <sub>3</sub> P (20)	91
9	1.0	40	Pd <sub>2</sub> dba <sub>3</sub> (2.5)	[3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ] <sub>3</sub> P (20)	99
10	1.0	40	Pd <sub>2</sub> dba <sub>3</sub> (1.5)	[3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ] <sub>3</sub> P (12)	93

<sup>a</sup> Reaction conditions: **1** (0.36 M in THF, 0.7 mmol), **2a** (0.7 mmol).<sup>b</sup> Yield determined by GC analysis using dodecane as internal standard.

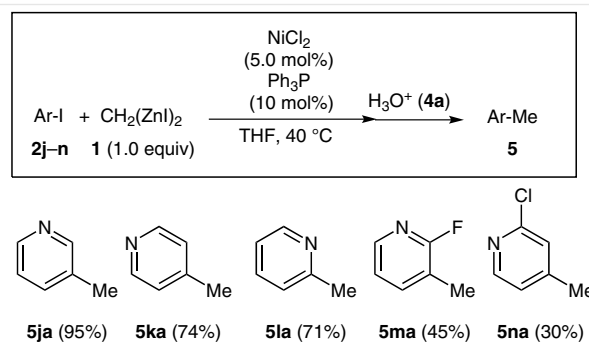
To achieve high yield in the cross-coupling reaction of 3-iodopyridine, the use of nickel catalyst instead of a palladium catalyst was shown to be effective (Table 2). Especially, the catalyst prepared from NiCl<sub>2</sub> (5 mol%) and Ph<sub>3</sub>P (10 mol%) gave the cross-coupling product in 99% yield (entry 8).

**Table 2** Optimization of Zinciomethylation of **2j**<sup>a</sup>

Entry	Catalyst [metal (mol%), ligand (mol%)]	<b>5ja</b> (%) <sup>b</sup>
1	Pd <sub>2</sub> dba <sub>3</sub> (2.5), [3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ] <sub>3</sub> P (20)	20
2	Pd <sub>2</sub> dba <sub>3</sub> (2.5), (2-furyl) <sub>3</sub> P (20)	10
3	NiCl <sub>2</sub> dppp (5)	40
4	NiCl <sub>2</sub> dppe (5)	38
5	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (5)	76
6	NiCl <sub>2</sub> (5), [3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ] <sub>3</sub> P (10)	2
7	NiCl <sub>2</sub> (5), (2-furyl) <sub>3</sub> P (10)	38
8	NiCl <sub>2</sub> (5), Ph <sub>3</sub> P (10)	99

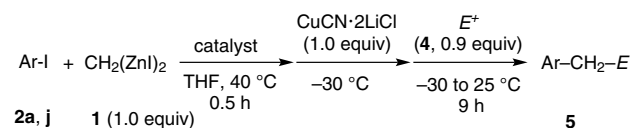
<sup>a</sup> Reaction conditions: **1** (0.36 M in THF, 0.7 mmol) and **2j** (0.7 mmol).<sup>b</sup> Yield determined by GC analysis using decane as internal standard.**Scheme 2** Zinciomethylation of iodoarenes bearing a functional group

As shown in Scheme 3, a range of iodopyridines were examined as substrate for the cross-coupling reaction with *gem*-dizinc **1** in the presence of nickel catalyst. Fluoro and chloro groups did not disturb the reaction (**5ma**, **5na**).

**Scheme 3** Zinciomethylation of iodopyridines

The copper-mediated reactions of the arenymethylzinc reagents, which had been prepared from iodoarenes (**2a,j**) and *gem*-dizinc **1**, with various electrophiles are shown in Table 3. Allyl- and propargyl bromide gave the coupling compounds regioselectively. The use of benzoyl cyanide gave arenymethyl phenyl ketones in good yields. Instead of benzoyl cyanide, the use of benzoyl chloride resulted in the formation of 4-benzoyloxy-1-halobutane, which was formed by a ring-opening of THF.

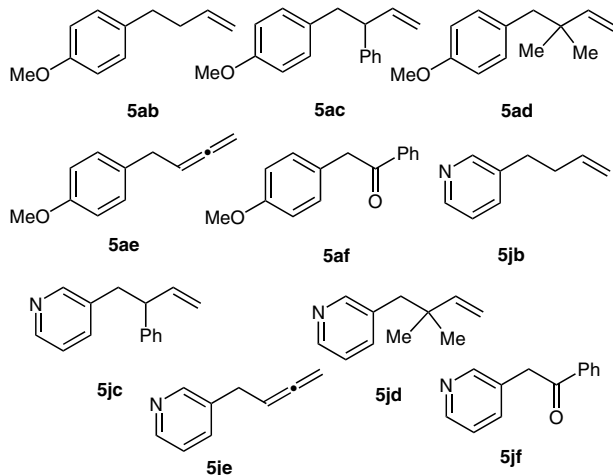
**Table 3** Sequential Reaction of Arenylmethylzinc with Electrophiles Mediated by Copper Salt<sup>a</sup>



**2a, j**    **1** (1.0 equiv)

**5**

Entry	<b>2</b>	Catalyst (mol%)	Electrophile	<b>5</b> (%) <sup>b</sup>
1	<b>2a</b>	Pd (3)	allyl bromide ( <b>4b</b> )	91 ( <b>5ab</b> )
2	<b>2a</b>	Pd (3)	cinnamyl bromide ( <b>4c</b> )	68 ( <b>5ac</b> )
3	<b>2a</b>	Pd (3)	prenyl bromide ( <b>4d</b> )	81 ( <b>5ad</b> )
4	<b>2a</b>	Pd (3)	propargyl bromide ( <b>4e</b> )	91 ( <b>5ae</b> )
5	<b>2a</b>	Pd (3)	benzoyl cyanide ( <b>4f</b> )	91 ( <b>5af</b> )
6	<b>2j</b>	Ni (5)	allyl bromide ( <b>4b</b> )	65 ( <b>5jb</b> )
7	<b>2i</b>	Ni (5)	cinnamyl bromide ( <b>4c</b> )	75 ( <b>5jc</b> )
8	<b>2j</b>	Ni (5)	prenyl bromide ( <b>4d</b> )	59 ( <b>5jd</b> )
9	<b>2j</b>	Ni (5)	propargyl bromide ( <b>4e</b> )	61 ( <b>5je</b> )
10	<b>2i</b>	Ni (5)	benzoyl cyanide ( <b>4f</b> )	55 ( <b>5jf</b> )

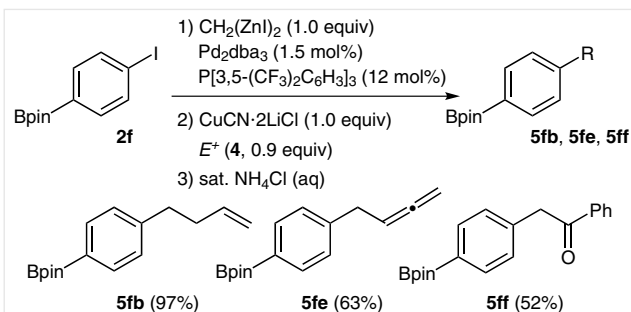


<sup>a</sup> Reaction conditions: **1** (0.36 M in THF, 1.0 mmol), **2** (1.0 mmol), CuCN·2LiCl (1.0 mmol), electrophile (0.9 mmol).

<sup>b</sup> Isolated yield.

As described above, the merit of the present method is the functional group tolerance. As shown in Scheme 4, the Bpin group remained intact throughout the whole transformation. Starting from the pinacol ester of 4-iodophenylboronic acid **2f**, the iodozinciomethylation and the copper-mediated coupling with a range of halides afforded various organoboronic acid esters.<sup>11</sup> These products can be transformed into various aromatic compounds through the Suzuki–Miyaura coupling reaction.

In conclusion, we have shown a novel method that can be used to prepare the arenylmethylzinc reagent bearing functional groups. The introduction of the C–Zn bond was performed by zinciomethylation through transition-metal-



**Scheme 4** Reaction of the pinacol ester of 4-iodophenylboronic acid

catalyzed cross-coupling reaction, so the higher functional tolerance compared with the existing methods was demonstrated.

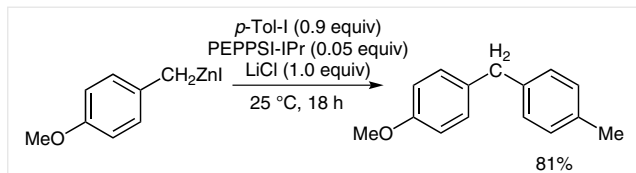
## Acknowledgment

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- To perform the cross-coupling between the formed arenylmethylzinc iodide and iodoarene by Pd catalyst, we found that LiCl (1.0 equiv) plays a crucial role. As shown in Scheme 5, 4-methoxyphenylmethylzinc iodide, which was prepared from 4-methoxy-1-iodobenzene and bis(iodozincio)methane in the presence of Pd catalyst, was treated with *p*-tolyl iodide in the presence of a stoichiometric amount of LiCl and an additional Pd catalyst (PEPPSI-IPr) to afford 1-methoxy-4-(4-methylbenzyl)benzene in 81% yield. Without the addition of LiCl, no cross-coupling product was observed, see: Shimada, Y.; Matsubara, S.;

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Scheme 5

- (11) **Preparation of 1-Phenyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-one (5ff)** To a mixture of  $\text{Pd}_2\text{dba}_3$  (0.015 mmol, 13.7 mg) and  $\text{P}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_3$  (0.12 mmol, 74.4 mg) in THF (2 mL), a solution of **2f** (1.0 mmol, 330 mg) in THF (2.0 mL) was added. The mixture was stirred for 5 min at 25 °C, then a solution of bis(iodozincio)methane (0.36 M in THF, 1.0 mmol, 2.8 mL) was added. The resulting mixture was stirred for 1 h at the same temperature. The mixture was cooled to –30 °C, then a solution of  $\text{CuCN}\cdot 2\text{LiCl}$  (1.0 M in THF, 1.0 mmol, 1.0 mL) was added and the resulting mixture was stirred for 15 min at the same temperature. A solution of benzoyl cyanide (0.9 mmol, 118 mg) in THF (0.5 mL) was added

at the same temperature and the mixture was stirred for 10 h at 25 °C. Aqueous work-up (sat. aq.  $\text{NH}_4\text{Cl}$ ) followed by extraction with  $\text{Et}_2\text{O}$  gave the crude product. Purification by silica gel column chromatography (5 wt% boric acid) gave the title compound (168 mg, 52%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  = 8.00 (d,  $J$  = 8.0 Hz, 2 H), 7.78 (d,  $J$  = 8.0 Hz, 2 H), 7.54 (dd,  $J$  = 8.0, 8.0 Hz, 1 H), 7.44 (dd,  $J$  = 8.0, 8.0 Hz, 2 H), 7.29 (d,  $J$  = 8.0 Hz, 2 H), 4.30 (s, 2 H), 1.33 (s, 12 H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  = 197.4, 137.7, 136.4, 135.1, 133.1, 130.1, 128.8, 128.6, 128.4, 83.7, 45.8, 24.8. HRMS (ESI):  $m/z$  [ $\text{M} + \text{K}$ ] $^+$  calcd for  $\text{C}_{20}\text{H}_{23}\text{O}_3\text{B}$ : 361.1372; found: 361.1359.

**2-[4-(But-3-en-1-yl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5fb)**:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  = 7.78 (d,  $J$  = 8.5 Hz, 2 H), 7.23 (d,  $J$  = 8.5 Hz, 2 H), 5.9–5.8 (m, 1 H), 5.06 (ddt,  $J$  = 17.0, 1.5, 1.0 Hz, 1 H), 5.00 (dd,  $J$  = 10, 1.5, 1.0 Hz, 1 H), 2.75 (t,  $J$  = 7.5 Hz, 2 H), 2.40 (dt,  $J$  = 7.5, 7.5, 1.0 Hz, 2 H), 1.36 (s, 12 H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  = 145.2, 137.9, 134.8, 127.9, 114.9, 83.6, 35.5, 35.3, 24.8. HRMS (ESI):  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{16}\text{H}_{23}\text{O}_2\text{B}$ : 281.1683; found: 281.1683.

**2-[4-(Buta-2,3-dien-1-yl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5fe)**:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  = 7.76 (d,  $J$  = 8.5 Hz, 2 H), 7.26 (d,  $J$  = 8.5 Hz, 2 H), 5.27 (dt,  $J$  = 7.0, 7.0 Hz, 1 H), 4.73 (dt,  $J$  = 7.0, 3.0 Hz, 2 H), 3.38 (dt,  $J$  = 7.0, 3.0 Hz, 2 H), 1.35 (s, 12 H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  = 143.6, 135.2, 134.9, 128.0, 127.8, 89.2, 83.6, 75.2, 35.2, 24.8. HRMS (ESI):  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{16}\text{H}_{21}\text{O}_2\text{B}$ : 279.1527; found: 279.1515.