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# A practical cobalt-catalyzed cross-coupling of benzylic zinc reagents with aryl and heteroaryl bromides or chlorides†

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**A catalytic system consisting of 5 mol% CoCl<sub>2</sub> and 10 mol% isoquinoline allows a convenient cross-coupling of benzylic zinc reagents with various aryl and heteroaryl bromides or chlorides leading to poly-functionalized diaryl- and aryl-heteroaryl-methane derivatives.**

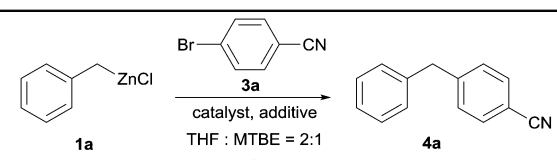
Pd-Catalyzed cross-couplings between organozinc reagents and various organic halides constitute a major C–C bond formation methodology (Negishi cross-coupling).<sup>1</sup> Due to the high price and toxicity of palladium, related transition metal-catalyzed cross-couplings involving zinc organometallics and Ni-, Fe- or Co-catalysts have been examined.<sup>2–4</sup> Furthermore, the use of zinc organometallics is of special synthetic interest due to the high functional group compatibility of zinc reagents.<sup>5</sup> Recently, we have reported several preparation methods of benzylic zinc halides and demonstrated that these reagents undergo smooth Negishi cross-couplings.<sup>6</sup> Also Bedford reported that benzylic halides undergo useful Fe-catalyzed cross-couplings with aryl-zinc reagents.<sup>7</sup> Gosmini has shown in one-pot procedures that arylzinc reagents generated *in situ* via a cobalt-catalyzed zinc insertion undergo cross-couplings with benzyl chlorides.<sup>8</sup> Interestingly, Ingleson has described a transition metal free cross-coupling between relatively non-functionalized diaryl-zincs with benzylic bromides and chlorides performed in the absence of coordinating ethereal solvents.<sup>9</sup>

Herein, we report a practical cobalt-catalyzed cross-coupling promoted by 10 mol% of isoquinoline between various benzylic zinc reagents with aryl and heteroaryl bromides or chlorides resulting in the formation of valuable diaryl- and arylheteroaryl-methane derivatives.<sup>10</sup> Preliminary control experiments performed with benzylzinc chloride (**1a**; prepared *via* the oxidative insertion

of magnesium turnings into benzyl chloride (**2a**) in the presence of LiCl and ZnCl<sub>2</sub>)<sup>11</sup> and 4-bromo-benzonitrile (**3a**) in a 2:1 THF:MTBE mixture<sup>12</sup> (MTBE = methyl *tert*-butyl ether) show that in the absence of transition catalysts no reaction is observed at 50 °C in 2 h (Table 1, entries 1 and 2). Also, Fe-catalysts such as Fe(acac)<sub>3</sub>, Fe(acac)<sub>2</sub> or FeCl<sub>2</sub> were inefficient (Table 1, entries 3–5).<sup>13</sup> However, the use of 5 mol% CoBr<sub>2</sub>, Co(acac)<sub>2</sub> and CoCl<sub>2</sub> show the formation of the desired cross-coupling product (**4a**) in 47–76% GC-yield (Table 1, entries 6–8).<sup>14</sup>

Previously reported additives like 4-fluorostyrene,<sup>15</sup> TMEDA<sup>16</sup> or isoquinoline<sup>17</sup> indicate a very positive effect of 10 mol% isoquinoline<sup>18</sup> leading to an isolated yield of 82% for **4a** (Table 1, entry 11; compared with entries 9 and 10). Decreasing the amount of isoquinoline to 5 mol% reduces somewhat the yield of **4a**

**Table 1** Screening of catalysts for the palladium-free cross-coupling of benzylzinc chloride (**1a**) with 4-bromobenzonitrile (**3a**)



Entry	Catalyst (mol%)	Additive (mol%)	Yield <sup>a,b</sup>
1	None	None	0
2	None	Isoquinoline (10)	0
3	Fe(acac) <sub>3</sub> (5)	None	0
4	Fe(acac) <sub>2</sub> (5)	None	Traces
5	FeCl <sub>2</sub> (5)	None	Traces
6	CoBr <sub>2</sub> (5)	None	47
7	Co(acac) <sub>2</sub> (5)	None	70
8	CoCl <sub>2</sub> (5)	None	76
9	CoCl <sub>2</sub> (5)	4-Fluorostyrene (10)	66
10	CoCl <sub>2</sub> (5)	TMEDA (10)	68
11	CoCl <sub>2</sub> (5)	Isoquinoline (10)	87 (82) <sup>c</sup> (72) <sup>d</sup>
12	CoCl <sub>2</sub> (5)	Isoquinoline (5)	75
13	CoCl <sub>2</sub> ·2LiCl (5)	Isoquinoline (10)	69
14	CoCl <sub>2</sub> ·2LiCl (5)	None	65

<sup>a</sup> 1.1 equiv. of benzylzinc chloride (**1a**) was used. <sup>b</sup> Determined by GC-analysis with tetradecane as an internal standard. <sup>c</sup> Isolated yield of pure product. <sup>d</sup> CoCl<sub>2</sub> with a purity of 99.999% was used.

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(Table 1, entry 12). Also, we found that the use of  $\text{CoCl}_2 \cdot 2\text{LiCl}^{19}$  was not advantageous (Table 1, entries 13 and 14). Additionally, we have examined the influence of the commercial origin of  $\text{CoCl}_2$  as well as its purity. Thus,  $\text{CoCl}_2$  having a purity of 99.999% provides under the same conditions (50 °C, 2 h) the diarylmethane **4a** in 72% yield (compared to 82%; see Table 1, entry 11).<sup>20,21</sup> The addition of MTBE as a cosolvent usually decreases the amount of homo-coupling and therefore enhances the product yield. However, large amounts of MTBE reduce the reaction rate. We found the solvent mixture THF:MTBE 2:1 to be optimal.<sup>22</sup> Concerning the need of isoquinoline as ligand, an extensive screening showed that N-heterocycles behave best, whereas various phosphines did not promote the cross-coupling.<sup>23</sup>

With these optimized conditions in hand, we studied the reaction scope of the cross-coupling between various benzylic zinc chlorides (**1a–i**) with a broad range of aryl and heteroaryl bromides or chlorides. First, the treatment of benzylic zinc reagents (**1a,b**) in the presence of 5 mol%  $\text{CoCl}_2$  and 10 mol% isoquinoline with 4-bromobenzonitrile (**3a**) at 50 °C within 2 to 4 h is leading to the diarylmethane derivatives **4a,b** in 77–82% (Table 2, entries 1 and 2). Furthermore, the cross-coupling of an *ortho*-substituted benzylzinc chloride (**1c**) with **3a** afforded the desired arene (**4c**) in 74% yield (Table 2, entry 3). Similarly, the two functionalized benzylic zinc reagents (**1d,e**) cross-coupled with **3a** giving the products **4d,e** in 70–79% (Table 2, entries 4 and 5). The ester-substituted benzylzinc chloride (**1f**) underwent a smooth cross-coupling with **3a** leading to the functionalized diaryl-methane **4f** in 62% yield (Table 2, entry 6). Additionally, the cross-couplings of the more electron-donating benzylic zinc reagents (**1g,h**) with 4-bromo-benzonitrile (**3a**) furnished the arenes **4g,h** in 65–82% yield (Table 2, entries 7 and 8).

The reaction scope of this cross-coupling proved to be quite broad. Thus, 2-bromo-benzophenone (**3b**) underwent the cobalt-catalyzed cross-coupling with the benzylzinc chloride (**1b**) yielding to the corresponding ketone **5a** in 64% yield (Table 3, entry 1). Similarly, the coupling of ethyl 4-bromo-benzoate (**3c**) with the two benzylic zinc reagents (**1e,g**) led to the functionalized diaryl-methane derivatives (**5b,c**) in 54–70% yield (Table 3, entries 2 and 3). Remarkably, 2-chloropyridines react well with various benzylic zinc reagents (Table 3, entries 4–9). The cross-couplings of the benzylzinc chlorides (**1b,e**) with ethyl 2-chloronicotinate (**3d**) proceeded smoothly under these conditions affording the 2,3-disubstituted pyridines (**5d,e**) in 60–95% yield (Table 3, entries 4 and 5). Also, 3-(ethoxycarbonyl)benzyl-zinc chloride (**1f**) underwent the coupling with the 2,3-di-substituted pyridine (**3d**) giving the functionalized aryl-hetero-arylmethane **5f** in 68% yield (Table 3, entry 6). Furthermore, the cross-couplings of the benzylic zinc reagents (**1d,g,i**) with 2-chloro-nicotinonitrile (**3e**) led to the desired benzylated pyridines (**5g–i**) in 67–77% yield (Table 3, entries 7–9). Finally, the reaction of 3-fluorobenzylzinc chloride (**1d**) with ethyl 5-bromofuran-2-carboxylate (**3f**) afforded within 3 h the 2,5-disubstituted furan (**5j**) in 60% yield (Table 3, entry 10). The use of aryl bromides bearing electron-donating substituents led to low yields.<sup>24</sup>

Moreover, such benzylic zinc reagents undergo high yield cross-couplings with various chloro- or bromo-N-heterocycles.

**Table 2** Isoquinoline-promoted Co-catalyzed cross-coupling of benzylic zinc reagents (**1a–h**) with 4-bromobenzonitrile (**3a**)

Entry	Benzylic zinc reagent <sup>a</sup>	Electrophile	Product, yield <sup>b,c</sup>
1			 <b>4a</b> : 82%, 2 h
2			 <b>4b</b> : 77%, 4 h
3			 <b>4c</b> : 74%, 18 h
4			 <b>4d</b> : 79%, 1 h
5			 <b>4e</b> : 70%, 2 h
6			 <b>4f</b> : 62%, 18 h
7			 <b>4g</b> : 82%, 2 h
8			 <b>4h</b> : 65%, 18 h

<sup>a</sup> 1.3–1.5 equiv. of benzylic zinc reagent were used. <sup>b</sup> Isolated yield of pure product. <sup>c</sup> Less than 15% of homo-coupling of the zinc reagent was observed.

Thus, the reaction of 4-methoxybenzylzinc chloride (**1g**) with 2-bromopyrimidine (**3g**) and the two substituted pyridines, 2-chloro-5-(trifluoromethyl)pyridine (**3h**) and 2-chloro-6-fluoropyridine (**3i**),



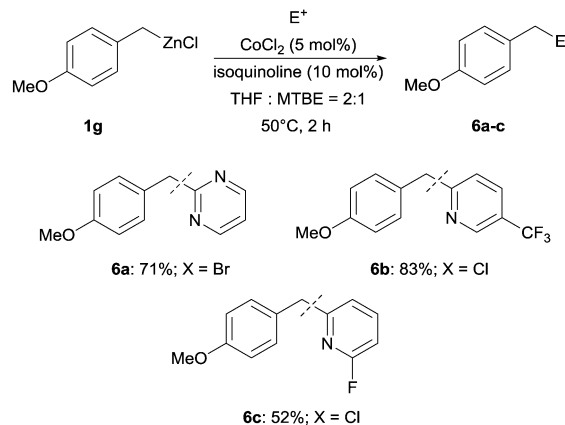
**Table 3** Co-Catalyzed cross-coupling reactions of benzylic zinc reagents with aryl and heteroaryl halides

FG = 4- <sup>t</sup> Bu, 3-F, 3-CF <sub>3</sub> , 3-CO <sub>2</sub> Et, 4-OMe, 4-Br		
Entry	Benzylic zinc reagent <sup>a</sup>	Electrophile
1		
	<b>1b</b>	<b>3b</b>
	 <b>5a</b> : 64%, 4 h	
2		
	<b>1e</b>	<b>3c</b>
	 <b>5b</b> : 54%, 18 h	
3		
	<b>1g</b>	<b>3c</b>
	 <b>5c</b> : 70%, 1 h	
4		
	<b>1b</b>	<b>3d</b>
	 <b>5d</b> : 95%, 4 h	
5		
	<b>1e</b>	<b>3d</b>
	 <b>5e</b> : 60%, 2 h	
6		
	<b>1f</b>	<b>3d</b>
	 <b>5f</b> : 68%, 18 h	
7		
	<b>1d</b>	<b>3e</b>
	 <b>5g</b> : 67%, 3 h	
8		
	<b>1g</b>	<b>3e</b>
	 <b>5h</b> : 77%, 2 h	

**Table 3** (continued)

FG = 4- <sup>t</sup> Bu, 3-F, 3-CF <sub>3</sub> , 3-CO <sub>2</sub> Et, 4-OMe, 4-Br		
Entry	Benzylic zinc reagent <sup>a</sup>	Electrophile
9		
	<b>1i</b>	<b>3e</b>
	 <b>5i</b> : 68%, 18 h	
10		
	<b>1d</b>	<b>3f</b>
	 <b>5j</b> : 60%, 3 h	

<sup>a</sup> 1.3–1.5 equiv. of benzylic zinc reagent were used. <sup>b</sup> Isolated yield of pure product. <sup>c</sup> Less than 15% of homo-coupling of the zinc reagent was observed.

**Scheme 1** Isoquinoline-promoted cross-coupling of the benzylic zinc reagent **1g** with selected N-heterocycles (**3g–i**).

led rapidly (within 2 h) to the functionalized aryl-heteroaryl methanes (**6a–c**) in 52–83% yield (Scheme 1).

In summary, we have reported a new practical Co-catalyzed, isoquinoline-promoted cross-coupling of various benzylic zinc chlorides with a range of aryl and heteroaryl bromides and chlorides, producing polyfunctionalized diaryl- or arylheteroaryl-methane derivatives. This method tolerates a variety of functional groups, such as esters, nitriles or ketones, and proceeds smoothly at 50 °C within 1–18 h. Remarkably, the combination of MTBE (MTBE = methyl *tert*-butyl ether) as co-solvent and isoquinoline as additive led only to small amounts of homo-coupling. In most cases, shorter reaction times and improved yields could be obtained. Further investigations towards the synthesis and applications of benzylic organo-metallics are underway in our laboratories.



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- The obtained yield difference using the high purity CoCl<sub>2</sub> (99.999%) instead of the commercial CoCl<sub>2</sub> ( $\geq 97\%$ , Sigma Aldrich) is attributed to the difference of solubility of these two salts. The CoCl<sub>2</sub> with the highest purity is significantly less soluble than the 97% pure CoCl<sub>2</sub>. In fact, this control reaction was performed in only THF.
- For a corresponding solvent screening, see: ESI,† Table S1.
- For an extensive ligand screening, see: ESI,† Table S2.
- Mechanistic studies are underway to explain these phenomena.

