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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% CoCl₂ 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.

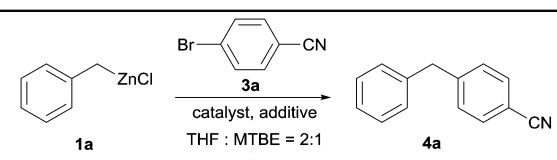
Pd-Catalyzed cross-couplings between organozinc reagents and various organic halides constitute a major C–C bond formation methodology (Negishi cross-coupling).¹ Due to the high price and toxicity of palladium, related transition metal-catalyzed cross-couplings involving zinc organometallics and Ni-, Fe- or Co-catalysts have been examined.^{2–4} Furthermore, the use of zinc organometallics is of special synthetic interest due to the high functional group compatibility of zinc reagents.⁵ Recently, we have reported several preparation methods of benzylic zinc halides and demonstrated that these reagents undergo smooth Negishi cross-couplings.⁶ Also Bedford reported that benzylic halides undergo useful Fe-catalyzed cross-couplings with aryl-zinc reagents.⁷ 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.⁸ 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.⁹

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.¹⁰ 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 ZnCl₂)¹¹ and 4-bromo-benzonitrile (**3a**) in a 2:1 THF:MTBE mixture¹² (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)₃, Fe(acac)₂ or FeCl₂ were inefficient (Table 1, entries 3–5).¹³ However, the use of 5 mol% CoBr₂, Co(acac)₂ and CoCl₂ show the formation of the desired cross-coupling product (**4a**) in 47–76% GC-yield (Table 1, entries 6–8).¹⁴

Previously reported additives like 4-fluorostyrene,¹⁵ TMEDA¹⁶ or isoquinoline¹⁷ indicate a very positive effect of 10 mol% isoquinoline¹⁸ 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 ^{a,b}
1	None	None	0
2	None	Isoquinoline (10)	0
3	Fe(acac) ₃ (5)	None	0
4	Fe(acac) ₂ (5)	None	Traces
5	FeCl ₂ (5)	None	Traces
6	CoBr ₂ (5)	None	47
7	Co(acac) ₂ (5)	None	70
8	CoCl ₂ (5)	None	76
9	CoCl ₂ (5)	4-Fluorostyrene (10)	66
10	CoCl ₂ (5)	TMEDA (10)	68
11	CoCl ₂ (5)	Isoquinoline (10)	87 (82) ^c (72) ^d
12	CoCl ₂ (5)	Isoquinoline (5)	75
13	CoCl ₂ ·2LiCl (5)	Isoquinoline (10)	69
14	CoCl ₂ ·2LiCl (5)	None	65

^a 1.1 equiv. of benzylzinc chloride (**1a**) was used. ^b Determined by GC-analysis with tetradecane as an internal standard. ^c Isolated yield of pure product. ^d CoCl₂ 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 CoCl_2 as well as its purity. Thus, 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).^{20,21} 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.²² 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.²³

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% 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 benzylic zinc 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 benzylic zinc 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 benzylic zinc 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 benzylic zinc 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.²⁴

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 ^a	Electrophile	Product, yield ^{b,c}
1			 4a : 82%, 2 h
2		3a	 4b : 77%, 4 h
3		3a	 4c : 74%, 18 h
4		3a	 4d : 79%, 1 h
5		3a	 4e : 70%, 2 h
6		3a	 4f : 62%, 18 h
7		3a	 4g : 82%, 2 h
8		3a	 4h : 65%, 18 h

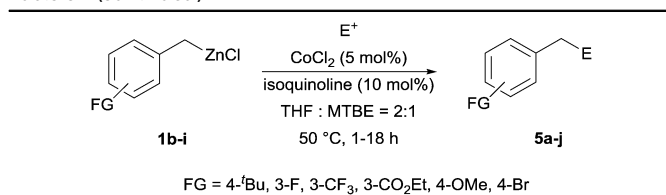
^a 1.3–1.5 equiv. of benzylic zinc reagent were used. ^b Isolated yield of pure product. ^c Less than 15% of homo-coupling of the zinc reagent was observed.

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**),



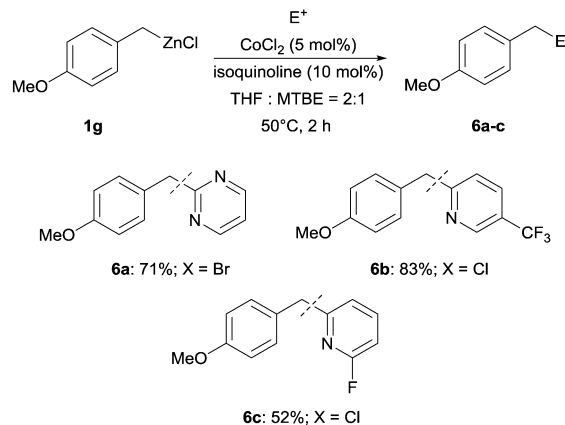
Table 3 Co-Catalyzed cross-coupling reactions of benzylic zinc reagents with aryl and heteroaryl halides

Benzylic zinc Entry reagent ^a	Electrophile	Product, yield ^{b,c}
	E^+ CoCl ₂ (5 mol%) isoquinoline (10 mol%) THF : MTBE = 2:1 50 °C, 1-18 h	
FG = 4- ^t Bu, 3-F, 3-CF ₃ , 3-CO ₂ Et, 4-OMe, 4-Br		
1	 1b	 3b
		 5a : 64%, 4 h
2	 1e	 3c
		 5b : 54%, 18 h
3	 1g	3c
		 5c : 70%, 1 h
4	 1b	 3d
		 5d : 95%, 4 h
5	 1e	3d
		 5e : 60%, 2 h
6	 1f	3d
		 5f : 68%, 18 h
7	 1d	 3e
		 5g : 67%, 3 h
8	 1g	3e
		 5h : 77%, 2 h

Table 3 (continued)

Benzylic zinc Entry reagent ^a	Electrophile	Product, yield ^{b,c}
 1i	3e	 5i : 68%, 18 h
 1d	 3f	 5j : 60%, 3 h

^a 1.3–1.5 equiv. of benzylic zinc reagent were used. ^b Isolated yield of pure product. ^c 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 CoCl₂ (99.999%) instead of the commercial CoCl₂ (≥97%, Sigma Aldrich) is attributed to the difference of solubility of these two salts. The CoCl₂ with the highest purity is significantly less soluble than the 97% pure CoCl₂. 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.

