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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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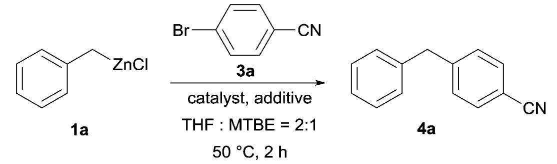
A catalytic system consisting of 5 mol% $CoCl_2$ and 10 mol% isoquinoline allows a convenient cross-coupling of benzylic zinc reagents with various aryl and heteroaryl bromides or chlorides leading to polyfunctionalized diaryl- and aryl-heteroaryl-methane derivatives.

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 arylzinc 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 diarylzincs 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 $ZnCl_2$)[11] and 4-bromo-benzonitrile (**3a**) in a 2 : 1 THF : MTBE mixture[12] (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 $FeCl_2$ were inefficient (Table 1, entries 3–5).[13] However, the use of 5 mol% $CoBr_2$, $Co(acac)_2$ and $CoCl_2$ 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] TMEDA[16] or isoquinoline[17] indicate a very positive effect of 10 mol% isoquinoline[18] 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	$CoCl_2 \cdot 2LiCl$ (5)	Isoquinoline (10)	69
14	$CoCl_2 \cdot 2LiCl$ (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] $CoCl_2$ with a purity of 99.999% was used.

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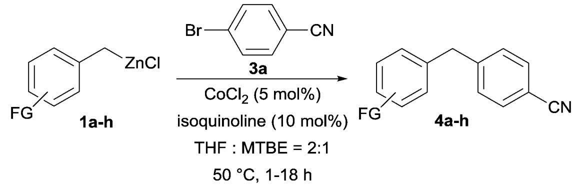
(Table 1, entry 12). Also, we found that the use of $CoCl_2\cdot 2LiCl$[19] was not advantageous (Table 1, entries 13 and 14). Additionally, we have examined the influence of the commercial origin of $CoCl_2$ as well as its purity. Thus, $CoCl_2$ having a purity of 99.999% provides under the same conditions (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 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).

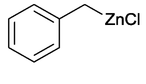
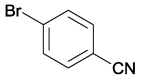
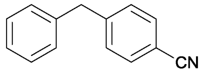
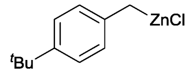
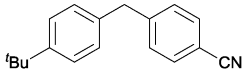
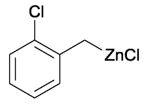
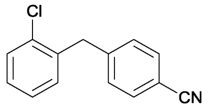
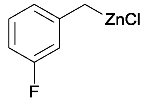
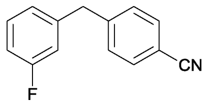
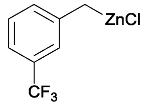
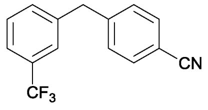
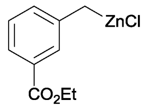
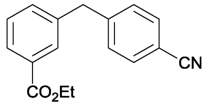
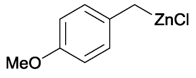
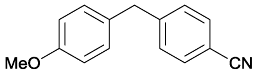
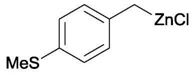
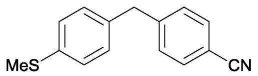
The reaction scope of this cross-coupling proved to be quite broad. Thus, 2-bromo-benzophenone (**3b**) underwent the cobalt-catalyzed cross-coupling with the benzylzinc chloride (**1b**) yielding to the corresponding ketone **5a** in 64% yield (Table 3, entry 1). Similarly, the coupling of ethyl 4-bromo-benzoate (**3c**) with the two benzylic zinc reagents (**1e**,**g**) led to the functionalized diarylmethane 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.[24]

Moreover, such benzylic zinc reagents undergo high yield cross-couplings with various chloro- or bromo-N-heterocycles. 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-fluoro-pyridine (**3i**),

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

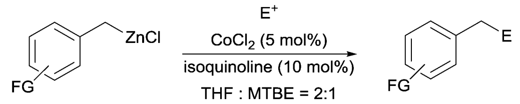


FG = 4-^{t}Bu, 2-Cl, 3-F, 3-CF_3, 3-CO_2Et, 4-OMe, 4-SMe

Entry	Benzylic zinc reagent[a]	Electrophile	Product, yield[b,c]
1	 **1a**	 **3a**	 **4a**: 82%, 2 h
2	 **1b**	3a	 **4b**: 77%, 4 h
3	 **1c**	3a	 **4c**: 74%, 18 h
4	 **1d**	3a	 **4d**: 79%, 1 h
5	 **1e**	3a	 **4e**: 70%, 2 h
6	 **1f**	3a	 **4f**: 62%, 18 h
7	 **1g**	3a	 **4g**: 82%, 2 h
8	 **1h**	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.

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



1b-i **5a-j**

FG = 4-^{t}Bu, 3-F, 3-CF_3, 3-CO_2Et, 4-OMe, 4-Br

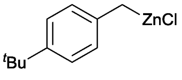
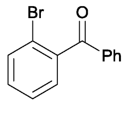
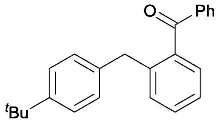
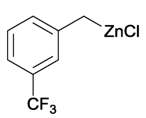
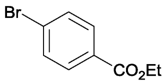
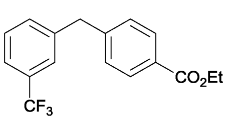
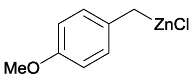
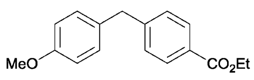
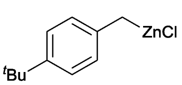
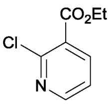
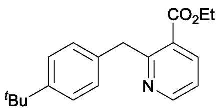
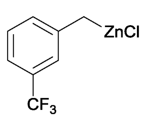
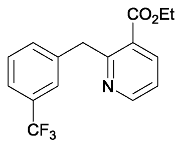
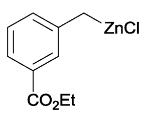
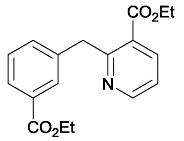
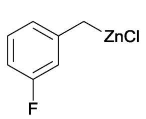
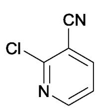
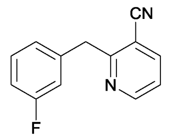
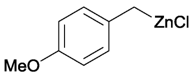
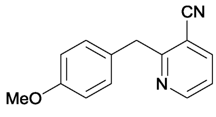
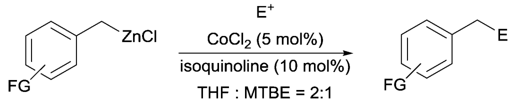
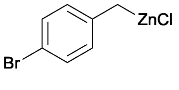
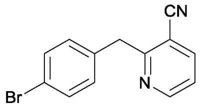
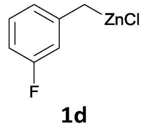
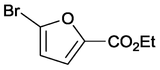
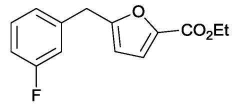
Entry	Benzylic zinc reagent[a]	Electrophile	Product, yield[b,c]
1	 **1b**	 **3b**	 **5a**: 64%, 4 h
2	 **1e**	 **3c**	 **5b**: 54%, 18 h
3	 **1g**	3c	 **5c**: 70%, 1 h
4	 **1b**	 **3d**	 **5d**: 95%, 4 h
5	 **1e**	3d	 **5e**: 60%, 2 h
6	 **1f**	3d	 **5f**: 68%, 18 h
7	 **1d**	 **3e**	 **5g**: 67%, 3 h
8	 **1g**	3e	 **5h**: 77%, 2 h

Table 3 (*continued*)

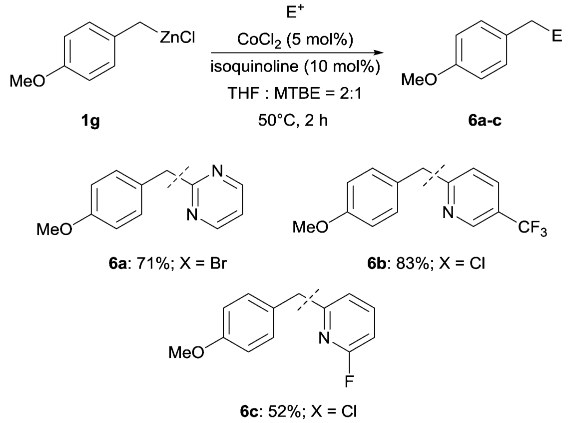


1b-i **5a-j**

FG = 4-^{t}Bu, 3-F, 3-CF_3, 3-CO_2Et, 4-OMe, 4-Br

Entry	Benzylic zinc reagent[a]	Electrophile	Product, yield[b,c]
9	 **1i**	3e	 **5i**: 68%, 18 h
10	 **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-heteroarylmethanes (**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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22 For a corresponding solvent screening, see: ESI,† Table S1.

23 For an extensive ligand screening, see: ESI,† Table S2.

24 Mechanistic studies are underway to explain these phenomena.