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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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Cite this: *Chem. Commun.*, 2016, 52, 3171

Received 14th December 2015, Accepted 20th January 2016

DOI: 10.1039/c5cc10272c

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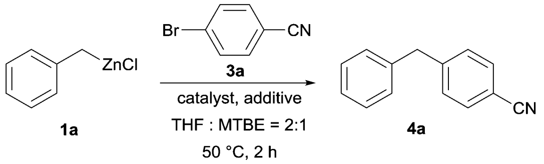
**A catalytic system consisting of 5 mol% $CoCl_2$ and 10 mol% isoquinoline allows a convenient cross-coupling of benzylic zinc reagents with various aryl and heteroaryl bromides or chlorides leading to polyfunctionalized diaryl- and aryl-heteroaryl-methane derivatives.**

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 | $CoCl_2·2LiCl$ (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] $CoCl_2$ with a purity of 99.999% was used.

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[b] *Laboratoire de Chimie Moléculaire, CNRS, Ecole Polytechnique, Université Paris Saclay, 91128 Palaiseau, France. E-mail: corinnne.gosmini@polytechnique.edu; Fax: +33-1-6933-4440; Tel: +33-1-6933-4412*

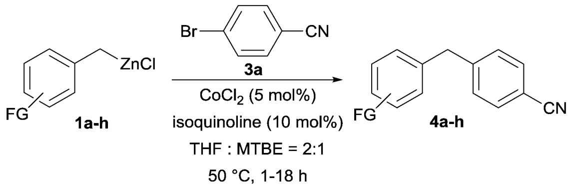
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5cc10272c

(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]

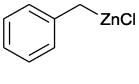
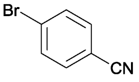
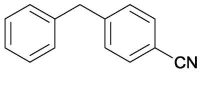
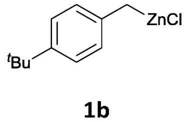
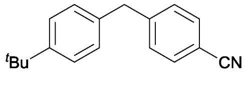
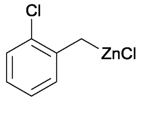
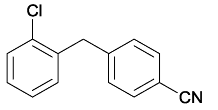
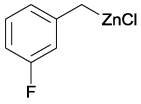
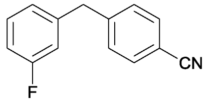
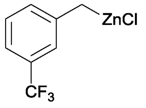
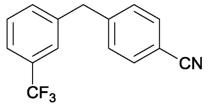
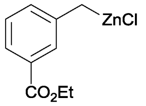
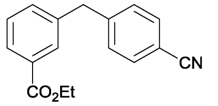
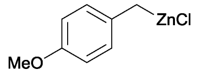
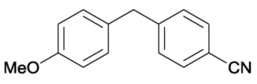
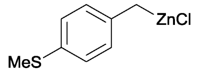
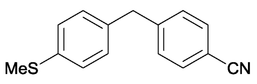
With these optimized conditions in hand, we studied the reaction scope of the cross-coupling between various benzylic zinc chlorides (**1a–i**) with a broad range of aryl and heteroaryl bromides or chlorides. First, the treatment of benzylic zinc reagents (**1a**,**b**) in the presence of 5 mol% $CoCl_2$ 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]

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



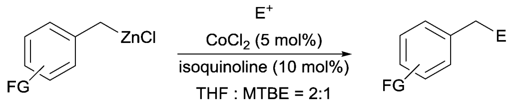
FG = 4-$^t$Bu, 2-Cl, 3-F, 3-$CF_3$, 3-$CO_2$Et, 4-OMe, 4-SMe

| 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.

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 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

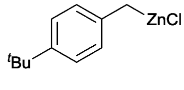
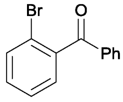
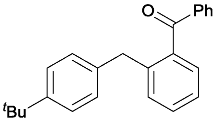
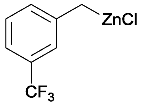
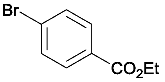
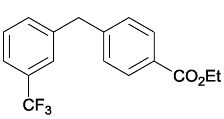
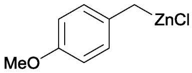
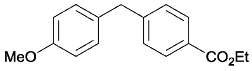
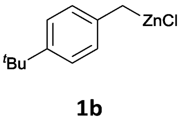
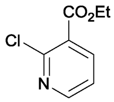
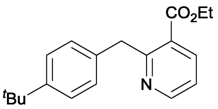
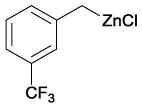
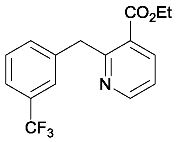
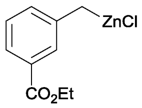
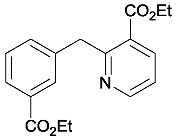
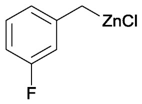
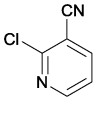
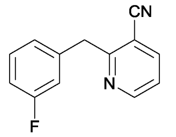
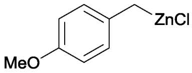
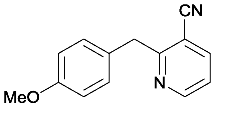
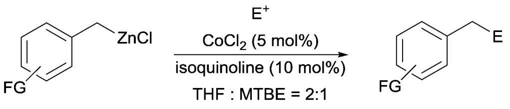
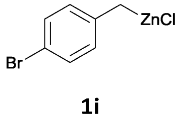
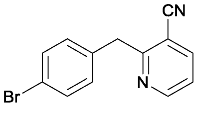
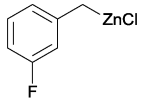
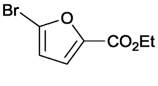
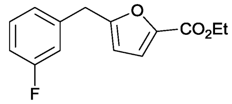
| Entry | Benzylic zinc reagent[a] | Electrophile | Product, yield[b,c] |
|---|---|---|---|
| 1 |  **1b** |  **3b** |  **5a**: 64%, 4 h |
| 2 |  **1e** |  **3c** |  **5b**: 54%, 18 h |
| 3 |  **1g** | 3c |  **5c**: 70%, 1 h |
| 4 |  **1b** |  **3d** |  **5d**: 95%, 4 h |
| 5 |  **1e** | 3d |  **5e**: 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*)

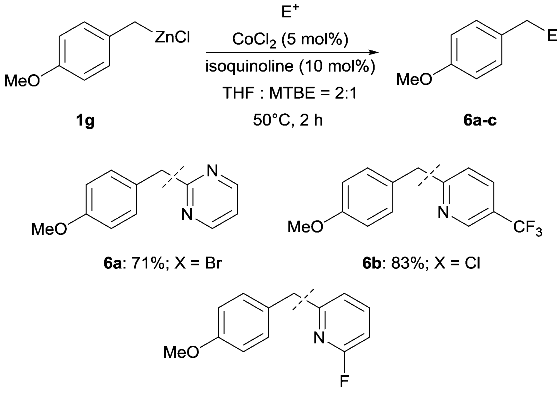


**1b-i** **5a-j**

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.

We would like to thank the DFG for financial support. We also thank BASF SE (Ludwigshafen, Germany) and Rockwood Lithium GmbH for the generous gift of chemicals.

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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.