Synthesis of functionalised diarylmethanes *via* a cobalt-catalysed cross-coupling of arylzinc species with benzyl chlorides†

Muriel Amatore[a] and Corinne Gosmini*[b]

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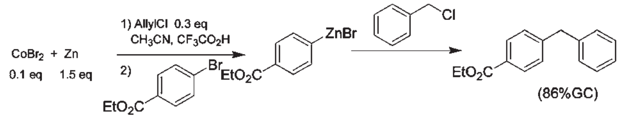
A new cobalt-catalysed reductive coupling of aryl halides with benzyl chlorides is reported; a variety of diarylmethanes can be prepared in good to excellent yields under mild reaction conditions using $CoBr_2$ as catalyst and Zn dust; this new cobalt-catalysed coupling represents a practical and interesting alternative to previously known methods for the synthesis diarylmethanes.

Diarylmethanes have been shown to possess interesting biological and medicinal properties and are ubiquitous structural constituents in pharmacologically important molecules[1] such as papaverine and beclobrate. These compounds also frequently appear as subunits in supramolecular structures such as macrocycles, catenanes, and rotaxanes.[2] A common synthetic method for obtaining diarylmethanes includes the Friedel–Crafts alkylation of aromatic compounds with benzylic halides.[3] Additionally, transition metal-catalysed cross-coupling reactions provide powerful tools for the formation of carbon–carbon bonds.[4] The most general procedures for diarylmethane synthesis are the transition metal-catalysed cross-coupling between aryl halides and benzylic metals[5] (usually prepared from benzylic halides). However, cross-coupling reactions of an aryl-metal with a benzyl halide or derivative such as benzyl phosphates or carbonates are reported less frequently.[6] The main difficulty with these methods remains the preliminary preparation of the organometallic reagent, especially when the aromatic ring bears reactive functional substituents. These preformed organometallic reagents often consist of a Grignard, borane, manganese, stannane or zinc derivative and the cross-coupling generally requires an expensive rhodium or palladium catalyst, or a toxic nickel catalyst and typically sophisticated ligands. Some interesting copper-catalysed reactions have also been shown to form the methylene-linked biphenyl species.[7] Alternatively, the use of cobalt as a highly reactive catalyst for carbon–carbon bond-forming reactions has been recently demonstrated by Cahiez,[8] Knochel,[9] Oshima,[10] Cheng[11] and our group.[12]

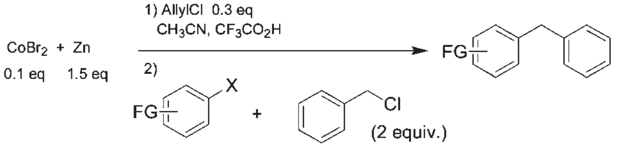
Herein, we wish to report a new Co(II)-mediated cross-coupling reaction devoted to the direct synthesis of diarylmethanes, using variously functionalized aromatic halides and benzylic chlorides in a very efficient manner. To the best of our knowledge, this is the first cobalt-catalysed reductive coupling of aryl halides and benzyl halides to form diarylmethane. Our initial efforts were directed towards finding an appropriate reaction using benzyl chloride as a model substrate for coupling with various aryl bromides. Stemming from our previous results concerning the reactivity of arylzinc species obtained under cobalt catalysis,[13] we believed that methylene-linked biaryls could be obtained *via* the cross-coupling of arylzinc derivatives with benzyl chlorides under suitable conditions. We first investigated a two-step coupling reaction, involving formation of 4-(ethoxycarbonyl)phenylzinc bromide from ethyl 4-bromobenzoate and subsequent coupling with benzyl chloride without further addition of cobalt catalyst, leading to the corresponding diarylmethane at room temperature. The coupling product was detected in 86% yield (GC), while the homocoupling product formed only in a small amount (Scheme 1).



Scheme 1 Two-step procedure for the reductive cross-coupling of $p\text{-}EtO_2CC_6H_4Br$ with $PhCH_2Cl$.

We next set our sights on developing an operationally simplified Barbier-type procedure for the synthesis of diarylmethanes from aryl bromides or iodides without the need for preforming the arylzinc reagent and avoiding the formation of the corresponding homocoupling product (Ar–Ar). Since both aryl and benzyl halides competitively form organozinc species resulting in undesired homocoupled products, selective diarylmethane formation was pursued by using an excess (2 equiv.) of the more reactive benzyl chloride coupling partner. Results are reported in Scheme 2 and Table 1.

As shown, the reaction was broadly successful, affording good yields with a range of electron-withdrawing or -donating groups on the aryl halide. Interestingly, the substituent position had no influence on yields as revealed in the case



Scheme 2 Reductive cross-coupling of ArX (X = Br or I) with $PhCH_2Cl$.

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[a] *Equipe Electrochimie et Synthèse Organique, Institut de Chimie et des Materiaux Paris Est, ICMPE, C.N.R.S-Université Paris 12 val de Marne, UMR 7182, 2, rue Henri Dunant, 94320 Thiais, France*
[b] *Laboratoire « Hétéroéléments et Coordination », Ecole Polytechnique, CNRS, 91128 Palaiseau Cedex, France. E-mail: corinne.gosmini@polytechnique.edu; Fax: +33 1-6933-4440; Tel: +33 1-6933-4412*

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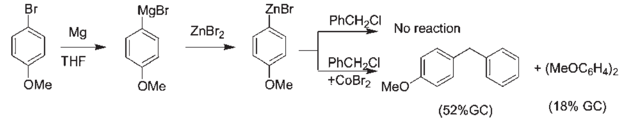
Table 1 Barbier-type reductive cross-coupling of ArBr with $PhCH_2Cl$

Entry	FG	Isolated yield (%)	GC yield (%)
1	p-CO_2Et	77	88
2	m-CO_2Et	75	85
3	o-CO_2Et	75	80
4	p-CN	71	92
5	m-CN	74	97
6	o-CN[a]	76	81
7	p-COMe	75	87
8	p-CF_3	85	91
9	p-Cl	77	86
10	p-Cl[b]	77	86
11	p-OMe	71	76
12	p-OMe[b]	—	70
13	o-OMe	68	76
14	p-NMe_2	70	90

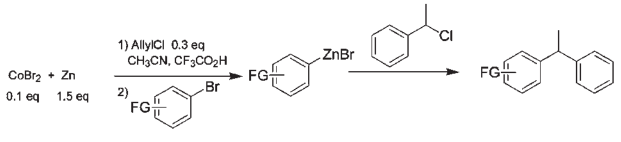
[a] Reaction at 50 °C. [b] X = I.

of ethyl bromobenzoate (Table 1, entries 1, 2 and 3), bromobenzonitrile (Table 1, entries 4, 5 and 6) and bromoanisole (Table 1, entries 11 and 13). Aryl iodides lead to similar yields (Table 1, entries 10 and 12). All the reactions were conducted at room temperature except for *o*-bromobenzonitrile (Table 1, entry 6). In this last case, the aryl bromide was totally consumed only after 17 hours at room temperature. Heating the medium to 50 °C led to a decrease in reaction time with a similar yield (6 h instead of 17 h). This presumably reflects steric and chelation effects.

We have shown that the behavior of our arylzinc compounds synthesised *via* cobalt catalysis in acetonitrile was similar to traditional arylzinc species obtained *via* a transmetallation reaction with $ZnBr_2$ from the corresponding organomagnesium compound in tetrahydrofuran. In this case no reaction was observed after adding benzyl chloride in the medium. However, this last arylzinc species could react with benzyl chloride due to the presence of $CoBr_2$ to afford the cross-coupling product and Ar–Ar in a large amount (Scheme 3). These results demonstrate that in our case, cobalt salts used for the preparation of arylzinc derivatives are also involved in this Negishi-type cross-coupling.



Scheme 3 Cross-coupling of ArZnBr derived from ArMgBr with $PhCH_2Cl$.



Scheme 4 Reductive cross-coupling of ArBr with PhCH(Me)Cl.

Table 2 Reductive cross-coupling of ArZnBr with PhCH(Me)Cl

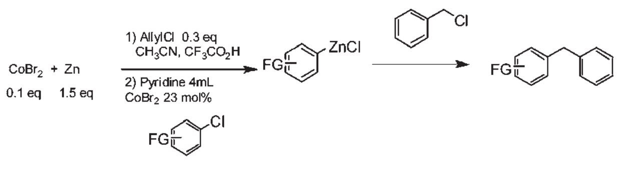
Entry	FG	Isolated yield *vs.* ArBr (%)	GC yield (%)
15	p-CO_2Et	75	77
16	o-CO_2Et	60	61
17	p-CN	67	74
18	o-CN	—	0
19	p-CF_3	70	79
20	p-OMe	65	68

The reaction scope was then investigated with a secondary benzylic chloride. Results are reported in Scheme 4 and Table 2. Interestingly, the α-substitution considerably modified the reactivity of the benzyl chloride, leading to a rapid oxidative addition of cobalt in the corresponding C–Cl bond and eventually to low selectivity. Under a Barbier-type procedure, the cross-coupling of *p*-ethylbromobenzoate afforded the desired diarylmethane in a modest 61% yield (GC). Alternatively, the cross-coupling could be conducted in a two-step procedure. As highlighted in Table 2, the corresponding diarylmethanes were generally obtained with good yields regardless of the electronic nature of the substituents. However, sterics had small impact on the reaction, especially in the case of *o*-bromobenzonitrile (Table 2, entries 15, 16 and 17, 18).

Recently, we have established that cobalt catalysis allows the simple and high-yielding preparation of a broad range of functionalised arylzinc species from readily available corresponding chlorides.[14] To the best of our knowledge, there is no previous example of any versatile chemical cobalt-catalysed reductive coupling from arylzinc chlorides. Due to the low reactivity of aryl chlorides as compared with aryl bromides, homocoupling of the benzyl chloride was a potential issue. However, it could be circumvented *via* a two-step procedure without additional cobalt catalyst. In this case, the presence of pyridine is required to avoid the fast disproportionation of Co(I) and allow its oxidative addition into the C–Cl bond as previously described.[14a]

On the basis of this observation, the scope of aryl chlorides bearing an electron-withdrawing group was investigated. Results are reported in Scheme 5 and Table 3. Satisfactory yields were observed and again the substituent position had only a slight influence on yields.

In conclusion, we have developed a new, alternative method for preparing diarylmethanes from the corresponding functionalised aryl iodide, bromide or chloride *via* an intermediate



Scheme 5 Reductive cross-coupling of ArZnCl with $PhCH_2Cl$.

Table 3 Reductive cross-coupling of ArCl with $PhCH_2Cl$

Entry	FG	Isolated yield *vs.* ArCl (%)	GC yield *vs.* ArCl (%)
21	p-CN	57	87
22	o-CN	55	85
23	p-CO_2Me	68	77
24	p-COMe	83	93

arylzinc species and benzyl chloride using an eco-friendly and inexpensive cobalt-catalyst. To the best of our knowledge, this represents the first cobalt-catalysed reductive cross-coupling involving a functionalised arylzinc chloride. Depending on the nature of substrates involved, this versatile process even allows the synthesis of a wide variety of diarylmethanes in a Barbier-fashion for more convenience. Finally, this practical, efficient and functional group tolerant procedure compares favorably with other palladium or rhodium catalysed methods.

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