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Cobalt-catalyzed Formation of functionalized diarylmethanes from benzylmesylates and aryl halides

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Abstract. A simple cobalt-catalyzed reductive coupling protocol allowing the synthesis of functionalized diarylmethanes from benzyl mesylate is described. The possibility to directly use the benzyl alcohol thanks to a 2-steps reaction is also presented. This method tolerates a variety of functional groups. The involvement of a benzyl radical is likely.

Keywords: Reductive coupling; cobalt; diarylmethane; benzyl alcohol; aryl halide

The success of cross coupling reactions generally relies on nickel and palladium catalysts but cobalt has emerged as a powerful alternative.^[1] The reactions generally employ organic halides as coupling partners.^[2] However, these reagents generate halogenated waste and their access in some advanced synthetic intermediates is sometimes difficult. These different drawbacks could be overcome using alternative partners such as C-O electrophiles.^[3] The availability, low toxicity and natural abundance of alcohols allow them to be powerful alternatives to organic halides^[3b, 4] Moreover, the low price of the alcohols compared to the more reactive corresponding halides is a strong driving force towards the discovery of new processes. For several years, our group has been interested in the synthesis of diarylmethane motifs due to their presence in many pharmacologically active compounds, agrochemicals and supramolecular sub-units such as catenanes and rotaxanes.^[5] Most approaches imply a pre-formed organometallic reagent either a benzylmetal or an aryl metal species. Among the different methods reported in the literature to synthesize these products starting from various functionalized benzyl chlorides,^[6] our group has already reported some Co-catalyzed cross-coupling synthesis either from arylzinc species or directly from aryl halides.^[7] A practical cobalt catalyzed cross-coupling of benzylzinc reagent with (hetero)aryl halides was also described.^[8] However,

other cross-coupling reactions using alternative benzyl reagents have been reported.^[9] Thus, Weix described the synthesis of various diarylmethanes thanks to a dual Ni/Co catalysis in which the cobalt phthalocyanine forms via a S_N2 mechanism the radical specie from benzyl mesylates.^[10] This elegant method however requires two catalysts. Ackermann^[11] and Yoshikai^[12] also reported cobalt-catalyzed ortho C-H benzylations of heteroarenes or aryl amines respectively. Few years ago, we already demonstrated that aryl sulfonates, especially aromatic triflates, are suitable reagents for cobalt catalysis to form either biaryl compounds or the corresponding organozinc species after transmetalation with zinc bromide.^[13] Nevertheless no reaction occurred with aryl mesylates in the described conditions because of their greater stability. Benzyl mesylates are more reactive than the corresponding aryl and would be easy-to access coupling partners.

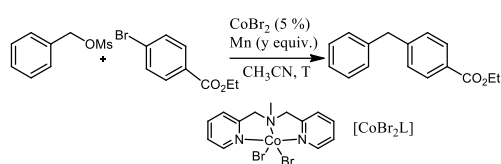
In this present contribution, we report a very simple Co-catalyzed cross-coupling protocol to form various diarylmethanes using benzyl mesylates instead of benzyl chlorides and aryl bromides. To our delight, we demonstrate that the more easily accessible and less reactive benzyl mesylates can advantageously replace benzyl halides. Furthermore, it is also possible to conduct the cross-coupling reaction in a very simple manner from the benzyl alcohol without isolating the corresponding mesylate.

First, we initiated our studies by investigating the reductive cross-coupling reaction of the benzyl mesylate with ethyl 4-bromobenzoate (Table 1). In the conditions established for the coupling of benzyl chlorides,^[7b] the reaction is slow but efficient (Table 1, entry 1). Raising the temperature to 45°C shorten the reaction but also decrease the yield (Table 1, entry 2). Better yields were obtained by diluting the reaction mixture (Table 1, entry 3-4). Increasing the temperature to 50°C, slightly decreases both the reaction time and the yield (Table 1, entry 5). Adding 4 equivalents of Mn as reductant instead of 2.2 does not significantly modify the yield nor the reaction time

(Table 1, entry 6). No improvement was observed by employing cobalt complex with nitrogen ligands (Table 1, entry 6-7). It should be noted that in these reactions manganese is activated by traces of trifluoroacetic acid. Without this activation, same yields of coupling products can be obtained at 45 °C but longer time is required (Table 1 entry 9).

The optimized reaction conditions (Table 1, entry 4) allow the arylation of benzyl mesylates as efficiently as that of benzyl chlorides however higher reaction temperature and longer time are necessary. Other electrophiles such as carbamates, carbonates, acetates were non-reactive under these conditions.

Table 1. Optimization study.



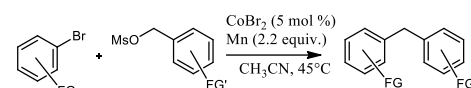
Entry	T °C	[ArBr]	Reaction time	GC yield%
1	r.t.	1.25 M	70h	71(85 ^d)
2	45	1.25 M	6h	51
3	45	0.83 M	17h	60
4	45	0.625 M	21h	82
5	50	0.625 M	15h	66
6 ^a	45	0.625 M	19h	75
7 ^b	45	0.625 M	15h	66
8 ^c	45	0.625 M	8h	33
9	45	0.625 M	36h	79

^a conducted with 4 equiv. of Mn. ^b using [CoBr₂L]. ^c using [CoBr₂(bpy)]. ^d From benzyl chloride.

Encouraged by these results, we examined the scope of this reaction employing substituted benzylmesylates and arylhalides (Table 2). Both electron-donating and electron-withdrawing functional groups, including potentially sensitive ones such as ester, nitrile, were tolerated. Good yields were generally observed. The position of the substituent on the coupling partner generally does not influence much the efficiency of the reaction (Table 2, entries 1/2, 4/6, 8/13, and 9/12). With a less electron-withdrawing on aryl bromide such as *p*-CF₃, the coupling with benzyl mesylate requires heating at 65° C (Table 2, entry 5). With electron-donating groups, the reactivity decreases. Then, a valuable alternative is therefore to use the corresponding aryl iodide (Table 2, entries 7, 11 and 19). Concerning the benzyl, the presence of electron donor favors the dimerization of the benzyl radical to form the dibenzyl derivative, as already observed with benzyl chlorides. In this case, dropwise addition of the benzyl mesylate or use of the more reactive aryl iodide in order to limit this side reaction (Table 2, entry 17-18) did not give a better result. However, with chlorine on the benzyl moiety (Table 2, entries 8-16), good yields are obtained except in entry 15.

Coupling of hetero-aromatic halides was also attempted (Scheme 1). Reactions with 2-bromopyridines were efficient. However reactions with 2-bromothiophene failed.

Table 2. Substrate scope

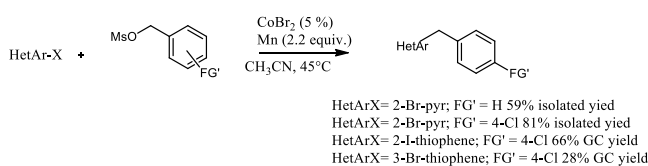


Entry	FG	FG'	Reaction Time (h)	Isolated Yield (%)
1	4-CO ₂ Et	H	21	78
2	3-CO ₂ Et	H	24	71
3	4-COMe	H	20	60
4	4-CN	H	16	76
5	4-CF ₃ ^a	H	16	53
6	2-CN	H	12	82
7	4-OMe ^b	H	16	72
8	4-CO ₂ Et	4-Cl	19	65
9	2-CN	4-Cl	20	88
10	H	4-Cl	24	85 ^{c,d}
11	4-OMe ^b	4-Cl	19	77
12	2-CN	2-Cl	16	82
13	4-CO ₂ Et	2-Cl	17	71
14	3-F	2-Cl	19	70
15	4-OMe ^b	2-Cl	16	27 ^c
16	4-SO ₂ Me	2-Cl	20	77 ^{c,e}
17	2-Cl	4-Me	16	47 ^c /48 ^{c,f}
18	4-CO ₂ Et	4-Me	17	51 ^c /55 ^{c,b}
19	4-OMe ^b	4-CO ₂ Me	15	84
20	4-CO ₂ Me	4-CN	16	52

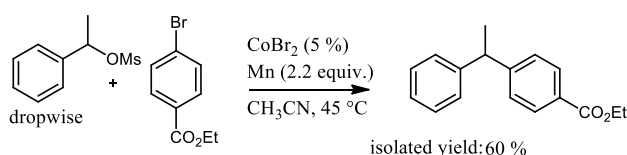
^a Reaction conducted at 65° C ^b Reaction conducted with ArI. ^c GC yield. ^d Inseparable from benzyl dimerization product. ^e Inseparable from ArH. ^f Dropwise addition of benzyl derivative

Using 2-iodo-thiophene, a satisfactory coupling with *p*-Cl benzyl mesylate took place, but not with *o*-Cl benzyl derivative. In the same manner coupling with 3-Br furan failed. Compared to our previous study using benzyl chlorides the coupling with hetero-aryl is as expected more difficult and less general. Nevertheless, we found no precedent report of coupling between benzylmesylate and bromo-pyridine using a base-metal catalyst. This works quite nicely with this simple methodology. We also try to couple a benzyl mesylate featuring an heteroaromatic ring but those from 2- and 3-thiophenemethanol as well as that from 3-pyridinylmethanol decomposes rapidly in the reaction mixture. The reaction of mesylated 2-pyridinyl methanol mostly gave dibenzyl homocoupling product when reacting with 4-bromobenzonitrile. With a dropwise addition of ethyl 4-iodobenzoate, the coupling product forms only in 15 % GC yield. Thus reactions with mesylated heteroaromatic methanol were disappointing.

Scheme 1. Coupling with hetero-aromatic halides.



However, a better result was obtained when coupling an α -substituted benzyl mesylate (Scheme 2). Due to its enhanced reactivity towards cobalt, the mesylate formed from 1-phenylethanol was added dropwise to a reaction mixture containing the catalytic system and the ethyl 4-bromobenzoate to give the coupling product in 60 % yield. This reaction is as effective as that described with a secondary benzyl chloride.^[7b]



Scheme 2. Cross-coupling with α -substituted benzyl.

In order to widen the applicability of this synthetic method we wish to avoid the isolation of the mesylate and develop a procedure from the benzyl alcohol.

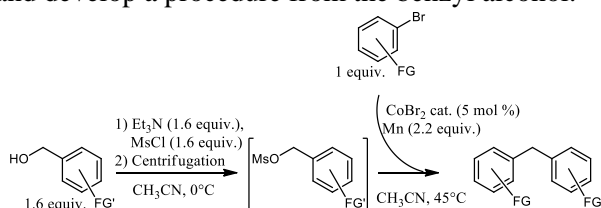


Table 3. Coupling reaction from benzyl alcohols.

Entry	ArBr	FG'	GC Yield (%)
1	4-CO ₂ Et-C ₆ H ₄ Br	H	66 (78) ^a
2	2-CN-C ₆ H ₄ Br	H	79 (82) ^a
3	4-CO ₂ Et-C ₆ H ₄ Br	4-Cl	73(71) ^a
4	2-CN-C ₆ H ₄ Br	4-Cl	92 (94) ^a
5	4-CO ₂ Et-C ₆ H ₄ Br	2-Cl	61 (76) ^a
6	4-CO ₂ Et-C ₆ H ₄ Br	4-F	61/57 ^b
7	4-CO ₂ Et-C ₆ H ₄ Br	3-F	58/53 ^b
8	C ₅ H ₅ Br	4-OCF ₃	73 ^c
9	4-CO ₂ Et-C ₆ H ₄ Br	4-OCF ₃	76/72 ^b
10	2-CN-C ₆ H ₄ Br	4-OCF ₃	84/77 ^b
11	2-Br- C ₅ H ₅ N	4-Cl	81 (88) ^a

^a GC yield starting from isolate benzyl mesylate. ^b Isolated yield. ^c Not separated from the homocoupling product of the benzyl derivative.

The key to success was to employ a stoichiometric amount of triethylamine and mesylate chloride in the first step, a slight excess indeed yielded low yields of coupling products. As often observed for reactions with CoBr₂ salt, acetonitrile was the best solvent. With

these conditions it was possible to perform the coupling from the benzyl alcohol. The mesylate is formed in a first step, then the ammonium salt is removed by centrifugation and the obtained solution added to a second reaction flask containing the aryl bromide, the cobalt catalyst and the reductant (Mn). With this 2-step procedure satisfactory to good yields were obtained (Table 3). Indeed the coupling of benzyl alcohol with 4-bromo-ethylbenzoate proceeds with a GC yield of 66% to compare with 78% obtained when using an isolated benzyl mesylate. The decrease in efficiency is thus pretty low (Table 3, entries 1-5) and often the observed GC yields are comparable. This has allowed realizing other reductive couplings (table 3, entries 6-10) employing variously substituted benzyl alcohols and aryl halides bearing an electron-withdrawing group. Again the position of the substituent does not have any appreciable influence on the coupling efficiency. Coupling with 2-bromopyridine worked nicely, whereas it was not satisfactory for aryl halides bearing an electron donating substituent.

As previously mentioned, we postulate a reaction mechanism similar to that from benzyl halides. The active catalyst should be cobalt(I) complex formed by reduction of the Co^{II} precatalyst with Mn. The oxidative addition of the C-X bond leads to a Co^{III} complex which is reduced to Co^{II} by manganese allowing its reaction with the benzyl radical to give a cobalt(III) complex from which the diarylamethane is released by reductive elimination allowing the regeneration of the cobalt(I) catalyst. To prove the involvement of a radical specie, control experiments were done in presence of TEMPO (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) or glavinoxyl as radical trap (see SI for details). Their inhibitory effect on the reaction was observed. Nevertheless, at this stage the generation of the benzyl radical was not studied, the intermediacy of a benzyl halide formed thanks to the metallic halide salts (Co and Mn) present in the reaction mixture is hypothesized.

To conclude we describe a very simple synthetic protocole using cobalt bromide (5 mol %) and stoichiometric amounts of manganese (2.2 equiv.) to achieve the reductive coupling of benzylmesylates and arylhalides at 45°C. Yields are moderate to excellent. The reaction tolerates a variety of functional groups and is not much sensitive to the position of the substituent. Interestingly this procedure can also be conducted in a 2-step manner directly from the benzylalcohol without the isolation of the benzylmesylate.

Experimental Section

To a solution of aryl bromide (5.0 mmol) and benzyl mesylates (7.5 mmol) in CH₃CN (8.0 mL) manganese powder (2.2 equiv., 11.0 mmol, 605 mg) was added. Trifluoroacetic acid (0.1 mL) was added to it, in order to activate manganese followed by the addition of dodecane or n-decane (0.1 mL) as internal standard. The reaction mixture was stirred for approximately 10 min. Then, CoBr₂ (5 mol%, 0.25 mmol, 55 mg) was added and the resulting reaction mixture was stirred at 45°C until the disappearance of either of the starting materials. Upon completion, the

mixture was then quenched with a solution of 2M HCl (25 mL) or with saturated NH₄Cl solution (in case basic nitrogen containing compounds) and was stirred vigorously until layers turned clear. The solution was then extracted with CH₂Cl₂ or EtOAc (3 x 25 ml), dried over MgSO₄, filtered and concentrated in vacuo. Purification of the resulting oil or solid by flash chromatography over silica with petroleum ether/ethyl acetate mixtures afforded the pure compounds.

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