Cobalt-catalyzed C–SMe bond activation of heteroaromatic thioethers†

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Cobalt-catalyzed activation of methylthio-substituted N-heterocycles facilitates either cross-coupling reactions with aryl- or benzylzinc compounds or synthesis of the corresponding zinc compounds.

Transition metal-catalyzed cross-coupling reactions allowing the formation of C–C bonds,[1] particularly in the formation of biaryl structural motifs, underlie the synthesis of key intermediates from natural products synthesis[2] to supramolecular chemistry.[3] Classically, most approaches require the use of an organometallic reagent (such as organoboron, organomagnesium, organostannane or organozinc reagents) in conjunction with an organic halide or pseudo halide. The major difficulties of these reactions lie in the preparation of the functionalized organometallic compounds and in the limited availability and stability of some halide derivatives, especially heteroaryl halides. Therefore, it can be worthwhile to use new types of heteroaromatic partners to extend the scope of these versatile reactions. Thioorganic derivatives, particularly thioether derivatives, are interesting compounds due to their stability, their availability, and their attractive prices as compared with the corresponding halide derivatives. These cross-coupling methodologies are heavily dominated by the use of palladium and nickel complexes, presenting an excellent compatibility with many functional groups. Thus, since the seventies, some research groups have worked toward the development of new cross-coupling reactions involving thioether derivatives as heteroaromatic partners. Grignard reagents have been successfully coupled for the first time with thioether derivatives using nickel[4] and palladium[5] complexes as catalysts. Likewise, organoboron reagents[6] or organostannane reagents[7] could be involved in palladium-catalyzed cross-coupling with thioether derivatives insofar as a stoichiometric amount of copper(I) carboxylates was present. With sufficiently thiophilic organozinc compounds, the cross-coupling reaction with thioether derivatives occurs without the requirement of a stoichiometric Cu^I carboxylate activator using nickel or palladium catalysts.[8] However, these catalysts have some disadvantages resulting from the cost,[9] the toxicity[10] and the need for ancillary ligands to stabilize and activate these catalytic species. Fortunately, over the past few years, new sustainable catalytic systems based on iron[11] or cobalt[12] have been developed without these drawbacks and have shown their efficiency in such cross-coupling reactions. However, to our knowledge, cobalt has never been used as catalyst to activate the C–SMe bond. Herein, we report, in the first part, our results concerning the $CoBr_2$-catalyzed cross-coupling reactions involving various arylzinc species and thioether derivatives and, in the second part, the formation of heteroarylzinc species from some corresponding 2-thiomethyl heterocycles.

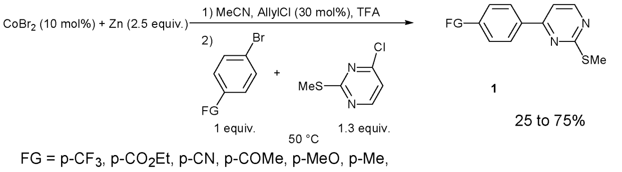
Within the framework of our studies concerning the $CoBr_2$-catalyzed cross-coupling reaction of arylzinc reagents with chlorodiazines,[13] we extended the cross-coupling in Barbier conditions, using 10 mol% $CoBr_2$ as catalyst, of various functionalized aryl bromides and 2-methylthio-4-chloropyrimidine leading to corresponding 2-methylthio-4-arylpyrimidine **1** (Scheme 1).

However, in all cases, we also noticed traces of another by-product that turned out to be a 2,4-diarylpyrimidine **2** coming from the disubstitution of both the Cl and the SMe groups positions.

From this encouraging observation, we concluded that it is possible to activate the C–SMe bond on the 2-methylthio-4-chloropyrimidine using $CoBr_2$ as catalyst to perform a cross-coupling reaction with organozinc reagents.

Then, we obtained the disubstituted pyrimidine in good yield by increasing the amount of $CoBr_2$. Indeed, the cross-coupling reaction performed with 10 mol% of $CoBr_2$ led to a 2-methylthio-4-arylpyrimidine. However, we observed the formation of the 2,4-diarylpyrimidine **2** as the major product of the reaction when we carried out the same reaction using 30 mol% of $CoBr_2$, even with one equivalent of the aryl bromide (36% yield). The only by-products we observed were the reduction product (ArH) and the homocoupling product (ArAr) and no formation of the 2-methylthio-4-arylpyrimidine **1** occurred. We extended this reaction to the cross-coupling of other functionalized aryl bromides bearing electron-withdrawing groups using two equivalents of the aryl bromide and one equivalent of the 2-methylthio-4-chloropyrimidine as shown in Scheme 2. Our results are indicated in Table 1.

In this way we isolated the expected disubstitution products in average yields of 60% whatever the aryl bromide derivative bearing an electron-withdrawing group.



Scheme 1 Co-catalyzed cross-coupling reaction of 2-methylthio-4-chloropyrimidine with various arylzinc reagents in a Barbier fashion.

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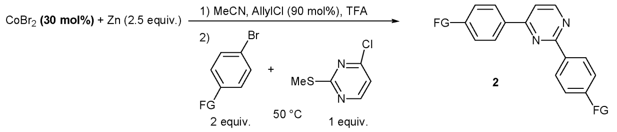


Scheme 2 Co-catalyzed formation of different 2,4-diarylpyrimidines from various aryl bromides.

Table 1 Formation of various 2,4-diarylpyrimidines from 2-methylthio-4-chloropyrimidine

Entry	FG-C_6H_4Br FG	Reaction times/h	Product No.	Yields %[a]
1	*p*-CF_3	5.5	**2a**	61
2	*p*-EtO_2C	4	**2b**	60
3	*p*-CN	4	**2c**	60

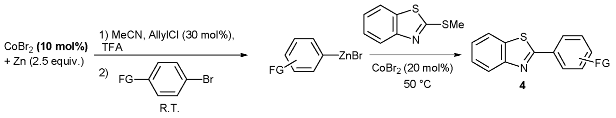
[a] Isolated yield *vs.* 2-methylthio-4-chloropyrimidine.

The special reactivity of the thioether group in the $CoBr_2$-catalyzed cross-coupling reaction allowed us to attempt to synthesize 2,4-diarylpyrimidines bearing two different aromatic rings. The reaction conditions were optimized for the coupling of the 2-methylthio-4-arylpyrimidines (**1b**) obtained using 10 mol% of $CoBr_2$ with *p*-bromoanisole.

Then, we worked out an operationally simplified Barbier-type procedure involving *p*-bromoanisole and the monosubstituted product (**1**) using cobalt catalysis avoiding the preliminary formation of the *p*-$MeOC_6H_4ZnBr$. In these conditions, we isolated 64% yield of the disubstitution product. Nevertheless we showed that it was not necessary to purify the 2-methylthio-4-arylpyrimidine derivatives; these cross-couplings were carried out with the crude product. With an optimized reaction in hand, a number of cross couplings with various aryl bromides were examined (Scheme 3).

Our results are reported in Table 2. The best yields were obtained for the reactions with *p*-bromoanisole whereas lower yields were observed in the case of cross-couplings with less reactive arylzinc species such as ethyl *p*-bromobenzoate or *p*-bromobenzotrifluoride.[14]

These results let us imagine the possibility of using different thioether derivatives as heteroaromatic partners in $CoBr_2$-catalyzed cross-coupling reactions. Moreover, the high price of 2-bromo- and 2-chlorobenzo[*b*]thiazole compared to 2-methylthiobenzo[*b*]thiazole was a major obstacle to the use of these halogenated compounds in cross-coupling reaction.[15]



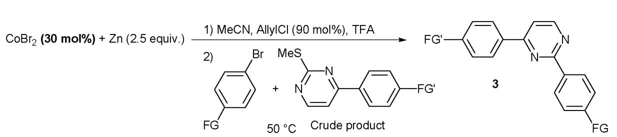
Scheme 5 Co-catalyzed cross-coupling of arylzinc bromides with 2-methylthiobenzo[*b*]thiazole.

Then, benzylzinc reagents (obtained *in situ* from the corresponding benzyl chlorides) could be successfully coupled with 2-methylthiobenzo[*b*]thiazole using similar conditions to lead to 2-benzylbenzo[*b*]thiazole derivatives in a Barbier procedure (Scheme 4).

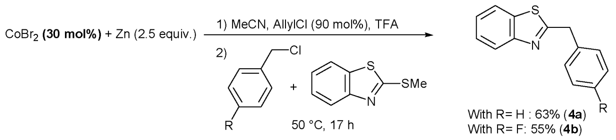
However, the cross-coupling of arylzinc reagents with 2-methylthiobenzo[*b*]thiazole required some modifications of the reaction conditions.

Indeed, the reaction didn't afford the expected cross-coupling product when it was performed using Barbier conditions. The formation of the arylzinc reagent from the corresponding aryl bromide was not observed in the presence of 2-methylthiobenzo[*b*]thiazole in the reaction medium. On the other hand, we noticed that the latter tended to react at the same time with zinc powder in these reaction conditions to give the corresponding 2-benzo[*b*]thiazole zinc reagent. Thus, we next set our sights on performing the reaction in two steps involving formation of the arylzinc reagent from the corresponding aryl bromide using 10 mol% of $CoBr_2$, and subsequent coupling with 2-methylthiobenzo[*b*]thiazole with further addition of $CoBr_2$. In these conditions, the expected 2-arylbenzo[*b*]thiazole (Scheme 5) was synthesized.

The nature of the functional group borne by the aryl bromides (Table 3) or benzyl chlorides (Scheme 4) didn't affect the yield of the reaction. On the contrary, the position of the substituent on the aromatic ring seemed to influence dramatically the reaction. Indeed, no coupling product could be obtained with 2-bromoanisole (Table 3, entry 2) whereas the coupling of 4-bromoanisole with 2-methylthiobenzothiazole afforded the expected 2-arylbenzothiazole derivative in a 60% yield (Table 3, entry 1). We could also notice that the cross-coupling



Scheme 3 Co-catalyzed formation of various unsymmetrical 2,4-diarylpyrimidines from various aryl bromides.



Scheme 4 Co-catalyzed cross-coupling of benzylzinc chloride with 2-methylthiobenzo[*b*]thiazole in a Barbier fashion.

Table 2 Formation of unsymmetrical 2,4-diarylpyrimidines **3**

Entry	FG-C_6H_4Br FG	**1** FG′	Reaction time/h	Product No.	Yield %[a]
1	*p*-OMe	*p*-CO_2Et **1b**	7	**3a**	65
2	*p*-CF_3	*p*-CO_2Et **1b**	5	**3b**	44
3	*p*-OMe	*p*-CF_3 **1a**	7	**3c**	53
4	*p*-CO_2Et	*p*-CF_3 **1a**	7	**3d**	30
5	*p*-OMe	*p*-CN **1c**	5	**3e**	75

[a] Yields *vs.* FG′C_6H_4Br.

Table 3 Formation of 2-arylbenzo[*b*]thiazole from various arylzinc bromides

Entry	FG-C_6H_4Br FG	Reaction time/h	Product No.	Yield %[a]
1	*p*-OMe	12	**4c**	60
2	*o*-OMe	72	**4d**	0
3	*p*-EtOCO	6	**4e**	57
4	*p*-CF_3	4	**4f**	50
5	*p*-CN	6	**4g**	45

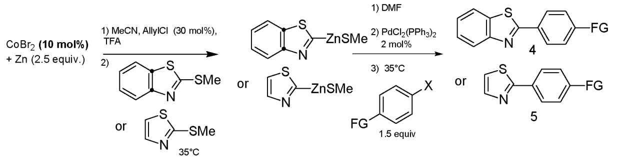
[a] Isolated yields.

reaction involving benzyl chloride derivatives requires longer reaction times than the coupling with aryl bromides.

As we just observed in the case of coupling, it was also possible to activate the C–SMe bond of 2-methylthiobenzo[*b*]thiazole or 2-methylthiothiazole to form the corresponding zinc compound by activation of zinc dust by trifluoroacetic acid in the presence of $CoBr_2$. The resulting organozinc compounds were converted into iodide species by addition of iodine for GC titration using an internal standard (alkane). Then, the cross-coupling reaction between the organozinc species from 2-methylthiobenzo[*b*]thiazole or 2-methylthiothiazole with an aryl bromide was also possible using palladium catalyst $PdCl_2(PPh_3)_2$.

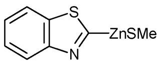
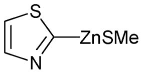
However, these corresponding well-known Negishi couplings proceeded in good yields exclusively if another solvent such as DMF was added to the solution to improve solubility (Scheme 6). The replacement of DMF by THF decreased the yields. This coupling process was conducted at 35 °C since the organozinc species from 2-methylthiothiazole was not stable at 50 °C. Then, results are correct and reported in Table 4. To our knowledge, this is the first reported synthesis of organozinc species from the C–SMe bond.

These organozinc species were obtained in good yields of 90% but the cross-coupling with various aryl iodides or bromides should be improved with different palladium complexes in order to increase the yield of cross-coupling.



Scheme 6 Pd-catalyzed cross-coupling of organozinc species from 2-methylthiobenzo[*b*]thiazole or 2-methylthiothiazole with aryl halides.

Table 4 Formation of 2-arylbenzo[*b*]thiazole or 2-arylthiazole

Entry	HetArZnSMe	FG-C_6H_4X FG	Product No.	Yield (%)
1		*p*-OMe	**4c**	70[a]
2		*p*-EtOCO	**4e**	65[a]
3		*p*-CN	**4g**	50[a] (55)[b]
4		*p*-CF_3	**4f**	55[a]
5		*p*-OMe	**5a**	55[a](0)[b]
6		*p*-EtOCO	**5b**	29[a]
7		*p*-CN	**5c**	34[a](49)[b]
8		*p*-CF_3	**5d**	0[a]

[a] Isolated yield from the corresponding ArI. [b] Isolated yield from the corresponding ArBr.

The coupling yields were generally better with aryl iodides except in the case of iodobenzonitrile. In fact, more homo-coupling product from iodobenzonitrile was obtained, decreasing the cross-coupling yield.

In conclusion, we have devised an expedient route to cobalt-catalyzed activation of the C–SMe bond of various methylthio-substituted N-heterocycles. This catalytic process involves a simple, inexpensive and environmentally friendly cobalt halide without ligand and allows the cross-coupling of these compounds with various aryl or benzylzinc halides. This activation of C–SMe also leads to the synthesis of the corresponding organozinc species in good yields.

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