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Cobalt-Catalyzed Cross-Coupling Reaction between Functionalized Primary and Secondary Alkyl Halides and Aliphatic Grignard Reagents

Gérard Cahiez,[a,*] Christophe Chaboche,[a] Christophe Duplais,[a] Arianna Giulliani,[a] and Alban Moyeux[a]

[a] Laboratoire de Synthèse Organique Sélective et de Chimie Organométallique (SOSCO), UMR 8123
CNRS-UCP-ESCOM, 5 Mail Gay-Lussac, Neuville s/Oise, 95092 Cergy-Pontoise, France
Fax: (+33)-1-3425-7383; e-mail: gerard.cahiez@u-cergy.fr

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Abstract: The coupling of primary and secondary unactivated alkyl bromides with alkyl-Grignard reagents was performed in good yields under mild conditions by using a new catalytic system: consisting of cobalt chloride and tetramethylethylenediamine ($CoCl_2 \cdot 2LiI$, 4TMEDA). The reaction is very chemoselective since ketone, ester and nitrile functions are tolerated.

Keywords: aliphatic Grignard reagents; alkyl-alkyl; cobalt-catalyzed reaction; cross-coupling; secondary alkyl bromides

Transition metal-catalyzed cross-coupling reactions have been extensively developed in the last years. They are frequently used on a laboratory as well as on an industrial scale and they are irreplaceable tools for the elaboration of carbon-carbon bonds.[1,2] Alkyl-alkyl cross-coupling using unactivated primary alkyl halides is one of the oldest reactions in this field.[3]

Thus, it has been known since 1968 that copper-mediated alkyl-alkyl coupling reactions (stoichiometric[4a,b] or catalytic[4c] amounts of copper) are very efficient with primary alkyl halides.[4] Recently, we,[5a] then Kambe,[5b] have shown that the use of additives (respectively, NMP and 1-phenylpropyne) allows the yield and the chemoselectivity of the reaction to be improved, sometimes dramatically. Nevertheless, only primary alkyl halides can be coupled successfully according to the previous procedures. It is interesting to note that the only example of copper-catalyzed coupling reactions between a Grignard reagent and an unactivated secondary alkyl halide was performed using Mn/Cu catalysis.[6] It should be noted that a sophisticated tridentate diamino-organomanganese(II) complex (NCN-MnCl·LiCl) is used as a co-catalyst.

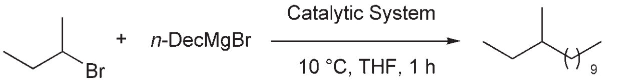
Few coupling reactions between alkyl-Grignard reagents and secondary alkyl halides under palladium[7a,b] or nickel[8a,b] catalysis were also reported. Moreover, the reactions are mainly limited to cycloalkyl halides that give better yields than linear secondary alkyl halides.[9] In fact, after many decades, the coupling of unactivated secondary alkyl halides is still a challenge since it is well-known that these substrates undergo very slow oxidative addition whereas the secondary alkyl-metal intermediates involved in the catalytic cycle undergo rapid β-elimination.[9,10] Thus, there is no general method for the metal-catalyzed coupling of unactivated secondary alkyl halides with aliphatic Grignard reagents.[11]

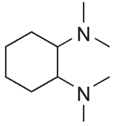
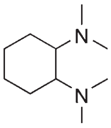
As a solution to this problem, we report herein our results concerning the first example of a cobalt-catalyzed alkyl-alkyl cross-coupling reaction from unactivated secondary halides.[11b]

Recently, we[12] and others[13] have reported that secondary alkyl halides can be coupled with aryl-Grignard reagents in the presence of a catalytic amount of iron or cobalt salts. The presence of an amine like TMEDA,[13c] or even better tandem TMEDA-HMTA,[12] is essential in order to obtain good yields. Thus, we decided to evaluate the potential of such catalytic systems to couple alkyl-Grignard reagents with secondary alkyl halides. Our attempts to couple 2-bromobutane with decylmagnesium bromide in the presence of iron salts [$Fe(acac)_3$-TMEDA and $Fe(acac)_3$-TMEDA-HMTA] resulted in failure.[14]

With cobalt chloride or an ate complex $CoCl_2 \cdot 2LiX$ ($X = Cl$ or I)[15] as a catalyst, the expected coupling product was only obtained in a trace amount (Table 1, entries 1 and 2). However, we were pleased to note that in the presence of 20 mol% TMEDA, the reac-

Table 1. Comparison of various catalytic systems.



Entry	Catalytic System[a]	Yield [%][b,c]
1	$CoCl_2$	Traces
2	$CoCl_2 \cdot 2LiX$ (X = Cl or I)	Traces
3	$CoCl_2$, 4 TMEDA	35
4	$CoCl_2 \cdot 2LiCl$, 4 TMEDA	27
5	$CoCl_2 \cdot 2LiBr$, 4 TMEDA	30
6	$CoCl_2 \cdot 2LiI$, 4 TMEDA	79
7	$CoCl_2 \cdot 2MgI_2$, 4 TMEDA	79
8	$CoCl_2$, 4 	28
9	$CoCl_2 \cdot 2$ LiI, 4 	75

[a] 5 mol% of catalyst were used.
[b] GC yield (pentadecane as an internal standard).
[c] The starting halide was completely consumed in all experiments.

tion led to a 35% yield (Table 1, entry 3). This result encouraged us to continue our investigations. We thus tried to combine TMEDA and ate complexes such as $CoCl_2 \cdot 2LiX$. No significant change was observed by using lithium chloride or bromide (respectively $CoCl_2 \cdot 2LiCl$ and $CoCl_2 \cdot 2LiBr$. Table 1, entries 4 and 5). On the other hand, with lithium iodide or magnesium iodide (Table 1, entries 6 and 7) the yield jumped from 35 to 79%. It is important to note that, contrary to the results reported by Oshima[13g] in the case of the coupling of secondary alkyl halides with aryl-Grignard reagents, the use of *N,N,N′N′*-tetramethyl-1,2-cyclohexanediamine in place of TMEDA does not allow us to improve the yield of the alkyl-alkyl coupling product (Table 1, entries 8 and 9).

With 2-iodobutane, the coupling can be performed successfully in the presence of $CoCl_2 \cdot 2LiI$ or $CoCl_2 \cdot 2LiCl$ (Scheme 1). This is not very surprising since, in this case, metallic iodides are formed *in situ* as soon as the reaction begins.

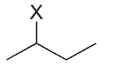
This is the first time that such a beneficial influence of iodide anion as a ligand has been evidenced in the case of cobalt-catalyzed coupling reactions.[16]

This interesting observation prompted us to explore the scope of the cobalt-catalyzed alkyl-alkyl coupling reaction by using $CoCl_2 \cdot 2LiI$, 4 TMEDA as a catalytic system (Table 2).

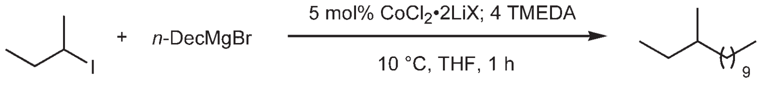
Acyclic secondary alkyl bromides (Table 2, entries 1 to 10) gave moderate to good yields of cross-coupling product. It is important to note that the influence of steric effects is determinant. Thus, 2-bromopentane gave a better yield than 3-bromopentane (Table 2, en-

Table 2. Cobalt-catalyzed cross-coupling reaction between unactivated primary and secondary alkyl halides and aliphatic Grignard reagents.

$$\text{RBr} + \text{R'MgBr} \xrightarrow[\text{10 °C, THF, 1 h}]{\text{5 mol\% CoCl}_2\text{•2 LiI, 4 TMEDA}} \text{R-R'}$$

Entry	Alkyl Halide	Grignard Reagent	Yield [%][a]
1	2-Bromopropane	*n*-OctMgBr	82
2	2-Bromopropane	*n*-DecMgBr	89
3	2-Bromobutane	*n*-OctMgBr	69
4	 X = Cl	*n*-DecMgBr	≤1[b]
5	X = Br	*n*-DecMgBr	79
6	X = I	*n*-DecMgBr	75
7	2-Bromopentane	*n*-OctMgBr	62[c]
8	3-Bromopentane	*n*-DecMgBr	45[c]
9	2-Bromoheptane	*n*-DecMgBr	47[c]
10	2-Bromodecane	*n*-BuMgBr	57[c]
11	Cyclohexyl bromide	*n*-OctMgBr	87
12	*n*-PentBr	*n*-OctMgBr	96
13	*n*-OctBr	*n*-PentMgBr	97
14	*n*-DecBr	*n*-PentMgBr	98
15	*n*-BuBr *n*-BuBr		70
16	*t*-PentBr	*n*-OctMgBr	0[b]
17	*n*-DecBr	*s*-BuMgBr	20[d]
18	*n*-DecBr	*t*-BuMgBr	0[d]

[a] Yield of isolated product.
[b] No reaction.
[c] A mixture R (±H) was obtained as side product from RBr.
[d] A mixture of decane and 1-decene was mainly obtained.



LiX = LiCl: 68%
LiX = LiI: 75%

Scheme 1. Reaction from 2-iodobutane.

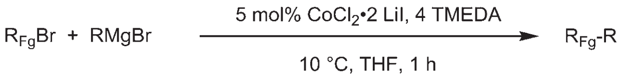
tries 7 and 8). Similarly, the results obtained with various 2-bromoalkanes clearly depend on the length of the alkyl chain (Table 2, entries 2, 5 and 9). As expected,[10] cyclic alkyl bromides gave higher yields than acyclic secondary alkyl bromides (Table 2, entries 7 and 11). Finally, it is possible to use alkyl iodides in place of the bromides whereas the corresponding chlorides do not react (Table 2, entries 4 to 6). The reaction has been extended to primary alkyl bromides, for which it should be noted that excellent yields were obtained (Table 2, entries 12 to 15). On the other hand, tertiary alkyl bromides do not react (Table 2, entry 16). It should be noted that only primary alkyl-Grignard reagents gave satisfactory yields (Table 2, entries 17 and 18).

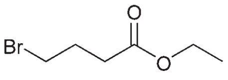
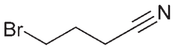
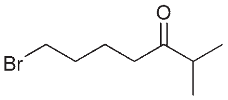
Interestingly, the presence of various functional groups like ester, nitrile and even ketone is tolerated (Table 3).

The reaction depicted in Scheme 2 is the first example of a chemoselective alkyl-alkyl coupling from a functionalized secondary alkyl bromide.

In summary, we have disclosed herein the first example of a cobalt-catalyzed chemoselective alkyl-alkyl coupling reaction. It is worthy of note that this procedure is now the best way to couple secondary alkyl halides with alkyl-Grignard reagents in satisfactory yields. An unprecedented and beneficial influence of iodides on this coupling reaction is described.

Table 3. Cobalt-catalyzed cross-coupling reaction between unactivated functionalized primary alkyl halides and aliphatic Grignard reagents.



Entry	Alkyl Halide	Grignard Reagent	Yield [%][a]
1		EtMgBr	78
2		*n*-DecMgBr	75
3		*n*-BuMgBr	82
4		*n*-PentMgBr	73

[a] Yield of isolated product.

Currently, sustainable development must be taken into account in the development of new chemical procedures. Thus, in the last few years considerable efforts have been made to replace palladium or nickel complexes by iron or manganese salts that are less expensive and more acceptable for the environment. As catalysts, cobalt salts are probably the most interesting candidates after iron and manganese derivatives. Moreover, it should be noted that the three metals deserve to be studied in parallel since they can exhibit some specific reactivities. The results reported above in the case of the alkyl-alkyl coupling are good evidence for such a difference between iron- and cobalt-catalyzed reactions. The cobalt-catalyzed cross-coupling reaction presented above is part of our efforts to propose new eco-friendly and economical metal-catalyzed procedures.

Experimental Section

Typical Procedure: Preparation of 3-Methyltridecane (Scheme 1)

A dry and nitrogen-flushed 250-mL four-necked flask, equipped with a mechanical stirrer, a thermometer, a nitrogen inlet and a septum, was charged with THF (25 mL), 2-bromobutane (6.85 g, 50 mmol), $CoCl_2$ (325 mg, 5 mol%), TMEDA (1.16 g, 20 mol%) and LiI (700 mg, 10 mol%). The reaction mixture was cooled to 10 °C then a solution of *n*-decylmagnesium bromide in THF (61 mL, 0.9 M, 55 mmol) was added in 80 min. After the end of the addition, the reaction mixture was stirred for 30 min then quenched with aqueous HCl (1 M, 100 mL). The aqueous phase was extracted with ether (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The crude product was purified by distillation at a reduced pressure (116 °C, 10 Torr) affording 3-methyltridecane as a colorless oil; yield: 7.8 g (79%).

Acknowledgements

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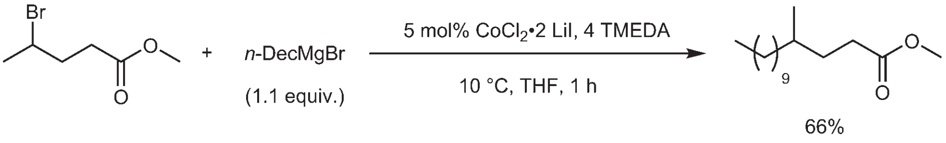

Scheme 2. Cobalt-catalyzed chemoselective alkylation of methyl 4-bromopentanoate.

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[16] We have verified that bromine-iodine exchange is very slow under our conditions. Thus, by stirring our catalytic system (CoCl$_2$·2LiI, 4TMEDA) with 2-bromooctane (ratio LiI/*s*-OctBr = 1:1), only 4% of 2-iodobutane were detected after 16 h at room temperature.