

Cobalt-Catalyzed $C_{sp^3}-C_{sp^3}$ Homocoupling

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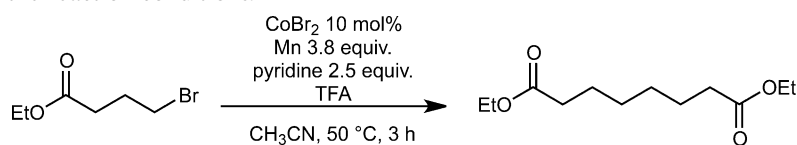
Abstract: An efficient and easy method for $C_{sp^3}-C_{sp^3}$ homocoupling was developed using cobalt bromide as catalyst. A series of functionalized alkyl bromides and alkyl chlorides were coupled in high yields under mild conditions. This reaction seems to involve a radical intermediate.

Keywords: alkyl-alkyl coupling; cobalt; dimerization; homocoupling; manganese

With the progress of biological science, the demand for efficient dimerization processes increases, since many natural products are dimers or pseudodimers.^[1] The dimerizations of olefins,^[2] alkynes,^[3] carbonyl compounds^[4] and aryl halides^[5] have been well developed in the last decades and a variety of efficient methodologies has been reported. However, compared to the methods mentioned above, the dimerization of alkyl halides has been relatively poorly investigated. The traditional Wurtz coupling was an important tool but it suffers from limited functional group

tolerance due to the harsh reaction conditions.^[6] In 2010, Leigh and co-workers first described a tridentate nitrogen-donor atom ligands-assisted Ni-catalyzed homocoupling of alkyl bromides under mild reaction conditions.^[7] Almost at the same time, Weix and co-workers published a more general method for reductive dimerization of alkyl halides/pseudohalides,^[8] using a Ni/terpy-catalyzed system. A series of functionalized substrates was tolerated and led to moderate to excellent yields, including primary and secondary alkyl halides, benzyl chlorides and allylic acetates. Later, Wang and co-workers established another Ni-catalyzed method for alkyl-alkyl homocoupling, used for sophisticated molecules with a Ni/ethyl crotonate or Ni/bipy system.^[9] More recently, Ando and co-workers showed that a Rh-catalyzed $C_{sp^3}-C_{sp^3}$ homocoupling reaction of benzyl halides could be involved instead of a nickel catalyst.^[10] For a few years, our group has already reported efficient Co-catalyzed reductive cross-couplings, such as aryl-aryl, aryl-alkyl, allyl-alkyl cross couplings,^[11] and homocoupling of aryl halides.^[12] Therefore, we investigated an alternative $C_{sp^3}-C_{sp^3}$ homocoupling reaction using a simple cobalt catalyst with the objective to develop a more

Table 1. Optimization of the reaction conditions.



Entry	Deviation from Standard Conditions	GC Yield [%]
1	none	84^[a]
2	no pyridine	< 10
3	pyridine 5 equiv.	42
4	2-picoline instead of pyridine	84^[a]
5	CoBr ₂ 5 mol%	53
6	Mn 1.9 equiv.	56
7	CoBr ₂ 20 mol%	50
8	r.t.	20 ^[b]
9	addition of 40 mol% allyl chloride before TFA	30

^[a] Isolated yield.

^[b] Conversion is 40% after 18h.

practical method, since Co is more environmentally friendly than nickel, much cheaper than rhodium, and Co-catalyzed reactions often do not need ligands.

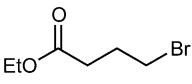
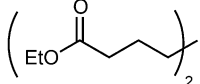
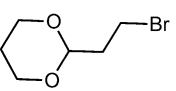
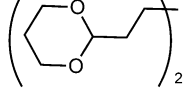
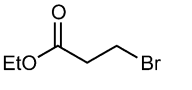
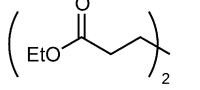
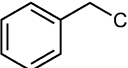
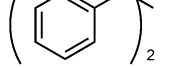
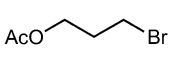
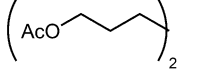
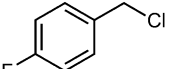
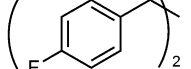
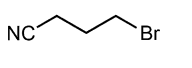
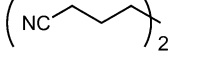
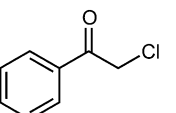
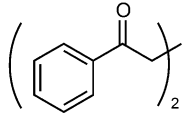
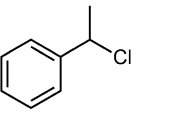
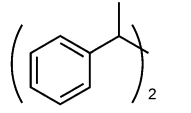
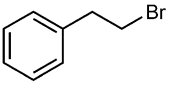
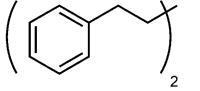
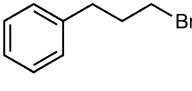
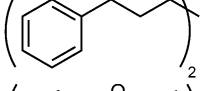
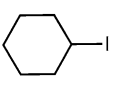
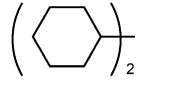
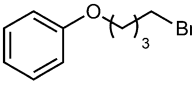
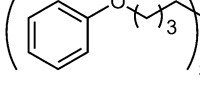
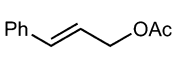
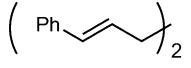
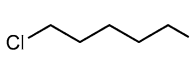
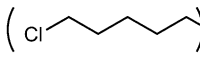
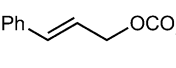
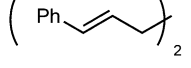
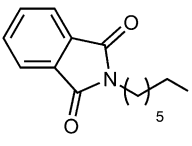
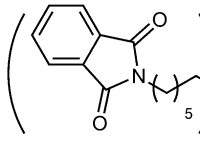
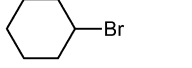
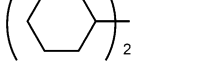
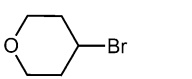
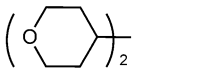
We first carried out a model study using ethyl 4-bromobutyrate as the starting reagent. We identified that a combination of $\text{CoBr}_2/\text{Mn}/\text{pyridine}$ in CH_3CN ,

as previously reported for the allyl-alkyl cross-coupling reaction,^[13] afforded the desired coupling product in 84% yield (Table 1, entry 1). Without pyridine, the reduction product was rapidly the main product (Table 1, entry 2). Increasing the pyridine amount reduced the catalytic ability and decreased the yield

Table 2. Scope of substrates.

$$\text{Alkyl-X} \xrightarrow[\text{CH}_3\text{CN/pyridine, TFA, 50 }^\circ\text{C, 4-6 h}]{\text{CoBr}_2 \text{ 10 mol\%, Mn 3.8 equiv.}} \text{Alkyl-Alkyl}$$

X = I, Br, Cl, OTs, OAc, OCO₂Me

Entry	Substrate	Product	Yield [%]	Entry	Substrate	Product	Yield [%]
1			84 ^[a,b]	13			87 ^[b]
2			66 ^[b]	14			82 ^[a]
3			83 ^[a]	15			79 ^[b] (68 ^[a,e])
4			88 ^[b] (65 ^[a])	16			50 ^[a] (trace ^[b])
5	$n\text{-C}_{10}\text{H}_{21}\text{Br}$	$n\text{-C}_{20}\text{H}_{42}$	87 ^[a]	17			78 ^[a]
6			74 ^[b] (37 ^[a])	18	$n\text{-C}_7\text{H}_{15}\text{I}$	$n\text{-C}_{14}\text{H}_{30}$	60 ^[a]
7			70 ^[b] (57 ^[a])	19			53 ^[a,b]
8			76 ^[b]	20			82 ^[a]
9			56 ^[b] (80 ^[a,e])	21			72 ^[a]
10			79 ^[a]	22	$n\text{-C}_7\text{H}_{15}\text{Cl}$	$n\text{-C}_{14}\text{H}_{30}$	70 ^[a,c] (37 ^[b,c])
11			68 ^[a] (48 ^[b,e])	23	$n\text{-C}_7\text{H}_{15}\text{OTs}$	$n\text{-C}_{14}\text{H}_{30}$	80 ^[a,d]
12			95 ^[b] (49 ^[a,e])				

^[a] Using pyridine.

^[b] Using 2-picoline.

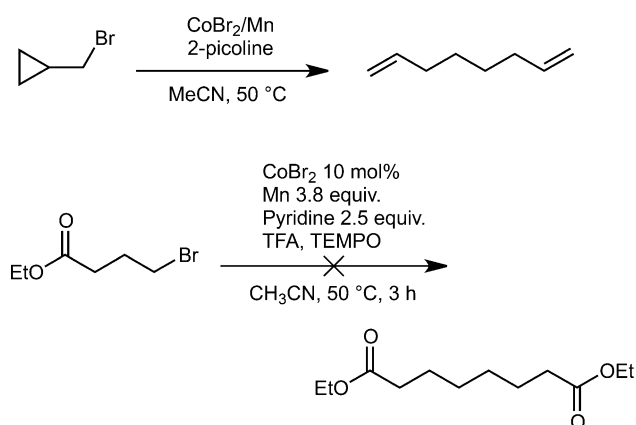
^[c] 0.5 equiv. of NaI added, at 80 °C, 72 h.

^[d] 0.5 equiv. of NaI added.

^[e] Yield on GC.

(Table 1, entry 3). It is noteworthy that when 2-picoline was used instead of pyridine, the same yield was obtained (Table 1, entry 4). Decreasing either the catalyst loading or the amount of Mn led to lower yields (Table 1, entry 5 and 6), while increasing the catalyst loading gave no positive effect (Table 1, entry 7). A low yield was obtained at room temperature (Table 1, entry 8). Addition of allyl chloride in a first step had no positive effect in this homocoupling reaction whereas the reduction product was decreased in cobalt-catalyzed reductive aryl-aryl homocoupling reactions in its presence.^[12] In contrast, more reduction product was observed and the reaction rate was diminished (Table 1, entry 9).

With these optimized conditions in hand, we next investigated the scope of alkyl halides. Primary alkyl bromides were well tolerated, good to excellent yields were obtained with or without functionalities (Table 2, entries 1–10). In most cases, 2-picoline gave better yields than pyridine. Alkyl bromides bearing electron-donating groups and electron-withdrawing groups, such as ester (Table 2, entries 1 and 2), acetate (Table 2, entry 3), nitrile (Table 2, entry 4), phenyl (Table 2, entries 6 and 7), ether (Table 2, entry 8), chloride (Table 2, entry 9), ketal (Table 2, entry 13) efficiently reacted. Interestingly, whereas isoindole-1,3-dione and ketone groups were not tolerated in the cobalt-catalyzed allyl-alkyl cross-coupling reactions,^[13] they provided moderate to good yields in this homocoupling reaction (Table 2, entries 10 and 16). Benzyl chloride, which is more reactive, could also be used in this reaction (Table 2, entries 14 and 15). However, the coupling of more reactive functionalized benzyl chlorides bearing electron-withdrawing groups, such as 4-(chloromethyl)benzotrile and 4-methylsulfonylbenzyl chloride, only afforded the reduction product. No better result was obtained at room temperature. Unreactive alkyl chlorides did not react under these conditions. However, as already reported in some Ni-catalyzed reductive couplings,^[8,14] addition of sodium iodide led to the coupling product. In our case, alkyl chloride dimerized smoothly at higher temperature in the presence of NaI (Table 2, entry 22). This additive also had a positive influence on the homocoupling of alkyl tosylates, which did not react under standard reaction conditions (Table 2, entry 23). Some secondary alkyl bromides, such as cyclohexyl bromide and 4-bromotetrahydropyran, coupled smoothly under these conditions (Table 2, entries 11 and 12), but *tert*-butyl 4-bromopiperidine-1-carboxylate was not homocoupled and only the reduction product was isolated. Besides, primary and secondary alkyl iodides reacted and led to moderate yields (Table 2, entries 18 and 19). To our delight, cinnamyl acetate and carbonate were well dimerized in this protocol (Table 2, entries 20 and 21). However, an hindered substituted al-

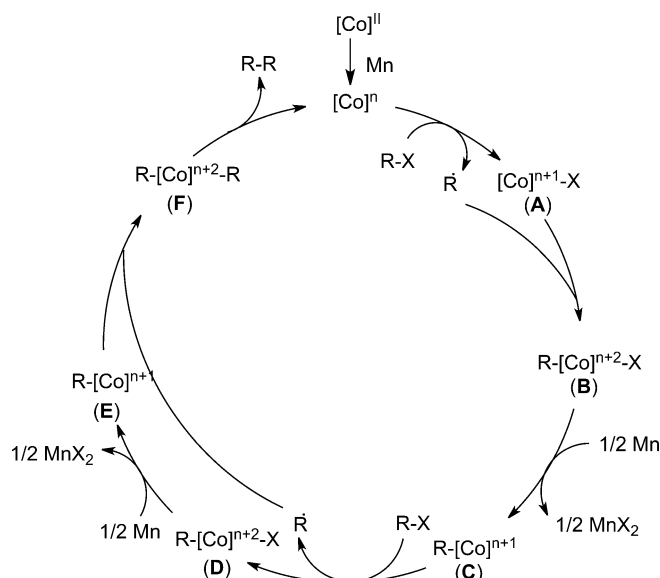


Scheme 1. Mechanism study.

lylic acetate, for example, (*E*)-hex-2-en-1-yl acetate did not react.

Some experiments were conducted to provide insights into the mechanism of this homocoupling reaction (Scheme 1). When bromomethylcyclopropane was used as starting material, the dimer of the ring-opened product was the sole product identified by NMR. Moreover, the addition of a free radical scavenger such as 2,2,6,6-tetramethylpiperine 1-oxyl (TEMPO) after the activation of manganese inhibited the homocoupling reaction. These results suggest that a radical intermediate is involved in this reaction.

Therefore we proposed a mechanism of the reaction as shown in Scheme 2. First, cobalt(II) is reduced by manganese. Then, an alkyl radical is generated from alkyl halide by its reaction with this low valent cobalt and a cobalt complex (**A**) is formed. This last complex (**A**) reacts with the alkyl radical to form an-



Scheme 2. Proposed mechanism.

other cobalt complex (**B**). After reduction of the complex (**B**) by manganese, a similar procedure leads to a cobalt-bialkyl complex (**F**). Finally a reductive elimination gives the desired homocoupling product and regenerates the catalyst.

In conclusion, a novel approach for $C_{sp^3}-C_{sp^3}$ homocoupling has been developed using a simple cobalt bromide as catalyst. A large variety of functionalities on the alkyl halides was tolerated and good to excellent yields were obtained even with reactive benzyl chlorides and allyl acetate/carbonate. However, the addition of sodium iodide is required to obtain the homocoupling product of unactivated alkyl chlorides and tosylates with good yields. This method is very easy to implement and no sophisticated ligand is necessary. Further applications are under investigation in our laboratory.

Experimental Section

General Procedure

To a solution of $CoBr_2$ (10 mol%, 0.25 mmol, 55 mg) and manganese powder (3.8 equiv., 9.5 mmol, 500 mg) in CH_3CN (3 mL) was added at room temperature the alkyl halide (2.5 mmol). Manganese powder was activated by traces of trifluoroacetic acid (50 μ L) and the mixture was then stirred at room temperature for 5 min until smoke disappeared. At this time, pyridine or 2-picoline (0.5 mL) was added and the mixture was stirred at 50 °C until the alkyl halide was consumed (3 to 6 h). The mixture was then quenched with a solution of 2 M HCl (30 mL) and was stirred vigorously until the layers turned clear. The solution was extracted with Et_2O or $EtOAc$ (3 \times 50 mL), washed with brine and dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting oil or solid by chromatography over silica with petroleum ether/diethyl ether (or ethyl acetate) mixtures afforded the pure compounds.

Acknowledgements

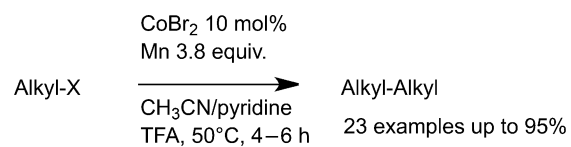
We thank the Ministère de l'Enseignement Supérieur et de la Recherche (PhD grants to Y. C. and X. Q.). This work was supported by CNRS and Ecole Polytechnique.

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X = I, Br, Cl, OTs, OAc, OCO₂Me

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