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Dehalogenation and desulfonation from aryl and alkyl compounds with a cobalt catalyst in presence of alcohol.

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Abstract: Easy dehalogenation of bromo, chloro-aryl and alkyl derivatives is performed in presence of a cobalt catalyst, manganese as reductant, and alcohol as hydrogen donor. This method tolerates a variety of functional groups with different electronic properties. Noteworthy examples of desulfonation are also reported.

The substitution of a halogen by a hydrogen atom, the so-called hydrodehalogenation, is an important transformation in organic chemistry due to the detrimental impact of halogen derivatives on the environment. It is classically achieved by reduction with metal derivatives that can, in some cases, be difficult to handle and may generate byproducts.^[1] Transition metal catalyzed processes with various reductant such as silane,^[2] dihydrogen gas,^[3] or metal derivative^[4] offer a valuable alternative. The reaction can also be conducted in presence of a metal alkoxide and alcohol serving both as base and hydrogen donor. Such transfer hydrodehalogenation were described with noble^[5] or base metals.^[6] Alcohol also allows the reduction of aryl halides by single electron transfer in presence of a base and a radical initiator,^[7] or under UV light.^[8] Dehalogenation thanks to photoactivation was reported without any catalyst^[9] or with a molecular catalyst^[10] as well as nanomaterials.^[11] The dehalogenation of aryl halides can also be achieved by electrochemical processes.^[12]

The presence of cobalt in the active site of reductive dehalogenases has stimulated the study of those enzymatic systems,^[13] the development of bio-inspired catalysts,^[14] and the study of their operating mechanism.^[15] Moreover cobalt porphyrins were shown to achieve the hydrodebromination of aryl derivatives,^[16] while low-valent cobalt complexes catalyze the hydrodefluorination of perfluoroarenes^[17] or the hydrodechlorination of pesticides.^[18] More recently, cobalt in combination with a biomass derived material was shown to catalyze the hydrodehalogenation of alkyl- and hetero-arenes using hydrogen gas at 120°C.^[19] As we demonstrated that low-valent cobalt generated from cobalt salts and a metal reductant is able to activate aryl or alkylhalides to deliver the corresponding reductive coupling products, we were interested in developing a user-friendly protocol allowing the dehalogenation of bromide or chloride aryl and alkyl derivatives. Indeed, we have proved that CoBr₂ in presence of a metal reductant is able to activate aryl or alkylhalides to deliver the corresponding reductive coupling products.^[20] We reasoned that the use of this catalytic system in presence of alcohol should allow to isolate hydrodehalogenation products. The result of this

study is presented below: aryl and alkyl bromides or chlorides were dehalogenated at room temperature in user-friendly conditions with a good functional tolerance. As the cobalt-catalyzed reduction of arylsulfone using a cobalt NHC complex in combination with alkylmagnesium reagents was recently described,^[21] we also investigated the hydrodesulfonation of sulfonate compounds, which reacted already efficiently using cobalt catalysis.^[20a, 22]

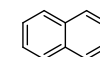
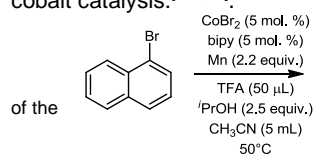
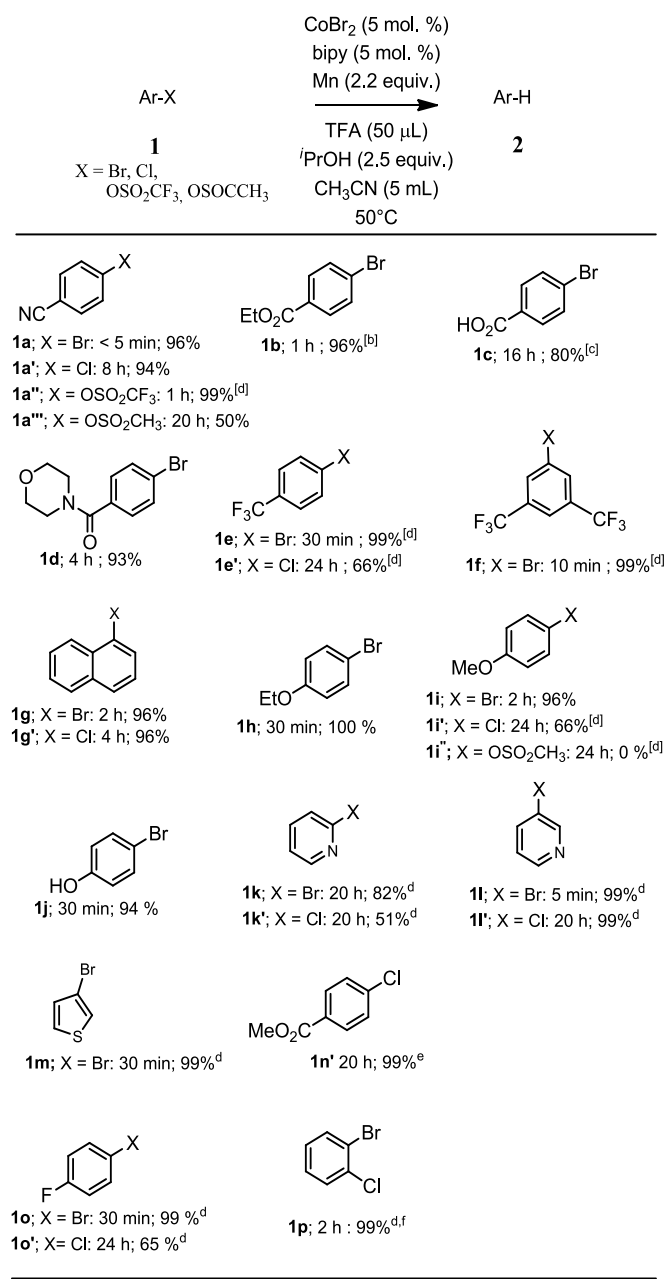


Table 1. Optimization dehalogenation of 1-bromonaphthalene.^[a]

Entry	Conditions modifications	t (h)	Conv. ^[b] (%)
1	No bipy	5	99 (0) ^[c]
2	None	2	99/96^[d] (96) ^{[c], [d]}
3	NiBr ₂ (bipy) as catalyst	5	43
4	No CoBr ₂ or no Mn	24	0
5	No TFA	6	99
6	Mn (1 equiv.)	24	69
7	Mn (0.2 equiv.)	24	31
8	T = 35 °C	4	99
9	T = 20 °C	6	99
10	DMF and pyridine instead of CH ₃ CN	24	9
11	iPrOH as solvent	24	20

^[a] Reactions carried out in a sealed vial on 2 mmol of 1-bromonaphthalene; ^[b] Conversion into naphthalene measured by GC using *n*-dodecane as standard. ^[c] From naphthalene chloride; ^[d] Isolated yield.

The optimization of the reaction conditions was done on the debromination of 1-bromonaphthalene. It started with conditions close to those we used for the dimerization of aryl bromides.^[23] First reaction was conducted in presence of CoBr₂ (5% mol.), manganese as reductant (2.2 equivalents) in acetonitrile at 50 °C, in presence of isopropanol (2.5 equiv.). Total conversion was



Scheme 1. Reactivity of aryl electrophiles.^[a]

^[a] All reactions were carried out on a 2 mmol scale in a sealed vial. Unless otherwise stated, isolated yield are indicated; ^[b] ethanol was used instead of isopropanol to avoid transesterification; ^[c] incomplete conversion due to low solubility of 4-bromobenzoic acid; ^[d] Yield determined by GC; ^[e] methanol was used instead of isopropanol to avoid transesterification; ^[f] without bipy

achieved within 5 h. Addition of one equivalent of bipyridine ligand per cobalt center (Entry 2) accelerates the reaction and naphthalene was isolated in 96 % yield after 2 h. Using [NiBr₂(bpy)] in the same conditions only led to 43% in 5 h (Entry 3). In the absence of cobalt salt or manganese, no reaction was observed (Entry 4). Without the addition of trifluoroacetic acid (used to activate the reductant) the reaction was much slower requiring 20 h to complete (entry 5). In the same manner, the

reduction of the manganese amount to 1 or 0.2 equivalent led to a less efficient reaction with conversion of 69% and 31% respectively after one day (Entries 6 and 7). The modification of the temperature affects the reaction duration, which lasts 6 h at room temperature, and 4 h at 35 °C (entries 8 and 9). The solvent plays also a major role: when conducted in DMF in presence of pyridine, previously successfully used for some coupling reactions^[20a, b, 24] only 9% conversion was observed after one day (Entry 10). The use of isopropanol as the unique solvent only gave 20% of dehalogenated product for the same duration (Entry 11).

We finally chose to use the conditions of entry 2, with bipyridine, since this additive accelerates the reaction from aryl bromide and is necessary to achieve the conversion of aryl chlorides (as already observed in other cobalt catalyzed processes^[23, 25]).

The scope of this dehalogenation process was then extended to variously substituted arylbromides. For electron-withdrawing group-substituted derivatives (**1a-f**, scheme 1), the reaction is rapid allowing the isolation of more than 95 % of the debrominated product after at maximum 1 h reaction. For the ester **1b** the reaction was conducted in presence of ethanol instead of isopropanol to avoid transesterification.

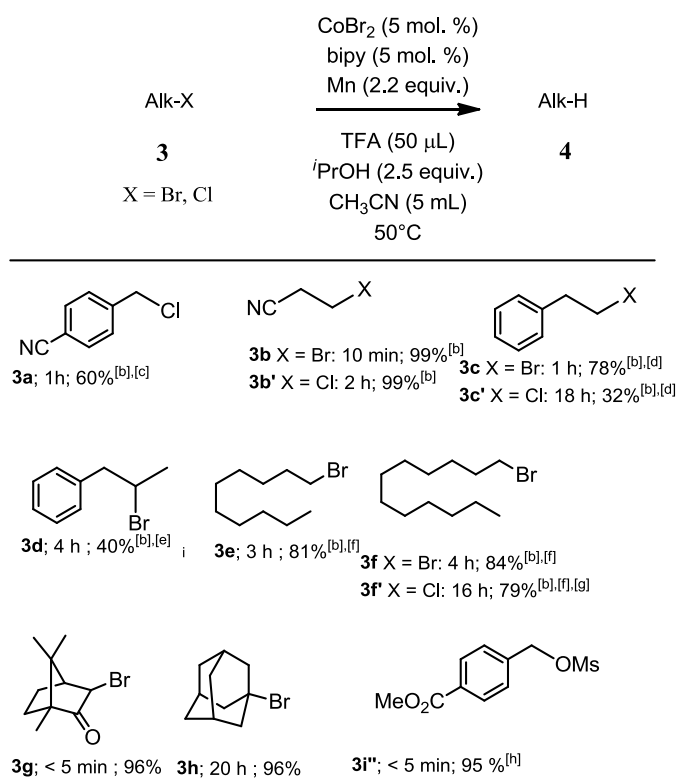
The benzoic acid was isolated in lower yield (80 %) even after longer reaction time because of the low solubility of **1c** in the reaction mixture. The conversion of the amide **1d** is efficient but requires longer time. Rapid and total reaction also occurred with trifluoromethyl substituted bromoaryls (**1e** and **1f**). For electron-rich arylbromides bearing oxygenated substituent (ethoxy (**1h**), methoxy (**1i**), or hydroxyl group (**1j**)), the reaction works well. In the same manner, the debromination of heterocyclic halides leads to high conversions but reaction time varies. 3-bromopyridine (**1l**) and 3-bromothiophene (**1m**) react rapidly, whereas for 2-bromopyridine (**1k**) 82% conversion was observed after 20 h. We already observed such differences using 2-halopyridine.^[20a]

Importantly the dechlorination proceeds also smoothly, provide that one equivalent of bipyridine is present in the reaction mixture. For **1a'**, **1g'**, **1i'**, **1l'** dechlorination gives yields similar to debromination but requires longer reaction time. Noteworthy, ester **1n'** was totally dechlorinated within 1 h in presence of methanol to avoid transesterification reaction.

For *p*-trifluoromethyl derivative (**1e'**) and 2-chloropyridine (**1k'**) lower conversion were obtained compared to the corresponding bromide derivative (66 % vs 99% from **1e** and 51 % vs 82% from **1k**). For fluorobenzene derivatives, defluorination is not observed, debromination is quantitative (from **1o**) and rapid while dechlorination (from **1o'**) took one day and yielded 65% of fluorobenzene. For *o*-chlorobromobenzene (**1p**) only debromination occurred without bipyridine (total conversion within 2 h). In presence of bipyridine, dechlorination took place, once debromination finished, but only 20 % benzene is observed after 20 h.

Interestingly, sulfonate derivatives also react but the efficiency depends on the sulfonate group: total conversion was observed from *p*-cyanophenyltriflate (**1a''**) within 1 h whereas the less reactive mesylate derivative (**1a'''**) only gave 50% conversion after 20 h.

We then tested the dehalogenation of alkylhalides and were pleased to find that the reaction proceeds smoothly from bromo or chloro derivatives (Scheme 2). *p*-cyanobenzyl chloride was converted within 1 h but 1,2-diphenylethane derivative forms concomitantly to toluene in a 1: 1.5 ratio. From primary (**3c**) and secondary (**3d**) alkylbromides, the reaction is rapid but accompanied by the formation of styrene and allylbenzene respectively. Traces of the corresponding α -olefin are also observed from **3e** and **3f** derivatives. Conversion of chloroalkyles takes longer time and gives in some cases lower yield (compare **3b** and **3b'**, **3c** and **3c'**, **3f** and **3f'**). From **3f'**, addition of excess lithium bromide was necessary to ensure efficient conversion. Steric hindrance does not hamper the reaction since camphor and adamantane were isolated in high yield from **3g** and **3h**, but the latter requires much longer time to react. Moreover the desulfonation of benzylmesylate bearing an ester function **3i''** is rapid and high yielding.



Scheme 2. Reactivity of alkyl electrophiles.^[a]

^[a] All reactions were carried out on a 2 mmol scale in a sealed vial Unless otherwise stated, isolated yield are indicated; ^[b] Yield determined by GC; ^[c] total conversion but formation of CNPhCH₂CH₂PhCN and CNPhCH₃ in ratio 1:1.5; ^[d] styrene formed concomitantly to ethylbenzene; ^[e] allyl benzene: propyl benzene: 1.5:1; ^[f] traces of α -olefin observed; ^[g] run with 10 equiv. of LiBr; ^[h] methanol was used instead of isopropanol to avoid transesterification.

From a mechanistic point of view, the involvement of radicals was already proved when using alkyl halides for coupling reactions using this catalytic system.^[20c] This is in agreement with the side products identified during the dehalogenation of alkyl halides. Starting from arylhalides the dehalogenation may originate from the alcoholysis of the arylcobalt formed after oxidative addition.

We therefore described a very user-friendly protocol to realize the dehalogenation of aryl and alkyl compounds using

cobalt salt in association with manganese as reductant in presence of alcohol in acetonitrile. Various electron-withdrawing or donating functions were nicely tolerated. This method compares favorably with other strategies described in the literature given the scope and the simplicity of the procedure.

Experimental Section

To a solution of 2,2'-bipyridine (5 mol%, 0.1 mmol, 16 mg), CoBr₂ (5 mol%, 0.1 mmol, 22 mg) in CH₃CN (5 mL), manganese powder (2.2 equiv., 4.4 mmol, 242 mg) was added. Trifluoroacetic acid (50 μ L) was added to it in order to activate manganese followed by addition of dodecane (0.1 mL) serving as internal standard. Organic halide/sulfonate (1.0 equiv, 2 mmol) was then added, followed by ⁱPrOH (2.5 equiv, 5.0 mmol, 0.385 mL). The vial was then stirred at 50 °C on a hotplate using an aluminum block. The reaction was monitored by GC. After completion of reaction, the reaction medium was diluted with CH₂Cl₂ and filtered through a pad of silica gel and evaporated. The crude product was purified by flash chromatography and characterized by NMR spectroscopy (¹H, ¹³C). Column purification is not required when only one isomer is formed with complete conversion.

Acknowledgements

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Keywords: alcohol; catalysis; cobalt; reduction; hydrodehalogenation

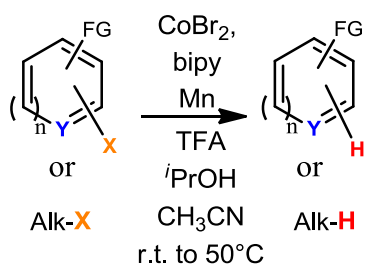
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Supporting Information bibliographical references

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Entry for the Table of Contents



X = Br, Cl, OMs, OTf 33 examples

Y = CH, S, N

n = 0 or 1

A very simple and user-friendly procedure allowing dehalogenation or desulfonation of aryl-, heteroaryl-, and alkyl-halide-, pseudohalide, and -sulfonate derivatives is presented. The reaction proceeds in presence of CoBr₂ as catalyst, manganese as reductant and isopropanol as hydrogen donor in acetonitrile at room temperature or 50°C.