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A Simple Preparation of Alkylzinc Reagents Compatible with Carbonyl Functions

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Abstract. Herein, we report a direct and straightforward method to prepare alkylzinc compounds from functionalized alkyl bromides using cobalt catalysis under mild conditions. This procedure only requires a simple catalytic system composed of CoBr₂ and bipyridine as ligand in a mixture of acetonitrile/pyridine. This reaction is stable under air and moisture conditions opening the way to an easy and accessible procedure. A wide range of functional groups such as esters, cyano and halogens on primary and secondary alkyl bromides was well tolerated and gave high yields of the corresponding alkylzinc compounds. Additionally, we managed to form unprecedented alkylzinc reagents bearing sensitive functional groups such as ketones and aldehydes with good yields. The direct application of these alkylzinc derivatives in palladium-catalyzed Negishi cross-coupling with various functionalized aryl bromides proved the efficiency and robustness of this methodology.

Keywords: Carbonyl function; Cobalt-catalysis; Negishi cross-coupling; alkylzinc.

Organometallics are one of the most useful reagents in organic synthesis. In particular, organozinc compounds are very attractive for various transformations and have been extensively used in Negishi cross-couplings via Pd,^[1] Ni^[2] and more recently Co^[3] catalysis. The main advantage offered by organozinc reagents compared to other organometallics, such as Grignard reagents, is their excellent functional group compatibility both with organometallic species and with coupling partners that makes these compounds very attractive. For example, Baran^[4] recently reported the cross-coupling of dialkylzinc species with redox active esters, demonstrating that organozinc reagents are still powerful reagents of great interest. For several years, the synthesis of arylzinc compounds has been well studied throughout various methodologies.^[5] However, the lower reactivity of alkyl halides resulted in challenging synthetic pathways to form alkylzinc reagents. For this purpose, different

interesting strategies have been reported to prepare alkylzinc derivatives: the transmetallation, the halogen/metal exchange and the direct insertion of metallic zinc, which is the most widely employed method. However, most of them require strict anaerobic and anhydrous conditions. Firstly, Knochel demonstrated the formation of benzylic zinc chlorides^[6] and alkylzinc bromides^[7] by transmetallation of a Grignard intermediate in the presence of LiCl and ZnCl₂. However, the use of a Grignard reagent limits the tolerance of sensitive functionalities on the alkylzinc reagent. In order to overcome this drawback, a methodology for the stereoselective preparation of cyclic^[8] and acyclic^[9] diorganozinc derivatives through a boron-zinc exchange was reported to lead to enantiopure molecules.^[10] Alkylzinc reagents can also be prepared through a halogen/metal exchange strategy in the presence of Et₂Zn.^[11] Furthermore, the most used method to form organozinc halide species was firstly described by Rieke.^[12] This reaction involves the direct insertion of activated metallic zinc into a C-X bond even though primary alkyl bromides are usually reluctant to the direct insertion of zinc dust. A highly reactive metallic zinc was obtained by the lithium naphthalenide reduction of ZnCl₂ which requires strong conditions to achieve activated zinc.^[13] Efficient methods were also developed by Knochel to synthesize alkylzinc iodides and bromides^[14] as well as benzylic zinc chlorides^[15] by the direct insertion of commercially available zinc powder in the presence of LiCl in THF. This efficient methodology tolerates many functionalities and proceeds under mild conditions. However, the activation of the metallic zinc requires several steps under strict and inert conditions. At the same time, Huo^[16] reported the formation of alkylzinc bromides and chlorides by the direct insertion of metallic zinc activated with a catalytic amount of I₂, into alkyl bromides in a polar aprotic solvent **at high temperature**.^[17] This method is also efficient but necessitates the use of aprotic solvent, in particular DMF, which is not always compatible for cross-coupling reactions with alkylzinc reagents. The direct insertion strategy

requires multiple activation of metallic zinc under strict anaerobic and anhydrous conditions limiting the functional group compatibility.

In order to prepare stable and easy to handle organozinc reagents, our group reported in 2003 a direct and simple cobalt-catalysed preparation of arylzinc compounds from aryl bromides.^[18] This procedure occurs in the presence of a catalytic amount of a simple cobalt bromide salt in acetonitrile under atmospheric and mild conditions. Delighted to see the efficiency of this Co-catalysed methodology and its compatibility with various functionalized groups, we decided to expand it to less reactive alkyl bromide substrates. Therefore, in this paper, we describe a direct and straightforward procedure to prepare alkylzinc derivatives from the direct insertion of metallic zinc into alkyl halides in the presence of cobalt catalysis under air and moisture conditions.

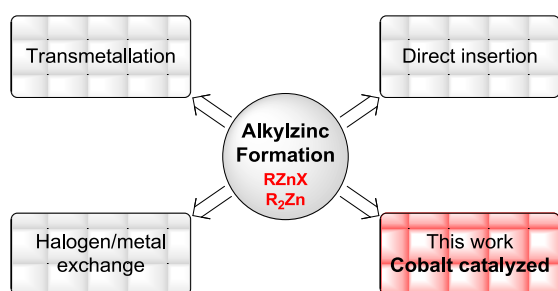
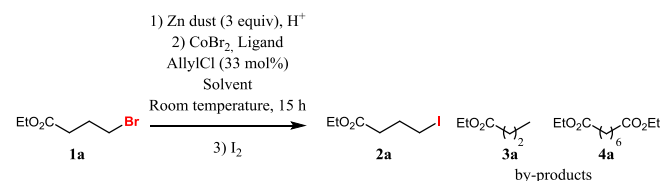


Figure 1. Methods to prepare alkylzinc reagents.

This investigation started by the optimization of the reaction conditions for the formation of alkylzinc compounds using ethyl-4-bromobutyrate (**1a**) as the model compound and solvents without regards to oxygen and water contamination. The yield of the organozinc (**2a**) formation is analysed after 16 h of reaction by gas chromatography after iodolysis of an aliquot, using decane as internal standard. The main expected by-products were the reduced product (**3a**) and/or the homocoupling product (**4a**).

First, similar experimental conditions previously described for arylzinc formation^[18] was attempted using 5 mol% of CoBr₂ without ligand in undistilled acetonitrile at room temperature under air. Unfortunately, no conversion of the starting material was detected (Table 1, Entry 1). No improvement was observed with distilled solvent. Different co-solvents were tested such as DMSO, DMF or THF and no conversion of **1a** was observed (Table 1, Entry 2 to 4). However, we were pleased to discover that the addition of pyridine in the acetonitrile media (MeCN/pyridine = 4:1 ratio) allowed the conversion of **1a** into **2a** with a good yield of 66% (Table 1, Entry 5), along with 2% of **3a**, 4% of **4a** and the remaining starting materials. Changing the ratio of the mixture MeCN/Py to 3:2 allowed a slight increase of the yield (74%) (Table 1, Entry 5 and 6) along with the same quantity of by-products.

Table 1. Optimization for the formation of alkylzinc



compounds.

Entry	CoBr ₂ (mol%)	Ligand (mol%)	Solvent (1.5 M)	Yield of 2a (%) ^a	Yield of 3a (%) ^a	Yield of 4a (%) ^a
1	5	/	MeCN	0	0	0
2	5	/	MeCN/ DMSO 4:1	0	0	0
3	5	/	MeCN/ DMF 4:1	0	0	0
4	5	/	MeCN/ THF 4:1	0	0	0
5	5	/	MeCN/Py 4:1	66	2	4
6	5	/	MeCN/Py 3:2	74	2	4
7	5	PPh ₃ 5	MeCN/Py 4:1	48	2	0
8	5	Phen 5	MeCN/Py 4:1	52	1	0
9	5	Bipy 5	MeCN/Py 4:1	56	0	0
10	5	PPh ₃ 10	MeCN/Py 4:1	55	2	0
11	5	Phen 10	MeCN/Py 4:1	73	2	0
12	5	Bipy 10	MeCN/Py 4:1	85 (64) ^b	0 (0) ^b	0 (0) ^b
13	5	Bipy 10	MeCN/Py 3:2	84	0	0
14	5	Bipy 10	MeCN	2	0	0
15	1	Bipy 2	MeCN/Py 4:1	81	0	0
16	10	Bipy 20	MeCN/Py 4:1	88	0	0
17	15	Bipy 30	MeCN/Py 4:1	92	0	0

7.5 mmol scale reaction. ^a) GC yield after iodolysis using decane as internal standard. ^b) Reaction performed without allylCl.

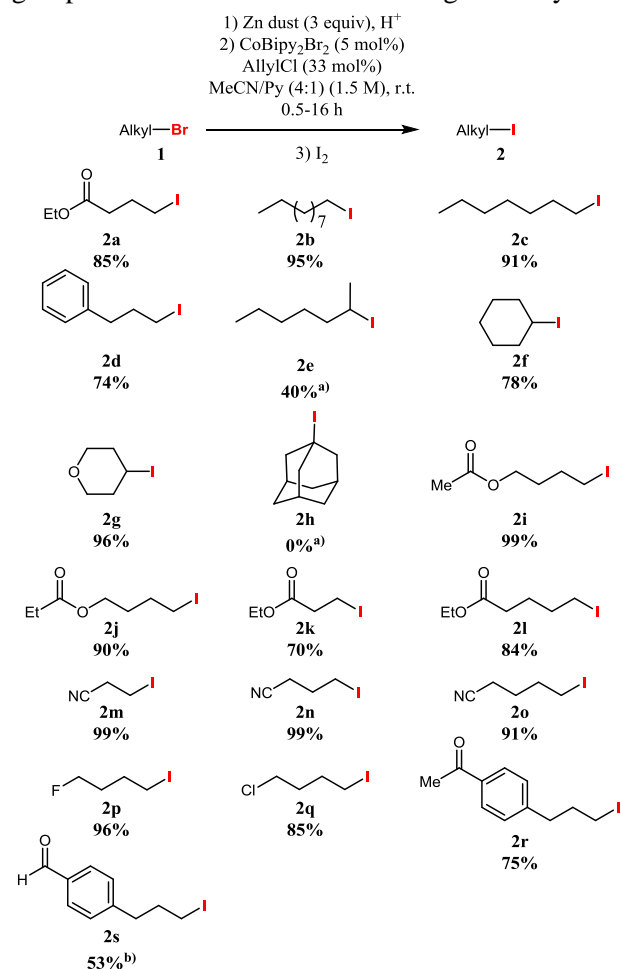
Then, the addition of a ligand into the catalytic system was investigated. With 1 equivalent per Co of PPh₃, phenanthroline or bipyridine, a slight decrease of the **1a** to **2a** conversion was observed (Table 1, Entry 7 to 9). However, this additional ligand seemed to prevent the formation of the reduced by-product **3a**. Therefore, the ratio of CoBr₂/ligand was modified from a ratio of 1:1 to 1:2 and afforded, in case of *N*-heterocyclic ligand, an increase of the conversion notably due to the absence of the reduced by-product **3a**. Thus, **2a** could be obtained with 73% and 85%

yields when phenanthroline or bipyridine were respectively used as ligand (Table 1, Entry 11 and 12). This catalytic system employing 5 mol% of CoBr_2 and 10 mol% of bipyridine gave similar yields in a 4:1 or 3:2 ratio mixture of MeCN/pyridine (Table 1, entry 12 and 13). However, the absence of pyridine in the reaction media completely inhibited the activity of the catalytic system leading to no conversion of **1a** which demonstrates the major importance of this co-solvent in the alkylzinc formation (Table 1, entry 14).

The pyridine seemed necessary for the conversion of the alkyl bromide and to stabilize cobalt intermediates in the catalytic cycle. This reaction was also attempted without allylchloride demonstrating a similar conversion of **1a** of 95%, however a decrease to 64% yield of **2a** was observed (Table 1, Entry 12 in brackets). No by-product **3a** and **4a** was observed by GC, the 31% of difference might correspond to decomposition products. Allylchloride seems to play a role of activating agent in this reaction and might help to avoid some decomposition. The role of pyridine and allylchloride in the mechanism was not exactly determined and further mechanistic investigations would be required to fully understand it. Although cobalt was necessary (See Table S3, Entry 1), decreasing the catalytic loading of the reaction to 1 mol% led to a similar yield of 81% (Table 1, Entry 15). However, reproducibility issues were observed. With no surprise, increasing the catalytic loading to 10 and 15 mol% gave higher yields, respectively 88% and 92% (Table 1, Entry 16 and 17). Finally, in order to decrease the reaction time, higher temperatures (40 °C or 80 °C) were tested and only decomposition was observed compared to room temperature (See Table S4).

With these optimized conditions in hand, the applicability of this methodology was investigated with various alkyl bromides (Scheme 1). The observed products were the corresponding alkyl iodides after iodolysis of the organozinc compound. We were delighted to see that the reaction tolerated a wide range of functional groups. Primary alkyl bromides gave high yields of the corresponding compounds (**2b** 95%, **2c** 91% and **2d** 75%). Pleas to see these excellent results, the reaction was attempted on secondary alkyls. With 2-bromoheptane, it was necessary to perform the reaction at 0 °C to prevent the decomposition of the starting material. We managed to obtain a moderate yield of 40% of the corresponding alkyl iodide compound (**2e**). However, when cyclic secondary alkyl bromides were used, higher yields were obtained (78% **2f** and 96% **2g**). The use of a tertiary alkyl bromide derivatives, such as 2-bromoadamantane, only led to the decomposition of the starting material even though the reaction was carried out at 0 °C (**2h**). This method was then applied on various bromo ester and cyano compounds (**2i** to **2o**) and led to the desired alkyl iodides with very good to excellent yields of 70 to 99%. It is noted that the length of the carbon chain had no real effect on the performance of the reaction. Moreover, the reaction tolerated very well other

halogens such as fluorine or chlorine which gave access to their corresponding alkyl iodides respectively with 96% (**2p**) and 85% (**2q**) yields. Finally, this methodology also allowed to reach organozinc bearing highly sensitive carbonyl-based functional groups. Indeed, ketone (**2r**) and aldehyde (**2s**) were very well tolerated and the corresponding alkyl iodides were synthesized with a moderate to excellent yields (53% and 75%). The high functional group tolerance of this original synthetic



methodology allowed the synthesis of unprecedented organozinc compounds bearing notably aldehyde moiety, opening a new pathway in cross-coupling reaction.

Scheme 1. Scope of alkyl iodides corresponding to alkylzinc compounds. 7.5 mmol scale reaction. GC yield after iodolysis. ^{a)} 0 °C. ^{b)} 15 mol% at 0.75 M.

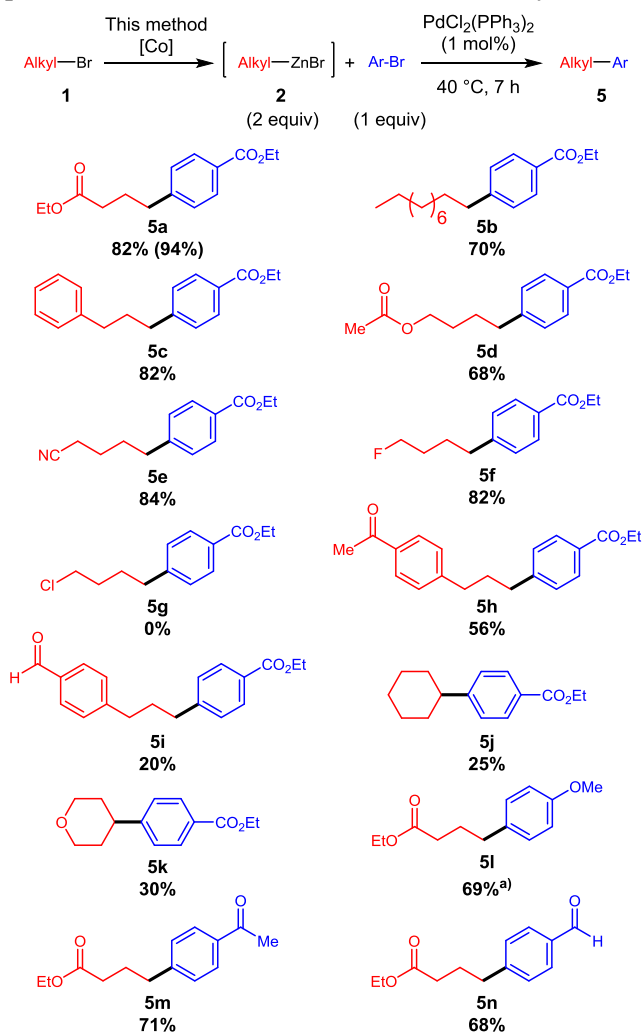
To prove the value of this methodology, these prepared organozinc reagents were engaged in classical reaction conditions of Negishi cross-coupling with aryl bromides (Scheme 2). In order to have a straightforward and simple method, we decided to directly introduce the aryl bromide cross-coupling partner and the palladium catalyst, $\text{PdCl}_2(\text{PPh}_3)_2$, into the crude mixture of the alkylzinc preparation without any addition of ligand, solvent or any treatment. The cross-coupling reaction was performed using a 2:1 ratio of alkylzinc reagent/aryl

halide with a very low catalytic loading (1 mol%) under mild conditions (40 °C). We were pleased to see the formation of the coupling product which demonstrated the compatibility of the cobalt-based catalytic system used for the formation of the alkylzinc with the palladium one employed for the Negishi cross-coupling.

Various functionalized alkylzinc derivatives were successfully coupled with the ethyl-4-bromobenzoate to give the corresponding coupling products in high yields (**5a** 82%, **5b** 70%, **5c**, 82%, **5d** 68%, **5e** 84% and **5f** 82%). However, the presence of chlorine atom on the alkylzinc seemed to inhibit the coupling reaction since only the unreacted starting materials were observed (**5g** 0%). Regarding the organozinc reagents bearing ketone and aldehyde moiety (**5h** and **5i**), we were also pleased to observe the corresponding coupling products. However, moderate and low yields were reached (56% and 20%), in this unoptimized Negishi cross-coupling reaction conditions. This could be due to the high sensitivity of the organozinc compound at 40 °C, leading to the degradation of these latter during the cross-coupling reaction which could certainly be avoided in other condition reactions. When a secondary alkyl was employed, surprisingly, the main product observed was the homocoupling product of the aryl bromide (75% and 70%), rather than the cross-coupling products which was isolated with moderate yields of

25% for **5j** or 30% for **5k**.

Scheme 2. Scope of the Negishi cross-coupling product. 3.75 mmol scale reaction. Isolated yields. GC yields in bracket. ^{a)} 80 °C.



Furthermore, both aryl bromides bearing an electro-withdrawing or -donating group were efficiently coupled with the alkylzinc reagent (**2a**) (**5a** 82% and **5l** 69%). In the same way as for the organozinc formation, aryl bromides bearing ketone and aldehyde substituents were well tolerated and the coupling products were successfully isolated in good yields (71% (**5m**) and 68% (**5n**)). This observation confirmed the high sensitivity of the organozinc compounds bearing aldehyde and ketone toward the temperature which will require deeper investigations of the Negishi cross-coupling reaction conditions.

In conclusion, we report a direct and simple cobalt-catalysed procedure to form alkylzinc compounds under mild conditions from alkyl bromides. This method tolerates broad functionalities such as esters, cyano and halogens, as well as primary and secondary alkyl bromide derivatives. This procedure also allows to access organozinc reagents bearing carbonyl functions. A key point of this method is its stability under air and moisture conditions making it easy and simple to handle. These alkylzinc demonstrated their applicability in Negishi cross-coupling with various substituted aryl bromides under palladium catalysis. This straightforward and robust methodology easily grants the access to functionalized molecules. Some mechanistic studies of the formation of the alkylzinc reagent are currently being investigated in order to understand the wide functional group tolerance of this methodology.

Experimental Section

General information: All solvents and reagents were used as received from commercially available suppliers (Acros Organics, Alfa Aesar, Fluorochem and Sigma Aldrich) without further purification unless otherwise noticed. Flash chromatography was performed using an Isolera Prime Biotage preparative chromatography machine equipped with UV detector and using pre-packaged Biotage silica column of 50 μm particle size. TLC were realized using TLC silica gel plates from Merck (60 F254) and visualized by UV detector and permanganate solution heated as developing agent. NMR spectra were recorded on a Bruker AC-300 SY spectrometer at 300 MHz for ^1H , 75 MHz for ^{13}C and 290 MHz for ^{19}F . Solvent peaks were used as internal references for ^1H and ^{13}C chemical shifts (ppm). Unless otherwise mentioned, NMR spectra were recorded at 300 K. The abbreviations used to indicate the multiplicity of signals are: s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintuplet), m (multiple) or a combination of the above. The coupling constants J were expressed in hertz. The spectra were analyzed with MestReNova software. Gas chromatography (GC) was performed on a Perichrom PR2100 2317 Series chromatogram equipped with a split mode, capillary injection system, flame ionization detector and an IDBP5 apolar SGE column (25 m x 0.33 mm). Mass spectrometry experiments were performed on a Tims-TOF mass

spectrometer (Bruker, France). Electrospray source has been used in positive and negative modes. Samples are prepared in acetonitrile with 0.1 % formic acid at μM concentration. 2 to 10 μL were introduced without separation with Elute UHPLC module (Bruker) at a 100 $\mu\text{L min}^{-1}$ flow rate into the interface of the instrument. Capillary and end plate voltages were set at 4.5 kV and 0.5 kV for ESI experiments. Nitrogen was used as the nebulizer and drying gas at 2 bar and 8 L min^{-1} , respectively, with a drying temperature of 220 $^{\circ}\text{C}$ for ESI source. Tuning mix (Agilent, France) was used for calibration. The IR analyses were performed with an FT-IR Nicolet IS5 spectrometer (Thermo Scientific) equipped with a Pike MIRacle module for ATR measurements in the spectral range from 4000 to 600 cm^{-1} and operated with the Omnic software for IR spectroscopy.

General procedure for alkylzinc formation: Zinc powder (1.5 g, 23 mmol, 3 equiv.), CoBr_2 (82 mg, 0.375 mmol, 5 mol%) and MeCN (4 mL) were vigorously stirred for 5 min. Then, allyl chloride (200 μL , 2.45 mmol, 33 mol%) followed by TFA (100 μL , 1.3 mmol, 17 mol%) were added. Reaction mixture was let to cool down to room temperature and pyridine (1 mL), bipyridine (117 mg, 0.75 mmol, 10 mol%) and alkyl bromide (7.5 mmol, 1 equiv.) were added. Reaction mixture was stirred at room temperature until full consumption of alkyl bromide. Reaction mixture was analyzed by gas chromatography after iodolize. Conversion and yields were determined by GC using decane as internal standard.

Iodolysis procedure: Iodine was introduced in a tube, heated to sublimation and cooled down to room temperature. Sample of the reaction mixture was poured on the sublimated iodine. EtOAc was added followed by a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$. Organic layer was passed through a pipette filled with silica and the sample was analyzed by GC.

General procedure of Negishi cross-coupling: Alkylzinc compounds were prepared using previous procedure. Aryl bromide (3.75 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (26 mg, 0.0375 mmol, 1 mol%) were added to the crude mixture of alkyl zinc and reaction mixture was stirred at 40 $^{\circ}\text{C}$ for 7 h. Then HCl solution (2 M, 20 mL) and EtOAc (20 mL) were added and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous MgSO_4 and concentrated under reduced pressure. Crude product was purified by flash column chromatography (PE/EtOAc) leading to the desired product.

Acknowledgements

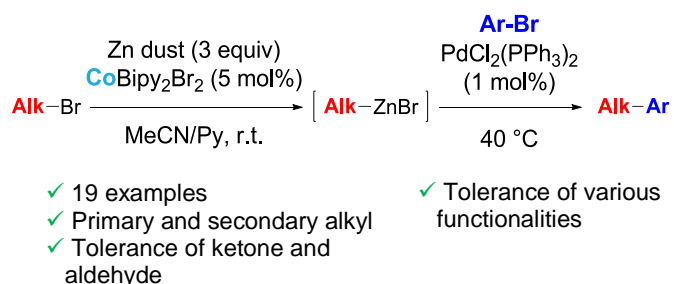
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