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Arylcalcium halides as substrates in Kumada-type cross-coupling reactions

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ABSTRACT

A precondition of a Kumada-type cross-coupling reaction with arylcalcium halides is the easy availability of these organometallics. Arylcalcium halides are accessible with high yields via reduction of arylhalides with activated calcium in ethers such as tetrahydrofuran. In order to demonstrate the generality of this Grignard-type reduction of haloarenes, $[(4\text{-BrC}_6H_4)CaI(thf)_4]$ (**1**) and $[(\beta\text{-naphthyl})CaBr(thf)_4]$ (**2**) are prepared. First investigations regarding arylcalcium halides as substrates in cross-coupling reactions are undertaken choosing $[(C_6H_5)CaI(thf)_4]$ (**3**) and $[(4\text{-CH}_3C_6H_4)CaI(thf)_4]$ (**4**) as the organometallic substrate in a cross-coupling with chlorobenzene and 4-chlorotoluene. The nickel-mediated conversion of arylcalcium iodides and chloroarenes to (substituted) biphenyls proceeds with moderate yields and significant amounts of homo-coupling products are observed.

1. Introduction

Calcium-based organometallics are currently gaining importance due to many factors [1]. First of all, suitable minerals for the calcium production are widespread and available in enormous quantities; guaranteeing its worldwide accessibility at low prices. Furthermore, the calcium cation is considered non-toxic regardless of its concentration [2], making calcium-based reagents and catalysts an interesting choice for the synthesis of drugs and other compounds with potential medical applications, since residual calcium contents in the products do not add health risks and therefore do not have to be removed. Consequently, calcium-based catalysis attracted much attention and led to the development of calcium-mediated hydroamination, hydrosilylation, hydrophosphanylation, and other catalytic processes in recent years [3].

The attractiveness of organocalcium reagents is also based on the low electronegativity (comparable to lithium leading to very heteropolar Ca—C bonds with a high reactivity) and the possibility of d-orbital participation (comparable to early transition metals with catalytic activity). In case of arylcalcium derivatives, improvements of the direct Grignard-type synthesis and refined protocols for subsequent derivatizations led to a tremendous development of their organocalcium chemistry [4].

In contrast to the related benzylcalcium and allylcalcium derivatives [5], the potential of arylcalcium reagents in organic syntheses remained almost uninvestigated. Only one example of a directed ortho-metalation reaction [6] and one of an oligomerization reaction of nitriles involving arylcalcium compounds have been briefly mentioned [7]. Here we investigate if arylcalcium halides can serve as substrates in nickel-catalyzed Kumada-type cross-coupling reactions. In general nickel-mediated cross-coupling reactions represent a powerful tool for the formation of C—C bonds involving sp^2- and also sp^3-hybridized carbon atoms [8,9]. Typically, in the presence of catalytic amounts of Ni^0 (or Pd^0) complexes the reaction of the Grignard reagent R-Mg-X with R′-X yields R—R′. The reaction mechanism of this Kumada-type coupling is discussed in detail in several general text books and reviews [10,11].

2. Results and discussion

2.1. Availability of arylcalcium halides

The use of arylcalcium halides as substrates in organic synthesis requires a straight forward approach to these calcium-based reagents. Although the synthesis of first derivatives via a Grignard-analogous reaction dates back to the beginning of the 20th century [12], reliable and easily applicable protocols based on those early results were just developed within the last decade [13] and recently refined to overcome existing limitations e.g. in case of halosubstituted polycyclic aromatic carbons as substrates [14].

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Finely divided calcium powders, generated by dissolution of the bulk metal in ammonia and subsequent reduction of the resulting solution to dryness, are nowadays commonly used and allow the synthesis of a variety of arylcalcium iodides and bromides [4]. Doubly metalated derivates are also accessible [15]. Chloroarenes are not suitable as substrates for Grignard-type reactions with activated calcium, in contrast to magnesium. THF and THP are the most commonly used solvents. In order to demonstrate the generality of this Grignard-type reduction of haloarenes, we prepared $[(4\text{-BrC}_6H_4)\text{CaI(thf)}_4]$ (**1**) and $[(\beta\text{-naphthyl})\text{CaBr(thf)}_4]$ (**2**) showing that even halogeno-substituted arylcalcium halides are accessible by this procedure (Scheme 1).

The molecular structures and numbering schemes of $[(4\text{-BrC}_6H_4)\text{CaI(thf)}_4]\cdot 0.5$ THF (**1**) and $[(\beta\text{-naphthyl})\text{CaBr(thf)}_4]$ (**2**) are depicted in Figs. 1 and 2. In contrast to the closely related derivatives $[(\alpha\text{-naphthyl})\text{Ca}(\mu\text{-Br})(\text{thf})_3]_2$ [16] and $[(\text{phenanthryl})\text{Ca}(\mu\text{-Br})(\text{thf})_3]_2$ [14b], compound **2** is monomeric in solid state as it was also observed for $[(C_6H_5)\text{CaBr(thf)}_4]$ [17] and $[(\text{phenanthryl})\text{CaBr(thp)}_4]$ [14b]. In **1** and **2**, the aryl group and the halide ion are trans-arranged due to electrostatic reasons. The structure of **2** contains a crystallographic mirror plane containing the naphthylcalcium-bromide fragment. The Ca—C bond lengths of 257.2 (6) and 256.9 (5) pm lie in the expected region [4].

For our first investigations regarding arylcalcium halides as substrates in cross-coupling reactions we have chosen $[(C_6H_5)\text{CaI(thf)}_4]$ (3) [17] and $[(4\text{-CH}_3C_6H_4)\text{CaI(thf)}_4]$ (**4**) [17] in order to limit side-reactions caused by any functional groups.

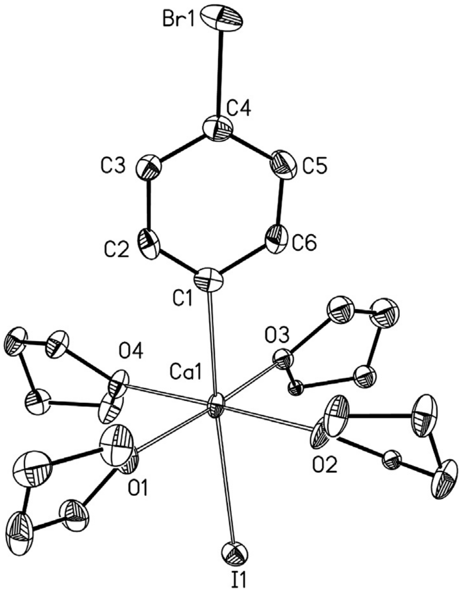


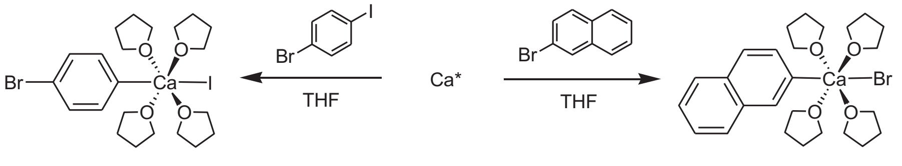
Fig. 1. Molecular structure and numbering scheme of $[(4\text{-BrC}_6H_4)\text{CaI(thf)}_4]\cdot 0.5$ THF (**1**). The ellipsoids represent a probability of 40%, H atoms are omitted for clarity reasons. In addition, the THF molecule in the gap between the calcium-based organometallics is neglected. Selected bond lengths (pm): Ca1—C1 257.2(6), Ca1—I1 311.81(12), Ca1—O1 238.2(4), Ca1—O2 235.0(4), Ca1—O3 243.3(9), Ca1—O4 239.7(4), Br1—C4 194.8(7); angle (deg.): C1—Ca1—I1 173.59(14).

2.2. Nickel-mediated cross-coupling reaction with arylcalcium iodides

In absence of a suitable nickel- or palladium-based catalyst, $[(C_6H_5)\text{CaI(thf)}_4]$ (3) does not react with chlorobenzene to form biphenyl in a Wurtz-type reaction (Table 1, entry 1). The corresponding experiment with iodobenzene (Table 1, entry 2) did not result in biphenyl formation either [18], although biphenyl was observed as a by-product in the synthesis of **3** in an earlier investigation [19]. In order to confirm this fact, the mother liquor of the synthesis of **3** was hydrolyzed, extracted with chloroform and analyzed by gas chromatography. Biphenyl and unreacted iodobenzene are the only high boiling by-products observed. Together with the above mentioned experiment, it can be concluded that this biphenyl formation is rather the result of a reaction of metallic calcium and iodobenzene than of a reaction between phenylcalcium iodide and iodobenzene. It is likely that its formation is closely related to the radical conditions of the Grignard-type reaction.

The catalytic coupling experiments were performed in 0.1M solution of the arylcalcium iodides $[(C_6H_5)\text{CaI(thf)}_4]$ (**3**) or $[(4\text{-CH}_3C_6H_4)\text{CaI(thf)}_4]$ (**4**) in THF with equimolar amounts of either chlorobenzene or 4-chlorotoluene. $[(\text{dppp})\text{NiCl}_2]$ [dppp = 1,3-bis(diphenylphosphanyl)-propane] was employed as the precatalyst (see Scheme 2 and Table 1).

Using 5 mol% of $[(\text{dppp})\text{NiCl}_2]$, the nickel-mediated homocoupling of phenylcalcium iodide with chlorobenzene as well as of 4-tolylcalcium iodide with 4-chlorotoluene gave conversion rates of 62% and 67% of the haloarenes after 24 h and yielded the corresponding symmetric products biphenyl and 4,4′-dimethylbiphenyl in yields of 56% and 52%, respectively. Although complete conversion of the halobenzenes was not anticipated because 10% of the arylcalcium reagent is expected to be consumed in the activation process of the precatalyst, the observed conversion is significantly lower than the achievable mark of 90%. A possible explanation is the known instability of arylcalcium reagents in THF at ambient temperature. It was reported that around 15% of tolylcalcium iodide decomposes within 24 h in THF at room temperature via solvent degradation reactions [14a]. The performed cross-coupling experiments of phenylcalcium iodide **3** with 4-chlorotoluene led to the formation of all possible biphenyl derivatives, namely biphenyl, 4-methylbiphenyl, and 4,4′-dimethylbiphenyl with a ratio of 23:23:5. In a complementary experiment, using **4** and chlorobenzene (see Table 1, entry 5), the three products were detected in a ratio of 7:32:21. In both cases, the desired product 4-methylbiphenyl is accompanied by large amounts of the homo-coupling product derived from the arylcalcium component of the reaction. Part of these homo-coupling products stems from the activation of the precatalyst $[(\text{dppp})\text{NiCl}_2]$ by arylcalcium iodide yielding $[(\text{dppp})\text{Ni(Ar)}_2]$ followed by the reductive elimination of biphenyls and formation of catalytically active Ni^0 species. The contribution of this activation reaction to the overall formation of homo-coupling products can be minimized by reduction of the catalyst loading. However, the



1

2

Scheme 1. Syntheses of **1** and **2**.