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An Opportunity for Mg-Catalyzed Grignard-Type Reactions: Direct Coupling of Benzylic Halides with Pinacolborane with 10 mol % of Magnesium

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Abstract: Mg in catalytic amounts as the only metal permits the reductive coupling between benzyl halides and pinacolborane. HBpin acts both as an electrophile and as a reducing agent to regenerate an organomagnesium species *in situ*. An hydride oxidation mechanism is proposed on the basis of DFT calculations.

The functionalization of organic halides with electrophiles mediated by Mg^0 (the Grignard reaction) is a ubiquitous process in organic chemistry.[1] Among mechanistic studies describing the nature of magnesium intermediate species,[2] there has not yet been, to our knowledge, any example describing such a reductive coupling in which the Mg^0 could be recycled, most likely because reduction of Mg^{II} species to Mg^0 is too energetically demanding. In the course of our studies on the reductive borylation of organic halides,[3] we found the first example of a Mg-catalyzed coupling reaction. We present here our results on the borylation of benzyl halides by pinacolborane (pinBH) in the presence of 10 mol % of Mg, as well as our hypothesis on its intriguing mechanism.

Boronic acids and esters are highly valuable reagents in organic synthesis, mainly as intermediates for the Suzuki−Miyaura coupling and other transition-metal-catalyzed C−C bond forming reactions.[4]

Access to organoboronic acids and their derivatives is classically carried out in two steps, involving the formation of Grignard or lithium reagents from the corresponding halides and their further reaction with trialkoxyboranes B(OR)$_3$ generally at low temperatures.[5] Alternative methods for the preparation of organoboronic esters are now available, based on transition-metal-catalyzed coupling reactions (using Pd, Ir, Rh, and Cu complexes) between organic halides and pinacolborane (HBpin)[6,7] or bispinacolatodiboron (pinB-Bpin).[8] The direct borylation of arenes benzylic C−H bonds with Ir or Rh complexes involving C−H activation is a very active field.[9,10]

Within the development of alternative electroreductive methods to access organoboronic acids and esters *via* the functionalization of organic halides with either trialkylborates or pinacolborane,[3] we investigated the possibility of using Mg^0 as the only metallic species involved. In a first approach using 1 equiv of Mg^0, the borylation of several aryl and benzyl halides with pinacolborane was carried out efficiently and led to the corresponding boronic esters in yields of 75−98%.[11] Interestingly, we found that, in several cases, the Mg metal was not completely consumed during the reaction, despite the total consumption of the organic halide. We therefore tested several reactions with catalytic amounts of Mg^0. In the case of benzyl chlorides and bromides, the reductive coupling could be carried out with only 2 to 10 mol % of Mg^0, as the only catalytic species! Optimization of this Mg-catalyzed reductive coupling process was carried out with 4-methylbenzyl bromide and pinacolborane in several solvents (THF, diethyl ether, THF−DMF mixtures) and different bases (NEt$_3$, *t*-BuOK, or 2,6-di-*tert*-butylpyridine). The best yields were obtained in refluxing THF with NEt$_3$ (Scheme 1).

Scheme 1. Preparation of Boronic Derivatives from Benzyl Halides Using Catalytic Amounts of Mg^0

$$\underset{\textbf{1a-k}}{\mathrm{ArCH_2X}} + \underset{\textbf{2}}{\mathrm{HBpin}} \xrightarrow[\mathrm{NEt_3(1\ equiv.)}]{\mathrm{Mg^0\ (10\ mol\%)}} \underset{\textbf{3a-k}}{\mathrm{ArCH_2Bpin}}$$

$$\mathrm{THF}$$

Table 1 presents the application of this Mg-catalyzed process to the synthesis of benzylboronic pinacol esters **3** from a series of benzylic halides **1** and pinacolborane.[12] Generally good conversions and yields were obtained. Very interestingly, the formation of benzylic dimers (Wurtz coupling) and of benzyl triethylammonium salts was avoided; the only byproduct was the reduced ArCH$_3$, easily removed from the reaction mixture.

4-Methylbenzylboronic pinacol ester **3a** was isolated in 92% yield using 10 mol % of Mg^0 (turnings, entry 1). With only 2 mol % of Mg^0, the coupling still proceeded efficiently and led to **3a** in 86% yield. The borylation of methyl- or alkyl-substituted benzyl bromides (entries 1−4) was carried out in good yields, although a lower efficiency was observed for the *ortho*-substituted substrate (entry 3).

The borylations of 4-chloro- or 4-bromo-benzyl bromide **1f** (respectively **1g**) were completely chemoselective, yielding **3f** and **3g** in respectively 90% and 88% yield (entries 6−7), without any reduction of the aromatic halide. The secondary benzyl bromide **1h** and chlorobenzyl derivatives **1i**−**1k** reacted smoothly, affording the boronic esters in 40−42% yields (entries 9−11).

The Mg catalytic borylation of **1a** was tested with several commercial Mg sources[13] to check whether transition metal impurities in the magnesium could influence the results. In all cases, the yields of **3a** were in the range 89−92%.

Mechanism. These results constitute, to our knowledge, the first example of a Barbier-type reaction carried out with recycling of the Mg species. They raise interesting questions on the mechanism. We have considered several hypotheses (Figure 1) that all begin with the formation of a boronate complex **C**[14] from borane **A** and benzylmagnesium bromide **B**. We confirmed the occurrence of **C** by ^{11}B NMR experiments ($\delta = -9.7$ ppm, $J = 86$ Hz).[11,15]

From **C**, several pathways can be proposed, and we performed DFT calculations[16] to support the discussion (Figure 1).

The calculated Gibbs energy for the formation of **C** itself through $\mathbf{TS_{(AB)C}}$ proceeded with a barrier of 8.6 kcal/mol, the step being exothermic by 10.5 kcal/mol.

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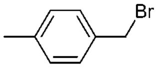
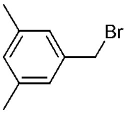
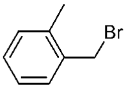
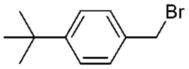
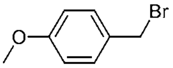
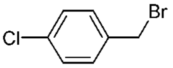
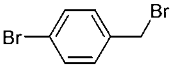
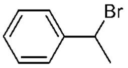
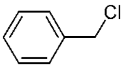
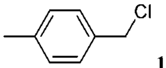
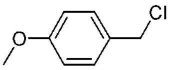
Table 1. Magnesium-Catalyzed (10 mol %) Borylation of Benzyl Halides **1** to Benzylboronic Pinacol Esters **3**[12]

entry	substrate	conditions	conv.	yield
1[a]	 **1a**	THF, reflux, 15 h	100%	92%
2	 **1b**	THF, reflux, 15 h	90%	85%
3	 **1c**	THF, reflux, 15 h	80%	62%
4	 **1d**	THF, reflux, 15 h	90%	76%
5	 **1e**	THF, reflux, 15 h	100%	75%
6	 **1f**	THF, reflux, 15 h	100%	90%
7	 **1g**	THF, reflux, 15 h	100%	88%
8	 **1h**	THF, 0°C, 15 h	40%	30%
9	 **1i**	DME, reflux, 24 h	42%	41%
10	 **1j**	DME, reflux, 24 h	42%	40%
11	 **1k**	DME, reflux, 24 h	41%	39%

[a] With only 2 mol % of Mg, yield of **3a** of 86%.

We considered first that **C** could yield HMgBr (**K**)[17] and the benzylboronic ester **G** (Figure 1, left-hand cycle, dotted lines). It is a slightly exothermic step, leading to **K** (associated with **G**) through transition state $\mathbf{TS_{(C)KG}}$ with a low 5.1 kcal/mol barrier. HMgBr **K** features a highly ionic H−Mg bond: NPA (Natural Population Analysis) charges are −0.83 e for Br, 1.55 e for Mg, and −0.71 e for H (compare with −0.79, 1.68, and −0.12 in boronate **C**, respectively).

But how could HMgBr **K** and benzyl bromide **D** regenerate the organomagnesium species **B**? Analogous with transition-metal chemistry, HMgBr in the presence of triethylamine could yield Mg^0 through reductive elimination. Nevertheless, the redox potential of Mg/Mg^{2+} (−2.37 V) makes this very unlikely. DFT calculations predict that the transformation from ($HMgBr + NH_3$) to ($Mg^0 + NH_4Br$) would be endothermic by 54 kcal/mol.[18]

Alternatively, reaction of HMgBr (**K**) and benzyl bromide **D** could lead directly to the formation of the organomagnesium species **B** and HBr (**F**) instead of the intuitively expected reduction (Figure 1, left-hand cycle). All attempts to find a calculated pathway for this direct reaction failed.[11] Instead, we actually came up with the hydride reduction of the benzyl bromide **D** to toluene **I** through $\mathbf{TS_{(K)I+J}}$ with a barrier of 20.2 kcal/mol. Thus, although the formation of HMgBr (**K**) is computationaly plausible, we did not find any solution involving this species that could account for the experimental outcome of the reaction.

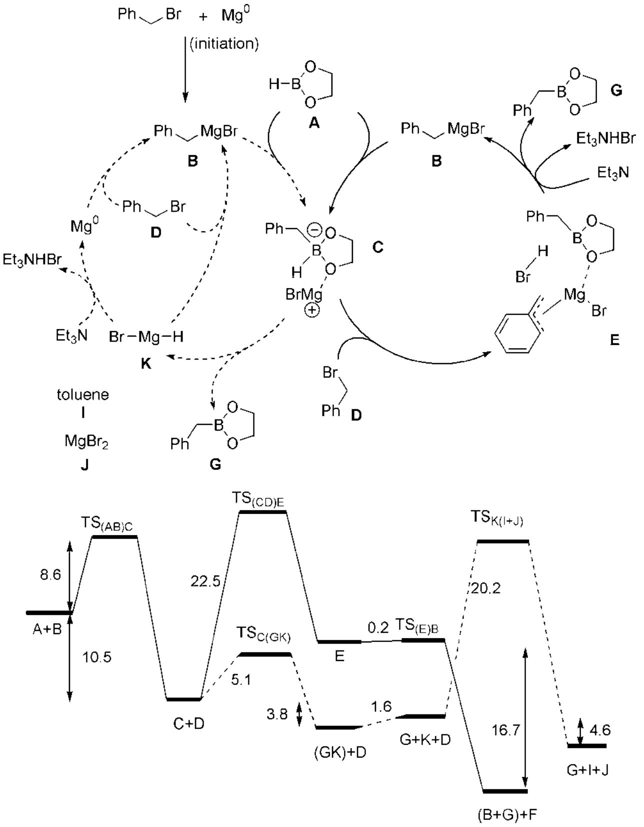


Figure 1. Hypotheses and corresponding DFT calculations for two hypothetic mechanisms of the Mg-catalyzed borylation of benzylic halides with pinacolborane. Dotted lines: mechanism through HMgBr **K**. Plain lines: direct reaction of boronate **C**. Values are Gibbs free energy (kcal/mol) calculated at the B3LYP/6-31G(d) level, with the PCM procedure for solvent effect.

We considered a third mechanism in which the regeneration of the benzyl organomagnesium reagent **B** could derive from the direct reaction of intermediate **C** with fresh benzyl bromide (Figure 1, right-hand cycle). This approach actually permitted the determination of a transition state $\mathbf{TS_{(CD)E}}$ leading to the formation of a new benzylmagnesium bromide **B** with a barrier of 22.5 kcal/mol, via intermediate **E** (Figures 1, 2).

During the transition **C** + **D** → **E** (Figure 1), the B−H bond breaks (4.60 Å in **E** compared to 1.26 Å in **C**) as well as the C−Br bond (2.88 Å in **E**, 2.01 Å in **D**), and the charge at H (initially bonded to boron atom) in **E** becomes +0.15 e. Then **E** proceeds exothermically by an almost barrierless rearrangement to the expected boronic ester **G**, phenylmagnesium bromide **B**, and HBr (trapped by triethylamine), thus closing the catalytic cycle.

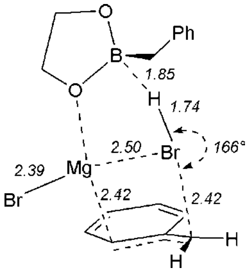


Figure 2. Transition state $\mathbf{TS_{(CD)E}}$.

Noticeably, in the transition state $\mathbf{TS_{(CD)E}}$ (Figure 2) the interaction of the Mg^{II} atom with the incoming benzyl bromide involves not only the coordination of Br to Mg and elongation of the C−Br bond but also a strong interaction of Mg^{II} with the benzylic system: Mg is very close to the *ortho*-phenyl carbon (C−Mg is 2.42 Å). Ionic interaction of the boronate with the Mg atom brings the electron pair of the B−H bond in close vicinity to the Br atom, facilitating the transfer of these electrons to Br with concomitant cleavage of the Br−C bond of the incoming benzyl bromide **D**.

Thus, in order to explain the unusual outcome of this new reaction, we propose a mechanism in which an unusual magnesium dialkoxy-alkyl-borohydride intermediate **C** reacts with a benzylic C−Br bond to form benzylmagnesium bromide instead of toluene. When confronted with DFT calculations, this hypothesis led to the experimentally obtained products through a coherent reaction pathway.

In conclusion, a novel catalytic, extremely simple, direct, efficient, and clean one-step procedure for the preparation of benzylboronic pinacol esters from the corresponding halides and pinacolborane in the presence of Mg^0 has been developed, without the need of any transition-metal catalyst. We explored an exciting example in which the association of pinacolborane and Mg^0 allowed the catalytic coupling of benzyl halides to benzyl boronic esters with the *in situ* recycling of the organomagnesium species, generally used in 10 mol %. The double activity of pinacolborane as an electrophile and as a reducing agent constitutes an interesting feature in the field of Grignard reagents and in organoboron chemistry. The illustrated possibility of carrying out "catalytic Grignard-type" reactions opens the field for further analogous developments in catalysis using inexpensive and simple metal catalysts, of particular interest in large-scale syntheses.

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Supporting Information Available: Full calculation data (pathway for protolysis, additional calculations for alternatives, and Cartesian coordinates), ^{11}B NMR experiments, and characterization of benzylboronic esters. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) See Supporting Information.

(12) General borylation procedure: Magnesium (turnings, 0.1 mmol) in distilled THF (10 mL), the benzyl halide (1 mmol), triethylamine (1 mmol), and pinacolborane (1 mmol) were successively introduced in a round-bottom flask under a nitrogen atmosphere. The solution was stirred for 15 h at reflux. The crude mixture was hydrolyzed and extracted with diethyl ether. The organic layer was washed with water and dried with $MgSO_4$. After solvent evaporation, the benzylboronic pinacol ester was purified by silica gel chromatography.

(13) Mg Turnings (Prolabo, 99.8%) were successively rinsed with 0.1 M aqueous HCl, water, 0.1 M aqueous HCl, water, and acetone and then dried in an oven at 70 °C. Magnesium powder (Alfa, 99.6%,−100 +200 mesh) was used as received. Both Mg sources gave similar results.

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