Magnesium-catalyzed hydroboration of terminal and internal alkynes

Marc Magre, Bholanath Maity, Alban Falconnet, Luigi Cavallo* and Magnus Rueping*

Abstract: A magnesium-catalyzed hydroboration of alkynes providing good yields and selectivities for a wide range of terminal and symmetrical and unsymmetrical internal alkynes has been developed. The compatibility with many functional groups makes this magnesium catalyzed procedure attractive for late stage functionalization. Experimental mechanistic investigations and DFT calculations reveal insights into the reaction mechanism of the magnesium catalyzed protocol.

The synthesis of organoboron compounds is an important task due to the facile conversion of carbon-boron bonds into various carbon-carbon and carbon-heteroatom bonds.[1] In particular, transition-metal catalysis has emerged as an important synthetic strategy for the synthesis of vinylboranes through the hydroborylation of alkynes. Although precious transition-metals have played an important role in achieving the borylation of unsaturated bonds,[2] the use of more earth-abundant metals has attracted considerable attention in recent years.[3-6]

In this context group 2 alkaline-earth metals such as magnesium and calcium are among the most abundant metals in the earth's crust. However, their application in homogeneous catalysis has been scarce. Regarding the functionalization of alkenes and alkynes, the application of group 2 metals has been mainly focused on the inter- and intramolecular hydroaminations of activated alkenes, using Ca^{II}, Sr^{II} and Ba^{II} as catalysts.[7]

Regarding hydroboration of unsaturated bonds, in the last decade, diorganomagnesium catalysts have emerged as an alternative for the hydroboration of polarized unsaturated bonds in aldehydes, ketones, esters, imines, nitriles, sulfones and pyridines, among others.[7-8]

Magnesium-hydride species remained unknown until 2010, when Jones and Stasch reported the first structurally characterized Mg-hydride complexes.[9] Since then, many efforts have been made to fully understand the alkaline-earth metal hydride chemistry and their application to catalytic transformations in which a metal-hydride center is involved.[10]

Although the magnesium hydroboration of polarized unsaturated bonds has been widely studied, to the best of our knowledge, there is no example in the literature describing the Mg^{II}-

catalyzed hydroboration of non-polarized unsaturated carbon-carbon bonds.[11] Herein, we report an efficient method for the synthesis of vinyl boranes *via* a $MgBu_2$-catalyzed hydroboration of terminal and internal alkynes (Scheme 1).
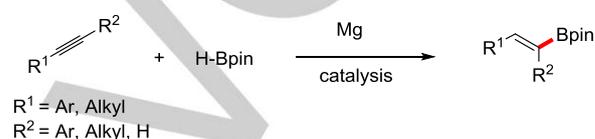
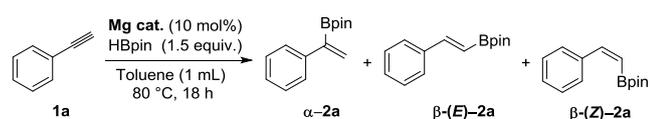**Scheme 1.** Magnesium-catalyzed hydroboration of terminal and internal alkynes.

We began our investigations of the magnesium catalyzed hydroboration of phenyl acetylene **1a** by evaluating the catalytic activity of readily available $MgBu_2$ in the presence of **L1** and **L2** diketimine ligands[12] (Table 1).
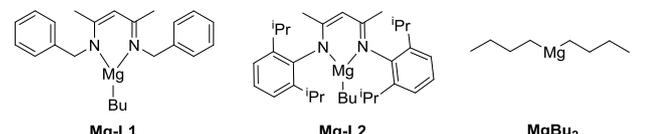
Performing the reaction with ligand **L1** in toluene at 80 °C afforded the corresponding β-(*E*)-vinyl borane **2a** in moderate yield and excellent selectivity (Table 1, entry 2). When ligand **L2** was tested, the product β-(*E*)-**2a** was obtained in higher yield (Table 1, entry 2 *vs* entry 7). To our surprise, use of $MgBu_2$ as the catalyst proved to be more active than the corresponding **L1-Mg** and **L2-Mg** complexes (Table 1, entry 8).[13-14] Finally, by decreasing the catalyst loading (7 mol%) and increasing the concentration, the desired β-(*E*)-vinyl borane **2a** was obtained in 83% yield (Table 1, entry 10).

With the optimized reaction conditions in hand we explored the scope and limitations of this alkaline-earth metal catalyzed hydroboration of terminal alkynes (Table 2). We started investigating different phenyl acetylene derivatives and were pleased to see that substituents with different electronic properties on the aromatic ring (**1a-1g**) did not influence the catalytic activity. It is worth mentioning the good yield attained for the hydroboration of phenyl acetylene derivative **1g**, containing an amino group. We assume that $MgBu_2$ shows milder reactivity compared to the corresponding aluminium catalyst, which failed in the hydroboration of **1g**-type alkynes.[5] We also observed that the presence of different substituents in the *ortho*-position of the aromatic ring (**1h-1m**) did not decrease the good yields.

Next, we studied the scope of the transformation by applying terminal alkynes bearing alkyl substituents (**1n-1r**), which behaved similarly to the corresponding phenyl acetylene derivatives. When increasing the steric demand on the alkyl substituent (**1n-1q**), the yields were maintained.

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        Supporting information for this article is given via a link at the end of
        the document.

Table 1. Optimization of Mg-catalyzed hydroboration of phenyl acetylene.[a]

Entry	Catalyst (mol%)	Solvent	Selectivity β-(E)-2a (%)[b]	Yield (%)[c]
1[d]	Mg-L1 (10)	Toluene	>99	10
2	Mg-L1 (10)	Toluene	>99	55
3	Mg-L1 (10)	THF	n.d.	<5
4	Mg-L1 (10)	Hexane	>99	37
5	Mg-L1 (10)	Cyclohexane	>99	52
6	Mg-L1 (10)	MTBE	>99	47
7	Mg-L2 (10)	Toluene	>99	74
8	MgBu₂ (10)	Toluene	>99	80
9[e]	MgBu₂ (10)	Toluene	>99	88
10[e]	**MgBu₂ (7)**	**Toluene**	**>99**	**86 (83)**
11[e]	MgBu₂ (5)	Toluene	>99	50
12	-	Toluene	n.d.	<5

[a] MgBu₂ (1M in heptane) (10 mol%), L1 or L2 (12 mol%), phenyl acetylene (1a, 0.5 mmol), 1.5 equiv. of HBpin, solvent (1 mL, 0.5M), at 80 °C for 18 h. [b] Determined by GC and ¹H NMR spectroscopy. [c] Determined by GC using n-dodecane as internal standard. Yield after isolation in parentheses. [d] Reaction at 60 °C. [e] 1M reaction concentration.

We also observed that even hydroboration of terminal dialkyne **1s** took place smoothly, providing **2s** in good yield. Finally, we tested the efficiency of the Mg-catalyzed hydroboration of terminal alkynes **1t-1v** containing functional groups. Importantly, the iPr₃Si-group as well as hydroxyl groups were well tolerated, affording the corresponding vinyl borane **2t-v** in good yields. Thus, the magnesium-catalyzed protocol is rather general and provides good yields and selectivities in the the hydroboration of a wide range of terminal alkynes, bearing different aromatic as well as alkyl substituents. In addition, different functional groups are tolerated under the mild reaction conditions which could not be afforded with other catalysts reported in the literature.[4-5]
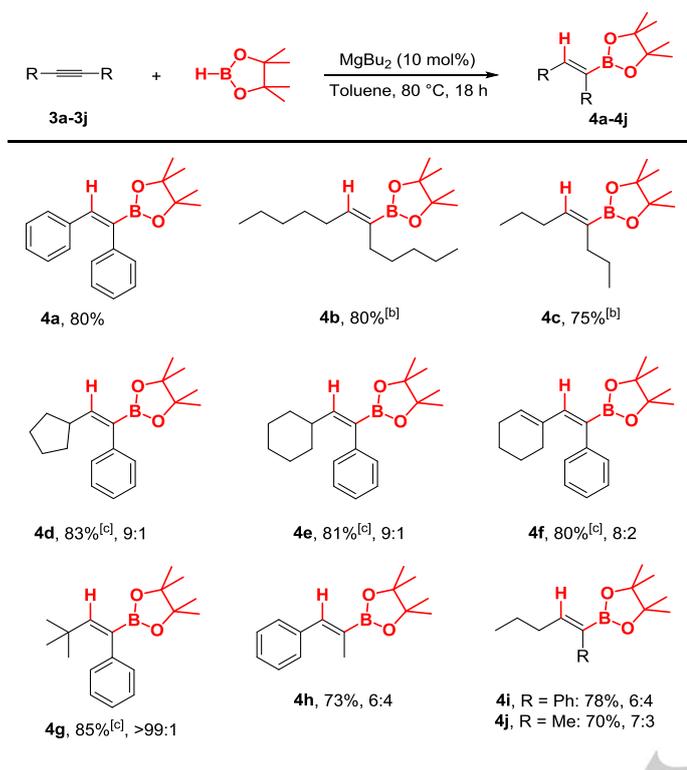
In order to further expand the substrate scope, we decided to examine the Mg-catalyzed hydroboration of internal alkynes (Table 3). We started our investigation by testing symmetric alkynes as model substrates. In this case, slightly higher catalyst loading (10 mol%) and in some cases longer reaction times were required to achieve good yields for diaryl and dialkyl alkynes **3a-3c**.

Table 2. MgBu₂-catalyzed hydroboration of terminal alkynes.[a]

[a] Reaction conditions: **1a-1v** (1 mmol), 1.5 equiv. HBpin, MgBu₂ (7 mol%), toluene (1 mL), 80 °C for 18 h. [b] 2.5 equiv. of HBpin. Yields after purification.

We also tested challenging unsymmetrical alkynes **3d-3j**, which can feature problems of regioselectivity, leading to a mixture of α- and β-vinyl boranes. We were delighted to see that MgBu₂ can successfully catalyze the hydroboration of internal aryl-alkyl alkynes **3d-3g** leading to α-vinyl boranes **4d-4g** with regioselectivities from 8:2 to >99:1.[15] It is interesting to note that the corresponding aluminum-hydride species were not able to hydroborate this type of unsymmetrical internal alkynes.[4,5,16] Moreover, and in contrast to sterically hindered alkynes **3d-3g**, the predominant regioisomer for the hydroboration of less bulky internal alkyne **3h** is the β-vinyl borane. Furthermore, by replacing a methyl with an n-propyl group (**3h** vs **3i**), the regioselectivity is inverted, meaning that the size of the alkyl substituent plays a dominant role in controlling the regioselectivity.

**Table 3.** MgBu$_2$-catalyzed hydroboration of internal alkynes.[a]

4a, 80%

4b, 80%[b]

4c, 75%[b]

4d, 83%[c], 9:1

4e, 81%[c], 9:1

4f, 80%[c], 8:2

4g, 85%[c], >99:1

4h, 73%, 6:4

4i, R = Ph: 78%, 6:4
4j, R = Me: 70%, 7:3

[a] Reaction conditions: **3a-3j** (1 mmol), 1.5 equiv. HBpin, MgBu$_2$ (10 mol%), toluene (1 mL), 80 °C for 18 h. Regioselectivities determined by ^{1}H NMR spectroscopy; [b] 70 °C; [c] 48 h. Yields after purification.

In order to gain a better understanding of the reaction mechanism we performed DFT calculations at the M06/Def2-TZVPP//BP86/Def2-SVP level of theory (for computational details see Supporting Information). Phenylacetylene **1a** and diphenylacetylene **3a** were used as terminal and internal alkynes, respectively. In case of **1a** two alternative pathways were considered (Scheme 2): i) *mechanism A*, starting with reaction of MgBu$_2$ with the terminal C–H bond of **1a** to give the active species **A**, and ii) *mechanism B*, starting with reaction of MgBu$_2$ with HBpin to give the active species **B**. The energy profiles for formation of the active species **A** and **B** are displayed in the Supporting Information (Figure S1 and S2). The highest activation barrier for the formation of the active species **A** is 25.4 kcal/mol (Figure S1), while the highest activation barrier for formation of the active species **B** is only 8.9 kcal/mol (Figure S2). This indicates that formation of **B** is remarkably favored over formation of **A**.

Mechanism A starts with exergonic coordination of two HBpin molecules to **A**. The resulting intermediate **A$_2$** undergoes hydroboration of the C≡C bond, with one of the coordinated HBpin molecules, via the [2σ+2π] addition type transition state **[A$_2$-A$_3$]‡** (Figure 1 for geometry). This step has an activation free energy of 36.5 kcal/mol (Figure S3), leads to the vinyl intermediate **A$_3$**, and it is exergonic by 8.6 kcal/mol. Substitution

of the second HBpin molecule of **A$_3$** by a **1a** molecule triggers deprotonation of **1a** via transition state **[A$_4$-A$_5$]‡**, leading to intermediate **A$_5$** with a moderate free energy barrier of 25.0 kcal/mol from **A$_3$**. The product is liberated from **A$_5$** to regenerate the active species **A**. Roesky[4] proposed a similar mechanism for the aluminum catalyzed hydroboration of terminal alkynes.

Within *mechanism B* the reaction starts with hydrometalation of **1a** by the active species **B**, which leads to the Mg-vinyl intermediate **B$_1$**, 24.2 kcal/mol lower in energy. This step requires a free energy barrier of 20.2 kcal/mol to overcome transition state **[B-B$_1$]‡**. The next step consist in nucleophilic migration of the vinyl group to the boron atom of the coordinated HBpin, to give the zwitterionic intermediate **B$_2$**, 4.9 kcal/mol more stable than **B$_1$**. Thereafter, reverse hydride migration from boron to magnesium generates **B$_3$**. The significantly lower energy barriers of 8.2 and 5.8 kcal/mol connected to transition states **[B$_1$-B$_2$]‡** and **[B$_2$-B$_3$]‡** suggest that the successive vinyl migration and reverse hydride migration are easy. Finally, the product is liberated from **B$_3$** to regenerate the active catalyst **B** for the next catalytic cycle.
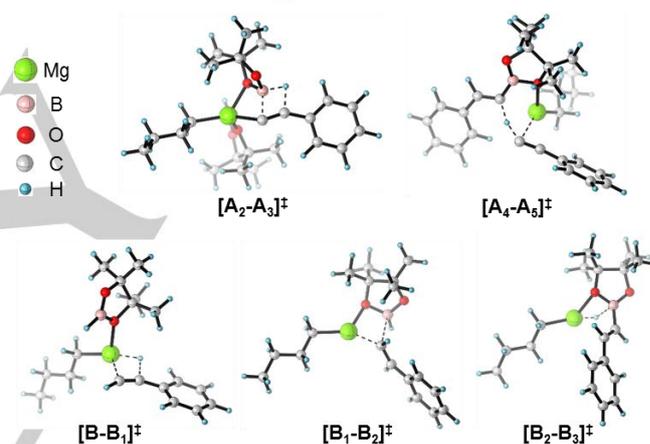
Figure 1. Optimized geometries of transition states involved in *mechanism A* and *mechanism B* for **1a**.

Comparison of the energetics of active species formation from MgBu$_2$, and of the reactivity within the catalytic cycles reveals that *mechanism B* is favored over *mechanism A*, both at the level of active species formation ($\Delta\Delta G^‡$ is 16.5 kcal/mol) and within the cycle ($\Delta\Delta G^‡$ is 16.3 kcal/mol). Moreover, while *mechanism A* can only explain the reactivity of terminal alkynes, *mechanism B* has the advantage of explaining the reactivity of both, terminal and internal alkynes. Finally, to assess the viability of *mechanism B* for the hydroboration of internal alkynes, we investigated the hydroboration of the internal alkyne **3a**, which resulted in a smooth energy profile, similar to that calculated for **1a** (Figure S5).

Scheme 2. Proposed mechanism for the MgBu$_2$-catalyzed hydroboration of terminal alkynes. Catalytic cycle for the active catalyst **A** represented by **_mechanism A_** while catalytic cycle for active catalyst **B** is represented as **_mechanism B_**. In parenthesis the relative free energies (in kcal/mol) of intermediates with respect to active catalysts **A** and **B** as 0.0 kcal/mol are presented. In square bracket, the activation free energy barriers for the corresponding steps are given.

To support _mechanism B_, a series of stoichiometric and catalytic experiments were performed (Scheme 3). When MgBu$_2$ was mixed with HBpin, the formation of Bpin-Bu was observed, corroborating the presence of the active species **B** (Scheme 3a). When equimolar amounts of phenylacetylene **1a** were added (Scheme 3b), quantitative yield of the desired product was detected.

Stoichiometric Experiments

a) Formation of BuMgH active species

b) BuMgH active species: mechanism B

c) Reaction of MgBu$_2$ with 1a

d) Conversion of A to the BuMgH

Scheme 3. Control experiments for mechanistic study.

Furthermore, when a 1:1 mixture of MgBu$_2$ and **1a** was prepared, species **A** was observed at 23°C (Scheme 3c), in line with the DFT results (Figure S1). However, treatment of **A** with 5 equiv. HBpin provides the BuMgH as indicated by the NMR spectra (Scheme 3d), which is in agreement with the DFT calculations for the interconversion of **A** into **B** (Figure S6). Therefore, these

stoichiometric experiments indicate that **B** is the active catalyst and _mechanism B_ is operative instead of _mechanism A_.

In summary, we report an active and selective system for the hydroboration of terminal and internal alkynes and demonstrate that commercially available MgBu$_2$ is an active catalyst for achieving good yields and selectivities under relatively mild reaction conditions and low catalyst loadings (7-10 mol%). The developed Mg-catalyzed hydroboration of alkynes shows tolerance for functional groups, making this transformation very attractive for late stage functionalization. Moreover, mechanistic studies employing DFT calculations together with experiments show that the hydroboration of alkynes takes place through the hydrometalation of an _in situ_ formed BuMgH species, followed by Mg/B exchange, regenerating the active BuMgH species and releasing the corresponding vinylborane product. Based on the experimental results and mechanistic insights we anticipate the development of further new magnesium catalyzed C-H-functionalizations.

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[14] For the first time, MgBu$_2$ hydroboration of unsaturated bonds is reported without the use of ligand.

[15] Usually alkylphenylacetylenes tend to produce β-vinylboranes. In our case, bulky alkyl substituted internal alkynes provided selectively the α-regioisomer, whereas less bulky alkyl substituents provided the β-vinylborane as the predominant regioisomer (with reduced regioselectivity).

[16] The aluminum-dihydride species reported by Yang, Parameswaran and Roesky *et al.* (ref. 4) did not succeed in the hydroboration of internal alkynes. The DIBAL-H / AlEt$_3$·DABCO reported by Thomas and Cowley *et al.* (ref. 5) were applicable to symmetrical and unsymmetrical alkyl-alkyl internal alkynes, but not to aryl-alkyl internal alkynes.

COMMUNICATION

MgBu$_2$ proved to be an efficient catalyst for the hydroboration of terminal and internal alkynes, achieving **good** yields and selectivities, competing with the best reports in the literature. The compatibility with many functional groups makes the Mg-catalyzed hydroboration of alkynes very attractive as a late stage functionalization protocol. Moreover, experimental investigations together with DFT calculations provide insight into the reaction mechanism.

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