Magnesium complexes in hydroelementation and reduction catalysis: 
Opportunities and Challenges

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Abstract:

The addition of a Y-H (Y= B, Si, Sn, N, P and O) bonds and H₂ to unsaturated bonds is a powerful and atom economic method for the synthesis of fine chemicals. In the recent years, magnesium-based organometallic complexes have appeared as an alternative to transition metal catalysts for the hydrofunctionalization and hydrogenation of unsaturated systems. This review focuses on the progress of magnesium catalysis for the hydrofunctionalization and hydrogenation of unsaturated bonds, provides a critical assessment of the state-of-the-art research, highlights the major developments achieved in the past three years and provides an overview of the challenges and opportunities.

Keywords:
sustainable catalysis, green chemistry, magnesium, hydroboration, hydrosilylation, hydrogenation,

1. Introduction:

In the last decade, the application of the group 1 and group 2 metal complexes in the hydroelementation and hydrogenation of unsaturated systems has evolved rapidly.[1] Fueled by the magnesium abundance in the Earth’s crust [2], the interest in research of magnesium in catalytic processes has increased tremendously. [3] Magnesium-based organometallic complexes are known to be very reactive due to their high nucleophilic character and Brønsted basicity, thus providing the basis for their applicability as catalysts for organic transformations that are traditionally catalyzed by transition metal complexes, which can be expensive, toxic and environmentally harmful. Although the use of magnesium complexes in hydrofunctionalization catalysis has increased in the last decade, their application is often limited due to their tendency to undergo Schlenk-type equilibrium, which leads to catalytically inactive species.[4] With regard to catalyst design, sterically demanding monoanionic ligands have been used for the stabilization of alkaline-earth abundant metals. Particularly, β-
diketimine ligands [5] have been widely employed in group 2 metal catalysis as their sterically demanding ligands tend to suppress any kind of ligand redistribution. As a result of the +2 oxidation state, magnesium [6] complexes are proven not to undergo oxidative addition and reductive elimination processes as often observed the transition metal catalysis. Therefore, their general reactivity is typically based on redox-neutral reaction pathways.[7,8] This review highlights the recent advances in the field and describes the progress made within the past three years. We have organized this review depending on the nature of the magnesium catalyzed Y-H bond forming reactions, involving hydridic reagents used in the hydroboration and hydrosilylations; protic Y-H reagents used in the hydrophosphination and less studied hydrofunctionalizations including hydrostannation, hydroalkoxylation as well as hydrogenation reactions.

2. Hydroboration of unsaturated bonds

2.1 Hydroboration of carbonyl compounds

Hydrometallations belong to the most important reactions and are frequently used in synthesis and catalysis to functionalize carbonyl groups, their derivatives as well as olefins. Although the magnesium-catalyzed hydrometallation of unsaturated bonds was not the first heterofunctionalization reported, it has become one of the most frequently studied reactions. [9] In the following we describe the recent advances on the magnesium-catalyzed hydroboration of polarized (C=O and C=N) and non-polarized unsaturated bonds (C=C and C≡C) and start with the hydroboration of carbonyl compounds (Figure 1a). A comparative study of hydroboration of p-methoxybenzaldehyde using N-adamantyl-iminopyrolyl complexes 1-5 with group 1 and group 2 metals was carried out by Panda et al. (Figure 1b) [10]. The study showed that both magnesium 4 and calcium 5 complexes exhibited good reactivity. However, group 1 analogues (1-3) displayed a better performance. Based on earlier work by Stasch et al. who introduced magnesium(I) complexes [11,12], Ma et al. prepared a series of unsymmetrical β-diketiminato-magnesium (I) complexes 6-8 (Figure 1c) for the hydroboration of aldehydes and ketones under mild reaction conditions.[13] The authors also proposed that dimeric Mg(I) complex 8 reacts with HBpin to form a dimeric magnesium boryloxide complex 9, which then reacts with another molecule of HBpin providing the catalytically active Mg(II)-complex 10. Given that β-diketiminato complexes can be easily tuned which is highly relevant for catalyst optimization, Vanka, Sen, et al. incorporated a pyridyl moiety in the ligand backbone to further stabilize the alkaline earth metal. β-Diketiminate-magnesium and calcium complexes 11 and 12 were subsequently tested in the hydroboration of aldehydes and ketones (Figure 1d) [14] and provided improved catalytic activity. Interestingly, DFT calculations suggest that the pyridyl moiety is responsible for HBpin activation. While these initial studies relied on new Mg-complexes and thoughtful ligand design, Rueping et al. applied readily available MgBu2 13 as an efficient catalyst for the chemoselective hydroboration of α,β-unsaturated ketones (Figure 1e) [15]. Compared to the other Mg-complexes previously applied for hydroboration of α,β-unsaturated compounds [16,17], dibutyl magnesium MgBu2 13 provided better conversions in shorter
Recently, Grignard reagents such as MeMgBr (14) have also effectively been applied by Ma et al. in the hydroboration of aldehydes and ketones.[18]

Figure 1. Mg-complexes in the hydroboration of aldehydes and ketones.
2.1.1 Catalytic enantioselective hydroboration of carbonyl compounds

The use of chiral Mg-complexes in asymmetric catalysis is still rare. The first example of enantioselective magnesium catalyzed hydroboration of prochiral ketones was reported by Rueping et al. using the Mg-BINOL complex 15.[19] The in situ formed catalyst from MgBu₂ and 3,3-disubstituted BINOL derivatives provided excellent yields and enantioselectivities for a range of acetophenone and 1-indanone derivatives (Figure 2). Moreover, catalyst 15 could also be applied for the hydroboration of α,β-unsaturated ketones, with exclusive 1,2-addition, achieving excellent enantioselectivities in the reduction of enones as well as yrones. Similarly, Gade et al. developed Mg-boxmi complex 16 (boxmi = bis(oxazolinyl-methylidene)-isoindoline) for the asymmetric hydroboration of a wide range of acetophenone derivatives (Figure 2) [20]. Mechanistic investigation provided insight into the activation mode. While both studies describe a Mg-coordination to the hydride donor HBpin to facilitate the hydride transfer, the study involving the chiral Mg-BINOL complex was proposed to occur via a metal-ligand cooperative activation [19] while a zwitterionic Mg-hydridoborate was suggested for the Mg-boxmi complex.[20] These studies clearly demonstrate the applicability of chiral Mg-complexes in asymmetric hydrofunctionalizations and provided first insights into the activation mode. However, the procedures have still substantial limitations regarding the substrate scope and applicability and better mechanistic understanding is required.

![Mechanistic insights: HBpin activation](image)

![Mg-BINOL cooperative activation](image)

![Zwitterionic Mg-hydridoborate](image)

Figure 2. Enantioselective Mg-catalyzed hydroboration of carbonyl compounds.
2.2 Magnesium catalyzed hydroboration of esters, nitriles, carbonates, carbamates, and carbon dioxide

Following the successful hydroboration of ketones and aldehydes, the groups of Ma and Rueping group extended the magnesium-catalyzed protocols to the hydroboration of more challenging carbonyl compounds such as esters, nitriles, carbonates, carbamates and carbon dioxide (Figure 3).

Ma et al. applied the dimeric Mg(I)-complex 7 to the hydroboration of nitriles.[13] A wide variety of aliphatic and aromatic nitriles was converted to the corresponding N-borylated amines in excellent yields (Figure 3a). The improved catalytic activity of 7 compared to previously applied magnesium catalysts is noteworthy.[21,22] The authors suggested that the reduced steric hindrance around the metal center in 7 provides better accessibility, thus increasing its reactivity. The same authors also applied dimeric Mg(I)-complex 17 to the hydroboration of esters.[23] Under mild reaction conditions, full reaction conversion was obtained for different esters (Figure 3a), showing the effectiveness of the low-valent Mg(I)-dimers, comparable to the best results reported by Sadow [24,25] and Nabenna [26] using Mg(II)-catalysts.

Due to the high stability of carbonates, examples of their reduction has been scarce. In this regard, the first example of a hydroboration using magnesium catalysis has been recently reported by Rueping and co-workers.[27] Commercially available MgBu$_2$ 13 was showed to be active for the hydroboration of linear and cyclic carbonates (Figure 3b). This efficient reduction of carbonates provides an indirect route towards the conversion of CO$_2$ into methanol and valuable diols. Importantly, magnesium 13 was also active for the depolymerization of polycarbonates. Similarly, Ma and co-workers subsequently reported the efficient hydroboration of carbonates catalyzed by dimeric Mg(I)-complex 17.[23]

Following the successful hydroboration of carbonates, Rueping and co-workers turned their attention to carbamates, often found as protecting groups of amines. As such, they are rather stable and difficult to be reduced. However, Rueping and co-workers successfully applied MgBu$_2$ 13 to the hydroboration of secondary and tertiary linear and cyclic carbamates to obtain N-methyl amines which are common structural moieties in pharmaceuticals.[28] Therefore, the hydroboration is an excellent alternative to conventional methylation reactions. Significantly, N-Boc protected amines were converted to the corresponding N-methyl amines in excellent yields. Application of DBpin resulted in the corresponding N-trideuteromethylated amines which are otherwise difficult to be accessed (Figure 3c).

The reduction of CO$_2$ to methanol is an important transformation. As such, Rueping[27] and Ma[23] groups applied their successful catalytic systems (MgBu$_2$ 13 and dimeric Mg(I)-17) to the hydroboration of carbon dioxide (Figure 3d). Although these magnesium precursors showed better activities than the first magnesium complex reported by Hill and co-workers[29], the magnesium catalyst developed by Okuda[16] is the most active to date.
Whereas the magnesium-catalyzed hydroboration of highly polarized unsaturated bonds (C=O) has now been widely studied, the successful examples on the hydroboration of alkynes are rare.
a) Hydroboration of esters and nitriles:

\[ R\text-N + \ H\text-B-O\text-O \overset{7 \text{ (1 mol\%)} }{\longrightarrow} \ R\text-N\text-B\text{pin} \]

83-99% yield

[Chemical structure]

R = alkyl
(2 equiv.)

\[ R\text-O\text-R^2 + \ H\text-B-O\text-O \overset{17 \text{ (1 mol\%)} }{\longrightarrow} \ R^1\text-O\text-B\text{pin} \]

>95% conv.

R\text{} = alkyl, aryl
R\text{} = alkyl
(2 equiv.)

b) Hydroboration of carbonates and polycarbonates:

\[ \text{Bu}_2\text{Mg} \overset{3 \text{ mol\%)}{\longrightarrow} \text{CH}_3\text{OBpin} \]

[Chemical structure]

\[ \text{HBpin} \overset{3.1 \text{ equiv.)}{\longrightarrow} \text{pinBO} + \text{OBpin} \]

91% yield

c) Hydroboration of carbamates:

[Chemical structure]

pharmaceuticals containing N-methyl moieties

Viagra

AVP-786

d) Hydroboration of carbon dioxide:

\[ \overset{\text{MgBu}_2 \text{ or } 17}{\overset{1 \text{ atm.)}}{\longrightarrow}} \text{H}_2\text{C-OBPin} + \text{Bpin}\overset{\text{O}}{\longrightarrow}\text{Bpin} \]

> 95% yield

e) Hydroboration of internal and terminal alkynes:

83% yield, >9:1

80% yield

82% yield

f) Regiodivergent hydroboration of epoxides and oxetanes:

\[ \overset{\text{MgL}_2}{\overset{L = \text{NTf}_{18} \text{ or } \text{Bu}_{13}}{\overset{\text{HBpin}}{\longrightarrow}}} \]

R\text{} = alkyl, aryl
R\text{} = alkyl, aryl
Figure 3. Catalytic hydroboration of esters, nitriles, carbonates, carbamates, carbon dioxide, alkynes and epoxides.

The first example was reported by Ma and coworkers applying the unsymmetrical Mg(I)-dimer 7.[13] Despite the harsh reaction conditions, excellent yields for terminal alkynes were achieved. Rueping and co-workers applied the readily available MgBu$_2$ 13 in the hydroboration of a wide range of terminal and internal alkynes[30] to obtain the corresponding products with excellent functional group tolerance and good-to-excellent regioselectivities for unsymmetrical internal alkynes (Figure 3e). Recently, Rueping group has reported the first example of s-block metal-catalyzed hydroboration of epoxides and oxetanes.[31] The authors established that the regioselectivity depends on the nature of the magnesium catalyst (Figure 3f). Whereas MgBu$_2$ 13 provided the corresponding branched alcohols, Mg(NTf$_2$)$_2$ 18 led to the linear regioisomer. Experimental mechanistic investigations and DFT calculations provided further insight into the observed regiodivergence. Whereas MgBu$_2$ 13 (bearing alkyl ligands) undergoes bimolecular ring opening via activation of the borohydride, the more Lewis acidic Mg(NTf$_2$)$_2$ 18 isomerizes 2,2-disubstituted epoxides to the corresponding aldehyde (via a 1,2-H shift) which is subsequently reduced to the corresponding alcohol. In both cases, excellent yields and regioselectivities were obtained for a wide range of epoxides. Later, Ma and co-workers reported the successful application of unsymmetrical Mg(I)-dimers to the hydroboration of epoxides.[32]

3. Magnesium catalyzed hydrosilylation, hydrophosphination, hydroalkoxylation, hydrostannation, hydroarylation and hydrogenation of unsaturated bonds.

Whereas magnesium catalyzed hydroboration of unsaturated bonds has been widely studied, there are only few recent examples on other hydroelementations of unsaturated compounds. Recently, Hill and co-workers reported the use of $\beta$-diketiminate magnesium 19 for the successful hydrosilylation of alkenes and internal alkynes.[33,34] Despite the broader substrate scope compared to work by Parkin and co-workers[35], catalyst 19 showed to be less active, requiring long reaction times (Figure 4a). In an effort to expand the hydroelementation Harder et al. reported the application of highly Lewis acidic cationic magnesium complex 20 for the hydrophosphination of alkynes (Figure 4b).[36] Cationic complex 20, which can be seen as a frustrated Lewis pair (FLP), is able to catalyze the hydrophosphination of phenylacetylene with diphenylphosphine. Interestingly the hydrophosphination of terminal alkynes provides exclusively the Z-isomer. However, in this first study, internal alkynes did not react and the use of dialkylphosphines provided only traces of product.

A new approach for the hydroalkoxylation was recently reported by Hevia et al. Potassium magnesiate 21 showed excellent activity towards the intramolecular hydroalkoxylation of alkynols (Figure 4c).[37] The authors found that catalytic amounts of crown ethers dramatically increase the activity of 21. It was suggested that that the crown ether species does not fully sequester the alkali metal, thus
allowing for π-interactions with the anionic moiety. In this regard, a wide range of terminal alkynols underwent cyclisation in excellent yields and regioselectivities.

Transition metal-catalyzed hydrostannylation of unsaturated bonds have been widely studied.[38] However, the use of alkali or abundant alkaline-earth metals is limited to only one recent example of a magnesium catalyst. Rueping and co-workers reported the use of readily available MgBu$_2$ 13 for the stereoselective hydrostannylation of internal and terminal alkynes (Figure 4d).[39] Under relatively mild reaction conditions, excellent yields and regio- and stereoselectivities were achieved for a broad range of terminal and internal alkynes, even for more challenging unsymmetrical substrates.

An interesting hydroarylation of alkynes with aniline derivatives was recently reported by Magre et al.[40] Mg(NTf$_2$)$_2$ 18 in HFIP was used as the catalyst (Figure 4e). Excellent yields and ortho-regioselectivities were achieved for a wide range of terminal alkynes and N-free and N-substituted anilines. Interestingly, magnesium 18 showed similar activities to its widely studied calcium analogue. Control experiments showed that in the presence of a sterically hindered base (2,6-tert-butylpyridine) the reaction was not scavenged, ruling out the possibility of Brønsted acid catalysis. Deuterium labeling experiments showed that Lewis acidic magnesium 18 activates ortho-positions of aniline. Thus, the authors proposed a mechanism based on a dual activation: (i) coordinated HFIP activates the C≡C as Gandon and Leboeuf previously proposed [41,42], while (ii) Mg(NTf$_2$)$_2$ 18 activates the aniline via ligand-NH interaction.

A general trend in alkaline earth metal hydrofunctionalization reactions shows that conversion rates increase with the metal size. Whereas magnesium had initially shown to be almost inactive towards H$_2$-activation, Ca, Sr and Ba catalysts provided hydrogenation products. Hence, there are only few examples of alkaline-earth abundant metal catalysts which are active towards reduction of alkenes. Harder et al. reported the efficient aldimine hydrogenation with simple alkaline earth metal catalysts (Figure 4f).[43] Comparing all group 2 metal catalyst analogues, the authors underpinned the observation that an increase in metal size (Mg < Ca < Sr < Ba) leads to better reactivity. Whereas Mg[N(SiMe$_3$)$_2$]$_2$ 22 showed catalytic activity, harsher conditions were required compared to the calcium analogue. The low activity of Mg towards H$_2$ activation was also observed in the hydrogenation of alkenes,[44] in which the magnesium catalyst provided only traces of the desired hydrogenated product, in contrast to their heavier analogues.
a) Hydrosilylation of alkenes:

\[
R = H_3SiPh \quad 19 \quad 4-44 \text{ days}
\]

b) Hydrophosphination of alkynes:

\[
\text{Ph} = H + HPPh_2 \quad 20 \quad \text{(10 mol\%)}
\]

c) Intramolecular hydroalkoxylation of alkynols:

\[
R = \quad 21 \quad \text{(5 mol\%)}
\]

Mechanistic insight: cyclisation via an allene intermediate

d) Hydrostannation of terminal and internal alkynes:

\[
\text{SnBu}_3 \quad \text{(terminal)} \quad \text{SnBu}_3 \quad \text{(internal)}
\]

e) Hydroarylation of alkynes with anilines:

\[
\text{Ar} + 18 \quad \text{(5 mol\%)}
\]

N-free and N-substituted anilines

f) Hydrogenation of unsaturated bonds:

\[
22 \quad \text{(10 mol\%)} \quad \text{H}_2 \quad \text{(6 bar)}
\]

Heavier A* metals were found to be more active than Mg

Figure 4. Mg-catalyzed hydroelementation and hydrogenation of unsaturated bonds.
4. Conclusions and outlook

In the last decade, alkaline-earth abundant metals have emerged as redox-neutral alternatives to transition metal catalysts for the hydrofunctionalization of unsaturated bonds. To this end, different magnesium-catalyzed hydroelementation reactions including hydroborations, hydrosilylations, hydrophosphinations, hydroalkoxyulations, hydrostannation as well as hydrogenations have been developed. Since the first example of a Mg-catalyzed hydrofunctionalization reaction, the research of magnesium catalysis in this field has grown fast. Magnesium complexes bearing neutral, monoanionic and dianionic ligands have been successfully reported as active and selective catalysts. Moreover, the use of commercially and readily available organomagnesium compounds as catalysts have attracted attention. Among the Mg-catalyzed hydroelementation reaction, the hydroboration has become the most widely studied reaction. The first examples of highly enantioselective transformations have paved the way for future applications of chiral Mg-complexes in asymmetric catalysis, a topic that will certainly attract further interest. In addition, Mg-catalysts show a good functional group tolerance as demonstrated by the various applications; they are often readily available and non-toxic leading to ecologically and economically favorable alternative procedures if compared to transition metal catalyzed protocols. The latter is of particular relevance in pharmaceutical and fine chemical industry in which the replacement of expensive and harmful transitions metals due to restrictions and regulations is becoming increasingly important. However, despite the advances made in Mg-catalysis, the underlying reaction mechanisms and catalytic active species are often not fully understood. Thus, further research in this area is required that will provide a better understanding of the catalytic processes and will allow to better address the reactivity and selectivity issues leading to improved catalysts. Aside from further progress in the magnesium catalyzed hydroelementation reactions, there are opportunities of applying magnesium catalysts in other further cutting-edge catalytic transformations, such as Mg-catalyzed C-H activation and functionalization reactions.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.
5. References

Papers of particular interest, published within the period of review, have been highlighted as:
* of special interest
** of outstanding interest


The first application of dimeric Mg(I) complex in catalytic hydroboration.


The first enantioselective magnesium-catalyzed hydroboration.


Enantioselective magnesium-catalyzed reduction of ketones.


Excellent yields, excellent functional group tolerance and good-to-excellent regioselectivities for a wide range of terminal and internal alkynes.

The first magnesium-catalyzed hydroboration of epoxides. Besides, an unprecedented regiodivergent ring opening behaviour was observed.

Excellent yields and selectivities as well as mechanistic studies.

Excellent yields, excellent functional group tolerance and good-to-excellent regioselectivities for a wide range of terminal and internal alkynes.

The first example of successful magnesium-catalyzed hydrogenation of aldimines.


TOC graphic