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# Generation of organo-alkaline earth metal complexes from non-polar unsaturated molecules and their synthetic applications

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Organomagnesium compounds, represented by the Grignard reagents, are one of the most classical yet versatile carbanion species which have widely been utilized in synthetic chemistry. These reagents are typically prepared *via* oxidative addition of organic halides to magnesium metals, *via* halogen–magnesium exchange between halo(hetero)arenes and organomagnesium reagents or *via* deprotonative magnesiation of prefunctionalized (hetero)arenes. On the other hand, recent studies have demonstrated that the organo-alkaline earth metal complexes including those based on heavier alkaline earth metals such as calcium, strontium and barium could be generated from readily available non-polar unsaturated molecules such as alkenes, alkynes, 1,3-enynes and arenes through unique metallation processes. Nonetheless, the resulting organo-alkaline earth metal complexes could be further functionalized with a variety of electrophiles in various reaction modes. In particular, organocalcium, strontium and barium species have shown unprecedented reactivity in the downstream functionalization, which could not be observed in the reactivity of organomagnesium complexes. This perspective will focus on the newly emerging protocols for the generation of organo-alkaline earth metal complexes from non-polar unsaturated molecules and their applications in chemical synthesis and catalysis.

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## 1. Introduction

As part of the larger movement towards sustainable and green chemistry, transition-metal free methodologies have attracted

much attention in the fields of synthetic chemistry and catalysis. In this context, leveraging of alkali/alkaline earth metals to drive desired synthetic processes is extremely attractive due to their abundance in nature and lower toxicity. Organomagnesium reagents, typified by the Grignard reagents, are one of the most classical yet versatile carbanion species, which have widely been utilized in synthetic chemistry.<sup>1,2</sup> These reagents are typically prepared *via* oxidative addition of organic halides to magnesium metals (Scheme 1A)<sup>3</sup> or *via* halogen–magnesium exchange between halo(hetero)arenes and alkylmagnesium

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Scheme 1 Conventional preparation methods of organomagnesium reagents.

reagents (Scheme 1B).<sup>4–8</sup> Deprotonative magnesiation of (hetero)arenes has also been developed for the direct preparation of arylmagnesium reagents, while it commonly needs prefunctionalization at a suitable position of the (hetero)arene substrates (Scheme 1C).<sup>9,10</sup>

Recently, synthesis and structural characterization of various molecular magnesium(II) hydrides has successfully been achieved.<sup>11</sup> Employment of sterically hindered ligands (L) is the key to stabilize molecular magnesium(II) hydrides [L-Mg-H] kinetically from their Schlenk equilibrium to homoleptic magnesium-anionic ligand complexes [MgL<sub>2</sub>] and insoluble magnesium hydride [MgH<sub>2</sub>]<sub>n</sub> of the bulk lattice due to its higher lattice energy.<sup>12</sup> Thermally stable lower valent magnesium(I) dimers [L-Mg-Mg-L] could also be designed and synthesized with the aid of bulky anionic ligands.<sup>13–15</sup> The reactivity assessments of these magnesium(II) hydride and magnesium(I) dimer complexes have led to the discovery of unprecedented magnesiation processes of non-polar unsaturated carbon systems such as alkenes, alkynes and arenes, which could be applied in chemical synthesis and catalysis mainly *via* downstream functionalization of the resulting organomagnesium intermediates with various electrophiles. On the other hand, *in situ* generation of active

magnesium hydride species could be mediated by  $\sigma$ -bond metathesis of hydrosilanes or pinacolborane with organomagnesium complexes or counter ion metathesis between sodium hydride (NaH)<sup>16</sup> and magnesium iodide (MgI<sub>2</sub>) without the use of ligands, facilitating unique molecular transformations of non-polar unsaturated compounds. Moreover, heavier alkaline earth metal hydride complexes based on calcium, strontium and barium have also been designed and prepared.<sup>17,18</sup> These hydride complexes commonly display more hydridic reactivity for hydrometallation to non-polar unsaturated molecules to generate organo-heavier alkaline earth metal intermediates.<sup>19,20</sup> These species further perform unprecedented molecular transformations and catalysis, which are not often observed in the reactivities of organomagnesium complexes. The purpose of this perspective is to highlight recent advances in the development of new metallation methods of non-polar unsaturated systems with alkaline earth metal reagents and the applications of the resulting organo-alkaline earth metal intermediates in chemical synthesis and catalysis.<sup>21</sup> It should be noted that this perspective does not include the preparation methods of the key alkaline earth metal complexes that are used for the metallation of non-polar unsaturated systems. Readers can find the protocols in the corresponding references.

## 2. Organomagnesium complexes

### 2.1. Transformation of alkenes

The terminal magnesium hydride carborane complex **1** having a tris[(1-isopropylbenzimidazol-2-yl)dimethylsilyl]methyl ligand was recently synthesized by Parkin and it was found to serve as a catalyst for the Markovnikov hydrosilylation and hydroboration of styrene (**2**) through hydromagnesiation and ensuing  $\sigma$ -bond metathesis of the resulting alkylmagnesium intermediate with hydrosilane **3** (PhSiH<sub>3</sub>) or pinacolborane (**4**) [HB(pin)] (Scheme 2).<sup>22</sup> The turnover frequency of the hydrosilylation was identified as 0.9 h<sup>-1</sup>, whereas that of the hydroboration was 0.3 h<sup>-1</sup>.

In contrast,  $\beta$ -diketiminato magnesium hydride dimer **7** (ref. 23) performed *anti*-Markovnikov hydromagnesiation of



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reactions and molecular functions featuring element-based characteristics.



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Scheme 2 Catalytic hydrosilylation and hydroboration of styrene (Parkin, 2017).

unactivated aliphatic terminal alkenes in good efficiency to afford the corresponding organomagnesium complexes 8–10 (Scheme 3A).<sup>24</sup> The *anti*-Markovnikov regioselectivity and the reaction rate are primarily governed by the steric effect. In turn, the hydromagnesiation of styrene (2) gave a 55 : 45 mixture of linear and branched organomagnesium species 11 and 12 (Scheme 3B). Although 1,2-disubstituted alkenes were generally inert toward hydromagnesiation, strained bicyclic alkene, norbornene (13) showed good reactivity with magnesium hydride 7 to afford 2-norbornylmagnesium 14 (Scheme 3C). A domino sequence of hydromagnesiation and 5-*exo* carbomagnesiation was observed in the reaction of 1,5-hexadiene (15), affording cyclopentylmethylmagnesium 17 *via* 5-hexenylmagnesium 16 (Scheme 3D).

Thus, this hydromagnesiation of non-activated alkenes with magnesium hydride 7 could be applied for the catalytic hydrosilylation using  $\text{PhSiH}_3$  3, which is responsible to undergo rate-determining  $\sigma$ -bond metathesis with the organomagnesium intermediates generated by hydromagnesiation to maintain the catalytic turnover (Scheme 4).

Jones and Maron revealed that magnesium(I) dimers 20 (ref. 25) and 21 (ref. 26) supported by  $\beta$ -diketiminato ligands showed unprecedented reactivity toward alkenes. For example, 1,1-diphenylethylene (22) underwent oxidative insertion into the  $\text{Mg(I)}\text{-Mg(I)}$  bond of 20 and 21 to form 1,2-dimagnesioethane complexes 23 and 24, respectively. At ambient temperature, this process was found reversible *via* reductive elimination of 1,1-diphenylethylene (22) (Scheme 5).<sup>27</sup>

Treatment of the 1,2-dimagnesioethane complex 23 with  $\text{H}_2$  resulted in regioselective hydrogenation at the  $\text{Mg-CPh}_2$  moiety to liberate alkylmagnesium 25 and magnesium hydride dimer 26, while the reaction of 23 with ethylene induced its insertion into the  $\text{Mg-CPh}_2$  bond, providing 1,4-dimagnesiobutane 27 (Scheme 6A). Interestingly, in the reaction of 24 with CO,

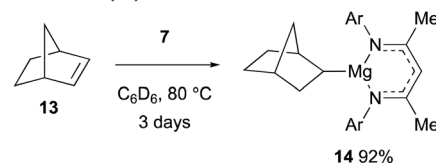
#### A. With non-activated terminal alkenes



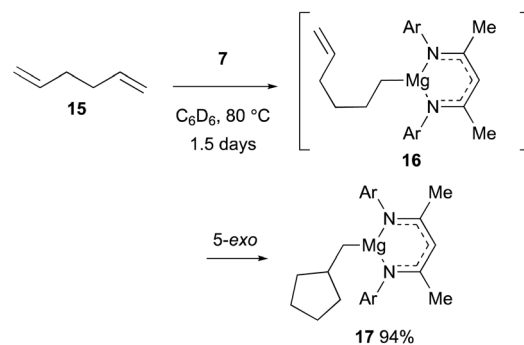
#### B. With styrene (2)



#### C. With norbornene (13)



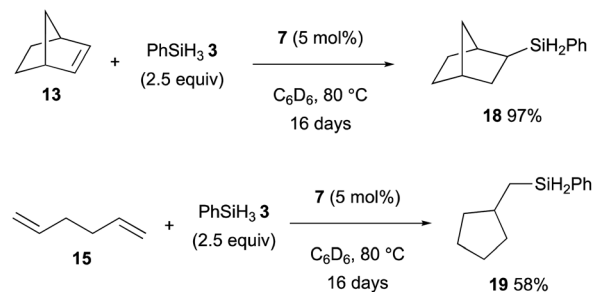
#### D. With 1,5-hexadiene (15)



Scheme 3 Hydromagnesiation of alkenes with magnesium hydride 7 (Maron and Hill, 2019).

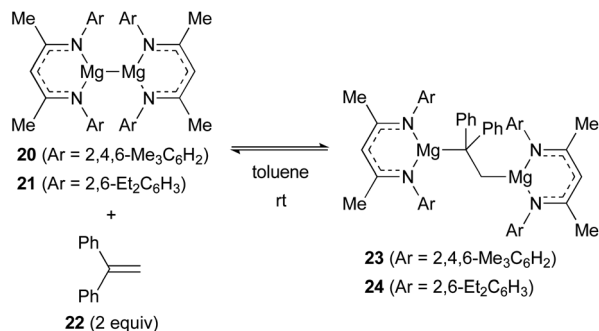
cyclobutenediolate 28 was formed *via* sequential incorporation of two molecules of CO and cyclization (Scheme 6B).

In the presence of an *N*-heterocyclic carbene ligand that can coordinate with  $\text{Mg(I)}$  centers as a Lewis base, the magnesium(I)



Scheme 4 Catalytic hydrosilylation of alkenes with 7 (Maron and Hill, 2019).





Scheme 5 Reversible insertion of 1,1-diphenylethylene into the Mg(I)–Mg(I) bond (Jones and Maron, 2017).



Scheme 7 Reductive activation of ethylene with Mg(I) dimer 20 (Jones and Maron, 2020).

#### A. With H<sub>2</sub> or ethylene



#### B. With carbon monoxide



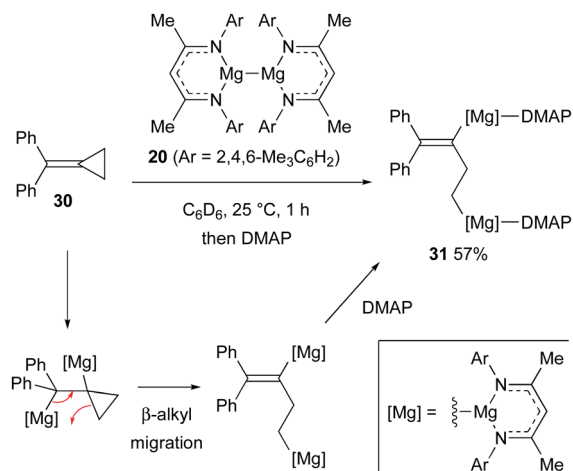
Scheme 6 Unique reactivity of 1,2-dimagnesiobutane complexes 23 and 24 (Jones and Maron, 2017).

dimer 20 could reductively activate even inert ethylene, forming 1,4-dimagnesiobutane 29 in 43% yield (Scheme 7).<sup>28</sup>

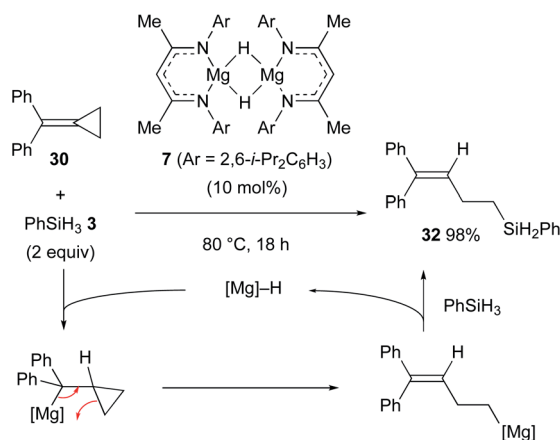
Treatment of alkylidene cyclopropane 30 with magnesium(I) dimer 20 resulted in the formation of 1,3-dimagnesiobutene 31 via 1,2-dimagnesiobutene followed by  $\beta$ -alkyl migration associated with the ring-opening of the

cyclopropane ring (Scheme 8A).<sup>29</sup> A combination of hydromagnesiation of alkenes and this  $\beta$ -alkyl migration led to the development of catalytic hydrosilylation of alkylidene cyclopropane 30 using magnesium hydride 7 and hydrosilane 3, affording homoallylsilane 32 in high yield (Scheme 8B).

#### A. Reaction with Mg(I) dimer



#### B. Catalytic hydrosilylation with Mg(II) hydride



Scheme 8 1,2-Dimagnesiobutene of alkylidene cyclopropane 30 with Mg(I) dimer 20 followed by  $\beta$ -alkyl migration and its catalytic variant with Mg(II) hydride 7 (Crimmin, 2020).

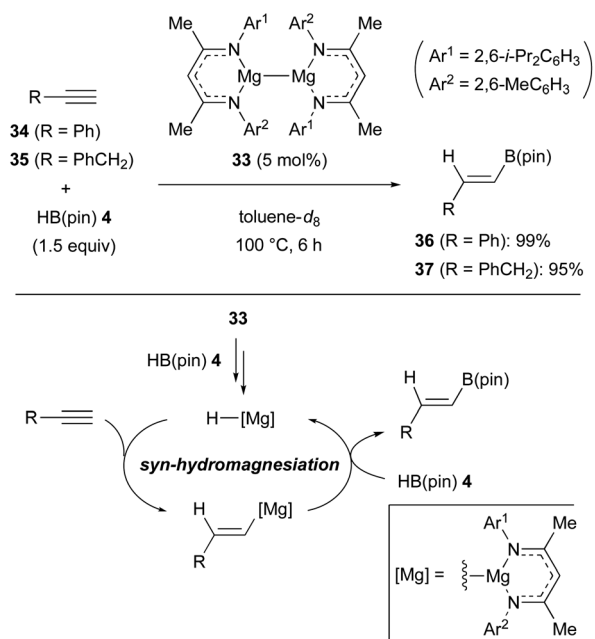


## 2.2. Transformation of alkynes

The magnesium(I) dimer **33** containing unsymmetrical  $\beta$ -diketiminate ligands was found to be an effective pre-catalyst for the *anti*-Markovnikov hydroboration of terminal alkynes such as **34** and **35** with pinacolborane (**4**) [HB(pin)] (Scheme 9).<sup>30</sup> In these processes, it was proposed that the magnesium(I) dimer pre-catalyst **33** is converted into magnesium hydride *via* the reaction with **4**, although the precise mechanism is unclear. The resulting magnesium hydride underwent *syn*-hydromagnesiation of the alkyne to form an alkenylmagnesium intermediate. Finally,  $\sigma$ -bond metathesis of alkenylmagnesium with HB(pin) **4** liberated the alkenylborane products such as **36** and **37** along with the regeneration of the magnesium hydride.<sup>31</sup>

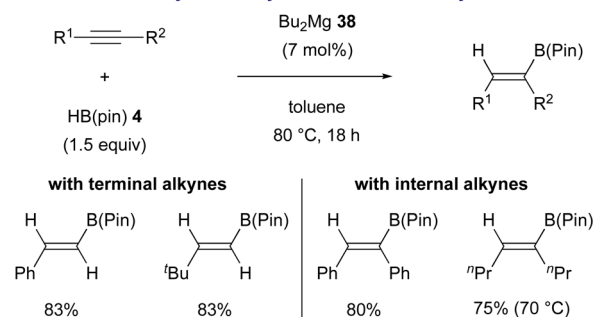
Rueping and Cavallo discovered that a catalytic amount of dibutylmagnesium (**38**) (Bu<sub>2</sub>Mg), in the presence of HB(pin) **4**, is able to effect the *syn*-selective hydroboration of both terminal and internal alkynes in good yields (Scheme 10A).<sup>32</sup> In the case of unsymmetrical internal alkynes such as (cyclohexylethynyl) benzene (**39**), the regioselectivity was controlled by the steric difference of the substituents (see Scheme 10B for the regioselective formation of **40** over **41**). The active catalytic species was estimated as butylmagnesium hydride coordinated with HB(pin) **4**, which could be generated *in situ* through  $\sigma$ -bond metathesis between Bu<sub>2</sub>Mg (**38**) and HB(pin) **4** (Scheme 10C). The *syn*-hydromagnesiation of the alkyne generated the vinyl magnesium intermediate, which underwent another  $\sigma$ -bond metathesis with HB(pin) **4**, to regenerate butylmagnesium hydride species with the release of the hydroborated product.<sup>33</sup>

Solvothermal treatment of sodium hydride (**42**) with magnesium iodide (**43**) in THF was found to allow for counter ion metathesis, generating highly reactive magnesium hydride (**44**) [MgH<sub>2</sub>]<sub>n</sub>, which could induce unprecedented *anti*-

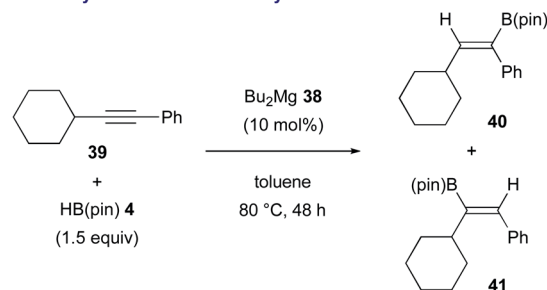


Scheme 9 Catalytic hydroboration of alkynes with unsymmetrical Mg(I) dimer **33** (Ma, 2018).

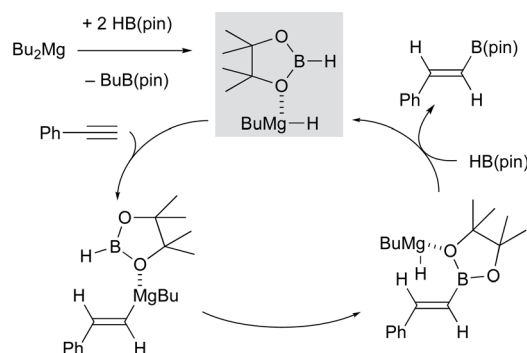
## A. With terminal alkynes and symmetrical internal alkynes



## B. With unsymmetrical internal alkynes



## C. A proposed catalytic cycle

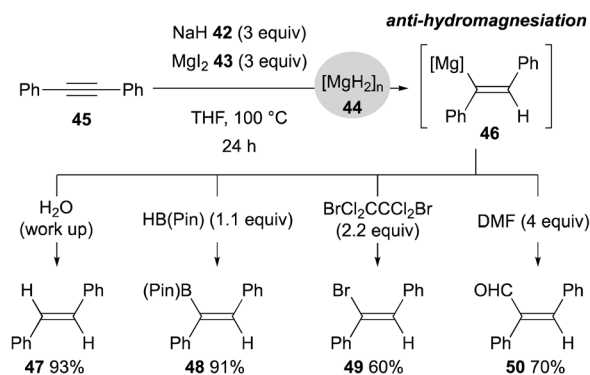


Scheme 10 Catalytic hydroboration of terminal and internal alkynes with Bu<sub>2</sub>Mg (Rueping and Cavallo, 2019).

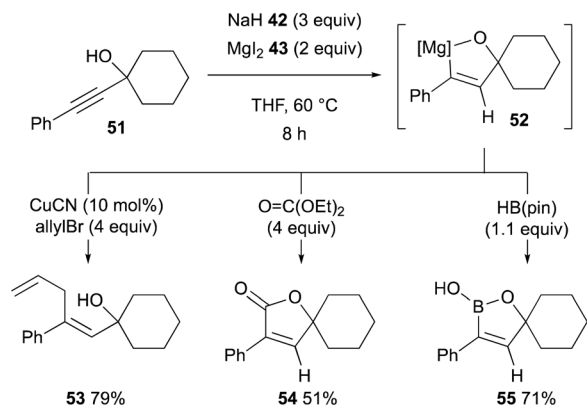
hydromagnesiation of arylalkynes such as diphenylacetylene (**45**) (Scheme 11A).<sup>34</sup> The resulting alkenylmagnesium intermediate **46** could be trapped with a series of electrophiles such as water (for **47**), HB(pin) **4** (for **48**), 1,2-dibromotetrachloroethane (for **49**) and dimethylformamide (DMF) (for **50**) to afford stereochemically well defined functionalized alkenes. In turn, the reactions of propargyl alcohols such as **51** underwent *anti*-hydromagnesiation with perfect diastereoselectivity *via* 5-membered ring magnesiumocycles such as **52**, and ensuing treatment with electrophiles allowed for further downstream functionalization (see Scheme 11B for the synthesis of **53–55**). The DFT calculation using a MgH<sub>2</sub> dimer as a model active species suggested that the reaction *via* transition state **TS<sub>anti</sub>** is the favored process, where the polar hydride transfer mechanism is involved, to afford the *anti*-alkenylmagnesium species (Scheme 11C). On the other hand, the large distortion of diphenylacetylene is required in **TS<sub>syn</sub>**, making the *syn*-hydromagnesiation unfavorable.



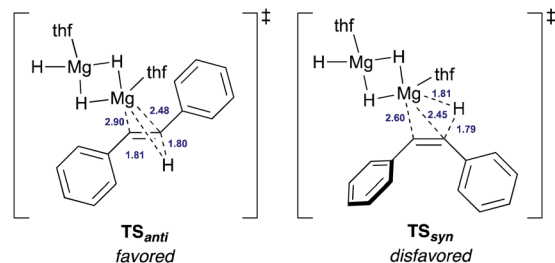
## A. With internal alkynes



## B. With propargyl alcohols



## C. Elucidation of stereoselectivity of hydromagnesiation

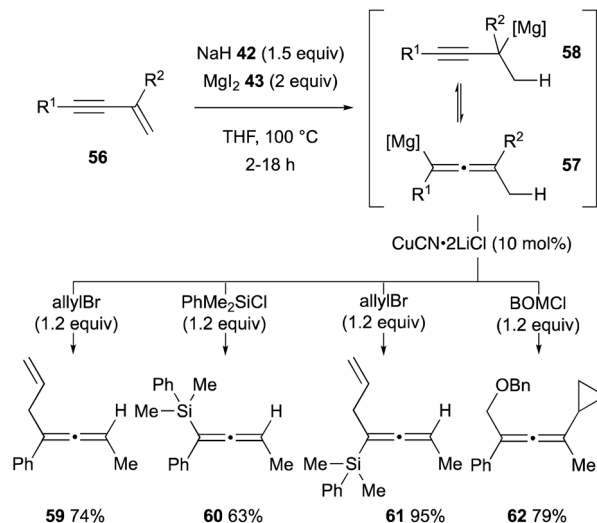


Scheme 11 Anti-hydromagnesiation of arylalkynes by *in situ* generated MgH<sub>2</sub> from NaH and MgI<sub>2</sub> (Chiba and Takita, 2020).

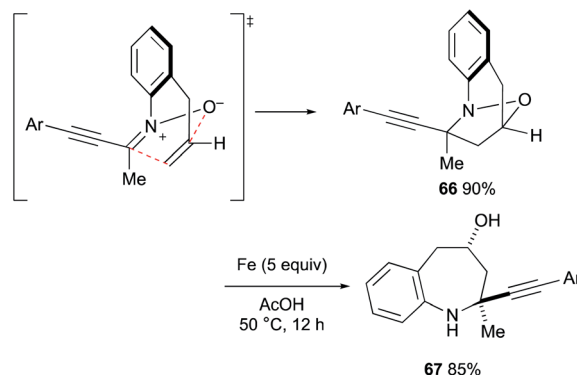
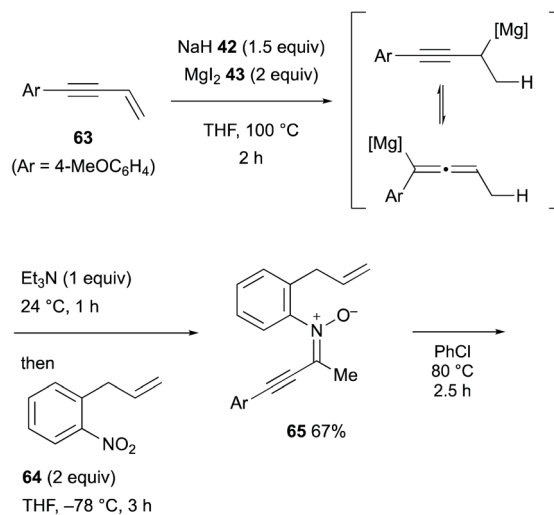
## 2.3. Transformation of 1,3-enynes

The unique hydridic reactivity of magnesium hydride (**44**) generated *in situ* from sodium hydride (**42**) and magnesium iodide (**43**) was extended further to regioselective hydromagnesiation of 1,3-enynes **56** to form an equilibrium mixture of allenylmagnesium **57** and propargylmagnesium **58** (Scheme 12).<sup>35</sup> Downstream functionalization of the resulting organomagnesium intermediates **57** and **58** was demonstrated by subsequent treatment with a series of alkyl and silyl halides in the presence of CuCN as a catalyst, affording polysubstituted allenes **59–62**.

In turn, downstream treatment of the allenyl/propargylmagnesium intermediates derived from hydromagnesiation of 1,3-enynes with organo nitro compounds<sup>36,37</sup> enabled engagement of propargylmagnesium species for the



Scheme 12 Hydromagnesiation of 1,3-enynes with MgH<sub>2</sub> and downstream functionalization for the synthesis of substituted allenes (Chiba and Takita, 2021).



Scheme 13 Hydromagnesiation of 1,3-enynes with MgH<sub>2</sub> and downstream functionalization for the synthesis of nitrones (Chiba, 2021).



amination, resulting in the formation of  $\alpha$ -alkynyl nitrones (Scheme 13).<sup>38</sup> The  $\alpha$ -alkynyl nitronone **65** derived from 1,3-enyne **63** and 1-allyl-2-nitrobenzene (**64**) underwent intramolecular 1,3-dipolar cycloaddition to afford tetrahydro-1,4-epoxybenzo[*b*]azepine **66** as the major product and the ensuing reductive N–O bond cleavage delivered diastereomerically pure tetrahydro-1*H*-benzo[*b*]azepin-4-ol **67**.

#### 2.4. Transformation of arenes

Two new strategies have recently emerged to convert inert arenes into the corresponding arylmagnesium complexes with *in situ* generated magnesium(i) radical species.

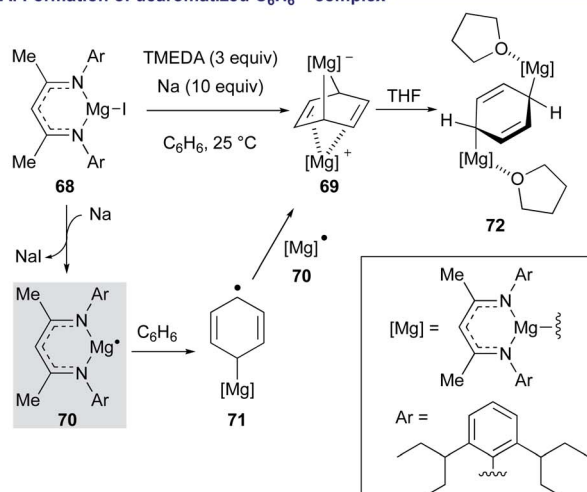
Reduction of magnesium iodide complex **68** with a super bulky  $\beta$ -diketiminate ligand having 2,6-diisopentylphenyl groups on the imine nitrogen by sodium (Na) in the presence of tetramethylethylenediamine (TMEDA) in benzene generated

cyclohexandienediyl bridged magnesium complex **69** (dearomatized C<sub>6</sub>H<sub>6</sub> dianion sandwiched between divalent magnesium cations) (Scheme 14A).<sup>39</sup> The reaction was initiated by the generation of doublet magnesium(i) radical **70** and its subsequent addition to benzene to form cyclohexadienyl anion radical **71**, which was further reduced by **70** to liberate **69**. The use of the bulky ligand and bidentate TMEDA is the key to kinetically stabilize the magnesium(i) radical **70** and prevent its dimerization. Addition of THF to **69** led to the formation of centrosymmetric flat C<sub>6</sub>H<sub>6</sub> dianion THF adduct **72**. The reaction of this dearomatized C<sub>6</sub>H<sub>6</sub> dianion complex **69** in toluene at 120 °C for 3 days gave phenylmagnesium **73** and magnesium hydride species **74** (Scheme 14B).

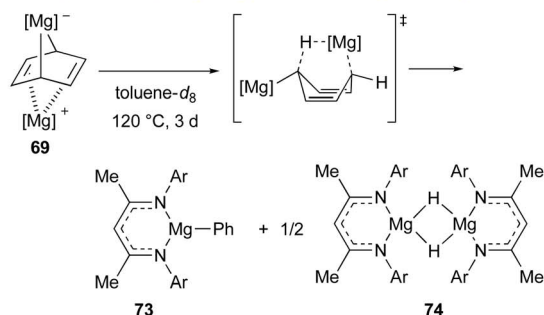
The C<sub>6</sub>H<sub>6</sub> dianion complex **69** also displayed highly reducing reactivity. For example, addition of fluorobenzene (**75**) to **69** induced reductive cleavage of the C–F bond to give magnesium fluoride **76** and phenylmagnesium **73** with the release of benzene (Scheme 14C).

On the other hand, Maron and Jones discovered that photoexcitation of magnesium(i) dimer **77** induced homolysis of the Mg–Mg bond to generate a highly reactive magnesium(i) radical **78**, which could be used for reductive dearomatization of benzene to form cyclohexandienediyl bridged magnesium complex **79** (Scheme 15A).<sup>40</sup> Similarly, **79** could be readily converted into phenylmagnesium **80** and magnesium hydride complex **7** upon gentle heating at 60 °C (Scheme 15A). Interestingly, the photoinduced magnesiation reactions of

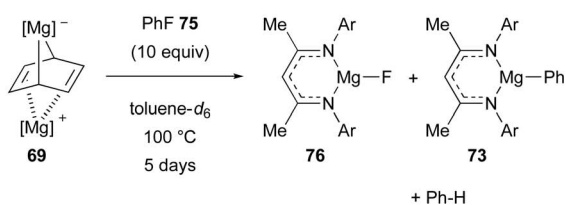
##### A. Formation of dearomatized C<sub>6</sub>H<sub>6</sub><sup>2-</sup> complex



##### B. Decomposition to phenylmagnesium and magnesium hydride

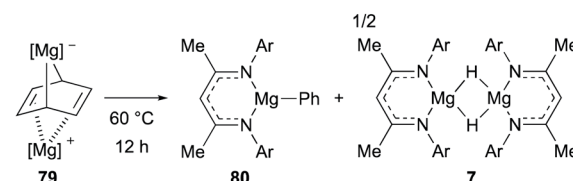
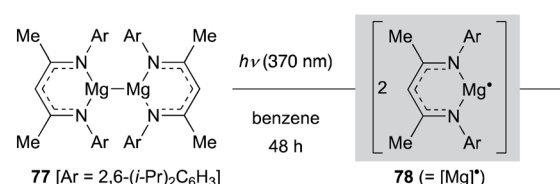


##### C. Reductive cleavage of fluorobenzene

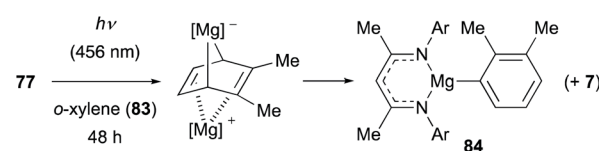
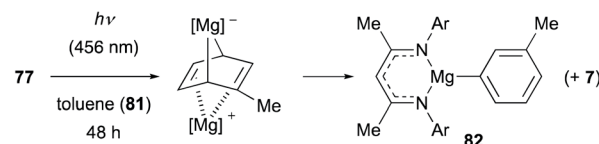


Scheme 14 Reductive magnesiation of benzene with magnesium(i) radical **70** (Harder, 2019).

##### A. Photoinduced reductive dearomatization of benzene



##### B. Photoinduced regioselective magnesiation of toluene and o-xylene



Scheme 15 Reduction and C–H magnesiation of inert arenes using photochemically generated magnesium(i) radical **78** (Maron and Jones, 2021).



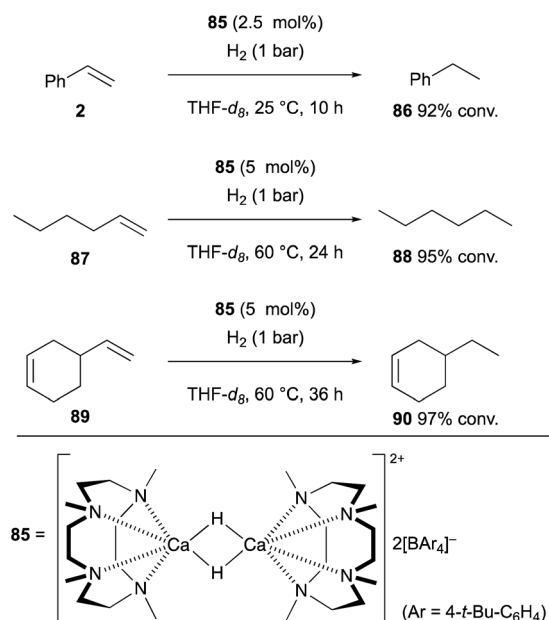
substituted arenes with **77** were observed to be regioselective. For example, the magnesiation of toluene (**81**) was observed at the *meta*-position to form **82**, whereas that of *o*-xylene (**83**) afforded *ortho*-magnesiated product **84** as a single product (Scheme 15B).

### 3. Organo-heavier alkaline earth metal complexes

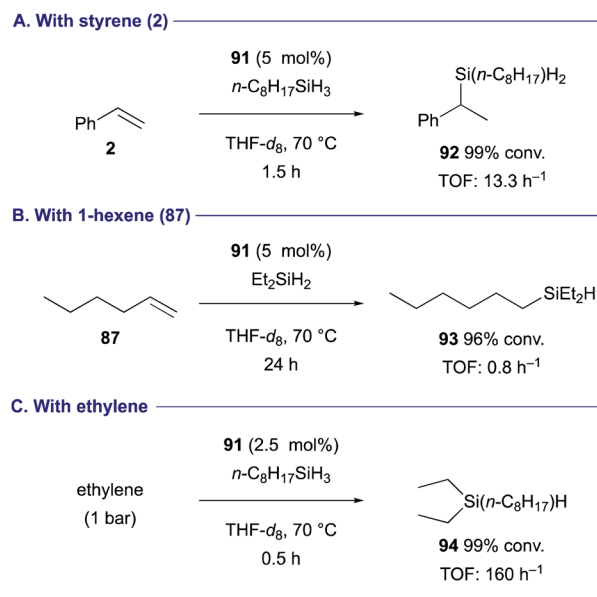
This section highlights recent selected examples for the generation of organo-heavier alkaline earth metal complexes from non-polar unsaturated molecules and their exotic reactivities in chemical synthesis and catalysis.

Maron and Okuda recently developed cationic dinuclear calcium hydride complex **85** supported by 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclododecane as the neutral tetradentate macrocyclic nitrogen ligand and tetraarylborate as the counter anion.<sup>41</sup> This calcium hydride complex functioned as a catalyst for the hydrogenation of terminal alkenes such as styrene (**2**) and 1-hexene (**87**) under a hydrogen atmosphere, whereas internal alkenes could be kept intact (Scheme 16). Thus, in the reaction of skipped diene **89**, selective hydrogenation of the terminal alkene moiety was observed to afford **90** as the sole product. It was speculated that the process is initiated by hydrometallation of terminal alkenes by the cationic calcium hydride complex **85** to form organocalcium intermediates, which are subsequently protonated with molecular hydrogen *via* heterolysis of the H–H bond to give the hydrogenation products along with the regeneration of the calcium hydride complex **85** to maintain the catalytic turnover.

The regioselectivity of the hydrometallation of terminal alkenes is determined by the electronic nature of the alkenes.

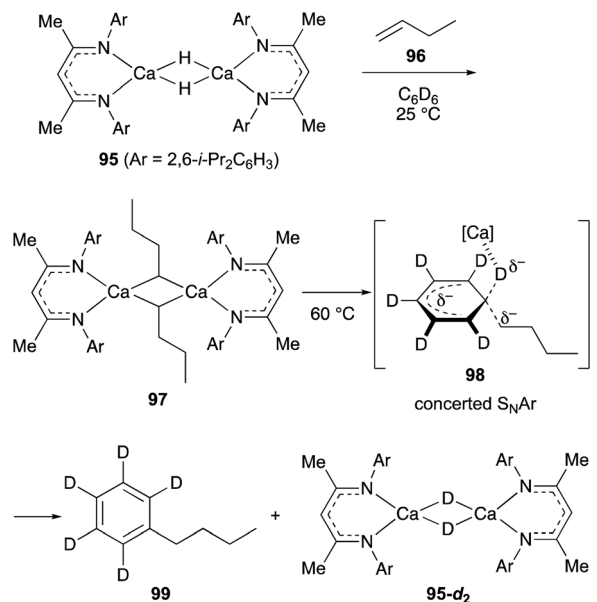


Scheme 16 Hydrogenation of alkenes catalyzed by cationic calcium hydride dimer **85** (Maron and Okuda, 2017).



Scheme 17 Hydrosilylation of alkenes catalyzed by cationic calcium hydride dimer **91** (Okuda, 2020).

Okuda demonstrated hydrosilylation of terminal alkenes using the cationic dinuclear calcium hydride complex **91** as the catalyst in the presence of hydrosilanes (Scheme 17). The reaction with styrene (**2**) proceeded in the Markovnikov manner to form



Scheme 18 Hydrometallation of non-activated terminal alkenes and the following  $S_NAr$  alkylation of benzene promoted by calcium hydride dimer **95** (Maron, 2017).





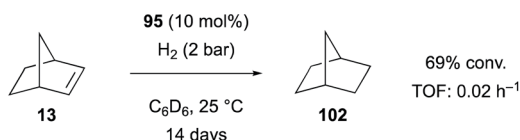
## Perspective

branched benzylsilane **92** as the product (Scheme 17A), whereas *anti*-Markovnikov selectivity was observed in the hydrosilylation of non-activated terminal alkenes such as 1-hexene (**87**) (Scheme 17B).<sup>42</sup> It should also be noted that this catalytic system is amenable to the hydrosilylation of ethylene (Scheme 17C). A more recent study revealed that the employment of 1,4,7,10,13-pentamethyl-1,4,7,10,13-pentaazacyclopentadecane as the pentadentate macrocyclic ligand could enhance the catalytic activity of the calcium hydride complex toward the hydrogenation and hydrosilylation.<sup>43</sup>

Maron discovered that  $\beta$ -diketiminato calcium hydride dimer **95** with no THF solvation on the calcium center undergoes hydrometallation of non-activated terminal alkenes such as 1-butene (**96**) in  $C_6D_6$  at ambient temperature to form alkylcalcium dimer **97** (Scheme 18).<sup>44</sup> Further treatment of **97** at 60 °C liberated *n*-butylbenzene **99** along with the regeneration of the calcium deuteride dimer **95-d<sub>2</sub>**. This unusual alkylation of benzene was characterized as the concerted nucleophilic aromatic substitution reaction where an alkyl carbanion is installed with concurrent elimination of a hydride on  $sp^2$  hybridized carbon *via* the transition state **98**.<sup>45</sup>

Hill and Maron demonstrated that under a hydrogen atmosphere,  $\beta$ -diketiminato calcium hydride dimer **95** could function as the catalyst for the hydrogenation of terminal alkenes such as allylbenzene (**100**) as well as some activated internal alkenes such as norbornene (**13**) (Scheme 19A).<sup>46</sup> Based on the

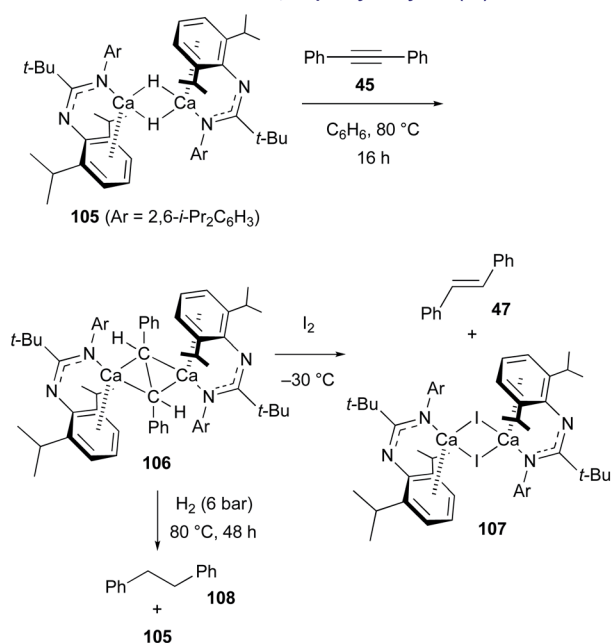
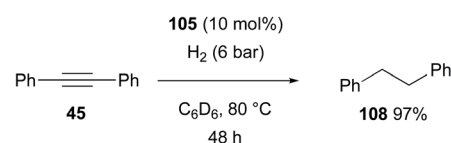
## A. Catalytic hydrogenation of alkenes



## B. Proposed mechanisms

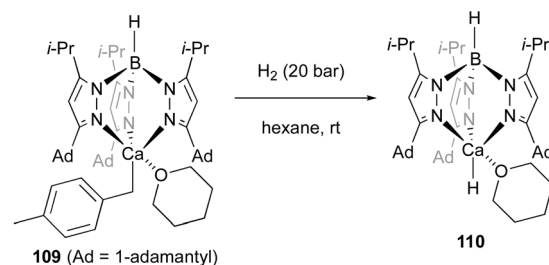


Scheme 19 Hydrogenation of alkenes catalyzed by calcium hydride dimer **95** (Hill and Maron, 2018).

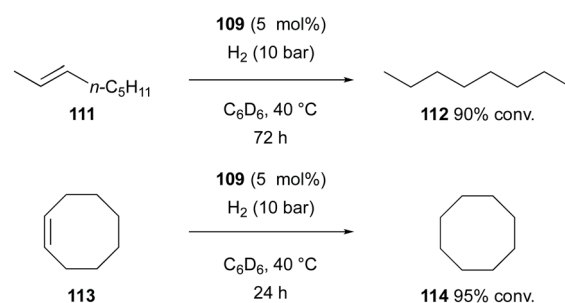
A. Stoichiometric reduction of 1,2-diphenylacetylene (**45**)B. Catalytic hydrogenation of 1,2-diphenylacetylene (**45**)

Scheme 20 Hydrogenation of alkynes with amidinato calcium hydride dimer **105** (Harder, 2017).

## A. Generation of calcium hydride species



## B. With unactivated internal alkenes



Scheme 21 Hydrogenation of alkenes with mononuclear calcium hydride **110** (Cheng, 2020).



experimental observations and the DFT calculations, it was proposed that the dimeric structure of the calcium complex is likely maintained during the catalytic cycle (Scheme 19B). Upon insertion of one molecule of alkene to calcium hydride dimer **95**, the resulting alkyl hydride dicalcium complex **103** liberates the reduced alkane *via* subsequent deprotonation of H<sub>2</sub>. Alternatively, the alkyl hydride dicalcium complex **103** can also undergo the second alkene insertion to generate the dialkyl complex **104**, prior to deprotonation of H<sub>2</sub> to release the reduced alkane with the regeneration of the dimeric calcium hydride species **95**.

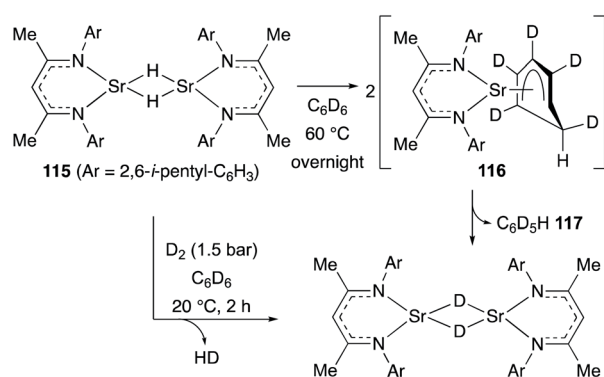
Amidinato calcium hydride dimer complex **105** developed by Harder<sup>47</sup> was found to react with diphenylacetylene (**45**) at 80 °C in benzene to form organocalcium complex **106** symmetrically bridged by a stilbene dianion (Scheme 20A).<sup>48</sup> Oxidation of **106** with I<sub>2</sub> gave *trans*-stilbene (**47**) with calcium iodide dimer **107**. In turn, the treatment of **106** under a H<sub>2</sub> atmosphere (6 bar) resulted in the formation of 1,2-diphenylethane (**108**) along with the regeneration of the calcium hydride dimer complex **105** *via* deprotonation of H<sub>2</sub>. Thus, the organocalcium complex **105** could be employed as the catalyst for hydrogenation of

diphenylacetylene (**45**) to 1,2-diphenylethane (**108**) under a H<sub>2</sub> atmosphere (6 bar) (Scheme 20B).

Cheng revealed that benzylcalcium complex **109** with a trispyrazolyl borate ligand is converted into the mononuclear calcium hydride complex **110** under a H<sub>2</sub> atmosphere (Scheme 21A).<sup>49</sup> The resulting calcium hydride **110** could serve as an active catalyst for the hydrogenation of alkenes including non-activated internal alkenes such as *trans*-2-octene (**111**) and cyclooctene (**113**) (Scheme 21B).

A strontium hydride dimer **115** having extremely bulky β-diketiminato ligands was found to display higher hydridic reactivity toward benzene by Harder (Scheme 22).<sup>50</sup> The stoichiometric reaction of **115** with C<sub>6</sub>D<sub>6</sub> induces unprecedented hydride addition to C<sub>6</sub>D<sub>6</sub> to form dearomatized anionic intermediate **116**, which undergoes re-aromatization *via* elimination

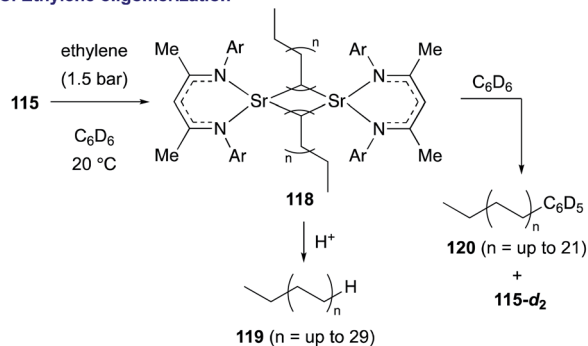
#### A. Reactivity toward benzene



#### B. Catalytic deuteration of benzene

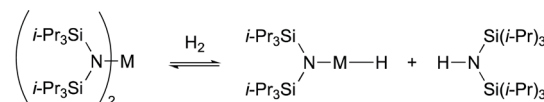


#### C. Ethylene oligomerization



Scheme 22 Nucleophilic hydrogenation and alkylation of benzene promoted by strontium hydride dimer **115** (Harder, 2019).

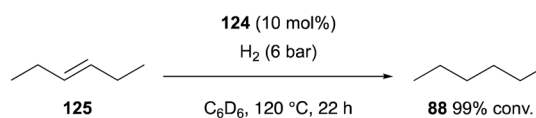
#### A. Reversible generation of alkaline earth metal hydrides under H<sub>2</sub>



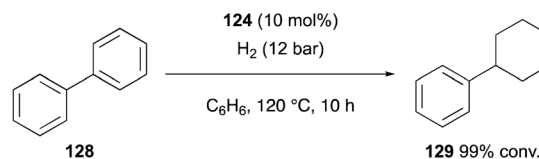
**121** (M = Mg); **122** (M = Ca)

**123** (M = Sr); **124** (M = Ba)

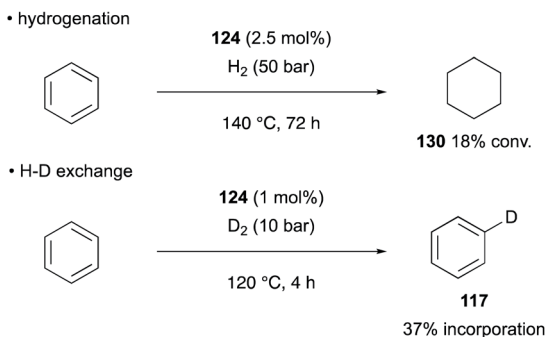
#### B. Hydrogenation of unactivated internal alkenes



#### C. Hydrogenation of conjugated arenes



#### D. Hydrogenation and deuterium incorporation of benzene



Scheme 23 Hydrogenation of non-activated alkenes and arenes with a barium hydride complex having a bis(triisopropylsilyl)amide ligand (Harder, 2020).



of deuteride to form strontium deuteride dimer **115-d<sub>2</sub>** and C<sub>6</sub>D<sub>5</sub>H **117** (Scheme 22A). On the other hand, the strontium hydride dimer **115** performed fast deprotonative H–D exchange under a D<sub>2</sub> atmosphere (1.5 bar) at ambient temperature. Thus, these reactivities could be combined to develop catalytic deuteration of benzene under a D<sub>2</sub> atmosphere by **115** (Scheme 22B). In turn, under an ethylene atmosphere (1 bar) in C<sub>6</sub>D<sub>6</sub> at ambient temperature, the strontium hydride dimer **115** is quickly converted into alkylstrontium complexes **118** having ethyl, butyl, hexyl and higher ethylene oligomers, which could be confirmed by the detection of the corresponding alkanes **119** by GC-MS analysis. Furthermore, these alkylstrontium complexes **118** undergo nucleophilic aromatic substitution with C<sub>6</sub>D<sub>6</sub> to form alkylated arenes **120** and **115-d<sub>2</sub>** (Scheme 22C).

Harder recently exploited alkaline earth metal complexes **121–124** having an extremely bulky bis(triisopropylsilyl)amide ligand as the precatalyst for the alkaline earth metal hydrides capable of catalytic hydrogenation of alkenes under a H<sub>2</sub> atmosphere (Scheme 23A).<sup>51</sup> The barium complex **124** was found to be most reactive, performing hydrogenation of even unactivated internal alkenes such as *trans*-3-hexene (**125**) (Scheme 23B). Moreover, the barium amide **124** complex could perform hydrogenation of conjugated arenes such as naphthalene (**126**) and biphenyl (**128**) to tetralin (**127**) and phenylcyclohexane (**129**), respectively (Scheme 23C). This catalytic system was found to be amenable to the hydrogenation of benzene to cyclohexane (**130**) (Scheme 23D). With 2.5 mol% of **124** under higher H<sub>2</sub> pressure (50 bar) at 140 °C, 18% conversion of benzene to cyclohexane (**130**) was attained after 3 days. On the other hand, treatment of benzene with 1 mol% of **124** under milder pressure of D<sub>2</sub> (10 bar) at 120 °C allowed for H/D exchange of benzene at 37% incorporation rate within 4 h.<sup>52</sup>

## 4. Conclusions

In this perspective, we have highlighted the protocols for the generation of organomagnesium complexes from non-polar unsaturated compounds and their unique reactivities in chemical synthesis and catalysis. The key enabling advance in these transformations takes advantage of well-defined molecular magnesium(II) hydrides or magnesium(I) dimer complexes, which are supported by the sophisticated sterically hindered anionic ligands. The method for *in situ* generation of active magnesium hydrides *via* either  $\sigma$ -bond metathesis between pinacolborane and dibutylmagnesium or counter ion metathesis between sodium hydride and magnesium iodide without the use of any supporting ligands also enabled concise transformation of alkynes and 1,3-enynes into various scaffolds *via* hydromagnesiation and ensuing downstream functionalization with electrophiles. Engagement of heavier alkaline earth metal hydride complexes having well-defined bulky ligands allowed for metallation of non-activated internal alkenes and arenes including benzene. The resulting organo-heavier alkaline earth metal complexes have shown exotic and unique reactivities in the downstream functionalization. Given the versatile reactivities of organo-alkaline earth metal complexes to drive the unprecedented chemical processes which have been dominated

by transition-metal catalysts, we view that more unique and capable synthetic methods, especially catalysis, that leverage organo-alkaline earth metal complexes as the key components, will be devised and engaged in various synthetic endeavours.

## Author contributions

S. C. and R. T. conceived the contents of the perspective. All the authors contributed to the preparation of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- 1 D. Seyferth, *Organometallics*, 2009, **28**, 1598–1605.
- 2 *The Chemistry of Organomagnesium Compounds*, ed. Z. Rappaport and I. Marek, Wiley-VCH, Weinheim, Germany, 2008.
- 3 J. F. Garst and M. P. Soriaga, *Coord. Chem. Rev.*, 2004, **248**, 623–652.
- 4 S. D. Robertson, M. Uzelac and R. E. Mulvey, *Chem. Rev.*, 2019, **119**, 8332–8405.
- 5 D. Tilly, F. Chevallier, F. Mongin and P. C. Gros, *Chem. Rev.*, 2014, **114**, 1207–1257.
- 6 T. Klatt, J. T. Markiewicz, C. Sämann and P. Knochel, *J. Org. Chem.*, 2014, **79**, 4253–4269.
- 7 H. Ila, O. Baron, A. J. Wagner and P. Knochel, *Chem. Lett.*, 2006, **35**, 2–7.
- 8 P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis and V. A. Vu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4302–4320.
- 9 M. Balkenhohl and P. Knochel, *SynOpen*, 2018, **2**, 78–95.
- 10 P. Knochel, M. A. Schade, S. Bernhardt, G. Manolikakes, A. Matzger, F. M. Piller, C. J. Rohbogner and M. Mosrin, *Beilstein J. Org. Chem.*, 2011, **7**, 1261–1277.
- 11 D. Mukherjee and J. Okuda, *Angew. Chem., Int. Ed.*, 2018, **57**, 1458–1473.
- 12 Physical Constants of Organic Compounds, in *CRC Handbook of Chemistry and Physics*, ed. J. R. Rumble, CRC Press/Taylor & Francis, Boca Raton, FL, 102nd edn (Internet Version), 2021.
- 13 C. Jones, *Nat. Rev. Chem.*, 2017, **1**, 0059.
- 14 M. Westerhausen, *Angew. Chem., Int. Ed.*, 2008, **47**, 2185–2187.
- 15 S. P. Green, G. Jones and A. Stasch, *Science*, 2007, **318**, 1754–1757.
- 16 For the generation of zinc hydrides through counter ion metathesis between NaH and zinc halides, see: D. Y. Ong,



- Z. Yen, A. Yoshii, J. R. Imbernon, R. Takita and S. Chiba, *Angew. Chem., Int. Ed.*, 2019, **58**, 4992–4997.
- 17 D. Mukherjee, D. Schuhknecht and J. Okuda, *Angew. Chem., Int. Ed.*, 2018, **57**, 9590–9602.
- 18 S. Harder, *Chem. Rev.*, 2010, **110**, 3852–3876.
- 19 M. Westerhausen, A. Koch, H. Görls and S. Krieck, *Chem.–Eur. J.*, 2017, **23**, 1456–1483.
- 20 M. Westerhausen, *Coord. Chem. Rev.*, 2008, **252**, 1516–1531.
- 21 M. S. Hill, D. J. Liptrot and C. Weetman, *Chem. Soc. Rev.*, 2016, **45**, 972–988.
- 22 M. Rauch, S. Rucolo and G. Parkin, *J. Am. Chem. Soc.*, 2017, **139**, 13264–13267.
- 23 S. P. Green, C. Jones and A. Stasch, *Angew. Chem., Int. Ed.*, 2008, **47**, 9079–9083.
- 24 L. Garcia, C. Dinoi, M. F. Mahon, L. Maron and M. S. Hill, *Chem. Sci.*, 2019, **10**, 8108–8118.
- 25 S. J. Bonyhady, C. Jones, S. Nembenna, A. Stasch, A. J. Edwards and G. J. McIntyre, *Chem.–Eur. J.*, 2010, **16**, 938–955.
- 26 R. Lalrempuia, C. E. Kefalidis, S. J. Bonyhady, B. Schwarze, L. Maron, A. Stasch and C. Jones, *J. Am. Chem. Soc.*, 2015, **137**, 8944–8947.
- 27 A. J. Boutland, A. Carroll, C. A. Lamsfus, A. Stasch, L. Maron and C. Jones, *J. Am. Chem. Soc.*, 2017, **139**, 18190–18193.
- 28 K. Yuvaraj, I. Douair, L. Maron and C. Jones, *Chem.–Eur. J.*, 2020, **26**, 14665–14670.
- 29 R. Y. Kong and M. R. Crimmin, *J. Am. Chem. Soc.*, 2020, **142**, 11967–11971.
- 30 J. Li, M. Luo, X. Sheng, H. Hua, W. Yao, S. A. Pullarkat, L. Xu and M. Ma, *Org. Chem. Front.*, 2018, **5**, 3538–3547.
- 31 J. W. Clary, T. J. Rettenmaier, R. Snelling, W. Bryks, J. Banwell, W. T. Wipke and B. Singaram, *J. Org. Chem.*, 2011, **76**, 9602–9610.
- 32 M. Magre, B. Maity, A. Falconnet, L. Cavallo and M. Rueping, *Angew. Chem., Int. Ed.*, 2019, **58**, 7025–7029.
- 33 Dibutylmagnesium was also found to function as a catalyst to induce a regio- and stereoselective hydrostannylation of both internal and terminal alkynes, while this process unlikely involves magnesium hydride species, see: M. Magre, M. Szewczyk and M. Rueping, *Org. Lett.*, 2020, **22**, 1594–1598.
- 34 B. Wang, D. Y. Ong, Y. Li, J. H. Pang, K. Watanabe, R. Takita and S. Chiba, *Chem. Sci.*, 2020, **11**, 5267–5272.
- 35 B. Wang, Y. Li, J. H. Pang, K. Watanabe, R. Takita and S. Chiba, *Angew. Chem., Int. Ed.*, 2021, **60**, 217–221.
- 36 G. Bartoli, E. Marcantoni and M. Petrini, *J. Org. Chem.*, 1992, **57**, 5834–5840.
- 37 G. Bartoli, E. Marcantoni, M. Petrini and R. Dalpozzo, *J. Org. Chem.*, 1990, **55**, 4456–4459.
- 38 Y. Li, J. S. Ng, B. Wang and S. Chiba, *Org. Lett.*, 2021, **23**, 5060–5064.
- 39 T. X. Gentner, B. Rösch, G. Ballmann, J. Langer, H. Elsen and S. Harder, *Angew. Chem., Int. Ed.*, 2019, **58**, 607–611.
- 40 D. D. L. Jones, I. Douair, L. Maron and C. Jones, *Angew. Chem., Int. Ed.*, 2021, **60**, 7087–7092.
- 41 D. Schuhknecht, C. Lhotzky, T. P. Spaniol, L. Maron and J. Okuda, *Angew. Chem., Int. Ed.*, 2017, **56**, 12367–12371.
- 42 D. Schuhknecht, T. P. Spaniol, L. Maron and J. Okuda, *Angew. Chem., Int. Ed.*, 2020, **59**, 310–314.
- 43 T. Höllerhage, D. Schuhknecht, A. Mistry, T. P. Spaniol, Y. Yang, L. Maron and J. Okuda, *Chem.–Eur. J.*, 2021, **27**, 3002–3007.
- 44 A. S. S. Wilson, M. S. Hill, M. F. Mahon, C. Dinoi and L. Maron, *Science*, 2017, **358**, 1168–1171.
- 45 S. Rohrbach, A. J. Smith, J. H. Pang, D. L. Poole, T. Tuttle, S. Chiba and J. A. Murphy, *Angew. Chem., Int. Ed.*, 2019, **58**, 16368–16388.
- 46 A. S. S. Wilson, C. Dinoi, M. S. Hill, M. F. Mahon and L. Maron, *Angew. Chem., Int. Ed.*, 2018, **57**, 15500–15504.
- 47 A. Causero, G. Ballmann, J. Pahl, H. Zijlstra, C. Färber and S. Harder, *Organometallics*, 2016, **35**, 3350–3360.
- 48 A. Causero, H. Elsen, G. Ballmann, A. Escalona and S. Harder, *Chem. Commun.*, 2017, **53**, 10386–10389.
- 49 X. Shi, C. Hou, L. Zhao, P. Deng and J. Cheng, *Chem. Commun.*, 2020, **56**, 5162–5165.
- 50 B. Rösch, T. X. Gentner, H. Elsen, C. A. Fischer, J. Langer, M. Wiesinger and S. Harder, *Angew. Chem., Int. Ed.*, 2019, **58**, 5396–5401.
- 51 J. Martin, C. Knüpfer, J. Eyselien, C. Färber, S. Grams, J. Langer, K. Thum, M. Wiesinger and S. Harder, *Angew. Chem., Int. Ed.*, 2020, **59**, 9102–9112.
- 52 J. Martin, J. Eyselien, S. Grams and S. Harder, *ACS Catal.*, 2020, **10**, 7792–7799.

