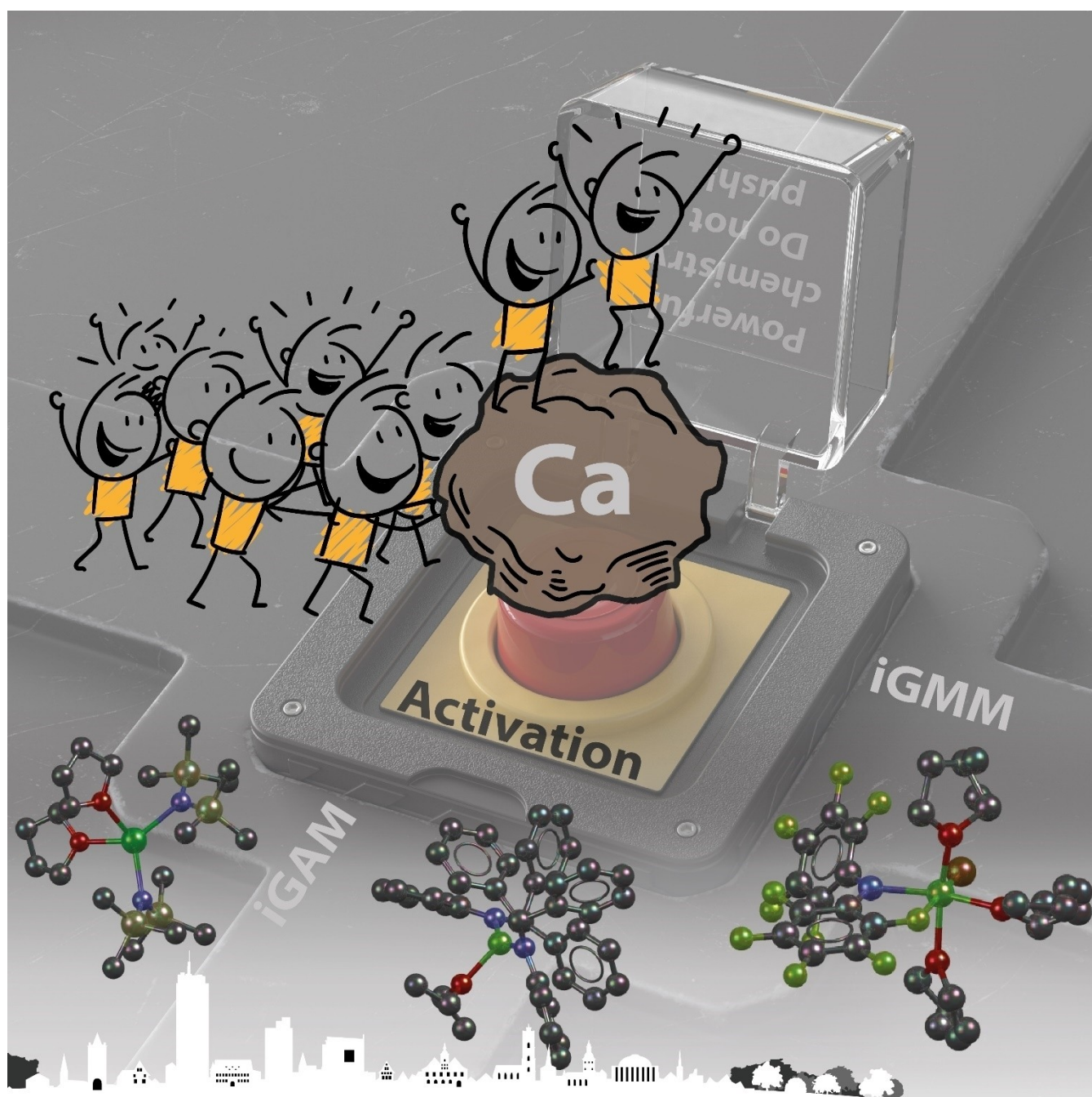


# In Situ Generation of Magnesium- and Calcium-Based Grignard Reagents for Amide Synthesis

Philipp Schüler,<sup>[a]</sup> Simon Sengupta,<sup>[a]</sup> Sven Kriek,<sup>[a]</sup> and Matthias Westerhausen<sup>\*[a]</sup>



**Abstract:** The alkaline-earth metals Mg and Ca are too inert for the direct metalation of primary and secondary amines. Consequently, activation prior to use is required. Alternatively, the *Grignard* reagents RMgX (R = alkyl, aryl, X = halide) can be applied in metalation of amines. However, such a straightforward procedure for the synthesis of alkylcalcium reagents is disadvantageous due to diverse side reactions, including *Wurtz*-type C–C coupling and ether degradation reactions. Therefore, suspensions of magnesium or calcium with amine

can be treated in a smooth reaction with ethyl bromide in an ethereal solvent at room temperature. Intermediately formed R<sub>Ae</sub>X (Ae = alkaline-earth metal, i.e., Mg, Ca) either metalates amines yielding the corresponding amides in an in situ *Grignard* metalation method (iGMM) or adds across C=N bonds of imines in an in situ *Grignard* addition method (iGAM). The amides R'<sub>2</sub>N-AeX (Ae = Mg; *Hauser* bases) undergo *Schlenk*-type ligand exchange reactions yielding homoleptic Ae(NR'<sub>2</sub>)<sub>2</sub> and potentially sparingly soluble AeX<sub>2</sub>.

## 1. Amides of Magnesium and Calcium

Amides of magnesium and calcium are widely used reagents with a broad portfolio of applications. Recent developments focus on reactive magnesium amide reagents<sup>[1]</sup> that can react regio- and chemoselectively, depending on substitution pattern and reaction conditions, and on more reactive calcium-based metalation reagents.<sup>[2]</sup> In addition, new magnesium- and calcium-based electrolytes in the quest for novel magnesium and calcium batteries are of vastly growing interest.<sup>[3]</sup> Beyond stoichiometric applications, calcium amides are applied as (pre)catalysts in ring-opening polymerization<sup>[4]</sup> and hydrofunctionalization processes such as for example addition of amines (hydroamination), phosphines (hydrophosphination, hydrophosphanylation) or phosphine oxides (hydrophosphorylation) onto alkynes.<sup>[5]</sup> The alkaline-earth metals Mg and Ca combine advantageous properties including lack of toxicity and global abundance but show a rather low reactivity in direct metalation reactions, i.e. metalation of H-acidic compounds with the metals itself.<sup>[6]</sup> Beyond these homometallic reagents also heterometallic mixed s-block metal compounds (A = alkali, Ae = alkaline-earth metal) such as *turbo-Hauser* bases (R<sub>2</sub>N–Mg–X–LiX),<sup>[7]</sup> alkali metal tris(amido)magnesiates<sup>[7a,8]</sup> and tris- or tetrakis(amido)calcates<sup>[9]</sup> A<sub>n</sub>[Ae(NR<sub>2</sub>)<sub>m</sub>] (n = 1, 2; m = n + 2) as well as inverse crowns [A(NR<sub>2</sub>)/Ae(NR<sub>2</sub>)<sub>2</sub> mixtures] gain vastly growing attention due to altered reactivity and metalation force.<sup>[10]</sup> In addition, heterobimetallic cage compounds containing combinations of magnesium or calcium with another main group metal and zinc have been studied thoroughly.<sup>[11]</sup>

The scope of this review focusses on homo- and heterobimetallic s-block metal amides with respect to synthesis, structures and applications of their homo- and heteroleptic derivatives. The in situ generation of magnesium- and calcium-based *Grignard*

reagents in the presence of substrates for subsequent derivatization reactions offers an advantageous straightforward protocol. The historical advancement of magnesium- and calcium-based *Grignard* reactions is summarized, too, illustrating the challenges related to the chemistry of these organometallics. An exhaustive literature overview is not intended but representative examples will be discussed in more detail. In addition, alkaline-earth metal imides of the type [(L)AeN–R]<sub>n</sub> with central Ae<sub>n</sub>N<sub>n</sub> cages are discussed elsewhere and hence neglected in this overview.<sup>[12]</sup>

### 1.1. Properties of magnesium and calcium metal

A brief visualization of the properties of the alkaline-earth metals underlines the striking differences between the reactivity of the homologs magnesium and calcium. Selected properties of these metals are compared in Table 1.<sup>[13]</sup> On the one hand, the atomization enthalpy of calcium is significantly larger than the values of the neighboring alkaline-earth metals, leading to a higher melting point. On the other hand, decreasing ionization energy with increasing radius of the alkaline-earth metal eases reduction reactions.

The thermodynamic counterpart in homogenous reactions is solvation of the cations by *Lewis* bases (donor, D). Increasing size compels larger distances between cation and *Lewis* base which leads to smaller electrostatic attraction and binding energy. Thus, the coordination of a THF molecule to Mg<sup>2+</sup> is much more beneficial than the addition of this base to a Ca<sup>2+</sup> ion.<sup>[14]</sup>

**Table 1.** Comparison of selected properties of the alkaline-earth metals.

	Be	Mg	Ca	Sr	Ba
EN <sup>[a]</sup>	1.47	1.23	1.04	0.99	0.97
1. IE <sup>[b]</sup>	9.321	7.642	6.111	5.695	5.211
2. IE <sup>[b]</sup>	18.21	15.03	11.87	11.03	10.00
AE <sup>[c]</sup>	324.6	147.70	178.2	164.4	180
m.p. <sup>[d]</sup>	1278	648.8	839	768	710
r(Ae) <sup>[e]</sup>	111.3	159.9	197.4	215.1	224
r(Ae <sup>2+</sup> ) <sup>[f]</sup>	59	86	114	132	149

[a] EN = *Allred-Rochow* electronegativity values. [b] IE = First and second ionization energy [eV]. [c] AE = Atomization enthalpy [kJ mol<sup>-1</sup>]. [d] m.p. = Melting point [°C]. [e] Radii *r* of the alkaline-earth metal atoms [pm]. [f] Radii *r* of the alkaline-earth metal ions with coordination number of 6 [pm].

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## 1.2. Conventional synthesis of s-block metal amides

For the synthesis of alkaline-earth metal amides several synthetic procedures have been established as exemplary depicted for calcium bis(amide) in Scheme 1. The method with the highest atom efficiency would be the direct metalation of the amine using the elemental metal, but the relative inertness of elemental Mg and Ca spoils this protocol. To enhance the reactivity especially of calcium diverse procedures have been developed such as distillation of the metal prior to application,<sup>[15]</sup> cocondensation of calcium and substrate,<sup>[16]</sup> reduction of calcium halides (*Rieke* method, reductant: lithium biphenylide),<sup>[17]</sup> or activation via a metastable anthracene complex (*Bogdanovic* method),<sup>[18]</sup> these procedures are depicted in Scheme 2.<sup>[19]</sup> These methods need special equipment or have low atom efficiency.

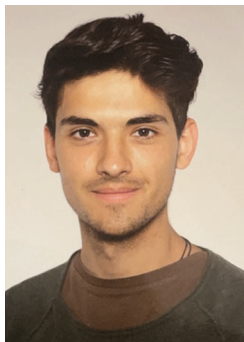
Therefore, alternative routes have been developed. A commonly used method for the synthesis of alkaline-earth metal bis(amides) is the salt metathesis reaction using alkali metal amides (mainly potassium amides) and alkaline-earth

metal halides (e.g.,  $(D)_x\text{Ca}_2$ <sup>[20]</sup> or  $(D)_x\text{Sr}_2$ <sup>[21]</sup>), Ae metal sulphonates<sup>[22]</sup> or heavier alkaline-earth metal alcoholates as educts.<sup>[23]</sup> This method is straightforward due to the simple synthesis of the starting materials using commercially available metathesis reagents. However, an exact stoichiometric ratio of the substrates is mandatory to avoid formation of side products such as heterobimetallic metalates because already small amounts of these compounds commonly change the reactivity of the target amides significantly. The commercial availability of dibutylmagnesium and some alkylmagnesium halides allows a straightforward access to magnesium bis(amides) via organometallic metalation reactions. Transmetalation of heavy metal amides (e.g., of Sn and Hg) with calcium leads to solvent-free or donor-containing adducts, depending on the solvent, of calcium bis(amides) under precipitation of elemental heavy metal.<sup>[24]</sup> The low atom efficiency and the high toxicity of Sn and Hg compounds are severe drawbacks of this method. An efficient way to synthesize alkaline-earth metal bis(amides) is the transamination of the appropriate amine with stronger, easily available amides (e.g., with the hmcs compounds

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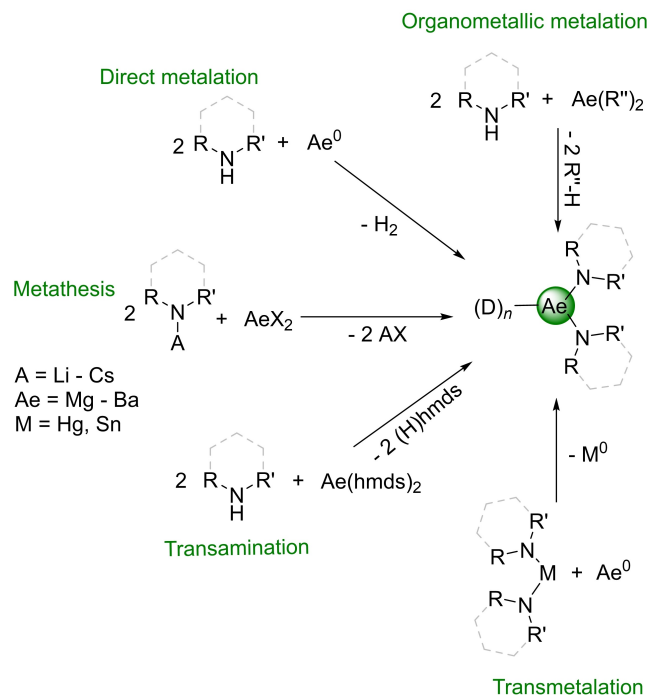
*Sven Kriek (born 1983) studied chemistry at the Friedrich Schiller University Jena, Germany, and received his Ph.D. degree in 2010. After a post-doctoral research period at the Karl Franzens University Graz, Austria, he returned to the Friedrich Schiller University Jena. He is interested in the synthesis of heavy Grignard reagents, their stabilization via agostic and  $\pi$ -interactions and their application for the synthesis of heterobimetallic compounds. He is in charge with teaching and organization of the curricula of chemistry studies for students with chemistry major and beyond.*



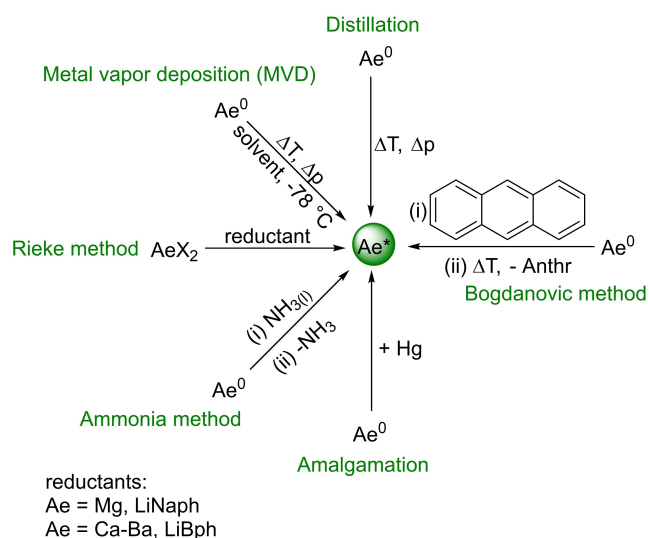
*Matthias Westerhausen (born 1959) studied chemistry at the Philipps University Marburg, Germany, and received his Ph.D. degree in 1987. After a post-doctoral period at the University of New Mexico in Albuquerque, USA, in 1987/1988 he performed his habilitation at the University on Stuttgart, Germany. Thereafter he was appointed to a professorship at the Ludwig Maximilians University of Munich in 1996 where he was also vice-president from 2001 to 2004. In 2004 he accepted the Chair of Inorganic Chemistry I at the Friedrich Schiller University Jena, Germany. His research focuses on coordination compounds of s-block and selected transition metals as well as on organic phosphorus compounds. In collaboration with the medicine faculty, he became also interested in bilirubin degradation end products and carbon monoxide-releasing molecules.*







**Scheme 1.** Synthetic methods for the synthesis of alkaline-earth metal bis(amides).



**Scheme 2.** Methods for activation of alkaline earth metals.

$Ae(hmnds)_2$ ). To overcome the disadvantages of the described methods a novel strategy has been established using the in situ organometallic metalation of amines in a straightforward one-pot reaction starting with the metals. This method is described in-depth in a later chapter.

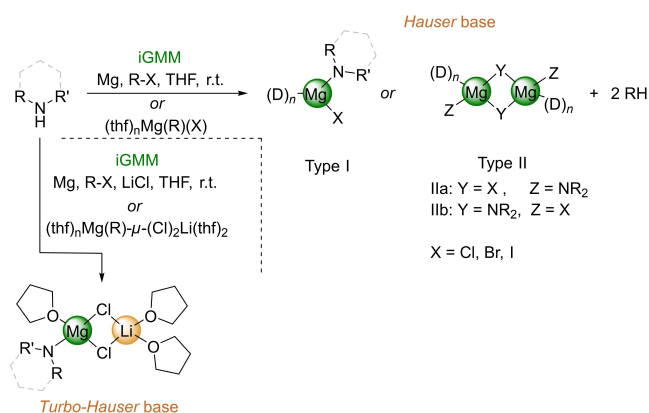
### 1.3. Hauser bases

Deprotonation of amines with *Grignard* reagents leads to halide-containing solutions and occasionally to mixtures of magnesium bis(amides) and amidomagnesium halides. However, homoleptic and heteroleptic compounds exhibit different reactivity. This observation has initiated an intensive study of the homoleptic magnesium bis(amides)  $[(D)_n Mg(NR_2)_2]$  and of heteroleptic amides of the type  $[(D)_n Mg(NR_2)X]$ , so-called *Hauser* bases. The *Hauser* bases can be divided structurally into two types (Scheme 3), monomeric (type I) and dimeric, halide-bridged compounds (type II). Type I is preferred for bulky amides or amides with secondary interactions such as carbazates,<sup>[3f]</sup> substituted carbazoles [tetra-*tert*-butylcarbazolate<sup>[25]</sup> or 2,9-diaryl-4,7-di-*tert*-butylcarbazolate (aryl = Mes,<sup>[25]</sup> 9'-Ph-Anthr), Ph = phenyl],<sup>[26]</sup> and perfluorinated diphenylamides.<sup>[27]</sup>

Type IIa is found for small amides like di-*iso*-propylamide (dipa)<sup>[28]</sup> and type IIb for amides with larger steric demand such as 2,2,6,6-tetramethylpiperidide (tmp)<sup>[7c]</sup> or substituted diphenylamides.<sup>[29]</sup>

The *Hauser* bases have become very popular and are highlighted by the group of *Knochel*, who shows that the reactivity of the *Hauser* bases  $[(D)_n Mg(NR_2)X]$  (Scheme 3, type II) can be enhanced significantly via addition of lithium chloride.<sup>[10a]</sup> These *turbo-Hauser* or *Knochel-Hauser* bases with  $NR_2 = 2,2,6,6$ -tetramethylpiperidide (tmp) have been characterized by X-ray diffraction studies<sup>[7c]</sup> and for solution structures by ECC-DOSY NMR,<sup>[30]</sup> verifying a dimeric structure in the solid state and in solution. For the heavier congeners, only  $[(tmeda)Ca(tmp)(\mu-I)]_2$  is known for a heavy *Hauser* base.<sup>[20b]</sup> However, the low solubility of the heavy alkaline-earth metal halides in ethereal solvents shifts the *Schlenk*-type equilibrium nearly quantitatively to the side of soluble homoleptic calcium bis(amides) and precipitating halides.

In alkali metal amide chemistry the analogy to *Hauser* bases  $[A(NR_2)] \cdot [AX]$  has not been investigated yet in detail. Recent findings in the reactivity of methyllithium shows an increase with (sub-stoichiometric) amounts of lithium halide.<sup>[31]</sup> The



**Scheme 3.** Synthesis and solid-state structures of *Hauser* and *turbo-Hauser* bases.

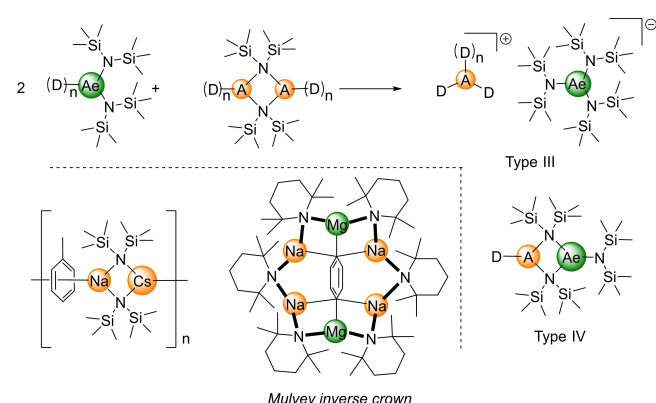


mixture of alkali metal amides and alkaline-earth metal bis(amides) leads to formation of so-called metalates. The generation of these compounds is based on different electronegativity values of the metals. In polar donor solvents often solvent-separated ion pairs of the type  $[A(D)_n][Ae(NR_2)_2]$  (K/Ca,<sup>[32]</sup> K/Mg,<sup>[33]</sup> Na/Mg,<sup>[8a]</sup> Scheme 4, type III) or heterobimetallic compounds  $[(D)A(\mu-NR_2)_2Ae(D)_n(NR_2)]$  (K/Ca,<sup>[9e,20e,34]</sup> Li/Ca,<sup>[9g,34]</sup> Li/Mg,<sup>[33a,34–35]</sup> Na/Mg,<sup>[33a]</sup> K/Mg,<sup>[36]</sup> Scheme 4, type IV) are observed.<sup>[34]</sup> Without Lewis basic donors  $[Li(\mu\text{-}\{N(SiMe_3)_2\}_2)Ae\{N(SiMe_3)_2\}]$  crystallizes and is stabilized by agostic Li–H interactions. Combinations of  $ANR_2/Ae(NR_2)_2$  have thoroughly been studied by Mulvey and coworkers and they have established the fascinating chemistry of inverse crowns with an extraordinary reactivity and metalation power (Scheme 4).<sup>[10a,f–h,35a,37]</sup>

The large electronegativity difference ( $\Delta EN(Li,Cs) = 0.11$ <sup>[13]</sup>) within the alkali metal group causes the formation of metalates and in hydrocarbons coordination polymers of the dimers are observed for the Li/Cs and the Na/Cs mixtures (Scheme 4).<sup>[38]</sup> In ethereal solvents Li/Na and Li/K metalates arrange in solvated dimeric structures.<sup>[39]</sup> For the alkaline-earth metal congeners only very few examples have been recognized. The heterobimetallic magnesium calcite crystallizes as  $[(hmds)Ca(\mu\text{-}hmds)_2]Mg(hmds)_2$ .<sup>[9d]</sup> Treating a 1:1 mixture of  $Mg(hmds)_2$  and  $Ba(hmds)_2$  with  $PhSiH_3$  allows the isolation of an amide-containing mixed metal hydride  $(Mg_3Ba_4H_{11}(hmds)_7)$ .<sup>[40]</sup>

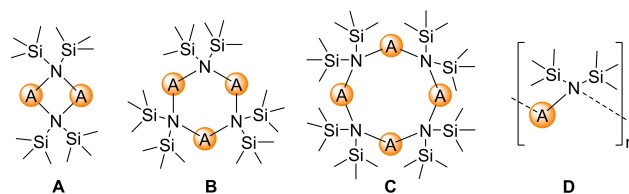
#### 1.4. Structures of s-block metal amides

The structural diversity of s-block metal amides is presented exemplarily at the bis(trimethylsilyl)amide complexes (Scheme 5). The donor-free compounds and Lewis base adducts can be divided into seven principal structural types. Donor-free alkali metal bis(trimethylsilyl)amides form tetramers, trimers and dimers. With increasing size of the metal ions the dimer becomes favored (type A with  $A=K$ ,<sup>[41]</sup> Rb,<sup>[42]</sup> Cs,<sup>[42]</sup> type B with

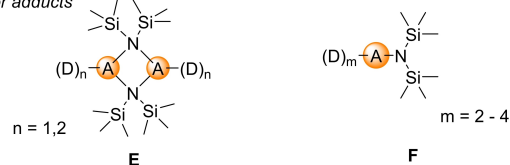


**Scheme 4.** Synthesis and molecular structures of heterobimetallic bis(trimethylsilyl)amides such as solvent-separated alkaline-earth metalates (type III), contact ion pairs (type IV), inverse crowns with a central doubly 1,4-deprotonated benzene (Mulvey reagent) and an example of a coordination polymer of a mixed alkali metal amide.

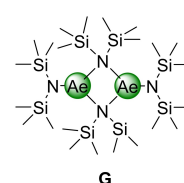
#### Donor-free compounds



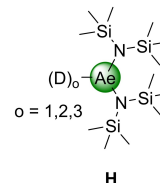
#### Donor adducts



#### Donor-free compounds



#### Donor adducts



**Scheme 5.** Structural motives of (homoleptic) donor-free complexes and Lewis base adducts of homometallic hmds compounds of the alkali (A) and alkaline-earth metals (Ae).

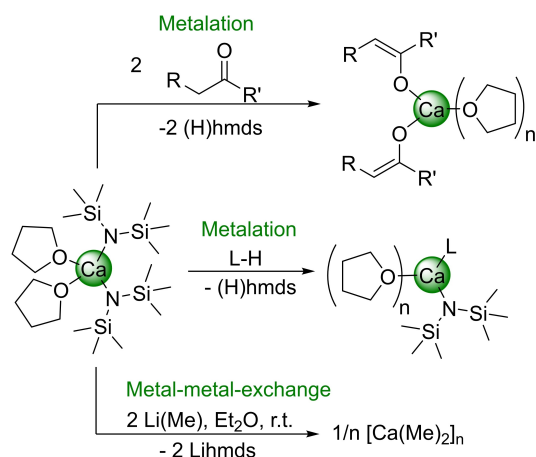
$A=Li$ ,<sup>[43]</sup> Na,<sup>[44]</sup> type C with  $A=Li$ ,<sup>[45]</sup> type D with  $A=Na$ .<sup>[46]</sup> The alkaline-earth metal complexes exclusively crystallize with dimeric structures (type G with  $Ae=Mg$ ,<sup>[47]</sup> Ca,<sup>[48]</sup> Sr,<sup>[48]</sup> Ba<sup>[49]</sup>).

The dimeric nature of the alkali metal species is maintained during addition of monodentate Lewis bases, the number of ligated bases depends on their steric demand. The dimeric heavier alkali metal amides bind mono- and bidentate bases (type E with for example  $NH_3$ ,<sup>[50]</sup>  $Et_2O$ ,<sup>[51]</sup>  $Me_4THF$  (THF: tetrahydrofuran),<sup>[52]</sup> THF,<sup>[53]</sup> THP (tetrahydropyran),<sup>[54]</sup> MTBE (methyl-*tert*-butyl ether),<sup>[54]</sup> isonitriles,<sup>[55]</sup> DME (1,2-dimethoxyethane),<sup>[56]</sup> TMEDA (tetramethylethylenediamine [1,2-bis(dimethylamino)ethane]),<sup>[41b,56–57]</sup> 1,4-dioxane,<sup>[58]</sup> carbenes,<sup>[59]</sup> pyridine,<sup>[35b]</sup> TEMPO (2,2,6,6-tetramethylpiperidinyloxy),<sup>[60]</sup> phosphane oxides,<sup>[61]</sup> ketones,<sup>[62]</sup> fluorinated arenes,<sup>[63]</sup> and crown ethers).<sup>[41b]</sup> However, bi- and polydentate ligands generally stabilize mononuclear complexes (Type F with for example 1,4-dioxane,<sup>[64]</sup> TMEDA,<sup>[56,57b]</sup> DME,<sup>[65]</sup> DMMEA,<sup>[57b]</sup> PMDETA,<sup>[66]</sup> crown ethers,<sup>[24a,67]</sup> and sparteine).<sup>[68]</sup> The alkaline-earth metal bis[bis(trimethylsilyl)amides] crystallize with monodentate and polydentate ligands as monomers with various numbers of donor molecules (type H with carbenes,<sup>[69]</sup> THF,<sup>[49,70]</sup>  $Me_4THF$ ,<sup>[21e]</sup> THP,<sup>[71]</sup> DME,<sup>[48,57b]</sup> DMMEA,<sup>[57b]</sup> TMEDA,<sup>[20b,57b,71a]</sup> PMDETA,<sup>[71a]</sup> imidazoles,<sup>[72]</sup> ketones,<sup>[73]</sup> pyridines,<sup>[74]</sup> and imides<sup>[75]</sup>). In general, s-block metal ions enhance their coordination number by agostic H–A/Ae-interactions with the methyl groups of the amides (see for example Ref. [76]).

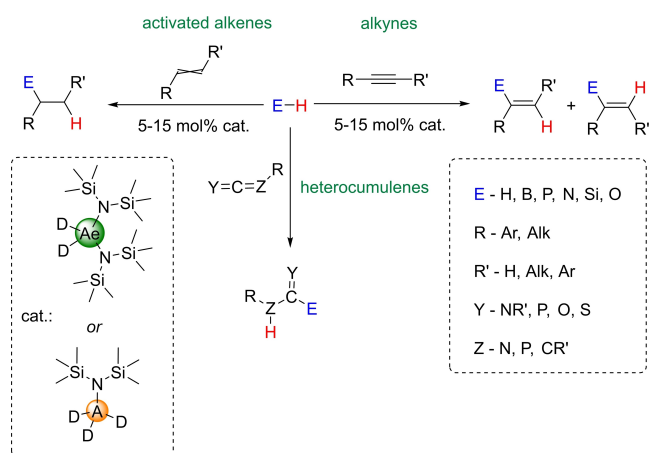
### 1.5. Application in Stoichiometric and Catalytic Reactions

s-Block metal amides have versatile application fields in synthetic chemistry.<sup>[5]</sup> Alkali metal amides such as Li(hmde), Li(dipa), Li(tmp) or K(hmde) are intensively used as metalating reagents in organic and metalorganic syntheses. Together with *Hauser* and *turbo-Hauser* bases like [(thf)Mg(tmp)(μ-Cl)<sub>2</sub>Li(thf)<sub>2</sub>], a plethora of metalation reagents with different base strengths are available. In contrast, the heavy congeners are only sparingly used in coordination chemistry despite their enormous reactivity. The calcium bis(amides) react as metalating reagents for the synthesis of new compounds with higher reactivity or selectivity (Scheme 6). In addition, the heavier alkaline-earth metal bis(hexamethyldisilazanes) can be considered as soluble surrogates for sparingly soluble halides and enable the preparation of highly reactive alkyl compounds like polymeric dimethylcalcium [CaMe<sub>2</sub>]<sub>∞</sub>.<sup>[77]</sup>

Due to their high solubility in organic solvents and their base strength, alkaline-earth metal bis[bis(trimethylsilyl)amides] are versatile precatalysts for hydrofunctionalization, i.e. the



**Scheme 6.** Exemplary stoichiometric applications of (thf)<sub>2</sub>Ca(hmde)<sub>2</sub>.



**Scheme 7.** Hydroelementation of unsaturated compounds using the bis(trimethylsilyl)amides of the alkali or alkaline-earth metals as precatalysts.

addition of diverse element-hydrogen bonds across multiple bond systems (Scheme 7), examples being hydrogenation (E=H),<sup>[75,78]</sup> hydroboration (E=BR<sub>2</sub>),<sup>[79]</sup> hydroacetylation (E=C≡C-R),<sup>[80]</sup> hydroamination (E=NR<sub>2</sub>),<sup>[81]</sup> hydroalkoxylation (E=OR),<sup>[82]</sup> hydrosilylation (E=SiR<sub>3</sub>),<sup>[83]</sup> hydrophosphination (hydrophosphanylation, E=PR<sub>2</sub>),<sup>[84]</sup> and hydrophosphorylation (E=P(O)R<sub>2</sub>).<sup>[84e,85]</sup> Additional examples are *Michael* additions,<sup>[86]</sup> [2,2]-cycloadditions<sup>[87]</sup> or *Claisen-Tishchenko*-reactions<sup>[88]</sup> which can be catalyzed efficiently by s-block metal amides, too.<sup>[89]</sup>

As catalysts in ring opening polymerization reactions, non-toxic s-block metal amides substitute very efficiently the established hazardous tin(II) octanoate. The amides react as precatalysts initially with an alcohol under formation of an alcoholate. The fact that many heavier alkaline-earth metal alcoholates are insoluble coordination polymers, in situ prepared alcoholates have to be used in polymerization catalysis.<sup>[4a,f,81e,90]</sup>

## 2. In Situ Generation of Magnesium- and Calcium-Based Grignard Reagents

The inertness of the metals magnesium and calcium themselves hinders a direct metalation of amines and hence more reactive metalation reagents are required for the preparation of amides. Hitherto, the synthesis of calcium amides succeeded via diverse procedures which posed drawbacks of different kinds such as toxic heavy metal substrates, sophisticated preparative protocols, metal activation prior to use and others.

### 2.1. Formation and properties of Grignard reagents

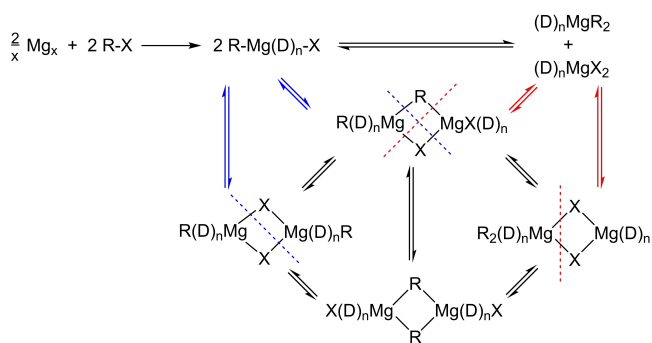
More than 120 years ago, magnesium organometallics have been established and are still fascinating and widely used reagents<sup>[91]</sup> which are easily available. The detailed mechanism of formation in an ethereal suspension of magnesium turnings and organyl halide is repeatedly attracting interest.<sup>[92]</sup>

In addition, *Grignard* reagents show solvent dependent *Schlenk* equilibria interconverting heteroleptic RMgX into homoleptic MgR<sub>2</sub> and MgX<sub>2</sub> as depicted in Scheme 8.<sup>[93]</sup> In Table 2, solvation enthalpies of Et<sub>2</sub>Mg, EtMgBr and MgBr<sub>2</sub> in diethyl ether and in stronger *Lewis* basic THF are compared. The electrophilicity decreases in the order MgBr<sub>2</sub> > EtMgBr > Et<sub>2</sub>Mg. In Et<sub>2</sub>O, 2 mol of EtMgBr (−62 kJ) are favored compared to 1 mol of Et<sub>2</sub>Mg and 1 mol of MgBr<sub>2</sub> (−56 kJ) whereas in THF the

**Table 2.** Solvation enthalpy of compounds involved in the *Schlenk* equilibrium of EtMgBr in diethyl ether and THF [kJ mol<sup>−1</sup>].

Solvent	Et <sub>2</sub> Mg	EtMgBr	MgBr <sub>2</sub>	K <sup>[a]</sup>
Et <sub>2</sub> O	−24	−31	−32	480
THF	−36.6	−68.3	−109	5.09

[a] The equilibrium constant K was determined for the formation of the Grignard reagent from the homoleptic compounds according to the equation MgEt<sub>2</sub> + MgBr<sub>2</sub> ↔ 2 EtMgBr.



**Scheme 8.** The *Grignard* reaction of magnesium with organyl halide yielding ligated  $\text{RMgX}$  which undergoes ligand scrambling in the *Schlenk* equilibrium via dinuclear magnesium complexes.

homoleptic compounds are favored ( $-145.6 \text{ kJ}$ ) compared to 2 mol of  $\text{EtMgBr}$  ( $-136.6 \text{ kJ}$ ).<sup>[94]</sup>

Besides the influence of the solvent on the *Schlenk* equilibrium, also the group  $\text{R}$  influences the equilibrium constant with larger values for longer alkyl chains.<sup>[94]</sup> Phenylmagnesium bromide shows smaller  $K$  values for the formation of the *Grignard* reagent from the homoleptic compounds according to the equation  $\text{MgPh}_2 + \text{MgBr}_2 \leftrightarrow 2 \text{PhMgBr}$  (in  $\text{Et}_2\text{O}$ : 55, in THF: 3.8).<sup>[94]</sup> Addition of 1,4-dioxane ( $\text{dx}$ ) allows to isolate dialkylmagnesium as halide-free dioxane adduct because the magnesium halides  $[(\text{dx})_2\text{MgX}_2]_\infty$  ( $\text{X}=\text{Cl}, \text{Br}$ ) are coordination polymers with layered structures and precipitate quantitatively.<sup>[95]</sup>

The reducing properties of *Grignard* reagents in diethyl ether have been investigated as well. Thus, the standard oxidation potentials also depend on the alkyl group ( $E^\circ$  for  $\text{RMgBr}$ :  $\text{R}=\text{Me} -0.25$ ,  $\text{Et} -0.66$ ,  $\text{Bu} -0.53$ , and  $\text{Ph} 0.0 \text{ V}$  vs. NHE).<sup>[96]</sup> Thus,  $\text{RMgX}$  can transfer an electron on the substrate  $\text{R}'\text{Y}$  yielding  $\text{RMgX}^+$  as well as  $\text{R}^*$  and  $\text{Y}^-$ , followed by a  $\text{C}-\text{C}$  coupling reaction and formation of  $\text{R}-\text{R}'$  as well as  $\text{MgXY}$ . Mechanistically, several competing pathways are possible which are discussed in detail elsewhere and hence neglected in this report.<sup>[91c]</sup>

In most cases the *Grignard* reaction proceeds with satisfactory to excellent yields, and the amount of  $\text{C}-\text{C}$  coupling side products is insignificant and negligible. Therefore, this reaction belongs to a standard reaction for all students studying chemistry major.

## 2.2. Organometallic calcium reagents

The synthesis of calcium-based *Grignard* reagents (post-*Grignard* reagents or heavy *Grignard* reagents) poses severe challenges. After electrochemical production of calcium metal, *Beckmann* reacted calcium shavings with iodobenzene and iodoethane in diethyl ether and reported the synthesis of phenylcalcium iodide and “rather air-stable” ethylcalcium iodide.<sup>[97]</sup> Twenty years thereafter, *Gilman* and *Schulze* disputed these results and they observed that (i) the reaction of  $\text{Ca}$  with

$\text{RI}$  was sluggish and irregular, (ii) was restricted to iodides and (iii) to primary alkyl halides, (iv) the yields were far from satisfactory, (v) formation of  $\text{R}-\text{R}$  was a pronounced side reaction, and (vi) organocalcium iodides were soluble in ether.<sup>[98]</sup> They also claimed the synthesis of diethylcalcium via transmetalation of diethylzinc with calcium turnings.<sup>[99]</sup> The reaction of calcium shavings with iodomethane in pyridine gave highly colored solutions and *Payne* and *Sanderson* reported the isolation of dimethylcalcium via extraction of the precipitate with pyridine.<sup>[100]</sup> Later, it was stated by another research group that this “report of the isolation of  $\text{MMe}_2$  ( $\text{M}=\text{Ca}, \text{Sr}, \text{Ba}$ ) is apparently in error”.<sup>[101]</sup> At the same time, *Bryce-Smith* and *Skinner*<sup>[102]</sup> as well as *Kawabata* and coworkers<sup>[103]</sup> prepared alkyl- and phenylcalcium iodide in THF and noticed that very low temperatures were highly beneficial and that sodium impurities in calcium were disadvantageous. Even toluene proved to be a suitable solvent in their hands.<sup>[104]</sup> Despite the report that “calcium appears unable to displace mercury from organomercury compounds”,<sup>[102]</sup> diarylcalcium was prepared by transmetalation of diarylmercury with calcium in THF.<sup>[105]</sup> Due to these challenges and inconsistent results, the interest in organocalcium chemistry ceased. To overcome the inertness of calcium metal, cocondensation of calcium vapor and organyl halides was studied by *Mochida* and coworkers.<sup>[16,106]</sup> In a typical procedure, calcium vapor was condensed at  $77 \text{ K}$  and then THF slurries were produced that were reacted with organyl halides. Yields were determined via the amount of  $\text{RH}$  after hydrolysis with diluted hydrochloric acid. A comparable procedure and solvent exchange yielded  $[(\text{dx})_2\text{Ca}\{\text{CH}(\text{SiMe}_3)_2\}_2]$ , the first structurally authenticated alkylcalcium compound.<sup>[107]</sup> The mechanochemical synthesis of *Grignard* reagents ( $\text{Mg}$ ,<sup>[108]</sup>  $\text{Ca}$ )<sup>[109]</sup> in a ball mill reduced significantly the amount of required solvent and hence, only solvent quantities had to be present to allow the coordinative saturation of the metal cations. Thereafter, metathetical approaches of  $\text{KR}$  with  $\text{CaI}_2$  allowed isolation and structural characterization of for example  $[\text{Ca}\{\text{C}(\text{SiMe}_3)_3\}_2]$ <sup>[110]</sup> and  $[(\text{thf})_2\text{Ca}\{\text{CH}(\text{SiMe}_3)_2\}_2]$ ,<sup>[111]</sup> stabilized electronically and sterically by bulky trimethylsilyl groups. The metathetical approach became the preferred route for the preparation of organocalcium reagents and dimethylcalcium as well as methylcalcium iodide were accessible by a metathetical variant.<sup>[77]</sup> The calcium-based *Grignard* reaction required at least one trimethylsilyl group and the reaction of  $\text{Me}_3\text{SiCH}_2\text{X}$  ( $\text{X}=\text{Br}, \text{I}$ ) with calcium gave trimethylsilylmethylcalcium halides whereas methylcalcium halide could not be prepared via direct synthesis due to the dominating *Wurtz*-type  $\text{C}-\text{C}$  coupling reaction.<sup>[19,112]</sup> Thus, the direct synthesis of organocalcium compounds remained limited to aryl halides and trimethylsilylmethyl halide<sup>[113]</sup> and alternative routes had to be developed to overcome the discrepancy between the inertness of the calcium metal and the enormous reactivity of organocalcium compounds leading to dominating side reactions such as ether cleavage<sup>[114]</sup> and *Wurtz*-type  $\text{C}-\text{C}$  coupling reactions.

This aspect suggests that organocalcium compounds should be prepared within a short time and used immediately to suppress side reactions. To avoid work-up procedures of highly air- and moisture sensitive organocalcium compounds, inter-

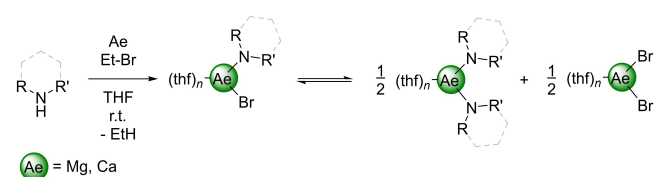


mediate preparation in the presence of another substrate seems advantageous to also circumvent large concentrations of potentially sparingly soluble  $\text{RCaX}$  and  $\text{CaR}_2$ . In addition, low reaction temperature decelerates ether cleavage reactions.

### 2.3. General procedure of the in situ generation of magnesium and calcium amides

Since magnesium and calcium are not able to directly metalate (H)hmds (hexamethyldisilazane [bis(trimethylsilyl)amide]) and other amines, the in situ *Grignard* metalation method (iGMM) offers an easily controllable and scalable straightforward synthesis to form the corresponding alkaline-earth metal amides.<sup>[115]</sup>

In a general procedure, commercial magnesium or calcium turnings (without purification or activation) and amine are suspended in THF and 1.0 equiv. of ethyl bromide is added at once at room temperature (Scheme 9). After an induction period, a visible, smooth gas evolution occurs due to the formation of ethane regardless of the amount of the substrates. In case of magnesium, the solution remains clear; in contrast, the calcium substrate leads to a turbid reaction mixture due to precipitating nearly insoluble calcium halide (Figure 1). The hardly soluble calcium halide shifts the *Schlenk*-type equilibrium toward the homoleptic alkaline-earth metal bis(amides).<sup>[20b]</sup> Ceasing gas evolution indicates the completion of the reaction. The conversion rate can be determined by titration of a hydrolyzed aliquot of the reaction solution with 0.1 N sulfuric acid against phenolphthalein. In some cases, for example using (H)hmds, the conversion rate can be increased by addition of a second equiv. of ethyl bromide in the presence of excess of alkaline-earth metal. In very rare cases, significant amounts of side products such as alkylated amines (coupling of  $\text{RX}$  with  $\text{MNR}_2$ ) and ether degradation reactions reduce the practicability of this protocol.



**Scheme 9.** General procedure of the iGMM showing the formation of alkaline-earth metal amides and the *Schlenk*-type equilibria between heteroleptic and homoleptic compounds.



**Figure 1.** Reaction course of the iGMM, using calcium, (H)hmds and EtBr. The reaction starts with a slight gas evolution, followed by a turbidity, due to the formation of THF-insoluble  $\text{CaBr}_2$ .

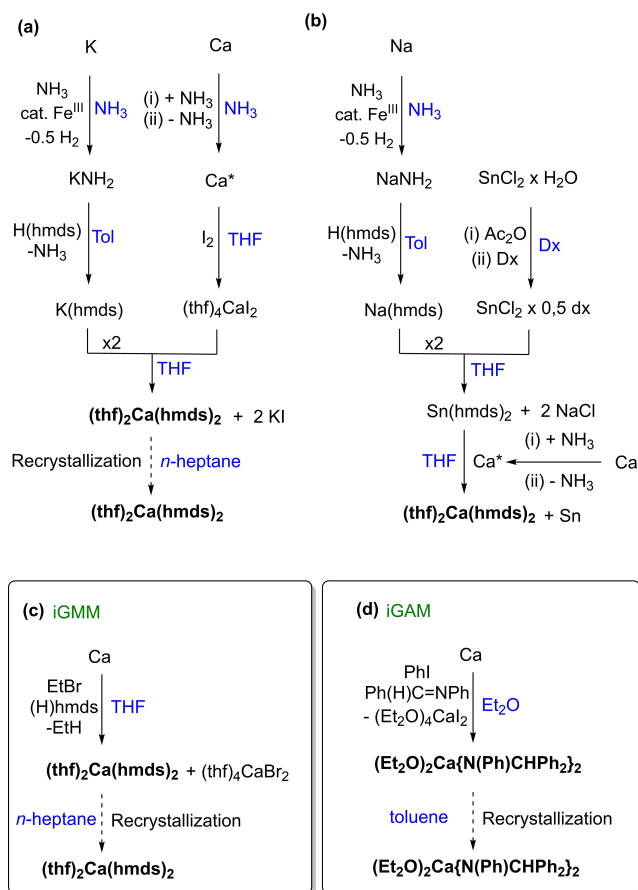
The extension of the iGMM to other donor solvents has also been investigated. Screening of the benchmark reaction of the alkaline-earth metal with (H)hmds shows that the iGMM with magnesium also leads to the formation of the *Hauser* base  $(\text{D})_n\text{Mg}(\text{hmds})\text{Br}$  in other monodentate ethers (e.g., 2-MeTHF,  $\text{Et}_2\text{O}$ , MTBE) with high conversion rates (Table 3).<sup>[27]</sup> Using calcium, only THF represents an advantageous solvent whereas significantly lower yields have been achieved in all other tested solvents.<sup>[97]</sup> The reaction can be performed with other organohalides, too, but EtBr is the reagent of choice because good yields and only volatile side products (ethane, ethene) are observed. The small amounts of ethene are formed via  $\beta$ -hydride elimination during the formation of the *Grignard* reagent or degradation of THF if the reaction is performed using this solvent.<sup>[27]</sup>

To shed light on advantages and atom economic aspects of the method, Scheme 10 illustrates a comparison of the iGMM with other established synthetic protocols for the synthesis of  $(\text{thf})_2\text{Ca}(\text{hmds})_2$ . Firstly, the iGMM (c) shows an obviously smaller number of reaction steps compared to salt metathetical procedures (a) and transmetalation reactions (b). This smaller number of reaction steps also reduces the sum of required chemicals (substrates as well as solvents) and the amount of energy. In addition, these beneficial conditions ease upscaling of the synthesis. Furthermore, exact stoichiometric ratio of the substrates is unnecessary as far as excess of metal and ethyl bromide is applied to avoid mixtures of amines and amides. For salt metathesis protocols an exact stoichiometry must be maintained to avoid the formation of calciates. Transmetalation of tin amides leads to formation of finely divided (colloidal) tin powder. During the transmetalation of mercury amides elemental mercury leading to a rather solid calcium amalgam. In addition, the formed secondary products in the straightforward iGMM are insoluble (potentially valuable anhydrous  $[(\text{thf})_4\text{CaBr}_2]$ , which can be used for organometallic reactions) or volatile (ethane, ethene) and therefore easy to remove. This fact also offers the opportunity to reuse the solvent without elaborate purification.

**Table 3.** Solvent screening for the synthesis of  $(\text{D})_n\text{Ca}(\text{hmds})_2$  using the iGMM and the comparison of this reaction with magnesium and calcium metal.

Entry	Solvent <sup>[a]</sup>	Conv [%], iGMM with Mg	Conv [%], iGMM with Ca
1	THF	92	46, > 95 <sup>[b]</sup>
2	$\text{Et}_2\text{O}$	94	0
3	2-MeTHF	92	0
4	MTBE	93	n.d.
5	CPME	n.d.	0
6	1,3-dioxolane	71	0
7	Methylal	23	0
8	DME	21	17
9	Triglyme	57	n.d.
10	Toluene	n.d.	0

[a] Me = methyl, Methylal = 1,1-dimethoxymethane, CPME = cyclopentylmethylether, MTBE = methyl-*tert*-butylether, 2-MeTHF = 2-methyltetrahydrofuran, triglyme = triethyleneglycoldimethylether. [b] Reaction was performed using an additional equivalent of EtBr.



**Scheme 10.** a–c) Comparison of the different synthetic strategies for the synthesis of  $(\text{thf})_2\text{Ca}(\text{hmnds})_2$  starting from *s*-block metals. d) Synthesis of  $(\text{Et}_2\text{O})_2\text{Ca}(\text{N}(\text{Ph})\text{CHPh}_2)_2$  starting from calcium.

## 2.4. Scope of the in situ Grignard metalation method (iGMM)

In addition to reaction optimization, studies have been also conducted to broaden the substrate spectrum. Besides  $(\text{H})\text{hmnds}$ , which has been used to develop the iGMM, other silyl amines, cyclic and acyclic amines, anilines, and *N*-heterocycles, *N,N'*-diarylamidines, cyclopentadienes and other CH-acidic substrates have been tested as depicted in Scheme 11. The iGMM with magnesium metal leads in almost all cases to high conversion rates. Using calcium, the reaction is limited in some cases, but offers an easily accessible and advantageous synthesis route of amides and other homoleptic calcium compounds at room temperature using THF as donor solvent.

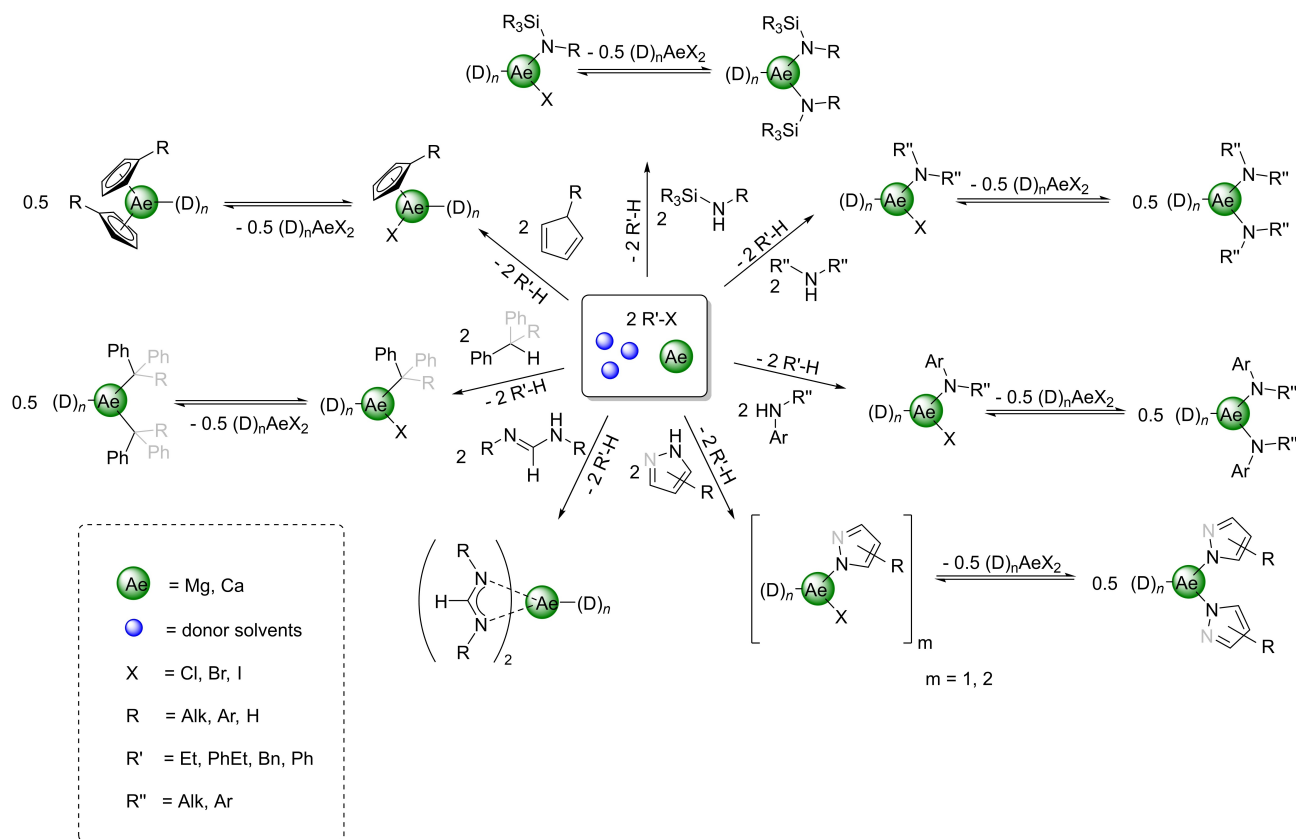
The reaction of magnesium with  $(\text{H})\text{hmnds}$  and  $\text{EtBr}$  yields the *Hauser*-type complex  $(\text{D})_n\text{Mg}(\text{Br})(\text{hmnds})$  in nearly quantitative conversion. Running the iGMM with  $(\text{H})\text{hmnds}$  and calcium, the conversion can be enhanced up to  $>95\%$  by addition of another equivalent of  $\text{EtBr}$ . Other silylamines represent suitable substrates, too, and lead to the corresponding amides in high yields. Trialkylsilyl substituents enhance the  $\alpha$ -anion stability via hyperconjugation, stabilizing the negative charge on the nitrogen atom. Increased steric demand of the *N*-bound trialkylsilyl substituents limits the applicability of this reaction.

Dialkylamides are accessible via iGMM, however, lower reaction temperatures and diluted solutions give significantly higher conversion rates. The preparation of the (*turbo*)-*Hauser* base  $(\text{tmp})\text{MgX}/(\text{tmp})\text{MgX}\cdot\text{LiCl}$  and the homoleptic calcium bis(amide)  $\text{Ca}(\text{tmp})_2$  is a highlight of the method because the straightforward synthesis yields powerful and widely applied deprotonation reagents (utility amides).<sup>[116]</sup> For example, in established synthesis protocols of  $(\text{tmp})\text{MgCl}\cdot\text{LiCl}$ , which are reported and used in numerous applications by *Knochel* and co-workers, the synthesis of  $i\text{PrMgCl}\cdot\text{LiCl}$  via *Grignard* reaction is necessary prior to the application of this metalation reagent. Although the solutions are commercially available, the iGMM offers a simple way to prepare (*turbo*)-*Hauser* bases within very few hours starting from elemental magnesium.<sup>[117]</sup>

Exchange of an alkyl substituent by an aryl group (i.e. aniline derivatives) leads to suitable substrates in the iGMM. It is noteworthy that aniline itself does not react under the common reaction conditions but an activation of the amine by further substitution at the nitrogen atom is necessary to enable the reaction. Again, stabilizing trimethylsilyl substituents support the formation of anilides. Using the iGMM, magnesium anilides are accessible with high yields, whereas the calcium species can only be obtained with moderate yields. In case of magnesium, *p*-methylaniline as a primary aniline derivative is a suitable substrate and a hexanuclear magnesium imide with a hetero-adamantane-like structure is formed after addition of 1,4-dioxane.<sup>[27]</sup>

Furthermore, the iGMM enables the metalation of nitrogen-containing heterocycles. Indole and pyrazoles are valuable substrates for the preparation of magnesium and calcium amides, whereas methyl substituents significantly increase the yields. On the contrary, aryl substituents impede the reaction. Pyrroles behave very similar to pyrazoles but show generally lower yields in the iGMM with calcium. Carbazole and phenothiazine react with magnesium in quantitative conversion, while calcination was impossible. *N*-Heterocycles, containing more than two nitrogen atoms in the ring, behave inert. Beside heterocycles, *N,N'*-diarylamidines expand the scope of this reaction to acyclic unsaturated amines. For example, *N,N'*-di(2,6-diisopropylphenyl)formamidine is a suitable substrate for the formation of the homoleptic magnesium bis(amidinate) in moderate yields. In the case of calcium metal, no reaction occurs due to the high steric demand of the formamidine.

To broaden the scope of the iGMM from NH-acidic to CH-acidic substrates, reactions with phenyl-substituted methane, fluorene and indene derivatives have been studied. While calcium diphenylmethanide can be prepared in low conversions, toluene and triphenylmethane show no reactivity under the described conditions. In the reaction with indene and fluorene derivatives no deprotonation occurs, even introduction of a trimethylsilyl substituent does not enhance the yield significantly. In contrast to these findings, the conversion of cyclopentadienes occurs smoothly in moderate to excellent yields using the iGMM. For example,  $\text{CpH}$ ,  $^{\text{TMS}}\text{CpH}$  and  $^{\text{TIPS}}\text{CpH}$  can be metalated with this method. The formed cyclopentadienides underlie a *Schlenk*-type equilibrium in ethereal solutions as described for cyclopentadienylmagnesium bromides in



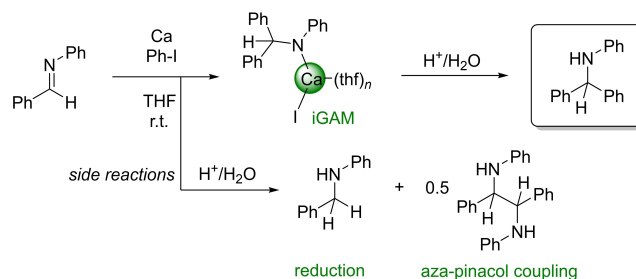
**Scheme 11.** Overview of the substrate screening of NH- (silyl amines, dialkylamines, aniline derivatives, *N*-heterocycles and formamidines) and CH-acidic (phenyl-substituted methane and cyclopentadienes) compounds to illustrate the scope of the iGMM.

previous studies employing the iGMM.<sup>[118]</sup> In case of calcium, the equilibrium lies on the side of homoleptic calcoenes; heteroleptic cyclopentadienylcalcium bromides were only observed as intermediate species.<sup>[119]</sup> Enhancing the steric bulk of the substituents is disadvantageous.

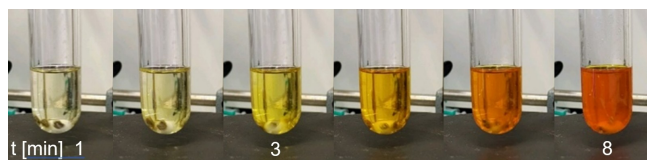
## 2.5. Scope of the in situ Grignard addition method (iGAM)

For the synthesis of sterically congested alkaline-earth metal amides another procedure than the iGMM has been developed. The intermediately formed heavy *Grignard* reagents cannot only be used for deprotonation of H-acidic compounds but also in addition reactions onto imines, the iGAM.<sup>[120]</sup> As proof of concept,  $[(Et_2O)_2Ca\{N(Ph)CHPh_2\}_2]$  has been prepared by the addition of previously isolated and recrystallized phenylcalcium iodide onto *N*-benzylideneaniline in diethyl ether. To avoid the isolation of the very reactive heavy *Grignard* reagent and to minimize side reactions, a one-pot procedure has been established, reacting calcium metal, phenyl iodide and *N*-benzylideneaniline in THF at room temperature in a smooth manner (Scheme 12).

The reaction started directly after addition of phenyl iodide to the suspension of calcium and imine in THF. During the first eight minutes, a color change from slightly yellow to deep orange indicates the start of the conversion (Figure 2). Stirring



**Scheme 12.** General procedure of the iGAM followed by hydrolysis to yield the addition product *N*-benzhydrylaniline.



**Figure 2.** Starting period of the iGAM, using calcium, *N*-benzylideneaniline and phenyl iodide in THF solution.

overnight and subsequent hydrolysis of the finally red-brown reaction mixture allows the isolation of *N*-benzhydrylaniline with high yield. Minor side products are traces of 1,2-dianilino-



1,2-diphenylethane (*aza*-pinacol coupling product) and benzylaniline (two-electron reduction). Solvent screening using different ethereal solvents shows that in contrast to THF, the reaction in Et<sub>2</sub>O, 2-MeTHF and CPME leads to mixture of addition and *aza*-pinacol coupling products. Furthermore, a mechanochemical ball milling procedure, using calcium granules, imines and an organyl halide, is successful.<sup>[120]</sup>

Beside phenyl iodide other aryl (e.g. tolyl, anisyl, naphthyl) and alkyl (e.g. ethyl, butyl, isopropyl) iodides are suitable for the iGAM leading to addition products in moderate to high yields. Increasing steric demand of the aryl halide by introduction of *ortho*-substituents (e.g. mesityl and 2,4,6-tri(*tert*-butyl)phenyl iodide) favors the formation of the *aza*-pinacol coupling product. Exchange of the iodine by bromine also enhances the amount of 1,2-dianilino-1,2-diphenylethane. In addition to the calcium-based iGAM, the reaction can also be performed with strontium yielding a rather similar product distribution. The reaction with barium metal enhances the *aza*-pinacol coupling product, yielding *N*-benzhydrylaniline and 1,2-dianilino-1,2-diphenylethane in nearly equimolar amounts.

The product distribution can easily be understood considering two competing reaction pathways. The projected reaction is the straightforward addition of R<sub>A</sub>E<sub>X</sub> (or AeR<sub>2</sub>) across the N=C double bonds. Alternatively, a single-electron transfer from calcium metal onto the imine leads to a radical anion. Recombination with the organic radical R<sup>•</sup> yields the intended amide. However, recombination of two imine radical anions leads to formation of *aza*-pinacol coupling products which can be the dominating side reaction. Furthermore, another electron transfer onto the imine radical anion gives a dianion; such a two-electron transfer onto an imine with calcium metal has been recognized earlier.<sup>[121]</sup> This species can react with still present substrate RX again leading to the projected alkaline-earth metal amide. Due to the presence of this dianion during hydrolytic work-up also very minor amounts of the reduced imine, a secondary amine, are observed. Despite the complexity of the iGAM, many alkaline-earth metal amides can be prepared with satisfying yields at room temperature in ethereal solvents under straightforward reaction conditions.

### 3. Proposed Mechanism for Formation of Magnesium and Calcium Amides

The synthesis of magnesium and calcium amides involves many sequential reaction steps which are shown in Scheme 13. The initial step is the single electron transfer (SET) from the alkaline-earth metal particle onto the organyl halide yielding the halide ion and an organyl radical. The organic radical can directly be trapped by the metal and subsequent solvation by *Lewis* basic solvent molecules D yield the (heavy) *Grignard* reagent [(D)<sub>n</sub>Ae(R)X] (Ae=Mg, Ca). To ensure sufficiently soluble calcium species strongly basic THF is the preferred solvent whereas for magnesium compounds other ethers are suitable as well. The mechanism of the *Grignard* reaction has been studied in depth for magnesium and also for calcium.<sup>[122]</sup> Magnesium- and

calcium-based organometallics show solvent dependent *Schlenk*-type equilibria leading to a mixture of heteroleptic R<sub>A</sub>E<sub>X</sub> as well as homoleptic AeR<sub>2</sub> and AeX<sub>2</sub>. The insolubility of CaX<sub>2</sub> in organic solvents shifts the equilibrium in favor of the homoleptic calcium derivatives. The heavy *Grignard* reagents CaR<sub>2</sub> and RCaX are highly reactive and cannot be stored due to incipient ether degradation processes. The quantum chemically calculated ionicity of 89% for the Ca–C bond can be compared with the value of 87% for Li–C bonds whereas the ionicity of 77% for the Mg–C bond is significantly smaller,<sup>[123]</sup> a finding that is also in agreement with the expectation based on electronegativity values. Therefore, one would assume very similar reaction behavior of lithium- and calcium-based organometallics which is more aggressive than the magnesium congeners.

#### 3.1. iGMM

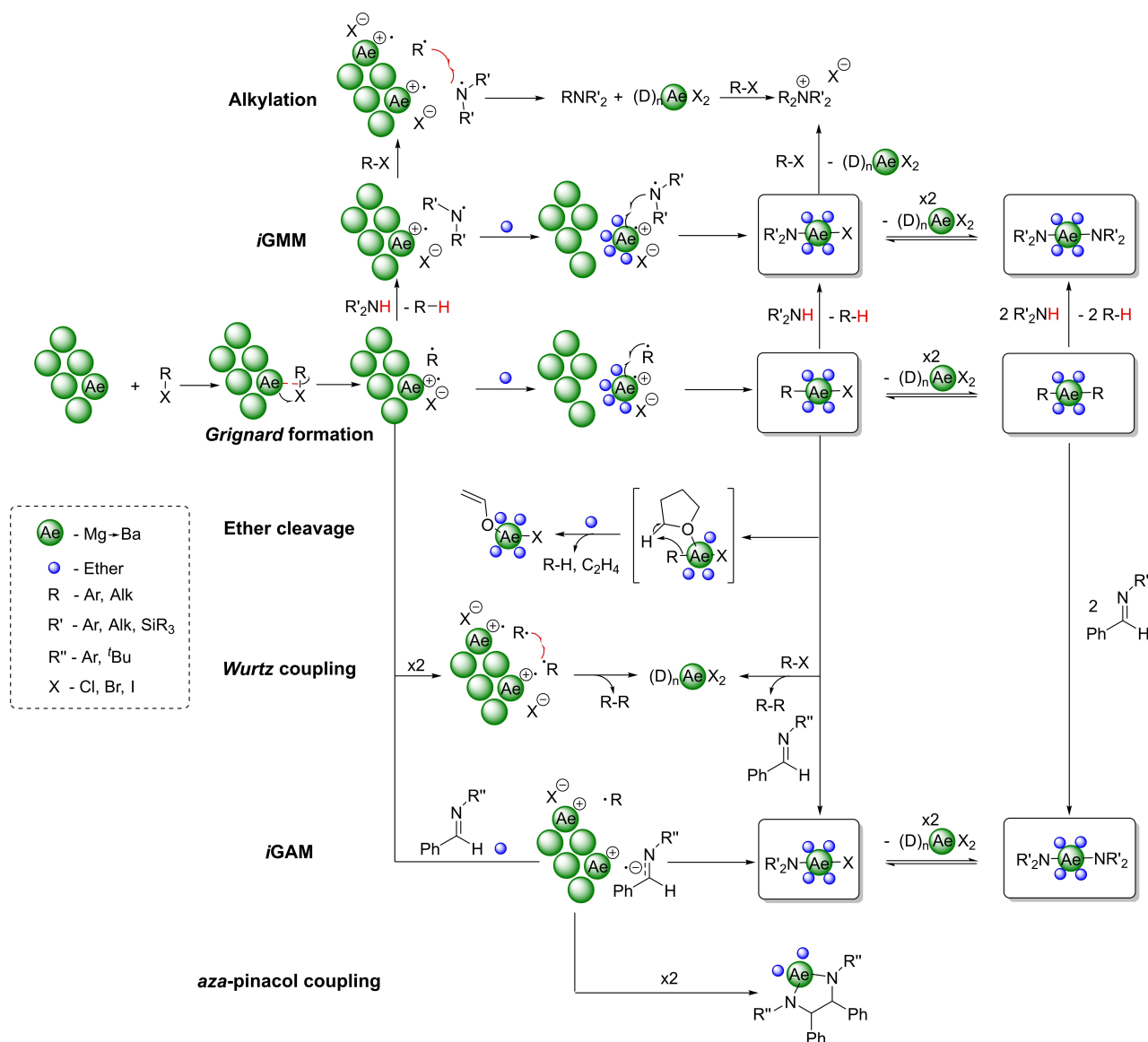
These intermediately formed heavy *Grignard* reagents can metalate H-acidic compounds such as amines yielding the corresponding amides. Whether CaR<sub>2</sub> or RCaX performs the metalation reaction depends on the competition between the *Schlenk* equilibrium and the metalation process. In Scheme 13 the *Schlenk*-type ligand scrambling is depicted in the right two columns. Regardless of the active species, calcium bis(amides) form due to insolubility of calcium halides in ethereal solvents. Solvation of the metal ions by strong *Lewis* bases is a required driving force and therefore, weaker ethers or hydrocarbons are unsuitable solvents for the iGMM. Precipitation of sparingly soluble products onto the metal particles stops the reaction, and in these cases, the ball milling procedure seems to be advantageous.

An alternative pathway is the attack of the organyl radical R<sup>•</sup> at the amine leading to the formation of RH and an aminyl radical. The aminyl species can be trapped on the particle surface, finally leading to ligated R'<sub>2</sub>N–CaX which again undergoes a *Schlenk*-type ligand exchange due to the formation of very sparingly soluble calcium halides.

The major side reaction leads to the formation of the *Wurtz*-type C–C coupling product R–R via recombination of two organyl radicals. Another side reaction involves the formation of RNR'<sub>2</sub> due to the N–C coupling reaction of R'<sub>2</sub>N–CaX with RX. Another equivalent of RX may even form ammonium salts of the type NR<sub>2</sub>R'<sub>2</sub><sup>+</sup> X<sup>–</sup> as shown at the top of Scheme 13.

#### 3.2. iGAM

The addition of the organocalcium component onto an imine yields calcium amides. Depending on the fact whether PhCaX or CaPh<sub>2</sub> reacts with Ph–CH=NPh either solvated Ph<sub>2</sub>CH–N(Ph)–CaX or [Ca{N(Ph)–CHPh<sub>2</sub>}<sub>2</sub>] is formed. As mentioned above, the insolubility of calcium halides only allows the isolation of the calcium bis(amide) [Ca{N(Ph)–CHPh<sub>2</sub>}<sub>2</sub>] regardless of the reacting calcium reagent. In Scheme 13 the heteroleptic complex is depicted for simplicity reasons which is however only accessible



**Scheme 13.** Summary of processes in a reaction of alkyl(aryl) halides with alkaline-earth metals and amines (iGMM) or imines (iGAM).

for the magnesium-based iGAM. As mentioned above, recombination of two imine radical anions leads to the formation of the aza-pinacol coupling product, a substituted 1,2-bis(amido)ethane derivative which is depicted in the bottom line of Scheme 13. The two-electron transfer from calcium onto the imine is neglected in this picture because it plays a very minor role in this reaction regime. The transfer of an electron onto an anion is a highly disadvantageous reaction for electrostatic reasons and cannot compete with the other pathways described above.

#### 4. Conclusion

The in situ *Grignard* reagent formation circumvents diverse difficulties related to the preparation of organic amides of the

benign, environmentally friendly and globally abundant alkaline-earth metals magnesium and calcium. On the one hand, inertness of these metals often requires activation procedures prior to their application in synthetic chemistry. On the other hand, magnesium- and especially calcium-based organometallics are highly reactive not only toward moisture (hydrolysis) and air (oxidation) but side reactions with substrates and solvents often reduce the product yields. The following side reactions have been observed during the reduction of alkyl halides with these alkaline-earth metals:

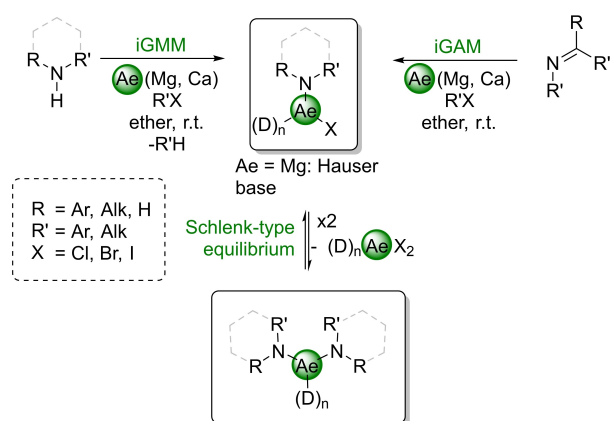
- *Wurtz*-type C–C coupling reactions of  $RAeX$  with  $RX$  yield  $R-R$  and thermodynamically strongly favored and occasionally sparingly soluble  $AeX_2$ .
- Ether degradation occurs via deprotonation in  $\alpha$ - or  $\beta$ -position of THF or diethyl ether and other ethers leading to formation of alcohols.

- $\beta$ -Hydride elimination from EtAeX (or *n*-alkylalkaline-earth metal derivatives) intermediately forms HAeX and ethene, a very minor and often neglected process in organomagnesium chemistry.

Due to these degradation reactions stock solutions of alkylcalcium compounds cannot be prepared (and hence are not available commercially). For the synthesis of magnesium and calcium amides two complementary pathways offer promising strategies (Scheme 14). To avoid large amounts and concentrations of highly reactive RAeX, these compounds are consumed immediately after formation by a substrate already present in the reaction mixture. If primary or secondary amines are available, metalation by the in situ prepared *Grignard* reagent (iGMM) yields the corresponding amides. In the presence of an imine substrate the addition of the *Grignard*-type reagent onto the C=N double bond (iGAM) gives amides, too. As minor side reactions these amides R<sub>2</sub>N-AeX and Ae(NR'<sub>2</sub>)<sub>2</sub> can react with RX leading to R-NR'<sub>2</sub> via a C-N coupling reaction. Therefore, volatile RX is beneficial because it is easily removed in vacuo after complete conversion.

Reaction conditions must be chosen which ease the synthesis of the projected amides but decelerate detrimental side reactions. Low reaction temperatures below room temperature make ether cleavage processes slow and almost negligible. The formation of the *Grignard*-type reagent proceeds usually within a few hours whereas metalation of amines (iGMM) and addition onto imines (iGAM) are much faster reactions. Ethereal solvents are required to ensure the formation of soluble ether adducts. Insoluble or very sparingly soluble products and side products often precipitate onto the surface of the alkaline-earth metal particles and hence the reduction of RX ceases. For calcium-based *Grignard*-type reactions only THF proves to be a generally suitable solvent whereas for magnesium-based chemistry other monodentate ethers can also be used for these procedures.

These reactions are accompanied by *Schlenk*-type equilibria which interconvert heteroleptic RAeX and R'<sub>2</sub>N-AeX into homoleptic AeR<sub>2</sub> and Ae(NR'<sub>2</sub>)<sub>2</sub> with simultaneous formation of AeX<sub>2</sub>. For magnesium derivatives the equilibrium constant depends



**Scheme 14.** Presentation of complementary iGMM (left) and iGAM (right) for the synthesis of alkaline-earth metal amides via in situ *Grignard* reagent formation in ethereal solvents at room temperature.

on the solvent and can lie in favor of RMgX (*Grignard* reagent) and R'<sub>2</sub>N-MgX (*Hauser* base). Addition of 1,4-dioxane shifts the equilibrium toward the homoleptic congeners because [(dx)<sub>2</sub>MgX<sub>2</sub>] is insoluble in organic solvents. In contrast, CaX<sub>2</sub> is generally only very sparingly soluble in ethereal solvents and precipitates quantitatively during iGMM and iGAM.

Alternative promising routes for the preparation of amides of calcium involve ball milling processes. In this procedure, calcium turnings, RX and amine or imine are treated in the presence of a very small amount of ether, preferably THF, in a ball mill at room temperature in an inert atmosphere. After several hours, the slurry is washed out from the reaction vessel with an ethereal solvent and common work-up procedures allow isolation of calcium bis(amides). Due to the fact that calcium also acts as a reducing agent toward imines, the product distribution differs from iGAM protocols.

## Acknowledgements

Open Access funding enabled and organized by Projekt DEAL.

## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

**Keywords:** amides · *Grignard* reaction · in situ *Grignard* metalation method · in situ *Grignard* addition method · organocalcium reagents

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Manuscript received: March 15, 2023

Accepted manuscript online: May 16, 2023

Version of record online: June 16, 2023