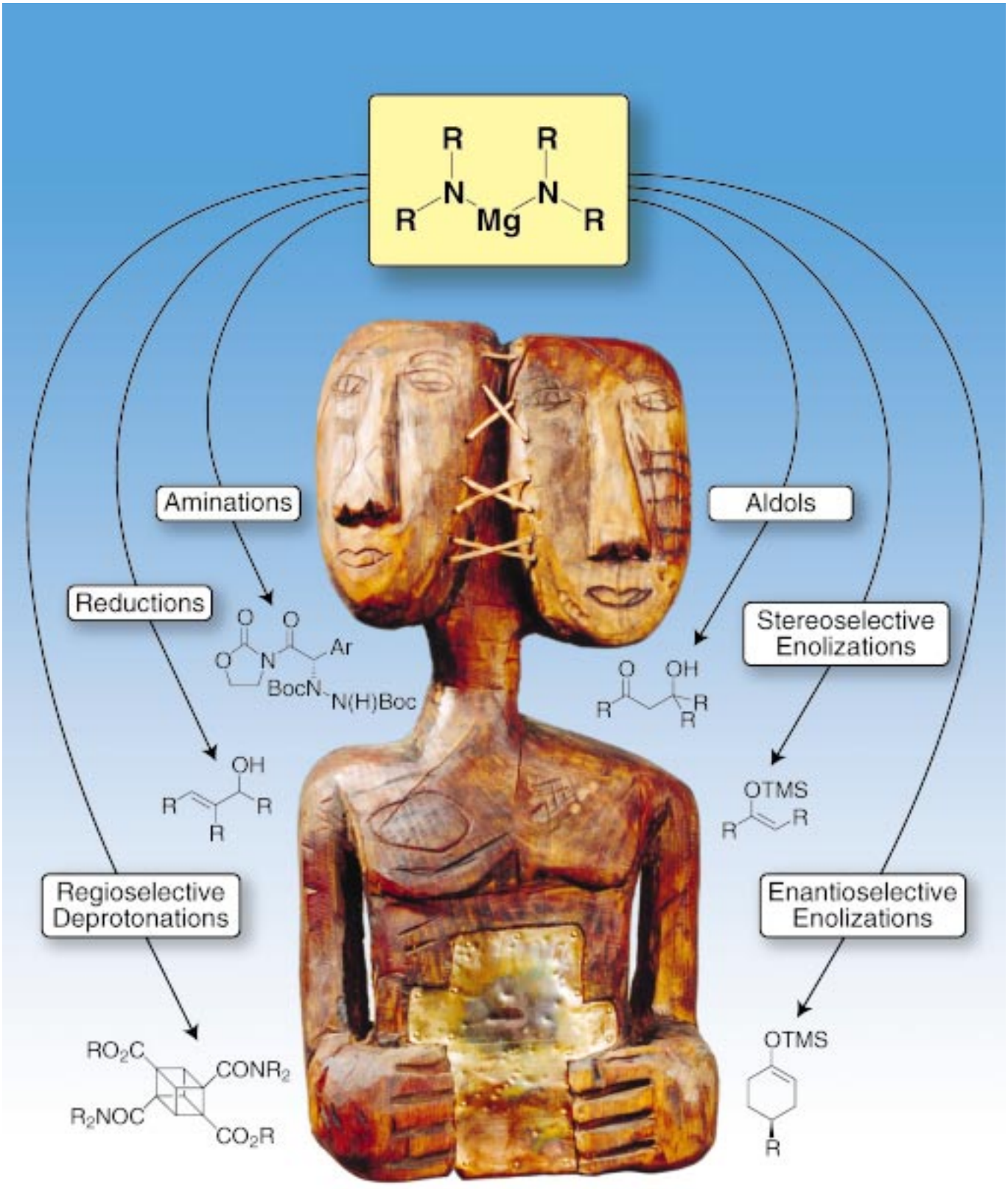

The above figure shows various transformations possible using magnesium bisamides in organic synthesis. Additionally, the image "Doppelkopf" (1997), by the Scottish artist Margaret Hunter, is used here to depict the divalent nature of magnesium; this artist is represented within The Collins Gallery at the University of Strathclyde.

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Magnesium Bisamides as Reagents in Synthesis

Kenneth W. Henderson*[a] and William J. Kerr*[a]

Abstract: As part of the continued requirement for more selective reagents in organic synthesis, magnesium bisamides are becoming established as a class of organometallic bases with considerable potential. Their relatively mild reactivity, combined with their high degree of steric congestion, leads to a distinct class of reagents with significantly different chemo-, regio-, stereo- and enantioselectivities when compared with existing species and protocols.

Keywords: aldol reaction · amination · asymmetric synthesis · magnesium · N ligands

Introduction

Magnesium bisamides, $(R_2N)_2Mg$, have recently emerged from relative obscurity and are fast becoming significant agents for use in organic synthesis. In particular, their utility thoroughly complements the use of lithium amides, R_2NLi, which are firmly established as one of the premier classes of organometallic reagents.[1]

With respect to the preparation of Mg anion (or bisanion) species, traditionally a typical process would involve initial lithiation of a substrate followed by a transmetallation reaction with either a Grignard reagent or a metal halide to introduce the desired cation.[2] Clearly such methodologies are problematic; the identity of the reactive organometallic is somewhat ambiguous and commonly the generation of salts within the reaction mixture introduces added complications, especially in subsequent processes. These problems may be overcome by the use of various 'pure' organometallic reagents. In this respect, the use of magnesium–nitrogen complexes in synthesis has mainly concentrated on the readily prepared Hauser bases, R_2NMgX (where X = halide); these are simply accessed by the direct reaction of an amine with a Grignard reagent.[3] Indeed, these Hauser bases have been shown to be highly efficient in the formation of Mg enolates, which further react in a wide variety of coupling processes.[4] On the other hand, a problem with these Hauser species is their complex solution behaviour, where Schlenk-type equilibria occur.[5] Nonetheless, now with the advent of simple synthetic methods for the facile preparation of ether-free and halide-free Mg bisamides, this latter family of compounds is beginning to be studied as a distinct class of reagents in their own right. In this respect, five key features of Mg bisamides combine to make them excellent candidates as reagents in synthesis: 1) their solution aggregation is generally simple and predictable, 2) both homo- and heteroleptic Mg organometallics are readily attainable, 3) the divalency of magnesium, coupled with the previous point, allows for the use of both a reactive anion and a spectator anion, 4) they are easily prepared in highly purified form, and 5) they are less reactive and more thermally stable than their lithium analogues leading, in turn, to selectivity differences between the two different sets of bases. This article will detail the methods available for the preparation of Mg bisamides, highlight a series of applications in which these bisamides have been found to be useful and, in addition, give a flavour of the nature of the organometallic intermediates involved in their reactions.

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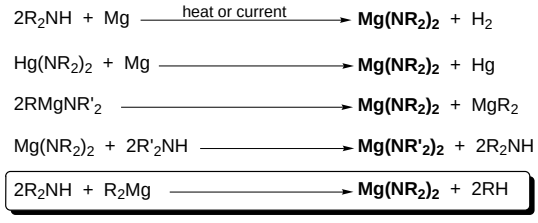
Preparation of Magnesium Bisamides

A number of routes to Mg bisamides have been developed. These include the direct reaction between the metal and a protic amine,[6, 7] various transmetallation strategies,[8] disproportionation of alkylmagnesium amides,[9] and transamination reactions[10] (Scheme 1). On the other hand, the most straightforward and most routine synthesis involves the reaction of a dialkylmagnesium with two equivalents of



Scheme 1. General preparative methods for magnesium bisamides.

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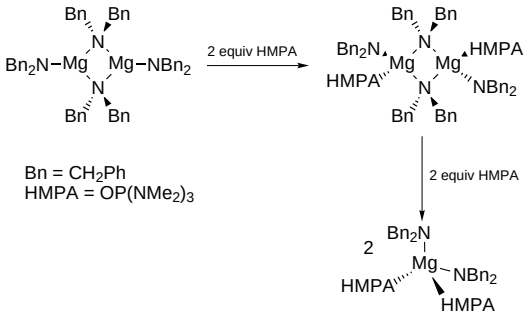
amine.[11] In some instances, the amination reaction ceases after the transfer of one amino function but gentle heating of the reaction mixture is usually sufficient to ensure complete conversion to the bisamide. Without doubt, this route is now the method of choice since ether-free Bu_2Mg (supplied as a 1:1 mixture of *n*- and *s*-butyl, with 5% *n*-octyl, in heptane) has become commercially available (Aldrich).[12]

Solution and Solid-State Structures of Magnesium Bisamides

The simple bisamide $(Me_2N)_2Mg$ is believed to be polymeric in structure and consists of linked Mg_2N_2 rings.[11] However, when bulky amides are utilised, the aggregation of the complexes is generally limited to either monomers or dimers.[13] Indeed, this specific feature will be advantageous in the use of these complexes as selective reagents, since easily reproducible solution aggregation is possible. In turn, this will allow transformations to be accomplished in an identical physical environment for each molecule. Importantly, this is in stark contrast to the well-studied and highly complex solution chemistry of the analogous lithium reagents.[14]

With the Mg systems, the position of the solution equilibria is dependent on the size and nature of the amide, the concentration and polarity of the solution, and the stoichiometry and denticity of any Lewis bases present (e.g. Scheme 2).[13] In general, monomers are prevalent in highly polar solvent media or in the presence of two or more equivalents of strong Lewis bases such as hexamethylphosphoramide (HMPA). Higher aggregation of magnesium-nitrogen complexes can however be achieved using specialised ligand systems such as dianionic amides and imides (RN^{2-}).[15]



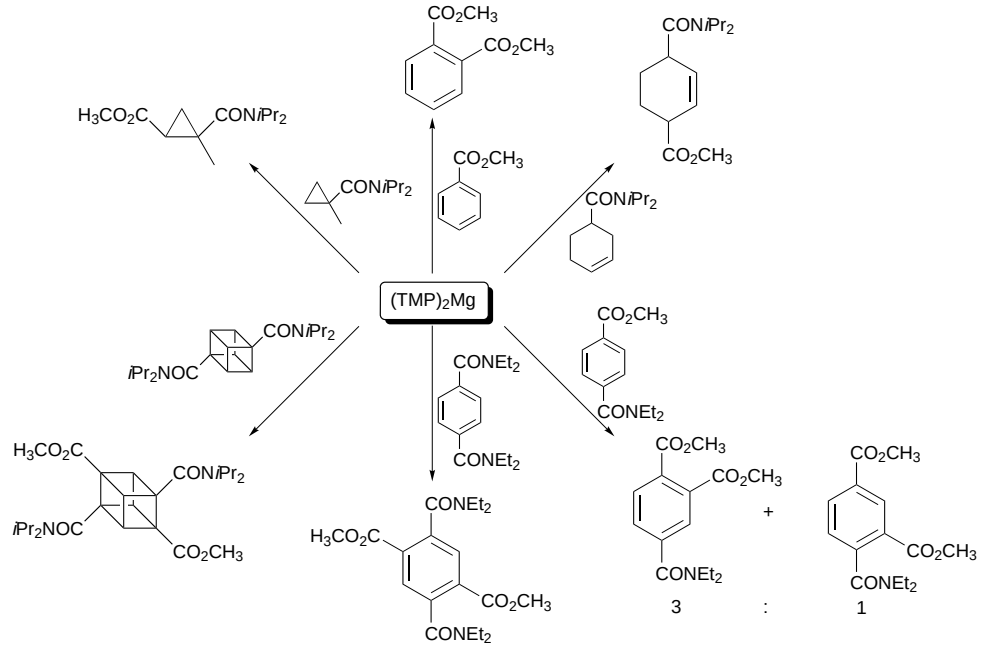
Scheme 2. Magnesium bisamide aggregation dependence on HMPA solvation.

Reaction Chemistry of Magnesium Bisamides

Magnesiation: Removal of an acidic proton by a Mg bisamide is a versatile reaction akin to that of the widely used lithium amides. However, the reactivity (and thermal stability) differences between the bases leads to differing and complementary selectivity in many instances.

Eaton first developed the use of magnesium bis(2,2,6,6-tetramethylpiperamide), $(TMP)_2Mg$, as a selective proton abstractor (Scheme 3).[16] Of particular note, is the ease with which *ortho*-magnesiation reactions can be accomplished in the presence of esters, which are normally more susceptible to nucleophilic attack using conventional Li-based reagents. Furthermore, the mild reactivity of the Mg reagents allows the carbocubane systems to be selectively monometallated (adjacent to each amide unit) and subsequently carboxylated.

As can also be noted in Scheme 3, THF solutions of the base $(TMP)_2Mg$ were found to be stable on heating to reflux over several hours, opening up its application with relatively unreactive or low solubility substrates. In a similar 'high-



Scheme 3. Carboxylation reactions using $(TMP)_2Mg$. Reagents and conditions: THF, CO_2, CH_2N_2, temperatures: between room temperature and reflux, 45 min to 2 h. Yields: >80%.

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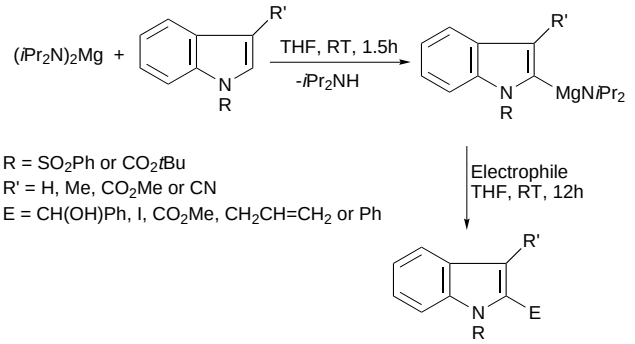
temperature' metallation strategy, indoles may be deprotonated exclusively at the 2-position by $(i\mathrm{Pr}_2\mathrm{N})_2\mathrm{Mg}$. Subsequent quenching with a variety of electrophiles leads to 2-subsituted indoles in good to excellent yields (Scheme 4).[17]

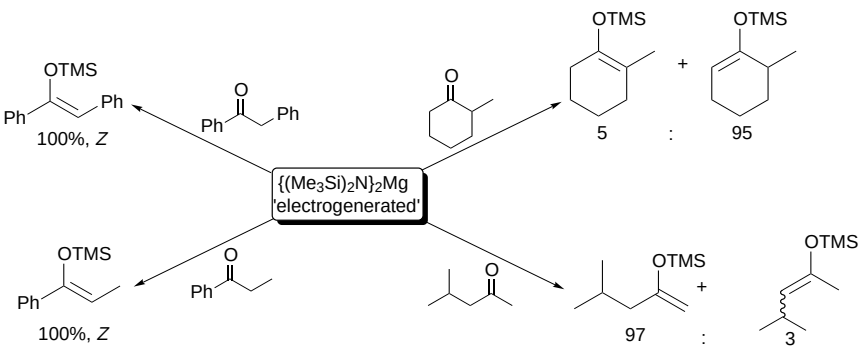


Scheme 4. Substiution of 1- and 1,3-substituted indoles. Yields: 44–93%.

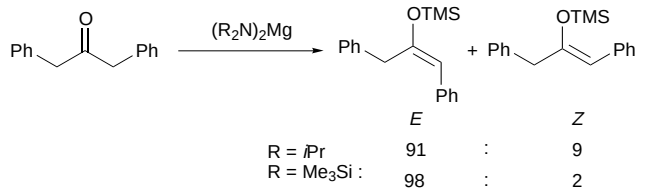
Overall, the main advantage of the Mg base approach for direct magnesiation is the ability to carry out these reactions at ambient temperature, whereas the lithium-mediated reactions are routinely conducted at low temperatures due to the instability of the reagent or metallated substrate.

Regio- and stereoselective formation of enolates: Mg bisamides can also be used as strong and selective bases in the formation of synthetically useful enolates. In this respect, Bordeau et al. have demonstrated that Mg salts of 2-pyrrolidone and hexamethyldisilazane, formed by electrochemical methods, react with a range of unsymmetrical ketones in a highly regioselective fashion to give predominately the kinetic enolates (Scheme 5).[6,18]

In addition, these bases afford high levels of selectivity in a stereochemical sense. Interestingly, by utilising magnesium bisdiisopropylamide, $(i\mathrm{Pr}_2\mathrm{N})_2\mathrm{Mg}$, prepared from $\mathrm{Bu}_2\mathrm{Mg}$ and diisopropylamine, high levels of (*E*)-silyl enol ethers may be prepared from benzylic ketones (Scheme 6).[18c] Our own work in this area has concentrated on utilising $\{(\mathrm{Me}_3\mathrm{Si})_2\mathrm{N}\}_2\mathrm{Mg}$, prepared from $\mathrm{Bu}_2\mathrm{Mg}$ and hexamethyldisilazane, as a sterically encumbered base.[19] These studies indicate that even higher levels of regio- and stereoselectivity can be achieved compared with the electrochemically generated base or $(i\mathrm{Pr}_2\mathrm{N})_2\mathrm{Mg}$. Furthermore, we have also crystallographically



Scheme 5. Regio- and stereoselective enolization reactions. Reagents and conditions: dimethoxyethane (DME), HMPA, $\mathrm{Et}_4\mathrm{NBF}_4$, $\mathrm{Me}_3\mathrm{SiCl}$, $-78\,^\circ\mathrm{C}$, 3 h. Conversions: >95%.



Scheme 6. Highly *E*-stereoselective enolization reactions. Reagents and conditions: heptane, THF, $\mathrm{Me}_3\mathrm{SiCl}$, -78 or $0\,^\circ\mathrm{C}$ to room temperature, 3–18 h. Conversions: >90%.

characterized the organometallic produced in the reaction of $\{(\mathrm{Me}_3\mathrm{Si})_2\mathrm{N}\}_2\mathrm{Mg}$ with propiophenone (Figure 1).[19] The complex is dimeric and, significantly, contains a 65:35 ratio of *E* to *Z* isomers of the enolate, which represents an unusually high level of stereoselection for the kinetic product of this enolate.[20]

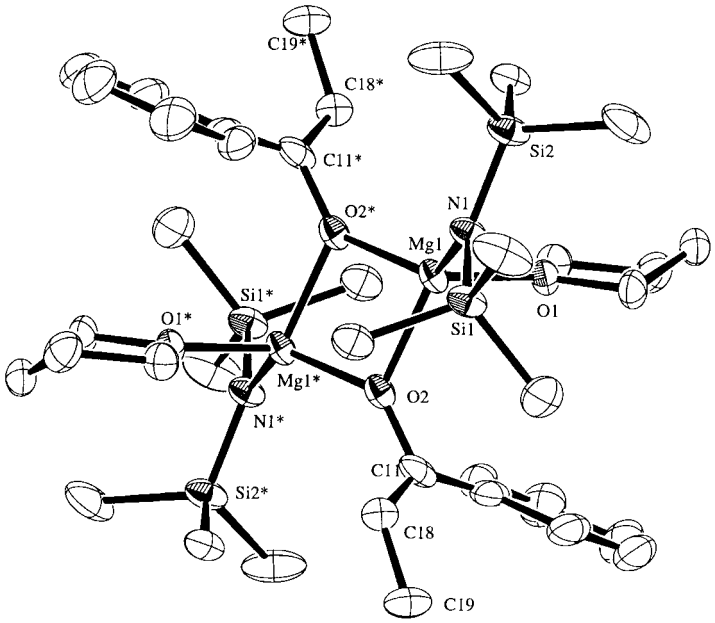
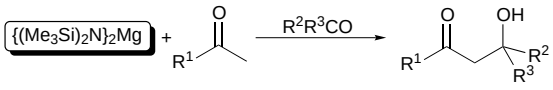


Figure 1. Molecular structure of $[\{(\mathrm{Me}_3\mathrm{Si})_2\mathrm{NMg}\{\mu\text{-OC(Ph)=CHMe}\}\cdot\mathrm{THF}\}_2]$ (only the *E* isomer is shown).

Aldol additions: We have recently shown that Mg enolates generated from Mg bisamides can be utilised in aldol addition reactions using alkyl, aryl and cyclic ketones.[21] As shown in Scheme 7, these reactions are significant in that the self-coupling of ketones in aldol reactions to give tertiary β-hydroxyketones are also possible. More specifically, these transformations are achieved principally by the use of relatively high reaction temperatures ranging between 25 °C and 60 °C. Such conditions are a notable departure from the widely used lithium-mediated aldol additions, where increas-



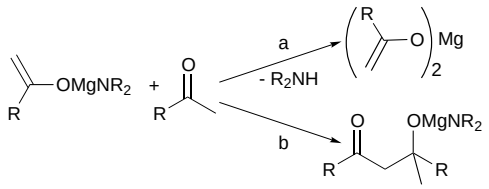
Scheme 7. Aldol additions mediated by $\{(Me_3Si)_2N\}_2Mg$. Reagents and conditions: hexane, $-78\,^{\circ}C$, 30 min for aldehyde additions; room temperature to reflux for ketone additions. Yields: 38–94%. R^1 = alkyl or aryl; and $R^2 = R^1$, $R^3 = Me$; or $R^2 = Ph$, $R^3 = H$.

ing the reaction temperature results in retro-aldol processes and also elimination of LiOH to give enone products.[2]

The thermal stability of the Mg aldolates is most likely a consequence of the strong chelation of the carbonyl function with the highly Lewis acidic metal within their dimeric structures. The amide/aldolate shown in Figure 2 is derived from the self-coupled aldol reaction between pinacolone and $\{(Me_3Si)_2N\}_2Mg$.

An interesting point to note is that the bisamide has mediated the reaction of two equivalents of ketone to produce an aldol product, even though a reactive amide function is still attached to the enolate intermediate (cf. Figure 1). The preference for the aldol addition is rooted in the preferential energetics of this transformation compared to bisenolate formation. However, we recently revealed that bisenolate formation can, indeed, be a viable alternative reaction pathway on the addition of two equivalents of ketone to a Mg bisamide (Scheme 8).[22] The specific outcome of these reactions is determined by a combination of factors including the steric and electronic nature of the ketone, the solvent media employed, and the reaction temperature.

Bisenolate formation has been definitively confirmed through the structural analysis of the product of the reaction between 2,4,6-trimethylacetophenone and $\{(Me_3Si)_2N\}_2Mg$



Scheme 8. Formation of a) bisenolate or b) amido(aldolate) via an amido(enolate).

(Figure 3). A fascinating aspect of this unusual tetrameric complex is the coordination of ketone in the presence of enolate, that is, this can be viewed as a pre-aldol intermediate.[23] This supports the assessment that formation of an aldol product in this instance is unfavoured. The elucidation of these 'intermediates' has proved, and will continue to be, vital

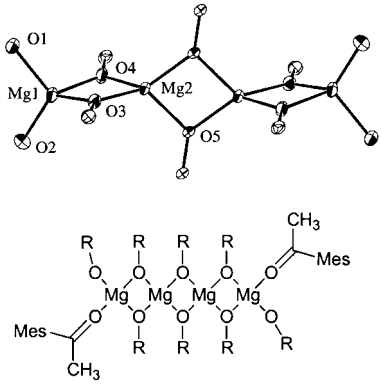


Figure 3. Molecular structure of $[Mg_4\{OC(Mes)=CH_2\}_8\{O=C(Mes)Me\}_2]$, where $RO = (Me_3C_6H_2)C(O)=CH_2$, $Mes = 2,4,6\text{-}MeC_6H_2$. All carbon atoms are omitted for clarity, except the α-carbon atoms of the bridging enolates.

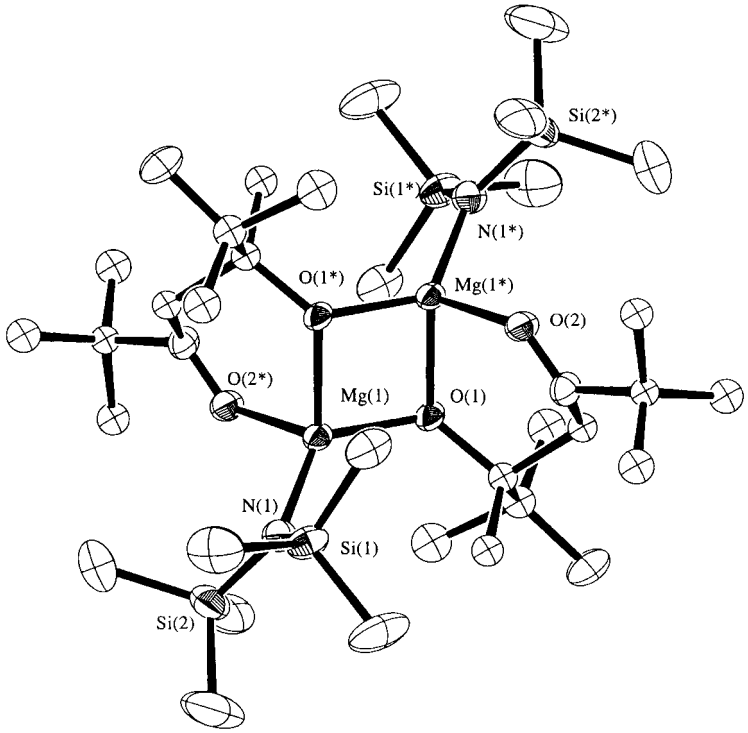


Figure 2. Molecular structure of $[\{(Me_3Si)_2NMg(\mu\text{-}OC(Me)t\text{Bu}CH_2C(t\text{Bu})=O)\}_2]$.

in aiding our understanding of the reactivity and selectivity of these Mg-mediated reactions.

A final point to note about these reactions is that aldehyde can be added to the base before addition of the ketone, without the formation of aldimine or other addition products.[24] This allows the use of an in situ trap for the enolate, which has a close parallel with the Corey internal quench procedure for the synthesis of silyl enol ethers in lithium-mediated enolization reactions.[25]

Asymmetric synthesis: Evans and Nelson first illustrated the potential of Mg bisamides in asymmetric synthesis by the enantioselective amination of

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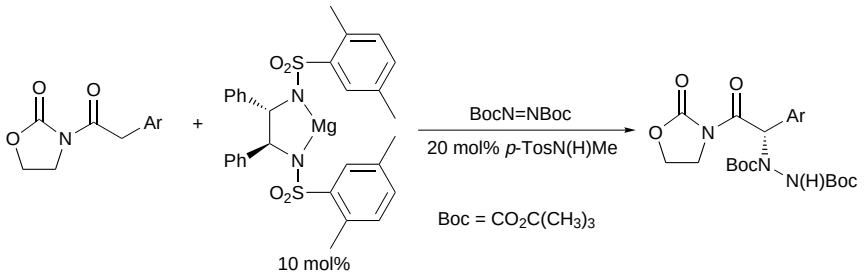


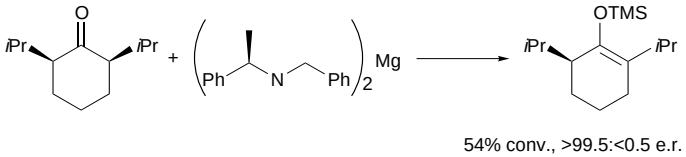
Scheme 9. Enantioselective amination reactions. Where Ar is for example Ph, *p*-F-C_6H_4, *p*-CH_3O-C_6H_4, 2-$C_{10}H_7$. Reagents and conditions: CH_2Cl_2, $-65\,^{\circ}C$, 48–72 h. Yields: >80% and e.r. values range between 90:10 and 95:5.

N-acyloxazolidinones (Scheme 9).[26] These reactions are not only highly enantioselective but are also catalytic in the chiral reagent.

Our own efforts in this area have concentrated on the enantioselective deprotonation of conformationally locked ketones. Initial results in this field have proved to be highly promising and, as Scheme 10 shows, very high levels of enantioselection can be achieved.[27]

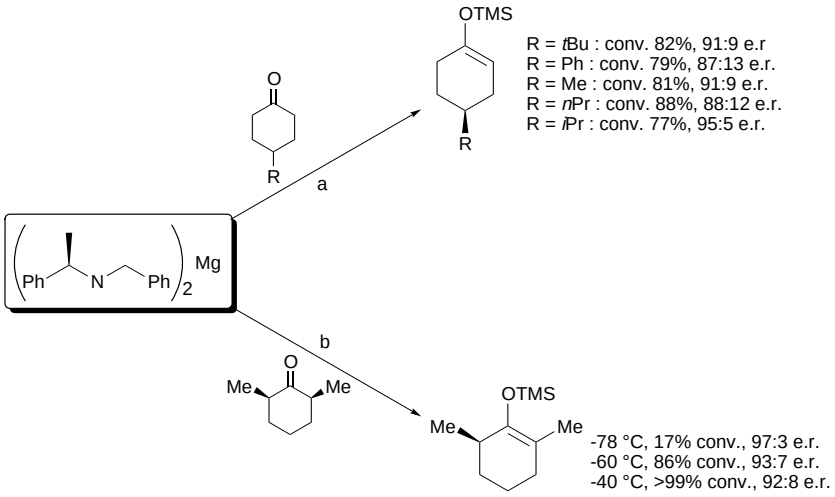
The most remarkable feature of these reactions is the level of asymmetric induction produced using a structurally very simple amide base. For comparison, the enantioselective deprotonation of *tert*-butylcyclohexanone using the lithiated derivative of the same amine, (*R*)-*N*-benzyl-α-methylbenzylamine, gives a much-reduced enantiomeric ratio of 75.5:24.5.[28] The Mg-based approach offers an advantage to existing methods in that the amine is commercially available (Aldrich) and is relatively inexpensive. In addition, the more practically acceptable additive *N*,*N*′-dimethyl-*N*,*N*′-propylene urea (DMPU) may be used to replace HMPA with comparable conversions (R = *t*Bu; 89%) and enantioselectivity (R = *t*Bu; 90:10 e.r.).

The deprotonation of *cis*-2,6-dimethylcyclohexanone shows an excellent e.r. of 97:3 using the Mg base, and is a dramatic improvement over the analogous lithium-mediated reaction using the same base, where a very modest 64.5:35.5 e.r. was achieved using acetic anhydride as a trapping agent.[29] Furthermore, the high degree of selectivity of the Mg-based transformation is not unduly affected by significantly raising the reaction temperature ($-78\,^{\circ}C$ to $-40\,^{\circ}C$) but the conversion achieved increases substantially (17% to >99%). The potential to carry out these reactions at elevated temperatures is clearly exciting in terms of the more widespread use of the Mg reagents. Also of note, is that by changing the ketone to *cis*-2,6-diisopropylcyclohexanone we have been able to achieve the highest asymmetric induction yet observed for such an enantioselective deprotonation reaction (Scheme 11).[30]



Scheme 11. Enantioselective deprotonation of 2,6-diisopropylcyclohexanone. Reagents and conditions: THF, 0.5 equiv HMPA, TMSCl, $-78\,^{\circ}C$, 39 h.

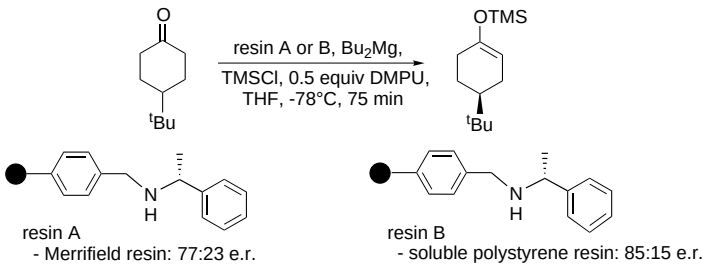
Finally, the development of solid-supported chiral amines, and ultimately supported Mg amides, affords certain practical and economic advantages: 1) ease of reagent removal and subsequent chiral analysis, 2) re-use of the valuable amine moiety, and 3) the possible development of libraries of chiral amine units. Our initial studies in this area have shown that the chiral Mg amide reagents derived from reaction of Merrifield or soluble polystyrene resins (A and B) with Bu_2Mg, have already proved capable of inducing good levels of enantioselection (Scheme 12).[31]



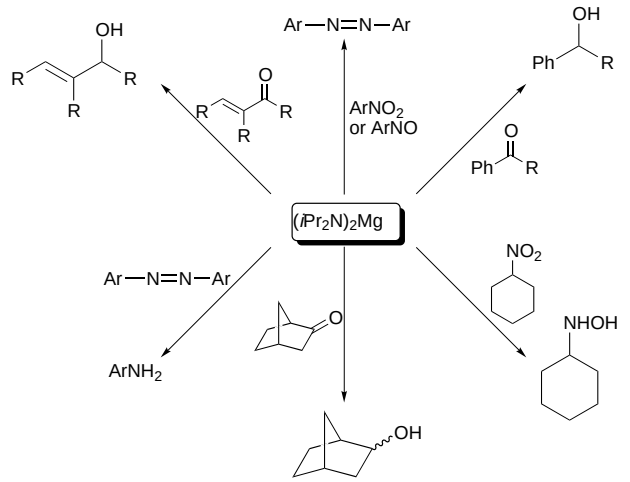
Scheme 10. Enantioselective deprotonation and silyl enol ether formation. Reagents and conditions: a) THF, 0.5 equiv HMPA, trimethylsilyl chloride (TMSCl), $-78\,^{\circ}C$, 1 h; b) THF, 0.5 equiv HMPA, TMSCl, 6 h.

Other transformations: Sanchez and co-workers have developed the use of Mg bisamides containing a β-hydrogen atom to act as selective reducing agents.[32] By using $(i\mathrm{Pr}_2\mathrm{N})_2\mathrm{Mg}$ in nonsolvating media, such as cyclohexane or *n*-heptane, the reductions of carbonyl, nitro, nitroso and azo compounds are possible (Scheme 13). These reactions exemplify the inherent weaker metallation ability of the Mg bases compared with their Li counterparts, which lead to alternative reaction pathways.[1]

Amidations are also possible through the direct reaction of a

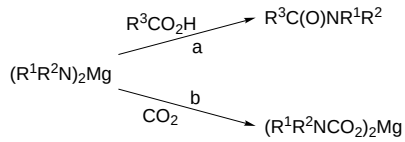


Scheme 12. Solid-supported enantioselective deprotonation reactions.



Scheme 13. Reduction reactions. Reagents and conditions: cyclohexane or heptane, $>75\,^{\circ}C$, 1.5 to 48 h.

Mg bisamide with a carboxylic acid or carbon dioxide, resulting in the formation of carboxamides and bis(*N*,*N*′-diorganocarbamoxy) compounds respectively, in good yields (Scheme 14).[33] These procedures again provide an alternative to existing, and more traditional methods.



Scheme 14. Amidation reactions. Reagents and conditions: a) heptane/CH_2Cl_2, 65 °C, yields: 52–89 %; b) alkenes, room temperature, yields: 60–89 %.

Conclusion

In summary, Mg bisamides offer an exciting alternative to existing metal bases in a number of applications. In combination, their properties of strong basicity, weak nucleophilicity, good thermal stability, high steric encumbrance, and more simple solution aggregation behaviour, lead to them possessing excellent properties as highly selective reagents in synthesis. The divalency of the metal, allowing formal bonding with two anionic ligands, clearly also has significant consequences on both the reactivity and selectivity of the Mg bisamides compared with similar lithium reagents. Indeed, the Mg reagent can be designed to formally bond simultaneously to two dissimilar units, each with potentially differing reactivities, opening up numerous possible heteromolecular transformations. Indeed, our current work on asymmetric addition reactions indicates that this methodology is robust. The future of these reagents in organic synthesis certainly lies in their use in a variety of stereoselective and asymmetric applications, and those outlined in this review already show outstanding promise.

Acknowledgements

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