

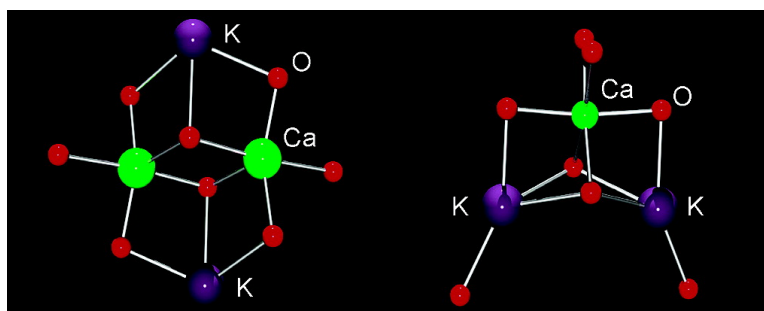
Communication

Ketone Deprotonation Mediated by Mono- and Heterobimetallic Alkali and Alkaline Earth Metal Amide Bases: Structural Characterization of Potassium, Calcium, and Mixed Potassium–Calcium Enolates

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Ketone Deprotonation Mediated by Mono- and Heterobimetallic Alkali and Alkaline Earth Metal Amide Bases: Structural Characterization of Potassium, Calcium, and Mixed Potassium–Calcium Enolates

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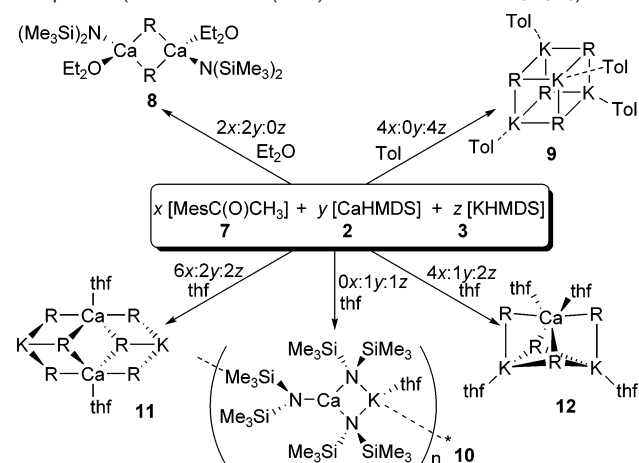
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The use of metal enolates in carbon–carbon bond-forming reactions is a cornerstone of modern organic synthesis.¹ In large part this can be attributed to the development of lithium amide reagents as strong, non-nucleophilic bases.² Our groups and others have become interested in the use of alternative metal base systems to improve upon the general levels of selectivity found for the lithium species.² In particular, we have focused on magnesium bisamides, (R₂N)₂Mg, which have proven to be valuable reagents in the regio-, stereo-, and enantioselective deprotonation of ketonic substrates.² As yet, the utility of heavier alkaline earth metal organometallics in organic synthesis has not been investigated to any significant extent, mainly due to perceived accessibility and handling issues.³ Nevertheless, heavier group 2 metal complexes are potentially attractive candidates as reagents due to their increased reactivity and varying local coordination environments at the metal centers compared with their magnesium analogues.⁴ Furthermore, mixed-metal amide reagents of the type M¹M²(NR₂)₃ (where M¹ = Li, Na, or K, and M² = Mg or Zn) have recently been developed by Mulvey, and these bases have been shown to display remarkable synergistic reactivity.⁵ From a synthetic perspective the most notable of these reactions are the completely regioselective 2,5-double deprotonation of arenes⁶ and the 1,1',3,3'-tetrametalation of ferrocene.⁷ We now report on the successful application of homoleptic hexamethyldisilazido, (Me₃Si)₂N⁻, compounds of calcium, potassium, and mixed potassium–calcium combinations to mediate enolate formation.

4-*tert*-Butylcyclohexanone, **1**,² was employed as a benchmark ketone for the initial enolization and subsequent silyl enol ether-trapping reactions using five base systems: Ca(HMDS)₂, **2**, KHMSD, **3**, KCa(HMDS)₃, **4**, K₂Ca(HMDS)₄, **5**, and Mg(HMDS)₂, **6**. Each base (1 mmol) was dissolved in 10 mL of THF, cooled to 0 °C, followed by the dropwise addition of **1** (0.9 mmol) as a solution in THF (5 mL). TMSCl (4 mmol) was then added, and the reactions were monitored by GC–MS. Reactions using bases **2**–**5** resulted in quantitative conversion to the silyl enol ether in <10 min. However, magnesium reagent **6** required substantially longer trapping times to achieve high conversions (5% conversion after 10 min, ~80% after 24 h). The reactivity difference between **2** and **6** illustrates a significant practical advantage for the calcium-based methodology.

Next, we undertook a study to uncover the structure of the metalated enolate intermediates. 2',4',6'-Trimethylacetophenone, **7**, was chosen as a model ketone for deprotonation since we have previously found that its enolate has excellent crystallization properties with a variety of metal centers.⁸ A summary of the reactions resulting in the successful isolation and structural identification of intermediates is detailed in Scheme 1. The stoichiometric reaction

Scheme 1. Structurally Characterized Amide and Enolate Complexes (where R is OC(Mes)=CH₂ and Tol is CH₃C₆H₅)



of **7** with **2** in hexane/Et₂O solution allowed the isolation of the amidocalcium enolate complex [(Me₃Si)₂NCaOC(Mes)=CH₂·Et₂O]₂, **8**. Single-crystal X-ray analysis determined that **8** adopts a centrosymmetric dimeric structure where the metals are tetracoordinated through bonding to a pair of bridging enolates, transoid terminal amides, and a diethyl ether molecule of solvation.⁹ The heteroleptic character of **8** demonstrates a substantial difference compared with the corresponding magnesium chemistry, where only the bisenolate could be identified in the solid state due to disproportionation.^{8a}

For comparative purposes the monometallic potassium enolate [(KOC(Mes)=CH₂·Tol)₄], **9**, was prepared from the reaction of **3** with **7** in toluene.¹⁰ The structure of **9** proved interesting in its own right, revealing a distorted cubane stabilized by toluene solvation.⁹ Only a handful of homometallic potassium enolate crystal structures have been reported, and they adopt solvent-separated,¹¹ monomeric¹¹ or hexameric structures.¹² Therefore, **9** represents a new aggregation mode in the solid state for a potassium enolate. Both the arenes of solvation and the enolate olefin bonds are involved in a profusion of π -contacts to the metals.¹³ Additionally, we were able to confirm that mixing the monometallic amides **2** and **3** in hexane/THF solution resulted in the formation of a heterobimetallic complex, i.e. [KCa(HMDS)₃·THF] _{∞} , **10**.⁹ The structure is composed of central CaKN four-membered rings with calcium also carrying a terminal amide unit, and with the potassium sites monosolvated by THF. A set of agostic K···C(Me) interdinuclear interactions between the terminal amide units and the potassium centers gives rise to a polymeric chain structure. Previously, discrete molecules, contact ion pairs, and one-dimensional chains utilizing bridging metal–N motifs have been found for such trisamides.¹⁴

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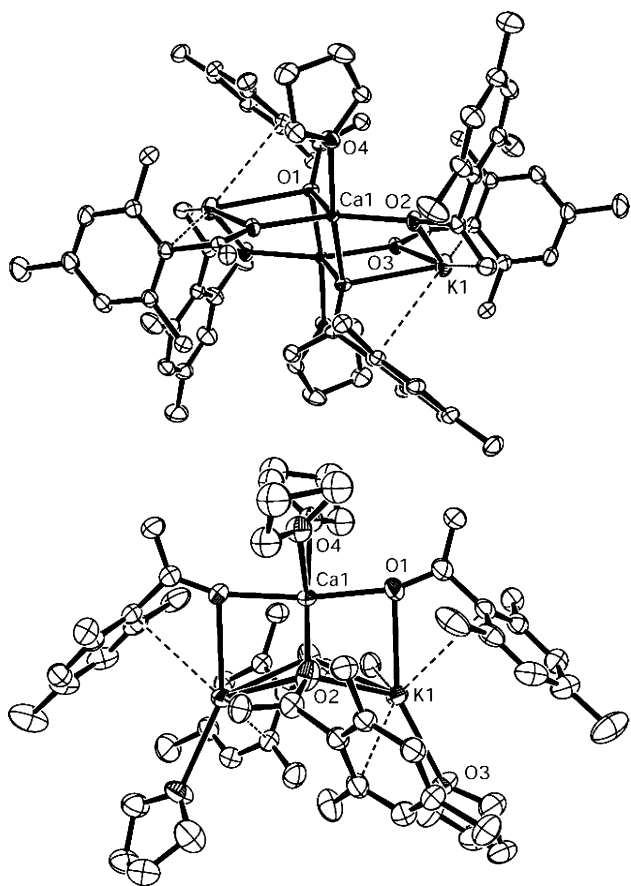


Figure 1. Molecular structures of **11** (top) and **12** (bottom) with hydrogens omitted for clarity (hashed lines indicate the direction of the π -contacts with the metal).

Next, we investigated the use of **4** and the stoichiometric variant **5** as bases in the enolization of **7**. These reactions resulted in the successful preparation and structural characterization of the 2:2 and 2:1 heterobimetallic enolates $[\text{K}_2\text{Ca}_2\{\text{OC}(\text{Mes})=\text{CH}_2\}_6\cdot 2\text{THF}]$, **11**, and $[\text{K}_2\text{Ca}\{\text{OC}(\text{Mes})=\text{CH}_2\}_4\cdot 4\text{THF}]$, **12**, respectively (Figure 1).

The core skeleton of THF-deficient **11** is comparable with the series of “inverse crown” complexes $[\{\text{M}^1\text{M}^2(\text{NR}_2)_2\}_2(\text{X})]$, where M^1 is an alkali metal (Li, Na, or K), M^2 is a divalent metal (Mg or Zn), NR_2 is a bulky secondary amide, and X is oxo (O^{2-}), peroxy (OO^{2-}), or a pair of alkoxides (RO^-) or hydrides (H^-).^{5a,15} All of these complexes are heteroleptic, whereas complex **11** is homoleptic, carrying solely enolate anions. The calcium centers in **11** achieve pentacoordination by bonding to four enolates (mean Ca–O 2.271 Å; range, 2.208(2)–2.348(2) Å, cf. 2.276(3) Å in **8**) and a THF molecule (Ca–O4, 2.406(2) Å). Revealingly, the potassium centers interact only relatively weakly with the anionic oxygens, where the three closest K–O(enolate) distances lie at 2.633(2), 2.702(2), and 2.842(2) Å for K1–O2, K1–O3, and K1–O1* respectively. In comparison, the K–O distances in the homometallic enolate **9** lie in the range 2.528(6)–2.706(6) Å (mean 2.631 Å). The remainder of potassium’s coordination sphere is filled with numerous π -interactions with both the olefin and the aryl rings from the enolates (six K–C distances <3.5 Å).

Several similarities are immediately apparent on comparing the structure of **12** with that of **11**. Again, calcium maximizes the number of contacts to the anionic oxygens by binding to all four enolates (Ca1–O1, 2.243(2) Å; Ca1–O2, 2.286(2) Å), and additionally it binds a pair of THF molecules (Ca1–O4, 2.297(5)

Å). The potassium centers interact even more weakly with the anionic oxygens than in **11**, with K–O(enolate) distances of 2.726(3), 2.729(3), and 2.852(3) Å for K1–O1, K1–O2, and K1–O2*, respectively. In fact, the closest contact to the potassium cations in **12** is with the THF molecule (K1–O3, 2.697(3) Å). Despite the presence of THF the potassium cations again form a series of π -interactions with the surrounding olefin and arenes (seven K–C distances <3.5 Å). Such contacts to alkali and alkaline earth metal cations, in particular Na^+ , K^+ , and Ca^{2+} , have recently been the subject of considerable attention due to their possible role in ion transport in biological systems.¹³ In this regard, the identification of **11** and **12** provides a rare opportunity to compare the bonding and structural preferences for the periodic neighbors potassium and calcium within heterobimetallic molecular complexes.¹⁰ The positions adopted by the metals clearly illustrate the substantial increase in Lewis acidity of the calcium cations compared with potassium (due to increased charge density). These observations are in accord with the recent work of Gokel who demonstrated that the ability of the cations to form π -complexes with lariat ethers increases in the sequence $\text{Ca}^{2+} < \text{Na}^+ < \text{K}^+$.¹³ Overall, complexes **11** and **12** have anchoring CaO σ -bonds which frame the structures into dinuclear and mononuclear arrangements, respectively, while the softer potassium cation affixes to these frameworks, though weaker, more π -based ancillary bonding.⁵

Further studies are presently underway to investigate the scope and utility of heavy groups 1 and 2 metal amides as reagents in stereoselective organic synthesis.

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Supporting Information Available: Full experimental, spectral and crystallographic data concerning compounds **8**–**12** (CIF and PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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