Heavier group 2 element-catalysed hydroamination of isocyanates†

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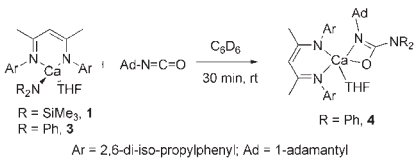
The heteroleptic calcium amides [{ArNC(Me)CHC(Me)NAr}-Ca(NR$_2$)(THF)] (Ar = 2,6-di-*iso*-propylphenyl, R = SiMe$_3$, Ph) and the homoleptic heavier alkaline earth amides, [M{N(SiMe$_3$)$_2$}$_2$] (M = Ca, Sr and Ba) are reported as pre-catalysts for the hydroamination of isocyanates.

The importance of the urea functional group to biological systems was well known before Wöhler's 1828 landmark synthesis.[1] Whilst this latter discovery overturned the theory of vitalism and arguably led to the birth of organic chemistry, in the countless studies that have followed urea derivatives have found myriad applications in synthetic, pharmaceutical and industrial chemistry. Despite their obvious significance, catalytic, atom-efficient, methods for the synthesis of ureas remain limited to a small number of protocols. Important examples include, (i) the transition-metal catalysed oxidative carbonylation of amines with CO in the presence of an oxidant such as O_2 or I_2,[2,3] (ii) the reductive coupling of nitro compounds with amines and CO mediated by transition-metals or elemental sulfur or selenium,[4,5] (iii) the carbonylation of amines with CO_2 in the presence of catalytic Ph_3SbO–P_4S_{10},[6] and (iv) the ruthenium-mediated dehydrogenative coupling of formamides and amines.[7]

Notable by its absence in these studies is the potential synthesis of ureas by the catalytic hydroamination of isocyanates. Whilst readily achievable under uncatalysed conditions,[8] this reaction is often limited to nucleophilic amines, where preparations frequently require elevated reaction temperatures or prolonged reaction times to afford the urea products in high yield. As such, homogeneous catalysis may offer the potential for improved substrate scope and reaction kinetics. In this regard, although previous studies upon well-defined organolanthanide(III) amides have demonstrated that these species undergo insertion reactions with isocyanates to form the corresponding metal ureido complexes,[9] this reactivity has not been extended to a catalytic synthesis of ureas. Rather, a number of *f*-block (and similarly *s*-block) mediated isocyanate oligomerisation or polymerisation reactions have been reported.[10,11]



Scheme 1 Reaction of **1** and **3** with 1-adamantyl isocyanate.

Our current interest lies in developing, understanding and exploiting the reaction chemistry of heavier alkaline earth complexes (M = Ca, Sr and Ba). In this regard we have previously reported Chisholm *et al.*'s β-diketiminate calcium amide [{ArNC(Me)CHC(Me)NAr}Ca{N(SiMe$_3$)$_2$}(THF)] (Ar = 2,6-di-*iso*-propylphenyl, **1**)[12] as a suitable pre-catalyst for the hydroamination and hydrophosphination of alkenes, alkynes and carbodiimides.[13] We now report the preliminary findings from our studies upon the application of **1** and the simple heavier alkaline earth amides [M{N(SiMe$_3$)$_2$}$_2$]$_2$ (**2a**, M = Ca; **2b**, M = Sr; **2c**, M = Ba) to the catalytic hydroamination of isocyanates to form unsymmetrical ureas.

To investigate the feasibility of the controlled single insertion of an isocyanate into a calcium–nitrogen bond,[14] the reaction of both **1** and [{ArNC(Me)CHC(Me)NAr}Ca{NPh$_2$}(THF)] (**3**) with 1-adamantyl isocyanate in C_6D_6 was monitored by ^{1}H and ^{13}C NMR. Although in both instances consumption of the starting materials was observed at the first point of analysis, only the diphenylamide compound **3** gave the desired insertion product in effectively stoichiometric yield (Scheme 1, **4**).

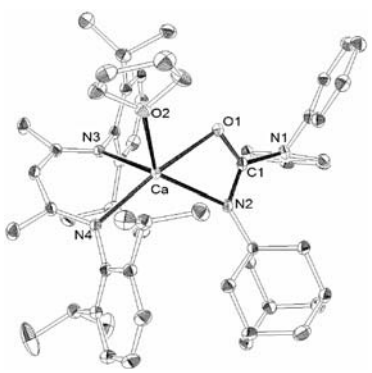


Fig. 1 ORTEP representation of **4**. Thermal ellipsoids at 20% probability. H-atoms and disordered atoms omitted for clarity. Selected bond lengths (Å) and angles (°), Ca–O(1) 2.2805(14), Ca–(3) 2.3383(16), Ca–N(4) 2.3546(16), Ca–O(2) 2.3670(15), Ca–N(2) 2.4356(16), N(1)–C(1) 1.450(2), N(1)–C(2) 1.302(3), O(1)–C(1) 1.280(2), N(3)–Ca–N(4) 81.36(5), O(1)–Ca–N(2) 56.59(5).

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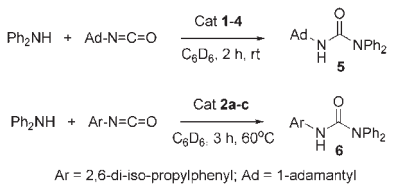

Scheme 2 Group 2-catalysed hydroamination of isocyanates.

The proposed structure of **4** (Fig. 1) was confirmed unambiguously, following its synthesis and isolation on a preparative scale,‡ by a single crystal X-ray diffraction analysis.§ In the solid state **4** consists of a penta-coordinate calcium centre in which coordination is provided by the bidentate β-diketiminate and ureido ligands and a single molecule of THF. The metal demonstrates approximate trigonal bipyramidal geometry ($\tau = 0.84$).[15] Although bond lengths and angles about the β-diketiminate chelate are comparable to previously characterised five-coordinate heteroleptic β-diketiminate/guanidinate complexes of calcium,[16] the ureido ligand binds *via* a κ^2-*O*,*N*-chelate and is the first example in calcium coordination chemistry.

Catalyst turnover may be envisaged by a further protonolysis reaction of **4** with diphenylamine to regenerate the amide **3** and liberate the hydroamination product 1,1′-diphenyl-3-(1-adamantyl)urea (**5**). Accordingly, the addition of 5 mol% **4** to diphenylamine and 1-adamantyl isocyanate at room temperature in C_6D_6 gave, after 2 h, **5** in 92% yield as monitored by ^{1}H NMR spectroscopy. Similarly, both **1** and **3** proved catalytically active and yielded the product in 89% and 93%, respectively under identical reaction conditions (Scheme 2). The structure of the urea **5** was confirmed by multinuclear NMR and infrared spectroscopy, mass spectrometry and single crystal X-ray diffraction (see ESI Fig. S1†) following a preparative scale synthesis. A background experiment, conducted in C_6D_6, demonstrated no reaction between diphenylamine and 1-adamantyl isocyanate over a period of 4 weeks at room temperature or 16 h at 80 °C further underscoring the efficacy of catalysis.

Previous studies upon the catalytic hydroamination of carbodiimides, have demonstrated that homoleptic group 2 metal amide complexes are suitable pre-catalysts for this transformation and it is proposed that the reaction products may act as ligands to not only kinetically stabilise intermediate group 2 species but also increase their solubility in hydrocarbon solvents.[13c] The reactions of diphenylamine with both 1-adamantyl isocyanate and 2,6-di-*iso*-propylphenyl isocyanate with 5–6 mol% **2a** in C_6D_6 were monitored by ^{1}H NMR spectroscopy. In these instances kinetic analyses, using the liberated hexamethydisilazane (formed quantitatively) or tetrakis(trimethylsilyl)silane as an internal standard, demonstrated that the hydroamination reaction proceeded cleanly with simultaneous consumption of the substrates and production of the urea (Fig. 2a). Whilst the hindered aryl isocyanate required slightly more forcing conditions (60 °C) than the alkyl-substituted analogue (25 °C), in both instances monitoring the isocyanate and amine concentrations over the reaction period revealed no significant polymerisation or oligomerisation side-reactions of the heterocumulene, with both substrates being consumed at equal rates (Fig. 2a and b, and ESI Fig. S2†).

In both reactions, product concentrations plateaued at high conversions and yields of the urea did not reach greater than 86% and 62% for **5** and **6** respectively as deduced by NMR (isolated yields 48–70%). Consideration of the plot of the logarithm of substrate concentration *versus* time for the reaction with 1-adamantyl isocyanate provides an explanation for this effect. The reaction is not first-order in either amine or isocyanate. Importantly, at longer reaction times (or higher conversion) the rate of the reaction begins to slow leading to the observed *pseudo* first-order data. We propose that this effect is due to product inhibition of catalysis and, whilst the change in the chemical shift of the diphenylamine *–NH* resonance over the course of the reaction (Fig. 3, $t = 5$ min, $^{1H}\delta = 5.2$ ppm; $t = 40$ min, $^{1H}\delta = 5.6$ ppm) provides evidence for the formation of intermolecularly hydrogen-bonded adducts between the product and substrates, it is likely this effect is due to the urea acting as a ligand for the catalytically active calcium species and hindering substrate coordination and activation at the metal.

Extension of this catalytic reactivity to the heavier congeners of the alkaline earths, strontium and barium, employing **2b** and **2c**, provided notable results. Following the reaction of 2,6-di-*iso*-propylphenyl isocyanate with diphenylamine, using 6 mol% **2a–c** in C_6D_6 at 60 °C with near constant catalyst [40–45 mM] and substrate starting concentrations [0.65–0.70 M], by ^{1}H NMR spectroscopy revealed an apparent effect of ionic radius on the course of the reaction (Fig. 2c). Although, in

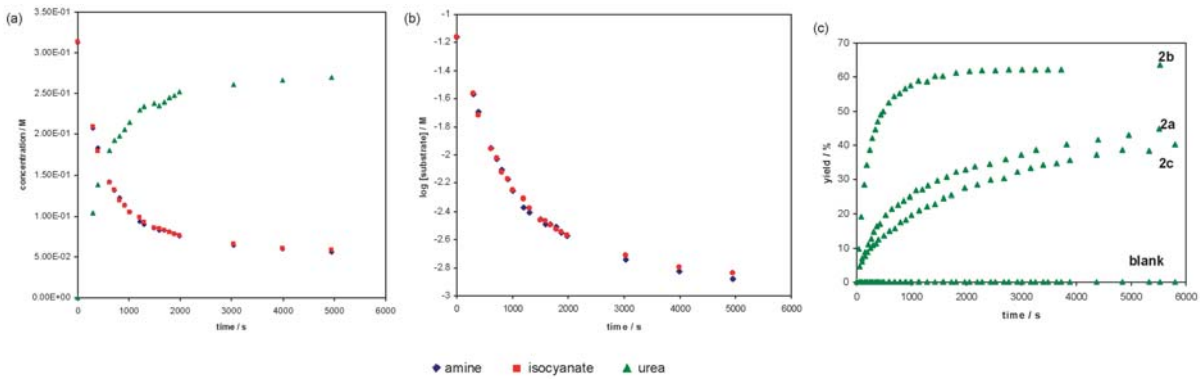

Fig. 2 Plot of (a) [substrate] and [product] *versus* time and (b) log [substrate] *versus* time for the reaction of 1-adamantyl isocyanate, diphenylamine and 5 mol% $[Ca\{N(SiMe_3)_2\}_2]_2$ at rt. (c) Plot of yield *versus* time for the reaction of 2,6-di-*iso*-propylphenyl isocyanate, diphenylamine and 6 mol% $[M\{N(SiMe_3)_2\}_2]_2$ (M = Ca, Sr and Ba) or no catalyst at 60 °C.

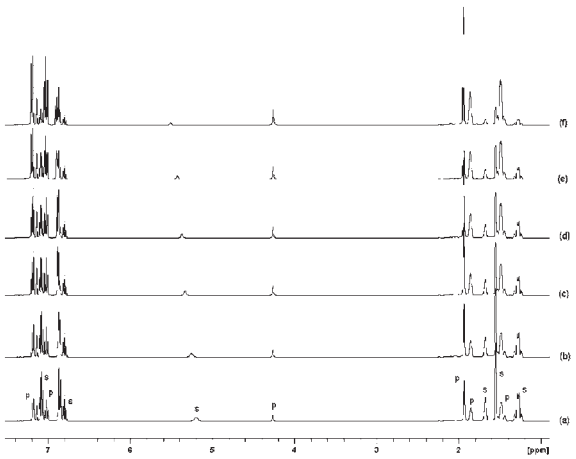

Fig. 3 Stack plot of ^{1}H NMR data from the reaction of 1-adamantyl isocyanate and diphenylamine with 5 mol% **2a** at rt. Spectra recorded at (a) 5 (b) 7 (c) 11 (d) 14 (e) 22 and (f) 40 min. Substrate (s) and product (p) peaks annotated.

accordance with previous studies upon the hydroamination of carbodiimides,[13d] the strontium analogue **2b** provided a higher yield and a faster rate of reaction than the calcium amide **2a**, catalytic reactions employing the barium compound **2c** were accompanied by the precipitation of a colourless solid. Although this material was not characterised further, it is most likely that the increased dicationic radius of barium (1.35 Å)[17] allows the formation of insoluble polymeric amide or ureido species, the precipitation of which depletes the potentially catalytically active species from solution.

In summary, we have demonstrated that inexpensive and easily prepared alkaline earth amides of calcium and strontium may be applied to catalytic urea synthesis *via* an amide–isocyanate coordination–insertion mechanism. Although our studies are presently limited to the catalytic assembly of diphenylamine and relatively sterically demanding organic isocyanates, we are continuing to broaden the scope of our studies and these results will be communicated in subsequent publications.

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Notes and references

‡ To a solution of **3** (0.85 g, 1.22 mmol) in hexane (15 mL) was added a solution of 1-adamantyl isocyanate (0.22 g, 1.24 mmol) in the same solvent (10 mL). The reaction mixture was stirred for 4 h at room temperature and the solvent volume reduced to *ca.* 15 mL. The product was isolated by hot recrystallisation from this concentrated solution. Filtration gave colourless crystals of **4** (0.38 g, 0.43 mmol, 36% unoptimised). ^{1}H NMR (C_6D_6, 400 MHz, 298 K) 1.16–1.20 (m, 6H), 1.19 (d, 12H, J = 6.8 Hz), 1.23 (m, 4H, *THF*), 1.34 (d, 12H, J = 6.4 Hz), 1.40–1.49 (m, 6H), 1.69–1.72 (m, 3H), 1.72 (s, 6H), 3.25 (broad heptet, 4H, J = 6.4 Hz), 3.72 (m, 4H, *THF*), 4.79 (s, 1H), 6.84 (*t*, 2H, J = 7.2 Hz), 6.93 (d, 4H, J = 8.0 Hz), 7.06–7.09 (m, 4H), 7.13–7.16 (m, 6H); ^{13}C NMR (C_6D_6, 100 MHz, 298 K) 24.5, 24.8, 25.0, 25.3, 28.3, 30.4, 36.8, 44.1, 51.7, 70.4, 93.5, 122.0, 122.5, 124.2, 124.4, 129.4, 141.5, 146.6, 146.8, 165.3, 165.5. Elemental analysis calc. for $C_{56}H_{74}CaN_4O_2$: C, 76.77; H, 8.45; N, 6.40%. Found C, 76.77; H, 8.43; N, 6.31%.

§ X-Ray diffraction data for **4**. $C_{56}H_{74}CaN_4O_2$, M = 875.27, monoclinic, $P2_1/n$, a = 12.3837(2) Å, b = 19.3136(3) Å, c = 21.3459(4) Å, β = 93.5240(10)°, V = 5095.73(15) Å^3, Z = 4, ρ = 1.141 g cm^{-3}, Temperature 150(2) K, R_1 [$I > 2\sigma(I)$] = 0.0532, wR_2 [$I > 2\sigma(I)$] = 0.1118, R_1 [all data] = 0.0935, wR_2 [all data] = 0.1313, measured reflections = 51 119, unique reflections = 11 481, R_{int} = 0.0843.

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