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Heavier Group-2-Element Catalyzed Hydroamination of Carbodiimides

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The heteroleptic calcium amide [{ArNC(Me)CHC(Me)NAr}Ca{N(SiMe$_3$)$_2$}(THF)] (Ar = 2,6-diisopropylphenyl) and the homoleptic heavier alkaline earth amides, [M{N(SiMe$_3$)$_2$}$_2$(THF)$_2$] (M = Ca, Sr and Ba) are reported as competent pre-catalysts for the hydroamination of 1,3-carbodiimides. Whilst the reaction scope is currently limited to reactions of aromatic amines with 1,3-dialkylcarbodiimides, in most cases preparations in hydrocarbon solvents proceed rapidly at room temperature with catalyst loadings as low as 0.2 mol-% and the guanidine reaction products crystallize directly from the reaction mixture. Initial studies are consistent with the intermediacy of heavier group-2 guanidinate complexes.

Introduction

Over the past few years a useful reaction chemistry of the organometallic compounds of the heavier alkaline earths (M = Ca, Sr and Ba) has begun to emerge.[1] Studies within our group, and elsewhere, have demonstrated the application of heavier group-2 species to the catalytic hydroamination,[2] hydrophosphination,[3] hydrosilylation,[4] and polymerization[5] of substrates containing unsaturated carbon–carbon bonds. In addition, a number of group-2 mediated catalytic reactions have been reported that employ substrates containing carbon–heteroatom multiple bonds. These include the polymerization of lactides and lactones,[6] the trimerisation of phenyl isocyanate,[7] the dimerisation of aldehydes (Tischenko reaction)[8] and the hydrophosphination of 1,3-carbodiimides.[9]

Guanidines have received considerable attention not only for use as ancillary ligands in f-block and transition-metal chemistry,[10] but also due to their appearance as functional groups in many natural products and synthetic pharmaceuticals.[11] Despite this, catalytic syntheses of these molecules remain limited to a handful of examples. These include the early transition metal,[12] lanthanide[13] and group 1[14] mediated hydroamination of carbodiimides and group 4 imido catalyzed transamination of guanidines.[12a] As part of a preliminary study toward the catalytic hydroamination of heterocumulenes, we recently reported that β-diketiminato calcium amides, [{ArNC(Me)CHC(Me)NAr}Ca{NR$_2$}(THF)] (Ar = 2,6-diisopropylphenyl, NR$_2$ = NHAr, NPh$_2$, NHCH$_2$CH$_2$OMe), readily undergo insertion reactions with 1,3-dialkylcarbodiimides to yield the corresponding heteroleptic calcium guanidinate complexes. Furthermore, these latter complexes could be synthesized through a one-pot procedure from addition of the amine and carbodiimide to [{ArNC(Me)CHC(Me)NAr}Ca{N(SiMe$_3$)$_2$}(THF)] (**1**) in hydrocarbon solutions.[15] We now describe the extension of this work to the group-2 catalyzed synthesis of guanidines by the hydroamination of 1,3-carbodiimides.

Results and Discussion

Hydroamination Catalysis

An initial NMR experiment was conducted between 2-fluoroaniline (δ_{19F} = –135.8 ppm), 1,3-diisopropylcarbodiimide and [Ca{N(SiMe$_3$)$_2$}$_2$(THF)$_2$] (**2a**) in [D$_6$]benzene. Addition of an excess of both 2-fluoroaniline and 1,3-dialkylcarbodiimide to the pre-catalyst resulted in an instant crystallization of a colorless reaction product from the NMR tube. Whilst this event prevented the acquisition of satisfactory multinuclear NMR spectroscopic data on the reaction mixture, following work-up of the tube, isolation and characterization revealed the solid to be the guanidine [{(2-FC$_6$H$_5$)N}C{NH*i*Pr}$_2$] (δ_{19F} = –125.1 ppm) formed in 44% isolated yield from the catalytic hydroamination of 1,3-diisopropylcarbodiimide followed by, or concominant with, a 1,3-proton shift. The structure of the product was confirmed by single-crystal X-ray diffraction (Figure 1). A

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background experiment between 2-fluoroaniline and 1,3-diisopropylcarbodiimide demonstrated no reaction after 7 d at room temperature (Scheme 1).[16]

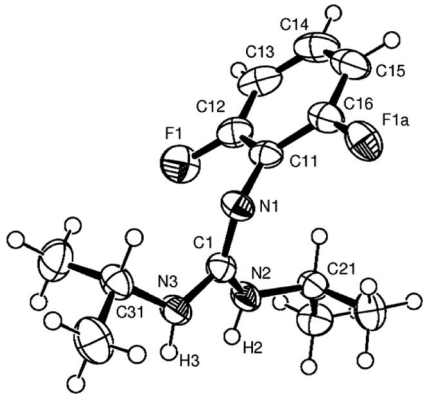
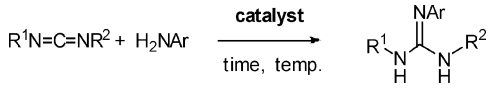


Figure 1. ORTEP representation (50%) of [{(2-FC_6H_5)N}C{NH*i*Pr}$_2$]. Selected bond lengths [Å] and angles [°]. C(1)–N(1) 1.306(2), C(1)–N(2) 1.364(3), C(1)–N(3) 1.363(3), N(1)–C(1)–N(3) 118.73(19), N(1)–C(1)–N(2) 127.06(19), N(3)–C(1)–N(2) 114.15(18). Disordered fluorine atoms modelled over two sites.



Scheme 1. Group-2 catalyzed hydroamination of carbodiimides.

On the basis of this observation a series of reactions were conducted in benzene solutions. The heteroleptic calcium amide **1** and the series of homoleptic heavier alkaline earth amides [M{N(SiMe$_3$)$_2$}$_2$(THF)$_2$] (M = Ca, **2a**; Sr, **2b**; Ba; **2c**) were applied to the catalytic hydroamination of 1,3-diisopropylcarbodiimide with 2-fluoroaniline. Although it has proven to be a remarkably useful prototype for the elaboration of stoichiometric calcium reactivity, in the current context, use of the β-diketiminato complex **1** offers no advantage over the homoleptic calcium amide **2a** in terms of either activity or ease of utility. Indeed it is likely that the β-diketiminate ligand is protonated and effectively removed during the early stages of catalytic turnover to provide common catalytic intermediates (viz. the homoleptic guanidinate complexes **3a** and **3b**, vide infra). Reactions were conducted using 2 mol-% catalyst and based upon initial substrate concentrations of 0.15 M. Although, in all cases, crystallization of the product from solution was observed at room temperature, the reaction yield of the isolated guanidine was consistently low (37–68%). This latter limitation could be overcome, however, by changing the conditions for what is effectively a crystallization of the reaction product upon mixing starting materials and catalyst. In this manner, increasing the concentrations of the substrates to 0.3 M and changing the reaction solvent to hexane yielded the hydroamination product [{(2-FC_6H_5)N}C{NH*i*Pr}$_2$] in 71–84%. Again **1** and **2a**–**c** proved catalytically active with most reactions taking less than 5 min at room temperature (Table 1, Entries 1–4).

A number of anilines and 1,3-carbodiimides were investigated under these reaction conditions and the results of this study are presented in Table 1. The hydroamination of both symmetric and unsymmetric carbodiimides was achieved at room temperature using 2 mol-% of the calcium amide **2a**. Choice of pre-catalyst was dictated by its ease of synthesis and low cost. Both electron-rich and electron-deficient anilines react readily and, in most cases, following crystallization the guanidine products could be isolated by a simple filtration. Catalytic hydroamination reactions employing sterically demanding substrates, such as 1,3-di-*tert*-butylcarbodiimide (Table 1 Entries 8, 9) and 2,6-diisopropylaniline (Table 1, Entry 17, 18) however, could only be achieved at higher reaction temperatures. These observa-

Table 1. Group 2 catalyzed hydroamination of carbodiimides.

Entry	R^1	R^2	Ar	Catalyst [mol-%]	Time [h]	Yield [%][a]
1	*i*Pr	*i*Pr	2-FC_6H_4	**1** (2)	0.1	84
2	*i*Pr	*i*Pr	2-FC_6H_4	**2a** (2)	0.1	77
3	*i*Pr	*i*Pr	2-FC_6H_4	**2b** (2)	0.1	80
4	*i*Pr	*i*Pr	2-FC_6H_4	**2c** (2)	1	67
5	Cy	Cy	2-FC_6H_4	**2a** (2)	0.1	79
6	*t*Bu	Et	2-FC_6H_4	**2a** (2)	12	91
7	*t*Bu	Et	2-FC_6H_4	**2a** (2)	0.25[b]	74[b]
8	*t*Bu	*t*Bu	2-FC_6H_4	**2a** (4)	24	37[c]
9	*t*Bu	*t*Bu	2-FC_6H_4	**2a** (4)	24	46[b,c]
10	*i*Pr	*i*Pr	4-MeC_6H_4	**2a** (2)	12	71
11	Cy	Cy	4-MeC_6H_4	**2a** (2)	4	81
12	*i*Pr	*i*Pr	Ph	**2a** (2)	1	74
13	Cy	Cy	Ph	**2a** (2)	0.1	81
14	*i*Pr	*i*Pr	2-$MeOC_6H_4$	**2a** (2)	12	85
15	Cy	Cy	2-$MeOC_6H_4$	**2a** (2)	12	80
16	*i*Pr	*i*Pr	1-naphthyl	**2a** (2)	72	57
17	Cy	Cy	2,6-*i*PrC_6H_3	**2a** (4)	2	55[c]
18	Cy	Cy	2,6-*i*PrC_6H_3	**2a** (4)	2	82[b,c]

[a] Isolated yield following crystallization of the product from hexane at 25 °C. [b] Yield determined by ^{1}H NMR spectroscopy in [D_6]benzene using tetrakis(trimethylsilyl)silane as an internal standard. [c] Reaction conducted at 80 °C.

tions are consistent with those previously made in stoichiometric heavier group-2 chemistry. For example, although the calcium amide [{ArNC(Me)CHC(Me)NAr}Ca{NHAr}(THF)] reacts readily with 1,3-diisopropyl- and 1,3-dicyclohexylcarbodiimide at room temperature, this latter complex does not undergo an insertion reaction with 1,3-di-*tert*-butylcarbodiimide even after being heated to 60 °C for 12 h.[15] Initial attempts to extend the catalytic methodology to primary alkylamines proved unsuccessful. Although stoichiometric reactions using **1** in these instances provided the expected heteroleptic calcium guanidinate complexes,[15] these species did not undergo catalytic turnover.

Previous catalytic syntheses of guanidines employing early transition metal, group 1 or f-block-based catalysts typically require long reaction times and/or elevated reaction temperatures to achieve the hydroamination of 1,3-carbodiimides.[13–14] For instance the reaction of aniline with 1,3-diisopropylcarbodiimide to yield [$(C_6H_5N)C\{NHiPr\}_2$] is reported to be catalyzed by [$Li\{N(SiMe_3)_2\}$] (2 mol-%, 18 h, room temp., 96% yield) and [$\{Me_2Si(C_5Me_4)NPh\}Y(CH_2SiMe_3)(THF)_2$] (1 mol-%, 24 h, 50 °C, 92% yield). Encouraged by the synthetic ease of the procedure detailed herein, we therefore sought to investigate the limits of this catalytic reaction. A series of reactions were conducted at room temperature based upon a 60 mmol quantity of 1,3-dicyclohexylcarbodiimide and aniline using 0.2–2 mol-% of **2a**. These experiments demonstrated that whilst the reaction proceeds rapidly at catalyst loadings as small as 0.5 mol-% (82%, 0.5 h), at even lower catalyst loadings product yields diminish quickly and the catalyst reaches a limit at 0.2 mol-% (56%, 48 h). In all cases, as with the small scale reactions, the product crystallizes directly from the reaction mixture.

To inform our understanding of these catalytic processes a series of stoichiometric reactions were performed. Addition of 2 equiv. of aniline and 1,3-diisopropylcarbodiimide to **2a** in [D_8]toluene yielded, in addition to 2-phenyl-1,3-diisopropylguanidine, a new calcium species, **3a**, which could also be synthesized by addition of two equivalents of the free guanidine to the pre-catalyst **2a**. Crystallization of **3a** from a hexane/THF solvent mixture allowed the isolation of single crystals. An X-ray diffraction experiment revealed the product **3a** to be a homoleptic calcium guanidinate complex with coordination at the metal provided by two unsymmetrically chelated κ^2-*N*,*N*-guanidinate ligands and two molecules of tetrahydrofuran (Figure 2 and Table 2). The complex possess pseudooctahedral geometry at the six-coordinate calcium center with the two tetrahydrofuran ligands demonstrating a *cisoid* geometry [O(1)–Ca–O(2) 89.54(4)°] with repect to one another. Calcium–nitrogen bond lengths [av. Ca–N 2.418 Å] and the guanidinate ligand bite angles [N(1)–Ca–N(2) 56.13 and N(4)–Ca–N(5) 55.90°] are consistent with those reported in the only previously reported homoleptic calcium guanidinate complex [$\{(Me_3Si)_2N\}C(NCy)_2]_2Ca(OEt_2)$ (**4**) [av. Ca–N 2.381 Å; av. N–Ca–N 56.39°].[17] In addition, bond lengths and bond angles within the two guanidinate ligands of **3a** suggest a significant degree of delocalisation of the non-coordinated nitrogen lone pair across the π-framework of the ligand.

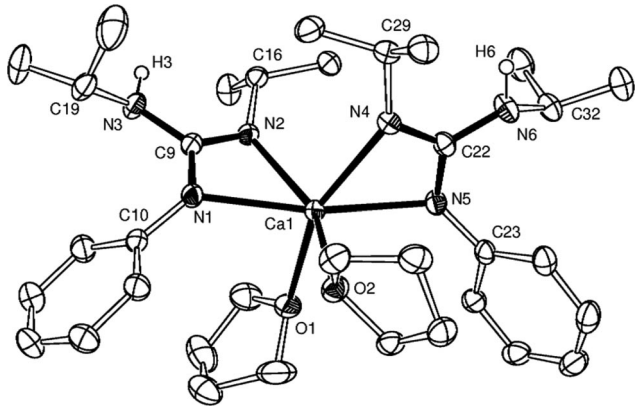


Figure 2. ORTEP representation (40%) of **3a**. H-Atoms with the exception of NH protons omitted for clarity. Selected bond lengths [Å] and angles [°]. Ca–N(1) 2.4215(11), Ca–N(2) 2.4179(10), Ca–N(4) 2.4202(11), Ca–N(5) 2.4291(11), Ca–O(1) 2.4106(10), Ca–O(2) 2.4194(10); N(1)–Ca–N(2) 56.13(3), N(1)–C(9)–N(2) 115.81(11), N(1)–C(9)–N(3) 121.53(11), N(2)–C(9)–N(3) 122.65(11), O(1)–Ca–O(2) 89.54(4).

Table 2. Selected bond lengths [Å] and bond angles [°] in complexes **3a**–**b**.

	3a	**3b**
Ca–N (terminal)	2.4215(11) 2.4179(10) 2.4202(11) 2.4291(11)	2.3604(11) 2.3748(11)
Ca–N (bridging)	–	2.4009(11) 2.4269(11)
Ca–O	2.4106(10) 2.4194(10)	–
N–C–N (terminal)	115.81(11) 121.53(11) 122.65(11) 122.90(12) 121.37(11) 115.70(11)	121.24(11) 115.97(11) 122.75(12)
N–C–N (bridging)	–	123.99(12) 116.52(11) 119.49(12)
N–Ca–N (terminal)	56.13(3) 55.90(4)	57.45(4)
N–Ca–N (bridging)	–	55.08(4)

In solution **3a** demonstrated a level of complexity that was not consistent with the solid-state data. Variable temperature NMR studies upon a [D_8]toluene solution of **3a** showed a number of reversible changes. At 298 K four independent isopropyl signals were observed by ^{1}H NMR spectroscopy. In the high-temperature limit (353 K) these resonances coalesced to give only two isopropyl environments. Although coalescence of the apparent two sets of twin resonances occurred at two independent temperatures [T_A = 318 K; T_B = 338 K] with two independent frequencies [k_A = 34 Hz; k_B = 117 Hz], these data gave a single activation energy [$\Delta G^{\ddagger}$ = 68 kJ mol^{-1}] characterising one fluxional process. The complexity of these observations was re-

solved by the synthesis of a solvent-free analogue of **3a**. Reaction of two equivalents of [(PhN)C{NH*i*Pr}$_2$] with [Ca{N(SiMe$_3$)$_2$}$_2$] in toluene yielded the dimeric calcium guanidinate complex **3b**. An X-ray crystallograpic study revealed **3b** to consist, in the solid-state, of a centrosymmetric dimer in which five-coordinate calcium centers are bridged by unsymmetric Ca–N–Ca′ interactions (Figure 3 and Table 2). The N–C–N chelate rings are disposed with and *anti*-configuration with respect to the dimer core giving rise to an S_2-symmetric tricylic ladder structure. Further coordination at calcium is provided by terminal guanidinate ligands. As with **3a** the guanidinate ligands in both terminal and bridging positions in **3b** coordinate as unsymmetric κ^2-*N*,*N*-chelates. The calcium–nitrogen bond lengths of the non-bridging interactions [av. 2.379 Å] are slightly shorter than those observed in **3a** due to the higher coordination number at calcium in the former complex. The guanidinate bite angles within **3b** [N(3)–Ca–N(1) 57.45° and N(6)–Ca–N(4) 55.08°] also differ slightly from those in the monomeric species with the terminal ligands demonstrating a more obtuse bite-angle than those in the bridging positions.

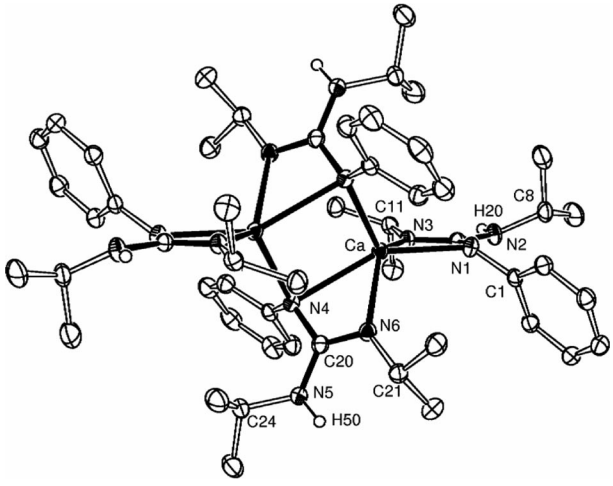


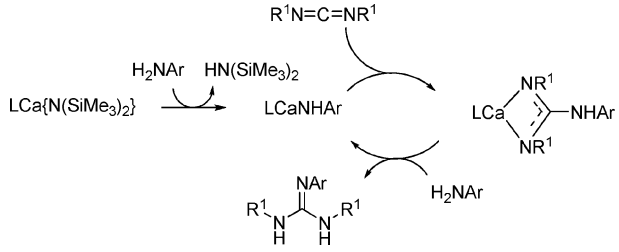
Figure 3. ORTEP representation (40%) of **3b**. H-Atoms with the exception of NH protons omitted for clarity. Selected bond lengths [Å] and angles [°]. Ca–N(3) 2.3604(11), Ca–N(1) 2.3748(11), Ca–N(6) 2.4009(11), Ca–N(4) 2.4269(11), Ca–N(4)′ 2.5590(11), N(3)–Ca–N(1) 57.45(4), N(6)–Ca–N(4) 55.08(4), Ca–N(4)–Ca′ 89.31(4).

Complex **3b** demonstrated identical variable-temperature ^{1}H NMR spectroscopic data to **3a** in [D$_8$]toluene solutions, indicating that **3a** also undergoes dimerisation in solution with the exclusion of THF from the coordination sphere. Whilst alternative fluxional modes cannot be discounted, this behaviour may be explained by considering the equilibration of bridging and terminal ligands within a robust dimeric species with the guanidinate maintaining a preference for unsymmetrical coordination. Consistent with this hypothesis ^{13}C NMR spectroscopic data demonstrated two guanidinate ligand environments at 298 K, characterized by the quaternary carbon resonances of the N$_3$C cores [$^{13}C_{quat.}$ = 151.5, 154.9 ppm]. Further qualitative evidence for the dimeric nature of **3** in solution was provided by the fact that $\Delta G^{\ddagger}$ was found to be independent of sample concentration.

Although it has previously been reported that [{(Me$_3$Si)$_2$N}C(NCy)$_2$]$_2$Ca(OEt$_2$) (**4**) is susceptible to reversible decomposition with reformation of a carbodiimide and calcium amide,[17] the attempted crossover reaction of [{(2-FC$_6$H$_5$)N}C{NH*i*Pr}$_2$], 1,3-dicyclohexylcarbodiimide and 2 mol-% **2a** yielded no new reaction products after 12 h at room temperature as monitored by ^{19}F NMR spectroscopy. Similarly, a mixture of [{(2-FC$_6$H$_5$)N}-C{NH*i*Pr}$_2$], 4-methylaniline and 2 mol-% **2a** demonstrated no signs of crossover reaction products over the same period. These experiments suggest that, under the catalytic reaction conditions, the calcium guanidinate complexes are kinetically stable and guanidine formation is non-reversible.

Proposed Catalytic Cycle

The isolated guanidinate complexes **3a** and **3b** were also applied to the catalytic hydroamination of 1,3-diisopropylcarbodiimide with aniline. Although, both compounds proved catalytically active the isolated yields of the guanidine products (**3a**, 1 h, 62%; **3b**, 1 h, 79%) differed slightly from those of the amide pre-catalyst [Ca{N(SiMe$_3$)$_2$}$_2$-(THF$_2$)] (**2a**, 1 h, 74%), most likely due to differences in the crystallization conditions of the reaction product. This observation, and consideration of our previous studies on the hydrophosphination of carbodiimides,[9] suggests that the catalytic hydroamination chemistry proceeds via fast catalyst initation via silylamide protonation and carbodiimide insertion to form a group-2 guanidinate complex. Protonolysis of this latter species with 1 equiv. of aniline, liberates the guanidine product and reforming the transient group-2 amide complex (Scheme 2)



Scheme 2. Proposed catalytic cycle.

Although the calcium guanidinate complexes may be dimeric in solution, the nuclearity of the active catalyst species is likely to be a function of not only the substrates but also the group-2 metal employed.

Conclusions

Homoleptic group-2 amides [M{N(SiMe$_3$)$_2$}$_2$(THF)$_2$] (M = Ca, Sr and Ba) are reported as highly competent pre-catalysts for the catalytic hydroamination of carbodiimides with anilines. Although initial attempts to extend this reaction chemistry to primary amines has been unsuccessful, the chemistry detailed herein represents a practical and scalable synthetic approach to guanidines. Coordination

chemistry studies upon the catalytic species (M = Ca) suggest the involvement of homoleptric dimeric guanidinate complexes in solution, with catalytic turnover occurring, by analogy to our previous work,[9] with fast Brønstead acid–Brønstead base and Lewis acid–Lewis base ligand-exchange processes at the metal center, and carbon–nitrogen bond formation proceeding by σ-bond metathesis and insertion reaction steps. We are continuing to investigate this reaction and the application of heavier group-2 species in this and related catalytic processes.

Experimental Section

General Procedures: All manipulations were carried out using standard Schlenk line and glovebox techniques under either dinitrogen or argon. All solvents were distilled under dinitrogen and dried with conventional drying agents. Anilines were purchased from Sigma–Aldrich and used without further purification, with the exception of aniline, 2-fluoroaniline, 2-methoxyaniline and 2,6-diisopropylaniline which were dried with calcium hydride and distilled before use. All carbodiimides were purchased from Sigma–Aldrich and used without further purification. The β-diketiminate ligand precursor, ArNHC(Me)CHC(Me)NAr (Ar = 2,6-diisopropylphenyl),[18] heavier alkaline earth amides [M{N(SiMe$_3$)$_2$}$_2$(THF)$_2$] (M = Ca, Sr and Ba),[19] and the heteroleptic calcium amide **1**[6a] were prepared by literature procedures.

Preparative Scale Experiments: In a glovebox, the aniline (1.584 mmol) and carbodiimide (1.584 mmol) were dissolved in hexane (1 mL). In a separate vial, [Ca{N(SiMe$_3$)$_2$}$_2$THF$_2$] (0.032 mmol, 2 mol-%) was dissolved in hexane (1 mL).The catalyst solution was then transferred to a test tube, the substrate solution was added and the total volume made up to ca 5 mL. The reaction mixture was mixed thoroughly and formed a homogeneous, colorless, solution. The test tube was sealed with a septum and the reaction left for the specified time. Upon crystallization of the product, the sample was removed from the glovebox and the guanidine isolated by filtration, washed with cold hexane and dried in a desiccator. Literature known compounds gave satisfactory multinuclear data (see Supporting Information).

NMR-Scale Experiments: In a glove box, accurately weighed tetrakis(trimethylsilyl)silane (TMSS, ca. 2 mg), aniline (0.25 mmol) and carbodiimide (0.25 mmol) were dissolved in [D$_6$]benzene (0.5 mL) and transferred to a Youngs tap NMR tube. The initial concentrations of reagents were measured by ^{1}H NMR spectroscopy, following which the catalyst (2–5 mol-%) was added and the reaction monitored by ^{1}H and ^{19}F NMR spectroscopy. Yields were calculated by reference to TMSS.

1,3-Dicyclohexyl-2-(2-fluorophenyl)guanidine [{(2-FC$_6$H$_5$)N}C{NHCy}$_2$]: The product crystallized as a colorless solid (397 mg, 1.25 mmol, 79%) after 5 min. ^{1}H NMR ([D$_6$]benzene, 400 MHz, 298 K): δ = 0.78–0.95 (m, 6 H), 1.04–1.14 (m, 4 H), 1.33–1.38 (m, 2 H), 1.44–1.50 (m, 4 H), 1.91–1.94 (m, 4 H), 3.40–3.52 (broad m, 2 H), 3.56–3.58 (broad m, 2 H), 6.68–6.73 (m, 1 H), 6.93 (ddd, J = 7.7, 7.6, 1.3 Hz, 1 H), 7.03 (ddd, J = 10.8, 8.1, 1.3 Hz, 1 H), 7.15–7.20 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]benzene, 100 MHz, 298 K): δ = 25.2. 25.9, 33.9, 50.5, 116.3 (d, J = 20.6 Hz), 122.1 (d, J = 7.1 Hz), 124.9 (d, J = 3.4 Hz), 126.5 (d, J = 2.6 Hz), 139.2 (d, J = 12.7 Hz), 150.1, 156.3 (d, J = 242.6 Hz) ppm. ^{19}F NMR ([D$_6$]benzene, 298 K): δ = –124.9 ppm. IR (DCM film) 1265, 1490, 1517, 1598, 1625, 2856, 2933, 2985, 3054, 3442 ppm. MS (ESI, +ve): m/z (%) = 318 (100) [M + H]$^+$. HRMS calcd. for $C_{19}H_{29}FN_3$ 318.2346 found 318.2338. M.p. (hexane) 154–156 °C. $C_{19}H_{28}FN_3$ (317.45): calcd. C 71.82, H 8.82, N 13.23; found C 71.40, H 8.86, N 13.00.

1,3-Dicyclohexyl-2-(2-methoxyphenyl)guanidine [{(2-MeOC$_6$H$_5$)N}C{NHCy}$_2$]: The product crystallized as a colorless solid (414 mg, 1.26 mmol, 80%) after 12 h. ^{1}H NMR ([D$_6$]benzene, 400 MHz, 298 K): δ = 0.85–0.97 (m, 6 H), 1.08–1.18 (m, 4 H), 1.36–1.39 (m, 2 H), 1.48–1.52 (m, 4 H), 3.46 (s, 3 H), 3.40–3.60 (apparent broad s, 2 H), 3.56 (broad s, 2 H), 6.79 (d, J = 7.8 Hz, 1 H), 6.93 (ddd, J = 7.8, 7.5, 1.8 Hz, 1 H), 6.98 (ddd, J = 7.5, 7.4, 1.5 Hz, 1 H), 7.21 (d, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]benzene, 100 MHz, 298 K): δ = 25.3, 26.0, 34.1, 50.6, 55.6, 113.2, 122.1, 122.2, 125.2, 140.9, 149.5, 153.0; IR (DCM film) 1031, 1049, 1238, 1255, 1452, 1490, 1548, 1585, 1621, 2852, 2927, 3054, 3286 ppm. MS (ESI, +ve): m/z (%) = 330 (100) [M + H]$^+$. HRMS calcd. for $C_{20}H_{32}N_3O$ 330.2542 found 330.2545. M.p. (hexane) 113–114 °C. $C_{20}H_{31}N_3O$ (329.48): calcd. C 72.91, H 9.48, N 12.75; found C 72.30, H 9.48, N 12.50.

3-*tert*-Butyl-1-ethyl-2-(2-fluorophenyl)guanidine [{(2-FC$_6$H$_5$N)}C{NHEt}{NH*t*Bu}]: On a Schlenk line, a solution of **2a** (16 mg, 0.032 mmol, 2 mol-%) in toluene (2 mL) was added to a toluene (2 mL) solution of 1-*tert*-butyl-3-ethylcarbodiimide (200 mg, 1.58 mmol) and 2-fluoroaniline (176 mg, 1.58 mmol). The reaction mixture was stirred overnight, and then exposed to air. The solvent was removed in vacuo and the crude dissolved in diethyl ether (30 mL) and washed with water (3 × 10 mL). The organic layer was dried with magnesium sulfate, filtered and the solvent removed in vacuo. The resultant oil was deemed pure by multinuclear NMR spectroscopy and mass spectrometry. Further purification was achieved by bulb-to-bulb distillation (150 °C, 3.3×10^{-1} mbar) to give the product as a yellow oil (340 mg, 1.43 mmol, 91%).The reaction monitored by ^{1}H and ^{19}F NMR showed a 74% yield after 15 min at room temperature. ^{1}H NMR ([D$_6$]benzene, 300 MHz, 298 K): δ = 0.65 (t, J = 7.2 Hz, 3 H), 1.31 (s, 9 H), 2.63 (q, J = 7.2 Hz, 3 H), 3.43 (broad s, 2 H), 6.68–6.72 (m, 1 H), 6.91 (ddd, J = 7.6, 7.6, 1.4 Hz, 1 H), 7.00 (ddd, J = 10.8, 8.1, 1.6 Hz, 1 H), 7.08 (ddd, J = 8.4, 8.1, 1.7 Hz, 1 H) ppm. ^{19}F NMR ([D$_6$]benzene, 298 K): δ = –125.4 ppm. ^{13}C NMR ([D$_6$]benzene, 100 MHz, 298 K): δ = 14.9, 29.8, 37.1, 50.8, 116.3 (d, J = 20.6 Hz), 122.0 (d, J = 7.1 Hz), 124.8 (d, J = 3.7 Hz), 126.3 (d, J = 3.2 Hz), 139.0 (d, J = 12.8 Hz), 150.6, 156.2 (d, J = 242.5 Hz) ppm. IR (DCM film): $\tilde{\nu}$ = 749, 1214, 1361, 1450, 1489, 1526, 1599, 1632, 2923, 2970, 3420. MS (ESI, +ve): m/z (%) = 238 (100) [M + H]$^+$. HRMS calcd. for $C_{13}H_{21}FN_3$ 238.1719 found 238.1704.

1,3-Di-*tert*-butyl-2-(2-fluorophenyl)guanidine [{(2-FC$_6$H$_5$N)}C{NH*t*Bu}$_2$]: On a Schlenk line, a solution of **2a** (32 mg, 0.064 mmol, 4 mol-%) in toluene (2 mL) was added to a toluene (2 mL) solution of 1,3-*tert*-butylethylcarbodiimide (246 mg, 1.58 mmol) and 2-fluoroaniline (176 mg, 1.58 mmol). The Schlenk tube was sealed, removed from the glovebox and heated to 80 °C for 24 h, after which point the reaction product was treated as moisture stable and the volatiles removed. Purification was achieved by bulb-to-bulb distillation (175 °C, 3.0×10^{-1} mbar) to give the product as a yellow oil (156 mg, 37%). Monitoring of the reaction by ^{1}H and ^{19}F NMR showed a 46% yield after 24 h at 80 °C. ^{1}H NMR ([D$_6$]benzene, 300 MHz, 298 K): δ = 1.20 (s, 18 H), 3.66 (broad s, 2 H), 6.65–6.72 (m, 1 H), 6.88 (ddd, J = 7.6, 7.6, 1.4 Hz, 1 H), 6.95–7.03 (m, 2 H) ppm. ^{19}F NMR ([D$_6$]benzene, 298 K): δ = –125.1 ppm. ^{13}C NMR ([D$_6$]benzene, 75 MHz, 298 K): δ = 30.0, 50.8, 116.3 (d, J = 20.6 Hz), 122.1 (d, J = 7.1 Hz), 124.7 (d, J = 3.7 Hz), 126.1 (d, J = 3.1 Hz), 139.0 (d, J = 12.9 Hz), 150.7, 156.0 (d, J = 242.2 Hz) ppm. IR (DCM film): $\tilde{\nu}$ = 749, 1210, 1436, 1490, 1520, 1600, 1635, 2962, 3472 cm^{-1}. MS (ESI, +ve): m/z (%) =

266 (100) $[M + H]^+$. HRMS calcd. for $C_{15}H_{24}FN_3$ 266.2033 found 266.2045.

Calcium Guanidinate 3a: To a solution of **2a** (0.253 g, 0.5 mmol) in THF (15 mL) was added a solution of 1,3-diisopropyl-2-phenylguanidine (0.219 g, 1.0 mmol) in THF (10 mL). After 12 h at room temperature the solvent was evaporated and the compound was recrystallized from hexane/THF (10 mL/1 mL) at –20 °C yielding colorless crystals of **3a** (0.174 g, mmol, 60%). M.p. (10:1 hexane/THF) 158–159 °C. Multinuclear NMR spectroscopic data as below with additional resonances attributed to non-coordinated THF. $C_{34}H_{56}CaN_6O_2$ (620.41): calcd. C 65.77, H 9.09, N 13.53; found C 65.69, H 8.97, N 13.62. M.p. (hexane/THF, 10:1) 158–159 °C.

Calcium Guanidinate 3b: Toluene (10 mL) was added to a solid mixture of $[Ca\{N(SiMe_3)_2\}_2]_2$ (164 mg, 0.46 mmol) and 1,3-diisopropyl-2-phenylguanidine (200 mg, 0.92 mmol). The mixture was stirred for 30 min, filtered and the solvent volume reduced to induce crystallization. The product **3b** was isolated as a colorless crystalline solid (127 mg, 0.133 mmol, 58%) by slow cooling of a hot toluene solution to 5 °C. M.p. (toluene) 153–158 °C. ^{1}H NMR ([D$_8$]toluene, 298 K, 400 MHz): δ = 0.71 (d, J = 6.8 Hz, 12 H), 0.91 (apparent s, 12 H), 1.13 (d, J = 6.2 Hz, 12 H), 1.18 (d, J = 6.3 Hz, 12 H), 3.15 (hept, J = 6.3 Hz, 2 H), 3.27 (hept, J = 6.2 Hz, 2 H), 3.37 (hept, J = 6.8 Hz, 2 H), 3.41 (broad s, 4 H, *NH*), 3.58 (multiplet, 2 H), 6.75–6.79 (m, 2 H), 6.77–6.81 (m, 2 H), 7.07–7.14 (m, 8 H), 7.15–7.23 (m, 8 H) ppm. ^{1}H NMR ([D$_8$]toluene, 353 K, 400 MHz): δ = 0.82 (apparent broad s, 12 H), 1.14 (d, J = 6.0 Hz, 12 H), 3.25 (multiplet, 2 H), 3.44 (multiplet, 2 H), 3.57 (broad s, 4 H, *NH*), 6.72 (broad t, 4 H), 6.96–7.01 (m, 8 H), 7.06–7.13 (m, 8 H) ppm. ^{13}C NMR ([D$_8$]toluene, 298 K, 100 MHz): δ = 24.4, 24.5, 26.3, 27.2, 115.9, 118.4, 121.6, 122.7, 123.7, 130.4, 151.5, 154.9, 163.3, 164.9 ppm. $C_{52}H_{80}Ca_2N_{12}$ (952.59): calcd. C 65.45, H 8.39, N 17.62; found C 65.53, H 8.33, N 17.57. M.p. (toluene) 155–158 °C.

Xray Diffraction Data:[20] Data for **[{(2-FC$_6$H$_5$)N}C{NH*i*Pr}$_2$]** and **3a**, **3b** were collected at 150 K with a Nonius Kappa CCD diffractometer equipped with a low-temperature device, using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Data were processed using the Nonius Software.[21] Structure solution, followed by full-matrix least-squares refinement was performed using either the WinGX-1.70 suite of programs[22] or the programme suite X-SEED.[23] Notes on refinement: **3**: F occupies both ortho positions in the ratio 60:40. **3a**: C3/C3a represent 65:35 disorder over 2 sites. H3 and H6 located and refined at 0.9 Å from the parent nitrogen atoms.

[{(2-FC$_6$H$_5$)N}C{NH*i*Pr}$_2$]: $C_{13}H_{20}FN_3$, M = 237.32, monoclinic, $P2_1/a$, a = 8.5380(5) Å, b = 11.2920(7) Å, c = 14.0080(10) Å, β = 94.402(3), V = 1346.54(15) Å^3, Z = 4, ρ = 1.171 g cm^{-3}, R_1 [$I > 2\sigma(I)$] = 0.0498, wR_2 [$I > 2\sigma(I)$] = 0.115, R_1 [all data] = 0.0913, wR_2 [all data] = 0.1358, measured reflections = 12160, unique reflections: 2358. R_{int} = 0.0889.

3a: $C_{34}H_{56}CaN_6O_2$, M = 620.93, triclinic, $P\bar{1}$, a = 8.2890(1) Å, b = 12.1250(2) Å, c = 18.3840(3) Å, α = 87.296(1), β = 81.426(1), γ = 77.981(1), V = 1786.72(5) Å^3, Z = 2, ρ = 0.213 g cm^{-3}, R_1 [$I > 2\sigma(I)$] = 0.0432, wR_2 [$I > 2\sigma(I)$] = 0.0988, R_1 [all data] = 0.0653, wR_2 [all data] = 0.1097, measured reflections: 38968, unique reflections = 10421. R_{int} = 0.041.

3b: $C_{52}H_{80}Ca_2N_{12}$, M = 953.44, monoclinic, $C2/c$, a = 21.4319(3) Å, b = 13.2981(2) Å, c = 20.0986(3) Å, β = 107.9810(10), V = 5448.40(14) Å^3, Z = 4, ρ = 1.162 g cm^{-3}, R_1 [$I > 2\sigma(I)$] = 0.0361, wR_2 [$I > 2\sigma(I)$] = 0.0832, R_1 [all data] = 0.0481, wR_2 [all data] = 0.0901, measured reflections: 44403, unique reflections: 6262. R_{int} = 0.0425.

Supporting Information (see also the footnote on the first page of this article): Complete experimental details and spectra of all isolated compounds and ^{1}H and ^{13}C{^{1}H} NMR spectra of isolated guanidine compounds.

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