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Calcium amido-bisoxazoline complexes in asymmetric hydroamination/cyclisation catalysis†

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Calcium complexes bearing bis(oxazolinylphenyl)amine (BOPA) ligands have been prepared, and their redistribution chemistry studied. The complexes [Ca(R-BOPA){N(SiMe$_3$)$_2$}(THF)] (R = ^{i}Pr **1a**, Ph **1b** and Bn **1c**) are active in hydroamination catalysis and give the highest enantioselectivity reported for a calcium complex.

The development of calcium-based molecular catalysts is expanding at an ever increasing rate.[1] Whilst being late in its development, the discovery of well-defined calcium complexes such as the β-diketiminato (nacnac) complex reported by Chisholm began a new era of calcium in catalysis,[2] that has been fuelled by the search for inexpensive and benign alternatives to ubiquitous precious metal systems. Calcium complexes have found application in various catalytic reactions: the calcium nacnac complex was found to be remarkably efficient in the hydroamination/cyclisation of amino-olefins,[3] the report of which has subsequently driven further developments in calcium-catalysed hydroamination,[4–7] hydrosilylation,[4,8] ring-opening polymerisation (ROP),[2,9] and hydrogenation.[10]
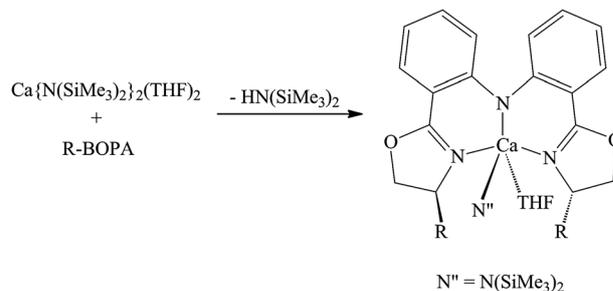
With such an impressive array of catalytic applications being reported for calcium, attention has naturally turned to the development of enantioselective derivatives; although high enantioselectivities have been reported for magnesium[11a] and in calcium-mediated Lewis acid catalysis,[11b–e] asymmetric variants of the afore-mentioned reactions has been a challenging, and largely elusive facet of calcium-mediated catalysis. The lower levels of selectivity observed with calcium, compared to magnesium, presumably arises from the greater tendency of alkaline earth complexes to undergo redistribution as the group is descended. The successful development of asymmetric calcium catalysts is a pivotal objective, if calcium is to become a mainstream metal in catalytic transformations.

Harder and coworkers pioneered asymmetric hydroamination catalysis using calcium complexes in 2008 using chiral nacnac and bisoxazoline (BOX) supported amide complexes.[4] In these cases ligand redistribution proved to be rapid, affording a mixture of

the heteroleptic complex [Ca(L){N(SiMe$_3$)$_2$}(THF)$_n$] and homoleptic complex [Ca{N(SiMe$_3$)$_2$}$_2$(THF)$_n$] alongside the catalytically inactive [Ca(L)$_2$]. This redistribution process understandably results in low enantioselectivities (6–10% ee). Replacing the oxazoline rings with imidazolines allowed the equilibrium to be controlled although selectivities remained at around 12%.[7b]

Sadow reported an improvement in stereoselectivity with trisoxazoline complexes (18%);[6] more recently we have reported 26% ee with the amino-amide ligands,[7a] which represents the current benchmark in this process when catalysed by calcium. Notwithstanding the current advances in asymmetric calcium catalysis, selectivities remain invariably low and have thus far resisted improvement. In this communication we report a doubling of the stereoselectivity, using calcium amido complexes supported by bis(oxazolinylphenyl)amine (BOPA) ligands,[12] and for the first time (for calcium) attaining 50% ee in the hydroamination/cyclisation of amino-olefins.

The complexes [Ca(R-BOPA){N(SiMe$_3$)$_2$}(THF)] (R = ^{i}Pr **1a**, Ph **1b**, Bn **1c**) were prepared by the reaction of [Ca{N(SiMe$_3$)$_2$}$_2$-(THF)$_2$] with the protio-ligand in benzene, with the concomitant elimination of one molar equivalent of hexamethyldisilazane (Scheme 1). The ^{1}H and ^{13}C{^{1}H} NMR spectra of the complexes indicate a C_2 symmetric product, consistent with the proposed structure. Samples of **1a–c** were found to undergo a slow but spontaneous redistribution into an equilibrium mixture of [Ca(R-BOPA){N(SiMe$_3$)$_2$}(THF)], [Ca(R-BOPA)$_2$] (R = ^{i}Pr **2a**, Ph **2b**, Bn **2c**) and [Ca{N(SiMe$_3$)$_2$}$_2$(THF)$_2$] (Scheme 2), thus preventing the isolation of pure samples of **1a–c**. Upon analysing *in situ* prepared samples of the phenyl and benzyl derivatives **1b** and **1c**, only traces (<5%) of the respective homoleptic complexes were observed after an hour at ambient
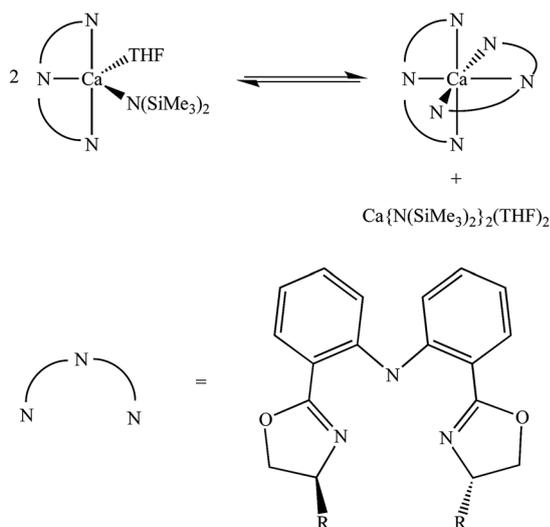
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Ca{N(SiMe$_3$)$_2$}$_2$(THF)$_2$ + R-BOPA → (− HN(SiMe$_3$)$_2$)

N″ = N(SiMe$_3$)$_2$

Scheme 1 Preparation of [Ca(R-BOPA){N(SiMe$_3$)$_2$}(THF)] (R = ^{i}Pr **1a**, Ph **1b**, Bn **1c**). N″ = N(SiMe$_3$)$_2$.

$$2 \ N{-}Ca{-}N(SiMe_3)_2 \ \rightleftharpoons \ N{-}Ca{-}N \ + \ Ca\{N(SiMe_3)_2\}_2(THF)_2$$

Scheme 2 Schematic showing ligand redistribution in [Ca(R-BOPA)-{N(SiMe₃)₂}(THF)].

temperature; heating the samples to 50 °C forced the mixtures to their equilibrium positions (**1b** : **2b** = 20 : 80; **1c** : **2c** = 15 : 85). In contrast, the isopropyl derivative **1a** was found to undergo redistribution at a significantly faster rate, in which NMR spectra recorded after 15 min. indicated an appreciable quantity of both **1a** and **2a**; heating the sample to 50 °C afforded the equilibrium mixture of essentially only **2a**. The more facile redistribution in this case is presumably attributed to the less sterically demanding nature of the isopropyl stereodirecting groups, compared to either phenyl or benzyl. Although pure samples of **1a–c** or **2a–c** could not be isolated, NMR data were collected *in situ* and high resolution mass spectra were obtained for all of the homoleptic complexes **2a–c**.

The redistribution of supporting ligands is commonplace in calcium complexes, and is thought to be one of the principal reasons for the low levels of enantioselectivity in calcium-mediated catalysis, as exemplified by the BOX and BIM complexes.[4,7b] The striking difference between the BOX/BIM equilibria and the BOPA complexes is that the redistribution is much slower with the BOPA complexes. Although samples of **1** were found to contain small amounts of **2** immediately, the transformation occurs slowly, taking several hours for the final equilibrium position to be attained, whereas the BOX and BIM complexes reach their respective equilibrium positions within minutes.

Whilst isolated samples of **1** invariably contained varying quantities of **2**, single crystals of [Ca(Bn-BOPA)₂] **2c** suitable for X-ray diffraction were grown by cooling a saturated solution of the equilibrium mixture in hexanes. The molecular structure is shown in Fig. 1, along with principal bond lengths and angles.‡ The structure contains two orthogonal BOPA moieties, each adopting a meridianal geometry with the two amido nitrogens located in *trans* positions. The amido nitrogens have approximate trigonal planar geometry (sum of angles subtended at N(1) and N(4) are 358.3(3) and 359.9(3)° respectively), although the plane of the amido nitrogens is somewhat offset from the plane formed by the calcium and oxazoline donors 57.1 and 49.3° for N(1) and N(4) respectively. The geometry of the calcium centre is best described as a highly distorted octahedral, the
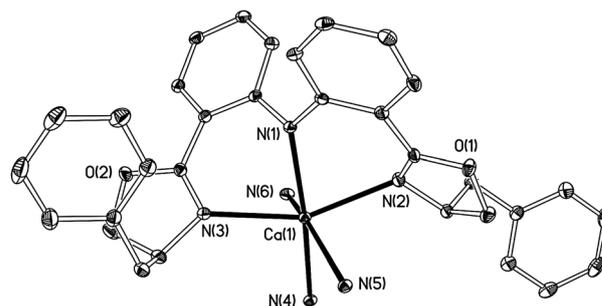
Fig. 1 Molecular structure of **2c**, H atoms omitted for clarity, and only the coordinating atoms of the second BOPA moiety are shown. Thermal ellipsoids are drawn at 25% probability. Selected bond lengths (Å) and angles (°): Ca(1)–N(1) 2.3979(12), Ca(1)–N(2) 2.4530(14), Ca(1)–N(3) 2.4418(14), Ca(1)–N(4) 2.3963(12), Ca(1)–N(5) 2.4502(13), Ca(1)–N(6) 2.4199(13), N(1)–Ca(1)–N(2) 74.59(4), N(1)–Ca(1)–N(3) 75.64(4), N(2)–Ca(1)–N(3) 149.50(4), N(1)–Ca(1)–N(4) 173.42(4), N(4)–Ca(1)–N(5) 75.05(4), N(4)–Ca(1)–N(6) 76.14(4), N(5)–Ca(1)–N(6) 149.52(4).

bond angles subtended at calcium deviating significantly from the ideal 90°. This is largely owing to the restricted bite angle of the BOPA ligand, as inferred by the N_{amide}–Ca–$N_{oxazoline}$ angles of *ca.* 75°. The phenyl rings that make up the ligand backbone are twisted in a helical fashion; the sense of the helical twist is such that the benzyl groups are arranged *exo*, which is presumably favoured on steric grounds.

Complexes **1a–c** were probed for their effectiveness in the calcium-catalysed asymmetric intramolecular hydroamination/cyclisation of amino-olefins. In light of the rearrangement, deemed likely to reduce the stereoselectivity of the reaction, the catalysis reactions were performed on samples of **1a–c** prepared at ambient temperature *in situ*, immediately prior to adding the substrate. The catalytic performances are summarised in Table 1 for 2,2′-diphenyl-1-aminopent-4-ene; interestingly, complexes **1a–c** were found to be completely inactive when the corresponding dimethyl substrate (2,2′-dimethyl-1-aminopent-4-ene) was employed, under a range of catalyst loadings and temperatures.

In general, the enantioselectivities when a particular ligand is used are relatively constant; being largely independent of temperature, *e.g.* compare entries 1–3, 4–12 and 13–15. The isopropyl and benzyl derivatives **1a** and **1c** give comparable selectivities of *ca.* 14–26% ee, which is commensurate with the very best of the previously reported calcium catalysts for this reaction. Most notable is the phenyl derivative, **1b**, which consistently gives ≥ 40% ee (entries 4–12), and for the first time enantiomeric excesses of 50% are reported (entry 10). Such selectivity is unprecedented in calcium-catalysed hydroamination, the highest reported example being 26% ee.[7] The higher level of selectivity with **1b** presumably has roots in the larger and more rigid phenyl stereodirecting group.

Whilst we have demonstrated that calcium-catalysed hydroamination/cyclisation is making remarkable progress in the formation of pyrrolidines, the *stereoselective* formation of the corresponding piperidines has only been reported for magnesium.[3c,11a] Initial studies using 2,2′-diphenyl-1-amino-hex-5-ene are presented in Table 2. As expected, the reaction rates were significantly slower than for the corresponding pyrrolidines, as predicted by Baldwin's rules.[14] No reactivity was found for the phenyl precatalyst **1b**, and given the relatively

Table 1 Asymmetric hydroamination using [Ca(R-BOPA){N(SiMe₃)₂}-(THF)] (R = ^{i}Pr **1a**, Ph **1b**, Bn **1c**)
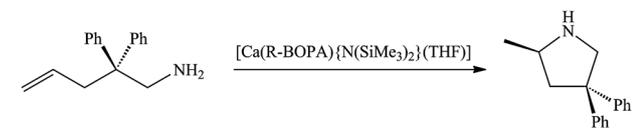
Entry	Precat.	Cat. mol%	Time[a]	Temp.[b]	Conv.[c]	ee[d]
1	**1a**	10	24 h	30	51	14
2	**1a**	10	24 h	40	> 99	22
3	**1a**	10	72 h	50	82	24
4	**1b**	10	24 h	30	79	40
5	**1b**	10	24 h	40	> 99	40
6	**1b**	10	24 h	50	> 99	34
8	**1b**	20	24 h	30	> 99	42
9	**1b**	20	24 h	40	> 99	46
10	**1b**	20	24 h	50	> 99	50
11	**1b**	25	24 h	30	> 99	44
12	**1b**	30	24 h	30	> 99	48
13	**1c**	10	24 h	21	> 99	25
14	**1c**	10	24 h	30	> 99	26
15	**1c**	10	24 h	40	88	20

[a] Time until no further reaction observed for at least 6 h. [b] °C. [c] Determined from ¹H NMR spectra. [d] Determined by ¹H NMR spectroscopy using (R)-(−)-O-acetylmandelic acid.[13]

Table 2 Asymmetric hydroamination using [Ca(R-BOPA){N(SiMe₃)₂}-(THF)] (R = ^{i}Pr **1a**, Ph **1b**, Bn **1c**)
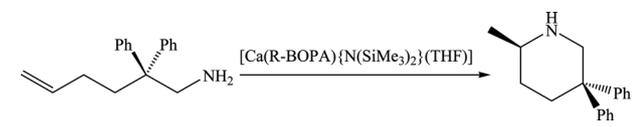
Entry	Precat.	Cat. mol%	Time[a]	Temp.[b]	Conv.[c]	ee[d]
1	**1a**	10	5 d	80	14	0
2	**1a**	20	24 h	50	26	8
3	**1a**	20	5 d	80	83	6
4	**1b**	20	24 h	80	Nil	—
5	**1c**	10	5 d	80	Trace	—
6	**1c**	10	24 h	50	Nil	—
7	**1c**	20	5 d	80	14	16

[a] Time until no further reaction observed for at least 6 h. [b] °C. [c] Determined from ¹H NMR spectra. [d] Determined by ¹H NMR spectroscopy using (R)-(−)-O-acetylmandelic acid.[13]

harsh conditions required to effect any reaction (no reaction was observed at ambient temperature) the phenyl ligand is possibly too sterically demanding for the larger substrate. Modest selectivities were obtained, 6–8% ee for **1a** (entries 2 and 3) although the benzyl congener **1c** gave a somewhat higher selectivity of 16% (entry 7). Given that this is the first time piperidines have been prepared stereoselectively using calcium, these modest selectivities make a useful and insightful addition to the field of asymmetric calcium catalysis.

In summary, we have demonstrated that the BOPA ligands represent a significant improvement in supporting chiral calcium complexes. This is demonstrated by the substantially higher stereoselectivity in the asymmetric hydroamination of amino-olefins, compared to previously reported systems.[16] We conclude that the relatively slow rate of ligand redistribution may be an important factor in the attainment of this level of selectivity,

and further preventing such processes may lead to even higher selectivities than those reported herein.

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