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Chiral calcium catalysts for asymmetric hydroamination/cyclisation†

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Calcium complexes supported by chiral 1,2-diamines have been shown to be efficient catalysts for the asymmetric hydroamination of amino-olefin substrates; the calcium complexes [Ca(NN^{R}){N(SiMe$_3$)$_2$}(THF)] (R = ^{t}Bu, ^{i}Pr, Ph, 4-C$_6$H$_4$F) give enantioselectivities of up to 26% which marks a significant increase based upon literature precedence. The structure of [Ca(NN^{Ph}){N(SiMe$_3$)$_2$}(py)] has been computed with density functional methods.

Whilst the coordination chemistry of the alkaline earth (AE) metals is well established, the development of well-defined complexes which can be successfully adapted to catalysis has only become apparent in the last few years.[1] The primary reason behind this late development of AE metals in catalysis is their propensity to undergo rapid Schlenk-type ligand redistribution processes,[2] thus rendering catalytically active species either inactive, or else removing the possibility of regio- or stereoselectivity. As such, the rich chemistry associated with the AE metals has been somewhat neglected outside the context of stoichiometric reagents.

Advances in the last five years have demonstrated that a further understanding of their coordination chemistry is likely to propel the catalytic applications of the AE metals, particularly calcium, into new and exciting directions. In this regard, remarkable advances in the area have been made, particularly with β-diketiminato ligands which have proven remarkably successful in supporting well-defined calcium complexes (Fig. 1a).[3] These, and related, AE complexes have been shown to be active in hydroamination,[4] hydrosilylation,[5] hydrogenation,[6] and ring opening polymerisation[3,7] catalysis. Despite the significant advances in this area, the use of chiral ligands to effect asymmetric catalysis remains much less developed, particularly in complexes in which strongly basic amide- or alkyl co-ligands are present.[8] Recently Buch and Harder prepared calcium amide complexes supported by the ubiquitous bisoxazoline (BOX) ligands, [Ca(BOX){N(SiMe$_3$)$_2$}(THF)] (Fig. 1b).[9] These complexes were screened in asymmetric hydroamination and hydrosilylation catalysis; despite being able to prepare and structurally characterise these complexes, ligand redistribution proved to be rapid in solution, reforming the achiral homoleptic complex Ca{N(SiMe$_3$)$_2$}(THF)$_2$ alongside the catalytically inactive [Ca(BOX)$_2$], thus rendering the enantioselectivities low (5–10% ee). Such observations have led to the hypothesis that ligand redistribution must be completely suppressed in order to generate acceptable enantioselectivities. Even more recently, Sadow *et al.* have reported somewhat higher enantioselectivities when using trisoxazoline magnesium and calcium complexes,[10] with the highest enantioselectivities being obtained with the magnesium complexes at elevated temperatures. It is in this context that we have sought to prepare simple and readily available chiral ligands that provide greater stereocontrol in hydroamination catalysis with calcium.

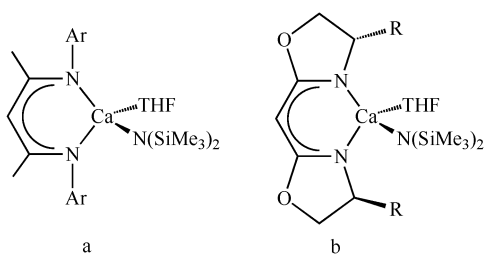

Fig. 1 Calcium complexes used in hydroamination catalysis.

A series of chiral ethylene diamine derivatives H$_2$NCH(^{i}Pr)CH$_2$NHR (HNN^{R}, R = ^{t}Bu **1a**, ^{i}Pr **1b**, Ph **1c** and 4-C$_6$H$_4$F **1d**) have been prepared from L-valine according to Scheme 1. This route utilises the amidation of an acid chloride with a series of primary amines or anilines. We have found that using thionyl chloride is the most convenient method of converting phthalimide-protected valine into the acid chloride, and does not give rise to epimerisation of the chiral acid; the protected valinoyl chloride can be readily prepared on a 100 g scale and is therefore convenient for the preparation of large quantities of diamines. The acid chloride can be converted into an N-substituted amide by adding a primary amine or aniline in THF. The addition of triethylamine allows this reaction to proceed under ambient conditions, although the yields are often much improved with the addition of catalytic *N*,*N*-dimethylaminopyridine (DMAP). The reduction of the amides to afford diamines was effected on a small scale with BH$_3$(THF) (using commercial 1 M solution). However, on increasing the scale of the reaction, this required the use of excessively large quantities of solvent, causing problems with heat transfer and unnecessary dilution. The reaction was less effective with BH$_3$(SMe$_2$) (10 M), whilst this enabled the

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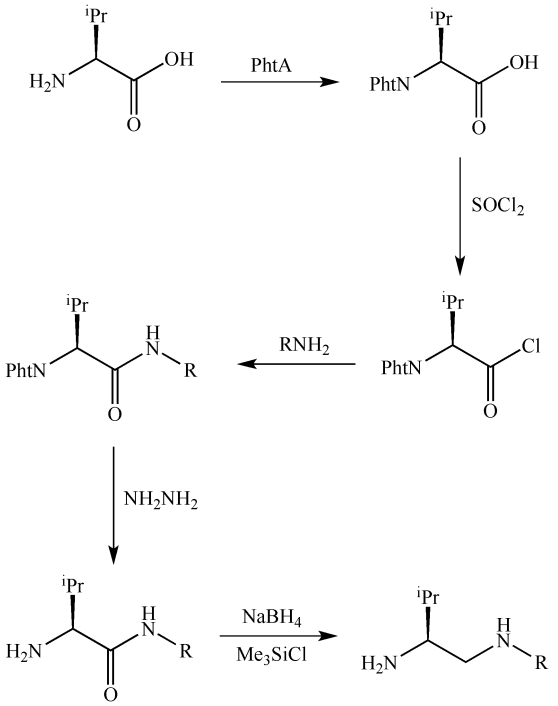


Scheme 1 Synthesis of chiral diamines **1a–d**.

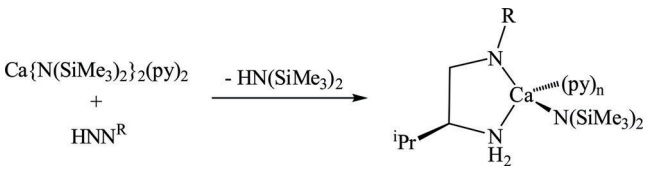
reaction to be scaled up safely, these conditions resulted in significantly lower yields, in addition to by-products arising from the degradation of the THF solvent. Conversely, the use of $NaBH_4/Me_3SiCl$ was found to give excellent yields,[11] with much more control over the reaction concentration; this procedure has been demonstrated to be successful on a scale of up to 12 g in 250 ml solvent. This simple multistep method allows a series of diamines (HNN^R) to be prepared in which the R substituent can be varied in a modular fashion, without introducing additional synthetic complexity.

Reaction of the protio-ligands **1a–d** with $Ca\{N(SiMe_3)_2\}_2(THF)_2$ in C_6D_6 afforded pale yellow precipitates, which although are suitable precursors for hydroamination catalysis (*vide infra*), were difficult to unambiguously characterise since they were found to be extremely labile in THF-d_8, but are insoluble in hydrocarbon solvents and C_6D_5Cl, and unstable in $CDCl_3$ and CD_2Cl_2. In order to determine the extent of base coordination, the complexes were prepared using the pyridine analogue $Ca\{N(SiMe_3)_2\}_2(py)_2$ in the presence of an excess of pyridine.[12] These complexes are formulated as $[Ca(NN^R)\{N(SiMe_3)_2\}(py)_n]$ (**2a–d**) (Scheme 2).

As with the THF complexes, the pyridine adducts were found to be only sparingly soluble in benzene and toluene, and decomposed in chloroform and dichloromethane. The NMR spectra in THF-d_8 were broad at ambient temperature, but nevertheless showed three clear signals (albeit without fine structure) for the diamine backbone protons. The presence of a single bis(trimethylsilyl)amide moiety was also evident from the relative integration of the signal at *ca.* 0 ppm. The fluxional process, presumably arising from the lability of the NN^R ligands, could not be completely "frozen out" using low temperature NMR analyses, within our instrumental capability (500 MHz, −90 °C), however NMR tube scale reactions carried out *in situ* demonstrated the elimination of one molar equivalent of $HN(SiMe_3)_2$, thus supporting the formation of a heteroleptic complex containing one deprotonated diamine moiety and one remaining bis(trimethylsilyl)amide ligand. Most noteworthy was the relative intensity of the pyridine, coordinated to the calcium centre. In each case, the complexes were dried *in vacuo* to 4×10^{-2} mbar, in order to ensure a consistent level of base coordination. Remarkably, when the alkyl-substituted diamines were employed (**2a** and **2b**), the number of pyridine ligands was less reproducible, ranging from 0.3–0.6. This suggests that the pyridine is only weakly bound to the calcium, and so we attempted to prepare the base-free complex $[Ca(NN^R)\{N(SiMe_3)_2\}]$ by subjecting the complex to vacuum overnight, but in all cases we were unable to completely remove the pyridine. In contrast, approximately one molar equivalent of coordinated pyridine was observed in complexes **2c** and **2d**, which decrease less after extended periods *in vacuo*. It is unclear as to the observed differences in pyridine coordination between alkyl and aryl systems, although we tentatively suggest that the difference may lie in the difference in steric constraints imposed by the different N-substituents. Given the different degrees to which pyridine coordinates to the calcium and the extremity of the NN^R lability, we cannot categorically rule out the possibility that complexes **2a–2d**, existing as dimers/oligomers; we suggest that the actual structure could be a complex mixture of monomeric and oligomeric species. Such a phenomenon is not unexpected, given the propensity of Grignard reagents to undergo such redistribution processes.[2] Attempts to crystallographically characterise complexes **2a–2d** were unsuccessful, yielding only redistributed calcium species without the NN^R ligand.

When $Ca\{N(SiMe_3)_2\}_2(py)_2$ was reacted with *two* equivalents of HNN^R, two equivalents of $HN(SiMe_3)_2$ were eliminated, forming the homoleptic complex $[Ca(NN^R)_2]$ (R = ^{t}Bu **3a** or 4-C_6H_4F **3b**). Again, the NMR spectra were broad at both ambient and low temperatures. Although we cannot completely rule out the possibility that the homoleptic complexes $[Ca(NN^R)_2]$ form in solution from the redistribution of ligands in **2**, it is unlikely that this represents a major component since complexes **2** were found to be catalytically active in the hydroamination/cyclisation of amino-olefins, whereas **3a** and **3b** were found to be completely inactive.

In order to gain insight into the structure of the proposed mononuclear species, and especially to determine which of the



Scheme 2 Preparation of $[Ca(NN^R)\{N(SiMe_3)_2\}(Py)_n]$ **2a–d**.

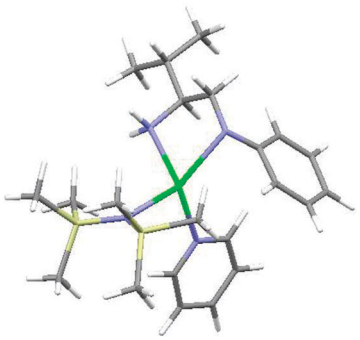
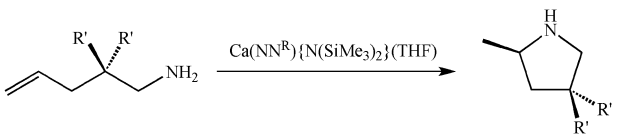


Fig. 2 Calculated structure of [Ca(NN^{Ph}){N(SiMe$_3$)$_2$}(py)] **2c$_{calc}$**.

amine moieties is likely to be preferentially deprotonated in the NN^R ligands, the structure of the [Ca(NN^{Ph}){N(SiMe$_3$)$_2$}(py)] **2c$_{calc}$** was calculated using density functional methods.† The computed structure is displayed in Fig. 2. The two possible structures, with the primary and secondary amines deprotonated, were calculated, however the structure with the secondary amine deprotonated, as shown in Fig. 2, was found to be significantly more stable, by *ca.* 13 kcal. In addition, the structure indicates a significant deviation of the amido nitrogen from the expected trigonal planar geometry; the consequence is that the phenyl ring is orientated so as to provide a chiral environment at the calcium centre, which may well explain the effective stereocontrol in hydroamination catalysis.

Complexes **2a–2d** were tested as precatalysts for the enantioselective hydroamination of the amino-olefin substrates **A** and **B** (Scheme 3). The activities and enantioselectivities of these catalytic reactions‡ are summarised in Table 1. For each of the ligands **2a–2c** the reaction proceeded significantly slower than with the homoleptic bis amide complex Ca{N(SiMe$_3$)$_2$}-(THF)$_2$ (23 h for **A** and 20 min for **B** at ambient temperature), as is expected when adding a sterically demanding spectator ligand. Interestingly, when the *para*-fluorophenyl ligand **2d** was employed, no activity was observed at all over a two week period (entries 7 and 8). The same was true of ligand **2c**, although only with the dimethyl-substrate **A** (entry 5). Most noteworthy is catalyst **2c** (phenyl N-substituent) with substrate **B** (entry 6), in



Scheme 3 Hydroamination catalysis (R′ = Me **A** or Ph **B**).

Table 1 Catalytic hydroamination of amino-olefins using [Ca(N$_2$N^R){N(SiMe$_3$)$_2$}(THF)]‡

Entry	Ligand	Substrate	Time[a]	Conv.[a] %	ee[b] %
1	**1a**	A	7 d	90	0
2	**1a**	B	24 h	>99	6
3	**1b**	A	5 d	>99	12
4	**1b**	B	1 h	>99	5
5	**1c**	A	21 d	0	—
6	**1c**	B	3 d	80	26
7	**1d**	A	14 d	0	—
8	**1d**	B	14 d	0	—

[a] Determined from ^{1}H NMR spectra when no further conversion observed. [b] Determined by ^{1}H NMR using R-(−)-*O*-acetylmandelic acid.[13]

which the chiral pyrrolidine is formed in 26% ee. This level of enantioselectivity represents a remarkable increase from the 5–10% obtained with calcium BOX complexes[8] and is also higher than the calcium complexes reported by Sadow *et al.*[10] It is thus far unclear as to why the enantioselectivity in this case far exceeds the other diamine–substrate combinations tested, however the phenyl-substituted diamine/phenyl-substituted substrate combination suggests that π–π stacking may be an important feature in one of the intermediate steps of the catalytic cycle. Such interactions may well explain the lack of selectivity in the entries 2 and 4; as well as the lack of selectivity in any entry involving the methyl-substituted substrate **A**. It is clear however that further investigations into the detailed mechanism are warranted, for such studies will undoubtedly facilitate further developments in stereoselective catalysis with calcium complexes.

Chiral 1,2-diamines have been shown to be efficient stereodirecting ligands in the calcium-catalysed intramolecular hydroamination of amino-olefins. Whilst there is clearly room for improvement, the enantioselectivities described herein represent a significant advance in calcium-mediated stereoselective catalysis. Further work in this area, particularly to probe the structure of these complexes, is currently underway.

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Notes and references

‡ 70 μmol [Ca(NN^R){(N(SiMe$_3$)$_2$}(THF)], 0.7 mmol substrate, 0.5 ml C_6D_6, rt. Reaction progress monitored by ^{1}H NMR spectroscopy. Enantiomeric excesses determined by ^{1}H NMR spectroscopy after the addition of R-(−)-*O*-acetylmandelic acid. See ref. 13.

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