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Zirconium catalysed enantioselective hydroamination/cyclisation†

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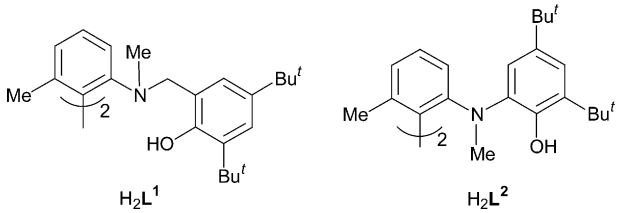
A chiral zirconium alkyl cation catalyses the cyclisation of certain aminoalkenes with enantioselectivity up to 82%, the highest thus far observed for such a process.

Cyclisation of aminoalkenes *via* hydroamination of the double bond is a very attractive approach for the synthesis of *N*-heterocycles.[1] Organolanthanide catalysts have provided the only examples thus far of the enantioselective variant of this reaction; Marks' original report based on chiral *ansa*-metallocenes,[2] which gave up to 74% ee, is yet to be improved upon in terms of enantioselectivity, despite intense efforts from several groups.[3] It would seem that as a result of the large size and the geometrical flexibility of organolanthanide compounds, sufficiently precise control of the metal coordination sphere is difficult to achieve.[4] The group 4 metals could fare better in this respect, but have thus far only been shown to catalyse the rather less thermodynamically-challenging addition of amines to alkynes and allenes to generate (achiral) imines.[5] We postulated that the group 4 *alkyl cations*, the active species in Ziegler-type alkene polymerisations,[6] may be more potent as a result of their enhanced Lewis acidity. Cationic (or cation-like) metallocene catalysts have also been used in a limited number of organic transformations,[7] including Buchwald's enantioselective hydrogenation of alkenes.[8]

We have recently reported[3] the development of chiral aminophenol proligands $H_2\mathbf{L^1}$ and $H_2\mathbf{L^2}$ as robust alternatives to the analogous Schiff-bases.[9] Reactions of these proligands with $[Zr(NMe_2)_2Cl_2(THF)_2]$ in dichloromethane generated the colourless complexes $[Zr\mathbf{L^1}Cl_2]$ and $[Zr\mathbf{L^2}Cl_2]$. The former was shown by X-ray crystallography to adopt the *trans* structure, which is unlikely to be of use in catalyses such as that under study here where mutually *cis* coordination sites are required. We thus focussed our efforts on $[Zr\mathbf{L^2}Cl_2]$ which gave the favourable[10] unsymmetrical *cis*-β structure as shown in Fig. 1.‡ It is interesting to note that the coordinated amine groups in $[Zr\mathbf{L^2}Cl_2]$ have mutually opposite configurations within the same molecule and that the *N*–Me groups are in close proximity to the metal centre [Zr–C(15) 3.498 Å and Zr–C(30) 3.036 Å]. NMR spectra were also consistent with *cis*-β configuration.



The reaction between $H_2\mathbf{L^2}$ and $[Zr(CH_2Ph)_4]$ gave a single complex species. Two pairs of AB doublets from diastereotopic methylene groups were apparent in the ^{1}H NMR spectrum, but only one Zr–CH_2Ph group was present. The second methylene group arises from a metallated *N*–Me group (*i.e.* N–CH_2–Zr). Assuming that the first formed species in this reaction is the expected $[Zr\mathbf{L^2}(CH_2Ph)_2]$ (**1**, Scheme 1), then it seems that close proximity to the zirconium centre of a relatively acidic N–Me group (*vide supra*) has encouraged protonolysis of one Zr–CH_2Ph bond to form the metallacycle $[Zr(\mathbf{L^{2\prime}})(CH_2Ph)]$ **2**. The proton source $[PhNMe_2H][B(C_6F_5)_4]$ reacted cleanly with **2** to give the desired

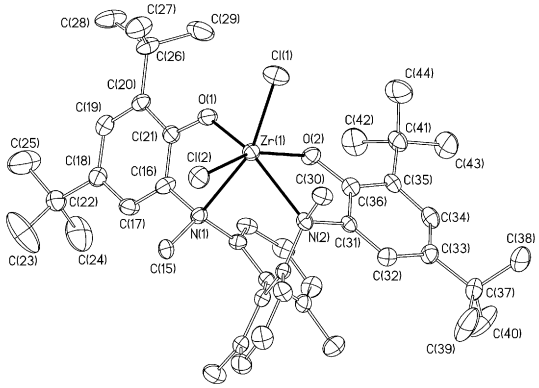
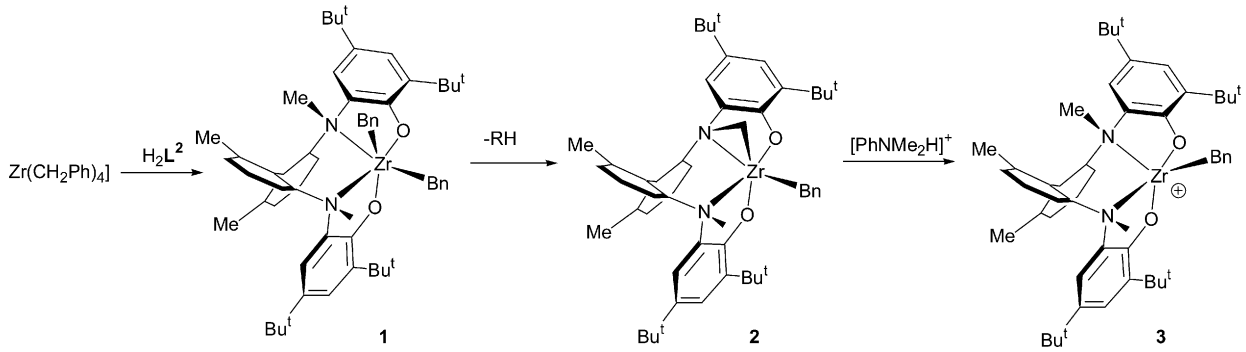


Fig. 1 Molecular structure of $[Zr\mathbf{L^2}Cl_2]$. Selected bond lengths (Å) and angles (°): Zr–O(1) 1.949(3), Zr–O(2) 1.977(3), Zr–Cl(1) 2.421(15), Zr–Cl(2) 2.443(15), Zr–N(1) 2.541(4), Zr–N(2) 2.483(4), O(1)–Zr–O(2) 98.58(15), N(1)–Zr–N(2) 88.43(13), Cl(1)–Zr–Cl(2) 92.91(5)

† Electronic Supplementary Information (ESI) available: experimental details and characterising data for complexes and substrates, catalytic protocol, determination of ee, crystal data for $[Zr\mathbf{L^2}Cl_2]$. See http://www.rsc.org/suppdata/cc/b4/b401493f/



Scheme 1 Synthesis of $[Zr\mathbf{L^2}CH_2Ph][B(C_6F_5)_4]$ **3**.

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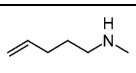
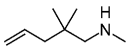
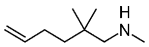
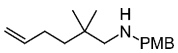
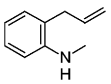
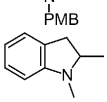
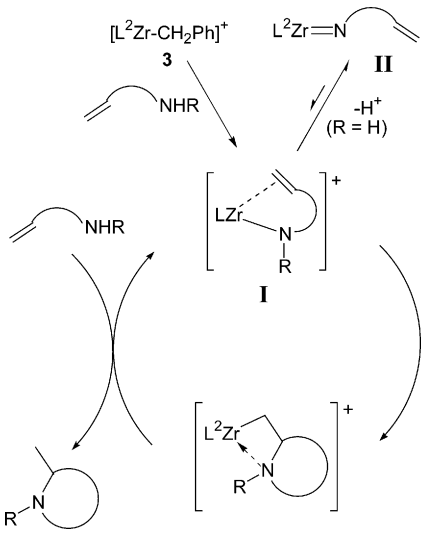
Table 1 Hydroamination/cyclisation catalysed by **3**[a]

Entry	Substrate	Product	*t*/h[c]	ee (%)[d]
1			4	64
2[b]			48	14
3			3	82
4			192	nd
5			3	20

[a] C_6D_5Br at 100 °C, *ca.* 10 mol% catalyst. [b] 5 mol% catalyst, 70 °C. 30% alkene isomerisation product. [c] Time for 100% conversion of substrate. [d] NMR analysis of (*R*)-(+)-Mosher's acid salt (see ESI).



Scheme 2 Possible mechanism for hydroamination/cyclisation catalysed by **3** (R = Me).

alkyl cation complex, orange [Zr**L²**(CH_2Ph)][$B(C_6F_5)_4$] **3** *in situ*.§ We were pleased to find that **3** showed no signs of decomposition on heating to 100 °C overnight; a remarkable level of stability for a non-metallocene.

Treatment of **3** with 10 equivalents of candidate aminoalkenes containing primary amine groups led to no conversion to the corresponding heterocycles (*vide infra*). Nevertheless, various secondary amine substrates were found to undergo hydroamination/cylisation in the presence of chiral non-racemic [Zr[(*S*)-**L²**](CH_2Ph)][$B(C_6F_5)_4$]. All catalyses gave 100% conversion (Table 1).

1-(*N*-Methylamino)pent-4-ene (entry 1) gave a similar ee to the best observed thus far for the primary amino analogue.[2] Surprisingly, the similar *gem*-dimethyl compound (entry 2) gave a disappointing ee; we suspect that a different mechanism is in operation for this substrate since it is the only one thus far which undergoes significant double-bond isomerisation with this catalyst (see ESI). The aminoalkene 1-(*N*-methylamino)-2,2-dimethylhex-5-ene (entry 3) gave the highest ee thus far recorded for any hydroamination/cyclisation reaction.[11] The analogous *p*-methyoxybenzyl substituted amine (entry 4) cyclised much more slowly, presumably as a result of steric protection of the N atom, and we were in any event unable to determine the ee. *N*-Methyl-2-allylaniline (entry 5) was cyclised quite efficiently, and although the ee obtained was modest, this appears to be the first reported enantioselective cyclisation of this type of substrate.

On the basis that this reactions is proceeding by a similar mechanism (Scheme 2) to that proposed by Marks[2] for the lanthanide catalyses, then a critical issue is the binding of the alkene group to the metal in the amido complex **I**. This determines the geometry of insertion into the amide–metal bond and thus the configuration of the stereogenic centre in the resultant heterocycle. Strong olefin activation, as well as efficient expression of chirality from the ligand to the active sites are required. It would seem that our employment of the zirconium alkyl cation in **3** here has provided the former and to a great extent the latter. For primary amine substrates however, the cationic nature of the catalyst species means that amido NH deprotonation is possible. The resultant *neutral* imido species **II**, similar to that implicated in aminoalkyne hydroamination,[12] is unable to activate the alkene sufficiently for insertion. We are currently addressing this problem.

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Notes and references

‡ Crystal data: $C_{51}H_{66}Cl_2N_2O_2Zr$, M = 901.18, monoclinic, a = 22.7186(9), b = 10.2902(4), c = 20.7759(9) Å, β = 99.4450(10), U = 4791.1(3) Å^3, T = 180 K, space group $P2(1)/c$, Z = 4, μ(Mo-K_α) = 0.381 mm^{-1}, 30886 reflections measured, 11948 unique (R_{int} = 0.1341). Final $R1$ = 0.0842 [$I > 2\sigma(I)$]. CCDC 230266. See http://www.rsc.org/suppdata/cc/b4/b401493f/ for crystallographic data in .cif or other electronic format.
§ It is unclear as yet whether the co-product $PhNMe_2$ is coordinated to the metal centre in this product.

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