Catalytic alkene cyclohydroamination *via* an imido mechanism†

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Chiral-at-metal half-sandwich diamide complexes catalyse enantioselective cyclohydroamination of aminoalkenes at unexpectedly high rates given their high coordination number and steric bulk; substantial evidence is presented which argues against the established σ-bond insertion process and is strongly indicative of an imido [2+2] cycloaddition mechanism.

The development of catalysts for the enantioselective cyclohydroamination of aminoalkenes is a subject of intense study.[1] The pioneering work by Marks in this area using chiral lanthanide metallocene complexes[2] was followed some years later by non-cyclopentadienyl systems,[3] cationic Zr catalysts,[4] and neutral catalysts based on the same metal.[5] It is apparent however that the Zr catalysts are sluggish in comparison with the f element/group 3 systems. This is unfortunate since transition metal systems are more readily accessible to non-specialist synthetic chemists than are organolanthanides. A step change is thus required in terms of reactivity so that the potential of these less sensitive systems can be exploited.

Most if not all such cyclohydroamination catalysts operate *via* intramolecular migratory insertion of alkene into an M–N amido σ-bond.[6] For some Zr catalysts a Bergman type [2+2] cycloaddition[7] of alkene at an imido centre M=N–R has been suggested.[8] However in no case thus far has the well-established σ-process been excluded, and very recently it has been argued[6] that it is not necessary to invoke the thermodynamically challenging imido/alkene [2+2] cycloaddition process; such reactions of group 4 imido units are rare[9] in comparison with the analogous reactions of alkynes and allenes.[10]

We recently reported[11] a polymerisation catalyst for which the resting state is six-coordinate $[Cp^*LZr^{IV}Me]^+[BAr^F_4]^-$ (L = achiral κ^2-salicyloxazolinato). The sluggish (but well-defined) catalysis by this species stems from its reluctance to bind alkene (ΔG *ca.* −2 kcal mol^{-1}) *cf.* the metallocene $[Cp_2ZrMe]^+$ (*ca.* −20 kcal mol^{-1}). We therefore set out to see if the neutral six-coordinate species $[Cp^*LZr^{IV}{=}NR]$ and thus perhaps an imido mechanism would also be supported by this system. The outcome of these investigations is a new class of enantioselective and unusually active Zr catalyst whose properties are inconsistent with the amido σ-process, but which argue strongly for an imido/alkene cycloaddition mechanism.

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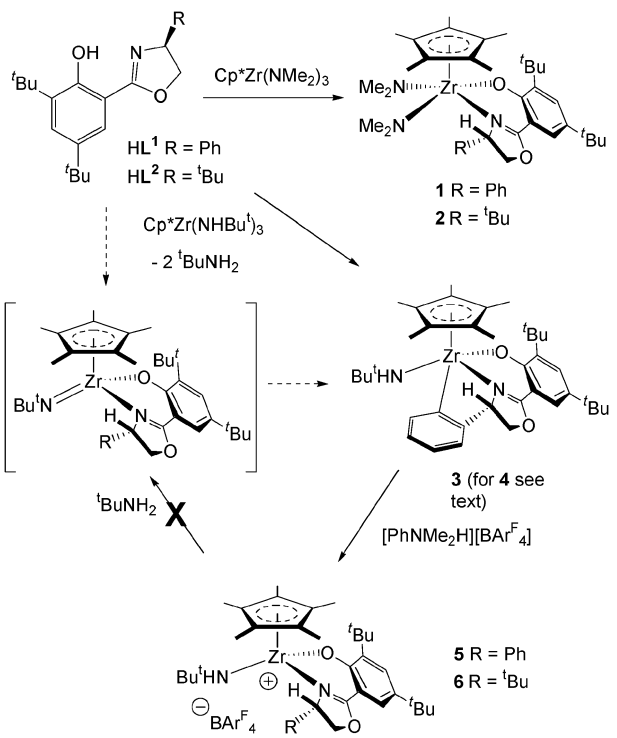
† Electronic supplementary information (ESI) available: Full experimental details and characterizing data; bond lengths and angles for **2**; kinetic plots of cyclizations in KIE studies. CCDC 669262. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b718373a

Treatment of $Cp^*Zr(NMe_2)_3$[12] with (*S*)-HL^n (n = 1, R = Ph; n = 2, R = ^{t}Bu)[13] gives clean and complete conversion to the half-sandwich oxazoline complexes (S_{Zr},S_C)-$[Cp^*L^1Zr(NMe_2)_2]$ **1** and (S_{Zr},S_C)-$[Cp^*L^2Zr(NMe_2)_2]$ **2** (Scheme 1). High solubility of the complexes hampered efficient isolation.

The diastereoselection for configuration at Zr in **1** is essentially perfect. Only one set of resonances is observed in the ^{1}H NMR spectrum for the Cp* and oxazoline units, and two separate dimethylamido singlets are observed at *ca.* δ 2.4 and 3.3 ppm. It is apparent from the molecular structure of **2** (Fig. 1)‡ and molecular models derived therefrom that the diastereomers (R_{Zr},S_C)-$[Cp^*L^nZr(NMe_2)_2]$ would be sterically untenable; the oxazoline substituents overlap spatially with the Cp* ligand.

Treatment of geminally substituted primary aminoalkenes **I** and **II** with 10 mol% of **1** and **2** at 110 °C (toluene-d_8) caused rapid conversion to the respective heterocycle with a range of enantioselectivities as shown in Table 1.

Complexes **1** and **2** thus give active catalysts despite the lack of the accessible coordination site as required for the σ-bond insertion mechanism;[6] indeed this catalysis is *promoted* by



Scheme 1 Synthesis of the half-sandwich complexes **1–6**.

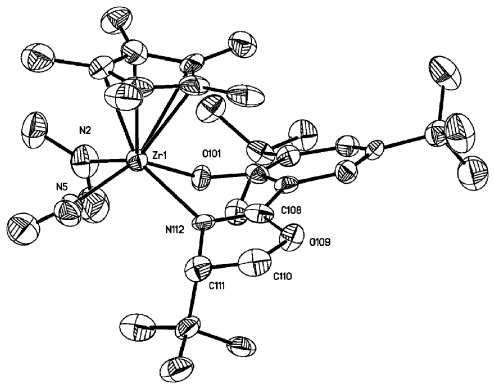
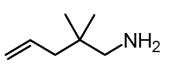
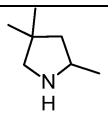
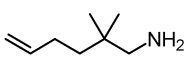
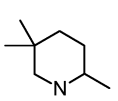


Fig. 1 Molecular structure of **2**.‡ Only one molecule of the asymmetric unit is shown. Hydrogen atoms omitted for clarity. Displacement ellipsoids are at the 50% probability level. Selected bond lengths (Å) and angles (°): Zr(1)–N(2) 2.078(9), Zr(1)–N(5) 2.144(9), Zr(1)–N(112) 2.361(8), Zr(1)–O(101) 2.140(7), Zr(1)–Cp*$_{cent}$ 2.305; N(2)–Zr(1)–N(5) 88.7(4), N(5)–Zr(1)–N(112) 87.3(3), N(2)–Zr(1)–O(101) 82.0(3).

steric crowding, in contravention of the otherwise universal trend of faster cyclo-hydroamination catalysis by systems with greater metal accessibility.[6]§ For example, unlike $Zr(NMe_2)_4$,[14] six-coordinate $Cp^*Zr(NMe_2)_3$[12] and $L^1{}_2Zr(NMe_2)_2$[13] show little and no conversion, respectively. Chiral amidate[5,15] and phosphinic/thiophosphinic amidate[16] catalysts are sterically unsaturated but are nevertheless substantially slower than **1** and **2**. A preliminary kinetic investigation of the cyclization of **I** by **1** (see ESI†) led to a turnover frequency N_t of 2.35 h^{-1} (90 °C), over 30× higher than the less congested (CGC)$ZrMe_2$ (N_t = 0.07 h^{-1} at 100 °C; CGC = $Me_4C_5SiMe_2NBu^t$) for which a σ-bond insertion mechanism is strongly substantiated.[6] Finally in this context we observe that of the new catalysts, the most congested **2** is the faster (Table 1).

Marks showed that (CGC)$Zr(NMe_2)Cl$ with its single aminolysable amido site was also a competent catalyst, and was significantly faster than (CGC)$ZrMe_2$ for steric reasons. This argues strongly against an imido mechanism in that system.[6] We synthesized the analogous compound [Cp*$L^1Zr(NMe_2)Cl$] as a 2.3 : 1 diastereomeric mixture, the isomers differing only in the site substituted by NMe_2 (see ESI†). This mixture was

Table 1 Hydroamination catalysed by **1** and **2**

Entry	Cat.[a]	Substrate	Product	t/min[b]	ee (%)[c]
1[d]	**1**	 **I**		50	51
2	**2**			20	70
3	**1**	 **II**		60	58
4	**2**			30	14

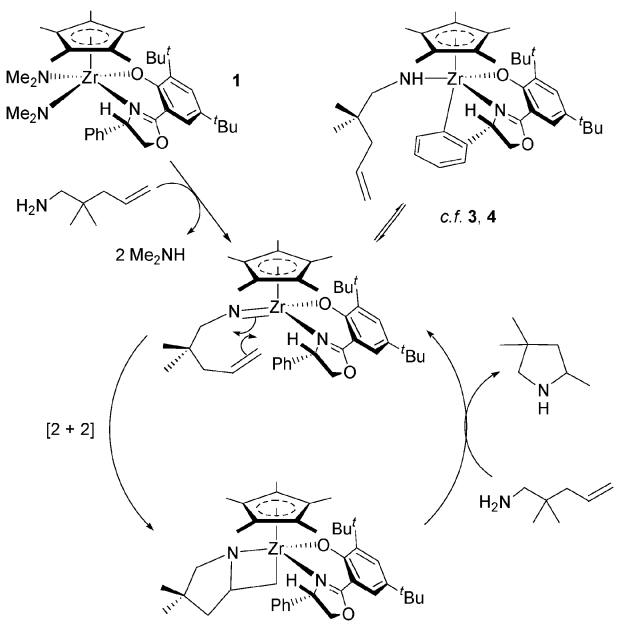
[a] 10 mol% catalyst, toluene, 110 °C. [b] Time for >95% conversion. [c] Determined by NMR as Mosher amides (see ESI†). [d] N_t = 2.35 h^{-1} and k_H/k_D = 3.0 (both 90 °C).

completely inactive as a catalyst for cyclohydroamination. Furthermore, in contrast with various CGC catalysts, compounds **1** and **2** are inactive for the cyclohydroamination of secondary amine substrates, for which there is no obvious route to imido intermediates.

Measurement of the rate of cyclization of *N*-deuteriated **I** with **1** led to N_t = 0.78 h^{-1} (after a period of induction) and thus a KIE k_H/k_D = 3.0 at 90 °C, rather less than that observed (7.3) in a unimolecular α-elimination process at a Zr amido system at the same temperature.[17] These figures will however be affected strongly by the precise structure and of course the identity of the transition state, neither of which has yet been determined.

We set out to explore the possibility of synthesis of an imido species [Cp*L^nZr=NR]. Reactions of (*S*)-HL^n with $Cp^*Zr(NH^tBu)_3$ at 60 °C proceeded cleanly to give the metallacyclic products of [Cp*$L^{n'}Zr(NH^tBu)$] **3** and **4** (Scheme 1); no intermediates were observed. Since diamides **1** and **2** are stable with respect to metallacyclisation it is highly unlikely that the expected first-formed products of these reactions, *viz*. [Cp*$L^nZr(NH^tBu)_2$], are reactive enough for this purpose. We thus propose that these secondary amides decompose by α-elimination to [Cp*L^nZr=N^{t}Bu] and that these imido units are responsible for the C–H activation giving **3** and **4**; a familiar process.[17,18] The metallacycles are nevertheless expected to be susceptible to aminolysis under catalytic conditions and indeed when employed in the cyclisation of **I**, they gave very similar rates of catalysis to the analogous **1** and **2**. Hence catalytic resting states similar in structure to seven-coordinate **3** and **4** are thus implicated in our mechanism (Scheme 2); productive intramolecular [2+2] cycloaddition competes with intramolecular C–H activation.

We have previously noted that the complexes [Cp*LZrMe]$^+$[$BAr^F{}_4$]$^-$ are not precatalysts for cyclohydroamination.[11] We thus set out to explore the origin of this behaviour. Treatment of **3** and **4** with [$PhNMe_2H$][$BAr^F{}_4$]



Scheme 2 Proposed imido mechanism as drawn for **1**.

yielded the complexes $[Cp^*L^nZr(NH^tBu)][BAr^F{}_4]$ (**5** and **6**, respectively, Scheme 1) *via* protonolysis of the metallacyclic alkyl. These rare examples of cationic amides are thermally stable. In common with Sita's related observations,[19] and despite their coordination number being lower than the neutral starting materials, **5** and **6** are not catalysts for cyclohydroamination of primary or secondary aminoalkenes. For secondary amines the lack of σ-insertion catalysis is of course due to the absence of an accessible coordination site.[4] For primary amine substrates which may react *via* the imido mechanism the reasons are less obvious; retardation of catalysis by adduct formation[19] is an unlikely cause since less bulky $[Cp^*ZrLMe]^+[BAr^F{}_4]^-$ does not readily bind C_2H_4 or $PhNMe_2$.[11] We have observed however that cation **5** is stable with respect to reaction with excess amine **I** under catalytic conditions, *i.e.* it is not deprotonated at secondary amide to give $[Cp^*L^1Zr{=}NR]$ or indeed the more stable **3**. The lack of catalysis is thus most probably due to the inaccessibility of the imido species from **5**.

In summary, we have presented substantial evidence that this new class of high coordination number catalyst is not operating *via* the established σ-bond insertion process. Observations are instead strongly indicative of the imido mechanism of Scheme 2. Ongoing synthetic, kinetic, theoretical and labelling investigations will cast further light on this process, *e.g.* the identity and structure of the transition state. Our future researches will focus not on coordinatively unsaturated systems but on bulky complexes with the right orbital availability to support reactive imido units. By this means we may be able to deliver fast *and* highly enantioselective cyclohydroamination catalysts using transition metals.

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Notes and references

‡ $C_{70}H_{118}N_6O_4Zr_2$, $M = 1290.14$, monoclinic, $P2_1$, colourless block, $a = 9.9465(7)$, $b = 9.9106(7)$, $c = 36.050(3)$ Å, $\beta = 95.098(2)^\circ$, $U = 3539.6(4)$ Å^3, $Z = 2$, $T = 180(2)$ K, 21778 total reflections, 9976 unique ($R_{int} = 0.0631$), $R_1 = 0.0804$ (obs. data), $wR_2 = 0.1649$ (all data), GOF 1.105.

§ The observation of substantial ee in the catalysis argues strongly against creation of a free coordination site by dissociation of the stereogenic oxazoline unit.

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