A new homogeneous zinc complex with increased reactivity for the intramolecular hydroamination of alkenes[†]

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The new zinc compound *N*-cyclohexyl-2-(cyclohexylamino)troponiminate zinc methyl, $[(Cy)_2ATI]ZnMe$ (2), was synthesized and showed a superior reactivity in the intramolecular hydroamination reaction of non-activated alkenes compared to previously reported homogeneous zinc complexes.

The synthesis of nitrogen-containing molecules is of particular interest because a huge number of natural products and pharmaceuticals include amine or amide moieties.¹ Traditionally, the synthesis of these compounds requires multistep synthesis resulting in the production of many side products and waste. Thus, the direct addition of N–H bonds to C–C multiple bonds (hydroamination) (Scheme 1) constitutes an environmentally friendlier and potentially more economic method.² Many metals and catalysts have been employed for this transformation, especially the lanthanides,^{2b,3} group IV transition metals,^{2b,c,4} the platinum metals⁵ and also calcium⁶ and gold.⁷

Recently we introduced *N*-isopropyl-2-(isopropylamino)troponiminate zinc methyl (1) as a catalyst for the intramolecular hydroamination.⁸ This complex possesses several advantages in comparison to the well-established catalysts: it shows unprecedented tolerance towards polar functional groups and it is relatively stable towards air and moisture. Furthermore zinc is an inexpensive and non-toxic metal which makes its use in catalysis attractive.

On our course to find more reactive complexes for the catalytic hydroamination reaction we focused our interest on simple modifications of the aminotroponiminate ligand system. We



Scheme 1 Intramolecular hydroamination of amines.



Scheme 2 *Reagents and conditions:* for R = Cy: a) cyclohexylamine (neat), 0 °C to rt, 16 h, 92%; b) 1. Et₃OBF₄, CH₂Cl₂, rt, 3 h; 2. cyclohexylamine (exc.), 0 °C to rt, 16 h, 90%; c) ZnMe₂ (1.7 eq.), toluene, rt, 3 h, 88% (Cy = cyclohexyl); for R = iPr see ref. 8.

therefore substituted the isopropyl by a cyclohexyl group. Thus, the ligand was prepared in two steps from 2-tosyloxytropone following a modified literature procedure.⁹ Both steps can be accomplished in high yields of 92 and 90%, respectively. The synthesis of the corresponding zinc complex **2** is also high yielding (Scheme 2).[‡]

The structure of 2 was established by single crystal X-ray diffraction analysis (Fig. 1). Compound 2 is a monomer in the solid state, thus the zinc atom displays trigonal planar geometry. The bond lengths and angles are in the expected range.

The activity of compound 2 was further investigated in the intramolecular hydroamination reaction. We were pleased to find that 2 is indeed highly reactive in this reaction. In most of the investigated cases it shows a much higher activity than complex 1



Fig. 1 Perspective ORTEP-view of the molecular structure of 2. Thermal ellipsoids are drawn to encompass 50% probability. Hydrogen atoms are omitted for clarity. Selected distances [pm] and angles [°]: Zn–N1 197.0(2), Zn–N2 1.96.6(2), Zn–C20 194.4(3); Zn–N1–C1 114.8(2), Zn–N1–C8 123.5(2), Zn–N2–C7 114.77(2), Zn–N2–C14 124.5(2), N2–Zn–C20 137.12(11), N–Zn1–C20 140.47(11), N1–Zn–N2 82.17(8).

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bearing isopropyl groups. All reactions were run at 80 °C with a catalyst loading of only 2.5 mol% and 2.5 mol% of [PhNMe₂H][B(C₆F₅)₄] as a cocatalyst. Excellent isolated yields of more than 80% were obtained in each case (Table 1). There is a notable substrate dependence on the reaction time, resulting in a timescale from ten minutes to four weeks for substrates bearing chelating functional groups. In the case of the strained norbornene derivatives (entries 1–2) the cyclization took place solely at the terminal double bond. With the second generation catalyst **2** both substrates were cyclized with short reaction times. It is noteworthy

that the reaction with catalyst **1** took around ten times longer for complete conversion to be reached. However, no diastereo-selectivity was observed with either catalyst, leading to an inseparable 1 : 1 mixture of diastereoisomers. Substrates bearing bulky substituents in the β position with respect to the amine cyclized with short reaction times of 10–20 minutes, respectively (entries 3–4). Changing from a thiophene to a furan moiety resulted in a 15 times longer reaction time for both catalysts (entries 4–5). These prolonged reaction times could be explained by the more effective chelation of the aminofuran to the zinc catalysts.

Fable 1	Synthesized	pyrrolidines	and comparison	of the	catalysts ^a
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			Catalyst 1		Catalyst 2	
Entry	Substrate	Product	Time	Conversion	Time	Conversion
1	N S S	N S	30 h	93% ^b	2 h	96% ^b 86% ^c
2	N H NTS	N Ts N	20 h	quant. ^b	3 h	quant. ^b 90% ^c
3	Ph Ph H	Ph///N	95 min	quant. ^b	20 min	quant. ^b 91% ^c
4	Ph Ph H S	Phu, N S	20 min	quant. ^{b,d}	10 min	quant. ^{b,d} 97% ^c
5	Ph Ph H O	Phu, N O	6 h	quant. ^b	2.5 h	quant. ^b 95% ^c
6	H		4.5 h	quant. ^b	75 min	quant. ^b 88% ^c
7	Me Me H	Merry N	13 h	60% ^b	13 h	quant. ^b 83% ^c
8	S S H OMe	S N OMe	13 d 27 d	36% ^b 49% ^b	13 d 27 d	84% ^b 97% ^b 95% ^c
9	Me Me H	Phr. N	20 d	86% ^b	7 d	85% ^b 82% ^c
10	Ph Ph H	Ph///NNN	21 d	quant. ^b	18 d	quant. ^b 96% ^c

^{*a*} Reagents and conditions: Substrate (430 µmol), catalyst (2.5 mol%), [PhNMe₂H][B(C₆F₅)₄] (2.5 mol%), C₆D₆, 80 °C. ^{*b*} Determined by ¹H NMR. ^{*c*} Isolated yield of > 95% purity. ^{*d*} The reaction was performed with 0.8 mol% [PhNMe₂H][B(C₆F₅)₄].

However, by using catalyst 2 the reaction time could be halved in both cases. A cyclohexane derivative was cyclized to the corresponding spiro compound three times faster with the new catalyst (entry 6). Even with slowly reacting substrates (entries 7-8) substantial differences in the reactivity between the zinc catalysts 1 and 2 were observed. In both cases quantitative conversion could only be obtained when the second generation catalyst was employed. We attribute this to a higher stability of catalyst 2. An amine bearing a disubstituted double bond took seven days to reach 85% conversion with catalyst 2, however the same amount was reached with catalyst 1 after three weeks (entry 9). Only in the case of the ortho-substituted pyridine (entry 10) did minor differences in reaction time occur. It is noteworthy that in the cases of previously reported substrates (entries 3 and 6) the reactions with our new zinc catalyst 2 were performed at significantly lower reaction temperature (80 °C compared to 120 °C) but were nevertheless faster.^{5d} In principle there are two possibilities for the mechanism of the reaction: activation of the double bonds by zinc or activation of the amine by forming a zinc amide moiety. So far we have not been able to clearly ascertain which of the two mechanisms operates in the zinc catalyzed hydroamination. Mechanistic investigations are currently in progress.

In conclusion, a new homogeneous zinc complex, its synthesis and crystal structure have been reported. We have demonstrated that subtle changes in the ligand structure can lead to a strong effect on the reactivity of the catalyst. The latter is available from low-cost starting materials in a high yielding procedure. In most of the investigated cases the new catalyst 2 showed superior reactivity in the hydroamination of non-activated alkenes and a higher stability in solution compared to the first generation catalyst 1, which makes its application to catalysis more useful.

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Notes and references

 \ddagger Dimethyl zinc solution was purchased from Aldrich. [PhNMe_2H] [B(C_6F_5)_4] was purchased from Strem.

N-Cyclohexyl-2-(cyclohexylamino)troponiminate zinc methyl, $[(Cy)_2ATI]ZnMe$ (2). A solution of ZnMe₂ (2.0 M in toluene, 4.5 mL, 9.0 mmol) was diluted in toluene (15 mL) at rt. A solution of $[(Cy)_2ATI]H$ (150 mg, 5.27 mmol) in toluene was added slowly. The reaction mixture was stirred for 3 h, then the solution was filtered and the solvent evaporated under reduced pressure. The resulting yellow solid was washed with *n*-pentane and dried *in vacuo*. Yield: 169 mg (88%). X-ray quality crystals can be grown from toluene at -40 °C. (Found: C, 65.7; H, 8.7; N, 7.3. $C_{20}H_{30}N_2Zn$ requires C, 66.0; H, 8.3; N, 7.7%); $\delta_H(400 \text{ MHz}, C_6D_6)$ 0.08 (3 H, s), 1.05–1.91 (20 H, m), 3.50–3.59 (2 H, m), 6.38 (1 H, t, *J* 9.1), 6.73 (2 H, d, *J* 11.6), 6.99 (2 H, dd, *J* 9.1, *J* 11.6); $\delta_C(100 \text{ MHz}, C_6D_6)$ 1.1, 25.7, 26.0, 35.2, 57.1, 111.3, 117.5, 134.1, 159.9 (C_q); *m/z* (EI) 362 [M⁺] (17%), 347 [M - CH₃⁺] (11), 284 [M - ZnCH₃⁺] (16).

Crystal data for 2: C₂₀H₃₀N₂Zn, M = 363.83, triclinic, space group $P\overline{1}$, a = 973.58(7) pm, b = 1100.97(8) pm, c = 2007.60(13) pm, $\alpha = 76.685(5)$, $\beta = 86.477(6)$, $\gamma = 64.209(5)^\circ$, $V = 1883.6(2)10^6$ pm³, T = 200(2) K, Z = 4, $\mu = 0.711$ mm⁻¹, 14223 reflections collected, 6621 unique, R1 = 0.0341($I > 2\sigma(I)$), wR2 = 0.0874 for all 6621 data, 417 parameters, all non hydrogen atoms calculated anisotropic; the positions of the H atoms were calculated for idealised positions. The structure was solved and refined using SHELXS-97 and SHELXL-97.¹⁰ CCDC 609557. For crystallographic data in CIF or other electronic format see DOI: 10.1039/ b607597e

General Procedure for the zinc-catalyzed hydroamination. A predried NMR-tube was charged with the aminoalkene (430 µmol). A solution of **2** (4 mg, 11 µmol, 2.5 mol%) and [PhNMe₂H][B(C₆F₅)₄] (9 mg, 11 µmol, 2.5 mol%) in 0.5 mL C₆D₆ was added under a nitrogen atmosphere. The NMR-tube was flamesealed under vacuum. The reaction mixture was then heated to 80 °C for the stated time. The reaction progress was monitored by ¹H NMR. When the reaction was judged to be completed, the crude reaction mixture was directly subjected to column chromatography on silica.

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