Enantioselective hydroamination/cyclization of aminoalkenes by (bis)-C₂ symmetric and (mono)-C₂ symmetric anionic tetraamide complexes of La(III)

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ABSTRACT

Enantioselective hydroamination/cyclizations of several monosubstituted and disubstituted aminoalkenes have been achieved, catalyzed by tetracoordinate anionic La(III) complexes.

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The intramolecular hydroamination of alkenes constitutes a powerful and atom-economical method for the synthesis of nitrogen-containing heterocycles.^{1,2} Both neutral and anionic complexes of Y(III) have shown utility in the asymmetric variation of this process.^{3a,b} We recently disclosed that neutral chelating diamide complexes of several group 3 metals prepared from simple *N*-(diaryl)methyl substituted diamide motifs derived from (*R*)-1,1'-binaphthyl-2,2'-diamine are effective catalysts for enantioselective hydroamination/cyclization.⁴ We subsequently demonstrated that (*R*)-*N,N'*-dibenzosuberyl-1,1'-binaphthyl-2,2'-diamine (**1**) is a vastly superior proligand for this process and showed that the chelating diamide complexes derived from La(III), the largest lanthanide metal, provided higher enantioselectivities than the more sterically congested Y(III) congeners.⁵ In this communication, we describe the reactivity and enantioselectivity for intramolecular hydroamination catalyzed by a new family of Y(III) and La(III) ate-complexes originating from enantiopure **1** and achiral amide ligands.

Catalyst Generation:

The catalytic complexes, **8a,b**, **9a,b** and **10a-d** utilized in this study were prepared by the following procedure.

Sequential treatment of YCl₃(THF)_{3.5} or LaCl₃(THF)_{1.5} (1 equiv each) with Me₃SiCH₂Li (4 equiv) in THF generated solutions of the corresponding anionic homoleptic alkyl (Me₃SiCH₂)₄M⁻Li⁺ complexes (**4a**: M=Y, **4b**: M=La). Immediate addition of **1** (1 equiv, 20 min, 23 °C) delivered the preformed solutions of **4a,b**. Addition of supporting ligands **6**, **7** or **1** (1 equiv each) subsequently afforded solutions of the anionic complexes **8a,b**, **9a,b** and **10a,b**. The anionic complex **10c** (M₁=La, M₂=Na) was generated by the sequential treatment of **1** (2 equiv) with La[N(*t*-Bu)(TMS)]₃ (1 equiv) followed by NaN(TMS)₂ (1 equiv), whereas the neutral complex **10d** was prepared by the treatment of **1** (2 equiv) with La[N(*t*-Bu)(TMS)]₃ (1 equiv). The tetra(amide) complexes **5a** and **5b** were directly prepared by amine elimination involving the sequential exposure of YCl₃(THF)_{3.5} or LaCl₃(THF)_{1.5} to LiN(*t*-Bu)(SiHMe₂) (4 equiv) followed by **1** (1 equiv). The selection of the -N(*t*-Bu)(SiHMe₂) ligand was based on the documented propensity of this substituent to engage in agostic bonding of the Si-H moiety to group 3 metals.⁶ After complex formation was complete, THF was removed in vacuo and replaced by C₆D₆ prior to the addition of the aminoalkenes (Scheme 1).

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Enantioselective Hydroamination Studies:

We initiated this investigation by examining the enantioselective hydroamination/cyclization of aminoalkene **11a** catalyzed by anionic *ate*-complexes **4a** and **4b**. Cyclization of **11a** in the presence of the Y(III) complex **4a** proceeded comparatively slowly (60 °C, 24 h) and provided pyrrolidine **12a** in 72% ee (Table 1, entry 1). The corresponding La(III) complex **4b** proceeded more slowly, and with roughly identical enantioselectivity (23 °C, 8 d, 73% ee) (entry 2). The anionic complex **4b** possessed much lower catalytic activity and stereoselectivity than the corresponding neutral complex.⁵

Alternative anionic complexes derived from **4a** and **4b** were subsequently evaluated as catalysts along with the anionic Y(III) complexes **5a** and **5b** derived from *tert*-butyldimethylsilyl amine. Complex **5a** showed no improvement in reactivity and exhibited diminished enantioselectivity (Table 1, entry 3). However, the bis(monoamide) *ate* complex **5b** is much more active than the analogous complex **4b** (23 °C, 5 h), with the enantioselectivity being improved (78% ee, entry 4). The modification of the metal steric environment was subsequently

examined using chelating diamide ligands. The four-membered Y(III) chelate **8a** derived from diamine **6** and the five-membered Y(III) chelate **9a** from diamine **7** led to inferior cyclization activity and as well as enantioselectivity (8% and 51% respectively) (entries 5 and 7). These results further emphasize the sensitivity of Y(III) complexes to increased steric congestion. Significantly, the use of the La(III) complex **10b** ($M_1 = \text{La}$, $M_2 = \text{Li}$) coordinated by *two* binaphthylamines **1**, led to an improved cyclization rate along with high enantioselectivity (82%, entry 10). It is also noteworthy that the La(III) complex **9b** which possesses only one *chiral* diamide ligand was virtually identical in its reactivity profile to **10b**.

A compilation of reaction times and enantioselectivities observed for the hydroamination of aminoalkene **11b** catalyzed by anionic complexes **4a**, **5a**, **8a**, **9** and **10a-c** (5 mol%, C_6D_6) are presented in Table 2. As expected, improved conversion rates were usually observed when anionic La(III) complexes were employed.⁵ Out of the ten anionic complexes that were evaluated, the *ate*-complex **9b** proved to be the most reactive (Table 2, entry 8) while **10b** proved the most enantioselective in the cyclization of aminoalkene **11b** (entry 10). The lack of bicycle

formation in the case of **11b** is consistent with the suppression of this process by the presence of LiCl.⁵ The role of the alkali metal counter ion was subsequently probed by the use of the anionic complex **10c** ($M_1=\text{La}$, $M_2=\text{Na}$). In this instance enantioselectivity was suppressed, leading to **12b** in 55% e.e. In addition, the use of the neutral complex **10d** provided **12b** in 59% e.e. In both of these cases, hydroamination/cyclization was rapid ($t = 30$ min).

Table 1: Enantioselective hydroamination/cyclization of aminoalkene **11a**.

Entry	Precatalyst	t^a	Temp (°C)	ee[%] ^b
1	4a	21 h	60	72
2	4b	192 h	23	73
3	5a	25 h	60	60
4	5b	5 h	23	78
5	8a	20 h	60	8
6	8b	9 h	23	77
7	9a	40 h	60	51
8	9b	3 h	23	81
9	10a	16 h	60	73
10	10b	3 h	23	82

^a >95 % conversion as determined by ¹H NMR spectroscopy with *p*-xylene as the internal standard. ^b Enantiomeric excess, calculated by ¹⁹F from Mosher's amides.

Table 2: Enantioselective hydroamination/cyclization of aminoalkene **11b**.

Entry	Precatalyst	t^a	Temp (°C)	ee[%] ^b
1	4a	15 h	23	64
2	4b	1 h	23	50
3	5a	5 h	23	33
4	5b	5 h	23	64
5	8a	5 h	23	31
6	8b	2 h	23	67
7	9a	4 h	23	16
8	9b	15 min	23	63
9	10a	4 h	23	52
10	10b	30 min	23	72

^a >95 % conversion as determined by ¹H NMR spectroscopy with *p*-xylene as the internal standard. ^b Enantiomeric excess, calculated by ¹⁹F from Mosher's amides.

1,2-Disubstituted alkenes are known to be less reactive toward hydroamination/cyclization catalyzed by complexes of the group 3 metals.^{7,8a,b} Accordingly, the aminostyrene **11c** was subjected to cyclization in the presence of 5 mol% of the anionic Y(III) and La(III) complexes (Table 3). As expected, improved conversion rates were observed with the La(III) *ate*- complexes (entries 2,4,6,8,10). As observed with alkene **11a**, the anionic complexes **9b** and **10b** were superior catalysts for the hydroamination/cyclization of **11c** (Table 3, entries 8 and 10). Unexpectedly, the bis(trimethylsilylmethyl) bearing La(III) *ate*-complex **4b** performed remarkably well as a catalyst in the case of **11c** (entry 2).

Table 3: Asymmetric hydroamination/cyclization of aminostyrene **11c**.

Entry	Precatalyst	t^a	Temp (°C)	ee[%] ^b
1	4a	216 h	60	23
2	4b	24 h	45	64
3	5a	110 h	60	32
4	5b	110 h	23	65
5	8a	110 h	60	9
6	8b	134 h	23	63
7	9a	146 h	60	12
8	9b	69 h	23	70
9	10a	163 h	60	30
10	10b	62 h	45	66

^a >95 % conversion as determined by ¹H NMR spectroscopy with *p*-xylene as the internal standard. ^b Enantiomeric excess, calculated by ¹⁹F from Mosher's amides.

The catalytic activity of the anionic complexes was subsequently examined in the cyclization 4-(methoxy)aminostyrene **11d**. The chelating diamide complexes **9b** and **10b** provided good enantioselectivities (74% and 82% ee) (Table 4, entries 4 and 5) although hydroamination/cyclization proceeded more slowly than was the case for **11c**. As before, the bis(monoamide) La(III) complex **5b** possessed remarkably good reactivity and enantioselectivity (entry 2).

Table 4: Enantioselective hydroamination/cyclization of 4-(methoxy)aminostyrene **11d**.

Entry	Precatalyst	t ^a	Temp (°C)	ee[%] ^b
1	4b	192 h	45	71
2	5b	110 h	45	81
3	8b	348 h	45	62
4	9b	103 h	45	74
5	10b	103 h	45	82

^a >95 % conversion as determined by ¹H NMR spectroscopy with *p*-xylene as the internal standard. ^b Enantiomeric excess, calculated by ¹⁹F from Mosher's amides.

The hydroamination/cyclization of the heteroarene bearing substrate **11e** catalyzed by anionic amide complexes was then investigated. Significantly, the cyclization of **11e** proceeded more rapidly (Table 5, entries 4 and 5) than the aminostyrene **11c** and the 4-(methoxy)aminostyrene **11d**. As in the case of **11c**, the bis(trimethylsilylmethyl) bearing La(III) ate- complex **4b** proved a superb catalyst (entry 1).

Table 5: Enantioselective hydroamination/cyclization of **11e**.

Entry	Precatalyst	t ^a	Temp (°C)	ee[%] ^b
1	4b	2 h	23	78
2	5b	16 h	45	79
3	8b	24 h	23	73
4	9b	5 h	23	68
5	10b	14 h	23	77

^a >95 % conversion as determined by ¹H NMR spectroscopy with *p*-xylene as the internal standard. ^b Enantiomeric excess, calculated by ¹⁹F from Mosher's amides.

In conclusion, we have shown that anionic La(III) (tetraamide) complexes have significantly higher catalytic activity and enantioselectivity than the corresponding anionic Y(III) complexes. In general, the La(III) anionic complexes **9b** and **10b** proceeded with faster cyclization rates, and higher enantioselectivities, although the latter catalysts offer little advantage when compared to the previously reported neutral complexes.⁵ Hydroamination/cyclization of the heteroarene substituted aminoalkene **11e** proceeded with very high efficiency, as has been previously demonstrated using simple group 3 amide complexes of the type $M[N(TMS)_2]_3$.^{8a,b}

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References and notes

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