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# Insight into the structure of the precatalyst and active species for samarium iodo binaphtholate catalysed aminolysis of epoxides

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Dedicated to Professor Kagan on the occasion of his 80th birthday

ABSTRACT

Samarium iodo binaphtholate is an efficient Lewis acid catalyst for the enantioselective carbon–nitrogen bond formation such as aza-Michael reactions and the aminolysis of epoxides allowing highly enantioenriched aminoalcohols and aminoacids building blocks to be prepared. Various studies including the relationship between enantiomeric excess and temperature and observation of non linear effects for these reactions indicate the importance of the amine for the formation of the catalytic species. Results support the proposal of dimeric or more aggregated structures for samarium iodo binaphtholate and of a bimetallic active species for the aminolysis of epoxides.



## 1. Introduction

Amongst the wide range of chiral ligands investigated over the last decades, bidentate ligands with axial chirality based on the binaphthyl skeleton have been widely developed.[1] Binaphthol and a variety of substituted binaphthols have been successfully employed as ligands for enantioselective catalysis with numerous metals[2] and especially with rare earths.[3] Different modes of coordination of the ligand are found in rare earth complexes, with binaphthol linked to the same metal or to two different metals and a variety of structures have been described.[3b,4] In our group the use of samarium diodide as a precatalyst promoting various carbon–carbon and carbon–nitrogen bonds formation as well as sequential reactions was first investigated.[5] The preparation of chiral lanthanide iodides based on binaphthol for the enantioselective catalysis of the above reactions was next studied.[6] Samarium iodo binaphtholate proved to be a highly efficient enantioselective catalyst for iminoaldolisation,[7] aza-Michael reactions,[8] and aminolysis of epoxides,[9] allowing β-aminoalcohols or β-aminoesters derivatives with enantiomeric excesses over 90% to be prepared. Different methods for the preparation of lanthanide iodo binaphtholates have been studied and the complexes have been characterized by NMR and elemental analysis but numerous trials for obtaining crystals suitable for X-ray analysis were unsuccessful.[6,9a] Elucidation of the structures of the precatalyst and the species involved in asymmetric catalysis is important to improve asymmetric induction and design new catalysts. Herein the influence of additives and the relationships between enantiomeric excesses of products and temperature or enantiomeric excesses of ligand are analyzed for a better understanding of the structure of the samarium iodo binaphtholate used as precatalyst and of the mechanism of aminolysis of epoxides.

## 2. Results and discussion

We have shown previously that samarium iodo binaphtholate catalyses a Mannich type reaction involving a glyoxylic imine and a ketene silyl acetal. After optimisation of the system high enantioselectivity was obtained (Scheme 1).[7] The use of amines as additives had a dramatic influence on the enantiomeric excess of the β-amino ester, the best results being recorded with aniline. Indeed the highest enantiomeric excess (90%) was observed at 30 °C when glyoxylic imine and aniline were stirred with the catalyst during 4 h before addition of ketene silyl acetal. Due to the high number of coordination of lanthanides, amine probably modifies the structure of the catalyst.

A similar effect was observed during our investigations concerning the synthesis of β-aminoalcohols by enantioselective aminolysis of *meso* epoxides in the presence of samarium iodo binaphtholate **1**. The addition of the amine on the catalyst prior to the epoxide had a strong influence on the asymmetric induction.[9] To optimise the enantiomeric excess we examined the effect of temperature on selectivity for the aminolysis of cyclohexene oxide **2a** by *o*-anisidine catalysed by complex **1**. We found that variation of the enantiomeric excess of aminoalcohol **4aa** was not monotonous since the enantiomeric excess increased first when temperature was decreased to reach a maximum value of 91% at −40 °C and then decreased at lower temperatures. The Eyring plot for this reaction is represented in Figure 1 and shows an inversion temperature ($T_{inv}$) at −39 °C. Inversion temperatures can be explained by a reaction pathway with at least two enantioselective

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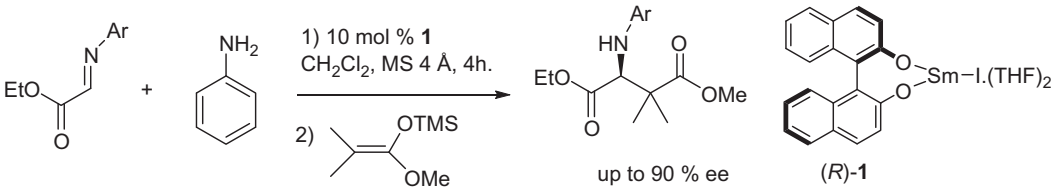



**Scheme 1.** Iminoaldolisation catalysed by samarium complex **1**.

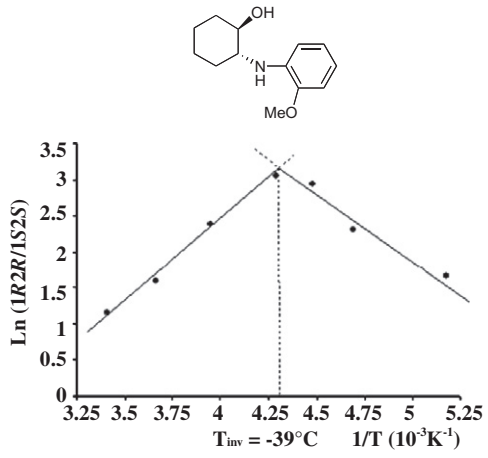



**Figure 1.** Eyring plot for the aminolysis of cyclohexene oxide with *o*-anisidine catalysed by samarium complex **1**.

steps weighted differentially according to the temperature or alternatively by interconversion between two different catalytic species such as solvation clusters.[10] In the aminolysis of epoxides catalysed by samarium iodo binaphtholate several catalytic species with variable numbers of THF molecules and/or amines coordinated can be envisaged.

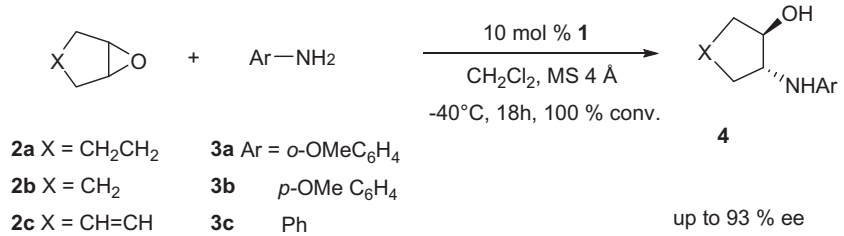
Various enantioselective aminolyses of epoxides were then performed in the optimised conditions and total conversions in β-aminoacohols with enantiomeric excesses up to 93% were observed after one night at −40 °C (Scheme 2). Thus, samarium iodo binaphtholate **1** is a very active and enantioselective catalyst for the aminolysis of cyclic *meso* epoxides and compares well for the preparation of enantioenriched β-aminoalcohols **4** to catalysts recently described for the asymmetric ring-opening of epoxides by amines.[11,12]

In subsequent studies we found that samarium iodo binaphtholate is an efficient catalyst for aza-Michael additions of aromatic amines to *N*-alkenoyl oxazolidinones (Scheme 3).[8] It is noteworthy that the order of introduction of substrates and the variation of temperature modifies strongly the asymmetric induction as for the aminolysis of epoxides. The highest ee are also obtained when amine is added to the catalyst prior to *N*-alkenoyl oxazolidinone.

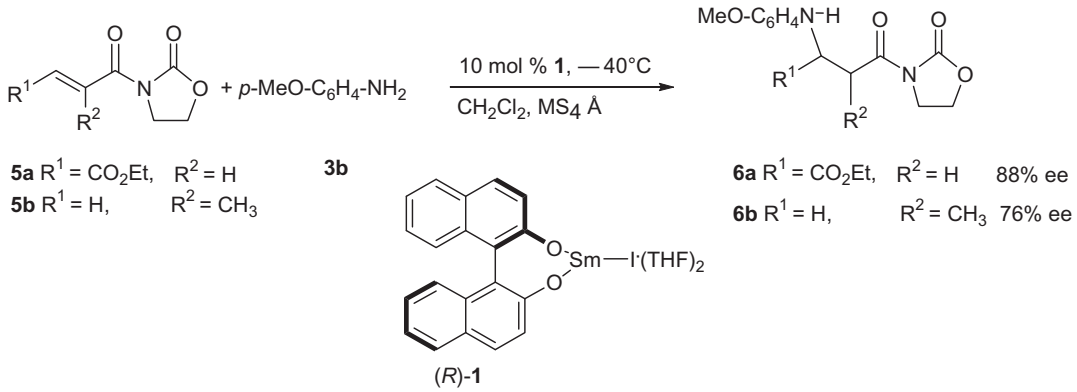
The effect of temperature on the enantiomeric excess of aza-Michael addition product **6** was studied for two reactions, the addition of *p*-anisidine on *N*-fumaroyl oxazolidinone **5a** ($R^1 = CO_2Et$, $R^2 = H$) and on α,β-unsaturated oxazolidinone **5b** ($R^1 = H$, $R^2 = CH_3$) from −78 °C to room temperature. As described above for the aminolysis of cyclohexene oxide we found that the variation of enantiomeric excesses was not monotonous with the temperature. The enantiomeric excess increased first upon decrease of temperature to reach maximum values of respectively 88% for **6a** and 76% for **6b** at −40 °C. Reactions performed at lower temperatures gave lower asymmetric inductions. An isoinversion effect was observed and the inversion temperature, determined from the Eyring plot (−39 °C) was the same for these two reactions as for the ring-opening of cyclohexene oxide with *o*-anisidine.

The determination of an identical value for inversion temperature in different reactions leads to attribute these phenomena to the formation of several catalytic species rather than to several reaction pathways. Both aza-Michael reaction and aminolysis of epoxides involve aromatic amines which could coordinate to samarium to form the active catalytic species.

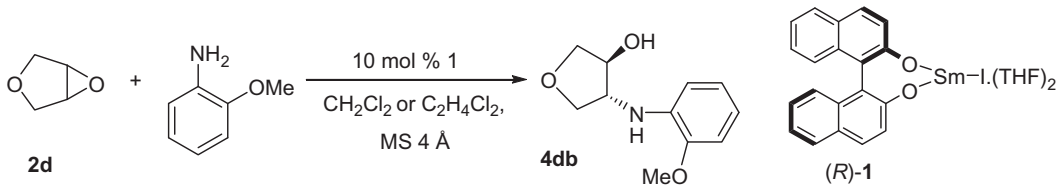
Enantioselective aminolyses of *meso* epoxides including an heteroatom were further studied.[9b] For the reaction of 2,5-dihydrofuran oxide **2d** and *o*-anisidine catalysed by 10 mol % of samarium iodo binaphtholate **1** in methylene chloride in the presence of molecular sieves higher temperatures and longer reaction times than for cyclic *meso* epoxides **2a–c** were required for total conversion. The presence of the heteroatom probably increases the coordination of the epoxide to samarium and slows down the reaction. Moreover, a higher ee value (48%) was obtained at 40 °C than at room temperature (30%) (Scheme 4, Table 1, entries 1 and 2). The reactions were further performed at higher temperature which led to small decreases in the enantiomeric excesses (entries 3–5). The variation of the enantiomeric excesses with temperature is not monotonous, with an isoinversion effect and ee maximal at 40 °C. At this temperature the aminolysis of epoxide **2d** afforded the highest enantioselectivities. For the reaction of epoxide **2d** with *p*-anisidine an enantiomeric excess of 70% was obtained while for epoxide **2e** the highest ee was recorded with *o*-anisidine (62%) (Scheme 5). These results differ from those obtained with unfunctionalised cyclic *meso* epoxides and could indicate the role of functionalized epoxides in the formation of the catalytic species. The presence of *O* or *N*-heterocycles in epoxides decreases their reactivity and only a few enantioselective catalysts have been reported




**Scheme 2.** Aminolysis of unfunctionalised epoxides catalysed by samarium complex **1**.




**Scheme 3.** Aza-Michael reaction catalysed by samarium complex **1**.

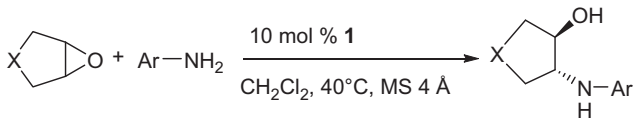



**Scheme 4.** Aminolysis of 2,5-dihydrofuran catalysed by samarium complex **1**.

**Table 1**
Influence of the temperature on the enantioselectivity of ring-opening of epoxide **2d** by *o*-anisidine catalysed by samarium complex **1**[a]

| Entry | Solvent | *T* (°C) | *t* (h) | Yield[b] | ee[c] |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 25 | 80 | 77 | 30 |
| 2 | $CH_2Cl_2$ | 40 | 48 | 55 | 48 |
| 3 | $C_2H_4Cl_2$ | 40 | 48 | 54 | 41 |
| 4 | $C_2H_4Cl_2$ | 60 | 40 | 55 | 34 |
| 5 | $C_2H_4Cl_2$ | 80 | 40 | 63 | 30 |

[a] Reactions performed with 10 mol % catalyst **1** and ratio **3**/**2**:1.2.
[b] Isolated yield (%), 100% conversion.
[c] Enantiomeric excess (%) determined by HPLC.




**Scheme 5.** Aminolysis of functionalised epoxides catalysed by samarium complex **1**.

for the aminolysis of these epoxides. Niobium coordinated by substituted binaphthol catalyses the aminolysis of epoxides **2d** and **2e** with high enantioselectivities but aniline is the sole amine used for these reactions.[12f]

The coordination of complex **1** by two molecules of THF as shown by NMR spectra and elemental analysis leads to a coordination number of five for a monomer, and the formation of a dimer or of more aggregated species can be envisaged. This hypothesis is in agreement with $^1$H NMR and $^{13}$C NMR spectra of samarium iodo binaphtholate **1** which show large signals corresponding to aromatic protons or carbons.[13] The patterns of these spectra differ from those corresponding to lanthanide diiodo complexes with binaphthol monocoordinated. The X-ray structure of lanthanum diiodo binaphtholate complex revealed a monomeric structure.[6] A tentative explanation for isoinversion effects is a dimeric structure for the catalytic species or an equilibrium between monomer and dimer or more associated species.

Non linear variation of enantiomeric excesses of ligands with that of products (NLE), first observed by Kagan et al. for the Sharpless epoxidation of geraniol can be synthetically useful and moreover bring informations on the mechanism of reactions.[14,15] The formation of dimeric species in a number of cases is the explanation for positive non linear effects, if the heterochiral dimers are stable and unreactive. In asymmetric reactions catalysed by lanthanides non linear effects have been frequently observed and were attributed to the Lewis acidity and the large coordination number of lanthanides which favour self organisation, aggregation and self assemblies of chiral complexes.[16] Non linear effects were detected in Ln(OTf)$_3$/binol catalysed Diels–Alder reactions,[17] Yb[(*R*)-BNP]$_3$ catalysed hetero Diels–Alder reactions,[18] Ln(O*i*Pr)$_3$/binol catalysed epoxidation of enones.[13,19] On the basis of kinetic studies and observation of amplification a bimetallic pathway has been proposed by Jacobsen for the ring-opening of epoxides by TMSCN catalysed by Yb(Cl)$_3$/pybox.[20] The strong positive non linear effect observed for the scandium-bipyridine catalysed aminolysis of epoxides was explained by aggregation of catalytic species.[21]

To get informations on the structure of catalyst **1**, the relationship between ee of products and ee of samarium iodo binaphtholate was investigated for several reactions. Catalysts of various enantiomeric purities were prepared from scalemic binaphthol. For each reaction the studies have been performed with substrates and in conditions leading to the highest values of enantiomeric excesses, at inversion temperature. Aza-Michael addition of *p*-anisidine on *N*-acyl oxaxolidinone **5b** was studied at −40 °C,[8] aminolysis of cyclohexene oxide with *o*-anisidine at −40 °C and aminolysis of 2,5-dihydrofuran oxide with *p*-anisidine at 40 °C. The results are indicated in Figures 2–4.

A strong negative non linear effect was observed for the aza-Michael reaction leading to **6b** while for the aminolysis of cyclohexene oxide by *o*-anisidine at −40 °C the negative non linear effect

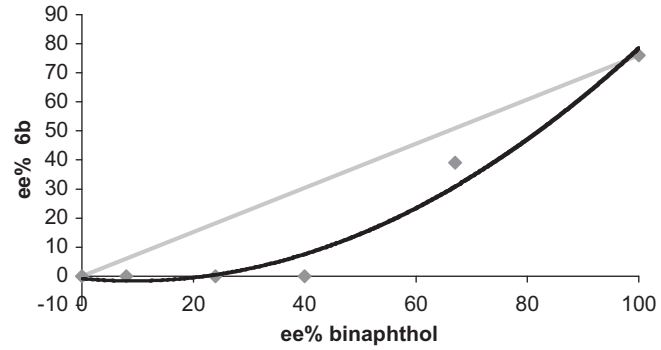



**Figure 2.** Correlation between the enantiomeric excess of binaphthol and the enantiomeric excess of aza-Michael adduct **6b** at −40 °C.

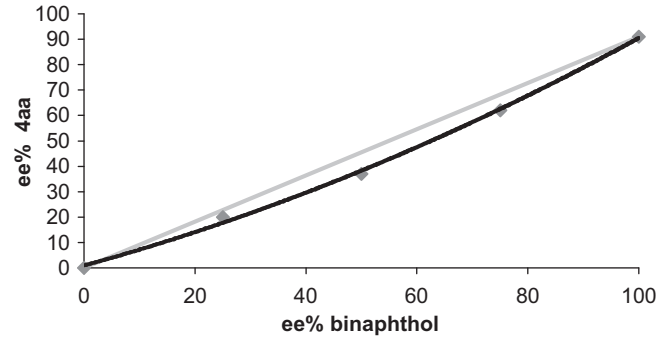



**Figure 3.** Correlation between the enantiomeric excess of binaphthol and the enantiomeric excess of β-aminoalcohol **4aa** at −40 °C.

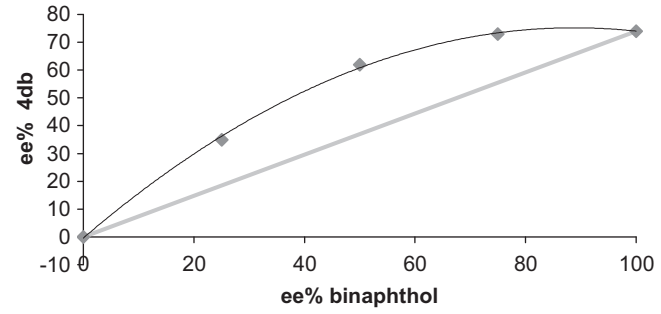



**Figure 4.** Correlation between the enantiomeric excess of binaphthol and the enantiomeric excess of β-aminoalcohol **4db** at 40 °C.

was of smaller amplitude. In contrast, a strong amplification was observed for the aminolysis of 2,5-dihydrofuran by *p*-anisidine at 40 °C. Since varying temperatures affords strong variations of the enantiomeric excesses, the difference in the sense of non linear effects could also be due to temperature. The study of the influence of the enantiomeric purity of binaphthol on the enantiomeric excess of the Michael product **6b** was then realized at 0 °C and at room temperature. In both cases negative non linear effects were observed. Different NLE for aza-Michael reaction and aminolysis of epoxides using the same catalyst are not surprising since different mechanisms take place. However the change of the sense of NLE between the ring-opening of the two epoxides **2a** and **2d** was intriguing. In such reactions both reagents can play the role of ligand for samarium. 2,5-Dihydrofuran oxide **2d** contains an oxygen heterocycle and could coordinate to samarium replacing a tetrahydrofuran molecule. Alternatively the different non linear effects for the two aminolysis reactions could be due to different coordinating properties of the aromatic amines used as substrates. The chelating *o*-anisidine should favour the dissociation of dimers.

To determine the role of substrates in the aminolysis of epoxides we studied different aminolyses using catalyst **1** prepared from binaphthol with an enantiomeric excess of about 50%. The reactions of three epoxides, cyclohexene oxide and epoxides containing heterocycles with *O*- and *N*-Boc group with *o*- and *p*-anisidine were examined. The results are indicated in Table 2. The enantiomeric excesses are compared with values calculated by linear correlation with enantiomeric excesses provided by catalyst **1** prepared from enantiopure binaphthol. For the aminolysis of epoxide **2d** by *o*-anisidine a negative non linear effect was observed as for cyclohexene oxide **2a** (entries 1 and 4) while for epoxide **2e** containing a nitrogen heterocycle a positive NLE was found for the reaction with *o*-anisidine (entry 8). For aminolyses realized with *p*-anisidine enantiomeric excesses measured were higher than those calculated showing an amplification with this amine whatever the epoxide employed (entries 2, 3, 5 and 9). We checked also for the ring-opening of cyclohexene oxide by *p*-anisidine that at room temperature a positive non linear effect was observed as at −40 °C (entries 2 and 3). These results indicate that both reagents play an important role in the formation of the active species. Similarly to our observations for samarium iodo binaphtholate catalysed aminolysis of epoxides, substrate-dependent NLE effects have been reported in literature.[22] Kobayashi found also linear correlation or negative NLE in $Yb(OTf)_3$/binol catalysed Diels–Alder reactions according to the additives employed.[17]

**Table 2**
Comparison of ee of β-aminoalcohols prepared with catalyst (*R*)-**1** and with scalemic catalyst **1**[a]

| Entry | Epoxide | Amine | *T* (°C) | ee **1**[b] | ee cat[c] | ee calcd | ee **2**[d] |
|---|---|---|---|---|---|---|---|
| 1 | **2a** | **3a** | −40 | 91 | 47 | 43 | 37[e] |
| 2 | **2a** | **3b** | −40 | 85 | 55 | 47 | 69[e] |
| 3 | **2a** | **3b** | 25 | 58 | 55 | 32 | 52[e] |
| 4 | **2d** | **3a** | 40 | 48 | 55 | 26 | 10[e] |
| 5 | **2d** | **3b** | 40 | 68 | 52 | 35 | 62[e] |
| 6 | **2d** | **3b** | 40 | 68 | 40 | 27 | 54[f] |
| 7 | **2d** | **3b** | 40 | 68 | 50 | 34 | 44[g] |
| 8 | **2e** | **3a** | 40 | 62 | 47 | 29 | 46[e] |
| 9 | **2e** | **3b** | 40 | 56 | 55 | 31 | 40[e] |

[a] Reactions performed with 10 mol % catalyst **1** and ratio **3**/**2**:1.2.
[b] Enantiomeric excess for a reaction performed with (*R*)-**1**.
[c] Enantiomeric excess of binaphthol determined after reaction by HPLC.
[d] Enantiomeric excess (%) determined by HPLC.
[e] Reaction performed with a catalyst prepared from a mixture of (*R*)-binaphthol and (*S*)-binaphthol.
[f] Reaction performed with a mixture of catalysts (*R*)-**1** and (*S*)-**1** prepared respectively from (*R*)-binaphthol and (*S*)-binaphthol.
[g] Reaction performed as for *f* but each catalyst (*R*)-**1** and (*S*)-**1** was separately premixed with *p*-anisidine in the ratio 0.1/1.2 before mixing catalysts (*R*)-**1** and (*S*)-**1**.

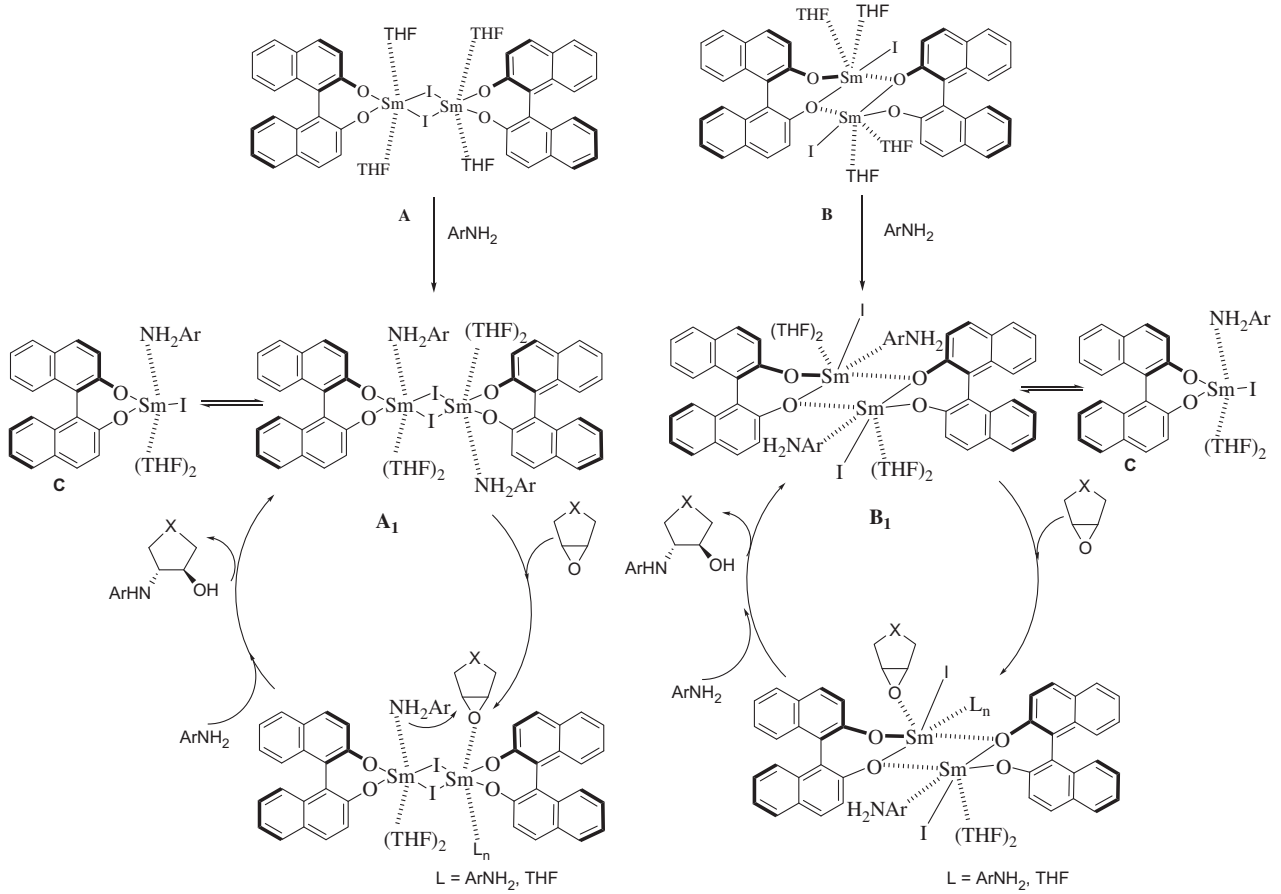
As indicated above, the occurrence of positive or negative non linear effects in all aminolyses of epoxides can be indicative of the presence of dimers. If we assume that the structure of samarium iodo binaphtholate **1** is dimeric, the use of scalemic binaphthol for the preparation of catalysts would lead to the formation of heterochiral [(*R*)-**1**–(*S*)-**1**] and homochiral dimers [(*R*)-**1**–(*R*)-**1**] and [(*S*)-**1**–(*S*)-**1**]. The method of preparation of catalysts can also influence non linear effects as shown by Kobayashi for the aminolysis of aziridine by aniline catalysed by titanium or zirconium complexes coordinated by substituted binaphthol using water as additive.[23] For these reactions an amplification was observed with catalysts prepared from scalemic ligand while using mixtures of enantiopure catalysts precoordinated by water led to enantiomeric excesses in linear correlation with those of catalysts. Addition of water on the mixtures of enantiopure catalysts led to a positive non linear effect but in a lesser extent than with the first method.

This was explained by the formation of active species from the homochiral dimer that are unstable in solution and by some organisation of the catalyst in the presence of water. We have now performed the aminolysis of 2,5-dihydrofuran oxide by *p*-anisidine at 40 °C with a mixture of complexes (*R*)-**1** and (*S*)-**1** of 40% ee. This catalyst afforded the β-aminoalcohol **4db** with 54% ee (entry 6), a value indicating a positive ENL corresponding exactly to that expected for a catalyst prepared from scalemic binaphthol (Fig. 4). This experiment is in agreement with dissociation of homochiral dimers [(*R*)-**1**–(*R*)-**1**] and [(*S*)-**1**–(*S*)-**1**] followed by reorganisation to form heterochiral dimer [(*R*)-**1**–(*S*)-**1**] under reaction conditions. Preparing catalyst by a mixture of complexes (*R*)-**1** and (*S*)-**1** of 50% ee, each complex (*R*)-**1** or (*S*)-**1** being independently treated with *p*-anisidine before mixing led to an enantiomeric excess of 44% indicating an ENL of lower amplitude than in previous cases. This indicates that the presence of *p*-anisidine does not prevent the reorganisation of the catalyst otherwise a linear correlation should be observed.

Since homochiral dimers [(*R*)-**1**–(*R*)-**1**] and [(*S*)-**1**–(*S*)-**1**] are dissociated in reaction conditions an equilibrium between monomers and dimers probably takes place and both of them can be envisaged as active species. For complex **1** association either through bridging iodines **A** or through oxygens of binaphthols **B** might account for dimeric structures as indicated in Scheme 6. Lanthanum complexes with bridging bisphenoxide ligands have been isolated and characterized by X-ray structures.[24] Addition of amine would lead to the dimeric species **A1** and **B1** in equilibrium with monomeric species **C** coordinated by one or two molecules of amine.[25]A key role for the amine to reorganize the catalyst structure and form active species has been established for titanium/binol catalysed aminolysis of epoxides.[12c]

We next realized the aminolysis of 2,5-dihydrofuran oxide catalysed by complex **1** using different amine/epoxide ratios and observed different trends depending on the amine. With *o*-anisidine enantiomeric excess decreased when ratio amine/epoxide increased (50% ee with 0.8 equiv *o*-anisidine vs 31% ee with 2 equiv) while similar enantiomeric excesses were obtained with different ratios amine/epoxide with *p*-anisidine (71% with 1.2 equiv and 69% with 2 equiv). Since dissociation of dimers occurs probably in a larger extent with chelating *o*-anisidine than with *p*-anisidine these experiments are in agreement with an equilibrium between monomers and dimers. The decrease of the enantiomeric excess with an excess of *o*-anisidine can be due to the formation of monomeric species less enantioselective than dimer species. For the reaction involving *p*-anisidine monomers and dimers could lead to similar enantiomeric excesses or the catalytic pathway involving dimers could predominate.

Considering the results described above, positive NLE observed for aminolyses of epoxides by *p*-anisidine probably cannot be attributed to the dissociation of homochiral dimer [(*R*)-**1**–(*R*)-**1**] in monomeric species while minor enantiomer of catalyst would be trapped as a stable heterochiral dimer [(*R*)-**1**–(*S*)-**1**]. The positive non linear effect would be better explained by assuming an higher activity for homochiral than for heterochiral dimer for reactions involving *p*-anisidine and epoxides **2a**, **2d** and **2e** (Table 2, entries 2, 5 and 9). NLE effects for reactions involving *o*-anisidine are more difficult to explain. The negative non linear effects observed with cyclohexene oxide and 2,5-dihydrofuran oxide (Table 2, entries 1 and 4) could be due to the dissociation of [(*R*)-**1**–(*S*)-**1**]. Since positive NLE have been observed in reaction involving nitrogen heterocyclic epoxide **2e** (Table 2, entry 8) different activities between homochiral and heterochiral dimeric species would offer




**Scheme 6.** Proposed dimeric species for the aminolysis of epoxides catalysed by samarium iodo binaphtholate **1**.

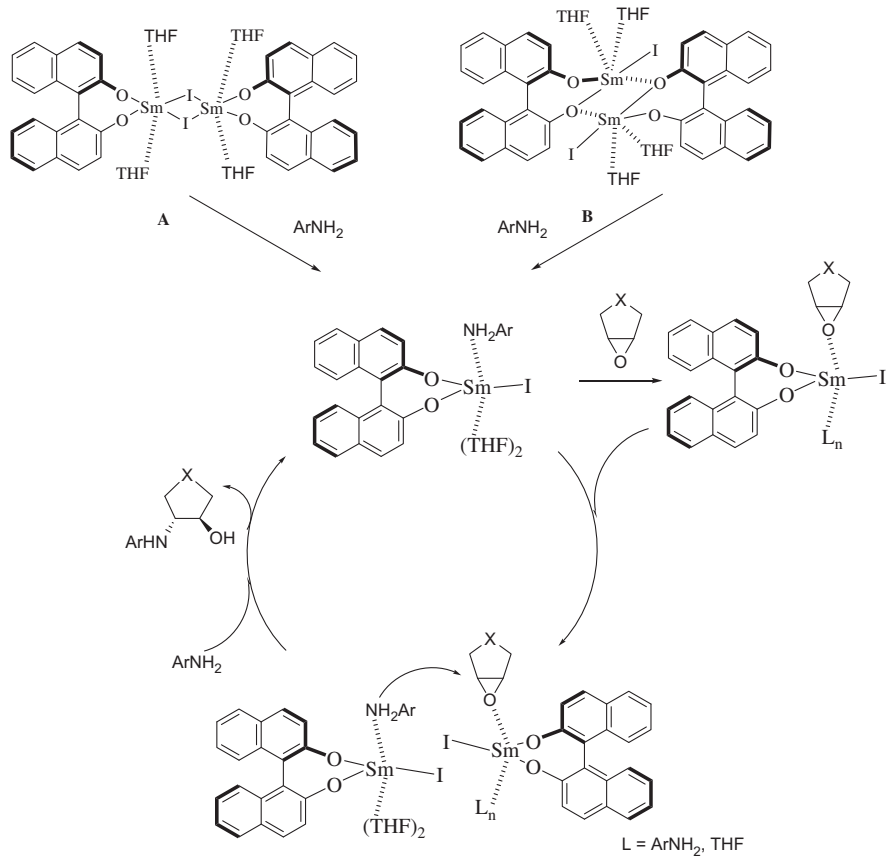
a better explanation. Different structures for the dimeric species could be also envisaged, especially involving coordination of epoxide.[26]

Mechanistic investigations for the enantioselective ring-opening of epoxides by trimethylsilyl azide for chromium/salen and zirconium/triisopropanolamine catalysed reactions have indicated bimetallic pathways.[27] These proposals were supported by observations of positive NLE. Several reports on enantioselective ring-opening of epoxides catalysed by lanthanides have led to similar conclusions. For the cyanation of epoxides catalysed by ytterbium/pybox a bimetallic mechanism was proposed on the basis of a positive NLE and mechanistic studies.[20] Thus samarium iodo binaphtholate catalysed aminolysis of epoxides might also proceed by a bimetallic mechanism. If epoxide is coordinated to a dimer **A1** or **B1** as represented in Scheme 6, a dimeric (or more aggregated) active species should be involved. Alternatively a bimetallic pathway with each substrate, amine and epoxide, coordinated to a different monomeric samarium species can be suggested, as shown in Scheme 7.

A comparison of monomeric and dimeric Cr/salen complexes for the catalysis of ring-opening of epoxides by trimethylsilyl azide has shown acceleration in the latter case demonstrating a cooperative effect between the two metal centers.[28] A dinuclear Ti-based catalytic system for the enantioselective transformation of epoxides in hydroxynitriles by trimethylsilyl cyanide has been reported, and selectivity for C–C versus N–C bond formation attributed to an intramolecular pathway.[29] For scandium/bipyridine catalysed aminolysis of epoxides the strong positive non linear effect was explained by aggregation of the catalyst.[21] Dimeric or oligomeric samarium catalytic species with a cooperative reactivity between metals have been suggested by Shibasaki for the enantioselective ring-opening of epoxyketones by trimethylsilyl azide.[30] It is thus tempting to assume that pathways described in Scheme 6 occur preferently to that described in Scheme 7 and that intermediates **A1** or **B1** are the most active and enantioselective species. This hypothesis takes into account the isoinversion and non linear effects observed in the aminolysis of epoxides. Complex **1** has a dimer or more associated structure and in the presence of amines an equilibrium with monomers occurs. The high activity and enantioselectivity of samarium iodo binaphtholate for aminolysis of epoxides is tentatively ascribed to its dimeric (or oligomeric) structure and to the high affinity of samarium towards aromatic amines.

## 3. Conclusion

Samarium iodo binaphtholate revealed as an efficient enantioselective catalyst for various C–C or C–N bond formation after reaction conditions such as the use of amines as additives, the order of addition of substrates and reaction temperature have been determined. The identical value for inversion temperature obtained for different reactions implying amines leads to attribute these phenomena to the formation of several catalytic species. The observation of non linear effects with catalysts prepared under different conditions led us to propose a dimer structure (or more aggregated) for samarium iodo binaphtholate and an equilibrium between monomers and dimers in the presence of amine. A bimetallic pathway is suggested for the aminolysis of epoxides catalysed by samarium iodo binaphtholate with a dimeric active species.




**Scheme 7.** Proposed bimetallic pathway for the aminolysis of epoxides catalysed by samarium iodo binaphtholate **1**.

## 4. Experimental

### 4.1. General

All manipulations were carried out under an argon atmosphere using standard Schlenk or glove box techniques. Dichloromethane and dichloroethane were distilled from $CaH_2$ and degassed immediately prior to use. The method for preparing samarium iodo binaphtholate **1** had been previously described.[9a] Catalysts have been prepared from enantiopure (*R*)-1,1-binaphthol except for the study of non linear effects (see below). Epoxide **2d** was synthesised according to the literature procedures.[31] *N*-*tert*-Butyloxycarbonyl-3-pyrroline oxide **2e** was obtained by the reaction of commercially available 3-pyrroline with *t*-butyl dicarbonate followed by epoxidation.[32] Epoxides and amines were distilled and degassed or recrystallised prior to use. All β-aminoalcohols **4** have been described previously.[9]

$^1H$ and $^{13}C$ NMR spectra were recorded on Bruker AM 360, AM 300 and AM 250 spectrometers, operating at 360, 300 and 250 MHz for $^1H$ and at 90.6, 75 and 62.5 MHz for $^{13}C$ in $CDCl_3$. Chemical shifts for $^1H$ and $^{13}C$ spectra were referenced internally according to the residual solvent resonances and reported in ppm relative to $CDCl_3$ (7.27 ppm for $^1H$ and 77 ppm for $^{13}C$). Infrared spectra were recorded on a Perkin Elmer 1000 FT-IR spectrometer as KBr disks or in $CHCl_3$ solution using $CaF_2$ cells and reported in $cm^{-1}$. High resolution mass spectra were measured on a Finnigan MAT 95 S spectrometer or at 70 eV (EI) with a Trace DSQ Thermo Electron spectrometer. Optical rotations were measured by using a Perkin Elmer 241 polarimeter at room temperature in a cell of 1 dm length at the sodium D line ($\lambda = 589$ nm) and were reported as follows: $[\alpha]_D^{20}$ (*c* in g per 100 mL, $CHCl_3$). HPLC analyses were performed on a Thermo Separation Product Pompe P100 with an UV detector and chiral stationary phase columns (Whelk O1, Chiralcel OD-H, Chiralpak IA). All the crude products were purified by preparative thin layer chromatography on silica gel 60 $PF_{254}$ (heptane/ethyl acetate).

### 4.2. Typical procedure for the aminolysis of epoxides

In the glove box, samarium iodo binaphtholate **1** (32.5 mg, 0.05 mmol) and molecular sieves 4 Å (100 mg) were weighed in a Schlenk tube and dichloromethane (4 mL) was added. *o*-Anisidine **3a** (74 mg, 0.6 mmol) was added to the solution, which was stirred at room temperature for 15 min. Outside the glove box, the reaction was heated at 40 °C and a solution of *N*-*tert*-butyloxycarbonyl-3-pyrroline oxide **2e** (92.5 mg, 0.5 mmol) in dichloromethane (1 mL) was then added by syringe. After stirring at 40 °C for 72 h, the reaction mixture was hydrolyzed with 0.1 M HCl, diluted with $CH_2Cl_2$ and neutralized with 0.1 M NaOH. The aqueous layer was extracted with EtOAc. The crude product was purified by preparative thin layer chromatography on silica gel (heptane/EtOAc 50:50). 86 mg, 56% yield. The enantiomeric excesses of product **4ea** (and of binaphthol for NLE studies) were determined by HPLC analysis as described below.

#### 4.2.1. (3*R*,4*R*)-*tert*-Butyl 3-hydroxy-4-(2-methoxyphenylamino)-pyrrolidine-1-carboxylate 4ea

Mp: 123–126 °C. $[\alpha]^{20} = +15.7$ (*c* 1.00, $CHCl_3$) for 62% ee. IR (KBr) ($cm^{-1}$): *ν* 3478, 2945, 1682, 1601, 1513, 1413, 1233, 1161, 1120, 1024, 742. $^1H$ NMR (300 MHz, $CDCl_3$): *δ* (ppm) 1.48 (9H, s), 3.26–3.50 (2H, m), 3.58–3.71 (1H, m), 3.73–3.98 (2H, m), 3.84 (3H, s), 4.21–4.33 (1H, m), 6.68–6.88 (4H, m). $^{13}C$ NMR (62.5 MHz, $CDCl_3$, rotamers): *δ* (ppm) 28.5, 50.1, 50.5, 51.7, 52.3, 55.3, 58.7, 59.0, 73.0, 73.8, 79.8, 109.5, 110.1, 117.2, 121.2, 136.3, 146.7, 154.9. MS (ESI) *m*/*z*: 331.1 ($MNa^+$, 100%). HRMS calcd for $C_{14}H_{21}O_4NNa$ ($MNa^+$): 308.1731, found: 308.1725.

### 4.3. HPLC determination of enantiomeric excesses

#### 4.3.1. (1*R*,2*R*)-2-(2-Methoxyphenylamino)-cyclohexanol: 4aa

HPLC: (Chiralcel OD-H column, flow rate = 1 mL $min^{-1}$, hexane/isopropanol 85/15, $\lambda = 254$ nm), $t_{R(minor)} = 7.3$ min, $t_{R(major)} = 16.2$ min.

#### 4.3.2. (1*R*,2*R*)-2-(4-Methoxyphenylamino)-cyclohexanol: 4ab

HPLC: (Chiralcel OD-H column, flow rate = 1 mL $min^{-1}$, hexane/isopropanol 85/15, $\lambda = 254$ nm), $t_{R(minor)} = 7.9$ min, $t_{R(major)} = 11.2$ min.

#### 4.3.3. (1*R*,2*R*)-4-Oxa-2-(2-methoxyphenylamino)cyclopentanol: 4da

HPLC: (Whelk O1 column, flow rate = 0.8 mL $min^{-1}$, hexane/ethanol 95/5, column temperature = 15 °C, $\lambda = 254$ nm), $t_{R(minor)} = 24.9$ min, $t_{R(major)} = 26.4$ min.

#### 4.3.4. (1*R*,2*R*)-4-Oxa-2-(4-methoxyphenylamino)cyclopentanol: 4db

HPLC: (Chiralpak IA column, flow rate = 0.7 mL $min^{-1}$, hexane/isopropanol 85/15, $\lambda = 254$ nm), $t_{R(minor)} = 17.7$ min, $t_{R(major)} = 20.0$ min.

#### 4.3.5. (3*R*,4*R*)-*tert*-Butyl 3-hydroxy-4-(2-methoxyphenylamino) pyrrolidine-1-carboxylate: 4ea

HPLC: (Chiralpak IA column, flow rate = 0.5 mL $min^{-1}$, hexane/isopropanol 85/15, $\lambda = 254$ nm), $t_{R(minor)} = 13.1$ min, $t_{R(major)} = 14.2$ min.

#### 4.3.6. (3*R*,4*R*)-*tert*-Butyl 3-hydroxy-4-(4-methoxyphenylamino) pyrrolidine-1-carboxylate: 4eb

HPLC: (Chiralpak IA column, flow rate = 0.5 mL $min^{-1}$, hexane/isopropanol 95/5, $\lambda = 254$ nm), $t_{R(minor)} = 44.7$ min, $t_{R(major)} = 47.6$ min.

### 4.4. Preparation of catalysts for the study of non linear effects

#### 4.4.1. Preparation of catalysts from mixtures of (*R*)- and (*S*)-binaphthols

The following procedure describes the synthesis of 0.15 mmol catalyst with an enantiomeric excess of 50%. In the glove box, (*R*)-binaphthol (32 mg, 0.11 mmol) and (*S*)-binaphthol (11 mg, 0.04 mmol) were dissolved in 3 mL THF and diphenylmethyl potassium (62 mg, 0.3 mmol) was added slowly under magnetic stirring. After 2 h of agitation, the orange colour of the reaction mixture disappeared and the suspension was added within 5 min to a suspension of $SmI_3(THF)_3$ (112 mg, 0.15 mmol) in 3 mL THF. After 18 h stirring, KI was separated by centrifugation and THF evaporated under vacuum. The residue was dissolved in 3 mL dichloromethane and an aliquot of 1 mL used for a catalytic experiment.

#### 4.4.2. Preparation of catalysts from mixtures of (*R*)- and (*S*)-iodo binaphtholate 1

For the preparation of catalyst with an enantiomeric excess of 50% in the glove box, (*R*)-samarium iodo binaphtholate **1** (26.5 mg, 0.0375 mmol) and (*S*)- samarium iodo binaphtholate **1** (8.8 mg, 0.0125 mmol) were dissolved in 2 mL dichloromethane and used as described above.

#### 4.4.3. Preparation of catalysts from mixtures of (*R*)- and (*S*)-iodo binaphtholate 1 premixed with 2a

For the preparation of catalyst with an enantiomeric excess of 50% in the glove box, (*R*)-samarium iodo binaphtholate (26.5 mg, 0.0375 mmol) and *p*-anisidine (55.5 mg, 0.45 mmol) were dissolved in 2 mL dichloromethane. Similarly, a solution of (*S*)-samarium

iodo binaphtholate (8.8 mg, 0.0125 mmol) with *p*-anisidine (18.5 mg, 0.15 mmol) in 1 mL dichloromethane was prepared. After 30 min stirring the two solutions were mixed in a Schlenk tube. Outside the glove box, the reaction was heated at 40 °C and a solution of 2,5-dihydrofuran oxide **2d** (43 mg, 0.5 mmol) in dichloromethane (1 mL) was then added by syringe. After 72 h, the solution was treated as previously described and the crude product was purified by preparative thin layer chromatography on silica gel (heptane/EtOAc 50:50). The enantiomeric excesses of product **4db** and of binaphthol were determined by HPLC analysis as described above.

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25. If monomeric and dimeric catalytic species promoting the reaction with different asymmetric inductions are in equilibrium the ratio of these species and thus the enantiomeric excess of the product should vary with the concentration of reaction mixture. However when the ring opening of 2,5-dihydrofuran oxide **2d** with *p*-anisidine **3b** was performed at various concentrations the variation of the enantiomeric excess of aminoalcohol **4db** was too small for supporting our proposal.
26. To probe the possibility of the involvement of enantioenriched β-aminoalcohol in the active species the enantiomeric excess of product was monitored during the aminolysis of **2d** with *p*-anisidine. No significant variation was observed when measuring enantiomeric excesses of **4db** on aliquots of reaction mixture and it was not possible to conclude on the possible role of β-aminoalcohol as a samarium ligand in these reactions.
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