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Chiral Lewis Acid Catalysed Asymmetric Nucleophilic Ring Opening of Cyclohexene Oxide

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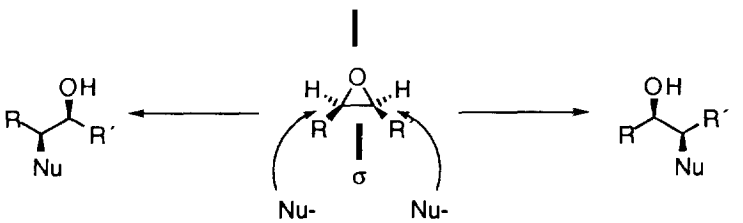
Abstract: Titanium and zirconium complexes of bispicolinic amides catalyze the ring opening of cyclohexene oxide with trimethylsilyl azide as nucleophile. The product, 1-azido-2-trimethylsilyloxycyclohexane, was obtained in up to 71% enantioselectivity when a catalyst prepared from (*S,S*)-*N,N'*-bis(2-pyridinecarboxamide)-1,2-diphenylethane and zirconium tetra-*t*-butoxide was employed under optimum conditions, which included the addition of a small amount of diethylamine in the catalyst preparation step. The nature of the catalyst is still unknown, but it seems probable that oligomeric metal species are involved.

INTRODUCTION

The field of asymmetric catalysis is continously growing and the number of sophisticated methods and reactions used to achieve high stereoselectivity is infinitely increasing. Chiral Lewis acids have been used as catalysts in a variety of asymmetric reactions, such as Diels-Alder , [2 + 2] cycloaddition and ene reactions, and the hydrocyanation of aldehydes.[1] The catalysts are often prepared in situ and consist of traditional Lewis acids modified by chiral ligands.

Nucleophilic ring opening of epoxides is another reaction where Lewis acids play an important roll as catalysts. Epoxides are useful building blocks in organic synthesis and a large variety of chiral epoxides are available due to the work of e g Sharpless.[2,3] The ability to control the regio- and stereochemistry in the ring opening of epoxides is of major importance for their further elaboration, and by using Lewis acids as catalysts it is possible to achieve the desired products.



Scheme 1: Nucleophilic cleavage of *meso* epoxides R = R'

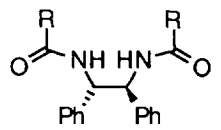
The nucleophilic ring opening of *meso* epoxides assisted by chiral Lewis acids has the advantage of simultaneously producing two stereogenic centers (Scheme 1). In order to achieve this, the metal center of the catalyst is thought to coordinate to the epoxide oxygen atom while the chiral ligand directs the incoming nucleophile to one of the enantiotopic carbon atoms of the oxirane. By choosing appropriate nucleophiles, several types of useful enantiomerically pure substances can be prepared in this way. So far, the catalysts used in these reactions have been early transition metals combined with chiral ligands predominantely having oxygen atoms as donor groups.[4,5]

The coordination properties of bispicolinic amides, derived from picolinic acid and diamines, have been widely investigated.[6] Despite this, examples of the use of metal complexes of this class of ligands as catalysts in organic reactions are scarce, consisting of only a few oxidation reactions.[7]

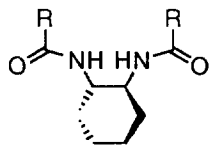
We have previously prepared and studied the coordination behaviour of a number of macrocyclic ligands based on the dipyridylmethane structural unit.[8] In this paper, we present some new C_2- and *pseudo* C_2-symmetric ligands derived from picolinic acids and chiral amines, together with studies of the catalytic activity of some early transition metal complexes of the ligands in the Lewis acid catalyzed ring opening of cyclohexene oxide.[9]

RESULTS AND DISCUSSION

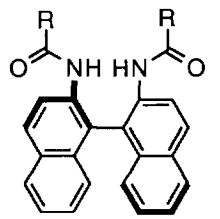
The ligands used in this investigation are picolinic- or bispicolinic amides, with structures **1-9** (Figure 1). With the exception of **4**, the ligands consist of two pyridyl derivatives and two amide groups, thus having the possibility to act as either N_2O_2- or N_4-donors. Furthermore, the ligands can act as either neutral donors or be deprotonated and act as combined ionic and neutral donors.[10] The ligands represent three different topologies. Ligands **1-7** are C_2-symmetric bis-amides without connectivity between the pyridine rings, ligand **8** is a 13-membered macrocycle and ligand **9** is analogous to **8** but with the connectivity between the two amide groups absent.



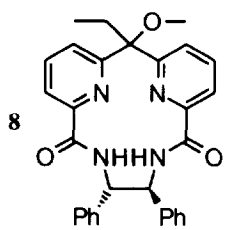
1. R = 2-pyridyl
2. R = 6-methyl-2-pyridyl
3. R = 2-quinolinyl
4. R = Ph



5. R = 2-pyridyl



6. R = 2-pyridyl
7. R = 2-quinolinyl



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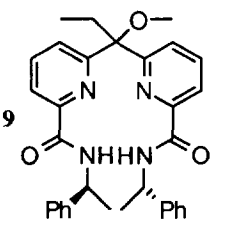

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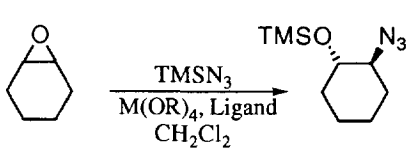
Figure 1

Titanium and zirconium complexes of the bispicolinic amides were investigated as catalysts in the nucleophilic ring opening of cyclohexene oxide. The catalysts were either prepared in situ by mixing the metal alkoxide with the appropriate ligand prior to reaction, or preformed and isolated and thereafter used in the catalytic reaction.

Preparation of the bispicolinic amides. All ligands were prepared via condensation of the parent acid or acid chloride and commercially available chiral amine or diamines. Ligands **1**,[6a] **2**, **3**, **5**,[6b] **6**[6c] and **7** were prepared via coupling of the parent acid and the diamine in the presence of triphenylphosphite. Ligand **4** was prepared by condensation of benzoyl chloride with (*S*,*S*)-stilbenediamine in the presence of triethylamine. The *pseudo* C_2-symmetric macrocyclic ligand **8** was prepared from 1,1-bis(6-chloroformyl-2-pyridyl)-1-methoxypropane and (*S*,*S*)-stilbenediamine using high dilution technique. The yield in this reaction was very low compared to the yields of previously prepared compounds of this class of macrocycles,[8] possibly due to the energetically unfavourable staggered conformation of the diamine in the transition state of the cyclisation process. This is supported by the formation of oligomeric amides as byproducts. Ligand **9** was prepared from 1,1-bis(6-chloroformyl-2-pyridyl)-1-methoxypropane and two equivalents of (*S*)-1-methylbenzylamine in presence of triethylamine.

Catalytic reactions. The catalytic process studied in this investigation is the Lewis acid mediated ring opening of cyclohexene oxide with trimethylsilyl azide as nucleophile, yielding *trans*-1-azido-2-trimethylsilyloxycyclohexane (Scheme 2).

Scheme 2



The reactions were performed using different strategies. As a first screening, a series of experiments was performed whereby the ligands were mixed with equimolar amounts of either a titanium or a zirconium alkoxide prior to the addition of cyclohexene oxide and trimethylsilyl azide. The reaction mixture was stirred at ambient temperature and monitored by TLC. The results from the experiments with different ligands are summarized in Table I.

Table I. Lewis Acid Catalysed Cleavage of Cyclohexene Oxide with Trimethylsilyl Azide.[a]

	$Ti(OPr^i)_4$			$Zr(OBu^t)_4$		
Ligand	**yield(%)**[b]	**ee(%)**[c]	**time(d)**	**yield(%)**[b]	**ee(%)**[c]	**time(d)**
1	38	57 (1*S*,2*S*)	12	45	56 (1*S*,2*S*)	4
2	43	15 (1*S*,2*S*)	7	65	17 (1*S*,2*S*)	7
3	19	3 (1*S*,2*S*)	7	21	15 (1*S*,2*S*)	7
4	20	1 (1*S*,2*S*)	12	34	1 (1*S*,2*S*)	7
5	42	36 (1*R*,2*R*)	21	33	35 (1*R*,2*R*)	7
6	22	1 (1*R*,2*R*)	7	15	1 (1*R*,2*R*)	7
7	13	0	7	28	0	7
8	21	0	15	19	1 (1*S*,2*S*)	7
9	17	0	7	25	0	7

[a] All runs contain cyclohexene oxide (1 eq), trimethylsilyl azide (1.05 eq), ligand (0.1 eq) and $M(OR)_4$ (0.1 eq), CH_2Cl_2 (3 mL), ambient temperature. [b] Isolated yield after liquid chromatography. [c] Determined by GLC analysis. Configuration of major enantiomer in parantheses.

Using the method described above with ligand **1** and titanium tetraisopropoxide as the metal precursor resulted in the formation of (1*S*,2*S*)-1-azido-2-trimethylsilyloxycyclohexane with 57% ee. Changing the substituents on the diamide to bulkier pyridyl derivatives resulted in a dramatic decrease in both conversion and enantioselectivity. This is illustrated by ligands **2** and **3**, where the ring opened product is formed with 15 and 3% ee, respectively. Replacing the heterocycle with a phenyl ring (ligand **4**), resulted in a dramatic decrease in the enantioselectivity (1%). Ligand **5**, where (1*R*,2*R*)-diaminocyclohexane serves as the chiral handle, produced (1*R*,2*R*)-1-azido-2-trimethylsilyloxycyclohexane with 36% ee. Ligands **6-9** gave low yields and no selectivity at all. The reaction rates in all experiments examined were very low. Running the same reaction as above using ligand **1** and zirconium tetra-*t*-butoxide as the catalyst precursor gave the ring opened product with 56% ee in 45% yield. The more sterically hindered ligands **2** and **3** as well as ligand **4** resulted also in this case in lower enantioselectivity in the conversion of cyclohexene oxide, although the yield of the silyl protected azido cyclohexanol using **2** was slightly improved. The enantioselectivity achieved with ligand **5** was comparable to the above titanium case. Complexes of ligands **6-9** showed no selectivity at all. The rates and yields were poor also in these reactions.

Catalytic reactions with ligand 1. The first screening experiments showed that the most promising results were obtained using ligand **1**, although the rate and the yield in the catalytic reactions were not satisfying. Since formation of the active catalyst seemed to be slow, preparation and isolation of metal complexes of **1**, prior to use in the catalytic reaction, were attempted. This precatalyst was prepared by refluxing the ligand and the metal alkoxide in toluene while removing the alcohol by azeotropic distillation. The ^1H NMR spectra of the isolated titanium and zirconium complexes showed that the amides were deprotonated, but were too complicated for further assignment.

Use of the catalysts in the nucleophilic ring opening of cyclohexene oxide with trimethylsilyl azide resulted in an increased reaction rate (see Table II, method C). The titanium complex gave a quantitative yield of 1-azido-2-trimethylsilyloxycyclohexane after only 42 h, whereas use of the zirconium complex gave the product in 93% yield after 5.5 days. The stereoselectivity, however, decreased substantially to 9% when titanium was used and in the case of zirconium to 44%. The zirconium complex is obviously sensitive since repeating the experiment under the same conditions on a different day gave a lower yield, 62% after 6 days,

although with a slightly higher enantiomeric excess (48%). Performing the reaction at low temperature gave, surprisingly, a lower enantiomeric excess (entry 11). Influenced by the results of Nugent,[5a] small amounts of acetic acid and trifluoroacetic acid were added to the reaction mixture. This, however, did not affect the rate or the selectivity of the reaction.

As a comparison, the metal complex of **3** and zirconium tetra-*t*-butoxide was prepared using method C as described above. Running the catalytic reaction in the presence of this complex resulted in 35% conversion of cyclohexene oxide to the ring opened product. The enantiomeric excess, 6 %, was slightly higher than that for the reaction with the *in situ* prepared catalyst (method A).

Table II. Nucleophilic Cleavage of Cyclohexene Oxide Catalysed by Chiral Lewis Acids Derived from Ligand 1.[a]

Entry	MX_4	yield(%)[b]	ee(%)[c]	solvent	conditions	method[d]
1	$Ti(OPr^i)_4$	38	28	CH_2Cl_2	RT, 6 d[e]	A
2	$Ti(OPr^i)_4$	29	35	CH_2Cl_2	RT, 8 d[f]	A
3	$Ti(OPr^i)_4$	19	35	THF	RT, 4 d	A
4	$Ti(OPr^i)_4$	100	9	CH_2Cl_2	RT, 42 h	C
5	$Ti(OPr^i)_4$	74	17	CH_2Cl_2	0°C, 17 d	C
6	$TiCl_4$	58	17	CH_2Cl_2	RT, 10 d	A
7	$Zr(OBu^t)_4$	56	35	THF	RT, 4 d	A
8	$Zr(OBu^t)_4$	83	24	CH_2Cl_2	RT, 5 d	B
9	$Zr(OBu^t)_4$	93	44	CH_2Cl_2	RT, 5.5 d	C
10	$Zr(OBu^t)_4$	62	48	CH_2Cl_2	RT, 6 d	C
11	$Zr(OBu^t)_4$	83	26	CH_2Cl_2	0°C, 7 d	C
12	$Zr(OBu^t)_4$	68	43	CH_2Cl_2	RT, 6 d[g]	C
13	$Zr(OBu^t)_4$	56	44	CH_2Cl_2	RT, 6 d[h]	C
14	$Zr(OBu^t)_4$	21	44	toluene	RT, 7 d	C

[a] Conditions: Cyclohexene oxide (1 eq), trimethylsilyl azide (1.05 eq), ligand **1** (0.1 eq) and MX_4 (0.1 eq). [b] Isolated yield after chromatography. [c] Determined by GLC analysis. [d] Methods: **A**; **1** and MX_4 were mixed in the solvent before substrate and reagent were added. **B**; Isolated catalyst, ligand deprotonated with *t*-BuLi before $Zr(OBu^t)_4$ was added. C; Isolated catalyst, prepared by azeotropic distillation of ROH from toluene. [e] 4Å molecular sieves added. [f] HOAc (0.4 eq) added. [g] HOAc (0.1 eq) added. [h] TFA (0.1 eq) added.

The influence of secondary amines. The low degree of conversion and the long reaction times in the above reactions led us to further investigate other methods to achieve more active catalysts. The addition of a catalytic amount of a secondary amine during the catalyst preparation step was found to increase the reaction rate as well as, in certain cases, the stereoselectivity of the product formed. The catalyst prepared from titanium tetraisopropoxide, ligand **1** and a secondary amine gave results similar to those described above, however, significantly better results were obtained with a catalyst prepared from zirconium tetra-*t*-butoxide.

The general method for preparing the active catalyst consisted of mixing the ligand, the metal alkoxide, $TMSN_3$ and a secondary amine, stirring for 24 h and then adding the substrate. The results from these reactions are presented in Table III. The amount of secondary amine seems to play an important role for the selectivity in the reaction. When using up to 10% of diethylamine relative to the amount of zirconium tetra-*t*-butoxide, the enantioselectivity of the formed product was as high as 65%. Increasing the amount of amine drastically decreased the selectivity. This can be explained by assuming that a nonchiral amine complex is formed in addition to the desired catalyst, thus offering an alternative catalytic pathway which lowers the enantioselectivity. Using other secondary amines like diisopropylamine and pyrrolidine resulted in similar yields and selectivities as in the case of diethylamine. Performing the catalytic ring cleavage reaction at 0°C increased the enantioselectivity to 71% (entry 7). It should be noted that the ligand could, in all of the above reactions, be recovered by simple recrystallization from ethanol.

Table III. Nucleophilic cleavage of cyclohexene oxide catalysed by chiral Lewis acids derived from ligand 1 in the precense of secondary amines.

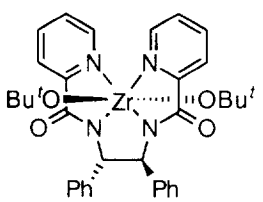
Entry	$M(OR)_4$	yield(%)[b]	ee(%)[c]	amine[d]	eq[e]	conditions
1	$Ti(OPr^i)_4$	48	44	DEA	0.01	RT,48 h
2	$Ti(OPr^i)_4$	58	39	DIPA	0.01	RT, 4 d
3	$Ti(OPr^i)_4$	84	39	pyrrolidine	0.01	RT, 4 d
4	$Zr(OBu^t)_4$	54	61	DEA	0.001	RT, 5 d
5	$Zr(OBu^t)_4$	86	61	DEA	0.005	RT, 5 d
6	$Zr(OBu^t)_4$	66	65	DEA	0.01	RT, 48 h
7	$Zr(OBu^t)_4$	60	71	DEA	0.01	0°C, 5 d
8	$Zr(OBu^t)_4$	99	20	DEA	0.1	RT, 46 h
9	$Zr(OBu^t)_4$	78	10	DEA	0.2	RT, 46 h
10	$Zr(OBu^t)_4$	64	67	DEA	0.01	RT, 48 h[f]
11	$Zr(OBu^t)_4$	95	62	DIPA	0.01	RT, 4 d
12	$Zr(OBu^t)_4$	99	57	pyrrolidine	0.01	RT, 4 d

[a] Conditions: cyclohexene oxide (1 eq), trimethylsilyl azide (1.05 eq), ligand **1** (0.1 eq) and $M(OR)_4$ (0.1 eq) in CH_2Cl_2. [b] Isolated yield after chromatography. [c] Determined by GLC analysis. [d] Diethylamine (DEA), diisopropylamine (DIPA). [e] Number of amine equivalents relative to cyclohexene oxide. [f] Ligand **1** (0.2 eq).

Solvent effects. The influence of the solvent in the reaction was also investigated. Use of an *in situ* generated titanium or zirconium catalyst (method A) in THF resulted in lower yield and lower selectivity compared to the same reactions performed in dichloromethane (entry 3 and 7, Table II). In nitrobenzene, with the catalysts prepared in the presence of diethylamine, the stereoselectivity was slightly lower in the case of titanium (36 %), and substancially lower with zirconium as the catalyst precursor (7 %). Changing from dichloromethane to toluene, using a zirconium catalyst prepared according to method C, resulted in a lower yield of the product, leaving the stereoselectivity essentially the same (entry 14, Table II).

Spectroscopic investigations. In order to gain further information about the nature and the role of the catalyst in the mechanism of the nucleophilic ring cleavage of epoxides, spectroscopic investigations were performed. The stoichiometric reaction was followed by NMR spectroscopy, using those reaction conditions giving the highest ee in the catalytic experiments above, i.e. ligand **1** (1 eq), zirconium tetra-*t*-butoxide (1 eq), diethylamine (0.1 eq), trimethylsilyl azide (2 eq) and cyclohexene oxide (2 eq) added to $CDCl_3$ at intervals. Initially, after mixing **1** and zirconium tetra-*t*-butoxide, the ^1H NMR spectrum showed a mixture of three major species, identified as the free ligand, a complex where one of the two amides was deprotonated, and finally a 1 : 1 metal to ligand complex of $Zr(OBu^t)_4$ and **1** in which both amide groups were deprotonated, believed to have the C_2-symmetric structure **10**.

10



The addition of diethylamine to this solution resulted in essentially complete conversion to **10**. The spectrum changed drastically upon addition of trimethylsilyl azide, showing a mixture of the above **10** and signals from four different ligands in a 1 : 1 : 1 : 1 ratio, three of them having deprotonated amide groups and one containing amide protons, all of them conserving their C_2 symmetry. To ascertain whether monomeric or oligomeric complexes were involved, the same reaction was repeated using racemic **1**. If dimers were to form, a

mixture of homochiral and heterochiral complexes would be expected, resulting in an NMR spectrum showing a new set of signals in addition to that originating from the enantiomerically pure ligand, whereas a considerably more complicated spectrum (up to eight sets of signals) is expected if a tetramer is formed. The actual spectrum showed unchanged signals for **10**, in accordance with the monomeric structure suggested, whereas one new set of signals, in addition to those of complexes of enantiomerically pure **1**, was observed for the four remaining ligands. These observations suggest that two different dimers were formed, even if the formation of a limited number of all possible tetramers (e g with *R*R*R*R** and *R*R*S*S** configuration) cannot be excluded. However, since the inherent C_2 symmetry of ligand in no case was destroyed, we favor the suggestion that dimers were formed, since it is difficult to envisage any tetramer with these structural constraints. Upon addition of cyclohexene oxide, the signals of the oligomeric complex(es) did not change. The reaction was monitored for several days and no change in the metal complex was observed and, most remarkably, no transformation of the epoxide to the ring opened product could be detected. Two additional equivalents of trimethylsilyl azide were then added, resulting within a few days, in the formation of a 1 : 1 mixture of 1-azido-2-trimethylsilyloxycyclohexane and the corresponding zirconium alkoxide. Performing the reaction using the same conditions as above but having a two-fold excess of zirconium alkoxide, resulted in the formation of **10** as the major complex, and almost no conversion of the epoxide to the ring opened product, even after addition of another two equivalents of trimethylsilyl azide. With a two-fold excess of ligand, the oligomeric product was the major complex observed, but unfortunately precipitation occurred before any epoxide was added, and the experiment was therefore aborted.

An IR spectrum of a solution of the dimeric complexes showed two new bands in the azide region, both shifted to lower energy compared to free azide. Whether the azides are terminal or bridging cannot be determined from this spectrum.[11] The amide N-H stretch from the ligand was absent and a new band, interpreted as a N-H stretch of the complex appeared at higher wavenumber.

Proposed mechanism. The mechanism of this reaction with azide as nucleophile has previously been investigated with titanium azides.[5f,12] The authors suggest that the epoxide is inserted into the Ti-N_3 bond yielding an azido-alkoxy ligand binding to the titanium ion through the alkoxy group. The silylprotected azido-alkohol is then removed from the metal by a substitution reaction with trimethylsilyl azide yielding a new titanium azide. This is in contrast to the findings of the present investigation, since in this case the first two equivalents of azide are consumed in the preparation of the zirconium complexes observed by NMR spectroscopy, with the epoxide undergoing nucleophilic attack only by the third equivalent of azide. It is therefore assumed that the nucleophilic attack occurrs by an azide ion not previously coordinated to the metal ion. This seems reasonable, since direct insertion of the epoxide into the metal-azide bond, yielding the *trans* isomer of the ring opened product, should be stereochemically highly unfavorable.

At the present stage, it is not possible to conclude which complex is the catalytic active species. However, there seems to be a relationship between the amount of the above proposed dimers and the rate of the reaction, indicating that at least one of these complexes acts as the active catalyst. If this is the case, a nonlinear relationship between the enantioselectivity of the reaction and the enantiomeric purity of the ligand might be expected. This was not observed, though, and therefore further conclusions about the catalytically active species can not be drawn. That the active catalyst is probably not monomeric is supported by the observation that macrocyclic ligand **8** does not result in any enantioselectivity.

EXPERIMENTAL

General Methods. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100.6 MHz respectively, in $CDCl_3$ unless otherwise stated. Chemical shifts are reported relative to Me_4Si and $CDCl_3$. Liquid chromatography was performed using silica gel (Merck 230-400 mesh). Enantiomeric excess values were determined with GLC on a Chrompak CP-cyclodextrin-β-2,3,6-M-19 column. Melting points are uncorrected. All catalytic reactions were performed under a dry nitrogen atmosphere.

Materials. *(R,R)-N,N'*-bis(2-pyridinecarboxamide)-1,2-cyclohexane (**5**)[6b] and *(R)-N,N'*-bis(2-pyridinecarboxamide)-2,2'-binaphthalene (**6**)[6c] were synthesized according to previously described methods. Dichloromethane was distilled from P_2O_5.

General procedure for the preparation of ligands 1, 2, 3 and 7. To a hot solution of the acid (2 eq) and triphenylphosphite (2 eq) in pyridine was added a solution of the diamine (1eq) in pyridine. The reaction mixture was left at 100 °C for 4 h, cooled to ambient temperature and poured into water. The resulting precipitate was filtered off and recrystallized or chromatographed.

(*S,S*)-*N,N'*-Bis(2-pyridinecarboxamide)-1,2-diphenylethane (1).[13] Purification: recrystallisation from EtOH. m.p. 223 °C. Small white needles. $[\alpha]_D^{20}$ +10 (*c* 0.6, $CHCl_3$). ^1H NMR δ 5.61 (AA'part of AA'XX', 2H, CH), 7.16-7.27 (m, 10H, phenyl), 7.34 (ddd, 2H, *J* = 7.7, 4.8 and 1.0 Hz, 5-pyridyl), 7,74 (td, 2H, *J* = 7.7 and 1.7 Hz, 4-pyridyl), 8.08 (td, 2H, *J* = 7.7 and 1.0 Hz, 3-pyridyl), 8.52 (ddd, 2H, *J* = 4.8, 1.7 and 1.0 Hz, 6-pyridyl), 8.93 (XX'part of AA'XX', 2H, NH); ^{13}C NMR δ 58.9, 122.2, 126.1, 127.8 (6C), 128.6 (4C), 137.1, 138.8, 148.2, 149.6, 164.6.

(*S,S*)-*N,N'*-Bis(6-methyl-2-pyridinecarboxamide)-1,2-diphenylethane (2). Yield: 124 mg (28%). Purification: column chromatography (hexane: EtOAc, 1:1). m.p. 55 °C. $[\alpha]_D^{20}$ -38 (*c* 0.4, $CHCl_3$). ^1H NMR δ 2.53 (s, 3H, CH_3), 5.62 (AA'part of AA'XX', 2H, CH), 7.15-7.32 (m, 12H, phenyl and 5-pyridyl), 7.60 (t, 2H, *J* = 7.6 Hz, 4-pyridyl), 7.91 (dd, 2H, *J* = 7.6 Hz, 3-pyridyl), 9.02 (XX'part of AA'XX', 2H, NH); ^{13}C NMR δ 24.3, 58.7, 119.2, 125.9, 127.8, 128.3, 129.8, 137.2, 138.9, 148.9, 157.3, 164.7.

(*S,S*)-*N,N'*-Bis(2-quinolinecarboxamide)-1,2-diphenylethane (3). Yield 296 mg (60 %). Purification: recrystallisation from EtOH. m.p. 209 °C. Pale yellow needles. $[\alpha]_D^{20}$ -21 (*c* 0.5, $CHCl_3$). ^1H NMR δ 5.73 (AA'part of AA'XX', 2H, CH), 7.21-7.35 (m, 10H, phenyl), 7.56 (ddd, 2H, *J* = 8.1, 6.9 and 1.2 Hz, 6-quinolinyl), 7,74 (ddd, 2H, *J* = 8.5, 6.9 and 1.2 Hz, 7-quinolinyl), 7.78 (dd, 2H, *J* = 8.1 and 1.2 Hz, 5-quinolinyl), 8.14 (dd, 2H, *J* = 8.5 and 1.2 Hz, 8-quinolinyl), 8.16 (d, 2H, *J* = 8.5 Hz, 3- or 4-quinolinyl), 8.20 (d, 2H, *J* = 8.5 Hz, 3- or 4-quinolinyl), 9.20 (XX'part of AA'XX', 2H, NH); ^{13}C NMR δ 58.9, 118.8, 127.6, 127.9 (4C), 127.9 (4C), 128.6 (4C), 129.3, 130.0, 130.1, 137.3, 138.8, 146.5, 149.4, 164.8. Anal. Calcd. for $C_{34}H_{26}N_4O_2$: C, 78.14; H, 5.01; N, 10.72. Found: C, 78.13; H, 5.01; N, 11.05.

(*R*)-*N,N'*-Bis(2-quinolinecarboxamide)-2,2'-binaphthalene (7). Yield 107 mg (51%). Purification: recrystallisation from EtOH. m.p. 223 °C. Pale yellow needles. $[\alpha]_D^{20}$ -89 (*c* 0.5, $CHCl_3$). ^1H NMR δ 7.28 (br d, 2H, *J* = 8.5 Hz, 5-naphthyl), 7.32 (ddd partly hidden, 2H, *J* = 8.5, 6.6 and 1.3 Hz, 6-quinolinyl), 7.39 (br d, 2H, *J* = 8.5 Hz, 5-quinolinyl), 7.46 (ddd, 2H, *J* = 8.1, 6.6 and 1.3 Hz, 7-quinolinyl), 7.50 (ddd, 2H, *J* = 8.1, 7.0 and 1.3 Hz, 7-naphthyl), 7.65 (ddd, 2H, *J* = 8.5, 7.0 and 1.3 Hz, 6-naphthyl), 7.70 (ddd, 2H, *J* = 8.1, 1.3 and 0.5 Hz, 8-naphthyl), 8.10 (d, 2H, *J* = 8.1 Hz, 8-quinolinyl), 8.13 (app. s, 4H, 3- and 4-quinolinyl), 8.35 (d, 2H, *J* = 9.1 Hz, 3- or 4-naphthyl), 9.29 (d, 2H, *J* = 9.1 Hz, 3- or 4-naphthyl), 10.49 (br s, 2H, NH). ^{13}C NMR δ 118.1, 119.2, 119.6, 125.3, 125.5, 127.3, 127.5, 128.0, 128.3, 129.1, 129.8, 130.0, 130.2, 131.3, 133.1, 135.7, 137.5, 145.9, 149.1, 162.1. Anal. Calcd. for $C_{40}H_{26}N_4O_2$: C, 80.79; H, 4.41; N, 9.42. Found: C, 80.01; H, 4.44; N, 9.83.

(*S,S*)-*N,N'*-Bis(benzenecarboxamide)-1,2-diphenylethane (4). Benzoyl chloride (274 µL, 2.36 mmol) was added dropwise to a solution of (*S,S*)-1,2-diamino-1,2-diphenylethane (200 mg, 0.94 mmol) and triethylamine (328 µL, 2.36 mmol) in 20 mL CH_2Cl_2. The reaction mixture was stirred at ambient temperature for 16 h and the resulting precipitate was filtered and washed with EtOH. The crude product was recrystallized from EtOH to yield 284 mg (72%) of **4** as white fluffy crystals. m.p. > 270 °C. $[\alpha]_D^{20}$ -105 (*c* 0.5, DMSO). ^1H NMR (DMSO-d_6) δ 5.68 (AA'part of AA'XX', 2H, CH), 7.14 (t, 2H, *J* = 7.3 Hz, 4'-phenyl), 7.24 (t, 4H, *J* = 7.3 Hz, 3'- and 5'-phenyl), 7.38 (d, 4H, *J* = 7.3 Hz, 2'-and 6'-phenyl), 7.45 (t, 4H, *J* = 7.2 Hz, 3- and 5-phenyl),7.51 (t, 2H, *J* = 7.2 Hz, 4-phenyl), 7.72 (d, 4H, *J* = 7.2 Hz, 2- and 6-phenyl), 9.05 (XX'part of AA'XX', 2H, NH); ^{13}C NMR (DMSO-d_6) δ 57.2, 126.7, 127.1, 127.2, 127.8, 128.1, 131.1, 134.7, 140.6, 166.3. Anal. Calcd. for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 80.05; H, 5.54; N, 6.60.

(4*S*,5*S*)-2,7-Dioxo-4,5-diphenyl-1,8,9,10,11,12,14,15,16,17,18,19-dodecadehydro-13-ethyl-13-methoxy-3,6,18,19-tetraazatetracyclo[12.3.1.1^{8,12}]nonadecane (8). To a solution of triethylamine (440 µL 3.16 mmol) in 250 mL CH_2Cl_2 was added simultaneously, over a period of 3 h, (*S,S*)-1,2-diamino-1,2-diphenylethane (335 mg, 1.58 mmol) and 1,1-bis[6-(chloroformyl)-2-pyridyl]-1-methoxypropane (558 mg, 1.58 mmol) in 40 mL CH_2Cl_2 respectively. The reaction mixture was stirred at ambient temperature for an additional 16 h, after which time half of the amount of solvent was evaporated and the remaining solution was washed with H_2O (3 x 100 mL) and dried ($MgSO_4$). The crude product was dissolved in CH_2Cl_2 (15 mL) and purified by acidic extraction with 4M HCl (aq, 3 x 15 mL). The acidic water phase was treated with K_2CO_3 (s) and extracted with CH_2Cl_2 (3 x 30 mL) and dried ($MgSO_4$), to yield 63 mg (8%) of **8** as white crystals. m.p. 150 °C. $[\alpha]_D^{20}$ -195 (*c* 0.4, $CHCl_3$). ^{1}H NMR δ 0.70 (t, 3H, *J* = 7.4 Hz, CH_3), 2.26 (qd, 1H, *J* = 14.8 and 7.4 Hz, CH_2), 2.45 (qd, 1H, *J* = 14.8 and 7.4 Hz, CH_2), 3.45 (s, 3H, CH_3), 5.47 (dd, 1H, *J* = 8.7 and 2.8 Hz, CH), 5.72 (dd, 1H, *J* = 10.7 and 2.8 Hz, CH), 7.19-7.28 (m, 3H, phenyl), 7.31 (t, 1H, *J* = 7.3 Hz, 4´-phenyl), 7.38 (t, 2H, *J* = 7.3 Hz, 3´- and 5´-phenyl), 7.45 (d, 2H, *J* = 7.3 Hz, 2´- and 6´-phenyl), 7.80 (dd, 1H, *J* = 7.8 and 1.0 Hz, 3´- or 5´-pyridyl), 7.85-7.93 (m, 3H, pyridyl), 7.92 (t partly hidden, 1H, *J* = 7.8 Hz, 4´-pyridyl), 8.03 (dd, 1H, *J* = 7.8 and 1.0 Hz, 3´- or 5´-pyridyl), 9.43 (br d, 1H, *J* = 10.7 Hz, NH), 9.45 (br d, 1H, *J* = 8.7 Hz, NH); ^{13}C NMR δ 7.8, 35.0, 52.9, 58.7, 58.9, 86.0, 119.6, 120.4, 123.8, 124.2, 126.38 (2C), 126.44 (2C), 127.6, 127.8, 128.6 (2C), 129.0 (2C), 138.0, 138.3, 141.0, 141.4, 149.1, 149.2, 159.2, 159.8, 164.2, 164.6. Anal. Calcd. for $C_{30}H_{28}N_4O_3 \cdot H_2O$: C, 70.57; H, 5.92; N, 10.97. Found: C, 70.62; H, 5.40; N, 10.49.

1,1-Bis[[6-(*N*-(*S*)-1-phenylethyl)carboxamido]-2-pyridyl]-1-methoxypropane (9). To a solution of (*S*)-1-phenethylamine (308 µL, 2.38 mmol) and triethylamine (333 µL, 2.38 mmol) in 170 mL CH_2Cl_2 was added dropwise 1,1-bis[6-(chloroformyl)-2-pyridyl)-1-methoxypropane (422 mg, 1.08 mmol) in 50 mL CH_2Cl_2. After an additional 30 min of stirring half of the amount of solvent was evaporated and the remaining solution was washed with H_2O (3x50 mL) and dried ($MgSO_4$). The crude product was chromatographed with EtOAc as eluent, to yield 339 mg (56%) of **9** as a pale yellow oil. $[\alpha]_D^{20}$ +87 (*c* 0.5, $CHCl_3$). ^{1}H NMR δ 0.76 (t, 3H, *J* = 7.4 Hz, CH_3), 1.44 (d, 3H, *J* = 6.9 Hz, CH-C*H*$_3$), 1.55 (d, 3H, *J* = 6.9 Hz, C´H-C*H*$_3$), 2.64 (qd, 1H, *J* = 14.8 and 7.4 Hz, CH_2), 2.68 (qd, 1H, *J* = 14.8 and 7.4 Hz, CH_2), 3.18 (s, 3H, CH_3), 5.20 (qd, 1H, *J* = 8.2 and 6.9 Hz, CH), 5.22 (qd, 1H, *J* = 8.5 and 6.9 Hz, C´H), 7.16-7.33 (m, 10H, phenyl), 7.62 (dd, 1H, *J* = 7.8 and 1.1 Hz, 5-pyridyl), 7.75 (dd, 1H, *J* = 7.8 and 1.2 Hz, 5´-pyridyl), 7.77 (t, 1H, *J* = 7.8 Hz, 4-pyridyl), 7.82 (t, 1H, *J* = 7.8 Hz, 4´-pyridyl), 8.03 (dd, 1H, *J* = 7.8 and 1.2 Hz, 3´-pyridyl), 8.05 (dd, 1H, *J* = 7.8 and 1.1 Hz, 3-pyridyl), 8.09 (d, 1H, *J* = 8.5 Hz, C´H-N*H*), 8.16 (d, 1H, *J* = 8.2 Hz, CH-N*H*); ^{13}C NMR δ 7.1, 22.4, 22.8, 25.5, 48.6, 48.8, 50.9, 85.6, 120.4, 120.6, 124.5, 124.8, 125.7 (2C), 125.9 (2C), 127.3, 127.4, 128.7 (2C), 128.8 (2C), 137.7 (2C), 143.2, 143.4, 148.4, 148.5, 161.6, 161.7, 163.3, 163.4.

Catalytic reactions: General procedure for catalytic ring opening of cyclohexene oxide.

Method A. To a dried flask containing 0.1 eq of ligand was added CH_2Cl_2 (3 mL) and 0.1 eq of the appropriate metal alkoxide. After 1 h, cyclohexene oxide (1 eq) and trimethylsilyl azide (1.05 eq) were added. The reaction mixture was stirred at ambient temperature for 4 - 21 d and monitored with TLC (EtOAc : Hexane 1 : 1). The workup was made by chromatography (hexane : EtOAc 92 : 8) and the enantiomeric excess was determined by GLC analysis.

Method B. Ligand **1** (0.1 eq) was dissolved in THF, cooled to -78 °C and *t*-butyllithium (0.2 eq) was added. $Zr(OBu^t)_4$ (0.1 eq) was added after 25 min, and 15 min later the cooling bath was removed. The reaction mixture was stirred at ambient temperature for 15 h after which time the solvent was evaporated. The crude white crystalline product was dissolved in CH_2Cl_2 (3 mL) and used immediately in the catalytic reaction using the procedure described above.

Method C. Ligand **1** (0.1 eq) was dissolved in toluene (5 mL) and the metal alkoxide (0.1 eq) was added. The solution was refluxed for 1 h and then the solvent was evaporated at atmospheric pressure to yield a pale yellow crystallinic product. This was dissolved in CH_2Cl_2 or toluene (3 mL) and used immediately according to the procedure described in method A.

With secondary amines. Ligand 1 (0.1 eq) was dissolved in CH_2Cl_2 (3 mL), 0.01 eq of the secondary amine, 0.1 eq of the metal alkoxide and 1.05 eq of trimethylsilyl azide were added. The mixture was stirred for

24 h and cyclohexene oxide (1 eq) was added. The reaction was stirred at ambient temperature and monitored by TLC. The workup is described under method A.

Spectroscopic studies. General procedure. The stoichiometric reactions monitored with NMR spectroscopy were performed under an atmosphere of dry argon, using NMR sample tubes equipped with rubber septa. Ligand 1 (1 eq) was dissolved in 1 mL $CDCl_3$ and $Zr(OBu^t)_4$ (1 eq) was added. A ^1H NMR spectrum was recorded and directly thereafter, diethylamine (0.1 eq) was added. Trimethylsilyl azide (2 eq) was added after 27 h and cyclohexene oxide (2 eq) after an additionally 72 h. Spectra were recorded at intervals of approximatively 24 h. After 6 days an additional 2 eq of trimethylsilyl azide was added. When the reaction was completed the solution was chromatographed using the procedure described for the catalytic experiments above, and the enantioselectivity was measured.

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