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Synthesis of Yb Complexes with Amino-Acid-Armed Ligands for Direct Asymmetric Tandem Aldol Reduction Reactions

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A synthetic route to a series of C_2-symmetric chiral ligands armed with selectively protected amino acids have been developed with the aim to study the potential of the corresponding Yb(III) complexes for enantioselective direct aldol reactions. These ligands, which contain chiral bis(ester) or bis(amide) moieties, were readily prepared in enantiomerically pure form by the reaction of (*S*,*S*)-hydrobenzoin or (*S*,*S*)-diphenylethylenediamine with various chiral amino acids. In this article, the asymmetric aldol-reduction reaction leading to 1,3-diols (known as the aldol–Tishchenko reaction) has been performed with an elaborated family of ligands. This unique tandem reaction was catalysed by chiral Yb complexes that promote both the aldol reaction of unactivated carbonyl compounds and the Evans–Tishchenko reduction of the aldol intermediates. 1,3-*anti*-Diols with three stereogenic centers have been isolated as a result of the condensation of aliphatic ketones with aromatic aldehydes with up to 64 % *ee*. Additional detailed investigations of the nature of the binding of both class of ligands have also been carried out with high-resolution ^{1}H-, ^{13}C-, and ^{14}N-NMR techniques.

Introduction

Lewis acid-catalyzed reactions are of great interest because of their unique reactivities and selectivities and mild reaction conditions used.[1] In particular, Lewis acids having chiral ligands are becoming more important as catalysts for selective and asymmetric organic transformations. The influence of ligands coordinated to Lewis acid-type catalysts on the rate and particularly the enantioselectivity of organic reactions is one of the most extensively studied topics in modern organic chemistry. Among the many Lewis acids developed so far, lanthanide triflates have received growing attention because of the combination of their strong Lewis acidity with their mildness and usually high selectivity.[2] The use of chiral lanthanide complexes as new catalysts in asymmetric synthesis is currently of intense interest,[3] but knowledge about their interaction with chiral ligands remains narrow, and the number of tested structures is still restricted.[4]

Despite the vast current interest in the biological aspects of lanthanide coordination chemistry, relatively few investigations have been carried out with amino acid derivatives as ligands. Considering the natural abundance of α-amino acids, it is somewhat surprising that their use as ligands in Lewis-acid catalysis remains largely unexplored.[5]

One of the promising fields of application of such amino acid-lanthanide complexes is the direct asymmetric aldol reaction. The aldol condensation is a key C–C bond-forming reaction, creating the β-hydroxy carbonyl structural unit found in many natural products and drugs.[6] From the several methods available for the asymmetric aldol reaction,[7] the direct condensation of an aldehyde with a ketone is a most attractive approach since it does not require the isolation of preformed enolates.[8] In particular, heterodimetallic complexes have been found to be suitable catalysts for the direct asymmetric aldol reaction.[9] These catalysts can be regarded as enzyme mimics of metal-containing, type-II aldolases which, in turn, are built essentially from amino acid-type elements. In this light, it is surprising that, despite the increasing acceptance of chiral lanthanide complexes as direct aldol reaction catalysts,[10] the application of modified amino acids as chiral ligands is limited mainly to zinc complexes.[11] One example of a chiral lanthanide complex application is the direct, asymmetric, aldol–Tishchenko reaction promoted by chiral Yb complexes.[12]

Our success in this field was the discovery of a selective catalyst for the asymmetric aldol–Tishchenko reaction of aliphatic ketones with aldehydes.[13] In this unique, one-step, tandem process, aldehydes reacted with methylene ketones to give 1,3-diols with three adjacent stereogenic centers (Scheme 1).[14] Despite the enormous synthetic potential of the aldol–Tishchenko reaction of unmodified ketones with aldehydes leading directly to an important class of 1,3-diols, its enantioselective variant needs further exploration. Interestingly, in all the known procedures of coupling unmodified ketones and aldehydes, only chiral lanthanide complexes were used with any success.[15] From

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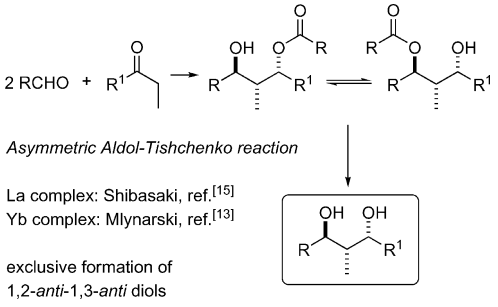
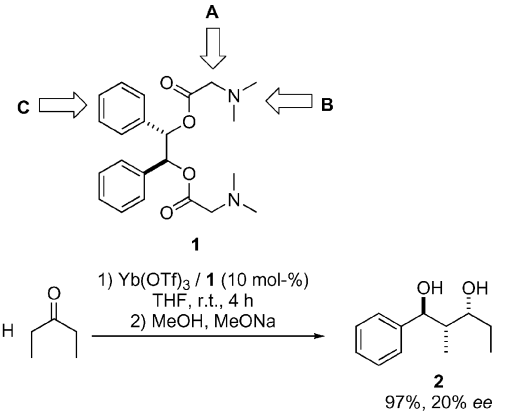
a practical perspective, however, there remains much room for improvement in the available methodology. Some limitations are still encountered including high catalyst loading (15–20%), difficulties in obtaining high enantioselectivity, and the substrate scope being limited to activated aromatic aldehydes. Therefore, a new catalyst for the asymmetric aldol–Tishchenko reaction is needed especially in terms of improved catalyst efficiency. Despite the creative efforts described above, the design and synthesis of new catalysts remains a considerable challenge. Herein, we report the synthesis and application of new Yb-based catalysts, armed with chiral amino acids, to enantioselective direct aldol reactions leading directly to 1,3-diols.



Scheme 1. Condensation of ketones with aldehydes by means of a catalytic aldol–Tishchenko reaction.

Results and Discussion

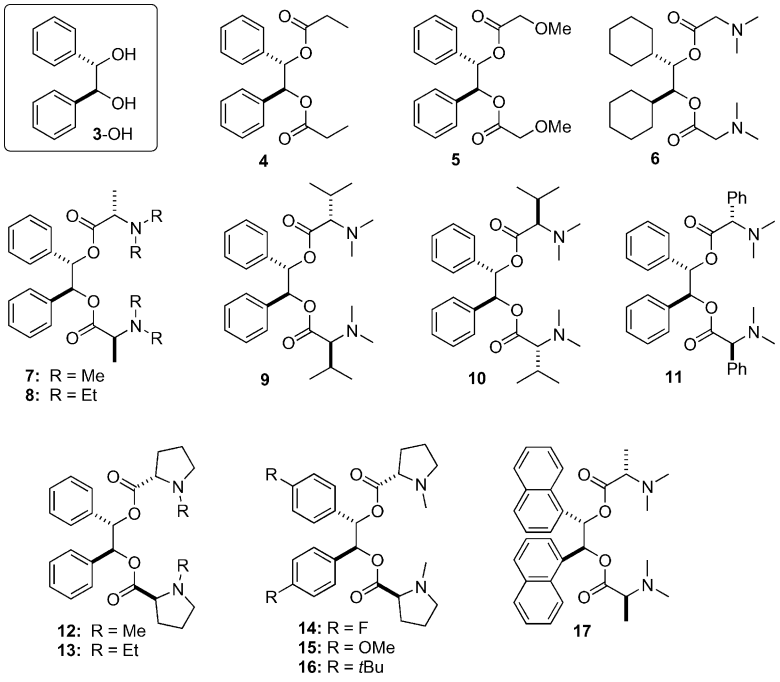
Previously, we reported our initial attempt at the asymmetric aldol–Tishchenko reaction with a glycine-based chiral ligand complexed with Yb salts, by which the direct asymmetric aldol reaction of 3-pentanone was efficiently



Scheme 2. Asymmetric aldol–Tishchenko reaction promoted by the ligand **1**–Yb complex.

accomplished.[12] In our preliminary experiments, we could not achieve satisfactory enantioselectivity (20% *ee*, Scheme 2). This finding motivated us to further tune the catalyst and investigate the possible catalytic efficiency of a more complex ligand composed of selectively blocked chiral amino acids. We speculated that substitution of the amino-acid arm at the C-2 position (Scheme 2, arrow A) would lead to more enantioselective Yb catalysts on the basis of an interaction with an additional stereogenic center in the catalyst. Additionally, we modified the protecting groups on the amino groups (Scheme 2, arrow B) and tested how changes within the aromatic backbone influenced the reactivity and enantioselectivity of the resulting Yb complex (Scheme 2, arrow C).

To realize this concept, we prepared a series of ligands based on the chiral (*S*,*S*)-hydrobenzoin backbone (**3**-OH,



Scheme 3. Chiral ligands derived from (*S*,*S*)-hydrobenzoin.

Scheme 3). To this backbone were added side arms composed of alkyl groups (**4**–**5**) or amino acids with dialkylamino groups at the termini. To provide a better understanding of the requirements for catalyst reactivity, we prepared both types of ligands. Ligands **4**–**17** were efficiently prepared by the DIC-promoted esterification of chiral (*S*,*S*)-hydrobenzoin. In addition, the analogous 1,2-dicyclohexylethanediol derivative **6** was also prepared for comparison with the hydrobenzoin derivatives.[16] *para*-Substituted hydrobenzoins were prepared with the Sharpless hydroxylation protocol.[17] All di-*N*-ethyl- and -methyl-protected amino acids (glycine, alanine, phenylalanine, valine, and proline) were prepared under standard conditions.[18]

With a diverse range of ligands in hand, we then examined each of them in the direct, asymmetric, aldol–Tishchenko reaction. The results of the catalytic reaction of benzaldehyde with 3-pentanone in THF with a catalyst composed of $Yb(OTf)_3$ and the prepared ligands (1:1, 20 mol-%) are collected in Table 1.

Table 1. Asymmetric aldol–Tishchenko reaction of benzaldehyde and 3-pentanone, promoted by Yb complexes with the ligands depicted in Scheme 3.

Entry	Ligand	% Yield[a]	% *ee*
1	**4**	n.d.	–
2	**5**	n.d.	–
3	**6**	15	5
4	**7**	95	40 (1*S*,2*S*,3*R*)[b]
5	**8**	68	0
6	**9**	98	0
7	**10**	97	0
8	**11**	70	9
9	**12**	98	40
10	**13**	66	0
11	**14**	55	23
12	**15**	35	14
13	**16**	13	27
14	**17**	92	30

[a] Yield of isolated diol **2**. [b] The absolute configuration was determined by HPLC and CD techniques.[13c]

The ligands without a tertiary amine group were inferior in this application (Table 1, Entries 1 and 2). Therefore, it appears that the presence of a basic coordination site in the ligand is essential for catalyst reactivity. The ligand derived from glycine and 1,2-dicyclohexyloethanediol led to a small increase in reactivity and enantioselectivity and afforded diol **2** in 5% *ee* only. Thus, the aromatic substituents in the catalyst backbone were indispensable for reactivity. The most promising levels of enantioselectivity (40% *ee*) and yield were obtained with ligands composed of dimethylalanine (**7**, Table 1, Entry 4) and methylproline (**12**, Table 1, Entry 9). For both ligands, diols with a (1*S*,2*S*,3*R*) configuration predominated. The level of asymmetric induction was similar to that observed with ligands lacking stereogenic centers in the amino-acid arms.

Unfortunately, the further modification of the ligand structures at the α position in the amino-acid arms was not productive. The application of amino acids with bulkier substituents like valine (**9** and **10**) and phenylalanine (**11**) was not promising. Surprisingly, tuning at the nitrogen termini turned out even more troublesome. Ligands **8** and **13**, having ethyl groups, were unselective, affording racemic diol **2** (Table 1, Entries 5 and 10).

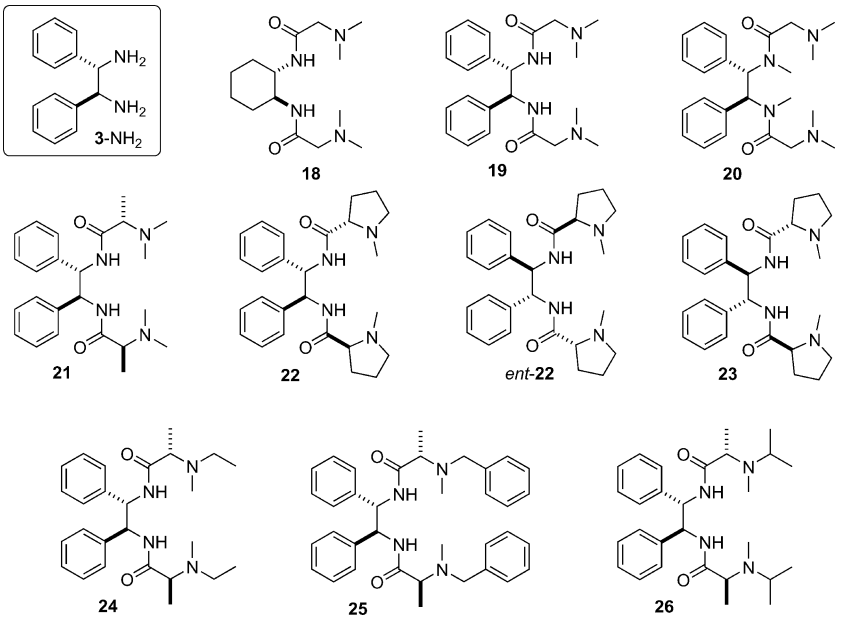
We speculated that *para* substitution of the backbone phenyl rings could change the catalyst reactivity and selectivity by altering the complexation properties of the benzylic oxygens. Unfortunately, attaching electron-donating or electron-withdrawing substituents at the *para* positions of ligands **14**–**16** yielded moderate enantioselectivities but lowered the reactivities of the catalysts. The application of ligand **17**, having naphthyl groups, was also not promising (Table 1, Entry 17).

To improve the enantioselectivity in the tandem aldol reaction and provide a better understanding of the requirements for a good asymmetric induction, we changed ligand structure to tune the character of the binding atoms around the catalytic center. Our means of limiting the number of available transition states in the enantiodetermining step was to restrict the number of degrees of freedom in the metal–ligand complex. One degree of freedom results from rotation about the carbon–oxygen bond in the esters. This may be rigidified by going to the analogous amide linkage. Moreover, in the development of Yb-containing catalysts, the use of *N*,*N*-donor ligands seemed attractive, as they would allow for the systematic tuning of both steric and electronic properties. In order to realize this concept, we prepared amide ligands **18**–**26** from the corresponding, readily available, enantiomerically pure diamine **3**-NH_2[19] (Scheme 4).

Optically pure 1,2-diaminocyclohexane and diphenylethylenediamine were acylated with the appropriately protected amino acids using DIC to give the corresponding chiral ligands. (1*S*,2*S*)-N^1,N^2-Dimethyl-1,2-diphenylethane-1,2-diamine, the substrate for ligand **20**, was prepared according to literature procedure.[20] *N*-Ethyl-, *N*-benzyl-, and *N*-isopropyl-*N*-methyl alanine were also prepared by known protocols.[21] Table 2 summarize the application of these ligands to the reaction of Scheme 2.

As we observed for the ester-type ligands, aromatic substituents in the ligand backbone were essential for catalyst reactivity. Diaminocyclohexane derivative **18** was not suitable as a ligand. The amide-based catalyst with glycine side arms led to increased enantioselectivity (30% *ee*, Table 2 Entry 2 vs. 20% *ee*, Scheme 2), albeit at the expense of the yield. Additional *N*-methyl groups in the ligand backbone adversely affected the catalyst reactivity (Table 2, Entry 3). Further improvements in the selectivity were achieved for the chiral amino acids. Alanine-based ligand **21** afforded the product with a 30% *ee*, while the *N*-methyl-proline-based ligand **22** resulted in a 50% *ee*. To study the catalytic effect of inverting stereocenters in the ligand, we prepared ligand **23** from the (*R*,*R*)-amine, but the resulting ligand was unreactive. This indicates that the diastereomeric catalyst **22** with matched configurations (*R*,*R*) between the backbone and side-arm stereocenters was better than catalyst **23** with a mismatched configuration (*R*,*S*).

Additionally, various ligands with two different alkyl groups attached to the *N* termini were tested. Although the



Scheme 4. Amine-derived chiral ligands.

Table 2. Asymmetric aldol–Tishchenko reaction of benzaldehyde and 3-pentanone promoted by Yb complexes with the ligands depicted in Scheme 4.

Entry	Ligand	% Yield[a]	% *ee*
1	**18**	23	0
2	**19**	42	30
3	**20**	n.d.	–
4	**21**	46	40
5	**22**	51	50 (1*S*,2*S*,3*R*)
6	*ent*-**22**	50	48 (1*R*,2*R*,3*S*)
7	**23**	n.d.	–
8	**24**	91	46
9	**25**	95	10
10	**26**	55	10

[a] Yield of isolated diol **2**.

N-ethyl-*N*-methyl combination did not alter the enantioselectivity significantly, the yield was much better than that observed for the other amide-type ligands (Table 2, Entry 8). For this ligand, as little as 5 mol-% of the catalyst was sufficient to produce a high yield. Replacing the ethyl group with a benzyl or isopropyl group resulted in the loss of enantioselectivity (Table 2, Entries 9 and 10).

In all cases, THF was the solvent of choice. Changing the reaction medium to more or less polar or coordinating solvents decreased the reactivity. In general, the reaction was not temperature-dependent. Decreasing the reaction temperature to 0 °C affected only the yield, since a reaction at 40 °C was much faster. In both cases, the selectivity was unchanged. Other metal sources tested in this reaction with ligand **22** gave either less satisfactory results [$Sc(OTf)_3$, $Er(OTf)_3$, and $Eu(OTf)_3$] or failed to react altogether [$Pr(OTf)_3$, $La(OTf)_3$, $Yb(O\text{-}iPr)_3$, and $YbCl_3$].

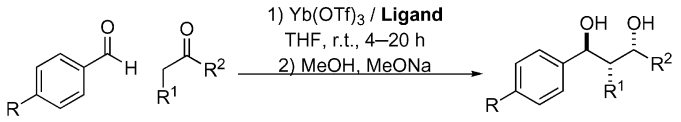
The combination of $Yb(OTf)_3$ with the best ligands **12**, **22**, and **24** was subsequently employed in the tandem aldol-reduction reactions of various ketones and aldehydes (Table 3). For several substrates, a higher catalyst loading was necessary to obtain higher yields. All the aromatic aldehydes tested gave useful product yields. In addition to benzaldehyde, other aromatic substrates reacted effectively to give diols in good yields with high *anti* selectivities. A less electrophilic anisaldehyde delivered diols in slightly lower yields but with higher enantiocontrol of 64% *ee* (Table 3, Entries 11–13). A number of aliphatic (**K1**–**K3**) and aromatic (**K4**–**K6**) ketones can be used as a donors without a loss of efficiency or enantiocontrol. Moreover, the catalysts exhibited similar efficiencies without considerable deterioration of enantiocontrol for more demanding substrates (dibutyl- and dipropylketone).

To shed light on the possible structure of the catalysts and the catalytic action of species formed in situ, we gained insight into the NMR spectra of Yb complexes with representative examples of both classes of tested ligands. We first examined the ^1H and ^{13}C NMR spectra of a complex of glycine-based (bis)ester **1** and $Yb(OTf)_3$ in a 1:1 mole ratio. To maintain the reaction conditions, all spectra were recorded in [D_8]THF.

The ^1H and ^{13}C NMR spectra of this catalyst show unequivocal downfield shifts of all the signals (Figure 1). The most interesting shift was that of the methylene signals at δ = 3.18 ppm. These diastereotopic protons generated separate NMR signals in an AB pattern at 4.15 and 4.61 ppm (Figure 1).

Such a change must have resulted from a restrained rotation in the amino-acid arms. This observation and the C_2 symmetry of the complex, deduced from the NMR spectra, suggest coordination of the Yb to both nitrogens. To support this speculation, we also recorded the ^{14}N spectrum of the complex. The results of this experiment confirmed the complexation of the Yb cation to the tertiary amines. In the measured complex, the nitrogens were shifted downfield by

Table 3. Asymmetric reaction of aldehydes with ketones, catalyzed by Yb(III) triflate and ligands **12**, **22** and **24**.



Entry	Ketone	Aldehyde R	Product	Ligand	Catalyst loading [mol-%]	Yield[a] [%]	*e.r.*
1	**K1**	H	**27**	**12**	20	98	70:30
2	**K1**	H	**27**	**22**	20	48	75:25
3	**K1**	H	**27**	**22**	30	97	75:25
4	**K1**	H	**27**	**24**	10	54 (72)[b]	73:27
5	**K1**	H	**27**	**24**	20	92	73:27
6	**K2**	H	**28**	**24**	20	74	78:22
7	**K3**	H	**29**	**24**	20	95	77:23
8	**K1**	CH_3	**30**	**22**	40	98	78:22
9	**K2**	CH_3	**31**	**22**	40	69	78:22
10	**K3**	CH_3	**32**	**24**	30	54	76:24
11	**K1**	OCH_3	**33**	**22**	20	26	87:23
12	**K1**	OCH_3	**33**	**22**	30	75	87:23
13	**K1**	OCH_3	**33**	**22**	40	98	87:23
14	**K2**	OCH_3	**34**	**22**	40	44	75:25
15	**K1**	Br	**35**	**24**	20	84	65:35
16	**K1**	$C(CH_3)_3$	**36**	**22**	40	96	78:22
17	**K4**	H	**37**	**24**	20	79	75:25
18	**K5**	H	**38**	**24**	20	87	69:31
19	**K6**	H	**39**	**24**	20	44	77:23
20	**K4**	OCH_3	**40**	**24**	20	53	68:32

[a] Yield of isolated diol **2**. [b] The yield in parentheses was obtained at 40 °C.

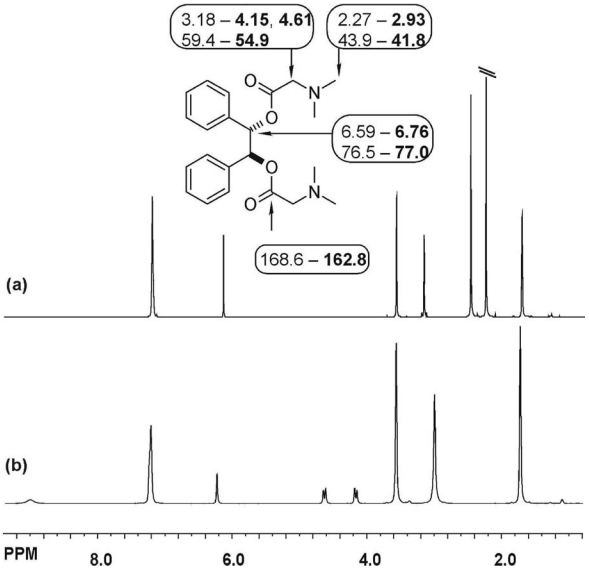


Figure 1. ^{1}H NMR spectra of ligand **1** (a) and the **1**–Yb(OTf)$_3$ (1:1) complex (b) in [D$_8$]THF. The scheme illustrates the NMR chemical shifts of ligand **1** and Yb complex (bold).

about 20 ppm relative to **1** (–344.2 and –364.3 ppm, respectively, Figure 2). This rather unexpected change in the chemical shifts of the N–metal complex vs. the free amino group was further investigated with a model experiment, in which the same rule was observed for the Yb complex of triethylamine. In the ^{14}N NMR, the nitrogen of the Yb(OTf)$_3$–Et$_3$N complex (1:1) was shifted downfield relative to that of triethylamine (Figure 2).

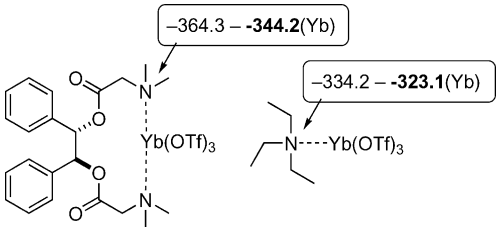


Figure 2. ^{14}N NMR chemical shifts of measured Yb complexes.

We made further deductions of the complex architecture based on the ^{1}H NMR spectra of **1** and Yb(OTf)$_3$ in various stoichiometric ratios. The chemical shift of the methylene protons changed when 0.5 equiv. of Yb(OTf)$_3$ was added to ligand **1** (Figure 3), indicating the formation of complexed chemical species among the uncomplexed ligand when less than 1.0 equiv. of Yb salt was added. Saturation was observed when 1.0 equiv. of Yb(OTf)$_3$ was added, indicating a 1:1 stoichiometric complexation of metal salt to ligand.

The ^{1}H NMR spectra of a complex composed of the structurally related amide ligand **19** showed similar features to those observed for the ester-based complex. In the ti-

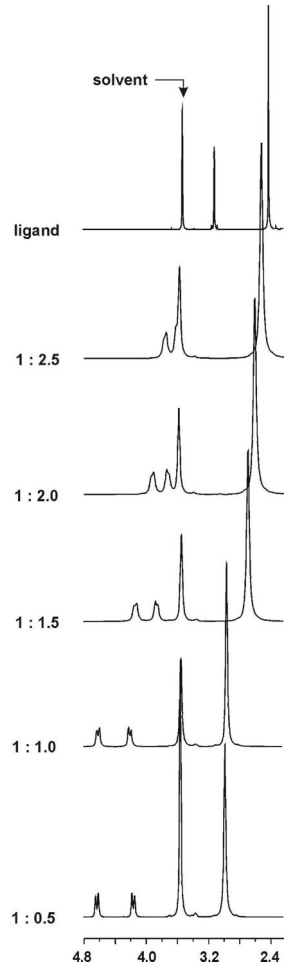


Figure 3. ^{1}H NMR titration of **1** with Yb(OTf)$_3$ in [D$_8$]THF (methylene region) at 25 °C.

tration experiment, saturation was observed for a 1:1 stoichiometric complexation of metal salt to ligand **19**. As a result of complexation, both diastereotopic methylene protons showed different chemical shifts, and the groups became magnetically non equivalent. This observation required a lower temperature NMR experiment (Figure 4). At $T > -10$ °C, the *N*-methyl signals coalesced, which was evidence for the fast inversion of the *N*-methyl nitrogen on the NMR time scale. Interestingly, this inversion was slower at around 0 °C.

The chemical shift of the NH proton changed upon complexation with the Yb salt from 7.89 ppm to 8.58 ppm but was still observed in the amide region. This suggested a nitrogen–Yb complexation with the hydrogen still attached to nitrogen. Such a complexation, although highly debatable, was previously postulated for Yb(III) triflate based on NMR and MS experiments.[22] Thus, based on our observations of similar reactivity of the ester- and amide-type ligands, the structures of the catalysts were tentatively assumed as shown in Figure 5. In both cases, the complexation of four heteroatoms is possible and is postulated based on NMR experiments (Figure 5, structure A). For the amide ligand, additional hydrogen bonding between the

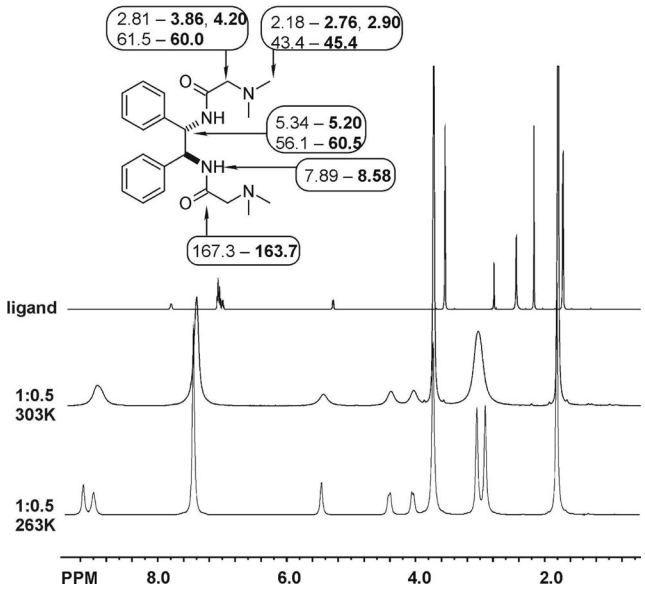


Figure 4. ^{1}H NMR spectra of complex **19**–Yb(OTf)$_3$ (1:1) in [D$_8$]-THF measured at 303 K and 263 K, compared with the spectrum of ligand **19**. The scheme illustrates the NMR chemical shifts of ligand **19** and its Yb complex (bold).

amide proton and the lateral amino groups can also be assumed, as shown in structure **B** in Figure 5. Unfortunately, suitable crystals of the complex could not be obtained for X-ray analysis.

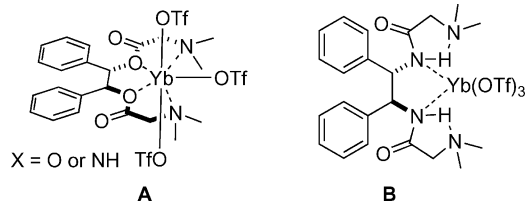


Figure 5. A plausible catalyst structure.

Conclusions

In conclusion, we have presented careful insight into a new class of Yb complexes with chiral bis(ester) and (bis)-amide ligands for a tandem asymmetric aldol reaction. A modular design of the catalyst is possible by varying the starting chiral backbone and amino-acid parts of the ligands. The most reactive ligand for this reaction was readily prepared (in two steps) from commercially available starting materials, and it can be obtained in both enantiomeric forms. Catalyst Yb^{III}-**24** was the most active for aliphatic ketone donors. Current studies are directed at further improving the enantioselectivity of the reactions and the practical application of the asymmetric aldol–Tischenko methodology to the synthesis more complex molecules.

Experimental Section

General: All reactions involving organometallic or other moisture-sensitive reagents were carried out under argon with standard vac-

uum line techniques and glassware that was flame dried and cooled under Ar before use. Solvents were dried according to standard procedures. All organic solutions were dried with Na_2SO_4. Thin-layer chromatography was performed with aluminum plates coated with 60 F_{254} silica (Merck). Plates were visualized with UV light (254 nm) and ethanolic phosphomolybdic acid solution or ethanolic ninhydrin solution followed by heating. Reaction products were purified by flash chromatography with silica gel 60 (240–400 mesh, Merck). Optical rotations were measured with a JASCO Dip-360 Digital Polarimeter at room temperature. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and in concentrations of grams per 100 mL. ^{1}H NMR spectra were recorded with a Varian-200, Varian-400, or Bruker-500 spectrometer in [D$_8$]THF or $CDCl_3$ with Me_4Si as an internal standard. High-resolution mass spectra were recorded with a Mariner PerSeptive Biosystems mass spectrometer with a time-of-flight (TOF) detector. IR spectra were recorded with a Perkin–Elmer FT-IR-1600 spectrophotometer as either a thin film on NaCl plates (film), as a KBr disc (KBr), or as chloroform solutions in 0.1 mm cells ($CHCl_3$), as stated.

General Procedure for the Preparation of Ester Ligands 4–17: A mixture of (1*S*,2*S*)-1,2-diarylethane-1,2-diol [for (*S*,*S*)-hydrobenzoin: 107 mg, 0.5 mmol, FLUKA], *N*,*N*-dimethylamino acid (2 mmol), 1,3-dicyclohexylcarbodiimide (412 mg, 2 mmol), and DMAP (6 mg, 0.05 mmol) in dry DCM (5 mL) was stirred magnetically under argon for 24 h. The precipitate was removed by filtration, and the residue was washed with DCM (5 mL). The solvent was evaporated, and the residue was purified by flash column chromatography to afford esters **4**–**17**.

(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl Dipropionate (4): Yield 160 mg, 98%. $[\alpha]_D^{20}$ = +21.5 (*c* = 1.03 in $CHCl_3$); R_f = 0.60 (Hex/AcOEt, 4:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.12 (t, *J* = 7.4 Hz, 6 H), 2.36 (q, *J* = 7.4 Hz, 4 H), 6.07 (s, 2 H), 7.10–7.25 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 9.1, 27.8, 77.0, 127.5, 128.1, 128.3, 136.3, 173.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3033, 2982, 2947, 1724, 1280, 1212, 1067, 1009, 701, 550 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{22}O_4$, $[M + Na]^+$ 349.1410; found 349.1398.

(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl Bis(2-methoxyacetate) (5): Yield 173 mg, 97%. $[\alpha]_D^{20}$ = +30.1 (*c* = 1.04 in $CHCl_3$); R_f = 0.60 (Hex/AcOEt, 1:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.40 (s, 6 H), 4.04 (s, 4 H), 6.18 (s, 2 H), 7.05–7.25 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 59.4, 69.7, 77.3, 127.5, 128.3, 128.6, 135.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2992, 2937, 2823, 1755, 1193, 1176, 1126, 778, 702, 594 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{22}O_6$ $[M + Na]^+$ 381.1309; found 381.1326.

(1*S*,2*S*)-1,2-Dicyclohexylethane-1,2-diyl Bis[2-(dimethylamino)acetate] (6): From (1*S*,2*S*)-1,2-dicyclohexyl-1,2-ethanediol.[16] Yield 149 mg, 75%. $[\alpha]_D^{20}$ = –18.3 (*c* = 0.52 in $CHCl_3$); R_f = 0.30 (AcOEt/MeOH, 9:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.80–1.70 (m, 22 H), 2.37 (s, 12 H), 3.22 (s, 4 H), 5.04 (d, *J* = 6.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 25.8, 26.1, 28.3, 29.1, 29.6, 38.4, 45.1, 59.9, 75.6, 170.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2924, 2852, 2817, 1751, 1450, 1187, 1158, 1058, 984, 854 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{41}N_2O_4$ $[M + H]^+$ 397.3061; found 397.3072.

(2*S*,2′*S*)-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl] Bis[2-(dimethylamino)propanoate] (7): Yield 166 mg, 86%. $[\alpha]_D^{20}$ = +6.5 (*c* = 1.02 in $CHCl_3$); R_f = 0.25 (DCM/MeOH, 95:5). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.24 (d, *J* = 7.2 Hz, 6 H), 2.25 (s, 12 H), 3.30 (q, *J* = 7.2 Hz, 2 H), 6.13 (s, 2 H), 7.05–7.30 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 15.3, 41.4, 62.5, 77.1, 127.4, 128.1, 128.3, 136.2, 172.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2979, 2937, 2834, 1730, 1456, 1173, 1149, 1109, 698, 598 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{32}N_2O_4$ $[M + Na]^+$ 435.2254; found 435.2237.

(2*S*,2′*S*)-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl] Bis[2-(diethylamino)-propanoate] (8): Yield 176 mg, 75%. $[\alpha]_D^{20}$ = –15.0 (*c* = 0.53 in $CHCl_3$); R_f = 0.50 (Hex/AcOEt, 1:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.99 (t, *J* = 7.0 Hz, 12 H), 1.24 (d, *J* = 7.2 Hz, 6 H), 2.30–2.70 (m, 8 H), 3.58 (q, *J* = 7.2 Hz, 2 H), 6.09 (s, 2 H), 7.00–7.20 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.1, 15.3, 44.4, 58.0, 77.1, 127.4, 128.0, 128.2, 136.3, 172.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2971, 2935, 1736, 1454, 1375, 1199, 1154, 1106, 1077, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{41}N_2O_4$ $[M + H]^+$ 469.3061; found 469.3081.

(2*S*,2′*S*)-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl] Bis[2-(dimethylamino)-3-methylbutanoate] (9): Yield 164 mg, 70%. $[\alpha]_D^{20}$ = +14.9 (*c* = 0.52 in $CHCl_3$); R_f = 0.50 (Hex/AcOEt, 7:3). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.77 (d, *J* = 6.4 Hz, 6 H), 0.94 (d, *J* = 6.6 Hz, 6 H), 1.80–2.10 (m, 2 H), 2.17 (s, 6 H), 2.73 (d, *J* = 10.6 Hz, 2 H), 6.12 (s, 2 H), 7.15–7.25 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.2, 19.9, 27.4, 41.4, 73.9, 77.1, 127.9, 128.0, 128.2, 136.6, 171.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2971, 2935, 1720, 1454, 1199, 1154, 1106, 1077, 698, 611 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{40}N_2O_4$ $[M]^+$ 468.2988; found 468.2999.

(*S*)-{(1*S*,2*S*)-2-[(*R*)-2-(Dimethylamino)-3-methylbutanoyloxy]-1,2-diphenylethyl} 2-(Dimethylamino)-3-methylbutanoate (10): Yield 176 mg, 75%. $[\alpha]_D^{20}$ = +46.2 (*c* = 0.54 in $CHCl_3$); R_f = 0.50 (Hex/AcOEt, 7:3). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.67 (d, *J* = 6.6 Hz, 6 H), 0.94 (d, *J* = 6.8 Hz, 6 H), 1.80–2.00 (m, 2 H), 2.21 (s, 6 H), 2.80 (d, *J* = 10.2 Hz, 2 H), 6.06 (s, 2 H), 7.10–7.25 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.7, 19.9, 28.1, 41.2, 73.9, 77.6, 127.6, 128.0, 128.1, 136.5, 171.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2963, 2937, 2792, 1723, 1456, 1145, 1121, 988, 700, 598 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{41}N_2O_4$ $[M + H]^+$ 469.3061; found 469.3062.

(2*S*,2′*S*)-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl] Bis[2-(dimethylamino)-2-phenylacetate] (11): Yield 81 mg, 30%. $[\alpha]_D^{20}$ = +48.6 (*c* = 0.52 in $CHCl_3$); R_f = 0.35 (Hex/AcOEt, 1:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.07 (s, 12 H), 3.87 (s, 2 H), 5.98 (s, 2 H), 6.85–6.95 (m, 4 H), 7.00–7.15 (m, 6 H), 7.20–7.35 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 43.1, 74.7, 76.9, 127.1, 127.8, 128.0, 128.2, 128.4, 128.7, 135.8, 136.2, 170.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2939, 2830, 2792, 1752, 1738, 1450, 1204, 1131, 1041, 699 cm^{-1}. HRMS (EI): calcd. for $C_{34}H_{36}N_2O_4$ $[M]^+$ 536.2675; found 536.2685.

(2*S*,2′*S*)-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl] Bis(1-methylpyrrolidine-2-carboxylate) (12): Yield 160 mg, 79%. $[\alpha]_D^{20}$ = –45.5 (*c* = 0.51 in $CHCl_3$); R_f = 0.35 (AcOEt/MeOH, 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.75–1.90 (m, 6 H), 2.00–2.15 (m, 2 H), 2.20–2.35 (m, 10 H), 3.00–3.15 (m, 2 H), 7.10–7.20 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.1, 29.4, 40.6, 56.1, 67.1, 77.0, 127.3, 128.1, 128.2, 136.2, 172.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3409, 2957, 2538, 1748, 1455, 1233, 1196, 997, 756, 700 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{33}N_2O_4$ $[M + H]^+$ 437.2434; found 437.2448.

(2*S*,2′*S*)-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl] Bis(1-ethylpyrrolidine-2-carboxylate) (13): Yield 174 mg, 75%. $[\alpha]_D^{20}$ = –52.9 (*c* = 0.10 in $CHCl_3$); R_f = 0.35 (Hex/acetone, 3:2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.98 (t, *J* = 7.2 Hz, 6 H), 1.75–1.95 (m, 6 H), 2.00–2.10 (m, 2 H), 2.30–2.39 (m, 4 H), 2.58–2.66 (m, 2 H), 3.05–3.15 (m, 2 H), 3.20–3.26 (m, 2 H), 6.14 (s, 2 H), 7.15–7.25 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.6, 23.1, 29.1, 48.3, 52.7, 65.3, 76.9, 127.2, 128.1, 128.2, 136.3, 173.0 ppm. IR (KBr): $\tilde{\nu}$ = 2988, 2806, 1735, 1455, 1244, 1175, 1067, 706, 593, 494 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{37}N_2O_4$ $[M + H]^+$ 465.2748; found 465.2738.

(2*S*,2′*S*)-[(1*S*,2*S*)-1,2-Bis(4-fluorophenyl)ethane-1,2-diyl] Bis(1-methylpyrrolidine-2-carboxylate) (14): Yield 185 mg, 78%. $[\alpha]_D^{20}$ = –54.3 (*c* = 0.52 in $CHCl_3$); R_f = 0.15 (AcOEt/MeOH, 9:1). ^{1}H

NMR ($CDCl_3$, 200 MHz): δ = 1.80–2.05 (m, 9 H), 2.15–2.40 (m, 9 H), 2.95–3.15 (m, 2 H), 6.09 (s, 2 H), 6.85–6.98 (m, 4 H), 7.05–7.15 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 23.2, 29.5, 40.7, 56.2, 67.1, 76.3, 115.2 (d, J = 21.5 Hz), 129.1 (d, J = 8.4 Hz), 131.9, 162.5 (d, J = 246.2 Hz) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2956, 2843, 2802, 1736, 1514, 1352, 1252, 1008, 847, 552 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{31}N_2O_4F_2$ $[M + H]^+$ 473.2246; found 473.2268.

(2*S*,2′*S*)-[(1*S*,2*S*)-1,2-Bis(4-methoxyphenyl)ethane-1,2-diyl] Bis(1-methylpyrrolidine-2-carboxylate) (15): Yield 163 mg, 66%. $[\alpha]_D^{20}$ = –60.1 (c = 0.27 in $CHCl_3$); R_f = 0.25 (AcOEt/MeOH, 9:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.75–1.98 (m, 6 H), 2.00–2.10 (m, 2 H), 2.20–2.40 (m, 10 H), 2.95–3.15 (m, 2 H), 3.75 (s, 6 H), 6.08 (s, 2 H), 6.65–6.80 (m, 2 H), 7.00–7.10 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 23.2, 29.4, 40.7, 55.1, 56.1, 67.2, 76.7, 113.5, 128.4, 128.8, 159.3, 172.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2960, 2839, 2785, 1739, 1516, 1255, 1200, 1174, 1029, 822 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{38}N_2O_6$ $[M + H]^+$ 497.2646; found 497.2658.

(2*S*,2′*S*)-[(1*S*,2*S*)-1,2-Bis(4-*tert*-butylphenyl)ethane-1,2-diyl] Bis(1-methylpyrrolidine-2-carboxylate) (16): Yield 214 mg, 78%. $[\alpha]_D^{20}$ = –50.0 (c = 0.15 in $CHCl_3$); R_f = 0.25 (AcOEt/MeOH, 9:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.25 (s, 18 H), 1.55–2.10 (m, 9 H), 2.15–2.35 (m, 9 H), 2.97–3.15 (m, 2 H), 6.21 (s, 2 H), 7.05–7.25 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 23.1, 29.4, 31.2, 34.4, 40.6, 56.1, 67.1, 77.6, 124.9, 126.5, 133.3, 150.9, 172.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2966, 2790, 1753, 1461, 1269, 1155, 1057, 833, 727, 569 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{49}N_2O_4$ $[M + H]^+$ 549.3687; found 549.3679.

(2*S*,2′*S*)-[(1*S*,2*S*)-1,2-Bis(naphthalen-1-yl)ethane-1,2-diyl] Bis[2-(dimethylamino)propanoate] (17): Yield 207 mg, 81%. $[\alpha]_D^{20}$ = –58.0 (c = 0.50 in $CHCl_3$); R_f = 0.20 (AcOEt/MeOH, 9:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.26 (d, J = 7.0 Hz, 6 H), 2.21 (s, 6 H), 3.36 (q, J = 7.0 Hz, 2 H), 7.12 (s, 2 H), 7.18–7.28 (m, 2 H), 7.31–7.50 (m, 6 H), 7.55–7.75 (m, 4 H), 8.15–8.25 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 15.3, 41.4, 62.5, 74.3, 123.3, 124.5, 125.5, 126.2, 126.4, 128.6, 129.1, 130.5, 132.3, 133.5, 172.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2934, 2869, 2791, 1740, 1451, 121, 1175, 1106, 969, 776 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{37}N_2O_4$ $[M + H]^+$ 513.2748; found 513.2738.

General Procedure for the Preparation of Amide Ligands 18–26: To a cooled solution of the *N*,*N*-dimethylamino acid (2 mmol) in dry DCM (4 mL), triethylamine (306 µL, 2.2 mmol) and ethyl chloroformate (192 µL, 2 mmol) were added at 0 °C. After 30 min, a solution of (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine[19] (213 mg, 1 mmol) in dry DCM (4 mL) was added. The mixture was stirred magnetically for 12 h under argon. The reaction mixture was washed with water (5 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate, concentrated with a rotary evaporator, and the residue was purified by flash column chromatography (AcOEt/MeOH, 4:1) to afford amides **18**–**26**.

***N*,*N*′-[(1*S*,2*S*)-Cyclohexane-1,2-diyl]bis[2-(dimethylamino)acetamide] (18):** Yield 94 mg, 33%. $[\alpha]_D^{20}$ = –57.2 (c = 0.49 in $CHCl_3$); R_f = 0.10 (AcOEt/MeOH, 4:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.15–1.40 (m, 4 H), 1.68–1.85 (m, 2 H), 1.95–2.15 (m, 2 H), 2.24 (s, 12 H), 2.87 (ABm, 2 H), 3.60–3.80 (m, 2 H), 7.20–7.40 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 24.7, 32.6, 45.8, 52.2, 63.0, 170.5 ppm. IR ($CHCl_3$): IR (KBr): $\tilde{\nu}$ = 3281, 2939, 1640, 1519, 1453, 1269, 1155, 1048, 866, 599 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{29}N_4O_2$ $[M + H]^+$ 285.2285; found 285.2282.

***N*,*N*′-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl]bis[2-(dimethylamino)-acetamide] (19):** Yield 344 mg, 90%. $[\alpha]_D^{20}$ = +37.3 (c = 0.65 in $CHCl_3$); R_f = 0.20 (AcOEt/MeOH, 4:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.24 (s, 12 H), 2.92 (s, 4 H), 5.20–5.40 (m, 2 H), 7.05–7.30 (m, 10 H), 7.95–8.05 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 45.9, 57.8, 63.1, 127.4, 127.5, 128.3, 138.8, 170.5 ppm. IR ($CHCl_3$): IR (KBr): $\tilde{\nu}$ = 3295, 2942, 2818, 1645, 1512, 1271, 1046, 865, 698, 553 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{31}N_4O_2$ $[M + H]^+$ 383.2442; found 383.2437.

***N*,*N*′-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl]bis[2-(dimethylamino)-*N*-methylacetamide] (20):** Yield 406 mg, 97%. $[\alpha]_D^{20}$ = +396.4 (c = 0.29 in $CHCl_3$); R_f = 0.30 (AcOEt/MeOH, 4:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.32 (s, 12 H), 2.76 (s, 6 H), 3.09 (s, 4 H), 6.75 (s, 2 H), 7.10–7.35 (m, 10 H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2944, 2825, 1639, 1454, 1404, 1320, 1038, 750, 701, 532 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{35}N_4O_2$ $[M + H]^+$ 411.2755; found 411.2775.

(2*S*,2′*S*)-*N*,*N*′-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl]bis[2-(dimethylamino)propanamide] (21): Yield 368 mg, 90%. $[\alpha]_D^{20}$ = +47.6 (c = 1.00 in $CHCl_3$); R_f = 0.25 (AcOEt/MeOH, 4:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.11 (d, J = 7.0 Hz, 6 H), 2.18 (s, 12 H), 2.97 (q, J = 7.0 Hz, 2 H), 5.15–5.30 (m, 2 H), 7.00–7.25 (m, 10 H), 8.05–8.20 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 10.9, 41.9, 58.2, 64.4, 127.3, 127.4, 128.2, 139.2, 174.0 ppm. IR (KBr): $\tilde{\nu}$ = 3310, 2937, 1646, 1508, 1454, 1204, 1158, 1099, 701, 580 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{35}N_4O_2$ $[M + H]^+$ 411.2755; found 411.2737.

(2*S*,2′*S*)-*N*,*N*′-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl]bis(1-methylpyrrolidine-2-carboxamide) (22): Yield 401 mg, 92%. $[\alpha]_D^{20}$ = –73.3 (c = 0.51 in $CHCl_3$); R_f = 0.30 (AcOEt/MeOH, 4:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.55–1.75 (m, 6 H), 2.05–2.18 (m, 2 H), 2.20–2.40 (m, 8 H), 2.82–2.94 (m, 2 H), 3.05–3.18 (m, 2 H), 5.20–5.35 (m, 2 H), 7.00–7.20 (m, 10 H), 8.10–8.25 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 24.3, 30.9, 41.9, 56.6, 57.7, 68.9, 127.2, 127.3, 128.2, 139.0, 174.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3298, 2943, 2733, 1648, 1504, 1314, 1255, 1048, 699, 550 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{35}N_4O_2$ $[M + H]^+$ 435.2755; found 435.2770.

(2*R*,2′*R*)-*N*,*N*′-[(1*R*,2*R*)-1,2-Diphenylethane-1,2-diyl]bis(1-methylpyrrolidine-2-carboxamide) (ent-22): Yield 404 mg, 93%. $[\alpha]_D^{20}$ = +75.0 (c = 0.50 in $CHCl_3$); R_f = 0.30 (AcOEt/MeOH, 4:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.55–1.75 (m, 6 H), 2.05–2.18 (m, 2 H), 2.20–2.40 (m, 8 H), 2.82–2.94 (m, 2 H), 3.05–3.18 (m, 2 H), 5.20–5.35 (m, 2 H), 7.00–7.20 (m, 10 H), 8.10–8.25 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 24.3, 30.9, 41.9, 56.6, 57.7, 68.9, 127.2, 127.3, 128.2, 139.0, 174.3 ppm. IR (KBr): $\tilde{\nu}$ = 3298, 2943, 2733, 1648, 1504, 1314, 1225, 1048, 699, 550 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{35}N_4O_2$ $[M + H]^+$ 435.2755; found 435.2770.

(2*S*,2′*S*)-*N*,*N*′-[(1*R*,2*R*)-1,2-Diphenylethane-1,2-diyl]bis(1-methylpyrrolidine-2-carboxamide) (23): Yield 399 mg, 92%. $[\alpha]_D^{20}$ = –96.5 (c = 0.59 in $CHCl_3$); R_f = 0.30 (AcOEt/MeOH, 4:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.73–1.90 (m, 6 H), 2.5–2.40 (m, 10 H), 2.75–2.85 (m, 2 H), 3.05–3.18 (m, 2 H), 5.15–5.35 (m, 2 H), 7.00–7.20 (m, 10 H), 8.05–8.15 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 24.2, 30.9, 41.5, 56.5, 57.6, 68.9, 127.2, 127.4, 128.2, 139.2, 174.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3298, 2943, 2733, 1648, 1504, 1314, 1225, 1048, 699, 550 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{35}N_4O_2$ $[M + H]^+$ 435.2755; found 435.2771.

(2*S*,2′*S*)-*N*,*N*′-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl]bis{2-[ethyl(methyl)amino]propanamide} (24): Yield 420 mg, 96%. $[\alpha]_D^{20}$ = +69.1 (c = 0.52 in $CHCl_3$); R_f = 0.30 (AcOEt/MeOH, 4:1). ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.00 (t, J = 7.1 Hz, 6 H), 1.11 (d, J = 6.9 Hz, 6 H), 2.13 (s, 6 H), 2.36 (q, J = 7.1 Hz, 4 H), 3.19 (q, J = 6.9 Hz, 2 H), 5.15–5.25 (m, 2 H), 6.95–7.20 (m, 10 H), 8.05–8.25 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 9.1, 13.1, 37.7, 47.9, 58.1, 62.2, 127.3, 127.3, 128.2, 139.2, 174.0 ppm. IR (KBr): $\tilde{\nu}$

= 3313, 2974, 2795, 1645, 1514, 1454, 1233, 1107, 701, 584 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{39}N_4O_2$ [M + H]$^+$ 439.3068; found 439.3078.

(2*S*,2′*S*)-*N*,*N*′-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl]bis{2-[benzyl-(methyl)amino]propanamide} (25): Yield 535 mg, 95%. $[\alpha]_D^{20}$ = +11.5 (*c* = 0.56 in $CHCl_3$); R_f = 0.30 (AcOEt/MeOH, 4:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.17 (d, *J* = 7.0 Hz, 6 H), 2.05 (s, 6 H), 3.20 (q, *J* = 7.0 Hz, 2 H), 3.44 (ABm, 4 H), 5.20–5.35 (m, 2 H), 7.00–7.40 (m, 20 H), 8.05–8.20 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 8.2, 37.9, 58.2, 58.4, 61.6, 127.1, 127.4, 128.3, 128.4, 128.6, 138.3, 139.0, 173.6 ppm. IR (KBr): $\tilde{\nu}$ = 3310, 3030, 2969, 2796, 1644, 1495, 1243, 1028, 739, 699 cm^{-1}. HRMS (ESI): calcd. for $C_{36}H_{43}N_4O_2$ [M + H]$^+$ 563.3381; found 563.3389.

(2*S*,2′*S*)-*N*,*N*′-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl]bis{2-[isopropyl-(methyl)amino]propanamide} (26): Yield 444 mg, 95%. $[\alpha]_D^{20}$ = +50.3 (*c* = 0.53 in $CHCl_3$); R_f = 0.30 (AcOEt/MeOH, 4:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.04 (d, *J* = 6.5 Hz, 12 H), 1.15 (d, *J* = 7.1 Hz, 6 H), 2.06 (s, 6 H), 2.84 (spt, *J* = 6.5 Hz, 2 H), 3.29 (q, *J* = 7.1 Hz, 2 H), 5.15–5.25 (m, 2 H), 6.98–7.20 (m, 10 H), 8.20–8.40 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.3, 19.3, 19.9, 32.5, 52.01, 57.86, 59.62, 127.26, 127.31, 128.17, 139.17, 174.70 ppm. IR (KBr): $\tilde{\nu}$ = 3300, 2968, 2937, 1645, 1515, 1245, 1132, 1105, 701, 557 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{43}N_4O_2$ [M + H]$^+$ 467.3381; found 467.3358.

General Procedure for the Aldol–Tishchenko Reaction: Yb(III) triflate (125 mg 0.20 mmol, 20 mol-%) was placed in an oven-dried flask with a magnetic stirring bar, and the flask was heated at 200 °C for 10 min in vacuo and then flushed with argon. After the flask was cooled to room temp., a solution of the appropriate ligand (0.20 mmol, 20 mol-%) in THF (2 mL) was added. The resulting solution was stirred for 30 min at room temp. under argon. To a solution of the catalyst, 3-pentanone (100 μL, 0.95 mmol) and benzaldehyde (101 μL, 1.00 mmol) were added successively. The resulting solution was stirred for 20 h at room temp. and then dissolved with MTBE and washed with water and brine. The organic layer was dried with Na_2SO_4, concentrated, and submitted to short column chromatography (Hex/AcOEt, 9:1) to afford a mixture of Tishchenko esters as an oil. The obtained esters were dissolved in MeOH (2 mL) and treated with NaOMe (5–10 mol-%) overnight. The resulting mixture was purified by column chromatography on silica gel (Hex/AcOEt, 3:2) to afford diol **2** and, with an analogous procedure, diols **27**–**40**.

Analytical data for diols **27**, **28**, **30**, **33**, **35**, **37**, **38**, and **40** were previously published.[13c]

(1*S*,2*S*,3*R*)-1-Phenyl-2-propylheptane-1,3-diol (29): Yield 119 mg, 95%. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.80–0.95 (m, 6 H), 1.15–1.50 (m, 10 H), 1.60–1.71 (m, 1 H), 3.12 (d, *J* = 4.7 Hz, 1 H), 3.70–3.77 (m, 2 H), 4.86 (t, *J* = 4.9 Hz, 1 H), 7.20–7.40 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.0, 14.2, 20.9, 22.6, 27.5, 28.4, 33.3, 48.1, 72.1, 76.0, 126.0, 127.1, 128.2, 143.9 ppm; HPLC [Chiralpak AS-H, Hex/*i*PrOH (9:1), flow rate = 1 mL/min, λ = 254 nm]: t_1 = 4.9 min, t_2 = 5.3 min (major peak).

(1*S*,2*S*,3*R*)-2-Ethyl-1-(4-methylphenyl)hex-1,3-diol (31): Yield 81 mg, 69%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.87 (t, *J* = 7.2 Hz, 3 H), 0.92 (t, *J* = 7.5 Hz, 3 H), 1.20–1.30 (m, 2 H), 1.32–1.46 (m, 2 H), 1.50–1.60 (m, 2 H), 1.61–1.67 (m, 2 H), 2.35 (s, 3 H), 2.70 (s, 2 H), 3.76–3.81 (m, 1 H), 4.86 (d, *J* = 6.1 Hz, 1 H), 7.14–7.18 (m, 2 H), 7.21–7.26 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.5, 14.0, 18.6, 19.5, 21.1, 35.6, 50.4, 71.8, 75.8, 126.1, 129.0, 136.9, 140.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3307, 2960, 2933, 2874, 1460, 1049, 1011, 844, 816, 773 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{24}O_2$ [M + Na]$^+$ 259.1668; found 259.1674; HPLC [Chiralpak AD-H, Hex/*i*PrOH (9:1), flow rate = 1 mL/min, λ = 254 nm]: t_1 = 6.4 min (major peak), t_2 = 7.4 min.

(1*S*,2*S*,3*R*)-2-Propyl-1-(4-methylphenyl)heptane-1,3-diol (32): Yield 71 mg, 54%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.85–0.89 (m, 6 H), 1.15–1.40 (m, 8 H), 1.48–1.56 (m, 2 H), 1.69–1.74 (m, 1 H), 2.34 (s, 3 H), 3.12 (s, 2 H), 3.72 (d, *J* = 7.2 Hz, 1 H), 4.82 (d, *J* = 6 Hz, 1 H), 7.14–7.26 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 14.2, 20.9, 21.1, 22.7, 27.7, 28.4, 33.2, 48.2, 7.2, 76.0, 126.0, 128.9, 136.7, 140.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3309, 2956, 2932, 2872, 1513, 1466, 1457, 1037, 1010, 815 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{28}O_2$ [M + Na]$^+$ 287.1981; found 287.1985; HPLC [Chiralpak AD-H, Hex/*i*PrOH (9:1), flow rate = 1 mL/min, λ = 254 nm]: t_1 = 6.1 min (major peak), t_2 = 6.8 min.

(1*S*,2*S*,3*R*)-2-Ethyl-1-(4-methoxyphenyl)hex-1,3-diol (34): Yield 55 mg, 44%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.86–0.93 (m, 6 H), 1.20–1.60 (m, 6 H), 1.62–1.68 (m, 1 H), 3.81 (s, 3 H), 4.83 (d, *J* = 6.3 Hz, 1 H), 6.87–6.91 (m, 2 H), 7.25–7.30 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.5, 14.0, 18.8, 19.5, 35.4, 50.5, 55.2, 71.9, 75.6, 113.7, 127.3, 136.0, 158.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3381, 3130, 2961, 2934, 2878, 1513, 1250, 1036, 842, 777 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{24}O_3$ [M + Na]$^+$ 275.16177; found. 274.1612; HPLC [Chiralpak AD-H, Hex/*i*PrOH (9:1), flow rate = 1 mL/min, λ = 254 nm]: t_1 = 8.1 min (major peak), t_2 = 9.7 min.

(1*S*,2*S*,3*R*)-1-(4-*tert*-Butylphenyl)-2-methylpentane-1,3-diol (36): Yield 120 mg, 96%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.82 (d, *J* = 7.1 Hz, 3 H), 0.90 (t, *J* = 7.3 Hz, 3 H), 1.31 (s, 9 H), 1.36–1.48 (m, 2 H), 1.50–1.60 (m, 1 H), 1.91 (qd, *J* = 7.1, 2.2 Hz, 1 H), 3.15 (s, 1 H), 3.68–3.75 (m, 1 H), 4.64 (d, *J* = 7.1 Hz, 1 H), 7.20–7.27 (m, 2 H), 7.33–7.38 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 10.7, 11.5, 26.5, 31.3, 34.4, 43.2, 74.0, 77.8, 125.1, 125.9, 140.7, 150.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3327, 2964, 2903, 2876, 1461, 1040, 1025, 965, 841, 773 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{26}O_2$ [M + Na]$^+$ 273.1825; found 273.1825; HPLC [Chiralpak AS-H, Hex/*i*PrOH (9:1), flow rate = 1 mL/min, λ = 254 nm]: t_1 = 4.5 min, t_2 = 5.52 min (major peak).

(1*S*,2*R*,3*S*)-1-(4-Methoxyphenyl)-2-methyl-3-phenylpropane-1,3-diol (39): Yield 60 mg, 44%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.71 (d, *J* = 7.1 Hz, 3 H), 2.10–2.25 (m, 1 H), 3.33 (dd, *J* = 14.2, 3.3 Hz, 2 H), 3.80 (s, 3 H), 4.60–4.70 (m, 1 H), 4.95 (br. s, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 7.25–7.40 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.5, 45.8, 55.2, 74.5, 77.8, 113.4, 126.3, 127.2, 127.5, 128.4, 134.6, 143.5, 158.6 ppm. IR (KBr): $\tilde{\nu}$ = 3560, 3351, 2979, 2903, 1511, 1246, 1006, 990, 704, 566 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{20}O_3Na$ [M + Na]$^+$ 295.1305; found 295.1293; HPLC [Chiralpak AD-H, Hex/*i*PrOH (4:1), flow rate = 1 mL/min, λ = 254 nm]: t_1 = 7.9 min, t_2 = 11.9 min (major peak).

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