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Ketopinic Acid Derived Bis(hydroxy amides) as Cheap, Chiral Ligands for the Enantioselective Ethylation of Aromatic Aldehydes

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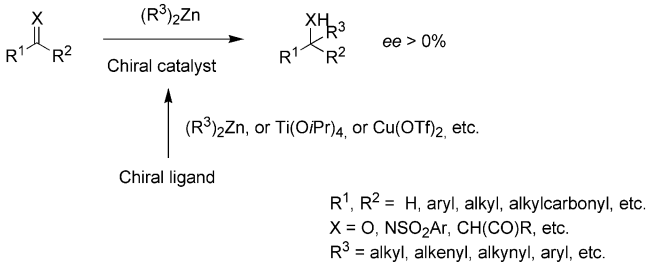
Readily accessible, C_2- and pseudo-C_2-symmetric bis(hydroxy amides), derived from commercially available (+)-ketopinic acid and protic diamines, are promising, cheap, chiral ligands for the synthetically valuable, enantioselective addition of organozinc reagents to carbon electrophiles. A series of ligands of this type, having key structural differences, has been synthesized and tested in the enantioselective ethylation of benzaldehydes and (*E*)-cinnamaldehyde, in order to gain information on the origin of ligand efficiency. The results obtained allow for the definition of a privileged structural pattern for the design of improved cheap ligands and support interesting models proposed for both the acting catalytic species and the controlling transition states. The most efficient ligands proved to be less efficient than commercially available (–)-MIB; nevertheless, an impressive efficiency level was obtained, which should sustain interest in this cheap type of ligands.

Introduction

Enantioselective Addition of Organozinc Reagents to Carbon Electrophiles

The enantioselective addition of organozinc reagents to carbon electrophiles (both 1,2- and conjugate additions), promoted by substoichiometric amounts of an enantioenriched, chiral ligand, is one of the most important reactions in asymmetric catalysis (Scheme 1).[1] In fact, the reaction can be considered a basic tool for the asymmetric construction of C–C bonds and, therefore, for the preparation of valuable, chiral, organic molecules.[2] The reaction presents the additional advantage of the easy preparation, stability, functional-group compatibility and structural diversity of the required organozinc reagents.[3]



Scheme 1. Enantioselective addition of organozinc reagents to carbon electrophiles.

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Since its discovery by Oguni and Omi[4] and the following development of its mechanistic rationalization by Noyori and co-workers,[5] intensive (and also extensive) research on this useful, asymmetric reaction has been performed.[1,6] This effort has mainly centered on developing efficient chiral ligands for less favored additions,[7] finding more versatile, chiral ligands,[8] achieving the coupling of a second asymmetric reaction by using the same chiral ligand (asymmetric tandem)[9] and, more recently, immobilizing the chiral ligand on an insoluble matrix without the loss of efficiency with the aim of optimizing the recovery and reuse of the ligand and designing reactors for flow chemistry.[10]

Nowadays, it is possible to accomplish the enantioselective alkylation, alkenylation, alkynylation and arylation of different types of aldehydes and α-oxo esters (the most electrophilic carbonyl compounds) by using different types of chiral ligands,[1] among which the most significant are the *N*,*N*-dialkylated β-amino alcohols [e.g. Nuggent's (–)-MIB (**1**)[8a] in Figure 1]. It is also possible to achieve enantioselective addition to some activated ketones and imines as well as addition to some activated Michael acceptors.[1] However, in these cases, more specific, chiral ligands and the employment of additional metals are generally required to gain efficiency. Thus, enantioselective addition to ketones can be realized by using Ti^{IV} and certain chiral hydroxysulfonamides such as C_2-symmetric **2** (Figure 1),[1g,8b,8c] whereas the 1,4-conjugate addition can mainly be accomplished with the use of Cu^{II}[7b] and certain tridentate, chiral ligands such as the hydroxy-imino-phosphane **3**, developed recently by Gau and co-workers (Figure 1).[7d]

With the interesting objective of improving both efficiency and versatility, new types of chiral ligand architectures (chiral carbon frameworks and/or involved functional

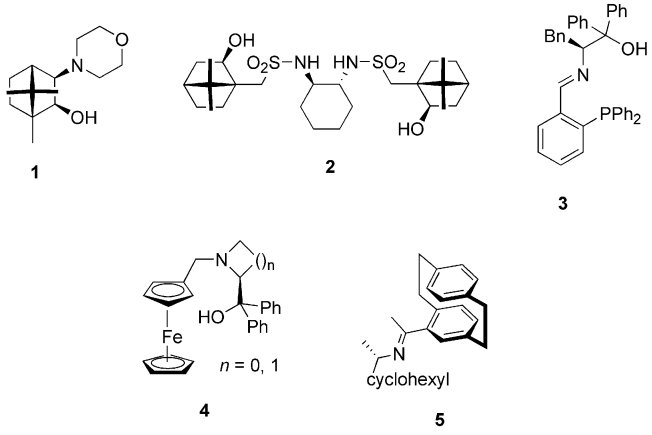


Figure 1. Some chiral ligands for the enantioselective addition of organozinc reagents to carbon electrophiles.

groupings) appear continuously in the literature.[6] In most cases, these ligands are extremely elaborate from a synthetic point of view, either due to their own structural complexity or because asymmetric syntheses or optical-resolution processes are required for their preparation (e.g. Wang's very versatile **4** and **5** in Figure 1).[11] This fact makes these new ligands expensive and, therefore, reduces the possibility of transferring them to industrial processes, as evidenced by the practically nonexistent industrial use of catalyzed, enantioselective addition of organozinc reagents to carbon electrophiles. In this sense, we strongly believe that one of the most important future research interests in this valuable reaction will be the establishment of procedures for its transfer to industry, including the development of cheap, efficient, chiral ligands.

Hydroxy Amides as Chiral Ligands for the Enantioselective Addition of Organozinc Reagents to Aldehydes

Some chiral, C_1-, C_2- and C_3-symmetric *N*-monosubstituted hydroxy amides (protic amide group) have been tested, generally in combination with titanium tetraisopropoxide, in the enantioselective alkylation and alkynylation of different aldehydes. These amides are based on either achiral carboxylic acids and chiral amino alcohols derived from α-amino acids (e.g. **6** and **7** in Figure 2),[12] chiral hydroxy acids and achiral amines (e.g. **8**)[13] or chiral hydroxy acids and chiral amines, including amino alcohols (e.g. **9**).[14]

In most cases, the enantioselectivities achieved are poor, with the exception of the results of Hui and co-workers in phenylethynylation with C_2-symmetric **6** (up to 95% *ee*),[12a] Du and co-workers in phenylethynylation with C_3-symmetric **7** (up to 92% *ee*)[12b] and Blay and co-workers with C_1-symmetric ligands **8** for methylation (up to 90% *ee*),[13] ethylation (up to 88% *ee*)[13] and alkynylation (up to 92% *ee*).[14a] In all these cases, the chiral hydroxy amide acts as an O/N ligand, coordinating a metal center in the catalytic organometallic species.[13]

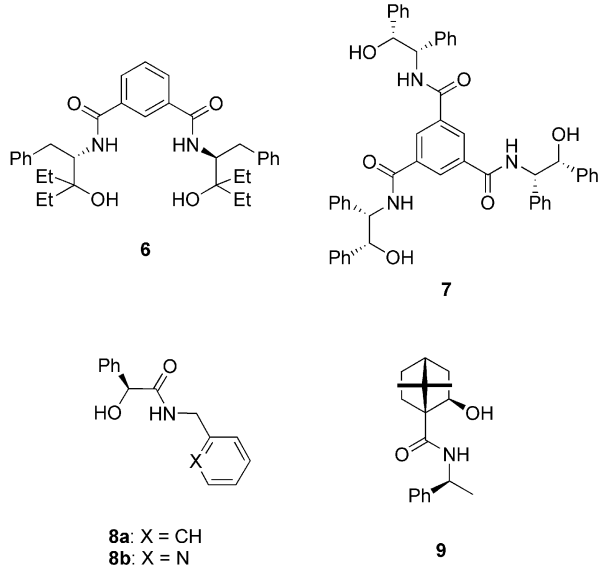
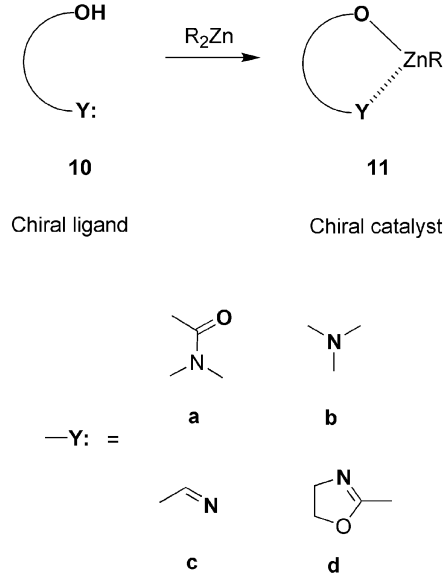


Figure 2. Some hydroxy amide based, chiral ligands having protic amides.

Two years ago, we became interested in testing *N*,*N*-disubstituted hydroxy amides **10a** (Scheme 2) as chiral ligands for the enantioselective addition of organozinc reagents to aldehydes in the absence of titanium. We then believed that the hydroxy-aprotic amide grouping should mimic some functional groupings, which have been successful in the titanium-free process described above [e.g. hydroxyamino (**10b**), hydroxyimino (**10c**) or hydroxyoxazolino (**10d**)].[1c] In these cases, the catalytic species is proposed to be a zinc alkoxide, which is chelated by the lone electron pair of the coordinating N (see **11b–d** in Scheme 2).[15] Therefore, whereas ligand types **10b–d** act as O/N ligands, we proposed that **10a** should act as an O/O ligand (compare **11b–d** with



Scheme 2. Different functional groupings in chiral ligands (**10**) and the corresponding Zn-chelate catalysts (**11**). Coordinating atoms are in bold.

11a in Scheme 2), since the amide oxygen atom (carbonyl group) should coordinate the Zn ion better than the amide N atom.

Chiral, *N*,*N*-disubstituted hydroxy amides **10a** have the additional advantage of being easily prepared by the amidation of simple starting materials (e.g. hydroxy acids and amines or acids and amino alcohols), which can be obtained in enantiopure form from the chiral pool (renewable, enantiopure, starting materials).[16] In other words, simple syntheses and cheap, readily accessible, enantiopure, starting materials make **10a** a cheap, potential, chiral ligand.

Once we established the idea that *N*,*N*-disubstituted hydroxy amide **10a** could constitute an interesting, new, cheap, chiral ligand for the enantioselective addition of organozinc reagents to carbon electrophiles under titanium-free conditions, we carefully looked for literature precedent on this utility. Only two precedents were found:[17] the seminal work of Oppolzer and co-workers using ketopinic acid derived **12** (Figure 3) for the ethylation of benzaldehyde (68% yield and 91% *ee*)[18] and the use of BINOL-derived **13** (Figure 3), reported by Katsuki and co-workers, for the ethylation of different aldehydes (up to 88% yield and 99% *ee* for benzaldehyde).[19] Less efficient ligand **12** is readily accessible from commercially available, camphor-derived (+)-ketopinic acid in only three synthetic steps,[18] whereas synthetic access to more efficient ligands **13** is much more complex.[19a] These two facts probably account for the early abandonment of studies on the catalytic use of ligands of type **10a**.

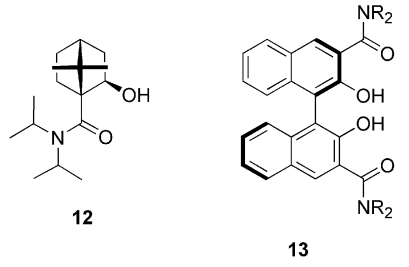


Figure 3. Previous ligands based on *N*,*N*-disubstituted hydroxy amides (type-**10a** ligands).

Gratifyingly, we have recently demonstrated in two preliminary communications a noticeable efficiency improvement in the ketopinic acid derived, hydroxy amide based ligand **12**, through the design of C_2-symmetric bis(hydroxy amides) derived from symmetric, secondary diamines hav-

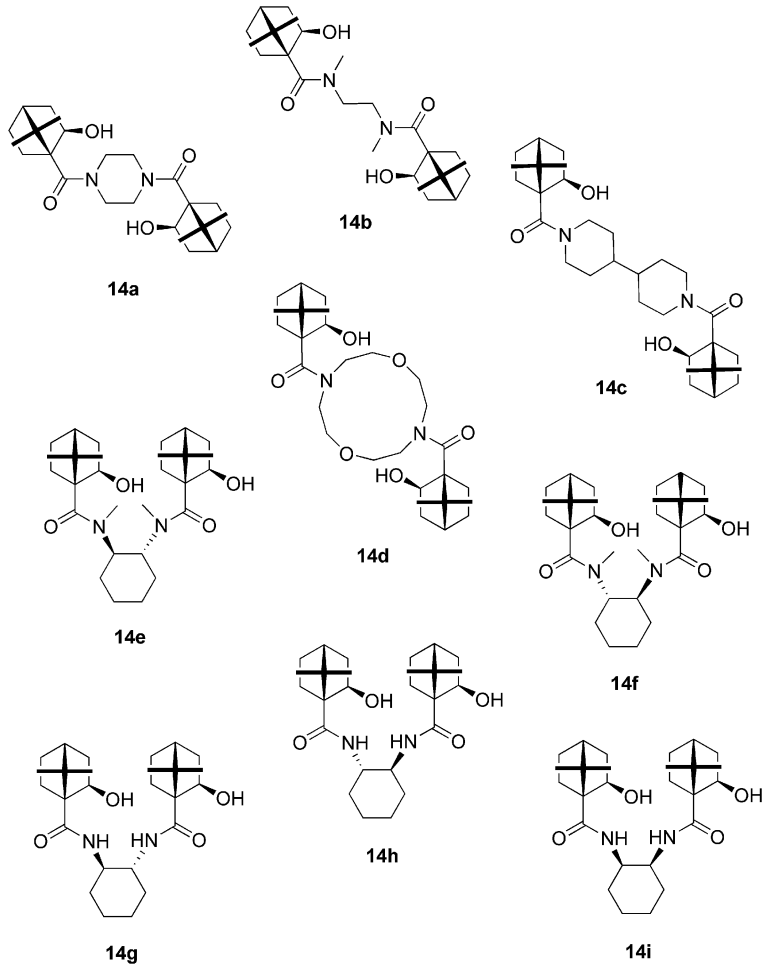


Figure 4. Selected library of symmetric, ketopinic acid derived bis(hydroxy amides).

ing low steric hindrance around the N atoms. Thus, piperazine-based ligand **14a** (Figure 4), our first, efficient, cheap, chiral ligand based on a hydroxy amide, is able to promote the titanium-free, enantioselective addition of diethylzinc to benzaldehyde in 97% yield and 90% *ee*.[20] The participation of the amide carbonyl groups in the coordination of a C_2-symmetric, zinc dialkoxide was proposed to be important for the high enantioselectivity obtained.[20]

In order to gain information on the key structural factors controlling the efficiency of these interesting, C_2-symmetric, bis(hydroxy amide)-based ligands, this paper gives insight into the importance of the bis(amide) chelation to the catalytic activity of these ligands as well as the effects of structural changes in the diamine spacer (length, flexibility and presence of protic N atoms or additional stereogenic centers) on ligand efficiency (yield and *ee*). Moreover, an interesting comparison between the catalytic activity of our most efficient ligands with well-known (–)-MIB (**1**) is included. All these studies have been realized by using the enantioselective ethylation of benzaldehyde as the test reaction.

Results and Discussion

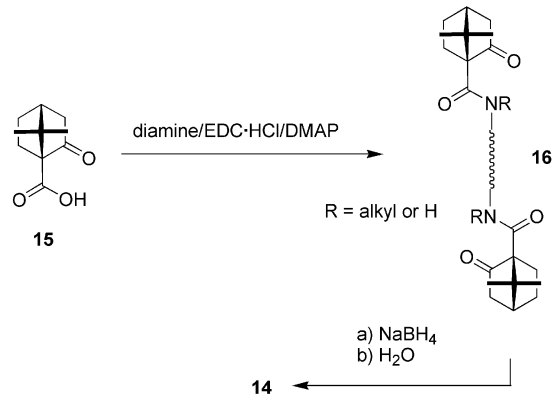
The small library of ketopinic acid derived bis(hydroxy amides) shown in Figure 4, which comprises the abovementioned structural variables for the diamine spacer, was chosen for the study. We then considered the following parameters for the library design: (1) the use of commercially available, symmetric diamines for ligand synthesis (short syntheses for cheap ligands) and (2) the use of reactive, nonaromatic amines (high conversions for cheap ligands). Previously described and tested **14a** and **14b**,[20] as well as the pseudo-C_2-symmetric **14i**, have been included in this study as referable comparison elements. Protic-amide-based ligands **14g** and **14h** have been previously synthesized by Uang and co-workers and tested in the enantioselective silylcyanation of aldehydes.[21]

Ligands **14a**–**i** were obtained through a simple, two-step synthetic process: the amidation of commercially available (+)-ketopinic acid (**15**) with the corresponding, commercially available diamine by standard acid activation with *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide (EDC),[20b,22] followed by the reduction of the intermediate bis(norbornan-2-one) **16** with $NaBH_4$.[20,23] This synthetic route is shown in Scheme 3. Table 1 reports the obtained yields.

In all these cases, high stereoselectivity was achieved in the reduction of **16** with $NaBH_4$,[24] since the bis(2-*exo*-hydroxy) stereoisomer **14** was obtained nearly exclusively (> 98% *de* by ^{1}H NMR spectroscopy of the isolated crude material and ca. 100% *de* after purification).

All the synthesized hydroxy amides **14a**–**i** have been tested in the enantioselective addition of diethylzinc to benzaldehyde. The obtained results are shown in Table 2.

Whereas protic-amide-based ligands **14g**–**i** exhibited poor efficiencies (10–24% *ee* and 43–65% yield, see Table 2), aprotic-amide-based **14a**,**b**,**e** and **f**, having 2-carbon spacers (see Figure 4) provided moderate to high efficiencies (73–94% *ee* and 92–99% yield, see Table 2). Nevertheless, a longer distance between the spacer N atoms (e.g. ligands **14c**–**d** in Figure 4) made such ligands lose substantial efficiency (40–52% *ee* and 25–62% yield, see Table 2).

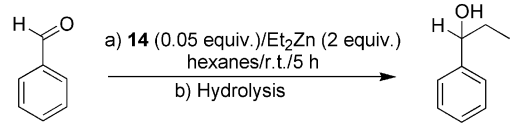


Scheme 3. Synthetic route to bis(hydroxy amides) **14**.

Table 1. Reaction yields for the preparation of ligands **14**.

Entry	Structure type	Chemical yields [%]		
		16	**14**	Overall
1	**a**	90	91	82
2	**b**	88	90	79
3	**c**	78	96	75
4	**d**	50	97	48
5	**e**	86	88	76
6	**f**	83	87	72
7	**g**	85	87	74
8	**h**	98	85	83
9	**i**	85	89	76

Table 2. Screening of ligands **14** for the enantioselective diethylzinc addition to benzaldehyde.[a]



Entry	Ligand	1-Phenylpropan-1-ol	
		Yield [%][b]	*ee* [%][c]
1	**14a**	97	90 (*R*)
2	**14b**	92	73 (*R*)
3	**14c**	25	40 (*R*)
4	**14d**	62	52 (*R*)
5	**14e**	95	94 (*R*)
6	**14f**	99	86 (*R*)
7	**14g**	43	24 (*R*)
8	**14h**	45	24 (*R*)
9	**14i**	65	10 (*R*)

[a] 5 mol-% of ligand, 2 equiv. of Et_2Zn (1.0 M in hexanes), 1 mL of additional hexane, 5 h at room temp. [b] Determined by GC with a capillary silicon-gum (SGL-1) column. [c] Determined by chiral HPLC (Chiralpak IC). Both elution peaks were previously assigned from a known mixture of stereoisomers, in which the configuration for the major isomer is known (assigned by the sign of the optical rotation of the mixture).

All these data agree with the previously proposed hypothesis of the formation of a privileged, diamide-chelated, C_2-symmetric, zinc dialkoxide catalyst (**17** in Figure 5) from C_2-symmetric, aprotic-amide-based bis(hydroxy amides).[20] Thus, the formation of this privileged catalyst should be favored for those ligands with short diamine spacers (e.g. 2-carbon spacers), whereas longer spacers should favor the formation of catalytic species without any centered zinc ion (e.g. dimetallic complex **18** in Figure 5). Note that the catalytic behavior of these decentered-zinc catalysts must be very similar to the behavior of the less efficient, C_1-symmetric catalysts, derived from C_1-symmetric hydroxy amides.[25]

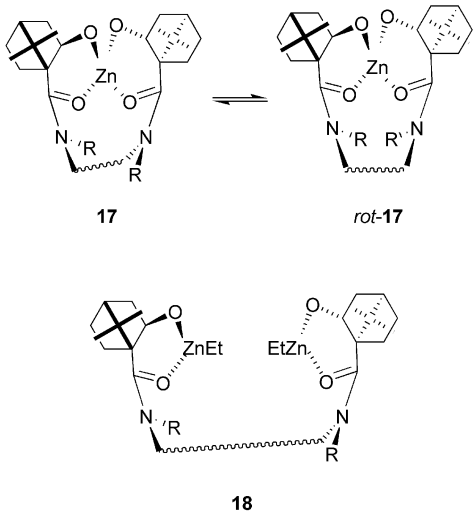


Figure 5. Proposed zinc-centered (**17** and *rot*-**17**) and zinc-decentered (**18**) catalysts for short and long diamine spacers, respectively. R ≠ H.

On the other hand, in the case of protic-amide-based bis(hydroxy amides), dimetallic, decentered-zinc catalysts **19** (Figure 6) must also be formed by the deprotonation of the amide groups,[26,27] which should make each single zinc center easily coordinated by two close oxide and amide groups when short diamine spacers are involved in the ligand structure (e.g. ligands **14g**–**i** in Figure 4).[28]

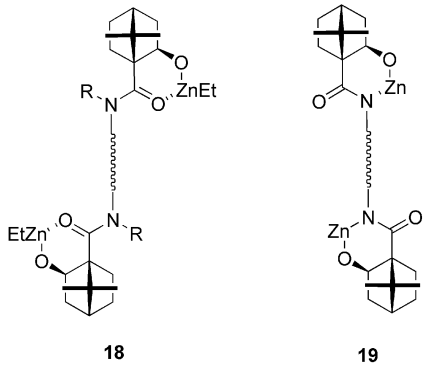


Figure 6. Proposed, zinc-decentered catalysts (**18**) for aprotic-amide-based ligands with long spacers (another perspective is represented in Figure 5) and protic-amide-based ligands (**19**).

On the other hand, for C_2-symmetric, aprotic-amide-based bis(hydroxy amide), the presence of diamine spacers allowing the existence of competitive, less-efficient, pseudo-C_2-symmetric, rotameric catalysts *rot*-**17** must decrease the ligand efficiency. This is the case for short-spacer ligand **14b** (see Figure 4). In this sense, conformationally restricted spacers (e.g. note the spacers of ligands **14e** and **14f** in Figure 4) or spacers with equally substituted N atoms (e.g. the spacer of **14a**) should help to maintain the C_2 symmetry of the corresponding zinc dialkoxide catalyst and, therefore, to provide a high catalytic efficiency (compare the efficiencies of **14a**,**e** and **f** versus that of **14b** in Table 2).

The catalytic behavior of all the studied aprotic-amide-based ligands (**14a**–**f** in Figure 4 and Table 2) demonstrates that both the length and the conformational flexibility of the diamine spacer are key structural factors controlling the catalytic activity, whereas the presence of additional stereogenic elements in the spacer does not seem to be very important at the ligand loading used (note the similar behavior of diastereomeric ligands **14e** and **14f** in Table 2).[29]

The stereodifferentiation preference for pro-(*R*) in all the studied cases (see Table 2), can be easily explained on the basis of the most stable diastereomeric transition states (controlling TS), shown in Figure 7; pro-(*R*) controlling TS **20**, generated from catalyst **17**,[20] explains the stereochemical outcome with the aprotic-amide-based ligands having 2-carbon spacers (**14a**,**b**,**e** and **f** in Figure 4). A similar, pro-(*R*) controlling TS **21** (Figure 7), generated from catalyst **18**,[25] can be proposed for aprotic-amide-based ligands having long spacers **14c**–**d** (see Figure 4). Both models are based on a previous one established by Oppolzer et al. for ligand **12** (see Figure 3).[18] Analogously to **21**, pro-(*R*) controlling TS **22** (Figure 7), derived from catalyst **19**, can also be proposed for protic-amide-based hydroxy amides **14g**–**i** (see Figure 4).

All these TSs are based on the seminal model proposed by Noyori and co-workers for explaining the stereochemical outcome of the isoborneol-based DAIB [3-*exo*-(dimethylamino)isoborneol].[5] This is the *endo-anti-anti*-type TS, in which the reactive molecules (benzaldehyde and diethylzinc) are coordinated to the isoborneol/zinc alkoxide catalyst on the less hindered *endo* face, far away from the catalyst hydrocarbon core (both lateral oxametallacycles are located in an *anti* disposition with respect to the central dioxadimetallacycle), and the (alkoxido)zinc moiety and the phenyl ring are *anti* (note this *endo-anti-anti* disposition in models **20**–**22** in Figure 7).

The centered-zinc character of the C_2-symmetric catalyst **17** (see Figure 5), generated from aprotic-amide-based, C_2-symmetric bis(hydroxy amides) having short spacers, impedes the formation of a competitive, diastereomeric, pro-(*S*) *exo-anti-anti* TS.[20] This undesired competition is possible for the decentered-zinc, C_2-symmetric catalyst **18** (see Figure 5), derived from aprotic-amide-based, C_2-symmetric bis(hydroxy amides) having long spacers (**14c**–**d** in Figure 4), which explains the lower enantioselectivity obtained with such ligands (compare **14c**,**d** versus **14a**,**b**,**e** and **f** in Table 2).

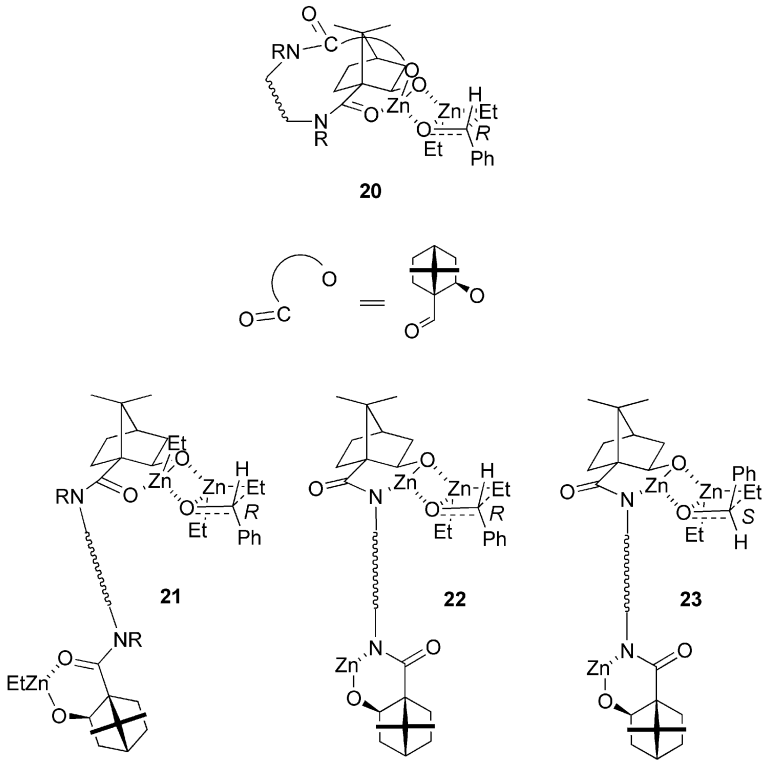


Figure 7. Proposed controlling TSs, derived from catalyst **17** (**20**), **18** (**21**) and **19** (**22** and **23**). R = alkyl.

The more naked character of the (alkoxido)zinc group of catalyst **19**, generated from protic-amide-based bis(hydroxy amides), when compared with the zinc centers of catalysts **17** and **18** (compare the coordinative groups around the zinc centers in Figure 5 and Figure 6), makes possible the competition of an undesired, pro-(*S*), *endo-anti-syn* TS (**23** in Figure 7) and explains the low enantioselectivity obtained with the protic-amide-based ligands **14g**–**i** (see Figure 4 and Table 2).

Before evaluating the versatility of the three best ligands (**14a**,**e** and **f**, see Table 2) for the ethylation of other aldehydes, an optimization of the reaction conditions for benzaldehyde ethylation was performed by using the cheapest ligand, **14a**. Table 3 shows the results of this optimization study.

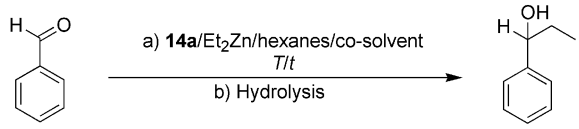
In contrast to the ligands **13** of Katsuki and co-workers (see Figure 3),[19] the efficiency of our *N*,*N*-substituted amide-based ligand **14a** decreases strongly when a coordinative solvent (THF) is used as a cosolvent in the enantioselective test addition (see Table 3). This fact supports the proposed, diamide-chelated, catalyst model for our ligands (**17**, Figure 5). Thus, whereas Katsuki et al. proposed for ligands **13** a catalyst model consisting of a solvent-coordinated zinc dialkoxide without any carbonyl chelation (although the amide carbonyl groups are proposed to be involved in the controlling TSs),[19] the diamide chelation in **17** is crucial for its catalytic activity, since the interruption of such chelation by the competitive THF coordination to the zinc center lowers both the yield and enantioselectivity (see Table 3).

Table 3 also shows that a temperature decrease from 20 °C to 0 °C results in an important loss of chemical yield, whereas the enantioselectivity does not practically change in the temperature interval between 0 °C and 40 °C. Additionally, the extra solvent can be removed without any significant loss of the reaction efficiency (only a slight loss of enantioselectivity is detected, see Table 3),[30] and the ligand loading can be decreased from 5 to 2 mol-% without the results suffering (see Table 3). The reaction time can also be diminished (from 5 h to 4 h, see Table 3) without any substantial loss of efficiency. Unfortunately, the amount of Et_2Zn cannot be decreased without a significant decrease in the yield (see Table 3).

Once we established the optimal reaction conditions, we tested the most efficient ligands **14a**,**e** and **f** in the ethylation of different stereoelectronically activated benzaldehydes as well as cinnamaldehyde under the same conditions (Table 4).The obtained results show that the selected hydroxy amides **14a**,**e** and **f** are able to efficiently promote (71–92% *ee* and 73–97% yield) the room-temperature ethylation of different aldehydes by using a low ligand loading (0.02 mol-%) and a short reaction time (4 h). Table 4 also shows that the different behavior of diastereomeric **14e** and **14f** we expected was only detected for the less efficient ethylations.

Finally, the catalytic activities of the most efficient ligands for the benzaldehyde ethylation (**14a**,**e** and **f**) have been compared with the catalytic activity exerted by well-known (–)-MIB (**1**) at a low ligand loading (0.005 equiv.). For such a comparison, the turnover number (TON), turn-

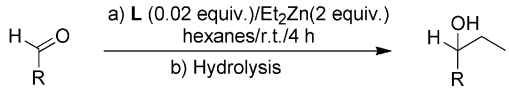
Table 3. Optimization of the reaction conditions.



Entry	**14a** [equiv.]	Et_2Zn [equiv.][a]	Cosolvent[b]	T [°C]	t [h]	1-Phenylpropan-1-ol Yield [%][c]	1-Phenylpropan-1-ol *ee* [%][d]
1	0.05	2.0	hexane	0	5	68	88 (*R*)
2	0.05	2.0	hexane	20	5	97	90 (*R*)
3	0.05	2.0	hexane	40	5	96	80 (*R*)
4	0.05	2.0	THF	20	5	38	14 (*R*)
5	0.05	2.0	CH_2Cl_2	20	5	90	84 (*R*)
6	0.05	2.0	–	20	5	97	84 (*R*)
7	0.10	2.0	hexane	20	5	85	80 (*R*)
8	0.02	2.0	hexane	20	5	95	90 (*R*)
9	0.01	2.0	hexane	20	5	90	86 (*R*)
10	0.01	1.5	hexane	20	5	64	92 (*R*)
11	0.01	1.0	hexane	20	5	30	88 (*R*)
12	0.02	2.0	hexane	20	5	96	90 (*R*)
13	0.02	2.0	hexane	20	4	95	90 (*R*)
14	0.02	2.0	hexane	20	3	90	90 (*R*)
15	0.02	2.0	–	20	4	91	88 (*R*)

[a] 1.0 M Et_2Zn in hexanes. [b] 1 mL of cosolvent was used. [c] Determined by GC (SGL1). [d] Determined by chiral HPLC (see Table 2).

Table 4. Screening of ligands **14a**, **14e** and **14f** (**L**) for the enantioselective, diethylzinc addition to different aldehydes.[a]



Aldehyde	**L**	Corresponding alcohol Yield (%)[b]	Corresponding alcohol *ee* (%)[c]
Benzaldehyde	**14a**	91	88 (*R*)
Benzaldehyde	**14e**	91	91 (*R*)
Benzaldehyde	**14f**	97	86 (*R*)
2-Chlorobenzaldehyde	**14a**	88	88 (*R*)
2-Chlorobenzaldehyde	**14e**	87	85 (*R*)
2-Chlorobenzaldehyde	**14f**	79	82 (*R*)
4-Chlorobenzaldehyde	**14a**	83	66 (*R*)
4-Chlorobenzaldehyde	**14e**	94	85 (*R*)
4-Chlorobenzaldehyde	**14f**	91	92 (*R*)
2-Methylbenzaldehyde	**14a**	73	88 (*R*)
2-Methylbenzaldehyde	**14e**	77	82 (*R*)
2-Methylbenzaldehyde	**14f**	76	89 (*R*)
4-Methylbenzaldehyde	**14a**	61	62 (*R*)
4-Methylbenzaldehyde	**14e**	83	79 (*R*)
4-Methylbenzaldehyde	**14f**	40	20 (*R*)
(*E*)-Cinnamaldehyde	**14a**	93	56 (*R*)
(*E*)-Cinnamaldehyde	**14e**	83	59 (*R*)
(*E*)-Cinnamaldehyde	**14f**	84	71 (*R*)

[a] 2 mol-% of ligand, 2 equiv. of Et_2Zn (1.0 M in hexanes), 4 h at room temp. [b] Determined by GC (SGL1). [c] Determined by chiral HPLC (Chiralpak IC or IA). Both elution peaks were previously assigned from a known mixture of stereoisomers, in which the configuration for the major isomer is known (assigned by the sign of the optical rotation of the mixture).

over frequency (TOF) and TOF × *ee* efficiency parameters have been calculated. The obtained results are shown in Table 5.

Table 5. Comparison of ligand activities at low ligand loading (0.5 mol-%).[a]

Entry	L	1-Phenylpropan-1-ol Yield [%][b]	1-Phenylpropan-1-ol *ee* [%][c]	TON[d]	TOF [h^{-1}][e]	TOF × *ee*	Relative (TOF × *ee*)[f]
1	**14a**	67	64 (*R*)	134	27	17.10^2	0.57
2	**14e**	46	4 (*R*)	92	18	72	0.02
3	**14f**	61	60 (*R*)	122	25	15.10^2	0.50
4	**1**	97	78 (*R*)	194	39	30.10^2	1.00

[a] 0.5 mol-% of ligand, 2 equiv. of Et_2Zn (1.0 M in hexanes), 1 mL of additional hexane, 5 h at room temp. [b] Determined by GC (SGL1). [c] Determined by chiral HPLC (see Table 2). [d] TON = equiv. of 1-phenylpropan-2-ol obtained/0.5. [e] TOF = TON/5. [f] Relative (TOF × *ee*) was determined relative to that of **1**.

Although Table 5 shows that the most efficient, ketopinic acid derived bis(hydroxy amides) are less efficient than **1**, a challenging activity for the cheaper piperazine-based **14a** is demonstrated. The different behavior of diastereomeric ligands **14e** and **14f** in the benzaldehyde ethylation is now highlighted at a low ligand loading, where **14f** is matched (61% yield and 60% *ee*), and **14e** is mismatched (46% yield and 4% *ee*).

Conclusions

A diversity of enantiopure, ketopinic acid derived, C_2-symmetric bis(hydroxy amides) can be easily obtained from cheap, commercially available, starting materials. A seminal screening on a selected library of these ligands by the enantioselective ethylation of benzaldehyde demonstrates that: (1) protic-amide-based bis(hydroxy amides) are less efficient than aprotic ones (*N*,*N*-disubstituted amides), (2) the effi-

ciency of aprotic-amide-based bis(hydroxy amides) having short diamine spacers (2-carbon length) is higher than the efficiency of related ligands having long spacers, (3) the efficiency of aprotic-amide-based bis(hydroxy amides) having conformationally restricted diamine spacers is higher than the efficiency of related ligands having flexible spacers and (4) additional chiral centers in the diamine spacer are not very important for ligand efficiency.

The results obtained are compatible with a C_2-symmetric, centered-zinc model for the organometallic, catalytic species generated from aprotic-amide-based bis(hydroxy amides) having short, diamine spacers and with a C_2-symmetric, decentered-zinc model for catalysts arising from aprotic-amide-based bis(hydroxy amides) having long, diamine spacers. Protic-amide-based ligands, having either short or long spacers, favored the centered-zinc model rather than the decentered-zinc one.

Controlling-TS models have been proposed for all the ligand cases. These models are based on previous ones proposed by the groups of Noyori and Oppolzer for related ligands. In all cases, the controlling TS is the pro-(*R*), *endo-anti-anti* diastereomer. C_2-Symmetric, centered-zinc catalysts prevent the participation of competitive, *exo* TSs, allowing high efficiencies, whereas C_2-symmetric, decentered-zinc catalysts, derived from protic-amide-based ligands, allow more participation by the pro-(*S*), *endo-anti-syn* TS, giving rise to low efficiencies.

The most efficient, ketopinic acid derived bis(hydroxy amide) **14a** turned out to be 1.7 times less efficient than (–)-MIB (in terms of TOF × *ee*) in the benzaldehyde ethylation. Nevertheless, the measured activity of the most efficient, aprotic-amide-based bis(hydroxy amides) (up to 97% yield and 94% *ee*) ensures that interest in the improvement and versatility of this interesting type of cheap ligands will remain strong. Further research on the use of other zinc reagents and other classes of aldehydes is in progress.

Experimental Section

General Considerations: Common solvents were dried and distilled by standard procedures. All starting materials and reagents were obtained from commercial sources and used without further purification. Flash chromatography purifications were performed on silica gel (230–400 mesh ASTM). NMR spectra were recorded at 20 °C, and the residual solvent peaks were used as internal standards. FTIR spectra were obtained by using the thin-layer technique. GC analyses were realized at 150 or 120 °C in a chromatograph equipped with an SGL-1 column, a flame ionization detector (FID), and N_2 as the mobile phase. Chiral-HPLC analyses were realized at room temp. in a chromatograph equipped with a capillary Chiralpak-IC or Chiralpack-IA column, a diode array detector (DAD), and hexane/2-propanol as the mobile phase. Mass spectra were recorded by using the EI (70 eV) or ESI techniques. HR mass spectra were obtained by using the peak-matching method (EI) or FTMS (ESI).

Synthesis of Bis(oxo amides) 16. Typical Procedure: Preparation of *N*,*N*′-Bis{[(1*S*,4*R*)-7,7-dimethyl-2-oxonorborn-1-yl]carbonyl}piperazine (16a): In a round-bottom flask, equipped with a magnetic stirrer, (1*S*)-ketopinic acid (0.55 g, 3.0 mmol), EDC hydrochloride (0.63 g, 3.3 mmol), DMAP (0.42 g, 3.3 mmol) and piperazine (0.13 g, 1.5 mmol) were dissolved in CH_2Cl_2 (10 mL), and the mixture was stirred at room temp. for 24 h. H_2O (5 mL) was then added, and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed successively with aqueous HCl (10%, 1 × 5 mL), H_2O (1 × 5 mL), aqueous NaOH (10%, 2 × 5 mL), H_2O (1 × 5 mL) and brine (1 × 5 mL) and dried with anhydrous $MgSO_4$. After filtration and solvent evaporation, pure **16a** (559 mg, 90% yield) was isolated as a white solid. M.p. 262–264 °C. $[\alpha]_D^{20}$ = –18.5 (*c* = 0.31, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.54 (br. s, 8 H, CH_2-N), 2.50 (ddd, *J* = 18.3, 2.3, 2.3 Hz, 2 H, CH_{exo}-C=O), 2.26–1.94 (m, 8 H) 1.94–1.85 (d, *J* = 18.3 Hz, 2 H, CH_{endo}-C=O), 1.51–1.37 (m, 2 H), 1.21 (s, 6 H, Me), 1.20 (s, 6 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 212.7 (C=O), 167.7 (N-C=O), 67.4 (C), 50.6 (C), 46.8 (N-CH_2), 43.7 (CH_2), 43.1 (CH), 27.2 (CH_2), 27.0 (CH_2), 21.2 (CH_3), 20.9 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 1740.8 (s), 1621.6 (s) cm^{-1}. MS (EI): *m*/*z* (%) = 414 (11), 165 (100). HRMS (EI): *m*/*z* = 414.2527 (calcd. for $C_{24}H_{34}N_2O_4$ 414.2519).

***N*,*N*′-Dimethyl-*N*,*N*′-bis{[(1*S*,4*R*)-7,7-dimethyl-2-oxonorborn-1-yl]-carbonyl}ethanediamine (16b):** White solid (549 mg, 88% yield). M.p. 165–167 °C. $[\alpha]_D^{20}$ = –48.9 (*c* = 0.62, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.82–3.35 (m, 4 H, CH_2-N), 3.06 (br. s, 6 H, Me-N), 2.48 (ddd, *J* = 18.4, 4.7, 2.8 Hz, 2 H, CH_{exo}-C=O), 2.35–1.95 (m, 8 H), 1.90 (d, *J* = 18.4 Hz, 2 H, CH_{endo}-C=O), 1.55–1.34 (m, 2 H), 1.20 (s, 6 H, Me), 1.18 (s, 6 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 212.2 (C=O), 169.1 (N-C=O), 67.5 (C), 50.5 (C), 47.0 (N-CH_2), 43.7 (CH_2), 43.2 (CH), 37.3 (N-CH_3), 26.9 (CH_2), 21.5 (CH_3), 20.8 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 1738.9 (s), 1624.5 (s) cm^{-1}. MS (EI): *m*/*z* (%) = 416 (1), 165 (100). HRMS (EI): *m*/*z* = 416.2666 (calcd. for $C_{24}H_{36}N_2O_4$ 416.2675).

***N*,*N*′-Bis{[(1*S*,4*R*)-7,7-dimethyl-2-oxonorborn-1-yl]carbonyl}-4,4′-bipiperidine (16c):** White solid (580 mg, 78% yield). Decomposes at 250 °C. $[\alpha]_D^{20}$ = –17.0 (*c* = 0.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.68 (br. s, 2 H, CH-N), 3.83 (br. s, 2 H, CH-N), 3.37–2.37 (br. s, 4 H, CH-N), 2.50 (ddd, *J* = 18.3, 4.9, 2.4 Hz, 2 H, CH_{exo}-C=O), 2.37–2.15 (br. s, 2 H), 2.15–2.01 (m, 4 H), 1.98 (dd, *J* = 4.4, 4.4 Hz, 2 H), 1.91 (d, *J* = 18.3 Hz, 2 H, CH_{endo}-C=O), 1.83–1.65 (m, 4 H), 1.60 (m, 2 H), 1.53–1.26 (m, 4 H), 1.23 (s, 6 H, Me), 1.21 (s, 6 H, Me), 1.26–0.96 (br. s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 212.6 (C=O), 167.2 (N-C=O), 67.4 (C), 50.6 (C), 46.8 (N-CH_2), 43.7 (CH_2), 43.1 (CH), 41.0 (N-CH_2CH_2CH), 29.6 (N-$CHCH_2$), 27.5 (CH_2), 27.0 (CH_2), 21.3 (CH_3), 21.0 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 1739.7 (s), 1619.9 (s) cm^{-1}. MS (EI): *m*/*z* (%) = 496 (16), 331 (100). HRMS (EI): *m*/*z* = 496.3306 (calcd. for $C_{30}H_{44}N_2O_4$ 496.3301).

***N*,*N*′-Bis{[(1*S*,4*R*)-7,7-dimethyl-2-oxonorborn-1-yl]carbonyl}-1,7-diaza-12-crown-4 (16d):** White solid (376 mg, 50% yield). M.p. 197–198 °C. $[\alpha]_D^{20}$ = –7.9 (*c* 0.21, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.10–2.90 (m, 16 H, O-CH_2CH_2-N), 2.47 (ddd, *J* = 18.4, 4.9, 2.4 Hz, 2 H, CH_{exo}-C=O), 2.23–1.93 (m, 6 H), 1.89 (d, *J* = 18.4 Hz, 2 H, CH_{endo}-C=O), 1.42 (m, 2 H), 1.24 (m, 2 H), 1.18 (s, 12 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 212.7 (C=O), 169.9 (N-C=O), 69.6 (CH_2-O), 67.9 (C), 50.7 (C), 48.7 (N-CH_2), 43.7 (CH_2), 43.0 (CH), 27.9 (CH_2), 27.0 (CH_2), 21.5 (CH_3), 20.7 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 1737.9 (s), 1623.6 (s) cm^{-1}. MS (ESI): *m*/*z* (%) = 503 (1), 525 (100). HRMS (ESI): *m*/*z* = 503.3116 (calcd. for $C_{28}H_{43}N_2O_6$ 503.3116).

(1*R*,2*R*)-*N*,*N*′-Dimethyl-*N*,*N*′-bis{[(1*S*,4*R*)-7,7-dimethyl-2-oxonorborn-1-yl]carbonyl}cyclohexane-1,2-diamine (16e): White solid (606 mg, 86% yield). M.p. 215–216 °C. $[\alpha]_D^{20}$ = +6.0 (*c* = 0.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.63 (dd, *J* = 4.9,

2.8 Hz, 2 H, CH-N), 2.72 (s, 6 H, Me-N), 2.49 (ddd, J = 18.4, 4.6, 2.2 Hz, 2 H, CH_{exo}-C=O), 2.35–2.17 (m, 2 H), 2.15–1.94 (m, 6 H) 1.90 (d, J = 18.4 Hz, 2 H, CH_{endo}-C=O), 1.83–1.66 (m, 4 H), 1.62–1.29 (m, 6 H), 1.21 (s, 6 H, Me), 1.13 (s, 6 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 212.0 (C=O), 169.1 (N-C=O), 68.1 (C), 53.2 (N-CH), 50.8 (C), 44.0 (CH_2), 43.4 (CH), 30.4 (N-CH_3), 29.0 (N-CHCH_2), 27.4 (CH_2), 26.8 (CH_2), 25.0 (N-CHCH$_2CH_2$), 22.0 (CH_3), 20.6 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 1738.9 (s), 1619.2 (s) cm^{-1}. MS (ESI): m/z (%) = 471 (2), 493 (100). HRMS (ESI): m/z = 471.3223 (calcd. for $C_{28}H_{43}N_2O_4$ 471.3217).

(1*S*,2*S*)-*N*,*N*′-Dimethyl-*N*,*N*′-bis{[(1*S*,4*R*)-7,7-dimethyl-2-oxonorborn-1-yl]carbonyl}cyclohexane-1,2-diamine (16f): White solid (585 mg, 83% yield). M.p. 198–200 °C. $[\alpha]_D^{20}$ = –77.0 (c = 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.67 (br. s, 2 H, CH-N), 2.77 (s, 6 H, Me-N), 2.47 (dd, J = 18.4, 2.6 Hz, 2 H, CH_{exo}-C=O), 2.28 (m, 2 H), 2.11–1.86 (m, 6 H), 1.86 (d, J = 18.4 Hz, 2 H, CH_{endo}-C=O), 1.68 (m, 4 H), 1.57–1.28 (m, 6 H), 1.20 (s, 6 H, Me), 1.15 (s, 6 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 211.2 (C=O), 169.0 (N-C=O), 68.2 (C), 53.3 (N-CH), 50.6 (C), 43.8 (CH_2), 43.6 (CH), 30.6 (N-CH_3), 29.7 (N-CHCH_2), 27.9 (CH_2), 26.7 (CH_2), 25.2 (N-CHCH$_2CH_2$), 21.6 (CH_3), 20.9 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 1739.7 (s), 1618.8 (s) cm^{-1}. MS (ESI): m/z (%) = 471 (3), 493 (100). HRMS (ESI): m/z = 471.3231 (calcd. for $C_{28}H_{43}N_2O_4$ 471.3217).

(1*R*,2*S*)-*N*,*N*′-Bis{[(1*S*,4*R*)-7,7-dimethyl-2-oxonorborn-1-yl]carbonyl}cyclohexane-1,2-diamine (16i): White solid (563 mg, 85% yield). M.p. 96–98 °C. $[\alpha]_D^{20}$ = +63.8 (c = 0.40, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.92 (m, 2 H, NH), 4.22 (m, 2 H, CH-N), 2.64–2.43 (m, 4 H), 2.22–2.02 (m, 4 H), 1.97 (d, J = 18.6 Hz, 1 H, CH_{endo}-C=O), 1.95 (d, J = 18.6 Hz, 1 H, CH_{endo}-C=O), 1.88–1.35 (m, 12 H), 1.25 (s, 3 H, Me), 1.24 (s, 3 H, Me), 0.99 (s, 3 H, Me), 0.98 (s, 3 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 217.4 (C=O), 217.1 (C=O), 168.7 (N-C=O), 168.6 (N-C=O), 64.6 (C), 64.5 (C), 50.1 (C), 49.8 (C), 48.33 (N-CH), 48.25 (N-CH), 43.73 (CH_2), 43.69 (CH_2), 43.2 (CH), 43.1 (CH), 29.3 (N-CHCH_2), 28.7 (N-CHCH_2), 28.4 (CH_2), 28.2 (CH_2), 27.67 (CH_2), 27.65 (CH_2), 22.5 (N-CHCH$_2CH_2$), 21.9 (N-CHCH$_2CH_2$), 20.9 (CH_3), 20.8 (CH_3), 20.4 (CH_3), 20.3 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 1725.9 (s), 1665.9 (s) cm^{-1}. MS (EI): m/z (%) = 442 (1), 261 (100). HRMS (EI): m/z = 442.2845 (calcd. for $C_{26}H_{38}N_2O_4$ 442.2832).

Synthesis of Bis(hydroxy amides) 14. Typical Procedure: Preparation of *N*,*N*′-Bis{[(1*S*,2*R*,4*R*)-7,7-dimethyl-2-hydroxynorborn-1-yl]-carbonyl}-1,7-diaza-12-crown-4 (14d): A two-necked, round-bottom flask, equipped with a magnetic stirrer and a H_2O condenser, was charged with bis(oxo amide) **16d** (0.25 g, 0.5 mmol), methanol (10 mL) and $NaBH_4$ (0.08 g, 2.0 mmol). The mixture was refluxed under argon for 24 h and cooled to room temp. H_2O (5 mL) was then added, and the resulting mixture was concentrated under reduced pressure (methanol elimination). The obtained residue was diluted with ethyl acetate (5 mL). H_2O (3 mL) was added, and the resulting layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine (1 × 5 mL) and dried with anhydrous $MgSO_4$. After filtration and solvent evaporation under reduced pressure, the residue was purified by flash column chromatography (silica gel, $CHCl_3$) to obtain **14d** (244 mg, 97% yield) as a white solid. Decomposes at 250 °C. $[\alpha]_D^{20}$ = –72.0 (c = 0.14, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.10 (dd, J = 8.2, 3.7 Hz, 2 H, CH-O) 4.27–2.60 (m, 18 H, N-CH_2CH_2-O and OH), 2.03–1.85 (m, 4 H), 1.84–1.69 (m, 4 H), 1.59–1.41 (m, 4 H), 1.36 (s, 6 H, Me), 1.18–1.01 (m, 2 H), 1.12 (s, 6 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.1 (N-C=O), 76.8 (CH-O), 69.8 (CH_2-O), 61.1 (C), 50.8 (C), 49.0 (N-CH_2), 44.6 (CH), 40.7 (CH_2), 29.9 (CH_2), 27.3 (CH_2), 22.4 (CH_3), 21.4 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3429.2 (br., w), 1622.3 (s) cm^{-1}. MS (ESI): m/z (%) = 507 (1), 529 (100). HRMS (ESI): m/z = 507.3423 (calcd. for $C_{28}H_{47}N_2O_6$ 507.3429).

***N*,*N*′-Bis{[(1*S*,2*R*,4*R*)-7,7-dimethyl-2-hydroxynorborn-1-yl]carbonyl}-4,4′-bipiperidine (14c):** White solid (239 mg, 96% yield). Decomposes at 250 °C. $[\alpha]_D^{20}$ = –4.0 (c = 0.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 700 MHz): δ = 4.47 (m, 4 H, CH-N and CH-O), 4.18 (m, 2 H, CH-N), 2.72 (m, 4 H, CH-N), 2.00 (ddd, J = 12.3, 12.3, 4.4 Hz, 2 H), 1.96–1.88 (m, 4 H), 1.87–1.77 (m, 4 H), 1.75 (m, 4 H), 1.63 (dd, J = 4.4, 4.4 Hz, 2 H), 1.54–1.50 (m, 2 H), 1.38 (s, 6 H, Me), 1.36–1.08 (m, 8 H) 1.15 (s, 6 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 175 MHz): δ = 171.4 (N-C=O), 78.0 (CH-O), 60.8 (C), 50.6 (C), 44.8 (CH), 44.7 (CH_2), 41.23 (N-CH_2CH_2CH), 41.22 (N-CH_2), 30.0 (N-CH_2CH_2), 29.8 (CH_2), 27.1 (CH_2), 22.3 (CH_3), 21.6 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3389.1 (br., w), 1596.0 (s) cm^{-1}. MS (ESI): m/z (%) = 501 (15), 236 (100). HRMS (ESI): m/z = 501.3684 (calcd. for $C_{30}H_{49}N_2O_4$ 501.3687).

(1*R*,2*R*)-*N*,*N*′-Dimethyl-*N*,*N*′-bis{[(1*S*,2*R*,4*R*)-7,7-dimethyl-2-hydroxynorborn-1-yl]carbonyl}cyclohexane-1,2-diamine (14e): White solid (208 mg, 88% yield). M.p. 222–223 °C. $[\alpha]_D^{20}$ = +22.0 (c = 0.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.72 (br. s, 2 H, CH-O), 4.20 (br. s, 2 H, CH-N), 2.92 (s, 6 H, Me-N), 2.01–1.69 (m, 14 H), 1.68–1.56 (m, 6 H), 1.40 (s, 6 H, Me), 1.43–1.30 (m, 2 H), 1.18–1.03 (m, 2 H), 1.09 (s, 6 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.8 (N-C=O), 77.1 (CH-O), 61.2 (C), 53.2 (N-CH), 50.8 (C), 44.7 (CH), 41.8 (CH_2), 29.7 (N-CH_3), 29.4 (CH_2), 26.9 (CH_2), 25.1 (CH_2), 22.2 (CH_3), 22.0 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3434.7 (br., w), 1601.4 (s) cm^{-1}. MS (ESI): m/z (%) = 475 (3), 497 (100). HRMS (ESI): m/z = 475.3525 (calcd. for $C_{28}H_{47}N_2O_4$ 475.3530).

(1*S*,2*S*)-*N*,*N*′-Dimethyl-*N*,*N*′-bis{[(1*S*,2*R*,4*R*)-7,7-dimethyl-2-hydroxynorborn-1-yl]carbonyl}cyclohexane-1,2-diamine (14f): White solid (205 mg, 87% yield). M.p. 130–131 °C. $[\alpha]_D^{20}$ = –63.0 (c = 0.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.72 (m, 2 H, CH-O), 4.17 (m, 2 H, CH-N), 3.24 (d, J = 6.6 Hz, 2 H), 2.91 (s, 6 H, Me-N), 2.86 (d, J = 2.0 Hz, 2 H), 1.92–1.29 (m, 18 H), 1.36 (s, 6 H, Me), 1.14 (s, 6 H, Me), 1.10–1.05 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.6 (N-C=O), 76.6 (CH-O), 61.2 (C), 53.4 (N-CH), 50.8 (C), 44.7 (CH), 41.6 (CH_2), 29.6 (N-CHCH_2), 29.5 (N-CH_3), 29.3 (CH_2), 27.0 (CH_2), 25.2 (N-CHCH$_2CH_2$), 22.5 (CH_3), 21.8 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3384.1 (br., w), 1608.7 (s) cm^{-1}. MS (ESI): m/z (%) = 475 (4), 497 (100). HRMS (ESI): m/z = 475.3532 (calcd. for $C_{28}H_{47}N_2O_4$ 475.3530).

(1*R*,2*S*)-*N*,*N*′-Bis{[(1*S*,2*R*,4*R*)-7,7-dimethyl-2-hydroxynorborn-1-yl]carbonyl}cyclohexane-1,2-diamine (14i): White solid (197 mg, 89% yield). M.p. 227–229 °C. $[\alpha]_D^{20}$ = –14.8 (c = 0.21, CH_2Cl_2). ^{1}H NMR (CD_3OD, 200 MHz): δ = 4.29 (br. s, 1 H, N-CH), 4.03 (dd, J = 7.4, 3.6 Hz, 2 H, N-CH and CH-O), 3.96 (dd, J = 7.4, 3.8 Hz, 1 H, CH-O), 2.41–2.15 (m, 2 H) 1.96–1.01 (m, 20 H), 1.20 (s, 3 H), 1.19 (s, 3 H), 0.98 (s, 3 H, Me), 0.96 (s, 3 H, Me) ppm. ^{13}C NMR (CD_3OD, 50 MHz): δ = 174.96 (N-C=O), 174.92 (N-C=O), 78.3 (CH-O), 77.8 (CH-O), 59.1 (C), 58.8 (C), 51.6 (C), 50.74 (C), 50.68 (N-CH), 49.6 (N-CH), 47.0 (CH), 46.9 (CH), 43.3 (CH_2), 42.9 (CH_2), 31.2 (N-CHCH_2), 31.0 (N-CHCH_2), 29.4 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 24.6 (N-CHCH$_2CH_2$), 22.2 (N-CHCH$_2CH_2$), 22.1 (CH_3), 22.0 (CH_3), 21.9 (CH_3), 21.8 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3250.3 (br., w), 1626.7 (s) cm^{-1}. MS (EI): m/z (%) = 446 (1), 97 (100). HRMS (EI): m/z = 446.3133 (calcd. for $C_{26}H_{42}N_2O_4$ 446.3145).

General Procedure for the Enantioselective Ethylation of Aldehydes: Under argon, into a 10 mL, round-bottomed flask, equipped with a magnetic stirrer and containing the corresponding bis(hydroxy

amide) (0.02 mmol), was added diethylzinc (2.00 mmol, 1.0 M in hexanes) at room temp. The mixture was stirred at room temp. for 5 min. The corresponding aldehyde (1.0 mmol) was then added, and the reaction mixture was stirred at room temp. for 4 h. The reaction was then quenched by the addition of aqueous NH_4Cl (1 M, 3 mL). The resulting mixture was extracted with diethyl ether (3 × 3 mL). The combined organic layers were submitted to Celite filtration and solvent evaporation. The obtained residue was dissolved in HPLC-grade hexanes and submitted to analysis by GC and chiral HPLC.

1-Phenylpropan-1-ol: Chiralpak IC, 260 nm, 2-propanol/hexanes (2:98), 1.3 mL/min. t_R = 7.3 (*R*), 7.8 (*S*) min.

1-(2-Chlorophenyl)propan-1-ol: Chiralpak IA, 260 nm, 2-propanol/hexanes (1:99), 1.3 mL/min. t_R = 12.7 (*R*), 13.4 (*S*) min.

1-(4-Chlorophenyl)propan-1-ol: Chiralpak IC, 260 nm, 2-propanol/hexanes (5:95), 1.3 mL/min. t_R = 4.3 (*R*), 4.5 (*S*) min.

1-(2-Methylphenyl)propan-1-ol: Chiralpak IA, 260 nm, 2-propanol/hexanes (2:98), 1.2 mL/min. t_R = 8.8 (*R*), 10.1 (*S*) min.

1-(4-Methylphenyl)propan-1-ol: Chiralpak IA, 260 nm, 2-propanol/hexanes (2:98), 1.2 mL/min. t_R = 10.4 (*R*), 11.7 (*S*) min.

1-Phenylpent-1-en-3-ol: Chiralpak IC, 260 nm, 2-propanol/hexanes (5:95), 1.3 mL/min. t_R = 6.4 (*R*), 7.2 (*S*) min.

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[22] A cheaper amidation of ketopinic acid can be achieved by acidic activation with thionyl chloride (ketopinoyl chloride generation). For example, see ref.[18,20a,21]

[23] Uang and co-workers have used L-selectride instead of $NaBH_4$ for the stereoselective reduction of **16g** and **16h** (see ref.[21]).
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[28] Note that the formation of an *N*-coordinated, zinc-centered complex (-CO-N-Zn-N-CO-) from a 2-carbon-spacer bis(hydroxy amide) should involve a rigid five-membered-ring spacer, whereas the carbonyl-chelated one (-N-C=O-Zn-O=C-N-) involves a less rigid, eight-membered-ring spacer.
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