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2-(Aminomethyl)-oxazolines: Highly Modular Scaffolds for the Preparation of Novel Asymmetric Ligands

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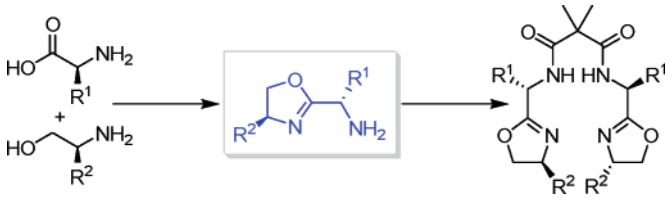

Highly modular chiral 2-(aminoalkyl)oxazolines have been prepared from α-amino acids and 1,2-amino alcohols. The amine-functionalized oxazolines were employed as scaffolds in the preparation of a number of different ligands with potential denticities varying from 2 to 5. The obtained ligands were employed and evaluated in the ruthenium-catalyzed asymmetric transfer-hydrogenation of acetophenone and in the titanium-catalyzed addition of diethylzinc to aldehydes. In the latter process, enantioselectivity up to 97% was obtained.

Introduction

Oxazolines or oxazoline-containing compounds have received an extensive amount of attention as ligands in asymmetric catalysis over the past decade.[1] The bisoxazolines introduced by the groups of Masamune,[2] Evans,[3] Pfaltz[4] and Corey[5] in the early 1990s represent one of the most useful classes of C_2-symmetric ligands. There are numerous catalytic applications where this ligand class is found superior to others in terms of generating highly active and selective catalysts.[1,6] The formation of chiral oxazolines is a straightforward process starting from a carboxylic acid or carboxylic acid derivative and a suitable chiral 1,2-amino alcohol. The ease with which α-amino acids can be transformed into 1,2-amino alcohols opens up a wide variety of enantiomerically pure ligand building blocks. Thus, vast structural variations of the oxazoline ligands can simply be achieved by the choice of 1,2-amino alcohol. We have recently described the preparation of C_2-symmetric bisoxazoline bisamides and the use of these compounds as ligands in the asymmetric addition of alkyl-zinc to aldehydes.[7] The central building block in this class of ligands is a highly modular asymmetric scaffold, 2-(aminomethyl)oxazoline (**1**).[8] To further extend our studies around this modular scaffold, we decided to explore the possibilities in forming a diverse library of ligands that could be of potential use in various asymmetric catalytic transformations. Herein we disclose our findings on the preparation of a novel series of ligands based on this oxazoline core. In addition, we demonstrate the effectiveness of these ligands in a typical asymmetric benchmark-reaction, the diethylzinc addition to aldehydes.

Results and Discussion

Ligand Preparation. 2-(Aminomethyl)oxazolines **1** (R^1 = H), conveniently prepared from α-amino acids (**3**) and 1,2-amino alcohols (**2**), have previously been used in various synthetic applications, e.g., peptide synthesis[9]

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(2) (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett*. **1990**, *31*, 6005−6008. (b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett*. **1991**, *32*, 7373−7376.

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(7) The preparation of C_2-symmetric tetradentate bisoxazoline ligands based on this strategy has previously been presented in: Pastor, I. M.; Adolfsson, H. *Tetrahedron Lett*. **2002**, *43*, 1743−1746.

(8) For two independent preparations of 2-(aminomethyl)oxazolines, see: (a) Rajaram, S.; Sigman, M. S. *Org. Lett*. **2002**, *4*, 3399−3401. (b) Gilbertson, S. R.; Lan, P. *Tetrahedron Lett*. **2002**, *43*, 6961−6965.

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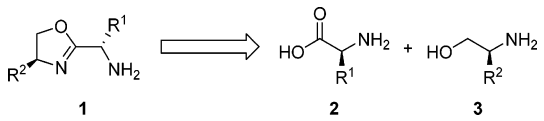
SCHEME 1



1 **2** **3**

and as substrates for asymmetric alkylation reactions.[10] Surprisingly, this highly modular class of oxazolines has not yet to any larger extent been applied as ligands in asymmetric catalysis.[7,11,12] The structure of 2-(aminomethyl)oxazolines, though, presents multiple opportunities for the preparation of ligands suitable for catalytically active transition metals. The parent compound **1** can be used by itself, functioning as a bidentate ligand, or the primary amine functionality can be further derivatized into a number of different interesting ligand structures. Since the basic structure is constructed from α-amino acids and 1,2-amino alcohols, the formation of 2-(aminomethyl)oxazolines containing two or three stereocenters is rather straightforward, taking advantage of the wide array of building blocks available in the chiral pool.[13] Hence, the highly modular scaffolds represented by 2-(aminomethyl)oxazolines are certainly qualified as ligands or ligand precursors for asymmetric catalysis.We have taken advantage of the ease with which enantiomerically pure 2-(aminomethyl)oxazolines are prepared and devised an array of ligand structures based on this precursor (Scheme 2). Employing **1** as the key building block, bi- and tridentate ligands containing a sulfon- (**4**) or carboxamide (**5**) were readily prepared. Tridentate Shiff base ligands (**6** and **7**) were synthesized from **1** and suitable aldehydes. Ligands **8**−**10** were obtained employing a suitable dicarboxylic acid as the linker between two units of 2-(aminomethyl)oxazoline. Thus, condensing **1** with either a 1,2- or a 1,3-dicarboxylic acid results in the tetradentate ligands **8** and **9**, whereas ligand **10** was prepared from pyridine 2,6-dicarboxylic acid.

With the goal set to prepare all of the different ligand structures presented in Scheme 2 we decided to initially limit the studies to ligands based on the amino acid L-valine. The chemistry presented herein will, however, be applicable to all other combinations of amino acids and amino alcohols. The preparation of **1** was conducted according to Scheme 3. Activation of the *N*-Boc-protected L-valine with isobutylchloroformate followed by the addition of a 1,2-amino alcohol led to the formation of amide **12**.[14] The *N*-protecting group was removed and in a functional group interconversion, the alcohol was replaced by chloride using thionyl chloride. The final ring closure to **1** was performed using basic conditions. Employing L-valine and L-valinol according to the above protocol resulted in the formation of **1a** in 54% overall yield. Exchanging the amino alcohol part to (*R*)-phenylglycinol gave **1b** in 60% overall yield.

All of the ligands depicted in Scheme 2 can in principle be prepared from oxazoline **1**, but because of various synthetic problems we decided to use a few different approaches for their formation. The crucial difference between the employed approaches is how and when in the synthesis the ring-closing step to the oxazoline occurred. The 2-(*p*-toluensulfonamido)methyloxazoline **4** was prepared in an efficient two-step synthesis starting with the formation of *N*-sulfonyl-L-valine (**15**).[15] The protected amino acid was thereafter conveniently reacted with L-valinol according to the Vorbrüggen protocol[16] to form ligand **4** in 78% overall yield starting from the amino acid (Scheme 4).[17] Initially we employed the procedure described in Scheme 3 for the preparation of ligand **4**, but because of nonselective coupling between the sulfonated amino acid and the amino alcohol, this route was abandoned.[18]

The potentially tri-dentate ligands **5**−**7** were prepared using two different routes (Schemes 5 and 6). For the preparation of ligand **5** we initially used the same route as for the formation of ligands **1**, but after removal of the Boc-group, the resulting amine **13a** was coupled with 2-picolinoyl chloride to yield the bisamide **16a**. After a functional group interconversion of the alcohol into a chloride, the resulting chloro-amide **17a** was treated with base to yield the desired tridentate ligand **5** (Scheme 5). The overall yield for the formation of **5** starting from **13a** was 58%.

Ligands **6** and **7** were prepared from 2-(aminomethyl)-oxazolines **1a** and **1b** respectively. The condensation to ligand **6** was readily performed using **1a** and 2-pyridinecarboxaldehyde in dry dichloromethane containing molecular sieves (4 Å), whereas ligand **7** was obtained in a Lewis acid [La(OTf)$_3$] catalyzed reaction of **1b** with 3,5-di-*tert*-butylsalicylaldehyde in the presence of $MgSO_4$ (Scheme 6).

The C_2-symmetric tetradentate ligands **8** and **9** were prepared using the routes presented in Schemes 7 and 8.[7] *N*-Protected amino acids were initially coupled with the proper 1,2-amino alcohols to yield the "dipeptide" compounds **13**. For the formation of ligand **8**, the alcohol present in **13** was exchanged for chloride and the resulting chloro-amide **14a** was reacted with oxalyl chloride to yield the tetraamide **18**. Treatment of this compound with sodium hydroxide in THF led to the formation of ligand **8**. For the formation of ligands **9a**−**f**, we found that significantly better overall yields were obtained if the hydroxyl-functionalized "dipeptides" **13** were directly coupled with dimethylmalonyl chloride instead of initially performing the functional group interconversion followed

(10) For the use of oxazolines in asymmetric synthesis, see: Meyers, A. I. *J. Heterocycl. Chem*. **1998**, *35*, 991−1002.

(11) (a) Jiang, Y.; Jiang, Q.; Zhang, X *J. Am. Chem. Soc*. **1998**, *120*, 3817−3818. (b) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237−2240. (c) McManus, H. A.; Barry, S. M.; Andersson, P. G.; Guiry, P. J. *Tetrahedron* **2004**, *60*, 3405−3416.

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(13) Blaser, H. U. *Chem. Rev*. **1992**, *92*, 935−952.

(14) This particular class of pseudo-dipeptides has successfully been employed as ligands in ruthenium-catalyzed transfer-hydrogenation of ketones; see: (a) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Commun*. **2002**, 2046−2047. (b) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Eur. J*. **2003**, *9*, 4031−4045. (c) Bøgevig, A.; Pastor, I. M.; Adolfsson, H. *Chem. Eur. J*. **2004**, *10*, 294−302.

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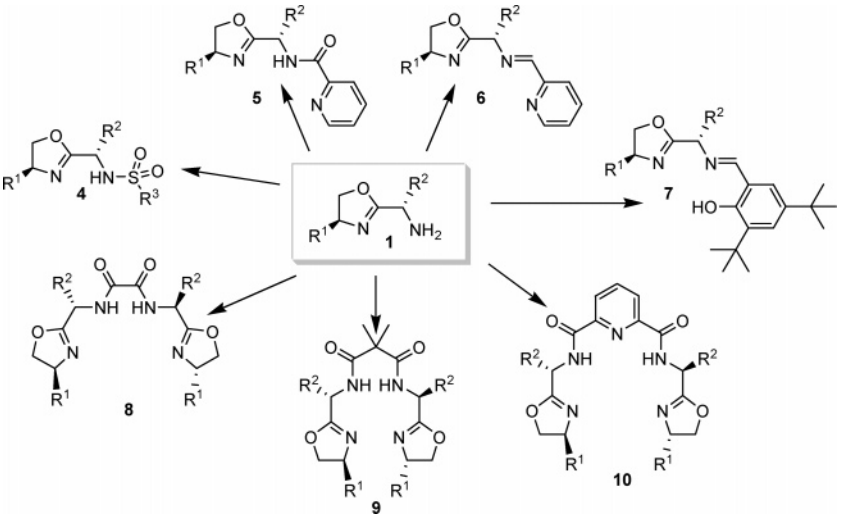
(16) (a) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353−9372. (b) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471−4474.

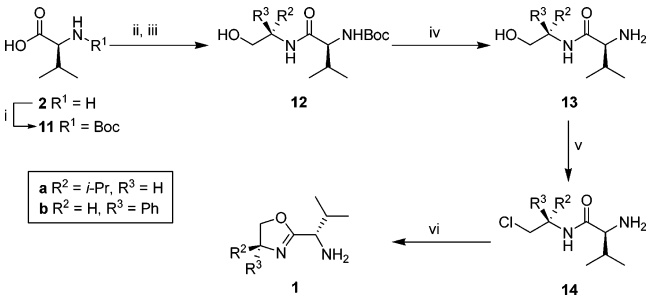
(17) A similar *N*-sulfonated (2-aminomethyl)oxazoline was previously prepared and used as an intermediate in the synthesis of the immunosuppressant FR901483; see: Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *5*, 765−767.

(18) The attempted coupling resulted predominantly in the acylation of the *N*-sulfonyl protected amino acid by the coupling reagent (isobutylchloro formate).

SCHEME 2

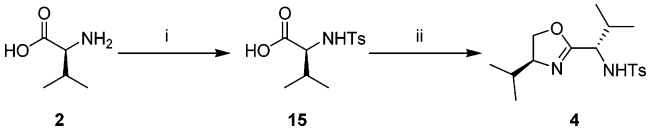


SCHEME 3[a]



[a] Reagents, conditions, and yield: (i) $(Boc)_2O$, NaOH, THF/ H_2O, 25 °C; (ii) Bu^iOCOCl, NMM, THF, −15 °C; (iii) 1,2-amino alcohol, THF, 25 °C (91% from **2**); (iv) HCl (aq, 3 M), MeOH (93%); (v) $SOCl_2$, 1,2-dichloroethane, 70 °C (90%); (vi) NaOH, EtOH, reflux (79% from **13**).

SCHEME 4[a]



[a] Reagents, conditions, and yield: (i) TsCl, Et_3N, 2 M NaOH, rt (97%); (ii) L-valinol, PPh_3, CCl_4, CH_3CN/pyridine, rt (81%).

by the coupling reaction. Hence, after initial formation of the tetraamides **19**, these compounds were treated with thionyl chloride to yield the bischloro compounds **20**. Subsequent base treatment of **20** facilitated the ring closure to the C_2-symmetric bisamidooxazolines **9** in overall yields up to 80% starting from **13**.

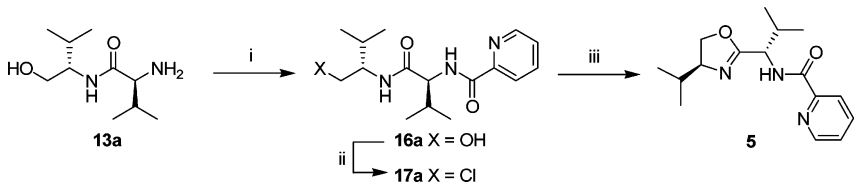
Compound **10**, which potentially can act as a pentadentate ligand, was prepared according to Scheme 9. The "dipeptide" **13a** was initially reacted with 2,6-di(chloroformyl)pyridine in the presence of triethylamine to yield tetra-amide **22**. Exchange of the alcohols for chlorides led to compound **23**, and submitting **23** to the standard ring-closing conditions (i.e., sodium hydroxide in ethanol) resulted in the formation of the C_2-symmetric ligand **10** in 76% overall yield.

As presented above, we have employed a number of different approaches for the formation of ligands **4**−**10**. The most convergent and perhaps most modular route is to start with 2-(aminoalkyl)oxazolines **1** and to connect these scaffolds with various electrophiles to obtain the desired ligand structures. However, the sensitivity of the oxazoline moiety in compound **1** makes further transformations and purifications involving this unit somewhat problematic, often leading to undesirable ring opening of the heterocycle. Despite these problems we chose to use this route for the preparation of ligands **6** and **7**, respectively, since the imine functionality present in these structures is even more sensitive toward decomposition. Another common intermediate that can be introduced at a late stage in the synthesis of the ligands is chloroamide **14**. The major problem encountered using chloroamide **14** as the key building block for the preparation of the various ligands is the nonproductive intramolecular side reaction leading to the formation of the piperazinone **24** (Scheme 10).

With these problems in mind, the slightly less convergent approach using hydroxy-amide **13** as the common intermediate turned out to be the most high-yielding and successful route into ligands **5**, **9**, and **10**, respectively. For example, ligand **9a** was initially prepared via coupling of chloroamide **14a** with dimethylmalonyl chloride, but when comparing the outcome with the route shown in Scheme 8, the preparation starting with **14a** gave about 20% lower overall yield. The chlorination of hydroxyamides **16**, **19**, and **22** were all high-yielding steps, resulting in >94% of the desired chloro-compounds. Hence, this strategy would certainly be useful also for other compounds where an amide linkage is formed during the ligand preparation.

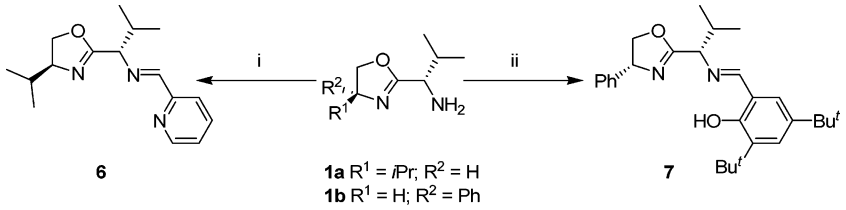
Catalytic Performance. With the plethora of chiral oxazoline-based ligands in hand we set out to investigate their abilities to influence the stereochemical outcome of an asymmetric catalytic transformation. Even though compounds **4**−**10** are based on the same structural motif, their coordinating ability can be expected to vary substantially, depending on both the choice of metal and the reaction conditions used in the complex formation or in the catalytic process. Compound **4** can be expected to coordinate a metal either solely through the oxazoline moiety or in a bidentate fashion upon sulfonamide-deprotonation. The potentially tridentate ligands **5**−**7**

SCHEME 5[a]



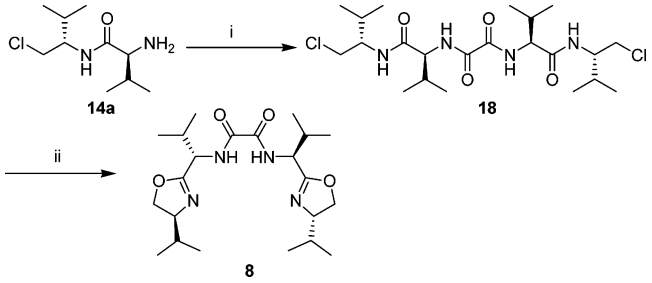
[a] Reagents, conditions, and yield: (i) 2-picolinoyl chloride, Et_3N, CH_2Cl_2 (99%); (ii) $SOCl_2$, 1,2-dichloroethane, rt (94%); (iii) NaOH, EtOH, reflux (62%).

SCHEME 6[a]



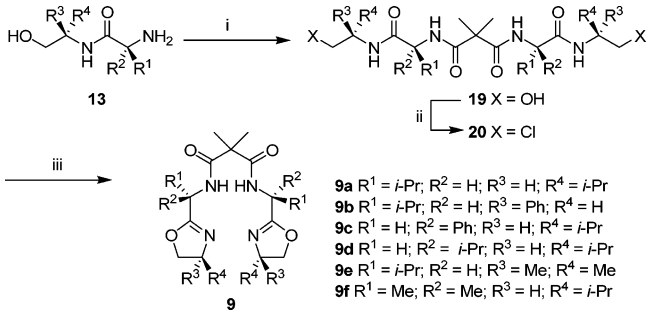
[a] Reagents, conditions, and yield: (i) 2-pyridinecarboxaldehyde, CH_2Cl_2, 4 Å MS, rt (85%); (ii) 3,5-di-*tert*-butylsalicylaldehyde, $MgSO_4$, $La(OTf)_3$, CH_2Cl_2, rt (37%).

SCHEME 7[a]



[a] Reagents, conditions, and yield: (i) oxalyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt; (ii) NaOH (0.5 M in MeOH), THF, reflux (89% from **14a**).

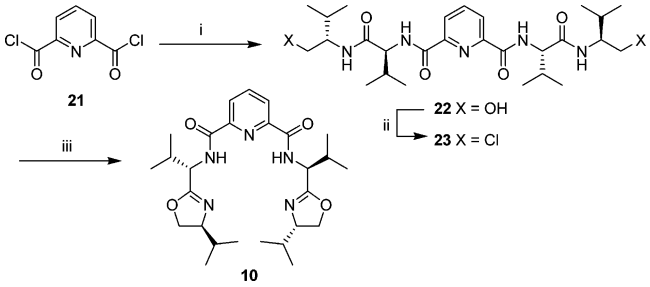
SCHEME 8[a]



[a] Reagents, conditions, and yield: (i) dimethylmalonyl dichloride, Et_3N, CH_2Cl_2, 0 °C to rt (90−93%); (ii) $SOCl_2$, CH_2Cl_2, 0 °C to rt; (iii) NaOH, EtOH, reflux (75−86% from **19**).

have an increased number of metal-coordinating possibilities, and an even larger set of coordination compounds can be expected from the use of ligands **8**−**10**. The choice of metal and type of catalytic reaction to study would thus instinctively be directed by the nature of the ligand. Guided by these arguments, the logic choice of a catalytic process for the polydentate ligands (**8**−**10**) is a reaction where the catalyst or a catalytic intermediate needs to be stabilized by a strong ligand field (for instance, an oxidation process using a highly oxidized

SCHEME 9[a]

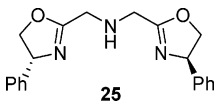


[a] Reagents, conditions, and yield: (i) **13a**, Et_3N, CH_2Cl_2, 0 °C to rt (94%); (ii) $SOCl_2$, CH_2Cl_2, 0 °C to rt (99.9%); (iii) NaOH, EtOH, reflux (81%).

SCHEME 10

transition metal), whereas ligands **4**−**7** would be applicable in a wider range of catalytic processes (i.e., additions, allylic substitutions, various oxidations and reductions).[1a] On the other hand, the diversity approach we used for preparing the compounds presented above opens for an unprejudiced investigation of all ligands in any catalytic reaction, where perhaps interesting results would be obtained from unexpected metal ligand combinations. Our previous studies employing libraries of chiral ligands in asymmetric reduction reactions prompted us to initially survey the new set of oxazoline-ligands in the ruthenium-catalyzed asymmetric transfer-hydrogenation of aryl alkyl ketones.[14,19]

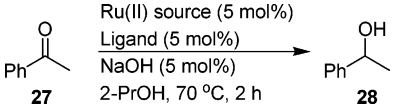
Besides, we were further encouraged by the excellent results obtained by Zhang and co-workers, who employed the structurally rather similar bisoxazoline **25** in combination with $Ru(PPh_3)_3Cl_2$ (**26**) for the asymmetric reduction of ketones under hydrogen transfer conditions.[20] Their results strengthen the hypothesis that the compounds presented in Scheme 2 would be good ligand



25

candidates for the same reaction. Thus, we performed the reduction of acetophenone employing **26** as ruthenium source and ligands **4**, **7**, and **9a**, respectively, as catalysts under the conditions shown in Scheme 11 ([acetophenone] = 0.2 M). The catalysts formed between ligand **4** or **7** and ruthenium(II)-precursor **26** gave the product alcohol in high yields, but unfortunately with no or low enantioselectivity (up to 24% ee). The catalyst formed between ligand **9a** and **26** completely inhibited the reaction and no product formation was observed. Changing the ruthenium-precursor to $[Ru(p\text{-cymene})Cl_2]_2$ did not improve the situation and even lower enantioselectivity was observed.[21]

SCHEME 11



27 **28**

The rather disappointing results obtained in the transfer-hydrogenation reaction led us to examine the influence of this ligand system in another typical asymmetric benchmark reaction, the addition of diethylzinc to aldehydes.[22] The addition of diethylzinc to benzaldehyde is certainly one of the most studied asymmetric reactions, and there are a number of ligands that catalyze the formation of the secondary alcohol product in excellent enantioselectivity. The fact that this reaction is so well-studied makes it a good choice for examining the activity of novel ligand structures. The typical reaction setup for addition of ethylzinc to aldehydes employs amino alcohol ligands, which in situ form the catalytically active zinc complexes. Performing the addition to benzaldehyde using 2 equiv of diethylzinc and 10 mol % of ligands **4**, **7**, **9a**, and **10**, respectively, resulted in the formation of 1-phenylpropanol in poor yield and enantioselectivity (entries 1, 6, 10, and 23, Table 1). An alternative reaction setup for the aldehyde addition is to use an additional Lewis acid (e.g., a titanium complex) in combination with diethylzinc, and these reactions tend to be more efficient and result in higher enantioselectivity.[23,24] The titanium-mediated protocol has previously been performed using various polydentate ligands[25] and should therefore be more suitable for the ligand system presented in Scheme 2. Thus, employing 10 mol % of ligands **4**, **7**, and **10**, respectively, as the chiral mediators together with a stoichiometric amount of titanium(IV)-isopropoxide for the diethylzinc addition to benzaldehyde resulted in a rather moderate improvement of the chemical yield in the case of ligands **4** and **7**, substantially better when ligand **10** was employed, but disappointingly in a lower enantioselectivity of the formed product

TABLE 1. Enantioselective Addition of Diethylzinc to Benzaldehyde[a]

entry	ligand	$Ti(OPr^i)_4$ (mol %)	T (°C)	yield[b] (%)	ee[c] (%)
1	**4**		−15	15	18 (*S*)
2	**4**	8	−15	12	14 (*S*)
3	**4**	100	−15	20	6 (*S*)
4	**5**	8	−15	37	1 (*R*)
5	**6**	8	−15	19	3 (*R*)
6	**7**		−15	14	17 (*S*)
7	**7**	8	−15	10	12 (*S*)
8	**7**	100	−15	21	8 (*S*)
9	**8**	8	−15	90	4 (*S*)
10	**9a**		−15	19	37 (*S*)
11[d]	**9a**	100	−15	56	54 (*S*)
12	**9a**	8	−15	87	78 (*S*)
13	**9a**	8	−78	no reaction	
14	**9a**	8	20	95	47 (*S*)
15[e]	**9a**	10	−15	61	64 (*S*)
16[e]	**9a**	5	−15	67	78 (*S*)
17[f]	**9a**	8	−15	65	75 (*S*)
18	**9b**	8	−15	85	70 (*S*)
19	**9c**	8	−15	90	79 (*S*)
20	**9d**	8	−15	93	73 (*R*)
21	**9e**	8	−15	92[g]	90 (S)
22	**9f**	8	−15	18	25 (*S*)
23	**10**		−15	47	54 (*R*)
24	**10**	8	−15	32	62 (*R*)
25	**10**	100	−15	90	10 (*R*)

[a] Reaction conditions: benzaldehyde (1 equiv), Et_2Zn (2 equiv), ligand (10 mol %), and $Ti(OPr^i)_4$ (8 mol %) in toluene. Reaction time 6 h. [b] Determined by GLC using internal standard. [c] Determined by chiral GLC (CP-Chirasil-Dex CB Chrompack 7503). [d] The catalyst was preformed prior to aldehyde addition. [e] Ligand **2a** (5 mol %). [f] $Zr(OBu^t)_4$ instead of $Ti(OPr^i)_4$. [g] Isolated yield.

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(21) It should be pointed out that only three ligands depicted in Scheme 2 were examined in the asymmetric transfer-hydrogenation of acetophenone. The structural resemblance between these and the other 2-(aminomethyl)oxazoline ligands suggest a similarly poor outcome of the reaction. In fact, in a recent report a similar oxazoline-based ligand made from L-proline was used in the same reaction and this resulted in poor yields and moderate enantioselectivity; see ref 11c.

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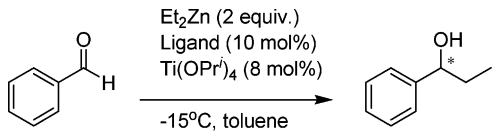
SCHEME 12



29 **30**

(entries 3, 8, and 25). On the other hand, using the same reaction setup with ligand **9a** gave improved yield and selectivity (entry 11). Optimizing the reaction conditions using ligand **9a** we found that upon decreasing the amount of titanium isopropoxide to 8 mol %, the yield and enantioselectivity of the product alcohol further increased (entry 12). This is highly contradictive to previous reports using titanium-based cocatalysts, where high yields and enantioselectivity only were achieved employing an excess of the Lewis acidic metal source.[23] Further results from the optimization showed that changing the reaction temperature to −78 °C completely inhibited product formation (entry 13), whereas performing the reaction at room temperature gave high yield but proved to be detrimental to the enantioselectivity (entry 14). The ratio of titanium versus ligand turned out to be crucial. As shown above, a full equivalent of the titanium alkoxide resulted in decreased conversion and selectivity. Performing the reaction with 5 mol % of the ligand and 10 mol % of the titanium source gave similar results (entry 15). Decreasing the amount of ligand and titanium isopropoxide to 5 mol % gave 1-phenylpropanol in slightly lower yield as compared to what we obtained in entry 12, but gratifyingly, the enantioselectivity remained unchanged (entry 16).[26] From this study we concluded that the optimized experimental conditions for the ethylzinc addition to benzaldehyde using the novel 2-(aminoalkyl)oxazoline-based ligands are as depicted in Scheme 12. Using these conditions and the other ligands described in Scheme 2 resulted in poor reactivity and selectivity in most of the cases. For example, the catalyst formed with the bidentate ligand **4** did not give better yield or selectivity (entry 2), nor did the catalysts based on the tridentate ligands **5**, **6**, or **7** (entries 4, 5, and 7). Employing the tetradentate ligand **8** gave 1-phenylpropanol in high yield but with no enantioselectivity (entry 9). The pentadentate ligand **10** performed distinctly better in terms of enantioselectivity, but the yield was on the other hand rather poor (entry 24). Interestingly, despite the homochirality existing between ligands **4**−**6**, **8**, **9a**, and **10**, different product isomers were obtained. In reactions using ligands **4**, **8**, and **9a**, the *S*-configured enantiomer of **30** was the dominant isomer, whereas using ligand **10** gave **30** with *R*-configuration as the major product. Even though the *R*-isomer was formed in slight excess in reactions performed with ligands **5** and **6**, the results are too small to be of any significance.

From the above study it is obvious that the best performance was obtained using the tetradentate ligand **9a**. Therefore, we logically continued the study by examining compounds with structural variations of this specific type of ligand. When performing the catalytic reaction with ligand **9b**, prepared from L-valine and (*R*)-2-phenylglycinol, high conversion and rather good enantioselectivity of **30** was obtained (entry 18). Surprisingly, the *S*-isomer of the product was formed in excess, although the absolute configuration of the chiral centers in the oxazoline parts of the ligand were interconverted. Replacing ligand **9b** for its regioisomer **9c** resulted in high yield and good enantioselectivity, again in favor of the *S*-isomer of the product (entry 19). The somewhat perplexing results obtained using ligands **9a**−**c** in the diethylzinc additions encouraged us to further study the effects of having different configurations of the four available stereocenters in this particular class of ligands. We therefore performed the catalytic reaction using ligand **9d**, where the configuration on the stereocenters next to the amide functionalities is reversed in comparison to its diastereomer **9a**. The outcome of the reaction resulted in the formation of the secondary alcohol **30** in high yield and with an ee (73%) similar to that previously obtained using **9a** (entry 20). In this case, however, the *R*-product was observed. Next we turned to ligands **9e** and **9f**, respectively, and using **9e** in the diethylzinc addition resulted in high yield and 90% enantioselectivity of adduct **30** (entry 21). When the regioisomer **9f** was employed, a huge drop in conversion and enantioselectivity was observed (entry 22). To conclude the ligand optimization it is apparent that the potentially tetradentate ligands (**9**) are the most efficient in the chirality transfer process. Out of the four stereocenters incorporated in ligands **9a**−**d**, it is clear that the chirality originating from the amino acid determined the absolute configuration of the product. Hence, ligands based on "natural" amino acids (**9a**−**c**, **e**) generated the product with *S*-configuration, and when an unnatural amino acid was present in the ligand (**9d**), the *R*-configured product was obtained. This is further accentuated in the result using ligand **9e**, where the highest enantioselectivity was obtained using a ligand lacking stereocenters in the oxazoline rings. Additionally, the results obtained above in the diethylzinc additions to benzaldehyde show a clear difference in comparison to previous studies on this particular reaction. The amount of titanium alkoxide necessary for efficient catalysis is dramatically deviating from earlier results. The use of a stoichiometric amount, or even an excess, of the titanium source has been considered as a highly important requirement for efficient catalysis. The increase in the reaction rate observed under those conditions was suggested to be a result of efficient removal of the product alkoxide, thereby reconstituting the active catalyst.[27,28] On the contrary, we observed a decrease in reaction rate and enantioselectivity when performing the reaction using 1 equiv of titanium isopropoxide. We believe this effect origin from either a different mechanism of the reaction and/or that the structure of the active catalyst is distinctively different. The latter seems more likely considering the nature of this novel class of ligands. The poly-denticity of the ligands provides plenty of room for the formation of bi- or even oligomeric homo- or heterometallic complexes. The important site of coordination, as suggested by the results presented in Table 1, is probably the bisamide part of ligand **9**. Regarding the structure of the

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TABLE 2. Enantioselective Addition of Diethylzinc to Different Aldehydes Catalyzed by Titanium Isopropoxide and Ligand 9e[a]

entry	substrate	yield (%)[b]	ee (%)[c]
1	benzaldehyde	92	90 (*S*)
2	2-methylbenzaldehyde	90	84 (*S*)
3	3-methylbenzaldehyde	95	91 (*S*)
4	4-methylbenzaldehyde	90	90 (S)
5	2-methoxybenzaldehyde	95	75 (*S*)
6	3-methoxybenzaldehyde	90	85 (*S*)
7	4-methoxybenzaldehyde	68	88 (*S*)
8	3-nitrobenzaldehyde	94	97 (*S*)
9	4-nitrobenzaldehyde	95	94 (*S*)
10	2-naphthaldehyde	96	89 (*S*)
11	3-pyridinecarboxaldehyde	95	15 (*S*)
12	*trans*-cinnamaldehyde	80	68 (*S*)
13	phenylpropargyl aldehyde	95[d]	48 (*S*)[e]
14	cyclohexanecarboxaldehyde	80[f]	89 (*S*)
15	nonylaldehyde	81[g]	84 (*S*)
16	pivalaldehyde	no reaction	

[a] Reaction conditions: aldehyde (1 equiv), Et_2Zn (2 equiv), ligand **9e** (10 mol %), and $Ti(OiPr)_4$ (8 mol %) in toluene. Reaction temperature −15 °C. Reaction time 6 h. [b] Isolated yields. [c] Determined by chiral GLC (CP-Chirasil-Dex CB Chrompack 7503). [d] Reaction time 3 h. [e] Determined by chiral HPLC (OD-H). [f] Reaction time 24 h. [g] Reaction time 12 h.

catalyst, we observed no complex formation when the ligand and titanium isopropoxide were mixed. However, upon addition of diethylzinc to this mixture, the amide protons were abstracted as observed by ^{1}H NMR spectroscopy. This observation further supports a bimetallic complex to be responsible for (1) the activation of the substrate by Lewis acid−base interaction and (2) transfer of the ethyl group. The structure of the catalyst is, however, currently unknown.

With the results from the optimization study described above, we continued with an examination of the substrate scope using ligand **9e**. A number of different aldehydes were submitted to the optimized experimental conditions, and the outcome is summarized in Table 2. With one exception, all the aromatic aldehydes we examined gave the corresponding secondary alcohol product in high yield. Regarding the stereochemical outcome, most products were obtained in high enantioselectivity, especially the electron-poor nitro-substituted benzaldehydes (Table 2, entries 8 and 9). Furthermore it should be noted that regardless of the electronic properties of the examined substrates, we obtained the *S*-configured secondary alcohol as the major isomer. This observation indicates that the same active catalyst is operating in all cases. In contrast to the electron-poor nitro-substituted benzaldehydes, the reaction with 3-pyridinecarboxaldehyde gave the product with low enantioselectivity, perhaps due to competing coordination between the zinc reagent and the substrate or the product (Table 2, entry 11). In the reaction between diethylzinc and *trans*-cinnamaldehyde, we obtained the secondary alcohol in good yield but only in moderate enantioselectivity (entry 12). The sterically nonhindered phenylpropargyl aldehyde reacted rapidly under these conditions, but the corresponding secondary alcohol was formed in significantly lower ee in comparison to the arylaldehydes. Furthermore, we performed the diethylzinc additions to some alkylaldehydes and in the cases where nonhindered substrates were used, the alcohol products were formed in good yields with moderate to good enantioselectivity (entries 14 and 15). Unfortunately we did not observe any product formation in the reaction with the sterically more demanding pivalaldehyde.

Conclusions

We have designed and prepared a novel set of chiral ligands based on a common, highly modular oxazoline scaffold, 2-(aminomethyl)oxazoline **1**. Based on this ligand motif we have constructed an array of compounds with varying denticity, from asymmetric bidentate up to C_2-symmetric potentially pentacoordinating oxazoline-based ligands. The ligands were readily synthesized in a straightforward fashion from commercially available enantiomerically pure starting materials using three different albeit similar routes. We have further demonstrated the use of these ligands in the titanium-catalyzed addition of diethylzinc to benzaldehyde. Depending on the reaction conditions employed, moderate to high enantioselectivity of the formed 1-phenylpropanol were obtained. The C_2-symmetric bisoxazoline **9e** was established as the best ligand and employing a catalytic mixture containing 10 mol % of this ligand together with 8 mol % of titanium isopropoxide, we conducted the addition-reaction of diethylzinc to a number of different aldehydes yielding the corresponding secondary alcohols in good chemical yield and with enantioselectivity up to 97%. The enantioselective addition of diethylzinc to aldehydes is most likely not the only catalytic process in which this new class of oxazoline ligands can be employed, and encouraged by the results presented above, we are currently investigating other asymmetric transformations using ligands based on the 2-(aminomethyl)-oxazoline core.

Experimental Section

(1*S*)-1-[(4*R*)-4-Phenyl-4,5-dihydrooxazol-2-yl]-2-methylpropylamine (1b). Compound **13b** (7.79 mmol, 1.58 g) was dissolved in CH_2Cl_2 (35 mL) and cooled to 0 °C, and $SOCl_2$ (18.7 mmol, 1.36 mL) was added dropwise. The reaction mixture was allowed to reach ambient temperature and stirred for 6 h at which time the temperature was again adjusted to 0 °C and aqueous $NaHCO_3$ (30 mL) was added. After 5 min of stirring, the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with Na_2SO_4. Evaporation of the solvent yielded 1.55 g of **14b** (7.00 mmol, 90% yield), which was used immediately in the next step. NaOH (10.0 mmol, 0.40 g) was added to a refluxing solution of **14b** (7.00 mmol, 1.55 g) in EtOH (50 mL). After 2 h the reaction mixture was cooled to room temperature and EtOH was evaporated under reduced pressure. CH_2Cl_2 (20 mL) and $NaHCO_3$ (20 mL) were added, the phases were separated and the aqueous phase was extracted with additional CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried with Na_2SO_4. Evaporation of CH_2Cl_2 yielded a yellow oil which was purified via column chromatography CH_2Cl_2/MeOH 9:1. After purification, 1.025 g **1b** was obtained as a yellow oil (5.56 mmol, 71% yield from **13b**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (6H, dd), 1.60 (2H, br s), 2.08 (1H, m), 3.45 (1H, dd), 4.12 (1H, t), 4.67 (1H, dd), 5.20 (1H, t), 7.23−7.42 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 19.7, 32.4, 55.7, 69.6, 75.2, 126.9, 127.8, 129.0, 142.4, 171.4.

(1*S*)-*N*-(4-Toluenesulfonyl)-1-[(4*S*)-4′-isopropyl-4,5-dihydrooxazol-2-yl)-2-methylpropyl-amine (4). Compound **15** (11 mmol, 2.98 mg), L-valinol (11 mmol, 1.17 g), Et_3N (33 mmol, 4.6 mL) and CCl_4 (44 mmol, 4.2 mL) were dissolved in CH_3CN/pyridine (1:1 22 mL), and to this solution was

slowly added triphenylphosphine (33 mmol, 8.75 g), dissolved in CH_3CN/pyridine (1:1 22 mL), over a period of 3 h. The resulting mixture was stirred for an additional 12 h and then quenched by addition of NaOH (0.5 M, 100 mL). The aqueous layer was washed with diethyl ether (2 × 25 mL) and CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under vacuum. The crude product was purified by column chromatography using toluene followed by toluene/EtOAc 6:1 as eluent. Evaporation of the solvents resulted in 3.0 g of **4** (8.9 mmol, 81% yield) as a white solid. Mp 108−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (3H, d), 0.74 (3H, d), 0.87 (3H, d), 0.97 (3H, d), 1.26 (1H, h), 2.00 (1H, m), 2.38 (3H, s), 3.54 (1H, m), 3.73 (1H, t), 3.81 (1H, q), 4.00 (1H, t), 5.24 (1H, d), 7.24 (2H, d), 7.72 (2H, d); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 18.5, 18.9, 19.0, 21.6, 32.1, 32.8, 56.9, 71.3, 71.9, 127.5, 129.6, 133.3, 143.4, 165.1; MS (MALDI-TOF) (*m/z*) 377.408 (MK^+), 361.412 (MNa^+), 339.401 (MH^+); elemental analysis calcd (%) for $C_{17}H_{26}N_2O_3S$, C 60.33, H 7.74, N 8.28; found, C 60.34, H 7.62, N 8.12.

***N*-[(1*S*)-2-Methyl-1-{(4*S*)-4-isopropyl-4,5-dihydro-oxazyl-2-yl}-propyl]-2-pyridine-carboxamide (5).** To a refluxing ethanol solution (25 mL) of **17a** (4.21 mmol, 1.37 g) was added NaOH (5.00 mmol, 0.20 g), and the resulting mixture was stirred under reflux for 2 h. The solvent was evaporated under reduced pressure. Aqueous $NaHCO_3$ (25 mL) and CH_2Cl_2 (30 mL) were added and the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with Na_2SO_4. After evaporation of the solvent, the crude product was purified with column chromatography using CH_2Cl_2/MeOH (19:1) as eluent. Compound **5** was isolated in 0.875 g as a yellow oil (2.60 mmol, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (6H, dd), 1.01 (6H, dd), 1.74 (1H, m), 2.26 (1H, m), 3.90−4.05 (2H, m), 4.27 (1H, t), 4.81 (1H, dd), 7.41 (1H, ddd), 7.83 (1H, td), 8.18 (1H, d), 8.53 (1H, br d), 8.58 (1H, d); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 19.0, 19.3, 19.9, 32.1, 32.8, 53.0, 70.6, 72.1, 122.5, 126.4, 137.4, 148.5, 150.0, 164.2, 165.9; MS (MALDI-TOF) (*m/z*) 290.316 (MH^+); elemental analysis calcd (%) for $C_{16}H_{23}N_3O_2$, C 66.41, H 8.01, N 14.52; found, C 66.65, H 8.12, N 14.68.

(1*S*)-*N*-(2-Pyridinylmethylene)-1-[(4*S*)-4′-isopropyl-4,5-dihydrooxazol-2-yl]-2-methylpropylamine (6). Compound **1a** (0.65 mmol, 120 mg) and 2-pyridinecarboxaldehyde (0.99 mmol, 94 μL) were dissolved in dry CH_2Cl_2 (3 mL) containing activated 4 Å MS (100 mg) and the mixture was stirred for 24 h at ambient temperature. The reaction solution was filtered to remove the molecular sieves, the solvent was evaporated and the resulting crude was triturated with *n*-pentane, filtrated and evaporated. The obtained yellow oil was immediately purified using column chromatography on SiO_2, initially using EtOAc as eluent to remove the excess 2-pyridinecarboxaldehyde and then with CH_2Cl_2/MeOH (10:1) to collect the product. After purification, 152 mg of compound **6** was isolated as a yellow oil (0.56 mmol, 85%). ^{1}H NMR (300 MHz, C_6D_6)[29] δ 0.75 (3H, d), 0.92 (3H, d), 0.99 (3H, d), 1.04 (3H, d), 1.51 (1H, m), 2.60 (1H, m), 3.55−3.70 (2H, m), 3.82 (1H, m), 3.93 (1H, m), 6.58 (1H, t), 6.98 (1H, t), 8.15 (1H, d), 8.43 (1H, d), 8.70 (1H,s); ^{13}C NMR (75 MHz, C_6D_6) δ 19.1, 19.3, 19.6, 20.2, 32.0, 33.5, 70.4, 72.9, 75.4, 121.6, 125.0, 136.3, 149.9, 155.2, 164.7, 166.2; MS (MALDI-TOF) (*m/z*) 312.206 (MK^+), 296.247 (MNa^+), 274.244 (MH^+); elemental analysis calcd (%) for $C_{16}H_{23}N_3O{\cdot}H_2O$, C 65.95, H 8.65, N 14.42; found, C 66.14, H 8.21, N 14.33.

2,4-Di-*tert*-butyl-6-{[(1*S*)-2-methyl-1-{(4*R*)-4-phenyl-4,5-dihydro-oxazyl-2-yl}-propylimino]-methyl}-phenol (7). Compound **1b** (3.45 mmol, 753 mg) and 3,5-di-*tert*-butylsalicylaldehyde (3.45 mmol, 816 mg) were dissolved in CH_2Cl_2 (50 mL), $MgSO_4$ (1.00 g) and La(OTf)$_3$ (0.173 mmol, 102 mg) were added to the solution, and the resulting mixture were stirred at ambient temperature for 24 h. The solvent was evaporated and the crude was purified by column chromatography using *n*-pentane/EtOAc (10:1) as eluent, to yield 522 mg of **7** as a yellow sticky solid (1.27 mmol, 37%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (6H, dd), 1.31 (9H, s), 1.46 (9H, s), 2.34 (1H, s), 2.41 (1H, q), 3.87 (1H, d), 4.12 (1H, t), 4.65 (1H, t), 5.22 (1H, t), 7.10−7.50 (7H, m), 8.44 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 19.9, 29.7, 31.8, 32.0, 34.3, 35.3, 69.5, 73.7, 74.9, 117.9, 126.6, 126.7, 127.5, 127.7, 127.8, 128.9, 137.0, 140.3, 142.2, 158.4, 167.9; elemental analysis calcd (%) for $C_{28}H_{38}N_2O_2$, C 77.38, H 8.81, N 6.45; found, C 77.23, H 8.57, N 6.50.

***N,N′*-Bis{(1*S*)-1-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-2-methylpropyl}-ethanediamide (8).** The chloroamide **14a** (5 mmol, 1.1 g) was dissolved in dry CH_2Cl_2 (10 mL) under inert atmosphere. The solution was cooled to 0 °C and Et_3N (12 mmol; 1.7 mL) was added. A solution of oxalyl chloride (2.5 mmol; 223 μL) in dry CH_2Cl_2 (2 mL) was added slowly to the reaction mixture (ca. 20 min), the ice bath was removed, and the mixture was stirred overnight. An additional amount of CH_2Cl_2 (10 mL) was added to dissolve the formed precipitate. The organic phase was then washed with HCl (1 M, 10 mL), $NaHCO_3$ (saturated solution, 10 mL) and brine (10 mL). In each case the aqueous layers were extracted with a portion of CH_2Cl_2 (10 mL). The resulting combined organic phases were dried over Na_2SO_4 and the solvent was removed under vacuum to yield **18**. This compound was used directly in the next step without further purification. The crude **18** was dissolved in dry THF (50 mL) and a solution of NaOH (0.5 M, 1.2 equiv of base) in MeOH was added. The solution was refluxed for 3 h, the solvent was removed under vacuum, and the resulting mixture was dissolved in CH_2Cl_2 (20 mL) and washed with brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under vacuum. The crude was purified by column chromatography using *n*-pentane/EtOAc 1:1 as eluent giving 0.94 g of the pure oily bisoxazoline **8** (2.2 mmol, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (6H, m), 0.96 (18H, m), 1.70 (2H, m), 2.17 (2H, m), 3.91 (2H, m), 3.99 (2H, def t, J = 8.4 Hz), 4.26 (2H, dd, J = 9.6 and 8.4 Hz), 4.55 (2H, dd, J = 9.2 and 5.6 Hz), 7.86 (2H, br d, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (2C), 18.4 (2C), 18.9 (2C), 19.1 (2C), 31.8 (2C), 32.8 (2C), 53,6 (2C), 70.7 (2C), 72.1 (2C), 159.3 (2C), 164.6 (2C); MS (MALDI-TOF) (*m/z*) 461.169 (MK^+), 445.178 (MNa^+), 423.201 (MH^+); elemental analysis calcd (%) for $C_{22}H_{38}N_4O_4{\cdot}H_2O$, C 59.97, H 9.15, N 12.72; found, C 59.69, H 8.59, N 12.70.

General Synthesis of Ligands 9a−f, Exemplified for the Preparation of Ligand 9a. *N,N′*-Bis[(1*S*)-1-{(2*S*)-1-hydroxymethyl-2-methylpropylcarbamoyl}-2-methylpropyl]-2,2-dimethyl-malonamide (19a). Triethylamine (10.3 mmol, 1.44 mL) and dimethylmalonyl chloride[30] (4.34 mmol, 0.575 mL) dissolved in dry CH_2Cl_2 (15 mL) were consecutively added dropwise to a solution of **13a** (8.69 mmol, 1.63 g) in dry CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C followed by an additional 12 h at room temperature. Aqueous NaOH (1 M, 100 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (4 × 100 mL). The organic phases were dried over Na_2SO_4, and the solvent was removed under vacuum, which resulted in 1.9 g of **19a** as a white crystalline product (4.1 mmol, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88−1.02 (24H, m), 1.50 (6H, s), 1.88 (2H, m), 2.20 (2H, m), 3.55−3.75 (6H, m), 4.17 (2H, t), 7.01 (2H, br d); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 19.4, 19.7, 23.8, 29.2, 30.4, 50.3, 57.4, 60.4, 63.1, 171.9, 174.2.

***N,N′*-Bis{(1*S*)-1-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-2-methylpropyl}-2,2-dimethylmalonamide 9a.** To a cooled solution (0 °C) of **19a** (3.92 mmol, 1.85 g) in CH_2Cl_2 (50 mL) was added dropwise $SOCl_2$ (18.9 mmol, 1.38 mL). The

(29) This compound proved to be rather sensitive towards hydrolysis. Performing NMR analysis in $CDCl_3$ resulted in substantial decomposition, presumable due to residual acid of the solvent.

(30) Dimethylmalonyl chloride was prepared from dimethylmalonic acid: Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544.

reaction mixture was stirred overnight at ambient temperature, cooled to 0 °C and quenched by addition of aqueous $NaHCO_3$ (70 mL). After an additional 5 min of stirring, the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried with Na_2SO_4, and the solvent was evaporated to give 1.99 g of **20a** (3.92 mmol, 99.9% yield). This compound was used directly without further purification for the preparation of **9a**. Thus, an ethanol (25 mL) solution of **20a** (3.20 mmol, 1.63 g) was heated to reflux, and NaOH (4.64 mmol, 0.186 g) was added. The resulting mixture was refluxed for 2 h and cooled to room temperature followed by evaporation of EtOH under reduced pressure. To the resulting crude was added CH_2Cl_2 (40 mL) and aqueous $NaHCO_3$ (40 mL), the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried with Na_2SO_4. Evaporation of CH_2Cl_2 yielded an oily, yellow crude product that was purified with silica column chromatography using EtOAC as eluent. After purification, 1.2 g of **9a** was isolated as white crystals (2.8 mmol, 86%). Mp 55−57.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (6H, d, J = 6.8 Hz), 0.93 (18H, def d, J = 6.8 Hz), 1.30 (6H, s), 1.70 (2H, m), 2.12 (2H, m); 3.88 (2H, m), 4.01 (2H, def t, J = 8.0 Hz), 4.25 (2H, dd, J = 9.6 and 8.8 Hz), 4.55 (2H, dd, J = 8.4 and 5.2 Hz), 7.30 (2H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (2C), 18.4 (2C), 18.8 (2C), 19.0 (2C), 24.2 (2C), 31.5 (2C), 32.9 (2C), 49.7, 53.2 (2C), 70.9 (2C), 71.7 (2C), 166.1 (2C), 173.5 (2C); MS (MALDI-TOF) (*m/z*) 503.193 (MK^+), 487.217 (MNa^+), 465.235 (MH^+); elemental analysis calcd (%) for $C_{25}H_{44}N_4O_4$, C 64.62, H 9.54, N 12.06; found, C 64.34, H 9.45, N 11.90.

***N,N′*-Bis{(2*S*)-1-[(4*S*)-4-isopropyl-4,5-dihydro-oxazol-2-yl)-2-methylpropyl]-pyridine-2,6-dicarboxamide (10).** An ethanol (30 mL) solution of **23** (2.34 mmol, 1.37 g) was heated to reflux, NaOH (5.84 mmol, 0.234 g) was added, and the reaction mixture was refluxed 1 h. After cooling, EtOH was evaporated under reduced pressure and CH_2Cl_2 (10 mL) and aqueous $NaHCO_3$ (10 mL) were added. The aqueous layer was separated and extracted with additional CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and upon evaporation of the solvent, 0.94 g (1.9 mmol, 81%) of **10** was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91−0.99 (12H, m), 1.02−1.10 (12H, m), 1.90 (2H, h), 2.08 (2H, br s), 2.38 (2H, m), 3.75 (4H, m), 4.41 (1H, t), 6.38 (2H, br s), 8.02 (1H, t), 8.33 (2H, d); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 18.3, 19.0, 19.3, 32.3, 32.8, 53.0, 70.6, 72.1, 125.4, 139.1, 148.9, 163.4; MS (MALDI-TOF) (*m/z*) 500.375 (MH^+); elemental analysis calcd (%) for $C_{27}H_{41}N_5O_4 \cdot 2H_2O$, C 60.54, H 8.47, N 13.07; found, C 61.03, H 8.30, N 13.12.

General Procedure for the Diethyl Zinc Addition to Aryl and Alkyl Aldehydes in the Presence of Ligand 9e (Table 2). Ligand **9e** (0.20 mmol) and titanium isopropoxide (0.16 mmol) were dissolved in toluene (10 mL) in a dry Schlenck tube, under inert atmosphere (N_2). The solution was cooled to 0 °C, diethylzinc (4.00 mmol, 1 M solution in hexane) was added and the resulting mixture was stirred for 1 h, when the temperature was lowered to −15 °C and benzaldehyde (2.00 mmol) was added. The reaction mixture was kept at −15 °C for 6 h and thereafter quenched with the addition of 1 M HCl (20 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried with Na_2SO_4 and the solvent was evaporated. Purification was performed with silica column chromatography using *n*-pentane/EtOAc (10:1) as the eluent. The product, 1-phenylpropanol, was analyzed by GLC (CP Chirasil DEX CB, hold 110 °C for 10 min, rate 80 °C/min to 200 °C and hold for 5 min). R_f = 0.32. Isolated yield: 0.249 g (92% yield, 90% ee). t_R(*R*-isomer) = 10.4 min, t_R(*S*-isomer) = 10.5 min. $[\alpha]_D$ −27.0 (*c* 1.0, methanol) (lit.[31] $[\alpha]_D$ −28 (*c* 1, methanol)).

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Supporting Information Available: Experimental procedures and characterization data for compounds **1a**, **9b**−**f**, **12a**, **12b**, **13a**, **13b**, **15**, **16a**, **17a**, **22**, and **23**; general procedure for the diethylzinc addition to benzaldehyde presented in Table 1; chromatographic separation data for the alcohols presented in Table 2; and ^{1}H and ^{13}C NMR spectra of compounds **1** and **4**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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