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Novel highly modular C_2-symmetric oxazoline ligands—application in titanium-catalyzed diethylzinc additions to aldehydes

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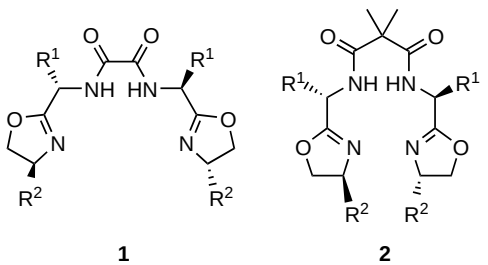
Abstract—Novel C_2-symmetric tetradentate bis-oxazoline ligands were efficiently prepared from α-amino acids, 1,2-amino alcohols and 1,2- or 1,3-diacids. The ligands were employed in the titanium-catalyzed addition of diethylzinc to benzaldehyde, and depending on conditions used, moderate to high enantioselectivities of the formed 1-phenylpropanol were obtained.

Herein we report on a novel class of highly modular C_2-symmetric oxazoline based ligands. The *chiral pool* serves as an outstanding and inexpensive source of asymmetric material for the preparation of ligands intended for metal-catalyzed reactions.[1] The heterocyclic compounds 2-substituted 4,5-dihydrooxazoles, or 2-oxazolines, originally introduced to the synthetic community as base-stable protecting groups for carboxylic acids,[2,3] are presently extensively used as ligand motifs in asymmetric catalysis.[4] The relative ease with which oxazolines are prepared (formally a fusion reaction between a carboxylic acid and an amino alcohol), combined with their metal coordinating ability, make these compounds highly attractive for catalytic applications. With a huge number of commercial non-racemic amino alcohols available, the oxazoline structure is easily modified for optimum catalytic activity and stereocontrol. We have designed a new class of tetradentate C_2-symmetric bis-oxazoline ligands based on the combination of a 1,2- or 1,3-diacid, an α-aminoacid and a 1,2-amino alcohol according to Scheme 1.[5]

The ligand structure can easily be modified by the proper choice of either the amino acid or the amino alcohol, hence this concept opens up a very modular approach towards finding efficient ligands providing the necessary prerequisites for asymmetric induction.

The ligands were efficiently prepared according to the general synthetic route outlined in Scheme 2, starting from the *N*-Boc protected α-amino acids L-valine or (*R*)-phenylglycine. The acids were coupled with the appropriate 1,2-amino alcohols to form amides **3**, using isobutyl chloroformate (**3a**; $R^1=R^2=$isopropyl, 89%, **3b**; $R^1=$isopropyl, $R^2=$(*R*)-phenyl, 91% and **3c**; $R^1=$(*R*)-phenyl, $R^2=$isopropyl, 82%). Boc-deprotection followed by chloride displacement of the alcohol functionality yielded the chloro-amides **4** (**4a**; 52%, **4b**; 43% and **4c**; 39%) which subsequently were coupled with either oxalyl chloride or dimethylmalonyl dichloride to form tetraamides **5** and **6**. The final step to the tetradentate ligands involved treatment of tetraamides **5** and **6** with a methanolic sodium hydroxide solution in THF to facilitate the ring closure to the oxazoline heterocycles (**1**; 57% from **4a**, **2a**; 83% from **4a**, **2b**; 71% from **4b** and **4c**; 75% from **2c**).



Scheme 1.

Initially, a different strategy was employed. We anticipated that 2-aminomethyloxazolines would serve as efficient building blocks for the tetradentate ligands.

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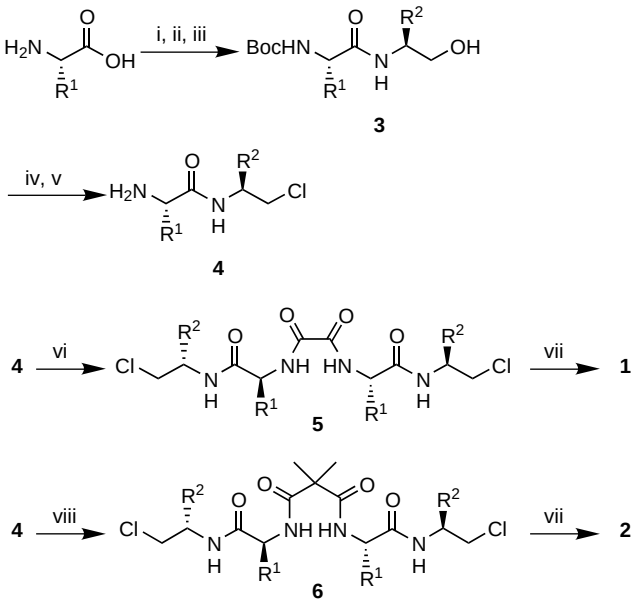
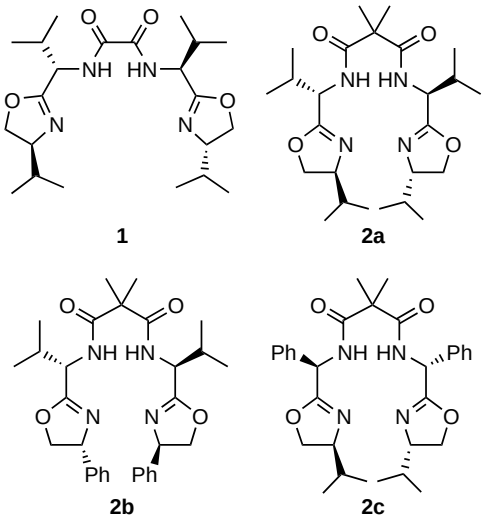
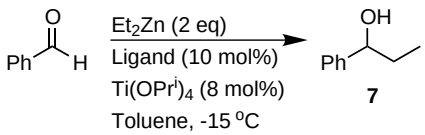


Scheme 2. *Reagents and conditions*: (i) Boc_2O, NaOH, THF/H_2O, rt; (ii) Bu^{t}OCOCl, THF, −15°C; (iii) 1,2-amino alcohol, rt; (iv) HCl (3 M, aq): MeOH (1:1), 0°C; (v) $SOCl_2$, 1,2-dichloroethane, rt; (vi) oxalyl chloride, Et_3N, CH_2Cl_2, 0°C to rt; (vii) NaOH (0.5 M in MeOH), THF, reflux; (viii) dimethylmalonyl dichloride, Et_3N, CH_2Cl_2, 0°C to rt.



Scheme 3.



Scheme 4.

The ring closure forming the oxazoline ring was, however, quite unselective and substantial amounts of by-products were observed. We therefore decided to perform the coupling with the 1,2- or 1,3-diacid prior to the formation of the oxazoline rings. The direct ring forming method reported by Vorbrüggen,[6] starting from either the hydroxy amide or from a *N*-Boc protected α-amino acid and a 1,2-amino alcohol using triphenyl phosphine and carbon tetrachloride, did not result in formation of 2-aminomethyloxazolines.

Thus, the tetradentate ligands prepared according to the above procedure are shown in Scheme 3. Ligand **1** was prepared from L-valine, (*S*)-valinol and oxalyl chloride. Ligands **2a**–**c** are based on dimethylmalonic acid and prepared from; L-valine and (*S*)-valinol (**2a**), L-valine and (*R*)-phenylglycinol (**2b**), and (*R*)-phenylglycine and (*S*)-valinol (**2c**).

With the tetradentate ligands in hand we decided to investigate their efficiency in a typical catalytic asymmetric *benchmark* reaction; the addition of diethylzinc to aldehydes.[7] This particular carbon–carbon bond forming reaction is a frequently studied system, and it serves well as a model for evaluating how ligand structure affects the enantioselectivity of the product. The experimental conditions chosen for the study are outlined in Scheme 4. The typical reaction setup employs zinc catalysts coordinated to amino alcohols, but the use of titanium based catalysts tends to be more efficient and selective.[8,9] Furthermore, the titanium-mediated protocol for the enantioselective addition of diethylzinc to aldehydes has previously been performed using tetradentate ligands.[10]

Thus, employing ligand **1** as the chiral mediator together with a catalytic amount of titanium isopropoxide for the diethylzinc addition to benzaldehyde, resulted in a high yield of 1-phenylpropanol (**7**), however, the enantioselectivity was very poor (Table 1, entry 1).[11] Replacing **1** with the malonic acid derived ligand **2a** resulted in good conversion to **7** and a significantly increased enantiomeric excess (entry 4). Interestingly, performing the reaction with a stoichiometric amount of titanium, resulted in lower conversion to the alcohol product (entry 3). A substantial decrease in enantioselectivity was also observed. This is highly contradictive to previous reports using the titanium system, where high yields and enantioselectivities were only achieved using an excess of the Lewis acidic metal source.

Excluding titanium isopropoxide from the reaction mixture resulted in low conversion to, and modest enantioselectivity of **7** (entry 2). Changing the temperature to −78°C completely inhibited product formation (entry 5), whereas performing the reaction at room temperature proved to be detrimental to the enantioselectivity (entry 6). 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 7). Employing equimolar amounts (5 mol%) of titanium isopropoxide and ligand **2a** gave the secondary alcohol **7** in slightly lower yield but the

Table 1. Enantioselective addition of diethylzinc to benzaldehyde[a]

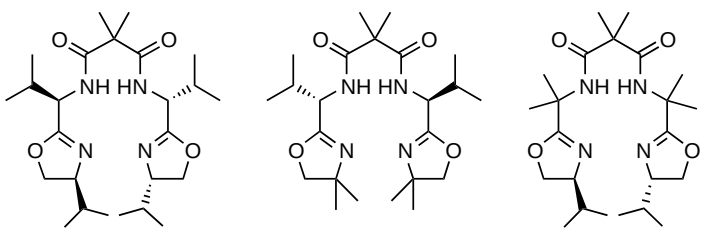
Entry	Ligand	$M(OR)_4$	T (°C)	Yield[b] (%)	ee[c] (%)
1	**1**	$Ti(OPr^i)_4$	−15	90	4 (*S*)
2	**2a**	–	−15	19	37 (*S*)
3[d]	**2a**	$Ti(OPr^i)_4$	−15	56	54 (*S*)
4	**2a**	$Ti(OPr^i)_4$	−15	87	78 (*S*)
5	**2a**	$Ti(OPr^i)_4$	−78	–	–
6	**2a**	$Ti(OPr^i)_4$	20	95	47 (*S*)
7[e]	**2a**	$Ti(OPr^i)_4$	−15	61	64 (*S*)
8[f]	**2a**	$Ti(OPr^i)_4$	−15	67	78 (*S*)
9	**2a**	$Zr(OBu^t)_4$	−15	65	75 (*S*)
10	**2b**	$Ti(OPr^i)_4$	−15	85	70 (*S*)
11	**2c**	$Ti(OPr^i)_4$	−15	90	79 (*S*)
12	**2d**	$Ti(OPr^i)_4$	−15	93	73 (*R*)
13	**2e**	$Ti(OPr^i)_4$	−15	83	89 (*S*)
14	**2f**	$Ti(OPr^i)_4$	−15	18	25 (*S*)

[a] Reaction conditions: benzaldehyde (1 equiv.), Et_2Zn (2 equiv.), ligand (10 mol%) and $M(OR)_4$ (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] $Ti(OPr^i)_4$ (1 equiv.). The catalyst was preformed prior to aldehyde addition.
[e] Ligand **2a** (5 mol%), $Ti(OPr^i)_4$ (10 mol%).
[f] Ligand **2a** (5 mol%), $Ti(OPr^i)_4$ (5 mol%).

enantioselectivity was however unchanged (entry 8).[12] When performing the catalytic reaction with ligand **2b**, prepared from L-valine and (*R*)-2-phenylglycinol, high conversion and good enantioselectivity of **7** was achieved (entry 10). 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 **2b** for its regioisomer **2c**, resulted in high yield and good enantioselectivity, again in favor of the (*S*)-isomer of the product (entry 11).

The somewhat puzzling results obtained using ligands **2a–c** in the diethylzinc additions encouraged us to further study the effects of having different configurations of the stereocenters in the ligands. We therefore prepared ligand **2d** (Scheme 5), from D-valine and (*S*)-valinol (prepared in 76% yield from **4d**), where the configuration on the stereocenters next to the amide functionalities are reversed in comparison to its diastereomer **2a**. The stereocenters in the oxazolines remain, however, the same. Performing the titanium-catalyzed diethylzinc addition to benzaldehyde in the presence of this ligand (**2d**), gave the secondary alcohol **7** in high yield and with a similar ee (73%) to that previously obtained using **2a** (entry 12). In this case, however, the (*R*)-product was observed. Next, we used ligands **2e** and **2f**, respectively, in the catalytic reaction. Ligand **2e**, prepared from the achiral amino alcohol 2-amino-2-methylpropanol and L-valine (prepared in 85% yield from **4e**), when used in the diethylzinc addition, resulted in high yield and good enantioselectivity of the adduct (entry 13). When instead the regioisomer **2f** (obtained in 77% yield from **4f**) was employed, a huge drop in conversion and enantioselectivity was observed (entry 14). The results obtained above in the diethylzinc additions to benzaldehyde show one clear difference in comparison to previous studies, the amount of titanium alkoxide necessary for efficient catalysis. The use of a stoichiometric amount, or even an excess, of the titanium source was in earlier work considered to be an 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.[13] On the contrary, we observed a decrease in reaction rate and enantioselectivity when performing the reaction using 1 equiv. of titanium isopropoxide.



2d **2e** **2f**

Scheme 5.

We believe this effect originates 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 bis-amide part of the ligand. In preliminary studies, we observed no complex formation upon mixing the ligand and titanium isopropoxide. However, upon addition of diethylzinc to this mixture, the amide-protons are 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 and further studies within this field are being performed.

To conclude, we have designed and prepared a novel class of C_2-symmetric oxazoline-based ligands. The ligands were readily synthesized in a straightforward fashion from commercially available enantiomerically pure starting materials. 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 enantioselectivities of the formed 1-phenylpropanol were obtained.

Acknowledgements

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11. General procedure for the addition of diethylzinc to benzaldehyde. Et_2Zn (2 equiv., 1.0 M solution in hexanes) was added to a cooled solution (–15°C) of the ligand (10 mol%; 0.1 mmol) and $Ti(OPr^i)_4$ (8 mol%; 0.08 mmol; 15 mg) in dry toluene (3 mL) under inert atmosphere. A solution of benzaldehyde (1 mmol; 1 mL of 1 M solution in dry toluene containing dodecane (20 μL/mmol of aldehyde as internal standard)) was added dropwise. Samples were taken at different time intervals (aliquots: 100 μL), quenched with HCl (1 M) and extracted with Et_2O. The yield and the enantioselectivity was determinated by chiral GLC (CP-Chirasil-Dex CB Chrompack 7530; 25 m×0.32 mm) using dodecane as internal standard. GLC conditions: injector: 200°C; detector: 200°C; *T* (initial): 110°C; *T* (final): 200°C; rate: 80°C/min; *t* (initial): 10 min. Retention times for benzaldehyde and the enantiomers of 1-phenylpropanol: benzaldehyde: 3.35 min; (*R*)-1-phenylpropanol: 10.98 min; (*S*)-1-phenylpropanol: 11.03 min.
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