An Efficient Synthesis of 1-Naphthylbis(oxazoline) and Exploration of the Scope in Asymmetric Catalysis

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Both enantiomers of 1-naphthylglycine were obtained in 99% *ee* by enzymatic resolution of the corresponding racemic amino acid amide, giving access to the novel ligands (*R*)- and (*S*)-naphthylbis(oxazoline). Initial studies provided insight into the scope and limitations of the (*S*)-naphthyl-substituted bis(oxazoline) and its steric influence compared to other bis(oxazolines) in catalytic asymmetric synthesis.

Introduction

During the last decade, bis(oxazoline) (box) based metal complexes[1] have emerged as highly enantioselective catalysts in a wide range of transformations such as Diels–Alder[2] and hetero-Diels–Alder reactions,[3] aldol reactions,[4] Michael additions,[5] and Friedel–Crafts reactions.[6] These conversions generally proceed via in situ formation of a chiral Lewis acid catalyst through bidentate complexation of the box ligand to a transition metal. So far, many variations at the core of the box ligand have been made, including variation of substituents (R^1) on the bridging methylene group,[7] and the introduction of additional stereocenters on the oxazoline rings (R^2, R^3) in such a way that the C_2-symmetry is maintained (type **A**, Figure 1).[8] A larger structurally deviating box-ligand features a bridging pyridine moiety resulting in tridentate coordinating box ligands (type **B**).[9] Generally, the commercially available box ligands of type **A** (with $R^2 = R^3 = H$) are most often used. Recently, the groups of Pfaltz, Helmchen and Williams independently developed a new type of non-C_2-symmetric oxazoline-based P,N-ligands (type **C**), suitable for application in palladium-catalyzed asymmetric reactions.[10]

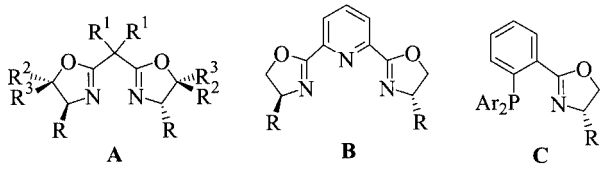

Figure 1. General structure of (bis)oxazoline-based ligands

Although many different substituted bis(oxazoline) ligands have been synthesized, only a few ligands of type **A** (R = isopropyl, *tert*-butyl, benzyl, phenyl with $R^2 = R^3 = H$) are frequently used. Despite the versatility of these ligands, there is not one single ligand that gives optimal results in every type of conversion; the most suitable ligand is usually identified by trial-and-error methods.

The frequently observed reversal of facial selectivity exhibited by alkyl- vs. aryl-substituted box ligands is remarkable. This phenomenon was first reported by the group of Jørgensen and was ascribed to a change in geometry of the metal center (from distorted square planar for *tert*-butyl-box to tetrahedral for phenyl-box).[11] Alternatively, the group of Evans performed solid-state crystallization studies on the phenyl-box and the *tert*-butyl-box·$Cu(H_2O)_2$ complex, both complexes having distorted square planar geometries (with an average distortion of −9° and +33°, respectively).[12] Therefore, Evans concluded that the phenyl-box complex exhibits a reduced propensity to deviate from square planarity than the *tert*-butyl-box complex. Although this forms no conclusive evidence for or against Jørgensen's proposal, it reduces the possibility of a planar-tetrahedral equilibrium in solution, based on a series of studies of bis(*N*-alkylsalicylaldiminato)copper(II) complexes.[13] Very recently, Jørgensen stated that the reversal of selectivity is mainly caused by differences in the flexibility and dynamics

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of the ligand. This includes not only the ability of the complex to interconvert between square-planar and tetrahedral conformations, but also the ability of the oxazoline substituent to flip between pseudo-axial and pseudo-equatorial positions.[14]

For the alkyl-substituents (R), it is generally found that with an increase of steric bulk of the substituent the enantioselectivity is increased. To the best of our knowledge, the steric influence of aryl-substituents has only once been extensively studied.[15] It was observed that the use of 2-naphthyl-box in combination with $Mg(OTf)_2$ induces a small increase in enantioselectivity in the Diels–Alder reaction of *N*-acryloyl-substituted oxazolidinone with cyclopentadiene compared to the use of phenyl-box (from 70 to 77% *ee*). Hence, the use of a more extended aromatic system on the chiral ligand appears to have a positive effect on the enantioselectivity of a tetrahedrally organized chiral catalyst. Moreover, a single example of the use of the bulky 1-naphthyl-box ligand in asymmetric Diels–Alder reactions has been described by the group of Evans.[16] Although the enantioselectivity was better than the phenyl-box ligand, it was still moderate and considerably lower than for the alkyl-substituted ligands. Surprisingly, the synthesis of this 1-naphthyl-substituted ligand has not been reported yet.

As part of a research project aimed at controlling the enantioselectivity of catalytic processes by variation of the electronic and steric properties of the substituents on the bis(oxazoline) ligands, we became interested in the 1-naphthyl-box ligand. Therefore, we performed PM3-level calculations[17] on the (*S*)-1-naphthyl- and (*S*)-phenyl-box ligand-copper(II) catalyst, choosing methyl pyruvate as the complexing compound since it is often used as the substrate in different types of reactions (Figure 2). In both cases, the complex adapted a distorted square-planar geometry in which one side of methyl pyruvate was blocked from attack by an incoming nucleophile, suggesting a favorable attack on the *Si*-face. A comparison of these complexes clearly shows an increase of shielding of the *Re*-face of methyl pyruvate in the complex with the 1-naphthyl-substituted ligand, predicting an enhanced enantioselectivity compared to the phenyl-box catalyst.

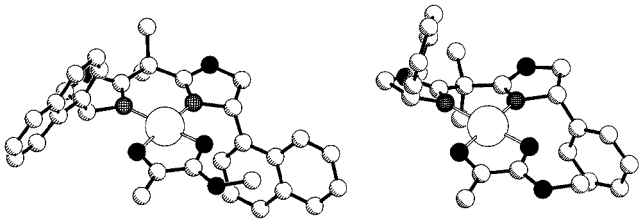
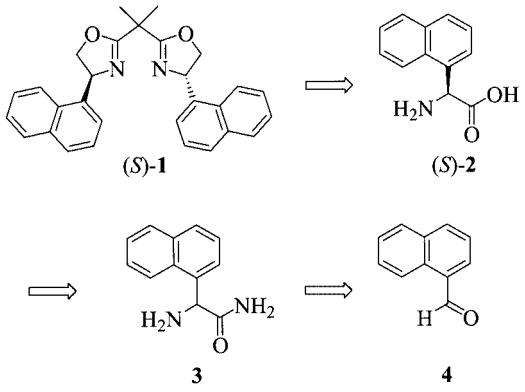


Figure 2. PM3 model of [Cu(*S*)-1-Np-box] and [Cu(*S*)-Ph-box] complex with methyl pyruvate

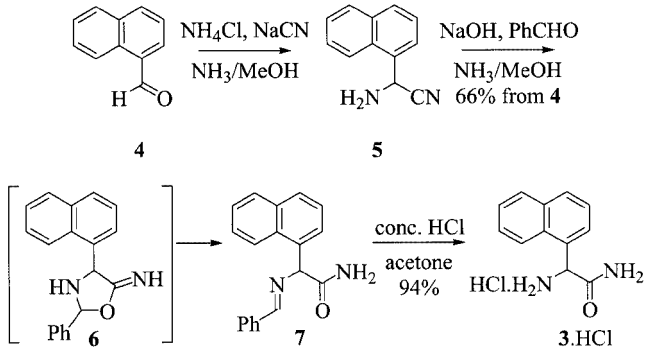
Considering the few experiments that have been carried out with the latter ligand, the promising PM3-model and the anticipated facile access to the required amino acid, we set out to develop a straightforward and efficient synthesis of the 1-naphthyl-box ligand and to explore its scope and limitations. A retrosynthetic analysis shows that ligand **1** is accessible from the corresponding enantiopure amino acid **2** (Scheme 1), which, in turn, is derived from the racemic amino acid amide **3** through an enzymatic resolution process that has been extensively studied in our group.[18] The amide was expected to be formed upon treatment of naphthaldehyde (**4**) under Strecker conditions, followed by partial hydrolysis of the resulting cyanide.



Scheme 1. Retrosynthesis of (*S*)-1-naphthylbis(oxazoline)

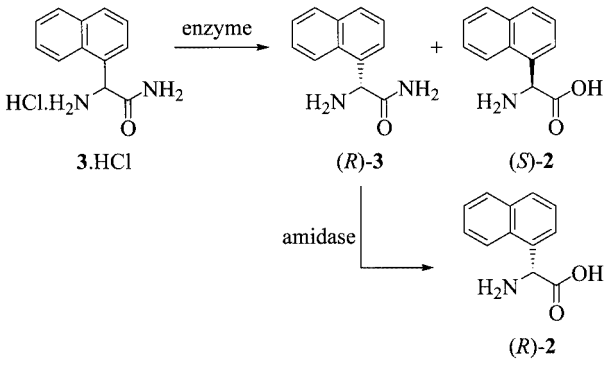
Results and Discussion

The synthesis of 1-naphthylglycine amide (**3**) started with a modified Strecker reaction (HCN prepared in situ from equimolar amounts of NH_4Cl and NaCN in concentrated ammonia) on freshly distilled 1-naphthaldehyde to give aminonitrile **5** (Scheme 2). After the reaction had finished, in situ reaction with benzaldehyde in the presence of NaOH (pH ≈ 10) led to conversion of the amino function into the Schiff base, with concomitant partial hydrolysis of the cyanide group (presumably via the five-membered ring *N*,*O*-acetal **6**).[19] Subsequent hydrolysis of the benzaldimine under the influence of concentrated HCl in acetone resulted in the crystalline HCl salt of the desired amino acid amide **3**. The whole sequence was efficiently carried out in 62% overall yield with only a single purification step at the end (precipitation from acetone).[18]



Scheme 2. Synthesis of 1-naphthylglycine amide

Table 1. Enzymatic resolution of amino acid amide **3**



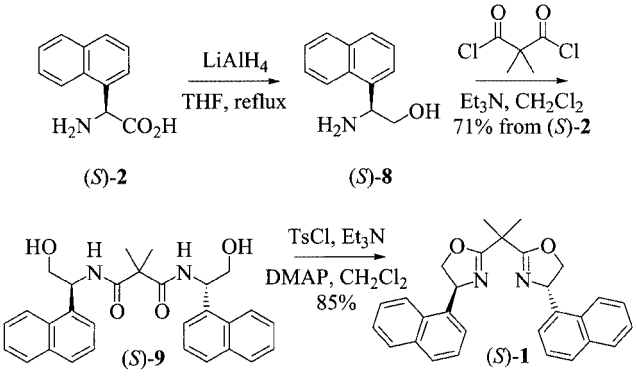
Enzyme source	(*S*)-**2** Yield (%)[a]	*ee* (%)[b]	(*R*)-**3** Yield (%)[a]	*ee* (%)[b]
P. putida ATCC 12633	86	89	90	99
O. anthropi NCIMB 40321	98	99	90	99

[a] Isolated yield. [b] Enantiomeric excess was determined by NMR spectroscopy.[29]

Treatment of racemic **3**·HCl with an L-specific aminopeptidase present in whole cells of the microorganism *Pseudomonas putida* ATCC 12633[18] (pH = 8.3, T = 37 °C) led to a mixture of the corresponding (*R*)-amide **3** and (*S*)-acid **2** in good yield and with high enantioselectivity [45% (99% *ee*) and 43% (89% *ee*), respectively; Table 1]. The amide and acid could be easily separated by a simple extraction with CH_2Cl_2 as a result of the low solubility of the amide in a basic aqueous environment. However, the low solubility of the amino acid amide caused the resolution (the enzyme optimum lies around pH 9) to proceed very slowly. The solubility problem was overcome by applying an L-specific amidase from the microorganism *Ochrobactrum anthropi* NCIMB 40321,[20] which has a good activity at pH 6.5 and is able to withstand a higher reaction temperature (50 °C). The use of this amidase resulted in an improvement of both yield and enantioselectivity giving the (*R*)-amide and (*S*)-acid in greater than 98% enantiopurity. Beside the synthesis of the (*S*)-acid **2**, the corresponding (*R*)-acid could also be obtained by hydrolysis of (*R*)-**3** with a non-selective amidase produced by *Rhodococcus erythropolis* NCIMB 11540.[21]

With the required amino acid in hand, the 1-naphthyl-box ligand (*S*)-**1** was synthesized according to a previously reported method (Scheme 3).[22] $LiAlH_4$ reduction of (*S*)-1-naphthylglycine (**2**) to the amino alcohol **8** and subsequent acylation with dimethylmalonyl dichloride resulted in diamide (*S*)-**9** in 71% yield. This diamide was then smoothly cyclized to the desired bis(oxazoline) via in situ formation of the bis(tosylate); recrystallization finally afforded enantiopure (*S*)-**1** in 60% overall yield starting from 1-naphthylglycine (**2**) and 37% yield from naphthyldehyde (**4**).

The scope and limitations of the (*S*)-1-naphthyl-box ligand in catalytic asymmetric synthesis were tested in a series of reactions and compared to results obtained with (*R*)-phenyl-box, (4*S*,5*S*)-diphenyl-box[23] and (*S*)-*tert*-butyl-box **1** (Figure 3). Furthermore, we anticipated being able to identify reactions that could especially benefit from the use of this particular ligand. These reactions were carried out with the [box-Cu^{II}] catalyst complexed to methyl pyruvate.



Scheme 3. Synthesis of (*S*)-1-naphthylbis(oxazoline) (*S*)-**1**

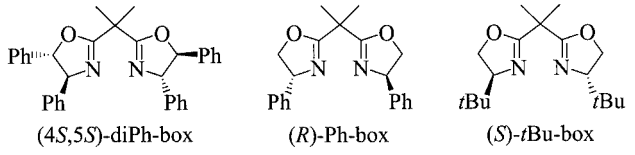
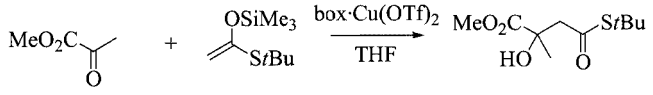


Figure 3. Reference box ligands

As a starting point, we tested the novel 1-Np-box ligand in the previously reported Mukaiyama aldol reaction of methyl pyruvate with silyl ketene acetal **11** in THF (Table 2).[24] However, use of this ligand-Cu(OTf)$_2$ complex resulted only in a decrease of enantioselectivity compared to Ph-box (19% vs. 24% *ee*). In contrast, a significantly higher *ee* was observed when using the (4*S*,5*S*)-diphenyl-

box and (*S*)-*t*Bu-box ligands (68% and 97% *ee*, respectively). Apparently, in this type of aldol reaction, the 4-aryl-substituted ligands do not have a crucial influence on the stereochemical outcome of the reaction.

Table 2. Results of the Mukaiyama aldol reaction



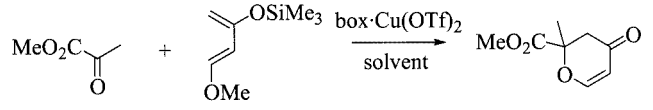
10 **11** **12**

Ligand	THF Yield (%)[a]	*ee* (%)[b]
(*S*)-1-Np-box	n.d.	19 (*S*)
(*R*)-Ph-box[c]	73	24 (*R*)
(4*S*,5*S*)-diPh-box	82	68 (*S*)
(*S*)-*t*Bu-box[c]	89	97 (*S*)

[a] Isolated yield. [b] Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD column (hexane/IPA, 99:1, 0.5 mL/min). [c] Data correspond to literature values.[24]

Another type of reaction in which methyl pyruvate was applied as the substrate in combination with box-Cu(OTf)$_2$ complexes is the hetero-Diels–Alder reaction with (*E*)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene, **13**; Table 3).[25] In both solvents, we observed no significant differences between the Ph- and the 1-Np-box ligand; a slight increase in CH_2Cl_2 (13% to 19% *ee*, respectively) and a slight decrease in THF (35% to 22% *ee*, respectively). In the case of the aryl-substituted box ligands, the selectivity was dependent on the solvent. This effect is in line with the results of Jørgensen.[14] In conclusion, the use of the 1-Np-box did not give the expected enhancement in enantioselectivity of this reaction.

Table 3. Results of the hetero-Diels–Alder reaction



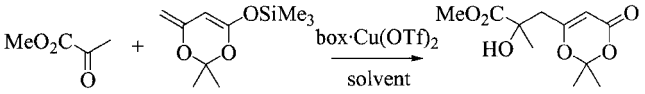
10 **13** **14**

Ligand	CH_2Cl_2 Yield (%)[a]	*ee* (%)[b]	THF Yield (%)[a]	*ee* (%)[b]
(*S*)-1-Np-box	n.d.	19 (*S*)	90	22 (*R*)
(*R*)-Ph-box[c]	n.d.	13 (*R*)	99	35 (*S*)
(*S*)-*t*Bu-box[c]	n.d.	>98 (*S*)	99	>95 (*S*)

[a] Isolated yield. [b] Enantiomeric excess was determined by chiral GC on a γ-CD column (110 °C). [c] Data correspond to literature values.[25]

In a search for factors that could favor the use of the 1-Np-box, we came across addition reactions with the silyl enol ether **15**[26] (Table 4). Use of this rather large nucleophile would give dioxenone **16**, which is an interesting building block for further transformations.[27] In this reaction, a significant increase in enantioselectivity was observed by replacing Ph-box by 1-Np-box (16% to 51% *ee* in CH_2Cl_2 and 17% to 43% *ee* in THF). The best result, however, for this addition was obtained with *t*Bu-box in THF (74% *ee*). In this reaction, a reversal of enantioselectivity in the presence of aryl-substituted box ligands compared to the alkyl-substituted analogues was observed, as discussed before. Thus, in this case the enantioselectivity of the 1-Np-box-induced addition closely approaches the result of the *t*Bu-box-Cu(OTf)$_2$ complex, particularly in CH_2Cl_2, affording the opposite enantiomer.

Table 4. Results of the addition reaction of silyl enol ether **15**



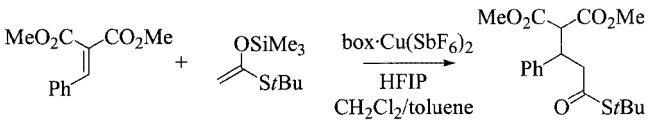
10 **15** **16**

Ligand	CH_2Cl_2 [a] Yield (%)[b]	*ee* (%)[c]	THF Yield (%)[b]	*ee* (%)[c]
(*S*)-1-Np-box	73	51 (*R*)	82	43 (*R*)
(*R*)-Ph-box	99	16 (*S*)	68	17 (*S*)
(*S*)-*t*Bu-box	90	49 (*S*)[d]	76	74 (*S*)

[a] In CH_2Cl_2 a mixture of Me_3Si-protected and unprotected alcohol was observed. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC on a Chiralpak AD column (heptane/2-propanol, 95:5, 0.5 mL/min). [d] The geometry of the major enantiomer was tentatively assigned based on the outcome of the Mukaiyama aldol and hetero-Diels–Alder reaction with methyl pyruvate, with the use of (*S*)-*t*Bu-box as ligand.

Finally, we decided to look into reactions where the reaction center is relatively remote from the coordination site and therefore may require an extended steric effect of the ligand, such as the Mukaiyama–Michael reaction (Table 5). Knoevenagel adduct **17** was used as the substrate in an addition reaction with silyl ketene acetal **11** catalyzed

Table 5. Results of the Mukaiyama–Michael addition



17 **11** **18**

Ligand	CH_2Cl_2 Yield (%)[a]	*ee* (%)[b]
(*S*)-1-Np-box	55	70 (*S*)
(*R*)-Ph-box[c]	67	56 (*S*)
(*S*)-*t*Bu-box[c]	99	>90 (*R*)

[a] Isolated yield after chromatography.[b] Enantiomeric excess was determined by HPLC on a Chiralpak AD column (heptane/2-propanol, 98:2, 1.0 mL/min). [c] Data correspond to literature values.[28]

by a box ligand with $Cu(SbF_6)_2$.[28] Indeed, we were pleased to find that catalysis with the 1-Np-box ligand afforded the addition product with good enantioselectivity (70% *ee*) and significant improvement of the *ee* compared to Ph-box (52% *ee*). Surprisingly, we observed a reversal in stereochemistry on going from the phenyl- to the naphthyl-box ligand. Again, the highest enantioselectivity so far was achieved with the *t*Bu-box ligand (>90% *ee*), but also in this case the product of opposite stereochemistry was obtained with the 1-Np-box ligand. Moreover, we expect that optimization studies on the use of 1-Np-box will further increase the enantioselectivity. From these results, it may be postulated that the use of 1-Np-box as a ligand is especially promising in reactions where the addition takes place at a functional group that is relatively remote from the coordination site.

Conclusions

Both (*S*)- and (*R*)-1-naphthylglycine were accessible through enzymatic resolution using enzymes from different sources, i.e. *Pseudomonas putida* and *Ochrobactrum anthropi*. These very useful amino acids could be effectively transformed into the enantiomerically pure 1-naphthylbis(oxazoline) ligand. (*S*)-1-Naphthyl-box was successfully synthesized in 60% yield from (*S*)-1-naphthylglycine and in 37% yield from 1-naphthaldehyde.

Studies of the scope of this novel 1-naphthyl-substituted ligand afforded several interesting results. Firstly, the influence of the enlarged 4-aryl substituent was not unambiguous. In the Mukaiyama aldol reaction and the hetero-Diels−Alder reaction, the enantiomeric excesses were comparably moderate for the use of 1-naphthyl- and phenyl-box as ligands. However, addition of a more bulky nucleophile, such as the silyl enol ether **15**, clearly showed the constructive influence of enlargement of the aryl substituent, resulting in a much higher enantioselectivity with 1-naphthyl-box than with phenyl-box. In this new addition reaction to methyl pyruvate, catalysis by 1-naphthyl- vs. *tert*-butyl-box resulted in similar enantioselectivity, particularly in CH_2Cl_2. We observed several cases of reversal of selectivity, which are similar to previously reported results. Nevertheless, the explanation for this inversion remains ambiguous since it appears to be dependent on a range of parameters, such as ligand, metal, solvent and substrate. Optimization studies on this reaction and follow-up chemistry are currently being performed.

Similarly, in the Mukaiyama−Michael reaction the effect of enlargement of the aryl substituent on the bis(oxazoline) was clearly observed. We now expect that our ligand could afford good results in reactions where the distance between reaction center and coordination site is relatively large. In this respect, the versatility of the 1-Np-box ligand is particularly enhanced by affording the opposite enantiomer than the *t*Bu-box-induced reaction.

Experimental Section

General: All reactions were carried out under an atmosphere of dry nitrogen or argon. Standard syringe techniques were applied for transfer of dry solvents and air- or moisture-sensitive reagents. Solvents were distilled from the appropriate drying agents immediately prior to use. Unless stated otherwise, all chemicals were purchased and used as such. 1-Naphthaldehyde and 2,2,6-trimethyl-1,3-dioxen-4-one were distilled before use. *S*,*S*-DBTAAN, whole cells of *Pseudomonas putida* ATCC 12633 and a cell-free extract containing the *Ochrobactrum anthropi* NCIMB 40321 L-amidase were kindly provided by DSM. Dowex 50 W × 4 (Fluka) was used for ion exchange with 2 N NH_4OH as the eluent and 2 N HCl as regeneration agent. IR spectra were recorded on an ATI Mattson Genesis Series FTIP spectrometer. Absorptions are reported in cm^{-1}. NMR spectra were recorded with Bruker DPX200 and DMX300 spectrometers from $CDCl_3$ solutions (unless otherwise reported) using TMS as internal standard. Shifts are given in ppm. Optical rotations were determined with a Perkin−Elmer 241 polarimeter. Mass spectra were measured with a Fisons (VG) Micromass 7070E apparatus. Melting points are uncorrected.

***N*-Benzylidene-1-naphthylglycine Amide (7):** Concentrated ammonia (90 mL, 25% in H_2O), NH_4Cl (6.50 g, 121 mmol) and 1-naphthaldehyde (19.90 g, 121 mmol) were added to a solution of NaCN (5.97 g, 122 mmol) in methanol (100 mL). After stirring for 5 h at room temperature, the reaction was complete according to TLC (Et_2O/heptane, 1:1). Toluene (100 mL), aqueous NaOH (122 mL, 122 mmol, 1.0 equiv., 1 N) and benzaldehyde (12.9 g, 121 mmol, 0.99 equiv.) were then added to the reaction mixture. After stirring for 1 h, a precipitate was formed, which was collected by filtration, washed with heptane and dried in vacuo. Benzaldimine **7** was isolated as a white solid (23.0 g, 66% from 1-naphthaldehyde) and used directly for the next step. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz): δ = 8.25 (s, 1 H, C*H*=N), 7.88−7.47 (m, 12 H, Ar-*H*), 7.24 (br., 1 H, N*H*), 5.94 (br., 1 H, N*H*), 5.67 (s, 1 H, C*H*) ppm. ^{13}C NMR ($CDCl_3$, 298 K, 50 MHz): δ = 174.52 (*C*=O), 163.25 (*C*=N), 135.61, 135.41, 134.28, 131.57, 131.12, 128.99 (Ar-*C*), 128.90 (2C, Ar-*C*), 128.77 (Ar-*C*), 128.56 (2C, Ar-*C*), 127.27, 126.63, 125.95, 125.53, 124.58 (Ar-*C*), 73.67 (*C*−N) ppm. R_f (Et_2O): 0.21.

1-Naphthylglycine Amide (3): Concentrated HCl (3.7 mL, 37.5 mmol, 0.98 equiv.) was added to a solution of **7** (11.0 g, 38.2 mmol) in acetone (500 mL). After stirring for 1 h at room temperature, a precipitate was formed, which was collected by filtration, washed with acetone and dried in vacuo. The amide **6** was isolated as its HCl salt (8.48 g, 94%). Extraction of an aqueous solution of the hydrochloride (pH ≈ 10, 500 mL) with CH_2Cl_2 (3 × 200 mL) afforded the HCl-free product as a white, crystalline solid (8.01 g, 89% from **7**). **3**: IR: $\tilde{\nu}$ = 3263 cm^{-1} ($CONH_2$), 3318, 3064, 1657 ($CONH_2$), 1624 ($CONH_2$). ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz): δ = 8.15 (d, *J* = 7.6 Hz, 1 H, Ar-*H*), 7.84 (m, 2 H, Ar-*H*), 7.58−7.41 (m, 4 H, Ar-*H*), 6.84 (br., 1 H, NH_2), 5.69 (br., 1 H, NH_2), 5.19 (s, 1 H, C*H*) ppm. ^{1}H NMR (CD_3OD, 298 K, 300 MHz): δ = 8.23 (d, *J* = 8.5 Hz, 1 H, Ar-*H*), 7.85 (m, 2 H, Ar-*H*), 7.58−7.43 (m, 4 H, Ar-*H*), 5.21 (s, 1 H, C*H*) ppm. ^{13}C NMR (CD_3OD, 298 K, 75 MHz): δ = 178.90 (*C*=O), 138.54, 132.45, 129.92, 129.57, 127.49, 126.84, 126.54, 126.16, 124.54 (Ar-*C*), 56.92 (*C*−N) ppm. R_f ($CHCl_3$/MeOH/NH_3(25%), 60:45:20): 0.45. HRMS(EI$^+$): calculated for $(C_{12}H_{12}N_2O)^+$ 200.09496, found 200.09486.

Preparation of (*S*)-1-Naphthylglycine [(*S*)-2] and (*R*)-1-Naphthylglycine Amide [(*R*)-3] Using *Pseudomonas putida* L-Aminopeptidase: A

solution of **3**·HCl (2.28 g, 9.65 mmol) in H_2O (135 mL) was brought to pH 8.3 with aqueous KOH (5 M). After addition of aqueous $MnSO_4$ (11.5 mL, 10 mM) and whole cells of *Pseudomonas putida* ATCC 12633 (2.17 g), the mixture was shaken for 90 h at 37 °C. The mixture was cooled to room temperature and the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). Both layers were filtered through Hyflo to remove the enzyme residue. The aqueous layer was changed to pH ≈ 5 and purified by ion-exchange chromatography. Removal of the solvent afforded acid (*S*)-**2** as an off-white solid (834 mg, 43%). After removal of the solvent from the CH_2Cl_2 layer, amide (*R*)-**3** was obtained as a light brown solid (791 mg, 41%). The *ee* was determined by ^{1}H NMR spectroscopy to be 73% for (*S*)-**2** and 99% for (*R*)-**3**.[29]

Preparation of (*S*)-1-Naphthylglycine [(*S*)-2] and (*R*)-1-naphthylglycine Amide [(*R*)-3] Using *Ochrobactrum anthropi* L-Amidase: A solution of **3**·HCl (12.0 g, 50.7 mmol) in H_2O (85 mL) was brought to pH 6.5 with aqueous KOH (5 M). After addition of aqueous $ZnSO_4$ (1.5 mL, 80 mM) and a cell-free extract containing the L-amidase from *Ochrobactrum anthropi* NCIMB 40321 in water (2 mL), the total weight of the mixture was brought to 120 g by addition of water. The mixture was shaken for 70 h at 50 °C, after which an extra 2 mL of cell-free extract was added and the mixture was shaken for another 20 h. After cooling the mixture to room temperature, the mixture was filtered through Hyflo. The resulting clear solution was brought to pH ≈ 9 by addition of aqueous KOH (5 M) and extracted with CH_2Cl_2 (3 × 250 mL). The aqueous layer was then changed to pH ≈ 5 and purified by ion-exchange chromatography. Removal of the solvent resulted in isolation of acid (*S*)-**2** as an off-white solid (5.04 g, 49%). The *ee* was determined by ^{1}H NMR spectroscopy to be 99%.[29] (*S*)-**2**: IR: $\tilde{\nu}$ = 3047, 1695, 1618, 1570, 1514 cm^{-1}. ^{1}H NMR (D_2O, 298 K, 200 MHz): δ = 8.13−7.98 (m, 3 H, Ar-*H*), 7.66−7.54 (m, 4 H, Ar-*H*), 5.50 (s, 1 H, C*H*) ppm. ^{13}C NMR (CD_3OD, 298 K, 75 MHz): δ = 173.85 (*C*=O), 135.60, 133.72, 132.73, 130.64, 129.97, 127.96, 127.70, 127.16, 126.49, 124.32 (Ar-*C*), 56.45 (*C*−N) ppm. $[\alpha]_D^{25}$ = −7.9 (*c* = 0.05, H_2O) [ref.[30] for (*R*)-**2** $[\alpha]_D^{25}$ = +8.0 (*c* = 0.05, H_2O)]. R_f ($CHCl_3$/MeOH/NH_3(25%), 60:45:20): 0.65.

After removal of the solvent from the CH_2Cl_2 layer, (*R*)-**3** was obtained as a white solid (5.59 g, 43%). The *ee* was determined by ^{1}H NMR to be 99%.[29] (*R*)-**3**: ^{1}H NMR (CD_3OD, 298 K, 300 MHz): δ = 8.24 (d, *J* = 8.5 Hz, 1 H, Ar-*H*), 7.85 (m, 2 H, Ar-*H*), 7.56−7.41 (m, 4 H, Ar-*H*), 5.21 (s, 1 H, C*H*). $[\alpha]_D^{25}$ = −114 (*c* = 0.5, MeOH).

(*R*)-1-Naphthylglycine [(*R*)-2]: To a 5% solution of (*R*)-**3** (100 mg, 0.50 mmol) in a buffer (pH 8: 500 mL of 0.1 M NaH_2PO_4 + 467 mL of 0.1 M NaOH) was added 50 mg of dried whole cells of *Rhodococcus erythropolis* NCIMB 11540 and the reaction mixture was stirred at 37 °C for 48 h. The reaction mixture was filtered through Hyflo, the filtrate was acidified and purified by ion-exchange chromatography to give (*R*)-**2** (74 mg, 74%) as a white solid. Analytical data were identical to the literature data.[30]

(*S*)-1-Naphthylglycinol [(*S*)-8]: $LiAlH_4$ (6.70 g, 176 mmol) was added in four portions to a suspension of acid (*S*)-**2** (3.50 g, 17.4 mmol) in THF (250 mL). After refluxing for 17 h, the mixture was cooled to 0 °C and quenched by addition of H_2O (6 mL), aqueous NaOH (6 mL, 4 N) and H_2O (15 mL) over a period of 15 min. After stirring for 30 min at room temperature, the mixture was filtered. The residue was washed with EtOAc (3 × 150 mL) and the combined filtrates were concentrated in vacuo to yield amino alcohol (*S*)-**8** as a yellow solid (2.94 g, 90%). (*S*)-**8**: ^{1}H NMR ($CDCl_3$, 298 K, 300 MHz): δ = 8.11 (d, *J* = 8.9 Hz, 1 H, Ar-*H*), 7.88 (d, *J* = 7.5 Hz, 1 H, Ar-*H*), 7.79 (d, *J* = 8.2 Hz, 1 H, Ar-*H*), 7.62−7.46 (m, 4 H, Ar-*H*), 4.92 (dd, *J* = 3.9, 8.0 Hz, 1 H, C*H*), 3.96 (dd, *J* = 3.9, 10.7 Hz, 1 H, CH_2), 3.67 (dd, *J* = 8.0, 10.7 Hz, 1 H, CH_2) ppm. ^{13}C NMR (CD_3OD, 298 K, 75 MHz): δ = 138.83, 135.32, 132.43, 129.69, 128.75, 127.20, 126.56, 126.46, 124.16, 123.66 (Ar-*C*), 68.61 (CH_2), 53.76 (C*H*) ppm. $[\alpha]_D^{25}$ = +83 (*c* = 0.50, MeOH) [ref.[31] for (*R*)-**8** $[\alpha]_D^{25}$ = −85 (*c* = 0.50, MeOH)]. R_f ($CHCl_3$/MeOH/NH_3(25%), 60:45:20): 0.88.

(*S,S*)-*N,N′*-Bis[2-hydroxyl-1-(1-naphthyl)ethyl]-2,2-dimethyl-1,3-propanediamide [(*S*)-9]: A solution of amino alcohol (*S*)-**8** (1.20 g, 6.44 mmol) and Et_3N (4.6 mL, 33.2 mmol, 5.2 equiv.) in CH_2Cl_2 (40 mL) was cooled to 0 °C. A solution of 2,2-dimethylmalonyl dichloride[32] (0.562 g, 3.3 mmol, 0.52 equiv.) in CH_2Cl_2 (15 mL) was then added with a cannula. After stirring for 90 min, CH_2Cl_2 (40 mL) was added and the mixture was washed with aqueous HCl (150 mL, 1 N). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with brine (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting brown solid was recrystallized from EtOAc, yielding diamide (*S*)-**9** as an off-white solid (1.24 g, 79%). (*S*)-**9**: M.p. 99 °C. IR (solvent): $\tilde{\nu}$ = 3337 (OH), 3047, 2971, 2933, 2876, 1642 (C=O), 1522 cm^{-1}. ^{1}H NMR (CD_3Cl, 298 K, 200 MHz): δ = 8.04 (m, 2 H, Ar-*H*), 7.89−7.76 (m, 4 H, Ar-*H*), 7.48 (m, 4 H, Ar-*H*), 7.35 (m, 4 H, Ar-*H*), 7.18 (d, *J* = 7.9 Hz, 2 H, N*H*), 5.96 (m, 2 H, C*H*), 4.10−3.94 (m, 4 H, CH_2), 3.92 (br., 2 H, O*H*), 1.50 (s, 6 H, CH_3) ppm. ^{13}C NMR (CD_3Cl, 298 K, 50 MHz): δ = 174.09 (2C, *C*=O), 134.34, 134.03, 131.04, 129.08, 128.66, 126.79, 126.04, 125.34, 123.48, 122.91 (10C, Ar-*C*), 65.59 (2C, CH_2), 51.87 (2C, C*H*), 50.24 [*C*(CH_3)], 23.85 (2C, CH_3) ppm. $C_{29}H_{30}N_2O_4$·1/2H_2O: calcd. C 72.63, H 6.52, N 5.84; found C 72.36, H 6.32, N 5.67. $[\alpha]_D^{25}$ = −39 (*c* = 0.50, MeOH). R_f (EtOAc/MeOH, 95:5) = 0.41.

(*S,S*)-2,2-Bis{2-[4(*S*)-(1-naphthyl)-1,3-oxazolinyl]}propane [(*S*)-1]: A solution of tosyl chloride (1.98 g, 10.4 mmol, 2.1 equiv.) in CH_2Cl_2 (40 mL) was added via cannula to a solution of (*S*)-**9** (2.32 g, 4.93 mmol), DMAP (65 mg, 0.53 mmol, 11 mol %) and triethylamine (3.5 mL, 25.2 mmol, 5.1 equiv.) in CH_2Cl_2 (125 mL). After stirring at room temperature for two days, the mixture was washed with saturated aqueous NH_4Cl (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (400 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to yield the crude product as an off-white solid. Purification by column chromatography (EtOAc/heptane, 4:6) resulted in isolation of (*S*)-**1** as a white solid (1.82 g, 85%). The product was purified by recrystallization (EtOAc/heptane) and was used as such for catalysis. (*S*)-**1**: M.p. 59 °C. IR (solvent): $\tilde{\nu}$ = 3057, 2981, 2893, 1657 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz): δ = 7.90−7.75 (m, 6 H, Ar-*H*), 7.60−7.40 (m, 8 H, Ar-*H*), 5.99 (dd, *J* = 8.1, 10.1 Hz, 2 H, C*H*), 4.96 (dd, *J* = 8.0, 10.2 Hz, 2 H, CH_2), 4.13 (t, *J* = 8.1 Hz, 2 H, CH_2), 1.80 (s, 6 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 298 K, 300 MHz): δ = 170.58 (2C, *C*=N), 138.35, 133.82, 130.52, 129.02, 127.83, 126.23, 125.74, 125.56, 123.44, 122.69 (20C, Ar-*C*), 75.06 (2C, CH_2), 66.17 (2C, C*H*), 39.33 [*C*(CH_3)$_2$], 24.61 (2C, CH_3) ppm. HRMS(EI$^+$): calculated for $(C_{29}H_{26}N_2O_2)^+$ 434.1994, found 434.1996. $C_{29}H_{26}N_2O_2$·1/4H_2O: calcd. C 79.34, H 6.08, N 6.38; found C 79.36, H 5.84, N 6.23. $[\alpha]_D^{25}$ = +180 (*c* = 0.50, $CDCl_3$). R_f (EtOAc/heptane, 4:6) = 0.23.

General Method for the Preparation of Methyl 3-(2,2-Dimethyl-6-oxo-6*H*-[1,3]dioxin-4-yl)-2-hydroxy-2-methylpropionate (16): (2,2-dimethyl-6-methylene-6*H*-[1,3]dioxin-4-yloxy)trimethylsilane (**15**) was prepared according to the method published by Krohn and Schafer.[33] Box ligand (11 mol %) and $Cu(OTf)_2$ (7 mg, 10 mol %) were weighted under Ar. After stirring for 1 h under Ar, solvent (2 mL) was added and the stirring under Ar was continued for overnight. After cooling the solution to −78 °C, methyl pyruvate (19 μL, 0.21 mmol) was added. After stirring for 30 min at −78 °C, enol **15** (50 μL, 1.1 equiv.) was added and the mixture was allowed to warm to room temperature overnight and then stirred for another night. After addition of saturated aqueous $NaHCO_3$ (10 mL) and solvent (10 mL), the layers were separated and the organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. This afforded a mixture of addition product **16** and its TMS-protected analogue.

Optional Procedure: TBAF (0.2 mL, 1.0 equiv., 1 M in THF) was added to a solution of the crude mixture (0.21 mmol) in THF (10 mL) at −78 °C and the orange solution immediately became green. After stirring for four days at room temp., saturated aqueous NH_4Cl (5 mL) was added and the color of the solution immediately changed to orange/brown. The mixture was extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$) and concentrated in vacuo. This afforded unprotected alcohol **16** as a yellow oil. Purification by column chromatography (EtOAc/heptane, 1:4) resulted in alcohol **16** as a colorless oil. Yields were determined after catalysis (without treatment with TBAF). The TMS/H ratio was determined by NMR analysis of the methoxy signal ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (O*H*), 3.73 ppm [OSi(CH_3)$_3$]. **16**: IR (solvent): $\tilde{\nu}$ = 3491 (OH), 2997, 2953, 2251, 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$, 298 K, 300 MHz): δ = 5.24 (s, 1 H, α-C*H*), 3.74 (s, 3 H, CO_2CH_3), 3.50 (br. s, 1 H, O*H*), 2.79 (d, *J* = 14.7 Hz, 1 H, CH_2), 2.52 (d, *J* = 14.7 Hz, 1 H, CH_2), 1.59 (s, 6 H, 2 × CH_3), 1.42 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 298 K, 75 MHz): δ = 175.56 (*C*=O), 166.60 (*C*=O), 160.42 (C=*C*−O), 106.49 [*C*(Me)$_2$], 95.87 (*C*H), 72.76 (*C*−OH), 52.86 (*C*H$_2$), 43.50 (O−*C*H$_3$), 27.00 (*C*H$_3$), 25.77 (*C*H$_3$), 24.04 (*C*H$_3$) ppm. The enantiomeric excess was determined by HPLC analysis on a chiralpak AD column (heptane/2-propanol, 95:5, 0.5 mL/min, 35 °C), t_R = 37.5 min, 46.6 min.

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