DOI: 10.1002/ejoc.200601053

Stabilizing Factors for Vanadium(IV) in Amavadin

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Dedicated to R. A. Sheldon on the occasion of his 65th birthday

Keywords: Amavadin / Vanadium / Reductive hydroxylamination / Hydroxylamines / Nitrones / Mass spectrometry

Six secondary *N*-hydroxy amino acids (amavadin-based ligands) have been prepared through a strategy with nitrone reduction as its key step. Two of these amino acids are the new amavadin ligand analogues **4a** and **4b** containing either a phenyl or a benzyl group in combination with a small backbone substituent. In addition, the monoester **5** of the amavadin ligand as well as three *N*-alkylated *N*-hydroxy amino acids **6** were prepared. Complexation studies with the new tri- and bidentate ligands using HRMS revealed that only amavadin and its two analogues with ligands **4a** and **4b** are stable in aqueous and aerobic environments and that the complexation of vanadium(IV) with ligands **5** and **6** does not lead to air-stable vanadium(IV) non-oxo compounds. An interesting spin-off of the synthetic work on nitrones is an effective and easily applicable method for the synthesis of racemic *N*-hydroxy amino acid esters.

Introduction

One of the most prominent examples of a vanadium-containing natural compound is amavadin. In 1972, Bayer and Kneifel isolated this compound from the mushroom *Amanita muscaria*.[1] The chemical synthesis of amavadin[2,3] and investigations of its electrochemistry,[4] catalytic properties[5–8] and structure[9,10] have been reported. The modifications to amavadin that have been reported mainly concern the replacement of the natural vanadium. The natural ligand **1** or its simplified achiral analogue **2** has been employed to complex the early transition metals Ti, Zr, Nb, Ta and Mo.[11] In one particular case, a ligand with ethyl groups on the backbone was prepared (**3**) and its complexation with V and Mo studied (Figure 1).

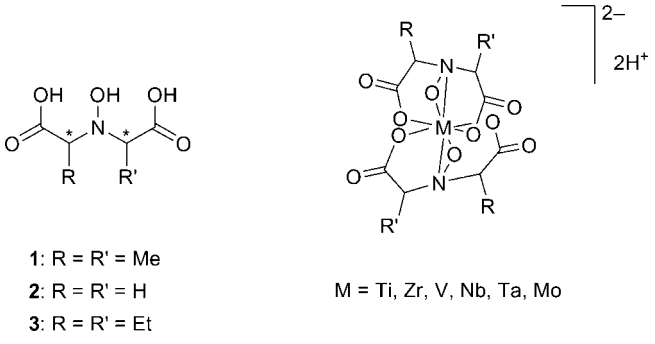

Figure 1. Amavadin analogues **1**–**3** reported in the literature.

A remarkable feature of amavadin is that it is an air-stable non-oxo vanadium(IV) complex in which the two *N*-hydroxy groups act as η^2 ligands. It has previously been shown that the modified ligands **2** and **3** do not affect the basic structure of amavadin,[12,13] but that the *N*-hydroxy groups are essential for the formation of the non-oxo vanadium(IV) nucleus.[14] In order to establish what other factors are important, we focused our attention on the roles of the carboxylate groups and the large substituents on the backbone. With this in mind, we aimed to synthesize ligands **4**–**6** (Figure 2) in which one of the backbone methyl groups of **1** is replaced by a phenyl or a benzyl group (**4**) or in which one of the coordinating groups of **1** is replaced by a weaker coordinating centre (**5**) or by a non-coordinating alkyl group (**6**).

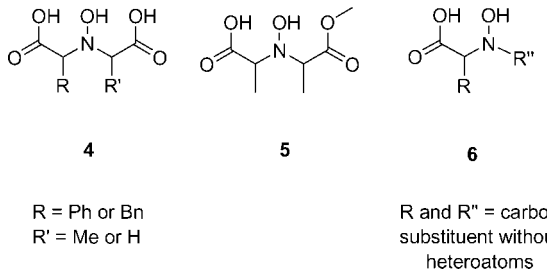

Figure 2. Amavadin-based ligands **4**–**6**.

Thus, our two objectives with respect to ligand synthesis were the introduction of new groups on the ligand backbone and the modification of one of the carboxylate groups

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of **1**. Our synthetic strategy initially focused on the *N*-alkylation of a primary hydroxylamine,[15,16] the method on which the traditional synthesis of the amavadin ligand is based.[2,3] As a second route, nitrones were used as intermediates.[15,17–19] The synthesis of the monoester **5** and the *N*-alkylated *N*-hydroxy amino acids **6** have no precedent in the literature, although a few reports exist on the synthesis of other *N*-alkylated *N*-hydroxy amino acids.[20–23] Studies on the interaction of vanadium with *N*-hydroxy amino compounds are limited to the inorganic hydroxylamine ligand[24,25] (H_2NOH) and its *N*-methyl[26] and *N*,*N*-dimethyl analogues.[27,28] There are no reports on vanadium complexation by *N*-hydroxy amino acids and derivatives thereof.

Results and Discussion

N-Alkylation of Hydroxylamine and Cyanide Addition to Nitrones

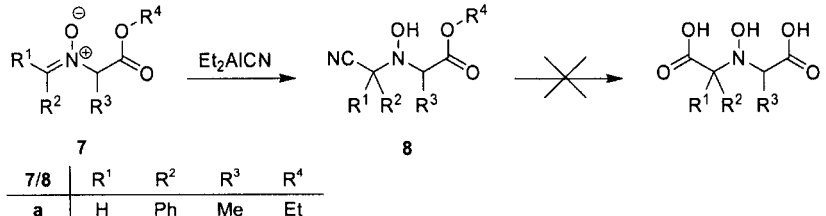
The *N*-alkylation of hydroxylamines is useful for the synthesis of *N*-hydroxy α-amino acids and derivatives thereof.[15,23,29–31] Although the double S_N2 substitution of hydroxylamine on two molecules of α-bromopropionic acid did not yield enantiopure **1**,[2,13,32,33] the application of triflate as a leaving group did enable the enantioselective synthesis of **1**.[3] We attempted S_N2 substitutions of α-triflate esters with an *i*Pr, Ph or Bn substituent at the α position, but the desired derivatives of **1** were not formed. When repeating the syntheses of **1** and **2** starting from the α-bromo carboxylic acids, both compounds were isolated in yields comparable to those reported in the literature. However, extension of this method to α-bromo acids with an *i*Pr, Ph or Bn substituent at the α position was not successful. Therefore, we decided to focus on nitrones as intermediates of the desired amavadin-based ligands.[15,17–19] Our first approach comprised the addition of cyanide[34] to nitrones **7**, which afforded the α-cyano secondary hydroxylamines **8** (Scheme 1). However, the hydrolysis of **8** to the corresponding amavadin ligand analogues was unsuccessful. Refluxing in concentrated HCl, the common procedure for the hydrolysis of nitriles in the Strecker reaction, resulted in the complete degradation of **8**. The application of milder conditions[35] or the use of a platinum-based catalyst designed to convert nitriles into amides did not afford the desired products either.[36]

Synthesis of Amavadin-Based Ligands

Our second approach to the use of nitrones as intermediates comprised nitrone reduction.[37–41] We prepared the nitrones by condensation of an *N*-hydroxy amino acid ester with an aldehyde or ketone and in situ reduction using $NaCN{\cdot}BH_3$. This method may therefore be called a "reductive hydroxylamination" process, stressing the analogy with the well-known reductive amination to obtain secondary amines.

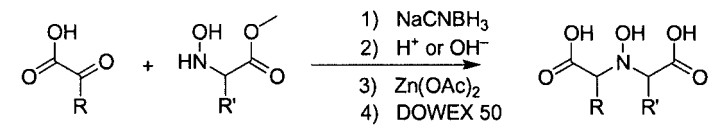
Synthesis of the Tridentate Ligands 4

The required nitrones could be generated quickly and effectively by using α-keto acids (Scheme 2). The first application of the method was the reaction of (racemic) *N*-hy-



7/8	R^1	R^2	R^3	R^4
a	H	Ph	Me	Et
b	H	Ph	Ph	Et
c	H	Me	Me	Me
d	Me	Me	H	Me
e	H	Me	H	Et
f	H	*i*Bu	H	Et

Scheme 1. Attempts to obtain amavadin ligand analogues by the addition of cyanide to nitrones.



R = H, Me or Ph

9: R' = Me
10: R' = Ph
11: R' = Bn

1: R = R' = Me 43% yield
4a: R = Me, R' = Ph 47% yield
4a: R = Ph, R' = Me 21% yield
4b: R = Bn, R' = H 41% yield

Scheme 2. Synthesis of tridentate ligands **4**.

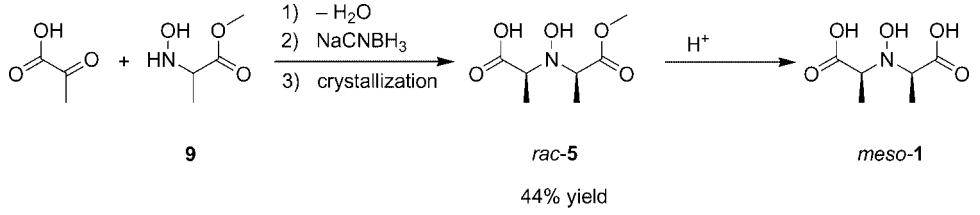
droxyalanine methyl ester (**9**) with pyruvic acid in order to prepare the natural amavadin ligand **1**. Subsequent addition of $NaCN{\cdot}BH_3$ (instantaneous reaction) and evaporation of the solvent yielded a white solid, which was then refluxed in concentrated HCl to hydrolyze the ester. Further workup was performed according to a procedure reported previously:[3] the crude ligand was precipitated with 1 equiv. of $[Zn(OAc)_2]$ followed by isolation of the intermediate zinc salt (49% yield) and release of the pure ligand **1** by ion-exchange chromatography and lyophilization. The overall yield of **1** was 43%, and ^1H NMR spectroscopy showed a slight preference for the formation of the *meso* isomer (*de* ≈ 20%). When starting from racemic *N*-hydroxyphenylglycine methyl ester (**10**) and pyruvic acid, the acid-catalyzed ester hydrolysis caused complete degradation of the product (smell of benzaldehyde), but on switching to alkaline conditions compound **4a** was isolated in 47% yield as a mixture of two diastereomers in a ratio of 1:5. Compound **4a** was also isolated when the reaction sequence was performed with (racemic) *N*-hydroxyalanine methyl ester (**9**) and phenylglyoxylic acid. A benzyl group could be introduced at the ligand backbone by starting with *N*-hydroxyphenylalanine methyl ester (**11**) and glyoxylic acid. After hydrolysis of the ester under reflux in 1 N HCl, the desired product **4b** was isolated in 41% yield. The use of optically pure **11** did not result in optically pure **4b**. Racemization of the chiral centre is likely to take place in the nitrone intermediate, although refluxing in hydrochloric acid could also induce such a racemization.

Synthesis of the Bidentate Ligands 5 and 6

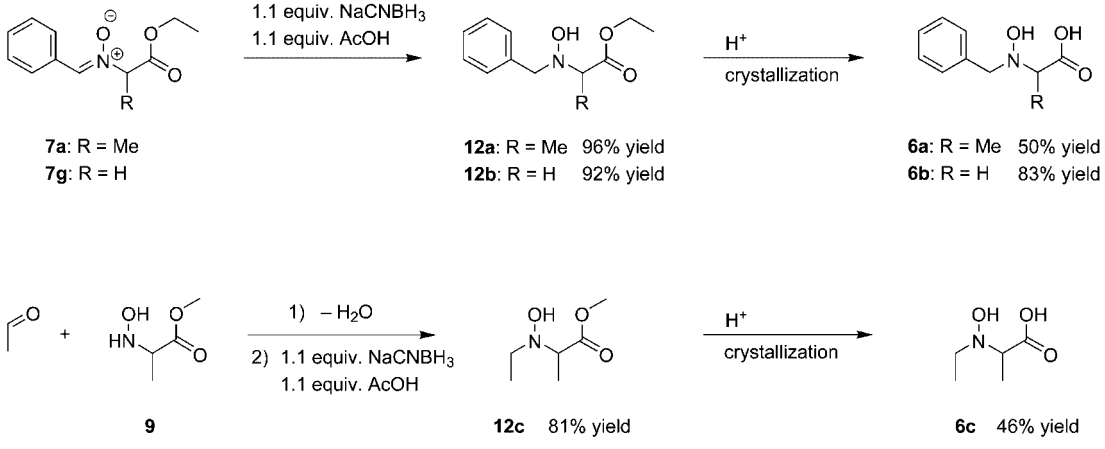
An important feature of the method depicted in Scheme 2 is that the monoester of the desired ligand is one of the intermediates. When synthesizing ligand **1** by this method, we could isolate **5** in a yield of 44% with a *dr* of 99:1 (NMR) by crystallization from the quenched reaction mixture after the reduction step. To identify its stereochemistry, **5** was hydrolyzed to the amavadin ligand **1**. Comparison of the NMR spectroscopic data with those of enantiopure and racemic **1** revealed **5** to be in the *meso* form (Scheme 3).[42] Thus, *meso*-**1** was prepared from *rac*-**5** for the first time.

The *N*-alkylated *N*-hydroxy amino acids **6** could also be synthesized by $NaCN{\cdot}BH_3$ reduction of the appropriate nitrones. The secondary hydroxylamines **12a** and **12b** thus obtained could be isolated in high yields. Subsequent hydrolysis gave the corresponding *N*-benzyl-*N*-hydroxy amino acids **6a** and **6b** (Scheme 4). Although the stable nitrones **7a** and **7g** could be isolated prior to their reduction, other nitrones can often only be prepared in situ and therefore require the "reductive hydroxylamination" sequence. Accordingly, we generated the nitrone of acetaldehyde and **9** and reduced this in situ to secondary hydroxylamine **12c**. Subsequent hydrolysis yielded *N*-ethyl-*N*-hydroxyalanine (**6c**).

The reductive hydroxylamination method strongly depends on the availability of the appropriate hydroxylamine. We prepared the racemic *N*-hydroxy amino acid esters **9**



Scheme 3. Synthesis of bidentate ligand **5** and *meso*-**1**.



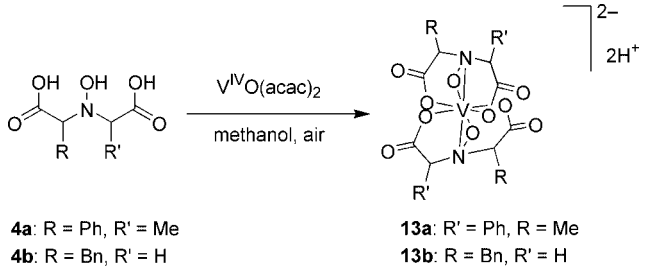
Scheme 4. Synthesis of bidentate ligands **6**.

and **10** by *N*-alkylation of (*Z*)-benzaldoxime[43,44] and enantiopure **11** by indirect *N*-oxidation of the enantiopure phenylalanine methyl ester.[45,46] At a later stage, we could improve the first procedure by using the cheap and commercially available acetaldoxime instead of (*Z*)-benzaldoxime, which resulted in a convenient three-step one-pot procedure towards **9** and **10**.

Vanadium Complexation by Amavadin-Based Ligands

Vanadium Complexation by Tridentate Ligands 4

The in situ complexation of ligand analogues **4a** and **4b** to $[VO(acac)_2]$ in methanol gave solutions with an intense blue colour reminiscent of the blue solutions of amavadin. HRMS (ESI) confirmed the presence of the amavadin analogues **13a** and **13b** (Scheme 5). Both complexes were stable in air and no oxidation occurred. At the start of the project, we anticipated that large R groups would improve the solubility of these complexes in organic solvents, but this appears not to be the case. The V^V analogues of **13a** and **13b** were isolated as the PPh_4 salts after oxidation with $[(NH_4)_2Ce(NO_3)_6]$[3] and ^1H, ^{13}C and ^{51}V NMR spectroscopy of these complexes confirmed their great similarities with amavadin. The complexes with ligands **1**, **2**, **3**, **4a** and **4b** all have vanadium shifts between δ = –230 and –290 ppm, while the distinct resonances observed in the ^1H and ^{13}C NMR spectra could be assigned to the ligands unambiguously.[47] This demonstrates that ligands **4a** and **4b** behave similarly to **1**, **2** and **3** and that the presence of larger backbone substituents still leads to an air-stable non-oxo vanadium(IV) nucleus.



Scheme 5. Formation of the amavadin analogues **13a** and **13b** from ligands **4a** and **4b**.

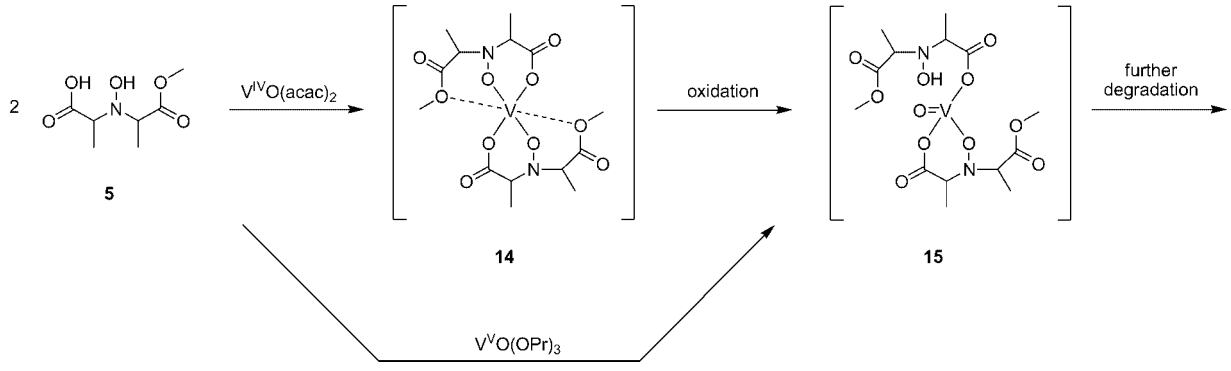
Vanadium Complexation by Bidentate Ligands 5 and 6

In compound **5** one of the carboxylate groups of ligand **1** is protected as the methyl ester; it is thus an ideal compound to study whether all the hydroxy groups in **1** need to be deprotonated in order to complex vanadium(IV) as a non-oxo complex. The complexation was performed by mixing **5** and $[VO(acac)_2]$ in a 2:1 molar ratio in methanol after which a brown solid was isolated. The molecular mass (ESI HRMS) corresponded to a non-oxo vanadium complex with two ligands of **5**. This was tentatively assigned to a formal dimethyl ester of amavadin[48] such as **14** with a hexacoordinate vanadium (Scheme 6). No significant changes were seen in the MS when larger ligand/vanadium ratios were used. The transient intermediate **14** was oxidized to complex **15**,[49] which can also be obtained directly by mixing the V^V precursor $[VO(OPr)_3]$ with **5**. However, **15** was not stable either; it slowly degraded and was therefore not fully characterized. ^{51}V NMR spectroscopy of the unstable product gave a large resonance at δ = –651 ppm, accompanied by smaller resonances at δ = –605, –623 and –704 ppm. Similarly, the ^1H and ^{13}C NMR spectra showed several species but did not allow the exact identification of the complexes. Evidently, **5** does not form an amavadin-like complex with vanadium(IV).

The complexation of **6a**–**6c** with V^{IV} and V^V nuclei was performed by mixing the ligand with either $[VO(acac)_2]$ or $[VO(OPr)_3]$ in different molar ratios (2:1–4:1) in methanol. Given the results described above, it is not surprising that the vanadium was immediately oxidized and a complex mixture was obtained. Thus, ligands **6** are not able to stabilize the V^{IV} nucleus either.

Conclusions

The aim of this study on the non-oxo vanadium(IV) nucleus in amavadin was to investigate if large ligand backbone substituents can be accommodated and to what extent the carboxylate groups are essential. The complexation studies showed that increasing the size of the methyl backbone substituents with a phenyl or a benzyl group still gives non-oxo V^{IV} complexes that are analogous to amavadin. In contrast, the protection of one carboxylate group per ligand does not give a stable non-oxo vanadium(IV) compound.



Scheme 6. Schematic representation of the tentative V^{IV} and V^V complexes formed from ligand **5**.

Instead, the initially obtained complex is slowly oxidized in air. Complete absence of one of the carboxylic acid groups results in immediate oxidation. In conclusion, these results show that in addition to the secondary *N*-hydroxy group, two unprotected carboxylate groups are also necessary to obtain an air-stable non-oxo vanadium(IV) nucleus in amavadin analogues.

We have also demonstrated that reductive hydroxylamination is a versatile method for preparing secondary *N*-hydroxy amino acid ligands. A one-pot three-step non-stereoselective synthesis has been developed to prepare the natural ligand and two of its derivatives with a phenyl or a benzyl backbone substituent. Moreover, the amavadin ligand monoester and *N*-alkylated *N*-hydroxy amino acids are also accessible by this strategy.

Experimental Section

Methods and Materials: Column chromatography was carried out with silica gel 0.060–0.200 mm, pore diameter approx. 6 nm (Fluka silica gel 60). TLC was performed on 0.20 mm silica gel aluminium sheets (Merck silica gel 60 F_{254}). Elution was carried out with mixtures of petroleum ether (PE; boiling range 40–65 °C) and ethyl acetate (EtOAc). The plates were developed by dipping them into either a ninhydrin bath (1.5 g of ninhydrin in 100 mL of ethanol) in which the hydroxylamines gave pale red to yellow spots or an iodine/silica gel bath (prepared as a mixture of 5 g of iodine and 300 g of silica gel). Ion-exchange chromatography was carried out with DOWEX 50WX8-200 resin. ^{1}H and ^{13}C NMR spectra were recorded with a Varian VXR400S (400 MHz) or a Varian Unity Inova 300 (300 MHz) instrument. Chemical shifts of the ^{1}H and ^{13}C nuclei are expressed in ppm (δ) relative to tetramethylsilane (in $CDCl_3$ or DMSO) or relative to *t*BuOH (in H_2O). Chemical shifts of the ^{51}V nuclei are expressed in ppm (δ) relative to the external reference $VOCl_3$. Coupling constants (J) are expressed in Hz. The abbreviations used are as follows: s (singlet), d (doublet), t (triplet) and q (quartet). Low-resolution mass spectrometry was performed with a Micromass Quattro LC-MS spectrometer (ESI). High-resolution mass spectrometry was performed with a Thermo LTQ Orbitrap spectrometer; resolution 50000; mass accuracy < 2 ppm; samples were diluted with a 1:1 methanol/water solution; injection volume: 10 μL; flow rate: 50 μL/min; eluent: 1:1 methanol/water. Optical rotations were obtained using a PerkinElmer 241 polarimeter. Melting points were measured with a Büchi 510 apparatus and are uncorrected. The CHN elemental analyses were performed at the Dr. Verwey Chemical Laboratory in Rotterdam, The Netherlands. The α-bromo acids,[50,51] α-hydroxy acid esters,[52,53] *N*-hydroxyglycine ethyl ester[54] and (*R*)-*N*-phenylalanine methyl ester (**11**)[46] were prepared according to literature procedures. We have previously reported the synthesis of **13b** and the NMR spectroscopic data of its PPh_4 salt after oxidation to V^V.[42] All other chemicals and dry solvents were obtained from Aldrich or Merck and were used as received. Other solvents were purchased from Baker. Petroleum ether (PE) with a boiling range of 40–65 °C was used. Ultrapure water (MilliQ) was used.

Synthesis of Amavadin Ligands 1 and 2 by Substitution of α-Bromo Acids: The synthesis was performed according to a literature procedure with modifications.[33] A pH-controlled automatic burette was charged with a 4 M NaOH solution. With the aid of this setup, a stirred solution of hydroxylamine hydrochloride and the α-bromo acid in water was brought to pH = 7.2. At this point, the reaction started and the pH of the reaction mixture was kept at 7.2 by the controlled addition of a 4 M NaOH solution with the temperature being kept at 30–35 °C. When the reaction was complete, the pH of the mixture was lowered to 4.4 with dilute HCl. A solution of $[Zn(OAc)_2{\cdot}2H_2O]$ in 40 mL of water was added to precipitate the ligand. The milk-white suspension was washed with water (a cycle of centrifugation, decanting the supernatant and suspending the residue in water was performed three times) and dried in vacuo, after which the zinc complex was obtained as a fine white powder. It was then dissolved in 20 mL of 6 N HCl (or the minimum amount that was necessary for complete dissolution) and the solution was added to a column of H^+-loaded DOWEX-50 ion-exchange resin that had previously been washed with water until a neutral pH was obtained. Elution with water first gave an eluate with a pH < 1, then the pH was increased to 3.4, and when the pH was decreased again the eluate was collected. After concentration and lyophilization, a white powder was obtained.

Ligand 1: From (*R*)-2-bromopropionate (19.122 g, 125 mmol), hydroxylamine hydrochloride (3.474 g, 50 mmol) and $[Zn(OAc)_2{\cdot}2H_2O]$ (10.975 g, 50 mmol), the zinc complex (6.841 g, 28.44 mmol, 57%) was obtained. The reaction was carried out in water (110 mL) and was complete after 40 h. Ion-exchange chromatography yielded 4.312 g (24.34 mmol, 49% overall yield) of **1**. M.p. 137–138 °C. $[\alpha]_D^{20}$ = +21.3 (c = 1, H_2O). MS: m/z = 178.3 (ES^+, [M + 1]), 176.3 (ES^-, [M – 1]). NMR spectroscopy showed that the ratio of *meso*-**1**/**1** was approximately 1:4 (*de* = 60%). The ^{1}H and ^{13}C NMR spectra of **1** are identical to those of **1** described in the literature.[3] The ^{1}H and ^{13}C NMR data for *meso*-**1** are identical to those of *meso*-**1** described below.

Ligand 2: From bromoacetic acid (34.738 g, 250 mmol), hydroxylamine hydrochloride (6.949 g, 100 mmol) and $[Zn(OAc)_2{\cdot}2H_2O]$ (21.950 g, 100 mmol), the zinc complex (11.600 g, 54.6 mmol, 55%) was obtained. The reaction was carried out in water (150 mL) at room temp. instead of 30–35 °C and was complete after 24 h. The free ligand was released batchwise; ligand **2** (1.180 g, 7.91 mmol, 79%) was obtained as a white solid (43% starting from bromoacetic acid and hydroxylamine hydrochloride) from the zinc complex (2.125 g, 10 mmol). M.p. 137 °C. ^{1}H NMR (D_2O, 300 MHz, 25 °C): δ = 3.80 (s, 4 H, 2 × NCH_2) ppm. ^{13}C NMR (D_2O, 75 MHz, 25 °C): δ = 173.33 (2 C, 2 × COOH), 61.49 (2 C, 2 × NCH_2) ppm. MS: m/z = 150.3 (ES^+, [M + 1]), 148.3 (ES^-, [M – 1]). $C_4H_7NO_5$ (149.10): calcd. C 32.22, H 4.73, N 9.39; found C 32.30, H 4.59, N 9.28.

Synthesis of Nitrones 7: The nitrones **7a**, **7b** and **7g** were synthesized and isolated according to literature procedures.[43,54]

Nitrone 7a: Yield: 2.14 g (48%), white crystals. M.p. 112 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.28 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.78 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 4.26 (m, J = 7.1 Hz, 2 H, CH_2CH_3), 4.75 (q, J = 7.0 Hz, 1 H, $CHCH_3$), 7.42 (m, 3 H, C_6H_5), 7.48 (s, 1 H, N=CH), 8.25 (m, 2 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 167.96 (1 C, COOEt), 134.95 (1 C, N=CH), 130.72, 130.27, 128.86, 128.54 (6 C, C_6H_5), 73.30 (1 C, $CHCH_3$), 62.26 (1 C, OCH_2CH_3), 15.61 (1 C, OCH_2CH_3), 14.03 (1 C, $CHCH_3$) ppm.

Nitrone 7b: Yield: 643 mg (42%), white crystals. M.p. 114 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.30 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.33 (m, 2 H, CH_2CH_3), 5.82 (s, 1 H, CHC_6H_5), 7.39 (m, 8 H, 2 × C_6H_5), 7.49 (s, 1 H, N=CH), 8.17 (m, 2 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 167.10 (1 C, COOEt), 135.76 (1 C, N=CH), 131.12, 130.98, 130.25, 129.85, 129.71,

129.43, 129.18, 128.44 (12 C, C_6H_5), 81.71 (1 C, CHC_6H_5), 62.53 (1 C, OCH_2CH_3), 14.03 (1 C, OCH_2CH_3) ppm.

Nitrone 7g: Yield: 3.45 g (60%), white crystals. M.p. 30 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.31 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 4.28 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 4.71 (s, 2 H, NCH_2), 7.42 (m, 3 H, C_6H_5), 7.43 (s, 1 H, N=CH), 8.24 (m, 2 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.70 (1 C, COOEt), 137.13 (1 C, N=CH), 130.96, 130.08, 128.84, 128.54 (6 C, C_6H_5), 68.14 (1 C, NCH_2), 62.34 (1 C, OCH_2CH_3), 14.07 (1 C, OCH_2CH_3) ppm.

Nitrones **7c**–**7f** were generated in situ prior to further reaction and were not subjected to further analysis. Their formation from *N*-hydroxy amino acid esters could be monitored by TLC as they generally have a very strong UV absorption and R_f values of < 0.05, whereas the *N*-hydroxy amino acid esters are readily visualized with iodine and ninhydrin at higher R_f values. The exact procedures for the in situ generation of the nitrones is described in the procedures of the respective reductive hydroxylamination (see below).

Synthesis of *N*-Hydroxy Amino Acid Esters 9 and 10 by the "Acetaldoxime Route": Sodium was dissolved in dry methanol (50 mL) under nitrogen. After addition of the acetaldoxime and the appropriate α-bromo methyl ester, the mixture was stirred overnight. By then the pH of the solution had decreased to almost neutral, as indicated by wet pH paper. After addition of the hydroxylamine hydrochloride, TLC (PE/EtOAc, 1:1) showed complete and immediate conversion of the nitrone. The solvent was evaporated, the residue was dissolved in 1 N HCl (30 mL) and was then washed with diethyl ether (5 × 30 mL). Saturated $NaHCO_3$ solution was added to the aqueous layer and the product was then extracted with diethyl ether until TLC could not detect any further product in the aqueous layer. The combined layers were dried with Na_2SO_4, after which the *N*-hydroxy amino acid methyl ester was isolated.

***N*-Hydroxy Amino Acid Ester 9:** Because of the high solubility of the product in water, the extraction with diethyl ether after the addition of $NaHCO_3$ was difficult. Instead, the water was evaporated, the residue suspended in diethyl ether and dried with Na_2SO_4. From methyl 2-bromopropionate (19.674 g, 117.80 mmol), acetaldoxime (6.627 g, 112.19 mmol), sodium (2.579 g, 112.19 mmol) and hydroxylamine hydrochloride (3.898 g, 56.10 mmol), compound **9** (4.174 g, 35.04 mmol, 31%) was obtained as white crystals. The analytic data match the values reported in the literature.[46] M.p. 29–30 °C. ^{1}H NMR (H_2O, 300 MHz, 25 °C): δ = 1.27 (d, J = 7.2 Hz, 3 H, $CHCH_3$), 3.75 (q, J = 7.2 Hz, 1 H, $CHCH_3$), 3.77 (s, 3 H, OCH_3), 6.04 (br., 2 H, NHOH) ppm.

***N*-Hydroxy Amino Acid Ester 10:** From methyl 2-bromo-2-phenylacetate (5.249 g, 22.91 mmol), acetaldoxime (1.301 g, 22.03 mmol), sodium (0.507 g, 22.03 mmol) and hydroxylamine hydrochloride (1.531 g, 22.03 mmol), compound **10** (1.275 g, 7.04 mmol, 32%) was obtained as a white solid. The analytic data match the values reported in the literature.[55] M.p. 71 °C. ^{1}H NMR (H_2O, 300 MHz, 25 °C): δ = 3.75 (s, 3 H, OCH_3), 4.78 (s, 1 H, CHC_6H_5), 5.89 (br., 2 H, NHOH), 7.34 (s, 5 H, C_6H_5) ppm.

Synthesis of α-Cyano Secondary Hydroxylamines 8a and 8b: A 1 M Et_2AlCN solution was added to a solution of the nitrone in dry CH_2Cl_2 (40 mL) under nitrogen. The mixture was stirred for 10 min after which TLC (PE/EtOAc, 8:2) showed full conversion of the nitrone. After the addition of saturated $NaHCO_3$ (50 mL) and 10 min of fast stirring (viscous suspension), the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The collected extracts were dried with Na_2SO_4 and traces of toluene needed to be removed by stripping with dichloromethane.

Hydroxylamine 8a: From **7a** (1.921 g, 8.68 mmol) and a 1 M $AlEt_2CN$ toluene solution (9.12 mL, 9.12 mmol), hydroxylamine **8a** (2.069 g, 8.33 mmol, 96%) was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.29, 1.30 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.45, 1.47 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 3.73, 3.74 (q, J = 7.1 Hz, 1 H, $CHCH_3$), 4.20, 4.22 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 5.12, 5.13 (s, 1 H, CHC_6H_5), 5.63, 5.68 (s, 1 H, NOH), 7.42 (m, 3 H, C_6H_5), 7.56 (m, 2 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 172.04, 171.91 (1 C, COOEt), 132.54, 132.31, 129.47, 129.38, 128.97, 128.91, 128.77, 128.69, (6 C, C_6H_5), 116.40, 115.73 (1 C, N≡C), 62.96, 62.29, 61.40, 61.29, 61.19, 59.84 (3 C, $CHCH_3$, OCH_2CH_3, CHC_6H_5), 15.25, 14.73 (1 C, $CHCH_3$, OCH_2CH_3), 14.12 (1 C, $CHCH_3$, OCH_2CH_3) ppm. $C_{13}H_{16}N_2O_3$ (248.28): calcd. C 62.89, H 6.50, N 11.28; found C 62.79, H 6.32, N 11.38.

Hydroxylamine 8b: From **7b** (629 mg, 2.22 mmol) and a 1 M $AlEt_2CN$ toluene solution (2.33 mL, 2.33 mmol), hydroxylamine **8b** (659 mg, 2.12 mmol, 96%) was obtained as white crystals. M.p. 142–143 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.17 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.10 (m, 2 H, CH_2CH_3), 4.59, 4.80 (2 × s, 2 H, CHC_6H_5), 5.81 (s, 1 H, NOH), 7.36–7.47 (m, 8 H, 2 × C_6H_5), 7.59–7.62 (m, 2 H, 2 × C_6H_5) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 170.09 (1 C, COOEt), 133.57, 132.80, 130.01, 129.72, 129.22, 128.84, 128.53 (12 C, 2 × C_6H_5), 115.05 (1 C, N≡C), 74.30, (1 C, N≡C*C*H), 61.78, 59.41 (2 C, OCH_2CH_3, CHC_6H_5), 14.13 (1 C, OCH_2CH_3) ppm. $C_{18}H_{18}N_2O_3$ (310.35): calcd. C 69.66, H 5.85, N 9.03; found C 69.57, H 5.71, N 8.81.

Synthesis of α-Cyano Secondary Hydroxylamine 8c: Sodium (0.644 g, 28.00 mmol) was dissolved in dry methanol (50 mL) under nitrogen. After the addition of acetaldoxime (1.654 g, 28.00 mmol) and methyl 2-bromopropionate (4.911 g, 29.41 mmol), the mixture was stirred overnight. By then the pH of the solution had decreased to almost neutral, as indicated by wet pH paper. Because of the instability of the nitrone, subsequent steps were performed quickly. The methanol was evaporated and CH_2Cl_2 was added to precipitate the NaBr, which was then removed by filtration. Concentration yielded a mixture of the nitrone and the oxime ether as a yellow oil. Petroleum ether was added to form a biphasic system, and the oxime ether was separated from the nitrone by removing the colourless upper layer using a pipette. The remaining yellow oil was dissolved in CH_2Cl_2 (50 mL) under nitrogen, and a 1 M Et_2AlCN solution in toluene (8 mL, 8 mmol) was added in one portion. TLC (PE/EtOAc, 8:2) showed a complete and immediate conversion of the nitrone ($R_f < 0.05$; strong UV absorption) and formation of a new product (R_f = 0.4; ninhydrin). After the addition of saturated $NaHCO_3$ (50 mL) and 10 min of fast stirring (viscous suspension), the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The collected extracts were dried with Na_2SO_4 and traces of toluene and the oxime ether were removed by stripping with CH_2Cl_2. The resulting yellow oil became a solid at –18 °C and after washing with a mixture of petroleum ether/diethyl ether hydroxylamine **8c** (1.363 g, 7.92 mmol, 28%) was obtained as white crystals. Recrystallization gave 0.605 g (3.51 mmol, 13%) of **8c** as a single diastereoisomer. M.p. 107–108 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.35 (d, J = 7.0 Hz, 3 H, $NCHCH_3$), 1.61 (d, J = 6.9 Hz, 3 H, $NCHCH_3$), 3.76 (q, J = 6.9 Hz, 1 H, $NCHCH_3$), 3.77 (s, 3 H, OCH_3), 3.94 (q, J = 7.0 Hz, 1 H, $NCHCH_3$), 6.23 (s, 1 H, NOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.84 (C, COOEt), 116.85 (1 C, N≡C), 64.34 (1 C, $NCHCH_3$), 52.36 (1 C, OCH_3), 49.99 (1 C, $NCHCH_3$), 17.12, 15.03 (2 C, $NCHCH_3$) ppm. $C_7H_{12}N_2O_3$ (172.18): calcd. C 48.83, H 7.02, N 16.27; found C 48.87, H 6.99, N 16.18.

Synthesis of α-Cyano Secondary Hydroxylamine 8d: The same procedure as used for the synthesis of **8c** was applied. By allowing sodium (0.841 g, 36.60 mmol), methyl bromoacetate (5.821 g, 38.05 mmol) and acetone oxime (2.649 g, 36.24 mmol) to react, the formation of the intermediate nitrone was complete within 2 h. After its isolation as a yellow oil and the immediate addition of a 1 M Et_2AlCN solution in toluene (4.5 mL, 4.5 mmol), hydroxylamine **8d** (319 mg, 1.85 mmol, 5%) was isolated as white crystals. M.p. 95 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.56 (s, 6 H, $NC(CH_3)_2$), 3.68 (s, 2 H, NCH_2), 3.78 (s, 3 H, OCH_3), 6.48 (s, 1 H, NOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.34 (C, COOMe), 119.90 (1 C, N≡C), 59.53, 56.19 [2 C, N*C*$(CH_3)_2$, NCH_2], 52.51 (1 C, OCH_3), 25.41 [2 C, N$(CH_3)_2$] ppm. $C_7H_{12}N_2O_3$ (172.18): calcd. C 48.83, H 7.02, N 16.27; found C 48.91, H 6.99, N 16.12.

Synthesis of α-Cyano Secondary Hydroxylamines 8e and 8f: The *N*-hydroxyglycine ethyl ester and the aldehyde were condensed in CH_2Cl_2 (20 mL) under nitrogen with the aid of Na_2SO_4 as drying agent. When TLC (PE/EtOAc, 1:1) showed full conversion of the ester to the intermediate nitrone (R_f < 0.05; strong UV absorption), a 1 M Et_2AlCN solution in toluene was added in one portion. TLC showed a complete and immediate conversion of the nitrone and formation of a new product. After the addition of saturated $NaHCO_3$ (50 mL) and 10 min of fast stirring (viscous suspension), the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The collected extracts were dried with Na_2SO_4 and traces of toluene were removed by stripping with petroleum ether. The resulting yellow oil became a solid at –18 °C, which was purified by recrystallization from a mixture of petroleum ether/diethyl ether.

Hydroxylamine 8e: From *N*-hydroxyglycine ethyl ester (0.350 g, 2.94 mmol), acetaldehyde (0.142 g, 3.23 mmol) and a 1 M Et_2AlCN solution in toluene (3.4 mL, 3.4 mmol), hydroxylamine **8e** (430 mg, 2.50 mmol, 85%) was obtained as white crystals. During the condensation, the mixture was cooled with ice to prevent evaporation of the acetaldehyde. Initially, the condensation reaction proceeded slowly, but it could be promoted by the addition of one drop of dilute HCl and was complete after 4 h. M.p. 35–36 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.30 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.56 (d, J = 7.2 Hz, 3 H, $CHCH_3$), 3.55 (J = 16.5 Hz, 1 H, NCH_2), 3.75 (J = 16.5 Hz, 1 H, NCH_2), 3.90 (q, J = 7.2 Hz, 1 H, $CHCH_3$), 4.23 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 6.73 (s, 1 H, NOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 169.48 (1 C, COOEt), 117.39 (1 C, N≡C), 61.69 (1 C, OCH_2CH_3), 58.70, 54.30 (2 C, NCH_2, N*C*HCN), 17.02 (1 C, $CHCH_3$), 14.34 (1 C, OCH_2CH_3) ppm. $C_7H_{12}N_2O_3$ (172.18): calcd. C 48.83, H 7.02, N 16.27; found C 48.94, H 6.99, N 16.02.

Hydroxylamine 8f: From *N*-hydroxyglycine ethyl ester (0.119 g, 1.00 mmol), freshly distilled valeraldehyde (0.095 g, 1.10 mmol) and a 1 M Et_2AlCN solution in toluene (1.15 mL, 1.15 mmol), hydroxylamine **8f** (173 mg, 0.81 mmol, 81%) was obtained as white crystals. The condensation was complete after 1 h. M.p. 87 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.96, 0.99 [2 × d, J = 7.1 Hz, 6 H, $CH(CH_3)_2$], 1.30 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.69–1.97 [m, 3 H, $NCCH_2$, $CH(CH_3)_2$], 3.55 (d, J = 16.5 Hz, 1 H, NCH_2), 3.76 (d, J = 16.5 Hz, 1 H, NCH_2), 3.82 (dd, J = 7.1 Hz, J = 7.2 Hz, 1 H, NCH), 4.23 (q, J = 7.2 Hz, 2 H, OCH_2), 6.40 (s, 1 H, NOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 169.27 (1 C, COOEt), 116.70 (1 C, N≡C), 61.40 (1 C, OCH_2CH_3), 58.60, 57.76 (2 C, NCH_2, N*C*HCN), 39.48, 24.84, 22.52, 21.91 [4 C, $CH_2CH(CH_3)_2$], 14.13 (1 C, OCH_2CH_3) ppm. $C_{10}H_{18}N_2O_3$ (214.26): calcd. C 56.06, H 8.47, N 13.07; found C 56.04, H 8.44, N 12.95.

Synthesis of Ligands 1, 4a and 4b by Reductive Hydroxylamination: The *N*-hydroxy amino acid ester and the α-keto acid were stirred in methanol until TLC (PE/EtOAc, 1:1) showed full conversion of the *N*-hydroxy amino acid ester. After the addition of $NaCN{\cdot}BH_3$, TLC showed a complete and immediate conversion of the nitrone (R_f < 0.05; strong UV absorption). Evaporation of the methanol yielded a white solid, which was then hydrolyzed under acidic (**1** and **4b**) or basic (**4a**) conditions. $[Zn(OAc)_2{\cdot}2H_2O]$ was added to precipitate the ligand, and the resulting milk-white suspension was washed with water (a cycle of centrifugation, decanting the supernatant and suspending the residue in water was performed three times) and dried in vacuo. It was then dissolved in 3 N HCl (using the minimum amount that was necessary for complete dissolution) and added to a column of H^+-loaded DOWEX-50 ion-exchange resin that had previously been washed with water until neutral pH. Elution with water first gave an eluate with a pH < 1, after which the pH increased again. When the pH started to decrease for the second time, the eluate was collected. After concentration, the solution was either lyophilized (**1**) or concentrated to dryness and stripped with CH_2Cl_2 (**4a** and **4b**; both are slightly soluble in CH_2Cl_2).

Ligand 1: The synthesis was performed by using **9** (357 mg, 3.00 mmol), pyruvic acid (280 mg, 3.18 mmol), $NaCN{\cdot}BH_3$ (211 mg, 3.36 mmol) and $[Zn(OAc)_2{\cdot}2H_2O]$ (659 mg, 3.00 mmol). The hydrolysis step was performed by stirring the mixture in 10 N HCl (11 mL) at 110 °C for 6 h. After evaporation of the aqueous HCl, the mixture was dissolved in water and the pH was adjusted to 4.4 with aqueous NH_4OH before adding $[Zn(OAc)_2{\cdot}2H_2O]$. The zinc complex was obtained as a fine white powder in a yield of 350 mg (1.46 mmol, 49%), from which the free ligand **1** was obtained in an overall yield of 229 mg (1.29 mmol, 43%). M.p. 120 °C (decomp.). ^{1}H and ^{13}C NMR show the presence of two diastereomers in a ratio of A/B = 6:4, with A being the *meso* compound. In all other respects, the ^{1}H NMR, ^{13}C NMR, and mass spectra are identical to those of **1** obtained by substitution on 2-bromopropionate as described above.

Ligand 4a (Starting from 10): The synthesis was performed by using **10** (336 mg, 1.85 mmol), pyruvic acid (171 mg, 1.94 mmol), $NaCN{\cdot}BH_3$ (128 mg, 2.04 mmol) and $[Zn(OAc)_2{\cdot}2H_2O]$ (407 mg, 1.85 mmol). The hydrolysis step was performed by stirring in 0.5 M NaOH at room temp. for 5 h. The pH was then adjusted to 1.80 with aqueous HCl after which the mixture was concentrated. Precipitation with $[Zn(OAc)_2{\cdot}2H_2O]$ yielded 265 mg (0.88 mmol, 47%) of the zinc complex as a fine white powder, from which **4a** was obtained as a white solid in an overall yield of 172 mg (0.72 mmol, 47%). NMR spectra showed the presence of **4a** as two isomers in a ratio of A/B = 1:5. The assignment of the ^{1}H and ^{13}C resonances was based on this ratio. M.p. 115 °C (decomp.). ^{1}H NMR (DMSO, 300 MHz, 25 °C): δ = 1.13^B, 1.35^A (d, J = 6.9 Hz, 3 H, $CHCH_3$), 3.09^B, 3.24^A (q, J = 6.9 Hz, 1 H, $CHCH_3$), 4.54^A, 4.99^B (s, 1 H, CHC_6H_5), $7.33–7.50^{A+B}$ (m, 5 H, C_6H_5) ppm. ^{13}C NMR (DMSO, 75 MHz, 25 °C): δ = 173.12^B, 172.83^B (2 C, 2 × COOH), 136.84^B, 129.47^B, 129.21^B, 129.09^B (6 C, C_6H_5), 73.23^B (1 C, CHC_6H_5), 59.11^B (1 C, $CHCH_3$), 16.66^B (1 C, $CHCH_3$) ppm. HRMS (ESI): calcd. for $C_{11}H_{14}NO_5$ $[M + H]^+$ 240.0867; found 240.0863. It was possible to obtain **4a** as one diastereoisomer analogously to the synthesis of *meso*-**1**: one diastereoisomer of the intermediate monoester was selectively crystallized and then hydrolyzed to the diacid. The NMR spectra correspond to isomer B of **4a**. This diastereomerically pure sample of **4a** was used for the complexation to vanadium.

Ligand 4a (Starting from 9): The procedure was identical to the one used for the synthesis of **4a** starting from **10**, but during the condensation step the use of $MgSO_4$ as a drying agent appeared to

be necessary. The methanol was therefore substituted by the low-boiling dichloromethane. When the condensation was complete, the reaction mixture was filtered, concentrated and the reduction was performed after the addition of methanol. From **9** (380 mg, 3.19 mmol), phenylglyoxylic acid (508 mg, 3.38 mmol), $NaCN{\cdot}BH_3$ (225 mg, 3.57 mmol) and $[Zn(OAc)_2{\cdot}2H_2O]$ (701 mg, 3.19 mmol), **4a** was obtained as a white solid in an overall yield of 161 mg (0.67 mmol, 21%). M.p. 118 °C (decomp.). ^1H NMR, ^{13}C NMR and the mass spectra are identical to those of **4a** obtained by starting from **10**.

Ligand 4b: The synthesis was performed by using (*R*)-*N*-hydroxyphenylalanine methyl ester (408 mg, 2.09 mmol), glyoxylic acid·H_2O (202 mg, 2.19 mmol), $NaCN{\cdot}BH_3$ (144 mg, 2.29 mmol) and $[Zn(OAc)_2{\cdot}2H_2O]$ (459 mg, 2.09 mmol). The hydrolysis step was performed by refluxing in 1 N HCl (15 mL) for 1 h. After evaporation of the aqueous HCl, the mixture was dissolved in water and the pH was then adjusted to 1.80 with aqueous NH_4OH after which the mixture was concentrated. After precipitation with $[Zn(OAc)_2{\cdot}2H_2O]$, **4b** was obtained as a white solid in an overall yield of 206 mg (0.86 mmol, 41%). M.p. 130 °C (decomp.). $[\alpha]_D^{20}$ = –5.0 (*c* = 1, EtOH). ^1H NMR (DMSO, 300 MHz, 25 °C): δ = 2.92–2.97 (m, 2 H, $CH_2C_6H_5$), 3.60–3.66 (m, 3 H, NCH, NCH_2), 7.16–7.29 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (DMSO, 75 MHz, 25 °C): δ = 172.51, 171.69 (2 C, 2 × COOH), 139.04, 129.92, 128.81, 126.83 (6 C, C_6H_5), 71.56 (1 C, NCH), 59.04 (1 C, NCH_2), 35.73 (1 C, $CH_2C_6H_5$) ppm. HRMS (ESI): calcd. for $C_{11}H_{14}NO_5$ $[M + H]^+$ 240.0867; found 240.0864.

Synthesis of Ligand *rac*-5: *N*-Hydroxy amino acid ester **9** (580 mg, 4.87 mmol) and pyruvic acid (455 mg, 5.16 mmol) were stirred in methanol until TLC (PE/EtOAc, 1:1) showed full conversion of **9**. After the addition of $NaCN{\cdot}BH_3$ (343 mg, 5.45 mmol), TLC showed a complete and immediate conversion of the nitrone (R_f < 0.05; strong UV absorption). Evaporation of the methanol yielded a white solid which was then dissolved in water (5 mL). To remove the cyanide, aqueous HCl (1–2 equiv.) was added and the mixture stirred in the open vessel at 60 °C in the fumehood for 20 min. The pH of the mixture was brought to 1.9 using NH_4OH solution, it was concentrated and left to crystallize at 0 °C after the addition of a small amount of ethanol. This yielded 330 mg (2.13 mmol, 44%) of *rac*-**5** as white crystals. M.p. 137–138 °C (decomp.). ^1H NMR (H_2O, 300 MHz, 25 °C): δ = 1.34, 1.35 (2 × d, *J* = 6.9 Hz, 6 H, 2 × $CHCH_3$), 3.74 (s, 3 H, OCH_3), 3.87, 4.01 (2 × q, *J* = 6.9 Hz, 2 H, 2 × $CHCH_3$) ppm. ^{13}C NMR (H_2O, 75 MHz, 25 °C): δ = 176.00, 174.01 (2 C, 2 × *C*OOH, *C*OOMe), 62.28, 61.88 (2 C, 2 × N*C*H), 52.73 (1 C, O*C*H_3), 14.51, 14.09 (2 C, 2 × N*C*H_3) ppm. HRMS (ESI): calcd. for $C_7H_{14}NO_5$ $[M + H]^+$ 192.0867; found 192.0863. HRMS (ESI): calcd. for $C_7H_{13}NO_5Na$ $[M + Na]^+$ 214.0686; found 214.0680.

Synthesis of *meso*-1: A solution of *rac*-**5** (146 mg, 0.76 mmol) in 1 N HCl (3 mL) was refluxed for 1 h. The pH of the mixture was brought to 4.2 with a 0.5 M NaOH solution and the product was precipitated with $[Zn(OAc)_2{\cdot}2H_2O]$ (168 mg, 0.76 mmol). Compound *meso*-**1** was released by ion-exchange chromatography according to the procedures reported above for **1** and was isolated as a white solid in a yield of 48 mg (0.27 mmol, 35%). ^1H and ^{13}C NMR spectra showed the presence of one diastereomer which was identified as the *meso*-form of **1** after comparison with the NMR spectroscopic data of **1** obtained by substitution of (*R*)-2-bromopropionate as described above. ^1H NMR (D_2O, 400 MHz): δ = 1.43 (d, *J* = 6.0 Hz, 6 H, $CHCH_3$), 4.08 (q, *J* = 6.0 Hz, 1 H, $CHCH_3$) ppm. ^{13}C NMR (D_2O, 100 MHz): δ = 175.91 (2 C, COOH), 64.58 (2 C, CH), 14.76 (2 C, CH_3) ppm.

Synthesis of Secondary Hydroxylamines 12a and 12b: $NaCN{\cdot}BH_3$ (1.1 equiv.) and acetic acid (1.1 equiv.) were added to a solution of the nitrone **7** in methanol (20 mL). The reaction was complete after 24 h (TLC). The solvent was then evaporated, saturated aqueous $NaHCO_3$ was added, the product was extracted with CH_2Cl_2 (3 × 20 mL) and dried with $MgSO_4$.

Hydroxylamine 12a: From nitrone **7a** (574 mg, 2.59 mmol), $NaCN{\cdot}BH_3$ (179 mg, 2.85 mmol) and acetic acid (171 mg, 2.85 mmol), hydroxylamine **12a** (557 mg, 2.49 mmol, 96%) was obtained as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.29 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.41 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 3.55 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 3.86 (*J* = 13.2 Hz, 1 H, NCH_2), 3.99 (*J* = 13.2 Hz, 1 H, NCH_2), 4.20 (q, *J* = 7.2 Hz, 1 H, $CHCH_3$), 5.75 (s, 1 H, NOH), 7.26–7.36 (m, 5 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 173.09 (1 C, COOEt), 137.23, 129.48, 128.33, 127. 44 (6 C, C_6H_5), 63.87, 60.80, 60.71 (3 C, NCH, NCH_2, OCH_2CH_3), 14.22, 14.12 (2 C, OCH_2CH_3, $CHCH_3$) ppm. HRMS (ESI): calcd. for $C_{12}H_{18}NO_3$ $[M + H]^+$ 224.1282; found 224.1277.

Hydroxylamine 12b: From nitrone **7g** (574 mg, 2.77 mmol), $NaCN{\cdot}BH_3$ (191 mg, 3.05 mmol) and acetic acid (183 mg, 3.05 mmol), hydroxylamine **12b** (531 mg, 2.54 mmol, 92%) was obtained as white crystals. M.p. 73 °C. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.26 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 3.50 (s, 2 H, NCH_2COOEt), 3.92 (s, 2 H, $NCH_2C_6H_5$), 4.18 (q, *J* = 7.1 Hz, 1 H, CH_2CH_3), 6.49 (s, 1 H, NOH), 7.25–7.38 (m, 5 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 170.03 (1 C, COOEt), 136.38, 129.68, 128.39, 127.66 (6 C, C_6H_5), 63.86, 60.85, 60.11 (3 C, $NCH_2C_6H_5$, NCH_2COOEt, OCH_2CH_3), 14.16 (1 C, OCH_2CH_3) ppm. $C_{11}H_{15}NO_3$ (209.24): calcd. C 63.14, H 7.23, N 6.69; found C 62.95, H 7.16, N 6.48. HRMS (ESI): calcd. for $C_{11}H_{16}NO_3$ $[M + H]^+$ 210.1125; found 210.1121.

Synthesis of Secondary Hydroxylamine 12c: *N*-Hydroxy amino acid ester **9** (385 mg, 3.23 mmol), acetaldehyde (157 mg, 3.55 mmol) and acetic acid (213 mg, 3.55 mmol) were stirred in CH_2Cl_2 (20 mL) under nitrogen at 0 °C using Na_2SO_4 as a drying agent. When TLC (PE/EtOAc, 1:1) showed full conversion of the ester to the intermediate nitrone (R_f < 0.05; strong UV absorption), $NaCN{\cdot}BH_3$ (223 mg, 3.55 mmol) was added. The reaction was complete after 1 h (TLC). The solvent was then evaporated, saturated aqueous $NaHCO_3$ was added, the product was extracted with CH_2Cl_2 (3 × 20 mL) and dried with $MgSO_4$. Compound **12c** was isolated in a yield of 385 mg (2.62 mmol, 81%) as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.18 (t, *J* = 7.0 Hz, 3 H, NCH_2CH_3), 1.36 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 2.70 (dq, 1 H, $NCHHCH_3$), 2.88 (dq, 1 H, $NCHHCH_3$), 3.56 (q, *J* = 7.0 Hz, 1 H, $NCHCH_3$), 3.75 (s, 3 H, OCH_3), 5.91 (br., 1 H, NOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 173. 73 (1 C, COOMe), 64.81 (1 C, NCH), 51.91, 50.60 (2 C, OCH_3, NCH_2), 14.02, 12.16 (2 C, $CHCH_3$, CH_2CH_3) ppm. HRMS (ESI): calcd. for $C_6H_{14}NO_3$ $[M + H]^+$ 148.0969; found 148.0966.

Synthesis of Ligands 6a–6c: A solution of the appropriate methyl ester (**12a**–**12c**) in 1 N HCl (20 mL) was stirred at 125 °C for 1 h, the reaction was monitored by TLC (PE/EtOAc, 4:1). The solvent was then evaporated and the residue stripped twice with water to remove residual HCl. After dissolving the residue in water (10 mL), the pH of the solution was brought to 2.4 using NH_4OH solution. The solution was concentrated and left to crystallize at 0 °C after the addition of a small amount of ethanol.

Ligand 6a: The hydrolysis required 3 N HCl instead of 1 M. From **12a** (465 mg, 2.08 mmol), ligand **6a** (189 mg, 1.04 mmol, 50%) was obtained as white crystals. M.p. 147 °C (decomp.). ^1H NMR (D_2O,

Table 1. HRMS (ESI) data for amavadin analogues **13a** and **13b** using ligands **4a** and **4b** (= L).

Product	Ionization	Molecular ion Empirical formula	Calcd. *M*	$[VO(acac)_2]$ + 2 L Found *M*
13a	$[M + H]^+$	$C_{22}H_{23}N_2O_{10}V$	526.0787	526.0788
	$[M – H]^–$	$C_{22}H_{21}N_2O_{10}V$	524.0641	524.0639
13b	$[M + H]^+$	$C_{22}H_{23}N_2O_{10}V$	526.0787	526.0786
	$[M – H]^–$	$C_{22}H_{21}N_2O_{10}V$	524.0641	524.0639

Table 2. HRMS (ESI) data for tentative complexes **14** and **15** using ligand **5** (= L).

Product	Ionization	Molecular ion Empirical formula	Calcd. *M*	$[VO(acac)_2]$ + 2 L Found *M*	$[VO(OPr)_3]$ + 2 L Found *M*
14	$[M + H]^+$	$C_{14}H_{23}N_2O_{10}V$	430.0787	430.0787	n.a.
	$[M – H]^–$	$C_{14}H_{21}N_2O_{10}V$	428.0641	–	
15	$[M + H]^+$	$C_{14}H_{24}N_2O_{11}V$	447.0815	447.0813	447.0814
	$[M – H]^–$	$C_{14}H_{22}N_2O_{11}V$	445.0668	445.0663	445.0663

300 MHz, 25 °C): δ = 1.53 (d, J = 7.2 Hz, 3 H, CHCH_3), 3.91 (q, J = 7.1 Hz, 1 H, CHCH$_3$), 4.46 (s, 2 H, NCH$_2$) 7.43–7.51 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (D_2O, 75 MHz, 25 °C): δ = 175.59 (1 C, COOH), 132.89, 131.49, 130.86, 130.57 (6 C, C_6H_5), 68.23, 62.46 (2 C, NCH, NCH$_2$), 14.17 (1 C, CHCH$_3$) ppm. HRMS (ESI): calcd. for $C_{10}H_{14}NO_3$ $[M + H]^+$ 196.0969; found 196.0967.

Ligand 6b: From **12b** (209 mg, 1.00 mmol), ligand **6b** (150 mg, 0.83 mmol, 83%) was obtained as white crystals. M.p. 135 °C (decomp.). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 3.74 (s, 2 H, NCH_2C$_6$H$_5$), 4.35 (s, 2 H, NCH_2COOH), 7.33–7.38, 7.47–7.51 (m, 5 H, C_6H_5), 12.47 (s, 2 H, COOH, NOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 171.09 (1 C, COOH), 131.62, 129.70, 129.54, 128.62 (6 C, C_6H_5), 62.84, 60.14 (2 C, NCH$_2$C$_6$H$_5$, NCH$_2$COOH) ppm. HRMS (ESI): calcd. for $C_9H_{12}NO_3$ $[M + H]^+$ 182.0812; found 182.0811.

Ligand 6c: The hydrolysis step required 1.5 h instead of 1 h. As crystals could not be obtained (oily precipitate), the solution was concentrated to dryness and the raw product was then extracted with THF. The product was then crystallized from a water/ethanol mixture. From **12c** (335 mg, 2.28 mmol), ligand **6c** (140 mg, 1.05 mmol, 46%) was obtained as white crystals. M.p. 146 °C (decomp.). ^{1}H NMR (DMSO, 300 MHz, 25 °C): δ = 1.03 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3), 1.17 (d, J = 6.6 Hz, 3 H, CHCH_3), 2.61 (dq, 1 H, NCHHCH$_3$), 2.71 (dq, 1 H, NCHHCH$_3$), 3.29 (q, J = 6.6 Hz, 1 H, CHCH$_3$), 7–12 (br., 2 H, COOH, NOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 174.40 (1 C, COOH), 65.61 (1 C, NCHCH$_3$), 51.02 (1 C, NCH$_2$), 14.76, 13.07 (2 C, CHCH$_3$, CH$_2$$CH_3$) ppm. HRMS (ESI): calcd. for $C_5H_{12}NO_3$ $[M + H]^+$ 134.0812; found 134.0811.

Synthesis of Vanadium(IV) Complex 13a: $[VO(acac)_2]$ (22 mg, 0.084 mmol) was added to a solution of **4a** (44 mg, 0.184 mmol) in methanol (15 mL). The mixture immediately turned deep brown for a few seconds. After stirring for 20 min, the mixture became clear blue-purple and the smell of Hacac was noticed. All volatiles were removed by rotary evaporation and the residue was stripped twice with methanol. The dry residue was then washed twice with dichloromethane, yielding 42 mg (0.080 mmol, 96%) of **13a** as a glittering blue solid. M.p. 200 °C (decomp.). HRMS (ESI): calcd. for $C_{22}H_{23}N_2O_{10}$ $[M + H]^+$ 526.0787; found 526.0786. HRMS (ESI): calcd. for $C_{22}H_{21}N_2O_{10}$ $[M – H]^–$ 524.0641; found 524.0636.

Oxidation of 13a to the Vanadium(V) Complex $[VL_2]^–[PPh_4]^+$ (L = Ligand): The oxidation and isolation processes were carried out according to the procedure reported earlier for amavadin.[3] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.946 [4 × d (overlapping), 6 H, CHCH_3], 4.88, 4.89, 5.11, 5.13 [4 × q (overlapping), 2 H, CHCH$_3$], 5.82, 5.83, 6.07, 6.10 (4 × s, 2 H, CHC$_6$H$_5$), 7.30–7.46 (m, 10 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 174.09, 173.97, 172.81, 171.98, 171.91, 170.72 (4 C, COOH), 136.95, 136.80, 136.76, 129.86, 129.70, 129.03 (12 C, C_6H_5), 80.63, 80.49, 79.70, 79.51 (2 C, CHC$_6$H$_5$), 72.96, 72.80, 72.38, 72.17 (2 C, CHCH$_3$), 18.87 (2 C, CHCH$_3$) ppm. ^{51}V NMR (79 MHz, $CDCl_3$, 25 °C): δ = –243 ppm.

Complexation of Ligands 5and 6 to $[VO(acac)_2]$. Solutions for HRMS Measurements: $[VO(acac)_2]$ (0.010 mmol) was added to a solution of the ligand (0.021 mmol) in methanol (0.8 mL). The mixtures were stirred in an open flask for 1 h, after which they were analyzed by electrospray HRMS.

Complexation of Ligands 5 and 6 to $[VO(OPr)_3]$. Solutions for HRMS Measurements: $[VO(OPr)_3]$ (0.035 mmol) was added to a solution of the ligand (0.074 mmol) in methanol (2 mL). The mixtures were stirred in an open flask for 1 h, after which they were analyzed by electrospray HRMS.

High-Resolution Electrospray MS Data: The HRMS (ESI) data recorded for the vanadium complexes are shown in Table 1 (tridentate ligands **4a** and **4b**) and Table 2 (bidentate ligand **5**).

Acknowledgments

We gratefully acknowledge TNO in Zeist, The Netherlands, for the high-resolution mass spectrometry measurements. T. H. thanks the Netherlands Research School Combination Catalysis (NRSC-C) for financial support.

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Received: December 5, 2006
Published Online: April 4, 2007

