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Modular synthesis of chiral pentadentate bis(oxazoline) ligands

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Abstract—Highly modular N,Y,Z,Y,N-ligands (Y=N, O, S; Z=N, NO, OH, OMe) have been prepared using bis(oxazoline) building blocks either as nucleophiles or as electrophiles in coupling reactions with central aromatic units. This way, a great variety of pentadentate bis(oxazoline) ligands in diastereo- and enantiomerically pure form become readily available, which are useful for the construction of helical metal complexes with predetermined chirality.

1. Introduction

Modular ligand design allows for the facile tailoring of properties of the corresponding metal complexes for a given application. This concept has especially been utilized in asymmetric catalysis for the fine-tuning of reactivity as well as the geometric environment of a chiral catalyst.

One of the most successful ligand motifs for this purpose over the last decades has been the oxazoline moiety.[1] Since their chiral information in most cases stems from readily available enantiopure amino acids, oxazoline ligands with broad stereochemical diversity are available. Beyond this intrinsic modularity, many successful oxazoline-based ligand systems have been developed with additional degrees of structural variability.[2–5] Generally, oxazoline ligands are build up by coupling of an amino acid derivative—most prominently amino alcohols—to a backbone followed by cyclization, the latter step often requiring forcing conditions. The incorporation of already preformed oxazoline moieties into a backbone has hardly been explored so far,[6] despite the potential advantage of a more convergent assembly of such structures. Difficulties with respect to the stability of the oxazoline units are often encountered in such transformations,[6a,6h] which have prevented by enlarge the identification of suitable oxazoline building blocks as transferable units and reaction conditions amenable for such an approach.

We recently reported on metal complexes of pentadentate bis(oxazoline) ligands **1** (Z=pyridinyl) for the construction of enantiomerically pure helical assemblies, including mononuclear metal complexes as well as polymeric organic–inorganic hybrid materials.[7] As part of our efforts to extend the versatility of this system we have worked out a modular synthesis for a variety of diverse bis(oxazoline) ligands of the general structure **1** (Scheme 1), demonstrating the use of oxazolines both as nucleophilic and electrophilic building blocks.

The generic structure **1** features a number of attractive characteristics to be explored for metal complexes. Firstly, the range of central units Z can be broadly varied. Besides a pyridine moiety that proved to be useful to generate a number of mononucleating complexes,[7] we also aimed at the synthesis of ligands with pyridine-*N*-oxide and related phenol/anisol building blocks being known to be able to accommodate two metal centers in close proximity, which could lead to binucleating ligands that could bear significance for a number of applications like asymmetric catalysis[8] or bioinorganic chemistry.[9] Secondly, the benzylic heteroatoms Y allow for facile variation of the donor set around the metal. In addition, they also serve as the nucleophilic part in the connection of the central unit Z and the peripheral oxazolines via a synthetically universal nucleophilic displacement reaction (Scheme 1, reaction between **2** and **5**, **4** and **7**). Thirdly, the variation of R^1 and R^2 on the oxazoline moieties enables the tuning of the steric bulk around the metal center in a straightforward manner.

The outlined synthetic strategy has the following advantages: (a) Generation of diversity is efficiently achieved in the final assembly step by the coupling of entire oxazoline units with the central building blocks Z. This appears to be more economic than in many other oxazoline containing systems with early introduction of the diversifying element (usually amino alcohols) followed by subsequent manipulations

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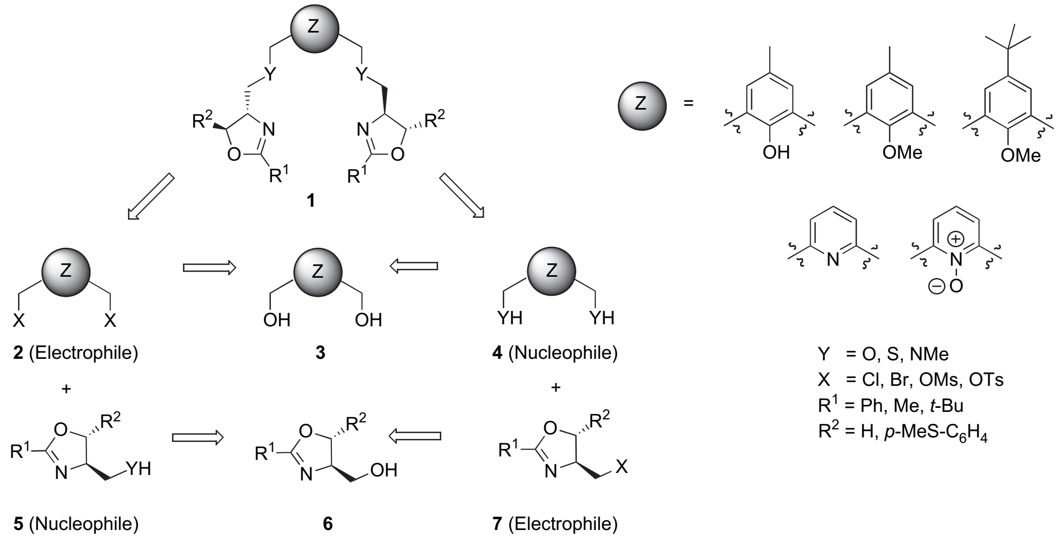


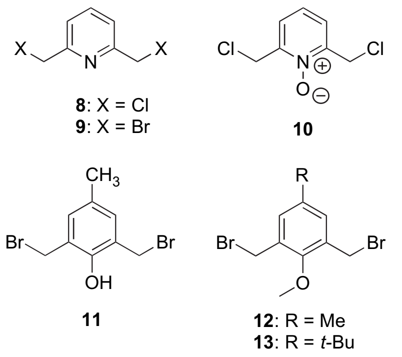
Scheme 1. Synthetic strategy for the modular bis(oxazoline) ligand system **1**.

(e.g., ring closure to the oxazoline); (b) The final S_N2 reaction in principle has an almost universal scope. In addition, the reaction partners Z and the oxazoline can both serve as nucleophiles (**4** or **5**), as well as electrophiles (**2** or **7**), making this process very flexible. Conveniently, each set of building blocks can be derived from common precursors (Scheme 1, **3** for **2** and **4**, **6** for **5** and **7**).

2. Results and discussion

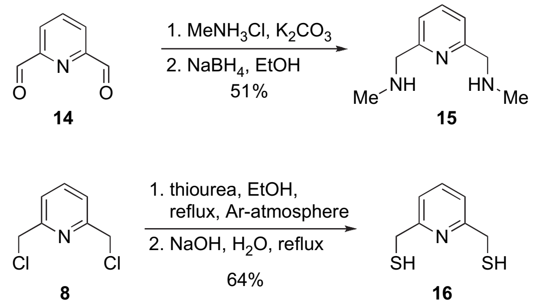
2.1. Synthesis of the central units

For the synthesis of the electrophilic pyridine building blocks (Scheme 2), commercially available 2,6-bis(hydroxymethyl)pyridine was converted to the dibenzyl chloride **8** with $SOCl_2$ and subsequent treatment with base.[10] The corresponding *N*-oxide **10** was prepared under standard conditions with $AcOH/H_2O_2$.[11] The more reactive dibenzyl bromide **9** was accessible from 2,6-lutidine by radical bromination with NBS.[12] The phenol- or anisol-based electrophilic building blocks **11–13** were readily accessible from 4-methyl- and 4-*tert*-butylphenol.[13]



Scheme 2. Pyridine, phenol, and anisol building blocks used as electrophiles.

The preparation of nucleophilic pyridine building blocks again started from 2,6-bis(hydroxymethyl)pyridine (Scheme 3). Oxidation with SeO_2[14] to bis(aldehyde) **14** and formation of the bis(imine) with methylamine in analogy to a reported procedure[15] was followed by reduction with $NaBH_4$ to yield the previously unknown air-sensitive bis(amine) **15**. Equally air-sensitive bis(thiol) **16** was accessible with improved yields from dibenzyl chloride **8** in a modified[7d] two-step procedure reported by Chiotellis[10] and co-workers.

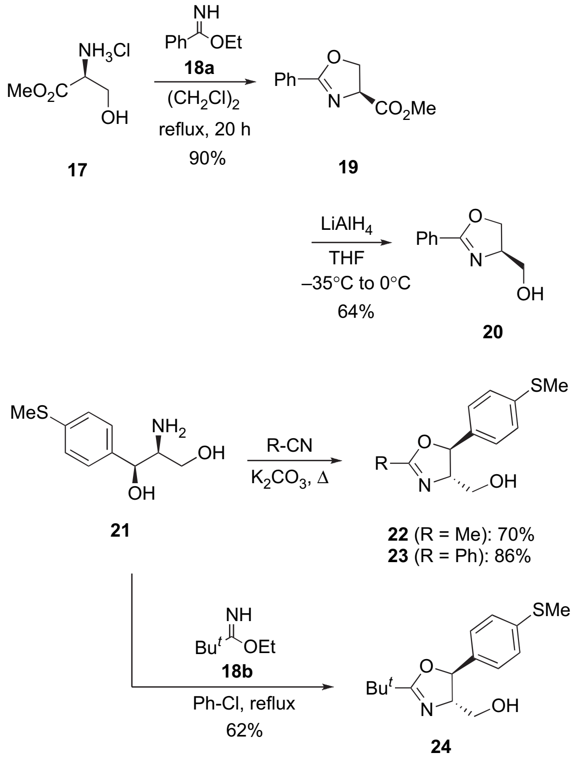


Scheme 3. Synthesis of pyridine building blocks used as nucleophiles.

2.2. Synthesis of the oxazoline units

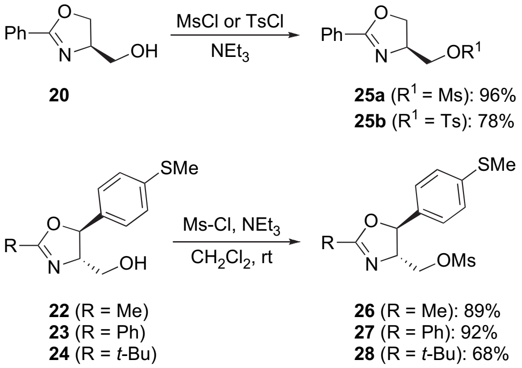
The range of nucleophilic oxazoline units was restricted to compounds of type **6** having alcohol functionalities. The corresponding primary amines and thiols proved to be unstable due to the formation of the corresponding imidazolines and thiazolines by attack on the oxazoline ring. The stable primary alcohol building blocks **20**, **22–24** were prepared from amino alcohols and imidates or nitriles (Scheme 4). Compound **20** was synthesized by condensation of imidate **18a** with (*S*)-serine methyl ester hydrochloride (**17**), followed by reduction of the corresponding methyl ester **19** with $LiAlH_4$.[16] Oxazoline **23** was accessible starting from benzonitrile and commercially available aminodiol **21**.[17] The methyl substituted analog **22** could also be prepared by this methodology, whereas the *tert*-butyl derivative **24** required the use of more reactive imidate **18b** instead of pivalonitrile.

Transformation of these nucleophilic building blocks to electrophiles was conveniently achieved by their conversion



Scheme 4. Synthesis of oxazoline building blocks used as nucleophiles.

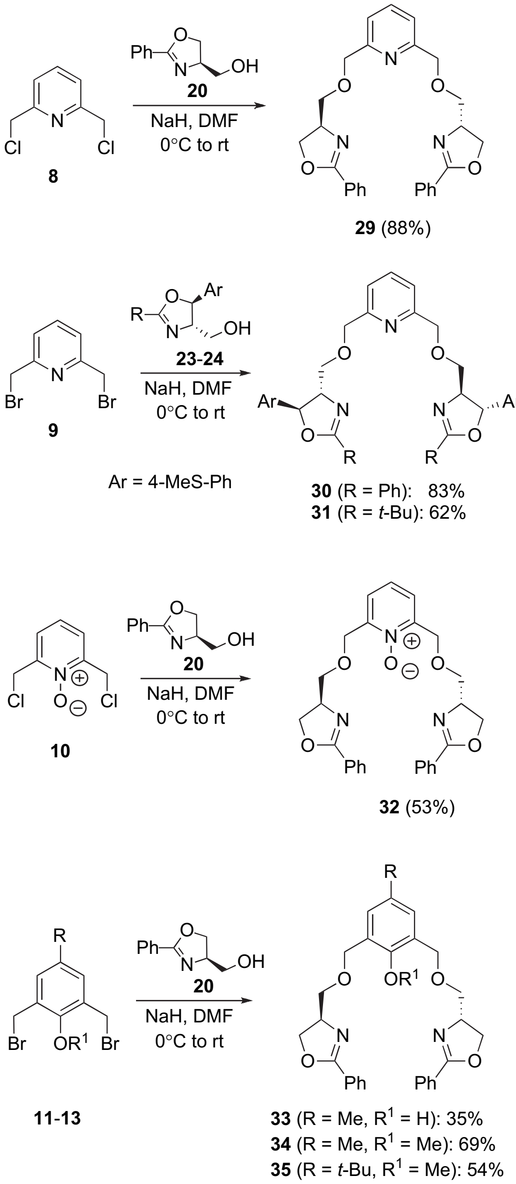
to the corresponding sulfonic acid esters (Scheme 5). Compounds **25a**[18a] and **25b**[18b] were synthesized according to literature precedence. For the sterically more hindered oxazolines **22–24**, the tosylates proved to be ineffective in subsequent transformations. Therefore, the more reactive mesylates **26–28** were prepared.



Scheme 5. Synthesis of oxazoline building blocks used as electrophiles.

2.3. Assembly of the bis(oxazoline) ligands

The connection between the central aromatic unit and the peripheral oxazolines was achieved via S_N2 displacement reactions, combining the appropriate electrophilic and nucleophilic building blocks. Oxazolines **20**, **23**, and **24** smoothly reacted as nucleophiles upon deprotonation with sodium hydride with the biselectrophiles **8–13** to give rise to the bis(oxazolines) **29**,[7b] **30–35** (Scheme 6). Likewise, oxazolines **25–28** could be reacted as nucleophiles to yield the ligands **36**,[7d] **37–41** (Scheme 7), however, for the bis-amine **15** K_2CO_3 instead of NaH had to be employed.

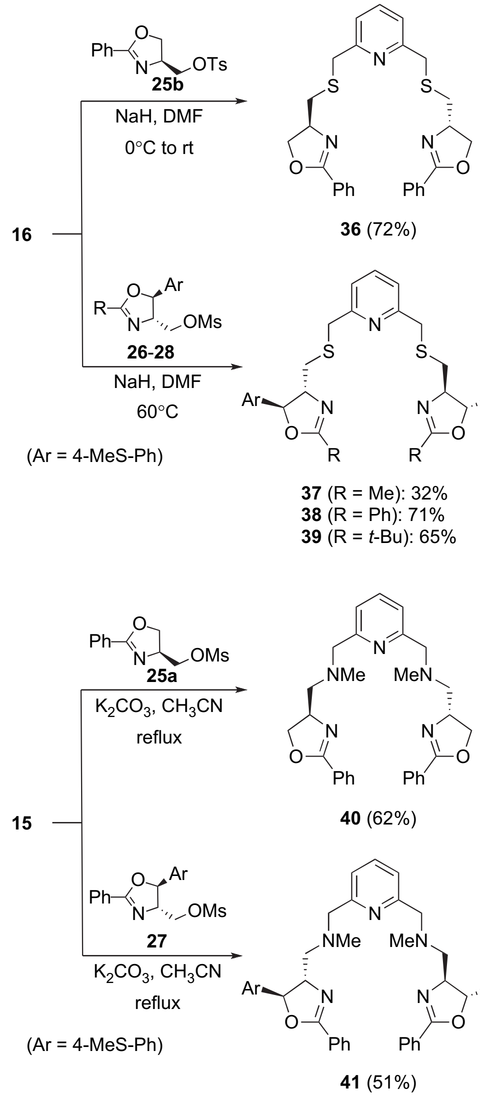


Scheme 6. Ligand synthesis with nucleophilic oxazoline building blocks.

While with **20**, **23**, and **24** the reactions proceeded already at 0 °C, the sterically more hindered oxazolines **26–28** required elevated temperatures (70–80 °C) and more reactive electrophiles (benzyl bromide **9** and mesylates **26–28**). In the case of 2-methyl substituted oxazolines **22** and **26**, only the thioether ligand **37** (reaction of **16** with **26**) but not the corresponding oxoether ligand (reaction of **9** with **22** in analogy to the preparation of **30–31**) could be obtained and only in low yield, presumably due to side reactions originating from competing deprotonation at the methyl group.

All ligands were obtained as single stereoisomers, as judged by their NMR spectra, HPLC traces, and spectroscopical data (NMR, CD) of their corresponding metal complexes.[7] Consequently, no racemization of the oxazoline building blocks introduced here for the modular assembly of the pentadentate bis(oxazoline) ligands should have occurred.

In conclusion, we have developed oxazoline building blocks that can be employed both as nucleophiles as well as



Scheme 7. Ligand synthesis with electrophilic oxazoline building blocks.

electrophiles, this way opening up a facile strategy to new structures containing such moieties. This approach was applied to the synthesis of pentacoordinating bis(oxazoline) ligands containing a central pyridine unit, which have shown a rich coordination chemistry to arrive at helical metal complexes.[7] Moreover, the strategy could be extended to novel ligands with central pyridine-*N*-oxide, phenol, and anisole units that might have potential for the construction of binucleating complexes.

3. Experimental

3.1. General

All reactions were carried out under a dry, oxygen-free atmosphere of N_2 using Schlenk technique, unless otherwise noted. Commercially available reagents were used as received. DMF, CH_3CN, and CH_2Cl_2 were distilled over P_4O_{10} and stored under N_2 over molecular sieves 3 Å. EtOH and MeOH were dried over Mg and stored under N_2. THF, 1,4-dioxane, and Et_2O were dried with Na/benzophenone and stored over Na wire under N_2. EtOAc, CH_2Cl_2, MeOH, and hexanes for chromatographic separations were distilled before use. For column chromatography silica gel Geduran 60 (Merck, 0.063–0.200 mm) was used. TLC analysis was done on silica gel 60 F_{254} (Merck) coated on aluminum sheets.

3.1.1. 2,6-Bis(*N*-methylaminomethyl)pyridine (15). A solution of methylamine hydrochloride (3.95 g, 58.5 mmol, 2.4 equiv) in MeOH (100 mL) was cooled to 0 °C and treated with K_2CO_3 (9.42 g, 68.2 mmol, 2.8 equiv). After stirring for 1 h in an ice bath, pyridine-2,6-dicarbaldehyde (**14**) (3.29 g, 24.3 mmol, 1.0 equiv) was added. The mixture was stirred at ambient temperature for further 3 h and the solvent was evaporated. The solid residue was taken up in 150 mL CH_2Cl_2 and the suspension stirred for 1 h. After filtering off the solid, the solvent was evaporated to yield 2,6-bis(methyliminomethyl)pyridine as a yellow oil (2.97 g, 76%). No further purification of the product was necessary for the next step. The analytical data correspond with the literature.[15] ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.32 (s, 1H), 7.85 (d, J=7.7 Hz, 2H), 7.68 (t, J=7.7 Hz, 1H), 3.48 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.0, 154.2, 137.0, 121.9, 48.0.

To a solution of 2,6-bis(methyliminomethyl)pyridine (2.62 g, 16.3 mmol, 1.0 equiv) in dry EtOH (40 mL) was added $NaBH_4$ (1.23 g, 32.5 mmol, 2.0 equiv) in portions. The solution was stirred for 16 h and water (40 mL) was added cautiously. This solution was extracted with 3×40 mL CH_2Cl_2, the combined organic phases dried ($MgSO_4$), and the solvent evaporated. The residue was distilled (bp 97–100 °C/0.08 mbar) to yield **15** as a yellow oil (1.81 g, 67%), which was stored under nitrogen at 4 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (t, J=7.6 Hz, 1H), 7.16 (d, J=7.6 Hz, 2H), 3.85 (s, 4H), 2.48 (s, 6H), 1.78 (br s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 159.3, 136.7, 120.4, 57.2, 36.2; MS (DCI, NH_3): m/z (%)=167.2 (10), 166.2 (100); HRMS (EI) calcd for $C_9H_{14}N_3$ $[M-H]^+$ 164.1188, found 164.1189.

3.1.2. 2,6-Bis(mercaptomethyl)pyridine[10] (16). 2.49 g (14.2 mmol, 1.0 equiv) of 2,6-bis(chloromethyl)pyridine (**8**) was reacted under Argon atmosphere with 2.16 g (28.4 mmol, 2.0 equiv) of thiourea in refluxing ethanol (30 mL, degassed) for 30 min. After cooling to ambient temperature, 11.2 mL of 5 M NaOH (degassed) was added and the solution was refluxed for additional 4 h. Afterward the pH was adjusted to 5–6 with 6 M HCl and the mixture extracted twice with 30 mL $CHCl_3$. The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent followed by vacuum Kugelrohr distillation afforded 1.53 g (9.0 mmol, 63%) of **16** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (t, J=7.7 Hz, 1H), 7.21 (d, J=7.7 Hz, 2H), 3.82 (d, J=8.0 Hz, 4H), 2.03 (t, J=8.0 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 159.9, 137.8, 120.5, 30.8.

3.1.3. (4*S*,5*S*)-4-Hydroxymethyl-2-methyl-5-(4-methylsulfanylphenyl)-oxazoline (22). (1*S*,2*S*)-2-Amino-1-(4-methylsulfanylphenyl)-1,3-propandiol (**21**) (5.00 g, 23.4 mmol, 1.00 equiv) and K_2CO_3 (0.500 g, 3.60 mmol, 0.15 equiv) were suspended in a mixture of ethylene glycol (10 mL) and glycerine (5 mL). Acetonitrile (2.5 mL, 1.92 g, 46.8 mmol, 2.0 equiv) was added and the resulting mixture stirred at 110 °C for 24 h. The product crystallized upon cooling to room temperature. The crystallization was completed by adding water (100 mL). The precipitate was collected on a Büchner funnel, washed with water (100 mL), and *n*-hexane (50 mL). The crude product was recrystallized from dichloromethane yielding **22** as a colorless solid (3.87 g, 70%). R_f 0.27 (CHCl$_3$/MeOH 19:1); mp 99–100 °C; $[\alpha]_D^{20}$ −154.0 (*c* 1.01, CHCl$_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27–7.20 (m, 4H), 5.24 (d, J=6.3 Hz, 1H), 4.88 (t, J=5.7 Hz, 1H), 3.80–3.74 (m, 1H), 3.61–3.54 (m, 1H), 3.45–3.38 (m, 1H), 2.45 (s, 3H), 1.97 (d, J=1.3 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 163.3, 138.2, 137.7, 126.1, 126.0, 82.0, 76.6, 63.0, 14.7, 13.6; IR (KBr): 3240, 2950, 2921, 2867, 1673; MS (PI-DCI, NH$_3$): *m*/*z* (%)=238.0 (100, [MH]$^+$); elemental analysis calcd (%) for $C_{12}H_{15}NO_2S$ (237.32): C 60.73, H 6.37, N 5.90, found: C 60.49, H 6.21, N 5.84.

3.1.4. (4*S*,5*S*)-4-Hydroxymethyl-5-(4-methylsulfanylphenyl)-2-*tert*-butyl-oxazoline (24). 2,2-Dimethyl-propionimidic acid ethyl ester (**18b**) (0.381 g, 2.95 mmol, 1.0 equiv) was dissolved in dry chlorobenzene (10 mL) and (1*S*,2*S*)-2-amino-1-(4-methylsulfanylphenyl)-1,3-propandiol (**21**) (0.756 g, 3.54 mmol, 1.2 equiv) was added. The resulting mixture was refluxed for 18 h. After cooling to room temperature, the solvent was evaporated and the residue purified by column chromatography (SiO$_2$, hexanes/EtOAc 1:3) to yield **24** (0.513 g, 62%) as a colorless solid. R_f 0.12 (hexanes/EtOAc 1:3); mp 66–68 °C; $[\alpha]_D^{20}$ −62.6 (*c* 1.25, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.23–7.15 (m, 4H), 5.20 (d, J=7.5 Hz, 1H), 3.97 (ddd, J=7.5, 4.4, 4.3 Hz, 1H), 3.82 (dd, J=11.6, 4.3 Hz, 1H), 3.64 (dd, J=11.6, 4.4 Hz, 1H), 2.44 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 175.5, 138.6, 137.8, 126.9, 126.1, 82.5, 76.4, 63.9, 33.5, 27.9, 15.8; IR (KBr): 3360, 3222, 2974, 2930, 2870, 1735, 1657, 1600; MS (CI, NH$_3$): *m*/*z* (%)=280.1 (100, [MH]$^+$); elemental analysis calcd (%) for $C_{15}H_{21}NO_2S$ (279.40): C 64.48, H 7.58, N 5.01, found: C 64.01, H 7.21, N 4.68.

3.1.5. (*S*)-2-Phenyl-4-mesyloxymethyl-oxazoline (25a). Under N$_2$ (*R*)-4-hydroxymethyl-2-phenyl-oxazoline (**20**) (3.01 g, 17.0 mmol, 1.0 equiv) was dissolved in 40 mL dry THF and cooled to −25 °C (external temperature). Dry NEt$_3$ (2.60 mL, 1.89 g, 18.7 mmol, 1.1 equiv) and methanesulfonyl chloride (1.38 mL, 2.04 g, 17.8 mmol, 1.05 equiv) were added subsequently. The mixture was stirred at −25 °C for 30 min, before water (50 mL) and CH$_2$Cl$_2$ (80 mL) were added. The organic layer was separated, dried (MgSO$_4$), and the solvent evaporated under reduced pressure. The crude yellow oil (4.17 g, 96%) was used for the subsequent steps without further purification. An analytical sample of **25a** was obtained by column chromatography (SiO$_2$, hexanes/EtOAc 1:1). $[\alpha]_D^{20}$ +54.5 (*c* 1.56, CH$_2$Cl$_2$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.00–7.88 (m, 2H), 7.57–7.36 (m, 3H), 4.69–4.49 (m, 2H), 4.47–4.30 (m, 3H), 3.03 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 166.1, 131.9, 128.5, 128.4, 127.0, 70.4, 69.3, 65.4, 37.6; IR (film): 3080, 3040, 2980, 2950, 2920, 1728, 1645, 1603, 1580, 1496, 1452, 1356, 1277, 1242, 1174, 1061, 1025, 961, 833, 786, 695; MS (DCI, NH$_3$): *m*/*z* (%)=258.2 (9), 257.2 (20), 256.1 (100, [MH]$^+$); HRMS (EI) calcd for $C_{11}H_{13}NO_4S$ ([M]$^+$) 255.0565, found 255.0565.

3.2. General procedure (GP1) for the synthesis of mesylates 26–28

The oxazoline (**22–24**) (1.0 equiv) and triethylamine (2.0 equiv) were dissolved in dry dichloromethane (20 mL) and cooled down to 0 °C. Methanesulfonyl chloride (2.0 equiv) was added dropwise. The mixture was allowed to warm up to room temperature and stirred for additional 12 h, before satd NaHCO$_3$ (20 mL) was added. The organic phase was separated and the aqueous layer was extracted three times with dichloromethane (20 mL). The combined organic layers were dried (MgSO$_4$) and the solvent evaporated under reduced pressure. The crude product was purified by chromatography or recrystallization.

3.2.1. (4*S*,5*S*)-2-Methyl-4-mesyloxymethyl-5-(4-methylsulfanylphenyl)-oxazoline (26). Compound **22** (1.00 g, 4.21 mmol) was reacted according to GP1 to yield **26** (1.18 g, 89%) as a colorless solid after recrystallization from CH$_3$CN. R_f 0.41 (CHCl$_3$/MeOH 19:1); mp 70–73 °C; $[\alpha]_D^{20}$ −46.5 (*c* 0.99, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.28–7.18 (m, 4H), 5.28 (d, J=6.9 Hz, 1H), 4.39 (dd, J=10.4, 4.6 Hz, 1H), 4.34 (dd, J=10.4, 5.0 Hz, 1H), 4.21 (dddq, J=6.9, 5.0, 4.6, 1.3 Hz, 1H), 3.06 (s, 3H), 2.48 (s, 3H), 2.11 (d, J=1.3 Hz, 3H); ^{13}C NMR (62.0 MHz, CDCl$_3$): δ 166.8, 139.5, 136.2, 126.9, 126.2, 82.7, 73.4, 69.8, 37.7, 15.7, 14.2; IR (KBr): 3011, 2928, 1672; MS (PI-DCI, NH$_3$): *m*/*z* (%)=316.0 (100, [MH]$^+$); elemental analysis calcd (%) for $C_{13}H_{17}NO_4S_2$ (315.41): C 49.50, H 5.43, N 4.44, found: C 48.97, H 5.41, N 4.34.

3.2.2. (4*S*,5*S*)-4-Mesyloxymethyl-5-(4-methylsulfanylphenyl)-2-phenyl-oxazoline (27). Compound **23** (0.500 g, 1.67 mmol) was reacted according to GP1 to yield **27** (0.58 g, 92%) as a slightly yellow solid after recrystallization from CH$_3$CN. R_f 0.34 (hexanes/EtOAc 1:1); mp 102–104 °C; $[\alpha]_D^{20}$ +29.6 (*c* 0.90, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.05–8.00 (m, 2H), 7.59–7.40 (m, 3H), 7.34–7.28 (m, 4H), 5.50 (d, J=6.6 Hz, 1H), 4.52–4.47 (m, 2H), 4.46–4.38 (m, 1H), 3.05 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 165.3, 139.5, 136.3, 132.0, 128.6, 128.5, 126.9, 126.7, 126.2, 82.7, 73.8, 69.9, 37.7, 15.6; IR (KBr): 3012, 2923, 1645, 1494, 1450, 1357, 1329, 1170, 1090, 1063, 978, 958, 916, 844, 800, 692, 534; MS (PI-DCI, NH$_3$): *m*/*z* (%)=378.1 (100, [MH]$^+$); elemental analysis calcd (%) for $C_{18}H_{19}NO_4S_2$ (377.48): C 57.27, H 5.07, N 3.71, found: C 57.26, H 5.06, N 3.79.

3.2.3. (4*S*,5*S*)-4-Mesyloxymethyl-5-(4-methylsulfanylphenyl)-2-*tert*-butyl-oxazoline (28). Compound **24** (0.500 g, 1.79 mmol) was reacted according to GP1 to yield **28** (0.436 g, 68%) as a slightly yellow solid after purification by column chromatography (SiO$_2$, hexanes/EtOAc 1:1). R_f 0.44 (hexanes/EtOAc 1:3); mp 107–108 °C; $[\alpha]_D^{20}$ −103.8 (*c* 1.05, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.29–7.23 (m, 2H), 7.20–7.15 (m, 2H), 5.28 (d, J=6.5 Hz, 1H), 4.40 (dd, J=10.3, 4.0 Hz, 1H), 4.32 (dd, J=10.3, 5.5 Hz, 1H), 4.19 (ddd, J=6.5, 5.5, 4.0 Hz, 1H), 3.06 (s, 3H), 2.48 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 176.2, 139.2, 136.9, 126.8, 126.0, 82.4, 73.3, 70.1, 37.6, 33.5, 27.8, 15.7; IR (KBr): 3431, 2962, 2929, 2372, 2734, 1656, 1600, 1489, 1474, 1414, 1344, 1209, 1175, 1141, 1082, 1032, 1000, 977, 953, 881, 827, 809, 771, 714, 530, 447;

MS (CI, NH_3): *m*/*z* (%)=358.1 (100, $[MH]^+$); elemental analysis calcd (%) for $C_{16}H_{23}NO_4S_2$ (357.49): C 53.76, H 6.48, N 3.92, found: C 53.68, H 6.08, N 3.75.

3.3. Assembly of the bis(oxazoline) ligands

3.3.1. Ligand 29. (*R*)-4-Hydroxymethyl-2-phenyl-oxazoline (**20**) (13.86 g, 78.2 mmol, 2.2 equiv) was dissolved in dry DMF (200 mL) under N_2 and cooled to 0 °C. NaH (60% suspension in mineral oil) (3.27 g, 81.5 mmol, 2.3 equiv) was added in portions and the mixture was stirred for 15 min. 2,6-Bis(chloromethyl)pyridine (**8**) (6.26 g, 35.6 mmol, 1.0 equiv) was added as a solid and the ice bath was removed. Stirring was continued at ambient temperature for 20 h. Water (200 mL) and CH_2Cl_2 (150 mL) were added cautiously and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2×150 mL). The combined organic layers were washed with water (3×100 mL) and dried (Na_2SO_4). After removal of the solvent in vacuo the residue was purified by column chromatography (SiO_2, EtOAc to EtOAc/MeOH 24:1) to yield **29** as a colorless solid (14.37 g, 88%). Mp 68–69 °C; $[\alpha]_D^{20}$ +62.5 (*c* 0.80, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 8.00–7.86 (m, 4H), 7.65 (t, *J*=7.7 Hz, 1H), 7.51–7.35 (m, 6H), 7.31 (d, *J*=7.7 Hz, 2H), 4.68 (s, 4H), 4.61–4.46 (m, 4H), 4.41–4.34 (m, 2H), 3.88–3.80 (m, 2H), 3.66–3.58 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.0, 157.7, 137.2, 131.4, 128.31, 128.30, 127.6, 120.0, 74.2, 72.9, 70.5, 66.4; IR (KBr): 3060, 3040, 2985, 2958, 2947, 2936, 1642; MS (DCI, NH_3): *m*/*z* (%)=459.2 (25), 458.1 (100, $[MH^+]$); elemental analysis calcd (%) for $C_{27}H_{27}N_3O_4$ (457.52): C 70.88, H 5.95, N 9.18, found: C 70.73, H 5.93, N 9.04.

3.4. General procedure (GP2) for the synthesis of ligands 30, 31, 33–35, 37–39

NaH (2.2 equiv, 60% suspension in mineral oil) was suspended in dry DMF (3–7 mL) and cooled to 0 °C. The nucleophile (**16**, **20**, **23** or **24**) was dissolved in dry DMF (5–10 mL) under N_2 and added dropwise. The mixture was stirred until the evolution of hydrogen had ceased. The electrophile (**9**, **11–13**, **26–28**) was dissolved in dry DMF (5–10 mL) and also added dropwise. The ice bath was removed and stirring was continued at ambient temperature or at 60 °C (reactions with **26–28**) overnight. DMF was evaporated and water (10 mL) and EtOAc (20 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (3×20 mL) and dried ($MgSO_4$). After removal of the solvent in vacuo, the residue was purified by chromatography and/or recrystallization.

3.4.1. Ligand 30. Compound **23** (0.659 g, 2.20 mmol) and **9** (0.265 g, 1.00 mmol) were reacted according to GP2 to yield **30** (0.588 g, 83%) as a colorless solid after recrystallization from CH_3CN. R_f 0.14 (EtOAc); mp 128–129 °C; $[\alpha]_D^{20}$ +24.1 (*c* 0.94, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.07–8.01 (m, 4H), 7.71–7.63 (m, 1H), 7.56–7.48 (m, 2H), 7.47–7.40 (m, 4H), 7.37–7.22 (m, 10H), 5.55 (d, *J*=6.8 Hz, 2H), 4.72 (s, 4H), 4.39 (ddd, *J*=6.8, 6.7, 4.3 Hz, 2H), 3.93 (dd, *J*=9.8, 4.3 Hz, 2H), 3.77 (dd, *J*=9.8, 6.7 Hz, 2H), 2.47 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.3, 157.7, 138.7, 137.6, 131.7, 128.5, 128.4, 127.4, 126.8, 126.5, 126.3, 120.0, 83.6, 74.9, 74.2, 72.5, 15.8; IR (KBr): 3429, 3247, 3059, 2919, 2869, 1899, 1648; MS (ESI): *m*/*z* (%)=702.3 (100, $[MH^+]$); elemental analysis calcd (%) for $C_{41}H_{39}N_3O_4S_2$ (701.90): C 70.16, H 5.60, N 5.99, found: C 70.17, H 5.75, N 5.71.

3.4.2. Ligand 31. Compound **24** (0.307 g, 1.10 mmol) and **9** (0.132 g, 0.50 mmol) were reacted according to GP2 to yield **31** (0.205 g, 62%) as a colorless solid after recrystallization from CH_3CN. R_f 0.13 (EtOAc); mp 98–99 °C; $[\alpha]_D^{20}$ −122.7 (*c* 0.88, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (t, *J*=7.7 Hz, 1H), 7.34 (d, *J*=7.7 Hz, 2H), 7.28–7.17 (m, 8H), 5.36 (d, *J*=6.3 Hz, 2H), 4.69 (s, 4H), 4.16 (ddd, *J*=6.8, 6.3, 3.8 Hz, 2H), 3.84 (dd, *J*=9.6, 3.8 Hz, 2H), 3.65 (dd, *J*=9.6, 6.8 Hz, 2H), 2.48 (s, 6H), 1.30 (s, 18H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 174.8, 157.8, 138.4, 138.3, 137.2, 126.8, 126.0, 119.8, 83.2, 74.4, 75.1, 72.7, 33.4, 27.8, 15.9; IR (KBr): 2964, 2920, 2876, 1656, 1595; MS (ESI): *m*/*z* (%)=662.4 (100, $[MH^+]$); elemental analysis calcd (%) for $C_{37}H_{47}N_3O_4S_2$ (661.92): C 67.14, H 7.16, N 6.35, found: C 66.87, H 6.76, N 6.20.

3.4.3. Ligand 33. Compound **20** (372 mg, 2.1 mmol) and **11** (294 mg, 1.0 mmol) were reacted according to GP2 to yield **33** (171 mg, 35%) as a slightly yellow oil after column chromatography (SiO_2, hexanes/EtOAc 1:1). R_f 0.19 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$ +106.6 (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.32 (br s, 1H), 8.05–7.90 (m, 4H), 7.47–7.35 (m, 6H), 6.96 (s, 2H), 4.73–4.43 (m, 8H), 4.27 (dd, *J*=7.3, 6.5 Hz, 2H), 3.74 (dd, *J*=9.9, 5.4 Hz, 2H), 3.64 (dd, *J*=9.9, 6.1 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.2, 152.1, 131.6, 129.7, 128.6, 128.4, 128.4, 127.4, 123.8, 72.4, 70.5, 70.4, 66.4, 20.4; IR (ATR): 3371, 3063, 2904, 2863, 1644, 1484, 1450, 1358, 1267, 1220, 1086, 1061, 963, 693 cm^{-1}; MS (ESI): *m*/*z* (%)=509.3 (15), 488.3 (33), 487.3 (100); HRMS (EI) calcd for $C_{29}H_{30}N_2O_5$ ($[M^+]$) 486.2155, found 486.2154.

3.4.4. Ligand 34. Compound **20** (186 mg, 1.05 mmol) and **12** (154 mg, 0.50 mmol) were reacted according to GP2 to yield **34** (173 mg, 69%) as a colorless oil after purification by column chromatography (SiO_2, hexanes/EtOAc 1:2). R_f 0.18 (hexanes/EtOAc 1:2); $[\alpha]_D^{20}$ +26.1 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.99–7.92 (m, 4H), 7.52–7.36 (m, 6H), 7.12 (s, 2H), 4.63–4.30 (m, 10H), 3.85–3.78 (m, 2H), 3.72 (s, 3H), 3.60–3.52 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.9, 154.6, 133.7, 131.4, 130.7, 130.5, 128.3, 128.3, 127.6, 72.6, 70.8, 68.4, 66.5, 62.8, 20.8 ppm. IR (ATR): 2957, 2904, 2867, 1648, 1477, 1359, 1231, 1098, 1009, 694 cm^{-1}; MS (ESI): *m*/*z* (%)=502.2 (33), 501.2 (100); HRMS (EI) calcd for $C_{30}H_{32}N_2O_5$ ($[M^+]$) 500.2311, found 500.2308.

3.4.5. Ligand 35. Compound **20** (186 mg, 1.05 mmol) and **13** (175 mg, 0.50 mmol) were reacted according to GP2 to yield **35** (147 mg, 54%) as a colorless solid after purification by column chromatography (SiO_2, hexanes/EtOAc 1:2). R_f 0.24 (hexanes/EtOAc 1:2); mp 123–126 °C; $[\alpha]_D^{20}$ +23.2 (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.99–7.92 (m, 4H), 7.52–7.36 (m, 6H), 7.32 (s, 2H), 4.66–4.30 (m, 10H), 3.84–3.77 (m, 2H), 3.73 (s, 3H), 3.64–3.53 (m, 2H), 1.24 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.0, 154.4, 146.9, 131.5, 130.3, 128.4, 128.3, 127.5, 126.8, 72.4, 70.8, 68.6, 66.4, 62.6, 34.4, 31.4. IR

(ATR): 2961, 2901, 2856, 1647, 1483, 1450, 1356, 1086, 1058, 1025, 735, 694 cm^{-1}; MS (EI): *m/z* (%)=542.2 (6), 383.2 (26), 382.2 (100), 205.1 (40), 161.1 (47), 146.1 (22), 118.1 (11), 105.0 (51), 91.0 (13); HRMS (EI) calcd for $C_{33}H_{38}N_2O_5$ ([M^+]) 542.2781, found 542.2780.

3.4.6. Ligand 37. Compound **16** (0.087 g, 0.51 mmol) and **26** (0.354 g, 1.12 mmol) were reacted according to GP2 to yield **37** (0.098 g, 32%) as a colorless solid after recrystallization from CH_3CN. R_f 0.29 (EtOAc/MeOH 9:1); mp 62–65 °C; $[\alpha]_D^{20}$ +8.7 (*c* 0.87, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (t, *J*=7.7 Hz, 1H), 7.25–7.11 (m, 10H), 5.13 (d, *J*=6.5 Hz, 2H), 4.06 (dddd, *J*=8.0, 6.5, 5.0, 1.4 Hz, 2H), 3.75 (s, 4H), 2.85 (dd, *J*=13.2, 5.0 Hz, 2H), 2.62 (dd, *J*=13.2, 8.0 Hz, 2H), 2.47 (s, 6H), 2.05 (d, *J*=1.4 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.0, 158.0, 138.7, 137.4, 137.3, 126.7, 126.3, 121.3, 85.0, 74.1, 38.0, 36.5, 15.8, 14.1; IR (KBr): 3399, 3081, 2920, 1653; MS (CI, NH_3): *m/z* (%)=610.1 (100, [MH^+]); HRMS (EI) calcd for $C_{31}H_{35}N_3O_2S_4$ ([M^+]) 609.1612, found 609.1613.

3.4.7. Ligand 38. Compound **16** (0.142 g, 0.83 mmol) and **27** (0.689 g, 1.83 mmol) were reacted according to GP2 to yield **38** (0.430 g, 71%) as a colorless solid after recrystallization from CH_3CN. R_f 0.19 (hexanes/EtOAc 1:1); mp 124–125 °C; $[\alpha]_D^{20}$ +87.5 (*c* 1.94, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.03–7.96 (m, 4H), 7.56–7.37 (m, 7H), 7.28–7.14 (m, 10H), 5.36 (d, *J*=6.3 Hz, 2H), 4.31 (ddd, *J*=8.2, 6.3, 4.7 Hz, 2H), 3.81 (s, 4H), 3.00 (dd, *J*=13.4, 4.7 Hz, 2H), 2.74 (dd, *J*=13.4, 8.2 Hz, 2H), 2.46 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.8, 158.1, 138.7, 137.4, 137.3, 131.6, 128.5, 128.4, 127.4, 126.7, 126.4, 121.4, 84.9, 74.7, 38.1, 36.5, 15.8; IR (KBr): 3071, 2919, 2806, 1635, 1605; MS (ESI): *m/z* (%)=734.2 (100, [MH^+]); elemental analysis calcd (%) for $C_{41}H_{39}N_3O_2S_4$ (734.03): C 67.09, H 5.36, N 5.72, found: C 67.01, H 5.24, N 5.78.

3.4.8. Ligand 39. Compound **16** (0.044 g, 0.26 mmol) and **28** (0.227 g, 0.63 mmol) were reacted according to GP2 to yield **39** (0.117 g, 65%) as a colorless solid after recrystallization from CH_3CN. R_f 0.47 (EtOAc); $[\alpha]_D^{20}$ −32.6 (*c* 0.92, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.57–7.50 (m, 1H), 7.28–7.12 (m, 10H), 5.16 (d, *J*=6.0 Hz, 2H), 4.10 (ddd, *J*=8.2, 6.0, 4.2 Hz, 2H), 3.79 (s, 4H), 2.89 (dd, *J*=13.3, 4.2 Hz, 2H), 2.64 (dd, *J*=13.3, 8.2 Hz, 2H), 2.47 (s, 6H), 1.28 (s, 18H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 174.4, 158.1, 138.4, 138.0, 137.3, 126.7, 126.1, 121.3, 84.4, 74.2, 38.2, 36.7, 33.4, 27.8, 15.8; IR (KBr): 3441, 2968, 2921, 1590; MS (ESI): *m/z* (%)=694.2 (100, [MH^+]); HRMS (EI) calcd for $C_{37}H_{47}N_3O_2S_4$ ([M^+]) 693.2551, found 693.2546.

3.4.9. Ligand 32. (*R*)-4-Hydroxy-2-phenyl-oxazoline (**20**) (3.70 g, 20.9 mmol, 2.0 equiv) was dissolved in dry DMF (30 mL) under nitrogen and the solution was cooled to 0 °C. NaH (60% suspension in mineral oil) (923 mg, 23.0 mmol, 2.2 equiv) was added in portions and the mixture was stirred for 15 min. A solution of 2,6-bis(chloromethyl)-pyridine-*N*-oxide (**10**) (2.00 g, 10.4 mmol, 1.0 equiv) in dry DMF (5 mL) was added and the ice bath was removed. Stirring was continued at ambient temperature for 20 h. Water (50 mL) and CH_2Cl_2 (70 mL) were added cautiously and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with water (3×20 mL) and dried (Na_2SO_4). After removal of the solvent in vacuo the residue was purified by column chromatography (SiO_2, EtOAc to EtOAc/MeOH 5:2) to yield a colorless solid (2.62 g, 53%). Mp 112 °C; $[\alpha]_D^{20}$ +66.8 (*c* 1.29, EtOH); ^1H NMR (300 MHz, $CDCl_3$): δ 8.01–7.99 (m, 4H), 7.53–7.04 (m, 8H), 7.25 (t, *J*=7.7 Hz, 1H), 4.84–4.83 (m, 4H), 4.62–4.43 (m, 6H), 3.92–3.87 (m, 2H), 3.83–3.78 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 165.13, 148.77, 131.54, 128.36, 127.55, 125.67, 121.22, 73.45, 70.19, 67.50, 66.44; MS (ESI, NH_4OAc): *m/z* (%)=474.3 (100, [$MH]^+$), 475.3 (31); elemental analysis calcd (%) for $C_{27}H_{27}N_3O_5$ (473.52): C 68.48, H 5.75, N 8.87, found: C 68.12, H 5.63, N 8.75.

3.4.10. Ligand 40. A solution of (*S*)-2-phenyl-4-mesyloxymethyl-oxazoline (**25a**) (1.11 g, 4.35 mmol, 2.1 equiv) in 20 mL dry CH_3CN was added dropwise to a solution of 2,6-bis(*N*-methylaminomethyl)pyridine (**15**) (0.342 mg, 2.07 mmol, 1.0 equiv) in 10 mL dry CH_3CN. K_2CO_3 (1.14 g, 8.28 mmol, 4.0 equiv) was added and the mixture was heated to reflux for 31 h. After cooling down, the suspension was filtered and the solvent evaporated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 19:1) to give **40** as a yellow oil (623 mg, 62%) that eventually solidified after a few weeks. $[\alpha]_D^{20}$ −14.6 (*c* 0.84, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 7.98–7.84 (m, 4H), 7.59 (t, *J*=7.7 Hz, 1H), 7.50–7.33 (m, 6H), 7.30 (d, *J*=7.7 Hz, 2H), 4.56–4.38 (m, 4H), 4.32–4.17 (m, 2H), 3.81 (d, *J*=14.3 Hz, 2H), 3.68 (d, *J*=14.3 Hz, 2H), 2.90–2.74 (m, 2H), 2.66–2.47 (m, 2H), 2.37 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.2, 158.7, 136.8, 131.3, 128.3, 128.2, 127.8, 121.2, 72.0, 65.4, 64.5, 62.1, 43.5; IR (film): 3420, 3076, 2952, 2908; MS (DCI, NH_3): *m/z* (%)=485.3 (27), 484.2 (100, [$MH]^+$), 337.1 (7); HRMS (EI) calcd for $C_{29}H_{33}N_5O_2$ ([M^+]) 483.2634, found 483.2635.

3.4.11. Ligand 41. A mixture of (4*S*,5*S*)-4-mesyloxymethyl-5-(4-methylsulfanylphenyl)-2-phenyl-oxazoline (**27**) (100 mg, 0.26 mmol, 2.2 equiv), 2,6-bis(*N*-methylaminomethyl)pyridine (**15**) (20 mg, 0.12 mmol, 1.0 equiv), and K_2CO_3 (66 mg, 0.48 mmol, 4.0 equiv) in 5 mL dry CH_3CN was heated to reflux for 72 h. After cooling down, the suspension was filtered and the solvent evaporated. The residue was purified by column chromatography (SiO_2, EtOAc) to yield **41** as a colorless solid (45 mg, 52%). R_f 0.08 (EtOAc); mp 143–145 °C; $[\alpha]_D^{20}$ +35.7 (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.03–7.96 (m, 4H), 7.62–7.55 (m, 1H), 7.52–7.46 (m, 2H), 7.44–7.35 (m, 4H), 7.33–7.19 (m, 10H), 5.41 (d, *J*=6.6 Hz, 2H), 4.31 (ddd, *J*=8.6, 6.6, 4.9 Hz, 2H), 3.80 (d, *J*=14.0 Hz, 2H), 3.70 (d, *J*=14.0 Hz, 2H), 2.88 (dd, *J*=12.6, 4.9 Hz, 2H), 2.68 (dd, *J*=12.6, 8.6 Hz, 2H), 2.46 (s, 6H), 2.30 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.5, 158.6, 138.4, 138.1, 136.7, 131.5, 128.3, 128.4, 127.2, 126.8, 126.3, 121.3, 84.9, 74.0, 64.6, 43.3, 15.8; IR (KBr): 3460, 3062, 2919, 1647; MS (ESI): *m/z* (%)=728.5 (100, [MH^+]); HRMS (EI) calcd for $C_{43}H_{45}N_5O_2S_2$ ([M^+]) 727.3015, found 727.3012.

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