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Chiral ditopic receptors. Application to palladium-catalyzed allylic alkylation

Jean Bourguignon,[a] Ulf Bremberg,[b] Georges Dupas,[a] Kristina Hallman,[b] Lars Hagberg,[b] Laurent Hortala,[a] Vincent Levacher,[a] Serghey Lutsenko,[b] Emmanuel Macedo,[b] Christina Moberg,[b,*] Guy Quéguiner[a] and Fredrik Rahm[b]

[a]*IRCOF, INSA, Laboratoire de Chimie Organique Fine et Hétérocyclique, UMR 6014, BP 08, F 76131 Mt St Aignan, France*
[b]*Department of Chemistry, KTH, Organic Chemistry, SE 100 44 Stockholm, Sweden*

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Abstract—Chiral pyridinooxazoline, quinolinooxazoline, bis(oxazolino)pyridine (pybox), and bisoxazoline (box) derivatives containing crown ether residues were prepared. Some of the ligands were assessed in substrate binding studies and in palladium catalyzed allylic alkylations.

1. Introduction

Ligands capable of simultaneously being involved in two binding interactions are attracting current interest due to their applications in various situations involving molecular recognition.[1] Bifunctional ligands may also have versatile properties in stereoselective catalysis due to their ability to be engaged in secondary interactions with the substrate undergoing reaction. Such interactions may enhance the reactivity as well as the selectivity of the catalytic system.[2] Several Lewis acid–Lewis base bifunctional catalysts were recently presented by Shibasaki et al.[3] A ferrocene derivative with planar chirality endowed with a crown ether function was used in palladium-catalyzed allylic alkylations by Ito et al.[4] Higher enantioselectivity and higher yield were observed with the bifunctional catalyst than with one lacking the crown ether moiety, indicating formation of a ternary complex. Similar ferrocenylphosphines with pendant crown ether moieties were also designed for rhodium-catalyzed hydrogenations.[5] Hydrogenation employing rhodium complexes of ligands capable of simultaneously coordinating to boron was also reported.[6] Furthermore, a salen ligand with binding sites for titanium and palladium was synthesized;[7] another bimetallic complex with the same ligand, containing titanium and rhodium, was later employed in hydroformylations.[8]

Another possible application of this type of ligands consists of the selective transformation of one functional group in a multifunctional substrate,[9] or selective transformation of one particular substrate out of a mixture of substrates.[10] We have previously found that a dipyridylmethanol derivative substituted with a crown ether ring exhibits selective complexation of ω-olefinic carboxylic acids, although no chemical transformation using that system was demonstrated.[11]

In order to enable studies of the possibility to achieve selective substrate binding as well as increased stereoselectivity and reactivity in catalytic reactions we needed ligands containing a binding site with chelating nitrogen donors and a crown ether moiety. Several crown ethers with nitrogen binding sites have been reported,[12] but since they are achiral they did not serve our purpose. The preparation of chiral nitrogen ligands with pendant crown ether rings is described here together with preliminary binding studies of ω-carboxylic acid olefins and preliminary studies of the use of some of the new compounds in palladium-catalyzed allylic alkylations.

2. Results and discussion

2.1. Preparation of ligands

Ligands **1**–**6**, having the oxazoline and crown ether rings as common structural features, were selected as suitable ditopic ligands. Pyridinooxazoline ligand **1** was obtained by esterification of (4′*R*)-2-(4′,5′-dihydro-4′-phenyl-2′-oxazolyl)-6-(hydroxymethyl)pyridine[13] (**7**) with 4-carboxybenzo-18-crown-6 (**8**) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), and quinoline

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* Corresponding author. Tel.: +46-8-790-9036; fax: +46-8-791-2333; e-mail: kimo@kth.se

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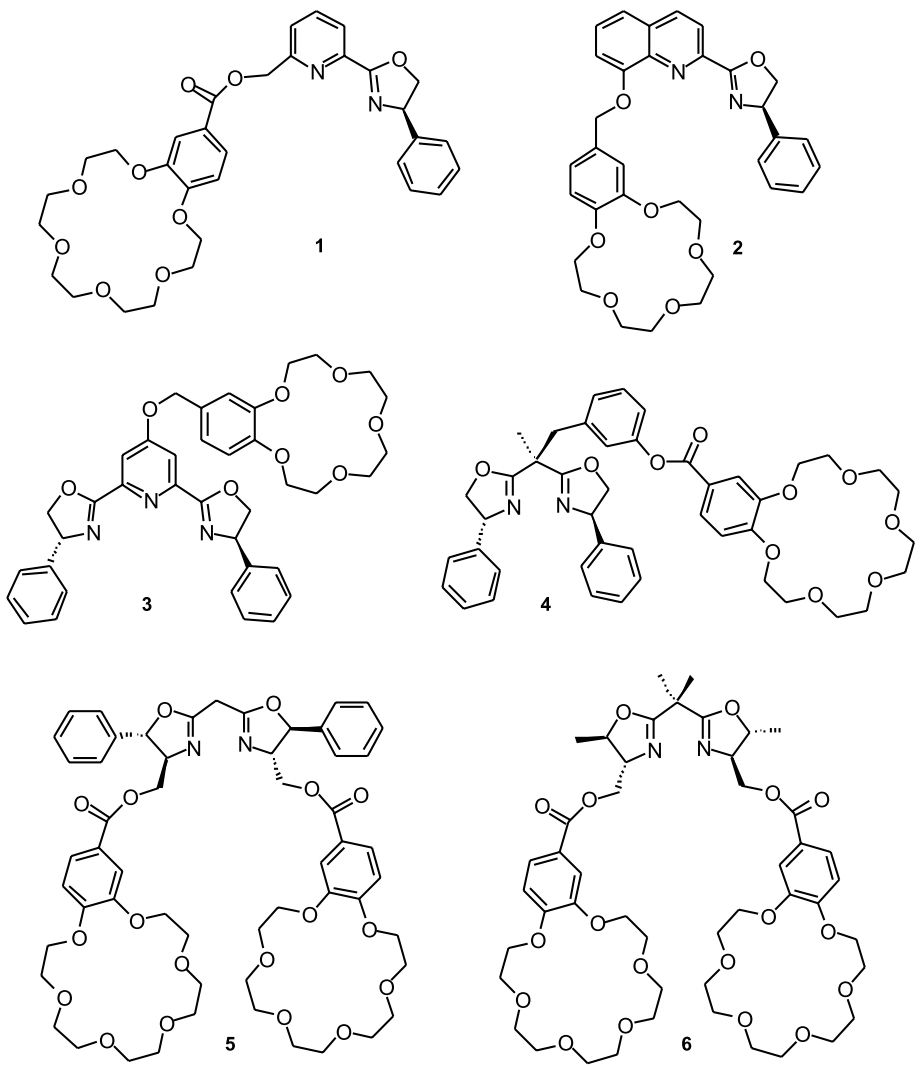
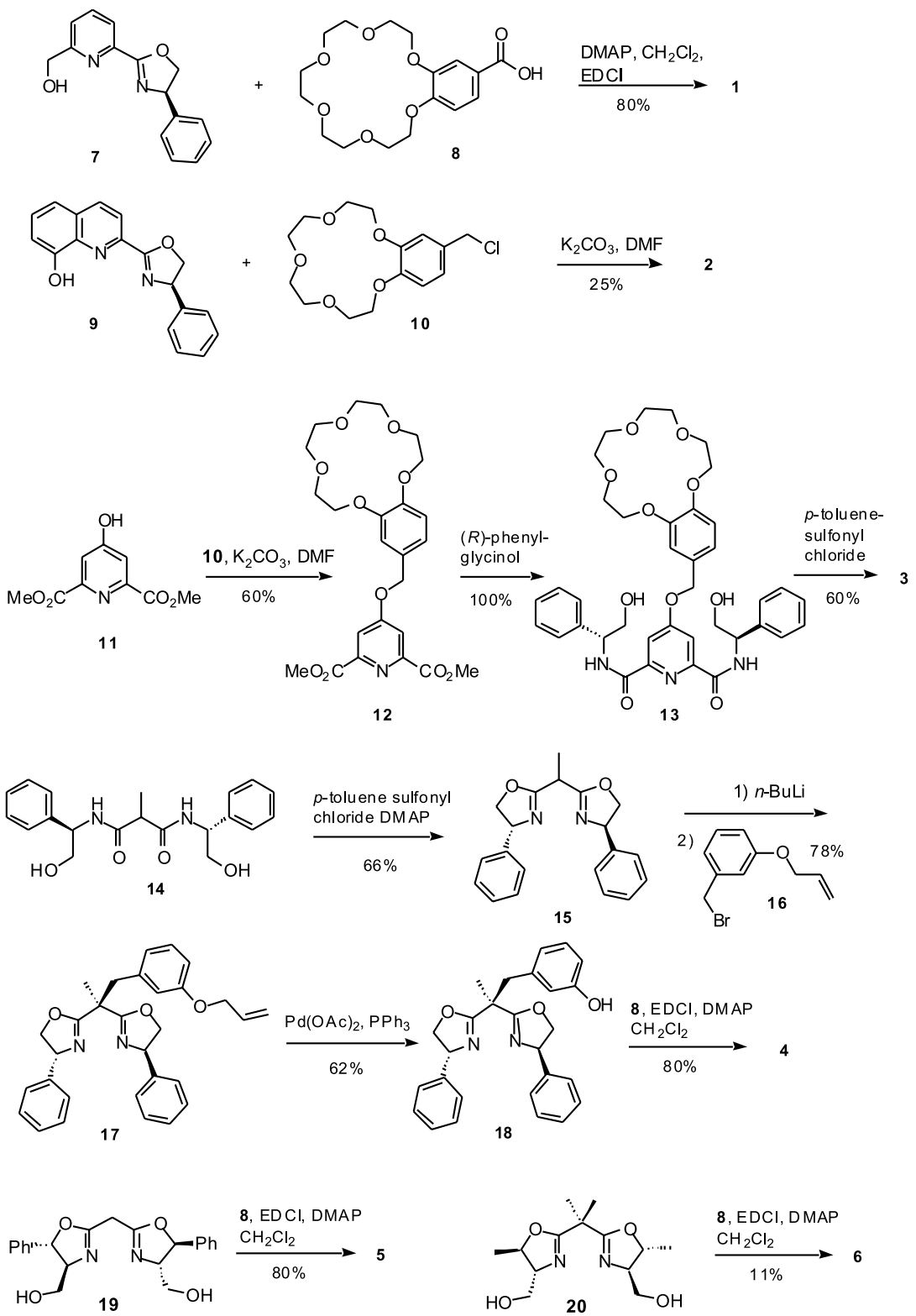


Chart 1.

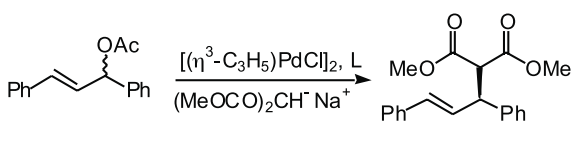
derivative **2** by *O*-alkylation of (4′*R*)-2-(4′,5′-dihydro-4′-phenyl-2′-oxazolyl)-8-hydroxyquinoline[13] (**9**) with 4-(chloromethyl)benzo-18-crown-6 (**10**).[14] The synthesis of pybox derivative **3** was achieved by O-alkylation of chelidamic acid dimethyl ester (**11**) with **10** to give **12**, which was transformed to amide **13** using (*R*)-phenylglycinol. Tosylation of the alcohol functions and final ring closure gave **3**. For the preparation of bisoxazoline **4** two routes were considered. The first involved initial alkylation of dimethyl methylmalonate with a protected 3-hydroxybenzyl halide followed by transformation of the ester groups to oxazoline rings, whereas the second involved alkylation of a preformed bisoxazoline with the phenolic compound. The first route was recently employed for the preparation of a polymer-bound bisoxazoline ligand.[15] However, we found the second route to be more convenient, affording the product with the same yield but involving fewer reaction steps. Thus, amide **14** was prepared from dimethyl methylmalonate and (*R*)-phenylglycinol. This was followed by cyclization of **14** to form bisoxazoline **15**. Alkylation of bisoxazoline **15** with allyl-protected 3-(bromomethyl)-phenol **16** using butyl lithium as the base resulted in the formation of alkylated bisoxazoline **17**, which was deprotected using palladium acetate and triphenylphosphine in ethanol to yield **18**. Final esterification gave the desired ligand **4**. The C_2-symmetric ligand **5**, incorporating two crown ether groups, was obtained from the known bisoxazoline **19**[16] via esterification. Ligand **6** was obtained by an analogous procedure starting from **20** (Chart 1 and Scheme 1).[17]

2.2. Catalytic reactions

In order to study the effect of the presence of a crown ether function on the selectivity and reactivity of the catalytic system, ligand **1** was assessed in palladium-catalyzed alkylations of *rac*-1,3-(*E*)-diphenyl-2-propenyl acetate with the sodium salt of dimethyl malonate, prepared employing sodium hydride, under a variety of different reaction conditions using bis[(π-allyl)palladium chloride] as the palladium source. The cation of the nucleophile was assumed to be trapped by the crown ether, resulting in close proximity of the nucleophile to the electrophilic allylic group. In order to judge whether this would affect the reactivity and selectivity of the catalytic reaction, the results were compared to those obtained using ligand **21** together with 1 equiv. of benzo-18-crown-6 (Scheme 2).



Scheme 1.

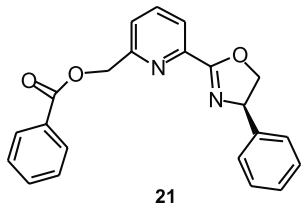


L: 1, 4, 21+benzo-18-crown-6, 22+benzo-18-crown-6

Scheme 2.

At low substrate concentration (0.024 M) in dichloromethane, slightly higher reactivity was observed for a catalyst containing ligand **1** than for a catalyst with ligand **21** and 1 equiv. of benzo-18-crown-6 (reactivity ratio 2:1). At higher substrate concentration (0.24 M) equal rates were observed for the two catalytic systems. In THF, a 2.5:1 ratio of the rates of reactions using ligands **1** and **21** (in the

absence of benzo-18-crown-6) was achieved at a substrate concentration of 0.1 M, whereas equal rates were observed at higher concentrations. The enantioselectivity was somewhat higher for reactions employing ligand **21** and benzo-18-crown-6 than for those with ligand **1** (75 and 67%, respectively). Comparison of ligands **6** and **22** in dichloromethane under slightly different conditions, where the nucleophile was generated in situ using BSA/KOAc, indicated no enhancement of selectivity or reactivity of the crown ether-containing ligand.



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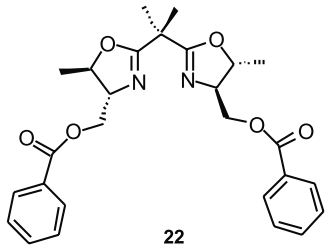

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2.3. Binding studies

A copper(I) complex of **4** was synthesized by treating **4** with 1 equiv. of $[Cu(MeCN)_4]PF_6$ in methanol under argon. When the resulting copper(I) complex was treated with the potassium salt of 10-undecanoic acid, the ^1H NMR signals of the olefinic protons shifted upfield indicating a complex being formed. Preliminary investigations showed that the same complex was not formed when the shorter 6-heptenoic acid was used, which suggests a 1:1 complex being formed with 10-undecanoic acid. Due to overlapping signals from the olefinic and oxazoline ring protons, quantitative determination of the binding could unfortunately not be made. The chemical shift of the terminal olefinic protons in CD_3OD shifted gradually when increasing the concentration of the olefin, from about δ 4.72 for a 0.5:1:1 olefin/metal/ligand mixture to δ 5.49 for a 5:1:1 olefin/metal/ligand mixture, whereas for analogous experiment with 6-heptenoic acid signals for the olefinic protons at about δ 5.30 were observed at all olefin/metal/ligand ratios. These results are in accordance with those previously found for a bispyridine-crown ether analogue, and suggest that a Cu(I) olefin complex was obtained only with the acid having a longer alkyl chain (Fig. 1).[11]

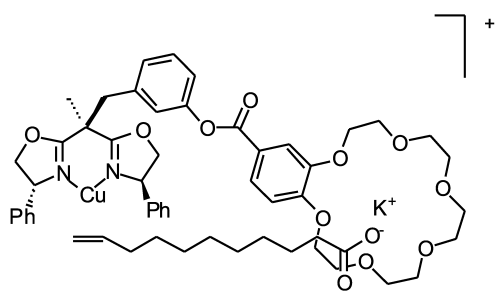

Figure 1. Complexation of 10-undecenoic acid to a Cu(I)–K(I) complex of **4**.

3. Conclusions

Chiral bidentate or tridentate nitrogen ligands containing at least one oxazoline ring as well as a crown ether residue, thereby capable of coordinating two metal ions, were prepared. The ligands were used in preliminary studies of enantioselective palladium-catalyzed allylic alkylations and substrate-selective binding of potassium salts of carboxylic acids containing a terminal olefinic group.

4. Experimental

4.1. General

4-(Chloromethyl)benzo-18-crown-6[14] (**10**), chelidamic acid dimethyl ester[18] (**11**) and bisoxazoline **19**[16] were prepared according to literature procedures. 3-Allyloxybenzyl bromide (**16**) was synthesized according to a procedure described for the 4-substituted isomer.[19] Other chemicals were purchased from Lancaster and used as received. Solvents were distilled according to standard procedures. Liquid chromatography was carried out using silica gel 60 (Merck 230–400 mesh). ^1H NMR spectra were recorded at 400 or 300 MHz and ^{13}C NMR spectra at 100.6 or 75.5 MHz in $CDCl_3$ with the solvent as internal standard, unless otherwise stated. HRMS spectra were recorded on a spectrometer of EB geometry equipped with FAB and EI/CI sources.

4.1.1. Ligand 1. Pyridinooxazoline **7**[13] (40.5 mg, 0.159 mmol), 4-carboxybenzo-18-crown-6 (**8**, 58.5 mg, 0.159 mmol) and DMAP (2.6 mg, 0.021 mmol) were dissolved in CH_2Cl_2 (0.5 mL). EDCI (35.2 mg, 0.180 mmol) was added and the reaction mixture was stirred at room temperature. After 6.5 h, additional CH_2Cl_2 (4 mL) was added and the mixture was extracted with brine (5 mL), 0.2 M HCl (5 mL) and saturated aqueous Na_2CO_3 (5 mL). The organic phase was dried (Na_2SO_4) and the solvent was evaporated in vacuo to give ester **1** (75 mg, 80%) as a thick oil. HRMS (FAB) calcd for $C_{32}H_{37}N_2O_9$ (MH^+), 593.2500. Found, 593.2497; $[\alpha]_D^{20}=+22.5$ (*c* 1.17 in CH_2Cl_2); IR (film): 1711, 1641 cm^{-1}; ^1H NMR (400 MHz): δ 8.12 (d, *J*=6.8 Hz, 1H), 7.83 (t, *J*=8.0 Hz, 1H), 7.74 (dd, *J*=8.4, 2.0 Hz, 1H), 7.60 (d, *J*=2.0 Hz, 1H), 7.57 (d, *J*=7.2 Hz, 1H), 7.38–7.28 (m, 5H), 6.88 (d, *J*=8.4 Hz, 1H), 5.57 (s, 2H), 5.45 (dd, *J*=10.2, 8.6 Hz, 1H), 4.91 (dd, *J*=10.4, 8.4 Hz, 1H), 4.41 (t, *J*=8.4 Hz, 1H), 4.22–4.19 (m, 4H), 3.96–3.91 (m, 4H), 3.79–3.76 (m, 4H), 3.73–3.70 (m, 4H), 3.68 (s, 4H); ^{13}C NMR (100.6 MHz): δ 165.8, 163.6, 156.7, 153.3, 148.3, 146.2, 141.7, 137.5, 128.8, 127.7, 126.8, 124.2, 123.6, 123.4, 122.2, 114.6, 112.1, 75.5, 70.94, 70.91, 70.8, 70.69, 70.65, 70.60, 70.3, 69.4, 69.3, 69.1, 68.9, 66.8.

4.1.2. Ligand 2. 8-Hydroxyquinoline-2-oxazoline[13] (**9**, 200 mg, 0.69 mmol), K_2CO_3 (290 mg, 2.1 mmol) and **10** (218 mg, 0.70 mmol) were heated at 60°C in DMF (4 mL) under nitrogen for 24 h. Water (2 mL) was added after

cooling, the aqueous phase extracted twice with CH_2Cl_2 and the organic phases dried ($MgSO_4$) to give a crude product, which was chromatographed on silica (eluent $CHCl_3$/MeOH 98:2). The slightly yellow product obtained was triturated with ether to give **2** as a white solid (100 mg, 25%). Anal. calcd for $C_{33}H_{34}N_2O_7$: C, 69.47; H, 5.96; N, 4.91. Found: C, 69.19; H, 5.85; N, 4.85%; $[\alpha]_D^{20}=+34.6$ (c 0.25 in CH_2Cl_2); ^{1}H NMR (300 MHz): δ 8.23 (d, J=8.6 Hz, 1H), 8.12 (d, J=8.6 Hz, 1H), 7.39 (d, J=8.2 Hz, 1H), 7.36–7.35 (m, 1H), 7.30–7.23 (m, 5H), 7.09 (s, 1H), 7.01 (d, J=7.1 Hz, 1H), 6.94 (d, J=8.2 Hz, 1H), 6.77 (d, J=8.2 Hz, 1H), 5.41 (dd, J=10.2, 8.8 Hz, 1H), 5.29 (s, 2H), 4.87 (dd, J=10.2, 8.4 Hz, 1H), 4.35 (t, J=8.6 Hz, 1H), 4.06–4.03 (m, 4H), 3.83–3.75 (m, 4H), 3.66 (d, 8H); ^{13}C NMR (37.6 MHz): δ 166.5, 157.0, 151.2, 150.5, 147.4, 143.9, 141.9, 138.6, 132.1, 132.0, 130.8, 130.4, 129.7, 128.9, 123.5, 121.9, 121.6, 115.8, 114.9, 113.0, 77.4, 73.0, 72.4, 71.5, 71.0, 70.7.

4.1.3. Compound 12. K_2CO_3 (314 mg, 2.28 mmol) was added to the chelidamic acid dimethyl ester (**11**) (160 mg, 0.76 mmol) in dry DMF (5 mL). After stirring for 20 min at 60°C the mixture was cooled and, after portionwise addition of compound **10** (241 mg, 0.76 mmol), again heated at 60°C for 4 h. The reaction was quenched by the addition of water (2 mL), the DMF was evaporated, and CH_2Cl_2 (5 mL) was added. The organic phase was washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent and trituration with ether gave **12** as a white solid (220 mg, 60%). Anal. calcd for $C_{24}H_{29}NO_{10}$: C, 58.65; H, 5.95; N, 2.85. Found: C, 58.08; H, 6.26; N, 2.81%; ^{1}H NMR (300 MHz): δ 7.84 (s, 2H), 6.97–6.84 (m, 3H), 5.12 (s, 2H), 4.14–4.11 (m, 4H), 3.98 (s, 6H), 3.89–3.87 (m, 4H), 3.73 (s, 8H); ^{13}C NMR (37.6 MHz): δ 167.6, 164.2, 151.2, 149.5, 139.6, 129.1, 128.3, 128.0, 127.2, 114.1, 114.0, 111.9, 71.2, 70.9, 70.5, 69.7, 69.1, 66.0, 56.4.

4.1.4. Compound 13. Diester **12** (200 mg, 0.4 mmol) and (*R*)-phenylglycinol (446 mg, 3.26 mmol) were heated at reflux in anhydrous toluene (4 mL) for 18 h. The solvent was evaporated, the residue dissolved in ethyl acetate, the organic phase washed with HCl (1 M) and $NaHCO_3$, and dried ($MgSO_4$) to give diamide **13** as a white solid (292 mg, 100%). HRMS (FAB) calcd for $C_{38}H_{44}N_3O_{10}$ (MH^+), 702.3027. Found, 702.2990; ^{1}H NMR (300 MHz): δ 8.69 (d, J=7.3 Hz, 2H), 7.81 (s, 2H), 7.27–7.36 (m, 10H), 6.91–6.83 (m, 3H), 5.20 (m, 2H), 5.05 (s, 2H), 4.10–3.97 (m, 4H), 3.95–3.87 (m, 8H), 3.74 (s, 8H); ^{13}C NMR (37.6 MHz): δ 167.6, 164.2, 151.2, 149.5, 139.6, 129.1, 128.3, 128.0, 127.2, 114.1, 114.0, 111.9, 71.2, 70.9, 70.5, 69.7, 69.1, 66.0, 56.4.

4.1.5. Ligand 3. *p*-Toluene sulfonyl chloride (170 mg, 0.89 mmol) was added to diamide **13** (292 mg, 0.41 mmol) and Et_3N (576 μL, 4.1 mmol) in CH_2Cl_2 (4 mL). After heating at reflux for 24 h, water (16 μL) was added and heating continued for another 1 h. The organic phase was washed with water and dried ($MgSO_4$) to give **3** (170 mg, 60%) as a white solid. HRMS (FAB) calcd for $C_{38}H_{40}N_3O_8$ (MH^+), 666.2816. Found, 666.2858; $[\alpha]_D^{20}=+28.0$ (c 0.25 in CH_2Cl_2); IR (film): 1641 cm^{-1}; ^{1}H NMR (300 MHz): δ 7.94 (s, 2H), 7.40–7.30 (m, 10H), 6.94–6.88 (m, 3H), 5.45 (app t, J=8.8 Hz, 2H), 5.13 (s, 2H), 4.93 (app t, J=8.8 Hz, 2H), 4.42 (app t, J=8.6 Hz, 2H), 4.15–4.12 (m, 4H), 3.93–3.90 (m, 4H), 3.76 (s, 8H); ^{13}C NMR (37.6 MHz): δ 166.1, 164.0, 149.8, 148.7, 142.1, 129.2, 128.4, 128.2, 127.3, 121.2, 114.3, 113.9, 113.5, 76.0, 71.5, 70.9, 70.7, 70.0, 69.4.

4.1.6. Diamide 14. A mixture of dimethyl methylmalonate (2.00 g, 13.7 mmol) and (*R*)-2-phenylglycinol (3.76 g, 27.4 mmol) was stirred at 110°C for 16 h. The solid obtained was crystallized from EtOH/$CHCl_3$ giving 4.12 g (84%) of the corresponding diamide **14** as a white solid: $[\alpha]_D^{20}=-37.8$ (c 1.66 in DMSO); mp 158°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.32–7.21 (m, 10H), 5.31–5.29 (m, 2H), 3.86 (m, 2H), 3.79 (m, 2H), 3.27 (q, J=7.0 Hz, 1H) 1.53 (d, J=7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.23, 170.15, 141.4, 141.3, 128.5, 128.4, 127.5, 127.4, 127.2, 127.1, 65.1, 65.0, 55.4, 55.2, 46.9, 15.3.

4.1.7. Bisoxazoline 15. A solution of *p*-toluene sulfonyl chloride (846 mg, 4.4 mmol) in dry CH_2Cl_2 (4 mL) was added to a solution of diamide **14** (712 mg, 2.0 mmol), Et_3N (2.2 mL, 16.5 mmol) and DMAP (24.4 mg, 0.2 mmol) in dry CH_2Cl_2 (6 mL). The resulting mixture was stirred for 48 h and then partitioned between EtOAc and 0.025 M aqueous HCl. The phases were separated, the organic layer was washed with saturated aqueous Na_2CO_3 and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography (eluent hexane/EtOAc/Et_3N 50:50:1) to give compound **15** (423 mg, 66%) as a yellow oil. HRMS (FAB) calcd for $C_{20}H_{21}N_2O_2$ (MH^+), 321.1604. Found, 321.1603; $[\alpha]_D^{20}=+69$ (c 0.92 in CH_2Cl_2); IR (film): 1659 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.35–7.25 (m, 10H), 5.24 (m, 2H), 4.743 (dd, J=10.2, 8.4 Hz, 1H), 4.741 (dd, J=10.2, 9.4 Hz, 1H), 4.24 (dd, J=8.3, 7.8 Hz, 1H), 4.23 (dd, J=9.3, 8.9 Hz, 1H), 3.82 (q, J=7.3 Hz, 1H), 1.70 (d, J=7.3 Hz, 3H); ^{13}C NMR (100.6 MHz): δ 168.8, 168.5, 143.82, 143.81, 130.3, 129.2, 128.3, 128.2, 128.1, 76.92, 76.90, 71.2, 71.1, 35.7, 17.0.

4.1.8. Bisoxazoline 17. *n*-BuLi (0.6 mL, 2.5 M in hexane, 1.50 mmol) was added to a solution of **15** (423 mg, 1.32 mmol) in dry THF (10 mL) at −78°C under nitrogen over a period of 5 min. The mixture was allowed to warm to 0°C and was then stirred for 0.5 h. At this temperature compound **16** (340 mg, 1.50 mmol) in THF (5 mL) was added dropwise. Stirring was continued for 20 min at 0°C followed by 5 h at room temperature. The reaction was quenched with brine and the reaction mixture extracted with EtOAc. The two phases were separated, the aqueous layer was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4. Evaporation in vacuo gave a yellow oil that was purified by flash chromatography on silica gel (eluent hexane/EtOAc 1:1) to give **17** (482 mg, 78%) as a yellow oil. ^{1}H NMR (400 MHz): δ 7.31–7.24 (m, 10H), 7.16 (m, 2H), 6.84 (m, 2H), 6.12–6.02 (m, 1H), 5.42 (d, J=17.3 Hz, 1H), 5.33–5.30 (m, 2H), 5.26 (d, J=10.1 Hz, 1H), 4.77 (dd, J=10.1, 8.6 Hz, 2H), 4.50 (d, J=5.3 Hz, 2H), 4.24–4.18 (m, 2H), 3.47 (s, 2H), 1.69 (s, 3H); ^{13}C NMR (100.6 MHz): δ 171.9, 171.7, 161.1, 144.9, 144.75, 140.6, 136.0, 131.7, 131.35, 131.25, 130.2, 130.1, 129.4, 125.9, 120.2, 119.9, 115.7, 78.4, 78.0, 77.95, 72.3, 72.2, 71.3, 46.4, 44.8, 24.3.

4.1.9. Bisoxazoline 18. A solution of **17** (482 mg,

1.03 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol) and PPh_3 (115 mg, 0.44 mmol) in ethanol (15 mL) was heated at reflux for 90 min. Silica (2 g) was then added at room temperature. After 15 min of stirring, the resulting mixture was filtered through Celite and the solvent was evaporated. The residue was purified by flash chromatography (eluent CH_2Cl_2/EtOAc 7:3) to yield compound **18** (271 mg, 62%) as a yellow oil. $[\alpha]_D^{20}=+115.8$ (*c* 0.52 in CH_2Cl_2); ^{1}H NMR (400 MHz): δ 8.12 (br s, 1H), 7.22–7.12 (m, 8H), 7.01 (m, 2H), 6.89 (t, *J*=8.0 Hz, 1H), 6.56 (d, *J*=7.6 Hz, 1H), 6.42 (m, 2H), 5.15 (dd, *J*=10.0, 8.4 Hz, 1H), 5.07 (dd, *J*=10.0, 7.6 Hz, 1H), 4.60 (dd, *J*=10.2, 8.4 Hz, 1H), 4.59 (dd, *J*=10.2, 8.4 Hz, 1H), 4.11 (dd, *J*=8.5, 7.6 Hz, 1H), 4.04 (t, *J*=8.5 Hz, 1H), 3.25 and 3.21 (AB spectrum, *J*=13.5 Hz, 2H), 1.48 (s, 3H); ^{13}C NMR (100.6 MHz): δ 170.10, 170.09, 157.0, 142.3, 142.2, 137.9, 129.6, 129.2, 129.1, 128.2, 128.1, 127.21, 127.19, 122.2, 118.3, 114.7, 75.84, 75.78, 69.9, 69.7, 44.3, 42.4, 21.9.

4.1.10. Ligand 4. Bisoxazoline **18** (271 mg, 0.64 mmol) was added in one portion to a solution of EDCI (135 mg, 0.70 mmol), 4-carboxybenzo-18-crown-6 (**8**, 230 mg, 0.64 mmol) and DMAP (8.5 mg, 0.07 mmol) in CH_2Cl_2 (10 mL). After 18 h of stirring, the mixture was partitioned between EtOAc and 0.025 M aqueous HCl. The phases were separated, the organic phase was washed with water, saturated aqueous Na_2CO_3, and brine, and dried over Na_2SO_4. After evaporation of the solvent the residue was purified by flash chromatography (eluent MeOH/CH_2Cl_2 1:10) followed by crystallization from ether/CH_2Cl_2 to yield **4** (391 mg, 80%) as a white solid: Anal. calcd for $C_{44}H_{48}N_2O_{10}$: C, 69.09; H, 6.33; N, 3.66. Found: C, 68.89; H, 6.40; N, 3.54; $[\alpha]_D^{20}=+56$ (*c* 0.70 in CH_2Cl_2); mp 58°C; IR (film): 1727, 1656 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.72 (dd, *J*=8.4, 2.0 Hz, 1H), 7.58 (d, *J*=2.0 Hz, 1H), 7.20 (m, 10H), 7.07 (m, 4H), 6.85 (d, *J*=8.6 Hz, 1H), 5.19 (dd, *J*=10.1, 7.7 Hz, 1H), 5.13 (dd, *J*=10.1, 8.4 Hz, 1H), 4.640 (dd, *J*=10.1, 8.1 Hz, 1H), 4.639 (dd, *J*=10.3, 8.4 Hz, 1H), 4.20–4.13 (m, 6H), 3.98–3.94 (m, 4H), 3.79–3.70 (m, 12H), 3.43 and 3.38 (AB spectrum, *J*=13.6 Hz, 2H), 1.59 (s, 3H); ^{13}C NMR (100.6 MHz): δ 168.4, 168.2, 164.0, 150.2, 147.8, 141.6, 141.4, 137.5, 128.3, 128.0, 127.9, 127.3, 126.9, 126.8, 126.0, 124.0, 123.2, 119.5, 114.2, 111.6, 74.7, 74.6, 70.30, 70.28, 70.15, 70.07, 70.04, 69.98, 68.96, 68.83, 68.78, 68.7, 43.0, 41.3, 21.0.

4.1.11. Ligand 5. A solution containing bisoxazoline **19** (100 mg, 0.273 mmol), 4-carboxybenzo-18-crown-6 (**8**, 292 mg, 0.82 mmol), EDCI (210 mg, 1.09 mmol) and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL) was stirred for 3 days. After evaporation of the solvent, the residue was dissolved in MeOH (5 mL) and the solution cooled to −78°C. The precipitated solid was filtered, washed with cold MeOH and dried. Recrystallization from EtOAc gave **5** (129 mg, 45%) as a white solid. Anal. calcd for $C_{55}H_{66}N_2O_{18}$: C, 63.33; H, 6.38; N, 2.69. Found: C, 62.88; H, 6.58; N, 2.74; mp 118°C; $[\alpha]_D^{20}=-38$ (*c* 0.90 in CH_2Cl_2); ^{1}H NMR (400 MHz): δ 7.53 (dd, *J*=8.4, 2.0 Hz, 2H), 7.41 (d, *J*=2.0 Hz, 2H), 7.23 (m, 10H), 6.71 (d, *J*=8.4 Hz, 2H) 5.32 (d, *J*=6.7 Hz, 2H), 4.50 (m, 2H), 4.37 (m, 4H), 4.08 (m, 8H), 3.82 (m, 8H), 3.65 (m, 24H), 3.57 (s, 2H); ^{13}C NMR (100.6 MHz): δ 166.5, 163.1, 153.6, 148.7, 140.1, 129.3, 129.0, 126.2, 124.4, 122.5, 114.7, 112.3, 84.9, 74.3, 71.35, 71.32, 71.2, 71.12, 71.1, 71.05, 69.8, 68.9, 69.4, 69.2, 66.0, 29.1.

4.1.12. Ligand 6. A solution of bisoxazoline **20**[17] (135 mg, 0.5 mmol), 4-carboxybenzo-18-crown-6 (**8**, 400 mg, 1.12 mmol), EDCI (315 mg, 1.64 mmol) and DMAP (24.4 mg, 0.2 mmol) in CH_2Cl_2 (9 mL) was stirred for 3 days and then partitioned between EtOAc and 0.025 M aqueous HCl. The phases were separated, the organic phase was washed with water, saturated aqueous Na_2CO_3 and brine, and dried over Na_2SO_4. After evaporation of the solvent the residue was purified by flash chromatography (eluent MeOH/CH_2Cl_2 1:10). The product was dissolved in EtOAc (1 mL) and ether (15 mL) was added. The milky mixture was kept for 16 h at 5°C. Decantation of the clear solution, evaporation of the solvent and recrystallization of the solid obtained from ether gave ligand **6** (52 mg, 11%) as a white solid. Anal. calcd for $C_{47}H_{66}N_2O_{18}$: C, 59.61; H, 7.02; N, 2.96. Found: C, 59.40; H, 7.15; N, 2.95%; mp 107°C; ^{1}H NMR (400 MHz): δ 7.56 (dd, *J*=8.2, 2.0 Hz, 2H), 7.45 (d, *J*=2.0 Hz, 2H), 6.79 (d, *J*=8.2 Hz, 2H), 4.42 (quint, *J*=6.3 Hz, 2H), 4.33 (dd, *J*=11.0, 4.6 Hz, 2H), 4.21 (dd, *J*=11, 6.0 Hz, 2H), 4.13 (m, 8H), 3.86 (m, 10H), 3.71 (m, 8H), 3.63 (m, 16H), 1.87 (s, 6H), 1.25 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (100.6 MHz): δ 166.5, 166.3, 153.65, 148.8, 124.4, 122.9, 115.0, 112.6, 79.4, 72.3, 71.4, 71.3, 71.2, 71.15, 71.1, 69.9, 69.8, 69.6, 69.3, 66.4, 21.4, 14.7.

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