The Synthesis of Novel 4-(Aminomethyl)oxazoline Ligands

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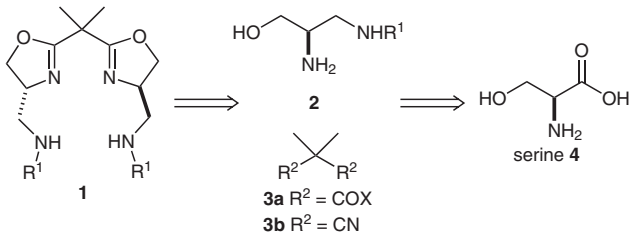
This paper is dedicated with respect to Professor Steven V. Ley on the occasion of his 60th birthday.

Abstract: A practical route to 2,3-bis(amino)-1-alcohols has been developed and utilized in the synthesis of a number of novel bis(oxazoline) ligands.

Key words: amines, amino alcohols, alkylations, ligands, asymmetric catalysis

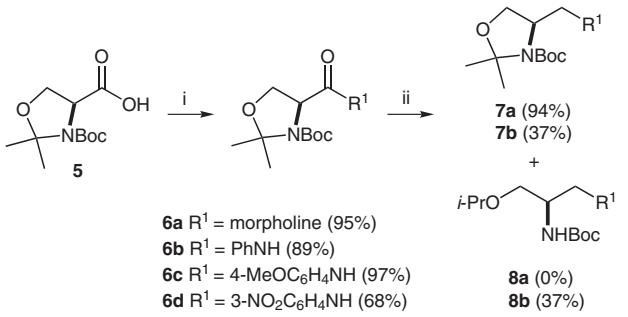
The concept of bifunctional catalysis is inspired by the mode of action of many enzymes, in that two reactive sites within a molecule act in concert to bring about a desired transformation.[1] Previously, we reported an example of a titanium–sulfoxide bifunctional catalyst.[2] Ultimately, whilst this complex produced a number of interesting results, it was not amenable to modification and optimization. As a result we wanted to design a ligand scaffold that was both simple to prepare and readily functionalized at a late stage. In this paper we report our initial results on the preparation of the 4-(aminomethyl)oxazoline moiety, which has the potential to fulfill these criteria.



Scheme 1 The synthesis of bis[4-(aminomethyl)oxazolines].

Oxazolines have an exceptional pedigree as chiral ligands[3] and they offer an excellent framework for the design of novel ligands. Surprisingly, there are few examples of their modification after ring formation as a means of increasing structural diversity.[4,5] We were interested in the bis[4-(aminomethyl)oxazolines] **1** (Scheme 1), as the amine moiety would allow further elaboration of the central core and has great potential in the formation of bifunctional catalysts.[6]

Oxazolines are normally prepared by the condensation of an amino alcohol and either a carboxylic acid derivative **3a** or a nitrile **3b** (Scheme 1). Therefore, the initial target was to develop a general route to the deceptively simple bis(amino) alcohols **2**. The obvious precursor for these densely functionalized molecules is the amino acid, serine **4**.



Scheme 2 *Reagents and conditions*: i. a) HOBt (1.1 equiv), EDCI (1.1 equiv), amine R^1 (1.1 equiv), DMF; b) Et_3N, r.t., overnight; ii. BH_3·THF, THF, 0 °C to reflux, 3 h.

Our initial strategy was based on the reductive amination of Garner's aldehyde[7] but in our hands this reaction proved unsatisfactory. Therefore, a two-step procedure involving amide formation and reduction was investigated. The known acid **5**[8] was converted to amides **6a–d** in excellent yields utilizing standard HOBt/EDCI coupling conditions (Scheme 2), but the reduction to amine **7** was far more problematic. The use of metal-based reducing agents, such as $LiAlH_4$ or DIBAL, gave highly capricious results, with yields varying erratically from 11–70%, and was deemed unsatisfactory. Believing that the problem was the coordination of the metal and the bis(amino) alcohol, reduction with BH_3·THF complex was attempted.[9] Reduction of the morpholine amide **6a** gave the protected bis(amino) alcohol **7a** in an excellent 94% yield. Unfortunately, the reduction of the aniline derivative **6b** resulted in the formation of an inseparable 1:1 mixture of the desired protected bis(amino) alcohol **7b** and the isopropyl ether **8b**. Presumably, the secondary amine somehow facilitates activation of the Boc-protected amine and permits the formation of an oxonium species that is reduced to the ether. It was clear that the use of the fully protected serine derivative **5** was going to thwart our attempts to devise a general route to the bis(amino) alcohols.

Whilst a plethora of protecting groups for the hydroxy functionality exist,[10] any one of which might be amenable to the preparation of **2**, their use is inefficient, adding extra steps to the synthesis and reduces the practicality of any synthesis. Consequently, a far more direct route avoiding the unnecessary alcohol protection was explored. After

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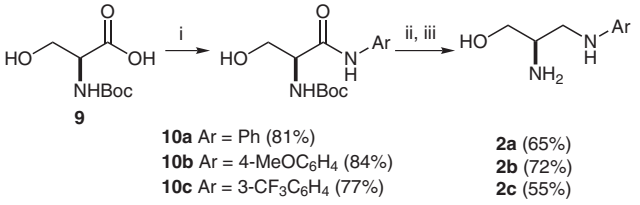
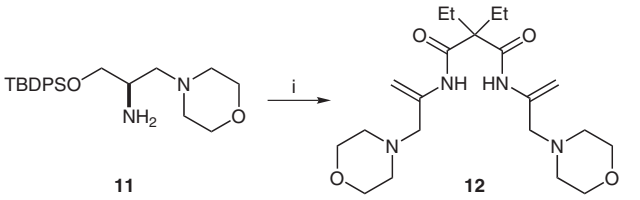


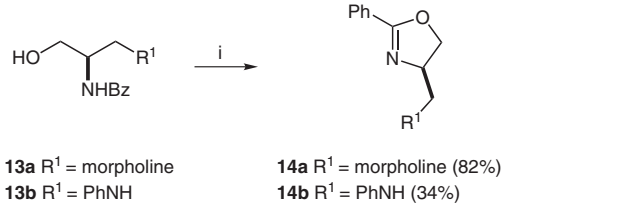
Scheme 3 *Reagents and conditions*: i. *i*-BuOCOCl, NMM, THF, –15 to 0 °C, overnight; ii. BH_3·THF, THF, reflux, 1 h; iii. TFA–H_2O, overnight.

extensive optimization it was found that *N*-Boc protected serine **9** could be readily coupled to a range of substituted anilines using *iso*-butyl chloroformate and *N*-methylmorpholine (NMM) under the conditions described by Katritzky[11] to give amides **10a–c** in excellent yields (Scheme 3). Direct reduction with BH_3·THF complex and subsequent treatment of the crude protected bis(amino) alcohol with TFA gave, after column chromatography, the desired bis(amino) alcohols **2a–c** in good yields.[12] It was vital that the reduction was stopped after 3 hours or reduction of the Boc group to *N*-methyl bis(amino) alcohol was observed.



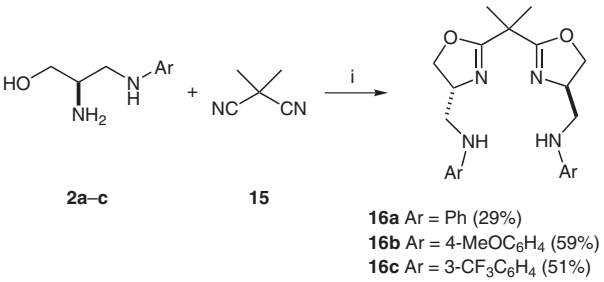
Scheme 4 *Reagents and conditions*: i. $Et_2C(COCl)_2$, Et_3N, –10 °C to r.t., overnight.

With a rapid, practical route to large quantities of the bis(amino) alcohols **2** in hand we turned our attention to oxazoline formation. The most reliable synthesis of the oxazoline moiety is via N-acylation and subsequent cyclization. Unfortunately, selective acylation of the bis(amino) alcohols was not possible; a mixture of N- and O-acylation was observed. Interestingly, acylation of silyl ether **11**, made from **7a** also failed, giving only the enamine **12**, the product of silyl alcohol elimination (Scheme 4). Even though the benzamides **13a** and **13b** could be synthesized by a low yielding (<30%), convoluted route and underwent smooth cyclization with DAST[13] to give the mono(oxazolines) **14a**,**b** in variable yields (34–82%), the acylation strategy was abandoned as it was judged to be impractical (Scheme 5).



Scheme 5 *Reagents and conditions*: i. DAST, K_2CO_3, CH_2Cl_2, –78 °C, 1 h.

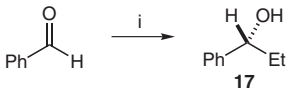
An alternative route to the oxazoline skeleton is via the direct condensation of a nitrile and an amino alcohol in the presence of $Cd(OAc)_2$.[14] Heating the three bis(amino) alcohols **2a–c** with dimethylmalononitrile **15** and $Cd(OAc)_2$ in chlorobenzene to reflux gave the bis(oxazolines) **16a–c** in moderate yields (Scheme 6). It is conceivable that cyclization results in the formation of the novel bis[4-(hydroxymethyl)imidazoline] instead of the desired bis(oxazoline). We believe that this is not the case primarily due to the ^{13}C NMR signal for C2 of the ring; in compounds **16a–c** this peak is above 170 ppm which appears to be indicative of an oxazoline ring[14,15] and not an imidazoline ring, in which this peak is normally closer to 160 ppm.[16] At present we cannot rule out the possibility of imidazoline formation.



Scheme 6 *Reagents and conditions*: i. $Cd(OAc)_2·2H_2O$, PhCl, reflux, overnight.

The five oxazoline ligands formed, **14a**,**b** and **16a–c**, have shown highly intriguing preliminary results when used in the catalytic addition of diethylzinc to benzaldehyde (Scheme 7). Firstly, an N–H bond is vital for reactivity; the reaction utilizing the morpholine substituted ligand **14a** failed to furnish any product. All the other ligands catalyzed alkylation. Secondly, the bis(oxazoline) ligands, **16a–c**, are generally superior to the mono(oxazoline) **14b** in terms of activity; all the bis(oxazolines) ligands double the yield of product formed. Mono(oxazoline) **14b** gives poor results furnishing the benzylic alcohol **17** in poor yield and selectivity (40% yield; 24% ee). This suggests that two zinc units must be coordinated within close proximity and then act in unison to bring about successful catalysis, which is in agreement with the results of Reiser who has made a similar observation when utilizing 4-(hydroxymethyl)oxazolines in the same reaction.[17] Thirdly, it is clear that the electronics of the amine moiety make a significant difference to the catalytic activity and selectivity of the ligands.[18] Not only does the electron poor amine **16c** produce a more reactive catalyst, ligand **16c** gives a 93% yield of **17** compared to only 72% of **17** when electron-rich **16b** is used, but it is significantly more enantioselective as well, giving over double the observed selectivity of electron rich amine **16b** (54% vs. 25%). It is interesting to speculate on the reasons for these differences. The most common mechanism[19] for the addition of diethylzinc to aldehydes requires electron donation from the ligand to activate one equivalent of diethylzinc, which would suggest the electron-rich ligand **16b**

should have made a better catalyst. The fact that the electron-poor ligand **16c** gives a more reactive catalyst might result from the increased Lewis acidity of the attached zinc centre but this still does not explain the increased selectivity. Clearly, more experimental evidence is required before an accurate working model can be formulated.



17

ligand = **14a** 0%; 0% ee
ligand = **14b** 40%; 24% ee
ligand = **16a** 83%; 45% ee
ligand = **16b** 72%; 25% ee
ligand = **16c** 93%; 54% ee

Scheme 7 *Reagents and conditions*: i. $ZnEt_2$ (2.5 equiv), ligand (0.1 equiv), toluene, –78 °C.

In conclusion, we have developed a general, practical route for the conversion of serine into valuable bis(amino) alcohols and have used these in the preparation of a number of novel bis(oxazoline) ligands. The ligands show interesting preliminary results in the addition of diethylzinc to benzaldehyde. Moreover, the basic 4-(aminomethyl)oxazoline scaffold should be highly amenable to further elaboration and we anticipate that derivatives of these ligands will have potential in numerous other transformations.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin 300 MHz spectrometer. IR spectra were recorded on a Perkin-Elmer SpectrumOne FT-IR Spectrophotometer. MS were obtained using VG Auto Spec Fisons Instruments and Bruker Daltonics Apex III. Mps were measured on a Gallenkamp Melting Point Apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 Polarimeter. All reactions were carried out in oven-dried flasks under a positive pressure of nitrogen. Chromatography refers to flash column chromatography on Merck Kieselgel 60 (230–400 mesh). Petroleum ether used had a bp range 40–60 °C. *N*-(*t*-Butyl)carbonyl L-serine **9** was prepared according to the literature.[20]

Coupling of *N*-(*tert*-Butyl)carbonyl L-Serine 9 with Aniline Derivatives; General Procedure

To a solution of *N*-(*tert*-butyl)carbonyl L-serine **9** (1.0 equiv) in THF (0.3 M) at 0 °C was added *N*-methylmorpholine (1.1 equiv). A solution of isobutyl chloroformate (1.1 equiv) in THF (2 M) was added slowly over 15 min. After stirring the mixture for a further 15 min, the aniline derivative (1.2 equiv) was added in one portion and the reaction was allowed to warm to r.t. overnight. The solvent was removed under reduced pressure, the residue was dissolved in EtOAc (150 mL), washed with sat. aq $NaHCO_3$ (90 mL), HCl (1 N; 90 mL), and brine (100 mL). The organic layer was dried ($MgSO_4$), the solvent removed under reduced pressure, and the residue purified via column chromatography (SiO_2; petroleum ether–EtOAc, 2:3).

(*S*)-*tert*-Butyl 3-Hydroxy-1-oxo-1-(phenylamino)propan-2-ylcarbamate (10a)

Yield: 17.89 g (81%); colorless solid; mp 82–84 °C; $[\alpha]_D^{27}$ –91.9 (*c* 1.04, $CHCl_3$).

IR ($CHCl_3$): 3310, 2977, 2931, 1671, 1600, 1537, 1499, 1445, 1392, 1367, 1298, 1163, 1060 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.85 (br s, 1 H, NH), 7.49 (d, *J* = 8.1 Hz, 2 H, ArH), 7.32–7.27 (m, 2 H, ArH), 7.11 (t, *J* = 7.4 Hz, 1 H, ArH), 5.78 (d, *J* = 7.4 Hz, 1 H, NHBoc), 4.38–4.26 (m, 1 H, H-3), 4.26–4.13 (m, 1 H, H-3), 3.85–3.66 (m, 1 H, H-2), 3.48–3.37 (br s, 1 H, OH), 1.48 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 137.8, 129.4, 125.1, 120.5, 81.4, 63.0, 55.7, 28.7.

MS (EI): *m*/*z* = 280 $[M]^+$, 93, 57.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{20}N_2O_4Na$ $[M + Na]^+$: 303.1315; found: 303.1318.

(*S*)-*tert*-Butyl 3-Hydroxy-1-(4-methoxyphenylamino)-1-oxopropan-2-ylcarbamate (10b)

Yield: 20.20 g (84%); colorless solid; mp 107–110 °C; $[\alpha]_D^{30}$ –95.9 (*c* 1.01, $CHCl_3$).

IR ($CHCl_3$): 3311, 2977, 2934, 2837, 1664, 1608, 1512, 1465, 1415, 1392, 1367, 1300, 1246, 1164, 1060, 1035 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (br s, 1 H, NH), 7.32 (d, *J* = 9.0 Hz, 2 H, ArH), 6.77 (d, *J* = 9.0 Hz, 2 H, ArH), 5.69 (br s, 1 H, NHBoc), 4.28–4.17 (m, 1 H, H-3), 4.17–4.05 (m, 1 H, H-3), 3.70 (s, 3 H, OMe), 3.70–3.57 (m, 1 H, H-2), 3.41–3.30 (br s, 1 H, OH), 1.40 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 157.0, 130.8, 122.3, 114.5, 81.3, 63.1, 55.8, 55.6, 28.7.

MS (EI): *m*/*z* = 310 $[M]^+$, 254, 123, 57.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{22}N_2O_5Na$ $[M + Na]^+$: 333.1421; found: 333.1421.

(*S*)-*tert*-Butyl 3-Hydroxy-1-oxo-1-(3-(trifluoromethyl)phenylamino)propan-2-ylcarbamate (10c)

Yield: 16.20 g (77%); colorless solid; mp 92–95 °C; $[\alpha]_D^{26}$ –77.1 (*c* 1.01, $CHCl_3$).

IR ($CHCl_3$): 3307, 3104, 2980, 2934, 1675, 1615, 1604, 1561, 1528, 1495, 1449, 1393, 1368, 1333, 1281, 1250, 1163, 1126, 1098, 1071 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.06 (br s, 1 H, NH), 7.82 (s, 1 H, ArH), 7.58 (d, *J* = 7.4 Hz, 1 H, ArH), 7.42–7.28 (m, 2 H, ArH), 5.83–5.69 (m, 1 H, NHBoc), 4.35–4.21 (m, 1 H, H-3), 4.21–4.10 (m, 1 H, H-3), 3.70 (br s, 1 H, OH), 3.25 (dd, *J* = 8.2, 4.5 Hz, 1 H, H-2), 1.42 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$; 2 rotamers): δ = 170.4, 157.3, 156.4, 138.4, 131.8 (q, *J* = 32.3 Hz, CCF_3), 129.9, 126, 123.4, 122.3, 121.5, 121.5, 117.1, 117.1, 81.7, 63.1, 62.8, 60.8, 56.4, 55.8, 28.6, 21.5, 14.6.

MS (EI): *m*/*z* = 348 $[M]^+$, 161, 104, 57.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{20}N_2O_4F_3$ $[M + H]^+$: 349.1369; found: 349.1357.

Amide Reduction and Deprotection; General Procedure

To a solution of amide **10** (1.0 equiv) in THF (0.1 M) at 0 °C was slowly added a solution of BH_3·THF complex (1 M in THF; 3.0 equiv). The mixture was heated to reflux for 1 h, then cooled in an ice-bath, and carefully quenched by the addition of MeOH (5 mL per mmol or until no reaction occurs). The solvent was removed under reduced pressure, the residue was taken up in a mixture of TFA–H_2O (19:1; 150 mL) and stirred for 1.5 h. The solvent was removed under reduced pressure, the residue dissolved in NaOH (2 M; 80 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and purified by column chromatography (SiO_2; CH_2Cl_2–MeOH–33% NH_4OH, 95:4.5:0.5).

(*R*)-2-Amino-3-(phenylamino)propan-1-ol (2a)
Yield: 10.09 g (65%); white solid; mp 108–110 °C; $[\alpha]_D^{31}$ +18.2 (*c* 1.03, $CHCl_3$).

IR (Nujol): 1605, 1582, 1497, 1331, 1258, 1178, 1129, 1109, 1088, 1074, 1054, 1016 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.29–7.13 (m, 2 H, ArH), 6.82–6.69 (m, 3 H, ArH), 3.76 (dd, *J* = 10.9, 4.4 Hz, 1 H, H-1), 3.65 (dd, *J* = 10.7, 5.4 Hz, 1 H, H-1), 3.35 (dd, *J* = 15.7, 8.3 Hz, 1 H, H-2), 3.21–3.12 (m, 2 H, H-3).

^{13}C NMR (75 MHz, CD_3OD): δ = 150.6, 130.4, 118.4, 114.3, 65.9, 53.5, 48.3.

MS (EI): *m*/*z* = 166 $[M]^+$, 106 $[M - CHNH_2CH_2OH]^+$, 77, 60 $[M - PhNHCH_2]^+$.

HRMS (EI): *m*/*z* calcd for $C_9H_{15}N_2O$ $[M + H]^+$: 167.1179; found: 167.1179.

(*R*)-2-Amino-3-(4-methoxyphenylamino)propan-1-ol (2b)
Yield: 8.57 g (72%); off-white solid; mp 84–87 °C; $[\alpha]_D^{30}$ +14.8 (*c* 1.05, MeOH).

IR (Nujol): 1580, 1509, 1334, 1269, 1238, 1174, 1126, 1104, 1035 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 7.0 Hz, 2 H, ArH), 6.60 (d, *J* = 6.7 Hz, 2 H, ArH), 3.73 (s, 3 H, OMe), 3.66 (dd, *J* = 10.9, 4.1 Hz, 1 H, H-1), 3.51 (dd, *J* = 10.7, 5.6 Hz, 1 H, H-1), 3.21–3.05 (m, 2 H, H-3), 2.99 (m, 1 H, H-2), 2.16 (br s, 3 H, 3 × NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.7, 142.8, 115.3, 114.8, 65.9, 56.2, 52.3, 49.1.

MS (EI): *m*/*z* = 196 $[M]^+$, 136 $[M - CHNH_2CH_2OH]^+$, 122, 108, 60 $[M - PhNHCH_2]^+$.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{16}N_2O_2Na$ $[M + Na]^+$: 219.1104; found: 219.1109.

(*R*)-2-Amino-3-[3-(trifluoromethyl)phenylamino]propan-1-ol (2c)
Yield: 5.14 g (55%); white solid; mp 94–97 °C $[\alpha]_D^{30}$ +12.3 (*c* 1.05, MeOH).

IR (Nujol): 1612, 1575, 1530, 1484, 1447, 1353, 1319, 1283, 1266, 1172, 1105, 1069, 1055 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.21 (t, *J* = 8.0 Hz, 1 H, ArH), 6.86–6.75 (m, 3 H, ArH), 3.59 (dd, *J* = 11.0, 4.8 Hz, 1 H, H-1), 3.49 (dd, *J* = 10.9, 5.7 Hz, 1 H, H-1), 3.20 (dd, *J* = 9.1, 7.4 Hz, 1 H, H-2), 3.08–2.92 (m, 2 H, H-3).

^{13}C NMR (75 MHz, CD_3OD): δ = 151.1, 132.8 (q, *J* = 31.4 Hz, CCF_3), 131.1, 126.4 (q, *J* = 271.5 Hz, CF_3), 117.1, 114.1, 110.0, 66, 53.4, 47.9.

MS (EI): *m*/*z* = 234 $[M]^+$, 174 $[M - CHNH_2CH_2OH]^+$, 60 $[M - CH_2NHC_6H_4CF_3]^+$.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{14}N_2OF_3$ $[M + H]^+$: 235.1053; found: 235.1051.

Bis(oxazoline); General Procedure
A solution of bis(amino) alcohol **2** (2.5 equiv), dimethylmalononitrile (1.0 equiv), $Cd(OAc)_2 \cdot 2H_2O$ (0.05 equiv) in chlorobenzene (0.3 M) was heated at reflux overnight. Upon cooling to r.t., the dark brown solution was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were washed with brine (40 mL) and dried ($MgSO_4$). After removing the solvent under reduced pressure the residue was purified by column chromatography (SiO_2; MeOH–CH_2Cl_2, 1.5–2.0%).

2,2-Bis{2-[(4*R*)-4-(phenylamino)methyl-1,3-oxazolinyl]}propane (16a)
Yield: 0.26 g (29%); pale yellow solid; mp 84–87 °C; $[\alpha]_D^{30}$ +155 (*c* 0.99, $CHCl_3$).

IR (Nujol): 3392, 2928, 1655, 1603, 1508, 1466, 1432, 1388, 1357, 1319, 1256, 1228, 1179, 1150, 1116, 1074, 972 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.08 (t, *J* = 8.4 Hz, 4 H, ArH), 6.63 (t, *J* = 7.3 Hz, 2 H, ArH), 6.54 (d, *J* = 7.8 Hz, 4 H, ArH), 4.50–4.38 (m, 2 H, H-4), 4.31 (dd, *J* = 9.6, 8.1 Hz, 2 H, H-5), 4.14 (dd, *J* = 7.9, 6.8 Hz, 2 H, H-5), 4.07 (br s, 2 H, 2 × NH), 3.26 (dd, *J* = 12.3, 4.2 Hz, 2 H, H-1′), 3.15 (dd, *J* = 12.2, 4.9 Hz, 2 H, H-1′), 1.48 (s, 6 H, 2 × Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 148.7, 129.6, 118, 113.5, 71.4, 65.8, 47.6, 39.4, 24.6.

MS (EI): *m*/*z* = 392 $[M]^+$, 287, 182, 106 $[M - PhNHCH_2]^+$, 77.

HRMS (EI): *m*/*z* calcd for $C_{23}H_{28}N_4O_2$ $[M + H]^+$: 393.2285; found: 393.2265.

2,2-Bis{2-[(4*R*)-4-(4-methoxyphenylamino)methyl-1,3-oxazolinyl]}propane (16b)
Yield: 0.27 g (59%); off-white solid; mp 78–80 °C; $[\alpha]_D^{25}$ +160.3 (*c* 1.18, $CHCl_3$).

IR ($CHCl_3$): 3369, 2929, 2832, 1655, 1514, 1465, 1357, 1302, 1236, 1117, 1037, 821 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 6.8 Hz, 4 H, ArH), 6.60 (d, *J* = 6.9 Hz, 4 H, ArH), 4.51–4.44 (m, 2 H, H-4), 4.39 (dd, *J* = 9.6, 7.9 Hz, 2 H, H-5), 4.24 (dd, *J* = 7.7, 6.8 Hz, 2 H, H-5), 3.83 (br s, 2 H, 2 × NH), 3.75 (s, 6 H, 2 × OMe), 3.30 (dd, *J* = 12.0, 4.1 Hz, 2 H, H-1′), 3.17 (dd, *J* = 12.0, 4.8 Hz, 2 H, H-1′), 1.57 (s, 6 H, 2 × Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 152.6, 142.9, 115.2, 114.8, 71.4, 65.9, 56.2, 48.7, 39.3, 24.6.

MS (EI): *m*/*z* = 452 $[M]^+$, 452, 136.

HRMS (EI): *m*/*z* calcd for $C_{25}H_{32}N_4O_4Na$ $[M + Na]^+$: 475.2316; found: 475.2287.

2,2-Bis{2-[(4*R*)-4-(3-(trifluoromethyl)phenylamino)methyl-1,3-oxazolinyl]}propane (16c)
Yield: 0.52 g (51%); clear oil; $[\alpha]_D^{30}$ +113.1 (*c* 1.12, $CHCl_3$).

IR ($CHCl_3$): 3391, 2928, 1655, 1617, 1497, 1445, 1344, 1319, 1283, 1249, 1162, 1118, 1069, 991, 784, 758, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 7.9 Hz, 2 H, ArH), 6.90 (d, *J* = 7.5 Hz, 2 H, ArH), 6.78 (s, 2 H, ArH), 6.70 (d, *J* = 8.0 Hz, 2 H, ArH), 4.59–4.48 (m, 4 H, H-4, 2 × NH), 4.40 (dd, *J* = 9.4, 8.4 Hz, 2 H, H-5), 4.21 (dd, *J* = 8.0, 6.4 Hz, 2 H, H-5), 3.37 (dt, *J* = 12.3, 3.8 Hz, 2 H, H-1′), 3.24 (ddd, *J* = 12.1, 7.0, 5.0 Hz, 2 H, H-1′), 1.56 (s, 6 H, 2 × Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 148.9, 131.8 (q, *J* = 31.6 Hz, CCF_3), 124.7 (q, *J* = 272.5 Hz, CF_3), 116.2, 114.3, 114.2, 109.7, 109.6, 109.6, 71.2, 65.7, 47.2, 39.5, 24.4.

MS (EI): *m*/*z* = 529 $[M + H]^+$, 490, 446, 355, 286, 174, 139, 113.

HRMS (EI): *m*/*z* calcd for $C_{25}H_{27}N_4O_2F_6$ $[M + H]^+$: 529.2032; found: 529.2024.

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