The Synthesis of AraBOX, a New 4,4′-Bis(oxazoline), from Novel Pentitol-Derived Bis-β-amino Alcohols

David Frain,[a] Fiona Kirby,[a] Patrick McArdle,[b] Patrick O'Leary*[a]

[a] School of Chemistry, SMACT (Synthetic Methods: Asymmetric Catalytic Transformations), National University of Ireland, Galway, Ireland
Fax +353(91)525700; E-mail: patrick.oleary@nuigalway.ie

[b] School of Chemistry, National University of Ireland, Galway, Ireland

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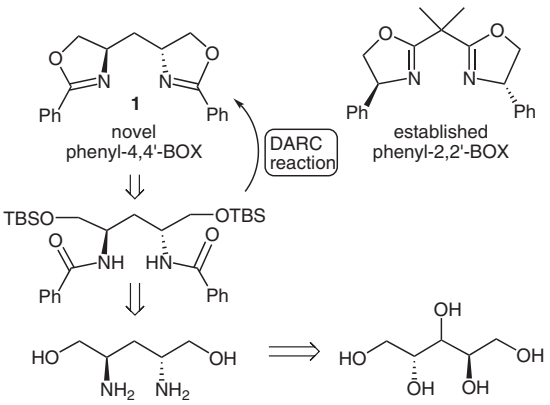
This letter is dedicated to Professor Richard N. Butler on the occasion of his 65th birthday.

Abstract: The preparation of a novel phenyl 4,4′-bis(oxazoline) [AraBOX] is described. The novel ligand is prepared in two efficient steps from a bis-[(*O*-silyl)β-amino alcohol], via conversion into an intermediate bis(benzamide) followed by a one-pot deprotection–activation–ring closure (DARC) oxazoline formation. To our knowledge, this is the first reported synthesis of an oxazoline ring via this DARC method. The synthesis of two precursor bis-β-amino alcohols, (2*R*,4*R*)- and *meso*-2,4-diaminopentane-1,5-diol, derived from D-(+)-arabitol and xylitol, respectively, is also described.

Key words: asymmetric synthesis, ligand, catalysis, oxazoline, chiral pool

The design of new asymmetric ligands remains an active area of chemical research.[1] These ligands have found use, generally as their metal complexes, as enantioselective catalysts for key synthetic transformations.[2] Many different ligand types have been reported, for example phosphines,[3] salens,[4] Binols,[5] BOXs (including Sasai's spiroBOXs which are the closest relative to the ligands described herein),[6] etc. Our recent research has focused on N-donor-based ligands including BOX and PYBOX ligands and their catalytically active metal complexes.[7] During the course of this work we became interested in altering the traditional BOX motif with the aim of addressing a problem which arises in the case of traditional BOX ligands with a methylene bridge.

Herein we report the synthesis of novel 4,4′-methylenebis[(4*R*)-2-phenyl-2-oxazoline] **1** with the methylene bridgehead of the ligand bound to the chiral sp^3-hybridised 4-position of the oxazoline rings. This ligand is a regioisomer of a standard 2,2′-BOX ligand and is synthesised from arabitol so we use the acronym (AraBOX). Regulating the electron density of the oxazoline rings in standard BOX ligands is difficult because of the potential for migration of the double bonds into conjugation.[8] This factor has traditionally limited the use of methylene-bridged BOXs and led to the use of gem-dimethyl-substituted bridges. The AraBOX ligand cannot undergo such a migration, which is a significant advantage. Obviously such a ligand is also likely to have more general application.



Scheme 1 Retrosynthetic analysis of the AraBOX **1** ligand

Chiral β-amino alcohols are often key components in the synthesis of oxazoline-based ligands and are commonly derived from amino acids such as phenylglycine or valine.[9] The AraBOX ligand synthesis would require the preparation of a new type of bis β-amino alcohol (Scheme 1). These bis-β-amino alcohols could be accessed from the widely available sugar-derived pentitols.

The preparation of novel bis-β-amino alcohols is of synthetic interest due to their potential application here, but also in a number of other contexts. Chiral amino alcohols, chiral amino diols and their derivatives have been reported as asymmetric catalysts for a number of reactions.[10] Amino diols are also a common structural motif in drug therapy.[11] They have also been used widely as starting materials for the synthesis of bioactive natural products.[12] In addition, structurally similar bisamino acids have been shown to have a useful cross-linking property which is of enormous potential for an application in the design and synthesis of conformationally constrained cyclic peptides.[13] The bis-β-amino alcohols in this study could be similarly applied.

We envisaged that the bis-β-amino alcohol shown could be elaborated to the AraBOX ligand (Scheme 1). The key step in the synthesis of the ligand would be a one-pot double deprotection–activation–ring-closure (DARC) reaction. This transformation would provide a facile synthetic route to our desired phenyl-AraBOX ligand.

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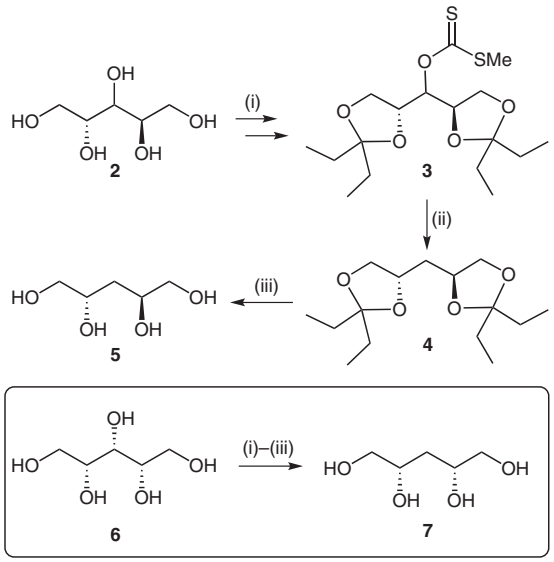
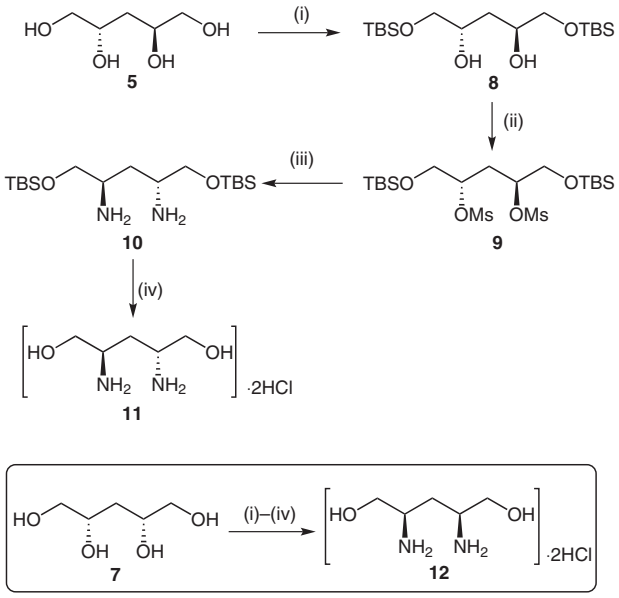
We initially studied the synthesis of the precursor bis-β-amino alcohols. A suitable starting point for the synthesis was identified as tetraol **5** (Scheme 2), which would provide the appropriate structural and stereochemical basis with overall C_2-symmetry. The preparation of **5** was achieved from D-(+)-arabitol **2** in four steps through a procedure modified from that of Linclau.[14] This process was also applied to xylitol **6**, yielding the *meso* diastereomer of the tetraol **7**. The main discussion will focus on the synthetic results of the chiral compounds. The *meso* synthesis is documented in Scheme 2 and Scheme 3.



Scheme 2 Synthesis of tetraol. *Reagents and conditions*: arabitol **2** conversion into tetraol **5** (i) as ref. 14, 68%; (ii) ACN, Bu_3SnH, toluene, reflux, 4 h, 95%; (iii) AcOH–H_2O–THF (3:2:1), 80 °C, 4 h, 90%. Xylitol **6** conversion into tetraol **7** (i) as ref. 14, 32%; (ii) 81%; (iii) 0.5 M H_2SO_4, EtOH, reflux, 4 h, 85%.

Kinetic acid-catalysed acetalisation of arabitol **2** with 3,3-dimethoxypentane yielded 1,2:4,5-bisacetalised arabitol as the major product. Sodium hydride mediated generation of the alkoxide at the 3-O-position in the presence of carbon disulfide and subsequent methylation using iodomethane provided xanthate **3** in high yield, as reported. Radical deoxygenation of **3** with tributyltin hydride was first attempted using AIBN as a radical initiator, but an increase in yield was observed when 1,1-azobis(cyclohexane-carbonitrile) (ACN) was used to initiate single electron transfer. Since **3** and **4** proved difficult to separate chromatographically, this increased yield in turn facilitated the process of column chromatography, given that less starting material needed to be separated from deoxygenated product **4**. Hydrolysis of both acetals occurred in a mixture of acetic acid, water, and tetrahydrofuran at 80 °C over four hours to yield desired **5**. The synthesis commencing from xylitol **6** was conducted in a similar fashion. The yield in the acetalisation reaction was found to be low (35%) in this case leading to a lower yield of the corresponding xanthate (32%).

Conversion of the secondary alcohols to amines could be achieved by activation as sulfonyl groups followed by S_N2 reaction involving azide transfer and reduction to amines leading to **10** (Scheme 3). The key transformation required to allow this to take place was selective protection of the primary hydroxyl groups of **5**. This was achieved by conversion to primary silyl ethers using *tert*-butyldimethylsilyl chloride, triethylamine, and dimethylaminopyridine in CH_2Cl_2 over a 40-hour period.

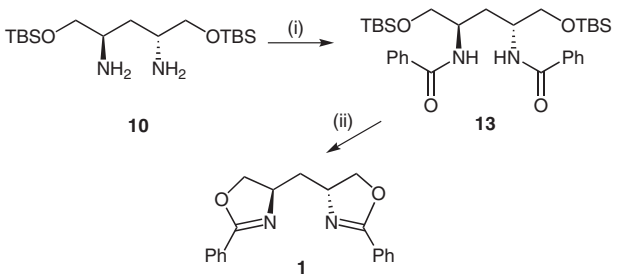


Scheme 3 Synthesis of bis-β-amino alcohol **11**. *Reagents and conditions*: (i) Et_3N, DMAP, TBSCl, CH_2Cl_2, –15 °C to r.t., 40 h, 65%; (ii) Et_3N, MsCl, CH_2Cl_2, 0 °C to r.t., 4 h, 99%; (iii) (a) NaN_3, DMF, 85 °C, 16 h; (b) H_2 (5 bar), 10% Pd/C, MeOH, 4 d, 76%; (iv) 1% HCl–MeOH, 4 h, 87%. Bis-β-amino alcohol **12** (i) 54%; (ii) 83%; (iii) 43%; (iv) 92%.

Mesylation of **8** gave **9**, in 99% yield, which could be carried through to the next step without purification. The treatment of **9** with sodium azide in *N*,*N*-dimethylformamide was seen to give complete displacement of sulfonate groups after 16 hours at 85 °C by ^{1}H NMR. The resultant diazido compound was not isolated but instead used in its crude form in the next step. Hydrogenation of the diazido compound gave diamine **10** after four days at 5 bar H_2 in the presence of 10% palladium on activated carbon.

Desilylation of **10** by treatment with 1% hydrochloric acid in methanol solution gave (2*R*,4*R*)-2,4-diaminopentane-1,5-diol **11** as the crystalline dihydrochloride salt which was suitable for X-ray crystal-structure determination.[15] The compound was optically active as expected. The absolute structure was determined in this case and the Flack parameter was –0.02(5). The X-ray crystal structure of a dication of *meso*-2,4-diaminopentane-1,5-diol **12**[16] was also determined.

Our attention then turned to the conversion of hydrogenation product **10** into novel ligand target **1**. Conventional oxazoline synthesis involves reaction between an acid



Scheme 4 Synthesis of phenyl 4,4′-bis(oxazoline) **1**. *Reagents and conditions*: (i) Et_3N, BzCl, 0 °C, 4 h, 76%; (ii) TsF, DBU, MeCN, reflux, 16 h, 75%.

chloride and an amino alcohol to yield a hydroxyamide, followed by activation with tosyl chloride, and subsequent base-promoted cyclisation. Hampering this approach with relation to **10** was the need to carry out desilylation of any resultant amide-type product prior to tosyl activation. DBU is known to catalyse the conversion of a TBS group into a tosyl group with *p*-toluenesulfonyl fluoride in refluxing MeCN.[17] We hoped that as well as catalysing the conversion from O-silyl to O-tosyl, employing a stoichiometric quantity of DBU would perhaps drive the reaction further, cyclising to the desired oxazoline.

The TBS protected β-amino alcohol **10** reacted with benzoyl chloride in high yield to give bis (*O*-silyl) benzamide **13** (Scheme 4).[18] The TsF-mediated double deprotection–activation–ring-closure reaction was then explored. We were pleased to find that bis (*O*-silyl) benzamide **13** refluxed overnight with 2.2 equivalents of both TsF and DBU in dry MeCN gave the desired double cyclisation product, phenyl 4,4′-BOX **1**,[19] in good yield (75%, Scheme 4). Recrystallisation from hot petroleum ether gave crystals suitable for crystallographic analysis.

In conclusion we have reported the synthesis of the first member of a new family of 4,4′-BOX ligands. The final step involved a TsF-mediated double deprotection–activation–ring-closure reaction which lead to the preparation of the ligand in high yield. We have also prepared novel bis-β-amino alcohols, which are of considerable synthetic interest. We will report in due course on the metal complexes of ligand **1** and their catalytic activity.

Acknowledgment

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(15) **(2*R*,4*R*)-2,4-Diaminopentane-1,5-diol Dihydrochloride (11)**
^{1}H NMR (400 MHz, D_2O): δ = 3.86 (2 H, dd, *J* = 12.4, 3.7 Hz 2 × one of C*H*$_2$OH), 3.71 (2 H, dd, *J* = 12.4, 6.0 Hz, 2 × one of C*H*$_2$OH), 3.56–3.50 (2 H, m, 2 × C*H*NH$_2$), 2.05 (2 H, t, *J* = 7.1 Hz, CHC*H*$_2$CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.2 (2 × CH_2OH), 49.4 (2 × CHN), 28.8 (CH*C*H$_2$CH) ppm. IR: 3512, 3333, 3048 (br), 2907, 1490, 1036 cm^{-1}. Anal. Calcd for $C_5H_{16}Cl_2N_2O_2$: C, 29.00; H, 7.79; N, 13.53. Found C, 29.17; H, 7.63; N, 13.71. $[\alpha]_D^{22}$ –46.5 (*c* 0.7, MeOH). The CIF file for this compound has been deposited

with the The Cambridge Crystallographic Data Centre (deposition number 719095).

(16) ***meso*-2,4-Diaminopentane-1,5-diol Dihydrochloride (12)**
^{1}H NMR (400 MHz, D_2O): δ = 3.84 (2 H, dd, *J* = 12.4, 3.7 Hz 2 × one of C*H*$_2$OH), 3.67 (2 H, dd, *J* = 12.6, 6.0 Hz, 2 × one of C*H*$_2$OH), 3.52–3.47 (2 H, m, 2 × C*H*NH$_2$), 2.08–1.88 (2 H m, CHC*H*$_2$CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.5 (2 × CH_2OH), 49.2 (2 × CHN), 28.9 (CH*C*H$_2$CH). IR: 3315 (br), 2927 (br), 1612, 1559, 1513 cm^{-1}. Anal. Calcd for $C_5H_{16}Cl_2N_2O_2$: C, 29.00; H, 7.79; N, 13.53. Found C, 28.37; H, 7.3; N, 12.53. The CIF file for this compound has been deposited with the The Cambridge Crystallographic Data Centre (deposition number 719096).

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(18) ***N*,*N*′-[(2*R*,4*R*)-1,5-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-pentane-2,4-diyl]benzamide (13)**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (4 H, d, *J* = 6.9 Hz, 4 × *ortho* ArH), 7.48–7.35 (6 H, m, 4 × *meta* ArH, 2 × *para* ArH), 7.05 (2 H, d, *J* = 7.8 Hz, 2 × NH), 4.19–4.12 (2 H, m, 2 × CHN), 3.88–3.81 (4 H, m, 2 × CH_2O), 2.07 (2 H, t, *J* = 6 Hz, CHC*H*$_2$CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5 (2 × HNC=O), 134.5 (2 × Ar*C*C=O), 131.5 (2 × *para* ArC), 128.6 (4 × *ortho* ArC), 127.0 (4 × *meta* ArC), 64.9 (2 × CH_2OSi), 49.2 (2 × *C*HNH$_2$), 33.4 (CH*C*H$_2$CH), 26.0 (6 × *C*H$_3$), 18.3 (2 × C), –5.3 [2 × Si(CH$_3$)$_2$]. IR: 3279, 2928, 1629, 1536, 1102, 777, 691 cm^{-1}. Anal. Calcd for $C_{31}H_{50}N_2O_4Si_2$: C, 65.25; H, 8.83; N, 4.91. Found: C, 65.25; H, 8.74; N, 4.77. $[\alpha]_D^{22}$ +52.2 (*c* 0.9, MeCN).

(19) To a solution of **13** (300 mg, 0.525 mmol) and TsF (140mg, 1.155 mmol) in dry MeCN (5 mL) was added DBU (185 μL, 1.115 mmol). The mixture was stirred at reflux overnight, cooled, and concentrated in vacuo. The residue was purified by flash chromatography on SiO_2 (PE–EtOAc, 80:20) to yield desired bis(oxazoline) **1** (120 mg, 75%).
4,4′-Methylenebis[(4*R*)-2-phenyl-2-oxazoline] (1)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (4 H, d, *J* = 6.9 Hz, 4 × *ortho* ArH), 7.49–7.38 (6 H, m, 4 × *meta* ArH, 2 × *para* ArH), 4.66 (2 H, app t, *J* = 8.5 Hz, 2 × one of CH_2O), 4.61–4.51 (2 H, m, 2 × CHN), 4.14 (2 H, app t, *J* = 8 Hz, 2 × one of CH_2O), 1.98 (2 H, t, *J* = 7 Hz, CHC*H*$_2$CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9 (2 × C=N), 131.4 (2 × *para* ArC), 128.4 (4 × *ortho* ArC), 128.3 (4 × *meta* ArC), 127.9 (2 × Ar*C*CN), 73.7 (2 × CHO), 65.5 (2 × CHN), 43.3 (CH*C*H$_2$CH). IR: 2924, 1720, 1642, 1080, 1025, 779, 688 cm^{-1}. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.15; H, 5.83; N, 8.75. $[\alpha]_D^{23}$ +57.1 (*c* 0.7, MeCN). The CIF file for this compound has been deposited with the The Cambridge Crystallographic Data Centre (deposition number 719094).