Tetrahedron 64 (2008) 10244–10249

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Convenient preparation of bifunctional pybox ligands

Mélanie Tilliet [a,b], Anders Frölander [a], Vincent Levacher [b,*], Christina Moberg [a,*]

[a] KTH School of Chemical Science and Engineering, Department of Chemistry, SE 100 44 Stockholm, Sweden
[b] UMR 6014 IRCOF, CNRS, Université et INSA de Rouen, BP 08, F 76131 Mont-Saint-Aignan Cédex, France

ARTICLE INFO

Article history:
Received 3 June 2008
Received in revised form 23 July 2008
Accepted 7 August 2008
Available online 9 August 2008

ABSTRACT

Starting from a common easily available pybox derivative, chiral ditopic ligands with pendant Lewis basic sites consisting of amine or phosphine oxide functions attached in the 4-positions of the oxazoline rings were prepared by simple synthetic procedures. From the same pybox derivative, a macrocyclic ligand containing a diaza-18-crown-6-ether ring linked via triazole groups was obtained employing 'click' chemistry.

1. Introduction

The incorporation of two or more reactive centers in a catalytic system may lead to increased selectivity and efficiency in catalytic applications.[1] For this reason, multifunctional catalysts have been the subject of numerous recent investigations.[2] Early examples described palladium catalysts equipped with crown ether side arms capable of binding and directing a nucleophile attacking an allyl group.[3] More recently, the combination of a Lewis acid and a Lewis base to activate both an electrophile and a nucleophile has been particularly well studied and applied to a variety of enantioselective catalytic processes.[4] In an alternative mode, the two binding sites of bimetallic complexes can be used for cooperative substrate binding, thereby enabling proper orientation of the substrate in a chiral environment.[5]

Incorporation of several binding sites in the same molecule requires advanced ligand design and synthesis, but may be necessary for certain applications, for example, to avoid undesired reaction of the Lewis acid with the Lewis base in Lewis acid–Lewis base catalyzed processes. For this reason, ditopic ligands based on wide-scope ligands such as binol,[6] salen,[7] and bisoxazoline[8] have been prepared and studied in catalytic applications.

Chiral oxazoline-containing ligands like pyridyloxazoline (pymox),[9] bisoxazoline (box)[10] 2,6-bis(oxazolyl)pyridine (pybox),[11] and phosphinooxazoline (PHOX)[12] derivatives, which are readily available in enantiopure form from amino alcohols, serve as highly versatile ligands in a variety of metal catalyzed asymmetric transformations. Numerous derivatives of the four types of ligands having substituents in the oxazoline rings as well as in other positions have been prepared. We have previously studied the effect of hydroxy and alkoxy functions in pymox,[13] box,[14] and PHOX[15] ligands and found that secondary interactions involving pendant hydroxy groups have pronounced effects on the stereochemistry of products obtained in Pd- and Ir-catalyzed asymmetric allylic alkylations. To allow further studies of catalytic reactions involving ditopic ligands, we needed simple methods for their synthesis. We decided to use the pybox skeleton as the common structural element for our studies since different substituents can easily be introduced at the 4- and 5-positions of the oxazoline rings, and thus the properties of the ligands can be readily tuned.

Here we report the preparation of six difunctional pybox compounds, **1a**–**e** and **2**, equipped with substituents containing Lewis basic groups together with triazole compounds **3a** and **b** and a macrocyclic ligand **3c**.

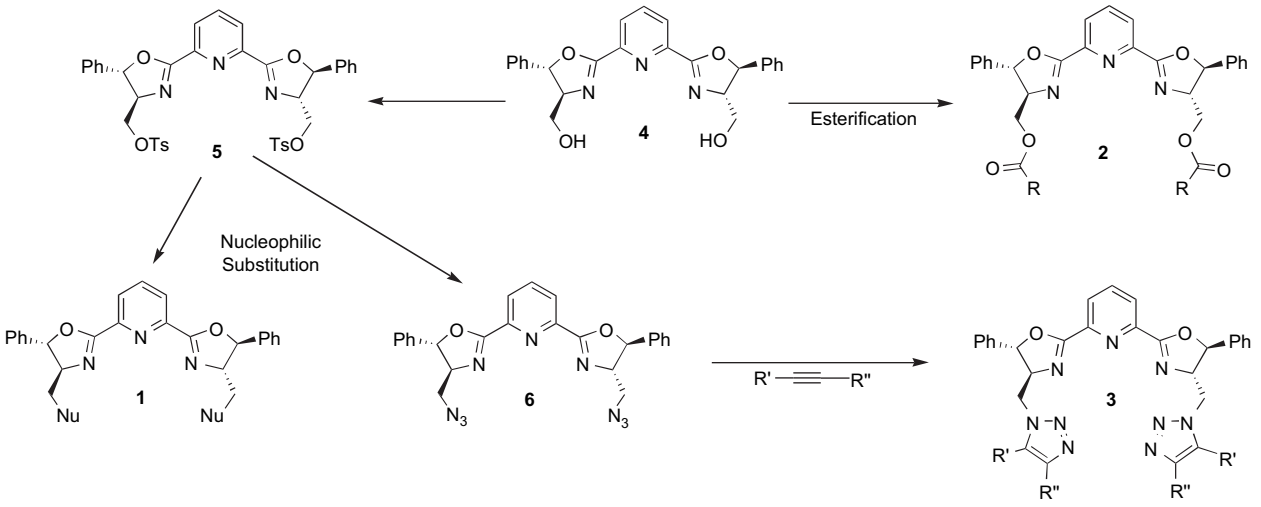
2. Results and discussion

(4′*S*,5′*S*)-2,6-Bis(4′-hydroxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl)pyridine (**4**) was selected as a suitable precursor for the synthesis of ditopic pybox ligands carrying structurally different pendant functionalities. This compound was obtained in two steps in good overall yield from 2,6-dicyanopyridine and (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol according to Desimoni et al.[16] For the introduction of the desired functionalities on **4** we identified two major routes, either nucleophilic substitution after modification of the hydroxy groups or ester formation. Substitution by *N*- or *P*-nucleophiles employing a suitable derivative of **4** (e.g., **5**) was assumed to give direct access to ditopic ligands **1**, whereas use of azide as nucleophile would result in a suitable precursor (**6**) for the linkage of other functionalities via 'click chemistry'[17] (Scheme 1).

To allow for nucleophilic substitutions, transformation of the hydroxy groups into suitable leaving groups was required. First, we tried a one-pot procedure involving initial formation of the

* Corresponding authors.
E-mail address: kimo@kth.se (C. Moberg).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.08.016

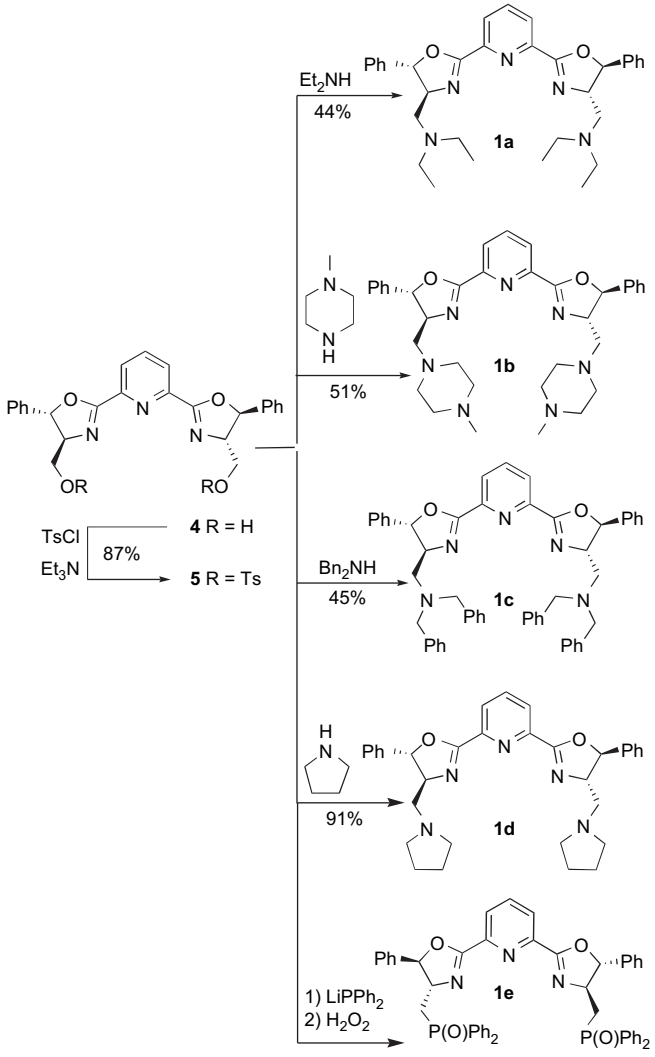


Scheme 1. General synthetic strategy.

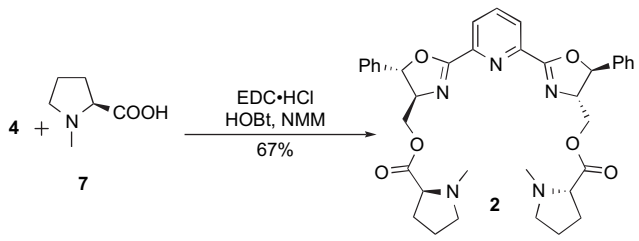
bistriflate using triflic anhydride, followed by addition of the secondary amine. Product formation was observed, but yields were poor. Searching for a better method we discovered that first converting **4** into the ditosylated compound **5** and then performing the nucleophilic substitution in a second step provided superior results. Compound **5** was thus obtained in 87% yield from **4** using TsCl and Et_3N. The four secondary amines diethylamine, 1-methylpiperazine, dibenzylamine, and pyrrolidine were selected as suitable nucleophiles, as they give rise to structurally different ligands. Thus, ligands **1a–d** were conveniently synthesized by reacting **5** with the appropriate amine in acetonitrile or DMF (Scheme 2). In order to get access to a ligand containing pendant phosphine oxide groups, which are particularly useful for the activation of silicon centers, ligand **1e** was prepared by reaction of in situ generated $LiPPh_2$ with the tosylate **5** followed directly by oxidation of the phosphine with hydrogen peroxide. Unfortunately, this ligand proved difficult to purify and could not be isolated in completely pure form but remained contaminated by some phosphinic acid.

A ligand containing a secondary amino function connected to the pybox moiety by a different linker was obtained by esterification of **4**. L-Proline was chosen as a suitable amino acid (Scheme 3). L-Proline was first converted into *N*-methyl-L-proline[18] (**7**) as secondary amines have been shown to be inferior as Lewis bases in catalytic reactions.[19] Coupling of compound **4** with **7** was achieved using EDC·HCl, HOBt, and *N*-methylmorpholine to give ligand **2** in 67% yield.

We next wanted to attach a crown ether function to the pybox nucleus. In order to obtain a rigid system with a defined distance between the binding sites, we decided to prepare a macrocyclic ligand by joining the 4-positions of the pybox compound to the nitrogen atoms of a diaza crown ether. For this purpose we selected the Huisgen [3+2] cycloaddition as a suitable reaction.[17] This chemistry has been used previously in our group to fix a pybox ligand on a polymer resin[20] and it was thought to be a good alternative to elaborate the substituents in the 4-positions of the



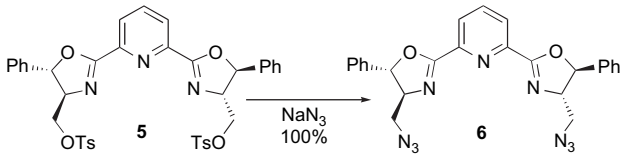
Scheme 2. Synthesis of ligands **1a–e**.



Scheme 3. Synthesis of ligand **2**.

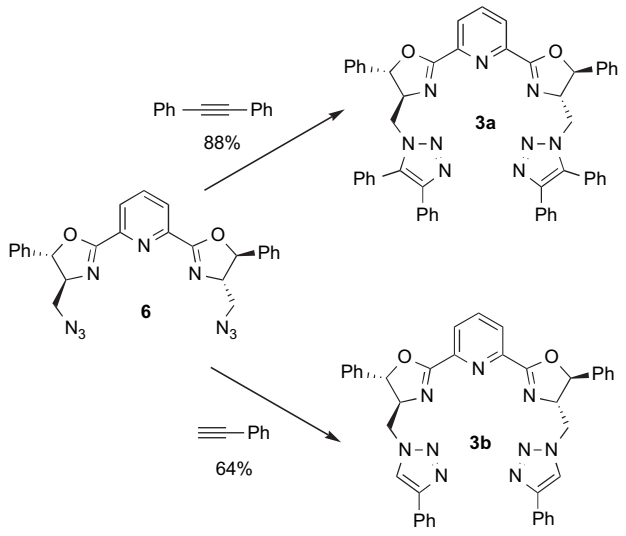
oxazoline rings, providing derivatives containing robust and rigid triazole groups.

Before undertaking the synthesis of a macrocyclic ligand we decided to probe the efficiency of the 'click chemistry' by attaching simple and readily available moieties onto a pybox ligand. We therefore started with the synthesis of **3a** and **b**. To allow for the Huisgen 1,3-dipolar addition we first had to install azide groups on the pybox. This was accomplished in quantitative yield by refluxing intermediate **5** with sodium azide in acetonitrile for 24 h (Scheme 4).



Scheme 4. Synthesis of intermediate **6**.

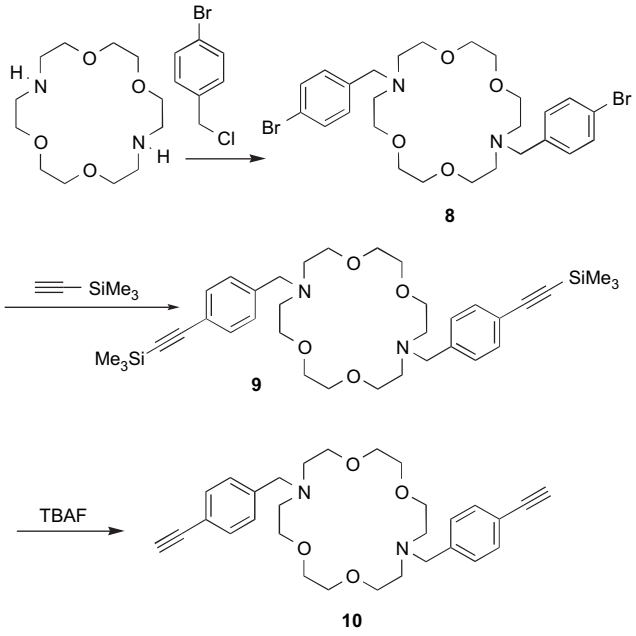
Intermediate **6** was subsequently reacted with diphenylacetylene under the thermal conditions of the Huisgen [3+2] cycloaddition to yield compound **3a** (88%). For the synthesis of compound **3b**, obtained in 64% yield, we used the Cu(I) catalyzed procedure, which results in selective formation of 1,3 triazoles in shorter times compared to the non-catalyzed reaction (Scheme 5).



Scheme 5. Synthesis of compounds **3a**,**b**.

With these results in hand, we undertook the functionalization of a diaza-18-crown-6 ether as shown in Scheme 6. First, 4-bromobenzyl groups were installed on the crown ether by N-functionalization using 4-bromobenzyl chloride, yielding **8** (91%). This allowed the Sonogashira coupling with trimethylsilylacetylene to be carried out. The trimethylsilyl moiety of product **9** could then be removed under mild conditions using TBAF in THF to afford intermediate **10** in 72% overall yield.

Following the model reaction developed to prepare ligand **3b**, we envisaged the Cu(I) catalyzed [3+2] cycloaddition of intermediates **6** and **10** (Scheme 7). To favor macrocyclization over oligomerization we performed the reaction under high dilution conditions. After 2 days the reaction did not seem to evolve further. A mixture of the macrocycle, in solution, and of precipitated oligomers was obtained. The latter were separated by filtration and the macrocycle could then be purified by column chromatography on deactivated silica (21% yield).



Scheme 6. Synthesis of intermediate **10**.

The ^{1}H and ^{13}C NMR spectra of macrocycle **3c** confirm the expected C_2-symmetrical structure, with pairwise identical protons and carbon atoms, respectively. The conformational mobility in **3c** is limited as shown by the lack of NOESY interaction between one of the diastereotopic protons in the methylene group connecting both oxazoline and triazole heterocycles and the proton in 5-position in the oxazoline ring. The protons in the aromatic rings incorporated in the macrocycle are pairwise chemically identical, demonstrating that the rings are freely rotating.

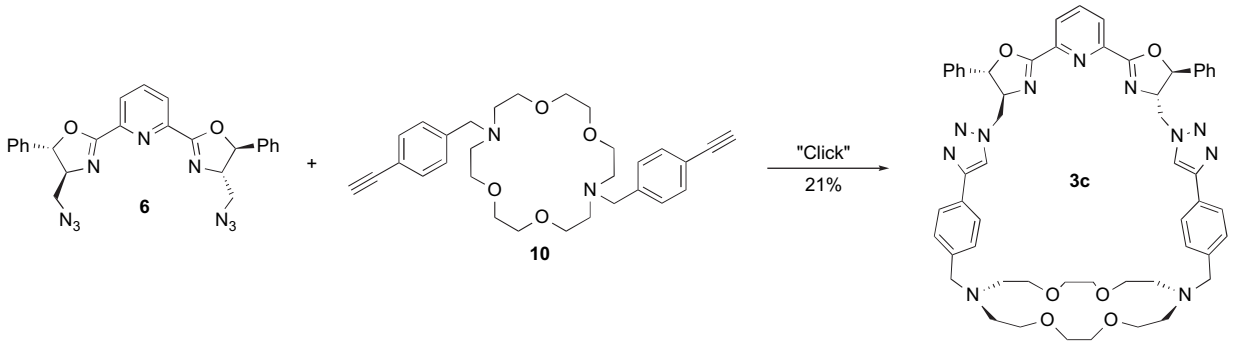
3. Conclusion

Simple procedures for the syntheses of pyridine-2,6-bis(oxazoline) derivatives carrying a variety of pendant groups have been developed starting from a common, easily available precursor. Six ditopic pybox ligands, which upon complexation to metal centers are expected to provide catalysts with Lewis acidic and Lewis basic sites, were synthesized in three or four steps from commercially available starting materials in good yields. Two ligands bearing bulky substituents as well as a macrocycle were obtained using the Huisgen cycloaddition. Further investigations of these newly prepared pybox ligands in bifunctional catalysis are being carried out in our laboratory.

4. Experimental section

4.1. General

All reactions sensitive to moisture and air were performed in oven-dried glassware under nitrogen atmosphere using freshly distilled solvents. Methylene chloride, triethylamine, and acetonitrile were distilled from CaH_2. Flash chromatography was performed using silica gel 60H treated with Et_3N or basic Al_2O_3. ^{1}H NMR spectra were recorded at 500, 400 or 300 MHz and ^{13}C spectra at 125 MHz. The ^{1}H and ^{13}C chemical shifts are reported relative to TMS. Melting points are uncorrected. Compounds **4**[16] and **7**[18] were synthesized according to the literature procedures.



Scheme 7. Synthesis of macrocycle **3c**.

4.2. Ligand synthesis

*4.2.1. (4′S,5′S)-2,6-Bis[4′-(p-toluenesulfonyl)oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**5**)*

Et_3N (2.43 mL, 17.46 mmol, 1.5 equiv) was added to a suspension of compound **4** (2.5 g, 5.82 mmol) in CH_2Cl_2 (30 mL) at −78 °C. A solution of TsCl (2.44 g, 12.81 mmol, 1.1 equiv) in CH_2Cl_2 (20 mL) was added and the mixture was allowed to slowly warm to rt and stirred for 16 h, giving an essentially clear solution. The mixture was absorbed on Al_2O_3 and purified by flash chromatography on basic Al_2O_3 (eluent: EtOAc/cyclohexane 1:1) to afford **5** (3.76 g, 87%) as a white solid. Mp 83 °C. $[\alpha]_D^{20}$ −0.46 (*c* 0.43, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 2.42 (s, 6H), 4.20 (dd, *J*=7.0, 10.1 Hz, 2H), 4.36–4.46 (m, 4H), 5.55 (d, *J*=7.3 Hz, 2H), 7.25–7.40 (m, 14H), 7.78 (m, 4H), 7.94 (t, *J*=7.9 Hz, 1H), 8.17 (d, *J*=7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 70.2, 73.9, 84.5, 126.0, 126.6, 128.2, 128.8, 129.0, 130.1, 132.6, 137.7, 139.3, 145.3, 146.6, 163.7. HRMS (FAB) *m*/*z* calcd for $C_{39}H_{36}N_3O_8S_2$ $[M+H]^+$: 738.1944, found: 738.1940.

*4.2.2. (4′S,5′S)-2,6-Bis[4′-(diethylamino)methyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**1a**)*

Diethylamine (1.0 mL, 9.67 mmol) was added to a solution of **5** (300 mg, 0.41 mmol) in acetonitrile (1 mL) and the solution was stirred at 60 °C for 24 h. The red mixture was diluted with CH_2Cl_2 (20 mL), washed with satd aq Na_2CO_3 (20 mL), dried with Na_2SO_4, and purified by flash chromatography on basic Al_2O_3 (eluent: EtOAc/pentane 1:3) to yield the product as a red oil. The product was dissolved in hexane (0.5 mL) and left to stand in the freezer for 2 h. The white precipitate formed was filtered off and washed with hexane to give **1a** (95.7 mg, 44%) as a white solid. Mp 90 °C. $[\alpha]_D^{20}$ +135.9 (*c* 0.37, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, *J*=7.1 Hz, 12H), 2.45 (dq, *J*=13.8, 7.0 Hz, 4H), 2.54–2.69 (m, 6H), 2.93 (dd, *J*=4.8, 12.9 Hz, 2H), 4.35 (ddd, *J*=4.8, 6.9, 9.7 Hz, 2H), 5.57 (d, *J*=6.9 Hz, 2H), 7.24–7.41 (m, 10H), 7.92 (t, *J*=7.8 Hz, 1H), 8.21 (d, *J*=7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.9, 47.4, 57.9, 74.3, 86.6, 126.0, 126.2, 128.1, 128.6, 137.5, 141.1, 147.3, 162.5. HRMS (FAB) *m*/*z* calcd for $C_{33}H_{42}N_5O_2$ $[M+H]^+$: 540.3339, found: 540.3336.

*4.2.3. (4′S,5′S)-2,6-Bis[4′-(4″-methyl-piperazine-1″-yl)methyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**1b**)*

1-Methylpiperazine (361 μL, 3.25 mmol) was added to a solution of **5** (400 mg, 0.54 mmol) in acetonitrile (3 mL) and the solution was stirred at reflux for 18 h. The red solution was concentrated and purified by flash chromatography on basic Al_2O_3 (eluent: EtOAc) to yield a red oil. On addition of cyclohexane, a solid was formed. The solid was filtered off and washed with cyclohexane to give **1b** (163.0 mg, 51%) as a white solid. Mp 105 °C. $[\alpha]_D^{20}$ +113.8 (*c* 0.22, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 2.00–2.26 (m, 4H), 2.28 (s, 6H), 2.38–2.60 (m, 14H), 2.86 (dd, *J*=4.5, 12.0 Hz, 2H), 4.35–4.42 (m, 2H), 5.55 (d, *J*=7.0 Hz, 2H), 7.24–7.42 (m, 10H), 7.91 (t, *J*=7.7 Hz, 1H), 8.20 (d, *J*=7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.1, 46.2, 55.2, 62.8, 73.7, 86.7, 126.1, 126.2, 128.2, 128.7, 137.5, 140.8, 147.3, 162.6. HRMS (FAB) *m*/*z* calcd for $C_{35}H_{44}N_7O_2$ $[M+H]^+$: 594.3556, found: 594.3551.

*4.2.4. (4′S,5′S)-2,6-Bis[4′-(dibenzylamino)methyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**1c**)*

Dibenzylamine (625 μL, 3.25 mmol) was added to a solution of **5** (400 mg, 0.54 mmol) in DMF (2 mL) and the solution was stirred at 100 °C for 24 h. A white solid precipitated upon cooling. The solid was filtered off and washed with acetone to yield **1c** (190 mg, 45%) as a white solid. Mp 151 °C. $[\alpha]_D^{20}$ +53.1 (*c* 0.24, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.77 (A part of ABX, *J*=8.4, 13.1 Hz, 2H), 2.89 (B part of ABX, *J*=3.9, 13.1 Hz, 2H), 3.45 (A part of AB, *J*=13.2 Hz, 4H), 3.67 (B part of AB, *J*=13.2 Hz, 4H), 4.42 (dt, *J*=3.9, 8.0 Hz, 2H), 5.22 (d, *J*=7.6 Hz, 2H), 7.12–7.37 (m, 30H), 7.79 (t, *J*=7.8 Hz, 1H), 8.07 (d, *J*=7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 57.2 (one signal missing due to overlap), 59.3, 74.2, 86.6, 126.0, 126.7, 127.2, 128.4, 128.7, 129.4, 137.3, 139.3, 140.7, 147.1, 162.4. HRMS (FAB) *m*/*z* calcd for $C_{53}H_{50}N_5O_2$ $[M+H]^+$: 788.3964, found: 788.3963.

*4.2.5. (4′S,5′S)-2,6-Bis[4′-(pyrrolidine-1″-yl)methyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**1d**)*

Pyrrolidine (178 μL, 2.17 mmol) was added to a solution of **5** (400 mg, 0.54 mmol) in acetonitrile (3 mL) and the solution was stirred at 80 °C for 24 h. The mixture was concentrated and purified by flash chromatography on silica treated with Et_3N (eluent: 2% EtOH in CH_2Cl_2) to yield **1d** (115 mg, 91%) as a slightly yellow solid. Mp 71 °C. $[\alpha]_D^{20}$ +108.2 (*c* 0.90, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 1.72–1.75 (m, 8H), 2.49–2.53 (m, 8H), 2.80 (A part of AB, *J*=8.8, 12.1 Hz, 2H), 2.86 (dd, *J*=5.5, 12.1 Hz, 2H), 4.28 (ddd, *J*=5.5, 7.3, 8.8 Hz, 2H), 5.56 (d, *J*=7.3 Hz, 2H), 7.29–7.37 (m, 10H), 7.90 (t, *J*=7.9 Hz, 1H), 8.22 (d, *J*=7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.7, 54.6, 60.6, 75.0, 86.5, 126.1, 126.2, 128.2, 128.7, 137.5, 140.8, 147.2, 162.4. HRMS (FAB) *m*/*z* calcd for $C_{33}H_{38}N_5O_2$ $[M+H]^+$: 536.3026, found: 536.3068.

*4.2.6. 2,6-Bis((4S,5R)-4-((diphenylphosphoryl)methyl)-5-phenyl-4,5-dihydrooxazol-2-yl)pyridine (**1e**)*

$ClPPh_2$ (180 μL, 1 mmol) and Li (48.58 mg, 7 mmol) were stirred in dry THF (2 mL) under N_2 for 5 h. $LiPPh_2$ solution (816 μL) was added slowly to pybox **5** (100 mg 0.136 mmol) in THF (0.5 mL) and cooled to −78 °C under N_2. After stirring overnight at −78 °C the reaction was quenched with Na_2CO_3 and the solution diluted with CH_2Cl_2. The phases were separated, the organic phase was washed with water and Na_2CO_3, dried over Na_2SO_4, and concentrated under vacuum. The crude mixture was diluted with of CH_2Cl_2 (2.5 mL) and aq H_2O_2 (0.5 mL, 30% w/w) was added. The mixture was stirred for 5 min at rt and then diluted with CH_2Cl_2 and water. The phases were separated, the organic phase was washed twice

with water, dried over Na_2SO_4, and concentrated under vacuum. The residue was chromatographed on deactivated silica (gradient EtOAc to EtOAc/MeOH 95:5) to obtain the product as a beige powder still contaminated with around 10% of diphenylphosphinic oxide. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.61 (ddd, J=10.3, 13.5, 14.7 Hz, 2H), 2.96 (ddd, J=3.5, 7.9, 11.7 Hz, 2H), 4.47–4.52 (m, 2H), 5.86 (d, J=5.7 Hz, 2H), 7.27–7.44 (m, 18H), 7.49–7.53 (m, 4H), 7.72–7.78 (m, 8H), 7.86 (t, J=7.8 Hz, 2H), 8.05 (d, J=7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.1 (d, J=68.7 Hz), 60.4, 70.1, 86.6, 126–132, 137.5, 139.6, 146.8, 162.5; ^{31}P NMR (202 MHz, $CDCl_3$): δ 29.14. HRMS (FAB) m/z calcd for $C_{49}H_{41}N_3O_4P_2Na$ $[M+Na]^+$: 820.2470, found: 820.2478.

4.2.7. (4′S,5′S,2″S)-2,6-Bis[4′-(1″-methyl-pyrrolidine-2″-carboxyl)oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**2**)

Compound **4** (300 mg, 0.70 mmol), compound **6** (198.5 mg, 1.54 mmol), HOBt (226.5 mg, 1.68 mmol), and *N*-methylmorpholine (184 μL, 1.68 mmol) were suspended in DMF (2 mL). EDC·HCl (308.0 mg, 1.61 mmol) was added and the mixture was stirred at rt for 16 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with H_2O (3×20 mL) and brine (20 mL), dried with Na_2SO_4, and purified by flash chromatography on basic Al_2O_3 (eluent: EtOAc) to yield **1e** (303.5 mg, 67%) as a white foam-like substance. $[\alpha]_D^{20}$ −22.7 (*c* 0.26, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69–1.78 (m, 2H), 1.83–1.93 (m, 4H), 2.01–2.12 (m, 2H), 2.28 (dt, J=7.8, 8.8 Hz, 2H), 2.34 (s, 6H), 2.98 (dd, J=6.5, 8.9 Hz, 2H), 3.05–3.12 (m, 2H), 4.38–4.45 (m, 2H), 4.49–4.57 (m, 4H), 5.52 (d, J=7.6 Hz, 2H), 7.29–7.39 (m, 10H), 7.94 (t, J=7.8 Hz, 1H), 8.24 (d, J=7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.3, 29.6, 40.9, 56.3, 65.5, 67.1, 74.1, 84.9, 126.2, 126.4, 128.7, 128.9, 137.6, 139.6, 146.8, 163.2, 173.6. HRMS (FAB) m/z calcd for $C_{37}H_{41}N_5O_6Na$ $[M+Na]^+$: 674.2954, found: 674.3167.

4.2.8. 2,6-Bis((4S,5S)-4-(azidomethyl)-4,5-dihydro-5-phenyloxazol-2-yl)pyridine (**6**)

Compound **5** (200 mg, 0.272 mmol) was dissolved in dry acetonitrile (3 mL). Sodium azide (141.5 mg, 2.177 mmol) was added. The mixture was stirred at 80 °C under N_2 for 24 h. The white precipitate formed was filtered off and the acetonitrile layer was concentrated under vacuum to afford the pure product in quantitative yield as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.53–3.64 (m, 4H), 4.43 (dt, J=5.5, 7.4 Hz, 2H), 5.54 (d, J=7.4 Hz, 2H), 7.34–7.36 (m, 10H), 7.95 (t, J=7.9 Hz, 1H), 8.25 (d, J=7.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.5, 75.2, 85.3, 126.4, 126.9, 129.1, 129.3, 138.0, 139.8, 147.0, 163.9; IR (neat, cm^{-1}): 2909, 2094, 1635, 1459, 1382, 1365, 1358, 1337, 1264, 1110, 1076, 1058, 943, 921, 882, 772, 706, 685, 649, 566. Anal. Calcd for $C_{25}H_{21}N_5O_2$: C, 62.62; H, 4.41; N, 26.29. Found: C, 62.77; H, 4.22; N, 25.57.

4.2.9. Compound **3a**

Compound **7** (100 mg, 0.21 mmol) and diphenylacetylene (149 mg, 0.84 mmol) were mixed in dry toluene (2 mL) and stirred at reflux for 1 week. The solvent was evaporated and the residue was purified by column chromatography (deactivated silica; cyclohexane/EtOAc 3:7) to afford 154 mg of the pure product as a white solid (88% yield). $[\alpha]_{436}^{25}$ +27.3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.43 (ddd, J=4.7, 7.6, 9.8 Hz, 2H), 4.58 (A part of ABX, J=9.8, 13.9 Hz, 2H), 4.73 (B part of ABX, J=4.7, 13.9 Hz, 2H), 5.74 (d, J=7.6 Hz, 2H), 7.00–7.03 (m, 8H), 7.24–7.55 (m, 22H), 7.92 (t, J=7.6 Hz, 1H), 8.12 (d, J=7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.4, 74.5, 85.3, 125.8, 126.3, 126.7, 127.2, 127.7, 128.4, 128.6, 129.3, 129.7, 129.8, 130.6, 134.3, 137.7, 139.0, 144.8, 146.4, 163.1 (1C missing due to overlap); IR (neat, cm^{-1}): 3858, 3822, 1640, 1575, 1456, 1445, 1355, 1239, 1111, 1073, 980, 778, 761, 731, 670. HRMS (FAB) m/z calcd for $C_{53}H_{42}N_9O_2[M+H]^+$: 836.3461, found: 836.3498.

4.2.10. Compound **3b**

Compound **7** (100 mg, 0.21 mmol), CuI (8 mg, 0.04 mmol), and phenylacetylene (46 μL, 0.84 mmol) were mixed in dry toluene (2 mL) and stirred at reflux for 23 h. The white precipitate formed was filtered off and rinsed with toluene to afford 92 mg of the pure product as a white solid (64% yield). Mp 251 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.71 (dt, J=7.9, 5.4 Hz, 2H), 4.84 (d, J=5.4 Hz, 4H), 5.61 (d, J=7.9 Hz, 2H), 7.14–7.40 (m, 16H), 7.76 (d, J=7.0 Hz, 4H), 7.89 (t, J=7.9 Hz, 1H), 7.99 (s, 2H), 8.12 (d, J=7.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.9, 75.2, 84.9, 121.5, 126.2, 126.4, 126.9, 128.6, 129.2, 129.4, 130.8, 138.4, 138.9, 146.7, 148.6, 164.0 (1C missing due to overlap); IR (neat, cm^{-1}): 3550, 3485, 3408, 3120, 3086, 3032, 1631, 1574, 1465, 1441, 1363, 1325, 1223, 1199, 1077, 955, 919, 763, 695, 619; HRMS (FAB^+) calcd for $C_{41}H_{33}N_9O_2$: 684.2848, found: 684.2835.

4.2.11. 7,16-Bis(4-bromobenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**8**)

Bromobenzylchloride (452 mg, 2.2 mmol) in acetonitrile (2.5 mL) was added dropwise to a mixture of diaza-18-crown-6 (262.34 mg, 1 mmol) and Na_2CO_3 (530 mg, 5 mmol) in dry acetonitrile (2.5 mL) under N_2 at rt. The reaction mixture was stirred at 90 °C for 19 h. After cooling the reaction mixture was filtered. The filtrate was concentrated and the residue redissolved in CH_2Cl_2 (20 mL). The organic phase was washed with water (3×20 mL), dried over $MgSO_4$, and concentrated to afford the pure product as white crystals in 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.78–2.80 (m, 8H), 3.59–3.61 (m, 16H), 3.63 (s, 4H), 7.22 (d, J=8.3 Hz, 4H), 7.40 (d, J=8.3 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 53.8, 59.3, 70.1, 70.8, 120.5, 130.5, 131.2, 139.0. HRMS (FAB) m/z calcd for $C_{26}H_{37}N_2O_4$ $[M+H]^+$: 599.1120, found: 599.1143.

4.2.12. Compound **9**

To a mixture of $Pd(PPh_3)_2Cl_2$ (5.62 mg, 0.008 mmol), PPh_3 (4.45 mg, 0.017 mmol), and CuI (3.17 mg, 0.017 mmol) in freshly distilled Et_3N (1 mL) was added compound **8** (100 mg, 0.167 mmol) followed by trimethylsilylacetylene (92 μL, 0.666 mmol). The reaction mixture was stirred under N_2 at 80 °C for 24 h. The reaction mixture was cooled, diluted with CH_2Cl_2, washed three times with water, dried over $MgSO_4$, and concentrated to yield **9**, which was used in the following step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.24 (18H), 2.78–2.80 (m, 8H), 3.58–3.60 (m, 16H), 3.66 (s, 4H), 7.27 (d, J=8.30 Hz, 4H), 7.39 (d, J=8.3 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 0.00, 53.9, 59.8, 70.1, 70.7, 93.7, 105.2, 121.5, 128.6, 131.8, 140.5.

4.2.13. Compound **10**

TBAF (0.67 mL of 1 M solution in THF, 0.67 mmol) and a drop of water were added to the crude compound **9** (0.167 mmol) in THF (1 mL). The mixture was stirred violently at rt for 2.5 h. The solvent was removed and the residue was diluted with CH_2Cl_2, washed three times with water, dried over $MgSO_4$, and concentrated under vacuum. The product was purified by column chromatography (basic Al_2O_3; EtOAc/hexane 3:7) to afford the pure product as a beige solid in 72% yield over two steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.79–2.82 (m, 8H), 3.05 (s, 2H), 3.59–3.62 (m, 16H), 3.68 (s, 4H), 7.31 (d, J=8.1 Hz, 4H), 7.43 (d, J=8.1 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 53.9, 59.8, 70.1, 70.8, 83.8, 120.5, 128.7, 132.0, 141.0 (1C missing). HRMS (FAB) m/z calcd for $C_{30}H_{39}N_2O_4$ $[M+H]^+$: 591.2910, found: 591.2878.

4.2.14. Macrocycle **3c**

2,6-Bis((4*S*,5*S*)-4-(azidomethyl)-4,5-dihydro-5-phenyloxazol-2-yl)pyridine (**7**) (119.9 mg, 0.25 mmol), compound **10** (122.7 mg, 0.25 mmol), CuI (4.76 mg, 0.025 mmol), and DIPEA (435 μL, 2.50 mmol) were dissolved in 5 mL of CH_2Cl_2 and acetonitrile

(40 mL) was rapidly added. This mixture was stirred for 2 days at rt under N_2. The solid formed was separated by filtration. The acetonitrile layer was concentrated under vacuum and the residue chromatographed on deactivated silica with a gradient CH_2Cl_2 to CH_2Cl_2/MeOH 9:1 to afford the pure product as a white powder in 21% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.79–2.81 (m, 8H), 3.59–3.63 (m, 16H), 3.73–2.74 (m, 4H), 4.69 (ddd, J=3.2, 4.7, 8.5 Hz, 2H), 4.80 (A part of ABX, J=4.7, 14.3 Hz, 2H), 4.92 (B part of ABX, J=3.2, 14.3 Hz, 2H), 5.50 (d, J=8.5 Hz, 2H), 7.36–7.41 (m, 14H), 7.67 (d, J=8.2 Hz, 4H), 7.84 (t, J=7.9 Hz, 1H), 7.94 (s, 2H), 8.03 (d, J=7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 51.9, 59.5, 54.1, 69.9, 70.8, 74.8, 83.6, 121.2, 125.6, 126.3, 126.5, 129.0, 129.2, 137.8, 138.4, 146.5, 148.1, 163.7 (3C missing). HRMS (FAB) m/z calcd for $C_{55}H_{60}N_{11}O_6$ $[M+H]^+$: 970.4728, found: 970.4725.

Acknowledgements

This work was supported by the Swedish Natural Science Research Council, the Swedish Foundation for Strategic Research, by the CNRS Région Haute-Normandie and by EGIDE—Programme Lavoisier of the French Foreign Ministry. Grants from Alliance Française and the Swedish Chemical Society made a stay by A.F. in Rouen possible.

Supplementary data

^{1}H and ^{13}C NMR spectra of **1a–e**, **2**, **5**, **6**, and **3a–c** and ^{31}P NMR spectrum of **1e** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.016.

References and notes

1. Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865–1882.
2. (a) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511–524; (b) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393–406.
3. Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857–871.
4. (a) Kanemasa, S.; Ito, K. *Eur. J. Org. Chem.* **2004**, 4741–4753; (b) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566–4583; (c) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491–1508; (d) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655–663.
5. (a) Börner, A.; Ward, J.; Kortus, K.; Kagan, H. B. *Tetrahedron: Asymmetry* **1993**, *4*, 2219–2228; (b) Fields, L. B.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1993**, *4*, 2229–2240; (c) Cernerud, M.; Wärnmark, K.; Moberg, C. *Tetrahedron Lett.* **1994**, *35*, 5473–5476; (d) Bourguignon, J.; Bremberg, U.; Dupas, G.; Hallman, K.; Hagberg, L.; Hortala, L.; Levacher, V.; Lutsenko, S.; Macedo, E.; Moberg, C.; Quéguiner, G.; Rahm, F. *Tetrahedron* **2003**, *59*, 9583–9589.
6. Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269–279.
7. (a) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668–12669; (b) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781–3784.
8. Takeuchi, K.; Takeda, T.; Fujimoto, T.; Yamamoto, I. *Tetrahedron* **2007**, *63*, 5319–5322.
9. (a) Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1–C3; (b) Brunner, H.; Obermann, U.; Wimmer, P. *Organometallics* **1989**, *8*, 821–826; (c) Brunner, H.; Kagan, H. B.; Kreutzer, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2177–2187.
10. (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005–6008; (b) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728–729; (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726–728.
11. (a) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846–848; (b) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119–3154.
12. (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566–568; (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769–1772; (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149–3150; (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.
13. Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1604–1609.
14. Hallman, K.; Frölander, A.; Wondimagegn, T.; Svensson, M.; Moberg, C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5400–5404; Similar processes were studied by Balavoine and co-workers but their interpretation of the results is different from the one provided by us: Hoarau, O.; Aït-Haddou, H.; Daran, J.-C.; Cramailère, D.; Balavoine, G. G. A. *Organometallics* **1999**, *18*, 4718–4723; Aït-Haddou, H.; Hoarau, O.; Cramailére, D.; Pezet, F.; Daran, J.-C.; Balavoine, G. G. A. *Chem.—Eur. J.* **2004**, *10*, 699–707.
15. Frölander, A.; Lutsenko, S.; Privalov, T.; Moberg, C. *J. Org. Chem.* **2005**, *70*, 9882–9891.
16. Desimoni, G.; Faita, G.; Guala, M.; Laurenti, A.; Mella, M. *Chem.—Eur. J.* **2005**, *11*, 3816–3824.
17. For a review on 'click chemistry', see: Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68.
18. Aurelio, L.; Box, J. S.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, M. M. *J. Org. Chem.* **2003**, *68*, 2652–2667.
19. Lundgren, S.; Wingstrand, E.; Moberg, C. *Adv. Synth. Catal.* **2007**, *349*, 364–372.
20. Tilliet, M.; Lundgren, S.; Moberg, C.; Levacher, V. *Adv. Synth. Catal.* **2007**, *349*, 2079–2084.