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The stereodivergent synthesis of chiral 4,5-disubstituted pybox ligands

Giovanni Desimoni,* Giuseppe Faita, Matilde Guala and Carmela Pratelli

Department of Organic Chemistry, University of Pavia-Viale Taramelli, 10-I-27100 Pavia, Italy

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Abstract—(1*R*,2*S*)-2-Amino-1,2-diphenylethanol and (1*R*,2*S*)-norephedrine are synthons for the stereodivergent syntheses of pybox ligands. The *trans*-isomers have been synthesised previously from the corresponding bis-amides derived from pyridine-2,6-dicarbonyl dichloride, the *cis*-4,5-disubstituted isomers are prepared for the first time from the same aminols and dimethyl pyridine–2,6-dicarboximidate. This protocol is also suitable for the synthesis of pybox derived from (*S*)-methioninol and (2*S*)-2-amino-2-(2′-naphthyl)ethanol.

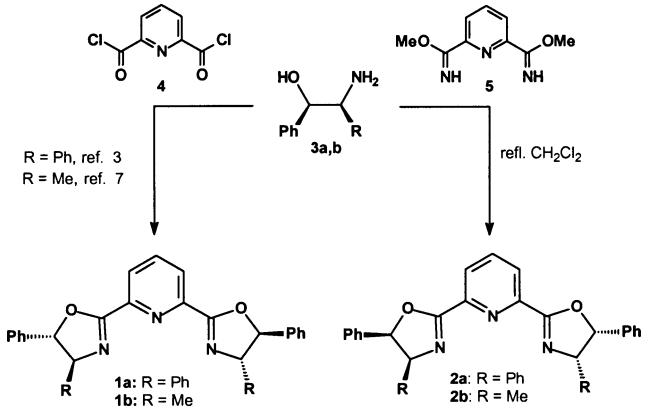
1. Introduction

Chiral pyridine-2,6-bis(oxazolines) (pyboxs) have proved useful as ligands for the preparation of catalysts for enantioselective reactions.[1] They differ from (2,2′-bisoxazoline)alkanes (box) in their behaviour as tridentate versus bidentate ligands in coordination with cationic centres,[2] and the involvement of three versus two nitrogen atoms increases the rigidity of the resulting complex with a better stereochemical outcome of the asymmetric catalysis.

In general, pybox ligands have a single substituent at the 4-position of the oxazoline ring, since it is closer to the cationic centre involved in the formation of the complex, and this is considered to have a strong influence on the stereoselectivity of the catalysed reaction. This is certainly true, but recently our group synthesised 2,6-bis[(4*S*,5*S*)-diphenyl-1,3-oxazolidin-2-yl]-pyridine **1a** [as well as its (4*R*,5*R*)-enantiomer (*enant*-**1a**)], with the phenyl groups *trans* to each other, which was found to be an excellent ligand for the preparation of catalysts for enantioselective Mukaiyama–Michael[3] and *exo*-Diels–Alder[4] reactions with alkenoyl-1,3-oxazolidin-2-ones as reacting substrates. These reactions emphasised the role of the substituent in position 5, suitably placed to block a single face of the coordinated reagent, and induce enantioselectivity. For this reason we aimed to synthesise 2,6-bis[(4*S*,5*R*)-diphenyl-1,3-oxazolidin-2-yl]-pyridine **2a** (the *cis*-pybox isomer of **1a**) for use as a further tool to test the influence of the substituent in position 5 on the stereoselectivity (Scheme 1).

2. Results and discussion

A pybox with a structure reported to be **2a** has already been described in the literature,[5] but all physical and spectroscopic data (mp, $[\alpha]_D$, ^{1}H NMR)[5b] were the same as reported for *enant*-**1a**.[3] Furthermore, the protocol for the preparation of the supposed **2a** reported the reaction of (1*S*,2*R*)-2-amino-1,2-diphenylethanol *enant*-**3a** with pyridine-2,6-dicarbonyl dichloride **4**, the mixture was treated first with $SOCl_2$, then with NaH to



Scheme 1.

* Corresponding author. Tel.: +39-0382-507313; fax: 39-0382-507323; e-mail: desimoni@chifis.unipv.it

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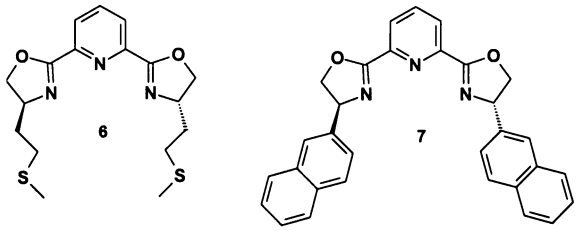
effect ring closure (ex-post with inversion of configuration).[5b] This sequence was very similar to the one reported for **1a**, but none of the intermediates described in the synthesis of the *trans* pybox (bis-amide, dichloride), together with the crystal structure of its lanthanum triflate complex,[3] were isolated in the supposed synthesis of *cis*-**2a**.

Several preparations of pybox ligands have been reported in the literature,[6] all suitable for the synthesis of 4-substituted derivatives. When these protocols were applied to the synthesis of 4,5-disubstituted pybox, even those effecting the conversion of the bis-amide under relatively weak conditions (120°C, $BF_3{\cdot}Et_2O$), gave ring closure with inversion of configuration and the bis-amide derived from (1*R*,2*S*)-norephedrine, gave the *trans*-pybox **1b**.[7]

Recently Müller and Bolèa[8] observed that diimidate **5**, derived from pyridine-2,6-dicarbonitrile, could be condensed with aminols in refluxing CH_2Cl_2 to afford pybox ligands in good yields. The only 4,5-disubstituted pybox synthesised with this protocol had a *trans* configuration, but this product simply retained the configuration of the starting aminol. Hence, dimethyl pyridine–2,6-dicarboximidate **5** was prepared[8] and this was heated under reflux in CH_2Cl_2 with 2 equiv. of **3a**. After 4 days, when the starting material had disappeared, the solvent was removed and the residue, worked up as described in Section 4, gave 2,6-bis[(4*S*,5*R*)-diphenyl-1,3-oxazolin-2-yl]pyridine **2a** in 75% yield, crystallised from ethyl acetate (Scheme 1). The same reaction starting from (1*S*,2*R*)-2-amino-1,2-diphenylethanol *enant*-**3a** afforded *enant*-**2a**. The analytical and spectral data of both enantiomers are reported in Section 4.

To test the limitations of this method, the same reaction was run with (1*R*,2*S*)-norephedrine **3b**, the same aminol that gave *trans*-pybox **1b**.[7] Again *cis*-2,6-bis[(4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolin-2-yl]pyridine **2b** was formed exclusively. A comparison of this pybox with a commercial sample of **1b**, nicely showed the clear difference between these two products.

The flexibility of the Müller–Bolèa protocol suggested to test it in the syntheses of two 4-substituted pybox ligands derived one from (*S*)-methioninol and the other from (2*S*)-2-amino-2-(2′-naphthyl)ethanol,[9] the latter one being impossible to be obtained at a satisfactory degree of purity by the typical bis-amide/dichloride method.[10] Both aminols reacted with **5** to give the two new pybox chiral ligands reported in Scheme 2: 2,6-bis[(4*S*) - 4 - (1 - methylthio)ethyl - 1,3 - oxazolin - 2 - yl]-pyridine **6** and 2,6-bis[(4*S*)-4-(2′-naphthyl)-1,3-oxazolin-2-yl]pyridine **7**, obtained in satisfactory overall yields.



Scheme 2.

3. Conclusion

We have reported a new application of a known procedure for the stereoselective synthesis of new chiral pybox ligands. These ligands represent basic structures to build new catalysts whose efficiency will be compared to that of catalysts already in use, having either the same substituents (but with different configuration on the oxazolidine ring), different substituents behaving as potential auxiliary ligands,[11] or substituents with less efficient shielding effects.[9] Their screening in enantioselective catalytic reactions is now under investigation.

4. Experimental

4.1. General method and materials

Melting points were determined by the capillary method and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, on a Bruker AC300 spectrometer; IR spectra were recorded on a Perkin–Elmer FT-IR Paragon 1000 spectrophotometer; optical rotations were measured at room temperature on a Perkin–Elmer 241 polarimeter with a 1 dm cell. Dichloromethane was the hydrocarbon-stabilised Aldrich ACS grade, distilled from calcium hydride and used immediately. Pyridine-2,6-dicarbonitrile, (1*R*,2*S*)-2-amino-1,2-diphenyl-ethanol **3a**, (1*S*,2*R*)-2-amino-1,2-diphenyl-ethanol *enant*-**3a**, (1*R*,2*S*)-norephedrine **3b**, (*S*)-methioninol and 2,6-bis[(4*S*,5*S*)-4-methyl-5-phenyl-1,3-oxazolin-2-yl]pyridine **1b** were commercial Aldrich products.

4.2. Synthesis of pybox ligands

4.2.1. Dimethyl pyridine-2,6-dicarboximidate, 5. This compound was prepared as described in the literature[8] and it was used without any further purification.

4.2.2. 2,6-Bis[(4*S*,5*R*)-diphenyl-1,3-oxazolin-2-yl]pyridine, 2a. A suspension of dimethyl pyridine-2,6-dicarboximidate **5** (0.265 g, 1.37 mmol) and (1*R*,2*S*)-2-amino-1,2-diphenylethanol **3a** (0.585 g, 2.75 mmol) in dichloromethane (15 mL) was heated under reflux with stirring for 4 days. The solvent was removed and the residue solidified when treated with methanol. The mixture was filtered, and the solid (crude **2a**) washed with water and then with methanol, then recrystallised from ethyl acetate to afford **2a** as a white crystalline solid (0.53 g, 75%): mp 225–226°C; $[\alpha]_D = -305$ (*c* 0.5 in chloroform). {2,6-Bis[(4*R*,5*S*)-diphenyl-1,3-oxazolin-2-yl]pyridine ***enant*-2a** has $[\alpha]_D = +305$ (*c* 0.5 in chloroform)}. HPLC analysis on CHIRALPAK AD column with hexane/2-propanol (2/1) as eluent (0.7

mL min^{-1}): the (4*S*,5*R*)-diphenyl pybox **2a** has $t_R = 31.7$ min; the (4*R*,5*S*) enantiomer has $t_R = 36.5$ min. IR (Nujol) ν 1664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ 5.86 (d, ^3J(H,H) = 10.3 Hz, 2H; CHN); 6.16 (d, ^3J(H,H) = 10.3 Hz, 2H, CHO); 6.95–7.10 (m, 20 H); 8.06 (t, ^3J(H,H) = 8.1 Hz, 1H, 4H pyridine); 8.45 (d, ^3J(H,H) = 8.1 Hz, 2H, 3,5H pyridine); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 74.8 (CHN oxazolidine), 86.8 (CHO oxazolidine), 126.8, 127.0 (C3 pyridine), 127.5, 127.7, 127.9, 128.0, 128.1, 128.3, 136.4, 137.6 (C4 pyridine), 138.1, 147.5 (C2 pyridine), 164.5 (C=N oxazolidine); elemental analysis calcd (%) for $C_{35}H_{27}N_3O_2$ (521.6) C, 80.59; H, 5.22; N, 8.06; found C, 80.73; H, 5.18; N, 7.98.

4.2.3. 2,6-Bis([(4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolin-2-yl]pyridine, 2b. A suspension of **5** (0.386 g, 2.00 mmol) and (1*R*,2*S*)-norephedrine **3b** (0.600 g, 4.00 mmol) in dichloromethane (20 mL) was heated under reflux for 5 days. After removal of the solvent, methanol was added to the residue and the white solid was filtered, washed and dried. The (4*S*)-methyl-(5*R*)-phenylpybox **2b** (0.686 g, 86%) was pure enough to be used without any further purification: mp = 176–177°C; $[\alpha]_D = -433$ (*c* 0.5 in chloroform). HPLC analysis on CHIRALPAK AD column with hexane/2-propanol (80/20) as eluent (1 mL min^{-1}): $t_R = 17.2$ min. IR (Nujol) ν 1672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ 0.95 (d, ^3J(H,H) = 7.0 Hz, 6H, CH_3); 4.77 (dq, ^3J(H,H) = 7.0, 9.9 Hz, 2H, CH-Me); 5.85 (d, ^3J(H,H) = 9.9 Hz, 2H, CH-Ph); 7.28–7.41 (m, 10 H); 7.94 (t, ^3J(H,H) = 7.8 Hz, 1H, 4H pyridine); 8.18 (d, ^3J(H,H) = 7.8 Hz, 2H, 3,5H pyridine); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.1 (CH_3), 65.1 (CHN oxazoline), 84.7 (CHO oxazoline), 125.2 (C3 pyridine), 125.8, 127.6, 127.8, 135.9, 137.2 (C4 pyridine), 146.4 (C2 pyridine), 161.5 (C=N oxazoline); elemental analysis calcd (%) for $C_{25}H_{23}N_3O_2$ (397.5) C, 75.54; H, 5.83; N, 10.57; found C, 75.68; H, 5.92; N, 10.71.

4.2.4. 2,6-Bis[(4*S*)-4-(1-methylthio)ethyl-1,3-oxazolin-2-yl]pyridine, 6. From a suspension of **5** (0.280 g, 1.45 mmol) and (*S*)-methioninol (0.390 g, 2.90 mmol) in dichloromethane (13 mL) heated under reflux for 5 days and worked up as previously described, **6** was obtained as white crystals from cyclohexane (0.36 g, 74%). mp = 59–60°C; $[\alpha]_D = -165$ (*c* 0.5 in chloroform). HPLC analysis on CHIRALPAK AD column with hexane/2-propanol (80/20) as eluent (1 mL min^{-1}), t_R = 26.2 min. IR (Nujol) ν 1676 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ 1.91 and 2.03 (m+m, 2H+2H, C-CH_2-C); 2.15 (s, 6H, CH_3); 2.71 (m, 4H, SCH_2); 4.17 (t, ^3J(H,H) = 8.1 Hz, 2H, CHO); 4.50 (m, 2H, CHN); 4.65 (dd, ^3J(H,H) = 8.1, 9.6 Hz, 2H, CHO); 7.90 (t, J = 7.8 Hz, 1H, 4H pyridine); 8.18 (d, ^3J(H,H) = 7.8 Hz, 2H, 3,5H pyridine); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.1 (CH_3-S), 30.3 (CH_2-S), 34.8 (C-CH_2-C), 65.5 (CHN oxazolidine), 72.7 (CHO oxazolidine), 125.3 (C3 pyridine), 137.0 (C4 pyridine), 146.2 (C2 pyridine), 162.0 (C=N oxazolidine); elemental analysis calcd (%) for $C_{17}H_{23}N_3O_2S_2$ (365.5) C, 55.86; H, 6.34; N, 11.50; found C, 56.04; H, 6.28; N, 11.67.

4.2.5. 2,6-Bis[(4*S*)-4-(2′-naphthyl)-1,3-oxazolin-2-yl]-pyridine, 7. From a suspension of **5** (0.168 g, 0.87 mmol) and (2*S*)-2-amino-2-(2′-naphthyl)ethanol[9] (0.326 g, 1.74 mmol) in dichloromethane (9 mL) heated under reflux for 6 days and worked up as previously described, **7** was obtained as white crystals from methanol (0.173 g, yield 43%). mp = 202–203°C; $[\alpha]_D = -289$ (*c* 0.5 in chloroform). HPLC analysis on CHIRALPAK AD column with hexane/2-propanol (2/1) as eluent (1 mL min^{-1}), $t_R = 31.7$ min. IR (Nujol) ν 1631 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ 4.54 (t, ^3J(H,H) = 8.6 Hz, 2H, CHN); 5.03 (dd, ^3J(H,H) = 8.6, 10.3 Hz, 2H, CHO); 5.68 (dd, ^3J(H,H) = 8.6, 10.3 Hz, 2H, CHO); 7.43–7.54 (m, 6H); 7.84–7.90 (m, 8H); 7.98 (t, ^3J(H,H) = 7.9 Hz, 1H, 4H pyridine); 8.42 (d, ^3J(H,H) = 7.9 Hz, 2H, 3,5H pyridine); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 70.0 (CHN oxazolidine), 75.0 (CHO oxazolidine), 124.2, 125.2, 125.5, 125.8, 126.0, 127.2 (C3 pyridine), 127.5, 128.4, 132.5, 133.0, 137.0 (C4 pyridine), 138.5, 146.4 (C2 pyridine), 163.2 (C=N oxazolidine); elemental analysis calcd (%) for $C_{31}H_{23}N_3O_2$ (469.5) C, 79.30; H, 4.94; N, 8.95; found C, 79.42; H, 4.99; N, 8.85.

Acknowledgements

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10. When (2*S*)-2-amino-2-(2′-naphthyl)ethanol (2 equiv.) was made to react with **4** (1 equiv.) in CH_2Cl_2, 2,6-

bis[(1*S*)*N*,*N*′-2-hydroxy-1-(2′-naphthyl)ethyl]pyridinedicarboxamide was obtained {mp 259–260°C from ethyl acetate, $[\alpha]_D = -169$ (*c* 0.8 in chloroform), ^1H and ^{13}C NMR data are fully consistent with the structure}. This product was converted, as described in Ref. 3, into 2,6-bis[(1*S*)*N*,*N*′-2-chloro-1-(2′-naphthyl)ethyl]pyridine–dicarboxamide in 56% yield after column chromatographic purification {mp 229–230°C from methanol, $[\alpha]_D = -157$ (*c* 0.5 in chloroform), ^1H and ^{13}C NMR fully consistent with the structure}. Ring-closure under basic conditions[3] was difficult since intermediate products and degradation by-products were often obtained. When **7** was isolated, the ^1H NMR spectrum was identical to that described above, but the product was a near-racemic mixture.

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