Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 22, pp. 3755–3764, 1997

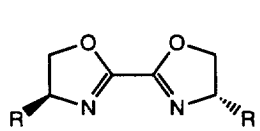
Printed in Great Britain
PII: S0957-4166(97)00499-0 0957-4166/97 $17.00 – 0.00

New homochiral bis(oxazoline) ligands for asymmetric catalysis

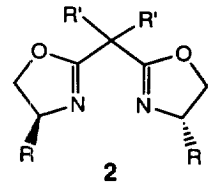
O. Hoarau, H. Aït-Haddou*, M. Castro and G. G. A. Balavoine* *
Laboratoire de Chimie de Coordination, CNRS, 205 rte de Narbonne, 31077 Toulouse Cedex, France

Abstract: Several homochiral bis(oxazolines), with asymmetric centers on the oxazoline rings and on the side chains, were prepared from (1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol in high yields. Asymmetric cyclopropanation of styrene with ethyl diazoacetate in the presence of 1 mol% of copper(I) triflate and the dibenzoyl bis(oxazoline) **5a**, gave ethyl 2-phenylcyclopropanecarboxylate in up to 85% ee. The same ligand **5a**, was used in the palladium catalysed enantioselective allylic substitution of the 1,3-diphenyl-2-propenyl acetate to give the desired product in up to 90% ee. © 1997 Elsevier Science Ltd

Catalytic enantioselective transformations have been the subject of numerous research efforts in recent years, and a variety of efficient chiral catalysts for different organic reactions have been introduced.[1] In particular, since the first reports by Brunner[2] and our group[3] the use of oxazolines as chiral ligands in asymmetric catalysis has been extensively developed.[4]



1



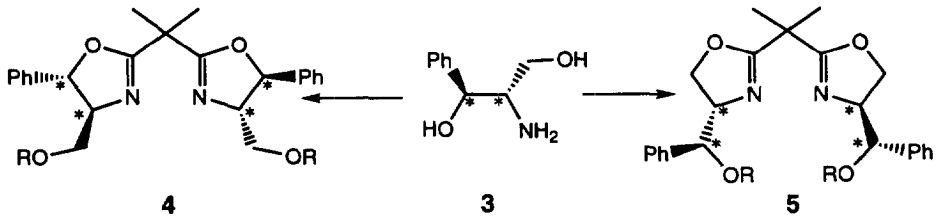
2

It is now recognised that chiral bis(oxazoline) ligands such as **1** and **2** have high synthetic potential owing to (i) their easy access from readily available chiral amino alcohols, (ii) the high enantioselectivity generally obtained in catalysis, and (iii) the enhanced reactivity of the metal catalysts in asymmetric transformations. For example, enantioselective cyclopropanation and aziridination,[5] hydrosilylation[6] and transfer hydrogenation of ketones,[7] Diels–Alder[8] cycloaddition, allylic alkylation reactions,[9] aldol additions of silylketene acetals to (benzyloxy)acetaldehyde,[10] and enantioselective copolymerization of *tert*-butylstyrene with carbon monoxide[11] have been reported to proceed with remarkably high levels of enantioselectivity. Herein, we report the synthesis of new bis(oxazoline) ligands **5** starting from the readily available and inexpensive (1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol **3** and the preliminary results obtained in catalytic asymmetric synthesis.

Recently, Pfaltz[9c] has reported the use of the bis(oxazoline) **4**, prepared from the (1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol **3**, in asymmetric palladium-catalyzed allylic alkylation (Scheme 1). With the chiral bis(oxazoline) **4** (R=$SiMe_2tBu$) the palladium complex was found to be the most efficient catalyst for the reaction of allylic acetates, such as 1,3-diphenyl-2-propenyl acetate, with dimethyl malonate (97% ee).

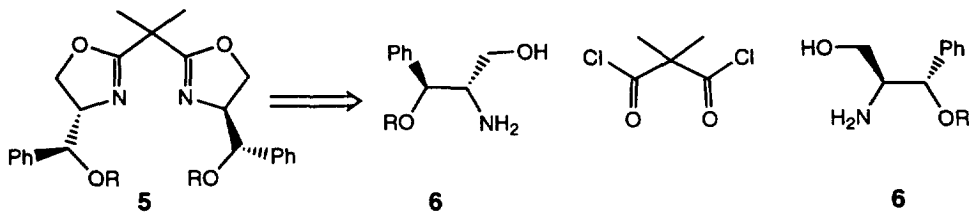
As part of ongoing work towards controlling the enantioselectivity of catalytic processes by using new C_2-asymmetric ligands, we have developed an efficient synthesis of new bis(oxazoline) ligands **5**, starting from **3**.[12] The oxazoline ring of **5** is formed after cyclisation involving the primary hydroxy group of **3**. The main features of this new kind of ligand is the presence of an asymmetric center on the side chains, with the possibility to adjust the steric and the electronic effect by changing the nature of the R group in order to fit the specific requirement of a particular reaction.

* Corresponding author. Email: balavoin@lcc-toulouse.fr



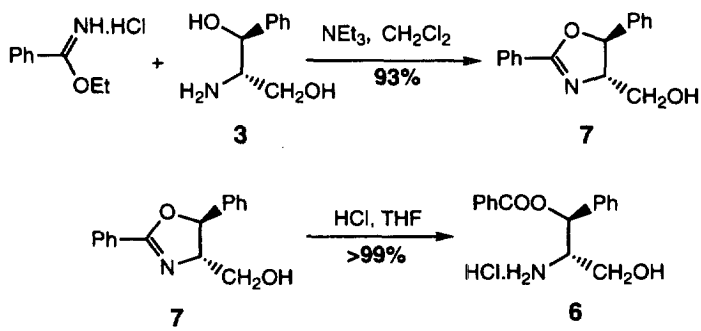
Scheme 1.

Several methods are reported for the preparation of oxazolines.[13] By using the amino diol **3**, the condensation with an imidate derivative of a carboxylic acid occurs selectively on the secondary hydroxy group.[3,13] Other methods involve a three step procedure, starting with hydroxy amide by condensation of acyl chloride and amino alcohols followed by activation of the hydroxy group and treament under basic conditions to produce the cyclisation. The application of this three step procedure to the amino diol **3** with 2,2-dimethylpropane-1,3-dioyl chloride yielded the mixture of products and the desired bis(oxazoline) **5** (R=H) was obtained in all cases in only 15–20% yield.[14] According to these results we turned to an alternative approach which is based on the synthesis of the monoprotected aminodiol **6** (Scheme 2).



Scheme 2.

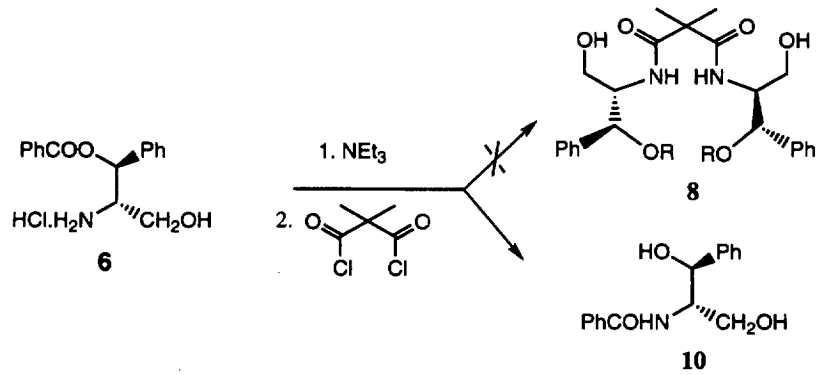
Starting from the amino diol **3** the selective protection of the secondary alcohol was carried out in two steps (Scheme 3). The oxazoline **7** was prepared as described[15] from the amino diol **3** and ethyl benzimidate with 94% isolated yield. The selective cleavage of the oxazoline ring by known methods[16] led to the amino ester hydrochloride **6** in quantitative yield.



Scheme 3.

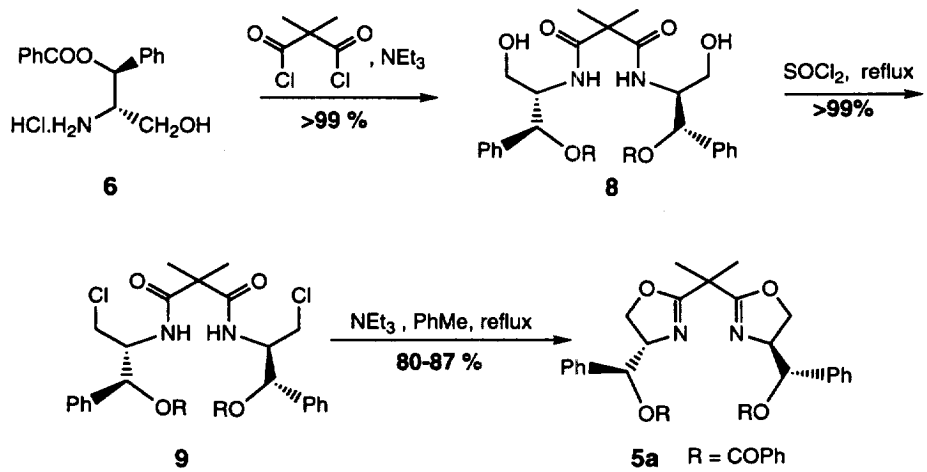
The use of classic conditions for the preparation of the diamide **8** which consist of combining **6** with 4 equivalents of triethylamine in dichloromethane at 0°C and slow addition of the 2,2-dimethylpropane-1,3-dioyl chloride (Scheme 4), yields exclusively the N-acyl diol **10**.

Such a reaction has been previously observed by Meyers in the case of the methyl ether of **6** in the presence of sodium bicarbonate.[17] This problem was solved by the addition of a mixture of 2,2-dimethylpropane-1,3-dioyl chloride and triethylamine to a suspension of monoprotected aminodiol **6**



Scheme 4.

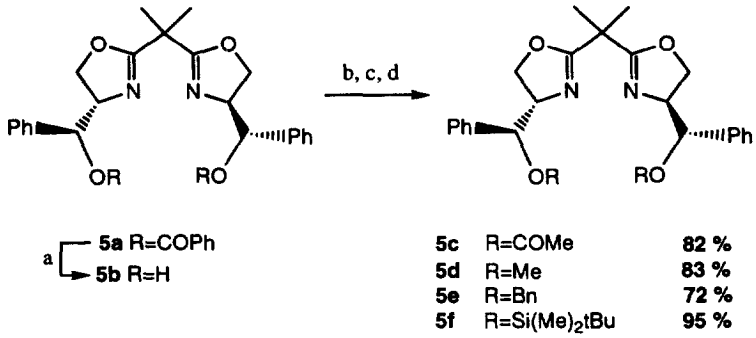
in dichloromethane at 0°C. This procedure resulted in the formation of **8** in excellent yield (Scheme 5). Diamide **8** was converted quantitatively to **9** by reaction with an excess of distilled $SOCl_2$ at reflux for 4 h. Reaction of the diamide **9** with 10 equivalents of triethylamine in toluene at reflux for 12 h using the conditions recently described by Denmark,[18] followed by extractive isolation and purification by chromatography (deactivated alumina, ethyl acetate:pentane=20:80) afforded **5a** as a white crystalline powder in a good overall yield.



Scheme 5.

Subsequent alkaline hydrolysis of **5a** produced the dihydroxy bis(oxazoline) **5b** in excellent yield. From this common intermediate, a large variety of chiral bis(oxazolines) can be obtained in high yield. As shown in the Scheme 6, the dihydroxy ligand **5b**, was transformed to its corresponding methyl ester (**5c**), methyl (**5d**), benzyl (**5e**) and silyl ether (**5f**) in good yield.

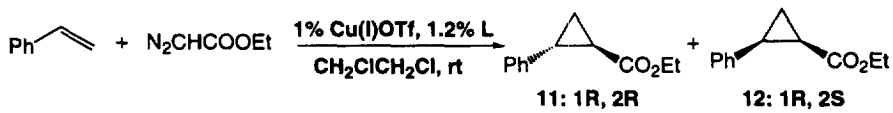
The ability of these new bis(oxazoline) ligands **5a–f** to provide asymmetric induction in metal-catalysed reactions was explored. We first examined copper-catalysed cyclopropanation of styrene with ethyl diazoacetate, which is the reaction most often studied with chiral oxazoline ligands. The asymmetric cyclopropanation was carried out in dichloroethane in the presence of 1 mol% of copper(I) catalyst generated *in situ* by mixing $CuOTf \cdot 0.5C_6H_6$[19] with the ligands, according to Evans' procedure. Ethyl 2-phenylcyclopropane-1-carboxylate was obtained as a mixture of *trans* and *cis* isomers (Scheme 7). The ratio of *trans/cis* isomers was determined by ^1H NMR and the enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Pharmacir 7C;



a) 1% NaOH in MeOH at rt; b) Acetic anhydride, DMAP, Et_3N in CH_2Cl_2 at 0 °C (5c);
c) NaH, MeI for (5d) and $PhCH_2Br$ for (5e) in THF; d) $tBuSi(Me)_2Cl$, Imidazole in DMF at rt (5f).

Scheme 6.

*i*PrOH:hexane=1:99). The absolute stereochemistry of the product was assigned to be (1R,2R) for the *trans*-**11** and (1R,2S) for the *cis*-**12** by measurement of the specific rotations and comparison with the literature values.[5b] The representative results are summarized in Table 1.



Scheme 7.

The levels of ee obtained so far are modest in comparison to the best literature values.[5,20] The most promising ligands were the diester derivative **5a**, and the dihydroxy **5b**, which gave the product in good yields and good to moderate enantiomeric excesses. The reaction using **5c** resulted in a dramatic lowering in enantioselectivity due to the instability of this ligand in the reaction conditions. The reaction using the diether ligands **5d–f**, (entries 4, 5 and 6) showed relatively poor asymmetric induction as compared with the dihydroxy ligand **5b**. These intriguing results could be explained by the formation, in the case of the diether ligands, of a mixture of catalytic species resulting probably from the coordination by the oxygen and the nitrogen atoms.[21]

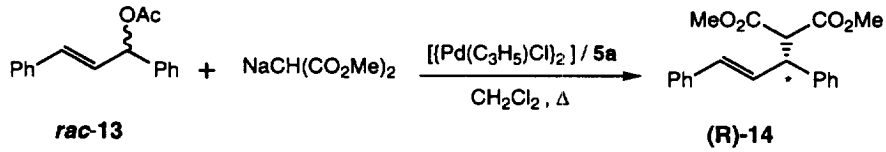
These preliminary results led us to explore the palladium catalyzed allylic alkylation which is the most asymmetric reaction available for C–C bond formation.[9c,22] This reaction (Scheme 8) involves nucleophilic attack by the malonate anion on a (distorted) square-planar complex formed from the chiral ligand, Pd(II), and racemic 1,3-biphenyl-2-propenyl acetate.

Our first study was concentrated on the use of the bis(oxazoline) **5a**, as a chiral ligand in this transformation. The catalytic process was initiated by addition of a mixture of 1% of allylic palladium

Table 1. Enantioselective cyclopropanation of styrene with ethyl diazoacetate according to Scheme 7

Entry	Ligand	Yield(%)[a]	*trans* : *cis*[b]	e.e.% *trans* (11)[c]	e.e.% *cis* (12)[c]
1	**5a**	83	62 : 38	75	85
2	**5b**	70	75 : 25	69	66
3	**5c**	85	70 : 30	18	17
4	**5d**	69	71 : 29	36	28
5	**5e**	91	65 : 35	57	51
6	**5f**	85	66 : 34	64	60

[a] Isolated yield after chromatography. [b] Determined by ^{1}HNMR. [c] Determined by HPLC analysis using a chiral column (Pharmacir 7C).



Scheme 8.

chloride dimer, 2% of chiral bis(oxazoline) and allylic acetate **13**, to a solution of sodium malonate in dichloromethane at 36°C. Under these conditions, the allylic acetate **13** was smoothly converted after 24 h to the desired product (R)-**14**, in essentially quantitative yield and in 90% ee.[23] The approach of the nucleophile is anti with respect to the palladium, and the attack is on the less-hindered terminus carbon of the π-allyl system. With oxazoline ligands attack at the other terminus carbon of the π-allyl system is hindered by one of the side chains on the oxazoline ring. We are currently working on the isolation and structure determination of the putative π-allyl intermediate.

In summary, we have found an efficient approach for the synthesis of new bis(oxazoline) ligands starting from the (1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol **3**. Preliminary results in asymmetric cyclopropanation of styrene with ethyl diazoacetate demonstrate the potential of these novel types of chiral bis(oxazoline) ligands. Further studies including modifications to ligand design and reaction conditions are in progress. The first result obtained with the ligand **5a** showed that these new chiral bis(oxazolines) can be effective for palladium-catalysed allylic substitution. We are currently studying other ligands **5b–f** (R=H, COMe, Me, $PhCH_2$, $Si(Me)_2tBu$) to clarify the effect of the substituents on the oxazoline ring on the control of the enantioselectivity, for the paladium allylic alkylation.

Experimental section

All reactions were carried out under an inert argon atmosphere. Melting points were taken using a Stuart Scientific apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded with Brucker AM-250 (250 MHz) and AC-200 (200 MHz) spectrometers for ^1H, and chemical shifts are reported in ppm downfield from Me_4Si. These instruments were also used for ^{13}C spectra. IR spectra were obtained from Perkin–Elmer 883 or FT-1725X spectrometers. Optical rotations were measured on Perkin–Elmer 241 MC in our laboratory. CI mass spectra were recorded with a quadripolar Nermag R10-10H instrument. Elemental analyses were performed by LCC (Laboratoire de Chimie de Coordination) Microanalytical Service. Column chromatogaphy purifications were performed with Merck alumina (70–230 mesh ASTM), deactivated with 8% of water or with Merck silica gel (230–400 mesh).

(4S,5S)-(+)-5 Phenyl-4 hydroxymethyl-2-phenyl oxazoline 7

(1S,2S)-(+)-2-Amino-1-phenyl-1,3-propanediol **3** (20 g, 120 mmol) and ethyl benzimidate hydrochloride (22.2 g, 120 mmol) were mixed in CH_2Cl_2 (150 ml). Triethylamine (16.7 ml, 120 mmol) was added dropwise and the solution was stirred for 15 h at room temperature. An additional portion of CH_2Cl_2 (200 ml) was then added, and the white precipitate (19 g) was filtered off. Slight concentration of the filtrate gave a second crop of oxazoline (9.8 g) which was used without further purification. Yield: 94%; m.p. 135°C; $[\alpha]_D^{20}$=+74.2 (c=1, DMSO); ^1H NMR ($CDCl_3$): δ=3.40 (s, 1H, OH), 3.77 (dd, J=3.6 Hz, 11.9 Hz, 1H, C*H*$_2$OH), 4.11 (dd, J=3.3 Hz, 11.9 Hz, 1H, C*H*$_2$OH), 4.23 (ddd, J=3.3 Hz, 3.6 Hz, 8.1 Hz, 1H, C*H*N), 5.57 (d, J=8.1 Hz, 1H, C*H*Ph), 7.24–7.45 (m, 8H, Ar–H), 7.88 (d, J=7.7 Hz, 2H, Ar–H); ^{13}C NMR (DMSO): δ=63.0, 77.0, 82.5, 125.5, 127.4, 128.0, 128.1, 128.7, 128.8, 131.7, 141.4, 162.3; DCI-MS (m/z): 272 (MH^+, 100%); Anal. Calcd for $C_{16}H_{15}NO_2$ (253.11): C, 75.87; H, 5.97; N, 5.53. Found: C, 75.89; H, 5.96; N, 5.44;.

(1S,2S)-(±)-2-Amino-3-benzoyloxy-3-phenyl-propan-1-ol **6**

To a solution of the alcohol (10 g, 39.5 g) in THF (400 ml) was added HCl (45 ml, 2 M, 90 mmol). The solution was stirred for 24 h at room temperature. Evaporation of the solvent and drying *in vacuo* left the ester hydrochloride (12.2 g, 39.4 mmol) as a white solid, which was used without further purification in the next step. Yield: >99%; m.p. 174°C; $[\alpha]_D^{20}=-38.8$ (c=1, CH_3OH); IR (neat, cm^{-1}) 2500–3500 (OH), 1715 (C=O); ^1H NMR (CD_3OD): δ=3.48 (dd, J=4.8 Hz, 11.7 Hz, 1H, CH_2OH), 3.75 (dd, J=3.4 Hz, 11.7 Hz, 1H, CH_2OH), 4.23 (ddd, J=3.4 Hz, 4.8 Hz, 9.7 Hz, 1H, C*H*NH_2), 6.25 (d, J=9.7 Hz, 1H, C*H*Ph), 7.40–7.80 (m, 8H, Ar–H), 8.25 (m, 2H, Ar–H); DCI-MS (m/z): 272 (MH^+, 100%); ^{13}C NMR (CD_3OD): δ=57.8, 59.6, 76.0, 128.8, 129.9, 130.3, 130.7, 130.9, 131.2, 135.0, 137.8, 167.0.

(−)-N,N′-Bis-[(2S,3S)-(3-phenylcarboxy-3-phenyl-1-hydroxypropyl)]-2,2-dimethyl-1,3 propanediamide **8**

Triethylamine (8.6 ml, 61.7 mmol) was added dropwise to a solution of dimethyl malonic chloride (2.6 g, 15.4 mmol) in CH_2Cl_2 (50 ml) at 0°C. The mixture was then added to suspension of amino ester **7** (9.5 g, 30.8 mmol) in CH_2Cl_2 (200 ml) at 0°C and stirred continuously for 3 h. After warming to room temperature the reaction medium was concentrated. The crude was then triturated in acetone (200 ml), and the insoluble salts were filtered off. Concentration of the filtrate and purification by silica gel chromatography with ethyl acetate as eluent furnished the diamide **8** (9.8 g, 15.3 mmol) as a white solid. Yield: 99%; m.p. 94°C; $[\alpha]_D^{20}=-4.3$ (c=1, CH_3OH); IR (neat, cm^{-1}): 3200–3600 (C–OH), 1723 (C=O), 1645 (C=O), ^1H NMR ($CDCl_3$): δ=1.15 (s, 6H, C(CH_3)$_2$), 1.90 (s, 2H, O*H*), 3.38 (dd, J=5.5 Hz, 11.4 Hz, 2H, CH_2O), 3.60 (dd, J=3.1 Hz, 11.3 Hz, 2H, CH_2O), 4.51 (ddd, J=3.3 Hz, 5.5 Hz, 7.7 Hz, 2H, C*H*NH), 6.18 (d, J=9.7 Hz, 2H, C*H*Ph), 6.98 (d, J=9.7 Hz, 4H, Ar–H), 7.26–7.58 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$): δ=22.8, 49.4, 55.1, 60.1, 74.8, 126.5, 127.9, 128.1, 129.0, 129.2, 132.9, 136.9, 165.5, 174.0; DCI-MS (m/z): 639 (MH^+, 100%); Anal. Calcd for $C_{37}H_{38}N_2O_8$ (638.73): C, 69.57; H, 6.00; N, 4.38. Found: C, 69.27; H, 5.93; N, 4.42.

(−)-N,N′-Bis-[(2S,3S)-(3-phenylcarboxy-3-phenyl-1-chloropropyl)]-2,2-dimethyl-1,3 propanediamide **9**

To a suspension of dihydroxy diamide **8** (3.07 g, 4.80 mmol) in dichloroethane (60 ml) was added freshly distilled thionyl chloride (3.6 ml, 48.0 mmol) via syringe. The resulting mixture was kept at reflux for 3 h. The solvent and excess of thionyl chloride were removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with a solution of K_2CO_3 (20 ml, 2 M), water (20 ml) and brine (20 ml), dried over Na_2SO_4, filtered and concentrated. The product was obtained as a white solid (3.33 g, 4.80 mmol) which was used without further purification in the next step. Yield: >99%; m.p. 162°C; $[\alpha]_D^{20}=-10.3$ (c=1, CH_3OH); IR (neat, cm^{-1}) 1723, 1712, 1664; ^1H NMR ($CDCl_3$): δ=1.15 (s, 6H, C(CH_3)$_2$), 3.32 (dd, J=3.4 Hz, 11.5 Hz, 2H, CH_2Cl), 3.65 (dd, J=3.6 Hz, 11.5 Hz, 2H, CH_2Cl), 4.76 (m, J=3.4 Hz, 3.6 Hz, 8.4 Hz, 2H, C*H*NH), 6.28 (d, J=8.2 Hz, 2H, C*H*Ph), 7.25–7.56 (m, 16H, Ar–H), 8.03 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$): δ=23.5, 44.5, 49.3, 54.2, 126.9, 128.4, 128.9, 129.0, 129.3, 129.8, 133.3, 136.3, 165.8, 173.3; DCI-MS (m/z): 675 (MH^+, 100%); Anal. Calcd for $C_{37}H_{36}ClN_2O_6$ (674.61): C, 65.78; H, 4.15; N, 5.37. Found: C, 65.73; H, 4.04; N, 5.33.

2,2-Bis-[2-((4S)-((1S)-1-phenylcarboxy-1-phenylmethyl)-1,3-oxazolinyl)] propane **5a**

A solution of diamide **9** (3.33 g, 4.9 mmol) and dry triethylamine (6 ml, 43.1 mmol) in dry toluene (60 ml) were heated to reflux overnight. After cooling to room temperature, ethyl acetate (50 ml) was added and the resulting mixture was washed with a saturated solution of $NaHCO_3$ (50 ml). The organic layer was separated, and the aqueous layer washed with ethyl acetate (3×50 ml). The combined organic layers were washed with brine (50 ml), dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification of the residue by column chromatography (Al_2O_3, ethyl acetate:pentane=35:65) afforded the bis(oxazoline) **5a** (2.44 g, 4.1 mmol) as a white solid. Yield: 83%;

m.p. 64°C; $[\alpha]_D^{20}$=+33.5 (c=1, CH_3OH); IR ($CHCl_3$, cm^{-1}): 1721 (C=O), 1655 (C=N); ^1H NMR ($CDCl_3$): δ=1.35 (s, 6H, $C(CH_3)_2$), 4.20 (dd, J=6.9 Hz, 12.9 Hz, CH_2O), 4.23 (dd, J=9.3 Hz, 12.9 Hz, CH_2O), 4.64 (ddd, J=4.9 Hz, 6.9 Hz, 9.3 Hz, 2H, CHN), 6.07 (d, J=4.9 Hz, 2H, CHPh), 7.13–7.57 (m, 16H, Ar–H), 8.05 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$): δ=23.9, 38.8, 69.1, 69.4, 73.3, 127.4, 128.2, 128.3, 128.4, 129.4, 129.8, 130.0, 133.2, 136.6, 165.4, 170.8; DCI-MS (m/z): 603 (MH^+, 100%); Anal. Calcd for $C_{37}H_{34}N_2O_6$ (602.69): C, 73.46; H, 5.69; N, 4.65. Found: C, 73.46; H, 5.66; N, 4.59.

2,2-Bis-[2-((4S)-((1S)-1-hydroxy-1-phenylmethyl)-1,3-oxazolinyl)] propane ***5b***

To a methanolic solution of NaOH (1% wt, 10 ml) was added the bis(oxazoline) **5a** (301 mg, 0.50 mmol) in one portion. After stirring 30 minutes at room temperature, the solvent was evaporated under reduced pressure and the crude residue was triturated in pentane. Removal of the pentane by filtration and purification of the solid by flash chromatography with ethyl acetate as eluent gave the dihydroxy bis(oxazoline) **5b** (190 mg, 0.49 mmol) as a white powder. Analytically pure product was obtained by crystallisation from $CHCl_3$ m.p. 136°C; $[\alpha]_D^{20}$=+105.6 (c=1, CH_3OH); IR ($CHCl_3$, cm^{-1}): 3200–3600 (C–OH), 1655 (C=N); ^1H NMR ($CDCl_3$): δ=1.42 (s, 6H, $C(CH_3)_2$), 4.04 (d, J=4.0 Hz, 2H, OH), 4.23 (m, 4H, CH_2O), 4.45 (m, 2H, CHN), 4.57 (dd, J=4.0 Hz, 5.5 Hz, CHPh), 7.26–7.36 (m, 10H, Ar–H); ^{13}C NMR ($CDCl_3$): δ=23.4, 39.2, 70.0, 71.3, 76.2, 126.4, 127.7, 128.1, 140.2, 171.3; DCI-MS (m/z): 395 (MH^+, 100%); Anal. Calcd for $C_{23}H_{26}N_2O_4$ (394.47): C, 70.03; H, 6.64; N, 7.10. Found: C, 69.31; H, 6.76; N, 7.08.

2,2-Bis-[2-((4S)-((1S)-1-methylcarboxy-1-phenylmethyl)-1,3-oxazolinyl)] propane ***5c***

Acetic anhydride (285 µl, 3 mmol) was added dropwise to a solution of **5b** (394 mg, 1.0 mmol), triethylamine (556 µl, 3.0 mmol) and 4-dimethylaminopyridine DMAP (2 mg) in CH_2Cl_2 (10 ml) at 0°C. The mixture was then stirred for 3 h at 0°C. After warming to room temperature the solvent was removed. The residue was dissolved in ether (10 ml), washed with water (2×10 ml), and dried over Na_2SO_4. Filtration and evaporation of the solvent afford the diacetyl bis(oxazoline) **5c** (400 mg, 15.4 mmol) as a colorless oil. Yield: 82%; $[\alpha]_D^{20}$= 117.5 (c=0.9, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1720 (C=0), 1655 (C=N); ^1H NMR ($CDCl_3$): δ=1.28 (s, 6H, $C(CH_3)_2$), 2.07 (s, 6H, $COCH_3$), 4.08 (d, J=8.2 Hz, 4H, CH_2O), 4.51 (dd, J=5.9 Hz, 8.2 Hz, 2H, CHN), 5.78 (d, J=5.9 Hz, 2H, CHPh), 7.28 (m, 10H, Ar–H); ^{13}C NMR ($CDCl_3$): δ=21.0, 23.7, 30.2, 38.6, 69.0, 76.0, 127.3, 128.1, 136.4, 169.7, 170.6; DCI-MS (m/z): 479 (MH^+, 100%); Anal. Calcd for $C_{27}H_{30}N_2O_6$ (478.20): C, 67.77; H, 6.32; N, 5.85. Found: C, 67.47; H, 6.89; N, 5.58.

2,2-Bis-[2-((4S)-((1S)-1-methyloxy-1-phenylmethyl)-1,3-oxazolinyl)] propane ***5d***

To a suspension of NaH (56 mg, 80% in mineral oil, 1.97 mmol) in THF (15 ml) was added bis(oxazoline) **5a** in two portions. The resulting mixture was heated at 36°C for 2h. After cooling to room temperature, methyl iodide (3 eq., 5,91 mmol) was added dropwise via syringe and stirring was continued overnight. The mixture was diluted with ether (20 ml), washed with brine (20 ml), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography (Al_2O_3, 20:80 ethyl acetate/pentane) afforded **5d** (2.44 g, 4.1 mmol) as a clear oil. Yield: 83%; $[\alpha]_D^{20}$=+131.7 (c=1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1650 (C=N); ^1H NMR ($CDCl_3$): δ=1.07 (s, 6H, $C(CH_3)_2$), 3.25 (s, 6H, OCH_3), 3.97 (dd, J=9.0 Hz, 9.6 Hz, 2H, CHPh), 4.07 (dd, J=6.7 Hz, 9.0 Hz, 2H, CH_2O), 4.30 (d, J=5.5 Hz, 2H, CHPh), 4.49 (ddd, J=4.9 Hz, 6.9 Hz, 9.3 Hz, 2H, CHN), 7.19–7.30 (m, 10H, Ar–H); ^{13}C NMR ($CDCl_3$): δ=23.6, 38.3, 57.0, 68.5, 69.5, 84.0, 127.7, 127.8, 127.9, 136.9, 170.2; DCI-MS (m/z): 423 (MH^+); Anal. Calcd for $C_{23}H_{30}N_2O_4$ (422.22): C, 71.07; H, 7.16; N, 6.63. Found: C, 70.92; H, 8.01; N, 5.92.

2,2-Bis-[2-((4S)-((1S)-1-phenylmethyloxy-1-phenylmethyl)-1,3-oxazolinyl)] propane ***5e***

To a suspension of NaH (16 mg, 80% in mineral oil, 0.55 mmol) in THF (8 ml) was added **5b** (100 mg, 0.25 mmol) in two portions. The resulting mixture was heated at 36°C for 2 h. After cooling to room temperaure, benzyl bromide (66 µl, 0.55 mmol) was added dropwise via syringe and stirring

was continued for 3 h. The mixture was diluted with ether (20 ml), washed with brine (20 ml), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography (Al_2O_3, ethyl acetate:pentane=20:80) afforded **5e** (105 mg, 0.29 mmol) as a clear oil. Yield: 72%; $[\alpha]_D^{20}$=+107.6 (c=0.95, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1650 (C=N); ^1H NMR ($CDCl_3$): δ=1.06 (s, 6H, $C(CH_3)_2$), 4.02 (m, 2H, C*H*N), 4.19 (dd, J=5.6 Hz, 9.1 Hz, CH_2O), 4.29 (d, J=12.1 Hz, 2H, CH_2Ph), 4.54 (m, 4H, C*H*Ph, $CH_2$0), 4.58 (d, J=12.1 Hz, 2H, CH_2Ph), 7.23–7.31 (m, 20H, Ar–H); ^{13}C NMR ($CDCl_3$): δ=23.6, 38.3, 68.7, 69.6, 70.6, 81.0, 127.6, 127.6, 127.9, 127.9, 128.3, 131.1, 138.1, 170.1; DCI-MS (m/z): 575 (MH^+, 100%).

2,2-Bis-[2-((4S)-((1S)-1-(1,1-dimethylethyl)dimethylsilyloxy-1-phenylmethyl)-1,3-oxazolinyl)] propane 5f

To a solution of the bis(oxazoline) **5b** (200 mg, 0.508 mmol), imidazole (103 mg, 1.524 mmol) in dry DMF (8 ml) was transfered a solution of *tert*-butyldimethylsilyl chloride (229 mg, 1.524 mmol) in DMF (2 ml) at room temperature via a cannula. The mixture was stirred for 48 h and then the solvent was removed under pressure. The residue was dissolved in ether (10 ml), washed with water (2×10 ml), dried over $MgS0_4$ and filtered. Evaporation of the solvent and purification of the residue by column chromatography (Al_2O_3, ethyl acetate:pentane=10:90) afforded **5f** (300 mg, 0.483 mmol) as a pale yellowish oil. Yield: 95%; $[\alpha]_D^{20}$=+75.4 (c=1.05, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1650 (C=N); ^1H NMR ($CDCl_3$): δ=−0.91 (s, 6H, $Si(CH_3)_2$), 0.21 (s, 6H, $Si(CH_3)_2$), 0.86 (s, 18H, Si^{t}Bu), 4.03 (dd, J=8.9 Hz, 9.8 Hz, 2H, CH_2O), 4.20 (dd, J=6.1 Hz, 8.9 Hz, 2H, CH_2O), 4.41 (ddd, J=4.7 Hz, 6.1 Hz, 8.9 Hz, 2H, C*H*N), 4.90 (d, J=4.7 Hz, 2H, C*H*Ph), 7.17–7.28 (m, 10H, Ar–H); ^{13}C NMR ($CDCl_3$): δ=−5.1, −4.8, 18.2, 23.4, 25.8, 38.3, 68.4, 71.2, 74.4, 127.3, 127.4, 139.7, 170.1; DCI-MS (m/z): 623 (MH^+, 100%); Anal. Calcd for $C_{35}H_{54}N_2O_4Si_2$ (622.36): C, 67.48; H, 8.74; N, 4.50. Found: C, 67.56; H, 9.08; N, 4.37.

General procedure for the cyclopropanation reaction

The ligand **5** (24 μmol) and $CuOTf{\cdot}0.5C_6H_6$ (20 μmol) were mixed in 5 ml of CH_2ClCH_2Cl and stirred for 1 h. The reaction mixture was filtered and the solution was added to styrene (1.1 ml, 10 mmol) at room temperature. Then, ethyl diazoacetate (0.2 ml, 2 mmol) in CH_2ClCH_2Cl (1.5 ml) was added at room temperature over a period of 7 h. It was stirred for 16 h. The solvent was removed and the crude residue was purified by column chromatography (SiO_2, ethyl acetate:hexane=5:95) to the the ethyl cyclopropyl in 69–91% yield. The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase column (Pharmacir 7C; *i*PrOH:hexane=1:99): t_R 6.7 min (1S,2S), t_R 7.8 min (1R,2R). 9.1 min (1R,2S), 13.1 min (1S,2R).

General procedure for the allylic alkylation reaction

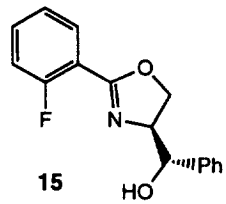
Ligand **5a** (12.0 mg, 0.02 mmol, 4 mol%), 3-acetoxy-1,3-diphenyl-1-propene (126 mg, 0.5 mmol) and $[\{Pd(C_3H_5)Cl\}_2]$ (1.8 mg, 0.005 mmol, 1 mol%) were dissolved in CH_2Cl_2 (2 ml) and stirred for 20 minutes. This mixture was added to the stirred suspension resulting from the addition of sodium hydride (34.5 mg, 1.5 mmol) on a solution of dimethyl malonate (0.175 ml, 1.5 mmol) in CH_2Cl_2 (3 ml) at room temperature. the whole mixture was then stirred at 36°C under argon. The reaction was monitored by TLC for disapperance of acetate. When all the acetate was converted to product, the reaction was quenched with a saturated aqueous NH_4Cl solution (20 ml), then extracted twice with CH_2Cl_2 (2×20 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give the crude product which was purified by chromatography (SiO_2, ethyl acetate:pentane=15:85). The enantiomeric excess was determined by ^1H NMR using the chiral shift reagent $Eu(hfc)_3$.

Acknowledgements

We are grateful to the CNRS for financial support of this work, and to the 'Ministère de l'Enseignement Supérieur et de la Recherche' for doctoral fellowships (H.O.).

References

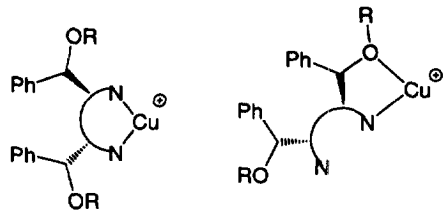
1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons: New York, 1994.
2. Brunner, H.; Obermann, U. *Organometallics* **1989**, *8*, 821.
3. Balavoine, G. G. A.; Clinet, J. C.; Lellouche, I. *Tetrahedron Lett.* **1989**, *31*, 6005.
4. (a) Bolm, C. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 542. (b) Doyle, M. P. in *Catalytic Asymmetric Synthesis*. (Ed.: Ojima, I.), VCH publishers, New York, 1993, p. 63.
5. (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (c) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (d) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 430. (e) Gant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36*, 8745. (e) Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 4073. (d) For the aziridination see: Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.
6. Helmchen, G.; Krotz, A.; Ganz, K.-F.; Hansen, D. *Synlett* **1991**, 257. For this purpose, see: Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Itoh, K. *Organometallics* **1989**, *8*, 846 and Nishiyama, H.; Kondo, M. Hakamura, T.; Itoh, K. *ibid* **1991**, *10*, 500.
7. Iridium-catalysed transfer hydrogenation of ketones, see ref. 5c and ref. 6.
8. (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. (b) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807. (c) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798.
9. (a) see ref. 5c. (b) Lentenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143. (c) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (d) von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A. and Macko, L.; Neuburger, M.; Zehnder, M. and Rüegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265.
10. Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814.
11. Brookhart, M.; Wagner, M. I. and Balavoine, G. G. A.; Aït-Haddou, H. *J. Am. Chem. Soc.* **1994**, *116*, 3641.
12. Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.
13. Gant T. G., and Meyers A. I. *Tetrahedron* **1994**, *50*, 2297.
14. While finishing this work, Helmchen and co-workers reported the synthesis of new oxazoline ligands of type **15**, starting from the (1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol **3** and using the method involving formation of an amide, transformation of the OH group into a leaving group and ring closure. This procedure was not applicable to the preparation of our bis(oxazoline) ligands, see: Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547.



15

15. Breton, P.; André-Barrès, C.; Langlois, Y. *Synth. Comm.* **1992**, *22*, 2543.
16. Meyers, A. I.; Schmidt, W.; Mckennon, M. J. *Synthesis* **1993**, 250.
17. Meyers, A. I.; Knaus, G.; Kamata, K. *J. Am. Chem. Soc.* **1974**, *96*, 268.
18. Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884 and references therein.
19. Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300.
20. (a) Uozumi, Y.; Kyota, H.; Kishi, E.; Kitayama, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1603. (b) Imai, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1997**, *38*, 2681.

21. We suppose that in the case of the diether bis(oxazoline) ligands, the complexation with the Cu(I) resulted in the formation of two catalytic species **A** and **B**.



A **B**

22. (a) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568. (b) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143. (c) Trost, B. M.; Marschner C. *Bull. Soc. Chim. Fr.* **1997**, *134*, 263. (d) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149. (c) Von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566. (e) Rieck, H.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2687. (f) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. (g) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395 and references therein.
23. The enantiomeric excess was determined by ^{1}H NMR in the presence of chiral shift reagent Eu(hfc)$_3$. The absolute configuration of the product was determined by comparison of the specific rotation with literature data: (a) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191. (b) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E. Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

(Received in UK 5 September 1997; accepted 9 October 1997)