Synthesis of Novel Chiral Bisoxazoline Ligands Containing 2,5-Diaryl-1,3,4-oxadiazole and Enantioselective Cyclopropanation of Styrene

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Abstract: Practical synthesis of chiral C_2-symmetric substituted bisoxazoline ligands containing 2,5-diaryl-1,3,4-oxadiazole units was investigated. Five chiral bisoxazoline ligands containing 2,5-diphenyl-1,3,4-oxadiazole have been synthesized from 2,5-di-(*o*-carboxylphenyl)-1,3,4-oxadiazole and amino alcohols by methanesulfonyl chloride or *p*-toluenesulfonyl chloride assisted cyclization via hydroxy amide intermediate. Preliminary examination of copper complexes of new ligands as chiral catalysts in the enantioselective cyclopropanation of styrene with ethyl diazoacetate was performed. Enantioselectivities up to 35% ee and 87% ee for *trans*- and *cis*-2-phenylcyclopropanecarboxylate, respectively were observed.

Key words: bisoxazoline, oxadiazole, enantioselective cyclopropanation

In recent years, the C_2-symmetric chiral bisoxazolines have become very useful ligands in the catalysis of many reactions.[2] High catalytic activities and enantiomeric excesses have been obtained for example in hydrosilylation of ketone,[3] allylic alkylation,[4] Michael addition,[5] Diels–Alder cycloaddition,[6] and cyclopropanation[7] mainly using C_2-symmetric chiral ligands in conjunction with a suitable transition metal ions. The conformational rigid framework of the metal chelate with the presence of stereocenters close to the donor nitrogen atoms provides a well-ordered chiral environment at the catalytic site. The size of the chelate in the metal complex of bisoxazoline is another important factor for the catalyst since it will control the orientation of the substituents on the two oxazolines around the metal ion. The design and synthesis of new chiral oxazoline ligands have inspired many scientists to work in this area. Our interest focuses on the studies of enantioselective transition-metal catalysis of heterocyclic ligands.[8] In the design of the new ligands it was crucial to have a rigid cyclic backbone, therefore a rigid system containing a 2,5-diaryl-1,3,4-oxadiazole unit was chosen. Hence, the incorporation of the 2,5-diaryl-1,3,4-oxadiazole unit and a chiral oxazoline unit in new ligands may result in unique properties for catalytic reaction. In this paper, the synthesis, structure, and catalytic enantioselective cyclopropanation of styrene with the aforementioned novel chiral bisoxazoline ligands containing 2,5-diaryl-1,3,4-oxadiazole units are reported.

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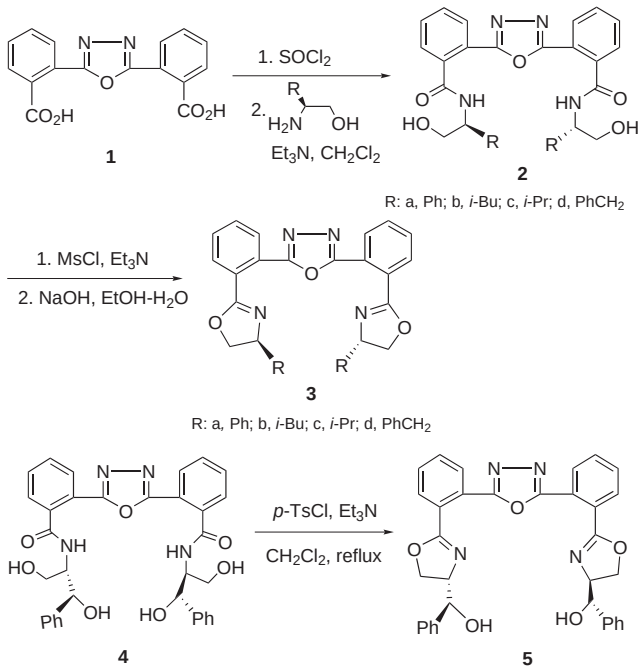
The usual method for preparation of chiral bisoxazoline is the reaction of diacid derivatives with chiral β-amino alcohols. The enantiomerically pure β-amino alcohols are either commercially available or easily obtained by reduction of the corresponding α-amino acids.[9] Many methods have been reported for the synthesis of oxazoline ligands.[10] We have attempted to use a one-pot condensation procedure of the diacid with the amino alcohol in the presence of triphenylphosphine, carbon tetrachloride and triethylamine,[11] but poor yields were obtained by this method for this series.

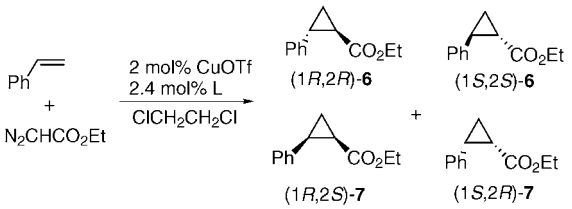
In the present work, the synthesis of ligands **3a**–**d** and **5** using a two-step procedure gave good yields in each step. Treatment of 2,5-di(*o*-carboxyphenyl)-1,3,4-oxadiazole with refluxing thionyl chloride afforded the diacyl dichloride, which was treated with β-amino alcohol and triethylamine to afford the corresponding chiral intermediate dihydroxy diamides **2a**–**d** as solids in 60–83% yields. Cyclization by activating the dihydroxy diamides with thionyl chloride can give the bisoxazoline, but this procedure cannot be repeated well on larger scale or even small scale. However, we found that when dihydroxy diamides **2a**–**d** were treated with methanesulfonyl chloride and triethylamine in dichloromethane at 0 °C afforded the corresponding bismesylates, which were then cyclized by heating in an aqueous methanolic solution of sodium hydroxide to give the desired bisoxazolines **3a**–**d** in 54–83% yields (Scheme 1). The latter procedure developed by Denmark[12] can work well on large scale and can be repeated well.

Diamide **4** was also synthesized according to the same procedure as dihydroxy diamides **2a**–**d** from 2,5-di-(*o*-carboxylphenyl)-1,3,4-oxadiazole **1** and (1*R*,2*S*)-(–)-2-amino-1-phenyl-1,3-propanediol, but with longer reaction time, refluxing for 36 hours. Diamide **4** when treated with methanesulfonyl chloride and triethylamine in dichloromethane did not afford the corresponding bisoxazoline **5**. However, treatment of diamide **4** with *p*-toluenesulfonyl chloride and triethylamine in refluxing dichloromethane[13] can give the desired bisoxazoline **5** in 46% yield.

In order to evaluate the efficiency of these bisoxazoline ligands in the copper(I)-catalyzed asymmetric cyclopropanation of olefins, we carried out the reaction of styrene with ethyl diazoacetate to give the *trans*- and *cis*-cyclopropanes **6** and **7**, as the model reaction. The reaction was



Scheme 1 Synthesis of new bisoxazolines **3a–d** and **5**



Scheme 2 Cyclopropanation reaction of styrene and ethyl diazoacetate

carried out at room temperature or 40 °C by slow addition of ethyl diazoacetate to a solution of styrene in 1,2-dichloroethane containing the copper(I)-bisoxazoline catalyst. This was prepared in situ by adding the appropriate amount of copper(I) trifluoromethanesulfonate benzene complex [Cu(OTf)·$(C_6H_6)_{0.5}$] to the ligand.

From the results given in Table 1, the following conclusions can be made:

(i) The diastereoselectivity of the reaction favors *trans* selectivity.

(ii) The enantioselectivity of the *cis*- isomer is higher than that of the *trans*-isomer, and the highest ee values for cyclopropane (1*R*,2*S*)-**7** were obtained with the benzyl substituted bisoxazoline **3d** however with moderate chemical yield. The best ee was up to 87% (entry 7).

(iii) The enantioselectivity was decreased when the temperature was raised (entries 6, 8, and 10 vs entries 5, 7, and 9).

(iv) The introduction of a phenyl substituent at the 4-position of the oxazoline ring has a pronounced effect on the enantioselectivity of the reaction.

(v) When a chiral substituent (phenylcarbinol) was introduced at the 4-position (ligand **5**), it also leads to a sharp decrease in the ee, this may be the effect of hydroxy group compared with benzyl group (entries 7, 8, 9, and 10).

(vi) The predominant formation of (1*R*,2*R*)-*trans*-cyclopropane **6** was observed irrespective of the reaction temperature (r.t. or 40 °C; entries 3 and 4). In contrast to this result, the preferred absolute configurations of *cis*-cyclo-

Table 1 Cyclopropanation of Styrene in the Presence of Diaryloxadiazole Bisoxazoline Ligands

Entry	Ligand	Temp	Time (h)	Yield[a] (%)	*trans*/*cis*[b]	% ee[c] (*trans*)	Config[d]	% ee[c] (*cis*)	Config[d]
1	**3a**	r.t.	24	8	73:27	0.2	–	0.5	–
2	**3a**	40 °C	24	48	76:24	0.3	–	0.5	–
3	**3b**	r.t.	24	13	87:13	15	1*R*,2*R*	70	1*S*,2*R*
4	**3b**	40 °C	24	41	67:33	21	1*R*,2*R*	71	1*R*,2*S*
5	**3c**	r.t.	24	44	88:22	15	1*S*,2*S*	57	1*R*,2*S*
6	**3c**	40 °C	24	37	67:33	8	1*S*,2*S*	9	1*S*,2*R*
7	**3d**	r.t.	24	25	74:26	20	1*R*,2*R*	87	1*R*,2*S*
8	**3d**	40 °C	24	37	68:32	35	1*R*,2*R*	66	1*R*,2*S*
9	**5**	r.t.	24	16	73:27	9	1*S*,2*S*	12	1*S*,2*R*
10	**5**	40 °C	24	53	69:31	2	1*S*,2*S*	7	1*S*,2*R*

[a] Isolated yield, based on ethyl diazoacetate for the mixture of *trans*- and *cis*-products.
[b] Determined by ^{1}H NMR of the crude product.
[c] By chiral HPLC using Chiralcel OD column.
[d] Based on the sign of optical rotation.[14]

propane **7** were changed from (1*S*,2*R*) to (1*R*,2*S*). This unusual stereochemical outcome may be ascribed to the temperature change, which affects the conformation of ligand and thus the complex. The same anomaly was also observed in entries 5 and 6. Furthermore, the preferred absolute configuration at C1 of *trans*-cyclopropane **6** was antipodal to that of *cis*-cyclopropane **7** when the reaction was conducted at room temperature (entries 3 and 5). Although the real reason is still unclear at present, this unusual result may be attributed to the fact that the solubility of the metal complex is low in the solvent, and different ligands have different solubility. Thus these homo and/or heterogeneous catalysts may have different ligand conformation which is correlated with the result of asymmetric induction.[15] Furthermore, we obtained moderate to good enantioselectivity for the *cis*-isomer **7** and need not to use the bulky adamantyl substituted bisoxazoline or bulky ester butyl diazocacetate. It is well known that the enantioselectivity of the metal catalyzed cyclopropanation is higher when the steric bulky ester is used,[16–18] so there exists potential to optimize the enantioselectivity.

In order to obtain a direct understanding of substituent effect of the new diaryl oxadiazole bisoxazoline ligands on the enantioselectivity, the stereostructure of ligands **3a** and **3b** were determined by X-ray crystal diffraction analysis.[19] Compounds **3a** and **3b** were obtained as air-stable, colorless plates, upon slow evaporation of a solution of **3a** or **3b** in ethyl acetate-petroleum ether (2:1). A perspective view of compound **3a** is shown in Figure 1. The diaryl 1,3,4-oxadiazole is in a twist conformation in compound **3a**. The C10-C12-C14 benzene ring has a dihedral angle with O3-N3-N4 oxadiazole ring of 57.7°, while the other benzene ring's dihedral angle with this oxadiazole ring is 135.4°. The two benzene rings are almost perpendicular to each other with a dihedral angle of 93.2° rather than coplanar. A perspective view of compound **3b** is shown in Figure 2. Compound **3b** has a similar stereostructure to that of compound **3a**, however, there are two independent molecules in each unit cell of this molecule. From the crystal structures of **3a** and **3b**, it turns out that larger substituent will result in a larger torsional strain between the two oxazoline units in corresponding copper(I) complex, and this can explain the dramatic decrease in ee. The conformation of the linking spacer may be affected by temperature, and thus the diaryl oxadiazole bisoxazoline copper(I) complex will result in different enantioselectivity at different temperatures.

In conclusion, an efficient synthetic procedure was found for synthesis of new chiral diaryl oxdiazole bisoxazoline ligands. Preliminary results in asymmetric cyclopropanation of styrene with ethyl diazoacetate have been obtained. The C_2-symmetric bisoxazoline **3a**–**d** and **5** derived from diaryl oxdiazole present markedly different reactivities in the asymmetric copper-catalyzed cyclopropanation. The highest enantioselectivity was obtained with benzyl substituted bisoxazoline **3d**. Although the yield is moderate and *trans* enantioselectivity is low, these results suggest that these novel diaryloxadiazole bisoxazolines have potential to be used as catalyst for asymmetric reaction. Further modification of the chemical structure and studies in other asymmetric reactions are in progress in our laboratory.

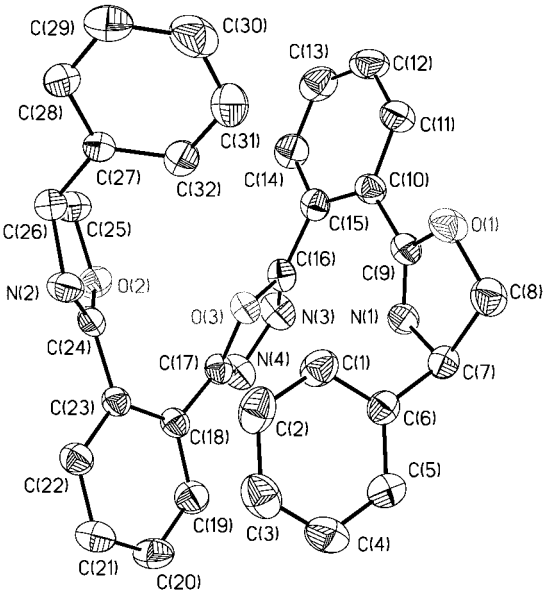


Figure 1 Perspective view of compound **3a**, showing 30% probability ellipsoids for the non-hydrogen atoms and the numbering scheme of the atoms in the molecule.

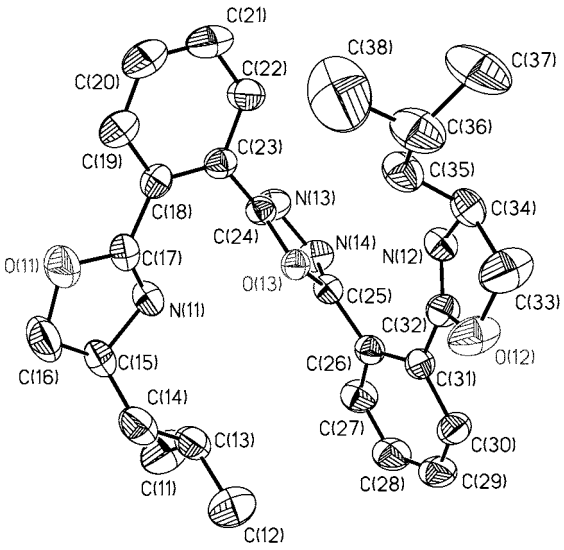


Figure 2 Perspective view of compound **3b**, showing 30% probability ellipsoids for the non-hydrogen atoms and the numbering scheme of the atoms in the molecule.

Melting points were measured on an XT-4 melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker ARX 400 spectrometer with tetramethylsilane (TMS) as the internal standard. Infrared spectra were obtained on a Bruker Vector 22 spectrometer. Mass spectra were obtained on a VG-ZAB-HS mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC spectrometer. Elemental analyses were carried out on an Elementar Vario EL instrument. The optical purities of *trans*- and

cis-cyclopropanes were determined by HPLC analysis using a chiral column (Daicel Chiralcel OD; eluent, hexane–*i*-PrOH 95:5; flow rate, 0.5 mL/min; UV detector, 220nm). The retention times for *trans*-isomers are 10.50 (1*R*,2*R*) and 13.34 (1*S*,2*S*) min, the *cis*-isomers are 9.83 (1*S*,2*R*) and 11.13 (1*R*,2*S*) min. The absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation. Solvents used were purified and dried by standard procedures. Petroleum ether used had a bp 60–90 °C. 2,5-Di(*o*-carboxyphenyl)-1,3,4-oxadizole was synthesized according to the literature produre.[20]

2,5-Bis{*o*-[*N*-(1′*R*)-(1′-phenyl-2′-hydroxyethyl)amido]phenyl}-1,3,4-oxadiazole (2a); General Procedure I

A solution of 2,5-di-(*o*-carboxyphenyl)-1,3,4-oxadiazole (1.9 g, 6.1 mmol) and $SOCl_2$ (34 mL) was refluxed for 8h. The excess $SOCl_2$ was removed under reduced pressure, benzene (20 mL) was added and the solvent was removed to afford the diacyl dichloride. The above diacyl dichloride dissolved in CH_2Cl_2 (100 mL) was added dropwise to a solution of *R*-phenylglycinol (1.65 g, 12.0 mmol) and Et_3N (6.9 mL) in CH_2Cl_2 (35 mL) at 0 °C and stirred at r.t. for 24 h. The precipitate was filtered and washed with Et_2O to afford **2a** as a colorless powder; 2.7 g (82.1%); mp 226–228 °C; $[\alpha]_D^{20}$ –105.0 (*c* 0.1, MeOH).

IR (KBr): 3327, 3058, 3034, 2945, 2857, 1648, 1601, 1553, 1531, 1493, 1079, 1042, 1038, 703 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.65 (4 H, m, CH_2), 4.89 (2 H, t, *J* = 5.6 Hz, OH), 5.04 (2 H, dd, *J* = 7.2, 14.2 Hz, CH), 7.20–7.71 (10 H, m, ArH), 7.51–7.72 (8 H, m, ArH), 8.93 (2 H, d, *J* = 8.2 Hz, NH).

FAB-MS: *m*/*z* (%) = 549 (M + 1, 20), 292 (10), 257 (10), 217 (60), 181 (40), 126 (70), 91 (100).

Anal. Calcd for $C_{32}H_{28}N_4O_5$: C, 70.06; H, 5.14; N, 10.20. Found: C, 69.88; H, 4.90; N, 10.05.

2,5-Bis{*o*-[*N*-(1′*S*)-(1′-isobutyl-2′-hydroxyethyl)amido]phenyl} -1,3,4-oxadiazole (2b)

Following general procedure I, 2,5-di-(*o*-carboxyphenyl)-1,3,4-oxadiazole (2.17 g, 7.0 mmol), $SOCl_2$ (40 mL), *S*-leucinol (1.64 g, 14.0 mmol) and Et_3N (8.0 mL) gave **2b** as a colorless solid; 2.8 g (78.6%); mp 173–175 °C; $[\alpha]_D^{20}$ –130.8 (*c* 1, $CHCl_3$).

IR (KBr): 3309, 3068, 2955, 2871, 1646, 1599, 1530, 1492, 1438 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.93 (12 H, d, *J* = 6.6 Hz, CH_3), 1.34 (2 H, m, CH_2), 1.52 (2 H, m, CH_2), 1.70 (2 H, m, CH), 3.50 (2 H, dd, *J* = 5.2, 11.3 Hz, CH_2), 3.79 (2 H, dd, *J* = 3.2, 11.3 Hz, CH_2), 4.03 (2 H, s, OH), 4.16 (2 H, m, CH), 6.54 (2 H, d, *J* = 8.1 Hz, CH_2), 7.48–7.60 (6 H, m, ArH), 7.80 (2 H, d, *J* = 5.0 Hz, ArH).

FAB-MS: *m*/*z* (%) = 509 (M + 1, 100), 491(10), 392(30), 292(90), 249(60), 160(70).

Anal. Calcd for $C_{28}H_{36}N_4O_5$: C, 66.12; H, 7.13; N, 11.02. Found: C, 66.23; H, 6.86; N, 10.92.

2,5-Bis{*o*-[*N*-(1′*S*)-(1′-isopropyl-2′-hydroxyethyl)amido]phenyl}-1,3,4-oxadiazole (2c)

Following general procedure I, 2,5-di-(*o*-carboxyphenyl)-1,3,4-oxadiazole (1.24 g, 4 mmol), $SOCl_2$(70 mL), *S*-valinol (0.83 g, 8 mmol) and Et_3N (4.6 mL) gave **2c** as a solid; 1.15 g (60%); mp 208–210 °C; $[\alpha]_D^{20}$ –107.6 (*c* 1, $CHCl_3$).

IR (KBr): 3420, 3240, 2920, 2860, 1620, 1500 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.86 (6 H, d, *J* = 6.8 Hz, CH_3), 0.88 (6 H, d, *J* = 6.8 Hz, CH_3), 1.88 (2 H, m, CH), 3.48 (4 H, t, *J* = 5.6 Hz, CH_2), 3.74 (2 H, m, CH), 4.56 (2 H, t, *J* = 5.4 Hz, OH), 7.61–7.72 (6 H, m, ArH), 7.89 (2 H, dd, *J* = 1.4, 7.4 Hz, ArH), 8.24 (2 H, d, *J* = 8.8 Hz, NH).

FAB-MS: *m*/*z* (%) = 481 (M + 1).

Anal. Calcd for $C_{26}H_{32}N_4O_5$: C, 64.98; H, 6.71; N, 11.67. Found: C, 64.83; H, 6.85; N, 11.92.

2,5-Bis{*o*-[*N*-(1′*S*)-(1′-benzyl-2′-hydroxyethyl)amido]phenyl}-1,3,4-oxadiazole (2d)

Following general procedure I, 2,5-di-(*o*-carboxyphenyl)-1,3,4-oxadiazole (2.17 g, 7.0 mmol), $SOCl_2$(40 mL), *S*-phenylalaninol(2.12 g, 14.0 mmol) and Et_3N (8.0 mL) gave **2d** as a colorless solid; 3.08 g (76.2%); mp 202–204 °C; $[\alpha]_D^{20}$ –135.8 (*c* 1, $CHCl_3$).

IR (KBr): 3300, 3060, 3028, 2955, 2919, 2867, 1645, 1599, 1554, 1532, 1494 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.74 (2 H, dd, *J* = 8.7, 13.6 Hz, CH_2), 2.91 (2 H, dd, *J* = 5.6, 13.7 Hz, CH_2), 3.38 (2 H, m, CH_2), 3.50 (2 H, m, CH_2), 4.08 (2 H, m, CH), 4.82 (2 H, t, *J* = 5.6 Hz, OH), 7.14–7.19 (2 H, m, ArH), 7.23–7.29 (8 H, m, ArH), 7.39 (2 H, dd, *J* = 1.2, 7.4 Hz, ArH), 7.59–7.68 (4 H, m, ArH), 7.87 (2 H, dd, *J* = 1.3, 7.5 Hz, ArH), 8.48 (2 H, d, *J* = 8.3 Hz, NH).

FAB-MS: *m*/*z* = 577 (M + 1).

Anal. Calcd for $C_{34}H_{32}N_4O_5$: C, 70.82; H, 5.59; N, 9.72. Found: C, 70.56; H, 5.71; N, 9.68.

2,5-Bis{*o*-[(4′*R*)-4′-phenyloxazolin-2′-yl]phenyl} -1,3,4-oxadiazole (3a); General Procedure II

To an ice-cold solution of dihydroxy diamide **2a** (1.1 g, 2.0 mmol) and Et_3N (1.4 mL, 10.1 mmol) in CH_2Cl_2 (30 mL) and DMF (10 mL) was added MsCl (0.36 mL, 4.6 mmol) via syringe. The reaction mixture was allowed to warm to r.t. and was stirred for 24 h, then poured into H_2O (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with brine, dried over anhyd Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to afford the crude bismesylate. The crude bismesylate was dissolved in EtOH (20 mL) and a solution of NaOH (0.5 g) in H_2O (20 mL) was added to it. The reaction mixture was refluxed for 3 h. The EtOH was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 50mL). The combined organic layers was washed with 3% HCl, then with 5% $NaHCO_3$, and brine, dried over anhyd Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give a pale yellow oil. The oil was purified by column chromatography on silica gel (EtOAc–petroleum ether, 2:3) followed by recrystallization from EtOAc–petroleum ether to give pure **3a**; 0.67g (65.4%); mp 156–158 °C; $[\alpha]_D^{20}$ +25.8 (*c* 1, $CHCl_3$).

IR (KBr): 2960, 2897, 1655, 1599, 1558, 1455, 1354, 1088 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.13 (2 H, t, *J* = 8.6 Hz, OCH), 4.68 (2 H, dd, *J* = 8.6, 10.2 Hz, OCH), 5.31 (2 H, dd, *J* = 8.6, 10.2 Hz, CHN), 7.19–7.24 (10 H, m, ArH), 7.50–7.66 (4 H, m, ArH), 7.77–7.86 (2 H, m, ArH), 7.97–8.01 (2 H, m, ArH).

FAB-MS: *m*/*z* (%) = 513 (M + 1, 100), 393 (20), 273 (70).

Anal. Calcd for $C_{32}H_{24}N_4O_3$: C, 74.99; H, 4.72; N, 10.93. Found: C, 74.87; H, 4.64; N, 10.93.

2,5-Bis{*o*-[(4′*S*)-4′-isobutyloxazolin-2′-yl]phenyl]-1,3,4-oxadiazole (3b)

Following general procedure II, dihydroxy diamide **2b** (1.1 g, 2.0 mmol), MsCl (0.36 mL, 4.6 mmol) and Et_3N (1.4 mL, 10.1 mmol) gave the crude bismesylate. The crude bismesylate was treated with a NaOH–EtOH–H_2O solution as above, column chromatography (silica gel; EtOAc–petroleum ether, 3:7) followed by recrystallization from EtOAc–petroleum ether gave **3b** as a colorless solid; 0.78 g (82.5%); mp 75–76 °C; $[\alpha]_D^{20}$ –145 (*c* 0.5, MeOH).

IR (KBr): 2957, 2868, 1653, 1602, 1472, 1358 cm^{-1}.

EI-MS: *m*/*z* = 473 (M + 1).

^{1}H NMR ($CDCl_3$): δ = 0.82 (12 H, d, *J* = 6.6 Hz, CH_3), 1.24 (2 H, m, CH_2), 1.54 (2 H, m, CH_2), 1.67 (2 H, m, CH), 3.89 (2 H, t, *J* = 7.7 Hz, CH_2), 4.27 (2 H, m, CH), 4.37 (2 H, dd, *J* = 7.8, 9.4 Hz, CH_2), 7.58–7.63 (4 H, m, ArH), 7.84–7.86 (2 H, m, ArH), 7.96–7.98 (2 H, m, ArH).

Anal. Calcd for $C_{28}H_{32}N_4O_3$: C, 71.16; H, 6.82; N, 11.86. Found: C, 71.30; H, 6.99; N, 11.64.

2,5-Bis{*o*-[(4′*S*)-4′-isopropyloxazolin-2′-yl]phenyl}-1,3,4-oxadiazole (3c)

Following general procedure II, dihydroxy diamide **2c** (0.96 g, 2.0 mmol), MsCl (0.36 mL, 4.6 mmol) and Et_3N (1.4 mL, 10.1 mmol) gave the crude bismesylate. The crude bismesylate was treated with a NaOH–EtOH–H_2O solution as above, column chromatography (silica gel; EtOAc–petroleum ether, 3:7) followed by recrystallization from EtOAc–petroleum ether gave **3c** as a colorless solid; 0.48 g (54%); mp 71–72 °C; $[\alpha]_D^{20}$ –82.7 (*c* 1, MeOH).

IR (KBr): 1680 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.83 (6 H, d, *J* = 6.8 Hz, CH_3), 0.91 (6 H, d, *J* = 6.8 Hz, CH_3), 1.74 (2 H, m, CH), 4.00 (4 H, m, CH_2), 4.27 (2H, m, NCH), 7.54–7.65 (4 H, m, ArH), 7.84–7.96 (4 H, m, ArH).

EI-MS: *m*/*z* = 444 (M^+).

Anal. Calcd for $C_{26}H_{28}N_4O_3$: C, 70.25; H, 6.35; N, 12.60. Found: C, 70.10; H, 6.30; N, 12.40.

2,5-Bis{*o*-[(4′*S*)-4′-benzyloxazolin-2′-yl]phenyl}-1,3,4-oxadiazole (3d)

Following general procedure II, dihydroxy diamide **2d** (2.3 g, 4.0 mmol), MsCl (0.75 mL, 9.5 mmol) and Et_3N (3.0 mL, 22.8 mmol) to afford the crude bismesylate. The crude bismesylate was treated with a NaOH–EtOH–H_2O solution as above, column chromatography on silica gel (EtOAc–petroleum ether, 5:4) gave **3d** as a colorless oil; 1.75 g (80.9%); $[\alpha]_D^{20}$ –87.2 (*c* 2.3, $CHCl_3$).

IR (KBr): 1670, 1520 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.64 (2 H, dd, *J* = 8.6, 13.6 Hz, CH_2), 3.08 (2 H, dd, *J* = 5.4, 13.6 Hz, CH_2), 4.01 (2 H, t, *J* = 8.6 Hz, CH_2), 4.20 (2 H, t, *J* = 8.6 Hz CH_2), 4.50 (2 H, m, CH), 7.09–7.30 (10 H, m, ArH), 7.56–7.65 (4 H, m, ArH), 7.84–7.99 (4 H, m, ArH).

EI-MS: *m*/*z* 541 (M + 1).

Anal. Calcd for $C_{34}H_{28}N_4O_3$: C, 75.54; H, 5.22; N, 10.36. Found: C, 75.34; H, 5.23; N, 10.21.

2,5-Bis{*o*-[*N*-(2′*S*, 3′*S*)-(1′,3′-dihydroxy-3′-phenylpropyl)amido]phenyl}-1,3,4-oxadiazole (4)

A solution of 2,5-di-(*o*-carboxyphenyl)-1,3,4-oxadiazole (2.17 g, 7.0 mmol) and $SOCl_2$ (40 mL) was refluxed for 12 h. The excess $SOCl_2$ was removed under reduced pressure, benzene (20 mL) was added and the solvent was removed to afford the diacyl dichloride. A solution of the above diacyl dichloride in CH_2Cl_2 (50 mL) was added dropwise to the suspension of (1*R*,2*S*)-(–)-2-amino-1-phenyl-1,3-propanediol (2.2 g, 13.0 mmol) and Et_3N (5.0 mL) in CH_2Cl_2 (80 mL) at 0 °C and stirred at r.t. for 36 h. The precipitate was filtered and washed with Et_2O to give **4** as a colorless solid; 3.3 g (83.3%); mp 200–202 °C; $[\alpha]_D^{20}$ +28.0 (*c* 0.1, MeOH).

IR (KBr): 3334, 3279, 3058, 3063, 2934, 2876, 1647, 1597, 1531, 1492, 1336, 1056 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.33 (2 H, m, OH), 3.54 (2 H, m, OH), 4.11(2 H, m, CHN), 4.70 (2 H, t, *J* = 10.8 Hz, CH_2), 4.90 (2 H, t, *J* = 4.4 Hz, CH_2), 5.41 (2 H, d, *J* = 4.8 Hz, CHPh), 7.17–7.40 (12 H, m, ArH), 7.57–7.69 (4 H, m, ArH), 7.88 (2 H, d, *J* = 8.4 Hz, ArH), 8.20 (2 H, d, *J* = 8.8 Hz, 2 H, NH).

FAB-MS: *m*/*z* (%) = 609 (M + 1, 6), 181 (100).

Anal. Calcd for $C_{34}H_{32}N_4O_7$: C, 67.09; H, 5.30; N, 9.21. Found: C, 66.90; H, 5.31; N, 9.23.

2,5-Bis(*o*-{(4′*S*)-4′-[(1*R*)-1-phenyl-1-hydroxymethyl]oxazolin-2′-yl}phenyl)-1,3,4-oxadiazole (5)

To a solution of diamide **4** (2.44 g, 4.0 mmol) and anhyd Et_3N (7 mL, 50.5 mmol) in CH_2Cl_2 (50 mL) was added MsCl and TsCl (2.3 g, 12.1 mmol) at r.t.. The reaction mixture was kept at reflux for 12 h. H_2O (4 mL) was added and the solution was heated to reflux for 1 h. After cooling the reaction mixture was extracted with H_2O (3 × 30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried over anhyd Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to afford the crude product. The crude product was purified by column chromatography on silica gel ($CHCl_3$–EtOAc, 1:2) to give **5** as a colorless solid; 1.06 g (46.3%); mp 88–90 °C; $[\alpha]_D^{20}$ –39.0 (*c* 0.1, $CHCl_3$).

IR (KBr): 3448, 1653, 1453, 1363, 1052, 958 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.94 (2 H, t, *J* = 8.2 Hz, CH_2), 4.11 (2 H, t, *J* = 9.2 Hz, CH_2), 4.34 (2 H, d, *J* = 7.6 Hz, CHPh), 4.55 (2 H, m, CHN), 5.34 (2 H, s, OH), 7.02–7.26 (10 H, m, ArH), 7.58–7.73 (4 H, m, ArH), 7.80 (2 H, dd, *J* = 1.4, 7.2 Hz, ArH), 8.14 (2 H, dd, *J* = 1.4, 7.6 Hz, ArH).

HR-FAB: *m*/*z* calcd for $C_{34}H_{28}N_4O_5$: 573.2132. Found: 573.2131.

Asymmetric Cyclopropanation of Styrene; Typical Procedure

To a solution of the ligand (2.4 mol%) in $ClCH_2CH_2Cl$ (1 mL) was added [Cu(OTf)$(C_6H_6)_{0.5}$] (2 mol%). After stirring at r.t. for 2 h, a solution of styrene (8 mmol) in $ClCH_2CH_2Cl$ (1 mL) was added, followed by ethyl diazoacetate solution (10 μL) and the mixture was heated to 50–60 °C to initiate the reaction. Then the solution was cooled to the desired temperature, the solution of ethyl diazoacetate (2 mmol) in $ClCH_2CH_2Cl$ (1 mL) was added dropwise over a period of 7 h. The mixture was stirred for another 15 h and then quenched with 10% NH_4Cl (5 mL). The mixture was diluted with EtOAc (25 mL), and then the organic phase was separated. The organic phase was washed with H_2O and brine, dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum ether–EtOAc, 60:1) to afford the mixture of *trans*- and *cis*-2-phenyl-cyclopropane-1-carboxylates as a colorless oil. The *trans*/*cis* ratio of this mixture was analyzed by ^{1}H NMR (200 MHz) in $CDCl_3$ using TMS as internal standard. The diastereomeric and enantiomeric excess were determined by HPLC with a chiral column (Daicel Chiralcel OD; eluent, hexane–*i*-PrOH, 95:5; flow rate, 0.5 mL/min; UV detector, 220nm).

X-ray Crystallographic Analysis

A colorless crystal was selected and mounted on a fine-focus sealed tube and used for data collection. Cell constants and an orientation matrix for data collection were obtained by least-squares refinement of the diffraction data from 25 reflections in the 2θ range from 2.52 to 27.48 degree for compound **3a** and 2.30 to 27.48 degree for compound **3b** in a Rigaku AFC6S diffractometer equipped with a graphite crystal incident beam monochromator. Data were collected at 293K using MoKα radiation (λ = 0.71073 Å) and the ω-2θ variable-scan mode. The intensity data obtained were corrected for Lorentz and polarization effects. An empirical absorption correction based on ψ-scan data was applied. The crystal structure was resolved by the direct method using SHELXS-97,[21] and full-matrix least-squares refinement on F^2 was performed with SHELXL-97 program.[22] All the non-hydrogen atoms were deduced from an E-map and refined anisotropically. The positions of hydrogen atoms were generated geometrically and included in structure factor calculations with assigned isotropic thermal parameters. All computations were performed on a FOUNDER FP$^+$ 5-166 586 personal computer.

3a

$C_{32}H_{24}N_4O_3$, F_W = 512.55, Monoclinic, space group P(2)1, a = 8.971(2), b = 15.404(3), c = 9.541 (2) Å; α = 90°, β = 95.86 (3)°, γ = 90°, V = 1311.6 (5) Å^3, Z = 2, F(000) = 536, Dc = 1.298 g/cm^3, μ = 0.085 mm^{-1}. Crystal size 0.50 × 0.40 × 0.35 mm; Index ranges 0≤h≤11, 0≤k≤20, –12≤l≤12; Reflections collected/unique, 3109/3109 (R_{int} = 0.0000); Data /restraints/parameters, 3109/1/353; Goodness-of-fit on F^2 0.845; Final R indices [I>2σ(I)]: R1 = 0.0299, wR2 = 0.0536; Extinction coefficient 0.034 (2); Largest diff. peak and hole, 0.101 and –0.091 eÅ^{-3}.

3b

$C_{28}H_{32}N_4O_3$, F_W = 472.58, Triclinic, space group P1, a = 12.7271(6), b = 12.8305(2), c = 9.6886(1) Å; α = 105.656 (3)°, β = 112.276 (2)°, γ = 101.700 (2)°, V = 1324.4 (5) Å^3, Z = 2, F(000) = 504, Dc = 1.185 g/cm^3, μ = 0.078 mm^{-1}. Crystal size 0.60 × 0.50 × 0.45 mm; Index ranges –16≤h≤16, –16≤k≤16, –12≤l≤11; Reflections collected/unique, 5986/5986 (R_{int} = 0.0229); Data/restraints/parameters, 5986/3/656; Max. and min. transmission 1.0613 and 0.9047; Goodness-of-fit on F^2 0.785; Final R indices [I>2σ(I)]: R1 = 0.0423, wR2 = 0.1046; Extinction coefficient 0.027 (3); Largest diff. peak and hole, 0.139 and –0.127 eÅ^{-3}.

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