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Journal of Organometallic Chemistry 603 (2000) 6–12

Journal of Organometallic Chemistry

Lanthanide-catalyzed asymmetric 1,3-dipolar cycloaddition of nitrones to alkenes using 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthol (BINOL-Box) ligands

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Received 18 November 1999; received in revised form 12 January 2000

Abstract

New BINOL-derived ligands, 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthols (BINOL-Box), bearing chiral bis-oxazoline at the 3,3′-carbons, were synthesized from commercially available 1,1′-bi-2-naphthol (BINOL). With the new ligands obtained, we found that asymmetric 1,3-dipolar cycloaddition reaction of *N*-benzylidenebenzylamine *N*-oxide (**2**) to 3-((*E*)-2-butenoyl)-1,3-oxazolidin-2-one (**1**) was catalyzed by BINOL-Box–scandium complexes to give isoxazolidine **3** in high yield with high diastereo- and enantioselectivity. For example, the reaction of **1** with **2** catalyzed by a 6 mol% (*S*,*R*)-**7d** and 5 mol% $Sc(OTf)_3$ complex proceeded to give the *endo*-3 as the major diastereomer with an *endo*:*exo* ratio of 97:3 and 87% *ee* of the *endo*-product in the presence of 4 Å molecular sieves. Interestingly, the absolute configuration of the major product was changed according to the kind of additive used.

Keywords: 1,3-Dipolar; Lanthanide catalysis; Isoxazolidine; 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthols

1. Introduction

The 1,3-dipolar cycloaddition of nitrones to alkenes is a useful and convenient method for the preparation of isoxazolidine derivatives, which are converted into amino alcohols [1], precursors to biologically important alkaloids, β-lactams, etc. [2]. In 1994, catalytic enantioselective 1,3-dipolar cycloaddition reactions by chiral catalysts were reported by Seerden or Jørgensen et al. In these reactions, the catalysts [3,4], which were Lewis acids with chiral ligands, were quite sensitive to a small amount of water. Previously, we reported that 1,3-dipolar cycloaddition reaction of nitrones with alkenes was catalyzed by phosphine–palladium complexes [5], which can be used in the presence of water. But this reaction needs to be stirred in chloroform under reflux to obtain the product in good yield. Moreover, Kobayashi et al. recently reported that a heterochiral ytterbium complex, which was prepared from $Yb(OTf)_3$, (*S*)-1,1′-bi-2-naphthol, and *N*-methyl-bis[(*R*)-1-(1-naphthyl)ethyl]amine, was quite effective in catalytic enantioselective 1,3-dipolar cycloaddition of nitrones [2c]. The reaction proceeded smoothly at room temperature (r.t.) in the presence of 20 mol% ytterbium triflate. In this reaction, the axial chirality of BINOL has been considered to be transmitted to the reaction site through the bulky amine, which binds to BINOL by a hydrogen bond, so in as much as the BINOL alone could not induce asymmetry in the product effectively. However, there was a problem, it was difficult to separate them from this reaction system including (*S*)-1,1′-bi-2-naphthol. In addition, recently, oxazoline ligands, which are at present widely used for various kinds of transition metal-catalyzed enantioselective reactions, have been reported [6].

Considering these results, we designed 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthols (BINOL-Box) as chiral ligands. The BINOL-Box ligands have chiral bis-oxazoline at the 3,3′-carbons of 1,1′-bi-2-naphthol through the σ-bond. Thus, a rigid asymmetric environment can be formed around the two hydroxyl moieties, which would work as coordinating groups to the metal center. Furthermore, the chiral oxazoline parts are eas-

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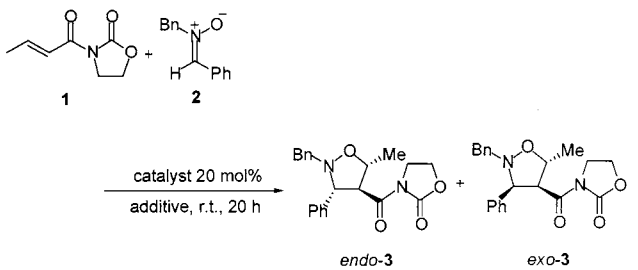
0022-328X/00/$ - see front matter
PII: S0022-328X(00)00024-3

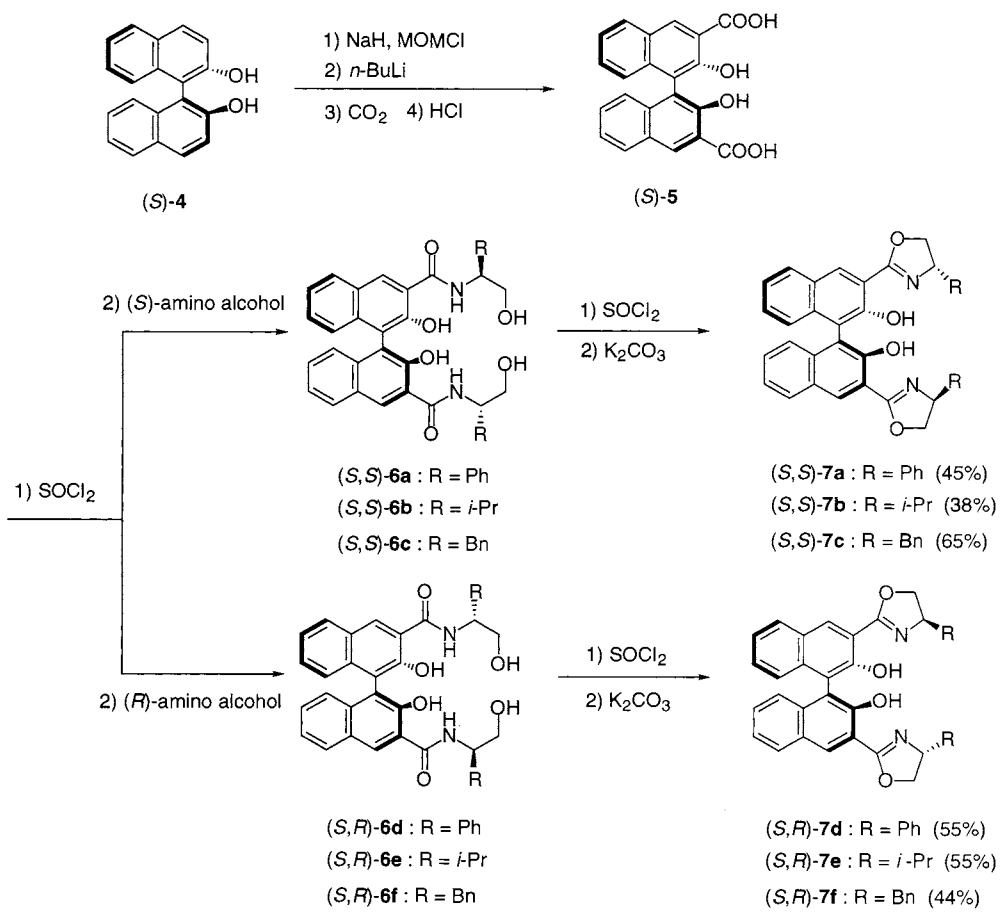
ily modified by changing the amino alcohol reagents in synthesis, which are conveniently obtained from natural α-amino acids. The effect of axial chirality of 1,1′-bi-2-naphthol and chirality at the carbon center of oxazolines is also easily examined for obtaining good selectivities. We found that the scandium-catalyzed asymmetric 1,3-dipolar cycloaddition of *N*-benzylidenebenzylamine *N*-oxide (**2**) to 3-((*E*)-2-butenoyl)-1,3-oxazolidin-2-one (**1**) [7] using these ligands proceeded in high yield with high diastereo- and enantioselectivity.



2. Results and discussion

2.1. Synthesis of 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthols (BINOL-Box)

Synthesis of the BINOL-Box ((*S*,*S*)-**7a**–**c**, (*S*,*R*)-**7d**–**f**) was started from commercially available (*S*)-1,1′-bi-2-naphthol ((*S*)-BINOL: (*S*)-**4**), as shown in Scheme 1. The hydroxy groups of (*S*)-**4** were protected as methoxymethyl ethers, and the resulting compound was subjected to ortholithiation [8], followed by carboxylation to give the corresponding 3,3′-dicarboxylic acid, which was hydrolyzed by treatment with hydrogen chloride in isopropyl alcohol–tetrahydrofuran to give (*S*)-**5** [9]. Then, the compound (*S*)-**5** was exposed to thionyl chloride, and the resulting acid chloride was treated with chiral amino alcohols to give the corresponding amides (**6a**–**f**). Moreover, amides **6a**–**f** were halogenated by the reaction with thionyl chloride, and



Scheme 1.

Table 1
Effect of $Ln(OTf)_3$ in 1,3-dipolar cycloaddition reaction [a]

Entry	$Ln(OTf)_3$	Yield (%) [b]	*endo*:*exo* [c]	*Ee* (%) [d]	Configuration [d,e]
1	$Sc(OTf)_3$	86	92:8	83	*R*,*S*,*R*
2	$Y(OTf)_3$	86	97:3	7	*S*,*R*,*S*
3	$La(OTf)_3$	77	95:5	9	*S*,*R*,*S*
4	$Pr(OTf)_3$	81	96:4	10	*S*,*R*,*S*
5	$Yb(OTf)_3$	88	94:6	5	*S*,*R*,*S*
6	$Lu(OTf)_3$	87	95:5	7	*S*,*R*,*S*

[a] Reaction conditions: the catalyst $Ln(OTf)_3$ (0.10 mmol) and (*S*,*R*)-**7d** (0.10 mmol) were stirred with powdered 4 Å molecular sieves (125 mg) in CH_2Cl_2 (1.5 ml) for 0.5 h, and the nitrone (0.50 mmol) and alkene (0.50 mmol) were added, and then the mixture was stirred for 20 h at room temperature.
[b] Based on 3-((*E*)-2-butenoyl)-1,3-oxazolidin-2-one.
[c] Determined by ^{1}H-NMR spectroscopy.
[d] *Ee* of the *endo*-product determined by HPLC analysis using a DAICEL CHIRALCEL OD-H column (eluent, 30:70 2–propanol-hexane; flow rate, 0.3 ml min^{-1}; detection, UV 220 nm).
[e] The order of 3,4,5-positions of isoxazolidine ring.

Table 2
$Sc(OTf)_3$-catalyzed 1,3-dipolar cycloaddition reaction [a]

Entry	Ligand	Solvent	Yield (%) [b]	*endo*:*exo* [c]	*Ee* (%) [d]	Configuration [d,e]
1	None	CH_2Cl_2	86	99:1		
2	(*S*)-**4**	CH_2Cl_2	81	98:2	30	*S*,*R*,*S*
3	(*S*,*S*)-**7a**	CH_2Cl_2	80	97:3	31	*R*,*S*,*R*
4	(*S*,*R*)-**7d**	CH_2Cl_2	86	92:8	83	*R*,*S*,*R*
5	(*S*,*R*)-**7d**	$CHCl_3$	82	97:3	67	*R*,*S*,*R*
6	(*S*,*R*)-**7d**	$PhCH_3$	89	97:3	8	*S*,*R*,*S*
7	(*S*,*R*)-**7d**	THF	86	93:7	6	*S*,*R*,*S*
8	(*S*,*R*)-**7e**	CH_2Cl_2	75	99:1	7	*S*,*R*,*S*
9	(*S*,*R*)-**7f**	CH_2Cl_2	43	84:16	72	*S*,*R*,*S*

[a] Reaction conditions: the catalyst $Sc(OTf)_3$ (0.10 mmol) and ligand (0.10 mmol) were stirred with powdered 4 Å molecular sieves (125 mg) in solvent (1.5 ml) for 0.5 h, and the nitrone (0.50 mmol) and alkene (0.50 mmol) were added, and then the mixture was stirred for 20 h at room temperature.
[b] Based on 3-((*E*)-2-butenoyl)-1,3-oxazolidin-2-one.
[c] Determined by ^{1}H-NMR spectroscopy.
[d] *Ee* of the *endo*-product determined by HPLC analysis using a DAICEL CHIRALCEL OD-H column (eluent, 30:70 2-propanol–hexane; flow rate, 0.3 ml min^{-1}; detection, UV 220 nm).
[e] The order of 3,4,5-positions of isoxazolidine ring.

the resulting compounds were cyclized in the presence of potassium carbonate to give the BINOL-Box **7a**–**f** in good yields (38–65% from (*S*)-**5**).

The structures of **7a**–**f** were confirmed by elemental and spectral analyses. Interestingly, signals of the phenolic protons appeared at around 12 ppm in ^{1}H-NMR. This shows that these phenolic protons have a hydrogen bond to the nitrogen atom, which is more basic than the oxygen atom, and these hydrogen bonds could make a rigid array of the oxazoline moieties.

2.2. Asymmetric Ln(OTf)$_3$-catalyzed 1,3-dipolar cycloaddition reaction by using BINOL-Box ligands

First, the effect of lanthanide triflates (scandium triflate ($Sc(OTf)_3$), yttrium triflate ($Y(OTf)_3$), lanthanum triflate ($La(OTf)_3$), praseodymium triflate ($Pr(OTf)_3$), ytterbium triflate ($Yb(OTf)_3$), and lutetium triflate ($Lu(OTf)_3$)) was examined. As shown in Table 1, lanthanide elements strongly influenced the enantioselectivities. The reaction of **1** with **2** catalyzed by 20 mol% (*S*,*R*)-**7d**–$Sc(OTf)_3$ complexes proceeded to give the *endo*-**3** as the major diastereomer with an *endo*:*exo* ratio of 92:8 and 83% *ee* of the *endo*-product (Table 1, Entry 1). On the other hand, when other lanthanide triflates were used, the enantioselectivities diminished largely (Table 1, Entries 2–6). Probably, the results were dependent on the enlargement of the ionic radii. Furthermore, the absolute configuration of the major product in the presence of $Sc(OTf)_3$ was 3*R*,4*S*,5*R*, while an adduct with absolute configuration of 3*S*,4*R*,5*S* was obtained in the presence of other lanthanide triflates.

Therefore, as models, we chose 3-((*E*)-2-butenoyl)-1,3-oxazolidin-2-one (**1**), *N*-benzylidenebenzylamine *N*-oxide (**2**) and scandium triflate $Sc(OTf)_3$ as a metal triflate. The reaction of **1** with **2** in the absence of a

ligand, only $Sc(OTf)_3$, proceeded to give the *endo*-**3** as the major diastereomer with an *endo*:*exo* ratio of 99:1 in 86% yield (Table 2, Entry 1). The product **3** was obtained from the reaction with a (*S*)-**4**–$Sc(OTf)_3$ complex in 81% yield with 30% *ee* of the *endo* isomer (*endo*:*exo* = 98:2) (Table 2, Entry 2). The application of (*S*,*S*)-**7a**, which has same axial chirality as (*S*)-**4**, led to similar yield, diastereoselectivity, and enantiomeric excess, but with the opposite configuration of the product **3** compared with the case of (*S*)-**4**. The use of (*S*,*R*)-**7d**, which is the diastereomeric isomer of (*S*,*S*)-**7a**, resulted in much higher enantioselectivity. From this result, it was apparent that (*S*,*R*)-configurated ligands give better results than (*S*,*S*)-configurated ligands. So, the effect of substituents on the oxazoline rings was examined by use of (*S*,*R*)-configurated ligands, such as (*S*,*R*)-**7d**, derived from (*R*)-phenylglicinol (phenyl), (*S*,*R*)-**7e**, derived from (*R*)-valinol (isopropyl), and (*S*,*R*)-**7f**, derived from (*R*)-phenylalaninol (benzyl) (Table 2, Entries 4, 8, and 9). The reaction using phenyl-substituted (*S*,*R*)-**7d** gave the best enantioselectivity, while the products from the reaction with isopropyl- or benzyl-substituted (*S*,*R*)-**7** had lower enantiomeric excesses and the opposite configuration. These results show that the chirality on the oxazoline ring affects both the enantiomeric excesses and absolute configuration of *endo*-**3**. The effect of solvents was examined for the reaction with (*S*,*R*)-**7d**. The reaction proceeded faster in dichloromethane or chloroform as a solvent, and enantioselectivities were much higher than that in toluene or tetrahydrofuran (Table 2, Entries 4–7), while in toluene or tetrahydrofuran enatioselectivities were lower (Table 2, Entries 6 and 7).

Jørgensen et al. reported [10,11] that both conversion and *endo*/*exo* selectivity of the $Yb(OTf)_3$ and $Sc(OTf)_3$ catalyzed reactions proved to be dependent on the amount of molecular sieves added and, on the other hand, in the Mg(II)-bisoxazoline catalyzed reaction, the absolute stereochemistry of the *endo*-product was changed in the presence and absence of 4 Å molecular sieves. So, the effects of 4 Å molecular sieves, magnesium sulfate, kinds of alcohols, and water as an additive were examined. In the absence of 4 Å molecular sieves, the reaction of **1** with **2** proceeded to give the *endo*-**3** as the major diastereomer with an *endo*:*exo* ratio of 72:23 and 38% *ee* of the *endo*-product, and the absolute stereochemistry of *endo*-3 was assigned to be (3*S*,4*R*,5*S*) (Table 3, Entry 1). Addition of 10 mg of 4 Å molecular sieves to the reaction mixture leads to an increase in the enantioselectivity (Table 3, Entry 2). Moreover, addition of 50 mg or 125 mg of 4 Å molecular sieves causes increase in *ee* compared with the use of 10 mg (Table 3, Entries 3 and 4), while the reaction did not proceed in the presence of 250 mg of 4 Å molecular sieves because of the sluggish mixture. But addition of magnesium sulfate leads to a decrease in *ee* (Table 3, Entry 5). Interestingly, in the presence of 4 Å molecular sieves or magnesium sulfate, the absolute stereochemistry of *endo*-**3** changed to (3*R*,4*S*,5*R*) in comparison with that from the reaction without an additive.

The above results show that a small amount of water in the reaction system may influence the selectivities of the reaction. So the reaction was performed by adding water (Table 3, Entries 6 and 7). Addition of a larger amount of water resulted in better enantioselectivities

Table 3
Effect of additives in $Sc(OTf)_3$-catalyzed 1,3-dipolar cycloaddition reaction [a]

Entry	Additive	Yield (%) [b]	*endo*:*exo* [c]	*Ee* (%) [d]	Configuration [d,e]
1	None	60	77:23	38	*S*,*R*,*S*
2	4 Å molecular sieves 10 mg	95	89:11	55	*R*,*S*,*R*
3	4 Å molecular sieves 50 mg	86	94:6	66	*R*,*S*,*R*
4	4 Å molecular sieves 125 mg	86	92:8	83	*R*,*S*,*R*
5	$MgSO_4$ 250 mg	83	87:13	37	*R*,*S*,*R*
6	H_2O 20 mol%	56	78:22	58	*S*,*R*,*S*
7	H_2O 40 mol%	20	80:20	88	*S*,*R*,*S*
8	MeOH 40 mol%	50	79:21	58	*S*,*R*,*S*
9	EtOH 40 mol%	72	87:13	6	*R*,*S*,*R*
10	*i*-PrOH 40 mol%	79	86:14	20	*R*,*S*,*R*
11	*t*-BuOH 40 mol%	84	91:9	58	*R*,*S*,*R*
12	$HO(CH_2)_2OH$ 40 mol%	64	90:10	34	*S*,*R*,*S*

[a] Reaction conditions: the catalyst $Sc(OTf)_3$ (0.10 mmol) and (*S*,*R*)-**7d** (0.10 mmol) were stirred with additive in CH_2Cl_2 (1.5 ml) for 0.5 h, and the nitrone (0.50 mmol) and the alkene (0.50 mmol) were added, and then the mixture was stirred for 20 h at room temperature.

[b] Based on 3-((*E*)-2-butenoyl)-1,3-oxazolidin-2-one.

[c] Determined by ^{1}H-NMR spectroscopy.

[d] *Ee* of the *endo*-product determined by HPLC analysis using a DAICEL CHIRALCEL OD-H column (eluent, 30:70 2-propanol–hexane; flow rate, 0.3 ml min^{-1}; detection, UV 220 nm).

[e] The order of 3,4,5-positions of isoxazolidine ring.

up to 88% *ee* less than 40 mol% of water as an additive, while the use of more water made the reaction mixture heterogeneous. Moreover, the effect of several alcohols, as an additive, was examined. In the presence of methanol, the reaction of **1** with **2** proceeded to give the *endo*-**3** as the major diastereomer with an *endo*:*exo* ratio of 79:21 and 58% *ee* of the *endo*-product (Table 3, Entry 8). When bulkier alcohols, for example, ethanol, isopropyl alcohol, *tert*-butyl alcohol and ethylene glycol, were used as an additive, the enantiomeric excesses and the absolute configuration were changed according to the bulkiness of the alcohol (Table 3, Entries 9–12). That is, the use of the smallest protic additive, i.e. water, resulted in *endo*-**3** with 88% *ee* of the (3*S*,4*R*,5*S*)-isomer, while the reaction with a bulkier additive gave *endo*-**3** with a higher ratio of the (3*R*,4*S*,5*R*)-isomer. The reaction with the bulkiest *tert*-BuOH yielded (3*R*,4*S*,5*R*)-**3** with 58% *ee*. These results suggested that addition of alcohols did not affect the catalytic activity, but caused some change in the coordination sphere of the scandium. According to Jørgensen et al. [11], in the octahedral lanthanide intermediate, including bidentate ligand and bidentate substrate, there are two free coordination sites, and additives, nitrones, or solvents coordinate to them. For the difference in coordinates to the two free coordination sites, coordination modes in the lanthanide intermediate may be different and, therefore, the absolute stereochemistry changed. So we thought that in the case of the large ligand preferring a *trans* coordination, the absolute stereochemistry of the *endo*-**3** was 3*R*,4*S*,5*R*, and in the case of the small ligand preferring a *cis* coordination, the absolute stereochemistry of the *endo*-**3** was 3*S*,4*R*,5*S*.

Moreover, the effect of the amount of catalyst was also examined. The catalyst $Sc(OTf)_3$ 5 mol% and (*S*,*R*)-**7d** 6 mol% was stirred with powdered 4 Å molecular sieves (125 mg) in CH_2Cl_2 (1.5 ml) for 0.5 h, and the nitrone **2** (0.50 mmol) and the alkene **1** (0.50 mmol) were added. After stirring for 48 h, the reaction proceeded to give the *endo*-**3** as the major diastereomer with an *endo*:*exo* ratio of 97:3 and 87% *ee* of the *endo*-product.

3. Conclusions

In conclusion, asymmetric 1,3-dipolar cycloaddition reaction of *N*-benzylidenebenzylamine *N*-oxide (**2**) to 3-((*E*)-2-butenoyl)-1,3-oxazolidin-2-one (**1**) catalyzed by new BINOL-Box–scandium complexes has been developed. The reaction of **1** with **2** catalyzed by 6 mol% (*S*,*R*)-**7d** and 5 mol% $Sc(OTf)_3$ in the presence of 4 Å molecular sieves proceeded to give **3** in 94% yield with an *endo*:*exo* ratio of 97:3 and 87% *ee* of the *endo*-product. We found that the choice of the additive and the ligand was very important in this reaction.

4. Experimental

All experiments were carried out under an argon atmosphere. Commercial reagents were used as received without further purification. All solvents were dried using standard procedures. The ^{1}H-NMR (400 MHz) spectra were recorded on a Jeol JNM A-400 spectrometer with TMS as an internal standard. Optical rotations were recorded with a Horiba SEPA-200 polarimeter. High-performance liquid chromatography (HPLC) was measured on a Hitachi L-7100. Chiral HPLC analysis was performed on the same apparatus with a chiral column, as described below. Preparation of (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxylic acid ((*S*)-**5**) was carried out according to the reported method [9].

4.1. Preparation of 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthols (BINOL-Box)

*4.1.1. (S,S)-3,3′-Bis(4-phenyloxazol-2-yl)-1,1′-bi-2-naphthol ((S,S)-**7a**)*

A solution of (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxylic acid (*S*)-**5** (1.87 g, 5.00 mmol) in thionyl chloride (15 ml) was refluxed for 4.5 h. After removal of the remaining thionyl chloride, the resulting acid chloride was dissolved in dichloromethane (20 ml). The mixture was added to a solution of (*S*)-phenylglicinol (1.51 g, 11.0 mmol) and triethylamine (0.81 g, 8.00 mmol) in dichloromethane (20 ml) at 0°C, and stirred for 24 h at r.t. Then, the reaction mixture was cooled to 0°C. Thionyl chloride (4.4 ml) in dichloromethane (13 ml) was added to this mixture, and the resulting solution was stirred for 24 h at r.t. Water was added to the reaction mixture, the separated organic layer was washed three times with water, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. To the crude residue in acetonitrile (50 ml) were added the distilled water (13 ml) and potassium carbonate (3.75 g, 27 mmol), and this mixture was refluxed for 24 h. After removal of the solvent, the residue was partitioned between dichloromethane and water. The organic layer was washed with 1.0 M hydrochloric acid. The water layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on silica gel (5:1 hexane–ethyl acetate) to give (*S*,*S*)-3,3′-bis(4-phenyloxazol-2-yl)-1,1′-bi-2-naphthol ((*S*,*S*)-**7a**) as a yellow solid (1.30 g, 45% from (*S*)-**5**): m.p. 173–175°C; MS *m*/*z* 576 (M^+). $[\alpha]_D^{23}$ + 144 (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 4.34 (t, $J = 8.8$ Hz, 2H), 4.90 (dd, $J = 8.8$ and 9.6 Hz, 2H), 5.52 (dd, $J = 9.6$ and 8.8 Hz, 2H), 7.20–7.34 (m, 16H), 7.90–7.92 (m, 2H), 8.50 (s, 2H), 12.22 (s, 2H, OH); IR (KBr): 3000, 1600, 1490, 1440, 1250, 1190, 1150, 1130, 1050, 930, 900,

700 cm^{-1}; HRMS Found: m/z 576.2024 (M^+). Anal. Calc. for $C_{38}H_{28}N_2O_4$: M^+, 576.2049.

In a similar manner, compounds **7b**–**7f** were prepared from (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxylic acid (*S*)-**5** and the corresponding amino alcohols.

*4.1.2. (S,R)-3,3′-Bis(4-phenyloxazol-2-yl)-1,1′-bi-2-naphthol ((S,R)-**7d**)*

Yield 55% (from **5**); m.p. 156–158°C; MS m/z 576 (M^+). $[\alpha]_D^{23}$ −189 (c 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 4.33 (t, $J=9.2$ Hz, 2H), 4.87 (t, $J=9.2$ Hz, 2H), 5.49 (t, $J=9.2$ Hz, 2H), 7.23–7.33 (m, 16H), 7.89–7.91 (m, 2H), 8.50 (s, 2H), 12.16 (s, 2H, OH); IR (KBr): 2800, 1600, 1500, 1450, 1330, 1250, 1200, 1150, 1130, 950, 900, 800, 750, 700 cm^{-1}; HRMS Found: m/z 576.2054 (M^+). Anal. Calc. for $C_{38}H_{28}N_2O_4$: M^+, 576.2049.

*4.1.3. (S,S)-3,3′-Bis(4-isopropyloxazol-2-yl)-1,1′-bi-2-naphthol ((S,S)-**7b**)*

Yield 38% (from **5**); m.p. 210–212°C; MS m/z 508 (M^+). $[\alpha]_D^{23}$ +66 (c 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 0.93 (d, $J=6.8$ Hz, 6H), 0.99 (d, $J=6.8$ Hz, 6H), 1.74–1.83 (m, 2H, CH_3CHCH_3), 4.41–4.17 (m, 4H), 4.54 (t, $J=8.0$ Hz, 2H), 7.14–7.32 (m, 6H), 7.88–7.90 (m, 2H), 8.42 (s, 2H), 12.43 (s, 2H, OH); IR (KBr): 3000, 1600, 1500, 1440, 1370, 1300, 1250, 1200, 1150, 1135, 1060, 950, 900, 750, 700 cm^{-1}; HRMS Found: m/z 508.2377 (M^+). Anal. Calc. for $C_{32}H_{32}N_2O_4$: M^+, 508.2362.

*4.1.4. (S,R)-3,3′-Bis(4-isopropyloxazol-2-yl)-1,1′-bi-2-naphthol ((S,R)-**7e**)*

Yield 55% (from 5); m.p. 254–256°C; MS m/z 508 (M^+). $[\alpha]_D^{23}$ −153 (c 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 0.93 (d, $J=6.8$ Hz, 6H), 0.99 (d, $J=6.8$ Hz, 6H), 1.70–1.82 (m, 2H, CH_3CHCH_3), 4.09–4.19 (m, 4H), 4.53 (t, $J=8.0$ Hz, 2H), 7.19–7.31 (m, 6H), 7.87–7.90 (m, 2H), 8.42 (s, 2H), 12.35 (s, 2H, OH); IR (KBr): 3000, 1630, 1500, 1440, 1340, 1300, 1260, 1220, 1200, 1150, 1135, 1060, 950, 900, 800, 750, 700 cm^{-1}; HRMS Found: m/z 508.2368 (M^+). Anal. Calc. for $C_{32}H_{32}N_2O_4$: M^+, 508.2362.

*4.1.5. (S,S)-3,3′-Bis(4-benzyloxazol-2-yl)-1,1′-bi-2-naphthol ((S,S)-**7c**)*

Yield 65% (from 5); m.p. 108–110°C; MS m/z 604 (M^+). $[\alpha]_D^{23}$ +70 (c 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.67–2.72 (m, 2H, $ArCH_2$), 2.94–2.99 (m, 2H, $ArCH_2$), 4.04 (t, $J=8.4$ Hz, 2H), 4.33 (t, $J=8.4$ Hz, 2H), 4.49–4.57 (m, 2H), 7.07–7.21 (m, 16H), 7.76–7.79 (m, 2H), 8.31 (s, 2H), 12.08 (s, 2H, OH); IR (KBr): 2900, 1630, 1490, 1440, 1350, 1200, 1050, 950, 790, 750, 700 cm^{-1}; Found: C, 79.17; H, 5.24; N, 4.33%. Anal. Calc. for $C_{40}H_{32}N_2O_4$: C, 79.45; H, 5.33; N, 4.63%.

*4.1.6. (S,R)-3,3′-Bis(4-benzyloxazol-2-yl)-1,1′-bi-2-naphthol ((S,R)-**7f**)*

Yield 44% (from 5); m.p. 143–145°C; MS m/z 604 (M^+). $[\alpha]_D^{23}$ −121 (c 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.76–2.81 (m, 2H, $ArCH_2$), 3.06–3.12 (m, 2H, $ArCH_2$), 4.17 (t, $J=8.8$ Hz, 2H), 4.47 (t, $J=8.8$ Hz, 2H), 4.61–4.69 (m, 2H), 7.17–7.30 (m, 16H), 7.86–7.88 (m, 2H), 8.41 (s, 2H), 12.13 (s, 2H, OH); IR (KBr): 2900, 1600, 1500, 1430, 1350, 1300, 1260, 1220, 1200, 1150, 1030, 950, 900, 800, 750, 700 cm^{-1}; Found: C, 79.39; H, 5.38; N, 4.34%. Anal. Calc. for $C_{40}H_{32}N_2O_4$: C, 79.45; H, 5.33; N, 4.63%.

4.2. A typical procedure for lanthanide-catalyzed asymmetric 1,3-dipolar cycloaddition reaction

The catalyst $Sc(OTf)_3$ (0.10 mmol) and (*S*,*S*)-**7d** (0.10 mmol) were stirred with powdered 4 Å molecular sieves (125 mg) in solvent (1.5 ml) for 0.5 h. Compounds **1** (0.50 mmol) and **2** (0.50 mmol) were added, and then the mixture was stirred for 20 h. Distilled water was then added to quench the reaction, and insoluble materials were filtered. The reaction mixture was extracted with dichloromethane, and dried on anhydrous sodium sulfate. The organic layer was evaporated to dryness and the residue was analyzed. The reaction yield and *endo*:*exo* ratio were determined by ^{1}H-NMR analysis, and the enantiomeric excess of the *endo* adduct was determined by HPLC analysis (DAICEL CHIRALCEL OD-H column (eluent, 30:70 2-propanol–hexane; flow rate, 0.3 ml min^{-1}; detection, UV 220 nm)). The absolute configuration was assigned by comparison of the optical rotation with that of the literature [3a].

Acknowledgements

We thank Dr Takayuki Yamashita for helpful discussions during the course of this work. We also thank undergraduate project students Takashi Okamoto and Yukiko Ogura. This work was partially supported by Doshisha University's Research Promotion Fund and a grant to RCAST at Doshisha University from the Ministry of Education, Japan.

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