# Bisoxazoline and Bioxazoline Chiral Ligands Bearing 4-Diphenylmethyl Shielding Substituents. Diels–Alder Reaction of Cyclopentadiene with 3-Acryloyl-2-oxazolidinone Catalyzed by the Aqua Nickel(II) Complex

**Shuji Kanemasa,* Kenji Adachi,† Hidetoshi Yamamoto,†† and Eiji Wada**

Institute of Advanced Material Study, Kyushu University, Kasugakoen, Kasuga 816-8580

†Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasugakoen, Kasuga 816-8580

††Department of Applied Chemistry, Faculty of Engineering, Yamaguchi University, Tokiwadai, Ube 755-8611

(Received July 9, 1999)

Enantiopure 2-amino-3,3-diphenyl-1-propanol has been synthesized by the hidantoin route starting from diphenylacetaldehyde, followed by subsequent functional group transformations and optical resolution by a chiral HPLC. This amino alcohol can be converted into two new chiral ligands: 4,4′-bis(diphenylmethyl)-2,2′-bioxazoline and 2,2′-isopropylidenebis(4-diphenylmethyloxazoline), and further to complexes with copper(II) trifluoromethanesulfonate and nickel(II) perchlorate hexahydrate. The nickel(II) aqua complex derived from the bisoxazoline effectively catalyzes the Diels–Alder reactions of cyclopentadiene with 3-acryloyl-2-oxazolidinone in high *endo*-selectivities and moderate enantioselectivities through a square planar transition structure.

We have reported the high synthetic utility of 2,2-dimethyloxazolidine chiral auxiliary having a diphenylmethyl shielding substituent at 4-position of the oxazoline ring.[1,2] In conjugate addition or dipolar cycloaddition reactions its $\alpha,\beta$-unsaturated amide derivatives have shown excellent diastereoselectivities in the absence of Lewis acid catalyst.[2–4] Two methyl substituents at 2-position serve to fix the amide nitrogen–carbonyl carbon bond as *Z*-conformation and the carbonyl carbon–vinyl carbon bond as *s-cis* conformation. One phenyl plane of the diphenylmethyl substituent shields one of the diastereofaces of the vinyl moiety as the reaction site.[1] This chiral shielding is so effective that single diastereomers of isoxazoline cycloadducts are produced in nitrile oxide 1,3-dipolar cycloadditions.[2]

On the other hand, 4-substituted oxazolines have found various successful applications as chiral ligand units in a wide variety of enantioselective syntheses: bioxazolines,[5] methylene- or isopropylidene-bridged bisoxazolines,[6,7] 2,6-pyridinediyl-2,2′-bisoxazolines,[7,8] 2,2′-(4,6-dibenzofurandilyl)-bis(4-phenyloxazoline),[9] and others are the chiral ligands included. The importance of oxazoline ligands is mainly based on the ready availability of the starting $\beta$-amino alcohols from naturally occurring, and usually inexpensive, $\alpha$-amino acids in enantiomerically pure forms. However, the shielding substituents are limited to phenyl, isopropyl, and *t*-butyl moieties.

We started the synthetic work of new oxazoline ligands having a diphenylmethyl substituent at 4-position of the oxazoline ring to examine the efficiency of chiral shielding by the diphenylmethyl substituent. This report presents the synthesis of pure enantiomers of 2-amino-3,3-diphenyl-1-propanol and new chiral oxazoline ligands such as 4,4′-bis(diphenylmethyl)-2,2′-bioxazoline (**1**) and 2,2′-isopropylidenebis(4-diphenylmethyloxazoline) (**2**) (Chart 1). Preparation of nickel(II) aqua complexes and synthetic applications to the asymmetric Diels–Alder reactions are briefly discussed.

**Synthesis of *rac*-2-Amino-3,3-diphenyl-1-propanol and Optical Resolution:** In our previous work, 2-amino-3,3-diphenyl-1-propanol (*rac*-**7**) was synthesized by reaction of the lithium enolate of ethyl *N*-benzylideneglycinate with diphenylmethyl bromide, followed by imine hydrolysis and reduction of the ester moiety.[1] However, this preparation route needed expensive reagents and resulted in a low-yield formation of the amino alcohol. Our new synthesis of *rac*-**7** in the present work is based on the usual Bücherer–Berg method (or hydantoin method)[10] starting from diphenylacetaldehyde (**3**), followed by subsequent hydrolysis, esterification, and reduction (Scheme 1). The starting aldehyde **3** was obtained in 74% yield by the pinacol rearrangement of 1,2-diphenyl-

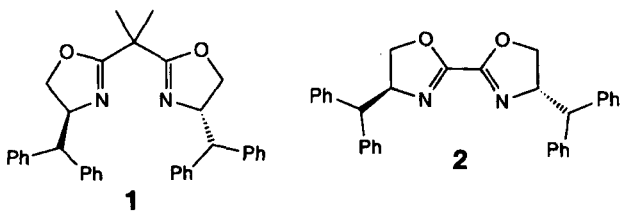
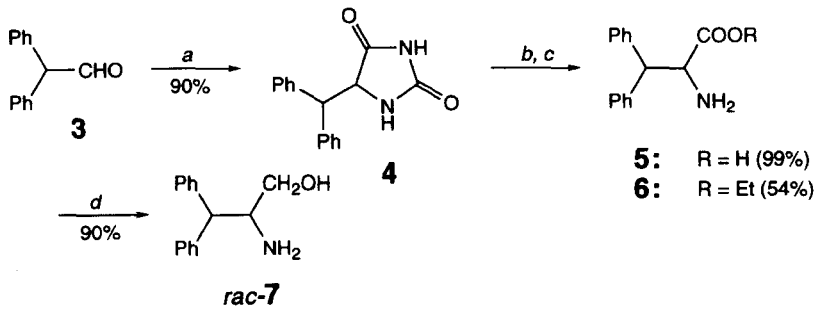
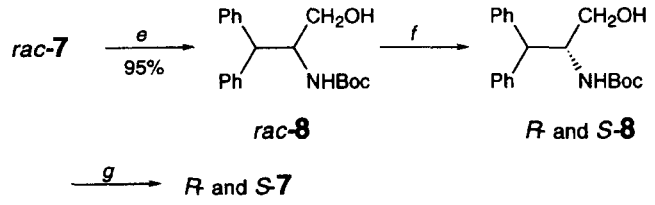



Chart 1.




*a*: NaCN, $(NH_4)_2CO_3$ in EtOH aq (50%), 50 °C, 12 h; *b*: NaOH aq, reflux, 18 h; *c*: $SOCl_2$ in EtOH, reflux, 24 h; *d*: $NaBH_4$ in EtOH aq (75%), rt, 23 h




*e*: $(Boc)_2O$, $Et_3N$, DMAP (cat) in $Et_2O$, 3 h; *f*: Chiral HPLC (Daicel OJ), hexane - *i*-PrOH = 6:1 v/v then crystallization from hexane - $Et_2O$; *g*: 2 M HCl in THF, 2 d

Scheme 1.

1,2-ethanediol and oxalic acid without solvent at 140 °C.[11] Most synthetic steps proceeded in more than 90% yields; the esterification of carboxylic acid **5** was the only low yield process, since steps of neutralization of the ester hydrochloride and extraction were not highly effective.

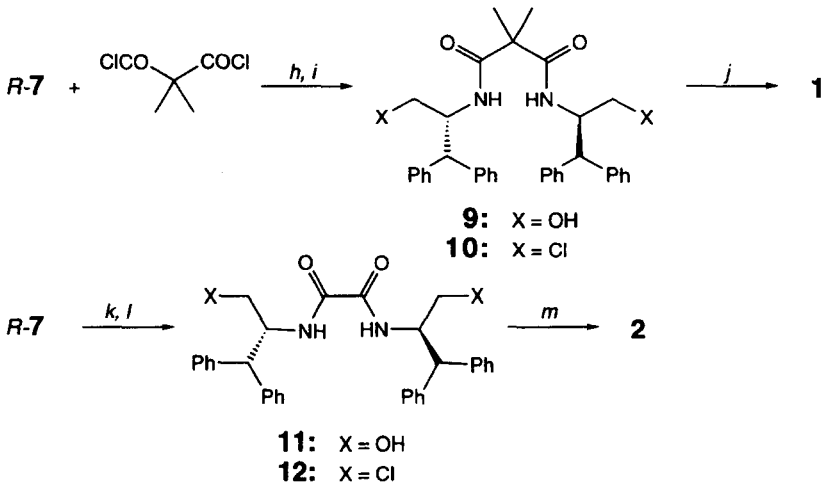
The direct optical resolution of $\beta$-amino alcohol *rac*-**7** by use of a chiral high-performance liquid chromatography (HPLC) was unsuccessful under various conditions. Not only was the peak separation of enantiomers ineffective, but also the solubility of *rac*-**7** was too low in the hexane–isopropyl alcohol mixture used as eluent. Therefore, *rac*-**7** was converted into *N*-Boc derivative *rac*-**8** which showed an improved solubility. By the HPLC operation on a chiral column (Daicel Chiral Cel OJ) with hexane–isopropyl alcohol (6 : 1 v/v) for *rac*-**8**, satisfactory separation was attained after one recycle of the eluent. When 50 mg of *rac*-**8** was charged, the initial fraction (20 mg) was obtained as a pure enantiomer and identified as *R*-enantiomer *R*-**8** on the basis of the optical rotation. Although the second fraction (20 mg) had an enantiopurity of only 80% ee, the pure enantiomer of *S*-**8** was given after crystallization from diethyl ether–hexane. Since it took only 50 min for one chromatographic operation to give 15 to 20 mg of both enantiomers of **8**, we believe that this chromatographic resolution is practical.

Removal of the Boc moiety from the pure enantiomers of **8** was easily performed quantitatively by treatment with diluted HCl in THF at room temperature without racemization to give enantiopure amino alcohol **7**.

**Synthesis of Enantiopure (*R*,*R*)-4,4′-Bis(diphenylmethyl)-2,2′-bioxazoline and (*R*,*R*)-2,2′-Isopropylidenebis(4-diphenylmethyloxazoline):** In the course of our work, the asymmetric synthesis of enantiopure (*R*)-2-amino-3,3-diphenyl-1-propanol (*R*-**7**) was reported by Koskinen and co-workers.[12] Therefore, we adopted the reported preparation method: *N*-Protection of (*S*)-serine with di-*t*-butyl carbonate was followed by esterification with diazomethane, acetalization with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid, Grignard reaction with excess phenylmagnesium bromide, reduction on palladium(II) hydroxide/charcoal in the presence of formic acid, and the final step of deprotection by alkaline hydrolysis gave *R*-**7**. It was confirmed that enantiomeric purity of *R*-**7** thus prepared was satisfactory enough to use in the following steps.

This enantiopure $\beta$-amino alcohol *R*-**7** was then applied to the synthesis of two chiral oxazoline ligands **1** and **2**. Reaction of *R*-**7** with dimethylmalonyl dichloride in the presence of triethylamine gave the corresponding diamide **9**, which was then chlorinated with thionyl chloride, producing **10** (Scheme 2). The base-mediated cyclization of **10** gave the 2,2′-isopropylidenebisoxazoline ligand **1** in 38% yield based on *R*-**7**. On the other hand, *R*-**7** was treated with dimethyl oxalate at 80 °C to give bisamide **11**. Similar chlorination with thionyl chloride followed by cyclization gave the bioxazoline ligand **2** in 33% yield based on *R*-**7**.

**The Diels–Alder Reaction Catalyzed by the Copper(II) and Nickel(II) Complexes, *R*,*R*-1·Cu(OTf)$_2$ and *R*,*R*-1·Ni(ClO$_4$)$_2$·*n*H$_2$O.** Metal complexes of bisoxazolines having a phenyl or *t*-butyl shielding substituent at 4-position of the oxazoline ring have been utilized in the asymmetric Diels–Alder reactions of cyclopentadiene with 3-acryloyl-2-oxazolidinone. The best result has been recorded in the reaction catalyzed by the copper(II) complex prepared from 2,2′-isopropylidenebis(4-*t*-butyloxazoline) and copper(II) trifluoromethanesulfonate to show an enantioselectivity better than




*h*: $Et_3N$, rt, 2 h in $CHCl_3$; *i*: $SOCl_2$, reflux, 5 h; *j*: NaOH in $CH_2Cl_2$ + aq MeOH, 40 °C, 3 d (38% for the three steps); k: Dimethyl oxalate, 80 °C; l: $SOCl_2$, reflux, 2 h, in toluene; m: 1 N NaOH, relux, 1.5 h in MeOH (33% for the three steps)

Scheme 2.

98% ee.[13] Corey and co-workers have found that the magnesium and iron(II) complexes of 2,2′-isopropylidenebis(4-phenyloxazoline) are also active catalysts.[14,15] It is interesting that the copper complex and the latter two complexes show the opposite enantioselectivities, indicating that the square planar substrate complex has been involved in the copper-(II)-catalyzed reaction,[16] while the tetrahedral or octahedral complexes were involved in the magnesium- or iron(II)-catalyzed reactions.[14,15] In the reactions proceeding through a square planar transition structure of the copper(II) complex-catalyzed reaction, the bulky *t*-butyl shielding substituent was more favored. We therefore expected that the bulky diphenylmethyl substituent would show a high enantioselectivity in the Diels–Alder reactions.

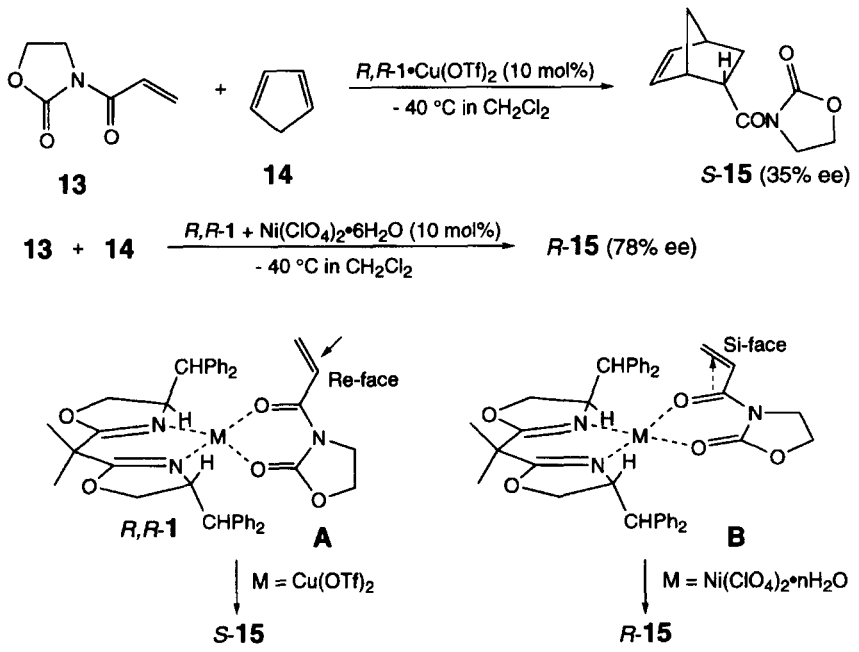
Equimolar amounts of *R,R*-**1** and copper(II) trifluoromethanesulfonate were stirred in dichloromethane at room temperature for 1 h under dry nitrogen to give a standard solution of the catalyst *R,R*-**1**·$Cu(OTf)_2$. Reaction of 3-acryloyl-2-oxazolidinone (**13**) with cyclopentadiene (**14**, 10 mol amt.) was performed in the above standard solution (catalytic loading: 10 mol%) at room temperature. A 79 : 21 mixture of *endo*- and *exo*-cycloadducts was obtained in 98% yield (Scheme 3). Enantioselectivity of the *endo*-cycloadduct **15** as major product was only 35% ee. Use of the complex catalyst derived from copper(II) hexafluoroantimonate having less coordinating counter anions did not improve the enantioselectivity (15% ee).

We therefore surveyed a variety of bisoxazoline complexes such as those prepared from the chiral ligand *R,R*-**1** and metal salts such as $MgI_2$ ($I_2$), $FeCl_2$ ($I_2$), $Mg(ClO_4)_2$, $Mn(ClO_4)_2$·$6H_2O$, $Fe(ClO_4)_2$·$nH_2O$, $Co(ClO_4)_2$·$6H_2O$, and $Zn(ClO_4)_2$·$6H_2O$. Although the complexes derived from $FeCl_2$ ($I_2$) and $Mg(ClO_4)_2$ showed high diastereoselectivities (*endo* : *exo* > 95 : 5) in the reaction at room temperature, no enantioselectivities were attained. Reactions catalyzed by the bisoxazoline complexes derived from $Mg(ClO_4)_2$, $Fe(ClO_4)_2$·$nH_2O$, $Mn(ClO_4)_2$·$6H_2O$, and $Zn(ClO_4)_2$·$6H_2O$ were poor both in diastereo- and enantioselectivities.

However, the aqua complex prepared from *R,R*-**1** and Ni-$(ClO_4)_2$·$6H_2O$ showed a high catalytic activity. The reaction between **13** and **14** catalyzed by the nickel(II) complex (10 mol%) in dichloromethane was completed in 30 min at room temperature, but both the diastereo- (*endo* : *exo* = 76 : 23) and enantioselectivities (21% ee for the *endo*-product) were not satisfactory. To our delight, the same reaction performed at −40 °C in dichloromethane gave a 93 : 7 mixture of *endo*- and *exo*-cycloadducts with the enantioselectivity of 78% ee for the *endo*-product **15**. Use of the anhydrous nickel(II) complex catalyst, prepared in situ from *R,R*-**1** (10 mol%), $NiBr_2$ (8 mol%), and $AgClO_4$ (16 mol%), at the same temperature did not improve either the catalytic activity or the enantioselectivity (93% yield, 75% ee for the *endo*-cycloadduct **15**); rather, a lower diastereoselectivity was recorded (*endo* : *exo* = 85 : 15).

The complex catalysts prepared from bioxazoline *R,R*-**2** and $FeCl_2$ ($I_2$), $Mg(ClO_4)_2$, and $Ni(ClO_4)_2$ were not so effective in the Diels–Alder reactions between **13** and **14**.

Although enantioselectivites were not so high in both cases, the aforementioned Diels–Alder reactions catalyzed by the copper(II) trifluoromethanesulfonate complex and the nickel(II) aqua complex produced *endo*-cycloadducts **15** with opposite chiralities. Based on the absolute configuration of the *endo*-cycloadducts **15** obtained,[17] we concluded that the copper(II) complex-catalyzed reaction and the nickel-(II) complex-catalyzed reaction have proceeded through a tetrahedral **A** and square planar transition structures **B**, respectively, as shown in Scheme 3. As described above, the bisoxazoline–copper(II) complex–catalyzed Diels–Alder reactions of 3-alkenoyl-2-oxazolidinones often take place through transition structures involving square planar substrate complexes.[16] Therefore, the present example provides a rare case; presumably the bulky diphenylmethyl shielding substituents of *R,R*-**1** are responsible for the reversal of enantioselectivity.[18]




Scheme 3.

It is now clear that the nickel(II) complex catalyst has activated the Diels–Alder reaction through the square planar substrate complex **B**.[19] On the other hand, the copper(II) complex was forced to have a rather unusual tetrahedral complex **A**.[18] The major reason for the low enantioselectivity observed in the copper(II) catalyzed Diels–Alder reactions would be the competitive participation of the square planar transition structure such as **B**. We therefore suspected that competitive participation of the tetrahedral complex would have contributed, to some extent, to the nickel(II) complex-catalyzed Diels–Alder reaction. If this is the case, introduction of two axial ligands to the square planar complex **B** would be effective to improve the enantioselectivity.

Addition of two mol amt. of triethylamine to the catalyst decelerated the reaction between **13** and **14** at −40 °C in the presence of 10 mol% of the aqua complex prepared from *R,R*-**1** and $Ni(ClO_4)_2 \cdot 6H_2O$, racemic cycloadducts being produced. The reaction rate (79% yield after 24 h at −40 °C) and enantioselectivity (54% ee for the *endo*-cycloadduct **15**) were not seriously affected in the presence of pyridine (two mol amt. to the catalyst) when the reaction was catalyzed by the nickel(II) aqua complex, while both the catalytic activity and enantioselectivity disappeared in the case of the anhydrous nickel(II) complex-catalyzed reaction (22% yield after 240 h at −40 °C, 0% ee for the *endo*-cycloadduct **15**). Although addition of phenyl isocyanide (two mol amt. to the catalyst), in the presence of both nickel(II) aqua and anhydrous complex catalysts, did not decrease the catalytic activity, enantioselectivity was much lowered (29 and 35% ee). Although the chirality control by the additional ligand coordination failed, the process teaches us that the nickel(II) aqua complex of *R,R*-**1** can survive as active catalyst in the presence of strongly coordinating additives such as pyridine and isonitrile.

In conclusion, we have synthesized enantiopure 2-amino-3,3-diphenyl-1-propanol by the hidantoin route starting from diphenylacetaldehyde, followed by subsequent functional group transformations and optical resolution by a chiral HPLC. This amino alcohol has been converted into two new chiral ligands: 4,4′-bis(diphenylmethyl)-2,2′-bioxazoline and 2,2′-isopropylidenebis(4-diphenylmethyloxazoline). The bisoxazoline complexes derived from copper(II) trifluoromethanesulfonate and nickel(II) perchlorate hexahydrate catalyze the Diels–Alder reactions of cyclopentadiene with 3-acryloyl-2-oxazolidinone. The nickel aqua complex catalyst leads to high *endo*-selectivities and moderate enantioselectivities through a square planar transition structure.

## Experimental

**General Procedure:** Melting points were recorded on a Yanagimoto melting point apparatus JANACO MP and are uncorrected. IR spectra were taken with a JASCO A-702 spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded with JEOL LA 600 ($^1H$ NMR: 600 MHz) and LA 400 (400 MHz for $^1H$ NMR and 100 MHz for $^{13}C$ NMR) instruments. Chemical shifts are reported in parts per million downfield ($\delta$) from internal tetramethylsilane at 27 °C unless otherwise stated. Mass spectra were recorded with a JEOL JMS-70 spectrometer operating at an ionization energy of 70 eV. Gas chromatography/mass spectra were recorded with Finnigan MAT GCQ apparatus. Elemental analyses were performed with a Hitachi 026 CHN analyzer. For preparative column chromatography, Wakogel C-200, Wako C-300, and Merck Silica gel 60 were employed. High-performance liquid chromatography (HPLC) was measured on Tosoh SC-8010 chromatograp attached by a column Hibar LiChrosorb$^R$ Si 60 (Cica Merck). Chiral HPLC analysis was performed on the same apparatus with a chiral column mentioned in each part of experimental procedures. Optical rotations were recorded with a Horiba SEPA-200 polarimeter. Flash chromatography was performed with an Eyera EF-10 apparatus on a 20×180 mm column packed with 0.04—0.063 mm silica gel 60. Micro vacuum distillation was performed with a Sibata GTO-250R Kugelrohr distilling apparatus.

**2-Amino-3,3-diphenylpropanoic Acid (5) and Ethyl 2-Amino-3,3-diphenylpropanoate (6):** A solution of diphenylacetaldehyde (**3**, 5.74 g, 29 mmol),[11] NaCN (2.13 g, 43.5 mmol), and $(NH_4)_2CO_3$ (9.75 g, 101.5 mmol) in aqueous ethanol (50% v/v, 30 ml) was heated at 50 °C for 8 h. The solvent was concentrated in vacuo. The dark colored precipitate of 5-diphenylmethylimidazolidine-2,4-dione (**4**, 6.94 g, 90%) was collected on a filter and washed with diethyl ether. This solid **4** (5.33 g, 20 mmol) was dissolved in aqueous solution of NaOH (1.6 g, 40 mmol in 16 ml) and heated under reflux for 18 h. After being cooled to room temperature, the mixture was neutralized with hydrochloric acid to give colorless solid of 2-amino-3,3-diphenylpropanoic acid[20] (**5**, 4.785 g, 99%). A solution of **5** (2.14 g, 8.9 mmol) in ethanol (50 ml) was treated with thionyl chloride (1.5 ml, 20 mmol) at 0 °C. After being stirred at room temperature for 30 min, the mixture was heated under reflux for 24 h. After the completion of reaction, the mixture was cooled down to room temperature, treated with aqueous NaOH (1 M, 10 ml) (1 M = 1 mol $dm^{-3}$), and then extracted with diethyl ether (30 ml×3). Evaporation of the dried ether gave ethyl 2-amino-3,3-diphenylpropanoate (**6**, 1.15 g, 54%). Colorless liquid; IR (neat) 3300—3400, 1730, 1600, 1495, 1455, 1375, 1180, 1030, 750, and 700 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ = 0.97 (3H, t, $J$ = 7.3 Hz, Me of COOEt), 1.52 (2H, br, $NH_2$), 3.96 (2H, q, $J$ = 7.3 Hz, $CH_2$ of COOEt), 4.21 (2H, m, H-2 and H-3), and 7.13—7.33 (10H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$ = 13.71 (Me of COOEt), 56.60 ($CH_2$ of COOEt), 58.73, 60.62 (each CH), 126.63, 126.88, 128.16, 128.30, 128.62, 140.50, 141.32 (each Ph), and 174.29 (COOEt). Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20%. Found: C, 75.88; H, 7.04; N, 5.17%.

**2-Amino-3,3-diphenyl-1-propanol (*rac*-7):** Ester **6** (2.69 g, 10 mmol) was added at 0 °C to the cooled aqueous ethanol solution (ethanol/water = 3/1 v/v, 50 ml) of $NaBH_4$ (1.5 g, 40 mmol). The mixture was stirred overnight at room temperature. The ethanol was evaporated in vacuo and the aqueous layer was extracted with dichloromethane (20 ml×5). The combined extracts were dried over $MgSO_4$ and chromatographed on silica gel with EtOAc–MeOH (3 : 1 v/v) to give 2-amino-3,3-diphenyl-1-propanol (***rac*-7**, 2.19 g, 90%): Colorless prisms; mp 120—122 °C; IR (KBr) 2800—3400, 1640, 1500, 1350, 1255, 1240, 1130, 1050, 940, 860, 810, and 715 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ = 2.20 (3H, br, OH and $NH_2$), 3.27 (1H, dd, $J_{gem}$ = 11.0 and $J_{1\text{-}2}$ = 6.6 Hz, one of H-1), 3.52 (1H, dd, $J_{gem}$ = 11.0 and $J_{1\text{-}2}$ = 2.9 Hz, the other of H-1), 3.63 (1H, ddd, $J_{2\text{-}3}$ = 10.3 and $J_{2\text{-}1}$ = 6.6, 2.9 Hz, H-2), 3.77 (1H, d, $J_{3\text{-}2}$ = 10.3 Hz, H-3), and 7.05—7.35 (10H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$ = 55.50, 56.40 (C-1 and C-3), 64.52 (C-2), 126.59, 126.75, 127.86, 128.24, 128.68, 128.91, and 142.15 (each Ph); MS (rel intensity, %) *m/z* 228 ($M^+$ + 1; 1), 196 (29), 180 (12), 179 (21), 178 (29), 168 (18), 167 (62), 166 (66), 165 (base peak), 164 (39), 152 (33), 151 (15), 118 (17), 115 (20), 100 (70), 99 (19), 91 (35), 90 (13), and 83 (19). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16%. Found: C, 79.24; H, 7.50; N, 5.94%.

***t*-Butyl *N*-(2-Hydroxy-1-diphenylmethylethyl)carbamate (8):** To a solution of 2-amino-3,3-diphenyl-1-propanol (**7**, 1.14 g, 5 mmol) and 4-dimethylaminopyridine (100 mg) in diethyl ether (100 ml) were added under nitrogen triethylamine (2.8 ml, 20 mmol) and di-*t*-butyl carbonate (1.15 ml, 5 ml). After stirring at room temperature for 3 h, the solvent and excess triethylamine were evaporated in vacuo and the residue was washed with diethyl ether (30 ml×3). The combined ether washings were removed by evaporation in vacuo to give *t*-butyl *N*-[2-hydroxy-1-diphenylmethylethyl]carbamate (**8**, 1.56 g, 95%): Colorless needles; mp 116—117 °C; $^1$H NMR ($CDCl_3$) $\delta$ = 1.33 (9H, s, *t*-Bu), 2.38 (1H, br, OH), 3.45 (1H, br d, $J_{gem}$ = 11.0 Hz, one of H-1), 3.37 (1H, br d, $J_{gem}$ = 11.0 Hz, the other of H-1), 4.15 (1H, d, $J_{3\text{-}2}$ = 10.6 Hz, H-3), 4.66 (1H, m, H-2), 4.68 (1H, br d, $J$ = 4.1 Hz, NH), and 7.17—7.33 (10H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$ = 28.26 (Me of *t*-Bu), 52.54 (C-3), 54.93 (C-1), 63.68 (C-2), 79.70 (q-C of *t*-Bu), 126.62, 126.79, 128.07, 128.45, 128.55, 128.84, 141.45, 142.01 (each Ph), and 156.121 (COO); MS (rel intensity, %) *m/z* 196 (23), 168 (32), 167 (base peak), 166 (44), 165 (58), 164 (16), 161 (12), 160 (54), 152 (24), 104 (35), 103 (13), and 91 (10). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28%. Found: C, 73.63; H, 7.53; N, 3.97%.

**Optical Resolution of 8 and Subsequent Hydrolysis Giving 7:** A solution of the racemic sample of the *N*-Boc-protected amino alcohol *rac*-**8** (50 mg in hexane–isopropyl alcohol 6 : 1 v/v (1.5 ml)) was charged into the HPLC apparatus equipped with a semipreparative chiral column (Chiralcel OJ, 1 cm×25 cm) and eluted with the same solvent (flow rate: 1.5 ml $min^{-1}$). After one recycle, the first fraction containing the *R*-enantiomer *R*-**8** was collected (32 min, 20 mg, almost pure *R*-**8**) and then the second fraction containing *S*-**8** (38 min, 20 mg, 80% ee). The *R*-enantiomer *R*-**8** ($[\alpha]_D^{23}$ = −22.3 (*c* 1 in MeOH)) was converted by the known Jones oxidation at 0 °C into (*R*)-2-(*t*-butyloxycarbonylamino)-3,3-diphenylpropanoic acid in 92% yield and its optical rotation ($[\alpha]_D^{23}$ = −34.2 (*c* 1 in MeOH)) was compared with the reported data.[21] The *R*-enantiomer *R*-**8** (0.082 g) was treated with 1 M HCl solution in THF (30 ml/30 ml) at room temperature for 24 h. The solution was neutralized with aqueous $NaHCO_3$ and extracted with chloroform (20 ml×2). The combined extracts were dried over $MgSO_4$ and evaporated to give *R*-**7** (56 mg, 100%) whose enantiopurity was determined by HPLC (Chiralcel OD-H, hexane–isopropyl alcohol 97 : 3 v/v). $[\alpha]_D^{23}$ = −26.5 (*c* 0.5 in MeOH).

**(*R*,*R*)-2,2′-Isopropylidenebis(4-diphenylmethyloxazoline) (*R*,*R*-1):** To a solution of (*R*)-2-amino-3,3-diphenyl-1-propanol (*R*-**7**, 1.137 g, 5 mmol) and triethylamine (1.7 ml, 12.5 mmol) in chloroform (5 ml) was added slowly at 0 °C dimethylmalonyl dichloride (0.423 g, 2.5 mmol). The mixture was stirred at room temperature for 2 h. After the mixture was cooled down to 0 °C, thionyl chloride (0.6 ml, 7.5 mmol) was added and this mixture was refluxed for 5 h. Saturated aqueous $NaHCO_3$ (20 ml) was added, followed by extraction with chloroform (25 ml×3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed over silica-gel chromatography with ethyl acetate to give (*R*,*R*)-*N*,*N*′-bis(2-chloro-1-diphenylmethylethyl)-2,2-dimethylmalonamide (*R*-**10**, 0.68 g, 46%): $^1$H NMR ($CDCl_3$) $\delta$ = 0.83 (6H, s, Me), 3.40 (2H, dd, $J_{gem}$ = 11.1 and $J_{2\text{-}1}$ = 2.7 Hz, one of H-2), 3.68 (2H, dd, $J_{gem}$ = 11.1 and $J_{2\text{-}1}$ = 3.3 Hz, the other of H-2), 4.26 (2H, d, $J_{CH\text{-}1}$ = 11.2 Hz, $Ph_2CH$), 5.02 (2H, m, H-1), 6.54 (2H, $J$ = 8.8 Hz, CONH), and 7.15—7.34 (20H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$ = 23.04 (Me), 47.01, 49.11, 51.84, 52.84, 127.25, 127.93, 128.10, 128.67, 129.03, 140.64, 140.78 (each Ph), and 172.71 (CON). A solution of this dichloride *R*-**10** (0.68 g, 1.16 mmol) in a mixture of aqueous NaOH (1 g in 4 ml of water) with dichloromethane (4 ml) was stirred at 40 °C for 3d. Saturated aqueous $NH_4Cl$ (40 ml) was added and the mixture was extracted with dichloromethane (30 ml×3). The combined extracts were dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel with hexane–diethyl ether (7 : 1 v/v) to give *R*,*R*-**1** (0.51 g, 86%). Colorless needles; mp 121—122 °C; $[\alpha]_D^{23}$ = 107.27 (*c* 1.003 in $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ = 1.28 (6H, s, Me), 4.02 (2H, dd, $J_{gem}$ = 8.7 and $J_{5\text{-}4}$ = 7.0 Hz, one of H-5), 4.02 (2H, d, $J_{CH\text{-}4}$ = 7.5 Hz, $Ph_2CH$), 4.26 (2H, dd, $J_{gem}$ = 8.7 and $J_{5\text{-}4}$ = 9.7 Hz, the other of H-5), 4.88 (2H, m, H-4), and 7.14—7.29 (20H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$ = 23.81 (Me), 38.61 (C), 56.09

(C-5), 69.17 ($Ph_2CH$), 71.35 (C-4), 126.36, 126.60, 128.15, 128.41, 129.02, 141.80 (each Ph), and 169.38 (C-2); MS (rel intensity, %) *m/z* 514 ($M^+$; 2), 348 (16), 347 (33), 207 (30), 193 (32), 181 (29), 178 (10), 168 (20), 167 (base peak), 166 (53), 165 (72), 164 (11), 152 (25), 151 (11), 137 (12), 111 (31), 110 (25), 91 (41), and 82 (12). Anal. Calcd for $C_{35}H_{34}N_2O_2$: C, 81.68; H, 6.66; N, 5.44%. Found: C, 81.68; H, 6.60; N, 5.42%.

**(*R*,*R*)-4,4′-Bisdiphenylmethyl-2,2′-bioxazoline (*R*,*R*-2):** A solution of (*R*)-2-amino-3,3-diphenyl-1-propanol (*R*-**7**, 2.27 g, 10 mmol) and dimethyl oxalate (2.36 g, 20 mmol) in toluene (30 ml) containing a few drops of 1,2-dichloroethane was heated at 80 °C under stirring for 9 h. The solvents were evaporated in vacuo to give a colorless solid of (*R*,*R*)-*N*,*N*′-bis(1-diphenylmethyl-2-hydroxyethyl)oxamide (*R*,*R*-**11**, 2.4 g, 94%, crystallized from ethanol): $^1$H NMR ($CDCl_3$) $\delta$ = 2.17 (4H, br, OH and NH), 3.62 (2H, dd, $J_{gem}$ = 11.4 and $J_{2\text{-}1}$ = 4.4 Hz, one of H-2), 3.62 (2H, dd, $J_{gem}$ = 11.4 and $J_{2\text{-}1}$ = 2.9 Hz, the other of H-2), 4.26 (2H, d, $J_{CH\text{-}1}$ = 10.6 Hz, $Ph_2CH$), 4.66 (2H, m, H-1), and 7.16—7.30 (20H, m, Ph). Thionyl chloride (3.3 ml, 45 mmol) was added to this amide *R*,*R*-**11** (2.3 g, 4.5 mmol in toluene 5 ml) at 0 °C and the mixture was heated under reflux for 2 h. On cooling down to room temperature, a colorless solid of *N*,*N*′-bis(2-chloro-1-diphenylmethylethyl)oxamide (*R*,*R*-**12**, 2.2 g, 90% crystallized from ethyl acetate) was obtained: $^1$H NMR ($CDCl_3$) $\delta$ = 3.49 (2H, dd, $J_{gem}$ = 11.4 and $J_{2\text{-}1}$ = 2.9 Hz, one of H-2), 3.62 (2H, dd, $J_{gem}$ = 11.4 and $J_{2\text{-}1}$ = 3.3 Hz, the other of H-2), 4.26 (2H, d, $J_{CH\text{-}1}$ = 10.6 Hz, $Ph_2CH$), 4.66 (2H, m, H-1), and 7.17—7.40 (20H, m, Ph). The dichloride (2 g, 3.7 mmol) in methanol (60 ml) containing 1 M NaOH (10 ml) was heated under reflux for 1.5 h. The solvents were evaporated in vacuo; the residue was extracted with diethyl ether (30 ml×3); the combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was crystallized from ethanol to give (*R*,*R*)-4,4′-bisdiphenylmethyl-2,2′-bioxazoline (*R*,*R*-**2**, 1.49 g, 85%): Colorless solid; mp 198—199 °C; $[\alpha]_D^{23}$ = 71.68 (*c* 1.003 in $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ = 4.04 (2H, d, $J_{CH\text{-}4}$ = 6.6 Hz, $Ph_2CH$), 4.07 (2H, dd, $J_{gem}$ = 9.2 and $J_{5\text{-}4}$ = 11.7 Hz, one of H-5), 4.42 (2H, dd, $J_{gem}$ = 9.2 and $J_{5\text{-}4}$ = 9.5 Hz, the other of H-5), 5.13 (2H, m, H-4), and 7.16—7.31 (20H, m, Ph); MS (rel intensity, %) *m/z* 474 (11), 473 (22), 472 ($M^+$; 28), 305 (10), 208 (17), 207 (28), 178 (12), 169 (17), 164 (64), 153 (30), 152 (base peak), 151 (48), 139 (13), 138 (33), 137 (13), and 128 (11). Anal. Calcd for $C_{32}H_{28}N_2O_2$: C, 81.33; H, 5.97; N, 5.93%. Found: C, 81.15; H, 6.16; N, 5.85%.

**Diels–Alder Reactions between Cyclopentadiene and 3-Acryloyl-2-oxazolidinone. The Copper(II) Complex-Catalyzed Reaction:** A mixture of ligand *R*,*R*-**1** (15.4 mg, 0.03 mmol) and copper(II) trifluoromethanesulfonate (9.5 mg, 0.03 mmol) in dichloromethane (2 ml) was stirred under dry nitrogen at room temperature for 1 h. To this mixture were added 3-acryloyl-2-oxazolidinone (0.042 g, 0.3 mmol) in dichloromethane (1 ml) at room temperature and cyclopentadiene (0.12 ml, 1.5 mmol) at −78 °C. The resulting mixture was allowed to stir under the reaction conditions specified. After the reaction was completed, saturated ammonium chloride aqueous solution was added and the mixture was extracted with dichloromethane (20 ml×2). The combined extracts were dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel with hexane–ethyl acetate (4 : 1 v/v) to give a mixture of *endo*- and *exo*-cycloadducts. The *endo* : *exo* ratio was determined on the basis of $^1$H NMR spectrum and the enantioselectivity was based on the chiral HPLC analysis by using Chiral Cel OD (hexane : isopropyl alcohol = 50 : 1 v/v).

**The Nickel(II) Complex-Catalyzed Reaction:** A mixture of ligand *R*,*R*-**1** (10.3 mg, 0.02 mmol) and nickel(II) perchlorate hexahydrate (6.4 mg, 0.02 mmol) in dichloromethane (2 ml) was stirred at room temperature for 2 h during which time the perchlorate dissolves to give a clear greenish blue solution. To this solution were added 3-acryloyl-2-oxazolidinone (0.028 g, 0.2 mmol) in dichloromethane (1 ml) at room temperature and cyclopentadiene (0.08 ml, 1 mmol) at −78 °C. The resulting mixture was allowed to stir under the reaction conditions specified. After the reaction was completed, saturated ammonium chloride aqueous solution was added and the mixture was extracted with dichloromethane (15 ml×2). The combined extracts were dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel with hexane–ethyl acetate (4 : 1 v/v) to give a mixture of *endo*- and *exo*-cycloadducts.

## References


1 S. Kanemasa and K. Onimura, *Tetrahedron*, **48**, 8631 (1992).

2 S. Kanemasa and K. Onimura, *Tetrahedron*, **48**, 8645 (1992).

3 S. Kanemasa, H. Suenaga, and K. Onimura, *J. Org. Chem.*, **59**, 6949 (1994).

4 S. Kanemasa, M. Nomura, S. Yoshinaga, and H. Yamamoto, *Tetrahedron*, **51**, 10463 (1995).

5 a) D. Muller, G. Umbricht, B. Weber, and A. Pfaltz, *Helv. Chim. Acta*, **74**, 232 (1991). b) Y. Ukaji, M. Miyamoto, M. Mikuni, S. Takeuchi, and K. Inomata, *Bull. Chem. Soc. Jpn.*, **69**, 735 (1996).

6 As a recent review: A. K. Ghosh, M. Mackiarajan, and J. Cappiello, *Tetrahedron Asymm.*, **9**, 1 (1998).

7 a) D. A. Evans, J. A. Murry, and M. C. Kozlowski, *J. Am. Chem. Soc.*, **118**, 5814 (1996). b) D. A. Evans, M. C. Kozlowski, and J. S. Tedrow, *Tetrahedron Lett.*, **37**, 7481 (1996). c) D. A. Evans, M. C. Kozlowski, C. S. Burgey, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **119**, 7893 (1997). d) D. A. Evans, T. Rovis, M. C. Kozlowski, and J. S. Tedrow, *J. Am. Chem. Soc.*, **121**, 1994 (1999).

8 a) H. Nishiyama, S. Yamaguchi, S.-B. Park, and K. Itoh, *Tetrahedron Asymm.*, **4**, 143 (1993). b) H. Nagashima, T. Ueda, H. Nishiyama, and K. Itoh, *Chem. Lett.*, **1993**, 347. c) H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **68**, 1247 (1995). d) S.-B. Park, N. Sakata, and H. Nishiyama, *Chem. Europ. J.*, **2**, 303 (1996). e) H. Brunner, C. Bluechel, and M. P. Doyle, *J. Organomet. Chem.*, **541**, 89 (1997). f) H. Nishiyama, T. Shimada, H. Itoh, H. Sugiyama, and Y. Motoyama, *J. Chem. Soc., Chem. Commun.*, **1997**, 1863. g) A. I. Sanchez-Blanco, K. V. Gothelf, and K. A. Jørgensen, *Tetrahedron Lett.*, **38**, 7923 (1997). h) A. Yanagisawa, K. Kimura, Y. Nakatsuka, and H. Yamamoto, *Synlett.*, **1998**, 958. i) D. A. Evans and J. S. Johnson, *J. Am. Chem. Soc.*, **120**, 4895 (1998). j) D. A. Evans, C. S. Burgey, N. A. Paras, T. Vojkovsky, and S. W. Tregay, *J. Am. Chem. Soc.*, **120**, 5824 (1998).

9 a) S. Kanemasa, Y. Oderaotoshi, H. Yamamoto, J. Tanaka, E. Wada, and D. P. Curran, *J. Org. Chem.*, **62**, 6454 (1997). b) S. Kanemasa, Y. Oderaotoshi, S.-I. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, and D. P. Curran, *J. Am. Chem. Soc.*, **120**, 3074 (1998). c) S. Kanemasa, Y. Oderaotoshi, and E. Wada, *Synth. Org. Chem. Jpn.*, **56**, 368 (1998). d) S. Kanemasa, Y. Oderaotoshi, J. Tanaka, and E. Wada, *Tetrahedron Lett.*, **39**, 7521 (1998). e) S. Kanemasa, Y. Oderaotoshi, J. Tanaka, and E. Wada, *J. Am. Chem. Soc.*, **120**, 12355 (1998).

10 E. Pierson, M. Giella, and M. Tishler, *J. Am. Chem. Soc.*, **70**, 1450 (1948).

11 Melting point of oxalic acid is 104 °C so that the reaction mixture melts at the reaction temperature applied.

12 A. M. Koskinen, H. Hassila, V. T. Myllymaki, and K. Rissanen, *Tetrahedron Lett.*, **36**, 5619 (1995).

13 D. A. Evans, S. J. Miller, and T. Lectka, *J. Am. Chem. Soc.*, **115**, 6460 (1993).

14 E. J. Corey, N. Imai, and H. Zhang, *J. Am. Chem. Soc.*, **113**, 728 (1991).

15 E. J. Corey and K. Ishihara, *Tetrahedron Lett.*, **33**, 6807 (1992).

16 a) A. S. Gokhale, A. B. E. Minidis, and A. Pfaltz, *Tetrahedron Lett.*, **36**, 1831 (1995). b) M. B. Andrus, A. B. Argade, X. Chen, and M. G. Pamment, *Tetrahedron Lett.*, **36**, 2945 (1995). c) M. Miura, M. Enna, K. Okuno, and M. Nomura, *J. Org. Chem.*, **60**, 4999 (1995). d) M. Johannsen and K. A. Jørgensen, *J. Org. Chem.*, **60**, 5757 (1995). e) M. Johannsen, and K. A. Jørgensen, *Tetrahedron*, **52**, 7321 (1996). f) R. Schumacher and H.-U. Reissig, *Liebigs Ann., Recl.*, 521 (1997). g) R. Schumacher, F. Dammast, and H.-U. Reissig, *Chem. Europ. J.*, **3**, 614 (1997). h) S. Yao, M. Johannsen, R. G. Hazell, and K. A. Jørgensen, *J. Org. Chem.*, **63**, 118 (1998).

17 For the determination of absolute configuration of (*S*)-**15**: Ref. 9b.

18 Reversal enantioselectivity of *t*-butyl vs. phenyl–substituted bisoxazoline–copper(II) complex catalyzed Diels–Alder and ene-reactions: D. A. Evans, J. S. Johnson, C. S. Burgey, and K. R. Campos, *Tetrahedron Lett.*, **40**, 2879 (1999).

19 For the nickel(II) complex catalyzed Diels–Alder reactions where square planar transition state geometries have been involved: A. K. Ghosh, H. Cho, and J. Capiello, *Tetrahedron Asymm.*, **9**, 3687 (1998).

20 H. G. Chen, V. G. Beylin, M. Marlatt, B. Leya, and O. P. Goel, *Tetrahedron Lett.*, **33**, 3293 (1992).

21 a) M. P. Sibi, P. K. Deshpande, A. J. L. Loggia, and J. W. Christensen, *Tetrahedron Lett.*, **36**, 8961 (1995). b) H. G. Chen, V. G. Beylin, M. Marlatt, B. Leja, and O. P. Goel, *Tetrahedron Lett.*, **33**, 3293 (1992).