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Preparation and application of bisoxazoline ligands with a chiral spirobiindane skeleton for asymmetric cyclopropanation and allylic oxidation

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Dedicated to Professor Jack Halpern on the occasion of his 80th birthday

Abstract—A new type of bisoxazoline ligand **4** (abbreviated as SpiroBOX) containing a chiral spirobiindane scaffold were easily prepared in high yields from enantiomerically pure 1,1′-spirobiindane-7,7′-diol (SPINOL) with 1,1′-spirobiindane-7,7′-dicarboxylic acid as the key intermediate. Ligands **4** were applied to the Cu-catalyzed asymmetric cyclopropanation of styrenes with menthyl diazoacetate and allylic oxidation of cyclic alkenes with *tert*-butyl perbenzoates. The copper complexes of ligands **4** showed high activities and moderate to good enantioselectivities.

1. Introduction

The synthesis of new chiral ligands is a focus of research in transition metal-catalyzed asymmetric reactions. A large number of chiral ligands have been developed over the last few decades, some of which have been successfully applied in the production of chiral compounds in industry.[1] There are many features that have to be considered in the design of new chiral ligands. Among them, an appropriate scaffold is a fundamental element for an efficient ligand. One of the excellent examples is that the axially chiral 1,1′-binaphthyl structure has been proven to be an ideal skeleton for many types of ligands.[2]

C_2-Symmetric bisoxazolines are the most popular chiral nitrogen ligands because of their convenient synthesis, modular nature, and more importantly wide applicability in metal-catalyzed transformations. Since Masamune and co-workers,[3] Pfaltz and co-workers,[4] and Evans et al.[5] reported the first bisoxazoline ligands **1** with a methylene bridge independently in the early 1990s, a variety of chiral bisoxazolines with different bridges and substituents have been developed.[6] The bisoxazolines with a chiral biphenyl, binaphthyl, and other backbones, such as ligands **2** and **3**, were also synthesized.[7] As the chiralities on the oxazoline ring and backbone match each other, the enantioselectivities of the ligands are normally enhanced. For instance, in the Pd-catalyzed Wacker-type cyclization of 2,3-dimethyl-2-butenylphenol, ligand (*S*,*S*)-**3** afforded dihydrobenzofuran product in 97% ee, while ligand **1** gave the same product in only 35% ee.[8] Over the last few years, we have developed a new series of chiral phosphorous ligands based on the spirobiindane scaffold and demonstrated that they are highly efficient for asymmetric hydrogenation[9] and C–C bond forming reactions.[10] Herein, we report the synthesis of the bisoxazoline ligands bearing a chiral spirobiindane scaffold, 7,7′-bis[(*S*)-4-alkyl-oxazolin-2-yl]-1,1′-spirobiindane **4** (abbreviated as SpiroBOX) (Scheme 1) and their applications in Cu-catalyzed asymmetric cyclopropanation of styrenes with menthyl diazoacetate and allylic oxidation of cyclic olefins with *tert*-butyl perbenzoates.

2. Results and discussion

2.1. Preparation of SpiroBOX ligands

Enantiomerically pure 1,1′-spirobiindane-7,7′-diol (SPINOL)[11] is a suitable starting compound for the preparation of chiral spiro ligands. SPINOL was firstly

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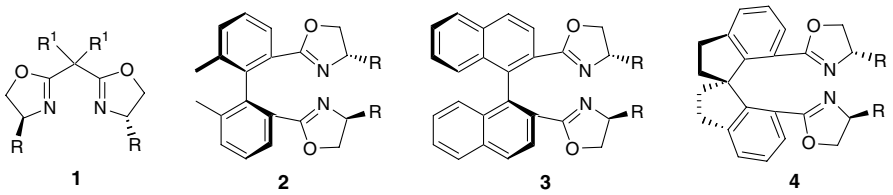


Scheme 1.

converted into bis(triflate) **5** in quantitative yield by treatment with trifluoromethane–sulfonic anhydride with the aid of pyridine. The reaction of compound **5** with $Zn(CN)_2$ catalyzed by $Pd(PPh_3)_4$ afford dicarbonitrile **6**. The utilization of $Zn(CN)_2$ as a cynation agent is crucial for this transformation. When KCN or NaCN, instead of $Zn(CN)_2$ was used, there was no target compound formed, even under harsh reaction condition. It was reported that the aromatic cyanides could react with amino alcohols in the presence of $ZnCl_2$ or other Lewis acid catalysts to construct oxazoline rings.[12] However, in our attempt, the dicarbonitrile **6** was found to be inert in the reaction with amino alcohols in virtue of the steric hindrance of the siprobiindane backbone. A step-wise strategy was finally taken to prepare dioxazolines. Dicarbonitrile **6** was hydrolyzed to the dicarboxylic acid **7** with dilute H_2SO_4, followed by treatment with optically active amino alcohols in the presence of dicyclohexyl-carbodiimide (DCC) and benzotriazol-1-ol (HOBt) to give amides **8** in almost quantitative yields. Amides **8** were subjected to oxazoline ring formation by the reaction with triphenylphosphine, carbon tetrachloride, and triethylamine to afford SpiroBOX ligands **4** in 73–97% yield.[13] As there are two stereogenic factors, one on the spirobiindane skeleton and the other on oxazoline rings, the SpiroBOX ligands **4** should have a pair of diastereomers. By using different enantiomers of SPINOL, both diastereomers of SpiroBOX ligands, (R_a,*S*,*S*)-**4** and (S_a,*S*,*S*)-**4**, were prepared in high yields (Scheme 2).

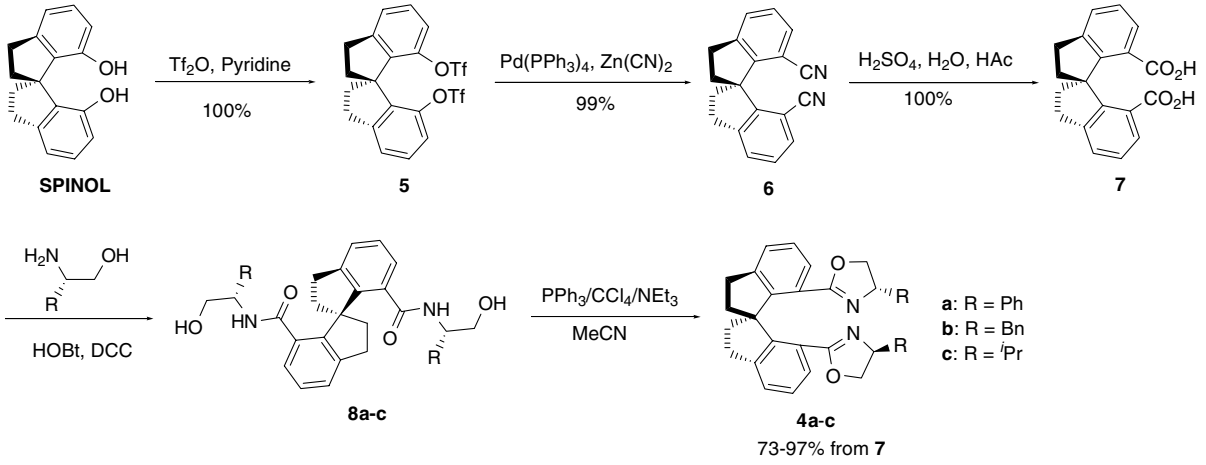
2.2. Asymmetric cyclopropanation of styrenes

Copper-catalyzed asymmetric cyclopropanation of styrenes with diazoacetates is a model reaction for the evaluation of efficiency of nitrogen ligands.[14] To test the activity and enantioselectivity of SpiroBOX ligands **4**, we first investigated the asymmetric cyclopropanation of styrene with (1*S*,2*R*,5*S*)-menthyl diazoacetate catalyzed by the copper complexes of SpiroBOX ligands. The reaction was carried out in dichloromethane with $(CuOTf)_2C_6H_6$ as a precatalyst at refluxing temperature. Comparison of the two diastereomers of SpiroBOX ligands clearly revealed that the ligand (R_a,*S*,*S*)-**4** has a matched combination of chiralities (Table 1, entries 1 and 2). Ligand (R_a,*S*,*S*)-**4c** gave the highest yield (93%), diastereoselectivity (cis/trans = 11:89) and ee value (70% ee for trans-isomer). When using chloroform as solvent, the reaction became sluggish and the yield decreased to 53% (Table 1, entry 5). The other copper salts, such as $CuPF_6(MeCN)_4$, $CuClO_4(MeCN)_4$, and CuCl, were also tried, with $(CuOTf)_2C_6H_6$ being the best choice of precatalyst.

Various *para*-substituted styrenes were examined in the cyclopropanation reaction. The results illustrated in Table 2 showed that the electron-withdrawing substituents on the styrene benefit enantioselectivity. The highest enantioselectivity (82% ee) was achieved by using 4-trifluoromethylstyrene substrate (Table 2, entry 1). In all cases, the trans/cis ratios were more than 80:20 and the electronic character of the substrate only had a slight influence on the diastereoselectivity.

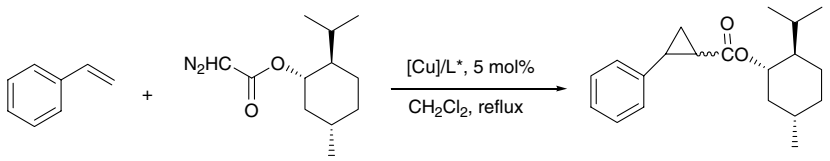
2.3. Asymmetric allylic oxidation of cycloalkenes

The copper-catalyzed asymmetric allylic oxidation of olefins with peresters provided an efficient route to prepare chiral allylic alcohols and their derivates, which are useful building blocks in organic synthesis. Since Pfaltz



Scheme 2.

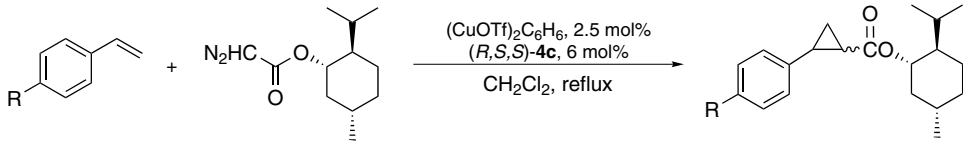
Table 1. Asymmetric cyclopropanation of styrene with (1*S*,2*R*,5*S*)-menthyl diazoacetate: optimizing reaction conditions[a]



Entry	Ligand	[Cu]	Time	Yield[b] (%)	cis/trans[c]	ee[c] (%)
1	(R_a,*S*,*S*)-**4a**	$(CuOTf)_2C_6H_6$	5 d	62	24:76	40/49
2	(S_a,*S*,*S*)-**4a**	$(CuOTf)_2C_6H_6$	6 d	71	25:75	11/13
3	(R_a,*S*,*S*)-**4b**	$(CuOTf)_2C_6H_6$	6 h	53	30:70	23/21
4	(R_a,*S*,*S*)-**4c**	$(CuOTf)_2C_6H_6$	3 h	93	11:89	62/70
5[d]	(R_a,*S*,*S*)-**4c**	$(CuOTf)_2C_6H_6$	3 d	53	21:79	77/68
6	(R_a,*S*,*S*)-**4c**	$CuPF_6(MeCN)_4$	3 h	86	12:88	65/69
7	(R_a,*S*,*S*)-**4c**	$CuClO_4(MeCN)_4$	24 h	30	20:80	47/31
8	(R_a,*S*,*S*)-**4c**	CuCl	24 h	37	25:75	9/31

[a] Reaction conditions: 5 mol % [Cu], 6 mol % ligands, 0.5 mmol menthyl diazoacetate, and 4 mmol styrene in dichloromethane at refluxing temperature.
[b] Isolated yield based on the menthyl diazoacetate.
[c] Determined by GC on HP-5 column.
[d] Chloroform as solvent at refluxing temperature.

Table 2. Asymmetric cyclopropanation of *para*-substituted styrene with (1*S*,2*R*,5*S*)-menthyl diazoacetate[a]



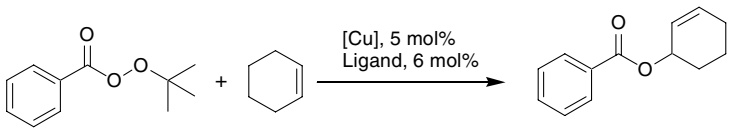
Entry	R	Yield (%)	cis/trans	ee (%)[b]
1	4-CF_3	56	14:86	82
2	4-Cl	54	14:84	82
3	4-Br	61	17:83	72
4	H	93	11:89	70
5	4-Me	67	18:82	55
6	4-OMe	55	15:85	53

[a] For reaction conditions and analyses, see Table 1 and Experimental section.
[b] Ee of trans-isomer.

and co-workers[15] and Andrus et al.[16] first introduced the chiral bisoxazolines into this reaction, it has drawn much attention to use bisoxazoline ligands for improving the activity and enantioselectivity of copper catalysts. Although great efforts have been made, only limited successful results have been achieved.[17] The major unsolved problems in asymmetric allylic oxidation include: (1) the activities of catalysts are too low, in most cases the reaction needs one or two weeks for completion and (2) the enantioselectivities of reactions are not high. Therefore, the search for new catalysts with high activity and enantioselectivity still remains to be a focus in the study of this important asymmetric transformation. To extend the scope of application of SpiroBOX ligands **4** in transition metal-catalyzed asymmetric reactions, we investigated the Cu-catalyzed allylic oxidation of cyclic olefins with perbenzoates, producing the corresponding allyl benzoate in moderate to good enantioselectivities.

A model reaction was established with cyclohexene as the standard substrate and *tert*-butyl perbenzoate as oxidant in acetone at room temperature in the presence of 5 mol % of copper (I) catalyst generated in situ from copper(I) salts and the ligands **4**. Comparison of ligands showed that the (R_a,*S*,*S*) ligands have matched chiralities for the asymmetric allylic oxidation (Table 3, entries 1 and 2), which is similar to that in the asymmetric cyclopropanation reaction. Ligand (R_a,*S*,*S*)-**4b**, which contained benzyl groups on the oxazoline rings, gave the highest enantioselectivity. Different copper salts, such as $CuPF_6(MeCN)_4$, $(CuOTf)_2C_6H_6$, and $Cu(OTf)_2$ could be used as a resource of catalyst. Further studies revealed that the reaction temperature has almost no influence on the ee value of product, but strongly impacted on the reactivity of the reaction. When the reaction temperature was increased to 40 °C, the reaction finished within 6 h without loss of yield or enantioselectivity (entry 7). This result represents one of the highest activities of Cu/bisoxazoline catalysts in the asymmetric allylic oxidation reaction. In addition to acetone, acetonitrile can also be used as a solvent to give a comparable activity, while the enantioselectivity became lower (entry 9).

Table 3. Asymmetric allylic oxidation of cyclohexene with *tert*-butyl perbenzoate: optimizing reaction conditions[a]



Entry	Ligand	[Cu]	Solvent	T (°C)	Time	Yield[b] (%)	ee[c] (%)
1	(R_a,*S*,*S*)-**4a**	$CuPF_6(MeCN)_4$	Acetone	rt	15 h	60	38
2	(S_a,*S*,*S*)-**4a**	$CuPF_6(MeCN)_4$	Acetone	rt	20 h	65	−15
3	(R_a,*S*,*S*)-**4b**	$CuPF_6(MeCN)_4$	Acetone	rt	2 d	58	70
4	(R_a,*S*,*S*)-**4c**	$CuPF_6(MeCN)_4$	Acetone	rt	25 h	59	2
5	(R_a,*S*,*S*)-**4b**	$(CuOTf)_2C_6H_6$	Acetone	rt	2 d	45	70
6	(R_a,*S*,*S*)-**4b**	$Cu(OTf)_2$	Acetone	rt	2 d	43	68
7	(R_a,*S*,*S*)-**4b**	$CuPF_6(MeCN)_4$	Acetone	40	6 h	57	70
8	(R_a,*S*,*S*)-**4b**	$CuPF_6(MeCN)_4$	Acetone	0	12 d	45	69
9	(R_a,*S*,*S*)-**4b**	$CuPF_6(MeCN)_4$	Acetonitrile	rt	2 d	69	58
10	(R_a,*S*,*S*)-**4b**	$CuPF_6(MeCN)_4$	Benzene	rt	2 d	57	14

[a] Reaction conditions: 5 mol % [Cu], 6 mol % ligands, 0.2 mmol *tert*-butyl perbenzoate, and 3 mmol cyclohexene.
[b] Isolated yield based on *tert*-butyl perbenzoate.
[c] Determined by HPLC on Chiralcel OD-H column.

Under the optimized conditions, cyclohexene and cyclopentene were oxidized with different perbenzoates and the results are illustrated in Table 4. The ring size of the cycloalkenes and the electronic characters of substituents at the *para*-position of *tert*-butyl perbenzoates only have a slight influence on the ee value of products. The properties of the substituent on the peresters have a great impact on the yield of oxidation products. For example, the introduction of a strong electron-withdrawing NO_2 group at the *para*-position of *tert*-butyl perbenzoate enhanced the yield of the allylic oxidation product to 80% (entry 5). However, a *ortho*-NO_2 group in the perester dramatically lowered the yield of oxidation product to 16%, indicating the steric hindrance of substituent has a negative impact to the reactivity of *tert*-butyl perbenzoate oxidant (entry 6).

3. Conclusion

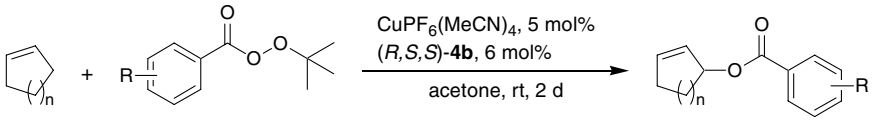
A series of C_2-symmetric chiral bisoxazoline ligands **4** with a spirobiindane scaffold were prepared from enantiomerically pure 1,1′-spirobiindane-7,7′-diol and 2-amino alcohols, in five steps, in high yields. These new types of bisoxazolines were evaluated in Cu-catalyzed asymmetric cyclopropanation of styrenes with menthyl diazoacetate, and high diastereoselectivities with moderate to good enantioselectivities were obtained. Ligands **4** were also proven to be efficient in the Cu-catalyzed asymmetric allylic oxidation of cyclic alkenes with *tert*-butyl perbenzoates, providing cycloalkenyl benzoates in moderate enantioselectivities.

4. Experimental

4.1. General methods

All reactions and manipulations were performed using standard Schlenk techniques. Acetone was distilled from 4 Å molecular sieves. Benzene was distilled from sodium benzophenone ketyl. Acetonitrile was distilled from calcium hydride. The cyclic olefins were distilled before use. The perbenzoates were prepared according to the previous method.[18] CuOTf, HOBt, and DCC were purchased from Aldrich and used directly. $CuPF_6$ was recrystallized from acetonitrile before use. NMR spectra were recorded with a Bruker or Varian spectrometer at 400 or 300 (^{1}H NMR), 100 or 75 (^{13}C NMR) MHz. Chemical shifts were reported in ppm down field from internal

Table 4. Asymmetric allylic oxidation of cyclic olefins with *tert*-butyl benzoates[a]



Entry	R	*n*	Yield (%)	ee (%)
1	H	1	58	70
2	H	2	58	70
3	4-OMe	2	67	67
4	4-Me	2	65	66
5	4-NO_2	2	80	67
6	2-NO_2	2	16	59

[a] For the reaction conditions and analyses, see Table 1 and Experimental section.

Me_4Si. Optical rotations were determined using a Perkin Elmer Model 341 polarimeter. Elemental analyses were performed on Yanaca CDRDER MT-3 instrument. Mass spectra were recorded on a LCQ Advantage spectrometer with ESI resource. GC analyses were performed using a Hewlett Packard Model HP 6890 Series. HPLC analyses were performed using a Hewlett Packard Model HP 1100 Series chromatography.

4.2. (*R*)-7,7′-Bis(trifluoromethanesulfonyloxy)-1,1′-spirobiindane (*R*)-5

To a solution of (*R*)-1,1′-spirobiindane-7,7′-diol (5.0 g, 19.8 mmol) and pyridine (7.0 mL, 86.7 mmol) in 100 mL of CH_2Cl_2, trfluoromethanesulfonic anhydride (8.2 mL, 43.7 mmol) was added slowly at 0 °C. The mixture was stirred at room temperature overnight. After removal of the solvent, the residue was diluted with CH_2Cl_2 (200 mL) and washed with 5% aqueous HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/petroleum ether = 1:20) to afford (*R*)-**5** (10.2 g, 100%) as a white solid; mp 62–64 °C; $[\alpha]_D^{20} = +143$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (m, 4H), 3.10 (m, 4H), 7.15 (dd, 2H, $J = 1.8$ and 6.6 Hz), 7.26–7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1 (CH_2), 38.6 (CH_2), 59.4 (CH), 115.9 (C), 118.5 (CF_3), 120.1 (CH), 124.4 (CH), 129.4 (CH), 138.2 (C), 145.8 (C), 147.7 (C); MS (EI) *m*/*z* (relative intensity) 516 (M^+, 100). Anal. Calcd for $C_{19}H_{14}F_6O_6S_2$: C 44.19, H 2.73. Found: C 43.97, H 2.83.

4.3. (*R*)-1,1′-Spirobiindane-7,7′-dicarbonitrile (*R*)-6

A mixture of bis(triflate) (*R*)-**5** (6.7 g, 13 mmol), $Zn(CN)_2$ (3.6 g, 30.1 mmol), and $Pd(PPh_3)_4$ (1.6 g, 1.38 mmol) in DMF (13 mL) was stirred at 140 °C for 24 h. The resulting mixture was diluted with ethyl acetate, washed sequentially with aqueous Na_2CO_3 and brine and dried over anhydrous $MgSO_4$. The dried organic layers were filtrated and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/petroleum ether = 1:7) to afford (*R*)-**6** (3.5 g, 99%) as white crystals; mp 194–195 °C; $[\alpha]_D^{20} = +144$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33–2.50 (m, 4H), 3.09–3.16 (m, 4H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.47–7.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1 (CH_2), 39.6 (CH_2), 61.8 (C), 108.3 (CH), 116.7 (CN), 128.5 (CH), 129.6 (CH), 132.0 (C), 146.0 (C), 151.1 (C); MS (EI) *m*/*z* (relative intensity) 270 (M^+, 100). Anal. Calcd for $C_{19}H_{14}N_2$: C 84.42, H 5.22, N 10.36. Found: C 84.42, H 5.36, N 10.56.

4.4. (*R*)-1,1′-Spirobiindanyl-7,7′-dicarboxylic acid (*R*)-7

Dinitrile (*R*)-**6** (3.5 g, 13.0 mmol) was added to a mixture of H_2O (90 mL), HOAc (30 mL), and H_2SO_4 (60 mL), and the mixture stirred at 145 °C for 48 h. The resulting mixture was diluted with water (600 mL), and extracted with ethyl acetate (3×100 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in reduced pressure. The residue was purified by flash chromatography (ethyl acetate/petroleum ether = 1:1) to give (*R*)-**7** (4.0 g, 100%). Further purification by recrystallization from toluene afforded a white solid; mp 230–231 °C; $[\alpha]_D^{20} = +303$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22–2.28 (m, 2H), 2.36–2.50 (m, 2H), 3.02–3.10 (m, 4H), 7.12 (t, $J = 7.5$ Hz, 2H), 7.39 (d, $J = 7.2$ Hz, 2H), 7.63 (d, $J = 7.5$ Hz, 2H), 9.8 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.9 (CH_2), 38.2 (CH_2), 63.2 (C), 125.2 (CH), 126.5 (CH), 128.8 (C), 129.5 (CH), 145.5 (C), 151.5 (C), 172.1 (COOH); MS (EI) *m*/*z* (relative intensity) 308 (M^+, 6), 290 (100). Anal. Calcd for $C_{19}H_{16}O_4$: C 74.01, H 5.23. Found: C 74.06, H 5.40.

4.5. (R_a,*S*,*S*)-*N*,*N*′-Bis(2-hydroxy-1-phenylethyl)-1,1′-spirobiindane-7,7′-diamide [(R_a,*S*,*S*)-8a]

A solution of (*R*)-**7** (308 mg, 1.0 mmol), dicyclohexylcarbodiimide (870 mg, 4.2 mmol), benzotriazol-1-ol (300 mg, 2.2 mmol), and (*S*)-2-amino-2-phenyl-ethanol (300 mg, 2.2 mmol) in dry THF was stirred at −5 °C for an hour and then at room temperature overnight. The resulting mixture was concentrated under reduced pressure, and purified by silica gel column chromatography (petroleum ester/ethyl acetate = 1:1) to give (R_a,*S*,*S*)-**8a** (550 mg, 1.0 mmol, 99%) as a white solid; mp 262–264 °C; $[\alpha]_D^{20} = +102$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83 (m, 2H), 2.28 (m, 2H), 3.09 (m, 6H), 3.46 (m, 2H), 3.59 (m, 2H), 4.99 (m, 2H, $J = 3.0$ Hz), 7.28 (m, 16H), 8.10 (d, 2H, $J = 9.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.1 (CH_2), 39.6 (CH_2), 54.5 (CH), 62.6 (C), 66.2 (CH_2), 126.4 (CH), 126.5 (CH), 126.8 (CH), 127.7 (CH), 129.0 (CH), 132.1 (C), 139.0 (C), 146.8 (C), 148.5 (C), 169.9 (C=O); MS (ESI): 547 (M+1). Anal. Calcd for $C_{35}H_{34}N_2O_4$: C 76.90, H 6.27, N 5.12. Found: C 77.07, H 6.29, N 5.25.

4.6. (S_a,*S*,*S*)-*N*,*N*′-Bis(2-hydroxy-1-phenylethyl)-1,1′-spirobiindane-7,7′-diamide (S_a,*S*,*S*)-8a

Compound (S_a,*S*,*S*)-**8a** was prepared by the same procedure for the preparation of (R_a,*S*,*S*)-**8a** from (*S*)-1,1′-spirobiindanyl-7,7′-dicarboxylic acid (*S*)-**7**. Yield (87%), as a white solid, mp 103–107 °C; $[\alpha]_D^{20} = -103$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (m, 2H), 2.26 (m, 2H), 2.48 (m, 2H), 2.86 (s, 2H), 3.00 (m, 4H), 3.56 (m, 4H), 4.45 (m, 2H), 6.97 (m, 6H), 7.14 (t, 2H $J = 7.6$ Hz), 7.26 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.8 (CH_2), 40.3 (CH_2), 57.1 (CH), 62.11 (C), 66.8 (CH_2), 126.4 (CH), 127.2 (CH), 127.4 (CH), 128.0 (CH), 128.9 (CH), 133.4 (C), 138.5 (C), 145.4 (C), 145.5 (C), 165.63 (C=O); MS (ESI): 547 (M+1). Anal. Calcd for $C_{35}H_{34}N_2O_4$: C 76.90, H 6.27, N 5.12. Found: C 77.05, H 6.31, N 5.27.

4.7. (R_a,*S*,*S*)-*N*,*N*′-Bis(1-benzyl-2-hydroxyethyl)-1,1′-spirobiindane-7,7′-diamide (R_a,*S*,*S*)-8b

Compound (R_a,*S*,*S*)-**8b** was prepared by the same procedure for the preparation of (R_a,*S*,*S*)-**8a** from (*S*)-2-

amino-3-phenylpropan-1-ol. Yield (99%), as a white solid, mp 213–215 °C; $[\alpha]_D^{20} = +90$ (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.62 (m, 2H), 2.24 (m, 2H), 2.77 (m, 4H), 3.03 (m, 8H), 3.28 (m, 2H), 4.04 (m, 2H), 6.87 (m, 2H), 7.06 (t, 2H, $J = 7.5$ Hz), 7.24 (m, 14H), 7.54 (d, 2H $J = 9.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.8 (CH_2), 36.8 (CH_2), 39.3 (CH_2), 51.1 (CH_2), 62.2 (C), 63.5 (CH), 125.9 (CH), 126.1 (CH), 126.3 (CH), 126.6 (CH), 128.5 (CH), 129.1 (CH), 132.0 (C), 137.9 (C), 146.4 (C), 148.0 (C), 169.7 (C=O); MS (ESI): 575 (M+1). Anal. Calcd for $C_{37}H_{38}N_2O_4$: C 77.33, H 6.66, N 4.87. Found: C 77.17, H 6.60, N 4.93.

4.8. (R_a,*S*,*S*)-*N*,*N*′-Bis(1-hydroxymethyl-2-methylpropyl)-1,1′-spirobiindane-7,7′-diamide (R_a,*S*,*S*)-8c

Compound (R_a,*S*,*S*)-**8c** was prepared by the same procedure for the preparation of (R_a,*S*,*S*)-**8a** from (*S*)-2-amino-3-methylbutan-1-ol. Yield (99%), as a white solid, mp 195–197 °C, $[\alpha]_D^{20} = +84$ (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (m, 6H), 0.93 (m, 6H), 1.57 (m, 2H), 1.74 (m, 2H), 2.25 (m, 2H), 3.13 (m, 8H), 3.41 (m, 4H), 7.13 (m, 4H), 7.32 (d, 2H, $J = 6.8$ Hz), 7.69 (d, 2H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4 (CH_3), 29.2 (CH_2), 31.0 (CH), 34.2 (CH_2), 39.3 (C), 56.1 (CH), 63.0 (CH_2), 126.1 (CH), 126.3 (CH), 126.7 (CH), 132.2 (C), 146.7 (C), 148.5 (C), 170.4 (C=O); MS (ESI): 479 (M+1). Anal. Calcd for $C_{29}H_{38}N_2O_4$: C 72.77, H 8.00, N 5.85. Found: C 72.56, H 7.97, N 6.01.

4.9. (R_a,*S*,*S*)-7,7′-Bis(4-phenyloxazolin-2-yl)-1,1′-spirobiindane (R_a,*S*,*S*)-4a

A solution of (R_a,*S*,*S*)-**8a** (234 mg, 0.42 mmol), triphenylphosphane (384 mg, 0.90 mmol), triethylamine (200 μL, 0.88 mmol), and tetrachloromethane (138 μL, 0.88 mmol) in dry acetonitrile was stirred overnight. After being concentrated in vacuum, the residue was dissolved with CH_2Cl_2, washed with water, dried over anhydrous magnesium sulfate, and then concentrated in vacuum. The residue was purified by silica gel column chromatography with petroleum/ethyl acetate (3:1) to give (R_a,*S*,*S*)-**4a** (204 mg, 95%) as a white solid; mp 130–132 °C; $[\alpha]_D^{20} = +93$ (*c* 0.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (dd, 2H, $J = 5.1$ and 6.9 Hz), 2.87 (m, 2H), 3.07 (m, 6H), 4.26 (dd, 2H, $J = 1.8$ and 8.4 Hz), 4.70 (t, 2H, $J = 10.5$ Hz), 7.09 (t, 2H, $J = 7.2$ Hz), 7.28 (m, 12H), 7.67 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.9 (CH_2), 39.0 (CH_2), 63.2 (C), 70.1 (CH_2), 74.0 (CH), 123.6 (CH), 126.0 (CH), 126.8 (CH), 127.1 (CH), 128.4 (CH), 128.5 (CH), 141.9 (C), 145.7 (C), 149.7 (C), 164.6 (C=N); MS (ESI): 511 (M+1). Anal. Calcd for $C_{35}H_{30}N_2O_2$: C 82.33, H 5.92, N 5.49. Found: C 82.22, H 6.07, N 5.59.

4.10. (S_a,*S*,*S*)-7,7′-Bis(4-phenyloxazolin-2-yl)-1,1′-spirobiindane (S_a,*S*,*S*)-4a

Compound (S_a,*S*,*S*)-**4a** was prepared by the same procedure for the preparation of (R_a,*S*,*S*)-**4a** from (S_a,*S*,*S*)-**8a**. Yield (93%), white solid, mp 167–169 °C; $[\alpha]_D^{20} = -322$ (*c* 0.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (dd, 2H, $J = 4.8$ and 7.2 Hz), 2.60 (m, 2H, $J = 10.8$ Hz), 3.05 (m, 4H), 3.37 (m, 2H), 3.72 (t, 2H, $J = 7.2$ Hz), 4.98 (dd, 2H, $J = 3.0$ and 6.9 Hz), 7.07 (m, 4H), 7.23 (m, 8H), 7.36 (d, 2H $J = 6.9$ Hz), 7.81 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.9 (CH_2), 38.9 (CH_2), 63.5 (C), 69.1 (CH), 74.5 (CH_2), 126.3 (CH), 126.8 (CH), 127.3 (CH), 127.4 (CH), 128.7 (CH), 128.9 (CH), 142.8 (C), 145.4 (C), 149.1 (C), 165.6 (C=N); MS (ESI): 511 (M+1). Anal. Calcd for $C_{35}H_{30}N_2O_2$: C 82.33, H 5.92, N 5.49. Found: C 82.17, H 6.12, N, 5.52.

4.11. (R_a,*S*,*S*)-7,7′-Bis(4-benzyloxazolin-2-yl)-1,1′-spirobiindane (R_a,*S*,*S*)-4b

Compound (R_a,*S*,*S*)-**4b** was prepared by the same procedure for the preparation of (R_a,*S*,*S*)-**4a** from (R_a,*S*,*S*)-**8b**. Yield (97%), colorless sticky oil; $[\alpha]_D^{20} = +111$ (*c* 0.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (dd, 2H, $J = 3.6$ and 8.1 Hz), 2.43 (dd, 2H, $J = 4.5$ 8.7 Hz), 2.66 (m, 2H), 2.89 (m, 4H, $J = 6.6$ Hz), 3.01 (m, 4H), 3.93 (m, 4H), 7.08 (d, 4H, $J = 6.9$ Hz), 7.26 (m, 12H), 7.64 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.70 (CH_2), 38.6 (CH_2), 41.4 (CH_2), 63.1 (C), 68.0 (CH_2), 71.6 (CH), 124.0 (CH), 125.8 (CH), 126.7 (CH), 128.1 (CH), 128.3 (CH), 129.1 (CH), 138.9 (C), 145.5 (C), 149.1 (C), 163.6 (C=N); MS (ESI): 539 (M+1). Anal. Calcd for $C_{37}H_{34}N_2O_2$: C 82.50, H 6.36, N 5.20. Found: C 82.31, H 6.30, N 5.29.

4.12. (R_a,*S*,*S*)-7,7′-Bis(4-isopropyloxazolin-2-yl)-1,1′-spirobiindane (R_a,*S*,*S*)-4c

Compound (R_a,*S*,*S*)-**4c** was prepared by the same procedure for the preparation of (R_a,*S*,*S*)-**4a** from (R_a,*S*,*S*)-**8c**. Yield (91%), as a colorless sticky oil. $[\alpha]_D^{20} = +155$ (*c* 0.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 0.66 (d, 6H, $J = 6.6$ Hz), 0.85 (d, 6H, $J = 6.6$ Hz), 1.41 (m, 2H), 2.23 (m, 2H), 2.74 (m, 2H, $J = 11.1$ Hz), 3.00 (m, 6H), 3.21 (m, 2H), 3.91 (m, 2H), 7.13 (t, 2H, $J =$ 7.5 Hz), 7.31 (d, 2H, $J = 7.2$ Hz), 7.52 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9 (CH_3), 19.7 (CH_3), 30.8 (CH_2), 32.7 (CH_2), 38.5 (CH), 63.2 (C), 70.0 (CH_2), 73.3 (CH), 124.1 (CH), 125.6 (CH), 126.4 (CH), 128.0 (C), 145.3 (C), 149.2 (C), 162.6 (C=N); MS (ESI): 443 (M+1). Anal. Calcd for $C_{29}H_{34}N_2O_2$: C 78.7, H 7.74, N 6.33. Found: C 78.80, H 7.57, N 6.47.

4.13. Typical procedure for copper(I) catalyzed asymmetric cyclopropanation of styrene

A mixture of $[(Cu(I)OTf)_2C_6H_6]$ (2.5 mg, 0.01 mmol) and ligand **4** (0.012 mmol) in dichloromethane (2.0 mL) was stirred at room temperature for 1 h under an argon atmosphere. After the addition of a styrene substrate (4 mmol), a solution of menthyl diazoacetate (112 mg, 0.5 mmol) in dichloromethane (2.0 mL) was added, and the reaction solution stirred at 40 °C for 1.5 h. The reaction mixture was filtered through a short silica pad. The filtrate was concentrated in vacuum to

give a crude product, which was chromatographed on a silica gel column with petroleum ether/ethyl acetate (20:1) to afford the product. The analyses were illustrated as follows.

4.13.1. (+)-Menthyl 2-phenylcyclopropanecarboxylate. Yield (93%), 62% ee for cis-isomer and 70% ee for trans-isomer [GC: HP-5 column (30 m); carrier gas, N_2 (0.7 mL/min); injection temp, 230 °C; initial column temperature, 150 °C; rate, 4 °C/min; final column temperature, 220 °C; cis-isomer: $t_R = 14.42$ min, $t_R = 14.54$ min; trans-isomer: $t_R = 15.38$ min, $t_R = 15.74$ min].

4.13.2. (+)-Menthyl 2-*p*-tolylcyclopropanecarboxylate. Yield (67%), 55% ee for trans-isomer [GC: HP-5 column (30 m); carrier gas, N_2 (0.7 mL/min); injection temp, 230 °C; initial column temperature, 40 °C; rate, 1 °C/min; final column temperature, 220 °C; trans-isomer: $t_R = 17.51$ min, $t_R = 17.89$ min].

4.13.3. (+)-Menthyl 2-(4-chlorophenyl)cyclopropanecarboxylate. Yield (54%), 82% ee for trans-isomer [GC: HP-5 column (30 m), carrier gas, N_2 (0.7 mL/min); injection temp, 230 °C; initial column temperature, 150 °C; rate, 4 °C/min; final column temperature, 220 °C; trans-isomer: $t_R = 19.68$ min, $t_R = 20.22$ min].

4.13.4. (+)-Menthyl 2-(4-bromophenyl)cyclopropanecarboxylate. Yield (61%), 72% ee for trans-isomer [GC: HP-5 column (30 m), carrier gas, N_2 (0.7 mL/min); injection temp, 230 °C; initial column temperature, 150 °C; rate, 4 °C/min; final column temperature, 220 °C; trans-isomer: $t_R = 22.72$ min, $t_R = 23.39$ min].

4.13.5. (+)-Menthyl 2-(4-methoxyphenyl)cyclopropanecarboxylate. yield (55%), 53% ee for trans-isomer [GC: HP-5 column (30 m), carrier gas, N_2 (0.7 mL/min); injection temp, 230 °C; initial column temperature, 150 °C; rate, 4 °C/min; final column temperature, 220 °C; trans-isomer: $t_R = 21.42$ min, $t_R = 22.00$ min].

4.13.6. (+)-Menthyl 2-(4-trifluoromethylphenyl)cyclopropanecarboxylate. Yield (56%), 82% ee for trans-isomer [GC: HP-5 column (30 m), carrier gas, N_2 (0.7 mL/min); injection temp, 230 °C; initial column temperature, 150 °C; rate, 5 °C/min; final column temperature, 220 °C; trans-isomer: $t_R = 14.93$ min, $t_R = 15.38$ min].

4.14. General procedure for the copper/SpiroBOX catalyzed asymmetric allylic oxidation of cyclic alkenes

A solution of $CuPF_6(MeCN)_4$ (3.7 mg, 0.01 mmol) and (R_a,*S*,*S*)-**4b** (6.4 mg, 0.012 mmol) in anhydrous acetone (2 mL) was stirred at room temperature for 1 h. Then 0.2 mL (3 mmol) of cyclohexene was added. After being stirred for 2 min, *tert*-butyl benzoate (38 μL, 0.2 mmol) was added. The reaction solution was then stirred at room temperature for two days, after which the reaction was quenched by addition of 1 mL water and extracted with ethyl acetate (10 mL, twice). The extract was washed by saturated $NaHCO_3$, water, and saturated brine, dried over $MgSO_4$, filtered, and concentrated to give a crude product. The crude product was purified by column chromatography with petroleum ester/ethyl acetate (40:1) to give benzoic acid cyclohex-2-enyl ester as a colorless oil. The analyses were illustrated as follows.

4.14.1. Cyclopent-2-enyl benzoate. Yield (58%), 70% ee [HPLC: chiralpak OD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 10,000:3, 0.8 mL/min, $t_R = 17.47$ min (*S*), $t_R = 21.41$ min (*R*)].

4.14.2. Cyclohex-2-enyl benzoate. Yield (58%), 70% ee [HPLC: chiralpak OD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 10,000:5, 0.8 mL/min, $t_R = 15.72$ min (*S*), $t_R = 16.51$ min (*R*)].

4.14.3. Cyclohex-2-enyl 4-methoxybenzoate. Yield (67%), 67% ee [HPLC: chiralpak OB column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 99:1, 0.8 mL/min, $t_R = 11.54$ min (*S*), $t_R = 13.44$ min (*R*)].

4.14.4. Cyclohex-2-enyl 4-methylbenzoate. Yield (65%), 66% ee [HPLC: chiralpak OD-H column (25 cm × 0.46 cm ID), *n*-hexane/*i*-PrOH = 10,000:5, 1 mL/min, $t_R = 16.91$ min (*S*), $t_R = 17.70$ min (*R*)].

4.14.5. Cyclohex-2-enyl 4-nitrobenzoate. Yield (80%), 67% ee [HPLC: chiralpak OB column (25 cm × 0.46 cm ID), *n*-hexane, 0.9 mL/min, $t_R = 33.38$ min (*S*), $t_R = 33.96$ min (*R*)].

4.14.6. Cyclohex-2-enyl 2-nitrobenzoate. Yield (16%), 59% ee [HPLC: chiralpak OB column (25 cm × 0.46 cm ID), *n*-hexane, 0.8 mL/min, $t_R = 51.6$ min (*S*), $t_R = 67.0$ min (*R*)].

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