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Enantioselective addition of diethylzinc to aldehydes catalyzed by monosubstituted [2.2]paracyclophane-based N,O-ligands: remarkable cooperative effects of planar and central chiralities

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Abstract—Diastereomeric monosubstituted [2.2]paracyclophane-based N,O-ligands, which unite the planar and central chiral elements, were optimized for the enantioselective diethylzinc addition to aldehydes. (*S*)-1-{(S_p)-[2.2]Paracyclophan-4-yl}methyl-2-pyrrolidine-α,α-diphenylmethanol (S_p,*S*)-**3** catalyzed the addition to give (*R*)-1-phenyl-1-propanol in a high yield and with a good enantioselectivity (91% ee).

1. Introduction

The asymmetric catalysis of organic reactions to provide enantiomerically enriched compounds has become one of the most powerful tools in modern synthetic organic chemistry. In particular, the enantioselective diethylzinc addition to benzaldehyde has been well studied as a carbon–carbon bond-forming reaction.[1,2] Many chiral ligands, which possess central, axial, and planar chiralities, have been developed, and excellent enantioselectivities have been achieved in recent decades. A large number of publications regarding the enantioselective diethylzinc addition[1,2] have been reported the use of [2.2]paracyclophane-based ligands for catalytic asymmetric processes over the last few years.[3,4] Some chiral N,O-ligands containing [2.2]paracyclophanes as chiral elements catalyze the enantioselective addition of diethylzinc to benzaldehyde. The first report of a [2.2]paracyclophane-based N,O-ligand for the enantioselective addition was reported in 2001 by Hou et al.,[5,6] who synthesized 4,13-disubstituted [2.2]paracyclophane derivatives, providing a 93% ee of 1-phenyl-1-propanol from diethylzinc and benzaldehyde. Ruzziconi et al. evaluated the quinolinophenylcarbinol as a catalyst in the enantioselective addition,[7] and, recently, they have reported improved carbinol catalysts, which have both planar and central chiralities.[8] Bräse et al. and Rozenberg et al. used 4,5-disubstituted [2.2]paracyclophane-based *N*,*O*-ketimine ligands[9–12] for asymmetric diethylzinc additions to aldehydes with moderate to high enantioselectivities. The ketimine ligands and their analogues also catalyze alkenylzinc[13] and alkynylzinc[14] addition to aldehydes, alkylzinc additions to imines,[15] and conjugate addition to α,β-unsaturated aldehydes and ketones[16] with excellent enantioselectivities. All of the [2.2]paracyclophane-based N,O-ligands are disubstituted derivatives; however, monosubstituted [2.2]paracyclophane-based N,O-ligands for the diethylzinc addition have not been reported.[†]

On the other hand, N-substituted prolinol derivatives have been well-studied as N,O-ligands for diethylzinc addition to aldehydes[17–27] and diphenylzinc addition to 4-chlorobenzaldehyde[28] with a low to excellent enantiomeric excess. The achiral N-substituents are methyl,[17–23,28] ethyl,[22,23] 2,2-dimethylpropyl,[21] benzyl,[22–25] mesitylmethyl,[28] and 9-anthrylmethyl,[28] while the chiral ones are 1-(ferrocenyl)ethyl[26] and 1-(2-phenyl-2-tosylamido)ethyl groups.[27]

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[†] Some planar chiral monosubstituted [2.2]paracyclophanes have been employed by Soai et al. in asymmetric autocatalytic diisopropylzinc additions to 2-(*tert*-butylethynylpyrimidine)-5-carbaldehyde to give an optically active pyrimidyl alkanol;[35,36] however, this reaction proceeds through a completely different process from the diethylzinc addition to aldehydes with N,O-ligands.[1,2]

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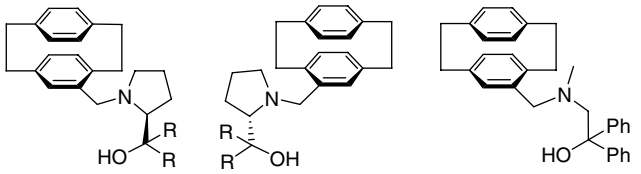


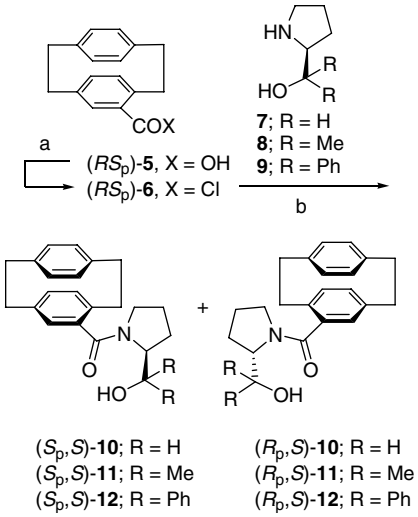
Figure 1. Monosubstituted [2.2]paracyclophane-based N,O-ligands.

Herein we report the efficacy of chiral monosubstituted [2.2]paracyclophane-based N,O-ligands **1**–**4** (Fig. 1) for the enantioselective diethylzinc addition to aldehydes. Ligands **1**–**3** are constructed with either (S_p)- or (R_p)-[2.2]paracyclophane and (*S*)-prolinol derivatives, and ligand (S_p)-**4** is based on a chiral monosubstituted [2.2]-paracyclophane without a stereogenic center. [2.2]Paracyclophanes **1**–**3** bearing chiral substituents would be expected to control the enantioselectivity of the addition because of the interplay between the planar chirality of the [2.2]paracyclophane and the central chirality of the substituents.

2. Results and discussion

As an easy route into [2.2]paracyclophane-based catalysts, ligands **1**–**3** were synthesized from racemic (RS_p)-[2.2]paracyclophane-4-carboxylic acid (RS_p)-**5**.[29,30] After the conversion of (RS_p)-**5** into [2.2]paracyclophane-4-carbonyl chloride (RS_p)-**6** by thionyl chloride, (RS_p)-**6** was reacted with (*S*)-prolinol derivatives (*S*)-**7**–**9** to afford the diastereomeric mixtures of amides (S_p,*S*)-**10**–**12** and (R_p,*S*)-**10**–**12** in good yields (Scheme 1). All of the amides could be readily separated by simple silica gel column chromatography thereby allowing the resolution of the planar chirality.

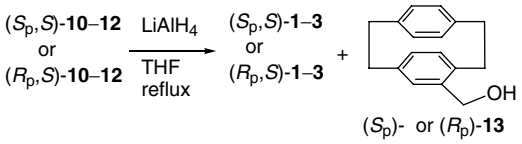
In order to determine the stereochemistry, amides (S_p,*S*)-**10** and (R_p,*S*)-**10** were hydrolyzed under acidic conditions (sulfuric acid/water/dioxane = 1:1:1, 100 °C, 15 h) to afford (S_p)-**5** and (R_p)-**5**, respectively. The absolute configurations of (S_p)-**5** and (R_p)-**5** were determined by the comparison of their reported specific rotations.[29] Acids (S_p)-**5** and (R_p)-**5** were converted to the corresponding methyl ester with (trimethylsilyl)diazomethane,[31] and their enantiomeric excesses were >98% ee, as measured by HPLC using Chiralcel OD. Next, we attempted to hydrolyze amides (S_p,*S*)-**11** and (S_p,*S*)-**12**; however, they were stable against the acidic conditions.[‡] To determine the stereochemistry, (S_p,*S*)-**11** and (S_p,*S*)-**12** were synthesized from acid chloride (S_p)-**6**, which was obtained from (S_p)-**5** using thionyl chloride. The absolute stereochemistries of (S_p,*S*)-**11**, (R_p,*S*)-**11**, (S_p,*S*)-**12**, and (R_p,*S*)-**12** were determined by the comparison of their diastereomeric ^{1}H NMR spectra with those of (S_p,*S*)-**11** and (S_p,*S*)-**12** obtained from (S_p)-**6**.



Scheme 1. Reagents and conditions: (a) $SOCl_2$, reflux; (b) Et_3N, DMAP, CH_2Cl_2, 0 °C to room temp.

The reduction of amides (S_p,*S*)-**10**–**12** and (R_p,*S*)-**10**–**12** with lithium aluminum hydride in refluxing THF gave the desired amino alcohols (S_p,*S*)-**1**–**3** and (R_p,*S*)-**1**–**3** (Table 1). In some of these reactions, (S_p)- and (R_p)-4-hydroxymethyl[2.2]paracyclophanes (S_p)-**13** and (R_p)-**13** were obtained as byproducts.[§]

Table 1. Reduction of amides **10**–**12**



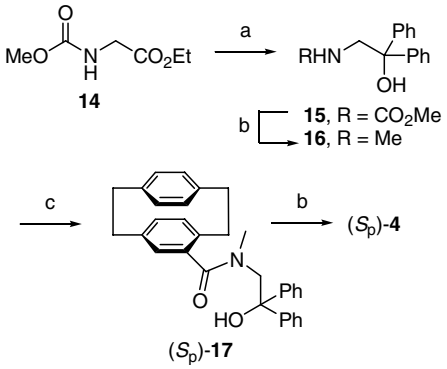
Entry	Substrate	Product (yield, %)	
1	(S_p,*S*)-**10**	(S_p,*S*)-**1** (91)	(S_p)-**13** (>5)
2	(R_p,*S*)-**10**	(R_p,*S*)-**1** (95)	(R_p)-**13** (>5)
3	(S_p,*S*)-**11**	(S_p,*S*)-**2** (64)	(S_p)-**13** (35)
4	(R_p,*S*)-**11**	(R_p,*S*)-**2** (82)	(R_p)-**13** (12)
5	(S_p,*S*)-**12**	(S_p,*S*)-**3** (64)	(S_p)-**13** (36)
6	(R_p,*S*)-**12**	(R_p,*S*)-**3** (83)	(R_p)-**13** (4)

Amino alcohol (S_p)-**4** was also synthesized as follows: 2-methylamino-1,1-diphenylethanol **16**[32,33] was obtained from *N*-methoxycarbonylglycine ethyl ester **14**[34] by the treatment of excess phenylmagnesium bromide, following the reduction with lithium aluminum hydride. Acid chloride (S_p)-**6** was reacted with amino alcohol **16** to give amide (S_p)-**17**. The reduction of (S_p)-**17** with lithium aluminum hydride in refluxing THF gave amino alcohol (S_p)-**4** (Scheme 2).

To investigate the catalytic properties of these N,O-ligands, the asymmetric addition of diethylzinc to benzaldehyde was carried out in toluene/hexane. All experiments were

[‡] Some [2.2]paracyclophane-based ketimines are also stable against acidic hydrolysis.[37]

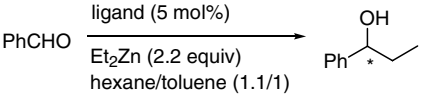
[§] Alcohol **13** has been obtained with reduction of a sulfamide derived from [2.2]paracyclophane-4-carboxylic acid.[31]



Scheme 2. Reagents and conditions: (a) PhMgBr (excess), THF, 0 °C, 30 min; (b) $LiAlH_4$, THF, reflux; (c) (S_p)-**6**, Et_3N, DMAP, CH_2Cl_2.

carried out at 0 °C for 2 h and then allowed to warm to room temperature for 16 h using a 5% molar amount of the ligands and 2 equiv of a 1 mol/L diethylzinc solution in hexane. The results on the catalyst efficiencies and the enantiomeric excess of the resulting 1-phenyl-1-propanol are presented in Table 2. Although the catalyst efficiencies of ligands (S_p,*S*)-**1**, (R_p,*S*)-**1**, and (S_p,*S*)-**2**, and (R_p,*S*)-**2** were insufficient (entries 1–4), those of ligands (S_p,*S*)-**3** and (R_p,*S*)-**3**, possessing α,α-diphenylmethanol moieties, were excellent, and the yields of the products using (S_p,*S*)-**3** and (R_p,*S*)-**3** were quantitative (entries 5 and 6). Surprisingly, the two enantiomeric excesses (91% ee and 1% ee) are completely different in spite of the high yields (>99%). In general, monosubstituted [2.2]paracyclophane-based ligands could adopt a large number of conformations.[3] Therefore, a potential explanation for the phenomena of the reaction using (R_p,*S*)-**3** (high yield and no selectivity) is that more than two active conformations of the catalyst exist in the reaction mixture and, as a result,

Table 2. Addition of diethylzinc to benzaldehyde

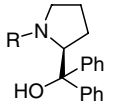


Entry	Ligand (5 mol %)	Product		
		Yield[a] (%)	ee (%)[b]	Abs. Config.[c]
1	(S_p,*S*)-**1**	20	54	*R*
2	(R_p,*S*)-**1**	5	1	*R*
3	(S_p,*S*)-**2**	6	8	*R*
4	(R_p,*S*)-**2**	40	36	*R*
5	(S_p,*S*)-**3**	>99	91	*S*
6	(R_p,*S*)-**3**	>99	1	*R*
7	(S_p)-**4**	99	41	*S*
8	(*S*)-**18**[d]	89	40[e]	*S*

[a] The yields were calibrated with the internal standard (Ph_3CH) by ^1H NMR integration.
[b] HPLC analysis (Chiralcel OD).
[c] The absolute configurations were determined by the comparison of the known elution order from a chiral OD column. See Experimental section.
[d] (*S*)-1-Benzyl-2-pyrrolidine-α,α-diphenylmethanol (Fig. 2).
[e] Using 5 mol % of (*S*)-**18** in hexane/toluene.[22,23] Various reaction conditions using (*S*)-**18** have been examined.[22–25]

(*R*)- and (*S*)-1-phenyl-1-propanols were synthesized with identical rates.

Next, we investigated the collaborative effects of the planar and central chiralities on the efficiency for the asymmetric diethyzinc addition to benzaldehyde. Ligand (S_p)-**4**, which has only (S_p)-planar chirality, provided the (*S*)-product with a 41% ee and a quantitative yield (entry 7). This enantioselectivity is due to the steric effect of the planar chirality. The effects of the stereogenic centers of ligands (S_p,*S*)-**3** and (R_p,*S*)-**3** could be estimated from the enantioselectivities of the reported values [(*S*)-1-phenyl-1-propanol, 40% ee] of (*S*)-1-benzyl-2-pyrrolidine-α,α-diphenylmethanol (*S*)-**18** (Fig. 2). The combination of the (S_p)-planar and (*S*)-central chiralities increased these moderate enantioselectivities (41% and 40% ee) to 91% ee [matched pair; (S_p,*S*)-**3**]; however, the combination of the (R_p)-planar and (*S*)-central chiralities decreased their effects [mismatched pair; (R_p,*S*)-**3**].



18, R = Bn
19, R = Et
20, R = Me

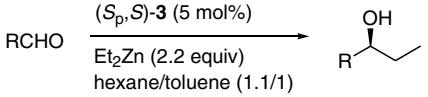
Figure 2. Ligands with stereogenic centers.

The addition of diethylzinc to benzaldehyde using (*S*)-1-ethyl- and (*S*)-1-methyl-2-pyrrolidine-α,α-diphenylmethanols **19**[22,23] and **20**,[17,20–23] respectively, has also been reported. For these ligands, the bulkiness of the N-substituents is in the order benzyl > ethyl > methyl, and the enantioselectivities[22,23] decrease with methyl (93% ee) > ethyl (87% ee) > benzyl (40% ee). In our study, a good enantioselectivity was observed using ligand (S_p,*S*)-**3**, even though it possessed a (S_p)-([2.2]paracyclophan-4-yl)methyl group, which is clearly bulkier than the benzyl group. Thus, the (S_p)-[2.2]paracyclophane moiety in the N,O-ligand (S_p,*S*)-**3** would form an effective chiral space with the (*S*)-pyrrolidine-α,α-diphenylmethanol moiety during the reaction.

Chiral ligand (S_p,*S*)-**3** was then examined for the asymmetric addition of a series of various aldehydes under the identical conditions to those of Table 2. The results are summarized in Table 3. The yields were high to moderate except *p*-chlorobenzaldehyde, 2-naphthaldehyde, and *trans*-cinnamaldehyde (entries 5, 9, and 11). In spite of the long reaction times (100 h), the yields were low to moderate (entries 6, 10, and 12). All the aldehydes gave the 1-aryl-1-propanols in high to moderate enantiomeric excesses except *p*-methoxybenzaldehyde (entry 1).[¶] The yields and enantiomeric excesses of 1-aryl-1-propanols

[¶] Although a lot of excellent ligands has been developed for the enatioselective addition of diethylzinc to benzaldehyde to give 1-phenyl-1-propanol in a high enantiomeric excess, some ligands give 1-aryl-1-propanols, for example, 1-(*p*-methoxyphenyl)-1-propanol, from arylaldehydes in low enantiomeric excesses exceptionally.[46–53]

Table 3. Addition of diethylzinc to various aldehydes using (S_p,S)-**3**



Entry	Aldehyde	Time (h)	Yield[a] (%)	ee[b,c] (%)
1	*p*-$MeOC_6H_4CHO$	16	58	4
2	*m*-$MeOC_6H_4CHO$	16	88	86
3	*o*-$MeOC_6H_4CHO$	16	93	57
4	*p*-BrC_6H_4CHO	16	54	80
5	*p*-ClC_6H_4CHO	16	6	—[d]
6	*p*-ClC_6H_4CHO	100	63	74
7	*o*-BrC_6H_4CHO	16	49	61
8	1-Naphthaldehyde	16	52	71
9	2-Naphthaldehyde	16	13	65
10	2-Naphthylaldehyde	100	43	62
11	PhCH=CHCHO[e]	16	<5	—
12	PhCH=CHCHO	100	33	73

[a] The yields were calibrated with the internal standard (Ph_3CH) by ^1H NMR integration.
[b] HPLC analysis (Chiralcel OD).
[c] The all absolute configurations were determined as (*S*) by comparison of the known elution order from a Chiralcel OD column. See Experimental section.
[d] Not determined.
[e] *trans*-Cinnamaldehyde.

from aldehydes using ligand (S_p,S)-**3** (Table 3) were lower than those of 1-phenyl-1-propanol from benzaldehyde (Table 2, entry 5).

N,O-Ligands (S_p,S)-**1**–**3** and (R_p,S)-**1**–**3** were synthesized easily from racemic (RS_p)-**5**. It has been pointed out that the progress of the application of [2.2]paracyclophanes in asymmetric catalysis is currently governed by the ease (or lack thereof) with which enantiomerically pure [2.2]paracyclophanes are synthesized.[3] For example, the synthesis of enantiomerically pure [2.2]paracyclophane-4-carboxylic acid **5** is dominated by classical resolution procedures, an approach that can be tedious and low yielding.[29,38–40] In fact, to synthesize the planar chiral ligand (S_p)-**4**, we needed enantiopure (S_p)-**5**. For the synthesis of N,O-ligands (S_p,S)-**1**–**3** and (R_p,S)-**1**–**3**, however, we did not need optically pure [2.2]paracyclophane-4-carboxylic acid **5** because diastereomeric mixtures of amides (S_p,S)-**10**–**12** and (R_p,S)-**10**–**12** were successfully separated with silica gel column chromatography. Thus, the stereogenic centers of the N,O-ligands were not only the active site of catalysts but also the origins of the separation.[‖]

3. Conclusions

In conclusion, the synthesis of planar chiral monosubstituted [2.2]paracyclophane-based N,O-ligands (S_p,S)-**3** and (R_p,S)-**3** containing central chiral 2-pyrrolidine-α,α-diphenylmethanol moieties has led to the development of a new family of ligands for the enantioselective addition of diethylzinc to benzaldehyde. Ligand (S_p,S)-**3** showed the best results (91% ee); however, a product with a low enantiomeric excess was obtained by using ligand (R_p,S)-**3**. The reaction using planar chiral ligand (S_p)-**4** gave the product in a 41% ee, and the reported enantiomeric excess using central chiral ligand (*S*)-**18** is 40% ee.[22,23] Therefore, ligand (S_p,S)-**3** has shown remarkable cooperative effects of the planar and central chiralities.

4. Experimental

Melting points were measured with a Yanaco MP-3 apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-140 polarimeter. IR spectra were recorded on a Hitachi 215 spectrophotometer. NMR spectra were obtained with JEOL JNM-GSX400 (^1H NMR: 400 MHz and ^{13}C NMR: 100 MHz), and JEOL JNM-AL300 (^1H NMR: 300 MHz) spectrometers using tetramethylsilane as an internal standard. MS and high-resolution MS (HR-MS) were taken on a JEOL JMS-DX302 spectrometer. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). Analytical TLC was performed on plates pre-coated with 0.25 mm layer of silica gel 60 F_{254} (Merck).

4.1. Synthesis of amides 10–12 (Scheme 1)

4.1.1. (*S*)-2-Hydroxymethyl-1-{(S_p)-[2.2]paracyclophane-4-carbonyl}pyrrolidine (S_p,*S*)-10 and (*S*)-2-hydroxymethyl-1-{(R_p)-[2.2]paracyclophane-4-carbonyl}pyrrolidine (R_p,*S*)-10. A solution of (*S*)-prolinol **7** (88.2 mg, 0.87 mmol), triethylamine (120 mg, 1.19 mmol), and DMAP (1.9 mg, 0.016 mmol) in dichloromethane (1.0 mL) was added dropwise to a solution of (RS_p)-**6**, which had been converted from (RS_p)-**5**[29] (200 mg, 0.79 mmol) by thionyl chloride just before use, in dichloromethane (1.0 mL) at 0 °C. After being stirred for 12 h while being allowed to warm to room temperature, the reaction mixture was poured into saturated aqueous ammonium chloride solution and extracted with dichloromethane. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate; 1:1) to give (S_p,S)-**10** [113 mg, 43% from (RS_p)-**5**] and (R_p,S)-**10** [120 mg, 45% from (RS_p)-**5**].

Compound (S_p,S)-**10**: Colorless solid, mp 125–126 °C. $[\alpha]_D^{24} = +3.3$ (*c* 0.7, $CHCl_3$). IR ($CHCl_3$): 3000, 2950, 1610, 1450, 1210 cm^{-1}. FABMS (glycerol) *m*/*z* 336 [$(M+1)^+$]. HRMS (FAB) (glycerol) Calcd for $C_{22}H_{26}NO_2$ (M+1): 336.1953. Found: 336.1964. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.52–1.75 (3H, m, NHCHC*H*H, $NHCH_2CH_2$), 2.06–2.14 (1H, m, NHCHCH*H*), 2.90–3.21 (10H, m, $ArCH_2CH_2$, $NHCH_2$), 3.73–3.85 (2H, m, $-CHCH_2OH$), 4.39 (1H, ddd, $J = 15.4$, 7.7, 2.9 Hz, $-NCHCH_2$), 5.40 (1H, br s, OH), 6.42–6.58 (6H, m, Ar), 6.98 (1H, dd, $J = 7.9$, 1.5 Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.6 (CH_2), 28.6 (CH_2), 33.9 ($ArCH_2$), 35.3

[‖] Some diastereomixtures of disubstituted [2.2]paracyclophanes[5,6,9,10,37,42–44] and monosubstituted [2.2]paracyclophanes[41,45] have been separated by silica gel column chromatography. Very recently, enantiomerically pure 4-substituted [2.2]paracyclophane derivatives (e.g., carboxylic acid **5**) were synthesized from one of the monosubstituted [2.2]paracyclophane by sulfoxide–metal exchange.[45]

(ArCH$_2$), 35.4 (ArCH$_2$), 35.5 (ArCH$_2$), 49.7 (NCH$_2$), 61.1 (NCH), 68.0 (CH$_2$OH), 130.3 (Ar, CH), 131.6 (Ar, CH), 132.3 (Ar, CH), 132.5 (Ar, CH), 132.9 (Ar, CH), 134.4 (Ar, CH), 134.7 (Ar, CH), 134.9 (Ar, C), 137.1 (Ar, C), 138.9 (Ar, C), 139.0 (Ar, C), 139.8 (Ar, C), 171.9 (C=O).

Compound (R_p,*S*)-**10**: Colorless solid, mp 201–202 °C. $[\alpha]_D^{24} = -119$ (*c* 0.8, CHCl$_3$). IR (CHCl$_3$): 3000, 2925, 1610, 1420, 1210 cm^{-1}. FABMS (glycerol) *m*/*z* 336 [(M+1)$^+$]. HRMS (FAB) (glycerol) Calcd for $C_{22}H_{26}NO_2$ (M+1): 336.1953. Found: 336.1964. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.51–1.73 (3H, m, NHCHC*H*H, NHCH$_2$C*H*$_2$), 2.04–2.19 (1H, m, NHCHCH*H*), 2.85–3.31 (10H, m, ArCH$_2$CH$_2$, –NHC*H*$_2$), 3.68–3.83 (2H, m, CHC*H*$_2$OH), 4.38 (1H, ddd, *J* = 15.4, 7.7, 2.8 Hz, NC*H*CH$_2$), 5.40 (1H, br d, *J* = 6.2 Hz, OH), 6.4 (1H, dd, *J* = 7.9, 1.7 Hz, Ar), 6.42 (1H, d, *J* = 7.7 Hz, Ar), 6.50–6.56 (4H, m, Ar), 7.04 (1H, dd, *J* = 8.1, 1.7 Hz, Ar). ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 24.6 (CH$_2$), 28.6 (CH$_2$), 33.9 (ArCH$_2$), 35.1 (ArCH$_2$), 35.2 (ArCH$_2$), 35.4 (ArCH$_2$), 50.0 (NCH$_2$), 61.1 (NCH), 67.6 (CH$_2$OH), 130.7 (Ar, CH), 131.6 (Ar, CH), 132.2 (Ar, CH), 132.2 (Ar, CH), 132.7 (Ar, CH), 133.2 (Ar, C), 134.4 (Ar, CH), 135.1 (Ar, CH), 137.2 (Ar, C), 138.9 (Ar, C), 139.3 (Ar, C), 139.7 (Ar, C), 172.0 (C=O).

4.1.2. (*S*)-2-(1-Hydroxy-1-methyl)ethyl-1-{(S_p)-[2.2]paracyclophane-4-carbonyl}pyrrolidine (S_p,*S*)-11 and (*S*)-2-(1-hydroxy-1-methyl)ethyl-1-{(R_p)-[2.2]paracyclophane-4-carbonyl}pyrrolidine (R_p,*S*)-11.

According to the procedure described above using (*S*)-1-methyl-1-(pyrrolidin-4-yl)ethanol **8** (113 mg, 0.87 mmol), which was synthesized from (*S*)-proline in three steps,[54] (S_p,*S*)-**11** [129 mg, 45% from (RS_p)-**5**] and (R_p,*S*)-**11** [130 mg, 45% from (RS_p)-**5**] were obtained. Hexane/ethyl acetate (2:1) was used for silica gel column chromatography.

Compound (S_p,*S*)-**11**: Colorless solid, mp 86–87 °C. $[\alpha]_D^{23} = -22.0$ (*c* 1.2, CHCl$_3$). IR (CHCl$_3$): 3300, 2900, 1600, 1430, 1380, 1170 cm^{-1}. FABMS (glycerol) *m*/*z* 364 [(M+1)$^+$]. HRMS (FAB) (glycerol) Calcd for $C_{24}H_{30}NO_2$ (M+1): 364.2276. Found: 364.2270. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.28 (6H, s, CMe$_2$), 1.41–1.75 (3H, m, NHCHC*H*H, NHCH$_2$C*H*$_2$), 2.08–2.17 (1H, m, NHCHCH*H*), 2.91–3.31 (10H, m, ArCH$_2$CH$_2$, NHC*H*$_2$), 4.30 (1H, t, *J* = 8.1 Hz, NC*H*CH$_2$), 6.44–6.58 (5H, m, Ar), 6.63 (1H, d, *J* = 1.8 Hz, Ar), 6.94 (1H, dd, *J* = 7.9, 1.7 Hz, Ar). ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 23.8 (Me), 24.6 (CH$_2$), 28.0 (Me), 28.8 (CH$_2$), 34.1 (Ar–CH$_2$), 35.2 (Ar–CH$_2$), 35.3 (Ar–CH$_2$), 35.3 (Ar–CH$_2$), 50.6 (N–CH$_2$), 67.8 (NCH), 73.8 (C–OH), 130.8 (Ar, CH), 131.5 (Ar, CH), 132.1 (Ar, CH), 132.4 (Ar, CH), 132.7 (Ar, CH), 134.3 (Ar, CH), 134.5 (Ar, CH), 135.2 (Ar, C), 137.3 (Ar, C), 138.6 (Ar, C), 138.9 (Ar, C), 139.8 (Ar, C), 172.5 (C=O).

Compound (R_p,*S*)-**11**: Colorless solid, mp 149–150 °C. $[\alpha]_D^{24} = -145$ (*c* 1.3, CHCl$_3$). IR (CHCl$_3$): 3300, 2950, 1610, 1420, 1400, 1180 cm^{-1}. FABMS (glycerol) *m*/*z* 364 [(M+1)$^+$]. HRMS (FAB) (glycerol) Calcd for $C_{24}H_{30}NO_2$ (M+1): 364.2276. Found: 364.2269. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.21 (3H, s, Me), 1.26 (3H, s, Me), 1.41–1.70 (3H, m, NHCHC*H*H, NHCH$_2$C*H*$_2$), 2.11–2.13 (1H, m, NHCHCH*H*), 2.79–3.41 (10H, m, ArCH$_2$CH$_2$, NHC*H*$_2$), 4.31 (1H, t, *J* = 10.5 Hz, NC*H*CH$_2$), 6.31 (1H, d, *J* = 10.5 Hz, Ar) 6.42–6.58 (5H, m, Ar), 7.07 (1H, d, *J* = 10.5 Hz, Ar). ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 23.4 (CH$_3$), 24.9 (CH$_2$), 27.7 (CH$_3$), 28.9 (CH$_2$), 34.0 (Ar–CH$_2$), 35.0 (Ar–CH$_2$), 35.1 (Ar–CH$_2$), 35.3 (Ar–CH$_2$), 51.2 (NCH$_2$), 67.5 (NCH), 73.8 (C–OH), 130.8 (Ar, CH), 131.6 (Ar, CH), 131.9 (Ar, CH), 132.2 (Ar, CH), 132.4 (Ar, CH), 132.5 (Ar, C), 134.5 (Ar, CH), 135.3 (Ar, CH), 137.9 (Ar, C), 138.7 (Ar, C), 139.4 (Ar, C), 139.5 (Ar, C), 172.7 (C=O).

4.1.3. (*S*)-2-(1,1-Diphenyl-1-hydroxy)methyl-1-{(S_p)-[2.2]paracyclophane-4-carbonyl}pyrrolidine (S_p,*S*)-12 and (*S*)-2-(1,1-diphenyl-1-hydroxy)methyl-1-{(R_p)-[2.2]paracyclophane-4-carbonyl}pyrrolidine (R_p,*S*)-12.

According to the procedure described above using (*S*)-α,α-diphenyl-2-pyrolidinemethanol (**9**) (221 mg, 0.87 mmol), we synthesized (S_p,*S*)-**12** [181 mg, 47% from (RS_p)-**5**] and (R_p,*S*)-**12** [181 mg, 47% from (RS_p)-**5**]. Hexane/ethyl acetate (10:1) was used for the silica gel column chromatography.

Compound (S_p,*S*)-**12**: Colorless solid, mp 181–182 °C. $[\alpha]_D^{25} = -7.1$ (*c* 1.0, CHCl$_3$). IR (CHCl$_3$): 3250, 3000, 2925, 1600, 1425, 1390, 1180 cm^{-1}. FABMS (magic bullet) *m*/*z* 488 [(M+1)$^+$]. HRMS (FAB) (magic bullet) Calcd for $C_{34}H_{34}NO_2$ (M+1): 488.2589. Found: 488.2590. ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 1.26–1.34 (2H, m), 1.89–1.94 (2H, m), 2.25–2.30 (1H, m), 2.60–2.73 (3H, m), 2.87–3.10 (6H, m) 5.14 (1H, t, *J* = 8.3 Hz, NC*H*CH$_2$), 6.29 (1H, d, *J* = 7.8 Hz, Ar), 6.42–6.50 (4H, m, Ar), 6.60 (1H, s, Ar), 6.70 (1H, d, *J* = 7.8 Hz, Ar), 7.19–7.54 (10H, m, Ar), 7.72 (2H, d, *J* = 7.6 Hz, Ar). ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 23.9 (CH$_2$), 30.7 (CH$_2$), 33.2 (Ar–CH$_2$), 35.2 (Ar–CH$_2$), 35.3 (Ar–CH$_2$), 35.6 (Ar–CH$_2$), 50.5 (NCH$_2$), 69.3 (NCH), 81.2 (C–OH), 126.9 (Ar, CH), 127.0 (Ar, CH), 127.3 (Ar, CH × 2), 127.46 (Ar, CH × 2), 127.52 (Ar, CH × 2), 127.61 (Ar, CH × 2), 130.64 (Ar, CH), 131.2 (Ar, CH), 132.1 (Ar, CH), 132.2 (Ar, CH), 133.0 (Ar, CH), 134.2 (Ar, CH), 134.4 (Ar, CH), 135.2 (Ar, C), 137.6 (Ar, C), 138.7 (Ar, C), 138.8 (Ar, C), 139.4 (Ar, C), 143.4 (Ar, C), 145.6 (Ar, C), 172.4 (C=O).

Compound (R_p,*S*)-**12**: Colorless solid, mp 199–200 °C. $[\alpha]_D^{26} = -70.9$ (*c* 1.4, CHCl$_3$). IR (CHCl$_3$): 3240, 2970, 2920, 1610, 1420, 1180 cm^{-1}. FABMS (magic bullet) *m*/*z* 488 [(M+1)$^+$]. HRMS (FAB) (magic bullet) Calcd for $C_{34}H_{34}NO_2$ (M+1): 488.2589. Found: 488.2590. ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 1.37–1.42 (2H, m), 1.84–1.90 (1H, m), 1.98–2.00 (1H, m), 2.63–2.82 (4H, m), 2.91–2.99 (2H, m), 3.08–3.10 (2H, m), 3.31–3.38 (2H, m), 5.20 (1H, t, *J* = 8.5 Hz, NC*H*CH$_2$), 5.66 (1H, s, Ar), 6.09 (1H, d, *J* = 7.8 Hz, Ar), 6.45 (1H, d, *J* = 7.8 Hz, Ar), 6.49 (2H, s, Ar), 6.91 (1H, d, *J* = 7.6 Hz, Ar), 7.25–7.34 (3H, m, Ar), 7.45–7.50 (5H, m, Ar), 7.72 (2H, d, *J* = 6.8 Hz, Ar). ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 24.4 (CH$_2$), 30.8 (CH$_2$), 34.2 (Ar–CH$_2$), 35.1 (Ar–CH$_2$), 35.2 (Ar–CH$_2$), 35.4 (Ar–CH$_2$), 51.4 (N–CH$_2$), 68.5 (NCH), 82.1 (C–OH), 126.9 (Ar, CH), 127.1 (Ar, CH), 127.4 (Ar, CH), 127.4 (Ar, CH), 127.5 (Ar, CH), 127.5 (Ar, CH), 127.69 (Ar, CH × 2), 127.71 (Ar, CH × 2), 131.2 (Ar, CH), 131.6 (Ar,

CH), 131.66 (Ar, CH), 131.73 (Ar, C), 132.2 (Ar, CH), 132.4 (Ar, CH), 134.5 (Ar, CH), 135.3 (Ar, CH), 138.6 (Ar, C), 138.7 (Ar, C), 139.2 (Ar, C), 139.6 (Ar, C), 143.3 (Ar, C), 145.2 (Ar, C), 172.2 (C=O).

4.2. Acidic hydrolysis of the amides (Table 1)

4.2.1. (S_p)-[2.2]Paracyclophane-4-carboxylic acid (S_p)-5. Amide (S_p,*S*)-**10** (40 mg, 0.12 mmol) was dissolved in dioxane (60 μL), and 50% w/w aqueous sulfuric acid (47 mg) was added to this solution. The resulting mixture was stirred for 14 h at 120 °C (bath temperature). After cooling to room temperature, the reaction mixture was alkalinized with 10% aqueous sodium hydroxide and washed with ethyl acetate. The aqueous layer was acidified with 10% hydrochloric acid and extracted with dichloromethane. The extracts were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate; 2:1) to afford (S_p)-**5** (18.5 mg, 62%) as colorless crystals. $[\alpha]_D^{22} = +158$ (*c* 0.7, $CHCl_3$). Ref. 29 $[\alpha]_D^{25} = +164$ (*c* 0.5, $CHCl_3$). ^1H NMR spectrum was in good agreement with that of (RS_p)-**5**.

4.2.2. (R_p)-[2.2]Paracyclophane-4-carboxylic acid (R_p)-5. According to the synthetic procedure for acidic hydrolysis of amide (S_p,*S*)-**10** described above, (R_p)-**5** (13.9 mg, 34%) was obtained from (R_p,*S*)-**10** (55.3 mg, 0.17 mmol). $[\alpha]_D^{19} = -159$ (*c* 0.4, $CHCl_3$). Ref. 29 $[\alpha]_D^{25} = -159$ (*c* 0.5, $CHCl_3$).

4.3. Reduction of amides 10–12 (Table 1)

4.3.1. (*S*)-[1-{(S_p)-[2.2]Paracyclophan-4-yl}methylpyrrolidin-2-yl]methanol (S_p,*S*)-1. Lithium aluminum hydride (32.6 mg, 0.86 mmol) was added to a solution of (S_p,*S*)-**10** (50.0 mg, 0.15 mmol) in THF (0.48 mL) at 0 °C, and the resulting mixture refluxed for 2 h. After cooling by use of an ice bath, water (33 μL) was added carefully, and 15% aqueous sodium hydroxide (33 μL) and then water (100 μL) were added to the reaction mixture with stirring. The mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the residue purified with silica gel column chromatograpy (hexane/ethyl acetate, 4:1) to afford (S_p,*S*)-**1** (43.6 mg, 91%) as a colorless solid. Mp 157–158 °C. $[\alpha]_D^{28} = +27.6$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$): 2950, 1600, 1120 cm^{-1}. FABMS (glycerol) *m*/*z* 322 [$(M+1)^+$]. HRMS (FAB) (glycerol) Calcd for $C_{22}H_{28}NO$ (M+1): 322.2171. Found: 322.2169. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.57–1.63 (2H, m), 1.74–1.89 (1H, m), 2.16 (1H, dd-like m), 2.62–2.66 (1H, m), 2.69–2.73 (1H, m), 2.82–2.88 (1H, m), 2.93–3.18 (7H, m), 3.44–3.50 (2H, m), 3.73 (1H, dd, $J = 10.7$, 3.4 Hz), 3.96 (1H, d, $J = 12.5$ Hz), 6.23 (1H, s, Ar), 6.38 (1H, dd, $J = 7.8$, 1.7 Hz, Ar), 6.44–6.53 (4H, m, Ar), 6.58 (1H, dd, $J = 7.8$, 1.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.4 (CH_2), 27.5 (CH_2), 33.3 (Ar–CH_2), 34.4 (Ar–CH_2), 34.9 (Ar–CH_2), 35.2 (Ar–CH_2), 54.4 (CH_2), 58.0 (CH_2), 61.9 (CH_2), 64.3 (N–CH) 128.8 (Ar, CH), 131.6 (Ar, CH), 131.8 (Ar, CH), 132.8 (Ar, CH), 133.0 (Ar, CH), 134.7 (Ar, CH), 135.2 (Ar, CH), 137.3 (Ar, C), 138.2 (Ar, C), 139.1 (Ar, C), 139.1 (Ar, C), 139.2 (Ar, C).

4.3.2. (*S*)-[1-{(R_p)-[2.2]Paracyclophan-4-yl}methylpyrrolidin-2-yl]methanol (R_p,*S*)-1. According to the synthetic procedure of (S_p,*S*)-**1** from (S_p,*S*)-**10** described above, (R_p,*S*)-**1** (45.7 mg, 95%) was obtained from (R_p,*S*)-**10** (50.0 mg, 0.15 mmol) as a colorless solid. Mp 124–125 °C. $[\alpha]_D^{24} = -93.4$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$): 2940, 1600, 1120 cm^{-1}. FABMS (glycerol) *m*/*z* 322 [$(M+1)^+$]. HRMS (FAB) (glycerol) Calcd for $C_{22}H_{28}NO$ (M+1): 322.2171. Found: 322.2166. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.62–1.69 (2H, m), 1.73–1.81 (1H, m), 1.84–1.93 (1H, m), 2.26 (1H, dd-like m), 2.73–2.80 (1H, m), 2.81–2.86 (1H, m), 2.91–3.17 (7H, m), 3.37–3.44 (2H, m), 3.51–3.61 (3H, m), 6.33 (1H, s, Ar), 6.39 (1H, dd, $J = 8.1$, 2.0 Hz, Ar), 6.42–6.50 (3H, m, Ar), 6.53 (1H, dd, $J = 7.8$, 2.0 Hz, Ar), 6.62 (1H, dd, $J = 7.8$, 2.0 Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.7 (CH_2), 28.1 (CH_2), 33.4 (Ar–CH_2), 34.5 (Ar–CH_2), 35.1 (Ar–CH_2), 35.4 (Ar–CH_2), 54.8 (CH_2), 56.7 (CH_2), 62.1 (CH_2), 64.5 (N–CH) 128.4 (Ar, CH), 131.2 (Ar, CH), 131.9 (Ar, CH), 133.1 (Ar, CH), 133.2 (Ar, CH), 134.3 (Ar, CH), 134.6 (Ar, CH), 137.4 (Ar, C), 138.0 (Ar, C), 139.0 (Ar, C), 139.4 (Ar, C), 139.8 (Ar, C).

4.3.3. (*S*)-1-Methyl-1-[1-{(S_p)-[2.2]paracyclophan-4-yl}-methylpyrrolidin-2-yl]ethanol (S_p,*S*)-2 and (S_p)-4-hydroxymethyl-[2.2]paracyclophane (S_p)-13. According to the synthetic procedure of (S_p,*S*)-**1** from (S_p,*S*)-**10** described above, (S_p,*S*)-**2** (30.7 mg, 64%) and (S_p)-**13** (12.2 mg, 35%) were obtained from (S_p,*S*)-**11** (50.0 mg, 0.14 mmol).

Compound (S_p,*S*)-**2**: Colorless solid, mp 79–80 °C. $[\alpha]_D^{27} = +32.7$ (*c* 0.3, $CHCl_3$). IR ($CHCl_3$): 2950, 1600, 1400, 1140 cm^{-1}. FABMS (glycerol) *m*/*z* 350 [$(M+1)^+$]. HRMS (FAB) (glycerol) Calcd for $C_{24}H_{32}NO$ (M+1): 350.2484. Found: 350.2492. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.15 (3H, s, Me), 1.24 (3H, s, Me), 1.57–1.70 (3H, m), 1.77–1.83 (1H, m), 2.37 (1H, dd, $J = 9.2$, 7.2 Hz), 2.68–2.74 (2H, m), 2.81–2.89 (1H, m), 2.93–3.16 (6H, m), 3.34 (1H, d, $J = 13.7$ Hz, –NC*H*HC), 3.54 (1H, t-like m), 4.10 (1H, d, $J = 13.4$ Hz, –NCH*H*C), 6.27 (1H, s, Ar), 6.36 (1H, dd, $J = 7.8$, 1.7 Hz, Ar), 6.42–6.54 (4H, m, Ar), 6.60 (1H, dd, $J = 7.8$, 1.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.0 (CH_2), 25.2 (Me), 27.9 (CH_2), 28.8 (Me), 33.7 (Ar–CH_2), 34.4 (Ar–CH_2), 35.2 (Ar–CH_2), 35.4 (Ar–CH_2), 55.4 (NCH_2CH_2), 62.8 (CCH_2N), 72.9 (C–OH), 73.6 (NCH), 128.8 (Ar, CH), 131.5 (Ar, CH), 131.9 (Ar, CH), 133.0 (Ar, CH), 133.1 (Ar, CH), 134.8 (Ar, CH), 134.9 (Ar, CH), 138.3 (Ar, C), 139.2 (Ar, C), 139.3 (Ar, C), 138.4 (Ar, C).

Compound (S_p)-**13**: Colorless solid, mp 111–112 °C. $[\alpha]_D^{28} = +67.6$ (*c* 0.9, $CHCl_3$). Ref. 55 $[\alpha]_D^{20} = +68$ (*c* 0.43, $CHCl_3$). IR ($CHCl_3$): 2920, 1600 cm^{-1}. EIMS *m*/*z* 238 (M^+, 64%), 134 (61), 119 (46), 105 (100), 104 (88), 91 (36). HRMS (EI) Calcd for $C_{17}H_{18}O$: 238.1358. Found: 238.1361. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.81–2.91 (1H, m), 2.96–3.19 (6H, m), 3.40 (1H, ddd, $J = 13.2$, 10.1, 2.4 Hz), 4.38 (1H, d, $J = 12.9$ Hz, OC*H*H), 4.71 (1H, d, $J = 12.7$ Hz, m, OCH*H*), 6.37–6.40 (2H, m, Ar), 6.45–6.55 (4H, m, Ar), 6.60 (1H, dd, $J = 7.9$, 1.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 32.9 (CH_2), 34.5 (CH_2), 35.2 (CH_2), 35.4 (CH_2), 64.6 (CH_2OH), 128.9 (Ar, CH), 131.97 (Ar, CH), 132.01 (Ar, CH), 132.2 (Ar, CH), 133.1 (Ar, CH), 133.2

(Ar, CH), 134.8 (Ar, CH), 137.3 (Ar, C), 139.1 (Ar, C), 139.1 (Ar, C), 139.4 (Ar, C), 139.6 (Ar, C). Enantiomeric excess was measured as >99% ee (S_p-enantiomer) by HPLC analysis (column; Chiralcel OD, eluent, hexane/*i*-PrOH, 4:1, flow rate; 0.5 mL/min, UV detector; 254 nm) [t_R(S_p-enantiomer) = 21.0 min, t_R(R_p-enantiomer) = 28.0 min].

4.3.4. (*S*)-1-Methyl-1-[1-{(R_p)-[2.2]paracyclophan-4-yl}-methyl-2-pyrrolidin-2-yl]ethanol (R_p,*S*)-2 and (R_p)-13. According to the synthetic procedure of (S_p,*S*)-**1** from (S_p,*S*)-**10** described above, (R_p,*S*)-**2** (39.6 mg, 82%) and (R_p)-**13** (4.2 mg, 12%) were obtained from (R_p,*S*)-**11** (50.0 mg, 0.14 mmol).

Compound (R_p,*S*)-**2**: Colorless solid, mp 69–70 °C. $[\alpha]_D^{27} = -85.1$ (*c* 0.8, $CHCl_3$). IR ($CHCl_3$): 2950, 1610, 1360, 1140 cm^{-1}. FABMS (glycerol) *m*/*z* 350 [$(M+1)^+$]. HRMS (FAB) (glycerol) Calcd for $C_{24}H_{32}NO$ (M+1): 350.2484. Found: 350.2492. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.20 (3H, s, Me), 1.33 (3H, s, Me), 1.58–1.71 (3H, m), 1.82–1.88 (1H, m), 2.24 (1H, td, $J = 10.5$, 6.8 Hz), 2.71–3.14 (9H, m), 3.31 (1H, t-like m), 3.70 (2H, dd, $J = 15.9$, 14.2 Hz), 6.34 (1H, dd, $J = 7.8$, 1.7 Hz, Ar), 6.40 (1H, d, $J = 7.8$ Hz, Ar), 6.46 (2H, d, $J = 7.6$ Hz, Ar), 6.54 (2H, dd, $J = 7.8$, 2.0 Hz, Ar), 6.65 (1H, dd, $J = 7.8$, 2.0 Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.1 (Me), 25.2 (CH_2), 27.9 (CH_2), 28.6 (Me), 33.4 (Ar–*C*H_2), 34.5 (Ar–*C*H_2), 35.2 (Ar–*C*H_2), 35.4 (Ar–*C*H_2), 55.4 (N*C*H_2CH_2), 60.3 (C*C*H_2N), 72.8 (C–OH), 73.1 (NCH), 128.1 (Ar, CH), 130.5 (Ar, CH), 131.6 (Ar, CH), 133.0 (Ar, CH), 133.1 (Ar, CH), 133.2 (Ar, CH), 134.3 (Ar, CH), 137.6 (Ar, C), 138.7 (Ar, C), 138.9 (Ar, C), 139.3 (Ar, C), 139.8 (Ar, C).

4.3.5. (*S*)-1-{(S_p)-[2.2]Paracyclophan-4-yl}methyl-2-pyrrolidine-α,α-diphenylmethanol (S_p,*S*)-3 and (S_p)-13. According to the synthetic procedure of (S_p,*S*)-**1** from (S_p,*S*)-**10** described above, (S_p,*S*)-**3** (362 mg, 64%) and (S_p)-**13** (109 mg, 36%) were obtained from (S_p,*S*)-**12** (585 mg, 1.2 mmol).

Compound (S_p,*S*)-**3**: Colorless solid, mp 204–205 °C. $[\alpha]_D^{25} = -17.9$ (*c* 0.8, $CHCl_3$). IR ($CHCl_3$): 2920, 2850, 1600, 1450, 1100 cm^{-1}. FABMS (magic bullet) *m*/*z* 474 [$(M+1)^+$]. HRMS (FAB) (magic bullet) Calcd for $C_{34}H_{36}NO_2$ (M+1): 474.2797. Found: 474.2787. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.43–1.52 (2H, m), 1.57–1.63 (1H, m), 1.72–1.80 (1H, m), 2.09–2.23 (2H, m), 2.46–2.50 (1H, m), 2.64–2.74 (3H, m), 2.91–3.06 (5H, m), 3.49 (1H, d, $J = 12.0$ Hz), 3.94 (1H, dd, $J = 9.3$, 5.4 Hz, NC*H*CH_2), 5.82 (1H, dd, $J = 7.8$, 1.7 Hz, Ar), 6.05 (1H, s, OH), 6.15 (1H, dd, $J = 7.8$, 2.0 Hz, Ar), 6.31–6.35 (2H, m, Ar), 6.39–6.42 (2H, m, Ar), 7.10–7.14 (2H, m, Ar), 7.22–7.28 (3H, m, Ar), 7.42–7.46 (2H, m, Ar), 7.58 (2H, dd, $J = 8.3$, 1.2 Hz, Ar), 7.94 (2H, dd, $J = 8.5$, 1.2 Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.5 (CH_2), 29.7 (CH_2), 33.1 (Ar–*C*H_2), 33.9 (Ar–*C*H_2), 35.0 (Ar–*C*H_2), 35.4 (Ar–*C*H_2), 55.6 (N*C*H_2CH_2), 61.9 (C*C*H_2N), 70.7 (NCH), 124.9 (Ar, CH × 2), 125.7 (Ar, CH × 2), 125.9 (Ar, CH), 126.5 (Ar, CH), 127.9 (Ar, CH × 2), 128.3 (Ar, CH × 2), 128.5 (Ar, CH), 131.9 (Ar, CH × 2), 132.8 (Ar, CH), 133.0 (Ar, CH), 134.6 (Ar, CH), 135.4 (Ar, CH), 138.2 (Ar, C), 138.7 (Ar, C), 139.0 (Ar, C × 2), 139.4 (Ar, C), 147.1 (Ar, C), 148.5 (Ar, C).

4.3.6. (*S*)-1-{(R_p)-[2.2]Paracyclophan-4-yl}methyl-2-pyrrolidine-α,α-diphenylmethanol (R_p,*S*)-3 and (R_p)-13. According to the synthetic procedure of (S_p,*S*)-**1** from (S_p,*S*)-**10** described above, (R_p,*S*)-**3** (473 mg, 83%) and (R_p)-**13** (12.1 mg, 4%) were obtained from (R_p,*S*)-**12** (585 mg, 1.2 mmol).

Compound (R_p,*S*)-**3**: Colorless solid, mp 154–155 °C. $[\alpha]_D^{25} = -59.8$ (*c* 0.4, $CHCl_3$). IR ($CHCl_3$): 2920, 2850, 1600, 1450, 1120 cm^{-1}. FABMS (magic bullet) *m*/*z* 474 [$(M+1)^+$]. HRMS (FAB) (magic bullet) Calcd for $C_{34}H_{36}NO_2$ (M+1): 474.2797. Found: 474.2787. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.50–1.56 (2H, m), 1.64–1.70 (1H, m), 1.82–1.90 (1H, m), 2.18 (1H, q, $J = 8.1$ Hz), 2.43–2.50 (1H, m), 2.63–2.77 (2H, m), 2.90–3.21 (8H, m), 4.08 (1H, dd, $J = 9.0$, 5.6 Hz, NC*H*CH_2), 5.62 (1H, dd, $J = 7.8$, 1.7 Hz, Ar), 5.96 (1H, dd, $J = 7.8$, 2.0 Hz, Ar), 6.09 (1H, s, OH), 6.29–6.37 (3H, m, Ar), 6.42 (1H, dd, $J = 7.8$, 1.7 Hz, Ar), 7.15 (1H, t, $J = 7.3$ Hz, Ar), 7.23–7.32 (4H, m, Ar), 7.44–7.48 (2H, m, Ar), 7.61 (2H, dd, $J = 8.3$, 1.2 Hz, Ar), 7.92 (2H, dd, $J = 8.8$, 1.2 Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.9 (CH_2), 29.8 (CH_2), 33.7 (Ar–*C*H_2), 34.7 (Ar–*C*H_2), 35.2 (Ar–*C*H_2), 35.4 (Ar–*C*H_2), 55.6 (N–*C*H_2–CH_2), 57.3 (C*C*H_2N), 70.6 (NCH), 125.2 (Ar, CH), 125.2 (Ar, CH), 125.8 (Ar, CH × 2), 126.0 (Ar, CH), 126.6 (Ar, CH), 128.0 (Ar, CH × 2), 128.2 (Ar, CH × 2), 128.5 (Ar, CH), 130.2 (Ar, CH), 131.8 (Ar, CH), 132.5 (Ar, CH), 132.9 (Ar, CH), 134.0 (Ar, CH), 134.1 (Ar, CH), 137.3 (Ar, C), 138.7 (Ar, C × 2), 139.01 (Ar, C × 2), 139.6 (Ar, C), 146.8 (Ar, C).

4.4. Synthesis of amino alcohol (S_p)-4 (Scheme 2)

4.4.1. Ethyl *N*-(2-hydroxy-2,2-diphenylethyl)carbamate 15. A solution of phenylmagnesium bromide in diethyl ether (3.0 mol/L, 14.3 mL, 42.8 mmol) was added dropwise to a solution of *N*-(ethoxycarbonyl)glycine ethyl ester **14**[34] (1.72 g, 10.7 mmol) in THF (21 mL) at 0 °C. After being stirred for 1 h at this temperature, the reaction was quenched with saturated aqueous ammonium chloride. The mixture was extracted with diethyl ether. The extracts were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo to give **15** (2.02 g, 70%) as a colorless solid. The solid was recrystallized from *tert*-butyl methyl ether, and the crystal was used for the spectrum analysis. Mp 124–125 °C. IR (KBr): 3390, 1690, 1540, 1450, 1345, 1260, 1180, 1065, 965 cm^{-1}. FABMS (glycerol) *m*/*z* 272 [$(M+1)^+$], 254 ($M-H_2O$). HRMS (FAB) (glycerol) Calcd for $C_{16}H_{18}NO_3$ (M+1): 272.1287. Found: 272.1277. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.17. Found: C, 70.91; H, 6.54; N, 4.95. ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.54 (3H, s, MeO), 3.63 (1H, br s, OH), 3.94 (2H, d, $J = 6.0$ Hz, CH_2), 5.11 (1H, br s, NH), 7.21–7.31 (2H, m, Ar), 7.28–7.31 (4H, m, Ar), 7.38–7.40 (4H, m, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 50.6 (NCH_2), 52.8 (Me), 78.1 (HOC), 125.9 (CH × 4, Ar), 127.1 (CH × 2, Ar) 128.2 (CH × 4, Ar), 144.3 (C × 2, Ar), 157.7 (C=O).

4.4.2. 2-Methylamino-1,1-diphenylethanol 16. A mixture of **15** (0.92 g, 3.43 mmol) and lithium aluminum hydride (0.26 g, 6.86 mmol) in THF (8.6 mL) was refluxed for 16 h. After cooling, the reaction mixture was diluted with diethyl ether (17 mL). Water (0.25 mL), 15% aqueous sodium hydroxide (0.25 mL), and then water (0.75 mL) were added. After being stirred for 1 h, the mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to give **16** (0.75 g, 96%) as a colorless solid. Mp 58–62 °C. IR ($CHCl_3$): 3400, 2980, 2940, 2840, 1445, 1115 cm^{-1}. EIMS *m*/*z* 227 (M^+, 1.7%), 183 (26), 105 (58), 77 (36), 44 (100). HRMS (EI) Calcd for $C_{15}H_{17}NO$: 227.1311. Found 227.1308. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.45 (3H, s, Me), 3.28 (2H, s, CH_2), 7.19–7.25 (2H, m, Ar), 7.29–7.33 (4H, t-like m, Ar), 7.45–7.47 (4H, d-like m, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 36.7 (Me), 61.2 (CH_2), 76.2 (C–OH), 125.9 (CH × 4, Ar), 126.8 (CH × 2, Ar), 128.1 (CH × 4, Ar), 145.5 (C × 2, Ar).

4.4.3. *N*-(2-Hydroxymethyl-2,2-diphenyl)ethyl-*N*-methyl-(S_p)-[2.2]paracyclophane-4-carboxamide (S_p)-17. Thionyl chloride (50 μL, 0.68 mmol) was added dropwise to a mixture of (*S*)-4-carboxy[2.2]paracyclophane (S_p)-**5** (44 mg, 0.18 mmol) and DMF (10 μL) in benzene (0.6 mL) in an atmosphere of argon at room temperature. After being stirred for 2 h at 70 °C, the reaction mixture was concentrated in vacuo.

Amino alcohol **16** (65 mg, 0.29 mmol), DMAP (2.6 mg) and triethylamine (54 mL, 0.39 mmol) were added to a solution of the residue in dichloromethane (0.65 mL) with stirring at 0 °C. The resulting mixture was stirred for 12 h and allowed to warm to room temperature. The resulting mixture was poured into saturated aqueous ammonium chloride solution and extracted with dichloromethane. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate; 1:1) to give (S_p)-**17** as a colorless amorphous foam. $[\alpha]_D^{23} = +28.8$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$): 3370, 3000, 2930, 1735, 1665, 1610, 1530, 1495, 1455 cm^{-1}. FABMS (glycerol) *m*/*z* 461 [$(M+1)^+$], 444 ($M-H_2O$). HRMS (FAB) (glycerol) Calcd for $C_{32}H_{32}NO_2$ (M+1): 462.2435. Found: 462.2425. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.26 (3H, s, Me), 2.73–2.80 (1H, m), 2.85–3.00 (4H, m), 3.08–3.20 (3H, m), 4.26 (1H, d, $J = 13.9$ Hz, NC*H*H), 4.55 (1H, d, $J = 13.9$ Hz, NCH*H*), 6.19 (1H, s, Ar), 6.32–6.39 (3H, m, Ar), 6.47–6.55 (3H, m, Ar), 6.99 (1H, m, Ar), 7.24–7.28 (2H, m, Ar), 7.33 (4H, m, Ar), 7.56 (2H, d, $J = 7.6$ Hz, Ar), 7.61 (2H, d, $J = 7.3$ Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 33.6 (CH_2), 35.26 (CH_2), 35.34 (CH_2), 35.4 (CH_2), 40.0 (Me), 60.4 (CH_2N), 79.1 (C–OH), 126.2 (CH_2 × 2, Ar), 126.3 (CH × 2, Ar), 126.9 (CH, Ar), 127.0 (CH, Ar), 127.9 (CH × 2, Ar), 128.0 (CH × 2, Ar), 130.6 (CH, Ar), 131.6 (CH, Ar), 132.2 (CH, Ar), 132.3 (CH, Ar), 132.5 (CH, Ar), 132.8 (CH, Ar), 134.4 (CH, Ar), 134.8 (CH, Ar), 137.7 (C, Ar), 138.9 (C, Ar), 139.1 (C, Ar), 139.7 (C, Ar), 145.3 (C, Ar), 145.8 (C, Ar), 174.5 (C=O).

4.4.4. 2-{*N*-Methyl-*N*-(S_p)-[2.2]paracyclophan-4-ylmethyl}-amino-1,1-diphenylethanol (S_p)-4. According to the synthetic procedure of (S_p,*S*)-**1** from (S_p,*S*)-**10**, (S_p)-**4** (25.7 mg, 77%) was obtained from (S_p)-**17** (34.3 mg, 0.074 mmol) as a colorless viscous oil. $[\alpha]_D^{26} = +24.9$ (*c* 0.5, $CHCl_3$). IR (film): 3000, 2930, 2850, 1600, 1495, 1453, 1380 cm^{-1}. FABMS (glycerol) *m*/*z* 448 [$(M+1)^+$], 221. HRMS (FAB) (glycerol) Calcd for $C_{32}H_{34}NO$ (M+1): 448.2642. Found: 448.2647. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.56–2.63 (1H, m), 2.71–2.79 (1H, m), 2.90–3.02 (m, 5H), 3.05 (1H, d, $J = 12.7$ Hz, NC*H*H), 3.25 (1H, t-like m), 3.34 (2H, s, NCH_2), 3.47 (1H, d, $J = 12.7$ Hz, NCH*H*), 6.09–6.20 (3H, m, Ar), 6.37–6.47 (4H, m, Ar), 7.16–7.25 (2H, m, Ar), 7.27–7.38 (4H, m, Ar), 7.56 (2H, d, $J = 16.3$ Hz), 7.58 (2H, d, $J = 16.6$ Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 33.4 (CH_2), 34.5 (CH_2), 35.1 (CH_2), 35.4 (CH_2), 44.0 (Me), 61.8 (CH_2), 67.8 (CH_2), 74.4 (C–OH), 125.6 (CH × 2, Ar), 125.7 (CH × 2, Ar), 126.5 (CH × 2, Ar), 128.0 (CH × 2, Ar), 128.1 (CH × 2, Ar), 131.5 (CH, Ar), 131.9 (CH, Ar), 132.9 (CH, Ar), 133.0 (CH, Ar), 134.6 (CH, Ar), 135.2 (CH, Ar), 137.3 (C, Ar), 138.4 (C, Ar), 139.1 (C, Ar), 139.2 (C, Ar), 139.4 (C, Ar), 147.1 (C, Ar), 147.2 (C, Ar).

4.5. General procedure for the addition of diethylzinc to benzaldehyde (Table 2)

A solution of diethylzinc in hexane (0.99 mol/L, 0.67 mL) was added dropwise to a solution of amino alcohol (S_p,*S*)-**1** (4.8 mg, 0.015 mmol) in toluene (0.6 mL) at 0 °C in an atmosphere of argon. After being stirred for 30 min, benzaldehyde (31.8 mg, 0.3 mmol) was added. The mixture was stirred for 2 h at 0 °C and then for 16 h while being allowed to warm to room temperature. The reaction was quenched with ice-cooled 5% hydrochloric acid, and the mixture was extracted with diethyl ether. The extracts were combined, dried over magnesium, filtered, and triphenylmethane (18.3 mg, 0.075 mmol) was added as an internal standard. The mixture was concentrated in vacuo, and the yield of 1-phenyl-1-propanol was calculated as 20% by ^1H NMR integral value. Enantiomeric excess was measured as 54% ee [(*S*)-enantiomer] by HPLC analysis.

4.6. General conditions for HPLC analysis of the chiral alcohols

Chiralcel OD column eluted with hexane/2-propanol (97:3, Method A or 98:2, Method B) at 0.5 mL/min using UV detector at 254 nm. All the absolute configurations were determined as (*S*) by the comparison of the known elution order from a chiral OD column.[56–60]

4.6.1. (*S*)-1-Phenyl-1-propanol. Method B: $t_R = 20.6$ min and $t_S = 24.3$ min.[57–59]

4.6.2. (*S*)-1-(*p*-Methoxyphenyl)-1-propanol. Method A: $t_R = 32.2$ min and $t_S = 38.3$ min (4% ee).[57–60]

4.6.3. (*S*)-1-(*m*-Methoxyphenyl)-1-propanol. Method B: $t_R = 49.3$ min and $t_S = 51.7$ min (86% ee).[57,60]

4.6.4. (*S*)-1-(*o*-Methoxyphenyl)-1-propanol. Method A: $t_R = 29.6$ min and $t_S = 26.1$ min (57% ee).[59,60]

4.6.5. (*S*)-1-(*p*-Bromophenyl)-1-propanol. Method A: t_R = 25.7 min and t_S = 23.5 min (80% ee).[58]

4.6.6. (*S*)-1-(*p*-Chlorophenyl)-1-propanol. Method A: t_R = 22.4 min and t_S = 20.2 min (74% ee).[57–59]

4.6.7. (*S*)-1-(*o*-Bromophenyl)-1-propanol. Method B: t_R = 30.4 min and t_S = 32.5 min (61% ee).[58]

4.6.8. (*S*)-1-Naphthyl-1-propanol. Method A: t_R = 91.8 min and t_S = 39.2 min (71% ee).[56–60]

4.6.9. (*S*)-2-Naphthyl-1-propanol. Method A: t_R = 57.9 min and t_S = 52.3 min (62–65% ee).[56–58,60]

4.6.10. (*S*,*E*)-1-Phenylpent-1-en-3-ol. Method A: t_R = 42.6 min and t_S = 81.4 min (73% ee).[56–59]

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