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Regulation of the flexibility of planar chiral [2.2]paracyclophane ligands and its significant impact on enantioselectivity in asymmetric reactions of diethylzinc with carbonyl compounds

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This paper is dedicated to Professor Chang Tao Qian on the occasion of his 70th birthday

Abstract—A series of planar chiral ligands derived from [2.2]paracyclophane were synthesized and applied as catalysts in enantioselective additions of diethylzinc to aldehydes and α,β-unsaturated ketones. When ligand **10** with a dimethyl hydroxymethyl as the substituent was used, the enantioselectivity of the reaction of diethylzinc with aldehydes was much higher than when using ligand **3c** with diphenyl hydroxymethyl as the substituent. The situation was the same with the 1,4-addition of diethylzinc to α,β-unsaturated ketones with 63–83% ee being obtained when the hydroxymethyl substituted ligand **7b** was used, while almost no enantioselectivity was afforded if ligand **3c** was used. The role of planar chirality is also studied.
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1. Introduction

Over the past few years, [2.2]paracyclophane derivatives have attracted growing attention as novel chiral ligands in asymmetric catalysis, with excellent asymmetric induction being realized in many types of asymmetric reactions.[1,2] These ligands, which have a framework of two benzene rings connected at the *para*-position by two ethylene chains, are chemically stable[3a] and undergo racemization only at relatively high temperature.[3b] Besides, planar chirality can be introduced when there is a substituent at any position of the benzene rings.[4] However, only a few structural characteristics of cyclophanes have been shown to influence the reactivity and enantioselectivity in asymmetric catalysis. For example, the [2.2]paracyclophane framework is usually considered to be rigid,[3c] but our understanding of the effect of this rigidity in asymmetric catalysis is not yet complete. As part of a program aimed at the synthesis and application of novel chiral ligands in asymmetric catalysis,[5] we previously synthesized several novel chiral *P*,*N*- and *N*,*O*-[2.2]paracyclophane ligands and used them in asymmetric catalysis.[2] We found that the location of the substituents on the ligands strongly affected the enantioselectivity of the reactions.[2a] We also found that *N*,*O*-[2.2]paracyclophane ligands were effective as catalysts in the enantioselective addition of diethylzinc to aldehydes.[2b] Unexpected results have been obtained in ongoing studies on the structure–reactivity relationships in chiral ligands,[5j] which has prompted us to study further the structure of [2.2]cyclophanes. Herein, we report the synthesis of new chiral cyclophane ligands and describe the unforeseen significant effect of the rigidity and flexibility of cyclophane-based ligands on the enantioselectivity of the reactions of diethylzinc with aldehydes and α,β-unsaturated ketones as well as the role of their planar chirality in these reactions.

2. Results and discussions

We have previously reported the synthesis of ligands **3** and **4** and their application in the enantioselective

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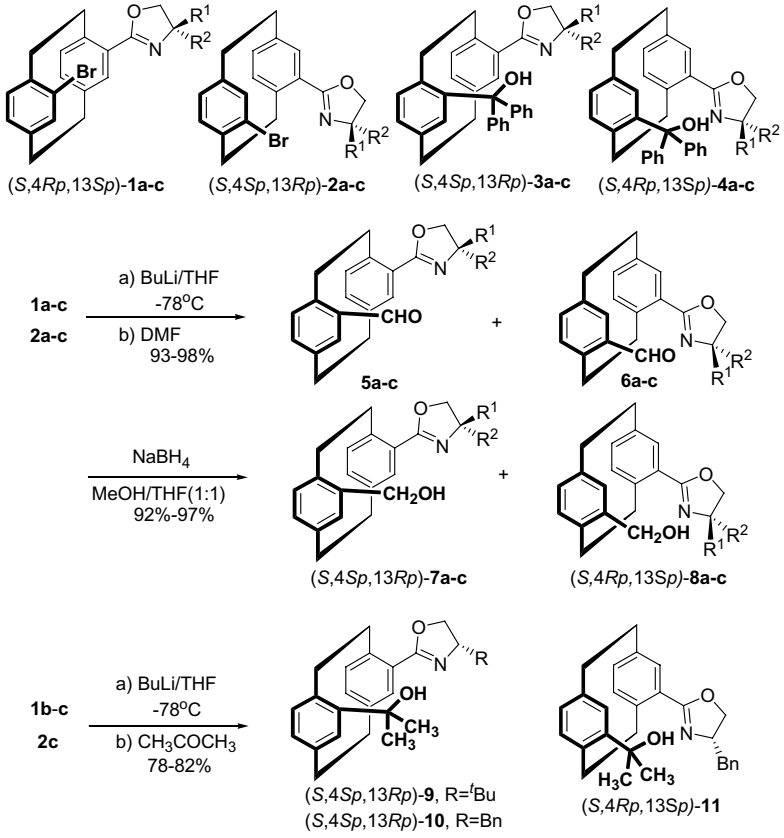
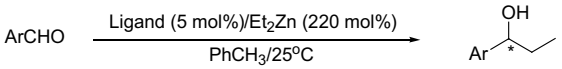
addition of Et_2Zn to aldehydes.[6] The synthesis of the new chiral [2.2]cyclophane ligands in this work is based on the same strategy that was used to obtain ligands **3** and **4**. Diastereoisomeric oxazolinlycyclophanes **1** and **2** are key intermediates for the synthesis of new planar chiral *N*,*O*-[2.2]paracyclophane ligands.[2b] Bromo-lithium exchange of **1** and **2** at −78 °C, followed by trapping of the anion with DMF gave compounds **5** and **6**. Reduction of **5** and **6** with $NaBH_4$ in MeOH and THF afforded the desired ligands **7** and **8** with a hydroxymethyl group as the substituent, which is smaller than the diphenylhydroxymethyl unit. To study further the effect of the rigid [2.2]paracyclophane backbone on asymmetric catalytic reactions, ligands **9**, **10**, and **11** were also synthesized. These ligands contain a dimethylhydroxymethyl group, which is medium-sized compared to the diphenylhydroxymethyl and hydroxymethyl groups (Scheme 1).

With these new ligands in hand, the addition reaction of diethylzinc to aldehydes was used to examine the effects of different substituents on the cyclophane on the reaction,[7] with the results shown in Table 1. It can be seen that ligands **7a**–**c**, with a hydroxymethyl moiety, gave enantioselectivities that were equal to or greater than with ligands **3a**–**c**, which have a diphenylhydroxymethyl moiety (Table 1, entries 1–6). Furthermore, while the planar chirality and central chirality in ligands **7** are matched, those in ligands **8** are not. However, ligands **9** and **10** with a dimethylhydroxymethyl group not only showed higher reactivity but also provided better enantioselectivities (97.9% and 98.4% ee, respectively) than ligands **3a**–**c** and **7a**–**c** (Table 1, entries 7 and 8 vs entries 3 and 5). The effectiveness of ligand **10** was further demonstrated when other aromatic aldehydes were used, with 96% ee being achieved regardless of the presence of electron-withdrawing or -donating groups on the benzene ring (Table 1, entries 10–13). These ee values are far better than those given by ligands **3**, with the ee values increasing as much as 14% and 15% in some cases (Table 1, entries 12 and 13). These results reflect the influence of changes in the ligand structure on the enantioselectivity of the reaction. There have already been many discussions on the effects of the rigidity and flexibility of ligands on enantioselectivity.[8–10] Most examples have shown that the enantioselectivity increases with an increase in the rigidity of the ligands.[8a–c] In particular, the introduction of a diphenylhydroxymethyl group into a chiral ligand usually leads to an increase in enantioselectivity in various reactions; a group of this type is known as a 'magic' group.[9] Only a few reports have noted that the introduction of flexibility has provided excellent enantioselectivity in the reaction.[10] Interestingly, in our case the less sterically demanding dimethylhydroxymethyl group gave better results than the more sterically demanding diphenylhydroxymethyl



Scheme 1.

Table 1. Enantioselective addition of diethylzinc to aldehydes with planar chiral *N*,*O*-ligands



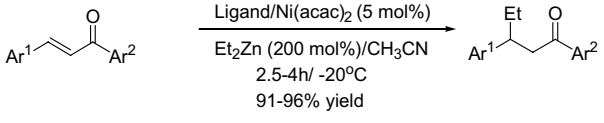
Entry	Ar	Ligand	Time (h)	Yield (%)[a,b]	Ee (%)[a,c]	Config.[d]
1	Ph	**7a** (**3a**)	5 (9)	94 (96)	91 (93)	*R* (*R*)
2	Ph	**8a** (**4a**)	24 (24)	49 (35)	25 (5)	*S* (*S*)
3	Ph	**7b** (**3b**)	7 (24)	93 (37)	94 (32)	*R* (*R*)
4	Ph	**8b** (**4b**)	24 (24)	46 (13)	36 (7)	*S* (*S*)
5	Ph	**7c** (**3c**)	5 (7)	94 (93)	91 (93)	*R* (*R*)
6	Ph	**8c** (**4c**)	24 (24)	51 (12)	45 (7)	*S* (*S*)
7	Ph	**9**	3.5	93	97.9	*R*
8	Ph	**10**	1.5	95	**98.4**	*R*
9	Ph	**11**	48	<5	—	—
10	*p*-ClC_6H_4	**10** (**3c**)	2 (8)	96 (96)	97.6 (94)	*R* (*R*)
11	*p*-BrC_6H_4	**10** (**3c**)	2 (9)	95 (95)	96.8 (93)	*R* (*R*)
12	*p*-$MeOC_6H_4$	**10** (**3c**)	3.5 (24)	94 (86)	96 (82)	*R* (*R*)
13	*o*-$MeOC_6H_4$	**10** (**3c**)	1 (4)	96 (94)	96 (81)	*R* (*R*)

[a] The yield, the ee value and the configuration in parenthesis were given using ligand **3** or **4**.[2b]
[b] Isolated yield based on aldehyde.
[c] Determined by HPLC (chiracel OD column).
[d] Configurations were assigned by comparison with the sign of specific rotation of known compounds.

group (Table 1, entries 10–13). It could be deduced that as the backbone of cyclophane is rigid, and the introduction of a more sterically demanding diphenylhydroxymethyl group into the rigid [2.2]paracyclophane backbone may have made the ligand even more rigid, then the dimethylhydroxymethyl group may have made the ligand more flexible, which enabled it to assume a more favorable conformation in the reaction. Similar results were obtained in our previously reported planar chiral *N*,*S* and *N*,*Se*-[2.2]paracyclophane ligand system and in *N*,*S*-ligands, with oxazoline, and thiophenyl groups at benzene and benzylic positions, in that benzylic-substituted ligands were more flexible than benzene ring-substituted ligands and provided far better reactivity and enantioselectivity.[2a]

The above results prompted us to extend the application of these new *N*,*O*-[2.2]paracyclophane ligands to the Ni-catalyzed asymmetric 1,4-addition reaction of diethylzinc reagent to chalcones.[11] In the presence of catalyst prepared in situ from 5 mol% of $Ni(acac)_2$ and 10 mol% of ligands **3** and **4**, the reaction gave the corresponding addition products in good yield, but the enantioselectivity was almost zero (Table 2, entry 1). Ligand **9**, which showed excellent enantioselectivity in the addition of diethylzinc to aldehydes, gave an enantiomeric excess of only 8% (Table 2, entry 2). This may be the result of it being difficult for chalcone to move close to the ligands and thus not be strongly affected by the chiral environment of the ligands; chalcone is more sterically demanding than benzaldehyde, so ligands **7** and **8** with

Table 2. Enantioselective 1,4-addition of diethylzinc to α,β-unsaturated ketones with planar chiral *N*,*O*-ligands



Entry	Ar^1	Ar^2	Ligand	Ligand (mol%)	Ee (%)[a]	Config.[b]
1	Ph	Ph	**3**–**4**	10	0	—
2	Ph	Ph	**9**	10	8	*S*
3	Ph	Ph	**7a** (**8a**)	10	52 (0)	*S* (−)
4	Ph	Ph	**7b** (**8b**)	10	63 (0)	*S* (−)
5	Ph	Ph	**7c** (**8c**)	10	53 (4)	*S* (*R*)
6	Ph	Ph	**7b**	20	75	*S*
7	*p*-MeC_6H_4	Ph	**7b**	20	63	—
8[c]	*p*-BrC_6H_4	Ph	**7b**	20	71	—
9	*p*-ClC_6H_4	Ph	**7b**	20	72	—
10	Ph	*p*-BrC_6H_4	**7b**	20	61	—
11	**Ph**	***p*-$MeOC_6H_4$**	**7b**	**20**	**83**	—

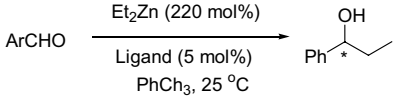
[a] Determined by chiral HPLC.
[b] Configurations were assigned by comparison with the sign of specific rotation of known compounds.
[c] The solvent is CH_3CN/CH_2Cl_2 (2/1).

an even less sterically demanding hydroxymethyl group might provide better results. Indeed, a significant increase in enantioselectivity was observed when ligands **7** and **8** were used as catalysts in this reaction (Table 2, entries 3–6). When 20 mol% of **7b** was used as a ligand, even higher enantioselectivity was achieved with the ee increasing from 63% to 75% (Table 2, entry 4 vs 6). Under the same reaction conditions, several chalcones were tested with ligand **7b** (entries 7–11) with up to 83% ee being obtained (Table 2, entry 11). These results suggest that introduction of the least sterically demanding hydroxymethyl group to ligand **7b** may have buffered the intrinsic rigidity in the [2.2]paracyclophane framework so that the enantioselectivity of the reaction was improved.

If we consider the above results along with those obtained previously in the *N*,*S*/*Se*-ligand system,[2a] we can see that an increase in the flexibility of the rigid [2.2]paracyclophane framework leads to a remarkable increase in enantioselectivity. This regulation of the flexibility of [2.2]paracyclophane ligands is very crucial for obtaining excellent results.

Furthermore, the results shown in Tables 1 and 2 also suggest the importance of matching the planar chirality and central chirality of the ligands.[2b,5e,12] To clarify further the effect of planar chirality, the *N*,*O*-ligands **15a** and **15b**, which possess only planar chirality, were synthesized using the methods depicted in Scheme 2.

First, ligands **15a** and **15b** were applied to the addition of Et_2Zn to benzaldehyde, and the product obtained in 93% and 92% ee, respectively (Eq. 1). These results contrast sharply with those using ligand **11**, which has planar chirality with the same configuration (Table 1, entry 9). These results unambiguously demonstrate that the planar chirality in cyclophane systems plays an important role in asymmetric catalysis. Based on the results of other studies[1f,m–p] and in our catalytic systems including *N*,*S*/*Se*[2a]- and *N*,*O*-ligands,[2b] the planar chirality in [2.2]paracyclophane ligands appears to play a greater role in asymmetric catalysis than that in planar chiral ferrocene ligands.[5a,e,12]



(1)

Ligand **15a**: 95% yield, 93% ee (*S*)
Ligand **15b**: 90% yield, 92% ee (*S*)

3. Conclusion

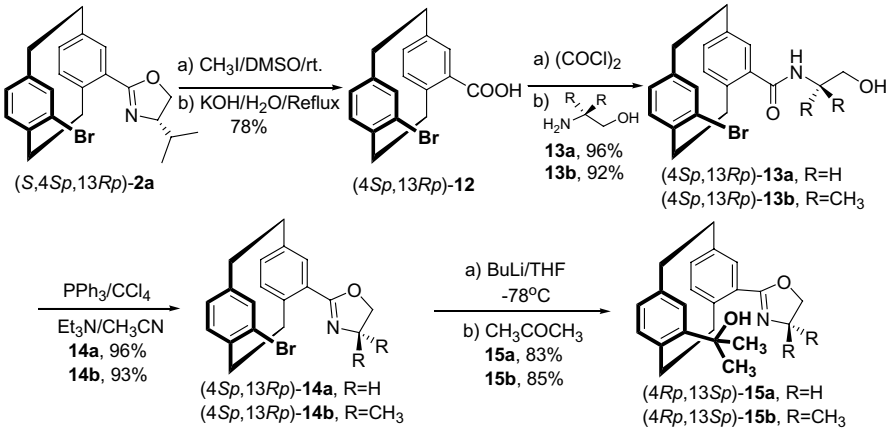
In summary, a series of ligands were synthesized and used in the addition reactions of the diethyl zinc reagent to aldehydes and chalcones. The importance of regulating the flexibility as well as the planar chirality of a rigid [2.2]paracyclophane ligand system in the reactivity and enantioselectivity of the reaction has been demonstrated. This information should be useful for the design and synthesis of new cyclophane ligands. Further investigations into the synthesis of chiral cyclophanes and their use in asymmetric catalysis are currently in progress.

4. Experimental

4.1. General methods

All reactions were performed under an argon atmosphere using oven-dried glassware. Solvents were treated prior to use according to standard methods. ^{1}H NMR spectra were recorded in $CDCl_3$ and CD_3SOCD_3. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard. IR spectra were measured in cm^{-1}. The commercially available reagents were used as received without further purification. Compound **1**, **2**, **3**, and **4** were prepared using our previously reported procedures.[2b] The α,β-unsaturated ketones were synthesized according to the similar procedure of chalcone.[13]

4.1.1. (*S*,4*Rp*,13*Sp*)-4-Formyl-13-(4-*iso*-propyl-oxazolin-2-yl)[2.2]paracyclophane 5a. *n*-BuLi (0.75 mL, 1.6 M in hexane, 1.2 mmol) was added dropwise to a solution of (*S*,4*Rp*,13*Sp*)-**1a** (398 mg, 1 mmol) in THF (10 mL) at −78 °C. The resulting mixture was stirred for 2 h at this



Scheme 2.

temperature. The mixture was treated with DMF (0.39 mL, 5 mmol) and stirred for another 1 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL). The organic layer was extracted twice with dichloromethane (15 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the crude product, which was purified by column chromatography (ethyl acetate/petroleum ether = 1/7) to give (*S*,4*Rp*,13*Sp*)-**5a** (330 mg, 95%) as a white solid: mp 130–132 °C; $[\alpha]_D^{20} = -62.3$ (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, $J = 6.7$ Hz, 3H), 1.08 (d, $J = 6.7$ Hz, 3H), 1.83–1.88 (m, 1H), 2.90–3.09 (m, 6H), 3.86–4.04 (m, 3H), 4.17–4.32 (m, 2H), 6.52–6.56 (m, 3H), 6.64 (dd, $J = 7.8$, 1.9 Hz, 1H), 6.93 (s, 1H), 7.00 (d, $J = 1.9$ Hz, 1H), 9.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 18.8, 19.9, 31.5, 33.1, 34.6, 34.7, 34.9, 70.1, 73.2, 128.8, 133.4, 134.4, 135.2, 135.8, 135.9, 136.5, 137.9, 139.2, 140.1, 140.5, 143.3, 162.8, 191.1; MS (EI) *m*/*z* (rel) 347 (M^+); IR (KBr): 2931, 1680, 1633, 1590, 1467 cm^{-1}; Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.77; H, 7.49; N, 3.90.

4.1.2. (*S*,4*Rp*,13*Sp*)-4-Formyl-13-(4-*tert*-butyl-oxazolin-2-yl)[2.2]paracyclophane 5b. Compound (*S*,4*Rp*,13*Sp*)-**1b** was allowed to react according to the procedure for **5a** to afford **5b** (98%) as a white solid: mp 134–136 °C; $[\alpha]_D^{20} = -34.6$ (*c* 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (s, 9H), 3.01–3.18 (m, 6H), 3.96–4.17 (m, 4H), 4.31–4.34 (m, 1H), 6.61–6.64 (m, 3H), 6.73 (dd, $J = 8.1$, 1.9 Hz, 1H), 7.01 (s, 1H), 7.06 (s, 1H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 26.2, 31.9, 33.9, 34.6, 34.7, 68.3, 76.0, 129.1, 133.2, 134.4, 135.6, 135.8, 136.0, 136.5, 137.5, 139.1, 140.0, 143.0, 163.3, 191.5; MS (EI) *m*/*z* (rel) 361 (M^+); IR (KBr): 2959, 1678, 1640, 1589, 1475 cm^{-1}; Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.70; H, 7.78; N, 3.69.

4.1.3. (*S*,4*Rp*,13*Sp*)-4-Formyl-13-(4-benzyl-oxazolin-2-yl)[2.2]paracyclophane 5c. Compound (*S*,4*Rp*,13*Sp*)-**1c** was allowed to react according to the procedure for **5a** to afford **5c** (96%) as a white solid: mp 105–106 °C; $[\alpha]_D^{20} = -19.0$ (*c* 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.88 (dd, $J = 13.7$, 9.2 Hz, 1H), 2.96–3.18 (m, 6H), 3.33 (dd, $J = 13.7$, 5.3 Hz, 1H), 4.05–4.61 (m, 5H), 6.60–6.70 (m, 3H), 6.72 (dd, $J = 7.6$, 1.8 Hz, 1H), 7.06 (s, 1H), 7.10 (s, 1H), 7.24–7.34 (m, 5H), 9.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 31.7, 34.6, 34.7, 34.8, 41.1, 68.1, 71.2, 126.3, 128.5, 128.6, 129.2, 133.4, 134.6, 135.6, 135.8, 135.9, 136.4, 137.8, 138.4, 139.3, 140.1, 140.7, 143.3, 163.3, 191.3; MS (EI) *m*/*z* (rel) 395 (M^+); IR (KBr) 2933, 1682, 1642 cm^{-1}; Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 81.82; H, 6.33; N, 3.43.

4.1.4. (*S*,4*Sp*,13*Rp*)-4-Formyl-13-(4-*iso*-propyl-oxazolin-2-yl)[2.2]paracyclophane 6a. Compound (*S*,4*Sp*,13*Rp*)-**2a** was allowed to react according to the procedure for **5a** to afford **6a** (93%) as a white solid: mp 114–116 °C; $[\alpha]_D^{20} = +59.6$ (*c* 0.545, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, $J = 6.7$ Hz, 3H), 1.00 (d, $J = 6.7$ Hz, 3H), 1.70–1.77 (m, 1H), 2.87–3.06 (m, 6H), 3.84 (t, $J = 9.1$ Hz, 1H), 3.96–4.06 (m, 2H), 4.22–4.3 (m, 2H), 6.48–6.65 (m, 4H), 6.84 (d, $J = 1.7$ Hz, 1H), 7.01 (d, $J = 2.0$ Hz, 1H), 9.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 18.5, 19.4, 30.8, 32.9, 34.6, 34.7, 35.0, 69.3, 73.4, 128.6, 133.2, 133.4, 134.2, 135.7, 135.8, 136.1, 138.0, 139.3, 139.9, 140.8, 143.9, 162.1, 190.0; MS (EI) *m*/*z* (rel) 347 (M^+); IR (KBr) 2960, 1679, 1639, 1630, 1589 cm^{-1}; Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.28; H, 7.42; N, 3.87.

4.1.5. (*S*,4*Sp*,13*Rp*)-4-Formyl-13-(4-*tert*-butyl-oxazolin-2-yl)[2.2]paracyclophane 6b. Compound (*S*,4*Sp*,13*Rp*)-**2b** was allowed to react according to the procedure for **5a** to afford **6b** (98%) as a white solid: mp 162–164 °C; $[\alpha]_D^{20} = +186.0$ (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 9H), 2.90–2.99 (m, 1H), 3.05–3.16 (m, 5H), 3.96–4.02 (m, 1H), 4.07–4.16 (m, 2H), 4.22–4.28 (m, 1H), 4.34–4.42 (m, 1H), 6.56 (d, $J = 8.0$ Hz, 1H), 6.64 (d, $J = 7.8$ Hz, 1H), 6.69–6.73 (m, 2H), 6.86 (s, 1H), 7.13 (s, 1H), 9.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 26.0, 30.1, 33.6, 34.6, 34.7, 35.3, 67.3, 76.8, 128.4, 131.7, 133.3, 133.9, 135.7, 135.8, 135.9, 138.2, 139.3, 139.8, 140.8, 144.2, 161.7, 189.2; MS (EI) *m*/*z* (rel) 361 (M^+); IR (KBr): 2946, 1688, 1675, 1639, 1591, 1479 cm^{-1}; Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.77; H, 7.67; N, 3.67.

4.1.6. (*S*,4*Sp*,13*Rp*)-4-Formyl-13-(4-benzyl-oxazolin-2-yl)[2.2]paracyclophane 6c. Compound (*S*,4*Sp*,13*Rp*)-**2c** was allowed to react according to the procedure for **5a** to afford **6c** (93%) as a white solid: mp 90–92 °C; $[\alpha]_D^{20} = +41.7$ (*c* 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.78 (dd, $J = 13.7$, 9.2 Hz, 1H), 2.97–3.20 (m, 6H), 3.30 (dd, $J = 13.4$, 5.0 Hz, 1H), 3.99 (t, $J = 8.4$ Hz, 1H), 4.07–4.21 (m, 1H), 4.24–4.32 (m, 2H), 4.55–4.66 (m, 1H), 6.58–6.73 (m, 4H), 6.97 (s, 1H), 7.07 (s, 1H), 7.21–7.35 (m, 5H), 9.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 31.4, 34.6, 34.7, 34.8, 41.5, 68.3, 71.1, 126.4, 128.4, 128.5, 129.1, 133.4, 134.4, 134.6, 135.7, 135.8, 136.2, 137.9, 138.4, 139.3, 140.0, 140.8, 143.6, 163.2, 190.7; MS (EI) *m*/*z* (rel) 395 (M^+); IR (KBr) 2949, 1676, 1629, 1589, 1496 cm^{-1}; Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 81.78; H, 6.27; N, 3.45.

4.1.7. (*S*,4*Sp*,13*Rp*)-4-(4-*iso*-Propyl-oxazolin-2-yl)-13-hydroxylmethyl[2.2]paracyclophane 7a. $NaBH_4$ (177.6 mg, 4.67 mmol) was added to a solution of (*S*,4*Rp*,13*Sp*)-**5a** (541 mg, 1.56 mmol) in methanol (10 mL) and THF (10 mL). The resulting mixture was stirred for 0.5 h at room temperature. After removal of the reaction solvent in vacuum, dichloromethane (15 mL) and water (10 mL) were added. The organic layer was extracted twice with dichloromethane (15 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the crude product, which was purified by column chromatography (ethyl acetate/petroleum ether = 1/4) to give (*S*,4*Sp*,13*Rp*)-**7a** (530 mg, 97%) as a white solid: mp 107–109 °C; $[\alpha]_D^{20} = -32.5$ (*c* 0.325, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (d, $J = 6.7$ Hz, 3H), 1.03 (d, $J = 6.7$ Hz, 3H), 1.80–1.87 (m, 1H), 2.81–2.90 (m, 1H), 3.01–3.31 (m, 6H), 3.61–3.71

(m, 1H), 4.07–4.15 (m, 2H), 4.29–4.50 (m, 3H), 4.85 (br, 1H), 6.45–6.52 (m, 3H), 6.60 (dd, $J=7.7$, 1.8 Hz, 1H), 6.77 (s, 1H), 7.00 (d, $J=1.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 18.5, 18.9, 32.7, 32.8, 33.2, 35.0, 35.1, 61.6, 70.9, 71.6, 126.6, 128.9, 131.0, 133.4, 134.7, 134.8, 135.8, 136.3, 139.8, 139.9, 140.0, 142.4, 166.7; MS (EI) *m/z* (rel) 349 (M^+); IR (KBr) 3290, 2955, 1627, 1594, 1419 cm^{-1}; Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 79.16; H, 8.01; N, 3.83.

4.1.8. (*S*,4*Sp*,13*Rp*)-4-(4-*tert*-Butyl-oxazolin-2-yl)-13-hydroxylmethyl[2.2]paracyclophane 7b. Compound (*S*, 4*Rp*,13*Sp*)-**5b** was allowed to react according to the procedure for **7a** to afford **7b** (94%) as a white solid: mp 133–134 °C; $[\alpha]_D^{20}=+99.2$ (*c* 0.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 9H), 2.80–2.90 (m, 1H), 3.01–3.31 (m, 6H), 3.56–3.65 (m, 1H), 4.10 (dd, $J=10.1$, 7.7 Hz, 1H), 4.21–4.35 (m, 2H), 4.41–4.49 (m, 2H), 5.30 (br, 1H), 6.46–6.57 (m, 3H), 6.62 (dd, $J=7.4$, 1.2 Hz, 1H), 6.79 (s, 1H), 7.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 26.0, 32.7, 32.8, 34.5, 35.0, 35.1, 61.5, 69.4, 75.1, 126.6, 128.9, 131.0, 133.4, 134.7, 134.8, 135.8, 136.3, 139.8, 139.9, 140.0, 142.6, 166.8; MS (EI) *m/z* (rel) 363 (M^+); IR (KBr 3286, 2949, 1627, 1593, 1482, 1477 cm^{-1}; Anal. Calcd for $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.85. Found: C, 79.45; H, 7.94; N, 3.78.

4.1.9. (*S*,4*Sp*,13*Rp*)-4-(4-Benzyl-oxazolin-2-yl)-13-hydroxylmethyl[2.2]paracyclophane 7c. Compound (*S*, 4*Rp*,13*Sp*)-**5c** was allowed to react according to the procedure for **7a** to afford **7c** (95%) as a white solid: mp 116–118 °C; $[\alpha]_D^{20}=+116.9$ (*c* 0.395, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.73–2.90 (m, 2H), 3.05–3.29 (m, 6H), 3.66–3.75 (m, 2H), 4.18 (dd, $J=8.6$, 6.9 Hz, 1H), 4.31–4.43 (m, 3H), 4.58–4.77 (m, 1H), 6.46–6.55 (m, 3H), 6.62 (dd, $J=7.7$, 1.8 Hz, 1H), 6.74 (s, 1H), 7.05 (d, $J=1.8$ Hz, 1H), 7.21–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) 32.8, 32.9, 35.0, 35.1, 41.6, 62.0, 68.2, 72.7, 126.3, 126.9, 129.0, 129.2, 129.5, 131.2, 133.2, 134.8, 135.3, 136.0, 136.5, 138.3, 139.8, 140.0, 140.2, 142.3, 166.8; MS (EI) *m/z* (rel) 397 (M^+); IR (KBr) 3271, 2920, 1637, 1456 cm^{-1}; Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.37; H, 6.96; N, 3.39.

4.1.10. (*S*,4*Rp*,13*Sp*)-4-(4-*iso*-Propyl-oxazolin-2-yl)-13-hydroxylmethyl[2.2]paracyclophane 8a. Compound (*S*, 4*Sp*,13*Rp*)-**6a** was allowed to react according to the procedure for **7a** to afford **8a** (96%) as a white solid: mp 110 °C; $[\alpha]_D^{20}=-123.9$ (*c* 0.355, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (d, $J=6.7$ Hz, 3H), 1.21 (d, $J=6.5$ Hz, 3H), 1.92–1.99 (m, 1H), 2.82–2.92 (m, 1H), 2.98–3.23 (m, 6H), 3.27–3.38 (m, 1H), 3.64–4.12 (m, 2H), 4.36–4.52 (m, 3H), 6.50–6.62 (m, 4H), 6.74 (s, 1H), 7.02(s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 19.0, 20.4, 32.7, 32.8, 33.1, 35.0, 35.1, 61.8, 71.1, 73.5, 126.4, 129.5, 131.1, 133.2, 134.7, 135.2, 135.9, 136.3, 139.6, 140.0, 140.1, 142.3, 166.4; MS (EI) *m/z* (rel) 349 (M^+); IR (KBr): 3459, 3197, 2953, 1635, 1590, 1471 cm^{-1}; Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 78.86; H, 7.81; N, 3.75.

4.1.11. (*S*,4*Rp*,13*Sp*)-4-(4-*tert*-Butyl-oxazolin-2-yl)-13-hydroxylmethyl[2.2]paracyclophane 8b. Compound (*S*, 4*Sp*,13*Rp*)-**6b** was allowed to react according to the procedure for **7a** to afford **8b** (94%) as a white solid: mp 121–123 °C; $[\alpha]_D^{20}=-103.9$ (*c* 0.425, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (s, 9H), 2.83–3.06 (m, 3H), 3.11–3.20 (m, 3H), 3.33–3.42 (m, 1H), 3.60–3.70 (m, 1H), 4.03–4.17 (m, 2H), 4.33–4.39 (m, 2H), 4.51 (d, $J=16.3$ Hz, 1H), 6.49–6.60 (m, 4H), 6.72 (s, 1H), 6,93 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 26.1, 32.3, 32.5, 33.3, 34.6, 34.7, 61.3, 68.2, 76.8, 126.0, 129.5, 130.8, 132.4, 134.3, 134.9, 135.5, 135.8, 139.1, 139.4, 139.6, 141.9, 165.6; MS (EI) *m/z* (rel) 363 (M^+); IR (KBr) 3263, 2930, 1634, 1592, 1478 cm^{-1}; Anal. Calcd for $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.85. Found: C, 79.01; H, 8.19; N, 3.58.

4.1.12. (*S*,4*Rp*,13*Sp*)-4-(4-Benzyl-oxazolin-2-yl)-13-hydroxylmethyl[2.2]paracyclophane 8c. Compound (*S*, 4*Sp*,13*Rp*)-**6c** was allowed to react according to the procedure for **7a** to afford **8c** (95%) as a white solid: mp 120–121 °C; $[\alpha]_D^{20}=-79.2$ (*c* 0.365, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.75–2.94 (m, 2H), 3.00–3.19 (m, 5H), 3.31–3.39 (m, 1H), 3.51 (dd, $J=13.8$, 4.7 Hz, 1H), 3.72–3.82 (m, 1H), 4.11 (t, $J=8.8$ Hz, 1H), 4.27–4.62 (m, 4H), 6.50–6.56 (m, 3H), 6.61 (dd, $J=7.7$, 1.9 Hz, 1H), 6.72 (s, 1H), 7.00 (d, $J=1.8$ Hz, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) 32.7, 32.8, 35.1, 35.2, 41.6, 61.9, 66.9, 72.0, 126.4, 126.9, 128.9, 129.2, 129.6, 131.2, 133.5, 134.8, 135.1, 135.9, 136.4, 137.7, 139.8, 140.0, 140.2, 142.3, 166.9; MS (EI) *m/z* (rel) 397 (M^+); IR (KBr): 3260, 2927, 1633, 1595, 1455 cm^{-1}; Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.45; H, 6.99; N, 3.44.

4.1.13. (*S*,4*Sp*,13*Rp*)-4-(4-*tert*-Butyl-oxazolin-2-yl)-13-(α,α-dimethylhydroxymethyl)[2.2]paracyclophane 9. Compound (*S*,4*Rp*,13*Sp*)-**1b** was allowed to react according to the procedure for **5a** and quenched with acetone to afford **9** (82%) as a white solid: mp 125–126 °C; $[\alpha]_D^{20}=+75.5$ (*c* 0.435, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 9H), 1.36 (s, 3H), 1.41 (s, 3H), 2.87–2.97 (m, 1H), 3.01–3.16 (m, 5H), 3.45–3.54 (m, 1H), 3.90–3.98 (m, 1H), 4.05–4.16 (m, 2H), 4.31–4,36 (m, 1H), 5.41 (br, 1H), 6.47–6.53 (m, 2H), 6.64–6.74 (m, 3H), 6.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 25.8, 31.8 31.9, 34.0, 34.5 34.7, 34.8, 36.0, 68.9, 71.7, 75.4, 127.0, 128.2, 131.3, 131.9, 134.8, 135.6, 136.8, 137.0, 138.9, 139.3, 140.0, 145.7, 167.7; MS (EI) *m/z* (rel) 391 (M^+); IR (KBr) 3251, 2953, 1645, 1628, 1589, 1478 cm^{-1}; HRMS: Anal. Calcd for $C_{26}H_{33}NO_2$: 391.2512. Found: 391.2521.

4.1.14. (*S*,4*Sp*,13*Rp*)-4-(4-Benzyl-oxazolin-2-yl)-13-(α,α-dimethylhydroxymethyl)[2.2]paracyclophane 10. Compound (*S*,4*Rp*,13*Sp*)-**1c** was allowed to react according to the procedure for **5a** to afford **10** (81%) as a white solid (except for being quenched with acetone): mp 108–110 °C; $[\alpha]_D^{20}=+52.5$ (*c* 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (s, 3H), 1.52 (s, 3H), 2.72–2.83 (m, 1H), 2.86–3.23 (m, 6H), 3.40 (dd, $J=13.8$, 4.2 Hz, 1H), 3.88–4.00 (m, 1H), 4.04–4.32 (m, 3H), 4.55–4.67 (m, 1H), 5.37 (br, 1H), 6.48 (s, 1H), 6.53 (s,

2H), 6.66 (d, $J=7.8$ Hz, 1H), 6.73 (dd, $J=8.0$, 1.9 Hz, 1H), 6.94 (s, 1H), 7.23–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) 31.0, 32.9, 33.7, 34.7, 35.0, 36.4, 41.6, 67.8, 71.5, 72.0, 125.9, 126.5, 127.8, 128.6, 129.0, 131.0, 131.8, 136.0, 136.2, 137.0, 137.7, 137.8, 138.8, 139.2, 141.0, 145.2, 166.2; MS (EI) *m/z* (rel) 425 (M^+); IR (KBr) 3248, 2920, 1645, 1587, 1457 cm^{-1}; Anal. Calcd for $C_{29}H_{31}NO_2$: C, 81.85; H, 7.34; N, 3.29. Found: C, 81.85; H, 7.61; N, 3.17.

4.1.15. (*S*,4*Rp*,13*Sp*)-4-(4-Benzyl-oxazolin-2-yl)-13-(α,α-dimethylhydroxymethyl)[2.2]paracyclophane 11. Compound (*S*,4*Sp*,13*Rp*)-**2c** was allowed to react according to the procedure for **5a** to afford **11** (78%) as a white solid (except for being quenched with acetone): mp 147 °C; $[\alpha]_D^{20}=+16.2$ (*c* 0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (s, 3H), 1.50 (s, 3H), 2.71–3.24 (m, 7H), 3.33 (dd, $J=13.8$, 5.2 Hz, 1H), 3.88–4.00 (m, 1H), 4.04 (t, $J=7.5$ Hz, 1H), 4.14–4.39 (m, 2H), 4.60–4.70 (m, 1H), 5.80 (br, 1H), 6.33 (s, 1H), 6.48–6.54 (m, 2H), 6.65 (d, $J=7.8$ Hz, 1H), 6.72 (dd, $J=7.8$, 1.8 Hz, 1H), 6.89 (d, $J=1.5$ Hz, 1H), 7.19–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) 29.9, 33.2, 33.8, 34.7, 35.0, 36.7, 41.6, 67.8, 70.9, 72.2, 125.6, 126.5, 127.8, 128.5, 129.2, 130.8, 132.0, 135.0, 136.4, 137.3, 137.5, 137.7, 138.8, 139.3, 141.5, 145.7, 165.7; MS (EI) *m/z* (rel) 425 (M^+); IR (KBr) 3158, 2934, 1654, 1454 cm^{-1}; Anal. Calcd for $C_{29}H_{31}NO_2$: C, 81.85; H, 7.34; N, 3.29. Found: C, 81.55; H, 7.47; N, 3.04.

4.1.16. (4*Sp*,13*Rp*)-4-Bromo-13-carboxy[2.2]paracyclophane 12. According to a literature procedure,[13] enantiomerically pure compound **12** (78%) was obtained as a white solid: mp 228–230 °C; $[\alpha]_D^{20}=+46$ (*c* 0.105, DMSO); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 2.94–3.05 (m, 5H), 3.07–3.13 (m, 1H), 3.32–3.40 (m, 1H), 4.29–4.34 (m, 1H), 6.60–6.62 (m, 2H), 6.65 (dd, $J=7.8$, 1.8 Hz, 1H), 6.68 (d, $J=7.8$ Hz, 1H), 6.75 (dd, $J=7.8$, 1.8 Hz, 1H), 7.26 (d, $J=1.2$ Hz, 1H), 12.36 (br, 1H); MS (EI) *m/z* (rel) 332 (M^++2), 330 (M^+); IR (KBr): 2934, 1673, 1587 cm^{-1}; Anal. Calcd for $C_{17}H_{15}BrO_2$: C, 61.65; H, 4.56. Found: C, 61.55; H, 4.49.

4.1.17. (4*Sp*,13*Rp*)-4-Bromo-*N*-(1-hydroxy-2-ethyl)[2.2]paracyclophane-13-carboxamide 13a. Using a literature procedure,[14] amide **13a** (96%) was achieved as a white solid: mp 170–172 °C; $[\alpha]_D^{20}=-22.7$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.51 (br, 1H), 2.83–3.17 (m, 6H), 3.52–3.67 (m, 3H), 3.86 (t, $J=4.9$ Hz, 2H), 3.99–4.09 (m, 1H), 6.53–6.63 (m, 5H), 7.08 (s, 1H); MS (EI) *m/z* (rel) 375 (M^++2), 373 (M^+); IR (KBr) 3308, 2952, 2857, 1616, 1586, 1463 cm^{-1}; Anal. Calcd for $C_{19}H_{20}BrNO_2$: C, 60.97; H, 5.39; N, 3.74. Found: C, 60.67; H, 5.53; N, 3.47.

4.1.18. (4*Sp*,13*Rp*)-4-Bromo-*N*-(1-hydroxy-2-methyl-2-propyl)[2.2]paracyclophane-13-carboxamide 13b. Using a literature procedure,[14] amide **13b** (92%) was achieved as a white solid: mp 200–200.5 °C; $[\alpha]_D^{20}=+32.4$ (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 3H), 1.48 (s, 3H), 2.83–3.20 (m, 6H), 3.55–3.62 (m, 1H), 3.71 (d, $J=5.8$ Hz, 2H), 3.94–3.98 (m, 1H), 5.25–5.29 (t, $J=6.1$ Hz, 1H), 5.79 (br, 1H), 6.53–6.65 (m, 5H), 7.13 (d, $J=1.7$ Hz, 1H); MS (EI) *m/z* (rel) 403 (M^++2), 401 (M^+); IR (KBr) 3420, 3321, 2920, 1640, 1592, 1454 cm^{-1}; Anal. Calcd for $C_{21}H_{24}BrO_2$: C, 62.69; H, 6.01; N, 3.48. Found: C, 62.64; H, 5.78; N, 3.34.

4.1.19. (4*Sp*,13*Rp*)-4-Bromo-13-(oxazolin-2-yl)[2.2]paracyclophane 14a. Amide **13a** was allowed to react according to a literature procedure [15] to afford compound **14a** (96%) as a white solid: mp 229–231 °C; $[\alpha]_D^{20}=+31.3$ (*c* 0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.94–3.10 (m, 6H), 3.51–3,61 (m, 1H), 4.03–4.10 (m, 2H), 4.34–4.55 (m, 3H), 6.52–6.66 (m, 5H), 7.25 (d, $J=1.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 33.4, 34.4, 34.8, 35.1, 55.0, 66.4, 126.1, 126.5, 131.6, 133.0, 134.8, 135.0, 135.8, 135.9, 138.6, 139.0, 140.6, 141.1, 164.5; MS (EI) *m/z* (rel) 357(M^++2), 355(M^+); IR (KBr) 2929, 1635, 1587, 1478 cm^{-1}; Anal. Calcd for $C_{19}H_{18}BrNO$: C, 64.06; H, 5.09; N, 3.93. Found: C, 63.98; H, 5.07; N, 3.73.

4.1.20. (4*Sp*,13*Rp*)-4-Bromo-13-(4,4-dimethyl-oxazolin-2-yl)[2.2]paracyclophane 14b. Amide **13b** was allowed to react according to a literature procedure [16] to afford **14b** (93%) as a white solid: mp 155–156 °C; $[\alpha]_D^{20}=+41.1$ (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 3H), 1.43 (s, 3H), 2.95–3.10 (m, 6H), 3.49–3.57 (m, 1H), 4.12 (dd, $J=18.6$, 7.9 Hz, 2H), 4.41–4.51 (m, 1H), 6.53–6.57 (m, 3H), 6.60 (dd, $J=7.8$, 1.8 Hz, 1H), 6.64 (s, 1H), 7.23(d, $J=1.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 28.0, 28.3, 32.7, 34.5, 34.8, 35.7, 67.5, 78.2, 126.9, 127.0, 131.3, 132.4, 134.7, 135.0, 135.9, 136.0, 138.5, 139.0, 140.4, 141.2, 162.0; MS (EI) *m/z* (rel) 385 (M^++2), 383 (M^+); IR (KBr): 2972, 2931, 1640, 1588 cm^{-1}; Anal. Calcd for $C_{21}H_{22}BrNO_2$: C, 65.63; H, 5.77; N, 3.64. Found: C, 65.80; H, 5.95; N, 3.42.

4.1.21. (4*Rp*,13*Sp*)-4-(Oxazolin-2-yl)-13-(α,α-dimethylhydroxymethyl)[2.2]paracyclophane 15a. Compound (4*Sp*,13*Rp*)-**14a** was allowed to react according to the procedure for **5a** to afford **15a** (83%) as a white solid (except for being quenched with acetone): mp 167–168 °C; $[\alpha]_D^{20}=-59.0$ (*c* 0.395, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 3H), 1.49 (s, 3H), 2.86–2.98 (m, 2H), 3.03–3.24 (m, 4H), 4.00–4.16 (m, 3H), 4.22–4.45 (m, 3H), 6.42 (s, 1H), 6.52 (s, 2H), 6.67 (d, $J=7.8$ Hz, 1H), 6.74 (dd, $J=7.2$, 1.8 Hz, 1H), 6.93 (d, $J=1.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 30.5, 33.6, 33.7, 35.1, 35.3, 36.7, 54.7, 67.1, 72.3, 126.2, 128.1, 131.2, 132.2, 135.3, 136.4, 137.4, 137.9, 139.0, 139.6, 141.4, 146.0, 166.8; MS (EI) *m/z* (rel) 335 (M^+); IR (KBr) 3166, 2932, 1648 cm^{-1}; Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.42; H, 7.77; N, 3.87.

4.1.22. (4*Rp*,13*Sp*)-4-(4,4-Dimethyl-oxazolin-2-yl)-13-(α,α-dimethylhydroxymethyl)[2.2]paracyclophane 15b. Compound (4*Sp*,13*Rp*)-**14b** was allowed to react according to the procedure for **5a** to afford **15b** (85%) as a white solid (except for being quenched with acetone): mp 99–100 °C; $[\alpha]_D^{20}=-41.4$ (*c* 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (s, 3H), 1.42 (s, 3H), 1.48 (s, 3H), 1.53

(s, 3H), 2.84–2.98 (m, 2H), 3.00–3.24 (m, 4H), 3.95–4.06 (m, 3H), 4.28 (t, $J=7.8$ Hz, 1H), 5.89 (br, 1H), 6.37 (s, 1H), 6.51–6.57 (m, 2H), 6.64 (d, $J=8.1$ Hz, 1H), 6.72 (dd, $J=8.1$, 1.8 Hz, 1H), 6.87 (s, 1H); MS (EI) *m/z* (rel) 363 (M^+); IR (KBr): 3362, 2958, 1627 cm^{-1}; Anal. Calcd for $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.85. Found: C, 79.20; H, 8.07; N, 3.57.

4.2. General procedure for the catalytic asymmetric addition of diethylzinc to various aldehydes

To a solution of the chiral *N*,*O*-[2.2]paracyclophane ligand (0.025 mmol) in toluene (2.0 mL) was added Et_2Zn (1.0 mL, 1.1 mmol, 1.1 M in toluene) at room temperature. After 1.0 h, the aldehyde (0.5 mmol) was added at the same temperature. After being stirred for an appropriate time, the reaction was quenched with 1 M HCl. The mixture was then extracted with dichloromethane (2×10 mL). The organic layer was washed with brine, dried, and evaporated under reduced pressure to give an oily residue. Purification of the residue by column chromatography gave rise to the optically active alcohol. The enantiomeric excess was determined by HPLC analysis using a Chiracel OD column. Configurations were assigned by comparison of the sign of the specific rotation of known compounds.

4.3. General procedure for catalytic asymmetric addition of diethylzinc to various α,β-unsaturated ketones

A solution of $Ni(acac)_2$ (3.2 mg, 0.0125 mmol) and the chiral *N*,*O*-[2.2]paracyclophane ligand (0.05 mmol) in CH_3CN (2 mL) was stirred at 35 °C for 1 h. The α,β-unsaturated ketone (0.25 mmol) was then added and the resultant solution stirred for another 30 min. After cooling to −20 °C, $ZnEt_2$ (0.5 mL, 1 M in hexane, 0.5 mmol) was added and the resulting mixture stirred at −20 °C for an appropriate time. The reaction was quenched with 1 M HCl. The mixture was extracted with dichloromethane (2×10 mL). The organic layer was washed with brine, dried and evaporated under reduced pressure to give an oily residue. Purification of the residue by column chromatography gave rise to the desired product. The enantiomeric excess was determined by HPLC analysis using a Chiracel AD column. Configurations were assigned by comparison of the sign of the specific rotation of known compounds.

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