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Planar- and Central-Chiral *N*,*O*-[2.2]Paracyclophane Ligands: Non-Linear-Like Effects and Activity

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Dedicated to Professor Dr. Dieter Enders on the occasion of his 60th birthday.

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Abstract: The non-linear-like effect (NLLE), activity, temperature dependence, and kinetics of hydroxy-[2.2]paracyclophane ketimine ligands have been investigated with the 1,2-addition reaction of diethylzinc to cyclohexanecarbaldehyde. A linear correlation between the enantiomeric excess of AHPC ketimine ligands bearing a phenylethyl side group and the product was observed with 0.5 mol % of catalyst loading. On increasing the catalyst loading to 4 mol %, a precipitate of the inactive heterochiral species was formed and resulted in a positive non-linear-like effect. The enantiomeric ratio was found to have linear temperature dependence.

Keywords: asymmetric catalysis; catalytic activity; non-linear-like effect; paracyclophanes

Asymmetric catalysis often displays a relationship between selectivity and reactivity. Intricate molecular mechanisms with a number of rate constants often lead to complex rate laws. The latter have not been elucidated in most cases although attempts have been made to unravel them.[1] Features such as non-linear effects,[2] autocatalysis,[3] reservoir effects, chiral poisoning,[4] and asymmetric activation[5] have been discovered in asymmetric catalytic reactions.[6] In particular, the strong non-linear effect associated with Noyori's DAIB ligand in the addition of diethylzinc to benzaldehyde has been thoroughly investigated.[7a]

Since the initial reports of Reich and Cram,[8] the field of [2.2]paracyclophane chemistry has grown considerably.[9] The chemical behavior of [2.2]paracyclophanes is currently well understood allowing predictable modification of this relatively stable class of molecules.[10–13]

Within the last few years, various new paracyclophane ligands have been used for asymmetric catalysis.[14–17] In particular, the asymmetric 1,2-addition reaction of zinc reagents[18] such as alkyl,[19–21] alkenyl,[22] aryl[23] and alkynyl[24] zinc reagents with aldehydes or imines,[19,20,23] can be efficiently controlled by the application of hydroxy[2.2]paracyclophane ketimine ligands.[17]

We recently reported the synthesis of the [2.2]paracyclophane-based ketimine ligands (R_P,*S*)-**2**, (S_P,*S*)-**2**, (R_P,*S*)-**3**, and (S_P,*S*)-**3** and their application in asymmetric catalysis such as the addition of zinc reagents to aldehydes.[19] During these studies, we observed not only that these ligands are highly active,[21,25] but also that they display mismatched and matched cases.[19,22] In general, the [2.2]paracyclophane backbone determines the configuration of the product. However, it was possible to fine-tune the ligand system by adjusting the side groups.

The successful applications of these [2.2]paracyclophane-based ligands led to further investigations of this system. In this manuscript, we disclose our findings which lead to a deeper understanding of this ligand class. We present studies of the non-linear-like effect (NLLE)[26] with the enantiomeric pairs **1** and **3**, respectively. In addition, we investigated the activity of the diastereomers (R_P,*S*)-**2** and (S_P,*S*)-**2** and the diastereomers (R_P,*S*)-**3** and (S_P,*S*)-**3**. Further, we performed studies on the temperature effect and kinetic studies of the system with (R_P,*S*)-**3** and (S_P,*S*)-**3**.

For the 1,2-addition reaction we chose cyclohexanecarbaldehyde ($C_6H_{11}CHO$) as the substrate. The corresponding secondary alcohol was transformed into an ester to achieve better separation on a GC chiral stationary phase.[27] The results for the different ketimine ligands are shown in Table 1.

The [2.2]paracyclophane-based ligands **1**–**3** showed complete conversion and enantiomeric excesses of 84% ee for ligands **1**, 95% and 93% ee for ligands **2** and 95% ee for ligands **3** in this reaction (Table 1). It is important to note that both enantiomers of the product with similar enantiomeric excesses can be produced by using diastereomers with a different planar-chiral type stereochemistry and the same stereogenic center (matched pair). As mentioned before, the paracyclophane backbone determines the configuration of the desired product: (R_P,*S*) and (R_P,*R*) ligands produced the

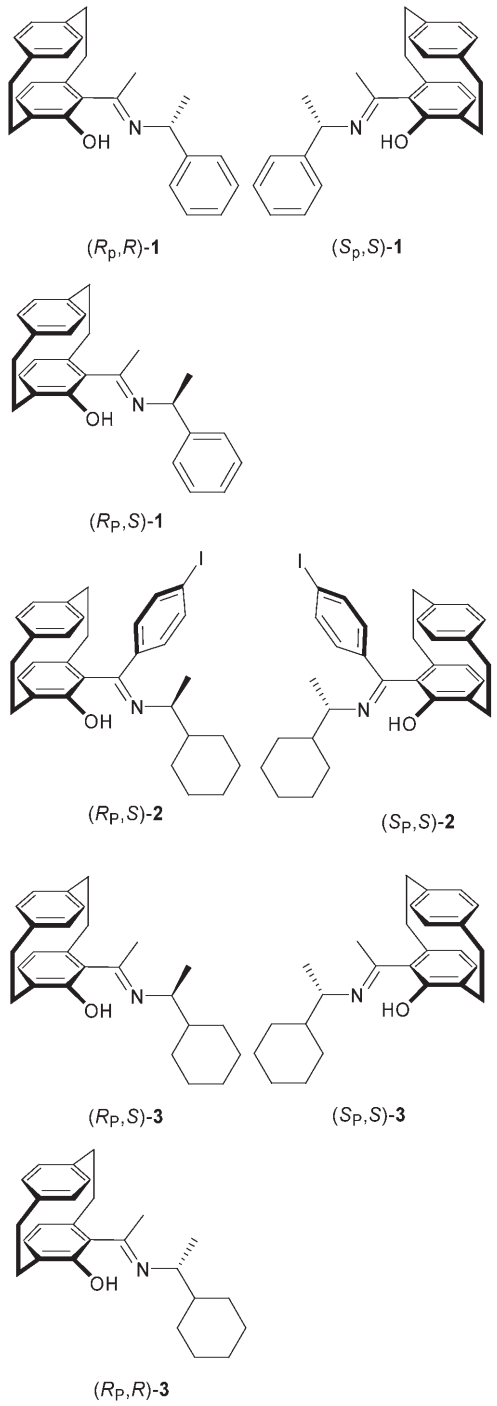
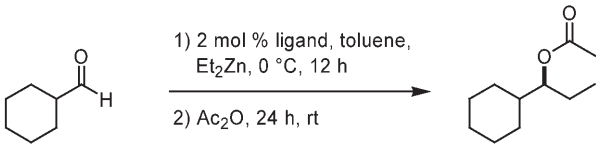


Figure 1. Planar- and central-chiral *N,O*-[2.2]paracyclophane ligands.

(*S*) product and the (S_P,*S*) ligands led to the formation of the (*R*) product.

The first NLLE studies were carried out with ligands (S_P,*S*)/(R_P,*R*)-**1** under standard conditions for this system, 2 mol % of the ligands (S_P,*S*)/(R_P,*R*)-**1** at 0 °C for 12 h with 1 mL of toluene as co-solvent. The results are shown in Figure 2. Unexpectedly, the ligand system showed a positive non-linear effect between the enantiomeric excess of the ligand and the enantiomeric excess of the desired product. Due to the bulkiness of the [2.2]paracyclophane system we expected a linear correlation between the enantiomeric excess of the ligand and the enantiomeric excess of the desired product. However, we observed precipitation of inactive heterochiral complexes (Scheme 1), especially with low enantiomeric excess of the ligand. We were not able to get suitable crystals for X-ray analysis from the precipitate. We also tried to filter the precipitate to determinate the actual enantiomeric composition of the ligands in solution. Unfortunately, the precipitate was too fine to remove it completely. However, we assume that the observed precipitate is the heterochiral dimer with two zinc species bridged between the alkoxy-oxygen atoms (see Scheme 1).[7a] Therefore, we observe a non-linear-like effect for this system described above.

Table 1. Results for the addition of diethylzinc to cyclohexanecarbaldehyde. 1) $C_6H_{11}CHO$ (0.5 mmol), 2 mol % of ligand, 1 mL of Et_2Zn (1 M in hexanes), 1 mL of toluene, 0 °C, 12 h; 2) Ac_2O, 24 h, room temperature.



Entry	Ligand	Conversion[a]	ee[b]
1	(S_P,*S*)-**1**	>99	84 (*R*)
2	(R_P,*R*)-**1**	>99	84 (*S*)
3	(R_P,*S*)-**1**	>99	84 (*S*)
4	(S_P,*S*)-**2**	>99	95 (*R*)
5	(R_P,*S*)-**2**	>99	93 (*S*)
6	(S_P,*S*)-**3**	>99	95 (*R*)
7	(R_P,*R*)-**3**	>99	95 (*S*)
8	(R_P,*S*)-**3**	>99	95 (*S*)

[a] Determined by GC.
[b] Determined by GC (CP-Chirasil-Dex).

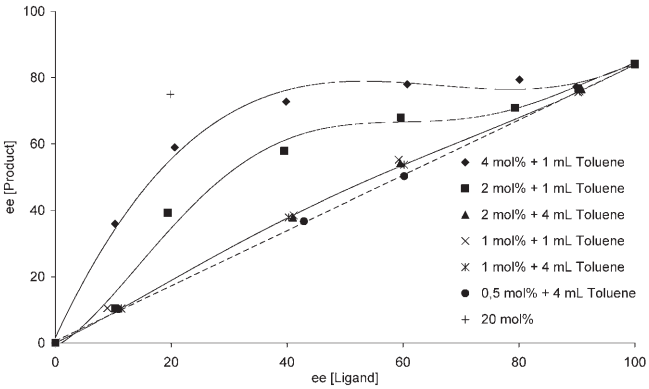
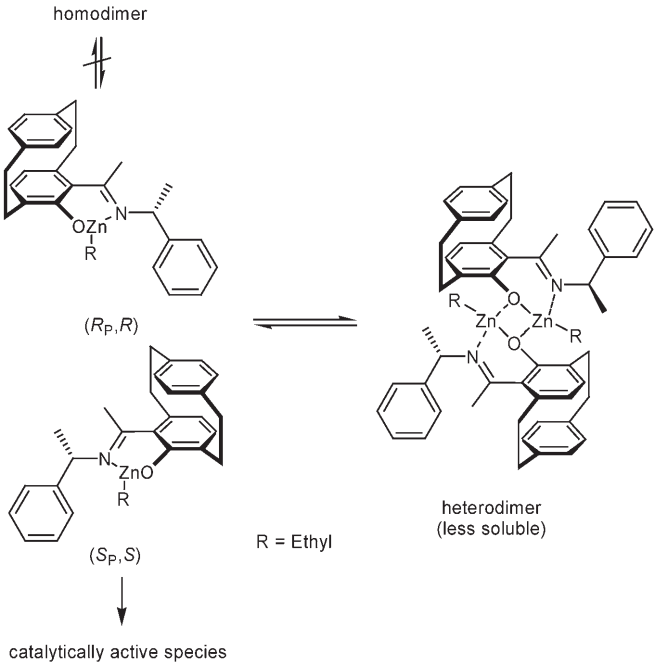


Figure 2. Results for the studies of the non-linear effect of the ligands (S_P,*S*)/(R_P,*R*)-**1**. 1) $C_6H_{11}CHO$ (0.5 mmol), 0.5–4 mol % of ligand, 1 mL of Et_2Zn (1 M in hexanes), 1–4 mL of toluene, 0 °C, 12 h; 2) Ac_2O, 24 h, room temperature.



Scheme 1. Equilibria of ligands **1**.

Based on this observation, it was necessary to determine whether this phenomenon was a result of increased catalyst loading or catalyst solubility. We carried out the same reaction while varying catalyst concentrations and solvent volumes. As shown in Figure 2, increasing the amount of the catalyst to 4 mol % led to a stronger positive non-linear-like effect. This trend was further supported by increasing the ligand loading to 20 mol % which resulted in an even stronger non-linear-like effect. To prevent the formation of the inactive heterochiral species, we increased the amount of the co-solvent toluene and decreased the catalyst loading. The results are also shown in Figure 2. We observed a nearly linear effect for 2 mol % of ligand and 4 mL of toluene [1 mL of Et_2Zn (1 M in hexanes), 0 °C, 12 h] and for 1 mol % ligand and 1 mL toluene. A linear effect was observed for 0.5 mol % and 4 mL of toluene (Figure 2). The positive non-linear-like effect described above can be completely attributed to the insolubility of the inactive dimer. On the other hand, by diluting the system, a linear effect is observed and no inactive heterochiral dimer is formed. At this point, it has to be mentioned that the described ligand systems display a high reactivity compared to most other ligand systems described in the literature.

To see if this observed effect with the enantiomeric pair (S_P,S)/(R_P,R)-**1** is transferable to other ligands we investigated the enantiomeric pair (S_P,S)/(R_P,R)-**3** more in detail. Interestingly, a positive non-linear effect was not observed when using the enantiomeric pair (S_P,S)/(R_P,R)-**3**, where a catalyst loading of 4 mol % with 1 mL of toluene showed a very slight negative

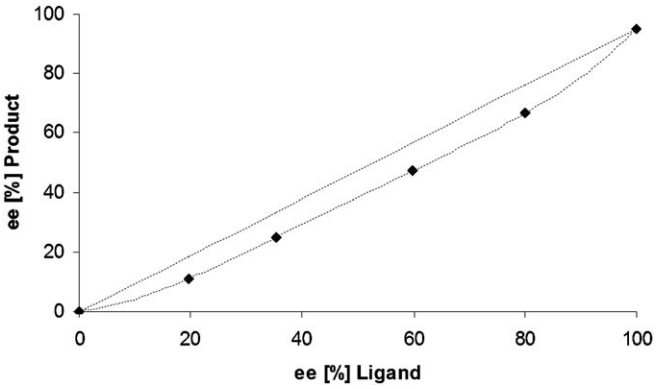


Figure 3. Results for the non-linear effect studies for the ligands (S_P,S)/(R_P,R)-**3**. 1) $C_6H_{11}CHO$ (0.5 mmol), 4 mol % of ligand, 1 mL of Et_2Zn (1 M in hexanes), 1 mL of toluene, 0 °C, 12 h; 2) Ac_2O, 24 h, room temperature.

non-linear effect (Figure 3). In this case, no inactive heterochiral dimer complexes were formed at any concentration investigated (up to 10%), and no solubility problems occurred. Presumably, the side chain of the ligand is responsible for this effect.

The general procedure for producing the ligands proceeds *via* the diastereomeric resolution.[11,19,21] Because of this we studied the difference in activity between the diastereomeric pair (R_P,S)-**2** and (S_P,S)-**2** and the diastereomeric pair (R_P,S)-**3** and (S_P,S)-**3** with the same 1,2-addition reaction. Confirming the results of the former study, it was found that the diastereomers showed similar selectivity.[19,22,28] Both diastereomers showed complete conversion after 12 h at 0 °C with similar enantiomeric excesses of 93% ee (*S*) and 95% ee (*R*) for (R_P,S)-**2** and (S_P,S)-**2**, respectively. The diastereomers **3** both reached enantiomeric excesses of 95% ee. To figure out if there are differences in the activity of the diastereomeric pairs we mixed the diastereomeric pairs in various ratios as shown in Table 2 and Table 3.

Table 2. Activity studies with different ratios between the diastereomeric pair (R_P,S)-**2** and (S_P,S)-**2**. 1) $C_6H_{11}CHO$ (0.5 mmol), 2 mol % of ligand, 1 mL of Et_2Zn (1 M in hexanes), 1 mL of toluene, 0 °C, 12 h; 2) Ac_2O, 24 h, room temperature.

Entry	de [(S_P,S)-**2**:(R_P,S)-**2**]	Conversion[a]	ee [%][b]
1	100	>99	95 (*R*)
2	60	>99	76 (*R*)
3	40	>99	64 (*R*)
4	0	>99	46 (*R*)
5	20	>99	40 (*R*)
6	40	>99	24 (*R*)
7	60	>99	1 (*S*)
8	80	>99	38 (*S*)
9	100	>99	93 (*S*)

[a] Determined by GC.
[b] Determined by GC (CP-Chirasil-Dex).

Table 3. Activity studies with different ratio between the diastereomeric pair (R_P,S)-**3** and (S_P,S)-**3**. 1) $C_6H_{11}CHO$ (0.5 mmol), 2 mol % of ligand, 1 mL of Et_2Zn (1 M in hexanes), 1 mL of toluene, 0 °C, 12 h; 2) Ac_2O, 24 h, room temperature.

Entry	de [(S_P,S)-**3**:(R_P,S)-**3**]	Conversion[a]	ee [%][b]
1	100	>99	95 (*R*)
2	81	>99	76 (*R*)
3	60	>99	62 (*R*)
4	41	>99	46 (*R*)
5	21	>99	30 (*R*)
6	20	>99	2 (*S*)
7	41	>99	22 (*S*)
8	57	>99	37 (*S*)
9	79	>99	63 (*S*)
10	100	>99	95 (*S*)

[a] Determined by GC.
[b] Determined by GC (CP-Chirasil-Dex).

The results are shown in Figure 4. The ketimine ligand (S_P,S)-**2** is more active than the ketimine ligand (R_P,S)-**2**, by the factor of 3.5.[29] A similar study showed that (S_P,S)-**3** is roughly 1.6 times faster than (R_P,S)-**3**. Therefore, we observed nearly the same activity for both diastereomers for the AHPC-based ligand **3**.

In addition, we investigated the temperature dependence of the enantiomeric excess of the product in the same 1,2-addition reaction. Within the temperature range we investigated (−20 °C to 50 °C), we found no intermediate maximum enantiomeric excess. A maximum would be explained by the principle of isoinversion developed by Scharf et al.[30,31]

Initial kinetic studies revealed that full conversion was achieved after 12 h, however the enantiomeric excess remained constant.

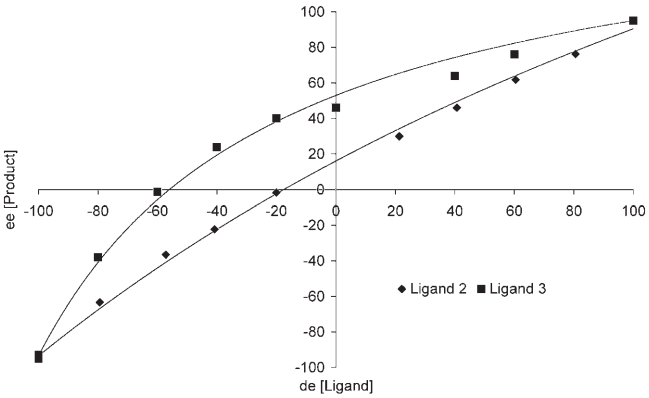


Figure 4. Activity studies with different ratios between the diastereomeric pair (*S*)-**2** and (*S*)-**3**, respectively. 1) $C_6H_{11}CHO$ (0.5 mmol), 2 mol % of ligand, 1 mL of Et_2Zn (1 M in hexanes), 1 mL of toluene, 0 °C, 12 h; 2) Ac_2O, 24 h, room temperature.

Table 4. Temperature dependence of the enantiomeric excess achieved by ligand (S_P,S)-**3**. 1) $C_6H_{11}CHO$ (0.5 mmol), 2 mol % of ligand, 1 mL of Et_2Zn (1 M in hexanes), 1 mL of toluene, 12 h; 2) Ac_2O, 24 h, room temperature.

Entry	Temperature [°C]	ee [%]
1	−20	96.0
2	−5	95.2
3	5	94.6
4	35	93.3
5	50	90.9

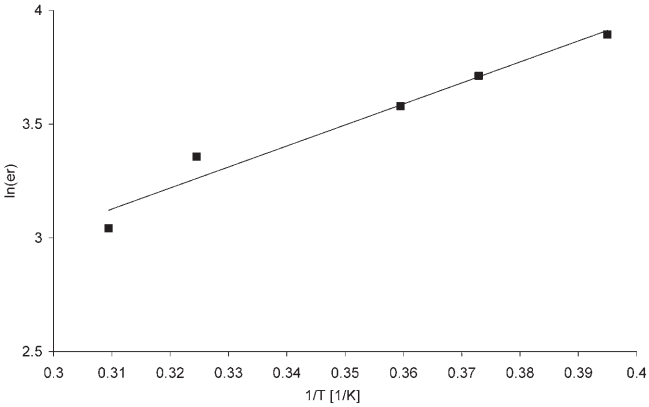


Figure 5. Eyring plot [ln(e_r) *vs.* 1/T]. Temperature dependence of the enantiomeric excess achieved by ligand (S_P,S)-**3**. 1) $C_6H_{11}CHO$ (0.5 mmol), 2 mol % of ligand, 1 mL of Et_2Zn (1 M in hexanes), 1 mL of toluene, 12 h; 2) Ac_2O, 24 h, room temperature.

In summary, we have presented the first selectivity and activity studies of various [2.2]paracyclophane ketimine ligands. To the best of our knowledge this is the first non-linear-like effect study reported in diethylzinc chemistry, which can be completely attributed to the insolubility of an inactive dimer being formed with certain diastereomers. Furthermore, we found no maximum for the enantiomeric excess over a wide range of temperature, while the enantiomeric excess remained constant over the reaction time. Due to their decreased tendency to dimerize and the very low loading necessary for catalyst activity, in comparison with other ligands, they present highly active catalysts for asymmetric 1,2-addition reactions due to the lack of dimerization. In contrast to other ligands having more than one stereogenic center such as ferrocene ligands, neither mismatched cases nor large differences in rate constants of two diastereomers can be observed.

Experimental Section

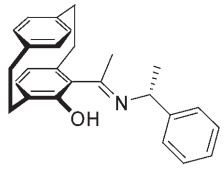
General Remarks

^{1}H NMR: Bruker AM 400 (400 MHz), Bruker DRX 500 (500 MHz); δ = 7.26 ppm for $CHCl_3$. Description of signals: s = singlet, bs = broad singlet, d = doublet, m = multiplet, dd = doublet of doublet, ddd = doublet of dd, q = quartet, p = quintet. The spectra were analyzed according to first order rules. All coupling constants are absolute values. ^{13}C NMR: Bruker AM 400 (100 MHz), Bruker DRX 500 (125 MHz); δ = 77.00 ppm for $CHCl_3$. IR: KBr pellets on a Bruker IFS88 IR; EI-HR-MS: Thermo Quest Finnegan MAT 90 (70 eV). GC analytical (achiral stationary-phase): Hewlett-Packard HP 5890 Series II, 12 m × 0.25 mm capillary column HP I (carrier gas N_2). Enantiomeric excesses were determined by GC on a chiral stationary phase (CP-Chirasil-Dex). Optical rotations were determined on a Perkin Elmer 241 polarimeter (Na, 589 nm). Melting points were measured with a MEL-TEMPII, Laboratory Devices Inc. USA. TLC: silica gel-coated aluminium plates (Merck, silica gel 60, F254). Detection under UV light at 254 nm. Chemicals, solvents, reagents, and chemicals were purchased from Acros, Aldrich, Fluka, and Merck.

General Procedure for the Catalysis Reaction

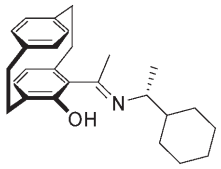
To a 10-mL vial under an argon atmosphere containing the appropriate amount of the chiral ligand dissolved in the appropriate amount of dry toluene as a co solvent, 1.0 mL of a 1 M solution of diethylzinc in hexane was added at room temperature. The mixture was stirred for 30 min at room temperature and cooled down to the desired temperature. After an additional 30 min at the desired temperature, 0.5 mmol of the aldehyde was added slowly and the reaction mixture was stirred for 12 h at the desired temperature. The reaction mixture was quenched with acetic anhydride and was allowed to stir for 24 h at room temperature. The reaction mixture was then quenched with saturated ammonium chloride solution, then diluted with diethyl ether, the organic phase was washed twice with water, once with brine, and then dried over $MgSO_4$.

(R_PR)-5-(1′-Phenylethyliminoethyl)-4-hydroxy[2.2]paracyclophane (1)



Enantiomerically pure (R_P)-5-acetyl-4-hydroxy[2.2]paracyclophane (AHPC) (0.10 g, 0.37 mmol) was dissolved in 50 mL of toluene and (*R*)-phenylethylamine (0.14 g, 1.13 mmol) was added. After adding a catalytic amount of dibutyltin diacetate, the reaction mixture was refluxed with a Dean–Stark apparatus for 40 h. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography to afford an orange solid; yield: 106 mg (78%); R_f = 0.14 (pentane/diethyl ether, 9:1); mp 153–154 °C; $[\alpha]_D^{20}$: +297 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, CDCl3): δ = 1.71 (d, *J* = 6.5 Hz, 3H), 2.28 (s, 3H), 2.41 (ddd, *J* = 12.9, 9.2, 7.1 Hz, 1H), 2.56 (ddd, *J* = 12.7, 10.1, 4.9 Hz, 1H), 2.86 (ddd, *J* = 13.8, 9.4, 7.1 Hz, 1H), 2.97 (ddd, *J* = 12.5, 9.4, 2.2 Hz, 1H), 3.04 (ddd, *J* = 13.4, 10.1, 2.7 Hz, 1H), 3.17–3.31 (m, 2H), 3.46 (ddd, *J* = 12.7, 10.0, 2.5 Hz, 1H), 4.88 (q, *J* = 6.5 Hz, 1H), 6.12 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.20 (d, *J* = 7.6, 1H), 6.44 (d, *J* = 7.3 Hz, 1H), 6.49 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.59 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.03 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.33–7.37 (m, 1H), 7.44–7.50 (m, 2H), 7.53–7.57 (m, 2H), 15.97 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.39, 24.98, 30.49, 33.91, 35.38, 37.23, 58.09, 122.24, 125.63, 126.49, 127.07, 127.33, 128.86, 129.47, 130.21, 131.47, 132.67, 136.27, 137.64, 139.95, 140.88, 163.27, 170.14; IR (KBr): ν = 3413 (br), 3067 (w), 3033 (w), 3011 (w), 2927 (m), 1582 (m), 1499 (w), 1436 (m), 1298 (m) cm^{-1}; MS (70 eV, EI): *m/z* (%) = 369 (95) [M+], 265 (58), 160 (63), 132 (7), 105 (100), 91 (5), 77 (5); HR-MS-EI: *m/z* = 369.2094 (calcd. for $C_{26}H_{27}NO$: 369.2093).

(R_PR)-5-(1′-Cyclohexylethyliminoethyl)-4-hydroxy[2.2]paracyclophane (3)



Enantiomerically pure (R_P)-5-acetyl-4-hydroxy[2.2]paracyclophane (AHPC) (0.10 g, 0.37 mmol) was dissolved in 50 mL of toluene and (*R*)-cyclohexylethylamine (0.14 g, 1.13 mmol) was added. After adding a catalytic amount of dibutyltin diacetate, the reaction mixture was refluxed with a Dean–Stark apparatus for 40 h. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography to afford an orange solid; yield: 113 mg (81%); R_f = 0.17 (pentane/diethyl ether, 9:1); mp 110–111 °C; $[\alpha]_D^{20}$: +611 (*c* 0.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.20 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.24–1.31 (m, 2H), 1.32–1.42 (m, 2H), 1.58–1.68 (m, 1H), 1.72–1.80 (m, 1H), 1.84–1.95 (m, 3H), 2.00–2.20 (m, 1H), 2.30 (s, 3H), 2.52 (ddd, *J* = 13.2, 10.6, 5.5 Hz, 1H), 2.67 (ddd, *J* = 13.3, 9.8, 5.5 Hz, 1H), 2.93 (ddd, *J* = 13.3, 9.5, 5.5 Hz, 1H), 3.01 (ddd, *J* = 13.1, 10.6, 2.8 Hz, 1H), 3.10 (ddd, *J* = 12.3, 9.7, 2.2 Hz, 1H), 3.17 (ddd, *J* = 12.6, 9.9, 5.1 Hz, 1H), 3.34–3.38 (m, 1H), 3.41 (ddd, *J* = 12.6, 10.1, 2.5 Hz, 1H), 3.60 (p, *J* = 6.5 Hz, 1H), 6.16 (d, *J* = 7.6 Hz, 1H), 6.35 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.41 (d, *J* = 7.6 Hz, 1H), 6.51 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.65 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.99 (dd, *J* = 7.8, 1.8 Hz, 1H), 16.70 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.60, 19.50, 26.36, 26.42, 26.68, 29.18, 30.10, 30.52, 33.88, 35.56, 37.42, 44.36, 58.02, 121.62, 124.94, 127.08, 129.90, 130.24, 131.42, 132.70, 136.20, 137.60, 140.16, 140.74, 165.44, 168.81; IR (KBr): ν = 2973 (s), 2932 (s), 2851 (s), 1869 (w), 1591 (m), 1443 (m) cm^{-1}; MS (70 eV, EI): *m/z* (%) = 375 (38) [M$^+$], 271 (100), 188 (50), 162 (44), 104 (55); HR-MS-EI: *m/z* = 375.2560 (calcd. for $C_{26}H_{27}NO$: 375.2562).

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