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Preparation of planar chiral amino phenols based on the [2.2]paracyclophane backbone

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Abstract—The synthesis of various planar and central chiral secondary and tertiary amino phenols based on the [2.2]paracyclophane backbone is described. Planar chiral tertiary amino phenols are prepared by reductive amination of 5-formyl-4-hydroxy[2.2]paracyclophane (FHPC) with secondary amines. The reduction of imine and ketimine precursors, as well as the 1,2-addition to these compounds is also described. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The element of planar chirality plays an important role in many modern ligand systems.[1–3] However, the majority of planar chiral ligands is based on ferrocene derivatives[2] or arene transition metal complexes.[3] So far, only limited attention has been paid to planar chiral ligands derived from [2.2]paracyclophane.[4]

Amino alcohol ligands are among the most versatile precursors for catalysts and can be applied in a variety of catalytic asymmetric reactions.[5] While the number of simple central chiral amino alcohols is very high because of their availability from natural sources or asymmetric synthesis (e.g. approximately 500 amino alcohols or amino alcohol derivatives have recently been review by Pu and Yu[6] as ligands in diethyl zinc additions to aldehydes), examples of more complex molecules such as planar chiral ferrocenes or axial chiral binaphthalenes are much fewer. The field of amino alcohol ligands based on the [2.2]paracyclophane backbone is more or less undeveloped.

As part of an ongoing study of [2.2]paracyclophane ligands in asymmetric catalysis, we have synthesized a variety of different secondary and tertiary amino phenols as potential ligands, either by reduction of imine or ketimine precursors, by 1,2-addition or by reductive amination. Herein, we report on the results of that study.

2. Results and discussion

One of the three key intermediates of our strategy is the 5-formyl-4-hydroxy[2.2]paracyclophane **4** (FHPC), which can be regarded as a planar chiral analogue of salicylaldehyde. The compound was first prepared by Rozenberg, Belokon et al.[7] followed by a number of reports on alternative routes to the racemic as well as the enantiomerically pure compound.[8]

The synthesis of FHPC was carried out according to Scheme 1 in a multi-stage reaction: bromination of the unsubstituted [2.2]paracyclophane **1**, lithium–halogen exchange with *n*-BuLi, quenching of the organometallic intermediate with trimethyl borate, and oxidative work-up furnished the hydroxy[2.2]paracyclophane **3**.[7b,9] The *ortho*-formylation of **3** catalyzed by $SnCl_4$ and Bu_3N according to the procedure of Belokon, Rozenberg et al.[7b] to give **4** only proceeds to 20–30% conversion. Although various Lewis acids were screened and the ratio of Lewis acid to amine was varied, we could not find better conditions.

We therefore chose to use the method of Hopf and Barrett,[8a] which proceeds via the formation of a

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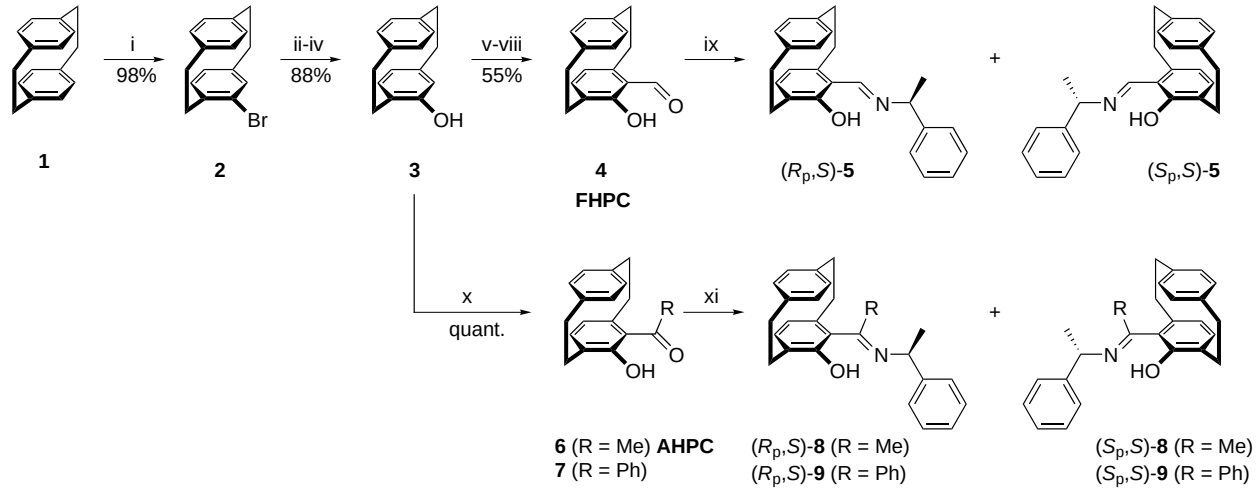


Scheme 1. Preparation of racemic and enantiomerically pure FHPC **4**, AHPC **6** and 5-benzoyl-4-hydroxy[2.2]paracyclophane **7**. In the resolution step, only the condensation with (*S*)-phenylethylamine is shown for clarity. (i) Br_2, Fe, CH_2Cl_2, reflux, 20 h; (ii) *n*-BuLi, THF, −50°C, 3 h; (iii) $B(OCH_3)_3$; (iv) H_2O_2, KOH; (v) diethylcarbamoyl chloride, DMAP, toluene, reflux, 16 h; (vi) *s*-BuLi, TMEDA, THF, −78°C, 3 h; (vii) DMF, −78°C to rt, 12 h; (viii) HCl (aq.); (ix) (*S*)-phenylethylamine, toluene, reflux, 40 h; (x) $TiCl_4$, RCOCl, CH_2Cl_2, 0°C to rt, 2 h; (xi) (*S*)-phenylethylamine, Bu_2SnCl_2 (R = Me) or $TiCl_4$ (R = Ph), toluene, reflux, 16–40 h.[7,9,10]

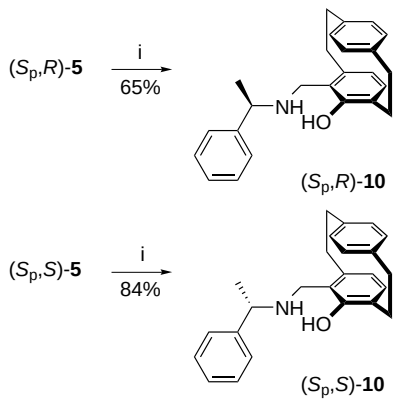
diethylcarbamate. *ortho*-Deprotonation of the latter with *s*-BuLi/TMEDA and subsequent reaction with DMF, delivered, after acidic work-up, the desired racemic FHPC (±)-**4** (Scheme 1).

The other key intermediates were the 5-acetyl-4-hydroxy[2.2]paracyclophane **6** and 5-benzoyl-4-hydroxy[2.2]paracyclophane **7**, which were synthesized by *ortho*-selective *Friedel–Crafts* acylation of phenol **3**.[10] The resolution of (±)-**4**,[7] (±)-**6** and (±)-**7**[10] was conducted according to literature procedures via their imines **5** or ketimines **8** and **9** with (*S*)- or (*R*)-phenylethylamine, respectively (Scheme 1). Enantiomerically pure **4** and **6** were obtained by hydrolysis of the corresponding imines and ketimines.

2.1. Reduction of imines and ketimines

The reduction of imines based on **4** was carried out under standard conditions with sodium borohydride in methanol at room temperature. The reaction proceeded smoothly affording the secondary amino phenols **10** in good yields (65–84%) (Scheme 2).

However, reduction of the ketimines was much slower (Scheme 3). The addition of acetic acid to the reaction mixture improved the formation of the product amino phenols. Ketimine (R_p,*S*)-**8** bearing a methyl substituent in the side chain was transformed to the product (R_p,*R*,*S*)-**11** with complete stereoselectivity regarding the newly formed stereogenic center (>98% d.e.). This corresponds to attack of borohydride from the unhindered 'bottom side' of the paracyclophane while the paracyclophane backbone efficiently shields the other side of the imine double bond. To test the dependency of the selectivity of the reduction on the size of the substituents in the side chain, ketimine (S_p,*S*)-**9** was also subjected to these reaction conditions. Although the latter is a diastereomer of (R_p,*S*)-**8** with opposite configuration of the planar chiral backbone, the outcome of the reaction should be determined by the backbone thus giving the (*S*)-configured product with respect to the newly formed stereocenter.

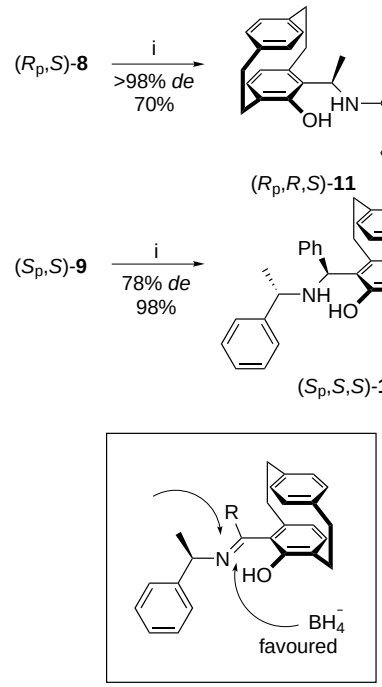


Scheme 2. Reduction of diastereomeric imines **5**. (i) $NaBH_4$, MeOH, rt, 12 h.

As expected, the larger phenyl ring of (S_p,*S*)-**9** interacts with the attacking borohydride much more strongly than the small methyl group leading to a diminished stereoselectivity of 78% d.e. (Scheme 3).

2.2. 1,2-Addition to imines and ketimines

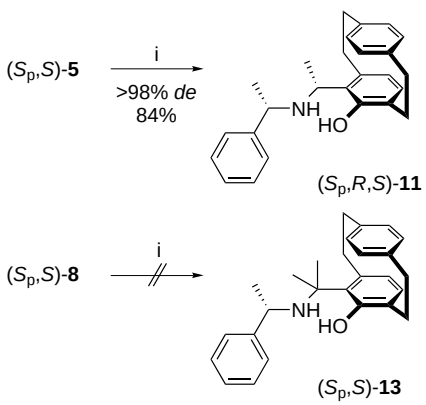
A further reaction yielding secondary amino phenols is the 1,2-addition to imines. As the stereochemical considerations are the same as for the borohydride reduction (Scheme 3), the attack of the nucleophile again occurs from the unhindered side of the paracyclophane.



Scheme 3. Reduction of ketimines **8** and **9**. (i) $NaBH_4$, AcOH, MeOH, rt, 5–12 h. The [2.2]paracyclophane backbone shields the upper side of the imine double bond.

Thus, the resulting amino phenol product (S_p,*R*,*S*)-**11** (Scheme 4) has the opposite configuration at the newly formed stereogenic center compared to the products obtained from the reduction of ketimines (Scheme 3). These methods are therefore complementary for the introduction of chirality in the paracyclophane side chain.[11]

However, the ketimine double bond was resistant to addition reactions ((S_p,*S*)-**8** in Scheme 4). Even in the presence of several equivalents of methyl lithium at room temperature, no reaction was observed and the starting material was recovered quantitatively after work-up.



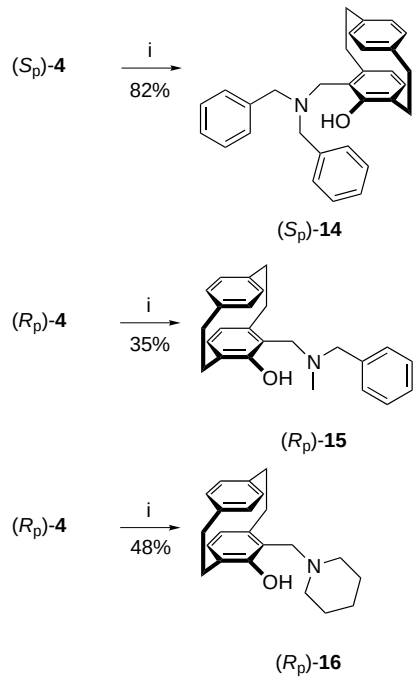
Scheme 4. 1,2-Addition to imines and ketimines. (i) MeLi, THF, −78°C to rt, 12 h.

2.3. Reductive amination

Reductive amination is a powerful method for the selective formation of secondary and tertiary amines. As secondary amino phenols could be obtained by reduction of the imine precursors in an acceptable fashion, the direct reductive amination of FHPC with secondary amines was examined.

The reaction proceeded smoothly in the presence of 5 equiv. of amine and 2 equiv. of HCl with $Na(CN)BH_3$ as reductant. The presence of HCl was necessary to form the iminium cation intermediate, which is the species that is selectively reduced by cyanoborohydride.

Compound (S_p)-**14** is a stable amino phenol, which was obtained as a white solid after chromatography on silica (Scheme 5). The less hindered amino phenols (R_p)-**15** and (R_p)-**16** however, are unusually acid sensitive and decompose on silica. Analytically pure samples could be obtained by chromatography on neutral aluminum oxide. The decomposition products obtained indicate, that upon protonation of the tertiary amine moiety, elimination and subsequent reactions of the paracyclophanyl methyl cation take place.



Scheme 5. Reductive amination. (i) Amine (5 equiv.), conc. HCl (2 equiv.), $Na(CN)BH_3$ (2 equiv.), MeOH, rt, 5–12 h.

3. Conclusion

In conclusion, we have demonstrated the formation of secondary and tertiary amino phenols based on the [2.2]paracyclophane backbone. Secondary amino phenols were synthesized by reduction of imines or 1,2-addition. Tertiary amino phenols could be obtained by reductive amination of FHPC **4** with secondary amines.

The tertiary amino phenol products **14**–**16** are especially interesting as chiral catalytic ligands for e.g. the addition of diethylzinc to aldehydes[12] and transfer hydrogenation reactions. The application of the amino phenols described herein as catalyst precursors is under examination and the results will be reported soon.

4. Experimental

4.1. General

All chemicals and solvents were used as received unless otherwise stated. THF (Na, benzophenone), toluene (Na, benzophenone), CH_2Cl_2 (CaH_2), methanol (Mg) were distilled under argon from the drying agent indicated. ^1H and ^{13}C NMR spectra were recorded with a Varian VXR 300 (300/75 MHz), Varian Unity 500 (500/125 MHz), Varian Inova (400/100 MHz) or Gemini 300 S (300/75 MHz) instrument. Abbreviations for ^1H NMR: s = singlet, d = doublet, t = triplet, m = multiplet, pc = paracyclophane backbone; abbreviations for ^{13}C NMR: p = primary, s = secondary, t = tertiary, q = quaternary carbon atom as determined by ATP and DEPT experiments. Preparative liquid chromatography was performed on straight phase silica gel (Merck 60, 230–400 mesh, 0.040–0.063 mm) or on neutral aluminum oxide (Merck, 60 PF_{254} Type E), with the eluent indicated. IR spectra were recorded on a Perkin–Elmer FT-IR 1750. Mass spectra were recorded on a Finnigan SSQ 7000 and HRMS on a Finnigan MAT 95, respectively. Optical rotations were measured with a Perkin–Elmer P 241 polarimeter in a 10 cm cell with the solvent indicated. FHPC **4**, AHPC **6** and 5-benzoyl-4-hydroxy[2.2]paracyclophane **7** were synthesized and resolved using literature procedures.[7,9,10]

4.2. Reduction of imines and ketimines

4.2.1. (S_p,*R*)-5-[(1′-Phenylethylamino)methyl]-4-hydroxy-[2.2]paracyclophane (S_p,*R*)-10. To a solution of (S_p,*R*)-5 - [(1′ - phenylethylimino)methyl] - 4 - hydroxy[2.2]paracyclophane (S_p,*R*)-**5** (100 mg, 0.29 mmol) in methanol (4 mL) was added $NaBH_4$ (38 mg, 1 mmol) at rt and the mixture was stirred for 12 h. After quenching with water, the mixture was extracted with dichloromethane and the combined organic layers were dried over $MgSO_4$. Chromatography on silica (1.7×20 cm, dichloromethane) afforded the title compound as a white solid (65 mg, 65%): R_f = 0.32 (pentane/ether = 1:1); $[\alpha]_D^{20}$ = −146 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.46 (d, *J* = 6.6 Hz, 3H, CH_3), 2.51–2.66 (m, 3H), 2.78–2.87 (m, 1H), 2.94–3.10 (m, 3H), 3.23 (d, *J* = 13.2 Hz, 1H, pcC*H*HN), 3.29–3.37 (m, 1H), 3.58 (d, *J* = 13.2 Hz, 1H, pcCH*H*N), 3.83 (q, *J* = 6.6 Hz, 1H, NC*H*(CH_3)Ph), 6.07 (d, *J* = 7.7 Hz, 1H), 6.37 (d, *J* = 7.7 Hz, 1H), 6.44–6.51 (m, 3H), 6.57 (dd, *J* = 7.7 Hz, 1.6 Hz, 1H), 6.85 (dd, *J* = 8.0 Hz, 1.7 Hz, 1H), 7.18–7.35 (m, 5H, H_{Ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.87 (p, NCH(*C*H_3)Ph), 29.70 (s), 32.56 (s), 33.94 (s), 34.07 (s, C-1, C-2, C-9, C-10), 47.13 (s, pc*C*H_2N), 57.67 (t, N*C*H(CH_3)Ph), 122.75 (q), 124.09 (t), 125.73 (q), 125.98 (t), 126.43 (t), 126.93 (t), 127.25 (t), 128.55 (t), 132.24 (t), 132.81 (t), 132.88 (t), 137.35 (q), 138.97 (q), 139.68 (q), 143.42 (q), 156.38 (q, C-4) ppm; IR (KBr): ν = 3305 (OH), 1598, 1430 cm^{-1}; MS (70 eV, EI), *m*/*z* (%): 357 (100) [M^+], 253 (24), 236 (25), 148 (26); 104 (72); HRMS $C_{25}H_{27}NO$ calcd: 357.2093, found: 357.2092.

4.2.2. (S_p,*S*)-5-[(1′-Phenylethylamino)methyl]-4-hydroxy-[2.2]paracyclophane (S_p,*S*)-10. The reaction was carried out as described for (S_p,*R*)-**10** starting from (S_p,*S*)-5-[(1′-phenylethylimino)methyl]-4-hydroxy[2.2]paracyclophane (S_p,*S*)-**5** (100 mg, 0.29 mmol). After chromatography on silica (1.7×20 cm, dichloromethane), the title compound was obtained as an oil (87 mg, 84%); R_f = 0.32 (pentane/ether = 1:1); $[\alpha]_D^{20}$ = −131 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (d, *J* = 6.8 Hz, 3H, CH_3), 2.44–2.66 (m, 3H), 2.71–2.85 (m, 1H), 2.91–3.10 (m, 3H), 3.19 (d, *J* = 14.0 Hz, 1H, pcC*H*HN), 3.28–3.37 (m, 1H), 3.54 (d, *J* = 14.0 Hz, 1H, pcCH*H*N), 3.66 (q, *J* = 6.6 Hz, 1H, NC*H*(CH_3)Ph), 6.09 (d, *J* = 7.7 Hz, 1H), 6.21 (d, *J* = 8.0 Hz, 1H), 6.39 (d, 7.7 Hz, 1H), 6.43 (s, br, 2H), 6.67 (d, br, *J* = 8.0 Hz, 1H), 7.29–7.46 (m, 5H, H_{Ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.55 (p, NCH(*C*H_3)Ph), 29.74 (s), 32.51 (s), 33.80 (s), 33.87 (s, C-1, C-2, C-9, C-10), 46.99 (s, pc*C*H_2N), 57.41 (t, N*C*H(CH_3)Ph), 122.16 (q), 124.04 (t), 125.70 (q), 126.09 (t), 126.67 (t), 126.95 (t), 127.49 (t), 128.59 (t), 132.08 (t), 132.55 (t), 132.76 (t), 137.11 (q), 139.25 (q), 139.54 (q), 143.00 (q), 156.46 (q, C-4) ppm; IR (KBr): ν = 3306 (OH), 1598, 1566, 1420 cm^{-1}; MS (70 eV, EI), *m*/*z* (%): 357 (100) [M^+], 253 (24), 236 (25), 148 (269; 104 (72); HRMS $C_{25}H_{27}NO$ calcd: 357.2093, found: 357.2092.

4.2.3. (R_p,*R*,*S*)-5-[1′-(1″-Phenylethylamino)ethyl]-4-hydroxy[2.2]paracyclophane 11. To a solution of (R_p,*S*)-[1′-(1″-phenylethylamino)ethyl]-4-hydroxy[2.2]paracyclophane (R_p,*S*)-**8** (100 mg, 0.27 mmol) in methanol/dichloromethane (2:1, 30 mL) was added $NaBH_4$ (38 mg, 1 mmol) at rt and dropwise conc. acetic acid (0.1 mL). The mixture was stirred for 5 h. After quenching with water, the mixture was extracted with dichloromethane and the combined organic layers were dried over $MgSO_4$. Chromatography on silica (1.7×20 cm, dichloromethane) afforded the title compound as a white solid (70 mg, 70%): R_f = 0.32 (pentane/ether = 1:1); $[\alpha]_D^{20}$ = +86 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, *J* = 6.6 Hz, 3H, NCH(CH_3)Ph), 1.59 (d, *J* = 6.9 Hz, 3H, pcCH(CH_3)N), 2.53–2.62 (m, 1H), 2.69–2.78 (m, 1H), 2.82–2.91 (m, 1H), 3.00–3.20 (m, 4H), 3.38–3.45 (m, 1H), 4.04 (q, *J* = 6.6 Hz, 1H, NC*H*(CH_3)Ph), 4.14 (q, br, *J* = 6.3 Hz, 1H, pcCH(CH_3)N), 6.07 (d, *J* = 7.7 Hz, 1H), 6.28 (d, *J* = 7.4 Hz, 1H), 6.50 (m, 2H), 6.64 (dd, *J* = 7.7 Hz, 1.6 Hz, 1H), 6.91 (dd, *J* = 8.0 Hz, 1.9 Hz, 1H), 7.31–7.46 (m, 5H, H_{Ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.75 (p, NCH(*C*H_3)Ph and pcCH(*C*H_3)N), 30.06 (s), 32.64 (s), 34.08 (s), 34.70 (s, C-1, C-2, C-9, C-10), 53.99 (s, pc*C*H_2N), 56.39 (t, N*C*H(CH_3)Ph), 125.92 (t), 126.14 (t), 127.46 (t), 127.51 (t), 127.82 (q), 128.94 (t), 129.68

(t), 132.74 (t), 133.96 (t), 134.02 (t), 137.26 (q), 138.35 (q), 140.60 (q), 144.43 (q), 155.71 (q, C-4) ppm; IR (KBr): $\nu = 3309$ (OH), 1593, 1566, 1430 cm^{-1}; MS (70 eV, EI), m/z (%): 371 (100) [M^+], 145 (96), 104 (97); HRMS $C_{26}H_{29}NO$ calcd: 371.2249, found: 371.2250.

4.2.4. (S_p,*S*,*S*)-5-[Phenyl-(1′-phenylethylamino)methyl]-4-hydroxy[2.2]paracyclophane 12. To a solution of (S_p,*S*)-5-[phenyl-(1′-phenylethylimino)methyl]-4-hydroxy[2.2]-paracyclophane (S_p,*S*)-**9** (100 mg, 0.23 mmol) in ethanol (10 mL) was added at rt $NaBH_4$ (38 mg, 1 mmol) and the mixture was stirred for 2 h. After quenching with water, the mixture was extracted with dichloromethane and the combined organic layers were dried over $MgSO_4$. After removal of the solvent, the title compound was obtained as a yellow oil (98 mg, 98%): major diastereomer (d.e. = 78%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (d, $J = 6.6$ Hz, 3H, CH_3), 2.41–2.51 (m, 1H), 2.54–2.64 (m, 1H), 2.73–2.92 (m, 2H), 3.00–3.23 (m, 3H), 3.39–3.47 (m, 1H, C-1, C-2, C-9, C-10), 4.00 (q, br, $J = 6.6$ Hz, 1H, NCH(CH_3)Ph), 4.86 (s, 1H, pcCH(Ph)N), 5.97 (d, $J = 7.4$ Hz, 1H), 6.30 (d, $J = 7.7$ Hz, 1H), 6.52 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 6.61 (dd, $J = 7.7$ Hz, 1.9 Hz, 1H), 6.78 (dd, $J = 7.7$ Hz, 1.9 Hz, 1H), 6.97–7.02 (m, 2H, H_{Ar}), 7.04 (dd, $J = 7.7$ Hz, 1.6 Hz, 1H, H_{pc}), 7.12–7.40 (m, 8H, H_{Ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.25 (p, NCH(CH_3)Ph), 29.99 (s), 33.69 (s), 34.02 (s), 34.17 (s, C-1, C-2, C-9, C-10), 55.20 (t, NCH(CH_3)Ph), 62.89 (t, pc$C$H(Ph)N), 123.66 (q), 125.79 (t), 126.26 (t), 126.31 (t), 127.08 (t), 127.19 (t), 127.36 (t), 127.43 (t), 127.65 (q), 128.50 (t), 128.65 (t), 128.68 (t), 132.30 (t), 133.68 (t), 138.04 (q), 138.65 (t), 140.25 (q), 143.16 (q), 143.50 (q), 156.75 (q, C-4) ppm.

4.3. 1,2-Addition to imines

4.3.1. (S_p,*S*,*R*)-5-[1′-(1″-Phenylethylamino)ethyl]-4-hydroxy[2.2]paracyclophane (S_p,*S*,*R*)-11. To a solution of (S_p,*S*)-5-[(1′-phenylethylimino)methyl]-4-hydroxy-[2.2]paracyclophane (S_p,*S*)-**5** (55 mg, 0.15 mmol) in THF (10 mL) was added at −78°C methyllithium (1 mL, 5% in Diethylether, 1.6 mmol) under argon. The solution was allowed to warm to rt over 15 h. The mixture was quenched with water and extracted with dichloromethane. After drying over $MgSO_4$ and removal of the solvent, the title compound was obtained as a white solid (50 mg, 84%): $R_f = 0.33$ (pentane/ether = 1:1); $[\alpha]_D^{20} = -140$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, $J = 6.3$ Hz, 3H, NCH(CH_3)Ph), 1.59 (d, $J = 6.6$ Hz, 3H, pcCH(CH_3)N), 2.50–2.63 (m, 3H), 2.84–2.93 (m, 1H), 2.97–3.07 (m, 2H), 3.10–3.18 (m, 1H), 3.39–3.47 (m, 1H), 3.73 (q, $J = 6.6$ Hz, 1H, NCH(CH_3)Ph), 3.99 (q, br, $J = 6.3$ Hz, 1H, pcCH(CH_3)N), 6.05 (d, $J = 7.7$ Hz, 1H), 6.20 (dd, $J = 8.0$ Hz, 1.9 Hz, 1H), 6.28 (d, $J = 7.7$ Hz, 1H), 6.46 (dd, $J = 8.0$ Hz, 1.9 Hz, 1H), 6.56 (dd, $J = 8.0$ Hz, 1.9 Hz, 1H), 7.33–7.51 (m, 5H, H_{Ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.29 (p, NCH(CH_3)Ph), 24.29 (p, pcCH(CH_3)N), 30.08 (s), 32.92 (s), 33.96 (s), 34.45 (s, C-1, C-2, C-9, C-10), 51.31 (t, pc$C$H(CH_3)N), 53.98 (t, NCH(CH_3)Ph), 125.91 (q), 126.25 (t), 126.27 (q), 127.11 (t), 127.57 (t), 127.68 (q), 128.79 (t), 129.16 (t), 132.43 (t), 133.77 (t), 134.11 (t), 136.92 (q), 138.22 (q), 140.21 (q), 142.86 (q), 155.34 (q, C-4) ppm; IR (KBr): $\nu = 3309$ (OH), 1593, 1565, 1430 cm^{-1}; MS (70 eV, EI), m/z (%): 371 (94) [M^+], 145 (100), 105 (31), 104 (99); HRMS $C_{26}H_{29}NO$ calcd: 371.2249, found: 371.2249.

4.4. Reductive amination

4.4.1. (S_p)-5-[(Dibenzylamino)methyl]-4-hydroxy[2.2]-paracyclophane (S_p)-14. To a solution of (S_p)-5-formyl-4-hydroxy[2.2]paracyclophane (S_p)-**4** (72 mg, 0.28 mmol) in methanol (10 mL) was added dibenzylamine (274 mg, 1.4 mmol) and 5 M HCl (100 μL) at rt. After stirring for 0.5 h, Na(CN)BH_3 (21 mg, 0.33 mmol) was added and the mixture was stirred for a further 2 h. The mixture was quenched with water, neutralized with $NaHCO_3$ solution and extracted several times with dichloromethane. After chromatography on silica (1.7× 20 cm, dichloromethane), the title compound was obtained as a white solid (100 mg, 82%): $R_f = 0.58$ (dichloromethane); $[\alpha]_D^{20} = -93$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43–2.58 (m, 2H, H_{pc}), 2.61–2.70 (m, 1H, H_{pc}), 2.91–3.01 (m, 3H, H_{pc}), 3.10 (d, $J = 13.2$ Hz, 2H, NCH_2Ph), 3.18 (d, $J = 14.6$ Hz, 1H, NCH_2pc), 3.28–3.36 (m, 1H, H_{pc}), 3.39 (d, $J = 14.3$ Hz, 1H, NCH_2pc), 3.95 (d, $J = 12.9$ Hz, 2H, NCH_2Ph), 5.84 (d, $J = 8.0$ Hz, 1H, H_{pc}), 6.11 (d, $J = 7.7$ Hz, 1H, H_{pc}), 6.33 (d, br, $J = 7.7$ Hz, 1H, H_{pc}), 6.40 (d, $J = 7.7$ Hz, 1H, H_{pc}), 6.41 (m, br, 2H, H_{pc}), 7.27–7.42 (m, 10H, H_{Ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.35, 33.10, 34.14, 34.18 (C-1, C-2, C-9, C-10), 53.87 (C-17), 58.82 (C-18), 121.21 (q), 124.61 (t), 125.92 (q), 126.14 (t), 127.43 (t, all C-Ar_{pc}), 128.01 (t), 128.86 (t), 130.00 (t, all C-Ar), 132.40 (t), 132.87 (t), 133.04 (t, all C-Ar_{pc}), 137.06 (q), 137.16 (q), 139.78 (q), 140.01 (q), 156.55 (C-4) ppm; IR (KBr): $\nu = 3026$, 1599, 1566, 1497, 1447, 1431 cm^{-1}; MS (70 eV, EI), m/z (%): 433 (100) [M^+], 329 (51), 238 (21), 196 (20), 106 (23), 104 (64), 91 (54); HRMS $C_{31}H_{31}NO$ calcd: 433.2406, found: 433.2406.

4.4.2. (R_p)-5-[(Benzylmethylamino)methyl]-4-hydroxy-[2.2]paracyclophane (R_p)-15. To a solution of (R_p)-5-formyl-4-hydroxy[2.2]paracyclophane (R_p)-**4** (100 mg, 0.40 mmol) in 10 mL of methanol was added at rt methylbenzylamine (242 mg, 2.0 mmol) and conc. HCl (80 μL). After stirring for 0.5 h, Na(CN)BH_3 (50 mg, 0.80 mmol) was added and the mixture was stirred for a further 2 h at rt. The mixture was quenched with water, neutralized with $NaHCO_3$ solution and extracted several times with dichloromethane. After chromatography on neutral aluminum oxide (1.7×20 cm, pentane/ether = 9:1), the title compound was obtained as a white solid (50 mg, 35%): $R_f = 0.6$ (pentane/ether = 9:1, neutral alox); $[\alpha]_D^{20} = +132$ (c 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H, CH_3), 2.51–2.74 (m, 3H), 2.94–3.08 (m, 4H), 3.24 (d, $J = 14.0$ Hz, 1H, NCH_2Ar), 3.28–3.36 (m, 2H), 3.38 (d, $J = 14.0$ Hz, 1H, NCH_2Ar), 3.74 (d, $J = 12.6$ Hz, 1H, NCH_2Ar), 6.11 (d, $J = 7.7$ Hz, 1H), 6.28 (d, br, $J = 7.7$ Hz, 1H), 6.41 (d, $J = 7.7$ Hz, 1H), 6.47 (s, br, 2H), 6.66 (d, br, $J = 8.0$ Hz, 1H), 7.27–7.40 (m, 5H, H_{Ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.96, 32.78, 34.15 (C-1, C-2, C-9, C-10),

42.29 (p, CH_3), 57.50 (s, pcCH_2N), 61.97 (s, br, NCH_2Ar), 121.45 (q), 124.34 (t), 125.67 (q), 126.11 (t), 127.24 (t), 127.80 (t), 128.64 (t, C-Ar), 129.52 (t, C-Ar), 132.44 (t), 132.88 (t), 133.00 (t), 137.00 (q), 137.32 (q), 139.64 (q), 139.89 (q), 156.48 (C-4) ppm; IR (KBr): $\nu = 3064$, 1600, 1569, 1498, 1454, 1423 cm^{-1}; MS (70 eV, EI), m/z (%): 357 (100) [M^+], 253 (67), 120 (32), 104 (69), 91 (22); HRMS $C_{25}H_{27}NO$ calcd: 357.2093, found: 357.2093.

4.4.3. (R_p)-5-[(Piperidinyl)methyl]-4-hydroxy[2.2]paracyclophane (R_p)-16. To a solution of (R_p)-5-formyl-4-hydroxy[2.2]paracyclophane (R_p)-**4** (100 mg, 0.40 mmol) in methanol (10 mL) at rt was added piperidine (170 mg, 2.0 mmol) and conc. HCl (80 μL). After stirring the mixture for for 0.5 h, $Na(CN)BH_3$ (50 mg, 0.80 mmol) was added and the mixture was stirred for another 2 h at rt. The reaction was quenched with water, neutralized with $NaHCO_3$ solution and extracted several times with dichloromethane. After chromatography on neutral aluminum oxide (1.7×20 cm, pentane/ether = 9:1), the title compound was obtained as a white solid (60 mg, 48%): $R_f = 0.5$ (pentane/ether = 9:1, neutral alox); $[\alpha]_D^{20} = +207$ (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.4 (s, br, 1H, OH), 1.52 (s, br, 6H), 2.44 (s, br, 4H, all H-piperidyl), 2.52–2.60 (m, 1H), 2.65–2.74 (m, 2H), 2.95–3.09 (m, 4H), 3.27–3.35 (m, 1H), 3.27 (d, $J = 12.0$ Hz, 2H, NCH_2pc), 6.09 (d, $J = 7.7$ Hz, 1H), 6.40 (d, $J = 7.7$ Hz, 1H), 6.52 (m, 2H), 6.68 (dd, $J = 7.7$ Hz, 1.4 Hz, 1H), 6.83 (dd, $J = 8.0$ Hz, 1.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.23, 26.07, 29.91, 32.67 (C-1, C-2, C-9, C-10), 34.24 (s), 54.45 (s), 59.46 (s, NCH_2pc), 121.42 (q), 124.19 (t), 125.41 (q), 126.11 (t), 127.15 (t), 132.60 (t), 132.87 (t), 133.02 (t), 137.54 (q), 139.66 (q), 140.04 (q, all C-Ar_{pc}), 156.69 (q, C-4) ppm; IR (KBr): $\nu = 2932$, 1598, 1567, 1500, 1451, 1432 cm^{-1}; MS (70 eV, EI), m/z (%): 321 (96) [M^+], 218 (16), 217 (100), 104 (37), 84 (45); HRMS $C_{22}H_{27}NO$ calcd: 321.2093, found: 321.2091.

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