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Synthesis of novel planar-chiral [2.2]paracyclophane derivatives as potential ligands for asymmetric catalysis

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Abstract

The synthesis of a variety of new 4,5-disubstituted [2.2]paracyclophane derivatives has been achieved employing different cross-coupling reactions. By this methodology, a heteroatom-variation of successful catalyst ligands was achieved, giving rise to a modular ligand system. The X-ray structure of 4-hydroxy-5-(1′-hydroxy-1′-phenylethyl)-[2.2]paracyclophane was determined to elucidate the configuration. Additionally, a diastereoselective synthesis of planar- and central-chiral 4-([2.2]paracyclophanyl)ethylamine was achieved, thus resulting in a planar- and central-chiral phenyl ethylamine analogue.

Keywords: [2.2]paracyclophane; Asymmetric catalysis; Cross-coupling reaction; Planar chirality

1. Introduction

The element of planar chirality plays an increasingly important role in modern Organometallic Chemistry. For example, ligands with a planar-chiral backbone are prominently used for the hydrogenation of carbon–carbon double-bonds, for the reduction of carbonyl and imino groups, for hydroboration, and others [1]. Especially, the field of [2.2]paracyclophane chemistry has developed considerably since these compounds first attracted the interest of chemists in the middle of the last century [2]. Recently, there has been notable progress, especially regarding the synthesis of new derivatives [3] and their applications in asymmetric catalysis [4]. In our group, we were able to employ 4,5-disubstituted bidentate N,O-ligands in the enantioselective organyl zinc addition to aldehydes [5], imines [6] and in the 1,4-addition to α,β-unsaturated aldehydes and ketones [7].

We herein report the synthesis of a variety of new 4,5-disubstituted [2.2]paracyclophane derivatives with different heteroatom combinations, providing potential ligands for the asymmetric catalysis.

2. Results and discussion

2.1. Variation of the substitution pattern in the 4-position

Our first target was to obtain variations of the successfully applied 4,5-disubstituted bidentate N,O-ligands (Fig. 1). We surmised that by changing the phenolic hydroxy-group to a softer amino function, we would obtain improved ligands for the 1,4-addition to α,β-unsaturated aldehydes or ketones (Fig. 1).

The strategy was to apply our newly developed Hartwig–Buchwald-amination for mono-substituted [2.2]paracyclophane-derivatives [8] towards 4,5-disubstituted [2.2]paracyclophane triflates [9] or nonaflates. These had to be synthesized starting from known phenols [10] (Table 1).

Reaction of 5-formyl-4-hydroxy[2.2]paracyclophane (FHPC) with sodium hydride and trifluoromethanesulfonic acid anhydride in toluene (entry 1) resulted in the desired product in very good 91% isolated yield [11]. Under the

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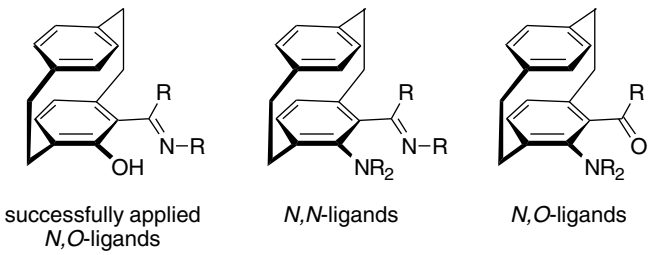


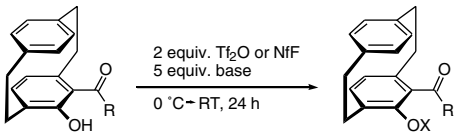
Fig. 1. Primary target molecules.

same reaction conditions, nonafluorobutanesulfonic acid fluoride (NfF) as reagent delivered no product (entry 2). By changing the solvent from toluene to DME, the corresponding nonaflate was isolated in excellent 95% yield (entry 3). By applying these conditions (DME and sodium hydride) and using Tf_2O instead of NfF, no triflate was obtained but the methoxy compound, 5-formyl-4-methoxy[2.2]paracyclophane, was synthesized (entry 4). This can either be explained by demethylation of monoglyme or by deprotonation of the monoglyme and elimination of methanolate and a subsequent nucleophilic aromatic substitution of the initially formed triflate with the methanolate. A direct application of respectively optimized conditions towards 5-benzoyl-4-hydroxy[2.2]paracyclophane (BHPC) resulted in the desired products in high yields (92% for the triflate and 99% for the nonaflate, entries 5 + 6). Further application of these conditions to enolizable 5-acetyl-4-hydroxy[2.2]paracyclophane (AHPC) did not result in the desired products. With sodium hydride as a strong base, the enolate was initially formed, which was subsequently converted to the α-trifluoromethanesulfonic- and α-nonafluorobutanesulfonic-derivative, respectively (entries 7 + 8). Applying weak amine bases like triethylamine, Hünig's base or pyridine resulted in no conversion. Only the use of the amidine base DBU (1,8-diazabicyclo[5.4.0]undecen-7-ene) gave trifluoromethanesulfonic acid-(5-acetyl-[2.2]paracyclophane-4-yl)ester in 25% yield (entry 9). To yield the corresponding imines, two approaches were possible: conversion of the literature known hydroxy-imines [12] to the triflates or condensation of the above synthesized triflates with α-chiral amines. For the AHPC- or BHPC-derived ketimines, the former was the method of choice (Scheme 1).

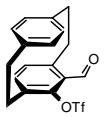
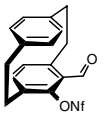
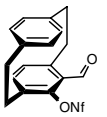
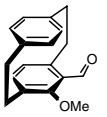
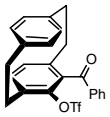
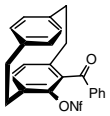
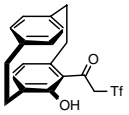
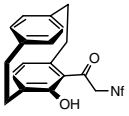
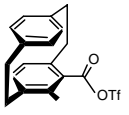
Starting from enantiomerically pure central- and planar-chiral ketimines **1** and **3**, the corresponding triflates **2** and **4** were synthesized in 49% and 41% isolated yield by the improved protocol of Table 1 without racemisation. For the FHPC-derived aldimines, the latter approach was superior (Scheme 2).

Condensation of the racemic aldehyde triflate **5** with enantiomerically pure (*S*)-phenyl ethylamine resulted in the diastereomeric aldimines (S_p,*S*)-**6** and (R_p,*S*)-**6** in 62% overall yield which could be separated by column chromatography. With these molecules in hand, we applied the BHPC triflate (Table 1, entry 5, **7**) exemplary in a Hartwig–Buchwald-reaction (Scheme 3).

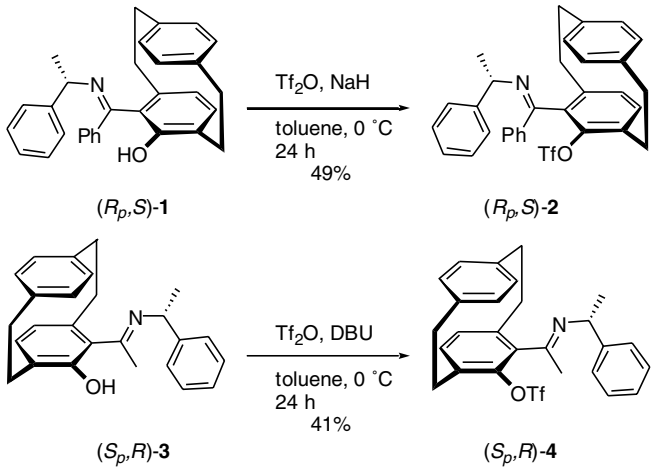
Table 1
Synthesis of perfluoroalkanesulfonic acid-(5-acyl-[2.2]paracyclophane-4-yl)esters



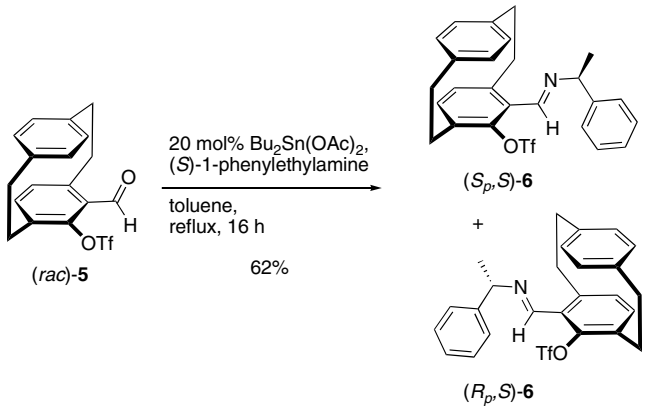
R= H, Ph, Me X = Tf or Nf

Entry	R	Base/ reagent	Solvent	Major Product	Yield [%]
1	H	NaH/ Tf_2O	Toluene		91
2	H	NaH/ NfF	Toluene		–
3	H	NaH/ NfF	DME		95
4	H	NaH/ Tf_2O	DME		84
5	Ph	NaH/ Tf_2O	Toluene		92
6	Ph	NaH/ NfF	DME		99
7	Me	NaH/ Tf_2O	Toluene		84
8	Me	NaH/ NfF	DME		79
9	Me	DBU/ Tf_2O	Toluene		25

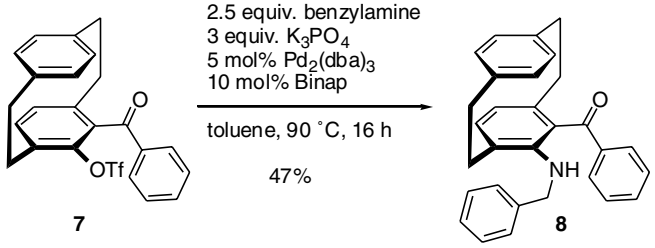
The reaction proceeded in 47% isolated yield with 5 mol% $Pd_2(dba)_3$ and 10 mol% racemic Binap as catalyst ligand, resulting in a novel 4,5-disubstituted *N*,*O*-[2.2]paracyclophane derivative. Standard transformations, like the condensation of **8** to an imine or the Hartwig–Buchwald-reaction of the imine triflate **4** to the aniline, will give rise to the second target class of Fig. 1, 4,5-disubstituted *N*,*N*-[2.2]paracyclophane derivatives. The synthesis of these derivatives is under investigation.



Scheme 1. Synthesis of the [2.2]paracyclophane ketimine triflates **2** and **4**.



Scheme 2. Synthesis of [2.2]paracyclophane aldimines triflate **6**.



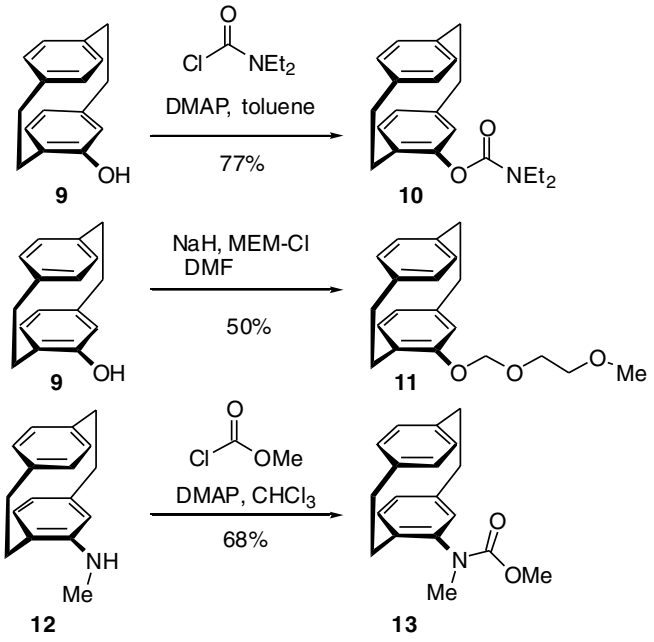
Scheme 3. Hartwig–Buchwald-reaction of a 4,5-disubstituted [2.2]paracyclophane triflate **7**.

2.2. Novel substitution patterns

One of the main problems in the synthesis of disubstituted [2.2]paracyclophanes is the lack of regioselectivity for the second substitution reaction. For example, the electrophilic bromination of 4-bromo[2.2]paracyclophane yields four different stereoisomers [13]. Until now, a general route for a variety of different 4,5-disubstituted [2.2]paracyclophanes is still elusive. Our approach incorporates the directed *ortho* metallation (D*o*M) of mono-substituted [2.2]paracyclophanes [14] and the subsequent reaction with an halide electrophile. These can then be used as starting materials for further variations via cross-coupling reactions. To achieve this goal, 4-substituted [2.2]paracyclophanes with *ortho* directing groups had to be synthesized initially [15] (Scheme 4).

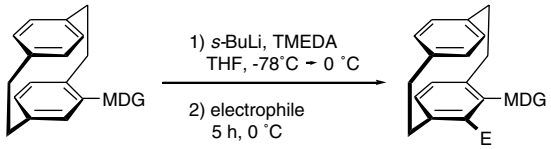
Both oxygen-bound derivatives **10** and **11** were prepared in 77% and 50%, respectively, starting from literature known 4-hydroxy[2.2]paracyclophane (**9**). Synthesis of nitrogen-bound [2.2]paracyclophane **13** underwent smoothly in 68% yield using (*N*-methyl)-(*N*-4-[2.2]paracyclophanyl)amine and methoxycarbamoylchloride in chloroform. Synthesis of the carbamic acid *t*-butylester with *t*-butylcarbamic acid anhydride, on the other hand, resulted in no conversion. The obtained [2.2]paracyclophane derivatives were applied in a D*o*M [16] with a subsequent electrophilic substitution (see Table 2).

Different combinations of electrophile and [2.2]paracyclophane derivative were tested. Reaction of iodine with the MEM-derivative gave no conversion (entry 1) whereas only the demethylation product, 4-[2.2]paracyclophanylcarbamic acid methylester, was obtained as a result of the reaction of the *N*-methylcarbamate with *s*-BuLi (entry 2). Only with *O*-(4-[2.2]paracyclophanyl) diethylcarbamate as substrate, the D*o*M succeeded. Where iodine as electrophile only resulted in poor 5% conversion towards the desired product (entry 3) and bromine resulted in no conversion at all (entry 4), 1,2-diiodoethane was the electrophile of choice. Here, a good conversion of 66% to the desired 4,5-disubstituted [2.2]paracyclophane-derivative was achieved (entry 5). With the product in hand, we were now able to apply it to a palladium-catalyzed C–S-bond-forming reaction (see Scheme 5).



Scheme 4. Synthesis of [2.2]paracyclophanes with *ortho* directing groups.

Table 2
Directed *ortho* metallation



MDG = metal directing group E = Br or I

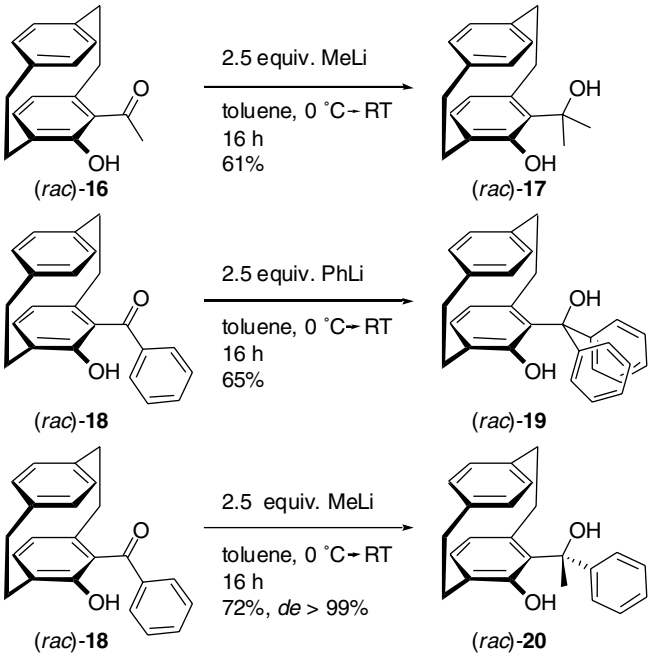
Entry	MDG	Electrophile	Yield (%)
1	OMEM	I_2	–
2	N(Me)C(O)OMe	ICH_2CH_2I	–[a]
3	$OC(O)NEt_2$	I_2	5
4	$OC(O)NEt_2$	Br_2	–
5	$OC(O)NEt_2$	ICH_2CH_2I	66 [17]

[a] Main product is the demethylation product.

The reaction of the sterically hindered *O*-(5-iodo-[2.2]paracyclophan-4-yl)diethyl carbamate (**14**) with triisopropylsilanylthiole (TIPS-SH), cesium carbonate and $Pd(PPh_3)_4$ in toluene at 100 °C resulted in the desired *O*-(5-(4-triisopropylsilanylsulfuryl)-[2.2]paracyclophanyl)diethyl carbamate (**15**) in 38% isolated yield [18]. This product is especially noteworthy because it can be synthesized as an enantiomerically pure compound, starting from known enantiomerically pure 4-hydroxy-[2.2]paracyclophane. Further investigations in this product are in progress.

Another interesting group of compounds are [2.2]paracyclophane derivatives with a stereogenic center in α-position to the [2.2]paracyclophane backbone [19]. With two substituents, these could be utilized as ligands in the asymmetric catalysis and mono-substituted as planar- and central-chiral phenyl ethylamine analogues. Initially, the nucleophilic attack of methyllithium and phenyllithium to AHPC and BHPC was tested (see Scheme 6).

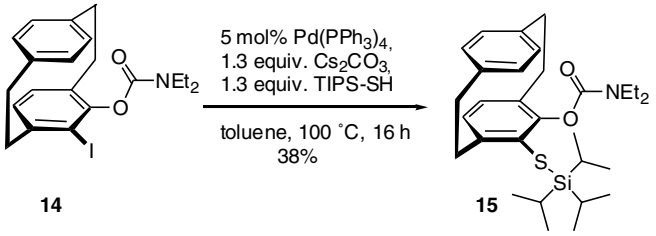
Both addition of methyllithium to AHPC (**16**) and of phenyllithium to BHPC (**18**) resulted in the corresponding tertiary alcohol in good yields (61% and 65%, respectively). Especially notable was the addition of methyllithium to **18**. The resulting product **20** was obtained in 72% yield as a single diastereomer. A X-ray analysis of the product proved, that the (S_p,*S*)-, (R_p,*R*)-diastereomer was the sole diastereomer obtained. This can be explained by the conformational fixation of the starting material due to hydrogen-bonding between the phenolic hydroxyl-group and the carbonyl-group (Fig. 2). The nucleophilic attack of the methyllithium is effectively blocked from one side by the [2.2]paracyclophane-backbone [20], which leads to the observed stereoselectivity.



Scheme 6. Nucleophilic addition to AHPC (**16**) and BHPC (**18**).

Compound **19** is another interesting product. Under weak acidic conditions like treatment with silica gel or acetic acid, water is eliminated resulting in a stable monodearomatized diphenylmethylenecyclohexa-2,4-dienone **21** (see Schemes 7).

The intermediary cation should be very stable due to the sterically demanding [2.2]paracyclophane as well as its electronic properties, comparable to the trityl cation.



Scheme 5. Palladium-catalyzed C–S-bond-formation of **14**.

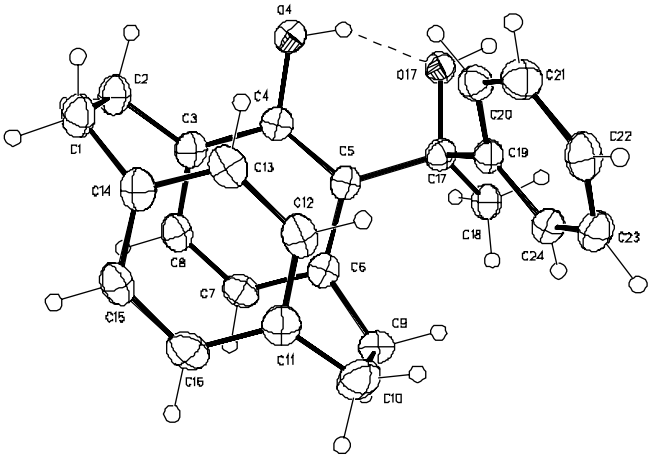
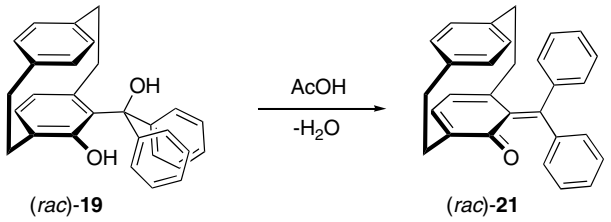


Fig. 2. X-ray structure of (R_p,*R*)/(S_p,*S*)-**20**, only one enantiomer is shown.

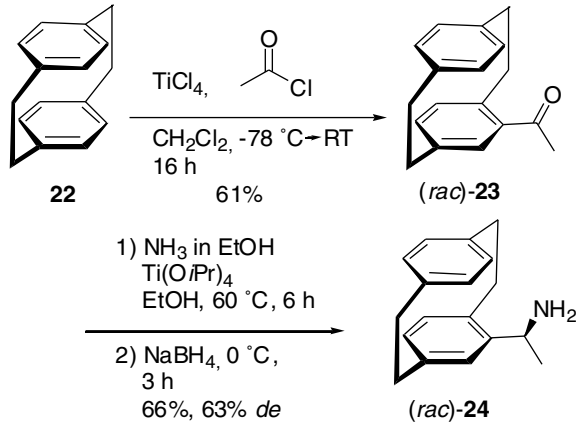


Scheme 7. Elimination of water from **19**.

Having established a route to disubstituted [2.2]paracyclophane-derivatives with a stereogenic center in α-position, we tried to synthesize the mono-substituted analogues (see Schemes 8).

Starting from [2.2]paracyclophane, the synthesis of 4-acetyl-[2.2]paracyclophane (**23**) with acetyl chloride and $TiCl_4$ proceeded in 61% isolated yield [21]. Reduction with $NaBH_4$ and $Ti(OiPr)_4$ resulted in the corresponding secondary alcohol in good 86% yield but poor 47% diastereomeric excess (not shown). Superior results could be achieved by reductive amination of **23** with NH_3 in ethanol and subsequent treatment with $NaBH_4$. The resulting planar- and central-chiral 1-[2.2]paracyclophane-4-ylethylamine (**24**) could be obtained in 66% yield and 63% diastereomeric excess. Further purification by column chromatography resulted in a diastereomeric excess >95%. Since the synthesis of enantiomerically pure **23** is known [22], **24** can be synthesized enantiomerically pure as well. An upscaling of the reaction to 5 g of starting material did not pose any obstacles, thus allowing the utilization of **24** as planar- and central-chiral phenyl ethylamine analogue for various applications.

In summary, we were able to synthesize a variety of 4,5-disubstituted 4-perfluoroalkanesulfonic acid- or 4-iodo-[2.2]paracyclophane derivatives as starting materials for two novel cross-coupling reactions. With two of these, a Hartwig–Buchwald-amination and a palladium-catalyzed C–S-bond forming reaction were exemplified, resulting in a heteroatom-variation of previously successfully employed catalyst ligands. Additionally, [2.2]paracyclophane derivatives with a stereogenic center in α-position to the [2.2]paracyclophane backbone were synthesized diastereoselectively. For one of these, 4-hydoxy-5-[1′-hydroxy-1′-phenylethyl)-[2.2]paracyclophane, the X-ray structure was determined to elucidate the three-dimensional structure and relative configuration.



Scheme 8. Diastereoselective synthesis of 1-[2.2]paracyclophane-1-yl-ethylamine (**24**).

3. Experimental

3.1. General procedure

All reactions were carried out under argon atmosphere. FHPC, AHPC and BHPC were synthesized according to literature. Other reagents were commercially available and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC300 (250 MHz/67 MHz), Bruker AM400 (400 MHz/100 MHz) or Bruker DRX500 (500 MHz/125 MHz), using $CDCl_3$ as the solvent and shift reference ($CHCl_3$ 7.26 ppm/77.00 ppm). Signals with an asterix * are interchangeable among themselves. The MS spectras were recorded on a Finnigan MAT 90. Elemental analyses were measured on a Heraeus CHN–O-Rapid. The IR spectras were recorded on a Bruker IFS 88. Optical rotations were determined on a Perkin Elmer 241 polarimeter (Na, 589 nm). Solvents were purified according to standard procedures.

3.2. General procedure for the synthesis of perfluoroalkanesulfonic acid esters

A 50-ml Schlenk-flask was flame-dried under a stream of argon and allowed to cool to room temperature. It was charged with hydroxy-[2.2]paracyclophane (1.0 equiv.) and mineral oil free NaH or DBU (5.0 equiv.) in abs. toluene or DME under an argon atmosphere. The reaction mixture was cooled to 0 °C and trifluoromethanesulfonic acid anhydride or nonafluorobutanesulfonic acid fluoride (2.5 equiv.) was added slowly. The suspension was stirred for another 5 min at 0 °C and was subsequently warmed to room temperature and stirred for 24 h. Saturated NH_4Cl_{aq} and diethyl ether were added and the mixture was transferred into a separatory funnel and the organic layer was washed with brine. The collected organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo.

3.3. Nonafluorobutanesulfonic acid-(5-formyl-[2.2]paracyclophane-4-yl)ester (Table 1, entry 3)

The product was synthesized in DME with NaH as base on a 100-mg (0.35 mmol) scale. The crude product was purified by flash chromatography (cyclohexane/DME 20:1) to yield 180 mg (0.34 mmol, 95%) of the title compound as a white waxy solid. $R_f = 0.19$ (cyclohexane/DME 20:1); ^1H NMR (250 MHz, $(CD_3)_2CO$): $\delta = 10.17$ (s, 1H, C*H*O), 7.07 (d, $J = 8.0$ Hz, 1H, H-7*), 6.94 (d,

$J = 8.0$ Hz, 1H, H-8*), 6.82 (dd, $J = 7.9$ Hz, 1.9 Hz, 1H, H_{Ar}), 6.77 (dd, $J = 8.0$ Hz, 1.9 Hz, 1H, H_{Ar}), 6.65 (dd, $J = 7.9$ Hz, 1.9 Hz, 1H, H_{Ar}), 6.45 (dd, $J = 7.9$ Hz, 1.9 Hz, 1H, H_{Ar}), 4.20–3.95 (m, 1H, CH_2), 3.55–2.95 (m, 7H, CH_2) ppm; ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$): $\delta = 189.8$ (*C*HO), 148.9 (q), 147.7 (q), 142.1 (q), 142.1 (t), 140.9 (t), 137.7 (t), 135.6 (t), 135.5 (q), 134.6 (t), 132.9 (t), 131.2 (q), 130.6 (t), 115–100 (m, 4C, C_4F_9), 35.3, 35.1, 34.3, 32.0 (Pc–C-1, C-2, C-9, C-10) ppm; ^{19}F NMR (376 MHz, $(CD_3)_2CO$): $\delta = -81.0$ to -81.1 (m, 3F, CF_3), -110.0 to -110.1 (m, 2F, CF_2), -121.1 to -121.2 (m, 2F, CF_2), -126.2 to -126.3 (m, 2F, CF_2) ppm; FTIR (KBr) $\nu = 2939$, 1689, 1596, 1474, 1398, 1354, 1205, 1143, 885 cm^{-1}, EI-MS *m*/*z* (relative intensity) 534 (34) [M^+], 251 (42) [M^+–Nf], 147 (47) [M^+–Nf–C_8H_8], 104 (100) [$C_8H_8^+$]; HRMS (*m*/*z*) $C_{21}H_{15}SO_4F_9$: calc. 534.0547, found 534.0551.

3.4. Trifluormethanesulfonic acid-(5-benzyl-[2.2]paracyclophane-4-yl)ester (Table 1, entry 5)

The product was synthesized in toluene with NaH as base on a 200-mg (0.61 mmol) scale. The crude product was purified by flash chromatography (cyclohexane/DME 20:1) to yield 258 mg (0.56 mmol, 92%) of the title compound as a white waxy solid. $R_f = 0.34$ (cyclohexane/DME 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 6.6$ Hz, 2H, Ph–H-2), 7.56 (tt, $J = 7.6$ Hz, 1.3 Hz, 1H, Ph–H-4), 7.41 (t, $J = 7.6$ Hz, 2H, Ph–H-3), 6.95–6.90 (m, 2H, Pc–H_{Ar}), 6.71 (d, $J = 7.9$ Hz, 1H, Pc–H-7 or H-8), 6.65–6.60 (m, 3H, Pc–H_{Ar}), 3.35 (ddd, $J = 13.7$ Hz, 10.0 Hz, 3.7 Hz, 1H, CH_2), 3.19 (ddd, $J = 13.2$ Hz, 9.8 Hz, 4.4 Hz, 1H, CH_2), 3.01 (ddd, $J = 13.1$ Hz, 10.1 Hz, 3.7 Hz, 1H, CH_2), 2.95–2.70 (m, 4H, CH_2), 2.53 (ddd, $J = 13.7$ Hz, 8.9 Hz, 4.9 Hz, 1H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 192.6$ (*C*HO), 144.0 (q), 142.2 (q), 139.4 (q), 138.7 (q), 138.1 (q), 137.4 (t), 133.9 (t), 133.8 (q), 133.6 (t), 132.6 (t), 132.2 (t), 132.1 (t), 131.2 (q), 130.5 (t, 2C, Ph–C-2*), 129.6 (t), 128.5 (t, 2C, Ph–C-3*), 118.3 (q, $J = 320.4$ Hz, 1C, *C*F$_3$), 34.9, 34.3, 34.2, 31.1 (Pc–C-1, C-2, C-9, C-10) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -73.8$ (s, 3F, CF_3) ppm; FTIR (KBr) $\nu = 2939$, 1670, 1597, 1420, 1215, 969, 882 cm^{-1}; EI-MS *m*/*z* (relative intensity) 460 (9) [M^+], 223 (16) [M^+ – Tf], 104 (18) [$C_8H_8^+$], 43 (100) [$C_2H_3O^+$]; HRMS (*m*/*z*) $C_{24}H_{19}F_3O_4S$: calc. 460.0956, found 460.0959.

3.5. Nonafluorobutanesulfonic acid-(5-benzyl-[2.2]paracyclophane-4-yl)ester (Table 1, entry 6)

The product was synthesized in DME with NaH as base on a 200-mg (0.61 mmol) scale. No further purification was necessary to yield 371 mg (0.608 mmol, 99%) of the title compound as a white waxy solid. ^{1}H NMR (250 MHz, $(CD_3)_2CO$): $\delta = 7.79$ (d, $J = 7.5$ Hz, 2H, Ph–H-2), 7.65–7.55 (m, 1H, Ph–H-4), 7.47 (t, $J = 7.5$ Hz, Ph–H-3), 6.9–6.7 (m, 6H, Pc–H_{Ar}), 3.5–2.5 (m, 8H, CH_2) ppm; ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$): $\delta = 193.9$ (*C*HO), 145.8 (q), 144.4 (q), 141.2 (q), 140.7 (q), 140.1 (q), 139.6 (t), 136.3 (t), 135.6 (q), 135.4 (t), 134.8 (t), 134.3 (t), 133.6 (t), 133.0 (q), 131.9 (t), 131.1 (t, 2C, Ph–C-2*), 130.4 (t, 2C, Ph–C-3*), 36.3, 35.8, 35.6, 32.6 (Pc–C-1, C-2, C-9, C-10) ppm; FTIR (KBr) $\nu = 2937$, 1672, 1597, 1423, 1242, 968, 883 cm^{-1}; EI-MS *m*/*z* (relative intensity) 610 (14) [M^+], 223 (43) [PcO^+], 105 (54) [$PhCO^+$], 104 (78) [$C_8H_8^+$], 43 (100) [$C_2H_3O^+$]; HRMS (*m*/*z*) $C_{27}H_{19}F_9O_4S$: calc. 610.0860, found 610.0865.

3.6. Trifluormethanesulfonic acid-(5-acetyl-[2.2]paracyclophane-4-yl)ester (Table 1, entry 9)

The product was synthesized in toluene with DBU as base on a 500-mg (1.88 mmol) scale. The crude product was purified by flash chromatography (cyclohexane/DME/triethylamine 20:1:1) to yield 188 mg (0.472 mmol, 25%) of the title compound as a white waxy solid in a mixture of ketone and enol form. $R_f = 0.35$ (cyclohexane/DME/triethylamine 20:1:1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.98$ (dd, $J = 7.9$ Hz, 1.5 Hz, 1H, H_{Ar}), 6.91 (d, $J = 7.9$ Hz, 1H, H_{Ar}), 6.5–6.0 (m, 4H, H_{Ar}), 3.5–2.2 (m, 8H, CH_2), 2.18 (s, 3H, Me) ppm, ^{13}C NMR (62.5 MHz, $CDCl_3$): A total attribution of the signals was not possible due to the keto-enol tautomerisation. Therefore only unambiguous carbonyl carbon of the keto form is given. $\delta = 204.4$ (*C*O) ppm; FTIR (KBr, tautomeric mixture) $\nu = 3506$, 2930, 2854, 1614, 1418, 1210, 909, 797, 732 cm^{-1}; EI-MS *m*/*z* (relative intensity) 398 (22) [M^+], 265 (15) [$M^+ - Tf$], 161 (62) [$M^+ - SO_2CF_3 - C_8H_8^+$], 104 (100) [$C_8H_8^+$]; HRMS (*m*/*z*) $C_{19}H_{17}F_3O_4S$: calc. 398.0799, found 398.0794.

3.7. (R_p,S)-Trifluormethanesulfonic acid-(4-[2.2]paracyclophanyl)-5-phenyl-(1′-phenylethyliminophenylmethyl)-ester (**2**)

The product was synthesized in toluene with NaH as base in a 200-mg (0.463 mmol) approach. The crude product was purified by flash chromatography (cyclohexane/DME/triethylamine 40:2:1) to yield 128 mg (0.227 mmol, 49%) of the title compound as an orange-yellow solid. $R_f = 0.38$ (cyclohexane/DME/triethylamine 40:2:1); $[\alpha]_{589}^{293} = +50.5°$ ($c = 1.00$ g/100 ml, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.6-7.5$ (m, 2H, H_{Ar}), 7.45–7.20 (m, 9 H, H_{Ar}), 6.82 (bd, $J = 8.0$ Hz, 1H, H_{Ar}), 6.70–6.65 (m, 2H, H_{Ar}), 6.58 (d, $J = 7.9$ Hz, 1H, Pc–H-7*), 6.48 (d, $J = 7.9$ Hz, 1H, Pc–H-8*), 5.13 (q, $J = 6.4$ Hz, 1H, NC*H*(Ph)-Me), 3.5–2.7 (m, 8H, CH_2), 1.83 (d, $J = 6.4$ Hz, 3H, Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.6$ (*C*N), 141.4 (q), 139.3 (q), 138.8 (q), 135.9 (q), 135.8 (t), 134.7 (t), 134.2 (q), 133.1 (q), 132.4 (t), 132.2 (t), 132.1 (t), 130.4 (t), 129.1 (t), 128.8 (2C, Ph–C-2*), 128.6 (q), 128.3 (2C, Ph–C-3*), 127.9 (2C, Ph–C-2*), 126.7 (t), 126.6 (2C, Ph–C-3*), 118.1 (q, 1C, *C*F$_3$), 61.8 (*C*HNMe), 34.7, 34.5, 33.5, 30.9 (Pc–C-1, C-2, C-9, C-10), 27.3 (Me) ppm; FTIR

(KBr) $\nu = 2936$, 1893, 1615, 1494, 1386, 1208, 963, 700 cm^{-1}; EI-MS m/z (relative intensity) 563 (2) [M^+], 430 (3) [$M^+ - Tf$], 105 (4) [$C_8H_9^+$], 43 (100) [$C_3H_7^+$]; HRMS (m/z) $C_{32}H_{28}F_3NO_3S$: calc. 563.1742, found 563.1747.

3.8. (R_p,S)-Trifluormethanesulfonic acid-(4-[2.2]paracyclophanyl)-5-(1'-phenylethyliminoethyl)ester (**4**)

The product was synthesized in toluene with DBU as base in a 250-mg (0.676 mmol) approach. The crude product was purified by flash chromatography (cyclohexane/DME/triethylamine 20:1:1) to yield 140 mg (0.279 mmol, 41%) of the title compound as an orange-yellow oil. $R_f = 0.47$ (cyclohexane/DME/triethylamine 20:1:1); ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 7.2$ Hz, 2H, Ph–H-2), 7.42 (t, $J = 7.2$ Hz, 2H, Ph–H-3), 7.31 (t, $J = 7.2$ Hz, 1H, Ph–H-4), 6.99 (dd, $J = 7.7$ Hz, 1.4 Hz, 1H, Pc–H_{Ar}), 6.76 (d, $J = 8.0$ Hz, 1H, Pc–H-7 or H-8), 6.65-6.55 (m, 2H, Pc–H_{Ar}), 6.46 (dd, $J = 7.9$ Hz, 1.8 Hz, 1H, Pc–H_{Ar}), 6.45-6.35 (m, 1H, Pc–H_{Ar}), 4.89 (q, $J = 6.6$ Hz, 1H, NC*H*(Ph)Me), 3.65 (ddd, $J = 14.0$ Hz, 9.5 Hz, 1.5 Hz, 1H, CH_2), 3.4–2.6 (m, 7H, CH_2), 2.24 (s, 3H, Me), 1.59 (d, $J = 6.6$ Hz, 3H, Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 161.5 (*C*N), 145.0 (q), 142.6 (q), 140.1 (q), 139.6 (t), 135.6 (t), 135.0 (q), 133.1 (t), 132.6 (q), 132.4 (q), 131.4 (t), 130.2 (t), 129.4 (q), 127.8 (t), 128.3 (2C, Ph–C-2*), 126.8 (2C, Ph–C-3*), 126.7 (t), 118.3 (q, 1C, *C*F_3), 60.4 (*C*H), 34.9, 34.4, 33.0, 30.7 (Pc–C-1, C-2, C-9, C-10), 26.9 (Me), 24.7 (Me) ppm; FTIR (KBr) $\nu = 2934$, 1579, 1420, 1204, 843 cm^{-1}; EI-MS m/z (relative intensity) 501 (2) [M^+], 161 (62) [$C_{10}H_{11}O_2^+$], 104 (59) [$C_8H_8^+$], 84 (100) [$C_5H_{10}N^+$]; HRMS (m/z) $C_{27}H_{26}F_3O_3NS$: calc. 501.1586, found 501.1588.

3.9. (R_p,S)- and (S_p,S)-Trifluormethanesulfonic acid-(4-[2.2]paracyclophanyl)-5-(1'-phenylmethyliminoethyl)ester (**6**)

To a stirred solution of (*rac*)-**5** (214 mg, 0.557 mmol) and dibutyltindiacetate (39 mg, 0.11 mmol) in 50 ml toluene, (*S*)-phenyl ethylamine (135 mg, 1.11 mmol) was added. The flask was equipped with a Dean–Stark-trap and a reflux-condenser and was refluxed for 24 h. Water and diethyl ether was added and the mixture was transferred into a separatory funnel and the organic layer was washed with brine. The collected organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (cyclohexane/triethylamine 33:1) to yield 167 mg (0.343 mmol, 62%) of the title compound as an orange oil. Due to partial (ca. 10%) degradation during the column chromatography back to the starting material, no NMR assignment of the signals was done. EI-MS m/z (relative intensity) 487 (4) [M^+], 354 (5) [$M^+ - Tf$], 105 (77) [$PhCO^+$], 104 (13) [$C_8H_8^+$], 43 (100) [$C_3H_7^+$]; HRMS (m/z) $C_{26}H_{24}F_3NO_3S$: calc. 487.1429, found 487.1424.

3.10. Benzyl-(5-benzoyl-[2.2]paracyclophane-4-yl)amine (**8**)

A sealable tube was charged with **7** (101 mg, 0.22 mmol, 1.0 equiv.), K_3PO_4 (140 mg, 0.66 mmol, 3.0 equiv.), $Pd_2(dba)_3$ (6 mg, 10 μmol, 5 mol%) and (*rac*)-Binap (14 mg, 20 μmol, 10 mol%). The vial was sealed afterwards. The sealed tube was evacuated and refilled with argon. This procedure was repeated three times. Dry toluene (5 ml) and benzyl amine (150 mg, 1.40 mmol, 6.4 equiv.) were added subsequently via syringe. The solution turned deep red and was warmed to 70 °C for 24 h. After cooling to room temperature, 5 ml of saturated aqueous Na_2CO_3 solution were added. The reaction contents were transferred to a separatory funnel and extracted twice with diethyl ether. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (cyclohexane/dichloromethane 2:1) to yield 43 mg (0.10 mmol, 47%) of the title compound as a yellow oil. $R_f = 0.06$ (cyclohexane/dichloromethane 2:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 7.5$ Hz, 2H, H_{Ar}), 7.50 (t, $J = 7.7$ Hz, 1H, H_{Ar}), 7.36 (t, $J = 7.7$ Hz, 2H, H_{Ar}), 7.20–7.05 (m, 4H, H_{Ar}), 6.59 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 6.55 (d, $J = 7.6$ Hz, 2H, H_{Ar}), 6.29 (d, $J = 7.7$ Hz, 1H, H_{Ar}), 4.30 (d, $J = 14.5$ Hz, 1H, C*H*HNH), 3.99 (d, $J = 14.5$ Hz, 1H, C*H*HNH), 3.42 (ddd, $J = 12.6$ Hz, 9.2 Hz, 2.8 Hz, 1H, Pc–CH_2), 3.22 (ddd, $J = 13.0$ Hz, 9.1 Hz, 6.3 Hz, 1H, Pc–CH_2), 3.1–3.0 (m, 1H, Pc–CH_2), 2.9–2.6 (m, 4H, Pc–CH_2), 2.55–2.45 (m, 1H, Pc–CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0 (*C*HO), 143.3 (q), 142.0 (q), 141.1 (q), 139.5 (q), 139.1 (t), 138.4 (q), 132.2 (t, 2C), 131.9 (t), 131.7 (q), 130.9 (t), 130.5 (q), 129.3 (t, 2C), 128.9 (t), 128.5 (t), 128.4 (q), 128.3 (t, 2C), 128.1 (t, 2C), 127.2 (t), 126.9 (t), 125.4 (q), 53.7 (*C*H_2N), 36.0, 34.9, 34.3, 34.1 (Pc–C-1, C-2, C-9, C-10) ppm; FTIR (KBr) $\nu = 3416$, 2929, 1623, 1575, 1495, 1285, 1101, 965, 698 cm^{-1}; EI-MS m/z (relative intensity) 417 (64) [M^+], 313 (35) [$M^+ - C_8H_8$], 312 (80) [$M^+ - C_7H_5O$], 234 (98) [$M^+ - C_6H_5 - C_7H_8N$] 131 (65) [$C_9H_9N^+$], 103 [$C_8H_7^+$]; HRMS (m/z) $C_{30}H_{27}ON$: calc. 417.2092, found 417.2094.

3.11. 4-(2-Methoxy-ethoxymethoxy)-[2.2]paracyclophane (**11**)

A 25-ml Schlenk-flask was flame-dried under a stream of argon and allowed to cool to room temperature. It was charged with 4-hydroxy-[2.2]paracyclophane (1.0 equiv.) and mineral oil-free NaH (96 mg, 4.0 mmol) in abs. DMF under an argon atmosphere. MEM-Cl (142 mg, 1.15 mmol) was added slowly over a period of 15 min. The reaction mixture was stirred for 16 h at room temperature. NH_{4aq} and diethyl ether were added and the mixture was transferred into a separatory funnel and the organic layer was washed with brine. The collected organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified

by column chromatography (cyclohexane/ethyl acetate 5:1) to yield 140 mg (0.50 mmol, 50%) of the title compound as a white solid. $R_f = 0.41$ (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.79$ (dd, $J = 7.8$ Hz, 1.8 Hz, 1H, H_{Ar}), 6.54 (dd, $J = 7.8$ Hz, 1.9 Hz, 1H, H_{Ar}), 6.46–6.38 (m, 3H, H_{Ar}), 6.29 (dd, $J = 7.7$ Hz, 1.6 Hz, 1H, H_{Ar}), 5.96 (d, $J = 1.8$ Hz, 1H, Pc–H-5), 5.27 (d, $J = 6.7$ Hz, 1H, OC*H*HO), 5.16 (d, $J = 6.7$ Hz, 1H, OC*H*HO), 4.00–3.80 (m, 2H, OCH_2CH_2), 3.60–3.57 (m, 2H, OCH_2CH_2), 3.50–3.35 (m, 1H, Pc–CH_2), 3.41 (s, 3H, Me), 3.15–2.95 (m, 6H, Pc–CH_2), 2.62 (ddd, $J = 12.9$ Hz, 8.6 Hz, 7.3 Hz, 1H, Pc–CH_2) ppm; FTIR (KBr) $\nu = 3362$, 2927, 1701, 1597, 1416, 1160, 718 cm^{-1}; EI-MS *m/z* (relative intensity) 312 (16) [M^+], 224 (33) [PcOH$^+$], 208 (10) [$M^+ - C_8H_8$], 120 (39) [$C_8H_8O^+$], 104 (100) [$C_8H_8^+$]; HRMS (*m/z*) $C_{20}H_{24}O_3$: calc. 312.1725, found 312.1727.

3.12. N-Methyl-(N-4-[2.2]paracyclophanyl)carbamic acid methyl ester (**13**)

A 50 ml flask was charged with *N*-methyl-(*N*-4-[2.2]paracyclophanyl)amine (41 mg, 0.17 mmol), DMAP (63 mg, 0.52 mmol) and methoxycarbamic acid chloride (33 mg, 0.35 mmol) in 1 ml pyridine and 10 ml $CHCl_3$. The reaction mixture was stirred for 16 h at room temperature. Water and diethyl ether were added and the mixture was transferred into a separatory funnel and the organic layer was washed with brine. The collected organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to yield 34 mg (0.12 mmol, 68%) of the title compound as a yellow solid. $R_f = 0.35$ (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.70$–6.60 (m, 2H, H_{Ar}), 6.53 (dd, $J = 8.0$ Hz, 1.5 Hz, 1H, H_{Ar}), 6.45–6.30 (m, 4H, H_{Ar}), 3.70 (bs, 3H, Me), 3.44 (s, 3H, Me), 3.20–2.90 (m, 8H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.2$ (*C*O), 141.1 (q), 139.7 (q), 139.6 (q), 139.2 (q), 139.1 (t), 135.2 (t), 135.0 (t), 132.8 (t), 132.3 (t), 132.1 (q), 132.0 (t), 128.1 (t), 37.5 (Me), 35.3, 35.2, 35.0 (C-1, C-9, C-10), 32.0 (Me), 26.8 (C-2) ppm; FTIR (KBr) $\nu = 3316$, 2927, 1703, 1595, 1448, 1347, 1152, 1063, 1016, 898, 797 cm^{-1}; EI-MS *m/z* (relative intensity) 295 (76) [M^+], 281 (16) [$M^+ - CH_3$], 191 (100) [$M^+ - C_8H_8$], 132 (50) [$C_8H_8NMe^+$]; HRMS *m/z* $C_{19}H_{21}NO_2$: calc. 295.1572, found 295.1570.

3.13. O-(5-(Iodo)-[2.2]paracyclophanyl)-N,N-diethylcarbamate (**14**)

A 25-ml Schlenk-flask was flame-dried under a stream of argon and allowed to cool to room temperature. It was charged with *O*-(4-[2.2]paracyclophanyl)-*N*,*N*-diethylcarbamate (200 mg, 0.62 mmol) and TMEDA (86 mg, 0.74 mmol) in abs. THF under an argon atmosphere. The solution was cooled to −78 °C and *s*-BuLi (1.3 M in hexane, 0.57 ml, 0.74 mmol) was added slowly over a period of 15 min. The solution was stirred for another 3 h at −78 °C. Diiodoethane (523 mg, 1.86 mmol) was added and the solution was allowed to slowly warm up to room temperature over a period of 5 h. 1 M hydrochloric acid and dichloromethane were added and the mixture was transferred into a separatory funnel and the organic layer was washed with brine. The collected organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (cyclohexane/DME 20:1) to yield 182 mg (0.41 mmol, 66%) of the title compound as a light yellow solid. $R_f = 0.12$ (cyclohexane/DME 20:1), ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.15$ (dd, $J = 7.9$ Hz, 1.6 Hz, 1H, H_{Ar}), 6.67 (dd, $J = 7.9$ Hz, 1.5 Hz, 1H, H_{Ar}), 6.58 (d, $J = 7.8$ Hz, 1H, H-7*), 6.56–6.51 (m, 2H, H_{Ar}), 6.44 (d, $J = 7.8$ Hz, 1H, H-8*), 3.80 (dq, $J = 14.2$ Hz, 7.1 Hz, 1H, NC*H*H), 3.56 (dq, $J = 14.2$ Hz, 7.1 Hz, 1H, NC*H*H), 3.50–3.35 (m, 7H, CH_2), 3.2–3.0 (m, 7H, CH_2), 2.9–2.8 (m, 1H, CH_2), 1.49 (t, $J = 7.1$ Hz, 3H, Me), 1.22 (t, $J = 7.1$ Hz, 3H, Me) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.6$ (q), 149.0 (q), 145.2 (q), 139.1 (q), 138.6 (q), 134.3 (t), 133.2 (t), 132.9 (t), 130.5 (t), 128.8 (t), 128.5 (t), 103.5 (C-4), 42.3 (N*C*H$_2$), 42.1 (N*C*H$_2$), 39.1, 34.5, 33.0, 31.7 (C-1, C-2, C-9, C-10), 14.7 (Me), 13.4 (Me) ppm; FTIR (KBr) $\nu = 2974$, 2933, 1720, 1421, 1239, 1153, 958, 799 cm^{-1}; EI-MS *m/z* (relative intensity) 449 (13) [M^+], 323 (30) [$M^+ - I$], 100 (100) [$CONEt_2^+$]; HRMS (*m/z*) $C_{21}H_{24}O_2NI$: calc. 449.0851, found 449.0847.

3.14. O-(5-(4-Triisopropylsilanylsulfuryl)-[2.2]paracyclophanyl)-N,N-diethylcarbamate (**15**)

A sealable tube was charged with **14** (270 mg, 0.601 mmol,), Cs_2CO_3 (255 mg, 0.781 mmol) and $Pd(PPh_3)_4$ (42 mg, 36 μmol, 5 mol%). The vial was sealed afterwards. The sealed tube was evacuated and refilled with argon. This procedure was repeated three times. Dry toluene (5 ml) and TIPS-SH (149 mg, 0.781 mmol) were added subsequently via syringe. The solution turned deep red and was warmed to 100 °C for 16 h. After cooling to room temperature, 5 ml of saturated aqueous NH_4Cl solution were added. The reaction contents were transferred to a separatory funnel and extracted twice with diethyl ether. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate 9:1) to yield 115 mg (0.225 mmol, 38%) of the title compound with ca. 20% deprotected arylthiol (due to deprotection during the column chromatography) as a yellow oil. $R_f = 0.28$ (cyclohexane/ethyl acetate 9:1); ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 6.97$ (dd, $J = 7.8$ Hz, 1.7 Hz, 1H, H_{Ar}), 6.86 (dd, $J = 7.8$ Hz, 1.9 Hz, 1H, H_{Ar}), 6.75–6.68 (m, 2H, H_{Ar}), 6.60–6.40 (m, 2H, H_{Ar}), 3.90 (q, $J = 7.1$ Hz, 1H, NC*H*HCH$_3$), 3.7–2.7 (m, 11H, CH_2), 1.55–1.40 (m, 3H, C*H*), 1.1–0.9 (m, 24H, Me) ppm; ^{13}C NMR (62 MHz, $CDCl_3$). Due to the arylthiol-byproduct a total assignment

of the aromatic signals was impossible, therefore only the aliphatic signals are given. $\delta = 42.1$, 35.2, 34.8, 34.5, 34.2, 31.6 (Pc–C-1, C-2, C-9, C-10, 2× NCH_2CH_3), 18.5 ($CHCH_3$), 18.1 (Me), 18.0 (Me), 17.6 ($CHCH_3$), 12.6, 12.2 (*C*H) ppm; FTIR (KBr) $\nu = 2934$, 2864, 1717, 1460, 1409, 1240, 1157, 883 cm^{-1}, EI-MS *m*/*z* (relative intensity) 511 (1) [M^+], 131 (100) [$C_6H_7OMe^+$], HRMS (*m*/*z*) $C_{30}H_{45}NO_2SSi$: calc. 511.2940, found 511.2940.

3.15. 4-Hydroxy-5-(1′-hydroxy-1′-methyl-ethyl)-[2.2]paracyclophane (**17**)

A 25-ml Schlenk-flask was flame-dried under a stream of argon and allowed to cool to room temperature. It was charged with **16** (300 mg, 1.13 mmol) in abs. toluene under an argon atmosphere. The solution was cooled to 0 °C and MeLi (1.6 M in diethylether, 1.7 ml, 2.7 mmol) was added slowly over a period of 5 min. The solution was allowed to slowly warm up to room temperature over a period of 16 h. It was again cooled to 0 °C and 10 ml water were added and the suspension was stirred for another 30 min. Water and dichloromethane were added and the mixture was transferred into a separatory funnel and the organic layer was washed with brine. The collected organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified crystallization in cyclohexane/dichloromethane to yield 194 mg (0.688 mmol, 61%) of the title compound as yellow crystals. ^{1}H NMR (500 MHz, $(CD_3)_2CO$): $\delta = 9.73$ (s, 1H, Pc–O*H*), 6.78 (dd, $J = 7.9$ Hz, 1.9 Hz, 1H, H_{Ar}), 6.69 (dd, $J = 7.9$ Hz, 1.8 Hz, 1 H, H_{Ar}), 6.65–6.55 (m, 2H, H_{Ar}), 6.20 (d, $J = 7.5$ Hz, 1H, H-7*), 6.04 (d, $J = 7.5$ Hz, 1H, H-8*), 5.22 (s, 1H, $C(Me)_2OH$), 3.35–3.25 (m, 2H, CH_2), 3.1–2.9 (m, 2H, CH_2), 2.51 (ddd, $J = 12.8$ Hz, 10.1 Hz, 6.0 Hz, 1H, CH_2), 1.85 (s, 3H, Me), 1.50 (s, 3H, Me) ppm; ^{13}C NMR (125 MHz, $(CD_3)_2CO$): $\delta = 157.2$ (q), 142.0 (q), 140.0 (q), 139.8 (q), 135.8 (t), 134.5 (t), 133.9 (t), 133.4 (t), 130.8 (q), 130.0 (q), 130.0 (q), 128.8 (t), 77.6 (*C*H), 37.4, 37.1, 35.6 (C-1, C-2, C-9*), 34.2 (Me), 31.6 (C-10*), 30.8 (Me) ppm; FTIR (KBr) $\nu = 3353$, 2931, 1600, 1416, 1145, 797 cm^{-1}; EI-MS *m*/*z* (relative intensity) 282 (1) [M^+], 264 (28) [$M^+ - H_2O$], 159 (100) [$M^+ - H_2O - C_8H_9$]; HRMS (*m*/*z*) $C_{19}H_{22}O_2$: calc. 282.1620, found 282.1625.

3.16. 4-Hydroxy-5-(hydroxy-diphenyl-methyl)-[2.2]paracyclophane (**19**)

A 25-ml Schlenk-flask was flame-dried under a stream of argon and allowed to cool to room temperature. It was charged with **18** (100 mg, 0.305 mmol) in abs. toluene under an argon atmosphere. The solution was cooled to 0 °C and PhLi (2.0 M in diethylether, 0.4 ml, 0.8 mmol) was added slowly over a period of 5 min. The solution was allowed to slowly warm up to room temperature over a period of 16 h. It was again cooled to 0 °C and 10 ml water were added and the suspension was stirred for another 30 min. Water and diethylether were added and the mixture was transferred into a separatory funnel and the organic layer was washed with brine. The collected organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (cyclohexane/DME 20:1) to yield 81 mg (0.20 mmol, 65%) of the title compound as light yellow crystals. $R_f = 0.14$ (cyclohexane/DME 20:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.53$ (d, $J = 7.2$ Hz, 2H, Ph–H_{Ar}), 7.36 (t, $J = 6.9$ Hz, 2H, Ph–H_{Ar}), 7.34 (t, $J = 8.1$ Hz, 1H, Ph–H_{Ar}), 7.30 (t, $J = 7.5$ Hz, 2H, Ph–H_{Ar}), 7.25–7.15 (m, 3H, Ph–H_{Ar}), 7.07 (d, $J = 6.6$ Hz, 2H, Ph–H_{Ar}), 6.94 (dd, $J = 7.8$ Hz, 1.9 Hz, 1H, Pc–H_{Ar}), 6.6–6.4 (m, 3H, Pc–H_{Ar}), 6.48 (d, $J = 7.5$ Hz, 1H, Pc–H-7*), 6.24 (d, $J = 7.5$ Hz, 1H, Pc–H-8*), 3.79 (s, 1H, O*H*), 3.26 (ddd, $J = 13.2$H, 10.0 Hz, 3.5 Hz, 1H, CH_2), 3.12 (ddd, $J = 13.2$ Hz, 9.4 Hz, 4.9 Hz, 1H, CH_2), 3.06 (ddd, $J = 13.2$ Hz, 10.2 Hz, 3.1 Hz, 1H, CH_2), 2.82 (ddd, $J = 13.0$ Hz, 10.3 Hz, 2.4 Hz, 1H, CH_2), 2.64 (ddd, $J = 13.3$ Hz, 10.3 Hz, 5.4 Hz, 1H, CH_2), 2.47 (ddd, $J = 13.2$ Hz, 9.9 Hz, 6.8 Hz, 1H, CH_2), 2.32 (ddd, $J = 14.1$ Hz, 9.9 Hz, 6.8 Hz, 1H, CH_2), 1.62 (ddd, $J = 14.1$ Hz, 9.8 Hz, 2.3 Hz, 1H, CH_2), ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 154.8$ (q), 149.4 (q), 146.0 (q), 141.7 (q), 139.8 (q), 139.0 (q), 135.4 (t), 133.2 (t), 132.1 (t), 131.7 (t), 129.2 (t), 128.1 (2C, Ph), 128.0 (2C, Ph), 127.7 (t), 127.0 (t), 126.9 (t), 126.6 (2C, Ph), 125.4 (2C, Ph), 81.1 (CR_3OH), 36.3, 35.9, 33.9, 29.9 (Pc–C-1, C-2, C-9, C-10) ppm; FTIR (KBr) $\nu = 3449$, 2925, 1624, 1501, 762, 697 cm^{-1}; EI-MS *m*/*z* (relative intensity) 404 (6) [M^+], 388 (46) [$M^+ - H_2O$], 283 (47) [$M^+ - C_8H_9 - H_2O$], 104 (10) [$C_8H_8^+$], 84 (100) [$C_5H_8O^+$].

3.17. (R_p,*R*) and (S_p,*S*)-4-Hydroxy-5-(1′-hydroxy-1′-phenyl-ethyl)-[2.2]paracyclophane (**20**)

A 25-ml Schlenk-flask was flame-dried under a stream of argon and allowed to cool to room temperature. It was charged with **18** (300 mg, 0.914 mmol) in abs. toluene under an argon atmosphere. The solution was cooled to 0 °C and MeLi (1.6 M in diethylether, 1.4 ml, 2.1 mmol) was added slowly over a period of 5 min. The solution was allowed to slowly warm up to room temperature over a period of 16 h. It was again cooled to 0 °C and 10 ml water were added and the suspension was stirred for another 30 min. Water and diethylether were added and the mixture was transferred into a separatory funnel and the organic layer was washed with brine. The collected organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by crystallization in cyclohexane/dichloromethane to yield 226 mg (0.657 mmol, 72%) of the title compound as yellow crystals. ^{1}H NMR (250 MHz, $(CD_3)_2CO$): $\delta = 9.90$ (s, 1H, PcO*H*), 7.86 (dd, $J = 7.7$ Hz, 1.3 Hz, 2H, Ph–H-2), 7.50 (t, $J = 7.7$ Hz, 2H, Ph–H-3), 7.39 (t, $J = 7.3$ Hz, 1H, Ph–H-4), 6.73 (d, $J = 7.9$ Hz, 1H, Pc–H_{Ar}), 6.55–6.50 (m, 2H, Pc–H_{Ar}), 6.22 (d, $J = 7.6$ Hz, 1H, Pc–H-7*), 5.96 (d, $J = 7.6$ Hz, 1H, Pc–H-8*), 5.77 (d, $J = 7.7$ Hz, 1H,

Pc–H_{Ar}), 5.77 (s, 1H, C(Me)(Ph)O*H*), 3.39 (ddd, $J = 12.7$ Hz, 9.6 Hz, 3.6 Hz, 1H, CH_2), 3.0–2.7 (m, 4H, CH_2), 2.5–2.2 (m, 3H, CH_2), 1.89 (s, 3H, Me) ppm; ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$): $\delta = 156.7$ (q), 148.8 (q), 141.5 (q), 140.8 (q), 140.1 (q), 136.2 (t), 134.1 (t), 133.6 (q), 133.6 (t), 133.6 (t), 130.5 (q), 130.0 (t), 129.8 (2C, Ph–C-2*), 129.6 (t), 129.2 (2C, Ph–C-3*), 128.9 (t), 80.8 (*C*HOH), 37.3, 36.1, 35.7, 32.6 (Pc–C-1, C-2, C-9, C-10), 28.5 (Me) ppm; FTIR (KBr) $\nu = 3395$, 2936, 1596, 1415, 1273, 1058, 993, 911, 705 cm^{-1}; EI-MS *m*/*z* (relative intensity) 344 (2) [M^+], 326 (5) [$M^+ - H_2O$], 221 (38) [$M^+ - H_2O - C_8H_9$], 104 (29) [$C_8H_8^+$], 57 (100) [$C_3H_5O^+$]; HRMS (*m*/*z*) $C_{24}H_{24}O_2$: calc. 344.1776, found 344.1778.

3.18. 6-Benzhydrylidene-tricyclo-[8.2.2.2^{4,7}]hexadeca-1(13),4(16),7(15),10(14),11-pentaen-5-one (**21**)

A 50-ml flask was charged with the crude product of the synthesis of **19** and ethyl acetate/acetic acid 10:1 and was stirred for 1 h at room temperature. It was concentrated in vacuo and the crude product was purified by column chromatography (cyclohexane/DME 20:1) to yield 64 mg (0.16 mmol, 54% over 2 steps) of the title compound as light yellow crystals. $R_f = 0.08$ (cyclohexane/DME 20:1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.4$–7.0 (m, 10 H, Ph–H_{Ar}), 6.9–6.7 (m, 4H, Pc–H_{Ar}), 6.04 (d, $J = 6.6$ Hz, 1H, Pc–H-7*), 5.47 (d, $J = 6.6$ Hz, 1H, Pc–H-8*), 3.1–2.6 (m, 5H, CH_2), 2.25–2.05 (m, 2H, CH_2), 1.82 (ddd, $J = 14.1$ Hz, 9.5 Hz, 5.2 Hz, 1H, CH_2) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 187.2$ (*C*O), 155.5 (q), 145.2 (q), 145.1 (q), 144.1 (q), 143.0 (q), 140.2 (q), 139.3 (q), 138.6 (t), 137.7 (q), 133.8 (t), 132.4 (t), 131.9 (t), 130.9 (t), 129.5 (t), 128.9 (t), 128.0 (t), 127.8 (t), 127.7 (t), 36.0, 34.9, 33.9, 29.5 (Pc–C-1, C-2, C-9, C-10) ppm; FTIR (KBr) $\nu = 2925$, 1742, 1606, 1479, 844, 804 cm^{-1}; EI-MS *m*/*z* (relative intensity) 388 (10) [M^+], 283 (84) [$M^+ - C_8H_9$], 104 (100) [$C_8H_8^+$].

3.19. 1-[2.2]Paracyclophan-4-yl-ethylamine (**24**)

A sealable tube was charged with **23** (125 mg, 0.500 mmol), ammonia (2 M in ethanol, 1.25 ml, 2.5 mmol) and Ti(O*i*Pr)$_4$ (284 mg, 1.00 mmol). The vial was sealed afterwards. The sealed tube was evacuated and refilled with argon. This procedure was repeated three times. The solution was heated to 50 °C and was stirred for 6 h. The solution was cooled down to 0 °C and $NaBH_4$ (28 mg, 0.75 mmol) was added and the reaction mixture was stirred for another 3 h. The solution was combined with a 2-M aqueous solution of NH_4OH and a white solid precipitated. The precipitate was then filtered and washed with dichloromethane. The organic layer was separated and was extracted three times with 1 M hydrochloric acid. The combined aqueous layers were basified with NaOH and extracted thrice with dichloromethane yielding 83 mg (0.33 mmol, 66%) of the title compound as a light yellow solid in 63% de. It was possible to separate the diastereomers by column chromatography (dichloromethane/cyclohexane 9:1, 1% triethylamine) to yield the excess diastereomer with no detectable traces of the minor diastereomer. Excess diastereomer (R_p,*S*), (S_p,*R*) respectively. $R_f = 0.17$ (dichloromethane/cyclohexane 9:1, 1% triethylamine); ^{1}H NMR (excess diastereomer (R_p,*S*) (S_p,*R*), 250 MHz, $CDCl_3$): $\delta = 6.6$–6.3 (m, 7H, H_{Ar}), 4.06 (q, $J = 6.6$ Hz, 1H, C-1), 3.55 (ddd, $J = 13.1$ Hz, 9.7 Hz, 2.3 Hz, 1H, CH_2), 3.2–3.0 (m, 6H, CH_2), 2.91 (ddd, $J = 13.2$ Hz, 10.7 Hz, 5.9 Hz, 1H, CH_2), 1.52 (d, $J = 6.6$ Hz, 3H, Me) ppm; ^{13}C NMR (excess diastereomer (R_p,*S*) (S_p,*R*), 100 MHz, $CDCl_3$): $\delta = 144.5$ (q), 139.7 (q), 139.0 (q), 138.9 (q), 136.8 (q), 135.1 (t), 133.0 (t), 132.6 (t), 131.6 (t), 131.1 (t), 129.4 (t), 128.4 (t), 46.8 (*C*H(NH_2)Me), 34.9, 34.8, 34.3, 32.9 (Pc–C-1, C-2, C-9, C-10), 20.9 (Me) ppm; minor diastereomer (R_p,*S*) (S_p,*R*) respectively $R_f = 0.25$ (dichloromethane/cyclohexane 9:1, 1% triethylamine); ^{1}H NMR (minor diastereomer (R_p,*R*) (S_p,*S*), 250 MHz, $CDCl_3$): $\delta = 6.6$–6.3 (m, 7H, H_{Ar}), 4.15 (q, $J = 6.6$ Hz, 1H, C-1), 3.41 (ddd, $J = 13.2$ Hz, 9.7 Hz, 2.1 Hz, 1H, CH_2), 3.2–3.0 (m, 6H, CH_2), 2.75–2.65 (m, 1H, CH_2), 1.19 (d, $J = 6.6$ Hz, 3H, Me) ppm; ^{13}C NMR (minor diastereomer (R_p,*R*) (S_p,*S*), 100 MHz, $CDCl_3$): $\delta = 145.8$ (q), 139.7 (q), 139.1 (q), 139.0 (q), 135.3 (q), 134.7 (t), 133.3 (t), 132.6 (t), 131.5 (t), 130.5 (t), 129.0 (t), 127.7 (t), 47.8 (*C*H(NH_2)Me), 34.9, 34.8, 33.8, 32.9 (Pc–C-1, C-2, C-9, C-10), 25.7 (Me) ppm; FTIR (KBr) $\nu = 3368$, 2928, 1594, 1500, 842, 716 cm^{-1}; EI-MS *m*/*s* (relative intensity) 251 (24) [M^+], 236 (100) [$M - CH_3^+$], 147 (25) [$M - C_8H_8^+$], 104 (28) [$C_8H_8^+$]; HRMS (*m*/*z*) $C_{18}H_{21}N$: calc. 251.1674, found 251.1677.

3.20. X-Ray structure analysis of (**20**)

$C_{24}H_{24}O_2$: colorless crystals, crystal dimension $0.05 \times 0.05 \times 0.40$ mm^3; $M = 344.43$; rhombohedral, space group R-3 (No. 148), $a = 18.0598(3)$ Å, $a = 116.341(1)°$, $V = 2853.23(8)$ Å^3, $Z = 6$, μ(MoKα) = 0.075 mm^{-1}, $T = 123(2)$ K, $F(000) = 1104.25552$ reflection up to $2\theta_{max} = 50°$ were measured on a Nonius KappaCCD diffractometer with MoKα radiation, 3346 of which were independent and used for all calculations. The structure was solved by direct methods and refined to F^2 anisotropically, the H atoms were refined with a riding model (H(O) free). The final quality coefficient $wR_2(F^2)$ for all data was 0.2082, with a conventional $R(F) = 0.0634$ for 241 parameters and 2 restraint. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-282766 (**20**). Copies of the data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambrigde CB2 1EZ, UK; Fax: +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk].

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