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Diastereoselective Hartwig–Buchwald Reaction of Chiral Amines with *rac*-[2.2]Paracyclophane Derivatives

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Dedicated to Professor Dr. Valeria Rozenberg

Abstract: A Hartwig–Buchwald addition of a variety of chiral amines to *rac*-4-bromo-[2.2]paracyclophane and *rac*-trifluoromethanesulfonic acid (4-[2.2]paracyclophane) ester was performed with high diastereoselectivities. Kinetic racemic resolution of the starting materials was achieved, providing a rapid access to enantiomerically enriched 4-bromo-[2.2]paracyclophane and the corresponding enantiomerically pure [2.2]paracyclophane amines. Additionally, the first reaction of a secondary amine with a [2.2]paracyclophane halide was achieved.

Keywords: asymmetric catalysis · catalyst screening · cross-coupling reaction · palladium · paracyclophanes

Introduction

Planar chirality plays an increasingly important role in modern organic chemistry.[1] Especially the field of [2.2]paracyclophane chemistry has developed considerably since they first attracted the interest of researchers in the middle of the last century.[2] Recently, there has been notable progress, particularly in the synthesis of new derivatives[3] and their applications in asymmetric catalysis.[4] Aryl amines are widespread chemicals; they are important intermediates in chemical synthesis and are often encountered in natural products. Although aryl amines are a relatively simple class of compounds, their synthesis is still cumbersome.[5] While the Hartwig–Buchwald reaction is a very powerful tool for their synthesis,[6] some starting materials, such as electron-rich aryl halides, still pose a challenge. Therefore, there are very few applications of the Hartwig–Buchwald reaction employing [2.2]paracyclophane halides and pseudo halides, although the resulting amines have interesting applications in biomedicine and catalysis.[7] To the best of our knowledge, there are only few examples of a successful palladium-catalysed cross-coupling reaction of nitrogen nucleophiles with [2.2]paracyclophanes. Rossen, Pye et al.[8] were able to react *rac*-4,12-dibromo-[2.2]paracyclophane with benzylamine under kinetic resolution and Gmeiner et al.[9] reacted diphenylhydrazone or piperazine with trifluoromethanesulfonic acid (4-[2.2]paracyclophane) ester.

Herein we want to report on the highly diastereoselective synthesis of planar and central chiral [2.2]paracyclophane amines via the Hartwig–Buchwald reaction of electron-rich racemic [2.2]paracyclophane bromide or triflate and a chiral amine. This reaction is also employed in the kinetic resolution of racemic 4-bromo-[2.2]paracyclophane. Finally, the first Hartwig–Buchwald reaction of a secondary amine with a [2.2]paracyclophane halide is described.

Results and Discussion

The Hartwig–Buchwald reaction is one of the most useful reactions for the synthesis of arylamines. A large variety of possible reaction systems is already existing in literature. However, none of them is close to providing a general protocol, which would be useful to obtain a large number of diverse compounds. Therefore we started with the screening of not only the ligands, but also bases, solvents and possible additives. We chose 4-bromo-[2.2]paracyclophane and achiral amines as the model system for the screening (Scheme 1).

We applied numerous mono- and bidentate phosphino ligands and a single aminophosphino ligand in the cross-coupling reaction (Figure 1).

The initial experiments with various bases, solvents and the monodentate ligands PPh_3, $P(t\mathrm{Bu})_3$ and di-*tert*-butylbi-

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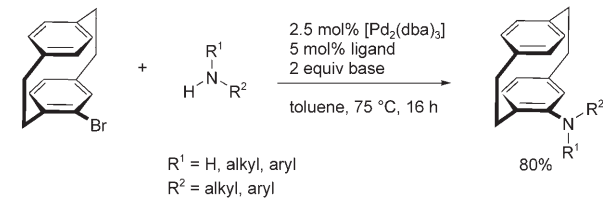


Scheme 1. Hartwig–Buchwald reaction of 4-bromo-[2.2]paracyclophane (PcBr) with amines.

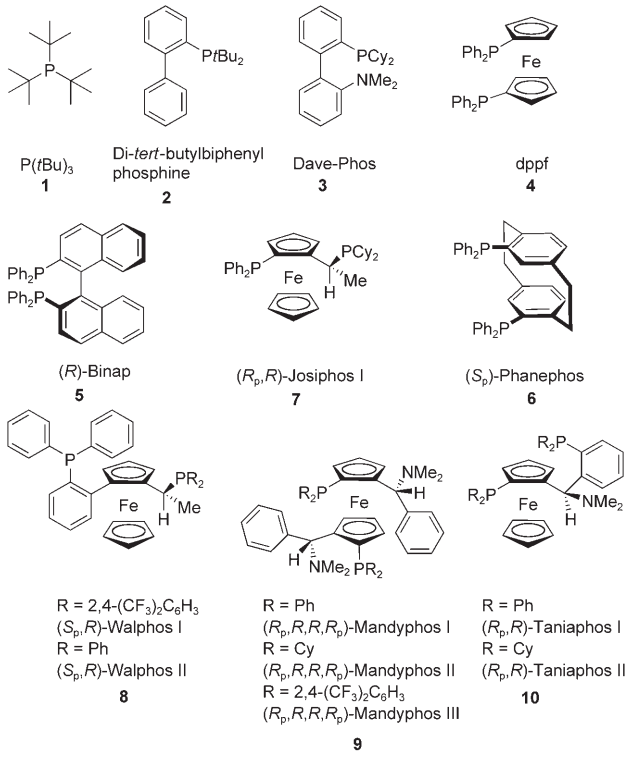


Figure 1. Ligands for the Hartwig–Buchwald reaction.

phenylphosphine were unsuccessful (Table 1, entries 1–3). Furthermore, the aminophosphino ligand Dave-Phos (entry 4) and the achiral dppf (entry 5) gave low yields, if any product at all, for various combinations of solvents and bases. The main reaction observed in these experiments was the β-hydride elimination leading to [2.2]paracyclophane. The desired [2.2]paracyclophane amines (Table 1) was only obtained with the chiral Binap ligand **5**. Among the various tested solvents, toluene gave superior results compared with dioxane, triethylamine or monoglyme. Weak bases such as Cs_2CO_3 (entry 7) or NEt_3 showed no conversion at all, whereas LiHMDS (lithiumhexamethyldisilazide, entry 8) promoted the β-hydride elimination, thus leaving NaO*t*Bu as the base of choice. Additives such as diglyme (entry 9) or [18]crown-6 failed to improve the reaction.

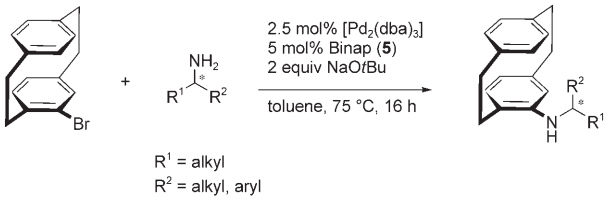
With these promising initial results, we tried to couple different chiral primary amines (Figure 2) by using 4-bromo-[2.2]paracyclophane as the substrate and Binap (**5**) as the chiral catalyst (Table 2).

Table 1. Catalytic cross-coupling of 4-bromo-[2.2]paracyclophane with achiral amines.[a]

Entry	Ligand	Amine	Yield [%][b]
1	PPh_3	morpholine	–
2	P(*t*Bu)$_3$ (**1**)	morpholine	traces
3	(*t*Bu)$_2$P(biphenyl) (**2**)	morpholine	traces
4	Dave-Phos (**3**)	morpholine	traces
5	dppf (**4**)	diphenylamine	traces
6	Binap (**5**)	morpholine	38
7[c]	Binap (**5**)	morpholine	–
8[d]	Binap (**5**)	morpholine	–
9[e]	Binap (**5**)	morpholine	38
10	Binap (**5**)	butylamine	74
11	Binap (**5**)	benzylamine	79
12	Binap (**5**)	methylammoniumchloride	70

[a] Reaction conditions: 1.0 equiv PcBr, 2.0 equiv NaO*t*Bu, 2.5 mol% $[Pd_2(dba)_3]$, 5 mol% ligand, 1.2 equiv amine in toluene at 75°C for 16 h. [b] Yield of isolated product. [c] As in [a] but with Cs_2CO_3 as base. [d] As in [a] but with LiHMDS as base. [e] As in [a] but with 1.0 equiv diglyme as additive.

Table 2. Binap-catalysed Hartwig–Buchwald reaction of 4-bromo-[2.2]paracyclophane with chiral amines **11**–**17**.[a]



Entry	Binap	Amine	Yield [%][b]	*de* [%]
1[c]	*rac*-**5**	*rac*-**11**	quant.	34
2	*rac*-**5**	(*S*)-**11**	96	31
3	(*S*)-**5**	(*S*)-**11**	94	45
4	(*R*)-**5**	(*S*)-**11**	96	9
5	*rac*-**5**	(*S*)-**12**	96	12
6	*rac*-**5**	(*S*)-**13**	96	24
7	(*S*)-**5**	(*S*)-**13**	92	62
8	(*R*)-**5**	(*S*)-**13**	94	13
9	*rac*-**5**	(*S*)-**14**	78	27
10	(*S*)-**5**	(*S*)-**14**	56	28
11	(*R*)-**5**	(*S*)-**14**	58	31
12[c]	*rac*-**5**	*rac*-**15**	quant.	57
13	(*S*)-**5**	(*S*)-**15**	98	47
14[c]	*rac*-**5**	*rac*-**16**	56	36
15[c]	*rac*-**5**	(*S*,*S*)-**17**	70[d]	98

[a] Reaction conditions: 1.0 equiv PcBr, 2.0 equiv NaO*t*Bu, 2.5 mol% $[Pd_2(dba)_3]$, 5 mol% Binap (**5**), 0.5 equiv amine in toluene at 75°C for 16 h. [b] Yield of product by GC-MS referring to amine. [c] As in [a] but with 1.2 equiv amine. Yield of product by GC-MS with referring to PcBr. [d] Yield of isolated product.

With 1-phenylethylamine (**11**) (entries 1–4), 1-(4-methoxyphenyl)ethylamine (**12**) (entry 5), 1-(4-fluorophenyl)ethylamine (entries 6–8) (**13**) and 1-(cyclohexyl)ethylamine (**15**), the reaction proceeded almost quantitatively with negligible amount of by-product due to β-elimination. The yield of the desired product decreased considerably in the case of 1-(2-naphthyl)ethylamine (**14**) where mostly β-elimination occurred (Scheme 2).

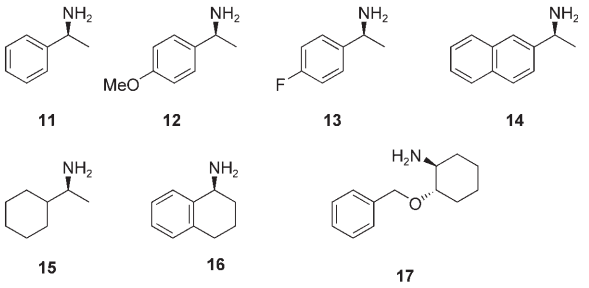
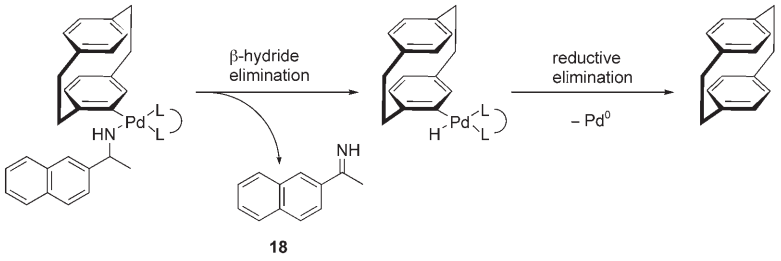
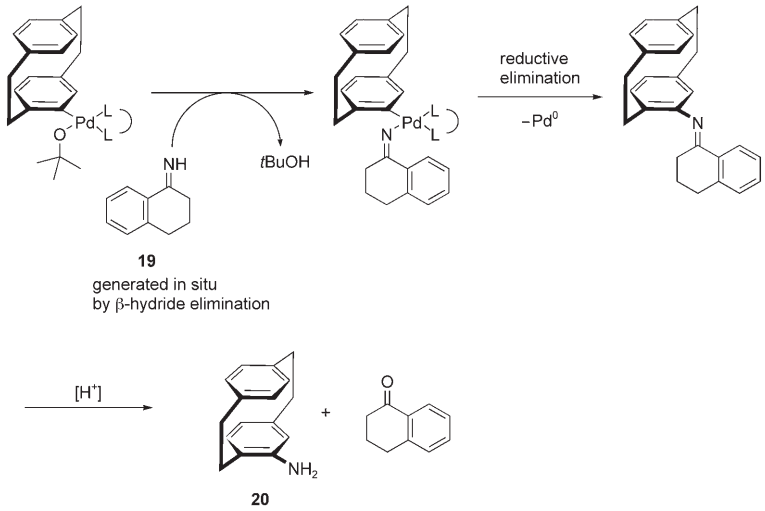


Figure 2. Primary chiral amines tested (only the *S* enantiomer is shown).



Scheme 2. Competitive β-hydride elimination side reaction with 1-(2-naphthyl)ethylamine.

The typical β-elimination by-products, [2.2]paracyclophane and 1-(2-naphthyl)ethylimine (**18**), could be consequently isolated in about 20% yield. The most surprising results were achieved by using 1,2,3,4-tetrahydronaphthalen-1-yl amine (**16**) as the coupling reagent (Scheme 3).

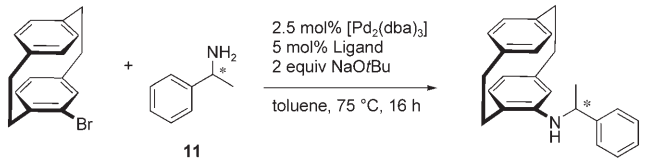


Scheme 3. Competitive reaction pathway with 1,2,3,4-tetrahydronaphthalen-1-yl amine.

Although the yield of the desired product decreased compared with the other amines, the major by-products were not the expected β-elimination products, but [2.2]paracyclophane and (3,4-dihydro-2*H*-naphthalen-1-ylidenyl)-(4-[2.2]paracyclophanyl)imine, the product of β-elimination and subsequent cross-coupling reaction. It could easily be hydrolysed into enantiomerically enriched 4-[2.2]paracyclophanylamine (**20**). With 1-*S*-*trans*-(*S*-2-benzyloxy)cyclohexylamine (**17**), the reaction proceeded in spite of the bulky amine in a satisfactory 70% yield with no traces of β-elimination by-products. For all chiral amines, the resulting excess diastereomer of the reaction was independent of the Binap enantiomer used. This shows that the product selectivity is superior to the catalyst selectivity. Measuring the optical rotation of the remaining PcBr after the kinetic resolution with (*S*)-1-phenylethylamine and comparing with the literature value gave (*S*)-4-bromo-[2.2]paracyclophane as the excess enantiomer. Consequently, the kinetic resolution (*R*)-1-phenylethylamine resulted in (*R*)-4-bromo-[2.2]paracyclophane as the excess enantiomer. As a result, the excess stereoisomer of the product is (R_p,*S*) with (*S*)-1-phenylethylamine and (S_p,*R*) with (*R*)-1-phenylethylamine, both are the same diastereomer, which could be seen in the NMR as well. Furthermore, 1-phenylethylamine (**11**) and 1-(4-fluorophenyl)ethylamine (**13**) showed a distinct matched–mismatched pair behaviour. While (*S*)-Binap showed a promising 62% *de* with (*S*)-1-(4-fluorophenyl)ethylamine (entry 7), the diastereoselectivity dropped dramatically via 24% *de* with *rac*-Binap (entry 6) to 13% *de* with the mismatched (*R*)-Binap (entry 8). The same trend, from 45% (entry 3) (*S*) via 31% (entry 2) *rac* to 9% *de* (entry 4) (*R*), could be observed with (*S*)-1-phenylethylamine. For these substrates, the correct combination of enantiomers is crucial for the diastereoselectivity of the reaction. An opposite example is (*S*)-1-(2-napthyl)-ethylamine (**14**). Its diastereoselectivity remained approximately constant (entries 9–11, 28% *de* (*S*), 27% *de* (*rac*), 31% *de* (*R*)), regardless of which enantiomer of Binap was used. Consequently for this substrate, only the product selectivity played a role in the stereoselectivity of the reaction. While (*S*)-1-(4-methoxyphenyl)ethylamine (**12**) showed poor selectivity (12% *de*), the selectivity of sterically more-demanding amines, such as (*S*)-1-cyclohexylethylamine (**15**) (57% *de* with *rac*-Binap) or 1-(*S*)-*trans*-(*S*-2-benzyloxy)cyclohexylamine (**17**) with almost total stereocontrol (98% *de* with *rac*-Binap), greatly surpassed this result.

With these good results using Binap as chiral catalyst ligand, we optimised the diastereoselectivity by varying the chiral catalyst ligand. We decided to employ 4-bromo-[2.2]paracyclophane and 1-(phenyl)ethyl amine (PEA) as a screening system (Table 3).

Table 3. Hartwig–Buchwald reaction of 4-bromo-[2.2]paracyclophane with 1-phenylethylamine.[a]



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Entry	Catalyst	*rac*-**11** *de* [%][b]	(*R*)-**11** *de* [%]	(*S*)-**11** *de* [%]
1	(*S*)-Binap (**5**)	34	9	45
2	(S_p)-Phanephos (**6**)	74	5	57
3	(R_p,*R*)-Josiphos I (**7**)	n.d.[c]		
4	(S_p,*R*)-Walphos I (**8**)	90 (92)[d]	n.d.[c]	86
5	(S_p,*R*)-Walphos II (**8**)	90 (91)[c,d]		
6	(R_p,*R*,*R*,R_p)-Mandyphos I (**9**)	61	57	54
7	(R_p,*R*,*R*,R_p)-Mandyphos II (**9**)	55		
8	(R_p,*R*,*R*,R_p)-Mandyphos III (**9**)	59		
9	(R_p,*R*)-Taniaphos I (**10**)	78 (75)[d]	69	47
10	(R_p,*R*)-Taniaphos II (**10**)	56		

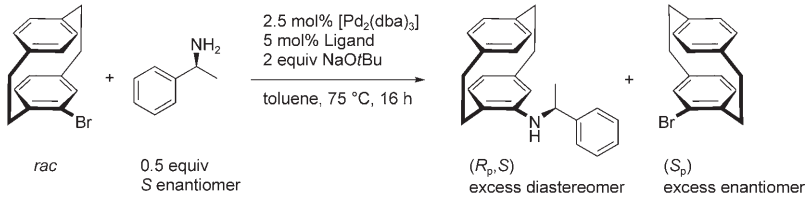
[a] Reaction conditions: 1.0 equiv PcBr, 2.0 equiv NaO*t*Bu, 2.5 mol% $[Pd_2(dba)_3]$, 5 mol% ligand, 0.5 equiv amine in toluene at 75°C for 16 h. [b] As in [a] but with 1.2 equiv amine. [c] Main product is [2.2]paracyclophane. [d] Results in parentheses for 10 mol% ligand and 5 mol% $[Pd_2(dba)_3]$.

We compared the purely stereoselective reaction with *rac*-1-phenylethylamine, whereby no decrease of the amount of any enantiomer occurs and a quantitative yield of product can be obtained with the kinetic resolution reaction with enantiomerically pure 1-phenylethylamine (Scheme 4).

In the first case, the resulting amine diastereomers can range from racemic to enantiomerically pure, whereas in the second case, the resulting product must be enantiomerically pure under the reasonable assumption that no racemisation occurs. In the latter case, the diastereomeric excess was usually lower, because the favoured Pc-Br enantiomer was decreased during the reaction. By changing the element of chirality from axial chiral Binap to planar chiral Phanephos, we were able to improve the selectivity from a modest 34% *de* (entry 1) to a good 74% *de* (entry 2). Here, the matched/mismatched differentiation became even more distinct, ranging from a hardly measurable 5% *de* for (*R*)-1-phenylethylamine to clear-cut 57% *de* for (*S*)-1-phenylethylamine. Consequently, we applied a variety of planar and central chiral diphosphine ligands in the reaction. With Mandyphos I–III and Taniaphos II (entries 6–8 and 10),[10] no improvement of the diastereoselectivity was observed, whereas application of Josiphos I (entry 3) led only to β-hydride elimination. This result is probably due to the bite angle of the diphosphine, which is quite inflexible (1,2-disubstituted ferrocene) and rather small. Mandyphos, on the other hand, has a very flexible bite angle (1,1′-disubstituted ferrocene), thus providing very high conversions but only moderate diastereoselectivities. An improvement of the result could be achieved with the more rigid 1,2-disubstituted ferrocene backbone, compared with the twistable 1,1′-ferrocene, but a bigger and more flexible bite angle than Josiphos I. With Taniaphos I (entry 9), the diastereomeric excess improved only slightly from 74 to 78% but the matched/mismatched effect was less pronounced and reversed to that of Phanephos resulting in a matched pair for (*R*)-1-phenylethylamine (69% *de*) and a mismatched pair for (*S*)-1-phenylethylamine (47% *de*). The best results were achieved with the Walphos ligands (entries 4 and 5). While, both Walphos I and Walphos II, gave excellent diastereoselectivities (both 90% *de* with *rac*-1-phenylethylamine), the more electron-rich Walphos II resulted in much lower yields, with the β-hydride elimination product [2.2]paracyclophane being the main product. With the electron poorer Walphos I, the selectivity remained constant, but the yield increased to about 55%. Distinction between the two 1-phenylethylamine enantiomers in a kinetic resolution reaction showed that while (*S*)-1-phenylethylamine resulted in excellent yields and selectivities (92% yield with respect to the amine and 86% *de*), (*R*)-1-phenylethylamine yielded mainly starting material and [2.2]paracyclophane. These results demonstrate that, of the four possible stereoisomers of (1-(phenyl)-ethyl)-(4-[2.2]paracyclophyl) amine only one is viable.

Based on these results, the feasibility of the improved reaction conditions towards two amines chosen with regard towards the conditions generality and substrate tolerance were tested. Furthermore, we examined the scope of the reaction with regards to other [2.2]paracyclophane derivates such as triflates and nonaflates (Table 4).

1-(4-Fluorophenyl)ethylamine (**13**) and 1-(4-methoxyphenyl)ethylamine (**12**) were chosen because they gave the most unsatisfactory results with *rac*-Binap as the catalyst ligand. By changing the catalyst from the axial chiral Binap (**5**) to the planar chiral Phanephos (**6**), the diasteromeric excess increased from a poor 12% to a reasonable 55% with 1-(4-methoxyphenyl)ethylamine as the reagent. For 1-(4-fluorophenyl)ethylamine, the more promising planar- and central chiral ferrocene ligands were tested. Walphos II (**8**) (entry 5)



Scheme 4. Kinetic resolution of *rac*-4-bromo-[2.2]paracyclophane with (*S*)-phenylethylamine.

Table 4. Hartwig–Buchwald reaction with other substrates.[a]

Entry	Substrate	Catalyst	Amine	*de* [%]
1[b]	PcBr	*S*-Phanephos (**6**)	(*R*)-**12**	55
2	PcBr	(R_p,*R*)-Taniaphos I (**10**)	*rac*-**13**	80
3[b]	PcBr	(R_p,*R*)-Taniaphos I (**10**)	(*S*)-**13**	58
4	PcBr	(S_p,*R*)-Walphos I (**8**)	*rac*-**13**	89
5	PcBr	(S_p,*R*)-Walphos II(**8**)	*rac*-**13**	71
6[d]	PcONf	*rac*-Binap (**5**)	*rac*-**11**	n.d.
7	PcOTf	*rac*-Binap (**5**)	*rac*-**11**	n.d.[c]
8[d]	PcOTf	*rac*-Binap(**5**)	*rac*-**11**	91

[a] Reaction conditions: 1.0 equiv PcX, 2.0 equiv NaO*t*Bu, 2.5 mol% $[Pd_2(dba)_3]$, 5 mol% ligand, 1.2 equiv amine in toluene at 75°C for 16 h. [b] As in [a] but with 0.5 equiv amine. [c] Main product is PcOH. [d] 1.0 equiv PcOTf, 3.0 equiv K_3PO_4, 5 mol% $[Pd_2(dba)_3]$, 10 mol% ligand, 1.2 equiv amine in toluene at 85°C for 72 h.

resulted in a diminished selectivity (71% *de*) with a similar low yield. Taniaphos I (**10**) gave a good selectivity of 80% *de* with *rac*-**13** and still a moderate selectivity of 58% *de* for (*S*)-**13**. The best selectivity was again achieved with Walphos I (**8**), resulting in a high diastereoselectivity of 89% for racemic 1-(4-fluorophenyl)ethylamine, thus showing that the improved reaction conditions for 1-phenylethylamine are successfully applicable to 1-(4-fluorophenyl)ethylamine. Following these successes, we tried to broaden the scope of the reaction to trifluoromethanesulfonic acid (4-[2.2]paracyclophane) ester (PcOTf) and nonafluorobutanesulfonic acid (4-[2.2]paracyclophane) ester (PcONf) which can be easily synthesised from 4-hydroxy-[2.2]paracyclophane. The cross-coupling of PcOTf and PcONf with 1-phenylethylamine and NaO*t*Bu as base resulted solely in the corresponding phenol while reaction with Cs_2CO_3 as base gave no reaction at all. Only K_3PO_4 generated the desired product with PcOTf as reactant in high selectivity (91% *de*, entry 8) and good 67% yield, while PcONf mainly reacted to [2.2]paracyclophane.

Conclusion

In summary, we have developed a highly diastereoselective Hartwig–Buchwald reaction of 4-bromo-[2.2]paracyclophane with chiral primary amines, showing diastereoselectivities of up to 98% *de*. This method is particularly noteworthy because of its experimental simplicity, high generality of chiral amines and because electron-rich aryl halides such as [2.2]paracyclophanes still pose a great challenge for the Hartwig–Buchwald reaction. Both enantiomers of 4-bromo-[2.2]paracyclophane can be obtained by a kinetic resolution reaction in good yields and via only one reaction step, whereas previously four steps[11] were needed. Furthermore, the first palladium-catalysed cross-coupling reaction of a secondary amine with a [2.2]paracyclophane halide was achieved. Additionally, we succeeded in coupling 1-phenylethylamine with trifluoromethanesulfonic acid (4-[2.2]paracyclophane) ester in 91% diastereomeric excess.

Experimental Section

General methods: All catalyses were performed in 10 mL vials under an argon atmosphere. Substrates were either purchased from commercial sources or were a gift from BASF (chiral amines) or Solvias (ligands) and were used without further purification. Enantiomeric excesses were determined by GC on a chiral stationary phase (CP-Chirasil-Dex or Lipodex E) or by comparison of optical rotation by literature known compounds on a Perkin Elmer 242 polarimeter (Na, 589 nm). GC-MS was measured on a HP 5890 Series II GC with a HP 5972 MS. Diastereomeric excesses were determined by NMR. $^1H/^{13}C$ NMR spectra were recorded on a Bruker AC250 (250 MHz/67 MHz), Bruker AM400 (400 MHz/100 MHz), Bruker DRX500 (500 MHz/125 MHz) or Bruker AVANCE 600 (600 MHz/150 MHz), using $CDCl_3$ as the solvent and residual $CHCl_3$ as shift reference ($CHCl_3$ 7.26 ppm/77.00 ppm). ^{19}F NMR spectra were recorded on a Bruker AM400 (376 MHz). Description of signals: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, ddd = doublet of dd, dt = doublet of triplets, Pc = [2.2]paracyclophanyl, Hn = hydronaphthyl, Cy = cyclohexyl, Mor = morpholyl, Bu = butyl, Bn = benzyl, t = tertiary, q = quaternary. NMR signals that are labeled with an asterix (*) are interchangeable within their corresponding numbers. Although the diastereomers were normally inseparable, the discrimination of the major and the minor diastereomer in the NMR spectra was possible. The MS spectra were recorded on a Finnigan MAT 90. The IR spectra were recorded on a Bruker IFS 88.

General procedure 1—Hartwig–Buchwald reaction of *rac*-4-bromo-[2.2]paracyclophane: A sealable tube was charged with *rac*-4-bromo-[2.2]paracyclophane (144 mg, 0.500 mmol, 1.0 equiv), NaO*t*Bu (96 mg, 1.0 mmol, 2.0 equiv), $[Pd_2(dba)_3]$ (7.0 mg, 13 μmol, 2.5 mol%) and the respective catalyst ligand (25 μmol, 5 mol%). Any solid racemic amine (0.6 mmol, 1.2 equiv) was added at this stage. 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 the racemic amine (0.6 mmol, 1.2 equiv), if liquid, were added subsequently via syringe. The solution turned deep red and was warmed to 75°C for 16 h. After cooling to room temperature, saturated aqueous Na_2CO_3 (5 mL) was added. The reaction mixture was transferred to a separatory funnel and extracted twice with diethyl ether (10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography.

General procedure 2—Kinetic resolution *rac*-4-bromo-[2.2]paracyclophane: Analogous to GP 1 except for a lower amount enantiomerically pure amine (0.25 mmol, 0.5 equiv) was used.

General procedure 3—Hartwig–Buchwald reaction of *rac*-trifluoromethanesulfonic acid (4-[2.2]paracyclophane) ester: A sealable tube was charged with *rac*-trifluoromethanesulfonic acid (4-[2.2]paracyclophanyl) ester (178 mg, 0.500 mmol, 1.0 equiv), K_3PO_4 (318 mg, 1.50 mmol, 3.0 equiv), $[Pd_2(dba)_3]$ (14 mg, 25 μmol, 5 mol%) and *rac*-Binap (**5**) (31 mg, 50 μmol, 10 mol%). The vial was sealed, evacuated and refilled with argon. This procedure was repeated three times. Dry toluene (5 mL) and *rac*-1-phenylethylamine (91 mg, 0.75 mmol, 1.5 equiv) were subsequently added via syringe. The solution turned deep red and was warmed to 90°C for 72 h. After cooling to room temperature, saturated aqueous Na_2CO_3 (5 mL) was added. The reaction mixture was 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).

1-(*S*)-*trans*-(*S*)-2-Benzyloxy)cyclohexyl 4-[2.2]paracyclophanylamine: The product was synthesised according to GP 2. It was purified by column chromatography (silica gel 60, cyclohexane/dichloromethane 1:1) yielding a yellow oil (71 mg, 0.17 mmol, 69%). R_f = 0.05 (cyclohexane/dichloromethane 1:1); ^1H NMR (600 MHz, $CDCl_3$): δ = 7.54 (d, J = 7.5 Hz, 2H, Ph H-2), 7.45 (dd, J = 7.5, 7.5 Hz, 2H, Ph H-3), 7.38 (t, J = 7.5 Hz, 1H, Ph H-4), 7.01 (dd, J = 7.8, 1.4 Hz, 1H, Pc H_{Ar}), 6.56 (dd, J = 7.8, 1.5 Hz, 1H, Pc H_{Ar}), 6.37 (dd, J = 7.8, 1.4 Hz, 1H, Pc H_{Ar}), 6.34 (dd, J = 7.8, 1.2 Hz, 1H, Pc H_{Ar}), 6.26 (d, J = 7.6 Hz, 1H, Pc H-8), 6.05 (d, J = 7.5 Hz, 1H, Pc H-7), 5.42 (s, 1H, Pc H-5), 4.90 (d, J = 11.6 Hz, 1H,

PhC*H*H), 4.64 (d, $J=11.6$ Hz, 1H, PhC*H*H), 3.99 (brs, 1H, N*H*), 3.52 (td, $J=9.2$, 3.7 Hz, 1H, C*H*NH), 3.18 (td, $J=9.1$, 3.7 Hz, 1H, C*H*O), 3.1–2.8 (m, 7H, PcCH_2), 2.66 (ddd, $J=14.1$ Hz, 10.6, 7.2 Hz, 1H, PcC*H*H), 2.4–2.3 (m, 1H, H_{Cy}), 2.3–2.2 (m, 1H, H_{Cy}), 1.9–1.8 (m, 1H, H_{Cy}), 1.7–1.5 (m, 2H, H_{Cy}), 1.5–1.3 (m, 2H, H_{Cy}), 1.1–1.0 (m, 1H, H_{Cy}); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 146.2, 140.9, 138.9, 138.7 (Pc C-4, C-6, C-11, C-14), 138.6 (Pc C_{Ar}), 135.0 (Pc C_{Ar}), 132.8 (Pc C_{Ar}), 132.5 (Pc C_{Ar}), 131.3 (Pc C_{Ar}), 128.5 (Ph C-2*), 128.1 (Ph C-3*), 128.0 (Ph C-1), 127.8 (Ph C-4), 123.7 (Pc C-3), 120.8 (Pc C-7), 117.0 (Pc C-5), 79.9 (*C*HOR), 70.7 (Ph *C*H_2), 56.1 (*C*HNH), 35.3 (Pc *C*H_2), 32.5 (Pc *C*H_2), 32.2 (Pc *C*H_2), 30.1 (Pc *C*H_2), 29.5 (Cy *C*H_2), 26.9 (Cy *C*H_2), 23.9 (Cy *C*H_2), 23.4 (Cy *C*H_2); FTIR (neat): $\tilde{\nu}$ = 3419, 2931, 1569, 1507, 1428, 1093, 689 cm^{-1}; EI-MS: *m*/*z* (%): 411 (15) [M^+], 208 (31) [Pc$^+$], 119 (45) [C_8H_8+NH_2^+], 104 (100) [$C_8H_8^+$], 77 (95) [Ph$^+$]; HRMS: *m*/*z*: calcd for $C_{29}H_{33}NO$: 411.2562; found: 411.2563.

4-[2.2]Paracyclophanylamine: The product was synthesised according to GP1 or GP 2 with 1-aminotetralin. The crude product was dissolved in methanol (10 mL) and conc. HCl (10 mL) and heated under reflux for 3 h. After cooling to room temperature, saturated aqueous Na_2CO_3 (50 mL) was added cautiously. The reaction mixture was transferred to a separatory funnel and extracted twice with diethyl ether. The collected organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel 60, cyclohexane/dichloromethane 1:1) yielding a waxy white solid (GP 1, 62 mg, 0.28 mmol, 56%). R_f = 0.1 (cyclohexane/dichloromethane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (dd, J = 7.8, 1.9 Hz, 1H, H_{Ar}), 6.59 (dd, J = 7.8, 1.9 Hz, 1H, H_{Ar}), 6.40 (dd, J = 7.9, 1.9 Hz, 2H, H_{Ar}), 6.27 (d, J = 7.7 Hz, 1H, H-7 or H-8), 6.14 (dd, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 5.39 (d, J = 1.7 Hz, 1H, H-5), 3.49 (brs, 2H, NH_2), 3.1–2.5 (m, 8H, PcCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 141.0, 138.9, 138.9 (C-4, C-6, C-11, C-14), 135.2, 133.4, 132,4. 131.4, 126.8 (C-8, C-12, C-13, C-15, C-16), 124.5 (C-3), 122.8 (C-7), 122.3 (C-5), 35.3, 34.9, 33.0, 32.2 (C-1, C-2, C-9, C-10); FTIR (neat): $\tilde{\nu}$ = 3476, 3389, 2926, 1615, 1426, 718 cm^{-1}; EI-MS: *m*/*z* (%): 223 (29) [M^+], 119 (100) [M^+−C_8H_8], 104 (7) [$C_8H_8^+$]; HRMS: *m*/*z*: calcd for $C_{16}H_{17}N$: 223.1361; found: 223.1358.

(1-Tetrahydronaphthyl)-(4-[2.2]paracyclophanyl)amine: The product was synthesised according to GP 1 or GP 2. It was purified by column chromatography (silica gel 60, cyclohexane/dichloromethane 2:1) yielding a white solid (GP 1, 67 mg, 0.19 mmol, 38%). R_f = 0.46 (both diastereomers, cyclohexane/dichloromethane 2:1); ^{1}H NMR (major diastereomer, 600 MHz, $CDCl_3$): δ = 7.36 (dd, J = 7.7, 7.6 Hz, 1H, Hn H-7*), 7.29 (dd, J = 7.6, 7.5 Hz, 1H, Hn H-8*), 7.25 (dd, J = 7.7, 1.4 Hz, 1H, Hn H-6**), 7.19 (d, J = 7.5 Hz, 1H, Hn H-9**), 6.63 (dd, J = 7.9, 1.7 Hz, 1H, Pc H_{Ar}), 6.55–6.45 (m, 1H, Pc H_{Ar}), 6.45–6.40 (m, 2H, Pc H_{Ar}), 6.29 (d, J = 7.6 Hz, 1H, Pc H-7***), 6.10 (d, J = 7.6 Hz, 1H, Pc H-8***), 5.59 (s, 1H, Pc H-5), 4.55 (brs, 1H, C*H*NH), 3.75 (brs, 1H, NH), 3.1–2.6 (m, 10H, PcCH_2 + Hn CH_2), 2.2–1.6 (m, 4H, Hn CH_2); ^{13}C NMR (major diastereomer, 125 MHz, $CDCl_3$): δ = 145.8 (q), 141.2 (q), 139.6 (q), 138.9 (t), 138.8 (q), 138.1 (q), 135.1 (t), 133.3 (q), 133.0 (t), 132.5 (t), 131.1 (t), 129.3 (t), 127.5 (t), 127.2 (t), 126.2 (t), 124.1 (q), 120.8 (t), 117.3 (t), 50.5 (Hn C-1), 35.7, 35.4, 33.0, 32.7, 29.4, 19.1, 15.3 (Hn C-2, C-3, C-4, PcC-1, C-2, C-9, C-10); ^{1}H NMR (minor diastereomer, 600 MHz, $CDCl_3$): δ = 7.20 (dd, J = 7.4, 7.3 Hz, 1H, Hn H-7*), 7.15 (d, J = 7.3 Hz, 1H, Hn H-6**), 7.12 (dd, J = 7.4, 7.4 Hz, 1H, Hn H-8*), 7.05 (d, J = 7.4 Hz, 1H, Hn H-9**), 6.61 (dd, J = 8.1, 2.2 Hz, 1H, Pc H_{Ar}), 6.55–6.45 (m, 1H, Pc H_{Ar}), 6.45–6.40 (m, 2H, Pc H_{Ar}), 6.30 (d, J = 7.3 Hz, 1H, Pc H-7***), 6.12 (d, J = 7.3 Hz, 1H, Pc H-8***), 5.50 (s, 1H, Pc H-5), 4.34 (brs, 1H, C*H*NH), 3.75 (brs, 1H, NH), 3.1–2.6 (m, 10H, PcCH_2 + Hn CH_2), 2.2–1.6 (m, 4H, Hn CH_2); ^{13}C NMR (minor diastereomer, 125 MHz, $CDCl_3$): δ = 145.0 (q), 141.4 (q), 139.0 (q), 138.8 (t), 138.2 (q), 137.5 (q), 135.2 (t), 133.3 (t), 133.1 (t), 131.3 (t), 129.2 (t), 129.0 (t), 128.8 (q), 128.3 (q), 127.1 (t), 126.2 (t), 121.3 (t), 117.1 (t), 51.6 (Hn C-1), 35.3, 33.1, 32.9, 30.1, 29.4, 27.5, 19.3 (Hn C-2, C-3, C-4, Pc C-1, C-2, C-9, C-10); FTIR (both diastereomers, neat): $\tilde{\nu}$ = 3415, 3012, 2853, 1594, 1506, 1425, 751 cm^{-1}; EI-MS: *m*/*z* (both diastereomers, %): 353 (19) [M^+], 249 (9) [M−$C_8H_8^+$], 223 (16) [PcNH_2^+], 208 (61) [Pc$^+$], 104 (100) [$C_8H_8^+$]; HRMS: *m*/*z*: calcd for $C_{26}H_{27}N$: 353.2143; found: 353.2140.

(1-(2-Naphthyl)ethyl)-(4-[2.2]paracyclophanyl)amine: The product was synthesised according to GP 1 or GP 2. It was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 5:1) yielding a waxy white solid (GP 1, 83 mg, 0.22 mmol, 44%). R_f = 0.23 (both diastereomers, cyclohexane/ethyl acetate 5:1); ^{1}H NMR (major diastereomer, 250 MHz, $CDCl_3$): δ = 8.1–7.2 (m, 7H, Naph H_{Ar}), 7.04 (dd, J = 7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.94 (dd, J = 7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.40 (dd, J = 7.7 Hz; 1.7 Hz, 1H, Pc H_{Ar}), 6.29 (d, J = 7.4 Hz, 1H, Pc H-7), 6.08 (dd, J = 7.7, 1.6 Hz, 1H, Pc H_{Ar}), 5.76 (dd, J = 7.8, 1.9 Hz, 1H, Pc H_{Ar}), 5.50 (d, J = 1.5 Hz, 1H, Pc H-5), 4.43 (q, J = 6.7, 1H, H-1), 3.96 (brs, 1H, NH), 3.4–2.7 (m, 8H, Pc CH_2), 1.59 (d, 3H, J = 6.7 Hz, Me); ^{13}C NMR (major diastereomer, 100 MHz, $CDCl_3$): δ = 146.7 (q), 143.3 (q), 141.3 (q), 138.7 (q), 138.6 (q), 134.8 (t), 133.5 (q), 133.2 (q), 133.0 (t), 132.8 (t), 132.4 (t), 131.3 (t), 128.4 (t), 128.3 (t), 127.9 (t), 127.7 (t), 127.7 (t), 125.7 (t), 125.1 (t), 124.8 (t), 124.3 (t), 123.7 (q), 121.2 (Pc C-7), 117.6 (Pc C-5), 54.3 (C-1), 35.6, 35.2, 33.3, 32.3 (Pc C-1, C-2, C-9, C-11), 24.0 (Me); ^{1}H NMR (minor diastereomer, 250 MHz, $CDCl_3$): δ = 8.1–7.2 (m, 7H, Naph H_{Ar}), 6.94 (dd, J = 7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.6–6.2 (m, 3H, Pc H_{Ar}), 6.32 (d, J = 7.4 Hz, 1H, Pc H-7), 6.06 (dd, J = 7.7, 1.7 Hz, 1H, Pc H_{Ar}), 5.20 (d, J = 1.4 Hz, 1H, Pc H-5), 4.61 (q, J = 6.7, 1H, H-1), 3.94 (brs, 1H, NH), 3.4–2.7 (m, 8H, Pc CH_2), 1.78 (d, 3H, J = 6.7 Hz, Me); ^{13}C NMR (minor diastereomer, 100 MHz, $CDCl_3$): δ = 145.3 (q), 142.5 (q), 140.9 (q), 139.5 (q), 139.0 (q), 134.9 (t), 133.4 (q), 133.0 (q), 133.0 (t), 132.7 (t), 132.6 (t), 130.8 (t), 128.4 (t), 127.7 (t), 127.7 (t), 127.5 (t), 127.1 (t), 126.2 (t), 125.8 (t), 125.3 (t), 124.0 (t), 123.7 (q),121.6 (Pc C-7), 117.2 (Pc C-5), 52.7 (C-1), 35.2, 35.2, 33.1, 32.7 (Pc C-1, C-2, C-9, C-11), 25.6 (Me); FTIR (both diastereomers, neat): $\tilde{\nu}$ = 3416, 2927, 1596, 1508, 1298, 749 cm^{-1}; EI-MS: *m*/*z* (both diastereomers, %): 377 (6) [M^+], 237 (18) [M−NaphCH_3^+], 208 (26) [Pc$^+$], 155 (12) [M−PcNH^+], 104 (100) [$C_8H_8^+$]; HRMS: *m*/*z*: calcd for $C_{28}H_{27}N$: 377.2143; found: 377.2140.

(1-(Phenyl)ethyl)-(4-[2.2]paracyclophanyl)amine: The product was synthesised according to GP 1 or GP 2. It was purified by column chromatography (silica gel 60, cyclohexane/dichloromethane 2:1) yielding a colourless oil (GP 1, 153 mg, 0.47 mmol, 94%). R_f = 0.23 (both diastereomers, cyclohexane/dichloromethane 2:1); ^{1}H NMR (major diastereomer, (R_p,*S*) or (S_p,*R*), 600 MHz, $CDCl_3$): δ = 7.63 (d, J = 7.4 Hz, 2H, Ph H-2), 7.50 (dd, J = 7.6, 7.4 Hz, 2H, Ph H-3), 7.38 (tt, J = 7.6, 1.2 Hz, 1H, Ph H-4), 6.83 (dd, J = 7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.54 (dd, J = 7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.38 (dd, J = 7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.26 (d, J = 7.6 Hz, 1H, Pc H-7), 6.06 (dd, J = 7.5, 1.5 Hz, 1H, Pc H_{Ar}), 5.79 (dd, J = 7.8, 1.8 Hz, 1H, Pc H_{Ar}), 5.44 (d, J = 1.3 Hz, 1H, Pc H-5), 4.25 (q, J = 6.7 Hz, 1H, H-1), 3.86 (brs, 1H, NH), 3.3–2.6 (m, 8H, Pc CH_2), 1.50 (d, J = 6.7 Hz, 3H, Me); ^{13}C NMR (major diastereomer, (R_p,*S*) or (S_p,*R*), 100 MHz, $CDCl_3$): δ = 146.6, 145.9, 141.3, 138.7, 138.6 (Pc C-4, C-6, C-11, C-14, Ph C-1), 134.8 (t), 132.9 (t), 132.4 (t), 131.4 (t), 128.7 (t), 128.1 (t), 127.3 (t), 126.7 (t), 123.7 (Pc C-3),121.6 (Pc C-7), 117.1 (Pc C-3), 54.1 (C-1), 35.3, 35.3, 33.4, 32.4 (Pc C-1, C-2, C-9, C-10), 24.0 (Me); ^{1}H NMR (minor diastereomer, (R_p,*R*) or (S_p,*S*), 500 MHz, $CDCl_3$): δ = 7.3–7.2 (m, 5H, Ph), 6.99 (dd, J = 7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.59 (dd, J = 7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.48 (dd, J = 7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.41 (dd, J = 7.6, 1.8 Hz, 1H, Pc H_{Ar}), 6.29 (d, J = 7.6 Hz, 1H, Pc H-7), 6.05 (dd, J = 7.4, 1.5 Hz, 1H, Pc H_{Ar}), 5.15 (d, J = 1.2 Hz, 1H, Pc H-5), 4.43 (q, J = 6.7 Hz, 1H, H-1), 3.86 (brs, 1H, NH), 3.3–2.6 (m, 8H, Pc CH_2), 1.70 (d, J = 6.7 Hz, 3H, Me); ^{13}C NMR (minor diastereomer, (R_p,*R*) or (S_p,*S*), 100 MHz, $CDCl_3$): δ = 145.4, 145.0, 141.0, 139.0, 138.6 (Pc C-4, C-6, C-11, C-14, Ph C-1), 135.0 (t), 133.3 (t), 132.7 (t), 130.9 (t), 128.5 (t), 127.2 (t), 126.7 (t), 125.8 (t), 123.3 (Pc C-3),121.2 (Pc C-7), 117.6 (Pc C-3), 52.6 (C-1), 35.3, 35.3, 33.1, 32.8 (Pc C-1, C-2, C-9, C-10), 25.7 (Me); FTIR (both diastereomers, neat): $\tilde{\nu}$ = 3416, 2927, 1595, 1508, 1427,701 cm^{-1}; EI-MS: *m*/*z* (both diastereomers, %): 327 (60) [M^+], 312 (15) [M−Me$^+$], 223 (100) [M−$C_8H_8^+$], 104 (96) [$C_8H_8^+$], 43 (98) [$C_2H_5N^+$]; HRMS: *m*/*z*: calcd for $C_{24}H_{25}N$: 327.1987; found: 327.1983; elemental analysis calcd (%) for $C_{24}H_{25}N$: C 88.03, H 7.70, N 4.28; found: C 87.43, H 7.39, N 3.45.

(1-(4-Methoxyphenyl)ethyl)-(4-[2.2]paracyclophanyl)amine: The product was synthesised according to GP 1 or GP 2. It was purified by column chromatography (silica gel 60, cyclohexane/dichloromethane 1:1) yielding a waxy white solid (GP 2, 61 mg, 0.17 mmol, 68%). R_f = 0.19 (both diastereomers, cyclohexane/dichloromethane 1:1); ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.5 Hz, 2H, Ph H-2*), 7.00 (d,

J=8.5 Hz, 2H, Ph H-3*), 6.82 (dd, J=7.7, 1.8 Hz, 1H, Pc H_{Ar}), 6.52 (dd, J=7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.35 (dd, J=7.8, 1.7 Hz, 1H, Pc H_{Ar}), 6.23 (d, 1H, J=7.5 Hz, Pc H-7), 6.03 (dd, J=7.5, 1.3 Hz, 1H, Pc H_{Ar}), 5.86 (dd, J=7.7, 1.7 Hz, 1H, Pc H_{Ar}), 5.42 (s, 1H, Pc H-5), 4.20 (q, J=6.8 Hz, 1H, H-1), 3.87 (s, 3H, OMe), 3.55 (s, 1H, NH), 3.2–2.5 (m, 8H, $PcCH_2$), 1.44 (d, J=6.8 Hz, 3H, Me); ^{13}C NMR (major diastereomer, 125 MHz, $CDCl_3$): δ=158.7 (Ph C-4), 146.6, 141.3, 138.7, 138.6, 138.0 (Pc C-4, C-6, C-11, C-14, Ph C-1), 134.8 (t), 132.8 (t), 132.4 (t), 131.4 (t), 127.9 (t), 127.7 (Ph C-2*), 123.7 (Pc C-3), 121.4 (t), 117.1 (t), 113.9 (Ph C-3*), 55.4 (OMe), 53.3 (C-1), 35.3, 35.3, 33.3, 32.4 (Pc C-1, C-2, C-9, C-10), 23.8 (Me); ^{1}H NMR (minor diastereomer, 500 MHz, $CDCl_3$): δ=7.17 (d, J=8.6 Hz, 2H, Ph H-2*[1]), 6.96 (dd, J=7.7, 1.7 Hz, 1H, Pc H_{Ar}), 6.79 (d, J=8.6 Hz, 2H, Ph H-3*[1]), 6.56 (dd, J=7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.45 (dd, J=7.7, 1.8 Hz, 1H, Pc H_{Ar}), 6.38 (dd, J=7.6, 1.8 Hz, 1H, Pc H_{Ar}), 6.26 (d, J=7.5 Hz, 1H, Pc H-7), 6.01 (dd, J=7.5, 1.1 Hz, 1H, Pc H_{Ar}), 5.14 (s, 1H, Pc H-5), 4.36 (q, J=6.8 Hz, 1H, H-1), 3.74 (s, 3H, OMe), 3.55 (s, 1H, NH), 3.2–2.5 (m, 8H, $PcCH_2$), 1.65 (d, J=6.8 Hz, 1H, Me); ^{13}C NMR (minor diastereomer, 125 MHz, $CDCl_3$): δ=158.3 (Ph C-4), 145.5, 141.0, 139.0, 138.7, 137.1 (Pc C-4, C-6, C-11, C-14, Ph C-1), 134.9 (t), 133.3 (t), 132.6 (t), 130.9 (t), 127.1 (t), 126.7 (Ph C-2*), 123.2 (Pc C-3), 121.1 (t), 117.6 (t), 113.9 (Ph C-3*), 55.2 (OMe), 52.0 (C-1), 35.3, 33.1, 32.7, 29.7 (Pc C-1, C-2, C-9, C-10), 25.7 (Me); FTIR (both diastereomers, neat): $\tilde{\nu}$ = 3412, 2927, 1570, 1511, 1245, 832 cm^{-1}; EI-MS: m/z (both diastereomers, %): 357 (34) [M^+], 342 (11) [$M-Me^+$], 135 (100) [$M-PcNH^+$], 119 (43) [$C_8H_8NH_2^+$], 104 (83) [$C_8H_8^+$]; HRMS: m/z: calcd for $C_{25}H_{27}NO$: 357.2093; found: 357.2089.

(1-(4-Fluorophenyl)ethyl)-(4-[2.2]paracyclophanyl)amine: The product was synthesised according to GP 1 or GP 2. It was purified by column chromatography (silica gel 60, cyclohexane/dichloromethane 2:1) yielding a colourless oil (GP 2, 76 mg, 0.22 mmol, 88%). R_f=0.12 (both diastereomers, cyclohexane/dichloromethane 2:1); ^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$): δ=7.65–7.55 (m, 2H, Ph H-2*), 7.20–7.10 (m, 2H, Ph H-2*), 6.79 (dd, J=7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.54 (dd, J=7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.38 (dd, J=7.7, 1.8 Hz, 1H, Pc H_{Ar}), 6.25 (d, J=7.6 Hz, 1H, Pc H-7), 6.06 (dd, J=7.8, 1.8 Hz, 1H, Pc H_{Ar}), 5.79 (dd, J=7.8, 1.8 Hz, 1H, Pc H_{Ar}), 5.37 (d, J=1.3 Hz, 1H, Pc H-5), 4.20 (q, J=6.7 Hz, 1H, C-1), 4.23 (brs, 1H, NH), 3.3–2.7 (m, 8H, Pc CH_2), 1.46 (d, J=6.7 Hz, 3H, Me); ^{13}C NMR (major diastereomer, 100 MHz, $CDCl_3$): δ=161.9 (d, J=245 Hz, C-F), 146.6 (q), 141.7 (d, J=3 Hz, Ph C-1), 141.3 (q), 138.7 (q), 138.6 (q), 134.8 (t), 133.3 (t), 132.8 (t), 131.3 (t), 128.1 (d, J=8 Hz, 2 C, Ph C-2), 127.9 (t), 123.8 (Pc C-3), 121.8 (t), 117.2 (t), 115.4 (d, J=21 Hz, 2H, Ph C-3), 53.7 (C-1), 35.3, 35.3, 33.4, 32.3 (Pc C-1, C-2, C-9, C-10), 24.3 (Me); ^{19}F NMR (major diastereomer, 376 MHz, $CDCl_3$): δ=−115–(−116) (m); ^{1}H NMR (minor diastereomer, 400 MHz, $CDCl_3$): δ=7.25–7.20 (m, 2H, Ph H-2*), 7.00–6.90 (m, 3H, Ph H-2*, Pc H_{Ar}), 6.57 (dd, J=7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.46 (dd, J=7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.37 (dd, J=7.7, 1.8 Hz, 1H, Pc H_{Ar}), 6.28 (d, J=7.6 Hz, 1H, Pc H-7), 6.04 (dd, J=7.7, 1.8 Hz, 1H, Pc H_{Ar}), 5.08 (d, J=1.3 Hz, 1H, Pc H-5), 4.40 (q, J=6.7 Hz, 1H, H-1), 4.23 (brs, 1H, NH), 3.3–2.7 (m, 8H, Pc CH_2), 1.66 (d, J=6.7 Hz, 3H, Me); ^{13}C NMR (minor diastereomer, 100 MHz, $CDCl_3$): δ=161.6 (d, J=244 Hz, C-F), 145.2 (q), 141.0 (q), 140.6 (d, J=3 Hz, Ph C-1), 139.0 (q), 138.6 (q), 135.0 (t), 132.7 (t), 132.4 (t), 130.8 (t), 127.1 (d, J=8 Hz, 2 C, Ph C-2), 127.1 (t), 123.3 (Pc C-3), 121.3 (t), 117.5 (t), 115.3 (d, J=21 Hz, 2H, Ph C-3), 52.0 (C-1), 35.3, 35.3, 33.0, 32.7 (Pc C-1, C-2, C-9, C-10), 25.8 (Me); ^{19}F NMR (minor diastereomer, 376 MHz, $CDCl_3$): δ=−116–(−117) (m); FTIR (both diastereomers, neat): $\tilde{\nu}$ = 3421, 2927, 1570, 1508, 1427, 1222, 837, 718 cm^{-1}; EI-MS: m/z (both diastereomers, %): 345 (56) [M^+], 330 (13) [$M-Me^+$], 421 (64) [$M-C_8H_8^+$], 123 (100) [$M-PcNH^+$], 104 (59) [$C_8H_8^+$]; HRMS: m/z: calcd for $C_{24}H_{24}NF$: 345.1893; found: 345.1891.

(1-(Cyclohexyl)ethyl)-(4-[2.2]paracyclophanyl)amine: The product was synthesised according to GP 1 or GP 2. It was purified by column chromatography (silica gel 60, cyclohexane/dichloromethane 2:1) yielding a colourless oil (GP 1, 136 mg, 0.41 mmol, 82%). R_f=0.41 (both diastereomers, cyclohexane/dichloromethane 2:1); ^{1}H NMR (major diastereomer, (R_p,R) (S_p,S), 400 MHz, $CDCl_3$): δ=7.01 (dd, J=7.4, 1.5 Hz, 1H, Pc H_{Ar}), 6.59 (dd, J=7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.4–6.3 (m, 2H, Pc H_{Ar}), 6.24 (d, J=7.6 Hz, 1H, Pc H-8), 6.03 (m, 1H, Pc H_{Ar}), 5.33 (s, 1H, Pc H-5), 3.38 (brs, 1H, NH), 3.3–2.6 (m, 10H, Pc CH_2, H-1, Cy H-1), 2.1–1.0 (m, 10H, Cy H-2,3,4), 1.00 (d, J=6.3 Hz, 3H, Me); ^{13}C NMR (major diastereomer, (R_p,R) (S_p,S), 100 MHz, $CDCl_3$): δ=146.0, 141.1, 138.8, 138.8 (Pc C-4, C-6, C-11, C-14), 134.9, 133.1, 132.4, 131.1, 127.6 (Pc C-8, C-12, C-131, C-15, C-16), 123.8 (Pc C-3), 120.3 (Pc C-7*), 117.3 (Pc C-5*), 52.7 (C-1), 43.8 (Cy C-1), 35.3, 33.1, 32.9, 30.2, 29.4, 26.7, 26.7 (Pc C-1, C-2, C-9, C-10, Cy C-2, C-3, C-4), 17.1 (Me); ^{1}H NMR (minor diastereomer, (R_p,S) or (S_p,R), 400 MHz, $CDCl_3$): δ=6.99 (dd, J=8.4, 1.9 Hz, 1H, Pc H_{Ar}), 6.59 (dd, J=7.6, 2.4 Hz, 1H, Pc H_{Ar}), 6.4–6.3 (m, 2H, Pc H_{Ar}), 6.24 (d, J=7.6 Hz, 1H, Pc H-8), 6.03 (m, 1H, Pc H_{Ar}), 5.30 (s, 1H, Pc H-5), 3.38 (brs, 1H, NH), 3.3–2.6 (m, 10H, Pc CH_2, H-1, Cy H-1), 2.1–1.0 (m, 10H, Cy H-2,3,4), 1.28 (d, J=6.7 Hz, 3H, Me); ^{13}C NMR (minor diastereomer, (R_p,S) or (S_p,R), 100 MHz, $CDCl_3$): δ=146.3, 141.1, 138.8, 138.7 (Pc C-4, C-6, C-11, C-14), 135.1, 133.2, 132.4, 131.0, 127.1 (Pc C-8, C-12, C-131, C-15, C-16), 123.2 (Pc C-3), 120.2 (Pc C-7*), 117.0 (Pc C-5*), 52.5 (C-1), 41.9 (Cy C-1), 35.4, 33.0, 32.9, 30.0, 27.4, 26.5, 26.3 (Pc C-1, C-2, C-9, C-10, Cy C-2, C-3, C-4), 17.8 (Me); FTIR (both diastereomers, neat): $\tilde{\nu}$ = 3405, 2922, 2851, 1886, 1593, 1505, 1425, 1137, 892, 796 cm^{-1}; EI-MS: m/z (both diastereomers, %): 333 (7) [M^+], 229 (15) [$M^+-C_8H_8$], 146 (6) [$M^+-C_8H_8-Cy$] 104 (100) [$C_8H_8^+$]; HRMS: m/z: calcd for $C_{24}H_{31}N$: 333.2459; found: 333.2456.

(4-[2.2]Paracyclophanyl)morpholine: The product was synthesised according to GP 1. It was purified by column chromatography (silica gel 60, cyclohexane for the separation of [2.2]paracyclophane followed by dichloromethane) yielding a colourless oil (56 mg, 0.19 mmol, 38%). R_f = 0.05 (cyclohexane); R_f = 0.6 (dichloromethane); ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.69 (dd, J=7.9, 1.7 Hz, 1H, Pc H_{Ar}), 6.54 (dd, J=7.9, 1.8 Hz, 1H, Pc H_{Ar}), 6.50–6.40 (m, 2H, Pc H_{Ar}), 6.35 (dd, J=7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.30 (dd, J=7.7, 1.7 Hz, 1H, Pc H_{Ar}), 5.73 (d, J=1.6 Hz, 1H, Pc H-5), 4.02 (ddd, J=11.1, 6.3, 3.2 Hz, 1H, C*H*HO), 3.98 (ddd, J=11.4, 6.2, 3.1 Hz, 2H, C*H*HO), 3.94 (ddd, J=11.0, 6.1, 3.1 Hz, 1H, C*H*HO), 3.44–3.21 (m, 2H, Pc CH_2), 3.12–2.66 (m, 10H, Pc CH_2, CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$): δ=150.4 (Pc C-4), 141.0, 139.8, 138.9 (Pc C-6, C-11, C-14), 136.3 (t), 133.2 (t), 132.8 (t), 132.2 (Pc C-3), 131.2 (t), 128.7 (t), 127.4 (t), 121.2 (t), 67.5 (*C*H_2O), 52.3 (*C*H_2N), 35.3, 35.2, 34.9, 34.1 (Pc C-1, C-2, C-9, C-10); FTIR (neat): $\tilde{\nu}$ = 3381, 2926, 2850, 1588, 1491, 1415, 1371, 1231, 1119, 988, 898, 716, 659 cm^{-1}; EI-MS: m/z (%): 293 (4) [M^+], 189 (3) [$M^+-C_8H_8$], 104 [$C_8H_8^+$], 44 (100) [$C_2H_6N^+$]; HRMS: m/z: calcd for $C_{20}H_{23}NO$: 293.1780; found: 293.1776.

Methyl-(4-[2.2]paracyclophanyl)amine: The product was synthesised according to GP 1 with methylammonium chloride as amine precursor and an additional equivalent of base. It was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 5:1) yielding a colourless oil (83 mg, 35 mmol, 70%). R_f=0.65 (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.89 (dd, J=7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.58 (dd, J=7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.41 (dd, J=7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.36 (dd, J=7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.29 (dd, J=7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.29 (d, J=7.6 Hz, 1H, Pc H-7), 6.11 (dd, J=7.6, 1.7 Hz, 1H, Pc H_{Ar}), 5.32 (d, J=1.6 Hz, 1H, Pc H-5), 3.64 (brs, 1H, NH), 3.13–2.60 (m, 8H, Pc CH_2), 2.76 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ=147.5 (Pc C-4), 141.3, 139.4, 139.1 (Pc C-6, C-11, C-14), 134.6 (t), 133.5 (t), 133.0 (t), 130.7 (t), 127.1 (t), 123.7 (Pc C-3), 120.9 (t), 116.0 (t), 35.3, 33.0, 32.8, 30.3, (Pc C-1, C-2, C-9, C-10,), 27.0 (Me); FTIR: $\tilde{\nu}$ = 3394, 2926, 2803, 1596, 1570, 1510, 1441, 1413, 1330, 1295, 1264, 1169, 1089, 1062, 972, 854, 796, 722, 666 cm^{-1}; EI-MS: m/z (%): 237 (28) [M^+], 133 (76) [$M^+-C_8H_8$], 104 (13) [$C_8H_8^+$], 43 (100) [$C_2H_5N^+$]; HRMS: m/z: calcd for $C_{17}H_{19}N$: 237.1517, found: 237.1514; elemental analysis calcd (%) for $C_{17}H_{19}N$: C 86.03, H 8.07, N 5.90; found: C 85.68, H 7.71, N 5.87.

Butyl-(4-[2.2]paracyclophanyl)amine: The product was synthesised according to GP 1. It was purified by column chromatography (cyclohexane) yielding a colourless oil (103 mg, 37 mmol, 74%). R_f=0.03 (silica gel 60, cyclohexane); ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.92 (dd, J=7.8, 1.8 Hz, 1H, Pc H_{Ar}), 6.59 (dd, J=7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.42 (dd, J=8.0, 2.0 Hz, 1H, Pc H_{Ar}), 6.38 (dd, J=7.9, 1.9 Hz, 1H, Pc H_{Ar}), 6.29 (d, J=7.6 Hz, 1H, Pc H-7), 6.10 (dd, J=7.6, 1.6 Hz, 1H, Pc H_{Ar}), 5.34 (d, J=1.2 Hz, 1H, Pc H-5), 3.64 (brs, 1H, NH), 3.70–2.60 (m, 10H, Pc CH_2 + Bu H-1, H-1′), 1.80–1.40 (m, 4H, Bu H-2, H-2′, H-3, H-3′), 1.05 (t, J=7.2 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ=146.9 (Pc C-4), 141.2, 138.8, 138.7 (Pc C-6, C-11, C-14), 134.7 (t), 133.3 (t), 132.3 (t), 130.8 (t),

127.2 (t), 123.5 (Pc C-3), 120.8 (Pc C-7), 116.4 (Pc C-5), 43.0 (Bu C-1), 35.5, 32.9, 32.6, 31.9 (Pc C-1, C-2, C-9, C-10), 26.9 (Bu C-2), 20.6 (Bu C-3), 14.0 (Bu C-4); FTIR: $\tilde{\nu}$ = 3427, 2927, 1570, 1509, 1428 cm^{-1}; EI-MS: *m*/*z* (%): 279 (4) [M^+], 175 (13) [$M^+-C_8H_8$], 58 (40) [$C_3H_8N^+$], 43 (100) [$C_2H_5N^+$]; HRMS: *m*/*z*: calcd for $C_{20}H_{25}N$: 279.1986; found: 279.1990.

Benzyl-(4-[2.2]paracyclophanyl)amine: The product was synthesised according to GP 1. It was purified by column chromatography (silica gel 60, cyclohexane) yielding a colourless oil (124 mg, 40 mmol, 79%). R_f = 0.05 (cyclohexane); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.49–7.32 (m, 5H, Bn H_{Ar}), 6.99 (dd, *J* = 7.9, 1.7 Hz, 1H, Pc H_{Ar}), 6.58 (dd, *J* = 7.8, 1.9 Hz, 1H, Pc H_{Ar}), 6.41–6.35 (m, 2H, Pc H_{Ar}), 6.30 (d, *J* = 7.6 Hz, 1H, Pc H-7), 6.13 (dd, *J* = 7.6 Hz,1.4 Hz, 1H, Pc H_{Ar}), 5.43 (s, 1H, Pc H-5), 4.25 (d, *J* = 13.1 Hz, 1H, Bn CH_2), 4.08 (d, *J* = 13.1 Hz, 1H, Bn CH_2), 3.77 (br s, 1H, NH), 3.15–2.62 (m, 8H, Pc CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5 (Pc C-4), 141.4, 139.4, 138.9, 138.8 (Pc C-6, C-11, C-14, Ph C-1), 134.8 (t), 133.3 (t), 132.5 (t), 130.8 (t), 128.7, 128.1 (Ph C-2, C-3), 127.4, 127.3 (t), 124.1 (Pc C-3), 121.6 (Pc C-7), 116.7 (Pc C-5), 48.1 (Bn C-1), 35.3, 35.2, 33.0, 32.6 (Pc C-1, C-2, C-9, C-10); FTIR: $\tilde{\nu}$ = 3429, 3032, 2924, 2853, 1890, 1595, 1570, 1506, 1474, 1427, 1327, 1299, 1249, 1120, 1096, 1064, 1028, 979, 937, 876, 797,718, 697, 666 cm^{-1}; EI-MS: *m*/*z* (%): 313 (70) [M^+], 209 (100) [$M^+-C_8H_8$], 104 (51) [$C_8H_8^+$]; HRMS: *m*/*z*: calcd for $C_{23}H_{23}N$: 313.1830; found: 313.1833; elemental analysis calcd (%) for $C_{23}H_{23}N\cdot H_2O$: C 83.34, H 7.60, N 4.23; found: C 83.85, H 7.24, N 4.02.

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