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Synthesis of planar chiral *pseudo–ortho*-substituted aryl[2.2]paracyclophanes by stepwise successive palladium-catalyzed coupling reactions

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ABSTRACT

Planar chiral aryl[2.2]paracyclophanyl-thioureas and -phosphine with a *pseudo–ortho* substitution pattern have been designed and efficiently synthesized by stepwise successive palladium-catalyzed cross-coupling reactions.

1. Introduction

The use of the planar chirality of the substituted [2.2]paracyclophanes as a source of asymmetric induction has recently attracted growing attention. The substituted [2.2]paracyclophanes serve as chiral building blocks from which some substituents protrude in various directions.[1,2] Of all such species, two functional groups in a *pseudo–ortho* relationship to each other in the [2.2]paracyclophane molecule seem to create the most effective chiral environment. Indeed, [2.2]PHANEPHOS, the *pseudo–ortho*-disubstituted [2.2]paracyclophane ligand possessing both identical substituents (a phosphinyl group) at the specified positions, has realized a highly enantioselective hydrogenation catalyzed by a rhodium or ruthenium complex in several unsaturated systems.[3] Some *pseudo–ortho*-disubstituted [2.2]paracyclophanes bearing two different functional groups have also proven to be effective ligands in asymmetric catalysis.[4] However, there have not yet been many examples of the use of *pseudo–ortho*-type cyclophane ligands compared to those bearing other substitution patterns (*mono*-,[5] *ortho*-di-,[6,7] or *pseudo-gem*-di-substitution),[8–11] probably due to a lack of their efficient synthetic methodology. Their preparation usually starts with the dibromination of [2.2]paracyclophane.[12] However, it is not always easy to catalytically transform only one of the two bromo groups of the resulting *pseudo–ortho*-dibromo-[2.2]paracyclophane,[13] while some methods via a single bromine–lithium exchange have been established.

We have been interested in the development of bifunctional[14] organocatalysts[15] based on the *pseudo–ortho*-substituted aryl-[2.2]paracyclophane backbone,[16] which is expected to construct a novel type of efficient asymmetric environment. Our design concept was as follows: (1) the [2.2]paracyclophane backbone would provide conformational rigidity; and (2) a spacer aryl group[17] connected to the *pseudo–ortho* position would offer not only a steric or electronic element, which interacts with the substrate and/or reactant, but also the conformational flexibility that makes the distance between two functional groups suitable for performing the dual activation of the substrate and reactant (Fig. 1).

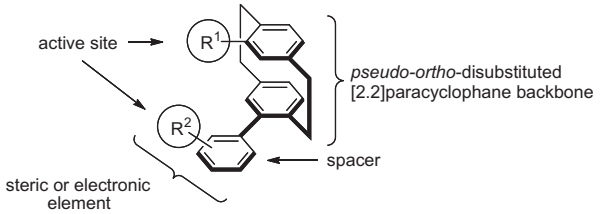

Figure 1.

Recently, Paradies et al. synthesized some enantiopure *pseudo-gem*-disubstituted [2.2]paracyclophanylthioureas, and demonstrated their potential in organocatalytic transformations.[18] These results prompted us to report the concise and efficient synthesis of chiral [2.2]paracyclophanyl-thioureas and -phosphines designed based on the aforementioned concept. The characteristic feature of our synthetic methodology is the stepwise successive palladium-catalyzed cross-coupling for the [2.2]paracyclophane bearing two different leaving groups in a *pseudo–ortho* relationship.

2. Results and discussion

Our common synthetic plan for the thiourea and phosphine derivatives is illustrated in Scheme 1. Triflation of the *pseudo–ortho*-bromo[2.2]paracyclophanol **3**, which is readily available in an enantiopure form, would set the stage for the stepwise successive palladium-catalyzed installation of two functional groups, that is, the polar functionality (R^1) to directly connect to the backbone and an aryl group equipped with the second functionality (R^2). The different leaving groups (Br and OTf) in **4** might make it easier to

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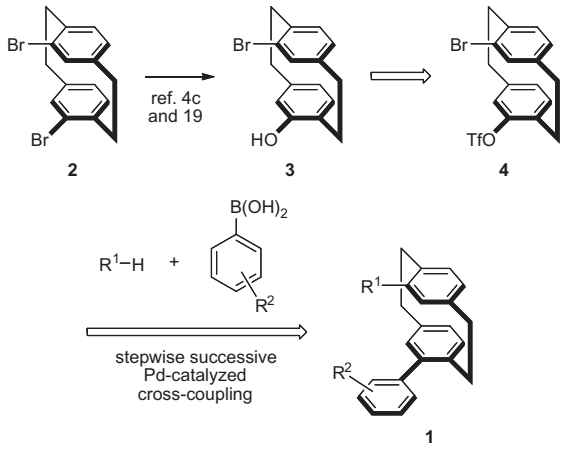
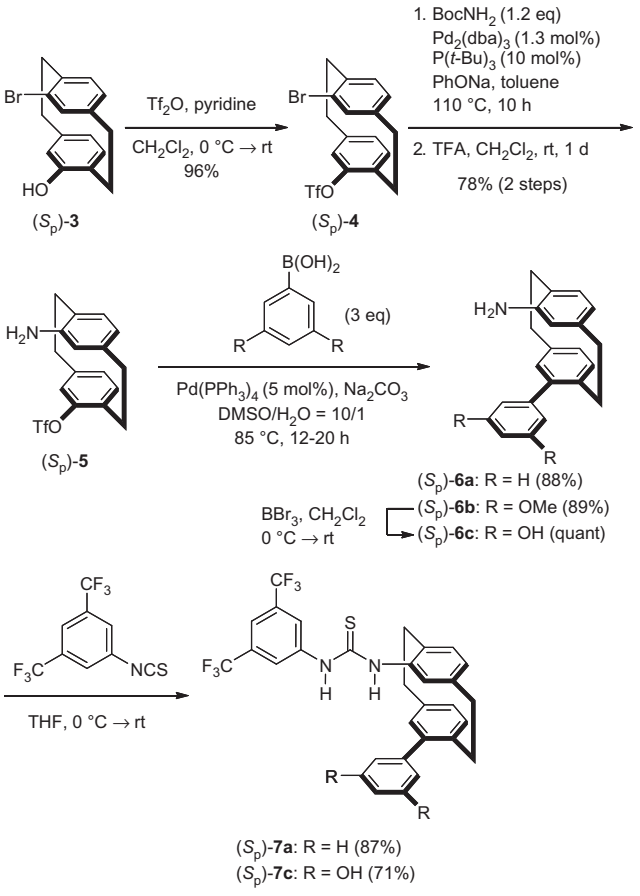


Scheme 1. Synthetic plan towards *pseudo–ortho*-substituted aryl[2.2]paracyclophanes **1**.

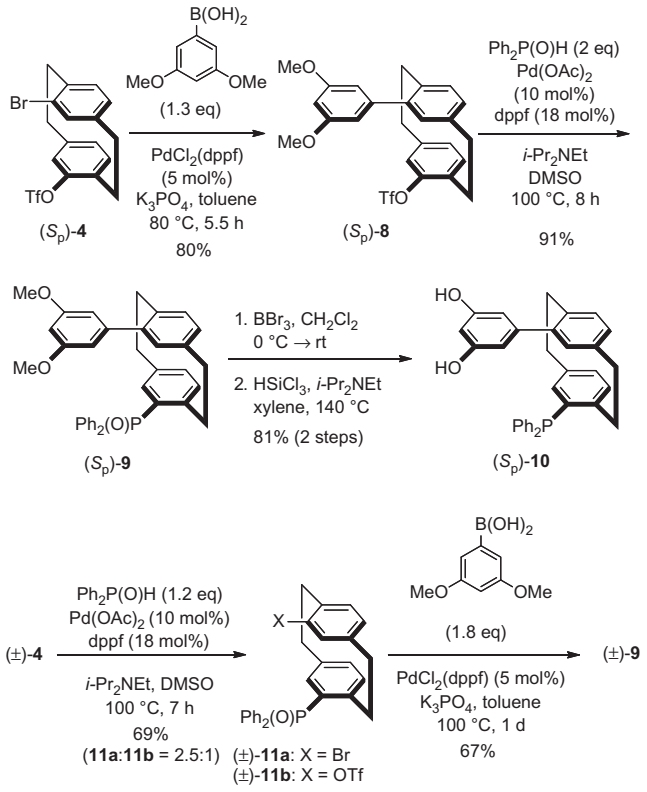
obtain the singly-coupled product, due to their different reactivities. Based on this plan, our initial investigation focused on the synthesis of optically active thioureas **1** [R^1 = $NHCSNHC_6H_3$-3,5-$(CF_3)_2$].

Compound (S_p)-**3**, prepared according to Rozenberg's procedure,[19] was triflated by conventional means (Scheme 2), and the palladium-catalyzed amination of the obtained (S_p)-**4** was investigated. As a result, a two-step procedure, which consists of the Buchwald–Hartwig amination using *N-tert*-butyl carbamate as the ammonia equivalent[20] and subsequent exposure to trifluoroacetic acid, was found to selectively give the desired *mono*-aminated cyclophanyl triflate (S_p)-**5** in good yield.[21,22] The next installation of an aryl group at the *pseudo–ortho* position was attained by conducting the Suzuki–Miyaura coupling. Thus, a nonfunctionalized phenyl group or a 3,5-dimethoxyphenyl one was introduced onto the cyclophane core in high yield using the corresponding boronic acid, and the latter product was demethylated using boron tribromide. Finally, treatment of the amine (S_p)-**6** with 3,5-bis(trifluoromethyl)phenyl isothiocyanate produced the corresponding thiourea (S_p)-**7**.

The synthesis of cyclophanylphosphine (S_p)-**10** was examined next. In this case, the installation of an aryl group by a Suzuki–Miyaura coupling was undertaken prior to the palladium-catalyzed phosphinylation (Scheme 3).[23] Thus, the reaction of (S_p)-**4** with 1.3 equiv of 3,5-dimethoxyphenyboronic acid in the presence of 5 mol % $PdCl_2$(dppf) and K_3PO_4 gave the monoarylated triflate (S_p)-**8** in 80% yield together with a trace amount of the diarylated one. Next, the palladium-catalyzed phosphinylation of (S_p)-**8** with diphenylphosphine oxide afforded the desired product (S_p)-**9** in 91% yield. Demethylation of the *pseudo–ortho*-aryl group and the subsequent reduction of the phosphine oxide with trichlorosilane gave the target compound (S_p)-**10**. An alternative sequence of the phosphinylation/Suzuki–Miyaura coupling was also screened. Thus, monophosphinylation of (±)-**4** with 1.2 equiv of diphenylphosphine oxide gave the desired coupling products as a 2.5:1 mixture of the bromide (±)-**11a** and triflate (±)-**11b** in 69% yield together with the recovered starting material (±)-**4** (20%) when 1,1′-bis(diphenylphosphino)ferrocene (dppf) was used as the bidentate ligand (Scheme 3).[24] Exposure of the resulting mixture (±)-**11a** and (±)-**11b** to the Suzuki–Miyaura coupling conditions afforded an arylated product (±)-**9** in 67% yield, and of the substrates, only triflate (±)-**11b** was recovered in 23%. The moderate yield of the desired product in each step was attributed to the insufficient reactivity of the phosphinylation[25] and excessively



Scheme 2. Preparation of *pseudo–ortho*-substituted cyclophanylthioureas (S_p)-**7**.



Scheme 3. Preparation of *pseudo–ortho*-substituted cyclophanylphosphine (S_p)-**10**.

low reactivity of the Suzuki–Miyaura coupling[23] by the trifluoromethanesulfonyloxy group. Therefore, the successive couplings in reverse order could have provided better results.

3. Conclusion

In conclusion, we have developed a concise and efficient synthetic method for preparing planar chiral *pseudo*–*ortho*-substituted aryl[2.2]paracyclophane molecules through the stepwise successive palladium-catalyzed coupling of the corresponding bromocyclophanyl triflate. The evaluation of the catalytic activity of the newly synthesized chiral cyclophanyl-thioureas and -phosphine based on the Morita–Baylis–Hillman reaction or other asymmetric catalysis is currently under investigation.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were measured in $CHCl_3$. ^1H NMR spectra were taken in $CDCl_3$ unless otherwise stated. $CHCl_3$ (7.26 ppm) for silyl compounds and tetramethylsilane (0.00 ppm) for compounds without a silyl group were used as internal standards. ^{13}C NMR spectra were recorded in $CDCl_3$ with $CDCl_3$ (77.00 ppm) as an internal standard. Reactions were carried out under a nitrogen atmosphere unless otherwise stated. Silica gel (Silica Gel 60, 230–400 mesh) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4. Compound (S_p)-**3** was prepared according to literature procedures.[4c,19]

4.2. (S_p)-12-Bromo[2.2]paracyclophan-4-yl trifluoromethanesulfonate (S_p)-4

To a solution of (S_p)-**3** (363 mg, 1.20 mmol) in CH_2Cl_2 (12 mL) were added pyridine (0.58 mL, 7.2 mmol) and Tf_2O (0.45 mL, 2.4 mmol) at 0 °C. After being stirred for 1.5 h at room temperature, the reaction mixture was quenched by the addition of water and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (10:1) to afford (S_p)-**4** (502 mg, 96%) as a colorless solid: mp 112–113 °C; $[\alpha]_D^{26} = +35.9$ (*c* 1.00, $CHCl_3$); IR 1420, 1207, 1140 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 6.94 (d, *J* = 1.4 Hz, 1H), 6.92 (d, *J* = 1.4 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.60 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 6.49 (dd, *J* = 7.6, 1.4 Hz, 1H), 3.49–3.39 (m, 2H), 3.17–2.99 (m, 4H), 2.86–2.76 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 148.1, 143.0, 141.3, 138.7, 136.1, 135.1, 133.8, 132.7, 131.8, 131.7, 126.6, 123.2, 118.7 (q, $J_{C\text{-}F}$ = 320.8 Hz), 35.4, 33.1, 32.4, 31.6; MS (EI): *m*/*z* (%) = 434 (31.9, M^+), 436 (31.4, M^+); HRMS calcd for $C_{17}H_{14}O_3F_3SBr$: 433.9799, found 433.9800; calcd for $C_{17}H_{14}O_3F_3S^{81}Br$: 435.9779, found 435.9779.

4.3. (S_p)-12-Amino[2.2]paracyclophan-4-yl trifluoromethanesulfonate (S_p)-5

To a solution of (S_p)-**4** (489 mg, 1.12 mmol), *t*-butyl carbamate (158 mg, 1.35 mmol), $Pd_2(dba)_3$ (12.8 mg, 0.0141 mmol), and NaOPh (196 mg, 1.69 mmol) in toluene (5.6 mL) was added P(*t*-Bu)$_3$ (10 wt % in hexane, 0.33 mL, 0.11 mmol) at room temperature under an argon atmosphere. After stirring for 10 h at 110 °C, the reaction mixture was cooled and diluted with saturated aqueous $NaHCO_3$. The whole was extracted with Et_2O and the extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (14:1) to afford the crude amide (668 mg) contaminated with PhOH. To a solution of the crude amide (668 mg) in CH_2Cl_2 (15 mL) was added TFA (0.92 mL, 12 mmol) at room temperature. The reaction mixture was stirred for 1 day, quenched by the addition of saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (20:1) to afford (S_p)-**5** (326 mg, 78% for two steps) as a colorless oil: $[\alpha]_D^{25} = -22.0$ (*c* 1.00, $CHCl_3$); IR 3470, 3389, 1420, 1207, 1142 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.07 (d, *J* = 1.4 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.49 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.32 (d, *J* = 7.9 Hz, 1H), 6.10 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.80 (s, 1H), 3.52 (br s, 2H), 3.36–3.28 (m, 1H), 3.16–3.07 (m, 2H), 3.06–3.01 (m, 1H), 3.00–2.93 (m, 1H), 2.92–2.85 (m, 1H), 2.81–2.72 (m, 1H), 2.71–2.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 144.9, 142.6, 141.1, 135.5, 135.3, 132.8, 131.0, 124.3, 122.8, 121.3, 118.2, 117.1, 33.4, 32.1, 31.9, 31.3; MS (EI): *m*/*z* (%) = 371 (14.6, M^+); HRMS calcd for $C_{17}H_{16}F_3NSO_3$: 371.0803, found 371.0805.

4.4. Typical procedure for the synthesis of (S_p)-4-amino-12-aryl [2.2]paracyclophane (S_p)-6

To a solution of (S_p)-**5** (36.2 mg, 0.0975 mmol), phenylboronic acid (37.4 mg, 0.307 mmol), and $Pd(PPh_3)_4$ (5.9 mg, 5.1×10^{-3} mmol) in DMSO (0.7 mL) was added aqueous Na_2CO_3 (2 M, 70 μL, 0.14 mmol) at room temperature under an argon atmosphere. After stirring for 12 h at 85 °C, the reaction mixture was cooled and diluted with saturated aqueous $NaHCO_3$. The whole was extracted with Et_2O and the extract was washed with brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–acetone (29:1) to afford (S_p)-**6a** (25.6 mg, 88%) as a pale yellow solid.

4.4.1. (S_p)-4-Amino-12-phenyl[2.2]paracyclophane (S_p)-6a

Mp 140–141 °C; $[\alpha]_D^{25} = +92.1$ (*c* 0.47, $CHCl_3$); IR 3462, 3383 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 2.1 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.43 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.41 (d, *J* = 7.9 Hz, 1H), 6.20 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.61 (d, *J* = 1.4 Hz, 1H), 3.56 (br s, 2H), 3.49–3.32 (m, 1H), 3.25–3.04 (m, 3H), 2.94–2.79 (m, 1H), 2.78–2.60 (m, 2H), 2.42–2.27 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.3, 141.5, 141.3, 140.7, 139.0, 136.2, 134.9, 134.8, 132.3, 129.5, 128.4, 127.7, 126.6, 124.5, 123.1, 117.9, 34.1, 34.0, 32.3, 32.2; MS (EI): *m*/*z* (%) = 299 (10.2, M^+); HRMS calcd for $C_{22}H_{21}N$: 299.1674, found 299.1675.

4.4.2. (S_p)-4-Amino-12-(3,5-dimethoxyphenyl) [2.2]paracyclophane (S_p)-6b

Compound (S_p)-**6b** was obtained as a colorless solid (89% yield): mp 158–159 °C; $[\alpha]_D^{25} = -78.7$ (*c* 1.00, $CHCl_3$); IR 3462, 3381 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, *J* = 1.8 Hz, 1H), 6.70–6.66 (m, 3H), 6.45 (t, *J* = 2.3 Hz, 1H), 6.44–6.36 (m, 2H), 6.19 (dd, *J* = 7.8, 1.8 Hz, 1H), 5.65 (d, *J* = 1.8 Hz, 1H), 3.86 (s, 6H), 3.61–3.43 (m, 3H), 3.20–3.06 (m, 3H), 2.91–2.81 (m, 1H), 2.80–2.68 (m, 2H), 2.51–2.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 144.2, 143.7, 141.3, 140.7, 139.0, 136.3, 134.9, 134.8, 132.4, 127.7, 124.5, 123.1, 118.0, 107.8, 98.3, 55.4, 34.2, 34.1, 32.3, 32.1; MS (EI): *m*/*z* (%) = 359 (14.0, M^+); HRMS calcd for $C_{24}H_{25}O_2N$: 359.1885, found 359.1880.

4.5. (S_p)-5-(12-Amino[2.2]paracyclophan-4-yl)resorcinol (S_p)-6c

To a solution of (S_p)-**6b** (30.0 mg, 0.0834 mmol) in CH_2Cl_2 (0.8 mL) was added BBr_3 (20.6 μL, 0.217 mmol) at 0 °C. The reaction mixture was stirred for 1 h, quenched by the addition of saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated to dryness. The residue

was chromatographed with hexane–AcOEt (3:2) to afford (S_p)-**6c** (28.9 mg, quant) as a colorless solid: mp 148–149 °C; $[\alpha]_D^{26} = -93.7$ (*c* 0.96, MeOH); IR 3595, 3312 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ 7.09 (d, *J* = 1.7 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 6.47 (d, *J* = 2.1 Hz, 2H), 6.39 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.32 (d, *J* = 7.6 Hz, 1H), 6.26 (t, *J* = 2.1 Hz, 1H), 6.07 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.65 (d, *J* = 1.7 Hz, 1H), 3.58–3.45 (m, 1H), 3.30–3.18 (m, 1H), 3.17–3.08 (m, 1H), 3.07–2.97 (m, 1H), 2.83–2.58 (m, 3H), 2.41–2.26 (m, 1H); ^{13}C NMR (150 MHz, CD_3OD): δ 159.3, 146.6, 145.3, 142.2, 142.1, 140.5, 137.3, 136.2, 136.1, 133.2, 128.4, 125.4, 123.2, 118.9, 109.1, 101.8, 35.4, 35.0, 33.2, 33.2; MS (EI): *m*/*z* (%) = 331 (53.7, M^+); HRMS calcd for $C_{22}H_{21}O_2N$: 331.1572, found 331.1578.

4.6. Typical procedure for the synthesis of thioureas (S_p)-7

To a solution of (S_p)-**6a** (10.8 mg, 0.0361 mmol) in THF (0.7 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (21.0 μL, 0.108 mmol) at 0 °C. The reaction mixture was stirred for 18 h at room temperature and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (10:1) to afford (S_p)-**7a** (17.9 mg, 87%) as a colorless solid.

4.6.1. (S_p)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*′-{12-phenyl[2.2]paracyclophan-4-yl}thiourea (S_p)-7a

Mp 78–79 °C; $[\alpha]_D^{25} = -21.2$ (*c* 0.48, $CHCl_3$); IR 3402, 3348 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.97 (s, 2H), 7.67 (s, 1H), 7.64 (s, 1H), 7.57 (s, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.43 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 2.1 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.76 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.51 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.35 (s, 1H), 3.54–3.46 (m, 1H), 3.40–3.33 (m, 1H), 3.33–3.24 (m, 1H), 3.14–3.07 (m, 1H), 3.00–2.86 (m, 3H), 2.63–2.55 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.4, 143.5, 141.9, 140.1, 139.7, 139.1, 136.9, 136.4, 136.0, 135.5, 133.5, 133.1, 132.6, 131.9 (q, J_{C-F} = 33.2 Hz), 129.3, 129.0, 128.1, 127.4, 127.4, 124.4, 122.9 (q, J_{C-F} = 274.6 Hz), 119.3, 34.0, 33.8, 33.4, 32.8; MS (EI): *m*/*z* (%) = 570 (1.5, M^+); HRMS calcd for $C_{31}H_{24}F_6N_2S$: 570.1564, found 570.1560.

4.6.2. (S_p)-*N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*′-{12-(3,5-dihydroxyphenyl)[2.2]paracyclophan-4-yl}thiourea (S_p)-7c

Compound (S_p)-**7c** was obtained as a colorless solid (71% yield): mp 103–104 °C; $[\alpha]_D^{25} = -211.5$ (*c* 0.30, $CHCl_3$); IR 3595, 3394, 3342 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.91 (s, 2H), 7.74 (br s, 1H), 7.69 (s, 1H), 7.66 (s, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.72 (s, 1H), 6.67 (d, *J* = 6.9 Hz, 1H), 6.65–6.59 (m, 2H), 6.56 (d, *J* = 2.1 Hz, 2H), 6.44 (dd, *J* = 7.9, 2.1 Hz, 1H), 6.35 (s, 1H), 3.49–3.39 (m, 1H), 3.36–3.24 (m, 1H), 3.24–3.13 (m, 1H), 3.12–3.02 (m, 1H), 3.01–2.84 (m, 2H), 2.83–2.74 (m, 1H), 2.64–2.54 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.4, 157.5, 143.6, 142.5, 141.7, 139.2, 138.8, 137.1, 136.0, 135.9, 134.2, 133.2, 133.0, 132.9, 132.1 (q, J_{C-F} = 33.2 Hz), 127.5, 127.3, 124.9, 122.8 (q, J_{C-F} = 274.6 Hz), 119.9 (q, J_{C-F} = 4.3 Hz), 109.0, 101.7, 34.0, 33.5, 33.3, 31.7; MS (EI): *m*/*z* (%) = 602 (6.3, M^+); HRMS calcd for $C_{31}H_{24}F_6N_2O_2S$: 602.1463, found 602.1461.

4.7. (S_p)-12-(3,5-Dimethoxyphenyl)[2.2]paracyclophan-4-yl trifluoromethanesulfonate (S_p)-8

To a mixture of (S_p)-**4** (101 mg, 0.232 mmol), 3,5-dimethoxyphenylboronic acid (54.8 mg, 0.301 mmol), $PdCl_2$(dppf) (9.5 mg, 0.012 mmol) and K_3PO_4 (148 mg, 0.696 mmol) was added toluene (2.3 mL) at room temperature under an argon atmosphere. After being stirred for 5.5 h at 80 °C, the reaction mixture was cooled and concentrated to dryness. The residue was chromatographed with hexane–CH_2Cl_2 (2:1) to afford (S_p)-**8** (91.5 mg, 80%) as a colorless solid: mp 149–152 °C; $[\alpha]_D^{23} = -58.8$ (*c* 1.00, $CHCl_3$); IR 1421, 1205, 1155, 1140 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 6.96 (s, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 1.4 Hz, 2H), 6.48–6.46 (m, 2H), 6.40 (s, 1H), 3.87 (s, 6H), 3.62–3.45 (m, 2H), 3.23–3.07 (m, 2H), 2.97–2.83 (m, 3H), 2.69–2.61 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.0, 147.7, 143.3, 142.5, 141.9, 139.2, 136.6, 135.9, 135.8, 132.8, 132.5, 131.9, 129.2, 124.6, 118.7 (q, J_{C-F} = 320.8 Hz), 107.3, 99.4, 55.4, 34.0, 33.8, 33.2, 31.8; MS (EI): *m*/*z* (%) = 492 (45.5, M^+); HRMS calcd for $C_{25}H_{23}F_3O_5S$: 492.1218, found 492.1213.

4.8. (S_p)-{12-(3,5-Dimethoxyphenyl)[2.2]paracyclophan-4-yl}diphenylphosphine oxide (S_p)-9

To a solution of (S_p)-**8** (70.8 mg, 0.144 mmol), $Ph_2P(O)H$ (58.2 mg, 0.288 mmol), $Pd(OAc)_2$ (3.2 mg, 0.014 mmol) and dppf (14.3 mg, 0.0259 mmol) in DMSO (0.7 mL) was added diisopropylethylamine (75 μL, 0.43 mmol) at room temperature under an argon atmosphere. After being stirred for 18.5 h at 100 °C, the reaction mixture was cooled, quenched by the addition of 10% aqueous HCl, and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (2:1) to afford (S_p)-**9** (71.7 mg, 91%) as a yellowish solid: mp 220–223 °C; $[\alpha]_D^{24} = -41.1$ (*c* 1.00, $CHCl_3$); IR 1180, 1155 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.76–7.70 (m, 4H), 7.46–7.34 (m, 6H), 7.17 (s, 1H), 6.86 (d, *J* = 2.1 Hz, 2H), 6.76 (d, *J* = 7.2 Hz, 1H), 6.71–6.65 (m, 3H), 6.59 (d, *J* = 6.9 Hz, 1H), 6.40 (s, 1H), 3.83 (s, 6H), 3.70 (td, *J* = 13.7, 9.6 Hz, 1H), 3.32–3.27 (m, 1H), 3.12 (t, *J* = 13.1 Hz, 1H), 3.02 (t, *J* = 11.7 Hz, 1H), 2.94 (dd, *J* = 13.1, 9.6 Hz, 1H), 2.81–2.73 (m, 2H), 2.36–2.31 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.7, 145.8 (d, J_{C-P} = 8.7 Hz), 142.6, 140.7, 139.8, 139.4 (d, J_{C-P} = 11.6 Hz), 136.7, 136.3, 136.2 (d, J_{C-P} = 102.6 Hz), 135.5 (d, J_{C-P} = 11.6 Hz), 135.1, 134.5 (d, J_{C-P} = 13.0 Hz), 133.4, 132.5, (d, J_{C-P} = 98.3 Hz), 132.2 (d, J_{C-P} = 8.7 Hz), 131.2, 131.1 (d, J_{C-P} = 2.9 Hz), 131.0 (d, J_{C-P} = 2.9 Hz), 130.9 (d, J_{C-P} = 10.1 Hz), 129.5 (d, J_{C-P} = 105.5 Hz), 128.2 (d, J_{C-P} = 11.6 Hz), 128.0 (d, J_{C-P} = 11.6 Hz), 107.9, 98.2, 55.4, 36.0 (d, J_{C-P} = 4.3 Hz), 35.4, 34.9, 33.7; ^{31}P NMR (161 MHz, $CDCl_3$): δ 24.1; MS (EI): *m*/*z* (%) = 544 (100.0, M^+); HRMS calcd for $C_{36}H_{33}O_3P$: 544.2167, found 544.2164.

4.9. (S_p)-{12-(3,5-Dihydroxyphenyl)[2.2]paracyclophan-4-yl}diphenylphosphine (S_p)-10

To a solution of (S_p)-**9** (47.9 mg, 8.80×10^{-2} mmol) in CH_2Cl_2 (0.9 mL) was added BBr_3 (83 μL, 0.88 mmol) at −78 °C. After being stirred for 2 h at room temperature, the reaction mixture was quenched by the addition of dry MeOH and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (1:1) to give the demethylation product (46.3 mg, quant.) as a brownish solid. To the demethylation product (46.3 mg) in xylene (0.9 mL) were added $HSiCl_3$ (0.50 mL, 3.0 mmol) and diisopropylethylamine (0.90 mL, 5.2 mmol) at 0 °C. After being stirred for 2 d at 140 °C, the reaction mixture was cooled and quenched by the addition of saturated aqueous $NaHCO_3$, filtered on Celite and extracted with AcOEt. The extract was washed with brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (3:1) to give (S_p)-**10** (35.9 mg, 81%) as a colorless solid: $[\alpha]_D^{20} = -113.8$ (*c* 0.81, $CHCl_3$); IR 3447, 3344, 3277 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74–7.69 (m, 2H), 7.47–7.33 (m, 5H), 7.22–7.19 (m, 3H), 6.95 (s, 1H), 6.67 (d, *J* = 7.3 Hz, 1H), 6.62–6.60 (m, 3H), 6.39 (d, *J* = 8.2 Hz, 1H), 6.24 (t, *J* = 2.3 Hz, 1H), 6.19 (d, *J* = 2.3 Hz, 2H), 4.55 (br s 2H), 3.49–3.27 (m, 3H), 3.13 (t, *J* = 10.0 Hz, 1H), 2.91 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.78–2.66 (m, 2H), 2.29–2.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 143.6 (d, J_{C-P} = 23.0 Hz), 143.5, 140.1, 139.9, 139.7 (d, J_{C-P}

= 11.5 Hz), 139.4, 137.9 (d, $J_{C\text{-}P}$ = 11.5 Hz), 137.0, 136.3 (d, $J_{C\text{-}P}$ = 23.0 Hz), 135.7, 135.5 (d, $J_{C\text{-}P}$ = 10.5 Hz), 134.7 (d, $J_{C\text{-}P}$ = 4.8 Hz), 133.1, 132.7 (d, $J_{C\text{-}P}$ = 1.9 Hz), 132.4 (d, $J_{C\text{-}P}$ = 20.1 Hz), 131.9, 130.2, 129.9 (d, $J_{C\text{-}P}$ = 2.9 Hz), 128.9 (d, $J_{C\text{-}P}$ = 8.6 Hz), 128.4 (d, $J_{C\text{-}P}$ = 11.5 Hz), 128.3, 108.5, 101.0, 36.0 (d, $J_{C\text{-}P}$ = 9.6 Hz), 35.2, 33.8, 33.2 (d, $J_{C\text{-}P}$ = 2.9 Hz); ^{31}P NMR (161 MHz, $CDCl_3$): δ −1.67; MS (EI): *m*/*z* (%) = 500 (100.0, M^+); HRMS calcd for $C_{34}H_{29}O_2P$: 500.1905, found 500.1903.

4.10. Phosphinylation of (±)-4

According to the procedure for the synthesis of (S_p)-**9**, (±)-**4** (100 mg, 0.230 mmol) was phosphinylated using $Ph_2P(O)H$ (55.8 mg, 0.276 mmol), $Pd(OAc)_2$ (5.2 mg, 0.023 mmol), dppf (23.0 mg, 0.0414 mmol) and diisopropylethylamine (0.12 mL, 0.69 mmol) to afford a mixture of (±)-**11a** and (±)-**11b** (80.3 mg, 69%, **11a**:**11b** = 2.5:1) as a colorless solid. Analytically pure (±)-**11a** and (±)-**11b** were obtained by careful column chromatography with CH_2Cl_2.

4.10.1. {12-Bromo[2.2]paracyclophan-4-yl}diphenylphosphine oxide 11a[4c]

IR 1180 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.74 (m, 2H), 7.58–7.52 (m, 3H), 7.48–7.43 (m, 3H), 7.39–7.35 (m, 2H), 7.28 (d, *J* = 1.8 Hz, 1H), 6.82 (dd, *J* = 14.6, 1.8 Hz, 1H), 6.66 (dd, *J* = 7.8, 4.1 Hz, 1H), 6.62 (s, 1H), 6.59 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 3.50–3.36 (m, 3H), 3.06–2.91 (m, 3H), 2.86–2.80 (m, 1H), 2.73 (ddd, *J* = 13.3, 10.5, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5 (d, $J_{C\text{-}P}$ = 7.7 Hz), 142.0, 138.9 (d, $J_{C\text{-}P}$ = 13.4 Hz), 138.5, 138.4, 137.2 (d, $J_{C\text{-}P}$ = 2.9 Hz), 135.5 (d, $J_{C\text{-}P}$ = 11.5 Hz), 135.2 (d, $J_{C\text{-}P}$ = 103.5 Hz), 133.8, 133.2 (d, $J_{C\text{-}P}$ = 13.4 Hz), 132.7 (d, $J_{C\text{-}P}$ = 9.6 Hz), 131.6 (d, $J_{C\text{-}P}$ = 102.6 Hz), 131.5 (d, $J_{C\text{-}P}$ = 2.9 Hz), 131.4 (d, $J_{C\text{-}P}$ = 9.6 Hz), 131.4 (d, *J* = 2.9 Hz), 130.9, 129.9 (d, $J_{C\text{-}P}$ = 105.4 Hz), 128.2 (d, $J_{C\text{-}P}$ = 11.5 Hz), 128.0 (d, $J_{C\text{-}P}$ = 11.5 Hz), 127.1, 35.7 (d, $J_{C\text{-}P}$ = 2.9 Hz), 35.7, 34.5, 32.2; MS (EI): *m*/*z* (%) = 486 (100.0, M^+), 488 (100.0, M^+); HRMS calcd for $C_{28}H_{24}OBrP$: 486.0748, found 486.0747; calcd for $C_{28}H_{24}O^{81}BrP$: 488.0728, found 488.0724.

4.10.2. {12-Trifluoromethanesulfonyloxy[2.2]paracyclophan-4-yl}diphenylphosphine oxide 11b

IR 1420, 1178, 1140 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.65 (m, 2H), 7.60–7.55 (m, 3H), 7.51–7.46 (m, 3H), 7.42–7.37 (m, 2H), 7.16 (d, *J* = 0.9 Hz, 1H), 6.69–6.59 (m, 4H), 6.53 (d, *J* = 14.7 Hz, 1H), 3.53–3.43 (m, 2H), 3.37 (ddd, *J* = 11.4, 9.6, 1.4 Hz, 1H), 3.10 (br t, *J* = 11.4 Hz, 1H), 3.01–2.93 (m, 1H), 2.90–2.83 (m, 2H), 2.78–2.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 145.3 (d, $J_{C\text{-}P}$ = 7.7 Hz), 143.9, 139.1 (d, $J_{C\text{-}P}$ = 12.5 Hz), 137.1 (d, $J_{C\text{-}P}$ = 2.9 Hz), 135.6 (d, $J_{C\text{-}P}$ = 11.5 Hz), 134.9, 134.6 (d, $J_{C\text{-}P}$ = 104.5 Hz), 134.0 (d, $J_{C\text{-}P}$ = 13.4 Hz), 133.3 (d, $J_{C\text{-}P}$ = 101.6 Hz), 132.1 (d, $J_{C\text{-}P}$ = 9.6 Hz), 131.8 (d, $J_{C\text{-}P}$ = 1.9 Hz), 131.7, 131.6 (d, *J* = 2.9 Hz), 131.4 (d, *J* = 9.6 Hz), 131.0, 129.7 (d, $J_{C\text{-}P}$ = 99.7 Hz), 129.0, 128.4 (d, $J_{C\text{-}P}$ = 8.6 Hz), 128.3 (d, $J_{C\text{-}P}$ = 8.6 Hz), 118.7 (q, $J_{C\text{-}F}$ = 321.1 Hz), 35.2 (d, $J_{C\text{-}P}$ = 4.8 Hz), 34.2, 32.9, 31.8; MS (EI): *m*/*z* (%) = 556 (100.0, M^+); HRMS calcd for $C_{29}H_{24}F_3O_4PS$: 556.1085, found 556.1083.

4.11. Suzuki–Miyaura cross-coupling of a mixture of (±)-11a and (±)-11b

To a mixture of (±)-**11a** and (±)-**11b** (2.5:1, 80.3 mg, 0.158 mmol) and 3,5-dimethoxyphenylboronic acid (54.6 mg, 0.300 mmol) in toluene (1.7 mL) were added $PdCl_2$(dppf) (6.8 mg, 8.3×10^{-3} mmol) and K_3PO_4 (106 mg, 0.498 mmol) at room temperature under an argon atmosphere. After being stirred for 23 h at 100 °C, the reaction mixture was cooled and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (10:1) to afford (±)-**9** (57.7 mg, 67%) as a colorless solid.

4.12. (±)-4,12-Bis(diphenylphosphinyl)[2.2]paracyclophane (±)-12[3a]

According to the procedure for the synthesis of (S_p)-**9**, (±)-**4** (387 mg, 0.888 mmol) was phosphinylated using $Ph_2P(O)H$ (360 mg, 1.78 mmol), $Pd(OAc)_2$ (20 mg, 8.9×10^{-2} mmol), dppf (89 mg, 0.16 mmol) and diisopropylethylamine (0.46 mL, 2.7 mmol) to afford (±)-**12** (336.3 mg, 65%) as a brownish solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.65 (m, 4H), 7.57–7.49 (m, 10H), 7.40–7.36 (m, 2H), 7.31–7.26 (m, 4H), 7.13 (dd, *J* = 14.7, 1.4 Hz, 2H), 6.77 (d, *J* = 7.8 Hz, 2H), 6.64 (dd, *J* = 7.3, 4.1 Hz, 2H), 3.39–3.32 (m, 2H), 3.22 (br t, *J* = 11.7 Hz, 2H), 3.02 (br t, *J* = 11.7 Hz, 2H), 2.73 (ddd, *J* = 12.8, 10.1, 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6 (d, $J_{C\text{-}P}$ = 8.6 Hz), 139.9 (d, $J_{C\text{-}P}$ = 13.4 Hz), 138.3 (d, $J_{C\text{-}P}$ = 12.4 Hz), 136.8 (d, $J_{C\text{-}P}$ = 102.6 Hz), 136.5 (d, $J_{C\text{-}P}$ = 2.9 Hz), 134.8 (d, $J_{C\text{-}P}$ = 11.5 Hz), 132.3 (d, $J_{C\text{-}P}$ = 8.6 Hz), 131.7 (d, $J_{C\text{-}P}$ = 103.5 Hz), 131.6 (d, $J_{C\text{-}P}$ = 2.9 Hz), 130.9, 130.8 (d, $J_{C\text{-}P}$ = 8.6 Hz), 129.9 (d, $J_{C\text{-}P}$ = 105.4 Hz), 128.0 (d, $J_{C\text{-}P}$ = 11.5 Hz), 127.9 (d, $J_{C\text{-}P}$ = 11.5 Hz), 36.2 (d, $J_{C\text{-}P}$ = 4.8 Hz), 34.7.

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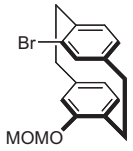
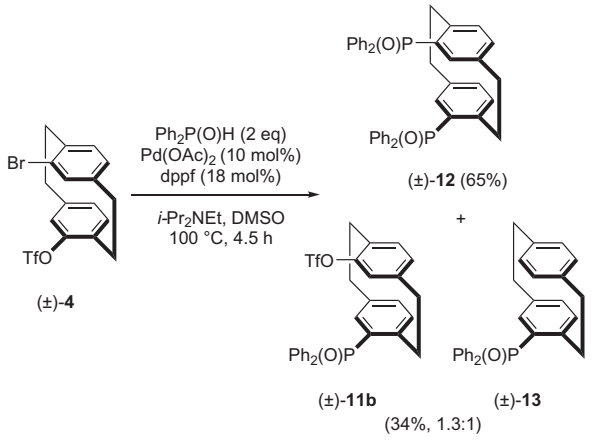
21. Before examination of the bromocyclophanyl triflate **4**, we explored the palladium-catalyzed amination reaction using the MOM-protected *pseudo–ortho*-bromo[2.2]cyclophanol (±)-**4′** as a substrate. As a result, the method using *N-tert*-butyl carbamate was shown to be more effective than those using benzylamine[3b] or benzophenone imine[13b] as an ammonia equivalent, and it was applied to the reaction of (S_p)-**4**.



4′

22. To the best of our knowledge, no systematic study of the palladium-catalyzed amination of haloaryl triflates has been reported. Buchwald et al. demonstrated that in the reaction of bromoaryl nonaflates, the selective substitution of the nonaflate moiety could be achieved in good yields with use of BINAP ligand. However, they also reported that in the reaction of 4-bromophenyl nonaflate with aniline, the amine was selectively substituted for the bromide in preference to the nonaflate with use of (2-biphenyl)di-*tert*-butylphosphine as the ligand. Anderson, K. W.; Mendez-Perez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563–9573.
23. In the case of Suzuki–Miyaura coupling reaction, aryl triflates are known to be less reactive than the corresponding bromides. (a) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201-2208. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
24. This reaction did not proceed when diphenylphosphinopropane (dppp), the most popular ligand for this type of reaction, was used. The use of 2 equiv of diphenylphosphine oxide under the influence of $Pd(OAc)_2$ and dppf gave the diphosphinylated product **12** in 65% yield together with a mixture of the monophosphinyl triflate **11b** and the hydrogenated phosphine oxide **13** (34%, 1.3:1). Since the diphosphinylated product **12** is known as a synthetic intermediate of [2.2]PHANEPHOS,[3a] this could be an alternative synthetic method for PHANEPHOS.



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