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A novel class of bidentate ligands with a conformationally flexible biphenyl unit built into a planar chiral [2.2]paracyclophane backbone

V. I. Rozenberg,* D. Yu. Antonov, R. P. Zhuravsky, E. V. Vorontsov and Z. A. Starikova

A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russia

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Abstract—We report the synthesis of a novel class of planar chiral bidentate aryl[2.2]paracyclophane ligands. For the first time in the [2.2]paracyclophanyl series the Pd-catalyzed Suzuki cross-coupling was employed for the formation of the arylparacyclophanyl skeleton. From the two possible approaches: (a) cross-coupling of [2.2]paracyalophanylboronic acids with aryl halides; (b) cross-coupling of [2.2]paracyclophanyl halides with arylboronic acids, the latter was found to be more efficient. This approach was successfully used for the synthesis of a wide range of aryl[2.2]paracyclophanes with different types of substitution patterns (*ortho*-, *pseudo-ortho*- or *pseudo-gem*-arrangement of the functionally-substituted aryl fragment with respect to the substituent in the paracyclophane ring).

One general strategy in the field of asymmetric synthesis is based on the application of catalysts constructed from *chirally rigid* ligands. A new powerful conceptual approach for asymmetric catalysis involves the design and application of catalysts, combining *conformationally flexible* ligands and a *chirally stable* stereogenic part.[1,2] These self-organized diastereomeric catalysts can provide better stereocontrol due to dynamic conformational behavior and, as a result, superior fine-tuning of the chiral environment. As a rule, the conformationally flexible part of these catalysts is played by a biphenyl unit or derivatives thereof.[2,3]

Earlier[4] we reported a number of effective approaches to the synthesis of a series of chiral bidentate ligands constructed from one or two [2.2]paracyclophane moieties and possessing not only planar chiral elements but also central ones (multichirality). In this study we describe a novel class of planar chiral bidentate ligands, with a conformationally flexible biphenyl unit built into a configurationally stable [2.2]paracyclophane backbone. In these ligands the biphenyl unit is formed by one aromatic ring of the [2.2]paracyclophane and the *ortho*-substituted benzene ring. The second functional group Y can be placed in any ring of the [2.2]paracyclophane backbone, but must be located in an *ortho*-position (Type **I**), a *pseudo-ortho*-position (Type **II**) or a *pseudo-gem*-position (Type **III**) towards the aryl substituent to allow chelation with a metal atom (Fig. 1).

For the synthesis of these types of bifunctional arylparacyclophanes[5] we used Suzuki cross-coupling, the most versatile, pragmatic and extensively utilized method for the synthesis of functionally substituted unsymmetrical biaryls.[6]

Synthesis of *ortho*-substituted aryl[2.2]paracyclophanes

We considered two possible synthetic routes to arylparacyclophanes of Type **I**, namely, cross-coupling of paracyclophanylboronic acid (obtained from 4-hydroxy[2.2]paracyclophane **1**) with bromoanisole and paracyclophanyl halides (from **1**) with arylboronic acids.

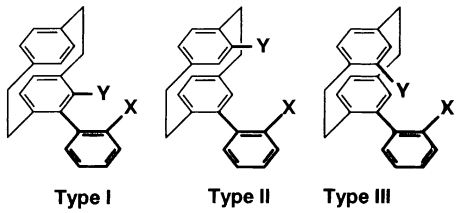

Figure 1.

* Corresponding author. Tel.: +7-095-135-9268; fax: +7-095-135-5085; e-mail: lera@ineos.ac.ru

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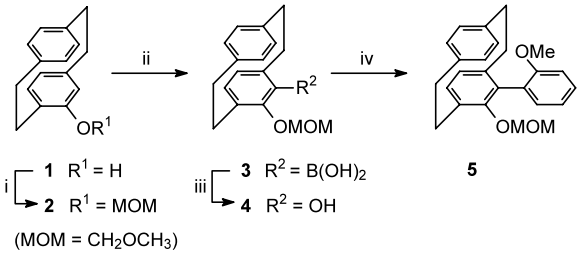
(a) Cross-coupling of paracyclophanylboronic acid and *ortho*-bromoanisole. Lithiation of MOM-protected paracyclophanol **2**[7] with *n*-BuLi in Et_2O followed by treatment of the reaction mixture with $B(OMe)_3$ resulted in the corresponding paracyclophanylboronic acid **3** which was then used in cross-coupling without isolation. The yield of **3** (50%) was estimated from the preparative yield of 5-hydroxy-4-methoxymethyleneoxy[2.2]paracyclophane **4** obtained by oxidation of **3** in situ with hydrogen peroxide in a basic medium (Scheme 1).

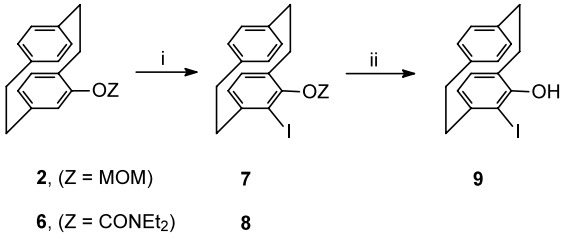
Cross-coupling of **3** and *ortho*-bromoanisole (2 equiv.) was carried out by refluxing the reagents in a toluene/$MeOH/H_2O$ mixture in the presence of Na_2CO_3 as base and $Pd(dppf)Cl_2$ as catalyst (10 mol%) to produce the desired biaryl **5** in up to 20% yield (Scheme 1).

(b) Cross-coupling of [2.2]paracyclophanyl halides and arylboronic acids. For the regioselective introduction of a halogen substituent into the molecule of phenol **1**, its derivatives **2**[7] and **6**[8] were *ortho*-lithiated and then Li was replaced with iodine (Scheme 2). Thus 4-iodo-5-methoxymethyleneoxy[2.2]paracyclophane **7** (80% as a mixture with 5% of unreacted **2**) and 5-diethylcarbamoyloxy-4-iodo[2.2]paracyclophane **8** (98%) were synthesized. Removal of the MOM protecting group in **7** with HCl/MeOH resulted in 5-hydroxy-4-iodo[2.2]-paracyclophane **9** in 80% yield.

Cross-coupling of halide **7** and *ortho*-anisylboronic acid **10** was performed under anhydrous conditions (toluene/K_3PO_4/$Pd(dppf)Cl_2$)[9] (Scheme 3). The aryl[2.2]-paracyclophane **5** was isolated by preparative chromatography on SiO_2 in 44% yield. The unreacted iodophenol **7** was recovered from the reaction mixture in 51% yield. The structure of **5** (CCDC 202651) was studied by X-ray diffraction analysis (Fig. 2).



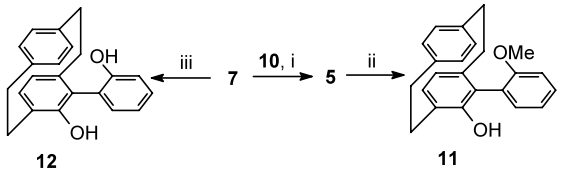
Scheme 1. *Reagents and conditions*: (i) NaH, DMF, rt; then MOMCl, 95%; (ii) *n*-BuLi, Et_2O, 0°C; then $B(OMe)_3$; (iii) H_2O_2, $NaOH/H_2O$, Et_2O, 50%; (iv) 2-BrC_6H_4OMe, $Pd(dppf)Cl_2$ (10 mol%), toluene/$MeOH/H_2O$, Na_2CO_3, reflux, up to 20%.



Scheme 2. *Reagents and conditions*: (i) Z = MOM: *n*-BuLi, Et_2O, 0°C; then I_2, 75%; Z = $CONEt_2$: *n*-BuLi, TMEDA, THF, −78°C; then I_2, 98%; (ii) HCl/MeOH, reflux, 80%.

In order to prepare the biphenol ligand **12**[11] from **5** we first removed the MOM protective group by hydrolysis using HCl/MeOH. The resulting **11** was obtained in quantitative yield; however, numerous Me-deprotection attempts under various conditions were unsuccessful. For instance, the cyclic [2.2]paracyclophano[4,5-*b*]benzofuran (55%) as the only product was obtained in the case of demethylation in HBr/AcOH (1:1) mixture. For this reason target **12** was synthesized by the cross-coupling reaction of **7** and *ortho*-methoxymethyleneoxyphenylboronic acid (instead of **10**) followed by hydrolysis of the intermediate double MOM-protected cyclophane (Scheme 3).

In principle, the three *ortho*-substituted biphenyl units in arylparacyclophanes of Type **I** can be either flexible or enantiomerically stable. Thus in the ^1H NMR spectrum of **5** only one set of the signals detected in the temperature range 293–383 K can probably be attributed to a chirally rigid structure. In the spectrum of the sterically less hindered **11** a double set of signals indicated the existence of two rapidly interconverting diastereomers. The energy barrier to rotation for **11** (17–18 kcal mol^{-1}) was estimated from the coalescence temperature (390 K) for the methoxy signals using the variable-temperature ^1H NMR technique.



Scheme 3. *Reagents and conditions*: (i) **10**, $Pd(dppf)Cl_2$ (2 mol%) and K_3PO_4 in toluene, 100°C, 44%; (ii) HCl/MeOH, 40°C, >98%; (iii) 2-$B(OH)_2$-C_6H_4OMOM, $Pd(dppf)Cl_2$ (2 mol%), K_3PO_4, toluene, 100°C; then HCl/MeOH, reflux, 39%.[10]

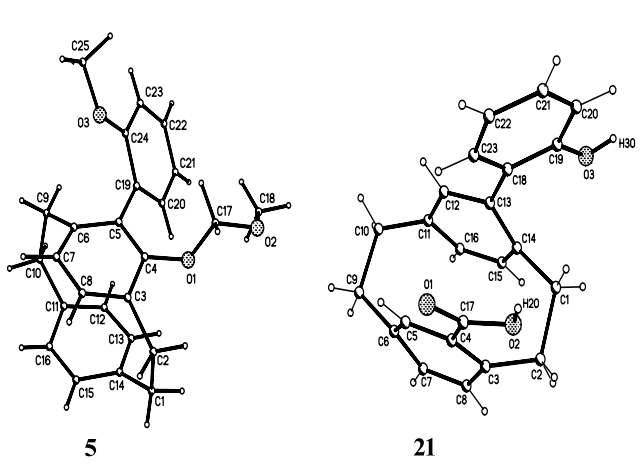


Figure 2. The X-ray crystal structures of **5** and **21**.

Thus we have found that both routes (a) and (b) can be used for the synthesis of disubstituted aryl[2.2]-paracyclophanes, however, the cross-coupling of paracyclophanyl halides with arylboronic acids is more effective. It should be noted that, arylparacyclophanes of Type **I** can be obtained from the enantiomers of **1**, the efficient resolution of which has recently been reported by us.[12]

Synthesis of *pseudo-ortho*-substituted aryl[2.2]paracyclophanes

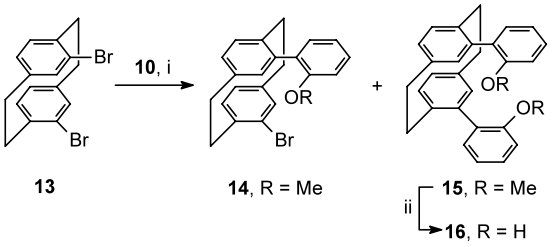
For the synthesis of *pseudo-ortho*-substituted aryl[2.2]-paracyclophanes (Type **II**) we chose *pseudo-ortho*-dibromo[2.2]paracyclophane **13** because of its easy synthetic access[13] and the possibility of obtaining it in optically pure form.[14]

Cross-coupling of **13** with **10** resulted in two products, **14** and **15** (Scheme 4), which were separated by preparative chromatography on SiO_2. The minor 4,12-bis(2-methoxyphenyl)[2.2]paracyclophane **15** (37%) resulted from cross-coupling at both bromine atoms. In contrast to *ortho*-substituted aryl[2.2]paracyclophane **11**, removal of the methyl groups in compound **15** with HBr/AcOH occurred smoothly and led to biphenol **16** in 80% yield (Scheme 4). This biphenol is the first example of a unique bidentate ligand with not only one, but *two conformationally flexible ortho*-functionally-substituted *biphenyl units* built into the chiral [2.2]paracyclophane skeleton.

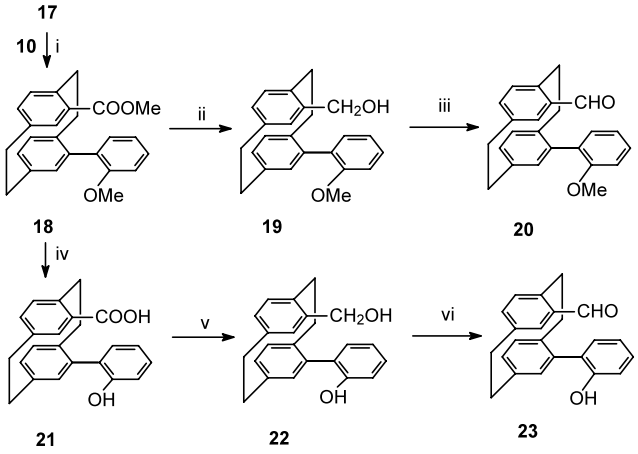
The major reaction product was 4-bromo-12-(2-methoxyphenyl)[2.2]paracyclophane **14**, isolated in 51% yield. The presence of a bromine substituent in **14** opens up considerable prospects for obtaining a series of *pseudo-ortho*-substituted arylparacyclophanes with various donor functional groups (-OH, -CHO, -SR, $-PR_2$, $-NR_2$, etc.).

Synthesis of *pseudo-gem*-substituted aryl[2.2]paracyclophanes

The 4-bromo-13-methoxycarbonyl[2.2]paracyclophane **17**[15] was used as starting compound for the synthesis aryl[2.2]paracyclophanes of Type **III**, because optically active **17** can be readily obtained from enantiomers of



Scheme 4. *Reagents and conditions*: (i) **10**, $Pd(dppf)Cl_2$ (2 mol%), K_3PO_4, toluene, 105°C, 51% of **14** and 37% of **15**; (ii) HBr (48%), AcOH, reflux, 80%.



Scheme 5. *Reagents and conditions*: (i) **10**, $Pd(dppf)Cl_2$ (2 mol%), K_3PO_4, toluene, 105°C, 80%; (ii) $LiAlH_4$, Et_2O, rt, >98%; (iii) DDQ, dioxane, rt, 98%; (iv) HBr (48%), AcOH, reflux, 98%; (v) $LiAlH_4$, Et_2O, rt, 98%; (vi) DDQ, dioxane, rt, 84%.

paracyclophanyl-4-carboxylic acid, whose efficient resolution has been reported many times.[16]

Cross-coupling of **17** and **10** led to 4-methoxycarbonyl-13-(2-methoxyphenyl)[2.2]paracyclophane **18** (80%), while the unreacted bromide **17** was recovered from the reaction mixture in 15% yield (Scheme 5).

It should be noted that aryl[2.2]paracyclophane **18** has vast synthetic potential due to the possibility of modification at the methoxycarbonyl group, which allows the synthesis of e.g. oxazoline, amino, hydroxy as well as many other functionalised ligands. Scheme 5 illustrates the first examples of the application of **18** as a new ligand precursor. Reduction of the ester group of **18** with $LiAlH_4$ resulted in methoxyarylcarbinol **19** in quantitative yield. Subsequent oxidation of **19** under mild conditions (DDQ, dioxane, room temperature) gave methoxyarylaldehyde **20**. Refluxing of compound **18** in a HBr/AcOH mixture led to a high yield of hydroxyarylcarboxylic acid **21**. The structure of **21** (CCDC 202652) was studied by X-ray diffraction analysis (Fig. 2). Reduction of **21** with $LiAlH_4$ in ether resulted in arylhydroxycarbinol **22** (98%). Oxidation of **22** with DDQ occurred analogously to the oxidation of carbinol **19** and gave hydroxyarylaldehyde **23** in 84% yield.

In summary, a number of planar chiral bidentate aryl[2.2]paracyclophane ligands of different types were obtained by Suzuki cross-coupling reactions. Since this method tolerates a broad range of functional groups it will be possible to synthesize a variety of aryl[2.2] paracyclophane ligands bearing different pairs of donor groups. Preparation of aryl[2.2]paracyclophanes in enantiomerically pure forms and their application in asymmetric catalysis are currently being investigated.

Acknowledgements

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10. General experimental conditions for the cross-coupling reactions of paracyclophanyl halides and arylboronic acids: A mixture of 0.71 mmol of **5** or **18** (or 0.35 mmol of **14**), 1.065 mmol of anisylboronic acid **10**, 0.015 mmol of $PdCl_2$ (dppf) and 1.42 mmol of K_3PO_4 in 5 ml of toluene under argon was stirred at 100–110°C (temperature in the oil bath) for 6 h for **5** (or 30 h for **20** or **16**). The reaction mixture was cooled, diluted with 10 ml of toluene and hydrolyzed with 10 ml of 1 M NaOH. The resulting mixture was extracted with toluene/THF (1/1) mixture, the combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by preparative chromatography on SiO_2. Analytical data for key compounds **5**, **14** and **18** are as follows: Compound **5**: $R_f=0.3$ (CH_2Cl_2). Mp 106.5–107°C. Anal. calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found C, 80.14; H, 7.11. ^{1}H NMR (400.13 MHz, $CDCl_3$; δ, ppm; J, Hz): 2.65–2.95 (m, 5H, -C***H***$_2$-C***H***$_2$-); 2.94 (s, 3H, -OCH$_2$OC***H***$_3$ or -OC***H***$_3$); 3.03–3.12 (m, 1H, -C***H***HC***H***$_2$-); 3.14–3.24 (m, 1H, -C***H***HC***H***$_2$-); 3.31–3.40 (m, 1H, -C***H***HC***H***$_2$-); 3.65 (s, 3H, -OCH$_2$OC***H***$_3$ or -OC***H***$_3$); 4.47 (d, $^2J=5.9$, 1H, -OC***H***HOCH$_3$); 4.56 (d, $^2J=5.9$, 1H, -OC***H***HOCH$_3$); 6.39 (d, $^3J=7.8$, 1H, PC-arom-***H***); 6.47 (d, $^3J=7.8$, 1H, PC-arom-***H***); 6.69 (m, 3H, PC-arom-***H***); 6.87 (br d, $^3J=7.8$, 1H, PC-arom-***H***); 6.94 (br d, $^3J=8.1$, 1H, arom-***H***); 7.15 (m, 1H, arom-***H***); 7.33 (m, 1H, arom-***H***); 7.82 (dd, $^3J=8.1$, $^4J=1.8$, 1H, arom-***H***). MS (EI, 70 eV), m/z: 374 (29, M$^+$), 239 (17), 238 (23), 225 (78), 195 (17), 165 (15), 105 (11), 104 (26). Compound **14**: $R_f=0.14$ (CCl_4). Mp 172–173°C. Anal. calcd for $C_{23}H_{21}BrO$: C, 70.24; H, 5.38; Br, 20.32. Found: C, 70.34; H, 5.49; Br, 20.44. ^{1}H NMR (400.13 MHz, $CDCl_3$; δ, ppm; J, Hz): 2.36–2.50 (m, 1H, -C***H***HC***H***$_2$-); 2.79–2.94 (m, 3H, -C***H***$_2$C***H***$_2$-); 3.07–3.23 (m, 3H, -C***H***$_2$C***H***$_2$-); 3.47–3.58 (m, 1H, -C***H***HC***H***$_2$-); 3.72 (s, 3H, -OC***H***$_3$); 6.51 (dd, $^3J=7.8$, $^4J=1.8$, 1H, PC-arom-***H***); 6.61 (d, $^3J=7.8$, 1H, PC-arom-***H***); 6.65 (m, 2H, PC-arom-***H***); 6.71 (d, $^4J=1.8$, 1H, PC-arom-***H***); 6.94 (d, $^3J=8.1$, 1H, arom-***H***); 6.99 (d, $^4J=1.8$, 1H, PC-arom-***H***); 7.21 (m, 1H, arom-***H***); 7.37 (m, 1H, arom-***H***); 7.99 (dd, $^3J=7.5$, $^4J=1.6$, 1H, arom-***H***). MS (EI, 70 eV), m/z: 394 (4, M$^+$), 392 (4, M$^+$), 313 (12, M$^+$–Br), 210 (42), 209 (100), 196 (10), 195 (41), 179 (24), 178 (17), 165 (12). Compound **18**: mp 182.5–183.5°C. Anal. calcd for $C_{25}H_{24}O_3$: C, 80.62; H, 6.49. Found: C, 80.57; H, 6.59. ^{1}H NMR (400.13 MHz, $CDCl_3$; δ, ppm; J, Hz): 2.72–2.83 (m, 1H, -C***H***HC***H***$_2$-); 2.94–3.09 (m, 3H, -C***H***$_2$C***H***$_2$-); 3.12–3.34 (m, 3H, -C***H***$_2$C***H***$_2$-); 3.51 (s, 3H, -OC***H***$_3$); 3.72 (s, 3H, -OC***H***$_3$); 3.89–3.99 (m, 1H, -C***H***HC***H***$_2$-); 6.54 (dd, $^3J=7.8$, $^4J=1.8$, 1H, PC-arom-***H***); 6.60 (d, $^4J=1.8$, 1H, PC-arom-***H***); 6.70 (m, 2H); 6.83 (dd, $^3J=7.8$, $^4J=1.8$, 1H, PC-arom-***H***); 6.88 (br d, $^3J=7.8$, 1H); 7.06 (m, 1H, arom-***H***); 7.31 (m, 2H, arom-***H***); 7.46 (dd, $^3J=7.5$, $^4J=1.6$, 1H, arom-***H***). MS (EI, 70 eV), m/z: 372 (38, M$^+$), 341 (12, M$^+$–OCH$_3$), 340 (31), 211 (16), 210 (82), 209 (100), 208 (16), 196 (26), 195 (84), 194 (29), 181 (16), 180 (15), 179 (67), 178 (61), 177 (24), 176 (12), 167 (19), 166 (20), 165 (45), 152 (31), 132 (11), 131 (23), 119 (15), 104 (16).
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