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The first regioselective double electrophilic substitution of the C_2-symmetric *pseudo-meta*-disubstituted [2.2]paracyclophanes

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Abstract—We report here the first examples of the regioselective double electrophilic substitution of chiral C_2-symmetric *pseudo-meta*-disubstituted [2.2]paracyclophanes. Thus, the double acylation of 4,15-dihydroxy[2.2]paracyclophane occurs *ortho*-regioselectively, whereas the double acylation of its respective dimethyl ether is completely *para*-regioselective. Double bromination of 4,15-dicarbomethoxy[2.2]paracyclophane regioselectively generates the *pseudo-gem*-substitution pattern. The approaches elaborated allow the synthesis of all three possible types of chiral bis-bifunctional compounds, which have two independent, although chemically and stereochemically equal, functional fragments with *pseudo-meta* mutual orientation of both pairs of identical substituents.

In our project aimed at developing chiral [2.2]paracyclophane derivatives to be used as planar chiral ligands in asymmetric catalysis,[1] we have been working on regioselective approaches to the functionalization of several monosubstituted [2.2]paracyclophanes.[1a,c,2] In particular, we have revealed the regularities of the *ortho*- and *para*-regioselective formylation and acylation of 4-hydroxy[2.2]paracyclophane and its methyl ether.[1a,c,2a,c] On the other hand, our recent interest in chiral C_2-symmetric bis-bifunctional [2.2]paracyclophanes, that is, those which contain in their structure two independent, although chemically and stereochemically identical functional fragments, has led us to set of multichiral cyclohexadienols, namely (*R*p,4*R*c,7*R*c,4,23*R*a,7,17*R*a)-*cis*-4,7-diarylsubstituted-4,7-dihydroxy-4,7-dihydro[2.2]paracyclophanes, which possess elements of planar, central, and axial chirality (Fig. 1).[3] In these ligands, the hydroxy groups attached to the [2.2]paracyclophane scaffold are paired with the functional groups of the aryl substituents to form two fragments, both of which are capable of coordination with a metal and so could work as chiral promoters,

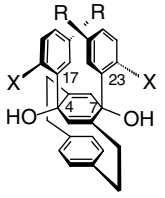

Figure 1. (*R*p,4*R*c,7*R*c,4,23*R*a,7,17*R*a)-*cis*-4,7-Diarylsubstituted-4,7-dihydroxy-4,7-dihydro[2.2]paracyclophanes.

as was demonstrated by the stereoselective diethylzinc addition to benzaldehydes (ees up to 93%).[3]

As another method to construct chiral C_2-symmetric bis-bifunctional compounds, we envisaged the location of both pairs of functional groups on the aromatic rings of the [2.2]paracyclophane scaffold. Here, we present the *ortho*-, *para*- and *pseudo-gem*-regioselective double electrophilic substitution of *pseudo-meta* disubstituted [2.2]paracyclophanes as a rational approach to tetrasubstituted [2.2]paracyclophanes, which correspond to three structurally diverse types of chiral bis-bifunctional compounds, two of which have never been described to our knowledge.

The double electrophilic substitution of [2.2]paracyclophanes with two equal functional groups looks very attractive from the synthetic point of view, however,

Keywords: Cyclophanes; Electrophilic substitution; Regioselectivity; Bis-bifunctional compounds.
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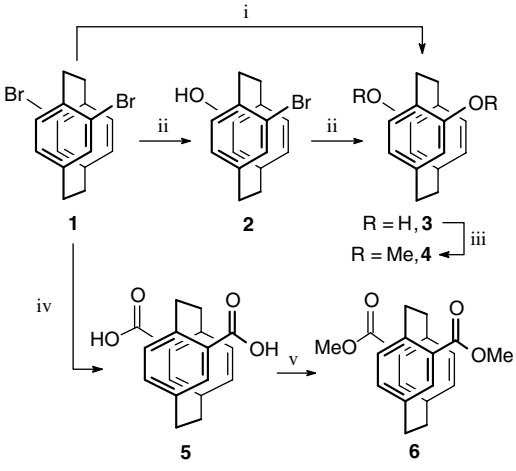
little attention has been paid to it so far. The known examples describe *pseudo-gem*-regioselective double chloromethylation of 4,7-dicarbomethoxy[2.2]paracyclophane (of the *para*-structure),[4] *ortho*-regioselective double acylation of 4,12-dihydroxy[2.2]paracyclophane (PHANOL, *pseudo-ortho*), and *para*-regioselective chlorosulfonation of its diacetate.[5] Dinitration of 4,12-dibromo[2.2]paracyclophane was *para*-regioselective,[5] whereas acylation, oxaloylation, and formylation of this substrate *para*-regioselectively produced monocarbonyl compounds only.[6]

As a model for investigation of the regioselectivity of the electrophilic substitution, the chiral *pseudo-meta*-substituted pattern was chosen. Compounds of this type, although planar chiral, have never been used in asymmetric synthesis, since their functional groups, situated on different sides of the plane passing through the four bridge carbon atoms, cannot coordinate with a metal. As a basic synthon, we used 4,15-dibromo[2.2]paracyclophane **1** (*pseudo-meta*). This compound is prepared by dibromination of [2.2]paracyclophane with Br_2 without catalyst and could be isolated with a chemical yield of 38–43% from the regioisomeric 4,16-dibromo-[2.2]paracyclophane (*pseudo-para*-, 33–40%) by fractional crystallization.[7]

The choice of functional substituents attached to the [2.2]paracyclophane scaffold (OH, OMe, and COOMe) was based on known regularities of the *ortho*-, *para*-[2a] and *pseudo-gem*-regioselective[8] electrophilic substitution, revealed earlier for the monosubstituted [2.2]paracyclophanes. The syntheses of 4,15-dihydroxy- and 4,15-dicarboxy[2.2]paracyclophanes (**3** and **5**) were carried out from the dibromide **1** by double lithiation/electrophilic exchange (Scheme 1). The 'classical' approach for the introduction of the hydroxy-group, namely Li/B exchange with trimethylborate and oxidation of the respective boronic esters with H_2O_2/NaOH failed to produce the expected diphenol **3**, and the parent



Scheme 1. Reagents and conditions: (i) 2 equiv *n*-BuLi, Et_2O, room temp.; then $PhNO_2$, −78 °C, 30%; (ii) 1 equiv *n*-BuLi, Et_2O, rt; then $B(OMe)_3$, H_2O_2/NaOH, 87%; (iii) NaH/DMF, then MeI, 80%; (iv) 2 equiv *n*-BuLi, THF, −78 °C; then CO_2, then HCl, 80%; (v) $SOCl_2$, $CHCl_3$; 61 °C, then MeOH, 78%.

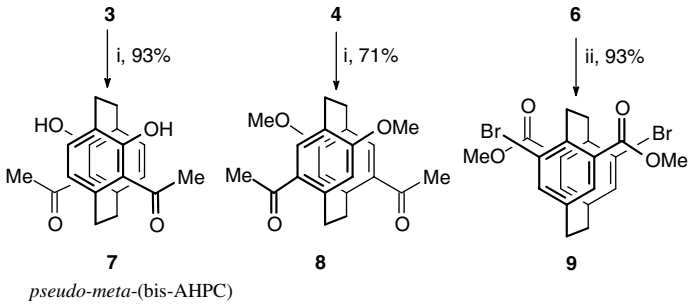
[2.2]paracyclophane (47%) and 4-hydroxy[2.2]paracyclophane (44%) were isolated. Oxidation of the dilithio derivative with nitrobenzene produced the target diphenol **3** in a low chemical yield (30%). An improved yield of **3** was achieved by application of a stepwise synthetic technique, including initial synthesis of 4-bromo-15-hydroxy[2.2]paracyclophane **2**, followed by the synthesis of the target diphenol **3** therefrom, carrying out each time the room temperature monolithiation in Et_2O, Li/B exchange, and oxidation. Diphenol **3** was next converted into 4,15-dimethoxy[2.2]paracyclophane **4**[9] via a standard methoxylation procedure.[10]

In contrast to the lack of the reactivity of the intermediate dilithio derivative with $B(OMe)_3$, its reaction with solid CO_2 followed by acidification of the reaction mixture smoothly produced 4,15-dicarboxy[2.2]paracyclophane **5**.[11a] The target 4,15-dicarbomethoxy-[2.2]paracyclophane **6**[11b] was obtained by methoxylation of the respective dichloroanhydride.

In our investigation of the reactivity and regioselectivity of electrophilic substitution of *pseudo-meta*-disubstituted [2.2]paracyclophane derivatives, we started with the acylation of diphenol **3**, bearing in mind the exclusive *ortho*-regioselective acylation revealed by us for 4-hydroxy[2.2]paracyclophane.[2a] Indeed, the reaction of **3** with 3 equiv of AcCl (3 equiv of $TiCl_4$, CH_2Cl_2, room temp) was *ortho*-regioselective producing a mixture of the respective mono- and diacylated diphenols (5,16-diacetyl-4,15-dihydroxy[2.2]paracyclophane **7** and 5-acetyl-4,15-dihydroxy[2.2]paracyclophane) and was accompanied by *O*-acylation. To achieve the chemoselective synthesis of the target **7** (93%), a solution of diphenol **3** was stirred with $TiCl_4$ for 1 h, and then AcCl was added (to avoid the formation of *O*-acylation products). In order to consume **3** and the intermediate monoacylated phenol completely, excess reagents (3 equiv of AcCl and 3 equiv of $TiCl_4$) were added and the reaction was carried out at 40 °C for 20 h (Scheme 2). The resulting C_2-symmetric diacylated phenol **7** possesses two functional fragments, each of which mimic the *ortho*-disubstituted functional part of 5-acetyl-4-hydroxy-[2.2]paracyclophane (AHPC),[2a] a well-known precursor for a series of efficient imino-type ligands.[12] These fragments are *pseudo-meta*-oriented with respect to each other and therefore, we refer to the compound **7** as *pseudo-meta*-(bis-AHPC).

As expected, the diacylation of the dimethoxy-derivative **4** with AcCl/$TiCl_4$ (1/6/6 reagents ratio, 20 h) was *para*-regioselective (as was the monoacylation of 4-methoxy[2.2]paracyclophane[2a]) and produced 7,12-diacetyl-4,15-dimethoxy[2.2]paracyclophane **8** as the sole product, isolated in a chemical yield of 71% (Scheme 2).

Next, we carried out the Fe-catalyzed room temperature bromination of the diester **6**.[13] The reaction with 2.4 equiv of Br_2 was quite slow and after three days ^{1}H NMR showed 80% conversion of the starting material and formation of the monobromination product. Therefore, a considerable excess of Br_2 (7.6 equiv) was added and the mixture was stirred for a further 10 days



pseudo-meta-(bis-AHPC)

Scheme 2. Reagents and conditions: (i) 6 equiv AcCl, 6 equiv $TiCl_4$, CH_2Cl_2, 40 °C, 20 h; (ii) Fe, 10 equiv Br_2, CH_2Cl_2, room temp., 13 d, 93%.

to reach full consumption (^{1}H NMR) of the starting **6** and of the intermediate monobromide. The only compound isolated from the reaction mixture in 93% yield was identified as 4,15-dibromo-8,13-dicarbomethoxy[2.2]paracyclophane **9**, the product of regioselective *pseudo-geminal* disubstitution. This compound, in our opinion, has great potential for further chemical transformations at the bromine atoms as well as at the carbomethoxy groups, thus providing scope for a wide range of novel [2.2]paracyclophane derivatives.

It is worthy of note that any C_2-symmetrical *pseudo-meta*-di-X-substituted [2.2]paracyclophane **A**, in principle, has three possible arrangements for the adoption of two *pseudo-meta*-oriented (with respect to each other) identical functional groups Y, thus allowing for formation of three C_2-symmetrical chiral tetrasubstituted patterns, **B**–**D**, respectively (Fig. 2). As is clear from Scheme 2, all three compounds **7**–**9**, being bis-bifunctional [2.2]paracyclophanes, represent these three patterns. Within each pattern, one could easily distinguish two identical fragments, constructed from two different functional groups (X = OH, Y = COMe in **7**; X = OMe, Y = COMe in **8**; X = COOMe, Y = Br in **9**), which are situated in close proximity to each other. Thus, starting from the *pseudo-meta*-disubstituted [2.2]paracyclophanes that, due to their structure, would be unable to undergo coordination with a metal, we have succeeded in arriving at three types of bis-bifunctional compounds; in each one, two independent functional fragments (X–Y) mimic the pattern of typical disubstituted chiral ligands, based on [2.2]paracyclophane (namely, *ortho*- in **B**, *pseudo-ortho*- in **C**, and *pseudo-gem*- in **D**).[14]

The construction of chiral bis-bifunctional chelating ligands of types **B**–**D** and their application in asymmetric catalysis are tasks of high priority. The other prospective area of investigations is their materials chemistry, namely, the design of the non-linearoptic and optoelectric,[15] as well as liquid crystalline materials[16] and polymers[17] from [2.2]paracyclophanes of types **B**–**D**.

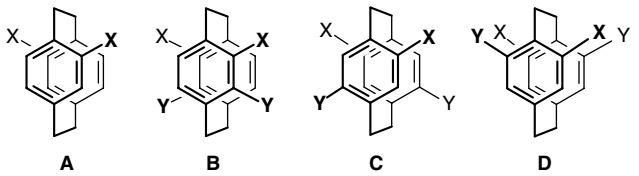


Figure 2. Three C_2-symmetric tetrasubstituted chiral patterns **B**–**D** with *pseudo-meta*-arrangement of identical substituents (X,X and Y,Y) originated from *pseudo-meta*-disubstituted [2.2]paracyclophane **A**.

In summary, we have for the first time investigated the reactivity and the regioselectivity of electrophilic substitution of chiral *pseudo-meta*-disubstituted [2.2]paracyclophanes. We have developed conditions for the chemoselective disubstitution, which can occur *ortho*-, *para*-, or *pseudo-gem*-regioselectively, giving rise to chiral bis-bifunctional compounds of types **B**–**D**. Further application of the regioselective double electrophilic substitution outlined above to novel *pseudo-meta*-disubstituted substrates, the chiral 4,7-[16] and the achiral 4,16-disubstituted[2.2]paracyclophanes (*para*- and *pseudo-para*-, respectively), and extension of the electrophilic reactions (formylation, oxaloylation, nitration, etc.) are underway.

Acknowledgements

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13. *pseudo-gem*-Regioselective bromination of 4,15-dicarbomethoxy[2.2]paracyclophane (**6**): A solution of Br_2 (0.05 mL, 0.9 mmol) in CCl_4 (2 mL) was prepared, and 0.3 mL of this solution and a suspension of iron powder (0.03 g, 0.54 mmol) in CH_2Cl_2 (5 mL) was stirred for 1 h in the absence of light. Then **6** (0.12 g, 0.37 mmol) in CH_2Cl_2 (15 mL) was added in one portion and the remaining Br_2/CH_2Cl_2 solution was added dropwise. After three days, an excess of Br_2 (0.15 mL, 2.7 mmol) was added and the reaction mixture was stirred at room temperature for an additional 10 days. The reaction mixture was washed with aq $NaHCO_3$ and dried with Na_2SO_4. The solvent was removed in vacuo and the solid residue was purified by preparative chromatography on SiO_2 (eluent CH_2Cl_2), to produce 4,15-dicarbomethoxy-8,13-dibromo[2.2]paracyclophane **9** (0.17 g, 93%). An analytically pure sample of **9** was obtained by recrystallization from hexane. Mp = 170.5–171 °C. Found (%): C, 49.64; H, 3.64; Br, 33.28. $C_{20}H_{18}Br_2O_4$. Calcd (%) C, 49.82; H, 3.76; Br, 33.14. MS (70 eV): *m*/*z* (%) = 483 (32) $[M]^+$, 482 (15) $[M]^+$, 481 (59) $[M]^+$, 479 (31), 466 (13), 243 (29), 242 (100), 240 (100), 239 (11), 227 (36), 226 (12), 225 (50), 223 (15), 211 (45), 210 (14), 209 (27), 203 (10), 202 (22), 201 (13), 200 (18), 199 (43), 198 (12), 197 (46), 189 (16), 184 (32), 183 (13), 182 (33), 162 (12), 129 (14), 115 (12), 104 (10), 103 (38), 102 (87). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 2.94–3.14 (m, 4H, bridge–CH_2–), 3.40–3.52 (m, 2H, bridge–CH_2–), 3.91 (s, 6H, 2-CH_3), 4.27–4.39 (m, 2H, bridge–CH_2–), 6.78 (d, ^4J = 1.8, 2H, H(5) and H(16)), 7.41 (d, ^4J = 1.8, 2H, H(7) and H(12)). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ = 27.70, 28.81, 48.07, 125.82, 127.30, 128.63, 135.16, 135.82, 137.95, 162.46.
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