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Improved Synthesis of Enantiopure 4-Hydroxy[2.2]paracyclophane

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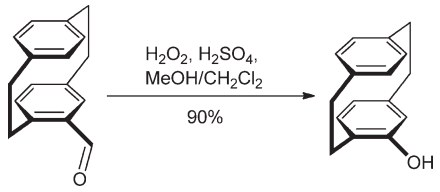


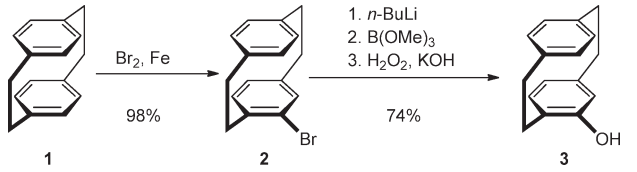
4-Hydroxy[2.2]paracyclophane is readily prepared via an improved synthetic protocol from unsubstituted [2.2]paracyclophane. The key step is a Dakin oxidation of 4-formyl-[2.2]paracyclophane. This allows a rapid access to large quantities of the product and an easy synthesis of the enantiopure form.

The synthesis of enantiopure ligands has attained considerable attention due to their pivotal role in asymmetric synthesis, and consequently, the need for efficient routes to such compounds is of increasing interest. In the field of asymmetric catalysis, mono- and bidentate ligands based on a [2.2]paracyclophane scaffold[1] (**1**) have been successfully employed as potent catalysts[2] in different kinds of reactions, like asymmetric hydrogenations,[3] addition reactions to aldehydes[4] and imines,[5] oxidations of thioethers,[6] trimethylsilylcyanation,[7] and allylboration.[8]

Most of such ligands can be described as derivatives of 4-hydroxy[2.2]paracyclophane (**3**) and are obtainable from this compound.

Since its first synthesis by Cram in 1955,[9] much effort has been made to develop more efficient synthesis protocols to this compound.[10,11] Today, **3** is usually prepared on a large scale by a method developed by Krohn and Hopf (Scheme 1).[12]

SCHEME 1. Conventional Synthesis of 3[12]



Starting from unsubstituted [2.2]paracyclophane (**1**), an aromatic substitution with bromine under iron catalysis is carried out. The obtained 4-bromo[2.2]paracyclophane (**2**) is then converted into the desired product by a one-pot procedure consisting of a Br−Li exchange, transmetalation onto boron, and an oxidative workup with a mixture of potassium hydroxide and hydrogen peroxide. Although this procedure is accomplishable, the second step is usually critical, and the yield ranges from 65[13] to 82%.[14]

In order to obtain enantiopure material, the subsequent resolution requires two additional steps. Auxiliaries known in the literature[15] for this purpose are acid chlorides, derived from camphanic acid (**4**)[16] and naproxene (**5**, Figure 1),[17] which convert **3** into the corresponding diastereomeric

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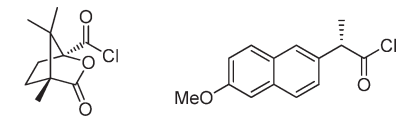
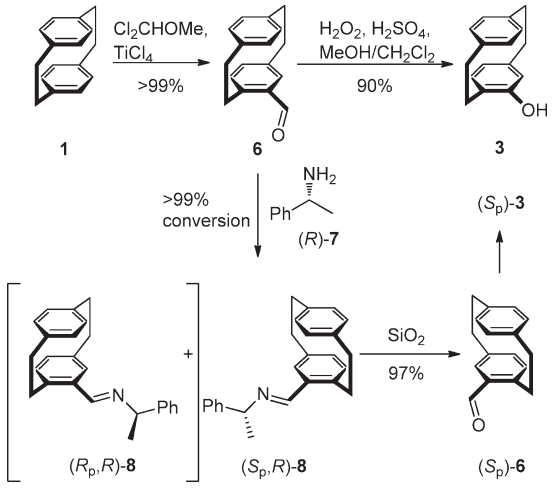


FIGURE 1. Common reagents for the resolution of **3**.

SCHEME 2. New Synthesis and Resolution Procedure for 3

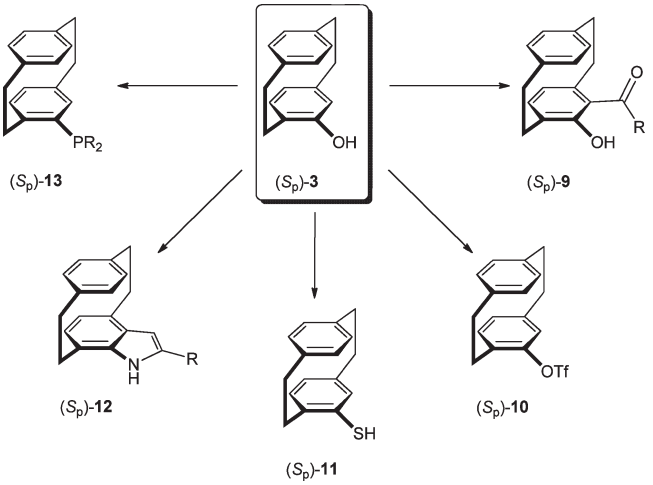


esters. The separation is achieved via fractional crystallization and delivers material of >98% de in 14−15% yield. Enantiopure 4-hydroxy[2.2]paracyclophane (**3**) is obtained after ester cleavage with $LiAlH_4$.

We discovered that **3** can be synthesized in a more effective way that also facilitates its synthesis in enantiopure form.

[2.2]Paracyclophanecarboxaldehyde (**6**), which is a key compound in our route, can be obtained by a Rieche formylation[18] of unsubstituted [2.2]paracyclophane (**1**) in quantitative yield and used without further purification in the next step.[19] It is known that aromatic phenols can be synthesized through a Dakin oxidation[20] of the corresponding aldehydes. To the best of our knowledge, this was not applied for the synthesis of 4-hydroxy[2.2]paracyclophane. We were able to show that racemic 4-hydroxy[2.2]paracyclophane (**3**) can be formed through oxidation of **6** with hydrogen peroxide and concentrated sulfuric acid on a large scale in an excellent yield of 90% (Scheme 2, upper row). The enantiomers of aldehyde **6** can be separated by a procedure developed by Quici.[21] Therefore, **6** is condensed with **7** by simple refluxing in benzene. The obtained diastereomeric imines **8** are separated by fractional crystallization in *n*-hexane. Only two crystallization steps are necessary to obtain analytically pure material of (S_p,*R*)-**8** in >98% de and 22% yield.[22]

SCHEME 3. Ligands prepared from (S_p)-3[16,18,24−26]



Since (S_p,*R*)-**8** is unstable under acidic conditions, it can be easily converted into the enantiopure aldehyde (S_p)-**6**. By filtration over a column of silica using dichloromethane as the eluent, it can be hydrolyzed and (S_p)-**6** is obtained in an almost quantitative yield. This enantiopure aldehyde can be oxidized under Dakin conditions into phenol (S_p)-**3**. The oxidation step occurs without racemization, which was verified by comparison of the enantiomeric excesses of substrate and product.

4-Hydroxy[2.2]paracyclophane is a key compound in the synthesis of [2.2]paracyclophane-based building blocks and ligands for asymmetric catalysis (Scheme 3).[2,23]

By an *ortho*-selective substitution reaction, for instance, ketones (S_p)-**9** and FHPC (R = H)[24] can be obtained that serve as starting materials for the synthesis of *N*,*O*-imine ligands.[4] The derivatization into the thiol (S_p)-**11** or indoles (S_p)-**12**[25] via the triflate (S_p)-**10**[17] is also possible. (S_p)-**10** can also be used for the synthesis of phosphine-based ligands like (S_p)-**13**.[17] Even chiral, nonracemic quinones are accessible.[26] In addition, the phenol **3** can itself serve as a chiral auxiliary.[27]

In conclusion, we have developed a new access to enantiopure 4-hydroxy[2.2]paracyclophane, which is a key compound in [2.2]paracyclophane chemistry. Our route offers an efficient synthesis since cheaper and safer reagents are used for the resolution/oxidation sequence.

Experimental Section

***rac*-4-Formyl[2.2]paracyclophane (6).** [2.2]Paracyclophane (**1**) (2.26 g, 10.8 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Titanium(IV) chloride (2.38 mL, 21.7 mmol) and

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(21) It was also shown that a resolution of the corresponding aldehyde (**6**) with enantiopure 1-phenyl-2-(4-methylphenyl)ethylamine proceeds in 29% yield over two steps: Banfi, S.; Manfredi, A.; Montanari, F.; Pozzi, G.; Quici, S. *J. Mol. Catal. A: Chem.* **1996**, *113*, 77–86.
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dichloromethoxymethane (1.00 mL, 11.3 mmol) were added subsequently. The mixture was stirred at room temperature for 6 h, poured into water (100 mL), and stirred for another 2 h. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product (2.56 g, >99%) was obtained as a colorless solid and used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.95 (s, 1H), 7.02 (d, J = 1.9 Hz, 1H), 6.73 (dd, J = 7.8 Hz, 1.9 Hz, 1H), 6.59 (d, J = 7.8 Hz, 1H), 6.56 (dd, J = 7.9 Hz, 1.8 Hz, 1H), 6.50 (dd, J = 7.9 Hz, 1.8 Hz, 1H), 6.43 (dd, J = 7.9 Hz, 1.8 Hz, 1H), 6.37 (dd, J = 7.9 Hz, 1.8 Hz, 1H), 4.10 (ddd, J = 11.8 Hz, 9.6 Hz, 1.5 Hz, 1H), 3.27 (ddd, J = 12.5 Hz, 10.4 Hz, 2.0 Hz, 1H), 3.21 (dd, J = 11.7 Hz, 4.5 Hz, 1H), 3.18 (dd, J = 11.7 Hz, 4.5 Hz, 1H), 3.14−2.97 (m, 3H), 2.95 (ddd, J = 13.1 Hz, 10.1 Hz, 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.1, 143.2, 140.6, 139.5, 139.4, 138.1, 136.6, 136.3, 136.1, 133.2, 132.9, 132.3, 132.1, 35.2, 35.1, 35.0, 33.6. Enantiopure material was prepared according to ref 21. HPLC conditions: OD column, *n*-heptane/2-propanol 98:2, 1 mL/min, 15 °C, 15.32 min (*S*); 22.27 min (*R*).

***rac*-4-Hydroxy[2.2]paracyclophane (3).** *rac*-4-Formyl[2.2]paracyclophane (5.00 g, 21.2 mmol) was dissolved in CH_2Cl_2 (100 mL) and MeOH (100 mL). Then concd H_2SO_4 (0.16 mL) and H_2O_2 (2.40 mL, 35% in water) were subsequently added, and the solution was stirred for 16 h. The solvent was evaporated under reduced pressure, and the residue was taken up in CH_2Cl_2 (100 mL) and water (100 mL). The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: cyclohexane/EtOAc, 1:1) to afford *rac*-4-hydroxy[2.2]paracyclophane (4.26 g, 90%) as a pale yellow solid. ^{1}H NMR (400 MHz,$CDCl_3$): δ = 7.01 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 6.54 (dd, J = 8.0 Hz, 1.9 Hz, 1H), 6.43 (dd, J = 8.0 Hz, 1.9 Hz, 1H), 6.38 (dd, J = 8.0 Hz, 1.9 Hz, 1H), 6.37 (d, J = 7.7 Hz, 1H), 6.24 (dd, J = 8.0 Hz, 1.9 Hz, 1H), 5.50 (d, J = 1.8 Hz, 1H), 4.54 (bs, 1H), 3.35−2.65 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 141.8, 139.4, 138.6, 135.2, 133.4, 132.6, 131.6, 127.7, 125.3, 124.8, 122.4, 35.2, 34.7, 33.8, 31.0. HPLC conditions: AS column, *n*-heptane/2-propanol 90:10, 1 mL/min, 10 °C, 7.44 min (*R*); 8.74 min (*S*).

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Supporting Information Available: General information and ^{1}H NMR spectra for compounds **3**, **6**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.