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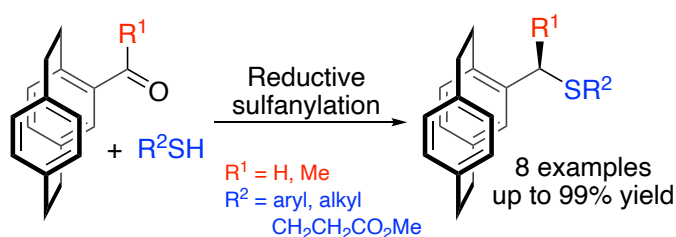
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Functionalization of [2.2]Paracyclophanes *via* a Reductive Sulfanylation Reaction

Damien Deschamps, Jean-François Lohier, Christopher J. Richards, Annie-Claude Gaumont
and Stéphane Perrio*

Graphical Abstract



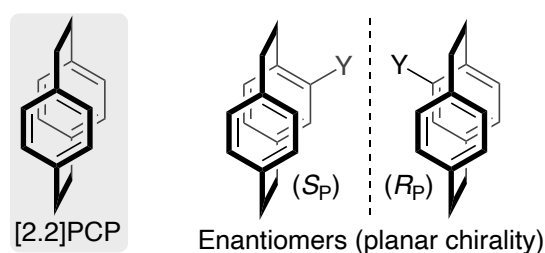
Abstract: An expeditious route to planar chiral sulfur-based scaffolds has been achieved in two operational steps from cheap and commercial [2.2]paracyclophane hydrocarbon. The sulfur atom was introduced in a specific benzylic position of the [2.2]paracyclophane according to a reductive sulfanylation reaction, which proceeds under two complementary reaction conditions with either the $\text{BF}_3 \cdot \text{OEt}_2 / \text{Et}_3\text{SiH}$ or $\text{TFA} / \text{BH}_3 \cdot \text{THF}$ combinations. The study was completed by the development on a highly efficient resolution approach by HPLC.

Introduction

Discovered by Brown and Farthing¹ seventy years ago, [2.2]paracyclophane ([2.2]PCP) is the parent hydrocarbon of a fascinating family of organic scaffolds (Figure 1).² It involves a compact arrangement of two co-facially stacked and strongly interacting benzene units, linked together at the *para* positions by ethylene groups. The unique structural, physical and electronic properties of [2.2]PCP derivatives have resulted in significant attention.³ They have been successfully applied in numerous fields, such as energy materials, functional poly-

p-xylylene (parylene) coatings, π -stacked polymers, and extensively used in asymmetric synthesis and catalysis.⁴ Indeed, an important facet of [2.2]PCP chemistry is related to the inherent planar chirality of these systems. The presence of a single substituent on the [2.2]PCP skeleton breaks the plane of symmetry of the molecule and generates enantiomers (Figure 1). As no asymmetric synthesis methods are available from the achiral [2.2]PCP hydrocarbon, approaches to enantiopure samples relies predominantly on the efficient resolution of racemates.⁵

Figure 1. Parent [2.2]paracyclophane and planar chiral monosubstituted derivatives

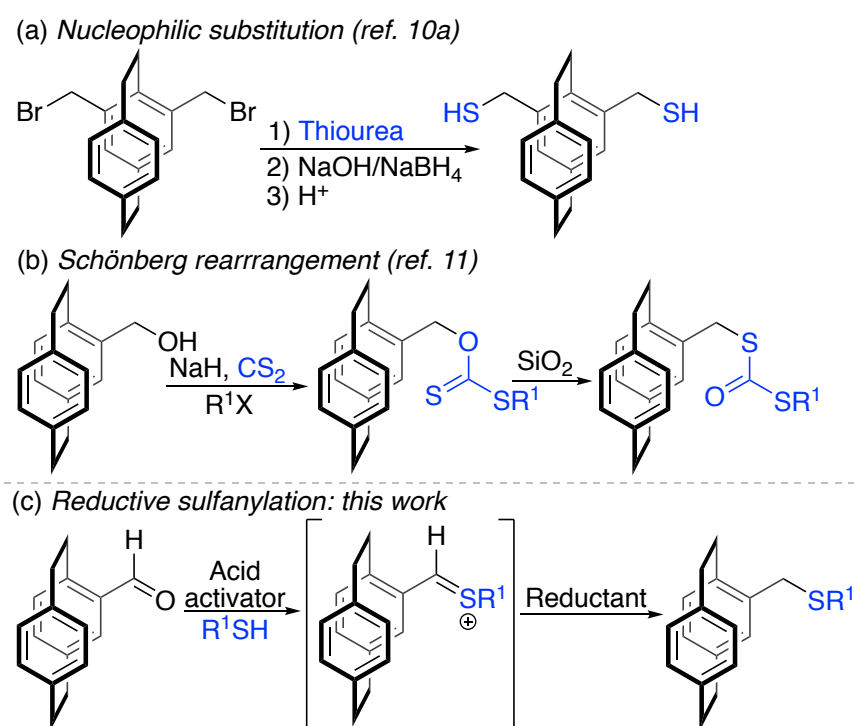


Despite the recent progress reported in selective functionalization of the [2.2]PCP core, unsolved synthetic challenges still remain, mainly due to the resistance they often exhibit for conventional chemical transformations.^{3a} Arguably, it is not always possible to transfer well-established aromatic chemistry to the [2.2]PCP series, without being faced with low yields, uncontrolled regioselectivities or unusual reactivities. As a consequence, special efforts are often required for optimization. Furthermore, [2.2]PCP derivatives exhibit a unique reactivity related to strong transannular interactions.

Inspired by our continuous interest in sulfur chemistry,⁶ we previously described the results of our investigations concerning the synthesis and the applications of monosubstituted sulfur-based [2.2]paracyclophanes.⁷ In the targeted structures, the heteroatom atom was directly attached to one aromatic deck of the [2.2]PCP ($Y = SR^1$, Figure 1). Considering the attractive reactivity of benzylic sulfur derivatives,⁸ we decided to turn out attention towards [2.2]PCP platforms, in which the sulfur center is located further from the ring, at a lateral

benzylic position ($Y = \text{CH}_2\text{SR}^1$, Figure 1).⁹ However, to the best of our knowledge, literature precedents for this subclasses of [2.2]PCP-based synthons remain surprisingly elusive. There are two common methodologies for the synthesis of such scaffolds, both of which provide racemic products. The most conventional one consists in a substitution reaction with displacement of a benzylic halogen atom in the presence of a nucleophilic sulfur source¹⁰ (Scheme 1a), whereas the other takes profit of the specific reactivity of thiocarbonyl derivatives with the so-called benzylic Schönberg rearrangement¹¹ (thione-thiol transformation, Scheme 1b).

Scheme 1. Literature Background and Strategy of this Work



Considering the versatile potential of these targets merging [2.2]PCP and benzylic heteroatom functionalities,¹² the development of a direct and practical strategy based on regioselective C–S bond formation on the [2.2]PCP platform is still warranted. An interesting feature would be to involve a readily available [2.2]PCP precursor, which could be prepared through a limited number of steps from the inexpensive and commercial [2.2]PCP hydrocarbon. As it is well established that the introduction of a carbonyl function to the

[2.2]PCP core can be directly achieved through an electrophilic substitution, we postulated that a reductive reaction approach¹³ could then allow incorporation of the sulfur atom (Scheme 1c). Indeed, the reductive sulfanylation is an elegant but overlooked reaction, which involves the reduction of a thionium¹⁴ species, formed from an aldehyde or ketone in the presence of a thiol and an activator. A limited number of examples, employing a Lewis/Brønsted acid with either a hydrosilane or borane reductant, have been described.^{13,14} In light of this, we present the results of our investigations.

Results and Discussion

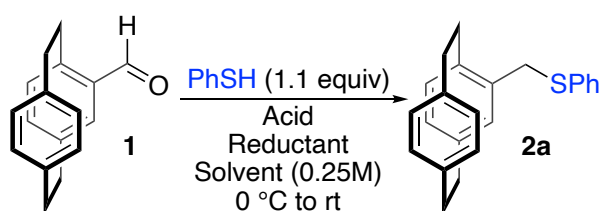
The racemic [2.2]paracyclophane-4-carboxaldehyde **1** building block was prepared in a single operational step (Rieche formylation) from parent [2.2]PCP, as previously described by Bräse.¹⁵ The synthesis was easily scaled up and allowed the isolation of ~10 g of substrate, from a single batch, in an excellent 85% yield.

In the initial study, thiophenol was chosen as the model sulfur reactant to optimize the reaction conditions (Table 1). In the first experiment (0.25 mmol scale), a stoichiometric amount of thiol and **1** was solubilized at 0 °C in CH₂Cl₂ (0.25 M). The reaction mixture was then reacted with commercial BF₃·2H₂O complex (2.1 equiv). After 5 min of reaction, triethylsilane (1.5 equiv) was added and the reaction mixture was stirred at room temperature for 3 h. Analysis of the crude mixture by ¹H NMR clearly indicated the formation of the anticipated [2.2]PCP thioether **2a**, according to the presence of the diagnostic AX pattern of the diastereotopic protons of the CH₂S group ($\delta = 3.83$ and 4.11 ppm, $^2J = 12.4$ Hz). Purification by chromatography on silica gel led to the isolation of **2a** in a satisfactory 75% yield (entry 1). The structure was then confirmed by X-Ray crystal structure analysis. Switching to BF₃·OEt₂ as the Lewis acid furnished a significant improvement to an 83% yield (entry 2). A similar reaction efficiency was observed employing a single equivalent of the BF₃·OEt₂ activator (entry 3). The effect of the solvent was then investigated. Whereas slightly

lower yields (71 and 75 %) were observed in 1,2-dichloroethane and toluene (entries 4 and 5), the reaction failed completely in a THF solution (entry 6).

We also explored activation by a Brønsted acid in the presence of a borane reductant. Use of a large excess of trifluoroacetic acid (TFA, 15 equiv) and pyridine·borane adduct (1 equiv) in CH₂Cl₂ furnished **2a** in a nice 80% yield (entry 7). A screening of other boron reagents and Brønsted acids was then investigated (entries 8–11). The best result was obtained in the presence of the borane·THF/TFA combination (92% yield, entry 9). Reducing the amount of TFA to 5 equivalents had a detrimental effect on the reaction efficiency (65% yield, entry 12). However, increasing the concentration of aldehyde **1** from 0.25M to 1M led to a much better 80% yield (entry 12). Finally, use of a single equivalent resulted in no product **2a** formation (entry 13). To summarize, the conditions of entries 3 and 9 in Table 1, were determined to be optimal for the synthesis of **2a**. In both cases, no erosion of reaction efficiency was noticed when experiments were carried out on a larger 1.2 mmol scale (entries 3 and 9).

Table 1. Optimization of the Reaction Conditions for the Reductive Sulfanylation^a



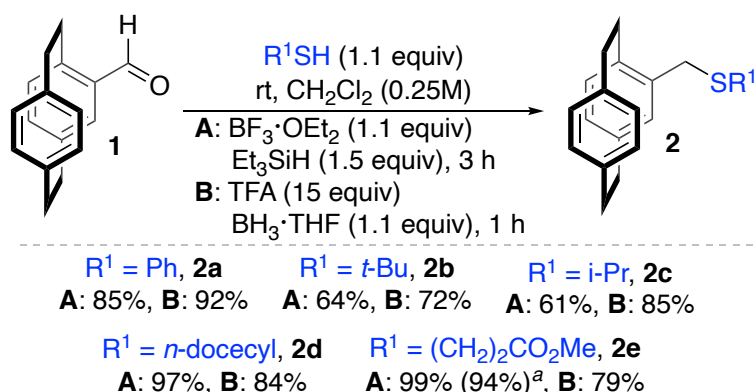
| Entry | Acid (equiv) | Reductant (equiv) | Solvent | Yield (%) |
|----------|---|--------------------------------|-------------------------------------|----------------------------|
| 1 | BF ₃ ·2H ₂ O (2.1) | Et ₃ SiH (1.5) | CH ₂ Cl ₂ | 75 |
| 2 | BF ₃ ·OEt ₂ (2.1) | Et ₃ SiH (1.5) | CH ₂ Cl ₂ | 83 |
| 3 | BF₃·OEt₂ (1.1) | Et₃SiH (1.5) | CH₂Cl₂ | 85 (83)^b |
| 4 | BF ₃ ·OEt ₂ (1.1) | Et ₃ SiH (1.5) | DCE ^c | 71 |
| 5 | BF ₃ ·OEt ₂ (1.1) | Et ₃ SiH (1.5) | PhMe | 75 |

| | | | | |
|----------|---|--|-------------------------------------|----------------------------|
| 6 | BF ₃ ·OEt ₂ (1.1) | Et ₃ SiH (1.5) | THF | — ^d |
| 7 | CF ₃ CO ₂ H (15) | BH ₃ ·Pyridine (1) | CH ₂ Cl ₂ | 80 |
| 8 | CF ₃ CO ₂ H (15) | BH ₃ ·Me ₂ S (1) | CH ₂ Cl ₂ | 85 |
| 9 | CF₃CO₂H (15) | BH₃·THF (1) | CH₂Cl₂ | 92 (88)^b |
| 10 | CH ₃ CO ₂ H (15) | BH ₃ ·THF (1) | CH ₂ Cl ₂ | — ^e |
| 11 | CF ₃ SO ₃ H (15) | BH ₃ ·THF (1) | CH ₂ Cl ₂ | 45 |
| 12 | CF ₃ CO ₂ H (5) | BH ₃ ·THF (1) | CH ₂ Cl ₂ | 65 (80) ^f |
| 13 | CF ₃ CO ₂ H (1.1) | BH ₃ ·THF (1) | CH ₂ Cl ₂ | — ^g |

^a Optimization with 0.25 mmol of **1**. ^b In brackets, reaction on a 1.2 mmol scale. ^c DCE = 1,2-dichloroethane. ^d Complex mixture. ^e No reaction. ^f In brackets, reaction with a concentration of 1M. ^g Reduction of **1** into the corresponding primary alcohol.

With optimal conditions in hand (conditions **A** with BF₃·OEt₂/Et₃SiH and **B** with TFA/BH₃·THF), the reaction scope with respect to the thiol was then investigated, as shown in Scheme 2. To our delight, the four aliphatic mercaptans tested reacted smoothly to afford the desired [2.2]PCP-based sulfides **2b-e** in good to excellent yields (64–99%). Worthy of note is the remarkable tolerance of the process to the ester function, with **2e** formed in a quantitative yield (conditions **A**). A comparison of the results obtained with both protocols shows the following trends. The use of conditions **A** is preferable with primary thiols (**2d** and **2e**), while conditions **B** brought about superior results with secondary, tertiary and aromatic thiols (**2a-c**). To explore the synthetic utility of the method, a scale-up reaction (7.5 mmol) of the [2.2]PCP derivative **1a** with 3-sulfanylpropionic acid methyl ester (R¹ = (CH₂)₂CO₂Me) was then conducted under conditions **A**, delivering 2.4 g of thioether **2e** in an excellent 94% yield.

Scheme 2. Substrate Scope through Variation of the Thiol

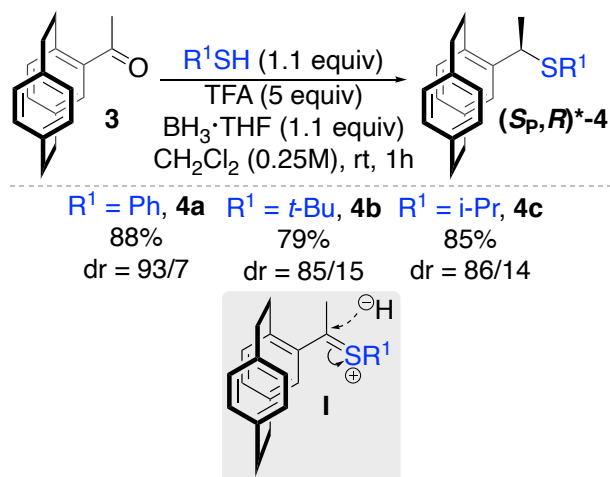


^a In brackets, yield at the 7.5 mmol scale.

We then turned our attention to extending the scope of this reductive sulfanylation reaction to the acetyl [2.2]PCP **3**, this offering a strategic entry to [2.2]PCP derivatives displaying both planar and central chirality (Scheme 3). This starting material was prepared in a 68% yield by a Friedel-Crafts acylation of [2.2]PCP with acetyl chloride/ AlCl_3 in dry dichloromethane.¹⁶ A preliminary set of experiments employing thiophenol rapidly indicated that the TFA/ $\text{BH}_3 \cdot \text{THF}$ system was more appropriate in this series (see the ESI[†]). Furthermore, a decrease of the amount of TFA to 5 equivalents improved markedly the reaction efficiency. The anticipated thioether **4a** was isolated in a pleasing 88% yield, as a mixture of two diastereoisomers in a 93/7 ratio. The products were readily separated by column chromatography on silica gel. Much to our delight, we succeeded in growing single crystals of the major diastereoisomer of **4a**, suitable for an X-ray diffraction analysis from which the relative (S_P, R)^{*} stereochemistry was unambiguously assigned. *tert*-Butanethiol and isopropanethiol gave the desired products **4b** and **4c**, in 79% and 85% yield, respectively, along with a similar level of diastereoselectivity (ratios of ~85/15). Separation of the diastereoisomers was again efficient on silica gel and the configurations were unambiguously assigned according to analytical similarities previously observed with **4a** (see the ESI[†]). To rationalize the preference for the (S_P, R)^{*} configured products, we suggest that the reaction

proceeds *via* thionium conformer **I**, with an attack of the reductant opposite to the CH₂CH₂ bridge (see the ESI† for additional details of the transition state model).

Scheme 3. Extension to 4-Acetyl[2.2]paracyclophane **3**

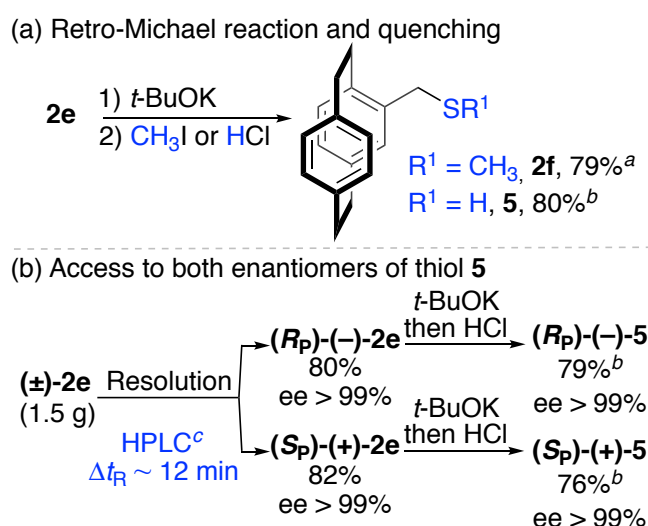


Cross-experiments were then investigated with stoichiometric amounts of the [2.2]PCP-based aldehyde **1**, ketone **3** and thiophenol (see the ESI†). Under the BF₃·OEt₂/Et₃SiH conditions, the reductive sulfanylation is totally chemoselective for the aldehyde function (ratio **2a:4a** of 100/0). The reaction led essentially to the isolation of the phenylsulfanyl [2.2]PCP **2a**. With the TFA/BH₃·THF system, competing reactivity of the acetyl group was observed, but the process is still highly in favor of the formyl substituent (ratio **2a:4a** of 88/12).

The highly efficient formation of sulfanyl ester **2e** provided great opportunities to use this functionalized [2.2]PCP derivative as a generally usable sulfur building block, through a methodology productively used in our group before^{7a-b,17} and which consists of a retro-Michael reaction and further electrophilic trapping of the generated anion. Accordingly, the treatment of **2e** at low temperature (−78 °C) with a 1M solution of *t*-BuOK in THF (1.2 equiv) afforded the corresponding benzylic thiolate (Scheme 4a). *In situ* quench with iodomethane

led to **2f** in a nice 79% yield. Notably, the synthesis of **2f** would have been problematic using directly the reductive sulfanylation reaction, as the use of gaseous methanethiol would have been required. Alternatively, quenching with an aqueous HCl solution afforded thiol **5** in an 80% yield. Thus, the precursor **2e** can be regarded as a valuable modular [2.2]PCP-based building block.

Scheme 4. Useful Transformations of Sulfanyl Ester **2e**



^a With 1.2 equiv of *t*BuOK. ^b With 2 equiv of *t*-BuOK. ^c Diacel Chiralpak IA column (i.d., 4.6 mm), *n*-heptane/EtOH (60:40 ratio) and flow rate of 1.0 mL/min.

As already mentioned, approaches to enantiopure samples relies predominantly on the efficient resolution of racemates, which can be tedious, especially when larger quantities are needed. We attempted the resolution of our racemate **(±)-2e** on an analytic scale by chiral high-performance liquid chromatography (HPLC). Using a Diacel Chiralpak IA column (i.d., 4.6 mm), with a mixture of *n*-heptane and EtOH in a 60:40 ratio (v/v) and a flow rate of 1.0 mL/min, a tremendous difference in retention times of 12 min for enantiomer **(*R*_P)-2e** and **(*S*_P)-2e** was observed, resulting in a baseline separation of the two enantiomers (see the ESI†). These conditions were then successfully applied on a semipreparative-scale, from 1.5 g

of starting material (Scheme 4b). This allowed the isolation of 596 mg of (**R_P**)-(-)-**2e** (t_R = 5.96 min, 80%, ee > 99%) and 613 mg of (**S_P**)-(+)-**2e** (t_R = 17.91 min, 82%, ee > 99%) (see the ESI†). Conversion into the corresponding thiols, according to the aforementioned retro-Michael reaction, was then carried out with the individual enantiomers of **2e**. This allowed the isolation of each enantiomer of thiol **5** in good yields (79% and 76%), as enantiopure products (see the ESI†). A single crystal suitable for X-ray diffraction analysis was obtained on the enantiopure thiol, derived from the first-eluting enantiomer of sulfanyl ester **2e** obtained by chiral HPLC, and this established unambiguously the configuration as (*R_P*) (Flack parameter = -0.01). Given the wide reactivity of the sulfanyl group, this highly efficient resolution process provides a promising entry to a collection of sulfur-based [2.2]PCP derivatives in both enantiomeric forms.¹⁸

Conclusions

In conclusion, through combining a Friedel-Crafts reaction and a reductive sulfanylation we have developed a reliable and high yielding method, which permits functionalization of the [2.2]PCP architecture at a specific benzylic position. Two complementary reaction conditions, promoted by either $\text{BF}_3 \cdot \text{OEt}_2 / \text{Et}_3\text{SiH}$ or $\text{TFA} / \text{BH}_3 \cdot \text{THF}$ combinations, were developed. The methodology allowed an efficient and straightforward access to a collection of relevant planar chiral sulfur-based [2.2]paracyclophanes. Furthermore, a highly efficient late stage resolution of the planar chirality led the isolation, in enantiopure forms, of both enantiomers of the related mercaptan, which can then serve as a versatile building block in the synthesis of more elaborated [2.2]PCP derivatives. These original scaffolds with the key features they display possess many application options that are to be explored.

Experimental Section

General Experimental. Dry THF and CH₂Cl₂ were obtained by a passage down an activated alumina column. All other reagents and solvents were used as purchased from commercial sources. All reactions were performed in oven-dried glassware, under an atmosphere of dry nitrogen. Due to the stench of thiols, all glassware and syringes were washed with bleach after use. Low reaction temperatures stated were those of the reaction mixtures. Reactions were purified by column chromatography with silica gel Si 60 (0.040–0.063 nm). Thin layer chromatography was carried out on silica gel 60 F₂₅₄ (1.1 mm) with spot detection under UV light or by I₂ oxidation. Melting points were obtained on a capillary apparatus and are uncorrected. All chemical shifts (δ) and coupling constants (J) in the NMR spectra are quoted in parts per million (ppm) and Hertz (Hz) respectively. The following abbreviations are used to designate the multiplicity of the signals: s = singlet; d = doublet; t = triplet; m = multiplet; and combinations thereof. The chemical shifts are calibrated to TMS (δ H 0.00) or residual proton and carbon resonances of the solvent CDCl₃ (δ H 7.26 and δ C 77.16). IR spectra were recorded on an ATR-FT-IR instrument equipped with a diamond ATR probe. Mass spectra were obtained with a QTOF LC/MS instrument. Semi-preparative separations of enantiomers were carried out on a chromatographic system with a 5 mL sample loop, equipped with a photodiode array detector (200–400 nm) and an IA column (5 mm; size 250 × 20 mm). Enantiomeric excesses were determined by chiral HPLC equipped with a photodiode array detector (200–400 nm) and an IA column (5 mm; size 250 × 4.6 mm). In all cases, the analysis was calibrated with a sample of the racemate. Optical rotations are reported in deg dm⁻¹ cm³ g⁻¹ and were measured at room temperature (20 °C) on a polarimeter using a 1 mL cell with a 1 dm path length at 589 nm (sodium D light).

Synthesis of the [2.2]PCP-based Precursors

[2.2]Paracyclophane-4-carboxaldehyde (1).¹⁵ The synthesis was carried out as reported in the literature. To a solution of [2.2]paracyclophane (10 g, 48 mmol, 1 equiv) in CH₂Cl₂ (450 mL) cooled to 0 °C, TiCl₄ (17.6 g, 92.8 mmol, 2 equiv, 10.2 mL) and Cl₂CHOCH₃ (4.5 mL, 50.8 mmol, 1 equiv) were successively added. The resulting mixture was allowed to warm up slowly to room temperature and then stirred at this temperature for 6 hours. Water (450 mL) was then added and stirring was maintained for 2 hours. The reaction mixture was extracted with CH₂Cl₂ and the combined organic phases were dried over MgSO₄, filtered and evaporated. The resulting solid was purified by column chromatography on silica gel with dichloromethane as eluent to obtain the desired aldehyde **1**. Yield 85% (9.61 g, 0.04 mol). White solid, mp: 148–149 °C (lit.¹⁵ mp 159 °C). TLC (CH₂Cl₂/pentane, 80:20) *R_f* = 0.59. ¹H NMR (400 MHz, CDCl₃) δ 9.96 (s, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 6.73 (dd, *J* = 7.8 and 1.8, 1H), 6.61–6.54 (m, 2H), 6.49 (dd, *J* = 7.8 and 1.6, 1H), 6.44 and 6.39 (AB part of ABXY pattern, *J* = 7.8 and 1.6, 1H each), 4.10 (ddd, *J* = 12.2, 10.3 and 1.8, 1H), 2.91–3.31 (m, 7H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 192.1, 143.4, 140.8, 139.5, 139.6, 138.2, 136.7, 136.5, 136.3, 133.4, 133.1, 132.5, 132.3, 35.4, 35.3, 35.1, 33.8. IR (cm⁻¹) ν: 719, 795, 875, 906, 1227, 1410, 1590, 1677 (C=O), 2751, 2850, 2925. MS (EI): *m/z* (%) 236 (84), 144 (21), 132 (21), 104 (100), 78 (38). HRMS (ESI) calcd for C₁₇H₁₇O [M+H]⁺: 237.1279, found: 237.1268.

4-Acetyl[2.2]paracyclophane (3).¹⁶ In two-necked round bottomed flask, equipped with a nitrogen inlet, a solution of [2.2]paracyclophane (4.16 g, 20 mmol, 1 equiv) in dry CH₂Cl₂ (22 mL) was cooled to –50 °C. A solution of acetyl chloride (3 mL, 42 mmol, 2.1 equiv) and AlCl₃ (4.67 g, 35 mmol, 1.75 equiv) was added dropwise. After stirring at –50 °C for 15 min, the reaction mixture was allowed to warm to –20 °C and stirred at this

temperature for an additional 15 min. The resulting mixture was poured into an aqueous 6N HCl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 30 mL). The organic fractions were combined, dried over MgSO₄, filtered and evaporated to dryness. The resulting crude product was then purified by column chromatography on silica gel (CH₂Cl₂/EtOAc, 99:1) to afford the expected ketone **3**. Yield 68% (3.40 g, 13.6 mmol). White solid, mp: 100–101 °C (lit.¹⁶ mp 107–109 °C). TLC (CH₂Cl₂/EtOAc, 99:1) *R_f* = 0.7. ¹H NMR (400 MHz, CDCl₃) δ 6.93 (d, *J* = 1.8, 1H), 6.66 (dd, *J* = 7.9 and 1.8, 1H), 6.58–6.49 (m, 4H), 6.39 (dd, *J* = 7.9 and 1.9), 3.98 (ddd, *J* = 12.6, 7.0 and 4.6, 1H), 3.25–3.11 (m, 4H), 3.10–2.97 (m, 2H), 2.90–2.79 (m, 1H), 2.47 (s, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 200.5, 141.8, 140.5, 140.0, 139.4, 138.1, 136.65, 136.60, 134.4, 133.3, 133.1, 132.3, 131.4, 36.3, 35.4, 35.3, 35.1, 29.0. IR (cm⁻¹) ν: 731, 793, 854, 902, 1185, 1266, 1349, 1552, 1679 (C=O), 2888, 2850, 2922, 2951. HRMS (ESI) calcd for C₁₈H₁₉O [M+H]⁺: 251.1436, found: 251.1441.

Synthesis of the [2.2]PCP-based Sulfides **2**

General procedure A – BF₃·OEt₂/Et₃SiH-mediated reductive sulfanylation: In a two-necked round bottomed flask, equipped with nitrogen inlet, a 0.25M solution of [2.2]paracyclophane-4-carboxaldehyde **1** (1 equiv) in CH₂Cl₂ and the appropriate thiol (1.1 equiv) were successively introduced. The stirred mixture was then charged successively dropwise with BF₃·OEt₂ (1.1 equiv) and triethylsilane (1.5 equiv). The reaction was then stirred at room temperature for an additional 3 h. After addition of a saturated NaHCO₃ aqueous solution, extraction with CH₂Cl₂ (20 mL), the organic layer was washed with H₂O (20 mL). The collected aqueous layers were extracted with CH₂Cl₂ (2 × 20 mL). The organic fractions were combined, dried over MgSO₄, filtered and evaporated to dryness. The resulting

crude product was then purified by column chromatography on silica gel to afford the anticipated sulfide **2**.

General procedure B – CF₃CO₂H/BH₃·THF-mediated reductive sulfanylation: In a two-necked round bottomed flask, equipped with a nitrogen inlet, a 0.25M solution of [2.2]paracyclophane-4-carboxaldehyde **1** (1 equiv) in CH₂Cl₂ and the appropriate thiol (1.1 equiv) were introduced. The stirred mixture was then charged dropwise successively with trifluoroacetic acid (15.6 equiv) and BH₃·THF (1.1 equiv). The reaction was then stirred at room temperature for an additional hour. After addition of an aqueous saturated NaHCO₃ solution, extraction with CH₂Cl₂ (20 mL), the organic layer was washed with H₂O (20 mL). The collected aqueous layers were extracted with CH₂Cl₂ (2 × 20 mL). The organic fractions were combined, dried over MgSO₄, filtered and evaporated to dryness. The resulting crude product was then purified by column chromatography on silica gel to afford the anticipated sulfide **2**.

4-(Phenylsulfanyl)methyl[2.2]paracyclophane (2a). Obtained following the general procedure **A** from aldehyde **1** (150 mg, 0.63 mmol), thiophenol (R¹ = Ph, 71 μL, 0.70 mmol), BF₃·OEt₂ (86 μL, 0.70 mmol) and triethylsilane (152 μL, 0.94 mmol) in CH₂Cl₂ (2.5 mL). Yield 85% (177.9 mg, 0.54 mmol). Obtained following the general procedure **B** from aldehyde **1** (59 mg, 0.25 mmol), thiophenol (R¹ = Ph, 28 μL, 0.275 mmol), trifluoroacetic acid (300 μL, 3.9 mmol) and BH₃·THF (1M solution, 275 μL, 0.275 mmol) in CH₂Cl₂ (1 mL). Yield 92% (76 mg, 0.54 mmol). White solid, mp: 88–89 °C. TLC (pentane/CH₂Cl₂, 70:30) R_f = 0.56. ¹H NMR (500 MHz, CDCl₃) δ 7.34–7.23 (m, 4H), 7.22–7.15 (m, 1H), 6.72 (dd, J = 7.8 and 1.8, 1H), 6.58 (dd, J = 7.8 and = 1.8, 1H), 6.55–6.48 (m, 3H), 6.45 (dd, J = 7.8 and 1.8, 1H), 6.37 (s, 1H), 4.11 (d, J = 12.4, 1H), 3.83 (d, J = 12.4, 1H), 3.43 (ddd, J = 13.7, 10.8 and 6.0, 1H), 3.22–3.12 (m, 1H), 3.12–2.93 (m, 5H), 2.86 (ddd, J = 13.7, 10.8 and 6.0, 1H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 140.2, 139.7, 139.4, 138.1, 137.1, 136.2, 135.3,

135.0, 133.5, 133.4, 132.3, 132.0, 129.6, 129.0, 128.9, 126.2, 38.1, 35.4, 35.1, 34.5, 33.4. IR (cm⁻¹) v: 714, 796, 897, 1412, 1485, 1592, 2849, 2922, 3006. HRMS (ESI) calcd for C₂₃H₂₂NaS [M+Na]⁺: 353.1340, found: 353.1338.

4-(tert-Butylsulfanyl)methyl[2.2]paracyclophane (2b). Obtained following the general procedure **A** from aldehyde **1** (150 mg, 0.63 mmol), *tert*-butanethiol (R¹ = *t*-Bu, 78 μL, 0.70 mmol), BF₃·OEt₂ (86 μL, 0.70 mmol) and triethylsilane (152 μL, 0.94 mmol) in CH₂Cl₂ (2.5 mL). Yield 64% (125.62 mg, 0.40 mmol). Obtained following the general procedure **B** from aldehyde **1** (118 mg, 0.5 mmol), *t*-butanethiol (R¹ = *t*-Bu, 62 μL, 0.55 mmol), trifluoroacetic acid (580 μL, 7.5 mmol) and BH₃·THF (1M solution, 550 μL, 0.55 mmol) in CH₂Cl₂ (2 mL). Yield 72% (112 mg, 0.36 mmol). White solid, mp: 81–82 °C. TLC (pentane/CH₂Cl₂, 80:20) R_f = 0.34. ¹H NMR (400 MHz, CDCl₃) δ 6.70 (dd, *J* = 7.8 and 1.6, 1H), 6.54 and 6.50 (AB part of ABMX pattern, *J*_{AB} = 7.9, *J*_{AM} = 1.6 and *J*_{BX} = 1.7, 2H), 6.48–6.41 (m, 3H), 6.31 (s, 1 H), 3.71 (d, *J* = 12.0, 1H), 3.47* (d, *J* = 12.0, 1H), 3.53–3.42* (m, 1H) (* signals overlapping), 3.23–3.13 (m, 1H), 3.13–2.93 (m, 5H), 2.88 (ddd, *J* = 13.5, 10.8 and 6.3, 1H), 1.35 (s, 9H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 140.0, 139.7, 139.4, 137.9, 137.5, 135.3, 135.1, 133.5, 133.4, 132.3, 131.6, 128.9, 42.6, 35.4, 35.1, 34.6, 33.5, 32.4, 31.0. IR (cm⁻¹) v: 715, 796, 870, 903, 1159, 1363, 1411, 1434, 1458, 1593, 2853, 2923, 3007. HRMS (ESI) calcd for C₂₁H₂₆NaS [M+Na]⁺: 333.1653, found 333.1663. Anal. calcd for C₂₁H₂₆S: C 81.23, H 8.44, S 10.33, found: C 81.42, H 8.31, S 10.30.

4-(Isopropylsulfanyl)methyl[2.2]paracyclophane (2c). Obtained following the general procedure **A** from aldehyde **1** (59 mg, 0.25 mmol), isopropanethiol (R¹ = *i*-Pr, 26 μL, 0.275 mmol), BF₃·OEt₂ (33 μL, 0.275 mmol) and triethylsilane (60 μL, 0.375 mmol) in CH₂Cl₂ (1 mL). Yield 61% (45 mg, 0.15 mmol). Obtained following the general procedure **B** from aldehyde **1** (118 mg, 0.5 mmol), isopropanethiol (R¹ = *i*-Pr, 52 μL, 0.55 mmol), trifluoroacetic acid (580 μL, 7.5 mmol) and BH₃·THF (1M solution, 550 μL, 0.55 mmol) in

CH₂Cl₂ (2.2 mL). Yield 85% (126 mg, 0.425 mmol). White solid, mp: 49–51 °C. TLC (pentane/CH₂Cl₂, 4:1) R_f = 0.30. ¹H NMR (400 MHz, CDCl₃) δ 6.69 (dd, J = 7.9 and 1.7, 1H), 6.55 and 6.50 (AB part of ABMX pattern, J_{AB} = 7.8, J_{AM} = 1.7 and J_{BX} = 1.8, 2H), 6.48–6.45 (m, 2H), 6.43 (dd, J = 7.9 and 1.8, 1H), 6.30 (s, 1H), 3.72 (d, J = 13.2, 1H), 3.45* (d, J = 13.2, 1H), 3.53–3.44* (m, 1H) (* signals overlapping), 3.24–3.13 (m, 1H), 3.13–2.94 (m, 5H), 2.87 (ddd, J = 13.5, 10.7 and 6.1, 1H), 2.69 (sept, J = 6.8, 1H), 1.24 (d, J = 6.8, 3H), 1.21 (d, J = 6.8, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 139.9, 139.6, 139.4, 137.95, 137.90, 135.3, 135.0, 133.5, 133.3, 132.2, 131.5, 128.9, 35.4, 35.1, 34.6, 34.5, 34.1, 33.5, 23.4 (a single signal for the two CH₃ of the i-Pr group). IR (cm⁻¹) ν: 715, 795, 870, 900, 1051, 1154, 1241, 1411, 1451, 1593, 2853, 2924, 2951. HRMS (ESI) calcd for C₂₀H₂₄NaS [M+Na]⁺: 319.1496, found: 319.1504.

4-(Dodecylsulfanyl)methyl[2.2]paracyclophane (2d). Obtained following the general procedure **A** from aldehyde **1** (150 mg, 0.63 mmol), dodecane-1-thiol (R¹ = CH₃(CH₂)₁₁, 166 μL, 0.70 mmol), BF₃·OEt₂ (86 μL, 0.70 mmol) and triethylsilane (152 μL, 0.94 mmol) in CH₂Cl₂ (2.5 mL). Yield 97% (259.4 mg, 0.61 mmol). Obtained following the general procedure **B** from aldehyde **1** (118 mg, 0.5 mmol), dodecane-1-thiol (R¹ = CH₃(CH₂)₁₁, 132 μL, 0.55 mmol), trifluoroacetic acid (580 μL, 7.5 mmol) and BH₃·THF (1M solution, 550 μL, 0.5 mmol) in CH₂Cl₂ (2.2 mL). Yield 84% (177 mg, 0.42 mmol). White solid, mp: 54–55 °C. TLC (pentane/CH₂Cl₂, 80:20) R_f = 0.45. ¹H NMR (400 MHz, CDCl₃) δ 6.68 (dd, J = 7.9 and 1.6, 1H), 6.56–6.41 (m, 5H), 6.28 (s, 1H), 3.71 (d, J = 13.2, 1H), 3.52–3.43 (m, 1H), 3.40 (d, J = 13.2, 1H), 3.24–3.13 (m, 1H), 3.12–2.94 (m, 5H), 2.93–2.81 (m, 1H), 2.32 (t, J = 7.4, 2H), 1.58–1.44 (m, 2H), 1.39–1.19 (m, 18H), 0.92 (t, J = 6.9, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 139.9, 139.6, 139.4, 137.95, 137.90, 135.25, 135.20, 133.5, 133.3, 132.2, 131.5, 129.0, 35.4, 35.2, 35.1, 34.5, 33.5, 32.0, 31.7, 29.85, 29.80, 29.7, 29.6, 29.55, 29.50, 29.3,

29.0, 22.8, 14.3. IR (cm⁻¹) ν : 717, 798, 872, 903, 945, 1412, 1432, 1464, 1593, 2850, 2919, 2949, 3007. HRMS (ESI) calcd for C₂₉H₄₂NaS [M+Na]⁺: 445.2905, found: 445.2925.

3-([2.2]Paracyclophan-4-yl)methylsulfanylpropionic Acid Methyl Ester (2e). Obtained following the general procedure **A** from aldehyde **1** (150 mg, 0.63 mmol), 3-sulfanylpropionic acid methyl ester (R¹ = (CH₂)₂CO₂Me, 77 μ L, 0.70 mmol), BF₃·OEt₂ (86 μ L, 0.70 mmol) and triethylsilane (152 μ L, 0.94 mmol) in CH₂Cl₂ (2.5 mL). Yield 99% (213.5 mg, 0.63 mmol). Obtained following the general procedure **B** from aldehyde **1** (118 mg, 0.5 mmol), 3-sulfanylpropionic acid methyl ester (R¹ = (CH₂)₂CO₂Me, 61 μ L, 0.55 mmol), trifluoroacetic acid (580 μ L, 7.5 mmol) and BH₃·THF (1M solution, 550 μ L, 0.55 mmol) in CH₂Cl₂ (2 mL). Yield 79% (135 mg, 0.4 mmol). White solid, mp: 58–59 °C. TLC (pentane/EtOAc, 80:20) R_f = 0.45. ¹H NMR (400 MHz, CDCl₃) δ 6.65 (dd, *J* = 7.8 and 1.8, 1H), 6.55–6.43 (m, 4H), 6.41 (dd, *J* = 7.8 and 1.8, 1H), 6.26 (s, 1H), 3.72 (d, *J* = 13.3, 1H), 3.67 (s, 3H), 3.42* (d, *J* = 13.3, 1H), 3.48–3.39* (m, 1H) (* signals overlapping), 3.22–3.12 (m, 1H), 3.12–2.94 (m, 5H), 2.86 (ddd, *J* = 13.6, 10.2 and 6.2, 1H), 2.61–2.57 (m, 2H), 2.51–2.46 (m, 2H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 172.4, 140.0, 139.5, 139.3, 137.9, 137.2, 135.3, 135.1, 133.5, 133.3, 132.2, 131.7, 128.9, 51.8, 35.3, 35.2, 35.0, 34.5, 34.4, 33.4, 26.4. IR (cm⁻¹) ν : 715, 794, 1238, 1344, 1434, 1592, 1724 (C=O), 2851, 2924, 3005. MS (ESI): *m/z* (%) 703 [(2M + Na)⁺, 31], 363 [(M + Na)⁺, 100], 341 [(MH)⁺, 38], 231 (29), 221 (79). HRMS (ESI) calcd for C₂₁H₂₅O₂S [M+H]⁺: 341.1575, found: 341.1576. Anal. calcd for C₂₁H₂₄O₂S: C 74.08, H 7.11, S 9.42, found: C 74.00, H 7.17, S 9.83.

Gram-Scale Synthesis of 2e. A two-necked round bottomed flask, equipped with nitrogen inlet, was charged successively with [2.2]paracyclophane-4-carboxaldehyde **1** (1.77 g, 7.5 mmol, 1 equiv), 3-sulfanylpropionic acid methyl ester (918 μ L, 8.25 mmol 1.1 equiv) and CH₂Cl₂ (30 mL). The resulting mixture cooled in an ice bath and BF₃·OEt₂ (1.02 mL, 8.25

mmol, 1.1 equiv) was added. After 5 minutes, triethylsilane (1,815 mL, 11,25 mmol, 1.5 equiv) was added. After removal of the cold bath, the reaction mixture was allowed to stir at room temperature for 3 h. After addition of a saturated NaHCO₃ aqueous solution, extraction with CH₂Cl₂ (20 mL), the organic layer was washed with H₂O (2 × 20 mL). The collected aqueous layers were extracted with CH₂Cl₂ (3 × 20 mL). The organic fractions were combined, dried over MgSO₄, filtered and evaporated to dryness. The resulting crude product was then purified by column chromatography on silica gel with pentane/ethyl acetate (9:1) to give sulfide **2e** (2.4 g, 94%).

Synthesis of the [2.2]PCP-based Sulfides **4**

General procedure: In a two-necked round bottomed flask, equipped with a nitrogen inlet, a 0.25M solution of 4-acetyl[2.2]paracyclophane **3** (1 equiv) in CH₂Cl₂ and appropriate thiol (1.1 equiv) was introduced. The stirred mixture was successively then charged dropwise with trifluoroacetic acid (5 equiv) and BH₃·THF (1.1 equiv). The reaction was then stirred at room temperature for an additional hour. After addition of a saturated NaHCO₃ aqueous solution, extraction with CH₂Cl₂ (20 mL), the organic layer was washed with H₂O (20 mL). The collected aqueous layers were extracted with CH₂Cl₂ (2 × 20 mL). The organic fractions were combined, dried over MgSO₄, filtered and evaporated to dryness. The resulting crude product was then purified by column chromatography on silica gel to afford the anticipated sulfide **4**.

4-[1'-(Phenylsulfanyl)ethyl][2.2]paracyclophane (**4a**). Obtained following the general procedure from ketone **3** (500 mg, 2 mmol), thiophenol (R¹ = Ph, 215 μL, 2.1 mmol), trifluoroacetic acid (750 μL, 10 mmol) and BH₃·THF (1M solution, 2.1 mL, 2.1 mmol) in CH₂Cl₂ (10 mL) as a mixture (93:7 ratio) of diastereoisomers. Yield 88% (604 mg, 1.76 mmol). Separation was achieved by column chromatography on silica gel (pentane/CH₂Cl₂,

90:10). (**S_p**, **R**)*-**4a** (major diastereoisomer). White solid, mp: 111–112 °C. TLC (pentane/CH₂Cl₂, 90:10) *R_f* = 0.08. ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.30 (m, 2H), 7.29–7.24 (m, 3H), 6.55–6.46 (m, 5H), 6.40–6.35 (m, 1H), 6.29 (s, 1H), 4.33 (q, *J* = 6.8, 1H), 3.66 (ddd, *J* = 13.6, 10.1 and 1.9, 1H), 3.27–3.17 (m, 1H), 3.15–2.88 (m, 6H), 1.67 (d, *J* = 6.8, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 140.0, 139.75, 139.70, 139.5, 138.3, 135.6, 134.8, 133.7, 133.5, 133.1, 132.15, 132.10, 130.4, 129.6, 128.8, 127.6, 44.5, 35.4, 35.3, 34.7, 33.9, 19.1. IR (cm⁻¹) ν: 738, 861, 1180, 1372, 1412, 1437, 1477, 1583, 1592, 2852, 2926, 3008. HRMS (ESI) calcd for C₂₄H₂₄NaS [M+Na]⁺: 367.1496, found: 367.1499. (**S_p**, **S**)*-**4a** (minor diastereoisomer). Colorless oil. TLC (pentane/CH₂Cl₂, 90:10) *R_f* = 0.16. ¹H NMR (400 MHz, CDCl₃) δ 7.67–7.63 (m, 2H), 7.44–7.38 (m, 2H), 7.35–7.29 (m, 1H), 6.91–6.86 (m, 1H), 6.69 (s, 1H), 6.60–6.58 (m, 2H), 6.46–6.39 (m, 3H), 4.46 (q, *J* = 6.7, 1H), 3.41 (ddd, *J* = 13.2, 9.3 and 3.7, 1H), 3.22–3.09 (m, 4H), 3.07–2.91 (m, 3H), 1.32 (d, *J* = 6.7, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 141.1, 140.5, 139.6, 139.1, 136.4, 136.2, 135.4, 133.3, 132.8, 132.6, 132.45, 132.40, 132.2, 130.1, 129.2, 127.3, 45.1, 35.6, 35.35, 35.30, 33.1, 25.3. IR (cm⁻¹) ν: 731, 860, 907, 1057, 1368, 1441, 1437, 1478, 1583, 2852, 2923, 3007. HRMS (ESI) calcd for C₂₄H₂₄NaS [M+Na]⁺: 367.1496, found: 367.1508.

4-[1'-(tert-Butylsulfanyl)ethyl]-[2.2]paracyclophane (4b). Obtained following the general procedure from ketone **3** (125 mg, 0.5 mmol), *t*-butanethiol (*R*¹ = *t*-Bu, 62 μL, 0.55 mmol), trifluoroacetic acid (193 μL, 2.5 mmol, 5 equiv) and BH₃·THF (1M solution, 550 μL, 0.55 mmol) in CH₂Cl₂ (2 mL) as a mixture (85:15 ratio) of diastereoisomers. Yield 79% (128 mg, 0.395 mmol). Separation was achieved by column chromatography on silica gel (pentane/CH₂Cl₂, 4:1). (**S_p**, **R**)*-**4b** (major diastereoisomer). White solid, mp: 117–118 °C. TLC (pentane/CH₂Cl₂, 4:1) *R_f* = 0.64. ¹H NMR (400 MHz, CDCl₃) δ 6.60–6.53 (m, 3H), 6.45–6.36 (m, 4H), 4.11 (q, *J* = 6.9, 1H), 3.60–3.51 (m, 1H), 3.25–2.89 (m, 7H), 1.84 (d, *J* = 6.9, 3H), 1.33 (s, 9H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 141.5, 139.9, 139.7, 139.4, 137.0,

135.6, 133.4, 132.9, 132.1, 131.9, 130.3, 130.1, 43.9, 38.8, 35.5, 35.3, 35.1, 33.6, 31.9, 22.5. IR (cm⁻¹) v: 750, 764, 794, 860, 1161, 1260, 1275, 1370, 1457, 1593, 2854, 2895, 2924, 3006. HRMS (ESI) calcd for C₂₂H₂₈NaS [M+Na]⁺: 347.1809, found: 347.1812. (**S_p**, **S**)*-**4b** (minor diastereoisomer). White solid, mp: 109–110 °C. TLC (pentane/CH₂Cl₂, 4:1) R_f = 0.84. ¹H NMR (400 MHz, CDCl₃) δ 6.95 (d, J = 7.8, 1H), 6.63–6.55 (m, 2H), 6.50 (s, 1H), 6.43 (d, J = 7.8, 1H), 6.35–6.29 (m, 2H), 4.09 (q, J = 6.8, 1H), 3.44–3.35 (m, 1H), 3.23–3.03 (m, 4H), 3.00–2.86 (m, 3H), 1.54 (s, 9H), 1.45 (d, J = 6.8, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 142.8, 140.2, 139.6, 139.0, 135.35, 135.30, 133.5, 132.6, 132.5, 132.1, 131.8, 130.1, 43.8, 38.6, 35.5, 35.25, 35.20, 33.0, 32.3, 29.1. IR (cm⁻¹) v: 750, 764, 1055, 1159, 1261, 1275, 1363, 1457, 1592, 2854, 2924. HRMS (ESI) calcd for C₂₂H₂₈NaS [M+Na]⁺: 347.1809, found: 347.1804.

4-[1'-(Isopropylsulfanyl)ethyl]-[2.2]paracyclophane (**4c**). Obtained following the general procedure from ketone **3** (125 mg, 0.5 mmol), isopropanethiol (R¹ = i-Pr, 52 μL, 0.55 mmol), trifluoroacetic acid (193 μL, 2.5 mmol, 5 equiv) and BH₃·THF (1M solution, 550 μL, 0.55 mmol) in CH₂Cl₂ (2 mL) as a mixture (86:14 ratio) of diastereoisomers. Yield 85% (131 mg, 0.425 mmol). Separation was achieved by column chromatography on silica gel (pentane/CH₂Cl₂, 4:1). (**S_p**, **R**)*-**4c** (major diastereoisomer). White solid, mp: 128–129 °C. TLC (pentane/CH₂Cl₂, 4:1) R_f = 0.62. ¹H NMR (400 MHz, CDCl₃) δ 6.56–6.50 (m, 3H), 6.46–6.37 (m, 4H), 4.04 (q, J = 6.8, 1H), 3.64–3.55 (m, 1H), 3.24–2.86 (m, 7H), 2.78 (sept, J = 6.7, 1H), 1.75 (d, J = 6.8, 3H), 1.27 (d, J = 6.7, 3H), 1.12 (d, J = 6.7, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 140.6, 140.0, 139.7, 139.5, 137.8, 135.5, 133.6, 133.0, 132.1, 131.8, 130.0, 129.9, 39.0, 35.5, 35.4, 34.9, 33.7 (2 signals overlapping), 23.8, 23.6, 19.7. IR (cm⁻¹) v: 750, 764, 861, 1260, 1275, 1452, 1592, 2854, 2925, 2954, 3007. HRMS (ESI) calcd for C₂₁H₂₆NaS [M+Na]⁺: 333.1653, found: 333.1652. (**S_p**, **S**)*-**4c** (minor diastereoisomer). White

solid, mp: 62–63 °C. TLC (pentane/CH₂Cl₂, 4:1) R_f = 0.82. ¹H NMR (400 MHz, CDCl₃) δ 6.88 (d, J = 7.9, 1H), 6.60–6.52 (m, 3H), 6.47 (d, J = 7.9, 1H), 6.39–6.33 (m, 2H), 4.07 (q, J = 6.8, 1H), 3.43–3.32 (m, 1H), 3.21–2.86 (m, 8H), 1.51 (d, J = 6.4, 3H), 1.42 (d, J = 6.8, 3H), 1.37 (d, J = 6.8, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 142.1, 140.3, 139.6, 139.1, 136.1, 135.3, 133.3, 132.8, 132.5, 132.2, 131.8, 130.3, 39.6, 35.5, 35.3, 35.2, 34.2, 33.2, 25.5, 23.9, 23.8. IR (cm⁻¹) ν: 750, 764, 1049, 1260, 1275, 1454, 1593, 2854, 2924, 2956, 3006. HRMS (ESI) calcd for C₂₁H₂₆NaS [M+Na]⁺: 333.1653, found: 333.1667.

Transformation of sulfanyl ester **2e**

4-(Methylsulfanyl)methyl[2.2]paracyclophane (2f). In a two-necked round bottomed flask, equipped with a nitrogen inlet, sulfanyl ester **2e** (194.7 mg, 0.57 mmol, 1 equiv) was diluted in dry THF (3 mL). After cooling to –78 °C, *t*-BuOK (686 μL of a 1M solution in THF, 1.2 equiv) was added dropwise. The reaction was stirred at –78 °C for 30 min and iodomethane (39 μL, 0.63 mmol, 1.1 equiv) was added. After an additional stirring of 20 min at –78 °C, water was added and the reaction mixture was allowed to warm to room temperature. Volatiles were removed under reduced pressure and the aqueous phase was extracted twice with CH₂Cl₂. The collected organic layers were dried over MgSO₄ and concentrated under vacuum. The resulting crude product was then purified by column chromatography on silica gel (pentane/CH₂Cl₂, 70:30) to afford the expected sulfide **2f**. Yield 79% (120.5 mg, 0.45 mmol). White solid, mp: 83–84 °C. TLC (pentane/CH₂Cl₂, 70:30) R_f = 0.32. ¹H NMR (400 MHz, CDCl₃) δ 6.67 (dd, J = 7.9 and 1.7, 1H), 6.56–6.45 (m, 4H), 6.43 (dd, J = 7.8 and 1.7, 1H), 6.27 (s, 1H), 3.71 (d, J = 13.4, 1H), 3.50–3.41 (m, 1H), 3.35 (d, J = 13.4, 1H), 3.23–3.14 (m, 1H), 3.13–2.95 (m, 5H), 2.87 (ddd, J = 13.6, 10.8 and 6.2, 1H), 1.92 (s, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 139.9, 139.6, 139.4, 137.9, 137.4, 135.25, 135.20, 133.5, 133.3, 132.2, 131.6, 129.0, 37.1, 35.4, 35.0, 34.4, 33.4, 15.1. IR (cm⁻¹) ν: 716,

753, 795, 868, 906, 1237, 1411, 1426, 1592, 2850, 2924, 3006, 3030. HRMS (ESI) calcd for $C_{18}H_{20}NaS$ $[M+Na]^+$: 291.1183, found: 291.1194. Anal. calcd for $C_{18}H_{20}S$: C 80.55, H 7.51, S 11.94, found: C 80.24, H 7.51, S 12.28.

([2.2]Paracyclophan-4-yl)methanethiol ((±)-5). In a two-necked round bottomed flask, sulfanyl ester (±)-**2e** (345.5 mg, 1.01 mmol, 1 equiv) was diluted in dry THF (5 mL). After cooling to -78 °C, *t*-BuOK (2 mL of a 1M solution in THF, 2 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 30 min and then directly poured onto an aqueous 1M HCl solution (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3×20 mL) and the collected organic layers were dried over $MgSO_4$ and concentrated under vacuum. The resulting crude product was then purified by column chromatography on silica gel (pentane/ CH_2Cl_2 , 80:20) to afford the expected thiol (±)-**5**. Yield 80% (204.2 mg, 0.80 mmol). White solid, mp: 143–144 °C. TLC (pentane/ CH_2Cl_2 , 80:20) $R_f = 0.22$. 1H NMR (400 MHz, $CDCl_3$) δ 6.63 (dd, $J = 7.8$ and 1.8, 1H), 6.53–6.44 (m, 4H), 6.41 (dd, $J = 7.8$ and 1.8, 1H), 6.30 (s, 1H), 3.73 (dd, $J = 13.1$ and 7.2, 1H), 3.49–3.38 (m, 2H), 3.23–3.13 (m, 1H), 3.12–2.94 (m, 5H), 2.93–2.82 (ddd, $J = 13.6$, 10.8 and 6.1, 1H), 1.54 (t, $J = 7.2$, 1H). ^{13}C $\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.5, 140.3, 139.7, 139.4, 137.1, 135.5, 134.1, 133.6, 133.4, 132.3, 131.8, 128.9, 35.4, 35.1, 34.5, 33.3, 27.8. IR (cm^{-1}) ν : 638, 794, 871, 1239, 1412, 1497, 1591, 2539, 2849, 2924. HRMS (ESI) calcd for $C_{17}H_{18}NaS$ $[M+Na]^+$: 277.1027, found: 277.1026. Anal. calcd for $C_{17}H_{18}S$: C 80.27, H 7.13, S 12.60, found: C 79.81, H 7.31, S 12.22.

Resolution protocol of sulfanyl ester (±)-**2e** by semi-preparative HPLC

The racemic sulfanyl ester (±)-**2e** (1.50 g, 4.41 mmol) was dissolved in the minimum amount of a 60:40 *n*-heptane/ethanol mixture. Aliquots of the resulting solution were repeatedly injected into the semi-preparative HPLC apparatus equipped with an IA column (5

μm ; size 250×20 mm) eluting with 60:40 *n*-heptane/ethanol at 1 mL min^{-1} ($20 \text{ }^\circ\text{C}$) and with UV monitoring at 229 nm. The collected fractions of each enantiomer, eluted at 5.96 and 17.91 min, were concentrated *in vacuo*. Individual fractions of enantiomers thus isolated were re-injected onto an analytical chiral IA column ($5 \mu\text{m}$; size 250×4.6 mm) to determine their enantiomeric purity. The absolute configuration within (-)-**2e** and (+)-**2e** was unambiguously assigned by chemical correlation to the related thiols (*vide infra*).

(R_P)-(-)-2e: as the first-eluted fraction in total yield of 596 mg (1.75 mmol, 100% ee), HPLC: $t_{\text{R}} = 5.96$ min, [IA column ($5 \mu\text{m}$; size 250×4.6 mm); flow rate = 1.0 mL min^{-1} ; *n*-heptane/ethanol 60:40; $20 \text{ }^\circ\text{C}$, 229 nm). $[\alpha]_{\text{D}}^{20} -14.2$ (*c* 0.01, CHCl_3). Other spectral data are similar to those previously given for the racemic sample.

(S_P)-(+)-2e: as the second-eluted fraction in total yield of 613 mg (1.80 mmol, 100% ee), HPLC: $t_{\text{R}} = 17.91$ min, [IA column ($5 \mu\text{m}$; size 250×4.6 mm); flow rate = 1.0 mL min^{-1} ; *n*-heptane/ethanol 60:40; $20 \text{ }^\circ\text{C}$, 229 nm). $[\alpha]_{\text{D}}^{20} +13.9$ (*c* 0.01, CHCl_3). Other spectral data are similar to those previously given for the racemic sample.

Deprotection into enantiopure thiols **5**

The deprotection was carried out as described before with the racemic material and the configuration of both enantiomers was unambiguously assigned by X-Ray crystallography.

(R_P)-(-)-5: Obtained from sulfanyl ester **(R_P)-(-)-2e**. Yield 79% (50.2 mg, 0.197 mmol, 100% ee). White solid, mp: $143\text{--}144 \text{ }^\circ\text{C}$. Spectral data are similar to those previously given for the racemic sample. HPLC: $t_{\text{R}} = 4.72$ min [Chiralpak Daicel IA column ($5 \mu\text{m}$; size 250×4.6 mm); flow rate = 1.0 mL min^{-1} ; *n*-heptane/EtOH 80:20; $20 \text{ }^\circ\text{C}$, 210 nm). $[\alpha]_{\text{D}}^{20} -37.6$ (*c* 0.01, CHCl_3).

(S_P)-(+)-5: Obtained from sulfanyl ester **(S_P)-(+)-2e**. Yield 76% (48.2 mg, 0.189 mmol, 100% ee). White solid, mp: 143–144 °C. Spectral data are similar to those previously given for the racemic sample. HPLC: $t_R = 6.38$ min [IA column (5 μ m; size 250 \times 4.6 mm); flow rate = 1.0 mL min⁻¹; *n*-heptane/EtOH 80:20; 20 °C, 210 nm). $[\alpha]_D^{20} +36.3$ (*c* 0.01, CHCl₃).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Optimization of the Reaction Conditions, Stereochemical Assignment and Transition State Model, and Cross-experiments and Chemoselectivity, Crystallographic Data for **2a**, **4a** and **(R_P)-5**, HPLC Chromatographs, and NMR Spectra for all new Products (PDF)

CCDC 1909740, 1909741 and 1909742 contain the supplementary crystallographic for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Brown, C. J.; Farthing, A. C. Preparation and structure of di-*p*-xylylene. *Nature* **1949**, *164*, 915–916.

(2) *Modern Cyclophane Chemistry*; Gleiter, R.; Hopf, H. Eds., Wiley-VCH:Weinheim, **2004**.

(3) For reviews, see: (a) Hassan, Z.; Spuling, E.; Knoll, D. M.; Bräse, S. Regioselective functionalization of [2.2]paracyclophanes: recent synthetic progress and perspectives. *Angew. Chem. Int. Ed.* **2020**, *59*, 2156–2170. (b) Weiland, K. J.; Gallego, A.; Mayor, M. Beyond simple substitution patterns – Symmetrically tetrasubstituted [2.2]paracyclophanes as 3D functional materials. *Eur. J. Org. Chem.* **2019**, 3073–3085. (c) Morisaki, Y.; Chujo, Y. Planar chiral [2.2]paracyclophanes: optical resolution and transformation to optically active π -stacked molecules. *Bull. Chem. Soc. Jpn.* **2019**, *92*, 265–274. (d) Hassan, Z.; Spuling, E.; Knoll, D. M.; Lahann, J.; Bräse, S. Planar chiral [2.2]paracyclophanes: from synthetic curiosity to applications in asymmetric synthesis and materials. *Chem. Soc. Rev.* **2018**, *47*, 6947–6963. (e) David, O. R. P. Syntheses and applications of disubstituted [2.2]paracyclophanes. *Tetrahedron* **2012**, *68*, 8977–8993. (f) Paradies, J. [2.2]Paracyclophane derivatives: synthesis and application in catalysis. *Synthesis* **2011**, 3749–3766. (g) Elacqua, E.; MacGillivray, L. R. From the decks to the bridges: optoelectronics in [2.2]paracyclophane chemistry. *Eur. J. Org. Chem.* **2010**, 6883–6894. (h) Aly, A. A.; Brown, A. B. Asymmetric and fused heterocycles based on [2.2]paracyclophane. *Tetrahedron* **2009**, *65*, 8055–8089. (i) Gibson, S. E.; Knight, J. D. [2.2]Paracyclophane derivatives in asymmetric catalysis. *Org. Biomol. Chem.* **2003**, *1*, 1256–1269.

(4) Selected recent examples of [2.2]PCP chemistry: (a) Moss, T.; Greiner, A. Functionalization of poly(para-xylylene)s—Opportunities and challenges as coating material. *Adv. Mater. Interfaces* **2020**, *7*, 1901858. (b) Zhao, Y.; Wang, H.; Wu, B.; Zhou, Y.-G. Synthesis of paracyclophanes with planar and central chirality: kinetic resolution of

[2.2]paracyclophane aldimines *via* palladium-catalyzed addition of arylboronic acids. *Org. Chem. Front.* **2019**, *6*, 3956–3960. (c) Wang, Y.; Zhao, C.-Y.; Wang, Y.-P., Zheng, W.-H. Enantioselective intramolecular dearomative lactonization of naphthols catalyzed by planar chiral iodoarene. *Synthesis* **2019**, *51*, 3675–3682.

(5) Rowlands, G. J. The synthesis of enantiomerically pure [2.2]paracyclophane derivatives. *Org. Biomol. Chem.* **2008**, *6*, 1527–1534.

(6) For recent investigations, see: (a) Martzel, T.; Lohier, J.-F.; Gaumont, A.-C.; Brière, J.-F.; Perrio, S. Sulfinato-organocatalyzed (3+2) annulation of allenyl sulfones with 1,1-dicyano olefins in the presence of a quaternary ammonium phase transfer agent. *Adv. Synth. Catal.* **2018**, *360*, 2696–2706. (b) Martzel, T.; Lohier, J.-F.; Gaumont, A.-C.; Brière, J.-F.; Perrio, S. Sulfinato-organocatalyzed (3+2) annulation reaction of propargyl or allenyl sulfones with activated imines. *Eur. J. Org. Chem.* **2018**, 5069–5073 (c) Martzel, T.; Lohier, J.-F.; Gaumont, A.-C.; Brière, J.-F.; Perrio, S. Unique reactivity of α -substituted electron-deficient allenes using sulfinato salts as Lewis base organocatalysts. *Adv. Synth. Catal.* **2017**, *359*, 96–106.

(7) (a) Lohier, J. F.; Foucoin, F.; Jaffrès, P.-A.; Garcia, J. I.; Sopková-de Oliveira Santos, J.; Perrio, S.; Metzner, P. An efficient and straightforward access to sulfur substituted [2.2]paracyclophanes: application to stereoselective sulfenate salt alkylation. *Org. Lett.* **2008**, *10*, 1271–1274. (b) Beqa, L.; Deschamps, D.; Perrio, S.; Gaumont, A.-C.; Knoppe, S.; Bürgi, T. Ligand exchange reaction on $\text{Au}_{38}(\text{SR})_{24}$, separation of $\text{Au}_{38}(\text{SR})_{23}(\text{SR}')_1$ regioisomers, and migration of thiolates. *J. Phys. Chem. C* **2013**, *117*, 21619–21625. (c) Vincent, A.; Deschamps, D.; Martzel, T.; Lohier, J.-F.; Richards, C. J.; Gaumont, A.-C.; Perrio, S. Enantiomerically pure [2.2]paracyclophane-4-thiol: a planar chiral sulfur-based building block readily available by resolution with an amino acid chiral auxiliary. *J. Org. Chem.* **2016**, *81*, 3961–3966.

(8) See for example: (a) Liu, Y.-F.; Zheng, L.; Zhai, D.-D.; Zhang, X.-Y.; Guan, B.-T. Dimeric potassium amide-catalyzed α -alkylation of benzyl sulfides and 1,3-dithianes. *Org. Lett.* **2019**, *21*, 5351–5356. (b) Yu, M.; Xie, Y.; Xie, C.; Zhang, Y. Palladium-catalyzed C–H alkenylation of arenes using thioethers as directing groups. *Org. Lett.*, **2012**, *14*, 2164–2167.

(9) In a previous study, we took profit of a [2.2]PCP precursor displaying a (*N,N*-dimethylamino)methyl substituent ($Y = \text{CH}_2\text{NMe}_2$, Figure 1) to generate a planar chiral *NC*-palladacycle with an excellent enantiomeric excess ($ee > 99\%$). Dendele, N.; Bisaro, F.; Gaumont, A.-C.; Perrio, S.; Richards, C. Synthesis of a [2.2]paracyclophane based planar chiral palladacycle by a highly selective kinetic resolution/C–H activation reaction. *J. Chem. Commun.* **2012**, *48*, 1991–1993.

(10) (a) Higuchi, H.; Kobayashi, E.; Sakata, Y.; Misumi, S. Photodimerization of benzenes in strained dihetera[3.3]metacyclophanes. *Tetrahedron* **1986**, *42*, 1731–1739. (b) Kannan, A.; Hopf, H.; Dix, I.; Jones, P. G.; Ernst, L. Synthesis, structure, and first reactions of a new class of thiacyclophanes. *Can. J. Chem.* **2017**, *95*, 278–285. (c) Kannan, A.; Dix, I.; Hopf, H.; Jones, P. G. [2.2]Dihydroisobenzothiophenophane. *Acta Crystallogr. Sect. E* **2005**, *61*, o3562–o3564. (d) Truesdale, E. A.; Cram, D. J. Macro rings. 49. Use of transannular reactions to add bridges to [2.2]paracyclophane. *J. Org. Chem.* **1980**, *45*, 3974–3981. (e) Kannan, N.; Otsubo, T.; Sakata, Y.; Misumi, S. Layered compounds. XXXV. Syntheses of triple-layered metaparacyclophanes. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3307–3313.

(11) Frank, D.; Nieger, M.; Friedmann, C.; Lahann, J.; Bräse, S. Functional paracyclophanes: synthesis of [2.2]paracyclophanemethyldithiocarbonates using thione–thiol rearrangement of *S,O*-dithiocarbonates (benzyl Schönberg rearrangement) at mild conditions. *Isr. J. Chem.* **2012**, *52*, 143–148.

(12) For a review dedicated to the recent progress of synthesis of enantioenriched chiral thioethers: (a) Chen, H.; Jian, W.; Zeng, Q. Recent advances in synthesis of chiral

thioether. *Chem. Rec.* **2020**, *20*, in the press. In addition, the [2.2]PCP sulfides could be readily transformed, through manipulation of the sulfur center, to a variety of synthetically valuable functional groups, including for example sulfoxides and sulfones. (b) Wojaczynska, E.; Wojaczynski J. Modern stereoselective synthesis of chiral sulfinyl compounds. *Chem Rev.* **2020**, *120*, 4578–4611. (c) Kaiser, D.; Klose, I.; Oost, R.; Neuhaus, J.; Maulide, N. Bond-forming and -breaking reactions at sulfur(IV): sulfoxides, sulfonium salts, sulfur ylides, and sulfinate salts. *Chem. Rev.* **2019**, *119*, 9701–8780. (d) Colomer, J. P.; Traverssi, M.; Oksdath-Mansilla, G. Oxidation of organosulfur compounds promoted by continuous-flow chemistry. *J. Flow Chem.* **2020**, *10*, 123–138.

(13) With $\text{BF}_3\cdot\text{H}_2\text{O}/\text{Et}_3\text{SiH}$: (a) Olah, G. A.; Wang, Q.; Trivedi, N. J.; Prakash, G. K. S. Boron trifluoride monohydrate catalyzed one-flask preparation of sulfides from carbonyl compounds with thiols and triethylsilane. *Synthesis* **1992**, 465–466. (b). Wang, Q.; Li, X.-y; Prakash, G. K. S.; Olah, G. A.; Locker, D. P.; Loker, K. B. Preparation of symmetric bis-sulfides via reductive thiolation of dicarbonyl with thiols or of carbonyl compounds with dithiols in the presence of triethylsilane and boron trifluoride monohydrate. *Arkivoc* **2001**, (viii), 116–128. (c) Procter, D. J.; Archer, N. J.; Needham, R. A.; Bell, D.; Marchington, A. P.; Rayner, C. M. Stereocontrolled synthesis of novel enantiomerically pure sulfides and selenides from (+)-camphor and (+)-camphor-10-sulfonyl chloride. *Tetrahedron* **1999**, *55*, 9611–9622. With TFA/ $\text{BH}_3\cdot\text{Pyridine}$: (d) Kikugawa, Y. A new synthesis of sulfides from thiols and aldehydes or ketones with pyridine-borane in trifluoroacetic acid. *Chem. Lett.* **1981**, 1157–1158. With TFA/ Et_3SiH : (e) Richter, L. S; Marsters Jr., J. C.; Gadek, T. R. Two new procedures for the introduction of benzyl-type protecting groups for thiols. *Tetrahedron Lett.* **1994**, *35*, 1631–1634. (f) Rudolph, J.; Theis, H.; Hanke, R.; Endermann, R.; Johannsen, L.; Geschke, F.-U. *seco*-Cyclothialidines: new concise synthesis, inhibitory activity toward bacterial and human DNA topoisomerases, and antibacterial properties. *J. Med. Chem.* **2001**,

44, 619–626. (g) Fyfe, M. C. T.; Rasamison, C. M. Reductive thiolation approach to pure cyclobutyl phenyl sulfide. *Org. Prep. Proced. Int.* **2005**, *37*, 194–197. With TfOH/Et₃SiH: (h) Gellert, B. A.; Kahlcke, N.; Feurer, M.; Roth, S. Triflic acid catalyzed reductive coupling reactions of carbonyl compounds with O-, S-, and N-nucleophiles. *Chem. Eur. J.* **2011**, *17*, 12203–11209.

(14) (a) Bondalapati, S.; Gogoi, P.; Indukuri, K.; Saikia, A. K. Diastereoselective Synthesis of substituted tetrahydrothiopyrans via (3,5)-thionium–ene cyclization reaction. *J. Org. Chem.* **2012**, *77*, 2508–2512. (b) Parnes, R.; Pappo, D. Reductive alkylation of arenes by a thiol-based multicomponent reaction. *Org. Lett.* **2015**, *17*, 2924–2927.

(15) Friedmann, C. J.; Ay, S.; Bräse, S. Improved synthesis of enantiopure 4-hydroxy[2.2]paracyclophane. *J. Org. Chem.* **2010**, *75*, 4612–4614.

(16) Mandal, S.; Mukhopadhyay, A.; Moorthy, J. N. Photochromism of acetyl-cyclophanochromene: intriguing stabilization of photogenerated colored *o*-quinonoid intermediates. *Eur. J. Org. Chem.* **2015**, 1403–1408.

(17) Gelat, F.; Jayashankaran, J.; Lohier, J.-F.; Gaumont, A.-C.; Perrio, S. Organocatalytic asymmetric synthesis of sulfoxides from sulfenic acid anions mediated by a *Cinchona*-derived phase-transfer reagent. *Org. Lett.* **2011**, *13*, 3170–3173.

(18) Performing an early resolution of 4-formyl[2.2]paracyclophane **1** would have been another option towards non-racemic substrates. (a) Delcourt, M.-L.; Turcaud, S.; Benedetti, E.; Micouin, L. Efficient and scalable kinetic resolution of racemic 4-formyl-[2.2]paracyclophane via asymmetric transfer hydrogenation. *Adv. Synth. Catal.* **2016**, *358*, 1213–1218. (b) Kramer, J. J. P.; Yildiz, C.; Nieger, M.; Bräse, S. Direct access to 4,5-disubstituted [2.2]paracyclophanes by selective ortho-halogenation with Pd-catalyzed C–H activation. *Eur. J. Org. Chem.* **2014**, 1287–1295. However, the ease of HPLC resolution of the sulfur-based [2.2]PCP compound **2e** makes this a simple alternative.

