Synthesis and Application of the First Planar Chiral Strong Brønsted Acid Organocatalysts

DIETER ENDERS,* MONIKA LUDWIG, AND GERHARD RAABE
Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany

ABSTRACT The synthesis of planar chiral strong Brønsted acid organocatalysts derived from [2.2]paracyclophane is described. Resolution was accomplished according to a modified protocol involving *pseudo-ortho*-substituted [2.2]paracyclophane-based sulfoxides for the synthesis of three new sulfonic acids. The first planar chiral phosphoric acid diester was obtained from the corresponding phenyl-substituted diol derived from enantiopure 4-bromo-12-hydroxy [2.2]paracyclophane. These new classes of catalysts were tested in an enantioselective Friedel–Crafts reaction as well as in a direct asymmetric Mannich reaction and gave yields of up to 93% and *ee*-values of up to 38%. *Chirality 24:215–222, 2012.*

KEY WORDS: paracyclophane; Brønsted acid; organocatalysis; planar chirality; Friedel–Crafts; Mannich

INTRODUCTION

The first synthesis of a planar chiral derivative of [2.2]paracyclophane was described in 1955 by Cram and Allinger.[1] However, it took 40 years to realize the potential of these structural elements in stereoselective synthesis,[2] but then resulting in numerous reports on applications of [2.2]paracyclophanes as chiral inducers such as ligands[3–5] and auxiliaries.[6,7]

The use of [2.2]paracyclophanes in catalysis was first reported in 2003 by Braddock et al., who utilized PHANOL (4,12-dihydroxy[2.2]paracyclophanediol) as a double hydrogen bond donor organocatalyst, but unfortunately no noticeable enantioselectivities were observed.[8,9]

In 2007, Kunz and coworkers[10] used enantiopure *N*-galactosyl[2.2]paracyclophane carbaldimines as organocatalysts in asymmetric Strecker reactions and obtained excellent enantiomeric excesses.

Recently, the application of a planar chiral thiourea hydrogen-bond catalyst[11] giving moderate enantioselectivities was described by Paradies and coworkers. Rowlands and coworkers reported on paracyclophane-derived *N*-oxides as Lewis base catalysts in enantioselective allylations giving likewise moderate enantioselectivities.[12] Besides these few examples, the application of [2.2]paracyclophanes in asymmetric organocatalysis has scarcely been investigated. To the best of our knowledge, synthesis or application of paracyclophane-derived stronger Brønsted acid organocatalysts has not been reported until now.

In the field of Brønsted acid organocatalysis, most of the utilized stronger acids such as phosphoric[13,14] and sulfonic acids[15] as well as *N*-triflyl phosphoramides[16] are derived from BINOL. Herein we report on the synthesis and first applications of three new sulfonic acids **1**, **2**, and **3** and one new phosphoric acid diester **4** (Fig. 1) derived from [2.2]paracyclophane as the first planar chiral strong Brønsted acid organocatalysts.

Because in binaphthol-derived catalysts sterically demanding substituents in 3- and 3′-position are crucial for a high stereocontrol in asymmetric transformations,[13] it was presumable that the [2.2]paracyclophane-backbone alone would not provide a suitable chiral environment. This assumption is also in accordance with previously published results.[9,11,12,17] We decided to add a sterically demanding group in *pseudo-ortho* position to the acid moiety. We assumed that especially in the case of sulfonic acids, steric hindrance to avoid free rotation of the acid is very important.

Enantiopure catalysts (R_P)-**1**, **2**, and **3** and (S_P)-**4** were obtained in several steps starting from commercially available [2.2]paracyclophane (**5**) and applied in asymmetric organocatalytic transformation.

EXPERIMENTAL

General Remarks

All reactions in which moisture-sensitive reagents were used were performed in oven-dried glassware under a slightly positive pressure of argon. Starting materials and reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. *rac*-4,12-Dibromo[2.2]paracyclophane (**7**), (R_P)-4-bromo-12-hydroxy[2.2]-paracyclophane ((R_P)-**21**), and (S_S)-(−)-*tert*-butyl-*tert*-butanethiosulfinate (**8**) were synthesized according to literature procedures (see text). All solvents were dried by conventional methods. Preparative column chromatography: Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical thin layer chromatography (TLC): silica gel 60 F254 plates from Merck, Darmstadt. Visualization of the developed TLC plates was performed with ultraviolet irradiation (254 nm) or by staining with a solution of phosphomolybdic acid in EtOH or potassium permanganate. ^{1}H- and ^{13}C-NMR spectra were recorded at ambient temperature on a Varian Mercury 300 instrument with tetramethylsilane as internal standard. Chemical shifts for ^{1}H-NMR and ^{13}C-NMR are reported in parts per million (ppm), with coupling constants reported in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, dt = doublet of triplet, q = quartet, qd = quartet of doublet, and m = multiplet. Mass spectra were acquired on a Finnigan SSQ7000 (EI 70 eV) spectrometer, electrospray ionization (ESI) spectra on a ThermoFinnigan LCQ Deca XP plus, and high resolution ESI spectra on a ThermoFisher Scientific LTQ-Orbitrap XL. IR spectra were taken on a PerkinElmer Spectrum 100 FTIR Spectrometer. The following

*Correspondence to: Dieter Enders, Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany.
E-mail: enders@rwth-aachen.de
Received for publication 6 June 2011; Accepted 2 November 2011
DOI: 10.1002/chir.21985
Published online 25 January 2012 in Wiley Online Library (wileyonlinelibrary.com).

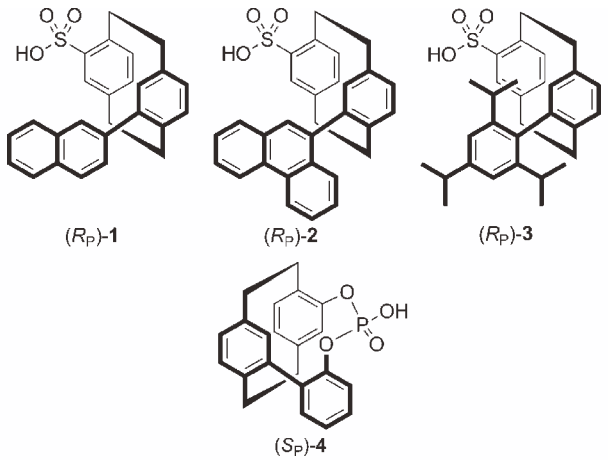


Fig. 1. New planar chiral Brønsted acids.

abbreviations are used: w = weak, m = medium, s = strong, and vs = very strong. Microanalyses were performed with a Vario EL element analyzer. Analytical high pressure liquid chromatography (HPLC) was carried out on a Hewlett-Packard 1050 Series instrument and Agilent 1100 Series instrument using chiral stationary phases. Optical rotation values were measured on a Perkin–Elmer 241 polarimeter.

(S_P,S_S)- and (R_P,S_S)-4-Bromo-12-*tert*-butylsulfinyl[2.2]paracyclophane ((R_P,S_S)-9 and (S_P,S_S)-9). To a solution of 4,12-dibromo[2.2]paracyclophane (**7**) (1.00 g, 2.73 mmol, 1 eq.) in anhydrous tetrahydrofuran (THF) (20 ml) at −78°C, *n*-BuLi (1.88 ml (1.6 M in *n*-hexane), 3.00 mmol, 1.1 eq.) was added dropwise via syringe pump. After stirring for 1 h at −78°C, the reaction mixture was transferred to a precooled (-78°C) solution of (S_S)-(−)-*tert*-butyl-*tert*-butanethiosulfinate (**8**) (800 mg, 4.09 mmol, 1.5 eq.) in anhydrous THF (2 ml) with a metal cannula and the resulting suspension was warmed to room temperature overnight. After addition of saturated aqueous NH_4Cl (10 ml) and methyl *tert*-butyl ether (MTBE) (10 ml) the phases were separated and the aqueous phase extracted with MTBE (3 × 20 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (*n*-pentane:ethyl acetate 4:1) with (R_P,S_S)-**9** being eluted first to obtain (R_P,S_S)-**9** (20%) and (S_P,S_S)-**9** (18%) as colorless crystals. (**R_P,S_S**)-9: m.p. 175°C; *de* > 99% (determined by NMR); $[\alpha]_D^{20}$ = –199 (*c* 1.0, $CHCl_3$); FTIR 2967 (m), 2934 (m), 2858 (m), 2297 (w), 2114 (w), 1585 (w), 1542 (w), 1453 (m), 1391 (m), 1390 (m), 1169 (s), 1133 (w), 1038 (vs), 955 (w), 909 (s), 864 (m), 820 (m), 794 (m), 711 (s), 676 (w) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.16 (d, *J* = 1.6 Hz, 1H.), 6.95 (d, *J* = 1.6 Hz, 1H), 6.62–6.54 (m, 3H), 6.50 (d, *J* = 7.8 Hz, 1H), 4.29 (ddd, *J* = 12.1 Hz, J_{cis} = 10.4 Hz, J_{trans} = 1.5 Hz, 1H), 3.50 (ddd, *J* = 13.1 Hz, J_{cis} = 9.8 Hz, J_{trans} = 1.8 Hz, 1H), 3.31–3.13 (m, 2H), 3.13–2.95 (m, 2H), 2.89–2.71 (m, 2H), 1.08 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 142.7, 142.3, 138.9, 138.5, 137.4, 137.2, 135.9, 134.9, 134.6, 130.9, 129.8, 127.1, 56.6, 35.6, 35.2, 34.4, 32.4, 23.1(3C); Analysis calculated for $C_{20}H_{23}BrOS$: C, 61.38; H, 5.92. Found: C, 61.12; H, 6.00.

(**S_P,S_S**)-9: m.p. 168°C; *de* > 99% (determined by NMR); $[\alpha]_D^{20}$ = +51 (*c* 1.0, $CHCl_3$); FTIR 3015 (w), 2930 (s), 2858 (m), 2315 (w), 1586 (w), 1543 (w), 1474 (m), 1454 (s), 1389 (m), 1362 (m), 1168 (s), 1137 (m), 1054 (s), 1023 (vs), 959 (w), 910 (s), 863 (m), 826 (s), 791 (m), 712 (s), 670 (m) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 1.8 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 6.64–6.42 (m, 4H), 3.56–3.43 (m, 2H), 3.32–3.19 (m, 1H), 3.15–3.03 (m, 3H), 2.89–2.72 (m, 2H), 1.04 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 140.8, 140.3, 138.9, 138.6, 138.5, 136.2 (2C), 134.8, 134.7, 131.0, 126.8, 126.6, 56.9, 35.9, 34.2, 33.5, 32.5, 22.6 (3C); Analysis calculated for $C_{20}H_{23}BrOS$: C, 61.38; H, 5.92; Found.: C, 61.48; H, 6.20.

(R_P)-4-Bromo-12-*tert*-butylsulfanyl[2.2]paracyclophane ((R_P)-10). To a solution of (R_P,S_S)-4-bromo-12-*tert*-butylsulfinyl[2.2]paracyclophane ((R_P,S_S)-**9**) (400 mg, 1.02 mmol, 1 eq.) and trichlorosilane (1.55 ml, 15.3 mmol, 15 eq.) in anhydrous toluene (6 ml) was slowly added triethylamine (1.42 ml, 10.2 mmol, 10 eq.) and the resulting yellow suspension stirred at reflux for 18 h. After cooling to 0°C, 2 N aqueous NaOH was added dropwise (*Caution*! Strong exothermic reaction occurs!) until the pH is below 7. After addition of MTBE (10 ml), the phases were separated and the aqueous phase extracted with MTBE (3 × 30 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (*n*-pentane:MTBE 20:1) to yield (R_P)-**10** (99%) as a colorless powder. m.p. 88°C; $[\alpha]_D^{20}$ = –140 (*c* 1.0, $CHCl_3$); FTIR 2959 (vs), 2929 (vs), 2855 (s), 2323 (w), 2107 (w), 1899 (w), 1729 (w), 1582 (s), 1539 (m), 1470 (s), 1451 (s), 1390 (s), 1360 (s), 1320 (w), 1269 (w), 1162 (vs), 1031 (vs), 953 (vs), 907 (s), 864 (s), 816 (s), 787 (s), 708 (vs), 669 (m) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.31 (d, *J* = 1.9 Hz, 1H), 6.67 (d, *J* = 1.7 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 6.55–6.49 (m, 2H), 6.47 (d, *J* = 7.8 Hz, 1H), 3.84–3.74 (m, 1H), 3.45 (ddd, *J* = 13.1 Hz, J_{cis} = 9.7 Hz, J_{trans} = 1.9 Hz, 1H), 3.19–3.08 (m, 1H), 3.08–2.97 (m, 3H), 2.86–2.73 (m, 2H), 1.18 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 145.4, 141.9, 139.7, 139.1, 138.7, 135.2, 134.9, 134.2, 133.8, 132.9, 131.3, 126.7, 46.5, 35.8, 35.5, 33.8, 32.4, 30.9 (3C); Analysis calculated for $C_{20}H_{23}BrS$: C, 63.99; H, 6.18; Found: C, 63.69; H, 6.22.

Sulfides (R_P)-14, (R_P)-15, and (R_P)-16

General method for the Suzuki cross-coupling. Method A: (R_P)-4-(2-Naphthyl)-12-*tert*-butylsulfanyl[2.2]paracyclophane ((R_P)-14). To a solution of (R_p)-4-bromo-12-*tert*-butylsulfanyl[2.2]paracyclophane ((R_P)-**10**) (850 mg, 2.26 mmol, 1 eq.), 2-naphthylboronic acid (**11**) (776 mg, 4.36 mmol, 1.9 eq) and tetrakis(triphenylphosphine)palladium(0) (270 mg, 0.23 mmol, 0.1 eq) in DMF (21 ml) was added 2 M aqueous Na_2CO_3 and the suspension was degased using the freeze-pump-thaw method and then heated to 100°C for 48 h. After cooling to room temperature, MTBE (100 ml) and saturated aqueous $NaHCO_3$ (100 ml) were added, the phases were separated and the aqueous phase extracted with MTBE (5 × 100 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (*n*-pentane:DCM 50:1) to yield (R_P)-**14** (58%) as a colorless powder. M.p. 175°C; *ee* = 98% (determined by chiral HPLC (Merck (s,s)-Whelk O1, 250 mm × 4.6 mm), *n*-heptane:isopropanol 98:2, 0.5 ml/min, t_R = 7.56 min (major), t_R = 8.23 (minor)); $[\alpha]_D^{20}$ = –20 (*c* 0.5, $CHCl_3$); FTIR 3035 (m), 2958 (s), 2926 (vs), 2855 (s), 2327 (m), 2205 (w), 1930 (w), 1896 (w), 1745 (w), 1625 (w), 1584 (s), 1501 (m), 1455 (s), 1389 (s), 1361 (s), 1261 (m), 1196 (m), 1162 (s), 1094 (w), 1049 (m), 1020 (m), 1020 (s), 949 (s), 907 (s), 863 (s), 824 (s), 801 (s), 751 (vs), 723 (vs), 682 (m) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.36 (d, *J* = 1.0 Hz, 1H), 8.03 (dd, *J* = 7.7 Hz, *J* = 1.0 Hz, 1H), 7.94–7.88 (m, 2H), 7.76 (dd, *J* = 8.5, *J* = 1.7, 1H), 7.57–7.48 (m, 2H), 6.88 (d, *J* = 1.8 Hz, 1H), 6.80 (d, *J* = 1.8 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 6.60 (dd, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 6.57 (dd, *J* = 7.7 Hz, *J* = 1.7 Hz, 1H), 3.89 (ddd, *J* = 12.4 Hz, J_{cis} = 9.3 Hz, J_{trans} = 2.1 Hz, 1H), 3.66–3.55 (m, 1H), 3.23–3.06 (m, 2H), 2.93–2.78 (m, 3H), 2.40–2.31 (m, 1H), 1.24 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 145.5, 141.2, 140.5, 140.1, 139.3, 138.7, 136.8, 135.9, 133.9, 133.8, 133.3, 132.4, 132.3, 131.8, 131.0, 128.6, 128.4, 128.3, 127.6, 127.5, 125.8, 125.7, 46.8, 35.9, 34.9, 34.0, 33.5, 31.1 (3C); HRMS calculated for $C_{30}H_{31}S$: 423.2141, Found: 423.2142.

(R_p)-4-(2-Phenanthryl)-12-*tert*-butylsulfanyl[2.2]paracyclophane ((R_P)-15). Compound (R_P)-**15** was prepared following method A using 9-phenanthrylboronic acid (**12**) (95%, colorless solid). M.p. 169°C; $[\alpha]_D^{20}$ = +217 (*c* 0.5, $CHCl_3$); FTIR 3303 (w), 3200 (w), 3064 (w), 2958 (s), 2924 (s), 2857 (m), 2327 (w), 2109 (w), 1580 (m), 1516 (w), 1439 (s), 1305 (s), 1206 (vs), 1158 (vs), 1054 (s), 950 (w), 906 (m), 867 (m), 731 (vs) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.78–8.71 (m, 2H), 8.70 (s, 1H), 8.26–8.19 (m, 1H), 7.95 (dd, *J* = 8.3 Hz, *J* = 1.2 Hz, 1H), 7.74–7.68 (m, 2H), 7.62 (ddd, *J* = 8.3 Hz, *J* = 6.9 Hz, *J* = 1.4 Hz, 1H), 7.45 (ddd, *J* = 8.2 Hz, *J* = 6.9 Hz, *J* = 1.3 Hz, 1H), 7.05 (d, *J* = 1.9, 1H), 6.88–6.85 (m, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.68–6.64 (m, 3H), 3.93 (ddd, *J* = 12.6 Hz, J_{cis} = 9.6 Hz, J_{trans} = 1.7 Hz, 1H), 3.29–3.08 (m, 2H), 2.91 (ddd, *J* = 12.7 Hz, J_{cis} = 10.3 Hz, J_{trans} = 6.9 Hz, 1H), 2.85–2.71 (m, 3H), 2.48–2.34 (m, 1H), 1.29 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 145.9, 140.4, 139.9, 139.7, 139.4, 137.5, 134.8, 134.0, 133.6, 132.7, 132.4 (2C), 132.3,

131.8, 131.0, 130.3, 129.9, 128.9, 128.6, 126.6, 126.5, 126.4, 126.3, 126.1, 122.7, 122.5, 46.8, 35.8, 34.8, 34.0, 33.7, 31.2 (3C); analysis calculated for $C_{34}H_{32}BS$: C, 86.39; H, 6.82; Found: C, 86.54; H, 7.16.

(R_p)-4-(2,4,6-Triisopropylphenyl)-12-*tert*-butylsulfanyl[2.2]paracyclophane ((R_P)-16). Compound (R_P)-**16** was prepared following method A using 2,4,6-triisopropylboronic acid (**13**) (16%). M.p. 138°C; $[\alpha]_D^{20}$ = +9 (*c* 0.5, $CHCl_3$); FTIR 3298 (w), 3193 (w), 2960 (m), 2873 (w), 2711 (w), 1575 (m), 1517 (w), 1434 (s), 1308 (vs), 1217 (vs), 1159 (s), 1057 (vs), 868 (m), 805 (m), 727 (m) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.13 (d, *J* = 1.9 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 6.81 (dd, *J* = 7.6 Hz, J = 1.9 Hz, 1H), 6.66 (d, *J* = 1.9 Hz, 1H), 6.47–6.40 (m, 3H), 3.92–3.70 (m, 2H), 3.30–3.21 (m, 1H), 3.02–2.65 (m, 7H), 2.16–2.01 (m, 1H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.43 (d, *J* = 6.6 Hz, 3H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.12 (s, 9H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.51 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 148.4, 147.2, 146.6, 146.4, 141.0, 139.2, 138.7, 137.5, 136.6, 134.4, 134.1, 133.7, 133.3, 132.5, 132.4, 129.5, 121.6, 120.7, 46.1, 36.2, 34.4, 34.0, 33.9, 33.2, 30.8 (3C), 29.7, 29.6, 26.6, 25.5, 24.2, 24.1, 24.0, 23.6; HRMS calculated for $C_{35}H_{47}S$: 499.3393, Found: 499.3398.

Thioacetates (R_P)-17, (R_P)-18, and (R_P)-19

General method for the acetylation. Method B: (R_P)-4-(2-Naphthyl)-12-acetylmercapto[2.2]paracyclophane ((R_P)-17). To a solution of (R_P)-4-(2-naphthyl)-12-*tert*-butylsulfanyl[2.2]paracyclophane ((R_P)-**14**) (300 mg, 0.71 mmol, 1 eq.) and acetyl chloride (0.36 ml, 4.97 mmol, 7 eq.) in anhydrous toluene (8 ml) was slowly added boron tribromide (0.852 ml (1 M in DCM), 0.85 mmol, 1.2 eq.). After stirring at room temperature overnight, saturated aqueous NH_4Cl (20 ml) and MTBE (50 ml) were added. The phases were separated and the aqueous phase extracted with MTBE (3 × 20 ml) and DCM (2 × 20 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (*n*-pentane:ethyl acetate 9:1) to yield (R_P)-**17** (99 %) as a colorless solid. M.p. 112°C; *ee* > 99% (determined by chiral HPLC (Chiralcel OD 10 μ (250 mm × 4.6 mm), *n*-heptane/isopropanol 95:5, 0.7 ml/min, t_R = 14.53 min (major), t_R = 20.80 min (minor)); $[\alpha]_D^{22}$ = +53 (*c* 0.5, $CHCl_3$); FTIR 3386 (w), 3059 (m), 2933 (m), 2852 (w), 2322 (m), 2084 (s), 1903 (w), 1701 (s), 1586 (m), 1476 (m), 1434 (m), 1347 (w), 1261 (m), 1198 (w), 1102 (s), 1053 (s), 947 (s), 898 (w), 862 (m), 814 (s), 728 (s), 669 (w), 608 (vs) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 1.1 Hz, 1H), 8.04–7.89 (m, 3H), 7.67 (dd, *J* = 8.5 Hz, *J* = 1.8 Hz, 1H), 7.61–7.51 (m, 2H), 6.85 (d, *J* = 1.9 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 1.8 Hz, 1H), 6.73–6.67 (m, 2H), 6.59 (dd, *J* = 7.8, *J* = 1.9, 1H), 3.67–3.59 (m, 1H), 3.50 (ddd, *J* = 13.1 Hz, J_{cis} = 9.6 Hz, J_{trans} = 1.4 Hz, 1H), 3.29–3.18 (m, 1H), 3.16–3.03 (m, 1H), 3.02–2.79 (m, 3H), 2.48 (s, 3H), 2.44–2.32 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 193.6, 143.2, 141.3, 140.5, 139.7, 138.4, 137.2, 136.3, 136.0, 134.9, 134.7, 133.8, 132.4, 132.2, 130.3, 128.4, 128.3, 128.2, 128.1 (2C), 127.6, 126.1, 125.9, 35.0, 34.8, 33.7, 33.6, 30.4; HRMS calculated for $C_{28}H_{24}ONaS$: 431.1440, Found: 431.1435.

(R_P)-4-(2-Phenanthryl)-12-acetylmercapto[2.2]paracyclophane ((R_P)-18). Compound (R_P)-**18** was prepared following method B using (R_P)-4-(2-phenanthryl)-12-*tert*-butylsulfanyl[2.2]paracyclophane ((R_P)-**18**) (99%, yellow solid); m.p. 151°C; $[\alpha]_D^{20}$ = +270 (*c* 0.5, $CHCl_3$); FTIR 3067 (w), 2926 (m), 2852 (w), 2317 (w), 2186 (w), 2161 (w), 2110 (w), 2058 (w), 2005 (m), 1930 (w), 1897 (w), 1702 (vs), 1583 (w), 1478 (m), 1447 (m), 1428 (m), 1351 (m), 1240 (w), 1202 (w), 1108 (s), 1047 (m), 948 (s), 899 (s), 866 (m), 813 (w), 726 (vs) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.80–8.71 (m, 2H), 8.17 (s, 1H), 8.17–8.12 (m, 1H), 7.89 (dd, *J* = 8.3 Hz, *J* = 1.0 Hz, 1H), 7.76–7.68 (m, 2H), 7.64 (ddd, *J* = 8.3, *J* = 6.9, *J* = 1.3, 1H), 7.46 (ddd, *J* = 8.2, *J* = 6.9, *J* = 1.2, 1H), 6.93 (d, *J* = 1.6 Hz, 1H), 6.90–6.85 (m, 2H), 6.74 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H), 6.72–6.65 (m, 2H), 3.57–3.45 (m, 1H), 3.34–3.22 (m, 1H), 3.16–2.89 (m, 2H), 2.88–2.68 (m, 3H), 2.51 (s, 3H), 2.47–2.34 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 193.5, 143.3, 140.7, 139.9, 139.7, 138.1, 137.5, 135.4, 135.0, 134.9, 134.7, 133.0, 131.9 (2C), 131.1, 130.4, 130.0 (2C), 128.9, 127.8, 126.8, 126.7, 126.6, 126.4, 126.3, 122.8, 122.5, 35.0, 34.7, 33.8, 33.7, 30.5; HRMS calculated for $C_{32}H_{26}ONaS$: 481.1597, Found: 481.1595.

(R_P)-4-(2,4,6-Triisopropylphenyl)-12-acetylmercapto[2.2]paracyclophane ((R_P)-19). Compound (R_P)-**19** was prepared following method B using (R_P)-4-(2,4,6-triisopropylphenyl)-12-*tert*-butylsulfanyl[2.2]paracyclophane ((R_P)-**16**) (77%, pale yellow solid). M.p. 170°C; $[\alpha]_D^{20}$ = +35 (*c* 0.5, $CHCl_3$); FTIR 3396 (w), 2957 (vs), 2866 (s), 2083 (w), 1889 (w), 1706 (vs), 1606 (m), 1579 (m), 1458 (s), 1380 (m), 1357 (s), 1313 (w), 1253 (w), 1199 (w), 1163 (w), 1105 (vs), 1051 (m), 1019 (s), 941 (s), 865 (s), 811 (m), 722 (s), 655 (w) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.14 (d, *J* = 1.6 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.93–6.88 (m, 2H), 6.58 (d, *J* = 1.2 Hz, 1H), 6.52–6.42 (m, 3H), 3.63–3.50 (m, 1H), 3.50–3.38 (m, 1H), 3.38–3.24 (m, 1H), 3.05–2.80 (m, 6H), 2.80–2.66 (m, 1H), 2.37 (s, 3H), 2.12–1.96 (m, 1H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.31 (d, *J* = 6.9 Hz, 6H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.54 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 193.6, 148.5, 147.4, 146.0, 143.6, 140.2, 138.9, 136.9, 136.7, 136.1, 134.6, 134.5, 134.3, 134.2, 132.6, 128.9, 128.1, 121.3, 121.0, 77.0, 35.3, 34.4, 33.9, 33.6, 33.1, 30.3, 30.2, 29.6, 26.4, 25.5, 24.1, 24.0 (2C), 23.6; HRMS calculated for $C_{33}H_{40}OKS$: 523.24315, Found: 523.2424.

Sulfonic Acids (R_P)-1, (R_P)-2, and (R_P)-3

General method for the deprotection of thioacetates and oxidation to sulfonic acids. Method C: (R_P)-4-(2-Naphthyl)[2.2]paracyclophane-12-sulfonic acid ((R_P)-1). (R_P)-4-(2-Naphthyl)-12-acetylmercapto[2.2]paracyclophane ((R_P)-**17**) (1.00 g, 2.45 mmol, 1 eq.) and freshly powdered KOH (2.00 g, 35.6 mmol, 14.5 eq.) were dissolved in MeOH (100 ml) and O_2 was bubbled through the solution for 72 h. The solvent was evaporated in vacuo, the residue dissolved in MTBE and 2 N aqueous HCl (50 ml) was added. The phases were separated and the aqueous phase extracted with MTBE (3 × 100 ml) and DCM (2 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (DCM:MeOH 9:1) to yield (R_P)-**1** (69%) as a yellow solid. To remove a possible contamination with alkali metals from the column, the product was dissolved in DCM, washed with 2 N aqueous HCl, and evaporated to give the free acid as a yellow-green foam. M.p. 142°C (decomposition); $[\alpha]_D^{22}$ = +79 (*c* 0.5, MeOH); FTIR 3407 (m), 2925 (vs), 2855 (s), 2090 (w), 1735 (vs), 1661 (w), 1589 (m), 1459 (s), 1370 (s), 1213 (vs), 1078 (s), 1021 (vs), 951 (m), 903 (m), 861 (m), 821 (s), 749 (s), 726 (s), 694 (m), 665 (w) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 1.3 Hz, 1H), 8.12 (dd, *J* = 6.7 Hz, *J* = 2.3 Hz, 1H), 7.90–7.86 (m, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.72 (dd, *J* = 8.5 Hz, *J* = 1.7 Hz, 1H), 7.50–7.42 (m, 2H), 7.25 (d, *J* = 1.4 Hz, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.63 (dd, *J* = 7.7 Hz, *J* = 1.7 Hz, 1H), 6.61–6.55 (m, 2H), 4.05–3.97 (m, 1H), 3.69–3.61 (m, 1H), 3.40–3.31 (m, 1H), 3.10–2.99 (m, 1H), 2.99–2.88 (m, 1H), 2.87–2.69 (m, 2H), 2.13–2.05 (m, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 142.5, 141.8, 141.2, 140.9, 139.9, 138.9, 138.1, 137.1, 136.6, 136.3, 135.4, 133.7, 132.8, 132.5, 129.7, 129.6, 129.5, 128.7, 128.6, 128.3, 126.7, 126.6, 36.3, 35.7, 34.9, 34.2; HRMS calculated for $C_{26}H_{21}O_3S$: 413.1206, Found: 413.1209.

(R_p)-4-(2-Phenanthryl)[2.2]paracyclophane-12-sulfonic acid ((R_P)-2). Compound (R_P)-**2** was prepared following method C using (R_p)-4-(2-phenanthryl)-12-acetylmercapto[2.2]paracyclophane ((R_P)-**18**) (80%, yellow solid). M.p. 68°C (decomposition); $[\alpha]_D^{20}$ = +195 (*c* 0.5, $CHCl_3$); FTIR 3838 (w), 3384 (m), 3069 (w), 2927 (s), 2859 (s), 2310 (w), 2166 (w), 2086 (m), 1995 (w), 1929 (w), 1715 (s), 1589 (m), 1451 (s), 1367 (w), 1260 (m), 1122 (s), 1075 (s), 1009 (s), 954 (w), 897 (s), 870 (s), 804 (m), 729 (vs) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.68–8.58 (m, 2H), 8.44 (s, 1H), 8.30 (dd, *J* = 7.1 Hz, *J* = 2.0 Hz, 1H), 7.84 (dd, *J* = 8.3 Hz, *J* = 1.0 Hz, 1H), 7.61–7.47 (m, 3H), 7.38–7.29 (m, 2H), 7.05 (d, *J* = 0.9 Hz, 1H), 6.71–6.64 (m, 2H), 6.64–6.54 (m, 2H), 3.95–3.62 (m, 1H), 3.36–3.18 (m, 2H), 3.14–2.98 (m, 1H), 2.96–2.81 (m, 1H), 2.81–2.59 (m, 2H), 2.32–2.10 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 140.2, 140.0, 139.5, 139.4, 137.6, 137.5, 137.3, 135.7, 135.4, 133.9, 132.5, 132.3, 132.0, 130.6, 130.1, 129.6, 129.3, 128.4, 126.9, 126.2, 126.1, 126.1, 125.9, 125.8, 122.5, 121.9, 35.1, 34.4, 33.8, 33.3; HRMS calculated for $C_{30}H_{23}O_3S$: 463.1362, Found: 463.1367.

(R_p)-4-(2,4,6-Triisopropylphenyl)[2.2]paracyclophane-12-sulfonic acid ((R_P)-3). Compound (R_P)-**3** was prepared following method C using (R_p)-4-(2,4,6-triisopropylphenyl)-12-acetylmercapto[2.2]-paracyclophane ((R_P)-**19**) (66 %, yellow solid). M.p: 139°C (decomposition); $[\alpha]_D^{20} = +32$ (*c* 0.5, $CHCl_3$); FTIR 2961 (s), 2927 (m), 2866 (m), 1722 (w), 1460 (m), 1382 (w), 1360 (w), 1259 (s), 1077 (vs), 1015 (vs), 868 (m), 796 (vs), 689 (m), 657 (w) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.13–7.04 (m, 2H), 6.95–6.87 (m, 2H), 6.87–6.62 (m, 1H), 6.62–6.49 (m, 3H), 3.92–3.33 (m, 3H), 3.26–2.63 (m, 7H), 1.92–1.72 (m, 1H), 1.43 (d, J = 6.9 Hz, 3H), 1.39 (d, J = 6.9 Hz, 3H), 1.27 (d, J = 6.9 Hz, 6H), 0.94 (d, J = 7.2 Hz, 3H), 0.51 (d, J = 7.2 Hz, 3H); ^{3}C-NMR (75 MHz, $CDCl_3$) δ: 148.3, 147.2, 146.9, 140.4, 139.2, 139.1, 137.4 (2C), 137.0, 136.8, 136.2, 134.1, 133.6, 132.2, 130.6, 128.8, 121.4, 120.6, 35.1, 34.5, 34.4, 33.9, 33.6, 30.2, 29.5, 26.0, 25.3, 24.1, 24.0, 24.0, 23.9; HRMS calculated for $C_{31}H_{37}O_3S$: 489.2458, Found: 489.2466.

(S_P)-4,12-Bis(2-hydroxyphenyl)[2.2]paracyclophane ((S_P)-22). To a solution of (S_P)-4-bromo-12-hydroxy[2.2]paracyclophane ((S_P)-**21**), 2-hydroxyphenylboronic acid (**21**) (245 mg, 1.78 mmol, 2.7 eq) and tetrakis(triphenylphosphine)-palladium(0) (38.8 mg, 0.034 mmol, 0.05 eq.) in DMF (7 ml) was added 2 M aqueous Na_2CO_3 (2.8 ml) and the suspension was degased using the freeze-pump-thaw method and then heated to 100°C for 48 h. After cooling to room temperature, MTBE (40 ml) and saturated aqueous $NaHCO_3$ (40 ml) were added, the phases were separated and the aqueous phase extracted with MTBE (5 × 40 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (*n*-pentane:ethylacetate 10:1) to yield (S_P)-**22** (53%) as a colorless powder. M.p. 58°C; $[\alpha]_D^{22} = -138$ (*c* 1.0, $CHCl_3$); FTIR 3404 (m), 2927 (m), 2854 (m), 1708 (w), 1654 (s), 1576 (s), 1485 (s), 1443 (s), 1418 (m), 1377 (w), 1339 (w), 1221 (s), 1096 (m), 1043 (m), 979 (m), 942 (w), 903 (m), 873 (s), 807 (m), 756 (vs), 660 (m) cm^{-1}; ^{1}H-NMR (300 MHz, CD_3OD): 7.53 (d, J = 7.3 Hz, 1H), 7.19 (ddd, J = 7.9 Hz, 7.4 Hz, J = 1.8 Hz, 1H), 7.02 (ddd, J = 7.6 Hz, 7.5 Hz, J = 1.2 Hz, 1H), 6.96 (d, J = 1.2 Hz, 1H), 6.87 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H), 6.58 (d, J = 7.7 Hz, 1H), 6.48 (d, J = 7.7 Hz, 1H), 6.37 (dd, J = 7.7 Hz, J = 1.8 Hz, 1H), 6.27 (dd, J = 7.7 Hz, J = 1.7 Hz, 1H), 5.75 (d, J = 7.3 Hz, 1H), 3.44 (ddd, J = −13.2 Hz, J_{cis} = 8.9 Hz, J_{trans} = 2.7 Hz, 1H), 3.17–2.97 (m, 3H), 2.97–2.85 (m, 1H), 2.79–2.68 (m, 1H), 2.68–2.57 (m, 1H), 2.49 (ddd, J = 13.1 Hz, J_{cis} = 10.3 Hz, J_{trans} = 4.8 Hz, 1H); ^{13}C-NMR (75 MHz, CD_3OD) δ: 156.1, 154.8, 143.3, 140.6, 139.5, 136.0, 135.2 (2C), 134.0, 130.2, 129.5 (2C), 125.6 (2C), 121.5 (2C), 120.3, 116.8, 35.2, 35.2, 34.4, 32.5; HRMS calculated for $C_{22}H_{21}O_2$: 317.1536, Found: 317.1531.

(S_P)-4-(Phenyl-2-yl)-[2.2]paracyclophane-12-yl-hydrogenphosphate ((S_P)-4). To a solution of (S_P)-4,12-bis(2-hydroxyphenyl)[2.2]-paracyclophane ((S_P)-**22**) (345 mg, 1.09 mmol, 1 eq.) in dry pyridine (35 ml), phosphoryl chloride (0.200 ml, 2.19 mmol, 2 eq.) was added slowly at room temperature and stirred overnight. After addition of water (15 ml) stirring was continued for another 24 h. The reaction mixture was diluted with DCM, the phases were separated and the aqueous phase extracted with DCM several times. The combined organic phases were thoroughly washed with 2 N aqueous HCl, dried over $MgSO_4$, and concentrated to yield (S_P)-**4** as a light red solid (48 %). M.p. 330°C (decomposition); $[\alpha]_D^{22} = -51.1$ (*c* 1.0, MeOH); FTIR 3286 (w), 3051 (w), 2963 (w), 2925 (m), 2853 (w), 2296 (w), 2142 (w), 2112 (w), 2073 (w), 2002 (w), 1920 (w), 1725 (w), 1630 (w), 1596 (m), 1565 (w), 1493 (m), 1467 (m), 1444 (s), 1411 (s), 1324 (w), 1259 (s), 1200 (s), 1095 (s), 1020 (vs), 965 (vs), 905 (m), 867 (m), 800 (s), 767 (s), 655 (w) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.42 (d, J = 1.8 Hz, 1H), 7.38 (ddd, J = 9.0 Hz, 7.4 Hz, J = 1.8 Hz, 1H), 7.27–7.19 (m, 2H), 7.19–7.13 (m, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.65 (dd, J = 7.7 Hz, J = 1.1 Hz, 1H), 6.56–6.52 (m, 1H), 6.51–6.43 (m, 2H), 3.37–3.26 (m, 1H), 3.21–3.06 (m, 2H), 3.03–2.64 (m, 5H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 150.5, 149.4, 142.5, 139.1, 138.3, 137.8, 135.3, 134.9, 134.4, 133.8, 130.5, 129.5, 129.4, 129.0, 128.3, 125.2, 124.1, 119.3, 35.1, 34.7, 32.9, 29.1; ^{31}P-NMR (121 MHz, DMSO-d_6) δ: −12.05; HRMS calculated for $C_{22}H_{19}O_4P$: 379.1094, Found: 379.1087.

General Procedure for the Catalytic Asymmetric Friedel–Crafts Reaction

N-Sulfonyl imine (0.1 mmol) and Brønsted acid (0.01 mmol) were placed in a dry Schlenk tube and dissolved in dry toluene (0.2 ml) under argon. After stirring for 15 min at room temperature the solution was cooled to −78°C and indole (0.5 mmol) was added. The reaction was warmed to −60°C for 20 min and then quenched by addition of sat. aqueous $NaHCO_3$. After extraction with ethyl acetate and drying over $MgSO_4$ the solvent was removed. The crude product was purified by column chromatography (*n*-pentane:ethylacetate 4:1).

***N*-(Indol-3-yl-phenylmethyl)-4-methylbenzenesulfonamide (25a).** ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.04 (s, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.32–7.05 (m, 8H), 7.09 (d, J = 8.0 Hz, 2H), 6.99 (t, J = 7.9 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 5.84 (d, J = 6.9 Hz, 1H), 5.18 (d, J = 6.9 Hz, 1H), 2.36 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 142.9, 140.2, 137.3, 136.5, 129.2, 128.3, 127.3, 127.2, 127.1, 125.3, 123.8, 122.4, 119.9, 119.2, 116.2, 111.2, 54.9, 21.4.

***N*-(5-Methoxy-indol-3-yl-phenylmethyl)-4-methylbenzenesulfonamide (25b).** ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.25–7.12 (m, 6H), 7.04 (d, J = 7.9 Hz, 2H), 6.82–6.76 (m, 2H, 1H), 6.58 (d, J = 2.6 Hz, 1H), 5.80 (d, J = 7.4 Hz, 1H), 5.56 (d, J = 7.4 Hz, 1H), 3.71 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 154.1, 142.9, 140.1, 137.4, 131.5, 129.7, 129.2, 128.3, 127.3, 127.1, 125.8, 124.5, 112.8, 111.9, 100.8, 55.7, 54.9, 21.4.

General Procedure for the Catalytic Asymmetric Mannich Reaction

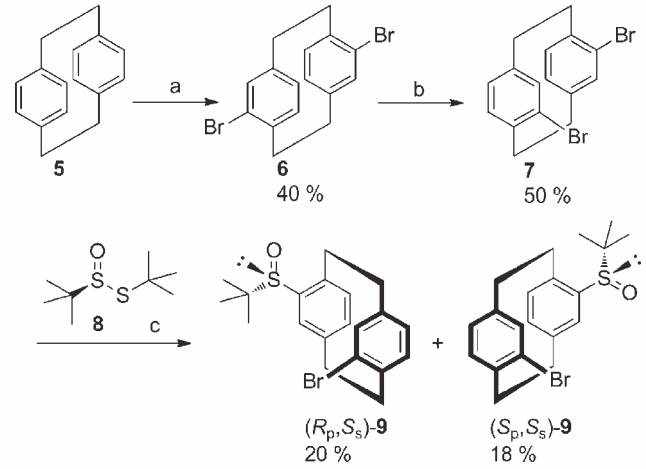
Aniline (36.5 µl, 0.4 mmol), 4-nitrobenzaldehyde (66.5 mg, 0.44 mmol), and Brønsted acid (0.008 mmol, 0.02 eq.) were dissolved in toluene (5 ml). After stirring for 30 min at room temperature the solution was cooled to 0°C and cyclohexanone (0.41 ml, 4 mmol) was added. The reaction was stirred for 2–3 days (until completion, monitored by TLC) and then quenched by addition of sat. aqueous $NaHCO_3$. After extraction with ethyl acetate and drying over $MgSO_4$ the solvent was removed. The crude product was purified by column chromatography (*n*-pentane:ethylacetate 8:1).

2-(4-Methoxyphenylamino)(4-nitrophenyl)methyl)cyclohexanone (30). Anti-diastereomer. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.18–8.12 (m, 2H), 7.61–7.54 (m, 2H), 7.13–7.04 (m, 2H), 6.70–6.64 (m, 1H), 6.53–6.47 (m, 2H), 4.88 (s, 1H), 4.71 (d, J = 5.3, 1H), 2.92–2.79 (m, 1H), 2.47–2.25 (m, 2H), 2.10–1.86 (m, 3H), 1.86–1.65 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 24.4, 27.7, 32.0, 42.4, 56.9, 57.7, 113.4, 118.0, 123.7, 128.2, 129.2, 146.6, 146.9, 149.8, 211.8. Syn-diastereomer. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.18–8.12 (m, 2H), 7.61–7.54 (m, 2H), 7.13–7.04 (m, 2H), 6.70–6.64 (m, 1H), 6.53–6.47 (m, 2H), 4.85 (d, J = 4.2, 1H), 4.59 (s, 1H), 2.92–2.79 (m, 1H), 2.47–2.25 (m, 2H), 2.14–1.86 (m, 3H), 1.72–1.47 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 24.9, 27.0, 29.0, 42.4, 56.1, 57.2, 114.0, 118.3, 123.6, 128.5, 129.2, 146.5, 146.9, 149.5, 210.6.

RESULTS AND DISCUSSION

Synthesis of Sulfonic Acids

To obtain enantiopure sulfonic acids, chiral sulfoxides seemed to be a good choice, because they offer a way for resolution and also provide a sulfur-containing moiety, which then can be converted to a sulfonic acid. The successful use of Ellman's[18] reagent (*tert*-butyl-*tert*-butanethiosulfinate (**8**)) as the chiral source in paracyclophanes was published recently[19] and the sulfoxide moiety was then converted into thiols.[20] Whereas the literature known synthesis used the mono-brominated paracyclophane as the starting material, we chose to use a dibromide for later insertion of a sterically demanding group. The *pseudo-ortho* 4,12-dibromo[2.2]paracyclophane (**7**) has often been used as starting material for a variety of substituted paracyclophane-derivatives.[5,21–23]



Scheme 1. Synthesis of the sulfoxide-precursor. Conditions: (a) Fe/Br2, DCM, reflux, 20 h; (b) triglyme, reflux, 6 h, (c) 1: *n*-BuLi, −78°C, THF, 1 h, 2: **8**, −78°C →r.t.

Starting from [2.2]paracyclophane (**5**), iron-catalyzed dibromination gave the *pseudo-para* isomer **6** as the main product, which is the only isolable isomer due to its insolubility in dimethylformamide.[22] After isomerization in refluxing triglyme, the desired *pseudo-ortho* isomer **7** was obtained. Lithiation with a slight excess of *n*-BuLi and addition of (S_S)-(−)-*tert*-butyl-*tert*-butanethiosulfinate (**8**) (*ee* > 97%) yielded the two diasteromers (R_P,S_S)-**9** and (S_P,S_S)-**9** in relatively low yields (Scheme 1). Interestingly, we were able to reisolate about 35% of the starting material. Conversely, using an excess of *n*-BuLi, less starting material but more disulfoxide was obtained. Since in published procedures by using monobrominated paracyclophane,[20] the yield of the obtained product was much higher with only one equivalent of *n*-BuLi, we believe that the additional bromine atom causes sterical hindrance to the electrophile due to its bulky *tert*-butyl moieties. The equilibrium during lithiation between *n*-bromobutane and lithiated paracyclophane could thus be less favorable for

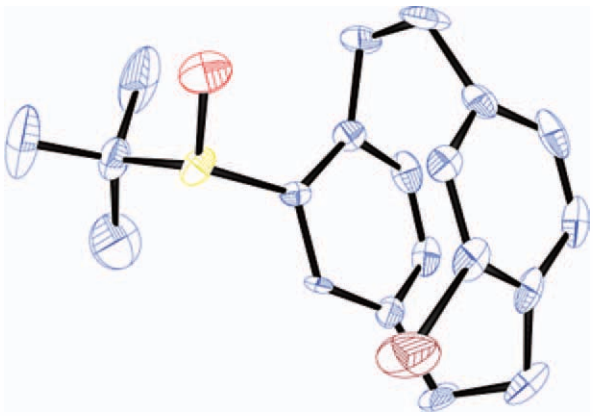
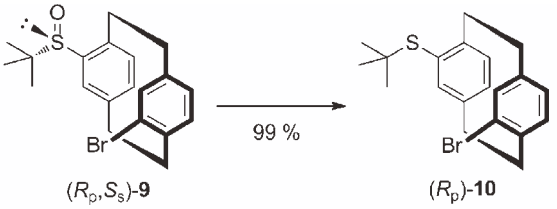


Fig. 2. ORTEP plot of (R_P,S_S)-**9**. The compound crystallizes with two symmetrically independent species in the asymmetric unit. Crystal data for (*RP*,*SS*)-9: Sum formula (C20H23BrOS)2, M_r = 782.75, space group *P212121* (19), Z = 4, a = 10.9767 (4) Å, b = 11.8188 (4) Å, c = 28.3255 (10) Å. Crystallographic data for the structure of (*RP*,*SS*)-**9** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 824753). Copies can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB12 1EZ, United Kingdom (Fax: 44-1223-336033 or email: deposit@ccdc.cam.ac.uk). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

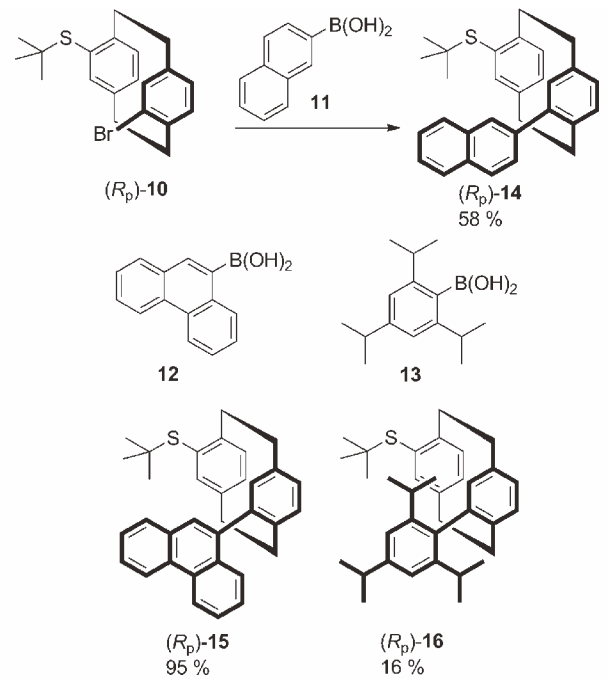


Scheme 2. Reduction of sulfoxide (*RP*,*SS*)-**9** to sulfide (*RP*)-**10**. Conditions: $HSiCl_3$, Et_3N, toluene, reflux, 24 h.

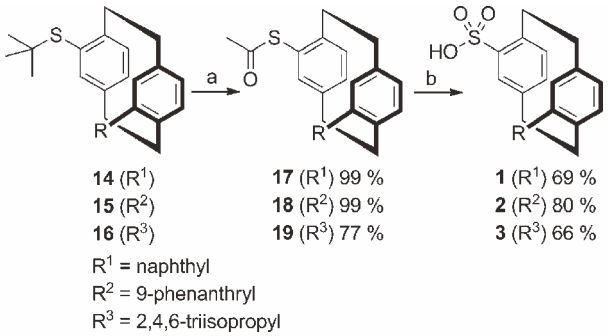
the desired product. By employing of an additional equivalent of *n*-BuLi, the generated product could favor a second lithiation thus leading to more disulfoxide. Considering the reisolation of unreacted starting material, the total yield of the two diasteromers was 58%. They could easily be separated by column chromatography, crystallized, and subjected to X-ray crystal structure analysis (Fig. 2) to determine the absolute configuration.

After the successful synthesis of the precursor (R_P,S_S)-**9**, we planned to introduce different sterically demanding groups by a Suzuki coupling with the corresponding boronic acid.

Initially, we tried to react the sulfoxide (R_P,S_S)-**9** directly with 2-naphthyl boronic acid (**11**) under standard Suzuki conditions. Unfortunately, the sulfoxide moiety was not stable under Suzuki conditions yielding a disulfide. Even though this observation was unprecedented, we found that sulfoxides can be pyrrolized by strong heating,[24] producing water and sulfides. Because in the proposed mechanism the sulfoxide-oxygen played a crucial role, we first reduced (R_P,S_S)-**9** to the sulfide (R_P)-**10** according to a known protocol[20] employing trichlorosilane and triethylamine (Scheme 2). The sulfide (R_P)-**10** was obtained almost quantitatively (99%).



Scheme 3. Suzuki-coupling of (*RP*)-**10** with different boronic acids. Conditions: $Pd(PPh_3)_4$, Na_2CO_3(aq.), DMF, 100°C, 48 h.



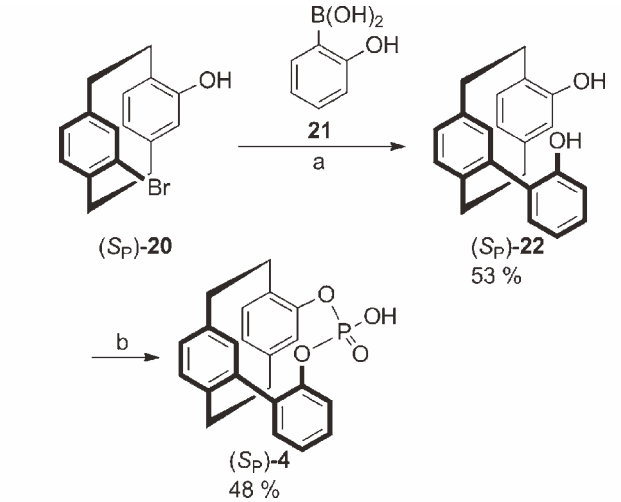
Scheme 4. Synthesis of new sulfonic acids (R_P)-**1**, (R_P)-**2,** and (R_P)-**3**. Conditions: (a) AcCl, BBr3, toluene, r.t., 12 h; (b) KOH, O2, #MeOH, r.t., 72 h.

We then tried the Suzuki coupling again, which this time was successful (Scheme 3). The 2-naphthyl-substituted derivative (R_P)-**14** was isolated in 58% yield and the 9-phenanthryl-substituted derivative (R_P)-**15** was obtained almost quantitatively (95%).

Unfortunately, the reaction of sulfide (R_P)-**10** with 2,4,6-triisopropylphenyl boronic acid (**13**) was challenging. Despite employing a large excess of boronic acid (**13**) and variation of solvents, we were not able to obtain more than 16% of the product (R_P)-**16**, which is most likely due to the steric hindrance of the triisopropyl groups.

The following conversion to the thioacetates proceeded smoothly by reaction of a mixture of the corresponding sulfides with acetyl chloride in toluene with boron tribromide,[20] producing quantitative yields for (R_P)-**17** (99%), (R_P)-**18** (99%) as well as 77% yield for the more sterically hindered (R_P)-**19** (Scheme 4).

In the next step, we tried the deprotection of the thioacetates (R_P)-**17**, (R_P)-**18**, and (R_P)-**19** by using potassium carbonate in methanol to obtain the corresponding thiols which could then be oxidized to the sulfonic acids. Interestingly, we noticed that the use of technical grade methanol produced 10–20% sulfonic acid along with the thiol and disulfide. We assume that traces of water could lead to the formation of potassium hydroxide from potassium carbonate which starts an autoxidation. The autoxidation of thiols to disulfides, sulfones and sulfonic acids under the influence of strong bases in polar solvents was previously published with the thiolate anion RS^- being the active species.[25,26] Carrying out the transformation with potassium hydroxide in methanol, we were able to deprotect the thioacetate and oxidize it to the corresponding sulfonic acid in one step. In this way, we obtained the target sulfonic acids (R_P)-**1**, (R_P)-**2**, and (R_P)-**3** with 69%, 80%, and 66% yield, respectively (Scheme 4).

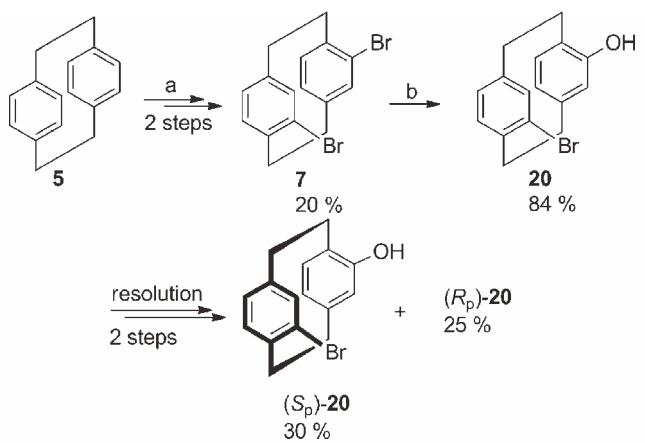


Scheme 6. Synthesis of enantiopure phosphoric acid diester (S_P)-**4**. Conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3(aq.), DMF, 100°C, 48 h; (b) 1: $POCl_3$, pyridine, r.t., 24 h; 2: H_2O, r.t., 24 h.

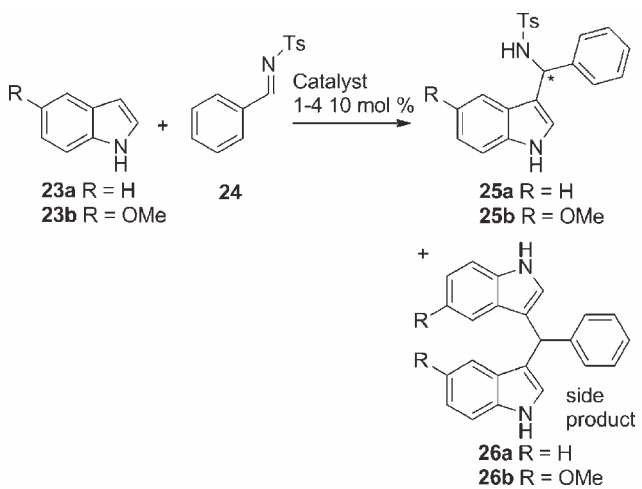
Synthesis of the Phosphoric Acid Diester

For the synthesis of the phosphoric acid diester, we started from enantiopure (S_P)-4-bromo-12-hydroxy[2.2]paracyclophane ((S_P)-**20**) which can be synthesized in five steps from [2.2]paracyclophane (**5**), involving a resolution employing the diastereomeric ester with (1*S*)-(−)-camphanic acid (Scheme 5). The resolution has been described previously by Rozenberg and coworkers.[27]

A Suzuki coupling of enantiopure (S_P)-**20** with 2-hydroxyphenyl boronic acid (**21**) gave the diol (S_P)-**22** in 70% yield



Scheme 5. Synthesis of resolved 4-bromo-12-hydroxy[2.2]-paracyclophanes ((S_P)- and (R_P)-**20**). Conditions: (a) see Scheme 1 condition (a) + (b); (b) 1: *n*-BuLi, −78°C, THF, 1 h; 2: $B(OCH_3)_3$, −78°C→r.t.; 3: H_2O_2, NaOH, r.t.; (c) 1: (*S*)-(−)-camphanic chloride, pyridine, r.t., 6 h; 2: separation by column chromatography of diastereomeric esters; 3: KOH, MeOH, r.t., 2 h.



Scheme 7. Asymmetric Friedel–Crafts reaction of indole **23** with *N*-tosylimine **24**. Conditions: (1) 0.1 mmol *N*-sulfonyl imine, 0.01 mmol Brønsted acid, 0.2 ml toluene, r.t., 15 min; (2) −78°C, 0.5 mmol indole, −78°C→−60°C, 20 min.

TABLE 1. Results of the Friedel-Crafts reactions

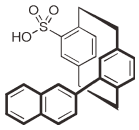
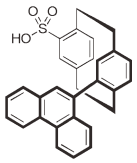
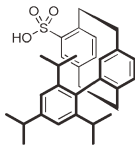
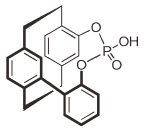
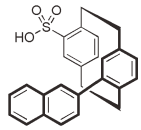
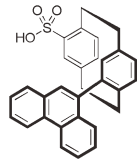
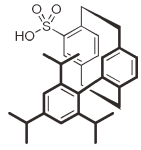
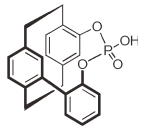
Entry	Catalyst	R	Yield (%)	*ee* (%)
1		H	56	6
2		H	31	3
3		H	75	14
4		H	80	34
		OMe	86	38

TABLE 2. Results of the Mannich reactions

Entry	Catalyst	Yield (%)	*de* (%)	*ee* % (*anti*)	*ee* % (*syn*)
1		93	23	2	6
2		93	30	15	5
3		92	39	20	2
4		62	12	7	7

(Scheme 6). This compound has been mentioned in the literature several times,[27–29] but no characterization has been published so far.

Reacting the diol (S_P)-**22** with phosphoryl chloride gave enantiopure acid (S_P)-**4** in 48% yield.

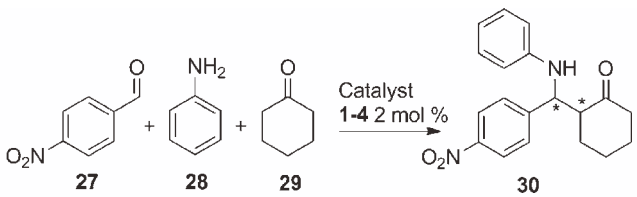
Applications in Asymmetric Transformations

The new enantiopure planar chiral Brønsted acids were then employed in asymmetric transformations. For our initial test reactions the known asymmetric Friedel–Crafts reaction of indoles **23** with *N*-tosylimine **24** was chosen (Scheme 7).[30]

The results are summarized in Table 1. As shown, all catalysts were able to catalyze the reaction in moderate to good yields with promising enantiomeric excesses of 3-38% with the phosphoric acid diester (S_P)-**4** showing the best result in both categories.

We assume that the sulfonic acids promote the formation of the bisindole sideproduct **26** thus leading to lower yields of **25**. In addition, the free rotation of the sulfonic acid in contrast to the strained phosphoric acid could explain the lower asymmetric induction, even though we constructed the sulfonic acids with bulkier groups. This assumption is in accordance to entry 3 (Table 1) of compound (R_P)-**3** achieving the highest enantiomeric excess within the sulfonic acids, which is possibly due to reduced rotation of the acid caused by the triisopropyl substituents.

We also employed the new catalysts in a direct asymmetric Mannich reaction[31] (Scheme 8).



Scheme 8. Asymmetric direct Mannich reaction. Conditions: 0.4 mmol aniline, 0.44 mmol 4-nitrobenzaldehyde, 0.008 mmol Brønsted acid, 5 ml toluene, 4 mmol cyclohexanone, r.t., 2–3 days.

As shown in Table 2, the reaction proceeded with good to excellent yields, moderate diastereoselectivities of 23–39% (anti) and enantiomeric excesses of 2-20%. It is noticeable that in this asymmetric transformation the sulfonic acid (R_P)-**3** shows the best enantioselectivity whereas the phosphoric acid (S_P)-**4** gives only a poor asymmetric induction.

In summary, the promising results of the initial test reactions clearly show the stereoselective activity of this new class of catalysts in asymmetric transformations.

CONCLUSION

In conclusion, we synthesized the first planar chiral strong Brønsted acid organocatalysts. Employing a modified protocol for the resolution of *pseudo-ortho*-substituted [2.2]paracyclophane-based sulfoxides, we obtained three sulfonic acids with different sterically demanding groups.

Starting from enantiopure (S_P)-4-hydroxy-12-bromo[2.2]-paracyclophane, the first planar chiral phosphoric acid diester was synthesized in only two steps. The results of the initial test reactions indicate that in principle asymmetric inductions can be obtained with these new classes of catalysts.

Further investigations of the effect of different sterically demanding groups in *pseudo-ortho* position as well as the activity of the new catalysts in other asymmetric organocatalytic reactions are currently underway in our laboratories.

LITERATURE CITED

1. Cram DJ, Allinger NL. Macro rings. XII. Stereochemical consequences of steric compression in the smallest paracyclophane. J Am Chem Soc 1955;77:6289–6294.

2. Rozenberg V, Sergeeva E, Hopf H. Cyclophanes as templates in stereoselective synthesis. In: Gleiter R, Hopf H, editors. Modern cyclophane chemistry. Weinheim: Wiley-VCH; 2004. p 435–462.

3. Gibson SE, Knight JD. [2.2]Paracyclophane derivatives in asymmetric catalysis. Org Biomol Chem 2003;1:1256–1269.
4. Hou X-L, Wu X-W, Dai L-X, Cao B-X, Sun J. Novel *N,S*- and *N,Se*-planar chiral [2,2]paracyclophane ligands: synthesis and application in Pd-catalyzed allylic alkylation. Chem Commun 2000:1195–1196.
5. Pye PJ, Rossen K, Reamer RA, Tsou NN, Volante RP, Reider PJ. A new planar chiral bisphosphine ligand for asymmetric catalysis: highly enantioselective hydrogenations under mild conditions. J Am Chem Soc 1997;119:6207–6208.
6. Rozenberg V, Kharitonov V, Antonov D, Sergeeva E, Aleshkin A, Ikonnikov N, Orlova S, Belokon Y. Scalemic 2-formyl-3-hydroxy[2.2]paracyclophane: a new auxiliary for asymmetric synthesis. Angew Chem Int Ed Engl 1994;33:91–92.
7. Antonov DY, Belokon YN, Ikonnikov NS, Orlova SA, Pisarevsky AP, Raevski NI, Rozenberg VI, Sergeeva EV, Struchkov YT, Tararov VI, et al. Synthesis, resolution and absolute configuration determination of (*S*)- and (*R*)-4-formyl-5-hydroxy [2.2]paracyclophane and its application in the asymmetric synthesis of α-amino acids. J Chem Soc Perkin Trans 1 1995:1873–1879.
8. Braddock DC, MacGilp ID, Perry BG. Planar chiral PHANOLs as organocatalysts for the Diels-Alder reaction via double hydrogen-bonding to a carbonyl group. Synlett 2003:1121–1124.
9. Braddock DC, MacGilp ID, Perry BG. Planar chiral PHANOLs as double hydrogen bonding donor organocatalysts: synthesis and catalysis. Adv Synth Catal 2004;346:1117–1130.
10. Negru M, Schollmeyer D, Kunz H. Enantioselective Strecker reaction catalyzed by an organocatalyst lacking a hydrogen-bond-donor function. Angew Chem Int Ed Engl 2007;46:9339–9341.
11. Schneider JF, Falk FC, Fröhlich R, Paradies J. Planar-chiral thioureas as hydrogen-bond catalysts. Eur J Org Chem 2010:2265–2269.
12. Fulton JR, Glover JE, Kamara L, Rowlands GJ. Facile synthesis of planar chiral *N*-oxides and their use in Lewis base catalysis. Chem Commun 2011;47:433–435.
13. Akiyama T. Stronger Brønsted acids. Chem Rev 2007;107:5744–5758.
14. Terada M. Chiral phosphoric acids as versatile catalysts for enantioselective transformations. Synthesis 2010:1929–1982.
15. Hatano M, Maki T, Moriyama K, Arinobe M, Ishihara K. Pyridinium 1,1′-binaphthyl-2,2′-disulfonates as highly effective chiral Brønsted acid–base combined salt catalysts for enantioselective Mannich-type reaction. J Am Chem Soc 2008;130:16858–16860.
16. Nakashima D, Yamamoto H. Design of chiral *N*-triflyl phosphoramide as a strong chiral Brønsted acid and its application to asymmetric Diels–Alder reaction. J Am Chem Soc 2006;128:9626–9627.
17. Schneider JF, Fröhlich R, Paradies J. Synthesis of enantiopure planar-chiral thiourea derivatives. Synthesis 2010:3486–3492.
18. Cogan DA, Liu G, Kim K, Backes BJ, Ellman JA. Catalytic asymmetric oxidation of *tert*-butyl disulfide. Synthesis of *tert*-butanesulfinamides, *tert*-butyl sulfoxides, and *tert*-butanesulfinimines. J Am Chem Soc 1998;120:8011–8019.
19. Hitchcock PB, Rowlands GJ, Seacome RJ. The synthesis and directed *ortho*-lithiation of 4-*tert*-butylsulfinyl[2.2]paracyclophane. Org Biomol Chem 2005;3:3873–3876.
20. Rowlands GJ, Seacome RJ. Enantiospecific synthesis of [2.2]paracyclophane-4-thiol and derivatives. Beilstein J Org Chem 2009;5:9.
21. Rossen K, Pye PJ, Maliakal A, Volante RP. Kinetic resolution of *rac*-4,12-dibromo[2.2]paracyclophane in a palladium [2.2]PHANEPHOS catalyzed amination. J Org Chem 1997;62:6462–6463.
22. Braddock DC, MacGilp ID, Perry BG. Improved synthesis of (±)-4,12-dihydroxy[2.2]paracyclophane and its enantiomeric resolution by enzymatic methods: planar chiral (*R*)- and (*S*)-phanol. J Org Chem 2002;67:8679–8681.
23. Focken T, Rudolph J, Bolm C. Planar chiral imidazolium salts in the asymmetric Rhodium-catalyzed 1,2-addition of arylboronic acids to aldehydes. Synthesis 2005:429–436.
24. Davis FA, Yocklovich SG, Baker GS. Synthesis of sulfenic acids: flash vacuum pyrolysis of aryl and alkyl *t*-butyl sulfoxides. Tetrahedron Lett 1978;19:97–100.
25. Wallace TJ, Schriesheim A. Solvent effects in the oxidation of thiols. IV. Base catalyzed oxidation of thiols and disulfides to sulfonic acids. Tetrahedron Lett 1963;4:1131–1136.
26. Wallace TJ, Schriesheim A. The base-catalysed oxidation of aliphatic and aromatic thiols and disulphides to sulphonic acids. Tetrahedron 1965;21:2271–2280.
27. Zhuravsky R, Starikova Z, Vorontsov E, Rozenberg V. Novel strategy for the synthesis of chiral *pseudo-ortho*-substituted hydroxy[2.2]paracyclophane-based ligands from the resolved 4-bromo-12-hydroxy[2.2]paracyclophane as a parent compound. Tetrahedron: Asymmetry 2008;19:216–222.
28. Vorontsova N, Zhuravsky R, Sergeeva E, Vorontsov E, Starikova Z, Rozenberg V. Planar chiral hydroxy derivatives of [2.2]paracyclophane as auxiliaries for asymmetric allylboration. Russ Chem Bull 2007;56:2225–2231.
29. Rozenberg V, Zhuravsky R, Sergeeva E. Design, classification, and strategies of synthesis of modular bidentate ligands based on aryl[2.2]paracyclophane backbone. Chirality 2006;18:95–102.
30. Kang Q, Zhao Z-A, You S-L. Highly enantioselective Friedel–Crafts reaction of indoles with imines by a chiral phosphoric acid. J Am Chem Soc 2007;129:1484–1485.
31. Guo Q-X, Liu H, Guo C, Luo S-W, Gu Y, Gong L-Z. Chiral Brønsted acid-catalyzed direct asymmetric Mannich reaction. J Am Chem Soc 2007;129:3790–3791.