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Co(II)-salen catalyzed stereoselective cyclopropanation of fluorinated styrenes

Serene Tai | Taber S. Maskrey | Prasanth R. Nyalapatla | Peter Wipf

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania

Correspondence
Peter Wipf, Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260.
Email: pwipf@pitt.edu

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Abstract

Three *cis*-selective Co(II)-salen complexes have been developed for the asymmetric cyclopropanation of *para*-fluorinated styrenes with ethyl diazoacetate. Increasing the steric reach of the C_2-symmetric ligand side chains improved the enantiomeric ratio of the reaction from 28:1 to 66:1. The methodology was exemplified by the gram-scale synthesis of a lead compound for the treatment of castration-resistant prostate cancer (CRPC), as well as a structurally related analog.

KEYWORDS

asymmetric synthesis, Co(II)-salen complex, fluorinated styrenes, JJ-450, stereoselective cyclopropanation

1 | INTRODUCTION

Due to their strain and rigidity, as well as their unique electronic properties, cyclopropanes cover a privileged space in natural products and pharmaceuticals.[1-3] Compounds possessing cyclopropane rings have been clinically investigated for CNS, antibacterial, and anticancer activity, among other therapeutic roles.[4,5] Cyclopropanes are also successfully used as bioisosteres for alkenes in pharmaceuticals, polyene natural products,[6] and in peptide mimetics.[7] In 2016, we disclosed the structure of a *cis*-cyclopropyl carboxamide, **JJ-450**, developed through an extensive structure-activity relationship (SAR) study, with single digit micromolar activity in a castration-resistant prostate cancer (CRPC) model.[8,9] Significantly, the two enantiomers of the *cis*-cyclopropane lead structure showed a 10-fold difference in activity, and the *trans*-cyclopropane was much less active (Figure 1).[8] Based on our goal to investigate the active enantiomer of **JJ-450** in further SAR and preclinical studies, we aspired to develop a convergent enantioselective synthesis of the core cyclopropyl carboxamide.

Metal-catalyzed cyclopropanation reactions have historically been well investigated, and several catalysts are available for both *trans*- and *cis*-selective variants.[10-12] The most common cyclopropanation method involves the reaction of a monosubstituted or disubstituted terminal olefin with a diazocarbonyl compound. In these catalytic cyclopropanations, a carbene is transferred to the alkene, resulting in the generation of two new stereogenic carbons. Diazo compounds substituted with electron-withdrawing groups are stable and frequently available from commercial sources. *Trans*-selective catalysts were introduced by Nishiyama (Ru),[13] Zhang (Ru),[14] Sunjic (Cu),[15] Furuta (Rh),[16] Woo (Fe),[17], Zhang (Co)[18], and Gallo (Co).[19] Optimizing both the ligand and metal catalyst has enabled nearly quantitative *trans*-selective transformations.

In comparison, fewer catalysts have been able to impart synthetically useful stereoselectivities and high yields for *cis*-cyclopropanations. Katsuki (Ru, Ir, Co),[20-23] Mezzetti (Ru),[24] Kim (Ru),[25] and Tilset (Rh)[26] have developed *cis*-selective metal/ligand systems, but there is still considerable room for improvement in terms of overall yields and enantiomeric ratios.[27] Furthermore, to the best of our knowledge, a general method for the *cis*-cyclopropanation of electron-deficient, fluorinated styrenes has not yet been reported.

This work is dedicated to the memory of Prof Koji Nakanishi, a true pioneer and outstanding leader in natural products chemistry and chemical biology.

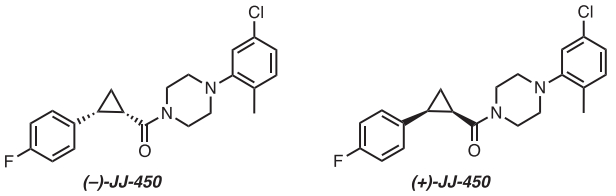


FIGURE 1 *Cis*-cyclopropanes (−)-**JJ-450** and (+)-**JJ-450** showed IC_{50} = 1.7μM and 15.2μM, respectively, in a luciferase reporter assay for the translocation of androgen receptor[8]

For the preparation of *cis*-cyclopropanes (−)-**JJ-450** and (+)-**JJ-450**, we considered the work of Katsuki et al with Co(II)-salen complexes as most relevant. The catalyst shown in Figure 2 delivered excellent yields and up to a 99:1 *cis*:*trans* ratio in the cyclopropanation of styrene with ethyl diazoacetate on a 0.5-mmol scale. Most importantly, the reaction afforded an enantiomeric ratio (*e.r.*) of 96:4 to 98:2.[22] Therefore, we selected this catalytic system to explore an enantioselective synthesis of our lead compound, (−)-**JJ-450,** and selected fluorinated analogs.

2 | MATERIALS AND METHODS

2.1 | General

All reagents and solvents were used as received unless otherwise specified. THF and Et_2O were distilled from sodium/benzophenone ketyl. Toluene and CH_2Cl_2 were distilled over CaH_2. Reactions were monitored by TLC analysis (precoated silica gel 60 F254 plates, 250-μm layer thickness) and visualization was accomplished with a 254/280-nm UV light and/or by staining with $KMnO_4$ solution (1.5-g $KMnO_4$ and 1.5-g K_2CO_3 in 100 mL of a 0.1% NaOH solution), or a PMA solution (5 g phosphomolybdic acid in 100-mL EtOH). Melting points were determined on a Mel-Temp II capillary melting point apparatus fitted with a Fluke 51 II digital thermometer. Infrared spectra were recorded on an ATR spectrometer. Specific rotations were determined using a Perkin-Elmer 241 polarimeter. Circular dichroism (CD) spectra were recorded on a JASCO J-815 instrument. NMR spectra were recorded on a 300, 400, 500, or 600 MHz instrument. Chemical shifts were reported in parts per million (ppm) with the residual solvent peak used as an internal standard, δ $^1H/^{13}C$ (Solvent): 7.26/77.16 ($CDCl_3$); 2.50/39.52 (DMSO-d6); ^1H NMR spectra are tabulated as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublets, app t = apparent triplet), coupling constant(s), number of protons. ^{13}C NMR spectra were obtained at 75, 100, or 125 MHz using a proton-decoupled pulse sequence and are tabulated by observed peak. HRMS (ESI+) data were obtained on a Thermo Scientific Exactive Orbitrap LC-MS coupled to a Thermo Scientific Accela HPLC system using a 2.5μM Waters XBridge C18 column (2.1 × 50 mm; 10-min gradient elution with MeCN/H_2O/MeOH containing 0.1% formic acid at a flow rate of 500 μL/min from 3:92:5 at 0-0.5 minutes to 93:2:5 at 4.0 minutes, back to 3:92:5 from 6.0 to 7.5 min). Chromatography on SiO_2 (Silicycle, Silia-P Flash Silica Gel or SiliaFlash P60, 40-63 μm) was used to purify crude reaction mixtures. High performance liquid chromatography (HPLC) analysis was performed on a Rainin instrument with a Chiralpak AD-H column (4.6 × 250 mm, 5 μm). Supercritical fluid chromatography (SFC) analysis was performed on a Mettler Toledo instrument with a Chiralpak IC column (10 × 250 mm, 5 μm). Calculations used Spartan 18 v.1.4.1 (Wavefunction, Inc) at the UHF 3-21G(*) level. For copies of ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra of new compounds, HPLC and SFC analyses with chiral stationary phases, and circular dichroism (CD) spectra, please see the Supporting Information.

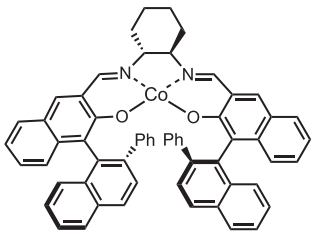


FIGURE 2 Katsuki's Co-salen catalyst for *cis*-selective enantioselective cyclopropanation[22]

2.2 | Synthesis of Co(II)-salen complexes

2.2.1 | (*S*)-2′-Hydroxy-[1,1′-binaphthalen]-2-yl trifluoromethanesulfonate (2)

General procedure A

To a mixture of (*S*)-(−)-1,1′-binaphthalene-2,2′-diol (**1**, 5.00 g, 17.3 mmol), 4-dimethylaminopyridine (0.254 g, 2.07 mmol) and *N*-phenyl-bis (trifluoromethanesulfonimide) (6.24 g, 17.3 mmol) was added 2,4,6-collidine (2.35 mL, 17.3 mmol) and anhydrous CH_2Cl_2 (70 mL). The reaction mixture was heated at reflux for 19 hours and then cooled to room temperature. The solution was concentrated in vacuo and purified by chromatography on SiO_2 (toluene) to afford **2** (4.78 g, 11.4 mmol, 66%) as a light orange viscous oil: $[\alpha]^{18}_D$ + 63.5 (*c* 2.05, MeOH); IR (CH_2Cl_2) 3538, 3061, 1417, 1206, 1136, 931, 728, 676 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 9.1 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.9 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.63-7.60 (m, 2H), 7.46-7.45 (m,

2H), 7.39-7.33 (m, 2H), 7.30 (app t, J = 7.7 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 4.94 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 146.1, 133.2 (2C), 132.9, 131.6, 131.4, 129.1, 128.5, 128.3, 128.2, 127.6, 127.0, 126.4, 125.2, 124.2, 123.8, 119.8, 118.4 (q, J C-F = 320 Hz), 117.9, 112.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −74.3 (s, 3F).[22]

2.2.2 | (*R*)-2′-Hydroxy-[1,1′-binaphthalen]-2-yl trifluoromethanesulfonate (25)

According to general procedure A, (*R*)-(−)-1,1′-binaphthalene-2,2′-diol (**24**, 3.00 g, 17.3 mmol), 4-dimethylaminopyridine (0.153 g, 1.26 mmol) and *N*-phenyl-bis (trifluoromethanesulfonimide) (3.78 g, 10.5 mmol) were combined with 2,4,6-collidine (1.42 mL, 10.5 mmol) and anhydrous CH_2Cl_2 (40 mL) to afford **25** (2.81 g, 6.72 mmol, 64%) as a yellow viscous foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 9.1 Hz, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.9 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.63-7.59 (m, 2H), 7.47-7.43 (m, 2H), 7.38-7.33 (m, 2H), 7.28 (ddd, J = 8.3, 6.9, 1.4 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 4.82 (s, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −74.4 (s, 3F); HRMS (ESI) m/z calcd for $C_{21}H_{14}F_3O_4S$ $[M + H]^+$ 419.0559, found 419.0558.[28]

2.2.3 | (*S*)-2′-Phenyl-[1,1′-binaphthalen]-2-ol (4)

General procedure B

To a mixture of (*S*)-2′-hydroxy-[1,1′-binaphthalen]-2-yl trifluoromethanesulfonate (**2**, 4.76 g, 11.4 mmol) and $NiCl_2$(dppe) (0.126 g, 0.228 mmol) in anhydrous diethyl ether (95 mL) under nitrogen was slowly added a solution of phenylmagnesium bromide in Et_2O (**3**, 3.0M, 19.0 mL, 56.9 mmol, 5 equiv.). The reaction mixture was heated at reflux for 3 hours, cooled to room temperature, quenched with aqueous NH_4Cl (60 mL) and extracted with Et_2O (2 × 60 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (60 mL), brine (2 × 60 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by chromatography on SiO_2 (1:3, hexanes:toluene) afforded **4** (3.15 g, 9.09 mmol, 80%) as a pale yellow foam: $[\alpha]^{20}_D$ −10.7 (*c* 2.15, $CHCl_3$); IR (CH_2Cl_2) 3503, 3056, 1619, 1596, 905, 726, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 8.5 Hz, 1H), 7.56-7.53 (m, 1H), 7.40-7.23 (m, 5H), 7.19-7.08 (m, 7H), 4.92 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 141.7, 140.9, 134.3, 133.3 (2C), 130.0, 129.5, 128.9, 128.8, 128.7 (3C), 128.3, 128.2, 127.8 (2C), 127.3, 127.1, 126.7, 126.5, 126.5, 125.1, 123.3, 117.8, 117.3.

2.2.4 | (*R*)-2′-(4-(Naphthalen-2-yl)phenyl)-[1,1′-binaphthalen]-2-ol (28)

According to general procedure B, (*R*)-2′-hydroxy-[1,1′-binaphthalen]-2-yl trifluoromethanesulfonate (**25**, 1.05 g, 2.51 mmol), $NiCl_2$(dppe) (26.8 mg, 0.0502 mmol), and a THF solution of (4-(2-naphthyl)phenyl)magnesium bromide (**26**, 0.34M, 14.8 mL, 5.02 mmol, 2 equiv.) afforded **28** (0.797 g, 1.69 mmol, 67%) as a pale yellow solid: $[\alpha]^{20}_D$ + 127.5 (*c* 0.38, $CHCl_3$); IR (CH_2Cl_2) 3506, 3055, 2917, 2849, 1620, 1597, 813, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.92 (s, 1H), 7.84-7.78 (m, 6H), 7.62 (dd, J = 8.6, 1.8 Hz, 1H), 7.53 (ddd, J = 8.1, 6.4, 1.7 Hz, 1H), 7.48-7.43 (m, 4H), 7.36-7.24 (m, 6H), 7.17 (d, J = 9.0 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 4.89 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 141.1, 139.9, 139.4, 137.8, 134.3, 133.6, 133.3, 133.2, 132.6, 129.9, 129.5 (2C), 129.2, 128.8, 128.6, 128.3, 128.2, 128.1, 127.6, 127.2, 126.7, 126.6 (2C), 126.5, 126.4, 126.2, 125.9, 125.6, 125.3, 125.0, 123.3, 117.7, 117.3.

2.2.5 | (*R*)-2′-(3-(Naphthalen-2-yl)phenyl)-[1,1′-binaphthalen]-2-ol (29)

According to general procedure B, (*R*)-2′-hydroxy-[1,1′-binaphthalen]-2-yl trifluoromethanesulfonate (**25**, 1.40 g, 3.35 mmol), $NiCl_2$(dppe) (35.7 mg, 0.0669 mmol), and a THF solution of (3-(2-naphthyl)phenyl)magnesium bromide (**27**, 0.45M, 14.8 mL, 6.62 mmol, 2 equiv.) in THF (5 mL) afforded **29** (1.16 g, 2.44 mmol, 73%) as a colorless solid: $[\alpha]^{20}_D$ −6.9 (*c* 0.79, $CHCl_3$); IR (CH_2Cl_2) 3497, 3427, 3055, 1619, 1596, 1380, 1205, 1146, 907, 731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.82-7.80 (m, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.55 (t, J = 8.5 Hz, 1H), 7.49-7.32 (m, 11H), 7.27-7.22 (m, 1H), 7.21 (d, J = 9.0 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 4.89 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 141.5, 141.3, 140.2, 138.1, 134.8, 133.7, 133.5, 133.4, 132.6, 130.1, 129.7, 129.0, 128.9, 128.6, 128.5, 128.4 (2C), 128.3, 128.2, 128.1, 127.7, 127.6, 127.4, 127.1, 126.7, 126.6, 126.2, 126.1, 125.9, 125.6, 125.5, 125.4, 123.6, 118.1, 117.6.

2.2.6 | (*S*)-2-(Methoxymethoxy)-2′-phenyl-1,1′-binaphthalene (5)

General procedure C

To a solution of (*S*)-2′-phenyl-[1,1′-binaphthalen]-2-ol (**4**, 3.10 g, 8.95 mmol) in distilled CH_2Cl_2 (35 mL) under nitrogen was added *N*,*N*-diisopropylethylamine (4.40 mL, 26.8 mmol) and chloromethyl methyl ether (2.00

mL, 26.8 mmol) at room temperature. The mixture was stirred for 24 hours, quenched with water (50 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with water (2 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by chromatography on SiO_2 (19:1, hexanes: Et_2O) to afford **5** (2.22 g, 5.69 g, 64%) as a white solid: $[\alpha]^{20}_D$ −60.4 (*c* 0.79, $CHCl_3$); IR (CH_2Cl_2) 3056, 2954,2847, 1592, 1506, 1241, 1147, 1012, 906, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.48-7.44 (m, 2H), 7.32-7.20 (m, 4H), 7.17-7.14 (m, 3H), 7.05-7.02 (m, 3H), 4.92 (d, *J* = 7.0 Hz, 1H), 4.79 (d, *J* = 7.0 Hz, 1H), 3.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 142.2, 140.1, 134.6, 133.3, 132.9, 131.9, 129.61, 129.47, 129.0 (2C), 128.4, 128.1, 128.1, 128.0, 127.4 (2C), 126.9, 126.6, 126.5, 126.3, 125.9, 125.8, 123.9, 123.1, 116.4, 95.2, 55.8.

2.2.7 | (*R*)-2-(Methoxymethoxy)-2′-(4-(naphthalen-2-yl)phenyl)-1,1′-binaphthalene (30)

According to general procedure C, (*R*)-2′-(4-(naphthalen-2-yl)phenyl)-[1,1′-binaphthalen]-2-ol (**28**, 0.920 g, 1.95 mmol), *N,N*-diisopropylethylamine (1.00 mL, 5.86 mmol) and chloromethyl methyl ether (0.450 mL, 5.86 mmol) in CH_2Cl_2 (10 mL) provided **30** (0.700 g, 1.35 mmol, 69%) as a white solid: $[\alpha]^{20}_D$ 168.5 (*c* 0.31, $CHCl_3$); IR (CH_2Cl_2) 3056, 2954,2847, 1592, 1506, 1241, 1147, 1012, 906, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.92 (s, 1H), 7.87-7.81 (m, 5H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.62 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.49-7.42 (m, 6H), 7.32 (t, *J* = 7.0 Hz, 1H), 7.29-7.19 (m, 6H), 4.96 (d, *J* = 7.0 Hz, 1H), 4.84 (d, *J* = 7.0 Hz, 1H), 3.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 141.2, 139.5, 138.8, 138.0, 134.5, 133.6, 133.2, 132.9, 132.5, 131.8, 129.6, 129.4, 129.3, 128.2 (2C), 128.1, 128.0, 127.9, 127.6, 126.8, 126.5, 126.2 (3C), 125.8, 125.7 (2C), 125.4, 125.3, 123.8, 123.0, 116.4, 95.0, 55.7; HRMS (ESI) *m/z* calcd for $C_{38}H_{28}O_2Na$ $[M + Na]^+$ 539.1982, found 539.1981.

2.2.8 | (*R*)-2-(Methoxymethoxy)-2′-(3-(naphthalen-2-yl)phenyl)-1,1′-binaphthalene (31)

According to general procedure C, (*R*)-2′-(3-(naphthalen-2-yl)phenyl)-[1,1′-binaphthalen]-2-ol (**29**, 1.13 g, 2.39 mL), *N,N*-diisopropylethylamine (1.20 mL, 7.17 mmol) and chloromethyl methyl ether (0.540 mL, 7.17 mmol) in CH_2Cl_2 (12 mL) afforded **31** (0.856 g, 1.66 mmol, 69%) as a colorless oil that generated a foam upon drying under vacuum: $[\alpha]^{20}_D$ 67.8 (*c* 0.58, $CHCl_3$); IR (CH_2Cl_2) 3054, 2924, 1593, 1507, 1264, 1148, 1013, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.91 (t, *J* = 7.4 Hz, 2H), 7.80-7.77 (m, 3H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 9.1 Hz, 1H), 7.48-7.24 (m, 13H), 7.18 (d, *J* = 8.4 Hz, 1H), 4.96 (d, *J* = 7.0 Hz, 1H), 4.80 (d, *J* = 7.0 Hz, 1H), 3.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 142.6, 140.0, 139.9, 138.4, 134.9, 133.7, 133.4, 133.1, 132.6, 132.1, 129.8, 129.6, 128.3, 128.24 (3C), 128.22, 128.17, 128.1 (2C), 128.0, 127.6, 127.0, 126.9, 126.4, 126.2, 126.1, 125.9, 125.8, 125.5 (3C), 124.1, 123.3, 116.7, 95.2, 55.9; HRMS (ESI) *m/z* calcd for $C_{38}H_{28}O_2Na$ $[M + Na]^+$ 539.1982, found 539.1980.

2.2.9 | (*S*)-2-(Methoxymethoxy)-2′-phenyl-[1,1′-binaphthalene]-3-carbaldehyde (6)

General procedure D

To a solution of *(S)*-2-(methoxymethoxy)-2′-phenyl-1,1′-binaphthalene (**5**, 2.20 g, 5.63 mmol) in THF (31 mL) at −78°C under nitrogen was added a solution of *t*-BuLi (1.65M in pentane, 7.50 mL, 12.4 mmol) by syringe dropwise. The mixture was stirred for 3 hours at −78°C. DMF (2.20 mL, 28.2 mmol) was added and the mixture was allowed to warm to room temperature and was stirred for an additional 1 hour. The reaction mixture was quenched with aqueous NH_4Cl (50 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by chromatography on SiO_2 (6:1, hexanes: Et_2O) afforded **6** (2.24 g, 5.35 mmol, 95%) as an off-white solid: $[\alpha]^{20}_D$ 23.3 (*c* 0.68, $CHCl_3$); IR (CH_2Cl_2) 3055, 2951, 2888, 1687, 1618, 1586, 1156, 960, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.43 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.35-7.24 (m, 4H), 7.10-7.02 (m, 5H), 4.60 (d, *J* = 6.0 Hz, 1H), 4.43 (d, *J* = 6.0 Hz, 1H), 2.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 153.2, 141.5, 140.8, 137.6, 133.2, 132.7, 131.3, 130.2, 129.3 (2C), 128.7 (4C), 128.4, 128.1, 127.5, 126.72 (2C), 126.69 (2C), 126.5, 125.9, 125.8, 99.6, 56.8.

2.2.10 | (*R*)-2-(Methoxymethoxy)-2′-(4-(naphthalen-2-yl)phenyl)-[1,1′-binaphthalene]-3-carbaldehyde (32)

According to general procedure D, (*R*)-2-(methoxymethoxy)-2′-(4-(naphthalen-2-yl)phenyl)-1,1′-binaphthalene (**30**, 0.650 g, 1.26 mmol), *t*-BuLi (1.65M in pentane, 1.50 mL, 2.52 mmol), DMF (0.50 mL, 6.30 mmol) and THF (7 mL)

afforded **32** (0.581 g, 1.07 mmol, 85%) as an off-white solid: $[\alpha]^{20}_D$ 39.6 (*c* 0.42, $CHCl_3$); IR (CH_2Cl_2) 3055, 2953, 2887, 1688, 1618, 1586, 1499, 1156, 1069, 961, 813, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.46 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.00 (t, *J* = 7.7 Hz, 2H), 7.92 (s, 1H), 7.84-7.80 (m, 3H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.62 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.49-7.40 (m, 6H), 7.35-7.32 (m, 2H), 7.27-7.21 (m, 3H), 4.64 (d, *J* = 6.0 Hz, 1H), 4.47 (d, *J* = 5.5 Hz, 1H), 2.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 153.3, 140.8, 140.5, 139.4, 137.96, 137.85, 133.8, 133.4, 132.9, 132.7, 131.7, 130.5, 130.4, 129.8, 129.6, 129.5, 129.4 (2C), 129.0, 128.9, 128.6, 128.4, 128.3 (2C), 127.7, 126.9, 126.8, 126.7 (2C), 126.6, 126.4, 126.1, 126.0 (2C), 125.7, 125.4, 99.8, 57.0; HRMS (ESI) *m*/*z* calcd for $C_{39}H_{28}O_3Na$ $[M + Na]^+$ 567.1931, found 567.1931.

2.2.11 | (*R*)-2-(Methoxymethoxy)-2′-(3-(napthalen-2-yl)phenyl)-[1,1′-binaphthalene]-3-carbaldehyde (33)

According to general procedure D, (*R*)-2-(methoxymethoxy)-2′-(3-(naphthalen-2-yl)phenyl)-1,1′-binaphthalene (**31**, 0.845 g, 1.64 mmol), *t*-BuLi (1.65M in pentane, 2.00 mL, 3.27 mmol), DMF (0.640 mL, 8.18 mmol) and THF (9 mL) afforded **33** (0.713 g, 1.31 mmol, 80%) as an off-white solid: $[\alpha]^{20}_D$ −28.5 (*c* 0.74, $CHCl_3$); IR (CH_2Cl_2) 3055, 2921, 2850, 1689, 1587, 1158, 1072, 964, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.49 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.78 (t, *J* = 6.9 Hz, 2H), 7.71 (t, *J* = 7.7 Hz, 2H), 7.55 (dt, *J* = 16.7, 8.1 Hz, 2H), 7.49-7.41 (m, 5H), 7.37-7.32 (m, 4H), 7.28 (d, *J* = 4.9 Hz, 2H), 7.11 (dd, *J* = 8.5, 1.5 Hz, 1H), 4.65 (d, *J* = 5.5 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 1H), 2.91 (s, 3H); ^{13}C NMR (125 MHz, CDC_{l3}) δ 191.0, 153.4, 142.1, 140.9, 140.0, 138.14, 138.01, 133.7, 133.4, 132.9, 132.6, 131.6, 130.7, 130.5, 129.9, 129.71, 129.67, 129.1, 129.0, 128.50, 128.47, 128.4, 128.24, 128.23, 128.1, 127.9, 127.7, 127.0, 126.9, 126.8, 126.3, 126.2, 126.1, 125.9, 125.8, 125.44, 125.36, 99.9, 57.0; HRMS (ESI) *m*/*z* calcd for $C_{39}H_{28}O_3Na$ $[M + Na]^+$ 567.1931, found 567.1940.

2.2.12 | (*S*)-2-Hydroxy-2′-phenyl-[1,1′-binaphthalene]-3-carbaldehyde (7)

General procedure E

A solution of (*S*)-2-(methoxymethoxy)-2′-phenyl-[1,1′-binaphthalene]-3-carbaldehyde (**6**, 2.22 g, 5.30 mmol) in anhydrous CH_2Cl_2 (45 mL) under nitrogen was treated with 4 Å molecular sieves (5 g) followed by bromotrimethylsilane (3.60 mL, 26.5 mmol). The reaction mixture was stirred for 1 hour, quenched with aqueous $NaHCO_3$ (50 mL), filtered, and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with water (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by chromatography on SiO_2 (3:7, hexanes:toluene) and subsequent recrystallization (CH_2Cl_2/hexanes) afforded **7** (1.42 g, 3.79 mmol, 71%) as a yellow crystalline solid: $[\alpha]^{20}_D$ 55.3 (*c* 0.70, $CHCl_3$); IR (CH_2Cl_2) 3196, 3056, 2848, 1655, 1630, 1340, 1292, 1115, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.44 (s, 1H), 10.08 (s, 1H), 8.15 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.34-7.26 (m, 4H), 7.23-7.21 (m, 2H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.05-7.02 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 153.6, 141.8, 140.7, 137.84, 137.78, 133.0, 132.6, 130.3, 129.8, 129.6, 128.6 (2C), 128.5, 128.3, 128.2, 127.4 (2C), 127.1, 126.6, 126.5, 126.0, 125.8, 125.4, 124.1, 121.5, 121.3; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{17}O_2$ $[M-H]^-$ 373.1223, found 373.1219.

2.2.13 | (*R*)-2-Hydroxy-2′-(4-(naphthalen-2-yl)phenyl)-[1,1′-binaphthalene]-3-carbaldehyde (34)

According to general procedure E, (*R*)-2-(methoxymethoxy)-2′-(4-(naphthalen-2-yl)phenyl)-[1,1′-binaphthalene]-3-carbaldehyde (**32**, 0.540 g, 0.991 mmol) and bromotrimethylsilane (0.670 mL, 4.96 mmol) in CH_2Cl_2 (8.5 mL) afforded **34** (0.356 g, 0.711 mmol, 77%) as a yellow crystalline solid: $[\alpha]^{20}_D$ −71.7 (*c* 1.00, $CHCl_3$); IR (CH_2Cl_2) 3200, 3055, 2923, 2851, 1656, 1680, 1501, 1339, 1291, 814, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.47 (s, 1H), 10.10 (s, 1H), 8.19 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.91 (s, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.83-7.80 (m, 3H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.61 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.47-7.41 (m, 4H), 7.38-7.28 (m, 6H), 7.18 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 153.8, 141.2, 140.4, 139.1, 138.1 (3C), 133.8, 133.2, 132.9, 132.7, 130.6, 130.1, 129.9, 129.3 (2C), 128.8, 128.4 (3C), 128.3, 127.7, 127.3, 126.8, 126.5 (2C), 126.4, 126.2, 126.0, 125.9, 125.6, 125.5, 125.4, 124.4, 121.8, 121.5; HRMS (ESI) *m*/*z* calcd for $C_{37}H_{25}O_2$ $[M + H]^+$ 501.1849, found 501.1849.

2.2.14 | (*R*)-2-Hydroxy-2′-(3-(naphthalen-2-yl)phenyl)-[1,1′-binaphthalene]-3-carbaldehyde (35)

According to general procedure E, (*R*)-2-(methoxymethoxy)-2′-(3-(naphthalen-2-yl)phenyl)-[1,1′-binaphthalene]-3-carbaldehyde (**33**, 0.689 g, 1.27 mmol) and bromotrimethylsilane

(0.850 mL, 6.33 mmol) in CH_2Cl_2 afforded **35** (0.535 g, 1.07 mmol, 85%) as a yellow crystalline solid: $[\alpha]^{20}_D$ −84.7 (*c* 0.75, $CHCl_3$); IR (CH_2Cl_2) 3187, 3054, 2851, 1655, 1630, 1505, 1340, 1290, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.51 (s, 1H), 10.07 (s, 1H), 8.16 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.77-7.74 (m, 3H), 7.56 (s, 1H), 7.53-7.21 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 153.7, 142.5, 140.8, 139.7, 138.3, 138.2, 138.1, 133.7, 133.2, 132.9, 132.6, 130.7, 130.2, 129.9, 128.8, 128.5, 128.3 (2C), 128.28, 128.26, 127.9, 127.8, 127.7, 127.4, 126.8, 126.3, 126.2, 126.1, 125.9, 125.7, 125.6, 125.4, 125.3, 124.4, 121.8, 121.7; HRMS (ESI) *m/z* calcd for $C_{37}H_{24}O_2Na$ $[M + Na]^+$ 523.1669, found 523.1667.

2.2.15 | Co(II)-salen complex 8

General procedure F

To a solution of (1*S*,2*S*)-(+)-l,2-cyclohexanediamine (0.180 g, 1.56 mmol) in EtOH (48 mL) was added (*S*)-2-hydroxy-2′-phenyl-[1,1′-binaphthalene]-3-carbaldehyde (**7**, 1.17 g, 3.12 mmol), and the reaction mixture was heated at reflux for 12 hours. The resulting light-yellow precipitate was filtered and dried under vacuum. This precipitate was added to a solution of $Co(OAc)_2$ (0.276 g, 1.56 mmol) in degassed EtOH (48 mL) under nitrogen. The mixture was heated at reflux for 18 hours and then cooled to room temperature. The resulting brown precipitate was filtered, washed with degassed EtOH under a nitrogen atmosphere, and dried under vacuum to give the corresponding Co(II)-salen complex **8** (1.07 g, 1.21 mmol, 78%) as a dark-brown solid: $[\alpha]^{20}_D$ 95.7 (*c* 0.70, $CHCl_3$); IR (CH_2Cl_2) 3051, 2935, 2860, 1590, 1546, 1425, 1330, 1297, 1146, 952, 818, 743 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{60}H_{44}CoN_2O_2$ [M + H] 883.2729, found 883.2733. Note: Co $(OAc)_2$ was prepared by heating Co $(OAc)_2 \cdot 4H_2O$ at 80°C under vacuum for 3 hours. The color of the solid turned from pink to purple.

2.2.16 | Co(II)-salen complex 36

According to general procedure F, (1*R*,2*R*)-(+)-l,2-cyclohexanediamine (0.030 g, 0.26 mmol), (*R*)-2-hydroxy-2′-(4-(naphthalen-2-yl)phenyl)-[1,1′-binaphthalene]-3-carbaldehyde (**34**, 0.260 g, 0.520 mmol), and $Co(OAc)_2$ (0.046 g, 0.26 mmol) in EtOH (16 mL) afforded **36** (0.222 g, 0.195 mmol, 75%) as a brown solid: $[\alpha]^{20}_D$ −382.9 (*c* 0.70, $CHCl_3$); IR (CH_2Cl_2) 3052, 2933, 2859, 1630, 1563, 1535, 1442, 1384, 1337, 1263, 942, 811, 734 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{80}H_{56}CoN_2O_2$ [M + H] 1135.3668, found 1135.3676.

2.2.17 | Co(II)-salen complex 37

According to general procedure F, (1*R*,2*R*)-(+)-l,2-cyclohexanediamine (0.030 g, 0.26 mmol), (*R*)-2-hydroxy-2′-(3-(naphthalen-2-yl)phenyl)-[1,1′-binaphthalene]-3-carbaldehyde (**35**, 0.260 g, 0.520 mmol), and $Co(OAc)_2$ (0.046 g, 0.26 mmol) in EtOH (16 mL) afforded **37** (0.254 g, 0.223 mmol, 86%) as a reddish-brown solid: $[\alpha]^{20}_D$ −45.7 (*c* 0.70, $CHCl_3$); IR (CH_2Cl_2) 3051, 2933, 2859, 1628, 1595, 1332, 1319, 1263, 1145, 947, 819, 795, 736 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{80}H_{56}CoN_2O_2$ [M + H] 1135.3668, found 1135.3667.

2.3 | Synthesis of *cis*-cyclopropanes

2.3.1 | Ethyl (1*S*,2*R*)-2-(4-fluorophenyl) cyclopropane-1-carboxylate (10)

General procedure G

To a stirred solution of Co(II)-salen complex **8** (27 mg, 0.027 mmol) in THF (1 mL) was added *N*-methylimidazole (0.97M in THF, 0.050 mL, 0.053 mmol). The reaction mixture was stirred for 2 minutes, treated with 1-fluoro-4-vinylbenzene (**9**, 0.095 mL, 0.80 mmol) and stirred for another 3 minutes before ethyl diazoacetate (0.064 mL, 0.53 mmol) was added. The solution was stirred for 25 hours at 23°C and the solvent was removed under reduced pressure. The crude product was purified by chromatography on SiO_2 (98:2, hexanes: EtOAc) to afford **10** (0.0830 g, 0.399 mmol, 75%) as a colorless oily liquid: $[\alpha]^{20}_D$ + 11.4 (*c* 1.42, $CHCl_3$); IR (CH_2Cl_2) 3279, 2983, 1725, 1513, 1383, 1228, 1182, 1154, 1096, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.20 (m, 2H), 6.97-6.92 (m, 2H), 3.89 (q, *J* = 7.1 Hz, 2H), 2.52 (q, *J* = 8.5 Hz, 1H), 2.06 (ddd, *J* = 9.1, 7.9, 5.6 Hz, 1H), 1.66 (dt, *J* = 7.4, 5.4 Hz, 1H), 1.32 (td, *J* = 8.2, 5.1 Hz, 1H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 161.8 (d, *J* = 244.7 Hz), 132.4 (d, *J* = 3.1 Hz), 130.9 (d, *J* = 8.0 Hz), 114.8 (d, *J* = 21.4 Hz), 60.3, 24.8, 21.8, 14.2, 11.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.2; HRMS (ESI+) *m/z* calcd for $C_{12}H_{14}O_2F$ [M + H] 209.0972, found 209.0969. The *cis:trans* diastereomeric ratio was determined to be >97:3 based on ^1H NMR.

2.3.2 | Ethyl (1*S*,2*R*)-2-(4-(trifluoromethyl) phenyl)cyclopropane-1-carboxylate (15)

According to general procedure G, Co(II)-salen complex **8** (0.037 g, 0.042 mmol), *N*-methylimidazole (0.50M in THF, 0.17 mL, 0.084 mmol), 1-(trifluoromethyl)-4-vinylbenzene (0.722 g, 4.19 mmol), and ethyl

diazoacetate (0.100 mL, 0.839 mmol) in THF (4.2 mL) afforded **15** (0.181 g, 0.701 mmol, 84%) as a colorless oil: $[\alpha]^{20}_D$ +17.0 (*c* 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 3.93-3.84 (m, 2H), 2.59 (q, *J* = 8.5 Hz, 1H), 2.14 (q, *J* = 7.6 Hz, 1H), 1.74 (q, *J* = 5.9 Hz, 1H), 1.40 (q, *J* = 7.1 Hz, 1H), 0.99 (t, *J* = 6.9 Hz, 3H); ^{19}F NMR ($CDCl_3$, 470 MHz) δ −62.4 (s, 3F). The *cis:trans* diastereomeric ratio was determined to be >95:5 based on ^{1}H NMR.

2.3.3 | Ethyl (1*R*,2*S*)-2-(4-(trifluoromethyl) phenyl)cyclopropane-1-carboxylate (38)

According to general procedure G, Co(II)-salen complex **36** or **37** (0.024 g, 0.021 mmol), *N*-methylimidazole (0.50M in THF, 0.085 mL, 0.042 mmol), 1-(trifluoromethyl)-4-vinylbenzene (0.361 g, 2.10 mmol), and ethyl diazoacetate (0.050 mL, 0.42 mmol) in THF (2.1 mL) afforded **38** (0.107 g, 0.416 mmol, 99%; Table 1, Entry 2) or **38** (0.0970 g, 0.376 mmol, 90%; Table 1, Entry 3) as a colorless oil: $[\alpha]^{20}_D$ −21.5 (*c* 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 3.94-3.85 (m, 2H), 2.59 (q, *J* = 8.4 Hz, 1H), 2.14 (ddd, *J* = 9.3, 7.9, 5.7 Hz, 1H), 1.74 (dt, *J* = 7.5, 5.4 Hz, 1H), 1.39 (ddd, *J* = 8.6, 7.9, 5.2 Hz, 1H), 0.99 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 470 MHz) δ −62.4 (s, 3F). The *cis:trans* diastereomeric ratio was determined to be >97:3 based on ^{1}H NMR for each Co (II)-salen complex.

2.3.4 | (1*S*,2*R*)-2-(4-Fluorophenyl)cyclopropane-1-carboxylic acid (11)

General procedure H

To a stirred solution of ethyl (1*S*,2*R*)-2-(4-fluorophenyl) cyclopropane-1-carboxylate (**10**, 0.080 g, 0.38 mmol) in MeOH (2 mL) was added NaOH (0.077 g, 1.9 mmol) at 23°C under a nitrogen atmosphere. The reaction mixture was heated at 55°C for 5 hours and then cooled to 23°C. The methanol was removed under reduced pressure, and the residue was poured into water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were discarded, and the aqueous layer was acidified with 4M HCl to pH > 2 and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford **11**, which was carried forward without further purification.

2.3.5 | (1*S*,2*R*)-2-(4-(Trifluoromethyl)phenyl)cyclopropane-1-carboxylic acid (16)

According to general procedure H, ethyl (1*S*,2*R*)-2-(4-(trifluoromethyl)phenyl)cyclopropane-1-carboxylate (**15**, 0.180 g, 0.697 mmol) and NaOH (0.139 g, 3.49 mmol) in MeOH (1.7 mL) afforded **16** which was carried forward without further purification.

2.3.6 | (1*R*,2*S*)-2-(4-(Trifluoromethyl)phenyl)cyclopropane-1-carboxylic acid (39)

According to general procedure H, ethyl (1*R*,2*S*)-2-(4-(trifluoromethyl)phenyl)cyclopropane-1-carboxylate (**38**, 0.095 g, 0.37 mmol) and NaOH (0.074 g, 1.8 mmol) in MeOH (1.5 mL) afforded **39** which was carried forward without further purification.

2.3.7 | (4-(5-Chloro-2-methylphenyl) piperazin-1-yl)((1*S*,2*R*)-2-(4-fluorophenyl) cyclopropyl)methanone (13, (−)-JJ-450)

General procedure I

To a stirred solution of (1*S*,2*R*)-2-(4-fluorophenyl)cyclopropane-1-carboxylic acid (**11**, 0.069 g, 0.38 mmol) and 1-(5-chloro-2-methylphenyl)piperazine monohydrochloride (**12**, 0.142 g, 0.570 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (0.16 mL, 1.2 mmol) at 0°C under a nitrogen atmosphere. Tripropylphosphonic anhydride (50 wt% solution in EtOAc, 0.34 mL, 0.57 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 30 minutes, allowed to warm to 23°C and stirred for 20 hours. The solution was diluted with CH_2Cl_2 (10 mL) and washed with 1M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (1:1, hexanes: EtOAc) to afford **(−)-JJ-450** (**13**, 0.130 g, 0.349 mmol, 91%) as a viscous oil: $[\alpha]^{20}_D$ −159.4 (*c* 1.67, $CHCl_3$); IR (CH_2C_{l2}) 2916, 2819, 1638, 1593, 1512, 1489, 1465, 1436, 1224, 1098, 1034, 941, 838, 815, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.10 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 7.01-6.92 (m, 3H), 6.72 (d, *J* = 2.0 Hz, 1H), 3.86-3.74 (m, 1H), 3.74-3.57 (m, 2H), 3.40-3.28 (m, 1H), 2.82-2.66 (m, 2H), 2.44 (q, *J* = 8.9 Hz, 1H), 2.35-2.26 (m, 1H), 2.26-2.14 (m, 5H), 1.82 (q, *J* = 5.8 Hz, 1H), 1.34 (td, *J* = 8.4, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 161.7 (d, *J* = 244.9 Hz), 151.9, 133.2 (d, *J* = 3.1 Hz), 132.0 (d, *J* = 19.9 Hz), 131.0, 129.2 (d, *J* = 7.9 Hz), 123.7, 119.8, 115.1 (d, *J* = 21.3 Hz), 51.9, 51.7, 45.6, 42.3, 23.9, 23.6, 17.4, 10.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ

−116.3; HRMS (ESI+) *m/z* calcd for $C_{21}H_{23}ON_2ClF$ [M + H] 373.1478, found 373.1488. The enantiomeric ratio was determined as 97:3 *er* by HPLC (Chiralpak AD-H, hexane:isopropanol (9:1), 23°C, 254 nm, flow rate: 1 mL/min; major isomer Rt 12.6 min; minor isomer Rt 15.3 min).[8]

2.3.8 | (4-(2-Methyl-5-(trifluoromethyl) phenyl)piperazin-1-yl)((1*S*,2*R*)-2-(4-(trifluoromethyl)phenyl)cyclopropyl) methanone (18)

According to general procedure I, (1*S*,2*R*)-2-(4-(trifluoromethyl)phenyl)cyclopropane-1-carboxylic acid (**16**, 0.170 g, 0.738 mmol), 1-(2-methyl-5-(trifluoromethyl)phenyl)piperazine monohydrochloride (**17**, 0.290 g, 1.03 mmol), triethylamine (0.31 mL, 2.2 mmol), and tripropylphosphonic anhydride (50 wt% solution in EtOAc, 0.78 mL, 1.1 mmol) in CH_2Cl_2 (7.4 mL) afforded **18** (0.249 g, 0.545 mmol, 74%) as a pale yellow oil: $[a]^{20}_D$ −123.5 (*c* 0.78, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54-7.52 (m, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.26-7.25 (m, 1H), 7.24-7.21 (m, 2H), 6.93 (s, 1H), 3.85-3.83 (br m, 1H), 3.69-3.67 (br m, 1H), 3.65-3.63 (br m, 1H), 3.34-3.33 (br m, 1H), 2.82-2.74 (br m, 2H), 2.53 (td, *J* = 8.9, 7.0 Hz, 1H), 2.30-2.26 (m, 5H), 2.16-2.13 (br m, 1H), 1.91 (q, *J* = 6.2 Hz, 1H), 1.43 (td, *J* = 8.4, 5.6 Hz, 1H); ^{19}F NMR ($CDCl_3$, 470 MHz) δ −62.5 (s, 3F), −62.5 (s, 3F); HRMS (ESI+) *m/z* calcd for $C_{23}H_{23}F_6N_2O$ (M + H) 457.1709, found 457.1711. The enantiomeric ratio was determined as 96.5:3.5 *er* by SFC (Chiralpak-IC (250 × 10 mm); 15% MeOH, 220 nm, 6.5 mL/min, 100 bar; Rt 6.15 min).

2.3.9 | (4-(2-Methyl-5-(trifluoromethyl) phenyl)piperazin-1-yl)((1R,2S)-2-(4-(trifluoromethyl)phenyl)cyclopropyl) methanone (40)

According to general procedure I (Table 1, Entry 2), (1*R*,2*S*)-2-(4-(trifluoromethyl)phenyl)cyclopropane-1-carboxylic acid (**39**, 0.075 g, 0.32 mmol), 1-(2-methyl-5-(trifluoromethyl)phenyl)piperazine monohydrochloride (**17**, 0.119 g, 0.424 mmol), triethylamine (0.14 mL, 0.98 mmol), and tripropylphosphonic anhydride (50 wt% solution in EtOAc, 0.35 mL, 0.49 mmol) in CH_2Cl_2 (3.3 mL) afforded **40** (0.131 g, 0.286 mmol, 88%) as a viscous oil that foamed up upon drying under vacuum. Table 1, Entry 3: (1*R*,2*S*)-2-(4-(Trifluoromethyl)phenyl)cyclopropane-1-carboxylic acid (**39**, 0.058 g, 0.25 mmol), 1-(2-methyl-5-(trifluoromethyl)phenyl)piperazine monohydrochloride (**17**, 0.092 g, 0.33 mmol), triethylamine (0.11 mL, 0.76 mmol), and tripropylphosphonic anhydride (50 wt% solution in EtOAc, 0.27 mL, 0.38 mmol) in CH_2Cl_2 (2.5 mL) afforded **40** (0.112 g, 0.245 mmol, 97%) as a viscous oil that foamed up upon drying under vacuum: $[\alpha]^{20}_D$ + 124.1 (c 0.75, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.25-7.21 (m, 2H), 6.93 (s, 1H), 3.85-3.83 (m, 1H), 3.71-3.60 (m, 2H), 3.36-3.32 (m, 1H), 2.82-2.74 (m, 2H), 2.52 (q, *J* = 8.0 Hz, 1H), 2.30-2.25 (m, 5H), 2.16-2.12 (m, 1H), 1.92 (q, *J* = 6.2 Hz, 1H), 1.43 (td, *J* = 8.4, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 151.0, 141.9, 136.8, 131.4, 129.1 (q, *J* = 32 Hz), 128.8 (q, *J* = 32 Hz), 127.9, 125.0 (q, *J* = 4 Hz), 124.2 (q, *J* = 270 Hz), 124.1 (q, *J* = 27 Hz), 120.4 (q, *J* = 4 Hz), 115.8 (q, *J* = 4 Hz), 51.8, 51.5, 45.5, 42.2, 24.5, 23.9, 17.8, 11.1; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −62.47 (s, 3F), −62.53 (s, 3F); HRMS (ESI+) *m/z* calcd for $C_{23}H_{23}F_6N_2O$ (M + H) 457.1709, found 457.1708. The enantiomeric ratio was determined as 98.5:1.5 *er* by SFC (Chiralpak-IC (250 × 10 mm); 30% MeOH, 220 nm, 7.0 mL/min, 100 bar; Rt 3.66 min).

2.4 | Gram-scale synthesis of (1*S*,2*R*)-*cis*-cyclopropane

2.4.1 | Ethyl (1*S*,2*R*)-2-(4-(pentafluorosulfanyl)phenyl)cyclopropane-1-carboxylate (20)

To a THF solution (5.7 mL) of Co(II)-salen complex **8** (0.167 g, 0.189 mmol) was added a THF solution of *N*-methylimidazole (0.5M, 0.750 mL, 0.377 mmol). The reaction mixture was stirred for 2 minutes, treated with pentafluoro(4-vinylphenyl)-λ^6-sulfane (**19**, 1.30 g, 5.66 mmol), stirred for another 3 minutes, and treated with ethyl diazoacetate (87 wt% in CH_2Cl_2, 0.450 mL, 3.77 mmol). The reaction mixture was stirred for 24 hours at room temperature and then concentrated in vacuo. The residue was precipitated with hexanes and filtered to recover the catalyst. The hexanes filtrate was concentrated and purified by chromatography on SiO_2 (9:1, hexanes: EtOAc) to afford **20** (1.10 g, 3.47 mmol, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 3.96-3.86 (m, 2H), 2.56 (q, *J* = 8.4 Hz, 1H), 2.15 (ddd, *J* = 9.2, 8.0, 5.7 Hz, 1H), 1.73 (dt, *J* = 7.5, 5.5 Hz, 1H), 1.41 (td, *J* = 8.3, 5.2 Hz, 1H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 470 MHz) δ 84.9 (quintet, *J* = 150 Hz, 1F), 63.1 (d, *J* = 150 Hz, 4F). The *cis:trans* diastereomeric ratio was determined to be >97:3 based on ^{1}H NMR.

2.4.2 | (1*S*,2*R*)-2-(4-(Pentafluorosulfanyl) phenyl)cyclopropane-1-carboxylic acid (21)

A solution of ethyl (1*S*,2*R*)-2-(4-(pentafluorosulfanyl)phenyl)cyclopropane-1-carboxylate (**20**, 1.80 g, 5.69 mmol) in MeOH (5.5 mL) was added to a solution of NaOH (1.14 g, 28.5 mmol) in MeOH (1.0 mL). The reaction mixture was heated at 55°C for 5 hours, cooled to room temperature and poured into water and extracted with CH_2Cl_2 (40 mL). The combined organic layers were discarded and the aqueous layer was acidified with 6M HCl and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford **21** (1.89 g, 6.10 mmol, quant) as a pale-yellow oil which was used in next step without further purification.

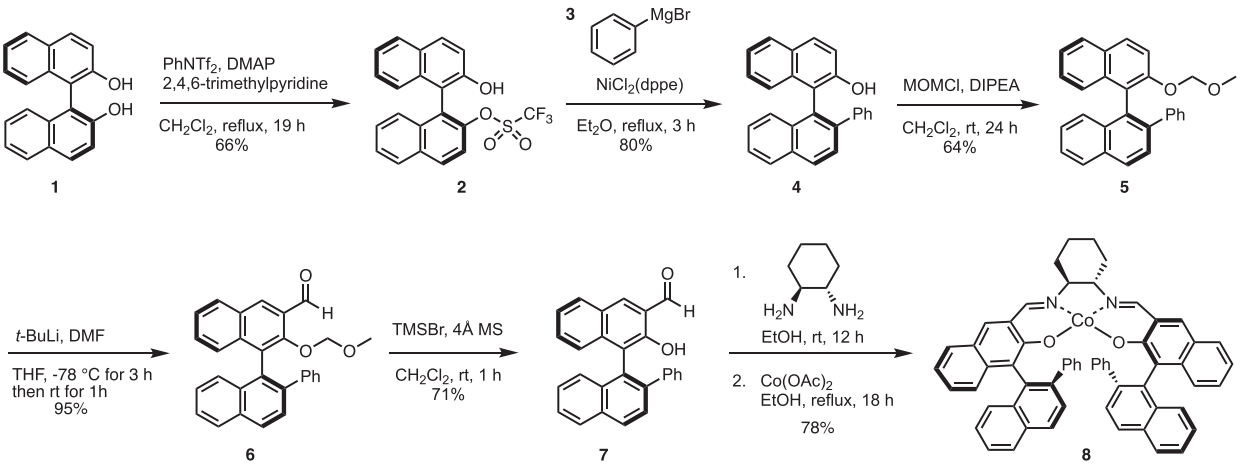
2.4.3 | (4-(5-Chloro-2-(trifluoromethyl) phenyl)piperazin-1-yl)((1*S*,2*R*)-2-(4-(pentafluorosulfanyl)phenyl)cyclopropyl) methanone (23)

A solution of (1*S*,2*R*)-2-(4-(pentafluorosulfanyl)phenyl) cyclopropane-1-carboxylic acid (**21**, 1.32 g, 4.26 mmol) and 1-(5-chloro-2-(trifluoromethyl)phenyl)piperazine monohydrochloride (**22**, 1.67 g, 5.54 mmol) in distilled CH_2Cl_2 (43 mL) was treated with Et_3N (1.80 mL, 12.8 mmol) at 0°C followed by dropwise addition of tripropylphosphonic anhydride (50 wt% in ethyl acetate, 4.50 mL, 6.39 mmol). The reaction mixture was stirred at 0°C for 30 minutes and allowed to warm to room temperature. After 16 hours, the solution was diluted with CH_2Cl_2 (50 mL) and washed with 1M HCl (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by chromatography on SiO_2 (1:1, hexanes: EtOAc) to afford **23** (1.98 g, 3.70 mmol, 87%) as a white solid: $[\alpha]^{20}_D$ −94.6 (*c* 4.69, MeOH); Mp 125.8-127.7°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.27-7.25 (m, 2H), 7.20 (d, *J* = 8.5 Hz, 1H), 6.93 (s, 1H), 3.99-3.96 (br m, 1H), 3.74-3.71 (br m, 1H), 3.56-3.52 (br m, 1H), 3.23-3.19 (br m, 1H), 2.79-2.74 (br m, 2H), 2.49 (q, *J* = 8.0 Hz, 1H), 2.29-2.22 (m, 2H), 1.98-1.94 (br m, 1H), 1.91 (q, *J* = 6.2 Hz, 1H), 1.45 (td, *J* = 8.4, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 152.6, 152.3 (t, *J* = 18 Hz), 142.1, 139.0, 128.4 (q, *J* = 5 Hz), 127.7, 126.0 (q, *J* = 29 Hz), 125.8 (t, *J* = 5 Hz), 125.6, 124.7, 122.5 (q, *J* = 273 Hz), 53.8, 52.8, 45.5, 42.2, 24.8, 23.7, 11.4; ^{19}F NMR ($CDCl_3$, 470 MHz) δ 84.8 (quintet, *J* = 150 Hz, 1F), 63.3 (d, *J* = 150 Hz, 4F), −60.4 (s, 3F); HRMS (ESI+) *m/z* calcd for $C_{21}H_{20}ClF_8N_2OS$ (M + H) 535.0852, found 535.0852. The enantiomeric ratio was enriched to 99:1 *er* after recrystallization from CH_2Cl_2:hexanes (HPLC Chiralpak AD-H (4.6 × 250 mm, 5 μm); hexanes:isopropanol (9:1), 254 nm, 1.0 mL/min; Rt 12.07 min).

3 | RESULTS AND DISCUSSION

In analogy to a protocol developed by Katsuki et al for the preparation of Co- and Mn-salen complexes,[22,28] we synthesized Co(II)-salen complex **8** in seven steps and 18% overall yield from (*S*)-(−)-1,1′-binaphthalene-2,2′-diol (Scheme 1). We expected catalyst **8** to be sufficiently reactive to provide the desired product stereoselectivity even with a fluorinated styrene.[22] To test this hypothesis, we selected the more potent enantiomer of our lead compound, **(−)-JJ-450**,[8] as the target compound (Scheme 2).

Reaction of 1-fluoro-4-vinylbenzene (**9**) with commercially readily available ethyl 2-diazoacetate in the presence of 5 mol% of Co(II)-salen complex **8** and



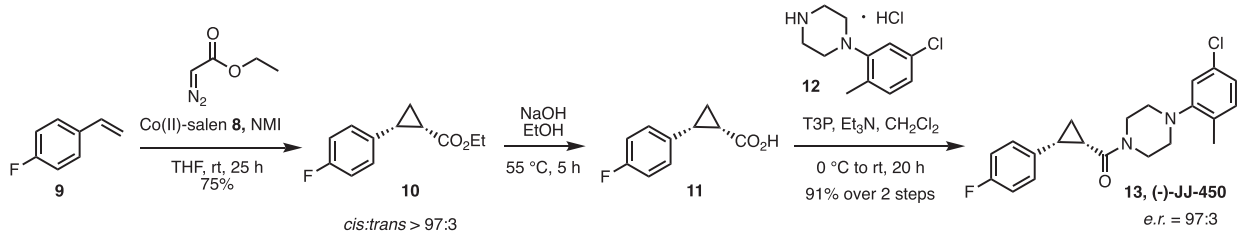
SCHEME 1 Synthesis of Co (II)-salen complex **8**

1-methylimidazole (NMI) provided *cis*-cyclopropane **10** in 75% yield. NMI was added to the reaction mixture as it was previously shown by Yamada et al. to act as an axial donor ligand and improve both the chemical and enantiomeric yields in a similar system.[29] Saponification of ester **10** with sodium hydroxide to carboxylic acid **11** and coupling with 1-(5-chloro-2-methylphenyl) piperazine monohydrochloride (**12**) in the presence of triethylamine and tripropylphosphonic anhydride (T3P) furnished target molecule **13**, (−)-**JJ-450**, in 91% yield over the two steps. The enantiomeric ratio was determined to be 97:3 by HPLC analysis and comparison to a racemic sample on a Chiralpak AD-H column (4.6 × 250 mm, 5 μm) with the mobile phase hexanes: isopropanol, 9:1, at a flow rate of 1 mL/min and UV monitoring at 254 nm.

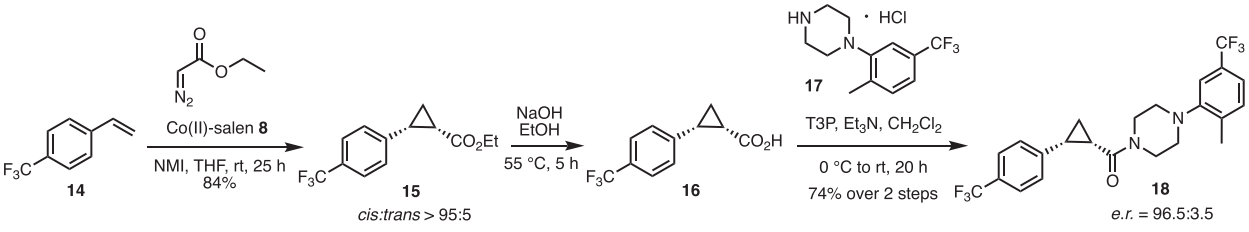
Previously, we had resolved the enantiomers in a time consuming and costly process by chiral stationary phase super-critical fluid chromatography (SFC).[8] Furthermore, we lost >50% of the product in this approach, and therefore the enantioselective *cis*-cyclopropanation of **9** represented a significant advancement over the resolution method.

For further synthetic validation, we expanded the asymmetric cyclopropanation to the preparation of highly electron-deficient trifluoromethylated styrene **14** (Scheme 3), and pentafluorosulfanyl styrene **19** (Scheme 4). In the presence of salen **8**, 1-(trifluoromethyl)-4-vinylbenzene (**14**) was converted to *cis*-cyclopropane (1*S*,2*R*)-**15** in 84% yield in a *cis:trans* ratio of >95:5 based on NMR analysis of the crude reaction mixture. Saponification of **15** with sodium hydroxide provided carboxylic acid (1*S*,2*R*)-**16** in quantitative yield. Subsequent coupling with 1-(2-methyl-5-(trifluoromethyl) phenyl)piperazine monohydrochloride (**17**) in the presence of triethylamine and T3P furnished analog (1*S*,2*R*)-**18** in an enantiomeric ratio of 96.5:3.5 based on SFC analysis. Analysis was performed using a Chiralpak-IC column (250 × 10 mm) with 15% MeOH modifier at a flow rate of 6.5 mL/min and monitoring at 220 nm.

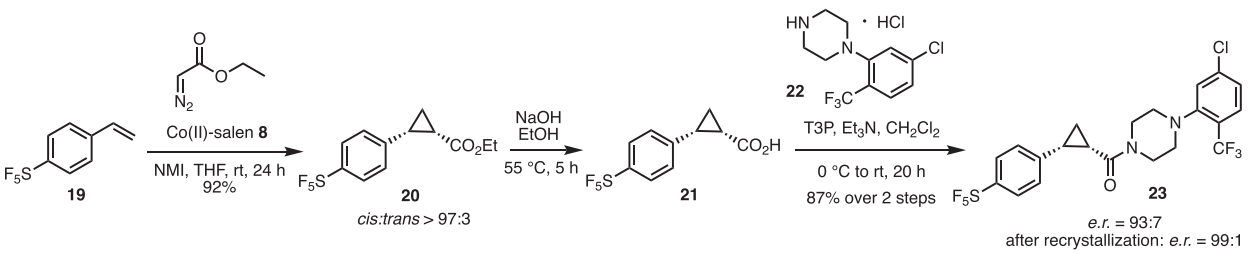
On a gram-scale, pentafluoro(4-vinylphenyl)-λ^6-sulfane (**19**) was reacted with ethyl 2-diazoacetate in the presence of 5 mol% Co(II)-salen complex **8** and NMI to provide *cis*-cyclopropane **20** in 92% yield (Scheme 4). Saponification of **20** with sodium hydroxide provided car-



SCHEME 2 Asymmetric synthesis of **13** ((−)-**JJ-450**) with *cis*-selective Co(II)-salen complex **8**



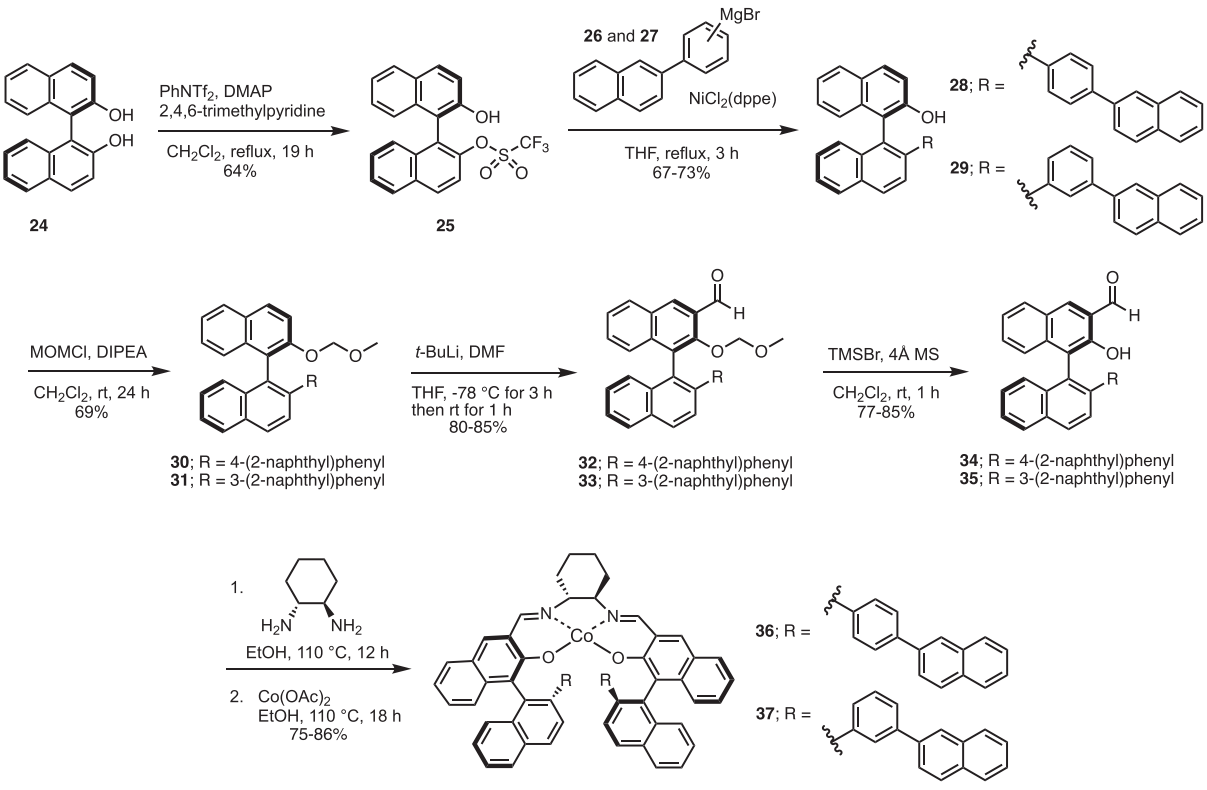
SCHEME 3 Asymmetric synthesis of (−)-**JJ-450** analog **18** with *cis*-selective Co(II)-salen complex **8**



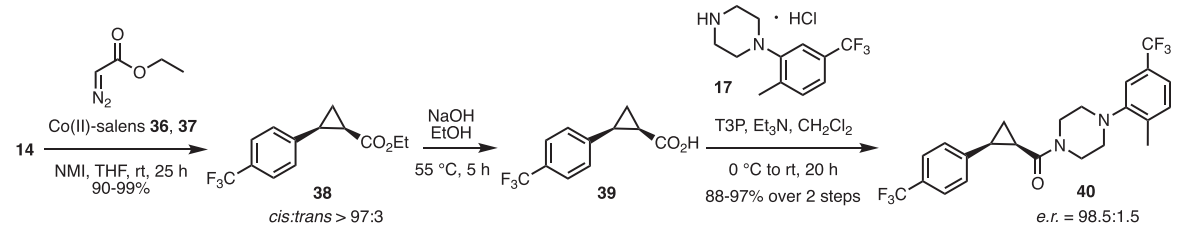
SCHEME 4 Asymmetric gram-scale synthesis of (−)-**JJ-450** analog **23** with *cis*-selective Co(II)-salen complex **8**

boxylic acid **21** in quantitative yield, and coupling of this acid with 1-(5-chloro-2-(trifluoromethyl)phenyl)piperazine monohydrochloride (**22**) in the presence of triethylamine and tripropylphosphonic anhydride led to desired pentafluorosulfanyl product **23** in 87% yield. The enantiomeric ratio of this product was determined by the previously described HPLC method to be 93:7, which could be further improved to 99:1 by recrystallization of **23** from dichloromethane and hexanes. The absolute configurations of **18** and **23** were assigned based on a comparison of the circular dichroism (CD) spectra to those of **13,** (-)-**JJ-450,** and (+)-**JJ-450**, for which we have also obtained an X-ray crystal structure.[30]

While an enantiomeric ratio of >9:1 is synthetically attractive, and, as shown for compound **23**, can be further improved by crystallization, impurity profiles in pharmaceutical products are subject to stringent guidelines by regulatory agencies, and >98:2 stereoisomer ratios are desirable in order to accomplish the goal of >98% purity.[31] Accordingly, we explored more bulky ligand designs and synthesized two additional, novel Co (II)-salen complexes, **36** and **37** (Scheme 5). By replacing the phenyl substituent in **8** with the much larger (4-(2-naphthyl)phenyl) and (3-(2-naphthyl)phenyl) groups in **36** and **37**, we hypothesized that the increased bulk provided by the naphthyl substituents would further increase *cis*-selectivity and enantiomeric ratios by guiding the ester alkyl group of the diazoacetate closer to the attacking olefin.[22] For future structure-activity relationship purposes in biological screens, we also switched the preferred chirality in these new ligands. Binaphthol triflate **25** was obtained from binaphthol **24** and *N*-phenyltriflimide in 64% yield. Nickel-catalyzed coupling with (4-(2-naphthyl)phenyl)magnesium bromide (**26**) or (3-(2-naphthyl)phenyl)magnesium bromide (**27**) provided chain-extended naphthols **28** and **29**, respectively, in



SCHEME 5 Synthesis of Co(II)-salen complexes **36** and **37** containing ligands with additional naphthyl side chains



SCHEME 6 Asymmetric synthesis of (+)-**JJ-450** analog **40** with highly *cis*- and enantioselective Co(II)-salen complexes **36** and **37**

TABLE 1 Asymmetric cyclopropanations of **14** using Co (II)-salen complexes **8**, **36**, and **37** to give cyclopropanes **15** and **38**.

Entry	Catalyst	Cyclopropanation Yield, %	Cis:Trans Ratio[a]	*e.r.*
1	**8**	84	>95:5	96.5:3.5[b]
2	**36**	99	>97:3	98.5:1.5[c]
3	**37**	90	>97:3	98.5:1.5[c]

[a]Determined by ^{1}H NMR analysis of **15** and **38**.

[b]Absolute configuration of analyte **18** is (1*S*,2*R*).

[c]Absolute configuration of analyte **40** is (1*R*,2*S*).

67% to 73% yield. Protection with MOM-Cl facilitated *ortho*-formylation of **30** and **31** with DMF to give aldehydes **32** and **33**. The MOM group was cleaved, and intermediates **34** and **35** were condensed with (1*R*,2*R*)-cyclohexane-1,2-diamine, followed by treatment with Co $(OAc)_2$ to give complexes **36** and **37**.

In the presence of salens **36** and **37**, *cis*-cyclopropane (1*R*,2*S*)-**38** was obtained in 99% and 90% yield, respectively, with a *cis:trans* ratio of >97:3 based on NMR analysis (Scheme 6). Further conversion of this ester to acid **39** and amide **40** was straightforward by routine transformations, and delivered a product enantiomeric ratio of 98.5:1.5 for both catalysts based on an analysis by the previously described SFC method. Absolute configurations were assigned by comparison of CD spectra to those of **18** and **23**. Table 1 summarizes the results with the three salens for the asymmetric cyclopropanation of styrene **14**. Among the salen complexes tested, the novel, bulky complex **36** provides a superior yield and *cis:trans* ratio, as well as an excellent

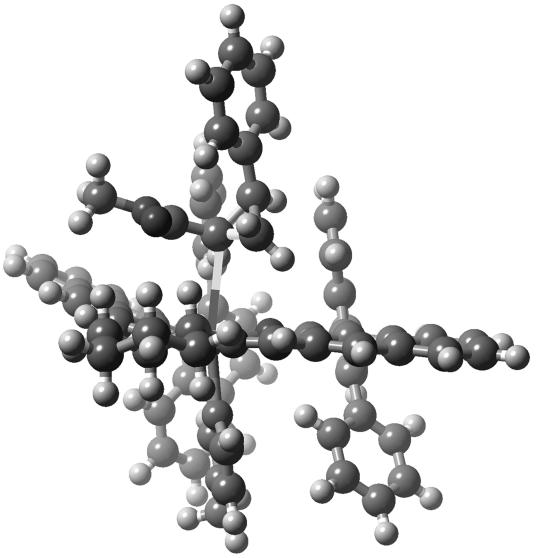
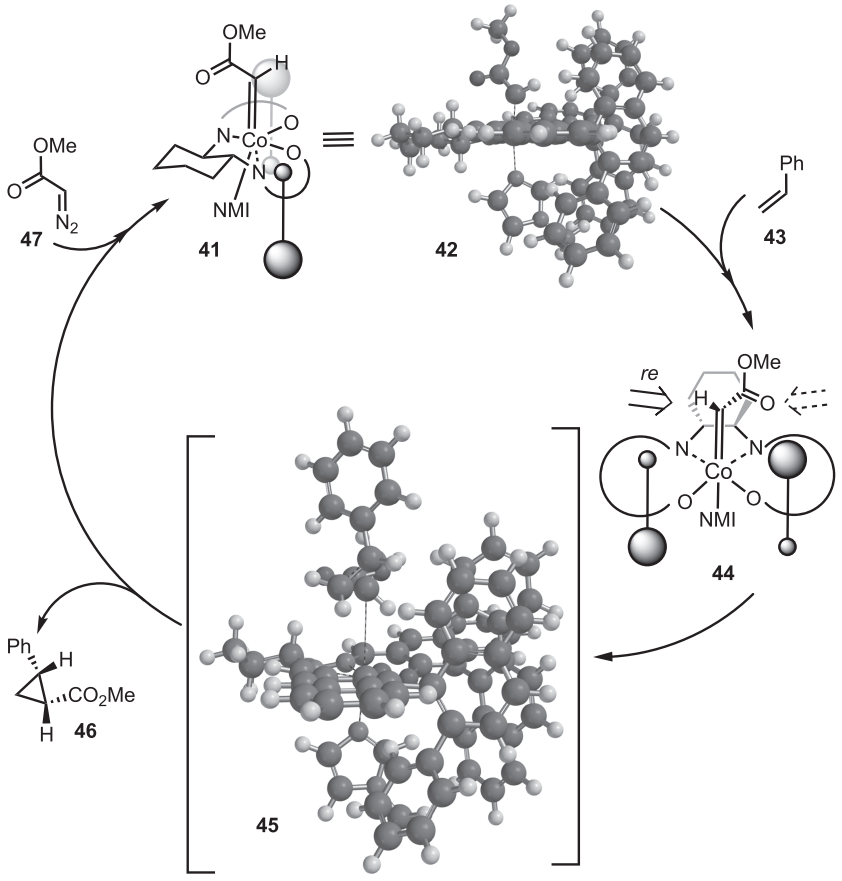


FIGURE 3 Perspective view of transition state **45**



SCHEME 7 Proposed catalytic cycle and computational ground state (**42**) and transition state (**45**) models (UHF 3-21G (*)) for the asymmetric cyclopropanation of styrene. NMI = N-methylimidazole

enantiomeric ratio as determined by the analysis of product amide **40**. These results are also particularly noteworthy in the context of the use of fluorinated styrenes, which have previously only rarely been studied in the asymmetric cyclopropanation reaction.

A mechanism and transition state model for the asymmetric cyclopropanation reaction with salens **36**, **37** are proposed in Scheme 7. The cobalt carbene complex **41**, also shown in the minimum-energy C_2-symmetric conformation **42** calculated by ground state UHF 3-21G(*) optimizations, adds styrene **43** on the less hindered *re*-face in **44**. The late-stage transition state **45**, obtained by transition state UHF 3-21G(*) calculations, has an elongated Co-C bond length of 3.36 Å versus 1.89 Å in ground state **42**, and is shown in Figure 3. Phenyl ring and ester are positioned *syn* in **45**, leading to the formation of *cis*-cyclopropane **46**, and after reaction with diazoester **47**, back to the beginning of the catalytic cycle with intermediate **41**.

4 | CONCLUSION

In summary, we have adapted and further developed an enantioselective *cis*-cyclopropanation reaction of styrenes with ethyl diazoacetate, utilizing Co(II)-salen complexes for the synthesis of the lead compound (−)-**JJ-450** and two highly fluorinated analogs. By switching from a phenyl to a naphthyl substituent in the cobalt salen ligands **36** and **37**, we were able to leverage the steric bulk of the catalyst for an increase in the *cis:trans* ratio from >95:5 to >97:3, and an improvement in the enantiomeric ratio of the product from 28:1 to 66:1. Furthermore, this approach is compatible with a variety of fluorinated, electron-poor styrene starting materials. Finally, we demonstrate that this protocol is sufficiently robust to synthesize a selected analog of our lead compound on a >1 gram scale with an enantiomeric ratio of 99:1 after recrystallization.

ACKNOWLEDGMENTS

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ORCID

Peter Wipf https://orcid.org/0000-0001-7693-5863

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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