

C–H Functionalization Approach for the Synthesis of Chiral C2 Symmetric 1,5-Cyclooctadienes Ligands

Bowen Zhang, Michael Hollerbach, [Simon Blakey](#), [Huw Davies](#)

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Chiral cyclooctadiene (COD) derivatives are readily prepared by rhodium-catalyzed allylic C-H functionalization of COD. Either mono or difunctionalization of COD is possible generating the products in high yield, diastereoselectivity and enantioselectivity.

File list (2)

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Supporting Information

C–H Functionalization Approach for the Synthesis of Chiral C_2 symmetric 1,5-cyclootadienes Ligands

Bowen Zhang, Michael R. Hollerbach, Simon Blakey,* and Huw M.L. Davies*

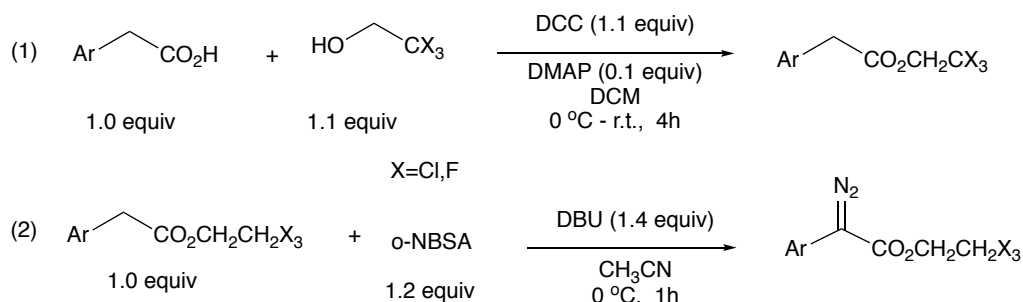
Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322

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General procedure for the diazo compound synthesis

Diazo compound **2-12** used in this work were pre-synthesized by group in storage following the general procedure below.

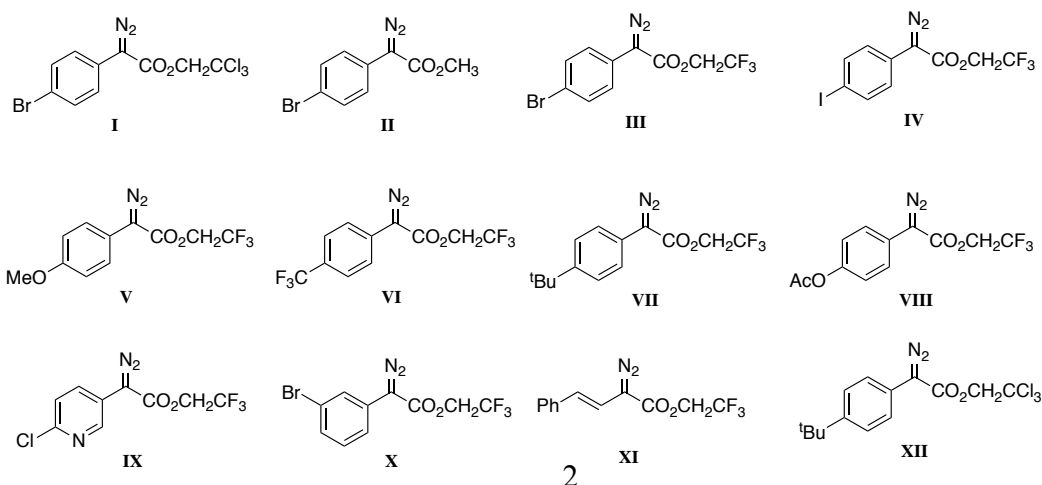


(1) Aryl acetic acid (1.0 equiv, 20 mmol) and 2,2,2-trihaloethanol (1.1 equiv, 22 mmol) were dissolved in 50 mL dichloromethane and stirred at 0 °C in ice/water bath. N,N'-Dicyclohexylcarbodiimide (DCC) (1.1 equiv, 22 mmol) was then added to the stirring solution carefully. Catalytic DMAP (0.1 equiv, 2.0 mmol) was then dissolved in 2 mL DCM and added to the solution. The white precipitation forms rapidly and the solution become milk color. The reaction was kept running for 4 h and warm to r.t. naturally. Filter and concentrate the solution give the crude ester product. Purify the ester with a quick silica plug (5% Et₂O/Pentane) and then concentrate under vacuum, yielding the ester as colorless oil, which is directly used for the following diazo transfer step.

(2) Ester from step (1) (1.0 equiv, 10 mmol) and ortho-nitrobenzenesulfonyl azide (o-NBSA) (1.2 equiv, 12 mmol) were dissolved in 30 mL anhydrous CH₃CN. The solution was kept stirring at 0 °C and DBU (1.4 equiv, 14 mmol) was added dropwise to the solution. The color of the solution gradually turned orange and it is quenched after 1 h by diluting with 100 mL Et₂O followed by adding 100mL NH₄Cl (sat.) solution. Extract the aqueous layer with Et₂O (30 mLx3), combined the organic layers and dry it over MgSO₄. Silica plug and concentrate give the crude diazo product as orange oil or solid. Further purification was done by flash column chromatography (2-5% Et₂O/Pentane)

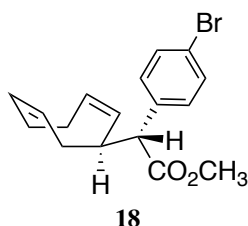
*For spectra information of these diazo compounds, refer to the references^[1-3].

(below are all diazo compounds involved. Notice the diazo compound **I** is **16** in the main context)



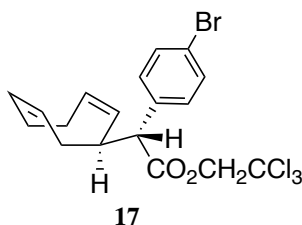
General Procedure for mono-allylic-insertion

To a 16 mL glass reaction vial was added stir bar, 1,5-cyclooctadiene (COD) (0.75 mmol, 2.5 equiv, 81 mg/~0.1 mL) and $\text{Rh}_2(\text{R-2-Cl,5-BrTPCP})_4$ (0.1 mol %). The vial was degassed and filled with Ar for several times. 2mL anhydrous DCM was then added to the vial and the solution was kept stirring at 0 °C for 5 min. Aryl diazo ester (0.3 mmol, 1.0 equiv) was dissolved in 4 mL DCM and added dropwise to the vial over 3 h via syringe pump. The reaction was kept running for 2 h after the addition of diazo compound is finished. The solution was concentrated to give oil mixture and the crude ^1H NMR was obtained for dr analysis. Further purification was done by column chromatography (0.8-10% Et_2O in pentane depending on substrate), giving product as colorless oil.



(R)-methyl 2-(4-bromophenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate 18: Derived from the reaction of diazo **II** (0.3 mmol, 77 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (2.5% Et_2O in pentane). Product: 74 mg, 73% yield; 72% ee.; 11.6:1 dr, colorless oil.

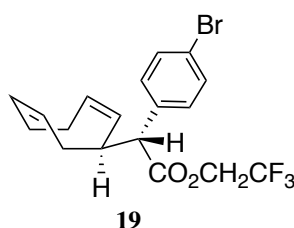
^1H NMR (600 MHz, CDCl_3) δ 7.43 (m, 2H), 7.22 (m, 2H), 5.57 (q, $J = 4.5$ Hz, 2H), 5.49 – 5.42 (m, 1H), 5.01 (dd, $J = 11.6, 6.9$ Hz, 1H), 3.67 (s, 3H), 3.51 – 3.44 (m, 1H), 3.39 (d, $J = 10.5$ Hz, 1H), 2.55 – 2.46 (m, 1H), 2.38 (dq, $J = 13.7, 3.6, 2.7$ Hz, 1H), 2.35 – 2.24 (m, 3H), 2.22 – 2.16 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 173.50, 136.55, 131.58, 130.46, 129.96, 129.35, 129.28, 127.23, 121.41, 57.48, 52.10, 42.16, 33.05, 27.91, 27.46. IR: 3010, 2949, 2885, 1732, 1488, 1433, 1340, 1266, 1153, 1073, 1011, 813, 763 (cm^{-1}); HRMS- (APCI) m/z : found at 335.0643 [$(\text{M}+\text{H})^+$: $[\text{C}_{17}\text{H}_{20}\text{O}_2\text{Br}]^+$ calculates to be 335.0641]; $[\alpha]_{\text{D}}^{20}$: -35.1° ($c=1.00$, CHCl_3);



(R)-2,2,2-trichloroethyl 2-(4-bromophenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate 17: Derived from the reaction of diazo **I** (0.2 mmol, 75 mg) and COD (0.5 mmol, 81 mg) following general procedure, purified by column chromatography (1-2% Et_2O in pentane). Product: 66 mg, 72% yield; 91% ee.; dr > 30:1, colorless oil. A large scale reaction was also performed for this reaction. Diazo **I** (3.0 mmol, 1.12 g) and COD (6.0 mmol, 650 mg)

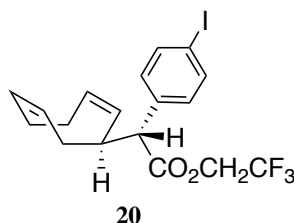
was reacted to generate the product at yield: 1.08 g, 80% yield; 89% ee.; dr > 30:1, colorless oil.

^1H NMR (600 MHz, CDCl_3) δ 7.45 (m, 2H), 7.26 (m, 2H), 5.58 (q, J = 6.1, 5.7 Hz, 2H), 5.48 (dt, J = 13.0, 7.1 Hz, 1H), 5.03 (dd, J = 11.6, 6.7 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H, **H of CH_2 next to CCl_3**), 4.66 (d, J = 12.0 Hz, 1H, **H of CH_2 next to CCl_3**), 3.58 (td, J = 10.4, 5.4 Hz, 1H), 3.53 (d, J = 10.5 Hz, 1H), 2.57 – 2.44 (m, 2H), 2.38 – 2.26 (m, 3H), 2.24 – 2.16 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 171.27, 135.60, 131.69, 130.62, 129.71, 129.43, 126.98, 121.77, 94.69, 74.21, 57.37, 41.80, 33.05, 27.91, 27.47. IR: 3012, 2888, 1749, 1488, 1428, 1407, 1371, 1270, 1200, 1134, 1074, 1012, 824 (cm^{-1}); HRMS-(APCI) m/z : found at 450.9632 $[(\text{M}+\text{H})^+ : [\text{C}_{18}\text{H}_{19}\text{O}_2\text{BrCl}_3]^+ \text{ calculates to be } 450.9629]$; $[\alpha]_D^{20}$: -24.8° ($c=1.00$, CHCl_3);



(R)-2,2,2-trifluoroethyl 2-(4-bromophenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate 19: Derived from the reaction of diazo **III** (0.3 mmol, 97 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (0.8-1.5% Et_2O in pentane). Product: 100 mg, 83% yield; 93% ee.; dr > 30:1, colorless oil.

^1H NMR (600 MHz, CDCl_3) δ 7.47 – 7.44 (m, 2H), 7.24 – 7.20 (m, 2H), 5.61 – 5.53 (m, 2H), 5.51 – 5.46 (m, 1H), 5.02 (dd, J = 11.6, 6.1 Hz, 1H), 4.56 (dq, J = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 4.35 (dq, J = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 3.53 – 3.46 (m, 2H), 2.49 (ddt, J = 17.9, 11.9, 5.7 Hz, 1H), 2.42 – 2.17 (m, 5H). ^{13}C NMR (151 MHz, CDCl_3) δ 171.48, 135.45, 131.75, 130.44, 129.82, 129.50, 129.30, 126.83, 122.79 (q, $J=277.8$ Hz, **C of CF_3**), 121.84, 60.48 (q, $J=36.7$ Hz, **C of CH_2 next to CF_3**), 56.93, 42.18, 32.71, 27.95, 27.35. IR: 3014, 2889, 1751, 1488, 1407, 1280, 1164, 1131, 1071, 1036, 1011, 978, 812 (cm^{-1}); HRMS-(APCI) m/z : found at 401.0361 $[(\text{M}-\text{H})^- : [\text{C}_{18}\text{H}_{17}\text{O}_2\text{BrF}_3]^- \text{ calculates to be } 401.0359]$; $[\alpha]_D^{20}$: -39.2° ($c=1.00$, CHCl_3);

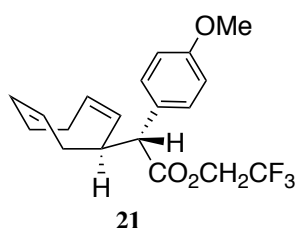


(R)-2,2,2-trifluoroethyl 2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)-2-(4-iodophenyl)acetate 20: Derived from the reaction of diazo **IV** (0.3 mmol, 111 mg) and COD (0.75 mmol, 81 mg)

following general procedure, purified by column chromatography (2% Et₂O in pentane).

Product: 117 mg, 78% yield; 95% ee.; dr > 30:1, colorless oil.

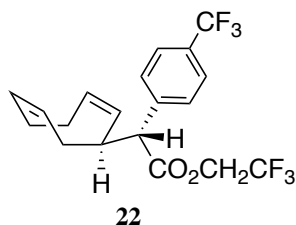
¹H NMR (600 MHz, CDCl₃) δ 7.72 – 7.60 (m, 2H), 7.14 – 7.04 (m, 2H), 5.56 (tq, *J* = 11.6, 5.9 Hz, 2H), 5.52 – 5.44 (m, 1H), 5.02 (dd, *J* = 10.9, 5.5 Hz, 1H), 4.56 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH₂ next to CF₃**), 4.34 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH₂ next to CF₃**), 3.53 – 3.44 (m, 2H), 2.48 (ddt, *J* = 17.6, 11.9, 5.7 Hz, 1H), 2.42 – 2.16 (m, 5H). ¹³C NMR (151 MHz, CDCl₃) δ 171.46, 137.72, 136.13, 130.69, 129.82, 129.50, 129.31, 126.83, 122.79 (q, *J* = 277.8 Hz, **C of CF₃**), 93.46, 60.48 (q, *J* = 36.7 Hz, **C of CH₂ next to CF₃**), 57.04, 42.12, 32.69, 27.95, 27.35. IR: 3013, 2887, 1750, 1485, 1404, 1279, 1164, 1129, 1062, 1006, 977, 810, 758 (cm⁻¹); HRMS-(APCI) *m/z*: found at 451.0379 [(M+H)⁺ : [C₁₈H₁₉O₂F₃I]⁺ calculates to be 451.0376]; [α]_D²⁰: -36.5° (c=1.00, CHCl₃);



(R)-2,2,2-trifluoroethyl 2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)-2-(4-

methoxyphenyl)acetate 21: Derived from the reaction of diazo **V** (0.3 mmol, 82 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (2-4% Et₂O in pentane). Product: 77 mg, 72% yield; 81% ee.; dr > 30:1, colorless oil.

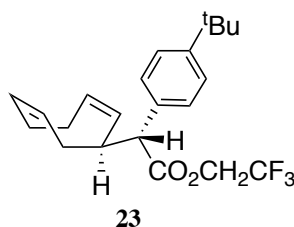
¹H NMR (600 MHz, CDCl₃) δ 7.25 (m, 2H), 6.88 – 6.82 (m, 2H), 5.61 – 5.53 (m, 2H), 5.51 – 5.43 (m, 1H), 5.06 (dd, *J* = 11.6, 6.3 Hz, 1H), 4.56 (dq, *J* = 12.7, 8.5 Hz, 1H, **H of CH₂ next to CF₃**), 4.33 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH₂ next to CF₃**), 3.79 (s, 3H), 3.55 – 3.45 (m, 2H), 2.51 (ddt, *J* = 17.2, 11.6, 5.8 Hz, 1H), 2.40 (dt, *J* = 15.1, 3.9 Hz, 1H), 2.36 – 2.24 (m, 3H), 2.20 (dq, *J* = 16.8, 4.8 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 172.14, 159.09, 129.86, 129.76, 129.35, 129.27, 128.48, 127.12, 122.90 (q, *J* = 277.4 Hz, **C of CF₃**), 113.98, 60.32 (q, *J* = 36.6 Hz, **C of CH₂ next to CF₃**), 56.69, 55.21, 42.10, 32.80, 27.98, 27.41. IR: 3012, 2891, 1750, 1610, 1511, 1465, 1407, 1283, 1249, 1163, 1128, 1034, 978 (cm⁻¹); HRMS-(APCI) *m/z*: found at 355.1517 [(M+H)⁺ : [C₁₉H₂₂O₃F₃]⁺ calculates to be 355.1516]; [α]_D²⁰: -34.5° (c=1.00, CHCl₃);



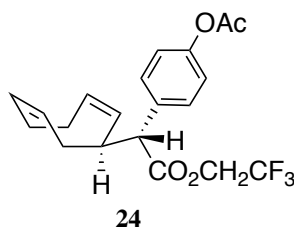
(R)-2,2,2-trifluoroethyl 2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)-2-(4-

(trifluoromethyl)phenyl)acetate 22: Derived from the reaction of diazo **VI** (0.3 mmol, 94 mg) and COD (0.75 mmol 81 mg) following general procedure, purified by column

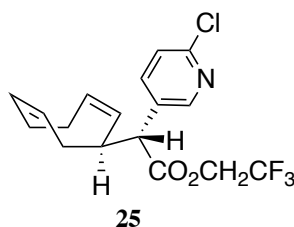
chromatography (1-2% Et₂O in pentane). Product: 91 mg, 78% yield; 94% ee.; dr > 30:1, white solid. (Single Crystal structure obtained for this compound); ¹H NMR (600 MHz, CDCl₃) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 5.63 – 5.53 (m, 2H), 5.49 (dddd, *J* = 11.6, 7.6, 5.9, 1.1 Hz, 1H), 5.01 (dd, *J* = 11.7, 6.8 Hz, 1H), 4.57 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH₂ next to CF₃ in ester**), 4.36 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH₂ next to CF₃ in ester**), 3.62 (d, *J* = 10.3 Hz, 1H), 3.54 (tt, *J* = 10.6, 5.5 Hz, 1H), 2.49 (ddt, *J* = 16.6, 11.8, 5.4 Hz, 1H), 2.43 – 2.18 (m, 5H). ¹³C NMR (151 MHz, CDCl₃) δ 171.25, 140.39, 130.02 (q, *J* = 32.5 Hz, **C on Ar ring next to CF₃**), 130.06, 129.59, 129.18, 129.06, 126.70, 125.54 (q, *J* = 3.7 Hz, **C on Ar ring next to the 130.02 C**), 124.01 (q, *J* = 272.3 Hz, **C of CF₃ on the Ar ring**), 122.75 (q, *J* = 277.7 Hz, **C of CF₃ in the ester**), 60.55 (q, *J* = 36.7 Hz, **C of CH₂ next to CF₃ in ester**), 57.29, 42.29, 32.65, 27.95, 27.31. IR: 3017, 2893, 1755, 1619, 1422, 1326, 1286, 1166, 1130, 1069, 1020, 980, 838 (cm⁻¹); HRMS-(APCI) *m/z*: found at 393.1284 [(*M*+*H*)⁺ : [C₁₉H₁₉O₂F₆]⁺ calculates to be 393.1284]; [*α*]_D²⁰: -43.5° (c=1.00, CHCl₃); m.p. 58-60 °C



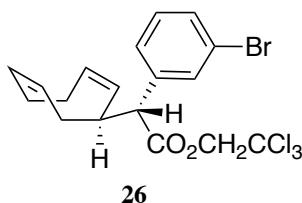
(R)-2,2,2-trifluoroethyl 2-(4-(tert-butyl)phenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate 23: Derived from the reaction of diazo **VII** (0.3 mmol, 90 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (0.8-1.5% Et₂O in pentane). Product: 98 mg, 85% yield; 88% ee.; dr > 30:1, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.30 (m, 2H), 7.27 – 7.23 (m, 2H), 5.63 – 5.52 (m, 2H), 5.51 – 5.43 (m, 1H), 5.08 (dd, *J* = 11.0, 5.5 Hz, 1H), 4.58 (dq, *J* = 12.7, 8.5 Hz, 1H, **H of CH₂ next to CF₃**), 4.30 (dq, *J* = 12.9, 8.5 Hz, 1H, **H of CH₂ next to CF₃**), 3.55 – 3.48 (m, 2H), 2.50 (ddt, *J* = 16.8, 11.2, 5.3 Hz, 1H), 2.45 – 2.17 (m, 5H), 1.30 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 172.08, 150.52, 133.23, 129.91, 129.40, 129.17, 128.31, 127.05, 125.47, 122.90 (q, *J* = 277.5 Hz, **C of CF₃**), 76.99, 60.31 (q, *J* = 37.1 Hz, **C of CH₂ next to CF₃**), 57.00, 42.09, 34.47, 32.54, 31.29, 28.04, 27.33. IR: 3014, 2964, 2890, 1753, 1508, 1408, 1365, 1283, 1166, 1131, 1062, 979, 841 (cm⁻¹); HRMS-(APCI) *m/z*: found at 381.2037 [(*M*+*H*)⁺ : [C₂₂H₂₈O₂F₃]⁺ calculates to be 381.2036]; [*α*]_D²⁰: -33.2° (c=1.00, CHCl₃);



(R)-2,2,2-trifluoroethyl 2-(4-acetoxyphenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate 24: Derived from the reaction of diazo **VIII** (0.2 mmol, 60 mg) and COD (0.5 mmol, 54 mg) following general procedure, purified by column chromatography (6-10% Et₂O in pentane). Product: 53 mg, 70% yield; 79% ee.; dr > 30:1, colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 7.38 – 7.32 (m, 2H), 7.09 – 7.02 (m, 2H), 5.62 – 5.52 (m, 2H), 5.48 (dddd, *J* = 11.7, 7.7, 6.0, 1.1 Hz, 1H), 5.05 (dd, *J* = 11.6, 6.5 Hz, 1H), 4.58 (dq, *J* = 12.7, 8.4 Hz, 1H), 4.33 (dq, *J* = 12.7, 8.4 Hz, 1H), 3.54 (d, *J* = 10.4 Hz, 1H), 3.49 (m, 1H), 2.49 (ddt, *J* = 17.9, 11.9, 5.8 Hz, 1H), 2.43 – 2.24 (m, 7H, 2.29 (s, **3H for Me in OAc**)), 2.24 – 2.17 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 171.68, 169.29, 150.17, 133.86, 129.78, 129.60, 129.51, 129.48, 126.90, 122.85 (q, *J* = 277.4 Hz, **C of CF₃**), 121.64, 60.43 (q, *J* = 36.6 Hz, **C of CH₂ next to CF₃**), 56.88, 42.31, 32.61, 28.00, 27.34, 21.16. IR: 3014, 2891, 1752, 1507, 1408, 1370, 1283, 1198, 1166, 1132, 1018, 978, 912 (cm⁻¹); HRMS-(APCI) *m/z*: found at 383.1465 [(M+H)⁺ : [C₂₀H₂₂O₄F₃]⁺ calculates to be 383.1465]; [α]_D²⁰: -32.4° (c=1.00, CHCl₃);



(R)-2,2,2-trifluoroethyl 2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)acetate 25: Derived from the reaction of diazo **IX** (0.3 mmol, 84 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (5-8% Et₂O in pentane). Product: 78 mg, 72% yield; 87% ee.; dr > 30:1, colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 8.31 (d, *J* = 2.4 Hz, 1H), 7.71 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 5.62 – 5.50 (m, 3H), 5.03 (dd, *J* = 11.6, 6.9 Hz, 1H), 4.58 (dq, *J* = 12.7, 8.3 Hz, 1H, **H of CH₂ next to CF₃**), 4.40 (dq, *J* = 12.7, 8.3 Hz, 1H, **H of CH₂ next to CF₃**), 3.58 (d, *J* = 9.8 Hz, 1H), 3.48 (p, *J* = 7.9 Hz, 1H), 2.44 (td, *J* = 13.6, 11.5, 8.5 Hz, 1H), 2.37 – 2.32 (m, 2H), 2.32 – 2.18 (m, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 170.88, 151.02, 150.02, 138.79, 131.08, 130.84, 129.67, 128.43, 126.44, 124.24, 122.67 (q, *J* = 278.6 Hz, **C of CF₃**), 60.68 (q, *J* = 36.8 Hz, **C of CH₂ next to CF₃**), 54.02, 42.35, 32.71, 27.89, 27.23. IR: 3014, 2891, 1752, 1584, 1565, 1462, 1410, 1391, 1278, 1166, 1138, 1107, 1023, 978 (cm⁻¹); HRMS-(APCI) *m/z*: found at 360.0971 [(M+H)⁺ : [C₁₇H₁₈O₂NCIF₃]⁺ calculates to be 360.0973]; [α]_D²⁰: -33.4° (c=1.00, CHCl₃);

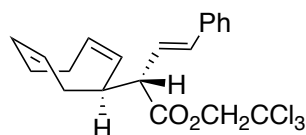


2,2,2-trichloroethyl (R)-2-(3-bromophenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate

26: Derived from the reaction of diazo **X** (0.3 mmol, 97 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (6-10% Et₂O in pentane).

Product: 78 mg, 64% yield; 63% ee.; dr > 30:1, colorless oil.

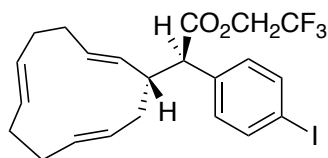
¹H NMR (600 MHz, Chloroform-*d*) δ 7.50 (t, *J* = 1.8 Hz, 1H), 7.42 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.28 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 5.63 – 5.53 (m, 2H), 5.53 – 5.47 (m, 1H), 5.04 (dd, *J* = 11.6, 6.3 Hz, 1H), 4.59 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH₂ next to CF₃**), 4.35 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH₂ next to CF₃**), 3.54 – 3.42 (m, 2H), 2.48 (ddt, *J* = 17.5, 11.8, 5.6 Hz, 1H), 2.43 – 2.17 (m, 5H). ¹³C NMR (151 MHz, CDCl₃) δ 171.35, 138.64, 131.80, 130.91, 130.10, 129.90, 129.58, 129.18, 127.42, 126.74, 122.78 (q, *J* = 277.3 Hz, **C of CF₃**), 122.60, 60.50 (q, *J* = 36.7 Hz, **C of CH₂ next to CF₃**), 57.03, 42.33, 32.53, 28.01, 27.27. IR: 3014, 2890, 1754, 1593, 1570, 1475, 1429, 1408, 1282, 1169, 1136, 1075, 997, 979 (cm⁻¹); HRMS-(APCI) *m/z*: found at 403.0510 [(M+H)⁺ : [C₁₈H₁₉O₂F₃Br]⁺ calculates to be 403.0515]; [α]_D²⁰: -39.9° (c=1.00, CHCl₃);



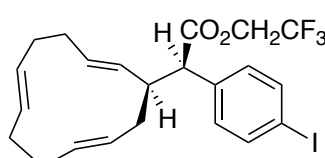
27

bis(2,2,2-trichloroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)(2S,2'S,3E,3'E)-bis(4-phenylbut-3-enoate) 27: Derived from the reaction of diazo **XI** (0.2 mmol, 67 mg) and COD (0.5 mmol, 54 mg) following general procedure, purified by column chromatography (6-10% Et₂O in pentane). Product: 53 mg, 67% yield; 88% ee.; dr > 30:1, colorless oil.

¹H NMR (600 MHz, CDCl₃) δ 7.40 – 7.37 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.23 (m, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.25 (dd, *J* = 15.8, 9.5 Hz, 1H), 5.67 – 5.61 (m, 1H), 5.61 – 5.54 (m, 2H), 5.42 (dd, *J* = 11.6, 6.8 Hz, 1H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 3.35 (td, *J* = 11.8, 7.1 Hz, 1H), 3.28 – 3.21 (m, 1H), 2.44 (dt, *J* = 16.8, 7.5, 4.4 Hz, 3H), 2.36 – 2.26 (m, 2H), 2.22 (dt, *J* = 15.4, 3.9 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 171.57, 136.58, 134.21, 129.88, 129.36, 129.15, 128.60, 127.81, 127.10, 126.48, 124.92, 94.88, 74.12, 55.29, 41.51, 32.82, 27.93, 27.53. IR: 3011, 2952, 2888, 1747, 1496, 1449, 1428, 1373, 1257, 1196, 1133, 966, 802 (cm⁻¹); HRMS-(APCI) *m/z*: found at 399.0682 [(M+H)⁺ : [C₂₀H₂₂O₂Cl₃I]⁺ calculates to be 399.0680]; [α]_D²⁰: -39.9° (c=1.00, CHCl₃);



37 (major)



37 (minor)

(R)-2,2,2-trifluoroethyl 2-((R,2E,6E,10E)-cyclododeca-2,6,10-trien-1-yl)-2-(4-iodophenyl)acetate 37 (major) & (R)-2,2,2-trifluoroethyl 2-((S,2E,6E,10E)-cyclododeca-2,6,10-trien-1-yl)-2-(4-iodophenyl)acetate 37 (minor): Derived from the reaction of diazo

IV (0.3 mmol, 111 mg) and Triene **36** (0.75 mmol, 122 mg) following general procedure, purified by column chromatography (2% Et₂O in pentane). Product: 118 mg (combined for **37 (major)** and **37 (minor)**), 78% yield; dr = 1:0.86 [**37 (major)**:**37 (minor)**]; 92% ee. for **37 (major)**, 96% ee. for **37 (minor)**; white solid. The 2 diastereomers were fully separated and characterized using prep HPLC. (Single crystal structure obtained for **37 (major)**.)

37(major):

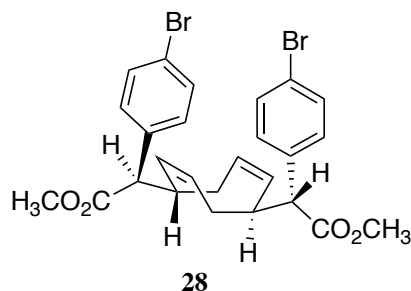
¹H NMR (600 MHz, CDCl₃) δ 7.69 – 7.58 (m, 2H), 7.03 – 6.98 (m, 2H), 5.08 – 4.91 (m, 4H), 4.88 (ddd, *J* = 14.7, 10.6, 3.9 Hz, 1H), 4.59 (ddd, *J* = 15.0, 9.9, 1.4 Hz, 1H), 4.52 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH₂ next to CF₃**), 4.35 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH₂ next to CF₃**), 3.47 (d, *J* = 9.8 Hz, 1H), 2.72 (qd, *J* = 10.0, 2.7 Hz, 1H), 2.25 – 2.17 (m, 3H), 2.18 – 2.12 (m, 1H), 2.05 – 2.00 (m, 1H), 1.90 – 1.82 (m, 2H), 1.82 – 1.74 (m, 2H), 1.67 (tdd, *J* = 13.2, 10.8, 2.9 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 171.54, 137.42, 136.24, 134.08, 132.30, 131.25, 130.89, 130.71, 129.60, 122.83 (q, *J* = 277.5 Hz, **C of CF₃**), 93.08, 65.86, 60.44 (q, *J* = 36.6 Hz, **C of CH₂ next to CF₃**), 56.15, 46.75, 37.32, 32.19, 32.14, 32.12, 31.92, 29.71, 15.28. IR: 2971, 2929, 2913, 2847, 1748, 1485, 1445, 1433, 1410, 1347, 1277, 1146, 1132, 1007, 981 (cm⁻¹); HRMS-(APCI) *m/z*: found at 505.0846 [(*M*+*H*)⁺ : [C₂₂H₂₅O₂F₃I]⁺ calculates to be 505.0846]; [α]_D²⁰: -175.5° (c=1.00, CHCl₃); m.p. 126-131°C

37 (minor):

¹H NMR (600 MHz, CDCl₃) δ 7.71 – 7.63 (m, 2H), 7.16 – 7.09 (m, 2H), 5.17 (ddd, *J* = 14.3, 10.0, 3.9 Hz, 1H), 5.05 – 4.94 (m, 3H), 4.93 – 4.84 (m, 2H), 4.44 (dq, *J* = 12.7, 8.5 Hz, 1H, **H of CH₂ next to CF₃**), 4.27 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH₂ next to CF₃**), 3.41 (d, *J* = 10.8 Hz, 1H), 2.63 (qd, *J* = 11.1, 3.0 Hz, 1H), 2.26 – 2.12 (m, 4H), 1.92 – 1.78 (m, 5H), 1.57 – 1.48 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 171.12, 137.81, 136.02, 133.64, 132.41, 131.80, 131.40, 131.18, 130.60, 130.60, 129.40, 122.87 (q, *J* = 277.4 Hz, **C of CF₃**), 93.38, 65.86, 60.39 (q, *J* = 36.6 Hz, **C of CH₂ next to CF₃**), 56.70, 47.21, 35.84, 32.22, 32.19, 32.13, 31.96, 29.71, 15.28; IR: 2912, 2844, 1753, 1485, 1436, 1404, 1279, 1168, 1128, 1063, 1007, 978, 958 (cm⁻¹); HRMS-(APCI) *m/z*: found at 505.0846 [(*M*+*H*)⁺ : [C₂₂H₂₅O₂F₃I]⁺ calculates to be 505.0846]; [α]_D²⁰: +103.2° (c=1.00, CHCl₃); m.p. 85-87°C

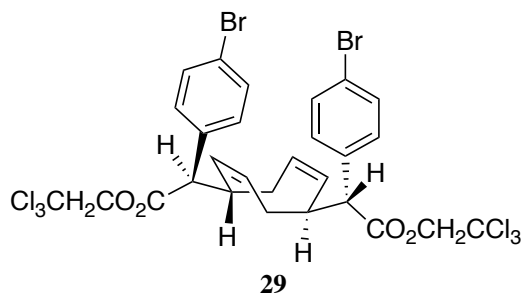
General Procedure for bis-allylic-insertion

To a 16 ml glass reaction vial was added stir bar, 1,5-cyclooctadiene (COD) (0.3 mmol, 1.0 equiv, 32 mg) and $\text{Rh}_2(2\text{-Cl},5\text{-BrTPCP})_4$ (0.1 mol%). The vial was degassed and filled with Ar for several times. 2mL anhydrous DCM was then added to the vial and the solution was kept stirring at 40 °C for 5min. Aryl diazo ester (0.9 mmol, 3.0 equiv) was dissolved in 4ml DCM and added dropwisely to the vial over 3 h via syringe pump. The reaction was kept running for 2 h after the addition of diazo compound is finished. The solution was concentrated to give oil crude, ^1H NMR was obtained for dr analysis. Further purification was done by column chromatography (2-4% Et_2O in pentane) or 5% AgNO_3 on silica column chromatography (4-10% Et_2O in pentane), giving product as sticky oil or white solid.



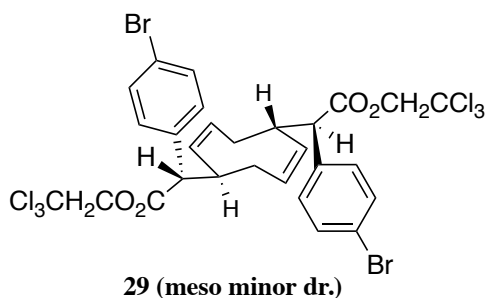
dimethyl 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)(2R,2'R)-bis(2-(4-bromophenyl)acetate) 28: Derived from the reaction of diazo **II** (0.9 mmol, 230 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by normal column chromatography (6-8% Et_2O in pentane). Product: 141 mg, 84% yield; >99% ee.; dr = 6.5:1, white foam solid.

^1H NMR (600 MHz, CDCl_3) δ 7.44 (d, J = 8.5 Hz, 4H), 7.20 (d, J = 8.5 Hz, 4H), 5.44 (ddd, J = 11.6, 7.9, 6.0 Hz, 2H), 5.04 (dd, J = 11.6, 6.6 Hz, 2H), 3.67 (s, 6H), 3.41-3.35 (m, 2H), 3.37 (d, J = 2.8 Hz, 2H), 2.28 – 2.11 (m, 4H). ^{13}C NMR (151 MHz, CDCl_3) δ 173.25, 136.21, 131.62, 130.44, 130.38, 128.37, 121.50, 57.37, 52.15, 42.03, 32.66. IR: 2950, 1734, 1590, 1488, 1434, 1407, 1339, 1264, 1156, 1073, 1011, 908, 819 (cm^{-1}); HRMS-(APCI) m/z : found at 561.0275 $[(\text{M}+\text{H})^+ : [\text{C}_{26}\text{H}_{27}\text{O}_4\text{Br}_2]^+ \text{ calculates to be } 561.0271]$; $[\alpha]^{20}_{\text{D}}$: -55.8° ($c=1.00$, CHCl_3); m.p. 66-70 °C



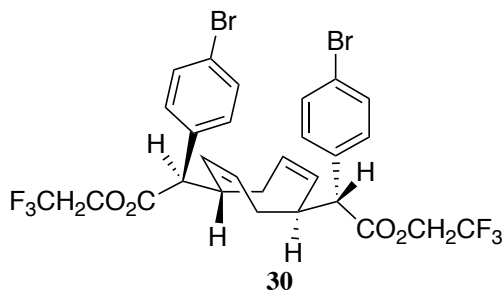
(2R,2'R)-bis(2,2,2-trichloroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)acetate) 29: Derived from the reaction of diazo **1** (0.9 mmol, 335 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by normal column chromatography (2% Et₂O in pentane). Product: 152 mg, 55% yield; >99% ee.; dr = 3.2:1, white foam solid. A larger scale of reaction at COD (0.8 mmol, 86 mg) and diazo **3** (2.4 mmol, 3.0 equiv, 893 mg) was performed, given 340 mg product, 53% yield, >99% ee. dr = 3.2:1.

¹H NMR (600 MHz, CDCl₃) δ 7.51 – 7.41 (m, 4H), 7.26 – 7.23 (m, 4H), 5.51 – 5.41 (m, 2H), 5.04 (dd, *J* = 11.3, 7.9 Hz, 2H), 4.76 (d, *J* = 12.0 Hz, 2H, **H of CH₂ next to CCl₃**), 4.68 (d, *J* = 12.0 Hz, 2H, **H of CH₂ next to CCl₃**), 3.67 (qd, *J* = 10.1, 8.0, 5.4 Hz, 2H), 3.47 (d, *J* = 10.2 Hz, 2H), 2.47 – 2.36 (m, 2H), 2.14 (ddd, *J* = 15.9, 12.5, 8.0 Hz, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 170.81, 135.21, 131.79, 130.58, 129.95, 128.56, 121.94, 94.66, 74.30, 57.71, 41.11, 33.38. IR: 2924, 1750, 1489, 1408, 1371, 1262, 1216, 1136, 1074, 1012, 826, 762, 719 (cm⁻¹); HRMS-(APCI) *m/z*: found at 792.8262 [(M+H)⁺ : [C₂₈H₂₅O₄Br₂Cl₆]⁺ calculates to be 792.8245]; [α]_D²⁰: +21.8° (c=1.00, CHCl₃); m.p. 48-52 °C



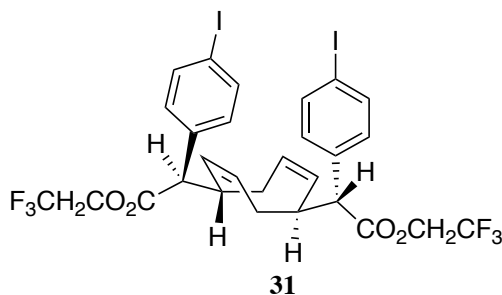
(2R,2'S)-bis(2,2,2-trichloroethyl) 2,2'-((1R,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)acetate) 29 (meso minor dr): Originally isolated from the reaction that give **29**. Larger preparation is derived from mono insertion product **17** (0.4 mmol, 181 mg, 1.0 equiv) and diazo **1** (0.8 mmol, 298 mg, 2.0 equiv) following general procedure using the different enantiomer of catalyst. Purify this meso product with column chromatography (2% Et₂O in pentane). Product: 168 mg, 53% yield, white foam solid.

¹H NMR (600 MHz, CDCl₃) δ 7.48 – 7.43 (m, 4H), 7.26 – 7.22 (m, 4H), 5.57 (dtd, *J* = 10.7, 8.8, 1.8 Hz, 2H), 5.15 (dd, *J* = 11.7, 4.3 Hz, 2H), 4.79 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 3.62 (d, *J* = 10.8 Hz, 2H), 3.24 – 3.15 (m, 2H), 2.53 (ddd, *J* = 13.9, 9.1, 4.7 Hz, 2H), 2.46 – 2.35 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 171.10, 135.26, 131.81, 130.89, 130.64, 127.33, 121.97, 94.63, 74.21, 56.04, 43.21, 30.23. IR: 2952, 2874, 1748, 1488, 1447, 1408, 1371, 1331, 1269, 1206, 1130, 1074, 1011 (cm⁻¹); HRMS-(APCI) *m/z*: found at 792.8262 [(M+H)⁺ : [C₂₈H₂₅O₄Br₂Cl₆]⁺ calculates to be 792.8245]; m.p. 50-55 °C



(2R,2'R)-bis(2,2,2-trifluoroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)acetate) 30: Derived from the reaction of diazo **III** (0.9 mmol, 290 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by AgNO₃ column chromatography (4-8% Et₂O in pentane). Product: 160 mg, 76 % yield; >99% ee.; dr = 6.5:1, sticky oil to half solid.

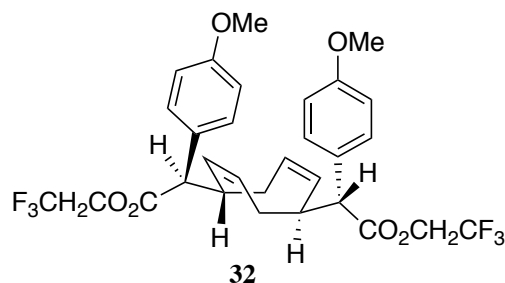
¹H NMR (500 MHz, CDCl₃) δ 7.53 – 7.42 (m, 4H), 7.24 – 7.14 (m, 4H), 5.46 (ddd, *J* = 12.6, 7.9, 5.3 Hz, 2H), 5.04 (dd, *J* = 11.5, 7.3 Hz, 2H), 4.50 (ddd, *J* = 13.1, 8.7, 4.5 Hz, 2H, **H of CH₂ next to CF₃**), 4.44 (ddd, *J* = 12.7, 8.7, 4.5 Hz, 2H, **H of CH₂ next to CF₃**), 3.58 – 3.47 (m, 3H), 3.46 (d, *J* = 10.0 Hz, 2H), 2.25 (dt, *J* = 15.4, 4.6 Hz, 2H), 2.14 (ddd, *J* = 15.5, 12.0, 8.2 Hz, 2H). ¹³C NMR (126 MHz, cdcl₃) δ 171.02, 134.97, 131.80, 130.36, 129.80, 128.54, 122.79 (q, *J* = 277.7 Hz, **C of CF₃**), 121.97, 60.54 (q, *J* = 36.6 Hz, **C of CH₂ next to CF₃**), 56.96, 41.60, 32.68. IR: 3017, 1753, 1489, 1408, 1282, 1168, 1138, 1074, 1012, 978, 817, 760, 644 (cm⁻¹); HRMS-(APCI) *m/z*: found at 694.9880 [(M-H)⁻ : [C₂₈H₂₃O₄Br₂F₆]⁺ calculates to be 694.9873]; [α]_D²⁰: -10.2° (c=1.00, CHCl₃);



(2R,2'R)-bis(2,2,2-trifluoroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-iodophenyl)acetate) 31: Derived from the reaction of diazo **IV** (0.9 mmol, 333 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by AgNO₃ column chromatography (4-8% Et₂O in pentane). Product: 156 mg, 66 % yield; >99% ee.; dr = 6.8:1, white solid.

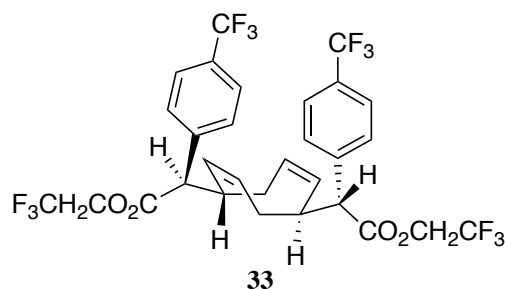
¹H NMR (600 MHz, CDCl₃) δ 7.68 – 7.64 (m, 4H), 7.08 – 7.05 (m, 4H), 5.46 (ddd, *J* = 12.4, 7.8, 5.4 Hz, 2H), 5.04 (dd, *J* = 11.5, 7.4 Hz, 2H), 4.50 (dq, *J* = 12.7, 8.4 Hz, 2H, **H of CH₂ next to CF₃**), 4.43 (dq, *J* = 12.7, 8.4 Hz, 2H, **H of CH₂ next to CF₃**), 3.55 – 3.47 (m, 2H), 3.44 (d, *J* = 10.0 Hz, 2H), 2.24 (dt, *J* = 15.3, 4.7 Hz, 2H), 2.14 (ddd, *J* = 15.6, 12.3, 8.2 Hz, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 171.02, 137.78, 135.66, 130.62, 129.83, 128.56, 122.81 (q, *J* = 277.7 Hz, **C of CF₃**), 93.61, 60.56 (q, *J* = 36.7 Hz, **C of CH₂ next to CF₃**), 57.08,

41.57, 32.67. IR: 3017, 1752, 1485, 1405, 1281, 1168, 1138, 1063, 1007, 978, 815, 757, 644 (cm^{-1}); HRMS-(APCI) m/z : found at 792.9745 $[(M+H)^+ : [C_{28}H_{25}O_4F_6I_2]^+]$ calculates to be 792.9741; $[\alpha]^{20}_D$: -7.1° ($c=1.00$, CHCl_3); m.p. 113-116 $^\circ\text{C}$;



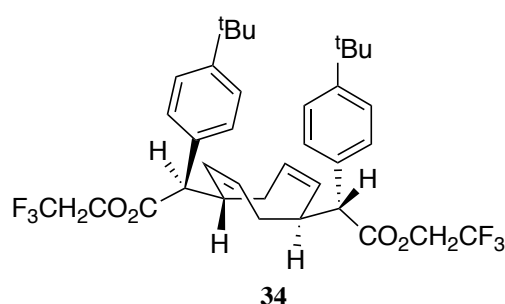
(2R,2'R)-bis(2,2,2-trifluoroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-methoxyphenyl)acetate) 32: Derived from the reaction of diazo **V** (0.9 mmol, 247 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by AgNO_3 column chromatography (4-8% Et_2O in pentane). Product: 96 mg, 53% yield; >99% ee.; dr = 4.2:1, white solid.

^1H NMR (600 MHz, CDCl_3) δ 7.26 – 7.23 (m, 4H), 6.90 – 6.83 (m, 4H), 5.45 (ddd, $J = 12.1, 7.7, 5.1$ Hz, 2H), 5.05 (dd, $J = 11.5, 7.6$ Hz, 2H), 4.49 (dq, $J = 12.7, 8.4$ Hz, 2H, **H of CH_2 next to CF_3**), 4.42 (dq, $J = 12.7, 8.4$ Hz, 2H, **H of CH_2 next to CF_3**), 3.80 (s, 6H), 3.63 – 3.52 (m, 2H), 3.44 (d, $J = 10.3$ Hz, 2H), 2.31 (dt, $J = 15.4, 4.5$ Hz, 2H), 2.19 (ddd, $J = 15.7, 12.3, 8.1$ Hz, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ 171.78, 159.17, 130.32, 129.69, 128.18, 122.92 (q, $J=277.7$ Hz, **C of CF_3**), 114.06, 60.39 (q, $J=36.6$ Hz, **C of CH_2 next to CF_3**), 56.94, 55.21, 41.56, 32.93. IR: 2962, 2839, 1750, 1610, 1511, 1464, 1408, 1283, 1249, 1164, 1133, 1034, 977 (cm^{-1}); HRMS-(APCI) m/z : found at 601.2021 $[(M+H)^+ : [C_{30}H_{31}O_6F_6]^+]$ calculates to be 601.2029; $[\alpha]^{20}_D$: -17.2° ($c=1.00$, CHCl_3); m.p. 89-93 $^\circ\text{C}$



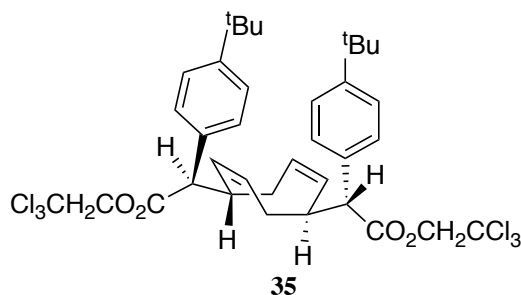
(2R,2'R)-bis(2,2,2-trifluoroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-(trifluoromethyl)phenyl)acetate) 33: Derived from the reaction of diazo **VI** (0.9 mmol, 281 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by AgNO_3 column chromatography (3-6% Et_2O in pentane). Product: 123 mg, 61 % yield; >99 % ee.; dr = 7.9:1, white solid.

^1H NMR (600 MHz, CDCl_3) δ 7.59 (d, J = 8.1 Hz, 4H), 7.45 (d, J = 8.1 Hz, 4H), 5.49 (ddd, J = 11.7, 8.0, 5.5 Hz, 2H), 5.06 (dd, J = 11.5, 7.0 Hz, 2H), 4.52 (dq, J = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 4.44 (dq, J = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 3.59 (d, J = 9.7 Hz, 2H), 3.58 – 3.50 (m, 3H), 2.25 (dt, J = 14.4, 4.3 Hz, 2H), 2.16 (ddd, J = 15.1, 11.6, 8.4 Hz, 2H). ^{13}C NMR (126 MHz, cdcl_3) δ 170.77, 139.84, 130.13 (q, J = 32.5 Hz, **C on Ar ring next to CF_3**), 129.61, 129.14, 128.70, 125.57 (q, J = 3.6 Hz, **C on Ar ring next to the 130.13 C**), 123.97 (q, J = 272.3 Hz, **C of CF_3 on the Ar ring**), 122.74 (q, J = 277.4 Hz, **C of CF_3 in the ester**), 60.60 (q, J = 36.7 Hz, **C of CH_2 next to CF_3 in ester**), 57.22, 41.75, 32.52. IR: 3021, 1754, 1619, 1422, 1325, 1285, 1163, 1127, 1069, 1020, 979, 827, 723 (cm^{-1}); HRMS-(APCI) m/z : found at 677.1551 $[(\text{M}+\text{H})^+ : [\text{C}_{30}\text{H}_{25}\text{O}_4\text{F}_{12}]^+]$ calculates to be 677.1556; $[\alpha]^{20}_{\text{D}}$: -35.8° (c = 1.00, CHCl_3); m.p. 96-101 $^\circ\text{C}$



(2R,2'R)-bis(2,2,2-trifluoroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-(tert-butyl)phenyl)acetate) 34: Derived from the reaction of diazo **VII** (0.9 mmol, 270 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by AgNO_3 column chromatography (2-6% Et_2O in pentane). Product: 150 mg, 76 % yield; >99 % ee.; dr = 6.8:1, sticky oil to half solid.

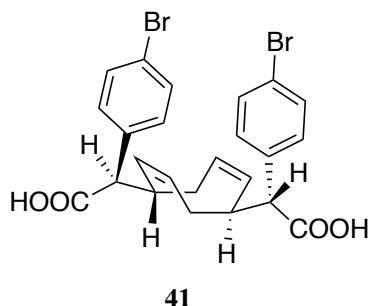
^1H NMR (600 MHz, CDCl_3) δ 7.35 – 7.29 (m, 4H), 7.25 – 7.22 (m, 4H), 5.45 (ddd, J = 12.6, 7.6, 5.7 Hz, 2H), 5.07 (dd, J = 11.6, 7.2 Hz, 2H), 4.51 (dq, J = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 4.37 (dq, J = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 3.53 (m, 2H), 3.48 (d, J = 10.2 Hz, 2H), 2.33 – 2.19 (m, 4H), 1.30 (s, 18H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.75, 150.59, 132.91, 130.36, 128.24, 128.08, 125.53, 122.90 (q, J = 277.6 Hz, **C of CF_3**), 60.36 (q, J = 36.5 Hz, **C of CH_2 next to CF_3**), 57.18, 41.59, 34.47, 32.56. IR: 2965, 1753, 1509, 1408, 1365, 1283, 1167, 1134, 1065, 1019, 978, 842, 823 (cm^{-1}); HRMS-(APCI) m/z : found at 653.3066 $[(\text{M}+\text{H})^+ : [\text{C}_{36}\text{H}_{43}\text{O}_4\text{F}_6]^+]$ calculates to be 653.3060; $[\alpha]^{20}_{\text{D}}$: -31.0° (c = 1.00, CHCl_3);



(2R,2'R)-bis(2,2,2-trichloroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-(tert-butyl)phenyl)acetate) 35: Derived from the reaction of diazo **XII** (0.9 mmol, 315 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by normal column chromatography (4-8% Et₂O in pentane). Product: 231 mg, 72 % yield; >99 % ee.; dr = 4.5:1, white foam solid. (Single crystal structure obtained for the reduction product of this compound.)

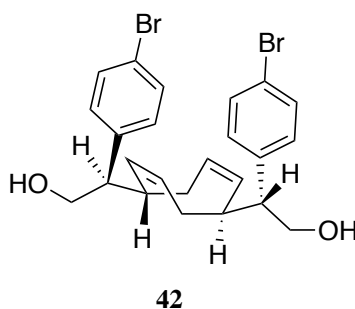
¹H NMR (600 MHz, CDCl₃) δ 7.36 – 7.27 (m, 9H), 5.46 (ddd, *J* = 11.9, 7.2, 4.9 Hz, 2H), 5.08 (dd, *J* = 11.6, 7.5 Hz, 2H), 4.73 (d, *J* = 12.0 Hz, 3H, **H of CH₂ next to CCl₃**), 4.69 (d, *J* = 12.0 Hz, 3H, **H of CH₂ next to CCl₃**), 3.78 – 3.68 (m, 2H), 3.50 (d, *J* = 10.5 Hz, 2H), 2.52 – 2.44 (m, 2H), 2.22 (ddd, *J* = 15.8, 12.2, 7.9 Hz, 2H), 1.31 (s, 18H). ¹³C NMR (151 MHz, CDCl₃) δ 171.56, 150.60, 133.19, 130.53, 128.47, 128.12, 125.53, 94.82, 74.25, 58.00, 41.03, 34.51, 33.43, 31.32. IR: 2963, 1749, 1516, 1461, 1366, 1269, 1200, 1131, 1058, 915, 827, 771, 721 (cm⁻¹); HRMS-(APCI) *m/z*: found at 749.1296 [(M+H)⁺ : [C₃₆H₄₃O₄Cl₆]⁺ calculates to be 749.1287]; [α]_D²⁰: +10.2° (c=1.00, CHCl₃); m.p. 72-77 °C

Derivatization for Bis-insertion C2 symmetric chiral COD ligand



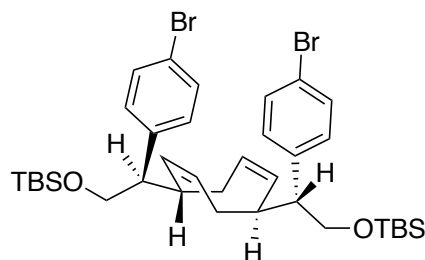
(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)acetic acid) 41: Bis-insertion compound **29** (0.053 mmol, 41.9 mg, 1.0 equiv.) was dissolved in 1 mL AcOH. Zn powder (34.4 mg, 10 equiv.) was added to the solution, and the suspension was kept stirring overnight. Crude material was obtained by filtration and concentration under reduced pressure. Further column chromatography (50% Et₂O in pentane with 0.5% AcOH) gave pure product as white powder 17.2 mg, 61% yield.

¹H NMR (600 MHz, CDCl₃) δ 7.46 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 8.6 Hz, 4H), 5.58 – 5.37 (m, 2H), 5.18 – 4.99 (m, 2H), 3.44 (d, *J* = 9.5 Hz, 2H), 3.40 – 3.25 (m, 2H), 2.49 – 2.31 (m, 2H), 2.32 – 2.21 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 178.89, 135.49, 131.75, 130.45, 130.30, 128.50, 121.83, 57.01, 42.16, 31.86, 20.58. IR: 2921, 2851, 1725, 1488, 1409, 1263, 1098, 1012, 800, 730 (cm⁻¹); HRMS-(APCI) *m/z*: found at 530.9817 [(M-H)⁻ : [C₂₄H₂₁O₄Br₂]⁻ calculates to be 530.9812]; [α]_D²⁰: -14.0° (c=1.00, acetone); m.p. > 200 °C



(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)ethan-1-ol) 42: Bis-insertion compound **29** (0.065 mmol, 51.9 mg, 1.0 equiv.) was dissolved in 1 mL anhydrous THF, and the solution was cooled to -78 °C. LiAlH₄ (1.0 M THF solution) (0.18 mL, 2.5 equiv.) was slowly added to the stirring solution. The reaction was kept running for 2 h at -78 °C, then raised to r.t. for 15 min and quenched with 1 mL sodium potassium tartrate solution (saturated) and 1.0 mL HCl (1.0 M). The organic phase was extracted with Et₂O multiple times, combined and dried over MgSO₄. Crude material was obtained through filtration and concentration under reduced pressure. Further column chromatography (60% Et₂O in pentane) gave pure product 27.5 mg as white powder, 84% yield.

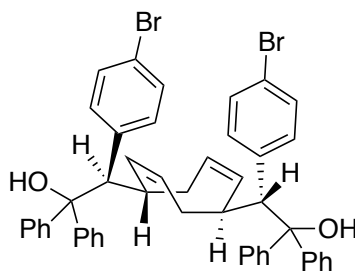
^1H NMR (600 MHz, CDCl_3) δ 7.40 (d, J = 8.5 Hz, 4H), 6.94 (d, J = 8.4 Hz, 4H), 5.54 (ddd, J = 11.4, 9.0, 7.4 Hz, 2H), 5.32 (dd, J = 11.4, 6.3 Hz, 2H), 3.83 (dq, J = 7.5, 4.1, 3.5 Hz, 4H), 2.73 (dp, J = 11.8, 5.7 Hz, 4H), 1.72 (ddd, J = 12.2, 7.1, 4.9 Hz, 2H), 1.64 (dt, J = 13.2, 6.8 Hz, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ 138.44, 131.18, 130.69, 129.52, 129.48, 120.73, 64.44, 53.00, 41.08, 31.63. IR: 3342 (broad OH), 3006, 2930, 2874, 1488, 1408, 1105, 1073, 1027, 1007, 819, 754 (cm^{-1}); HRMS-(APCI) m/z : found at 505.0376 $[(\text{M}+\text{H})^+]$: $[\text{C}_{24}\text{H}_{27}\text{O}_2\text{Br}_2]^+$ calculates to be 505.0372; $[\alpha]^{20}_{\text{D}}$: -129.2° (c =1.00, CHCl_3); m.p. 69-73 °C



43

(1Z,3S,5Z,7S)-3,7-bis((R)-1-(4-bromophenyl)-2-((tert-butyldimethylsilyl)oxy)ethyl)cycloocta-1,5-diene 43: The di-ol starting material **42** (0.063 mmol, 31.7 mg, 1.0 equiv.) was dissolved in 1 mL DCM, and the solution was cooled to 0 °C. Imidazole (0.158 mmol, 10.8 mg, 2.5 equiv.) and TBSCl (0.139 mmol, 21.0 mg, 2.2 equiv.) was added to the solution, and the solution was kept stirring overnight. Crude material was obtained by filtration and concentration under reduced pressure. Further column chromatography gave pure product as white solid. 42.0 mg, 90% yield.

^1H NMR (600 MHz, CDCl_3) δ 7.33 (d, J = 8.4 Hz, 4H), 6.92 (d, J = 8.4 Hz, 4H), 5.54 (ddd, J = 11.3, 8.7, 7.0 Hz, 2H), 5.32 (dd, J = 11.4, 7.1 Hz, 2H), 3.76 (dd, J = 10.0, 7.2 Hz, 2H), 3.70 (dd, J = 10.0, 6.0 Hz, 2H), 2.93 (dq, J = 12.6, 6.2 Hz, 2H), 2.59 (q, J = 6.4 Hz, 2H), 1.79 (dt, J = 12.2, 6.0 Hz, 2H), 1.61 (td, J = 14.0, 9.2 Hz, 2H), 0.84 (s, 18H), -0.03 (s, 6H), -0.04 (s, 6H). ^{13}C NMR (151 MHz, CDCl_3) δ 139.82, 130.72, 130.67, 129.92, 129.47, 120.14, 64.52, 52.96, 39.99, 32.09, 25.86, 18.21, 0.00, -5.50. IR: 3008, 2953, 2928, 2885, 2856, 1488, 1471, 1408, 1361, 1254, 1097, 1074, 1010 (cm^{-1}); HRMS-(APCI) m/z : found at 733.2095 $[(\text{M}+\text{H})^+]$: $[\text{C}_{36}\text{H}_{55}\text{O}_2\text{Br}_2\text{Si}_2]^+$ calculates to be 733.2102; $[\alpha]^{20}_{\text{D}}$: -109.0° (c =1.00, CHCl_3); m.p. 67-69 °C

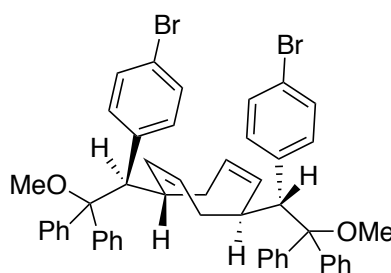


44

(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)-1,1-diphenylethan-1-ol) 44: The bis-insertion compound **28** (0.756 mmol, 380 mg, 1.0 equiv)

was dissolved in 4 mL anhydrous THF. The solution was kept stirring under Ar at -78 °C. PhLi (1.9 M purchased from Sigma Aldrich) in THF 2.6 mL was slowly added to the stirring solution over 30 min. The reaction was maintained at -78 °C for 3 h. After that, the solution was diluted with 4 mL Et₂O and quenched with HCl (1.0 M). The organic layer was extracted 3 times with Et₂O (1 mL), combined and dried over MgSO₄. Flash cotton pipette (a layer of silica) plug and concentration under reduced pressure gave crude sticky oil. Flash column chromatography (15% Et₂O/pentane) for the crude to remove nonpolar impurity and gave greenish yellow solid. Pure product was further obtained through recrystallization with ether/pentane system (40 °C cool to 0 °C) as white solid, 275mg, 50% yield.

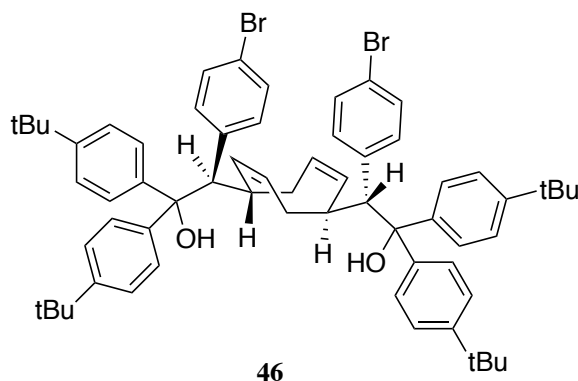
¹H NMR (600 MHz, CDCl₃) δ 7.55 (dd, *J* = 8.4, 1.1 Hz, 4H), 7.33 (t, *J* = 7.8 Hz, 4H), 7.24 – 7.19 (m, 6H), 7.18 – 7.14 (m, 4H), 7.11 – 6.99 (m, 8H), 6.93 (t, *J* = 7.3 Hz, 2H), 5.48 (dd, *J* = 11.3, 7.2 Hz, 2H), 5.45 – 5.36 (m, 2H), 3.58 (d, *J* = 3.3 Hz, 2H), 2.67 (s, 2H), 2.66 – 2.54 (m, 2H), 1.46 – 1.32 (m, 4H). ¹³C NMR (151 MHz, CDCl₃) δ 146.72, 146.05, 136.94, 133.10, 130.23, 130.04, 129.81, 128.54, 127.76, 126.76, 126.11, 125.42, 125.11, 120.34, 81.42, 58.20, 40.19, 33.32. IR: 3586(Broad), 3057, 3021, 2974, 2868, 1597, 1488, 1447, 1157, 1112, 1075, 1068, 1010 (cm⁻¹); HRMS-(ESI) *m/z*: found at 843.1261 [(M+Cl)⁻ : [C₄₈H₄₂O₂Br₂Cl]⁻ calculates to be 843.1246]; [α]_D²⁰: -94.3° (c=1.00, CHCl₃); m.p. > 200 °C



45

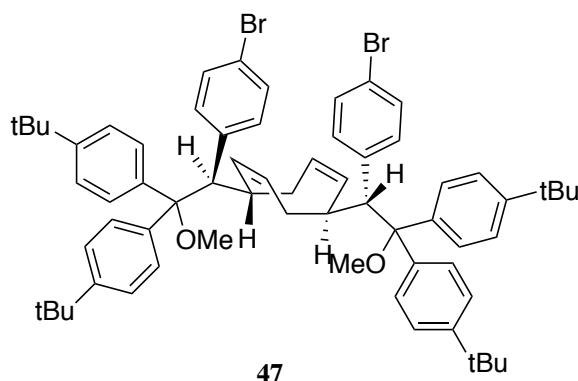
(1Z,3S,5Z,7S)-3,7-bis((R)-1-(4-bromophenyl)-2-methoxy-2,2-diphenylethyl)cycloocta-1,5-diene 45: The di-ol starting material **44** (59.7 mg, 0.074 mmol, 1 equiv) was dissolved in 1.5 mL anhydrous DCM. NaH (17.8 mg, 60% wt in mineral oil, 0.74 mmol, 10 equiv) was added into the solution, and the suspension was kept stirring at 0 °C. CH₃I (52.5 mg, 0.37 mmol, 5 equiv) was then added to the solution. The reaction was let warm up to r.t. naturally and run overnight. After that, the reaction was quenched with NH₄Cl(saturated) and extracted with Et₂O multiple times. The organic layer was combined and dried over MgSO₄. Crude material was obtained through filtration and concentration under reduced pressure. Further column chromatography gave pure product as white solid 50.8 mg, 82% yield.

¹H NMR (600 MHz, CDCl₃) δ 7.27 (s, 10H), 7.24 (d, *J* = 8.6 Hz, 4H), 7.22 – 7.11 (m, 10H), 6.80 (d, *J* = 7.8 Hz, 4H), 5.09 – 4.97 (m, *J* = 7.9 Hz, 4H), 3.32 (d, *J* = 4.1 Hz, 2H), 2.78 (s, 6H), 2.64 – 2.44 (m, 2H), 1.37 – 1.29 (m, 2H), 1.18 (td, *J* = 13.8, 7.6 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 141.29, 137.95, 133.89, 130.74, 129.57, 128.95, 127.97, 127.48, 127.38, 127.35, 127.16, 120.08, 87.29, 60.76, 52.53, 40.52, 34.10, 29.70. IR: 3021, 2929, 2826, 1488, 1446, 1407, 1193, 1074, 1010, 828, 756, 729, 702 (cm⁻¹); HRMS-(APCI) *m/z*: found at 871.1572 [(M+Cl)⁻ : [C₅₀H₄₆O₂Br₂Cl]⁻ calculates to be 871.1559]; [α]_D²⁰: -75.7° (c=1.00, CHCl₃); m.p. 91-96 °C



(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)-1,1-bis(4-(tert-butyl)phenyl)ethan-1-ol) 46: The bis-insertion compound **28** (0.1 mmol, 56.0 mg, 1.0 equiv.) was dissolved in 1 mL anhydrous THF, and the solution was cooled to -78 °C. ^tBuPhLi solution (prepared from Li and 4-^tBuPhBr, 0.94 M) (0.6 mL, 5.5 equiv.) was added to the stirring solution, and the reaction was let run for 2 h at -78 °C. After that, the reaction was quenched with NH₄Cl (saturated) 1 mL, HCl (1.0 M) 1 mL and extracted with Et₂O multiple times. The organic phase was combined, dried over MgSO₄, filtered and concentrated to obtain crude material. Further column purification (5-8% Et₂O in pentane) gave pure product as white powder 43.5 mg, 42% yield.

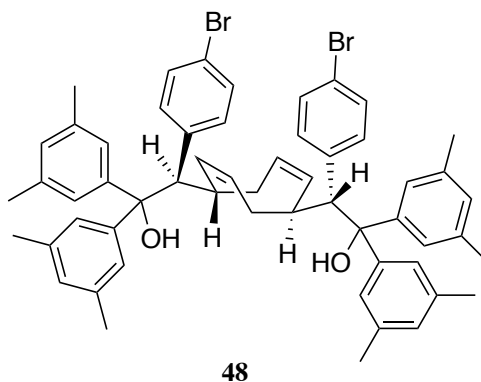
¹H NMR (600 MHz, CDCl₃) δ 7.44 (d, *J* = 8.6 Hz, 4H), 7.32 (d, *J* = 8.5 Hz, 4H), 7.16 (d, *J* = 8.7 Hz, 4H), 7.11 (d, *J* = 8.8 Hz, 4H), 7.03 (d, *J* = 8.8 Hz, 8H), 5.52 (dd, *J* = 11.3, 7.2 Hz, 2H), 5.46 – 5.35 (m, 2H), 3.51 (d, *J* = 3.3 Hz, 2H), 2.67 (s, 2H), 2.56-2.60 (m, 2H), 1.36 – 1.31 (m, 4H), 1.30 (s, 18H), 1.15 (s, 18H). ¹³C NMR (151 MHz, CDCl₃) δ 149.24, 148.64, 143.59, 143.29, 137.25, 133.14, 130.06, 129.71, 125.25, 125.12, 124.81, 124.57, 120.13, 81.20, 58.51, 40.33, 34.35, 34.12, 33.20, 31.35, 31.17. IR: 3580, 2962, 2867, 1509, 1487, 1404, 1363, 1269, 1109, 1076, 1010, 909, 839 (cm⁻¹); HRMS-(APCI) *m/z*: found at 1050.4424 [(M+NH₄)⁺ : [C₆₄H₇₈O₂NBr₂]⁺ calculates to be 1050.4394]; [α]_D²⁰: -98.5° (c=1.00, CHCl₃); m.p. > 200 °C



(1Z,3S,5Z,7S)-3,7-bis((R)-1-(4-bromophenyl)-2,2-bis(4-(tert-butyl)phenyl)-2-methoxyethyl)cycloocta-1,5-diene 47: The di-ol starting material **46** (37.9 mg, 0.037 mmol, 1 equiv) was dissolved in 1.5 mL anhydrous DCM. NaH (15 mg, 60% wt in mineral oil, 0.37 mmol, 10 equiv) was added into the solution, and the reaction was kept stirring at 0 °C. CH₃I (20.8 mg, 0.148 mmol, 4 equiv) was then added to the solution and the reaction

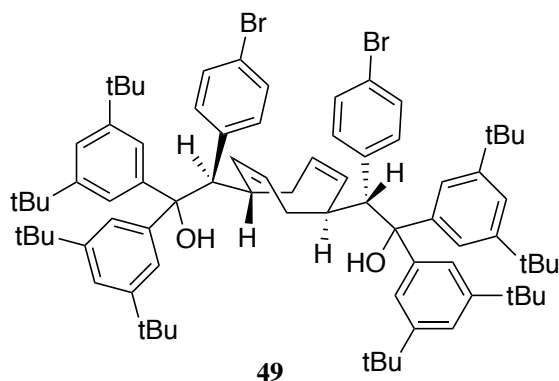
was let warm up to r.t. overnight. After that, the reaction was quenched with NH_4Cl (saturated) 1 mL and extracted with Et_2O multiple times. The organic layer was combined and dried over MgSO_4 , filtered and concentrated to yield crude material. Further column chromatography purification gave pure product 33.2 mg, 90% yield.

^1H NMR (600 MHz, CDCl_3) δ 7.28 (d, J = 8.7 Hz, 4H), 7.24 (dd, J = 8.8, 1.8 Hz, 9H), 7.09 (d, J = 8.8 Hz, 4H), 6.95 (d, J = 8.7 Hz, 8H), 5.12 (qd, J = 11.6, 7.0 Hz, 4H), 3.15 (d, J = 2.4 Hz, 2H), 2.82 (s, 6H), 2.29 – 2.19 (m, 2H), 1.30 (s, 18H), 1.24 (s, 18H), 1.11 – 0.95 (m, 4H). ^{13}C NMR (151 MHz, CDCl_3) δ 149.94, 149.56, 139.54, 138.40, 137.95, 134.15, 130.42, 129.68, 129.57, 128.41, 128.22, 124.35, 123.90, 119.99, 87.70, 60.93, 52.92, 41.22, 34.39, 34.30, 33.07, 31.37, 31.25. IR: 2962, 2903, 2868, 1508, 1486, 1403, 1363, 1271, 1110, 1083, 1011, 966, 833 (cm^{-1}); HRMS-(APCI) m/z : found at 1083.4276 $[(\text{M}+\text{Na})^+]$: $[\text{C}_{66}\text{H}_{78}\text{O}_2\text{Br}_2\text{Na}]^+$ calculates to be 1083.4261; $[\alpha]^{20}_{\text{D}}$: -132.7° (c =1.00, CHCl_3); m.p. 159-163 °C



(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)-1,1-bis(3,5-dimethylphenyl)ethan-1-ol) 48: Bis-insertion ester **28** (0.1 mmol, 56.0 mg, 1.0 equiv.) was dissolved in 1 mL anhydrous THF, and the solution was cooled to -78 °C. 3,5-diMePhLi solution (prepared from Li and 3,5-di-Methyl-4-Br-benzene, 0.73 M) (0.75 mL, 5.5 equiv.) was slowly added to the stirring solution, and the reaction was let run for 2 h at -78 °C. After that, the reaction was quenched with NH_4Cl (saturated) 1 mL, HCl (1.0 M) 1mL and extracted with Et_2O multiple times. The organic phase was combined, dried over MgSO_4 , and concentrated to give crude material. Further column purification (2-5% Et_2O in pentane) gave pure product as white solid 52.1 mg, 56% yield.

^1H NMR (600 MHz, CDCl_3) δ 7.16 (d, J = 8.7 Hz, 4H), 7.13 (s, 4H), 7.11 – 6.98 (m, 4H), 6.82 (d, J = 7.7 Hz, 6H), 6.56 (s, 2H), 5.51 (dd, J = 11.4, 7.1 Hz, 2H), 5.44 – 5.33 (m, 2H), 3.51 (d, J = 3.2 Hz, 2H), 2.54 – 2.49 (m, 2H), 2.50 (s, 2H), 2.29 (s, 12H), 2.10 (s, 12H), 1.38 – 1.27 (m, 4H). ^{13}C NMR (151 MHz, CDCl_3) δ 146.75, 146.21, 137.70, 137.40, 136.92, 133.13, 130.09, 130.03, 129.69, 128.33, 127.73, 123.38, 122.84, 120.11, 81.28, 58.39, 40.38, 33.36, 21.69, 21.45. IR: 3586, 2007, 2916, 1597, 1487, 1408, 1376, 1216, 1157, 1111, 1075, 1010, 843 (cm^{-1}); HRMS-(APCI) m/z : found at 920.2830 $[(\text{M})]$: $[\text{C}_{56}\text{H}_{58}\text{O}_2\text{Br}_2]$ calculates to be 920.2809; $[\alpha]^{20}_{\text{D}}$: -121.0° (c =1.00, CHCl_3); m.p. 140-144 °C

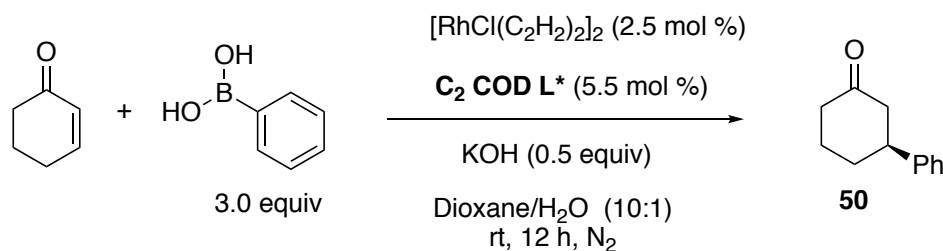


(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)-1,1-bis(3,5-di-tert-butylphenyl)ethan-1-ol) 49: Bis-insertion ester **28** (0.1 mmol, 56.0 mg, 1.0 equiv.) was dissolved in 1 mL anhydrous THF, and the solution was cooled to -78 °C. 3,5-ditBuPhLi solution (prepared from Li and 3,5-di-tBu-4-Br-benzene, 1.1 M) (0.5 mL, 5.5 equiv.) was slowly added to the stirring solution, and the reaction was let run for 4 h at -78 °C. After that, the reaction was quenched with NH₄Cl (saturated) 1 mL, HCl (1.0 M) 1mL. The organic phase was extracted with Et₂O multiple times, combined, dried over MgSO₄, and concentrated to give crude material. Further column purification (0-2% Et₂O in pentane) gave pure product as white solid 55.3 mg, 44% yield.

¹H NMR (600 MHz, CDCl₃) δ 7.42 (d, *J* = 1.7 Hz, 4H), 7.25 (t, *J* = 1.7 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 4H), 6.96 (dd, *J* = 13.7, 1.7 Hz, 10H), 5.46 (dd, *J* = 11.4, 6.7 Hz, 2H), 5.43 – 5.37 (m, 2H), 3.36 (d, *J* = 3.2 Hz, 2H), 2.60 – 2.53 (m, 2H), 2.55 (s, 2H), 1.44 – 1.32 (m, 4H), 1.30 (s, 36H), 1.09 (s, 36H). ¹³C NMR (151 MHz, CDCl₃) δ 150.17, 149.36, 145.00, 144.92, 137.31, 133.18, 130.16, 129.82, 129.59, 120.30, 120.23, 120.20, 120.02, 119.79, 82.28, 60.07, 40.76, 34.95, 34.70, 33.53, 31.55, 31.29. IR: 3609, 2962, 2904, 2866, 1598, 1487, 1477, 1393, 1362, 1248, 1109, 1076, 1011, 879 (cm⁻¹); HRMS-(APCI) *m/z*: found at 1279.6415 [(M+Na)⁺ : [C₈₀H₁₀₆O₂Br₂Na]⁺ calculates to be 1279.6452] [α]_D²⁰: -35.8° (c=1.00, CHCl₃); m.p. 128-131 °C

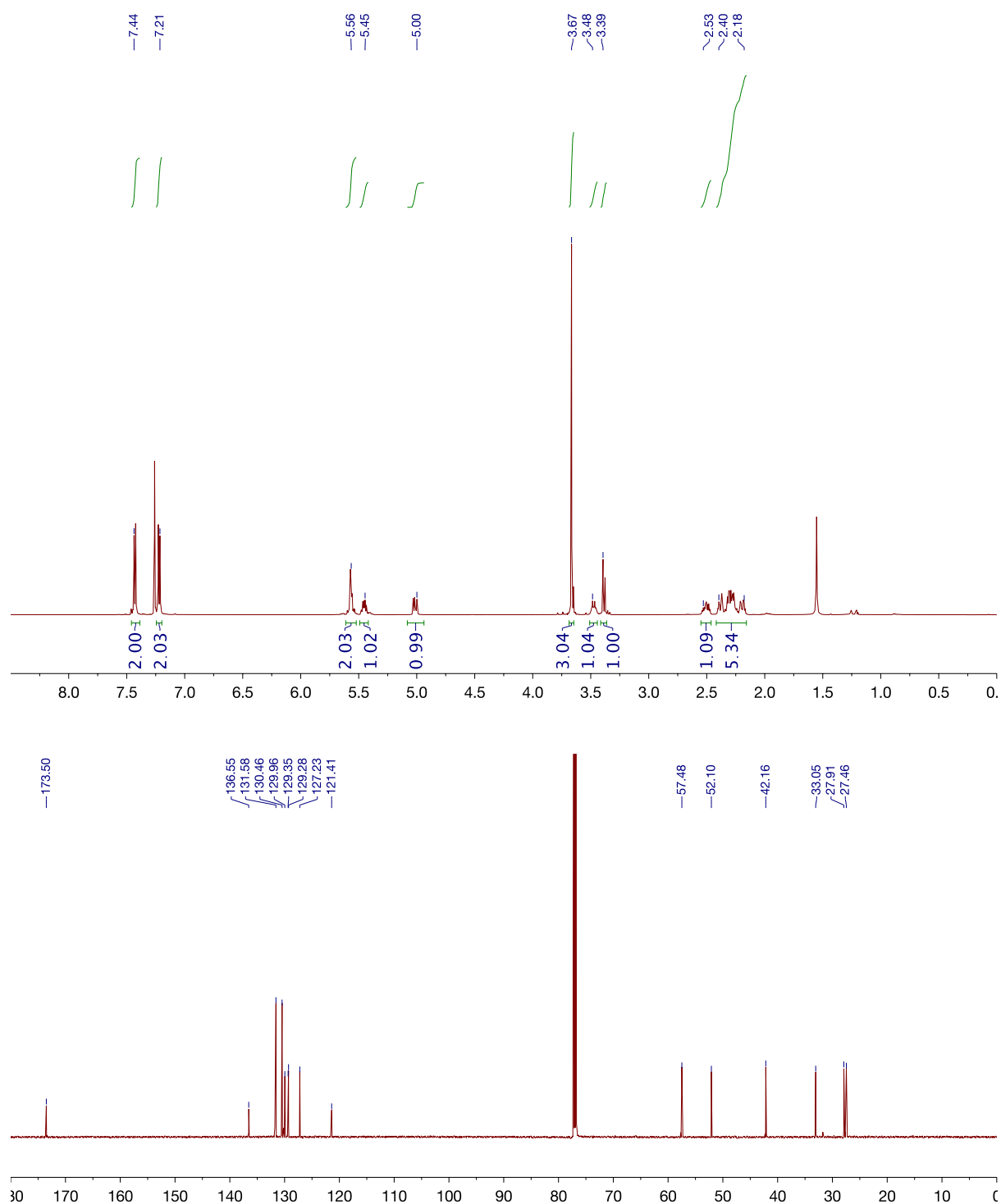
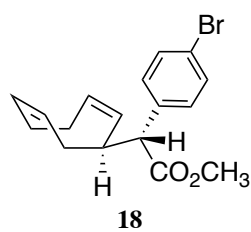
General Procedure for conjugate addition test (Arylation of cyclohex-2-enone)

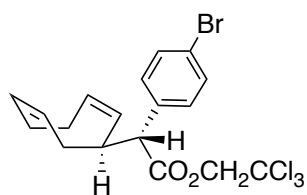
To an oven dried 4 mL vial with a stir bar was weighed di- μ -chlorotetraethylene dirhodium (0.025 equiv) and cyclooctadiene derived ligand (0.055 equiv). The vial was wrapped with Teflon™ thread tape, fitted with a septum cap and the atmosphere was exchanged for a dry N₂ atmosphere (3 cycles, 1 minute per cycle). Dry, nitrogen sparged 1,4-dioxane (1.8 mL) was then added to the vial and placed on a preheated hotplate at 50 °C to stir for 20 minutes under N₂. Aqueous potassium hydroxide (0.18 mL, 56.1 mg/mL, 0.50 equiv, sparged with N₂) was added to the reaction vial via syringe and allowed to stir for an additional 10 minutes at temperature. The vial was opened for addition of solid phenylboronic acid (3 equiv), then quickly resealed and the headspace was purged under positive pressure with addition of a vent needle for 1 minute. To the vial was added cyclohex-2-enone (0.2 mmol, 1 equiv) via syringe and the vial was fitted with a N₂ balloon and allowed to stir at temperature for 12 hours. The reaction was removed from heat, allowed to cool, and diluted with diethyl ether and passed through a silica plug. The combined organics were dried over sodium sulfate and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel in a gradient of Hexanes: EtOAc (97:3 \rightarrow 90:10) to afford the pure 3-phenylcyclohexan-1-one.



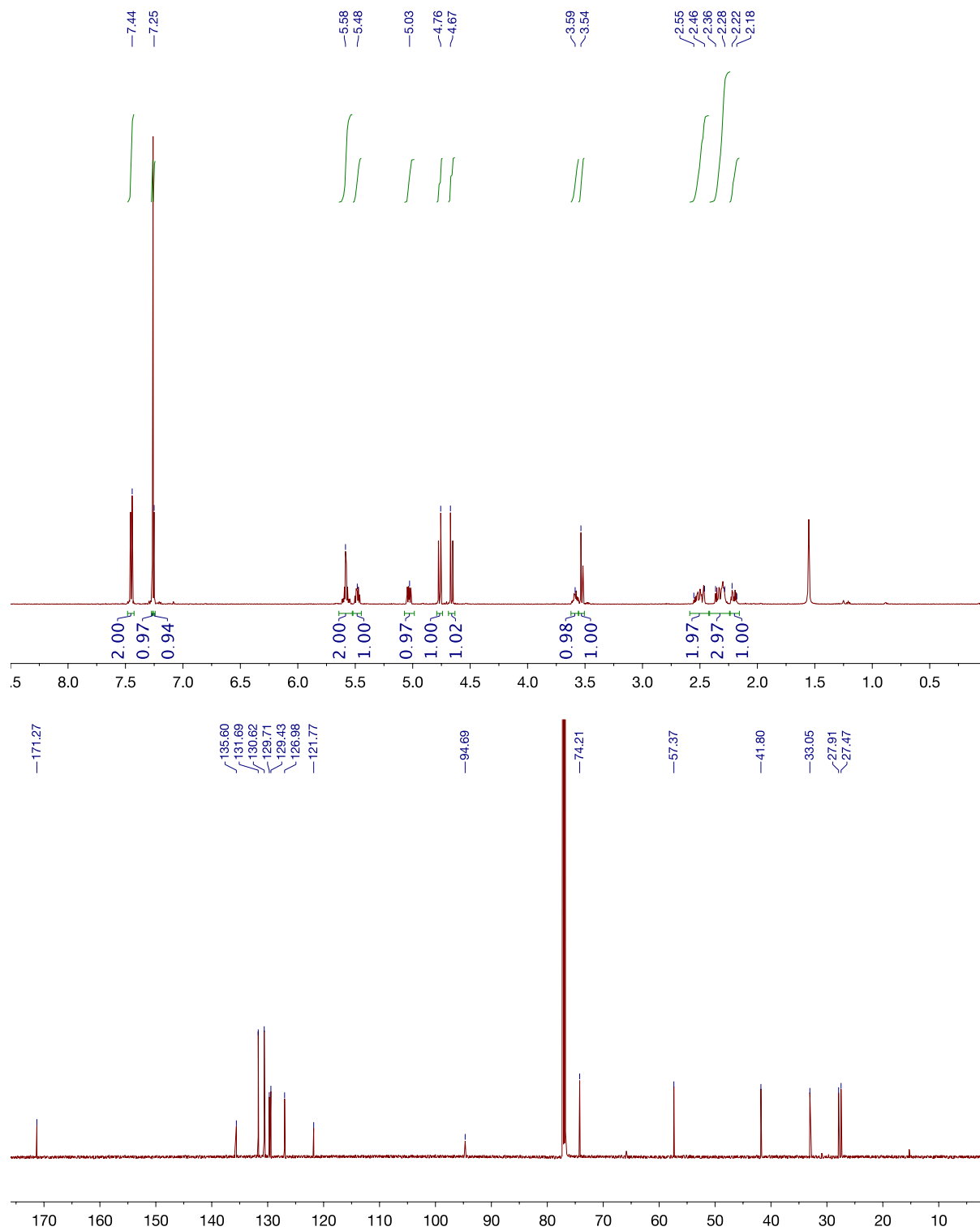
Ligand	28	29	30	31	32	33	34	41	42	43	44	45	46	47	48	49
yield	67	84	81	~2	68	60	45	43	61	78	58	32	69	81	63	63
ee.	39	34	36	45	30	33	22	27	26	53	47	60	69	59	41	76

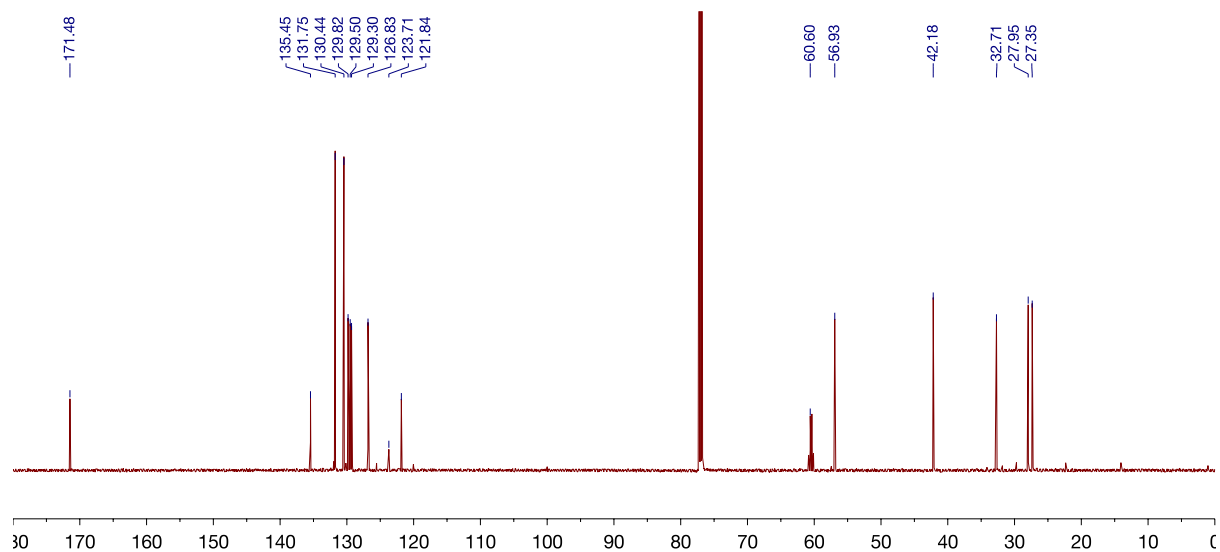
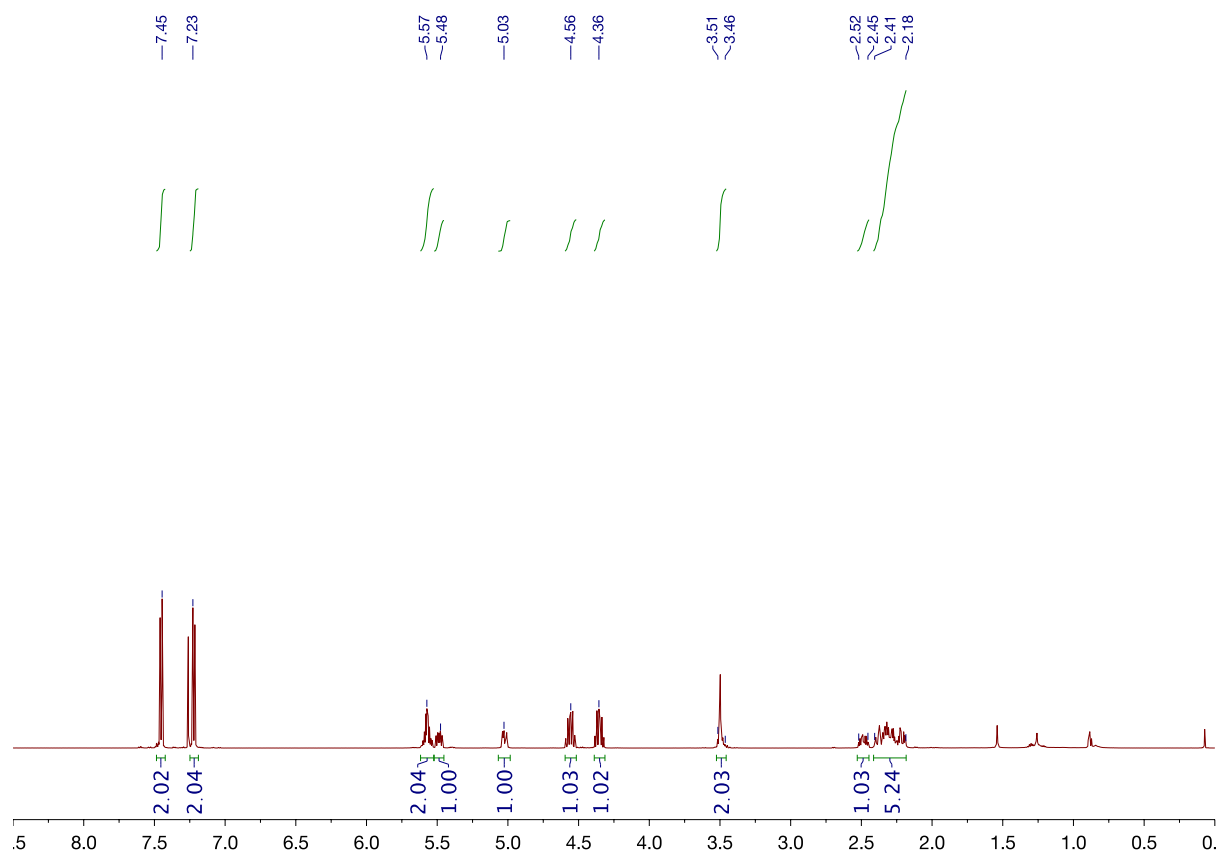
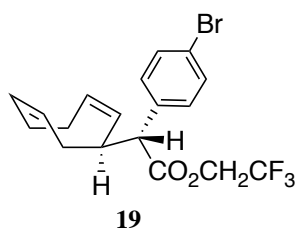
¹H & ¹³C spectra of mono- insertion products

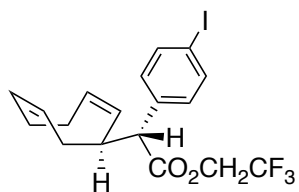




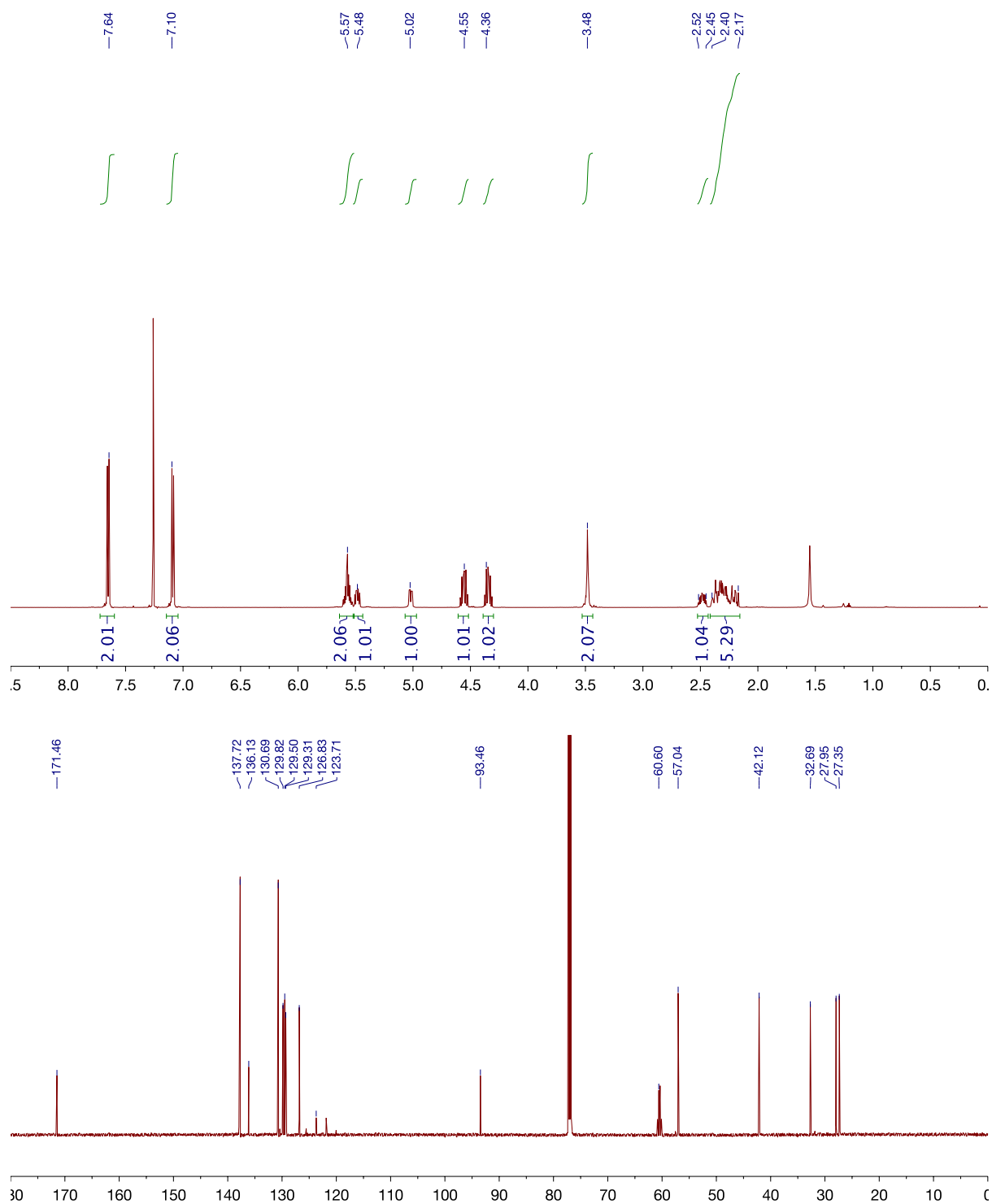
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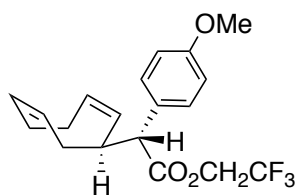




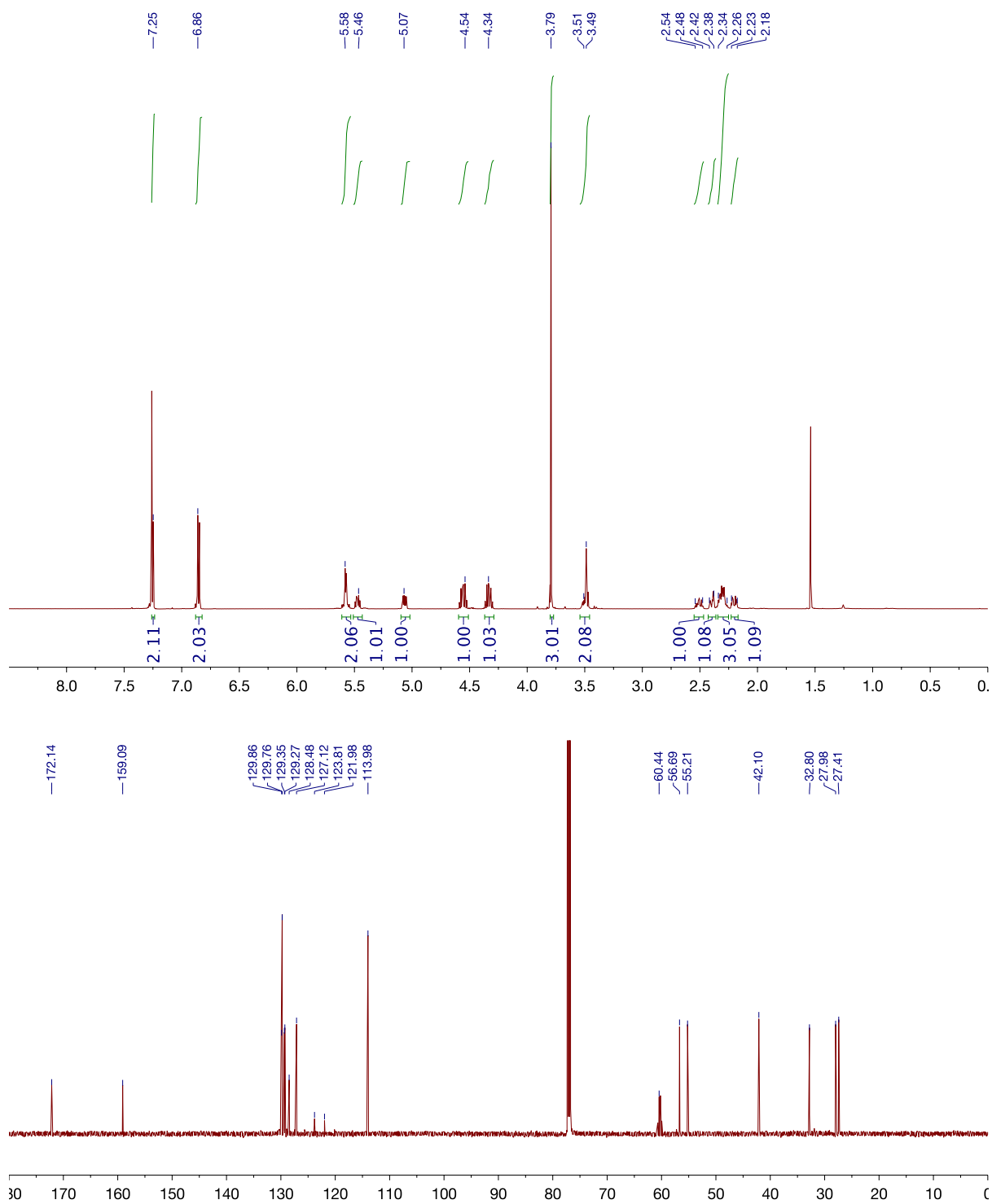


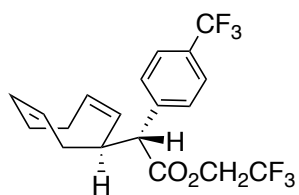
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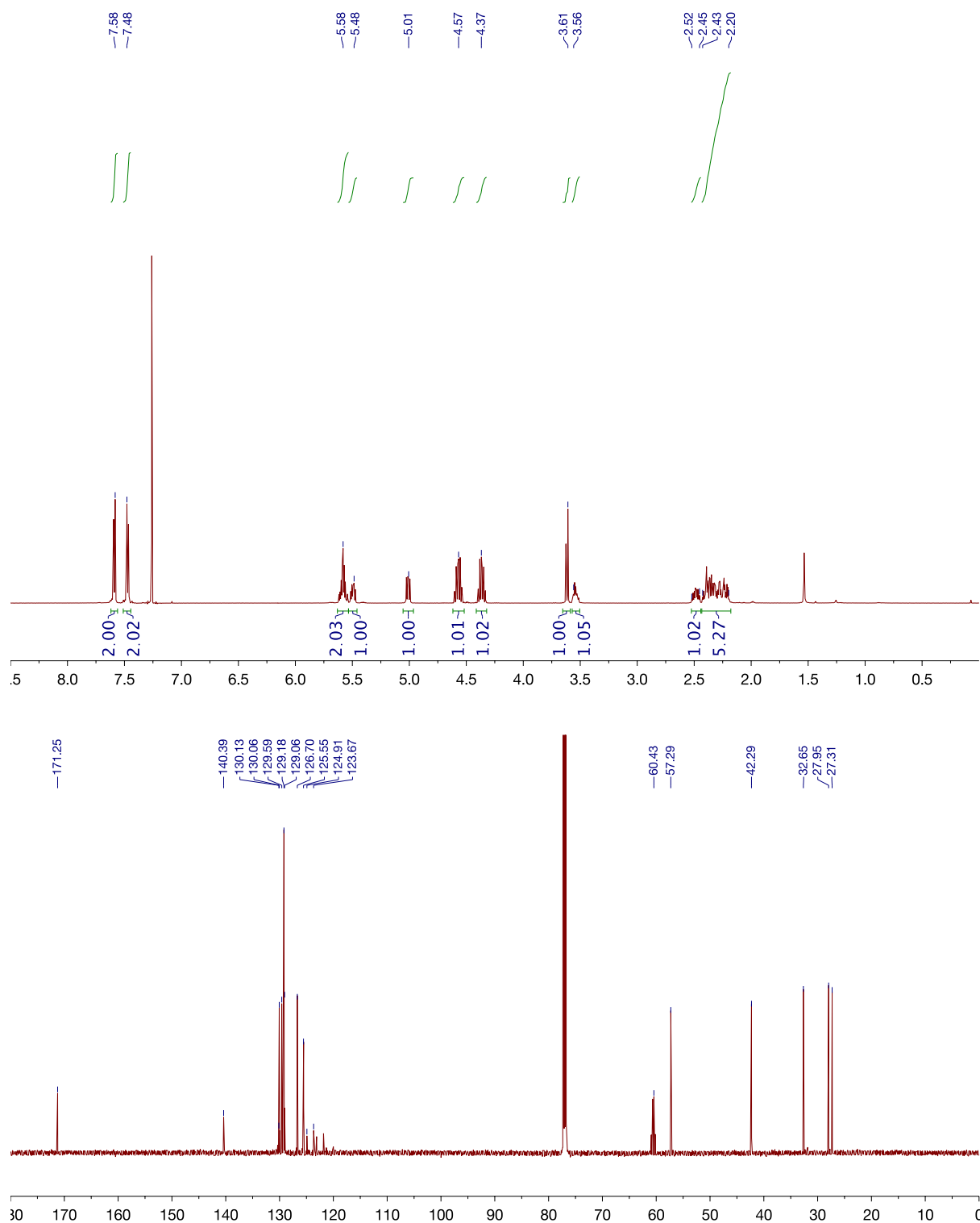


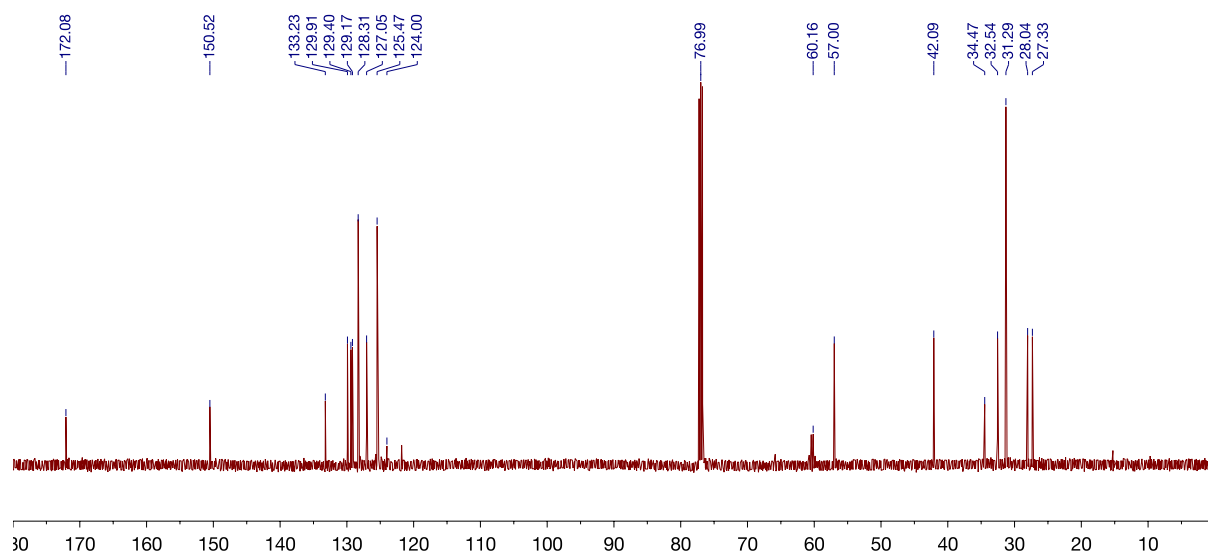
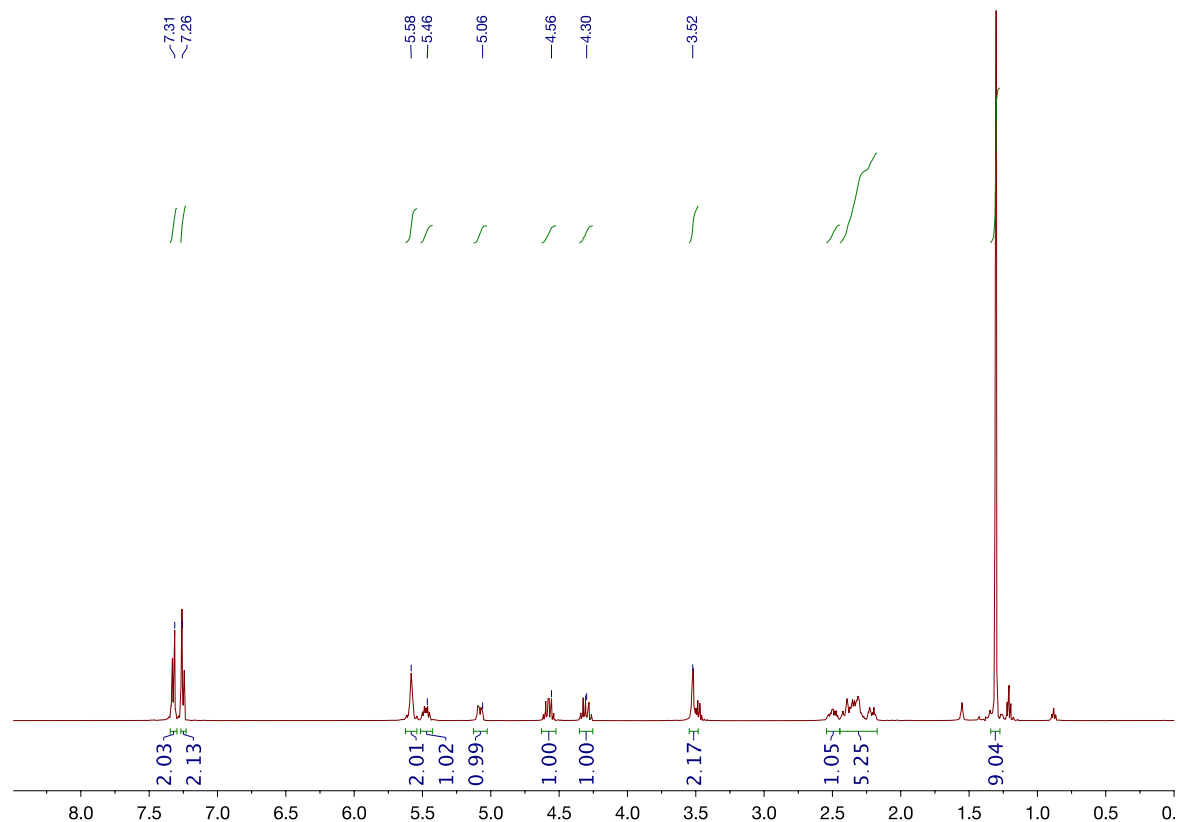
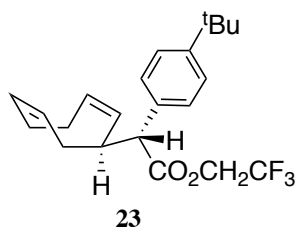
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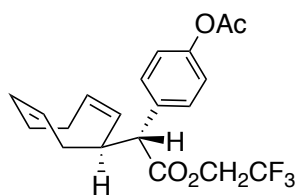




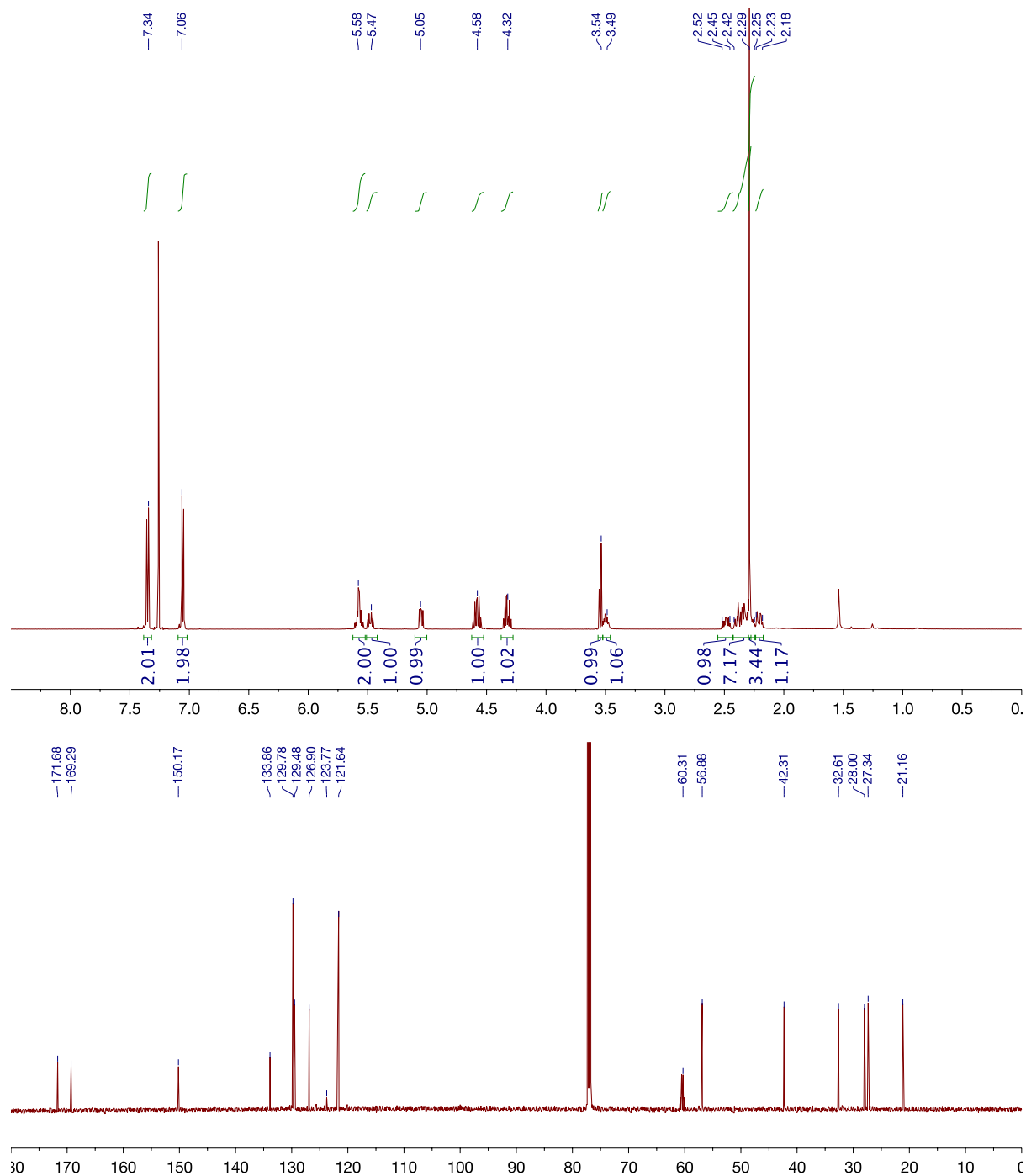
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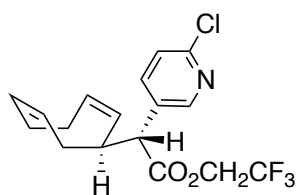




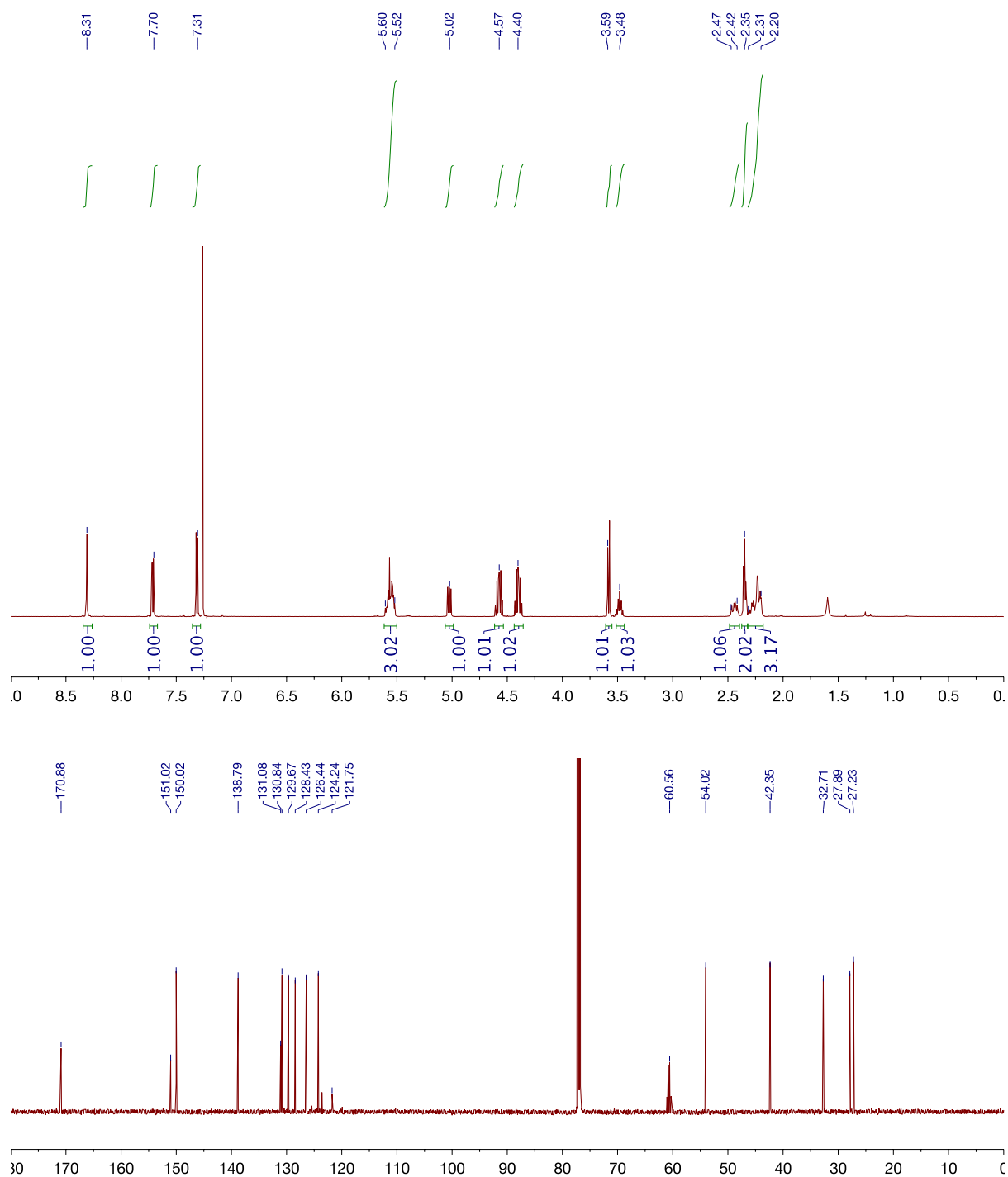


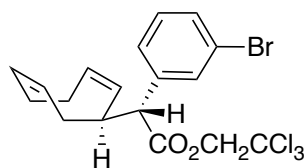
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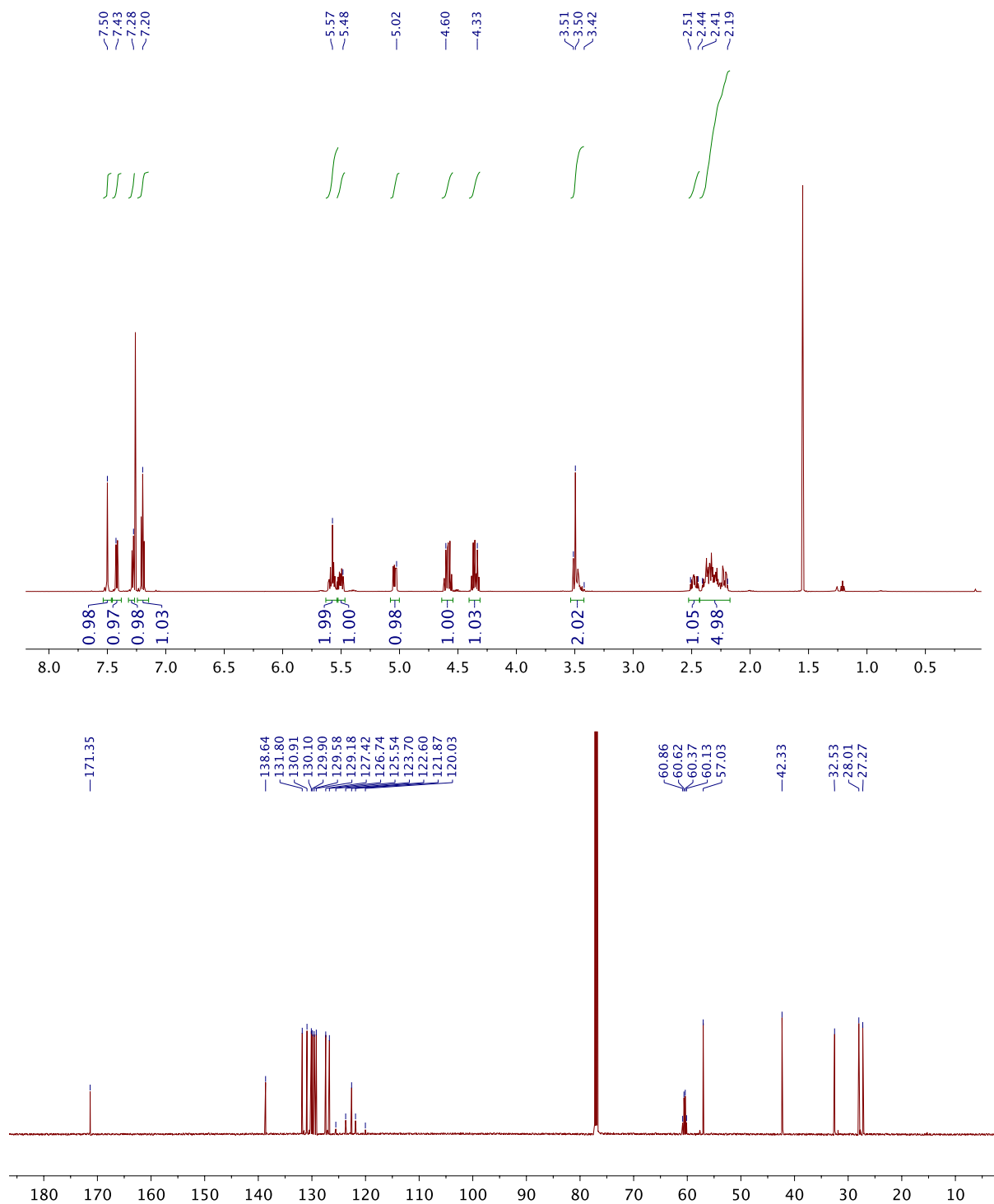


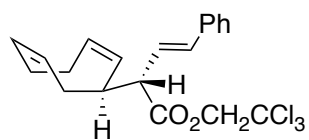
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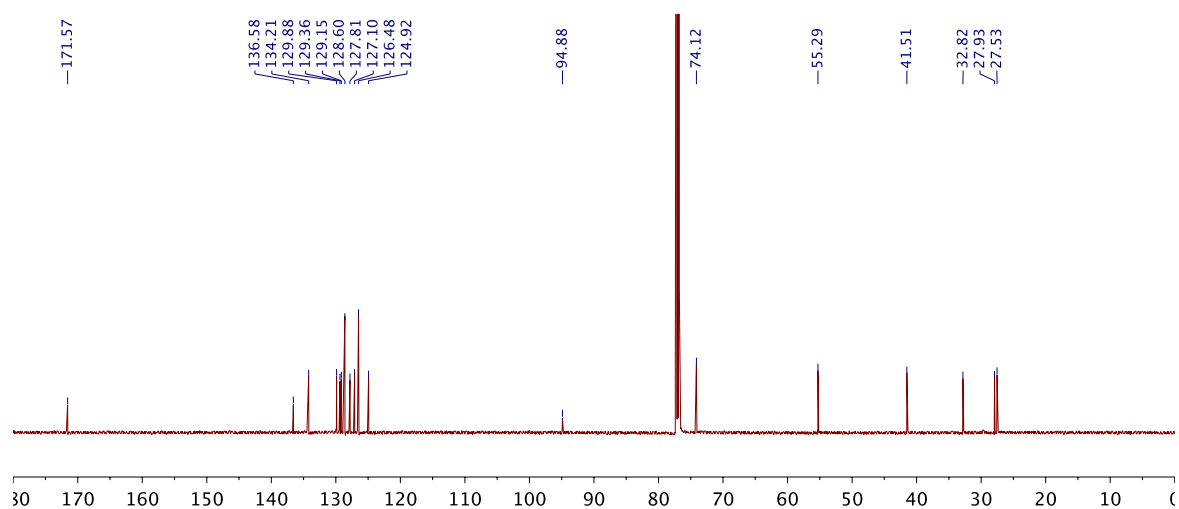
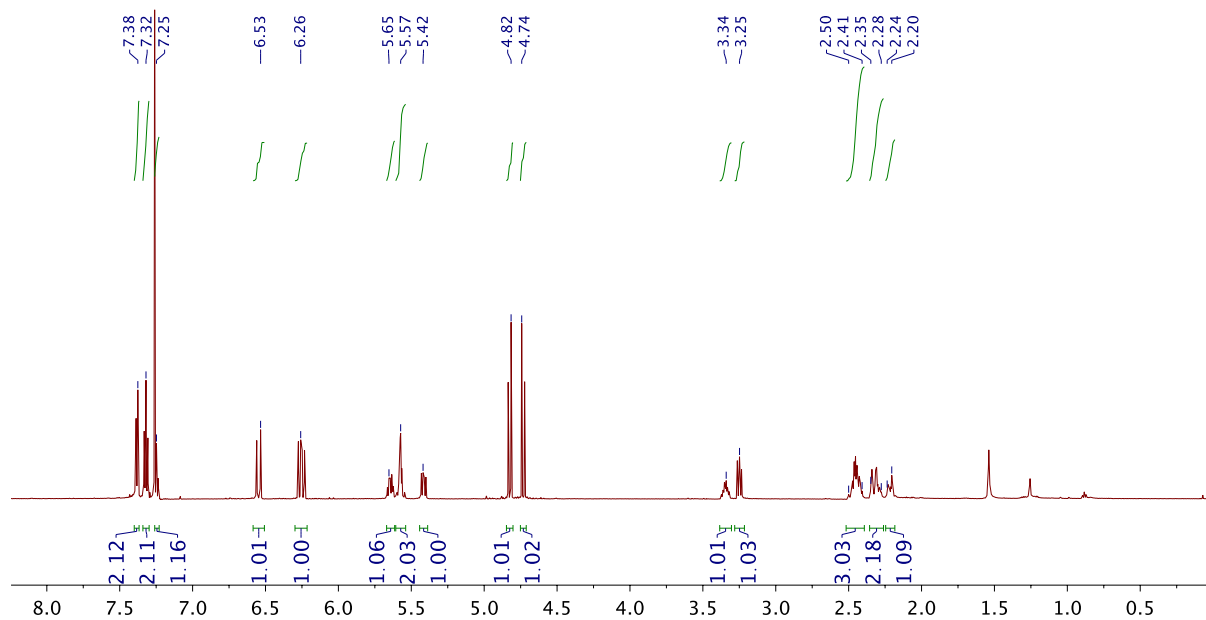


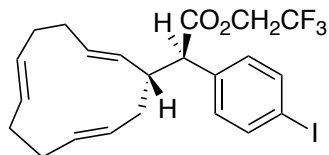
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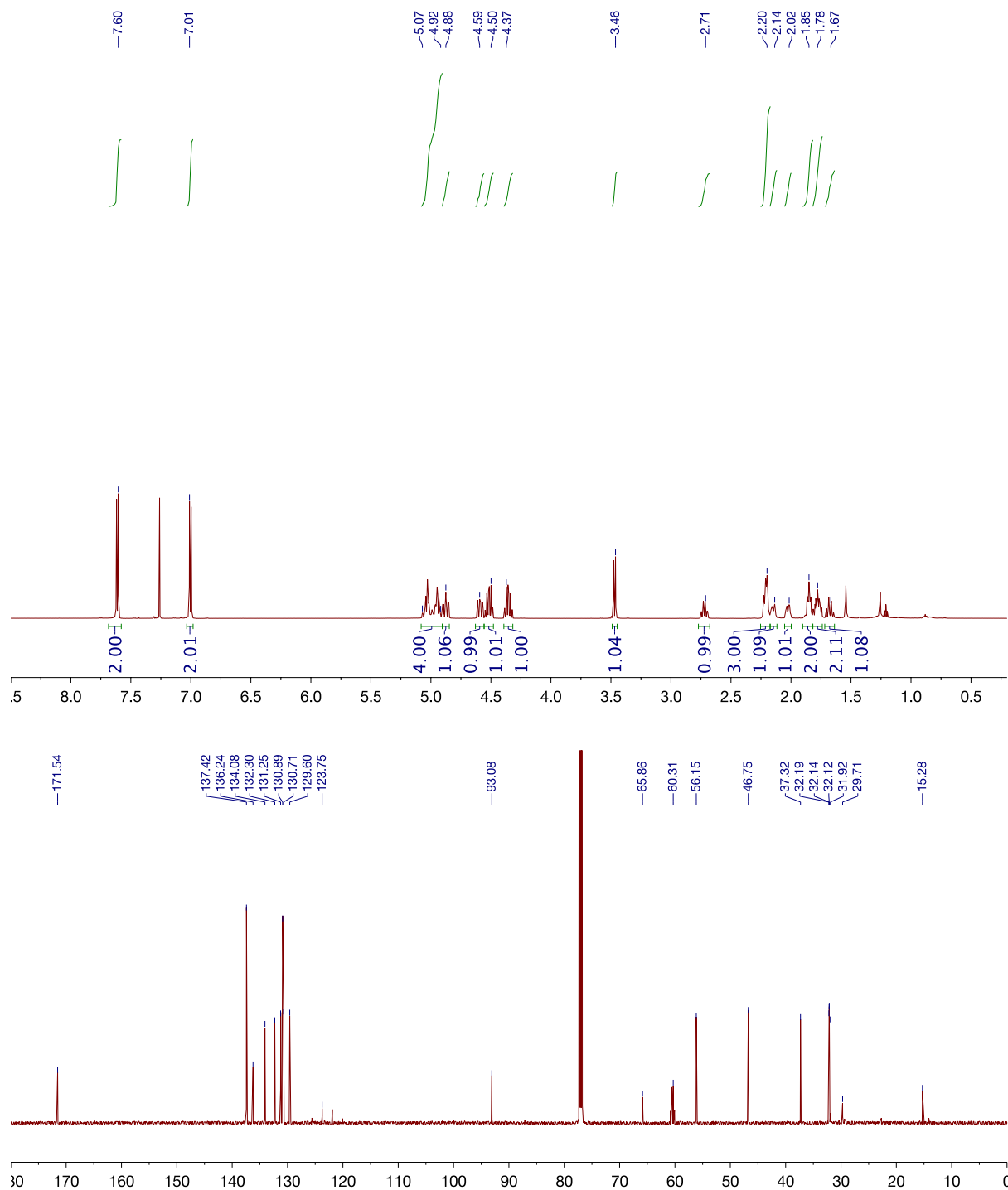


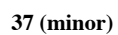
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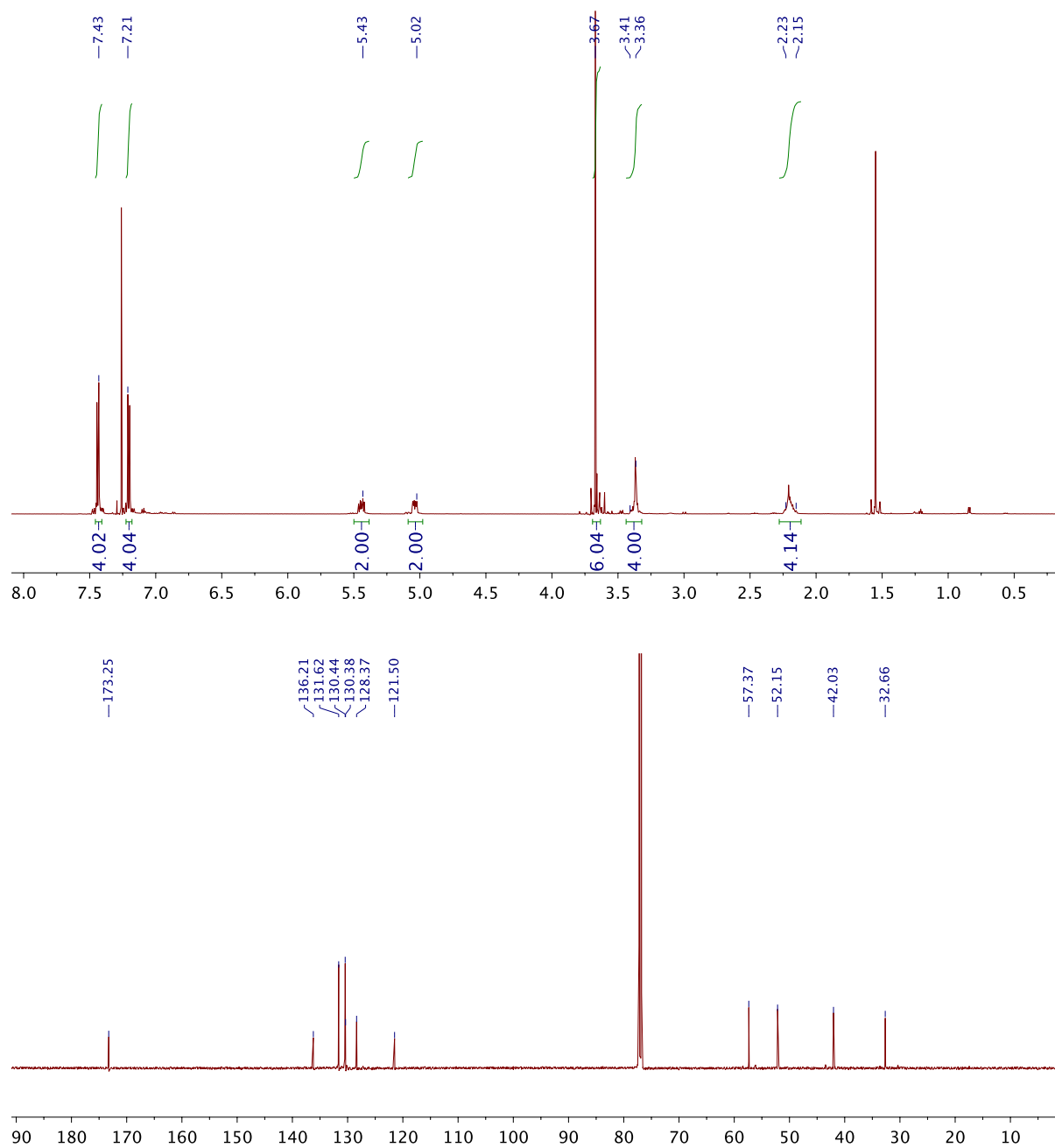
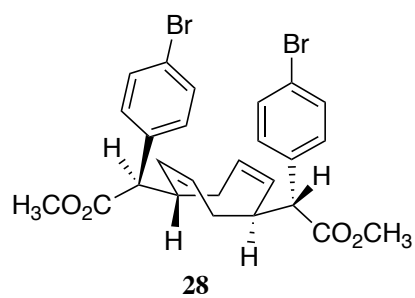


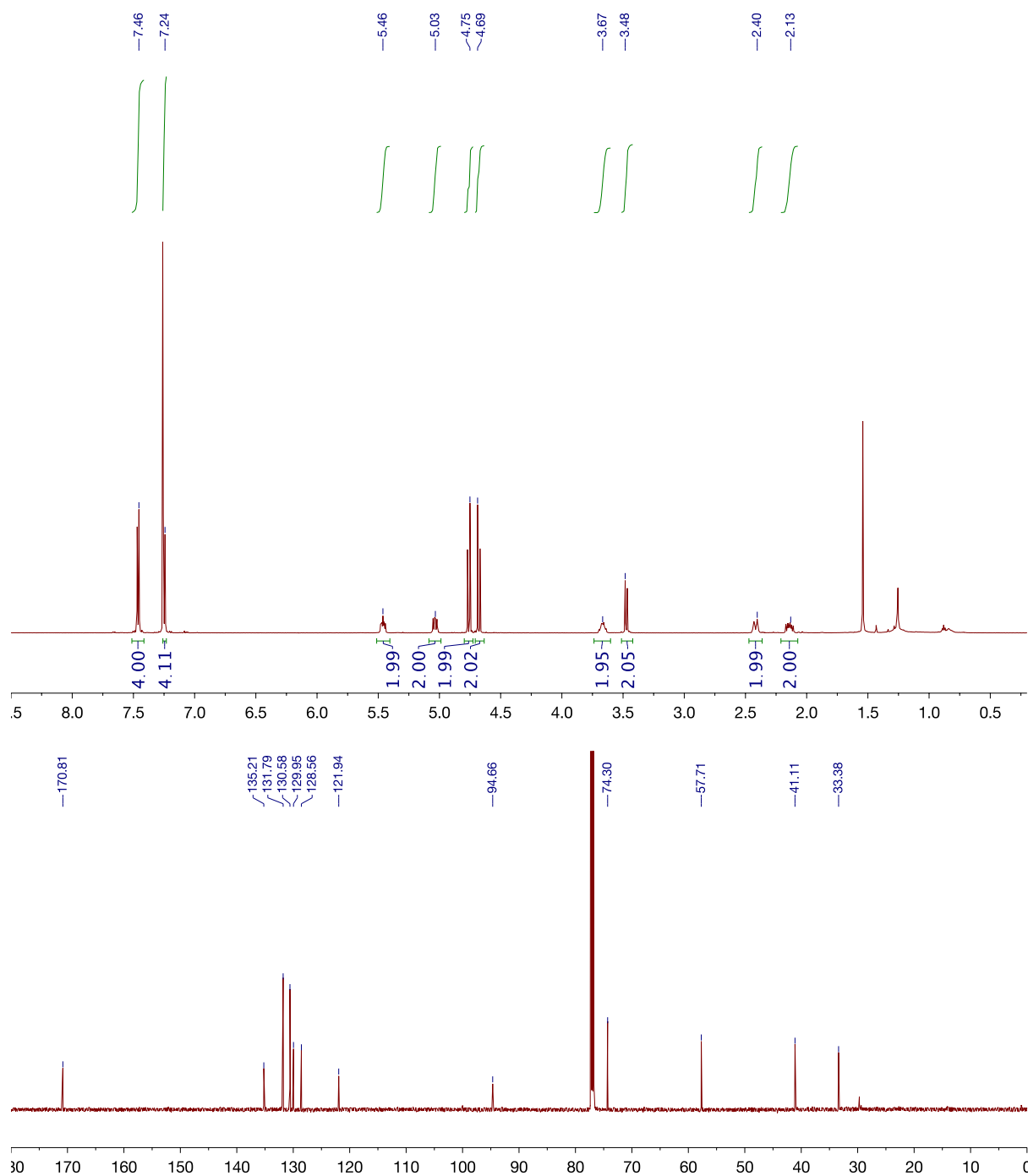
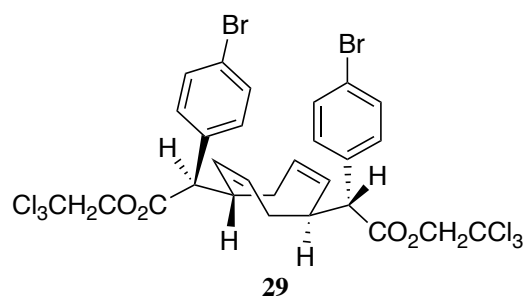
37 (major)

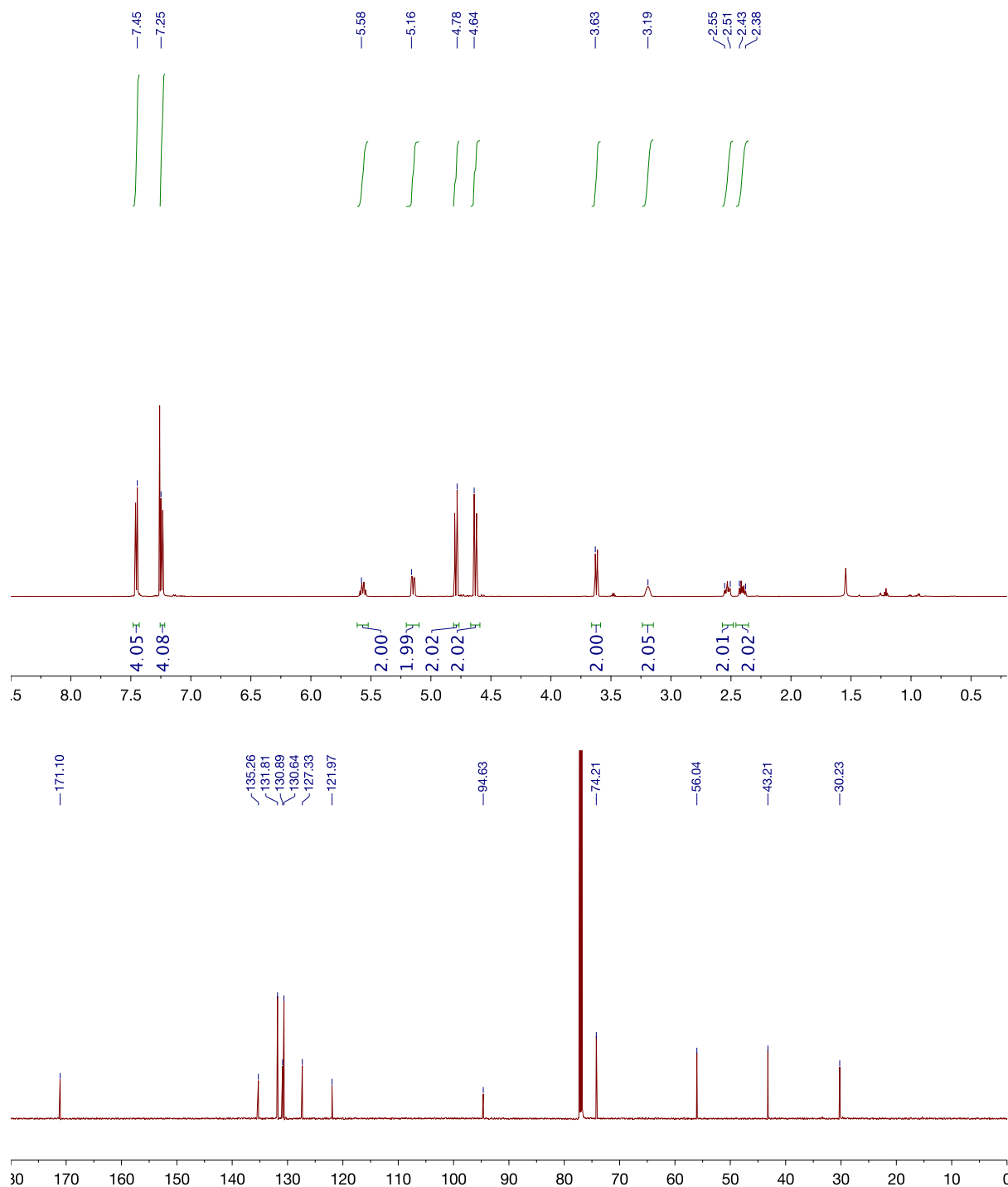
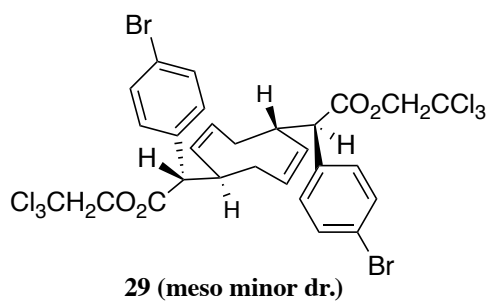


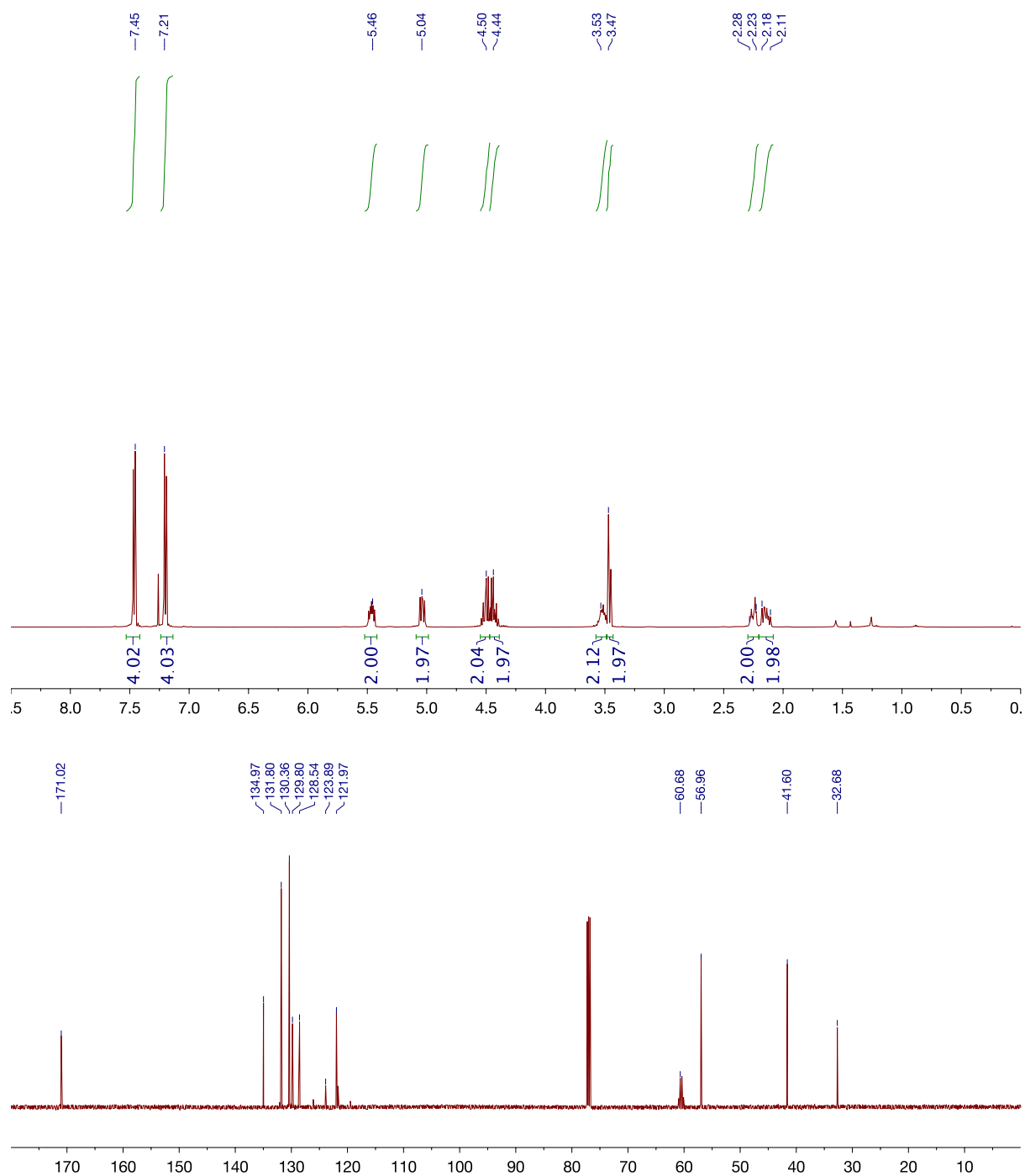
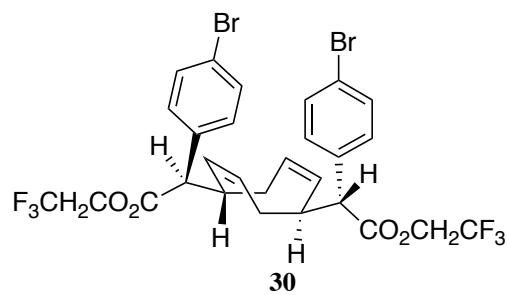


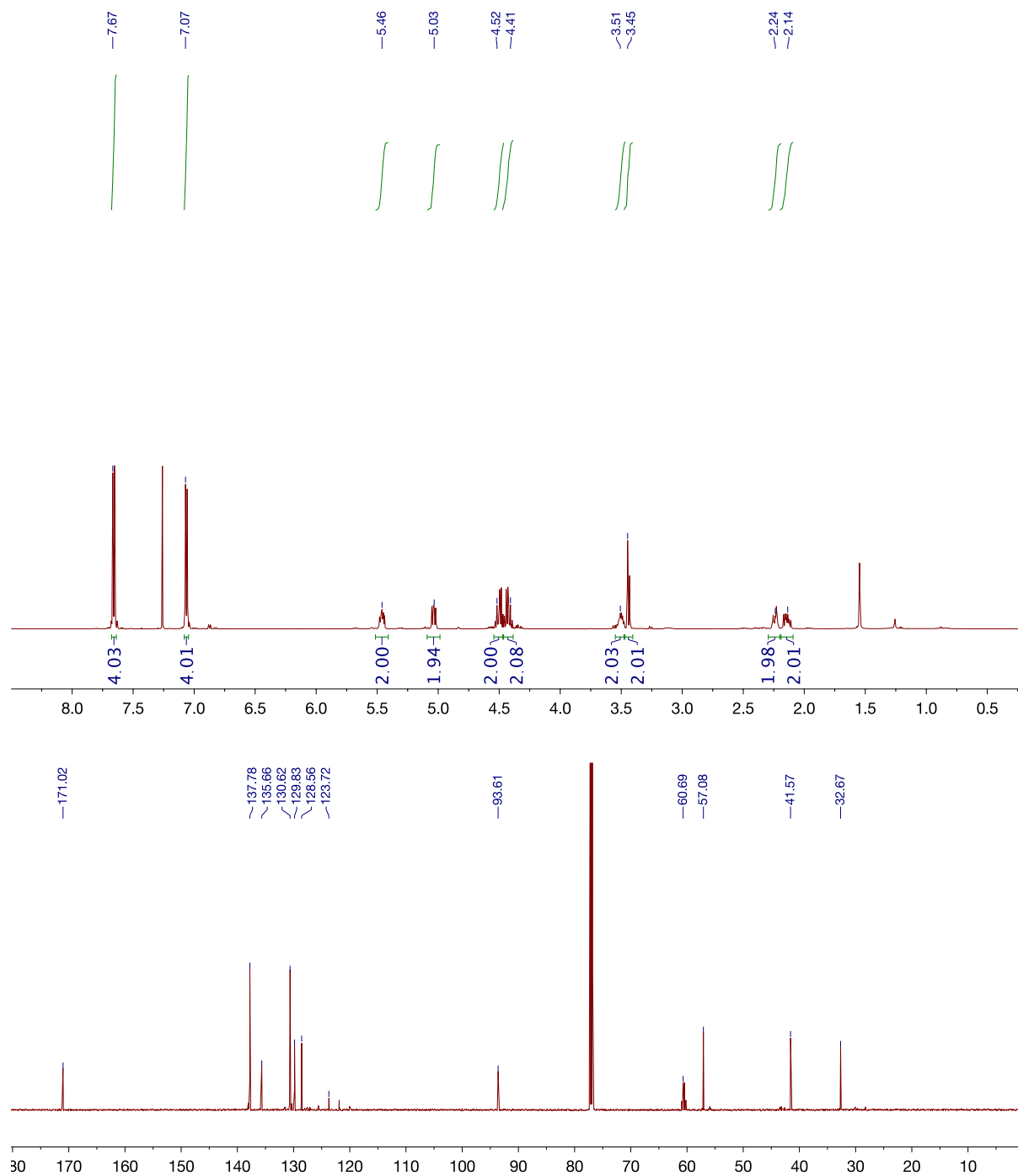
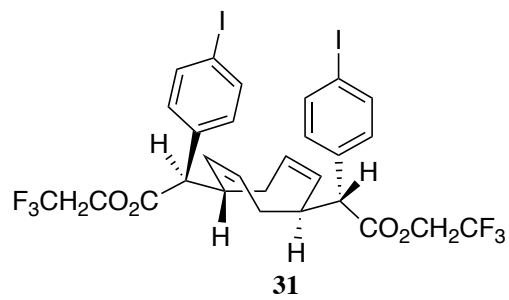
¹H & ¹³C spectra of di-insertion products

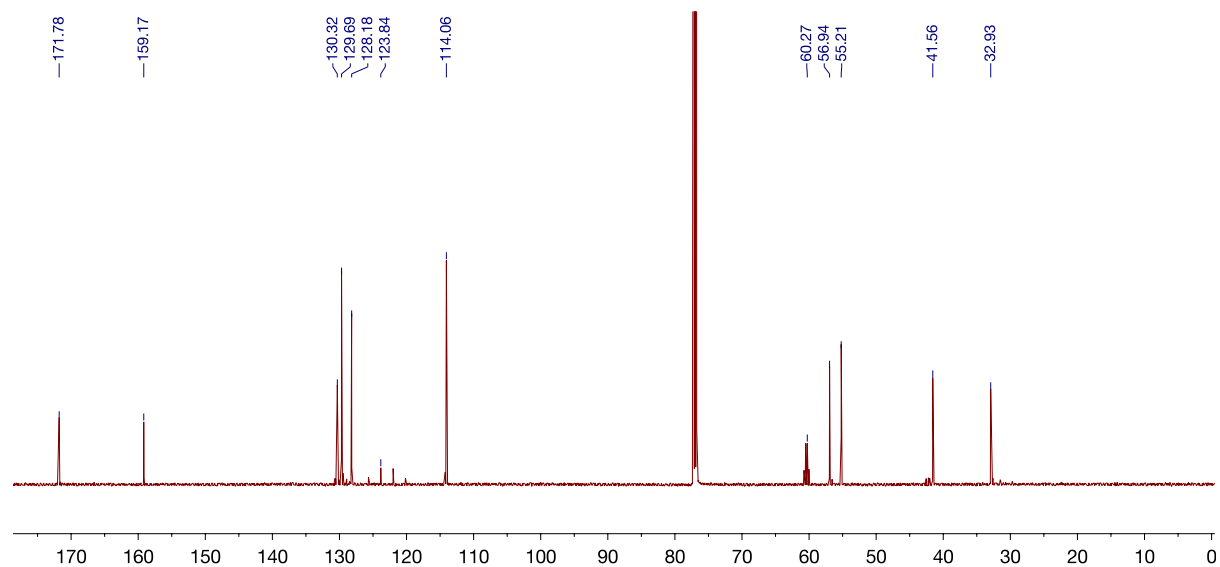
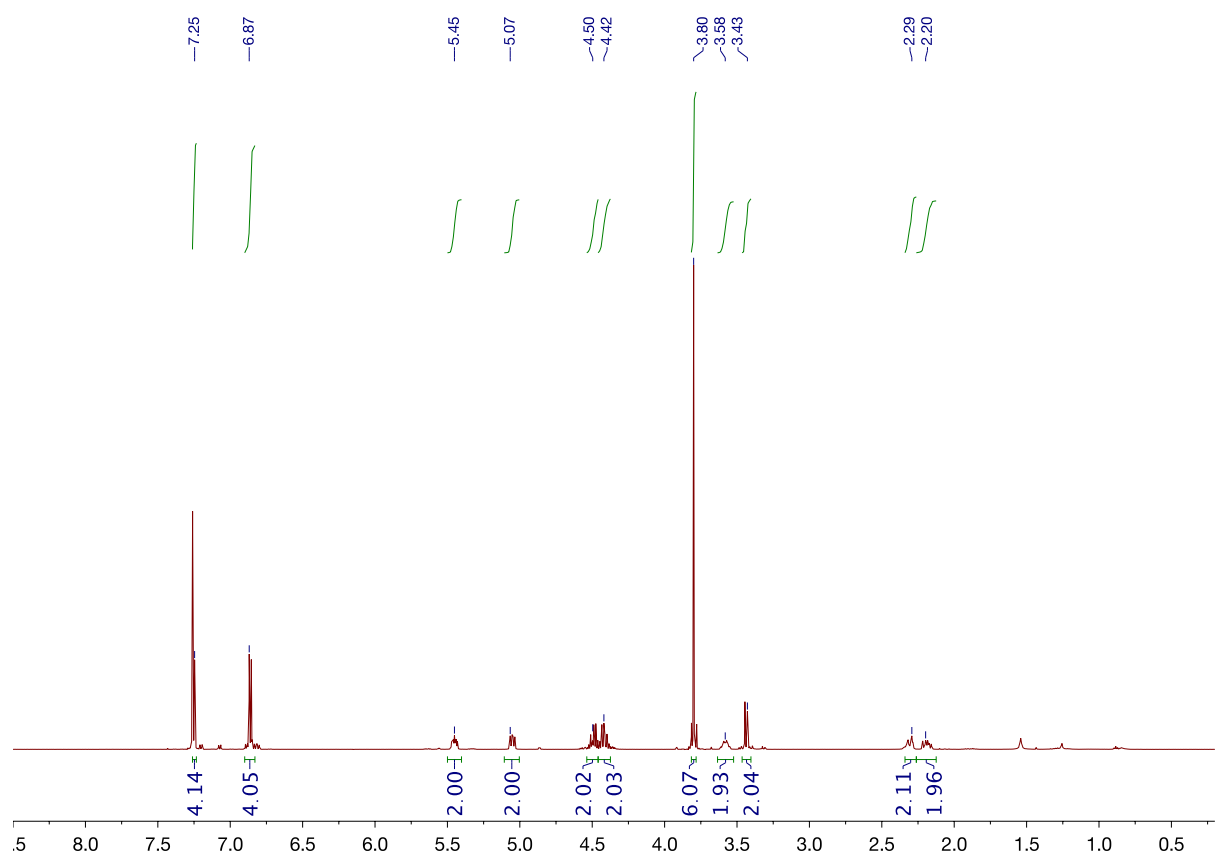
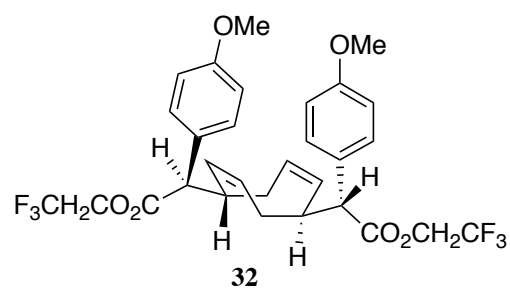


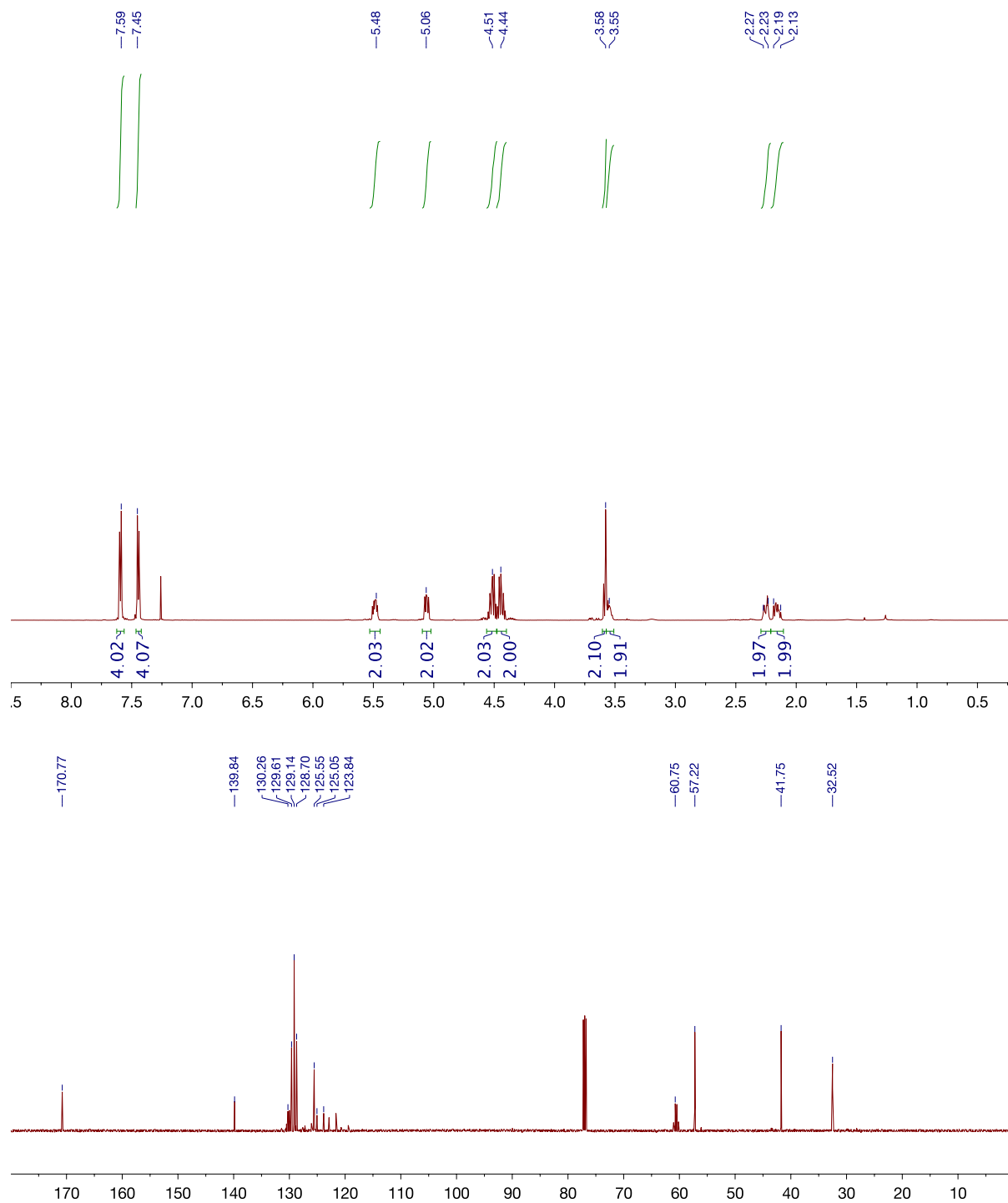
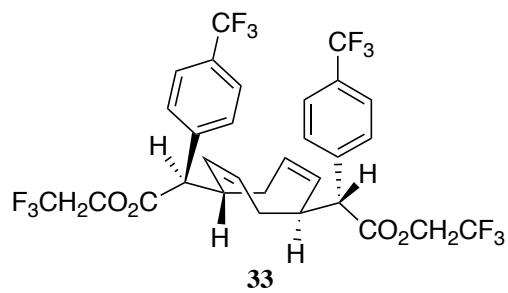


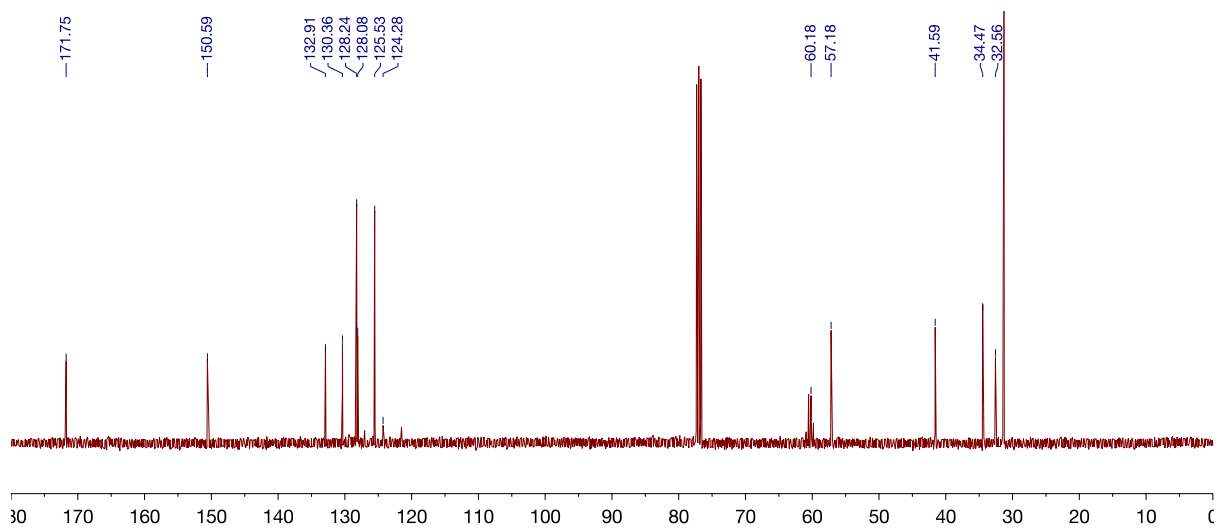
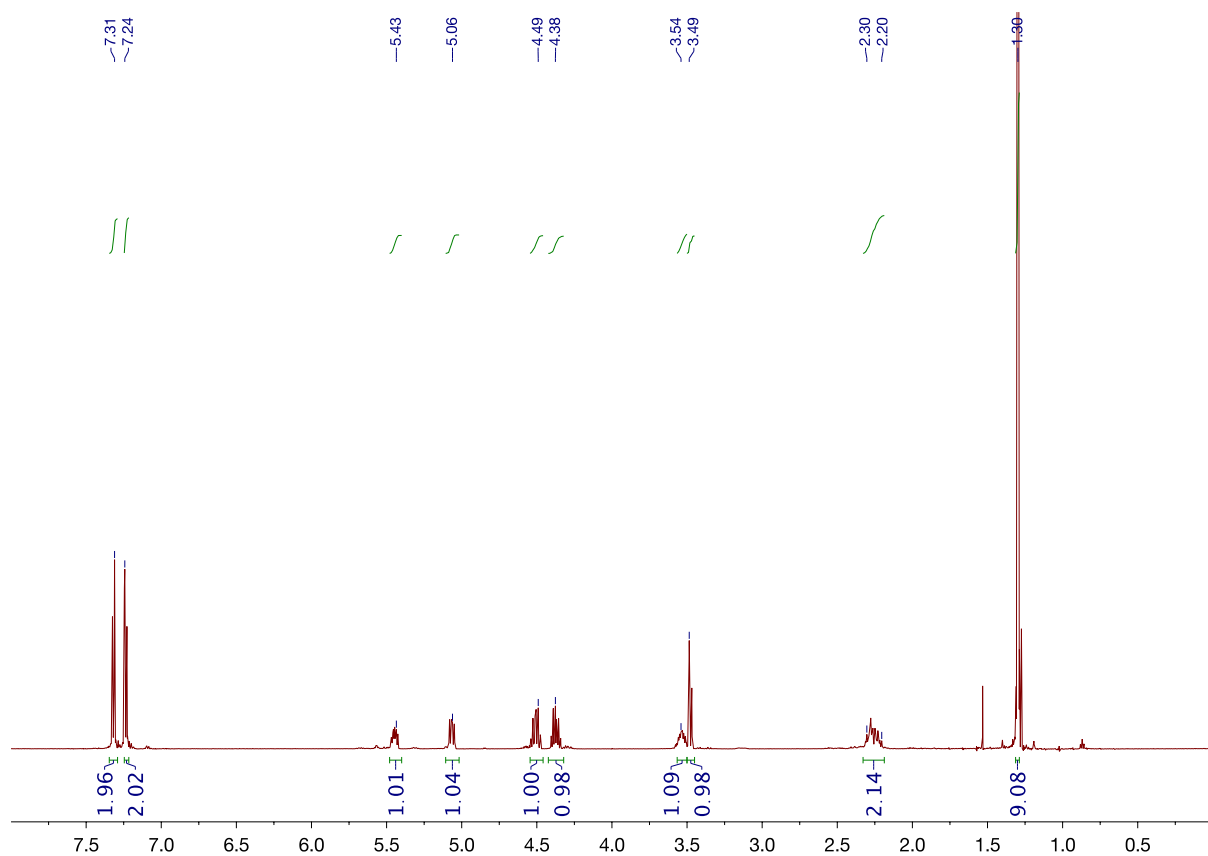
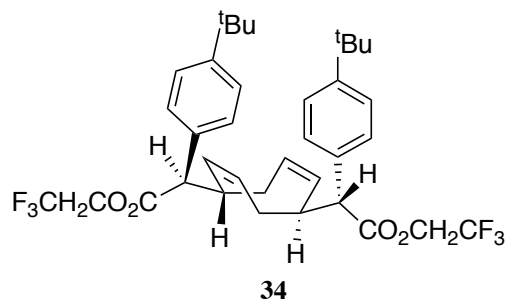


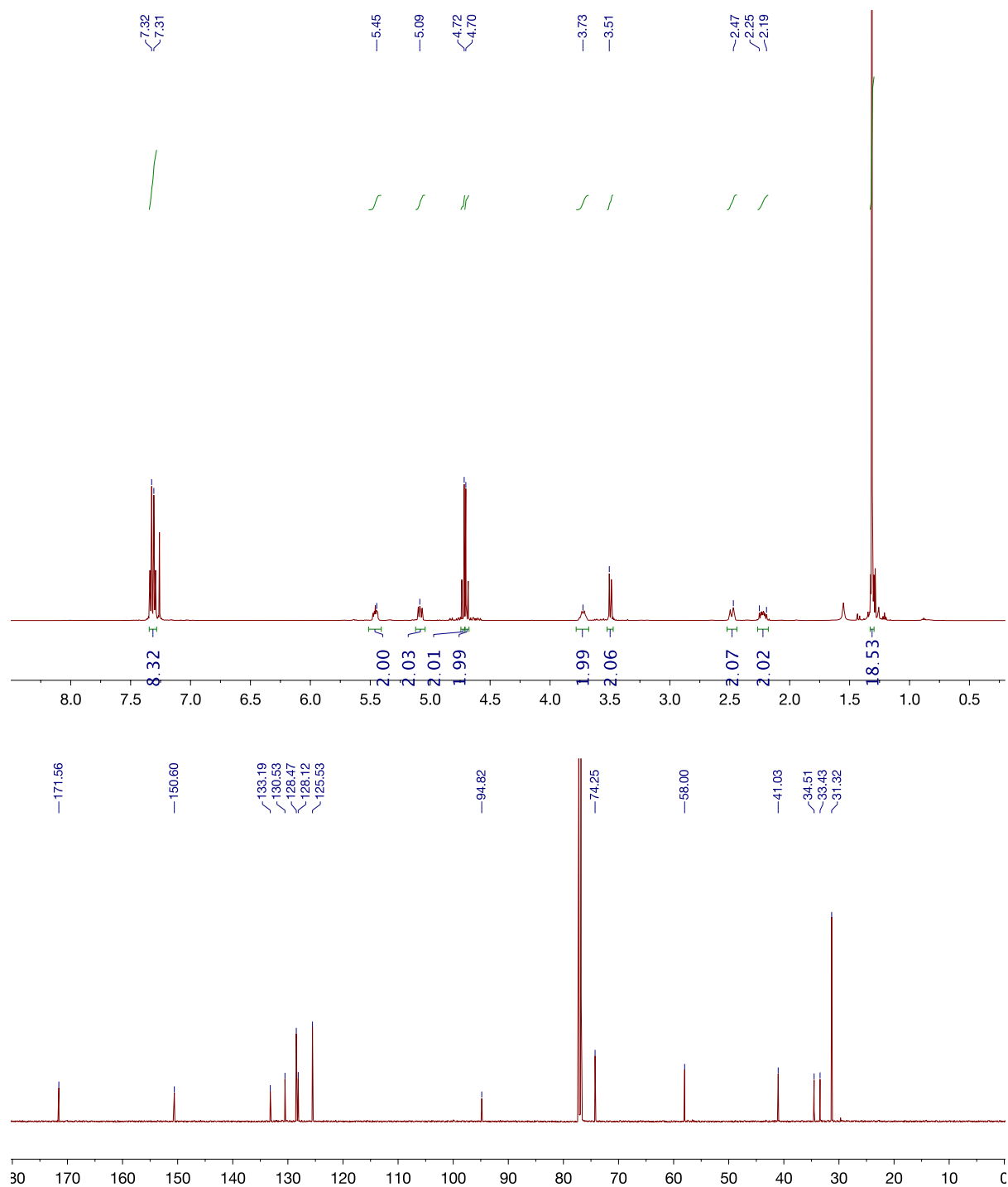
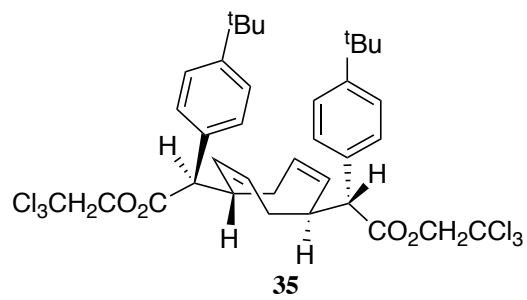




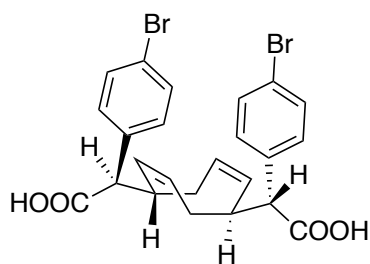




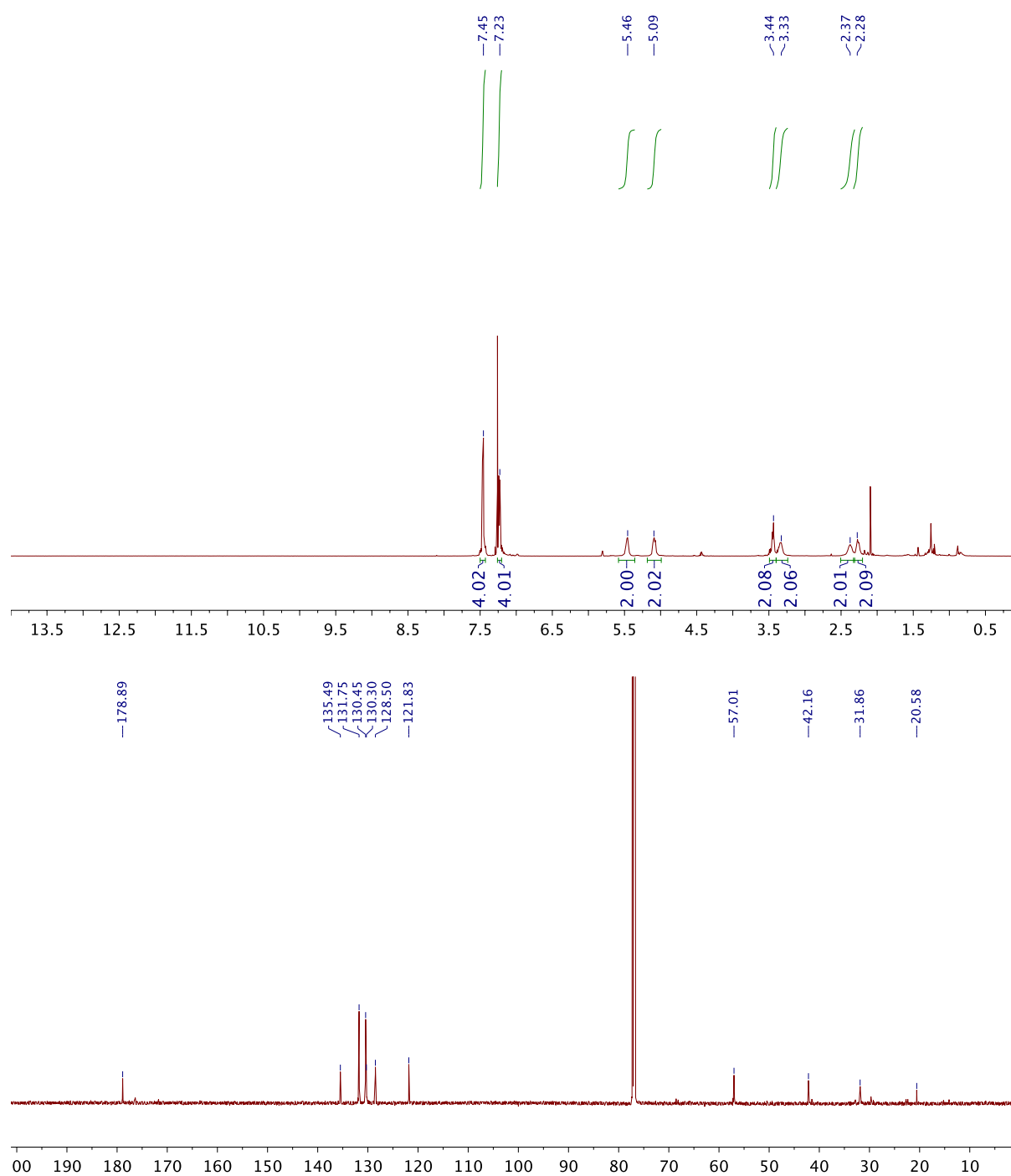


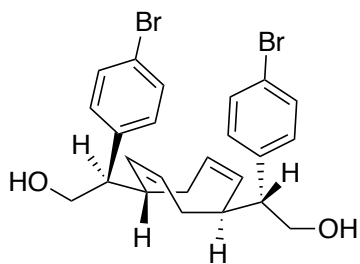


^1H & ^{13}C spectra of derivatization products.

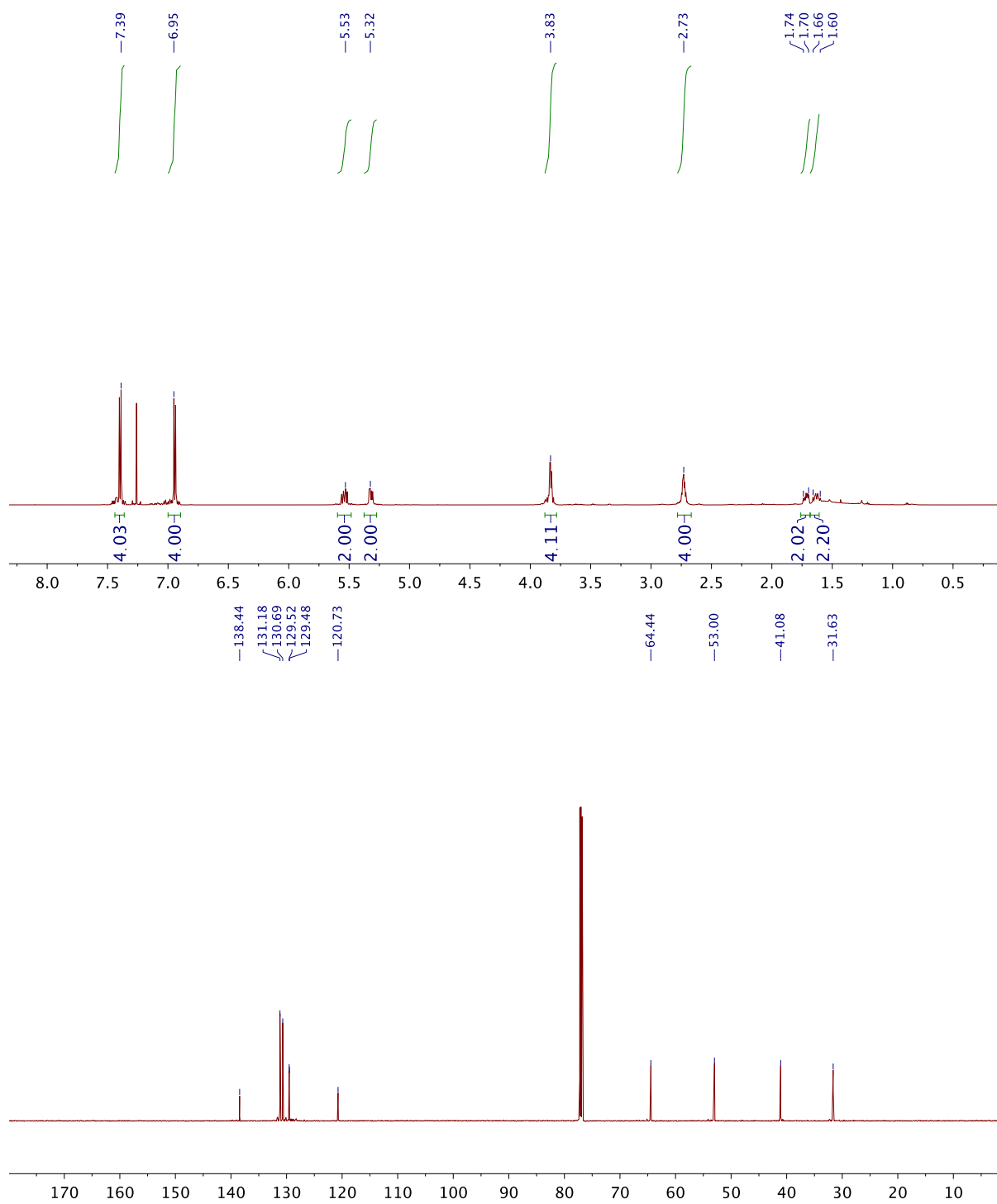


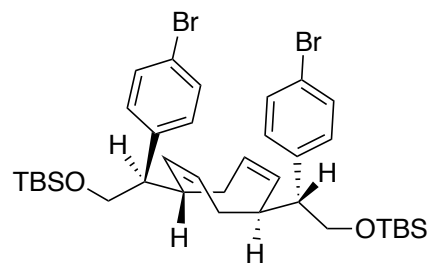
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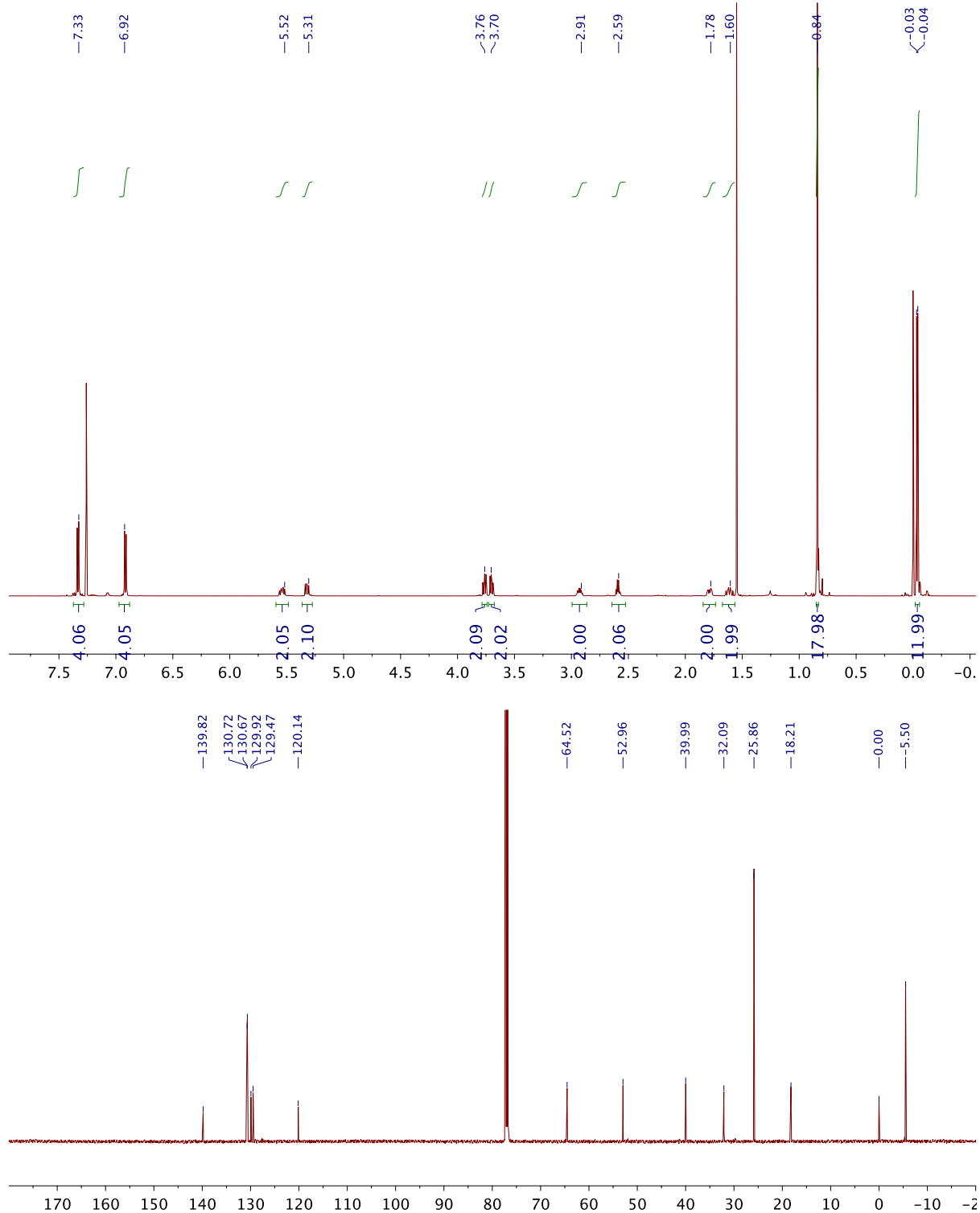


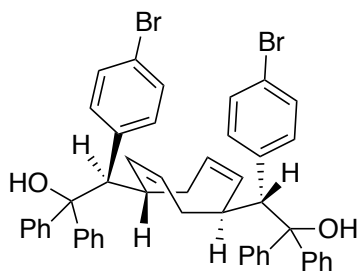
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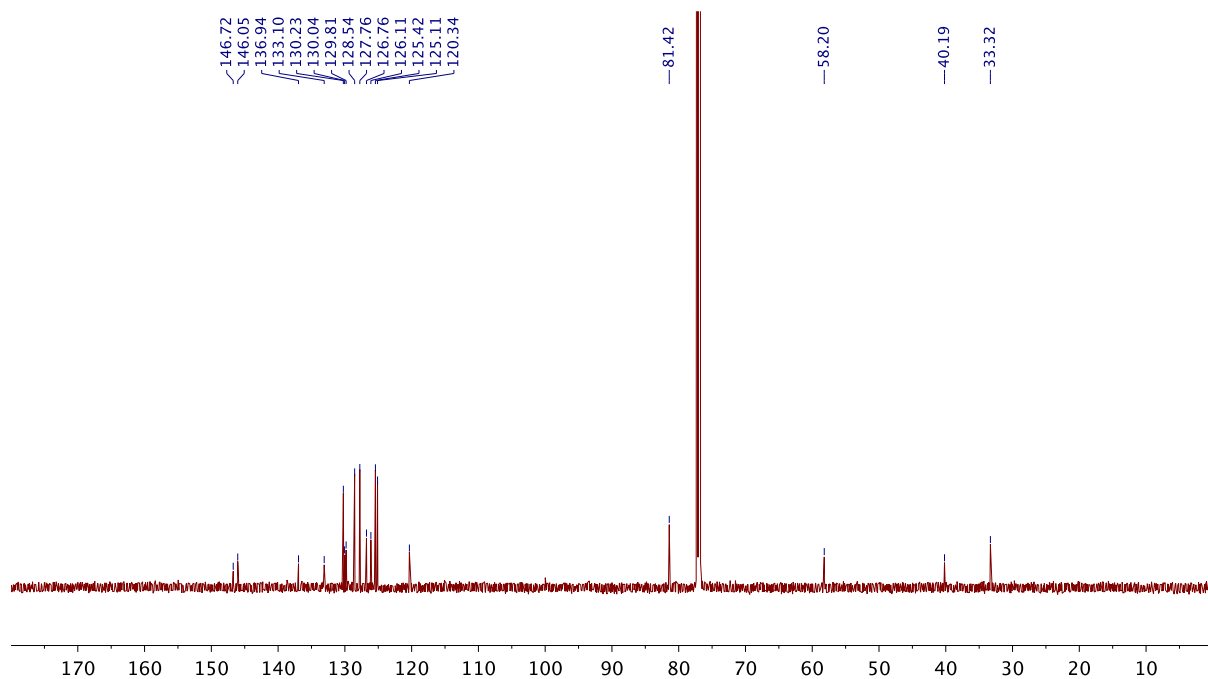
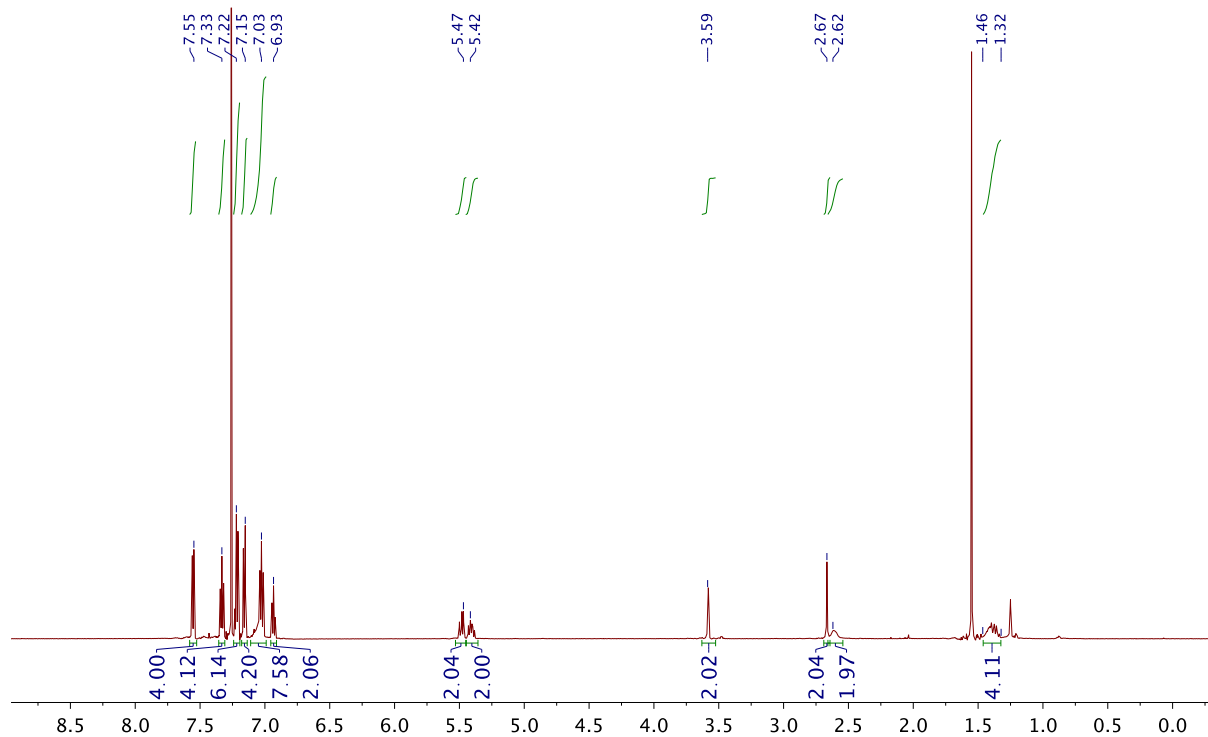


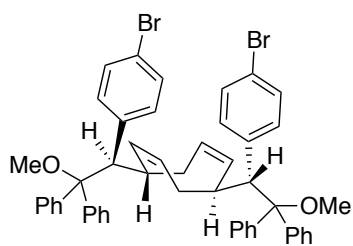
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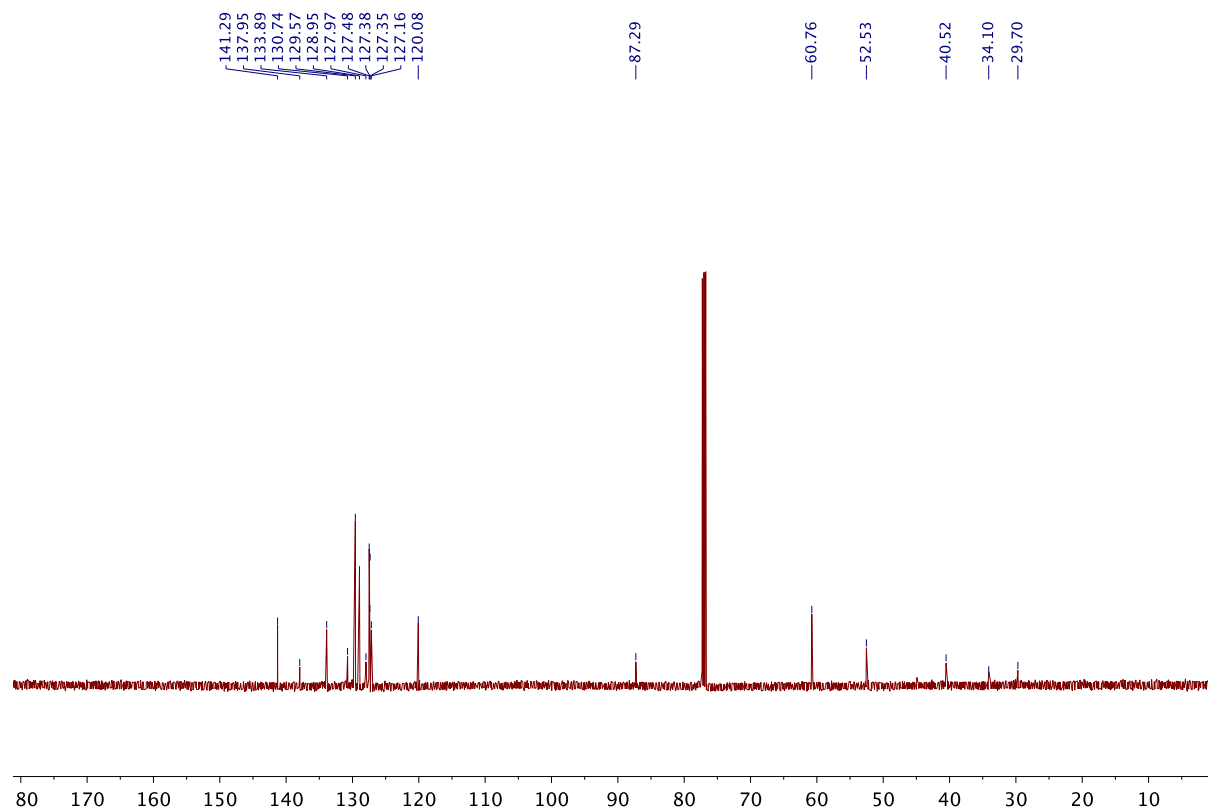
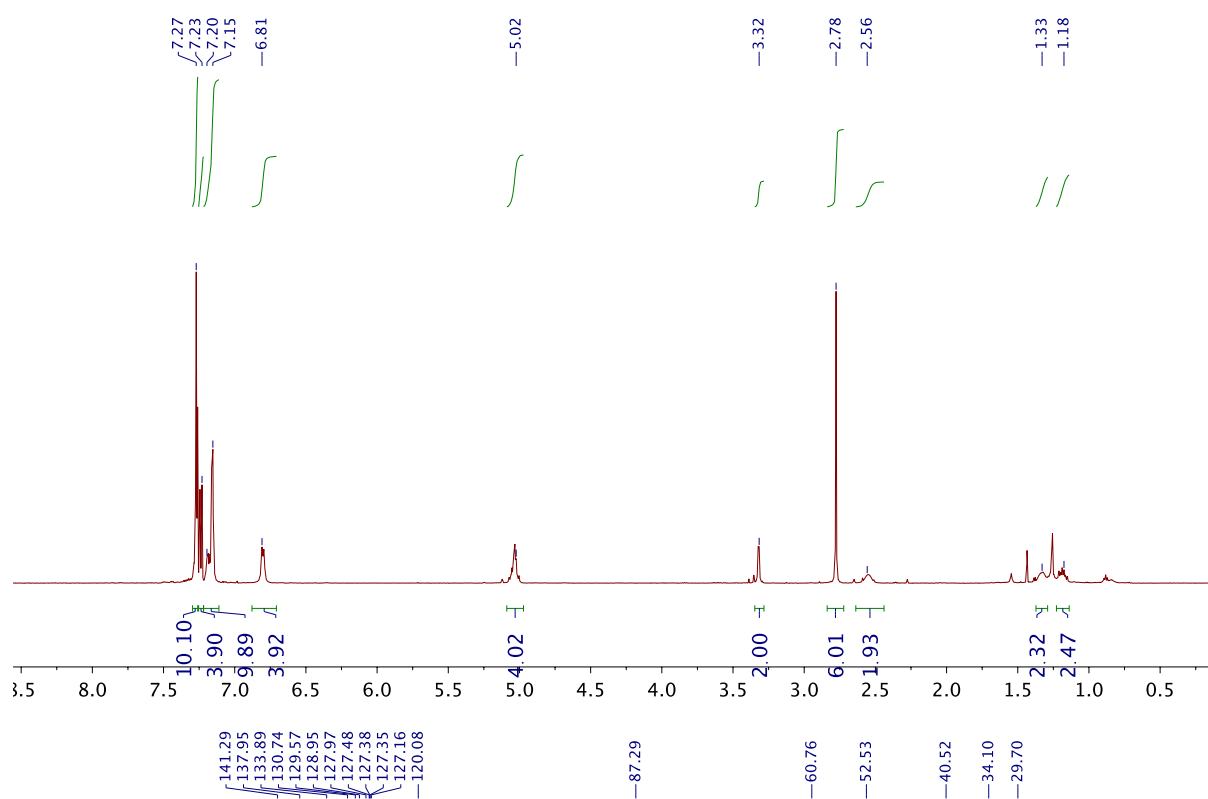


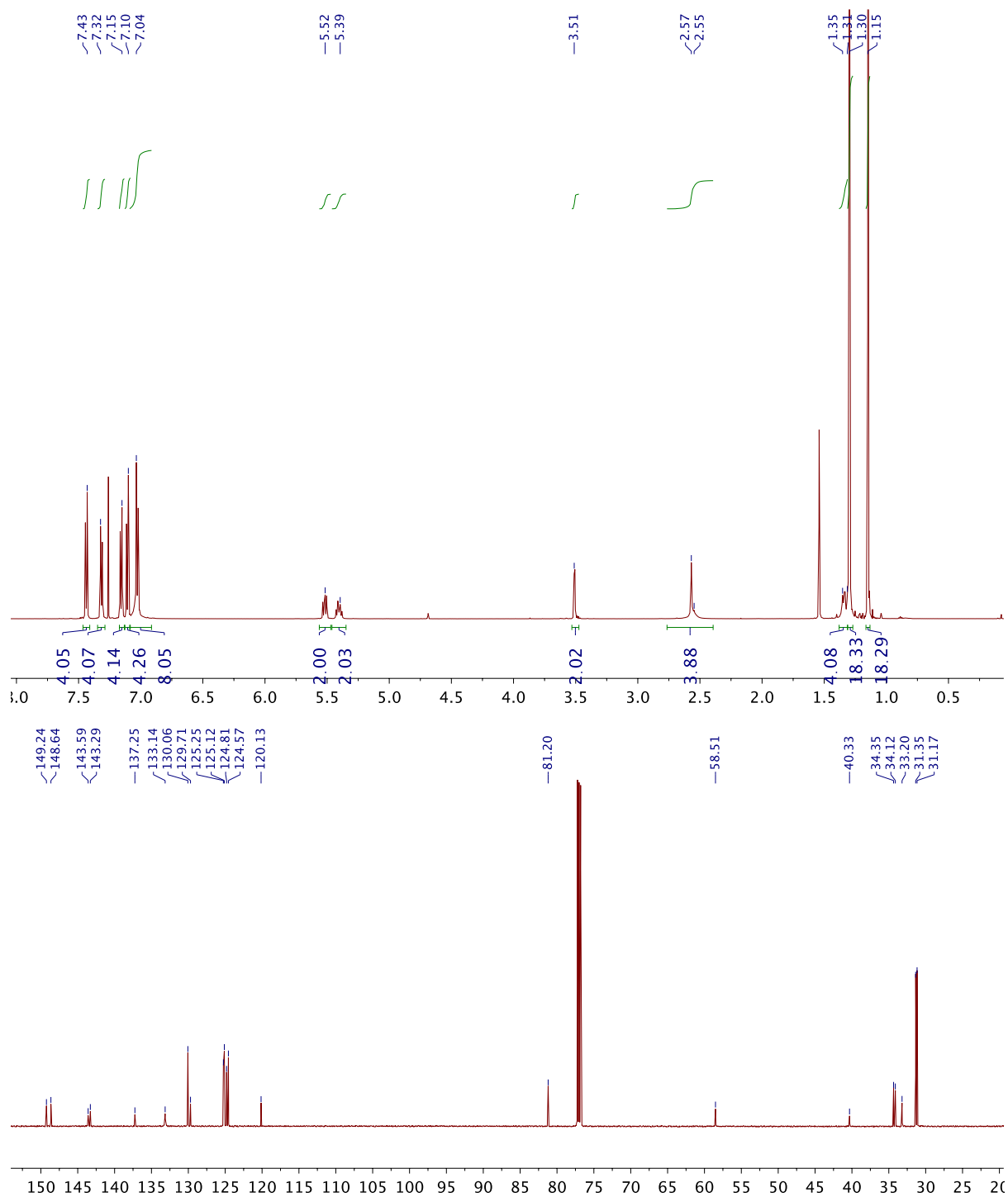
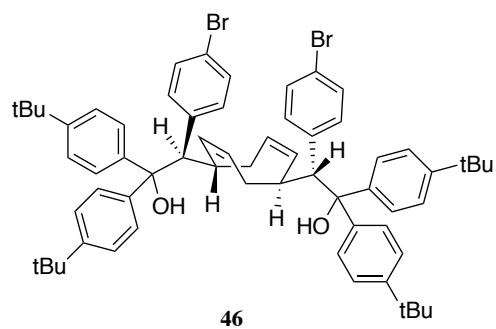
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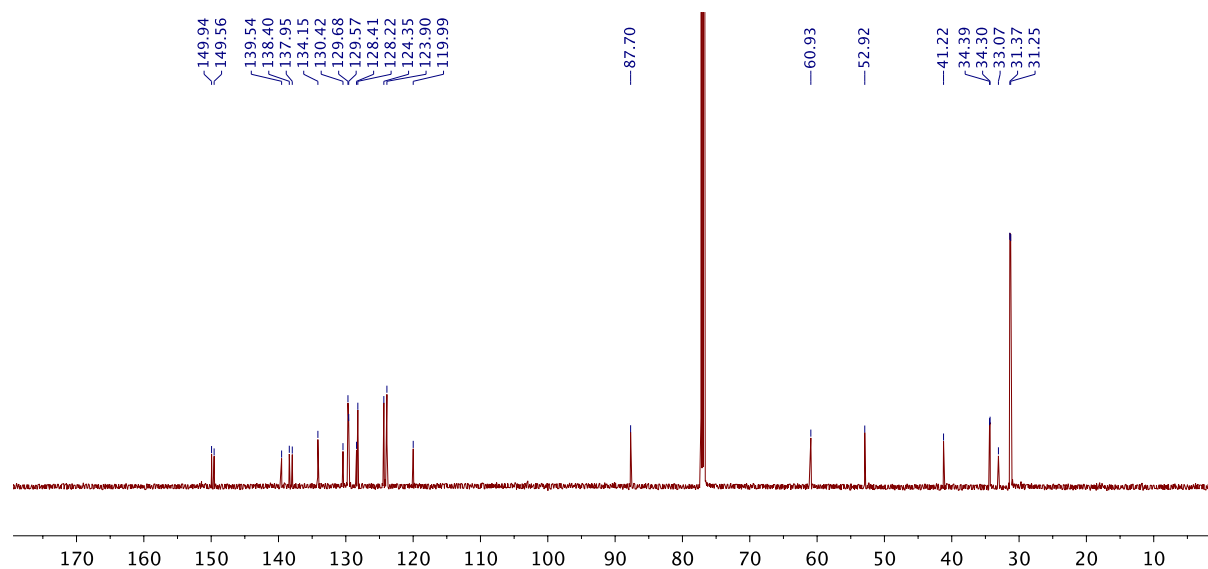
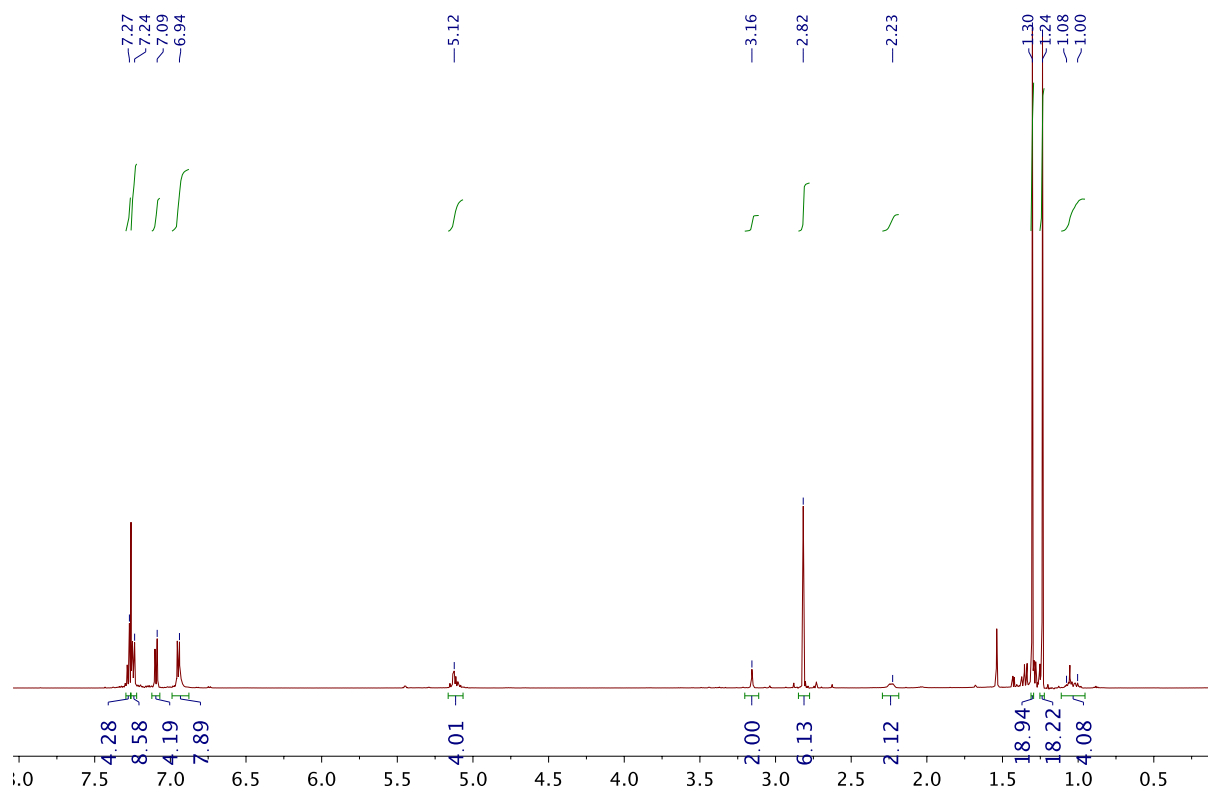
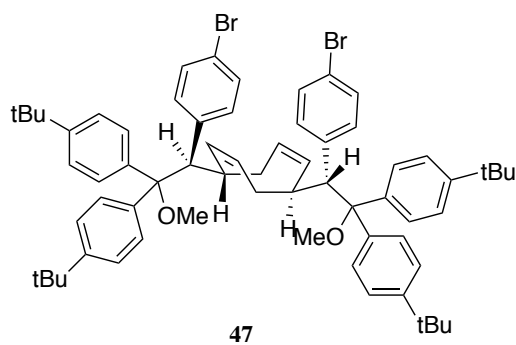


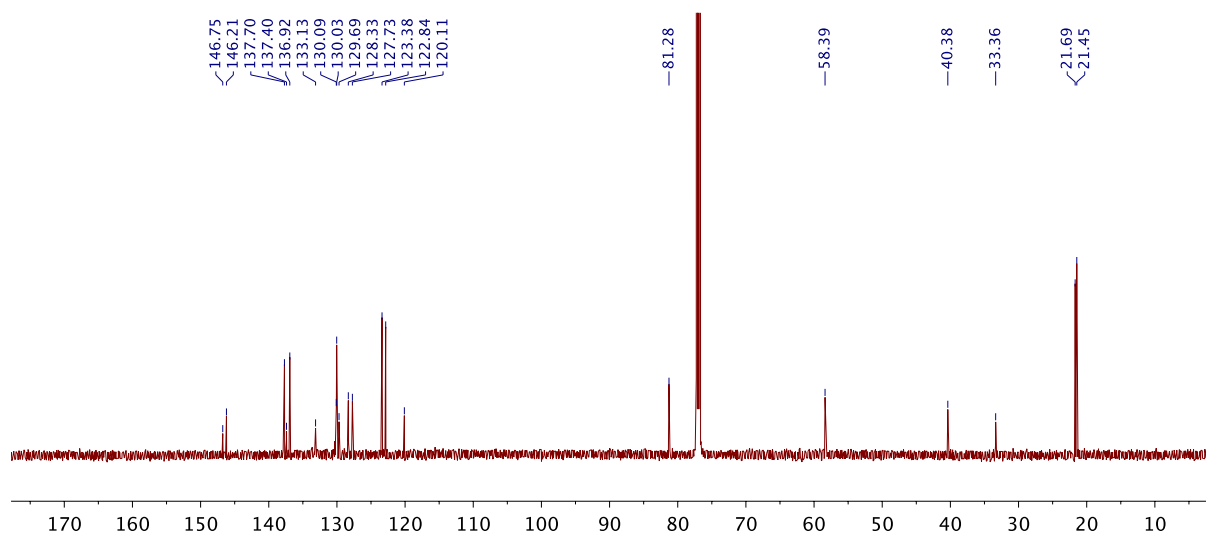
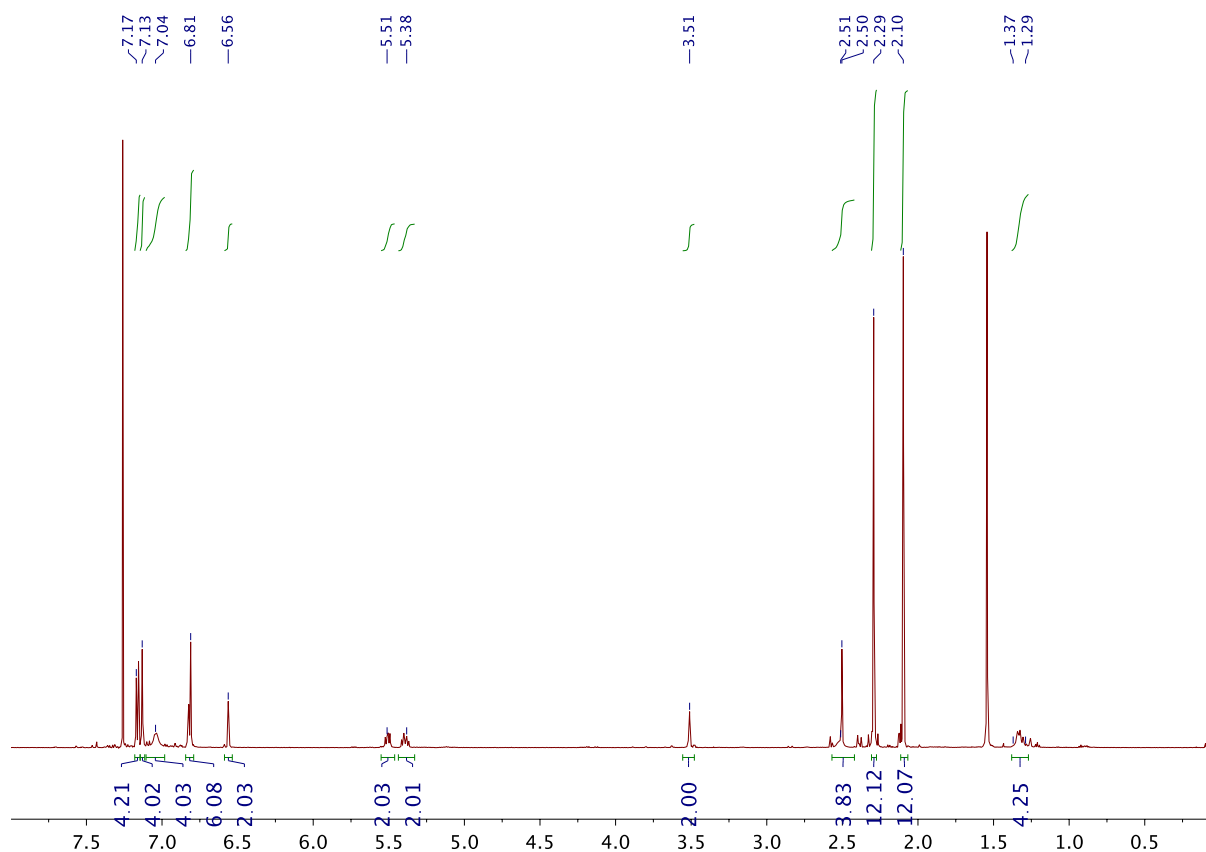
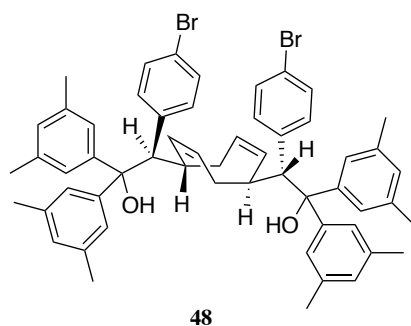


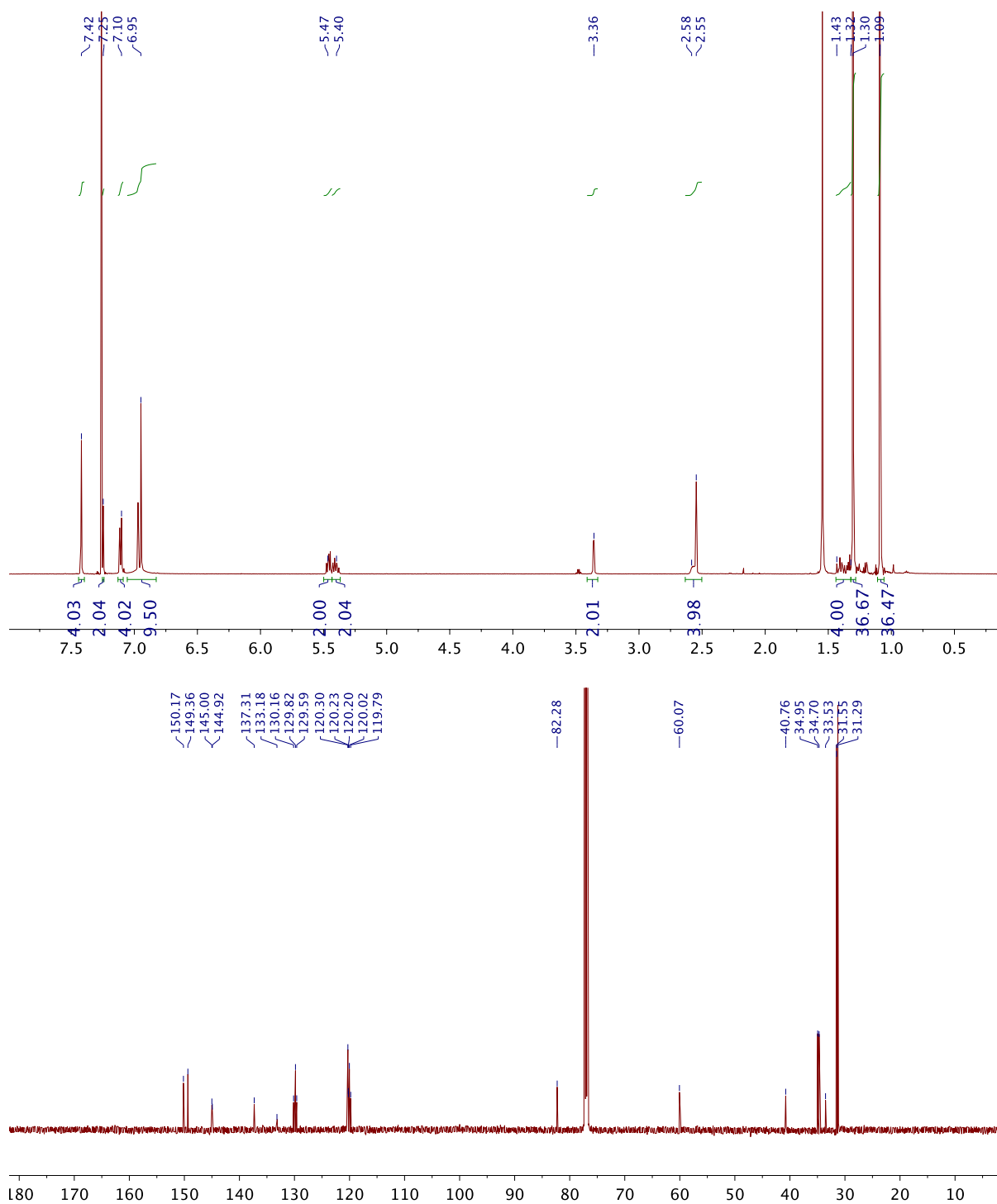
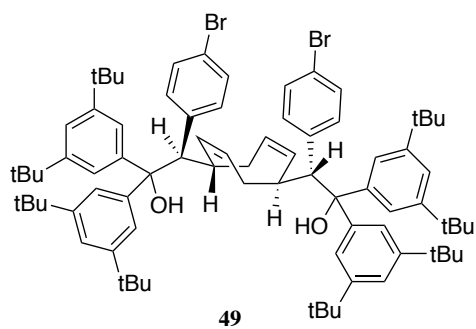
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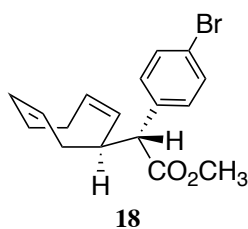








HPLC analysis for mono-insertion products



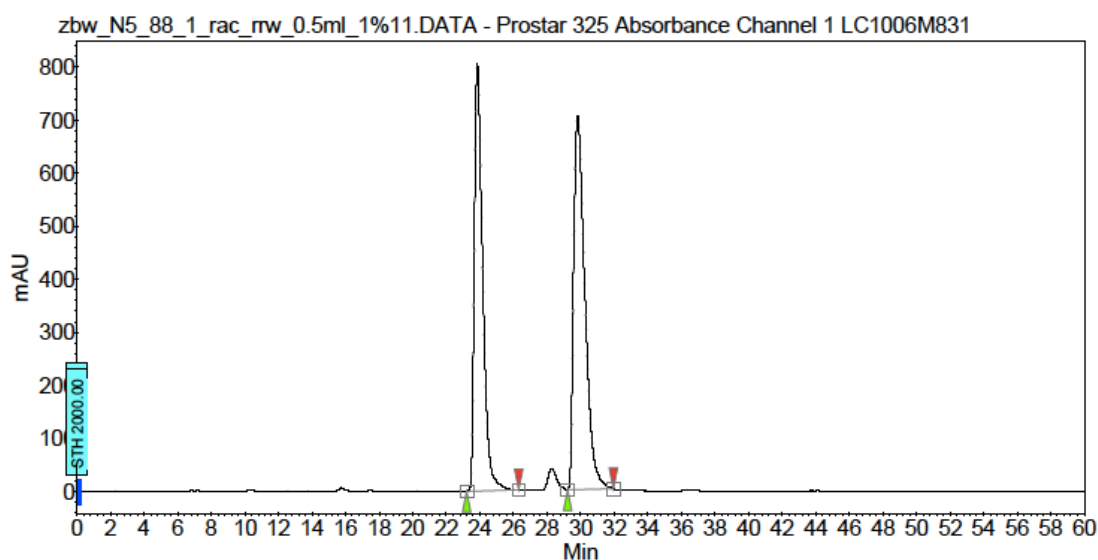
Rh₂(*R/S*-2-Cl,5-BrTPCP)₄ (R,R)-whelk_30min_0.5mL/min_1% **racemic**

(old machine, the system says S4900 column but actually we put RRw column there)

Chromatogram : zbw_N5_88_1_rac_rrw_0.5ml_1%11_channel1

System : Prostar LC System
Method : S4900_30min_0.5mL_1%_210_230
User : User1

Acquired : 9/9/2018 11:47:45 PM
Processed : 11/28/2018 3:54:37 PM
Printed : 11/28/2018 3:54:47 PM



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23.85	46.38	807.5	471.2	46.377
2	UNKNOWN	29.81	53.62	705.1	544.8	53.623
Total			100.00	1512.6	1016.0	100.000

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_30min_0.5mL/min_1% 72% ee.

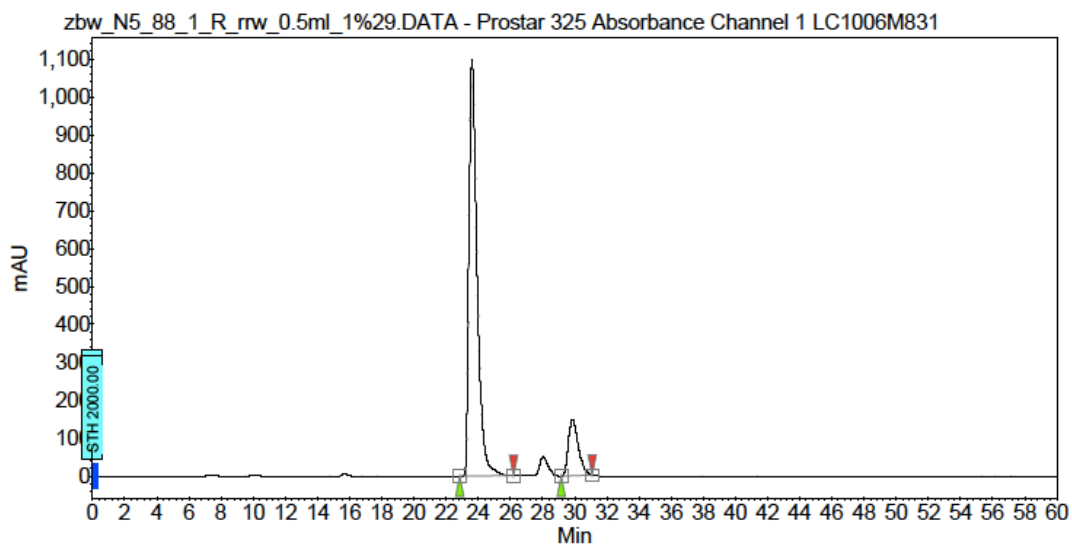
(old machine, the system says S4900 column but actually we put RRw column there)

Chromatogram :

zbw_N5_88_1_R_rrw_0.5ml_1%29_channel1

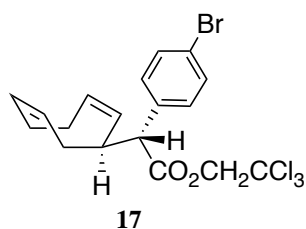
System : Prostar LC System
Method : S4900_30min_0.5mL_1%_210_230
User : User1

Acquired : 9/10/2018 8:24:43 PM
Processed : 11/28/2018 3:49:13 PM
Printed : 11/28/2018 3:52:53 PM



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23.60	85.95	1099.7	646.5	85.947
2	UNKNOWN	29.85	14.05	148.9	105.7	14.053
Total			100.00	1248.6	752.2	100.000



Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(R,R)-whelk_30min_0.5mL/min_0.5%

racemic

(old machine, the system says S4900 column but actually we put RRw column there)

Chromatogram : zbw_N5_55_racemic72_channel1

System : Prostar LC System

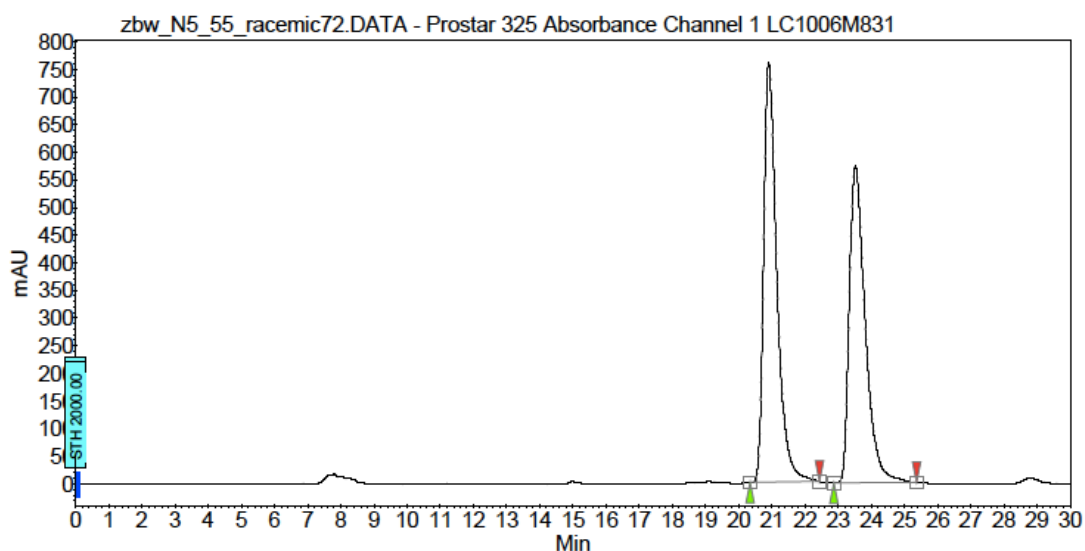
Method : S4900_30min_0.5mL_0.5%_210_230

User : User1

Acquired : 7/24/2018 7:56:46 PM

Processed : 11/28/2018 2:57:54 PM

Printed : 11/28/2018 2:58:29 PM



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20.91	52.35	760.5	350.6	52.347
2	UNKNOWN	23.52	47.65	573.4	319.1	47.653
Total			100.00	1333.9	669.7	100.000

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_30min_0.5mL/min_0.5% **91% ee.**

(old machine, the system says S4900 column but actually we put RRw column there)

Small scale (0.3 mmol diazo compound)

Chromatogram :

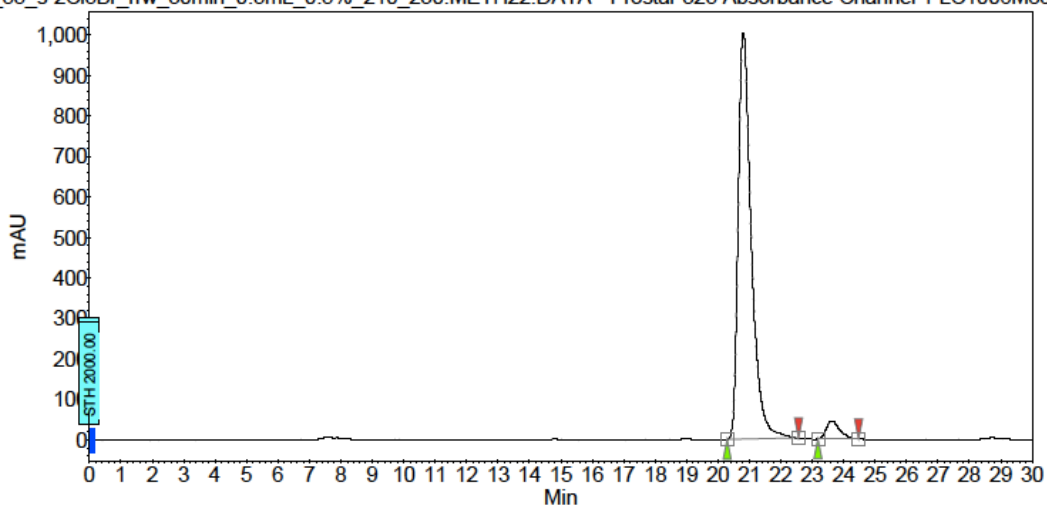
zbw_N5_55_s-2Cl5Br_rw_30min_0.5mL_0.5%_2

40-230.METH22 channel1

Method : S4900_30min_0.5mL_0.5%_210_230
User : User1

Acquired : 7/25/2018 8:59:49 PM
Processed : 7/30/2018 10:08:23 AM
Printed : 11/28/2018 3:01:14 PM

zbw_N5_55_s-2Cl5Br_rw_30min_0.5mL_0.5%_210_230.METH22.DATA - Prostar 325 Absorbance Channel 1 LC1006M831



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20.81	95.63	1003.9	484.7	95.627
2	UNKNOWN	23.62	4.37	44.0	22.2	4.373
Total			100.00	1047.9	506.8	100.000

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_30min_0.5mL/min_0.5% **89% ee.**

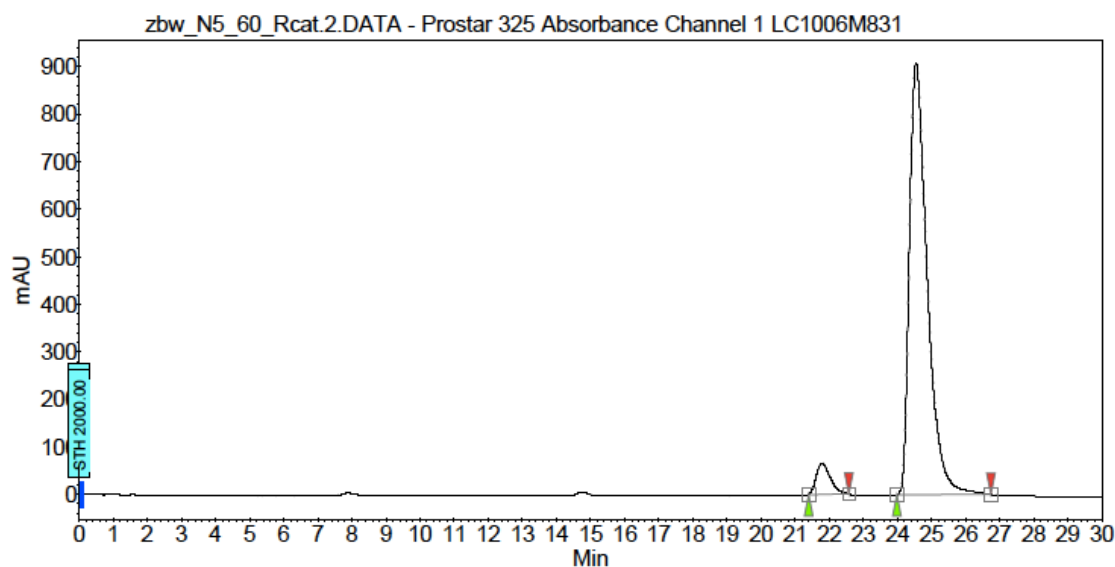
(old machine, the system says S4900 column but actually we put RRw column there)

Large scale (3 mmol diazo compound)

Chromatogram : zbw_N5_60_Rcat.2_channel1

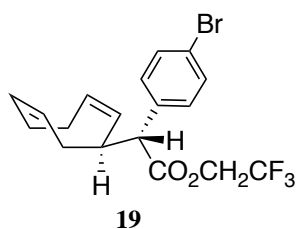
System : Prostar LC System
Method : S4900_30min_0.5mL_0.5%_210_230
User : User1

Acquired : 7/30/2018 1:02:21 AM
Processed : 7/30/2018 10:06:02 AM
Printed : 11/28/2018 3:06:12 PM



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	21.80	5.36	66.2	31.2	5.358
2	UNKNOWN	24.55	94.64	910.1	550.5	94.642
Total			100.00	976.3	581.6	100.000



Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(*R,R*)-whelk_30min_0.5mL/min_0.5%

racemic

(old machine, the system says S4900 column but actually we put RRw column there)

Chromatogram :

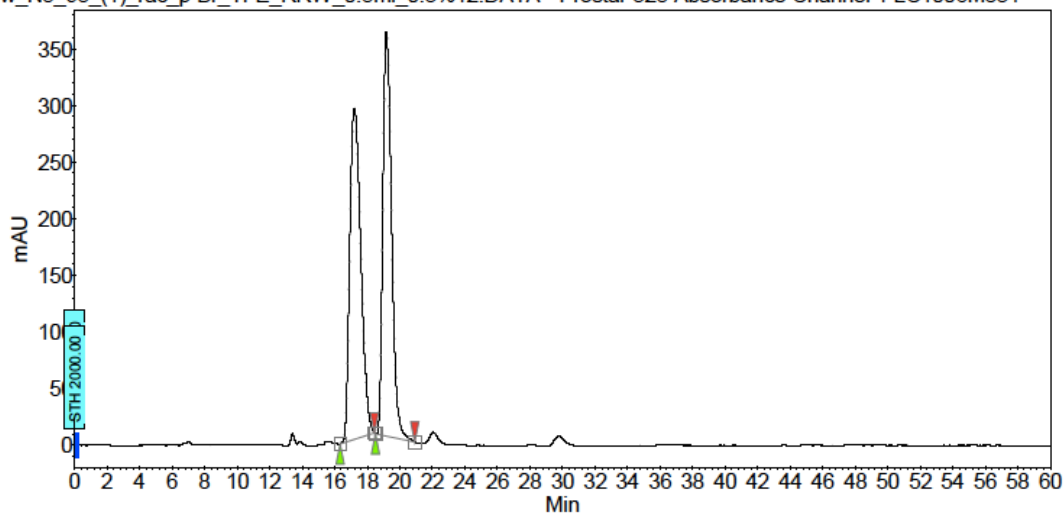
zbw_N5_95_(1)_rac_p-Br_TFE_RRW_0.5ml_0.3%

12 channel1

System : System
Method : S4900_30min_0.5mL_0.5%_210_230
User : User1

Acquired : 9/20/2018 1:23:37 PM
Processed : 11/28/2018 4:00:04 PM
Printed : 11/28/2018 4:00:15 PM

zbw_N5_95_(1)_rac_p-Br_TFE_RRW_0.5ml_0.3%12.DATA - Prostar 325 Absorbance Channel 1 LC1006M831



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17.21	50.88	292.8	230.5	50.882
2	UNKNOWN	19.19	49.12	357.7	222.5	49.118
Total			100.00	650.5	453.0	100.000

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_30min_0.5mL/min_0.5% **93% ee.**

(old machine, the system says S4900 column but actually we put RRw column there)

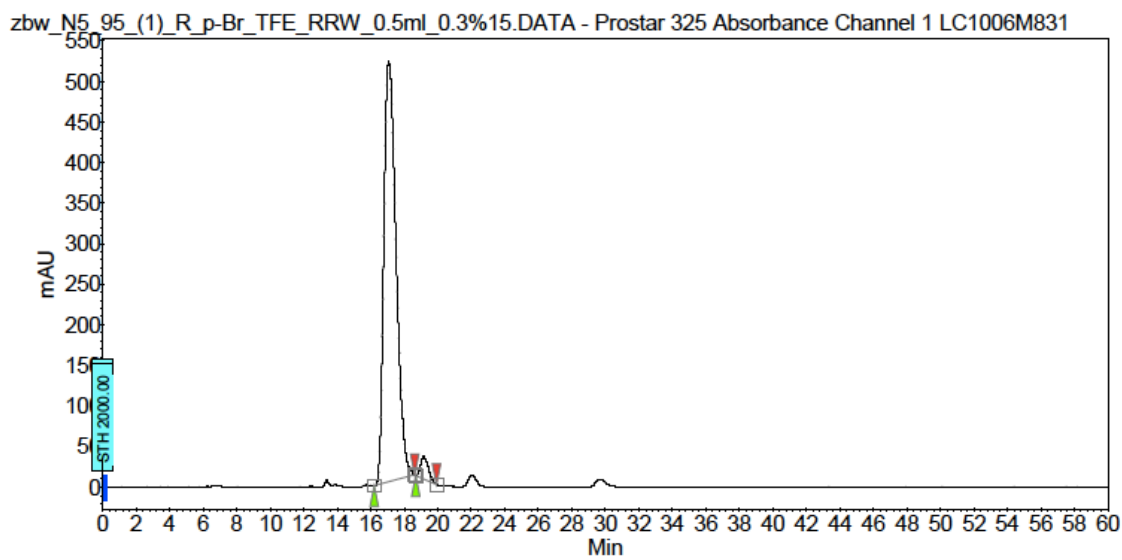
Chromatogram :

zbw_N5_95_(1)_R_p-Br_TFE_RRW_0.5ml_0.3%1

5 channel1

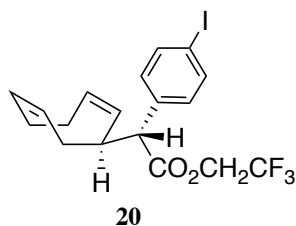
System
Method : S4900_30min_0.5mL_0.5%_210_230
User : User1

Acquired : 9/20/2018 3:11:43 PM
Processed : 11/28/2018 4:00:59 PM
Printed : 11/28/2018 4:01:08 PM



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17.08	96.74	519.5	436.9	96.736
2	UNKNOWN	19.19	3.26	27.3	14.7	3.264
Total			100.00	546.8	451.7	100.000



Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(*R,R*)-whelk_30min_0.5mL/min_0.5%

racemic

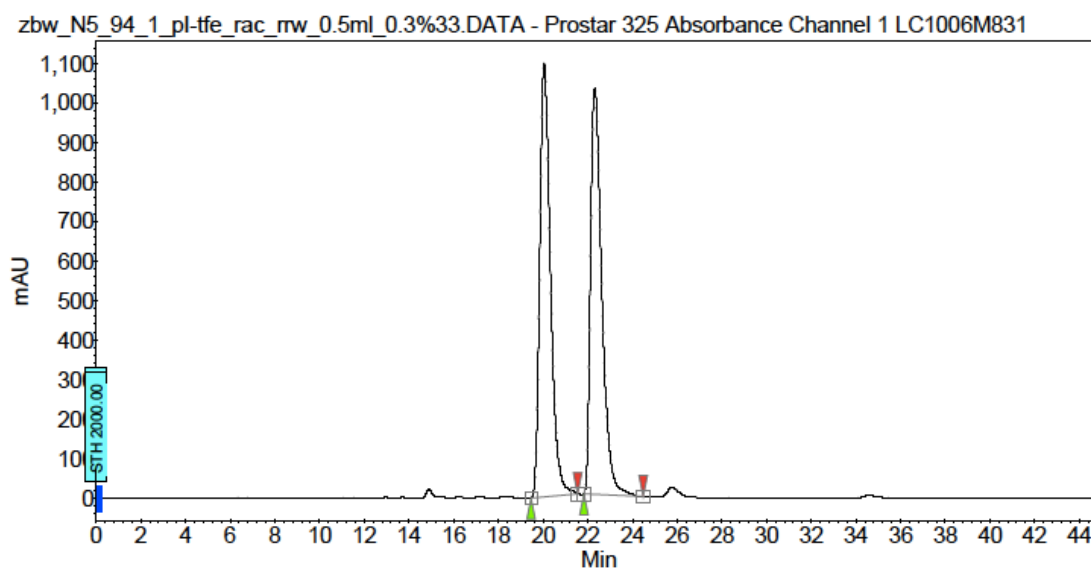
(old machine, the system says S4900 column but actually we put RRw column there)

Chromatogram :

zbw_N5_94_1_pl-tfe_rac_rrw_0.5ml_0.3%33_cha

Method : S4900_30min_0.5mL_0.5%_210_230
User : User1

Acquired : 9/16/2018 1:43:04 AM
Processed : 11/28/2018 3:35:34 PM
Printed : 11/28/2018 3:35:45 PM



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20.05	50.27	1096.8	608.0	50.270
2	UNKNOWN	22.31	49.73	1029.3	601.5	49.730
Total			100.00	2126.1	1209.5	100.000

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_30min_0.5mL/min_0.5% **95% ee.**

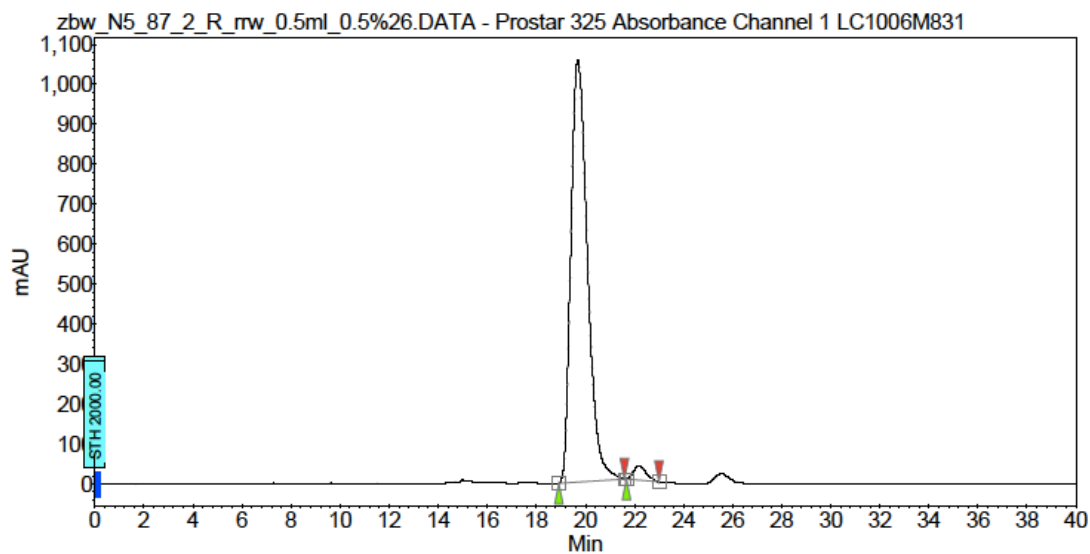
(old machine, the system says S4900 column but actually we put RRw column there)

Chromatogram :

zbw_N5_87_2_R_rrw_0.5ml_0.5%26_channel1

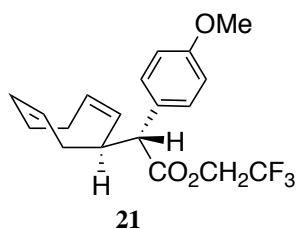
System : Prostar LC System
Method : S4900_30min_0.5mL_0.5%_210_230
User : User1

Acquired : 9/10/2018 6:57:05 PM
Processed : 11/28/2018 3:38:43 PM
Printed : 11/28/2018 3:38:54 PM



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	19.69	97.49	1057.2	826.3	97.488
2	UNKNOWN	22.19	2.51	34.4	21.3	2.512
Total			100.00	1091.6	847.6	100.000



Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(R,R)-whelk_30min_0.5mL/min_0.5%

racemic

(old machine, the system says S4900 column but actually we put RRw column there)

Chromatogram :

zbw_N5_93_2_p-OMe_rac_rrw_0.5ml_0.5%12_ch

Prostar LC System

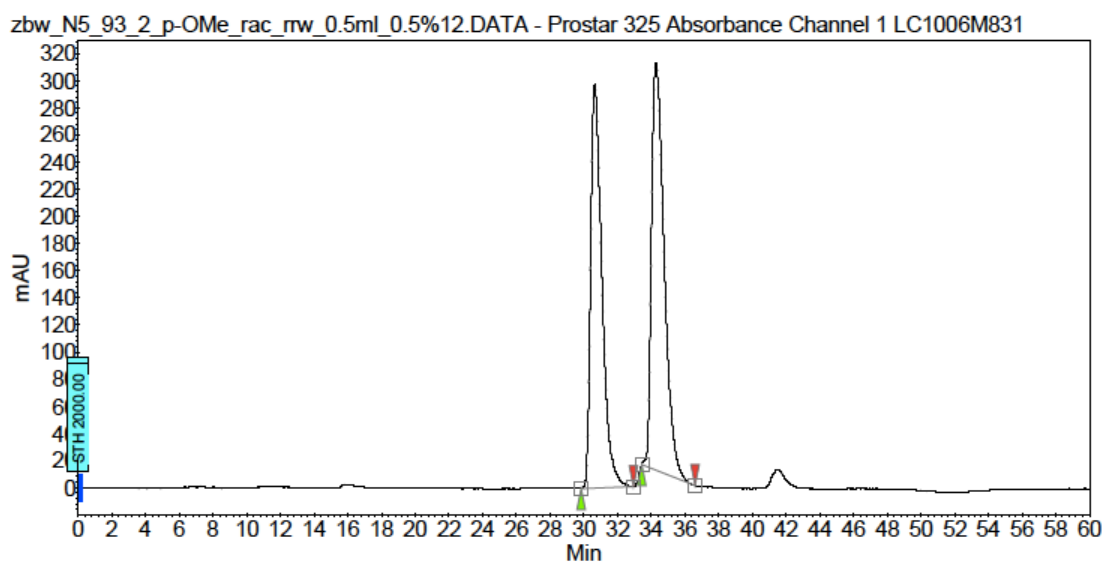
Method : S4900_30min_0.5mL_0.5%_210_230

User : User1

Acquired : 9/17/2018 6:40:29 PM

Processed : 11/28/2018 3:57:10 PM

Printed : 11/28/2018 3:57:23 PM



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	30.65	46.98	297.3	232.5	46.979
2	UNKNOWN	34.29	53.02	300.2	262.4	53.021
Total			100.00	597.5	494.9	100.000

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_30min_0.5mL/min_0.5% **81% ee.**

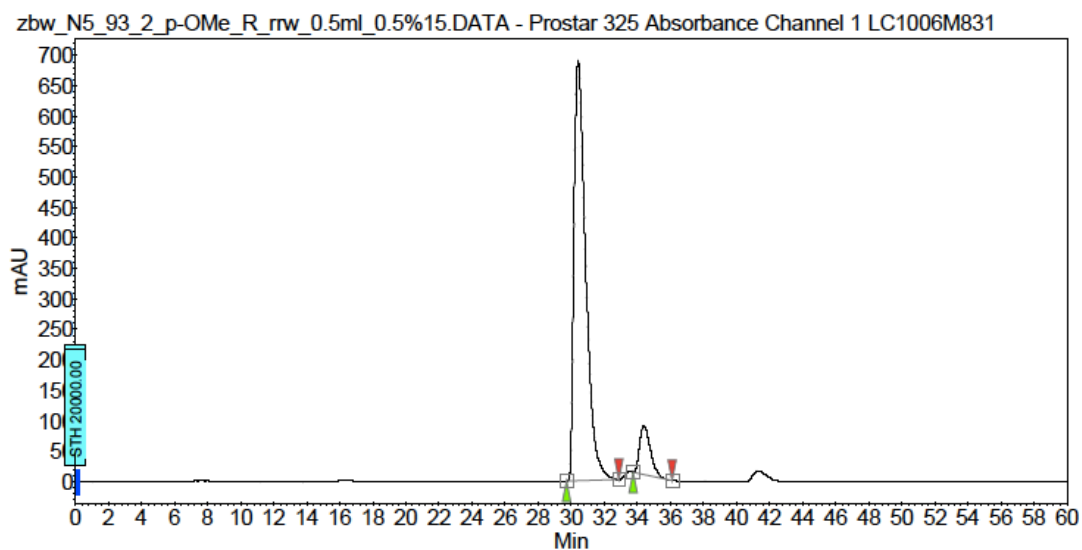
(old machine, the system says S4900 column but actually we put RRw column there)

Chromatogram :

zbw_N5_93_2_p-OMe_R_rrw_0.5ml_0.5%15_cha

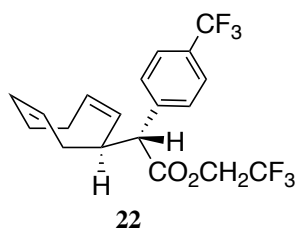
Prostar LC System
Method : S4900_30min_0.5mL_0.5%_210_230
User : User1

Acquired : 9/17/2018 8:28:46 PM
Processed : 11/28/2018 3:58:29 PM
Printed : 11/28/2018 3:58:42 PM



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	30.41	90.38	690.9	566.3	90.380
2	UNKNOWN	34.40	9.62	79.5	60.3	9.620
Total			100.00	770.4	626.5	100.000



Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(*R,R*)-whelk_60min_0.5mL/min_1%

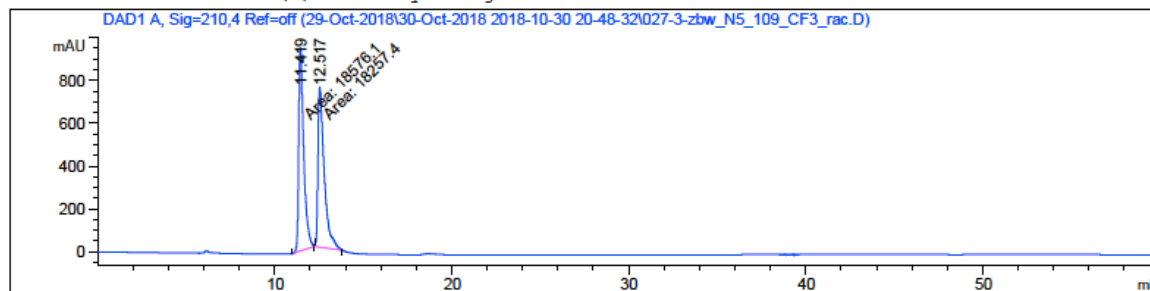
racemic

(new machine, the column is correct)

Data File C:\Chem32\...\Oct-2018\30-Oct-2018 2018-10-30 20-48-32\027-3-zbw_N5_109_CF3_rac.D

Sample Name: zbw_N5_109_CF3_rac

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   27
Acq. Instrument : Agilent 1100                Location  :    3
Injection Date  : 10/31/2018 11:17:02 AM      Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\29-Oct-2018\30-Oct-2018 2018-10-30 20-48-32\WHELK_60min_0.
                  50ML_0.1%.M (Sequence Method)
Last changed    : 6/29/2017 3:15:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.419	MM	0.3256	1.85761e4	950.78387	50.4326
2	12.517	MM	0.4072	1.82574e4	747.31641	49.5674

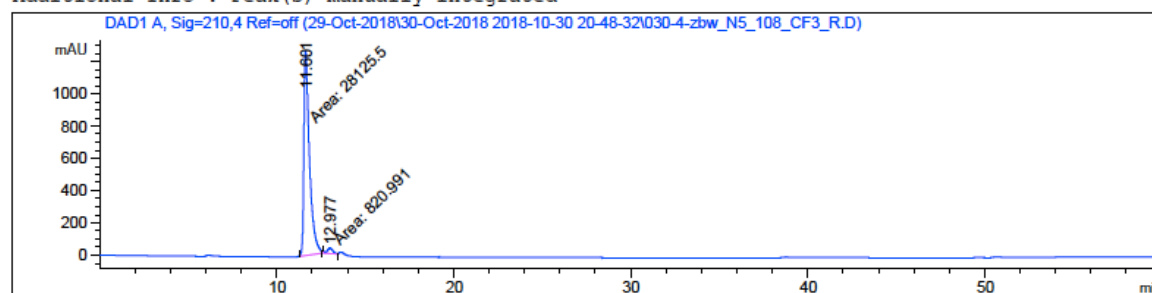
Totals : 3.68335e4 1698.10028

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_60min_0.5mL/min_1% **94% ee.**

(new machine, the column is correct)

Data File C:\Chem32\...9-Oct-2018\30-Oct-2018 2018-10-30 20-48-32\030-4-zbw_N5_108_CF3_R.D
Sample Name: zbw_N5_108_CF3_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   30
Acq. Instrument : Agilent 1100                Location  :    4
Injection Date  : 10/31/2018 1:00:08 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method          : C:\Chem32\1\Data\29-Oct-2018\30-Oct-2018 2018-10-30 20-48-32\WHELK_60min_0.
                  50ML_0.1%.M (Sequence Method)
Last changed    : 6/29/2017 3:15:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



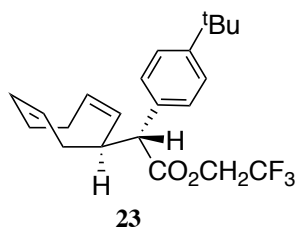
=====
Area Percent Report
=====

```
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.601	MM	0.3693	2.81255e4	1269.22559	97.1638
2	12.977	MM	0.3790	820.99097	36.10427	2.8362

Totals : 2.89465e4 1305.32986



Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(*R,R*)-whelk_60min_0.25mL/min_0.1%

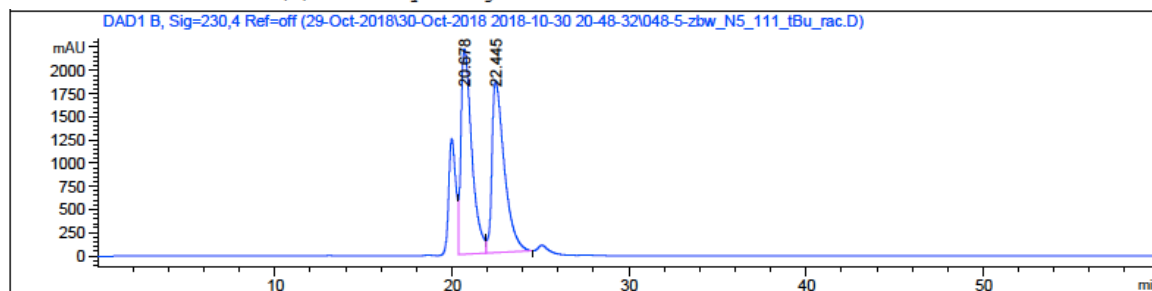
racemic

(new machine, the column is correct)

The racemic contains impurity peak, but not influence determination of 2 ee. peaks

Data File C:\Chem32\...\Oct-2018\30-Oct-2018 2018-10-30 20-48-32\048-5-zbw_N5_111_tBu_rac.D
Sample Name: zbw_N5_111_tBu_rac

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   48
Acq. Instrument : Agilent 1100                Location  :    5
Injection Date  : 10/31/2018 10:09:05 PM      Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\29-Oct-2018\30-Oct-2018 2018-10-30 20-48-32\WHELK_60min_0.
                25ML_0.1%.M (Sequence Method)
Last changed    : 6/29/2017 3:14:16 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.678	VV	0.5037	9.50120e4	2214.04614	51.2073
2	22.445	VB	0.5749	9.05319e4	1846.84668	48.7927

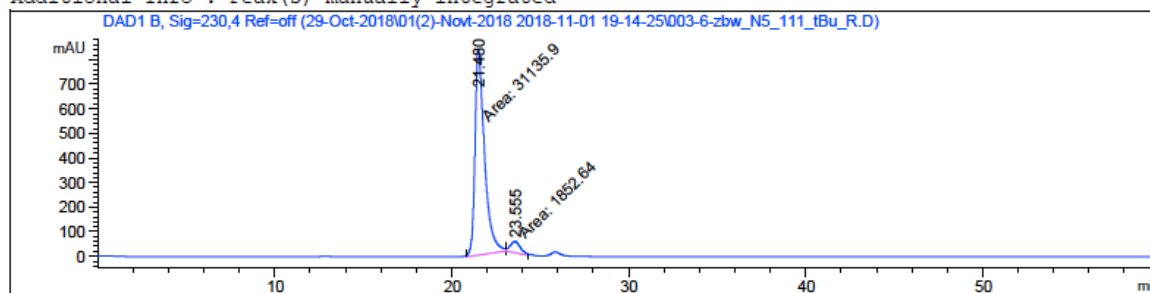
Totals : 1.85544e5 4060.89282

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_60min_0.25mL/min_0.1% 88% ee.

(new machine, the column is correct)

Data File C:\Chem32\...\t-2018\01(2)-Novt-2018 2018-11-01 19-14-25\003-6-zbw_N5_111_tBu_R.D
Sample Name: zbw_N5_111_tBu_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    3
Acq. Instrument : Agilent 1100                Location  :    6
Injection Date  : 11/1/2018 9:51:09 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\29-Oct-2018\01(2)-Novt-2018 2018-11-01 19-14-25\WHELK_
                  60min_0.25ML_0.1%.M (Sequence Method)
Last changed    : 6/29/2017 3:14:16 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



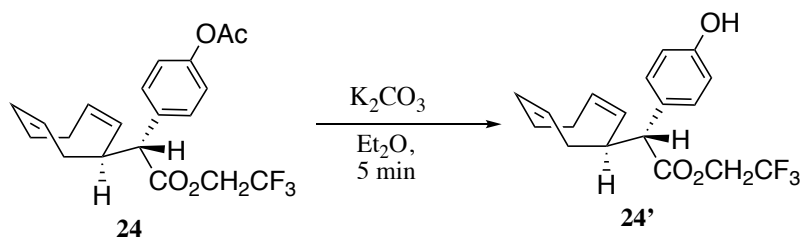
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.480	MM	0.6193	3.11359e4	837.87689	94.3840
2	23.555	MM	0.6690	1852.63745	46.15164	5.6160

Totals : 3.29886e4 884.02853



Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(R,R)-whelk_60min_0.5mL/min_2%

racemic

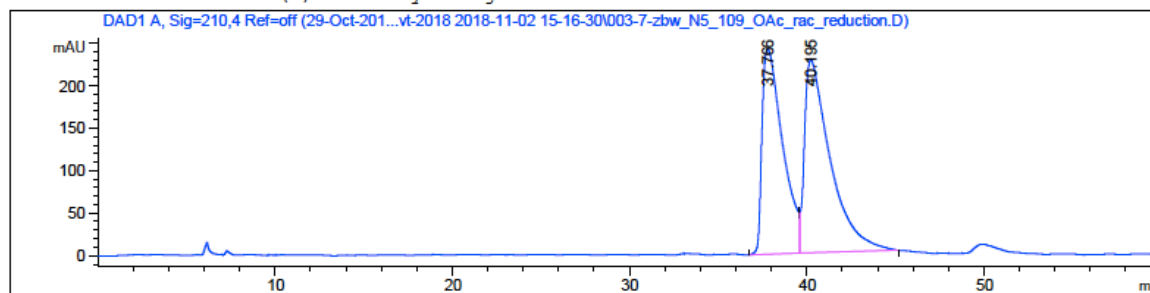
(new machine, the column is correct)

(ee. measured after hydrolysis of the OAc to OH)

Data File C:\Chem32\...\Novt-2018 2018-11-02 15-16-30\003-7-zbw_N5_109_OAc_rac_reduction.D
 Sample Name: zbw_N5_109_OAc_rac_reduction

```

=====
Acq. Operator   : SYSTEM                      Seq. Line :    3
Acq. Instrument : Agilent 1100                Location  :    7
Injection Date  : 11/2/2018 4:01:33 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\29-Oct-2018\02-Novt-2018 2018-11-02 15-16-30\WHELK_60min_0
                  .50ML_2%.M (Sequence Method)
Last changed    : 6/29/2017 3:17:04 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
  
```



Area Percent Report

```

=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
  
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.766	BV	0.9443	1.95137e4	241.85922	45.7811
2	40.195	VB	1.1899	2.31102e4	227.06458	54.2189

Totals : 4.26239e4 468.92380

Rh₂(*R*-2-Cl,5-BrTPCP)₄

chiral.

(R,R)-whelk_60min_0.5mL/min_2%

79% ee.

(new machine, the column is correct)

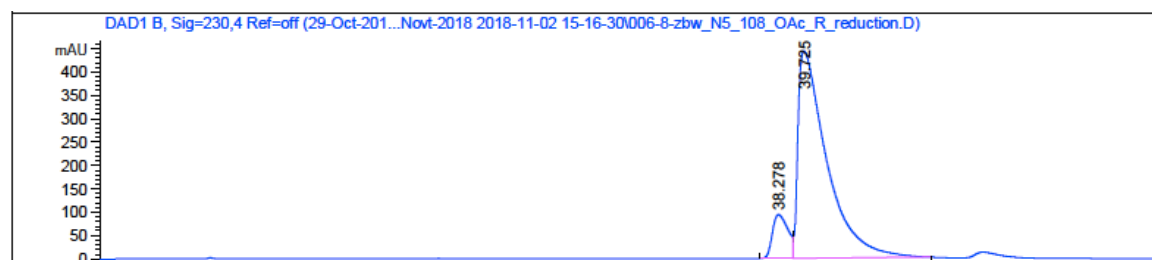
Data File C:\Chem32\...\02-Novt-2018 2018-11-02 15-16-30\006-8-zbw_N5_108_OAc_R_reduction.D
Sample Name: zbw_N5_108_OAc_R_reduction

```

=====
Acq. Operator   : SYSTEM                      Seq. Line :    6
Acq. Instrument : Agilent 1100                Location  :    8
Injection Date  : 11/2/2018 5:44:43 PM         Inj       :    1
                                           Inj Volume: 10.000 µl

Method          : C:\Chem32\1\Data\29-Oct-2018\02-Novt-2018 2018-11-02 15-16-30\WHELK_60min_0
                  .50ML_2%.M (Sequence Method)
Last changed    : 6/29/2017 3:17:04 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====

```



Area Percent Report

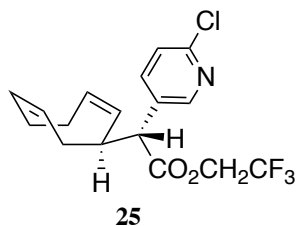
```

=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

```

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.278	BV	0.7143	5703.19141	93.73991	10.2297
2	39.725	VB	1.3202	5.00479e4	443.09872	89.7703
Totals :				5.57511e4	536.83864	



Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(*R,R*)-whelk_60min_0.5mL/min_1%

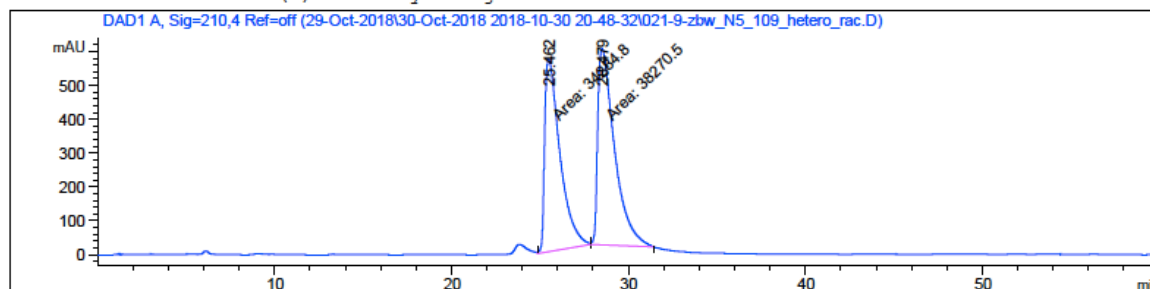
racemic

(new machine, the column is correct)

Data File C:\Chem32\...-2018\30-Oct-2018 2018-10-30 20-48-32\021-9-zbw_N5_109_hetero_rac.D

Sample Name: zbw_N5_109_hetero_rac

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   21
Acq. Instrument : Agilent 1100                Location  :    9
Injection Date  : 10/31/2018 7:50:35 AM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\29-Oct-2018\30-Oct-2018 2018-10-30 20-48-32\WHELK_60min_0.
                    50ML_1%.M (Sequence Method)
Last changed    : 6/29/2017 3:16:23 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.462	MM	1.0022	3.42848e4	570.16846	47.2534
2	28.479	MM	1.0996	3.82705e4	580.06543	52.7466

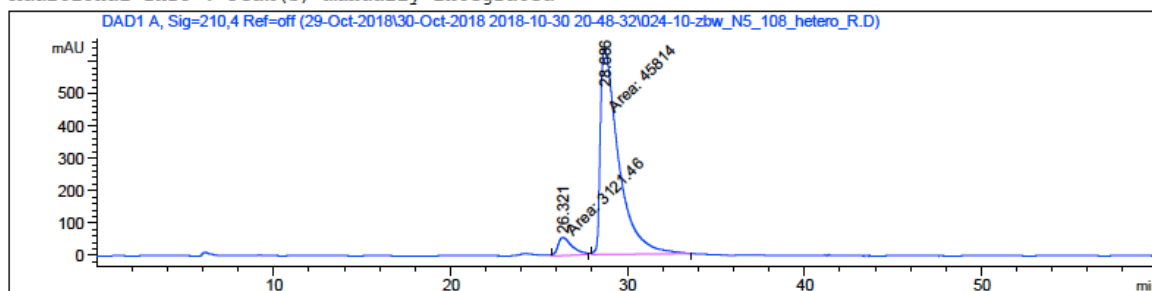
Totals : 7.25554e4 1150.23389

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_60min_0.5mL/min_1% **87% ee.**

(new machine, the column is correct)

Data File C:\Chem32\...\t-2018\30-Oct-2018 2018-10-30 20-48-32\024-10-zbw_N5_108_hetero_R.D
Sample Name: zbw_N5_108_hetero_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   24
Acq. Instrument : Agilent 1100                Location  :   10
Injection Date  : 10/31/2018 9:33:50 AM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\29-Oct-2018\30-Oct-2018 2018-10-30 20-48-32\WHELK_60min_0.
                  50ML_1%.M (Sequence Method)
Last changed    : 6/29/2017 3:16:23 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



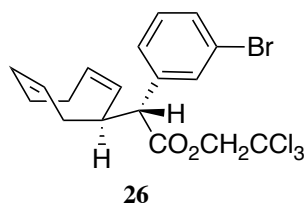
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.321	MM	0.9370	3121.46338	55.52421	6.3787
2	28.686	MM	1.2033	4.58140e4	634.56042	93.6213

Totals : 4.89355e4 690.08463



Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

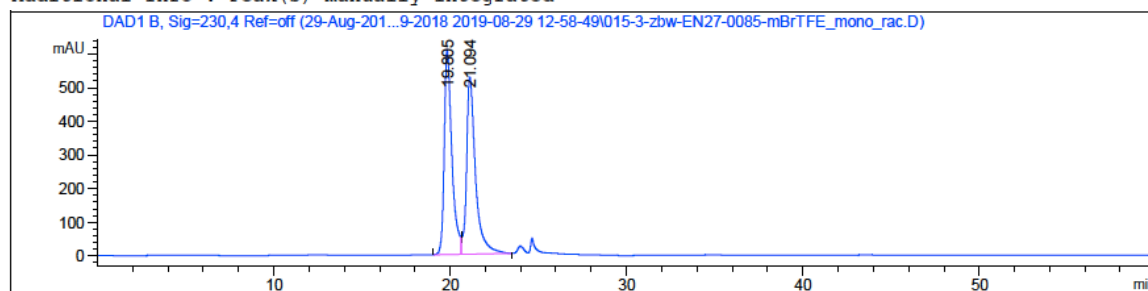
(*R,R*)-wheelk_60min_0.25mL/min_0.5%

racemic

(new machine, the column is correct)

Data File C:\Chem32\...t-29-2018 2019-08-29 12-58-49\015-3-zbw-EN27-0085-mBrTFE_mono_rac.D
Sample Name: zbw-EN27-0085-mBrTFE_mono_rac

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   15
Acq. Instrument : Agilent 1100                Location  :    3
Injection Date  : 8/29/2019 6:34:31 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method          : C:\Chem32\1\Data\29-Aug-2019\August-29-2018 2019-08-29 12-58-49\WHEELK_60min
                  _0.25ML_0.5%.M (Sequence Method)
Last changed    : 6/29/2017 3:15:04 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.805	BV	0.4304	1.83524e4	609.34955	49.7209
2	21.094	VB	0.4897	1.85584e4	527.24005	50.2791

Totals : 3.69108e4 1136.58960

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_60min_0.25mL/min_0.5% 63% ee.

(new machine, the column is correct)

Data File C:\Chem32\...ust-29-2018 2019-08-29 12-58-49\018-4-zbw-EN27-0085-mBrTFE_mono_R.D
Sample Name: zbw-EN27-0085-mBrTFE_mono_R

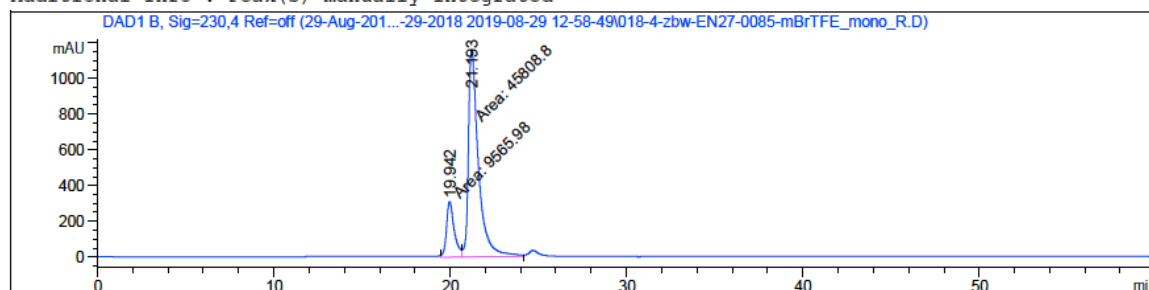
=====

Acq. Operator	: SYSTEM	Seq. Line	: 18
Acq. Instrument	: Agilent 1100	Location	: 4
Injection Date	: 8/29/2019 8:17:46 PM	Inj	: 1
		Inj Volume	: 10.000 µl

Method : C:\Chem32\1\Data\29-Aug-2019\August-29-2018 2019-08-29 12-58-49\WHELK_60min_0.25ML_0.5%.M (Sequence Method)

Last changed : 6/29/2017 3:15:04 PM by SYSTEM

Additional Info : Peak(s) manually integrated



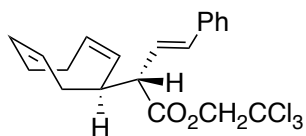
=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.942	MF	0.5108	9565.97754	312.13907	17.2750
2	21.193	FM	0.6580	4.58088e4	1160.35608	82.7250

Totals : 5.53747e4 1472.49515



27

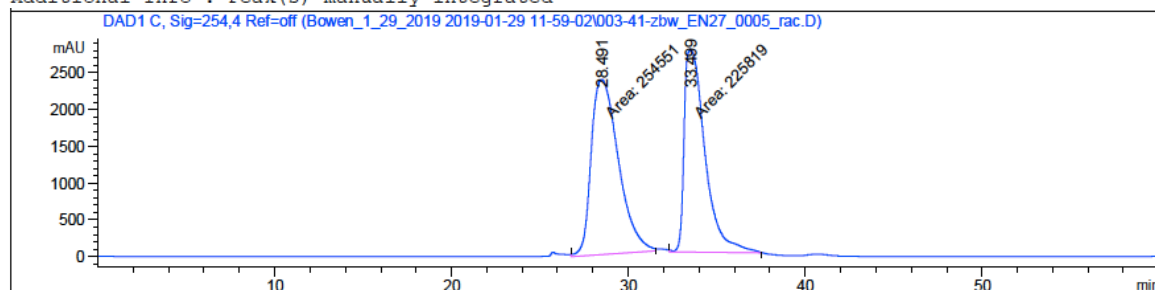
Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(*R,R*)-whelk_60min_0.25mL/min_0.5%

racemic

Data File C:\Chem32\1\Data\Bowen_1_29_2019 2019-01-29 11-59-02\003-41-zbw_EN27_0005_rac.D
Sample Name: zbw_EN27_0005_rac

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    3
Acq. Instrument : Agilent 1100                Location  :   41
Injection Date  : 1/29/2019 12:42:00 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\Bowen_1_29_2019 2019-01-29 11-59-02\WHELK_60min_0.25ML_0.5
                  %.M (Sequence Method)
Last changed    : 6/29/2017 3:15:04 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
```



Area Percent Report

```
Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs
```

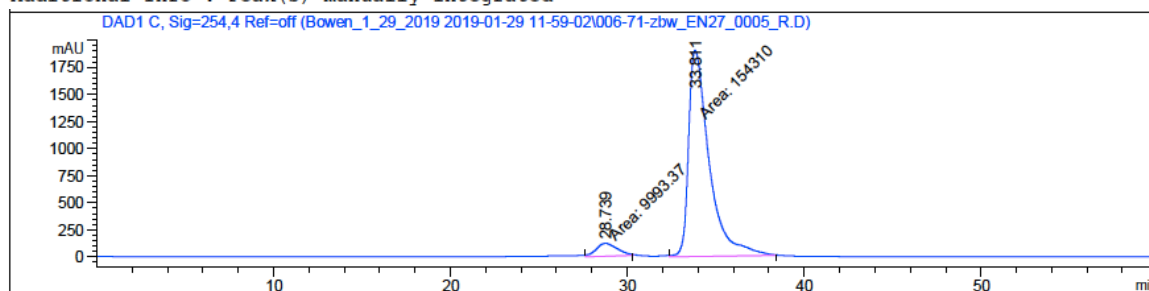
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.491	MM	1.7811	2.54551e5	2381.97681	52.9906
2	33.499	MM	1.3652	2.25819e5	2756.88794	47.0094

Totals : 4.80370e5 5138.86475

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_60min_0.25mL/min_0.5% 88% ee.

Data File C:\Chem32\1\Data\Bowen_1_29_2019 2019-01-29 11-59-02\006-71-zbw_EN27_0005_R.D
Sample Name: zbw_EN27_0005_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    6
Acq. Instrument : Agilent 1100                Location  :   71
Injection Date  : 1/29/2019 2:25:18 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\Bowen_1_29_2019 2019-01-29 11-59-02\WHELK_60min_0.25ML_0.5
                  %M (Sequence Method)
Last changed    : 6/29/2017 3:15:04 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```

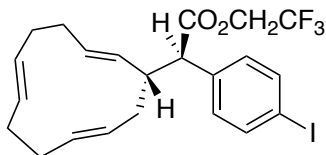


Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
Signal 3: DAD1 C, Sig=254.4 Ref=off
=====
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.739	MM	1.4017	9993.36816	118.82793	6.0822
2	33.811	MM	1.3512	1.54310e5	1903.36523	93.9178

Totals : 1.64304e5 2022.19316



37 (major)

Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(*R,R*)-whelk_60min_0.5mL/min_0.1%

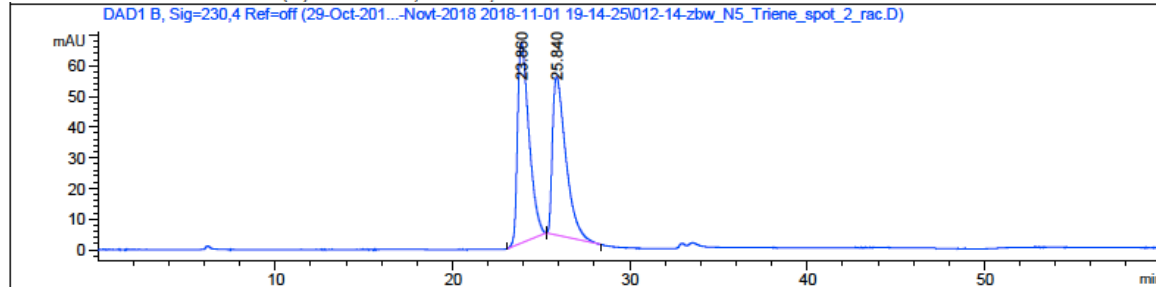
racemic

(new machine, the column is correct)

Data File C:\Chem32\...\(2)-Novt-2018 2018-11-01 19-14-25\012-14-zbw_N5_Triene_spot_2_rac.D

Sample Name: zbw_N5_Triene_spot_2_rac

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   12
Acq. Instrument : Agilent 1100                Location  :   14
Injection Date  : 11/2/2018 3:00:39 AM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\29-Oct-2018\01(2)-Novt-2018 2018-11-01 19-14-25\WHELK_
                  60min_0.50ML_0.1%.M (Sequence Method)
Last changed    : 6/29/2017 3:15:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
                  DAD1 B, Sig=230,4 Ref=off (29-Oct-2018-2018-11-01 19-14-25\012-14-zbw_N5_Triene_spot_2_rac.D)
=====
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.860	BB	0.5301	2938.78125	65.53732	51.8959
2	25.840	BB	0.6164	2724.05762	51.68593	48.1041

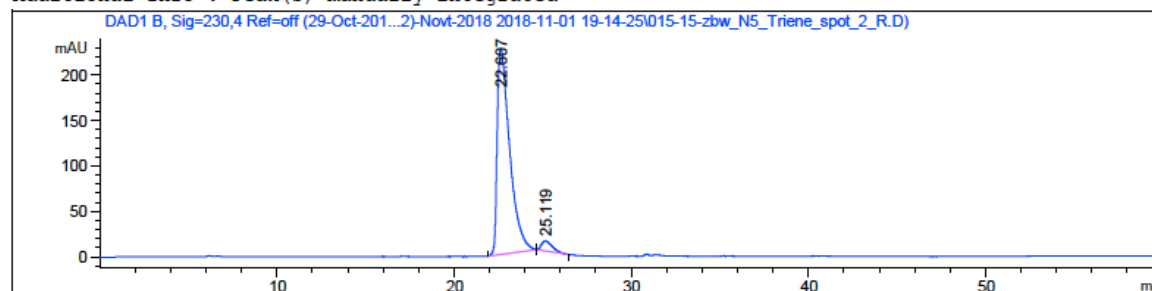
Totals : 5662.83887 117.22326

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_60min_0.5mL/min_0.1% 92% ee.

(new machine, the column is correct)

Data File C:\Chem32\...01(2)-Novt-2018 2018-11-01 19-14-25\015-15-zbw_N5_Triene_spot_2_R.D
Sample Name: zbw_N5_Triene_spot_2_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   15
Acq. Instrument : Agilent 1100                Location  :   15
Injection Date  : 11/2/2018 4:43:47 AM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\29-Oct-2018\01(2)-Novt-2018 2018-11-01 19-14-25\WHELK_
                  60min_0.50ML_0.1%.M (Sequence Method)
Last changed   : 6/29/2017 3:15:25 PM by SYSTEM
Additional Info : Peak(s) manually integrated
=====
```



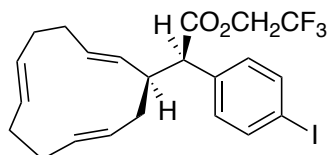
=====
Area Percent Report
=====

```
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.607	BB	0.6548	1.10904e4	225.90422	95.9992
2	25.119	BB	0.4957	462.19281	10.93318	4.0008

Totals : 1.15526e4 236.83741



37 (minor)

Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

(*R,R*)-whelk_60min_0.5mL/min_0.1%

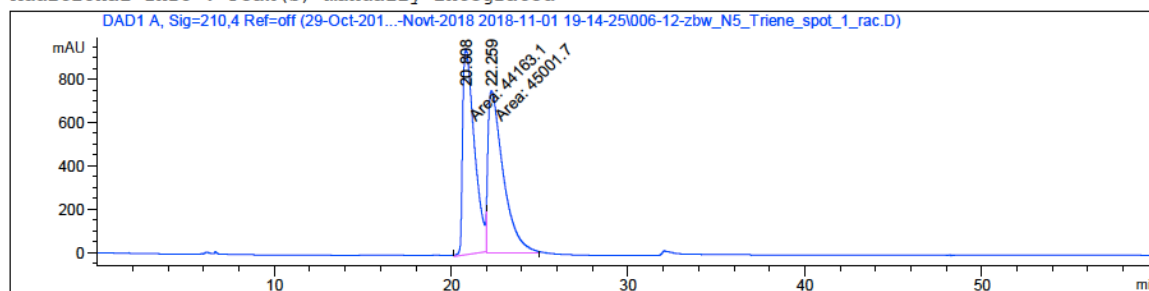
racemic

(new machine, the column is correct)

Data File C:\Chem32\...\(2)-Novt-2018 2018-11-01 19-14-25\006-12-zbw_N5_Triene_spot_1_rac.D
Sample Name: zbw_N5_Triene_spot_1_rac

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    6
Acq. Instrument : Agilent 1100                Location  :   12
Injection Date  : 11/1/2018 11:34:18 PM        Inj       :    1
                                           Inj Volume: 10.000 µl

Method          : C:\Chem32\1\Data\29-Oct-2018\01(2)-Novt-2018 2018-11-01 19-14-25\WHELK_
                  60min_0.50ML_0.1%.M (Sequence Method)
Last changed    : 6/29/2017 3:15:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.808	MM	0.7756	4.41631e4	948.97925	49.5297
2	22.259	MM	1.0038	4.50017e4	747.17798	50.4703

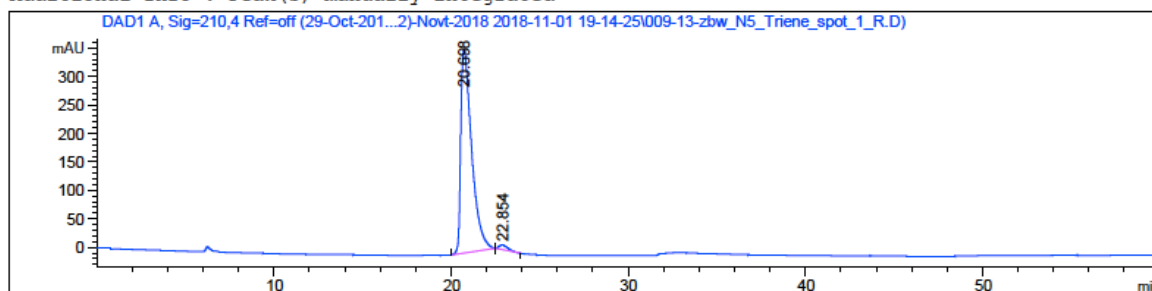
Totals : 8.91648e4 1696.15723

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. (R,R)-whelk_60min_0.5mL/min_0.1% 96% ee.

(new machine, the column is correct)

Data File C:\Chem32\...\01(2)-Novt-2018 2018-11-01 19-14-25\009-13-zbw_N5_Triene_spot_1_R.D
Sample Name: zbw_N5_Triene_spot_1_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    9
Acq. Instrument : Agilent 1100                Location  :   13
Injection Date  : 11/2/2018 1:17:27 AM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method          : C:\Chem32\1\Data\29-Oct-2018\01(2)-Novt-2018 2018-11-01 19-14-25\WHELK_
                  60min_0.50ML_0.1%.M (Sequence Method)
Last changed    : 6/29/2017 3:15:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

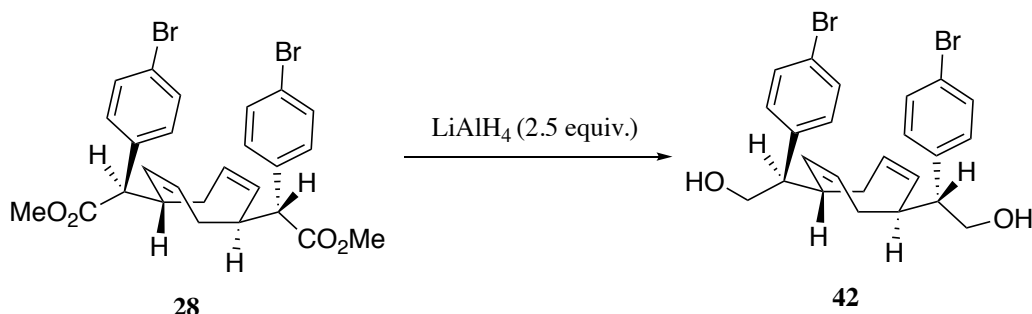
Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.698	BB	0.5894	1.52595e4	357.16669	98.0558
2	22.854	BB	0.4122	302.55719	8.61666	1.9442

Totals : 1.55621e4 365.78335

HPLC analysis for di-insertion products

* For 29, the pre-mixed racemic catalyst can generate isolable racemic sample, for others, the racemic reaction either give meso dr as major or too difficult to separate, therefore R and S catalyst were used to measure ee.



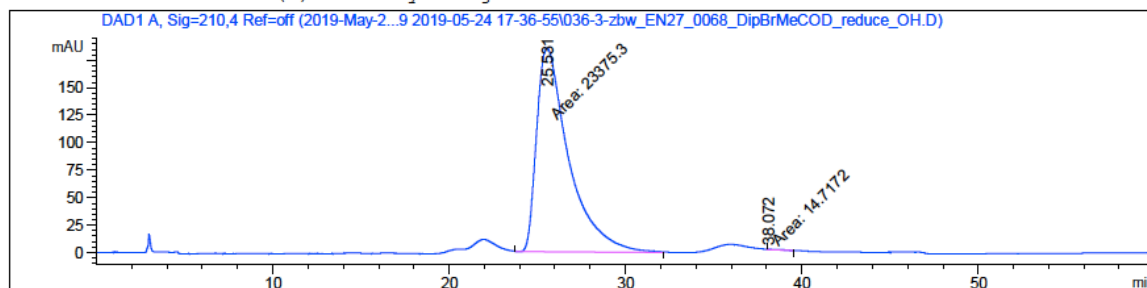
$\text{Rh}_2(R\text{-}2\text{-Cl,5-BrTPCP})_4$ chiral. OD_60min_1mL/min_10% >99% ee.

(new machine, the column is correct)

(ee. measured after reduction of di-ester to di-ol)

Data File C:\Chem32\...2019-05-24 17-36-55\036-3-zbw_EN27_0068_DipBrMeCOD_reduce_OH.D
Sample Name: zbw_EN27_0068_DipBrMeCOD_reduce_OH_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   36
Acq. Instrument : Agilent 1100                Location  :    3
Injection Date  : 5/25/2019 1:15:01 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\2019-May-24\24-May-2019 2019-05-24 17-36-55\OD_60min_1.OML
                                           _10%.M (Sequence Method)
Last changed    : 6/29/2017 2:56:25 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.531	MM	2.1037	2.33753e4	185.18878	99.9371
2	38.072	MM	0.6951	14.71724	3.52856e-1	0.0629

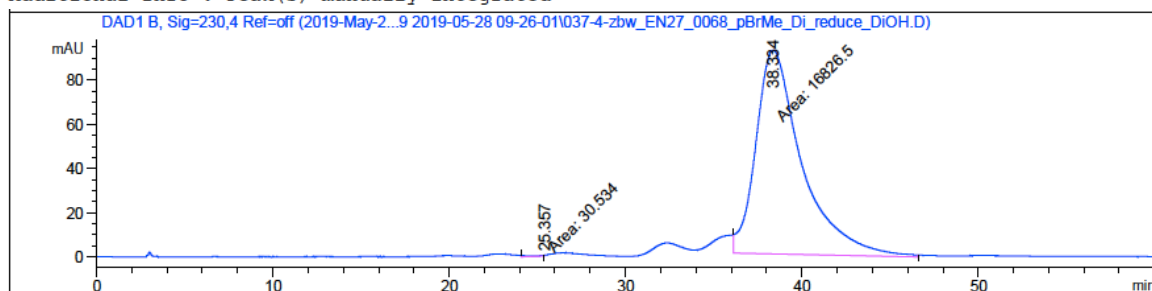
Totals : 2.33900e4 185.54164

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. OD_60min_1mL/min_10% >99% ee.

(new machine, the column is correct)

Sample Name: zbw_EN27_0068_pBrMe_Di_reduce_DiOH_Scat.

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   37
Acq. Instrument : Agilent 1100                Location  :    4
Injection Date  : 5/29/2019 12:47:30 AM       Inj       :    1
                                           Inj Volume: 10.000 µl
Method          : C:\Chem32\1\Data\2019-May-28\28-May-2019 2019-05-28 09-26-01\OD_60min_1.OML
                  _10%.M (Sequence Method)
Last changed    : 6/29/2017 2:56:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```

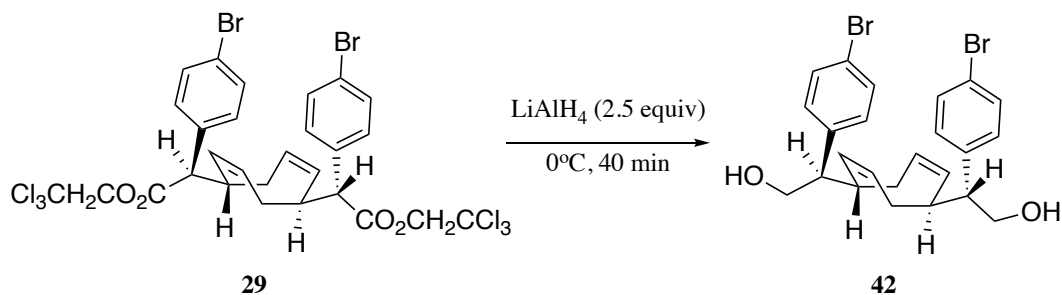


Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
Signal 2: DAD1 B, Sig=230,4 Ref=off
=====
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.357	MM	1.2413	30.53397	4.09984e-1	0.1811
2	38.334	FM	3.0343	1.68265e4	92.42507	99.8189

Totals : 1.68571e4 92.83506



Rh₂(*R/S*-2-Cl,5-BrTPCP)₄

OD_60min_1mL/min_10%

racemic

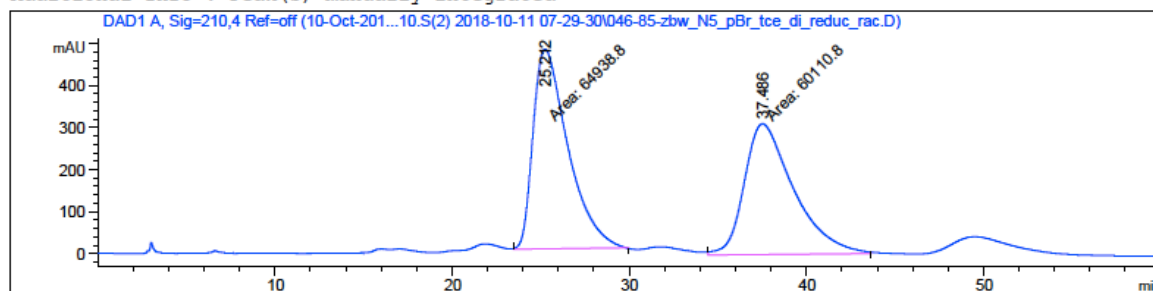
(new machine, the column is correct)

(ee. measured after reduction of di-ester to di-ol)

Data File C:\Chem32\...\ct.10.S(2) 2018-10-11 07-29-30\046-85-zbw_N5_pBr_tce_di_reduc_rac.D
 Sample Name: zbw_N5_pBr_tce_di_reduc_rac

```

=====
Acq. Operator   : SYSTEM                      Seq. Line :   46
Acq. Instrument : Agilent 1100                Location  :   85
Injection Date  : 10/12/2018 8:14:43 AM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\10-Oct-2018\2018.Oct.10.S(2) 2018-10-11 07-29-30\OD_60min_
                  1.0ML_10%.M (Sequence Method)
Last changed    : 6/29/2017 2:56:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
  
```



Area Percent Report

```

=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
  
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.212	MM	2.2808	6.49388e4	474.53320	51.9304
2	37.486	MM	3.2266	6.01108e4	310.49551	48.0696

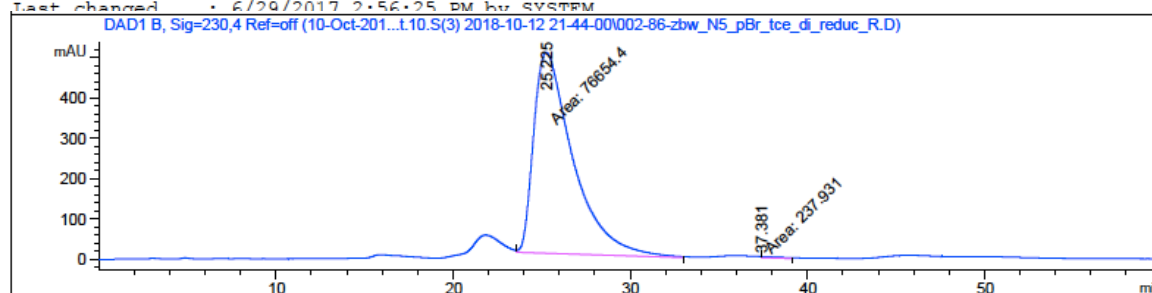
Totals : 1.25050e5 785.02872

Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. OD_60min_1mL_10% >99% ee.

(new machine, the column is correct)

Data File C:\Chem32\....Oct.10.S(3) 2018-10-12 21-44-00\002-86-zbw_N5_pBr_tce_di_reduc_R.D
Sample Name: zbw_N5_pBr_tce_di_reduc_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    2
Acq. Instrument : Agilent 1100                Location  :   86
Injection Date  : 10/12/2018 10:18:20 PM      Inj       :    1
                                           Inj Volume: 10.000 µl
Method          : C:\Chem32\1\Data\10-Oct-2018\2018.Oct.10.S(3) 2018-10-12 21-44-00\OD_60min_
                  1.0ML_10%.M (Sequence Method)
Last changed    : 6/29/2017 2:56:25 PM by SYSTEM
```



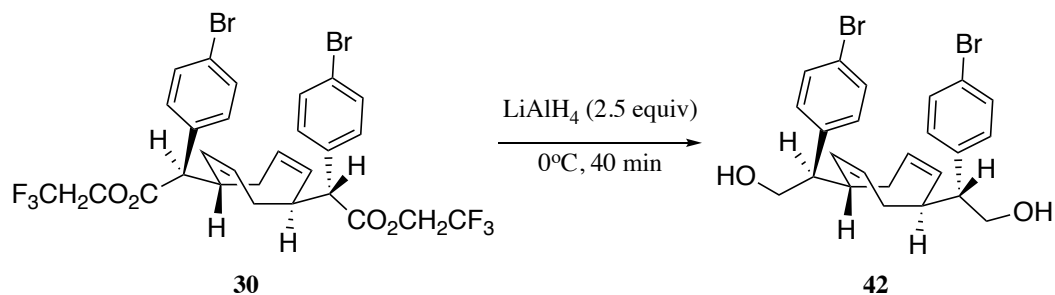
Area Percent Report

```
=====
Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.225	MM	2.5663	7.66544e4	497.81952	99.6906
2	37.381	MM	1.3720	237.93073	2.89031	0.3094

Totals : 7.68923e4 500.70983



$\text{Rh}_2(R\text{-}2\text{-Cl},5\text{-BrTPCP})_4$ chiral. OD_60min_1mL/min_10% >99% ee.

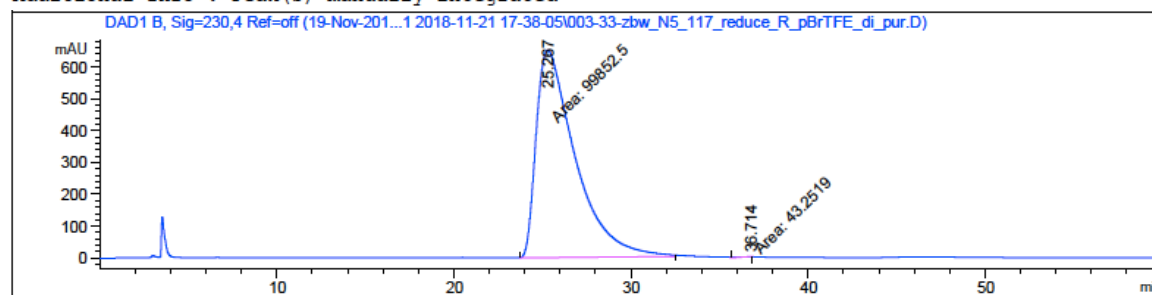
(new machine, the column is correct)

(ee. measured after reduction of di-ester to di-ol)

Data File C:\Chem32\...1.21 2018-11-21 17-38-05\003-33-zbw_N5_117_reduce_R_pBrTFE_di_pur.D
 Sample Name: zbw_N5_117_reduce_R_pBrTFE_di_pure

```

=====
Acq. Operator   : SYSTEM                      Seq. Line :    3
Acq. Instrument : Agilent 1100                Location  :   33
Injection Date  : 11/21/2018 6:21:05 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method          : C:\Chem32\1\Data\19-Nov-2018\2018.11.21 2018-11-21 17-38-05\OD_60min_1.0ML_
                  10%.M (Sequence Method)
Last changed    : 6/29/2017 2:56:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
  
```



Area Percent Report

```

=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
  
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.267	MM	2.5536	9.98525e4	651.70209	99.9567
2	36.714	MM	0.0000	43.25190	1.22331	0.0433

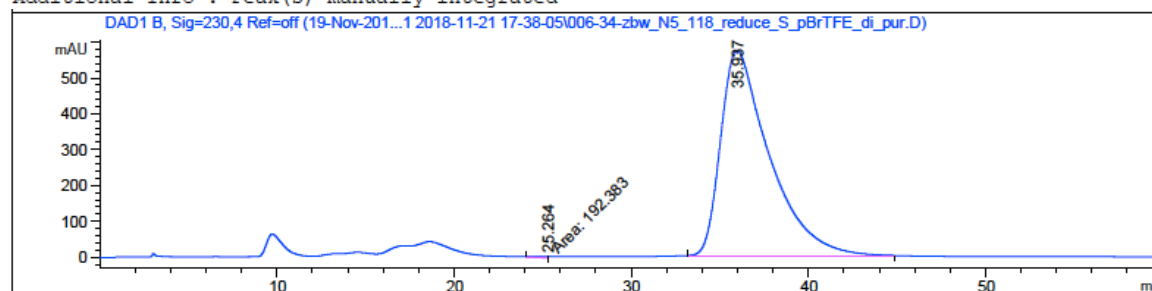
Totals : 9.98957e4 652.92540

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. OD_60min_1mL/min_10% >99% ee.

(new machine, the column is correct)

Data File C:\Chem32\...1.21 2018-11-21 17-38-05\006-34-zbw_N5_118_reduce_S_pBrTFE_di_pur.D
Sample Name: zbw_N5_118_reduce_S_pBrTFE_di_pure

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    6
Acq. Instrument : Agilent 1100                Location  :   34
Injection Date  : 11/21/2018 8:04:14 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method          : C:\Chem32\1\Data\19-Nov-2018\2018.11.21 2018-11-21 17-38-05\OD_60min_1.0ML_
                  10%.M (Sequence Method)
Last changed    : 6/29/2017 2:56:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



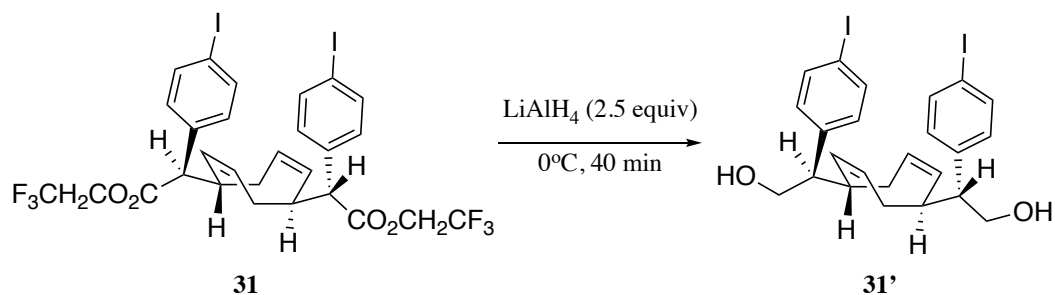
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.264	MM	0.7843	192.38348	4.08837	0.1762
2	35.937	BB	2.2251	1.08982e5	572.45422	99.8238

Totals : 1.09174e5 576.54260



$\text{Rh}_2(R\text{-}2\text{-Cl}, 5\text{-BrTPCP})_4$ chiral. OD_60min_1mL/min_10% >99% ee.

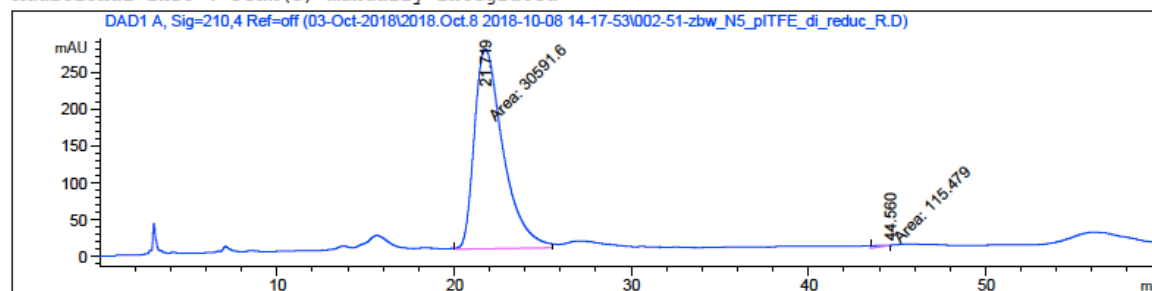
(new machine, the column is correct)

(ee. measured after reduction of di-ester to di-ol)

Data File C:\Chem32\...\018\2018.Oct.8 2018-10-08 14-17-53\002-51-zbw_N5_pITFE_di_reduc_R.D
 Sample Name: zbw_N5_pITFE_di_reduc_R

```

=====
Acq. Operator   : SYSTEM                      Seq. Line :    2
Acq. Instrument : Agilent 1100                Location  :   51
Injection Date  : 10/8/2018 2:51:56 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\03-Oct-2018\2018.Oct.8 2018-10-08 14-17-53\OD_60min_1.0ML_
                  10%.M (Sequence Method)
Last changed    : 6/29/2017 2:56:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
  
```



Area Percent Report

```

=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
  
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.719	MM	1.8870	3.05916e4	270.20322	99.6239
2	44.560	MM	72.5942	115.47887	2.65124e-2	0.3761

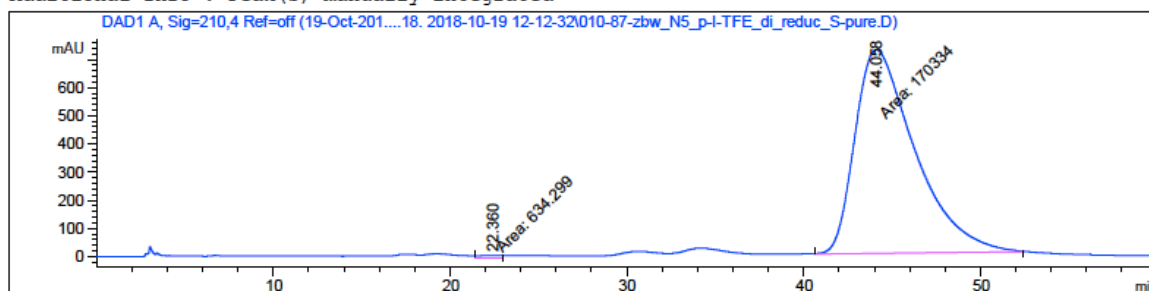
Totals : 3.07071e4 270.22973

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. OD_60min_1mL/min_10% >99% ee.

(new machine, the column is correct)

Data File C:\Chem32\...\Oct.18. 2018-10-19 12-12-32\010-87-zbw_N5_p-I-TFE_di_reduc_S-pure.D
Sample Name: zbw_N5_p-I-TFE_di_reduc_S-pure

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   10
Acq. Instrument : Agilent 1100                Location  :    87
Injection Date  : 10/19/2018 5:04:48 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\19-Oct-2018\2018-Oct.18. 2018-10-19 12-12-32\OD_60min_1.
                  OML_10%.M (Sequence Method)
Last changed    : 6/29/2017 2:56:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



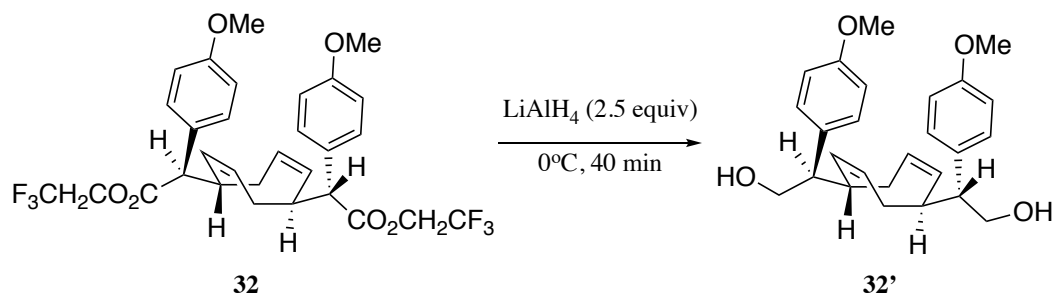
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.360	MM	1.4991	634.29938	7.05196	0.3710
2	44.058	MM	3.9277	1.70334e5	722.78461	99.6290

Totals : 1.70969e5 729.83657

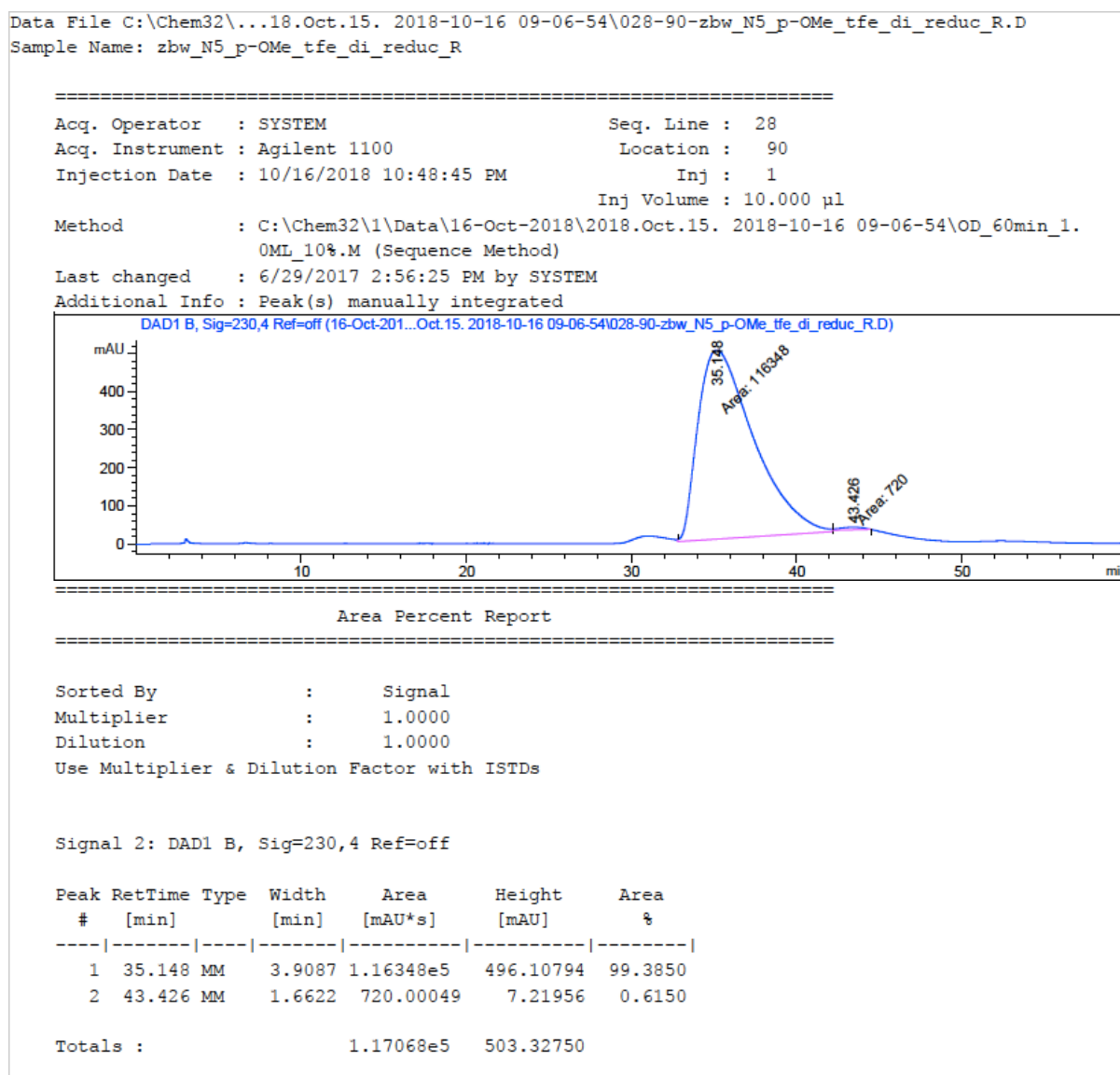


Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. OD_60min_1mL/min_10% **98% ee.**

(new machine, the column is correct)

(ee. measured after reduction of di-ester to di-ol)

in R product an impurity peak overlap with minor ee. peak position therefor influences the ee. see S cat. result for determining the correct ee.

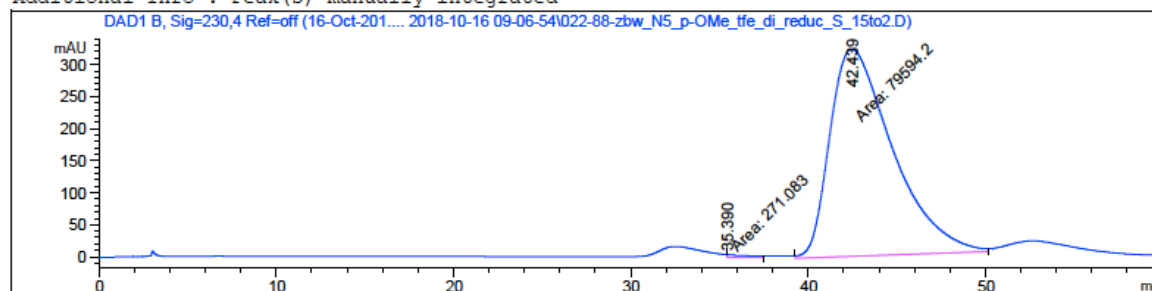


Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. OD_60min_1mL/min_10% >99% ee.

(new machine, the column is correct)

Data File C:\Chem32\....15. 2018-10-16 09-06-54\022-88-zbw_N5_p-OMe_tfe_di_reduc_S_15to2.D
Sample Name: zbw_N5_p-OMe_tfe_di_reduc_S_15to20

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   22
Acq. Instrument : Agilent 1100                Location  :   88
Injection Date  : 10/16/2018 7:22:06 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\16-Oct-2018\2018.Oct.15. 2018-10-16 09-06-54\OD_60min_1.
                  OML_10%.M (Sequence Method)
Last changed    : 6/29/2017 2:56:25 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



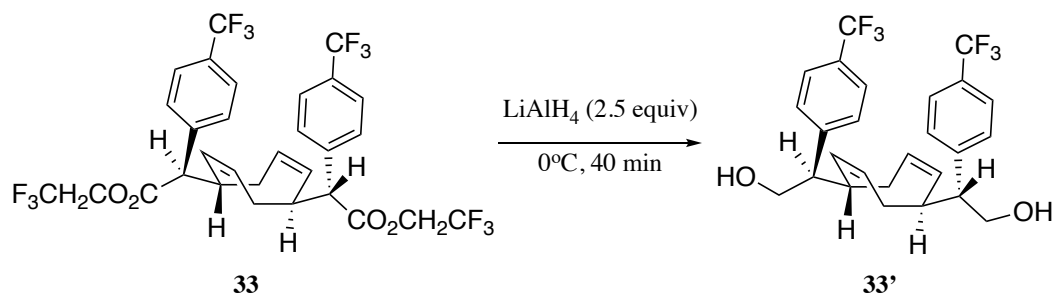
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.390	MM	1.2737	271.08316	3.54726	0.3394
2	42.439	MM	4.1005	7.95942e4	323.51260	99.6606

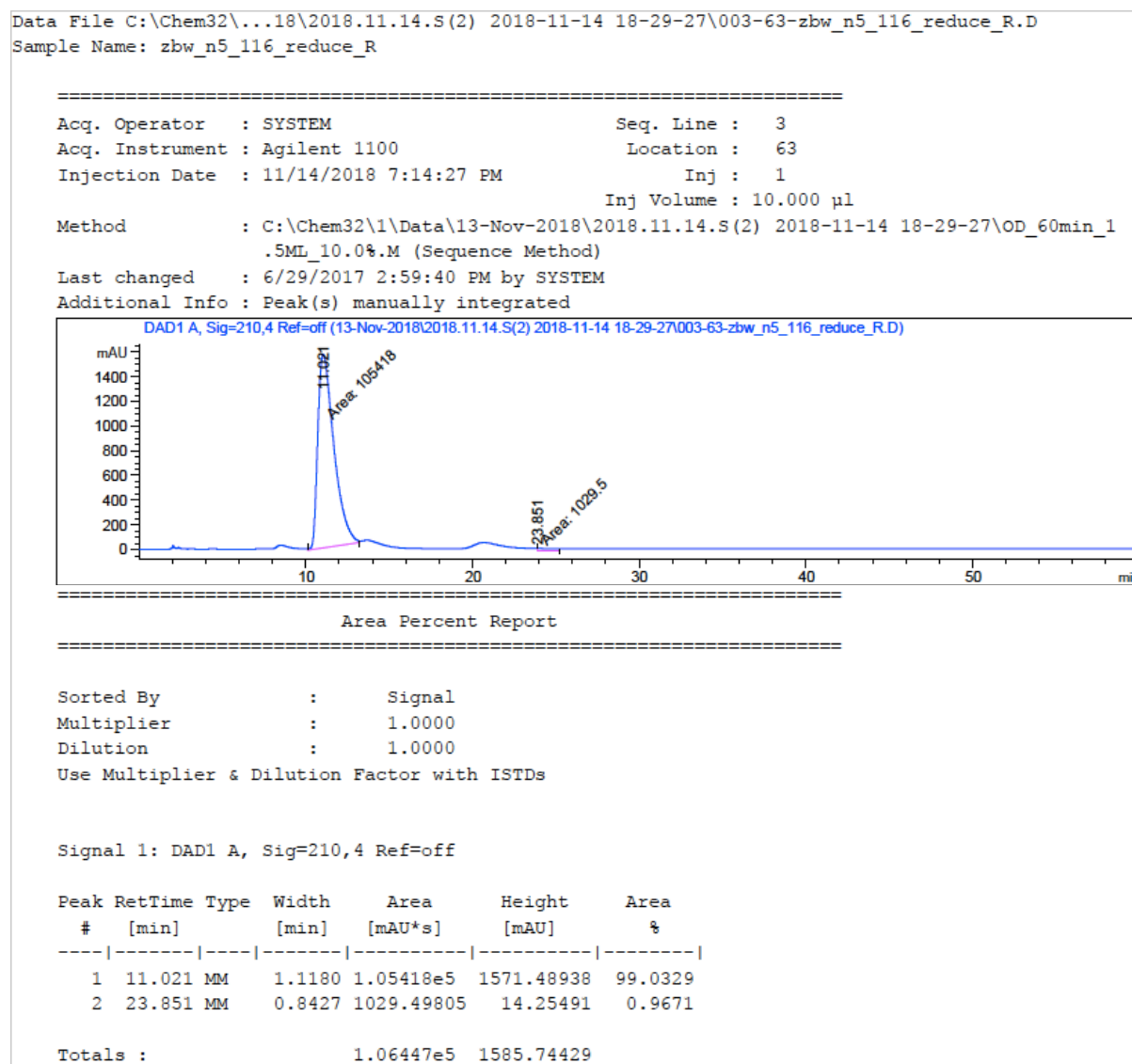
Totals : 7.98653e4 327.05986



$\text{Rh}_2(R\text{-}2\text{-Cl},5\text{-BrTPCP})_4$ chiral. OD_60min_1.5mL/min_10% >99% ee.

(new machine, the column is correct)

(ee. measured after reduction of di-ester to di-ol)

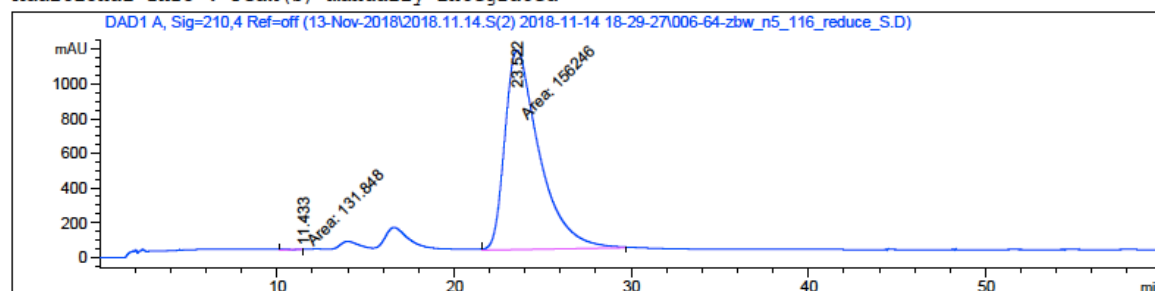


Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. OD_60min_1.5mL/min_10% >99% ee.

(new machine, the column is correct)

Data File C:\Chem32\...18\2018.11.14.S(2) 2018-11-14 18-29-27\006-64-zbw_n5_116_reduce_S.D
Sample Name: zbw_n5_116_reduce_S

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    6
Acq. Instrument : Agilent 1100                Location  :   64
Injection Date  : 11/14/2018 8:57:42 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\13-Nov-2018\2018.11.14.S(2) 2018-11-14 18-29-27\OD_60min_1
                  .5ML_10.0%.M (Sequence Method)
Last changed    : 6/29/2017 2:59:40 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



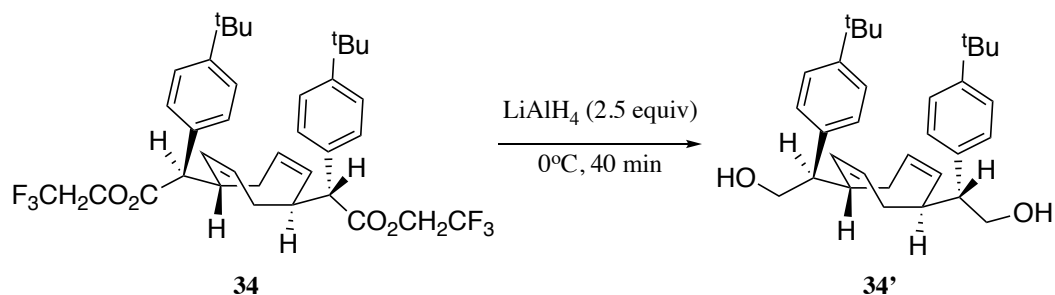
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.433	MM	0.0000	131.84846	1.04742	0.0843
2	23.522	MM	2.2612	1.56246e5	1151.63013	99.9157

Totals : 1.56377e5 1152.67755



$\text{Rh}_2(R\text{-}2\text{-Cl},5\text{-BrTPCP})_4$ chiral. OD_60min_1mL/min_5% **98.5% ee.**

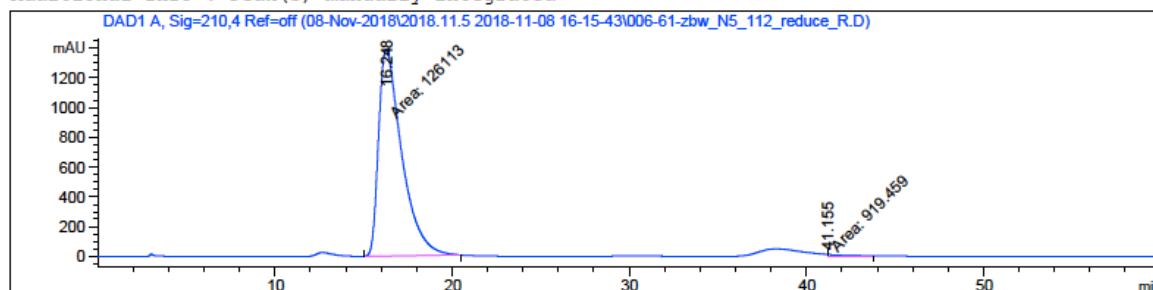
(new machine, the column is correct)

(ee. measured after reduction of di-ester to di-ol)

minor ee. peak slightly overlap with impurity, see S cat. for ee. determining

Data File C:\Chem32\...\Nov-2018\2018.11.5 2018-11-08 16-15-43\006-61-zbw_N5_112_reduce_R.D
Sample Name: zbw_N5_112_reduce_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    6
Acq. Instrument : Agilent 1100                Location  :   61
Injection Date  : 11/8/2018 6:13:48 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\08-Nov-2018\2018.11.5 2018-11-08 16-15-43\OD_60min_1.0ML_5
                  %M (Sequence Method)
Last changed    : 6/29/2017 2:57:33 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.248	MM	1.5131	1.26113e5	1389.08105	99.2762
2	41.155	MM	0.8866	919.45898	12.11218	0.7238

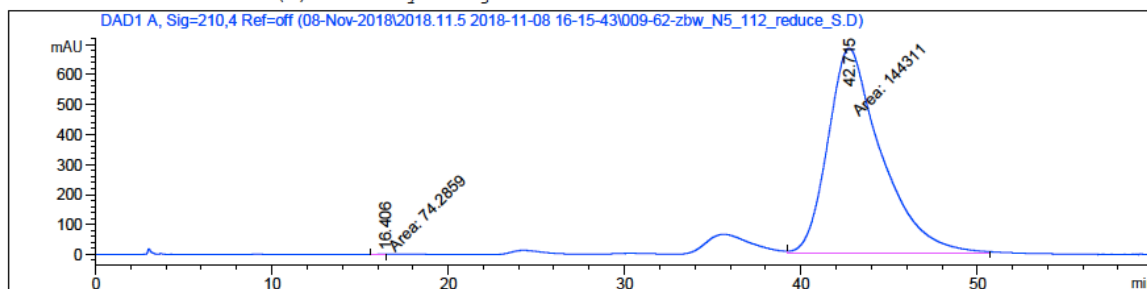
Totals : 1.27032e5 1401.19324

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. OD_60min_1mL/min_5% >99% ee.

(new machine, the column is correct)

Data File C:\Chem32\...\Nov-2018\2018.11.5 2018-11-08 16-15-43\009-62-zbw_N5_112_reduce_S.D
Sample Name: zbw_N5_112_reduce_S

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    9
Acq. Instrument : Agilent 1100                Location  :   62
Injection Date  : 11/8/2018 7:57:00 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\08-Nov-2018\2018.11.5 2018-11-08 16-15-43\OD_60min_1.0ML_5
                  %.M (Sequence Method)
Last changed    : 6/29/2017 2:57:33 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



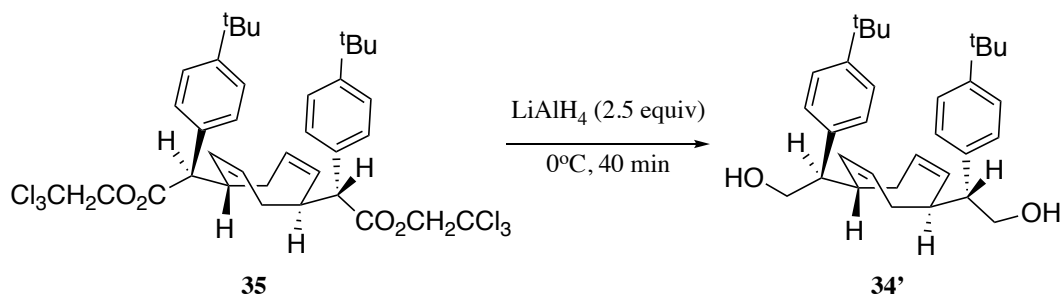
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.406	MM	0.6019	74.28591	2.05695	0.0514
2	42.715	MM	3.5182	1.44311e5	683.63403	99.9486

Totals : 1.44386e5 685.69099



Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. OD_60min_1mL/min_5% >99% ee.

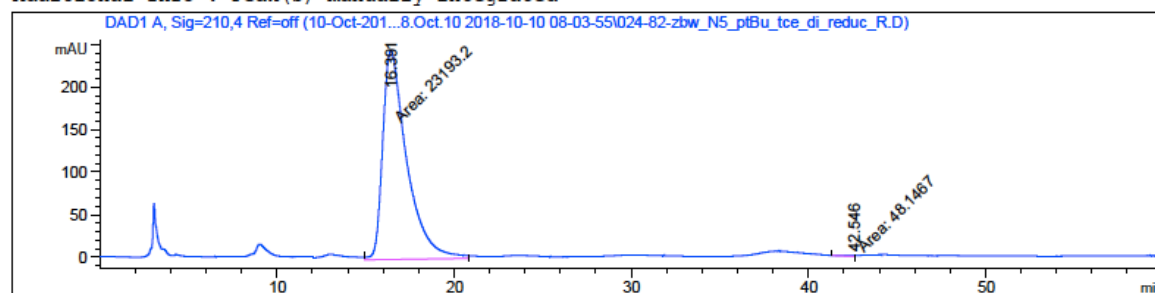
(new machine, the column is correct)

(ee. measured after reduction of di-ester to di-ol)

Data File C:\Chem32\...2018.Oct.10 2018-10-10 08-03-55\024-82-zbw_N5_ptBu_tce_di_reduc_R.D
 Sample Name: zbw_N5_ptBu_tce_di_reduc_R

```

=====
Acq. Operator   : SYSTEM                      Seq. Line :   24
Acq. Instrument : Agilent 1100                Location  :   82
Injection Date  : 10/10/2018 5:18:50 PM       Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\10-Oct-2018\2018.Oct.10 2018-10-10 08-03-55\OD_60min_1.0ML
                                           _5%.M (Sequence Method)
Last changed    : 6/29/2017 2:57:33 PM by SYSTEM
Additional Info : Peak(s) manually integrated
  
```



Area Percent Report

```

=====
Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs
  
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.391	MM	1.5732	2.31932e4	245.71730	99.7928
2	42.546	MM	0.5838	48.14667	1.37450	0.2072

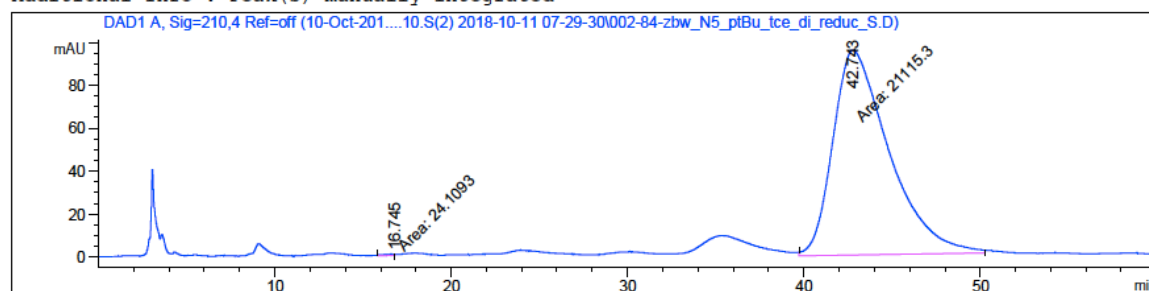
Totals : 2.32414e4 247.09180

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. OD_60min_1mL/min_5% >99% ee.

(new machine, the column is correct)

Data File C:\Chem32\...\Oct.10.S(2) 2018-10-11 07-29-30\002-84-zbw_N5_ptBu_tce_di_reduc_S.D
Sample Name: zbw_N5_ptBu_tce_di_reduc_S

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    2
Acq. Instrument : Agilent 1100                Location  :   84
Injection Date  : 10/11/2018 8:03:52 AM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\10-Oct-2018\2018.Oct.10.S(2) 2018-10-11 07-29-30\OD_60min_
                  1.0ML_5%.M (Sequence Method)
Last changed    : 6/29/2017 2:57:33 PM by SYSTEM
Additional Info : Peak(s) manually integrated
=====
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.745	MM	1.2428	24.10930	3.23316e-1	0.1140
2	42.743	MM	3.6889	2.11153e4	95.40105	99.8860

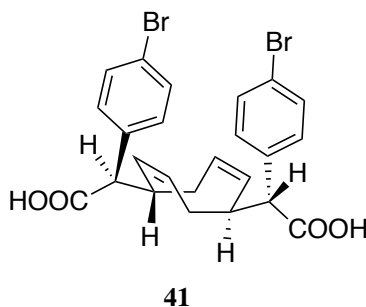
Totals : 2.11394e4 95.72436

HPLC for the derivatized product:

*42 is the reduced alcohol that has been shown before.

*43 is treated with TBAF, goes back to 42 and e.e. still over 99%

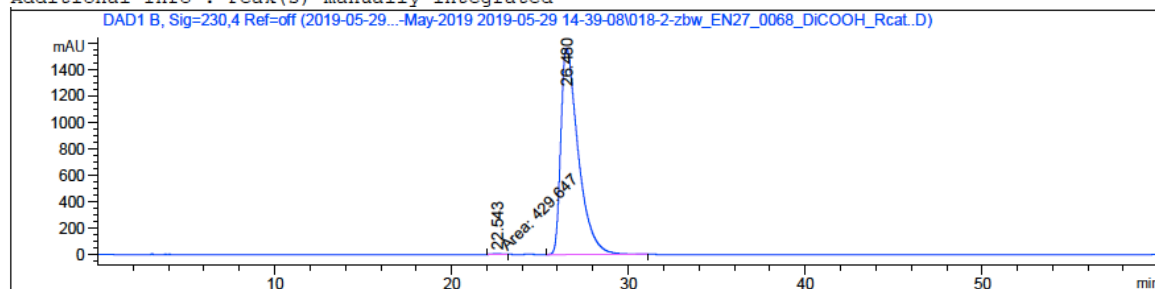
*for 41, 44-49 HPLC below, when it's no longer over 99% e.e. due to the derivatization, it's later on recrystallized to >99% ee. for conjugate addition test.



Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. ADH_60min_1mL/min_10% >99% ee.

Data File C:\Chem32\...\28-May-2019 2019-05-29 14-39-08\018-2-zbw_EN27_0068_DiCOOH_Rcat..
Sample Name: zbw_EN27_0068_DiCOOH_Rcat.

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   18
Acq. Instrument : Agilent 1100                Location  :    2
Injection Date  : 5/29/2019 10:59:40 PM       Inj       :    1
                                           Inj Volume: 10.000 µl
Method          : C:\Chem32\1\Data\2019-05-29\28-May-2019 2019-05-29 14-39-08\ADH_60min_1.0ML
                                           _10%.M (Sequence Method)
Last changed    : 6/29/2017 2:31:38 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



Area Percent Report

```
=====
Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

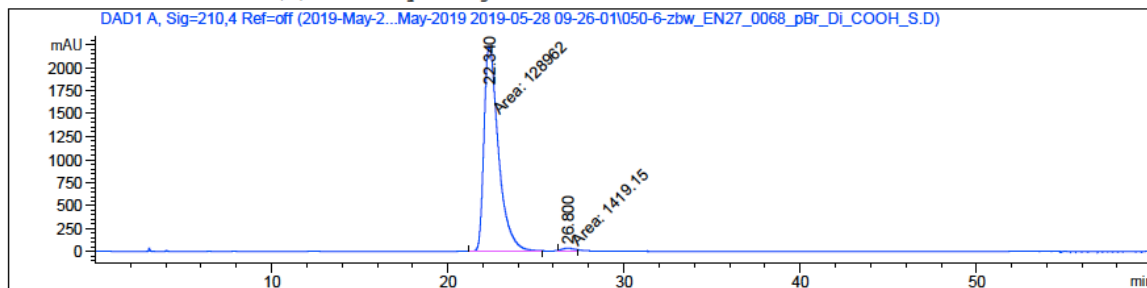
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.543	MM	0.8508	429.64722	8.41681	0.4017
2	26.480	BB	0.8031	1.06540e5	1558.46423	99.5983

Totals : 1.06969e5 1566.88104

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. ADH_60min_1mL/min_10% 98% ee.

Data File C:\Chem32\...\28-May-2019 2019-05-28 09-26-01\050-6-zbw_EN27_0068_pBr_Di_COOH_S.D
Sample Name: zbw_EN27_0068_pBr_Di_COOH_S

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   50
Acq. Instrument : Agilent 1100                Location  :    6
Injection Date  : 5/29/2019 7:51:25 AM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\2019-May-28\28-May-2019 2019-05-28 09-26-01\ADH_60min_1.
                  OML_10%.M (Sequence Method)
Last changed    : 6/29/2017 2:31:38 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



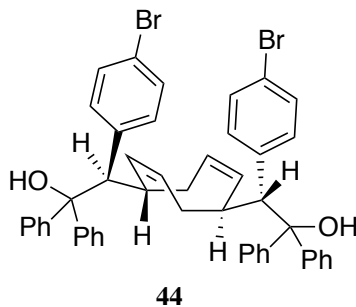
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.340	MM	0.9620	1.28962e5	2234.21387	98.9115
2	26.800	MM	0.7933	1419.14905	29.81648	1.0885

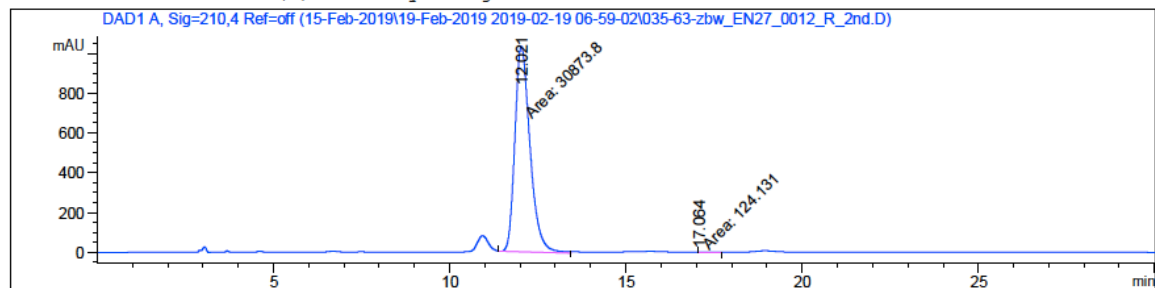
Totals : 1.30381e5 2264.03035



Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. ADH_30min_1mL/min_10% >99% ee.

Data File C:\Chem32\...b-2019\19-Feb-2019 2019-02-19 06-59-02\035-63-zbw_EN27_0012_R_2nd.D
 Sample Name: zbw_EN27_0012_R_2nd

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   35
Acq. Instrument : Agilent 1100                Location  :   63
Injection Date  : 2/19/2019 8:15:01 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\15-Feb-2019\19-Feb-2019 2019-02-19 06-59-02\ADH_30min_1.
                  OML_10%.M (Sequence Method)
Last changed    : 6/28/2017 4:48:38 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

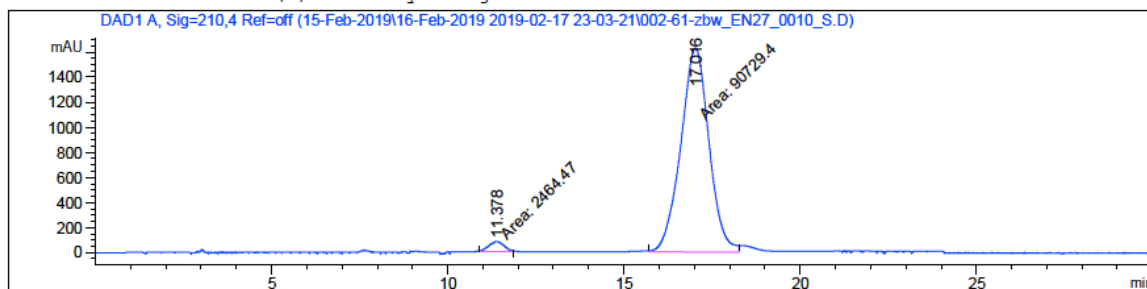
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.021	MM	0.4987	3.08738e4	1031.82483	99.5996
2	17.064	MM	0.6349	124.13059	3.25873	0.4004

Totals : 3.09980e4 1035.08356

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. ADH_30min_1mL/min_10% 95% ee.

Data File C:\Chem32\...5-Feb-2019\16-Feb-2019 2019-02-17 23-03-21\002-61-zbw_EN27_0010_S.D
Sample Name: zbw_EN27_0010_S

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    2
Acq. Instrument : Agilent 1100                Location  :   61
Injection Date  : 2/17/2019 11:37:32 PM       Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\15-Feb-2019\16-Feb-2019 2019-02-17 23-03-21\ADH_30min_1.
                  OML_10%.M (Sequence Method)
Last changed    : 6/28/2017 4:48:38 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



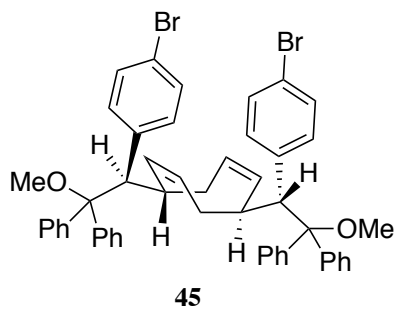
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.378	MM	0.5171	2464.46997	79.42877	2.6445
2	17.016	MF	0.9282	9.07294e4	1629.08740	97.3555

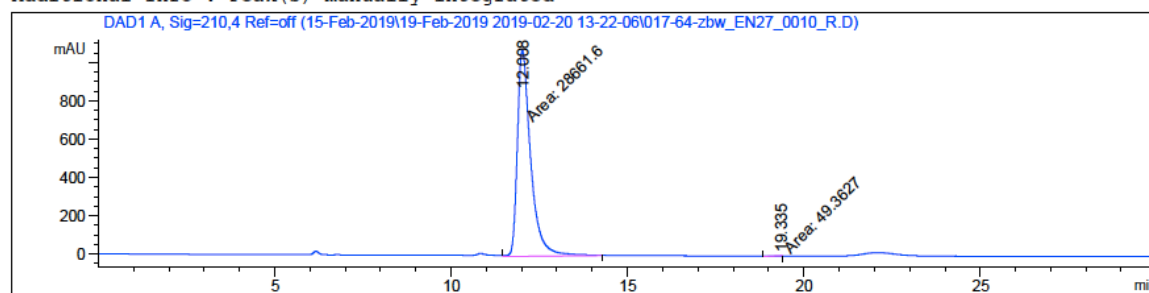
Totals : 9.31939e4 1708.51617



$\text{Rh}_2(R\text{-}2\text{-Cl,5-BrTPCP})_4$ chiral. ADH_30min_0.5mL/min_0.3% >99% ee.

Data File C:\Chem32\...5-Feb-2019\19-Feb-2019 2019-02-20 13-22-06\017-64-zbw_EN27_0010_R.D
Sample Name: zbw_EN27_0010_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   17
Acq. Instrument : Agilent 1100                Location  :    64
Injection Date  : 2/20/2019 7:19:34 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method          : C:\Chem32\1\Data\15-Feb-2019\19-Feb-2019 2019-02-20 13-22-06\ADH_30min_0.
                  50ML_0.3%.M (Sequence Method)
Last changed    : 7/26/2017 9:17:15 AM by SYSTEM
Additional Info  : Peak(s) manually integrated
```



Area Percent Report

```
Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

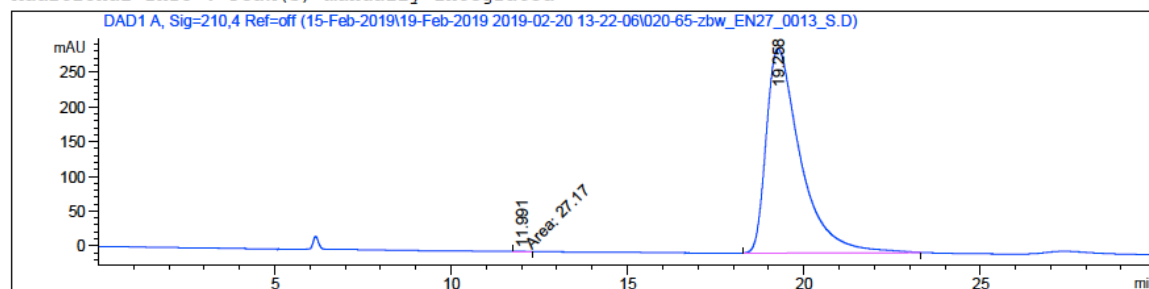
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.008	MM	0.4428	2.86616e4	1078.84436	99.8281
2	19.335	MM	0.0000	49.36269	6.57758e-1	0.1719

Totals : 2.87109e4 1079.50212

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. ADH_30min_0.5mL/min_0.3% >99% ee.

Data File C:\Chem32\...5-Feb-2019\19-Feb-2019 2019-02-20 13-22-06\020-65-zbw_EN27_0013_S.D
Sample Name: zbw_EN27_0013_S

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   20
Acq. Instrument : Agilent 1100                Location  :   65
Injection Date  : 2/20/2019 8:32:39 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\15-Feb-2019\19-Feb-2019 2019-02-20 13-22-06\ADH_30min_0.
                  50ML_0.3%.M (Sequence Method)
Last changed    : 7/26/2017 9:17:15 AM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



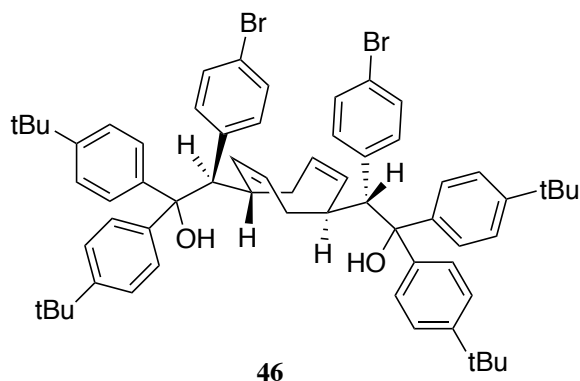
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.991	MM	0.4632	27.17001	9.77655e-1	0.1368
2	19.258	BB	0.7901	1.98394e4	294.23596	99.8632

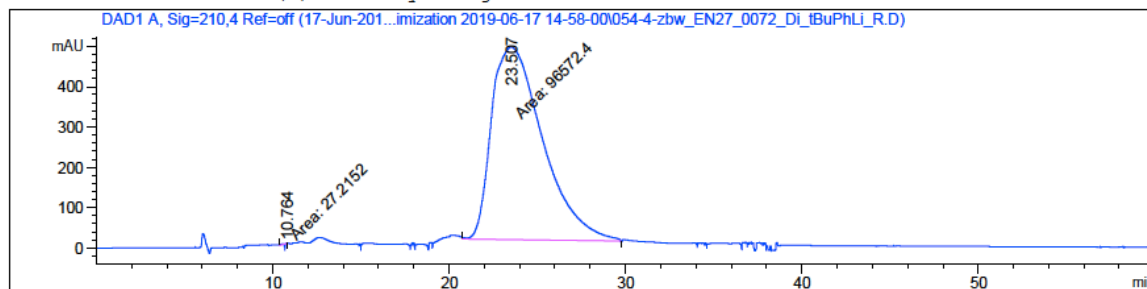
Totals : 1.98665e4 295.21362



$\text{Rh}_2(\text{R-2-Cl,5-BrTPCP})_4$ chiral. ADH_60min_0.5mL/min_5% >99% ee.

Data File C:\Chem32\...\optimization 2019-06-17 14-58-00\054-4-zbw_EN27_0072_Di_tBuPhLi_R.D
Sample Name: zbw_EN27_0072_Di_tBuPhLi_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   54
Acq. Instrument : Agilent 1100                Location  :    4
Injection Date  : 6/18/2019 5:35:33 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\17-Jun-2019\Janakiram_reaction optimization 2019-06-17 14-58-00\ADH_60min_0.5ML_5%.M (Sequence Method)
Last changed    : 6/29/2017 2:29:33 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



Area Percent Report

```
Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

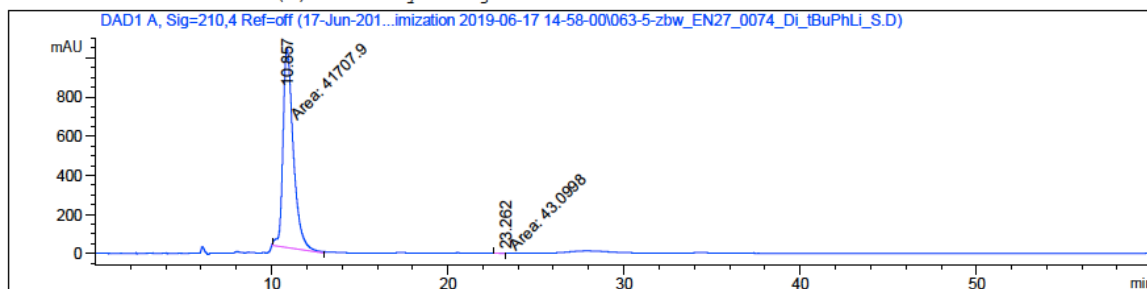
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.764	MM	0.5211	27.21519	6.20744e-1	0.0282
2	23.507	MM	3.3726	9.65724e4	477.24286	99.9718

Totals : 9.65997e4 477.86360

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. ADH_60min_0.5mL/min_5% >99% ee.

Data File C:\Chem32\...\optimization 2019-06-17 14-58-00\063-5-zbw_EN27_0074_Di_tBuPhLi_S.D
Sample Name: zbw_EN27_0074_Di_tBuPhLi_S

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   63
Acq. Instrument : Agilent 1100                Location  :    5
Injection Date  : 6/18/2019 10:45:58 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\17-Jun-2019\Janakiram_reaction optimization 2019-06-17 14-
                    58-00\ADH_60min_0.5ML_5%.M (Sequence Method)
Last changed    : 6/29/2017 2:29:33 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```



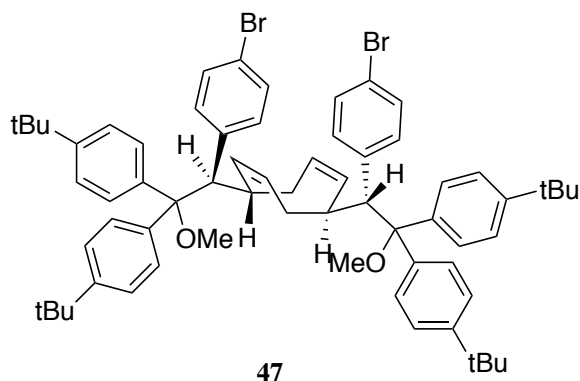
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

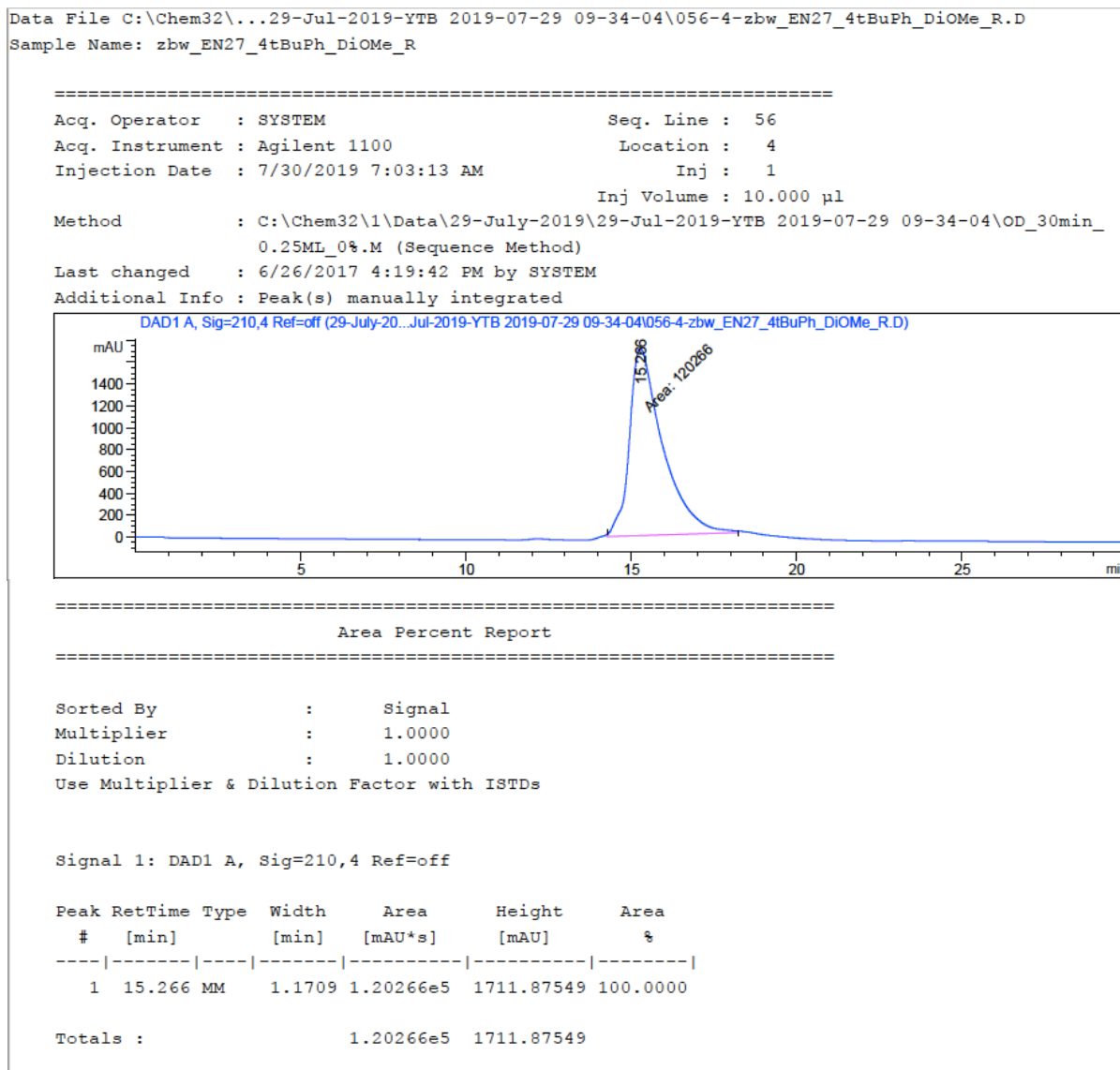
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.857	MM	0.6811	4.17079e4	1020.57922	99.8968
2	23.262	MM	0.2153	43.09983	3.33621	0.1032

Totals : 4.17510e4 1023.91543



$\text{Rh}_2(R\text{-}2\text{-Cl,5-BrTPCP})_4$ chiral. OD_30min_0.25mL/min_0%

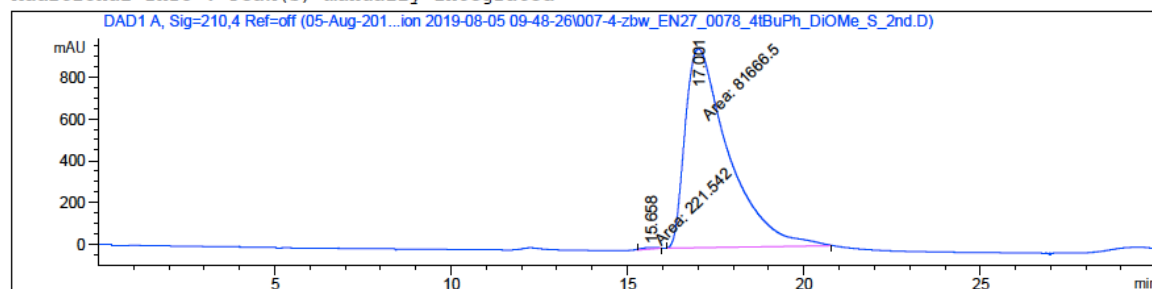
(should be >99% ee.) but the minor peak could be shielded by the tail of the major peak, therefore refer to the S catalyst product for ee. (2 peaks are close)



Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. OD_30min_0.25mL/min_0% >99% ee.

Data File C:\Chem32\...zation 2019-08-05 09-48-26\007-4-zbw_EN27_0078_4tBuPh_DiOMe_S_2nd.D
Sample Name: zbw_EN27_0078_4tBuPh_DiOMe_S_2nd

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :    7
Acq. Instrument : Agilent 1100                Location  :    4
Injection Date  : 8/5/2019 12:55:44 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\05-Aug-2019\Janakiram_reaction optimization 2019-08-05 09-
                48-26\OD_30min_0.25ML_0%.M (Sequence Method)
Last changed    : 6/26/2017 4:19:42 PM by SYSTEM
Additional Info : Peak(s) manually integrated
=====
```



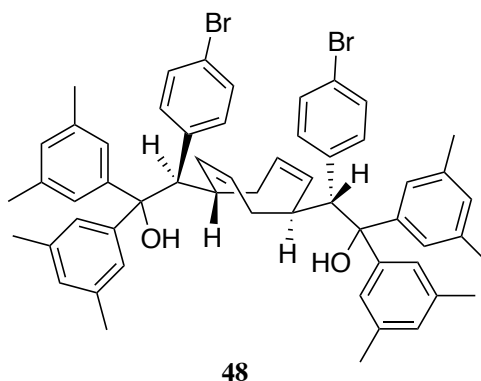
Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====
```

Signal 1: DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.658	MM	0.3815	221.54221	6.95205	0.2705
2	17.001	MM	1.4320	8.16665e4	950.52710	99.7295

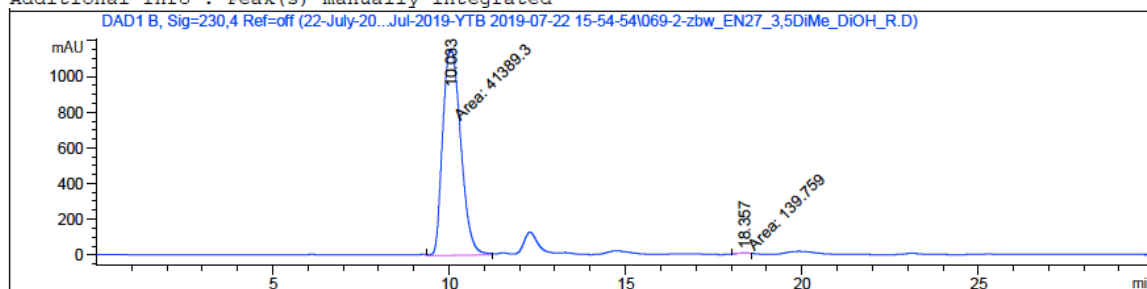
Totals : 8.18880e4 957.47915



Rh₂(*R*-2-Cl,5-BrTPCP)₄ chiral. ADH_30min_0.5mL/min_1% >99% ee.

Data File C:\Chem32\...\22-Jul-2019-YTB 2019-07-22 15-54-54\069-2-zbw_EN27_3,5DiMe_DiOH_R.D
Sample Name: zbw_EN27_3,5DiMe_DiOH_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   69
Acq. Instrument : Agilent 1100                Location  :    2
Injection Date  : 7/23/2019 7:27:55 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\22-July-2019\22-Jul-2019-YTB 2019-07-22 15-54-54\ADH_30min
                  _0.50ML_1%.M (Sequence Method)
Last changed    : 6/26/2017 4:49:12 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
Signal 2: DAD1 B, Sig=230,4 Ref=off
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.033	MM	0.5953	4.13893e4	1158.73865	99.6635
2	18.357	MM	0.3862	139.75879	6.03107	0.3365

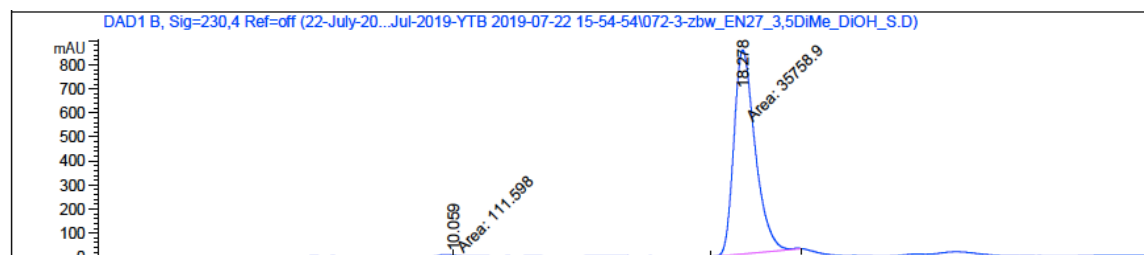
Totals : 4.15291e4 1164.76972

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. ADH_30min_0.5mL/min_1% >99% ee.

Data File C:\Chem32\...\22-Jul-2019-YTB 2019-07-22 15-54-54\072-3-zbw_EN27_3,5DiMe_DiOH_S.D
Sample Name: zbw_EN27_3,5DiMe_DiOH_S

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   72
Acq. Instrument : Agilent 1100                Location  :    3
Injection Date  : 7/23/2019 8:41:01 PM        Inj       :    1
                                           Inj Volume: 10.000 µl

Method          : C:\Chem32\1\Data\22-July-2019\22-Jul-2019-YTB 2019-07-22 15-54-54\ADH_30min
                  _0.50ML_1%.M (Sequence Method)
Last changed    : 6/26/2017 4:49:12 PM by SYSTEM
Additional Info  : Peak(s) manually integrated
=====
```

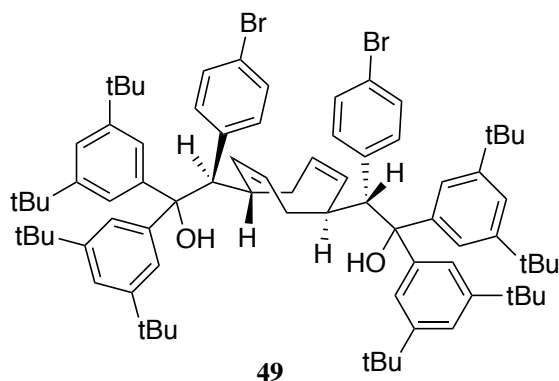


Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
Signal 2: DAD1 B, Sig=230,4 Ref=off
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.059	MM	0.1931	111.59756	6.79147	0.3111
2	18.278	MM	0.7001	3.57589e4	851.22589	99.6889

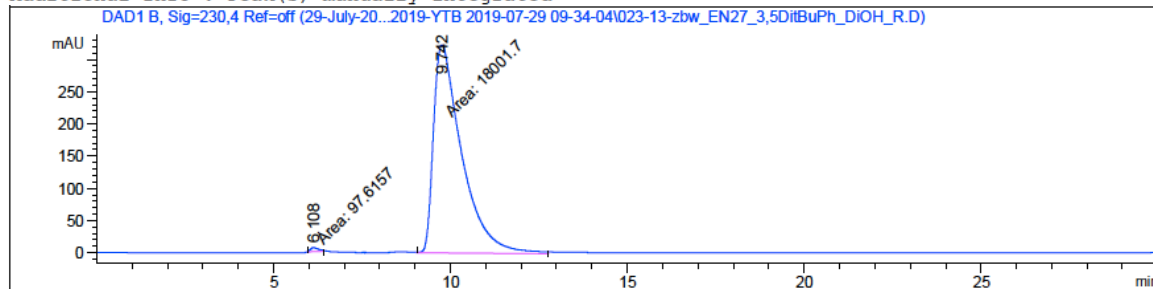
```
Totals :                      3.58705e4  858.01736
```



$\text{Rh}_2(R\text{-}2\text{-Cl,5-BrTPCP})_4$ chiral. OD_30min_0.5mL/min_0.3% **99% ee.**

Data File C:\Chem32\...ul-2019-YTB 2019-07-29 09-34-04\023-13-zbw_EN27_3,5DiTBuPh_DiOH_R.D
Sample Name: zbw_EN27_3,5DiTBuPh_DiOH_R

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   23
Acq. Instrument : Agilent 1100                Location  :   13
Injection Date  : 7/29/2019 5:58:24 PM         Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\29-July-2019\29-Jul-2019-YTB 2019-07-29 09-34-04\OD_30min_
                  0.5ML_0.3%.M (Sequence Method)
Last changed    : 6/21/2019 9:30:36 AM by SYSTEM
Additional Info : Peak(s) manually integrated
DAD1 B, Sig=230,4 Ref=off (29-July-20...2019-YTB 2019-07-29 09-34-04\023-13-zbw_EN27_3,5DiTBuPh_DiOH_R.D)
```



Area Percent Report

```
=====
Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 2: DAD1 B, Sig=230,4 Ref=off

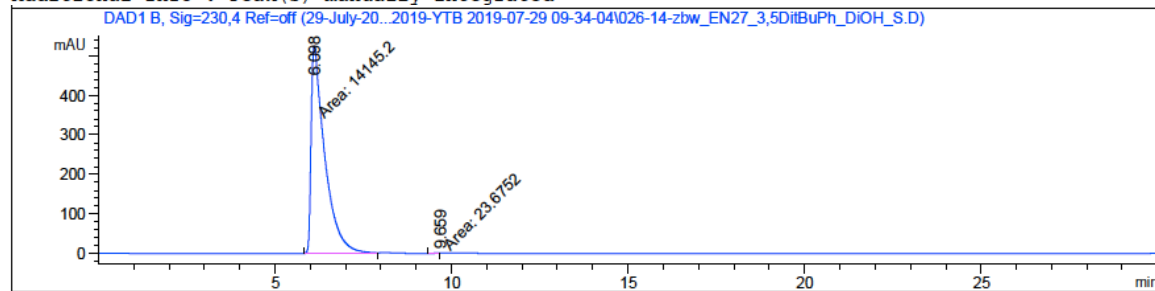
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.108	MM	0.2552	97.61575	6.37577	0.5393
2	9.742	MM	0.9276	1.80017e4	323.44415	99.4607

Totals : 1.80993e4 329.81992

Rh₂(*S*-2-Cl,5-BrTPCP)₄ chiral. OD_30min_0.5mL/min_0.3% >99% ee.

Data File C:\Chem32\...ul-2019-YTB 2019-07-29 09-34-04\026-14-zbw_EN27_3,5DitBuPh_DiOH_S.D
Sample Name: zbw_EN27_3,5DitBuPh_DiOH_S

```
=====
Acq. Operator   : SYSTEM                      Seq. Line :   26
Acq. Instrument : Agilent 1100                Location  :   14
Injection Date  : 7/29/2019 7:11:34 PM        Inj       :    1
                                           Inj Volume: 10.000 µl
Method         : C:\Chem32\1\Data\29-July-2019\29-Jul-2019-YTB 2019-07-29 09-34-04\OD_30min_
                  0.5ML_0.3%.M (Sequence Method)
Last changed    : 6/21/2019 9:30:36 AM by SYSTEM
Additional Info : Peak(s) manually integrated
DAD1 B, Sig=230,4 Ref=off (29-July-20...2019-YTB 2019-07-29 09-34-04\026-14-zbw_EN27_3,5DitBuPh_DiOH_S.D)
```



Area Percent Report

```
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

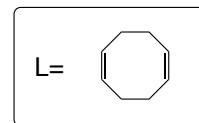
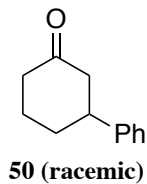
Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.098	MM	0.4497	1.41452e4	524.25287	99.8329
2	9.659	MM	0.2084	23.67523	1.89338	0.1671

Totals : 1.41689e4 526.14625

HPLC analysis for conjugate addition test (column: OJH_30min_1ml/min_1%)

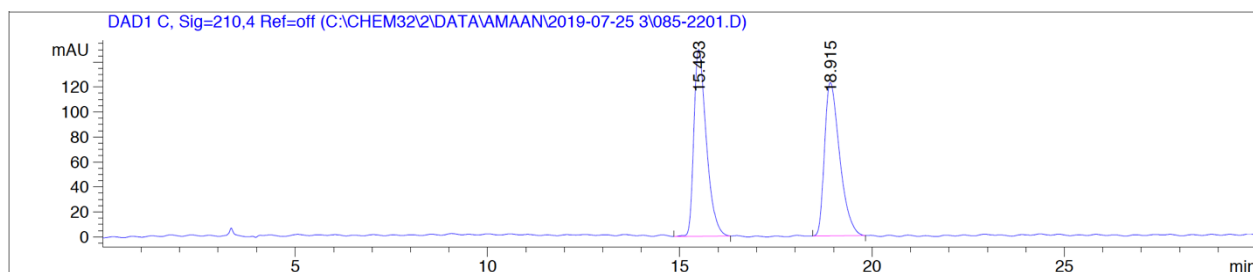
1. test with 1,5-Cyclooctadiene (racemic reaction)



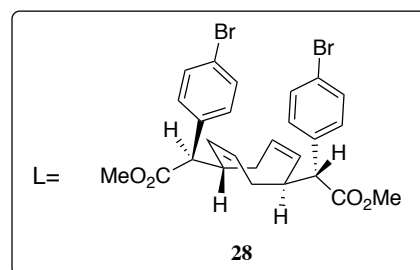
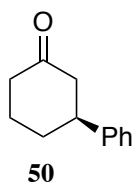
Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.493	VB	0.3441	3389.26660	149.71777	50.1511
2	18.915	BB	0.4216	3368.83813	122.95934	49.8489

Totals : 6758.10474 272.67712



2. test with C2-symmetric chiral COD ligands and their derivatives

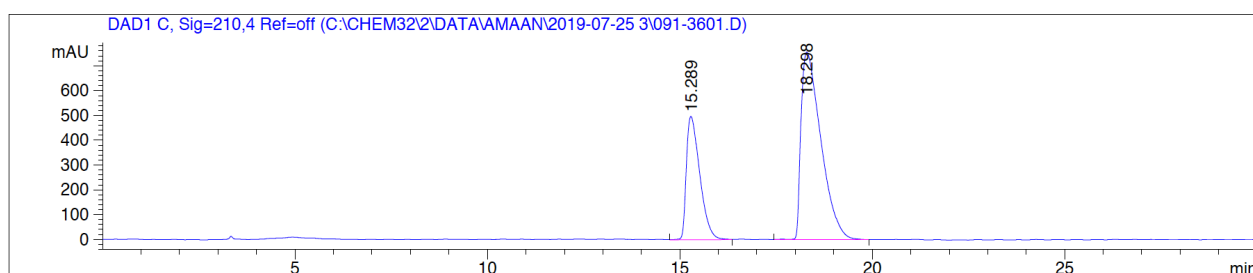


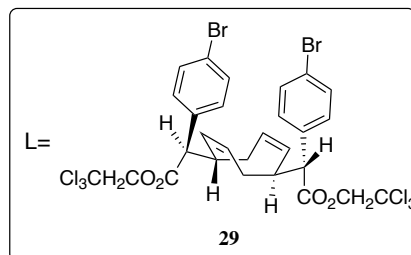
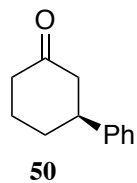
(1). L=28, 39% ee.

Signal 2: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.289	VB	0.3740	1.20196e4	497.26553	30.7100
2	18.298	BB	0.5639	2.71193e4	757.13055	69.2900

Totals : 3.91388e4 1254.39609



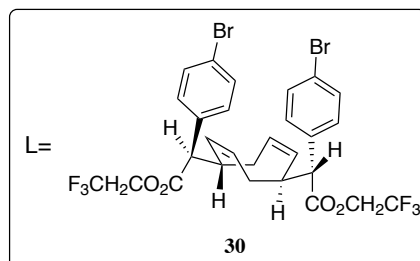
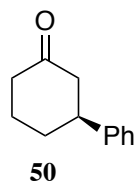
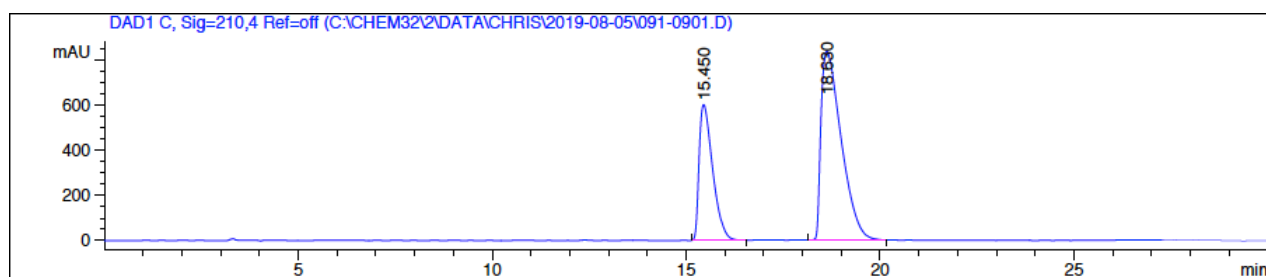


(2). L=29, 34% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.450	BB	0.3744	1.46869e4	602.50049	32.7329
2	18.630	BB	0.5526	3.01820e4	837.23248	67.2671

Totals : 4.48690e4 1439.73297

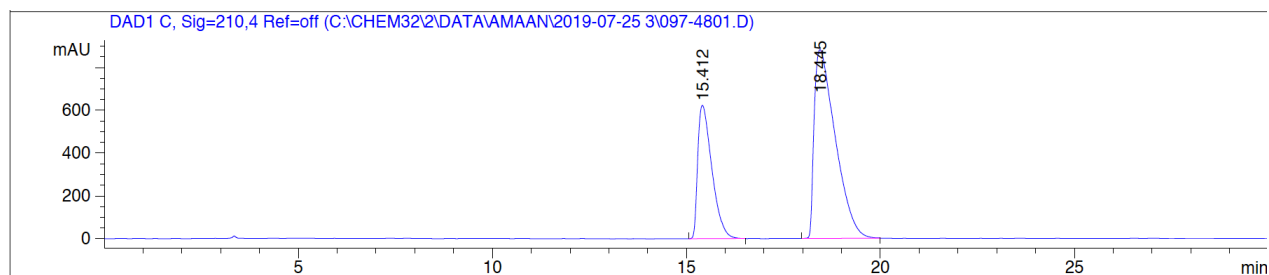


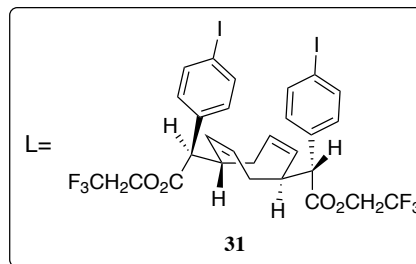
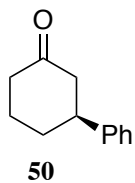
(3). L=30, 36% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.412	BB	0.3902	1.58306e4	623.60895	32.2460
2	18.445	BB	0.5778	3.32627e4	882.38849	67.7540

Totals : 4.90934e4 1505.99744



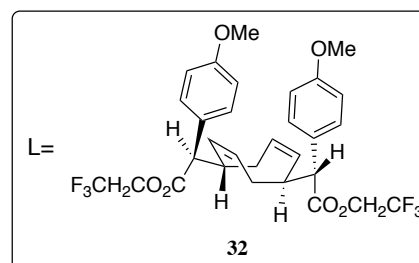
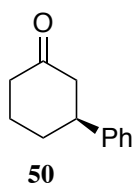
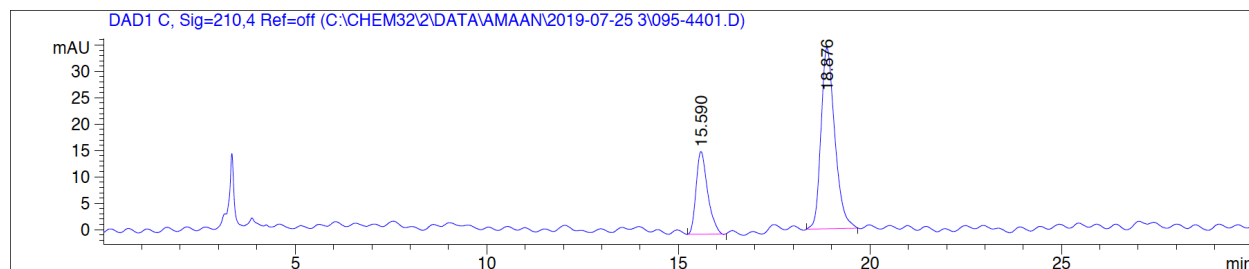


(4). L=31, 45% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.590	BB	0.3171	329.31805	15.67247	27.6779
2	18.876	BB	0.3805	860.50415	34.32642	72.3221

Totals : 1189.82220 49.99889

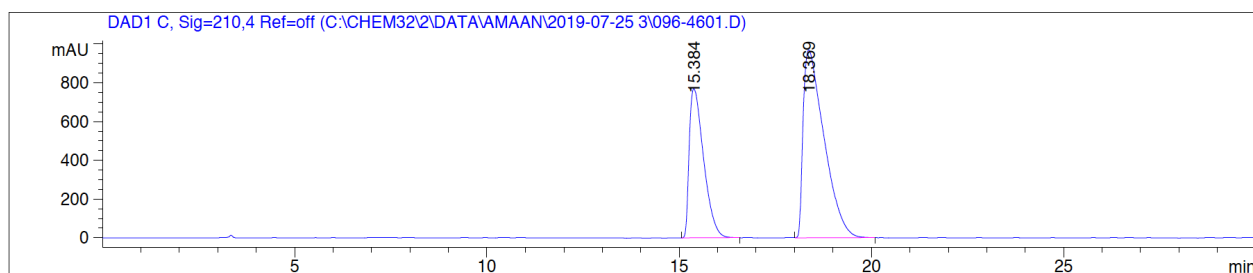


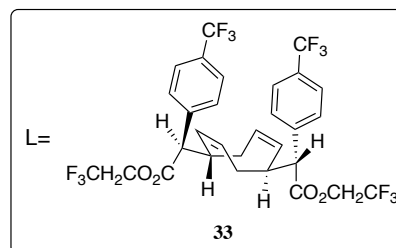
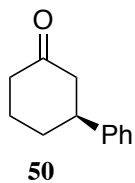
(5). L=32, 30% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.384	BB	0.3969	1.98576e4	770.04730	35.1377
2	18.369	BB	0.5576	3.66560e4	968.45874	64.8623

Totals : 5.65136e4 1738.50604



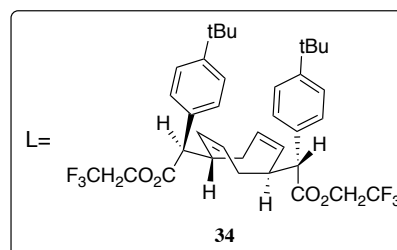
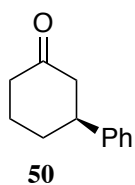
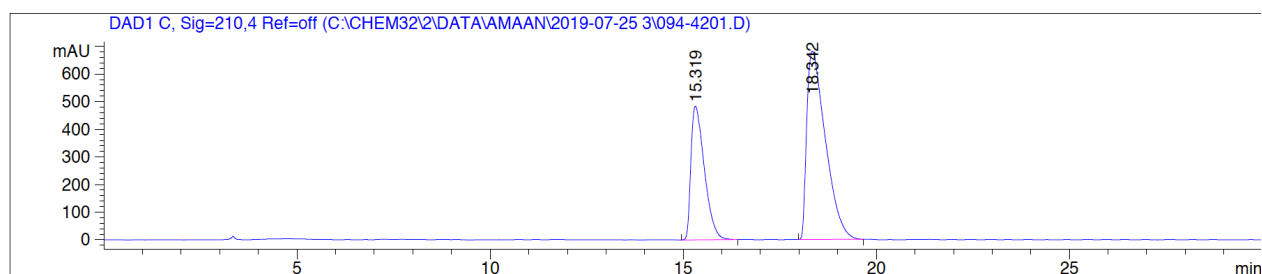


(6). L=33, 33% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.319	BB	0.3681	1.16148e4	483.75128	33.6101
2	18.342	BB	0.5086	2.29427e4	681.73700	66.3899

Totals : 3.45575e4 1165.48828

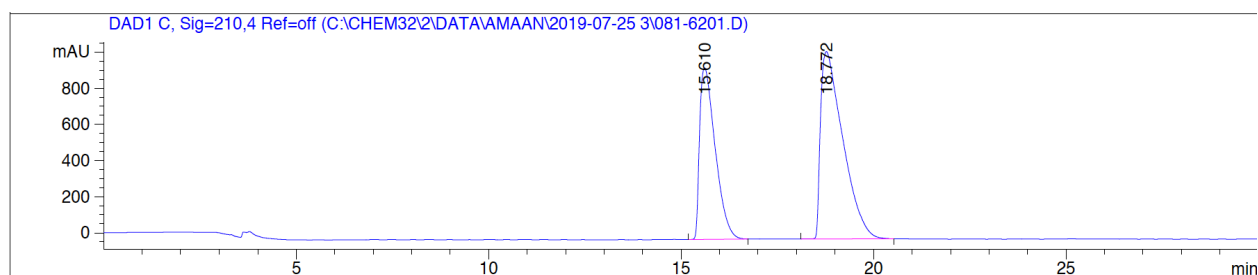


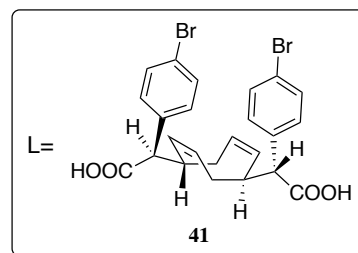
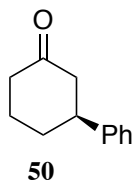
(7). L=34, 22% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.610	BB	0.4381	2.67188e4	949.94879	39.1501
2	18.772	BB	0.5890	4.15284e4	1037.52234	60.8499

Totals : 6.82472e4 1987.47113



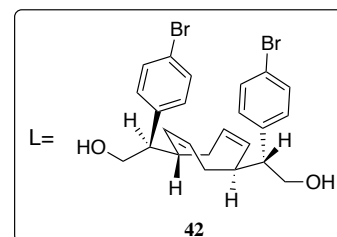
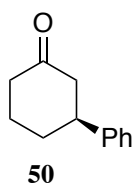
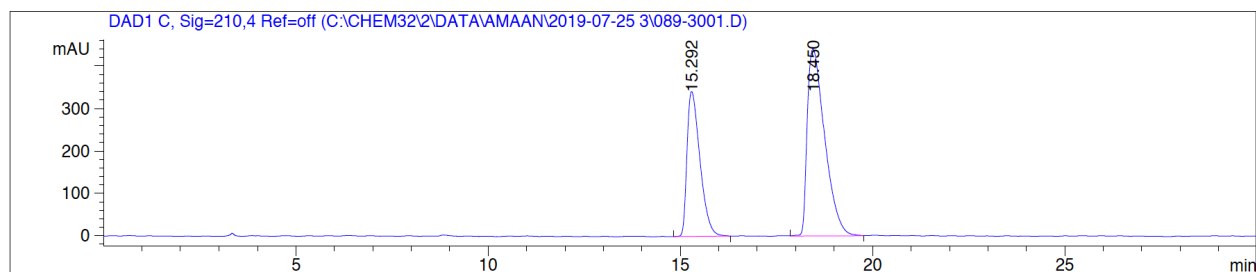


(9). L=41, 27% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.292	BB	0.3646	8040.54785	341.64832	36.5930
2	18.450	BB	0.4848	1.39324e4	440.72278	63.4070

Totals : 2.19729e4 782.37109

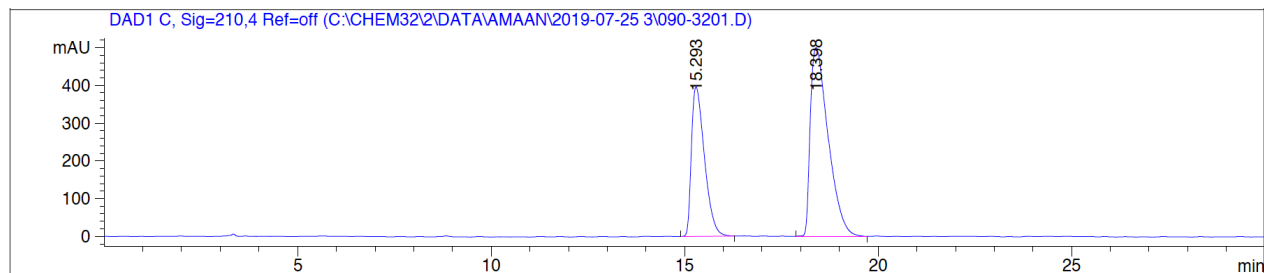


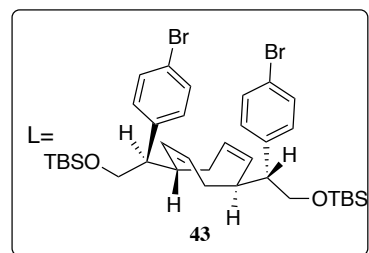
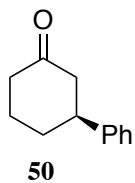
(8). L=42, 26% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.293	BB	0.3648	9337.66113	396.40738	36.7708
2	18.398	BB	0.4906	1.60566e4	500.13208	63.2292

Totals : 2.53942e4 896.53946



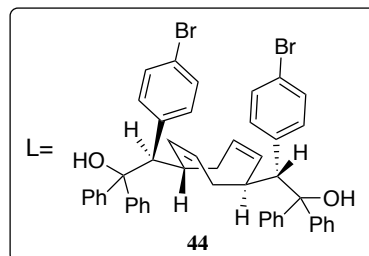
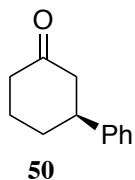
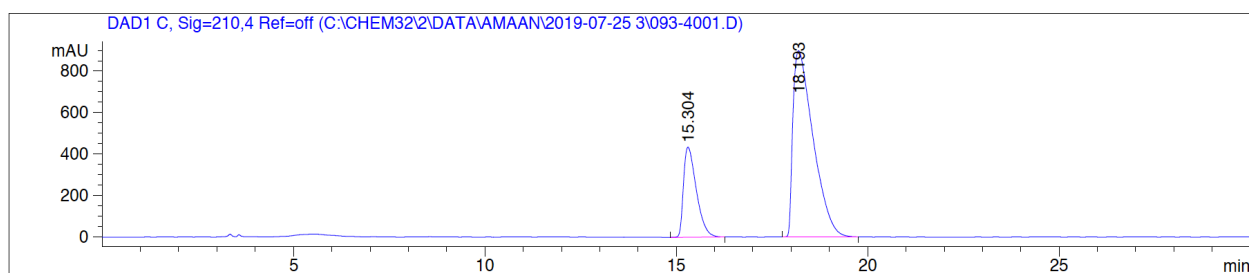


(12). L=43, 53% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.304	BB	0.3619	1.01920e4	434.13281	23.5753
2	18.193	BB	0.5715	3.30398e4	897.48987	76.4247

Totals : 4.32319e4 1331.62268

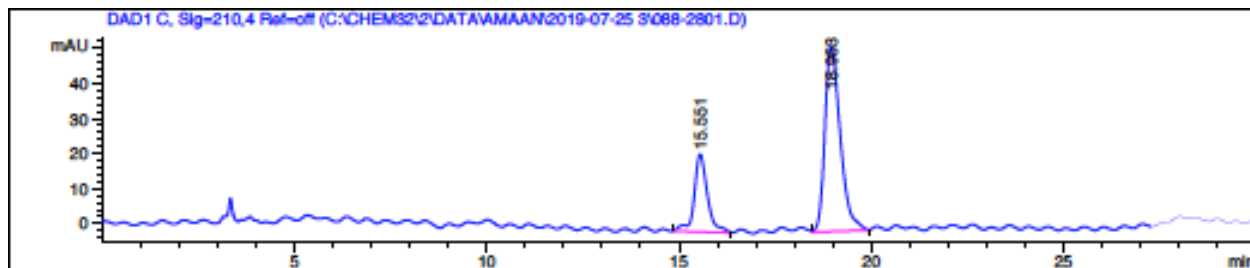


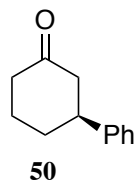
(10). L=44, 47% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

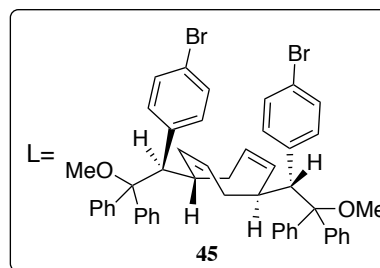
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.551	BB	0.3571	529.52753	22.13255	26.4121
2	18.953	VB	0.4298	1475.34106	52.82749	73.5879

Totals : 2004.86859 74.96004





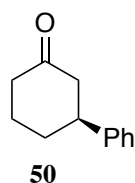
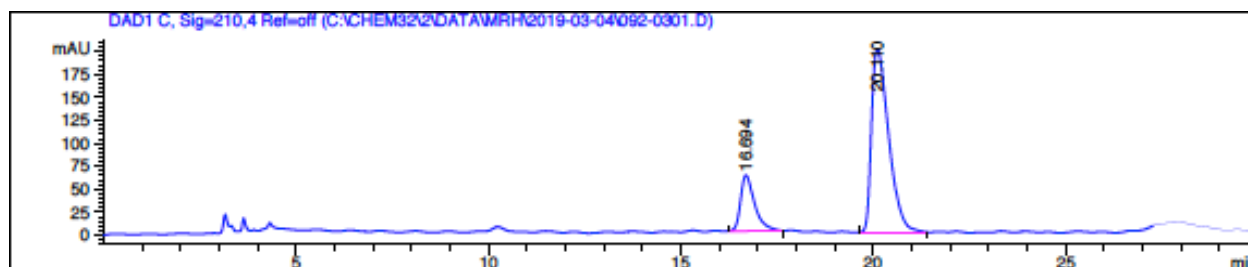
(11). L=45, 60% ee.



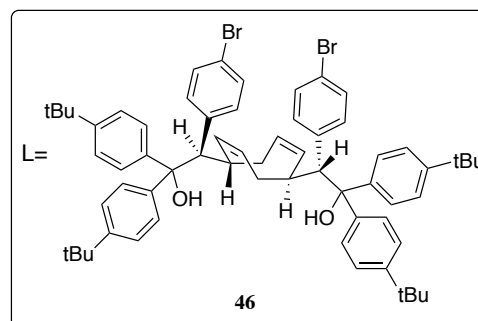
Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.694	BB	0.3768	1534.34827	60.72484	19.8006
2	20.110	BB	0.4812	6214.63330	199.64850	80.1994

Totals : 7748.98157 260.37334



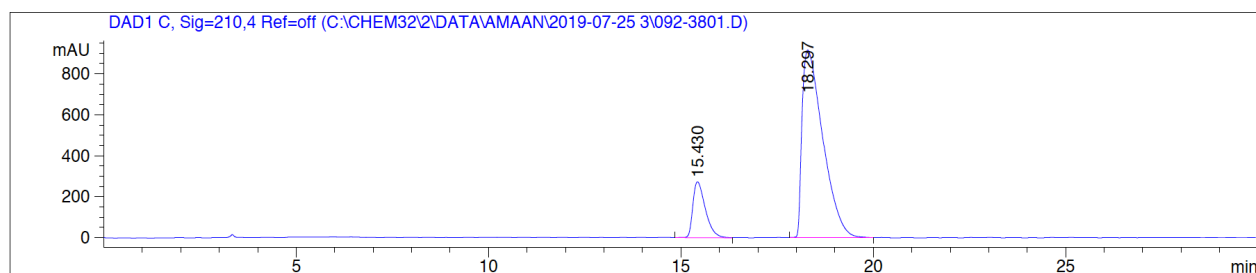
(13). L=46, 69% ee.

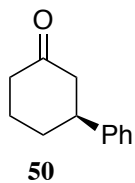


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.430	VB	0.3499	6226.05908	273.17520	15.2606
2	18.297	BB	0.5817	3.45722e4	917.27521	84.7394

Totals : 4.07982e4 1190.45041



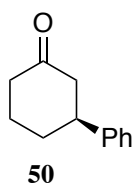
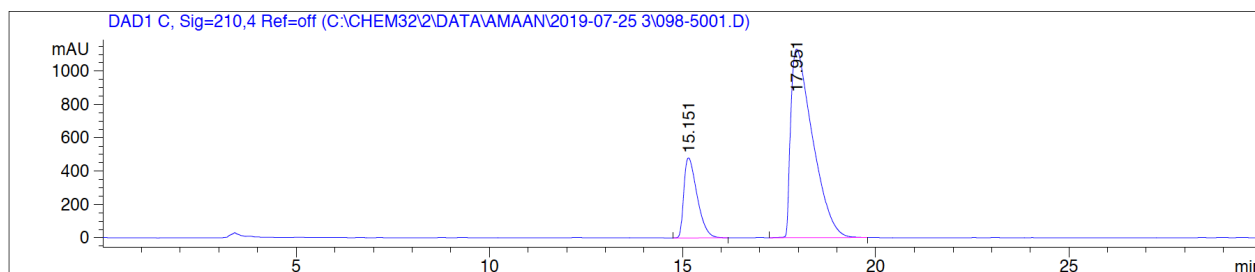
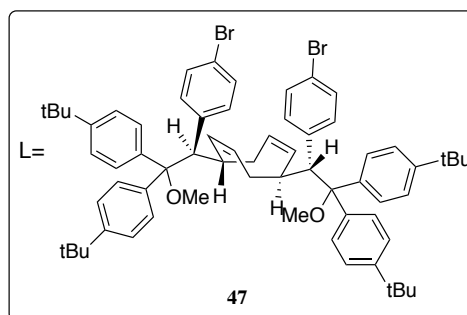


(14). L=47, 59% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.151	BB	0.3686	1.14708e4	480.38049	20.4964
2	17.951	VB	0.5870	4.44942e4	1130.92139	79.5036

Totals : 5.59650e4 1611.30188

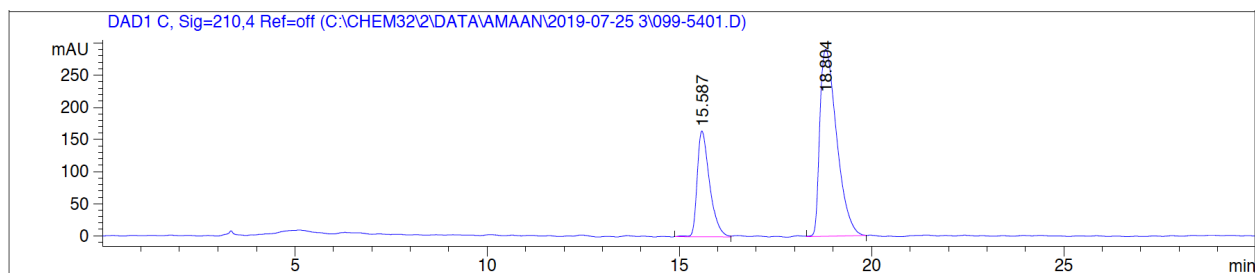
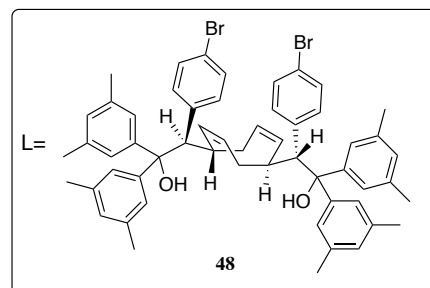


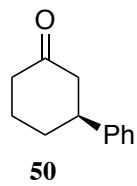
(15). L=48, 41% ee.

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.587	BB	0.3432	3716.06152	164.74695	29.6503
2	18.804	VB	0.4713	8816.89844	291.16553	70.3497

Totals : 1.25330e4 455.91248



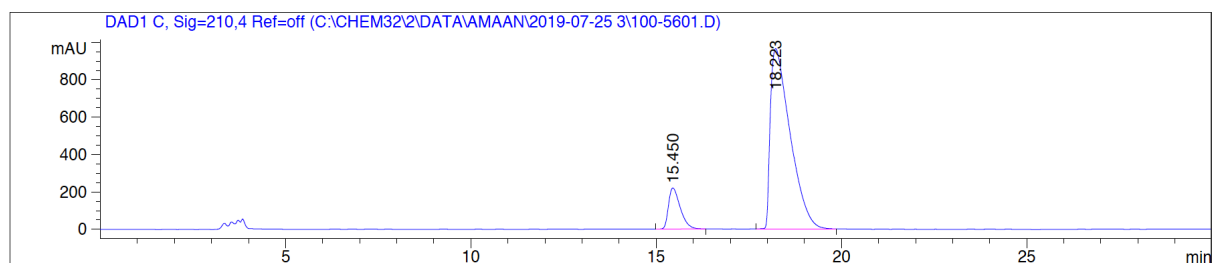
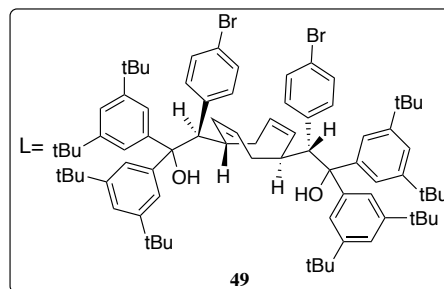


(15). L=49, 76% ee.

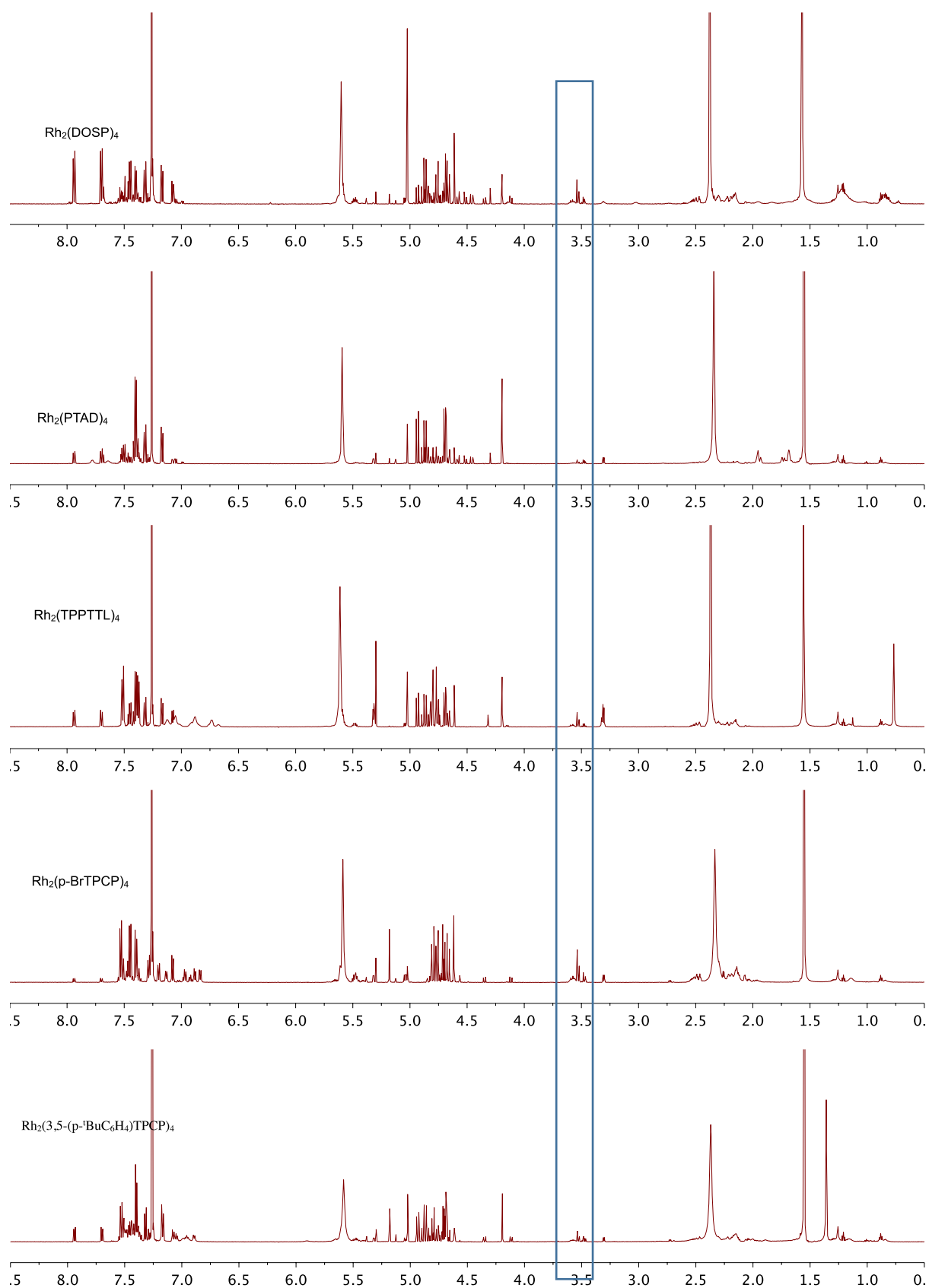
Signal 1: DAD1 C, Sig=210,4 Ref=off

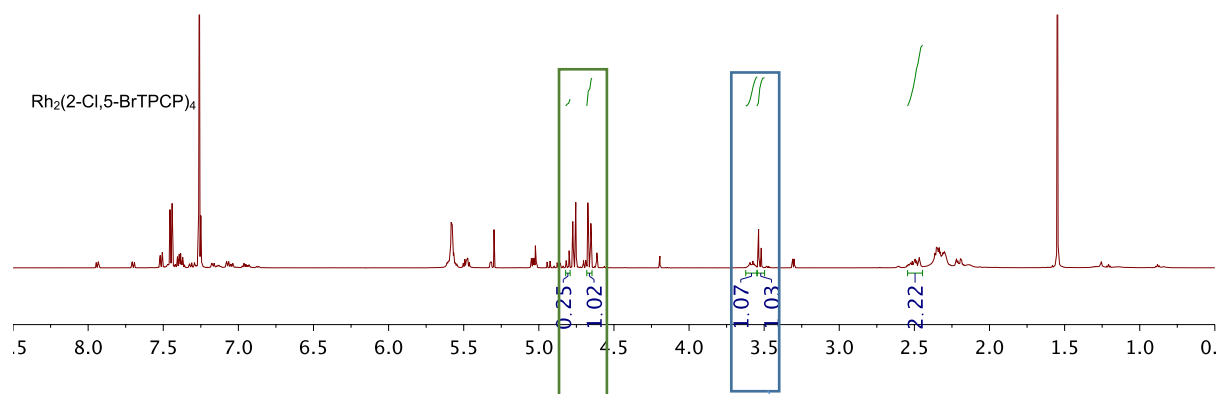
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.450	BB	0.3402	4872.13184	220.15059	11.9691
2	18.223	BB	0.5714	3.58338e4	964.50671	88.0309

Totals : 4.07059e4 1184.65730



Catalyst screen result for the initial mono-insertion test





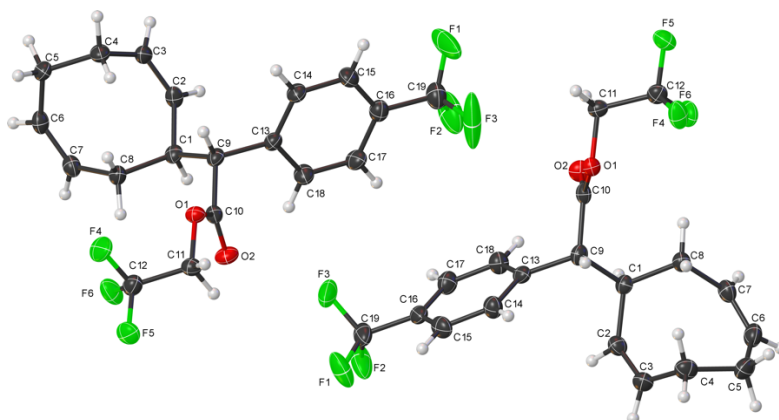
Left multiplet as the insertion C-H of the vinylogous site, right doublet as the benzylic C-H after the insertion.

As can be seen from the catalyst screening crude ^1H NMR, all catalyst indeed can generate the vinylogous insertion product, but the trichloroethyl CH_2 region can show the difference.

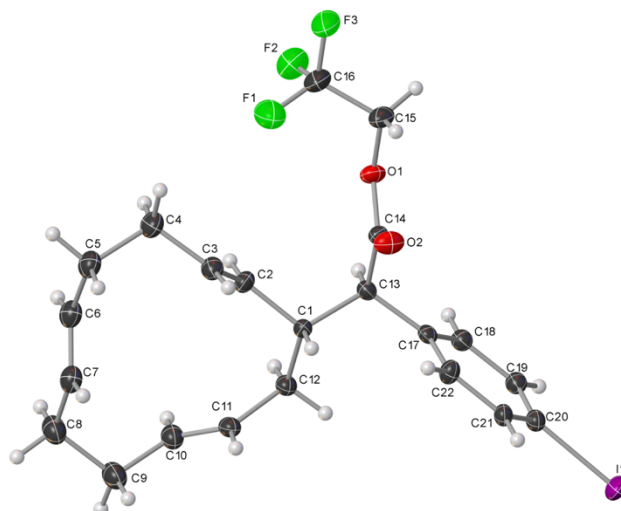
$\text{Rh}_2(2\text{-Cl},5\text{-BrTPCP})_4$ give the cleanest diastereotopic set of doublets, suggesting it to be the optimized catalyst for the reaction.

Single crystal structure for compound 22, 37 (major), 35 [after reduction]

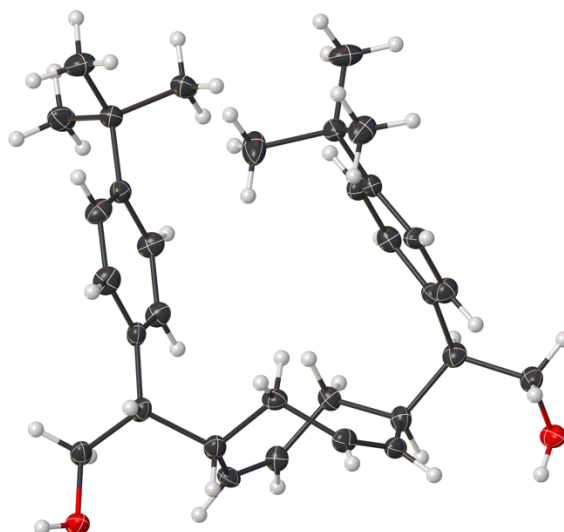
22 crystal structure



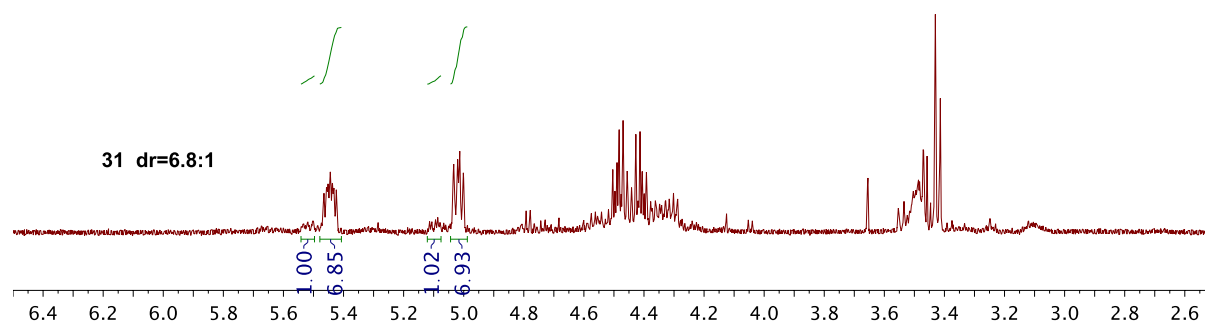
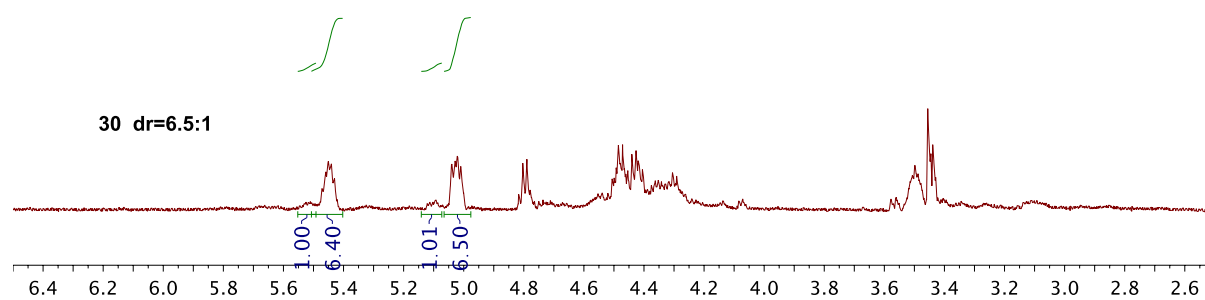
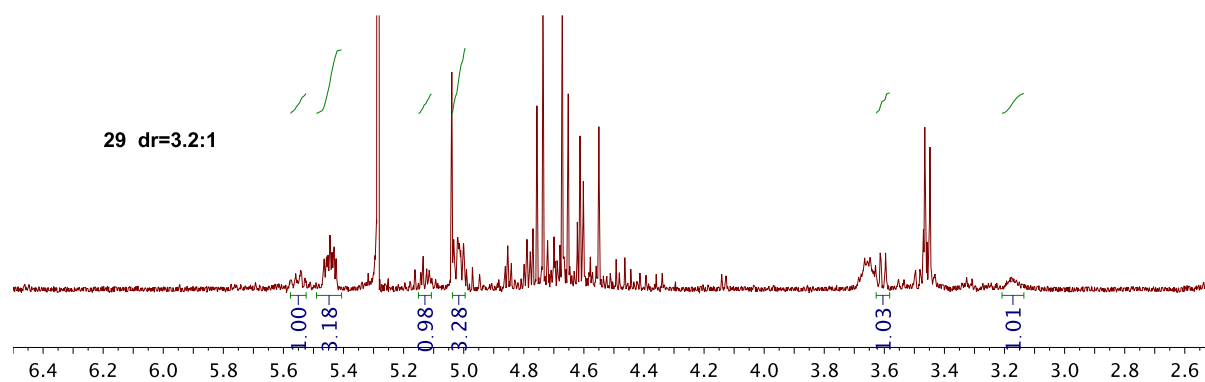
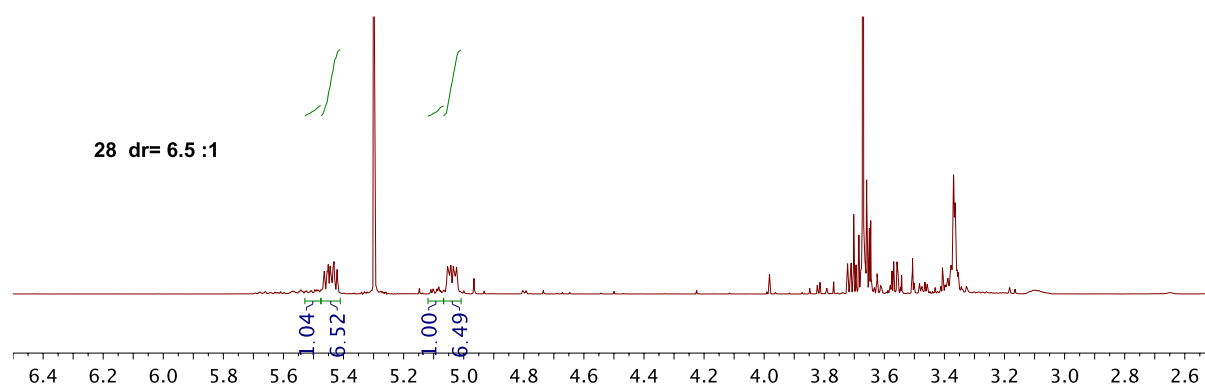
37 (major) crystal structure

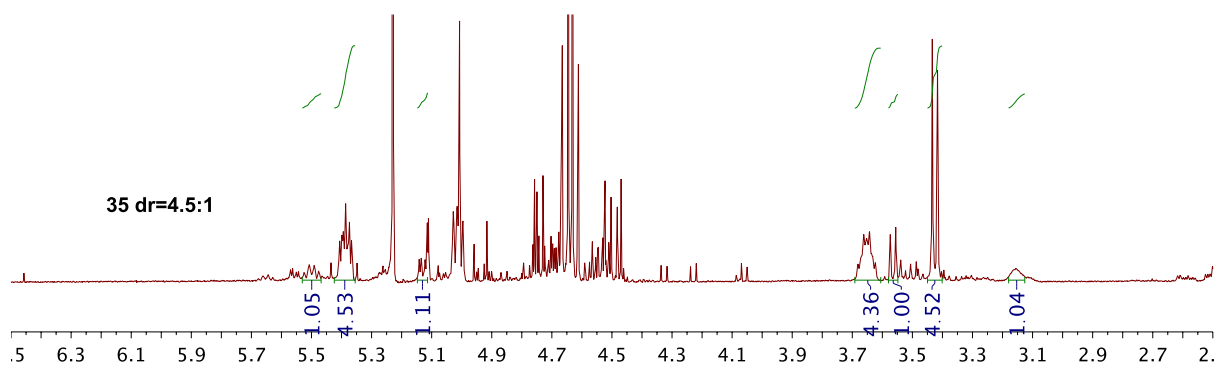
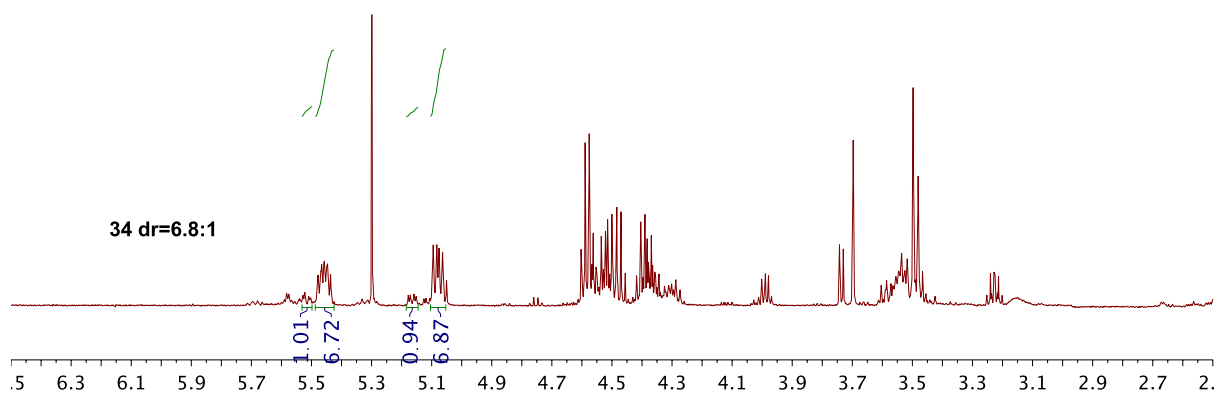
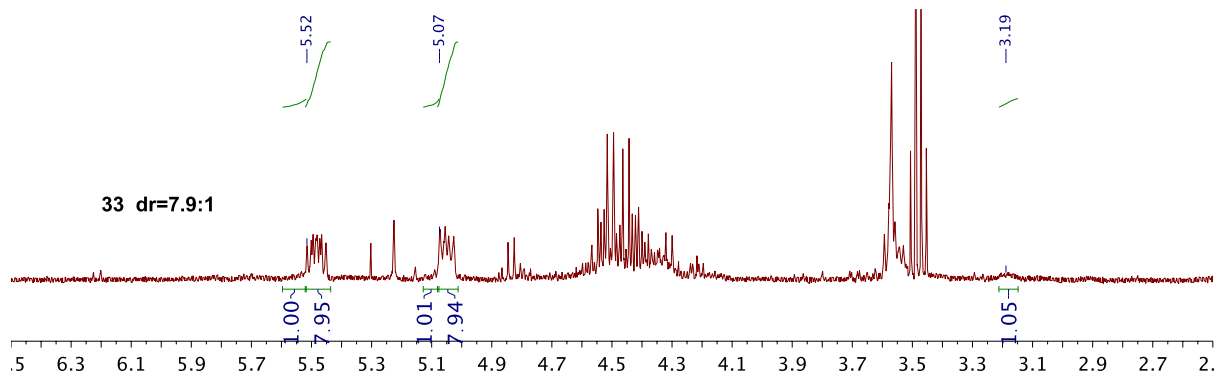
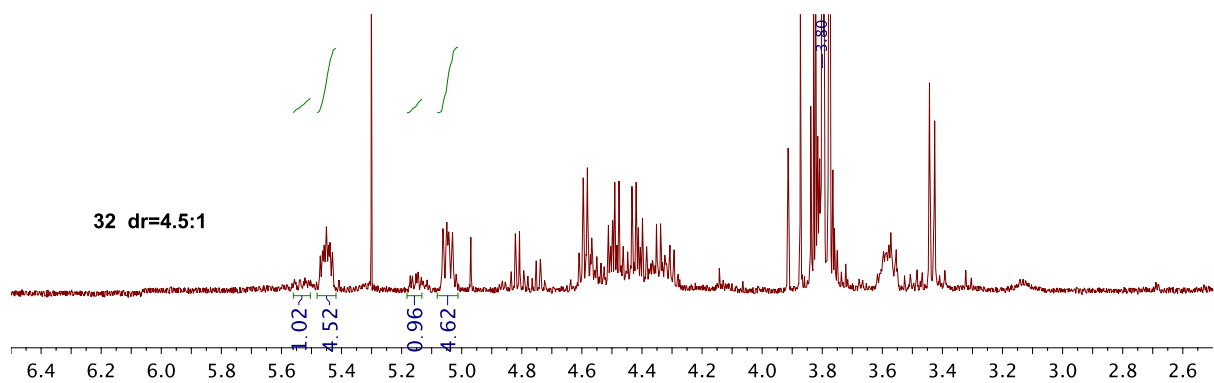


35 after reduction structure



dr. in crude ^1H NMR for di-insertion product



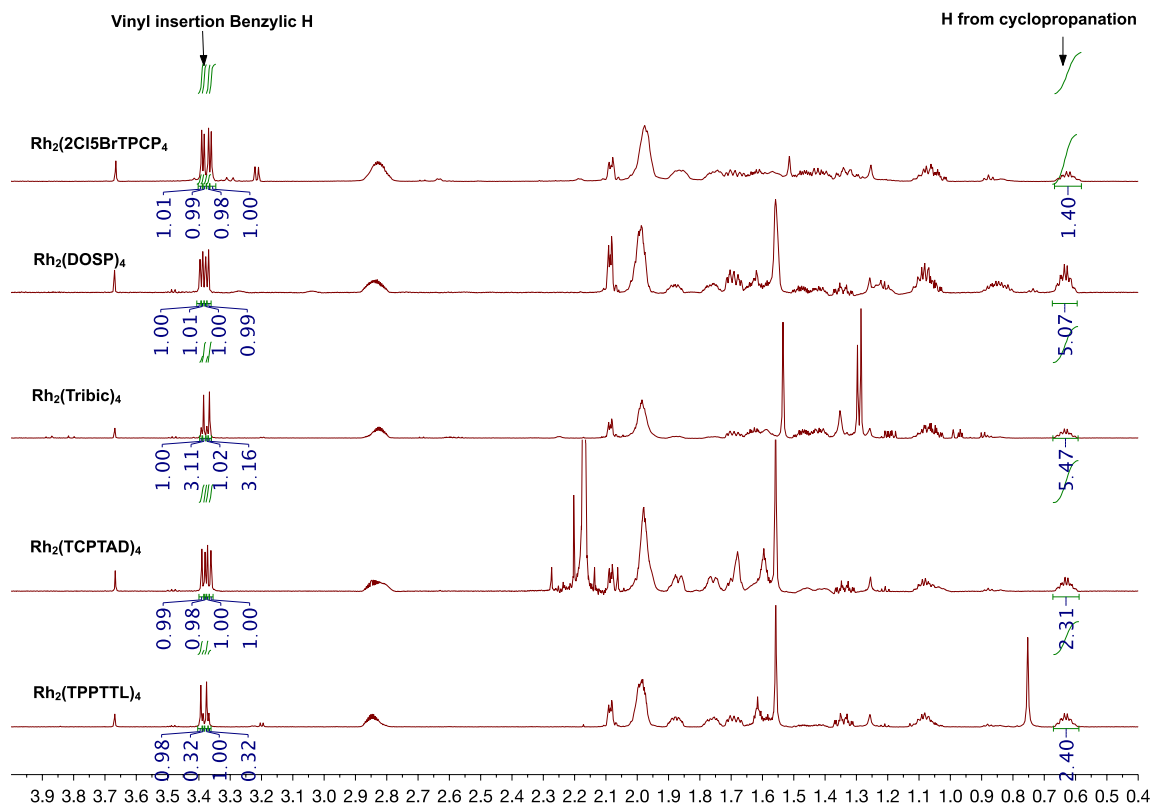


Comparison with other cyclic alkene & triene catalyst screening

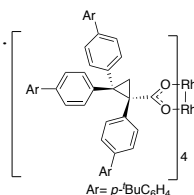
(1) Cyclohexene catalyst screening: cyclo:vinyI & vinyl dr from crude proton NMR

(dr. peaks of vinylogous insertion)

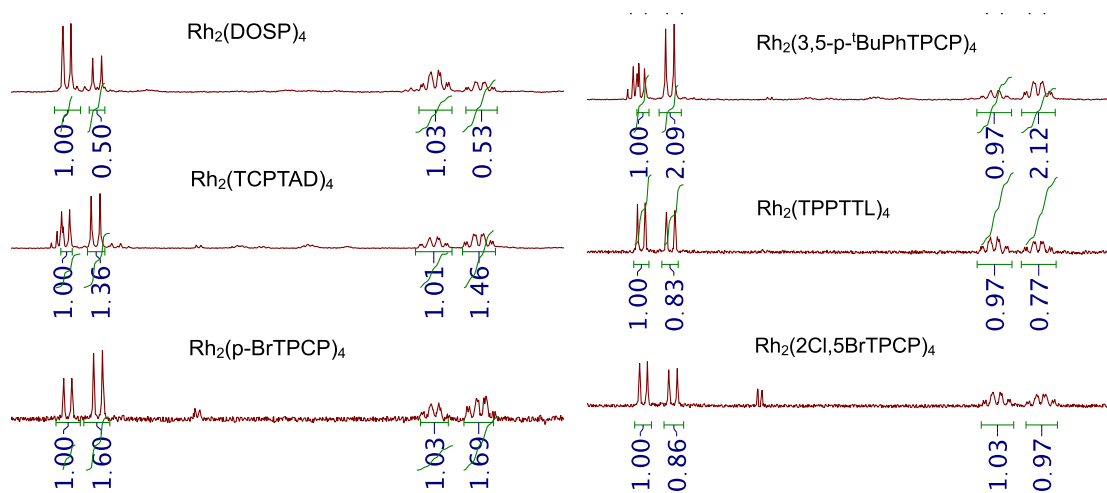
(cyclopropanation peak)



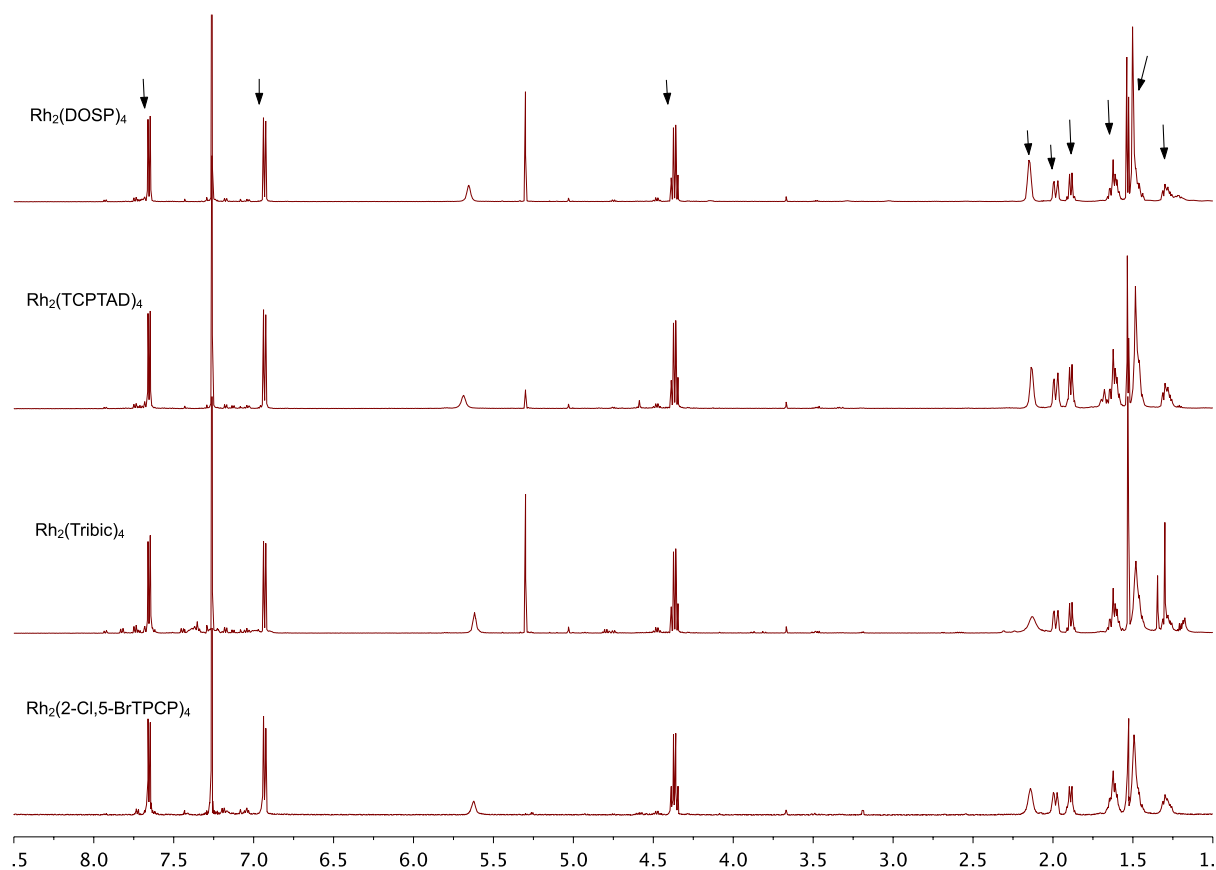
* $\text{Rh}_2(\text{Tribic})_4$ is a catalyst originally developed by our group for primary C-H insertion⁴.



(2) 1E, 5E, 9E-Cyclododecatriene catalyst screening: (dr. ratio)



(3) cis-Cyclooctene catalyst screening:



*The arrow peaks are for the cyclopropanation product. All catalysts give clean formation of cyclopropane.

References

1. Wenbin Liu et.al., *J. Am. Chem. Soc.*, **2018**, *140*, 12247–12255
2. Liangbing Fu et.al., *Chem. Eur. J.* **2017**, *23*, 1
3. David M. Guptill et.al. *J. Am. Chem. Soc.* **2014**, *136*, 17718
4. Liao, K.; Yang, Y.-F.; Li, Y.; Sanders, J. N.; Houk, K. N.; Musaev, D. G.; Davies, H. M. L. *Nature Chem.* **2018**, *10*, 1048.

SI COD_V15 Submitted version.pdf (13.49 MiB)

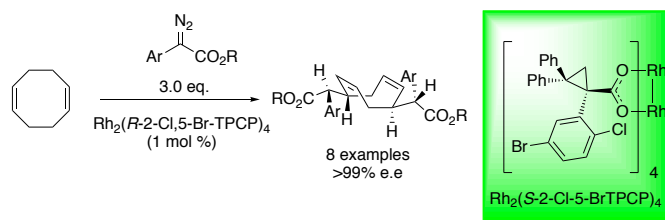
[view on ChemRxiv](#) • [download file](#)

C—H Functionalization Approach for the Synthesis of Chiral C₂ Symmetric 1,5-Cyclooctadiene Ligands

Bowen Zhang, Michael R. Hollerbach, Simon Blakey* and Huw M. L. Davies*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322

Supporting Information Placeholder



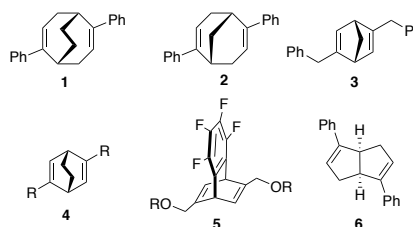
ABSTRACT: Chiral cyclooctadiene (COD) derivatives are readily prepared by rhodium-catalyzed allylic C—H functionalization of COD. Either mono or difunctionalization of COD is possible generating the products in high yield, diastereoselectivity and enantioselectivity. The double C—H functionalization generates C₂ symmetric COD derivatives with four new stereogenic centers in >99% ee, which can be readily converted to a series of chiral COD ligands. Preliminary evaluations revealed that the COD ligands can be used in rhodium-catalyzed asymmetric arylation of cyclohex-2-enone, leading to the conjugate addition products in up to 76% ee.

1,5-Cyclooctadiene (COD) is widely used as a ligand in transition metal complexes.¹ Metal-COD complexes are useful because many are sufficiently stable to be isolated and easily handled, often more robust than the related ethylene complexes because of chelation. Even though the metal-COD complexes were initially considered as stable precursors to active catalysts, it became clear in many instances that the COD ligand was not lost and was an integral part of the catalytic cycle.²⁻⁴ Consequently, there became interest in designing chiral COD ligands for chiral catalysis. The Chiral COD ligands **1** and **2** have shown considerable promise but their synthesis requires a multistep synthesis and a resolution.^{4b} This has led to the synthesis of other skipped cyclic dienes as chiral ligands,⁴⁻⁶ including a number of C₂ symmetric ligands **3-6**. However, all require a multistep synthesis and most involve a racemic synthesis followed by resolution⁴⁻⁶ (Scheme 1). In this paper we describe an enantioselective C—H functionalization method for the direct synthesis of C₂ symmetric COD derivatives **7**, with four stereogenic centers. Furthermore, we describe their derivatization to other C₂ symmetric COD derivatives **8** and their initial evaluation as chiral ligands for rhodium-catalyzed conjugate addition.

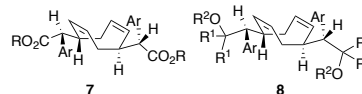
The motivation for this study was the realization that COD would be an intriguing substrate to challenge catalyst-controlled C—H functionalization by rhodium-stabilized donor/acceptor carbenes (Scheme 2).^{7,8} We have recently shown that dirhodium catalysts of defined shapes are capable of selecting between primary, secondary and tertiary unactivated

Scheme 1 Chiral cyclic diene ligands

A. Previous cyclic chiral diene:



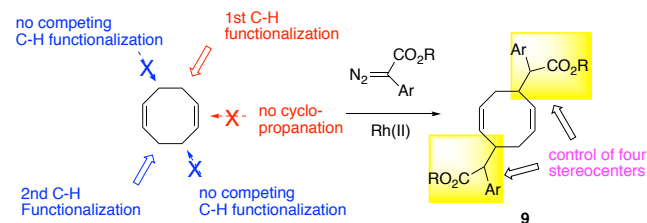
B. This work



C—H bonds.^{8a-e} We have also shown that catalysts can be designed that would select between different secondary C—H bonds.^{8c,f,g} COD was considered to be an interesting substrate because even though the methylene sites are allylic and relatively activated, the cis alkene would be expected to be a competing site for cyclopropanation. Therefore, we would need to identify a catalyst that would lead to selective C—H functionalization instead of cyclopropanation. Then, ideally once the mono C—H functionalization has occurred, the catalyst would select the C5 site for a second C—H functionalization, over the two other allylic methylene sites at C3 and C6 to generate the COD derivative **9**. For the overall

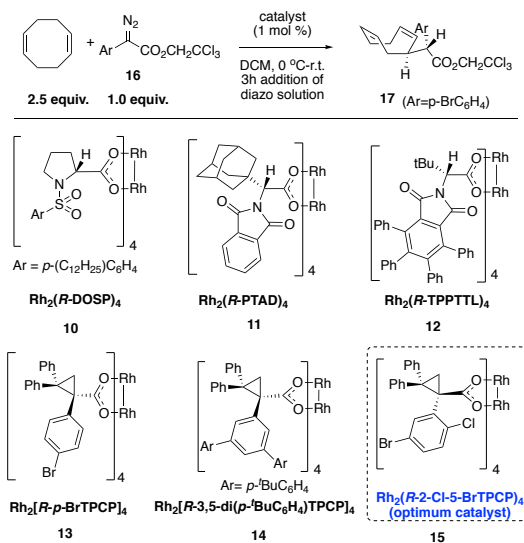
scheme to be useful we would need to be able to control the stereochemistry of the four newly formed stereogenic centers so that the C₂-symmetric form of **7** is generated.

Scheme 2. Synthetic Challenge



The first stage of the study focused on the mono-C—H functionalization reactions using the most promising catalysts in our tool box for selective reactions at methylene sites (Scheme 3). Rh₂(S-DOSP)₄ (**10**) is our original catalyst and has been shown to be broadly applicable for functionalization of activated methylene sites.^{7b} Rh₂(S-PTAD)₄ (**11**) is an uncrowded catalyst that can give different stereochemical results to Rh₂(S-DOSP)₄ at methylene C—H functionalization.^{7b} Rh₂(R-TPPTTL)₄ (**12**) has shown remarkable site selectivity for C3 over C4 C—H functionalization of alkylcyclohexanes.^{8f} The triphenylcyclopropanecarboxylates (TPCP) derivatives generate the most sterically crowded dirhodium tetracarboxylate catalysts. Rh₂(*R-p*-BrTPCP)₄ (**13**) was the first member of this class and preferentially reacts at less crowded C—H bonds.^{8a,b} Rh₂(*R*-3,5-(*p*-^tBuC₆H₄)TPCP)₄ (**14**) and Rh₂(*R*-2-Cl-5-BrTPCP)₄ (**15**) selectively react at the most accessible unactivated methylene site in linear alkanes.^{8c,g} We have recently found that C—H functionalization with donor/acceptor carbenes tend to proceed in higher yields when the acceptor group is a trihaloethyl derivative.^{8b} Therefore, the test reaction was initially conducted with the trichloroethyl aryldiazoacetate **16** and 2.5 equiv of COD. Most of the catalysts gave an undefined mixture of products, consisting of cyclopropanation, diastereomeric mono-insertion and likely diastereomeric and/or regioisomeric di-insertion products (see supplementary information for details). In contrast, the Rh₂(*R*-2-Cl-5-BrTPCP)₄-catalyzed reaction was relatively clean and the desired mono C—H functionalization product **17** could be isolated in 72% yield, >30:1 dr and 91% ee.

Scheme 3 Catalyst screening



The scope of the reaction was then examined with a range of aryldiazoacetates as summarized in Scheme 4. The first three systems examined the influence of the ester functionality. The methyl ester gave the C—H functionalization product **18** with lower diastereoselectivity and enantioselectivity compared to the trichloroethyl ester **17**, further underscoring the advantage of the trihaloethyl esters in C—H functionalization reactions. The trifluoroethyl derivative **19** was formed with the highest yield and enantioselectivity and retained the high diastereoselectivity. Therefore, the further studies focused on the trifluoroethyl derivatives. A series of *p*-substituted aryl (**20–24**) and a pyridyl derivative (**25**) were prepared and they were formed in high yield and dr, with the asymmetric induction in the range of 79–95% ee. The reaction with a *meta*-substituted aryldiazoacetate gave the mono-insertion product **26** but with decreased enantioselectivity (63% ee). We also examined the reaction with the styryldiazoacetate and it similarly gave an effective reaction to form **27** in 67% yield, >30:1 dr, 88% ee.

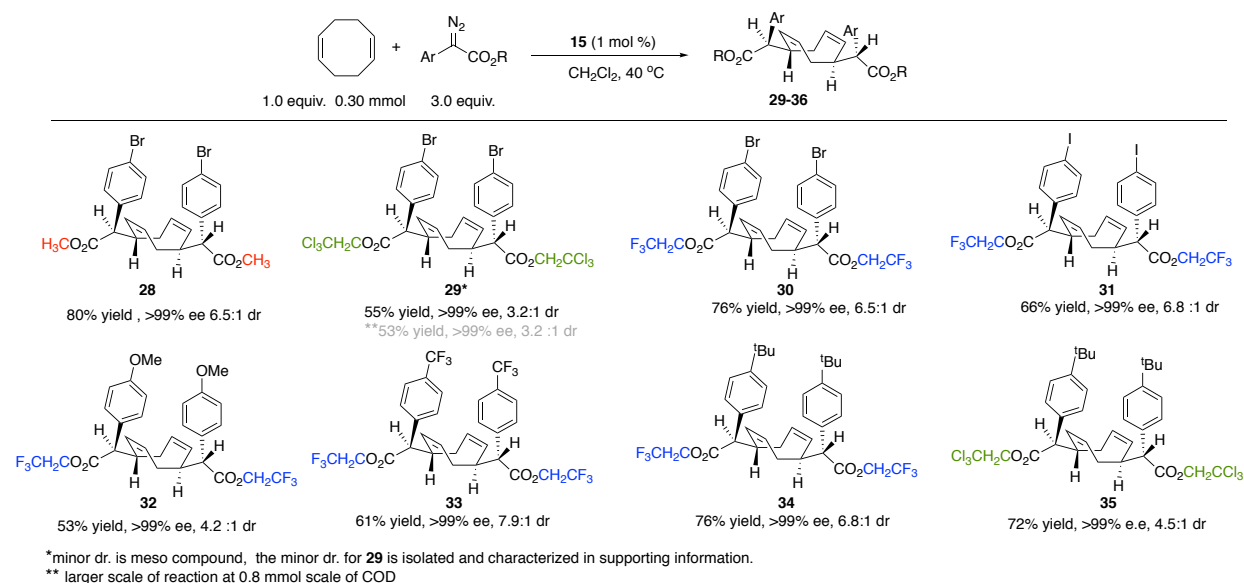
Scheme 4. Mono C—H functionalization of COD

product	R ₁	R ₂	yield, %	dr	ee, %
17	<i>p</i> -BrC ₆ H ₄	CH ₂ CCl ₃	72/80*	>30:1	91/89*
18	<i>p</i> -BrC ₆ H ₄	CH ₃	73	11.6:1	72
19	<i>p</i> -BrC ₆ H ₄	CH ₂ CF ₃	83	>30:1	93
20	<i>p</i> -IC ₆ H ₄	CH ₂ CF ₃	78	>30:1	95
21	<i>p</i> -(MeO)C ₆ H ₄	CH ₂ CF ₃	72	>30:1	81
22	<i>p</i> -(CF ₃)C ₆ H ₄	CH ₂ CF ₃	78	>30:1	94
23	<i>p</i> -tBuC ₆ H ₄	CH ₂ CF ₃	85	>30:1	88
24	<i>p</i> -(AcO)C ₆ H ₄	CH ₂ CF ₃	70	>30:1	79
25	6-(2-Cypridine)	CH ₂ CF ₃	72	>30:1	87
26	<i>m</i> -BrC ₆ H ₄	CH ₂ CF ₃	64	>30:1	63
27	styryl	CH ₂ CF ₃	67	>30:1	88

* larger scale reaction at 3.0 mmol of diazo compound

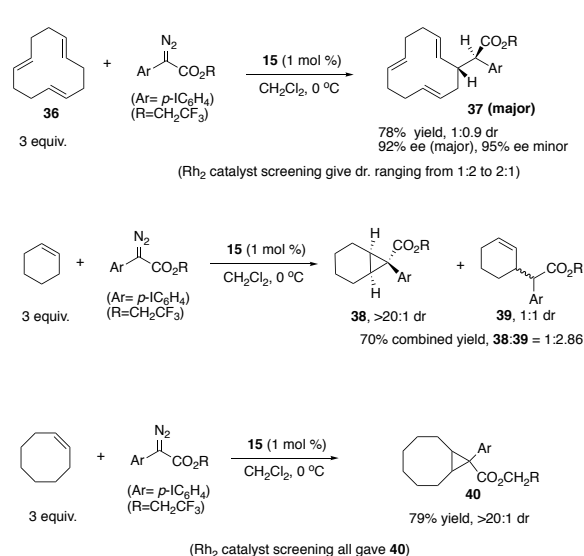
With the vision of designing chiral COD ligands, we decided to explore whether a double C—H functionalization could be achieved because this could be a direct way for the synthesis of C₂ symmetric ligands. At the onset of this work, it was considered to be a challenging C—H functionalization because a stereoselective reaction would be required at a specific allylic methylene site in the presence of two other allylic methylene sites and two cis-alkenes. Nevertheless, the double C—H functionalization turned out to be very effective (Scheme 5). The reaction was conducted using 3 equiv of the diazo compound at elevated temperature (40 °C), and under these conditions the bis C—H functionalization products **28–35** were formed in good yield. All the products are produced with very high levels of enantioselectivity (>99% ee) even though the enantiomeric purity of the mono C—H functionalization products was considerably lower (72–95% ee). This is because the minor enantiomer of the mono-insertion product is primarily transformed into the meso diastereomer of the final bis C—H insertion product during the second insertion. Also, imperfect asymmetric induction of the major enantiomer of the mono insertion product generates a diastereomer rather than an enantiomer of the final bis C—H insertion products. Consequently **28–35** are produced with very high enantioselectivity but with moderate diastereoselectivity. Fortunately, the desired major diastereomer is easily purified on silver-impregnated silica.

Scheme 5. Double C—H functionalization of COD



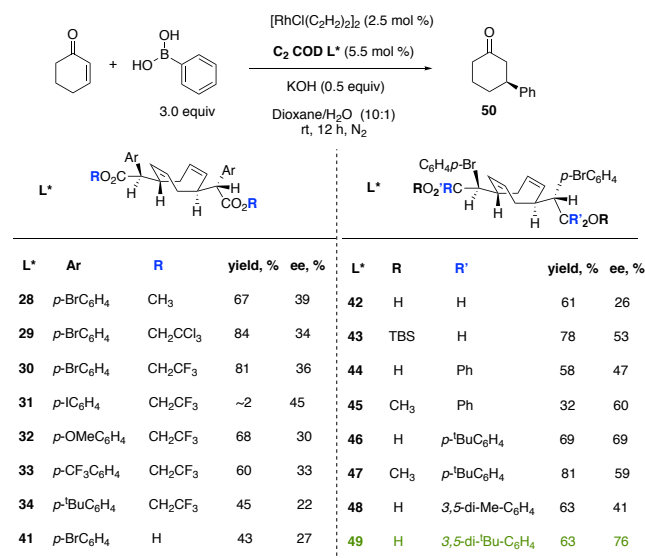
In order to understand the unprecedented site selectivity exhibited by COD, control experiments were conducted on related substrates using $\text{Rh}_2(2\text{-Cl}, 5\text{-BrTPCP})_4$ (**15**) as catalyst (Scheme 6). 1E,5E,9E-Cyclododecatriene (**36**) was found to be an effective substrate, forming the allylic C—H functionalization product **37** with poor diastereoselectivity but high enantioselectivity. The diastereomeric ratio could be altered slightly (2:1 – 1:2) with different dirhodium catalysts, but no catalyst rendered the reaction highly diastereoselective. The reaction with cyclohexene gave a mixture of cyclopropanation (**38**) and C—H functionalization products (**39**), ranging from 1.27:1 to 1:2.85, and the diastereoselectivity was also poor ranging from 3.11:1 to 1:3.12 dr (see supporting information for details). The reaction with cyclooctene, however, was very clean but the only product formed was the cyclopropane (**40**) (scheme 3). These results indicate that the structural features of COD are ideally suited for stereoselective allylic C—H functionalization, and other cycloalkenes can have a very different reactivity profile.

Scheme 6. Evaluation of related cycloalkenes



The bis C—H functionalization products can be further derivatized by either ester hydrolysis, ester reduction, or aryllithium addition, and the resulting alcohol products can be either methylated or silylated (See supporting information for details), leading to the formation of a variety of C₂-symmetric chiral COD ligands (**41-49**). A preliminary exploratory study was conducted to determine if these chiral COD ligands were compatible with rhodium-catalyzed conjugate addition of phenylboronic acid to cyclohexenone (Scheme 7). The reactions with all of the ligands, except for the aryl iodide derivative **31** resulted in the formation of conjugate addition product **50** in reasonable yield (32-84%) and variable levels of enantioselectivity (26-76% ee). Most of the direct double C—H insertion products gave about 30-40% ee but some of the ligands derived from the aryllithium addition gave higher levels of enantioselectivity. The most promising ligand to date has been **49**, which resulted in the formation of **50** in 63% yield and 76% ee.

Scheme 7. Enantioselective conjugate addition



In conclusion, a one-step enantioselective synthesis of C₂-symmetric chiral COD ligands was achieved by means of a double allylic C—H functionalization of COD. This transformation illustrates the capacity of C—H functionalization to rapidly generate synthetic complexity from a simple starting material. Initial evaluation of these chiral COD ligands along with their derivatives revealed they were effective in the rhodium-catalyzed asymmetric arylation of cyclohex-2-enone.

ASSOCIATED CONTENT

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

Complete experimental procedures and compound characterization are available in the Supporting Information. (PDF)

CIF file for **22** (CCDC 1960982), **35** (after reduction) (CCDC 1960983), **37** (major) (CCDC 1960993)

AUTHOR INFORMATION

Corresponding Author

* hmdavie@emory.edu

* sblakey@emory.edu

Notes

HMLD is a named inventor on a patent entitled, Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto (US 8,974,428, issued March 10, 2015). The other authors have no competing financial interests.

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