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Douglas Massashi Kavaguti April 9, 2023

An Investigation on the Diastereoselectivity of α-Methylstyrene Cyclopropanations Catalyzed by Dirhodium (II) Catalysts

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An abstract of
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Abstract

An Investigation on the Diastereoselectivity of α-Methylstyrene Cyclopropanations Catalyzed by Dirhodium (II) Catalysts

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Dirhodium (II) based catalysis have proven to be important tools for chemical syntheses, allowing for the development of bonds that would otherwise be difficult to obtain. In particular, rhodium-catalyzed cyclopropanations provide an efficient way to produce three-membered rings – scaffolds of interest in the context of pharmaceutics and natural synthesis. Though the Davies group has developed rhodium catalysts that allow these reactions to be performed efficiently and with high levels of selectivity, there are still gaps to be filled in these studies. This current study explores the diastereoselectivity of cyclopropanations between α-methylstyrene and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate in the presence of 11 different dirhodium (II) catalysts. The obtained results represent an initial step in the further refining of cyclopropanation-directed dirhodium (II) catalysts.

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Tables and Figures

1) Introduction

1.a) Rhodium (II) Catalysis

Dirhodium tetracarboxylate catalysts are valuable tools in asymmetric carbene-transfer reactions due to their chiral ligand environment. Because of this, the formation of one enantiomer over the other is preferred, a very desirable concept in both a chemical[1,2] and a pharmaceutical[3-5] context. Motivated by the catalytic potential of these species, the Davies group has developed several series of dirhodium (II) tetracarboxylate catalysts with different ligands.[6-10] Notable catalyst groups include the prolinato series, the phthalimido series, the triphenylcyclopropyl series, and the naphthalimido series (Figure 1).

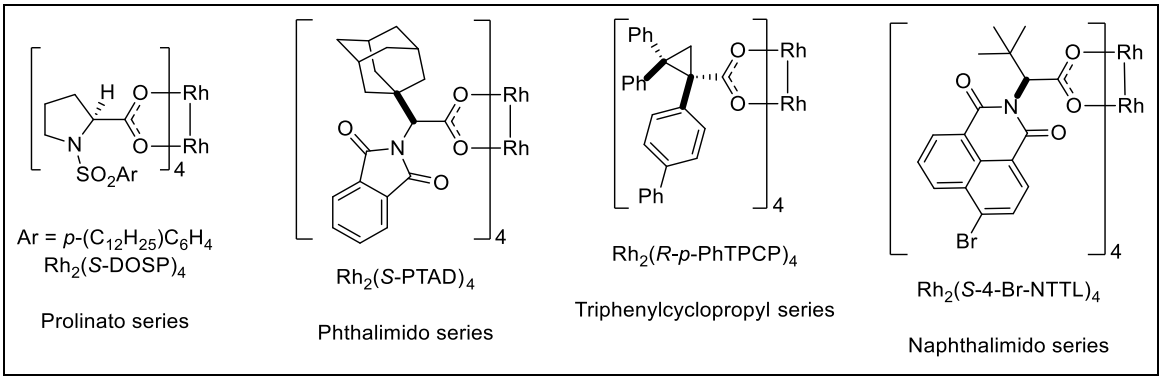


Figure 1. Selected dirhodium (II) catalysts.

These catalyst series each represent different stages of the work developed by the Davies group. The prolinato series – in particular, the Rh_2(*S*-DOSP)$_4$ catalyst with 4-dodecylphenyl sulfonyl-(L)-prolinato ligands – was a large step in making enantioselective and diastereoselective cyclopropanation reactions between styrene and aryldiazoacetates more accessible.[6] Phthalimido series catalysts such as Rh_2(*S*-TPPTTL)$_4$ have effectively been used in intermolecular cyclopropanations as well as in intramolecular and intermolecular C-H insertions[7], further expanding the capabilities of dirhodium catalysts. Catalysts from the

triphenylcyclopropyl series are able to target secondary C-H bonds over primary ones with high levels of enantioselectivity and diastereoselectivity.[8] They are also able to selectively catalyze cyclopropanation reactions between styrene and aryldiazoacetates.[8] The more recent naphthalimido series catalysts such as Rh_2(*S*-di-Ph-NTTL)$_4$ are capable of facilitating allylic C-H functionalization with triazoles, yielding great enantioselectivity levels.[9] Finally, a group of extended catalysts, including Rh_2(*S*-T-*p*-Br-TPPTTL)$_4$ and Rh_2(*S*-di-Ph-NTTL)$_4$, feature longer and bulkier ligands that form a rigid bowl-shaped structure around the dirhodium center, and are hypothesized to give greater diastereoselectivity than their predecessors in cyclopropanation reactions. Indeed, extended TPPTTL catalysts have been shown to yield exceptional site selectivity, enantioselectivity, and diastereoselectivity in the C-H functionalization of *tert*-butylcyclohexane.[10]

1.b) Cyclopropanation Reactions

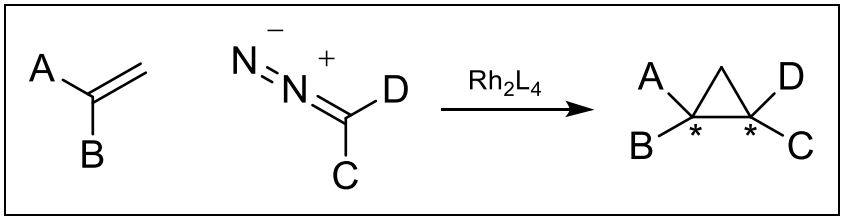


Figure 2. General cyclopropanation reaction involving an alkene and a diazo compound. Asymmetric centers are marked by asterisks.

Cyclopropane products are of great interest in the natural product[1,2] and pharmaceutical[3-5] industries due to the rigid geometry of their three-membered rings. Furthermore, when properly activated, they can serve as intermediates in the synthesis of more structurally complex derivatives via ring opening and cycloaddition reactions.[2] This synthetic potential has led to an increased need for the development of efficient and selective cyclopropanation reaction pathways. The Rh_2(*S*-DOSP)$_4$ catalyst can be highlighted as a breakthrough in these

investigations, as it facilitates highly enantioselective and diastereoselective cyclopropanation reactions between styrene and aryldiazoacetates. In a broader sense, it has been found that the chiral environment provided by an asymmetric catalyst favors a specific reaction pathway, in which the alkene substrate is only allowed to approach the carbene at a particular angle, increasing the enantioselectivity of the overall cyclopropanation reaction.

The catalytic cycle of a cyclopropanation reaction is shown below in Figure 3. After the catalyst-diazo complexation step (1), nitrogen gas (N_2) is released to produce a rhodium carbenoid (2). The rhodium-carbene intermediate and the alkene then perform a [2+1] cycloaddition to afford the desired cyclopropane product, while also regenerating the dirhodium catalyst. (3)[11]

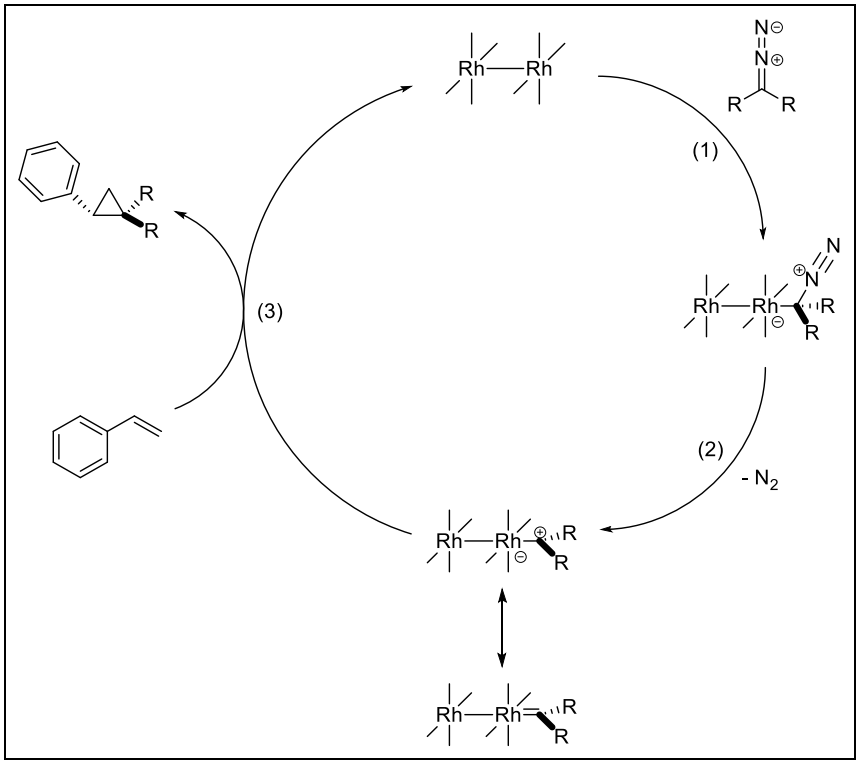


Figure 3. Scheme of the catalytic cycle of a cyclopropanation reaction.

1.c) Catalyst Screening with α-Methylstyrene

In 1996, Davies et al. explored the selectivity of cyclopropanation reactions between styrene and 2-diazo-4-phenylbutenoate in the presence of prolinate-derived dirhodium catalysts, finding very high diastereoselectivity (>40:1) and good yields (ranging from 46% to 91%), as well as high levels of enantiomeric excess (64% to 83%).[6] This current study followed a similar framework in order to investigate cyclopropanation reactions with α-methylstyrene and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (shown in Figure 4), in the presence of different dirhodium catalysts.

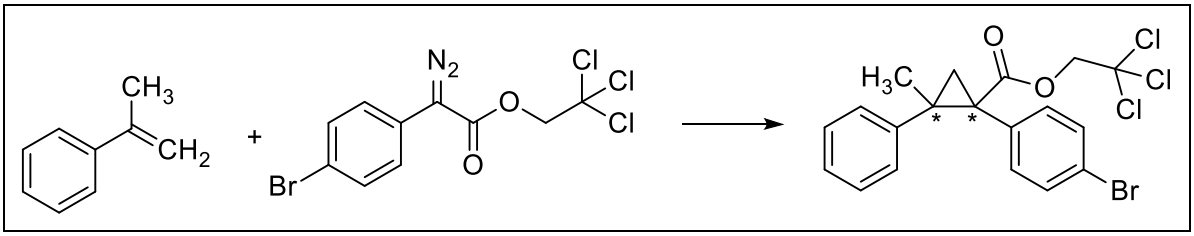


Figure 4. Cyclopropanation reaction investigated in this study.

1.d) Working Hypotheses

Compared to the previous styrene study[6], this current study introduced variables that make diastereoselectivity predictions less clear-cut. In particular, the additional methyl group on the styrene substrate is expected to interfere more with the sterics involved in the [2+1] cycloaddition step than a single hydrogen atom would. This implies that cyclopropanations with α-methylstyrene will give lower diastereoselectivity.

The screened catalysts included some with a rigid C_4-symmetric bowl shape, as well as others with more flexible C_4-, C_2-, or D_2-symmetric structures. It was expected that the rigid geometry of C_4-symmetric catalysts would lead to a greater steric factor in the cycloaddition step, leading to higher diastereoselectivity.

2) Results and Discussion

2.a) Screened Catalysts

The catalysts screened in this study are shown below, along with $Rh_2(OAc)_4$, used in a racemic reaction to obtain HPLC retention time data.

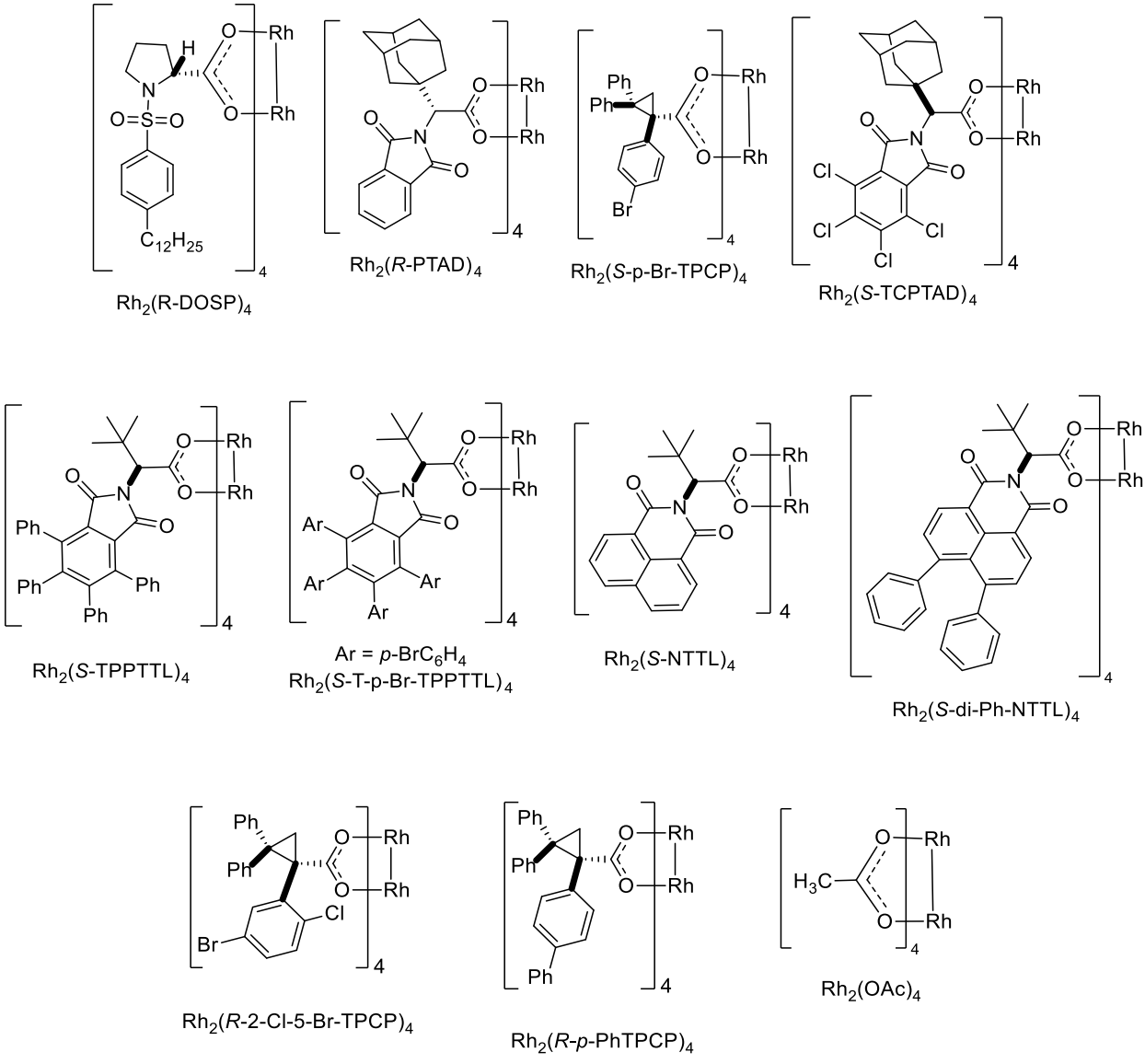


Figure 5. Dirhodium catalysts screened in this study.

This study originally intended to explore cyclopropanations with the first eight catalysts above in order to determine the validity of the hypotheses. Rh_2(*R*-2-Cl-5-Br-TPCP)$_4$ and Rh_2(*R*-*p*-Ph-TPCP)$_4$ were added to the catalyst list after Rh_2(*S*-*p*-Br-TPCP)$_4$ showed the best diastereoselectivity.

2.b) Cyclopropanation Reactions and Results

After purification, the cyclopropanation products were analyzed for yield, diastereomeric ratio (d.r.), and the enantiomeric excess (ee%) for the major and minor products. The obtained data is shown in Table 1 below.

Index #	**Catalyst**	**d.r.**	**Yield (%)**	**ee (%, major / minor)**
1	*R*-DOSP	8.6:1	64	+31 / +14
2	*R*-PTAD	5.5:1	73	-86 / -94
3	*S*-p-Br-TPCP	9.3:1	66	-85 / -82
4	*S*-TCPTAD	7.7:1	61	-31 / +42
5	*S*-TPPTTL	4.4:1	51	-14 / -14
6	*S*-T-*p*-Br-TPPTTL	5.0:1	42	+44 / +26
7	*S*-NTTL	4.0:1	64	+62 / +76
8	*S*-di-Ph-NTTL	3.3:1	71	+28 / +59
9	*R*-2-Cl-5-Br-TPCP	3.0:1	75	+52 / +77
10	*S*-*p*-Ph-TPCP	10.5:1	50	-92 / -87
11	$Rh_2(OAc)_4$	9.9:1	60	<5 / -8

Table 1. Cyclopropanation product data.

The performed α-methylstyrene cyclopropanation reactions were shown to be consistently less diastereoselective than their styrene counterparts, with d.r. values ranging from 3.0:1 to 10.5:1, much lower than the >40:1 values previously reported from styrene cyclopropanations.[6] This suggests that the methyl group does negatively impact the diastereoselectivity of the reaction.

The screened bowl-shaped rigid catalysts (**5-8**) were shown to give lower diastereoselectivity than more flexible catalysts (**1-4**, **9-10**), contrary to the original hypothesis. This may be related to the substrate's increased bulk as a result of the additional methyl group, which, coupled with the bowl catalysts' rigid structure, would make the catalysis of a singular pathway less favorable, lowering the reaction's diastereoselectivity.

A notable exception to be trend above was catalyst **9**, which gave similar d.r. levels to **5-8**. Catalyst **9** had the lowest d.r. out of the three screened TPCP-derived catalysts (**3, 9, 10**). This can be explained by its geometry: **3** and **10** are C_2-symmetric, while **9** is C_4-symmetric. This makes **9** more rigid than its counterparts, leading to lower diastereoselectivity.

2.c) Determination of Diastereoselectivity via ^{1}H NMR Analysis

The four theoretical cyclopropane products from the reaction of interest are shown in Figure 6. Products (A) and (B) are non-superimposable mirror images of each other and thus form a pair of enantiomers, as do (C) and (D). Other pairs are not mirror images of each other (changing only one of the two chiral centers), and are thus pairs of diastereomers.

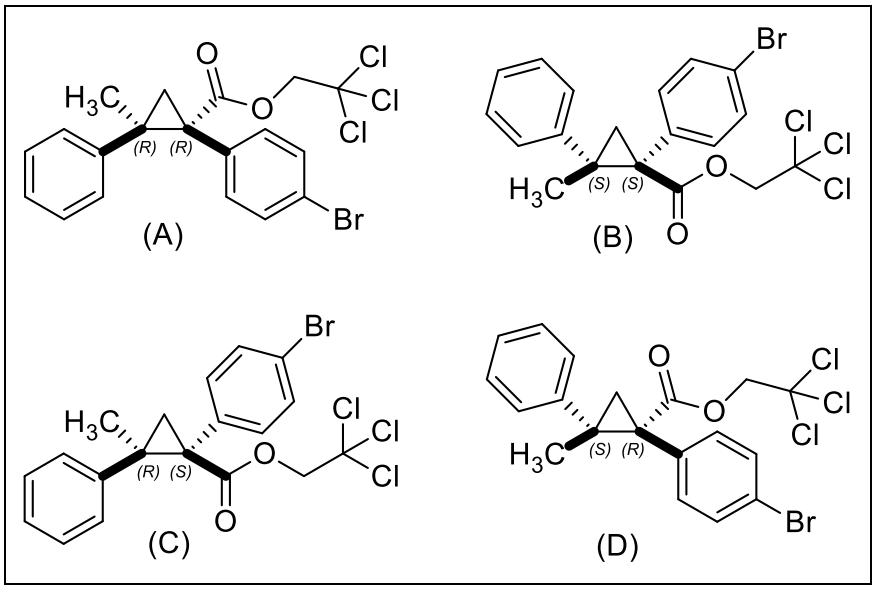


Figure 6. Theoretical products for cyclopropanation reaction, with stereochemistry indicated.

Enantiomers are mirror images of each other and have identical physical properties; they are thus indistinguishable in an NMR (nuclear magnetic resonance) spectrum. Diastereomers, on the other hand, due to the mismatch between their chiral centers, have slightly different properties, allowing them to be differentiated in an NMR spectrum. In the case of these cyclopropane products, this can be attributed to electronic effects.

The stereochemistry of the products is set in one of two ways with regards to the methyl and ester groups: either they are on the same side of the cyclopropane plane (as in the products (A) and (B) above), or they are on opposite sides (as in (C) and (D)). In the latter case, they would each be on the same side as a phenyl ring, whose π-system would interact with the methyl and methylene protons when under the strong magnetic field of an NMR instrument: the movement of π-electrons as a result of the applied magnetic field induces an opposing magnetic field, shielding the methyl's and ester's protons. This phenomenon, diamagnetic anisotropy[12], causes the peaks corresponding to the affected protons to be more shielded.

In practical terms, this property of the diastereomeric products causes their peaks to be shifted slightly on a ^{1}H NMR spectrum. The methyl and ester protons for (A) and (B) are downfield (i.e., show higher ppm values) compared to those for (C) and (D). The diastereoselectivity of a reaction can be measured by the corresponding diastereomeric ratio (d.r.), which is obtained by integrating the area under each signal separately and calculating the ratio between them.

This is exemplified by the spectra shown in Figures 7 and 8 below.

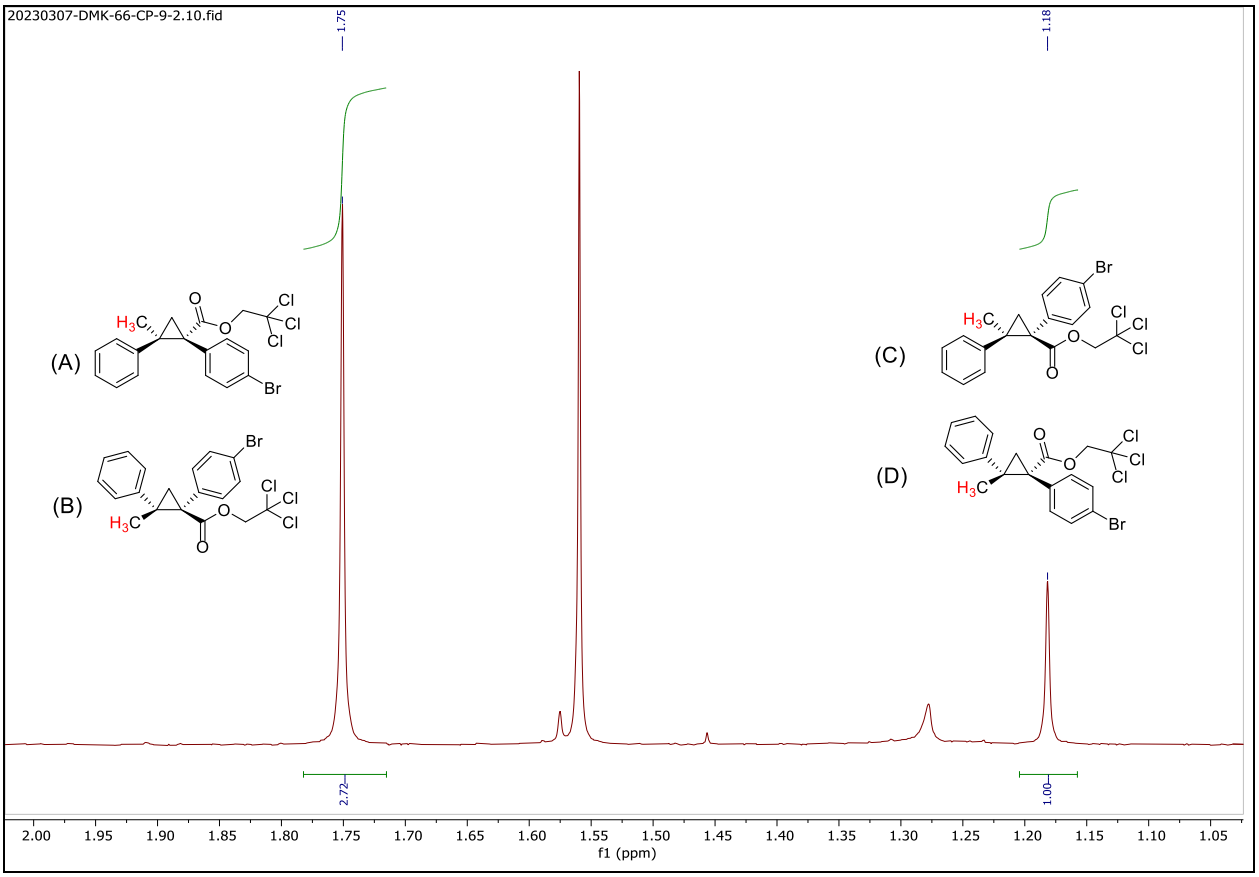


Figure 7. Spectrum highlighting the difference between the methyl proton signals of diastereomers. Relevant protons in red. Products A and B correspond to the signal at 1.75 ppm, while C and D correspond to the signal at 1.18 ppm. The d.r. of this reaction is calculated to be 2.7:1. The peak at 1.55 ppm corresponds to water.

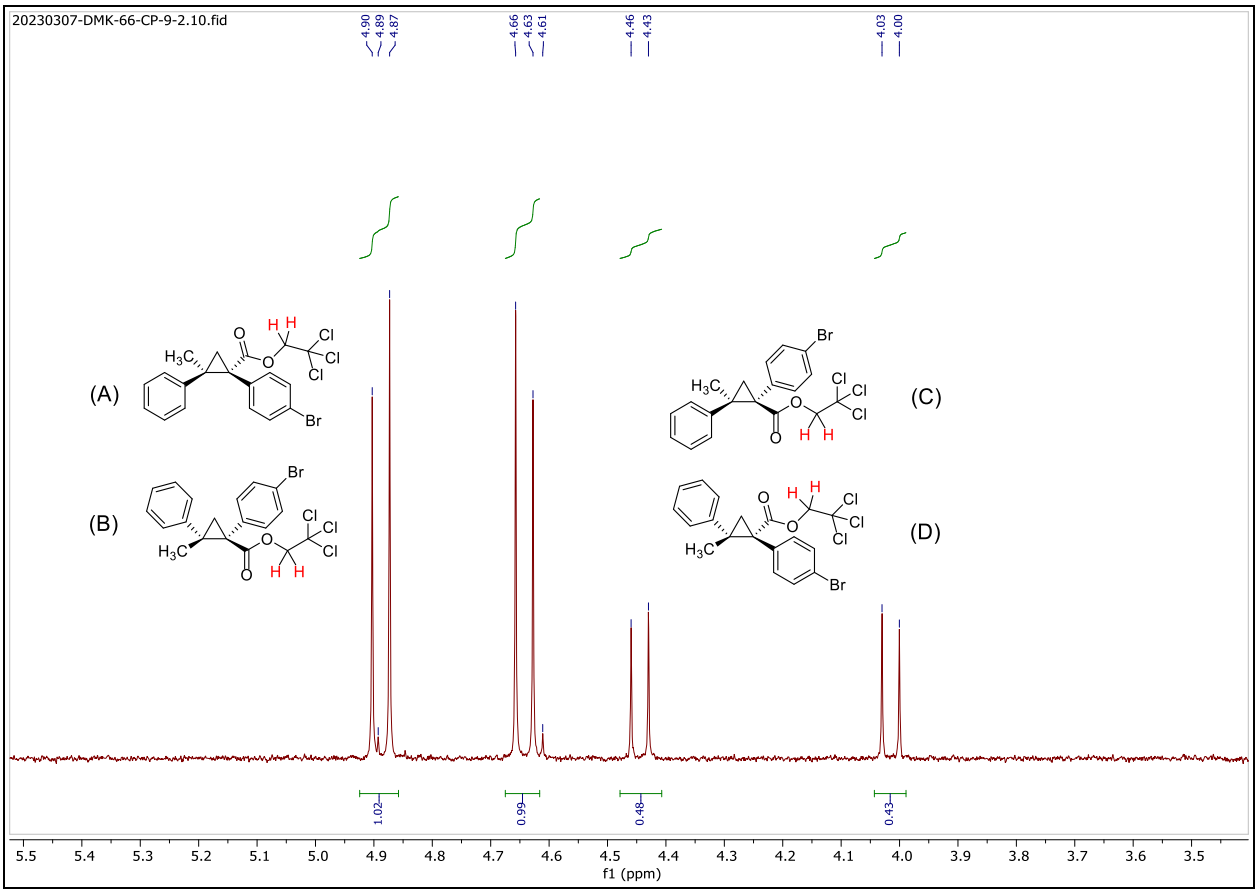


Figure 8. Spectrum highlighting the difference between the methylene proton signals of diastereomers. Relevant protons in red. Products A and B correspond to the signal centered at 4.77 ppm, while C and D correspond to the signal centered at 4.23 ppm.

3) Conclusions

The study has found that α-methylstyrene cyclopropanation reactions in the presence of dirhodium tetracarboxylate catalysts are less diastereoselective than styrene cyclopropanations, likely due to the steric factors introduced by the addition of a methyl group to the substrate.

It has also been found that rigid catalysts (e.g., the bowl-shaped Rh_2(*S*-di-Ph-NTTL)$_4$ or the C_4-symmetric Rh_2(*R*-2-Cl-5-Br-TPCP)$_4$) tend to give lower diastereoselectivity for α-methylstyrene cyclopropanations than more flexible catalysts (e.g., Rh_2(*S*-*p*-Br-TPCP)$_4$ and Rh_2(*S*-*p*-Ph-TPCP)$_4$), though it is unknown if this trend is specific to this substrate.

Further studies will focus on the diastereoselectivity of the cyclopropanation of less bulky styrene derivatives (or styrene itself) in the presence of rigid catalysts, and obtained results will the compared to those of the previous styrene study.[6] The cyclopropanation of other styrene derivatives (examples in Figure 9 below) is another possible option to explore steric and electronic factors in the cyclopropanation reaction.

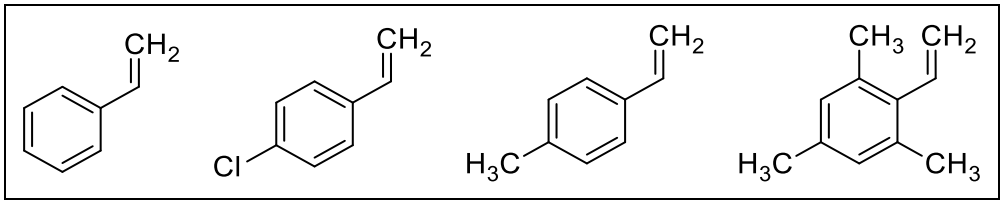
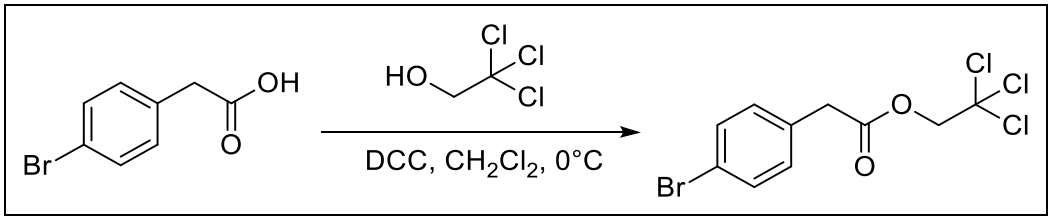


Figure 9. Styrene and selected styrene derivatives.

4) Experimental Section

4.a) Diazoacetate Synthesis Procedure:

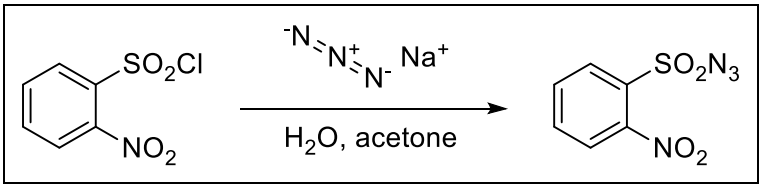
Synthesis of 2,2,2-trichloroethyl 2-(4-bromophenyl)acetate:



2-(4-bromophenyl)acetic acid (3.0 g, 14 mmol, 1 equiv.) and 2,2,2-trichloroethan-1-ol (2.5 g, 1.6 mL, 17 mmol, 1.2 equiv.) were added with 80 mL of CH_2Cl_2 to a 250 mL round-bottom flask. N,N'-dicyclohexylcarbodiimide (DCC, 3.2 g, 15 mmol, 1.1 equiv.) was carefully dissolved in 40 mL of CH_2Cl_2. The latter solution was slowly poured into the round-bottom flask at 0°C and left to stir overnight. The solution was filtered and washed with diethyl ether, and the solvent was evaporated under reduced pressure. The obtained crude product was purified via flash chromatography on silica gel (10% diethyl ether in hexanes) and concentrated, yielding a white crystalline solid (3.34g, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), δ 7.27 – 7.19 (m, 2H), δ 4.77 (s, 2H), δ 3.75 (s, 2H).[13]

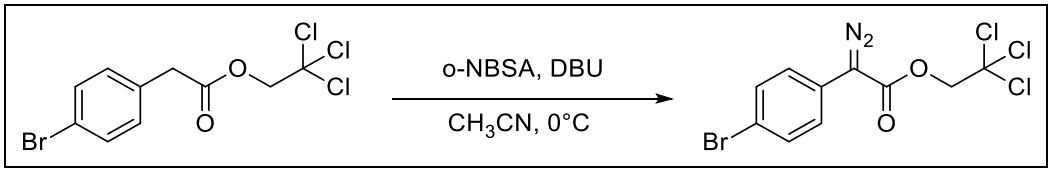
Synthesis of 2-nitrobenzenesulfonyl azide (o-NBSA):



Sodium azide (NaN_3, 1.6 g, 1.1 equiv., 25 mmol) was added to a 250 mL round-bottom flask via a plastic spatula, with trace NaN_3 being discarded in an appropriate azide waste container and the spatula being rinsed with acetone and water. Water (8.9 g, 8.9 mL, 0.5 mol, 22 equiv.) and acetone (12 g, 15 mL, 0.21 mol, 9 equiv.) were added to the same flask. 3-nitrobenzene chloride (5.0 g, 23 mmol, 1 equiv.) was dissolved in a separate 50 mL round-bottom flask with acetone (12 g, 15 mL, 0.21 mol, 9 equiv.). The solution in the 50 mL round-bottom flask was slowly added to the 250 mL round-bottom flask behind a blast shield. The solvent was evaporated under reduced pressure. The aqueous material was resuspended in water and diethyl ether, yielding a bilayer which was washed with water, then brine. The organic layer was extracted with diethyl ether and dried over $NaSO_4$ and filtered. The remaining solvent was evaporated behind a blast shield, yielding the product as a yellow crystalline solid (4.6 g, 90% yield). The ^{1}H NMR data matched the literature data.[13]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.20 (m, 1H), δ 7.98 – 7.81 (m, 3H).

Synthesis of 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate:

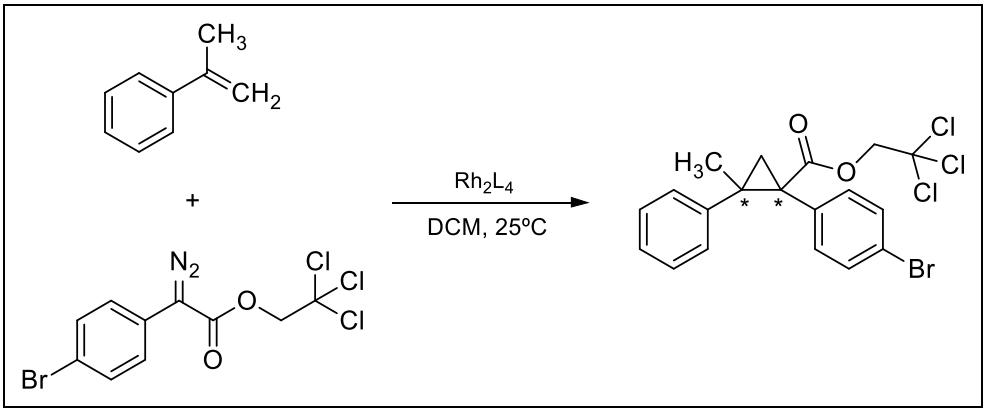


2,2,2-trichloroethyl 2-(4-bromophenyl)acetate (1.5 g, 4.33 mmol, 1 equiv.) and o-NBSA (1.48 g, 6.49 mmol, 1.5 equiv.) were added to a 250 mL round-bottom flask alongside 45 mL of acetonitrile. 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (DBU, 1.45 g, 1.42 mL, 9.53 mmol, 2.2 equiv.) was slowly added via syringe to the flask behind a blast shield, gradually turning the solution dark orange in color. After the slow addition, the solution was left to stir for an hour. The reaction was quenched with 50 mL of a solution of NH_4Cl and the organic layer

was extracted with diethyl ether (3 x 30 mL), then washed with water (2 x 30 mL) and brine (2 x 30 mL). The orange phase was concentrated, yielding an orange solid. This solid was purified via flash chromatography on silica gel (0% ether in n-hexane for 3 CV, 0-2% for 10 CV, 2% for 5 CV). The orange fractions were combined and concentrated, yielding the orange crystalline product (1.24 g, 77% yield). The ^{1}H NMR data matched the literature data.[13]

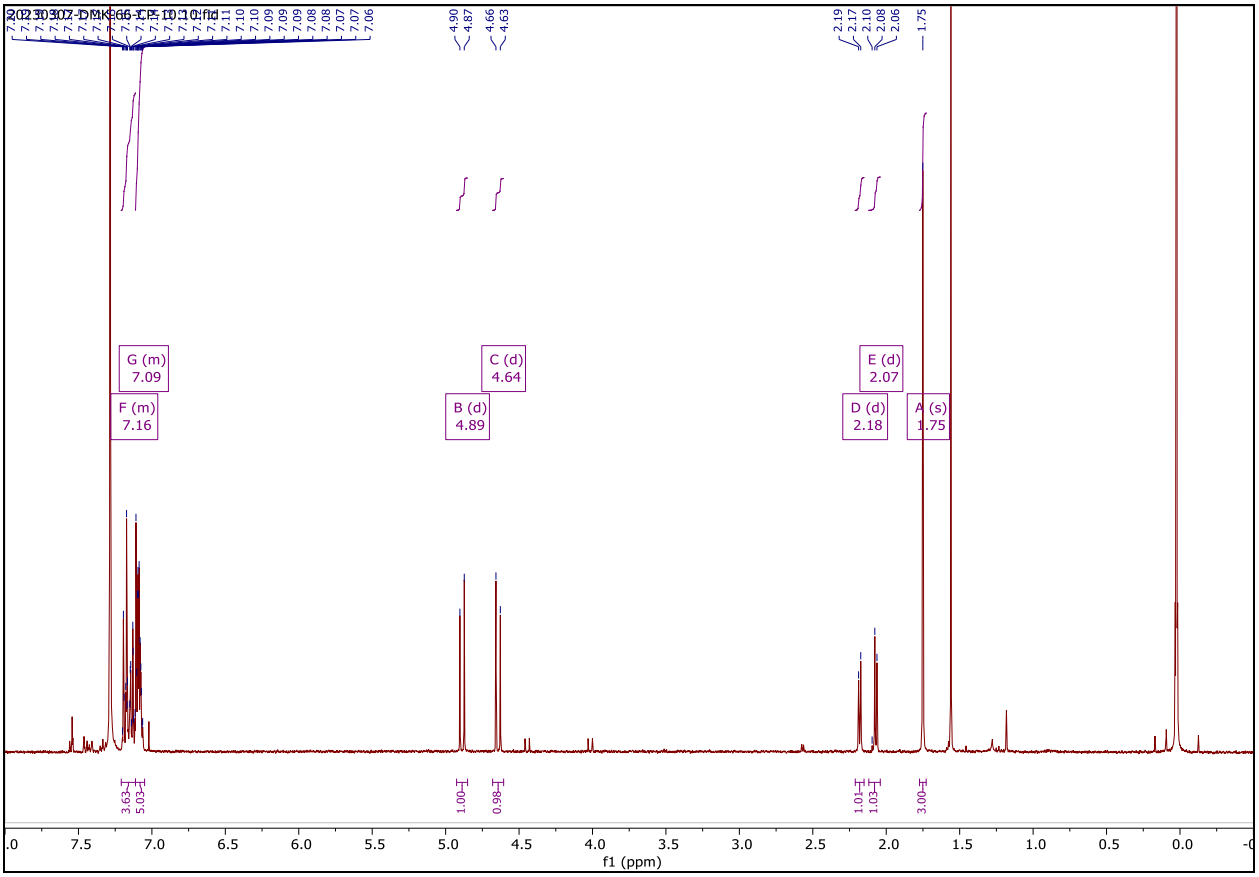
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2H), δ 7.44 – 7.37 (m, 2H), δ 4.93 (s, 2H).

4.b) General Cyclopropanation Reaction Procedure:



4Å molecular sieves and a stir bar were added to a 16 mL vial, which was subsequently flame-dried, purged, and left to return to room temperature. The dirhodium catalyst (0.002 mmol, 0.01 equiv.) was weighted and dissolved in 2 mL of dry CH_2Cl_2, then added to the vial. α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.) was added to the vial. The vial was placed in a pie-block, which was placed on a stirring plate. Slow stirring (100 rpm) of the solution was started. 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.) was dissolved in 2 mL of dry CH_2Cl_2, and slowly added to the stirring solution over 10 minutes via syringe. The solution was left to stir for an hour in room temperature. The obtained solution was filtered via a short pipette with celite using diethyl ether. Solvents were then evaporated under

reduced pressure. The obtained green crude product was purified via flash chromatography on silica gel (0% ether in n-hexane for 3 CV, 0-12% for 15 CV, 12% for 1.5 CV). The collected fractions were combined and concentrated, yielding the desired cyclopropane product as a white solid. The enantiomeric purity of the product was determined via chiral HPLC analysis.



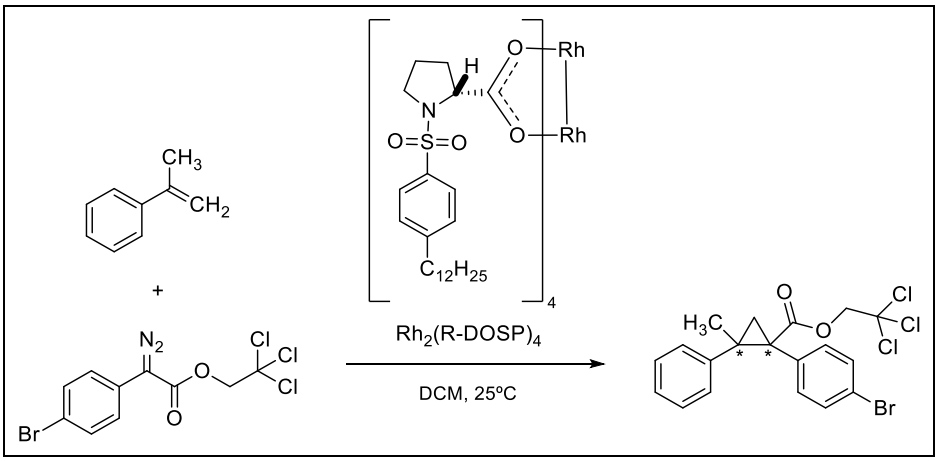
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.21 – 7.11 (m, 4H), δ 7.11 – 7.05 (m, 5H), δ 4.89 (d, J = 11.9 Hz, 1H), δ 4.64 (d, J = 11.9 Hz, 1H), δ 2.18 (d, J = 5.9 Hz, 1H), δ 2.07 (d, J = 5.8 Hz, 1H), δ 1.75 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ 169.64, δ 140.07, δ 134.71, δ 133.40, δ 130.49, δ 128.06, δ 127.85, δ 126.72, δ 121.13, δ 94.79, δ 74.78, δ 41.16, δ 37.52, δ 35.32, δ 26.07.

HRMS (+p APCI): calcd for $C_{19}H_{17}O_2{}^{79}Br{}^{35}Cl$ 460.9472 $[M+H]^+$, found 460.9480.

IR (neat): 2954, 1733, 1602, 1488, 1447, 1395, 1367, 1316, 1265, 1236, 1190, 1122, 1091, 1074, 1052, 1010, 889, 826, 805 cm^{-1}.

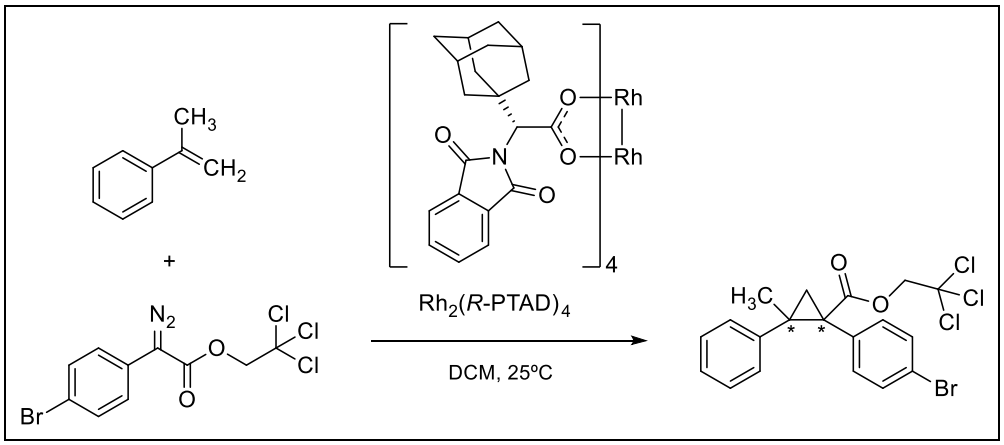
Rh_2(*R*-DOSP)$_4$ cyclopropanation



The reaction above was performed following general procedure **4.b** with Rh_2(*R*-DOSP)$_4$ (3.8 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (59 mg, 64% yield, 8.6:1 d.r.).

Chiral HPLC: enantiopurity was determined to be +31% ee for the major diastereomer and +14% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 11.5 min, Minor: 13.6 min, RT minor diastereomer: Major: 14.3 min, Minor: 20.2 min).

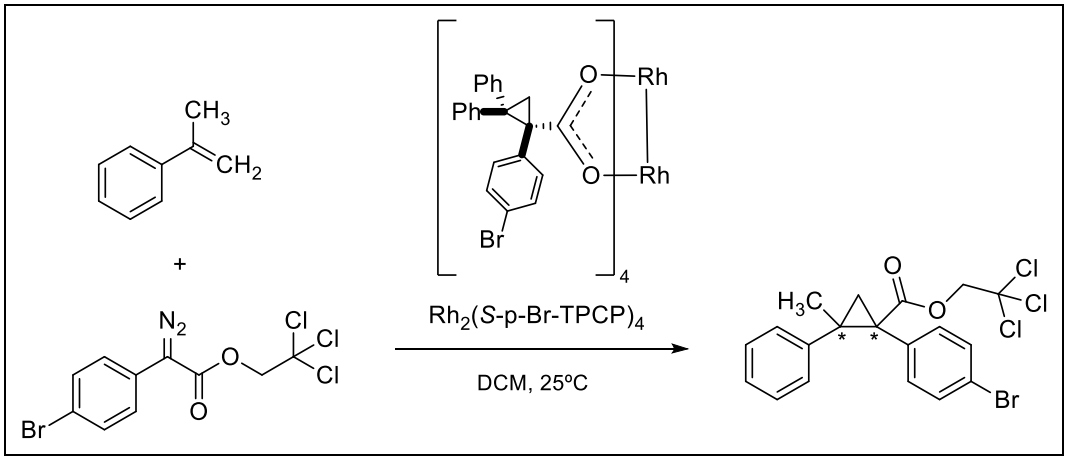
Rh_2(*R*-PTAD)$_4$ cyclopropanation



The reaction above was performed following general procedure **4.b** with Rh_2(*R*-PTAD)$_4$ (3.1 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (67 mg, 73% yield, 5.5:1 d.r.).

Chiral HPLC: enantiopurity was determined to be -86% ee for the major diastereomer and -94% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 13.2 min, Minor: 11.2 min, RT minor diastereomer: Major: 19.9 min, Minor: 13.8 min).

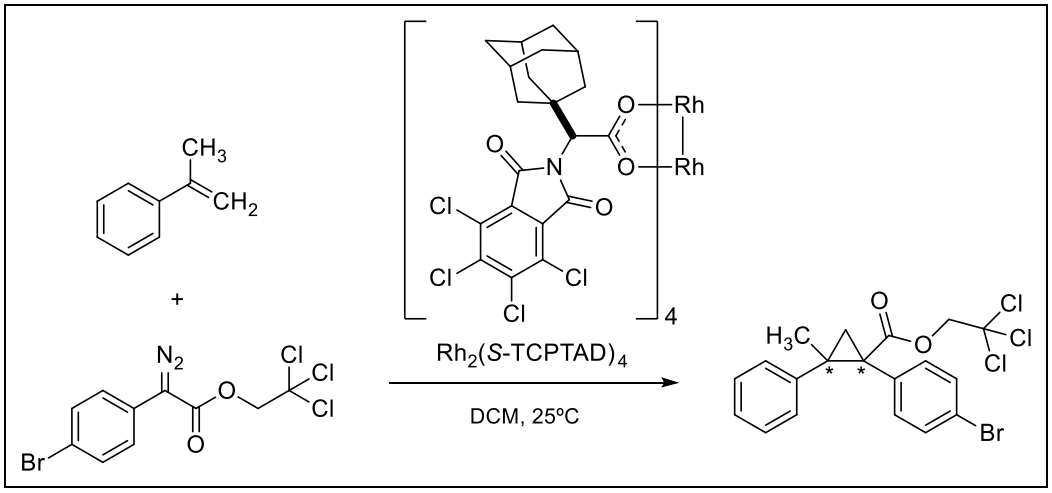
Rh_2(*S*-p-Br-TPCP)$_4$ cyclopropanation



The reaction above was performed following general procedure **4.b** with Rh_2(*S*-*p*-Br-TPCP)$_4$ (3.6 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (61 mg, 66% yield, 9.3:1 d.r.).

Chiral HPLC: enantiopurity was determined to be -85% ee for the major diastereomer and -82% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 13.4 min, Minor: 11.4 min, RT minor diastereomer: Major: 20.0 min, Minor: 14.0 min).

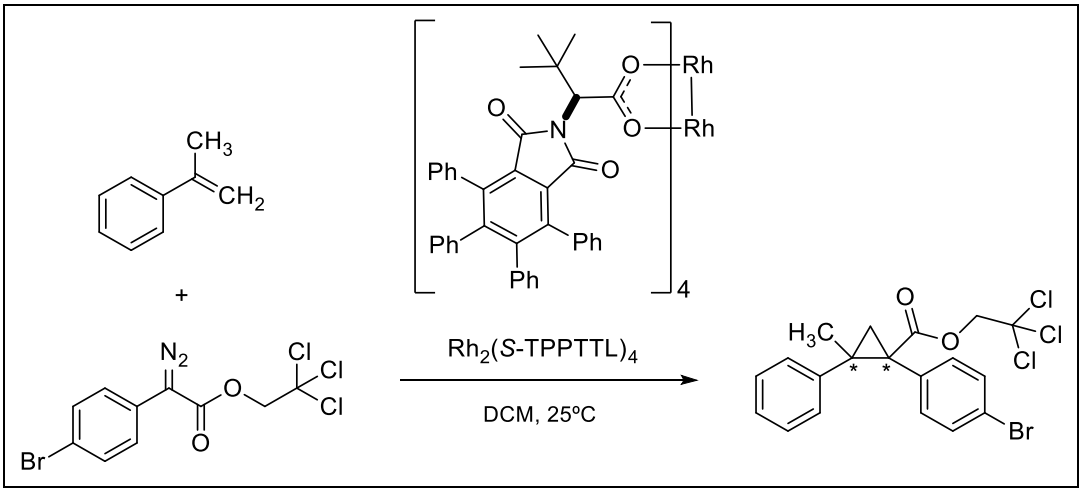
Rh_2(*S*-TCPTAD)$_4$ cyclopropanation



The reaction above was performed following general procedure **4.b** with Rh_2(*S*-TCPTAD)$_4$ (4.2 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (56 mg, 61% yield, 7.7:1 d.r.)).

Chiral HPLC: enantiopurity was determined to be -31% ee for the major diastereomer and +42% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 13.6 min, Minor: 11.4 min, RT minor diastereomer: Major: 14.2 min, Minor: 20.2 min).

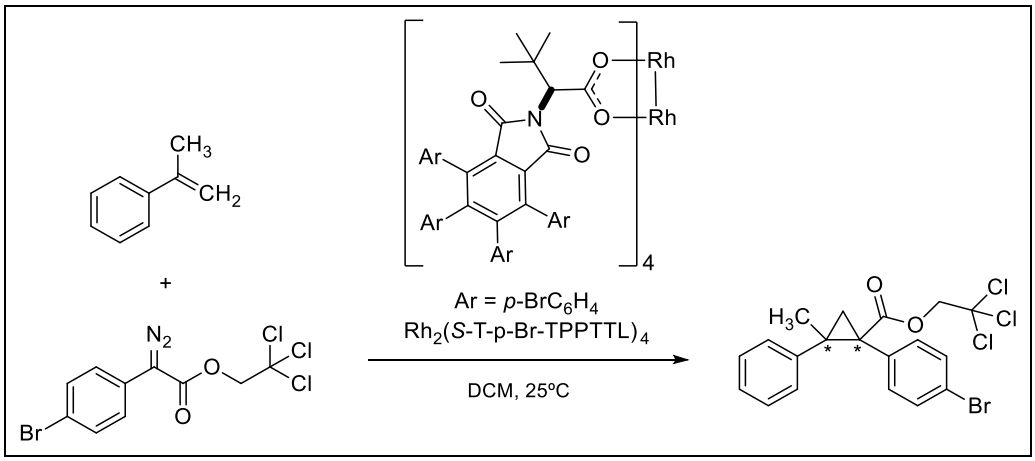
Rh_2(*S*-TPPTTL)$_4$ cyclopropanation



The reaction above was performed following general procedure **4.b** with Rh_2(*S*-TPPTTL)$_4$ (4.9 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (47 mg, 51% yield, 4.4:1 d.r.).

Chiral HPLC: enantiopurity was determined to be -14% ee for the major diastereomer and -14% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 13.6 min, Minor: 11.5 min, RT minor diastereomer: Major: 20.4 min, Minor: 14.3 min).

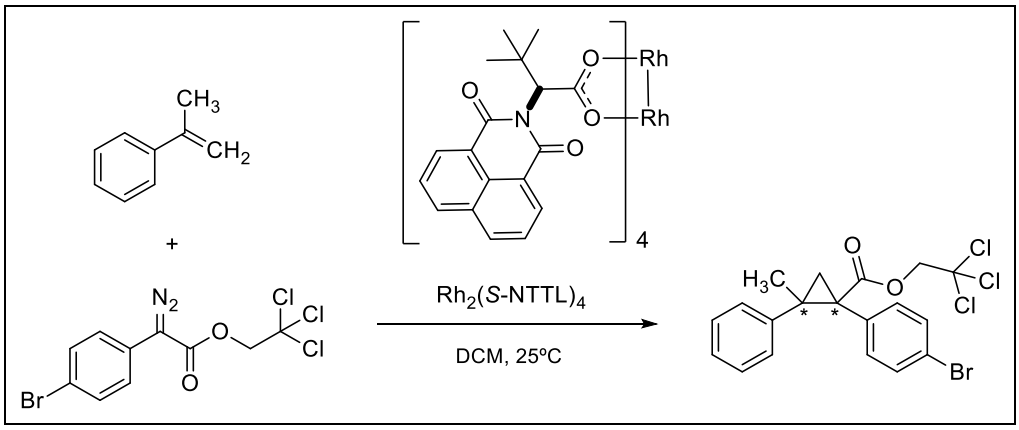
Rh_2(*S*-T-*p*-Br-TPPTTL)$_4$ cyclopropanation



The reaction above was performed following general procedure **4.b** with Rh_2(*S*-T-*p*-Br-TPPTTL)$_4$ (5.6 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (39 mg, 42% yield, 5.0:1 d.r.).

Chiral HPLC: enantiopurity was determined to be +44% ee for the major diastereomer and +26% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 11.2 min, Minor: 13.3 min, RT minor diastereomer: Major: 13.9 min, Minor: 20.1 min).

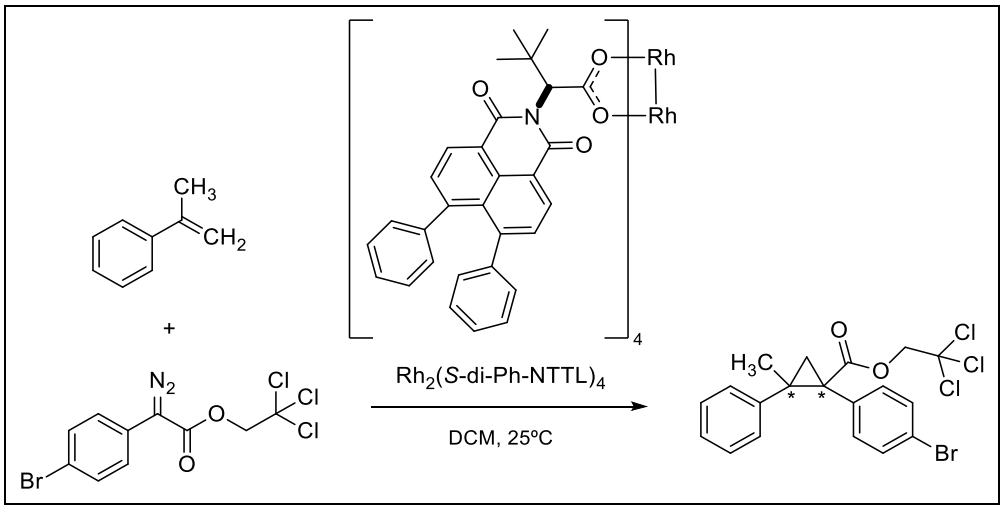
Rh_2(*S*-NTTL)$_4$ cyclopropanation



The reaction above was performed following general procedure **4.b** with Rh_2(*S*-NTTL)$_4$ (2.9 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (59 mg, 64% yield, 4.0:1 d.r.).

Chiral HPLC: enantiopurity was determined to be +62% ee for the major diastereomer and +76% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 11.4 min, Minor: 13.5 min, RT minor diastereomer: Major: 14.2 min, Minor: 20.5 min).

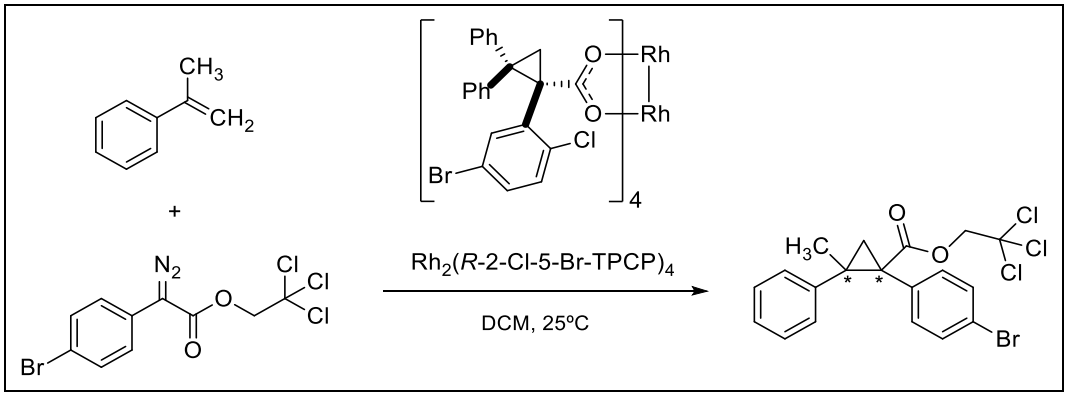
Rh_2(*S*-di-Ph-NTTL)$_4$ cyclopropanation



The reaction above was performed following general procedure **4.b** with Rh_2(*S*-di-Ph-NTTL)$_4$ (4.1 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (66 mg, 71% yield, 3.3:1 d.r.).

Chiral HPLC: enantiopurity was determined to be +28% ee for the major diastereomer and +59% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 11.3 min, Minor: 13.3 min, RT minor diastereomer: Major: 13.9 min, Minor: 20.0 min).

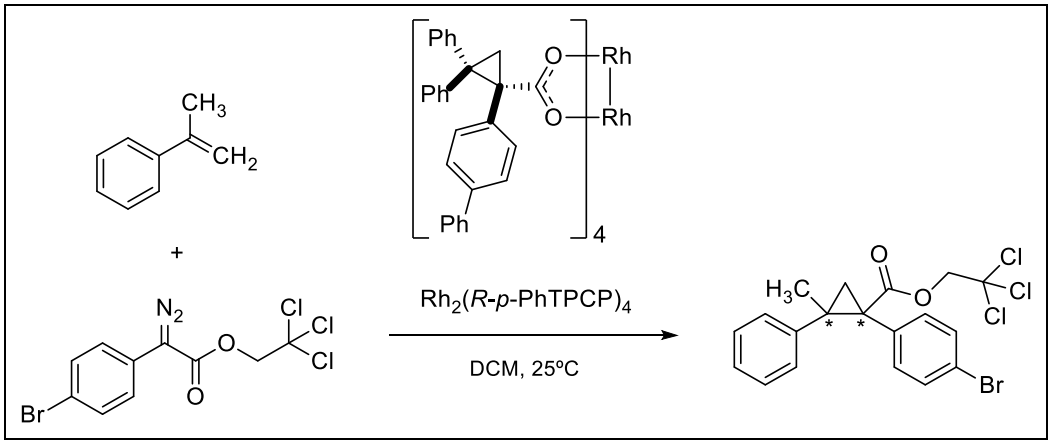
Rh_2(*R*-2-Cl-5-Br-TPCP)$_4$ cyclopropanation



The reaction above was performed following general procedure **4.b** with Rh_2(*R*-2-Cl-5-Br-TPCP)$_4$ (3.8 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (69 mg, 75% yield, 3.0:1 d.r.).

Chiral HPLC: enantiopurity was determined to be +52% ee for the major diastereomer and +77% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 11.2 min, Minor: 13.2 min, RT minor diastereomer: Major: 13.8 min, Minor: 19.9 min).

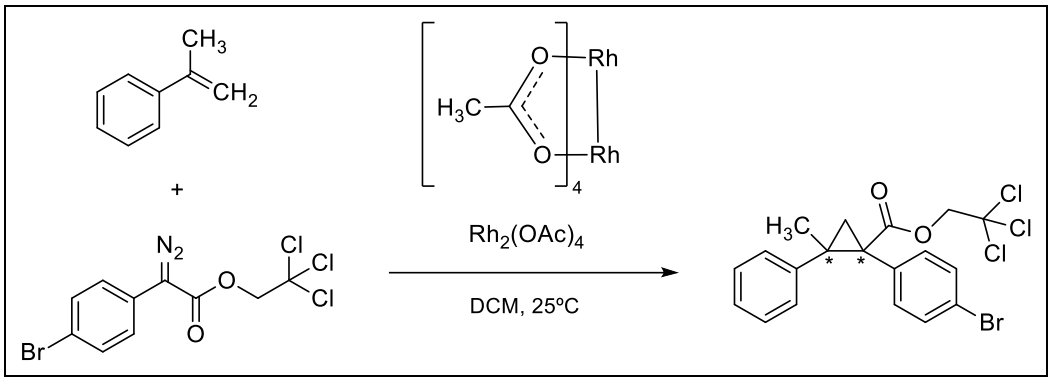
Rh_2(*S*-*p*-Ph-TPCP)$_4$ cyclopropanation



The reaction above was performed following general procedure **4.b** with Rh_2(*S*-*p*-Ph-TPCP)$_4$ (3.5 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (46 mg, 50% yield, 10.5:1 d.r.).

Chiral HPLC: enantiopurity was determined to be -92% ee for the major diastereomer and -87% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 13.4 min, Minor: 11.3 min, RT minor diastereomer: Major: 20.1 min, Minor: 14.0 min).

Rh_2(OAc)$_4$ cyclopropanation



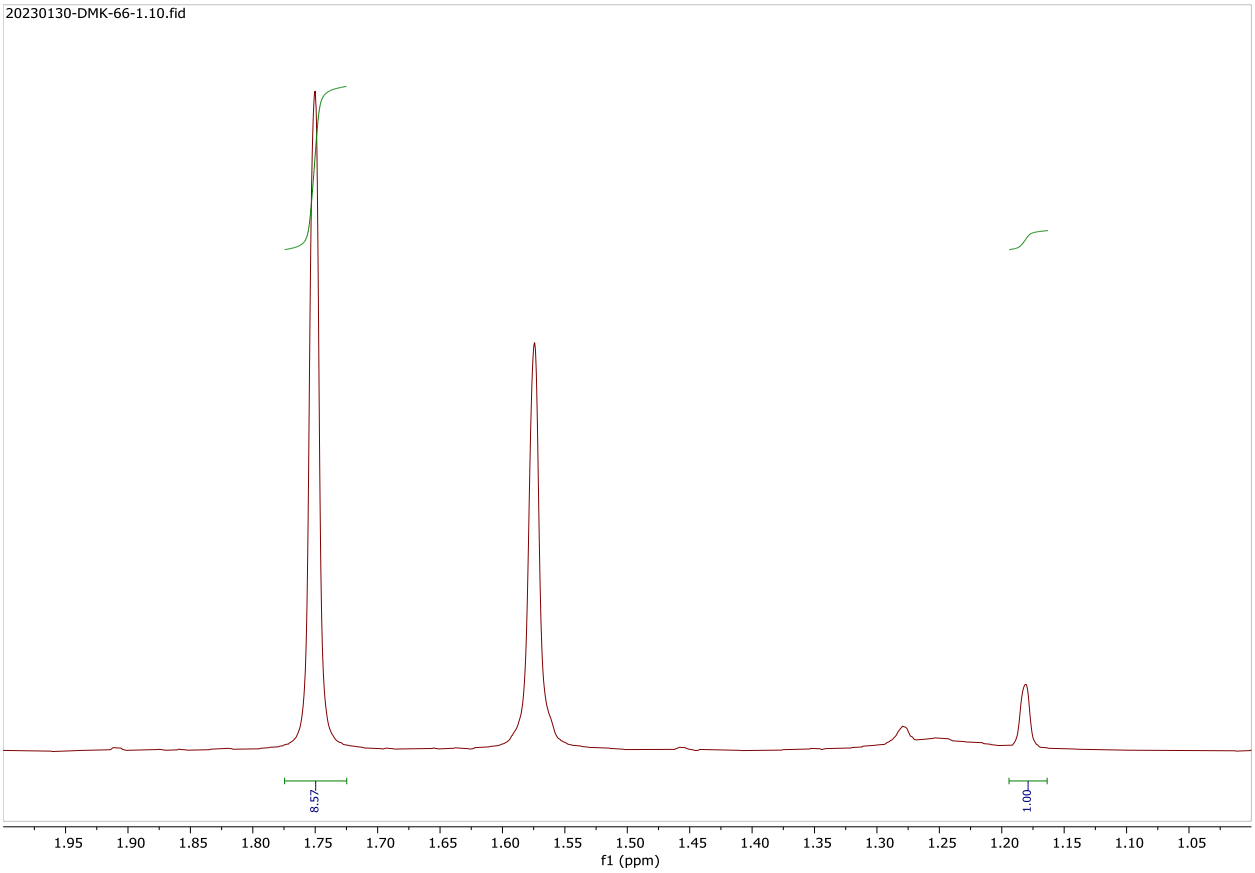
The reaction above was performed following general procedure **4.b** with $Rh_2(OAc)_4$ (0.9 mg, 0.002 mmol, 1 mol %) as the catalyst, α-methylstyrene (71 mg, 0.6 mmol, 3 equiv.), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazo acetate (75 mg, 0.2 mmol, 1 equiv.). After flash chromatography, the product was obtained as a white solid (56 mg, 60% yield, 9.9:1 d.r.).

Chiral HPLC: enantiopurity was determined to be <5% ee for the major diastereomer and -8% ee for the minor diastereomer by chiral HPLC analysis (Chiracel AD-H, 1.0% IPA/Hexanes, 0.5 mL/min, λ=230 nm, RT major diastereomer: Major: 11.3 min, Minor: 13.3 min, RT minor diastereomer: Major: 20.0 min, Minor: 13.9 min).

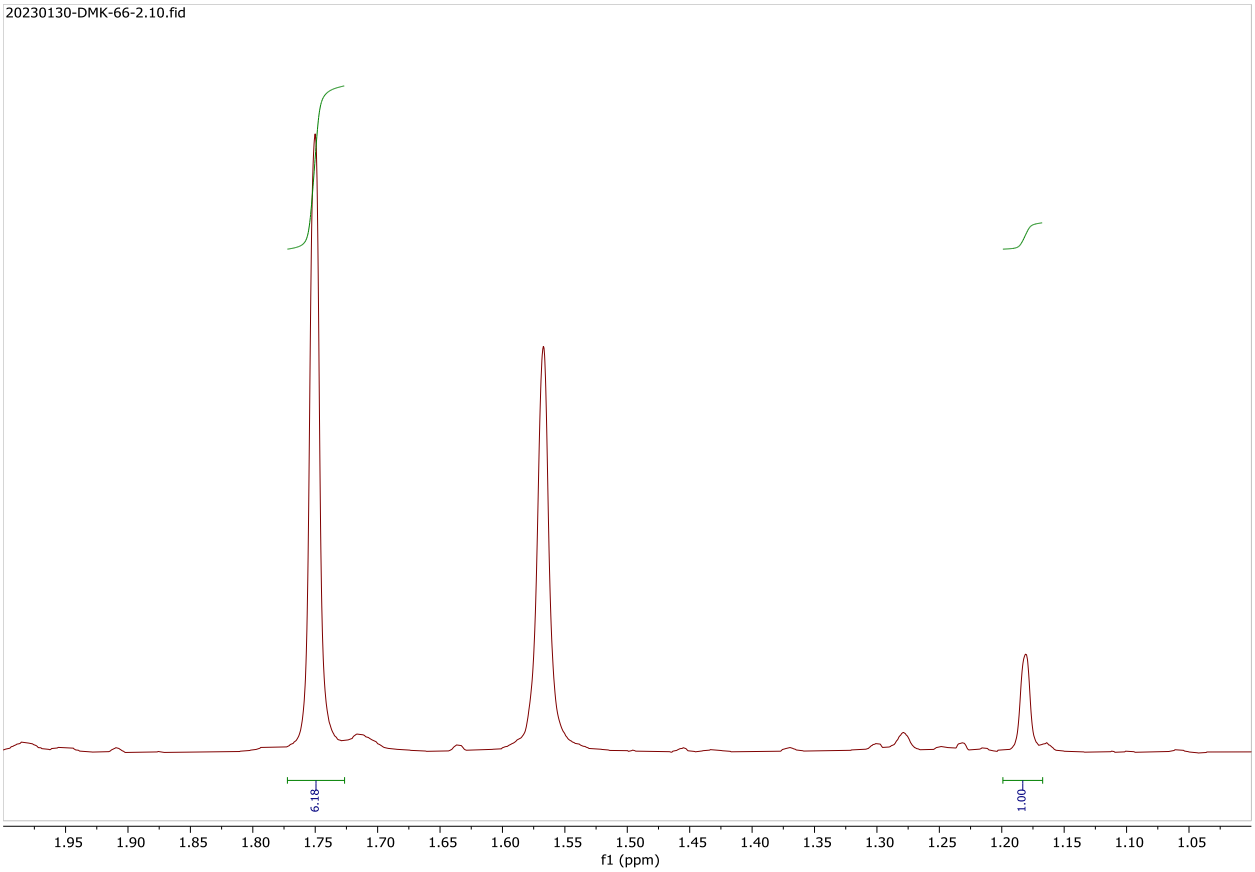
4.c) Cyclopropanation Product NMR Spectra:

The procedure described in section **2.c** was followed for each obtained cyclopropane product's NMR spectrum to determine the diastereoselectivity of the respective reaction.

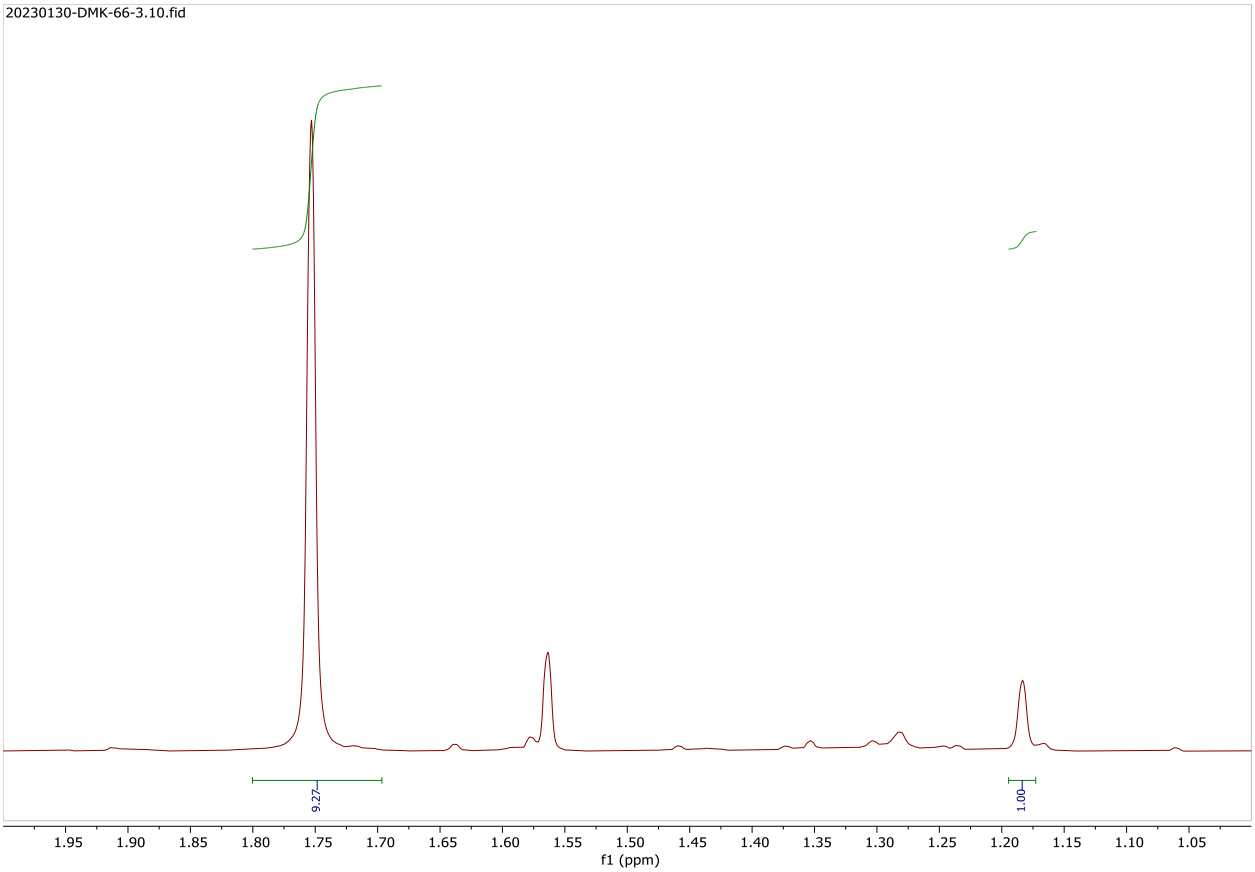
Rh_2(*R*-DOSP)$_4$ cyclopropanation



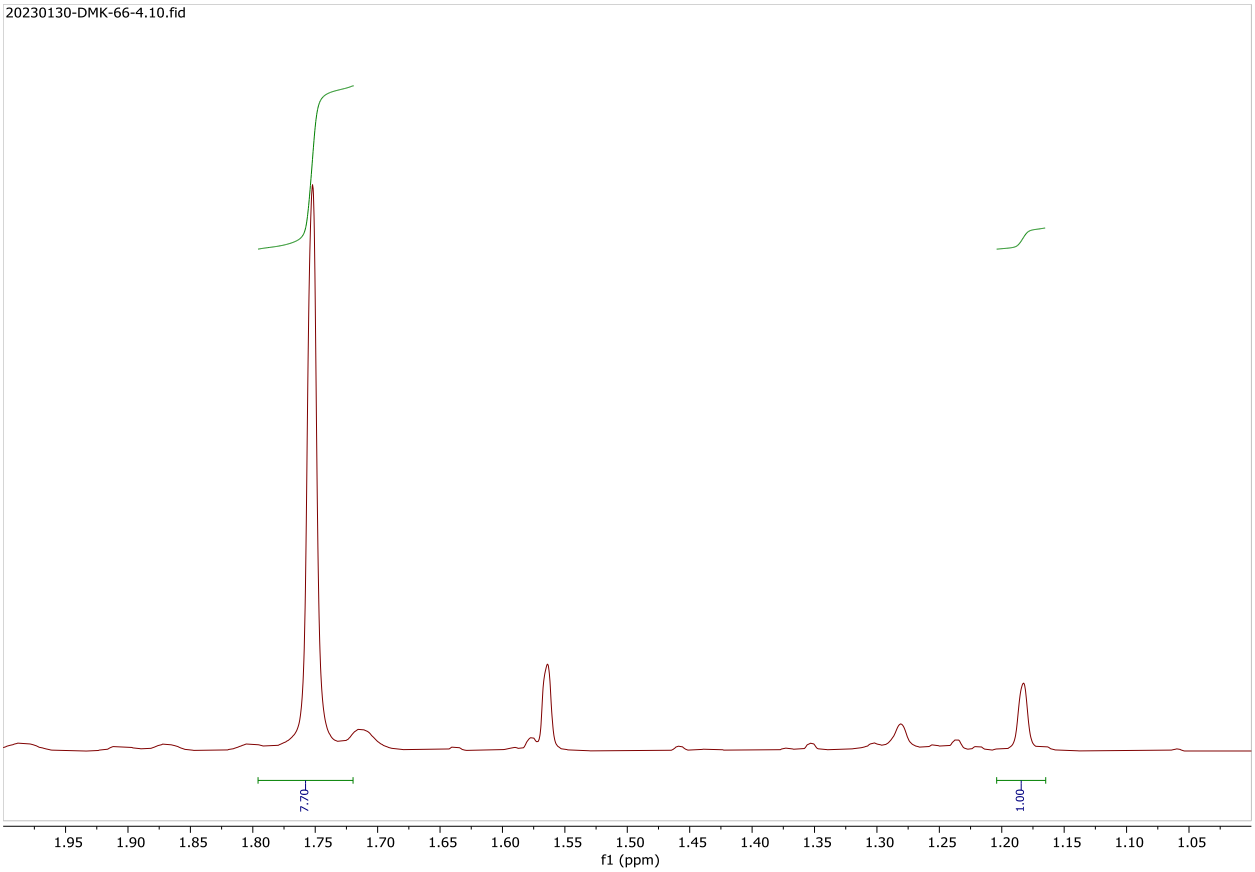
Rh_2(*R*-PTAD)$_4$ cyclopropanation



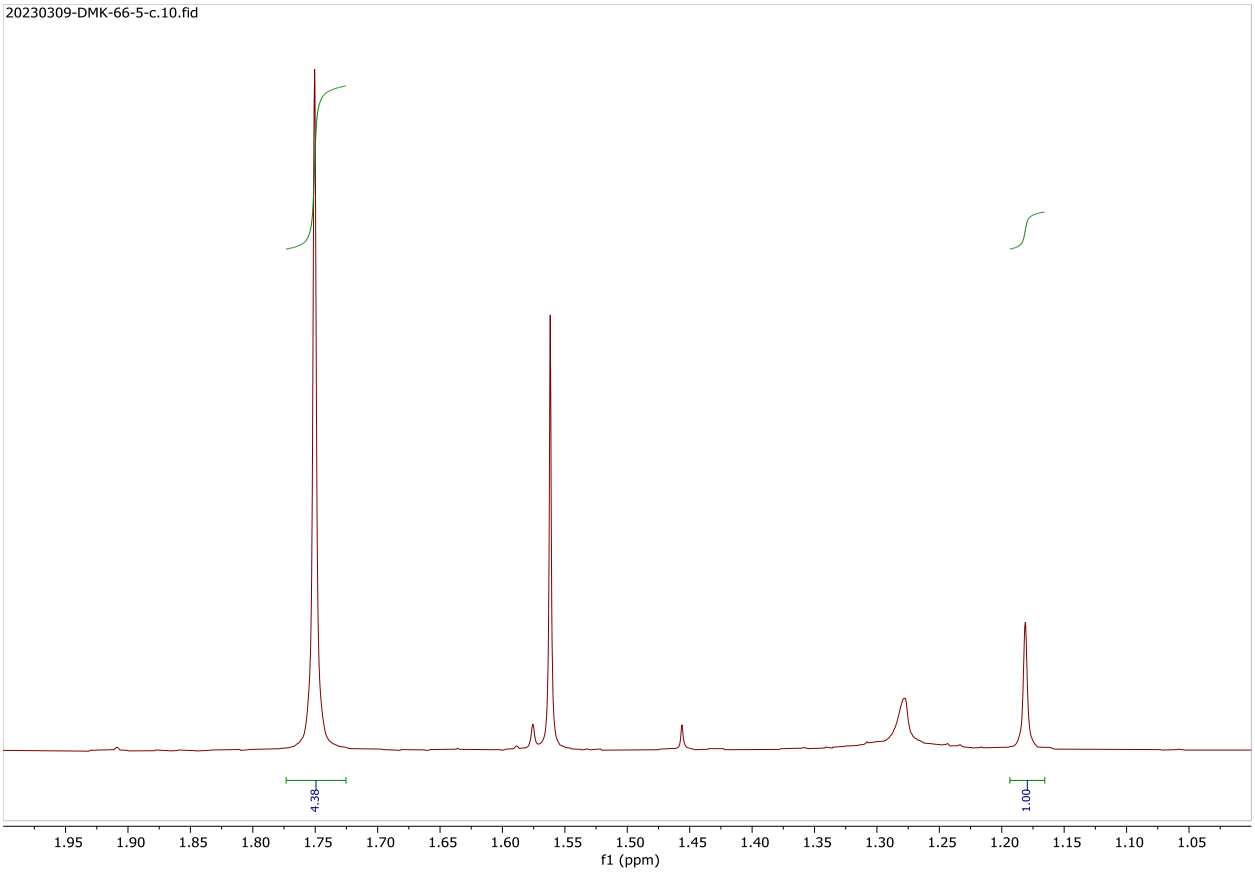
Rh_2(*S*-p-Br-TPCP)$_4$ cyclopropanation



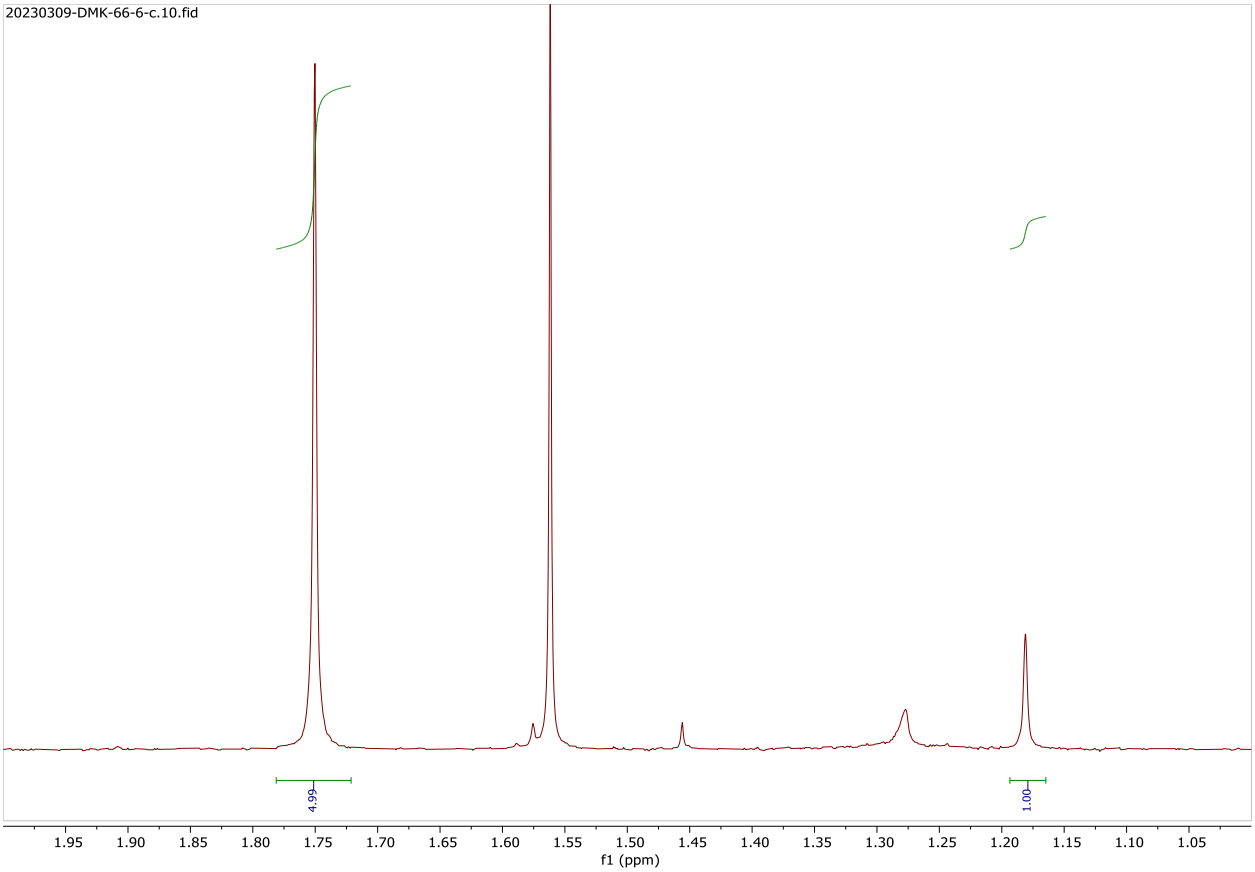
Rh_2(*S*-TCPTAD)$_4$ cyclopropanation



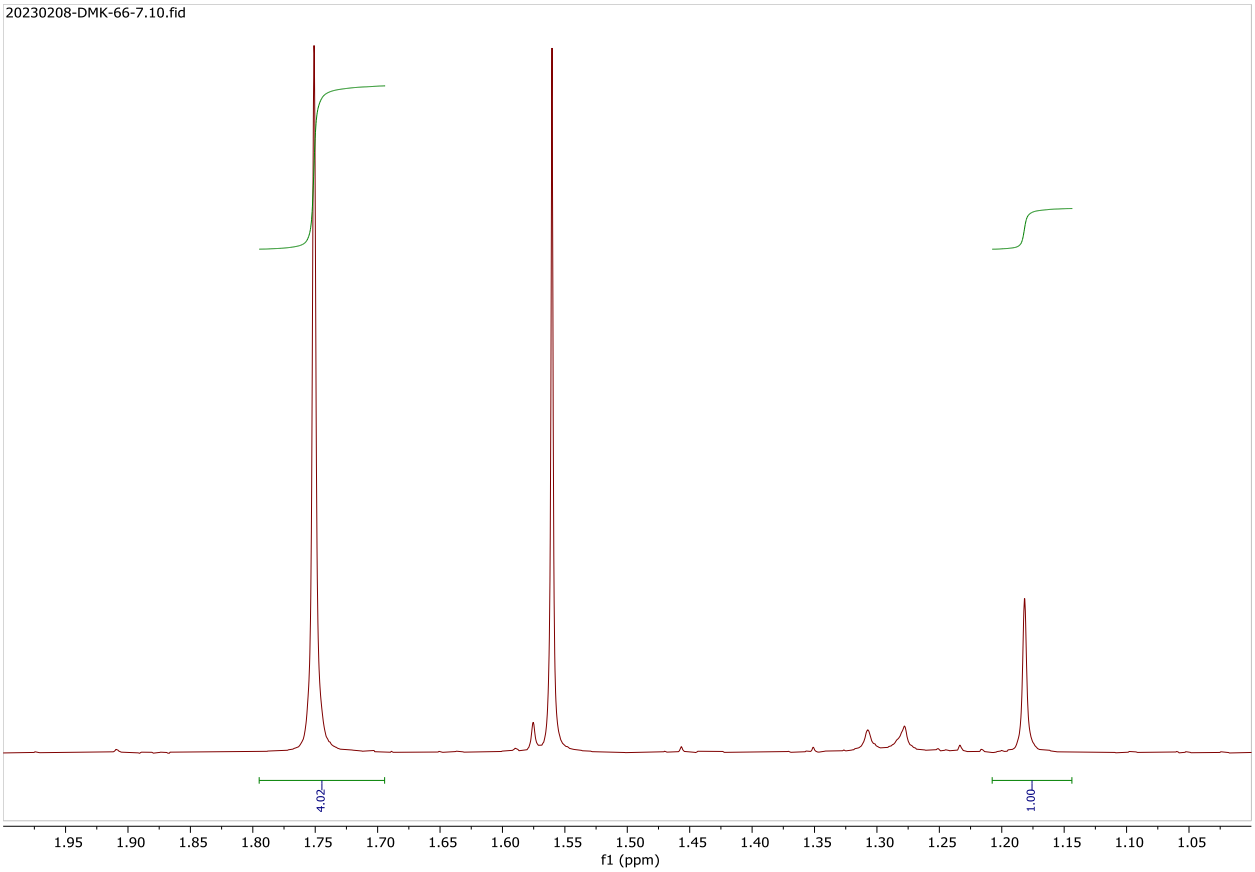
Rh_2(*S*-TPPTTL)$_4$ cyclopropanation



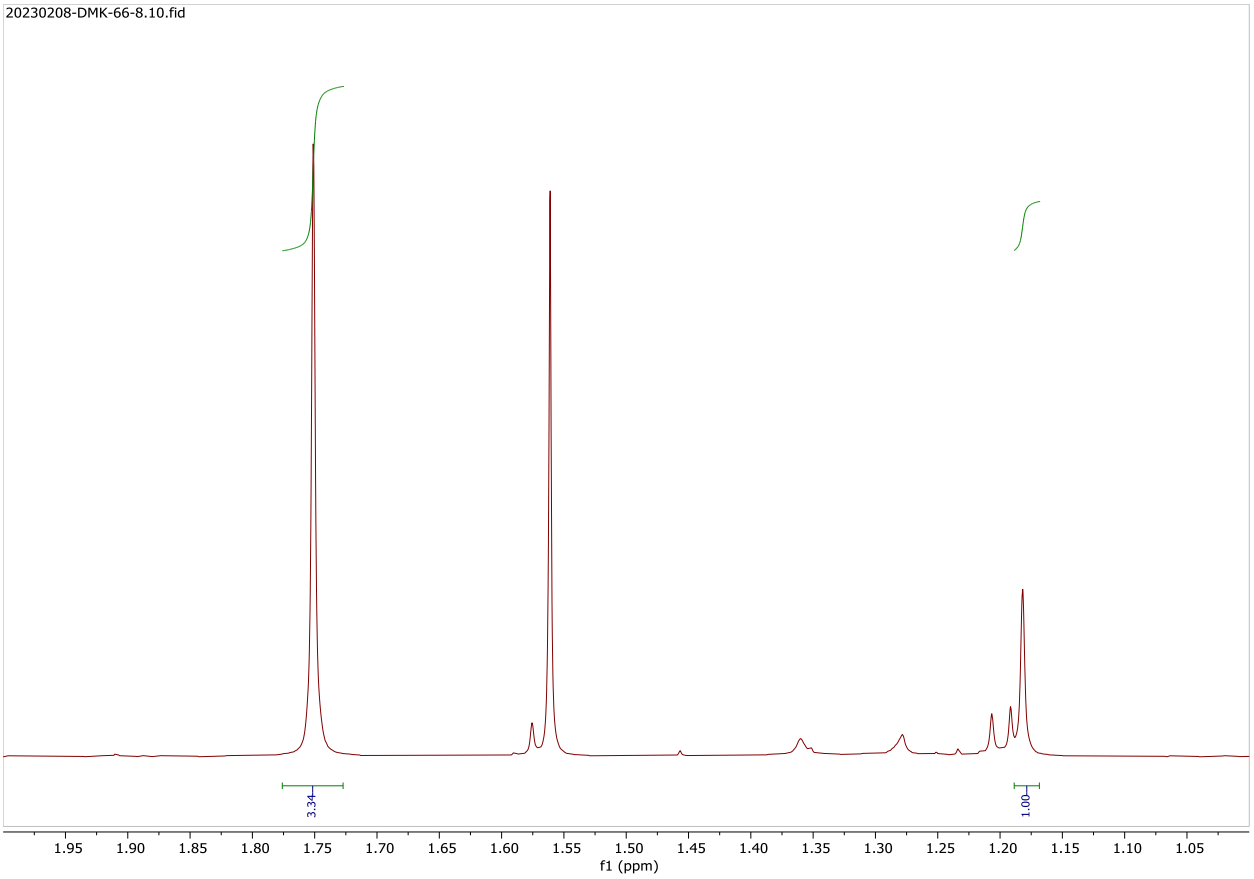
Rh_2(*S*-T-*p*-Br-TPPTTL)$_4$ cyclopropanation



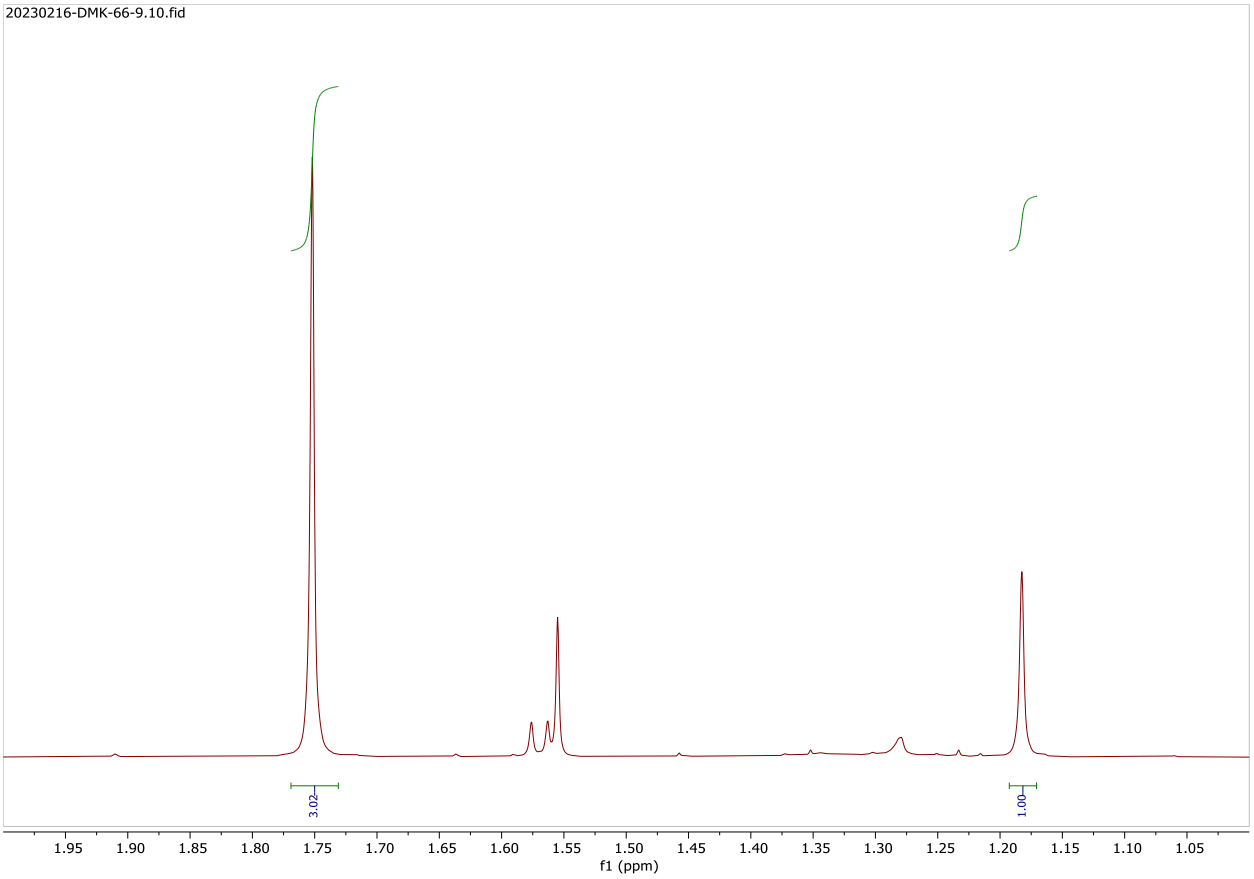
Rh_2(*S*-NTTL)$_4$ cyclopropanation



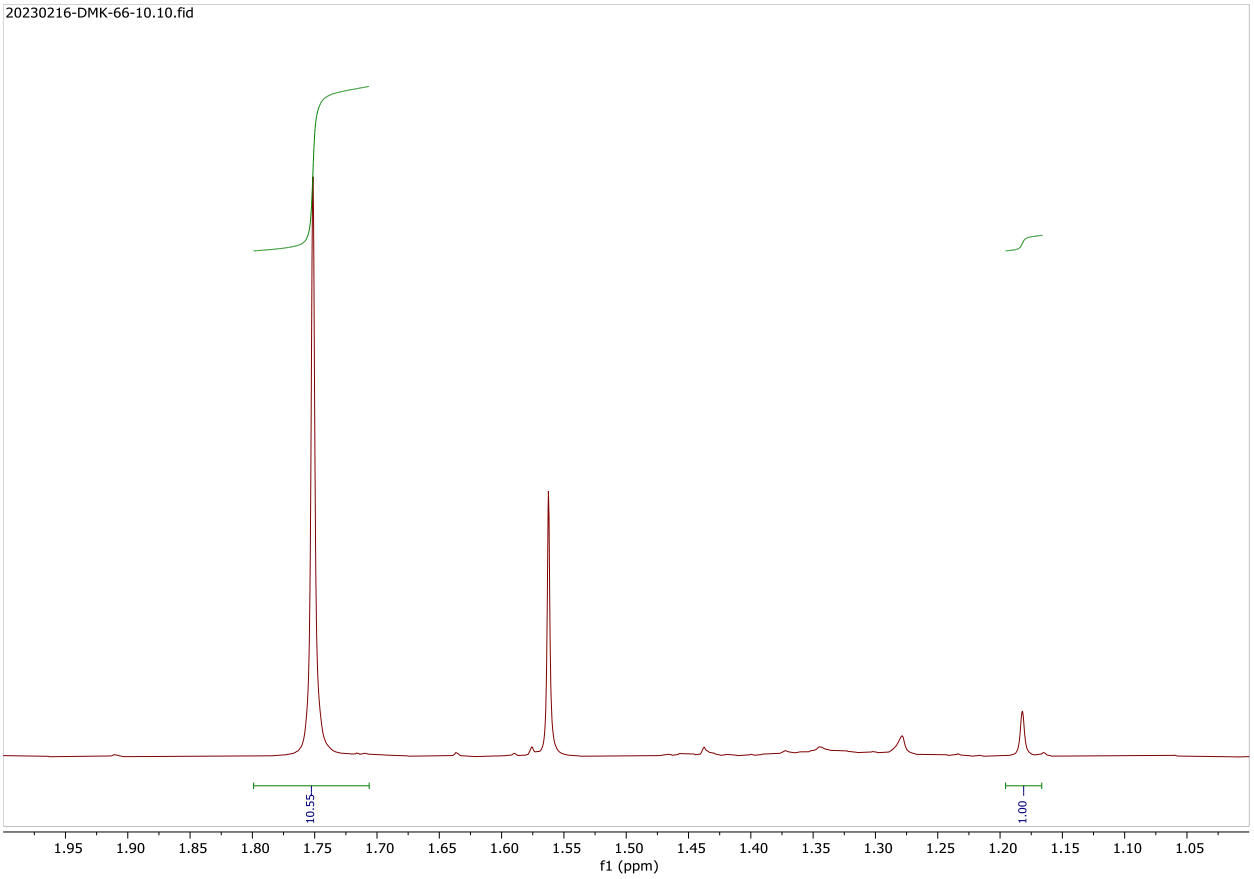
Rh_2(*S*-di-Ph-NTTL)$_4$ cyclopropanation



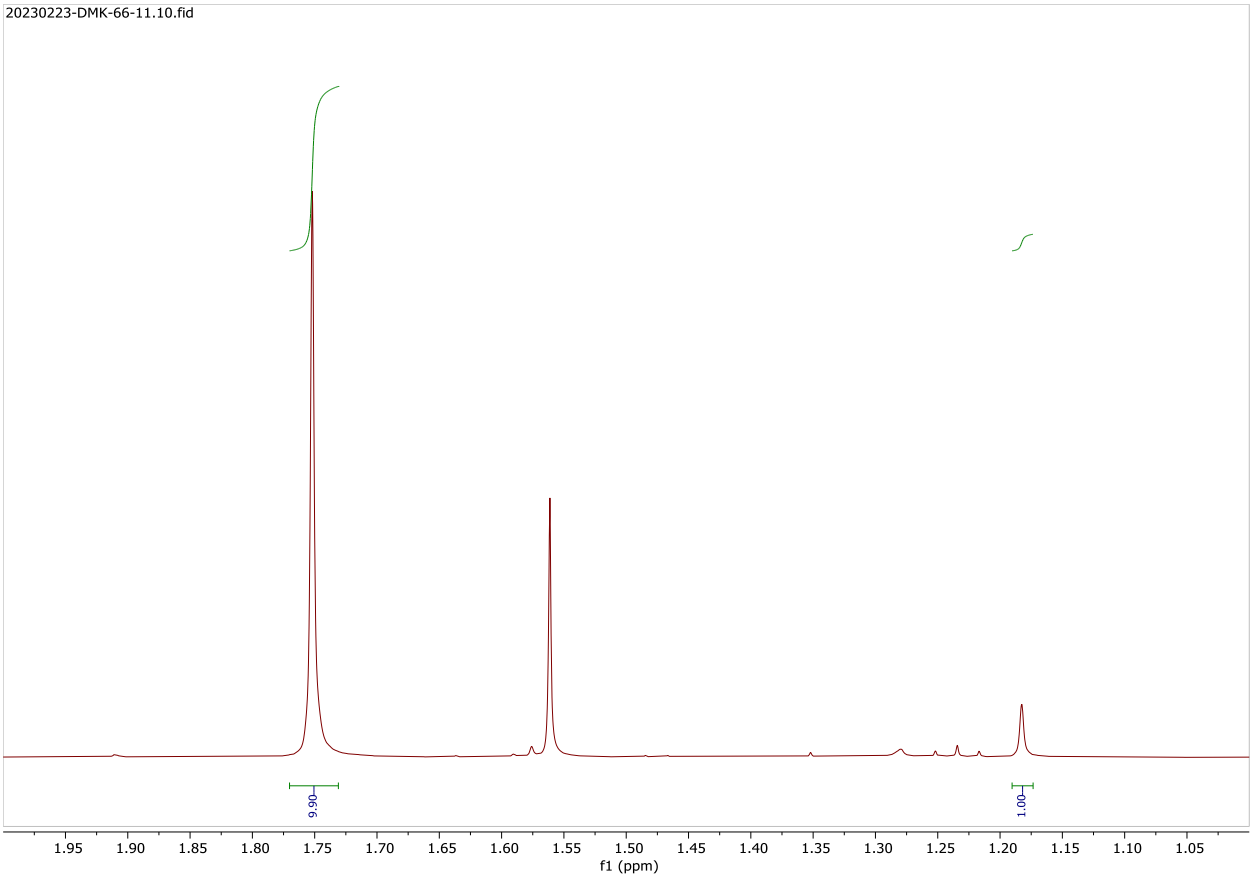
Rh_2(*R*-2-Cl-5-Br-TPCP)$_4$ cyclopropanation



Rh_2(*S*-*p*-Ph-TPCP)$_4$ cyclopropanation

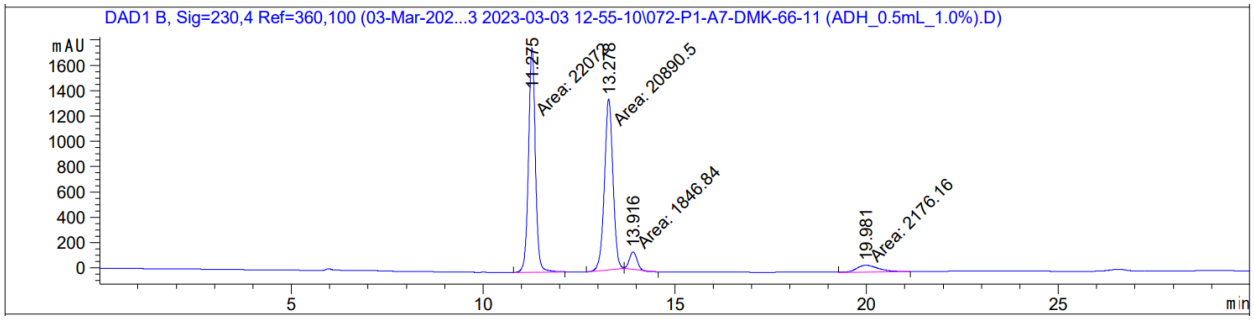


$Rh_2(OAc)_4$ cyclopropanation



4.d) HPLC Traces:

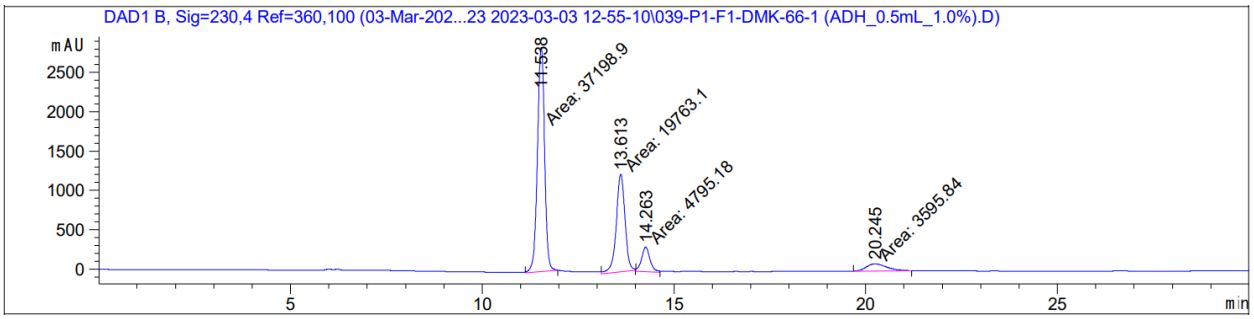
$Rh_2(OAc)_4$ (racemic) cyclopropanation product



Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.275	0.2077	22072.0	1770.8	46.98

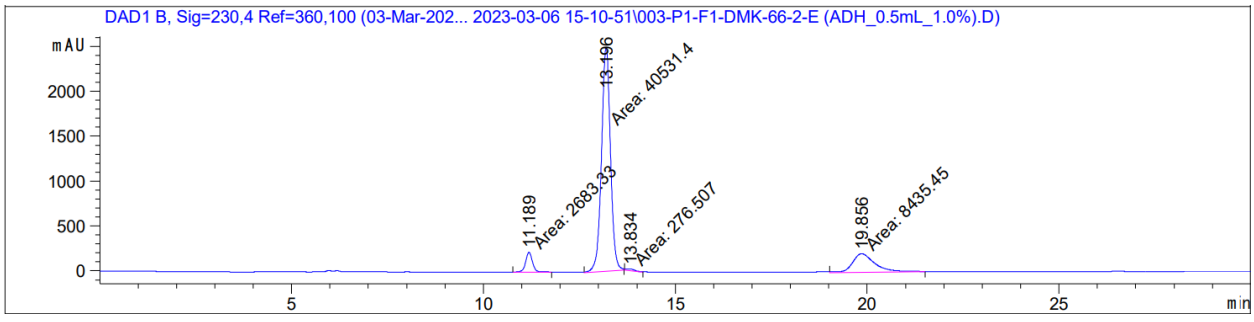
2	13.278	0.2584	20890.5	1347.4	44.46
3	13.916	0.2254	1846.8	136.6	3.93
4	19.981	0.6617	2176.2	54.8	4.63

Rh_2(*R*-DOSP)$_4$ cyclopropanation product



Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.538	0.2172	37198.9	2854.4	56.92
2	13.613	0.2651	19763.1	1242.4	30.24
3	14.263	0.2563	4795.2	311.8	7.34
4	20.245	0.6379	3595.8	94.0	5.50

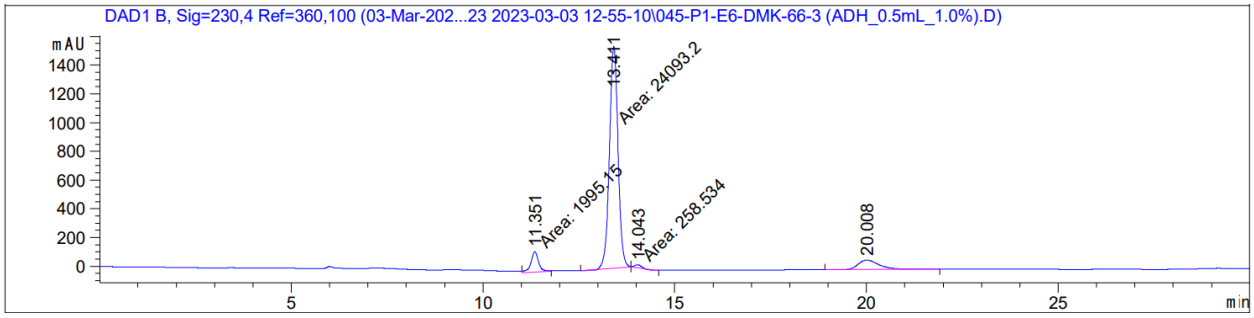
Rh_2(*R*-PTAD)$_4$ cyclopropanation product



Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.189	0.2037	2683.3	219.5	5.17
2	13.196	0.2711	40531.4	2492.1	78.06
3	13.834	0.2414	276.5	19.1	0.53

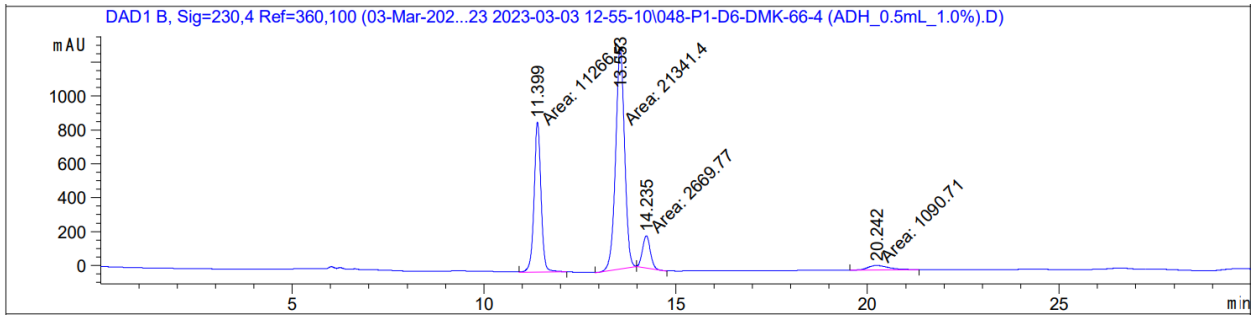
4	19.856	0.6831	8453.5	205.8	16.24

Rh_2(*S*-p-Br-TPCP)$_4$ cyclopropanation product



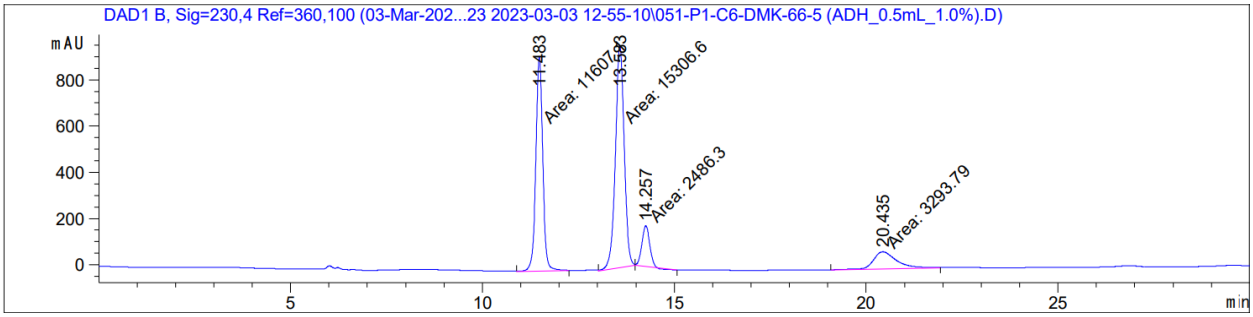
Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.351	0.2324	1995.2	143.1	6.90
2	13.411	0.2599	24093.2	1545.1	83.28
3	14.043	0.1948	258.5	22.1	0.89
4	20.008	0.5841	2584.3	66.7	8.93

Rh_2(*S*-TCPTAD)$_4$ cyclopropanation product



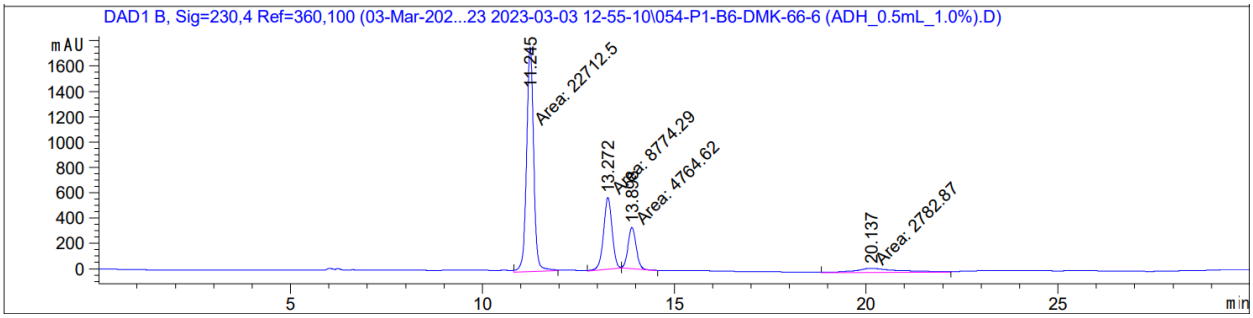
Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.399	0.2116	11266.4	887.4	30.98
2	13.553	0.2716	21341.4	1309.5	58.68
3	14.235	0.2343	2669.8	189.9	7.34
4	20.242	0.6709	1090.7	27.1	3.00

Rh_2(*S*-TPPTTL)$_4$ cyclopropanation product



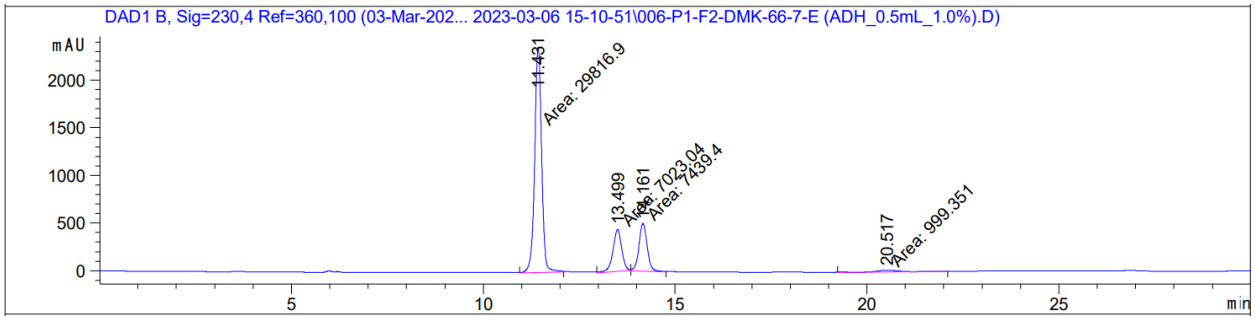
Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.483	0.2089	11607.1	926.2	35.50
2	13.583	0.2657	15306.6	960.0	46.82
3	14.257	0.2360	2486.3	175.6	7.60
4	20.435	0.7323	3293.8	75.0	10.07

Rh_2(*S*-T-p-Br-TPPTTL)$_4$ cyclopropanation product



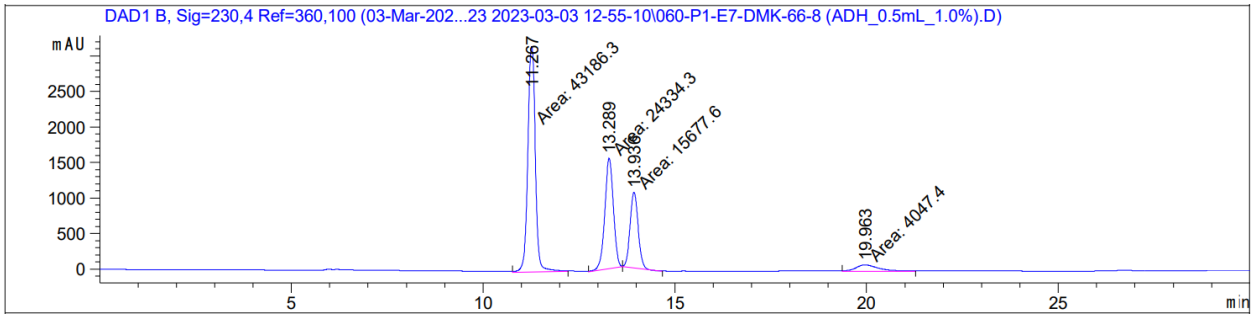
Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.245	0.2137	22712.5	1771.7	58.18
2	13.272	0.2586	8774.3	565.5	22.48
3	13.898	0.2444	4764.6	325.0	12.21
4	20.137	1.3905	2782.9	33.4	7.12

Rh_2(*S*-NTTL)$_4$ cyclopropanation product



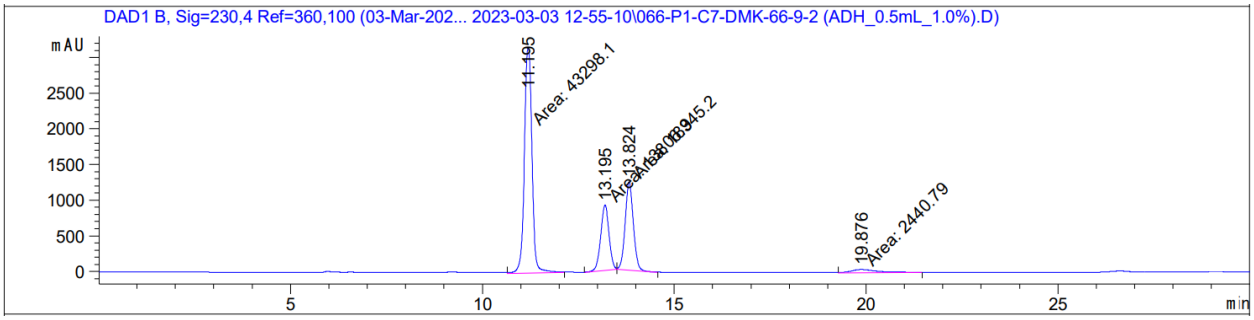
Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.431	0.2102	29816.9	2363.8	65.85
2	13.499	0.2665	7023.0	439.3	15.51
3	14.161	0.2490	7439.4	498.0	16.43
4	20.517	0.8462	999.4	19.7	2.21

Rh_2(*S*-di-Ph-NTTL)$_4$ cyclopropanation product



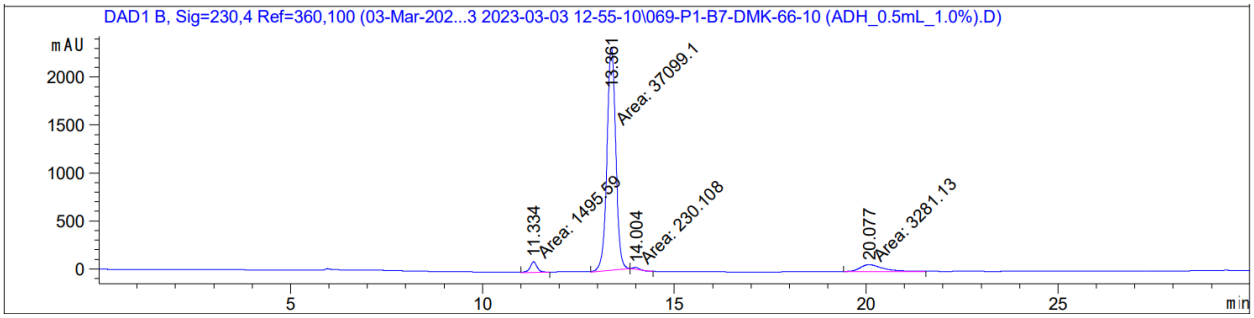
Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.267	0.2267	43186.3	3174.3	49.50
2	13.289	0.2606	24334.3	1556.2	27.89
3	13.936	0.2446	15677.6	1068.2	17.97
4	19.963	0.7323	4047.4	92.1	4.64

Rh_2(*R*-2-Cl-5-Br-TPCP)$_4$ cyclopropanation product



Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.195	0.2281	43298.1	3163.0	55.59
2	13.195	0.2518	13806.9	914.0	17.73
3	13.824	0.2472	18345.2	1236.6	23.55
4	19.876	0.8634	2440.8	47.1	3.13

Rh_2(*S*-p-Ph-TPCP)$_4$ cyclopropanation product



Peak #	RetTime (min)	Width (min)	Area (mAU*s)	Height (mAU)	Area %
1	11.334	0.2239	1495.6	111.4	3.55
2	13.361	0.2658	37099.1	2326.0	88.11
3	14.004	0.1886	230.1	20.3	0.55
4	20.077	0.7457	3281.1	73.3	7.79

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