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Kuo Zhang April 1, 2023

New Advances in Asymmetric Cyclopropanation and Drug Discoveries Using Dirhodium(II) Tetracarboxylates

by

Kuo Zhang

Dr. Huw M. L. Davies

Adviser

Chemistry

Dr. Huw M. L. Davies

Adviser

Dr. Frank McDonald

Committee Member

Dr. Brian Dyer

Committee Member

2023

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Kuo Zhang

Dr. Huw M. L. Davies

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Abstract
New Advances in Asymmetric Cyclopropanation and Drug Discoveries Using Dirhodium(II) Tetracarboxylates

By Kuo Zhang

Dirhodium(II) tetracarboxylate paddle-wheel complexes are robust catalysts that can achieve highly enantioselective intermolecular cyclopropanations for the reactions of donor-acceptor carbenes. The work performed by the Davies Group demonstrated that in the presence of these Rh(II) complexes, highly enantioselective, highly diastereoselective, and high-yielding reactions using a donor-acceptor carbene precursor and an electron-rich alkene could be achieved[5]. However, the new catalysts that were developed in the lab lack a complete cyclopropanation dataset, and it is not exactly clear how the catalysts would behave for a wide range of donor-acceptor carbenes. The first part of the thesis explores a series of screening reactions involving various dirhodium (II) catalysts, aryldiazoacetate (carbene precursor), and electron-rich alkene (trap). Also, the previous kinetic studies heavily focused on substituted phenyl group as the donor for aryldiazoacetate (carbene derivative). It was hypothesized that using a more electron-donating group as the donor would make the reaction faster while maintaining the robustness of the reaction (high e.e, d.r. and yield). The latter part of the thesis, therefore, expands to the kinetic studies of aryldiazoacetates with methoxy naphthalene as the donor group. The new substrates could potentially boost turnover numbers due to the methoxy-naphthalene motif, a more electron-rich and extended π-system, aiming to achieve and exceed the turnover numbers for this type of reaction using the new substrates. The product structure has high similarity to naproxen, implicating pharmaceutical relevance.

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Table of Contents

1.) Introduction

1.1) Carbenes/Carbenoids Chemistry & Davies Group Catalyst Development

Carbenes are reactive molecules in which a carbon atom has two bonds with two substituents respectively and carries a lone pair, leading to electron-deficient neutral species. Due to the lack of a full octet of electrons in their outer shell, carbene compounds react on stable chemical bonds that are usually unreactive[1]. An example of this is cyclopropanation. The substrate, usually an electron rich alkene, tends to donate electron density to the electron deficient carbon on carbene, while the substrate interacts with the higher energy lone pair of the carbene. By having this interaction, a cyclopropane is formed. The ring strain is associated with cyclopropanes, and their formation requires high energy molecules. Another example is C-H insertion, in which the carbene is inserted in between the C-H signma bond. Carbene is reactive enough to overcome the activation barrier for cyclopropanation and C-H insertion. Because of its hyperreactivity, free carbenes usually react unselectively and without an external chiral influence would result in racemic products.[1]

Diazo compounds, shown in the catalytic cycle in Figure 1.1, could act as precursors to carbenes and they can be induced to lose nitrogen to form metal-bound carbenes when they react with dirhodium (II) catalysts.[2] The stability of this complex is governed by the nature of the R_1 and R_2 groups on the carbene. The most used diazo compounds by the Davies group are "donor-acceptors," in which R_1 is electron donating, usually a phenyl ring, and R_2 is electron withdrawing, usually an ester. This unique combination makes the carbene more electron-deficient and reactive yet keeps its stability. A "donor-donor" compound donates electron density to the electrophilic carbene, stabilizing the carbene and making it less reactive.[3] An "acceptor-acceptor" is the

opposite, which makes the carbene more reactive. The "donor-acceptor" carbene has the ideal reactivity that allows Davies group's chemistry to happen.

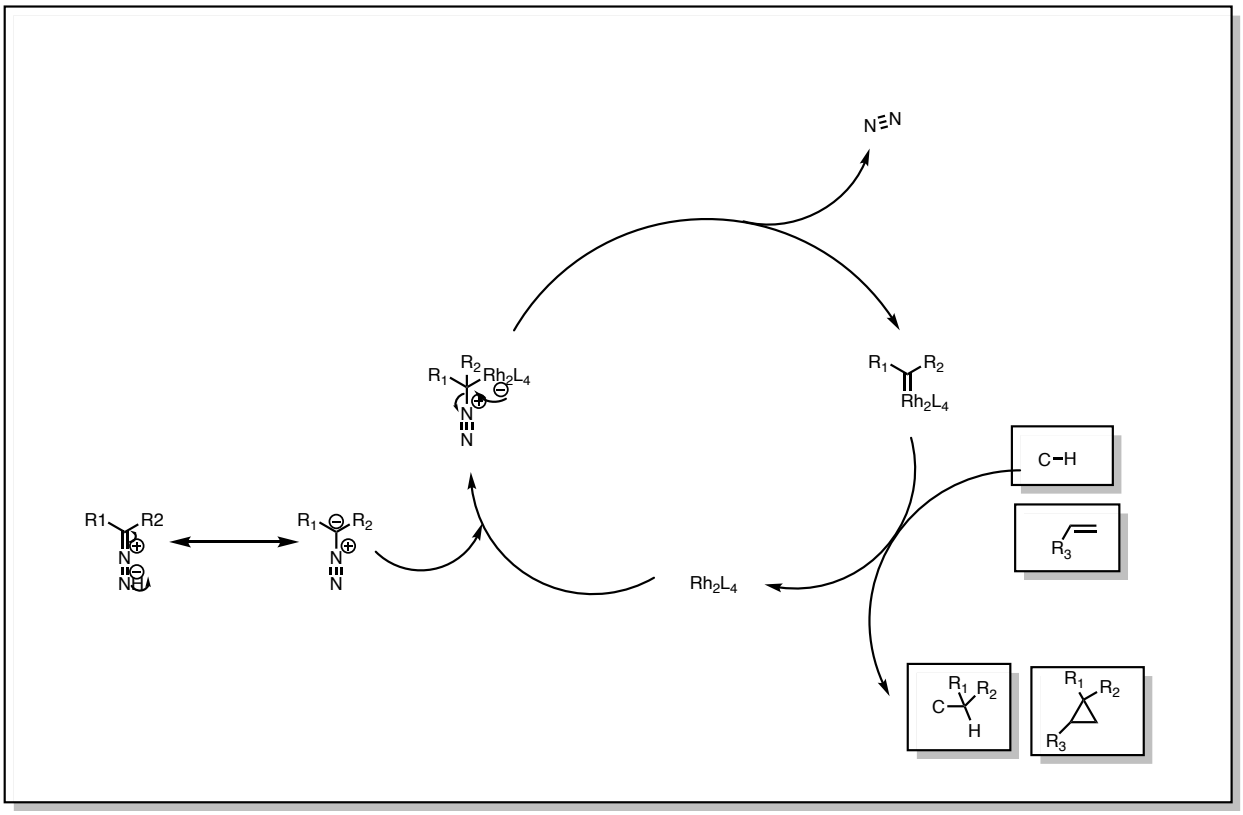


Figure 1.1: Typical catalytic cycle for Rh(II)-mediated C-H insertion and cyclopropanation of diazonium compounds

If a cyclopropanation reaction is to be controlled selectively, meaning favoring a specific stereochemistry over others, the generation of a stable carbenoid complex is crucial. If the complex is unstable, the reaction proceeds uncontrollably. Chiral dirhodium catalysts facilitates cyclopropanation in a controlled manner, in which the chirality of the catalyst forces the substrate to approach the complex in a specific orientation due to the steric environment imposed by the chiral ligands.[4] Thus the product would favor one stereochemistry over other possible stereoisomers.

The Davies group has developed a series of chiral dirhodium catalysts to control the reactivity of the carbenoid complex by having different steric reactive pockets to control the selectivity of the reactive species. These complexes typically adopt a paddlewheel/bowl shape that adopt higher symmetry such as D_2, C_4, and C_2. The catalysts developed by the Davies group aim to perform site-selective, diastereoselective and enantioselective C-H bond insertion and cyclopropanation, which would not be possible had the reaction not controlled by donor-acceptor carbene and bowl-shaped dirhodium catalysts[4].

A selection of representative catalysts is shown in Figure 1.2. These catalysts have different reactivity and selectivity profiles. Each catalyst has its own advantages; some are good for C-H insertion while others are good for cyclopropanation[4]. The key of succeeding a new reaction is finding the optimal catalyst for the desired transformation. The Davies group's philosophy is to create a library of catalysts and use them as a toolbox to the ideal catalyst that can tackle a particular site of any given molecule by using various chiral catalysts that impose different steric pockets.

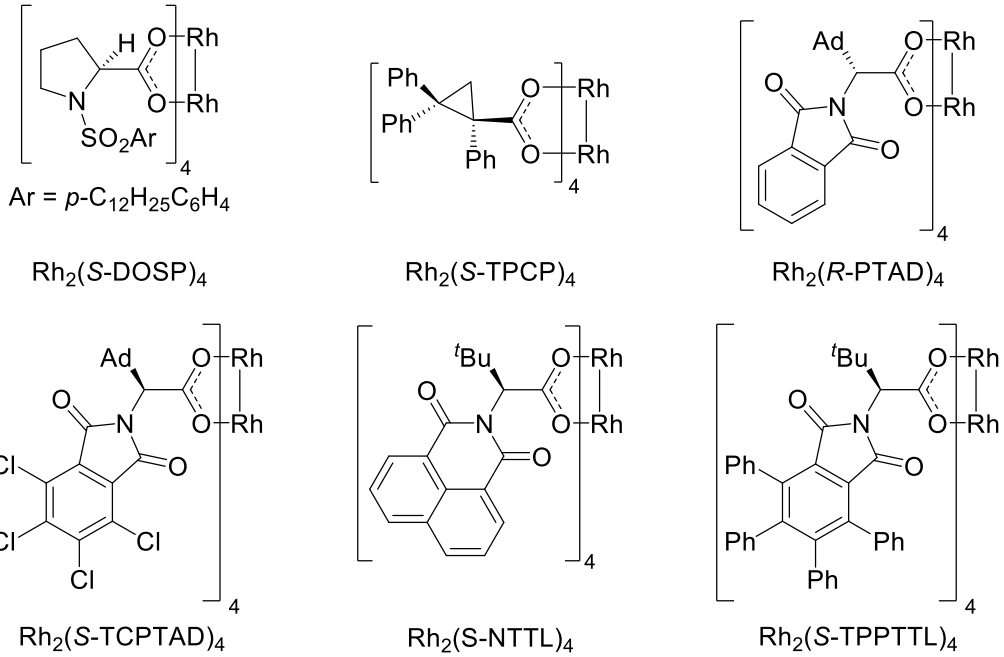


Figure 1.2: Representative catalysts developed by the Davies group[4]. Reprinted (adapted) with permission from {Davies, H. M. L. Finding Opportunities from Surprises and

1.2) Asymmetric Cyclopropanation using Bulky Dirhodium(II) Tetracarboxylate catalysts and its Kinetic Aspects

As mentioned, dirhodium(II) tetracarboxylate paddle-wheel complexes are robust catalysts that can achieve highly enantioselective intermolecular cyclopropanations for the reactions of donor-acceptor carbene. The work performed by the Davies Group demonstrated that in the presence of these Rh(II) complexes, highly enantioselective, highly diastereoselective, and high-yielding reactions using a donor-acceptor carbene precursor and an electron-rich alkene could be achieved. The dirhodium complex activates the diazo compound to enable the escape of nitrogen and generation of metal-carbene complex. When an electron-rich alkene is present, the reaction usually resorts to cyclopropanation formation. Figure 3 illustrates the mechanism for cyclopropanation formation when the diazo reacts with the dirhodium complex[5].

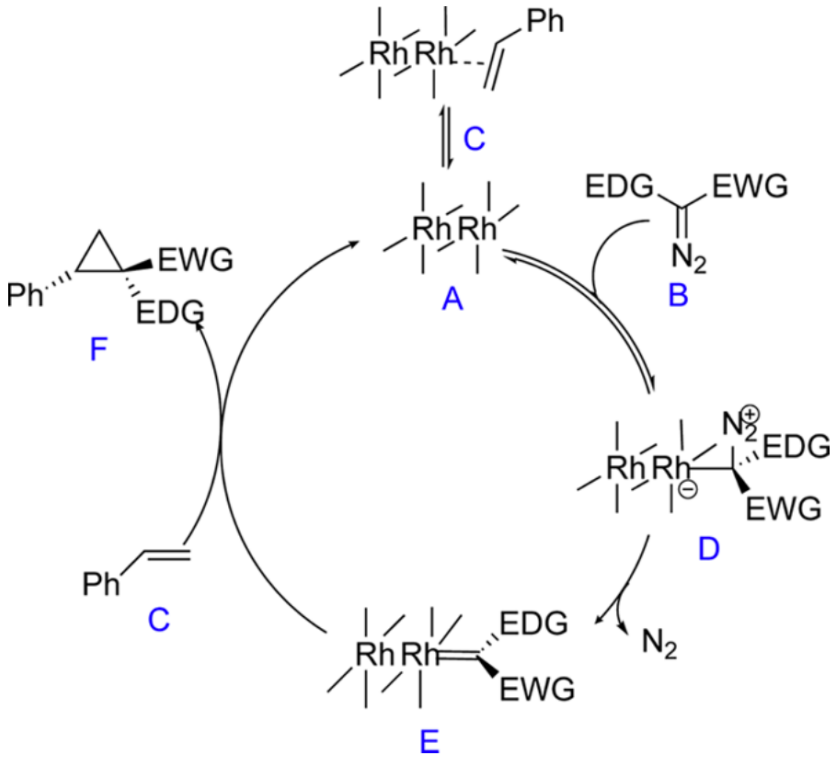


Figure 1.3: Catalytic Cycle for Cyclopropanation of Styrene[5]. Reprinted (adapted) with permission from {Wei, B.; Sharland, J. C.; Lin, P.; Wilkerson-Hill, S. M.; Fullilove, F. A.; McKinnon, S.; Blackmond, D. G.; Davies, H. M. L. In Situ Kinetic Studies of Rh(II)-Catalyzed Asymmetric Cyclopropanation with Low Catalyst Loadings. *ACS Catal.* 2020, *10* (2), 1161–1170. }. Copyright {2019} American Chemical Society.

While the reaction exhibits cyclopropanation in a selective manner, Davies group has found out that with dirhodium tetracarboxylate complexes, the donor-acceptor carbene could react with styrene with million turnover numbers or above. The robustness of these catalysts allows the reaction to proceed at an incredibly fast rate. At the same time, the catalyst loading could be as low as 0.001 mol% and yet still sufficient to drive the reaction to completion while maintaining high enantiomeric excess. This feature of the reaction gives interest to explore about the kinetics

of asymmetric cyclopropanation. The second part of this thesis, therefore, focuses on ways of improving the already fast kinetics of cyclopropanation using dirhodium tetracarboxylates and donor-acceptor carbene. It was hypothesized that using a more extended pi-system, such as methoxynaphthalene, as the donor group could potentially improve the kinetics with the same catalyst loading as low as 0.001 mol%. Figure 1.4 illustrates a typical cyclopropanation reaction[5].

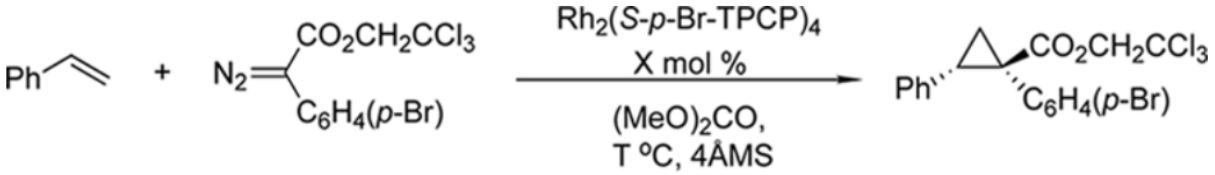


Figure 1.4: A Typical Cyclopropanation of Styrene using Dirhodium(II) Tetracarboxylates and Donor-acceptor Carbene[5]. Reprinted (adapted) with permission from {Wei, B.; Sharland, J. C.; Lin, P.; Wilkerson-Hill, S. M.; Fullilove, F. A.; McKinnon, S.; Blackmond, D. G.; Davies, H. M. L. In Situ Kinetic Studies of Rh(II)-Catalyzed Asymmetric Cyclopropanation with Low Catalyst Loadings. *ACS Catal.* 2020, *10* (2), 1161–1170. }. Copyright {2019} American Chemical Society.

The cyclopropane functionality is highly relevant in pharmaceutical industry, so a way of using dirhodium(II) tetracarboxylates to generate cyclopropane with high yield and exceptional enantiomeric excess has been an interesting area to explore. One example is the synthesis of Beclabuvir, an anti-viral drug for treating Hepatitis C (HCV) infection. Originally, the industrial process was to generate the cyclopropane with Rh_2(S-DOSP)$_4$ under 0.2 mol% catalyst loading, which achieved 94% yield and 83% enantiomeric excess. With optimized process done by Davies group, the reaction was able to achieve 96% ee with 0.001 mol% catalyst loading of Rh_2(S-*p*-Ph-TPCP)$_4$. The feature of high ee under incredibly low catalyst loading gave this reaction advantage for the drug synthesis.[5]

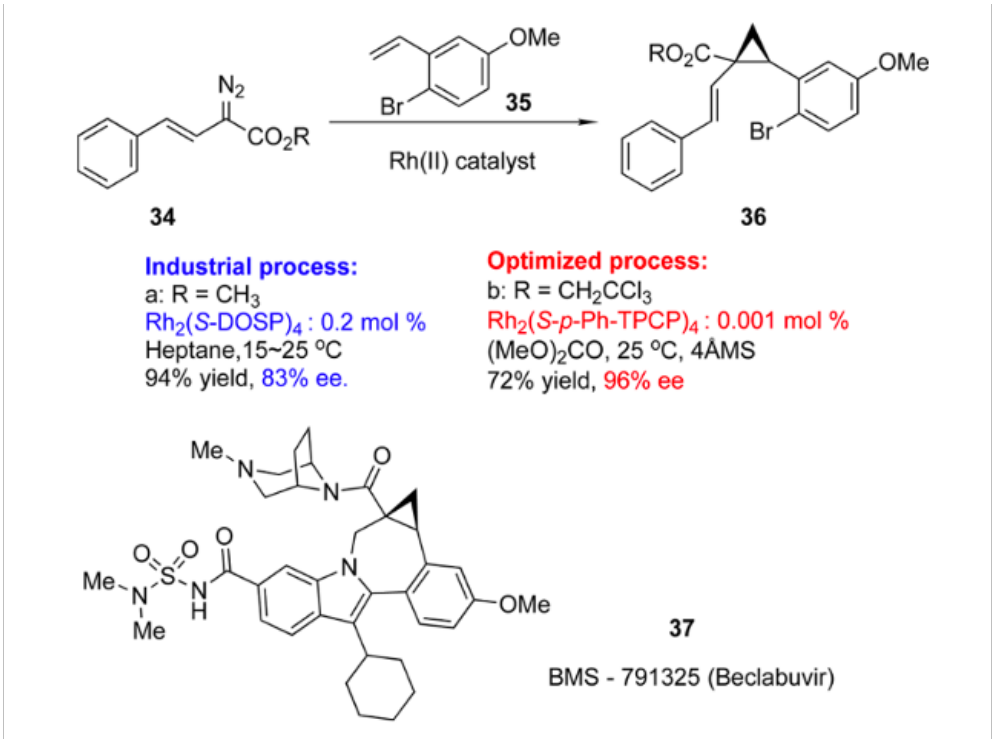


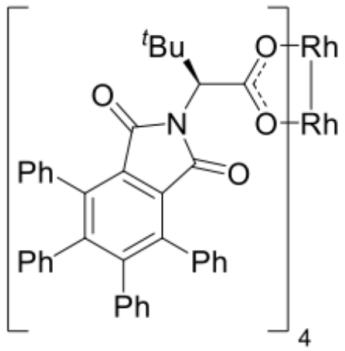
Figure 1.5 Asymmetric Cyclopropanation in a Key Step in the Synthesis of Beclabuvir[5]. Reprinted (adapted) with permission from {Wei, B.; Sharland, J. C.; Lin, P.; Wilkerson-Hill, S. M.; Fullilove, F. A.; McKinnon, S.; Blackmond, D. G.; Davies, H. M. L. In Situ Kinetic Studies of Rh(II)-Catalyzed Asymmetric Cyclopropanation with Low Catalyst Loadings. *ACS Catal.* 2020, *10* (2), 1161–1170. }. Copyright {2019} American Chemical Society.

2.) First Advance: Asymmetric Cyclopropanation using $Rh_2(TPPTTL)_4$ Catalysts

A key feature of our catalyst design is to surround the dirhodium core with four identical chiral carboxylate ligands that self-assemble to create complexes that adopt various symmetries such as D_2, C_2, and C_4[6]. *$Rh_2(TPPTTL)_4$*, a catalyst that has phthalimido scaffold, has C_4 symmetric bowl-shaped structure. This catalyst was identified as an ideal catalyst for selective C-H functionalization on alkylcyclohexane with exceptional diastereoselectivity and enantioselectivity.

The catalyst is special in that the 16 phenyl groups are tilted to render it a helical chirality, which is considered to be a factor in directing asymmetric C-H functionalization. The group expanded tetraarylphthalimido derived catalysts and studied their enhancement on site-selective and enantioselective C-H functionalization[6]. Yet it is worthwhile to explore about how these incredibly bulky bowl-shaped catalysts would perform for cyclopropanation and whether these reactions exhibit high diastereoselectivity and enantioselectivity as well. Many of the newly designed catalysts in Davies group, such as Rh_2(S-TPPTTL)$_4$ and its derivatives, have shown exceptional ability in directing selective C-H functionalization yet there is a lack of cyclopropanation data for those catalysts.

Three types most commonly used diazo carbene precursors, three types of electron-rich alkene traps, and three types of *Rh_2(TPPTTL)$_4$* derivatives were selected (Figure 2.1) to perform cyclopropanations and the results are shown below from Table 1 to Table 9.



Rh_2(*S*-TPPTTL)$_4$

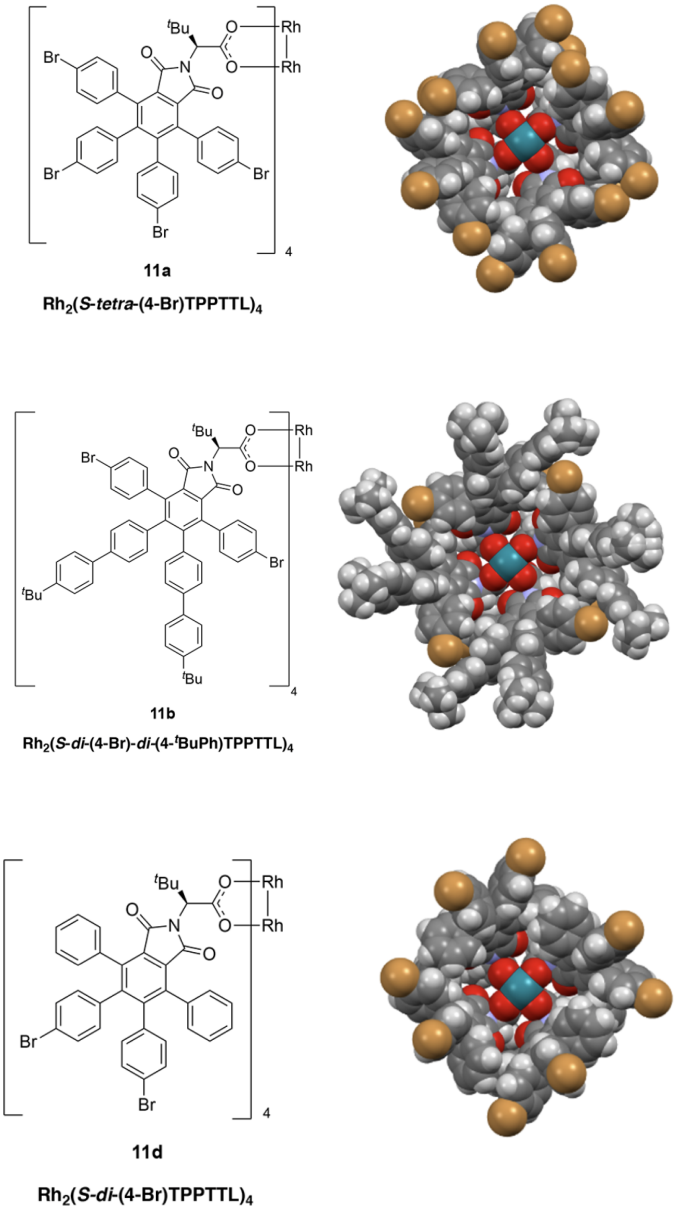
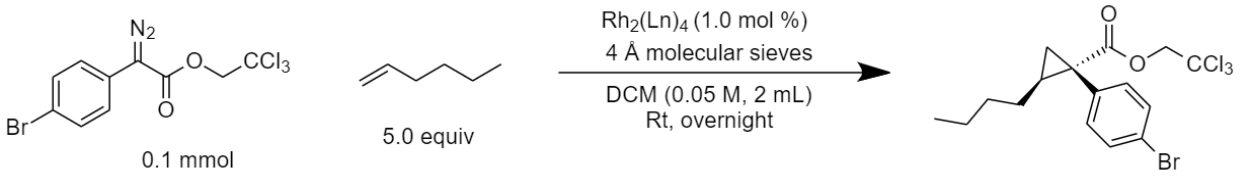


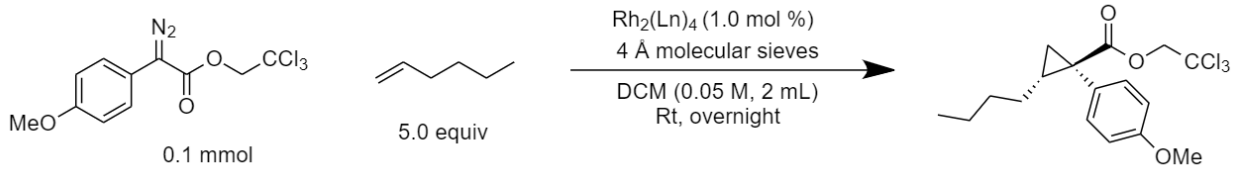
Figure 2.1: Rh_2(S-TPPTTL)$_4$ and the three bowled-shaped bulky derivatives selected. Reprinted (adapted) with permission from {Zachary J. Garlets, Yannick T. Boni, Jack C. Sharland, Randall P. Kirby, Jiantao Fu, John Bacsa, and Huw M. L. Davies. *ACS Catalysis* 2022 *12* (17), 10841-10848}. Copyright {2022} American Chemical Society.

Table 1. Reaction of 1-hexene and p-Br-TCE in the presence of various catalysts



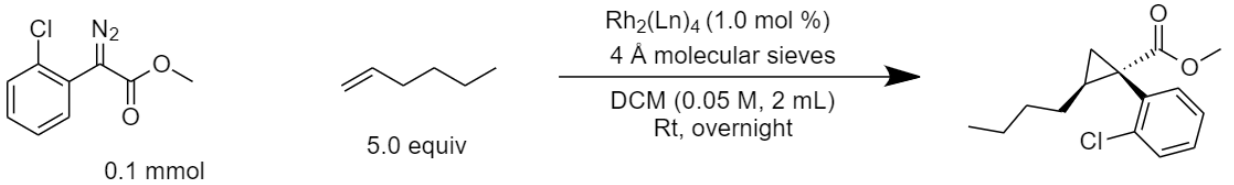
Entry	Catalyst	%yield	%ee
1	Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$	>90	98
2	Rh_2(S-*di*-(4-Br)TPPTTL)$_4$	62	97
3	Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$	49	97

Table 2. Reaction of 1-hexene and p-MeO-TCE in the presence of various catalysts



Entry	Catalyst	%yield	%ee
1	Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$	52	94
2	Rh_2(S-*di*-(4-Br)TPPTTL)$_4$	45	91
3	Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$	43	96

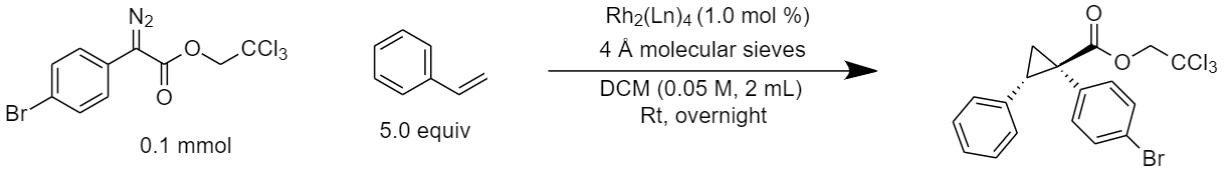
Table 3. Reaction of 1-hexene and o-Cl-MeO in the presence of various catalysts



Entry	Catalyst	%yield	%ee
1	Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$	44	64
2	Rh_2(S-*di*-(4-Br)TPPTTL)$_4$	27	27

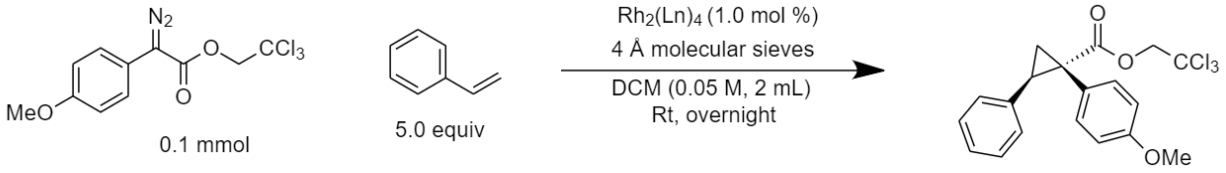
3	Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$	36	61

Table 4. Reaction of styrene and p-Br-TCE in the presence of various catalysts



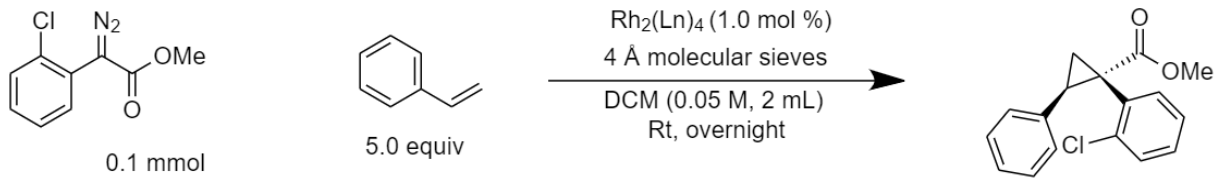
Entry	Catalyst	%yield	%ee
1	Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$	>90%	86
2	Rh_2(S-*di*-(4-Br)TPPTTL)$_4$	>90%	91
3	Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$	74%	87

Table 5. Reaction of styrene and p-MeO-TCE in the presence of various catalysts



Entry	Catalyst	%yield	%ee
1	Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$	58	77
2	Rh_2(S-*di*-(4-Br)TPPTTL)$_4$	54	92
3	Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$	62	80

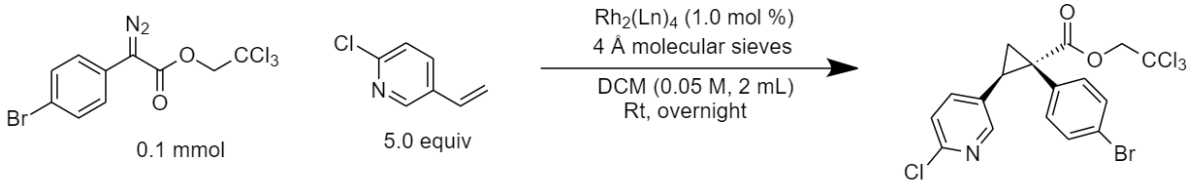
Table 6. Reaction of styrene and o-Cl-MeO in the presence of various catalysts



Entry	Catalyst	%yield	%ee

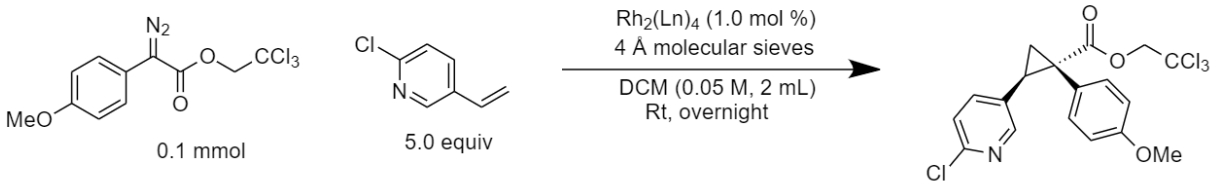
1	Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$	34	23
2	Rh_2(S-*di*-(4-Br)TPPTTL)$_4$	68	40
3	Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$	39	40

Table 7. Reaction of 2-chloro-5-vinylpyridine and p-Br-TCE in the presence of various catalysts



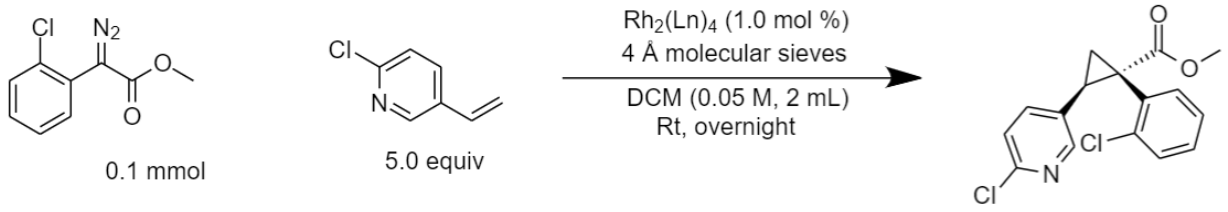
Entry	Catalyst	%yield	%ee
1	Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$	47	91
2	Rh_2(S-*di*-(4-Br)TPPTTL)$_4$	84	33
3	Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$	40	80

Table 8. Reaction of 2-chloro-5-vinylpyridine and p-MeO-TCE in the presence of various catalysts



Entry	Catalyst	%yield	%ee
1	Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$	53	93
2	Rh_2(S-*di*-(4-Br)TPPTTL)$_4$	75	82
3	Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$	15	88

Table 9. Reaction of 2-chloro-5-vinylpyridine and o-Cl-MeO in the presence of various catalysts



Entry	**Catalyst**	**%yield**	**%ee**
1	Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$	46	31
2	Rh_2(S-*di*-(4-Br)TPPTTL)$_4$	74	88
3	Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$	23	64

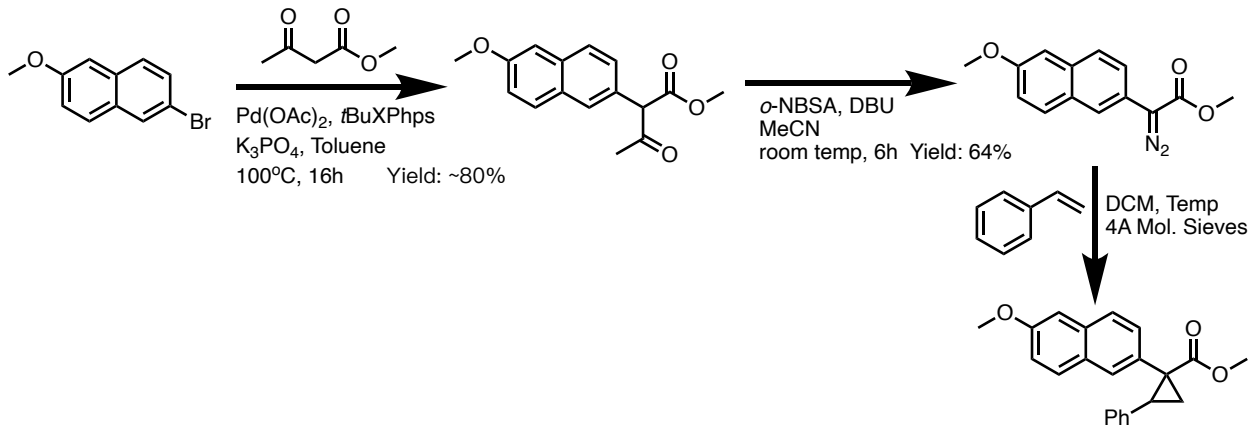
The reactions generally exhibited high enantioselectivity when using p-Br-TCE diazo and p-Methoxy-TCE diazo as substrates with styrene and 1-hexene as traps. Surprisingly, the e.e. drops significantly for reactions involving ortho-Cl diazo.

For the determination of the stereochemistry of the compound, it is crucial to observe the methylene peak of the tricholoro ethyl ester. In the cyclopropanation product, if the trichloro ethyl ester is on the same side with the aromatic group coming from the alkene trap, the anisotropy effect of the aromatic ring effectively de-shields the methylene peak. It would appear at around 5.0 ppm. Otherwise the methylene peak is more shielded by usually 0.5 ppm. Therefore, it is often useful to examine the crude NMR of the product to see if there are two methylene peaks present to determine the stereochemistry of the made product.

3.) Second Advance: Kinetic Studies via Cyclopropanation of methyl 2-diazo-2-(6-methoxynaphthalen-2-yl)acetate

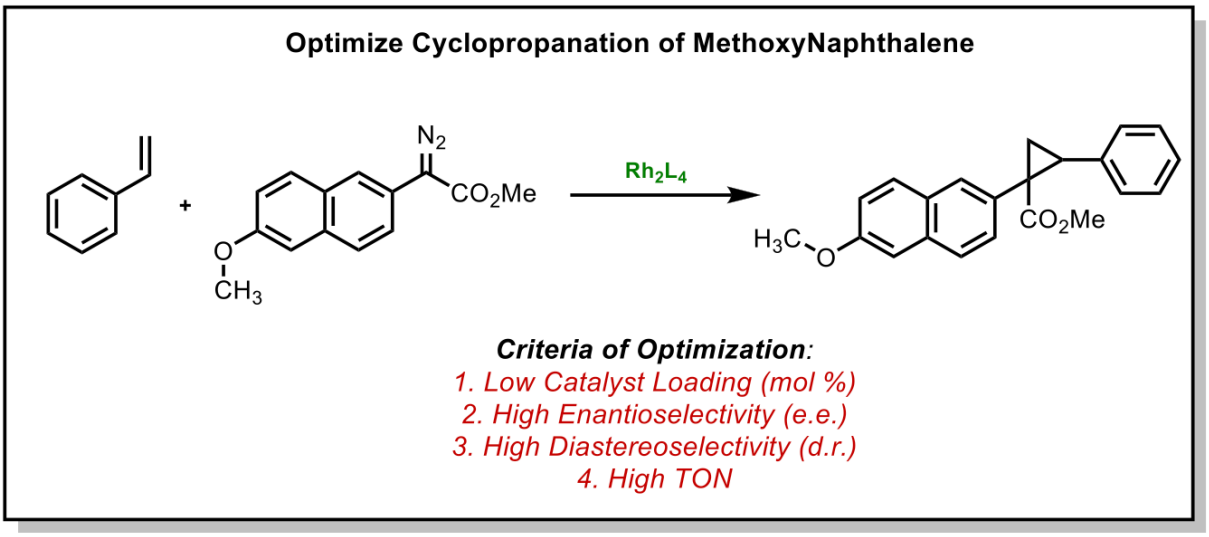
Another topic my thesis explores is to find out if the current turnover rates for cyclopropanation could be improved. It was hypothesized that adding a more extended electron-rich pi-system to the donor group of the donor-acceptor carbene could potentially improve the

stability of carbene, therefore improving the kinetics of cyclopropanation. To add an extended pi-system donor, methoxynaphthalene would be an ideal donor group choice due to the electron-donating nature of methoxy group and two aromatic rings conjugated with one another. Methyl 2-diazo-2-(6-methoxynaphthalen-2-yl)acetate was synthesized as the new substrate for measuring the kinetics of cyclopropanation shown in Scheme 1.



Scheme 1. Synthesis of Methyl 2-diazo-2-(6-methoxynaphthalen-2-yl)acetate and its subsequent cyclopropanation.

Though the fast kinetics of the reaction could be appealing, this feature should not sacrifice other criteria for the reaction, in which the criteria include high yield, high diastereoselectivity, and high enantiomeric excess. Therefore, a series of catalysts was screened for their ability to induce asymmetric cyclopropanation between styrene and the new substrate. It was found that Rh_2(S-*p*-Br-TPCP)$_4$ and Rh_2(S-*p*-Ph-TPCP)$_4$ are the two best catalysts that could give the reaction high yield and e.e..



Entry	$Rh_2(L)_4$	Temp. (°C)	Additive	Trap (eq)	Yield	e.e.	d.r.
1	Rh2(S-DOSP)4	25	4A MS	10	78.4%	75%	>20:1
2	Rh_2(R-PTAD)$_4$	25	4A MS	10	86.0%	-40%	>20:1
3	Rh_2(S-TPPTTL)$_4$	25	4A MS	10	78.5%	72%	>20:1
4	Rh_2(S-p-Br-TPCP)$_4$	25	4A MS	10	82.2%	86%	>20:1
5	Rh_2(R-p-Ph-TPCP)$_4$	25	4A MS	10	84.1%	-84%	>20:1
6	Rh_2(R-TCPTAD)$_4$	25	4A MS	10	86.0%	-13%	>20:1

Figure 2.2 Catalyst Screening Scheme and Results for methyl 2-diazo-2-(6-methoxynaphthalen-2-yl)acetate

Eventually, Rh_2(S-*p*-Br-TPCP)$_4$ was chosen as the best catalyst to perform REACT-IR, a method that detects the IR peak intensities of the reaction mixture as a measure of how fast the reaction proceeds. The diazo peak intensity (at around 2100 cm^{-1}) was measured over time using the new substrate to conduct kinetic studies. The parent p-Br TCE diazo's optimized kinetic experiments in the paper that Davies group published, *In-Situ Kinetic Studies of Asymmetric*

Cyclopropanation using Dirhodium(II) Tetracarboxylates, were repeated as shown in Figure 2.3. The reaction requires a dry, inert atomosphere because even a tiny amount of water could cause O-H insertion rather than cyclopropanation and has the risk of poisoning the catalyst, especially under catalyst loading as low as 0.001 mol%. Two attempts were made to finally match the reaction rate as close as possible to the rate indicated on the previous paper on kinetic studies that Davies group published.

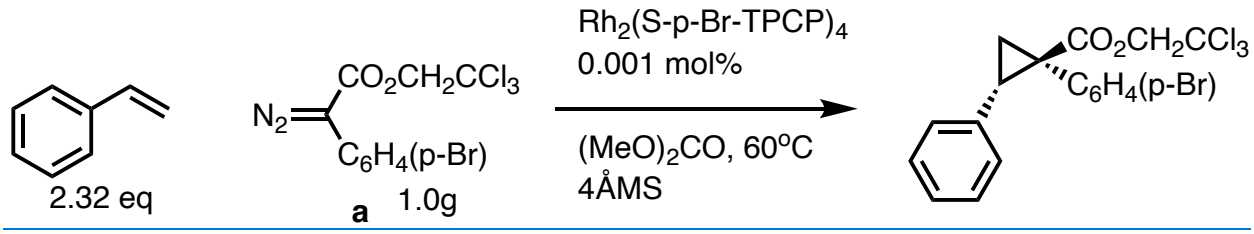
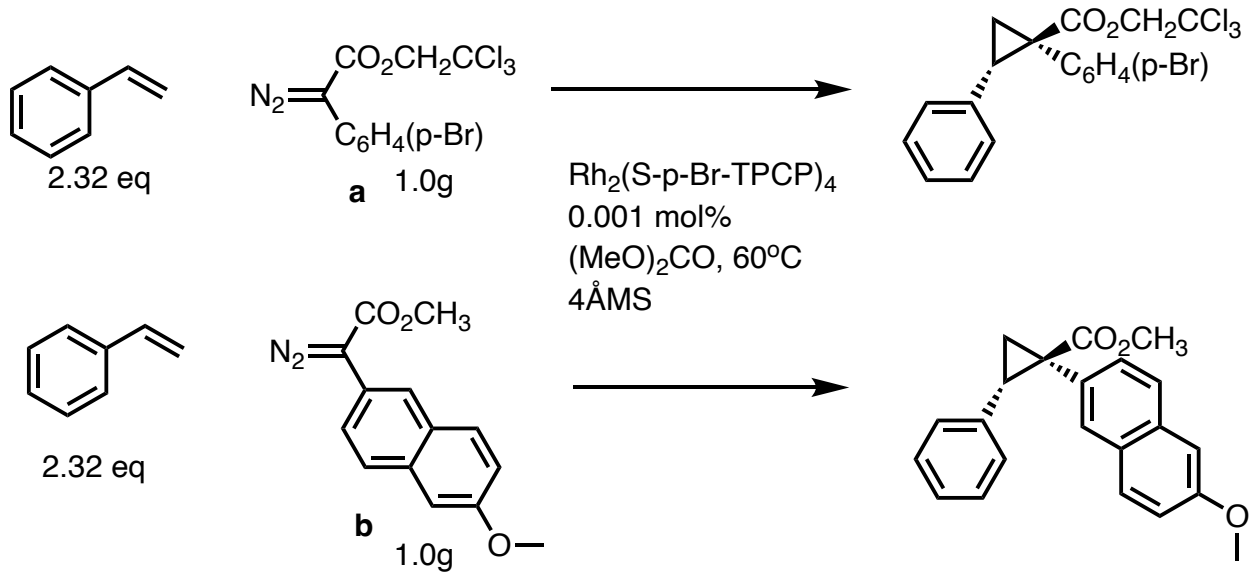


Figure 2.3: Repeat of p-Br TCE diazo kinetics with one gram of diazo compound as the limiting reagent and 2.32 eq styrene with 0.001 mol% catalyst loading in Dimethyl Carbonate under 60 °C.

After the optimization, the new substrate was prepared on REACT-IR using the same method. A comparison was drawn between the kinetics of the new substrate and p-Br TCE diazo. It was found that the new substrate does not differ significantly from the parent diazo indicated in Figure 2.4.



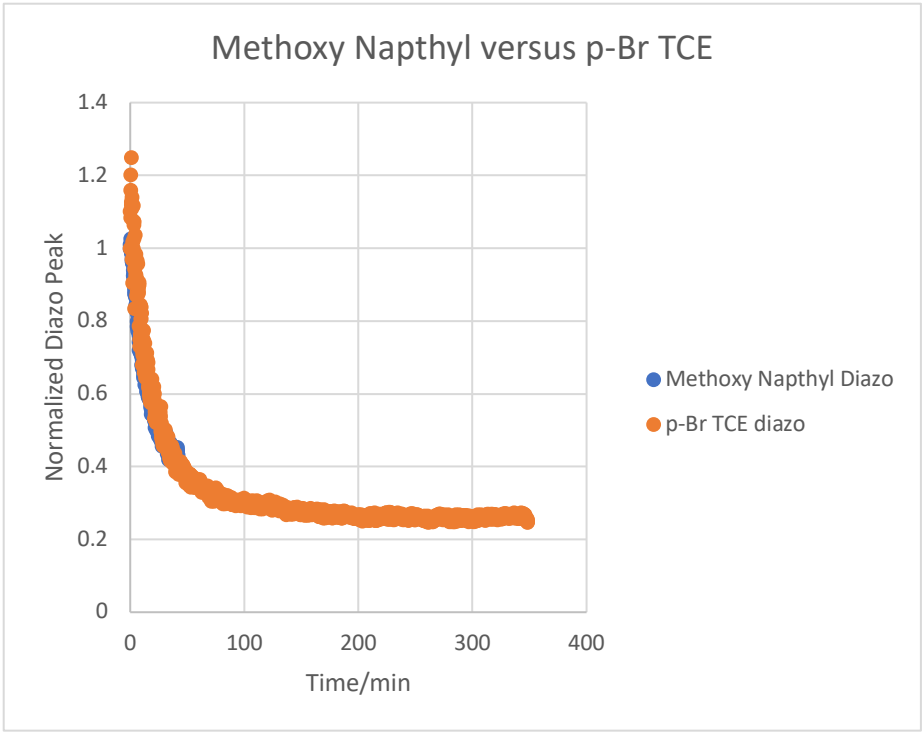


Figure 2.4a: Comparison of kinetics between cyclopropanation of methoxy napthyl diazo and p-Br TCE diazo.

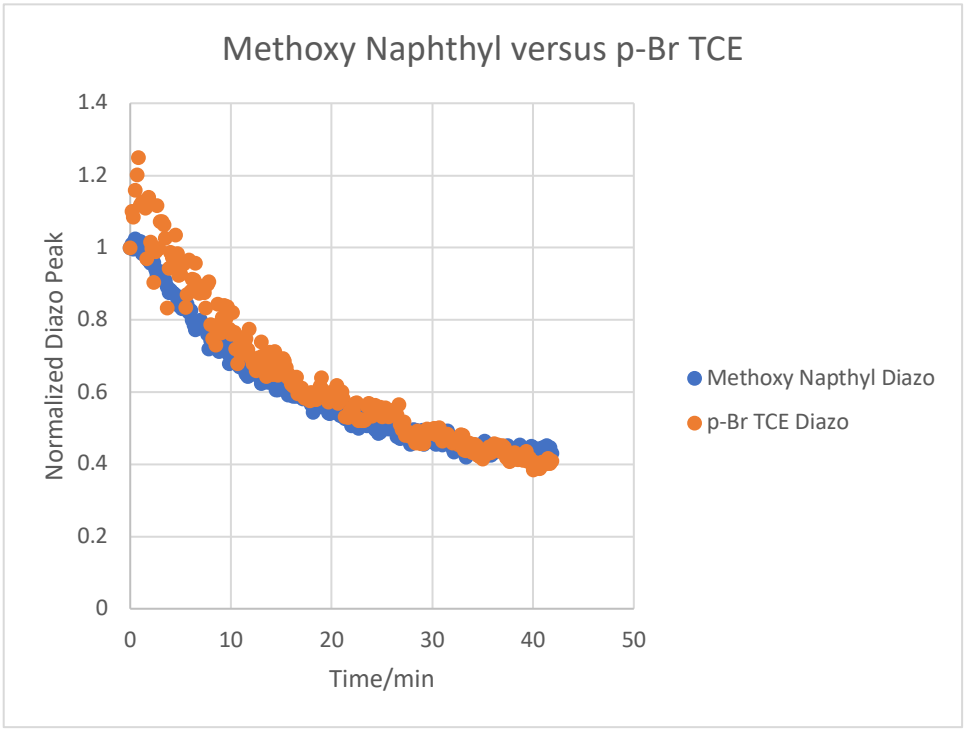


Figure 2.4b: Close examination of the reaction kinetics for the first 40 minutes of the reaction.

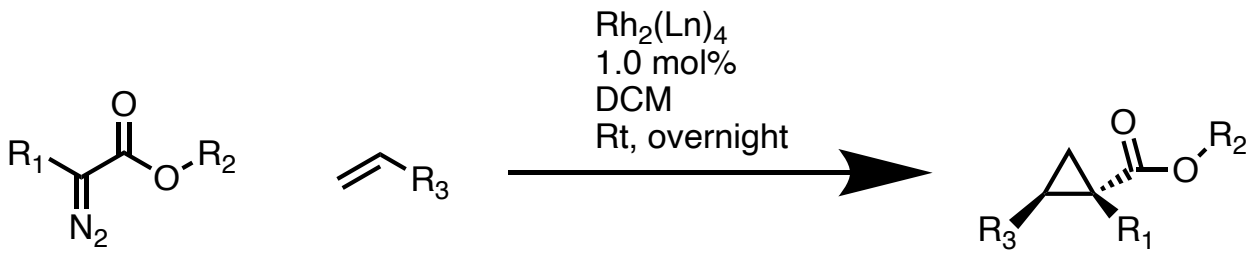
4.) Conclusions

The Rh_2(S-TPPTTL)$_4$ derivatives perform asymmetric cyclopropanation exceptionally, giving high enantiomeric excess (>80%) when p-Br tri-chloro ethyl ester diazo and p-methoxy tri-chloro ethyl ester diazo are the substrates as while as when styrene and 1-hexene are the traps. The e.e. drops when the ortho-chloro methyl ester diazo is the substrate. As for the kinetic aspects of asymmetric cyclopropanation, the new substrate, methyl 2-diazo-2-(6-methoxynaphthalen-2-yl)acetate, did not exceed the current turnover numbers Davies group has achieved so far. Yet given that the reaction was only performed under REACT-IR once, there is plenty of room to improve the current conditions to make the new substrate a better choice for performing fast asymmetric cyclopropanation. It would also be interesting to see if TCE ester could improve the functionality of the current substrate, which is a methyl ester.

5.) Experimental

5.1) Supporting Information for Asymmetric Cyclopropanation Screening using Rh_2(S-TPPTTL)$_4$

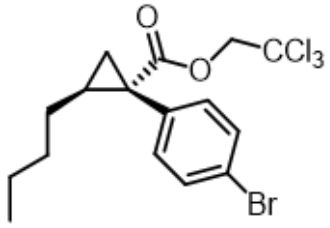
5.1.1) General Procedure for Asymmetric Cyclopropanation with Rh_2(TPPTTL)$_4$ derivatives.



A 4 ml vial equipped with a small stir bar and 4 Å activated molecular sieves was flame dried and evacuated. The flask was then purged with inert atmosphere (nitrogen) and the cycle was repeated an additional time prior to the addition of dirhodium catalyst (1.0 mol%, 0.001 mmol) to the vial. The purge cycle was repeated once more, then alkene (5 equiv, 0.50 mmol) was added via syringe. The mixture was then dissolved in DCM (1.0 ml). The solution was stirred for 5 mins under argon at rt to allow the reagents an opportunity to mix thoroughly. In a separate vial, the diazo compound (0.10 mmol) was dissolved in DCM (1.0 mL). The diazo solution was then loaded into a syringe. Then, the diazo compound solution was added to the stirring reaction mixture over 2 min via syringe and the mixture was left to run overnight. The next day, the solvent was evaporated and the crude material was subjected to flash column chromatography and product containing fractions were aggregated and solvent was removed *in vacuo* to yield the desired product. Asymmetric induction (% ee) was determined by chiral HPLC or SFC.

5.1.2) Compound Characterization

Known Products:



2,2,2-trichloroethyl (1S,2S)-1-(4-bromophenyl)-2-butylcyclopropane-1-carboxylate: Product was prepared according to general procedure 1 from the reaction between 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (32 mg, 0.10 mmol) and 1-hexene (21 mg, 0.25 mmol) in the presence of a variety of dirhodium tetracarboxylate catalysts. The product was obtained as a

clear colorless oil in up to 98% ee and 90% yield. Spectra and characterization matched literature reported values.[7]

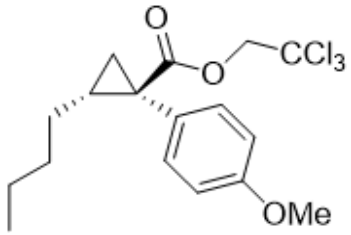
^{1}H NMR: (500 MHz, CDCl3) δ 7.88 – 7.83 (m, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.51 – 7.43 (m, 3H), 4.70 (ab-quartet, 2H), 2.02 (tdd, *J* = 9.1, 6.8, 4.7 Hz, 1H), 1.94 (dd, *J* = 9.0, 4.2 Hz, 1H), 1.47 – 1.30 (m, 3H), 1.28 – 1.14 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H), 0.65 – 0.54 (m, 1H).

^{13}C NMR: (151 MHz, CDCl3) δ 173.08, 133.18, 133.06, 132.70, 129.90, 129.86, 127.83, 127.64, 127.38, 125.94, 95.12, 74.22, 33.74, 31.32, 29.86, 29.85, 22.39, 21.90, 14.01.

IR(neat): 2956, 2930, 2858, 1735, 1620, 1506, 1435, 1367, 1260, 1236, 1217, 1160, 1128, 1099, 1047, 905, 858, 815, 753, 711, 657, 573, 478 cm^{-1}

Chiral HPLC: (Column AD-H, 15 min, 1ml/min, 1% IPA/Hexanes) RT: 4.9 min, 5.4 min.

HRMS: (+p APCI) calculated for C20H21O235Cl3 [398.06016] found [398.06017]



2,2,2-trichloroethyl (1R,2R)-2-butyl-1-(4-methoxyphenyl)cyclopropane-1-carboxylate

Product was prepared according to general procedure 1 from the reaction between 2,2,2-trichloroethyl 2-(4-methoxyphenyl)-2-diazoacetate and 1-hexene (42 mg, 0.5 mmol) in the presence of a variety of dirhodium tetracarboxylate catalysts. After isolation, product was obtained

as a clear colorless oil in up to 52% yield and 96% ee. Spectra and characterization matched literature reported values.[7]

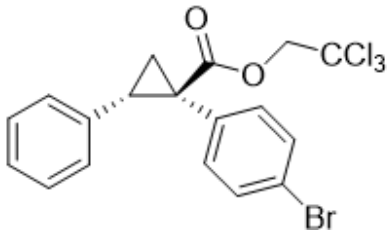
^{1}H NMR (400 MHz, CDCl3) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.70 (dd, *J* = 96.9, 11.9 Hz, 2H), 3.83 (s, 4H), 1.91 (ddd, *J* = 8.8, 6.6, 5.0 Hz, 1H), 1.85 (dd, *J* = 9.3, 3.9 Hz, 1H), 1.50 – 1.33 (m, 4H), 1.28 (dtd, *J* = 15.3, 7.4, 1.9 Hz, 2H), 1.20 (dd, *J* = 6.6, 4.0 Hz, 1H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.74 – 0.53 (m, 1H).

^{13}C NMR (101 MHz, CDCl3) δ 173.38, 158.70, 132.46, 127.37, 113.37, 95.18, 74.19, 55.23, 32.80, 31.28, 29.94, 29.64, 22.45, 21.99, 14.05.

IR(neat): 3004, 2955, 2930, 2858, 1736, 1612, 1581, 1515, 1441, 1366, 1292, 1244, 1217, 1158, 1101, 1034, 974, 889, 832, 813, 796, 753, 724, 640, 605, 574, 528 cm^{-1}

Chiral HPLC: (Column AD-H, 15 min, 1ml/min, 1% IPA/Hexanes) RT: 5.8 min, 6.3 min.

HRMS: (+p APCI) calculated for C17H22O335Cl3 [379.0629] found [379.06258]



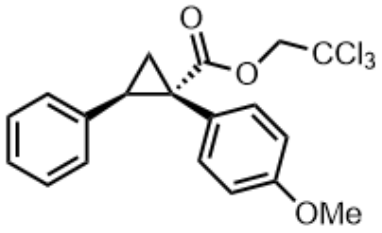
2,2,2-Trichloroethyl (1R,2S)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate

Product was prepared according to general procedure 1 from the reaction between 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (32 mg, 0.10 mmol) and styrene (5.0 equiv, 0.5 mmol, 52 mg, 60 ul). After isolation, product was obtained as a clear crystalline solid in up to 98% yield and 91% ee (98 μmol, 44.0 mg). Spectra and characterization matched literature reported values.[5]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.24 (m, 3H), 7.16 – 7.05 (m, 2H), 6.98 – 6.86 (m, 2H), 6.86 – 6.75 (m, 2H), 4.83 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 3.22 (dd, *J* = 9.4, 7.5 Hz, 1H), 2.28 (dd, *J* = 9.4, 5.2 Hz, 1H), 1.97 (dd, *J* = 7.5, 5.2 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.74, 135.35, 133.79, 133.07, 131.06, 128.23, 128.18, 127.02, 121.67, 95.10, 74.54, 36.74, 34.09, 20.32.

Chiral HPLC: (Column AD-H, 1mL/mL, 1% IPA/hexane, 15 min) RT: 6.7 min, 8.4 min.



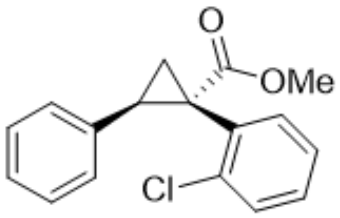
2,2,2-trichloroethyl (1S,2R)-1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate

Product was prepared according to general procedure 1 from the reaction between 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (32 mg, 0.10 mmol) and styrene (5.0 equiv, 0.5 mmol, 52 mg, 60 ul) After isolation, product was obtained as a clear colorless oil in up to 62% yield and 92% ee. Spectra and characterization matched literature reported values.[5]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 – 7.05 (m, 3H), 7.05 – 6.95 (m, 2H), 6.88 – 6.78 (m, 2H), 6.73 – 6.63 (m, 2H), 4.86 (d, *J* = 11.9 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H), 3.72 (s, 3H), 3.20 (dd, *J* = 9.4, 7.4 Hz, 1H), 2.29 (dd, *J* = 9.4, 5.0 Hz, 1H), 1.97 (dd, *J* = 7.4, 5.0 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.52, 158.82, 136.03, 133.21, 128.33, 127.99, 126.71, 125.94, 113.33, 95.33, 74.49, 55.25, 36.71, 34.07, 20.66.

Chiral HPLC: (*R,R*-Whelk , 45 min, 1 mL/min, 1 % iPrOH in hexanes, UV 230 nm) RT: 30.3 min,: 19.7 min,



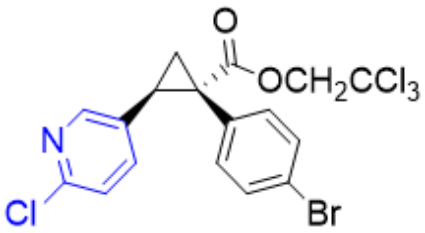
Methyl (1*S*,2*R*)-1-(2-chlorophenyl)-2-phenylcyclopropane-1-carboxylate

Product was prepared according to general procedure 1 from the reaction between methyl- 2-(2'-chlorophenyl)-2-diazoacetate (21 mg, 0.10 mmol) and styrene (5.0 equiv, 0.5 mmol, 52 mg, 60 ul). After isolation, enantio-enriched product was obtained as a clear colorless oil in up to 68% yield and 40% ee (68 µmol, 19.5 mg). Spectra and characterization matched literature reported values.[8]

^{1}H NMR (400 MHz, CDCl3) δ 7.15 (broad m, 4H), 7.08 (m, 3H), 6.87 – 6.76 (dd, *J* = 6.9, 2.0 Hz 2H), 3.70 (s, 3H), 3.34 (t, *J* = 8.4 Hz, 1H), 2.13 (s, 1H), 1.94 (dd, *J* = 7.5, 5.2 Hz, 1H).

^{13}C NMR (151 MHz, CDCl3) δ 173.4, 137.3, 133.3, 129.3, 128.6, 127.9, 129.4, 126.4, 126.1, 64.4, 52.7, 33.3, 25.4, 21.5

Chiral SFC: (OJ-3, 5 min, 2.5 mL/min, 5%(1:1 mixture of MeOH an *i*-PrOH + 0.2% FA)/CO2, UV 230 nm) RT: 0.94 min, 1.21 min



2,2,2-trichloroethyl (1*S*,2*R*)-1-(4-bromophenyl)-2-(6-chloropyridin-3-yl)cyclopropane-1-carboxylate.

Product was prepared according to general procedure 1 from the reaction between 2,2,2-trichloroethyl 2-(4-bromo)-2-diazoacetate and and 2-chloro-5-vinyl pyridine (5 equiv, 0.50 mmol, 80 mg)**.** After isolation, enantio-enriched product was obtained as an off-white greasy crystalline solid in up to 84% yield and 91% ee (0.084 mmol, 34 mg). Spectra and characterization matched literature reported values.[8]

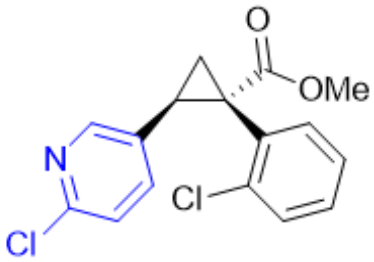
^{1}H NMR (600 MHz, CDCl3) δ 8.05 (d, *J* = 2.5 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.83 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.84 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 3.18 (dd, *J* = 9.4, 7.3 Hz, 1H), 2.34 (dd, *J* = 9.4, 5.5 Hz, 1H), 1.93 (dd, *J* = 7.3, 5.5 Hz, 1H).

^{13}C NMR (151 MHz, CDCl3) δ 171.1, 150.2, 149.9, 137.4, 133.7, 131.9, 131.7, 130.7, 123.7, 122.5, 94.9, 74.8, 37.0, 30.3, 20.5.

HRMS: (+p APCI) calculated for [C17H13O2N79Br35Cl4+] 481.8878, found 481.8878

IR(neat): 2954, 1737, 1587, 1561, 1490, 1464, 1396, 1367, 1349, 1237, 1210, 1156, 1111, 1071, 1057, 1024, 1011, 973, 909, 836, 801, 767, 740, 717, 646, 575, 521 cm^{-1}

Chiral HPLC: (OD-H, 60 min, 1 mL/min, 1% *i*-PrOH in *n*-hexane, UV 230 nm) RT: 30.65 min, 38.71 min.



Methyl (1*S*,2*R*)-1-(2-chlorophenyl)-2-(6-chloropyridin-3-yl)cyclopropane-1-carboxylate

Product was prepared according to general procedure 1 from the reaction between methyl- 2-(2'-chlorophenyl)-2-diazoacetate (21 mg, 0.10 mmol) 2-chloro-5-vinyl pyridine (5 equiv, 0.50 mmol, 80 mg). After isolation, enantio-enriched product was obtained as a clear colorless oil in up to 74% yield and 88% ee (0.074 mmol, 35.8 mg). Spectra and characterization matched literature reported values.[8]

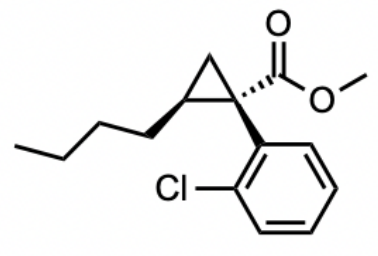
^{1}H NMR (400 MHz, CDCl3) δ 7.98 (d, *J* = 2.5 Hz, 1H), 7.49 – 7.27 (m, 1H), 7.25 – 7.12 (m, 3H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.87 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.68 (s, 3H), 3.30 (t, *J* = 8.4 Hz, 1H), 2.11 (t, *J* = 8.2 Hz, 1H), 1.89 (dd, *J* = 7.3, 5.4 Hz, 1H).

^{13}C NMR (151 MHz, CDCl3) δ 172.8, 149.6, 149.7, 137.2, 137.1, 132.5, 130.9, 129.9, 129.6, 126.9, 123.0, 53.1, 37.0, 29.7 **HRMS:** (+p APCI) calculated for [C16H14O2N35Cl2+] 322.0396, found 322.0399

IR(neat): 2923, 2852, 1720, 1586, 1561, 1464, 1434, 1397, 1348, 1269, 1250, 1208, 1165, 1143, 1110, 1034, 1023, 992, 968, 909, 885, 833, 802, 780, 741, 699, 660, 647, 586, 518, 470, 434 cm^{-1}

Chiral HPLC: (OD-H, 60 min, 1 mL/min, 1% *i*-PrOH in *n*-hexane, UV 230 nm) RT: 28.71 min, 32.79 min

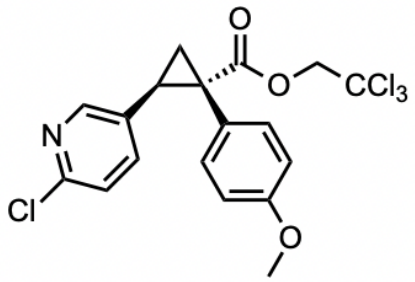
Novel compounds:



Methyl (1*S*,2*S*)-2-butyl-1-(2-chlorophenyl)cyclopropane-1-carboxylate.

Product was prepared according to general procedure 1 from the reaction between methyl- 2-(2'-chlorophenyl)-2-diazoacetate (21 mg, 0.10 mmol) and 1-hexene (42 mg, 0.5 mmol). After isolation, the product was obtained as a clear colorless oil in up to 44% yield and 64% ee (44 μmol, 11.7mg).

Chiral SFC (S,S-Whelk, 10 min, 2.5 mL/min, 1%(1:1 mixture of MeOH an *i*-PrOH + 0.2% FA)/CO2, UV 230 nm) RT: 1.81 min, 1.95 min



2,2,2-trichloroethyl(1*S*,2*R*)-2-(6-chloropyridin-3-yl)-1-(4-methoxyphenyl)cyclopropane-1-carboxylate.

Product was prepared according to general procedure 1 from the reaction between 2,2,2-trichloroethyl 2-(4-methoxyphenyl)-2-diazoacetate and 2-chloro-5-vinyl pyridine (5 equiv, 0.50 mmol, 80 mg)**.** After isolation, enantio-enriched product was obtained as a clear colorless oil in up to 75% yield and 93% ee (0.075 mmol, 32.6 mg).

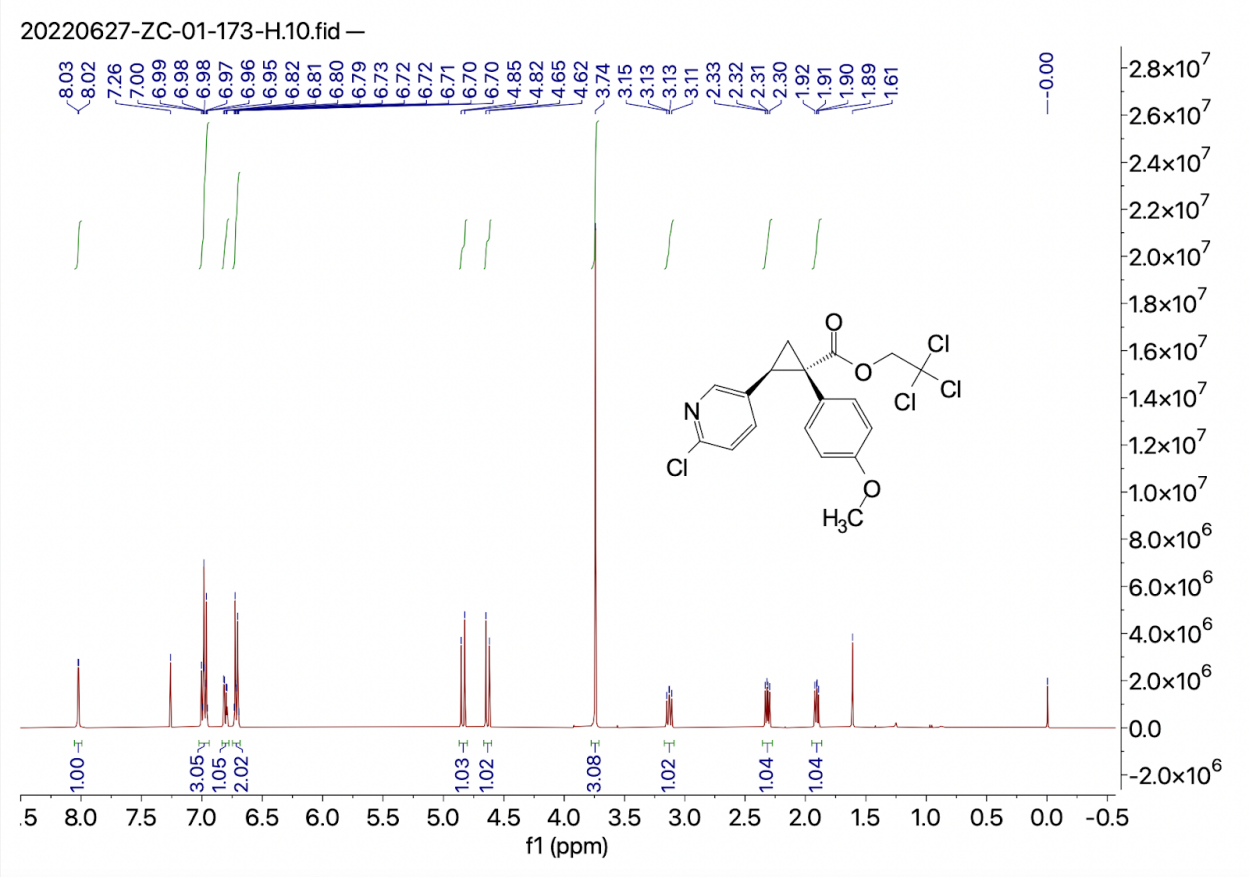
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.5 Hz, 1H), 6.98 (dd, *J* = 9.0, 7.5 Hz, 3H), 6.81 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.75 – 6.67 (m, 2H), 4.84 (d, *J* = 11.9 Hz, 1H), 4.63 (d, *J* = 11.9 Hz, 1H), 3.74 (s, 3H), 3.13 (dd, *J* = 9.4, 7.2 Hz, 1H), 2.31 (dd, *J* = 9.4, 5.3 Hz, 1H), 1.91 (dd, *J* = 7.2, 5.3 Hz, 1H).

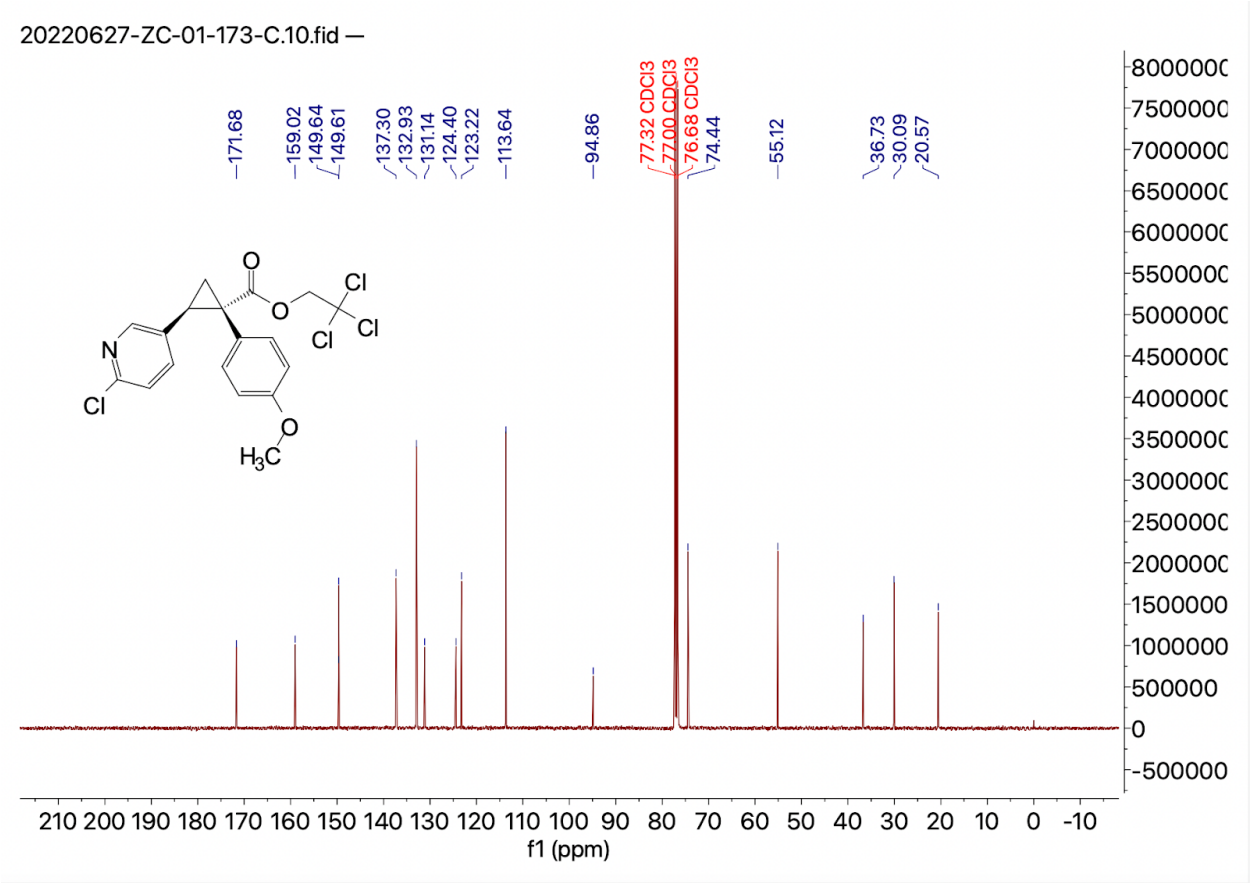
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.68, 159.02, 149.64, 149.61, 137.30, 132.93, 131.14, 124.40, 123.22, 113.64, 94.86, 74.44, 55.12, 36.73, 30.09, 20.57.

IR 535, 576, 605, 632, 652, 723, 737, 757, 799, 836, 972, 1033, 1057, 1110, 1155, 1209, 1247, 1294, 1348, 1367,1463, 1515, 1560, 1584, 1612, 1733, 2836, 2954.

Chiral SFC (AMY-1, 5 min, 2.5 mL/min, 10%(1:1 mixture of MeOH an *i*-PrOH + 0.2% FA)/CO2, UV 254 nm) RT: 2.33 min, 3.87 min

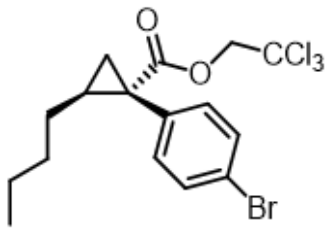
NMR Spectra:

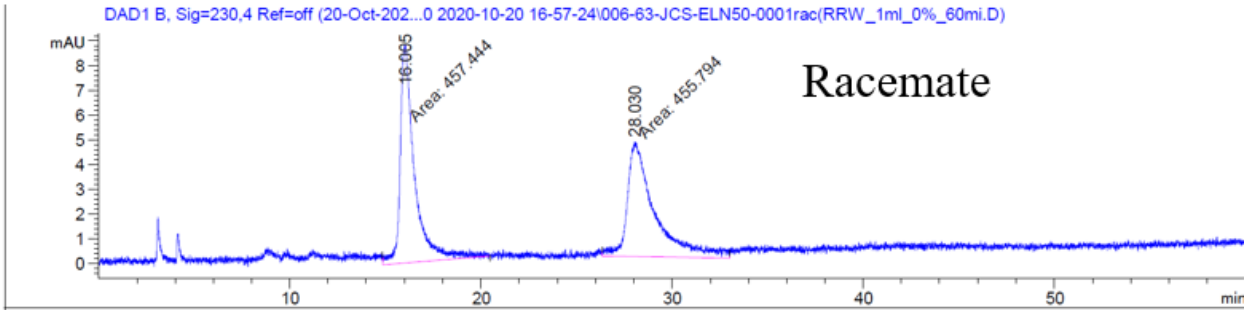

20220627-ZC-01-173-H.10.fid
8.03
8.02
7.26
7.00
6.99
6.98
6.98
6.97
6.96
6.95
6.82
6.81
6.80
6.79
6.73
6.72
6.72
6.71
6.70
6.70
4.85
4.82
4.65
4.62
3.74
3.15
3.13
3.13
3.11
2.33
2.32
2.31
2.30
1.92
1.91
1.90
1.89
1.61
-0.00
O
Cl
O
Cl
Cl
N
Cl
O
H3C
1.00
3.05
1.05
2.02
1.03
1.02
3.08
1.02
1.04
1.04
2.8×10^7
2.6×10^7
2.4×10^7
2.2×10^7
2.0×10^7
1.8×10^7
1.6×10^7
1.4×10^7
1.2×10^7
1.0×10^7
8.0×10^6
6.0×10^6
4.0×10^6
2.0×10^6
0.0
-2.0×10^6
.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

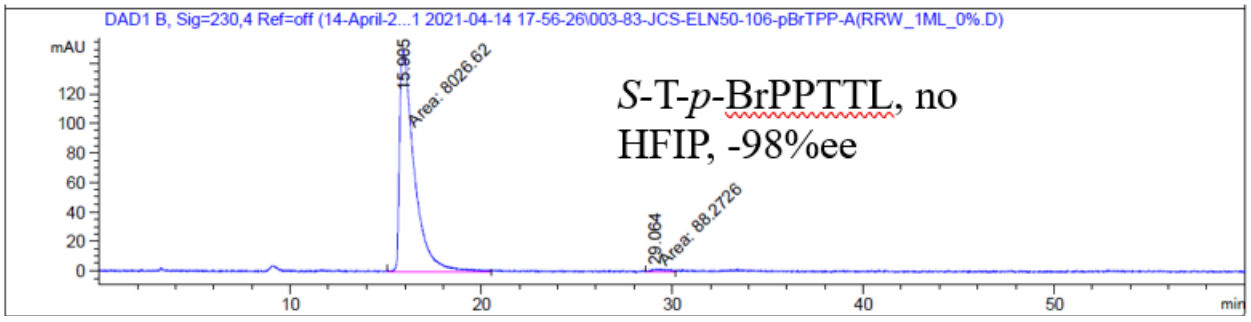


5.1.3) HPLC Traces

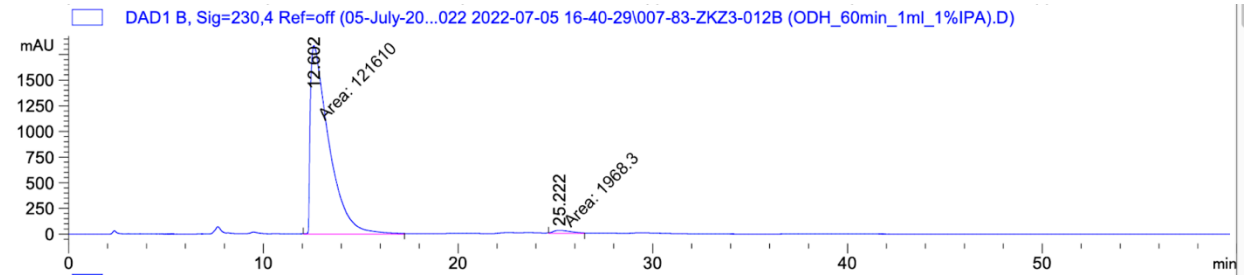
Determination of Enantioselectivity:







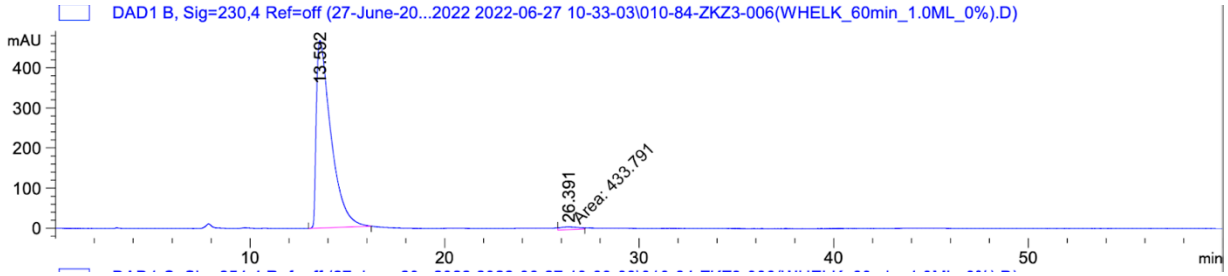
Rh_2(S-*di*-(4-Br)TPPTTL)$_4$, **97%**



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

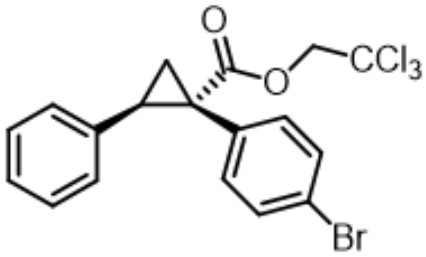
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.602	MM	1.1028	1.21610e5	1837.90063	98.4072
2	25.222	MM	1.0888	1968.30371	30.12941	1.5928
Totals :				1.23578e5	1868.03005	

Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$, **97%**

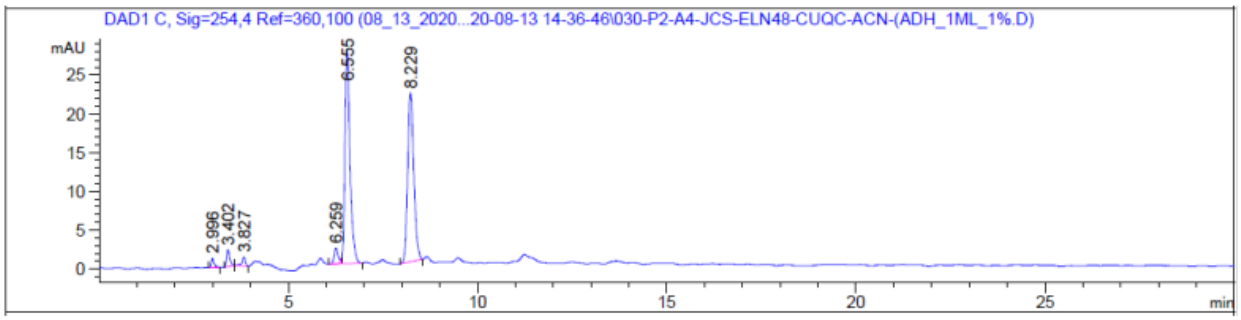


Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.592	VV R	0.6165	2.45609e4	467.43903	98.2645
2	26.391	MM	1.1058	433.79114	6.53838	1.7355
Totals :				2.49946e4	473.97740	

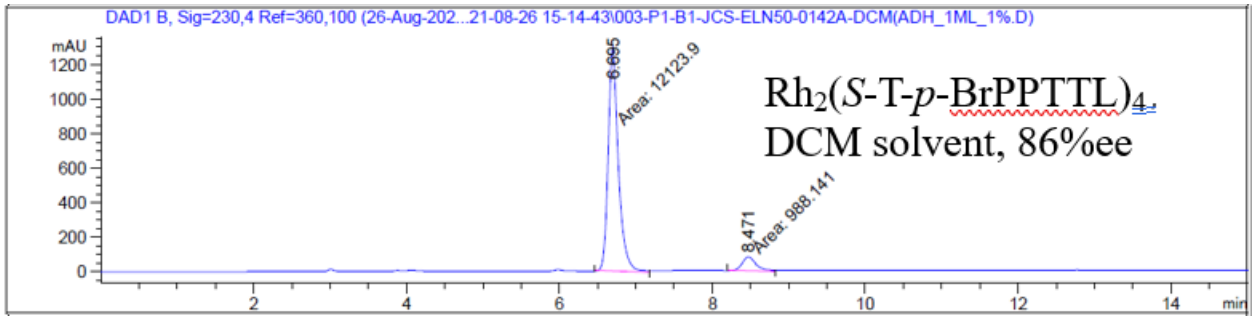


Racemate:

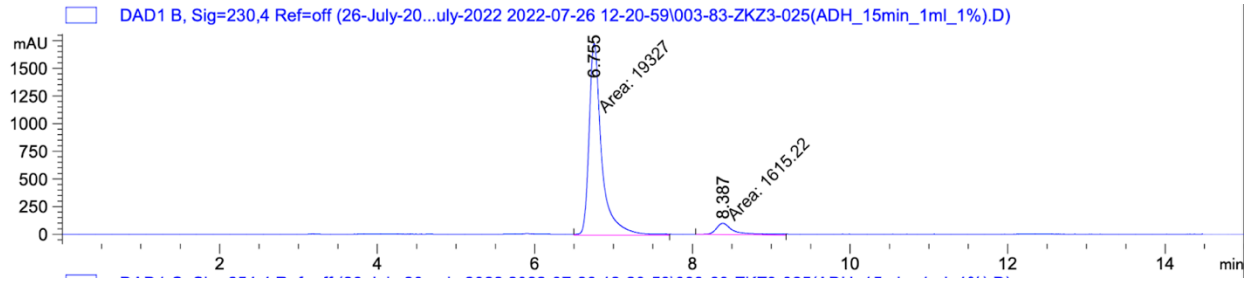


Sample Name: JCS-ELN48-CUQC-ACN-(ADH_1ML_1%_30MIN)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.555	MM	0.1498	4015.92651	446.79294	49.1184
2	8.229	MM	0.1961	4160.08594	353.50052	50.8816
Totals :				8176.01245	800.29346	



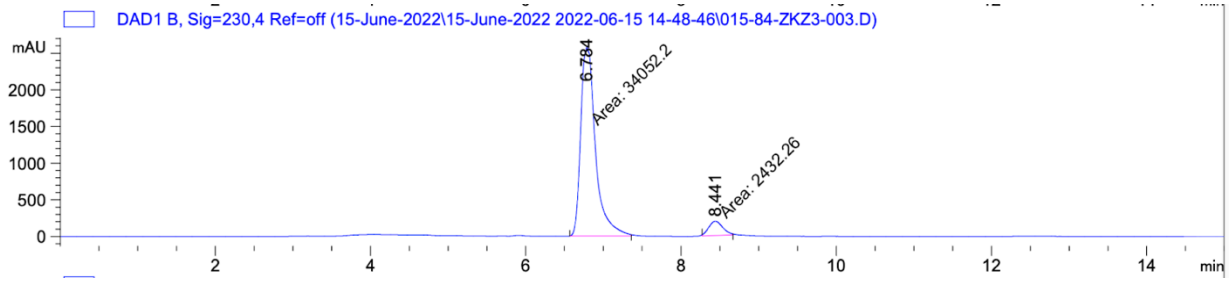
Rh_2(S-*di*-(4-Br)TPPTTL)$_4$, 91%



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

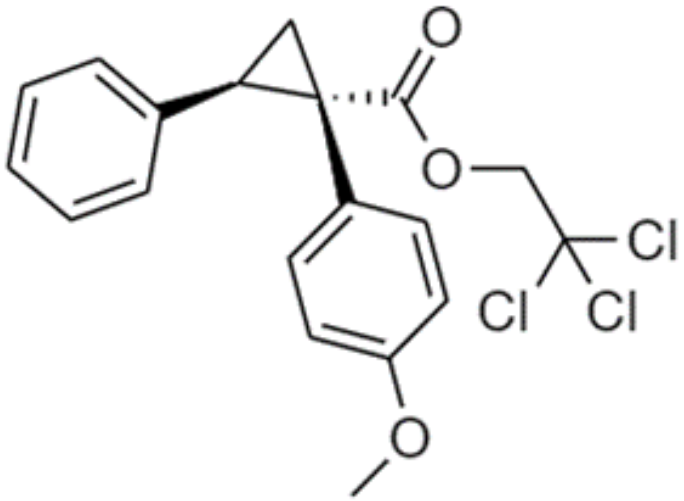
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.755	MM	0.1862	1.93270e4	1730.36694	92.2872
2	8.387	MM	0.2657	1615.22473	101.32029	7.7128
Totals :				2.09422e4	1831.68723	

Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$, 88%

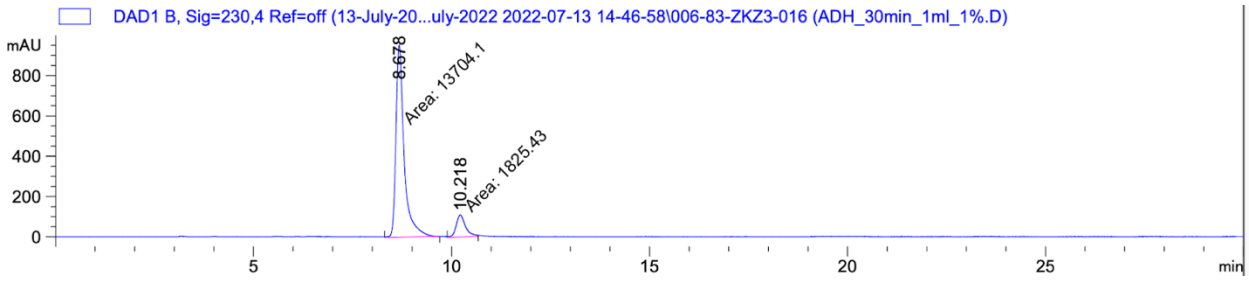


Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.784	MM	0.2207	3.40522e4	2572.08154	93.3334
2	8.441	MM	0.2086	2432.25830	194.33783	6.6666
Totals :				3.64844e4	2766.41937	



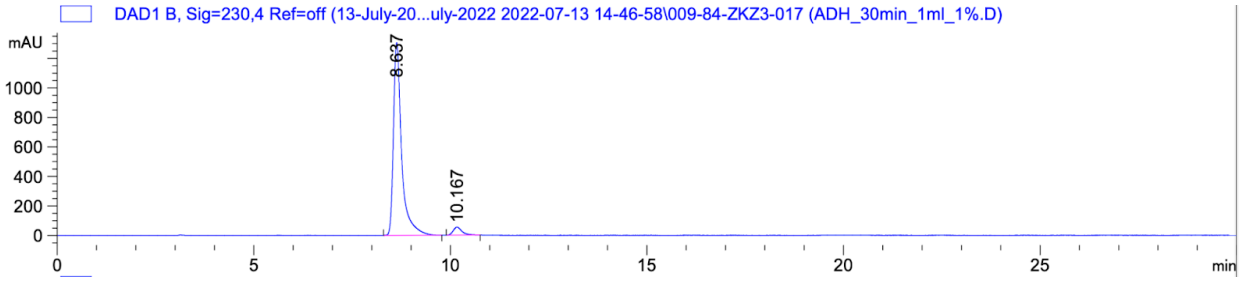
Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$ **,77%**



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.678	MM	0.2395	1.37041e4	953.81073	88.2454
2	10.218	MM	0.2783	1825.42908	109.30656	11.7546
Totals :				1.55295e4	1063.11729	

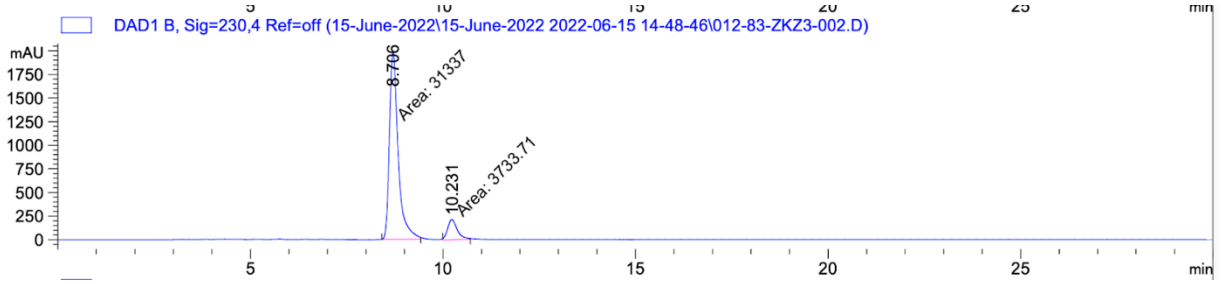
Rh_2(S-*di*-(4-Br)TPPTTL)$_4$**, 92%**



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

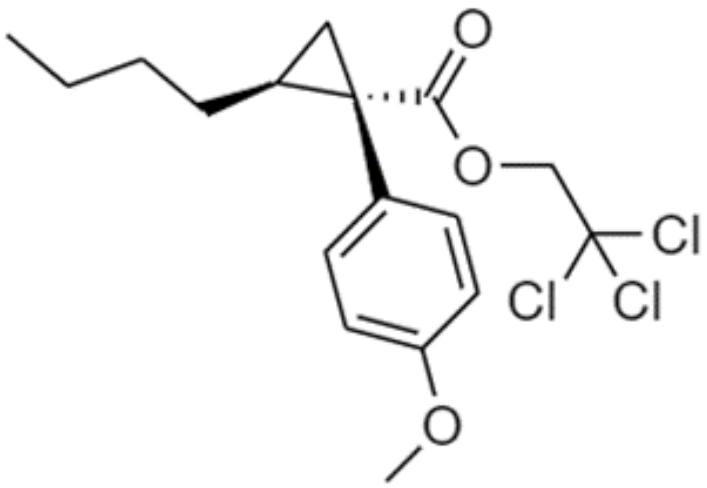
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.637	VV R	0.1999	1.88100e4	1306.73145	95.6017
2	10.167	BV R	0.1861	865.38220	55.44265	4.3983
Totals :				1.96754e4	1362.17410	

Rh$_2$(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$, **80%**

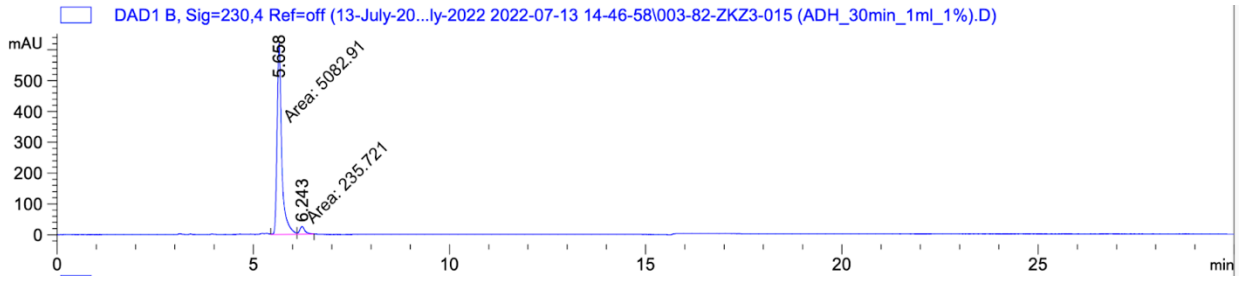


Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.706	MM	0.2652	3.13370e4	1969.36353	89.3538
2	10.231	MM	0.2919	3733.71118	213.20332	10.6462
Totals :				3.50707e4	2182.56685	



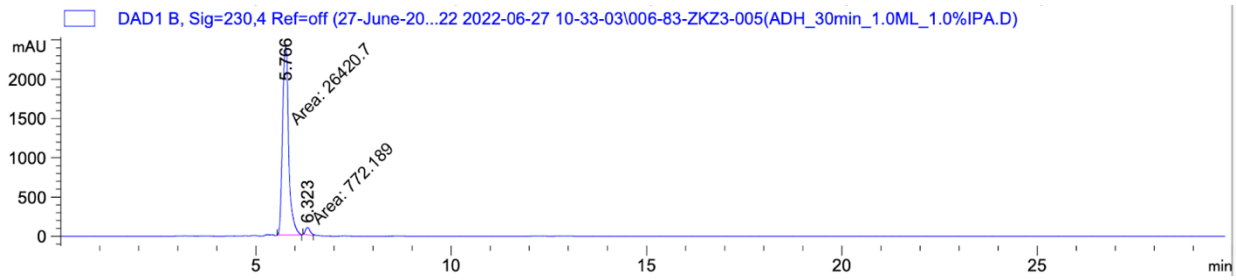
Rh_2(S-*di*-(4-Br)TPPTTL)$_4$, 91%



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

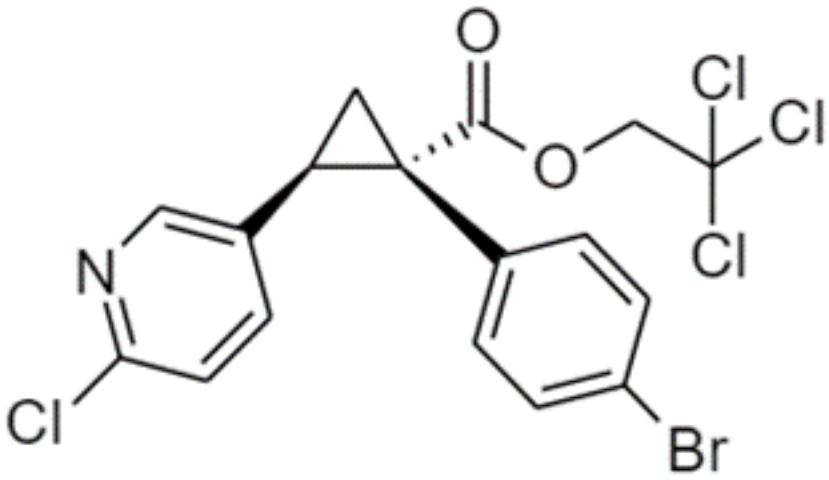
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.658	MF	0.1367	5082.91260	619.75354	95.5680
2	6.243	FM	0.1568	235.72090	25.05112	4.4320
Totals :				5318.63350	644.80466	

Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$, 96%

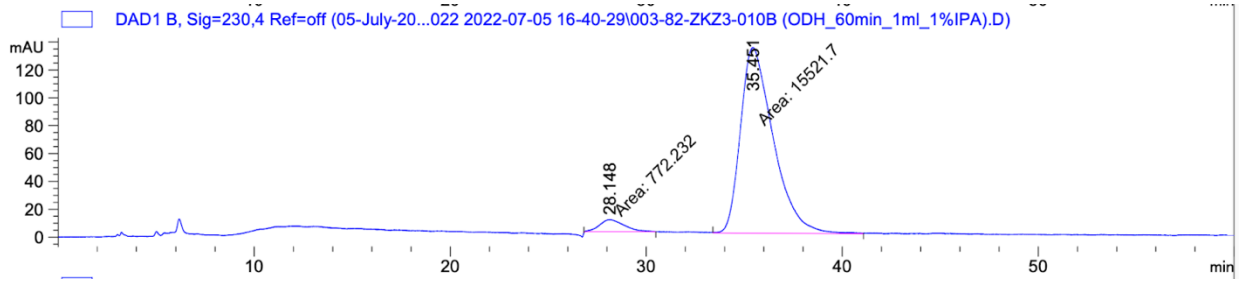


Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.766	MM	0.1836	2.64207e4	2398.61523	97.1603
2	6.323	MM	0.1364	772.18890	94.34519	2.8397
Totals :				2.71929e4	2492.96043	



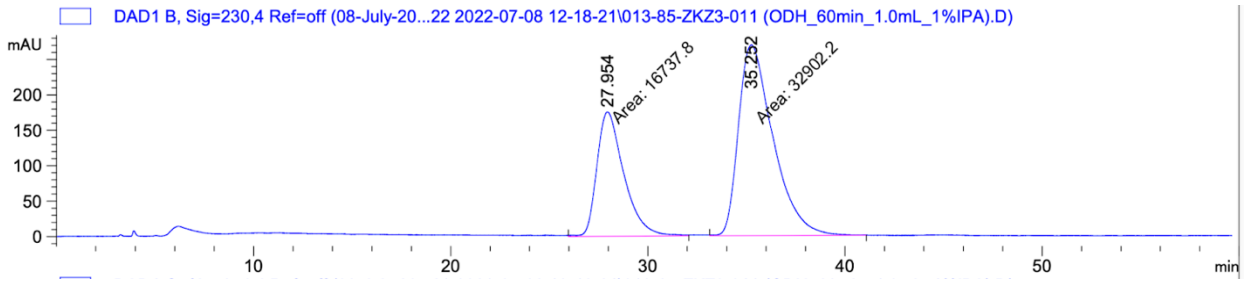
Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$, 91%



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.148	MM	1.4601	772.23151	8.81511	4.7394
2	35.451	MM	1.9396	1.55217e4	133.37469	95.2606
Totals :				1.62940e4	142.18980	

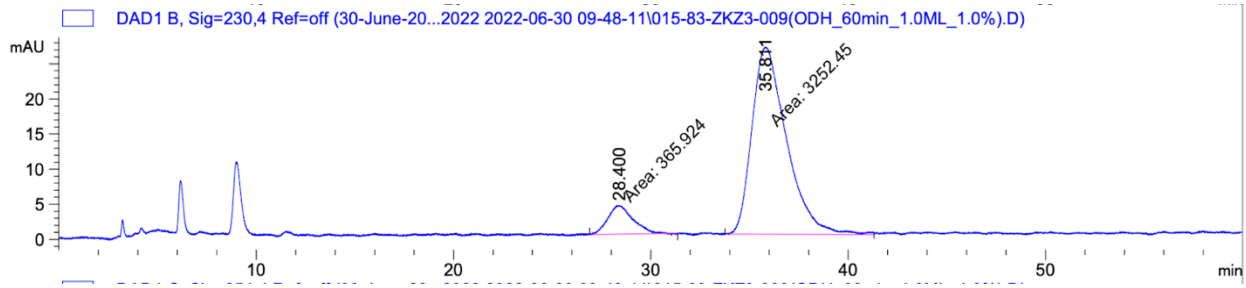
Rh_2(S-*di*-(4-Br)TPPTTL)$_4$, 33%



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

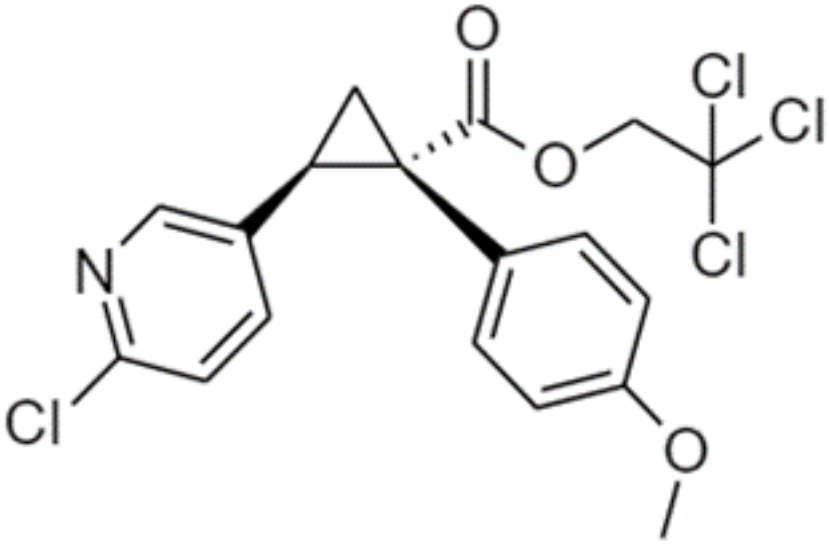
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.954	MM	1.5874	1.67378e4	175.73447	33.7183
2	35.252	MM	2.0338	3.29022e4	269.62573	66.2817
Totals :				4.96400e4	445.36020	

Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$, 80%

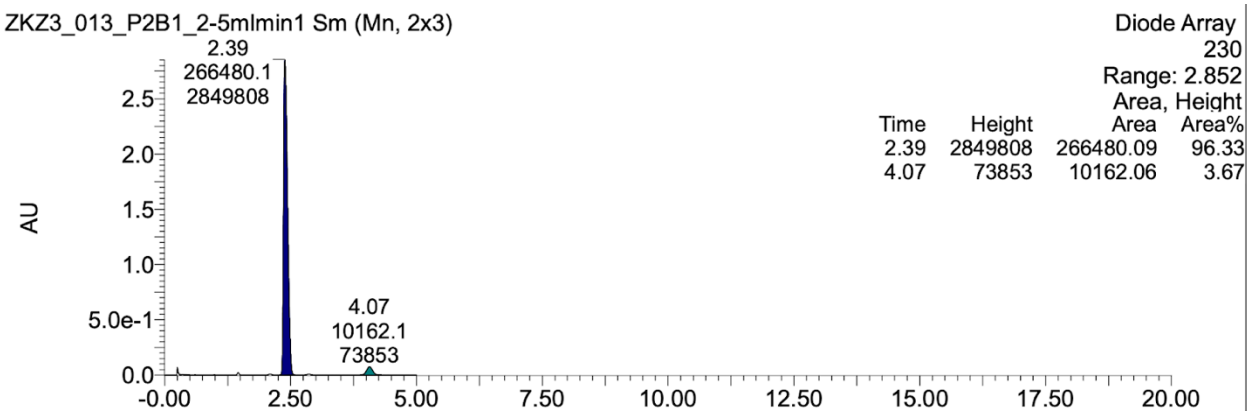


Signal 2: DAD1 B, Sig=230,4 Ref=off

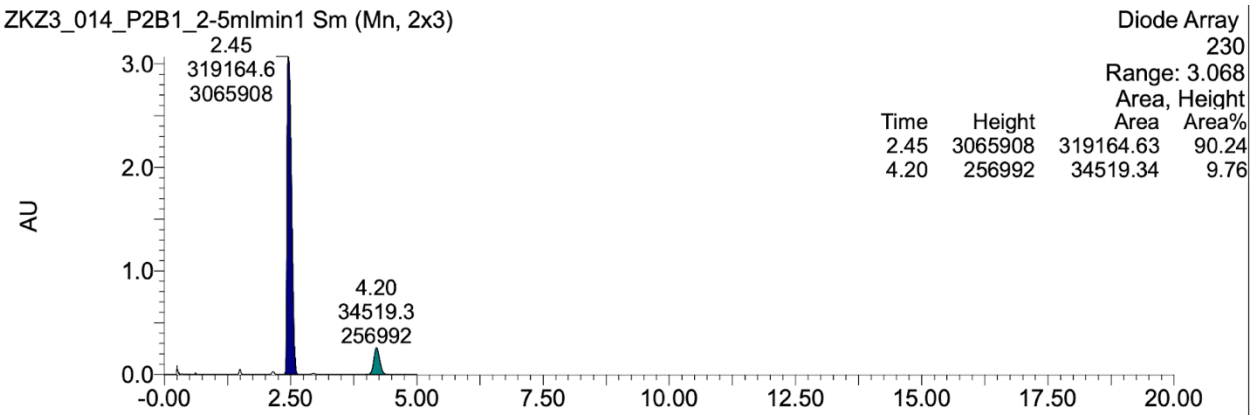
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.400	MM	1.4668	365.92389	4.15788	10.1129
2	35.811	MM	2.0331	3252.45264	26.66212	89.8871
Totals :				3618.37653	30.81999	



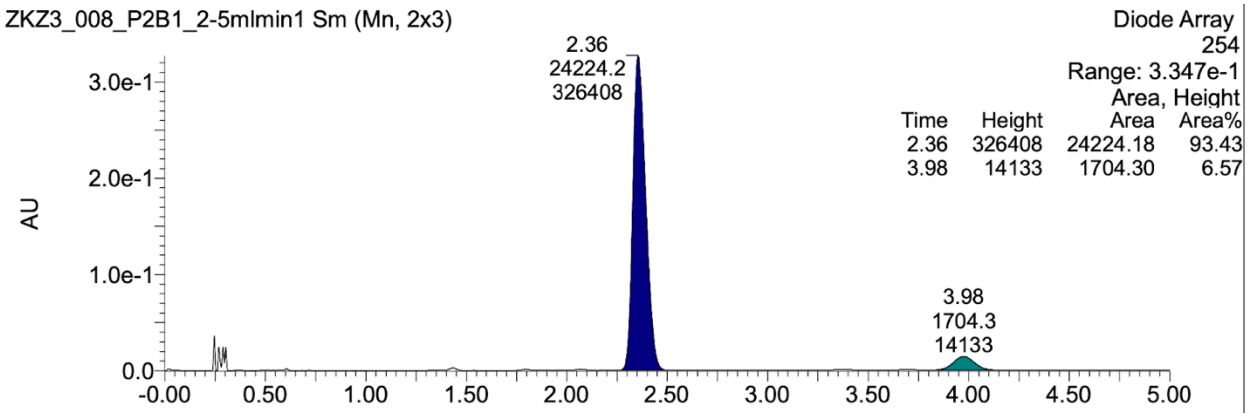
Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$, 93%

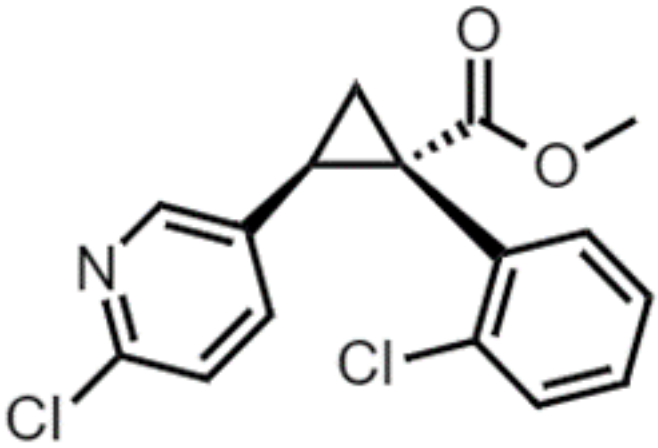


Rh_2(S-*di*-(4-Br)TPPTTL)$_4$, 82%

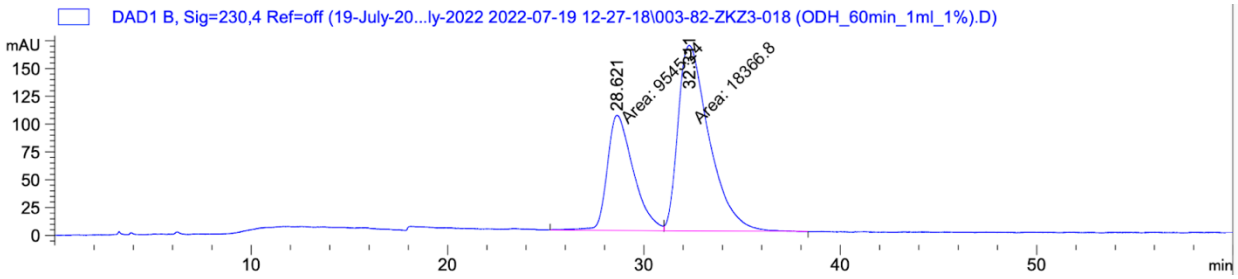


Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$, 88%





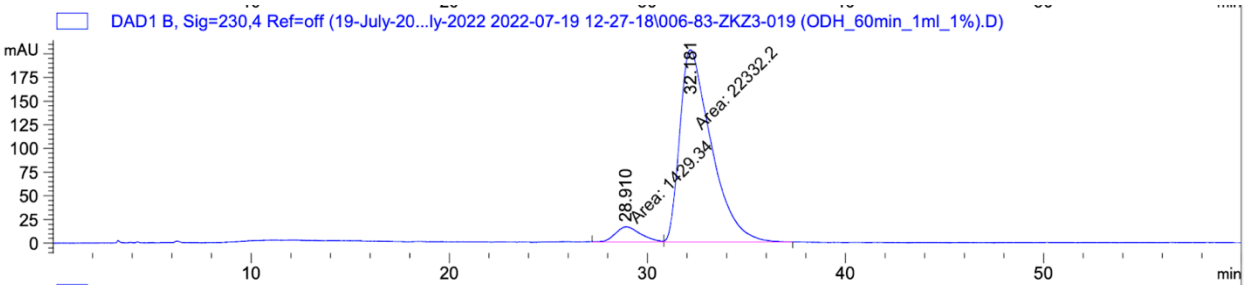
Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$, 31%



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.621	MF	1.5363	9545.24023	103.55520	34.1976
2	32.311	FM	1.8345	1.83668e4	166.86417	65.8024
Totals :				2.79120e4	270.41936	

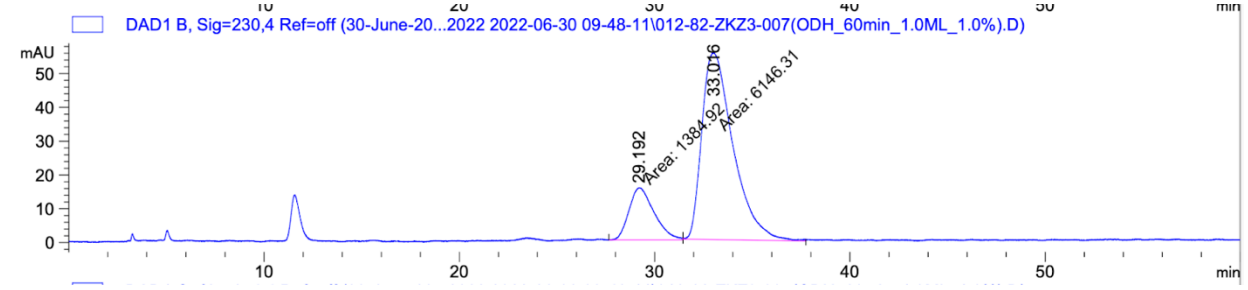
Rh_2(S-*di*-(4-Br)TPPTTL)$_4$, 88%



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

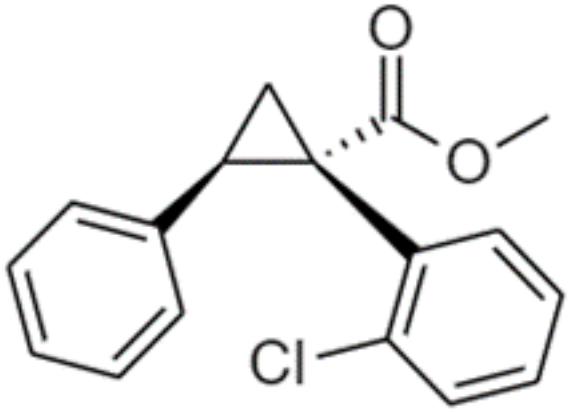
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.910	MM	1.4820	1429.34058	16.07476	6.0154
2	32.181	MM	1.8352	2.23322e4	202.81792	93.9846
Totals :				2.37615e4	218.89268	

Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$, 64%

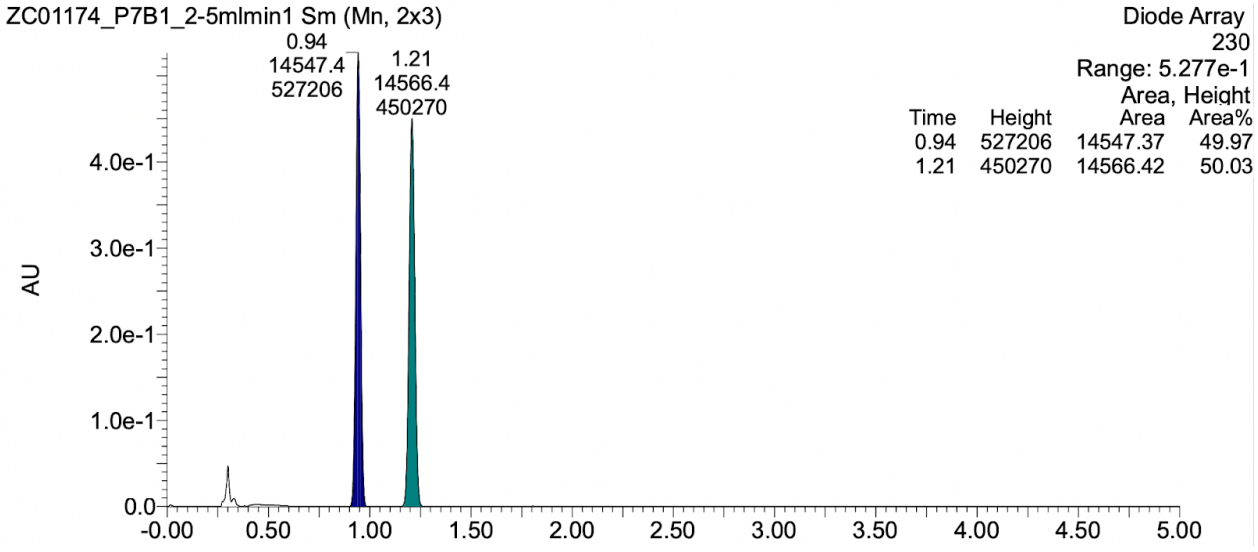


Signal 2: DAD1 B, Sig=230,4 Ref=off

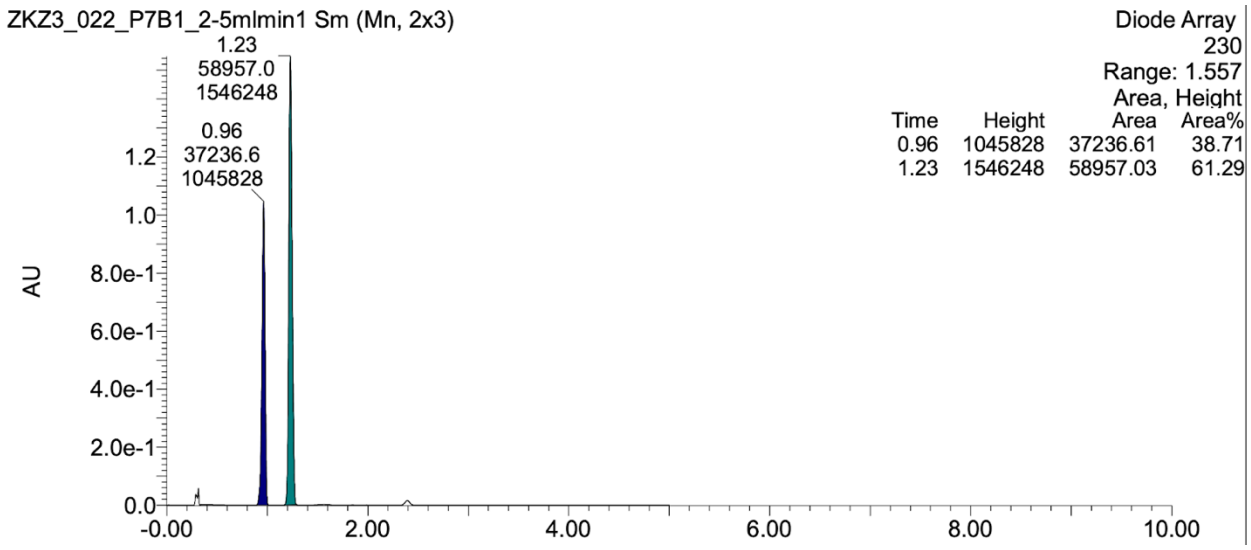
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.192	MM	1.4905	1384.92285	15.48647	18.3891
2	33.016	MM	1.8538	6146.30664	55.25809	81.6109
Totals :				7531.22949	70.74456	



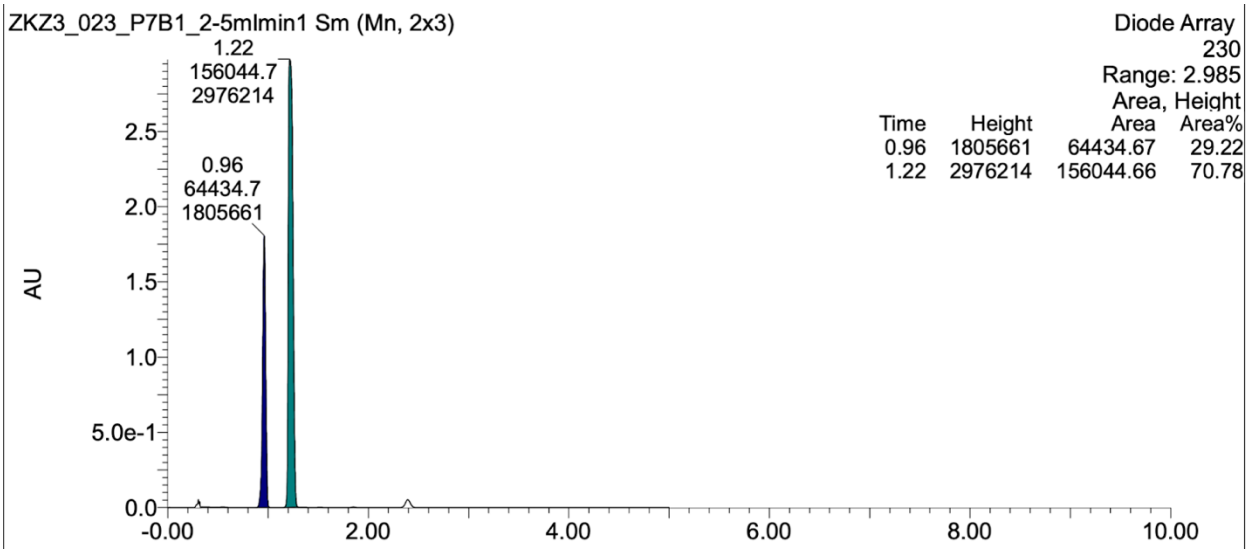
Racemate



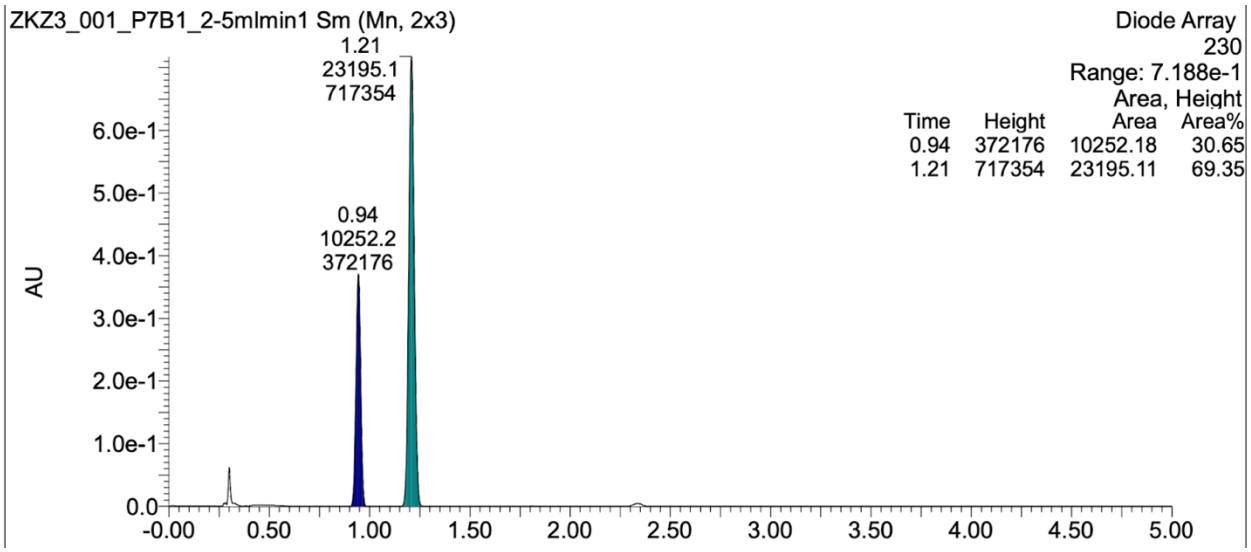
Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$, 23%

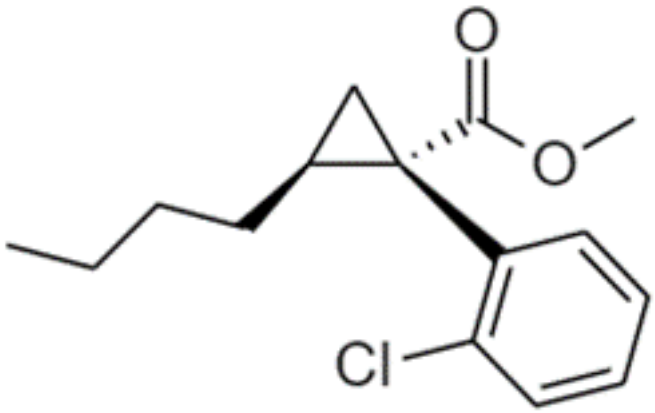


Rh_2(S-*di*-(4-Br)TPPTTL)$_4$, 40%



Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$, 40%


ZKZ3_001_P7B1_2-5mlmin1 Sm (Mn, 2x3)
Diode Array
230
Range: 7.188e-1
Area, Height
1.21
23195.1
717354
0.94
10252.2
372176
AU
Time Height Area Area%
0.94 372176 10252.18 30.65
1.21 717354 23195.11 69.35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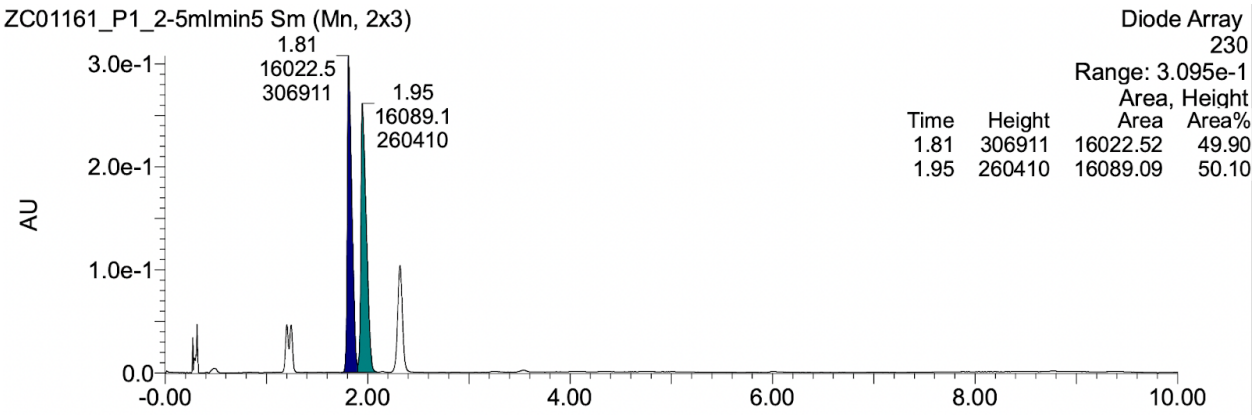
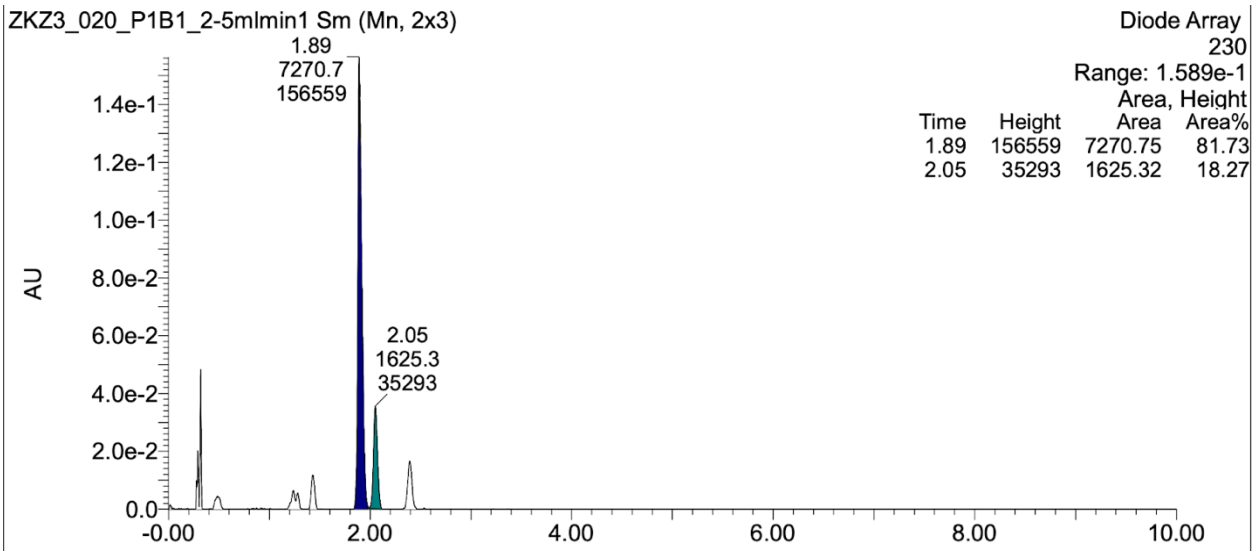
Cl

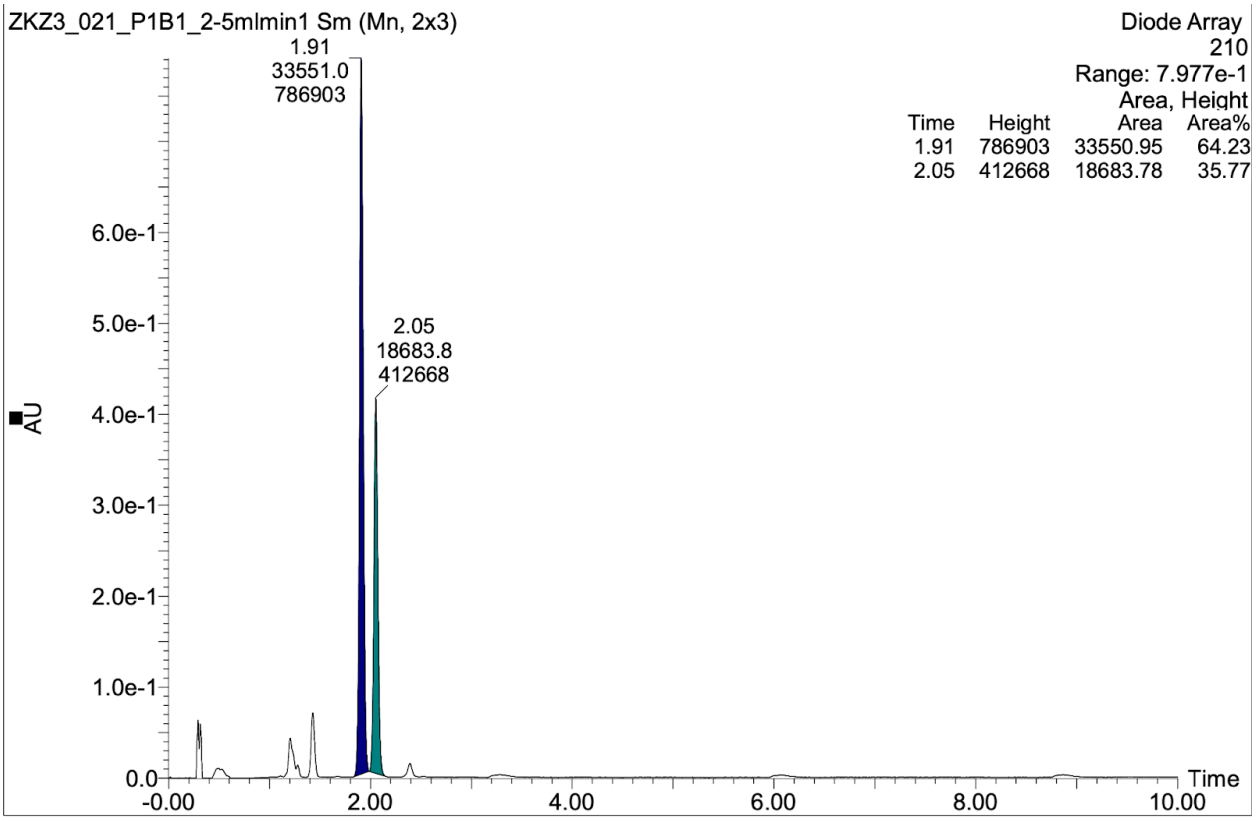
Racemate


ZC01161_P1_2-5mlmin5 Sm (Mn, 2x3)
Diode Array
230
Range: 3.095e-1
Area, Height
1.81
16022.5
306911
1.95
16089.1
260410
AU
Time Height Area Area%
1.81 306911 16022.52 49.90
1.95 260410 16089.09 50.10

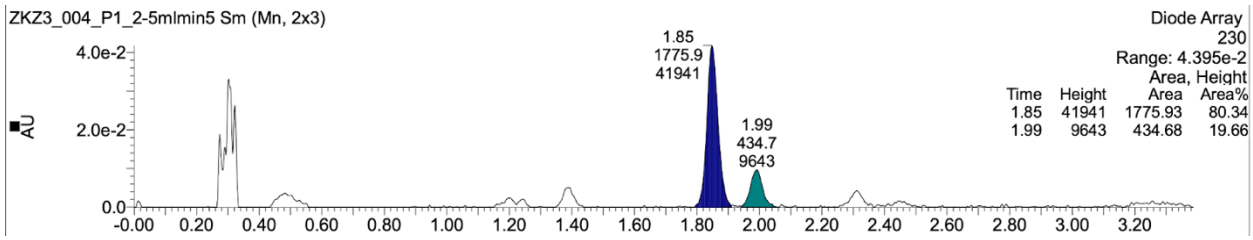
Rh_2(S-*tetra*-(4-Br)TPPTTL)$_4$, -64%



Rh_2(S-*di*-(4-Br)TPPTTL)$_4$, -27%



Rh_2(S-*di*-(4-Br)-*di*-(4-^{t}BuPh)TPPTTL)$_4$, -61%

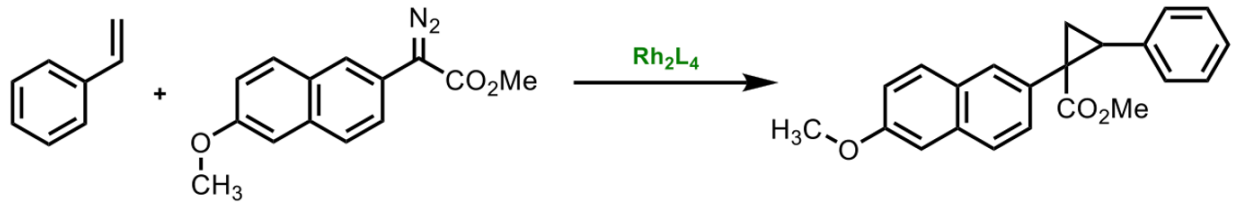


5.2) Kinetic Studies on Asymmetric Cyclopropanation with Low Catalyst Loading

General Remarks

All experiments were carried out in oven-dried glassware under argon atmosphere. Flash column chromatography was performed on silica gel. All solvents were distilled using a short-path distillation system the day before or the same day when the reactions were completed. Molecular sieves (4Å) were activated under vacuum at 300 °C over 3 hours and stored in the oven. *In situ* IR experiments were carried out with the Mettler Toledo ReactIR^{TM} 45m instrument. All chemicals were obtained commercially. Styrene was filtered through silica before each experiment. ^{1}H NMR spectra were obtained on a 400 and 600 MHz spectrometer in deuterated chloroform ($CDCl_3$), with residual chloroform taken as an internal standard (7.26 ppm for 1H, and 77.23 ppm for 13C), and were reported in parts per million (ppm). The abbreviations for multiplicity are as follows: s= singlet, d= doublet, t= triplet, q= quartet, p= pentet, m= multiplet, dd= doublet of doublet, etc. Coupling constants (J values) are obtained from the spectra. TLC was done on aluminum-back silica gel plates with UV light to visualize.

5.2.1) General Procedure for Catalyst Screening



A 20 ml vial equipped with a small stir bar and 4 Å activated molecular sieves was flame dried and evacuated. The flask was then purged with inert atmosphere (nitrogen) and the cycle was repeated an additional time prior to the addition of dirhodium catalyst (0.5 mol%, 0.0025 mmol) to the vial. The purge cycle was repeated once more, then alkene (10 equiv. 5.0 mmol) was added via syringe. The mixture was then dissolved in DCM (2.5mL). The solution was stirred for 5 mins under argon at rt to allow the reagents an opportunity to mix thoroughly. In a separate vial, diazo (0.500 mmol) was dissolved in DCM (2.5 ml). The diazo solution was then loaded into a syringe. Then diazo was added to the stirring solution over 2 mins via syringe and the mixture was left to run overnight. The next day, the solvent was evaporated and the crude material was subjected to flash column chromatography and product containing fractions were aggregated and solvent was removed *in vacuo* to yield the desired product. Asymmetric induction (%ee) was determined by chiral HPLC or SFC.

5.2.2) React IR Protocols

The ReactIR^{TM} instrument was filled with liquid nitrogen and allowed to equilibrate while the reaction flask was being set-up. An oven-dried 100 mL 3-neck round-bottom flask with 4 Å

molecular sieves was fitted with a rubber septum (left neck, 14/20), ReactIR^{TM} probe (center neck, 24/40 to 19/25 adapter, 19/25 neck), and argon inlet (right neck, 14/20)

Figure 5.1 REACT-ID Setup

The flask was cooled to room temperature under vacuum, and then backfilled with argon. The flask was placed in a water or oil bath, with the temperature of the stir plate set to the desired temperature and stir rate on 700 rpm. Once the reaction flask was at the desired temperature, the background and water vapor spectrum were taken via the ReactIR^{TM} instrument. The syringe and needle used for the solvent was primed with argon from the flask before adding solvent through the rubber septum. The data collection was started on the software, and the solvent was allowed to stir for 15 minutes. After a reference spectrum of the solvent was taken, styrene was added using a plastic syringe. The reaction mixture was allowed to stir while the diazo carbonyl compound was weighed out. A reference spectrum of styrene was taken after subtracting out the solvent spectrum, and then the diazo compound was added by removing and then quickly replacing the rubber septum.

A reference spectrum was taken of the diazo compound after subtracting out the reference spectrum of styrene, and the reaction mixture was allowed to stir for 15 minutes. 1 mL of the catalyst stock solution (created by measuring out the calculated amount of catalyst, dissolved in 25 mL of solvent, then 1 mL of the 25 mL was taken out and diluted to 10 mL to create the catalyst stock solution) was added to the reaction mixture and was allowed to stir until the complete consumption of the diazo compound, determined by the diazo stretching frequency (2103 cm^{-1}).

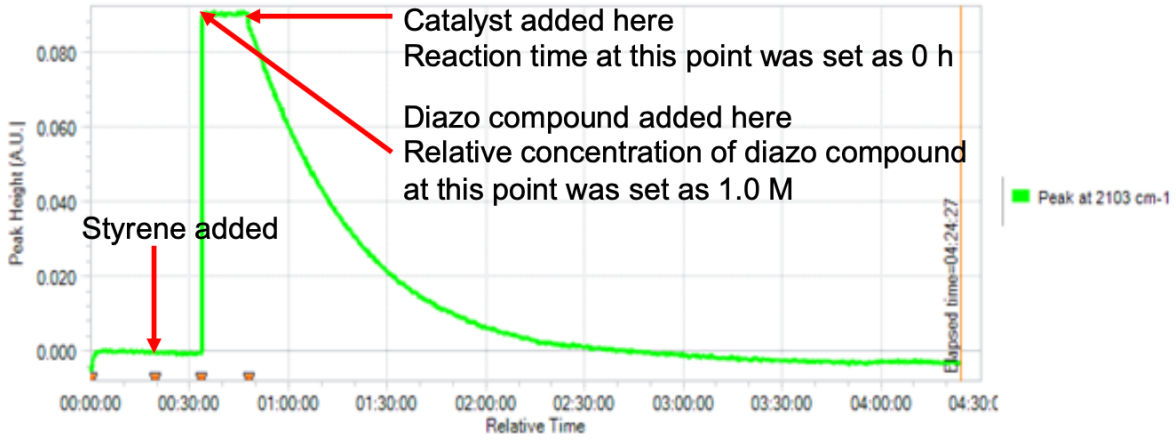


Figure 5.2 Sample data for REACT-IR

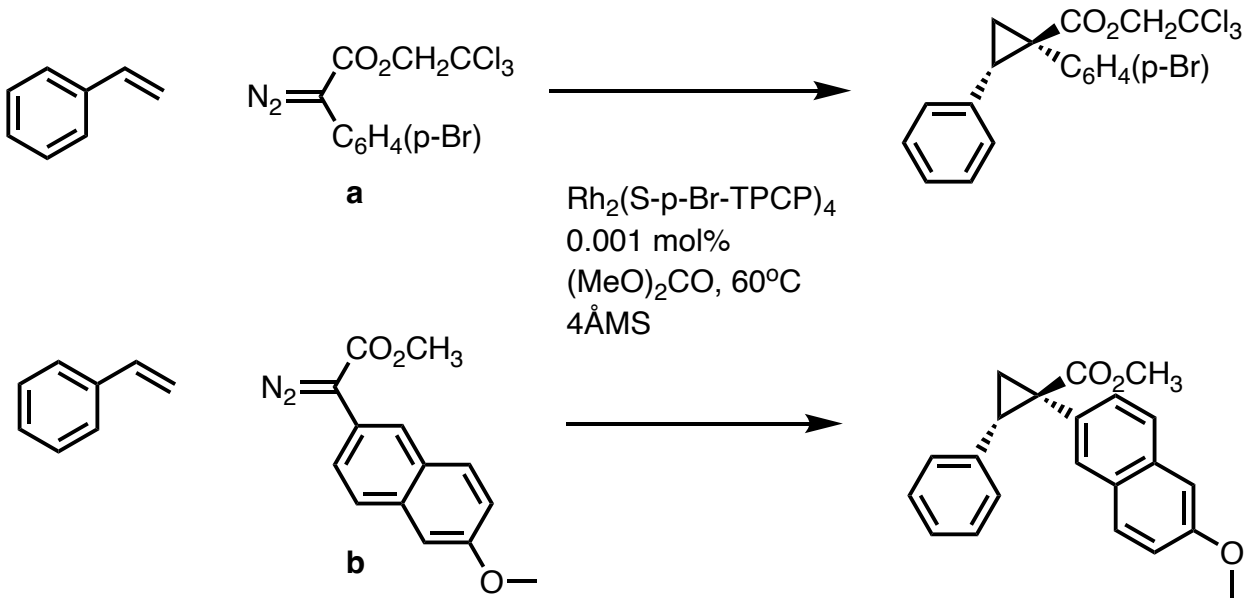
The data was extracted directly from the software as a text-file and copied into Microsoft Excel. The point at which the curve rises sharply at a right angle, around the 30-minute mark, is where the diazo carbonyl compound was added to the reaction mixture. Where the curve starts to decrease, around the 45-minute mark, is where the catalyst solution was injected. The absorbance point and relative time at which the catalyst was added, all the way until the end of the data collection period, set as the beginning of the diazo decomposition curve. The first time point in the diazo decomposition curve is set as “00:00:00” (HH:MM:SS) by subtracting the relative time at that

point from itself, and all subsequent time points are set by subtracting the relative time of the beginning of the data set from the relative time extracted from Figure 24. To normalize the absorbance, the absorbance of the first point in the data set is set as "1," obtained from dividing the absorbance of the first point by itself, and all subsequent absorbances are divided by the absorbance of the first point. In doing so, it is possible to get the relative concentration of diazo and to monitor the time of the diazo decomposition.

5.2.3) Preparation of Stock Solution for Low Catalyst Loading & General Procedure for Kinetic Cyclopropanation

catalyst	MW (g/mol)	Weight of catalyst.in 25ml stock solution (mg)
Rh_2(*S*-*p*-Br-TPCP)$_4$	1774.28	11.9

Catalyst wreight used in stock solution is shown in Figure. Given amount of catalyst (0.006725 mmol) was dissolved in 25 ml dichloromethane in a volumetric flask, then 2.5 mL out of the 25 mL was taken out and diluted up to 10 mL dichloromethane in a volumetric flask to create the catalyst stock solution, 0.00006725 mmol/ml. 0.4 ml of this solution was used to perform each reaction in order to achieve 0.001 mol% catalyst loading.



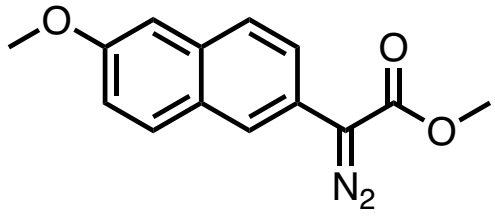
Following **general procedure 5.2.2**, the flask was placed in a 25 °C water bath. 27.0 ml dimethyl carbonate was added through the rubber septum. After a reference spectrum of diemthyl carbonate was taken, 0.72 ml (2.32 equiv, 6.24 mmol, 0.232 M) styrene was added. The reaction mixture was allowed to stir while the 1.000 g (1.0 equiv, 2.7 mmol, 0.1 M) diazo compound **a or b** was weighed out. The reaction was heated to 60 °C and equilibrated for 15 minutes. A reference spectrum of styrene was taken after subtracting out the solvent spectrum, and then the diazo compound **a or b** was added by removing and quickly replacing the rubber septum. The reaction mixture was allowed to stir for 15 min. 0.4 mL of the catalyst stock solution (Based on the weight of each catalyst as displayed in **Table**) was added to the reaction mixture and allowed to stir until the complete consumption of the diazo compound (as determined by disappearance of the characteristic peak at 2103 cm^{-1}) by ReactIR.

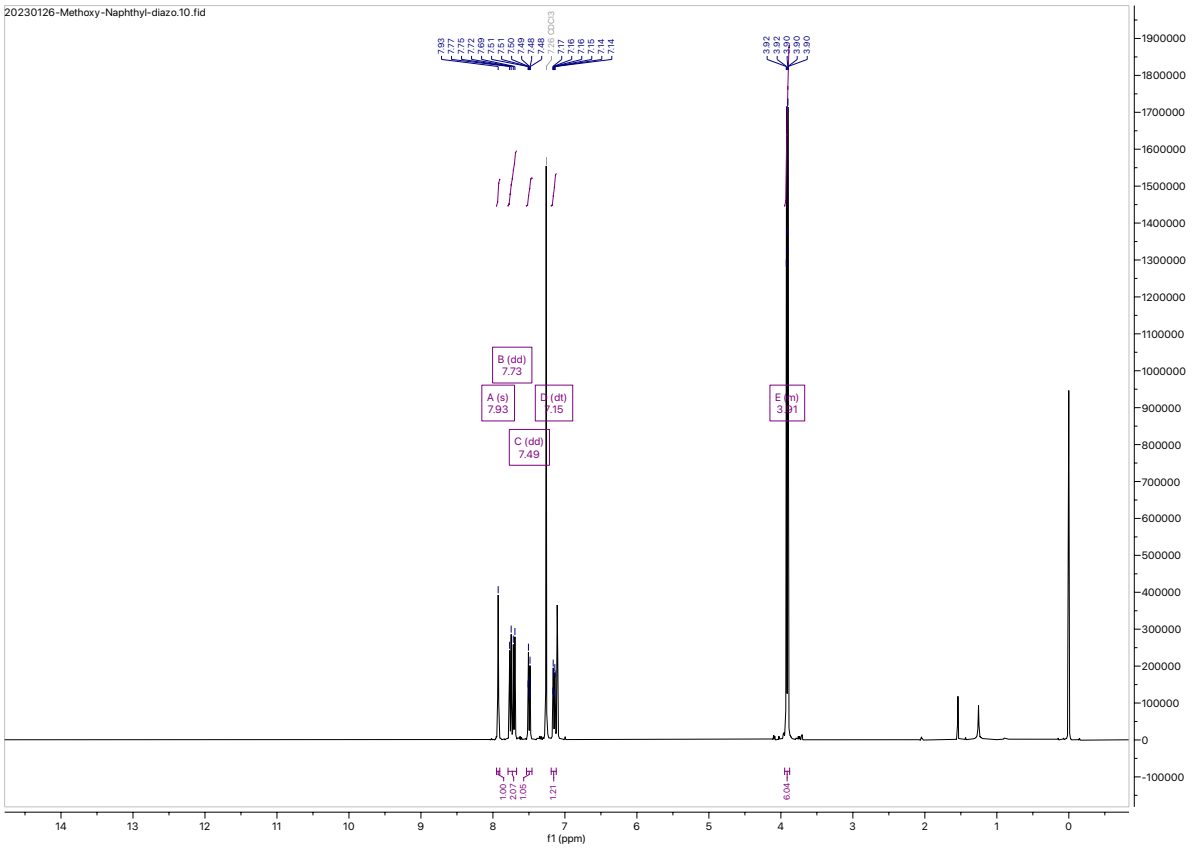
5.2.4) Experimental Methods for Diazo Synthesis of Scheme 1

To a flame dried RBF with a stir bar was added: 2-bromo-6-methoxynaphthalene (10 g, 1 Eq, 42 mmol), potassium phosphate (36 g, 4 Eq, 0.17 mol), di-tert-butyl Xphos (1.8 g, 0.1 Eq, 4.2 mmol) anddiacetoxypalladium (0.47 g, 0.05 Eq, 2.1 mmol). The reaction vessel was backfilled with N_2 three times. Toluene (3.9 g, 0.30 L, 0.14 molar, 1 Eq, 42 mmol) was syringed into the vessel, followed bymethyl 3-oxobutanoate (15 g, 14 mL, 3 Eq, 0.13 mol). The reaction vial was sealed under N2 atmosphere and heated under vigorous stirring at 100°C for 16h. 100mL of DI water was added to quench the reaction. The solution was diluted with EtOAc.The phases were separated. The organic layer was dried over $MgSO_4$, filtered and the solution was concentrated to dryness.

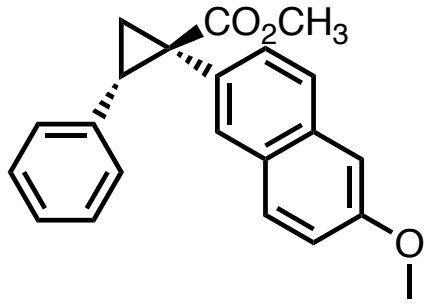
The crude mixture was directly subjected to the next step, which is diazo synthesis. Add 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (224 mg, 221 µL, 2 Eq, 1.47 mmol) in dichloromethane (62.4 mg, 7.34 mL, 0.1 molar, 1 Eq, 734 µmol) to a solution of methyl 2-(6-methoxynaphthalen-2-yl)-3-oxobutanoate (200 mg, 1 Eq, 734 µmol) and 2-nitrobenzenesulfonyl azide (335 mg, 2 Eq, 1.47 mmol) in dichloromethane (62.4 mg, 7.34 mL, 0.1 molar, 1 Eq, 734 µmol) at 0 °C. Stir the mixture for 6 hours at room temperature. Add 5% aqueous NaOH (10 mL) to the resulting mixture. Extract the mixture with Et_2O (2 x 50 mL). Wash the combined organic layer with water (30 mL) and brine (2 x 30 mL). Dry the combined organic layer over anhydrous Na_2SO_4. Filter the combined organic layer. Evaporate the combined organic layer in vacuo. Purify the crude product by column chromatography (silica gel, 15/1 hexane/EtOAc).

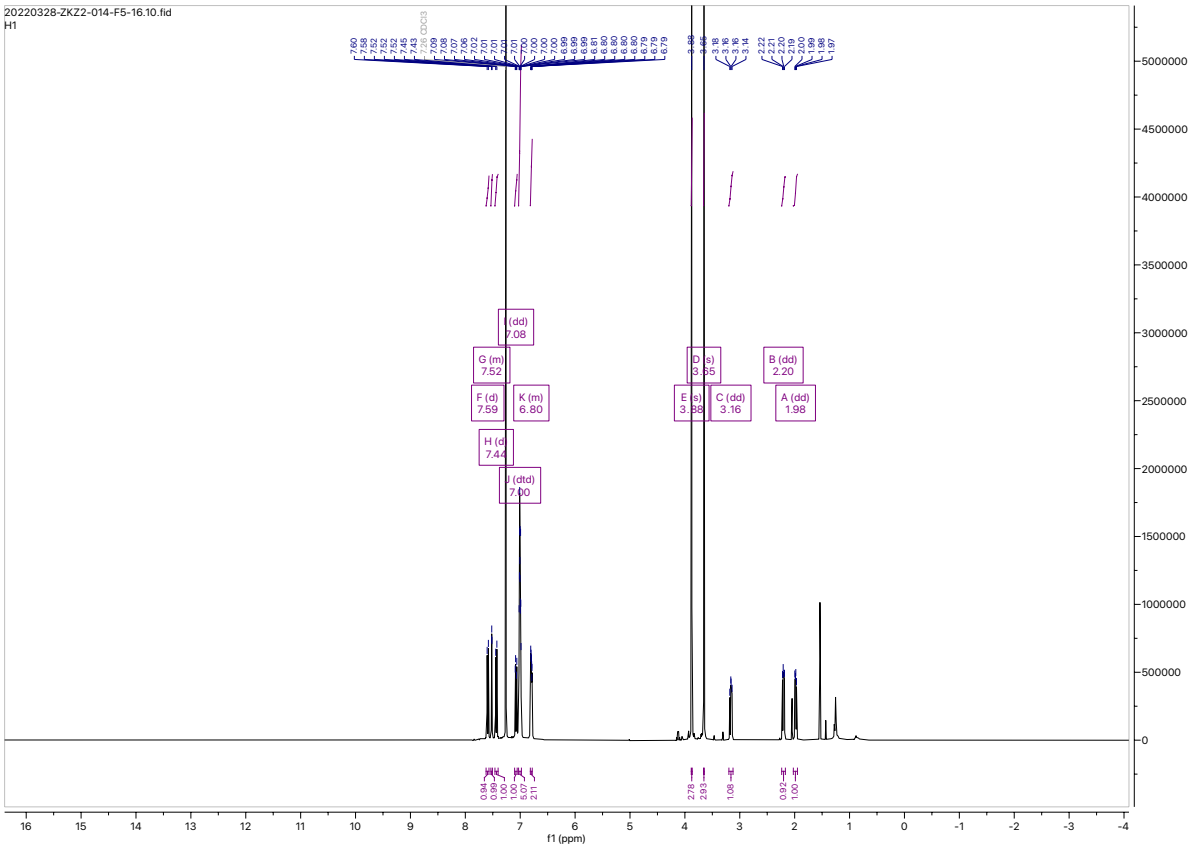
5.2.5) NMR Spectra





^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (m, 1H), 7.79 – 7.68 (dd, 2H), 7.50 (d, 1H), 7.18-7.13 (d, 1H), 7.11 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H).

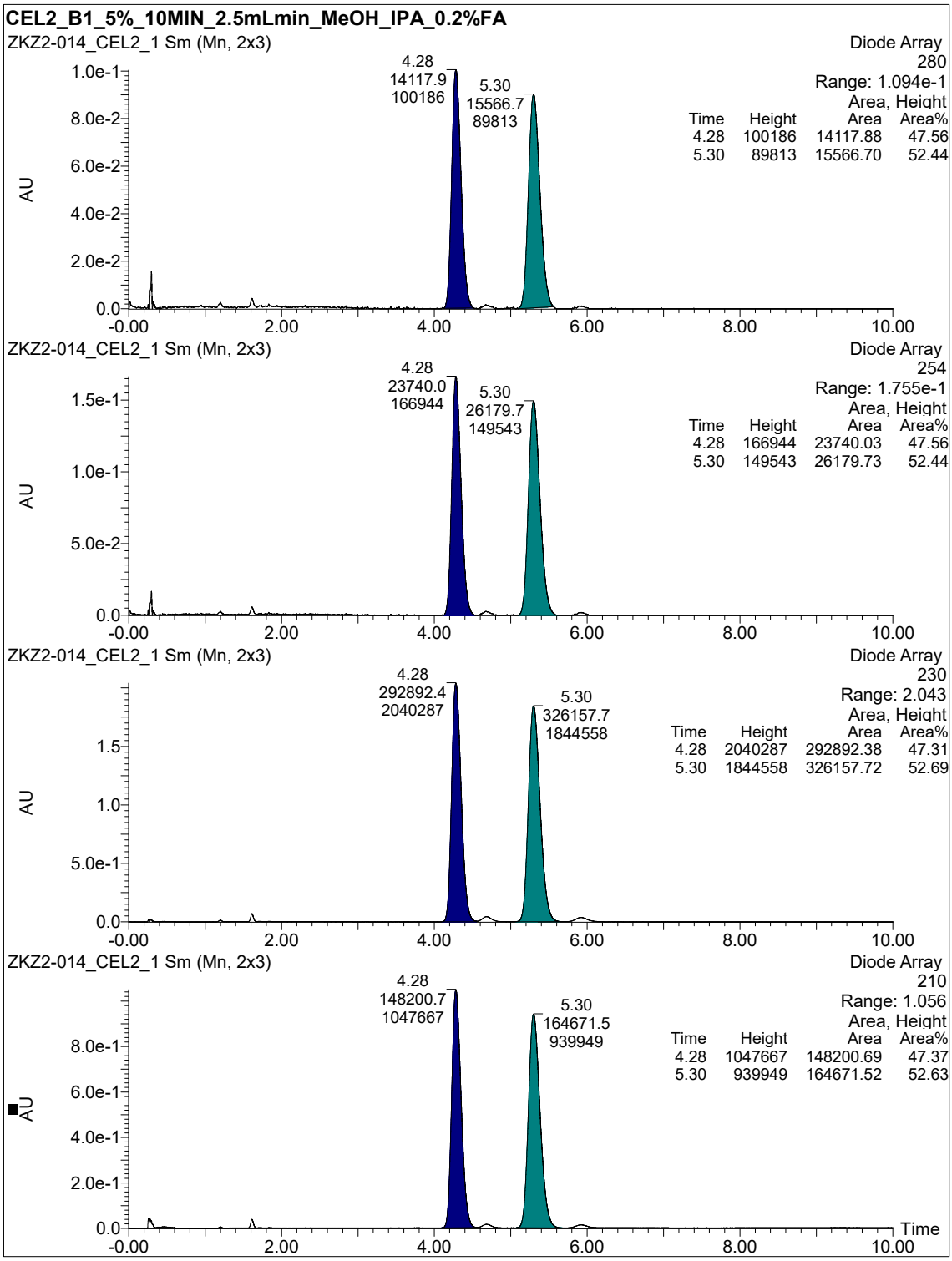




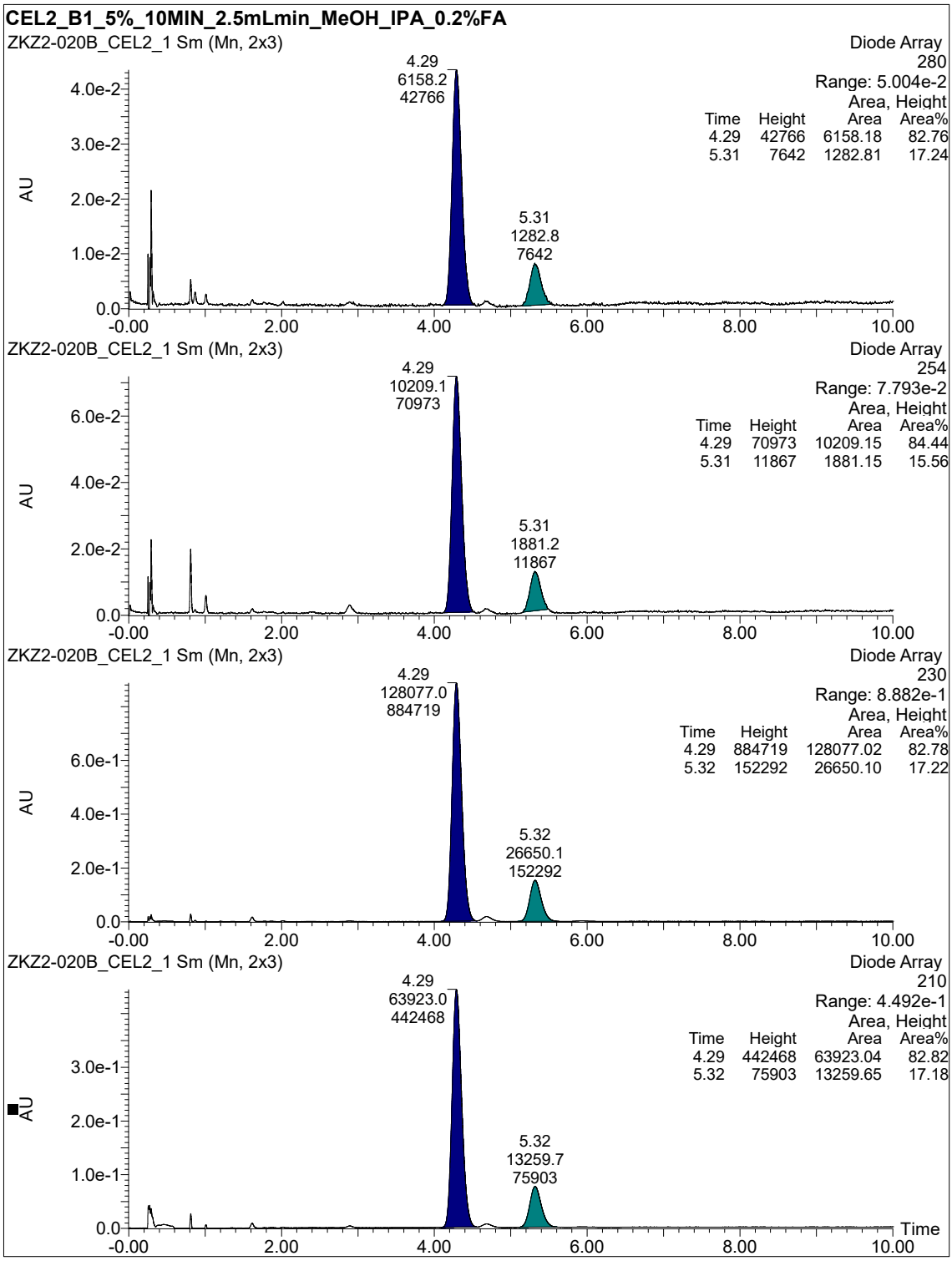
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 (d, 8.9 Hz, 1H), 7.52 (m, 1H), 7.44 (d, 8.5 Hz, 1H), 7.08 (dd, 8.9 Hz, 2.5Hz, 1H), 7.00 (m, 5H), 6.80 (m, 2H), 3.88 (s, 3H), 3.65 (s, 3H), 3.16 (dd, 9.3 Hz, 7.3 Hz, 1H), 2.20 Hz (dd, 9.3 Hz, 4.8 Hz, 1H), 1.98 (dd, 7.3 Hz, 4.8 Hz, 1H).

5.2.6) SFC Traces for Determination of Enantioselectivity (Catalyst Screening)

Rh_2(R/S-DOSP)$_4$


CEL2_B1_5%_10MIN_2.5mLmin_MeOH_IPA_0.2%FA
ZKZ2-014_CEL2_1 Sm (Mn, 2x3)
Diode Array
280
Range: 1.094e-1
Area, Height
4.28
14117.9
100186
5.30
15566.7
89813
Time Height Area Area%
4.28 100186 14117.88 47.56
5.30 89813 15566.70 52.44
AU
ZKZ2-014_CEL2_1 Sm (Mn, 2x3)
Diode Array
254
Range: 1.755e-1
Area, Height
4.28
23740.0
166944
5.30
26179.7
149543
Time Height Area Area%
4.28 166944 23740.03 47.56
5.30 149543 26179.73 52.44
AU
ZKZ2-014_CEL2_1 Sm (Mn, 2x3)
Diode Array
230
Range: 2.043
Area, Height
4.28
292892.4
2040287
5.30
326157.7
1844558
Time Height Area Area%
4.28 2040287 292892.38 47.31
5.30 1844558 326157.72 52.69
AU
ZKZ2-014_CEL2_1 Sm (Mn, 2x3)
Diode Array
210
Range: 1.056
Area, Height
4.28
148200.7
1047667
5.30
164671.5
939949
Time Height Area Area%
4.28 1047667 148200.69 47.37
5.30 939949 164671.52 52.63
AU
Time

Rh_2(S-DOSP)$_4$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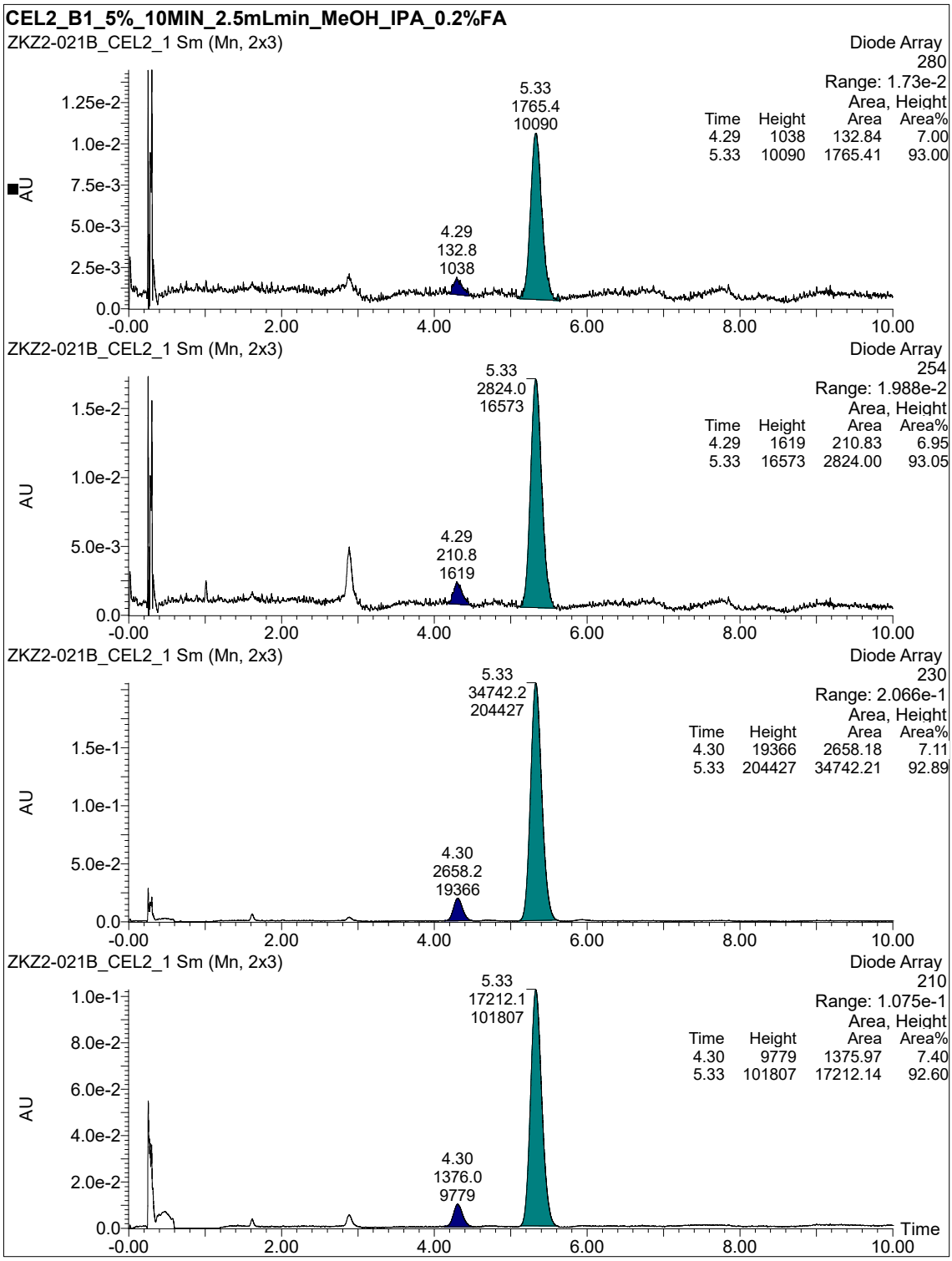
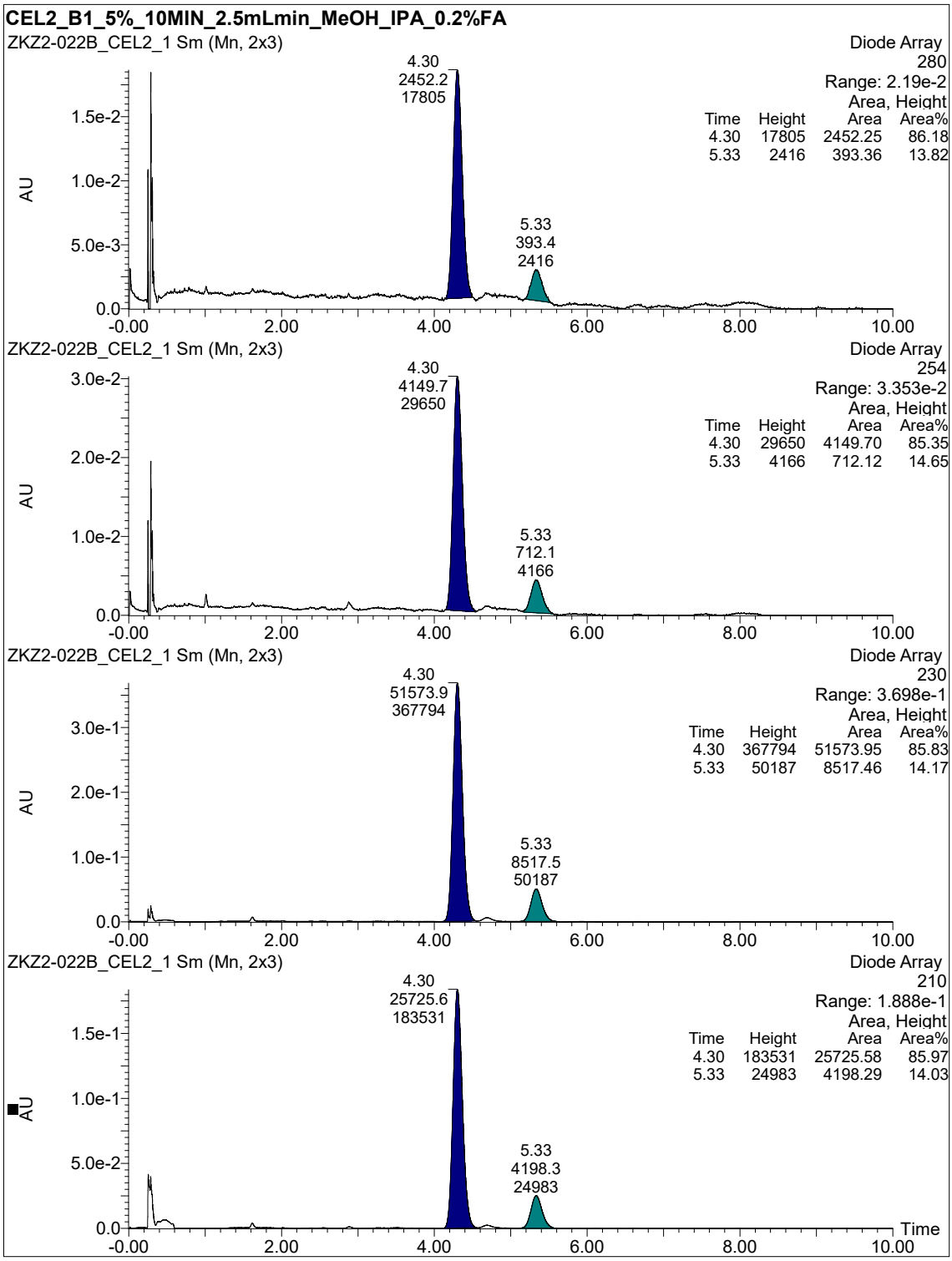
Diode Array
280
Range: 5.004e-2
Area, Height
Time Height Area Area%
4.29 42766 6158.18 82.76
5.31 7642 1282.81 17.24
4.29
6158.2
42766
5.31
1282.8
7642
AU
ZKZ2-020B_CEL2_1 Sm (Mn, 2x3)
Diode Array
254
Range: 7.793e-2
Area, Height
Time Height Area Area%
4.29 70973 10209.15 84.44
5.31 11867 1881.15 15.56
4.29
10209.1
70973
5.31
1881.2
11867
AU
ZKZ2-020B_CEL2_1 Sm (Mn, 2x3)
Diode Array
230
Range: 8.882e-1
Area, Height
Time Height Area Area%
4.29 884719 128077.02 82.78
5.32 152292 26650.10 17.22
4.29
128077.0
884719
5.32
26650.1
152292
AU
ZKZ2-020B_CEL2_1 Sm (Mn, 2x3)
Diode Array
210
Range: 4.492e-1
Area, Height
Time Height Area Area%
4.29 442468 63923.04 82.82
5.32 75903 13259.65 17.18
4.29
63923.0
442468
5.32
13259.7
75903
AU
Time

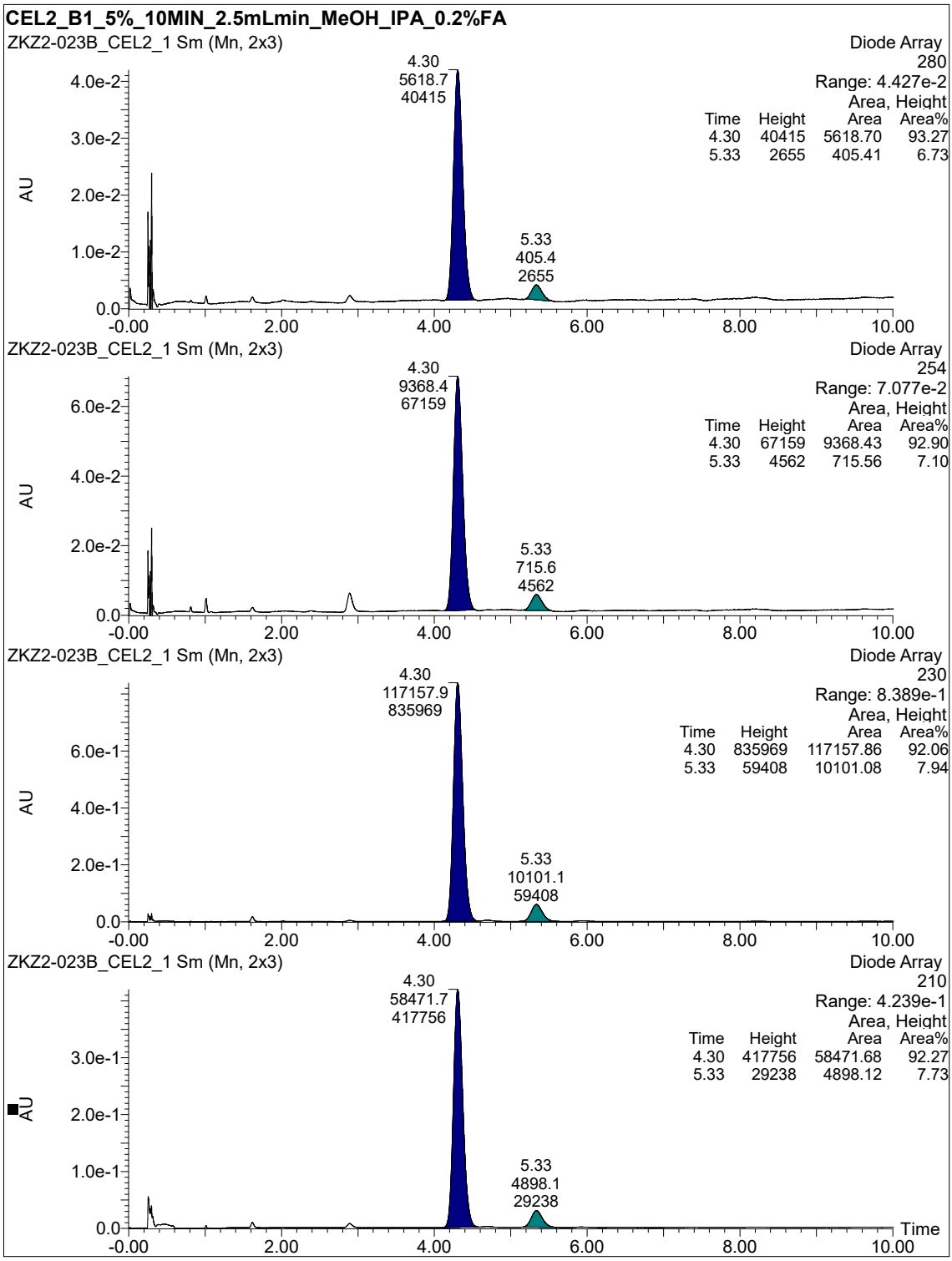
Rh_2(R-p-Ph-TPCP)$_4$



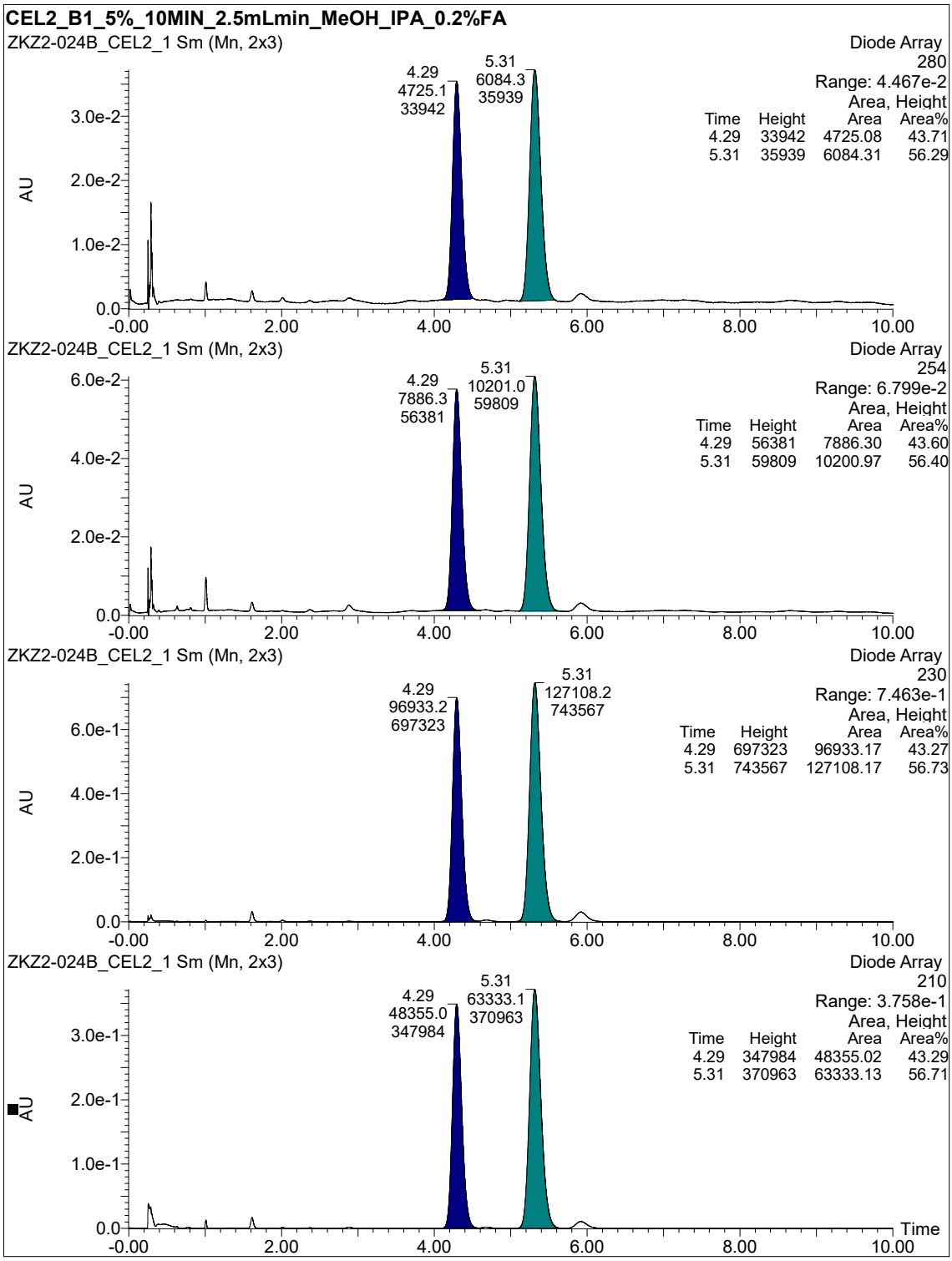
Rh_2(S-TPPTTL)$_4$



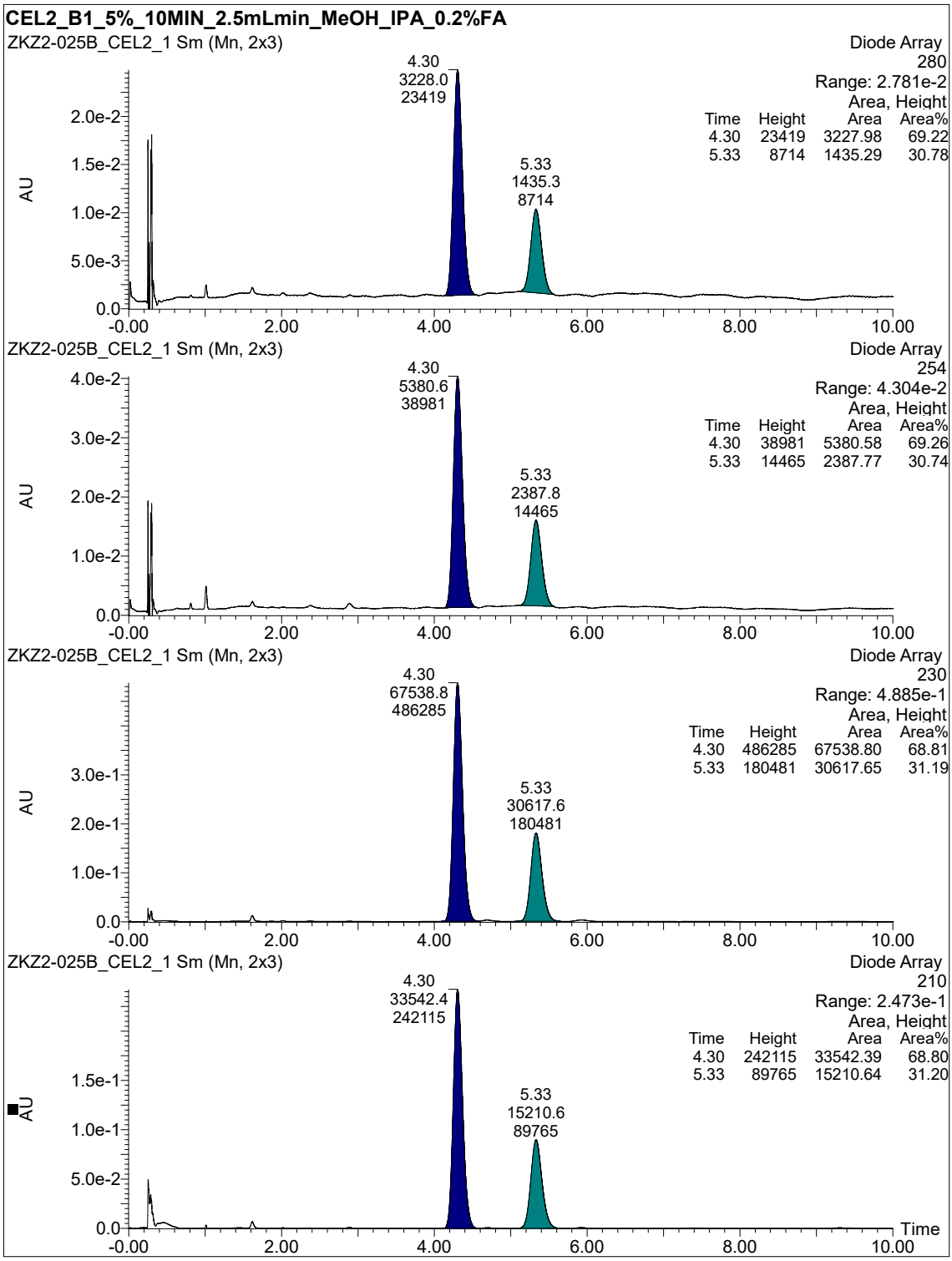
Rh_2(S-p-Br-TPCP)$_4$



$Rh_2(R\text{-}TCPTAD)_4$



Rh_2(R-PTAD)$_4$


CEL2_B1_5%_10MIN_2.5mLmin_MeOH_IPA_0.2%FA
ZKZ2-025B_CEL2_1 Sm (Mn, 2x3)
Diode Array
280
Range: 2.781e-2
Area, Height
Time Height Area Area%
4.30 23419 3227.98 69.22
5.33 8714 1435.29 30.78
4.30
3228.0
23419
5.33
1435.3
8714
AU
Time
ZKZ2-025B_CEL2_1 Sm (Mn, 2x3)
Diode Array
254
Range: 4.304e-2
Area, Height
Time Height Area Area%
4.30 38981 5380.58 69.26
5.33 14465 2387.77 30.74
4.30
5380.6
38981
5.33
2387.8
14465
AU
ZKZ2-025B_CEL2_1 Sm (Mn, 2x3)
Diode Array
230
Range: 4.885e-1
Area, Height
Time Height Area Area%
4.30 486285 67538.80 68.81
5.33 180481 30617.65 31.19
4.30
67538.8
486285
5.33
30617.6
180481
AU
ZKZ2-025B_CEL2_1 Sm (Mn, 2x3)
Diode Array
210
Range: 2.473e-1
Area, Height
Time Height Area Area%
4.30 242115 33542.39 68.80
5.33 89765 15210.64 31.20
4.30
33542.4
242115
5.33
15210.6
89765
AU
Time

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DOI: 10.1021/acscatal.2c03041

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