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Carolyn Ma April 3, 2023

Synthesis and Evaluation of Novel Phenyl-Adamantyl Dirhodium Catalyst for C-H Functionalization

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a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

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Phthalimide-based dirhodium catalysts PTAD and TCPTAD are capable of catalyzing highly selective cyclopropanation and C-H functionalization reactions. However, their synthetic routes are difficult and risky to carry out. A novel phenyladamantyl (PHAD) dirhodium catalyst was developed that features a 3-step synthesis that is safer and more straightforward than the syntheses of phthalimide-based catalysts. A crucial step of the synthesis of PHAD is a tertiary C-H functionalization reaction of adamantane that has been optimized to 3rd generation Davies Group methodologies. Dirhodium *p*-Br-PHAD was evaluated in a series of cyclopropanation and C-H functionalization reactions, exhibiting moderate levels of stereoselectivity and site selectivity. This work demonstrates that with further ligand optimization, dirhodium PHAD catalysts could offer a more accessible alternative to phthalimide-based dirhodium catalysts.

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1.) Introduction

1.1) Dirhodium-Catalyzed C-H Functionalization

C-H functionalization is a powerful synthetic tool that allows for the direct modification of C-H bonds to useful C-C or C-functional group bonds. Whereas traditional organic methods focus on conversion of specific functional groups on a molecule, C-H functionalization enables transformations along the molecule's skeleton. As such, C-H functionalization represents a paradigm shift in the logic of chemical transformations and synthesis.[1]

C-H functionalization was previously considered an unviable approach in synthesis because the high bond strength of C-H bonds makes them relatively inert to many common reagents.[2] It is the development of metal catalysts that has made useful C-H functionalization reactions possible. These catalysts can either directly insert in a C-H bond or help facilitate radical or carbene chemistry, and they have been successfully employed in a variety of C-H functionalization reactions.[3] Currently, the grand challenge in C-H functionalization is achieving site-selectivity. A given molecule typically contains numerous C-H bonds, each with similar reactivity; it is a challenging prospect to functionalization one given C-H bond without functionalizing the others as well. Several approaches have been developed to address this problem, including reliance on intramolecular reactions and the use of directing groups.[4,5]

Instead of these substrate-focused strategies, the Davies Group uses catalysts to control site-selectivity. Although it is challenging to design catalysts that can differentiate between C-H bonds with very small electronic and steric variances, this catalyst-controlled approach provides great versatility. Using dirhodium catalysts that form rhodium-carbene complexes, the Davies group has developed a method for conducting highly selective intermolecular C-H

functionalization and cyclopropanation reactions. Since 1996, the Davies Group has synthesized several powerful dirhodium (II) catalysts with various ligands (Figure 1).

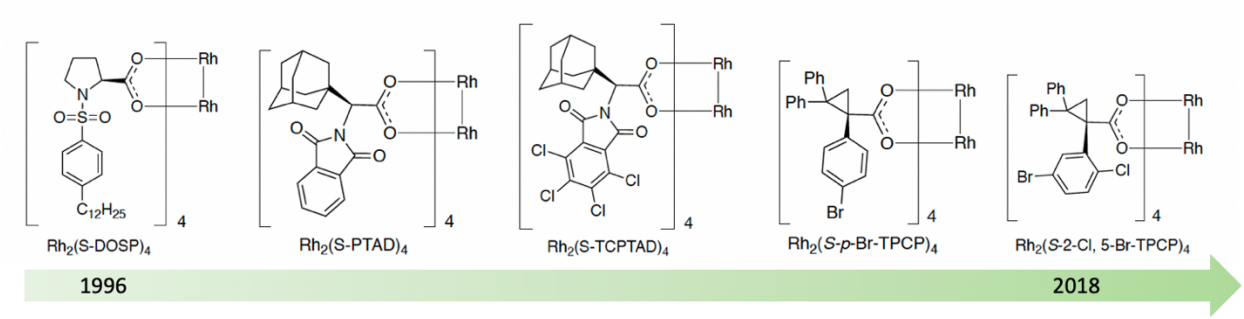


Figure 1. Davies Group dirhodium (II) catalyst timeline.

A common feature of these catalysts is their bowl-shaped conformation, with the chiral ligands of the catalyst contributing to the high levels of enantioselectivity. The first generation of catalysts have prolinate-based ligands, with $Rh_2(DOSP)_4$ exhibiting the ability to catalyze cyclopropanation reactions with very high diastereo- and enantioselectivity.[6] The second generation of dirhodium catalysts include phthalimide-based catalyst $Rh_2(PTAD)_4$ and are able to catalyze highly selective cyclopropanation reactions with a wider variety of donor/acceptor carbenes than the first generation.[7] The current, third generation of catalysts include $Rh_2(TCPTAD)_4$, $Rh_2(S\text{-}p\text{-Br-TPCP})_4$, and $Rh_2(S\text{-2-Cl-5-BrTPCP})_4$, which are able to selectively catalyze C-H functionalization reactions in addition to cyclopropanation reactions.[8]

Dirhodium catalyzed C-H functionalization and cyclopropanation reactions both proceed through the formation of a rhodium carbenoid complex, which is formed when the electron-rich central carbon of the diazo compound coordinates with the dirhodium catalyst. Backbonding from the catalyst leads to the loss of N_2 to drive the carbenoid complex formation, and from there the complex can interact with a substrate to perform a C-H functionalization or cyclopropanation reaction.

The known catalytic cycle of dirhodium-catalyzed cyclopropanation and C-H functionalization reactions are shown below (Figure 2).[10]

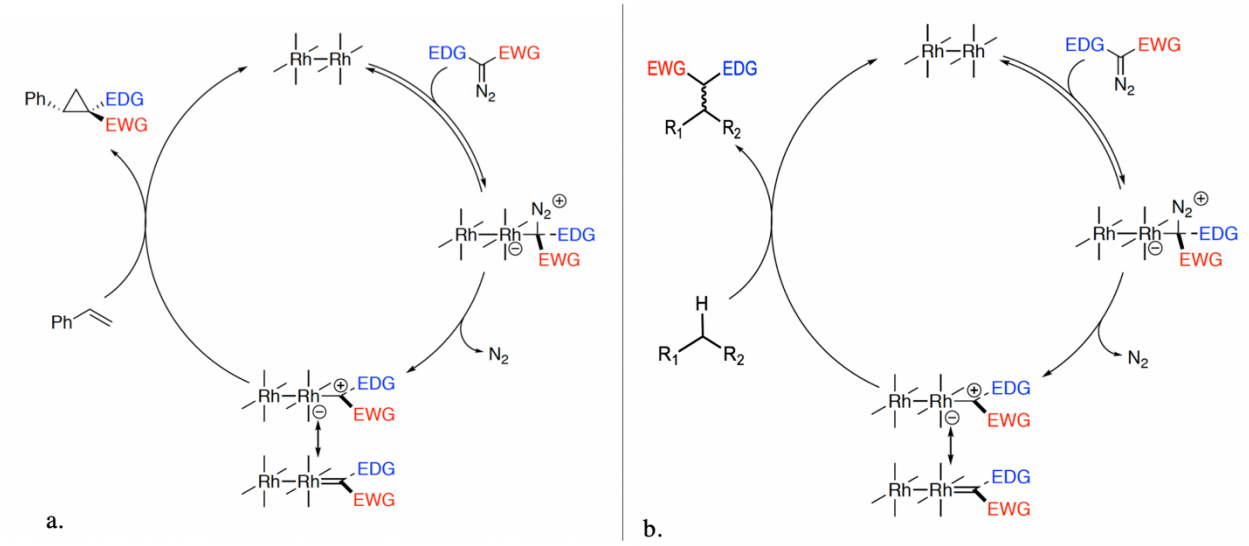
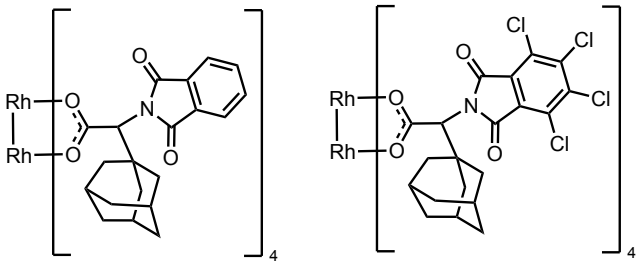


Figure 2. General mechanism for (a) dirhodium-catalyzed cyclopropanation and (b) dirhodium catalyzed C-H functionalization.

The substituents attached to the carbene carbon play a crucial role in influencing the stability of the carbenoid complex, as well as diastereoselectivity of the reaction. The Davies Group discovered that "donor-acceptor" carbenes, in which one substituent is an electron donating group and the other is an electron withdrawing group, are ideal for controlling both of these aspects.[9] "Acceptor-acceptor" carbenes are extremely reactive because of electron deficiency at the carbene center, which makes preventing dimerization and controlling selectivity of their reactions very difficult. On the other hand, "donor-donor" carbenes are stabilized by electron donation from substituents, making them relatively unreactive. "Donor-acceptor" carbenes are reactive enough to be used in a wide variety of reactions, while being far more selective and less prone to dimerization than acceptor-only carbenes.

1.2) Dirhodium PTAD and TCPTAD

The first phthalimide-based dirhodium catalyst series was originally developed by Hashimoto, which featured ligands consisting of a phthalimide and an alkyl group[11]. The Davies Group expanded on this catalyst series with the development of $Rh_2(PTAD)_4$ and $Rh_2(TCPTAD)_4$, which are among the best-performing catalysts developed by the Davies Group. The Davies Group has found that replacement of Hashimoto's smaller alkyl groups with adamantane led to a catalyst with greater enantioselectivity, likely because the increased bulk of adamantane better blocks substrate approach from the underside of the catalyst.[12]



$Rh_2(PTAD)_4$ $Rh_2(TCPTAD)_4$

Figure 3. Structures of $Rh_2(PTAD)_4$ and $Rh_2(TCPTAD)_4$.

PTAD was developed in 2006 as part of the 2nd generation of Davies Group catalysts, and it is capable of performing cyclopropanation reactions with high enantio- and diastereoselectivity.[7] However, it is not very useful in C-H functionalization because its conformational flexibility prevents PTAD from exhibiting high site selectivity. The corresponding tetrachlorophthalimido catalyst TCPTAD is a 3rd generation catalyst that is useful in both cyclopropanation and C-H functionalization reaction because it is conformationally rigid.[13] The addition of four chlorines expands the bowl of TCPTAD and causes the catalyst to adopt a stable C4 symmetric conformation. TCPTAD has been found to selectively functionalize tertiary C-H bonds, which are electronically preferred but are less sterically accessible.[14]

The original and currently used syntheses of PTAD are shown below (Figure 4).

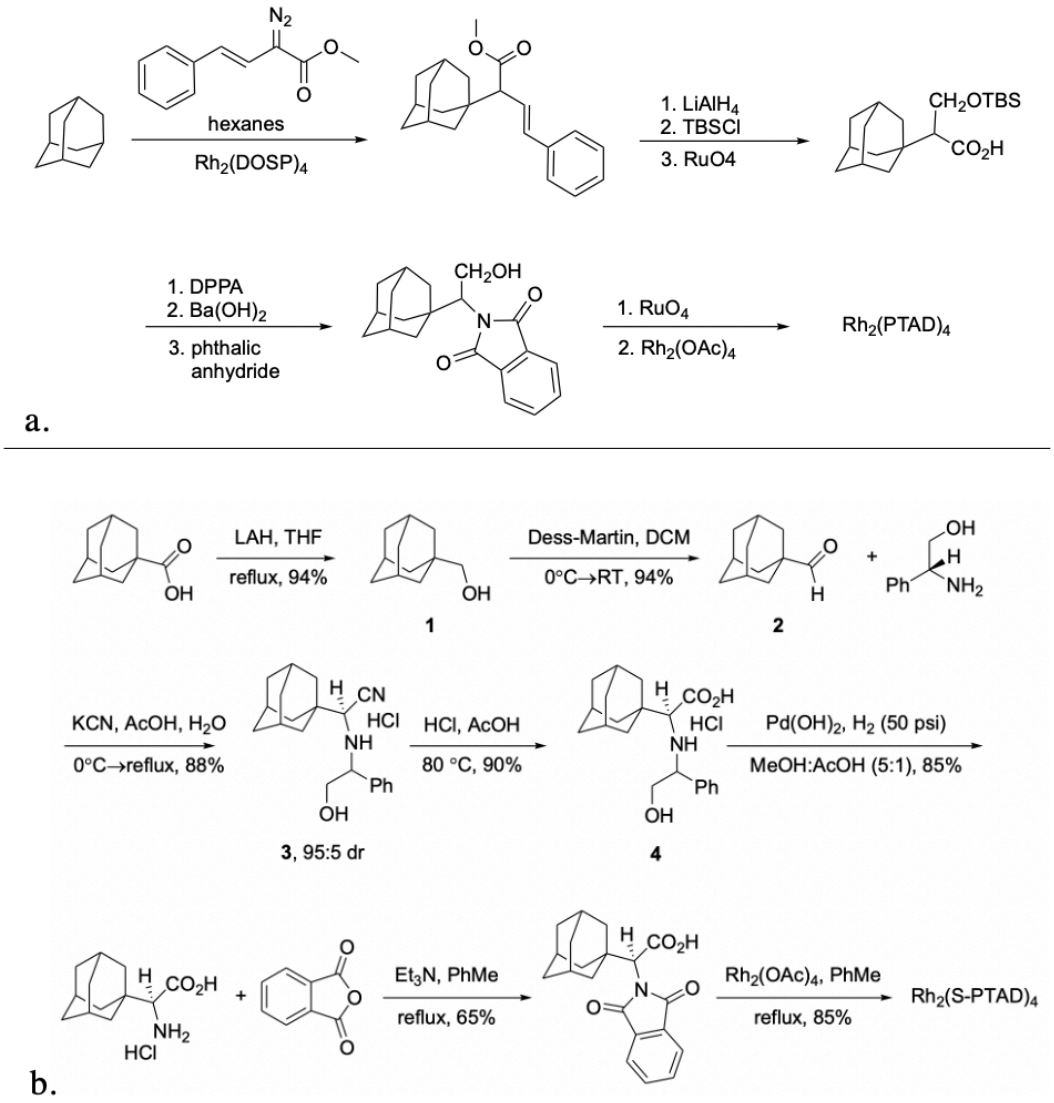


Figure 4. (a) Original synthesis $Rh_2(PTAD)_4$.[7] (b) Current Davies Group procedure for synthesis of $Rh_2(PTAD)_4$.

The published synthesis of PTAD (Figure 4a) was inspired by Davies C-H functionalization chemistry.[7] It is a challenging procedure, however, involving many steps. The key step of C-H functionalization of adamantane is followed by an ester reduction to an alcohol, protection of the alcohol as a silyl ether, and oxidative cleavage of the alkene. The resulting acid then undergoes a Curtius rearrangement to become an amine, which is converted to a

phthalimide. Finally, the alcohol is oxidized to an acid, which then undergoes ligand exchange with rhodium acetate to form $Rh_2(PTAD)_4$.

This synthesis has several limitations and is no longer used to make PTAD. Ruthenium tetroxide is used twice in the procedure as an oxidizing agent, and it is a highly toxic reagent. In addition, the C-H functionalization step must be heated to 69 °C and this dirhodium reaction is difficult to perform on a larger scale. Other steps are also difficult to scale up, and the Curtius rearrangement product is prone to undergoing undesired cyclizations. This approach generated the early small batches of $Rh_2(PTAD)_4$ but was not suitable for a multigram synthesis.

The current procedure used by the Davies Group (Figure 4b) can be performed on a much larger scale (50-100g). Instead of directly functionalizing adamantane, adamantylcarboxylic acid is used as a precursor and each step gives high yields. However, this synthesis is also not ideal. Specifically, a dangerous Strecker reaction is required to produce intermediate 3. The Strecker reaction uses potassium cyanide, which upon contact with water produces hydrogen cyanide gas, a volatile substance that can be fatal upon inhalation. Therefore, although this synthesis of PTAD is scalable, the safety issues associated with a large-scale Strecker reaction render it undesirable. Consequently, we became interested in exploring whether the C-H functionalization chemistry could be used to generate effective chiral dirhodium catalysts in a more direct and practical manner.

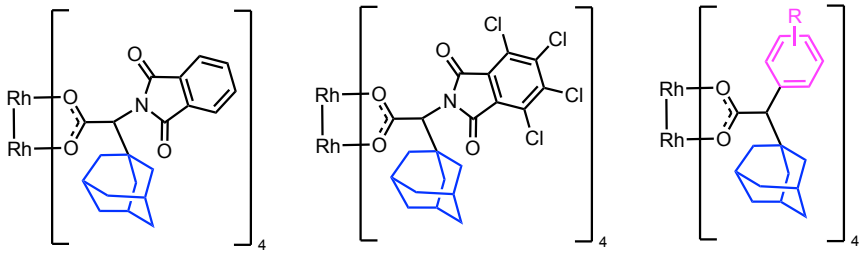
2.) Dirhodium PHAD Design and Synthesis

2.1) Catalyst Design Philosophy

PTAD is capable of carrying out highly enantio- and diastereoselective cyclopropanation reactions, while TCPTAD is also able to selectively functionalize tertiary C-H bonds. However,

these phthalimido catalysts are challenging and risky to synthesize. Therefore, there is a strong interest in developing a new catalyst that is as effective as the phthalimido catalysts but is also easier and safer to synthesize.

For this new catalyst, we envisioned a structure very similar to the PTAD family, retaining the adamantane group but replacing the phthalimide group with a phenyl (Figure 5).



$Rh_2(PTAD)_4$ $Rh_2(TCPTAD)_4$ this work: $Rh_2(PHAD)_4$

Figure 5. Structures of $Rh_2(PTAD)_4$, $Rh_2(TCPTAD)_4$, and $Rh_2(PHAD)_4$.

The retained adamantane will help improve selectivity of this catalyst as it did with PTAD and TCPTAD, by providing bulk to block one face of the catalyst. Meanwhile, elimination of the phthalimide group greatly improves the safety of the synthesis by negating the use of a Strecker reaction and potassium cyanide. Installation of the phenyl group can be achieved with the direct functionalization of adamantane using an aryl diazoacetate, which greatly shortens the synthesis. The goal of this project is to prepare a phenyladamantyl ligand (PHAD), generate the corresponding dirhodium catalyst, and evaluate it in enantioselective cyclopropanation and C-H functionalization. If these proof of principle experiments give reasonable levels of enantioselectivity, then future studies (beyond the scope of this study) will be conducted to generate a library of $Rh_2(PHAD)_4$ catalysts to identify the optimum structure for high asymmetric induction.

2.2) Dirhodium PHAD Synthesis

2.2.1) Overview of Synthesis

The synthesis of PHAD proceeds in a straightforward, 3-step procedure. (Figure 6).

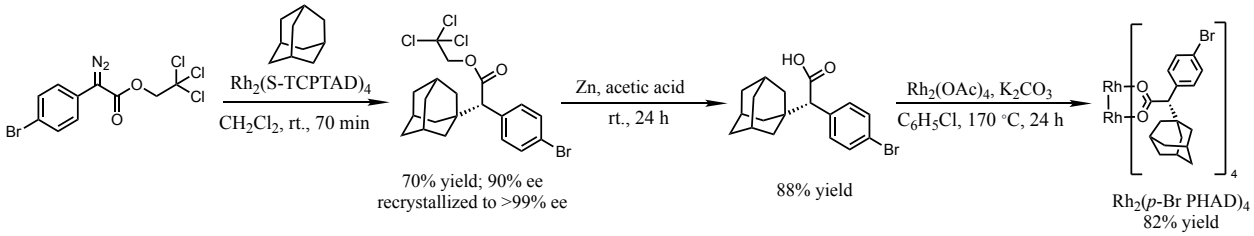


Figure 6. Synthetic route to Rh_2(*p*-Br-PHAD)$_4$.

A tertiary C-H functionalization of adamantane is performed using 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate with 70% yield and 90% ee. After recrystallization of the C-H insertion product to >99% ee, an ester cleavage is performed by stirring with zinc in glacial acetic acid. Finally, a ligand exchange with dirhodium acetate is performed to yield Rh_2(*p*-Br-PHAD)$_4$.

2.2.2) Optimization of Adamantane C-H Functionalization

Although direct C-H functionalization of adamantane was a challenging step in the original synthesis of PTAD, the use of 3rd generation methodologies significantly increases the practicality of this reaction. The C-H functionalization of adamantane using *p*-Br aryl diazoacetate was first reported by the Davies Group in 2000 using 1st generation methodologies (Figure 7).[15]

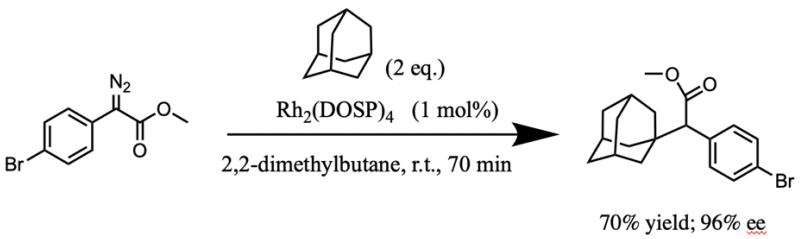


Figure 7. C-H insertion of adamantane using 1st generation methodologies (above).

A methyl-ester was used as the acceptor group for the aryl diazo acetate, and its C-H insertion into adamantane is performed by the catalyst DOSP with 2,2-dimethylbutane as solvent. The reaction gave a 70% yield overall with 96% ee. However, this reaction has several drawbacks and is difficult to reproduce, largely because of the limitations brought on by using DOSP as catalyst. Firstly, DOSP can achieve high selectivity using donor/acceptor carbenes, but only if the acceptor group is a methyl ester[12]. Methyl ester diazo compounds are effective, but cleavage of the ester to form a carboxylic acid requires a relatively tedious procedure. In addition, DOSP achieves greatest asymmetric induction in nonpolar solvents[16]. While the commonly used nonpolar solvent is pentane, the relative inertness of adamantyl C-H bonds compared to pentane requires a solvent with less-reactive C-H bonds. 2,2-dimethylbutane is therefore used as solvent to avoid undesired C-H functionalization of the solvent. However, the use of 2,2-DMB poses several problems. Firstly, 2,2- DMB is not a common solvent, and it is very expensive.[17,18] Secondly, commercial 2,2-DMB frequently suffers from contamination issues. While dirhodium catalysts form a green solution when dissolved in clean solvent, catalyst dissolved in the commercial 2,2-DMB forms a pink solvent (Figure 8).

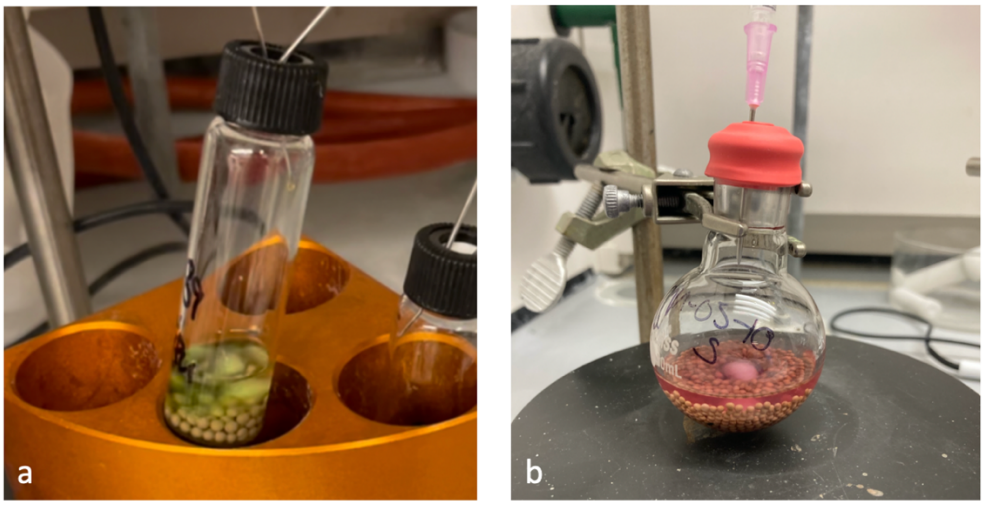
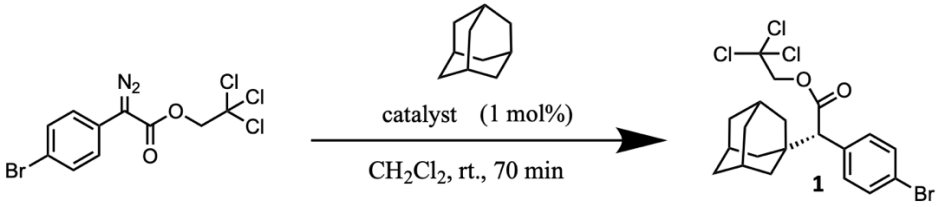


Figure 8. (a) dirhodium catalyst dissolved in clean dichloromethane (green). (b) dirhodium catalyst dissolved in contaminated 2,2-dimethylbutane solvent (pink).

This pink color is an indication of catalyst poisoning from the presence of heteroatom contaminants, and the color persists even after solvent distillation. This solvent contamination issue leads to a difficulty in replicating published yields, while solvent cost and diazo acceptor-group limitations decrease the practicality of this C-H functionalization method.

Fortunately, newer catalysts developed by the Davies Group are tolerant of a wide variety of acceptor groups and solvents. For the optimization reactions, 2,2,2-trichloroethyl ester (TCE) acceptor group aryldiazoacetates were chosen because cleavage of the TCE ester is straightforward.[19] Additionally, dichloromethane was chosen as solvent because of its convenience and cost effectiveness. A catalyst screen was performed to determine the optimal catalyst for these new conditions (Table 1).

Table 1. Optimization of C-H insertion of adamantane using 3rd generation Davies Group methodologies.



entry	catalyst	equivalents adamantane	yield (%)	ee (%)
1	Rh_2(S-DOSP)$_4$	2	46	50
2	Rh_2(S-PTAD)$_4$	2	58	-85
3	Rh_2(S-TCPTAD)$_4$	2	0	x
4	Rh_2(S-TPPTTL)$_4$	2	16	94
5	Rh_2(S-NTTL)$_4$	2	57	28
6	Rh_2(S-BTPCP)$_4$	2	46	22
7	Rh_2(S-TCPTAD)$_4$	5	34	90
8	Rh_2(S-TPPTTL)$_4$	5	16	x*
9	**Rh_2(S-TCPTAD)$_4$**	**10**	**70**	**90**

*further HPLC analysis in progress.

Unsurprisingly, the performance of DOSP was greatly decreased in these conditions, with a 50% ee (Entry 1). NTTL and BTPCP catalyzed these reactions with poor enantioselectivity (Entries 5 & 6), while the preferred enantiomer of PTAD was reversed compared to the other catalysts (Entry 2). TCPTAD resulted in the cleanest reaction by NMR with 90% ee (Entry 7). A 70% yield was achieved after increasing equivalents of adamantane to 10, which decreased side reactions like dimerization (Entry 9). Although TPPTTL catalyzed the reaction with 94% ee (Entry 4), a crude NMR showed a mixture of products and yield did not improve beyond 16%, even with additional equivalents of adamantane (Entry 8).

2.2.3) Final Steps to Completed Catalyst

The C-H insertion product was recrystallized from hexanes 3 times to achieve >99% ee. Crystals formed within 30 min, and the entire process could be completed within a few hours. The enantiopure product was then stirred in acetic acid overnight with 20 equivalents of zinc to deprotect the TCE ester with 88% yield. The ligand's enantiopurity was verified by HPLC before proceeding to the ligand exchange reaction. The ligand exchange reaction was conducted with dirhodium acetate in chlorobenzene under reflux, using a Soxhlet extractor containing potassium carbonate to remove acetic acid. PHAD was produced in 82% yield from this reaction.

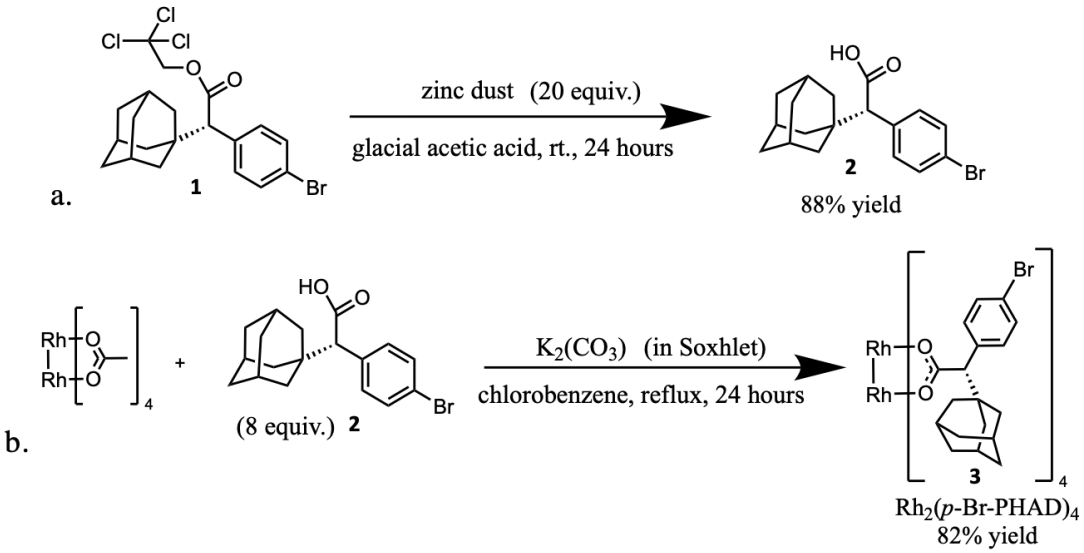


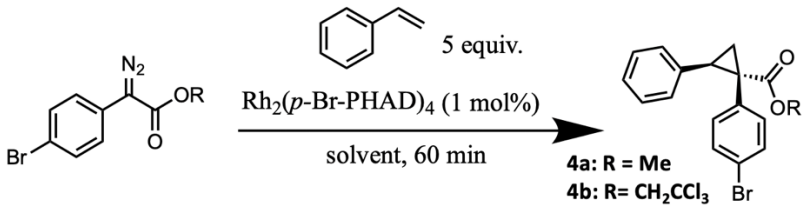
Figure 9. (a) Zinc cleavage of TCE ester. (b) Ligand exchange with dirhodium acetate to give *p*-Br-PHAD.

3.) Dirhodium PHAD Catalyst Evaluation

3.1) Optimization of Model Reaction

Dirhodium PHAD-catalyzed cyclopropanation of *p*-Br aryldiazoacetate with styrene was used as the model reaction for optimization. The reaction was studied with methyl ester and TCE ester acceptor group diazo compounds in the solvents dichloromethane, pentane, and HFIP. The reactions were conducted at room temperature and 0 °C with 4 angstrom molecular sieves were added to reactions in DCM and pentane to sequester any adventitious water.

Table 2. Optimization of model cyclopropanation reaction.



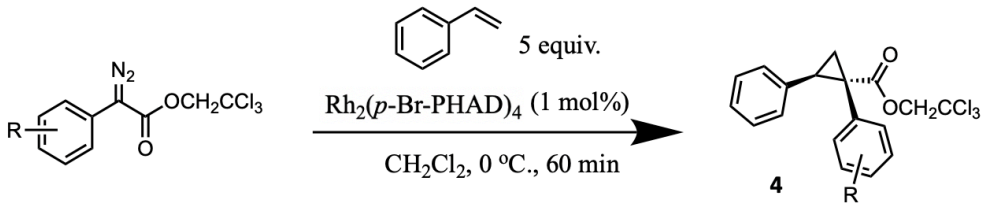
entry	R	solvent	additive	temperature (°C)	yield (%)	d.r.	ee (%)
1	CH_2CCl_3	CH_2Cl_2	4Å m.s.	25	77	>20:1	34
2	**CH_2CCl_3**	**CH_2Cl_2**	**4Å m.s.**	**0**	**63**	**>20:1**	**40**
3	CH_3	CH_2Cl_2	4Å m.s.	0	25	>20:1	16
4	CH_2CCl_3	pentane	4Å m.s.	0	40	>20:1	39
5	CH_3	pentane	4Å m.s.	0	16	>20:1	22
6	CH_2CCl_3	CH_2Cl_2	10 equiv. HFIP	25	81	>20:1	50
7	CH_2CCl_3	HFIP	none	25	84	>20:1	28

The reaction was first run with TCE ester diazo compound in dichloromethane at room temperature, which gave a 34% ee (Entry 1). When cooled to 0 °C, the ee of this reaction increased to 40% (Entry 2). Using methyl ester diazo compound in DCM at 0 °C resulted in a low enantiomeric excess of 16%, lower than that of the TCE ester (Entry 3). Because $Rh_2(PHAD)_4$ appears to be a relatively flexible catalyst like DOSP, we hypothesized that using pentane as solvent could increase enantioselectivity of the reaction as it does with DOSP. This hypothesis was supported by an increase in ee to 22% for the methyl ester diazo (Entry 5), although the TCE ester reaction in pentane remained about the same at 39% ee (Entry 4). the use of HFIP as solvent resulted in the highest yield reaction with 84% yield, but it resulted in a 28% ee (Entry 7). Finally, the addition of 10 equivalents of HFIP to the reaction of TCE diazo compound in dichloromethane led to an 81% yield and 50% ee, the highest of the test reactions (Entry 6). However, due to issues with the HPLC instrument, the beneficial effect of using HFIP as an additive was not discovered until subsequent test reactions were completed. Ultimately, the condition that resulted in the next-highest ee was TCE ester diazo in dichloromethane at 0 °C, with a 68% yield and 40% ee, and these conditions were used in subsequent test reactions.

3.2) Additional Test Reactions

After completion of optimization, a series of cyclopropanation and C-H functionalization test reactions were conducted to evaluate *p*-Br-PHAD. The substrates used were styrene, cyclohexane, and 4-ethyl toluene, and TCE diazo compounds with *p*-Br, *p*-OMe, and *o*-Cl substitutions on the aryl donor group were used. Cyclopropanation these diazo compounds with styrene resulted in moderate yields (Table 3).

Table 3. Styrene cyclopropanation reactions catalyzed by Rh_2(*p*-Br-PHAD)$_4$

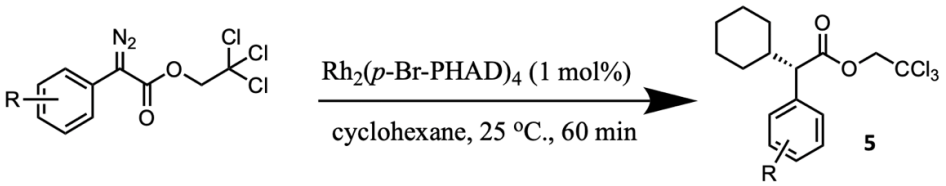


entry	R	yield (%)	d.r.	ee (%)	compound
1	*p*-Br	63	>20:1	40	4a
2	*p*-OMe	46	>20:1	36	4b
3	*o*-Cl	28	>20:1	4	4c

Cyclopropanation of the *p*-OMe diazo compound (Entry 2) resulted in a 36% ee, similar to that of *p*-Br aryldiazoacetate (Entry 1). However, cyclopropanation of styrene with *o*-Cl aryldiazoacetate (Entry 3) resulted in a nearly racemic reaction, giving only 4% ee.

C-H insertion of these aryldiazoacetates with cyclohexane was also performed (Table 4). *p*-Br aryldiazoacetate (Entry 1) resulted in a 45% yield with 42% ee. However, *p*-OMe aryldiazoacetate (Entry 2) gave only trace product by NMR, with starting material as the main component of product mixture. Finally, C-H insertion with *o*-Cl aryldiazoacetate (Entry 3) resulted in a 12% yield. Chiral resolution of this product is in progress.

Table 4. Cyclohexane C-H insertion reactions catalyzed by Rh_2(*p*-Br-PHAD)$_4$

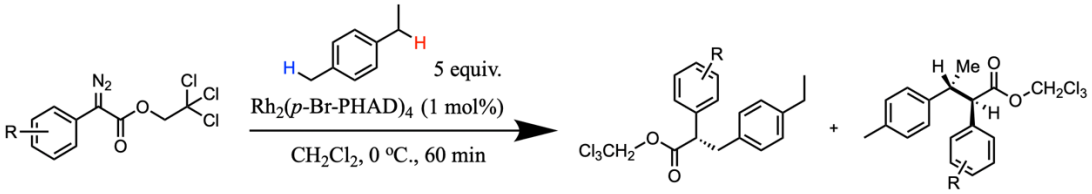


entry	R	yield (%)	ee (%)	compound
1	*p*-Br	45	42	5a
2	*p*-OMe	trace product	x	x
3	*o*-Cl	12	x*	5b

*Chiral resolution in progress.

C-H insertion with 4-ethyl-toluene was also performed in order to probe primary versus secondary site-selectivity of *p*-Br-PHAD (Table 4). Although *p*-OMe (Entry 2) and *o*-Cl aryldiazoacetates (Entry 3) did not undergo C-H insertion, *p*-Br aryldiazoacetate gave a 63% yield with 11:1 secondary-to-primary site selectivity.

Table 5. 4-ethyl-toluene C-H insertion reactions catalyzed by Rh_2(*p*-Br-PHAD)$_4$



entry	R	yield (%)	1°:2°	d.r.
1	*p*-Br	63	1:11	6:1
2	*p*-OMe	0	x	x
3	*o*-Cl	0	x	x

4.) Conclusions

Rh_2(*p*-Br-PHAD)$_4$ was synthesized and evaluated as a potential successor to Rh_2(PTAD)$_4$ and other phthalimide-based dirhodium catalysts, which are difficult and often dangerous to

synthesize. *p*-Br-PHAD was successfully synthesized in a straightforward, 3-step procedure with good yield and was able to catalyze cyclopropanation reactions of aryldiazoacetates with styrene with high diastereoselectivity and up to 50% ee. *p*-Br-PHAD was also able to perform C-H insertion reactions with cyclohexane and 4-ethyl toluene using *p*-Br aryldiazoacetate, the latter with 11:1 secondary to primary site selectivity. Future investigations would include finding additional diazo compounds that can undergo C-H functionalization reactions catalyzed by PHAD, as well as probing the additive effect of HFIP on additional reactions.

The phenyl-adamantyl ligand of *p*-Br-PHAD is a capable of inducing moderate levels of asymmetric induction, though further development of the ligand is necessary to improve enantioselectivity. A future direction would be to expand the bowl of the catalyst by adding bulky substituents to the aromatic ring, similar to the expanded bowl of TCPTAD compared with PTAD. Rh_2(3,5-diaryl-PHAD)$_4$ is a proposed catalyst that features 3,5 diphenyl substitution on the original aromatic ring (Figure 10). We hypothesize that the additional phenyl substituents would increase the rigidity of the PHAD catalyst and thus increase selectivity. We also propose that 3,5-diaryl-PHAD can be easily synthesized via the same synthetic route used for *p*-Br-PHAD by using a 3,5 dibromo substituted aryldiazoacetate and installing phenyl groups via a Suzuki cross coupling reaction after the ligand exchange[20].

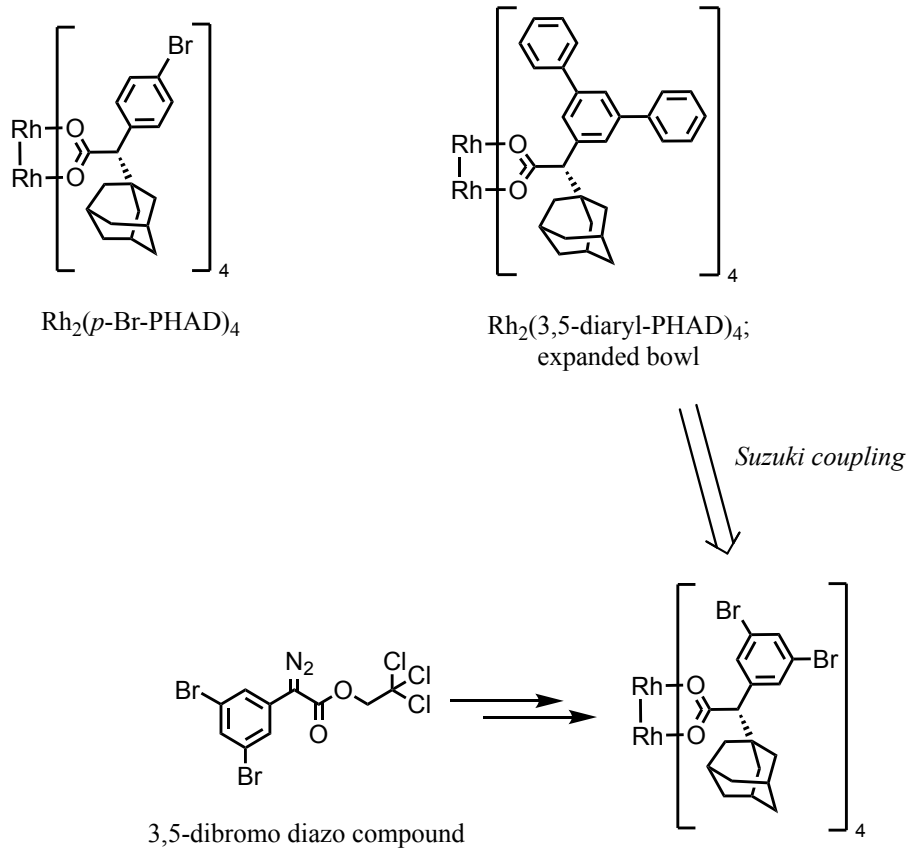


Figure 10. Structure of Rh_2(*p*-Br-PHAD)$_4$ and proposed catalyst Rh_2(3,5-diaryl-PHAD)$_4$, which features an expanded catalyst bowl.

5.) Experimental

5.1) General Considerations

All experiments were carried out in flame-dried glassware under nitrogen atmosphere unless otherwise stated. Flash column chromatography was performed on silica gel. 4Å molecular sieves were activated under vacuum at 300 °C for 4 hours then stored in an oven at 140 °C for future use. 2,2-dimethylbutane was distilled using a short-path distillation system and all solvents were stored over 4 Å molecular sieves under nitrogen atmosphere. All reagents were obtained from commercial sources and used as received without purification unless otherwise noted. Styrene was filtered through a silica plug before each experiment. ^{1}H and ^{13}C NMR spectra were recorded at either 400 MHz on VNMR 400 or Bruker NANO HD III 400 instrument, 500 MHz on INOVA 500 instrument, or 600 MHz on INOVA 600 or Bruker AVANCE 600 WB SSNMR instrument. NMR spectra were run in solutions of deuterated chloroform with residual chloroform taken as an internal standard (7.26 ppm for 1H and 77.23 ppm for ^{13}C) 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. Thin layer chromatography was performed on aluminum-back silica gel plates with UV light to visualize. IR spectra were collected on a Nicolet iS10 FT-IR spectrometer from Thermo Scientific and reported in unit of cm^{-1}. Mass spectra at Emory were taken on a Thermo Finnigan LTQ-FTMS spectrometer with APCI. Optical rotations were measured on a AUTOPOL® IV Automatic Polarimeter. Enantiomeric excess (% ee) data were obtained on an Agilent 1100 HPLC, an Agilent 1290 Infinity UHPLC, or a Waters SFC, eluting the purified products using a mixed

solution of HPLC-grade 2-propanol (i-PrOH) and n-hexane for HPLC and a mixed solution of i-PrOH or MeOH and supercritical CO2 for SFC.

5.2) Preparation of Diazo Compounds

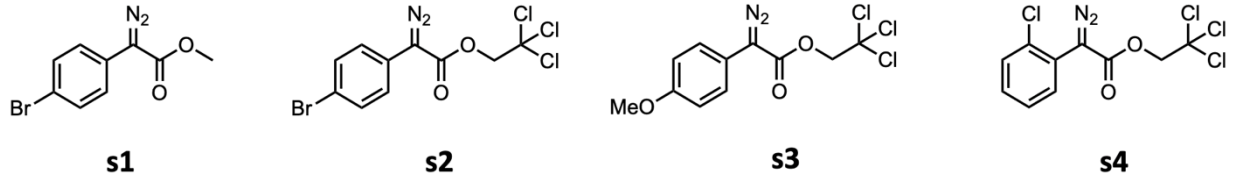


Figure S1. Scope of starting diazo compounds.

Diazo compound **s1** was prepared using the procedure reported in the literature and matched the reported spectra.[21]

Diazo compounds **s2** and **s3** were prepared using the procedure reported in the literature and matched the reported spectra.[22]

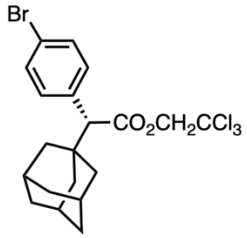
Diazo compound **s4** was prepared using the procedure reported in the literature and matched the reported spectra.[23]

5.3) General Procedure for C-H Functionalization and Cyclopropanation reactions

A round bottom flask was equipped with a stir bar and 4 Å molecular sieves and flame dried. A second round bottom flask was flame dried and both flasks were cooled under vacuum then backfilled with nitrogen. After cooling to room temperature, the empty flask was charged with diazo compound (1 equiv.) and solvent (10 mL per mmol diazo compound). The flask with the stir bar was loaded with Rh catalyst (1 mol%), substrate (varying equivalents), and solvent (same volume as flask with diazo, or 10 mL per mmol diazo compound). The solution of diazo compound was added dropwise via syringe pump to the solution of catalyst and adamantane over 40 minutes. The reaction was allowed to stir at least 10 minutes after the addition was complete,

but not longer than overnight. The crude product was purified by column chromatography. The General Procedure 1 was used to accomplish the C-H functionalization of adamantane (Table 1), cyclopropanation reactions (Table 2 & 3), C-H functionalization of cyclohexane (Table 4), and C-H functionalization of 4-ethyl toluene (Table 5).

2,2,2-trichloroethyl (*S*)-2-(adamantan-1-yl)-2-(4-bromophenyl)acetate (1)

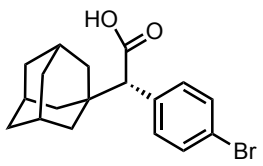


2,2,2-trichloroethyl (2*R*)-2-((1*S*,3*S*)-adamantan-1-yl)-2-(4-bromophenyl)acetate was prepared according to the general procedure for C–H functionalization reaction, using adamantane (20 mmol, 2.72 g, 10 equiv.) as the substrate and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (2 mmol, 745 mg, 1.0 equiv.) and catalyzed by Rh_2(*S*-TCPTAD)$_4$ (0.01 mmol, 35 mg, 1 mol%). The solvent used was dried dichloromethane. The reaction mixture was dried under vacuo and excess adamantane was removed by Kugelrohr at 90 ^oC. The residue was purified by flash chromatography (100% hexanes) to give 2,2,2-trichloroethyl (2*R*)-2-((1*S*,3*S*)-adamantan-1-yl)-2-(4-bromophenyl)acetate as a white solid (673 mg, 70% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.31 – 7.26 (m, 2H), 4.80 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 3.39 (s, 1H), 1.97 (m, 3H), 1.69 (m, 6H), 1.56 (m, 6H)

Chiral HPLC: (SUMICHIRAL OA-4900, 1% isopropanol in hexane, 1.0 mL/min, λ 210-230 nm) retention times of 6.211 min (major), 6.916 min (minor), 90% ee)

(*S*)-2-(adamantan-1-yl)-2-(4-bromophenyl)acetic acid (2)



A round bottom flask was equipped with a stir bar and charged with 2,2,2-trichloroethyl (2*R*)-2-((1*S*,3*S*)-adamantan-1-yl)-2-(4-bromophenyl)acetate (0.09 mmol, 42 mg, 1.0 equiv.), zinc dust (1.75 mmol, 114 mg, 20.0 equiv.), and 3.0 mL glacial acetic acid, and the resulting solution was stirred overnight at room temperature. The reaction mixture was partitioned between water and ethyl acetate, then extracted three times with ethyl acetate. The organic layer was dried with magnesium sulfate and then concentrated in vacuo to give 2-((3*R*,5*R*,7*R*)-adamantan-1-yl)-2-(4-bromophenyl)acetic acid as a white solid (27 mg, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.45-7.37 (m, 2H), 7.26-7.24 (m, 2H), 3.26 (s, 1H), 1.96 (s, 3H), 1.67 (t, J = 12.9 Hz, 6H), 1.55 (t, J = 11.65 Hz, 6H)

^{13}C NMR (150 MHz, $CDCl_3$) δ 176.8, 133.7, 132.2, 131.2, 121.9, 62.5, 40.1, 37.0, 36.5, 28.9, 0.4.

IR (neat): 2901, 2849, 1689, 1488, 1445, 1364, 1346, 1267, 1236, 1011, 850, 703, 645, 462 cm^{-1}

HR-MS: (+p APCI) calculated for [C18H21BrO2+] 348.06522 found 348.06478

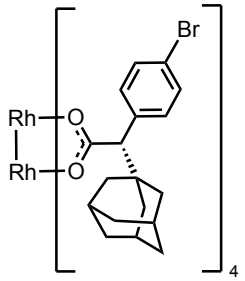
Specific Rotation: $[\alpha]_D^{20}$ -16.8 (*c* 0.5, $CHCl_3$)

Chiral HPLC:

Racemic ligand: (Regis (*S,S*) Whelk-O1, 30 min, 1% isopropanol in hexane, 1.0 mL/min, λ 210-230 nm) retention times of 5.002 min (major), 7.030 min (minor), 6% ee)

Enantiopure ligand: (Regis (*S,S*) Whelk-O1, 30 min, 1% isopropanol in hexane, 1.0 mL/min, λ 210-230 nm) retention time of 5.145 min, >99% ee).

dirhodium tetrakis ((*S*)-2-(adamantan-1-yl)-2-(4-bromophenyl)acetic acid) (3)



A round bottom flask was equipped with a stir bar and was charged with 2-((3*R*,5*R*,7*R*)-adamantan-1-yl)-2-(4-bromophenyl)acetic acid (2.4 mmol, 834 mg, 8.0 equiv.), rhodium (II) acetate (0.3 mmol, 132 mg, 1.0 equiv.), and 25 mL anhydrous chlorobenzene. A Soxhlet extractor filled with oven-dried potassium carbonate was fitted on top of the flask. The solution was heated at reflux for 24 hours. The solvent was removed under reduced pressure using a rotary evaporator then excess ligand was removed using a silica plug (100% $CHCl_2$). The remaining solid was purified by flash chromatography (0%-15% EtOAc in hexanes) to give dirhodium tetrakis (2-((3*R*,5*R*,7*R*)-adamantan-1-yl)-2-(4-bromophenyl)acetic acid) as a green solid (395 mg, 82% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 8H), 6.85 (d, *J* = 8.3 Hz, 8H), 2.92 (s, 4H), 1.74 (s, 12H), 1.52 (d, *J* = 12.1 Hz, 12H), 1.30 (d, *J* = 12.0 Hz, 12H), 1.23 (q, *J* = 11.9 Hz, 24H).

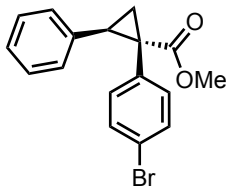
^{13}C NMR (150 MHz, CDCl3) δ 192.5, 182.25, 135.2, 133.5, 132.5, 132.0, 131.4, 130.7, 122.1, 121.1, 121.1, 65.9, 63.5, 40.3, 40.2, 37.2, 37.0, 36.9, 36.8, 36.6, 31.4, 29.1, 29.0, 28.9.

IR (neat): 2900, 2846, 1685, 1580, 1387, 1313, 1388, 1345, 1309, 1236, 1105, 850, 775, 646, 478, 435, 419, 402 cm^{-1}

HR-MS: (+p APCI) calculated for [C72H80O8Br4Rh2+] 1594.06913 found 1594.07463

Specific Rotation: $[\alpha]_D^{20}$ 24.6 (*c* 0.1, $CHCl_3$)

methyl (1*S*,2*R*)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate (4a)

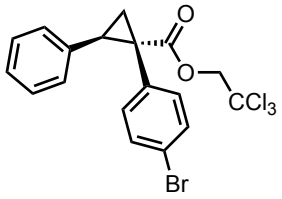


Methyl (1*S*,2*R*)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate was prepared according to the general procedure for cyclopropanation reaction, using styrene (1 mmol, 104 mg, 5 equiv.) as the substrate, methyl 2-(4-bromophenyl)-2-diazoacetate (0.2 mmol, 51 mg, 1.0 equiv.) and Rh_2(*p*-Br-PHAD)$_4$ catalyst (0.002 mmol, 3.2 mg, 1 mol %). The solvent used was dried pentane and the reaction flask was placed in an ice bath at 0 ºC. After flash chromatography (0%-5% Et_2O in hexanes) methyl (1*S*,2*R*)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate was obtained as a colorless oil (11.0 mg, 16% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.23 (m, 2H), 7.09-7.06 (m, 3H), 6.90-6.87 (m, 2 H), 6.78-6.75 (m, 2H), 3.65 (s, 3H), 3.11 (dd, J = 9.2, 7.3 Hz, 1H), 2.13 (dd, J = 9.2, 4.9 Hz, 1H), 1.83 (dd, J = 7.3, 4.9 Hz, 1H)

Chiral HPLC (Regis (*S,S*) Whelk-O1, 30 min, 1% isopropanol in hexane, 1.0 mL/min, λ 210-230 nm) retention times of 9.643 min (major), 12.279 min (minor), 14% ee)

2,2,2-trichloroethyl (1*S*,2*R*)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate (4b)



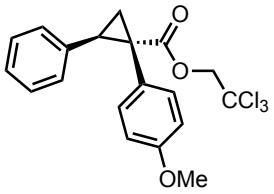
2,2,2-trichloroethyl (1*S*,2*R*)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate was prepared according to the general procedure for cyclopropanation reaction,

using styrene (1 mmol, 104 mg, 5 equiv.) as the substrate, 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (0.2 mmol, 74 mg, 1.0 equiv.) and Rh_2(*p*-Br-PHAD)$_4$ catalyst (0.002 mmol, 3.2 mg, 1 mol %). The solvent used was dried dichloromethane and the reaction flask was placed in an ice bath at 0 °C. After flash chromatography (0%-5% Et_2O in hexanes) 2,2,2-trichloroethyl (1*S*,2*R*)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate was obtained as a colorless oil (71.4 mg, 77% yield).

^{1}H NMR (500 MHz, $CDCl_3$) 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).

Chiral HPLC: (CHIRALPAK AD-H, 30 min, 1 mL/min, 1 % iPrOH in hexanes, λ 230 nm) retention times of 7.312 min (minor), 9.774 min (major), 22% ee).

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



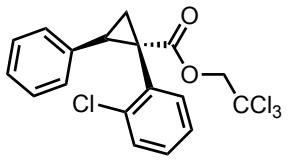
2,2,2-trichloroethyl (1*S*,2*R*)-1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate was prepared according to the general procedure for cyclopropanation reactions, using styrene (1 mmol, 104 mg, 5 equiv.) as the substrate, 2,2,2-trichloroethyl 2-diazo-2-(4-methoxyphenyl)acetate (0.2 mmol, 65 mg, 1.0 equiv), and Rh_2(*p*-Br-PHAD)$_4$ catalyst (0.002 mmol, 3.2 mg, 1 mol %). The solvent used was dried dichloromethane and the reaction flask was placed in an ice bath at 0 °C. After flash chromatography (0%-5% Et_2O in hexanes) 2,2,2-trichloroethyl (1*S*,2*R*)-1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate was

obtained as a clear oil (38.3 mg, 46% yield).

^{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), 3.2 (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).

Chiral HPLC: (Regis (*S,S*) Whelk-O1, 30 min, 1% isopropanol in hexane, 1.0 mL/min, λ 210-230 nm) retention times of 8.685 min (major), 10.202 min (minor), 36% ee)

2,2,2-trichloroethyl (1*S*,2*S*)-1-(2-chlorophenyl)-2-phenylcyclopropane-1-carboxylate (4d)

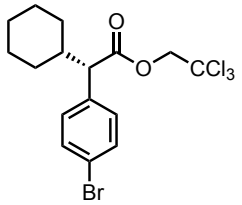


2,2,2-trichloroethyl (1*S*,2*S*)-1-(2-chlorophenyl)-2-phenylcyclopropane-1-carboxylate was prepared according to the general procedure for cyclopropanation reactions, using styrene (1 mmol, 104 mg, 5 equiv.) as the substrate, 2,2,2-trichloroethyl 2-(2-chlorophenyl)-2-diazoacetate (0.2 mmol, 66 mg, 1.0 equiv), and Rh_2(*p*-Br-PHAD)$_4$ catalyst (0.002 mmol, 3.2 mg, 1 mol %). After flash chromatography (0%-5% Et_2O in hexanes) 2,2,2-trichloroethyl (1*S*,2*S*)-1-(2-chlorophenyl)-2-phenylcyclopropane-1-carboxylate was obtained as a colorless oil (23.8 mg, 28% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.15 – 7.05 (m, 7H), 6.83 (dd, J = 7.77, 1.82 Hz, 2H), 4.73 (dd, J = 11.8, 6.52 Hz, 2H), 3.39 (t, J = 8.44, 1H), 2.26 (s, 1H), 2.02 (dd, J = 7.6, 5.3 Hz, 1H).

Chiral SFC: (Daicel CHIRALCEL OJ-3, 5 min, 5% methanol in isopropanol, 2.5 mL/min formic acid in heptane, λ 210-230 nm) retention times of 1.15 min (major), 1.63 min (minor), 4% ee)

2,2,2-trichloroethyl (*S*)-2-(4-bromophenyl)-2-cyclohexylacetate (5a)

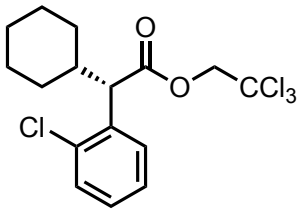


2,2,2-trichloroethyl (*S*)-2-(4-bromophenyl)-2-cyclohexylacetate was prepared according to the general procedure for C–H functionalization reaction, but the substrate cyclohexane was used as solvent. 2 mL of cyclohexane was used as the substrate 2,2,2-trichloroethyl 2-diazo-2-(4-methoxyphenyl)acetate (0.2 mmol, 65 mg, 1.0 equiv), and Rh_2(*p*-Br-PHAD)$_4$ catalyst (0.002 mmol, 3.2 mg, 1 mol %). After flash chromatography (0%-5% Et_2O in hexanes) 2,2,2-trichloroethyl (*S*)-2-(4-bromophenyl)-2-cyclohexylacetate was obtained as a colorless oil (34.6 mg, 45% yield).

^{1}H NMR (400 MHz, CDCl3) δ 7.47 – 7.42 (m, 2H), 7.26 – 7.22 (m, 2H), 4.76 (d, J = 12.0 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 3.35 (d, J = 10.6 Hz, 1H), 2.05 (qt, J = 11.1, 3.4 Hz, 1H), 1.86 (m, 1H), 1.75 (m, 1H), 1.70 – 1.58 (m, 2H), 1.43 – 1.25 (m, 2H), 1.22 – 1.04 (m, 3H), 0.82 – 0.72 (m, 1H).

Chiral SFC: (Trefoil AMY1, 5 min, 5% methanol in isopropanol, 2.5 mL/min formic acid in heptane, λ 210-230 nm) retention times of 1.31 min (minor), 1.70 min (major), 42% ee)

2,2,2-trichloroethyl (*S*)-2-(2-chlorophenyl)-2-cyclohexylacetate (5b)



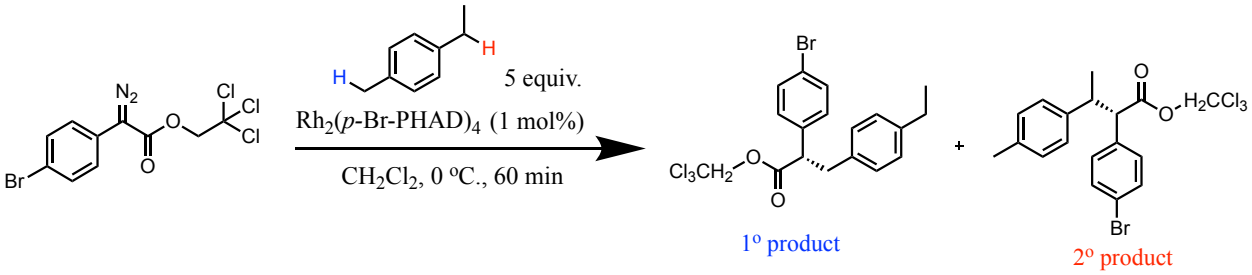
2,2,2-trichloroethyl (*S*)-2-(2-chlorophenyl)-2-cyclohexylacetate was prepared according to the general procedure for C–H functionalization reaction, but the substrate cyclohexane was used as

solvent. 2 mL of cyclohexane was used as the substrate with 2,2,2-trichloroethyl 2-(2-chlorophenyl)-2-diazoacetate (0.2 mmol, 66 mg, 1.0 equiv), and Rh_2(*p*-Br-PHAD)$_4$ catalyst (0.002 mmol, 3.2 mg, 1 mol %). After flash chromatography (0%-5% Et_2O in hexanes) 2,2,2-trichloroethyl (*S*)-2-(2-chlorophenyl)-2-cyclohexylacetate was obtained as a colorless oil (10.0 mg, 12% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38 (dd, *J* = 7.9, 1.5 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 11.9 Hz, 1H), 4.17 (d, *J* = 10.6 Hz, 1H), 2.11 (qt, *J* = 11.0, 3.3 Hz, 1H), 1.92 (d, *J* = 12.6 Hz, 1H), 1.81 – 1.58 (m, 4H), 1.04 (m, 5 H).

Chiral Separation: Chiral resolution is in progress.

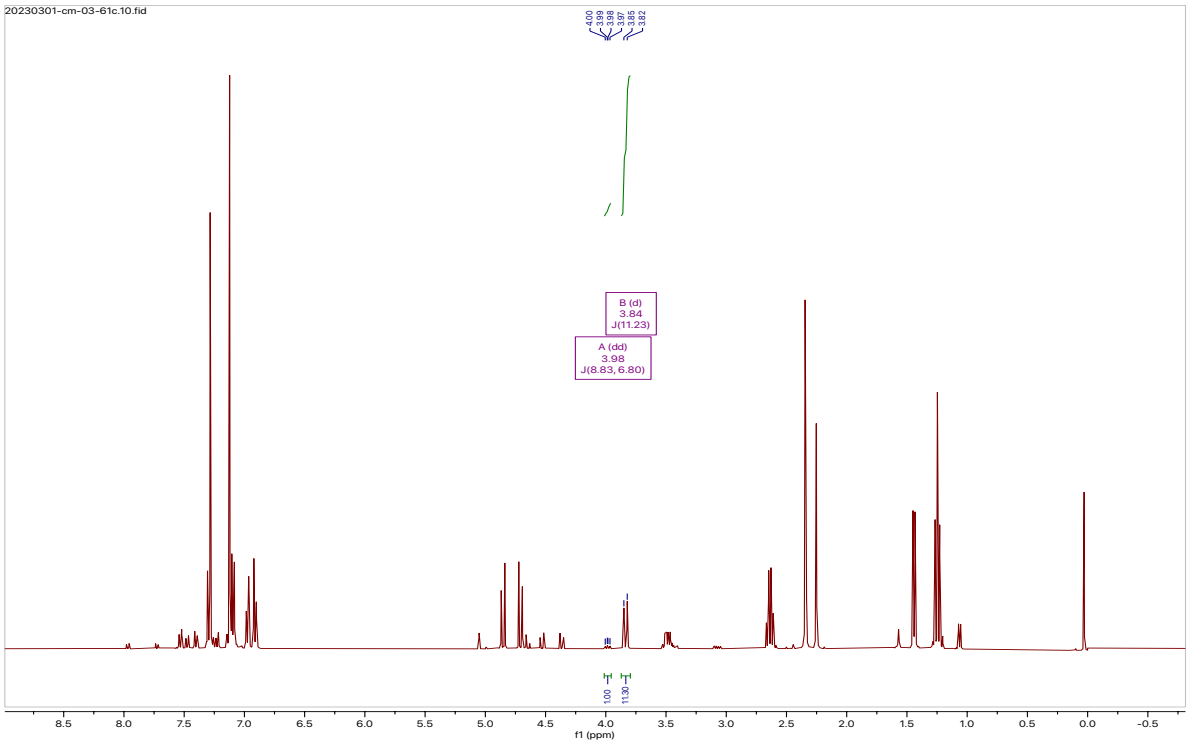
5.4) Site Selectivity Analysis

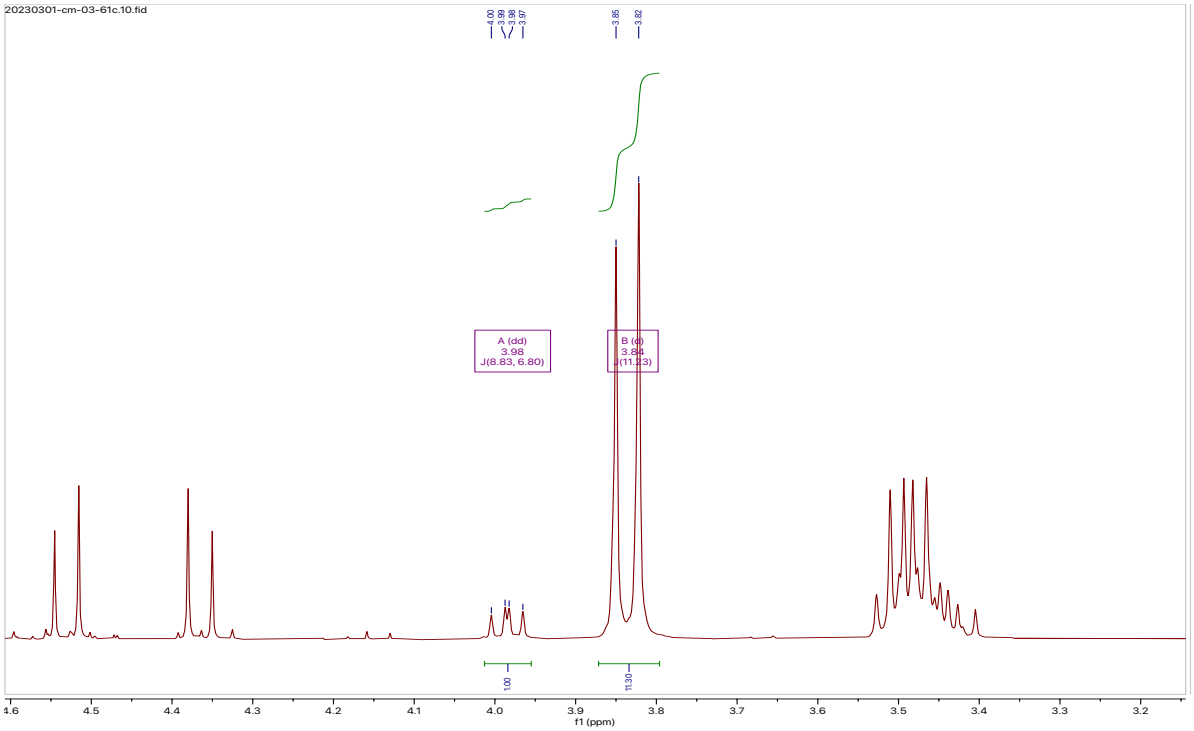


This reaction was carried out according to the general procedure for C–H functionalization reaction, using 4-ethyl toluene (1 mmol, 120 mg, 5 equiv.) as the substrate and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (2 mmol, 745 mg, 1.0 equiv.), and Rh_2(*p*-Br-PHAD)$_4$ catalyst (0.002 mmol, 3.2 mg, 1 mol %). The solvent used was dried dichloromethane and the reaction flask was placed in an ice bath at 0 °C. The reaction mixture was concentrated and a mixture of primary and secondary insertion product was obtained as a colorless oil (56.8 mg, 63% yield).

Site selectivity of this reaction was determined by NMR analysis, comparing integrations of the C-H insertion site proton of each product. The primary C-H insertion peak appears as a

doublet of doublets at 3.98 ppm, while the secondary C-H insertion peak is a double at 3.84 ppm. The respective integrations are 1 and 11.3, indicating a 1:11 ratio of primary to secondary C-H insertion for this reaction.

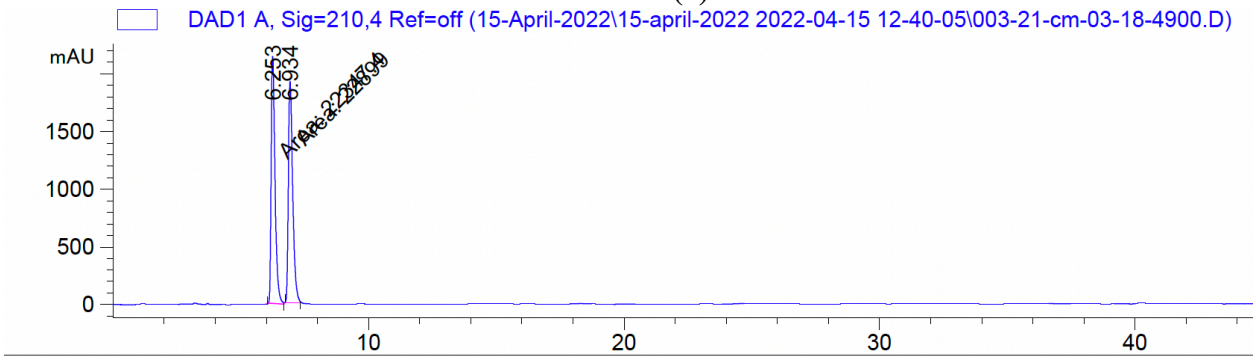




5.5) HPLC Traces

5.5.1) Traces Corresponding to Table 1

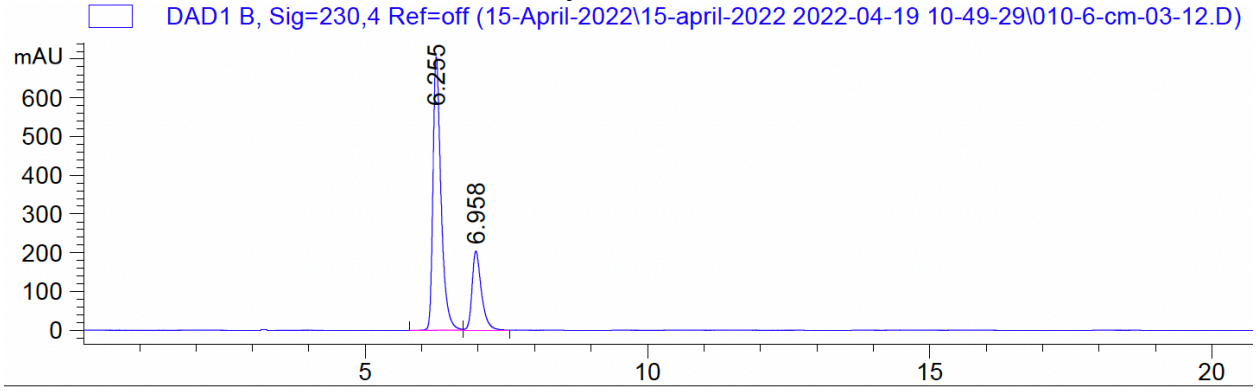
Racemic (1)



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.253	MM	0.1740	2.23474e4	2141.12524	49.3904
2	6.934	MM	0.1986	2.28990e4	1921.92395	50.6096

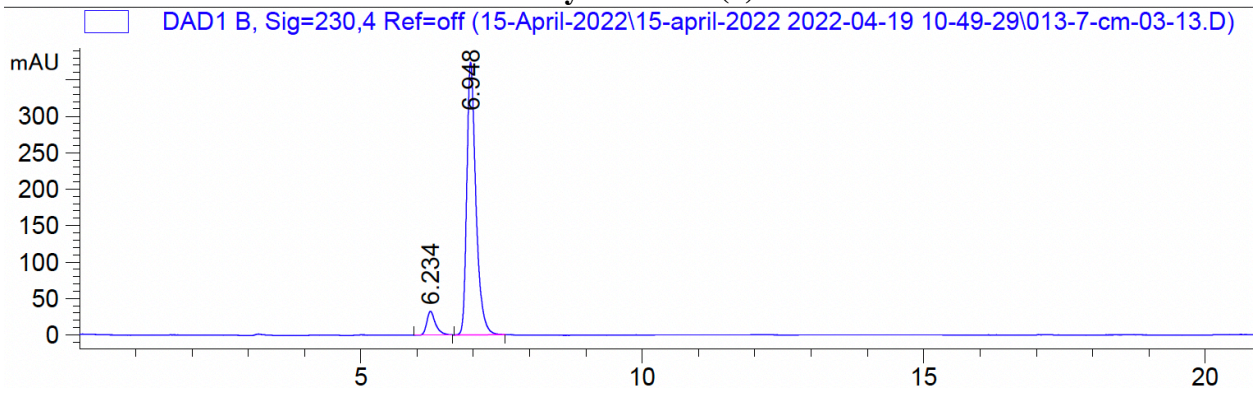
Entry 1: DOSP (1)



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.255	VV R	0.1504	7043.03760	706.12476	74.9471
2	6.958	VB	0.1730	2354.30811	204.18358	25.0529
Totals :				9397.34570	910.30833	

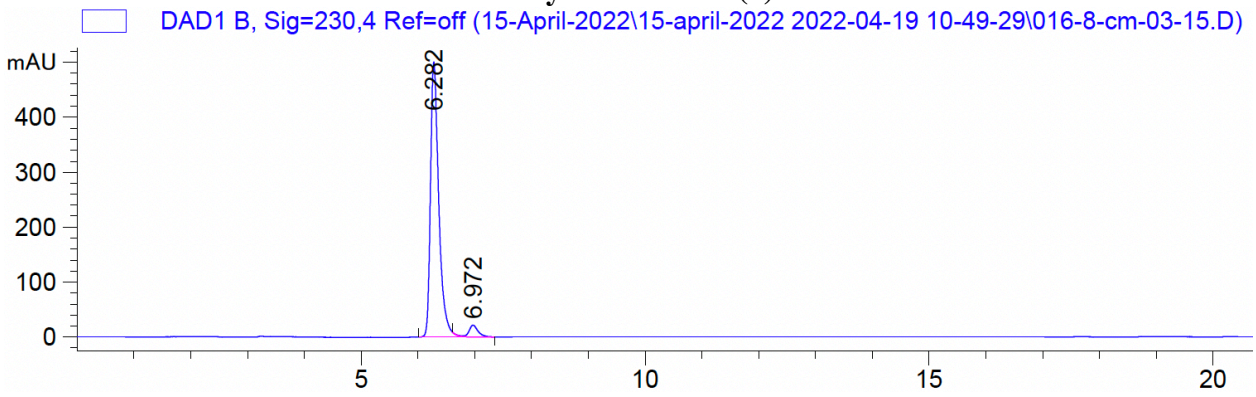
Entry 2: PTAD (1)



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.234	VB R	0.1604	352.05533	32.61884	7.7329
2	6.948	BB	0.1681	4200.61230	373.91599	92.2671
Totals :				4552.66763	406.53482	

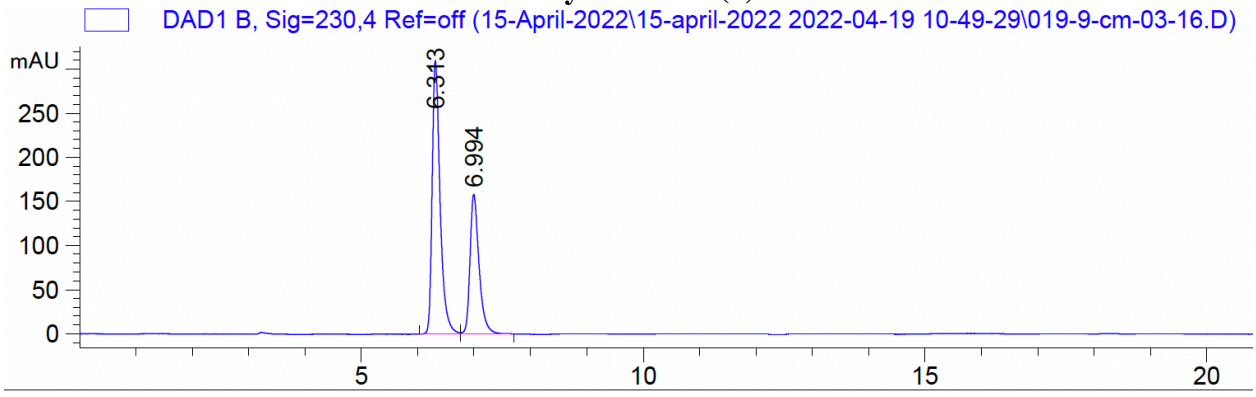
Entry 4: TPPTTL (1)



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.282	BV R	0.1523	5077.82764	500.80682	95.4920
2	6.972	VB E	0.1592	239.71483	21.40425	4.5080
Totals :				5317.54247	522.21107	

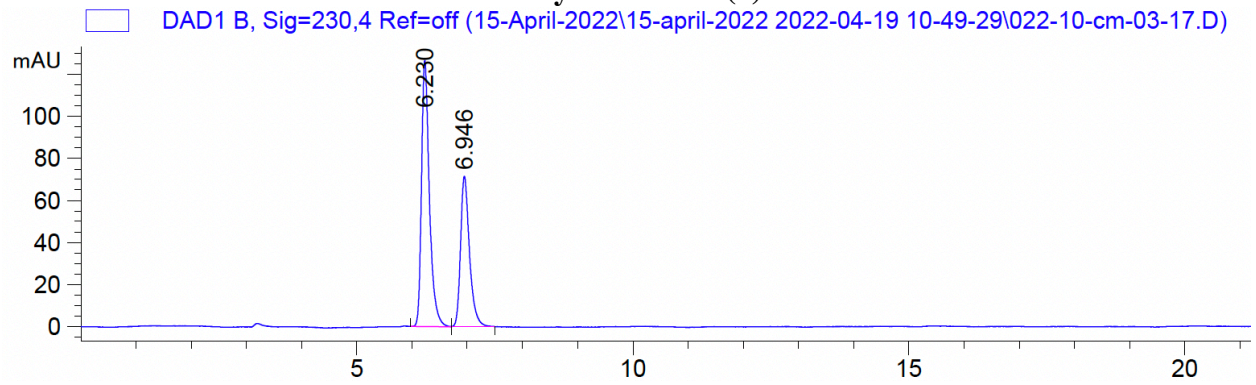
Entry 5: NTTL (1)



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.313	BV	0.1451	3016.87402	309.96722	63.0464
2	6.994	VV R	0.1664	1768.29248	158.17572	36.9536
Totals :				4785.16650	468.14294	

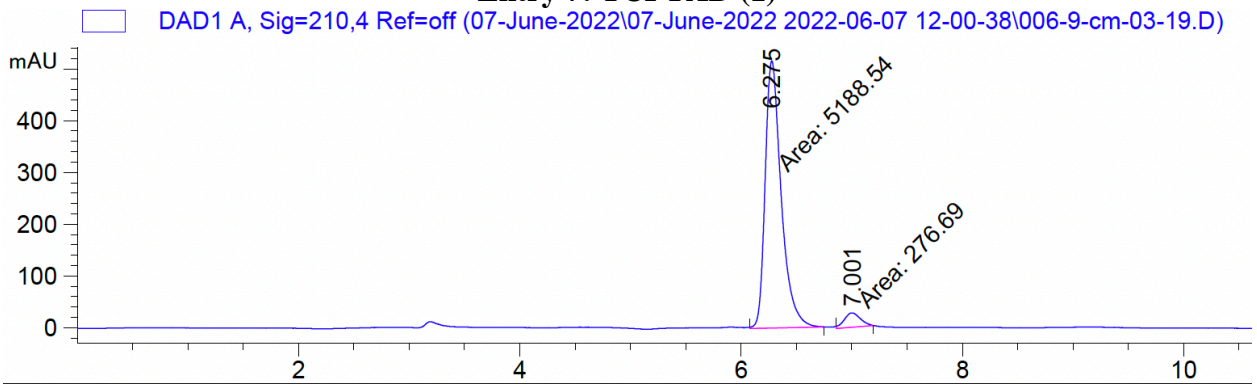
Entry 6: BTPCP (1)



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.230	BB	0.1499	1264.50635	126.69987	61.0227
2	6.946	BB	0.1691	807.68274	71.57931	38.9773
Totals :				2072.18909	198.27917	

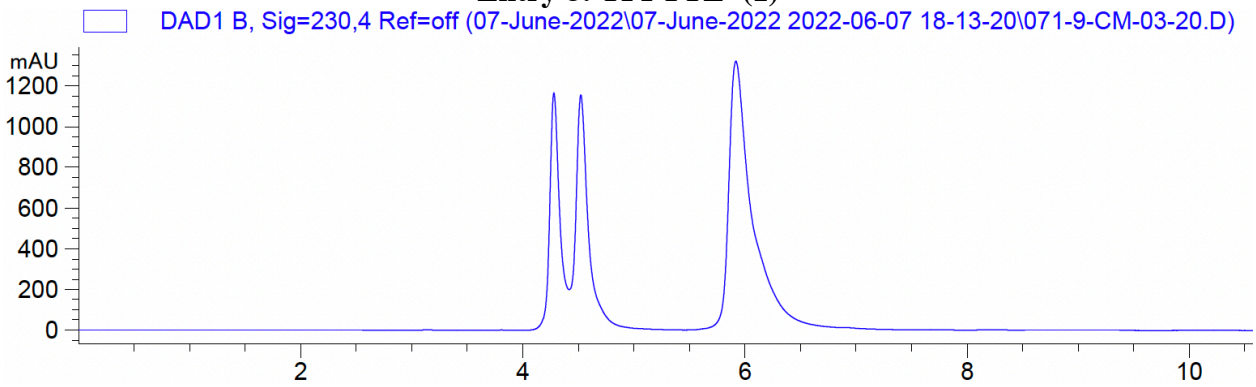
Entry 7: TCPTAD (1)



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

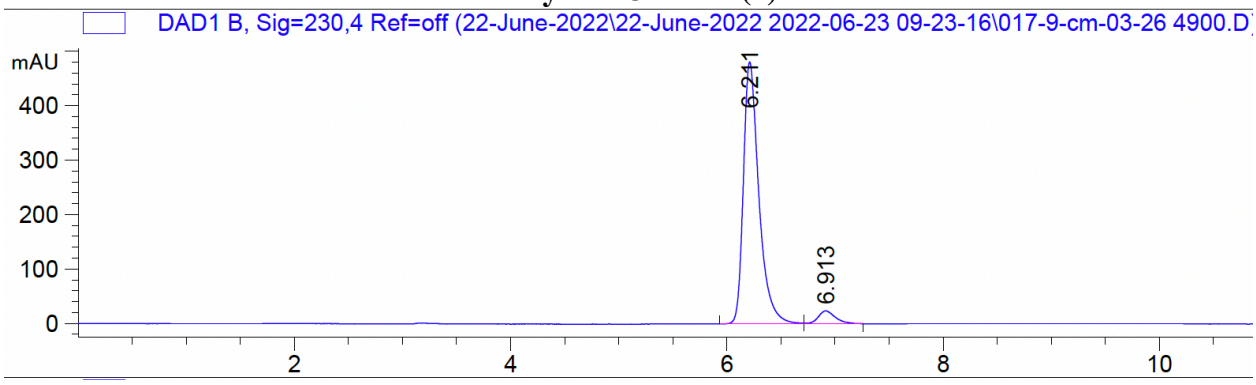
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.275	MM	0.1677	5188.54102	515.76843	94.9373
2	7.001	MM	0.1208	276.69019	27.56262	5.0627
Totals :				5465.23120	543.33105	

Entry 8: TPPTTL* (1)



*retention times do not match racemic; further analysis is in progress.

Entry 9: TCPTAD (1)

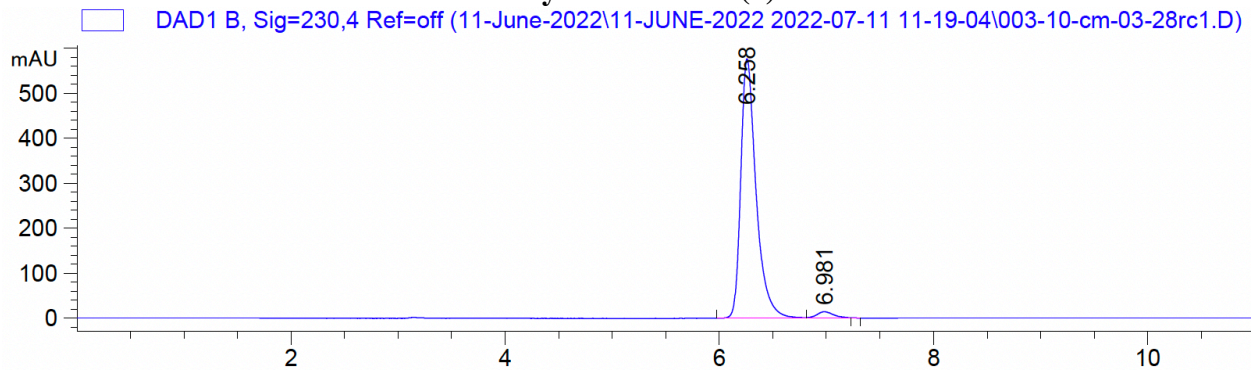


Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.211	VV R	0.1470	4785.16455	481.47177	94.8023
2	6.913	VV R	0.1485	262.35550	23.72196	5.1977
Totals :				5047.52005	505.19373	

5.5.2) Traces Corresponding to Recrystallization and PHAD Ligand

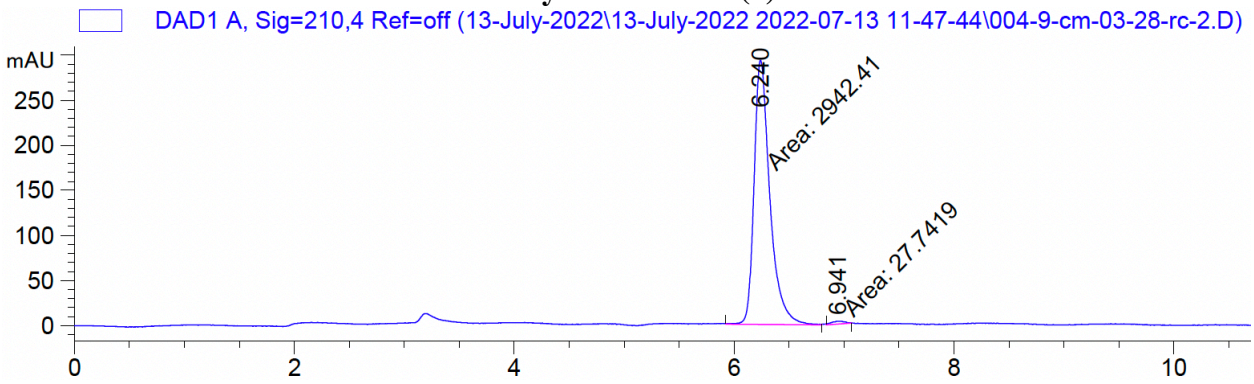
Recrystallization 1 (1)



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

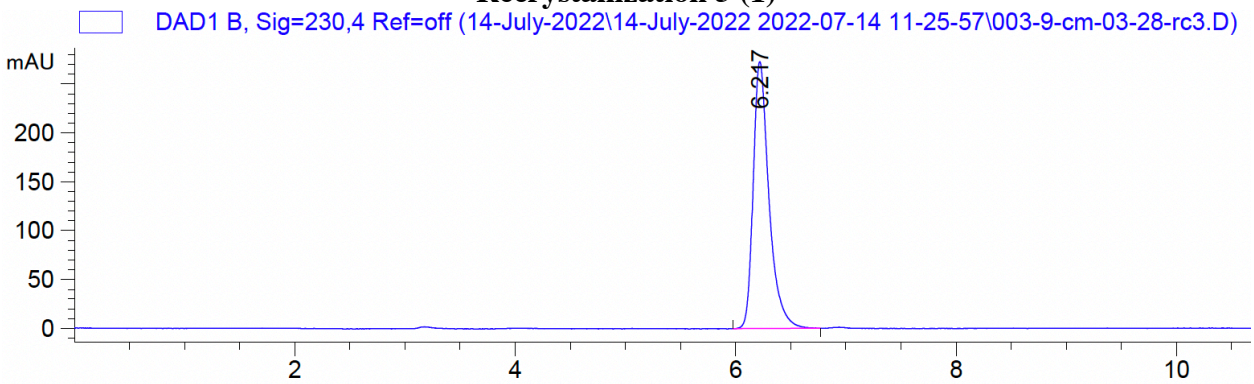
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.258	VV R	0.1499	5755.17969	576.63080	97.3538
2	6.981	VV E	0.1324	156.43521	14.27204	2.6462
Totals :				5911.61490	590.90284	

Recrystallization 2 (1)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.240	MM	0.1672	2942.40601	293.30371	99.0660
2	6.941	MM	0.1425	27.74191	3.24529	0.9340
Totals :				2970.14791	296.54900	

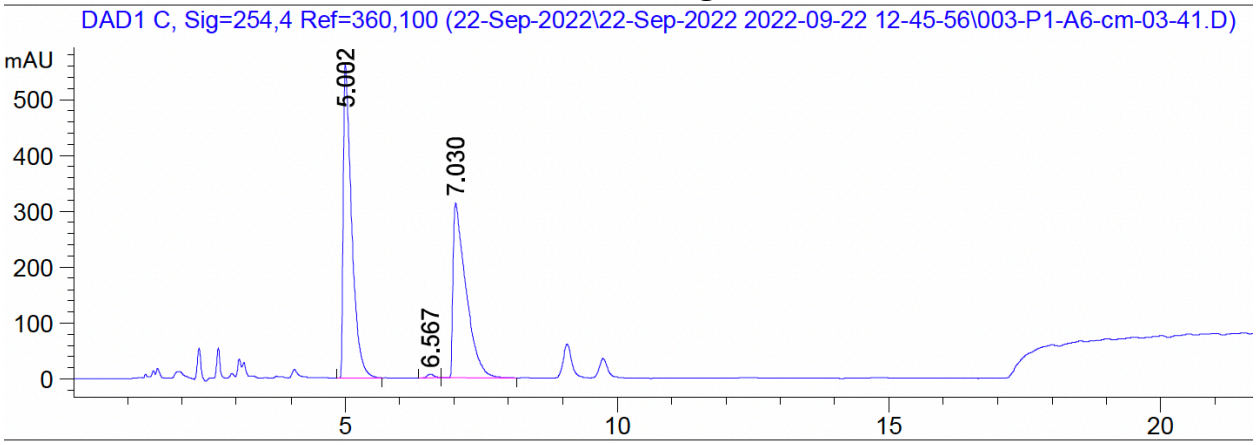
Recrystallization 3 (1)



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

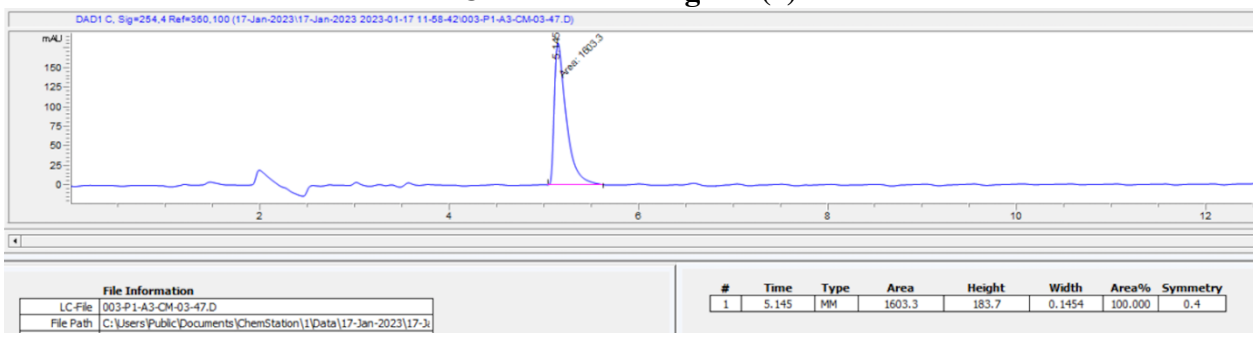
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.217	VV R	0.1484	2723.43213	272.96619	100.0000
Totals :				2723.43213	272.96619	

Racemic PHAD Ligand (2)



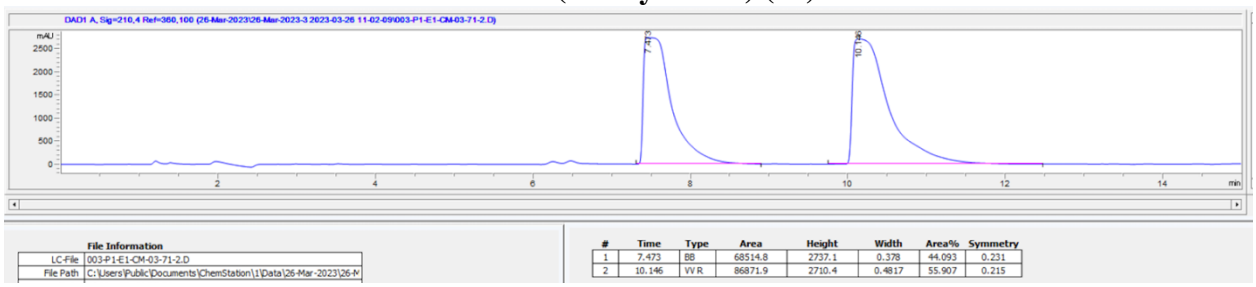
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.002	MM	0.1835	1091.76184	99.18152	53.4844
2	7.031	MM	0.2846	949.50848	55.59917	46.5156
Totals :				2041.27032	154.78069	

Chiral PHAD Ligand (2)



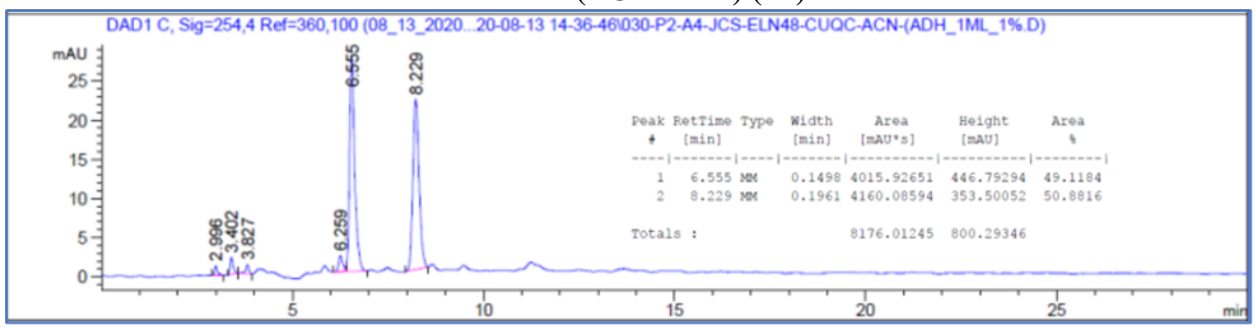
5.5.3) Traces Corresponding to Table 2

Racemic (Methyl Ester) (4a)*

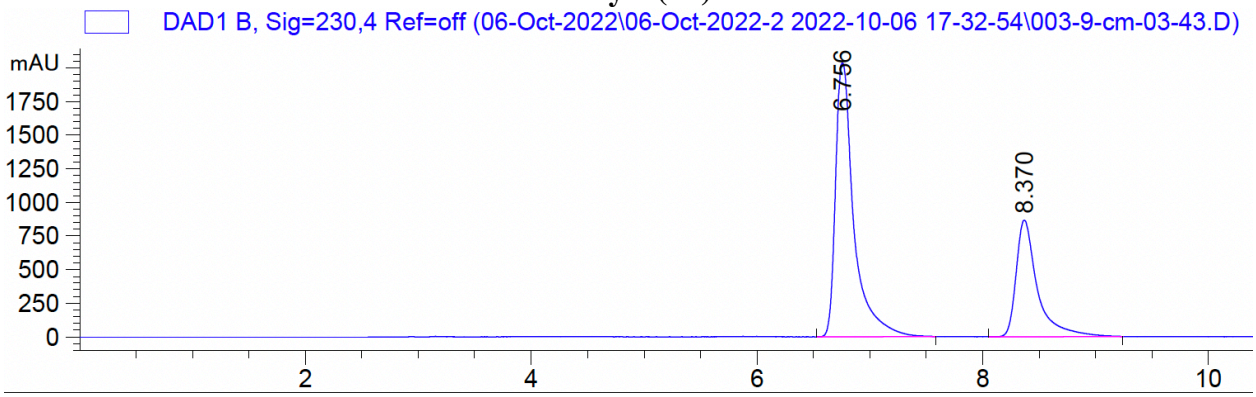


*This entry will be updated with a less-concentrated sample.

Racemic (TCE Ester) (4b)



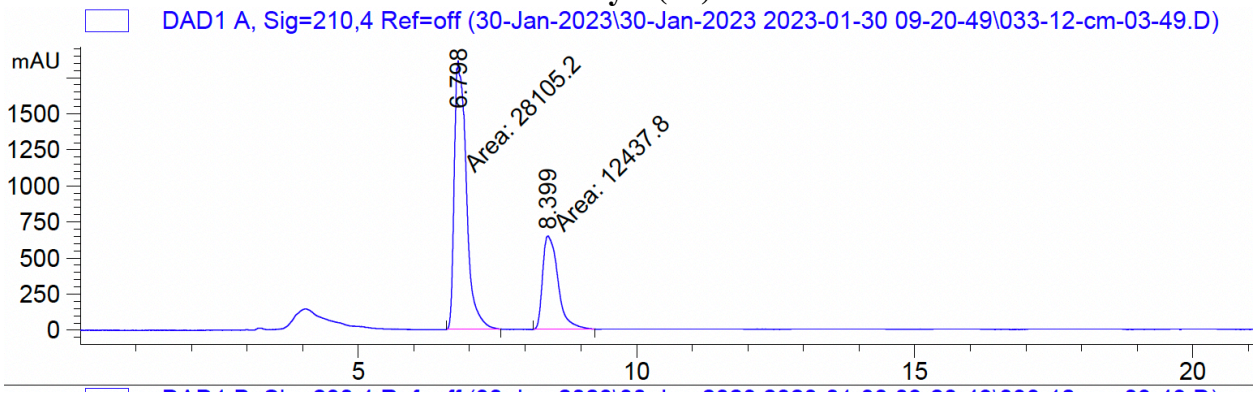
Entry 1 (4b)



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.756	VV R	0.1346	2.30483e4	2036.18970	67.0191
2	8.370	VV R	0.1784	1.13423e4	865.58759	32.9809
Totals :				3.43906e4	2901.77728	

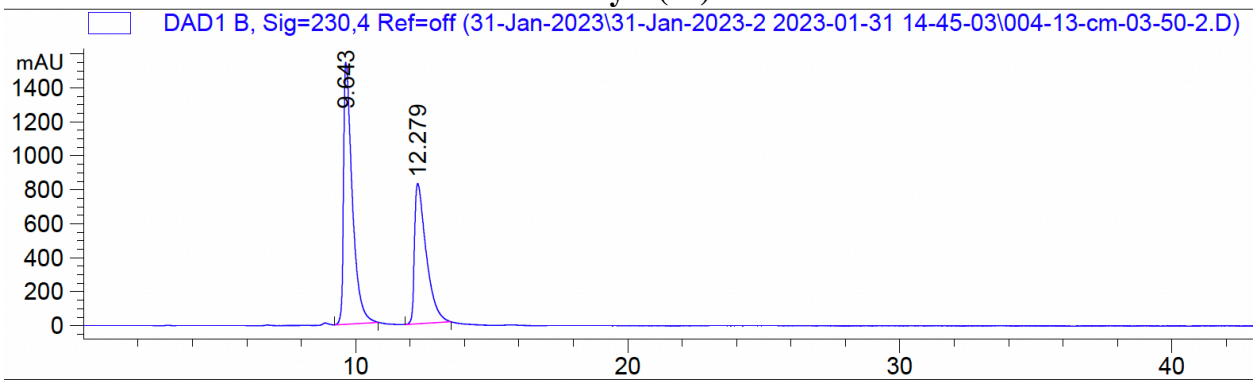
Entry 2 (4b)



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.798	MM	0.2515	2.81052e4	1862.57043	69.3219
2	8.399	MM	0.3203	1.24378e4	647.15430	30.6781
Totals :				4.05431e4	2509.72473	

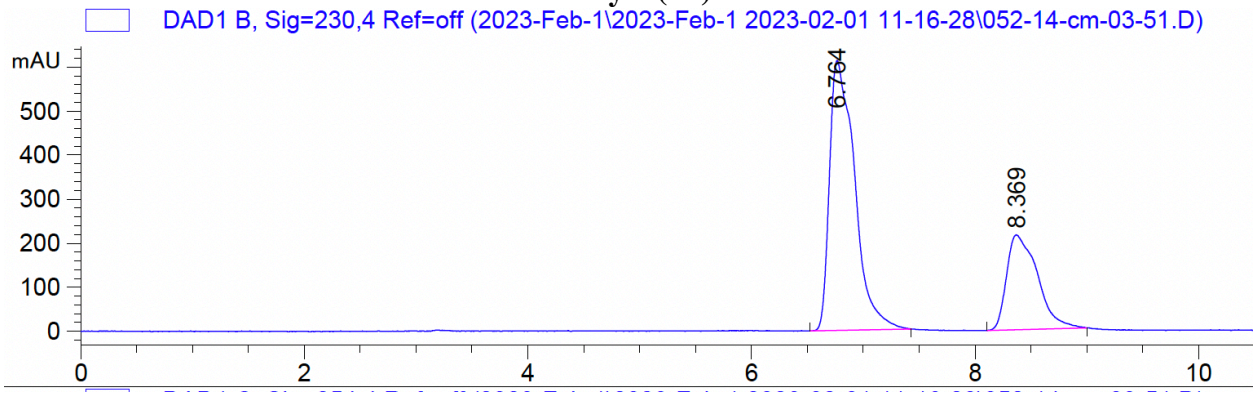
Entry 3 (4a)



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.643	VV R	0.2612	3.43327e4	1542.13367	58.1069
2	12.279	VV R	0.3517	2.47528e4	825.90149	41.8931
Totals :				5.90855e4	2368.03516	

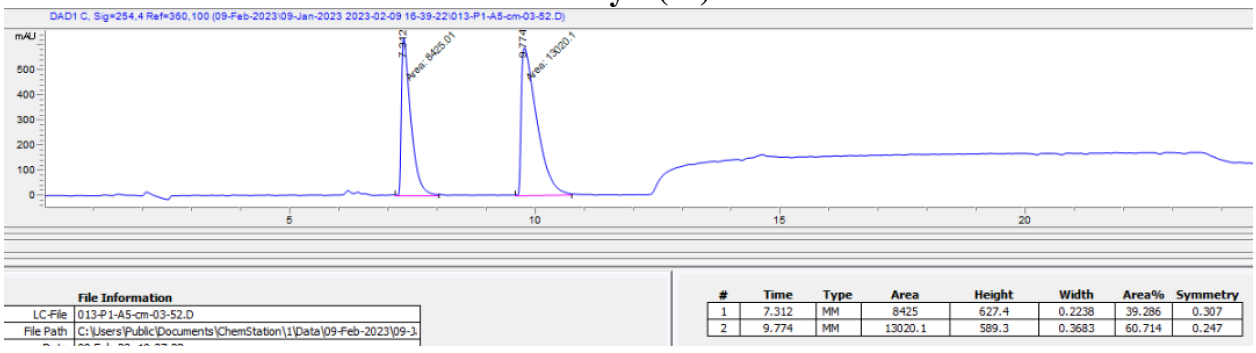
Entry 4 (4b)



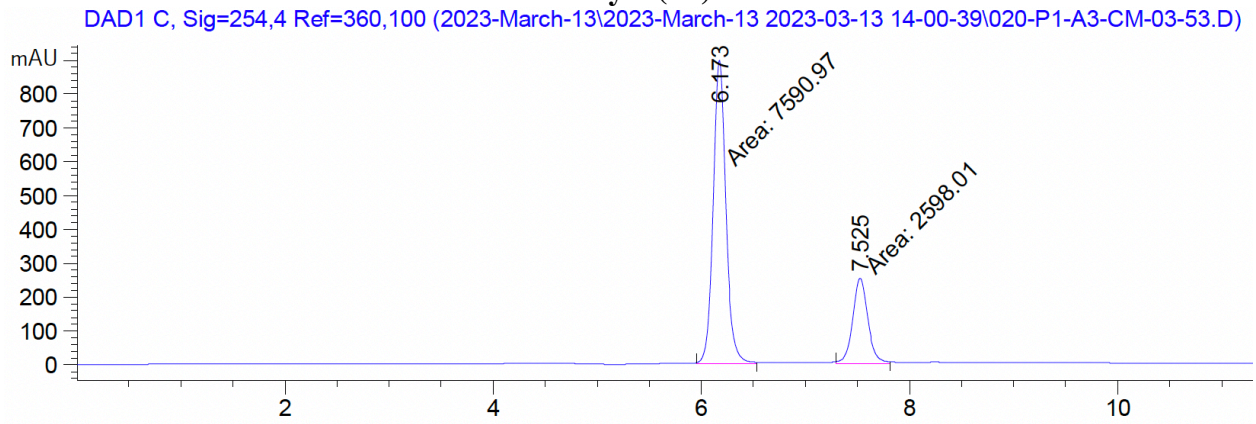
Signal 2: DAD1 B, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.764	BV R	0.1961	9572.45020	613.12555	69.8924
2	8.369	VV R	0.2259	4123.52734	215.38953	30.1076
Totals :				1.36960e4	828.51508	

Entry 5 (4a)



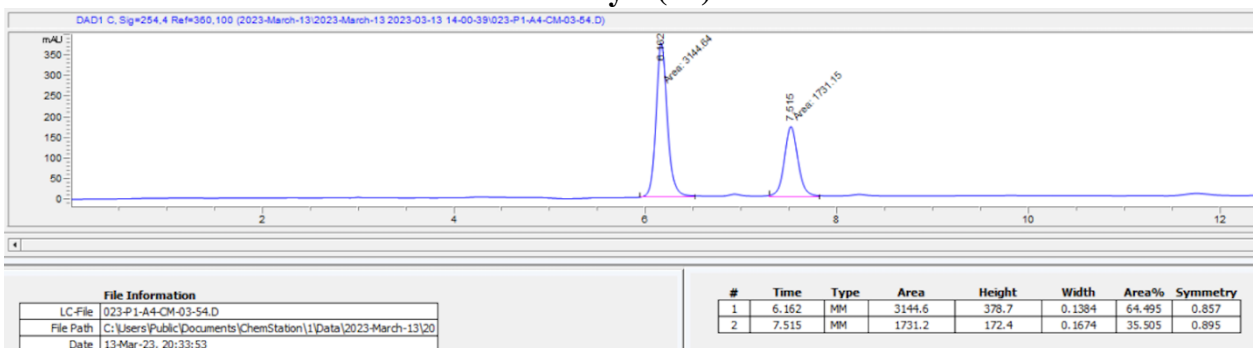
Entry 6 (4b)



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

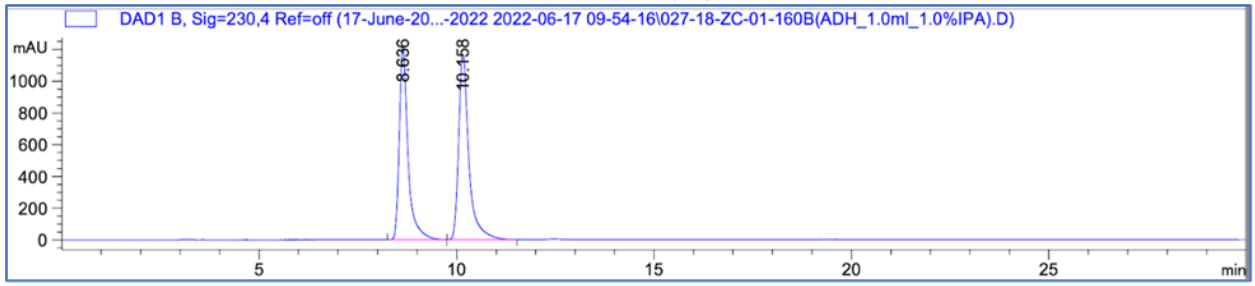
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.173	MM	0.1408	7590.97314	898.82208	74.5018
2	7.525	MM	0.1707	2598.00586	253.68669	25.4982
Totals :				1.01890e4	1152.50877	

Entry 7 (4b)

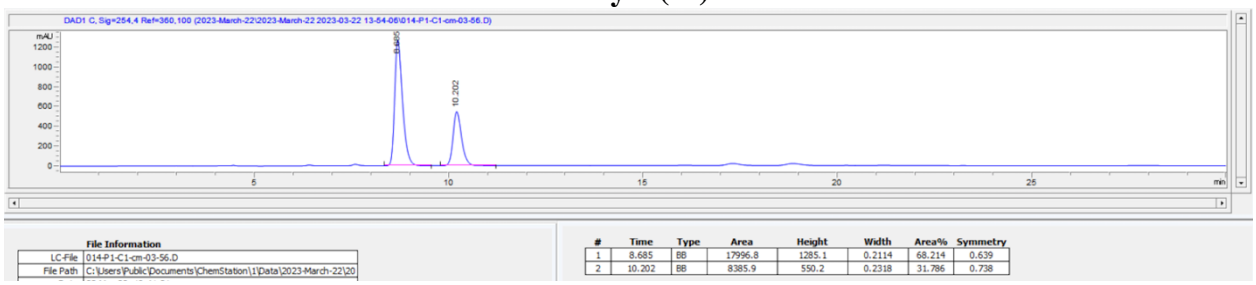


5.5.4) Traces Corresponding to Table 3

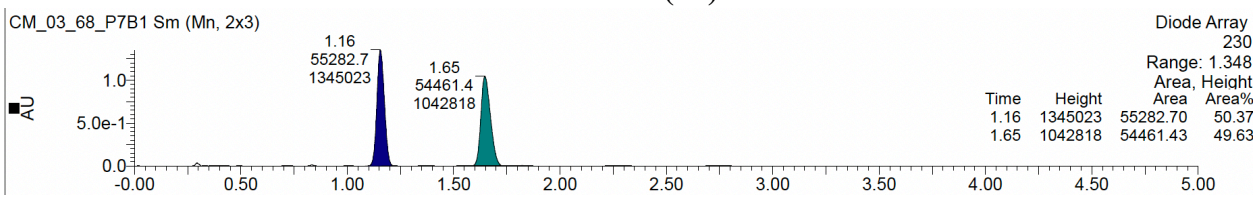
Racemic (4c)



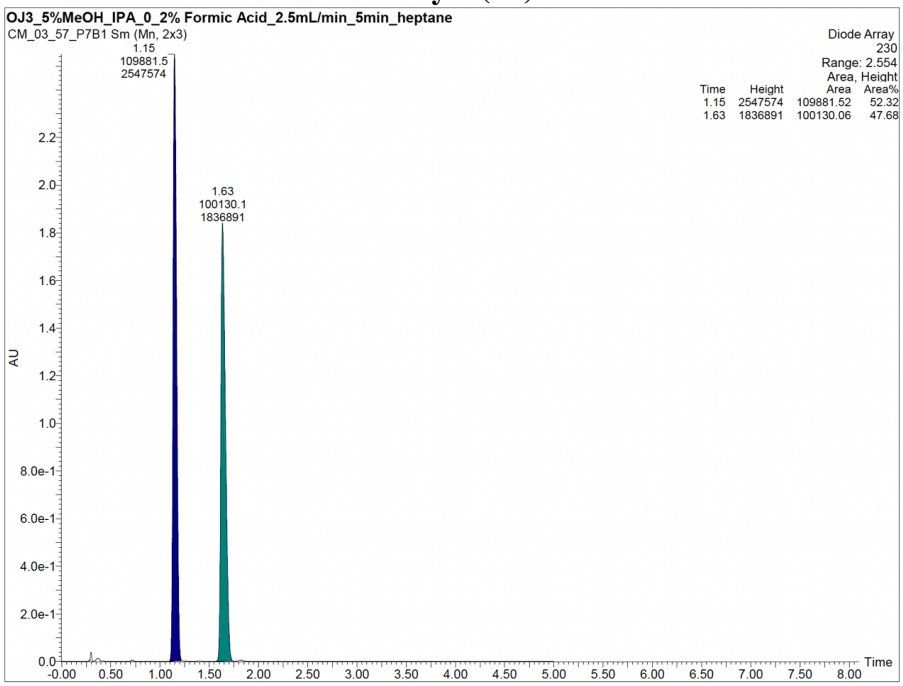
Entry 2 (4c)



Racemic (4d)

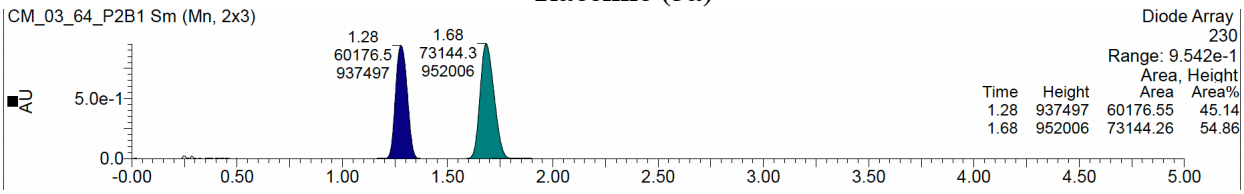


Entry 3 (4d)

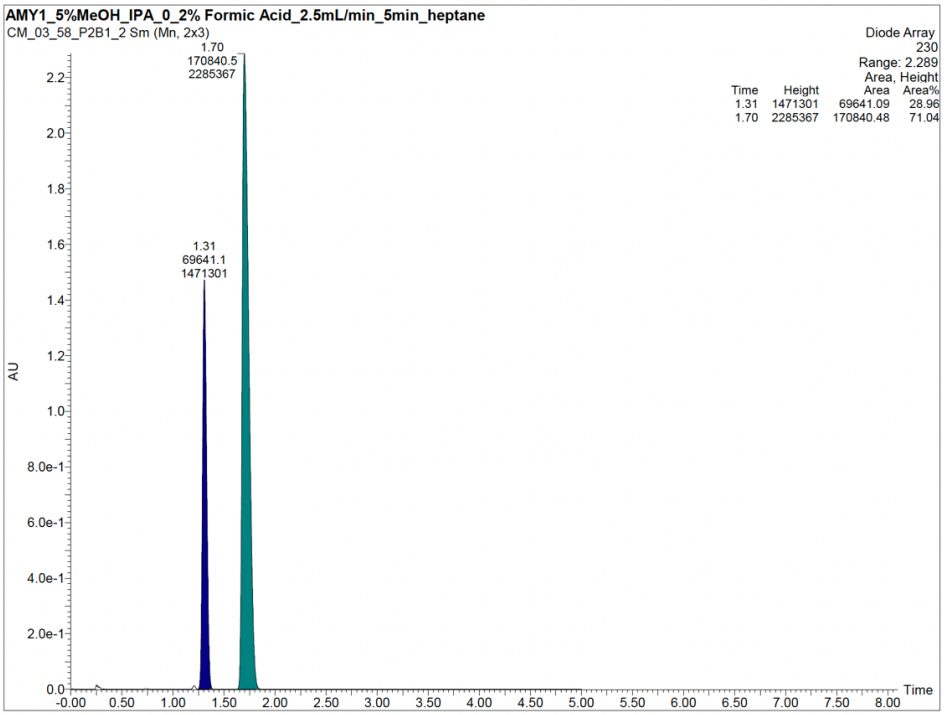


5.5.5) Traces Corresponding to Table 4

Racemic (5a)



Entry 1 (5a)



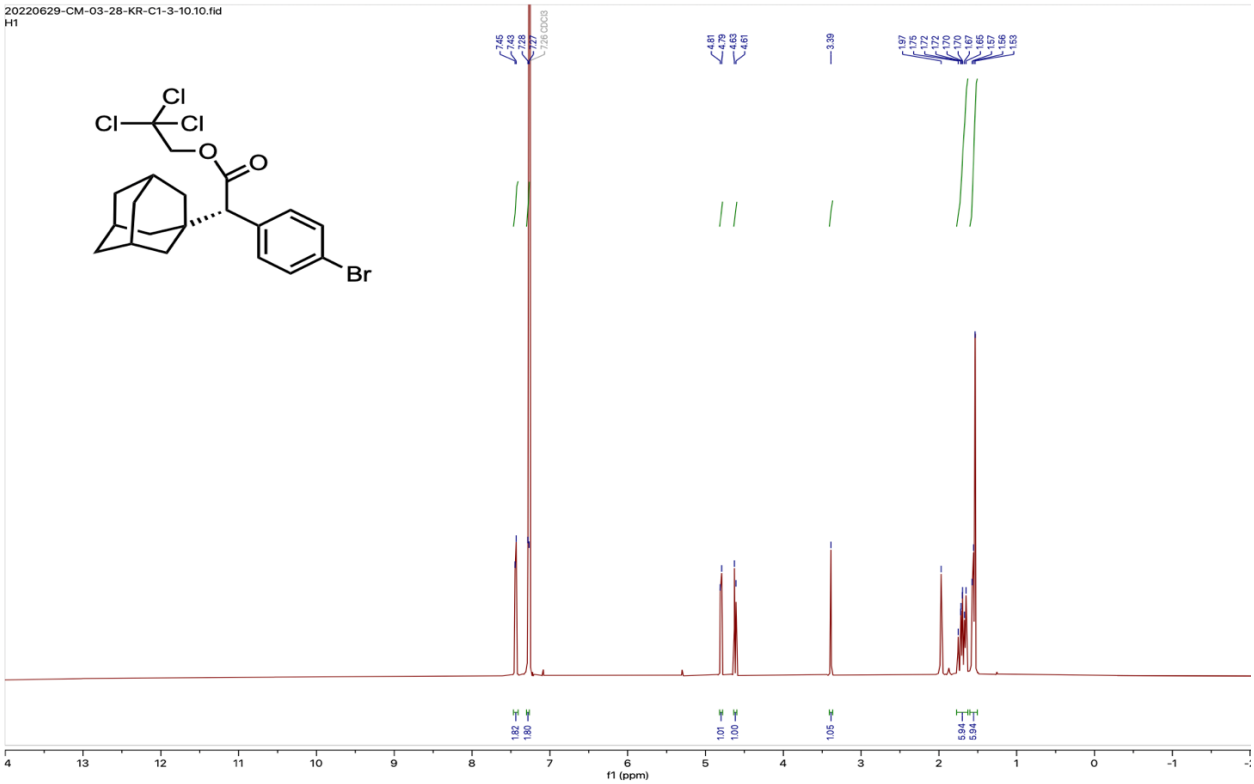
Racemic (5b)

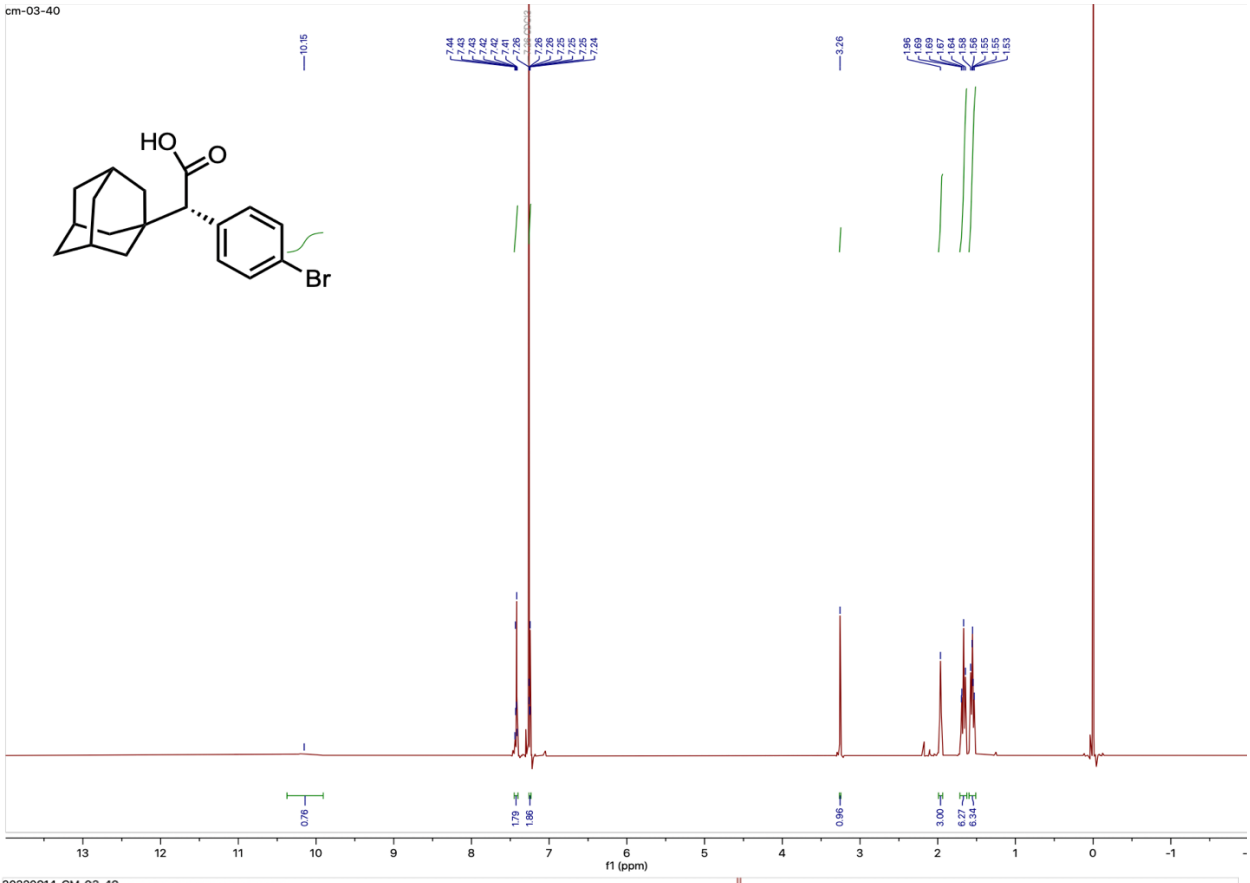
Chiral resolution is in progress.

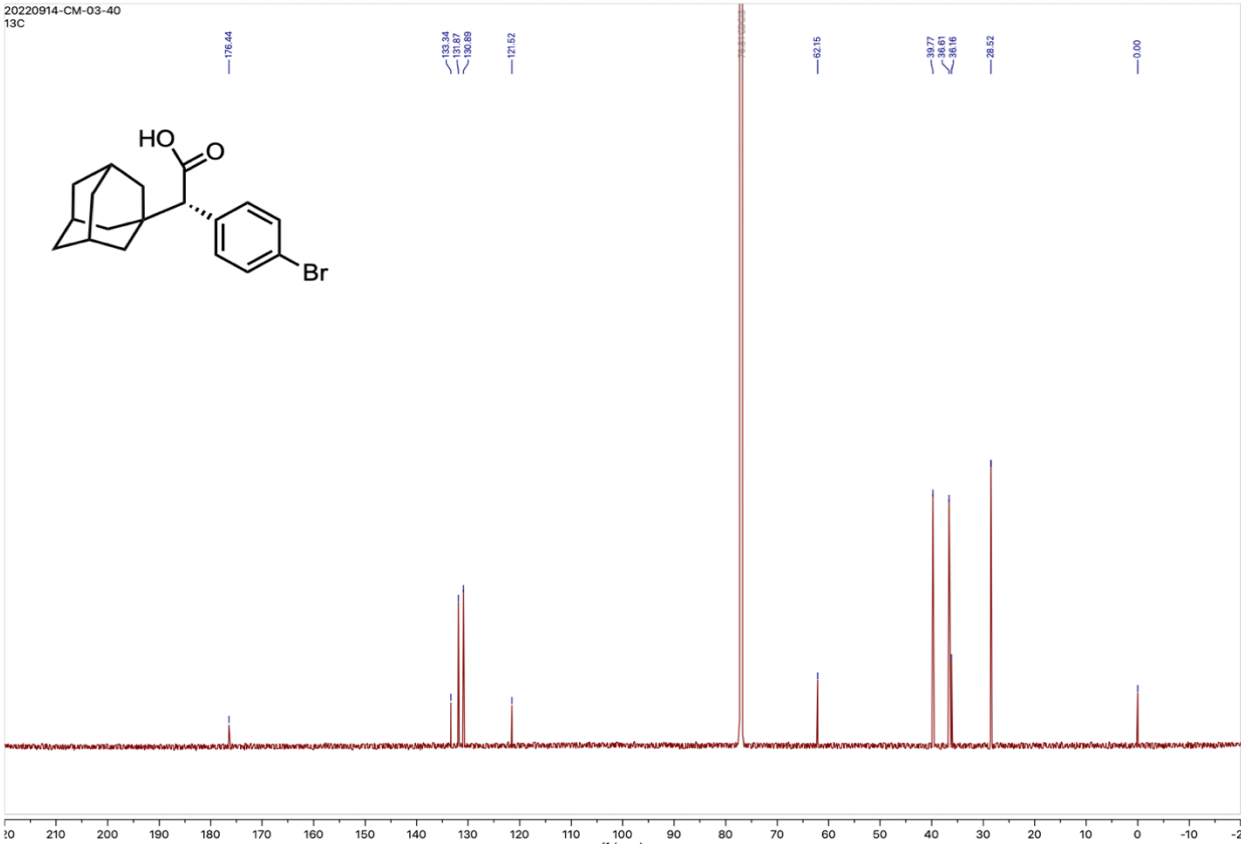
Entry 3 (5b)

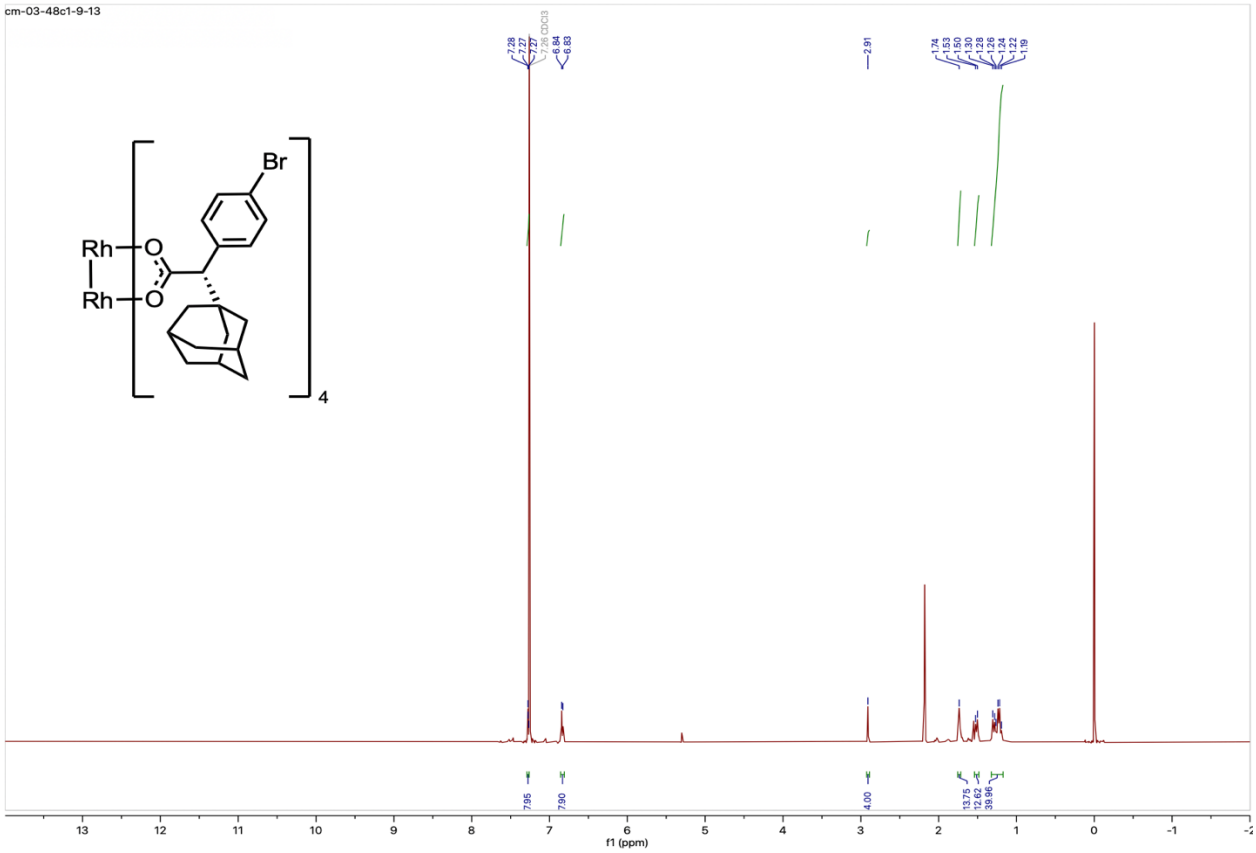
Chiral resolution is in progress.

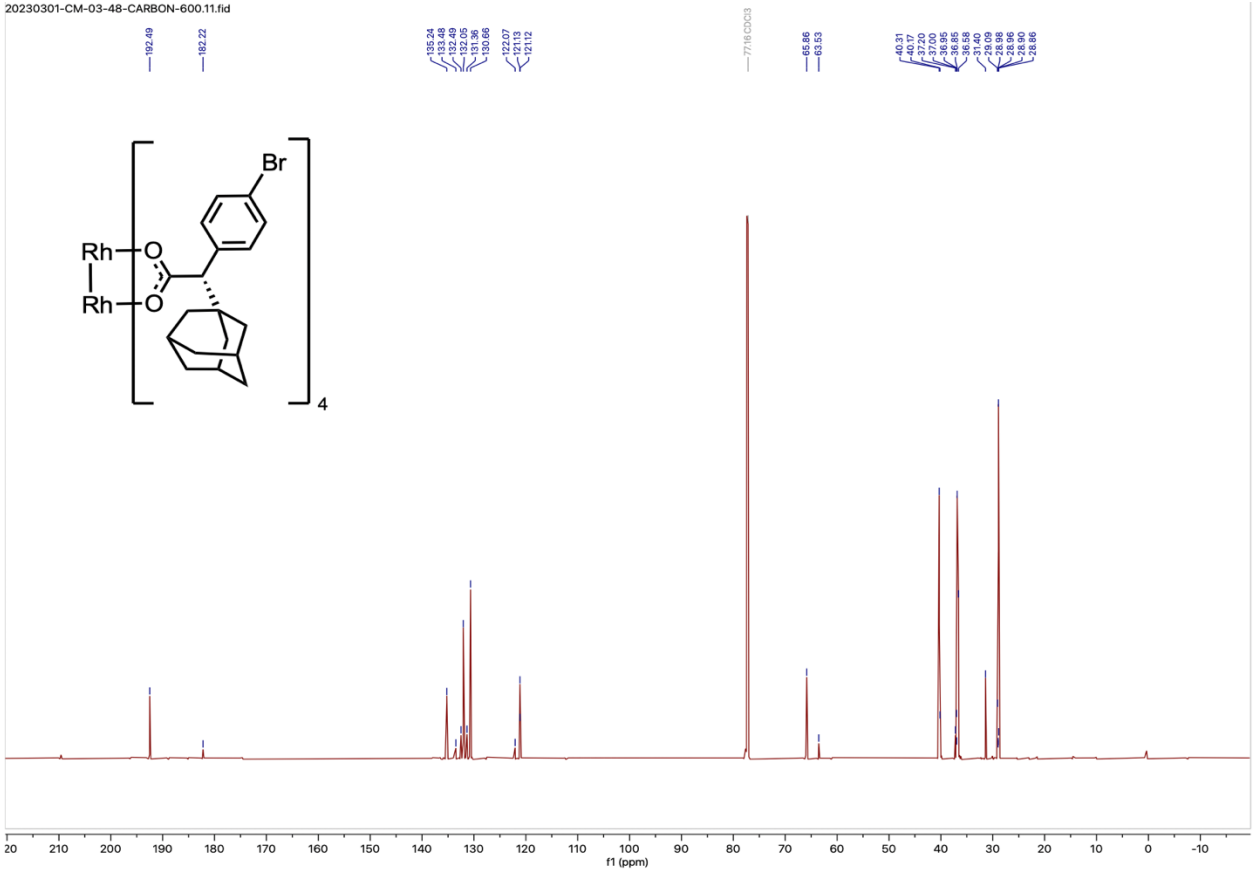
5.6) NMR Spectra

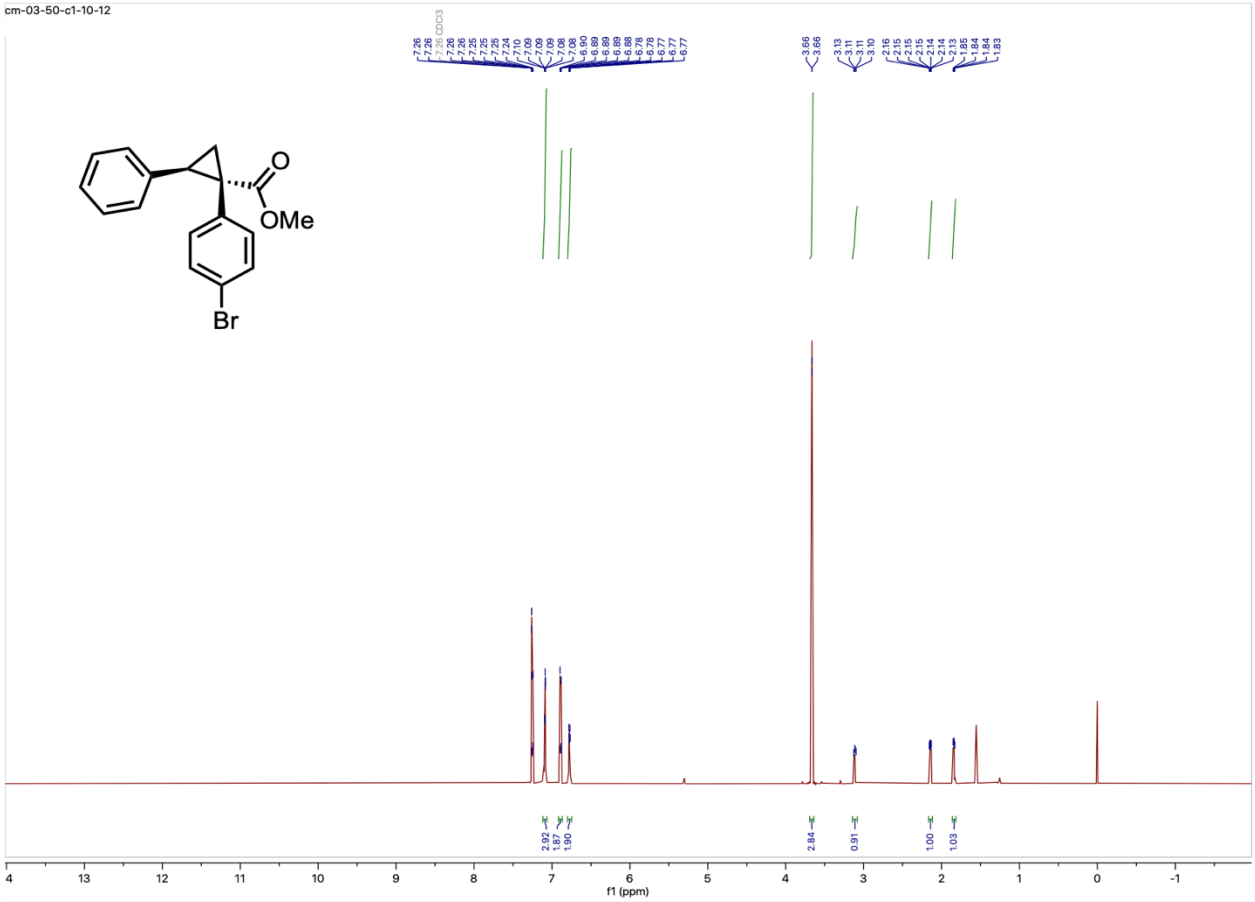


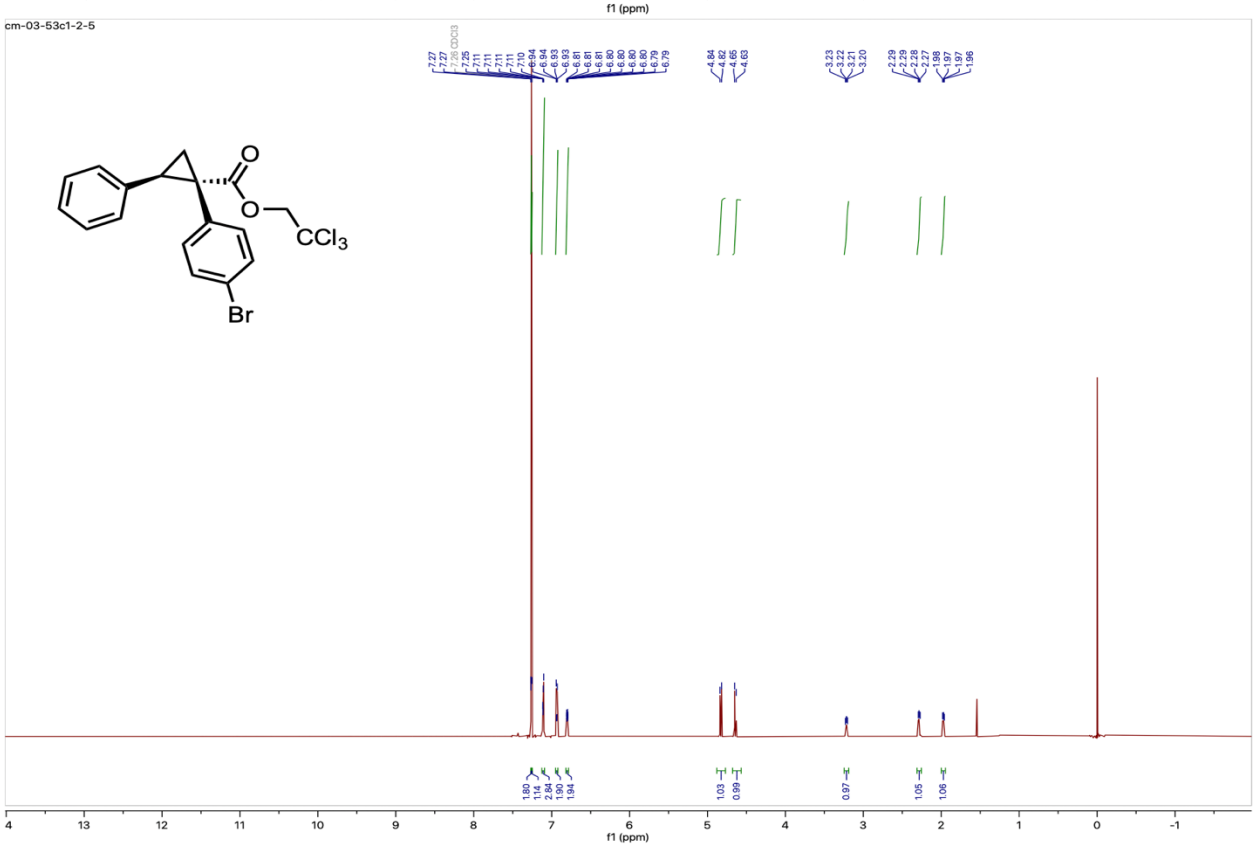

cm-03-40
HO
O
Br
f1 (ppm)

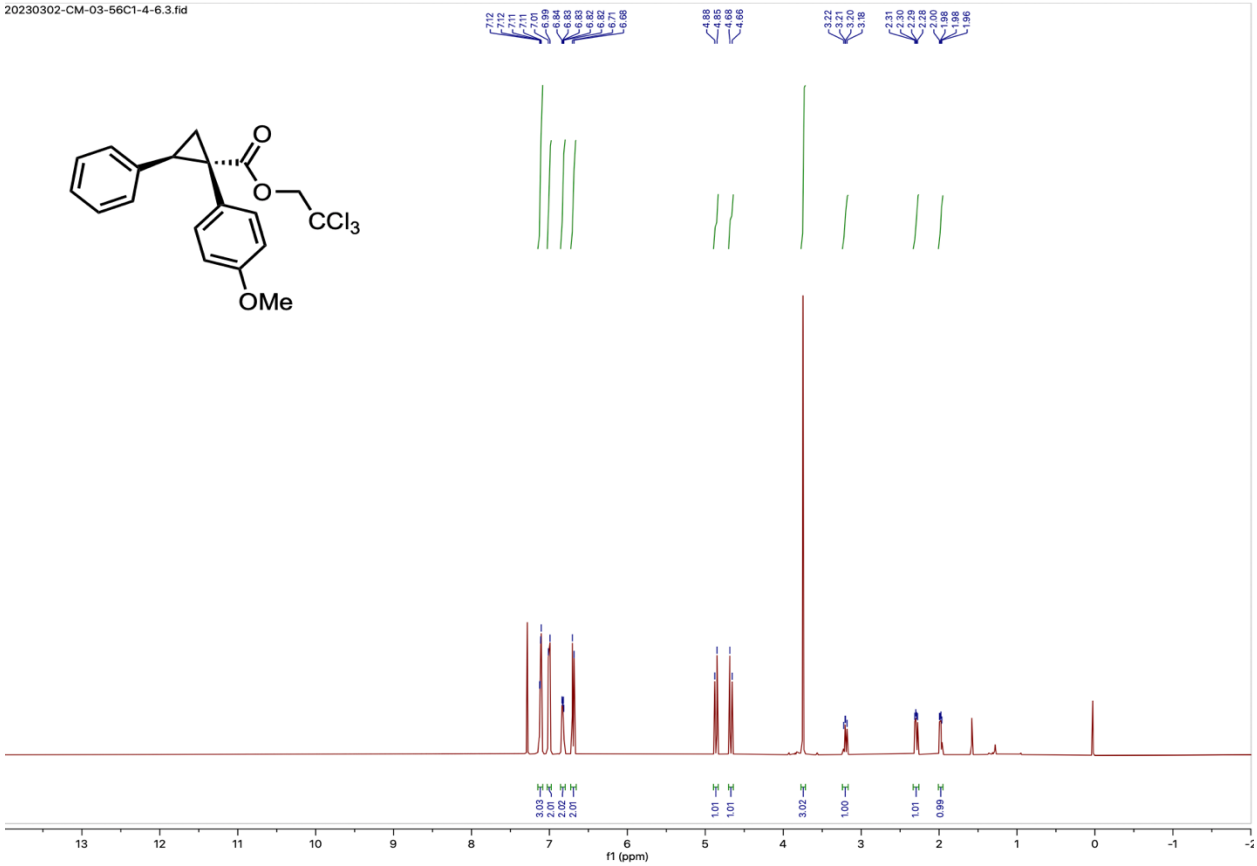

20220914-CM-03-40
13C
HO
O
Br

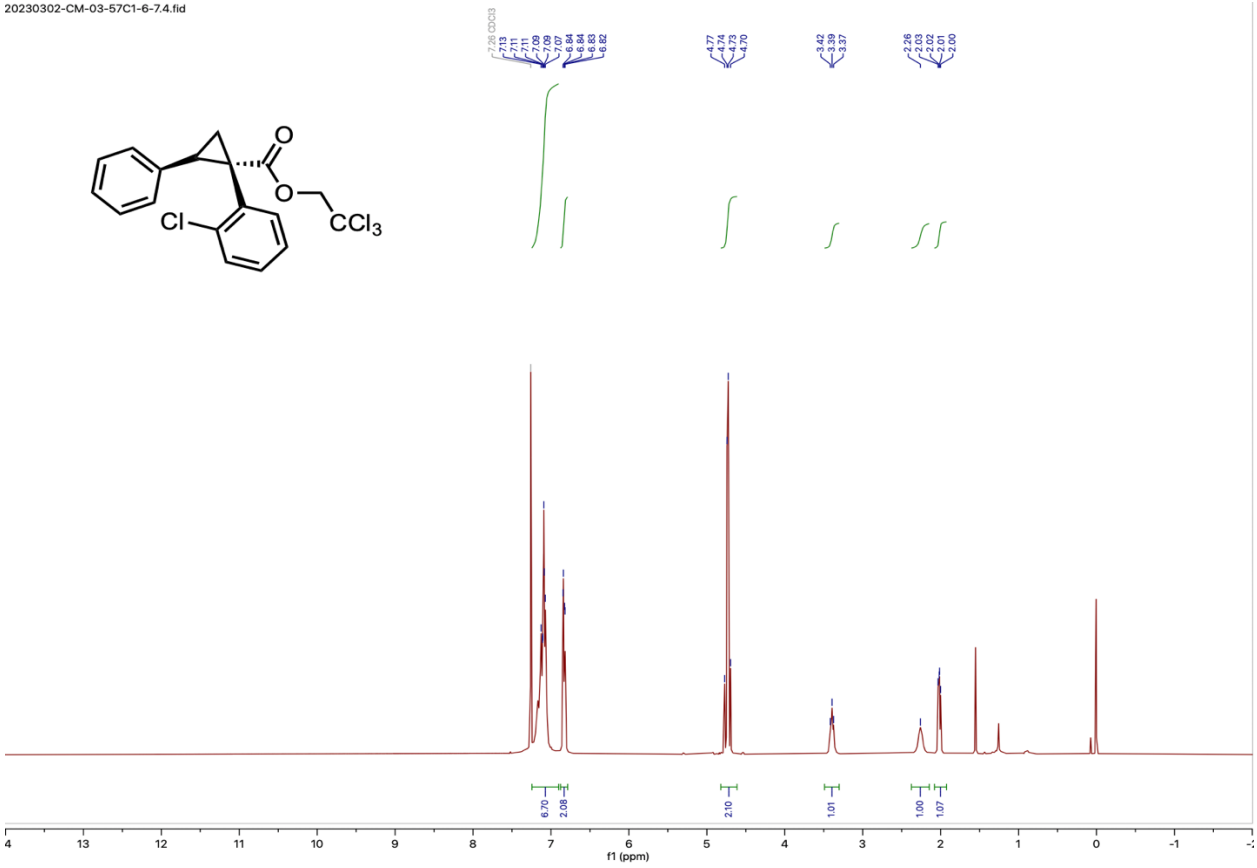

cm-03-48c1-9-13
Br
Rh
O
Rh
O
4
f1 (ppm)


20230301-CM-03-48-CARBON-600.11.fid
Br
Rh
O
Rh
O
4
f1 (ppm)


cm-03-50-c1-10-12
O
OMe
Br
f1 (ppm)


cm-03-53c1-2-5
O
O
CCl3
Br
f1 (ppm)


20230302-CM-03-56C1-4-6.3.fid
O
O
CCl3
OMe
f1 (ppm)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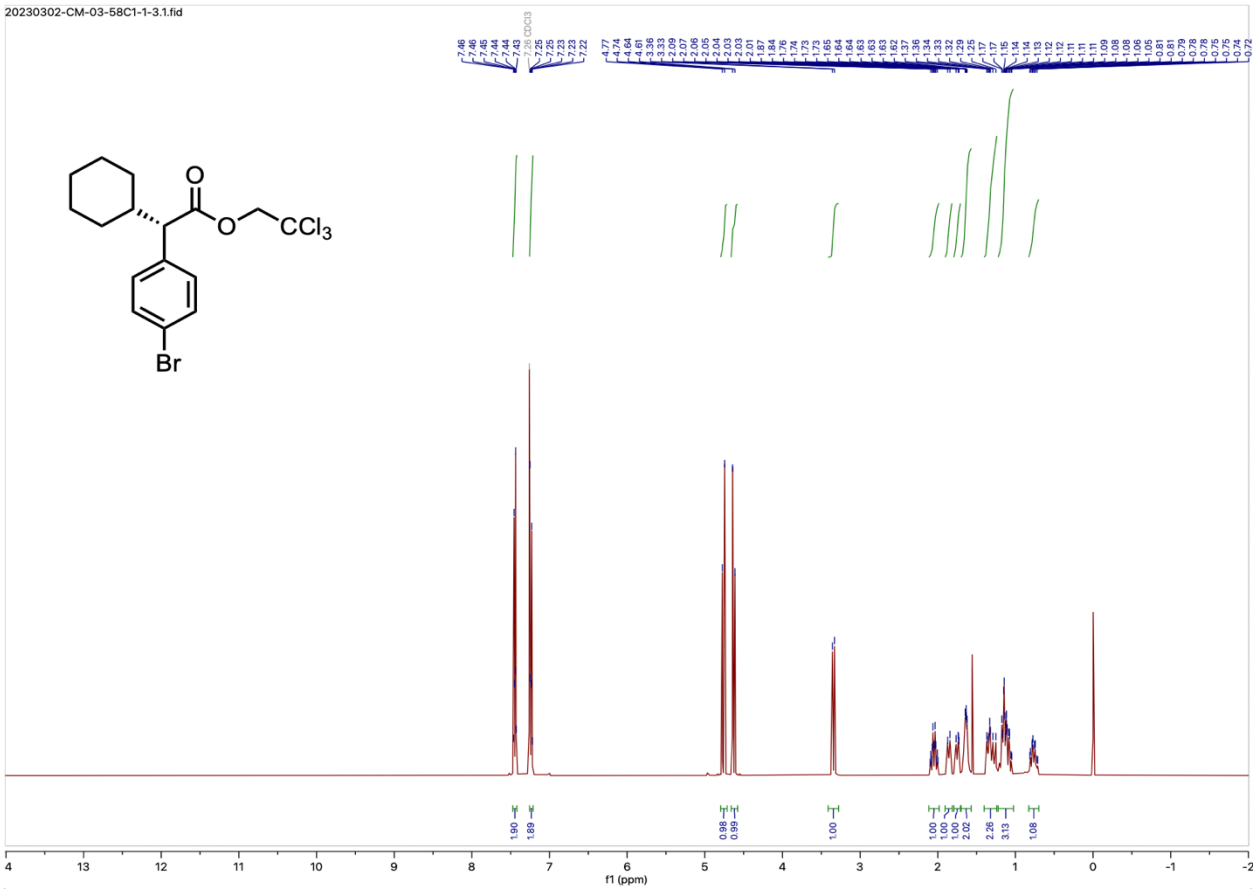
O
O
Cl
CCl3
f1 (ppm)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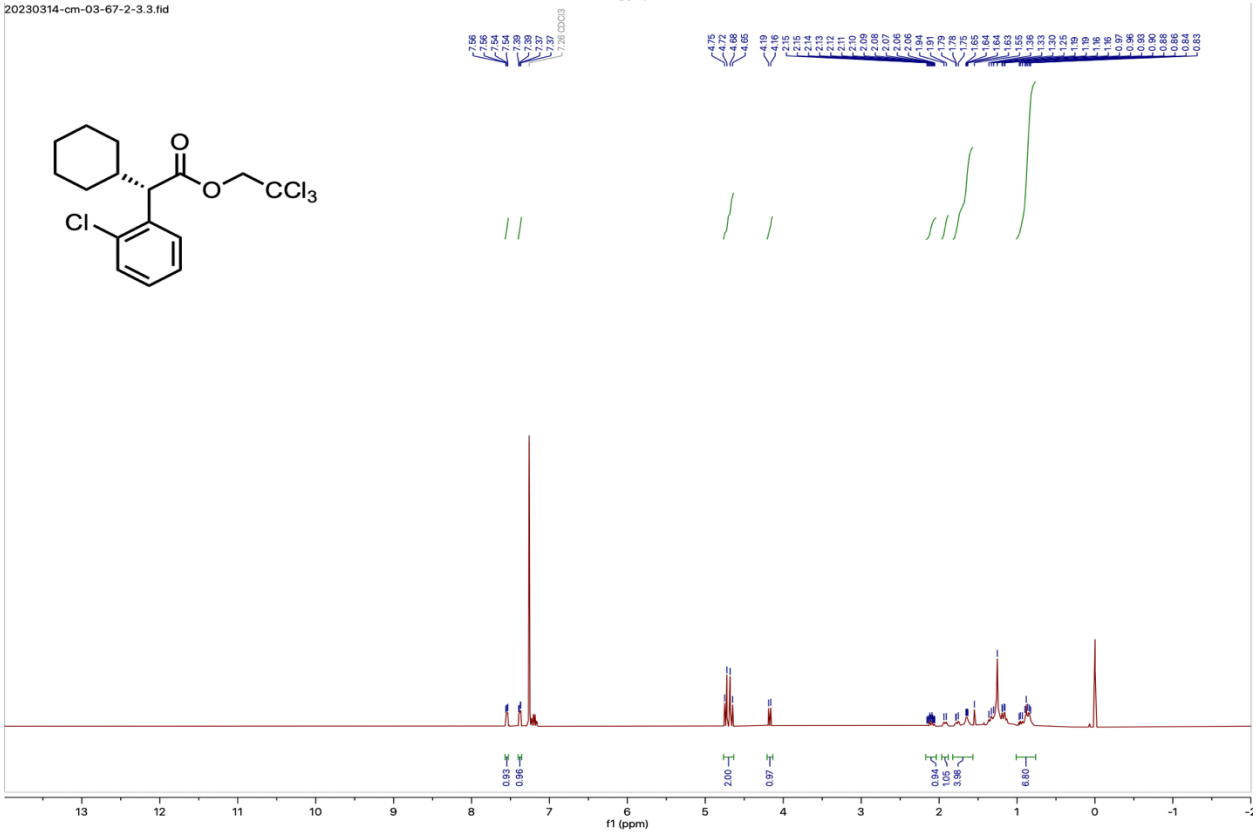
O
O
CCl3
Br
f1 (ppm)


20230314-cm-03-67-2-3.3.fid
O
O
CCl3
Cl
f1 (ppm)

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