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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
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Abstract

A Methodological Study of Enantioselective Dirhodium(II)-Catalyzed Cyclopropanations at Low Catalyst Loadings

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Dirhodium(II) catalyzed carbene chemistry has proven to be one of the most effective ways to selectively transform bonds that are traditionally difficult to functionalize. However, rhodium is a rare and expensive metal. With a serious demand for cost efficient methods in synthetic chemistry, rhodium must be used sparingly. This study investigates dirhodium(II) catalyzed cyclopropanations at low catalyst loading ranging from 0.001 mol% to 0.00001 mol% with a variety of dirhodium(II) catalysts, diazo substrates, solvents in order to optimize for reaction conditions that provide high turnover numbers (TONs) and excellent enantioselectivity. The best conditions for high turnover numbers yielded 5.7 million TONs with 20% ee. The best conditions for high enatioselectivity at low catalyst loading yielded 780,000 TONs with 85% ee.

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Acknowledgements

First of all, I would to thank my primary investigator, Dr. Huw Davies, for three great years of mentoring. He has supported my career in chemistry every step of the way. I'm grateful for having opportunity to do cutting-edge chemistry in his lab, and having the unique opportunity to do collaborative research in Nagoya Japan through the Davies lab. He has given me the tools to continue to be successful in graduate studies and I do not think I could have possibly asked for a better undergraduate research experience.

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Finally, I would like to thank the entire Davies group for providing me with an excellent learning environment.

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Figures and Tables

1) Introduction

1.1) Diazo Decomposition and Carbene Formation

Metal catalyzed decomposition of diazo compounds is one of the possible strategies to form highly reactive carbene intermediates.[1] A generally accepted mechanism for the decomposition of the diazo group is shown in Figure 1.

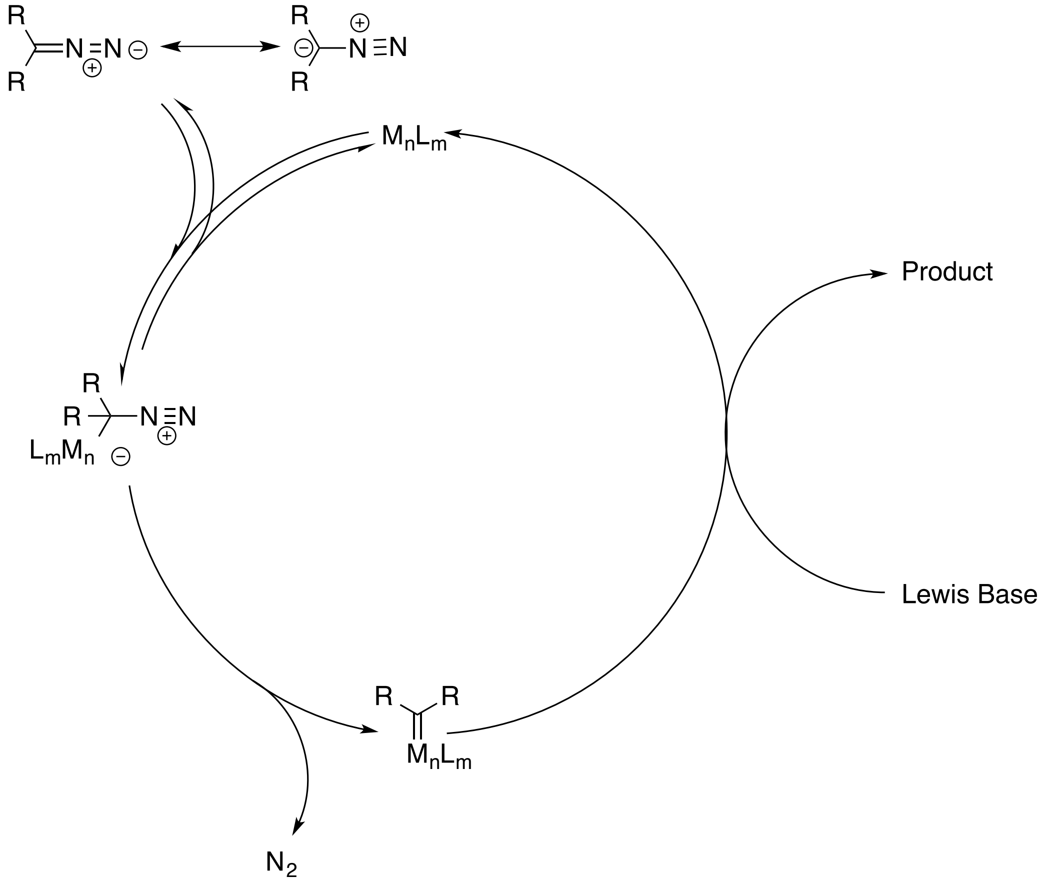


Figure 1: Mechanism for Diazo Decomposition

First, the electronegative diazo carbon coordinates to the metal via nucleophilic attack. Second the negatively charged metal forms the carbene intermediate and ejects the diazo leaving group as molecular nitrogen. Third, a Lewis base reacts with the carbene to regenerate the catalyst and synthesize the product. Carbene chemistry is capable of transforming many different kinds of bonds. A vast array of Lewis bases can be used to trap the carbene intermediate.[1] Cyclopropanation[2], C–H insertion[3] and ylide formation[4] reactions are just a few examples to represent the versatility of carbene reactivity.

Carbenes have been classified according to the substituents attached to the center of the carbene[5]. The three classifications of carbenes are acceptor carbenes, acceptor-acceptor carbenes, and donor-acceptor carbenes. Acceptor carbenes contain a single electron-withdrawing group that is attached to the carbene carbon. Acceptor-acceptor carbenes contain two electron-withdrawing groups that are attached to the carbene carbon. Donor-acceptor carbenes contain an electron-donating group and electron-withdrawing group that are attached to the carbene carbon. Figure 2 shows an example of the classes of carbene and qualitatively evaluates the reactivity and selectivity of each.

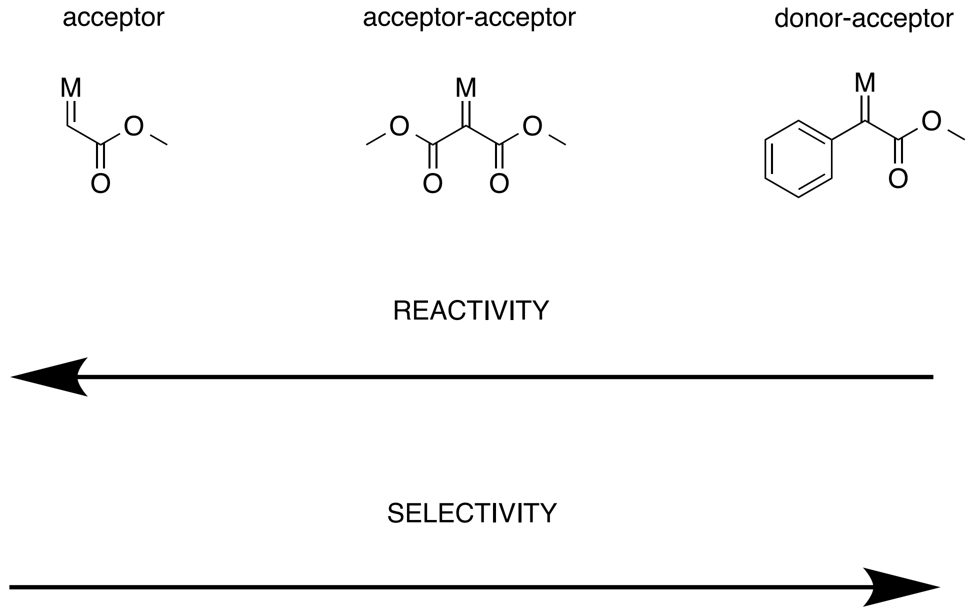


Figure 2: Classes of carbene compared in terms of reactivity and selectivity.

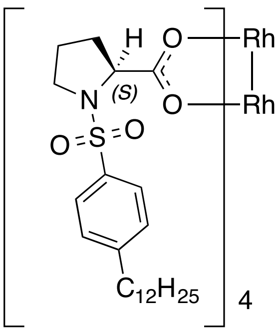
The donor-acceptor is the least reactive species because the electrophilic carbene carbon is stabilized by the electron-donating group. Consequently it is the most selective of the three classes of carbenes.[5] Donor-acceptor carbenes proved to be very effective for selective cyclopropanation, which will be discussed further in a later section.

1.2) Catalyst Structures and Background

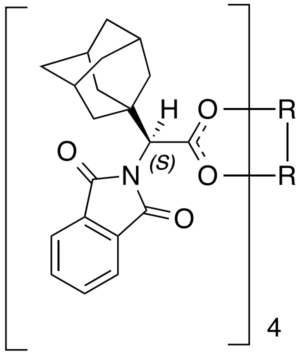
Reactivity of a carbene is also influenced by the nature of the metal in the carbene bond.[1] This metal must be Lewis acidic to accept electron density from the diazo carbon. Many metals have been used for carbene chemistry such as iron, cobalt, copper, palladium, ruthenium and rhodium.[1]

Rhodium is a particularly good choice for selective carbene functionalization because dirhodium(II) tetracarboxylate catalysts are easy to synthesize. Ever since dirhodium(II) tetraacetate was used to hydrogenate olefins,[6] dirhodium(II) tetracarboxylates have been extensively studied for carbene formation. Carboxylate ligands are very easy to synthesize and exchange on the dirhodium(II) catalysts, laying a well structured paddlewheel framework that can include enantiopure ligands.[3]

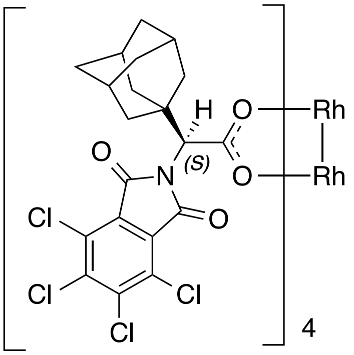
The Davies lab specializes in dirhodium(II) catalysis. The six catalysts in Figure 3 were used in this project.



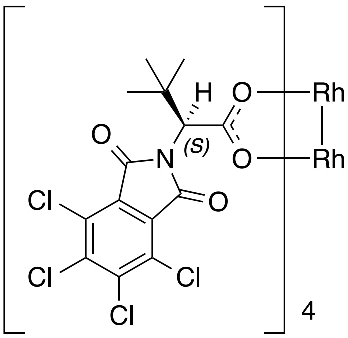
$\mathrm{Rh_2}(S\text{-DOSP})_4$



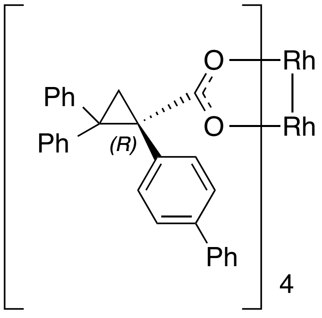
$\mathrm{Rh_2}(S\text{-PTAD})_4$



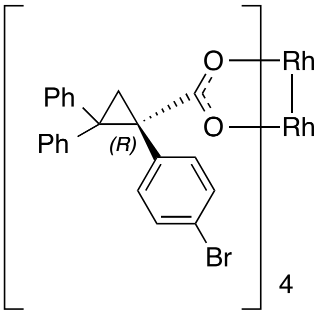
$\mathrm{Rh_2}(S\text{-TCPTAD})_4$



$\mathrm{Rh_2}(S\text{-TCPTTL})_4$



$\mathrm{Rh_2}(R\text{-BPCP})_4$



$\mathrm{Rh_2}(R\text{-BTPCP})_4$

Figure 3: The six dirhodium(II) catalysts used in this study

The first generation of chiral dirhodium(II) catalyst in the Davies lab was made with N-(arylsulfonyl)prolinate ligands. After a ligand screening for the para substituted group, the ligand with the dodecyl carbon chain, known as DOSP, was found to have extremely high performance in terms of enantioinduction and diastereoselectivity.[2] This catalyst is known as Rh_2(*S*-DOSP)$_4$. Rh_2(*S*-DOSP)$_4$ has been used to lay a lot of the foundation of carbene chemistry[5] and will be discussed in more detail in the cyclopropanation section.

A decade after the debut of Rh_2(*S*-DOSP)$_4$, two new chiral catalyst based on a phthalimido framework, Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-TCPTAD)$_4$ were synthesized.[7],[8] Rh_2(*S*-PTAD)$_4$ proved to be very enantioselective with cyclopropanation reactions and was considered an effective backup for Rh_2(*S*-DOSP)$_4$.[7] Rh_2(*S*-TCPTAD)$_4$ is the tetrachloro substituted version of Rh_2(*S*-PTAD)$_4$. Rh_2(*S*-TCPTAD)$_4$ was successful in preforming C–H selective amination reactions[8] and more recently has shown the capability of performing a double C–H insertion on a highly complex molecule.[9] Rh_2(*S*-TCPTTL)$_4$, derived from Hashimoto's catalyst Rh_2(*S*-PTTL)$_4$, was the original phthalimido catalyst to be chlorinated and excelled in performing C–H amidation chemistry.[10] The triarylcyclopropanecarboxylate catalysts, Rh_2(*R*-BPCP)$_4$ and Rh_2(*R*-BTPCP)$_4$ are created via asymmetric cyclopropanation carried out by Rh_2(*S*-DOSP)$_4$.[11,12] This class of catalyst has shown great success in selectively inserting in to primary C–H bonds[13] and cyclopropanating trichloro ethyl ester diazoaceate with high levels of enantioinduction.[14] These catalysts all have shown promise in unique reactivity where their predecessors have failed.

1.3) Cyclopropanation

Three membered carbon rings appear in numerous natural products,[15] and can be useful intermediates in syntheses requiring a highly stereoselective ring opening process.[16] Thus finding new methods to effectively synthesize cyclopropanated compounds is an exciting area in synthetic-organic chemistry. Moreover, most biologically active molecules have multiple stereo-centers, making highly diastereoselective and enantioselective catalysis desirable.

$Rh_2(S\text{-DOSP})_4$ was the first successful chiral dirhodium(II) catalyst to perform highly diastereo and enantioselective carbene facilitated cyclopropanation reactions.[2] This discovery, made by Davies, not only revolutionized the field of dirhodium(II) catalyzed carbene chemistry, but it also lead to the a mechanistic proposal shown in Figure 4.

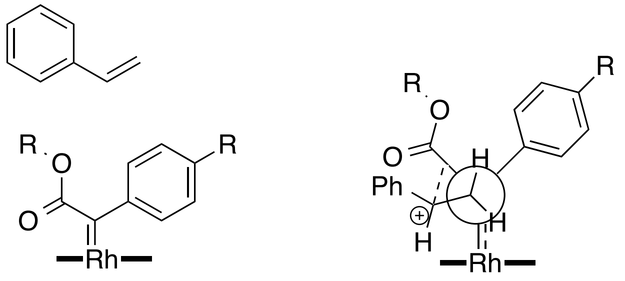


Figure 4: Davies' initial proposed mechanism to explain the stereochemistry of the product

The substrate approaches the carbene with the bulky substituents facing away from the surface of the catalyst due to steric crowding. This provides a reasonable explanation for why *trans*-alkenes do not successfully cyclopropanate through carbene facilitated chemistry.[2] The electron rich alkene group of styrene begins to donate electron density to the electron poor carbene carbon. While the bond begins to form between the primary carbon on styrene and the carbene carbon, partial positive charge on the secondary carbon on styrene is stabilized by the electronegative ester. This explains the transition state shown on the right hand side of figure 4. Simultaneously electron density from the carbene bond shifts toward the secondary carbon on styrene, completing the reaction with observed stereochemistry. The preferred stereochemistry of the cyclopropanated product leaves the aryl group from styrene and the ester from the diazo trans to one another.

1.4) High Turnover Numbers for Rh_2 Catalyzed Cyclopropanation

The reactivity and selectivity of chiral dirhodium(II) are excellent, but rhodium is a rare and precious metal. Sustainability is an important consideration for the future and application of carbene chemistry. There are three methods to push for more sustainable chemistry. First row transition metal catalysts are popular, since the material is much cheaper than the precious metal catalysts such as ruthenium, rhodium and palladium. Another approach is immobilizing the catalyst by attaching it to a solid support. Flow chemistry with solid supported Rh_2(*S*-DOSP)$_4$ derivative was previously accomplished in the Davies group.[17] Achieving high TONs is a way that precious metal catalysts can still be the most synthetically useful, when cost efficiency comes into question. This study focuses on the last approach.

With Rh_2(*S*-DOSP)$_4$ being the best catalyst for carbene facilitated cyclopropanation of alkenes in terms of diastereo and enantio control, tests were also conducted to see if the catalyst was capable of performing high turnover numbers (TONs) in the initial studies with this catalyst.[2] TONs can be calculated by Equation 1.

$$\frac{moles\ of\ desired\ product\ produced}{moles\ of\ catalyst} = TONs \qquad 1)$$

Rh_2(*S*-DOSP)$_4$ was able to perform 5000 TONs, 50% conversion at 0.0001 equivalents. However, the enantioselectivity significantly dropped from 92% ee to 50% ee. Chiral and achiral carboxylate additives were placed in reaction to see if the mechanism for drop in %ee was ligand exchange. Little change suggested that the catalyst was being poisoned instead.[2]

In the Davies lab, multiple studies have been done on cyclopropantion at low catalyst loadings, since the debut of Rh_2(*S*-DOSP)$_4$.[18,19] In particular, solvent free studies with donor-acceptor diazo compounds have shown that Rh_2(*S*-DOSP)$_4$ is capable of doing 900,000 TONs with 69% ee in 144 h and Rh_2(*S*-PTAD)$_4$ is capable of doing 1,800,000 TONs with 51% ee in 72 h for cyclopropanation reactions.[19] Although these results were impressive, in terms of turnover numbers, the enantioselectivity was mediocre.

The purpose of the following study is to investigate some of the newer dirhodium(II) paddlewheel catalysts, as well as new donor-acceptor diazo compounds try to achieve high TONs with good enantioinduction. A system was found that was capable of performing 5.7 million TONs with 20% ee. A more enantioselective system was found that was capable of performing 780,000 TONs with 85% ee.

2) Results and Discussion

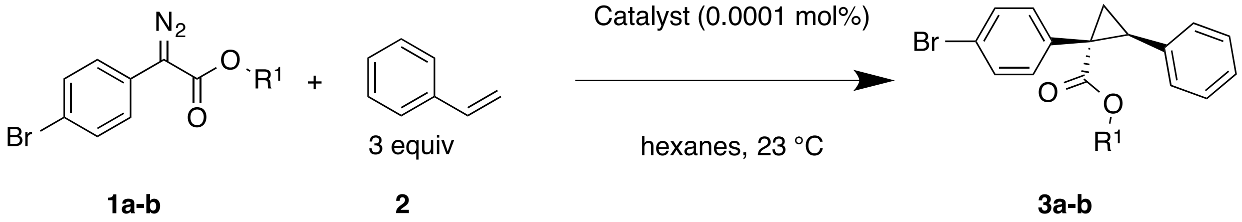
2.1) The Initial Cyclopropanation Study at 0.0001 mol% Catalyst Loading

There have been many great strides in the advancement of dirhodium(II) catalyst since the days when Rh_2(*S*-DOSP)$_4$ was first introduced. For instance, the phthalamido based ligand catalysts, Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-TCPTAD)$_4$.[7,8] Additionally, the cyclopropanated triphenyl products produced by the highly selective reactions with Rh_2(*S*-DOSP)$_2$ can be used as ligands in a second generation of catalysts, like Rh_2(*R*-BTPCP)$_4$.[12] These new catalysts have shown promise to be more robust than the first generation catalyst, and on that premise were selected as candidates to perform high TONs.

Advances in donor-acceptor diazo compounds have also been made. Trichloroethyl substituted diazo compounds have shown great success in functionalizing methyl ethers, whereas the traditional methylester diazo compounds have not performed as well. [20]

An initial screening of these four catalyst and two diazo compounds was performed at 0.0001 mol% catalyst loading. The purpose of this experiment was to simply see if any diazo/catalyst combination in particular stood out in terms of excellent reactivity or selectivity. Table 1 shows a summary of the results obtained from this experiment.

Table 1: Initial catalyst diazo screening at 0.0001 mol% catalyst loading.



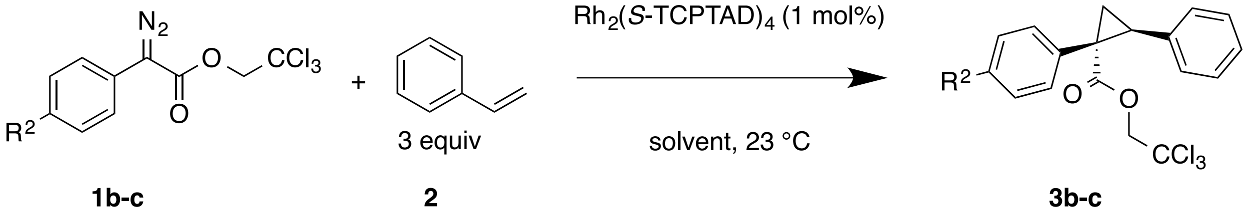
R^1	t (h)	Catalyst	Yield[a]	ee[b]
Me	185	Rh_2(*S*-DOSP)$_4$	-	-
Me	185	Rh_2(*S*-PTAD)$_4$	-	-
Me	185	Rh_2(*S*-TCPTAD)$_4$	-	-
Me	185	Rh_2(*R*-BTPCP)$_4$	-	-
CH_2CCl_3	22.5	Rh_2(*S*-DOSP)$_4$	8%	ND
CH_2CCl_3	22.5	Rh_2(*S*-PTAD)$_4$	8%	ND
CH_2CCl_3	22.5	Rh_2(*S*-TCPTAD)$_4$	88%	45%
CH_2CCl_3	185	Rh_2(*R*-BTPCP)$_4$	27%	ND

Reaction conditions: **2** (3 equivalents), hexanes, 23 °C, c=0.3 M. [a]Yields determined by ^{1}H NMR (400 MHz) with mesitylene and 1,3,5 trimethoxybenze as internal standards. [b]ee determined by HPLC.

The Rh_2(*S*-TCPTAD)$_4$ catalyzed cyclopropanation of the trichloro-ethyl substited diazoacetate showed remarkable reactivity, going to completion in less than 24 h. Even though this reaction had poor enantioinduction of 45% ee it was chosen for further studies on the premise that it could potentially do more TONs than reported in the previous literature and could be optimized for better enantioselectivity.

2.2) Optimization of Solvent and Substituent Effect at 1 mol% Catalyst Loading

The solvent effect and the effect of substituents in the para position were explored. These results are summarized in Figure 5.



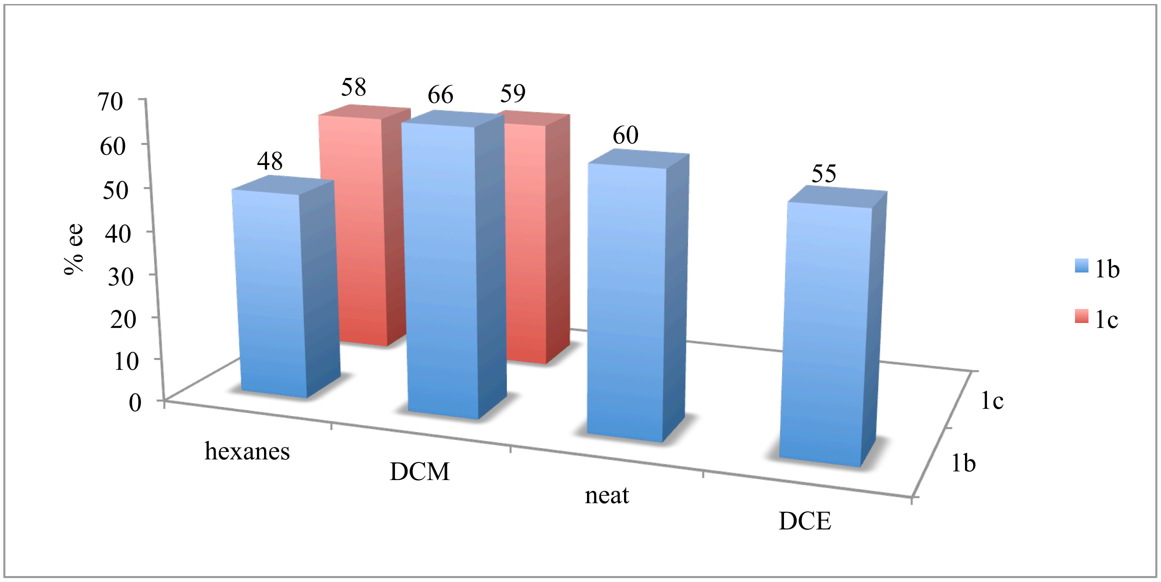


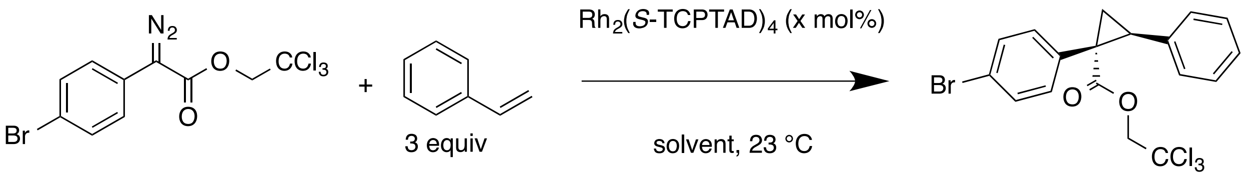
Figure 5: Optimization at 1 mol% catalyst loading

Reaction conditions: **2** (3 equivalents), 23 °C, c=0.3 M. Reactions went until completion. ee determined by HPLC. **1b** in hexanes and **1c** in hexanes and DCM were added over 3 h. Reactions all went to complete conversion.

The dirhodium(II) catalyzed cyclopropanation of para-bromo substituted diazoacetate in dichloromethane resulted in the highest levels of enantioinduction with 66% ee. Another interesting find from this study was that even at the catalyst loading of 1 mol% which is typical loading used for dirhodium(II) catalyzed cyclopropanations,[14] only 48% ee was found for cyclopropanation of the para-bromo substituted diazoacetate in hexanes. This signifies that unlike other chiral dirhodium(II) catalysts reported in previous studies,[2,18,19] Rh_2(*S*-TCPTAD)$_4$ is capable of going to very low catalyst loadings without experiencing a significant drop in enantioselectivity. The improved enantioselectivity of the Rh_2(*S*-TCPTAD)$_4$ catalyzed cyclopropanation of the para-bromo substituted diazoacetate in DCM, lead to a study of the decrease in enantioselectivity as a function of catalyst loading. The results of this study are displayed in Table 2.

2.3) The Effects of Low Catalyst Loading on Enantioinduction

Table 2: Enantioselectivity at different catalyst loadings and in different solvents



1b **2** **3b**

Entry	Catalyst loading (mol%)	Solvent	Time (days)	Yield[a]	Conversion[b]	ee[c]
1	1	hexanes	ND	ND	ND	48%
2	1	DCM	ND	ND	ND	66%
3[d]	0.0001	hexanes	1	88%	ND	45%
4[d]	0.0001	DCM	1	63%[e]	ND	52%
5[d]	0.00001	hexanes	7	57%	83%	20%
6[d]	0.00001	DCM	7	ND	38%	42%

Reaction conditions: **2** (3 equivalents), hexanes and DCM, 23 °C, c=0.3 M. [a]Yields determined by ^{1}H NMR (400 MHz) with mesitylene and 1,3,5 trimethoxybenze as internal standards. Conversion[b] is a qualitative measurement calculated with Equation 2. [c]ee determined by HPLC. [d]Additive was 4 Å molecular sieves. [e]Isolated yield.

$$\frac{\left(\frac{\text{cyclopropane integration}}{\text{number of equivalent hydrogens}}\right)}{\left(\frac{\text{cyclopropane integration}}{\text{number of equivalent hydrogens}}\right)+\left(\frac{\text{diazo integration}}{\text{number of equivalent hydrogens}}\right)}\times 100\% = {}^{1}H\ NMR\ conversion \tag{2}$$

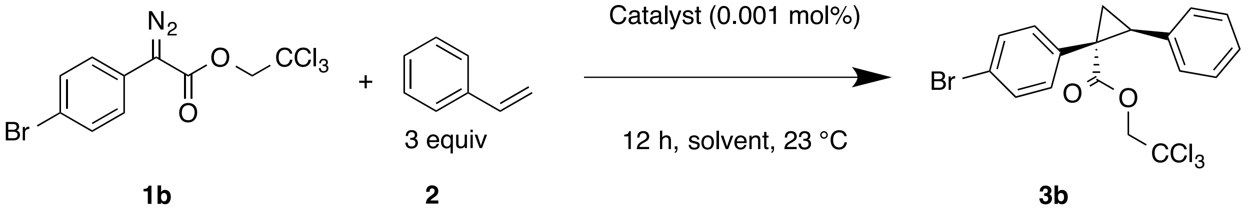
Equation 2 gives a qualitative measurement for conversion of the reaction by dividing the ^{1}H NMR estimation of products by the ^{1}H NMR estimation of products plus reactants.

Along with previously reported results from the previous two studies, this table contains the Rh_2(*S*-TCPTAD)$_4$ catalyzed cyclopropanation of para-bromo substituted diazoacetate at 0.0001 mol% in DCM and 0.00001 mol% in DCM and hexanes. Remarkably, Rh_2(*S*-TCPTAD)$_4$ was capable of achieving 5.7 million TONs with 20% ee in hexanes and approximately 3.8 million TONs with 42% ee in DCM. These TONs were significantly higher than those reported previously for dirhodium(II) catalyzed cyclopropanation in the literature.[19] An interesting feature of this study is the drop in enantioselectivity. There seems to be a consistent pattern in the dropping of enantioselectivity for reactions in DCM as opposed to little decrease in % ee for reactions in hexanes from 1 mol% to 0.0001 mol%, but a large drop in % ee from 0.0001 mol% to 0.00001 mol%.

Even though the TONs of these reactions were impressive, not much data was gathered on reaction rates, and the enantioselectivity was moderate to poor in general for Rh_2(*S*-TCPTAD)$_4$ catalyzed cyclopropanation. Therefore, it was necessary to do another systematic catalyst screening using insitu infrared monitoring (ReactIR®).

2.4) Systematic Cyclopropanation Study at 0.001 mol% Catalyst Loading

A set of experiments followed 5 cyclopropanation reations catalyzed by different dirhodium(II) complexs at 0.001 mol% catalyst loading via ReactIR® software. The ReactIR® data for diazo decomposition by Rh_2(*S*-TCPTTL)$_4$, Rh_2(*R*-BPCP)$_4$, Rh_2(Octanoate)$_4$ or Rh_2(Oct)$_4$, Rh_2(*S*-TCPTAD)$_4$, Rh_2(*S*-DOSP)$_4$ were treated using Microsoft Excel® and plotted against each other in Figure 6. The data from these reactions is compiled in Figure 7.



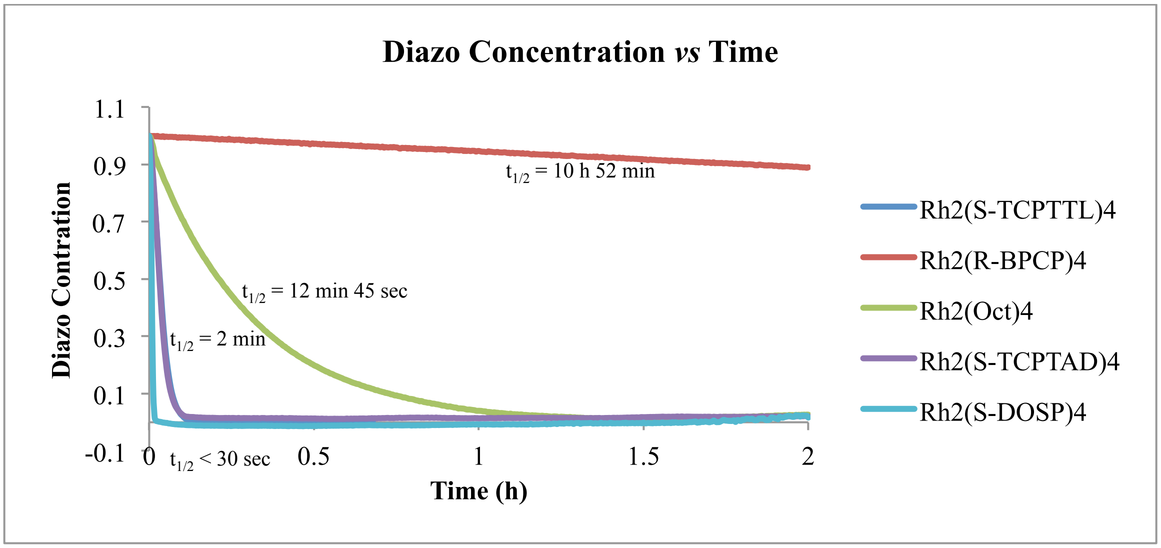


Figure 6: Diazo concentration following IR peak 2101 cm^{1-} on a relative scale *vs* time in h. Rh$_2$(*S*-TCPTAD)$_4$ and Rh$_2$(*S*-TCPTTL)$_4$ catalyzed reactions are overlapping.

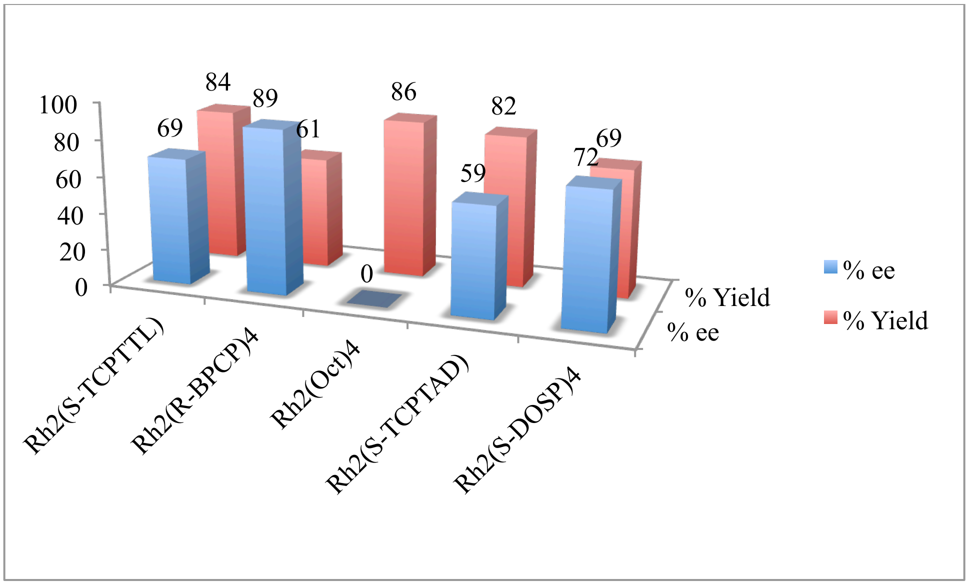


Figure 7: Catalyst screening for cyclopropanation at 0.001 mol% catalyst loading

Reaction conditions: **2** (3 equivalents), DCM and hexanes for Rh$_2$(*S*-DOSP)$_4$, 23 °C, c=0.3 M. Opposite enantiomer formed with Rh$_2$(*R*-BPCP)$_4$. Yields determined by mass of isolated product. ee determined by HPLC.

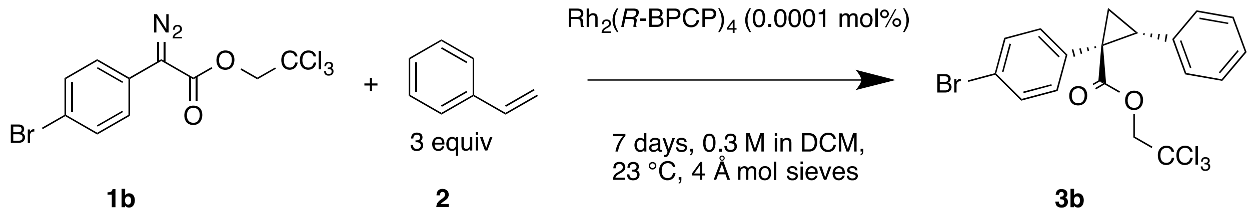
In all cases the signal relative to the diazo peak (2101 cm^{-1}) decreased with time following first order behavior. The Rh$_2$(*S*-DOSP)$_4$ catalyzed cyclopropanation in hexane was the fastest reaction, with the half-life of less than 30 sec. The Rh$_2$(*S*-TCPTAD)$_4$ and Rh$_2$(*S*-TCPTTL)$_4$ catalyzed cyclopropanation reactions had the half-life of 2 min each. The Rh$_2$(Oct)$_4$ catalyzed cyclopropanation reaction had the half life of 12 min and 45 sec. The Rh$_2$(*R*-BPCP)$_4$ catalyzed cyclopropanation reaction had the half life of 10 h and 52 min and did not go to completion in the 12 h ReactIR® monitoring period.

These 5 reations were evaluated in terms of reaction speed, based on reaction half-life and enantioselectivity. Rh$_2$(Oct)$_4$ was chosen to catalyze an achiral control reaction as a point of reference. Rh$_2$(*S*-DOSP)$_4$ being the catalyst that defined diastereoselective intermolecular cyclopropanation,[2] was chosen to be a point of comparison to the newer catalysts. The tetrachloro substituted phthalimido, Rh_2(*S*-TCPTAD)$_4$ and Rh_2(*S*-TCPTTL)$_4$, were successful at catalyzing the double C–H insertion reaction in the synthesis of Dictodendryn A,[9] and enantioselective C–H amidation.[10] Rh_2(*R*-BPCP)$_4$ showed excellent enantioselectivity in a recent catalyst screen for cyclopropanation at 1 mol%.[14]

There are a few key highlights to be noted from this study. First of all the Rh_2(*S*-DOSP)$_4$ catalyzed cyclopropanation was by far the fastest reaction, being more than halfway finished in 30 sec. Not only more reactive, the Rh_2(DOSP)$_4$ catalyzed reaction was also more selective than the Rh_2(*S*-TCPTAD)$_4$ and Rh_2(*S*-TCPTTL)$_4$ catalyzed reactions at this catalyst loading with 72% ee compared to 60% ee and 69% ee respectively. With the same reaction rate as the Rh_2(*S*-TCPTAD)$_4$ catalyzed reaction, Rh_2(*S*-TCPTTL)$_4$ becomes a superior choice of catalyst at this loading due to the increased enantioselectivity. Although the Rh_2(*R*-BPCP)$_4$ catalyzed reaction was the slowest, in the screening with the half-life of 10 h and 52 min, it was the most enantioselective reaction in the study with 89% ee. This result is supported by previous data showing that Rh_2(*R*-BPCP)$_4$ was the most successful catalyst for cyclopropanating trichloroethyl ester diazo compounds.[14]

Since Rh_2(*S*-DOSP)$_4$ has been studied extensively even at low catalyst loadings, it would be beneficial to study Rh_2(*R*-BPCP)$_4$ further and push for higher turnover numbers and optimize for better reactivity and enantioselectivity. A case could also be made for studying Rh_2(*S*-TCPTTL)$_4$ at much lower catalyst loadings. Since the diazoacetate used in this study is much more soluble in DCM than hexane, the reactions could be run at a high molarity and therefore proceed faster. This is also a promising path, considering Rh_2(*S*-TCPTAD)$_4$ a structurally and electronically similar catalyst can perform 5.7 million TONs and Rh_2(*S*-TCPTTL)$_4$ has very similar enantioselectivity to Rh_2(*S*-DOSP)$_4$ catalyzed cyclopropanation at 0.001 mol% catalyst loading.

2.5) Highly Selective Cyclopropanation at 0.0001 mol% Catalyst Loading



The reaction went to completion with a 78% yield and 85% ee. This is an incredible result because other chiral dirhodium(II) paddlewheel catalysts have not been able to main such high enantioselectivity for diazo facilitated cyclopropanation.[18,19] Even though Rh_2(*R*-BPCP)$_4$ catalyzes cyclopropanation at a relatively slow rate compared to other catalysts in these studies it conducts the reaction with far superior enantioinduction.

2.6) Discussion and Outlook

The preceding studies each accomplished something unique and useful to this project. The first study, reported in section 2.1, investigated the effect of the ester group of the diazoacetate substrates. Trichloroethyl ester diazoactates proved to be far superior to their methyl counterparts. The Rh_2(*S*-TCPTAD)$_4$ catalyzed reaction was also shown to be the most reactive at the low catalyst loading of 0.0001 mol%.

The second study, section 2.2, optimized the Rh_2(*S*-TCPTAD)$_4$ catalyzed reaction for enantioselectivity by trying multiple solvents and para-substituents for the diazoacetate at standard catalyst loading of 1 mol%. This study showed that the para-bromo phenyl diazoacetate was the best substrate in DCM for high levels of enantioinduction.

The third study, section 2.3, followed the level of enantioselectivity of the cyclopropanation reaction from 1 mol% to 0.00001 mol%. It demonstrated that Rh_2(*S*-TCPTAD)$_4$ is capable of 5.7 million turnovers in hexanes with 20% ee and approximately 3.8 million turnovers with 42% ee.

The poor enantioselectivity levels for these reactions lead to a systematic study of cyclopropanation catalyzed by various dirhodium(II) paddlewheel catalysts at 0.001 mol% to search for a more enantioselective catalyst. From this fourth study, section 2.4, the Rh_2(*R*-BPCP)$_4$ catalyzed reaction was the slowest but most enantioselective reaction with 89% ee performing 61,000 TONs. Moreover, the study showed that Rh_2(*S*-TCPTAD)$_4$ was in fact the least enantioselective chiral catalyst chosen in the study, and decomposed the diazoacetate at a slower rate than Rh_2(*S*-DOSP)$_4$ at 0.001 mol% catalyst loading. Rh_2(*R*-BPCP)$_4$ was chosen to attempt even lower catalyst loadings in a fifth study, section 2.5.

Finally carbene facilated cyclopronation was attempted at 0.0001 mol% catalyst loading with Rh_2(*R*-BPCP)$_4$. After one week the reaction performed 780,000 TONs with 85% ee. Amazingly, the enantioselectivity hardly changed when the catalyst loading was decreased by one order of magnitude.

There are still many challenges with these low catalyst-loading experiments and more areas to explore. One issue is the degradation of Rh_2 chiral catalyst in solution. For most of these experiments, a fresh solution was prepared immediately before the reaction was run. However, a couple of experiments, notably two in the initial study, were run with a Rh_2(*S*-DOSP)$_4$ solution that was made a couple weeks prior to the experiment. The high performance of Rh_2(*S*-DOSP)$_4$

at 0.001 mol%, 69,000 TONs in 1 min brings the result of only 80,000 TONs in 22.5 h at 0.0001 mol% catalyst loading into question. The reactions with Rh_2(*S*-DOSP)$_4$ at 0.001 mol% should definitely be repeated to confirm this surprising discrepancy.

For the ReactIR® study, new precautions were taken to ensure better catalyst solution longevity. For instance, the solvent used to make the solution was dried and kept over 4 Å molecular sieves until the solution was made. For the later experiments, solutions were also stored at room temperature, to avoid heavy condensation experienced in a freezer. An even better solution for doing experiments at low catalyst loading could be to immediately inject small aliquots of the solution into new vials, and concentrate the bulk of the solution and the small aliquots immediately in vacuo. This would not only allow the catalyst to have minimal exposure to possible contaminants in solution, but also allow for the >99% of the catalyst to be retrieved unscathed. This measure could significantly increase the cost efficiency of these experiments.

Another issue with these experiments is the volatility of dichloromethane. This problem is especially relevant to the 0.00001 mol% catalyst loading of Rh_2(*S*-TCPTAD)$_4$ experiment, where the DCM was replaced every other day in order to keep the reaction from drying out completely. Not only does evaporating solvent changes the kinetics of the reaction as a function of concentration, it also provides the more serious issue of reagents crashing out of solvent and stopping the reaction. TONs much higher than 3.8 million may very well be possible for Rh_2(*S*-TCPTAD)$_4$ in DCM if this problem can be avoided. Running reactions in Parafilm® sealed vials, as done in the fifth study can solve this problem since a plastic lid is much less porous than a rubber stopper.

Finally further optimization studies and more rigorous conditions could also be explored in order to achieve quicker, more selective reactions with higher TONs. Concentration, temperature, styrene substrate scope, and a larger diazoacetate scope could all be ways to optimize the low catalyst loading reactions for better reactivity and selectivity. An incredible feature of this low catalyst loading chemistry, is how reasonable, and non-rigorous the conditions were to achieve it. Although all reactions were run under argon gas, reagents were not subjected to argon-vacuum cycles, which could possibly do a better job of freeing the reagents of water vapor. Schlenk techniques could potentially perform than round bottom flasks for evacuating air. Glove box techniques would ultimately be the best in assuring air and water free reactions.

In future studies, hopefully this kind of low catalyst loading carbene chemistry can be applied to other systems, and potentially do C–H functionalization chemistry.

3) Conclusions

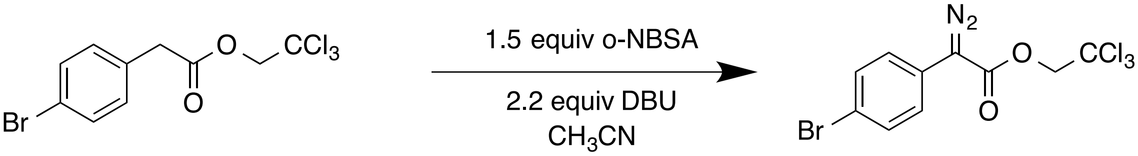
Dirhodium(II) catalyzed cyclopropanation reactions were optimized for high turnover numbers and enantioselectivity. Rh_2(*S*-TCPTAD)$_4$ was capable of doing more TONs for cyclopropanation than other dirhodium(II) catalysts previously reported in the literature with 5.7 million TONs. However the enantioinduction was lackluster at 20% ee. Further studies showed that Rh_2(*S*-TCPTAD)$_4$ is able to achieve 42% ee with approximately 3.8 million TONs by changing the solvent from hexanes to DCM. After a second systematic screening of dirhodium(II) catalysts, Rh_2(*R*-BPCP)$_4$ was found to be the most promising catalyst, yielding 89% ee after completing 61,000 TONs. At 0.0001 mol% this catalyst was able to perform 780,000 TONs with 85% ee. A catalyst as selective and robust as Rh_2(*R*-BPCP)$_4$ at low catalyst loading could be a powerful tool routinely used to carry out organic synthetic reactions in an industrial or academic setting in an efficient manner.

4) Experimental Part

4.1) General Remarks

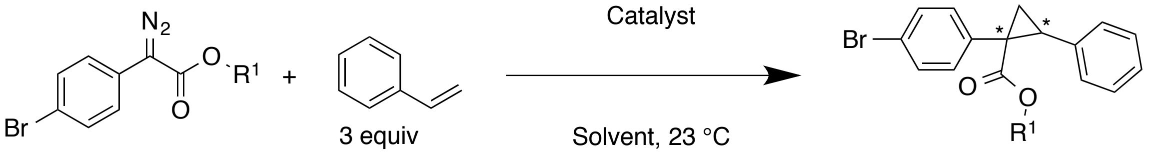
All solvents were purified and dried by a Glass Contour Solvent System unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded at either 400 MHz (^{13}C at 100 MHz) on Varian-400 spectrometer or at 500 MHz on a I-Nova spectrometer. NMR spectra were run in solutions of deuterated chloroform ($CDCl_3$) with residual chloroform taken as an internal standard (7.26 ppm for ^{1}H, and 77.16 ppm for ^{13}C), and were reported in parts per million (ppm). Abbreviations for signal multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublet, app t = apparent triplet, etc. Coupling constants (*J* values) were calculated directly from the spectra. IR spectra were collected on a Nicolet iS10 FT-IR spectrometer. Mass spectra were taken on a Thermo Finnigan LTQ-FTMS spectrometer with APCI, ESI or NSI. HPLC analysis was done with Varian Pro Star Model 410 instrument. Thin layer chromatographic analysis was performed with aluminum-backed silica gel plates, visualizing with UV light and/or staining with PMA stain. Melting points (mp) were measured in open capillary tubes with a Mel-Temp Electrothermal melting points apparatus and are uncorrected. *In situ* IR monitoring experiments were carried out with a Mettler Toledo ReactIR® 45m instrument equipped with a 9.5 mm x 12’’ AgX 1.5 m SiComp probe. Unless otherwise stated, all chemicals were obtained from Fluka, Aldrich or Acros and used as received or purified according to standard literature procedures. Styrene was always filtered through silica to remove anti-polymerization reagent. 4 Å molecular sieves were flame dried with argon vacuum cycles and stored in a 60 °C+ over. For 1 mol% catalyst loading reactions, the catalyst was weighed into flask and diazoacetate was added slowly in solution to the reaction mixture. ^{1}H NMR data for know compounds matched with the literature. Absolute stereochemistry predicted from known results.[14]

4.2) General Procedure for the Synthesis of Diazo Compounds



In a round bottom flask with a magnetic stir bar 5.1 g, 15 mmol of trichloroethyl ester and (5.0 g, 22 mmol of o-NBSA) were dissolved in 51 mL of acetonitrile. The reaction flask was cooled to 0 °C in an ice bath. (4.84 mL, 32 mmol) of DBU was slowly added to the reaction mixture. The reaction slowly warmed to room temperature and stirred for 80 min. 50 mL of saturated NH_4Cl (aq) was added to the reaction. The mixture was washed 3 times with 70 mL of diethyl ether, once with 100 mL distilled water and once with 100 mL of brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo onto silica. The product absorbed onto silica was loaded with hexanes eluted in 50:1 hexanes to diethyl ether as the column progressed, yielding 4.59 g, 84% of the theoretical yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.40 – 7.36 (m, 2H), 4.91 ppm (s, 2H). ^{1}H NMR data matched with that from the literature.[20]

4.3) General Procedure for Cyclopropanation Reactions



0.0015 mmol of Rh_2L_4 were dissolved in 50.00 mL of hexanes in a volumetric flask, to create a 0.00003 M solution. To a dry round-round bottom with a magnetic stir bar and activated 4 Å molecular sieves, 0.6 mmol of diazo compound (1 equivalent) were added. The reaction flask was purged with argon gas and kept under an argon-filled balloon. 1.8 mmol of styrene (3 equivalents) and 2.0 mL of hexanes were added. 20 µL of (0.00003 M) catalyst solution were injected into the reaction mixture using a 250 µL micro syringe.

4.4) General Procedure for Experimental and Data Analysis for ReactIR®

A Dry 25 mL two-neck flask with a magnetic stir bar was equipped with the ReactIR® probe inserted into one opening and a rubber stopper with an argon gas line inserted into the other opening. Distilled dichloromethane (DCM) was dried over 4 Å molecular sieves. 2.0 mL of DCM was added to the flask, and the ReactIR® started collecting data at 1 scan per 15 sec for 12 h. (3 equivalents, 3.6 mmol, 0.414 mL) of styrene was added to the flask. (1 equivalent, 1.2 mmol, 447 mg) of 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate was weighed into a 20 mL vial, dissolved in 1.5 mL of DCM and added to the reaction flask. The vial was rinsed with (0.4 mL) of DCM which and was added to reaction flask. 0.006 mmol of Rh_2L_4 was dissolved in 50.00 mL of dry DCM in a 50 mL volumetric flask. 100 L of the 0.00012 M Rh_2L_4 solution was added to the reaction flask using a 250 µL-micro syringe. After the reaction went to completion or for 12 h, the reaction mixture was concentrated under vacuo, dissolved in a small amount of DCM or eluent, and eluted through silica with a mixture of 15:1 pentane to diethyl ether.

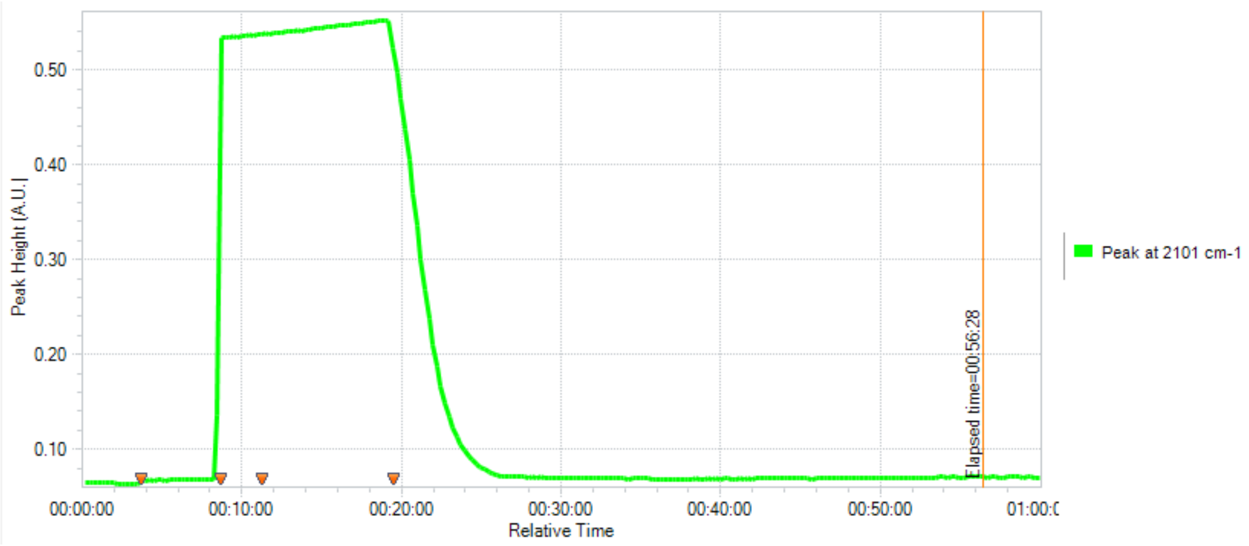
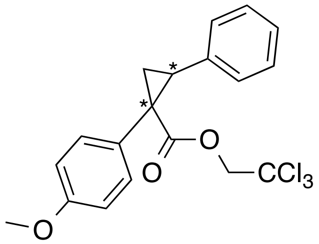


Figure 8: Untreated ReactIR® data, with absorbance at 2101 cm^{-1} *vs* time in h, min, and sec.

Figure 8 follows peak C-N stretch at 2101 cm^{-1} corresponding to the diazo peak. The baseline absorbance has the value of 0.07. The sharp increase of the peak at around 9 min corresponds to the addition of the diazo solution to the reaction mixture. The sharp decrease in the peak at around 20 min corresponds to the decomposition of the diazo upon addition of Rh_2(*S*-TCPTTL)$_4$. The steady increase in absorbance value between 9 min and 20 min should be noted. Evaporation of DCM as a result of the high argon pressure and leaks in the rubber stopper, was the probable cause of the increase in diazo concentration.

The data was extracted as a text file and imported to Microsoft Excel®. There were 3 necessary corrections that were made to this data. A baseline correction was made by taking the absorbance at 2101 cm^{-1} at a point right before the diazo was added, and subtracting that value from all other points. This effectively shows that when there is no diazo when the reaction is finished. Or if there is some diazo left after the 12 h, the figure will give an accurate representation of the progress of the reaction. Secondly, the whole absorbance data set was divided by the value of the intensity immediately before the catalyst was added. This normalizes the graph from values of 1 to 0 so all of the reactions are comparable. Thirdly the initial the time and temperature data was cut off before the addition of the catalyst and 2 h after the addition of the catalyst. This gave a reference point from which to compare all reactions.

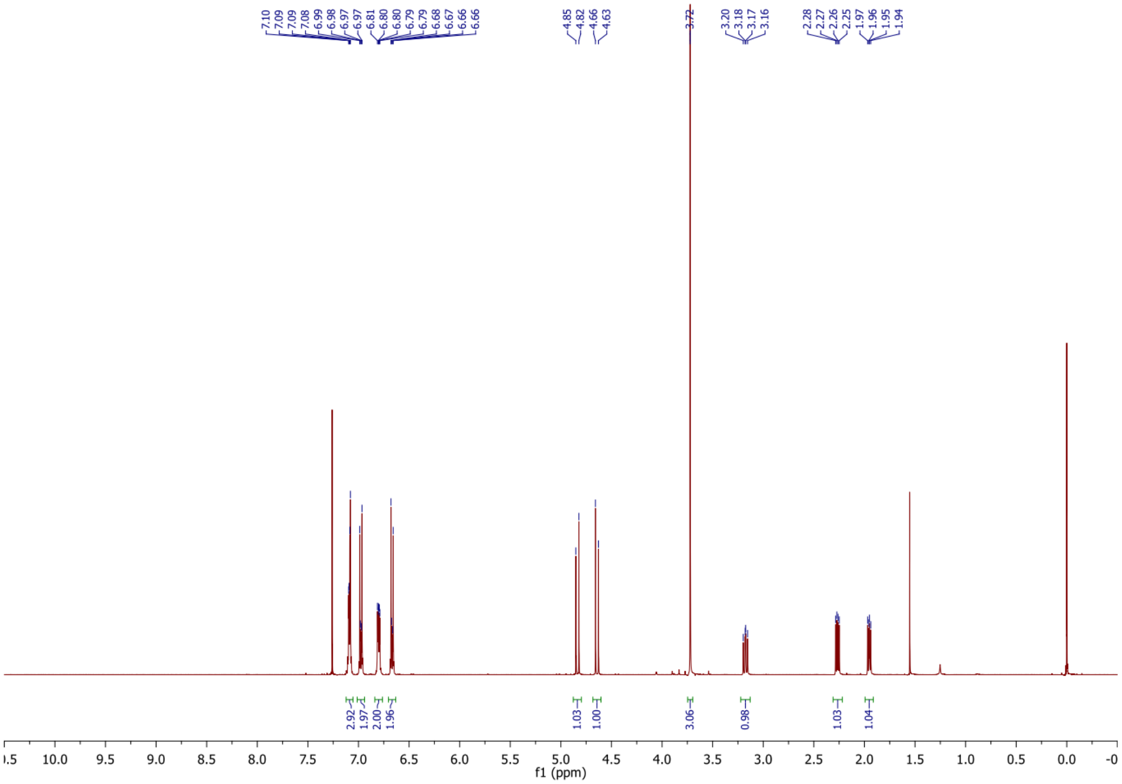
4.5) Analysis Data for 2,2,2-trichloroethyl 1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate



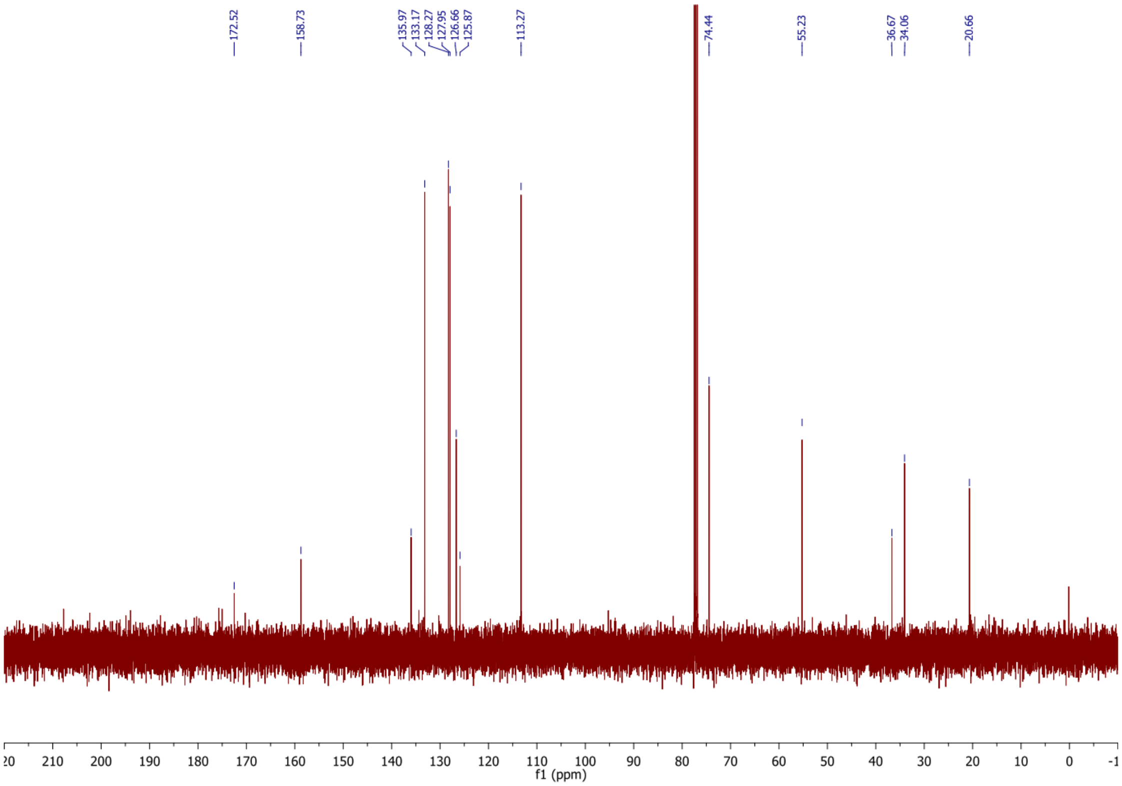
2,2,2-trichloroethyl 1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 – 7.05 (m, 3H), 7.01 – 6.94 (m, 2H), 6.84 – 6.76 (m, 2H), 6.70 – 6.63 (m, 2H), 4.84 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 3.72 (s, 3H), 3.18 (dd, *J* = 9.4, 7.4 Hz, 1H), 2.27 (dd, *J* = 9.4, 5.0 Hz, 1H), 1.95 (dd, *J* = 7.4, 5.1 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $cdcl_3$) δ 172.52, 158.7, 136.0, 133.2, 128.3, 128.0, 126.7, 125.9, 113.3, 74.4, 55.2, 36.7, 34.1, 20.7 ppm. IR ($CDCl_3$): 1733, 1516, 1265, 1152 cm^{-1}; FTMS (NSI) calc for $C_{19}H_{18}O_3Cl_3$ $(M+H)^+$ 399.03160 found 399.03186 m/z. HPLC: (SS_WHELK, 2% isopropanol in hexane, 1.0 mL/min) retention times of 10.7 (minor) and 15.1 major (major) min, 58 % ee. M.P. (58 – 60) °C

^{1}H NMR (CDCl$_3$, 400 MHz)

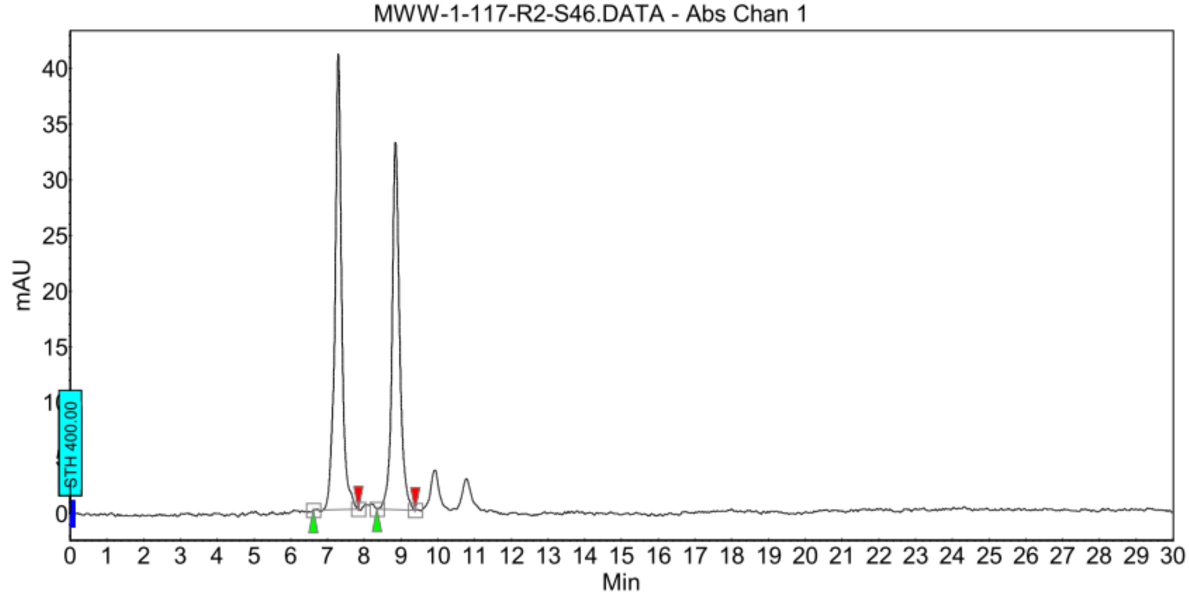


^{13}C NMR ($CDCl_3$, 101 MHz)



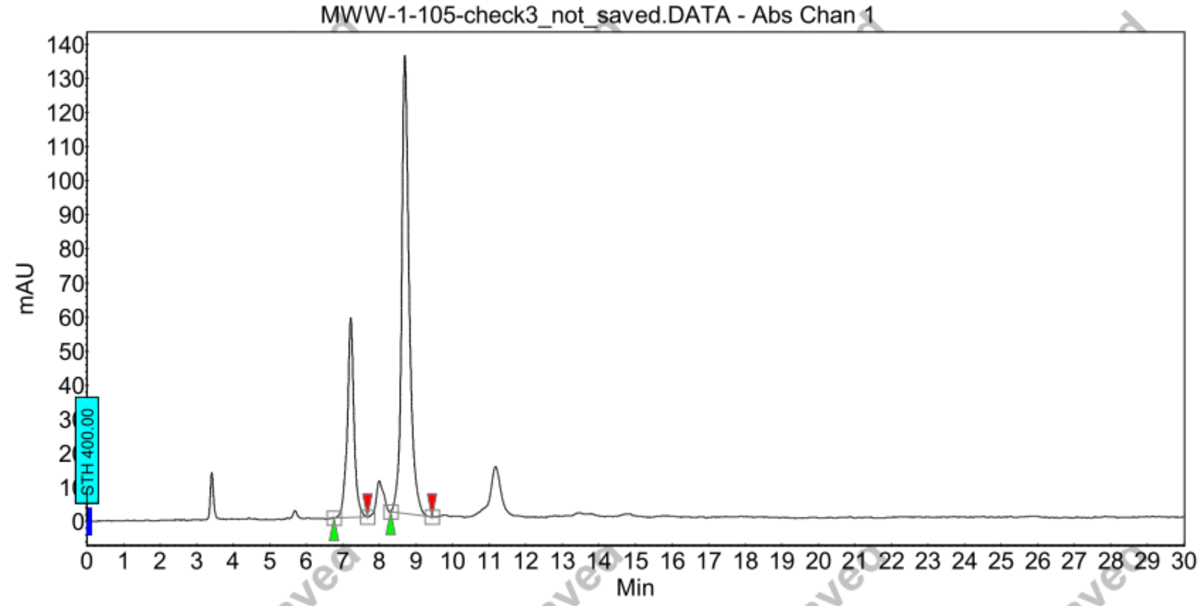
4.6) HPLC Traces

Data relevant to **2.1** and **2.3**



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	7.29	52.79	40.9	8.8	52.788
2	UNKNOWN	8.85	47.21	33.0	7.9	47.212
Total			100.00	73.9	16.7	100.000



Peak results :

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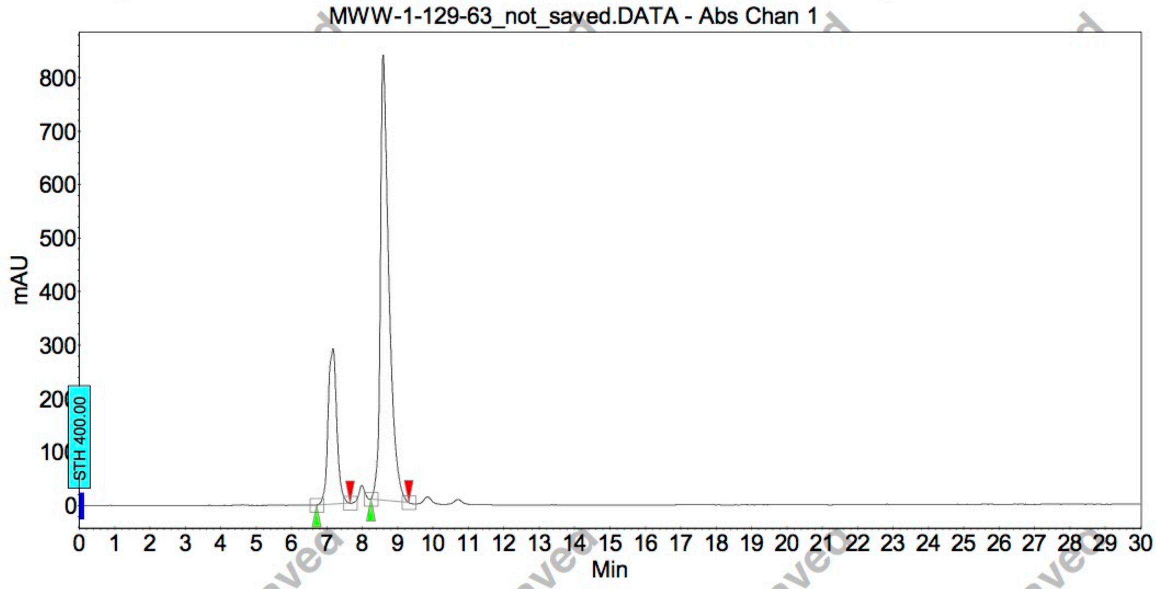
1	UNKNOWN	7.21	27.65	58.5	12.4	27.645
2	UNKNOWN	8.69	72.35	134.5	32.5	72.355
Total			100.00	193.0	44.9	100.000

Data relevant to **2.2** and **2.3**



Peak results :

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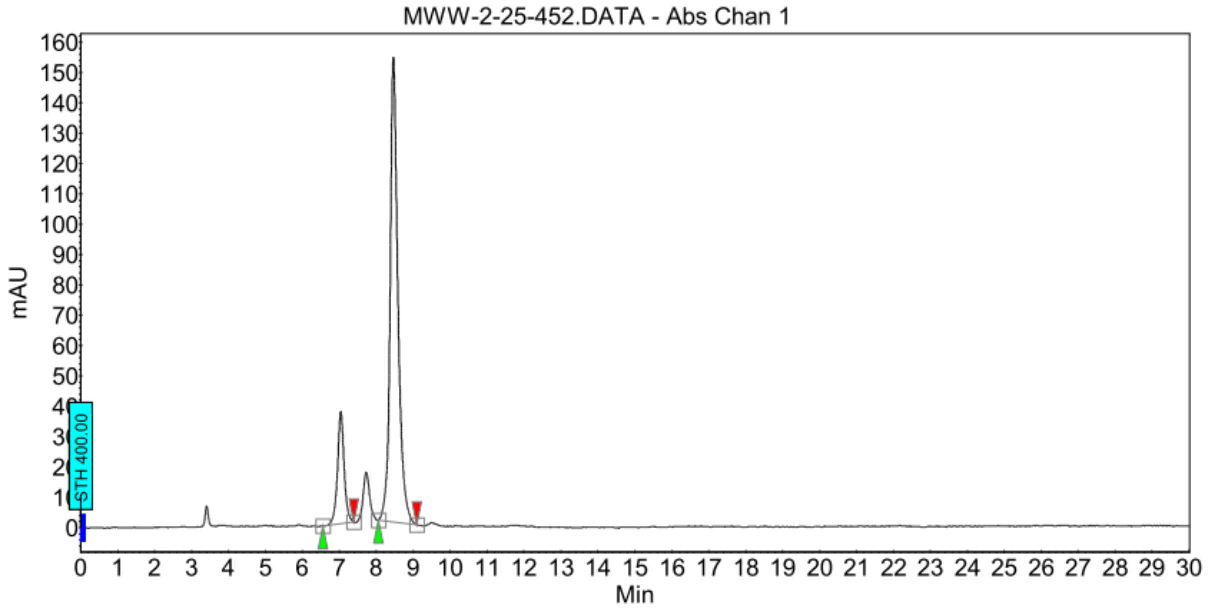
1	UNKNOWN	7.17	26.18	291.0	83.0	26.184
2	UNKNOWN	8.59	73.82	832.9	233.9	73.816
Total			100.00	1123.9	316.9	100.000



Peak results :

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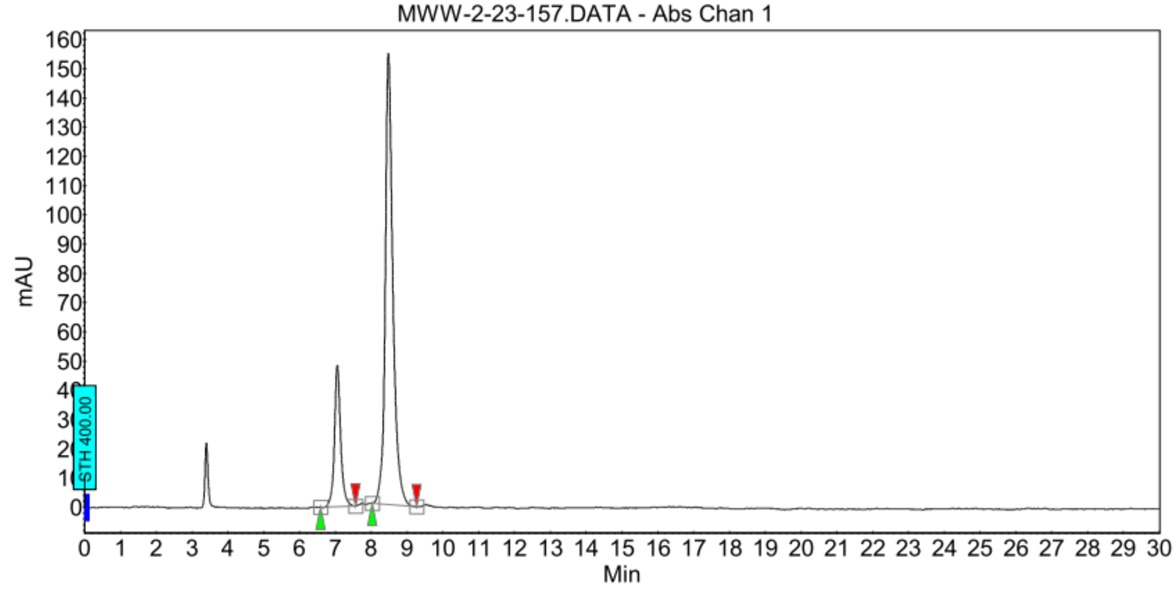
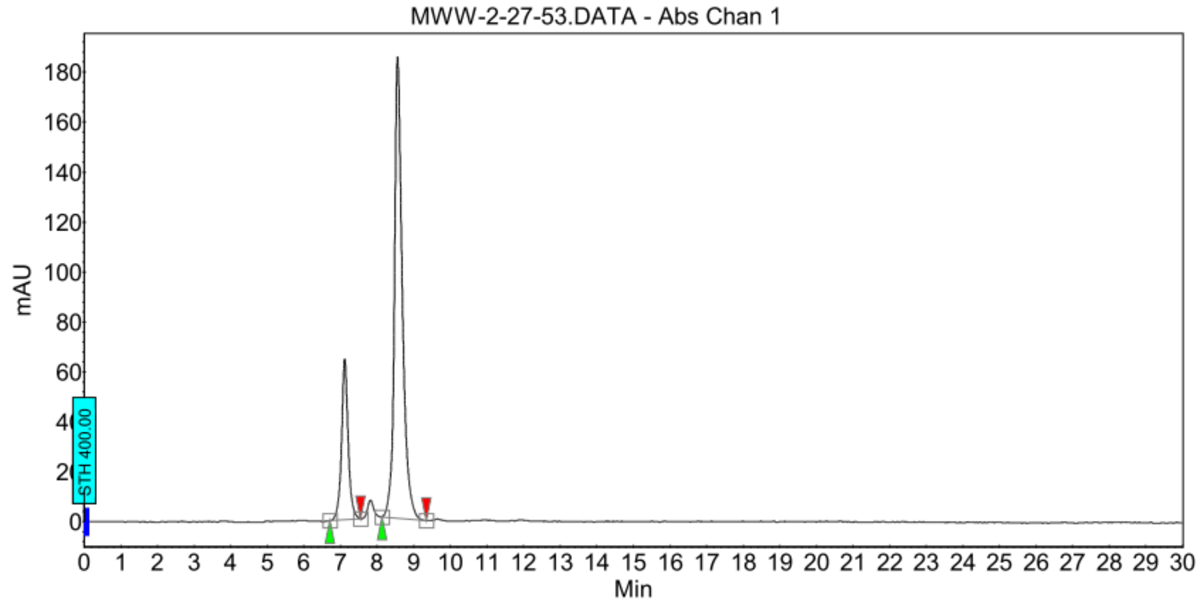
1	UNKNOWN	7.04	16.94	37.0	7.7	16.939
2	UNKNOWN	8.46	83.06	153.2	37.7	83.061
Total			100.00	190.3	45.4	100.000



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	7.05	20.16	48.4	9.7	20.155
2	UNKNOWN	8.48	79.84	154.4	38.3	79.845
Total			100.00	202.8	48.0	100.000



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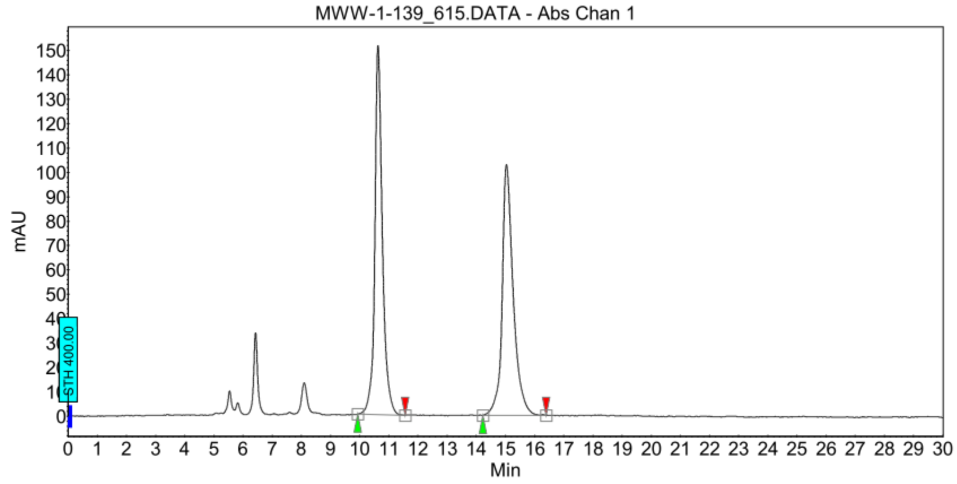
1	UNKNOWN	7.12	22.52	64.4	13.5	22.517
2	UNKNOWN	8.56	77.48	184.8	46.5	77.483
Total			100.00	249.2	60.0	100.000



Peak results :

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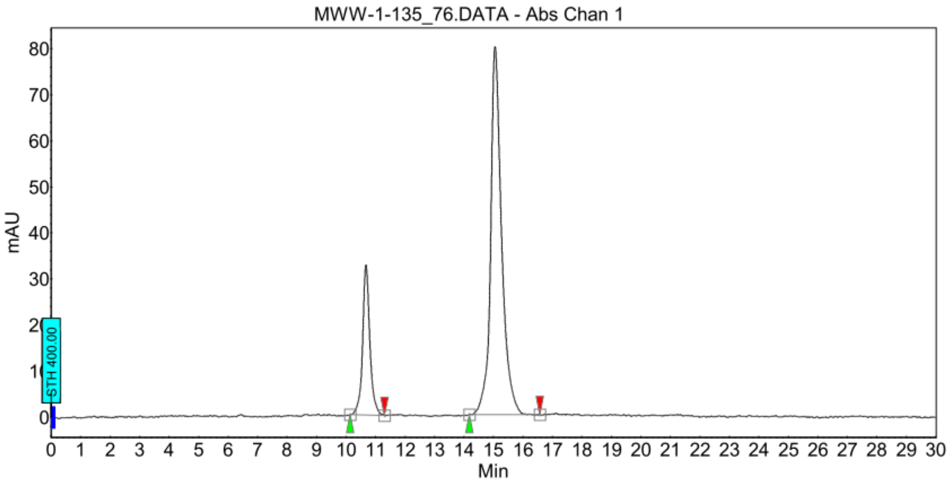
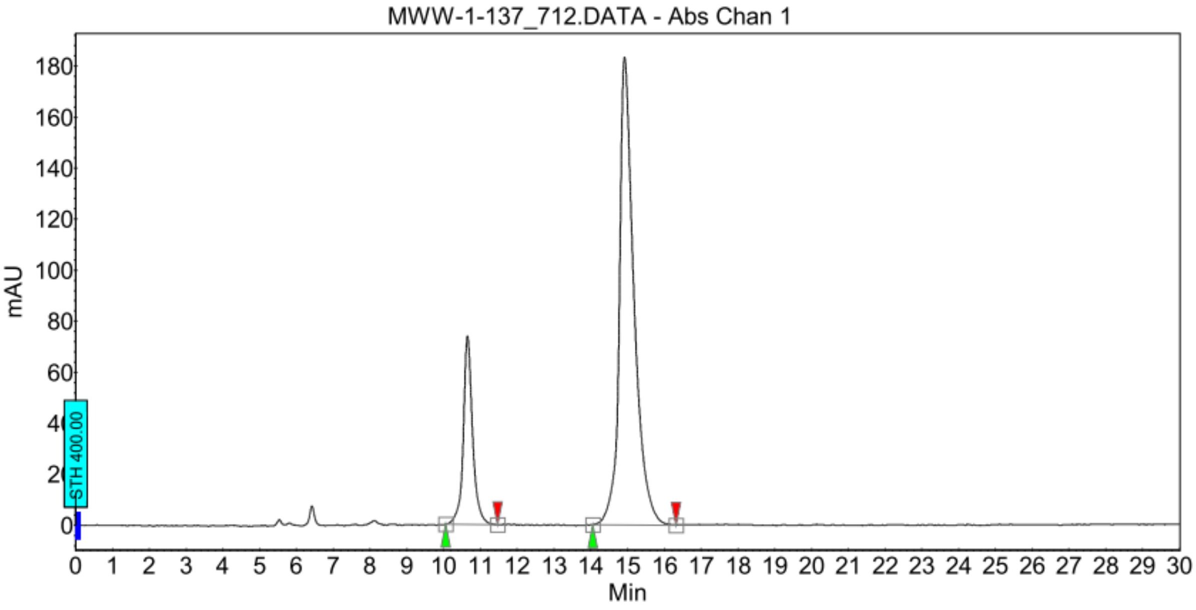
1	UNKNOWN	10.63	50.24	151.5	45.6	50.243
2	UNKNOWN	15.03	49.76	102.9	45.2	49.757
Total			100.00	254.3	90.8	100.000



Peak results :

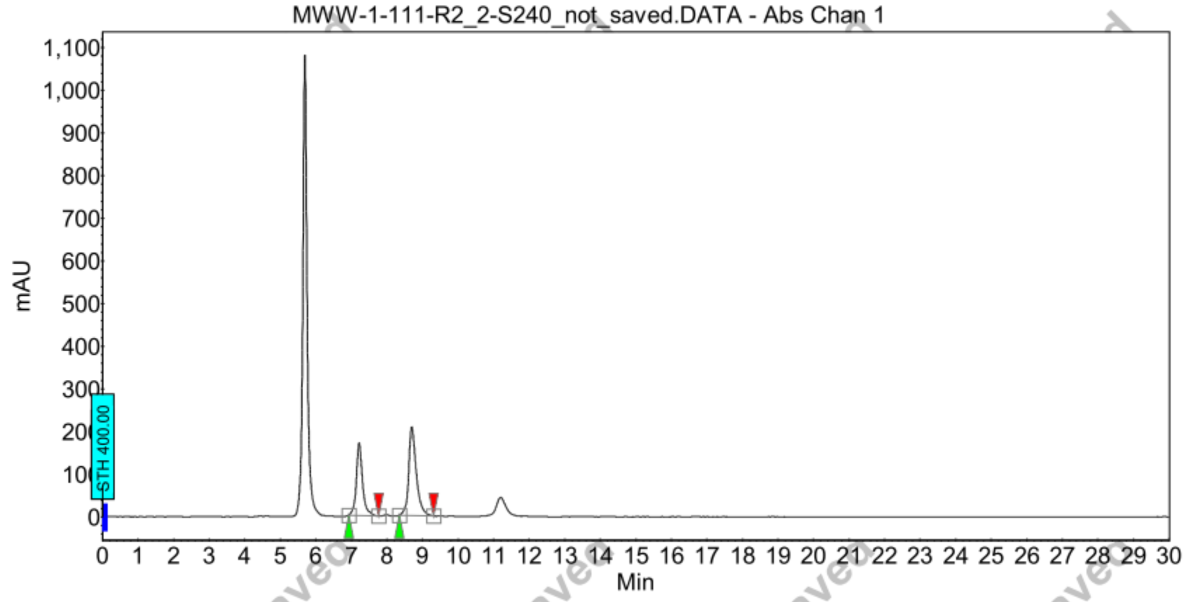
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.67	21.23	32.6	9.3	21.227
2	UNKNOWN	15.05	78.77	79.9	34.5	78.773
Total			100.00	112.4	43.8	100.000



Peak results :

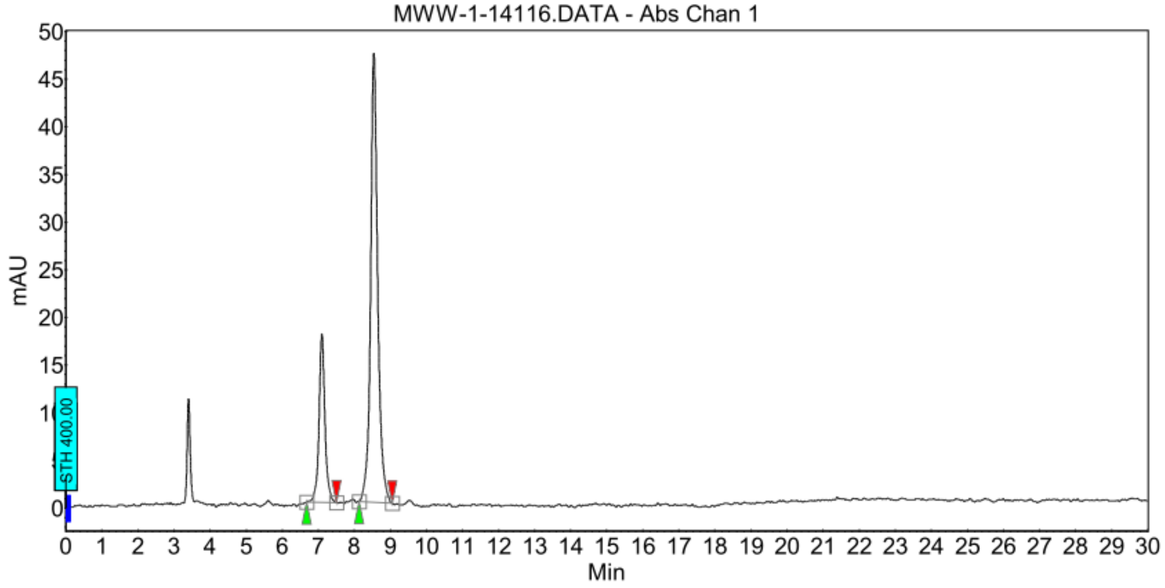
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.65	20.27	73.9	21.6	20.270
2	UNKNOWN	14.92	79.73	183.5	85.0	79.730
Total			100.00	257.3	106.5	100.000

Data relevant to **2.3**



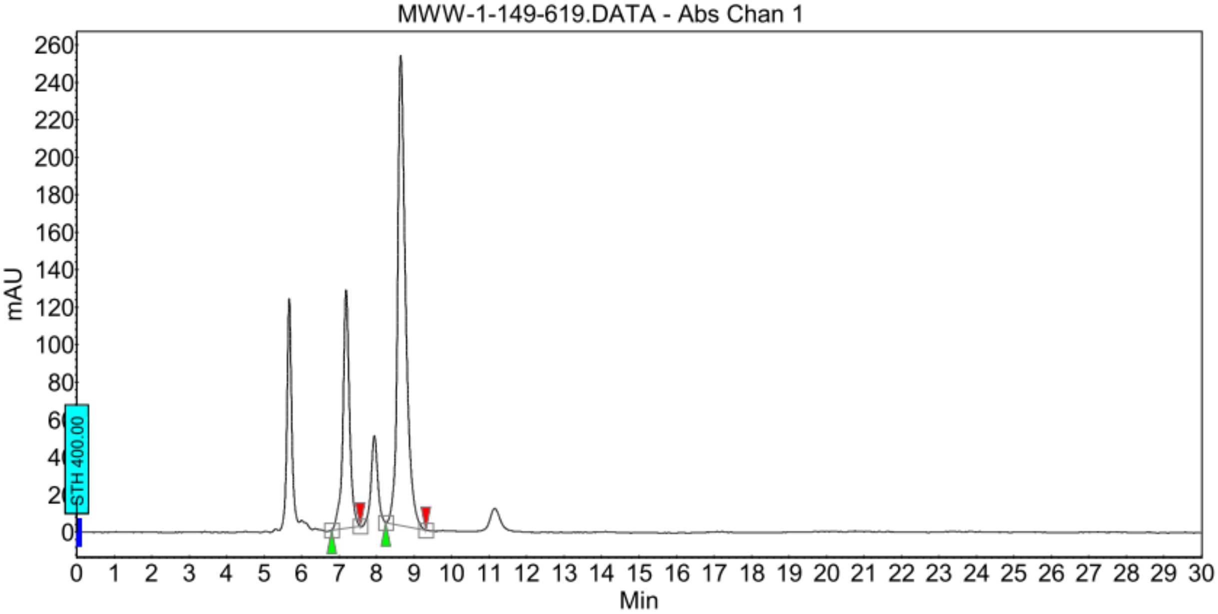
Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	7.22	39.93	169.6	34.2	39.935
2	UNKNOWN	8.70	60.07	208.1	51.4	60.065
Total			100.00	377.7	85.6	100.000



Peak results :

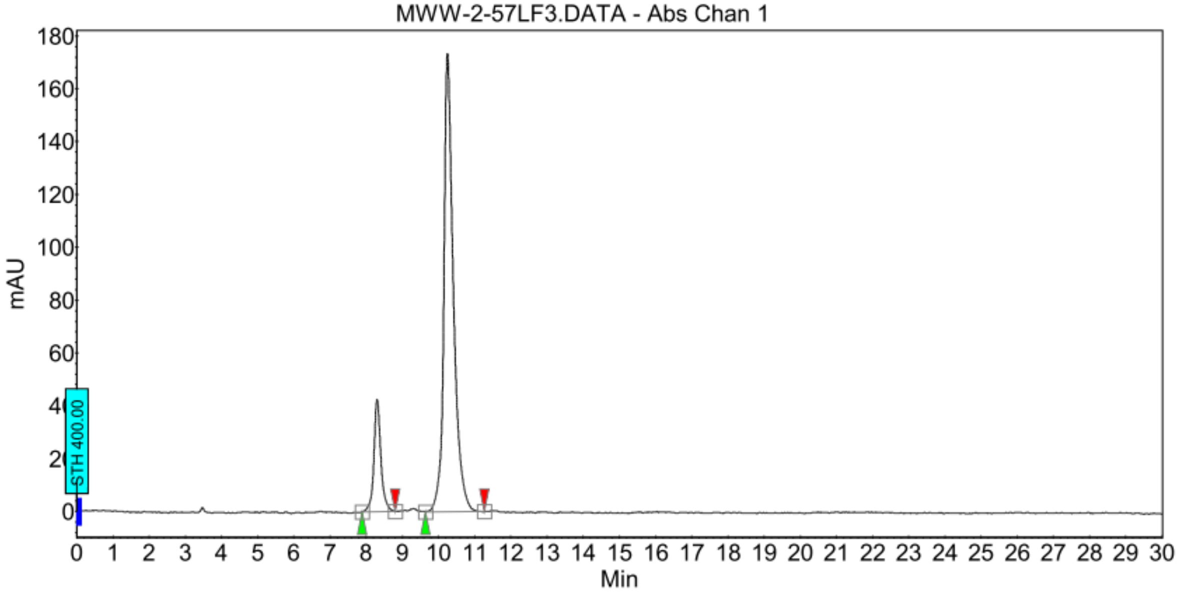
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	7.10	23.81	17.7	3.4	23.806
2	UNKNOWN	8.54	76.19	47.1	10.8	76.194
Total			100.00	64.8	14.1	100.000



Peak results :

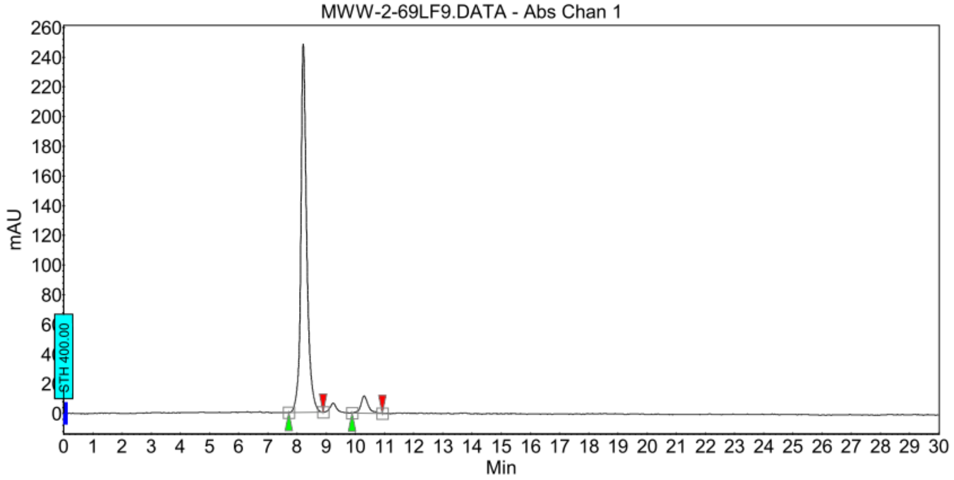
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	7.19	29.06	127.0	25.7	29.063
2	UNKNOWN	8.64	70.94	250.8	62.7	70.937
Total			100.00	377.8	88.4	100.000

Data relevant to **2.4**



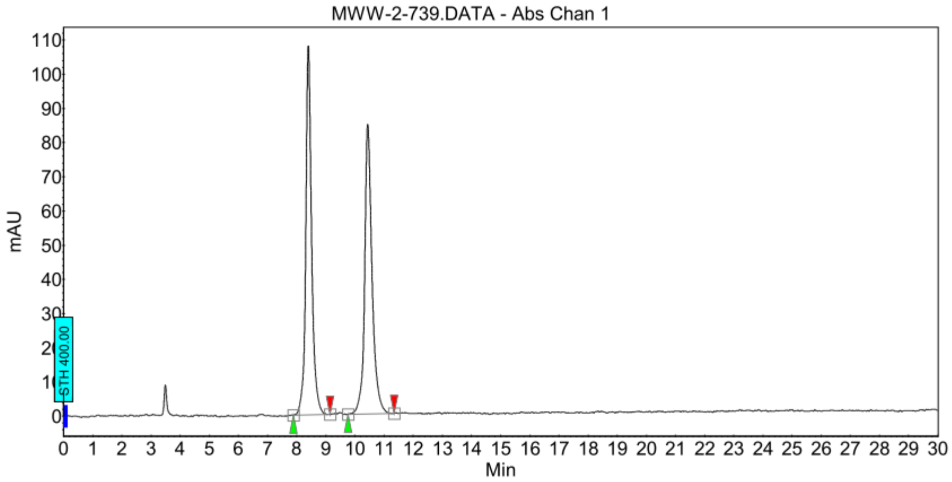
Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.30	15.20	42.6	9.6	15.202
2	UNKNOWN	10.25	84.80	173.5	53.3	84.798
Total			100.00	216.1	62.8	100.000



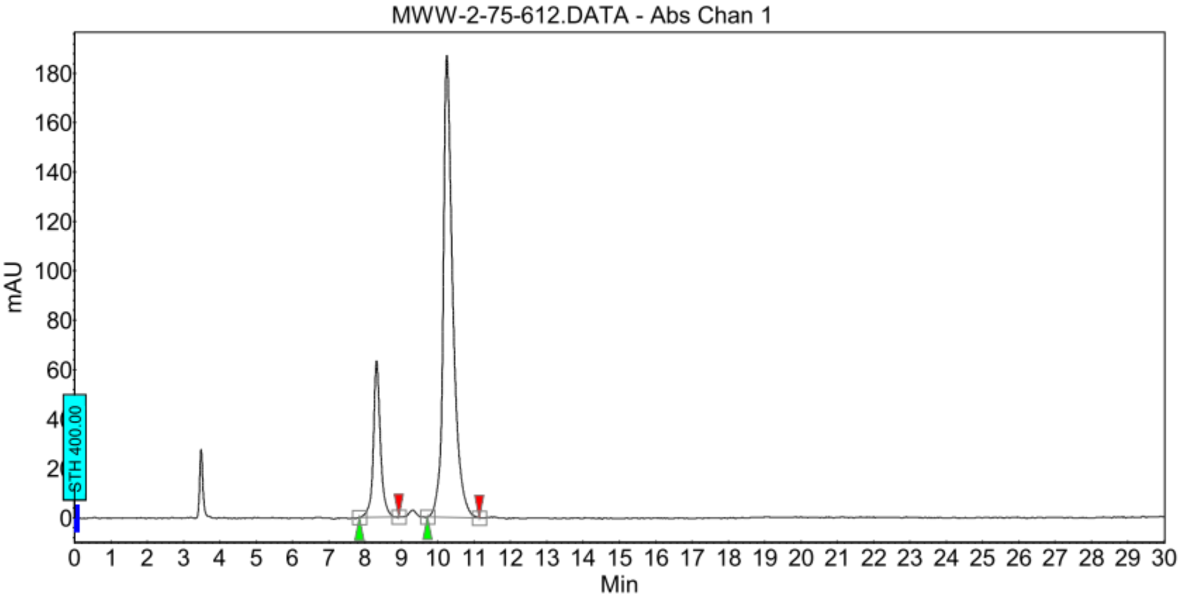
Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.21	94.59	248.1	58.0	94.587
2	UNKNOWN	10.30	5.41	11.6	3.3	5.413
Total			100.00	259.8	61.3	100.000



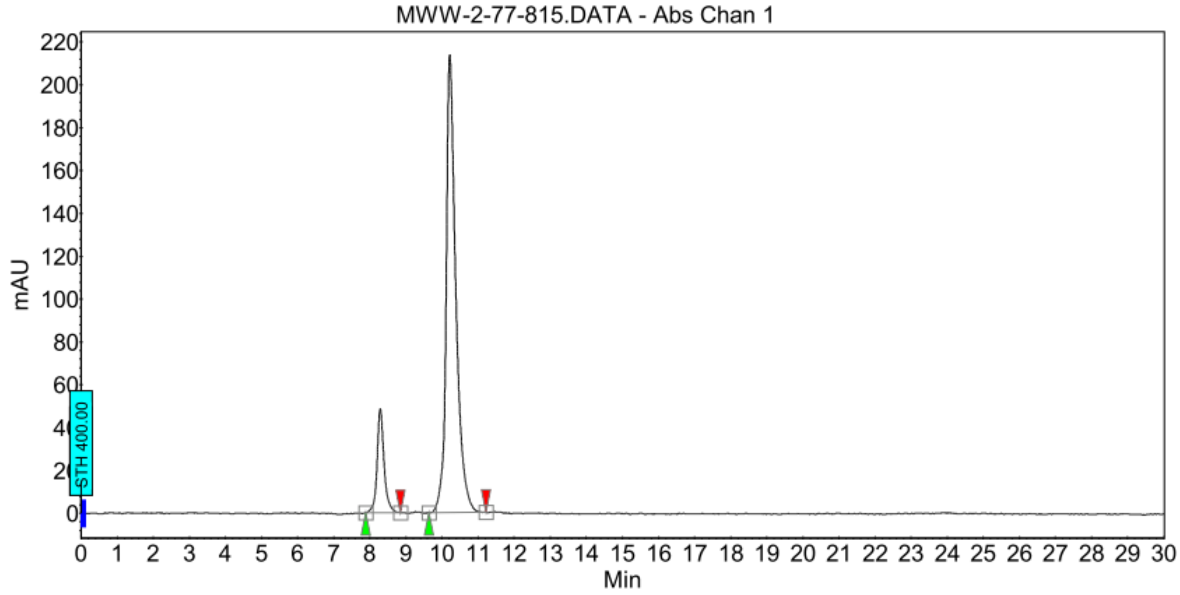
Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.40	50.11	107.9	25.1	50.113
2	UNKNOWN	10.44	49.89	84.7	24.9	49.887
Total			100.00	192.6	50.0	100.000



Peak results :

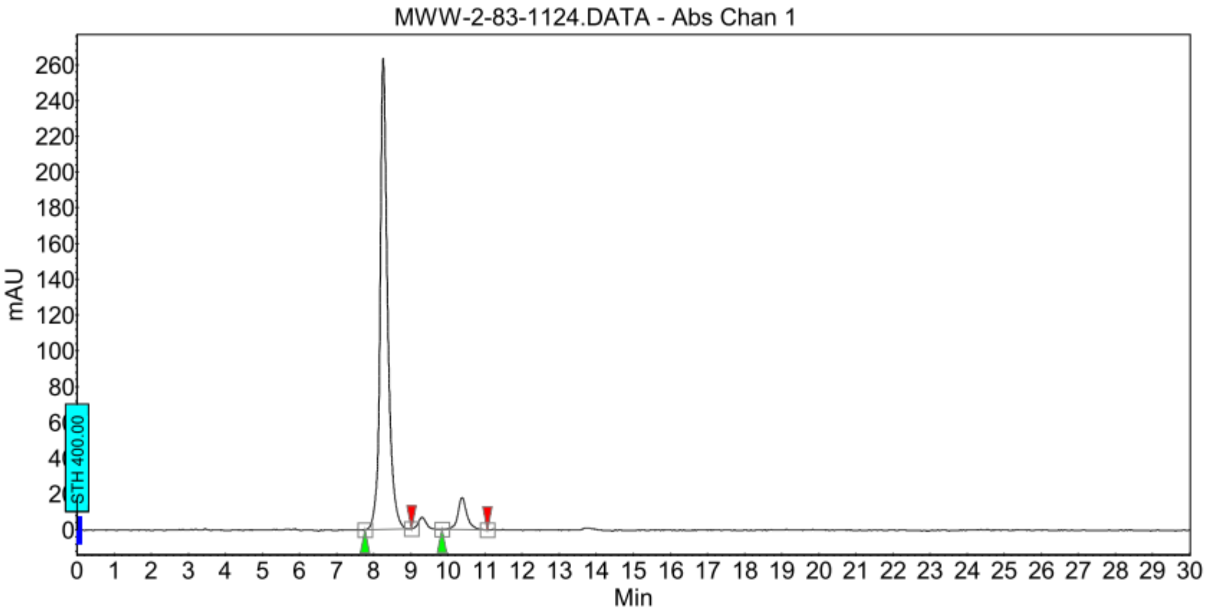
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.31	19.93	63.3	14.3	19.930
2	UNKNOWN	10.25	80.07	186.8	57.4	80.070
Total			100.00	250.1	71.7	100.000



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.29	14.06	48.4	10.8	14.058
2	UNKNOWN	10.21	85.94	213.6	66.3	85.942
Total			100.00	262.0	77.1	100.000

Data relevant to **2.5**



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.25	92.39	263.6	62.3	92.388
2	UNKNOWN	10.38	7.61	18.0	5.1	7.612
Total			100.00	281.6	67.4	100.000

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