Influence of Tethered, Axially Coordinated Ligands on Rh(II,II)-Catalyzed Carbene Transfer Reactions

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Abstract

Dirhodium (II,II) paddlewheel complexes have become ubiquitous in diazo-mediated carbene transfer reactions. The Rh(II,II)-carbene intermediate is capable of a large variety of transformations such as cyclopropanation, C-H and X-H (O, N, S, Si, B) insertion reactions, cyclopropenations, and ylide transformations. Cyclopropanation reactions resulting in the formation of functionalized cyclopropane structures has always been a major focus in Rh(II,II)-carbene chemistry. Improvements on catalytic performance in cyclopropanations has largely focused on the modification of the bridging ligands and has resulted in Rh(II,II) catalysts that exhibit high reactivity and selectivity in cyclopropanation reactions. However, high enantio- and diastereoselectivity is not easily achieved with all carbene types and other control elements on the catalyst, such as axial coordination, can possibly remedy this issue. Although there are some examples of axially coordinated Lewis Base additives affecting stereoselectivity, elucidation of the role the axial ligand plays in the reaction is still ambiguous. To gain more control over the axial stie and more accurately study the role axial coordination, the synthesis of axial ligands that are anchored to a bridging ligand site have been developed.

My work in the Darko group has focused on developing Rh(II,II) complexes that contain tethered, axially coordinated ligands (TACLs) and studying the effect the axial coordination has on diazo-mediated carbene transfer reactions, specifically cyclopropanations. Characterization in both the solid confirmed axial coordination. The complexes demonstrated higher cyclopropanation yields than control catalysts when using acceptor-type carbenes. It has also been determined that modifications to the axial ligands can have a small influence on the reaction’s sensitivity to changes in the substrate. Incorporation of chiral groups onto the pendant arm of the tethers resulted in improved enantioselectivity with donor/acceptor carbenes.

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List of Abbreviations

Bi – bismuth

Cu – copper

DCE – 1,2-dichloroethane

DFT – density functional theory

DCM – dichloromethane

dr – diastereomeric ratio

EDA – ethyl diazoacetate

EDG – electron-donating group

ee – enantiomeric excess

EtOH – ethanol

EWG – electron-withdrawing group

GC – Gas chromatography

HOMO – highest occupied molecular orbital

HPLC – High performance liquid chromatography

hr – hour

LUMO – lowest unoccupied molecular orbital

MeCN – acetonitrile

mg – milligram

mL – milliliter

MW – microwave

NMR – Nuclear Magnetic Resonance

NOESY – Nuclear Overhauser Effect Spectroscopy

OAc – acetate

Rh – rhodium

$Rh_2(OAc)_4$ – dirhodium tetraacetate

$Rh_2(Oct)_4$ – dirhodium(II) octanoate

Rh_2(*S*-BSP)$_4$ – dirhodium(II) tetrakis[[benzenesulfonyl]-prolinate]

Rh_2(*S*-DOSP)$_4$ – dirhodium(II) tetrakis[1-[[4-dodecylphenyl]sulfonyl]-prolinate]

Rh_2(*S*-MACIM)$_4$ – dirhodium(II) tetrakis[methyl 1-acetyl-2-oxoimidazolidine-4-carboxylate]

Rh_2(*S*-MCPIM)$_4$ –dirhodium(II) tetrakis{methyl 1-[3'*S*)-phenyl-2(*S*)cyclopropanecarbonyl]-2-oxo-imidazolidine-4(*S*)-carboxylate]

Rh_2(*S*-MEPY)$_4$ – dirhodium(II)tetrakis[methyl 2-pyrrolidone-5(*S*)-carboxylate]

Rh_2(*S*-MEOX)$_4$ – dirhodium(II) tetrakis[methyl 2-oxo-oxazolidine-4(*S*)-carboxylate]

Rh_2(*S*-NTTL)$_4$ – dirhodium(II) tetrakis[N-1,2-naphthaloyl-(*S*)-*tert*-leucinate]

Rh_2(*S*-PTA)$_4$ – dirhodium(II) tetrakis[N-phthaloyl-(*S*)-alaninate]

Rh_2(*S*-PTAD)$_4$ – dirhodium(II) tetrakis[(*S*)-(-)-(1-adamantyl)-(N-phthalimido)acetato]

Rh_2(S-PTPA)$_4$ – dirhodium(II) tetrakis[[N-phthaloyl-(S)-phenylalaninato]

Rh_2(*S*-PTTL)$_4$ – dirhodium(II) tetrakis[N-phthaloyl-(*S*)-*tert*-leucinate]

Rh_2(*S*-PTTL)$_3$TPA – dirhodium(II) tris[N-phthaloyl-(*S*)-tert-leucinate] triphenylacetate

Rh_2(*S*-TBSP)$_4$ - dirhodium(II) tetrakis[1-[4-*tert*-butylphenyl)sulfonyl]-(2S) pyrrolidinecarboxlate]

rt – room temperature

TBA – tetrabutylammonium

^{t}Bu – tert butyl

TFA – trifluoroacetic acid

THF – tetrahydrofuran

TLC – Thin-layer Chromatograph

Chapter 1 Introduction

Cyclopropanes are moieties consisting of three carbons in a triangular orientation with 60° bond angles that result in structures with high ring and torsional strain. Due to this co-planar structure, the C–H bonds in the ring are forced into an eclipsed conformation which leads to increased hydrophobicity.[1, 2] Cyclopropanes have had positive effects in pharmaceutical drugs such as aqueous solubility, metabolic stability, brain permeability, and lipophilicity.[3] They have also been known to be used as isosteres of phenyl rings.[1] Because of their unique properties, cyclopropanes play a pivotal role in the pharmaceutical industry. Of the 200 best-selling drugs on the market, 8 of them contain a cyclopropane ring and there are almost as many cyclopropane containing drugs as there are drugs that contain fluorine[1]. Some notable cyclopropane containing drugs are Tranylcypromine, Lenvatinib, Drospirenone, and Milnacipran (Figure 1.1a).[1] This prevalence has led to the development of different methods for synthesizing cyclopropanes. One of the most popular pathways towards cyclopropanes involve the formation of carbenes as intermediates (Figure 1.1b).[4-7] Free carbenes are highly reactive species that have caused issues with selectivity in these transformations. A way to mitigate this issue is using stabilized carbenoids derived from the coordination of diazo compounds onto transition metals. Fisher metal carbenoids have exhibited improved stability as intermediates in the cyclopropanation of olefins.[8] The catalytic cycle for this cyclopropanation is largely the same for different transition metals and is depicted in (Figure 1.2).[9] The cycle begins with association of the diazo onto the metal center (A). This is followed by extrusion of N_2, facilitated by the metal, to form the carbenoid species (B). A nucleophilic attack by the olefin onto the carbenoid in an asynchronous concerted step (C) then occurs, leading to the formation of a cyclopropane (D) and regeneration of the catalyst (E). A common and usually undesired side reaction can be observed when the metal carbenoid is trapped by another equivalent of the diazo compound, generating a homocoupled product (F).[10]

Group 9 and 11 transition metals, specifically copper and rhodium, have emerged as the most used metals for diazo-mediated cyclopropanation reactions. Copper complexes are inexpensive and have shown excellent stereoselective performance with a large library of ligand systems. However, these catalysts are hindered by a lack in the diversity of carbenes that they can catalyze, leading to limited applications. Another issue

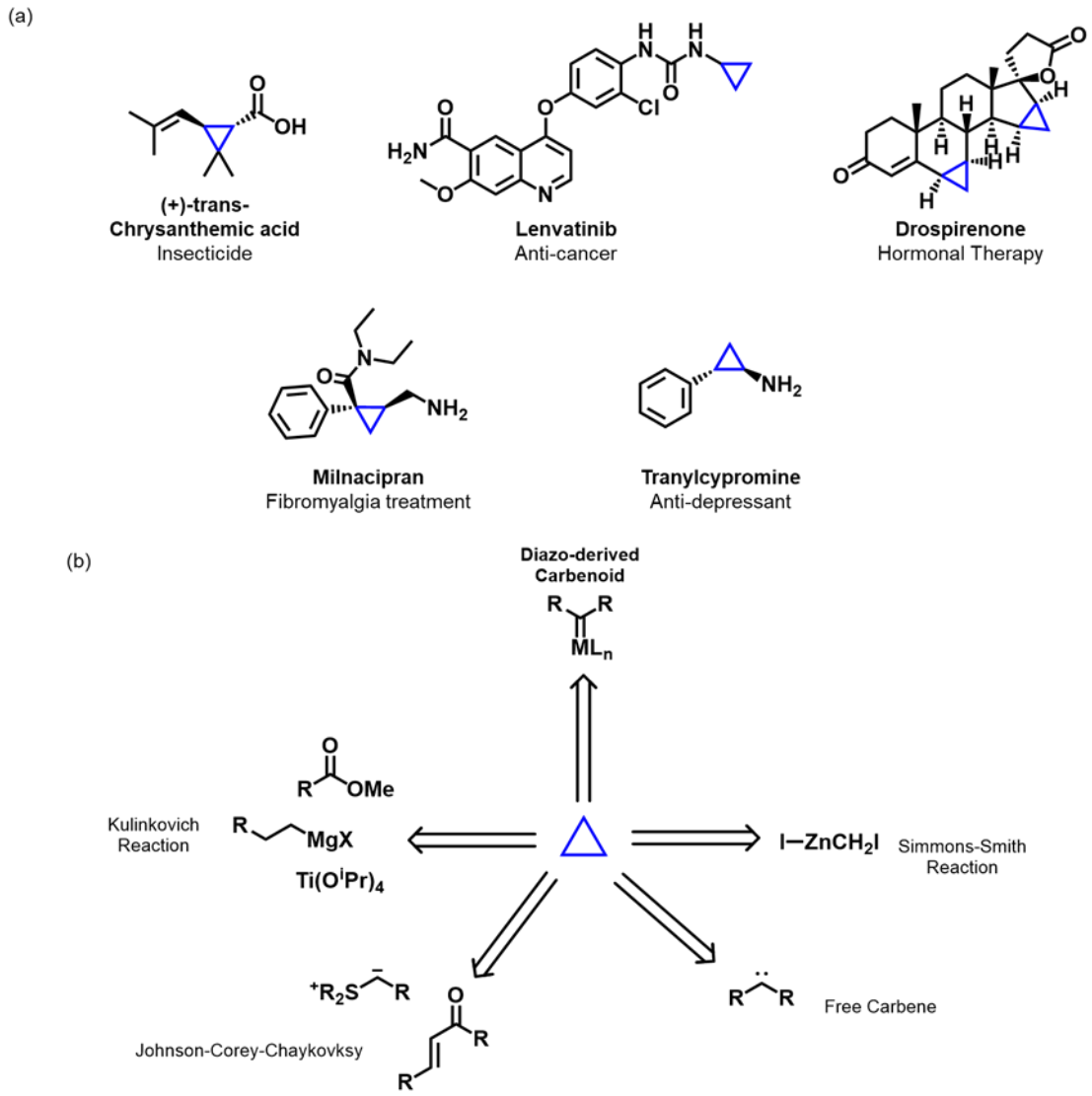


Figure 1.1 a) Examples of pharmaceutical and bioactive natural products that contain a cyclopropane ring and b) common methods for synthesizing cyclopropane rings

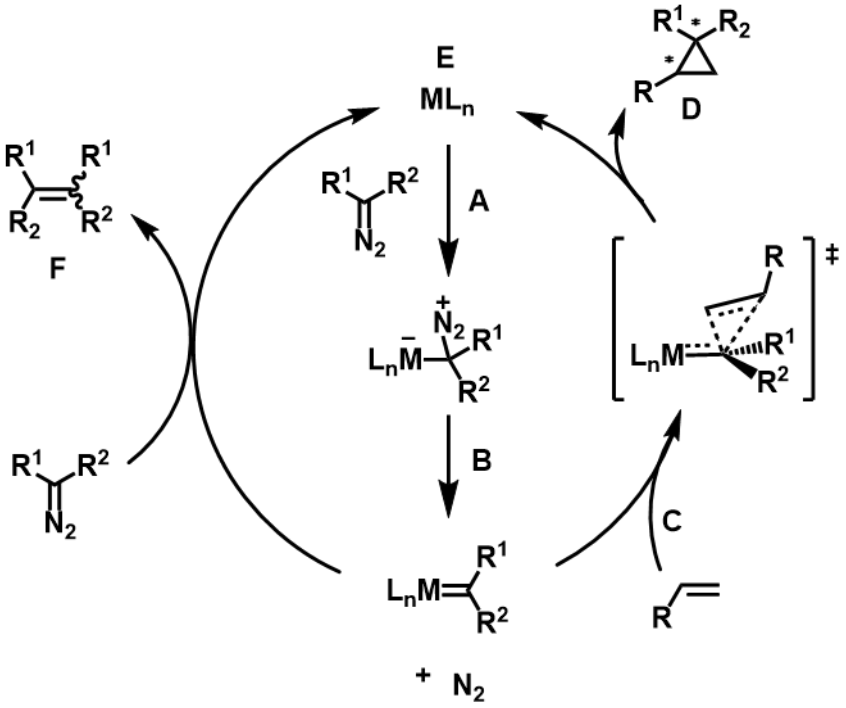


Figure 1.2 Catalytic cycle for metal-catalyzed carbene transfer cyclopropanation reactions

with copper catalysts is that the olefin substrates tend to bind to the metal and inhibit the catalyst.[11] The most common rhodium complexes for cyclopropanation reactions are dirhodium paddlewheel complexes (Rh(II,II)).[12]

1.1 Rh(II,II) Complexes

Rh(II,II) paddlewheel complexes are bimetallic structures consisting of a Rh–Rh bond that is surrounded by 4 bridging ligands and an axial site on each rhodium metal (Figure 1.3).[13, 14] This results in a complex in which each rhodium center has an octahedral geometry.[15] Various bridging ligand motifs have been developed such as: carboxylates,[16] carboxamidates,[17] *ortho*-metalated phosphines,[18] and amidinates.[19] The properties of the bridging ligand have been known to have a profound effect on the stereoelectronics and activity of the rhodium centers. The presence of more electron-withdrawing ligand leads to an increase in electrophilicity of the metal centers, while electron-rich ligands decrease it. This level of control through simple ligand modification has cemented Rh(II,II) paddlewheels as premiere catalysts in carbene transfer reactions. Ever since Teyssié and co-workers first decomposed diazo compounds with Rh(II,II) carboxylates,[20] catalytic applications of Rh(II,II) complexes have included C-H and X-H insertions (X = O, N, S, Si, B), cyclopropanations, and other diazo-mediated reactions.[20-26] The reactivity of the diazo species towards association onto the metal is increased with more electron-rich diazo substrates. Rh(II,II) carbenes can be classified into three major groups: acceptor/acceptor, donor/acceptor, and acceptor carbenes (Figure 1.4).[13, 14, 26] Reactivity of these metal carbenes is inverse to that of diazos and increases as the carbene center becomes more electron-deficient, while selectivity typically increases with more electron density.[14] Selectivity is also affected by the steric bulk of the carbene substrates creating asymmetric faces for catalysis. For example, donor/acceptor diazo compounds derived from aryl or vinyl diazoacetates exhibit incredible selectivity not seen in other types like acceptors, as a result, they have seen extensive use in stereoselective and chemoselective cyclopropanations and C-H insertions with chiral catalysts.[23, 27-30]

The bimetallic nature of Rh(II,II) paddlewheels results in a more complex relationship between the metal and carbene. Although formation of the carbene and subsequent catalysis occurs at one rhodium center, the other rhodium atom influences the electronics of the active metal. Berry and co-workers proposed that Rh(II,II)-carbenes follow a 3 center/4 electron (3c/4e) model.[31] This model suggests that the Rh–Rh–$C_{carbene}$

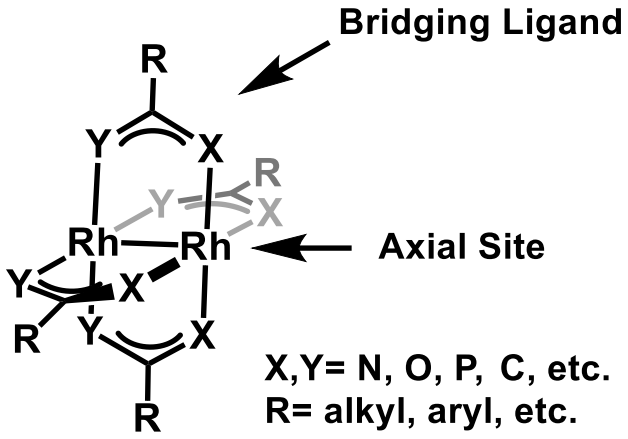


Figure 1.3 General structure of Rh(II,II) paddlewheel complexes

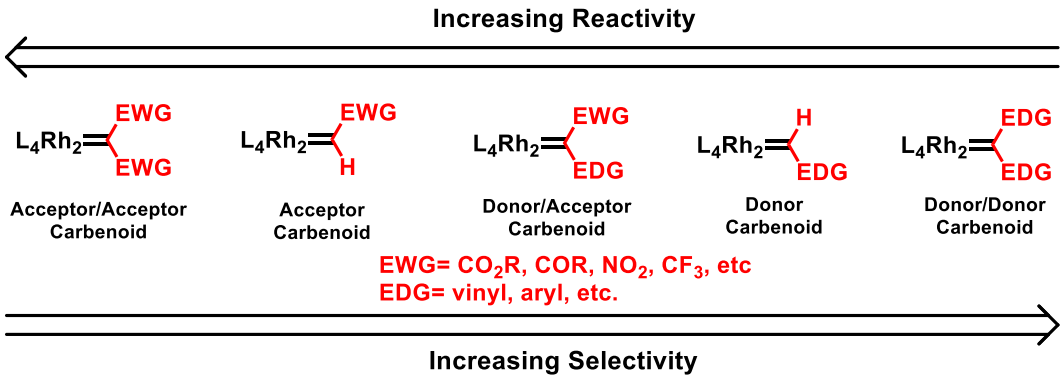


Figure 1.4 Classifications and reactivity trends of Rh(II,II)-carbenes

core contains two resonance structures, one in which the Rh–Rh bond is a 2 center/2 electron bond (2c/2e) with the carbene having a dative bond to one of the Rh metals. The other resonance structure has a formal oxidation of a Rh center (Rh(III)) and reduction of the other Rh (Rh(I)). This model essentially treats the Rh center that is not bound to the carbene as an electron sink and creates a dynamic environment when the Rh(II,II)-carbene is formed.

1.1.1 Synthesis of Rh(II,II) Complexes

Rh(II,II) paddlewheel complexes can be synthesized from Rh(I) or other Rh(II,II) species. One of the most common pathway towards making Rh(II,II) carboxylates in a paddlewheel structure involves the reduction of Rh(III) species.[32] Some of the first $Rh_2(O_2CR)_4L_n$ complex was synthesized by refluxing $[RhCl_6]^{3-}$ salts in an aqueous formic acid solution to form a Rh(II,II) formate paddlewheel complex (Figure 1.5a).[33, 34] Another method uses rhodium (III) hydrates in refluxing carboxylic acids or alcohol/carboxylic acid mixtures to make Rh(II,II) carboxylates. This results in subpar yields with large quantities of rhodium metal deposition.[35, 36] Since then, one of the most efficient synthesis of $Rh_2(OAc)_4$ is accomplished by refluxing $RhCl_3$ in ethanol with acetic acid and sodium acetate (Figure 1.5b).[37-39] Using this method with various acetates affords $Rh_2(O_2CR)_4L_n$ complexes at yields upwards of 85% or quantitative amounts when using a large excess of carboxylic acid.[37]

The synthesis of Rh(II,II) paddlewheels with functionalized bridging ligands has most commonly been through the substitution of the acetate ligands on $Rh_2(OAc)_4$ with carboxylates, carboxamidates, amidinates, and many other types of bridging ligands (Figure 1.5c).[13] The conditions for this ligand exchange typically require an excess of ligand to the Rh(II,II) tetraacetate in a high boiling, non-coordinating solvent such as chlorobenzene (PhCl). The mechanism of this ligand exchange is thought to begin with coordination of the new ligand to one of the axial sites (Figure 1.6, A), which then facilitates the release of an acetate ligand (Figure 1.6, B,C). This process is then repeated three more times for full conversion to the tetra-substituted complex. This mechanism has been supported by NMR studies conducted by Lahuerta and co-workers using orthometallated phosphine ligands exchanged on a very electrophilic $Rh_2(TFA)_4$ complex.[40] Formation of heteroleptic complexes with mono-, di-, and tri-substitution are also possible and the distribution of these products is largely dependent on the type of ligands utilized.[41] One

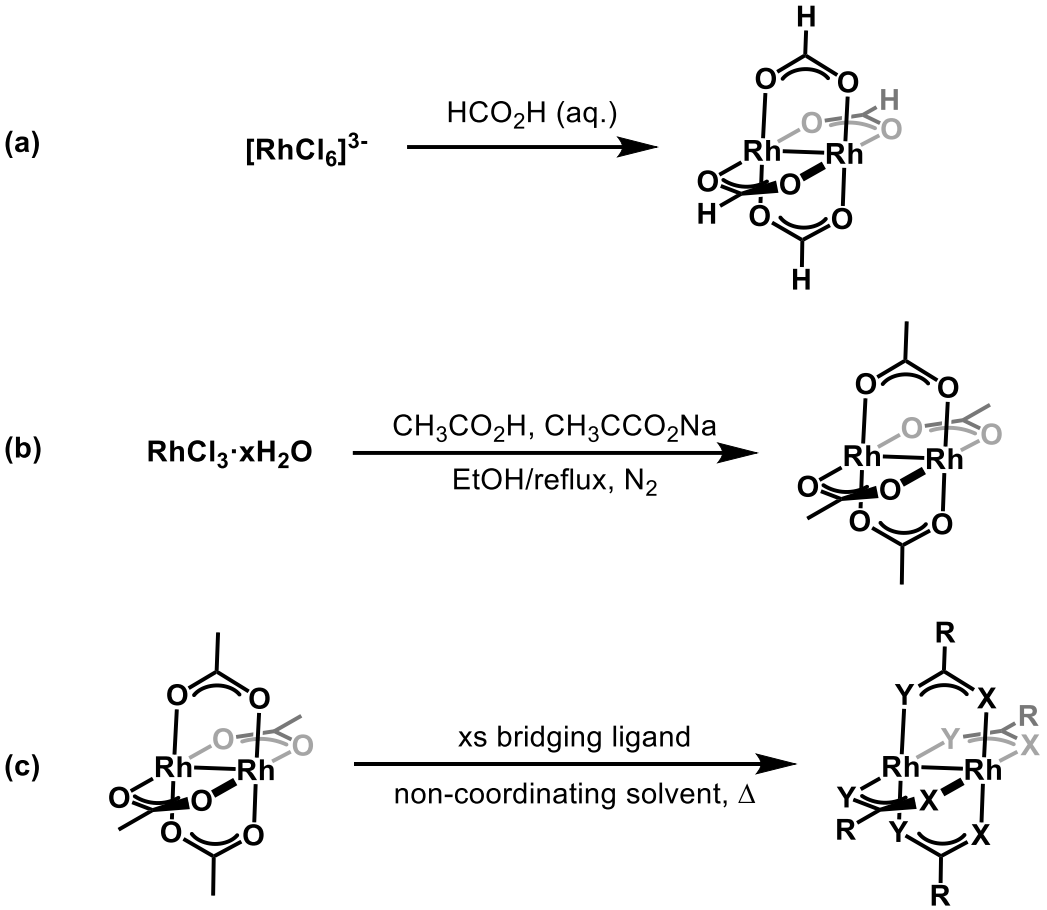


Figure 1.5 Synthesis of Rh(II,II) complexes from a) Rh(III) salts, b) Rh(III) hydrates, and c) other Rh(II,II) complexes

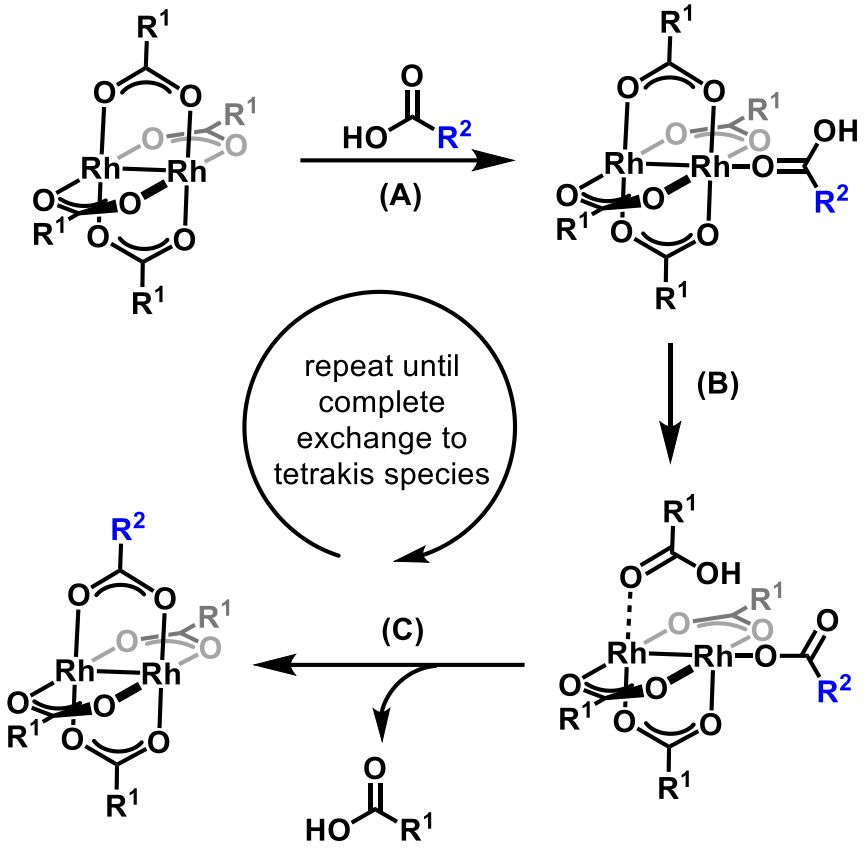


Figure 1.6 Mechanism of ligand exchange for Rh(II,II) complexes

NMR study determined that the relative rates of partially substituted products in the exchange of trifluoroacetic acid onto $Rh_2(OAc)_4$ was 1:2:0.1:0.25 for mono, di, tri, and tetrakis respectively.[42] To achieve complete exchange of bridging ligands, researchers' efforts have focused on the equilibrium of ligand exchange. Removal of the dissociated ligand, acetic acid in the case of $Rh_2(OAc)_4$, prevents it from coordinating to the complex again and displacing the newly associated ligands. This removal drives the equilibrium towards complete substitution. This process is achieved by fitting the reaction flask with a Soxhlet extractor that contains a thimble filled with an inorganic base to trap the released acetic acid that azeotropes with the refluxing PhCl solvent (Figure 1.7).[13, 43] The solvent is returns to the reaction flask, unaffected by the base.

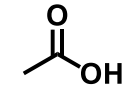
1.1.2 Asymmetric Cyclopropanation

With the prevalence and proficiency of Rh(II,II) complexes in diazo-mediated carbene transfer reactions, their potential for asymmetric catalysis has been a major focus. In the early 1980s it was determined that Rh(II,II) paddlewheels were capable of supporting chiral bridging ligands and were immediately applied towards diazo-mediated transformations, namely cyclopropanation and C-H insertions.[13] This section will summarize major advancements in the development of Rh(II,II) paddlewheel complexes and their applications towards asymmetric cyclopropanation reactions.

1.1.2.1 Chiral Rh(II,II) Complexes

As is the case for other chiral systems, symmetry plays an important role in how Rh(II,II) complexes are designed. Typically in metal catalysis, synthesizing high symmetry catalysts involves ligation of highly symmetric ligands such as C_2-symmetric bidentate binaphthyl or bisoxazoline (BOX) ligands, although less symmetric C_1 ligands can also be utilized.[44] In Rh(II,II) catalysis, C_1 ligands are commonly used because they are easy to synthesized and exchange onto the Rh(II,II) core.[27, 45-47] The Rh(II,II) core can be considered to intrinsically be highly symmetric and as such, exchange of low symmetry ligands can produce symmetric chiral catalysts. Once chiral ligands are ligated at the bridging sites, the introduction of sterically blocking groups on the ligands create chiral pockets of varying symmetries at each axial site. These groups are thought to be situated either at the up (α) face or the down (β) face relative to a "side-on" view of the complex. It was initially thought that the blocking groups cannot lie on the periphery of the complex

boiling points of solvent and acetic acid by-product

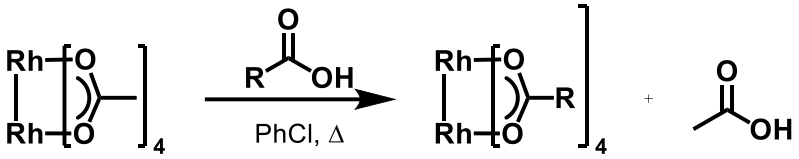


bp = 118°C

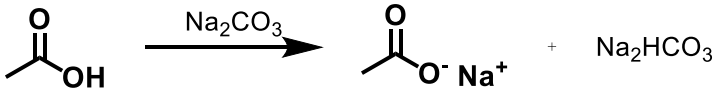
PhCl

bp = 132°C

acetate ligand displacement



acetic acid trapped by thimble charged with sodium carbonate



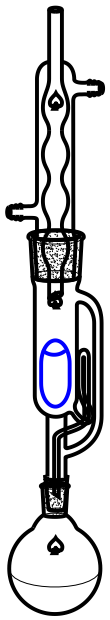


Figure 1.7 Soxhlet method of Rh(II,II) ligand exchange

as to avoid steric clash with an adjacent ligand (Figure 1.8a).[45, 48, 49] With these two faces in mind, four permutations of the ligands are possible: α,α,α,α (C_4-symmetry), α, α, α, β (C_1-symmetry), α, α, β, β (C_2-symmetry) and α, β, α, β (D_2-symmetry) (Figure 1.8b). Initially, it was believed that the C_1 and C_4 complexes would not be viable catalysts for enantiocontrol.[45, 48] This was because the C_1 conformation contains non-equivalent chiral pockets. While high stereoselectivity was expected for the α face with three blocking groups, the converse was expected for the β side with only one blocking group. The C_4 conformation has a face that has no sterically blocking groups to direct substrate attack and since this axial site is more kinetically active, no enantiocontrol is expected.[49] Even higher symmetry Rh(II,II) complexes can be achieved by ligating C_2 -symmetric ligands instead of C_1. These C_2 ligands can create D_2 or even D_4-symmetric catalysts by influencing both faces of the complex (Figure 1.8c).[45, 49] Efforts towards synthesizing and using chiral Rh(II,II) complexes has led to a vast library of diverse ligand architectures and catalyst designs that build upon previous breakthroughs. These have included prolinate, N-protected amino acid, phosphonate, and *ortho*-metallated phosphine derived systems. One of the first highly enantioselective chiral Rh(II,II) classes developed were Rh(II,II) carboxamidate complexes primarily pioneered by the Doyle group.[17, 50]

1.1.2.2 Chiral Rh(II,II) Carboxamidates

Rh(II,II) carboxamidate complexes contain ligands that bridge the two rhodium metals with an oxygen and a nitrogen atom instead of two oxygen atoms. As a result, multiple isomers are possible, but the *cis*-2,2 orientation is the preferred isomer (Figure 1.9).[51, 52] The rhodium centers of these complexes are also more electron rich than carboxylates due to the higher basicity of the nitrogen atoms on the carboxamidate ligands. This increase in electron density results in a catalyst that is less active in carbene reactions but with higher selectivity.[13, 53, 54] Initially, when attempting to develop chiral carboxamidate complexes, Doyle and co-workers found that ligand exchange of acyclic amides was largely not possible due to free rotation creating unfavorable amide configurations.[17, 55] This led to the use of cyclic carboxamidate ligands for exchange onto the paddlewheel and most Rh(II,II) carboxamidates use lactam rings. The Doyle group proceeded to make a large library of carboxamidate complexes derived from azetidinones, 2-oxazolidinones, N-acylimidazolin-2-ones, and 2-oxopyrrolidines (Figure 1.10).[14, 45] Rh(II,II) carboxamidates have been used extensively in asymmetric carbene transfer

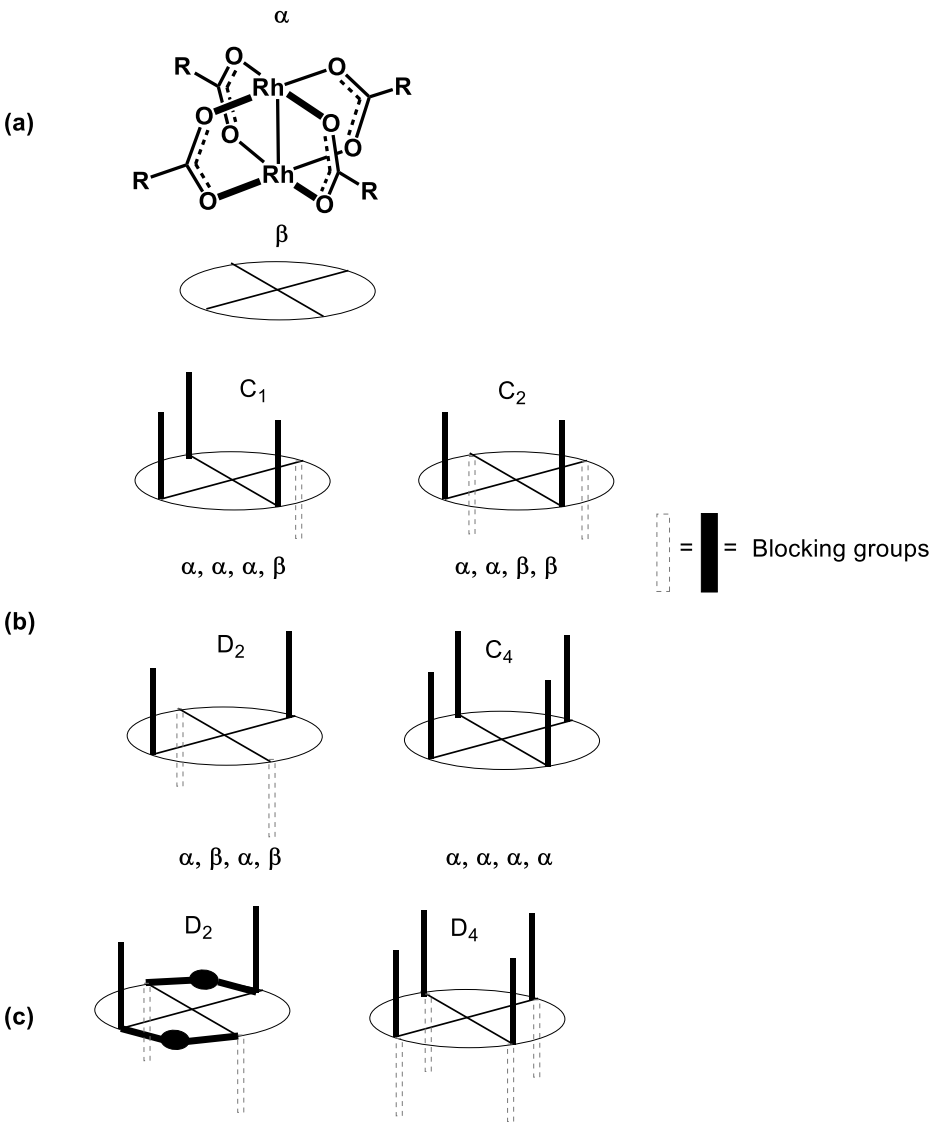


Figure 1.8 “Side-on” view of a Rh(II,II) paddlewheel, b) possible symmetry conformations for Rh(II,II) complexes, and c) symmetries of Rh(II,II) complexes with C_2-symmetric ligands

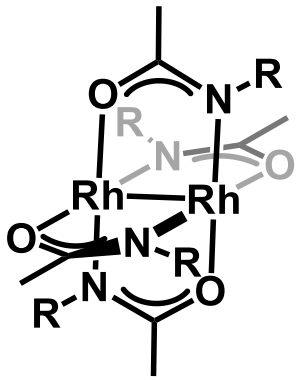


Figure 1.9 Cis-(2,2) isomer of Rh(II,II)-carboxamidates

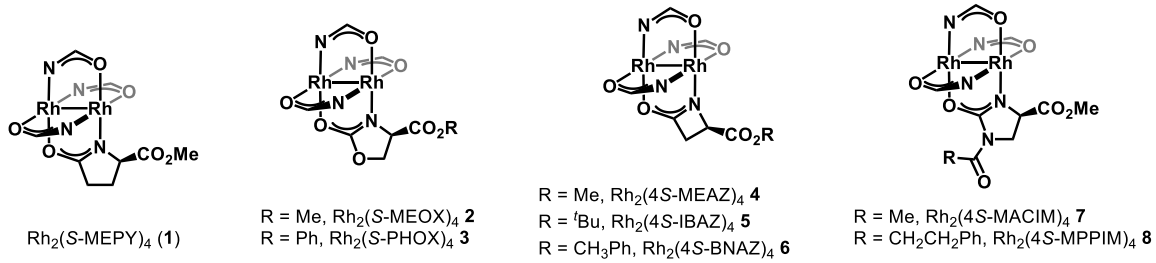


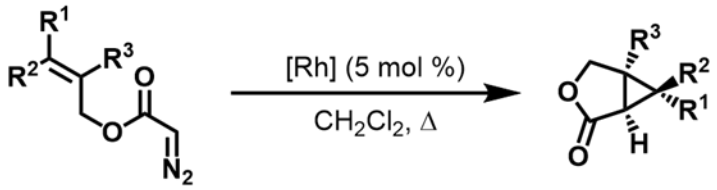
Figure 1.10 Rh(II,II)-carboxamidates derived from oxopyrrolidinones, oxazolidinones, azetidinones, and N-acylimidazolidinones

reactions where they have shown high proficiency in intramolecular allylic cyclopropanation reactions.[4] With Rh(II,II) carboxamidates and allylic diazoacetates, Doyle and coworkers were able to form bicyclic lactones in up to 90% yield and enantiomeric excesses (ee) reaching >95% (Table 1.1).[15, 17, 56] Rh_2(5*S*-MEPY$_4$) **1**, the first highly selective Rh(II,II) carboxamidate, was an efficient catalyst in this study with very high ee's while maintaining moderate to high yields with various substrates (Table 1.1, entries 1-3).[56] It should be noted that both the *S* and *R* enantiomers of the Rh_2(MEPY)$_4$ complex gave comparable enantiocontrol in the reaction but towards the opposite isomer (Table 1.1, entries 1 and 4). However, for the cases where it underperformed, the Rh_2(4*S*-MACIM)$_4$ **7** and Rh_2(4*S*-MPPIM)$_4$ **8** complexes improved enantiocontrol (Table 1.1, entries 5-7).[56]

Unlike the intramolecular allylic systems, chiral Rh(II,II) carboxamidates have struggled to achieve high selectivity in intermolecular ethyl diazoacetate (EDA) systems.[27, 57-59] Traditionally, EDA reactions are better accomplished by chiral Cu(I) BOX catalysts for high enantioselectivity.[17] Aside from a few examples, diastereoselectivity for EDA cyclopropanation using Rh(II,II) complexes is largely lacking.[9] With EDA, it was found that the oxopyrrolidine, oxazolidinone, and azetidinone complexes catalyzed the reaction with moderate enantioselectivities and, interestingly, exhibited preference for the thermodynamically less stable *cis*-cyclopropane (Table 1.2, entries 1-4).[57, 59] It should also be noted that all the carboxamidate complexes exhibited lower overall cyclopropane yields than the benchmark complex, Rh_2(OAc)$_4$ (Table 1.2, entry 5).

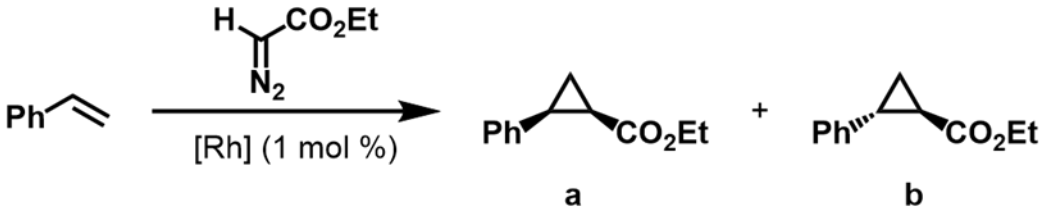
Rationalization for the observed stereoinduction involves the sterically blocking groups forming symmetric chiral pockets at each rhodium active site. Doyle and coworkers modeled these steric effects on the Rh_2(MEPY)$_4$ carbenoid species using X-ray crystallography and computational analysis.[60] It was determined that the chiral methyl ester blocking groups are arranged in an α, α, β, β (C_2-symmetric) conformation (Figure 1.11a). This arrangement creates active sites that contain two blocking groups, from adjacent bridging ligands, that form a barrier that directs substrate attack onto the carbene (Figure 1.11b). For intermolecular cyclopropanations, it is inferred that smaller diazo ester substituents, like the ethyl in EDA, are too small to be influenced by the blocking groups and will create racemic mixtures. Larger ester groups like the dicyclohexyl group of

Table 1.1 Intramolecular cyclopropanation of allylic diazoacetates using chiral Rh(II,II)-carboxamidates



entry	Catalyst	R^1	R^2	R^3	Yield (%)	% ee
1	Rh_2(5*S*-MEPY)$_4$ (**1**)	H	H	H	75	95
2	Rh_2(5*S*-MEPY)$_4$ (**1**)	CH_3	CH_3	H	89	98
3	Rh_2(5*S*-MEPY)$_4$ (**1**)	H	C_6H_5	H	70	≥94
4	Rh_2(5*R*-MEPY)$_4$ (**9**)	H	H	H	72	-95
5	Rh_2(5*S*-MEPY)$_4$ (**1**)	H	H	CH_3	72	7
6	Rh_2(4*S*-MACIM)$_4$ (**7**)	H	H	CH_3	90	78
7	Rh_2(4*S*-MPPIM)$_4$ (**8**)	H	H	CH_3	75	89

Table 1.2 Cyclopropanation of styrene with EDA using chiral Rh(II,II)-carboxamidates



a b

entry	Catalyst	Yield (%)	a/b	%ee
1	Rh_2(5*S*-MEPY)$_4$ **(1)**	59	44:56	33
2	Rh_2(*S*-PHOX)$_4$ **(3)**	41	66:34	57
3	Rh_2(4*S*-IBAZ)$_4$ **(5)**	62	69:31	76
4	Rh_2(4*S*-BNAZ)$_4$ **(6)**	74	58:42	60
5	$Rh_2(OAc)_4$	93	38:62	N/A

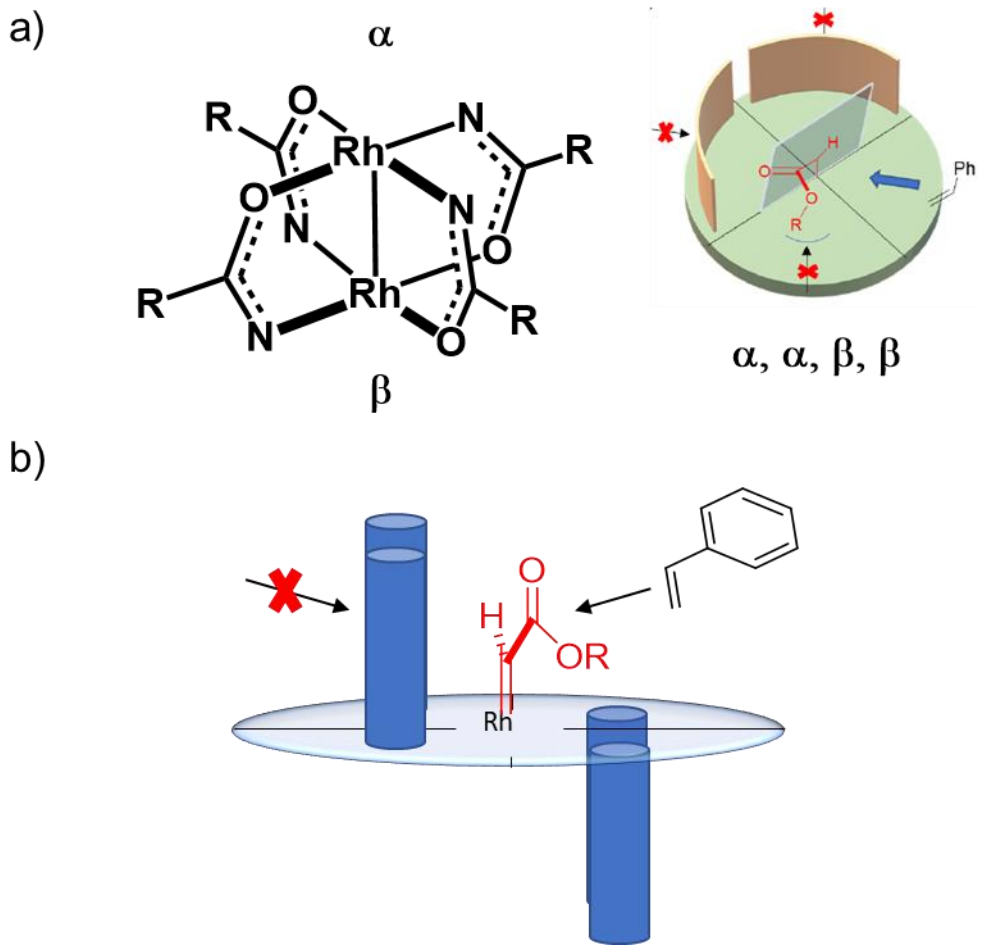


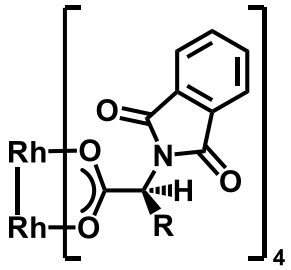
Figure 1.11 a) $Rh_2(4S\text{-}MEPY)_4$ conformation of methyl ester blocking groups b) approach of substrate directed by chiral blocking groups

dicyclohexyl diazoacetate (DCDA) will have higher steric clash and increase enantioselectivity.

1.1.2.3 Chiral Rh(II,II) Phthalimides

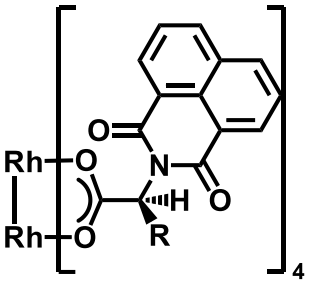
In the early 1990s, Hashimoto, Ikegami, and coworkers introduced chiral Rh(II,II) complexes with phthalimide protected amino acid ligands (Figure 1.12a**).**[13] Initially, alanine and phenylalanine derivatives, Rh_2(S-PTA)$_4$ **10** and Rh_2(PTPA)$_4$ **11** respectively, were developed and used to catalyze intramolecular C-H insertions.[61] A few years later they synthesized the *tert*-leucine derived Rh_2(*S*-PTTL)$_4$ **12** which exhibited high enantiocontrol in cyclopropanation and C-H insertion reactions and provided a structural blueprint for other successful chiral catalysts.[62-64] One of the initial hypotheses for this high enantiocontrol was the assumption that **12** adopts a C_2-symmetric conformation similar to Rh_2(*S*-MEPY)$_4$ in the solid state.[65, 66] Based on this assumption, Hashimoto proposed a general model for enantioinduction with **12** wherein the subsequent carbene sits in the active site with its bulky substituents pointed away from the two blocking groups.[67-69] The substrate attack is then directed towards the *re*-face resulting in the observed stereochemistry. Efforts towards improving this steric effect led to the Müller group developing the *N*-1,8-naphthaloyl *tert*-leucine derived catalyst, Rh_2(*S*-NTTL)$_4$ **14** (Figure 1.12b), which demonstrated impressive asymmetric cyclopropanation of donor/acceptor and acceptor/acceptor systems.[70-73] Another method of utilizing steric bulk on the bridging ligands involves modification of the α-carbon of the amino acid derivative. In fact, a decrease in enantioselectivity when decreasing the bulk at the α-carbon, *t*-butyl **12** (74% ee) vs. *i*-Pr **13** (51% ee) vs. Me **10** (35% ee), has been observed.[74, 75] The Davies group took notice of this and developed the L-adamantylglycine derived complex Rh_2(*S*-PTAD)$_4$ **15**.[76] The bulkier complex afforded enhanced enantioselectivity in various asymmetric reactions, including intermolecular cyclopropanations of donor/acceptor diazos [76-79] The Rh_2(*S*-PTAD)$_4$ complex proved to be the superior catalyst for the enantioselective intermolecular cyclopropanation of styrene with α-diazobenzylphosphonates, outperforming its *t*-butyl analog Rh_2(*S*-PTTL)$_4$ and the prolinate derived Rh_2(*S*-DOSP)$_4$ **16** (Table 1.3).[76] Around this time, the idea that only C_2 and D_2-symmetric complexes could afford high enantiocontrol was challenged by the Fox group when they obtained an X-ray crystal structure of Rh_2(*S*-PTTL)$_4$ and determined that it adopted an all-up α, α, α, α

(a)



R = Me, Rh_2(*S*-PTA)$_4$ **10**
R = Bn, Rh_2(*S*-PTPA)$_4$ **11**
R = ^{t}Bu, Rh_2(*S*-PTTL)$_4$ **12**
R = *i*-Pr, Rh_2(*S*-PTV)$_4$ **13**

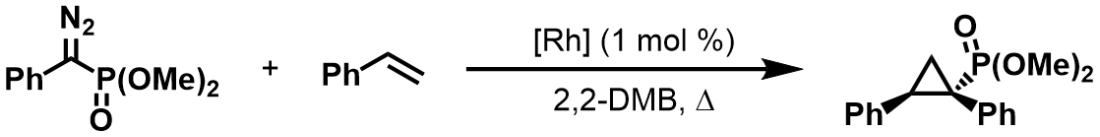
(b)



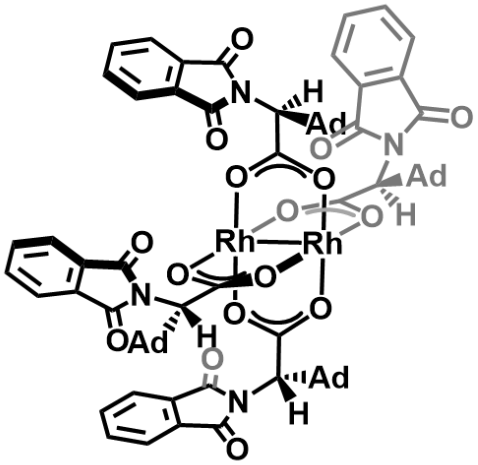
Rh_2(*S*-NTTL)$_4$ **14**

Figure 1.12 Rh(II,II) complexes derived from phthalimide protected amino acid ligands

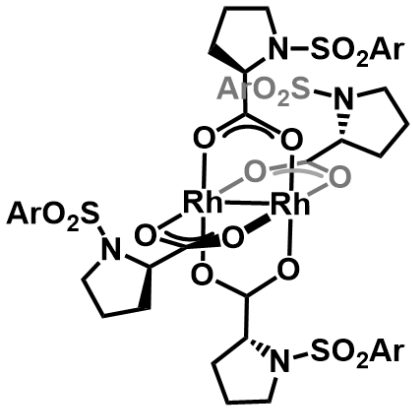
Table 1.3 Intermolecular cyclopropanation of styrene with a α-diazobenzylphosphonate catalyzed by Rh(II,II)-phthalimides and a Rh(II,II)-prolinate complex



entry	Catalyst	Yield (%)	d.r	ee, %
1	Rh_2(*S*-DOSP)$_4$ (**16**)	69	>30:1	34
2	Rh_2(*S*-PTTL)$_4$ (**12**)	85	>30:1	88
3	Rh_2(*S*-PTAD)$_4$ (**15**)	86	>30:1	99



Rh_2(*S*-PTAD)$_4$ **15**



Ar = 4-($C_{12}H_{25}$)C_6H_4
Rh_2(*S*-DOSP)$_4$ **16**

conformation instead of the predicted α, α, β, β (C_2-symmetric) conformation.[80, 81] However, this all-up conformation was not C_4-symmetric but C_2-symmetric as a result of the phthalimide rings creating a "chiral crown" configuration around one of the axial sites with a single ethyl acetate (EtOAc) solvent molecule coordinated (Figure 1.13a/b).[80] Fox and coworkers suggested that this chiral crown is maintained during catalysis and that the carbene orients itself in the chiral pocket in such a way that its *si*-face is open to attack by the substrate (Figure 1.13c). It was also suggested that the distal Rh active site is inaccessible due to steric blocking from the *t*-butyl groups.[80, 81] Although this theory is in accordance with the improved enantiocontrol observed with the bulkier **15**, several groups have challenged Fox's claims. The idea that the distal Rh site is completely restricted was disproven by Adly and coworkers when they reported an X-ray crystal structure of Rh_2(*S*-PTAD)$_4$ and found that it existed as a bis(EtOAc) adduct.[82] The Charette group conducted 2D heteronuclear NOESY experiments on **12** and discovered that the phthaloyl groups are flexible and can change conformation in solution, refuting Fox's claim (Figure 1.14).[63] The same study also determined that the replacement of the phthaloyl hydrogens with halogens, complexes **17-18** led to a more conformationally rigid complex with no observed rotation of the blocking groups and improved enantioselectivity in the intermolecular cyclopropanation of styrene and α-nitro diazoacetophenones (Table 1.4).[63]

1.1.2.4 Chiral Rh(II,II) Prolinates

The notion that C_2- and D_2-symmetric complexes, those with two equivalent active sites, will lead to high stereoselectivity was confirmed by the development of chiral Rh(II,II) prolinate complexes.[45, 48] McKervey and co-workers developed the first prolinate complex, Rh_2(*S*-BSP)$_4$ **23**, in the early 90s and saw good enantiocontrol in C-H insertion reactions.[83, 84] However, prolinate complexes didn't start realizing their potential until Davies expanded their use to cyclopropanations of donor/acceptor carbenes.[48, 85] Donor/acceptor carbenoids are stabilized by the donor groups, and as such, are considered to be less active. Davies and co-workers tested various Rh(II,II) prolinates in the cyclopropanation of alkenes with vinyl diazoacetates.[48] It was found that changing the arylsulfonyl group had a small effect on enantioselectivity in DCM (Table 1.5, entries 1-5). However, when the solvent was changed to pentane, Rh_2(*S*-TBSP)$_4$ **26** and Rh_2(*S*-DOSP)$_4$ **16** exhibited high enantiocontrol (Table 1.5, entries 6-7). This improved performance of **16** in non-polar solvents was also seen in C-H insertion reactions.[22, 49] Davies also tested acyclic N-

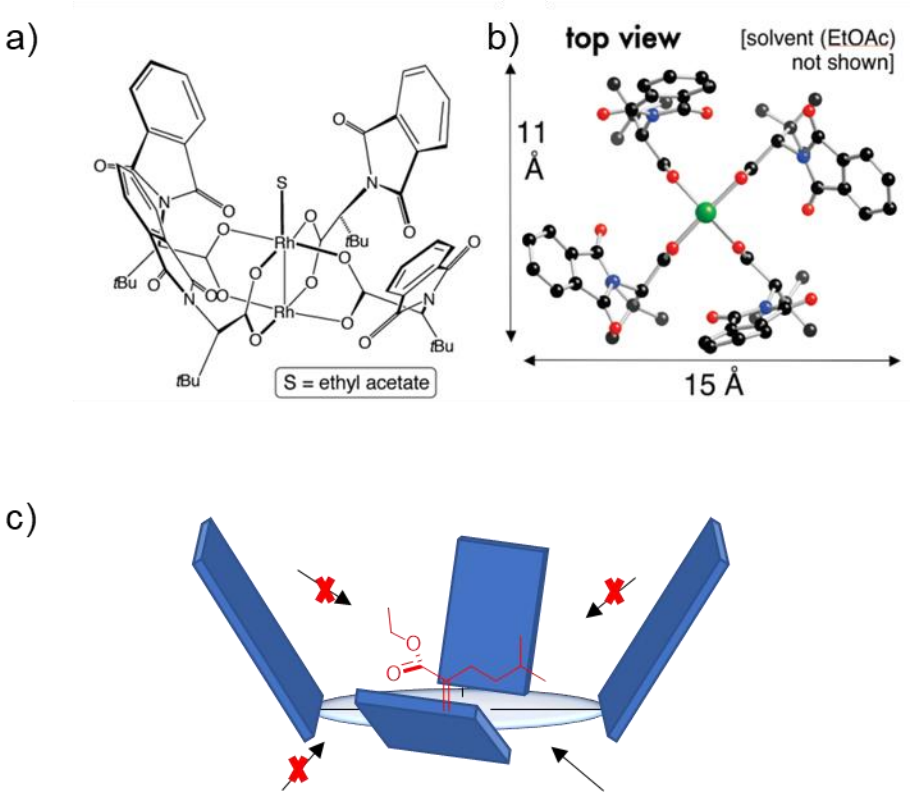
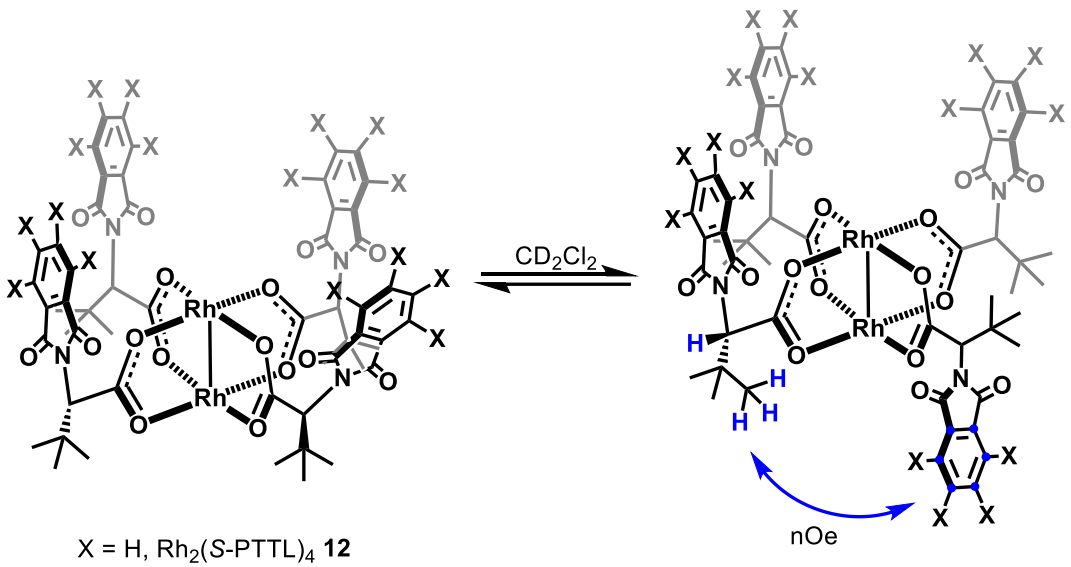


Figure 1.13 a) Side-on view of the “chiral crown” of Rh_2(*S*-PTTL)$_4$, b) a top-down view of the X-ray crystal structure, and c) a visual representation of the chiral pocket directing substrate attack.

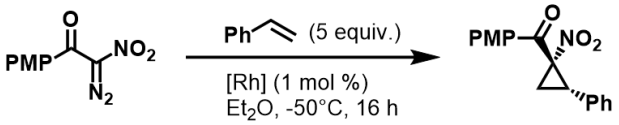
a/b): Reprinted with permission from DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M., Chiral Crown Conformation of Rh2(S-PTTL)4: Enantioselective Cyclopropanation with α-Alkyl-α-diazoesters. Journal of the American Chemical Society 2009, 131 (21), 7230-7231. Copyright 2009 American Chemical Society."

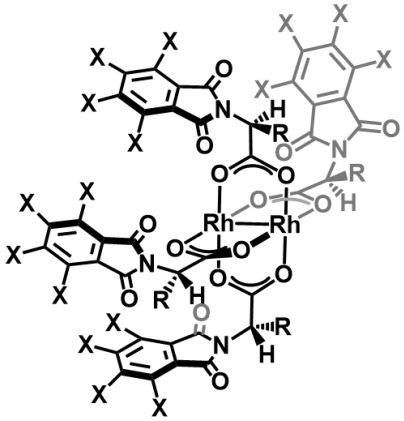


X = H, Rh_2(*S*-PTTL)$_4$ **12**
X = Cl, Rh_2(*S*-TCPTTL)$_4$ **17**
X = Br, Rh_2(*S*-TBPTTL)$_4$ **18**

Figure 1.14 Interaction between side chain protons and phthaloyl aromatic carbons in Rh(II,II)-phthalimide complexes. Confirmed by ^{1}H NMR NOESY experiments

Table 1.4 Asymmetric cyclopropanation of styrene with α-nitro diazoacetophenones with Rh(II,II)-phthalimide complexes

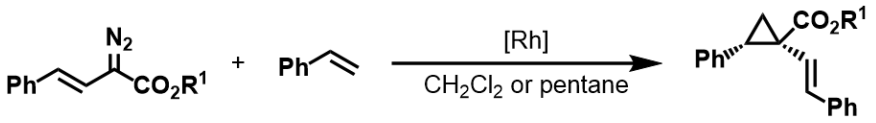




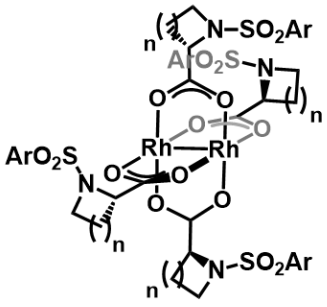
R= Me, X= Cl; Rh_2(*S*-TCPTA)$_4$ **19**
R= Bn, X= Cl; Rh_2(*S*-TCPTPA)$_4$ **20**
R= ^{i}Pr, X= Cl; Rh_2(*S*-TCPTV)$_4$ **21**
R= ^{i}Pr, X= Br; Rh_2(*S*-TBPTV)$_4$ **22**

entry	Catalyst	Yield (%)	cis/trans	ee (cis), %
1	Rh_2(*S*-PTA)$_4$ **(10)**	55	53:47	22
2	Rh_2(*S*-PTPA)$_4$ **(11)**	56	55:45	43
3	Rh_2(*S*-PTV)$_4$ **(13)**	76	72:28	16
4	Rh_2(*S*-PTTL)$_4$ **(12)**	80	33:67	2
5	Rh_2(*S*-TCPTA)$_4$ **(19)**	81	97:3	92
6	Rh_2(*S*-TCPTPA)$_4$ **(20)**	72	94:6	91
7	Rh_2(*S*-TCPTV)$_4$ **(21)**	82	98:2	91
8	Rh_2(*S*-TCPTTL)$_4$ **(17)**	70	99:1	93
9	Rh_2(*S*-TBPTV)$_4$ **(22)**	89	96:4	80

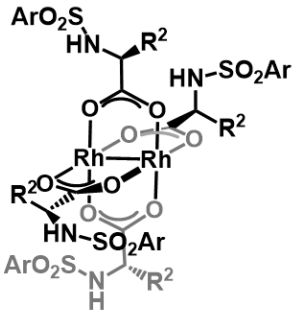
Table 1.5 Asymmetric cyclopropanation of styrene and vinyl diazoacetates by Rh(II,II)-prolinate complexes



entry	Catalyst	Ar	n	R^1	R^2	Solvent	ee, %
1	Rh_2(*S*-BSP)$_4$ **(23)**	Ph	2	Me	-	CH_2Cl_2	74
2	**(24)**	4-(OMe)C_6H_4	2	Me	-	CH_2Cl_2	76
3	**(25)**	4-(NO_2)C_6H_4	2	Me	-	CH_2Cl_2	83
4	Rh_2(*S*-TBSP)$_4$ **(26)**	4-(^{t}Bu)C_6H_4	2	Me	-	CH_2Cl_2	74
5	Rh_2(*S*-DOSP)$_4$ **(16)**	4-($C_{12}H_{25}$)C_6H_4	2	Me	-	CH_2Cl_2	79
6	Rh_2(*S*-TBSP)$_4$ **(26)**	4-(^{t}Bu)C_6H_4	2	Me	-	pentane	90
7	Rh_2(*S*-DOSP)$_4$ **(16)**	4-($C_{12}H_{25}$)C_6H_4	2	Me	-	pentane	92
8	**(27)**	4-(^{t}Bu)C_6H_4	-	Me	*i*Pr	CH_2Cl_2	30
9	**(28)**	4-(^{t}Bu)C_6H_4	-	Me	CH_2Ph	CH_2Cl_2	6
10	**(29)**	4-(^{t}Bu)C_6H_4	1	Me	-	pentane	81
11	**(30)**	4-(^{t}Bu)C_6H_4	3	Me	-	pentane	81
12	Rh_2(*S*-TBSP)$_4$ **(26)**	4-(^{t}Bu)C_6H_4	2	Et	-	pentane	84
13	Rh_2(*S*-TBSP)$_4$ **(26)**	4-(^{t}Bu)C_6H_4	2	^{t}Bu	-	pentane	50



Cyclic Prolinates



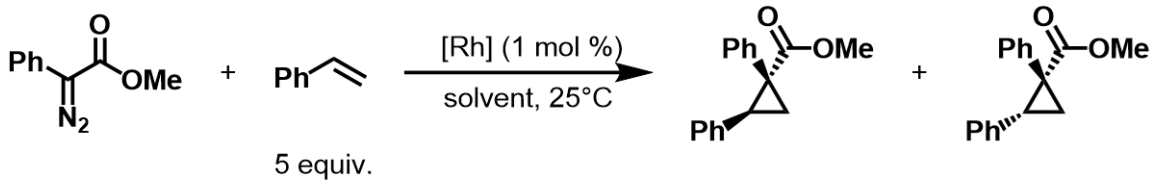
Acycic N-sulfonyl Carboxylates

sulfonyl carboxylates as catalysts in the cyclopropanation of alkenes (Table 1.5, entries 8-9) and found a substantial decrease in enantioselectivity, highlighting the necessity of a cyclic bridging ligand. Finally, ring size was also evaluated with azetidinecarboxylate (Table 1.5, entry 10) and picolinate (Table 1.5, entry 11) complexes. Although not as good as the five-membered prolinates, changes in ring size can be tolerated as evidenced by high enantioselectivities for both complexes. Increasing the steric bulk at the ester of the diazo also did not yield improved enantioselectivity (Table 1.5, entries 12-13).

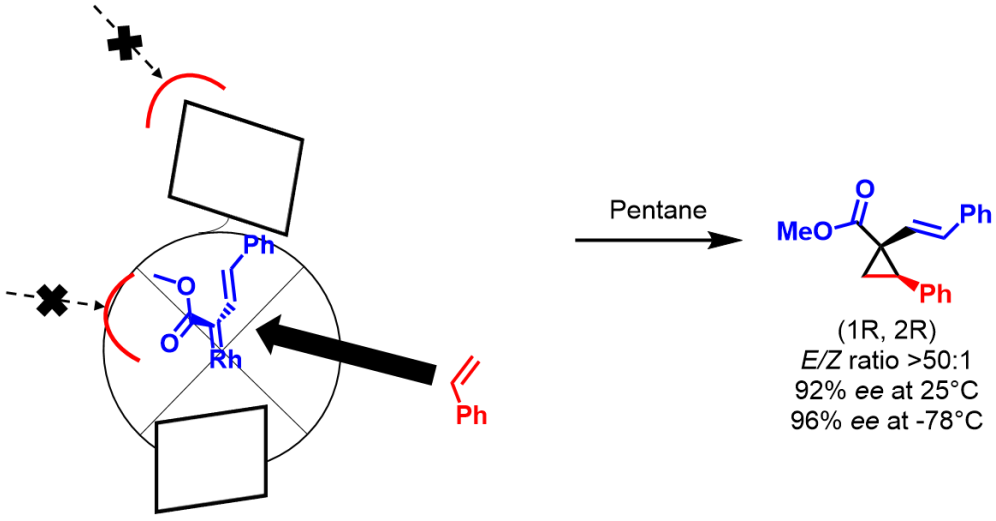
Rh(II,II) prolinate cyclopropanation is not just limited to vinyl diazoacetates and has also seen success with aryl diazoacetates. Both **26** and **16** demonstrated exceptional enantioselectivity in the cyclopropanation of styrene with methyl phenyldiazoacetate (Table 1.6).[85] As observed with the vinyl diazoacetates, catalyst performance can be further tuned through changes in solvents evidenced by non-polar solvents improving enantiocontrol (Table 1.6, entries 1-4). However, diastereoselectivity was largely independent of catalyst control. This was evidenced by comparable diastereomeric ratios (d.r.) between the chiral prolinate complexes and achiral complexes such as $Rh_2(OAc)_4$ (Table 1.6, compare entries 1-4 with 5). Increasing the electron-deficiency of the complex also had minimal change in product yield and diastereoselectivity (Table 1.6, entries 6).

High enantiocontrol with prolinate complexes has been attributed to the orientation of the arylsulfonyl groups. Rh(II,II) prolinate complexes likely adopt a D_2-symmetry in which the sterically blocking groups are in an α, β, α, β conformation. This conformation creates two identical active sites with blocking groups limiting certain trajectories for substrate attack and inducing stereoselectivity. Davies proposed a general model in which the 16 metal-carbene complex has its *si*-face blocked by one of the arylsulfonyl groups, forcing attack of the olefin to occur at the *re*-face (Figure 1.15a).[48] Another quadrant for approach is blocked by the sterics of the carbene ester group. Based on this stereochemical model, Davies and co-workers developed second generation D_2-symmetric prolinate complexes that locked the arylsulfonyl groups in a rigid α, β, α, β conformation by exchanging C_2-symmetric dicarboxylate ligands that link two prolinates together through a *meta*-benzene bridge (Figure 1.15b).[86, 87] These complexes exhibited high enantiocontrol in intermolecular cyclopropanations of methyl styryldiazoacetates, comparable to the first generation prolinates. Interestingly, the bridged complexes resulted

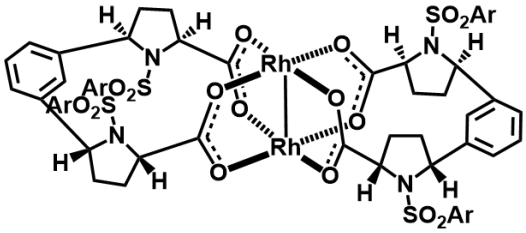
Table 1.6 Asymmetric cyclopropanation of styrene and methyl phenyldiazoacetate by Rh(II,II)-prolinate complexes



entry	Catalyst	solvent	trans:cis	Yield, %	ee **trans**, %
1	Rh_2(*S*-TBSP)$_4$ **(26)**	CH_2Cl_2	98:2	65	67
2	Rh_2(*S*-TBSP)$_4$ **(26)**	pentane	97:3	72	86
3	Rh_2(*S*-DOSP)$_4$ **(16)**	CH_2Cl_2	98:2	69	69
4	Rh_2(*S*-DOSP)$_4$ **(16)**	pentane	97:3	79	91
5	$Rh_2(OAc)_4$	CH_2Cl_2	98:2	69	-
6	$Rh_2(TFA)_4$	CH_2Cl_2	99:1	70	-



(b)



Ar = 2,4,6-tri-*i*PrC$_6$H$_2$, Rh$_2$(*S*-biTISP)$_2$ **31**
4-(C$_{12}$H$_{25}$)C$_6$H$_4$, Rh$_2$(*S*-biDOSP)$_2$ **32**

Figure 1.15 a) General model for the directed substrate attack on the Rh$_2$(S-DOSP)$_4$ carbene species responsible for the observed enantioselectivity b) Second generation Rh(II,II)-prolinates with linked prolinate rings.

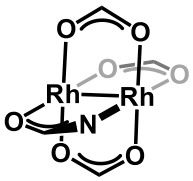
in the opposite enantiomer of cyclopropanes as the first generation prolinates. This was attributed to the carbene adopting a different conformation in the chiral pocket resulting in an olefin attack that is onto the *si*-face rather than the *re*-face.[49]

1.1.3 Heteroleptic Rh(II,II) Complexes

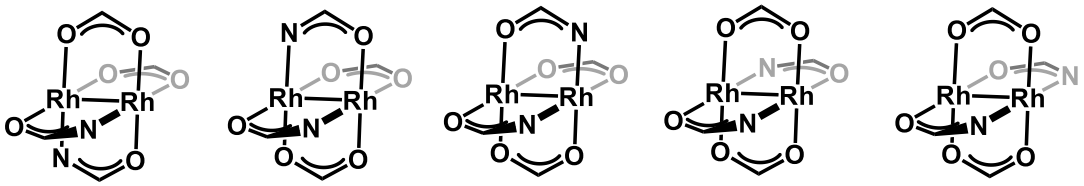
Incomplete substitution leads to a mixture of heteroleptic products that may also be separated into different isomeric structures. One example is in ligand exchanges with carboxamidate bridging ligands that contain a nitrogen and an oxygen atom coordinating to the rhodium metals.[17] In total, 14 different geometric isomers can be formed when considering all substitution possibilities. The mono-substituted product contains no isomers because all the other bridging ligands are identical (Figure 1.16, a).[88, 89] Bis-substituted complexes are characterized as *cis* if the two exchanged carboxamidate ligands are adjacent to each other or *trans* if they are exchanged at the opposite equatorial position. The di-substituted complexes, however, have much more complex mixtures of isomers (Figure 1.16, b). These isomers are classified as either *syn* or *anti* depending on whether the two nitrogens (one from each ligand) are on the same rhodium metal or on different metals. Another level of isomerism is observed with the *cis-anti* configurations in which two rotational isomers can exist.[88] If the rotation occurs in a clockwise fashion, it is regarded as a *P-cis-anti* isomer and if counterclockwise, *M-cis-anti* (Figure 1.16, b). Three-fold substitution can result in 4 isomers with no further complexity seen other than a general change in N and O pattern (Figure 1.16, c). Isomers are also possible with tetra-substituted complexes. The tetra-substituted complexes can be arranged with all the nitrogens on one rhodium metal and the oxygens on the other (4,0), three nitrogens (3,1), or two on each rhodium (2,2). The (2,2) complexes can be further isomerized between *cis* or *trans* relative to the positions of the nitrogen atoms on each metal. Ligand exchange towards the tetra-substituted isomer concluded that the *cis*-(2,2) isomer is the most thermodynamically favored product of the ligand exchange (Figure 1.16, d).[88, 90]

A common method for heteroleptic complex synthesis involves using a more labile bridging ligand to control the extent of ligand exchange and obtain the desired substitution pattern. This has been accomplished by using mixed acetate/trifluoroacetate complexes, $Rh_2(OAc)_n(TFA)_{4-n}$, as the starting material and exchanging the more labile trifluoroacetate ligands for the desired bridging ligand (Figure 1.17, a).[41] The bis-substituted species, $Rh_2(OAc)_2(TFA)_2$, can be synthesized as either a *cis* or *trans* isomer and has been used

(a)

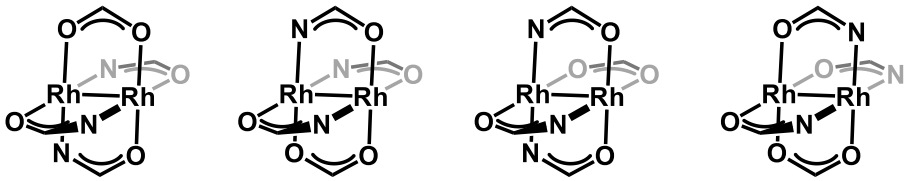


(b)

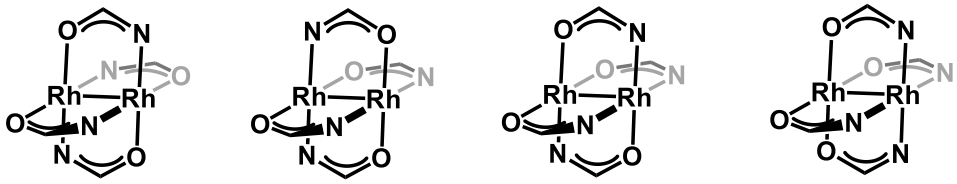


M-cis-anti *P-cis-anti* *cis-syn* *trans-anti* *trans-syn*

(c)



(d)



cis-(2,2) *trans-(2,2)* *(3,1)* *(4,0)*

Figure 1.16 Possible isomers for heteroleptic Rh(II,II) complexes at a) mono, b)di, c) tri, and d) tetra levels of substitution.

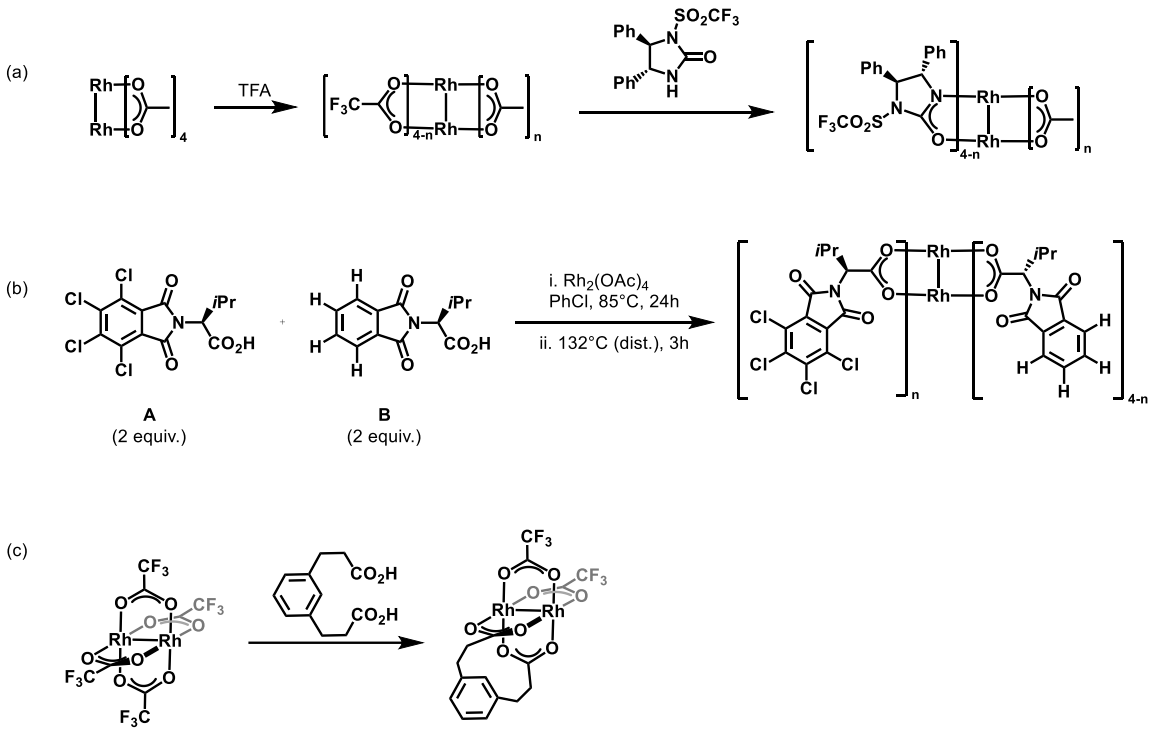


Figure 1.17 Synthetic methods towards heteroleptic complexes

by Corey and co-workers for the synthesis of diphenyl-*N*-triflylimidazolidinone (DPTI) ligated complexes, $Rh_2(DPTI)_{4-n}(OAc)_n$.[88] Charette and co-workers successfully synthesized heteroleptic complexes with different carboxylates by reacting $Rh_2(OAc)_4$ with two equivalents of ligands **A** and **B** in PhCl (Figure 1.17, b).[91] Ligand **A** contained a fully halogenated aryl ring which acts as a "polarity-control group" that affected the retention factor (R_f) of each substituted product. This resulted in well-defined chromatographic separation of products and subsequent isolation of each. Yields of the chloro- tris-substituted species was enhanced by a process of isolating the products that are not fully substituted and resubjecting them to the same reaction conditions. This process was repeated multiple times to achieve a desired substitution pattern.[91, 92] Another method of controlling substitution in heteroleptic complexes is using bidentate carboxylate ligands. This was first accomplished by the Taber group wherein they exchanged a benzenedipropanoic acid ligand onto a $Rh_2(TFA)_4$ complex, resulting in a bidentate Rh(II,II) heteroleptic complex as the only product (Figure 1.17, c).[93]

Heteroleptic complexes have exhibited utility in asymmetric catalysis, despite having a lower symmetry than their homoleptic counterparts.[41] Corey determined that using $Rh_2(DPTI)_3(OAc)$ **33** in the cyclopropanation of EDA and styrene afforded excellent ee's for both diastereomers, however, diastereoselectivity was lacking (Figure 1.18a).[94] The high enantioselectivity was theorized to be the result of a cleavage of the acetate ligand, forming a tri-bridged carbene species **34** (Figure 1.18b). This species allows for a stronger $Rh–C_{carbene}$ dπ-bond and creates a preference for either *cis* or *trans* orientation of the ester portion relative to the N or O of the DPTI ligands. The carbene subsequently prefers the orientation where the ester is *cis* to the oxygen of the DPTI ligand, locking it in a specific geometric isomer. This model was challenged a year later by Singleton in which they conducted kinetic isotope effect experiments and computational studies and found that the tri-bridged structure was 21.5 kcal/mol higher in energy than the tetra-bridged structure.[95]

Although Corey's intermediate was disproven, the report had implications for the use of heteroleptic complexes with chiral bridging ligands exchanged for an achiral ligand. Fox and co-workers synthesized the heteroleptic $Rh_2(S\text{-PTTL})_3TPA$ (TPA = triphenylacetate) from $Rh_2(S\text{-PTTL})_4$.[96] It was found that this complex exhibited comparable selectivity to homoleptic chiral complexes in the asymmetric cyclopropanation

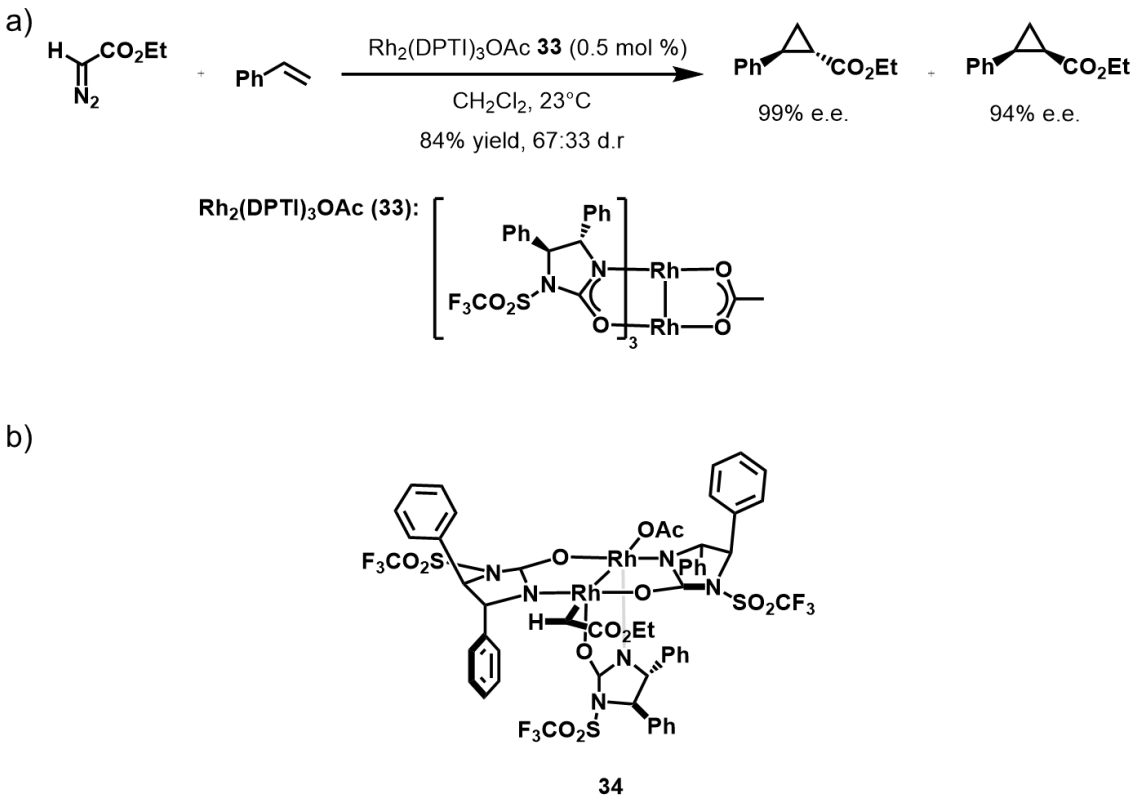


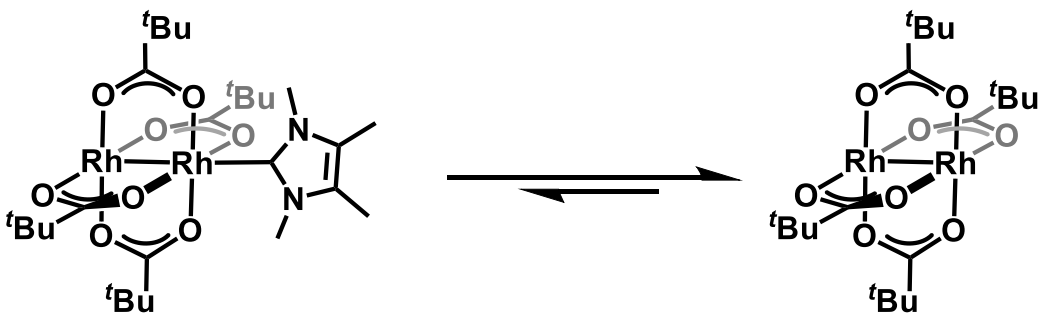
Figure 1.18 a) asymmetric cyclopropanation of styrene and EDA with $Rh_2(DPTI)_3OAc$ b) proposed tri-bridged carbene species responsible for observed enantioselectivity

of styrene with ethyl 2-diazobutanoate. The mixed-ligand complex resulted in lower yields but better enantio- and diastereoselectivity than the parent Rh_2(*S*-PTTL)$_4$, despite the loss of one of the chiral ligands.[96]

1.1.4 Axial Coordination

Most studies into axial coordination involve the use of exogenous Lewis bases (LB), but the weaker association of axially bound LBs compared to bridging ligands makes this approach problematic. Controlling formation of mono- and bis-adducts has proven difficult when axial coordination is facilitated by additives. Drago and coworkers found that at low concentrations of exogenous ligand, both free complex and 1:1 (ligand:catalyst) adducts are observed.[97] At high concentrations of exogenous ligand, a mixture of 1:1 and 2:1 adducts exist. Free complex, 1:1, and 2:1 adducts are all present when using intermediate concentrations of the ligand.[97] Indeed, studying axial coordination can be difficult since excess equivalents of the additive are needed for measurable effects, and as a result, determining the exact influence of the additive is more nuanced. There are reports of positive results in the presence of additives, while in other situations additives are a detriment. For example, using mild coordinative co-solvents such as tetramethyl urea or Hünig's base resulted in improvements in O-H insertion reaction yields,[98] but the use of dimethylaminopyridine (DMAP) in cyclopropanation reactions gave lower yields.[64] Recently, Davies and co-workers reported improved asymmetric cyclopropanation of heteroaryl diazos using a 2-chloropyridine additive that binds to the axial site, though the exact effect this additive has on enantioselectivity has not been extensively explored.[99] *N*-Heterocyclic carbene (NHC) additives were implemented as a way to ensure axial coordination due to their strong coordinating ability.[100] The first Rh(II,II) paddlewheel complexes with NHC axially ligated adducts were used in intramolecular cyclization reactions, but the improved performance was attributed to a free complex (Figure 1.19a).[100] This was later remedied by the incorporation of bulky wingtip groups, however, the use of NHC axial ligands for carbene transfer reactions generally resulted in comparatively lower product yields (Figure 1.19b).[101, 102] Lately, there have been renewed efforts to pursue an increased understanding of the role of axial coordination in carbene transfer reactions. For example, Laconsay and co-workers very recently disclosed a computational study on the effect of axial solvents on C–H insertion reactions and found that axial coordination affects barriers for N_2 extrusion and C–H insertion.[103]

(a)



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(b)

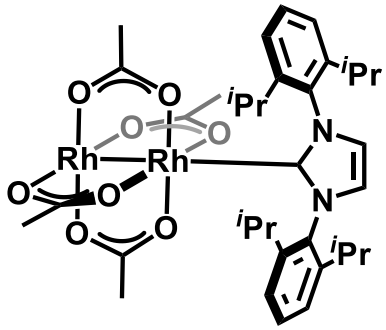

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Figure 1.19 First Rh(II,II)-NHC adduct synthesized and the proposed equilibrium during catalysis b) Rh(II,II)-NHC complex with bulky wingtip groups

Experimentally, studying axial coordination by tethering them to bridging ligands has emerged as a viable strategy to circumvent the weak interaction associated with axial ligands.[104-106] This provides a bias for the site of reactivity and ensures a high local concentration for axial coordination. These tethered ligands also take advantage of the chelate effect and allow for higher stability and stronger coordination to the axial site.As an example, Ball and co-workers developed Rh(II,II) metallopeptides that contain tripodal peptide bridging ligands with a histidine residue coordinated to the rhodium axial site (Figure 1.20) .[105] They found that tethering the bridging ligands to the axial ligand improved catalytic performance in diazo-mediated cyclopropanations over their previous mono-peptide, non-tethered catalysts.[105, 107] This improvement was theorized to be the result of controlling access to the axial site, as well as a conformational change in the peptide folding as a result of histidine binding to the rhodium metal.

1.2 Research Motivation

The synthesis of cyclopropanes has been an important area of research in the pharmaceutical and natural products industries for decades. A plethora of synthetic methods towards cyclopropanes have been developed, the most prevalent of which has been metal-catalyzed carbene transfer reactions. With this method, platinum group metal complexes have been the most common catalysts and Rh(II,II) paddlewheels have shown the most efficacy and versatility leading to their prevalence in these reactions. Although Rh(II,II)-catalyzed carbene transfer reactions have been extensively studied, efforts toward improving stereoselectivity have largely focused on bridging ligand modifications. Development of chiral bridging ligands with sterically bulky groups has been the predominant method for achieving higher levels of stereochemical control. Specifically, these studies have involved the use of homoleptic complexes with 4 identical bridging ligands and heteroleptic complexes have not been widely studied until recent years.[14, 41, 45]

A strategy of using non-covalent interactions to influence the chiral environment of the catalysts has been explored in recent years. Furuta and co-workers developed Rh(II,II) complexes that contain axially chiral binaphthothiophene bridging ligands (Figure 1.21). These ligands were shown to reduce conformational mobility and adopt a D_2 symmetric conformation through chalcogen-bonding interactions between the thiophene sulfur atoms and the carboxylate oxygens. This rigidification resulted in complexes that exhibit excellent

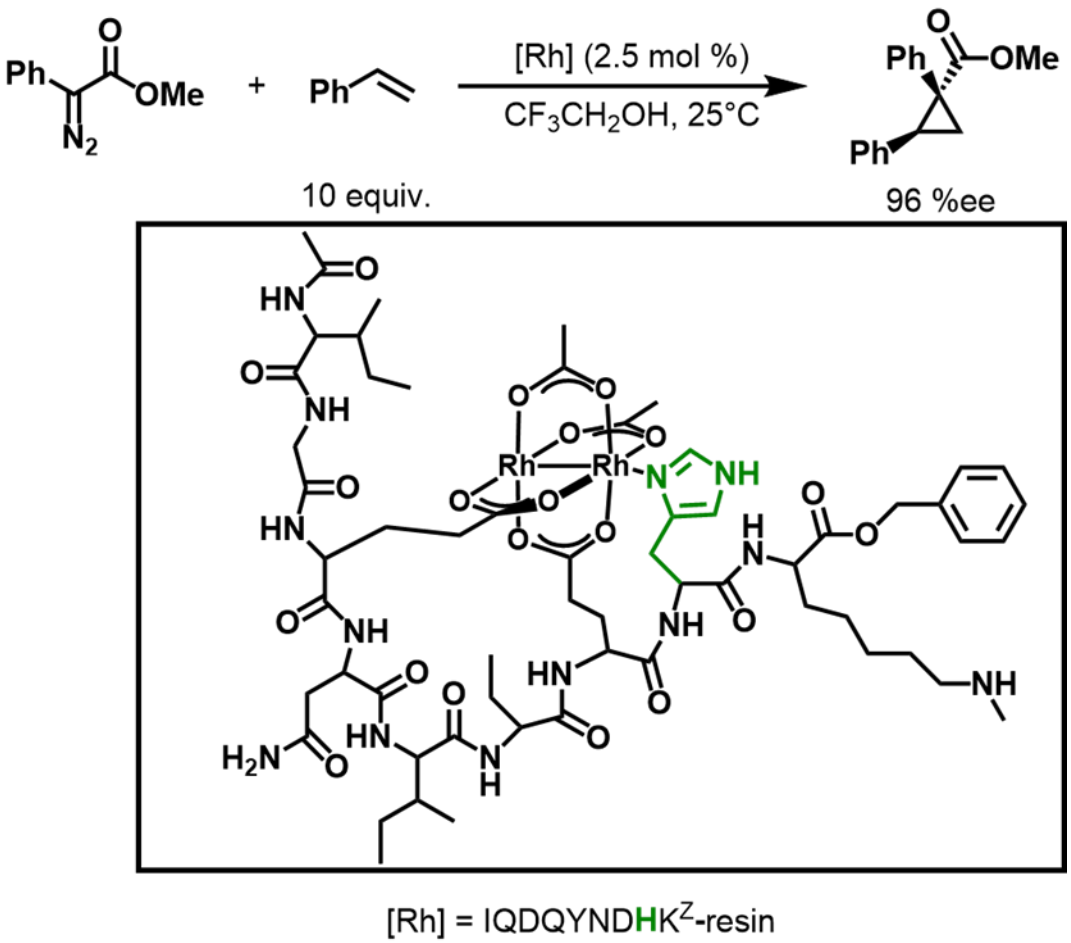


Figure 1.20 Asymmetric cyclopropanation with a Rh(II,II) metallopeptide

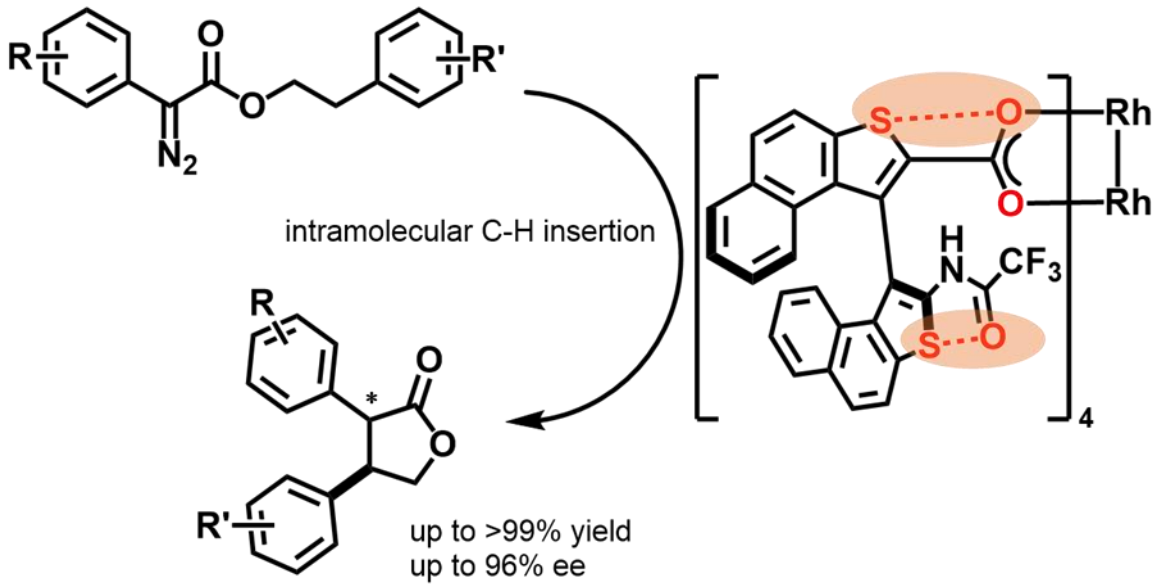


Figure 1.21 Intramolecular C–H insertion of aryl diazoacetates with Rh(II,II) complexes bearing axially chiral binaphthothiophene ligands

enantioselectivity in the intramolecular C–H insertion of α-aryl-α-diazoacetates towards diaryl γ-lactones while maintaining high yields.[108] The Fürstner lab also used non-covalent interactions to improve Rh(II,II) stereoselectivity. In 2022, they developed heteroleptic Rh(II,II) complexes with an amidate ligand that directs the orientation of the carbenoid through hydrogen bonding between the nitrogen and the carbonyl oxygen (Figure 1.22).[109] This stabilization of the carbenoid led to diastereodivergent asymmetric cyclopropanation of α-stannyl diazoacetates with excellent enantioselectivity for each diastereomer.

Not until recently have researchers made a large push towards understanding the influence of axial coordination and exploiting it to improve catalytic performance. The incorporation of additives that coordinate to the axial site has had mixed results with some additives improving reactivity and selectivity and other instances where they are a detriment. The influence of Lewis base coordination is complex and has not been widely studied. This is because it is difficult to accurately study the influence of the axial position with exogenous addition of the ligands in solution. An emerging method for axial coordination study is the development of axial ligands that are tethered to a bridging site through a linker. Recent developments in using bridging ligands with a tethered axial ligand moiety have inspired our group to develop heteroleptic Rh(II,II) complexes with tethered, axially coordinated ligands (TACLs). By tuning the electronics of the axial ligands and tethers, we hypothesized that we could more accurately study the impact of the axial position on carbene transfer reactions. The donation from the coordinated LB is expected to be communicated through the Rh-Rh bond and into the carbene, which can have a stabilizing effect in more reactive carbenes and possibly improve yields by reducing dimerization. The axial tether can also invoke steric and non-covalent influence closer to the axial site due to its proximity to the metal center. Our group proceeded to synthesize Rh(II,II)-TACLs complexes and in our seminal work, determined that these complexes could improve yields in cyclopropanation reactions.[110]

With an initial blueprint for synthesizing Rh(II,II)-TACLs complexes, we then proceeded to test the effect of the tether on an acceptor-type carbene, EDA. Chapter two highlights the synthesis and characterization of Rh(II,II)-TACLs complexes, along with spectroscopic, electrochemical, and structural analysis to elucidate the influences of the axial tether. Application towards the cyclopropanation of alkenes with EDA and evaluation

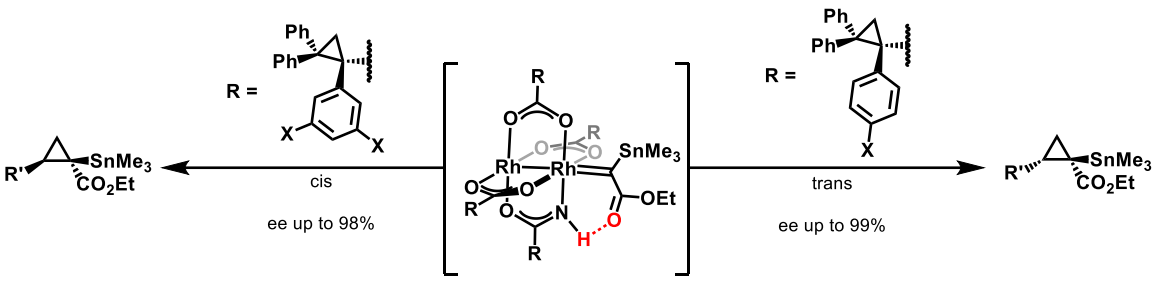


Figure 1.22 Heteroleptic Rh(II,II)-amidate complex for diastereodivergent asymmetric cyclopropanation of α-stannyl diazoacetate

of the tether's role in the catalysis is also presented. Chapter three focuses on kinetic analyses of the Rh(II,II)-TACLs, including linear free energy relationships (LFER) of competitive cyclopropanation reactions. Chapter four outlines our efforts to exchange TACLs onto chiral Rh(II,II) scaffolds and synthesize $Rh_2(A)_n(B)_{4-n}$ heteroleptic complexes where ligand A is a chiral bridging ligand and ligand B is a TACLs. Application of heteroleptic chiral Rh(II,II)-TACLs towards asymmetric cyclopropanations of various diazo reagents is also highlighted in this chapter. Finally, all the supplementary information, including NMR spectra, are in the appendices.

Chapter 2 Tuning Rh(II,II)-Catalyzed Cyclopropanation with Tethered Thioether Ligands

2.1 Disclosure

Portions of the following chapter were adapted from the article:

Cressy, D.; Zavala, C.; Abshire, A.; Sheffield, W.; Darko, A., Tuning Rh(II)-catalysed cyclopropanation with tethered thioether ligands. *Dalton Transactions* **2020**, *49* (44), 15779-15787.

In this work, Dr. Derek Cressy was responsible for the synthesis, X-ray structure elucidation, UV-Vis, and electrochemical analysis of the Rh(II,II) oxazolidinone catalysts, as well as manuscript preparation. Cristian Zavala was responsible for catalytic testing of the catalysts and in manuscript preparation. Anthony Abshire was responsible for all calculations and William Sheffield aided in characterization and manuscript preparation. Prof. Ampofo Darko advised the work.

2.2 Abstract

Rh(II,II) paddlewheel complexes have high utility in diazo-mediated cyclopropanation reactions and ethyl diazoacetate is one of the most commonly used diazo compounds in this reaction. In this study, we report our efforts to use tethered thioether ligands to tune the reactivity of Rh(II,II)-carbene mediated cyclopropanation of olefins with ethyl diazoacetate. Microwave methods enabled the synthesis of a family of Rh(II,II) complexes in which tethered thioether moieties were coordinated to axial sites of the complex. Different tether lengths and thioether substituents were screened to optimize cyclopropane yields and minimize side product formation. Furthermore, good yields were obtained when equimolar diazo and olefin were used. Structural and spectroscopic investigation revealed that tethered thioethers changed the electronic structure of the rhodium core, which was instrumental in the performance of the catalysts. Computational modelling of the catalysts provided further support that the tethered thioethers were responsible for increased yields.

2.3 Introduction

2.3.1 General Background

Rh(II,II) paddlewheel complexes have become ubiquitous in carbene chemistry since the Teyssié group first demonstrated that they were capable of decomposing diazo compounds.[8, 17, 20] The resulting Rh(II,II)-carbene is capable of a wide range of reactions including C–H and X–H (X = O, N, S, Si, B) insertion reactions, ylide transformations, and

cyclopropanation, which have made it a versatile synthetic tool.[20-26] Despite their wide utility, a common problem is the formation of side products due to competitive carbene dimerization (homocoupling).[13, 111] Carbenoids derived from EDA are particularly prone to side products derived from carbene dimerization[112, 113] and a well-used strategy to suppress dimer formation is to use an excess, typically 5–10 equivalents, of the substrate. This method can be problematic, however, in cases where precious substrates or late-stage applications are concerned.[114] Dimerization can also be mitigated by slow addition of the diazo into the reaction solution.[9] In the infancy of Rh(II,II) catalyzed carbene transfer reactions, EDA cyclopropanations were very prevalent and much of the pioneering work on Rh(II,II)-carboxylates was conducted on them.[11, 13, 20, 115-118] However, work on acceptor carbenes like EDA has significantly dropped and been replaced with acceptor/acceptors and donor/acceptors.[5, 14] This is because of the difficulty for EDA systems to attain high stereoselectivities, specifically in cyclopropanation reactions.[9, 28] As a result, acceptor carbenes are typically catalyzed by non-rhodium catalysts such as copper or ruthenium.[13, 14]

While bridging ligand design is a major focus in the development of Rh(II,II) complexes,[14, 17, 27, 47, 91, 93, 96, 119-121] we hypothesized that axial sites on the complex can be used to modulate Rh-carbene reactivity such that side products due to dimerization could be minimized. Early studies of the axial sites of Rh(II,II) complexes focused on the role of solvents and other Lewis bases and their effect on the Rh–Rh bond.[97, 122, 123] It was observed that coordination to the axial site occurs sequentially wherein the first equivalent binds stronger than the second due to the cooperative ability of the two Rh atoms.[124] Applying these fundamental studies to benefit catalytic performance has been somewhat ambiguous but has received attention as an alternative method for tuning Rh(II,II) catalysts.[125] It was clear that solvents such as acetonitrile (MeCN) decreased yields in catalytic applications by binding to the axial site and inhibiting catalysis.[97, 126, 127] There are situations, though, in which Lewis base additives have improved yields[98, 128] and selectivity[64, 129, 130] in diazo-mediated reactions. In these instances, axial coordination of the additives was believed to be playing a role. The addition of exogenous ligands, however, is complicated by the inherent weakness of axial site coordination of neutral donors. As a result, the coordination exists in solution as an equilibrium, leading to uncertainty as to whether axial coordination is involved in the catalytically active species.[131] One strategy to circumvent the issue is to add a large excess of additive to

increase the probability of axial coordination during catalysis.[132] Another method that has been explored is to implement a strong σ donor, such as N-heterocyclic carbenes,[101, 102] that will irreversibly bind to the axial site. Both strategies often lead to decreased catalyst performance or result in only marginal benefits in Rh(II,II)-carbene reactions.

2.3.2 Catalyst Design

To better utilize and enhance the effect of axial coordination on Rh(II,II) complexes, we have developed bridging ligands with tethered thioether moieties that are capable of axial coordination. Incorporation of a tether increases the local concentration of the axial coordinating group and gives significantly more control over the coordination to the axial site. The ligand design was inspired by similar scaffolds reported by Bera[106] and Ball,[105] in which tethered axial coordination resulted in interesting results in α-diazocarbonyl mediated C–H insertion and cyclopropanation. The first Rh(II,II) complexes with tethered, axially coordinated ligands (TACLs) synthesized contained benzoate bridging ligands that are tethered to a thioether LB (Figure 2.1a) The linker between the two ligands contained a gem-dimethyl group that uses the Thorpe-Ingold effect to reduce the flexibility of the linker and improve the chelate effect, leading to a stronger association to the axial site.[110] The second series of complexes developed have cyclic oxazolidinones at the bridging site that results in less electrophilic complexes due to donation from the nitrogen atom (Figure 2.1, b). These oxazolidinone complexes were theorized to be more electrophilic than pyrrolidinone based complexes due to the inductive effects invoked by the oxygen on ring. Our group initially considered using nitrogenous LBs at the axial site, however, it is known that they bind strongly to the axial site[133] and have reduced reactivity in some cases.[129] Weaker donors such as carbonyls, have been used as additives with little to no loss of reactivity and sometimes show improvements in stereoselectivity.[134] As a result, thioethers were chosen to be the axial moiety for our tethered complexes. Thioethers have been known to coordinate well to Rh(II,II) paddlewheels[135] and although they are not as modular as phosphines, the stereoelectronics of thioethers are fairly tunable.

Initial reports of our bespoke Rh(II,II) complexes proved that they were proficient in cyclopropanation[110] and Si–H insertion reactions[136] with donor/ acceptor carbenes (Figure 2.2, a and b respectively). Most importantly, we demonstrated that dimerization could be minimized by incorporating tethered, axially coordinated thioether groups. In the examples where cyclopropanation was concerned, excess substrate was required for

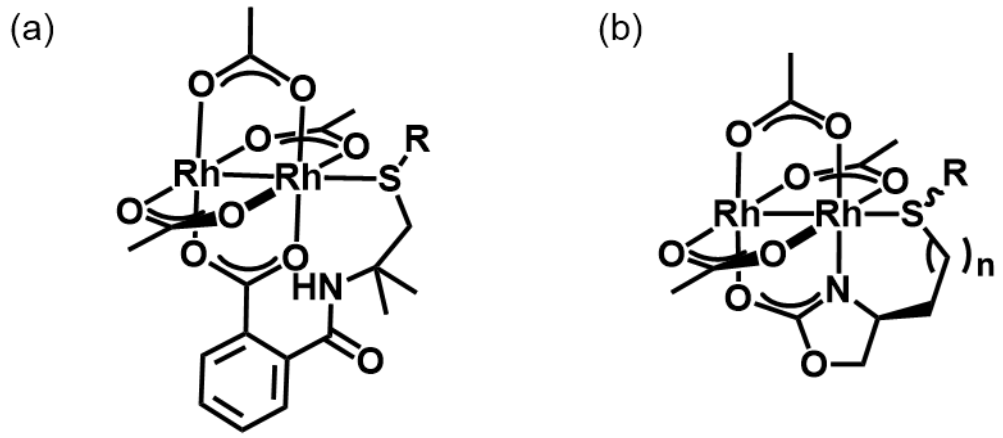


Figure 2.1 Rh(II,II)-TACLs complexes with thioether axial ligands and a)benzoate or b) oxazolidinone bridging ligands

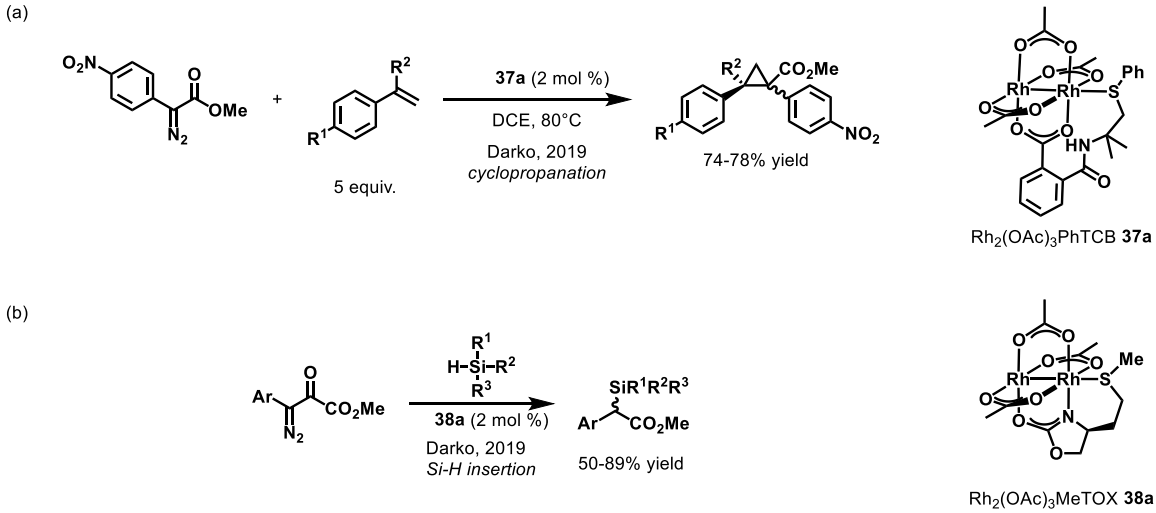


Figure 2.2 Application of Rh(II,II)-TACLs on diazo-mediated a) cyclopropanation and b) Si–H insertion reactions

adequate yields. Charette and co-workers were able to obtain good yields with 2 equivalents of alkene using conventional Rh(II,II) complexes in a biphasic system[137] but reports of good yields using equimolar alkene to diazo in Rh(II,II)-mediated intermolecular cyclopropanation reactions remain scarce.[26] To address this gap, we sought to fine-tune catalyst performance by varying tether lengths and thioether substituents on our oxazolidinone-based scaffold. Herein, we report the microwave-assisted synthesis of heteroleptic Rh(II,II) complexes comprised of oxazolidinone bridging ligands equipped with tethered thioether groups of varying tether lengths and substituents. The complexes were utilized to maximize yields in the cyclopropanation of alkenes with EDA. Further analysis of the complexes by UV-Vis, cyclic voltammetry, and computational chemistry was conducted to explain the observed reactivity.

2.4 Results and Discussion

2.4.1 Ligand Synthesis

As this study necessitated the use of our thiocarbamoylbenzoate (TCB) complexes, the synthesis of their ligands was required (Figure 2.3). Ligand **39** and its precursors were synthesized and characterized according to established procedures previously reported by our group (Figure 2.3a).[110] The methyl variant, **41**,was synthesized using some of the procedures used for **39** (Figure 2.3b). Thioetherification of 2-ammonio-2-methylpropyl sulfate in NaOH/H_2O resulted in formation of a methyl aminothioether **41**.[138] This is then followed by ring opening of phthalic anhydride with the aminothioether to arrive at the final **42** ligand.[110]

The thiooxazolidinone (TOX) ligands made for this study were primarily synthesized by Dr. Derek Cressy and William Sheffield (Figure 2.3c). These oxazolidinone ligands are derivatives of aspartic acid and contain two methylene unit linkers between the bridging and axial sites. The MeTOX ligand, **40**, and precursors were synthesized according to procedures outlined in our previous work.[110] Other thioether variants derived from aspartic acid were explored to study the effect modifications at the axial ligand have on catalysis. Compound **44** was made by esterification and subsequent carbamate formation from **43**. This was then reduced to a diol, **45**, which is cyclized to form an oxazolidinone, **46**. The oxazolidinone is tosylated to **47** and finally a nucleophilic substitution with a substituted thioether furnishes the final thiooxazolidinone, **48-49**.

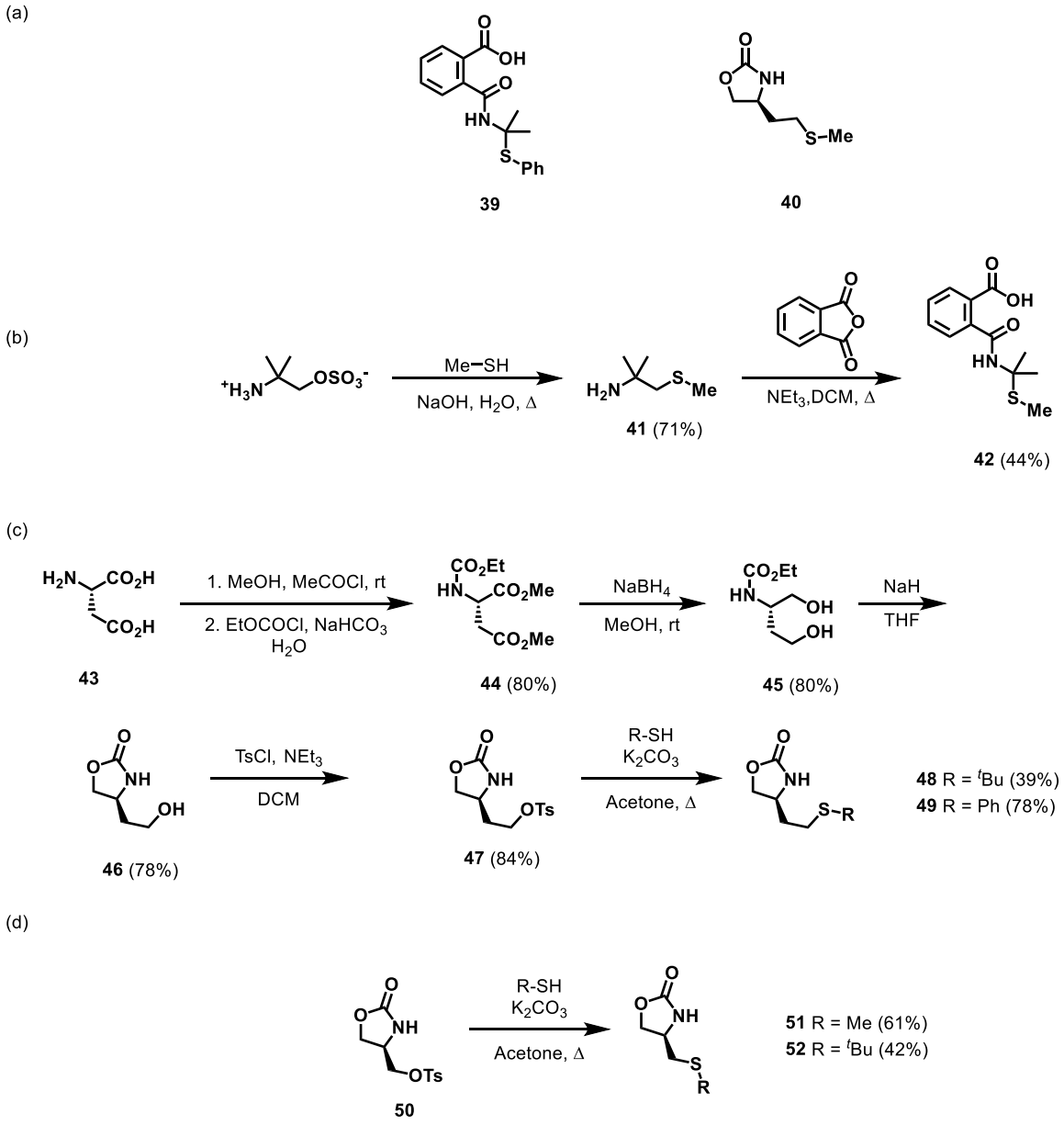


Figure 2.3 a) TCB and TOX ligands previously reported by our group b) synthesis of the methyl variant of **39** c) synthetic pathway for the synthesis of the aspartic acid-derived oxazolidinone series of ligands and d) the synthetic pathway for the synthesis of the serine-derived oxazolidinone ligands

Synthesis of the serine-derived ligands that contain just one methylene unit was similar to the aspartic acid derivatives with both methyl **51** and ^{t}butyl **52** thioethers made (Figure 2.3d).

2.4.2 Catalyst Synthesis

A challenge for the study of our axially coordinated catalysts is the need to synthesize heteroleptic complexes. Traditionally, homoleptic complexes are obtained through sequential substitution of the acetate bridging ligands of dirhodium acetate with the desired ligand.[13] Full ligand substitution is driven by the removal of displaced acetate through trapping methods. When using this strategy to produce heteroleptic complexes, results are hampered by a complex statistical mixture of products.[91, 96] Alternatively, one can start with a Rh(II,II) precursor with bridging ligands of varying aptitude for dissociation.[88, 139] Corey used this method to synthesize heteroleptic imidazolidinate complexes, however, the number of isomers was further complicated by the orientation of the N and O atoms around each Rh atom.[88, 90] We observed that the incorporation of the thioethers on our ligand scaffold significantly reduced the number of products in heteroleptic complex synthesis.[110] Each ligand substitution either slowed or blocked further ligand substitution such that only products from mono- and bis-tethered adducts were produced.

The synthesis of $Rh_2(OAc)_3$PhTCB **37a** and $Rh_2(OAc)_2(PhTCB)_2$ **37b/c** has been documented in our previous work and involves refluxing the PhTCB ligand and $Rh_2(OAc)_4$ in DCE with N,N-diisopropylethylamine (Hünig's base) (Figure 2.4a, R = Ph).[110] $Rh_2(OAc)_3$MeTCB **53a** and $Rh_2(OAc)_2(MeTCB)_2$ **53b/c** were obtained using the same procedure for the PhTCB (Figure 2.4a, R = Me). The sulfoxide version of the PhTCB complex, $Rh_2(OAc)_3$PhOTCB **54**, was previously synthesized by undergraduate student Kimberly Hollister and used as is (Figure 2.4b).[140] Both the methyl and phenyl TCB ligands gave moderate yields of the mono and bis-substituted products in just three hours. However, reaction times were a bit sluggish in the case of the oxazolidinate scaffold, so we turned to microwave synthesis to accelerate the process.

Microwave conditions have previously been implemented for expediting the synthesis of homoleptic Rh(II,II) paddlewheel complexes,[141, 142] and we were attracted to the microwave synthesis of each complex, even in small amounts, to facilitate rapid

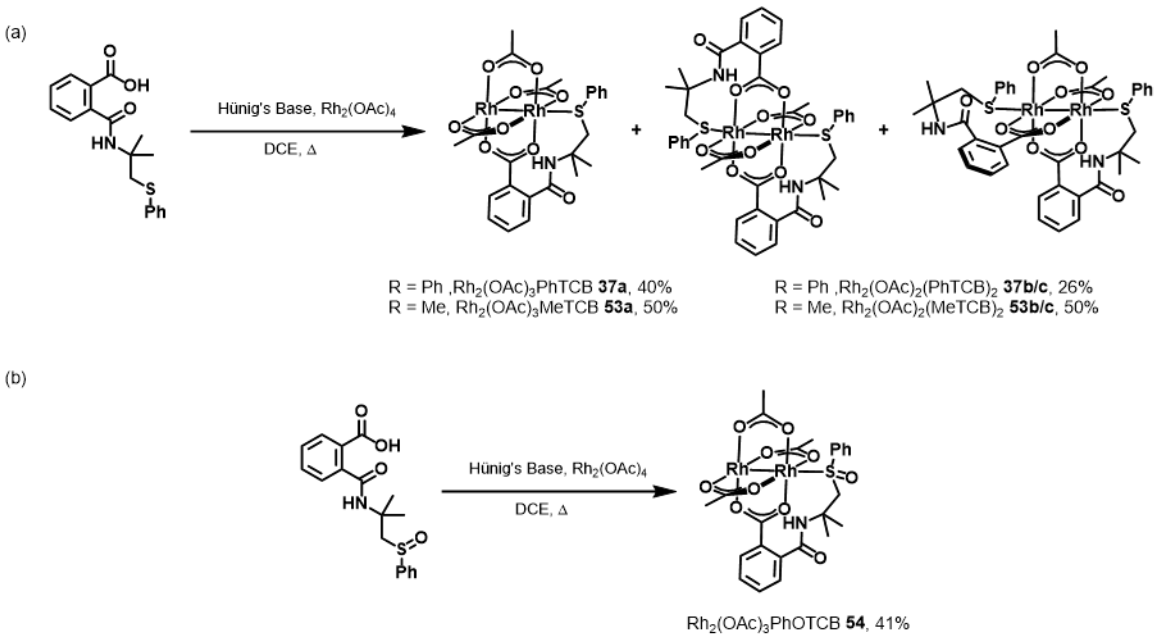
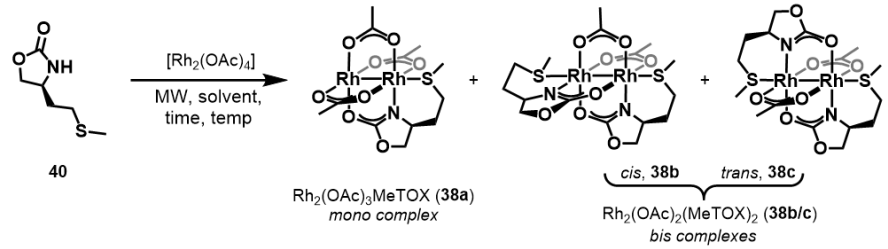


Figure 2.4 Synthesis of Rh(II,II)-TACLs complexes with a) TCB ligands and b) an oxidized TCB ligand

access to a range of catalysts for reaction studies. The synthesis of catalyst **38a**[110] and **38b/c** from ligand **40** and rhodium acetate was used for initial optimization studies. Product formation was initially observed in low yields at 160 °C (Table 2.1, entry 2). Prolonged time at 160 °C did not dramatically improve yields (Table 2.1, entries 3 and 4). Increased temperatures led to an increase in complexes **38a** and **38b/c** with preferred formation of **38** (Table 2.1, entry 5). A series of solvents with varied coordinating ability were then screened (Table 2.1, entries 5–9). Ethanol gave a high percent conversion (Table 2.1, entry 7) but provided low yields of **38a** and **38b/c** along with the presence of a grey solid. It has been reported that ethanol facilitates the reduction of Rh(II,II) to Rh(0), which would explain the grey solid residue in the reaction vessel.[35] As observed with other ligand exchange conditions, the weakly coordinating solvents DCE and chlorobenzene (PhCl) produced the highest yields (Table 2.1, entries 5 and 9). Although they gave similar yields, DCE was used in further reactions due to its convenience in reaction workup. A further increase in temperature to 190 °C afforded the optimal conversion and product yield while producing the desired mono-complex **38a** preferentially to the bis-complexes **38b** and **38c** (Table 2.1, entry 10). Continuing to increase the temperature did not significantly improve yields (Table 2.1, entry 11).

Ligand exchange reactions with the other TOX ligands using the optimized microwave conditions furnished complexes **55-57** (Figure 2.5). The mono-substituted complexes formed preferentially in all cases, but the ratio of mono-to-bis increased according to donating strength of the thioether substituent. More specifically, the stronger donating *t*-butyl group in ligand **48** furnished a 3:1 ratio of complexes **55a** to **55b/c** compared with 1.3:1 for **56a** to **56b/c** in which the sulfur substituent was phenyl. Higher overall yields were obtained when the tether length was one methylene unit compared to two methylene units, as evidenced by comparing yields of complexes from ligand **51** to those from ligand **40** It is worthy to note that while ligands with pendant thioethers proceeded readily with one equivalent of the ligand under microwave conditions, synthesis of mixed ligand oxazolidinate/carboxylate complexes without axial coordination required excess ligand to drive the reaction forward,[88, 136] suggesting that the tethered thioether facilitates ligand exchange.

Table 2.1 Optimization of microwave synthesis parameters for Rh(II,II)-TACLs complex synthesis



entry	Solvent	Time (min)	Temp (°C)	Yield **38a** (%)	Yield **38b/c** (%)	Conv. (%)
1	DCE	10	140	1	0	3
2	DCE	10	160	6	1	7
3	DCE	20	160	13	3	18
4	DCE	30	160	17	5	23
5	DCE	10	180	22	7	46
6	THF	10	180	4	2	9
7	EtOH	10	180	14	7	79
8	MeCN	10	180	18	5	29
9	PhCl	10	180	21	5	27
10	DCE	10	190	33	16	52
11	DCE	10	190	33	17	53

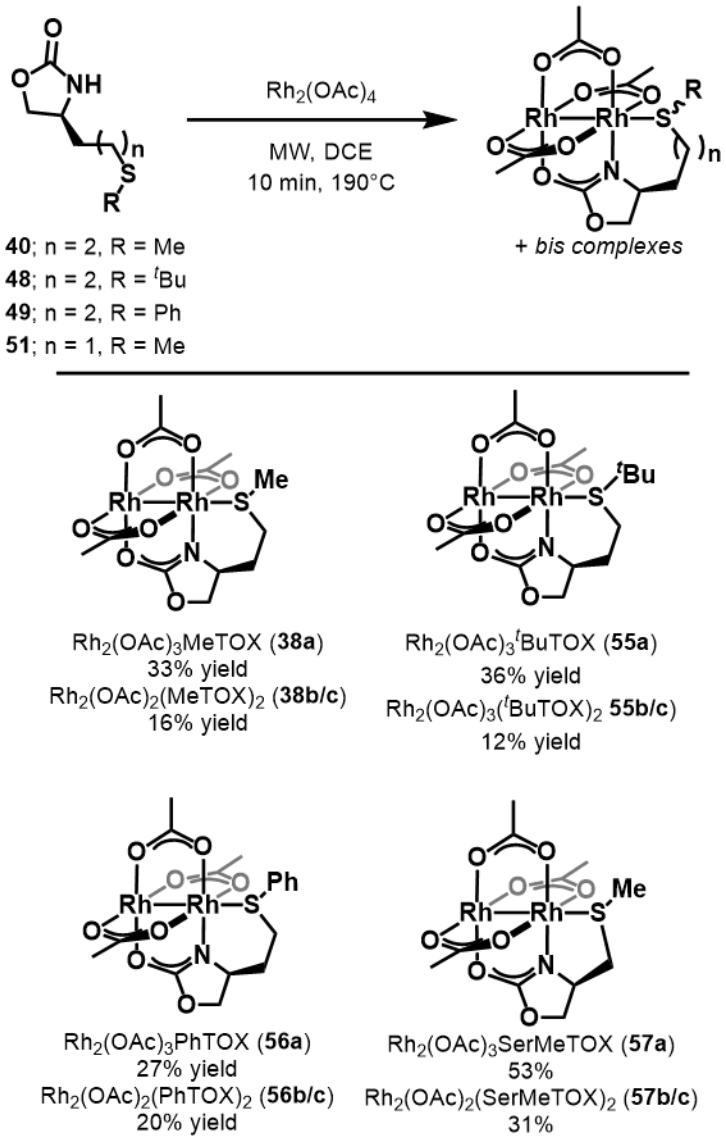


Figure 2.5 Rh(II,II)-TACLs with TOX ligands synthesized via microwave method

2.4.3 Characterization of Rh(II,II) TACLs

2.4.3.1 X-ray Structures

We have previously reported the X-ray structure for complex **38a**[110] and we were able to obtain suitable crystals for X-ray analysis for complex **56a** *via* slow evaporation of a 1:1 mixture of acetonitrile and toluene (Figure 2.6). Despite our efforts, we were unable to obtain X-ray quality crystals of the other new complexes. Unlike complex **38a**, $Rh_2(OAc)_3$PhTOX (**56a**) does not form an oligomeric chain in the solid state. Instead, the asymmetric unit is comprised of four distinct paddlewheel units in which the second axial site is occupied by acetonitrile (Figure 2.7). A stereogenic center is created at the sulfur atom upon coordination to the Rh centre.[143-146] As a result, a mixture of diastereomers is present, (S_C, R_S) and (S_C, S_S), due to the sulfur stereogenic center and the *S* configuration at the asymmetric carbon on the bridging oxazolidinate (Figure 2.6). Of the four paddlewheel units, two are (S_C, R_S) and two structures are (S_C, S_S), with minor structural variations between them. Representatives of each pair are shown in Figure 2.6. The Rh–Rh bond distances for each paddlewheel unit does not vary (average of 2.4217(5) Å) and is within the general range for Rh–Rh bonds in paddlewheel complexes, which are typically between 2.35–2.45 Å.[32] The Rh–S bond distances of complex **56a** range between 2.4730(12)–2.5195(12) Å. The observation that the Rh–S bonds are not constant suggests that the phenyl thioether axial ligand is in a fluxional state and is a weaker donor than the methyl sulfide in **38a**, in which the intramolecular Rh–S bond is 2.48 Å.[110] The Rh–N2 bond distance varies little and averages 2.236(4) Å between the paddlewheel structures, but pairs of the structures have differences in Rh–Rh–N angles. The (S_C, R_S) pair has slightly bent Rh–Rh–N angles of 171°, while the (S_C, S_S) pair has almost linear Rh–Rh–N angles of 175°. The variations are most likely a consequence of packing effects, but they give insight into the structural flexibility of the complex.

2.4.3.2 UV-Vis Spectroscopy

In general, axially coordinated molecules bind to the σ* orbital of the Rh–Rh center, which perturbs the π* to σ* HOMO–LUMO gap. This is manifested by shifts in the visible region of their UV-vis spectrum.[31] Figure 2.8 shows the overlaid UV-vis spectra of the mono-complexes **38a**, **55a**, **56a**, and **57a**. The colors of the mono-complexes are shades of violet and the local maxima of their bands in the visible region are clustered between 572 nm to 582 nm. The similarity between them suggests that varying the tether length

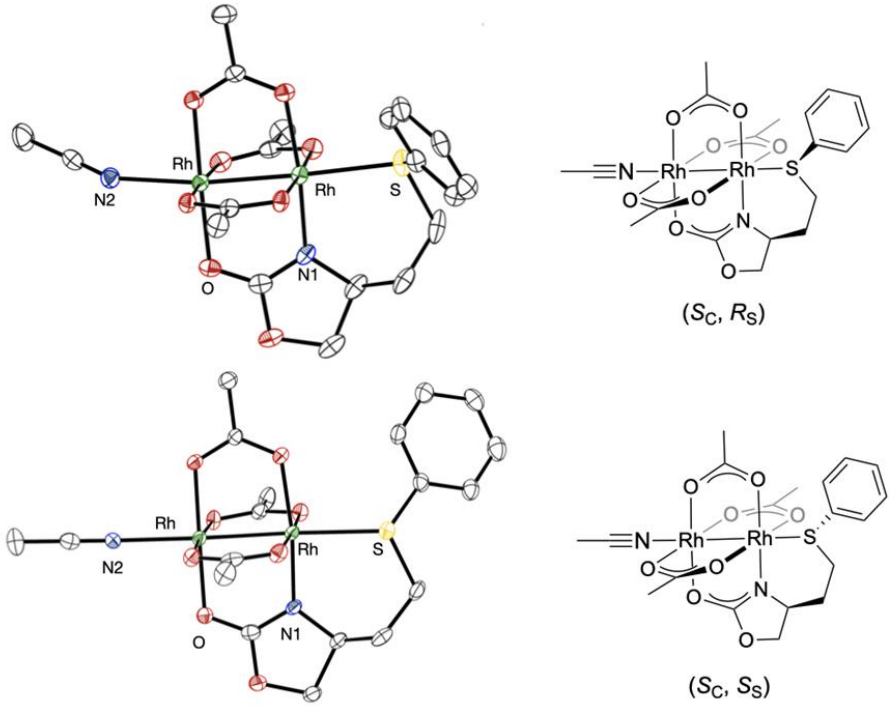


Figure 2.6 X-Ray structure of complex **56a** with thermal ellipsoids at 50% probability. Only two of the four molecules in the asymmetric unit are shown. Selected bond lengths and angles as an average of the four structures of the asymmetric unit: Rh–Rh 2.42 Å, Rh–S 2.50 Å, Rh–N2 2.24 Å, Rh–Rh–S 175.5°.

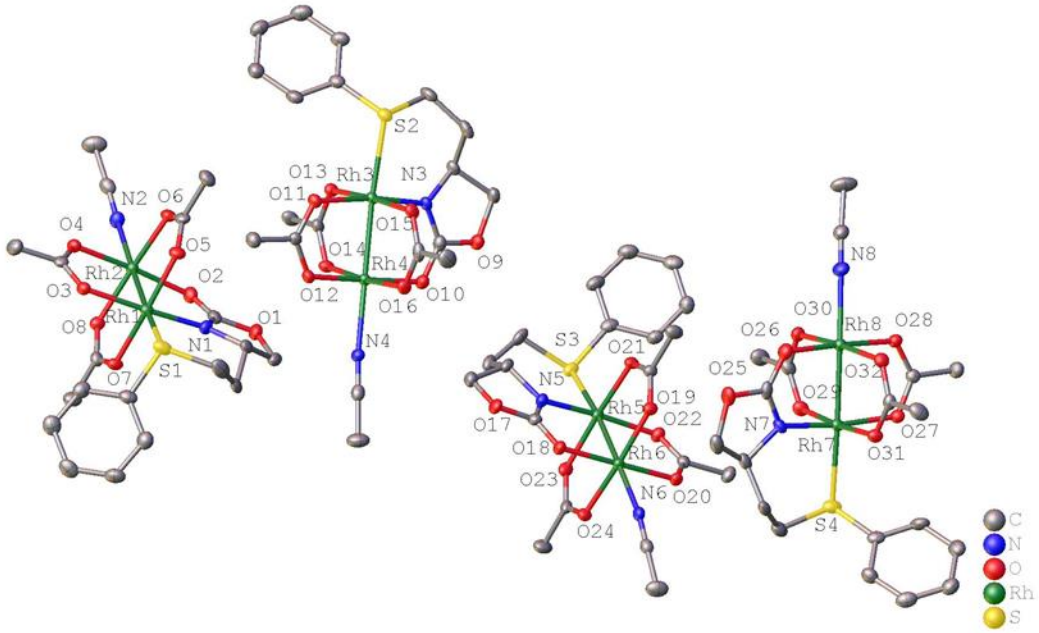


Figure 2.7 Asymmetric unit of $Rh_2(OAc)_3PhTOX{\cdot}CH_3CN$ (**36**·CH3CN) with ellipsoids shown at 50% probability level and protons omitted for clarity

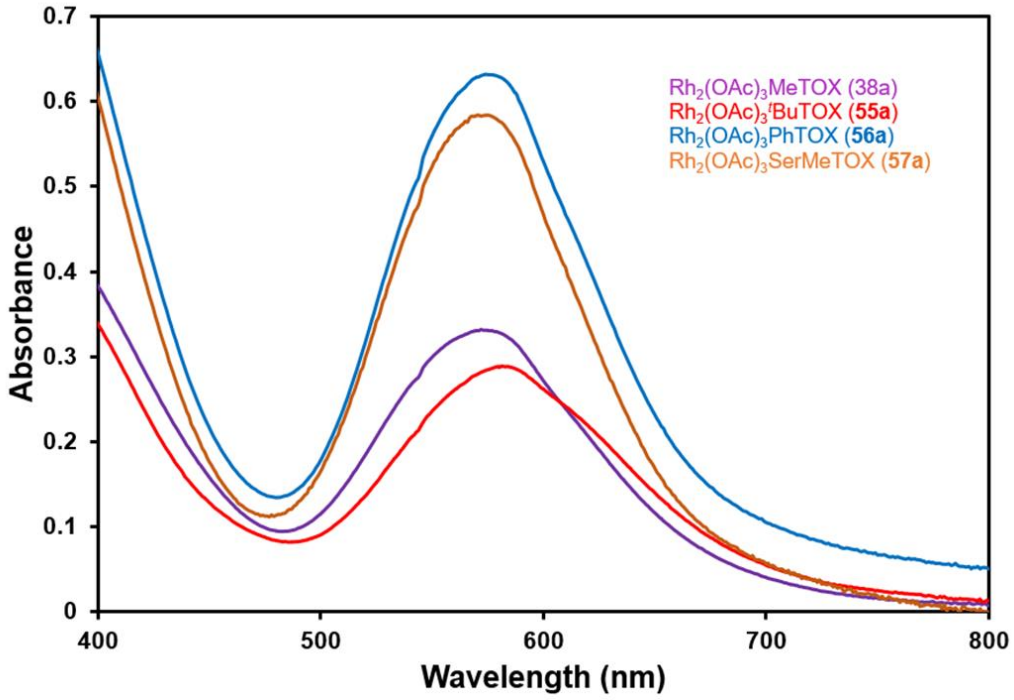


Figure 2.8 UV-Vis spectrum of complexes **38a**, **55a**. **56a**, and **57a**.

(between 1 or 2 methylene units) or varying the thioether substituent (Me, ^{t}Bu, or Ph) does not significantly alter the HOMO–LUMO energy gap of the complex (Figure 2.8).

2.4.3.3 Cyclic Voltammetry

Cyclic voltammetry experiments were performed to probe the effect of the tethered thioether ligands on the electronics at the Rh metal centers. Early studies demonstrated that the variance of the $Rh_2^{4+/5+}$ oxidation potential could be used as a metric for the strength of axial coordination.[126] Our analysis was conducted in 0.1 M [TBA][PF_6] in dichloromethane. Figure 2.9 is a stack of the cyclic voltammograms of the Rh(II,II) complexes. Each of the complexes displayed a reversible, or quasi-reversible, oxidation event assigned to the $Rh_2^{4+/5+}$ couple. Oxidation potentials of the mono-complexes followed the trend that increased σ donating ability of the tethered thioether corresponded to a higher oxidation potential (Figure 2.9). This is contrary to previous studies in which the sequential addition of exogenous axial ligands resulted in a lower oxidation potential.[127] This increased oxidation potential, though unexpected, is not unprecedented. We have shown this trend to be the case with respect to $Rh_2(OAc)_3$PhTCB **37** complexes which also contains a tethered thioether and showed a $Rh_2^{4+/5+}$ $E_{1/2}$ value 36 mV higher than $Rh_2(OAc)_3$OBz **59** (OBz = benzoate).[110] It is worth noting that the same trend was not observed when the CV experiments of complexes **38a**, **55a**, **56a**, and **57a** were conducted in MeCN confirming that the electrochemical study of the complexes is sensitive to coordinating solvents.

2.4.4 Cyclopropanation of Ethyl Diazoacetate

We initially explored the reactivity of the various rhodium catalysts in the cyclopropanation of styrene with ethyl diazoacetate (EDA) using optimal conditions from our previous studies.[110] We anticipated that performing the reactions with excess styrene would likely result in high yields of the cyclopropane product for most of the catalysts. Therefore, to better distinguish the performance of reaction conditions, reactions were conducted with equimolar amounts of styrene to EDA. In this way, selectivity between carbene dimerization and cyclopropanation could be evaluated. Initial optimization of reaction conditions with **37a** showed that cyclopropane yields are improved when the reaction is run at a higher concentration (Table 2.2, entries 1-2). Like our previous cyclopropanation work, DCE was found to be an adequate solvent while other chlorinated solvents gave subpar yields (Table 2.2, entries 3-4). A higher dielectric constant also

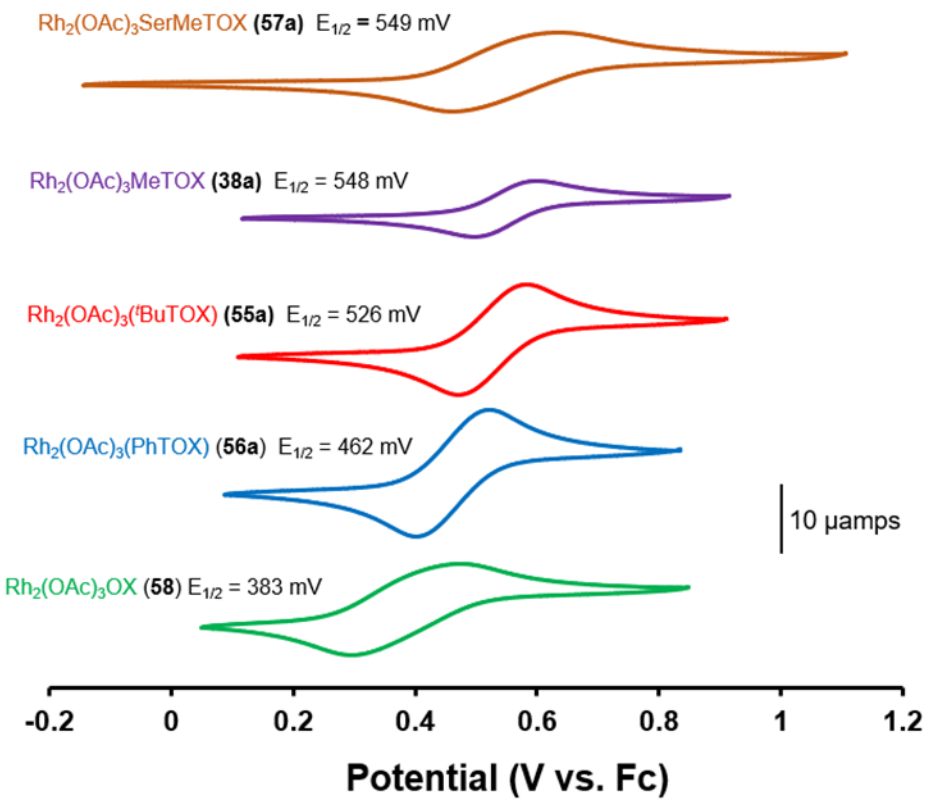
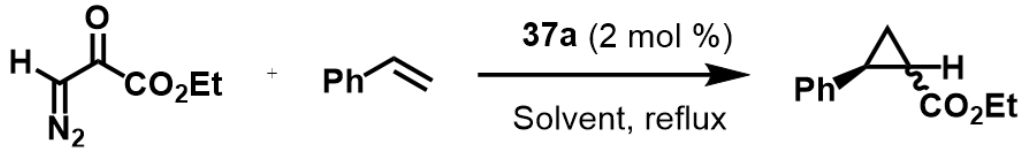


Figure 2.9 Cyclic voltammograms of complexes **38a**, **55a**, **56a**, **57a**, and $Rh_2(OAc)_3OX$. Electrolyte comprised of 0.1 M [TBA][PF_6] in DCM (scan rate of 100 mV s^{-1}).

Table 2.2 Optimization of reaction conditions in the cyclopropanation of styrene and EDA using **37a**



1 equiv., 0.1M 1mL/hr 1 equiv.

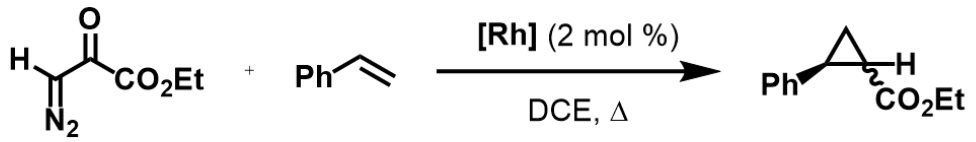
entry	Solvent	Total Volume (mL)	Additive	Yield (%)
1	DCE	7.7	-	51
2	DCE	2.2	-	54
3	DCM	2.2	-	43
4	PhCl	2.2	-	16
5	Acetone	2.2	-	10
6	DCE	2.2	Indole	21
7	DCE	2.2	Imidazole	Trace

seems to be detrimental to the reaction (Table 2.2, entry 5). The introduction of coordinating additives to the reaction solution either hindered the catalysis (Table 2.2, entry 6) or completely shut down the reaction all together (Table 2.2, entry 7). Strong binding of nitrogen to the axial site and formation of N-H insertion products are the most likely reasons for these results.

Once the reaction conditions were optimized, the next step was a catalyst screen to determine the optimal catalyst for the reaction. Reactions remained at equimolar amounts of styrene to EDA to better analyze differences with each catalyst. Both the methyl and phenyl TCB complexes gave moderate yields at 60% and 54% respectively (Table 2.3, entries 1-2). Oxidation of the thioether seemed to decrease its performance in the reaction (Table 2.3, entry 3). Similar to the cyclopropanation of donor/acceptor diazos[110], the tethered TCB complexes outperform both the benchmark rhodium acetate and heteroleptic, untethered control complex $Rh_2(OAc)_3OBz$ **59** (Table 2.3, entries 4-5).

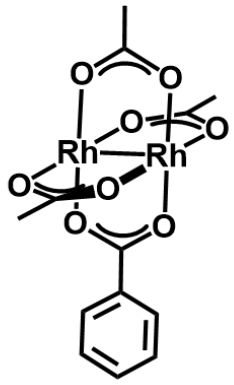
In contrast to previous work in our group demonstrating low reactivity for catalyst **38a** with donor/acceptor diazo compounds in the cyclopropanation of styrene,[110] it was a very competent catalyst when EDA was used, providing 63% yield of the cyclopropane and trace yields of dimer products (Table 2.4, entry 1). The length of the tether only had a minor influence on the yield of the cyclopropane, but the change resulted in increased dimer formation (Table 2.4, compare entries 1 and 2). The thioether substituent had a more pronounced effect on cyclopropane yield. Complex **56a** with a phenyl substituent on the thioether, provided the highest cyclopropane yield of the series (71%, Table 2.4, entry 3), while the complexes with alkyl substituents on the thioether (complexes **38a**, **55a**, and **57a**) gave essentially comparable yields (Table 2.4, entries 1–4). Except for complex **57a**, the mono-substituted tethered complexes had only trace amounts of dimer products. All of the tethered complexes outperformed rhodium acetate in cyclopropane yield (Table 2.4, entry 5). Compound **58** was also tested to eliminate the possibility that the bridging oxazolidinate ligand was responsible for the yield increases. However, **58** also obtained the cyclopropane in a lower yield compared to the tethered complexes, further implicating the tethered thioether as the reason for increased yields (Table 2.4, entry 6). As observed in our previous work, the mixed bis-substituted complexes **38b/c** exhibited greatly diminished catalytic activity (Table 2.4, entry 7).[110, 136] In this reaction, some carbene dimerization was observed along with a high percentage of unreacted EDA. The dual

Table 2.3 Initial screening of Rh(II,II)-TACLS catalysts for the cyclopropanation of styrene with EDA



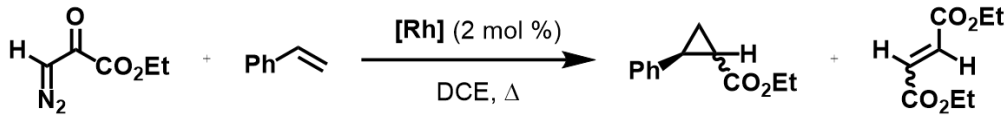
1 equiv., 0.1M 1mL/hr 1 equiv.

entry	Catalyst	Yield (%)
1	$Rh_2(OAc)_3$MeTCB **53a**	60
2	$Rh_2(OAc)_3$PhTCB **37a**	54
3	$Rh_2(OAc)_3$PhOTCB **54**	40
4	$Rh_2(OAc)_4$	33
5	$Rh_2(OAc)_3$OBz **59**	37



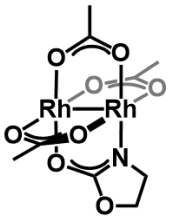
$Rh_2(OAc)_3$OBz **59**

Table 2.4 Screening of Rh(II,II) TOX catalysts in the cyclopropanation of styrene with EDA



1 equiv., 0.1M 1mL/hr 1 equiv.

entry	Catalyst	Catalyst Loading (mol %)	Yield (%)	Yield Dimer
1	$Rh_2(OAc)_3$MeTOX **38a**	2	63	<1
2	$Rh_2(OAc)_3$SerMeTOX **57a**	2	59	8
3	$Rh_2(OAc)_3$PhTOX **56a**	2	71	<1
4	$Rh_2(OAc)_3$^{t}BuTOX **55a**	2	57	<1
5	$Rh_2(OAc)_4$	2	33	3
6	$Rh_2(OAc)_3$OX **58**	2	38	3
7	$Rh_2(OAc)_2(MeTOX)_2$ **38b/c**	2	19	8
8	$Rh_2(OAc)_3$PhTOX **56a**	1	62	1
9	$Rh_2(OAc)_3$OX **58**	1	36	11
10	$Rh_2(OAc)_3$PhTOX **56a**	0.1	53	3
11	$Rh_2(OAc)_3$OX **58**	0.1	30	17



$Rh_2(OAc)_3$OX **58**

tether of the bis-substituted complex likely blocks both axial sites, requiring displacement before catalysis is possible and thereby reducing reaction yield. Dimerization yields were more of an issue for non-tethered complexes when catalyst loading was reduced, but the side product was kept minimal when complex **56a** was used, although a drop in cyclopropanation yield was observed (Table 2.4, entries 8–11). At 0.1 mol% of catalyst, complex **56a** provided a 53% yield with 3% of the dimer products, while **58** gave a 30% yield of cyclopropane and 17% yield of dimer products (Table 2.4, entry 10 and 11). This result is evidence that the thioether tether may assist with catalyst turnover, an issue that is present when ethyl diazoacetate is used as the diazo precursor.[147]

A substrate scope was conducted for the cyclopropanation reaction using 2 mol% of complex **56a** (Figure 2.10). Styrene derivatives **60-70** generally maintained good yields at 1 equivalent of olefin and high yields of cyclopropane when 5 equivalents were used. 4-*t*-Butylstyrene provided similar yields of product **62** compared to styrene, while 4-chlorostyrene gave a slightly lower yield of compound **61**. This is consistent with inductive withdrawing effects of the Cl resulting in a less nucleophilic olefin. Introduction of steric hindrance via disubstituted olefins also resulted in good to excellent yields, albeit slightly lower than monosubstituted olefins (**63** and **64**, Figure 2.10). Non-styrene derivatives were also tested. Most of the non-aryl olefins tested gave either trace amounts or no cyclopropane products (Figure 2.10, **65**-**68**). Non-styrene derivatives **69** and **70** performed well in the reaction when 5 equivalents of olefin were used. Using 5 equivalents of the electron-rich ethyl vinyl ether afforded quantitative amounts of cyclopropane **69**, but only 31% yield at 1 equivalent. We hypothesized that volatility of the vinyl ether was partly to blame for the low yield. Performing the experiment at room temperature slightly increased the yield to a 43% yield of **69**. The synthetically challenging norbornene afforded moderate yields of its respective cyclopropane (compound **70**) at 5 equivalents, but low yield at 1 equivalent. In all cases, the diastereomeric ratio of the cyclopropanes did not differ markedly from that observed in the literature.[5] This was anticipated as EDA generally gives low diastereoselectivities in Rh(II,II)-carbene cyclopropanation reactions (Figure 2.10).[9, 148-150]

2.4.5 Computational Analysis

DFT calculations were employed as a means of further understanding the electronic structure of the complexes. Theoretical calculations of the precursor complexes,

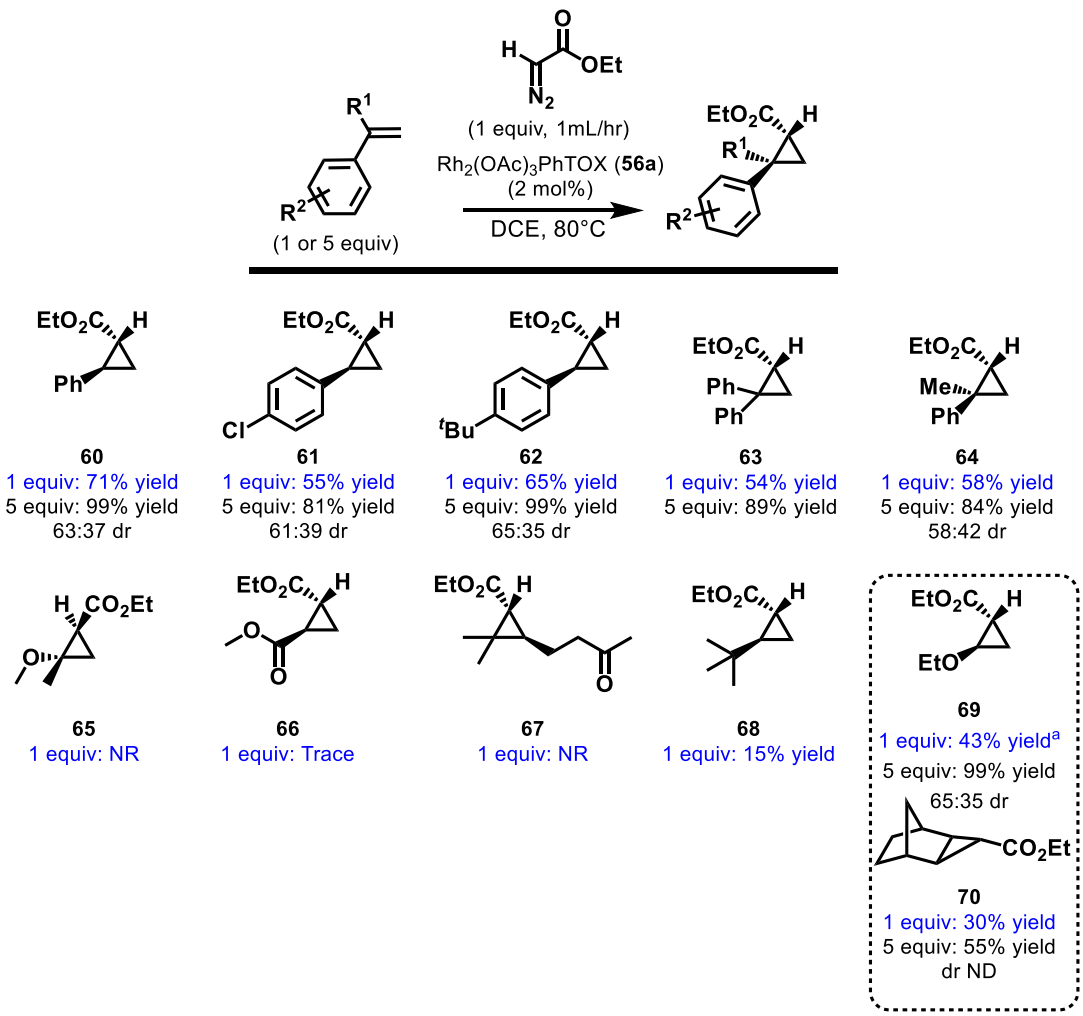


Figure 2.10 $Rh_2(OAc)_3$PhTOX (**56a**)-catalyzed cyclopropanation of EDA. All yields calculated by ^{1}H NMR except compounds **60** and **69**

as well as their carbene complexes with EDA, were calculated at the MO6-2X/def2-TZVPP level of theory. According to Berry's three center/four electron (3c/4e) bonding model, the addition of axial ligands has the most impact in the energy of the Rh–Rh σ* orbital, which is the LUMO of the complex.[31] The out of phase combination of the axial ligand's lone pair σ orbitals interact with the Rh–Rh σ* orbital and raise the energy of the Rh–Rh σ* LUMO. When comparing complex **56a** to **58**, the most dramatic change was in the destabilization of the Rh–Rh σ* LUMO due to their interaction with the thioether lone pairs (Figure 2.11). The extent of destabilization is greater with **38a**[136] than **56a**, hence, stronger axial interactions lead to greater destabilization, which is in agreement with the 3c/4e model.[31, 151] The effect of the axial ligands also raises the energy of the Rh–Rh π* HOMO, but this energy destabilization is minor compared to that of the LUMO. The combined effects lead to larger HOMO–LUMO gaps for the complexes with tethered thioethers when compared to **58**.

Upon analysis of the LUMO of the carbene species, we found interesting differences in the electronic structure of the tethered complexes (Figure 2.12). The LUMO of Rh-carbene **71** comprises of an interaction of the p orbital of the carbene with a filled Rh–Rh π* orbital, which is normally the case with axially free rhodium complexes.[152] The extent of π backbonding decreases the electrophilicity of the carbene, but this interaction is polarized towards the Rh, leading to "super electrophilic" carbenes.[31, 153] In the case of the tethered thioether carbene complex **72**, the LUMO seems to include a mixed electronic environment at the Rh core—π symmetry at the Rh–C and σ symmetry at the Rh–S. Such mixing of σ and π components in metal–metal bonding has been reported for triruthenium extended metal-atom chains (EMACs) in which bending of the linear structure introduces mixing of σ and π orbitals in the Ru_3 core.[154] In our case, the calculated S–Rh–Rh (176°) and Rh–Rh–C (168°) angles in **72** deviate from linearity compared to **71** (Rh–Rh–C~177°) and this reduction in symmetry may be the driving force for the interaction of the σ and π orbitals. A result of this distortion is an increase in the energy of the LUMO orbital of **72** compared to **71**. Although this is not a dramatic increase in energy (0.316 eV or 7.29 kcal mol^{-1}), it opens the possibility of further perturbing the Rh(II,II)-carbene LUMO energy with distal axial coordination.

The more significant energy destabilization occurs in the HOMO of the carbene complexes with tethered thioether ligands. The HOMO of the carbene from tethered

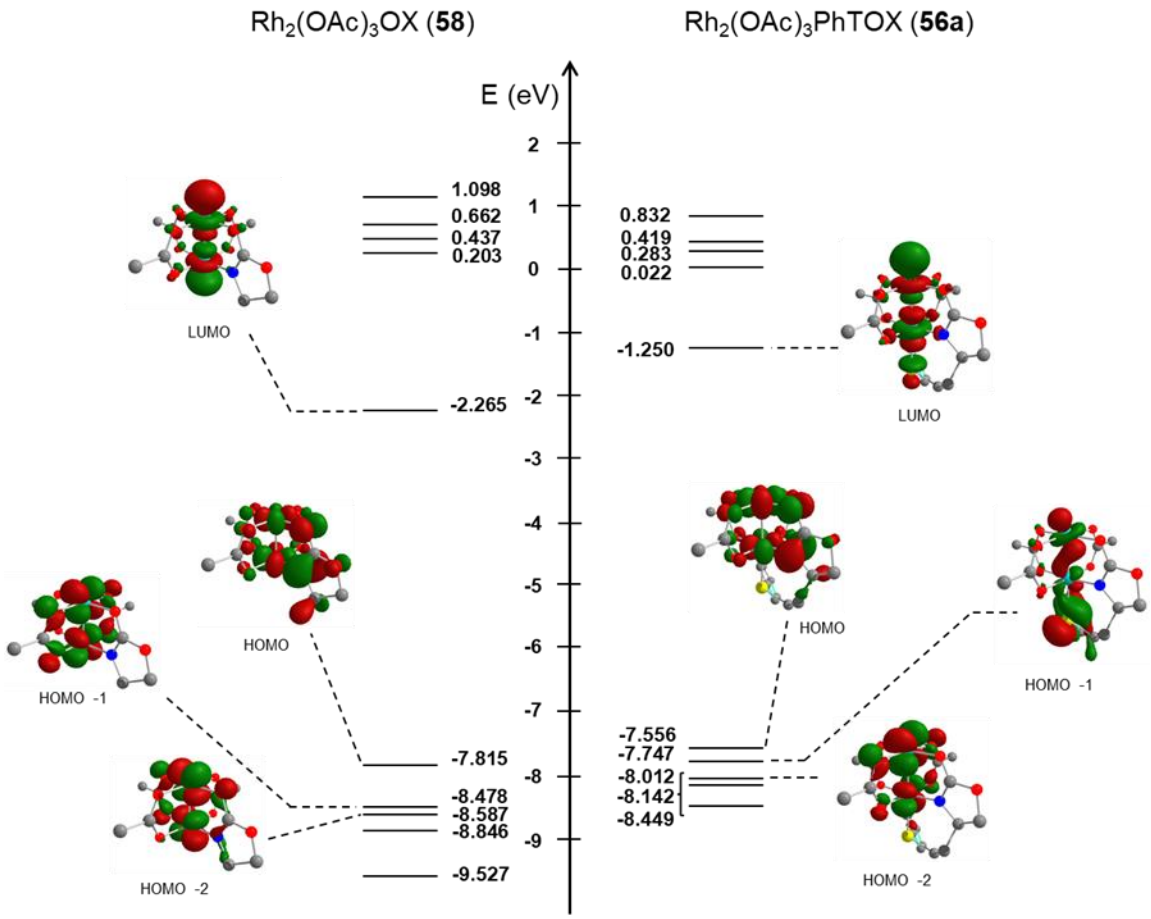


Figure 2.11 Molecular orbitals of complex **56** in comparison to **58** calculated at the MO6-2X/def2-TZVPP level of theory

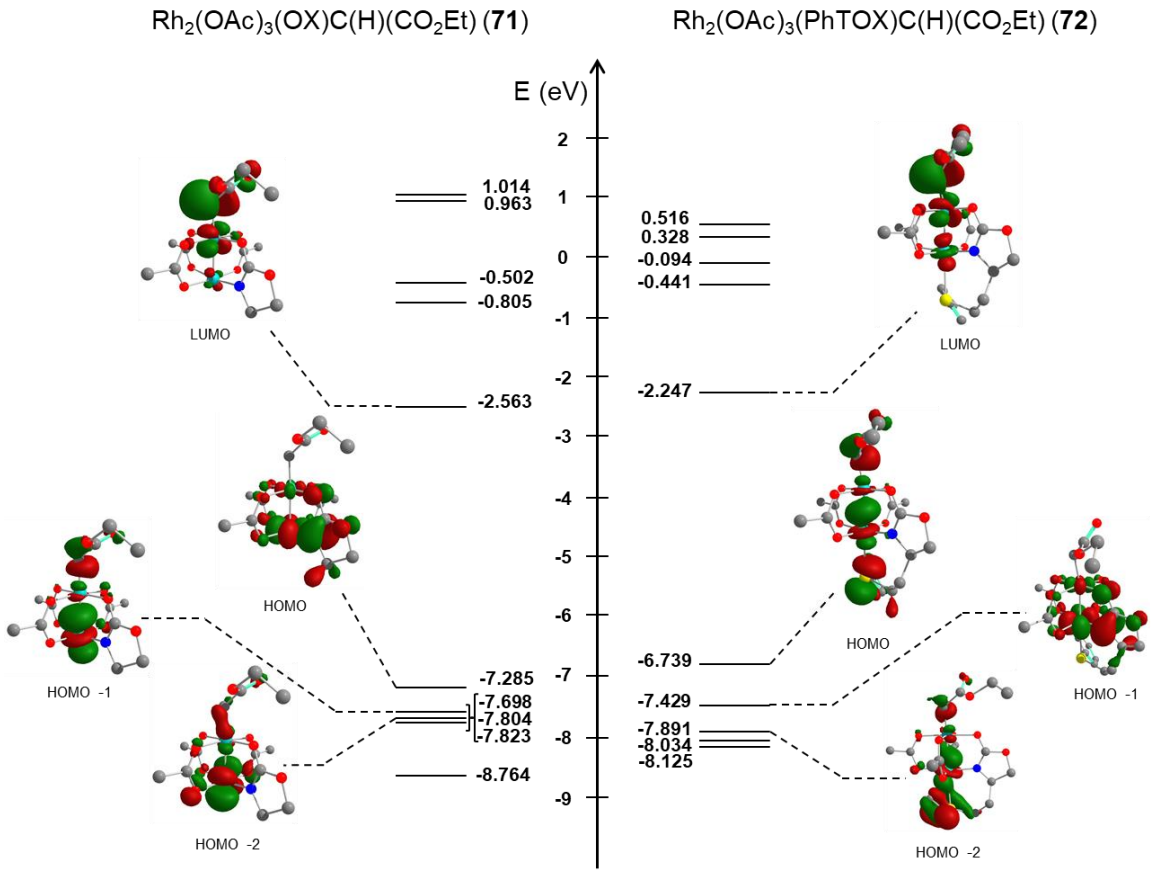


Figure 2.12 Calculated orbitals and energies of EDA carbenoid species **71** and **72.** Calculated at the MO6-2X/def2-TZVPP level of theory.

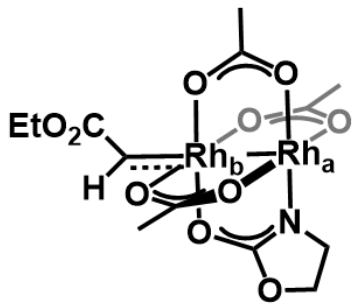
complex **72** is comprised of a Rh–Rh σ-bonding orbital with significant carbene character. Out-of-phase σ interactions characterize both the interaction of the tethered thioether and carbene with the Rh center. In contrast, in the untethered complex **71**, the HOMO is a Rh–Rh π* orbital with no carbene character. It is plausible that the difference in the HOMOs is an important factor in the enhanced reactivity of the complexes with tethered thioether ligands. A similar change in the electronic character of the HOMO was observed when carboxylate paddlewheel complexes with Rh–Rh and Rh–Bi metal centers were compared. Fürstner and co-workers observed extreme electrophilicity of Rh–Bi acceptor carbene complexes and implicated 3c/4e interactions in the σ framework as the major contributor.[153] Davies and co-workers also observed similar qualitative orbital topologies with Rh–Bi donor/acceptor carbene complexes and proposed that the HOMO of the Rh–Bi complex should result in a more nucleophilic carbenoid.[155] It is generally accepted that cyclopropanation occurs via a concerted, but asynchronous process that is initiated by nucleophilic attack on the carbene carbon by the olefin.[156] We speculate that since the HOMO of the tethered complexes partially lies on the carbene carbon, it could more readily facilitate the formation of the cyclopropane ring over other competing pathways.

Further support for σ interactions in the HOMO as a major factor is provided by the calculated bond distances for the carbene species, in which the tethered complex **72** possesses an elongated Rh–C bond in comparison to the untethered carbene complex **71** (Table 2.5). Natural population analysis of the carbene complexes shows increased electron density at the carbene carbon of **72** compared to **71** (0.095 vs. 0.174 respectively, Table 2.5), meaning that the tethered thioether can modulate the electron density at the distal carbene. This remote modulation of electron density could account for the reactivity and be a factor in reducing the barrier for the rate-limiting diazo extrusion step,[156, 157] thereby increasing catalyst turnover. Theoretical calculations are underway to better address the effects of tethered ligands on transition states and energy barriers in diazo-mediated transformations.

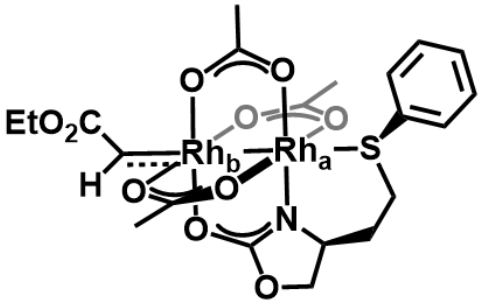
2.5 Conclusion

In conclusion, heteroleptic Rh(II,II) paddlewheel complexes containing axially coordinated thioether ligands were synthesized using base in reflux conditions and a microwave-assisted approach. We have demonstrated that catalyst synthesis and reactivity is influenced by the tether length and the substituent of the thioether. The

Table 2.5 Calculated geometric parameters and NBO analysis of **71** and **72**. Calculated at the MO6-2X/def2-TZVPP level of theory



71



72

Natural Population Analysis		
	71	72
Rh_a	0.523	0.407
Rh_b	0.625	0.592
$C_{carbene}$	0.174	0.095
S	-	0.394

Bond Distances (Å)		
Rha-Rhb	71	72
Rh_b-$C_{carbene}$	2.47	2.45
Rh_a-S	1.86	1.91
	-	2.76

tethered complexes achieved higher yields that their non-tethered counterparts in the cyclopropanation of styrene with ethyl diazoacetate, even demonstrating good yields with equimolar amounts of styrene substrate. Electronic studies and computational methods provided insight into the effect of the donating strength of the tethered ligands on the observed reactivity. The calculations were of relevance, revealing the importance of the effect of the tethered thioether on the HOMO of the Rh(II,II)-carbene complexes. Efforts to further understand the interplay between the donor of the tether and reactivity in Rh(II,II)-carbene mediated reactions are currently ongoing.

2.6 Experimental Procedures

2.6.1 General Considerations

Unless otherwise noted, all reagents were purchased and used as received from the manufacturer without further purification. 2-Ammonio-2-methylpropyl sulfate was synthesized from 2-amino-2-methylpropan-1-ol according to established procedures.[158] Ligand **39** was synthesized using established procedures previously reported in our group.[110] Ligands **40** and **51** were synthesized via established literature procedures.[159, 160] All products from previously reported procedures were verified, using ^{1}H NMR, against the values presented in the literature. Hexanes, THF, diethyl ether, DCM, and MeCN were dried with columns packed with alumnia using an Inert® PureSolv Micro Solvent Purification System and stored over molecular sieves. Reactions were monitored using TLC on Sorbent Technologies Silica XG TLC Plates. Column chromatography was performed using 60 Å, 40-63 μm silica from Sorbent Technologies. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury Vx 300 MHz or Varian VNMRS 500MHz spectrometers. All NMR chemical shifts are reported in ppm on the δ scale. Signals were referenced by residual solvent signal for ^{1}H NMR ($CHCl_3$ = 7.26 ppm, acetone = 2.05 ppm, acetonitrile = 1.94 ppm) and ^{13}C NMR ($CHCl_3$ = 77.16 ppm, acetone = 206.26 ppm, acetonitrile = 1.32 ppm). GC analysis was conducted using a Shimadzu GC-2010 instrument. HPLC analysis was performed on a Shimadzu LC-2030 Prominence-I instrument using a C18 column. Cyclic voltammetry experiments were performed inside an N_2-filled electrochemical cell in MeCN with 0.1 M [TBA][PF_6] as the supporting electrolyte. Anhydrous MeCN and electrochemical grade [TBA][PF_6] were purchased from Sigma-Aldrich and used as received. The voltammograms were recorded with a BASi Epsilon potentiostat, using a 2.5 mm (o.d.) 1.0 mm (i.d.) Pt-disk working electrode, Ag-

wire quasi-reference electrode, and a Pt wire auxiliary electrode. Reported potentials are referenced to the Fc/Fc^+ redox couple, added as an internal standard at the conclusion of each experiment. The mass spectra for the ligands and their precursors were obtained using an AccuTOF Mass spectrometer equipped with a DART ionization apparatus. The mass spectra for all Rh(II,II) complexes were obtained using a Water SYNAPT H2-*Si* MALDI-TOF Mass Spectrometer. X-ray diffraction experiments were conducted using a Bruker APEX-II CCD diffractometer and solved with OLEX2. UV-Visible data was obtained in a 10mm quartz cell using a Cary 5000 spectrophotometer.[161]

2.6.2 Ligand Synthesis

2-methyl-1-(methylthio)propan-2-amine (41)

To a stirring solution of 21% sodium thiomethoxide in water (0.994 g, 1.2 equiv.) was added 2-ammonio-2-methylpropyl sulfate (2 g, 1 equiv.) and NaOH (0.5 g, 1 equiv.). The mixture was stirred at 90°C for 16 hours at which time two layers had formed. The top layer was separated and diluted with 10 mL of DCM. The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo* to yield **41** as a colorless oil, (1 g, 8 mmol, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 2H), δ 2.04 (s, 3H), δ 1.40 (s, 2H), δ 1.02 (s, 6H).

2-((2-methyl-1-(methylthio)propan-2-yl)carbamoyl)benzoic acid (42)

The following ligand was prepared using a modified procedure developed by Tohnishi.[162] A solution of 2-methyl-1-(methylthio)propan-2-amine (509 mg, 4.26 mmol) in DCM (4 mL) was added to a stirring solution of phthalic anhydride (1 equiv.) in DCM (4 mL). Triethylamine (10 mol%) was added and the mixture was stirred at reflux for 20 hours. A 10 mL portion of DI water was added, and the resulting solution was extracted 3 X 20 mL EtOAc and dried over anhydrous Na_2SO_4 then concentrated *in vacuo*. Recrystallized by addition of boiling EtOAc then adding a few drops of hexane and placed in freezer overnight. Filtration afforded **42** as a white solid (498 mg, 1.86 mmol, 44% yield). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.03-7.92 (d, 1H), 7.75-7.55 (m, 3H), 6.86-6.58 (s, 1H), 3.18-3.15 (s, 2H), 2.28-2.23 (s, 3H), 1.56-1.52 (s, 6H).

(*S*)-4-((tert-butylthio)methyl)oxazolidin-2-one (48)

To a flame dried 5 mL flask equipped with a stir bar was added **47** (0.43 g, 1.5 mmol) followed by 2-methyl-2-propanethiol (1.5 mL, 13 mmol). The reagents were then dissolved

in 6 mL acetone and refluxed at 45 °C for 24 hours. The reaction was allowed to cool to room temperature, then concentrated in vacuo. The resulting mixture was dissolved in 10 mL deionized water and extracted twice with 5 mL DCM. The combined organic layers were then washed with 5 mL brine solution, followed by 5 mL saturated sodium bicarbonate solution. The organics were separated and dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude mixture was then purified by column chromatography (25% EtOAc/Hexanes to 50% EtOAc/Hexanes) to afford **48** as a pale-yellow oil (0.1181 g, 0.58 mmol, 39% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (s, 1H), 4.56 – 4.47 (m, 1H), 4.07 – 3.96 (m, 2H), 2.63 – 2.54 (m, 2H), 1.93 – 1.81 (m, 2H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.46, 70.24, 52.29, 42.69, 35.05, 30.97, 24.62. Calculated m/z: $[M+H]^+$ = 204.1014, found m/z: $[M+H]^+$ = 204.1069

(S)-4-(2-(phenylthiol)oxazolidin-2-one (49)

To a flame dried 5 mL flask equipped with a stir bar was added **47** (0.10 g, 0.36 mmol) followed by thiophenol (0.5 mL, 0.54 mmol). The reagents were then dissolved in 1 mL acetone and refluxed for 4 hours. The reaction was allowed to cool to room temperature, then concentrated in vacuo. The resulting mixture was dissolved in 2 mL DI water and extracted twice with 2 mL DCM. The organics were combined and washed with 1 mL brine solution, followed by 1 mL saturated sodium bicarbonate solution. The organics were separated, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude mixture was then purified by column chromatography (2.5% MeOH/DCM) to afford **49** as a yellow oil (68 mg, 0.29 mmol, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 4H), 5.73 – 5.65 (m, 1H), 4.55 – 4.47 (m, 1H), 4.09 – 3.99 (m, 2H), 2.97 (td, J = 7.0, 2.5 Hz, 2H), 1.99 – 1.83 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.18, 134.88, 129.88, 129.20, 126.79, 51.63, 34.33, 30.21. Calculated m/z: $[M+H]^+$ = 224.0701, found m/z: $[M+H]^+$ = 224.0691

2.6.3 Rh(II,II) Complex Synthesis

$Rh_2(OAc)_3$MeTCB (53a)

To a dry 25 mL Schlenk flask, was added $Rh_2(OAc)_4$ (1 equiv.) and dry DCE. To the mixture was added ligand **41** (1.1 equiv) and *N,N*-diisopropylethylamine (1.1 equiv). The mixture was then heated to reflux and stirred for 3 hours. The resulting solution containing the complexes was concentrated *in vacuo* and the products separated via column

chromatography (1:1 toluene/MeCN). Bis substituted complex **53b/c** eluted first as a mixture of *cis* and *trans* isomers. Mono complex **53a** eluted second as a blue-green solid (73.5 mg, 0.113 mmol, 45% yield).). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, 2H), 7.48-7.14 (m, 4H), 6.15 (s, 1H), 3.59 (s, 2H), 2.57 (s, 3H), 1.79 (s, 3H), 1.76 (s, 6H), 1.60 (s, 6H).

General Microwave Procedure for Rh(II,II)-TOX Synthesis. All microwave reactions were conducted in sealed reaction vials with a Biotage Initiator+ equipped with an IR sensor for determination of reaction temperature. Power input was adjusted by the instrument achieve and maintain the desired reaction temperature. Reaction times are presented as hold times, not total reaction time. A 2-5 mL microwave vial equipped with a magnetic stir bar was charged with $Rh_2(OAc)_4$ (15 mg, 34 mmol) and the desired ligand (34 mmol). The edges of the flask were rinsed with 4 mL DCE. The vial was then capped and heated at 190°C for 10 minutes. The mixture was allowed to cool to room temperature, transferred to a round-bottom flask using DCM, and concentrated *in vacuo*. The crude mixture was then purified by column chromatography using a 1:1 toluene/MeCN mobile phase. Bis substituted products eluted first as a mixture of cis and trans isomers. The bis fractions were then recrystallized in MeCN to remove excess oxazolidinone starting material. Mono products eluted next with no further purification needed. $Rh_2(OAc)_4$ eluted last. The product distribution for the ligand exchange reaction with ligand **40** was quantified via HPLC using 75% 1:1 MeCN:MeOH with 0.1% TFA/25% water on a C18 column. Calibration curves were generated for **38a**, **38b/c**, and $Rh_2(OAc)_4$. The yields for complexes **55-57** were determined by isolated material.

$Rh_2(OAc)_3$MeTOX (38a)

^{1}H NMR (500 MHz, $CDCl_3$/CD_3CN) δ 4.31 (s, 1H), 3.62 (s, 2H), 3.04 (s, 2H), 2.55 (s, 3H), 1.96 (ddd, *J* = 4.9, 2.4, 0.8 Hz, 1H), 1.94 (s, 3H), 1.86 (m, *J* = 9.7, 5.1 Hz, 1H), 1.83 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$/CD_3CN) δ 191.91, 191.36, 190.90, 168.37, 69.73, 59.30, 35.64, 30.30, 23.82, 23.76, 23.28, 17.90 ppm. Calculated *m/z*: $[M+H]^+$ = 543.9019, found *m/z*: $[M+H]^+$ = 543.9011. Anal. Calcd for $C_{14}H_{22}N_2O_8$ Rh_2S: C, 28.78; H, 3.80; N, 4.80; S, 5.49. Found: C, 28.62; H, 3.71; N, 4.30; S, 5.39.

$Rh_2(OAc)_2(MeTOX)_2$ (38b/c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 – 4.23 (m, 1H), 3.76 – 3.53 (m, 2H), 3.23 (dd, J = 13.3, 5.5, 2.1 Hz, 1H), 3.11 – 3.04 (m, 1H), 2.98 (td, J = 13.2, 12.5, 2.6 Hz, 1H), 2.62 (s, J = 8.6

Hz, 3H), 2.09 – 1.70 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.09, 191.77, 140.34, 135.25, 132.44, 131.66, 129.49, 128.98, 128.67, 128.52, 126.17, 54.57, 48.65, 28.36, 23.99. Calculated m/z: $[M+H]^+$ = 644.9319, found m/z: $[M+H]^+$ = 644.9269. Anal. Calcd for $C_{16}H_{26}N_2O_8Rh_2S_2$: C, 29.83; H, 4.08; N, 4.35; S, 9.96. Found: C, 29.20; H, 3.94; N, 4.18; S, 9.47.

$Rh_2(OAc)_3(^tBuTOX)$ (55a)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 – 4.39 (m, 1H), 3.76 – 3.65 (m, 1H), 3.11 (ddd, *J* = 12.7, 5.4, 2.7 Hz, 1H), 2.97 (td, *J* = 12.4, 3.0 Hz, 1H), 2.11 (dddd, *J* = 14.7, 5.4, 3.0, 1.3 Hz, 1H), 1.99 (s, 3H), 1.87 (s, 3H), 1.84 (s, 3H), 1.84 – 1.76 (m, 1H), 1.66 (s, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.82, 190.79, 189.00, 167.23, 70.04, 58.95, 49.59, 31.96, 29.15, 29.03, 24.07, 23.90, 23.34. Calculated *m/z*: $[M+H]^+$ = 585.9489 , found m/z: $[M+H]^+$ 585.9444. Anal. Calcd for $C_{15}H_{25}NO_8Rh_2S$: C, 30.79; H, 4.31; N, 2.39; S, 5.48. Found: C, 32.80; H, 4.79; N, 2.42; S, 5.18.

$Rh_2(OAc)_2(^tBuTOX)_2$ (55b/c)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 – 4.25 (m, 1H), 3.74 – 3.54 (m, 2H), 3.19 (m, J = 13.1, 5.7, 2.5 Hz, 1H), 2.97 (m, J = 12.2, 9.1, 2.8 Hz, 1H), 1.99 (m, J = 17.5, 5.6, 2.8, 1.3 Hz, 1H), 1.90 (s, 2H), 1.85 (s, 1H), 1.81 – 1.72 (m, 1H), 1.65 (s, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.25, 69.62, 59.84, 59.74, 48.19, 48.01, 32.70, 32.64, 29.84, 29.78, 29.75, 28.95, 23.94, 23.71. Calculated m/z: $[M+H]^+$ = 729.0257, found m/z: $[M+H]^+$ = 729.0233. Anal. Calcd for $C_{22}H_{38}N_2O_8Rh_2S_2$: C, 36.27; H, 5.27; N, 3.85; S, 8.81. Found: C, 39.08; H, 5.88; N, 3.62; S, 8.04

$Rh_2(OAc)_3$(PhTOX) (56a)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.89 (m, 2H), 7.44 – 7.40 (m, 3H), 4.45 – 4.38 (m, 1H), 3.83 – 3.73 (m, 2H), 3.55 (ddd, *J* = 13.1, 5.8, 2.3 Hz, 1H), 3.37 (ddd, *J* = 13.1, 11.8, 2.5 Hz, 1H), 2.18 (dddd, *J* = 14.8, 6.0, 2.6, 1.4 Hz, 1H), 2.02 (dddd, *J* = 14.6, 12.1, 9.9, 2.4 Hz, 1H), 1.96 (s, 3H), 1.88 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.27, 190.97, 189.55, 167.73, 133.00, 131.05, 129.04, 128.54, 69.89, 59.09, 37.26, 31.16, 23.94, 23.91, 23.35. Calculated *m/z*: $[M+H]^+$ = 605.9176 , found m/z: $[M+H]^+$ 605.9180. Anal. Calcd for $C_{17}H_{21}NO_8Rh_2S$: C, 33.74; H, 3.50; N,2.32; S, 5.30. Found: C, 37.79; H, 4.40; N, 2.51.

$Rh_2(OAc)_2(PhTOX)_2$ (56b/c)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.84 (m, 2H), 7.42 – 7.29 (m, 3H), 4.41 – 4.07 (m, 2H), 3.77 – 3.61 (m, 3H), 3.43 – 3.30 (m, 1H), 2.12 – 1.93 (m, 3H), 1.89 (s, 1H), 1.86 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.65, 168.30, 131.41, 131.06, 128.91, 127.86, 69.39, 59.67, 37.09, 31.53, 23.64 Calculated m/z: $[M+H]^+$ = 768.9632, found m/z: $[M+H]^+$ = Anal. Calcd for $C_{26}H_{30}N_2O_8Rh_2S_2$: C, 40.64; H, 3.94; N, 3.65; S, 8.35. Found: C, 41.49; H, 4.24; N, 3.45; S, 7.73

$Rh_2(OAc)_3$(SerMeTOX) (57a)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (t, J = 8.0 Hz, 1H), 4.11 (m, J = 11.4, 10.2, 7.8, 3.5 Hz, 1H), 3.98 (dd, J = 10.4, 8.2 Hz, 1H), 2.86 (dd, J = 12.2, 3.5 Hz, 1H), 2.55 (s, 3H), 2.26 (t, J = 12.0 Hz, 1H), 2.03 (s, 3H), 1.84 (d, J = 5.4 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.49, 192.22, 191.04, 72.96, 59.70, 41.16, 24.27, 24.18, 23.77, 16.27. Calculated m/z: $[M+H]^+$ = 529.8863, found m/z: $[M+H]^+$ = 529.3375. Anal. Calcd for $C_{11}H_{17}NO_8Rh_2S$: C, 24.97; H, 3.25; N,2.65; S, 6.06. Found: C, 29.71; H, 4.26; N, 2.74.

$Rh_2(OAc)_2(SerMeTOX)_2$ (57b/c)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 – 4.59 (m, 1H), 4.00 – 3.89 (m, 1H), 2.84 (m, J = 12.2, 5.8, 3.4 Hz, 1H), 2.59 (d, J = 9.2 Hz, 1H), 2.52 (d, J = 5.8 Hz, 2H), 2.31 – 2.18 (m, 1H), 1.97 – 1.90 (m, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 190.32, 167.65, 72.29, 59.69, 23.72, 15.76. Calculated m/z: $[M+H]^+$ = 616.9006 , found m/z: $[M+H]^+$ = 616.8975. Anal. Calcd for $C_{14}H_{22}N_2O_8Rh_2S_2$: C, 27.29; H, 3.61; N, 4.45; S, 10.41. Found: C, 28.92; H, 3.91; N, 4.33; S, 9.95.

2.6.4 Catalysis

General Procedure for the Cyclopropanation of Styrene with EDA. Under an atmosphere of N_2, a 25 mL Schlenk flask equipped with a magnetic stir bar was flame dried and charged with styrene (0.19 mL, 1.7 mmol, 1.0 equiv.), Rh(II,II) catalyst (2 mol%), and DCE (0.5 mL). The solution was then brought to the desired temperature, followed by slow addition of EDA (0.17 mmol, 0.1 M (1.7 mL), 1.0 equiv.) by syringe pump (1 mL/hr). Once addition was complete, 16.54 µL of mesitylene standard was added to the reaction mixture and stirred. The solution was then eluted through a Nylon66 0.2 µm syringe filter into a 2 mL glass GC vial. Yields and diastereoselectivity were determined by gas

chromatography using a multiple point internal standard of the cyclopropyl product and mesitylene as the internal standard.[163]

General Procedure for the Cyclopropanation of Olefin Substrates with 56a. Under an atmosphere of N_2, a 25 mL Schlenk flask equipped with a magnetic stir bar was flame dried and charged with olefin (1.0 or 5.0 equiv. with respect to EDA), **56a** (2 mol%), and DCE (0.5 mL). The solution was then heated to 80°C, followed by slow addition of EDA (0.17 mmol, 0.1 M (1.7 mL), 1.0 equiv.) by syringe pump (1 mL/hr). After addition was complete, the reaction solution was filtered through 1.5-inch silica plug and eluted with 4 mL of DCM. The eluent was then concentrated *in vacuo* with a rotary evaporator. 10 µL of mesitylene was then added as an internal standard for ^{1}H NMR determination of cyclopropane product yield and diastereoselectivity.

Cyclopropanation of Olefin Substrates: ^{1}H NMR Yield Calculations. Yield and diastereoselectivity for each cyclopropanation reaction was calculated by ^{1}H NMR using mesitylene as an internal standard. Normalized integration of the methyl protons of mesitylene (2.26 ppm) was compared to the integration of the diastereotopic protons of the methylene unit of the cyclopropane for the cis (2.06 ppm) and trans (1.90 ppm) isomers to give the total yield of the cyclopropane product.

Chapter 3 Effect of Tethered, Axially Coordinated Ligands (TACLs) on Dirhodium(II,II)-Catalyzed Cyclopropanation: A Linear Free Energy Relationship Study

3.1 Disclosure

Portions of the following chapter were adapted from the article:

Zavala, C.; Darko, A., Effect of Tethered, Axially Coordinated Ligands (TACLs) on Dirhodium(II,II) Catalyzed Cyclopropanation: A Linear Free Energy Relationship Study. *J. Org. Chem* **2022**, In revision.

Cristian Zavala was responsible for synthesis, characterization, catalytic screening of catalysts, and writing of the manuscript. Prof. Ampofo Darko advised the work.

3.2 Abstract

Hammett correlation experiments were used to determine the nature of the influence of Rh(II,II) paddlewheel complexes with tethered, axially coordinated ligands (TACLs) on the chemoselectivity of rhodium carbenoids using competitive cyclopropanation reactions. Reaction constants for the intermolecular cyclopropanation of ethyl diazoacetate with para-substituted styrene derivatives were found to differ when comparing TACLs complexes with conventional Rh(II,II) paddlewheel complexes. Although larger changes were observed when incorporating heteroleptic bridging ligands, the results suggest that Rh(II,II) paddlewheel complexes with TACLs are less sensitive to changes in electronics and reduce selectivity in cyclopropanation reactions with acceptor-substituted rhodium carbenoids. In addition, Hammett experiments with functionalized aryldiazoacetates resulted in a non-linear downward curvature of the Hammett plot. Hints of this deviation was also seen when para-substituents were modified on aryl thioethers on TACLs, suggesting a change in the rate-limiting step of the carbene transfer reaction in response to the changes.

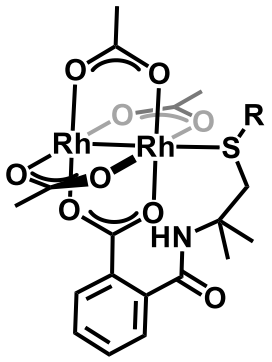
3.3 Introduction

Rhodium carbenoids, largely derived from α-diazocarbonyl precursors, have proven to be efficient and versatile intermediates in organic synthesis with applications in cyclopropanation reactions,[23] ylide reactions,[164] and X-H insertion reactions (X = C, S, O, N, Si).[13, 14, 23] The reactivity and selectivity of the complexes are driven by the selection of bridging ligands surrounding the bimetallic Rh(II,II) center. The choice of ligand can impart remarkable selectivity in carbene transfer reactions[53, 120, 165, 166] and has been leveraged in the synthesis of many complex molecules.[167-171] Although it has been known that changes

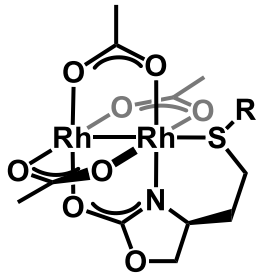
to the bridging ligands have a direct effect on the control of selectivity in Rh(II,II) carbene transfer reactions,[53, 120, 165] the effect of ligand coordination to the axial sites of Rh(II,II) catalysts on carbene transfer reactions are also important.[125] Over the years, it became apparent that an inductive effect as a result of Lewis Base (LB) coordination at one axial site is communicated through the Rh-Rh bond, which weakens Lewis acidity at the distal rhodium site.[31, 122, 123, 172, 173] The increased electron density at the other rhodium can effectively slow down association of another ligand. Indeed, introduction of axial ligands can have profound effects on the electronics of the carbenoid.[125, 157, 174]

Experimentally, studying axial coordination by tethering them to bridging ligands has emerged as a viable strategy to circumvent the weak interaction associated with axial ligands.[104, 105, 175] This provides a bias for the site of reactivity and ensures a high local concentration for axial coordination. Tethered axial coordination has also been implicated in the reaction mechanisms as in the case of a three-component reaction involving carbene transfer when $Rh_2(Oct)_4$ was used with Xantphos as the ligand.[176] We have investigated the role of axial coordination by designing bridging ligands that have pendant thioether moieties that are capable of axial coordination (complexes **37a**, **56a**, and **38a**, Figure 3.1).[110, 136, 177] The use of a thioether group, well-known as components of hemilabile ligand structures,[178-183] ensured that catalysis was not completely inhibited at the distal Rh active site. The use of these tethered, axially coordinated ligands (TACLs) resulted in improved Si–H insertion[136] and cyclopropanation[110, 177] yields compared to conventional Rh(II,II) catalysts (complexes **59** and **58** Figure 3.1). Our computational studies have also determined that the axial ligands could modulate the electron density of the carbene via electronic communication across the Rh-Rh bond.[177] To further evaluate this effect, we turned to linear free energy relationships (LFER) to determine the extent of the influence the axial tether has on the chemoselectivity of Rh(II,II) carbenes in competitive cyclopropanation reactions.

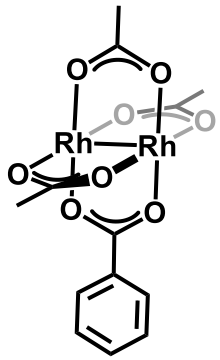
The use of Hammett constants to evaluate mechanisms in carbene transfer is precedented and has been used to confirm the electrophilic nature of Fisher-type metallocarbenoids[184, 185] or radical mechanisms in metal-catalyzed olefin cyclopropanation.[186] A breakthrough in selectivity with Rh(II,II) carbenes came with the use of donor/acceptor carbeniods. Davies and co-workers determined that vinyl and aryldiazoacetates were much more chemoselective than unsubstituted acceptor



R= Ph, **37a**
R = *p*-OMePh, $Rh_2(OAc)_3$(*p*-OMePhTCB) (**73a**)
R= *p*-CF_3Ph, $Rh_2(OAc)_3$(*p*-CF_3-PhTCB) (**74a**)
R= *p*-NO_2, $Rh_2(OAc)_3$(*p*-NO_2-PhTCB) (**75a**)



R= Ph, **56a**
R= Me, **38a**



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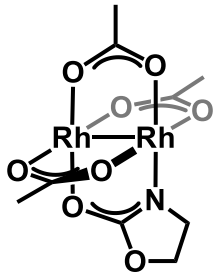


58

Figure 3.1 Rh(II,II)-TACLs complexes, **37a**, **73a-75a**, **56a**, and **38a**, and their heteroleptic control complexes **59** and **58**. Complexes **37a**,**38a**, **56a**, **58**, and **59** have been previously disclosed by our lab.

diazoacetates by comparing relative rates of cyclopropanations between styrene and substituted styrene derivatives (Figure 3.2).[28] Rho(ρ) values across various catalysts also indicated that chemoselectivity in the cyclopropanation is largely affected by the structure of the carbenoid and only slightly affected by the Rh(II,II) catalyst used.[28] It was theorized that introduction of an electron-donating group (EDG) likely stabilizes the electron-deficient carbene and creates a later transition state so that more charge builds up at the reaction center.[156] This extra stability has led to a number of applications, most notably in C-H functionalization,[187] for donor/acceptor carbenoids resulting in highly diastereo-, chemo-, and enantioselective transformations when combined with the appropriate chiral Rh(II,II) paddlewheel catalyst.[23, 85] Qu and co-workers also used Hammett correlations to gain more insight into the carbene transfer mechanism through pairwise competition reactions between a series of substituted aryldiazoacetates in a Si–H insertion reaction (Table 3.1).[188] In that study, ρ values were catalyst dependent, with electron-poor catalysts resulting in greater charge buildup in the reaction. While previous studies with Rh(II,II) carbenes have focused on the role of electronics on the carbenoid, described herein would be the first example of using Hammett correlations to study the effects of axial coordination on Rh(II,II)-catalyzed carbene transfer reactions. These experiments were conducted with previously reported Rh(II,II) TACLs complexes[110, 177] (complexes **37a**, **56a**, and **38a**, Figure 3.1) along with newly synthesized complexes for further fine-tuning at the axial site (complexes **73a-75a**, Figure 3.1).

3.4 Results and Discussion

3.4.1 Rh(II,II)-TACLs Synthesis

To evaluate the electronic influence of the axial ligand, aryl thiocarbamoyl benzoate (ArTCB) complexes with donating and withdrawing para substituents were synthesized. To this end, the necessary thiocarbamoylbenzoate ligands and their precursors were prepared using modified procedures from the literature (Figure 3.3a).[158, 162, 189] Sulfonation followed by Wenker aziridine synthesis leads to aminothioethers **76-78**. Subsequent ring-opening of phthalic anhydride leads to ligands **79**, **80**, and **81**. Complexes $Rh_2(OAc)_3$(*p*–OMe-ArTCB) **73a**, $Rh_2(OAc)_3$(*p*–CF_3-ArTCB) **74a** and $Rh_2(OAc)_3$(*p*–NO_2-ArTCB**) 75a** were synthesized using a modified procedure of our synthesis of $Rh_2(OAc)_3$ArTCB **37a** (Figure 3.3b).[110] Ligand exchange was facilitated by refluxing Rh(II,II) tetraacetate dimer in DCE with 1.1 equivalents of ligand in the presence of Hünig's base. At 1.1 equivalents

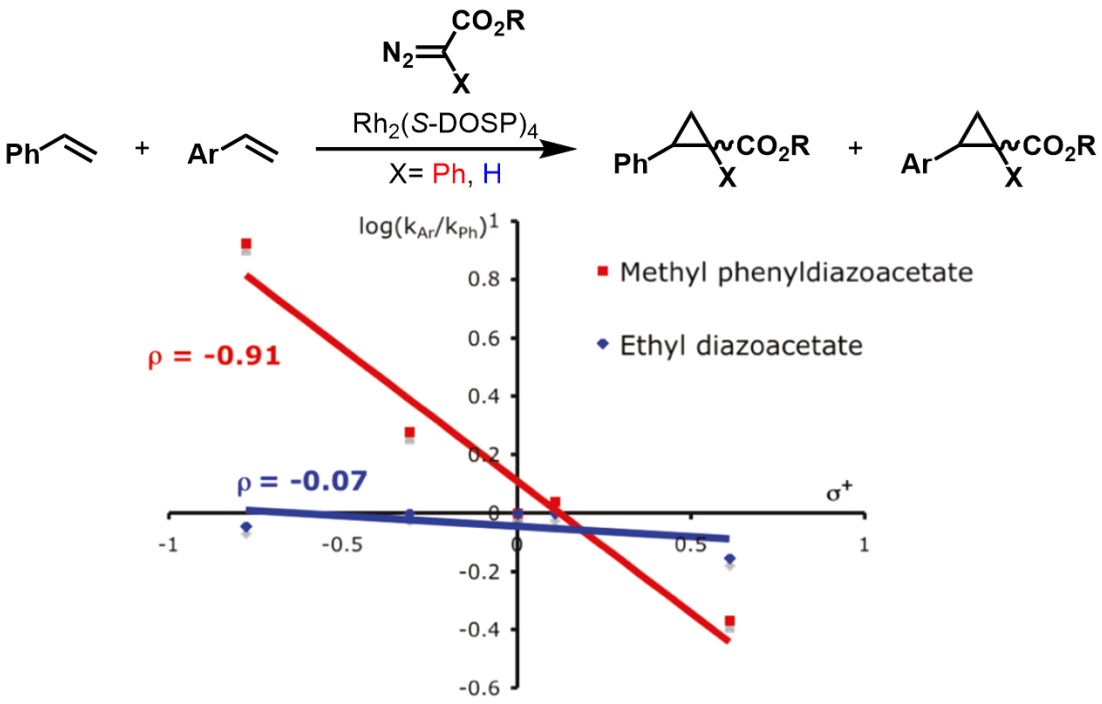
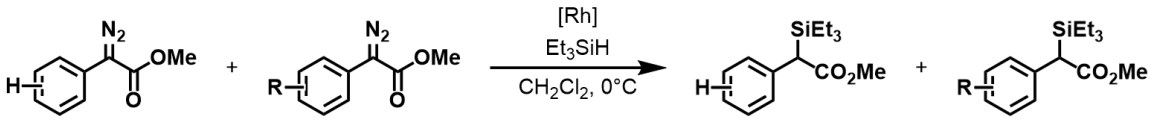
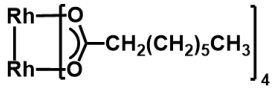


Figure 3.2 Competition reactions with styrene, using Rh(II,II)-carbenoids. Comparison of an acceptor carbenoid and a donor/acceptor carbenoid.

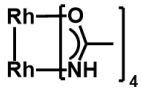
Table 3.1 Pairwise competition reactions between substituted aryl diazoacetates in a Si–H insertion reaction using Rh(II,II) complexes



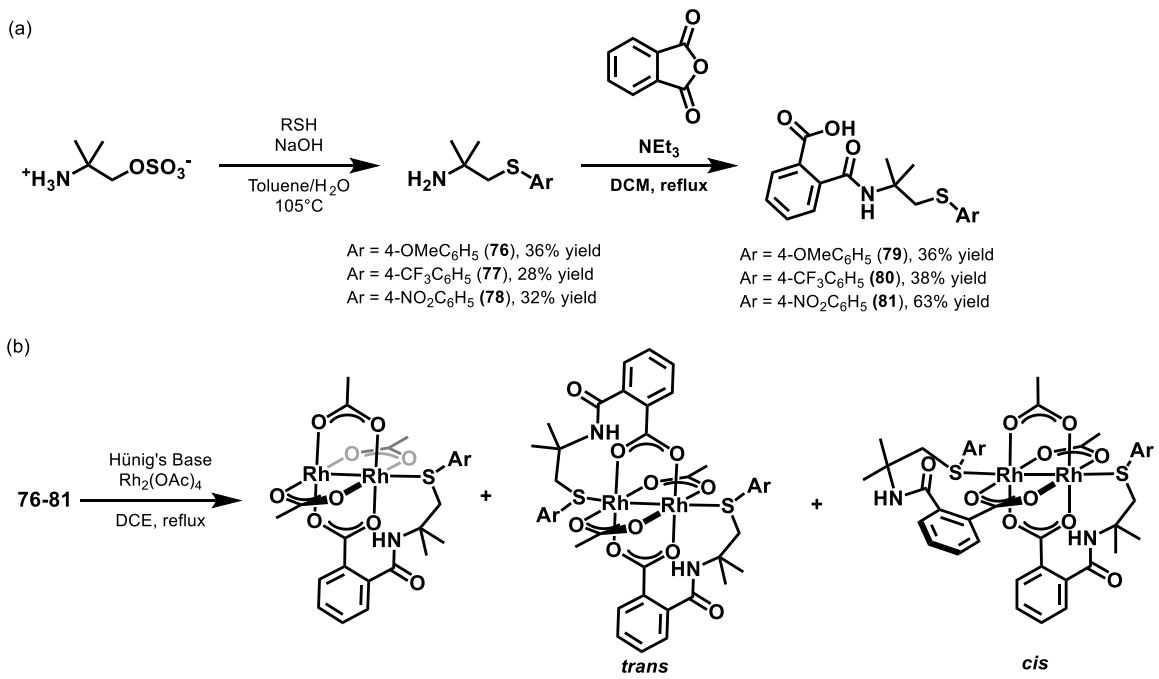
		k_{rel}			
entry	R	$Rh_2(OAc)_4$	$Rh_2(Oct)_4$	$Rh_2(acam)_4$	$Rh_2(TFA)_4$
1	*p*-OMe	10.5	12.3	7.58	16.4
2	*p*-Ph	1.35	1.73	1.65	1.32
3	*m*-Me	1.20	1.19	1.25	1.54
4	H	1.00	1.00	1.00	1.00
5	*m*-OMe	1.00	0.62	1.12	0.98
6	*p*-Br	0.84	0.90	0.74	0.65
7	*p*-NO_2	0.084	0.102	0.099	0.072
ρ	-	-1.29	-1.31	-1.18	-1.46



$Rh_2(Oct)_4$



$Rh_2(acam)_4$



$Rh_2(OAc)_3$(*p*-OMe-ArTCB) **(73a)**, 43% yield + $Rh_2(OAc)_2$(*p*-OMe-ArTCB)$_2$ **(73b/c)**, 36% yield
$Rh_2(OAc)_3$(*p*-CF_3-ArTCB) **(74a)**, 33% yield + $Rh_2(OAc)_2$(*p*-CF_3-ArTCB)$_2$ **(74b/c)**, 56% yield
$Rh_2(OAc)_3$(*p*-NO_2-ArTCB) **(75a)**, 25% yield + $Rh_2(OAc)_2$(*p*-NO_2-ArTCB)$_2$ **(75b/c)**, 26% yield

Figure 3.3 a) synthesis of ligands and b) Rh(II,II) complexes with TACLs

of ligand, exchange predominantly formed the monosubstituted species with a mixture of cis and trans isomers of the disubstituted product (**73b/c**, **74b/c** and **76b/c**) in smaller quantities.

3.4.2 EDA Cyclopropanation Linear Free Energy Relationship Study

Reaction constants for the Rh(II,II)-catalyzed cyclopropanation of EDA with a series of *para*-substituted styrene derivatives were measured by the pairwise competition of styrene and a styrene derivative in the presence of 1 mol% Rh(II,II) TACLs complex in DCE at room temperature. The relative amounts of cyclopropane products in the reaction were determined using NMR spectroscopy. The competition experiments were used as a method to obtain relative rate data *(1)*, which were then applied to the Hammett equation *(2)*. Plotting $\log(k_X/k_H)$ vs. σ obtains the reaction constant, ρ, which gives insight into the sensitivity of the reaction to changes in the electronic nature of the substituents compared to a reference reaction with styrene.

$$k_X/k_H = P_X/P_H \quad (1)$$

$$\log(k_X/k_H) = \rho \cdot \sigma \quad (2)$$

Initial experiments focused on evaluating changes in reaction sensitivity when incorporating an axial tethered thioether ligand. To this end, TACLs complexes **37a**, **73a-75a**, and **56a** were subjected to the above reaction conditions and relative rates were determined and compared to conventional complexes with no tether, $Rh_2(OAc)_3(OBz)$ **59** and $Rh_2(OAc)_3(OX)$ **58**. The negative slopes for all the complexes indicate the building of positive charge, although subtle, at the benzylic carbon center in the transition state (Figure 3.4a-f). The generally low ρ values for the complexes (Table 3.2) are common for EDA-mediated cyclopropanation reactions.[28, 190] When comparing carboxylate-bridged complexes, the use of non-tethered complex **59** resulted in a reaction that is more sensitive (more negative ρ value) to substituent changes with a slightly larger reaction constant compared to TACLs complexes **37a**, **73a**, and **75a**, indicating that axial coordination lowers this sensitivity. As the axial ligand becomes more electron-releasing, the ρ values for the reaction become less negative, indicating a decrease in positive charge build-up in the system, giving the catalyst ρ value trend: **73a** > **37a** > **75a** (Table 3.2).

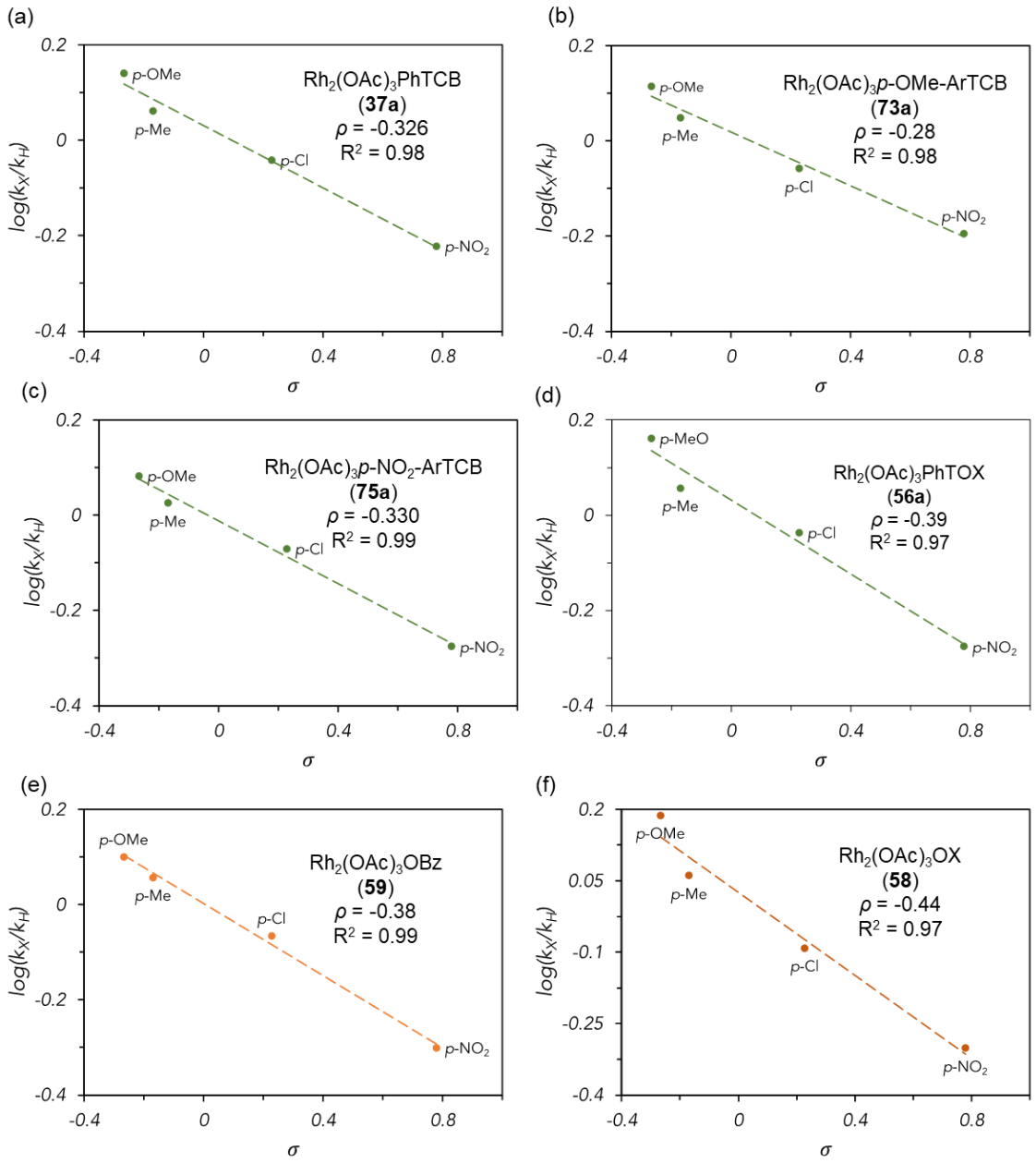
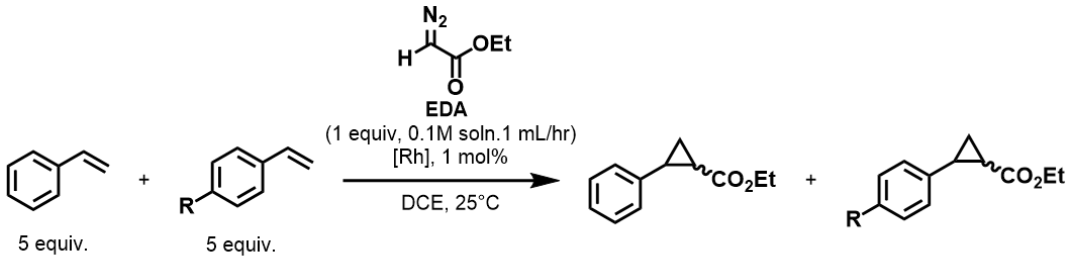


Figure 3.4 Hammett plots of competitive EDA cyclopropanation reactions of styrene vs. *para*-substituted styrenes using Rh(II,II) complexes, a) $Rh_2(OAc)_3$PhTCB **37a**, b) $Rh_2(OAc)_3$*p*-OMe-ArTCB **73a**, c) $Rh_2(OAc)_3$*p*-NO_2-ArTCB **75a**, d) $Rh_2(OAc)_3$PhTOX **56a**, e) $Rh_2(OAc)_3$OBz **59**, f) $Rh_2(OAc)_3$OX **58**

Table 3.2 Relative rates for the EDA cyclopropanation competition study



R	Relative rate versus styrene (k_X/k_H)						
	37a	**73a**	**74a**	**75a**	**56a**	**59**	**58**
OMe	1.33	1.32	1.15	1.21	1.37	1.28	1.48
Me	1.18	1.10	-	1.08	1.15	1.12	1.12
Cl	0.96	0.88	-	0.86	0.92	0.86	0.80
NO_2	0.65	0.69	-	0.56	0.58	0.51	0.48
ρ	-0.29	-0.25		-0.31	-0.34	-0.37	-0.44

It has previously been established that bridging ligands can have substantial influence on chemoselectivity in diazo-mediated Rh(II,II) catalysis.[53, 165] When comparing complex **37a** and complex **56a**, where both axial ligands contain a phenyl thioether moiety but differ in their bridging ligands and tether type, the reaction catalyzed by **56a** was determined to be more sensitive than **37a**. The difference in reaction constants between them ($\Delta\rho$(**37a** – **56a**) = 0.05) was found to be slightly smaller than the extremes of the para-substituted ArTCB complexes ($\Delta\rho$ (**73a** – **75a**) = 0.06). This larger difference indicates that changes at the axial site have larger impact on the system than at the bridging site of these catalysts, though an additional consideration is that both sites counteract each other electronically. There is an inverse relationship between the electron density trends for bridging ligand and axial ligand changes, evidenced by increased sensitivity when using the more electron-rich bridging ligand (compare ρ for **59** and **58**, Table 3.1) while the opposite was observed for electronic changes at the axial site (*vide supra*).

Interestingly, analysis of the selectivity for the individual competition reaction of 4-methoxystyrene and styrene across substituted ArTCB TACLs complexes revealed a Hammett plot with poor correlation (Figure 3.5a). The relatively small rho value also indicates that the axial site is marginally sensitive to electronic changes at the benzylic carbon. Poor correlations were also observed for the competition of styrene with *para*-Me, -Cl, and -CF_3 styrene derivatives but not with the *para*-NO_2 derivative (Figure 3.5b-d), which gave a very linear correlation. A feature of the poorly correlated Hammett plots is a decreased rate when the aryl thioether substituent is methoxy, resulting in a downwards trend in that portion of the plot (Figure 3.5b-c). Downward curving Hammett plots[191] are associated with a shift in the rate-determining step (RDS) in the mechanism.[192, 193] In Rh(II,II)-catalyzed cyclopropanations, the nitrogen extrusion step leading to the formation of the carbenoid is considered to be the RDS for Rh(II,II)-catalyzed cyclopropanations.[156, 157] Axial coordination likely contributes to destabilizing the diazo addition step,[103] but kinetic experiments are needed to confirm whether the addition step becomes the new slow-step

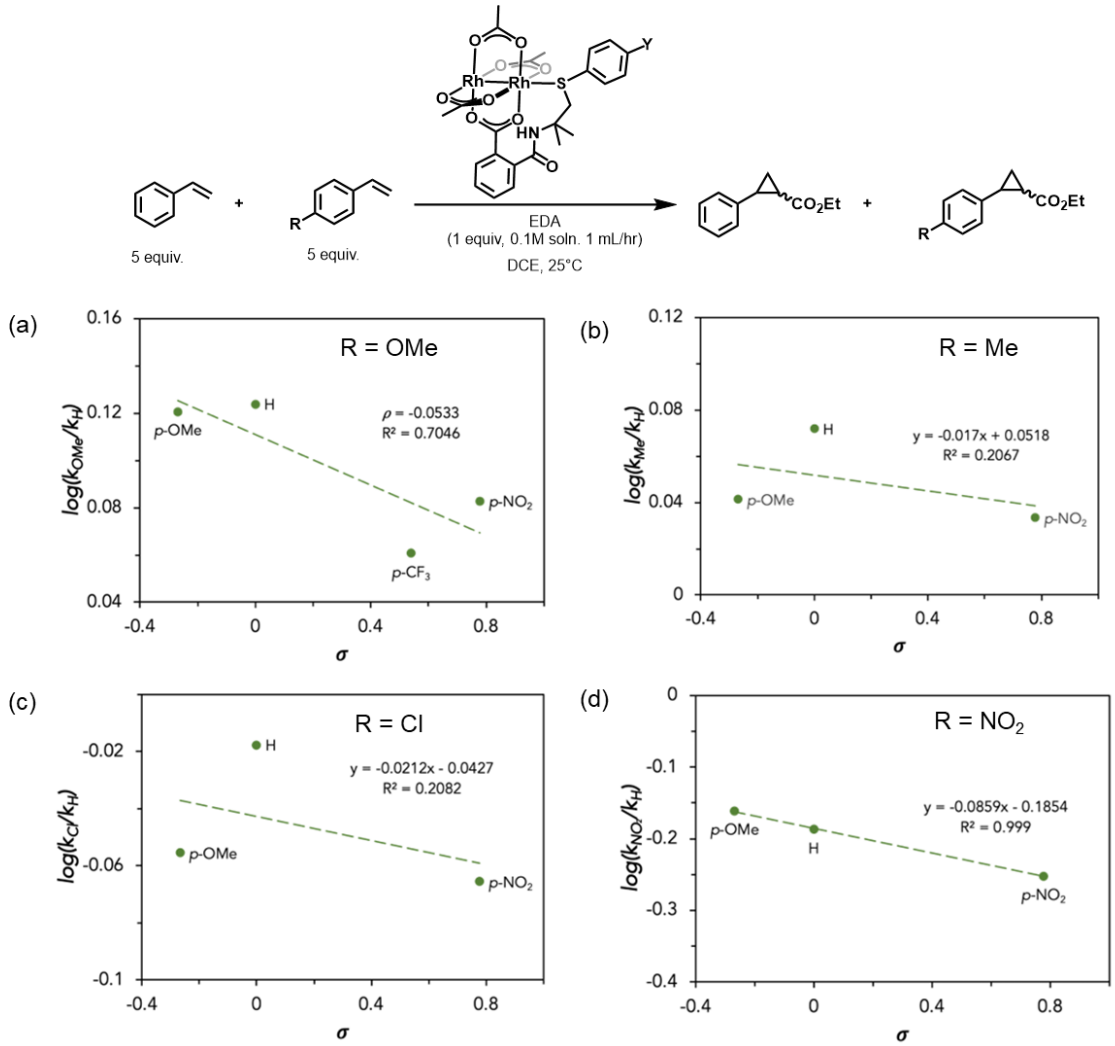
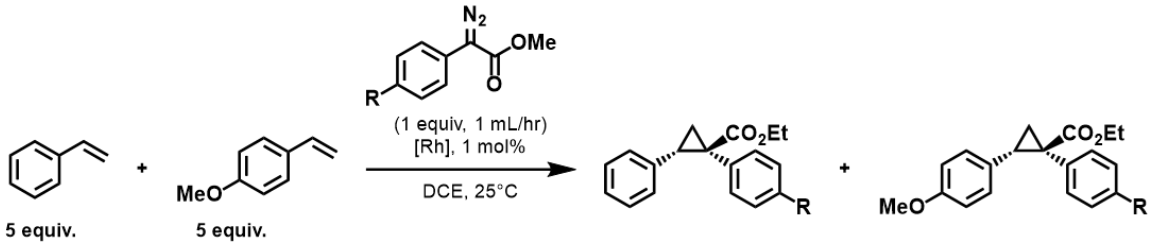


Figure 3.5 Hammett plots of individual competitions of styrene and a) 4-methoxystyrene, b) 4-methylstyrene, c) 4-chlorostyrene, and d) 4-NO_2styrene across substituted ArTCB TACLs complexes

3.4.3 Aryl Diazoacetate Cyclopropanation Linear Free Energy Relationship Study

To further investigate the effect carbene stabilization/destabilization has on the reaction, a linear free energy relationship was conducted with functionalized aryl diazoacetates in the pairwise competition of 4-methoxystyrene and styrene. Acquisition of reaction constants was achieved by reacting the desired para-substituted aryl diazoacetate with 1 mol% of a Rh(II,II) paddlewheel complex in the presence of both styrene and 4-methoxystyrene (Table 3.3). Relative rates were obtained with the same method as the EDA cyclopropanations. Complex **56a** and its conventional counterpart, complex **58a**, were used in this study since they were determined to be more sensitive to substituent changes than the carboxylate catalysts (Table 3.3). When plotting the relative rates for product distribution against substituent constants, a downwards curving Hammett plot was clearly observed for both complexes (Figure 3.6). A negative Hammett correlation was observed for electron-withdrawing substituents ($\sigma > 0$), while a positive Hammett correlation was observed for electron-releasing substituents ($\sigma < 0$). The positive slope indicates that the RDS has changed from one that builds positive charge to one that loses positive charge, as in the attack of the olefin to the carbenoid. This deviation was more pronounced than the ArTCB experiments and gives evidence that *inductive donation to the carbene, either from across the Rh(II)-Rh(II) bond or from the diazo substituents, causes a change in the RDS of Rh(II,II)-catalyzed cyclopropanation reactions*. The change in RDS when electronics are perturbed adjacent to the carbene carbon was independent of the catalyst used, since both the TACLs and conventional complexes exhibit this change, but the difference in the sensitivity of the two complexes was still determined. The positive and negative ρ values for the upward and downward trends were calculated separately for each complex and it was found that, in contrast to the EDA study, the system with the TACLs complex was more sensitive to substituent changes at the carbene center than the untethered complex (Figure 3.6). For electron-releasing substituents with complex **5**, σ substituent constants resulted in a better linear correlation, while σ^+ gave better correlation with the withdrawing groups (Figure 3.6a). This indicates that there is less of a mesomeric effect of the donating groups on the carbene when a tethered axial coordinating group is present. Results with complex **8**, on the other hand, produced a better correlation with σ^+ for both electron-withdrawing and electron-releasing substituents

Table 3.3 Relative rates for the cyclopropanation of styrene and 4-methoxystyrene using *para*-substituted aryl diazoacetate and σ and σ^+ scales for *para* substituents.



R	k_{OMe}/k_H (**56a**)	k_{OMe}/k_H (**58**)	σ	σ^+
OMe	7.84	7.26	-0.268	-0.778
Me	8.13	8.3	-0.17	-0.311
Cl	9.91	10.07	0.227	0.114
CF_3	7.52	8.3	0.54	0.612
NO_2	7.57	7.59	0.778	0.79

σ and σ^+ are Hammett constants for substituents, R

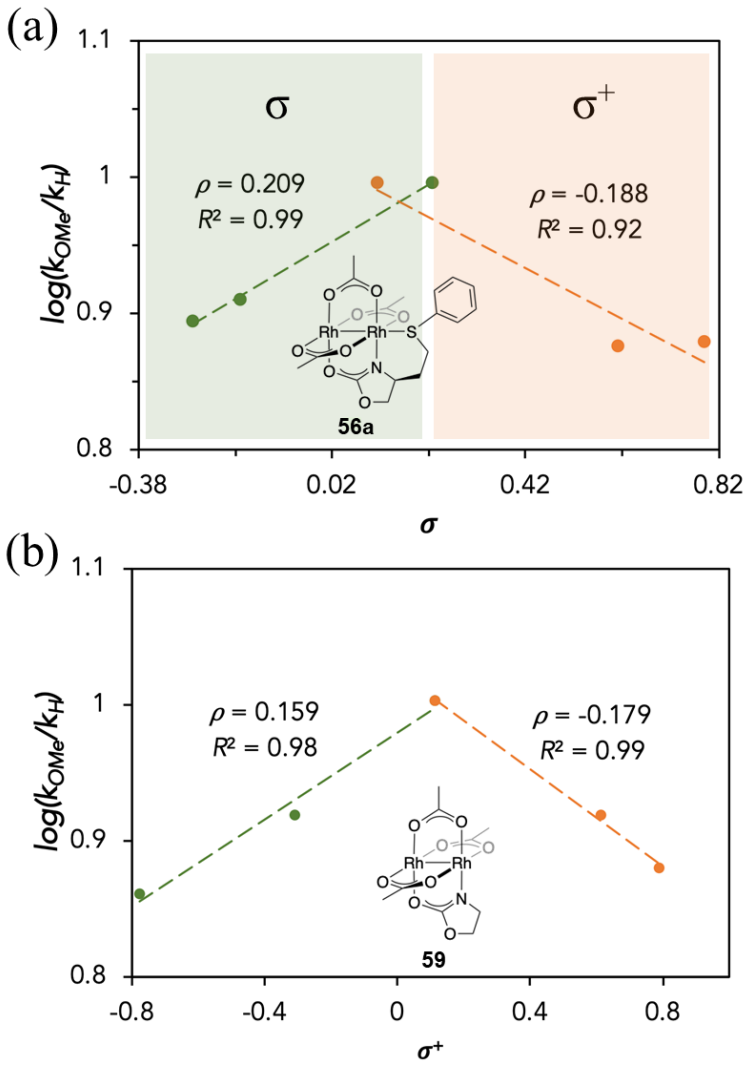


Figure 3.6 Hammett plots for the cyclopropanation of styrene and 4-methoxystyrene using *para*-substituted aryldiazoacetates catalyzed by a) complex **56a** and b) complex **59**

(Figure 3.6b). These results indicate that the tethered axial thioether ligands could play a beneficial role in enhancing selectivity when electronics are perturbed on the aryl diazo compound in donor/acceptor carbenes.

3.5 Conclusion

In conclusion, we have reported the use of linear free energy relationships in the form of Hammett experiments to determine the influence of tethered axially coordinated ligands on the chemoselectivity of Rh(II,II) catalyzed cyclopropanations. With the cyclopropanation of ethyl diazoacetate with styrene and styrene derivatives, it was determined that the reactions with conventional complexes were slightly more sensitive to electronic changes in the substrates. However, the differences across complexes were found to be minor. It also seems that a more sensitive reaction can be accomplished by decreasing electron donation into the axial site distal to the carbene. Larger changes were observed when bridging ligands were changed than the axial site. Hammett parameters were also applied to the cyclopropanation of a series of para-substituted phenyl diazoacetates, wherein a non-linear downward curvature was present in the Hammett plot. A downward deviation was observed when comparing the competition of styrene derivatives with various para-substituted ArTCB complexes. These deviations have been theorized to be the result of a change in the rate-determining step to the cyclopropanation step when using more electron-rich substituents adjacent to the carbene or at the distal axial site. Theoretical kinetic analysis of the transition states of these processes is currently underway in our lab to better understand the role the TACLs have on Rh(II,II) activity.

3.6 Experimental Procedures

3.6.1 General Considerations

Unless otherwise noted, all reagents were purchased and used as received from the manufacturer without further purification. 2-Ammonio-2-methylpropyl sulfate was synthesized from 2-amino-2-methylpropan-1-ol according to established procedures.[158] Methyl phenyldiazoacetate was prepared from benzylic acid according to established procedures.[194] Methyl 2-diazo-2-(4-methoxyphenyl)acetate,[189] methyl 2-diazo-2-(p-tolyl)acetate,[189] methyl 2-(4-chlorophenyl)-2-diazoacetate,[189] and methyl 2-diazo-(4-nitrophenyl)acetate were also prepared using literature procedures.[195]All products from previously reported procedures were verified, using ^{1}H NMR, against the values presented

in the literature. Hexanes, THF, diethyl ether, DCM, and MeCN were dried with columns packed with alumnia using an Inert® PureSolv Micro Solvent Purification System and stored over molecular sieves. Reactions were monitored using TLC on Sorbent Technologies Silica XG TLC Plates. Column chromatography was performed using 60 Å, 40-63 μm silica from Sorbent Technologies. ^{1}H NMR, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Mercury Vx 300 MHz, Varian VNMRS 500MHz, or Bruker AVANCE NEO 500 MHz spectrometers. All NMR chemical shifts are reported in ppm on the δ scale. Signals were referenced by residual solvent signal for ^{1}H NMR ($CHCl_3$ = 7.26 ppm, acetone = 2.05 ppm, acetonitrile = 1.94 ppm) and ^{13}C NMR ($CHCl_3$ = 77.16 ppm, acetone = 206.26 ppm, acetonitrile = 1.32 ppm). The mass spectra for the ligands and their precursors were obtained using an AccuTOF Mass spectrometer equipped with a DART ionization apparatus. The mass spectra for all Rh(II,II) complexes were obtained using a Water SYNAPT H2-*Si* MALDI-TOF Mass Spectrometer.

3.6.2 Ligand Synthesis

General Procedure A: Synthesis of Aminothioethers. Aminothioethers were synthesized with modified procedures from established protocols.[158] To a stirring solution of 2-ammonio-2-methylpropyl sulfate (1 equiv.) in 8 mL toluene:water (50/50) was added *para*-substituted thiophenol (1.5 equiv.). The mixture was heated to reflux at which point 4 mL of 2M aq. NaOH solution was added at 2 mL/hr by syringe pump. The reaction was stirred at reflux for 3 hours and then at 45°C for 17 hours. The toluene layer was separated and washed with 1M NaOH. The organic layer was dried over anhydrous MgSO4 and concentrated *in vacuo*. The residue was then partitioned between 20 mL EtOAc and 20 mL 1M HCl then stirred for 30 minutes. The aqueous layer was then separated and neutralized with 1M NaOH until white precipitate that forms persisted. Aqueous layer was then extracted 3 X 30 mL of EtOAc then dried over anhydrous MgSO4 and concentrated *in vacuo* to afford an oil.

1-((4-methoxyphenyl)thio)-2-methylpropan-2-amine (76)

General Procedure A was used with 4-methoxythiophenol (545 μL, 4.43 mmol) to obtain **76** as a yellow oil, (227 mg, 1.07 mmol, 36% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.8 Hz, 2H, Ar–H), 6.82 (d, *J* = 8.8, 2H, Ar–H), 3.76 (s, 3H, OCH_3), 2.93 (s, 2H, CH_2), 1.44 (s, 2H, NH_2) 1.16 (s, 6H, C(CH_3)$_2$), ^{13}C NMR (125 MHz) δ 158.8, 132.9, 128.2, 114.7,

55.4, 52.3, 51.0, 29.9. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{18}NOS$ 212.1104, Found 212.1084.

2-methyl-1-((4-(trifluoromethyl)phenyl)thio)propan-2-amine (77)

General Procedure A used with 4-trifluoromethylthiophenol (608 µL, 4.43 mmol) to obtain **77** as a yellow oil, (207 mg, 0.83 mmol, 28% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 28.1, 7.9, 4H, Ar–H), 3.07 (s, 2H, CH_2), 1.75 (s, 2H, NH_2), 1.24 (s, 6H, C(C*H*$_3$)$_2$), ^{13}C NMR (125 MHz) δ 143.2, 128.0, 127.8, 127.6, 125.4, 123.2, 121.0, 50.9, 48.6, 30.1, ^{19}F (470 MHz, $CDCl_3$) δ 62.5. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{15}F_3NS$ 250.0872, Found 250.0893.

2-methyl-1-((4-nitrophenyl)thio)propan-2-amine (78)

General Procedure A used with 4-nitrothiophenol (1.4 g, 9 mmol) to obtain **78** as an orange oil (433 mg, 1.9 mmol, 32% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.1, 2H, Ar–H), 7.37 (d, *J* = 8.5, 2H, Ar–H), 3.08 (s, 2H, CH_2), 1.54 (s, 2H, NH_2), 1.24 (s, 6H, C(C*H*$_3$)$_2$), ^{13}C NMR (125 MHz, CDCl3) δ 148.3, 145.1, 126.8, 123.9, 50.1, 47.6, 30.2. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_{15}N_2O_2S$ 227.0849, Found 227.0871.

General Procedure B: Synthesis of Thiocarbamoylbenzoate Ligands. The following ligands were prepared using a modified procedure developed by Tohnishi.[162] A solution of aminothioether in DCM(4 mL) was added to a stirring solution of phthalic anhydride (1 equiv.) in DCM (4 mL). Triethylamine (10 mol%) was added and the mixture was stirred at reflux for 20 hours. A 10 mL portion of DI water was added, and the resulting solution was extracted 3 X 20 mL EtOAc and dried over anhydrous Na_2SO_4 then concentrated *in vacuo*. Solids recrystallized by addition of boiling EtOAc then adding a few drops of hexane and placed in freezer overnight. Filtration afforded the thiocarbamoylbenzoates as white solids.

2-((1-((4-methoxyphenyl)thio)-2-methylpropan-2-yl)carbamoyl)benzoic acid (79)

General Procedure B used with 1-((4-methoxyphenyl)thio)-2-methylpropan-2-amine (219 mg, 1.04 mmol) to obtain **79** as a white solid (135 mg, 0.376 mmol, 36% yield). ^{1}H NMR (300 MHz, Acetone-d_6) δ 7.87 (d, *J* = 7.2, 1H, Ar–H), 7.63-7.33 (m, 5H, Ar–H), 6.89 (d, *J* = 9.5, 2H, Ar–H), 3.78 (s, 3H, OC*H*$_3$), 3.55 (s, 2H, CH2), 1.49 (s, 6H, C(C*H*$_3$)$_2$), ^{13}C NMR (125 MHz, Acetone-d_6) δ 169.7, 167.9, 159.7, 140.4, 133.3, 132.3, 130.8, 129.8, 128.9,

128.8, 115.5, 55.6, 46.1, 26.6. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{22}NO_4S$ 360.1270, Found 360.1242.

2-((2-methyl-1-((4-(trifluoromethyl)phenyl)thio)propan-2-yl)carbamoyl)benzoic acid (80)

General Procedure B used with 2-methyl-1-((4-(trifluoromethyl)phenyl)thio)propan-2-amine (53 mg, 0.211 mmol) to obtain **80** as a white solid (32 mg, 0.08 mmol, 38% yield). ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.86 (d, *J* = 8.6, 1H, Ar–H), 7.61 (s, 4H, Ar–H), 7.57-7.42 (m, 2H, Ar–H), 7.32 (d, *J* = 6.9, 1H, Ar–H), 3.78 (s, 2H, CH_2), 1.54 (s, 6H, C(CH_3)$_2$), ^{13}C NMR (125 MHz, Acetone-d_6) δ 169.8, 167.8, 144.9, 140.4, 132.3, 130.73, 130.5, 129.8, 128.8, 128.5, 127.4, 127.2, 126.5, 126.4, 126.4, 126.4, 55.1, 42.2, 26.7, ^{19}F (470 MHz, $CDCl_3$) δ 62.8. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{19}F_3NO_3S$ 398.1032, Found 398.1043.

2-((2-methyl-1-((4-nitrophenyl)thio)propan-2-yl)carbamoyl)benzoic acid (81)

General Procedure B used with 2-methyl-1-((4-nitrophenyl)thio)propan-2-amine (361 mg, 1.6 mmol) to obtain **81** as a yellow solid (374 mg, 1 mmol, 63% yield). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.15 (d, *J* = 8.8, 2H, Ar–H), 7.87 (d, *J* = 7.1, 2H, Ar–H), 7.68-7.33 (m, 5H, Ar–H), 3.85 (s, 2H, CH2), 1.56 (s, 6H, C(CH_3)$_2$), ^{13}C NMR (125 MHz, Acetone-d_6) δ 170.0, 169.9, 167.9, 149.5, 145.9, 140.4, 132.3, 130.7, 130.6, 129.85, 128.8, 127.7, 124.7, 124.6, 54.9, 41.8, 26.8. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{19}N_2O_5S$ 375.1015, Found 375.0988.

3.6.3 Rh(II,II) Complex Synthesis

General Procedure C: Synthesis of Rh(II,II)-TCB Complexes. To a dry 25 mL Schlenk flask, was added $Rh_2(OAc)_4$ (1 equiv.) and dry DCE. To the mixture was added ligand (1.1 equiv.) and *N,N*-diisopropylethylamine (1.1 equiv.). The mixture was then heated to reflux and stirred for 3 hours. The resulting solution containing the complexes was concentrated *in vacuo* and the products separated via column chromatography (1:1 toluene/MeCN). Bis substituted complexes **73b/c**, **74b/c**, and **75b/c**, eluted first as a mixture of *cis* and *trans* isomers. Bis complexes were further purified by crystallization by adding minimal hexanes to a mixture of toluene/MeCN and cooling in a freezer for 3 days. Mono complexes **73a**, **74a**, and **75a** eluted second with no further purification needed. Finally, unreacted $Rh_2(OAc)_4$ eluted last.

$Rh_2(OAc)_3$(*p*-OMe-ArTCB) (73a)

Isolated as a blue-green solid (36 mg, 0.049 mmol, 43% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 9.1, 2H, Ar–H), 7.73 (d, *J* = 7.9, 1H, Ar–H), 7.38 (t, 1H, Ar–H), 7.29 (d, *J* = 6.7, 1H, Ar–H), 7.20 (d, *J* = 6.9, 1H, Ar–H), 6.99 (d, *J* = 9.1, 2H, Ar–H), 5.64 (s, 1H, NH), 4.01 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 1.95 (s, 6H, $(CO_2)CH_3$-*cis*), 1.88 (s, 3H, (CO2)CH_3-*trans*), 1.73 (s, 6H, $C(CH_3)_2$), ^{13}C NMR (125 MHz) δ 192.4, 192.1, 170.8, 160.8, 160.5, 140.3, 134.8, 131.5, 130.1, 128.7, 128.4, 126.5, 126.1, 115.1, 55.6, 54.6, 49.9, 28.3, 24.1, 3.1. HRMS (ESI-TOF) *m/z*: $[M+K]^+$ Calcd for $C_{25}H_{29}KNO_{10}Rh_2S$ 779.9259, Found 779.9258.

$Rh_2(OAc)_2$(*p*-OMe-ArTCB)$_2$ (73b/c)

Isolated as a reddish-purple solid (21 mg, 0.020 mmol, 36% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.1, 4H, Ar–H), 7.75 (d, *J* = 6.8, 2H, Ar–H), 7.38-7.28 (m, 2H, Ar–H), 7.25-7.13 (m, 4H, Ar–H), 6.97 (d, *J* = 8.9, 4H, Ar–H), 5.70 (s, 2H, 2 × NH), 4.11 (s, 4H, 2 × CH_2), 3.85 (s, 6H, 2 × OCH_3), 1.88 (s, 6H, 2 × $(CO_2)CH_3$), 1.77 (s, 12H, 2 × $C(CH_3)_2$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 186.3, 171.1, 160.3, 140.2, 135.1, 131.0, 130.8, 128.9, 128.4, 127.5, 125.9, 115.0, 114.9, 55.6, 54.8, 49.9, 28.5, 28.3, 24.2. HRMS (ESI-TOF) *m/z*: $[M+K]^+$ Calcd for $C_{42}H_{46}KN_2O_{12}Rh_2S_2$ 1079.0239, Found 1079.0211.

$Rh_2(OAc)_3$(*p*-CF_3-ArTCB) (74a)

Isolated as a blue-green solid (18.3 mg, 0.023 mmol, 33% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7, 2H, Ar–H), 7.75 (d, *J* = 7.5, 2H, Ar–H), 7.69 (d, *J* = 8.0, 2H, Ar–H), 7.46-7.28 (m, 3H, Ar–H), 5.62 (s, 1H, NH), 4.13 (s, 2H, CH_2), 1.95 (s, 6H, $(CO_2)CH_3$-*cis*), 1.83 (s, 3H, $(CO_2)CH_3$-*trans*), 1.78 (s, 6H, $C(CH_3)_2$), ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 192.1, 185.2, 171.2, 140.5, 132.2, 132.0, 130.3, 129.4, 129.00, 128.9, 127.5, 126.6, 126.5, 126.5, 54.7, 47.6, 28.7, 24.3, 24.2, ^{19}F (470 MHz, $CDCl_3$) δ 62.8. HRMS (ESI-TOF) *m/z*: $[M+K]^+$ Calcd for $C_{25}H_{26}F_3KNO_9Rh_2S$ 817.9028, Found 817.9025.

$Rh_2(OAc)_2$(*p*-CF_3-PhTCB)$_2$ (74b/c)

Isolated as a reddish-purple solid (21.8 mg, 0.020 mmol, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.7, 4H, Ar–H), 7.68 (d, *J* = 7.5, 4H, Ar–H), 7.60 (d, *J* = 7.5, 2H, Ar–H), 7.39-7.32 (m, 3H, Ar–H), 7.19 (d, *J* = 8.0, 3H, Ar–H), 5.61 (s, 2H, 2 × NH), 4.37 (s, 2H, CH_2), 4.19 (s, 2H, CH_2), 1.84 (s, 6H, 2 × $(CO_2)CH_3$), 1.80 (s, 12H, $C(CH_3)_2$), ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 186.0, 171.0, 140.8, 140.1, 134.6, 131.6, 131.5, 131.4, 130.2,

129.90, 129.2, 128.8, 128.7, 128.5, 127.1, 126.4, 126.2, 126.1, 126.1, 125.3, 65.5, 54.6, 46.6, 28.6, 24.1, ^{19}F (470 MHz, $CDCl_3$) δ 62.6. HRMS (ESI-TOF) *m/z*: $[M+K]^+$ Calcd for $C_{42}H_{40}F_6N_2KO_{10}Rh_2S_2$ 1154.9776, Found 1154.9711.

$Rh_2(OAc)_3$(*p*-NO_2-PhTCB) (75a)

Isolated as a green solid (21 mg, 0.028 mmol, 25% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.8, 2H, Ar–H), 8.06 (d, *J* = 9.8, 2H, Ar–H), 7.79 (d, *J* = 8.1, 1H, Ar–H), 7.47-7.28 (m, 2H, Ar–H), 7.21 (d, *J* = 7.2, 1H, Ar–H), 5.61 (s, 1H, NH), 4.22 (s, 2H, CH_2), 1.94 (s, 6H, $(CO_2)CH_3$-*cis*), 1.84 (s, 3H, $(CO_2)CH_3$-*trans*), 1.79 (s, 6H, $C(CH_3)_2$), ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 192.2, 185.7, 170.9, 147.2, 144.2, 140.1, 131.2, 131.0, 128.9, 128.8, 124.4, 124.2, 54.4, 28.5, 28.3, 24.1, 23.9. HRMS (ESI-TOF) *m/z*: $[M+K]^+$ Calcd for $C_{24}H_{26}KN_2O_{11}Rh_2S$ 794.9004, Found 794.9016.

$Rh_2(OAc)_2$(*p*-NO_2-PhTCB)$_2$ (75b/c)

Isolated as a yellowish-purple solid (32 mg, 0.030 mmol, 26% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9, 4H, Ar–H), 8.06 (d, *J* = 8.9, 4H, Ar–H), 7.61 (d, *J* = 8.91, 2H, Ar–H), 7.38(t, 2H, Ar–H), 7.26 (t, 2H, Ar–H), 7.20 (d, *J* = 7.91, 2H, Ar–H), 5.61 (s, 2H, 2 × NH), 4.3 (s, 4H, 2 × CH_2), 1.81 (s, 12H, 2 × $C(CH_3)_2$), 1.56 (s, 6H, $(CO_2)CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 185.8, 170.9, 146.9, 144.5, 139.8, 131.5, 130.7, 130.6, 129.8, 128.6, 128.5, 126.4, 124.1, 54.2, 45.3, 28.4, 23.9. HRMS (ESI-TOF) *m/z*: $[M+K]^+$ Calcd for $C_{40}H_{40}KN_4O_{14}Rh_2S_2$ 1109.9730, Found 1109.9692.

3.6.4 Catalysis

General Procedure for EDA Linear Free Energy Relationship Study. Under an atmosphere of argon, a 25 mL Schlenk flask equipped with a magnetic stir bar was flame dried and charged with styrene (96.82 µL, 0.85 mmol, 5 equiv.), *p*-substituted styrene (0.85 mmol, 5 equiv.), Rh(II) catalyst (1 mol%), and DCE (0.5 mL). EDA (0.1 M (1.7 mL), 1.0 equiv.) was then added slowly by syringe pump (1 mL/hr). After addition was complete, the reaction was filtered through a 1.5-inch silica plug and eluted with 5 mL DCM. The eluent was then concentrated *in vacuo* with a rotary evaporator. The ratio of cyclopropane products was then determined using ^{1}H NMR to obtain relative rates and plot the Hammett relationship.

General Procedure for Aryl Diazoacetate Linear Free Energy Relationship Study. Under an atmosphere of argon, a 25 mL Schlenk flask equipped with a magnetic stir bar was flame dried and charged with styrene (96.82 µL, 0.85 mmol, 5 equiv.), 4-methoxystyrene (111.32 µL, 0.85 mmol, 5 equiv.), Rh(II,II) catalyst (1 mol%), and DCE (0.5 mL). To the stirring solution was added an aryl diazoacetate (0.17 mmol, 0.1 M (1.7 mL), 1.0 equiv.) by syringe pump (1 mL/hr). After addition was complete, the reaction was filtered through a 1.5-inch silica plug and eluted with 5 mL DCM. The eluent was then concentrated *in vacuo* with a rotary evaporator. The ratio of cyclopropane products was then determined using ^{1}H NMR to obtain relative rates and plot the Hammett relationship.

Chapter 4 Chiral Rh(II,II)-TACLs for Stereoselective Cyclopropanation

4.1 Disclosure

Portions of this chapter were adapted from the article:

Zavala, C, Abshire, A; Darko, A. “Chiral Rh(II,II) Complexes with Tethered, Axially Coordinated Ligands (TACLs) Improve Asymmetric Cyclopropanation with Methyl Phenyldiazoacetate” *Org Biomol Chem* **2022**. In preparation

Cristian Zavala was responsible for the synthesis, characterization, catalytic screening of catalysts, and preparation of the manuscript. Anthony Abshire assisted with scaling up the synthesis of the ligands and catalysts. Prof. Ampofo Darko advised the work.

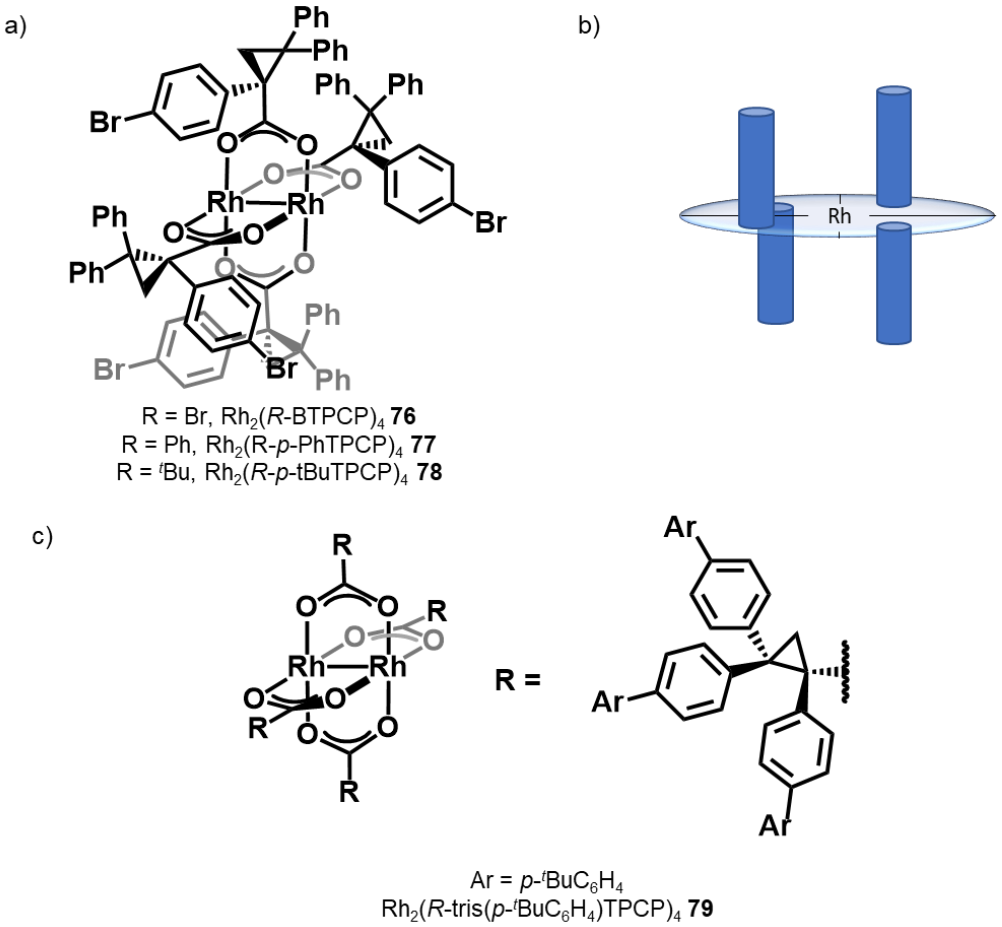
4.2 Abstract

Rh(II,II) paddlewheels are highly modular complexes that have been extensively used as catalysts in carbene transfer reactions using diazo precursors. Efforts towards stereoselective transformations have led to the development of chiral Rh(II,II) complexes that use sterically blocking groups to create symmetric chiral pockets at each rhodium metal. These catalysts have exhibited high enantiocontrol in C–H functionalization, cyclopropanation, and other diazo-mediated transformations. The use of axial coordination to influence stereoselectivity is not as developed as bridging ligand effects. The incorporation of tethered, axially coordinated ligands (TACLs) to chiral Rh(II,II) scaffolds can take advantage of steric and non-covalent interactions closer to the active site. Our group has previously developed Rh(II,II) complexes with thioether TACLs and applied them towards diazo-mediated cyclopropanation and Si–H insertion reactions. Herein, chiral Rh(II,II) TACLs complexes were synthesized to evaluate the influence of axial coordination on stereoselective diazo-mediated carbene transfer reactions. It was determined that incorporating axially tethered ligands with a chiral linker improves enantioselectivity in cyclopropanation reactions of styrene and donor/acceptor carbenes.

4.3 Introduction

The cyclopropane moiety exhibits unique properties that make them highly sought after in the pharmaceutical and natural products industries.[1, 2] As a result, chemo- and stereoselective transformations are imperative for the synthesis of cyclopropane containing pharmaceuticals or bioactive natural products.[196] The catalytic formation of

cyclopropanes via transition-metal carbene transfer reactions is one of the most common strategies and has been extensively studied for decades.[8, 14, 41, 197, 198] Dirhodium(II) paddlewheel catalysts are among the most effective catalysts used in diazo-mediated cyclopropanation reactions. Rh(II,II)-paddlewheel complexes are highly efficient at carbene transfer reactions with many types of diazo species.[12] As discussed in Section 1.1.2, stereoselective cyclopropanation reactions with Rh(II,II) complexes can be achieved by using diverse bridging ligand architectures. Early studies led by the Doyle lab demonstrated the effectiveness of Rh(II,II)-carboxamidates in intramolecular cyclopropanations of allylic diazos (Section 1.1.2.2).[4, 17] Chiral Rh(II,II)-carboxylates based on phthalimide-protected amino acids are generally efficient at asymmetric induction of various diazo types, but are most proficient at acceptor/acceptors (Section 1.1.2.3).[14, 27, 45] By far the most impressive complexes for stereoselective carbene transfer reactions of donor/acceptor diazos are the Rh(II,II) complexes developed by the Davies lab (Section 1.1.2.4).[14, 45, 46] Recently, Davies and co-workers have developed their "third generation" of carboxylate complexes, which are comprised of triarylcyclopropanecarboxylate (TPCP) bridging ligands (Figure 4.1a).[199] These complexes contain cyclopropane rings with sterically crowding aryl groups that give the catalyst the same α, β, α, β conformation as Rh_2(*S*-DOSP)$_4$ but with more conformational rigidity (Figure 4.1b). The first Rh(II,II)-TPCP complex synthesized, Rh_2(*R*-*p*-Br-TPCP)$_4$ **76**, was initially evaluated in the cyclopropanation of styryldiazoacetates with styrene (Table 4.1).[199] It was determined that the TPCP catalyst gave higher yields and enantioselectivity than the Rh_2(*S*-DOSP)$_4$ species in DCM (Table 4.1). Increasing the size of the ester substituent was found to improve the enantioselectivity of the reaction, likely due to increased steric clash at the active site (Table 4.1). Since this work, the Davies lab has developed even more sterically demanding TPCP complexes by the incorporation of larger groups on one of the aryl rings (Figure 4.1a).[30] This concept was expanded upon with the development of a complex with three *para*-substituted aryl rings on the cyclopropane, Rh_2(*R*-tris(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$ **79** (Figure 4.1c).[200] In a recent *in-situ* kinetic study conducted by the Davies lab, they were able to conduct cyclopropanation reactions with high enantioselectivity at low catalyst loadings with **76** (Table 4.2).[201] The same study found that the larger TPCP complexes decomposed the diazo much slower than the prolinate or phthalimide complexes (2-13 hrs. to ~2 minutes respectively) but obtained higher enantioselectivities. Most efforts with

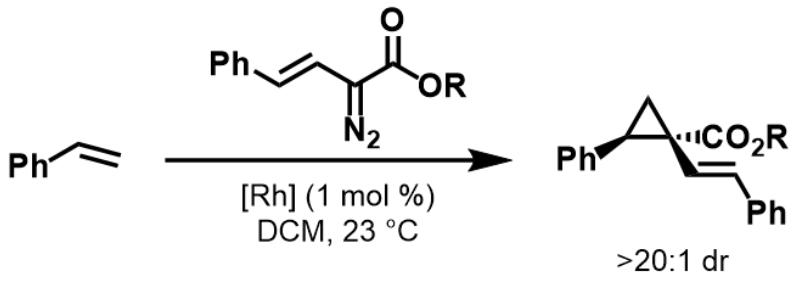


R = Br, Rh_2(*R*-BTPCP)$_4$ **76**
R = Ph, Rh_2(R-*p*-PhTPCP)$_4$ **77**
R = ^{t}Bu, Rh_2(*R*-*p*-tBuTPCP)$_4$ **78**

Ar = *p*-^{t}BuC$_6$H$_4$
Rh_2(*R*-tris(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$ **79**

Figure 4.1 a) General structure for Rh(II,II) TPCP complexes, b) D_2-symmettry of the Rh(II,II)-TPCP blocking groups, c) structure of the sterically encumbered Rh_2(*R*-tris(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$

Table 4.1 Asymmetric cyclopropanation of styrene with styryldiazoacetates and Rh_2(*R*-*p*-Br-TPCP)$_4$ **76**



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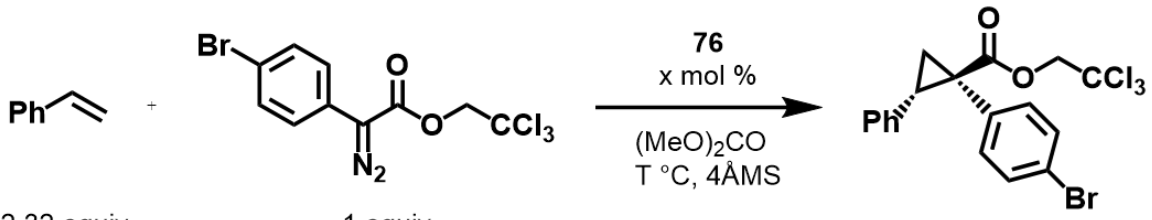
Entry	[Rh]	R[1]	Yield (%)	ee (%)
1	**76**	Me	86	91
2	**76**	Et	88	93
3	**76**	*t*Bu	87	95
4	Rh_2(*R*-DOSP)$_4$	Me	80	81
5	Rh_2(*R*-DOSP)$_4$	Et	84	75
6	Rh_2(*R*-DOSP)$_4$	*t*Bu	80	16

[a] 0.001 mol % [Rh]

Table 4.2 Asymmetric cyclopropanation of styrene with an aryl trichlorodiazoacetate using **76** at low catalyst loadings



2.32 equiv. 1 equiv.

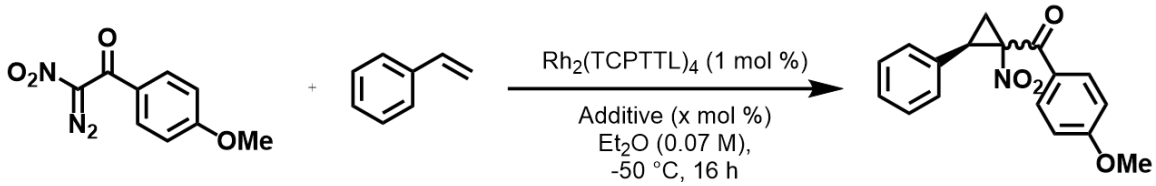
Entry	[Rh] loading %	Temp. °C	ee (%)
1	0.0025	25	97
2	0.0025	40	96
3	0.0025	60	96
4	0.001	60	94
5	0.00025	60	90
6	0.0001	60	81

the TPCP complexes, however, have been towards site-selective C-H functionalization reactions.

The control of the stereoselectivity is mostly dependent on steric factors that affect the axial site of the Rh(II,II) complex.[46, 47] However, this has mainly been accomplished through the development of chiral bridging ligands with large sterically hindering groups. Recent attempts at affecting the chiral pocket have led to a trend of using non-covalent interactions to either reduce conformational mobility, direct the substrates, or stabilize the carbene. This has been accomplished through hydrogen bonding,[202, 203] halogen bonding,[63, 91]chalcogen bonding,[108] and London dispersion forces.[204] Another method of perturbing the properties of the chiral pocket is through direct coordination at the axial sites. Axial ligand coordination is thought to slow catalysis by blocking the active sites of the catalyst, however, one axial site must be opened for catalysis to take place.[157] This would leave the other axial ligand at the distal rhodium to have electronic influence on the active Rh(II)-carbene. This influence and its role in asymmetric catalysis are not studied as bridging ligands in Rh(II,II) chemistry. The Charette lab has probed this influence in the cyclopropanation of acceptor/acceptor diazos with styrene (Table 4.3).[71, 129] With the cyclopropanation of α-nitro diazoacetates and styrene, the addition of nitrogenous LBs resulted in increased enantioselectivity, albeit with drops in diastereoselectivity and cyclopropane yields (Table 4.3, entries 1-3).[129] Additives that did not result in higher enantioselectivity maintained about the same yield, diastereoselectivity, and enantioselectivity (Table 4.3, entries 4-5). At higher temperatures, there is no difference in selectivity with or without additive, indicating that lower temperatures allow for association and full influence of the additive (Table 4.4, entries 6-7). Additives don't always result in an increase in enantioselectivity, however. In the same study, they also conducted cyclopropanations of styrene and methyl phenyldiazoacetate, a donor/acceptor diazo, and found that most additives either offered no change or decreased enantioselectivity (Table 4.4).[129]

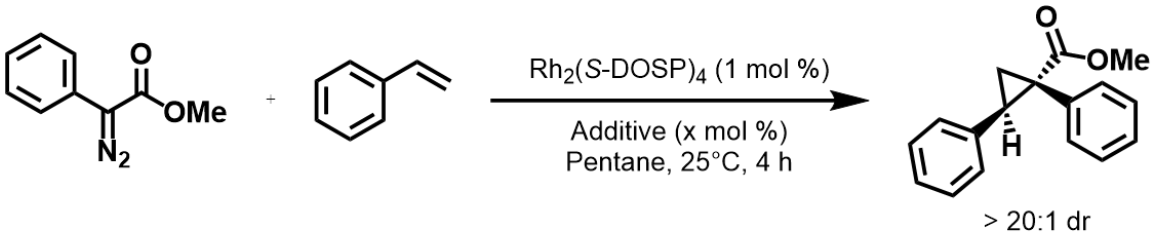
Indeed, elucidating the influence of the axial position on stereoselectivity is more nuanced than simply adding exogenous ligands. Previously, our group has used Rh(II,II) complexes with tethered, axially coordinated ligands (TACLs) to control the local concentration of the axially bound LB and more accurately assess its role in catalysis.[110, 136, 177] We have observed increased yields in cyclopropanation[110, 177] and Si–H insertion[136]

Table 4.3 Influence of nitrogenous Lewis base additives on the Rh(II,II)-catalyzed cyclopropanation of styrene and α-nitro diazoacetates



Entry	Additive (x)	Yield (%)	dr	er
1	None	80	49:1	27:1
2	DMAP (1)	78	32:1	39:1
3	Pyridine (1)	70	32:1	32:1
4	$TfNH_2$ (10)	85	49:1	28:1
5	$MsNH_2$ (10)	89	49:1	28:1
6[a]	None	68	16:1	14:1
7[a]	DMAP (1)	70	16:1	14:1

Table 4.4 Influence of nitrogenous Lewis base additives on the Rh(II,II)-catalyzed cyclopropanation of styrene and phenyl diazoacetates



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Entry	Additive (x)	Yield (%)	er
1	None	80	16:1
2	DMAP (1)	72	16:1
3	MeCN (10)	83	14:1
4	$TfNH_2$ (10)	88	8:1
5	$MsNH_2$ (10)	77	10:1
6	DMF (10)	86	13:1

reactions when using the TACLs complexes over untethered Rh(II,II) complexes with no axial tether. Changes in rate-determining steps are also possible when perturbing diazo substrate electronics. Herein, we report the development of Rh(II,II) complexes that incorporate TACLs onto chiral scaffolds. The influence of the axial tether's stereoelectronics on asymmetric catalysis was then probed.

4.4 Results and Discussion

4.4.1 Synthesis of Chiral Rh(II,II)-TACLs Complexes

Chiral heteroleptic Rh(II,II) complexes containing TACLs were synthesized using the carboxylate thiocarbamoyl benzoate (TCB) ligand template from our previously reported studies.[110] Phthalimide-protected amino acid derived chiral Rh(II,II) complexes were chosen as parent complexes for exchange with the tethered ligands due to their versatility in diazo-mediated cyclopropanation reactions and facile synthesis.[14] Specifically, Rh_2(*S*-PTTL)$_4$ has been widely studied and has previously shown success in asymmetric cyclopropanation reactions even when one of the chiral PTTL ligands was exchanged for an achiral ligand.[96] NTTL and PTPA were also attempted for added variety and the possibility for non-covalent interactions with the ligand π system. With this in mind, we proceeded to exchange the chiral TCB ligands onto the homoleptic ligands using our previously published conditions.[110] Attempts at exchanging the PhTCB ligand, **39**, onto PTTL were unsuccessful. However, exchange with the phenylalanine variant, Rh_2(*S*-PTPA)$_4$, furnished both mono and bis-substituted products by refluxing in DCE with base (Figure 4.2).

The pendant arm of the tether was modified to contain chiral centers that can aid in stereoinduction through non-covalent interactions and perturb the bridging ligand sphere. To this end, ligand **85** was synthesized through Mitsunobu coupling of (1*S*,2*R*)-2-amino-1,2-diphenylethan-1-ol **82** to aziridine **83**, followed by nucleophilic ring-opening with thiophenol to provide compound **84**. Finally, ring-opening of phthalic anhydride with compound **84** obtained the desired TCB ligand **85** (Figure 4.3a). Ligand **90** was also synthesized through an aziridine intermediate; however, a few steps were different. Synthesis of (S)-2-phenylaziridine **88** was achieved by first isolating an amino alcohol hydrogen sulfate **87** followed by nucleophilic ring-closing in basic conditions to arrive at

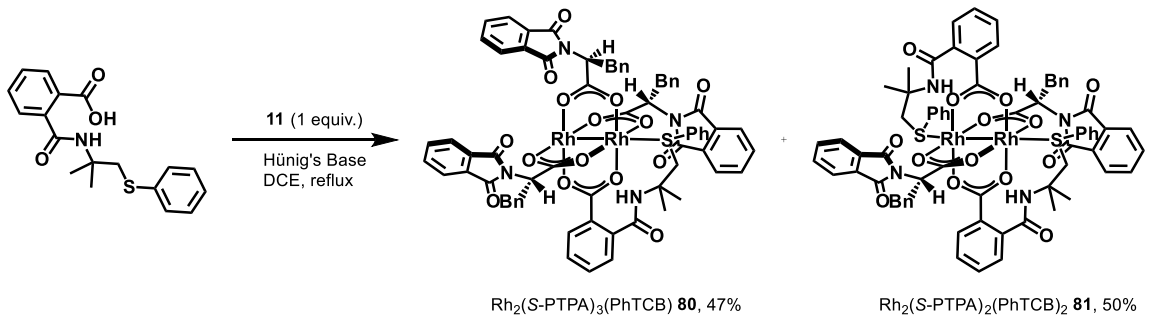


Figure 4.2 Synthesis of chiral Rh(II,II)-TACLs from Rh_2(*S*-PTPA)$_4$ and PhTCB ligands

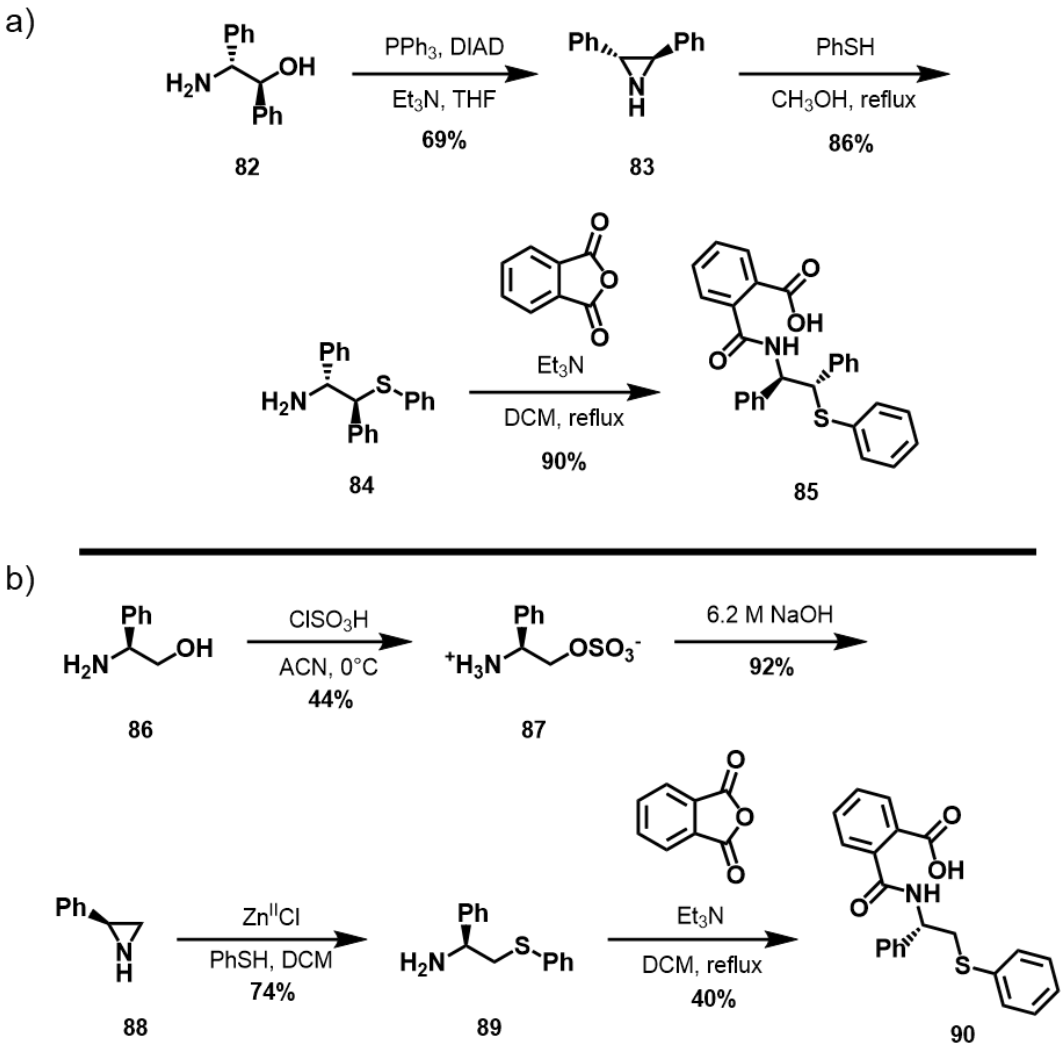


Figure 4.3 Synthesis of tethered, axially coordinated ligands with chiral pendant arms

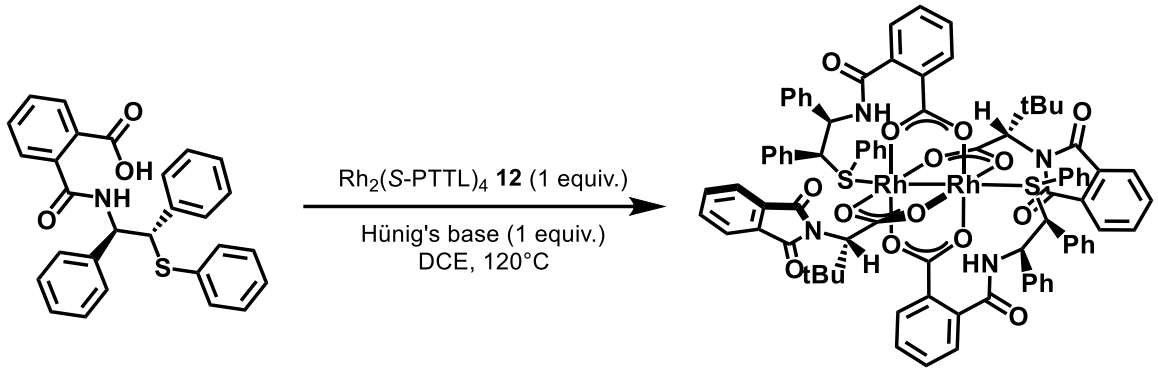
the subsequent aziridine **88**. Using a zinc(II) chloride mediated ring-opening of the aziridine with thiophenol resulted in formation of the aminothioether **89** which was then used to ring-open phthalic anhydride to arrive at ligand **90** (Figure 4.3b).

Attempts at exchanging the chiral tethered ligands were only successful with the Rh_2(*S*-PTTL)$_4$ complex. The parent homoleptic complex and chiral TCB ligands were stirred in a pressure tube with Hünig's base at 120°C in DCE overnight to furnish the bis-substituted species Rh_2(*S*-PTTL)$_2$(1*S*,2*R*-DPPhTCB)$_2$ **91** as the only product as a cis/trans mixture in a 10% yield (Figure 4.4**)**. The low yield for the bis complex could be a result of bulkiness of the chiral groups on the ligand. Low yields could also be due to a lack of the Thorpe-Ingold effect present in **39** from the gem-dimethyl groups. When ligand exchange with the glycine derived ligand **90** was attempted, we obtained the mono species, **92**, at an 11% yield as the only isolable product (Figure 4.5).

4.4.2 Asymmetric Cyclopropanation

The effect of the axial tether on enantioinduction was probed in the asymmetric cyclopropanation of styrene with EDA (Table 4.5). Cyclopropanation with **80** saw the enantioselectivity cut in half when compared to the Rh_2(*S*-PTPA)$_4$ parent complex at 0°C (Table 4.5, entries 1-2). Warming to room temperature did not exhibit a significant change in these results (Table 4.5, entries 3-4). The bis complex **81** gave essentially the same enantioselectivity as the mono species (Table 4.5, entry 5). Although enantioselectivity was not improved with the axial tether, diastereoselectivity for the reaction improved from 54:46 d.r. to 65:35 d.r. when using the bis-substituted **81**. Cyclopropanation with other phthalimide-derived homoleptic complexes did not show any vast changes in the stereoselectivity aside from the tetra-chlorinated Rh_2(TCPTPA)$_4$ **20**, which gave a 21% ee (Table 4.5, entries 6-8). When using the chiral TCB ligated **91**, a minor improvement in enantioselectivity was observed relative to the achiral PhTCB but a decrease compared to its homoleptic parent complex PTTL (Table 4.5, entry 9).

These results reaffirm the notion that asymmetric cyclopropanation of styrene with EDA using Rh(II,II) complexes proves to be a more difficult task than other diazos. To further explore the utility of axial tethers in asymmetric cyclopropanations, we applied our chiral Rh(II,II)-TACLs complexes with methyl phenyldiazoacetate. To this end, we first tested various chiral homoleptic Rh(II,II) complexes. Enantioselectivity for this cyclopropanation with Rh_2(*S*-PTTL)$_4$ was found to



1 equiv.

Rh_2(*S*-PTTL)$_2$(1*S*,2*R*-DPPhTCB)$_2$ **91**, 10%

Figure 4.4 Synthesis of the chiral Rh(II,II)-TACLs complex Rh_2(*S*-PTTL)$_2$(1*S*,2*R*-DPPhTCB)$_2$ **91**

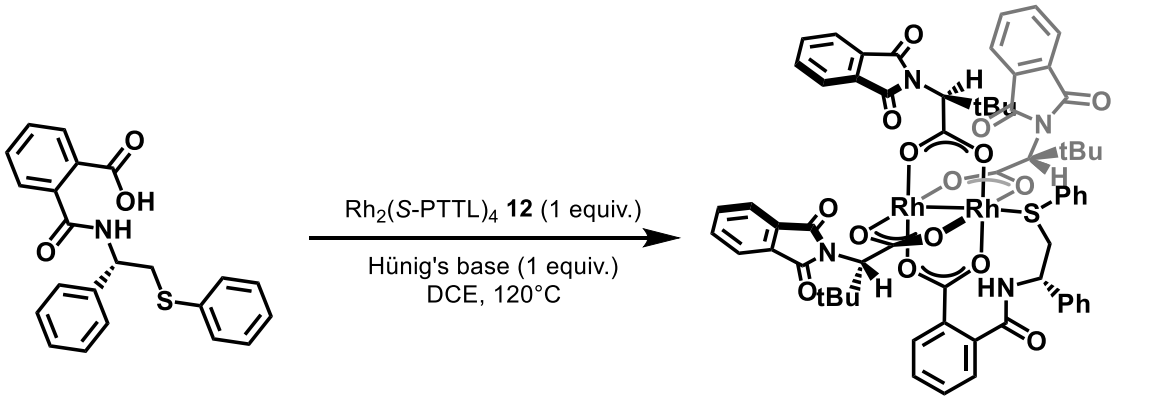
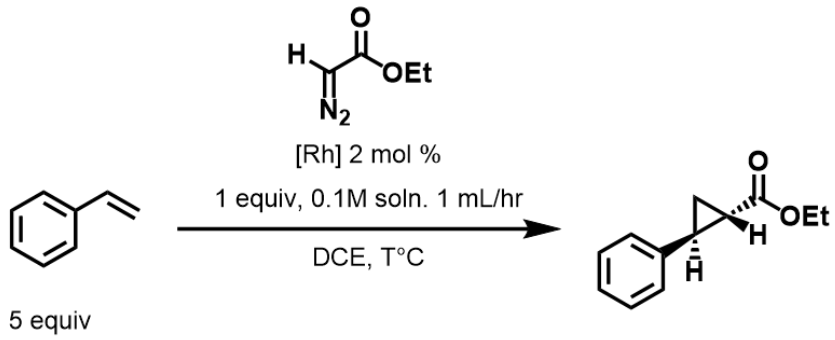


Figure 4.5 Synthesis of the chiral Rh(II,II)-TACLs complex Rh_2(*S*-PTTL)$_3$(1*S*-Ph-PhTCB) **92**

Table 4.5 Asymmetric cyclopropanation of styrene and EDA with chiral homoleptic Rh(II,II) complexes and chiral Rh(II,II)-TACLs complexes

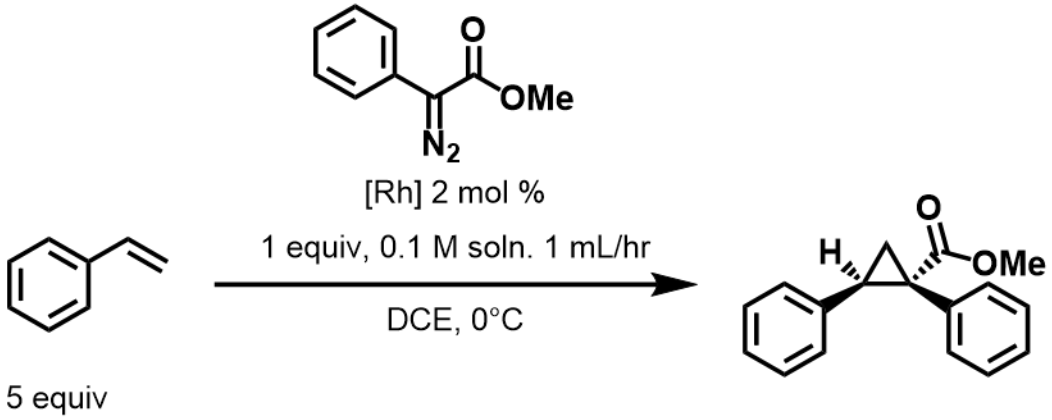


Entry	[Rh]	Temp. °C	Yield (%)	d.r	% ee
1	Rh_2(*S*-PTPA)$_4$ (**11**)	0	-	54:46	13
2	Rh_2(*S*-PTPA)$_3$(PhTCB) (**80**)	0	-	60:40	6
3	Rh_2(*S*-PTPA)$_4$ (**11**)	25	-	54:46	10
4	Rh_2(*S*-PTPA)$_3$(PhTCB) (**80**)	25	-	60:40	6
5	Rh_2(*S*-PTPA)$_2$(PhTCB)$_2$ (**81**)	25	-	65:45	7
6	Rh_2(TCPTPA)$_4$ (**20**)	0	-	54:46	21
7	Rh_2(*S*-PTTL)$_4$ (**12**)	0	84	53:47	13
8	Rh_2(*S*-NTTL)$_4$ (**14**)	0	73	54:46	8
9	Rh_2(*S*-PTTL)$_2$(1*S*,2*R*-DPPhTCB)$_2$ (**91**)	0	38	57:43	9

be in agreement with previous attempts in the literature[82, 205] with 32% ee observed at 0°C and 1 mL/hr addition rate of diazo (Table 4.6, entry 1). Cyclopropanation with the naphthyl analog, Rh_2(*S*-NTTL)$_4$, in the same conditions gave 42% ee, a marked improvement over previous attempts at room temperature in 2,2-DMB (Table 4.6, entry 2).[82, 205]. The phenylalanine derived complex, Rh_2(*S*-PTPA)$_4$ was also tested and found to exhibit the same enantioselectivity as the Rh_2(*S*-NTTL)$_4$ catalyst, 42 % ee (Table 4.6, entry 3). Cyclopropane yields for the homoleptic catalysts were low to moderate for all the homoleptic complexes tested. Similar to the EDA cyclopropanation, the PhTCB ligated **81** resulted in a decrease in % ee (Table 4.6, entry4). However, enantioinduction was improved to 46% with the Rh_2(*S*-PTTL)$_2$(1*S*,2*R*-DPPhTCB)$_2$ complex as a mixture of cis and trans isomers (Table 4.6, entry 5). Yields for the bis-TACLs complex were lower than the corresponding homoleptic species at 12%. This was most likely due to inhibition of both active sites, requiring a dissociation event to occur. The phenylglycinol-derived mono species, **92**, exhibited the same enantioselectivity as the PTTL parent complex and with increased cyclopropane yields (Table 4.6, entry 6).

Predictive models for the observed enantioinduction of Rh(II,II)-phthalimide complexes have primarily focused on the orientations of the sterically bulky groups of the chiral ligands. An early model put forth by Hashimoto and co-workers based on the x-ray structure of Rh_2(*S*-PTPA)$_4$ proposed that the bulky groups are aligned in an “up, up, down, down” C_2 configuration leading to two equivalent faces (one at each rhodium). Each of these faces influence the formation of the cyclopropane by blocking certain attack trajectories of the substrate and directing their approach.[65, 67] Later, Fox and co-workers reported the x-ray structure of Rh_2(*S*-PTTL)$_4$ and found that the sterically bulky groups adopted an “all-up” C_4 configuration. They proposed that the bulky *tert*-butyl groups at one face block access to the axial site and allow all enantioinduction to occur at the phthalimide occupied face. This theory, however, is not entirely accurate as other groups have shown that coordination at the *tert*-butyl face still occurs.[82] Without a crystal structure or computational results, a model for the improvements observed with the chiral TACLs complexes cannot be accurately made. However, we theorize that interactions at the axial site could involve π-π interactions on the ligand scaffold that could aid in creating a chiral environment for the substrates. With the bis-substituted complex, Rh_2(*S*-PTTL)$_2$(1*S*,2*R*-DPPhTCB)$_2$, one of the thioether ligands must be dissociated for catalysis to occur. Due to the axial ligand being tethered to the bridging ligand, and possible π-π interactions from

Table 4.6 Asymmetric cyclopropanation of styrene and methyl phenyldiazoacetate with chiral homoleptic Rh(II,II) complexes and chiral Rh(II,II)-TACLs complexes



Entry	[Rh]	Yield (%)	% ee
1	Rh_2(*S*-PTTL)$_4$ (**12**)	19	32
2	Rh_2(*S*-NTTL)$_4$ (**14**)	31	42
3	Rh_2(*S*-PTPA)$_4$ (**11**)	35	42
4	Rh_2(*S*-PTPA)$_2$(PhTCB)$_2$ (**81**)	-	32
5	Rh_2(*S*-PTTL)$_2$(1*S*,2*R*-DPPhTCB)$_2$ (**91**)	12	46
6	Rh_2(*S*-PTTL)$_2$(1*S*-Ph-PhTCB)$_2$ (**92**)	33	31

the aryl rings, it will likely stay in the proximity of the axial site and affect the chiral pocket. This would then influence the approach of the alkene substrate, leading to enhanced enantioselectivity.

4.5 Conclusion

In conclusion, we have developed chiral Rh(II) TACLs complexes that give improved enantioselectivity relative to its parent complex, $Rh_2(PTTL)_4$. A combination of steric factors and non-covalent interactions may be the deciding factors in the increase of selectivity. This is a result that expands the methods in which enantioselectivity can be achieved to include tethered, axial ligands. More examples of such heteroleptic complexes are currently being explored in our lab and will be reported in due course.

4.6 Experimental Procedures

4.6.1 General Considerations

Unless otherwise noted, all reagents were purchased and used as received from the manufacturer without further purification. Compounds **83** and **84** were synthesized via an established literature procedure.[206] Compounds **87**, **88**, and **89** were also synthesized according to literature procedures.[158, 207] Methyl phenyl diazoacetate was prepared from benzylic acid according to established procedures.[189] Hexanes, CH_2Cl_2 (DCM), tetrahydrofuran (THF), and acetonitrile (ACN) were dried with columns packed with alumina using an Inert® PureSolv Micro Solvent Purification System and stored over molecular sieves. Reactions were monitored using thin layer chromatography (TLC) on Sorbent Technologies Silica XG TLC Plates. Ligands were purified with column chromatography using 60 Å, 40-63 μm silica from Sorbent Technologies. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury Vx 300 MHz or Bruker AVANCE NEO 500 MHz spectrometers. All NMR chemical shifts are reported in ppm on the δ scale. Signals were referenced by residual solvent signal for ^1H NMR ($CHCl_3$ = 7.26 ppm, acetone = 2.05 ppm, acetonitrile = 1.94 ppm) and ^{13}C NMR ($CHCl_3$ = 77.16 ppm, acetone = 29.84 ppm, acetonitrile = 1.32 ppm. The mass spectra for all compounds, unless otherwise specified, were obtained using an AccuTOF Mass spectrometer equipped with a DART ionization apparatus.

4.6.2 Ligand Synthesis

2-(((1*S*,2*R*)-1,2-diphenyl-2-(phenylthio)ethyl)carbamoyl)benzoic acid (85)

To a stirring solution of phthalic anhydride (194 mg, 1.31 mmol) in dry CH_2Cl_2 (8 mL) was added a solution of (1*S*,2*R*)-1,2-diphenyl-2-(phenylthio)ethan-1-amine **84** (400 mg, 1.31) in dry CH_2Cl_2 (8 mL). Triethylamine (18 µL, 10 mol%) was added and the mixture was stirred at reflux for 41 hours. Reaction was cooled to room temperature and a 20 mL portion of DI water was added. The resulting solution was extracted 3 X 70 mL EtOAc. The organic portions were combined, dried over anhydrous Na_2SO_4, then concentrated *in vacuo* to a white solid without further purification (535 mg, 1.18 mmol, 90% yield). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.04 (s, 1H, Ar–H), 7.78 (d, 1H, Ar–H), 7.58-7.08 (m, 17H, Ar–H), 6.93 (d, 1H, Ar–H), 5.72 (t, 1H, N–C*H*–C), 4.94 (d, 1H, –C*H*–S); ^{13}C NMR (125 MHz, acetone-d_6) δ 168.7, 167.8, 140.8, 139.1, 135.7, 133.0, 132.1, 131.2, 130.8, 130.2, 129.7, 129.6, 129.1, 128.9, 128.9, 128.6, 128.3, 128.1, 127.9, 59.6, 58.4; HRMS (EI) *m/z*: calcd. for $C_{28}H_{24}NO_3S$ ($[M+H]^+$) 454.1477, found 454.1523.

(S)-2-((1-phenyl-2-(phenylthio)ethyl)carbamoyl)benzoic acid (90)

To a stirring solution of phthalic anhydride (94 mg, 0.635 mmol) in dry CH_2Cl_2 (3 mL) was added a solution of (S)-1-phenyl-2-(phenylthio)ethan-1-amine **89** (145 mg, 0.632 mmol) in dry CH_2Cl_2 (5 mL). Triethylamine (9 µL, 10%) was added and the mixture was stirred at reflux for 20 hours. The reaction was cooled to room temperature and a 20 mL portion of DI water was added. The resulting solution was extracted 3 X 25 mL EtOAc. The organic portions were combined, dried over anhydrous Na_2SO_4, then concentrated *in vacuo* to a yellow residue. Recrystallized by dissolving in hot EtOAc and adding hexanes then placing in a freezer. Product obtained as a white solid (93.5 mg, 0.248 mmol, 40% yield). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.86 (s, 1H, Ar–H), 7.52-7.41 (m, 7H, Ar–H), 7.32-7.21 (m, 7H, Ar–H), 4.77 (dd, *J* = 2.53, 1H, Ph–C*H*-), 4.00 (dd, *J* = 7.31, 1H, –C*H*H–), 3.86 (dd, *J* = 4.92, 1H, –CH*H*–); ^{13}C NMR (125 MHz, acetone-d_6) δ 169.9, 167.9, 140.9, 139.3, 137.1, 135.9, 132.2, 132.0, 131.3, 130.9, 130.8, 130.2, 129.9, 129.8, 129.7, 129.3, 129.2, 129.2, 129.1, 128.6, 128.3, 127.6, 127.3, 127.0, 126.2, 51.8, 45.5; HRMS (EI) *m/z*: calcd. for $C_{22}H_{20}NO_3S$ ($[M+H]^+$) 378.1158, found 378.1148.

4.6.3 Rh(II,II) Complex Synthesis

To a stirring solution of Rh_2(*S*-PTPA)$_4$ (50 mg, 0.032 mmol, 1 equiv.) in 10 mL dry DCE was added **39** (12 mg, 0.032 mmol, 1 equiv.) in a Schlenk flask under Argon. Hünig's base (6 µL, 0.032 mmol, 1 equiv.) was then added. The mixture was then heated to reflux and stirred for 3 hours. Upon completion, the reaction solution is concentrated in vacuo and purified via column chromatography (5% MeOH in DCM). The bis isomer, **81**, eluted first followed by the mono species, **80**.

Rh_2(*S*-PTPA)$_3$(PhTCB) (80)

Isolated a blue-green solid (28 mg, 0.018 mmol, 57% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.77, 1H), 7.76-7.43 (m, 16H), 7.33 (dd, *J* = 7.50, 1H), 7.22-6.98 (m, 17H), 6.92-6.85 (m, 1H), 5.94 (s, 1H), 5.20-5.02 (m, 3H), 3.57-3.21 (m, 4H), 1.65 (s, 3H), 1.57 (s, 3H).

Rh_2(*S*-PTPA)$_2$(PhTCB)$_2$ (81)

Isolated as reddish-purple solid (12 mg, 0.008 mmol, 50% yield). ^{1}H NMR (500 MHz, CD_3CN): δ 7.72 (dd, *J* = 3.37, 5H), 7.62-7.57 (m, 8H), 7.50 (d, *J* = 7.14, 4H), 7.41 (t, *J* = 5.93, 2H), 7.29 (d, *J* = 8.09, 2H), 7.22 (t, *J* = 7.14, 4H), 7.16 (t, *J* = 8.49, 2H), 7.08-7.02 (m, 6H), 7.01-6.96 (m, 4H), 6.28 (s, 2H), 4.94 (dd, *J* = 4.67, 2H), 3.42 (dd, *J* = 4.41, 2H), 3.08 (dd, *J* = 12.26, 2H), 1.56 (s, 6H), 1.45 (s, 6H).

Rh_2(*S*-PTTL)$_2$(1*S*,2*R*-DPPhTCB)$_2$ (91)

To a stirring solution of Rh_2(*S*-PTTL)$_4$ (100 mg, 0.08 mmol, 1 equiv.) in 10 mL dry DCE was added **85** (40 mg, 0.088 mmol, 1 equiv.) in a Schlenk tube with a Young's tap. Hünig's base (15.4 µL, 0.088 mmol) was then added. The tube was then sealed, and the mixture heated to 120°C and stirred overnight. The resulting solution was concentrated *in vacuo* and the products separated via a Biotage Selekt automated column using a EtOAc:hexanes gradient on a 10 g Biotage Sfär column. First the Rh_2(*S*-PTTL)$_4$ is separated using 1:1 hexane/EtOAc as the eluent. This is then followed by 9:1 toluene/ACN as the eluent to afford the bis-substituted complex **91** as a mixture of *cis* and *trans* isomers. Blue-green solid (13 mg, 0.008 mmol, 10% yield). ^{1}H NMR (500 MHz, CD_3CN): δ 7.70 (s, 9H, Ar–H), 7.68 (d, 5H, Ar–H), 7.33 (d, 6H, Ar–H), 7.20 (m, 15H, Ar–H), 7.08 (t, 3H, Ar–H), 6.86 (t, 8H, Ar–H), 6.56 (d, 1H, Ar–H), 4.92 (d, 2H, N–C*H*–C), 4.56 (d, 2H, –C*H*–S), 4.40 (s, 2H, NH), 4.22 (t, 2H, (CO_2)C*H*–N), 0.83 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (125 MHz,

$CDCl_3$): δ 168.0, 138.2, 133.8, 132.3, 129.9, 129.5, 128.9, 128.4, 128.3, 128.3, 128.1, 127.8, 127.8, 123.5, 65.8, 61.8, 58.4, 35.6, 29.0, 28.2; HRMS (EI) *m/z*: calcd. for $C_{84}H_{73}N_4O_{14}Rh_2S_2$ ([M+H]$^+$) 1631.2675, found 1631.2770.

Rh_2(*S*-PTTL)$_3$(*S*-PPhTCB) (92)

To a stirring solution of Rh_2(*S*-PTTL)$_4$ (564 mg, 0.41mmol, 1 equiv.) in 50 mL dry DCE was added **90** (189 mg, 0.5 mmol) in a Schlenk tube with a Young's tap. Hünig's base (87 µL, 0.5 mmol) was then added. The tube was then sealed, and the mixture heated to 120°C and stirred overnight. The resulting solution was concentrated *in vacuo* and the products separated via a Biotage Selekt automated column using a EtOAc:hexanes gradient on a 25 g Biotage Sfär column. The mono-substituted complex, **92**, was isolated as a Blue-green solid (61 mg, 0.045 mmol, 11% yield). ^{1}H NMR (500 MHz, CD_3CN): δ 8.58-8.54 (m, 1H, Ar–H), 8.10-8.04 (m, 1H, Ar–H), 7.84 (dd, *J* = 3.88, 2H, Ar–H), 7.87-7.47 (m, 14H, Ar–H), 7.36 (d, *J* = 7.91, 1H, Ar–H), 7.18-7.01 (m, 3H, Ar–H), 6.81-6.70 (m, 3H, Ar–H), 6.49 (d, *J* = 6.12, 2H, Ar–H), 6.03 (dt, *J* = 7.5, 3H, Ar–H), 5.76 (d, *J* = 7.76, 2H, Ar–H), 5.07 (s,1H, (CO_2)C*H*–N), 4.67 (s, 1H, (CO_2)C*H*–N), 4.47 (s, 1H, (CO_2)C*H*–N), 4.16 (dd, *J* = 9.45, 1H, N–C*H*–C), 3.59 (d, *J* = 5.11, 1H, CH–C*H*H–S), 3.11 (dt, *J* = 5.13, 1H, CH–CH*H*–S), 1.27 (s, 9H, C(CH_3)$_3$), 1.03 (s, 9H, C(CH_3)$_3$), 0.72 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.6, 188.0, 187.0, 186.5, 168.3, 168.1, 165.4, 139.3, 136.1, 134.0, 133.7, 133.1, 132.9, 132.6, 132.2, 132.0, 131.8, 130.5, 130.1, 128.4, 128.0, 127.7, 127.6, 127.3, 126.8, 126.7, 125.9, 124.9, 123.4, 123.2, 63.0, 62.6, 60.6, 58.7, 41.5, 36.2, 35.2, 34.5, 28.8, 28.2, 28.1, 28.0, 27.9.

4.6.4 Asymmetric Cyclopropanation

Under an atmosphere of argon, a 25 mL Schlenk flask equipped with a magnetic stir bar was flame dried and charged with styrene (0.845 mmol, 5 equiv), Rh(II,II) complex (2 mol%), and DCE (0.5 mL). The solution was then cooled to 0°C or maintained at room temperature. This is followed by slow addition of methyl phenyldiazoacetate or EDA (0.17 mmol, 1 equiv) as a 0.1 M solution in DCE by syringe pump (1 mL/hr). After addition was complete, the reaction solution was filtered through 1.5-inch silica plug and eluted with 4 mL DCM. The eluent was then concentrated *in vacuo* with a rotary evaporator. Yields were calculated by ^{1}H NMR using mesitylene as an internal standard. Normalized integration of the methyl protons of mesitylene (2.26 ppm) was compared to the integration of the

diastereotopic proton of the methylene unit of the cyclopropane. Enantioselectivity was determined by chiral HPLC analysis. Chiral HPLC analysis was performed on a Shimadzu LC-2030 Prominence-I instrument using a Chiralcel OJ-H column with a flow rate of 1 mL/min and 2% IPA/Hexanes mobile phase.[205]

Chapter 5 Conclusions

The work presented herein outlines our efforts towards elucidating the influence of axial coordination in Rh(II,II) catalyzed cyclopropanation reactions. This was accomplished by utilizing ligands that tether the axial site to a bridging ligand site to better control coordination and more accurately assess the influence on the catalyst. In Chapter 2, the synthesis and characterization of Rh(II,II)-TACLs complexes were discussed. Thiocarbamoylbenzoate and thiooxazolidinone ligands were successfully synthesized and ligated onto $Rh_2(OAc)_4$ to furnish mono and bis-substituted Rh(II,II)-TACLs complexes. These complexes demonstrated increased yields in the cyclopropanation of EDA when compared to conventional Rh(II,II) catalysts. Structural studies indicated that some of the tethered ligands seem to exist in a fluxional state in regard to their coordination to the axial site. Electronic and computational studies revealed that the axial coordination perturbs the HOMO of the Rh(II,II)-carbene species.

In Chapter 3, Hammett correlation experiments were conducted to determine the influence the tethered ligands have on the chemoselectivity of Rh(II,II)-catalyzed cyclopropanation reactions. It was observed that the changes to the axial position have a smaller effect on reaction sensitivity to substrate changes than the bridging position. Interestingly, when the Hammett parameters were applied to the aryl diazoacetates, a non-linear downward deviation was observed in the Hammett plot. We theorized that this could be the result of a change in the rate-determining step.

Finally, Chapter 4 highlighted our efforts to develop chiral Rh(II,II) complexes that contain TACLs and apply them towards asymmetric cyclopropanation reactions. Chiral Rh(II,II) complexes were successfully synthesized with achiral and chiral TACLs ligands. Unfortunately, catalysis with the achiral TACLs ligated complexes exhibited a decrease in enantioselectivity for the EDA reactions. However, diastereoselectivity seemed to improve when using the bis-substituted TACLs catalysts. When applied to the cyclopropanation with methyl phenyldiazoacetate, the chiral TACLs complexes increased the enantioselectivity relative to the homoleptic parent complexes. It's theorized that this improvement is the result of steric and non-covalent interactions occurring at a closer proximity to the active site. These interactions help to direct incoming substrates and stabilize the carbene intermediate.

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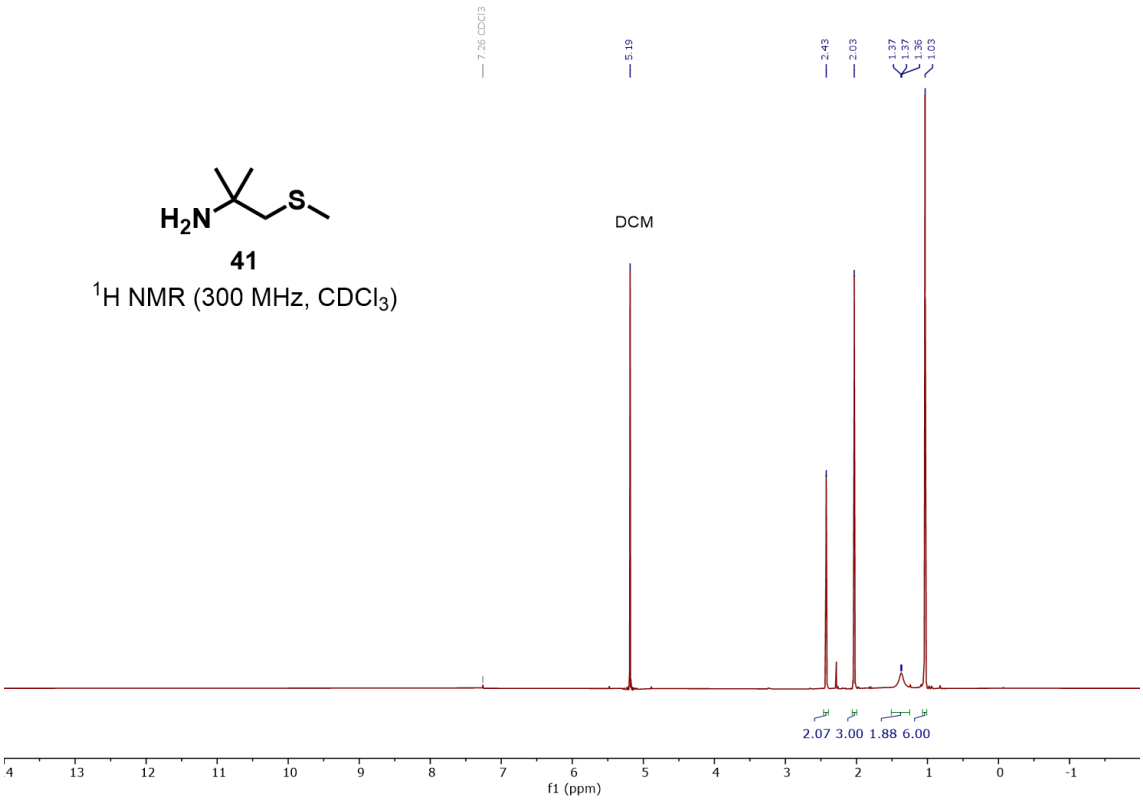
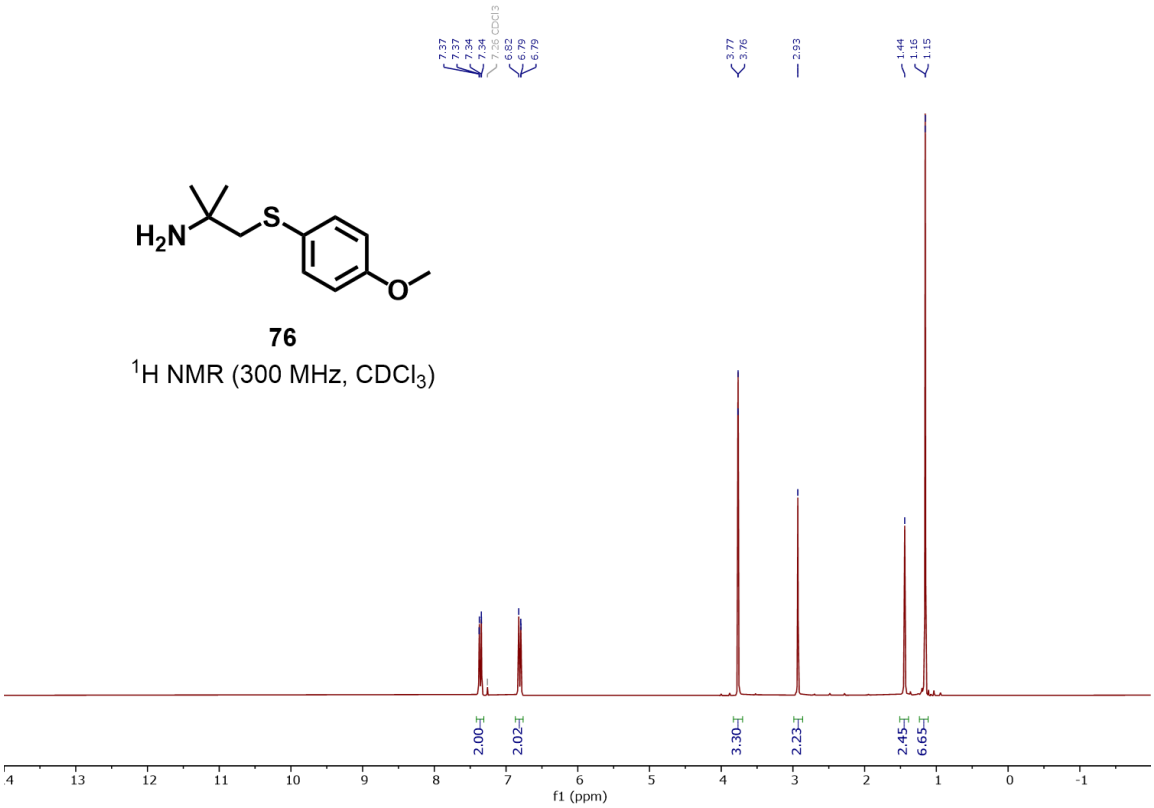
Appendix



41

^{1}H NMR (300 MHz, $CDCl_3$)

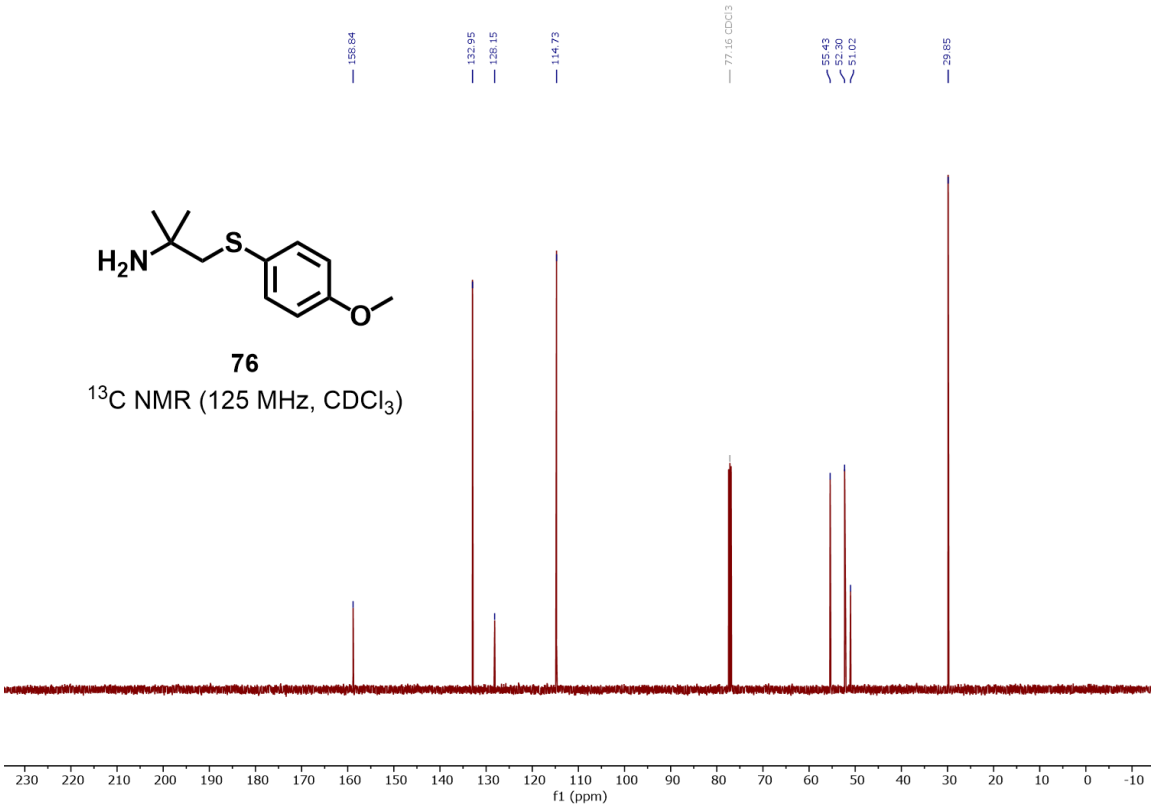
S 1 ^{1}H NMR spectrum of compound **41**



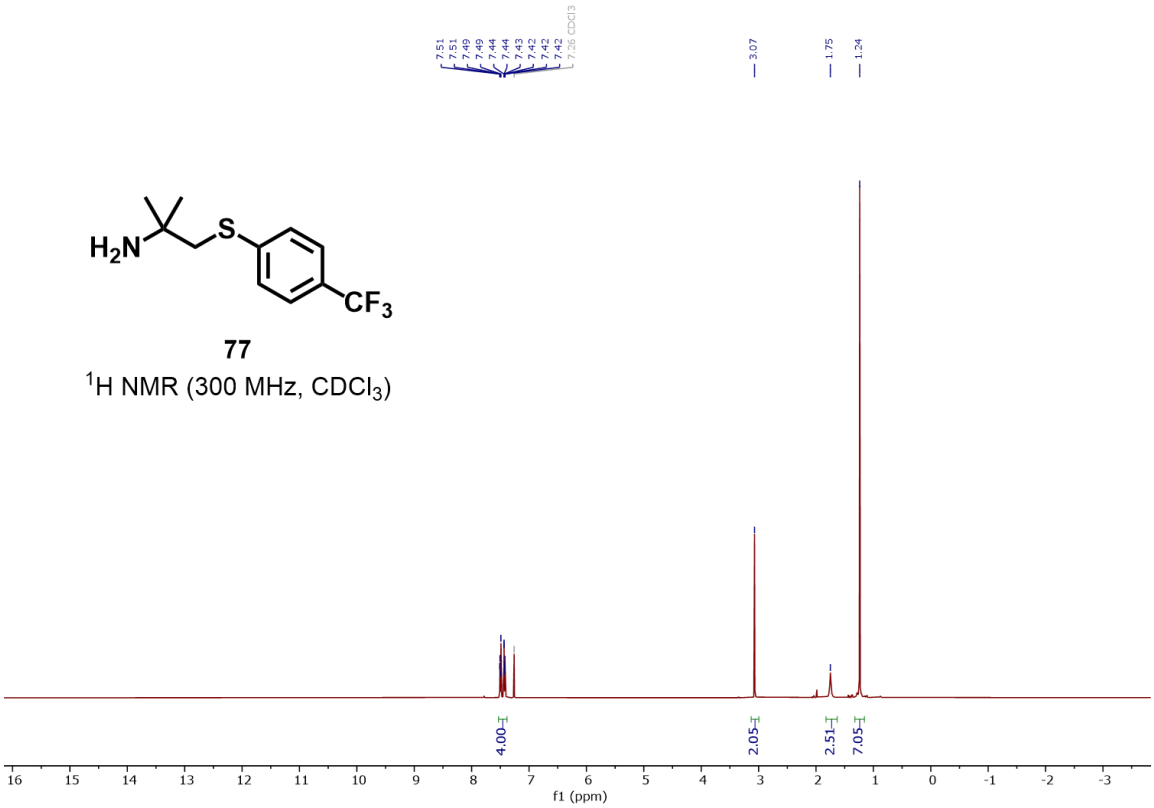
76

^{1}H NMR (300 MHz, $CDCl_3$)

S 2 ^{1}H NMR spectrum of compound **76**



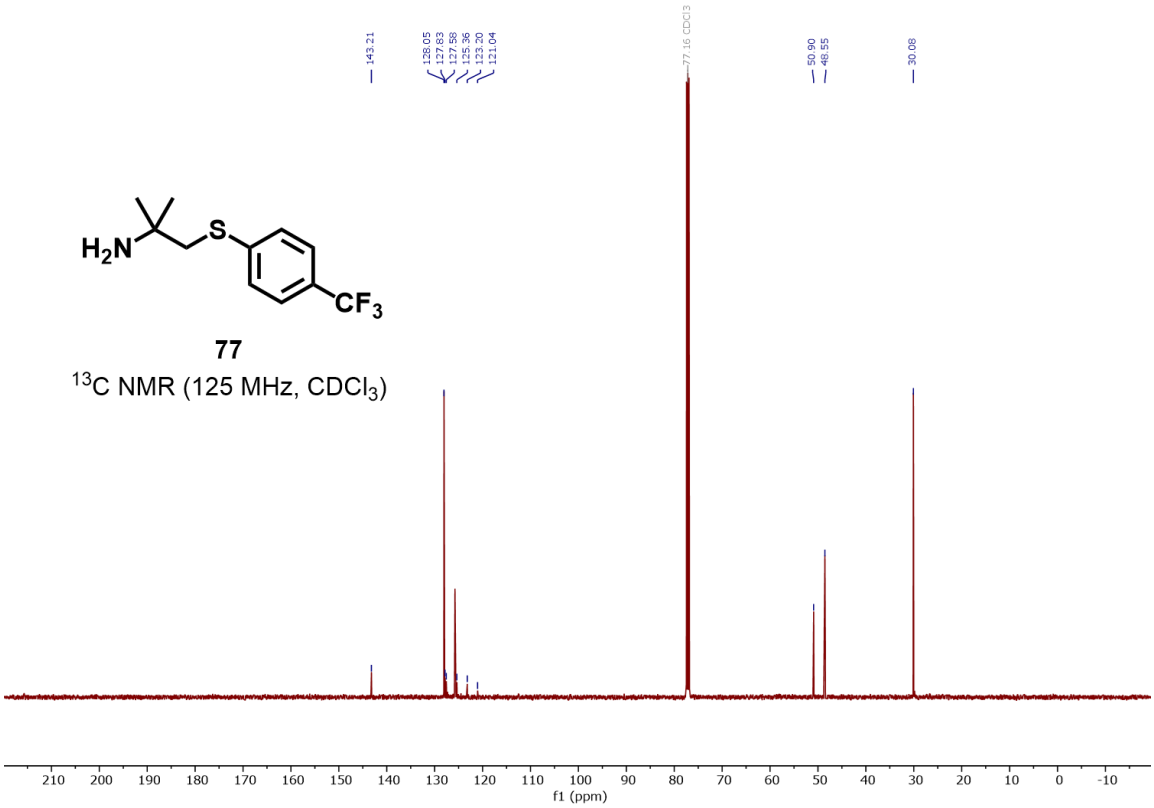
S 3 ^{13}C NMR spectrum of compound **76**



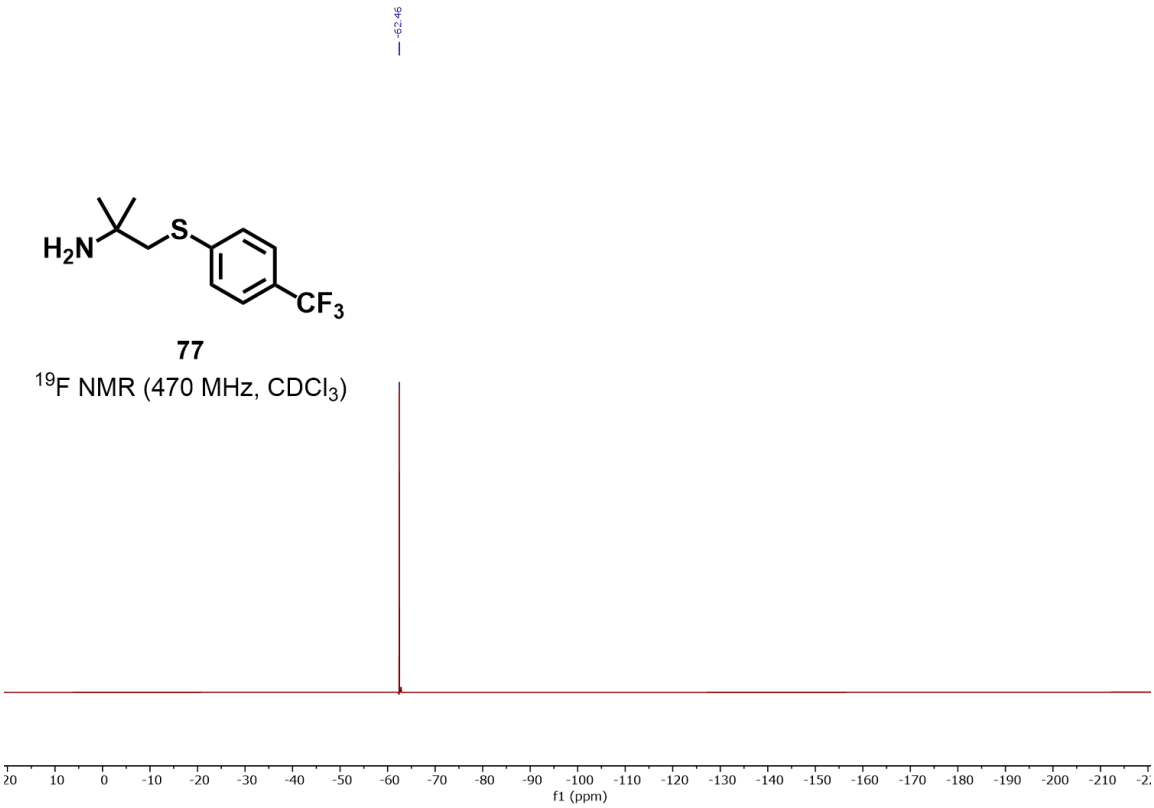
77

^{1}H NMR (300 MHz, $CDCl_3$)

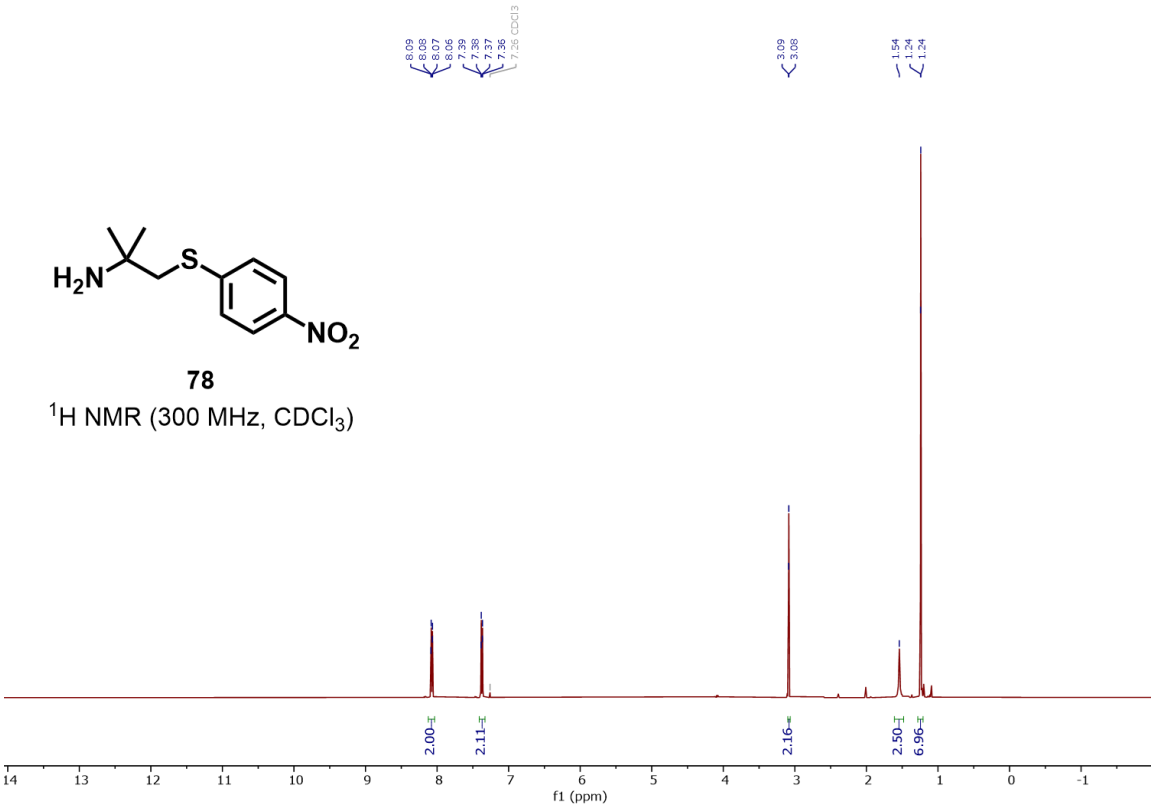
S 4 ^{1}H NMR spectrum of compound **77**



S 5 ^{13}C NMR spectrum of compound **77**



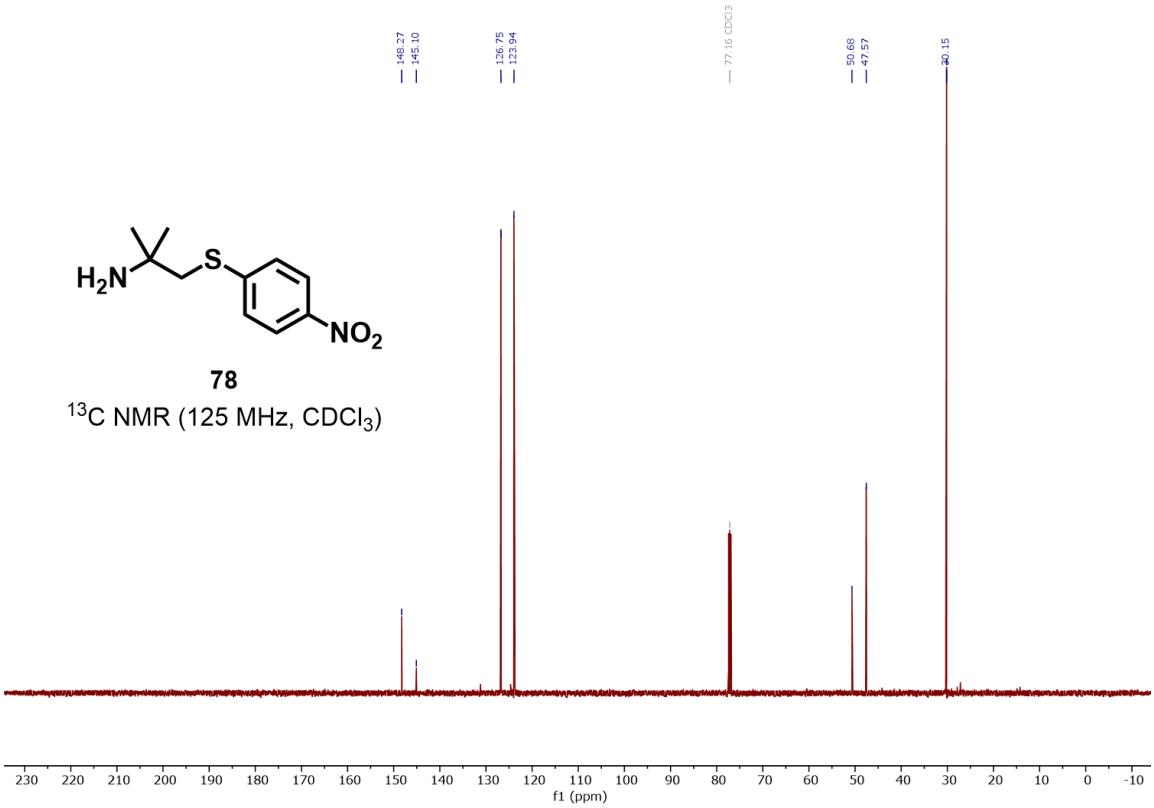
S 6 ^{19}F NMR spectrum of compound **77**



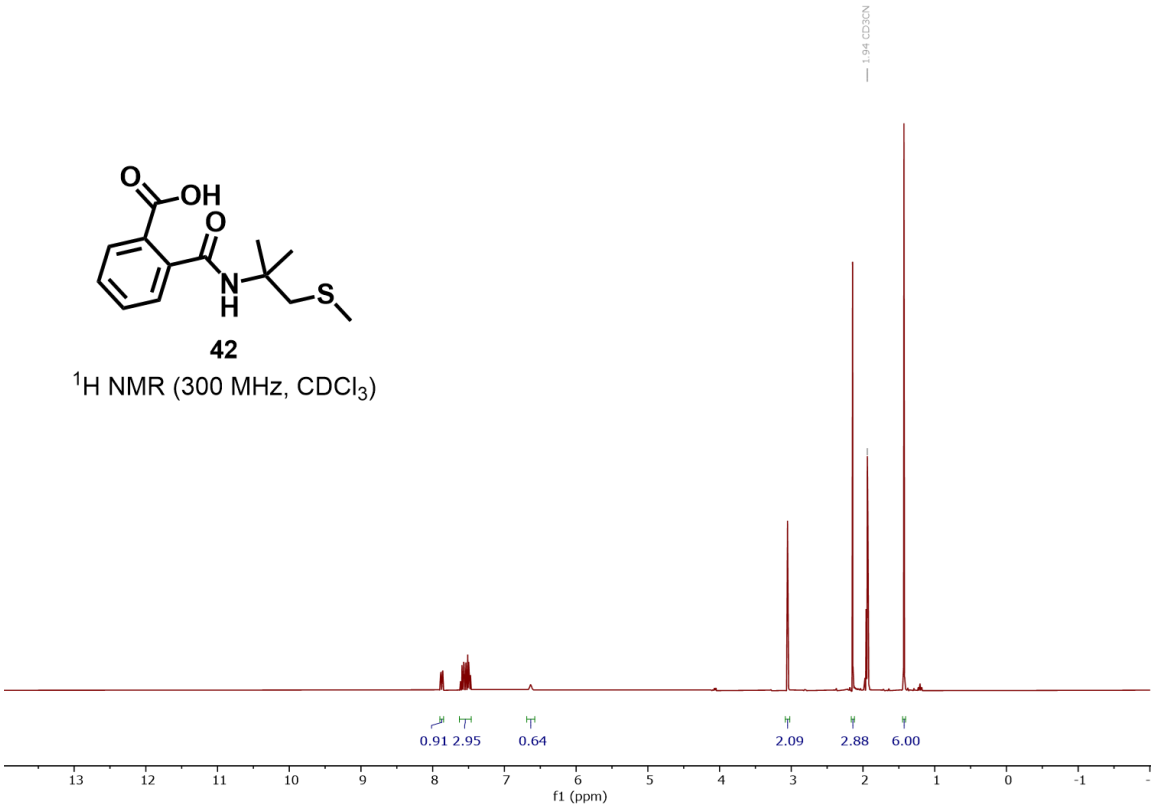
78

^{1}H NMR (300 MHz, $CDCl_3$)

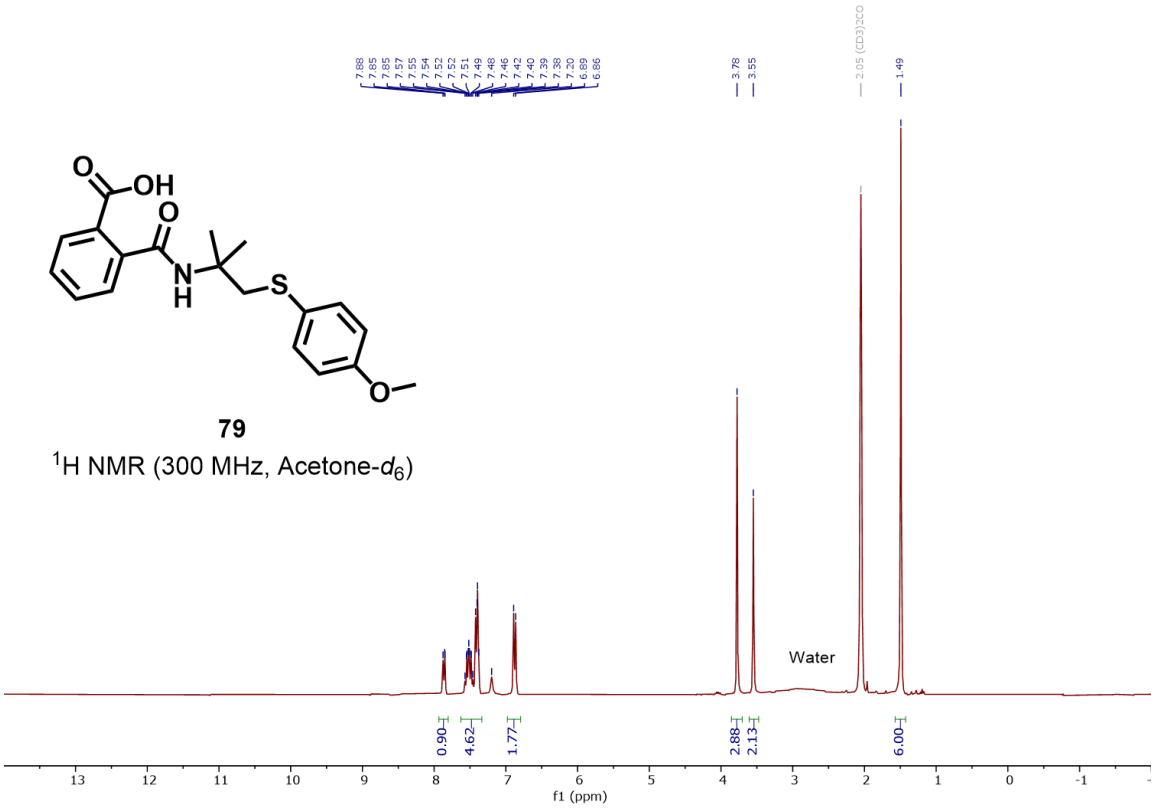
S 7 ^{1}H NMR spectrum of compound **78**



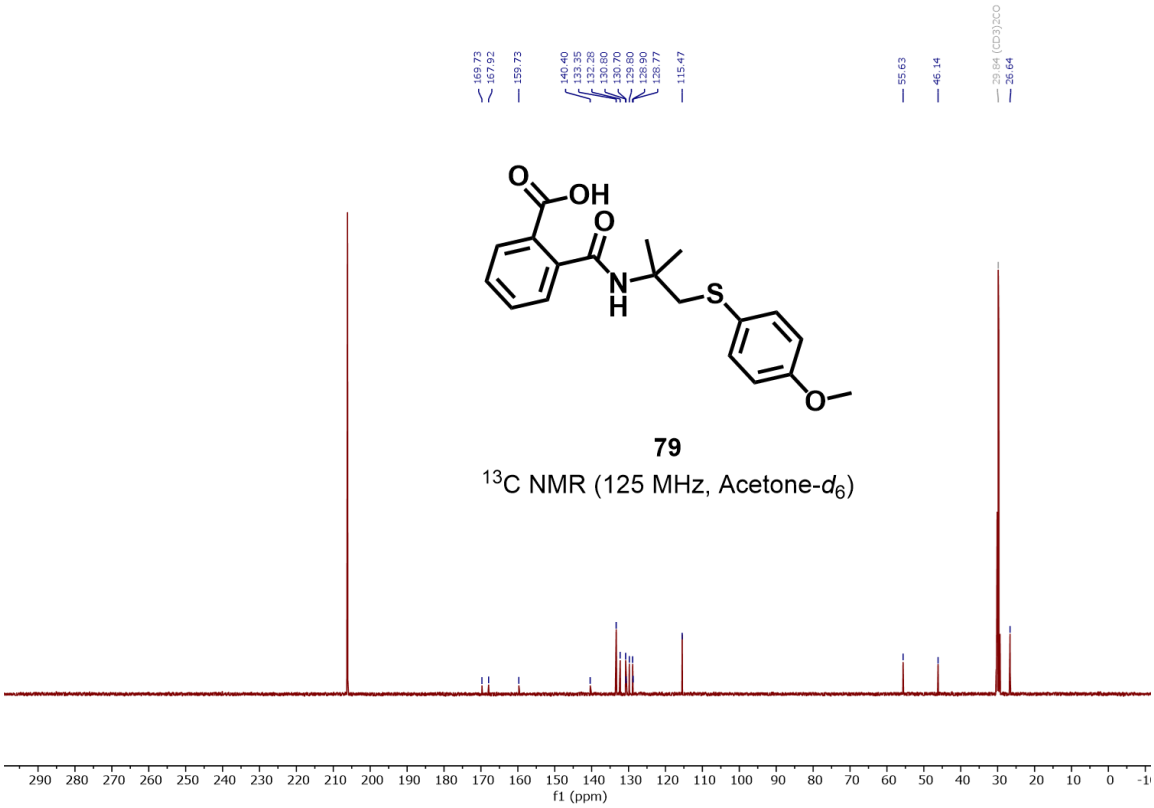
S 8 ^{13}C NMR spectrum of compound **78**



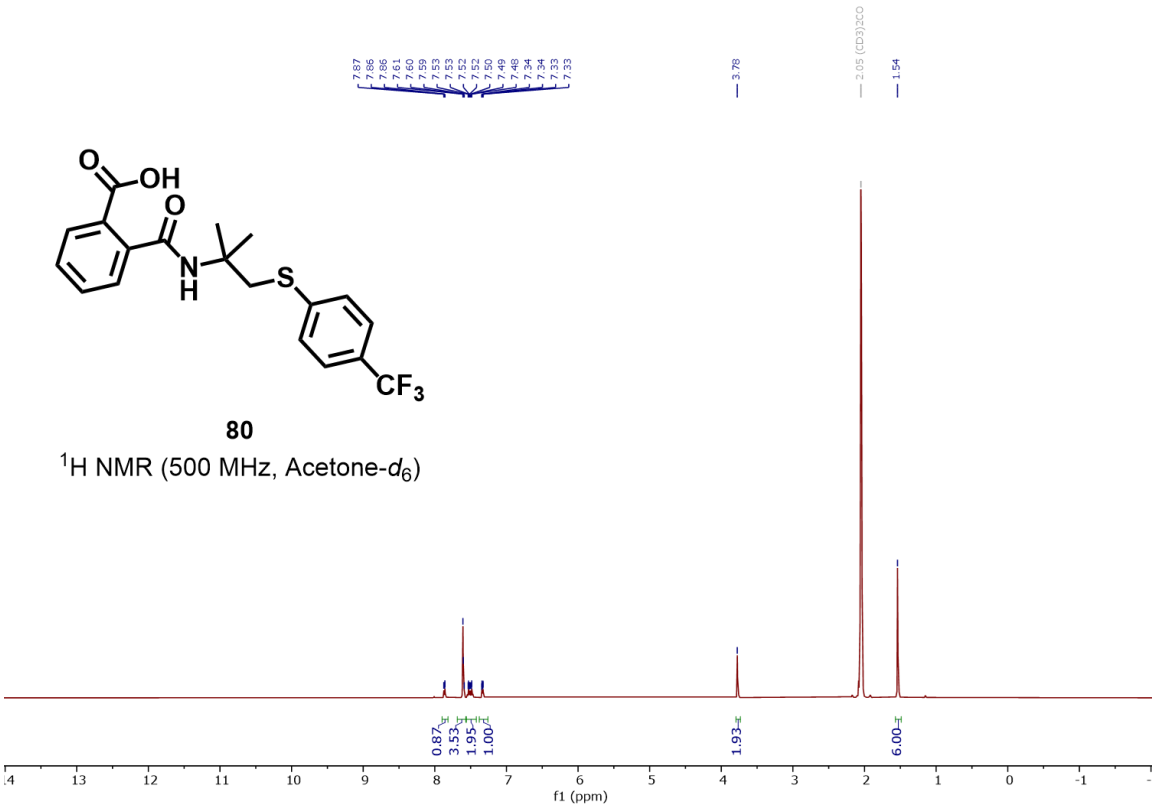
S 9 ^{1}H NMR spectrum of compound **42**



S 10 ^{1}H NMR spectrum of compound **79**



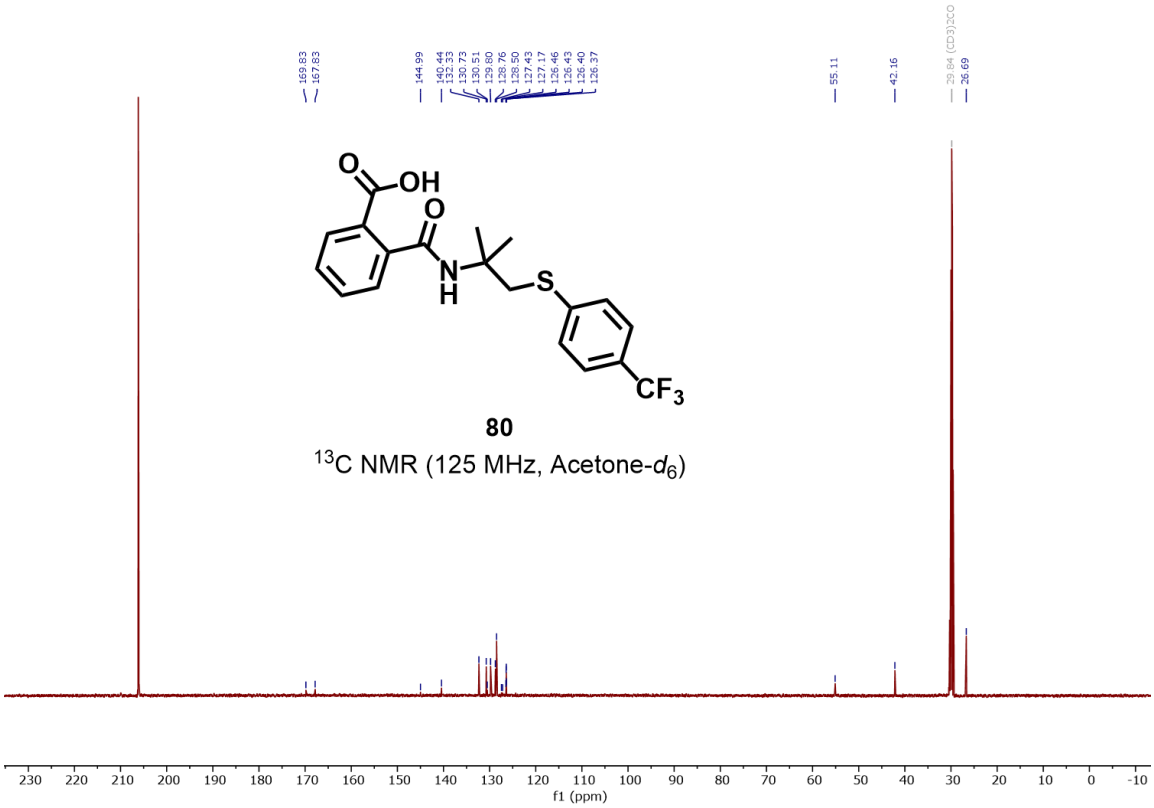
S 11 ^{13}C NMR spectrum of compound **79**



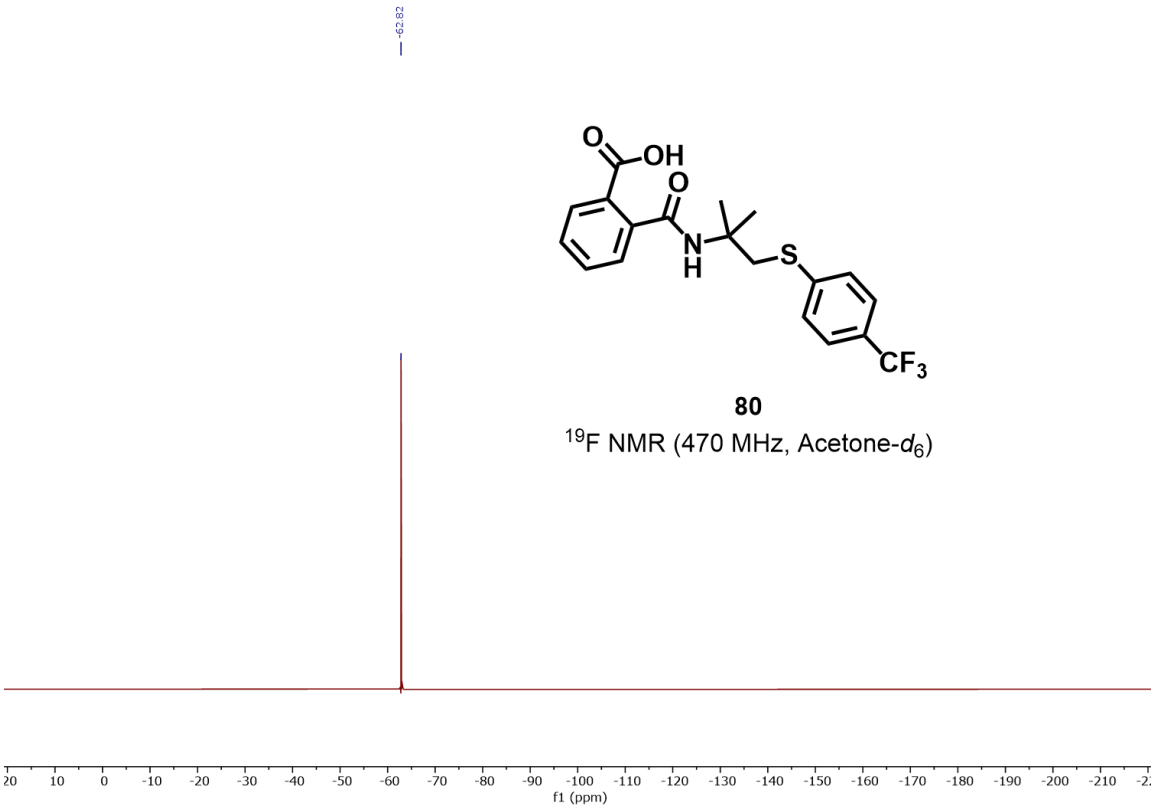
80

^{1}H NMR (500 MHz, Acetone-d_6)

S 12 ^{1}H NMR spectrum of compound **80**



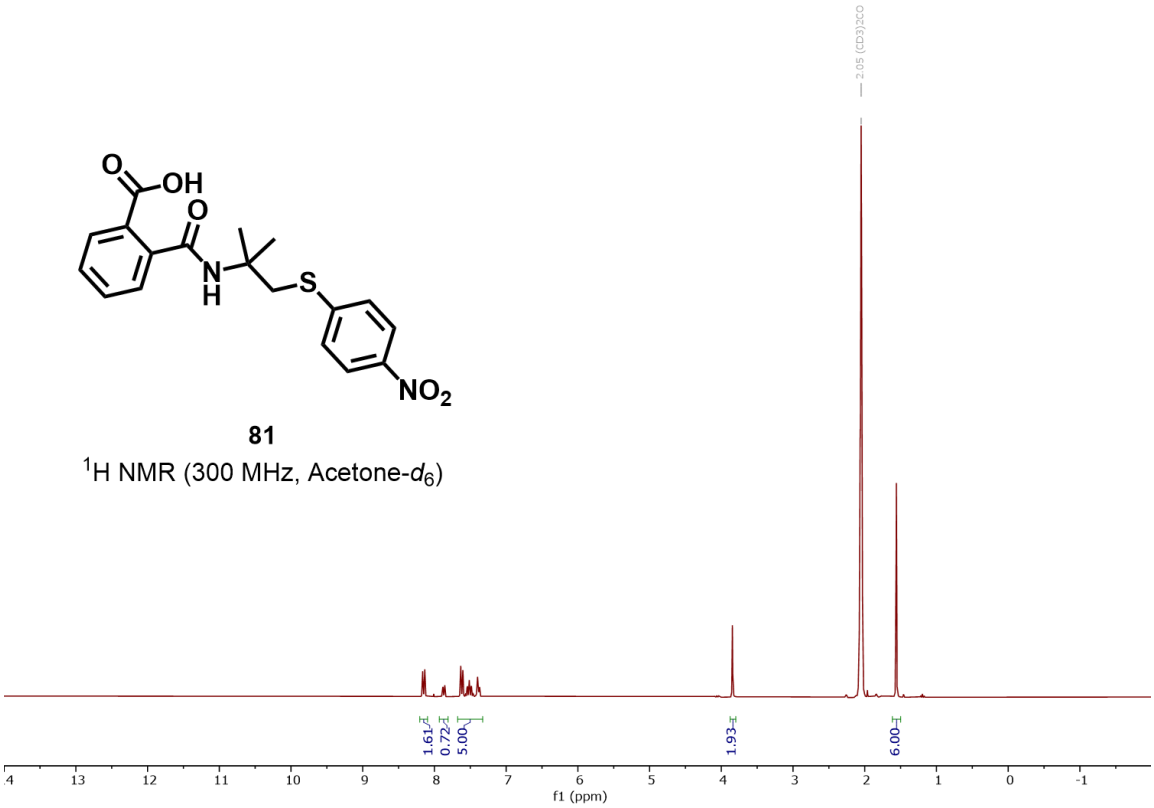
S 13 ^{13}C NMR spectrum of compound **80**



80

^{19}F NMR (470 MHz, Acetone-d_6)

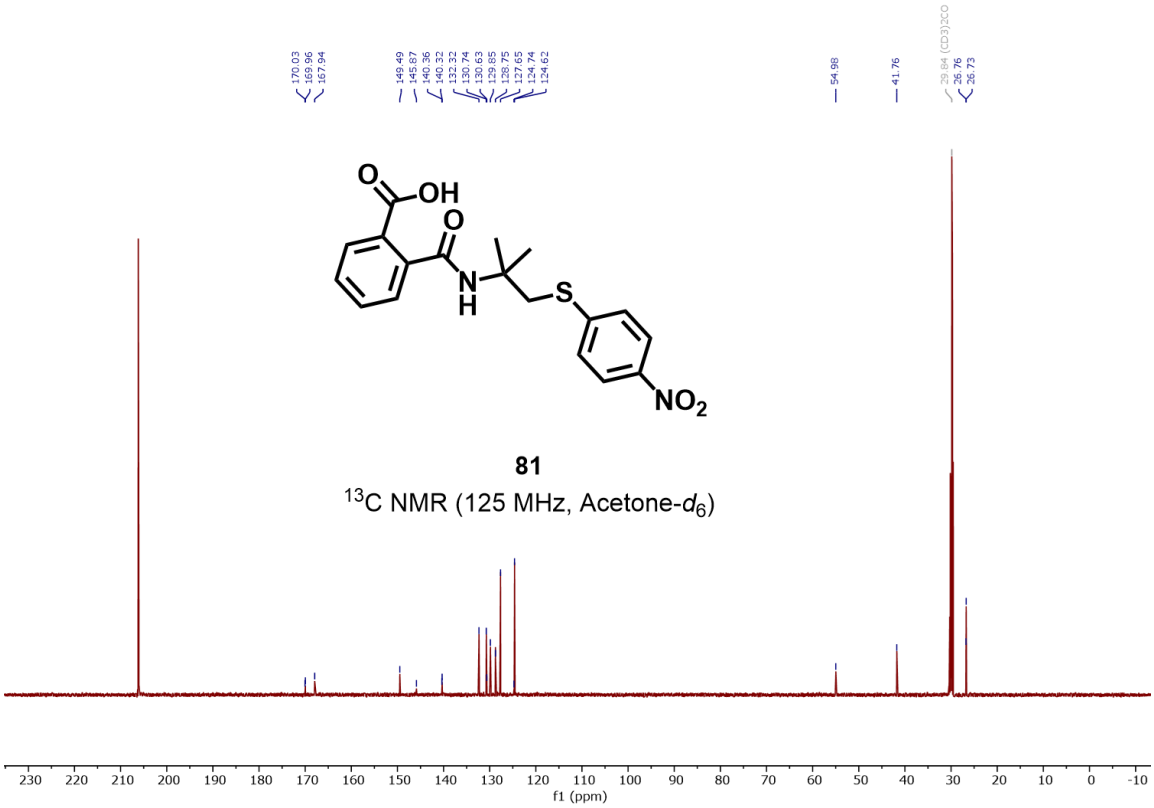
S 14 ^{19}F NMR spectrum of compound **80**



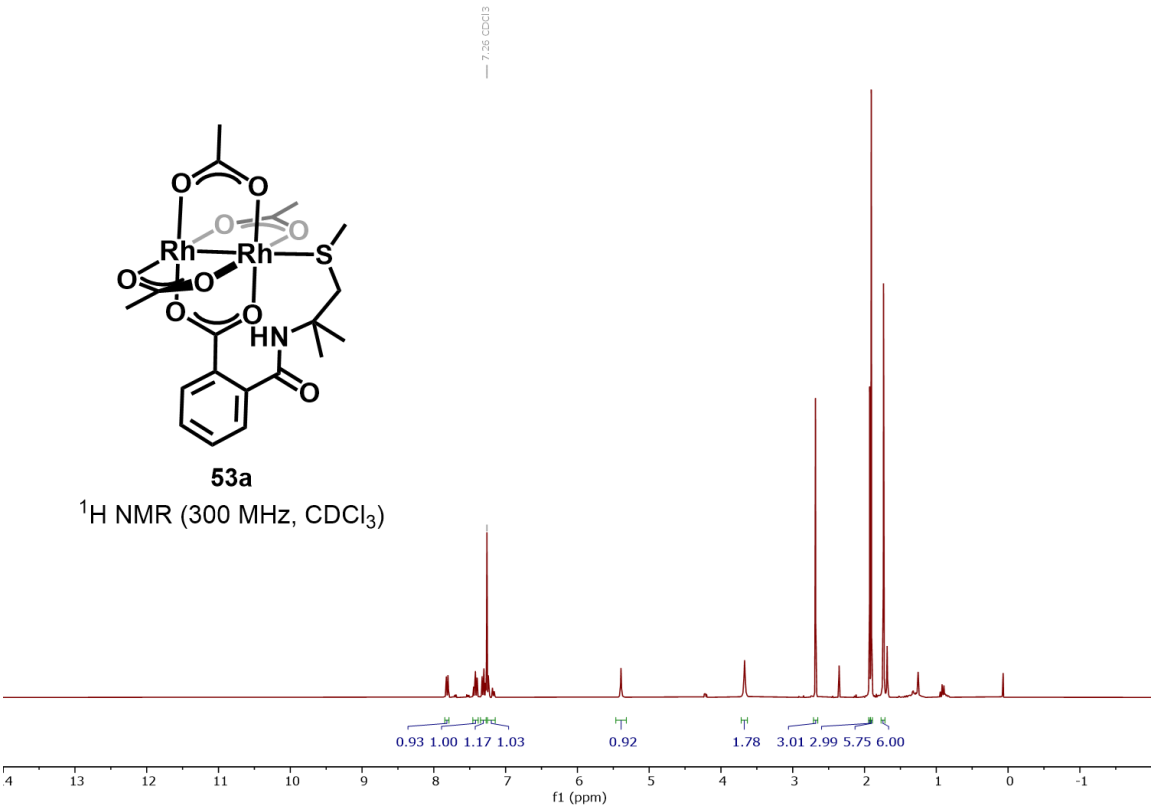
81

^{1}H NMR (300 MHz, Acetone-d_6)

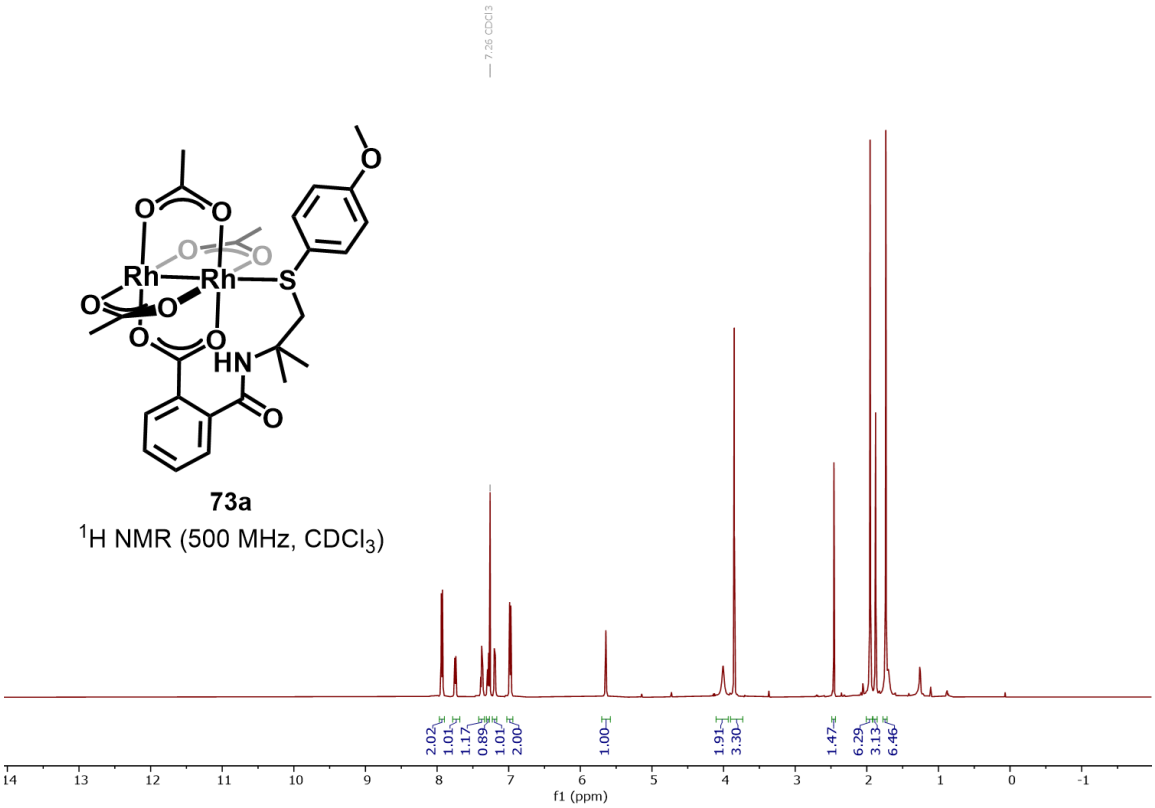
S 15 ^{1}H NMR spectrum of compound **81**



S 16 ^{13}C NMR spectrum of compound **81**



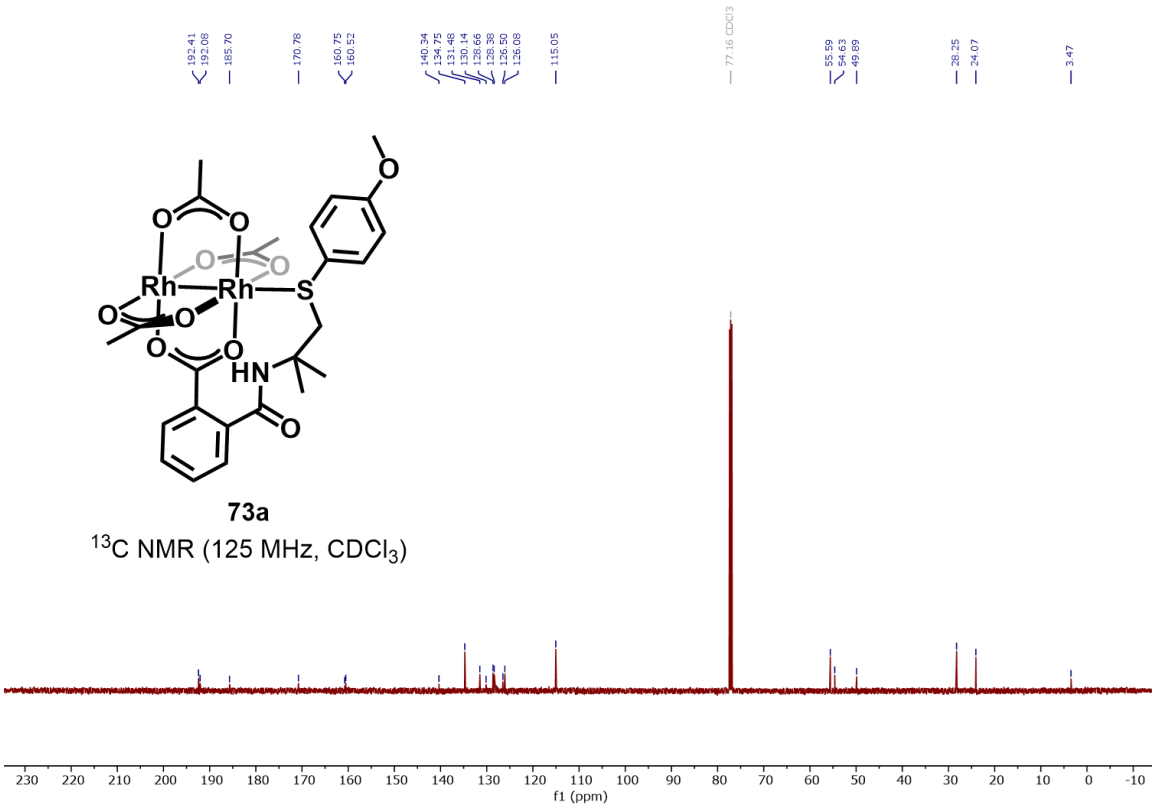
S 17 ^{1}H NMR spectrum of compound **53a**



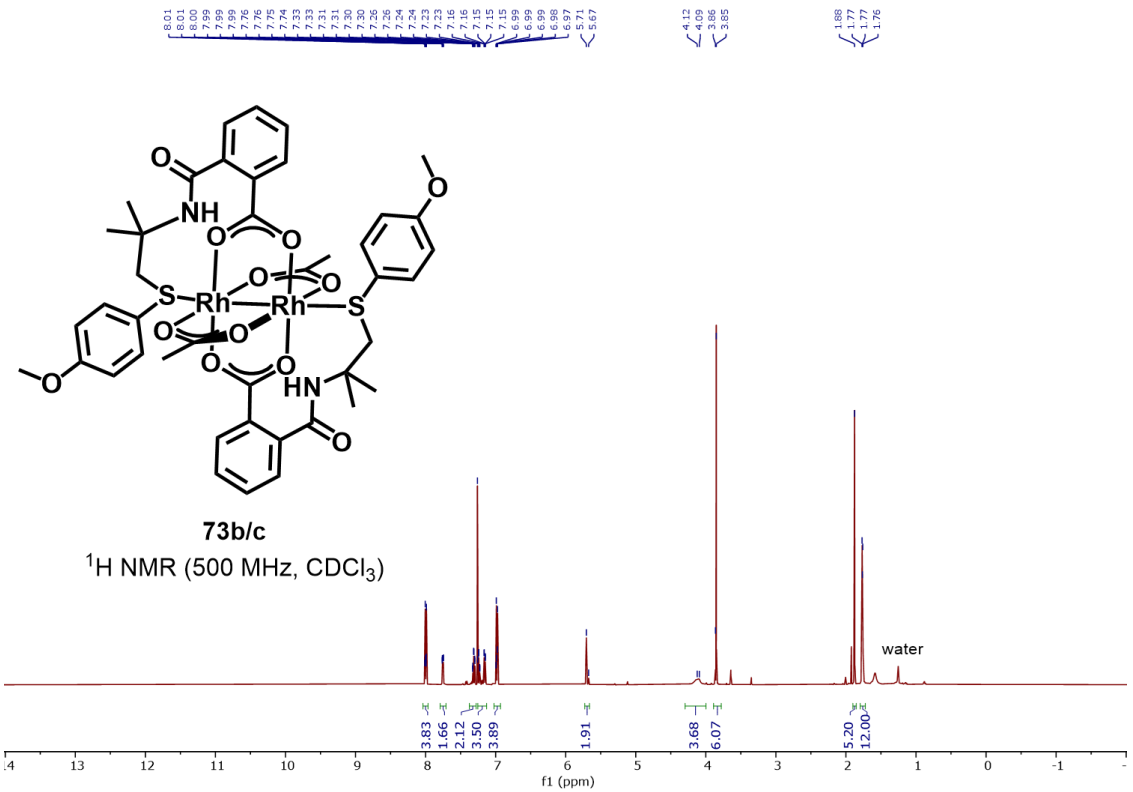
73a

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

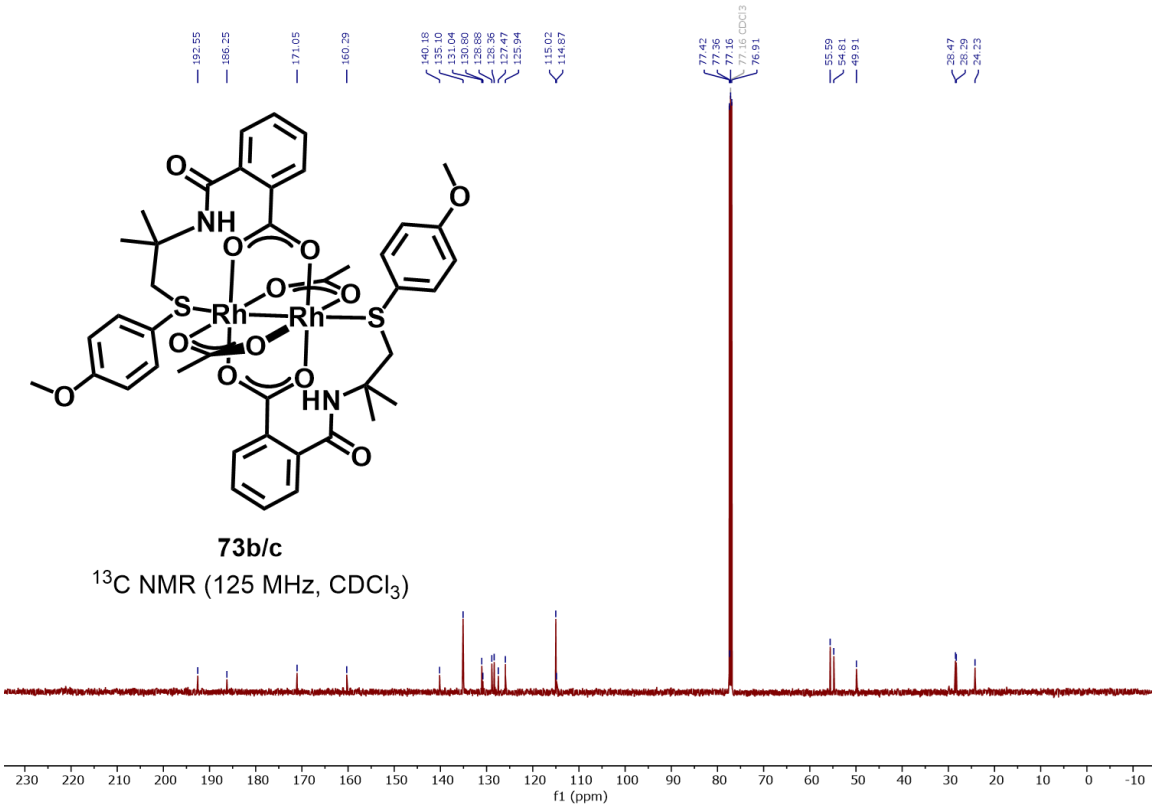
S 18 ^{1}H NMR spectrum of compound **73a**



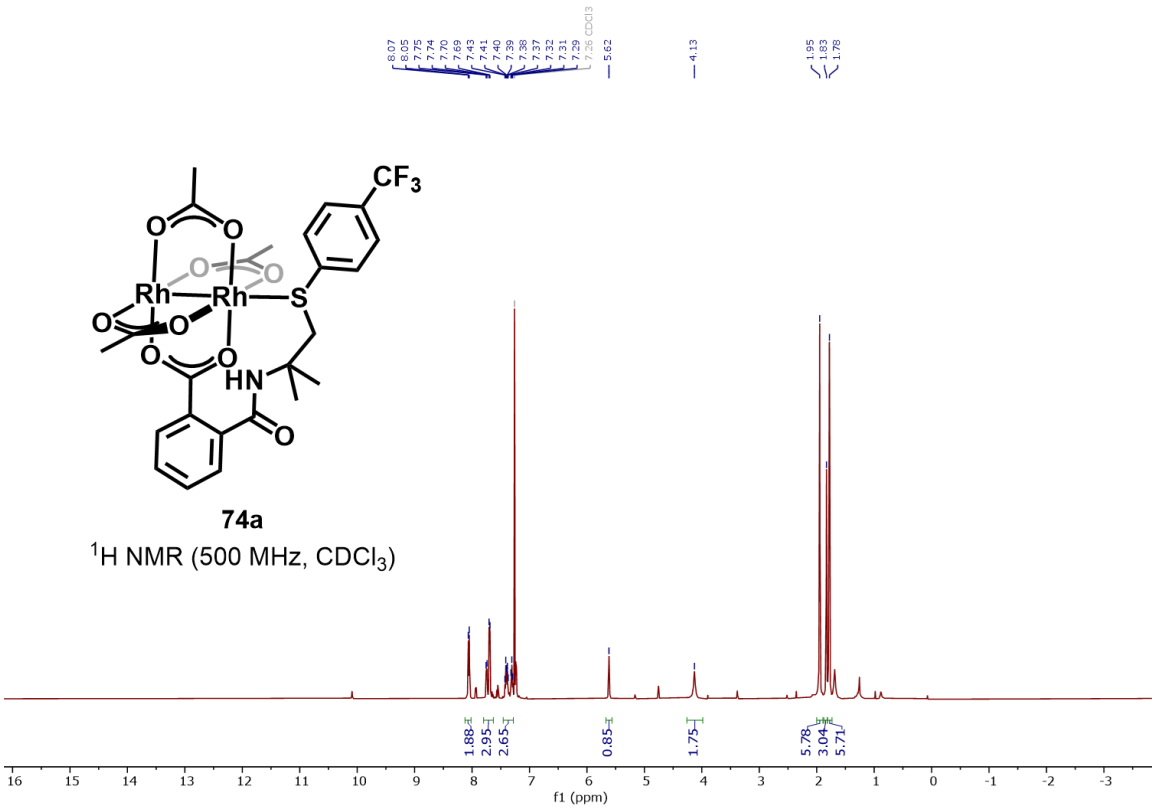
S 19 ^{13}C NMR spectrum of compound **73a**



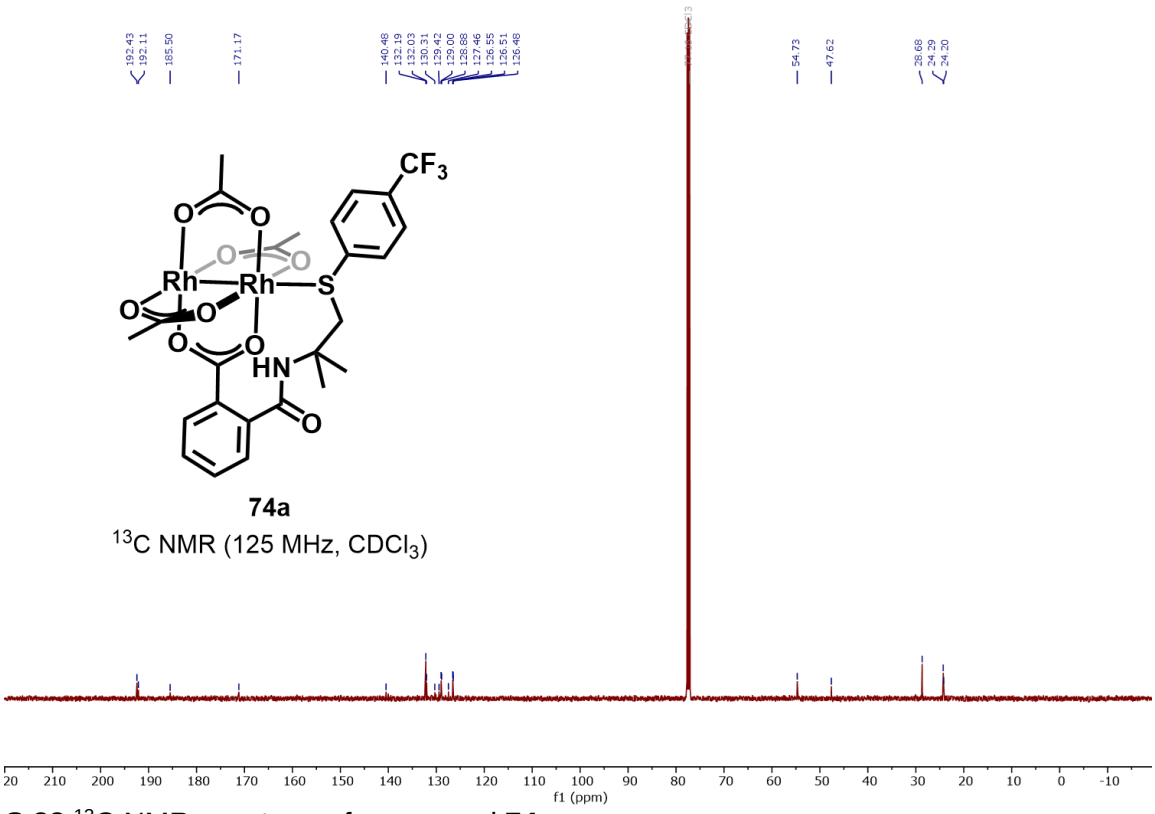
S 20 ^{1}H NMR spectrum of compound **73b/c**



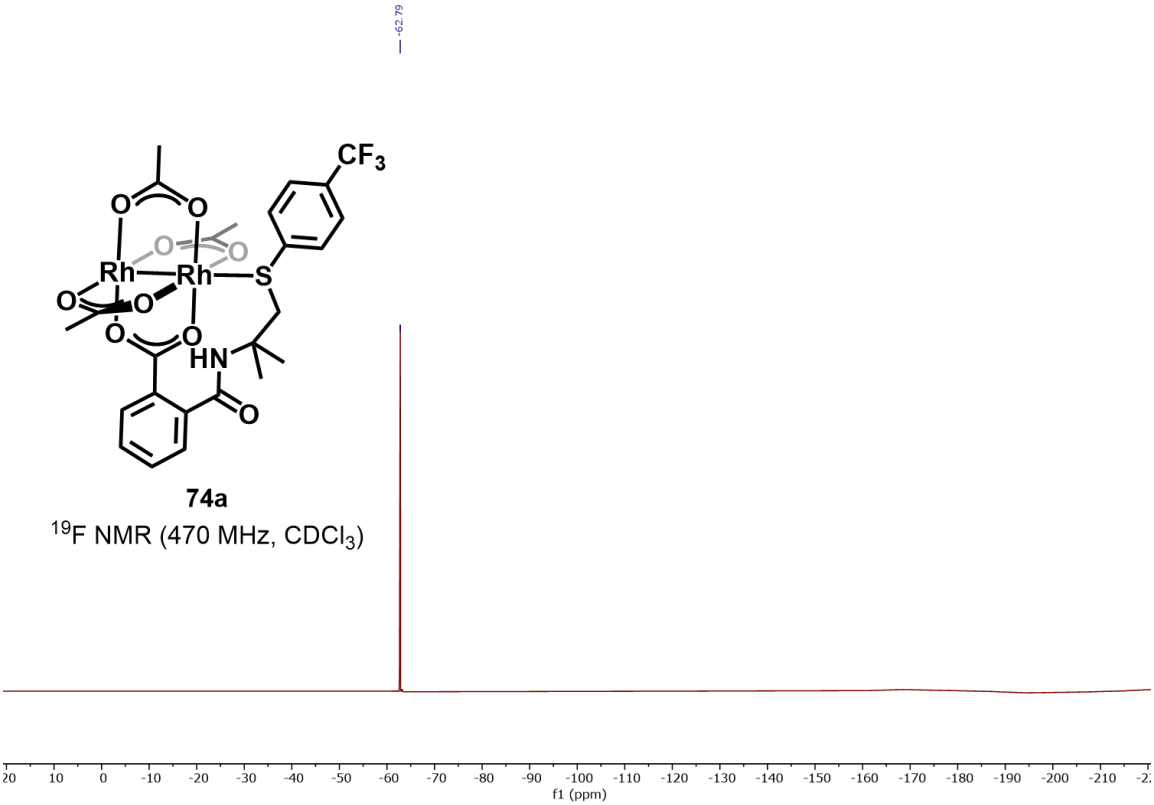
S 21 ^{13}C NMR spectrum of compound **73b/c**



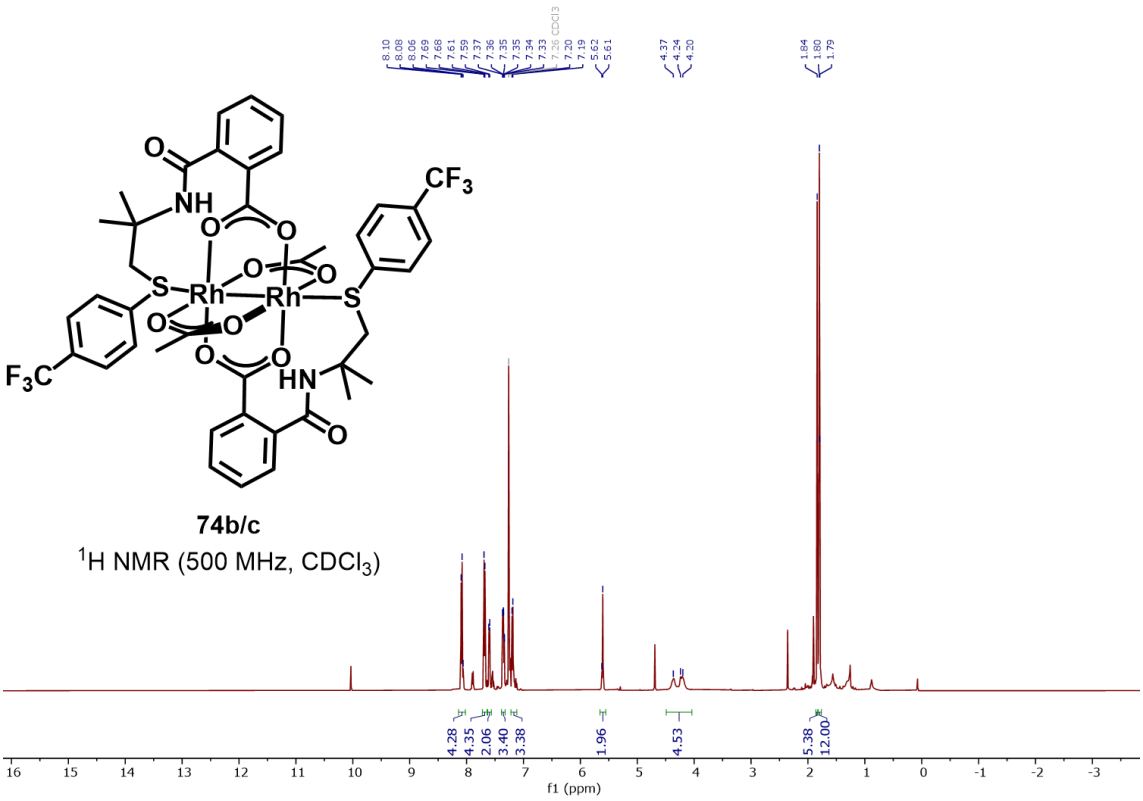
S 22 ^{1}H NMR spectrum of compound **74a**



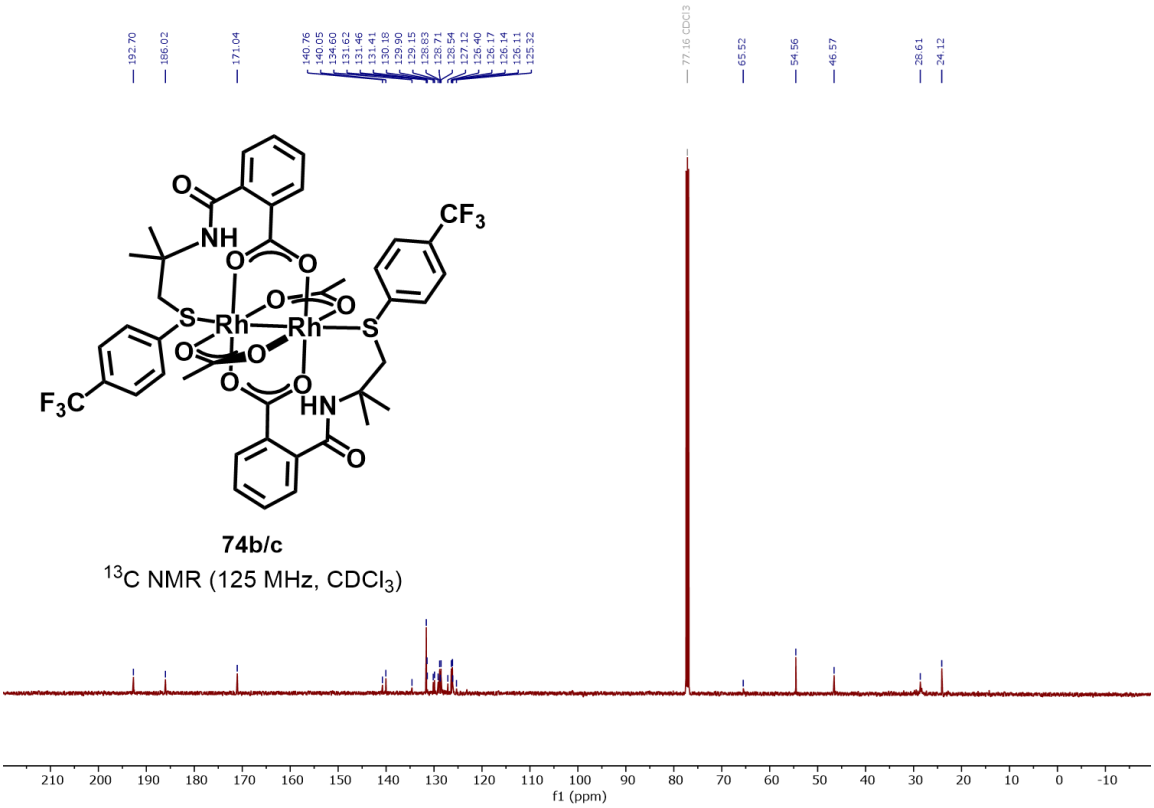
S 23 ^{13}C NMR spectrum of compound **74a**



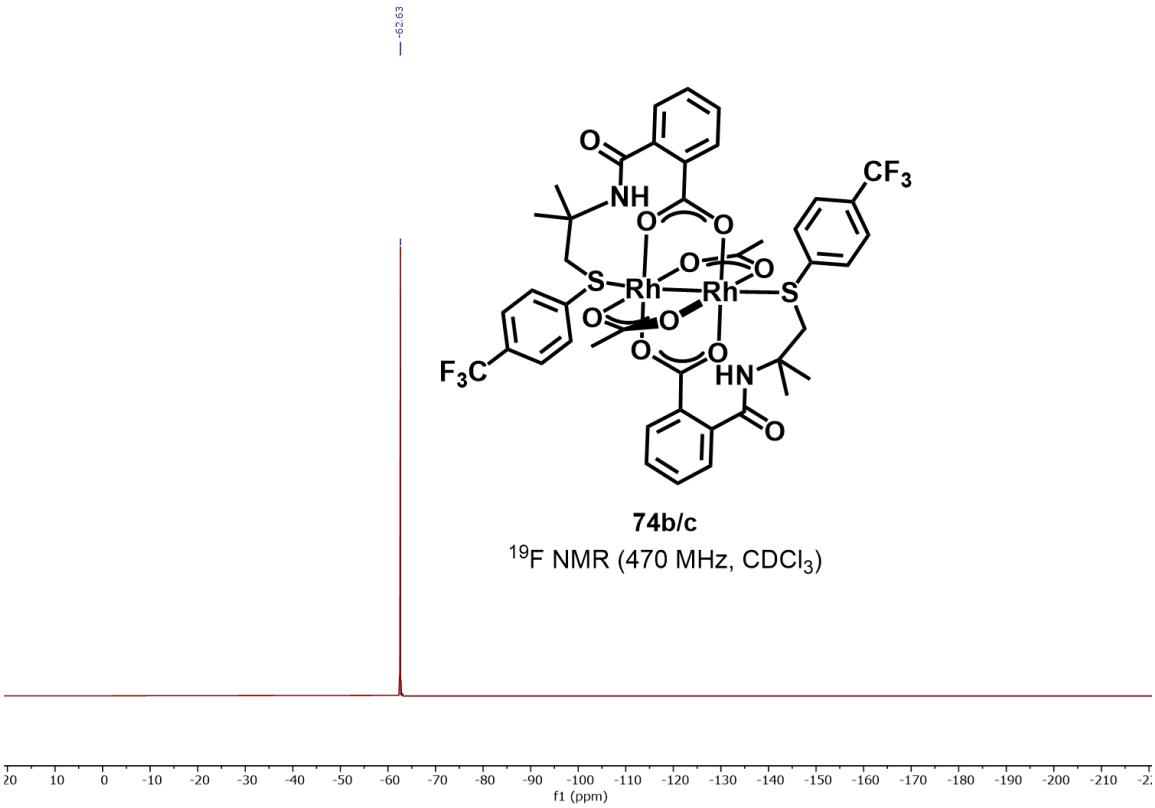
S 24 ^{19}F NMR spectrum of compound **74a**



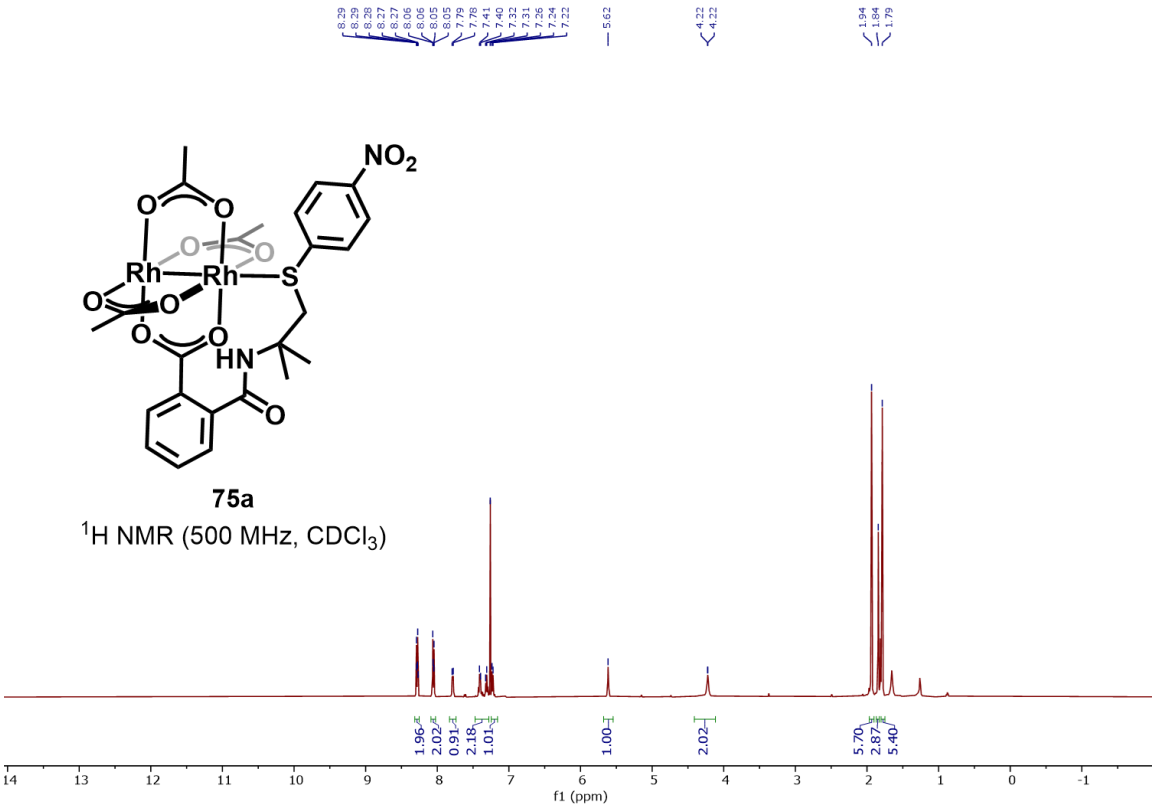
S 25 ^{1}H NMR spectrum of compound **74b/c**



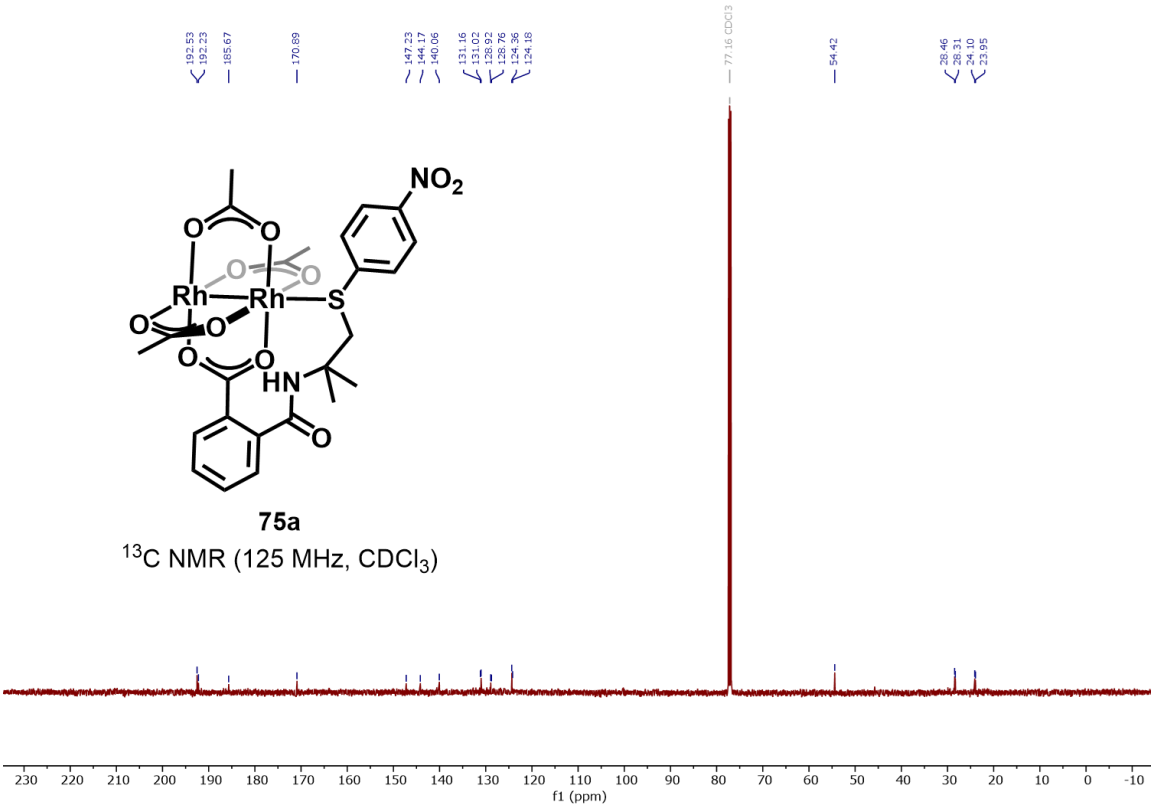
S 26 ^{13}C NMR spectrum of compound **74b/c**



S 27 ^{19}F NMR spectrum of compound **74b/c**



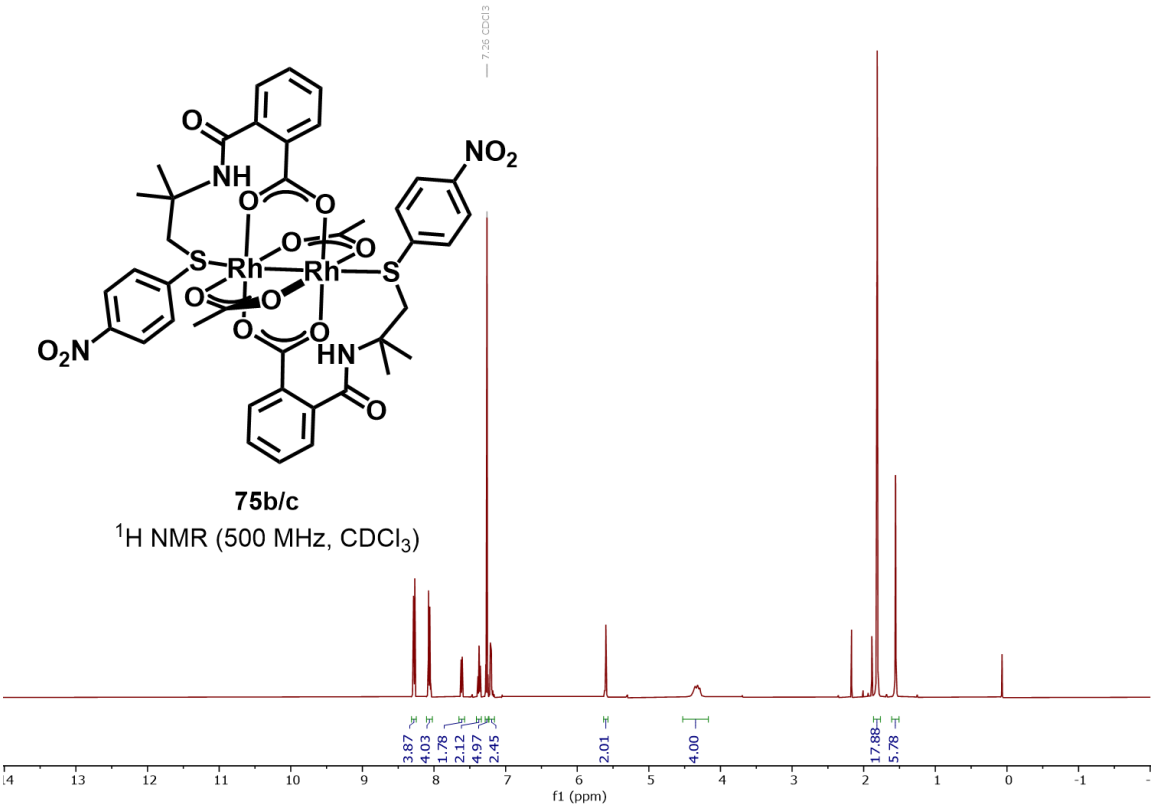
S 28 ^{1}H NMR spectrum of compound **75a**



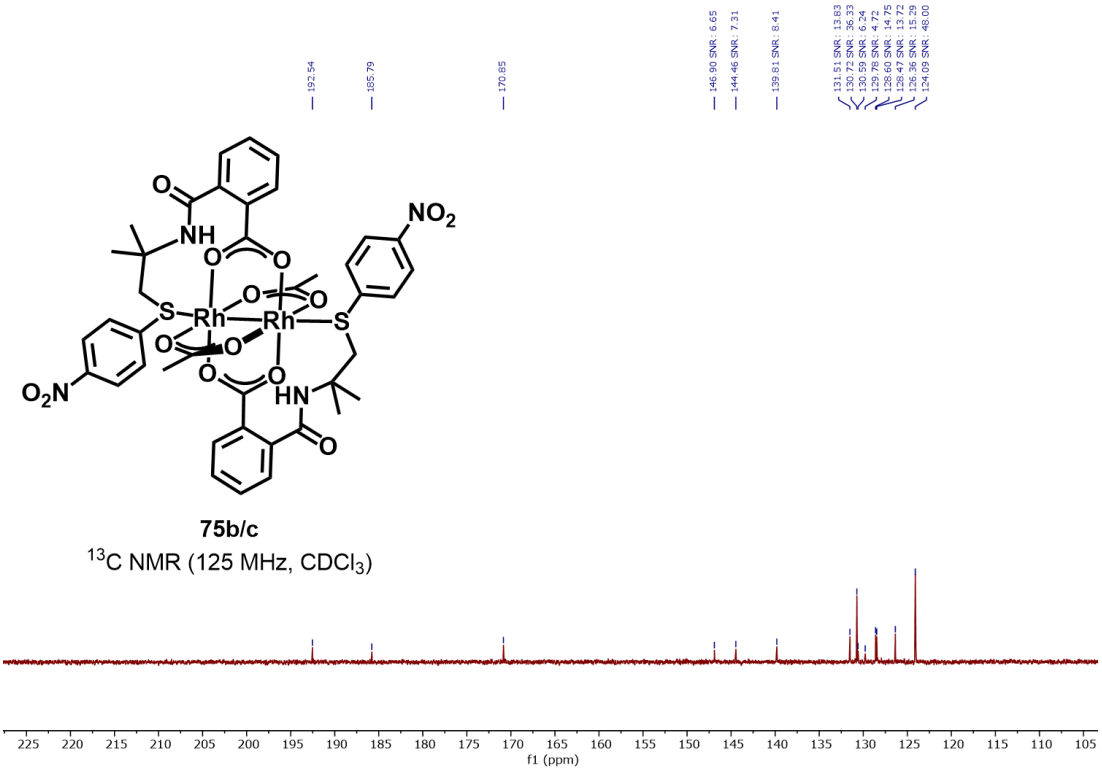
75a

^{13}C NMR (125 MHz, $CDCl_3$)

S 29 ^{13}C NMR spectrum of compound **75a**



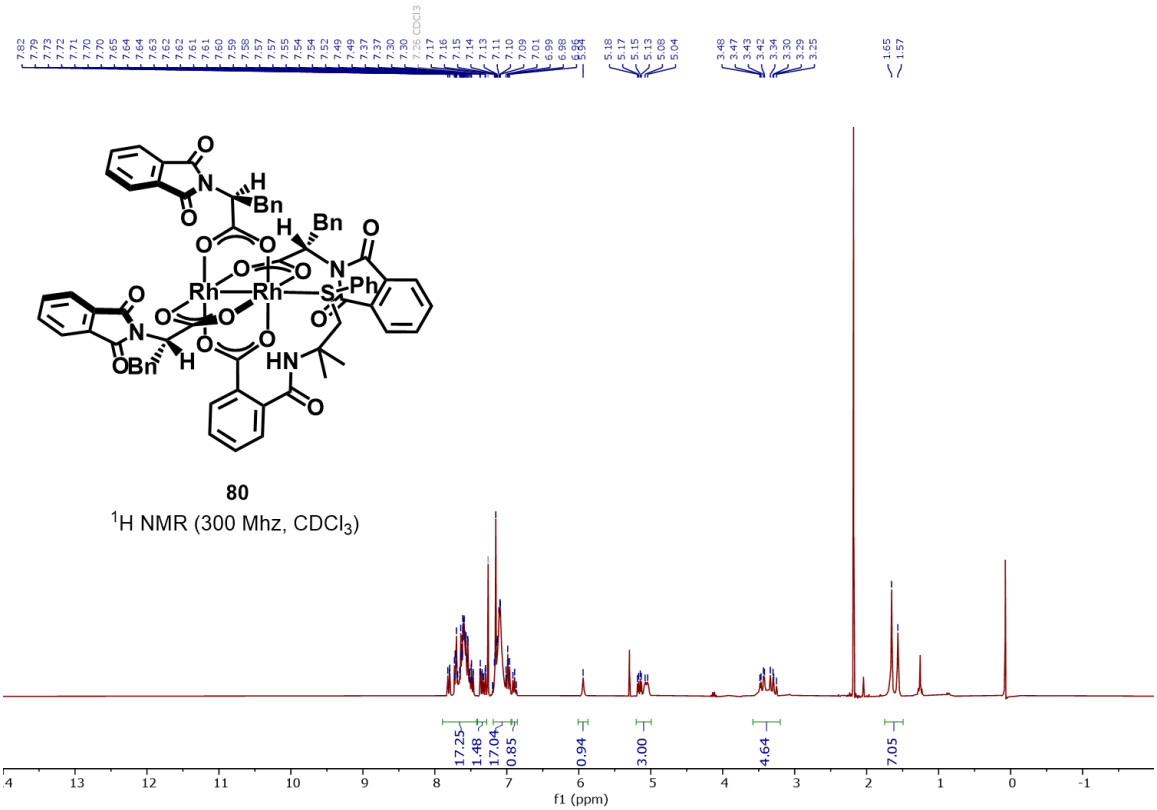
S 30 ^{1}H NMR spectrum of compound **75b/c**



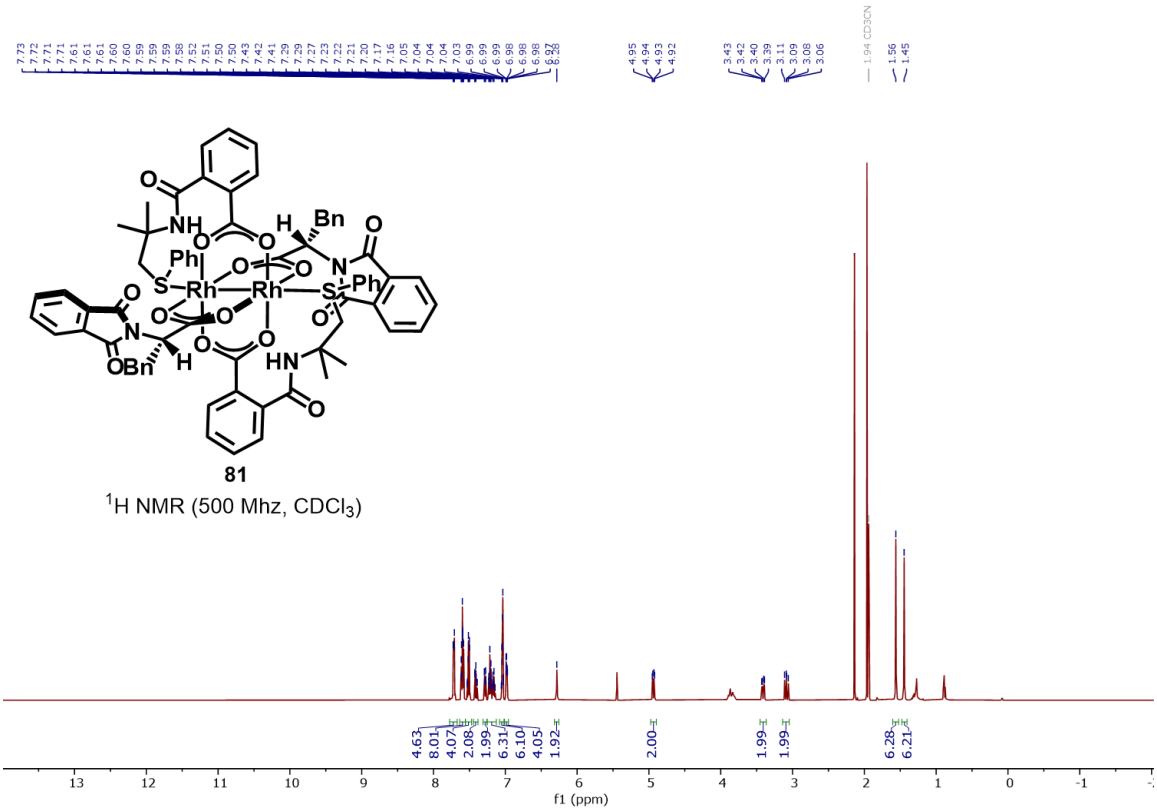
75b/c

^{13}C NMR (125 MHz, $CDCl_3$)

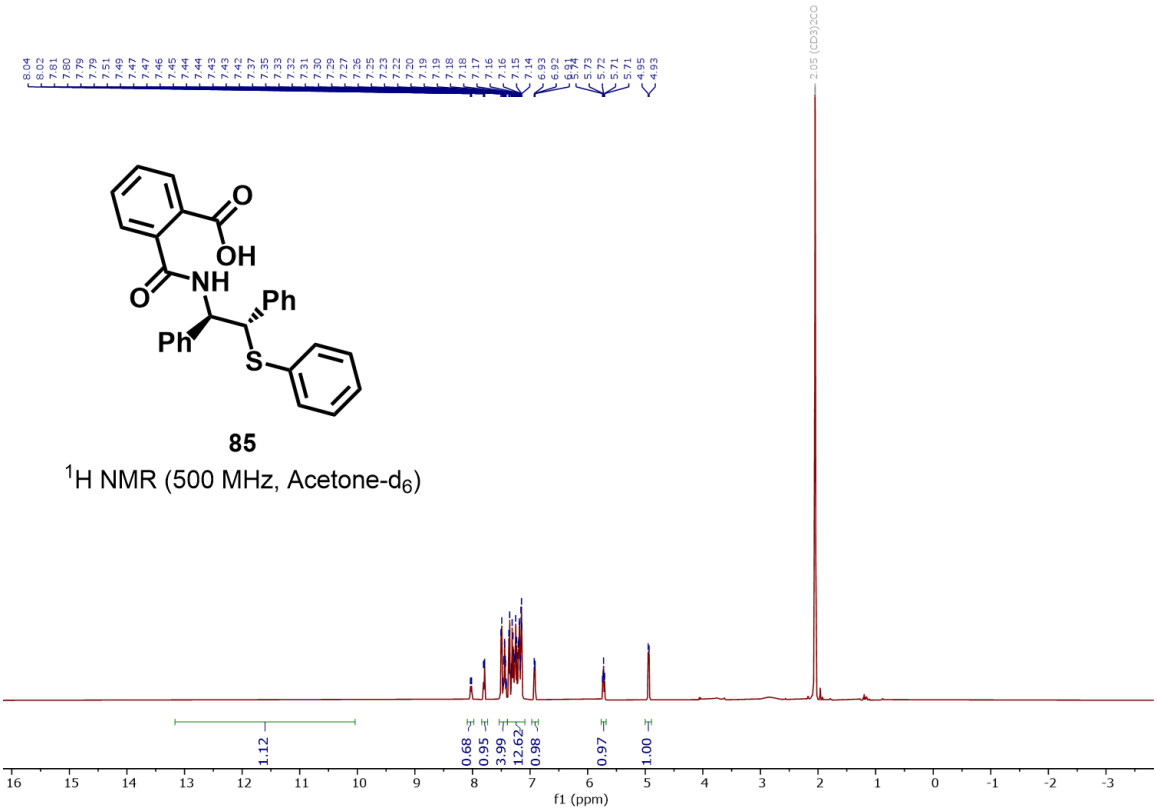
S 31 ^{13}C NMR spectrum of compound **75b/c**



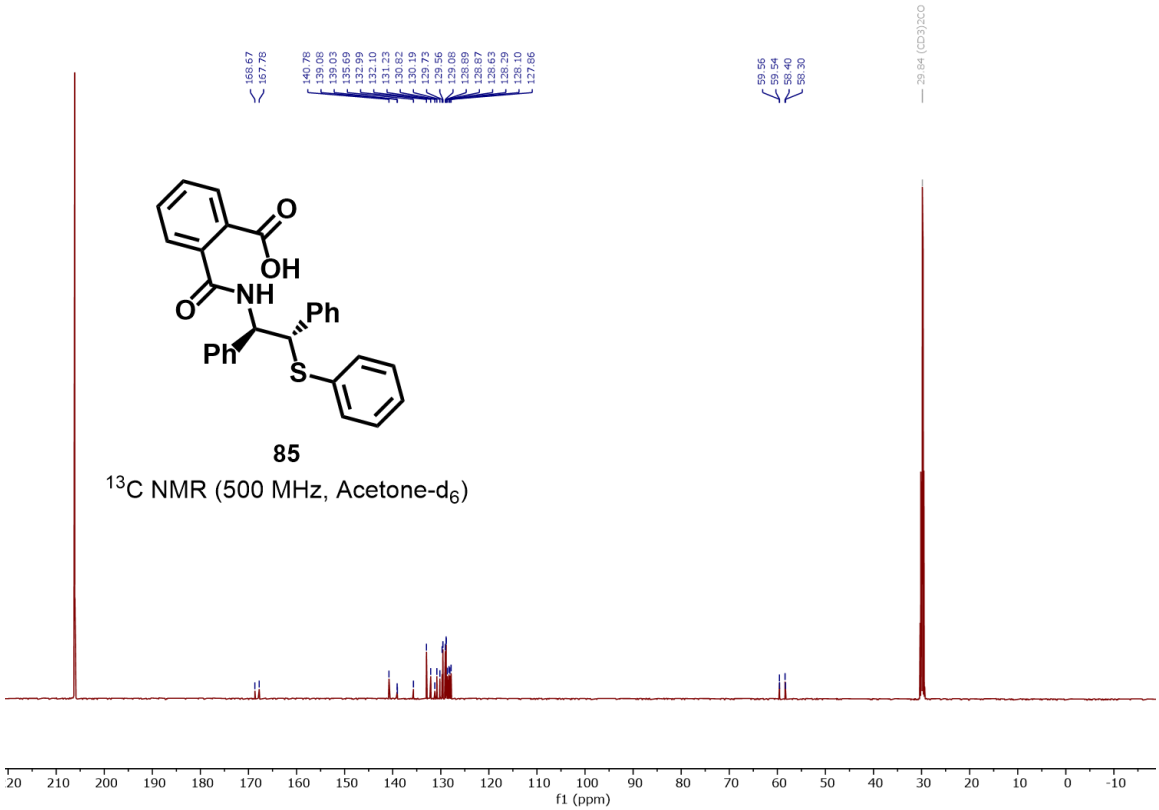
S-32 ^{1}H NMR spectrum of compound **80**



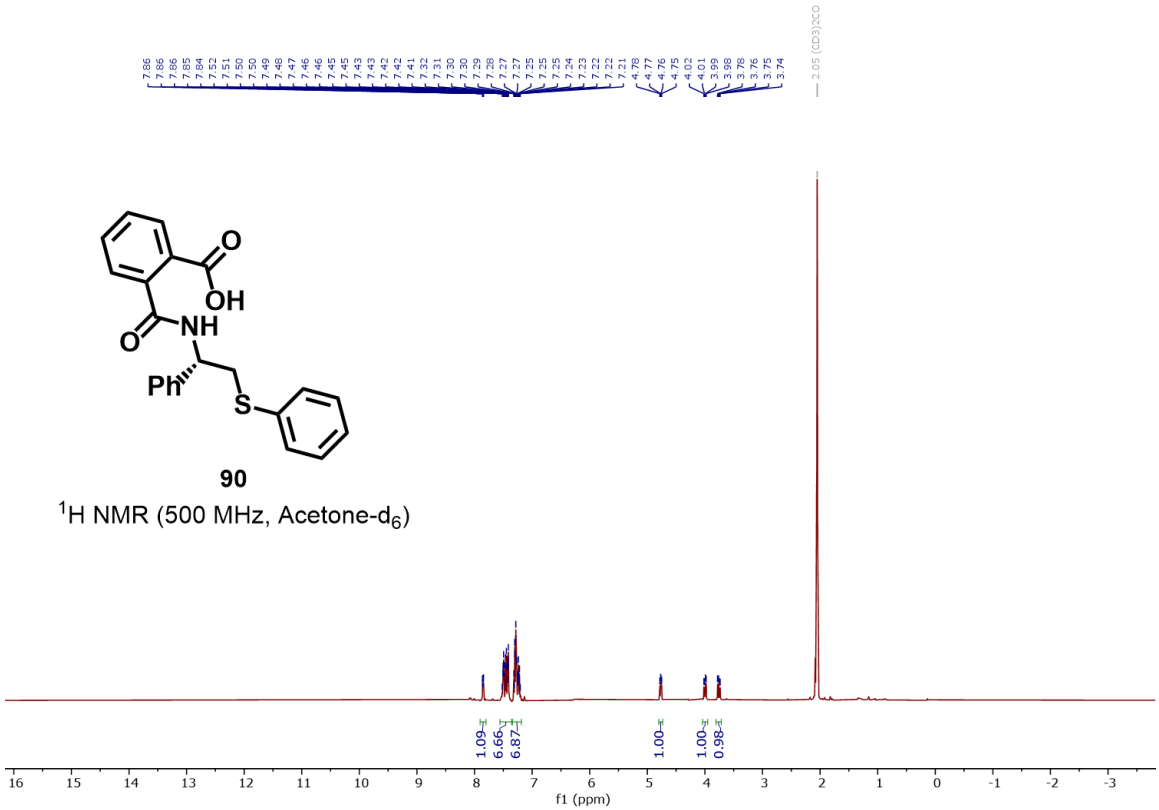
S-33 ^{1}H NMR spectrum of compound **81**



S-34 ^{1}H NMR spectrum of compound **85**



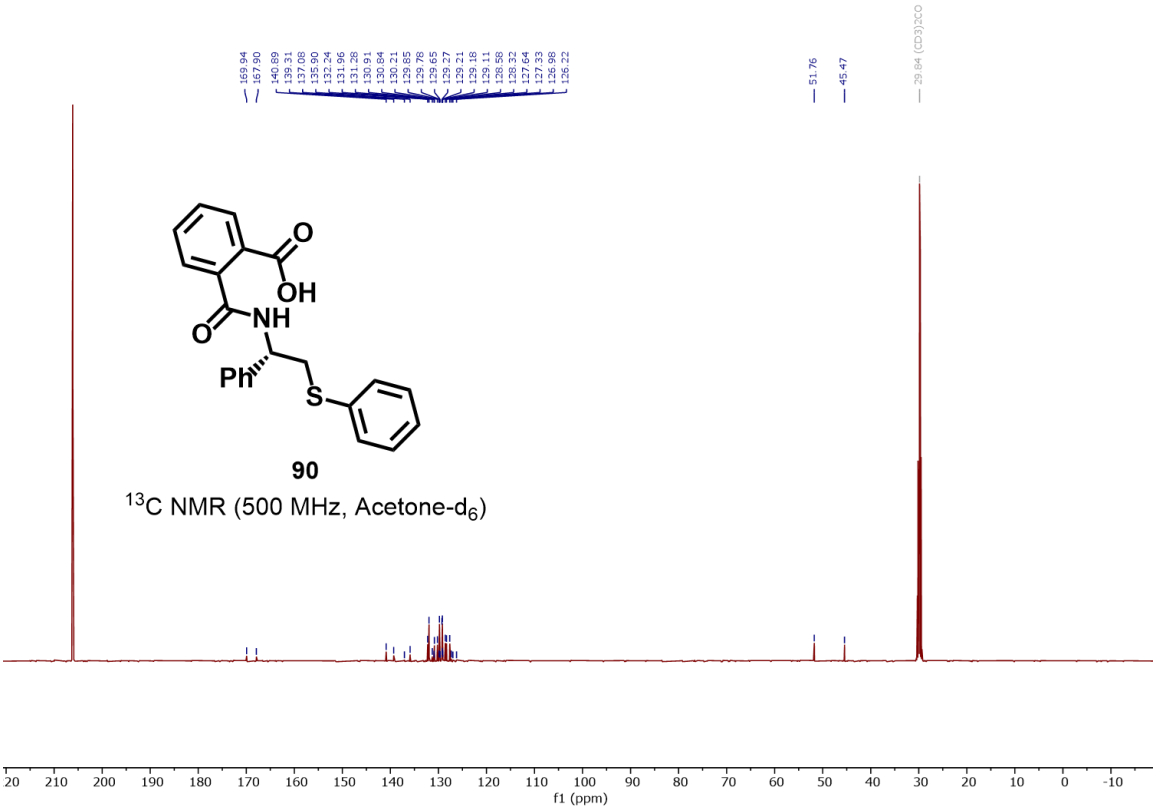
S-35 ^{13}C NMR spectrum of compound **85**



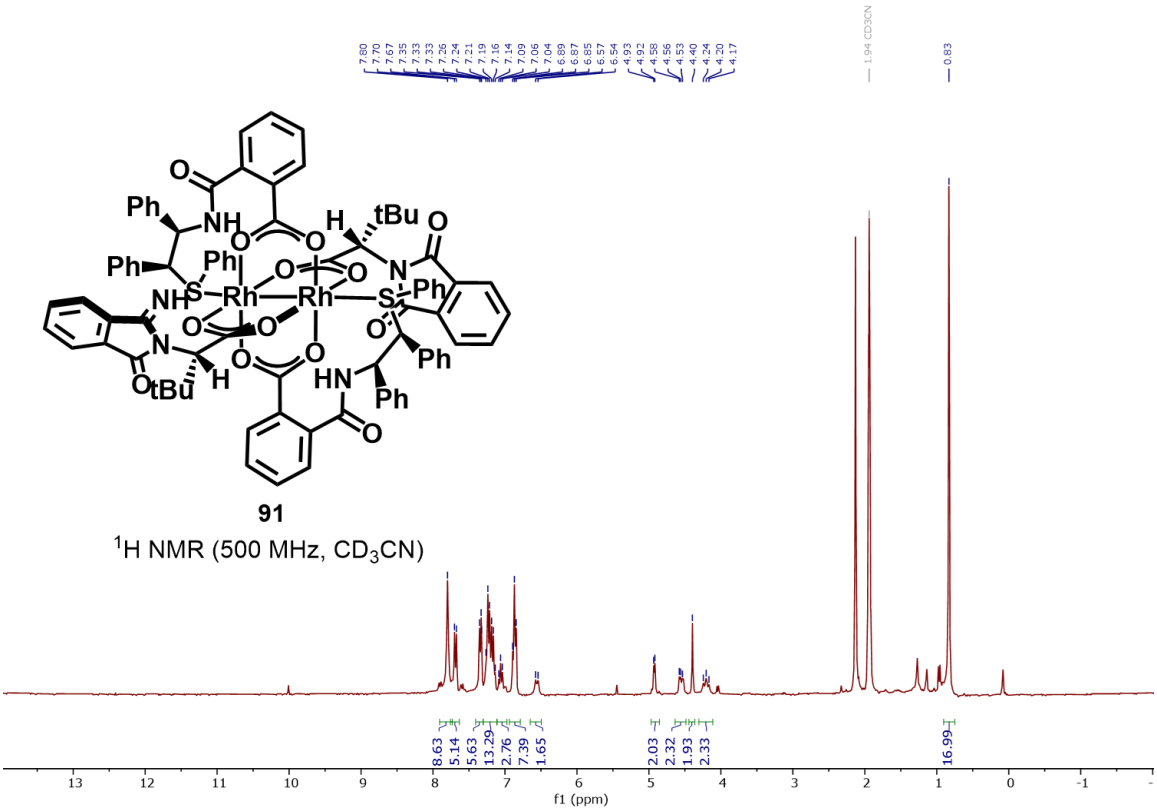
90

^{1}H NMR (500 MHz, Acetone-d_6)

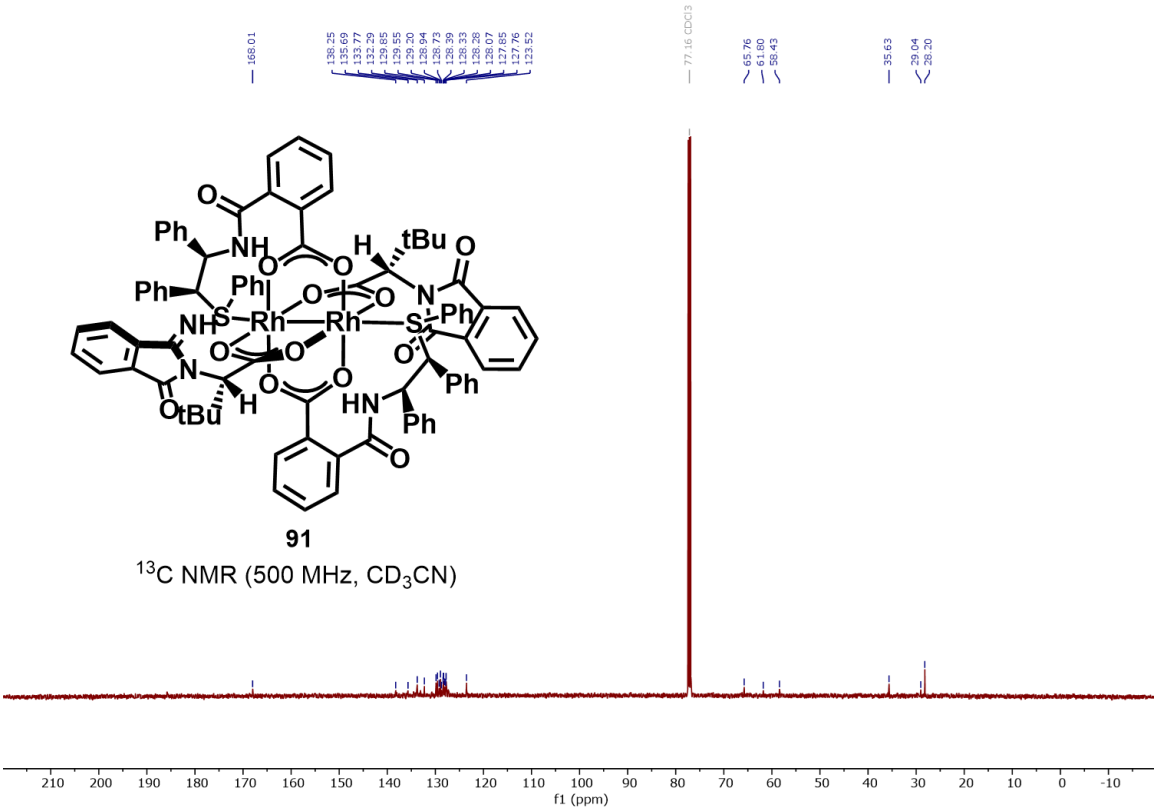
S-36 ^{1}H NMR spectrum of compound **90**



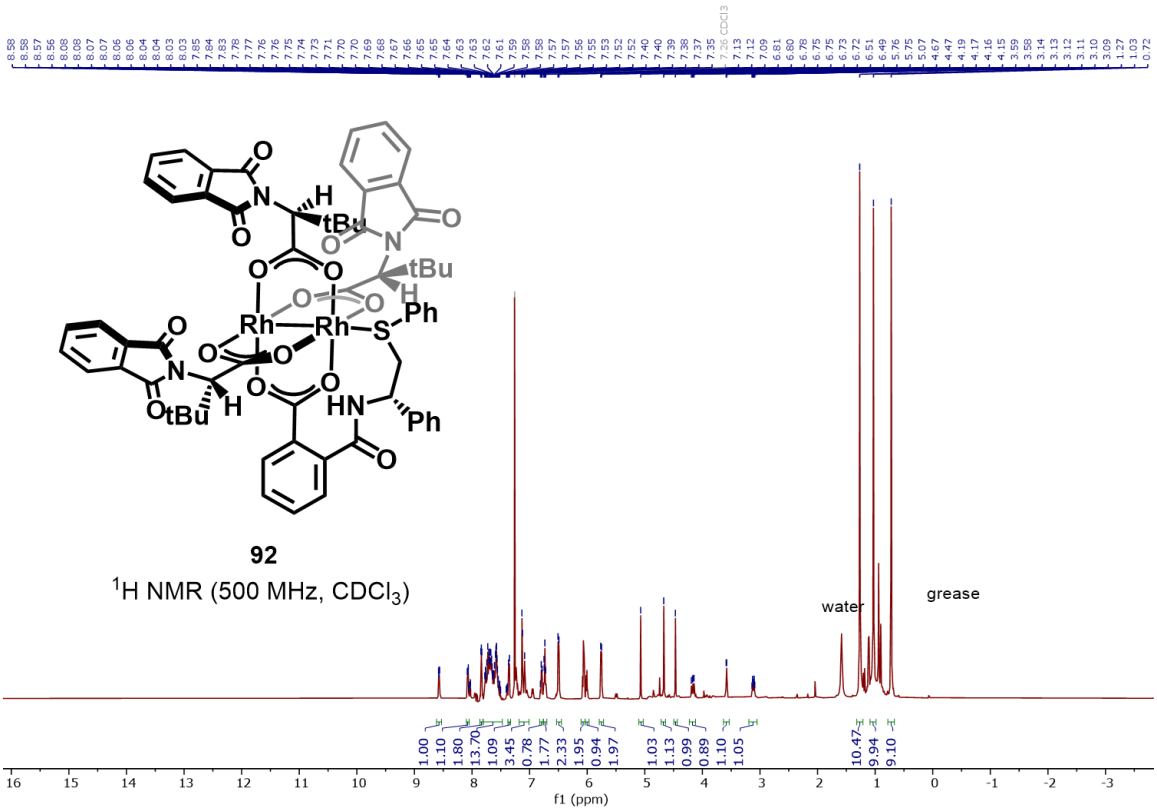
S-37 ^{13}C NMR spectrum of compound **90**



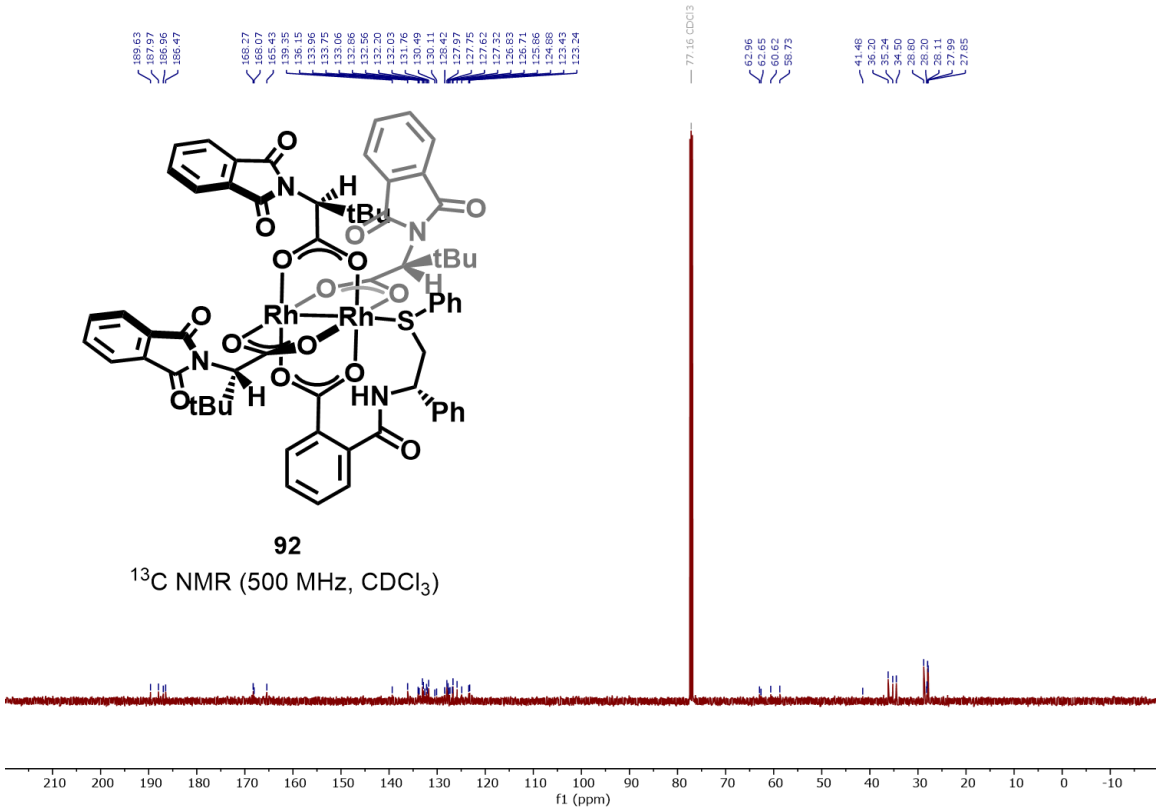
S-38 ^{1}H NMR spectrum of compound **91**



S-39 ^{1}H NMR spectrum of compound **91**



S-40 ^{1}H NMR spectrum of compound **92**



92

^{13}C NMR (500 MHz, $CDCl_3$)

S-41 ^{13}C NMR spectrum of compound **92**

Vita

Cristian Zavala was born in Miami, FL in 1994 to Hernan and Maritza Meraz. He graduated from Miami Sunset Senior High School in Spring of 2013. He then attended Florida International University where he received his B.S. in Biochemistry in 2017. In Fall 2017, he was accepted into the graduate school at the University of Tennessee to pursue a Ph.D. in Chemistry with a concentration in Organic Chemistry under the tutelage of Dr. Ampofo Darko. His research interest includes studying the effect of ligand architectures on Rh(II,II) catalysis.