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Paul Beasley Date

Metal Catalyst Methodology Development towards Carbon-Oxygen Bond Formation: Synthesis of Vinyl Ethers and Vinyl Esters

By

Paul Beasley

Doctor of Philosophy

Chemistry

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Advisor

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Date

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Paul Beasley

B.S., Earlham College, 2018

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An abstract of

a dissertation submitted to the Faculty of the Graduate School of Emory University

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Abstract

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Vinyl ethers and vinyl esters are versatile functional groups utilized in synthetic and bioorthogonal applications, and they are found in natural products with medicinal properties. Novel scorpionate Ru complexes were synthesized for vinyl ether synthesis, however they are unable to promote reactivity with alcohols. The novel scorpionate catalyst were applied towards vinyl ester synthesis, and a reactive system with tunable stereoselectivity depending on ligands of choice is described. Deuterium experiments were conducted, suggesting an alternative pathway for vinyl ester synthesis besides vinylidene formation. Finally, Chan-Lam coupling reactions were optimized and applied towards complex glycoside vinyl ether synthesis. Screening Chan-Lam reaction conditions provided insight into the obstacles preventing Chan-Lam from being a robust method for vinyl ether synthesis.

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For Toni Thompson, Taja and Nadia

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Abbreviations

Ac	acetyl
BTA	benzotriazole
Bz	benzoyl
COD	1,5-cyclooctadienyl
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet
DIPEA	N,N-Diisopropylethylamine
DCM	dichloromethane
DMA	dimethylacetamide
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformaide
DMSO	dimethylsulfoxide
DPPIsC	diplasmenylcholines
Equiv.	equivalent
Eq.	equation
EtOAc	ethyl acetate

Ft-IR	fourier transform infrared spectroscopy
Fur	furyl
HFIP	hexafluoro-2-propanol
HRMS	high-resolution mass spectroscopy
MCPBA	meta-Chloroperoxybenzoic acid
m	multiplet
mL	milliliter
mmol	millimole
MS	molecular sieves
Ph	phenyl
RNA	ribonucleic acid
rt	room temperature
s	singlet
Sat	saturated
TMP	trimethylolpropane
Tpz	trispyrazolylborate
TBAB	tetrabutylammonium bromide
Tf	triflate

Chapter 1

Ru Catalyst development towards complex vinyl ether synthesis

1.1 Introduction and Background

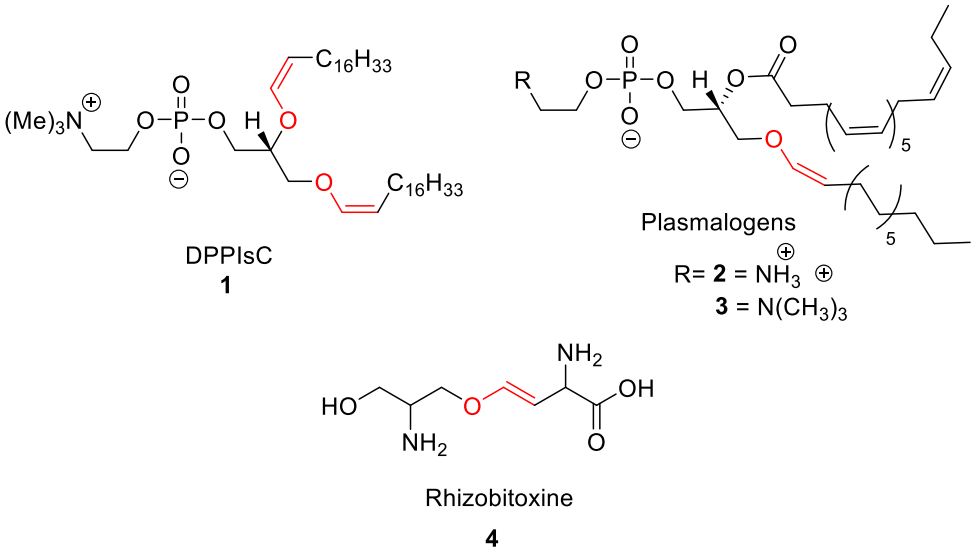


Figure 1: Vinyl ether natural products

1.1.1 Vinyl Ether

Vinylic ethers are versatile functional groups found in natural products and utilized as key intermediates in various organic methodologies. These electron-rich alkenes also occur in various natural products. Plasmalogens are a class of glycerophospholipids that function as a major components in biological membranes[1] (**Figure 1**). Content and molecular changes in plasmalogens are linked to pathological conditions ranging from inherited to metabolic and degenerative diseases. Plasmalogens are also utilized in synthetic plasmalogen replacement therapy,[2] which is demonstrated to restore plasmalogen levels and ameliorate disease phenotypes in different clinical conditions. Diplasmenylcholines (DPPIsC) are acid sensitive drug carrier liposomes. These drug carriers exhibit high biocompatibility and large loading capacity for hydrophilic or hydrophobic drugs.[3] Rhizobitoxine is a vinyl ether containing amino acid secreted from rhizobia bacteria.[4]

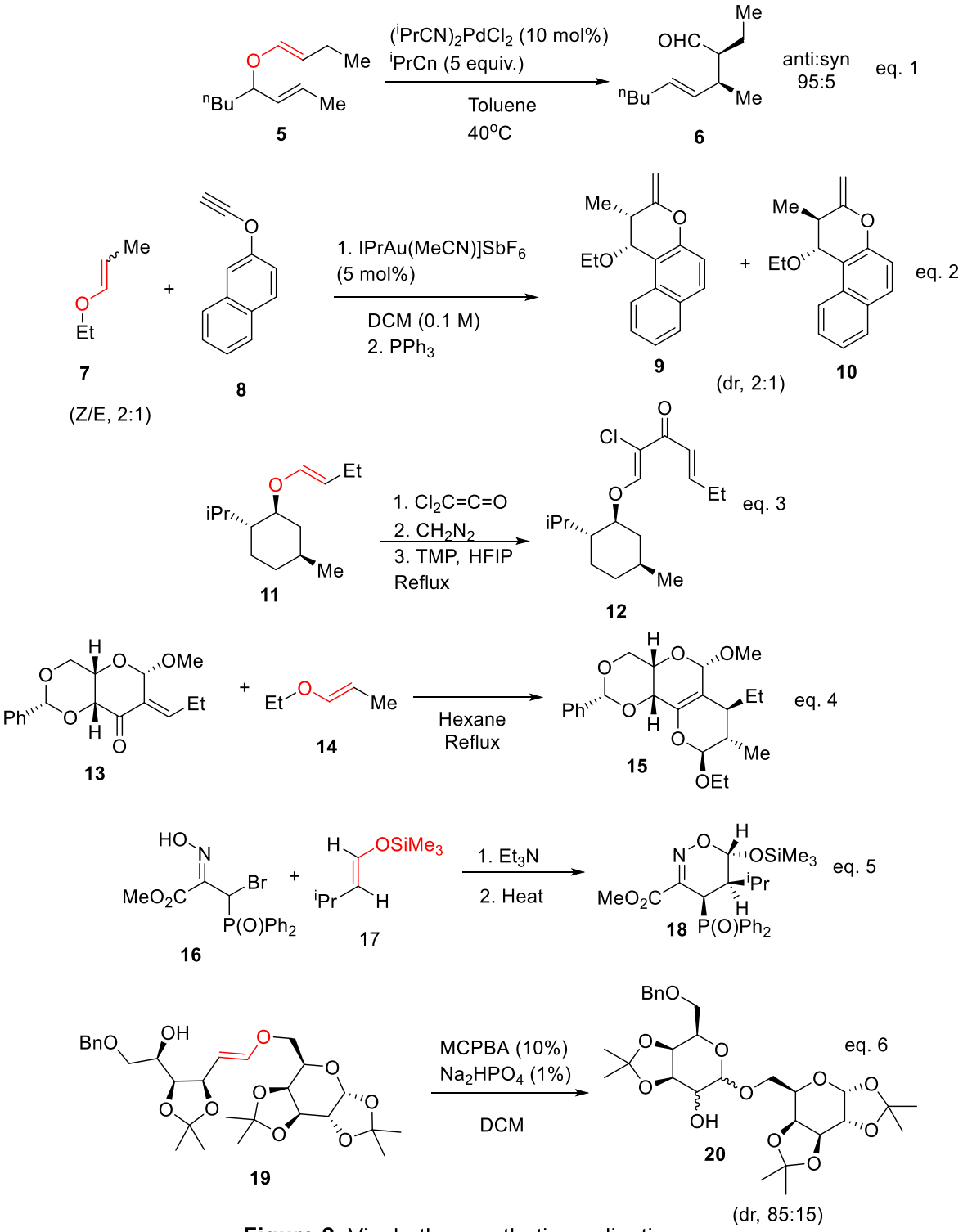


Figure 2: Vinyl ether synthetic applications

Vinyl ethers function as key intermediates in various synthetic methodologies (**Figure 2**) and bioorthogonal applications. Hetero-Diels-Alder cycloaddition methods were developed by

taking advantage of the electron rich alkene towards the synthesis of complex ring systems (eq. 4 & 5).[5-6] Nelson *et al*. designed a Pd(II) catalyzed Claisen rearrangement of acyclic allyl vinyl ethers to synthesize 2,3 anti disubstituted pentenal Claisen adducts with high diastereoselectivity (eq. 1). [7] Harmata *et al.* developed a method to cleave vinyl ethers via a retro-Nazarov reaction (eq. 3). [8] Vinyl ethers are also used in Au Catalyzed cycloaddition under mild conditions (eq. 2). [9] A method for stereoselective synthesis of glycosides is conducted through epoxidation of vinyl ethers followed by spontaneous intramolecular cyclization (eq. 6). [10]

Bioorthogonal chemistry also uses vinyl ether groups for medicinal applications (**Figure 3**). A technique for site specific prodrug release uses vinyl ether linkers for rapid drug incorporation and efficient drug release upon radiation. [11] Bioorthogonal tetrazine uncaging reaction with vinyl ethers are used to visualize and detect target RNA sequences.[12] Multiple bioorthogonal techniques take advantage of monosubstituted vinyl ethers, [13-14] but much like other organic methodologies, they arewa limited by the lack of methods for stereoselective E or Z selective synthesis of disubstituted vinyl ethers.

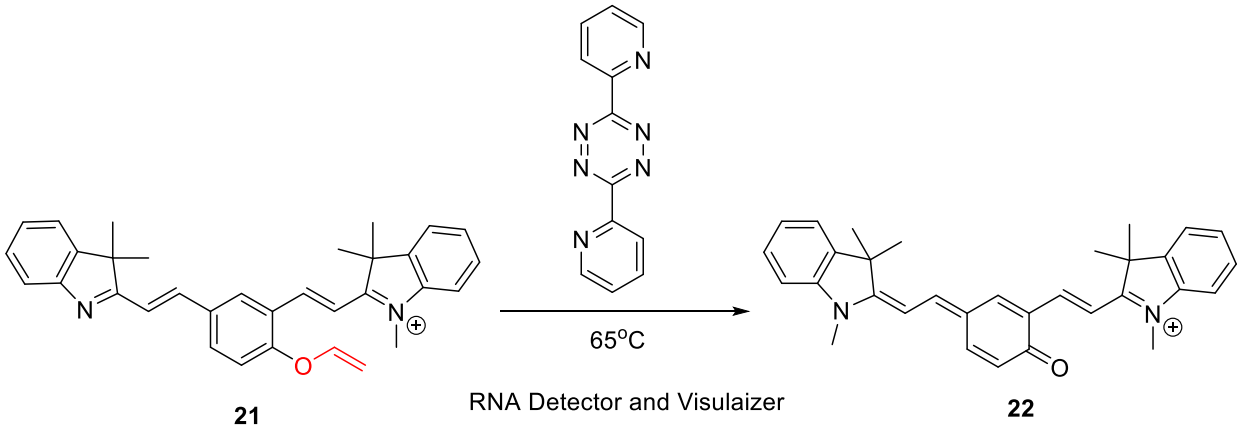


Figure 3: Vinyl ether bioorthogonal applications

Synthetic and biomedical applications of vinyl ethers are not well explored due to the limited methods for vinyl ether synthesis, especially acyclic 1,2-disubstituted vinylic ethers. Julia-Lythgoe-Kocienski olefination generates vinyl ethers, but with poor E/Z selectivity [15] (eq. 5). Current methods for vinyl ether synthesis are limited in scope and selectivity (**Figure 4**). Partial hydrogenation of ynol ethers indirectly gives E or Z vinyl ethers, but requires multiple steps [16] (eq. 3). Copper catalyzed cross-coupling of alcohols with alkenyl halides [17] or boron substrates (eq. 1 & 2) [18-19] generates vinyl ether, although this scope is limited to simple substrates. Ir catalyzed isomerization of diallyl ethers generates vinyl ethers, but this method is limited in scope to using simple allylic ethers [7] (eq. 4). Other classical methods require harsh conditions and are not compatible for complex vinyl ether synthesis.[20]

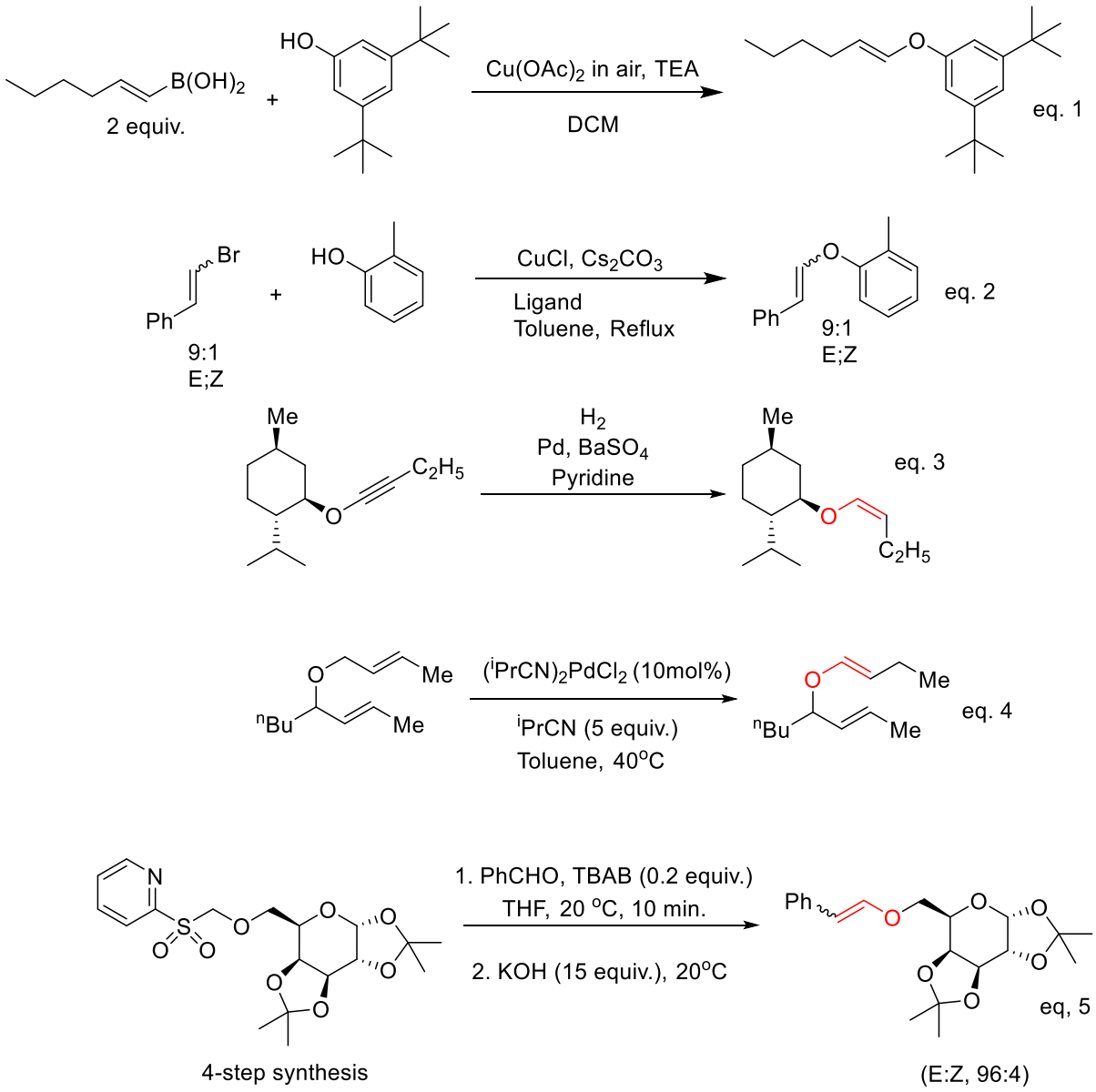


Figure 4: Current vinyl ether synthetic pathways

A direct and atom-economic route for vinyl ether synthesis, is an anti-Markovnikov hydroalkoxylation addition across an alkyne bond with an oxygen nucleophile. For this reaction, there is a regioselectivity between Markovnikov and anti-Markovnikov addition, and then there is a stereoselectivity for E or Z isomers. Markovnikov addition yields the terminal olefin isomer, while anti-Markovnikov addition has the possibility of generating E or Z vinyl ethers. Methodologies for Markovnikov hydroalkoxylation addition are well established, such as mercuric

salts and other Lewis acids,[21] but a consistent anti-Markovnikov method for synthesizing 1,2 disubstituted vinylic ethers remains elusive.

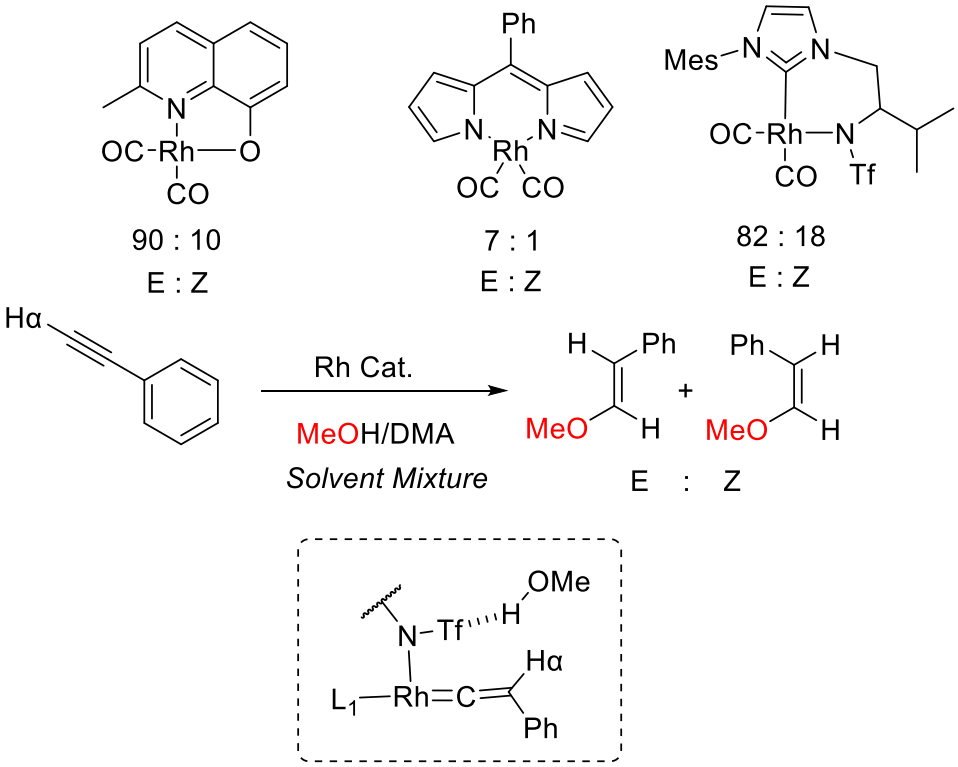


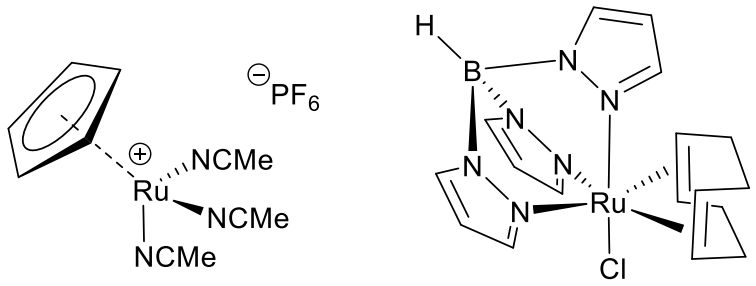
Figure 5: Vinyl ether synthesis via anti-Markovnikov addition

The primary methods for anti-Markovnikov vinyl ether synthesis utilize Rhodium catalyst. [22-23] These metal centers are known to rearrange terminal alkynes into vinylidene intermediates (**Figure 5**). The sp-sp_2 hybridized carbon intermediate reveals an electrophilic alpha-carbon that is prone to nucleophilic attack. Bera *et al*. describes the necessity of a proton acceptor ligand to assist methanol deprotonation and proton migration for promoting C-O bond formation and proton rearrangement from the beta-carbon to the alpha carbon. [22] The complex then generates a vinyl ether through a final rate limiting proton rearrangement guided by the H-bonding sites on the proton acceptor ligand. These methods are insightful, but are not practical because they require the alcohol to be a solvent. This work, along with mechanistic studies of 8-quinolinolato rhodium catalyst [24] reveals the significance of hydrogen bonding acceptor ligands, and how they mediate

proton rearrangement and lower the energy barrier required to generate vinyl ethers. Our lab aims to reduce the stoichiometry between the alcohol and alkyne to be 1:1, in order to accommodate structurally complex alcohols. The rhodium catalysts requires the attacking alcohol to also be the solvent or co-solvent. Requiring a large excess of the alcohol prevents these methods from being suitable for structurally complex vinyl ether synthesis. Rhodium is currently the most developed metal center for promoting anti-Markovnikov alkyne hydroalkoxylation, but expansion on its methodology is limited due to it being expensive and relatively inaccessible.

1.1.2 Vinyl Ester

Ruthenium is a cheaper alternative metal that has also been demonstrated to mediate C-O bond formation, presumably via vinylidene mechanisms. For example, ruthenium catalyst **23** mediates anti-Markovnikov addition between water and terminal alkynes to give aldehydes. [25] Catalyst **24** was demonstrated to synthesize vinyl esters via anti-Markovnikov addition between carboxylic acids and terminal alkyne [26] (**Figure 6**). These metal complexes demonstrate how ruthenium can catalyze C-O bond formation.



$[CpRu(NCCH_3)_3][PF_6]$ TPzRuClCOD

23 **24**

Hydration Hydroacyloxylation

Figure 6: Ruthenium catalyst for C-O bond formation

The mechanism for the vinyl ester synthesis is thought to proceed through displacement of the labile ligand to generate a vinylidene intermediate. [27-28] Once in proximity to the alcohol, the

alpha carbon undergoes nucleophilic attack, yielding (oxy)carbene intermediate. Then benzoic acid adds through either Markovnikov or anti-Markovnikov addition to yield vinyl esters. (**Figure 7**).

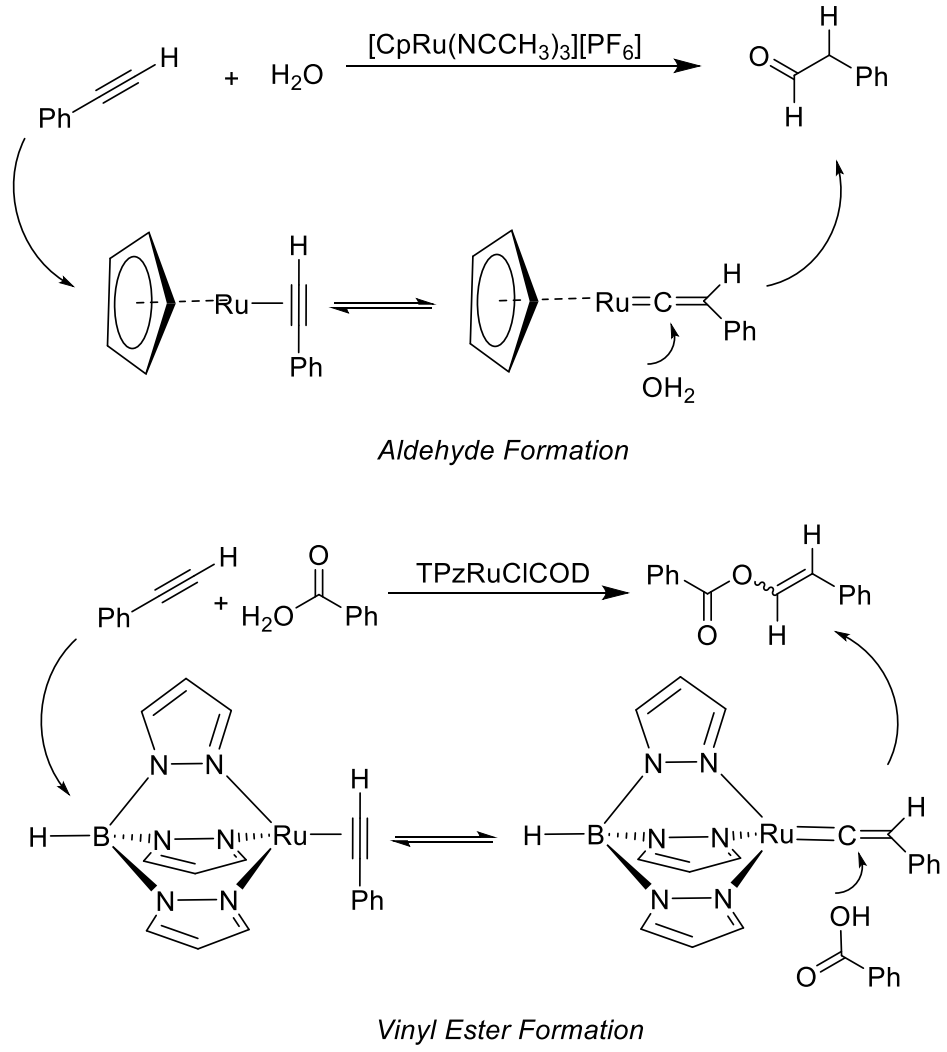


Figure 7: C-O bond formation via Ru vinylidene intermediate

1.2 Synthetic Strategy

We expect the alcohol nucleophile to function analogous to the carboxylic acid nucleophile, but the less acidic alcohols may be less nucleophilic. Therefore, we intend to utilize a modified scorpionate ligand with proton accepting properties to bring the alcohol closer to the alpha carbon

via electronic attraction for nucleophilic attack. This strategy is analogous to Rh catalyst that mediate vinyl ether synthesis, with excess alcohol. The specific aim is to develop a metal catalyst that catalyzes C-O bond formation via anti-Markovnikov addition between alcohols and terminal triple bonds. We sought to test two hypotheses: (1) design a ligand that increases the electrophilicity and reactivity of the metal-vinylidene intermediate to attract weaker nucleophiles such as alcohols, and (2) to use a suitable hydrogen bonding acceptor ligand to increase the nucleophilicity of the alcohol and mediate proton transfer steps. To test our hypothesis, we wanted to use a versatile metal ligand system that could be modified to test different conditions.

To achieve this, we initially planned to use 1,2,3-triazolyl rings as opposed to 1,2-pyrazoyl rings. We hypothesized that the lone pairs from the nitrogen atom will attract the proton on the attacking alcohol, increasing its nucleophilic properties. Also, the minimal difference compared to the control tpz ligand ensures that the changes in results can be confidently attributed to the new nitrogen replacing the carbon (**Figure 8a**).

Alternatively, hypothesized that decorating the tris-pyrazolyl borate ligand with electron withdrawing groups will induce a more electron deficient and reactive metal center (**Figure 8b**). This set of scorpionate ligands allowed us to test our hypothesis, and improve on a ruthenium catalyst system to allow for the addition of less reactive alcohol nucleophiles.

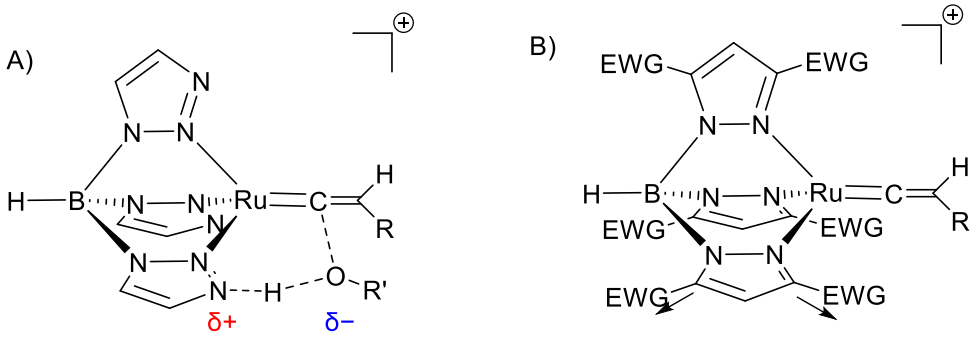
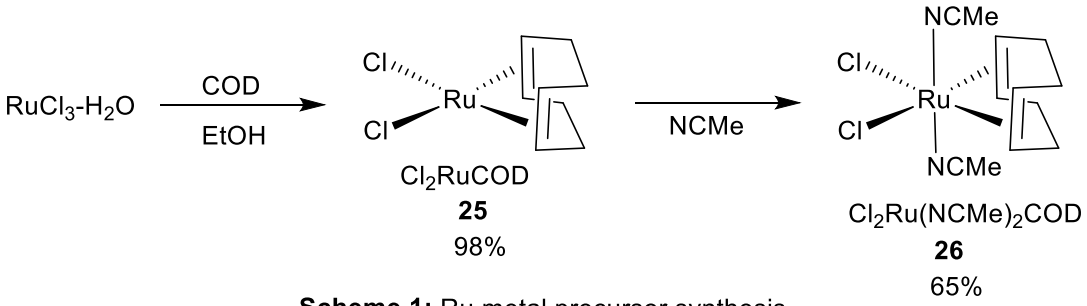


Figure 8: Modified scorpionate ligands designed for vinyl ether synthesis by alkyne hydroalkoxylation

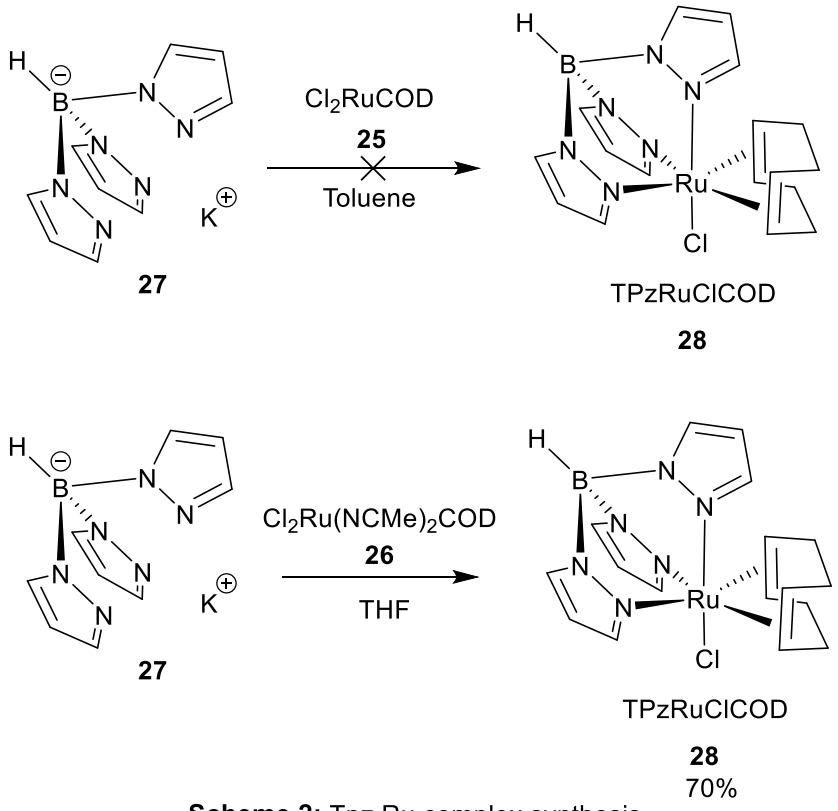
1.3 Catalyst Synthesis and Results

1.3.1 Preliminary Catalyst Synthesis (Synthesis of $HB(Pz)_3Ru(L)Cl$)



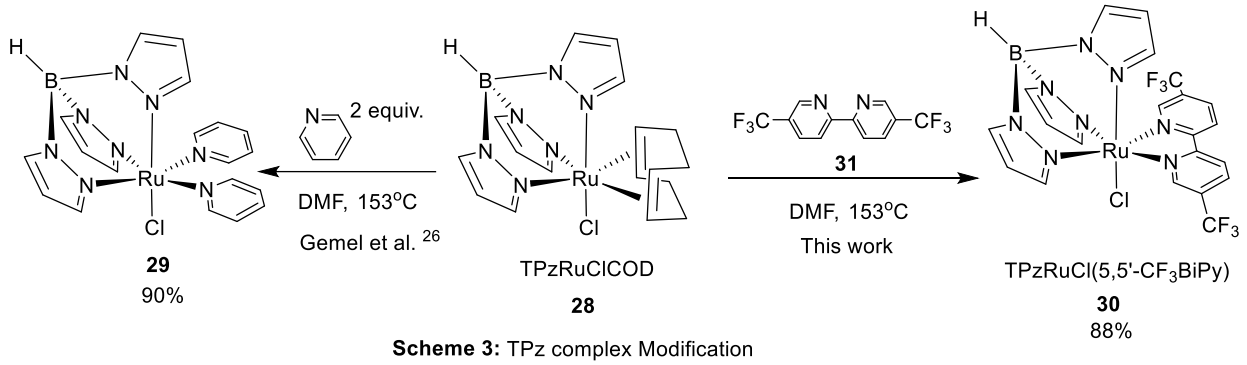
Scheme 1: Ru metal precursor synthesis

Metal catalyst TPzRu(COD)Cl **28** was the control system for catalyst synthesis and hydroalkoxylation experiments. The commercially available tris(pyrazolyl)borate ligand **27** was the basic skeleton we planned to build upon. Comparing the reactivity of TPzRu(COD)Cl **28** with its functionalized analogs allowed us to directly determine the impacts of our modifications. Air-stable complex **25** was used as a convenient starting material, which was synthesized from refluxing $RuCl_3$-H_2O with COD in ethanol (**Scheme 1**). [29] Rodriguez *et al*. reported synthesizing TPzRu(COD)Cl **28** from refluxing **27** and **25** in THF, followed by toluene extraction. [30] However, we were unable to reproduce this and pursued other methods. Complex **26** was subsequently synthesized from **25** refluxing in acetonitrile, and this complex proved to be a reliable synthetic precursor for our purposes. [31] We found that refluxing **26** and **27** in THF affords the desired product **28**, as reported in later literature (**Scheme 2**). [32]



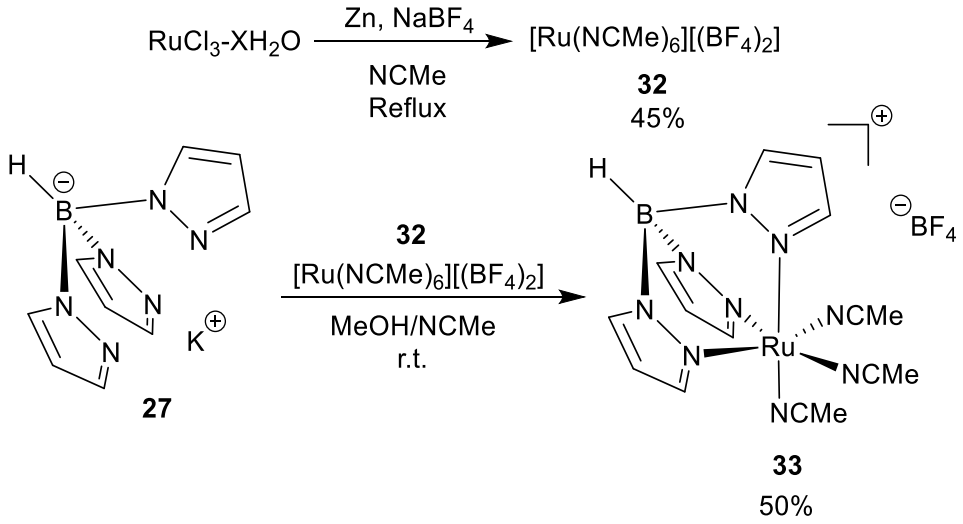
Scheme 2: Tpz Ru complex synthesis

Kirchner *w*. reports that the COD ligand on complex **28** can be substituted by refluxing with the desired ligand in DMF.[26] We hypothesized that establishing a method for substituting the COD ligand would expand our screening reaction scope for favorable reactivity. Refluxing **28** in DMF with excess pyridine yields **29**. This species is reported in literature,[26] and is known to catalyze the addition of benzoic acid or allylic alcohol with phenylacetylene. We wanted to use a ligand that has been demonstrated to promote carbon-oxygen bond formation via vinylidene intermediate. Herzon reports that commercially available ligand, 5,5'-bis(trifluoromethyl)-2,2'-bipyridine **31** was found to be the optimal ligand for promoting anti-Markovnikov phenylacetylene hydration. [25] An explanation for this is not discussed, but the ligand may assist with vinylidene formation and/or proton transfer, which is applicable for our studies. Boiling **28** with ligand **31** cleanly affords **30** upon workup (**Scheme 3**).



Scheme 3: TPz complex Modification

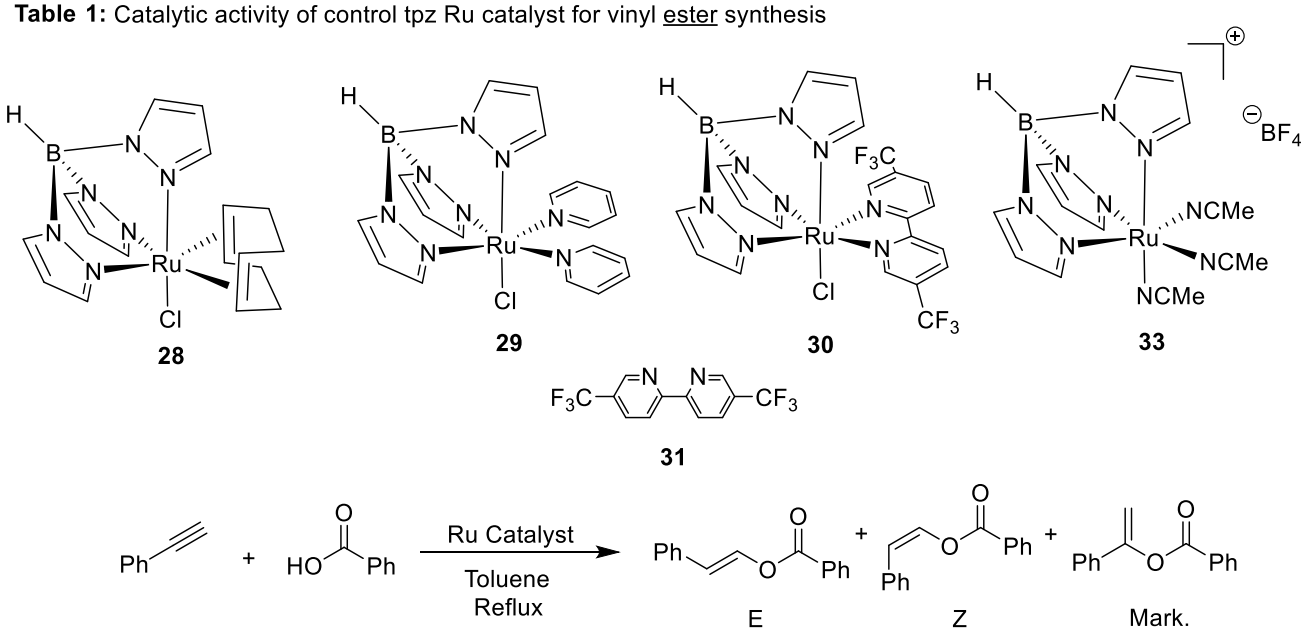
Tpz-ruthenium complex **28** and **29** are known to catalyze the hydroalkoxylation addition of benzoic acid to phenylacetylene. We intended to use this reaction as an initial screen to determine if complex **30** is a possible candidate for exploration. Complex **28** was reported to yield a mixture of E/Z/Markovnikov isomers at a 1.63 : 1.00 : 0.00 ratio when heated in toluene to reflux for 10 hours. When we replicated these conditions, we found that the complex generates an additional Markovnikov product with a ratio of 1.71 : 1.00 : 0.10. Complex **29** was reported to generate vinyl esters at a ratio of 1.20 : 1.00: 0.00. Complex **30** is novel and not reported in literature. The structure was confirmed by NMR and mass spectrometry. When we subject complex **30** to the same reactive conditions, it generated a E:Z ratio of 0.33 : 1.00, with trace amounts of Markovnikov product. Overall, however, the catalyst exhibited a significantly less yield compared to other catalyst at only 1%, but the favored selectivity switched from the E isomer to the Z. These early experiments confirm the significance of both the scorpionate ligand and the other accompanying ligand on yield and selectivity.



Scheme 4: Synthesis of tpz Ru complex with labile acetonitrile ligands

We decided to use complex **33** as another catalyst system to explore, because it expands our reaction screening towards finding a catalyst for vinyl ether synthesis. Although its reactivity for vinyl ester synthesis is not reported, we decided to use this system because the labile acetonitrile ligands allows us to test other ligands with in-situ methodologies. We aimed to generate $[TPzRu(NCMe)_3][BF_4]$ analogs with our library of scorpionate ligands to quickly assess the influence of ligand substituents on reactivity and expand our vinyl ether catalyst screening. [33] Metal complex $Ru(NCMe)_6(BF_4)_2$ **32** serves as the general precursor for generating these in-situ scorpionate catalyst. The catalyst is generated from refluxing $RuCl_3$-H_2O in acetonitrile with $NaBF_4$, mediated by Zn which reduces Ru(III) into Ru(II). Complex $[Ru(NCMe)_6][(BF_4)_2]$ **32** is synthesized in an acetonitrile/methanol mixture, and will serve as the control for in-situ methods (**Scheme 4**). It was found to be catalytically active for vinyl ester synthesis, generating a yield of 41% and a selectivity of 68 : 25 : 7 (E : Z : Mark.) when heated in toluene to 110^{o}C for 24 hours. When ligand **31** is added to the reaction the yield drops to 29 % but the selectivity changes to favor the Z isomer, 24 : 72 : 4 (E : Z : Mark.) (**Table 1**). This set of reactions show how selectivity can be controlled with the ligand choice, and we hoped to apply this towards vinyl ether synthesis.

Table 1: Catalytic activity of control tpz Ru catalyst for vinyl ester synthesis



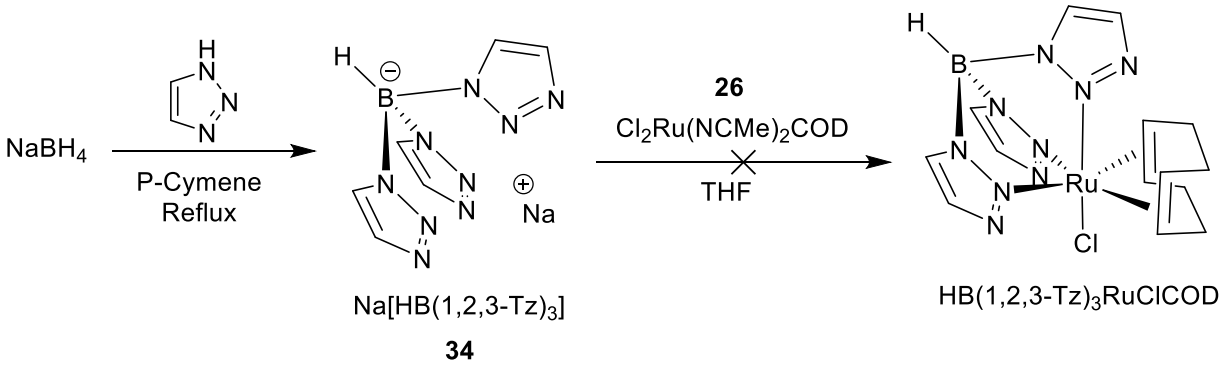
Catalyst	Ligand	Time (hr.)	Yield	E : Z : Mark.
28	None	10	96%	61 : 36 : 3
29	None	10	98%	55 : 45 : 0
30	None	18	1%	25 : 75 : trace
33	None	24	41%	68 : 25 :7
33	**31**	24	29%	24 : 72 :4

(a) Isolated yields (b) selectivity determined by ^{1}H NMR integrations of vinyl peaks

1.3.2 Hydrogen Bonding Accepting Catalyst Synthesis (Synthesis of HB(BzTz)$_3$Ru(L)Cl)

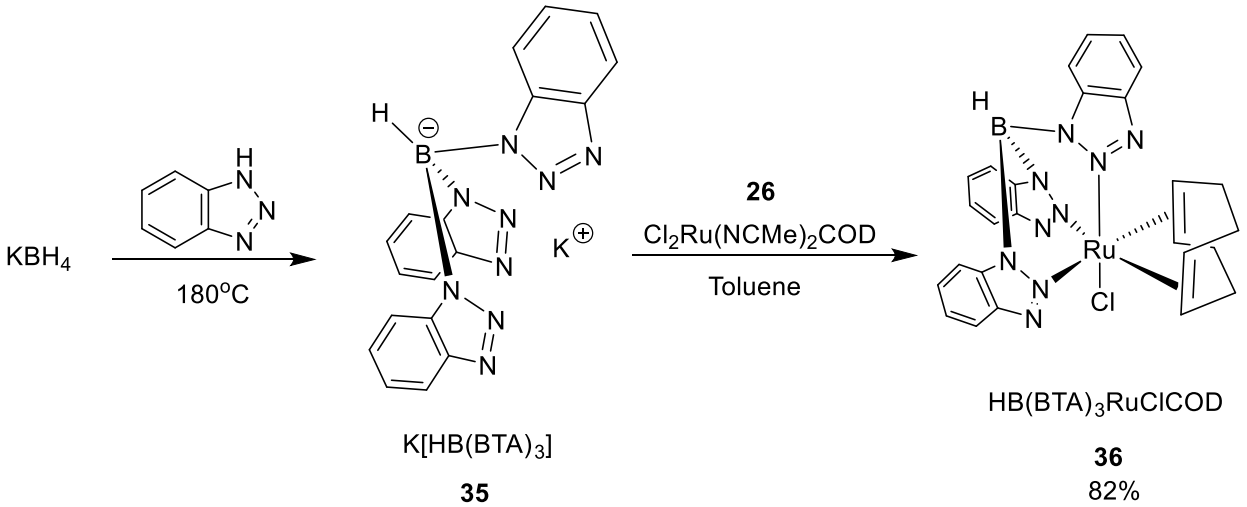
Our first approach is to develop a ligand with a hydrogen bonding accepting properties to promote nucleophilic attack. To achieve this, we planned to use tris(1,2,3-triazolyl)borate **34** ligands. We hypothesized that the alternative nitrogen atom will attract the proton on the attacking alcohol, increasing its nucleophilic properties. Also, the minimal difference compared to the control tpz ligand **27** ensures that the impacts can be confidently attributed to the new nitrogen replacing the carbon. Scorpionate ligand **34** was reported to be generated after refluxing $NaBH_4$

and (1,2,3)-triazole at 180°C in para-cymene for 1 week, followed by subsequent THF washes. [34] A method for chelating this ligand to ruthenium has not been reported, therefore the method to chelate **27** and **26** was initially applied. Due to significant solubility barriers, the resulting precipitates could not be analyzed (**Scheme 5**) with ligand **34**.



Scheme 5: Attempted synthesis of triazole Ru complex

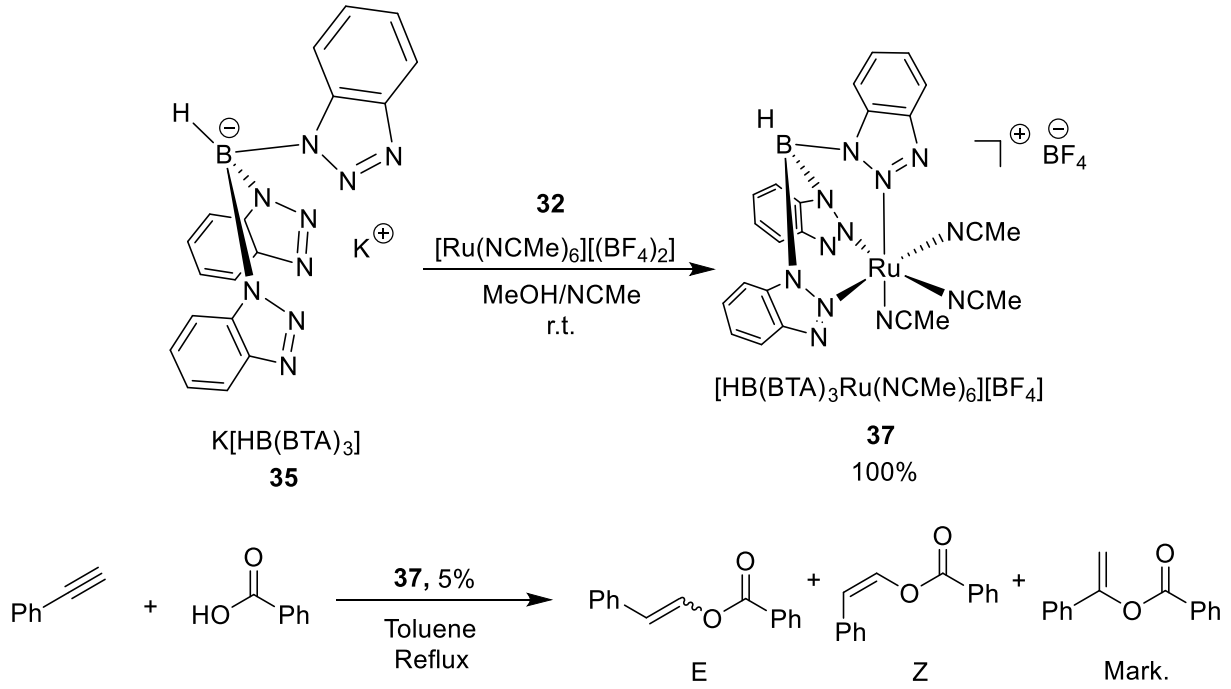
As chelation of **34** and **26** proved non-trivial, we decided to aim for an analog of **33** that has more carbon atoms, to increase its solubility. We decided to pursue tris(1,2,3-benzotriazoly)borate **35**, due to its literature precedents and precursor accessibility. [35a] Although found in literature, a comprehensive method and workup for generating ligand **35** was not clearly reported. Originally, we synthesized **11** from refluxing in para-cymene for a week, but this method was found to be difficult to reproduce, and time consuming. Therefore, we aimed to find a more comprehensive route. We found that heating KBH_4 and benzotriazole without any solvent overnight at 180°C, followed by DCM extraction and diethyl ether washes yields **35** in good yields. We found that refluxing **35** and **26** in toluene affords a solid, which upon DCM extraction yields a crude green product **36**. (**Scheme 6**).



Scheme 6: Synthesis of BTA Ru complex

The structure of the solid could not be determined with NMR due to insolubility in $CDCl_3$, DMSO, and MeOD, but was characterized with MS. Efforts to crystalize the solid were also unsuccessful. The structure of complex **36** is a proposal based on ^1H NMR of complex **37**, which shows symmetry among the BTA ligands that suggest tridentate coordination. We decided to use hydroalkoxylation experiments between benzoic acid and phenylacetylene to determine if the product is catalytically active and worth exploring with alcohol nucleophiles. The solid, presumably **36**, mediated vinyl ester synthesis with a selectivity of 35 : 59 : 6 (E : Z : Markovnikov) and a yield of 39%.

We wanted to screen $HB(BTA)_3Ru(NCMe)_3BF_4$ **37** for vinyl ether synthesis capabilities because the labile acetonitrile provide access to the Ru metal center and allow for in-situ ligand studies to hopefully promote reactivity. We used the method for synthesizing $TPzRu(NCMe)_3BF_4$ **33** by stirring a mixture of $K[HB(BTA)_3]$ **35** in methanol with the Ru metal precursor in acetonitrile until the desired product crashes out of solution. Diethyl ether washes cleanly afforded the desired material (**Scheme 7**).



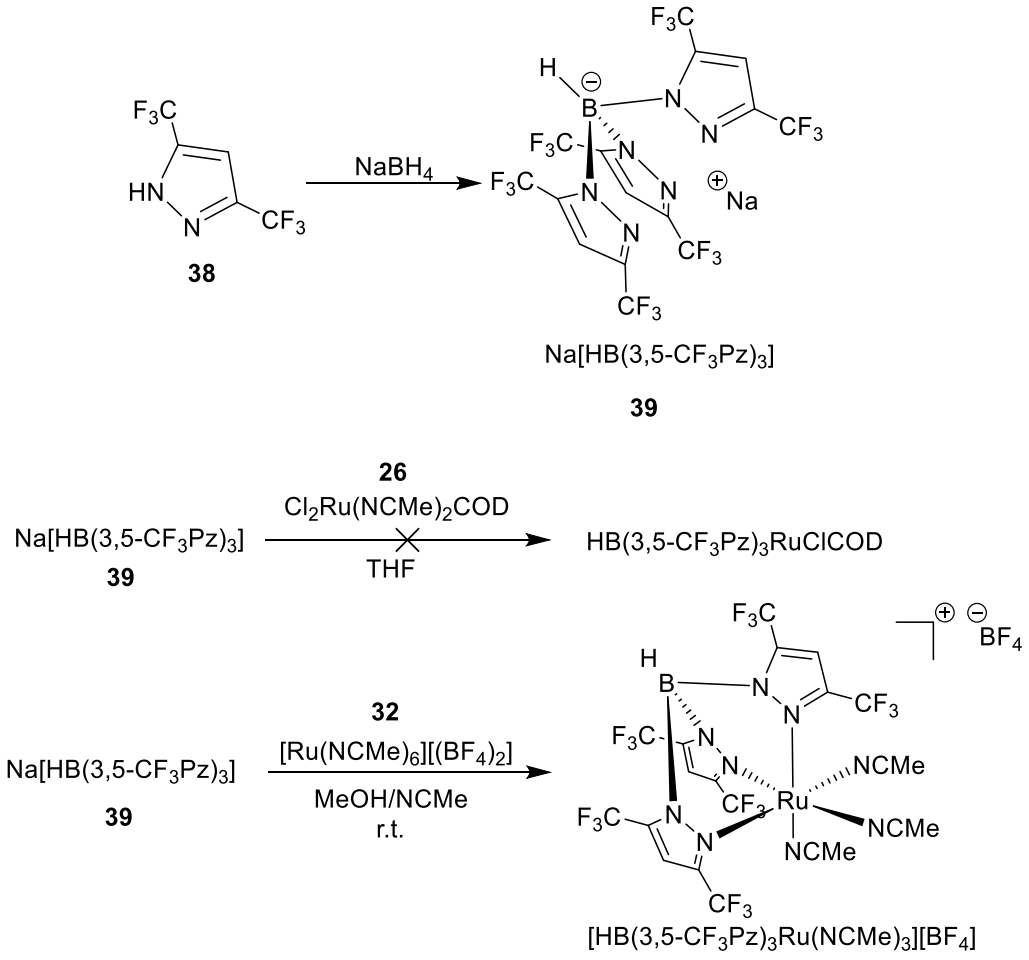
Scheme 7: Synthesis of BTA Ru complex with labile acetonitrile ligands

The complex **37** was characterized by NMR and we ran a vinyl ester synthesis experiment with benzoic acid and phenylacetylene. The symmetry of the NMR spectra indicated to us that there was a tridentate coordination with all BTA rings coordinating to the ruthenium center. The complex generated vinyl ester product with a yield of 25% and a selectivity of 43 : 50 : 7 (E : Z : Mark.). When the reaction was ran with ligand **31**, it formed product with a yield of 35% and shifted the selectivity to 29 : 67 : 4 (E : Z : Mark.). Other ligands such as COD, bipyridine, and triphenyl phosphine were unable to promote reactivity to occur.

1.3.3 Electron Deficient Metal Catalyst Synthesis

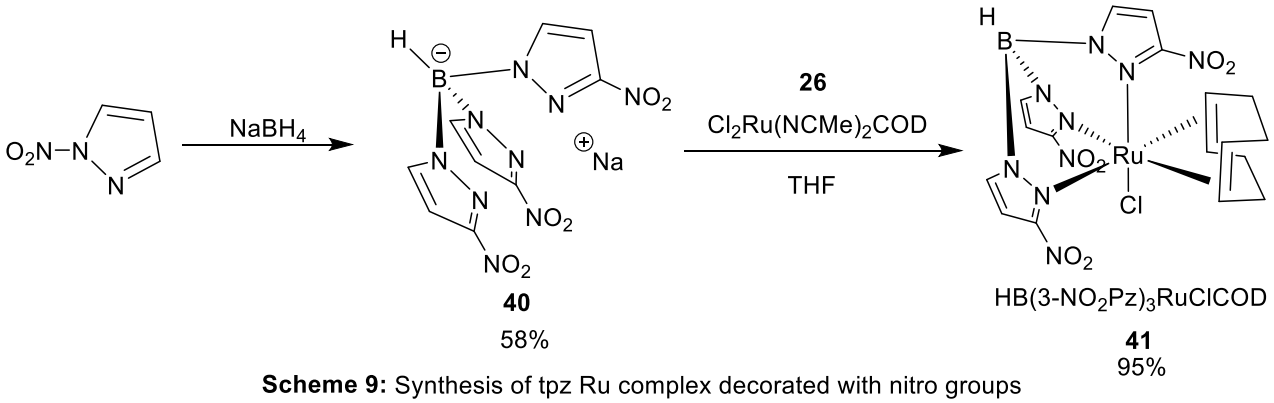
Our second approach is to increase the electron-deficiency of the ruthenium metal center. To achieve this, we decided to pursue tris(3,5-bis(trifluoromethyl)-pyrazole) borate **39** and tris(3-nitro)-pyrazole borate. These ligands are decorated with electron withdrawing groups, which we hypothesize will increase the electrophilicity of the chelated metal center and the partial positive

charge on the alpha carbon of the vinylidene intermediate, making it more likely for a nucleophile to attack. Ring precursor **38** was synthesized from refluxing hydrazine and hexafluoroacetylacetone in ethanol, followed by purification via sublimation. [36] As reported, **39** is synthesized from heating $NaBH_4$ and **15** to 190°C followed by sublimation purification. [37-38] We then tried to chelate **39** and **26**, but this has proven to be a difficult task. The methodology used to chelate **27** and **26** was attempted to chelate **39** with **26**, but this yields an unreactive crude oil. (**Scheme 8**).



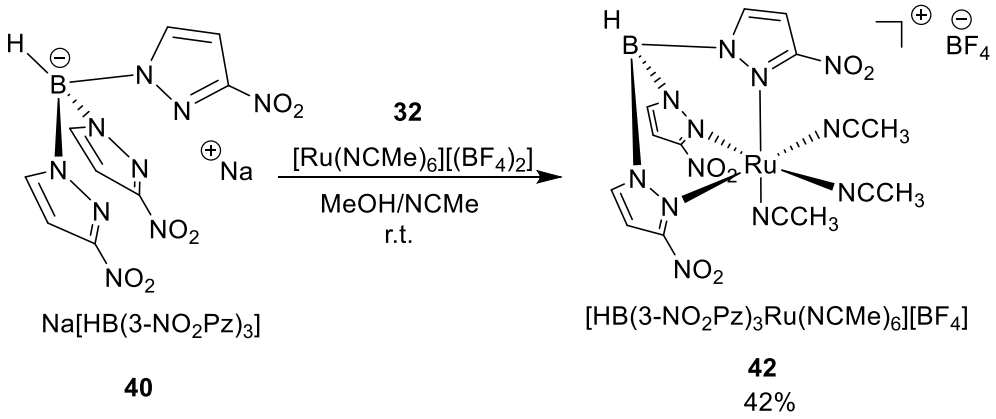
Scheme 8: Attempted synthesis of tpz Ru complex decorated with trifluoromethyl groups

To generate a reactive catalyst with the tris(3,5-bis(trifluoromethyl)-pyrazole) borate we attempted to chelate it with $[Ru(NCMe)_6][(BF_4)_2]$. Using the same method for chelating $K[HB(Pz)_3]$, a white solid was formed upon work up. Vinyl ester experiments were ran to determine reactivity, and found that the solid did not generate vinyl ester product between phenylacetylene and benzoic acid.



Scheme 9: Synthesis of tpz Ru complex decorated with nitro groups

Since ligand **39** was unsuccessful at forming a reactive catalyst for vinyl ether synthesis, we decided to shift our efforts towards tris(3-nitro)-pyrazole borate. [39] This scorpionate ligand is reported to be generated from heating the nitro pyrazole precursor with KBH_4 in anisole solvent at 180°C. This scorpionate ligand generated a reactive catalyst with $Ru(NCMe)_2Cl_2COD$ using an analogous method for chelating the tris(pyrazolyl)borate. (**Scheme 9**). Much like the BTA scorpionate catalyst, characterization of the structure was difficult and could not be resolved with NMR, because of its insolubility in DMSO, $CDCl_3$, and MeOD. Vinyl ester synthesis is used to determine if a reactive complex is obtained. This catalyst generated a yield of 79% with a selectivity of 46 : 42 : 12 (E : Z : Markovnikov). When used with ligand **31**, the selectivity switches to favor the Z isomer, 12 : 88 : 0 with a 71% yield . We then tried to expand this catalyst into vinyl ether synthesis. Unfortunately, we were unable to push this catalyst to generate vinyl ethers from phenylacetylene. Both methanol and benzyl alcohol returned starting material as the product.



Scheme 10: Synthesis of nitro tpz Ru complex with labile acetonitrile ligands

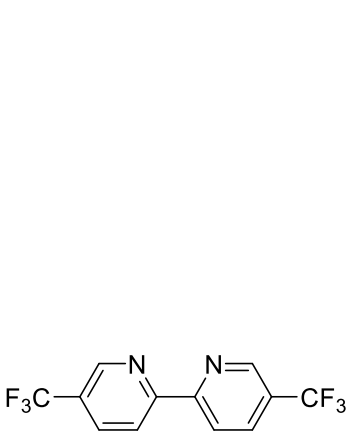
The next step in our investigation is to chelate our nitro scorpionate ligand with $[Ru(NCMe)_6][(BF_4)_2]$ **32** to expand our scope and explore complementary ligands to improve reactivity. Following the same methodology for the synthesis of $TPzRuNCMe_3BF_4$ **42**, a solution of the scorpionate ligand in methanol was added to a solution of the metal precursor in acetonitrile to generate our reactive solid (**Scheme 10**). The returned solid successfully catalyzed vinyl ester synthesis between phenylacetylene and benzoic acid with a 64% yield and a selectivity of 68 : 24 : 8.

1.3.4 Hydroalkoxylation Experiments

With 3 catalytically active products, we decided to test whether the catalysts are capable of mediating vinyl ether synthesis. We explored two methodologies to test the products catalytic activity: a method analogous to the Rh catalyst for vinyl ether synthesis with methanol, and a method analogous to the Ru catalyst for vinyl ester synthesis with benzyl alcohol. With methanol, we heated a reaction mixture of phenyl acetylene and the catalyst of choice dissolvent in a solvent mixture of methanol and DMA. The reactions with benzyl alcohol were conducted analogously to the vinyl ester experiments, expect benzoic acid was substituted for benzyl alcohol. After screening both reactions, our lab determined that the complexes are unable to catalyze hydroalkoxylation

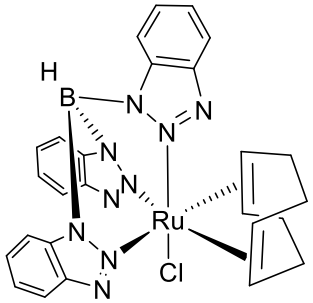
addition between acetylenes and alcohols as only the acetylene is returned in every case regardless of the conditions. The results from these experiments do not support hypothesis, and suggest that the differences in the scorpionate system are not significant enough to promote reactivity with weaker alcohol nucleophiles (**Table 2**).

Table 2: Attempted vinyl ether synthesis experiments



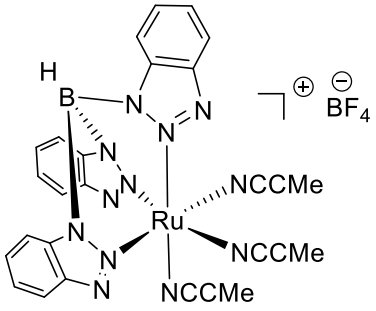
31

R_1 = -OCOPh
R_2 = -CH_3
R_3 = -CH_2Ph



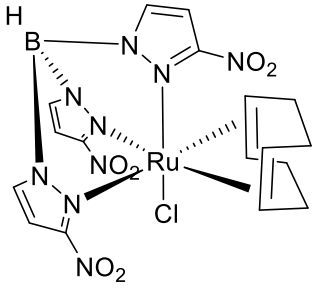
$HB(BTA)_3RuClCOD$

36



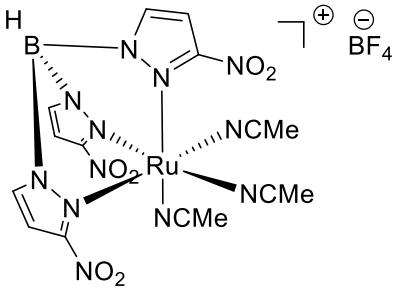
$HB(BTA)_3Ru(NCMe)_3BF_4$

37



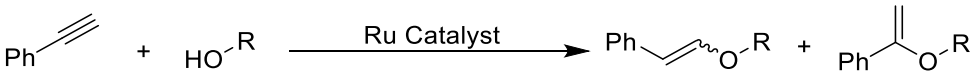
$HB(3\text{-}NO_2Pz)_3RuClCOD$

41



$[HB(3\text{-}NO_2Pz)_3Ru(NCMe)_6][BF_4]$

42



R	Catalyst	Ligand	Solvent	Temp. (C°)	Yield	E : Z : Mark.
Benzoic Acid	**36**	None	Toluene	110	39%	35 : 59 : 6
Methanol	**36**	None	DMA	110	-	No Reaction
	36	None	None	110	-	No Reaction
Benzyl Alcohol	**36**	None	Toluene	110	-	No Reaction
	36	None	DMA	110	-	No Reaction

Benzoic Acid	**37**	None	Toluene	110	25%	43 : 50 : 7
Methanol	**37**	None	DMA	110	-	No Reaction
	37	None	None	110	-	No Reaction
	37	**31**	DMA	110	-	No Reaction
Benzyl Alcohol	**37**	None	Toluene	110	-	No Reaction
	37	None	DMA	110	-	No Reaction
Benzoic Acid	**41**	None	Toluene	110	79%	46 : 42 : 12
Methanol	**41**	None	DMA	110	-	No Reaction
	41	None	None	110	-	No Reaction
	41	**31**	DMA	110	-	No Reaction
Benzyl Alcohol	**41**	None	Toluene	110	-	No Reaction
	41	None	DMA	110	-	No Reaction
Benzoic Acid	**42**	None	Toluene	110	64%	68 : 24 : 8
Methanol	**42**	None	DMA	110	-	No Reaction
	42	None	None	110	-	No Reaction
	42	**31**	DMA	110	-	No Reaction
Benzyl Alcohol	**42**	None	Toluene	110	-	No Reaction
	42	None	DMA	110	-	No Reaction

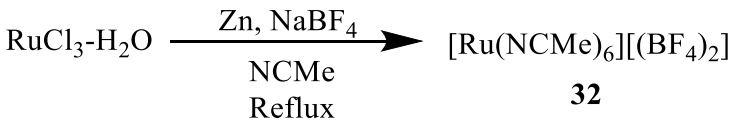
1.4 Conclusions

Our lab is interested in developing a comprehensive method for the complex synthesis of vinyl ethers via anti-Markovnikov hydroalkoxylation. We hypothesized that by modifying scorpionate Ru catalyst for vinyl ester synthesis, we could promote the addition of less reactive alcohols for the synthesis of vinyl ethers. Following the direction of present Rh catalyst that can generate vinyl ethers, we hypothesized that we could promote nucleophilic addition by attaching an additional nitrogen atom so the lone pairs can function as a hydrogen bonding accepting ligand for the

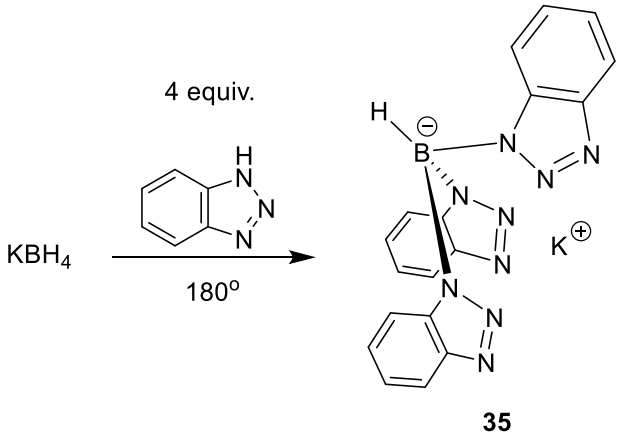
attaching alcohol. We also hypothesized that decorating the scorpionate ligand with electron withdrawing groups would induce a more electrophilic metal center and a more reactive vinylidene intermediate. We successfully at synthesized scorpionate compounds to test both hypothesis, and confirmed their reactivity via *vinyl ester* synthesis. However, we were unable to promote any *vinyl ether* synthesis with our Ru catalysts, as they all returned unreacted starting material. Through our screening we discovered a method to influence E and Z stereoselectivity depending on the ligands used. Although we were unable to use this technique for vinyl ether synthesis, we were able to apply this towards vinyl ester synthesis with terminal alkynes (*Chapter 2*).

1.5 Experimental Section

General Information: Proton and carbon NMR spectra were recorded INOVA-400 (400 MHz), INOVA-600 (600 MHz), or a BRUKER 600 (600 MHz) instrument equipped with cryogen probe. NMR spectra were recorded in solutions of deuterated chloroform (CDCl3) with the residual chloroform (7.27 ppm for ^{1}H NMR and 77.23 ppm for 13C NMR) taken as the internal standard, or in deuterated dimethyl sulfoxide (DMSO-d6) and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; m, multiplet. Thin layer chromatography (TLC) was performed on pre-coated glass-backed plates purchased from Whatman (silica gel 60F254; 0.25mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from Silicycle. All reactions were carried out with anhydrous solvents in oven-dried or flame-dried and argon-charged glassware unless otherwise specified. All anhydrous solvents were purchased from Sigma-Aldrich. Other solvents used in extraction procedures and chromatography were used as received from commercial suppliers without prior purification.

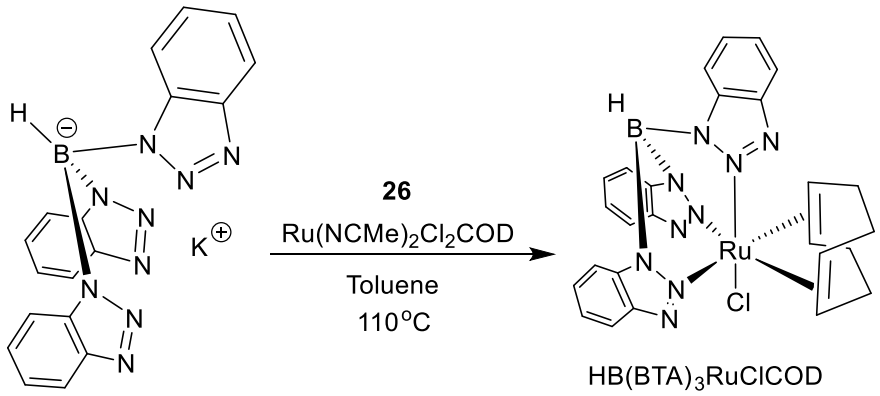


Synthesis of [Ru(NCMe)$_6$][(BF$_4$)$_2$] 32: In a dry 500 mL round bottom flask, $RuCl_3$-H_2O (2.0 g, 7.15 mmol), zinc (0.23 g, 3.60 mmol) and acetonitrile (150 mL) were heated to reflux for 30 min. Once cooled to room temperature, the solution was filtered through celite and $NaBF_4$ (1.65 g, 15.0 mmol) was subsequently added to the filtrate. The filtrate was then heated to reflux for 12 hrs. The solution was cooled to room temperature, filtered through celite, and reduced under rotary evaporation to yield brown solid. The solid was then washed with acetone to remove the salts, yielding the product as a yellow solid. Yield **32**: (1.49 g, 2.86 mmol, 45%). ^{1}H NMR spectroscopic data were in agreement with the literature.



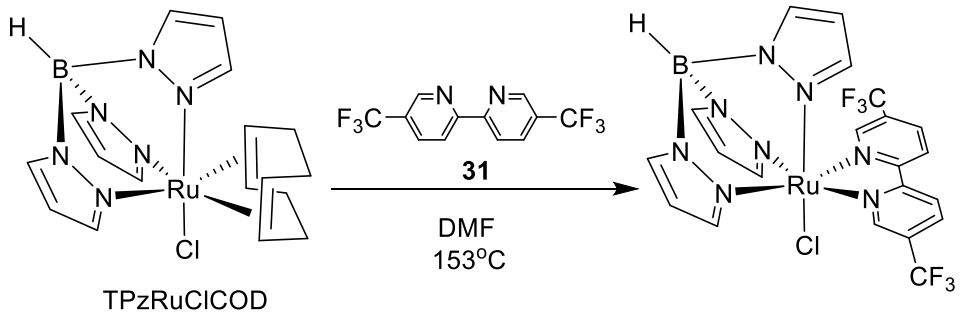
Synthesis of K[HB(C$_6$H$_4$N$_3$)$_3$] 35: KBH_4 (0.4 g, 7.40 mmol) and BTA (3.54 g, 29.60 mmol) were charged to a dry 50 mL round bottom with a stir bar under argon. The flask was heated to 190^O C for 15 hours. The flask is then removed from the heat and allowed to cool to room temperature. The resultant oil was suspended in DCM (15 mL) and sonicated it for 30 min. Filter the solution and collect the yellow filtrate. Next, remove the solvent with the rotary evaporator, and stir the oil

with diethyl ether (30 mL) overnight. The resultant white solid is filtered, washed with hexanes and hot toluene. The solid was then dried under high vacuum. Yield **35**: (2.752 g, 92%). ^{1}H NMR (DMSO, 400 MHz): δ 7.91 (m, 1H), 7.81 (m, 1H), 7.32-7.15 (m, 2H), ^{13}C NMR (DMSO, 100 MHz): δ_C 125.9, 124.0, 122.9, 118.6, 115.6, 113.0 ppm. HR-ESI-MS (*m/z*): $[L]^-$ $C_{18}H_{13}BN_9$ 366.13925 (calcd.); 366.13867 (found). IR: 3219, 2470, 1614, 1449, 1348, 1133, 1042, 740 cm^{-1}



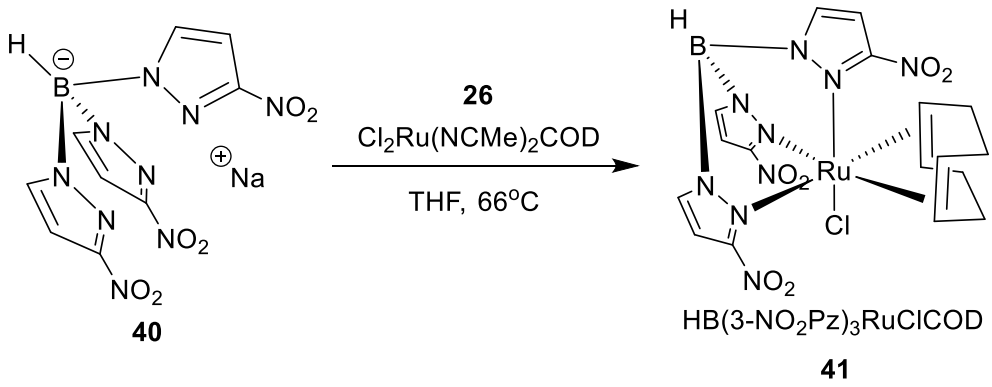
35 **36**

Synthesis of HB(BTA)$_3$RuCl(COD) 36: Ligand **35** (0.30 g, 0.82 mmol) and metal complex **26** (0.27 g, 0.74 m mol) are charged to a dry 50 mL round bottom under argon. Toluene (20 mL) then added to the flask and heated to reflux with stirring for 4 hours. The flask was removed from heat and once cooled to room temperature, the solid was collected via filtration and washed with hexanes and DI water. The solid was washed with DCM (20 mL) and the filtrate was collected. Addition of petroleum ether to the filtrate crashes out green solid **36**. Yield: (0.371 g, 0.61 mmol, 82 %). HR-ESI-MS (*m/z*): $[L]^-$ $C_{26}H_{25}N_9BCl_2Ru$ 646.0756 (calcd.); 646.0752 (found). A ^{1}H NMR spectrum could not be obtained due to insolubility in $CDCl_3$, DMSO, MeOD.



Synthesis of [TPzRuCl(bipy)] (bipy = $(C_6NF_3)_2$) 30: The metal complex **28** (0.15 g, 0.33 mmol) was added to a solution of DMF (15 mL) and ligand **31** (0.10 g, 0.34 mmol) in a dry 100 mL round bottom flask under argon**.** The solution was then heated to reflux for 1 hour. It was then cooled to room temperature and subsequently filtered. The filtrate was then reduced by rotary evaporation, and the resulting residue was dissolved in DCM (10 mL). Petroleum ether (25 mL) is added to the solution and the mixture sits in the refrigerator overnight. The resulting solid **30** is collected by filtration and washed with petroleum ether (20 mL). Yield: (0.19 g, 0.29 mmol, 88%). ^{1}H NMR (DMSO, 400 MHz): 9.05 (d, 2H, *J* = 8 Hz), 8.80 (s, 2H), 8.41 (d, 2H, *J* = 8 Hz) 8.05 (s, 2H) 7.89 (m, 3H), 6.50 (m, 2H), 6.11 (m, 1H), 5.94 (m, 1H). HR-ESI-MS (*m/z*): $[L]^-$ $C_{21}H_{16}N_8BClF_6Ru$ 636.02498 (calcd.); 636.02542 (found).

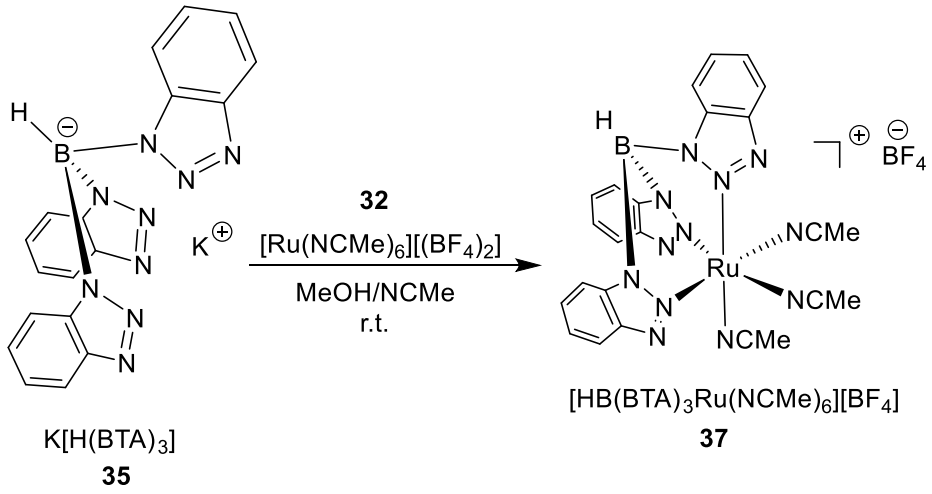
The symmetry of the proposed structure is supported from the ^{1}H spectrum. One pyrazole ring is apical and directly across from the chlorine atom. The other two of the pyrazole rings are across from the COD ligand. We expect these two pyrazole rings to show different chemical shifts in comparison to the one apical pyrazole ring. Since this is reflected in the ^{1}H NMR, we can infer that the symmetry is as predicted.



40 **41**

HB(3-NO_2Pz)$_3$RuClCOD

Synthesis of HB(3-NO_2Pz)$_3$RuCl(COD) 41: Ligand **40** (0.30 g, 0.81 mmol) and metal complex **26** (0.27 g, 0.74 m mol) are charged to a dry 50 mL round bottom under argon. THF (20 mL) is then added to the flask and heated to reflux with stirring for 24 hours. The solvent was removed via rotary evaporation and the residue is triturated with diethyl ether. The solid is collected via filtration and the diethyl ether wash is discarded. The solid was then dissolved with DCM (20 mL) and the filtrate was collected. Petroleum ether is then added to the filtrate and stored in the freezer overnight. The resulting solid **41** that crashes out of solution is then collected via filtration and washed with diethyl ether. Yield: (0.67 g, 1.18 mmol, 95 %). A ^{1}H NMR spectrum could not be obtained due to insolubility in $CDCl_3$, DMSO, MeOD.

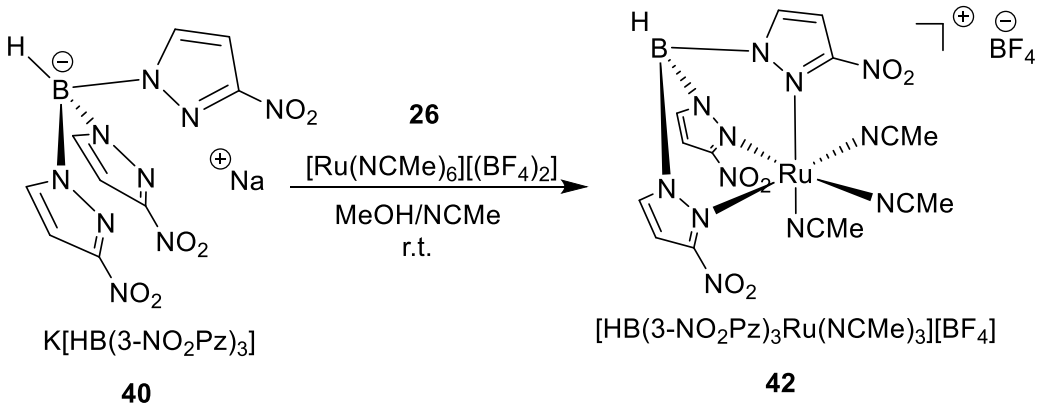


K[H(BTA)$_3$]
35

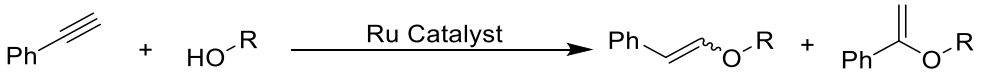
[HB(BTA)$_3$Ru(NCMe)$_6$][BF$_4$]
37

Synthesis of [HB(BTA)$_3$Ru(NCMe)$_3$][BF$_4$] 37: A solution of scorpionate ligand **35** (0.231 g; 0.35 mmol) in methanol (10 mL) was added by syringe to a solution of **32** (88.1 mg, 0.38 mmol) in acetonitrile (25 mL) and stirred for 2 hr. at room temperature. The desired product crashes out of solution over time. Once done, the solid is collected via filtration and washed with more diethyl ether yielding a white solid. **(**0.237 g, 0.35 mmol, 100%).

^{1}H NMR (DMSO, 400 MHz): 7.89 (d, 1H, *J* = 8 Hz), 7.27 (d, 1H, *J* = 8 Hz), 7.22-7.15 (m, 2H) 2.71 (s, 9H) ^{19}F NMR (DMSO, 400 MHz): δ - 148.3 (s)

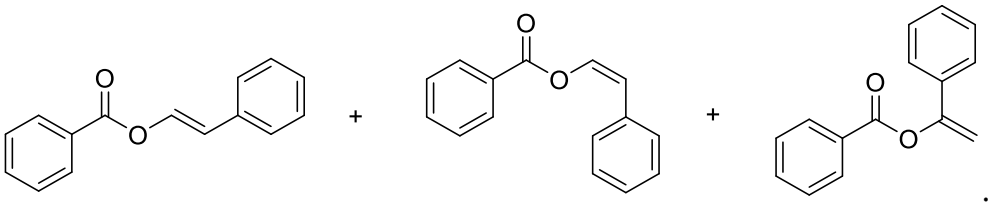


Synthesis of [HB(3-(NO$_2$)pz)$_3$Ru(NCMe)$_3$][(BF$_4$)] 42: A solution of the **40** (0.212 g, 0.84 mmol) in methanol (10 mL) was added by syringe to a solution of **26** (0.396 g, 0.76 mmol) in acetonitrile (25 mL) and stirred for 1 hr. at room temperature. Once done, the solvent was reduced by half and the residue was extracted with acetone. The filtrate was collected and reduced under rotary evaporation. Diethyl ether was subsequently added to promote **42** to crash out as a yellowish/white solid. The solid was collected via filtration and washed with more ether. Yield: (0.210 g, 0.32 mmol, 42%). A ^{1}H NMR spectrum could not be obtained due to insolubility in $CDCl_3$, DMSO, MeOD.



General Hydroalkoxylation Experiments Phenylacetylene (0.056 mL, 0.50 mmol) and benzoic acid (0.061 g, 0.50 mmol) – or benzyl alcohol (0.054 g, 0.50 mmol) – or co-solvent methanol (5 mL) are dissolved in toluene (5 mL) with the catalyst (0.01 mmol) and the additional ligand (0.01 mmol) when necessary. The mixture is then heated to reflux for 24 hours. Once complete, the solvent is removed by rotary evaporation and analyzed by ^{1}H NMR.

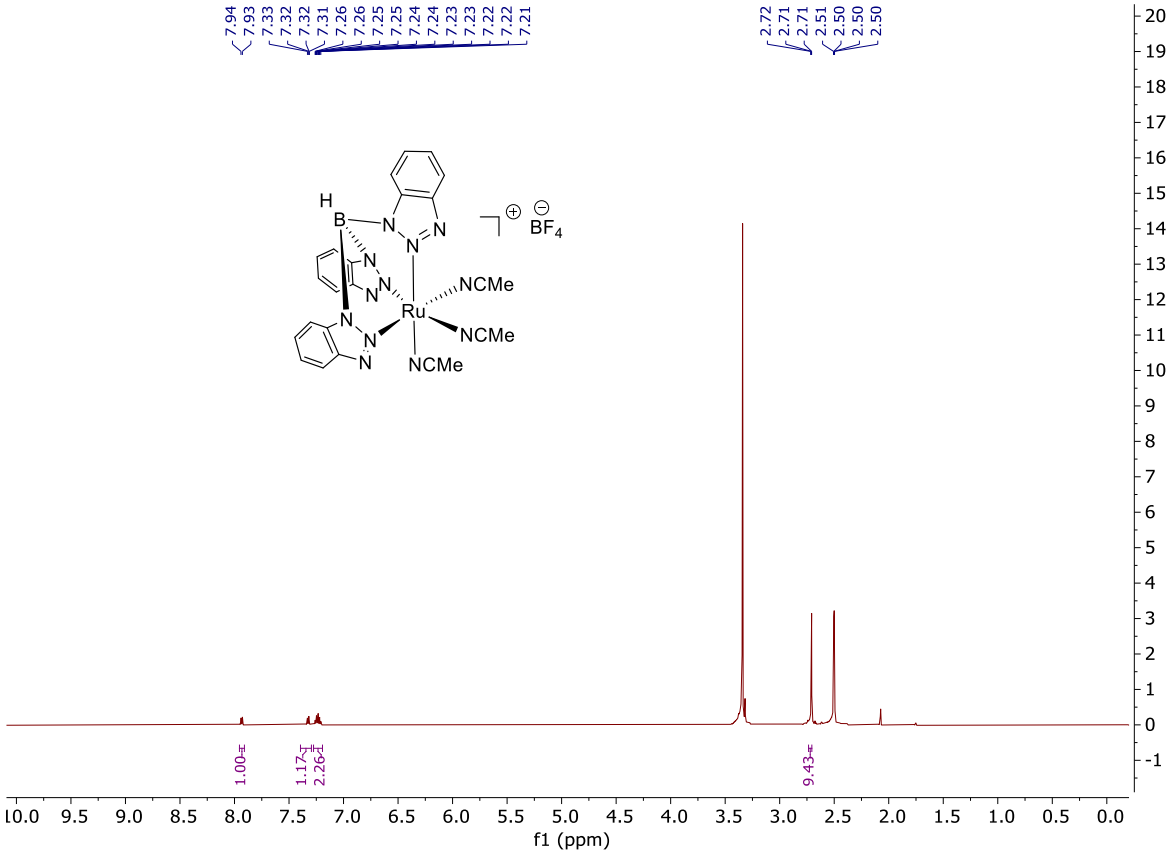
Reaction progression is monitored with TLC. Column chromatography with 8:2 Petroleum Ether/Ethyl Acetate, yielding a mixture of products as a red oil.

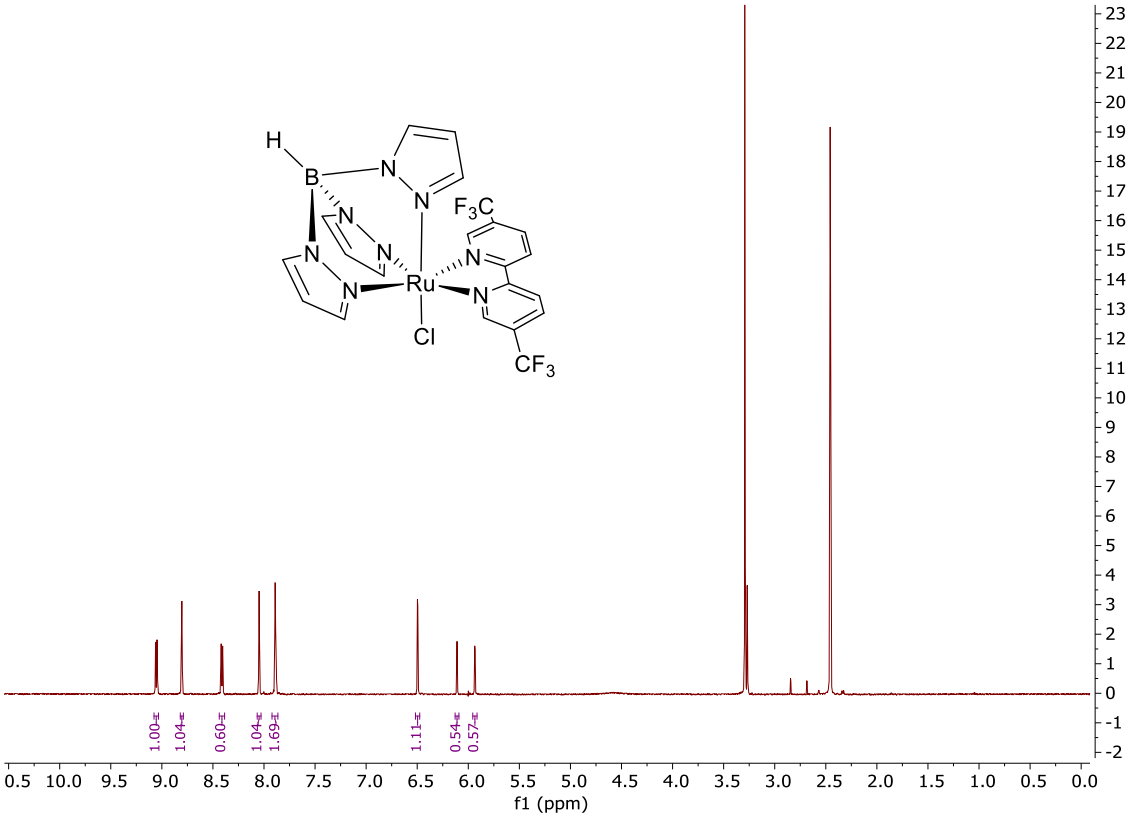


Spectroscopic data were in agreement with the literature.

^{1}H NMR (CDCl3, 400 MHz): δ **E**, 8.11 (m, 2H), 7.65-7.24 (m, 9H), 5.84 (d, 1H, *J* = 7.5 Hz); **Z** , 8.11 (m, 3H), 7.65-7.24 (m, 8H), 6.59 (d, 1H, *J* = 12.9 Hz); **Markovnikov**, 8.28 (m, 2H), 7.67-7.23 (m, 8H), 5.60 (d, 1H, *J* = 1.8 Hz), 5.17 (d, 1H, *J*) 1.8 Hz).

NMR Spectrum of Selected Product





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Chapter 2

Ligand and Substrate Effects on Regio- and Stereoselectivity of Carboxylic Acids and Terminal Alkyne Addition Catalyzed by Ruthenium(II) Complexes Towards Vinyl Ester Synthesis

2.1 Introduction

Vinyl esters are versatile functional groups utilized in various organic methodologies and found in natural products with medicinal applications. The electron rich alkene found in vinyl esters are used as key intermediates/reagents. Vinyl esters are reported to undergo regioselective hydrophosphonylation with P(O)H compounds via metal-free electrochemically induced strategies to generate Markovnikov type adducts (eq. 1). [1] Vinyl esters are capable of undergoing intermolecular C-H alkenylation of enamides with vinyl esters to access diverse functionalized ketones (eq. 2). [2] Reductive coupling between vinyl esters and ammonium salts to construct C-C bonds has been demonstrated (eq. 3). [3] Vinyl ester are also substrates for Rh(III) catalyzed dehydrogenative arylation with benzamid derivatives (eq. 4). [4] Enyne cyclization is possible with vinyl esters to give stereodefined [3,3,0]-bicyclooctenes (eq. 5),[5] and vinyl esters provide chiral alpha functionalized aldehydes via asymmetric hydroformylation (eq. 6). [6]

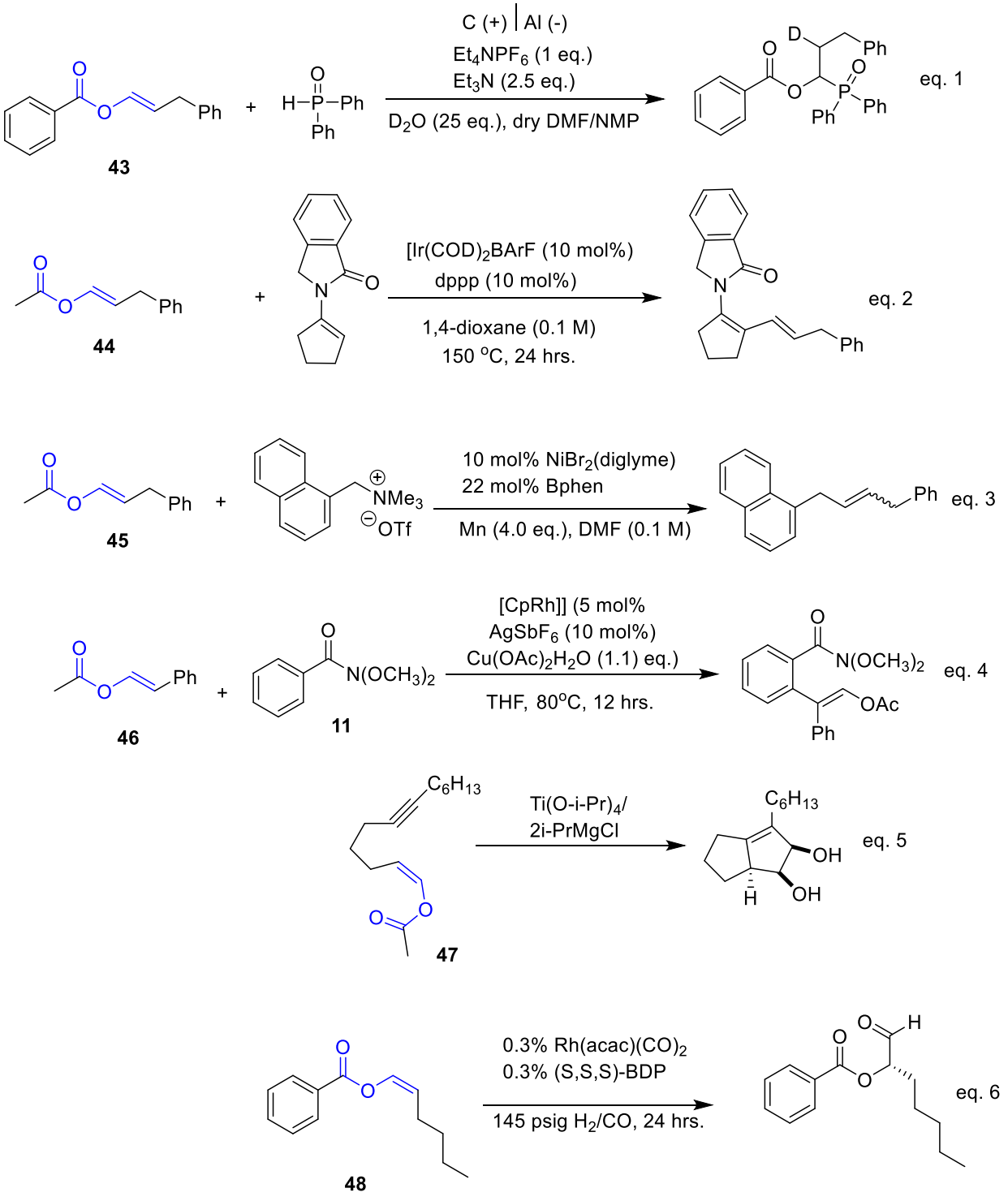


Figure 1: Synthetic applications of vinyl esters

This functional group is also found in natural products and biochemically relevant compounds (**Figure 2**). Vibsane-type diterpenoids with potent cytotoxic activity against A549 cells and HepG2 cells contain the electron rich vinyl ester group. [7] Nepetoidin B is a natural product discovered with anti-inflammatory effects. [8] Caulerpenyne is a sesquiterpene extracted from green algae that is known to be a unique structure among the family of 5-lipoxygenase (5-LO) inhibitors. [9] Although vinyl esters are versatile intermediates with multiple applications, further exploration into its uses is hindered due to the lack of synthetic methodologies for complex 1,2 di-substituted vinyl esters.

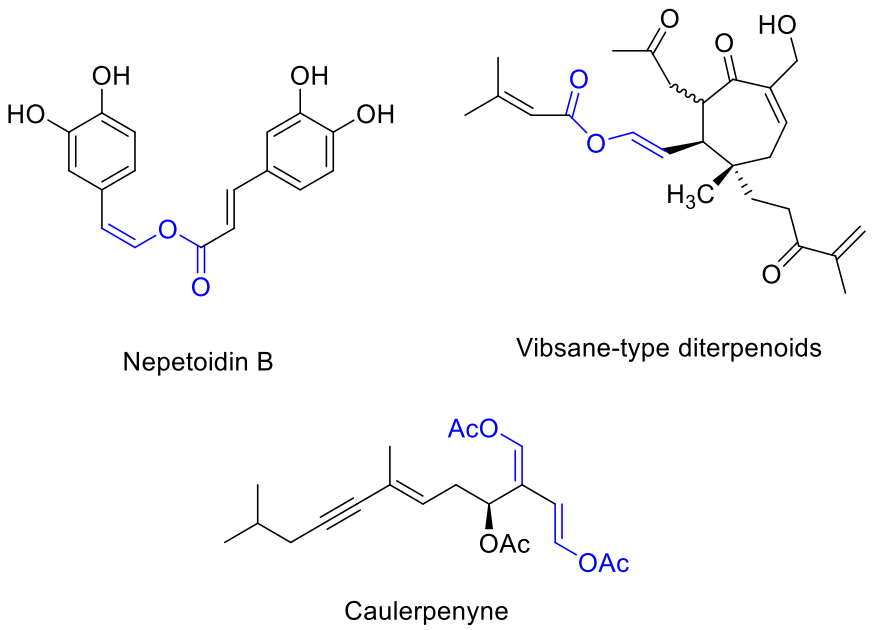
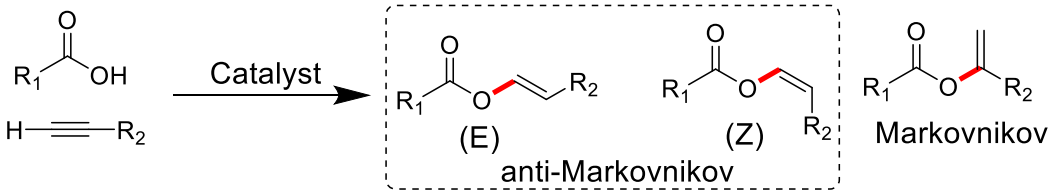


Figure 2: Natrual products containing vinyl esters

An atom-economical route to alkenyl esters is a single-step catalytic addition between a carboxylic acid and an alkyne. In addition to several methods giving Markovnikov regioselectivity,[10-11] some ruthenium- and rhodium-catalyzed methods favor the *anti*-Markovnikov products (**Figure 3**). A single example with benzoic acid and phenylacetylene

catalyzed by $Ru_3(CO)_{12}$ favors the (*E*)-alkenyl ester, [12] whereas most other *anti*-Markovnikov catalysts favor either Markovnikov or (*Z*) isomer products.



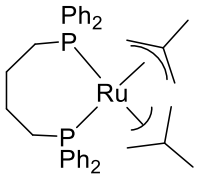
I. (E)-Selective Catalyst:

$Ru_3(CO)_{12}$

4.1 : 1[a]

(Shvo, 1983, ref. 24)

II. (Z)-Selective Catalyst



24 : 1[a]

(Dixneuf, 1995, ref. 13)

$[(COD)RhCl]_2$ + **PPh_2**

31 : 1[b]

(Breit, 2010, ref. 14)

$[(p\text{-cumene})RuCl_2]_2$ + $P(p\text{-Cl-}C_6H_4)_3$, **DMAP**

>50 : 1[a,b]

(Goossen, 2003, ref. 15)

$[(Cy_3P)_2(CO)RuHCl$ + **THF**

6.7 : 1[a]

(Yi, 2008, ref. 16)

a) Benzoic acid + Phenylacetylene; b) benzoic acid + 1-hexyne

Figure 3: Metal catalysts for stereoselective synthesis of vinyl esters

Regioselectivity is dependent on the choice of ligands,[13-14] additives,[15] and/or solvent.[16] Dixneuf has proposed that *anti*-Markovnikov regioselectivity arises from nucleophilic addition to metal-vinylidene reactive intermediates. Theoretical and experimental studies are consistent with vinylidene intermediates.[17] Fan and Tan demonstrated that the choice of ligand influences the electron density at the metal, and found that ligands that enhanced the electron density at the metal center favored Markovnikov product while ligands that reduced electron density generated anti-Markovnikov products.[18] Practical methods from Goosen *et al*. demonstrates this with a Ru system that generates Markovnikov product with tri-2-furyl phosphine ($P(Fur)_3$) and anti-Markovnikov (Z) isomer product with $P(p\text{-Cl-}C_6H_4)_3$.[15]

The regioselectivity of anti-Markovnikov vs. Markovnikov addition is well studied, but the selectivity between E and Z isomers is not as well understood. Also, practical catalyst systems that switches between (*Z*)- and (*E*)-selectivity while maintaining high *anti*-Markovnikov region-selectivity are still unknown, but could make a significant impact in synthetic applications. In this investigation, we explored substrate effects on Markovnikov vs. anti-Markovnikov selectivity and ligand effects on (*E*)- vs. (*Z*)-selectivity in ruthenium-catalyzed hydroacyloxyations of terminal alkynes.

Building on previous work with *anti*-Markovnikov regioselective intramolecular additions of terminal alkynes tethered to nucleophiles, we have begun to explore *intermolecular* nucleophilic additions to terminal alkynes, targeting metal vinylidene carbenes as reactive intermediates. We sought to initially test the hypothesis that a hydrogen bond-acceptor built into the ligand might promote nucleophilic addition to a vinylidene intermediate, screening catalysts with a 1 : 1 ratio of phenylacetylene (**1**) with benzoic acid (**2**).

2.2 Background

Comprehension of the mechanistic pathway is necessary to develop an effective synthetic strategy. Much like vinyl ether synthesis, the generation of vinyl ester is thought to proceed through a vinylidene intermediate. [21] However, a complete understanding of the mechanistic pathway towards the formation of key intermediates and the reasoning behind region- and stereoselectivity is still debated. Yi and Gao developed an effective catalyst for regioselective synthesis of vinyl ethers depending on the solvent of choice.[16] In the coordinating solvent THF, the catalyst generates Z vinyl esters, whereas in the non-coordinating solvent DCM, Markovnikov addition occurs generating terminal alkenes (**Figure 4**).

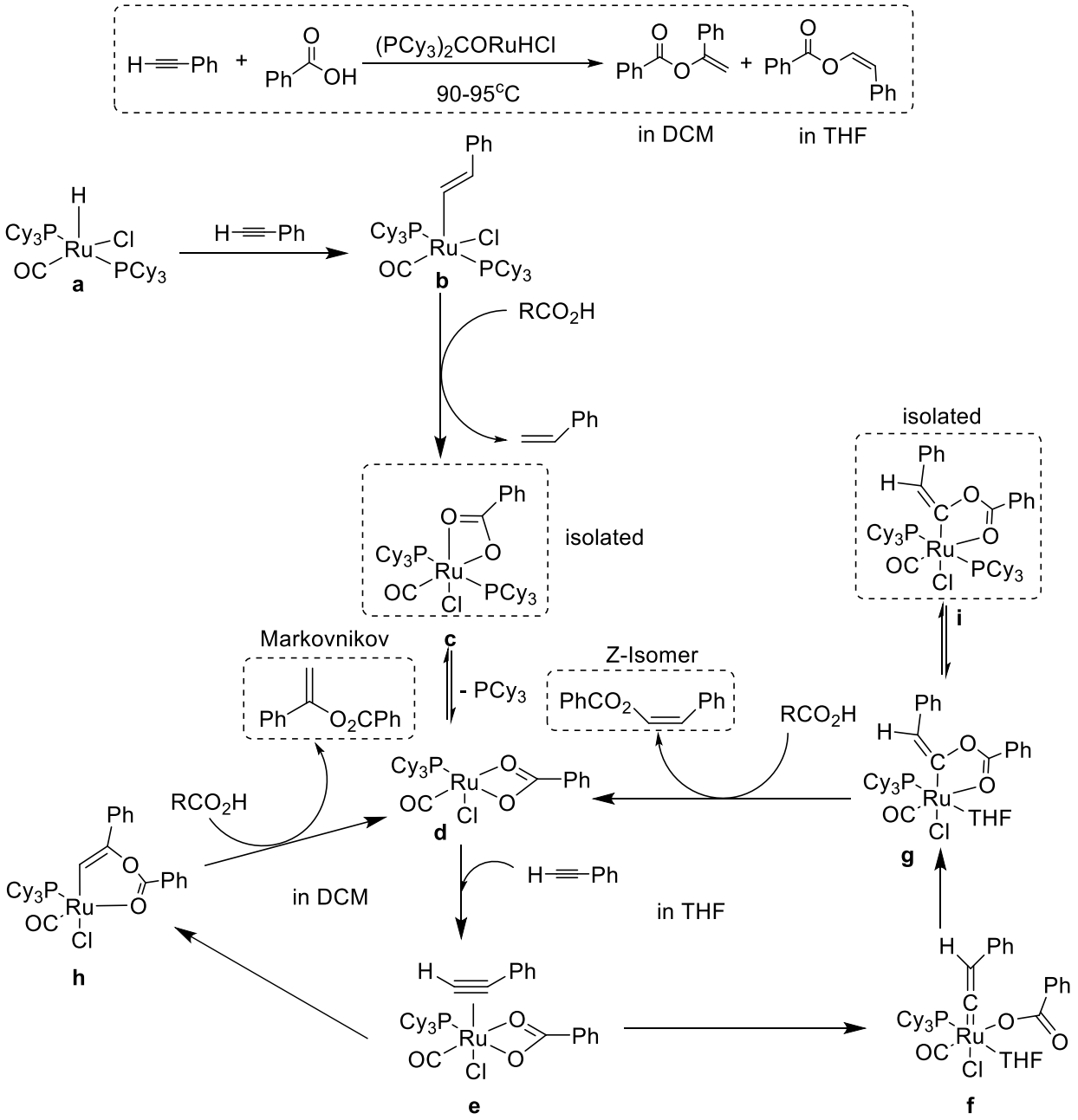


Figure 4: Yi and Gao proposed mechanistic pathway for vinyl ester synthesis

The mechanistic insight from this work is applied towards our synthetic strategy. For Yi and Gao's catalyst, they hypothesize that the first equivalent of phenylacetylene is consumed to generate complex **(b)**, which was isolated and characterized. The carboxylic acid then protonates the alkene ligand to generate the mono-substituted alkene and complex **(c)**. Regioselectivity is

affected by the choice of solvent. The coordinating THF solvent stabilizes the Ru metal during vinylidene formation. This allows the carboxylic acid to attack the electrophilic carbon while coordinated to the Ru metal sources to generate complex **(g)** and **(i)**, which was also isolated and characterized by x-ray crystallography. Without a coordinating ligand, the vinylidene intermediate cannot be stabilized, so direct migratory insertion of the carboxylate oxygen to the internal carbon of the alkyne substrate occurs. This catalyst system exclusively generates the Z isomer, and a source of the stereoselectivity is not given, generating the gem-isomer.

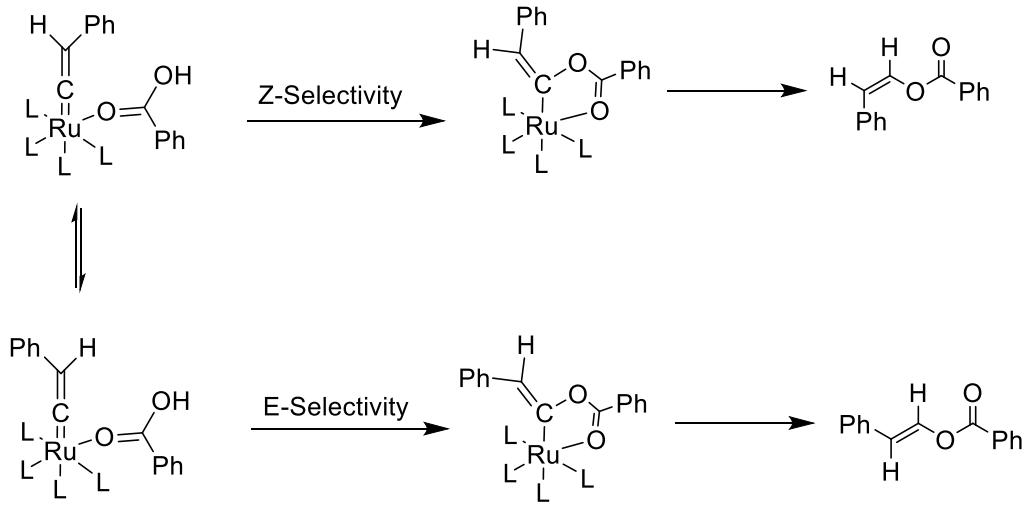


Figure 5: Our proposed key intermediates for stereoselectivity

Similar to our vinyl ether hypothesis, we wanted to test whether the substituents on our scorpionate ligand could impact the reactivity of the Ru metal center. Our lab was also interested in developing a stereoselective route towards E and Z vinyl esters. We hypothesize that the coordinated ligands have a steric impact on the vinylidene formation (**Figure 5**). When the steric bulk due to the coordinating ligands to the Ru metal is significant, then the vinylidene favors having the sterically larger substitute to face away from the coordinating ligands, forming the Z-isomer. If the coordinating ligands are not sterically significant, then we suspect that the vinylidene will favor facing away from the carboxylic group and forming the E-isomer. With our adaptable

catalytic Ru system, we sought to develop a tunable catalytic method that generates either E or Z isomers depending on the ligand of choice.

2.3 Results and Discussion

2.3.1 Catalyst and Ligand Screening

We began with two candidate complexes: a tris(benzotriazolyl)borate complex **37**, bearing additional nitrogen atoms adjacent to the site for ruthenium binding, and an *anti*-Markovnikov hydration catalyst generated *in situ* from $[CpRu(NCCH_3)_3]PF_6$ (**23**) and 5,5'-(CF_3)-bipyridine (**31**) (**Table 1**).[20] Complex **37** gave low conversion to produce a mixture of vinylic esters slightly favoring the (*Z*)-isomer, mixed with a measurable amount of the Markovnikov addition isomer (entry 10). In the presence of ligand **31**, the yield slightly improves with enhanced Z selectivity (entry 12). In contrast, when ligand **49** is used, reactivity is suppressed and only starting material is returned (entry 11). Control scorpionate complex **33** generate vinyl ester products favoring the E vinyl isomer. In the presence of ligand **31**, selectivity shifts to favor Z isomers while diminishing yield (entries 4, 5, 6). We tested catalyst **41** and **42** to investigate the influence of the electron withdrawing nitro groups. These catalyst followed the same pattern as the other scorpionate ligands, by favoring the E vinyl ester without ligand **31**, and favors the Z vinyl ester in the presence of **31** (entries 7, 9, 13 & 14). However, catalyst **41** is reactive with ligand **49**, but there is no E or Z stereoselectivity (entry 8). The combination of **41** and **31** gave the highest (*Z*)-selectivity in modest yield. To compare the effects of scorpionate ligands vs. cyclopentadienyl ligands, the ruthenium precursor $[CpRu(NCCH_3)_3]PF_6$ (**23**) was tested in the absence vs. the presence of the co-ligand **31**[20] (entries 11, 12). To test the significance of the scorpionate and bipyridine ligand, we tested metal catalyst **32**. We found that this catalyst generates the highest E selectivity and yield (entry 1).

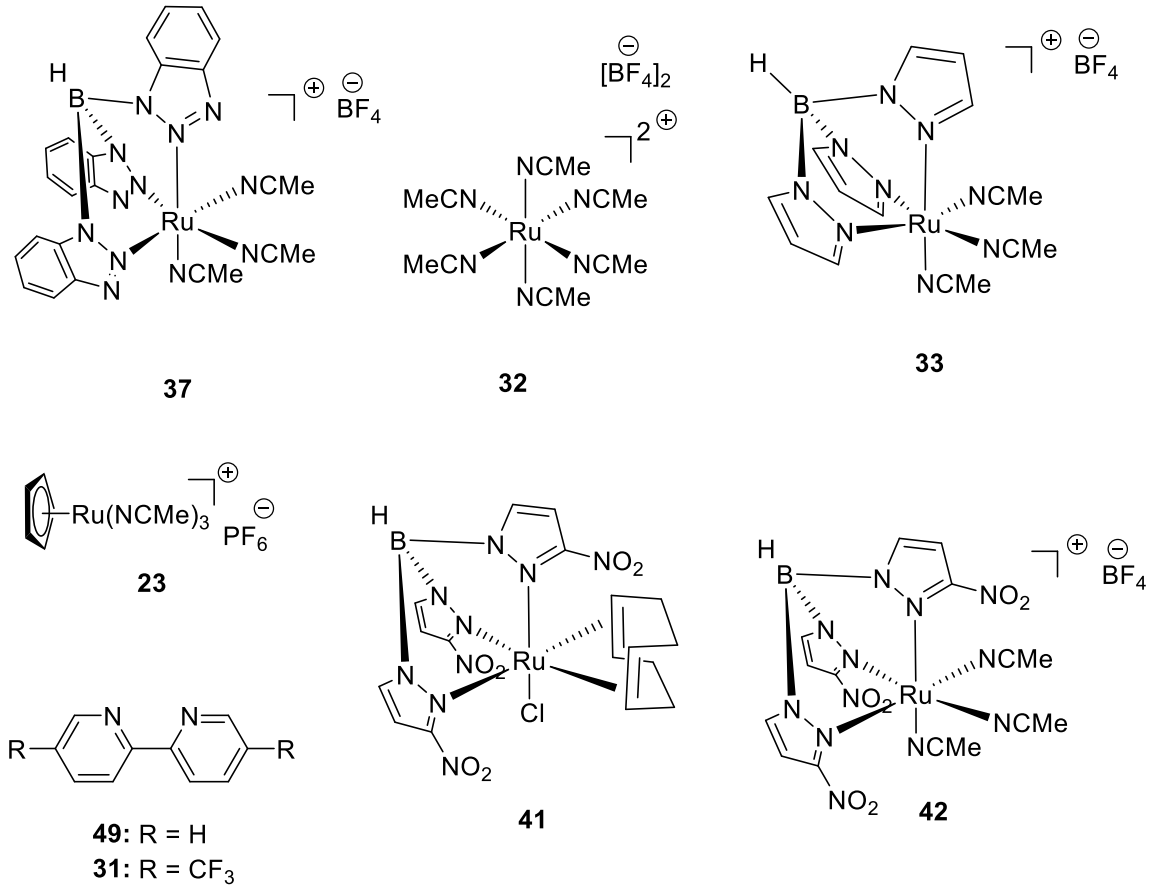
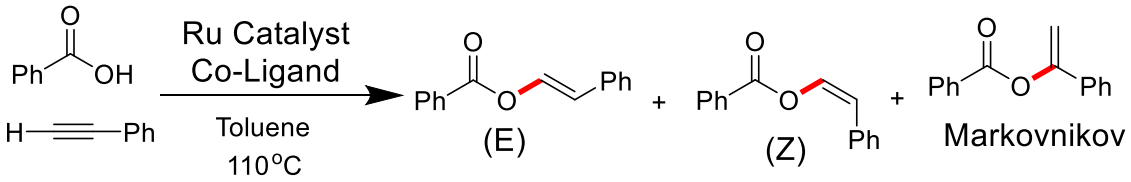


Figure 6: Ru catalyst for vinyl ester synthesis

Table 1: Ligand screening for vinyl ester synthesis



Entry	Catalyst (2%)	Co-Ligand (2%)	Yield	Selectivity
1	**32**	None	100%	73 : 20 : 7
2	**23**	None	56%	60 : 40 : 0
3		**31**	35%	17 : 83 : 0
4	**33**	None	41%	68 : 25 : 7
5		**49**	0%	Starting Material
6		**31**	29%	24 : 72 : 4
7	**42**	None	64%	68 : 24 : 8
8		**49**	52%	46 : 52 : 2
9		**31**	85%	22 : 70 : 8
10	**37**	None	25%	43 : 50 : 7
11		**49**	0%	Starting Material
12		**31**	35%	31 : 66 : 2
13	**41**	None	79%	46 : 42 : 12
14		**31**	71%	12 : 88 : 0

The results from these experiments provide insights into how the ligands of choice influences vinyl ester synthesis. The cp ligand is more reactive but less selective when compared to the scorpionate ligand entry 2 and 4, with catalyst **33** favoring the E isomer and generating some Markovnikov byproduct. When neither cp nor scorpionate ligand are present, the E selectivity increases along with the yield (entry 1). This indicates that any ligand presence slightly shifts the selectivity to favor the Z, suggesting a steric influence is necessary to generate the Z vinyl ester. Both complex **23** and **33** favor the Z isomer and express reduced yields once ligand **31** is used. These reactions reveal to us that the cp and scorpionate ligand play a role in overall reactivity, but the co-ligand has more influence on the stereoselectivity. Complex **37** gave reduced yields while favoring the Z isomer with and without ligand **31**. This supports our hypothesis that the steric bulk

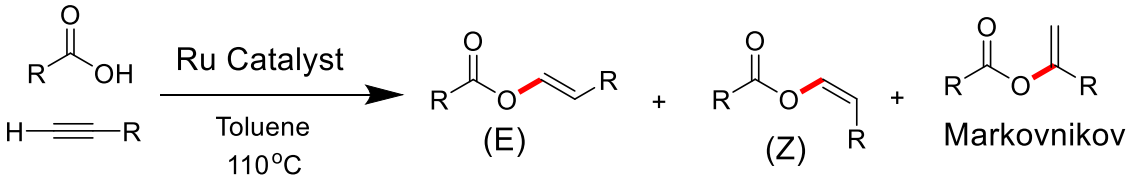
of the ligands induce an effect that favors the Z isomer, but does not support our hypothesis that the hydrogen bonding accepting properties of the nitrogen could improve nucleophilic addition (entry 10-12). Once the scorpionate ligand is decorated with electron withdrawing nitro groups however, reactivity is improved with very little change to stereoselectivity (entry 4 and 7). This supports our hypothesis that the electron withdrawing groups would induce a more electrophilic and reactive metal intermediate to promote vinyl ester synthesis. Ligand **31** continues to switch stereoselectivity to favor the Z isomer, but once neutral bipyridine ligand **49** is used, reactivity is either reduced or ceases. This reveals the significance of the trifluoromethyl groups on how the bipyridine co-ligand influences the overall reactivity and suggests and electronic influence on the mechanistic pathway.

2.3.2 Substrate Expansion

As the simple ruthenium source [12] rivalled the (*E*)-selectivity obtained from the various scorpionate catalysts **23**, **33**, and **42**, we explored the scope of **32** catalyzed hydroacyloxylation with other carboxylic acids and terminal alkynes (**Table 2**). We decided to compare the difference between **32** and **41** with **31** because they are our most stereoselective catalystSterically hindered benzoic acids give slightly less good selectivity for the E favorable method A (entry 7), but the Z favorable method B returns good selectivity. Non-aromatic carboxylic acids proceed with good selectivity and yields (entry 1). Electron rich carboxylic acids generate E isomers with good selectivity (entry 3), but the electron poor carboxylic acids generates more Markovnikov product at the expense of the (*E*) isomer (entry 5). Other phenylacetylene substrates convert in mild to good yields and in good selectivity with withdrawing aromatic group (entries 11). Non-aromatic and electron rich phenylacetylenes decreases anti-Markovnikov selectivity, generating less (*E)* isomer and more Markovnikov product (entries 9 & 13).

The TPz(3-NO2)RuClCOD complex **41** with the ligand **31** gave the highest Z selectivity, so we decided to continue exploring its reactivity. Z selectivity is preserved across carboxylic acid and acetylene aromatic substrates. Electron withdrawing and electron donating substrates have little impact on the stereoselectivity of the reaction, but donating groups generated slightly more product on the acetylene aromatic group. Alkyl carboxylic acid generated high Z selectivity, but alkyl acetylene substrates lost Z selectivity.

Table 2: Substrate scope of selective vinyl ester synthesis methods



Entry	Alkyne	Acid	Method	Yield	Selectivity
1	Ph -	- Cyclohexyl	A	79%	68 : 27 : 5
2			B	65%	19 : 81 : 0
3		- Ph-*p*-OMe	A	63%	81 : 13 : 6
4			B	41%	22 : 77 : 1
5		- Ph-*p*-CF_3	A	53%	57 : 23 : 20
6			B	41%	15 : 83 : 2
7		- Ph-2,4,6,Me	A	83%	55 : 39 : 6
8			B	73%	15 : 85 : 0
9	Cyclohexyl -	- Ph	A	69%	50 : 35 : 15
10			B	35%	37 : 50 : 13
11	F_3C-*p*-Ph -		A	73%	71 : 25 : 4
12			B	70%	20 : 79 : 1
13	MeO-*p*-Ph -		A	81%	33 : 13 : 54
14			B	82%	17 : 68 : 15

Method A: 1.0 mmol Acid, 1.1 mmol Acetylene, 2% **32**, 24 hrs., 1.5 mL toluene.

Method B; 1.0 mmol Acid, 1.1 mmol Acetylene, 2% **41** and 2% **31**, 24 hrs., 1.5 mL toluene.

It has been demonstrated that the two methods are capable of mediating several terminal alkyne and carboxylic acid substrates, but the cases with unexpected selectivity provides

mechanistic insights. Carboxylic acid with an electron withdrawing para trifluromethyl group generates more Markovnikov product at the expense of the E-isomer product with an overall decrease in reactivity with method A (entry 1 and 5). However, the more acidic carboxylic acid generates still favors the Z isomer with method B, suggesting that the mechanism for method A is different than method B. The electronic properties of the alkyne substrate has direct influence on the initial alkyne coordination to the Ru metal center and on the vinylidene intermediate formation. The results suggest that electron withdrawing groups favor vinylidene formation and electron donating groups disfavors the vinylidene formation since more Markovnikov product is formed, especially for method A (entry 13 and 14).

2.3.3 Deuterium Labeling Experiments

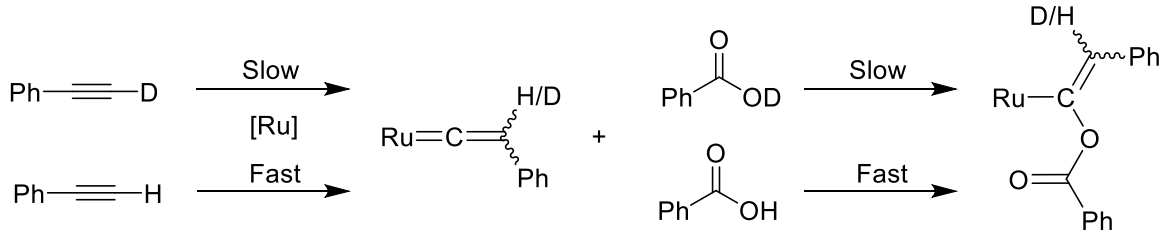


Figure 7: Kinetic isotope effect for mechanism analysis

Deuterium experiments were conducted to gain mechanistic insight of our catalytic system. If the ruthenium catalyst proceeds through a vinylidene intermediate, then the proton on the carboxylic acid should be H_a and the terminal alkyne proton should be found at H_b (**Figure 8**). However, previous mechanistic studies from Yi and Gao suggests that the ruthenium metal mediates H/D exchange between the carboxylic acid and the acetylene,[16] so scrambling between the substrates is expected. Kinetic isotope effects further complicates the analysis, as the carbon-deuterium bond impacts the vinylidene rearrangement rate and/or the nucleophilic addition of the carboxylic acid (**Figure 7**).

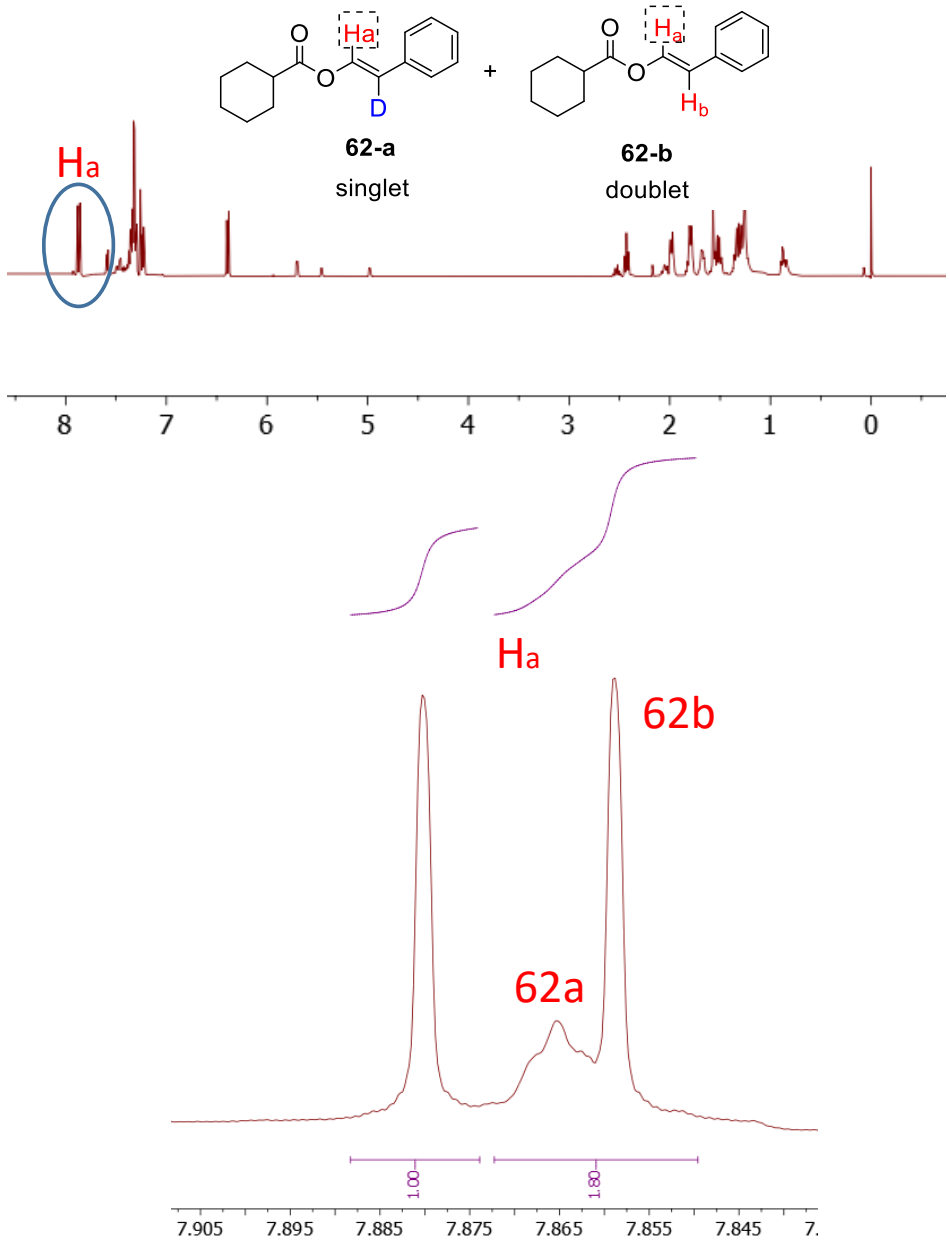
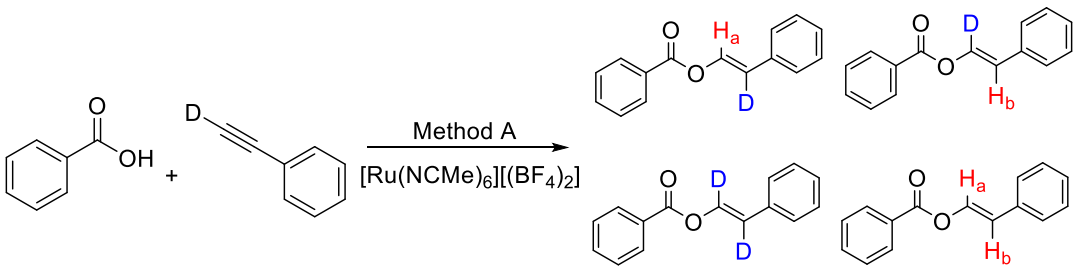


Figure 8: Example of single deuterated vinyl ester product mixed with dual protonated product

Analysis of the deuterium experiments were complicated because the deuterated reagents generates 4 products for each isomer. Okuyama *et al*. synthesized deuterated vinyl esters via acetolysis of iodonium salts. [24] They found that once deuterated, the alkene peaks on vinyl ester lose their chemical splitting and become singlets and a small change in chemical shift. This study informs us that the deuterated products will be overlapping with our protonated products. A

mixture of a dual protonated vinyl ester and a singular deuterated vinyl ester product is shown (**Figure 8**). H_a appears as a doublet when adjacent to a C-H bond, but becomes a small singlet with a change in chemical shift when adjacent to a C-D bond.

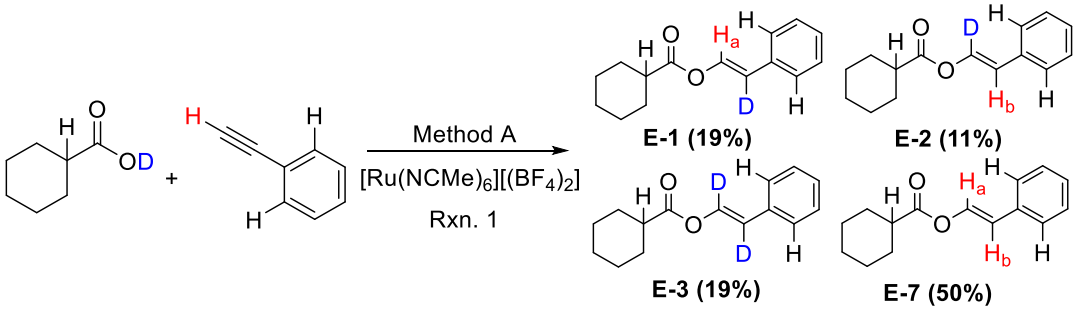


Scheme 1: Deuterated experiment with benzoic acid

Initial deuterium experiments were conducted with deuterated benzoic acid and deuterated phenylacetylene to determine NMR and reaction properties. NMR analysis confirms Okuyama *et al.* analysis of deuterated vinyl esters. [24] The vinyl esters with only one deuterium incorporated appear as a broad singlet with a small change in chemical shift. However, we cannot accurately analyze proton H_a because it overlaps with the aromatic peaks. Therefore, we decided to use cyclohexyl carboxylic acid as opposed to benzoic acid to separate the relevant peaks for analysis. The protons selected as standards generally had little to no overlap with other resonances.

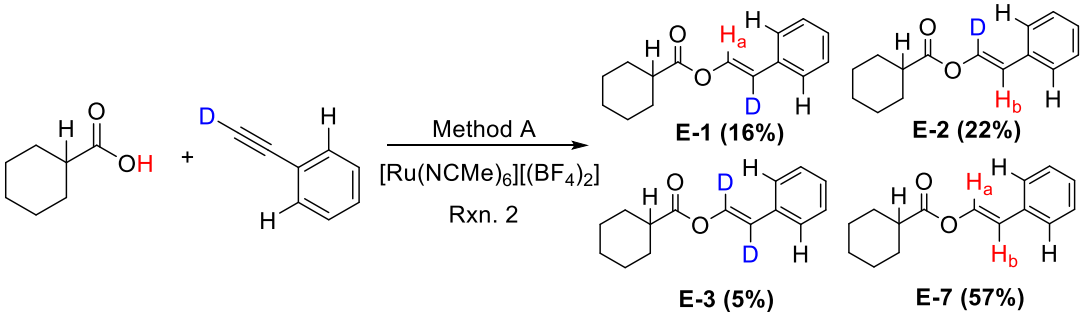
The standardized protons for the integration were either the ortho protons on the phenyl group (7.60 ppm), or the proton adjacent to the carbonyl on cyclohexyl group (2.49 ppm). The standard protons were chosen because they do not undergo proton or deuterium exchange. The standardized proton depended on which signal had the highest resolution and purity. To calculate the dual deuterated products E-**3** and Z-**6**, we looked at proton H_b (6.4 ppm – E isomer, 5.7 ppm – Z isomer) and determined how much the signal is depreciated due to E-**3** or Z-**6** and accounting for depreciation due to compounds E-**1** and Z-**4**. Z-**6** = [Control – (Z-**8** + Z-**5**)] – Z-**4**. The proton

signals for the single deuterated compounds resided usually in one of the doublet signals from E-**7** or Z-**8**. Separate integration of each signal of the doublet followed calculation of the difference between the peaks while accounting for the control, gives the integration of the proton adjacent to the deuterium.



Scheme 2: Deuterated cyclocarboxylic acid experiment with method A

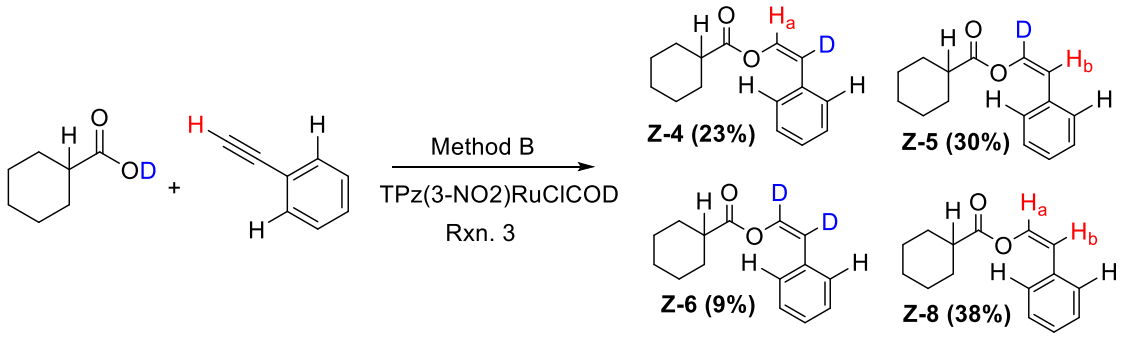
Reaction 1 uses deuterated cyclohexyl carboxylic acid and phenylacetylene with the E-selective method. The isomers for reaction 1 are divided as such: E-1 is 19%, E-2 is 11%, E-3 19%, and E-7 is 50%.



Scheme 3: Deuterated phenylacetylene experiment with method A

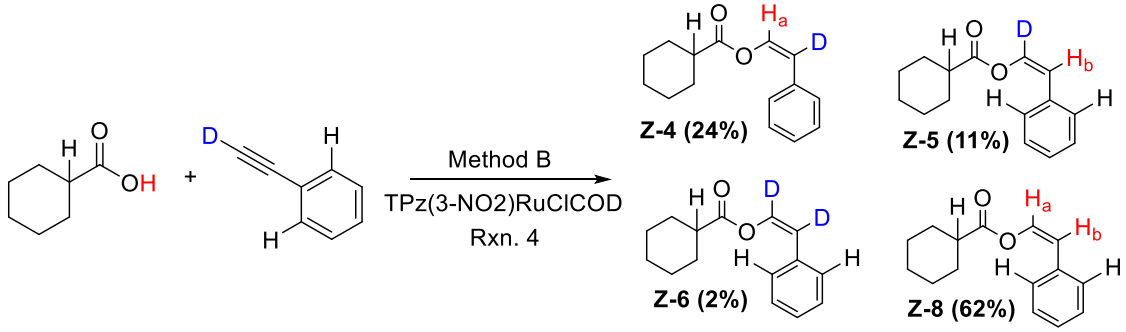
Reaction 2 uses deuterated phenylacetylene and cyclohexyl carboxylic acid with the following distribution: E-1 is 16 %, E-2 is. 22%, E-3 is 5%, and E-7 is 57% present. The results from the E catalyst does not support the vinylidene intermediate hypothesis.

Although, proton rearrangement occurs, we expect the proton on the carboxylic acid group to be incorporated to Ha, and the proton on the terminal acetylene should be incorporated to Hb. However, reaction 1 reveals that deuterated isomer E-1 is present the most when deuterated carboxylic acid is used. Reaction 2 shows that when deuterated acetylene is used, E-2 is present the most. Although primary kinetic isotope effects can account for some of this distribution, the data does not support the vinylidene hypothesis. Isomer E-7 and Z-8 being present the most suggests that the deuterium has a significant kinetic isotope effect on the mechanistic pathway.



Scheme 4: Deuterated cyclohexyl carboxylic acid experiment with method B

Reaction 3 uses the Z-selective methodology treated with deuterated cyclohexyl carboxylic acid and phenylacetylene generated the vinyl ester products in the following amounts: Z-4 is 23%, Z-5 is 30%, Z-6 is 9%, and Z-8 is 38% present.



Scheme 5: Deuterated phenylacetylene experiment with method B

Reaction 4 treated with deuterated phenylacetylene and cyclohexyl carboxylic acid with Z-4 at 24%, Z-5 at 11%, Z-6 at 2%, and Z-8 at 62%. The results from the deuterated Z-selective catalyst suggests that the mechanism proceeds through a vinylidene intermediate.

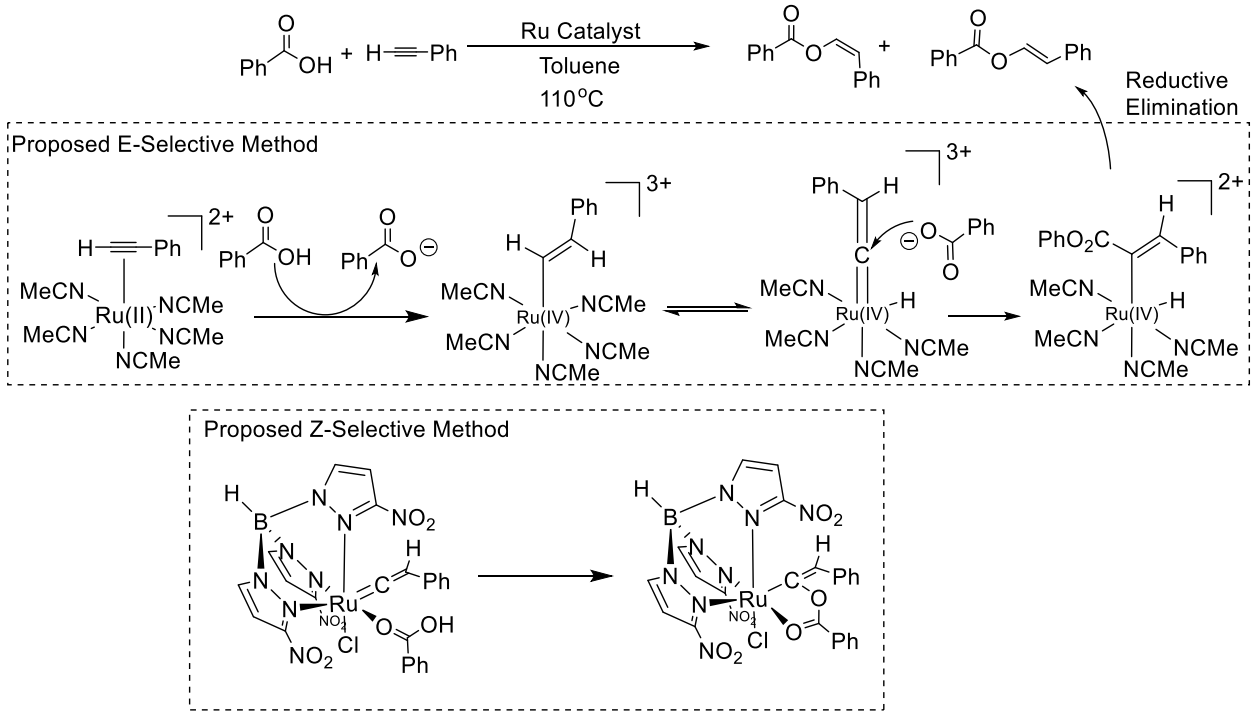


Figure 9: Proposed mechanistic pathways for produccts

We initially proposed that the Z selectivity is due to the syn geometry of the vinylidene-carboxylate addition, and then the E selectivity arise from to anti-geometry intermediate (**Figure 9**). However, our mechanistic studies suggest that there may be another pathway that generates the E-isomer. We propose that the steric hindrance experienced by the metal center plays a significant role on the stereoselectivity of the reaction, but the E-isomer may also be generated from an alternative mechanism. An alternative mechanism we propose is based on the mechanistic work done by Wakatsuki *et al.* [21] The mechanism begins with protonation of a Ru(II) π-alkyne species to give a Ru(IV)-vinyl species. The Ru(IV) then rearranges to a vinylidene intermediate that

experiences nucleophilic attack at the alpha carbon followed by reductive elimination to give the vinyl ester. Steric hindrance still plays a significant role in the stereoselectivity of the reaction because the alkene bond will favor the E-isomer to avoid steric clash with the other Ru ligands.

Steric hindrance is also essential for the Z favorable method. This is apparent because bulky scorpionate and bipyridine ligands favors the Z-isomer when used in the catalyst system. The electronic effects of the bipyridine ligand is significant because the catalyst system only works with electron withdrawing trifluoromethyl groups are bonded to the pyridine rings, but further mechanistic studies are required to gain an understanding of this significance. In contrast, the small and labile acetonitrile ligands on catalyst **32** or carbonyl ligands on $Ru_3(CO)_{12}$, allows for the anti- intermediate to be favored due to the lack of steric interference, generating more E isomers. The electronic characteristics of the substrates influenced the regioselectivity between anti-Markovnikov and Markovnikov addition. We hypothesize that the choice of alkyne directly impacts the rate of vinylidene formation. The data suggest that electron donating groups diminish vinylidene formation, as more gem alkene products are generated. We hypothesize that the electronic effects of the carboxylic acid group impacts the rate of nucleophilic addition. Further mechanistic studies are required to determine how the rate of nucleophilic addition impacts the overall reactivity and stereoselectivity.

2.4 Conclusions

Our lab has discovered a Ru catalyzed system for E or Z vinyl ester synthesis depending on the ligand system used. Most methods in literature are capable of synthesizing Z vinyl ether or gem-alkene synthesis from anti-Markovnikov addition with carboxylic acids and acetylenes, but our lab found a system that can synthesize E and Z vinyl ester. Initial Ru scorpionate catalyst designed for vinyl ester synthesis were used to explore vinyl ester reactivity, regio-, and

stereoselectivity. We found that the scorpionate ligand decorated with nitro groups along with the bipyridine ligand with trifluoromethyl groups promoted Z vinyl ester synthesis. The source of the stereoselectivity is hypothesized to be from the steric hindrance favoring vinylidene intermediates that promote syn addition. The benzotriazolyl scorpionate ligand reacted poorly with low selectivity. This does not support our hypothesis that the additional nitrogen lone pairs could promote hydroalkoxylation addition through electronic attraction of the alcohol. However, we discovered that a method for E favorable vinyl ester synthesis with $[Ru(NCH_3)_6][(BF_4)_2]$. We initially hypothesized that the lack of steric ligands allowed for the anti-addition to occur. Deuterium experiments suggest on the other hand, that the Z favorable method proceeds through a vinylidene intermediate and the E favorable method may proceed through a different mechanistic pathway. Further experimentation is necessary to make more mechanistic claims.

2.5 Experimental Section

General Information: Proton and carbon NMR spectra were recorded INOVA-400 (400 MHz), INOVA-600 (600 MHz), or a BRUKER 600 (600 MHz) instrument equipped with cryogen probe. NMR spectra were recorded in solutions of deuterated chloroform (CDCl3) with the residual chloroform (7.27 ppm for ^{1}H NMR and 77.23 ppm for 13C NMR) taken as the internal standard, or in deuterated dimethyl sulfoxide (DMSO-d6) and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; m, multiplet. Thin layer chromatography (TLC) was performed on pre-coated glass-backed plates purchased from Whatman (silica gel 60F254; 0.25mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from Silicycle. All reactions were carried out with anhydrous solvents in oven-dried or flame-dried and argon-charged glassware unless otherwise specified. All anhydrous solvents were purchased from Sigma-Aldrich. Other solvents used in extraction procedures and chromatography were used as received from commercial suppliers without prior purification

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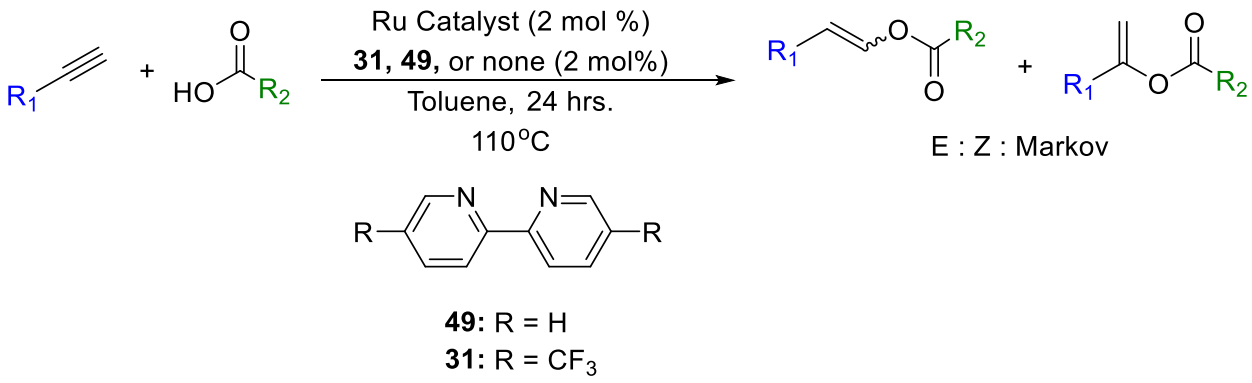
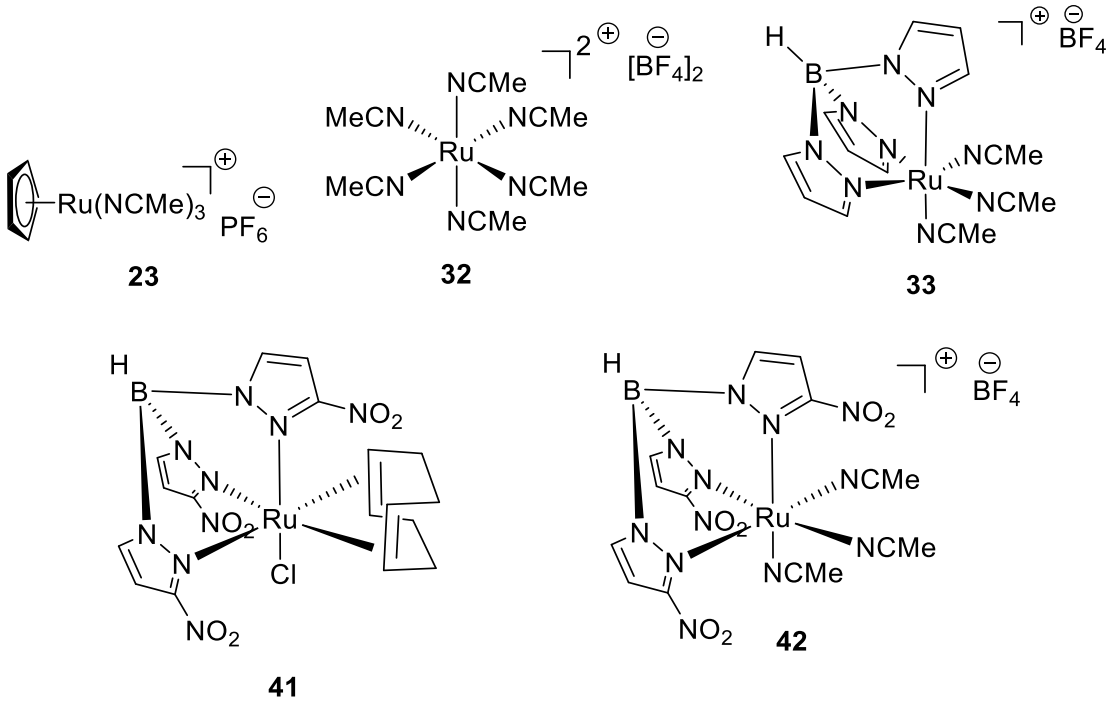
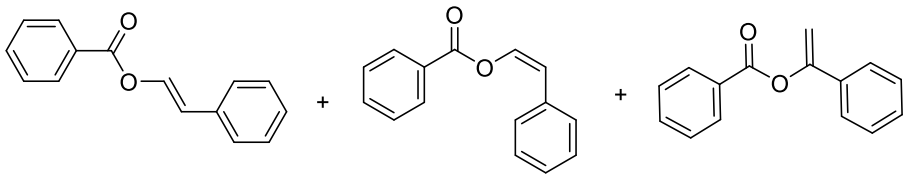


General Procedures for Vinyl Ester Synthesis:

The acetylene (1 mmol) and carboxylic acid (0.12 g, 1 mmol were dissolved in toluene (1.5 mL) with the Ru catalyst of choice (**23, 32, 33, 37, 41** or **42**) (2%) and the co-ligand (**31** or **49**) (2%) when necessary. The mixture is then heated to reflux for 24 hrs. Once complete, the solvent is removed by rotary evaporation and purified by column chromatography with 8:2 Pentane/Ethyl Acetate, to yield the isomer mixture of products as a red/yellow oil.



Experimental Data of Products



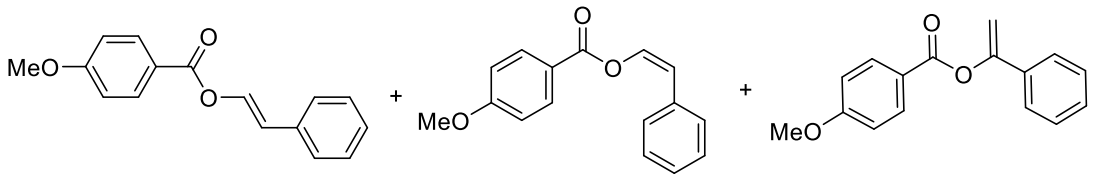
(E, Z)-styryl benzoate ***(50, 51, 52)***[19]

Following the general procedure, (0.11 ml, 1.00 mmol) and benzoic acid (122 mg, 1.00 mmol). Purification by flash-column chromatography a mixture of the vinyl ester isomers as a red oil (220 mg, 100%). E, Z and Markovnikov product are inseparable isomers. Previous literature also encounters chromatographic ally inseparable mixture of isomers.[15, 16, 19] Diagnostic peaks for NMR analysis are in bold.

^{1}H NMR (600 MHz, $CDCl_3$) δ E-Isomer: 8.27-8.19 (m, 3H, Ph & =CH), 7.64-7.31 (m, 8H, Ph & =CH), **6.54** (d, J = 12.7 Hz, =CH, E-isomer)

Z-Isomer: 8.27-8.19 (m, 2H), 7.64-7.31 (m, 8H, Ph & =CH), 7.38 (d, J = 7.3 Hz, =CH, Z-isomer), **5.55** (d, J = 7.2 Hz, =CH, Z-isomer),

Markovnikov isomer: 8.27-8.19 (m, 2H), 7.64-7.31 (m, 8H) **5.14** (d, J = 2.1 Hz, $=CH_2$) **4.99** (d, J = 2.1 Hz, $=CH_2$),



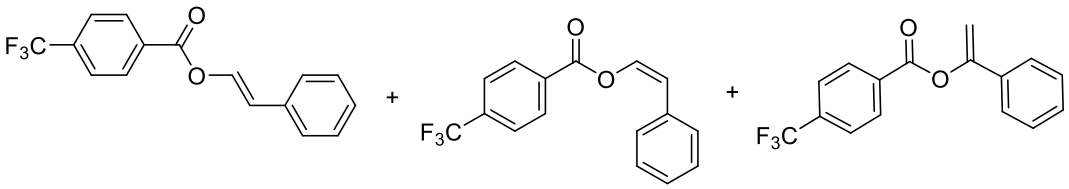
(E, Z)-styryl 4-methoxybenzoate ***(53, 54, 55)***[16]

Following the general procedure using phenylacetylene (0.11 ml, 1.00 mmol) and 4-methoxybenzoic acid (152 mg, 1.00 mmol). Purification by flash-column chromatography afforded a mixture of the vinyl ester isomers as a red oil (160 mg, 63%).

^{1}H NMR (600 MHz, $CDCl_3$) δ E-Isomer: 8.10-8.06 (m, 3H, $PhCO_2$), 7.39-7.35 (m, 2H, Ph), 7.33-7.30 (m, 2H, Ph) 7.24-7.21 (m, 1H, Ph) 6.95-6.92 (m, 2H, $PhCO_2$) **6.57** (d, J = 12.8 Hz, =CH, E-isomer) 3.88 (s, 3H, OCH_3)

Z-Isomer: 8.13-8.06 (m, 2H, $PhCO_2$), 7.82-7.72 (m, 2H), 7.52 (d, J = 7.2 Hz, =CH, Z-isomer) 7.42-7.34 (m, 2H, Ph), 7.33-7.29 (m, 2H, Ph) 7.28-7.18 (m, 1H, Ph) 7.00-6.92 (m, 2H, $PhCO_2$) **5.81** (d, J = 7.2 Hz, =CH, Z-isomer), 3.84 (s, 3H, OCH_3)

Markovnikov isomer: 8.16-8.05 (m, 2H, $PhCO_2$), 7.79-7.69 (m, 2H), 7.43-7.24 (m, 5H, Ph), 7.01-6.94 (m, 2H, $PhCO_2$), **5.57** (dd, 1H, J = 2.2, 1.1 Hz, $=CH_2$) **5.14** (dd, 1H, J = 2.4, 1.1 Hz, $=CH_2$), 3.84 (s, 3H, OCH_3)



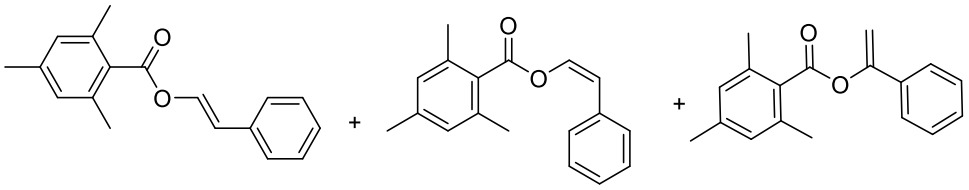
(E, Z)-styryl 4-(trifluoromethyl) benzoate ***(56, 57, 58)***[16]

Following the general procedure using phenylacetylene (0.11 ml, 1.00 mmol) and (Trifluoromethyl) benzoic acid (190 mg, 1.00 mmol). Purification by flash-column chromatography afforded a mixture of the vinyl ester isomers as a red oil (155 mg, 53%).

^{1}H NMR (600 MHz, $CDCl_3$) δ E-Isomer: 8.30-8.20 (m, 2H), 8.06 (d, J = 12.7 Hz, =CH, E-isomer) 7.82-7.72 (m, 2H), 7.46-7.27 (m, 5H, Ph), **6.60** (d, J = 12.7 Hz, =CH, E-isomer)

Z-Isomer: 8.28-8.24 (m, 2H, Ph), 7.78 (m, 2H, Ph), 7.53 (d, J = 7.2 Hz, =CH, Z-isomer), 7.43-7.25 (m, 5H, Ph), **5.90** (d, J = 7.2 Hz, =CH, Z-isomer),

Markovnikov isomer: 8.28-8.20 (m, 2H), 7.82-7.72 (m, 2H), 7.46-7.27 (m, 5H, Ph), **5.61** (d, J = 2.4 Hz, $=CH_2$) **5.19** (d, J = 2.4 Hz, $=CH_2$),



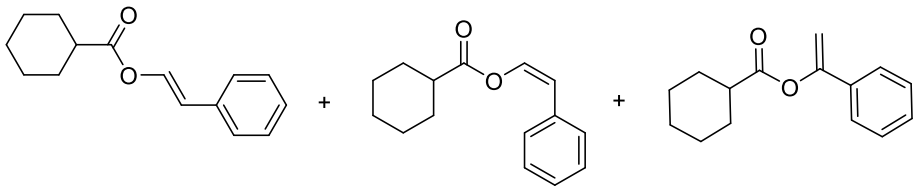
(E, Z)-styryl 2,4,6-trimethylbenzoate ***(59, 60, 61)***[23]

Following the general procedure using phenylacetylene (0.11 ml, 1.00 mmol) and 2,4,5-trimethylbenzoic acid (164 mg, 1.00 mmol). Purification by flash-column chromatography a mixture of the vinyl ester isomers as a red oil (220 mg, 83%).

^{1}H NMR (600 MHz, $CDCl_3$) δ E-Isomer: 8.11 (d, 1H, J = 12.8 Hz, =CH, E-isomer), 7.42-7.20 (m, 5H, Ph), 6.91-6.85 (m, 2H, $PhCO_2$), **6.47** (d, J = 12.8 Hz, =CH, E-isomer), 2.41-2.25 (m, 9H, $Ph(CH_3)_3$)

Z-Isomer: 7.55-7.52 (m, =CH, Z-isomer), 7.42-7.20 (m, 5H, Ph), 6.91-6.85 (m, 2H, $PhCO_2$), **5.79** (d, J = 7.4 Hz, =CH, Z-isomer), 2.41-2.25 (m, 9H, $Ph(CH_3)_3$)

Markovnikov isomer: 7.42-7.20 (m, 5H, Ph), 6.91-6.85 (m, 2H, $PhCO_2$), **5.54** (d, J = 1.4 Hz, $=CH_2$) **5.18** (d, J = 1.4 Hz, $=CH_2$), 2.41-2.25 (m, 9H, $Ph(CH_3)_3$)



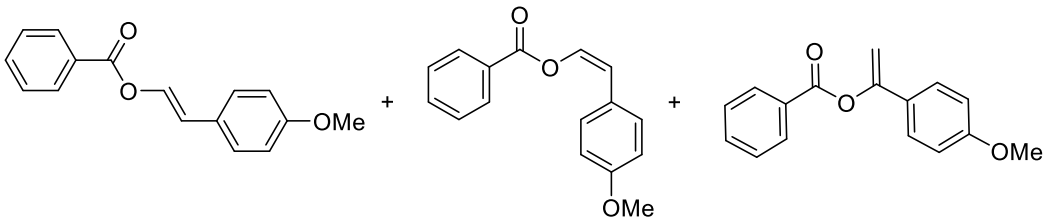
(E, Z)-styryl cyclohexane carboxylate ***(62, 63, 64)***[16]

Following the general procedure using phenylacetylene (0.11 ml, 1.00 mmol) and cyclohexane carboxylic acid (128 mg, 1.00 mmol). Purification by flash-column chromatography afforded a mixture of the vinyl ester isomers as a red oil (181 mg, 79%).

^{1}H NMR (600 MHz, $CDCl_3$) δ E-Isomer: 7.89 (d, J = 12.3 Hz, =CH, E-isomer) 1H, 7.51-7.20 (m, 5H, Ph), **6.41** (d, J = 12.3 Hz, =CH, E-isomer), 2.46 (tt, J = 3.8 & 11.3 Hz, 1H, CO_2CH, E-isomer), 10-1.95 (m, 2H), 1.86-1.78 (m, 2H), 1.74-1.63 (m, 1H), 1.61-1.45 (m, 2H), 1.42-1.22 (m, 2H)

Z-Isomer: 7.51-7.20 (m, 5H, Ph), 7.38 (d, J = 7.3 Hz, =CH, Z-isomer), **5.73** (d, J = 7.3 Hz, =CH, Z-isomer), 2.54 (tt, J = 3.8 & 11.3 Hz, 1H, CO_2CH, Z-isomer), 10-1.95 (m, 2H), 1.86-1.78 (m, 2H), 1.74-1.63 (m, 1H), 1.61-1.45 (m, 2H), 1.42-1.22 (m, 2H)

Markovnikov Isomer: 7.51-7.20 (m, 5H, Ph), **5.46** (d, J = 2.1 Hz, $=CH_2$, Markov.), **4.99** (d, J = 2.1 Hz, $=CH_2$, Markov.), 10-1.95 (m, 2H), 1.86-1.78 (m, 2H), 1.74-1.63 (m, 1H), 1.61-1.45 (m, 2H), 1.42-1.22 (m, 2H)



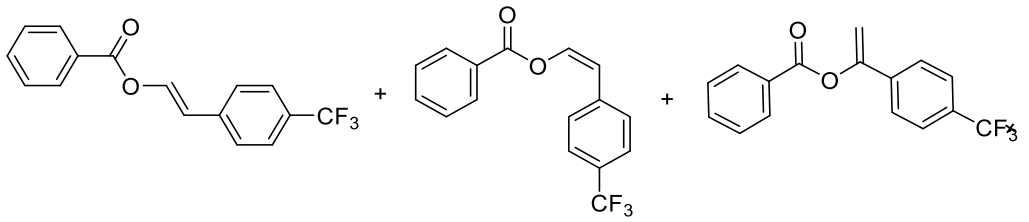
(E, Z)-4-methoxystyryl benzoate ***(65, 66, 67)***[16]

Following the general procedure using 4-ethynylanisole (0.14 ml, 1.00 mmol) and benzoic acid (122 mg, 1.00 mmol). Purification by flash-column chromatography afforded a mixture of the vinyl ester isomers as a red oil (183 mg, 82%).

^{1}H NMR (600 MHz, $CDCl_3$) δ E-Isomer: 8.38-8.25 (m, 2H) 7.71--7.48 (m, 7H, Ph & $PhCO_2$), **6.57** (d, 1H, J =12.7 Hz, =CH, E-isomer), 3.83 (s, 3H)

Z-Isomer: 8.38-8.25 (m, 2H) 7.71--7.48 (m, 7H, Ph & $PhCO_2$), 5.83 (d, 1H, J =7.1 Hz, =CH, Z-isomer), 3.85 (s, 3H)

Markovnikov isomer: 8.38-8.25 (m, 2H) 7.83-7.59 (m, 7H, Ph & $PhCO_2$), 5.50 (d, 1H, J =2.3 Hz, $=CH_2$), 5.08 (d, 1H, J =2.3 Hz, $=CH_2$), 3.81 (s, 3H)



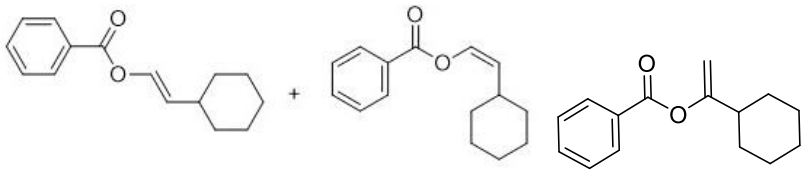
(E, Z)-4-(trifluoromethyl)styryl benzoate ***(68, 69, 70)***[16]

Following the general procedure using 4-ethynyl-trifluorobenzene (0.11 ml, 1.00 mmol) and benzoic acid (122 mg, 1.00 mmol). Purification by flash-column chromatography afforded a mixture of the vinyl ester isomers as a red oil (206 mg, 73%).

^{1}H NMR (600 MHz, $CDCl_3$) δ E-Isomer: 8.38-8.25 (m, 3H) 7.83-7.59 (m, 7H, Ph & $PhCO_2$), 6.74 (d, 1H, J =12.8 Hz, =CH, E-isomer)

Z-Isomer: 8.38-8.25 (m, 2H) 7.83-7.59 (m, 8H, Ph & $PhCO_2$), 6.03 (d, 1H, J =7.2 Hz, =CH, Z-isomer)

Markovnikov isomer: 8.38-8.25 (m, 2H) 7.83-7.59 (m, 7H, Ph & $PhCO_2$), 5.83 (d, 1H, J =2.6 Hz, $=CH_2$), 5.45 (d, 1H, J =2.6 Hz, $=CH_2$)



(E, Z)-2-cyclohexylvinyl benzoate ***(71, 72, 73)***[22]

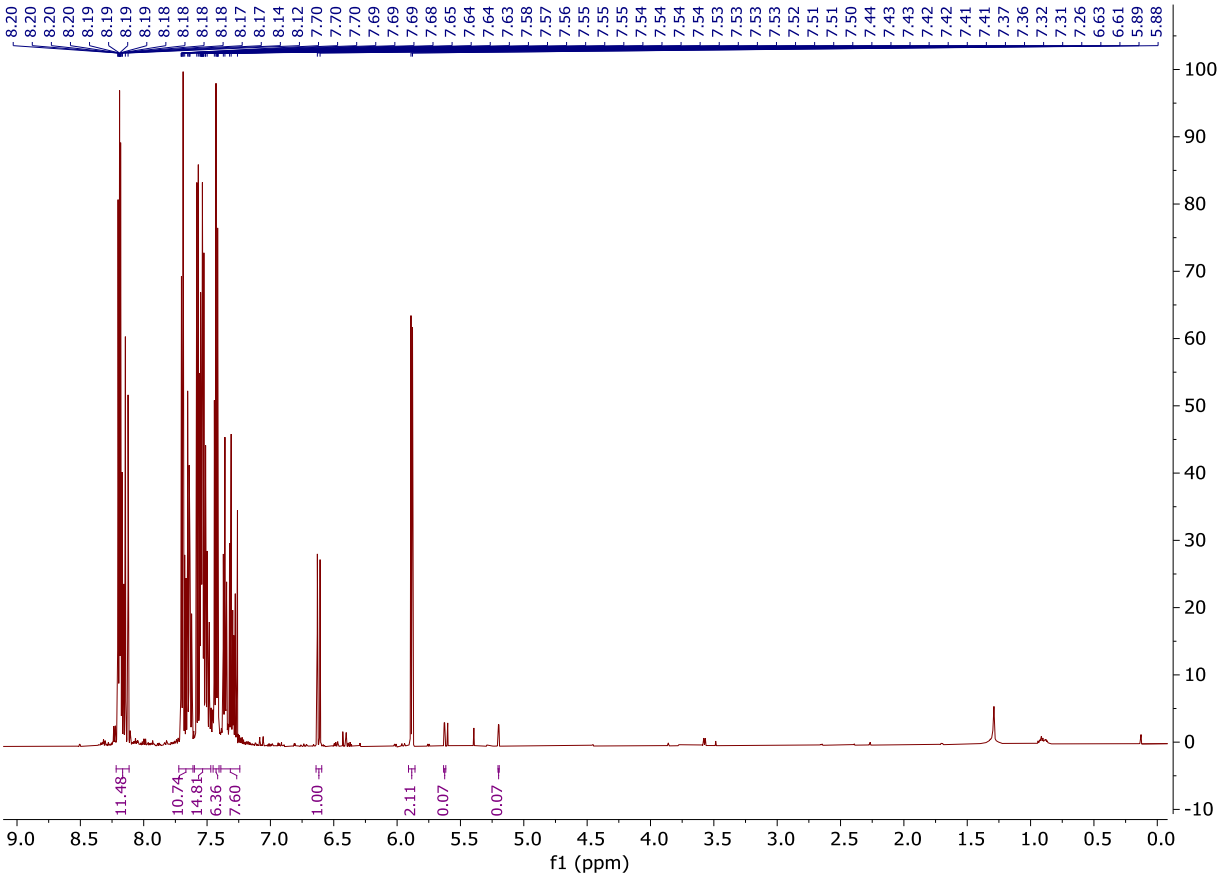
Following the general procedure using cyclohexyl acetylene (131 ml, 1.00 mmol) and benzoic acid (122 mg, 1.00 mmol). Purification by flash-column chromatography afforded a mixture of the vinyl ester isomers as a red oil (159 mg, 69%).

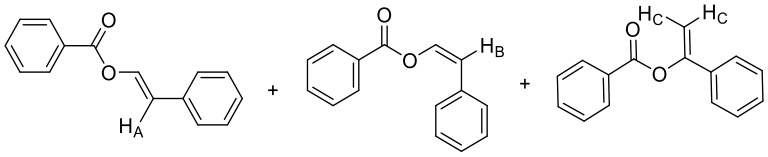
^{1}H NMR (600 MHz, $CDCl_3$) δ E-Isomer: 8.24-8.08 (m, 2H) 7.72-7.43 (m, 3H, $PhCO_2$), 7.35 (dd, 1H, J = 1.2 , 12.5 Hz, =CH, E-isomer) 5.61 (dd, J = 7.8 , 12.5 Hz, =CH, E-isomer), 2.34-1.96 (m, 1H, Cy), 1.87-1.64 (m, 2H, Cy), 1.47-1.10 (m, 8H, Cy)

Z-Isomer: 8.24-8.08 (m, 2H) 7.72-7.43 (m, 3H, $PhCO_2$), 7.21 (dd, 1H, J = 0.8 , 10.2 Hz, =CH, Z-isomer) 5.61 (dd, J = 6.4 , 10.2 Hz, =CH, Z-isomer), 2.34-1.96 (m, 1H, Cy), 1.87-1.64 (m, 2H, Cy), 1.47-1.10 (m, 8H, Cy)

Markovnikov isomer: 8.24-8.08 (m, 2H) 7.72-7.43 (m, 3H, $PhCO_2$), 4.87 (m, 1H, $=CH_2$), 4.85 (m, 1H, $=CH_2$), 2.34-1.96 (m, 1H, Cy), 1.87-1.64 (m, 2H, Cy), 1.47-1.10 (m, 8H, Cy)

NMR Spectra of Selected Products:





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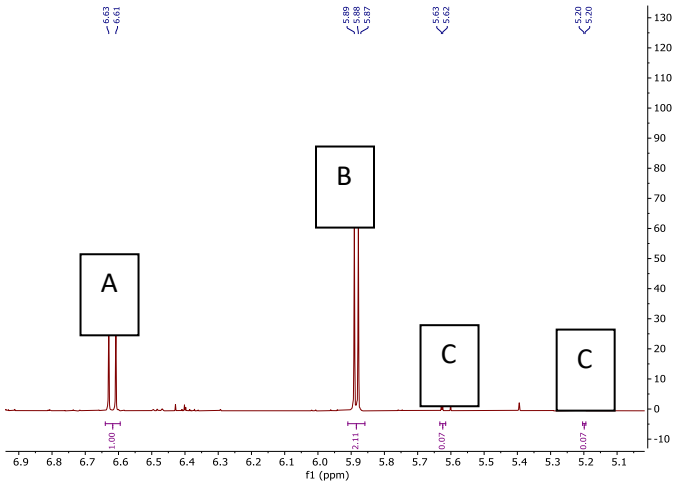
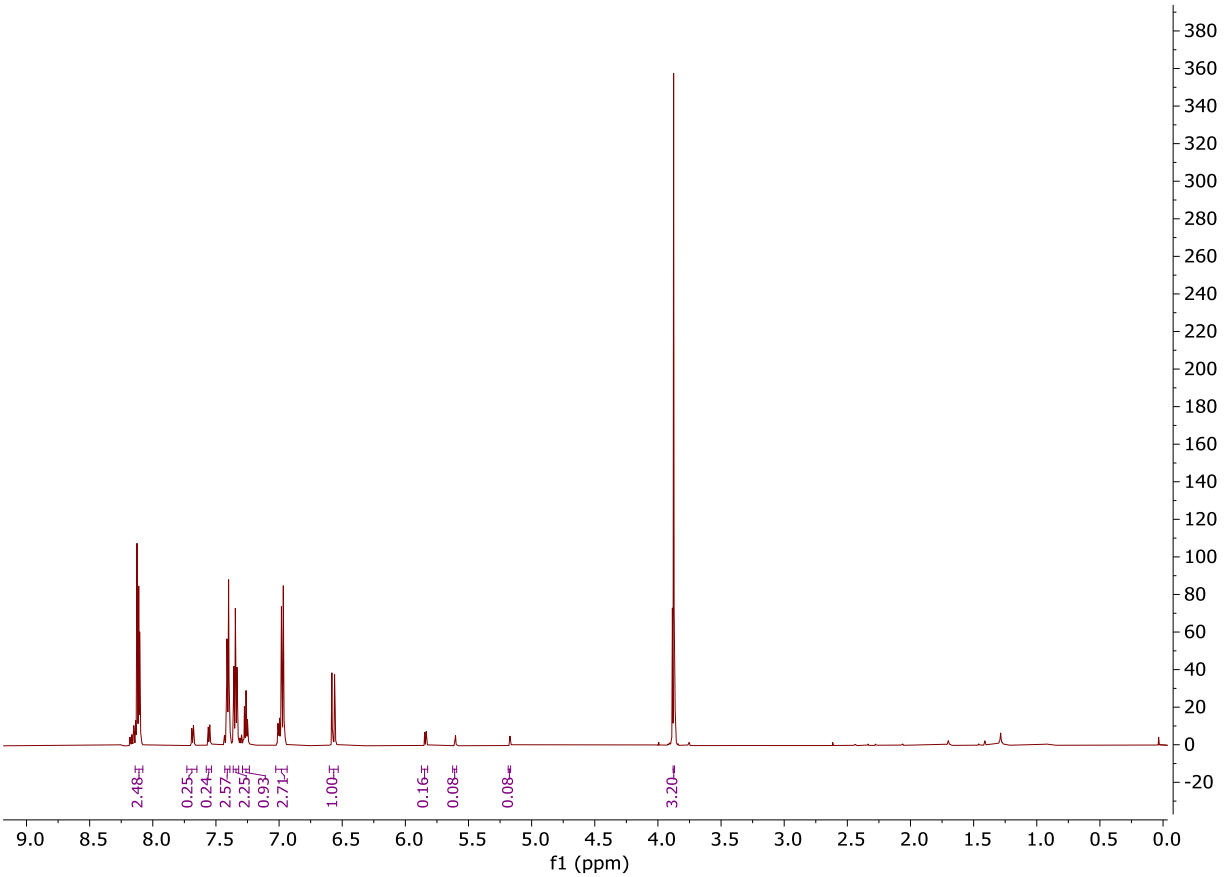
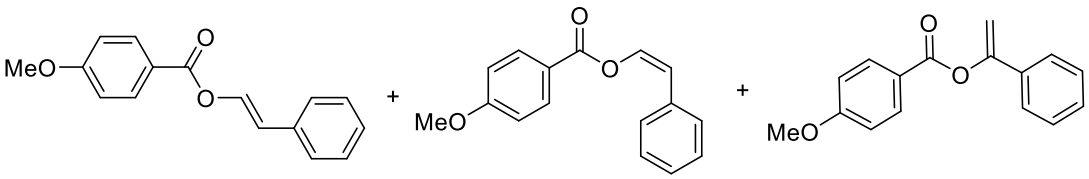
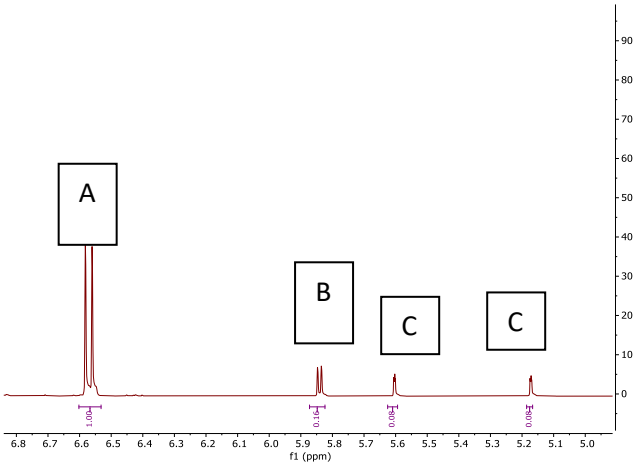
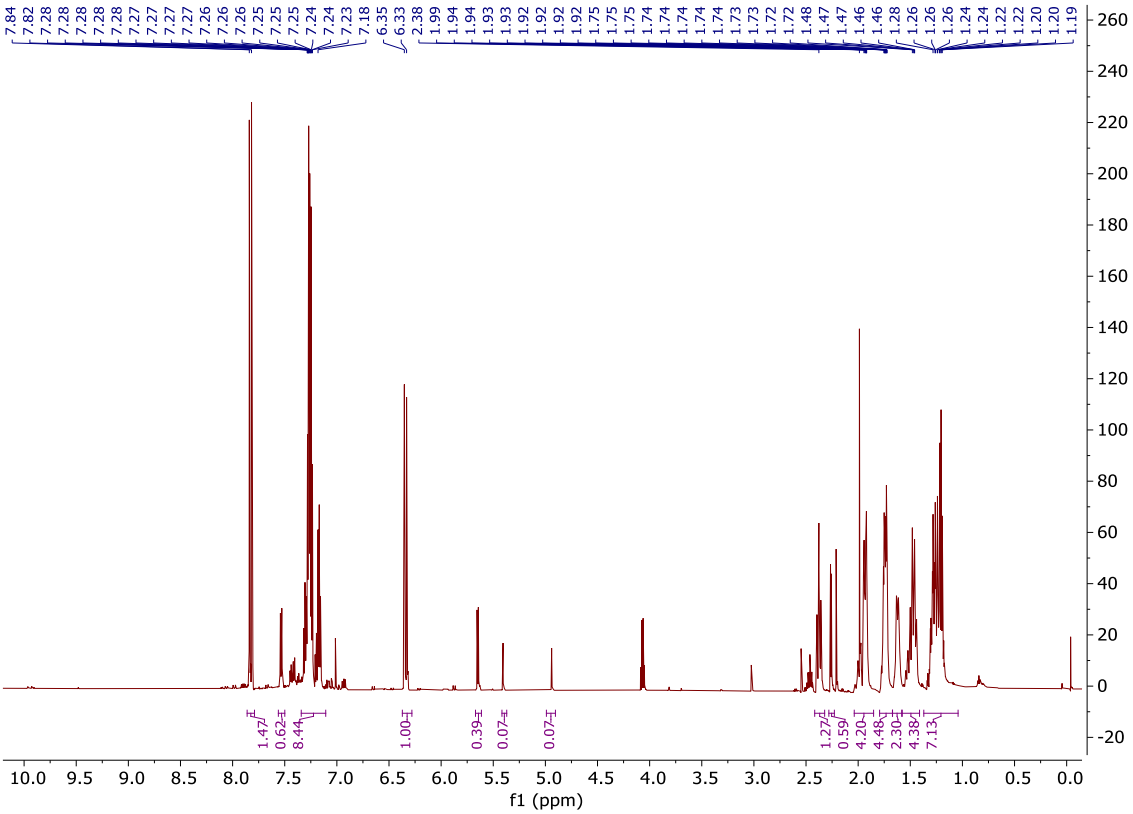


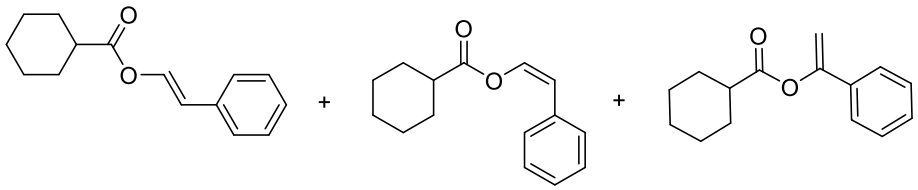




With $[Ru(NCMe)_6][(BF_4)_2]$







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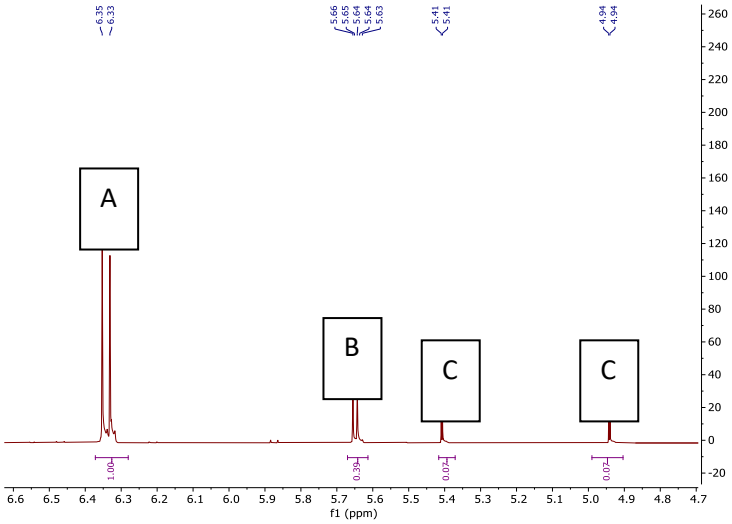

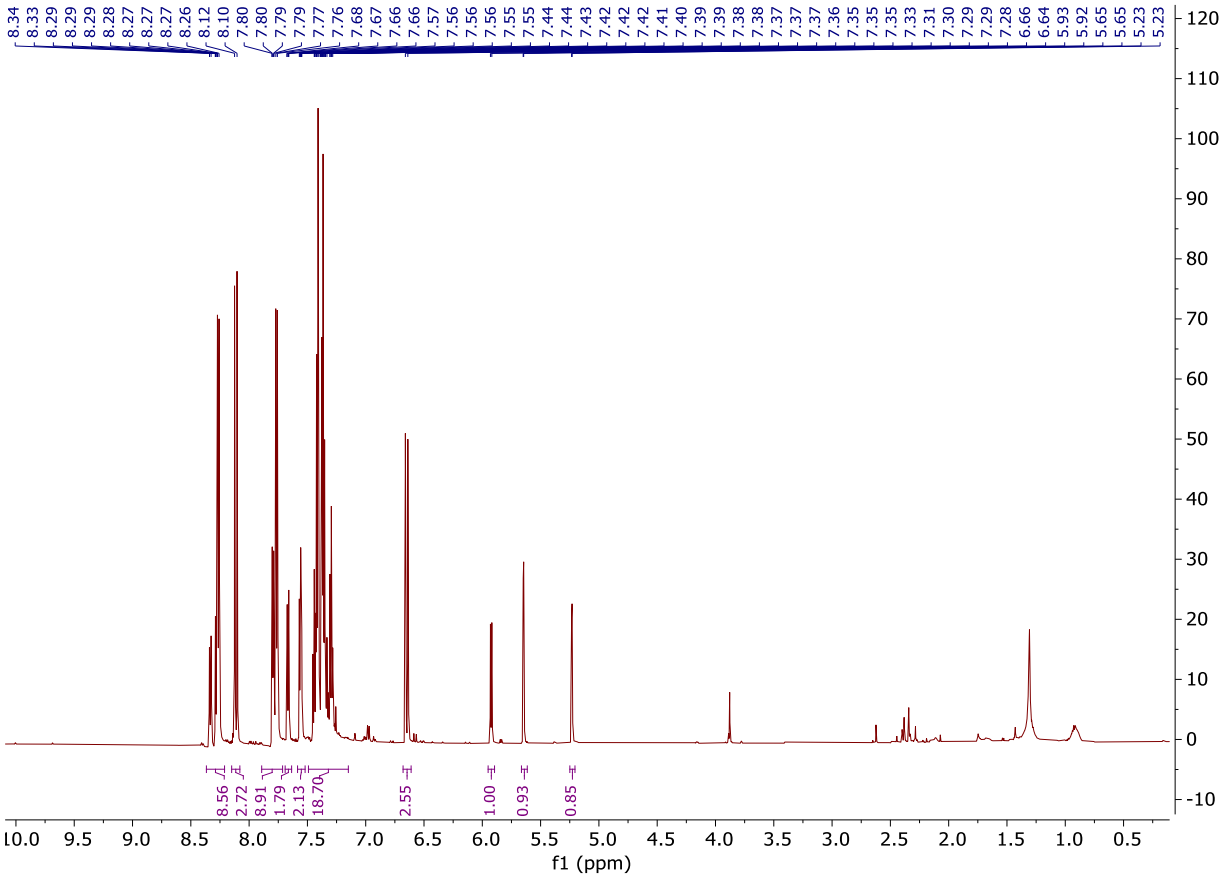

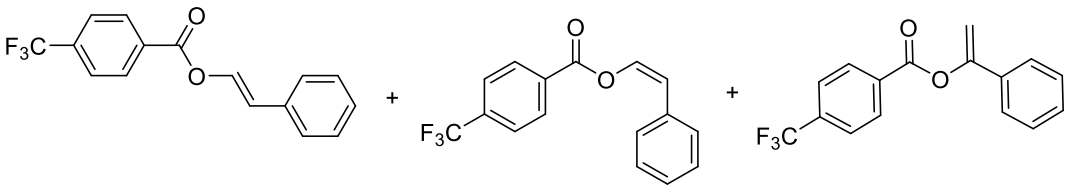

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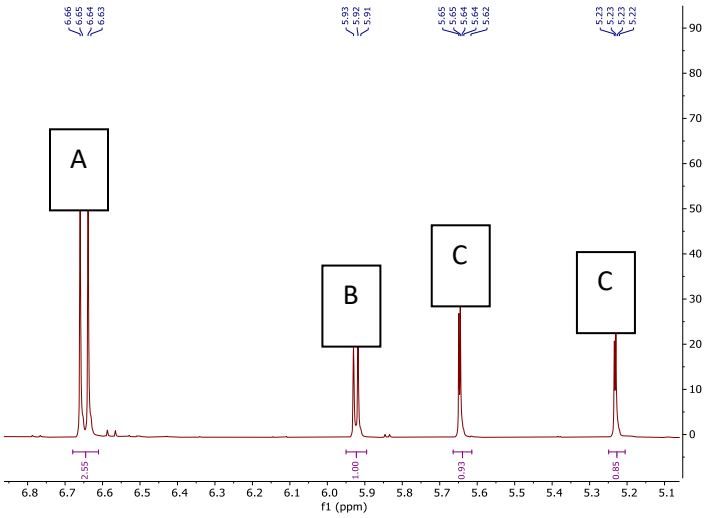

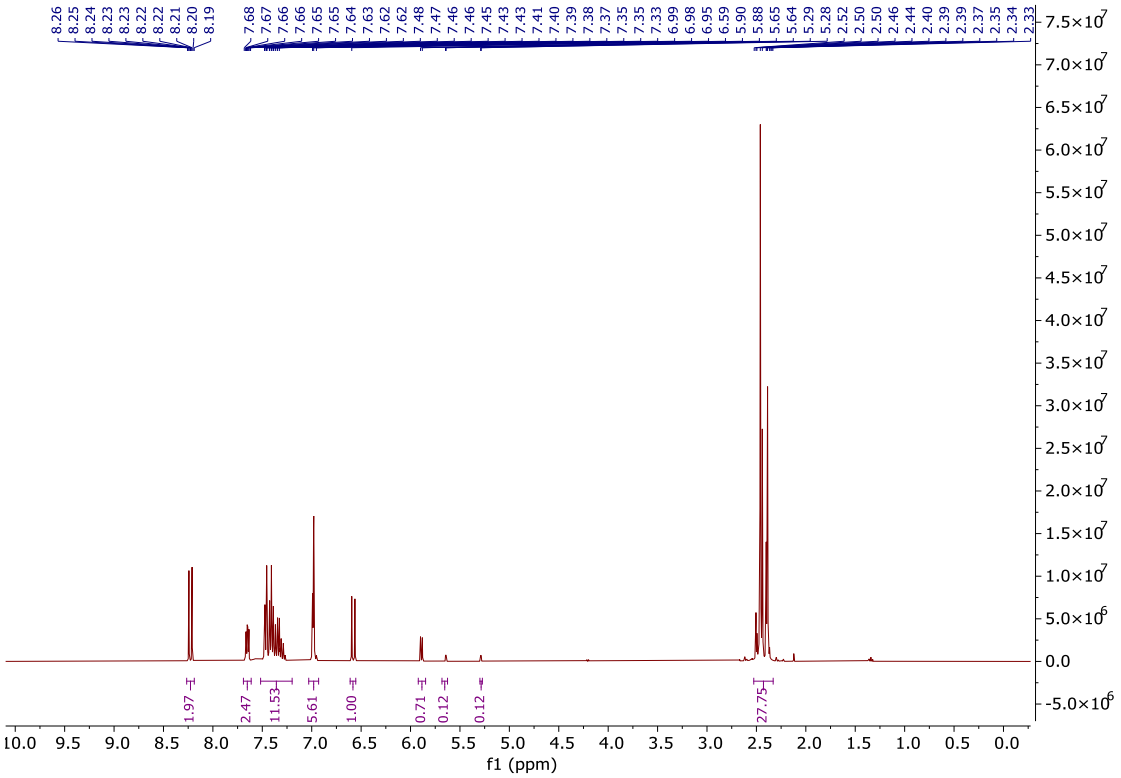

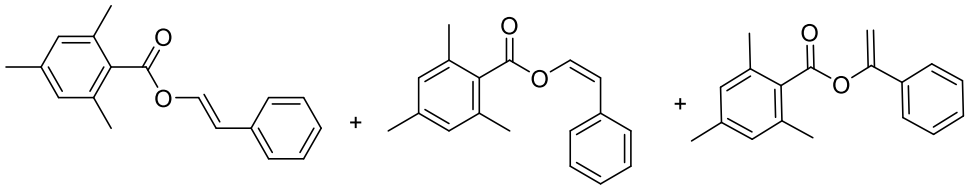

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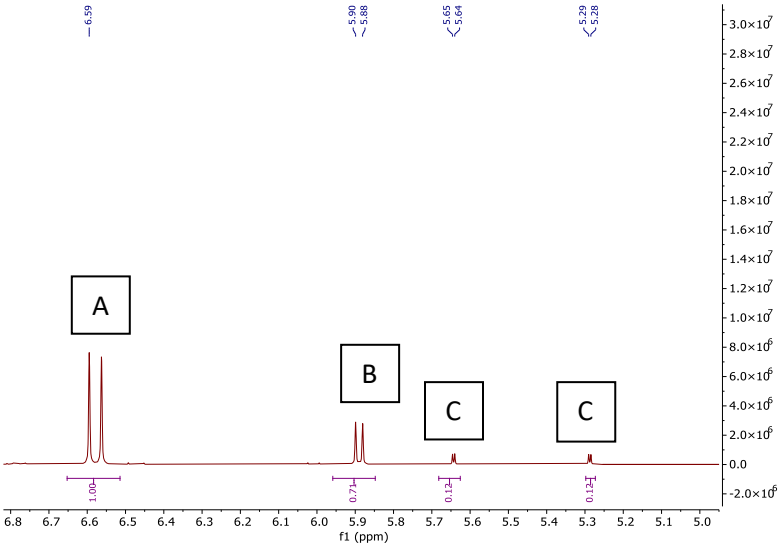

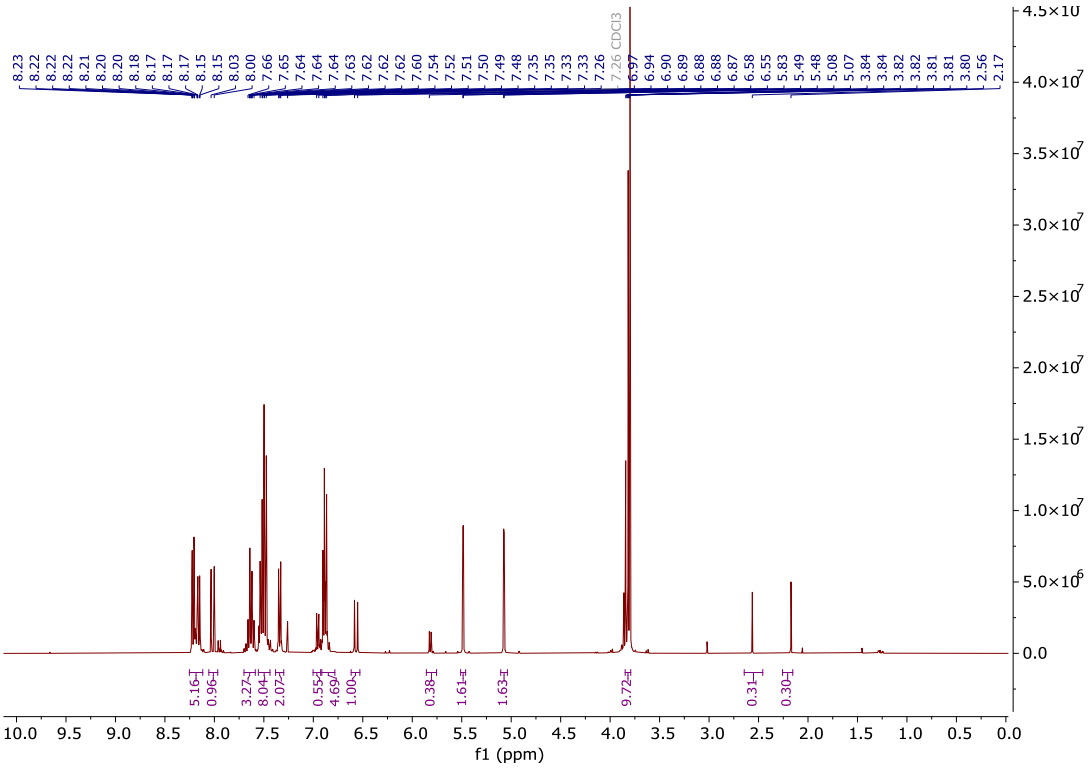

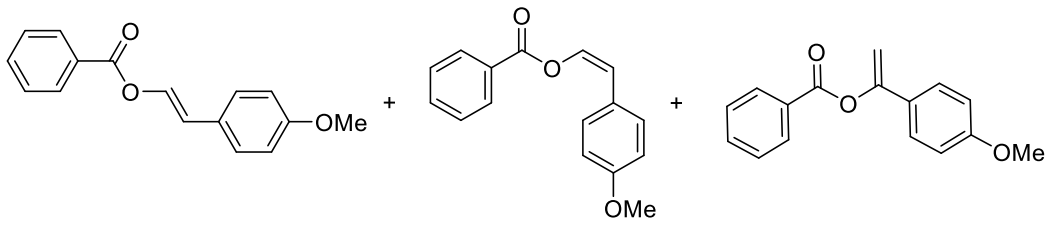

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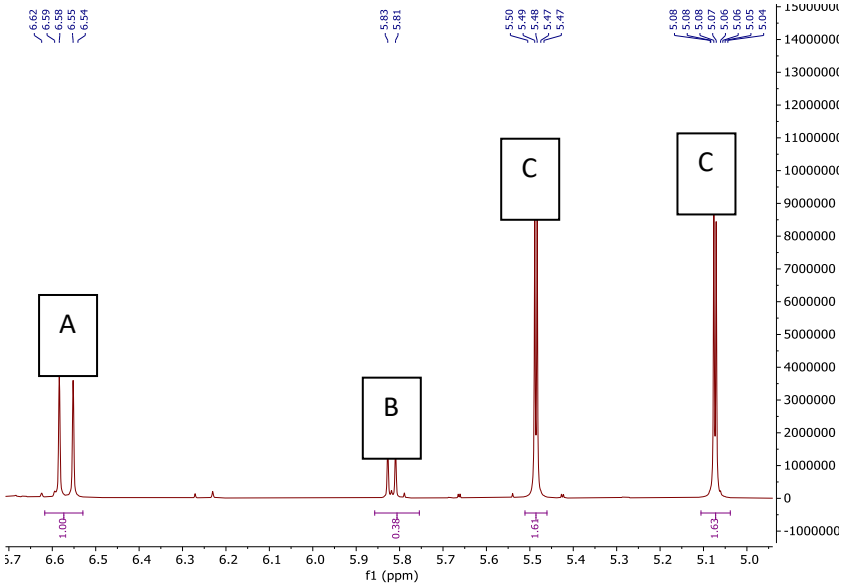
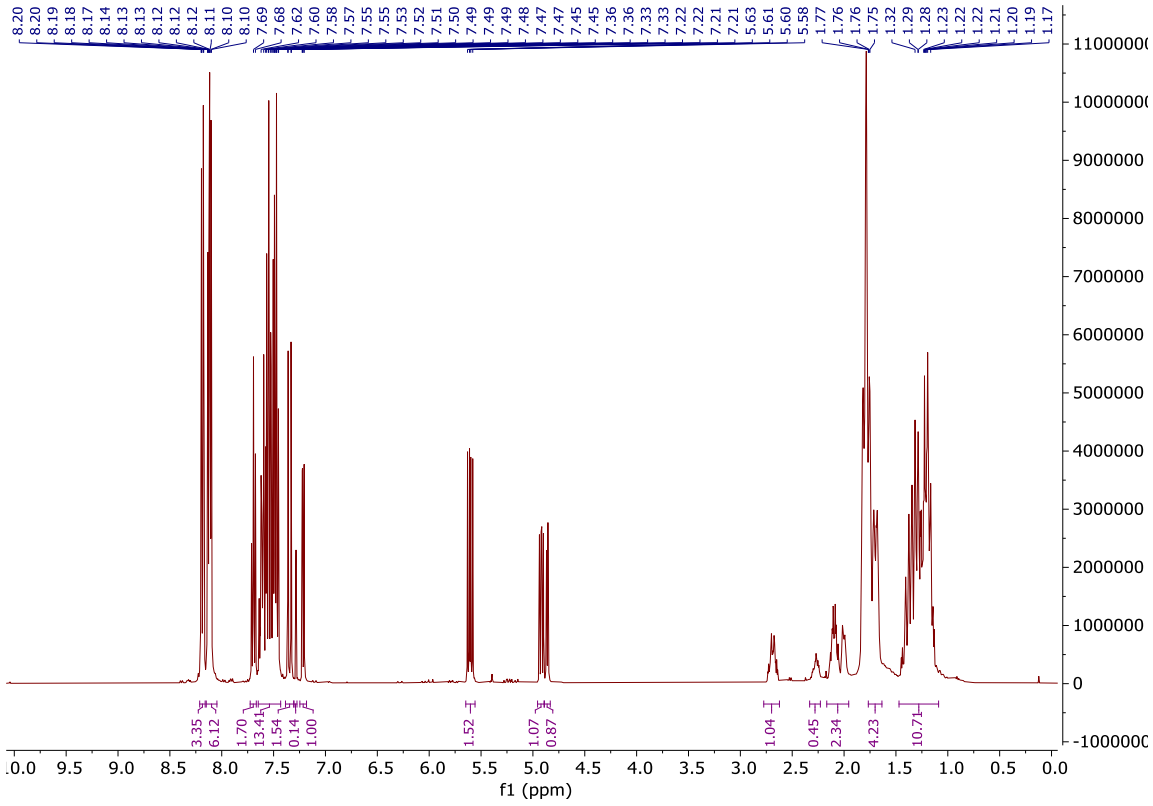
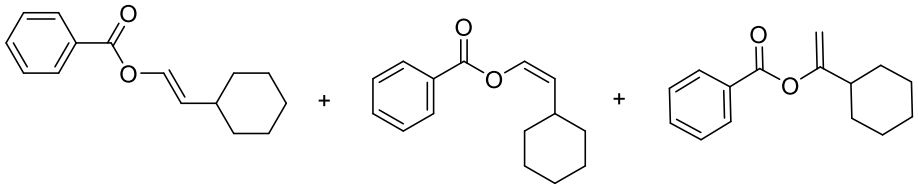
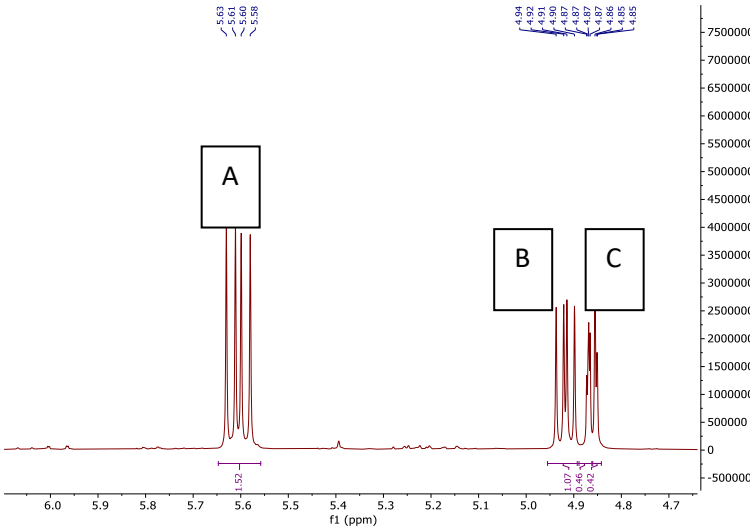
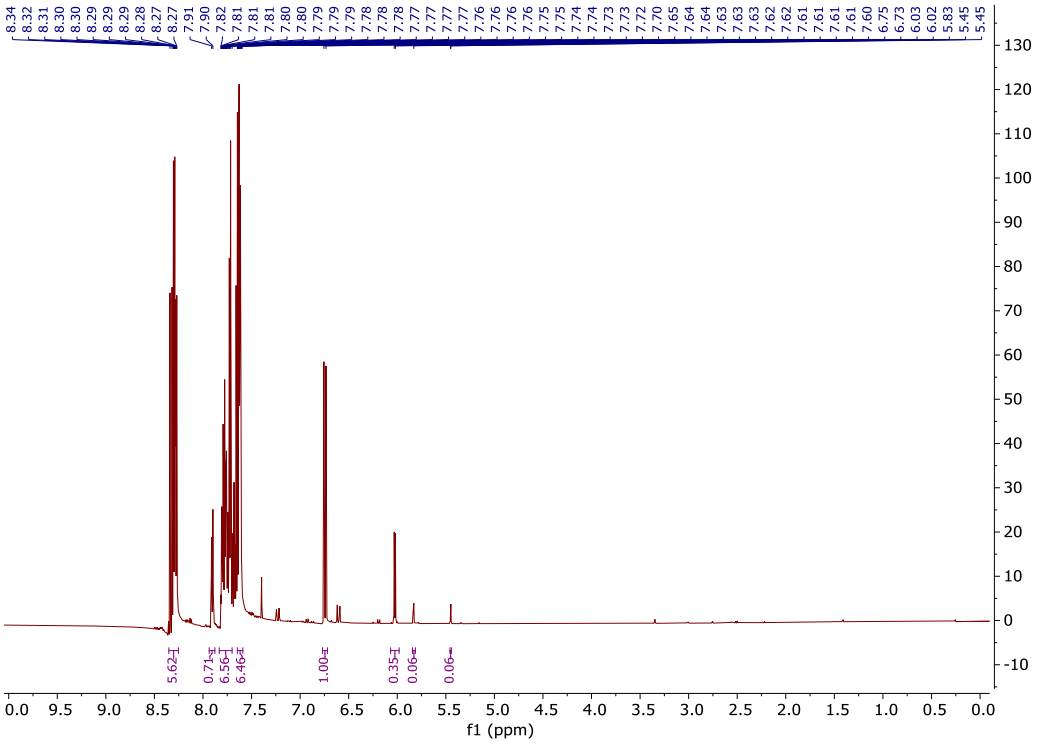


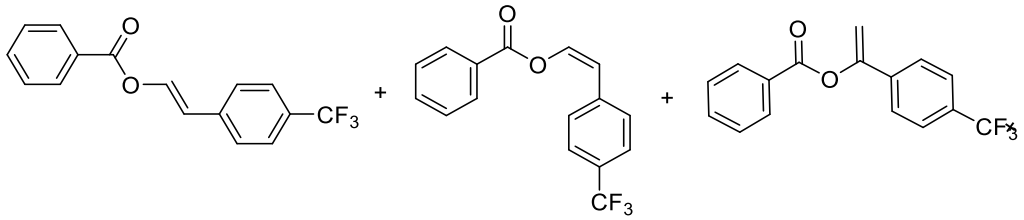




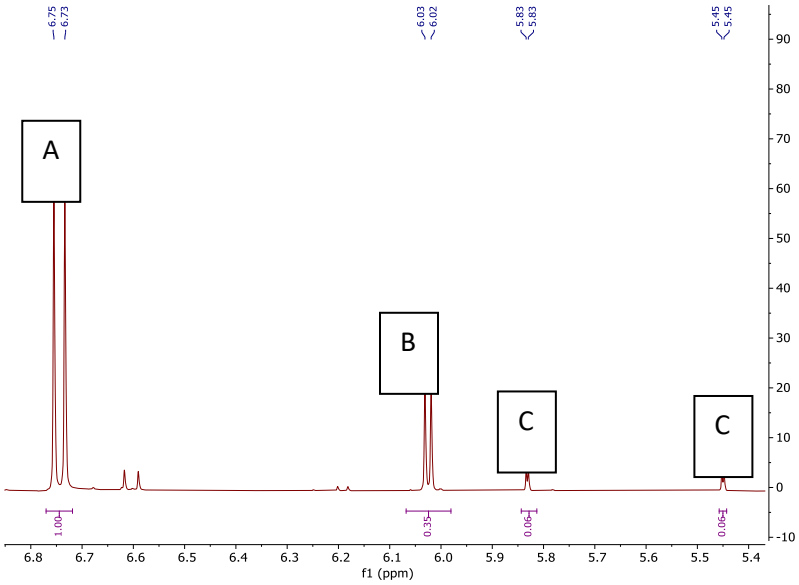
With $[Ru(NCMe)_6][(BF_4)_2]$







With $[Ru(NCMe)_6][(BF_4)_2]$



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Chapter 3

Optimizing Chan-Lam coupling for vinyl ether synthesis

3.1 Introduction

Our investigation aims to expand Chan-Lam coupling to synthesize complex 1,2 di-substituted vinyl ethers. Unable to catalyze anti-Markovnikov addition between alkyne and alcohol substrates with ruthenium, we decided to focus our efforts on optimizing copper catalyzed cross-coupling of alcohols with alkenyl reactants. One common method for forming carbon heteroatom bonds via transition metal-catalyzed cross-coupling reactions is Ullmann coupling reactions. However, along with exploring Ullmann coupling reactions, we decided to explore the capabilities of Chan -Lam coupling. Broadly defined, Chan-Lam coupling links organic boronic acids with nitrogen, oxygen, and hetero-nucleophiles. [1] Methods for coupling stronger nucleophiles such as N-H are well developed and understood. Weaker nucleophiles such as O-H especially sp^3 hybridized alcohols are not as well understood mechanistically. The published methods for vinylic ether synthesis are impractical for complex synthesis as they require the nucleophilic alcohol to be in excess or have limited substrate scope. [2] The objective is to extend the reactivity of Chan-Lam reactions to include the addition of alcohols and equimolar amounts of boron substrates towards the synthesis of complex vinyl ethers. To achieve this, we planned to utilize mechanistic insights from other Chan-Lam methods.

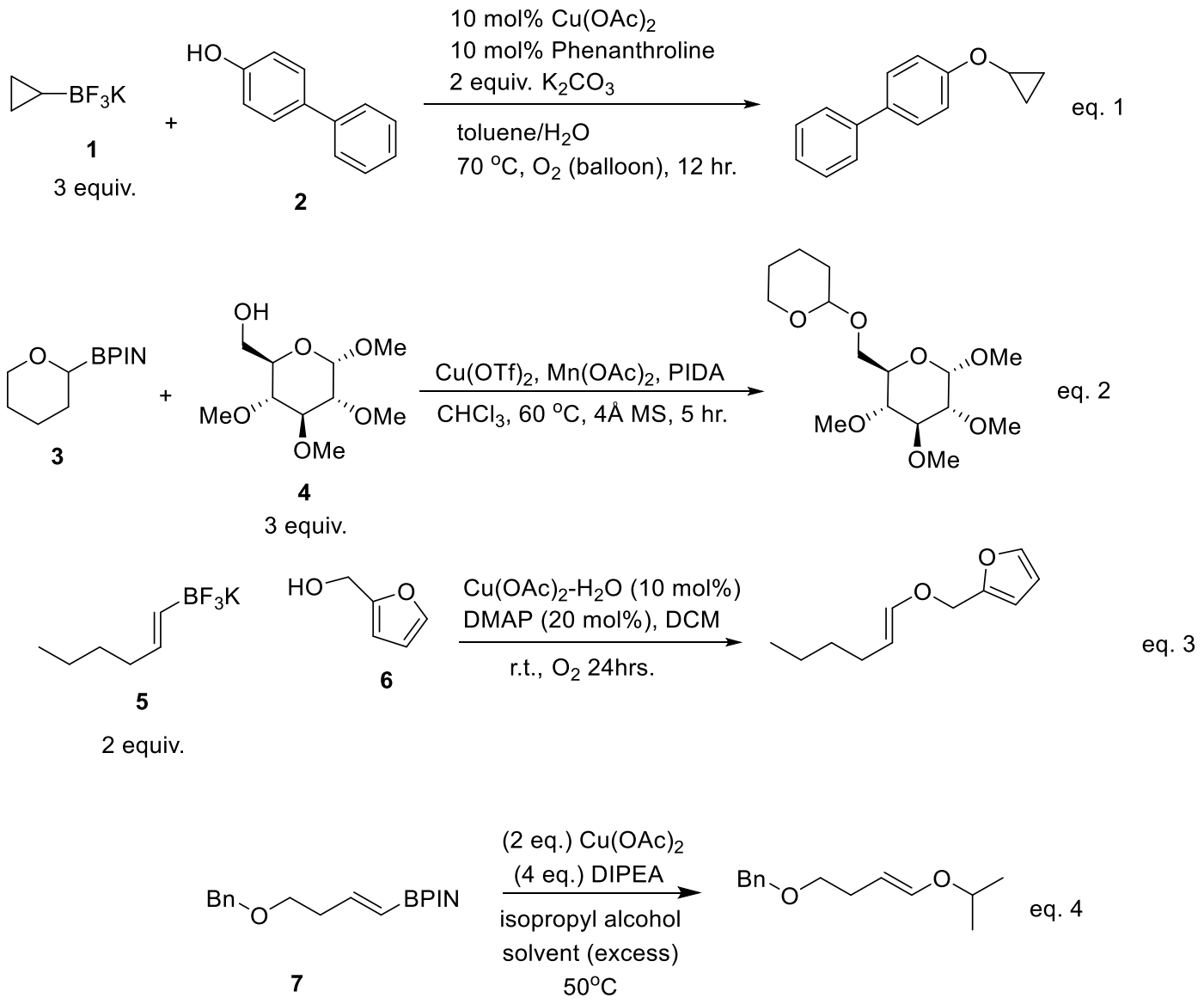


Figure 1: Chan-Lam methods for C-O bond formation

There are several Chan-Lam coupling methods developed for C-O bond formation, but these methods are too limited for our applications due to substrate and stoichiometry limitations (**Figure 1**). McAlpine *et al*. designed a Chan-Lam cyclopropylation reaction using potassium cyclopropyl trifluoroborate (eq. 1). [3] This method was capable of mediating Chan-Lam coupling

with 3 equiv. of the trifluoroborate, but was limited to only a cyclopropyl group. They found that bidentate ligand, 1,10-phenanthroline, drastically improves reactivity in comparison to bipyridine and pyridine. Walczak and Miller published an expanded Chan-Lam protocol for the acetalization of boronic esters to include C-sp^3 nucleophiles (eq. 2). [4] Batey and Quach report an efficient Chan-Lam reaction for alkyl trifluoroborate coupling with 2-furfuryl alcohol **8**. (eq. 3). [5] The best documented method for complex C-O bond formation via Chan-Lam coupling is the coupling of compound **10** and isopropyl alcohol or allyl alcohol (neat) in the presence of DIPEA or NEt_3 and $Cu(OAc)_2$ (eq. 4). [6] Chan-Lam methods for C-O bond formation are developed for aromatic alcohols and aromatic boronic acid substrates, but seldom methods are capable of mediating the addition of less acidic sp^3 hybridized alcohols with vinyl boron substrates.

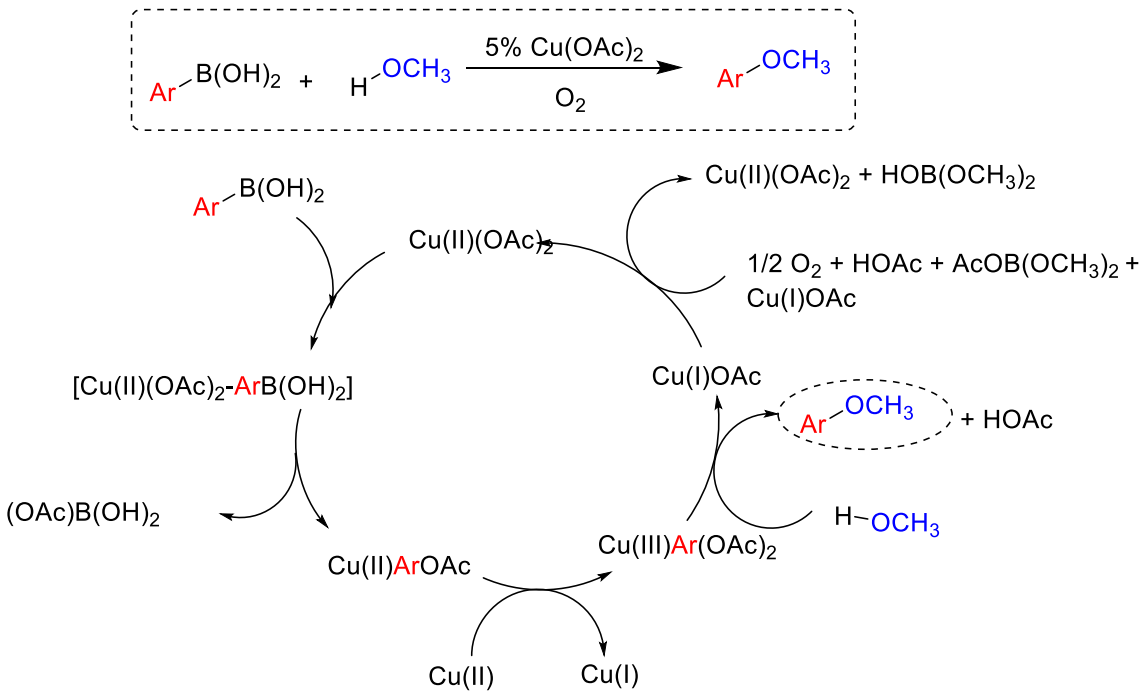


Figure 2: Stahl mechanism for Chan-Lam C-O bond formation

Stahl *et al*. conducted mechanistic studies on the cross coupling reaction between aromatic boric acid and methanol (**Figure 2**). They propose that the reaction is initiated by transmetalation

between the aryl group and Cu(II) to form an aryl Cu(II). This species is then oxidized by another Cu(II) to yield a Cu(III) aryl species that undergoes facile C-O bond formation. Finally, rapid aerobic oxidation of Cu(I) regenerates Cu(II) and the catalytic cycle continues. The rate determining step in the cycle is the transmetalation of the aryl group to the copper center.

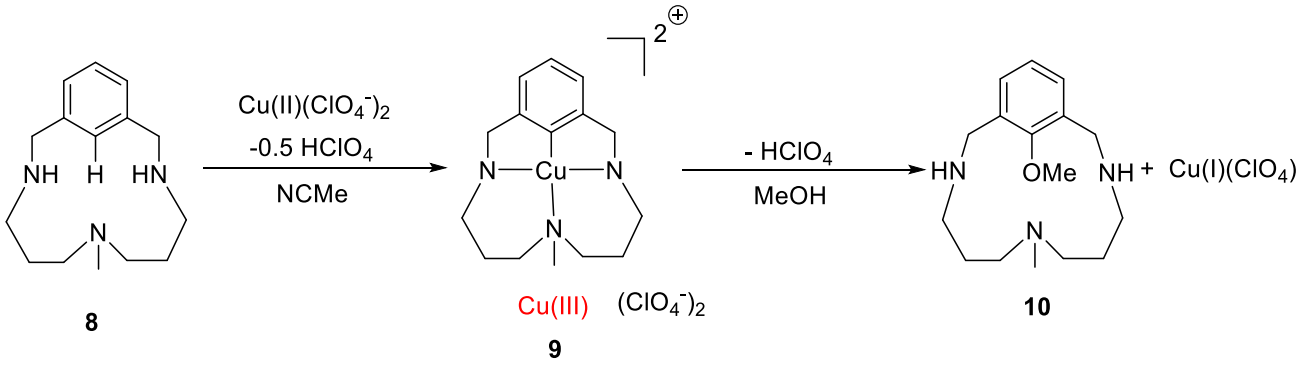


Figure 3: Example of Cu(III) in disproportionation

Arene complex **9** is an early example of a Cu species being used for methoxylation and amidation (**Figure 3**). Stahl *et al.* used this complex to establish the relevance of Cu(III) by isolating the product and characterizing it by X-ray crystallography, NMR, and UV-visible spectroscopy. When this complex is subjected to methanol, arene complex **10** forms, demonstrating how Cu(III) can be involved in redox disproportionation.

Transmetalation was determined to be the rare-determining step for copper catalyzed oxidative coupling. [7] EPR and kinetic studies of the reaction conditions suggest that the C-O bond formation occurs after the turnover-limiting step. EPR revealed a lack of strong aryl donor ligand and a presence of weak donor ligands during the resting state. This supports the kinetic experiments that determined a kinetic dependence on the $Cu(OAc)_2$ and the $ArB(OMe)_2$ and that transmetalation between the two is the rate- determining step. Although EPR studies cannot determine structural

assignment they hypothesized that complex **11** is the structure before transmetalation based on inhibitory effects of acetate and acetic acid on the catalytic rate. They propose that rate-determining transmetalation proceeds through a methoxide bridged intermediate. This suggests that the acetate ligand play a significant role in the promotion of transmetalation.

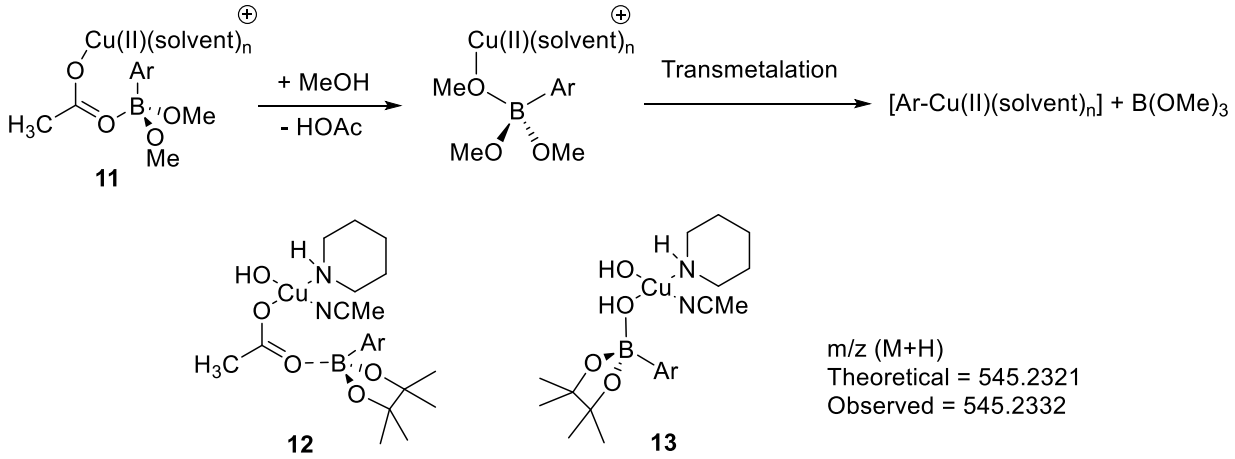


Figure 4: Stahl's proposed resting states/pre-transmetalation intermediates (**11**) and Watson observed intermediates (**12**) and (**13**)

Watson *et al*. conducted spectroscopic mechanistic studies on Chan-Lam amination to determine key intermediates in the mechanistic pathway (**Figure 4**). In the cross-coupling of aromatic boric acid and piperidine, they found mass ions consistent with their proposed pre-transmetalation intermediate structural isomers **12**. The investigation also describes a paddlewheel species that is initiated by acetic acid which inhibits the essential amine denucleation step through protonation of the amine, giving the hexa-acetate paddlewheel. These mechanistic studies provide insights that will guide our synthetic strategy.

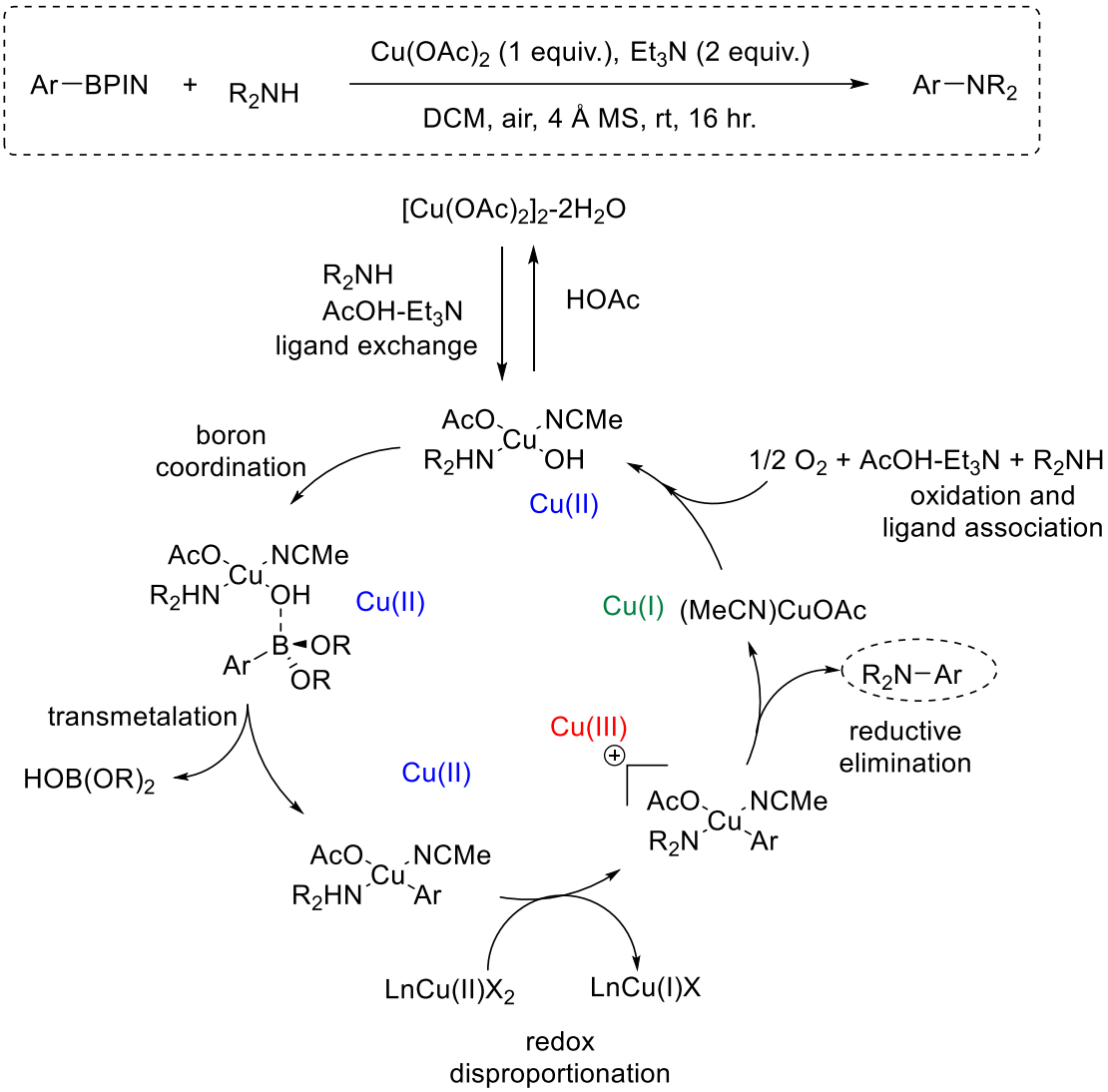


Figure 5: Watson proposed mechanism for Chan-Lam amination [8]

The use of Cham-Lam coupling to construct C-N bonds is better developed. We envisioned that the mechanistic insights might be used to develop a synthetic strategy for C-O bond formation (**Figure 5**). Watson *et al*. reports a cross-coupling method to synthesize N-arylsulfonamides, through previous mechanistic insight. [8] Based on Stahl etherification work and isolated stoichiometric experiments, Watson proposes a complete mechanistic description of the Chan-Lam amination. Previous mechanistic studies from Stahl *et al*. reveal that the initial paddlewheel denucleation is highly dependent on the Lewis basicity of the nitrogen substrate, and the nitrogen

association mediates the oxidative turnover of the Cu catalyst.[7] From these insights, they designed a method that utilized $Cu(MeCN)_4PF_6$ instead of $Cu(OAc)_2$ to avoid paddlewheel formation and bolster substrate ligation (**Figure 6**). This also suppressed organo-boron homocoupling and promoted oxidative turnover.

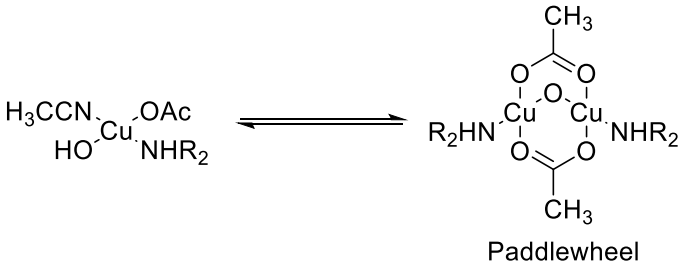


Figure 6: Paddlewheel formation

Merlic *et al*. reported $Cu(OAc)_2$ promoted coupling of a vinylic boronate with neat allyl alcohol. Currently, this method is limited and unable to synthesize complex vinyl ethers, because the alcohol has to be in large excess and only simple alcohols are demonstrated to synthesize 1,2 di-substituted vinyl ethers. The mechanistic understanding of this chemistry is under-development. Merlic proposes that the transmetalation and ligand exchange from $Cu(OAc)_2$ is followed by disproportionation and then reductive elimination. Their method uses triethylamine, which they postulate might quench the acetic acid without functioning as a ligand for the copper.

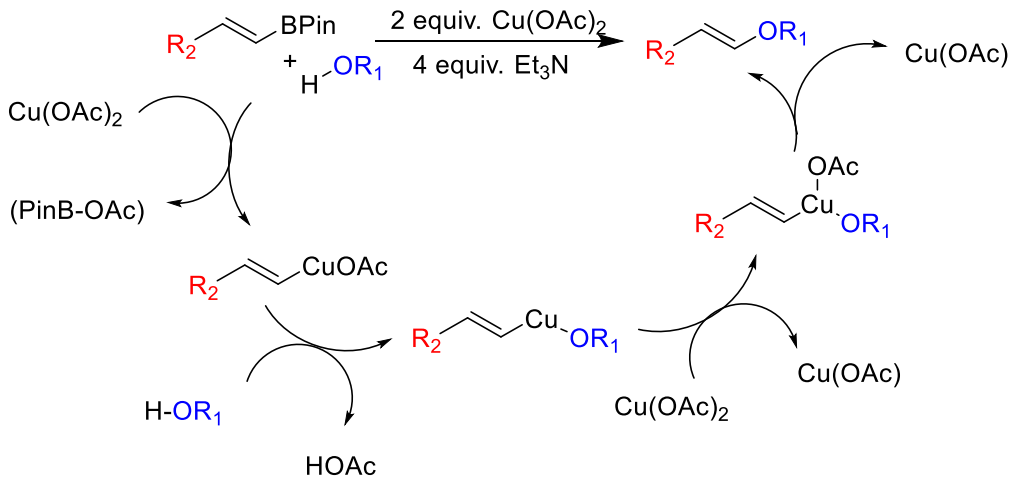


Figure 7: Merlic's proposed mechanism for Chan-Lam vinyl ether synthesis

Merlic's laboratory describes a mechanism for this process based on the mechanistic work from Stahl and Watson (**Figure 7**). The propose that the mechanism is similar to the mechanism proposed by Stahl, however Merlic describes a stoichiometric mechanism where the excess Cu(II) is required and the Cu(I)OAc generated is not re-oxidized back into Cu(II). It is hypothesized that the disproportionation step requires excess cupric acetate to oxidize Cu(II) into Cu(III). Merlic *et al*. found vinyl BPIN to be the best substrate for Chan-Lam coupling with alcohol, but this is in contrast with other Chan-Lam methods where boric acid is more suitable.

3.2 Synthetic Strategy

Our strategy is to use the mechanistic insights from other Chan-Lam methods and apply them to the Chan-Lam coupling between vinyl boron species and complex alcohols and expand reactivity. Our initial mechanistic proposal assumes that water plays a significant role in the activation of the boron substrate and the Cu catalyst (**Figure 8**). Initially, water reacts with the vinyl BPIN to give pinacol and the reactive vinyl boric acid. The boron substrate associates with the copper metal center and forms the intermediate analogous to the one proposed by Stahl *et al* followed by ligand exchange with water to give the reactive key intermediate that can undergo the

rate-determing transmetalation. With the presence of water and base, protodeboronation is a possible side reaction that can compete with our desired reaction of the transmetalation step is not fast enough. The Cu(II) intermediate then performs a redox disproportionation with another Cu(II) species to generate a Cu(III) that exchanges ligands with the nucleophilic alcohol to generate acetic acid. The Cu(III) undergoes reductive elimination to give the vinyl ether and Cu(I), which oxidizes to recycle the catalytic system.

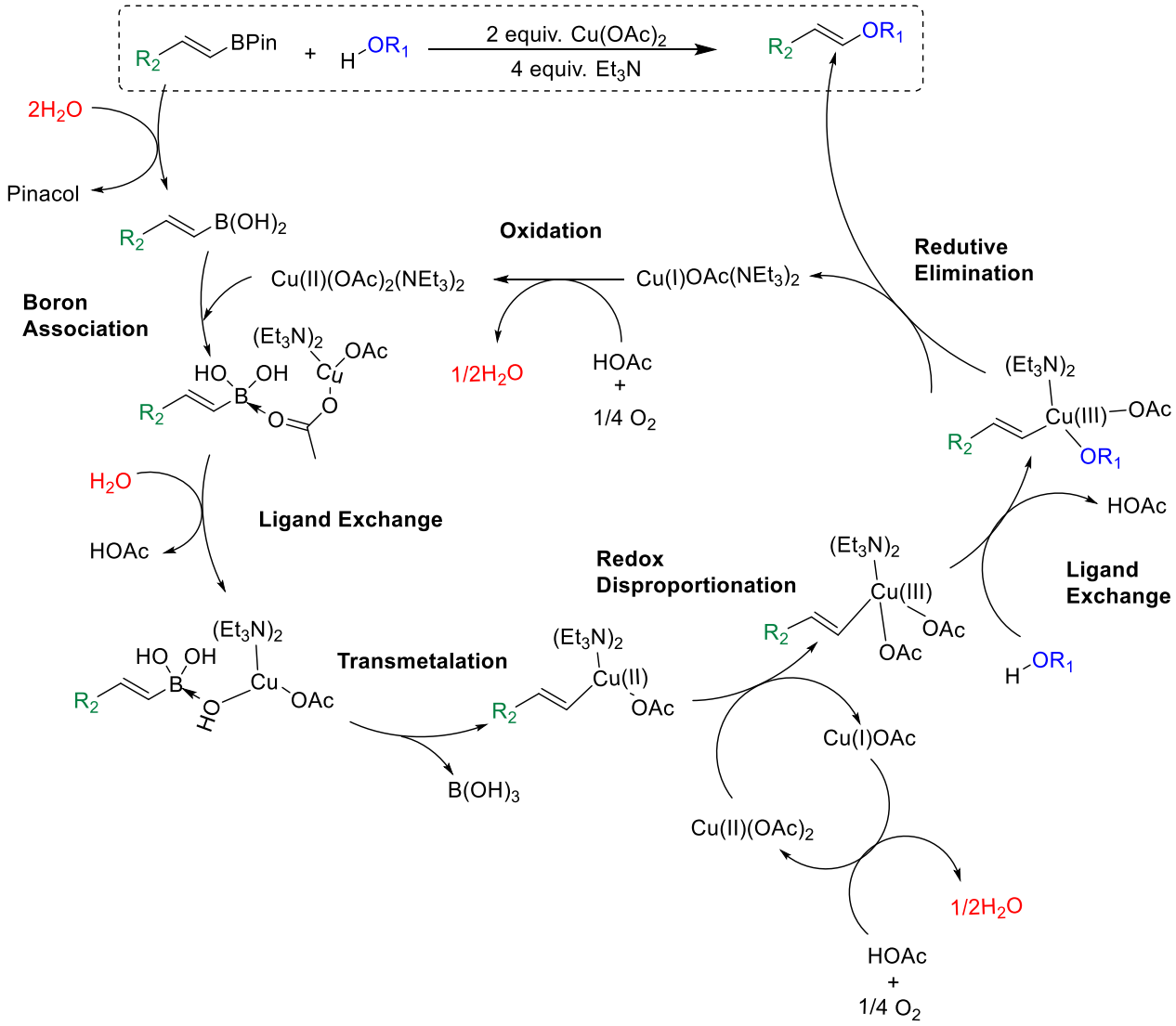


Figure 8: Our proposed hydrous Chan-Lam mechanism

From our proposed mechanism, we developed several routes to promote reactivity and generate

more vinyl ether product. A screening of solvent allows us to vary the temperature and solubility of the system, but an increase in temperature may promote more byproduct production. The choice of base is significant because we need one that promotes vinyl ether synthesis, but avoids proto-deboronation. The role of the base in the vinyl ether synthesis is unclear, but is clearly significant to promote reactivity.

The acetate ligand assists with the ligand exchange to generate the reactive intermediate for the rate-determining transmetalation, but the presence of acetic acid favors the unreactive paddlewheel compound. A copper catalyst screening may discover a catalyst that can avoid the paddlewheel compound and promote transmetalation. Our lab hypothesized that a stoichiometric screening of $Cu(OAc)_2$ may find conditions that promote transmetalation and reduce paddlewheel formation. The investigation of other copper catalyst for Chan-Lam coupling will further expand our options.

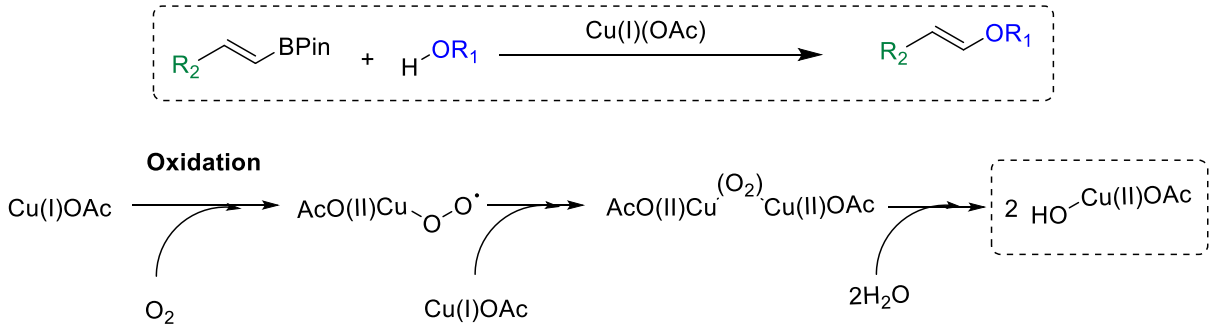


Figure 9: Cu(I) for Chan-Lam vinyl ether synthesis

We proposed to test Cu(I)OAc for vinyl ether synthesis, to control the presence of acetic acid and the paddlewheel formation (**Figure 9**). For this Cu catalyst, we propose a new mechanism with Cu(I)OAc that is initiated by oxidation with oxygen, followed by hydration to generate the reactive key intermediate for transmetalation. The mechanism then follows the same steps with redox disproportionation and ligand exchange with the alcohol. Reductive elimination generates

the vinyl ether, and the Cu is recycled ready to be oxidized. We hypothesize that less acetate ligand will suppress paddlewheel formation, while still promoting transmetalation. Further stoichiometric screening of Cu(I)OAc will allow us to further fine tune the reactivity.

Another approach we explored was an anhydrous Chan-Lam method. Water is initially required during ligand exchange to generate acetic acid and the reactive hydroxyl copper intermediate for the rate-determining transmetalation. However, water also promotes protodeboronation in the presence of base.[9-10] An anhydrous method may suppress this byproduct, and Merlic *et al*. hypothesize that the transmetalation may occur without water through the copper acetate intermediate.

Collman *et al*. describes a Cu(I) complex that promotes Chan-Lam amination with arylboronic acids. [11] The Cu catalyst featured a μ-hydroxo complex with nitrogen chelated bidentate ligands. We hypothesize that the hydroxo ligands will provide access towards the reactive intermediate before the rate-determining transmetalation (**Figure 10**). Collman developed a series of copper catalyst with various nitrogen bidentate ligands that can be screened for vinyl ether synthesis. We hypothesize that the choice of ligand will function analogously to the base and impact the rate of protodeboronation and transmetalation.

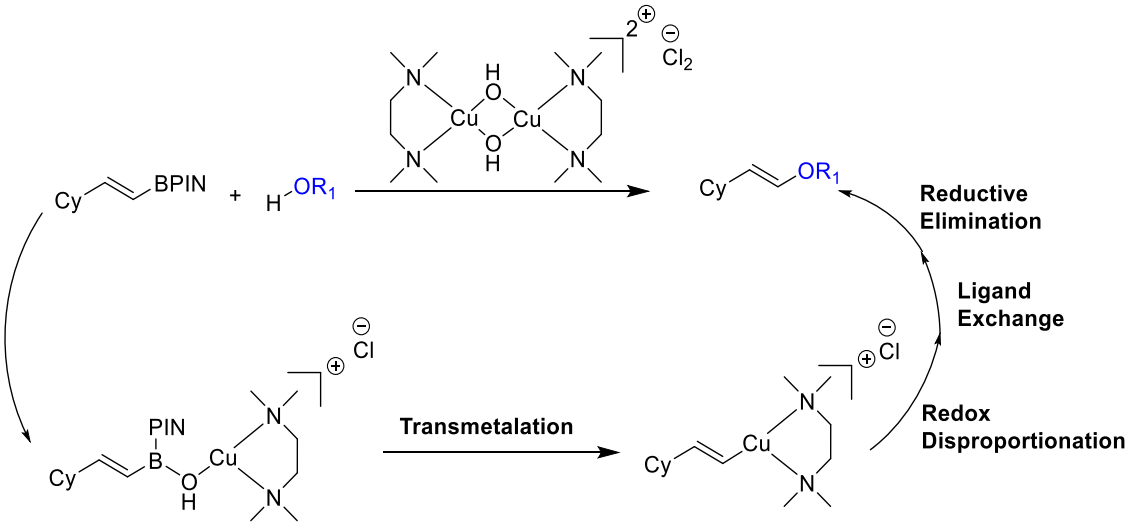


Figure 10: Proposed Chan-Lam mechanism with Collman catalyst

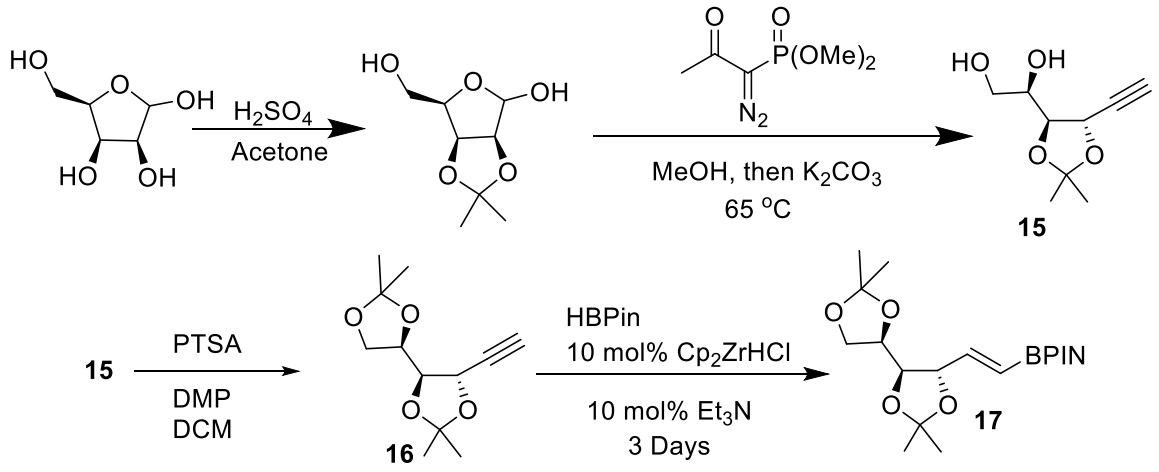
3.3 Results and Discussion

The goal of our investigation is to improve Chan-Lam coupling methods so that only equimolar amounts of boron substrate and alcohol are required and complex substrates are capable of undergoing reaction. Copper catalyst, solvent, base, temperature and catalyst loading screenings will allow us to tune conditions to promote vinyl ether generation and reduce byproduct formation. Control of the acetate ligand is essential to promote transmetalation, but also reduces reactivity due to paddlewheel formation. We hypothesize that this balance can be controlled through acetate ligand loading or by finding a copper catalyst that can promote transmetalation without an acetate ligand.

3.3.1 Sugar Synthesis

Our lab is interested in synthesizing vinyl ethers because this functional is essential for the stereoselective synthesis of glycosides. We decided to test Chan-Lam coupling methods for complex glycoside synthesis. Sugar diol complex **15** was synthesized based on our labs previously

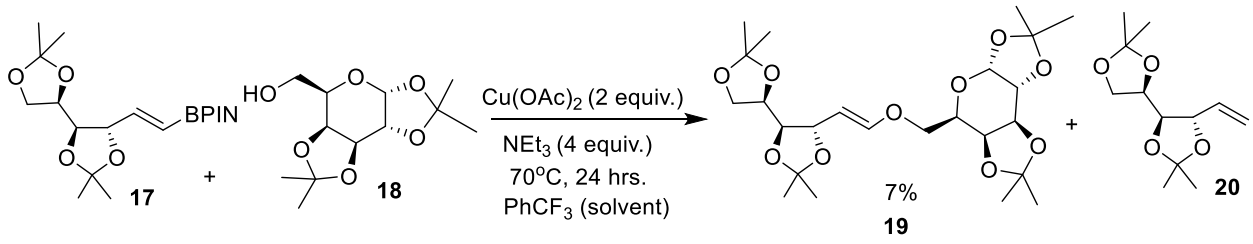
reported method with Bestmann-Ohira reagent. [12] Our lab has previously discovered that the refluxing conditions promote a alkynylation and a competing epimerization reaction. The Sugar diol was then protected to form acetonide sugar alkyne **16**. [13] The vinyl BPIN **17** was then synthesized via Zr-mediated hydroboration, but instead of overnight, the reaction mixture stirred for 3 days. [14] Complex **17** is a novel structure. Hydroboration was confirmed via ^{1}H NMR with the disappearance of the alkyne terminal hydrogen and the emergence of two new alkene C-H bonds at 6.60 and 4.77 ppm.



Scheme 1: Acetonide protected vinyl BPIN synthesis

We now wanted to test our optimal Chan-Lam conditions on coupling vinyl BPIN **17** with our sugar alcohol. We followed the reaction protocol developed by Merlic for vinyl ether synthesis via Chan-Lam coupling.[6] We decided to use trifluorotoluene as a solvent to dissolve the sugar alcohol **18** effectively. We also wanted a nonpolar solvent that could allow for reaction heating. Following Merlic's method, stirring at room temperature only returns unreacted **17** and **18**. We then heated the reaction mixture to 70°C. Formation of vinyl ether **19** was observed with the emergence of vinyl ether alkene peaks appearing at 6.62 and 4.49 ppm. We generated vinyl ether **19** with a yield of 7%. It appears that most of the vinyl BPIN underwent protodeboronation as

terminal alkene **20** and unreacted sugar alcohol were isolated from the reaction mixture. To confirm that coupling has occurred we ran HSQC experiments. The results found strong correlations between the alkene peaks and the sugar moiety. Although some product was formed, the prominent protodeboronation generating product **20** hinders this method from being an effective method for complex vinyl ethers synthesis and henceforth our lab's objective.

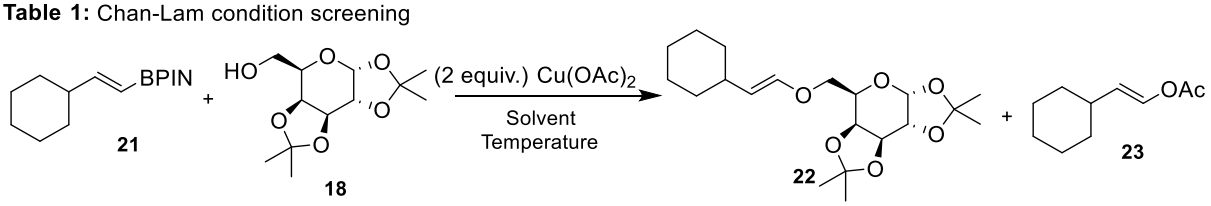


Scheme 2: Sugar vinyl ether synthesis

3.3.2 Cu(II)(OAc)$_2$ Optimization

Given the low yield of **19**, we engaged on an optimization study with simpler vinylic boronate. We decided to use 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose **18** as our nucleophilic alcohol to remain relevant towards our original objective. We were interested in bring the stoichiometry down from the alcohol functioning as the solvent, towards a 1:1 ratio between the alcohol and the boron substrate. DIPEA was found to be an effective base under Merlic conditions so our preliminary experiments utilized 4 equiv. of DIPEA and 2 equiv. of Cu(II)(OAc)$_2$.We explored these reaction conditions with cyclohexyl vinyl BPIN to stay consistent with Merlic conditions, but reduced the alcohol stoichiometry to 1:1. We decided to use cyclohexyl vinyl BPIN **21** because the simple 6-membered ring slightly mimics the steric bulk of vinyl BPIN **17**, and should provide relevant information towards our objective.

Table 1: Chan-Lam condition screening



Entry	Solvent	Temperature	Base	Atmosphere	18 : 19 : 20 : 21
1	None	r.t.	NEt_3 (4 equiv.)	Air	41 : 49 : 8 : 2
2	DMA	50	NEt_3 (4 equiv.)	Air	19 : 49 : 12 : 20
3	Acetone	40	NEt_3 (4 equiv.)	Air	6 : 56 : 24 : 2
4	$PhCF_3$	70	NEt_3 (4 equiv.)	Air	0 : 56 : 30 : 13
5	$PhCF_3$	70	DIPEA (4 equiv.)	O_2	20 : 80 : trace : trace
6	$PhCF_3$	70	NEt_3 (4 equiv.)	O_2	0 : 52 : 31 : 17

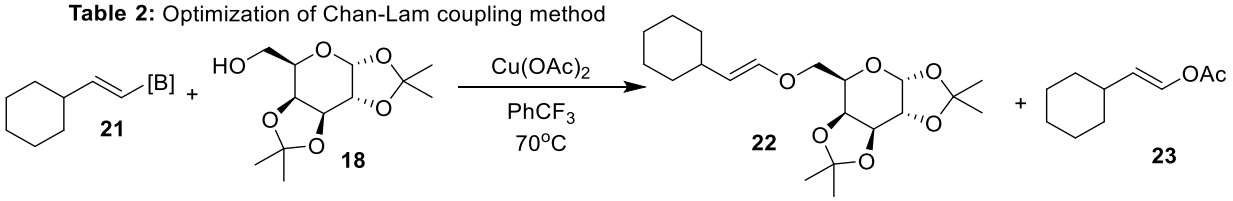
In air, we generated some vinyl ether product while retaining some of our vinyl BPIN starting material at room temperature (entry 1) with no solvent, but mostly unreacted vinyl BPIN and sugar alcohol were returned. (**Table 1**). A temperature and solvent screening revealed that higher temperature generates more of the desired vinyl ether product, but it also promotes decomposition of the vinyl BPIN, and the generation of unwanted byproducts: vinyl ester (entry 2-4). We found trifluorotoluene to be the best solvent because it has better solubility properties with the sugar alcohol, and it allows for a higher temperature to be reached. Air works better than argon because oxygen is most likely necessary for redox disproportionation [7] and catalyst regeneration. We found that triethylamine promotes vinyl ether synthesis under an oxygen atmosphere (entry 5). The best method developed after optimization uses 4 equiv. of triethylamine in trifluorotoluene under an oxygen atmosphere, generating a final product mixture of the vinyl ether **22** and vinyl ester **23** with a 45% isolated yield for the vinyl ether (entry 6). To calculate this,

we determined the ratio between vinyl ester and vinyl ether in the inseparable mixture. From this we calculated the mole ratio and determined how much of the vinyl ether is generated. The yield is then calculated relative to how much **18** was initially used. We attempted to further optimize this method through further stoichiometry and additive screenings.

The main problem with optimizing this reaction is the decomposition of our vinyl BPIN substrate through other side reactions before the vinyl ether synthesis can take place. We hypothesize that we are losing some vinyl BPIN to protodeboronation, generating a terminal alkene as demonstrated with the sugar synthesis, but is lost during purification due to its low molecular weight. Our lab also observes the generation of vinyl ester **23**, competing with our vinyl ester synthesis. Therefore, our main goal in optimizing this reaction is to suppress both protodeboronation and vinyl ester synthesis.

Screening $Cu(OAc)_2$ through various parameters provided insight into the mechanism (**Table 2**). Less $Cu(OAc)_2$ reduces vinyl ester generation, but also vinyl ether. Further reduction diminishes vinyl ether synthesis and generates more vinyl ester product (Entry 7-8). Vinyl boronic acid works just as well as vinyl BPIN, but vinyl BF_3K generates less product and loses more substrate to protodeboronation. $Cu(OAc)_2$ H2O with the BF_3K precursor only generates more vinyl ester product and less vinyl ether product, so we decided that BPIN was still the optimal boron species for $Cu(OAc)_2$. Further dehydration of the reaction with molecular sieves slows down the reaction returning some vinyl BPIN, but still generating the vinyl ester and vinyl ether in almost equal amounts. This supports our mechanism because water is necessary for the reaction to occur, but also promotes vinyl BPIN decomposition.

Table 2: Optimization of Chan-Lam coupling method

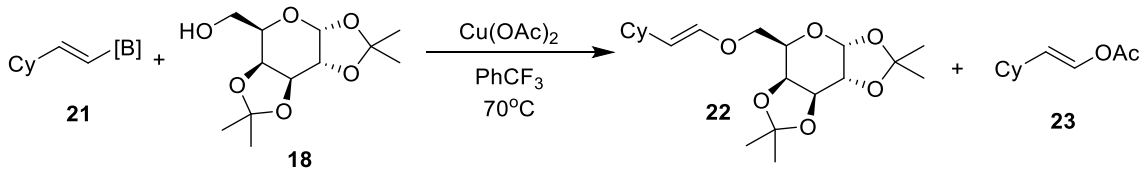


Entry	[B] : **18**	**[B]**	**Cu equiv.**	**Base**	**21 : 18 : 22 : 23**
7	1 : 1.1	BPIN	$Cu(OAc)_2$ (1 equiv.)	NEt_3 (4 equiv.)	0 : 60 : 33 : 7
8	1 : 1.1	$B(OH)_2$	$Cu(OAc)_2$ (0.5 equiv.)	NEt_3 (4 equiv.)	0 : 57 : 23 : 20
9	1 : 1.1	BF_3K	$Cu(OAc)_2$ (2 equiv.)	NEt_3 (4 equiv.)	0 : 73 : 22 : 5
10	1 : 1.1	BF_3K	$Cu(OAc)_2H_2O$ (0.5 eq.)	NEt_3 (4 equiv.)	0 : 67 : 15 : 18
11	1 : 1.1	BPIN	$Cu(OAc)_2$ (0.5 eq.) + Mol. Sieves	NEt_3 (4 equiv.)	12 : 47 : 24 : 17
12	1 : 1.1	$B(OH)_2$	$Cu(OAc)_2$ (2 equiv.)	NEt_3 (4 equiv.)	0 : 58 : 25 : 9
13	1 : 1.1	BPIN	$Cu(OAc)_2$ (2 equiv.)	DMAP	0 : 1 : 0 : 0
14	1 : 1.1	BPIN	$Cu(OAc)_2$ (2 equiv.)	TMEDA	0 : 1 : 0 : 0
15	1 : 1.1	BPIN	$Cu(OAc)_2$ (2 equiv.)	Cs_2CO_3	1.0 : 1.1 : 0 : 0
16	1 : 1.1	BPIN	$Cu(OAc)_2$ (2 equiv.)	NEt_3 (2 equiv.)	24 : 58 : 9 : 9
17	1 : 1.1	BPIN	$Cu(OAc)_2$ (2 equiv.)	None	1.0 : 1.1 : 0 : 0
18	2 : 1	BPIN	$Cu(OAc)_2$ (2 equiv.)	NEt_3 (4 equiv.)	0 : 41 : 26 : 33
19	1 : 2	BPIN	$Cu(OAc)_2$ (2 equiv.)	NEt_3 (4 equiv.)	0 : 73 : 22 : 5

We conducted a base screening with other bases utilized in Chan-Lam coupling with oxygen and nitrogen nucleophiles. Nitrogen base DMAP decomposed the vinyl BPIN substrate and didn't generate a product. Unreacted sugar **18** and unreacted vinyl boron substrate **21** were returned when Cs_2CO_3 was used. Reducing triethylamine equivalency to 2 only slows down the

reaction returning some vinyl BPIN and generating both vinyl ether and vinyl ester in equal amounts. Control test with no base returns the starting material **21** and **18** with no product formation. It is still unclear whether the base also function as a ligand for the copper metal, but it is essential for promoting reactivity. The main obstacle is still reducing vinyl ester synthesis without reducing vinyl ether generation.

Table 3: Additive Chan-Lam screening



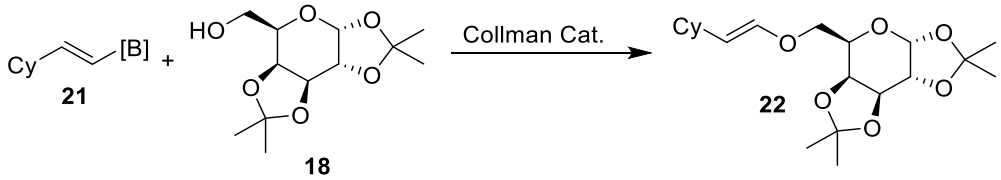
Entry	[B]	Additive	Base	21 : 18 : 22 : 23
20	BPIN	$B(OH)_3$	NEt_3 (4 equiv.)	0 : 1 : 0 : 0
21	BPIN	Mn(OAc)2 / PIDA	NEt_3 (4 equiv.)	1.0 : 1.1 : 0 : 0
22	BPIN	$Mn(OAc)_3$	NEt_3 (4 equiv.)	1.0 : 1.1 : 0 : 0
23	BPIN	3-Hexyne	NEt_3 (4 equiv.)	0 : 76 : 12 : 12
24	BPIN	K_2CO_3	Phenanthroline	10 : 71 : 10 : 9

We conducted a screening on reagents that have been used as additives in other Chan-Lam methods, in hopes of enhancing reactivity (**Table 3**). Watson *et al*. reports that boric acid sequesters acetate and pinacol in the amination reaction, preventing them from inhibiting reactivity, and it may accelerate Cu(I) oxidation to Cu(II). [8] However, in one case, the addition of boric acid only promotes vinyl BPIN decomposition, only returning the sugar alcohol reagent. Reagents $Mn(OAc)_2$ and $Mn(OAc)_3$ were used by Walczak *et al*. for copper catalyzed oxidative

acetalization of boric esters. It is demonstrated that the Mn assisted with the oxidation of Cu(I) to Cu(II), and we hypothesized that the Mn may also help with the disproportionation required for reductive elimination and product generation. [4] In our hands, the addition of Mn(II) and Mn(III) only returns vinyl boronate and the unreacted sugar, suppressing all reactivity. Simple alkenes and alkynes have been found to be important pi ligands for oxidative copper-based coupling by Merlic *et al*., with 3-hexyne being the most efficient. [18] Unfortunately, 3-hexyne only promotes vinyl BPIN decomposition and reduces vinyl ether and ester generation. Engle *et al*. developed a Chan-Lam coupling for O-cyclopropylation of phenols utilizing 1,10-phenanthroline and K_2CO_3. [3] These conditions didn't consume all of the vinyl BPIN, but some decomposition was observed with low yielding vinyl ether and ester.

3.3.3 Other Cu Catalyst Screening

Table 4: Collman catalyst screening for vinyl ether synthesis



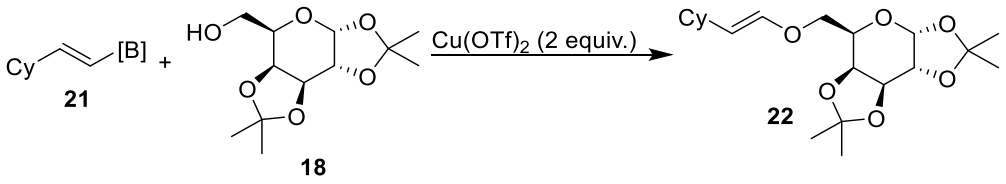
Entry	[B]	Catalyst	Additive	Base	21 : 18 : 22
25	BPIN	$[Cu(TMEDA)Cl]_2[(Cl)_2]$ (10%)	None	K_2CO_3 (20 %)	0 : 1.0 : 0.03
26	BPIN	$[Cu(TMEDA)OH]_2[(OTf)_2]$ (1 eq.)	None	K_2CO_3 (1 eq.)	0 : 1.0 : trace
27	BPIN	$[Cu(TMEDA)OH]_2[(OTf)_2]$ (10%)	None	K_2CO_3 (20 %)	0 : 1.0 : trace
28	BPIN	$[Cu(TMEDA)OH]_2[(OTf)_2]$ (10%)	None	K_2CO_3 (20 %)	0 : 1.0 : trace
29	$B(OH)_2$	$[Cu(TMEDA)OH]_2[(OTf)_2]$ (1 eq.)	None	NEt_3 (4 equiv.)	0 : 1.0 : 0.06
30	BPIN	$[Cu(DABCO)OH]_2[(OTf)_2]$ (1 eq.)	None	NEt_3 (4 equiv.)	1.0 : 1.1 : 0 : 0

Our lab synthesized several Collman catalyst to determine if the catalyst promotes Chan-Lam coupling and if the reactivity is controllable with ligand choice and reaction conditions. [11] The Collman and $Cu(OTf)_2$ catalysts are attractive because it they do not possess acetate ligand. The triflate ligands are non-nucleophilic and should not interfere with the proposed mechanism. Synthesis of the Collman catalysts were typically completed by stirring a mixture of the amine bidentate ligand of choice and the CuX metal source in 95% ethanol. The complexes were used for Chan-Lam coupling on the basis of the formula of $[Cu(OH)L]_2X_2$.

Screening of the Collman catalyst was conducted with conditions analogous to our optimal method (**Table 4**). Early experiments determined that $[Cu(TMEDA)Cl]_2[(Cl)_2]$ promotes vinyl BPIN decomposition and generates a vinyl chloride byproduct. We switched to using weakly nucleophilic triflate as the counter ion to avoid vinyl halogen synthesis. Regardless of the conditions however, decomposition of the vinyl BPIN is the only outcome with trace amounts of vinyl ether in some conditions.

Walczak *et al*. developed a protocol for acetalization of boronic esters utilizing $Cu(OTf)_2$ and $Mn(OAc)_2$. [4] We wanted to expand this procedure with $Cu(OTf)_2$ to mediate Chan-Lam coupling towards complex vinyl ether synthesis. Walczak hypothesizes that the $Mn(II)(OAc)_2$ salts are beneficial for copper catalyzed oxidation. We hypothesized that the $Mn(II)(OAc)_2$ also generates the pre-transmetalation intermediate in-situ with $Cu(OTf)_2$, due to the labile triflate ligands. Their method worked with BPIN and BF_3K, so we investigate both boron substrates, and we also explored various metal acetate salts beyond $Mn(II)(OAc)_2$ to expand our reaction scope.

Table 5: Chan-Lam coupling screening with $Cu(OTf)_2$

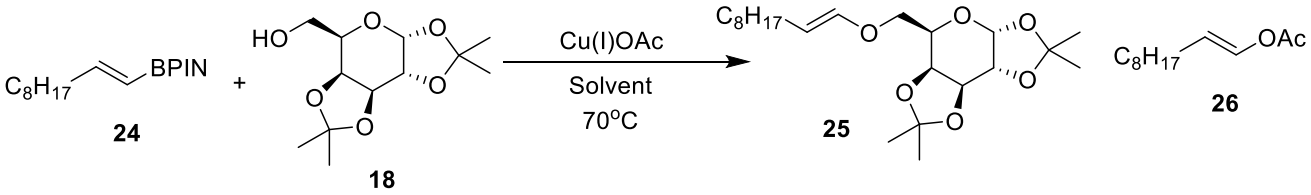


Entry	[B]	Additive	Base	21 : 18 : 22
31	BPIN	Na(OAc) (1 equiv.)	NEt_3 (4 equiv.)	18 : 75 : 5
32	BPIN	$Mn(OAc)_2$ (2 equiv.)	None	1.0 : 1.1 : 0
33	BPIN	$Mn(OAc)_3$ (2 equiv.)	None	1.0 : 1.1 : 0
34	BF_3K	None	NEt_3 (4 equiv.)	1.0 : 1.1 : 0
35	BF_3K	NaOAc (2 equiv.)	None	0 : 1.0 : trace
36	BF_3K	Na_2CO_3 (1 equiv.)	None	0 : 1.0 : trace
37	BF_3K	NaOAc (2 equiv.)	NEt_3 (4 equiv.)	0 : 1.0 : trace
38	BF_3K	Cs_2CO_3 (1 equiv.)	NEt_3 (4 equiv.)	0 : 1.0 : trace
39	BF_3K	AgOAc (2 equiv.)	NEt_3 (4 equiv.)	0 : 1.0 : trace

Our investigation found that $Cu(OTf)_2$ is not a suitable catalyst for Chan-Lam coupling alcohols and vinyl boron substrates (**Table 5**). Utilizing Walczak's protocol returns starting material, so we decided to explore other acetate metals. NaOAc and AgOAc promotes protodeboronation with minimal vinyl ether synthesis when NEt_3 is present and when it is not. Using less of NaOAc slows down the protodeboronation, but minimal vinyl ether is generated with some vinyl acetate. Metal carbonate species, such as Cs_2CO3 and Na_2CO_3 returns the same results. These results suggests that the acetate and carbonate metals function more as a base as opposed to a metal ligand during the reaction, promoting protodeboronation.

Next, we explored the possibility of using Cu(I)OAc for promoting Chan-Lam coupling (**Table 6**). We hypothesized that having less acetate ligand will reduce vinyl ester generation, but still promote vinyl ether synthesis. Unfortunately, we found that the stoichiometry does not assist with reducing vinyl ester synthesis, as more vinyl ester product is present. However, it is interesting to note the Cu(I)OAc was reactive as opposed to $Cu(II)(OAc)_2$. We hypothesize that this is due to the lack of paddlewheel complex formation due to less acetate ligand being present. Reactivity does improve when no solvent is used, but protodeboronation remains to be the overwhelming reaction.

Table 6: Chan-Lam coupling with Cu(I)OAc



Entry	Catalyst Loading	Solvent	Base	24 : 18 : 25 : 26
40	2 equiv.	$PhCF_3$	NEt_3 (4 equiv.)	14 : 73 : 5 : 8
41	20%	None	NEt_3 (40 %)	0 : 86 : 10 : 4
42	20%	None	NEt_3 (4 equiv.)	0 : 89 : 9 : 2

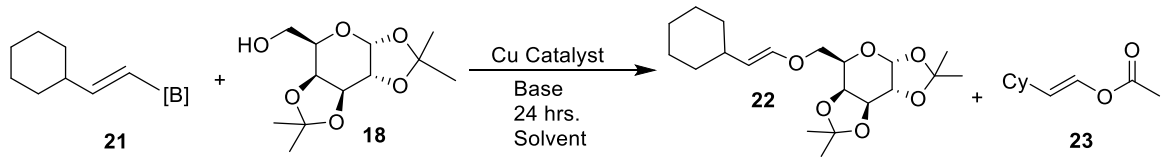
3.4 Conclusions

Our lab was interested in exploring Chan-Lam coupling for the complex synthesis of vinyl ethers, but our investigation found that the conditions are unsuitable. Current methods in literature require an excess of alcohol to successfully undergo Chan-Lam coupling, but we developed a protocol that uses equal amounts of alcohol and cyclohexyl vinyl BPIN for Chan-Lam coupling. This was achieved by using trifluorotoluene as the solvent and heating the reaction mixture to 70°C. However this method is out competed by protodeboronation and vinyl ester synthesis from

the copper acetate ligand. We attempted to reduce these byproduct formation with different copper catalyst and conditions, but none were able to synthesize vinyl ethers. Our experiments support the significance of the acetate ligand. Other Cu catalyst that did not have an acetate ligand were unable to promote Chan-Lam coupling. The acetate ligand is hypothesized to help promote the rate-determining transmetalation step. However, the acetate ligand also promotes vinyl ester synthesis at high temperatures. Also at high temperatures, protodeboronation decomposes our vinyl BPIN product. We hypothesize that not only does the basic conditions may promote protodeboronation but so does the nucleophilic alcohol. These disadvantageous will keep Chan-Lam coupling from fulfilling our overall objective of complex vinyl ether synthesis. Expanding Chan-Lam coupling scope to other metals may help avoid the protodeboronation obstacle. Ni has been demonstrated to promote Chan-Lam coupling, and further experimentation may improve reactivity to include more complex substrates without promoting protodeboronation or vinyl ester synthesis. [15-17]

3.5 Experimental Section

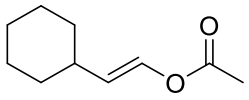
General Information: Proton and carbon NMR spectra were recorded INOVA-400 (400 MHz), INOVA-600 (600 MHz), or a BRUKER 600 (600 MHz) instrument equipped with cryogen probe. NMR spectra were recorded in solutions of deuterated chloroform (CDCl3) with the residual chloroform (7.27 ppm for ^{1}H NMR and 77.23 ppm for 13C NMR) taken as the internal standard, or in deuterated dimethyl sulfoxide (DMSO-d6) and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; m, multiplet. Thin layer chromatography (TLC) was performed on pre-coated glass-backed plates purchased from Whatman (silica gel 60F254; 0.25mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from Silicycle. All reactions were carried out with anhydrous solvents in oven-dried or flame-dried and argon-charged glassware unless otherwise specified. All anhydrous solvents were purchased from Sigma-Aldrich. Other solvents used in extraction procedures and chromatography were used as received from commercial suppliers without prior purification.



General Cham-Lam Coupling Protocol: Sugar 1**8** is suspended in a dry 5 mL round bottom flask with the Cu catalyst, solvent, base, and additive when necessary under the desired atmosphere. While stirring with a stir bar, vinyl BPIN **21** is then added to the mixture via syringe. The solution is then heated to the desired temperature and left to stir for 24 hours. Once completed, the reaction is diluted with ethyl acetate, filtered through celite and concentrated via rotary evaporation to yield

the crude product mixture to be analyzed via ^{1}H NMR. **22 (**0.214 g, 0.46 mmol, 45%), Compound **22** and **23** are inseparable via chromatography, and the relative ratios are based on alkene proton integrations.

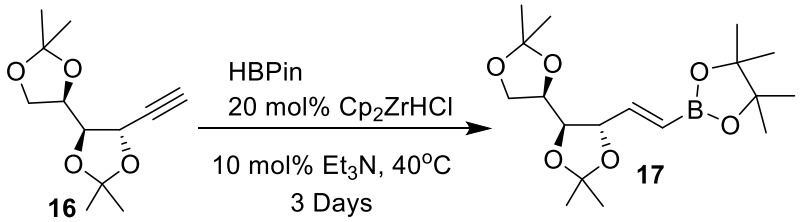
^{1}H NMR (600 MHz, $CDCl_3$) for **22**: **6.27** (dd, 1H, J_{HH} =12.7 Hz, 1 Hz), 5.52 (d, *J* = 5.0 Hz, 1H) **4.78** (dd, 1H, J_{HH} =12.7 Hz, 7.7 Hz), 4.63 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.34 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.28 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.04 (ddd, *J* = 7.2, 5.5, 1.9 Hz, 1H), 3.90 – 3.75 (m, 2H), 2.04-1.92 (1H, m, C*H*) , 1.74-1.62 (5H, m, C*H* $_2$), 1.55 (s, 3H), 1.48 (s, 3H) 1.33-1.03 (5H, m, C*H* $_2$), 1.28 (s, 3H)



23

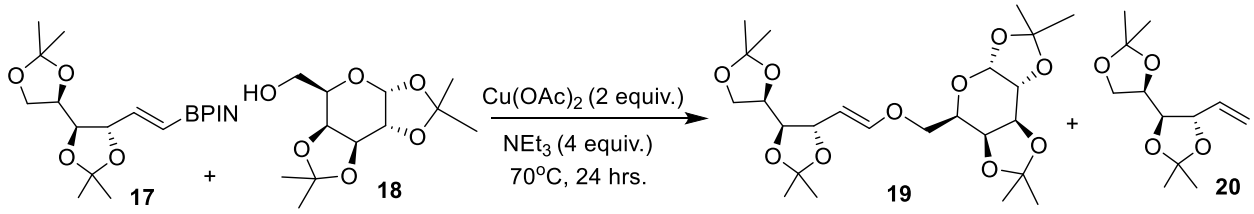
^{1}H (600 MHz, $CDCl_3$, ppm) for **23**: **7.08** (1H, dd, *J*= 12.6, 1.1 Hz, C*H*) , **5.38** (1H, dd, *J*= 12.5, 7.6 Hz, C*H*) , 2.10 (3H, s, C*H* $_3$) , 2.04-1.92 (1H, m, C*H*) , 1.74-1.62 (5H, m, C*H* $_2$) , 1.33-1.03 (5H, m, C*H* $_2$)

Poladura, B.; Martínez-Castañeda, Á.; Rodríguez-Solla, H.; Llavona, R.; Concellón, C.; del Amo, V. General Metal-Free Baeyer–Villiger-Type Synthesis of Vinyl Acetates. *Org. Lett.* **2013**, *15* (11), 2810–2813. https://doi.org/10.1021/ol401143q.



Preparation of vinyl BPIN 17: Compound **16** (0.56 g, 2.47 mmol) and HBPin (0.38 mL, 2.60 mmol) are charged to a dry 10 mL dry round bottom. Cp_2ZrHCl (0.128 g 0.50 mmol) were subsequently added to the mixture, and then left to stir at 50°C overnight. The next day, an additional Cp_2ZrHCl (0.128 g 0.50 mmol) is added to the reaction mixture and left to stir for two days. The mixture was then cooled to room temperature and diluted with hexanes. The solution was filtered through a celite plug, and the plug was washed with hexanes. The filtrate was collected and concentrated via rotary evaporation to yield the product as yellow oil. Yield: 0.403 g, 46%

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 17.9, 6.9 Hz, =CH, 1H), 5.77 (d, *J* = 17.9 Hz, =CH 1H), 4.31-4.27 (m, 1H), 4.16-4.11 (m, 1H), 3.99 – 3.93 (m, 1H), 3.79-3.75 (m, 1H), 3.74 – 3.69 (m, 1H), 1.42 (s, 6H), 1.41 (s, 6H), 1.36 (s, 3H), 1.26-1.23 (m, 9H).



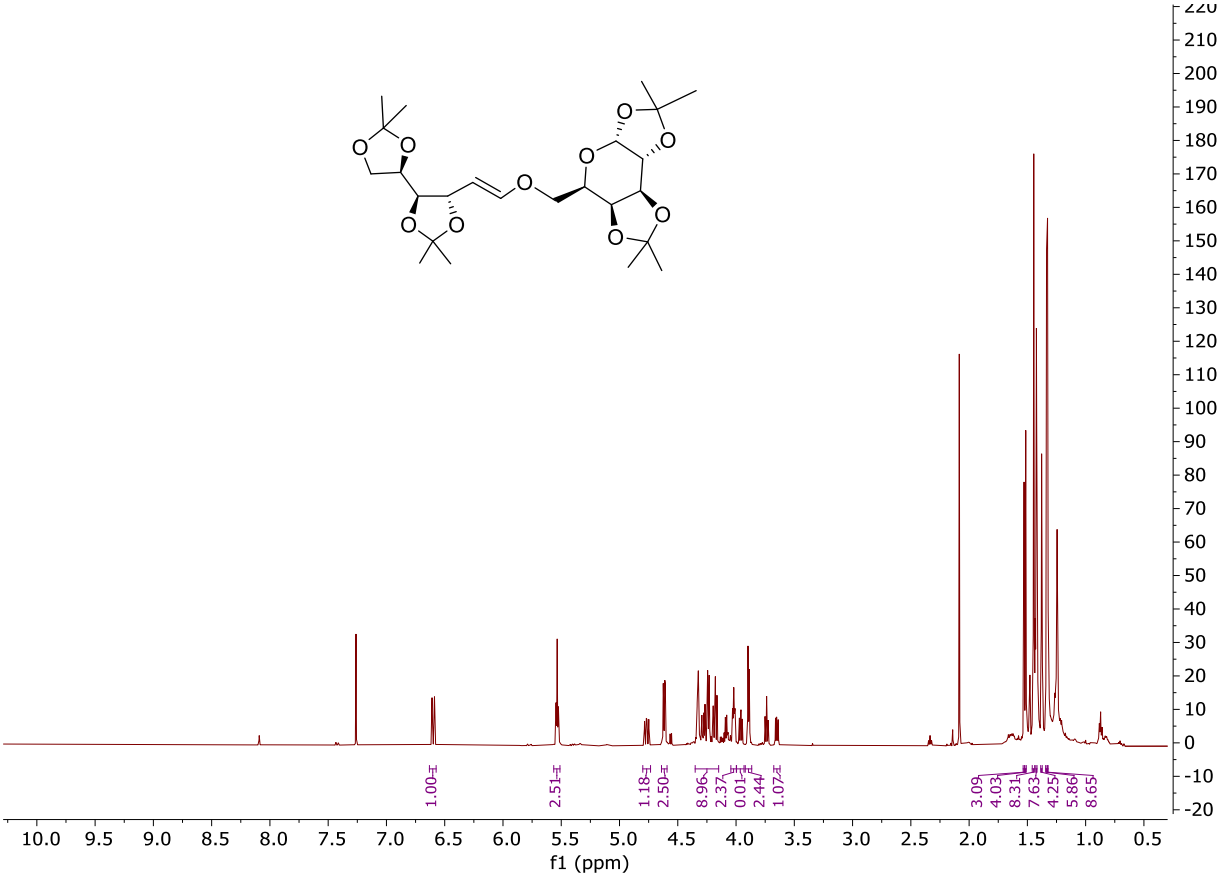
Scheme 2: Sugar vinyl ether synthesis

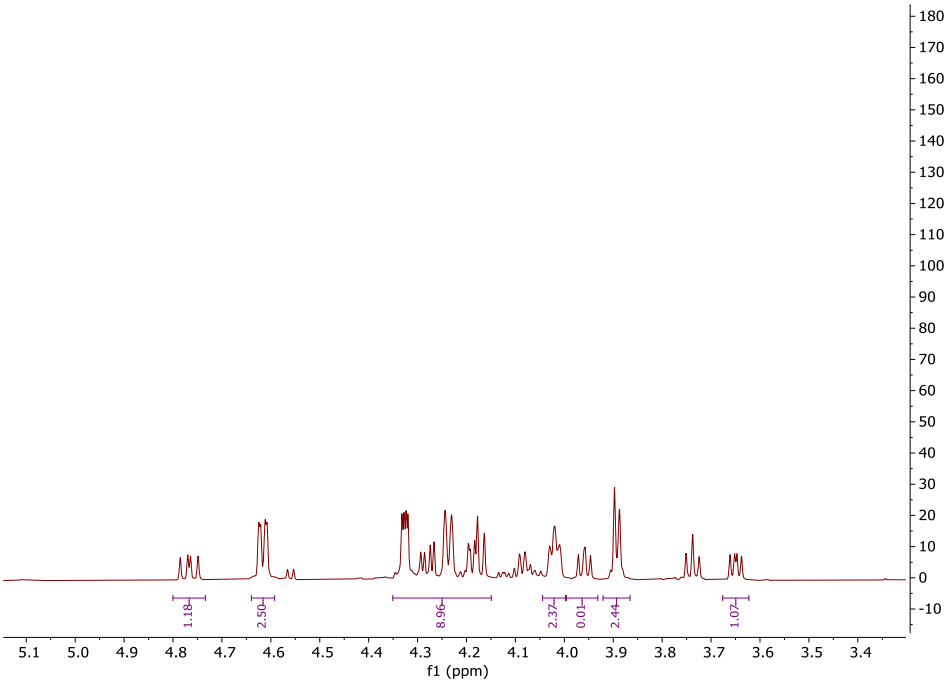
Preparation of vinyl ether 19: Vinyl BPIN **17** (0.20 g, 0.57 mmol) were charged to a dry 10 mL round bottom with **18** (0.162 g, 0.62 mmol). Subsequently, $Cu(OAc)_2$ (0.205 g, 1.13 mmol), NEt_3 (0.315 mL, 2.26 mmol), additives, and trifluorotoluene (0.5 mL) are added to the mixture. The reaction is then stirred for 24 hours at the desired temperature, with an air cooled condenser attached. Once completed, the reaction mixture is then diluted with ethyl acetate and washed with aq. sat. $NaHCO_3$ (x3), brine, and dried with Na_2SO_4. The organic filtrate is reduced via rotary evaporation to the crude material as a red oil. Column chromatography with 100% hexanes yields compound **20**, followed by 9:1 hexanes/ethyl acetate yields **19**.

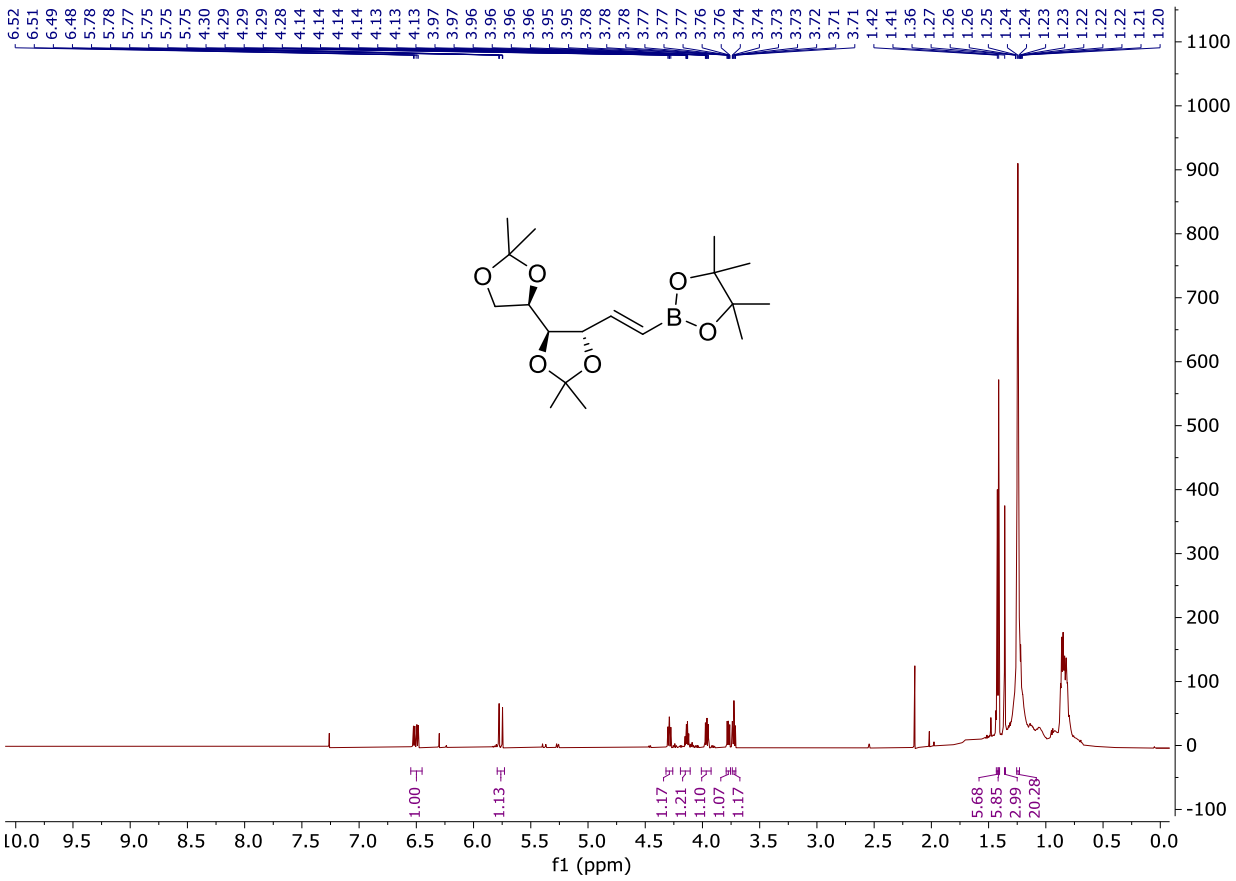
^{1}H NMR for **19** (600 MHz, $CDCl_3$) δ **6.60** (d, *J* = 12.6 Hz, =CH, 1H), 5.53 (d, *J* = 5.2 Hz, 1H), **4.77** (dd, *J* = 12.6, 9.2 Hz, =CH, 1H), 4.62 (dd, *J* = 7.9, 2.4 Hz, 2H), 4.37 – 4.14 (m, 4H), 4.04 - 4.00 (m, 2H), 3.92-3.86 (m, 2H), 3.65 (dd, *J* = 8.4, 5.6 Hz, 1H), 1.53 (s, 3H) 1,51 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H).

^{1}H NMR for **20** (600 MHz, $CDCl_3$) δ 5.82 (dddd, *J* = 17.1, 10.2, 7.7, 1.0 Hz, 1H), 5.40 (dd, *J* = 17.1, 1.0 Hz, 1H), 5.29 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.25 (dd, *J* = 8.5, 7.6, 1H), 4.13-4.10 (m, 1H), 3.99 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.77 – 3.72 (m, 2H). 1.45 (s, 6H), 1.43 (s, 3H), 1.39 (s, 3H).

NMR Spectra of Selected Products:



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1.21
1.10
1.07
1.17
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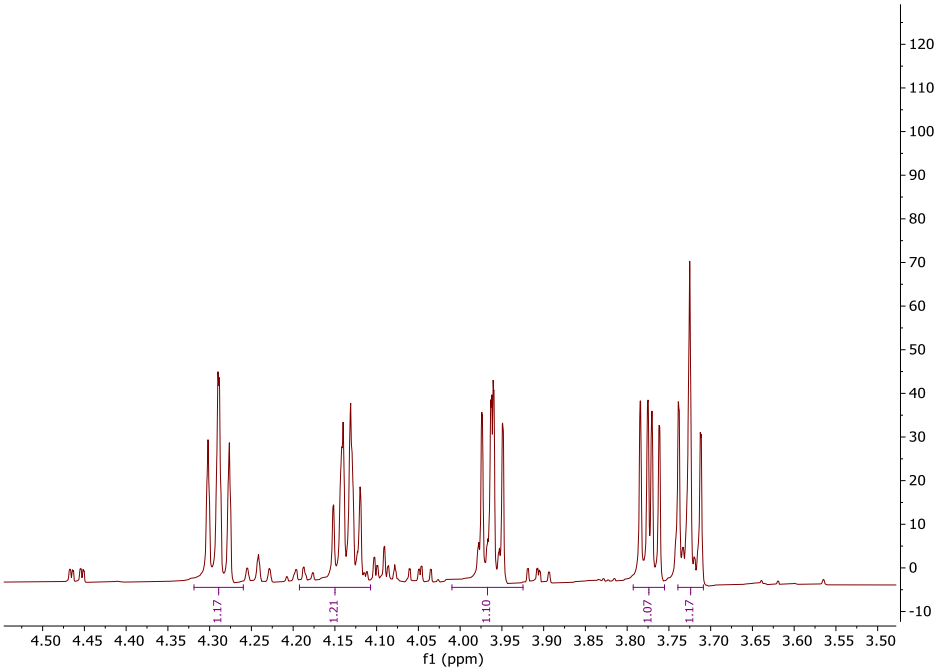
5.85
2.99
20.28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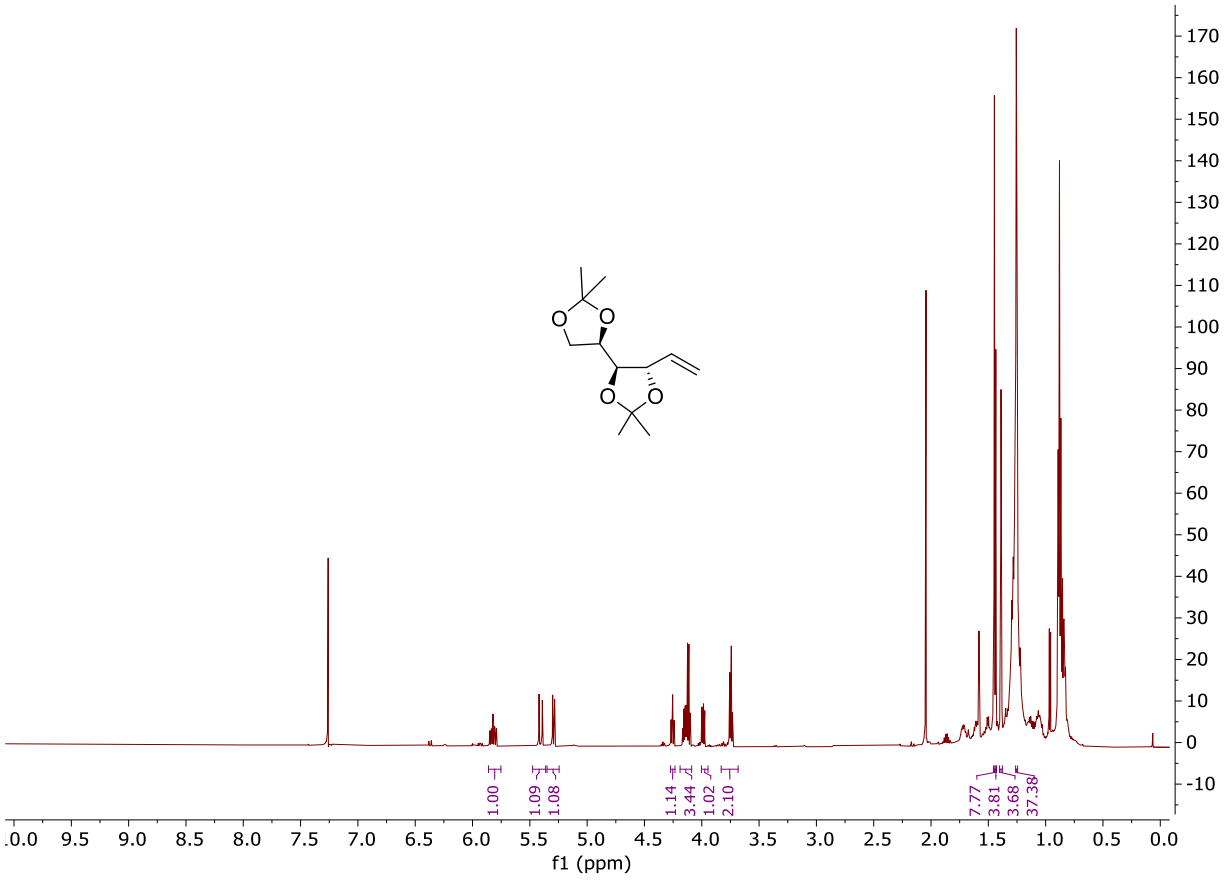
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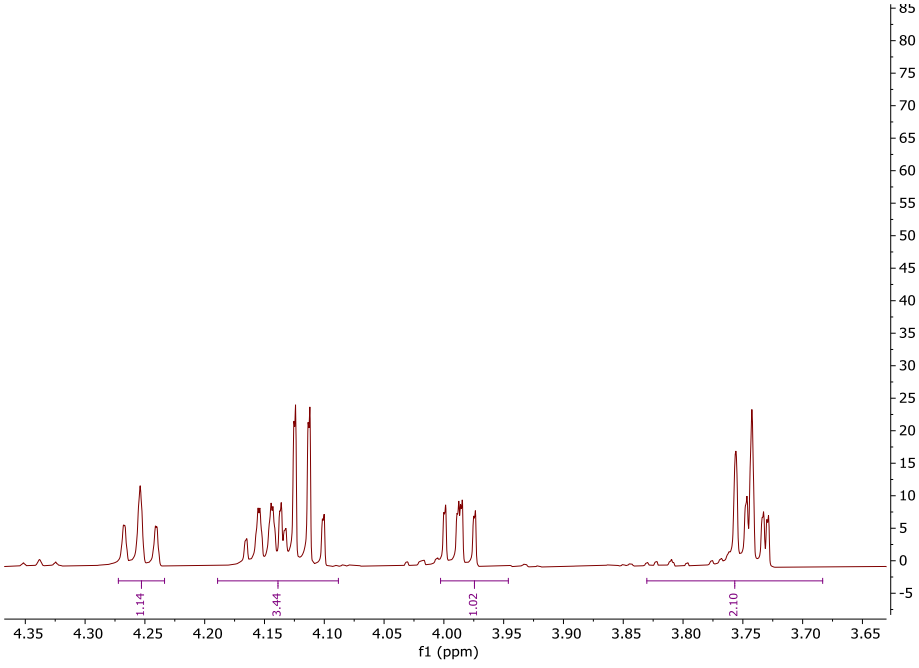
f1 (ppm)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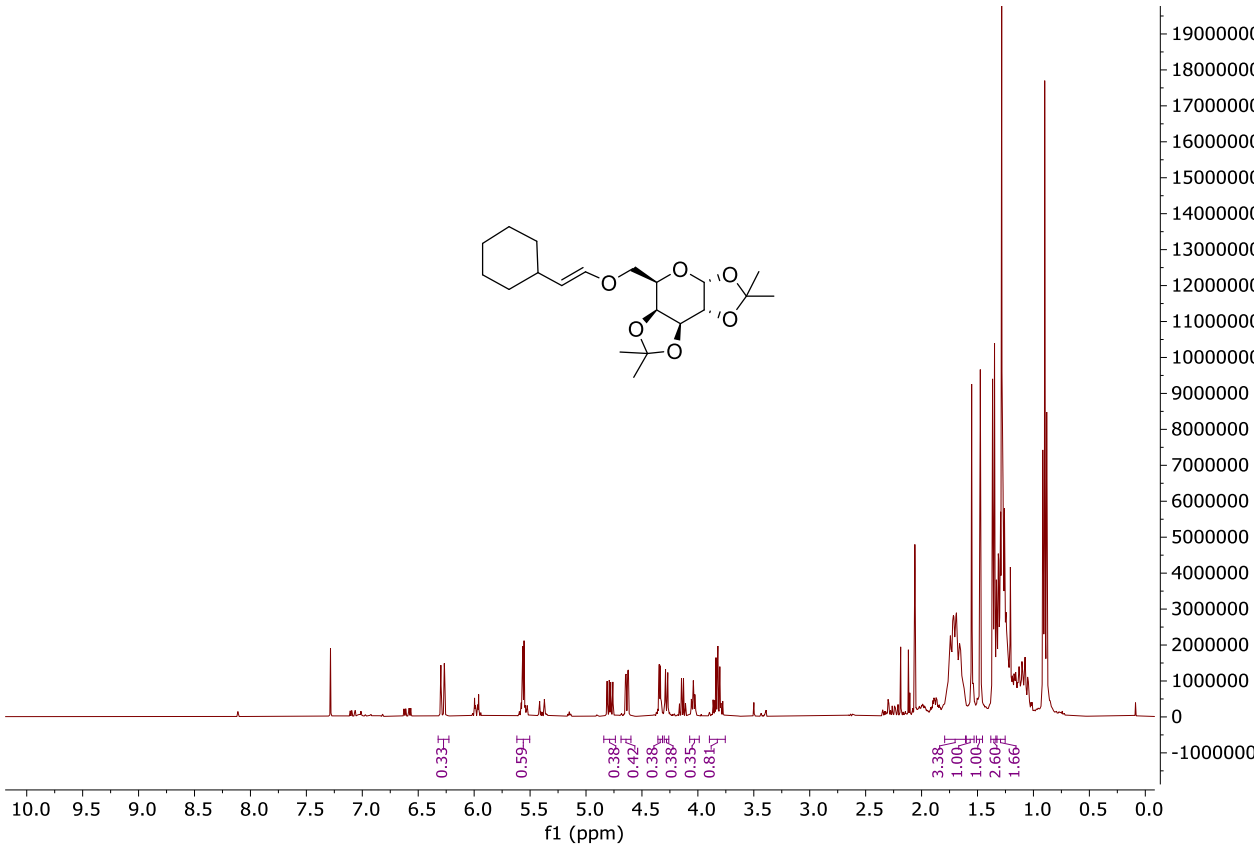
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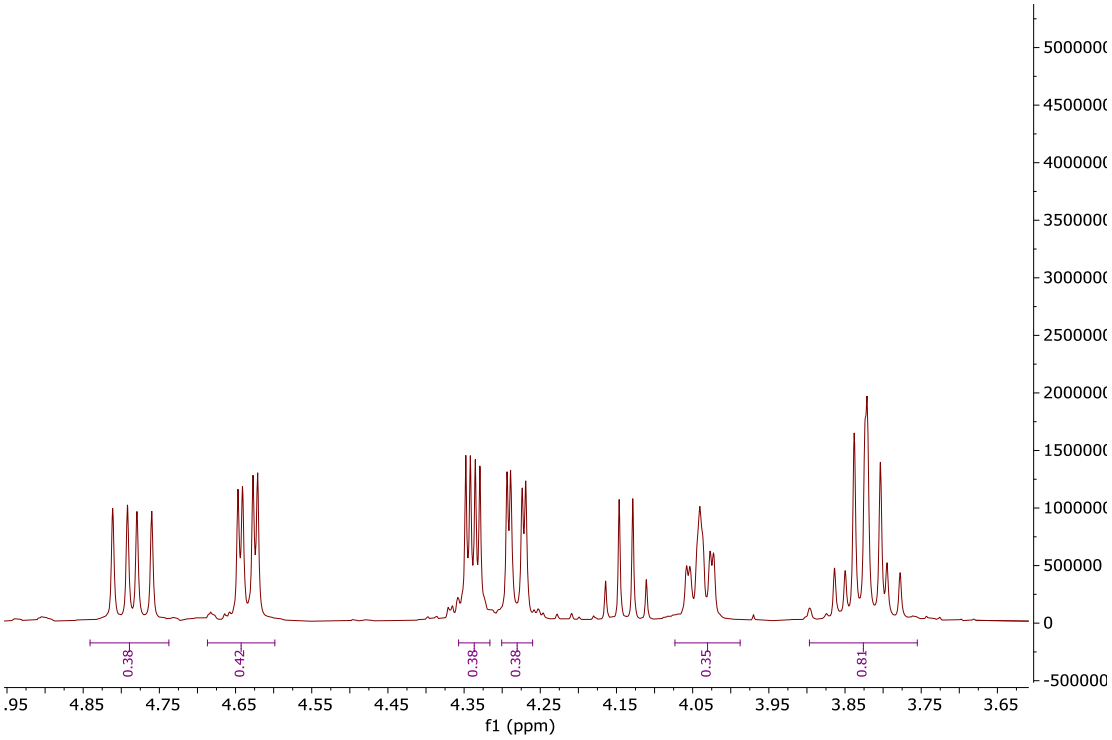
0.38
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f1 (ppm)

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