ZIRCONIUM-MEDIATED ALKYENE-ALDEHYDE COUPLING, RHODIUM-CATALYZED ALKENE HYDROTHIOLATION, AND COPPER-CATALYZED ALKYNE HYDROARYLATION: REACTION DEVELOPMENT AND MECHANISTIC INVESTIGATIONS

BY

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DISSERTATION

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Abstract

In the last 150 years, we have seen a boon in the development of new methodologies for the synthesis of organic compounds, which has led to the ability for one to synthesize any compound of interest given enough time and resources. Of course, time and resources are finite, thus development of methods that can reduce the time and resources required to synthesize libraries of compounds are of extreme import. This goal can be achieved by reducing step count, increasing the modularity by diverging from common synthetic intermediates, or by reducing waste from reaction byproducts. Our group is interested in developing transition-metal-catalyzed reactions which utilize ubiquitous starting materials such as alkynes and alkenes for the synthesis of compounds which are valuable synthetic intermediates or desirable final products which reduce the time and resources required compared to current methods.

α,β-unsaturated carbonyl compounds are common synthetic intermediates and pharmaceuticals targets which are often synthesized though the olefination of a carbonyl with an ylide. These reactions produce a stoichiometric amount of byproduct, such as triphenylphosphine oxide in the Wittig olefination. We sought the develop a zirconium–oxo-catalyzed alkyne-aldehyde coupling reaction to access α,β-unsaturated ketones as this would be a completely atom economical approach to this motif. Each step in the catalytic cycle was investigated stoichiometrically, and the scope of alkynes and aldehydes was explored. The most critical step of the transformation is a retro-[4+2]-cycloaddition from a dioxazirconacyclohexene. It was found that this step is thermodynamically unfavorable which prevented a catalytic reaction from being developed; however, by using chalcone as a trap for the zirconium-oxo, we were able to show that the retro-[4+2]-cycloaddition does occur and that the strong Zr–O bond in the dioxazirconacyclohexene can be broken via this mechanism.

The ability to access multiple products selectively from a single set of starting materials is a highly desirable process as it rapidly affords a vast library of compounds which can be utilized in drug discovery and structure activity relationships. We have discovered that allyl amines and imines undergo a rhodium-catalyzed regiodivergent hydrothiolation reaction to afford either 1,2- or 1,3-aminothioethers. The regiodivergence is a result of the ligand employed. Ligands with small bite angles afford the 1,3-isomer, while ligands with large bite angles afford the 1,2-isomer. Mechanistic experiments suggest that both reactions proceed through an oxidative addition into

the S–H bond, followed by migratory insertion, and finally reductive elimination. The regiodivergence in the reaction is a result of the selectivity for the migratory insertion. The anti-Markovnikov reaction undergoes a Rh–H insertion, followed by Rh–S reductive elimination, while the Markovnikov-selective conditions proceed by Rh–S insertion, followed by Rh–H reductive elimination.

The regio- and diastereoselective synthesis of trisubstituted olefins remains a challenge for organic chemists. Herein is reported the synthesis of 1,1-diaryl, trisubstituted olefins, which are commonly found in pharmaceutical compounds. The reaction is catalyzed by a copper/dppf complex and combines an *in situ* generated copper–hydride with an alkyne and an aryl iodide to afford trisubstituted olefins in good to excellent yields, excellent regioselectivities and as single diastereomers. The scope of the transformation is presented both in terms of alkyne and aryl iodide. Mechanistic studies suggest that the reaction proceeds through an initial hydrocupration followed by a two-electron oxidative addition/reductive elimination.

To Tracy

Acknowledgements

I first and foremost would like to thank Prof. Kami Hull. Without your training, I would not be the chemist that I have become today. From the lows of screening hundreds of different conditions trying to get a new reaction to work without any success, to the highs of discovering a new reaction and bringing it to a completed project, you were with me every step of the way, and for that I cannot express my gratitude enough. I would also like to thank the rest of my committee for pushing me to become a better chemist. From the classroom, TAing, seminar, prelim, and ORP you not only taught me fundamental chemistry concepts but also how to critically think about my research and the work of others.

To Tracy, our family members and all my friends, thank you so much for joining me on this journey. Thank you for listening (or pretending to listen) to everything I had to complain about and giving me so much support throughout our whole time here. Without all of you, I would not be the person I am today.

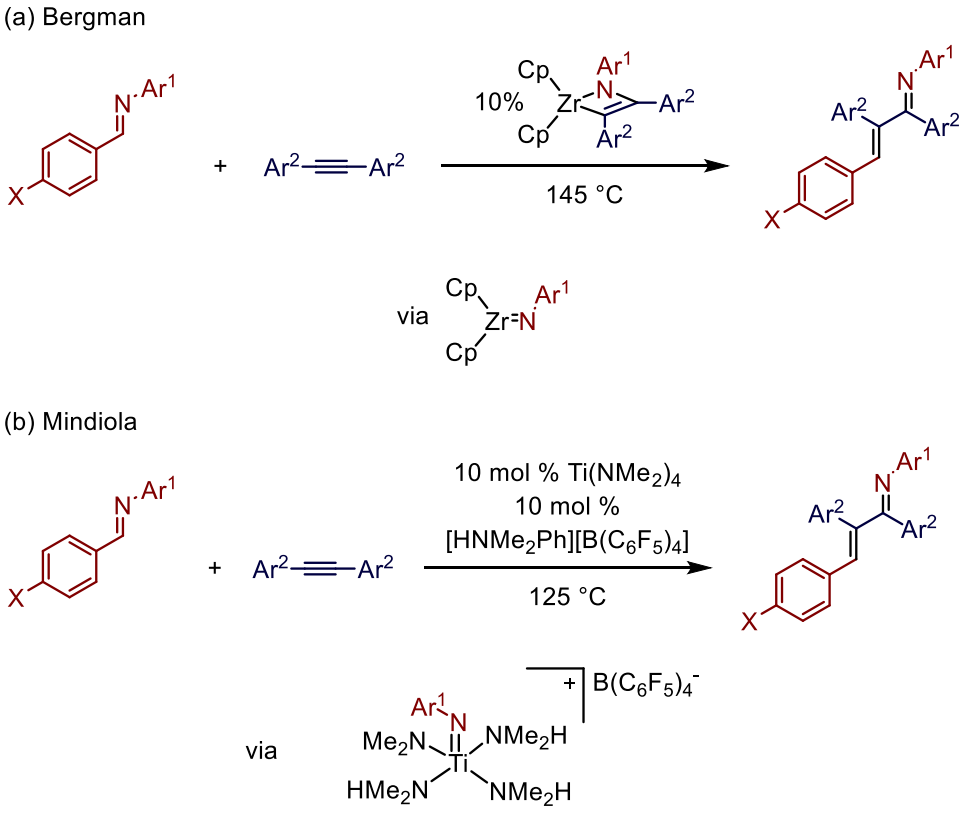
To my labmates, thank you all for your insightful comments during four-hour practice talks, group meetings, subgroups, chats at our hoods, and making late nights less miserable. Evan, from 357 to 370, I cannot thank you enough for all the talks we've had about chemistry and all the talks we had about not chemistry. It truly was an amazing time. I'd like to thank Jenni, Dr. Nguyen, Dr. Ensign, Andrew, Dr. Gupta, Evan, Sam, Travis and Lee for collaborating with me on the hydrothiolation project, the carboamination project and solving crystals.

Table of Contents

Chapter 1: Zirconium-Mediated Alkyne-Aldehyde Coupling*

1.1 Introduction.

Trisubstituted α,β-Unsaturated carbonyls are prominent functional groups and synthetic intermediates found throughout natural products, pharmaceuticals, agrochemicals, and organic materials;[1] however, regio- and stereoselective formation of such compounds can often be challenging.[2,3,4] Olefination reactions are one of the most widely used approached for the synthesis of α,β-unsaturated carbonyls. While being powerful transformations, they are wasteful, both requiring the synthesis of the ylide and generating significant quantities of stoichiometric byproducts, such as triphenyl phosphine oxide. Inspired by the group 4 metal−imido-mediated alkyne−imine coupling reactions reported by Bergman[5] and Mindiola,[6] (Scheme 1) our group was



Scheme 1: Alkyne-Imine Coupling Reactions Developed by Bergman and Mindiola.

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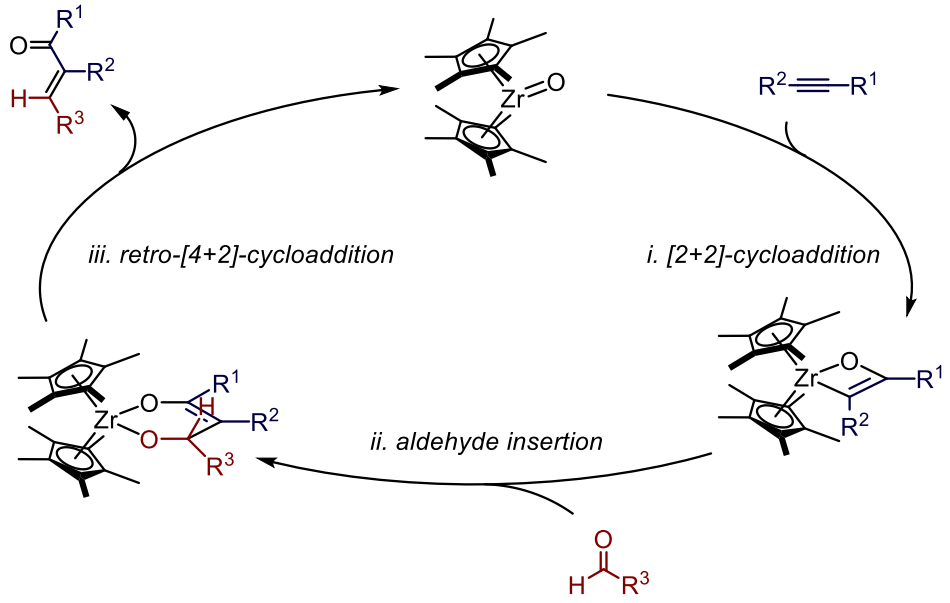
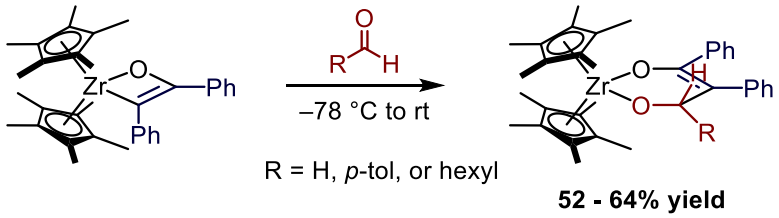
interested in developing a M=O-mediated coupling of an aldehyde and an alkyne for the synthesis of enones.[7] The proposed catalytic cycle (Scheme 2) involves (*i*) [2+2]-cycloaddition between [M]=O and the alkyne, followed by (*ii*) aldehyde insertion, and finally (*iii*) a [4+2]-retrocycloaddition to generate the enone and regenerate the [M]=O catalyst. Although examples



Scheme 2: Proposed Zr=O-Catalyzed Alkyene-Aldehyde Coupling Catalytic Cycle.

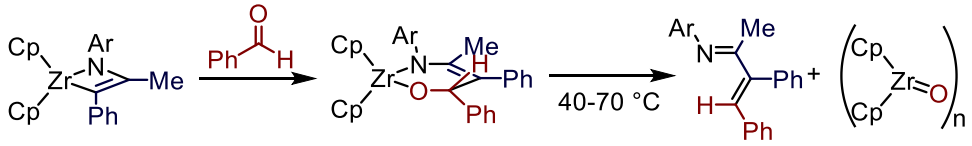
are limited, Bergman has demonstrated that in situ generated $Cp^*_2Zr=O$ undergoes the [2+2]-cycloaddition with simple alkynes[8,9] and Hillhouse has shown that the Zr–C bond can insert into p-tolualdehyde, n-heptanal, and paraformaldehyde.[10] However, the retro-[4+2]-



Scheme 3: Hillhouse's Oxazirconacyclobutene Aldehyde Insertion Conditions.

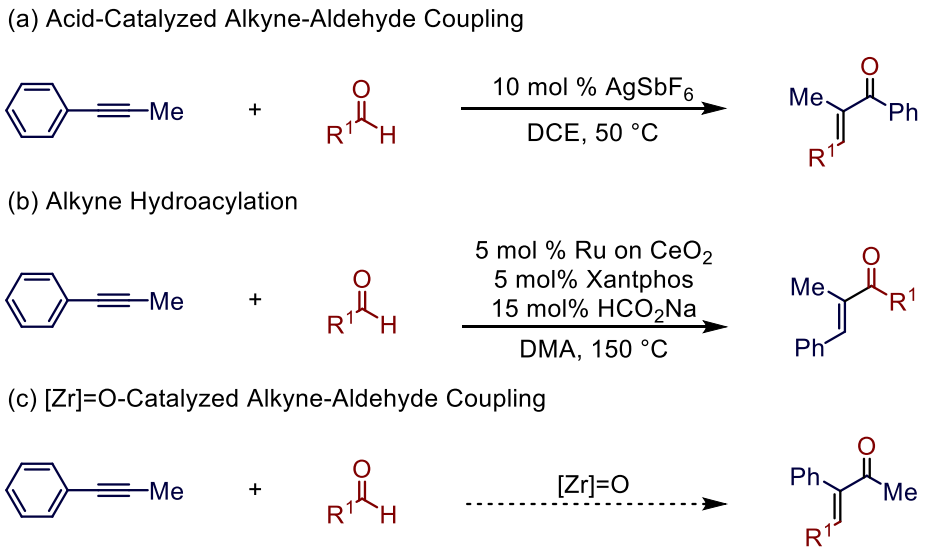
cycloaddition from dioxazirconacyclohexenes has not been reported. Promisingly, as seen in Scheme 1, the related reaction is known for the generation of α,β-unsaturated imines and $Cp_2Zr=O$/$Cp_2Zr=NR$ from azaoxazirconacyclohexenes/diazazirconacyclohexenes.[5] The desired

retro-[4+2]-cycloaddition occurs upon heating the zirconacycles to 45−135 °C. However, as a [Zr]−O bond is significantly stronger than a [Zr]−N bond,[11] our initial efforts have focused on studying the reactivity of dioxazirconacyclohexene complexes and identifying conditions which promote the retro-[4+2]-cycloaddition, with the long-term goal of identifying a catalytically active transition-metal complex.



Scheme 4: Bergman's Azaoxazirconacyclohexene Retro-[4+2]-Cycloaddition.

As the coupling of an aldehyde and alkyne to form an α,β-unsaturated carbonyl is redox neutral, coupling the two directly should allow for the synthesis of desired functionality in a single step without the requirement of a stoichiometric reductant. Additionally, as both components are readily available functional groups, accessing them requires minimal synthetic overhead. Strong acids, silver, and gold catalysts are known to couple alkynes and carbonyls directly and generate α,β-unsaturated carbonyls, via oxetene and/or carbocation intermediates.[7] Although useful, these reactions are limited to substrates that can stabilize carbocation intermediates. Late transition metals are also known to couple alkynes and aldehydes through well-known alkyne hydroacylation.[12] These reactions typically utilize precious metal catalysts, so an alternative early metal catalyst system would be beneficial. More importantly, the bond disconnection for the proposed Zr=O and for alkyne hydroacylation or acid catalyzed cyclization are complementary, as shown in Scheme 5. Starting with 1-phenyl-1-propyne, acid catalyzed alkyne-

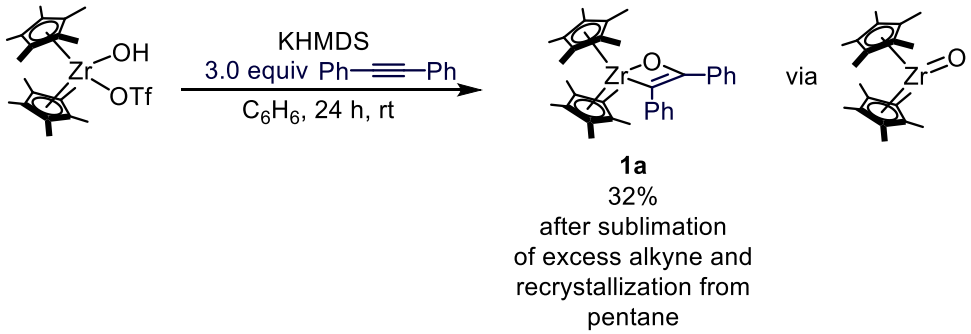


Scheme 5: Alkyne-Aldehyde Coupling Reactions.

aldehyde coupling (Scheme 5a), alkyne hydroacylation (Scheme 5b), and our proposed [Zr]=O mediated alkyne-aldehyde coupling (Scheme 5c) would all afford different products, allowing for one to selected the correct system for the desired product selectivity based on starting materials available and each system's substrates bias. To realize this project each step in the catalytic cycle was investigated. Most importantly, the key step in the catalytic cycle, the retro-[4+2]-cycloaddition was investigated for its feasibility as the Zr–O bond is very strong.

1.2 Reaction Optimization and Scope of [2+2]-Cycloaddition.

I began our investigations in the Zr=O-mediated alkyne-aldehyde coupling by investigating the [2+2]-cycloaddition between the Zr=O and alkynes and examining the scope of this reaction. Bergman's initial report for the synthesis of $Cp^*_2Zr{=}O$ involved the elimination of KOTf from $Cp^*_2Zr(OH)OTf$ (Scheme 6). As the yield for this synthetic pathway is low and removal of excess

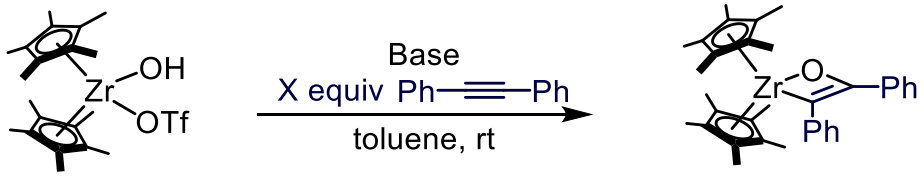


1a
32%
after sublimation
of excess alkyne and
recrystallization from
pentane

Scheme 6: Bergman's Initial [2+2]-Cycloaddition Reaction Conditions.

alkyne by sublimation is required due to its similar solubility in pentane to **1a**, I sought to optimize the base used in the reaction as it should increase the rate of elimination of MOTf. Surveying various hexamethyldisilazide bases revealed a periodic trend in the group I bases (Table 1). Starting from LiHMDS and moving to CsHMDS (Table 1, entries 1-3) reveals a drastic increase in yield and decrease in reaction time. This effect can be rationalized by the increased solubility of the larger cations and a weakening of the M–O (M = Li, K, Cs) bond allowing for a more facile elimination of MOTf.[13] Most importantly, the use of CsHMDS allows for the reduction of alkyne equivalents to 1 equiv. This reduction in alkyne equivalents also eliminates the necessity of removing the excess of alkyne by sublimation. I found that recrystallization from octane instead of pentane further improved the recovery of the product (Table 1, entry 6). These modifications lead to a 30% increase in the isolated yield of **1a** with a simpler purification procedure. With optimized conditions, the scope of alkynes which undergo the [2+2]-cycloaddition was investigated (Table 2). Both electron rich and electron poor diarylacetylenes undergo the [2+2]-cycloaddition in good yields. 4,4'-dimethoxyphenylacetylene undergoes the [2+2]-cycloaddition

Table 1: Base Screen for the [2+2]-Cycloaddition.

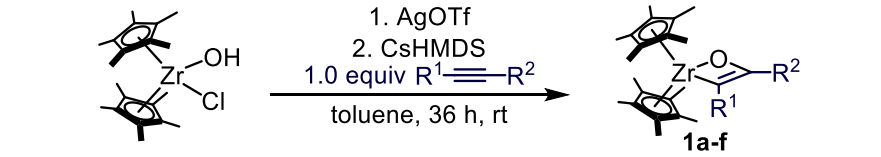


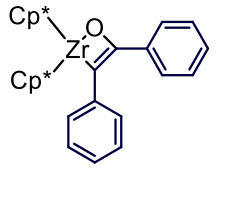
entry	base	PhCCPh equiv	time (h)	yield (%)[a]
1	KHMDS	4	24	60
2	NaHMDS	4	168	58
3	LiHMDS	4	168	10
4	tBuLi	4	24	0
5	CsHMDS	4	6	80
6	CsHMDS	1	36	62[b]

[a]Yield of the resulting phenylbenzylketone after protonolysis with excess pyridiniumhydrochloride was determined by GC analysis of the crude reaction mixture by comparison to 1-methylnaphathene as an internal standard. [b]Yield of purified dioxazirconacyclohexene after recrystallization from n-octane.

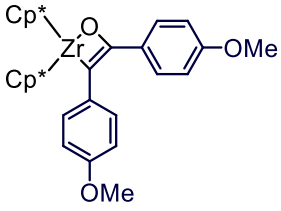
readily affording **1b** in an excellent 97% yield. 0.6 equivalents of alkyne is utilized for this substrate to improve the efficiency of the recrystallization as the alkyne has similar solubility to the **1b** in octane. Electron poor 4,4'-bistrifluoromethyldipheynlacetylene also undergoes the [2+2]-cycloaddition affording **1c** in a modest 39% yield due to a sluggish [2+2]-cycloaddition. When differentially substituted alkynes are used there is a possibility of the formation of two regioisomers. Excitingly, alkyl-substituted phenylacetylenes result in the formation of oxazirconacyclobutenes **1d**, **1e**, and **1f** as single regioisomers. The steric hindrance of the alkyl chain can be increased to an isopropyl with **1f** being obtained in a 39% yield. Pyridine can also be used to trap $Cp^*_2Zr{=}O$, with **2** being isolated in a 72% yield.

Table 2: Scope of [2+2]-Cycloaddition.[a]

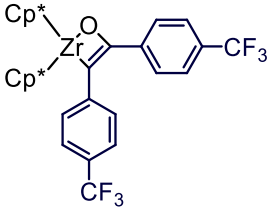




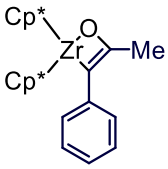
1a
62%



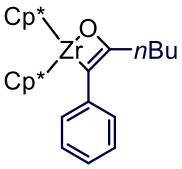
1b[b]
97%



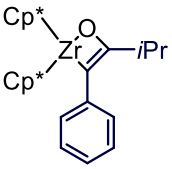
1c
39%



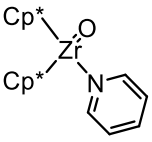
1d
25% >20:1 r.r.



1e
96% >20:1 r.r.



1f
39% >20:1 r.r.

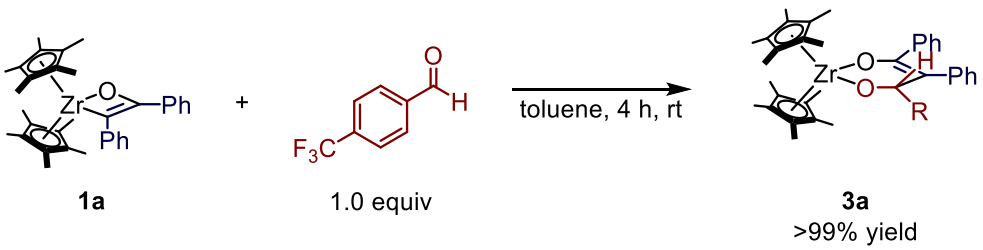


2[c]
72%

[a]Reaction Conditions: $Cp^*_2ZrCl_2$ (1.0 equiv), AgOTf (1.0 equiv) and toluene (0.10 M) were stirred for 0.75 h. The suspension was filtered and alkyne (1.0 equiv) and CsHMDS (1.0 equiv) were added and the reaction was stirred for 36 h. The resulting solution was concentrated under reduced pressure, redissolved in hexane, filtered through celite, and concentrated under reduced pressure. Recrystallization from octane resulted in a red powder. [b]0.60 equiv alkyne used. [c]30 equiv of pyridine used.

1.3 Scope of Aldehyde Insertion.

Originally, Hillhouse reported that aldehyde insertion required addition of the aldehyde at -78° C followed by warming to room temperature. As a catalytic reaction will likely not proceed at cryogenic temperatures because the retro-[4+2]-cycloaddition will likely not occur at such a low temperature,[5,6] I needed to determine if the aldehyde insertion could occur at ambient temperatures. Excitingly, 4-trifluoromethylbenzaldehyde readily inserts into **1a** at room temperature affording **3a** quantitatively by ^{1}H-NMR (Scheme 7). The structure of **3a** was confirmed by X-ray



Scheme 7: Insertion of 4-Trifluoromethylbenzaldehyde into 1a.

crystallography (Figure 1). The zirconium atom is pseudotetrahedral, as expected, and the metallacycle is in a boat-like conformation. O1, C23, C22, and C21 are coplanar and O2 and Zr1

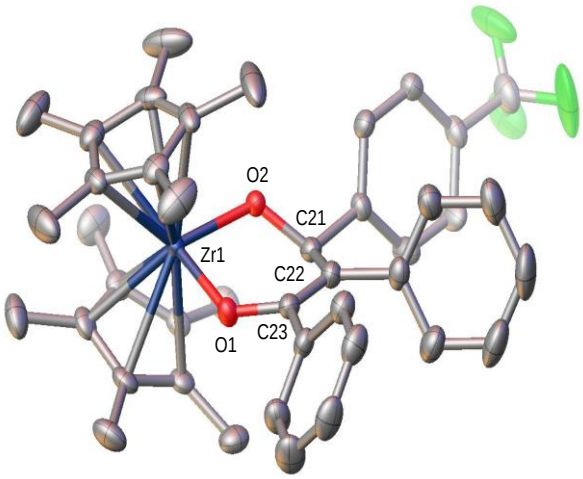
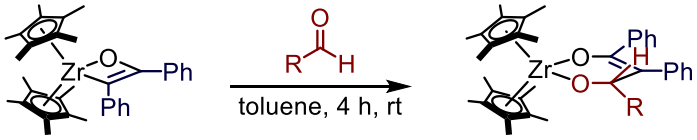


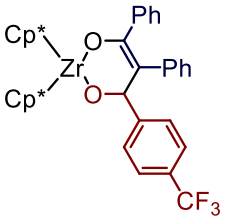
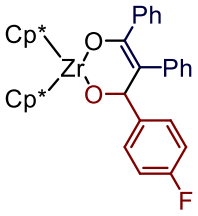
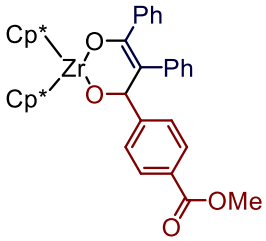
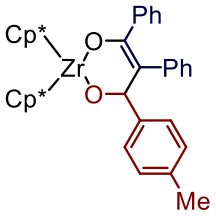
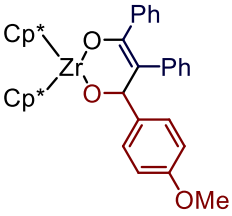
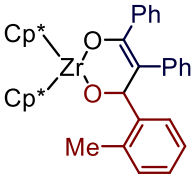
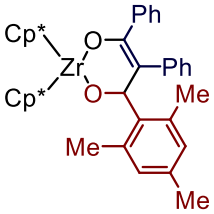
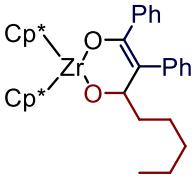
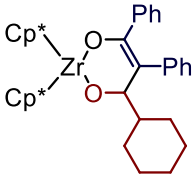
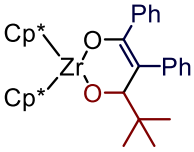
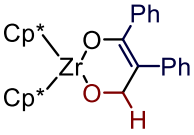
Figure 1: ORTEP Diagram of 3a. Hydrogen atoms and a benzene solvent molecule are omitted for clarity.

are located above the plane. The three aryl substituents are rotated out of conjugation to alleviate steric strain. With the aldehyde insertion now occurring at room temperature, the scope of aldehydes that undergo the insertion was investigated. Gratifyingly, electron poor and rich benzaldehydes all proceed to full conversion with 1.0 equiv of aldehyde affording **3a-3f**. Increasing the steric bulk of the aldehyde requires an increase of aldehyde equivalents to reach full conversion with 2-tolualdehdye requiring 1.6 equiv. Increasing the steric hinderance further to mesitaldehyde results in no reaction. Heating **2a** and mesitaldehyde results in the consumption of mesitaldehyde and the formation of an intractable mixture. Aldehydes which have enolizable protons are also incorporated into the product with excellent yields as hexanal and

cyclohexanecarboxaldehdye readily insert affording **3i** and **3j** in 99% and 91% yield, respectively. Carbonyl insertion does not occur with the more hindered pivalaldehyde; rather, the known metallacycle Cp*$_2$Zr[η^2-OCH(tBu)OCH(tBu)O] forms.[14] This undesired side reaction presumably occurs through a retro-[2+2]-cycloaddition to generate Cp*2Zr=O, which undergoes a subsequent reaction with pivaldehyde. Finally, paraformaldehyde can be used, yielding **3k** quantitatively.

Table 3: Scope of Aldehyde Insertion into 2a.[a]



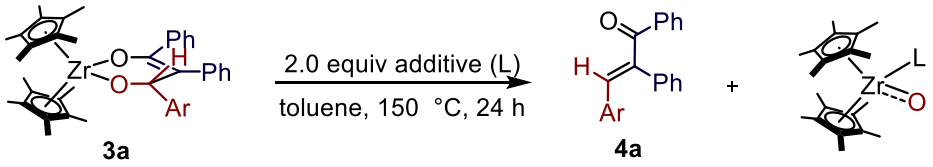
			
3a 99%	**3b** 99%	**3c** 99%	**3d** 99%
			
3e 99%	**3f** 70%[b]	**3g** 0%	**3h** 99%
			
3i 91%	**3j** 0%	**3k** 99%	

[a]Yield determined by ^{1}H NMR by comparision to 1, 3, 5-trimethoxybenzene. [b]1.6 equiv of aldehyde used.

1.4 Investigation of the Retro-[4+2]-Cycloaddition.

After exploring the scope of the [2+2]-cycloaddition and the aldehyde insertion, I turned my attention to the key step of the catalytic cycle, the retro-[4+2]-cycloaddition. I initially tested the retro-[4+2]-cycloaddition of **3a** under thermal conditions (Table 4, entry 1). Unfortunately. only a trace amount of **4a** was observed with the remainder of the mass balance being unreacted **3a**. I postulated that the reaction was in an equilibrium and the transiently formed Zr=O rapidly underwent a [4+2]-cycloaddition with **4a**. To affect this equilibrium various traps for the Zr=O were tested, including Lewis basic ligands such as pyridine, 4-dimethylaminopyridine, and PPh_3, which might be able to trap the Cp^*_2Zr=O intermediate. These additives did not greatly improve the reaction affording **4a** in 7%, 33% and 4% respectively and did not result in any trapped Zr=O (Table 4, entry 2-4). Similarly, when diphenylacetylene was used as a trap, only 4% of **3a** was

Table 4: Effect of Additives on the Retro-[4+2]-Cycloaddition.



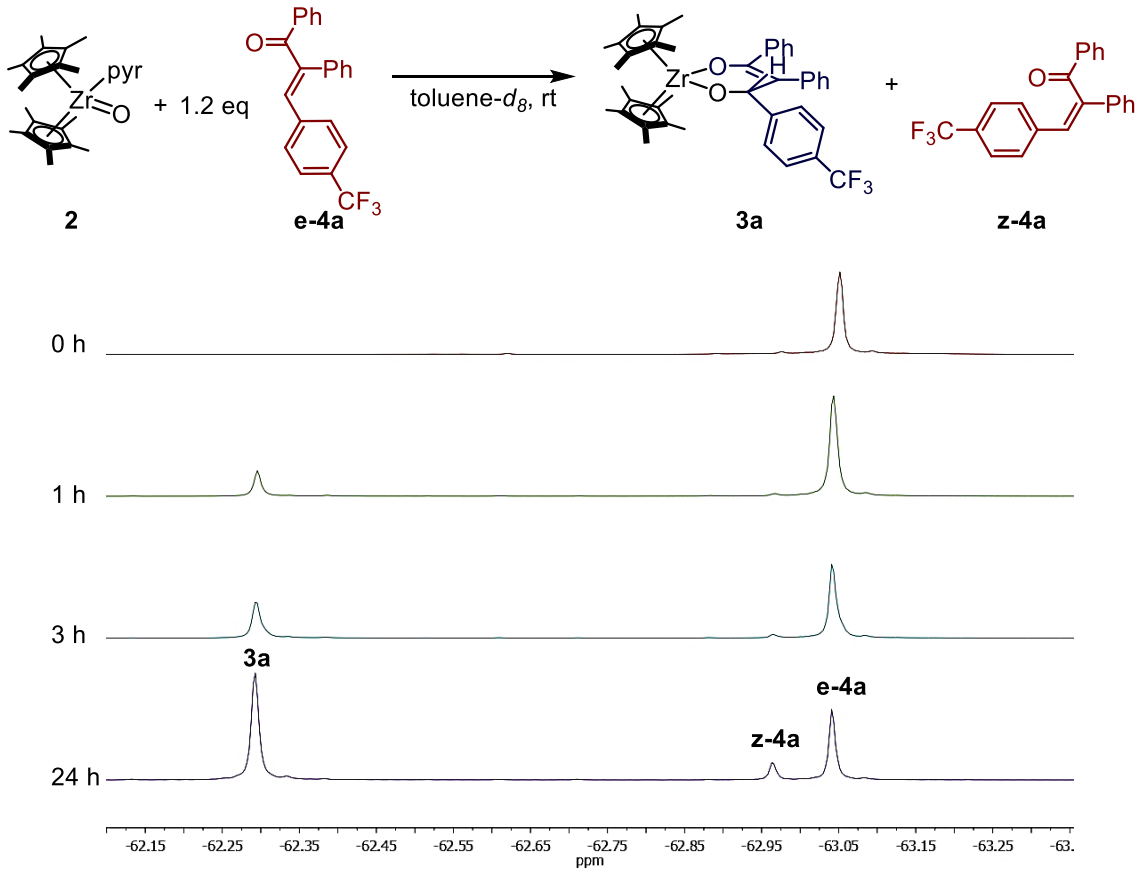
3a **4a**

Ar = 4-$CF_3C_6H_4$

entry	additive	remaining **3a** (%)[a]	yield of **4a** (%) (dr)[a]	yield of $Cp^*_2Zr(=O)L$ (%)[a]
1	None	95	4 (1.6:1)	<5[b]
2	Pyridine	91	7 (1.5:1)	<5[c]
3	DMAP	64	33 (1.6:1)	<5[c]
4	PPh_3	96	4 (1.6:1)	<5[d]
5	PhCCPh	96	4 (1.5:1)	<5[c]
6	PhCCPh[e]	65	35 (1.5:1)	<5[c]
7	Cp_2ZrCl_2	65[f]	4 (1.6:1)	<5[d]

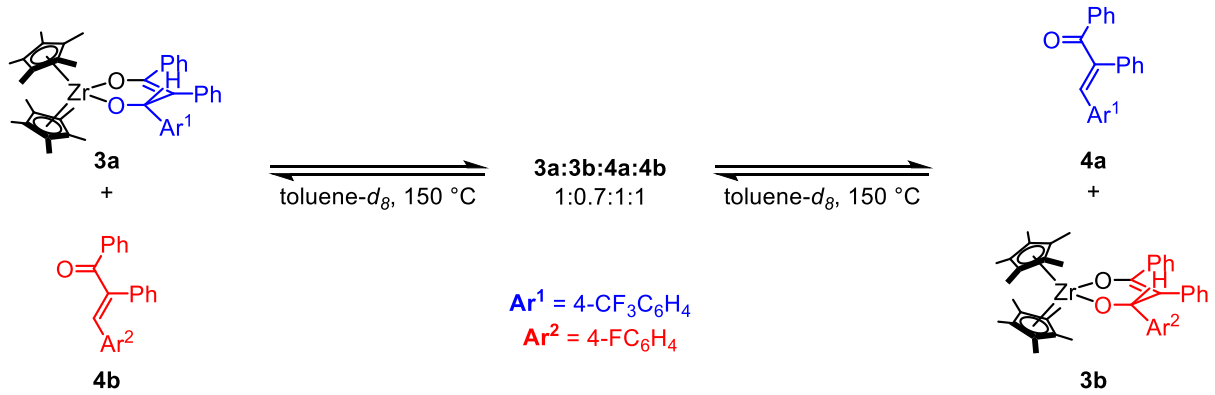
[a]In situ yields determined by comparison of the product to an internal standard in the ^1H or ^{19}F NMR. [b]Solid from resulting from Zr=O oligomerization was also not observed. [c]Not observed by ^1H NMR by comparison to an authentic sample of $Cp^*_2Zr(=O)L$. [d]An authentic sample for comparison could not be generated. [e]20 equiv of PhCCPh was added. [f]Decomposition of **3a** was observed, no other Zr containing products could be identified.

observed. Increasing the diphenylacetylene equivalents to 20 equiv does increase the yield of **4a** to 35%, but **1a** was not observed, rather an intractable mixture was formed. Finally, attempting to trap $Cp^*_2Zr{=}O$ with Cp_2ZrMe_2 which is known to react with $Cp_2Zr{=}O$ to form $[Cp_2Zr(Me)]_2O$ was not successful likely due to the steric bulk of the $Cp^*_2Zr{=}O$ compared to $Cp_2Zr{=}O$, instead an intractable mixture was observed under these conditions. Cp_2ZrMe_2 also does not react with **2**, confirming the hypothesis that $Cp^*_2Zr{=}O$ is too bulky to react with Cp_2ZrMe_2. Again, a mixture of decomposition products was observed. Because the remainder of the zirconium containing material could not be identified in entries 3, 6 and 7, I could not conclude that the retro-[4+2]-cycloaddition was occurring, as **4a** could instead be forming from other pathways such as protonolysis from adventitious water. I hypothesized that the oxo traps employed in Table 4 were simply incompetent traps compared to **4a** as it is a bidentate ligand and forms a highly stable six-membered metallacycle, with the equilibrium thereby greatly favoring **3a**. To test this hypothesis, **2** was reacted with **e-4a** at room temperature in toluene-d_8. Even at ambient temperature **4a** displaces pyridine and after 24 h full conversion of **2** to **3a** is observed. As this is the microscopic



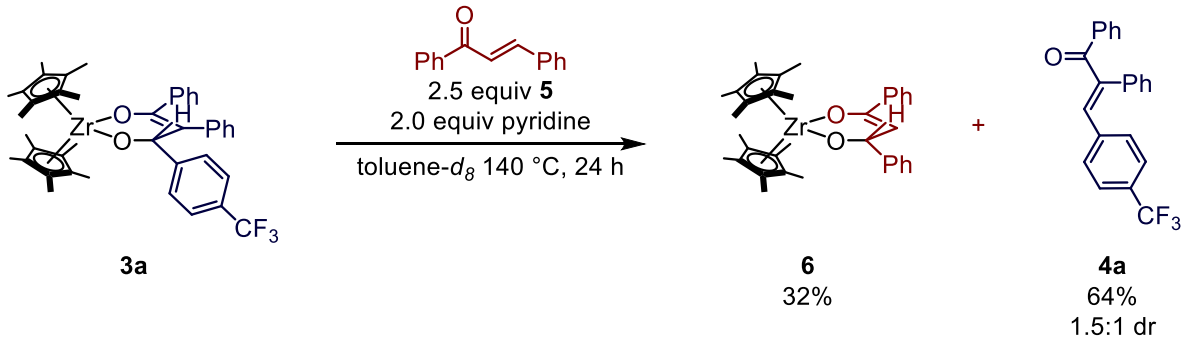
Scheme 8: ^{19}F NMR Spectrum of the Reaction of 2 with e-4a.

reverse of the retro-[4+2]-cycloaddition, the retro-[4+2]-cycloaddition should also be possible. Interestingly, I also observed the formation of **z-4a** during the reaction, suggesting that **4a** interacts reversibly with the zirconium. In order to further probe the retro-[4+2]-cycloaddition, I conducted an exchange experiment (Scheme 9) where **3a** was heated to 150 °C for 24 h in the presence of **4b**. The reaction could easily be monitored by ^{19}F NMR to determine if an exchange would take place. Excitingly, after 24 hours a 1:0.7:1:1 ratio of **3a**:**3b**:**4a**:**4b** was obtained. Approaching the equilibrium from the opposite direction by starting with **4a** and **3b** affords a nearly identical mixture indicating that an equilibrium has been reached and that the equilibrium does not have a significant electronic bias. As the crystal structure of **3a** shows a large degree of steric clash in the phenyl rings on the α,β-unsaturated carbonyl, I expected that an α,β-unsaturated carbonyl which has less $A^{1,3}$ strain would push the equilibrium to the desired product. Chalcone, **5**, is a readily available and inexpensive α,β-unsaturated carbonyl which does not have a substituent on the β-



Scheme 9: Investigating the Equilibrium of the Retro-[4+2]-Cycloaddition.

position and should significantly reduce the $A^{1,3}$ strain of the resulting dioxazirconacyclohexene. To test this hypothesis **3a** was heated to 140 °C in toluene-d_8 in the presence of 2.5 equivalents of chalcone for 24 h (Scheme 10). Excitingly, **4a** was obtained in a 64% yield and the chalcone



3a **6** 32% **4a** 64% 1.5:1 dr

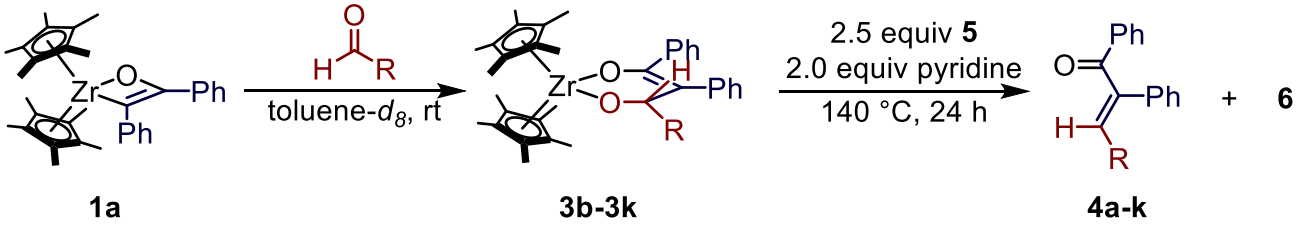
Scheme 10: Chalcone as a Trap for the Retro-[4+2]-Cycloaddition.

trapped Zr=O 6 was obtained in a 32% yield. Unfortunately, the diastereomeric ratio is quite low, though it is consistent with the thermodynamic mixture according to the calculated ground state energies. Now that it has been confirmed that the retro-[4+2]-cycloaddition does occur and that the resulting Zr=O can be trapped with chalcone, I explored the scope of aldehydes and alkynes that were amenable to the reaction.

1.5 Scope of the Retro-[4+2]-Cycloaddition.

Once conditions were identified for the formation of the α,β-unsaturated ketone **4a** and trapping of the $Cp^*_2Zr=O$ intermediate with **5**, the scope of both the aldehyde and the alkyne coupling partners was examined. A variety of aldehydes were subjected to the insertion reaction and then heated to 140 °C with **5** in a NMR tube sealed with a Teflon lined cap. Parasubstituted benzaldehyde derivatives with both electron-withdrawing and electron-donating groups undergo the reaction (Table 5, entries 1-4). The conditions are tolerant of fluoro, ester, and ether functional

Table 5: Scope of Aldehydes in the Retro-[4+2]-Cycloaddition.



1a **3b-3k** **4a-k**

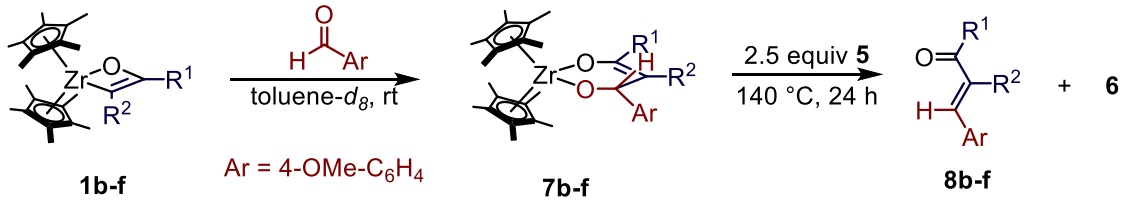
Entry	R	yield of 3 (%)[a]	Yield of 4 (%)[a]	Yield of 6 (%)[a]
1	4-F-C_6H_4 (**b**)	>99	56 (1.4:1)	34
2	4-MeO_2C-C_6H_4 (**c**)	>99	64 (1.8:1)	28
3	4-Me-C_6H_4 (**d**)	>99	82 (nd)[b]	57
4	4-MeO-C_6H_4 (**e**)	>99	>99 (1.4:1)	52
5	2-Me-C_6H_4 (**f**)	>70[c]	91 (1.1:1)	40
6	mesityl (**g**)	0[d]		
7	*n*-pentyl (**h**)	>99[e]	40 (1.4:1)	18
8	cyclohexyl (**i**)	>99	86 (1.3:1)	59
9	*t*-butyl (**j**)	0[f]		
10	H (**k**)	>99	0	0

[a]In situ yields determined by comparison of the product to an internal standard in the ^{1}H NMR. [b]The dr was not determined (nd) due to coincidental chemical shifts in the ^{1}H NMR. [c]1.6 equiv of 2-tolualdehyde was required for complete conversion. [d]No insertion was observed. [e]**1b** was used rather than **3** for the ease of calculating the in situ yield [f]Formation of $Cp^*_2Zr[\eta^2$-OCH(-*t*Bu)OCH(*t*Bu)O] and free PhCCPh was observed.

groups. Electron-rich aldehydes are especially efficient; namely, when p-methoxybenzaldehyde was used, the α,β-unsaturated ketone **4e** was formed in 99% yield and 1.1:1 dr. Ortho substitution is also tolerated (Table 5, entry 5), as the reaction between **1a** and o-tolualdehyde afforded a 91% yield and 1.4:1 dr of **4f**. Aliphatic aldehdyes n-hexanal and cyclohexanal undergo the reaction in

40% and 86% yields, respectively (Table 5, entry 7 and 8). Finally, relatively unhindered formaldehyde readily undergoes the insertion reaction to generate **3k** quantitatively. However, neither **4k** nor any decomposition of **3k** was observed after 24 h at 140 °C.

Finally, the scope of oxazirconacyclobutenes, and therefore, the alkynes that can undergo the coupling reaction, was examined. As seen in Table 6, entries 1 and 2, diaryloxazirconacyclobutenes **1b** and **1c** readily undergo insertion into 4-methoxybenzaldehyde, which was chosen due to the lack of side products in both the insertion and retro-[4+2]-cycloaddition steps (Table 5, entry 4). The subsequent retro-[4+2]-cycloaddition of the electron-rich **7b** affords the corresponding α,β-unsaturated ketone **8b** in 95% yield and 1.7:1 dr (Table 6, entry 1). Conversely, the bis-4-CF_3phenyl adduct **7c** was significantly slower **Table 6: Scope of Alkynes in the Retro-[4+2]-Cycloaddition.**



entry	R^1, R^2	yield of **7** (%)[a]	yield of **8** (%)[a]	yield of **6** (%)[a]
1	R^1, R^2 = 4-MeO-C_6H_4 (**b**)	>99	95 (1.7:1)	55
2	R^1, R^2 = 4-CF_3-C_6H_4 (**c**)	>99	49 (1.1:1)	12[b]
3	methyl, Ph (**d**)	>99	0	0
4	*n*-butyl, Ph (**e**)	>99	53 (1.2:1)	30
5	*i*-propyl, Ph (**f**)	73	95 (5.2:1)	65

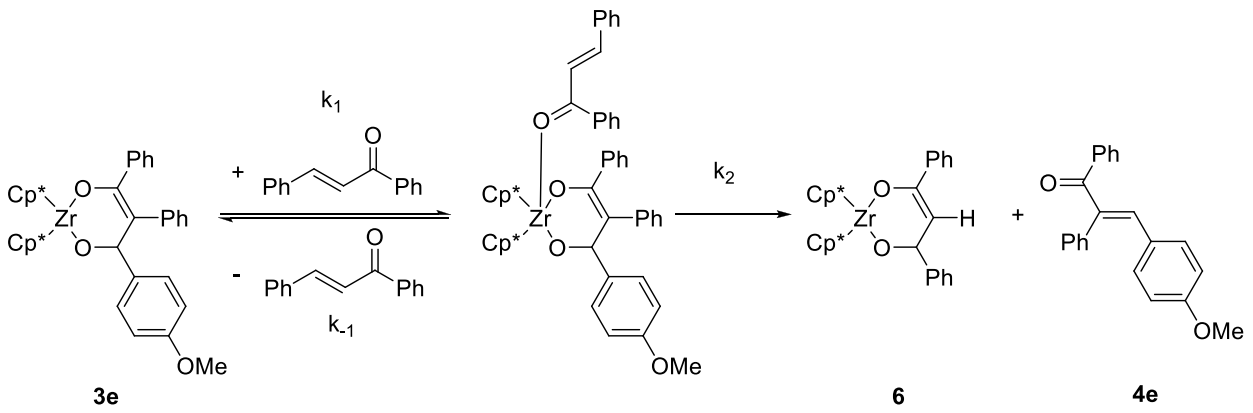
[a]See Table 5. [b]48 h.

at undergoing the retro-[4+2]-cycloaddition, as only 36% of **8c** was observed at 24 h along with 49% remaining starting material; after an additional 24 h **8c** was generated in 49% yield (67% brsm) (Table 6, entry 2). Extending the reaction time further for this substrate did not improve the yield. There are two possible constitutional isomers that could be formed when unsymmetrical alkynes are used; the selectivity of the reaction is dependent upon the [2+2]-cycloaddition. The

reaction between 1-phenyl-1-propyne and $Cp^*_2Zr{=}O$ is known to incorporate the phenyl group exclusively α to the [Zr] and the methyl α to the oxygen atom (**1d**);[8] therefore, it was expected that the α,β-unsaturated ketone would form as a single regioisomer. Likewise, when **1d** was subjected to the carbonyl insertion conditions, **7c** was observed in 99% yield as a single regioisomer, where R^1 = Me and R^2 = Ph (Table 6, entry 3). However, **8c** was not observed after heating at 140 °C for 24 h; rather, side products consistent with deprotonation of **8c** with the basic [Zr]=O to form the enolate were observed. When R^1 is n-butyl (**1e**) or isopropyl (**1f**), the retro-[4+2]-cycloaddition reaction does proceed, affording **8e** and **8f** in 53% and 95% yields, respectively, as single constitutional isomers (Table 6, entries 4 and 5). The increased steric hindrance of **8e** and **8f** relative to **8d**, slows the deprotonation of the α position relative to the [4+2]-cycloaddition with chalcone (**5**). Increasing the size of the group on the alkene increases the dr; when R^1 = *i*Pr, the dr is 5.2:1. The yields of the organic and organometallic products in Tables 5 and 6 were determined by comparison to an internal standard (1,3,5-trimethoxybenzene) in the ^{1}H NMR spectrum. This was necessary, as the α,β-unsaturated ketone is one of the decomposition products upon exposure of the dioxazirconacyclohexene to a GC injection port, proton source, or standard purification techniques such as silica gel chromatography, and, therefore, leads to artificially high yields of α,β-unsaturated ketones. To demonstrate the isolation of the organic products, the retro-[4+2]-cycloaddition of 3d, which is nearly quantitative by ^{1}H NMR, was scaled up to 0.33 mmol and **4e** was isolated in a 75% yield of a 1.1:1 mixture of diastereomers.

1.6 Mechanistic Investigations.

Two potential mechanisms were considered for the retro-[4+2]-cycloaddition. The first mechanism being an associative mechanism (Scheme 11) where **5** first coordinates to **3e** then **4e** is displaced from the zirconium center with co-formation of **6**.



Scheme 11: The Associative Mechanism for the Retro-[4+2]-Cycloaddition from 3e.

If the first step of the reaction is rate determining, at high concentrations of **5** the rate will be:

$$rate = k_1[\mathbf{3e}][\mathbf{5}]$$

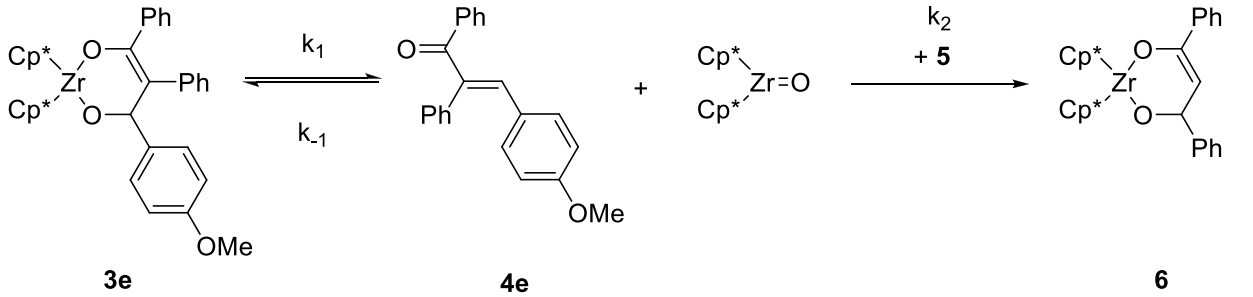
If the second step is rate determining the rate will be:

$$rate = k_{obs}[\mathbf{3e}][\mathbf{5}]$$

where $k_{obs} = \frac{k_2 k_1}{k_{-1}+k_2}$.

Thus, a first order dependence of **5** should be observed if the retro-[4+2]-cycloaddition is going through an associative mechanism regardless of whether the first step or second step is rate determining.

The second mechanism considered was a dissociative mechanism (Scheme 12). In the dissociative mechanism **3e** first undergoes the retro-[4+2]-cycloaddition forming **4e** and Zr=O,



Scheme 12: The Dissociative Mechanism for the Retro-[4+2]-Cycloaddition from 3e.

and second the formed Zr=O undergoes a rapid [4+2]-cycloaddition with **5** to form **6**. If the first step is rate determining the observed rate will be:

$$rate = k_1[\mathbf{3e}]$$

If the second step is rate determining the rate will be:

$$rate = \frac{k_1 k_2[\mathbf{3e}][\mathbf{5}]}{k_{-1}[\mathbf{4e}] + k_2[\mathbf{5}]}$$

When $k_2[\mathbf{5}] >> k_{-1}[\mathbf{4e}]$, the rate will reduce to:

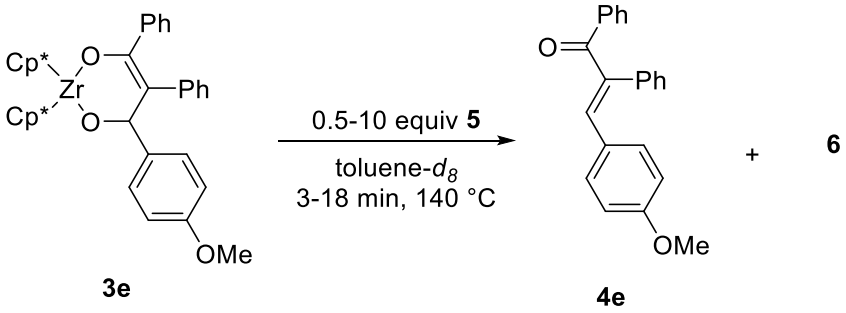
$$rate = k_1[\mathbf{3e}]$$

If $k_{-1}[\mathbf{4e}] >> k_2[\mathbf{5}]$, the rate equation will be:

$$rate = \frac{k_1 k_2[\mathbf{3e}][\mathbf{5}]}{k_{-1}[\mathbf{4e}]}$$

Thus if the retro-[4+2]-cycloaddition is going through a dissociative mechanism, the reaction will be zero order in **5** if the first step is rate determining or when $k_2[\mathbf{5}] >> k_{-1}[\mathbf{4e}]$ or first order in **5** if $k_{-1}[\mathbf{4e}] >> k_2[\mathbf{5}]$.

Given the differences in the two kinetic equations, rate studies should distinguish between the two possible mechanisms. The initial rate under each set of reaction conditions was obtained using the initial rates method, as product inhibition may complicate the kinetic analysis at higher conversions. Each reaction was run to ~20% conversion (as determined by ^{1}H NMR) and [**4e**] was plotted versus reaction time and the reported initial rate values are the average of two unique kinetic experiments. The results for the effect of **5** on the rate is shown in Figures 2 and 3.



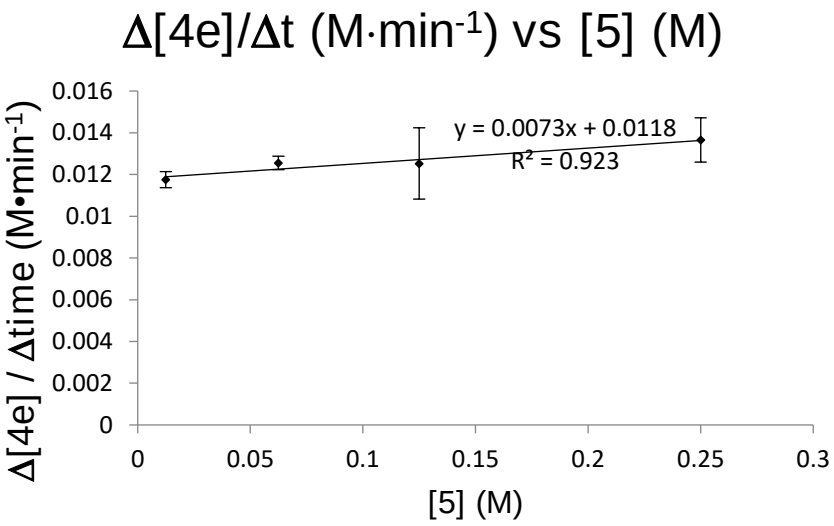


Figure 2: Order of Chalcone (5) on Retro-[4+2]-Cycloaddition of 3e to 4e.

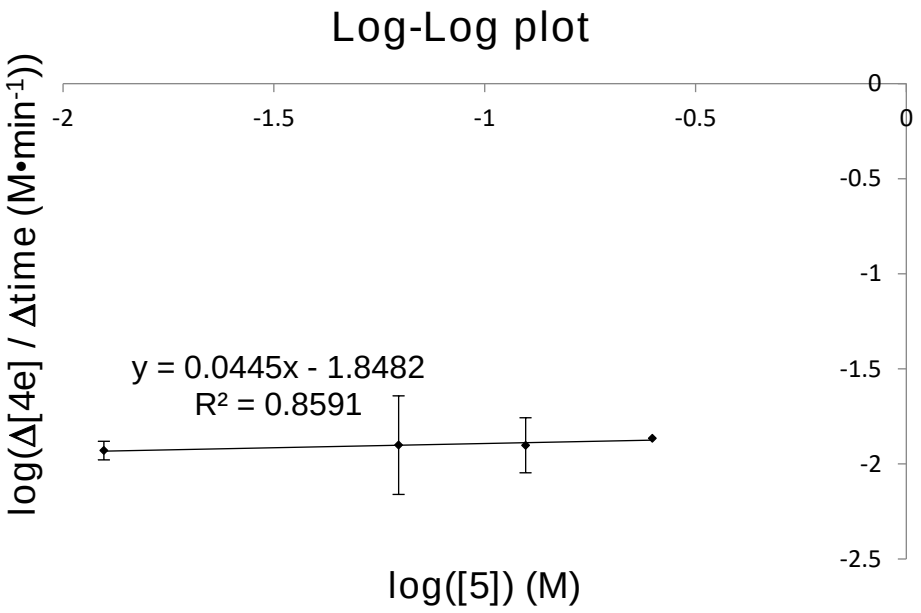
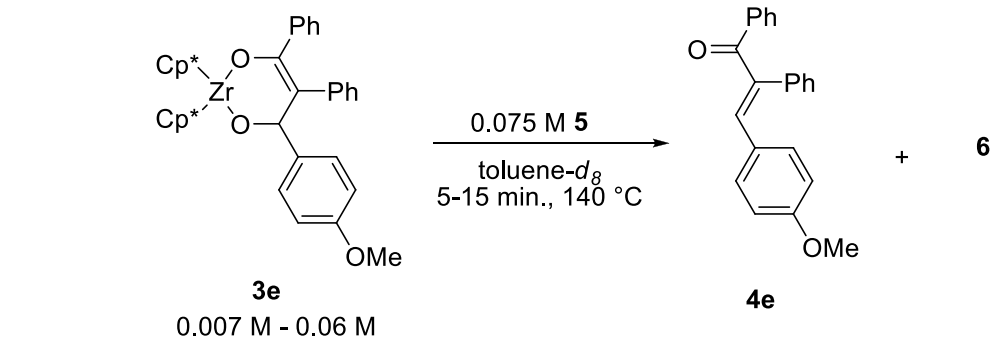


Figure 3: Plot of Log Δ4e/Δtime vs Log [5].

From the log-log plot (Figure 3), it was determined that the order in chalcone was 0.044 ± 0.013 (zero order), indicating that chalcone is not involved in the rate determining step, and thus favoring the dissociative mechanism. To further support the proposed mechanism, kinetic experiments were conducted to determine the order in **3e** and **4e**. I expected that the reaction would be first order in **3e** as the retro-[4+2]-cycloaddition should be rate limiting and **4e** should inhibit the reaction as the retro-[4+2]-cycloaddition between the [Zr]=O and **4e** was shown to be reversible in Scheme 9. The kinetics results for the order in **4e** are plotted in Figures 4 and 5.



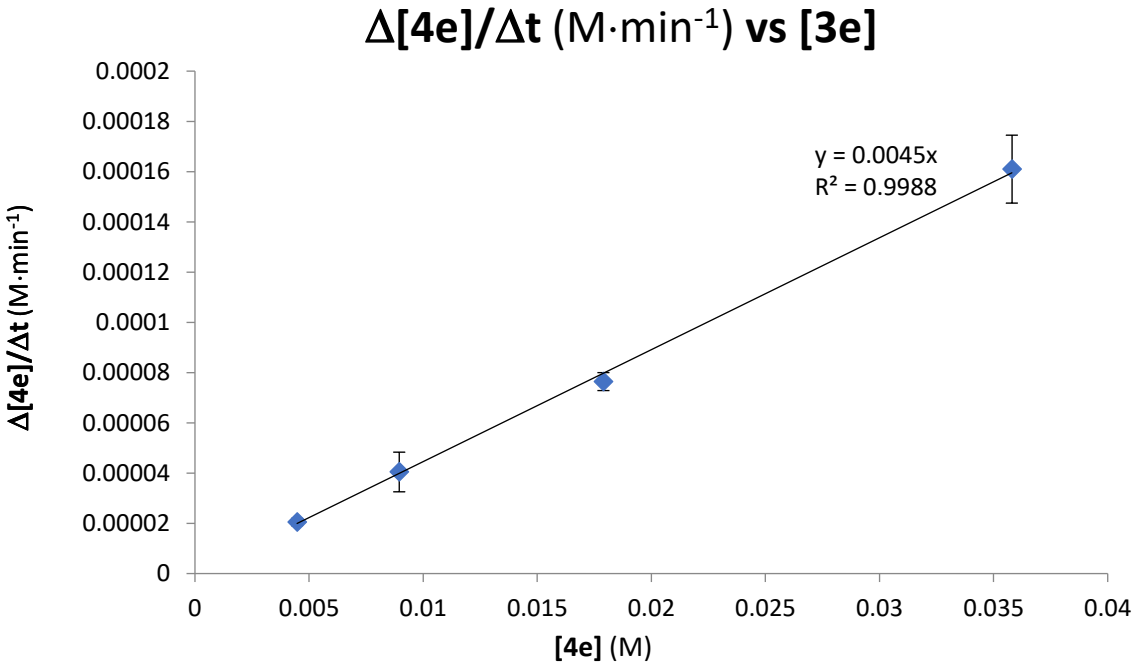


Figure 4: Order of 3e on Retro-[4+2]-Cycloaddition of 3e to 4e.

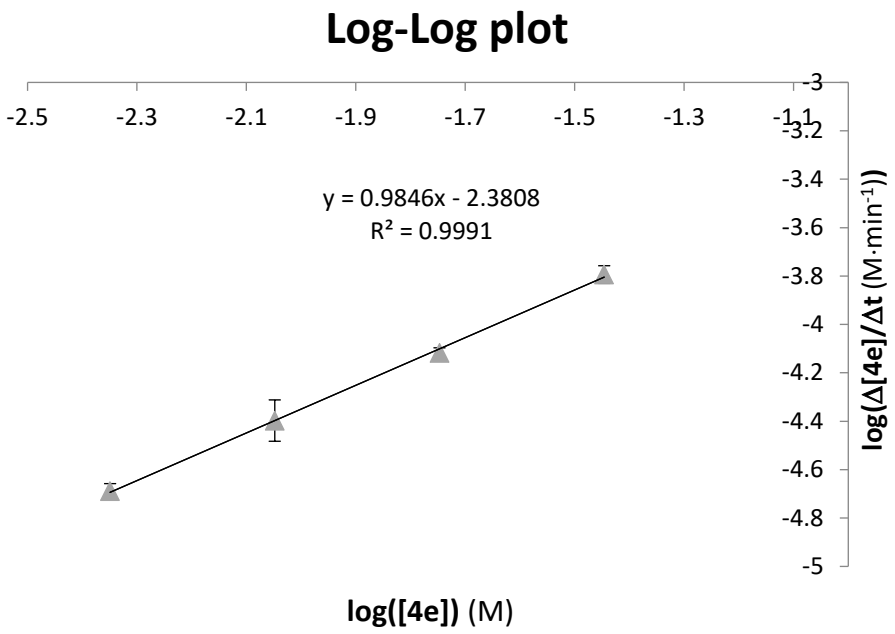


Figure 5: Plot of Log Δ4e/Δtime vs Log [3e].

From the log-log plot (Figure 5) it was determined that the order of **3e** in the retro-[4+2]-cycloaddition is 0.985 ± 0.020 (first order) indicating that **3e** is involved in the rate determining step. Furthermore, this proves that the zirconium species is monomeric. Finally the effect of **4e** on retro-[4+2]-cycloaddition is shown in Figure 6.

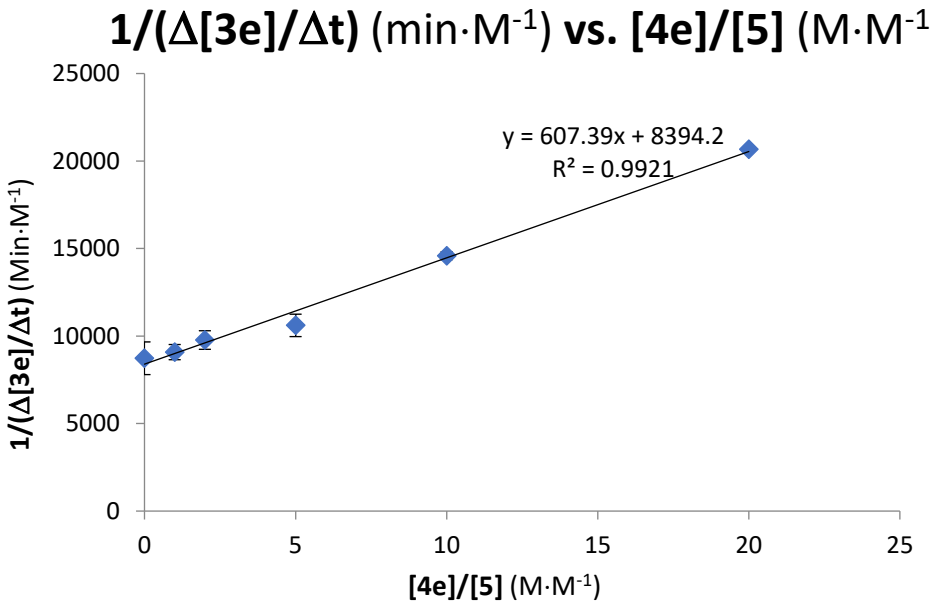


Figure 6: Plot of 1/(Δ[3e]/Δt) vs. [4e]/[5].

Plotting 1/Δ[3e]/Δt vs. [4e]/[5] results in a linear relationship with a non-zero intercept, confirming that the reaction is inhibited by **4e**. To summarize the results of the kinetic experiments, the retro-[4+2]-cycloaddition is zero order in **5**, first order in **3e** and is inhibited by **4e**. These results are all consistent with the dissociative mechanism (Scheme 12) and the retro-[4+2]-cycloaddition being the rate determining step.

1.7 Conclusions.

In conclusion, dioxazirconacyclohexene complexes are able to undergo a reversible retro-[4+2]-cycloaddition to afford α,β-unsaturated ketones and $Cp^*_2Zr{=}O$ and the equilibrium favors the dioxazirconacyclohexene. Using chalcone (**5**) to trap the $Cp^*_2Zr{=}O$ generates the α,β-unsaturated carbonyls in good to excellent yields as a thermodynamic mixture of olefin isomers. Moreover, each step of the proposed catalytic cycle; [2+2]-cycloaddition, carbonyl insertion, and retro-[4+2]-cycloaddition, has been demonstrated to occur under similar reaction conditions with a variety of alkynes and aldehydes. Kinetic experiments confirm that the retro-[4+2]-cycloaddition proceeds through a dissociative mechanism. To identify a M=O complex that will catalyze the alkyne-aldehyde coupling reaction, one should focus on discovering a metal–oxo which thermodynamically favors the M=O over the dioxametallocyclohexene. This will likely require a ligand scaffold which is more sterically demanding than the current Cp* ligand system.

1.8 Experimental Procedures.

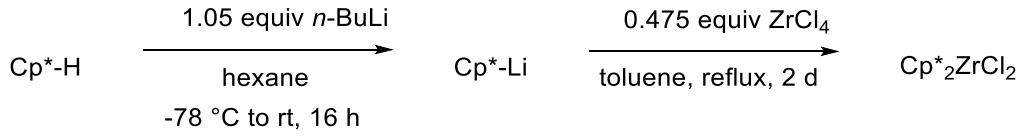
General Considerations: All reactions were carried out in flame- or oven-dried (at 140 °C, for at least 4 hours) glassware under an atmosphere of nitrogen unless otherwise indicated. Air or moisture sensitive materials were synthesized and stored in a nitrogen filled glove box. Column chromatography was performed with silica gel from Grace Davison Discovery Sciences (35-75 μm), packed as a slurry and run under positive pressure. Analytical thin-layer chromatography (TLC) was performed on pre-coated glass silica gel plates with F-254 indicator purchased from EMD Chemicals Inc. Visualization was done by short wave (254 nm) ultraviolet light. Distillations were performed using a 3 cm short-path column either under reduced pressure or under positive pressure of nitrogen.

Instrumentation: ^{1}H, ^{13}C, and ^{19}F NMR specta were recorded on a Varian Unity 400/500 MHz or a VXR-500 MHz (100/125 MHz respectively for ^{13}C, 376/470 MHz respectively for ^{19}F) spectrometer. Spectra were collected in $CDCl_3$, C_6D_6, or toluene-d_8 and were referenced using residual protic solvent (^{1}H NMR: δ 7.26, ^{13}C NMR: δ 77.16 ppm for $CDCl_3$, ^{1}H NMR: δ 7.16, ^{13}C NMR: δ 128.00 ppm for C_6D_6, and ^{1}H NMR: δ 2.10 ppm for toluene-d_8). ^{19}F NMR were referenced internally using C_6F_6 (^{19}F NMR: δ -164.9 ppm). Chemical shifts were reported in parts per million (ppm) and multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), and m (multiplet). Coupling constants (J) are reported in Hertz and integrations are provided. Analysis by Gas Chromatorgraphy- Mass Spectrometry (GC-MS) was performed using a Shimadzu GC-2010 Plus Gas Chromatograph equipped with a Shimadzu GCMS-QP2010 SE mass spectrometer using electron impact ionization (EI) ionization after traveling through a SHRXI-5MS- 30m x 0.25 mm x 0.25 μm column with helium carrer gas. Gas Chromatography (GC) was performed on a Shimadzu GC-2010 Plus gas chromatograph with SHRXI–MS- 15m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and a flame ionization detector (FID). High Resolution Mass Spectrometry was performed at the School of Chemical Sciences Mass Spectrometry Laboratory located at the University of Illinois at Urbana-Champaign. X-Ray crystallography was done at the George L. Clark X-Ray Facility and 3M Materials Laboratory at the University of Illinois at Urbana-Champaign. Microanalysis was performed at the School of Chemical Sciences Microanalysis Laboratory located at the University of Illinois at Urbana-Champaign and at Robertson Microlit Laboratories in Ledgewood, NJ. Microanalysis of

compounds were consistently low in carbon content which is indicative of hydrolysis of the sample or formation of zirconium carbide.

Materials: Solvents used for extraction, column chromatography and recrystallizations of air stable materials were reagent grade and used as received. Solvents for reactions, extractions and recrystallizations of air and water sensitive materials were dried on a Pure Process Technology Glass Contour Solvent Purification System equipped with activated stainless-steel columns following manufacture's recommendations for solvent preparation and dispensing. Solvents were then further dried by storing over 4 Å molecular sieves which had been activated by heating to 200 °C under dynamic vacuum for at least 24 h. Anhydrous pentane and octane for recrystallizations were purchased from Aldrich Chemical Co in a sure-seal® bottle, transferred to a nitrogen filled gloved box and used as received. Pyridine was dried by refluxing over calcium hydride for 24 h, distilled under an atmosphere of nitrogen, transferred to a nitrogen filled glove box and stored over activated molecular sieves for at least 24 h prior to use. C_6D_6 and toluene-d_8 were degassed by freeze-pump-thaw cycles and stored in a nitrogen filled glove box and dried over activated molecular sieves for at least 24 h prior to use. Aldehydes were distilled under reduced pressure or an atmosphere of nitrogen and immediately transferred to a nitrogen filled glove box where they were stored at room temperature until use. Hexanal was used immediately after distillation. diphenylacetylene was purchased from the Aldrich Chemical Company and used as received. 1-phenyl-1-propyne was purchased from the Aldrich Chemical Company and distilled prior to use. $ZrCl_4$ was purchased from Strem Chemical Company or Acros Organics and used as received. Cp*-H was obtained from Boulder Scientific and distilled prior to use. The following alkynes were synthesized by known literature procedures: 1,2-bis(4-methoxyphenyl)ethyne[15], 1,2bis(4-(trifluoromethyl)phenyl)-ethyne,[15] hex-1-ynylbenzene,[16] and (3-methylbut-1-ynyl)benzene.[17] CsHMDS was synthesized using literature procedure.[18]

Experimental procedures and characterization:



Synthesis of $Cp^*_2ZrCl_2$:[19]

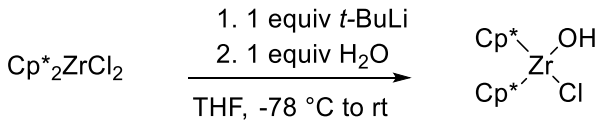
Step 1: To a 500 mL round bottom flask was added Cp*-H (9.81 g, 72.2 mmol, 1.00 equiv) and 350. mL hexane and a magnetic stir bar. The flask was then cooled to -78 °C in the glovebox coldwell with a dry ice/acetone bath. *n*-Butyllithium (1.6 M in hexane) (47.3 mL, 75.8 mmol, 1.05 equiv) was then added dropwise over 10 minutes with vigorous stirring. The solution was stirred at -78 °C for 30 minutes and removed from the coldwell and stirred at room temperature for 16 h. The light orange solid was filtered and washed with 2 x 50 mL hexane and dried in vacuo yielding a white solid (9.27 g, 65.3 mmol, 90.7% yield).

Step 2: To a 500 mL round bottom flask was added $ZrCl_4$ (8.32 g, 35.7 mmol, 1 equiv) and Cp*Li (10.7 g, 75.0 mmol, 2.10 equiv). The solids were suspended in 350. mL toluene, a stir bar was added, reflux condenser attached and a septum affixed a top the reflux condenser. The round bottom was then removed from the glovebox, put under N_2 and heated to 130 °C in an oil bath for 48 h. The solution was cooled to room temperature, the reflux condenser was removed and the solvent was removed *in vacuo*. The resulting brown solid was dissolved in $CHCl_3$ (400 mL) and transferred to a 1 L separatory funnel. The flask was rinsed with an additional 200. mL $CHCl_3$ and 100. mL 3 M HCl. The organic layer was washed with an additional 100 mL 3 M HCl, 100 mL H_2O, and 100 mL brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting yellow solid was transferred to the glovebox and used without further purification (13.7 g, 31.8 mmol, 89.0% yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 30H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 123.76, 12.09.

^{1}H and ^{13}C NMR matched reported literature spectra.[20]

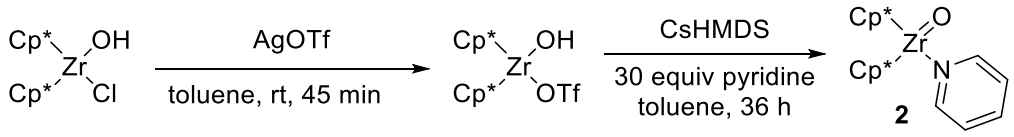


Synthesis of Cp*$_2$Zr(OH)Cl: To a 500 mL round bottom flask was added Cp*$_2$ZrCl$_2$ (7.48 g, 17.3 mmol, 1.00 equiv), a magnetic stir bar, and 400 mL THF. The solution was stirred at room temperature until all of the Cp*$_2$ZrCl$_2$ dissolved. The solution was next cooled to -78 °C in the glove box coldwell with a dry ice/acetone bath. Solid *tert*-butyllithium (1.11 g, 17.3 mmol, 1.00 equiv) dissolved in 15 mL hexane was then added dropwise over 10 minutes with vigorous stirring. A septum was affixed and the solution was stirred 16 h while allowing to slowly warm to RT. The round bottom was next removed from the glove box and put under N_2. With vigorous stirring H_2O (320. μL, 17.3 mmol, 1.00 equiv) was added to the dark brown/black solution (gas evolved) causing the solution to turn a light yellow. The solution was stirred for 4 hours and concentrated *in vacuo*. The resulting solid was dissolved in 400 mL DCM and filtered through a bed of celite to remove LiCl. The flask and filter cake was rinsed with an extra 2 x 100 mL DCM. The filtrate was concentrated in vacuo yielding an off white powder. (6.42 g, 15.5 mmol, 89.5% yield). Samples were typically contaminated with 5-10 % of Cp*$_2$ZrCl$_2$ or Cp*$_2$Zr(OH)$_2$. Attempts to further purify the material from either contaminate by recrystallization or sublimation were unsuccessful.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (s, 1H), 1.95 (s, 30H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 120.99, 11.42.

Signals corresponding to contaminates are omitted. ^{1}H and ^{13}C NMR matched reported literature spectra.[8]



Synthesis of Cp*$_2$Zr(O)(NC$_5$H$_5$) (2): Cp*$_2$Zr(OH)OSO$_3$CF$_3$ was generated *in situ* by modification of the procedure reported in reference 8. To a 20 mL scintillation vial was added Cp*$_2$Zr(OH)Cl (830 mg, 2.0 mmol, 1.0 equiv) followed by AgOSO$_3$CF$_3$ (514 mg, 2.0 mmol, 1.0 equiv), a magnetic stir bar, and 10 mL of toluene. The suspension was stirred for 45 minutes and filtered through a packed bed of celite in to a 100 mL round bottom flask. The scintillation vial was rinsed

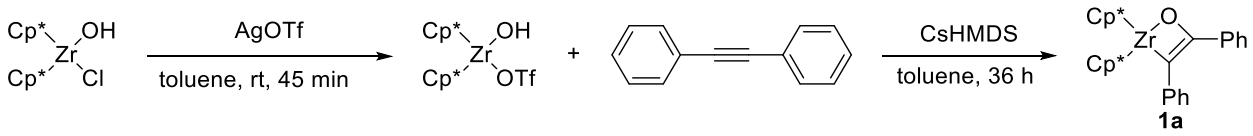
with 10 mL toluene and the filter cake was rinsed with 2 x 10 mL toluene or until the filtrate ran clear. To the yellow solution was added pyridine (5.0 mL, 60. mmol, 30. equiv) and CsHMDS (586 mg, 2.0 mmol, 1.0 equiv), which was stirred for 36 h. The solution was then concentrated in vacuo and the resulting solid was triturated with hexane (3 x 10 mL), redissolved in toluene (40 mL), filtered through celite, the round bottom was then rinsed with additional toluene (40 mL) and filtered through celite, the resulting filtrates were then concentrated yielding 650 mg (1.4 mmol, 72 % yield) of a tan solid.

^{1}H NMR (499 MHz, C_6D_6) δ 9.23 (d, $^{3}J_{HH}$ = 5.4 Hz, 1H), 7.55 (d, $^{3}J_{HH}$ = 5.3 Hz, 1H),6.76 (tt, $^{3}J_{HH}$ = 7.6, $^{5}J_{HH}$ = 1.6 Hz, 1H), 6.52 – 6.40 (m, 2H), 1.92 (s, 30H).

^{13}C NMR (126 MHz, C_6D_6) δ 157.97, 148.62, 137.69, 124.86, 122.97, 116.13, 11.53.

^{1}H and ^{13}C NMR matched reported literature spectra.[21]

Synthesis of Oxazirconacyclobutenes 1a-f:



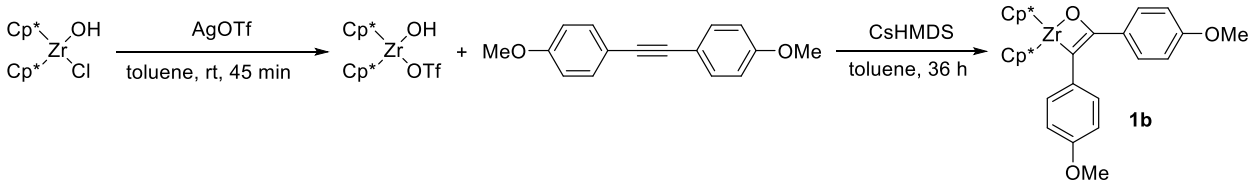
Synthesis of Cp*$_2$Zr(OC(Ph)=C(Ph)) (1a): 1a was synthesized with modification of the procedure reported in reference 8. Cp*$_2$Zr(OH)OSO$_3$CF$_3$ was generated *in situ* according to the following procedure: To a 20 mL scintillation vial was added Cp*$_2$Zr(OH)Cl (0.734 g, 4.19 mmol, 1.00 equiv) followed by AgOSO$_3$CF$_3$ (1.08 g, 4.19 mmol, 1.00 equiv), a magnetic stir bar, and 15.0 mL of toluene. The suspension was stirred for 45 minutes and filtered through a packed bed of celite in to a 100 mL round bottom flask. The scintillation vial was rinsed with 10 mL toluene and the filter cake was rinsed with 2 x 10 mL toluene or until the filtrate ran clear. To the yellow solution was added diphenylacetylene (745 mg, 4.19 mmol, 1.00 equiv) and CsHMDS (1.23 g, 4.19 mmol, 1.00 equiv). The orange solution was stirred for 36 h over which time it turned dark red and was concentrated *in vacuo*. The resulting red tacky solid was redissolved in 50 mL hexane and filtered through a packed celite bed. The flask and filter cake were rinsed with hexane until the filtrates ran clear. The hexane was removed in vacuo and the resulting tacky red solid was redissolved in minimal hot octane and slowly cooled to -35 °C resulting in the formation of 1.44 g (2.59 mmol, 61.8% yield) of red crystalline solid.

^{1}H NMR (499 MHz, C_6D_6): δ 8.01 (d, $^{3}J_{HH}$ = 7.3 Hz, 2H), 7.25 – 7.13 (m, 6H), 7.09 (t, $^{3}J_{HH}$ = 7.3 Hz, 1H), 6.96 (tt, $^{3}J_{HH}$ = 6.7, $^{5}J_{HH}$ =1.6 H, 1H), 1.80 (s, 30H).

^{13}C NMR (126 MHz, C_6D_6): δ 158.58, 144.11, 136.77, 136.04, 129.22, 128.05, 127.38, 122.69, 120.17, 11.17. Two sp^2 resonances could not be located.

HRMS (EI/TOF) *m/z*: [M^+] calculated for $C_{34}H_{40}OZr$, 554.2126; found, 554.2136

^{1}H and ^{13}C NMR matched reported literature spectra.[10]



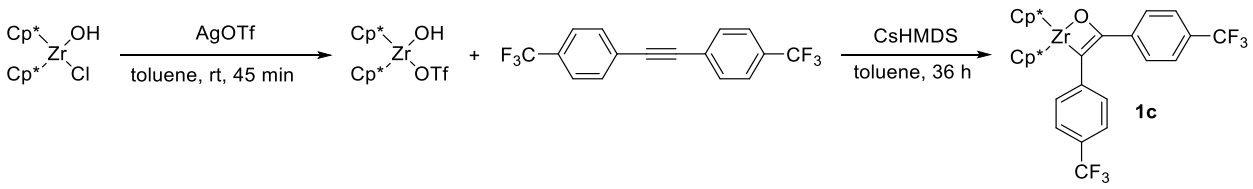
Synthesis of Cp*$_2$Zr(OC((4-OMe)C$_6$H$_4$)=C((4-OMe)C$_6$H$_4$)) (1b): Cp*$_2$Zr(OH)OSO$_3$CF$_3$ was generated *in situ* by modification of the procedure reported in reference 8. To a 20 mL scintillation vial was added Cp*$_2$Zr(OH)Cl (828 mg, 2.00 mmol, 1.67 equiv) followed by AgOSO$_3$CF$_3$ (514 mg, 2.00 mmol, 1.67 equiv), a magnetic stir bar, and 10 mL of toluene. The suspension was stirred for 45 minutes and filtered through a packed bed of celite in to a 100 mL round bottom flask. The scintillation vial was rinsed with 10 mL toluene and the filter cake was rinsed with 2 x 10 mL toluene or until the filtrate ran clear. To the yellow solution was added 1,2-bis(4-methoxyphenyl)ethyne (285 mg, 1.20 mmol, 1.00 equiv) and CsHMDS (586 mg, 2.00 mmol, 1.67 equiv). The orange solution was stirred for 36 h over which time it turned dark red and was concentrated *in vacuo*. The resulting red tacky solid was redissolved in 50 mL hexane and filtered through a packed celite bed. The flask and filter cake were rinsed with hexane until the filtrates ran clear. The hexane was removed in vacuo and the resulting tacky red solid was redissolved in minimal hot octane and slowly cooled to -35 °C resulting in the formation of 722 mg (1.17 mmol, 97% yield) of red crystalline solid (contaminated with 7% of 1,2-bis(4-methoxyphenyl)ethyne).

^{1}H NMR (500 MHz, C_6D_6) δ 7.99 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 7.17 (d, $^{3}J_{HH}$ = 8.8, 2H), 6.87 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.83 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 3.42 (s, 3H), 3.30 (s, 3H), 1.85 (s, 30H).

^{13}C NMR (126 MHz, C_6D_6) δ 159.42, 157.17, 156.20, 136.77, 134.22, 130.39, 130.06, 129.38, 119.92, 113.91, 113.62, 54.75, 54.68, 11.21.

HRMS (EI/TOF) *m/z*: [M^+] calculated for $C_{36}H_{44}O_3Zr$, 614.2237; found, 614.2202.

Anal. Calcd. for $C_{36}H_{44}O_3Zr$: C, 70.20; H, 7.20. Found: C, 68.42; H, 7.18. Repeated analysis of recrystallized samples were consistently low in carbon content.



Synthesis of $Cp^*_2Zr(OC((4\text{-}CF_3)C_6H_4)=C((4\text{-}CF_3)C_6H_4))$ (1c): $Cp^*_2Zr(OH)OSO_3CF_3$ was generated *in situ* by modification of the procedure reported in reference 8**Error! Bookmark not defined.**. To a 20 mL scintillation vial was added $Cp^*_2Zr(OH)Cl$ (414 mg, 1.00 mmol, 1.25 equiv) followed by $AgOSO_3CF_3$ (257 mg, 1.25 mmol, 1.00 eq.), a magnetic stir bar, and 10 mL of toluene. The suspension was stirred for 45 minutes and filtered through a packed bed of celite in to a 100 mL round bottom flask. The scintillation vial was rinsed with 10 mL toluene and the filter cake was rinsed with 2 x 10 mL toluene or until the filtrate ran clear. To the yellow solution was added 1,2bis(4-(trifluoromethyl)phenyl)ethyne (251 mg, 0.8 mmol, 1.00 equiv) and CsHMDS (293 mg, 1.00 mmol, 1.25 equiv). The orange solution was stirred for 36 h over which time it turned red and was concentrated *in vacuo*. The resulting red tacky solid was redissolved in 50 mL hexane and filtered through a packed celite bed. The flask and filter cake were rinsed with hexane until the filtrates ran clear. The hexane was removed in vacuo and the resulting tacky red solid was redissolved in minimal hot octane and slowly cooled to -35 °C resulting in the formation of 218 mg (0.315 mmol, 39% yield) of dark orange-red crystalline solid.

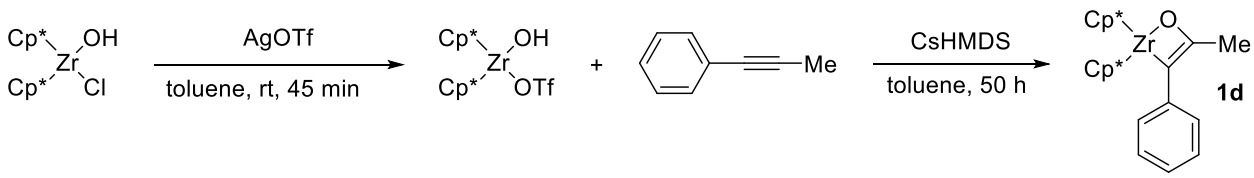
^{1}H NMR (499 MHz, C_6D_6) δ 7.78 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.36 (m, 4H), 6.92 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 1.69 (s, 30H).

^{13}C NMR (126 MHz, C_6D_6) δ 157.99, 147.80, 139.39, 137.41, 129.41 (d, $^2J_{CF}$ = 32.5 Hz), 128.99, 128.44, 126.78 (q, $^1J_{CF}$ = 273.8 Hz), 126.09 (q, $^1J_{CF}$ = 273.4 Hz), 125.16 (q, $^3J_{CF}$ = 3.6 Hz), 125.04 (q, $^3J_{CF}$ = 3.8 Hz), 120.67, 10.92. One resonance not located (**C**CF_3).

^{19}F NMR (470 MHz, C_6D_6) δ -61.70, -62.52.

HRMS (EI/TOF) *m/z*: [M^+] calculated for $C_{36}H_{38}F_6OZr$, 690.1873; found, 690.1738

Anal. Calcd. for $C_{36}H_{38}F_6O_3Zr$: C, 62.49; H, 5.54. Found: C, 61.66; H, 5.60. Repeated analysis of recrystallized samples were consistently low in carbon content.



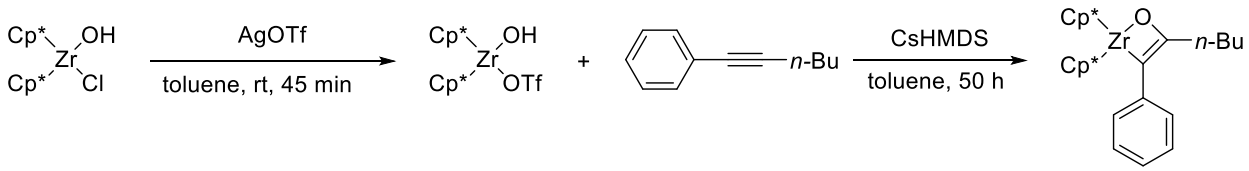
Synthesis of Cp*$_2$Zr(OC(Me)=C(Ph) (1d): Cp*$_2$Zr(OH)OSO$_3$CF$_3$ was generated *in situ* by modification of the procedure reported in reference 8. To a 20 mL scintillation vial was added Cp*$_2$Zr(OH)Cl (723 mg, 1.75 mmol, 1.00 equiv) followed by AgOSO$_3$CF$_3$ (449 mg, 1.75 mmol, 1.00 equiv), a magnetic stir bar, and 10 mL of toluene. The suspension was stirred for 45 minutes and filtered through a packed bed of celite in to a 100 mL round bottom flask. The scintillation vial was rinsed with 10 mL toluene and the filter cake was rinsed with 2 x 10 mL toluene or until the filtrate ran clear. To the yellow solution was added CsHMDS (511 mg, 1.75 mmol, 1.00 equiv). The orange solution was stirred for 24 h then 1-phenyl-1-propyne (202 mg, 1.75 mmol, 1.00 equiv) was added and the solution was stirred for an additional 36 h over which time it turned red and was then concentrated *in vacuo*. The resulting red tacky solid was redissolved in 50 mL hexane and filtered through a packed celite bed. The flask and filter cake were rinsed with hexane until the filtrate ran clear. The hexane was removed *in vacuo* and the resulting tacky red solid was redissolved in minimal hot pentane and slowly cooled to -35 °C resulting in the formation of 216 mg (0.437 mmol, 25% yield) of dark red crystalline solid.

^{1}H NMR (499 MHz, C_6D_6) δ 7.36 (t, $^3J_{HH}$ = 7.7 Hz, 2H), 7.15 (dd, $^3J_{HH}$ = 8.2, 1.1 Hz, 2H), 7.04 (tt, $^3J_{HH}$ = 7.3, $^5J_{HH}$ 1.1 Hz, 1H), 2.35 (s, 3H), 1.79 (s, 30H).

^{13}C NMR (126 MHz, C_6D_6) δ 156.09, 144.36, 137.61, 129.16, 123.19, 122.21, 119.75, 19.12, 11.18.

HRMS (EI/TOF) *m/z*: [M$^+$] calculated for $C_{29}H_{38}OZr$, 492.1969; found, 692.1830

^{1}H and ^{13}C NMR matched reported literature spectra.[8]



1e

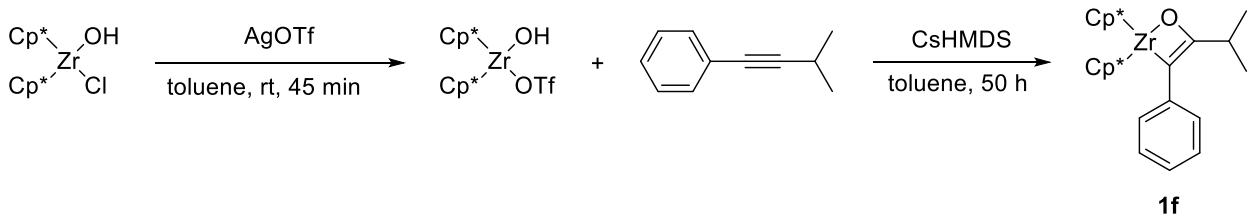
Synthesis of Cp*$_2$Zr(OC(Ph)=C(*n*-C$_4$H$_9$) (1e): Cp*$_2$Zr(OH)OSO$_3$CF$_3$ was generated *in situ* by modification of the procedure reported in reference 8. To a 20 mL scintillation vial was added Cp*$_2$Zr(OH)Cl (414 mg, 1.00 mmol, 1.00 equiv) followed by AgOSO$_3$CF$_3$ (257 mg, 1.00 mmol, 1.00 equiv), a magnetic stir bar, and 10 mL of toluene. The suspension was stirred for 45 minutes and filtered through a packed bed of celite in to a 100 mL round bottom flask. The scintillation vial was rinsed with 10 mL toluene and the filter cake was rinsed with 2 x 10 mL toluene or until the filtrate ran clear. To the yellow solution was added CsHMDS (293 mg, 1.00 mmol, 1.00 equiv). The orange solution was stirred for 24 h then hex-1-ynylbenzene (158 mg, 1.00 mmol, 1.00 equiv) was added and the solution was stirred for an additional 36 h over which time it turned red and was then concentrated *in vacuo*. The resulting red tacky solid was redissolved in 50 mL hexane and filtered through a packed celite bed. The flask and filter cake were rinsed with hexane until the filtrate ran clear. The hexane was removed *in vacuo* and the resulting tacky red solid was redissolved in minimal hot pentane and slowly cooled to -35 °C resulting in the formation of 514 mg (0.959 mmol, 96% yield) of dark red crystalline solid.

^{1}H NMR (499 MHz, C$_6$D$_6$) δ 7.35 (t, $^3J_{HH}$ = 8.2 Hz, 2H), 7.16 (dd, $^3J_{HH}$ = 8.2, $^5J_{HH}$ 1.4 Hz, 2H), 7.11 (tt, $^3J_{HH}$ = 7.3, $^5J_{HH}$ = 1.2 Hz, 1H), 2.76 – 2.69 (m, 2H), 1.97 – 1.84 (m, 2H), 1.77 (s, 30H), 1.45 (sextet, $^3J_{HH}$ = 7.3 Hz, 2H), 0.96 (t, $^3J_{HH}$ = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, C$_6$D$_6$) δ 156.03, 144.41, 140.95, 129.03, 128.19, 122.29, 119.71, 32.52, 31.08, 24.01, 14.35, 11.28.

HRMS (EI/TOF) *m/z*: [M$^+$] calculated for C$_{36}$H$_{44}$O$_3$Zr, 534.2439; found, 534.2310.

Anal. Calcd. for C$_{32}$H$_{44}$OZr: C, 71.72; H, 8.28. Found: C, 69.79; H, 8.17. Repeated analysis of recrystallized samples were consistently low in carbon content.



1f

Synthesis of Cp*$_2$Zr(OC(Ph)=C(*i*-Pr)) (1f): Cp*$_2$Zr(OH)OSO$_3$CF$_3$ was generated *in situ* by modification of the procedure reported in reference 8. To a 20 mL scintillation vial was added Cp*$_2$Zr(OH)Cl (414 mg, 1.00 mmol, 1.00 equiv) followed by AgOSO$_3$CF$_3$ (257 mg, 1.00 mmol, 1.00 equiv), a magnetic stir bar, and 10 mL of toluene. The suspension was stirred for 45 minutes and filtered through a packed bed of celite in to a 100 mL round bottom flask. The scintillation vial was rinsed with 10 mL toluene and the filter cake was rinsed with 2 x 10 mL toluene or until the filtrate ran clear. To the yellow solution was added CsHMDS (293 mg, 1.00 mmol, 1.00 equiv). The orange solution was stirred for 24 h then (3-methylbut-1-ynyl)benzene (158 mg, 1.00 mmol, 1.00 equiv) was added and the solution was stirred for an additional 36 h over which time it turned red and was then concentrated *in vacuo*. The resulting red tacky solid was redissolved in 50 mL hexane and filtered through a packed celite bed. The flask and filter cake were rinsed with hexane until the filtrate ran clear. The hexane was removed *in vacuo* and the resulting tacky red solid was redissolved in minimal hot pentane and cooled to -35 °C resulting in the formation of 202.8 mg (0.389 mmol, 39% yield) of dark red crystalline solid.

^{1}H NMR (500 MHz, C$_6$D$_6$) δ 7.37 (t, $^3J_{HH}$ = 7.8 Hz, 2H), 7.20 (dd, $^3J_{HH}$ = 8.1, $^5J_{HH}$ = 1.3 Hz, 2H), 7.04 (tt, $^3J_{HH}$ = 7.3, $^5J_{HH}$ = 1.1 Hz, 1H), 3.55 (hept, $^3J_{HH}$ = 6.8 Hz, 1H), 1.80 (s, 30H), 1.36 (d, J = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, C$_6$D$_6$) δ 154.62, 144.75, 144.48, 129.04, 128.17, 122.18, 119.75, 29.00, 22.38, 11.39.

HRMS (EI/TOF) *m/z*: [M$^+$] calculated for C$_{36}$H$_{44}$O$_3$Zr, 520.2282; found, 520.2144.

Anal. Calcd. for C$_{31}$H$_{42}$OZr: C, 71.34; H, 8.11. Found: C, 70.04; H, 7.99. Repeated analysis of recrystallized samples were consistently low in carbon content.

Synthesis of dioxazirconacylcobutenes, Retro-[4+2]-cycloaddition yields and characterization of products.

As the dioxazirconacyclohexenes are susceptible to hydrolysis if exposed to air, protic solvents or silica gel, NMR yields of the crude reactions were instead collected as to not artificially increase isolated yields by hydrolyzing unreacted **3a-k or 7b-f**. This artificial increase was also observed when attempting to collect GC yields of crude reaction mixtures (Table 7). Authentic products were either synthesized via aldol condensation (General procedure A described below), or by subjecting the appropriate dioxazirconacyclobutene to silica gel chromatography when the appropriate starting materials for the aldol condensation were not easily accessible. However, this procedure typically led to significant hydrolysis of the formed β-hydroxy ketone. Yields were determined by collecting an NMR after adding internal standard to determine the amount of starting material relative to internal standard. The internal standard integration was then used and compared to a relevant product peak to determine the yield.

Table 7: Comparison of NMR and GC yields for Select Substrates.[a]

Starting Metallocycle	NMR Yield (%)	Remaining Starting Material (%)	GC Yield (%)
3a	64	9	70
3d	66	0	67
8b	58	11	73

[a]See procedure below for reaction conditions. Reactions were conducted on 0.050 mmol, NMR yields were determined by comparison to 1,3,5-trimethoxybenene. GC yields were determined by comparison to 1-methylnaphthalene. GC samples were prepared in a nitrogen filled glove box in screw cap GC vials and run immediately after being removed from the glove box.

General procedure for aldehyde insertion and retro-[4+2]-cycloaddition

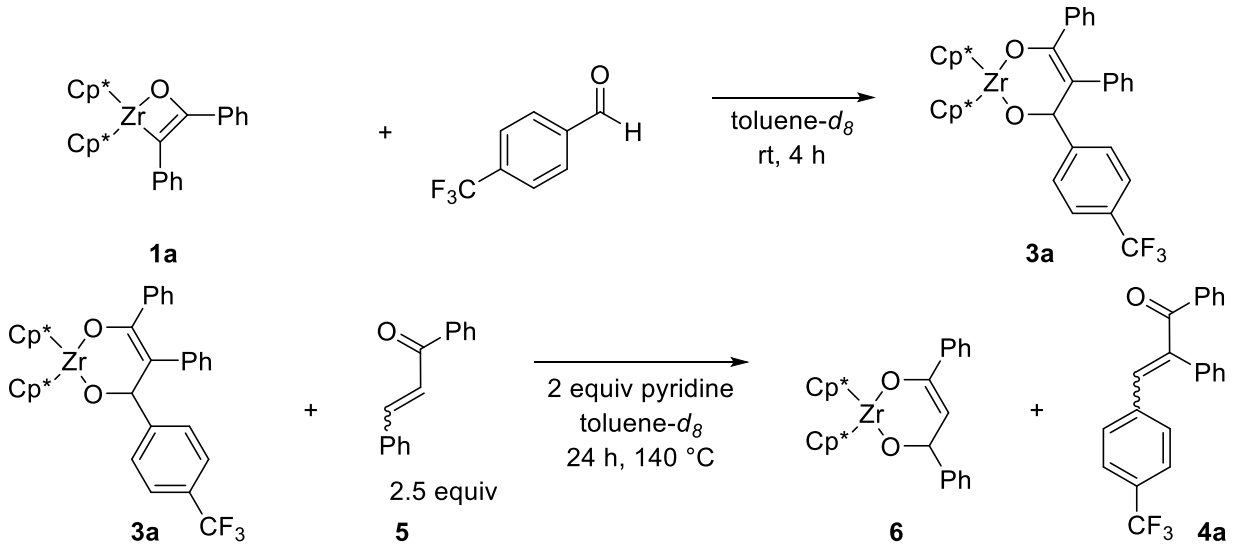
To a 4 mL scintillation vial was added oxazirconacyclobutene (**1a-f**) (0.050 mmol, 1.0 equiv) and aldehyde (0.50 mmol, 1.0 equiv) (if solid). Next 500 μL of toluene-d_8 was added followed by aldehyde (0.050 mmol, 1.0 equiv) (if liquid). The vial was capped and shaken until all solids were dissolved. The vial was left to react at rt for 4 h and then transferred to a screw capped NMR tube. The vial was rinsed with an additional 300 μL of toluene-d_8 and transferred to the NMR tube. A Teflon lined cap was affixed and the aldehyde insertion completion was confirmed by ^{1}H NMR. The NMR tube was returned to the glove box and chalcone (26 mg, 0.13 mmol, 2.5 equiv) was added followed by pyridine (8.1 μL, 0.10 mmol, 2.0 equiv) and the internal standard 1, 3, 5-trimethoxybenzene (8.4 mg, 0.050 mmol). The Teflon cap was affixed and the NMR tube was removed from the glovebox and placed in an oil bath heated to 140 °C for 24 h.

General Procedure (A): Synthesis of Authentic α,β-Unsaturated Carbonyl Compounds

To a 25 mL round bottom was added deoxybenzoin (490 mg, 2.5 mmol, 1.0 equiv), the appropriate aldehyde (2.5 mmol, 1.0 equiv), and benzene (9.0 mL, 2.8 M). Next glacial acetic acid (0.14 mL, 2.5 mmol, 1.0 equiv) and piperidine (0.050 mL, 0.5 mmol, 0.20 equiv) were added. A reflux condenser was attached and the solution was heated to reflux in an oil bath for 24 h. The solution was reduced to an oil and recrystallized from hexane yielding a white or yellow solid.

General Procedure (B): Racemization of α,β-Unsaturated Carbonyl Compounds

Occasionally only a single diastereomer was obtained from general procedure A and was racemized to a mixture of diastereomers using the following procedure: To a screw capped NMR tube was added α,β- unsaturated carbonyl (0.15 mmol, 1.0 equiv) followed by Cp*$_2$Zr(O)pyr (20 mg, 0.030 mmol, 0.010 equiv) and toluene-d_8 (0.5 mL). A Teflon lined cap was affixed to the NMR tube and it was reacted at room temperature until all Cp*$_2$Zr(O)pyr was consumed by NMR. The tube was then heated in an oil bath to 100 °C for 48 h. The NMR tube was then returned to the glove box and excess pyridine hydrochloride (20 mg, 0.17 mmol) was added. The solution was then directly loaded onto a silica gel column and the product was eluted with 10 % ethyl acetate in hexane.



Cp*$_2$Zr(O-C(Ph)=C(Ph)-CH((4-CF$_3$)C6H4)-O) (3a and 4a). **1a** 27.8 mg, 4-trifluoromethylbenzaldehyde 6.8 μL. C_6F_6 (10 μL, 0.086 mmol) was added in addition to 1,3,5-trimethoxybenene as an internal standard. C_6F_6 was used to determine the yield of **4a** and 1,3,5-trimethoxybenene was used to determine the yield of **6**. The NMR yield of **4a** was 64% (1.5:1 dr) and the NMR yield of **6** was 32% which was determined by comparison to internal standard.

An authentic sample of **4a** was obtained by general procedure B.

Characterization data for 3a

^{1}H NMR (500 MHz, C_6D_6) δ 7.46 (dd, $^3J_{HH}$ = 8.3, $^5J_{HH}$ = 1.4 Hz, 2H), 7.33 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.28 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.03 (dd, $^3J_{HH}$ = 8.3, $^3J_{HH}$ = 7.2 Hz, 2H), 6.93 – 6.85 (m, 3H), 6.81 (dd, $^3J_{HH}$ = 8.3, $^3J_{HH}$ = 6.9 Hz, 2H), 6.73 (tt, $^3J_{HH}$ = 7.3, $^5J_{HH}$ = 1.4 Hz, 1H), 6.54 (s, 1H), 1.87 (s, 15H), 1.79 (s, 15H).

^{13}C NMR (126 MHz, C_6D_6) δ 157.69, 150.81, 143.32, 140.90, 131.94, 129.65, 129.21, 128.42 (q, $^2J_{CF}$ = 32.3 Hz), 127.42, 126.58, 125.08 (q, $^1J_{CF}$ = 273.1 Hz), 125.43, 124.53 (q, $^3J_{CF}$ = 3.7 Hz), 121.56, 121.40, 113.21, 84.01, 11.35, 11.18. One sp^2 resonance was not located.

^{19}F NMR (470 MHz, C_6D_6) δ -62.20.

HRMS (EI/TOF) *m/z*: [M$^+$] calculated for $C_{36}H_{44}O_3Zr$, 728.2419; found, 728.2419.

Anal. Calcd. for $C_{42}H_{45}F_3O_2Zr$: C, 69.10; H, 6.21. Found: C, 67.96; H, 6.13. Repeated analysis of recrystallized samples were consistently low in carbon content.

Characterization data for 4a

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H, minor diastereomer), 7.97 (dd, $^3J_{HH}$ = 8.3, $^5J_{HH}$ = 1.4 Hz, 2H, minor diastereomer), 7.88 (dd, $^3J_{HH}$ = 8.3, $^5J_{HH}$ = 1.4 Hz, 2H), 7.56 (tt, $^3J_{HH}$ = 7.4, $^5J_{HH}$ = 1.2 Hz, 1H), 7.51 – 7.41 (m, 4H), 7.40 – 7.31 (m, 3H), 7.29 – 7.24 (m, 2H), 7.20 (dd, $^3J_{HH}$ = 9.4, $^5J_{HH}$ = 1.9 Hz, 3H).

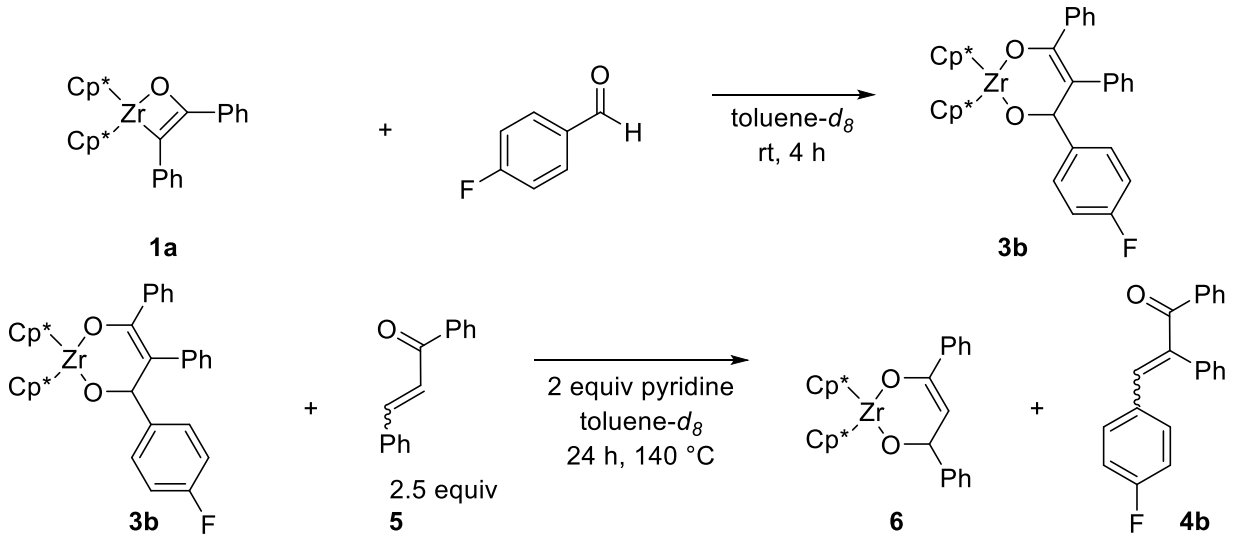
^{1}H NMR (499 MHz, Toluene-d_8) δ 7.95 (dd, $^3J_{HH}$ = 8.3, $^5J_{HH}$ = 1.5 Hz, 2H, minor diastereomer), 7.85 (dd, $^3J_{HH}$ = 8.3, $^5J_{HH}$ = 1.4 Hz, 2H), 7.37 (dd, $^3J_{HH}$ = 8.0, $^5J_{HH}$ = 1.7 Hz, 2H, minor diastereomer), 7.22 – 7.00 (m, 11H), 6.98 – 6.91 (m, 2H, minor diastereomer), 6.90 (s, 1H), 6.81 (s, 1H, minor diastereomer), 6.78 (d, $^3J_{HH}$ = 8.1 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.22, 143.03, 138.57, 137.63, 137.15, 135.86, 134.15, 132.73, 130.41 (d, $^2J_{CF}$ = 32.7 Hz), 130.44, 129.99, 129.80, 129.58, 129.11, 129.05, 128.87, 128.55, 128.50, 128.34, 126.53, 125.55 (q, $^3J_{CF}$ = 3.9 Hz, minor diastereomer), 125.29 (q, $^3J_{CF}$ = 3.8 Hz), 123.98 (d, $^1J_{CF}$ = 273.0 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ -63.13, -63.22.

^{19}F NMR (470 MHz, toluene-d_8) δ -62.99, -63.07.

HRMS (ESI/TOF) *m/z*: [M+H$^+$] calculated for $C_{22}H_{16}F_3O$, 353.1153; found, 353.1151.



Cp*$_2$Zr(O-C(Ph)=C(Ph)-CH((4-F)C$_6$H$_4$)-O) (3b and 4b). **1a** 27.8 mg, 4-Fluorobenzaldehdye 5.36 μL. C_6F_6 (10 μL, 0.086 mmol) was added in addition to 1, 3, 5-trimethoxybenzene as an internal standard. C_6F_6 was used to determine the yield of **4b** and 1, 3, 5-trimethoxybenzene was used to determine the yield of **6**. The NMR yield of **4b** was 56% (1.4:1 dr) and the NMR yield of **6** was 34% which was determined by comparison to internal standard.

An authentic sample of **4b** was obtained from general procedure A.

Characterization data for 3b

^{1}H NMR (499 MHz, C_6H_6) δ 7.53 (d, $^3J_{HH}$ = 7.4 Hz, 2H), 7.28 (dd, $^3J_{HH}$ = 8.5, $^5J_{HF}$ = 5.7 Hz, 2H), 7.08 (t, $^3J_{HH}$ = 7.7 Hz, 2H), 7.01 – 6.93 (m, 3H), 6.90 (dd, $^3J_{HF}$ = 8.3, $^3J_{HH}$ = 6.9 Hz, 2H), 6.82 – 6.74 (m, 3H), 6.61 (s, 1H), 1.92 (s, 15H), 1.84 (s, 15H).

^{13}C NMR (126 MHz, C_6D_6) δ 161.81 (d, $^1J_{CF}$ = 243.6 Hz), 157.15, 143.62, 142.30 (d, $^4J_{CF}$ = 3.0 Hz), 141.46, 131.91, 130.69 (d, $^3J_{CF}$ = 7.7 Hz), 129.78, 129.23, 127.39, 126.48, 125.25, 121.41, 121.30, 114.33 (d, $^2J_{CF}$ = 21.0 Hz), 113.71, 84.36, 11.37, 11.22.

^{19}F NMR (470 MHz, C_6D_6) δ -117.18.

Characterization for 4b

^{1}H NMR (499 MHz, $CDCl_3$) δ 8.01 (dd, $^3J_{HF}$ = 8.3, $^5J_{HH}$ = 1.4 Hz, 2H, minor diastereomer), 7.88 (dd, $^3J_{HF}$ = 8.3, $^5J_{HF}$ 1.4 Hz, 2H), 7.54 (tt, $^3J_{HH}$ = 7.5, $^5J_{HH}$ = 1.1 Hz, 2H), 7.52 – 7.43 (m, 6H), 7.42

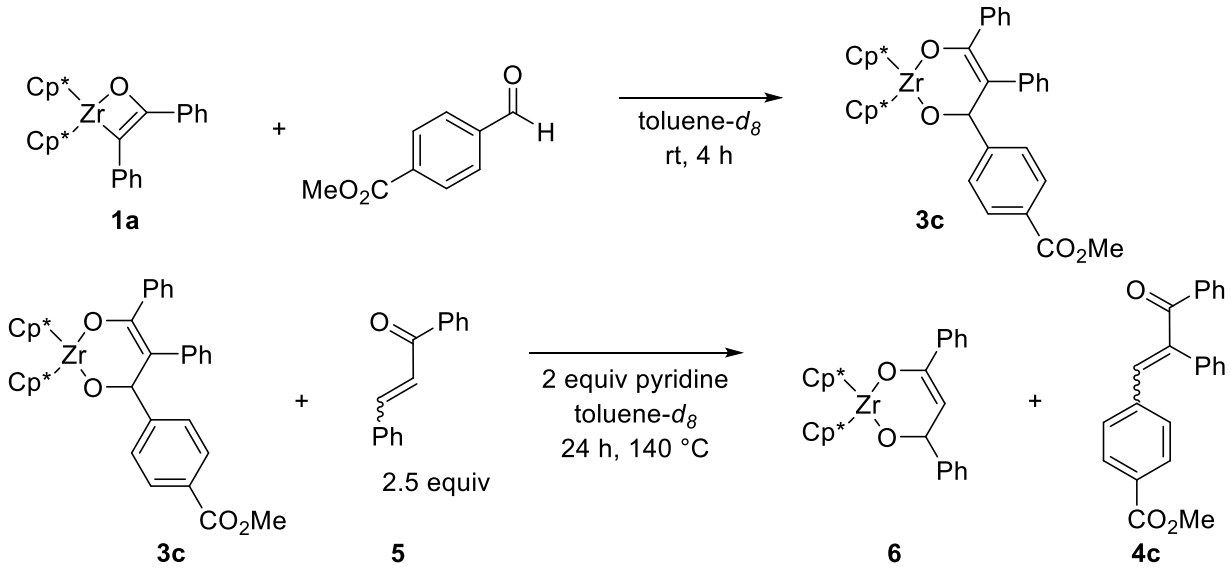
– 7.27 (m, 11H), 7.24 (s, 1H), 7.18 (s, 1H, minor diastereomer), 7.09 (dd, $^{3}J_{HH}$ = 8.7, $^{5}J_{HF}$ 5.6 Hz, 2H), 6.88 (td, $^{3}J_{HH}$ = 8.7, $^{5}J_{HH}$ = 1.8 Hz, 3H).

^{1}H NMR (499 MHz, toluene-d_8) δ 7.97 (dd, J = 8.3, 1.3 Hz, 2H, minor diastereomer), 7.83 (dd, J = 8.3, 1.4 Hz, 2H), 7.39 (dd, $^{3}J_{HF}$ = 8.2, $^{5}J_{HH}$ = 1.4 Hz, 2H, minor diastereomer), 7.21 (dd, $^{3}J_{HF}$ = 8.3, $^{5}J_{HH}$ = 1.6 Hz, 2H), 7.17 – 7.04 (m, 12H), 7.00 (s, 1H), 6.98 – 6.90 (m, 2H), 6.85 (s, 1H, minor diastereomer), 6.72 (dd, $^{3}J_{HH}$ = 8.6, $^{5}J_{HF}$ = 5.6 Hz, 2H), 6.55 – 6.44 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.31, 197.40, 162.84 (d, $^{1}J_{CF}$ = 250.6 Hz), 162.34 (d, $^{1}J_{CF}$ = 249.1 Hz), 140.87, 140.67, 138.90, 138.17, 137.90, 136.37, 136.31, 133.86, 132.31 (d, $^{3}J_{CF}$ = 8.6 Hz), 132.26, 131.73 (d, $^{4}J_{CF}$ = 3.4 Hz), 131.00 (d, $^{4}J_{CF}$ = 3.4 Hz), 130.63 (d, $^{3}J_{CF}$ = 8.3 Hz), 129.81, 129.73, 129.69, 128.99, 128.97, 128.88, 128.38, 128.36, 128.13, 126.39, 115.56 (d, $^{2}J_{CF}$ = 21.6 Hz), 115.45 (d, $^{2}J_{CF}$ = 21.5 Hz).

^{19}F NMR (470 MHz, toluene-d_8) δ -111.85, -113.31.

HRMS (ESI/TOF) *m/z*: [M+H$^+$] calculated for $C_{21}H_{16}FO$, 303.1185; found, 303.1180.



Cp*$_2$Zr(O-C(Ph)=C(Ph)-CH((4-C(O)OMe)C$_6$H$_4$)-O) (3c and 4c). **1a** 27.8 mg, methyl-(4-formyl)-benzoate 8.2 mg. The NMR yield of **4c** was 64% (1.8:1 dr) and the NMR yield of **6** was 28% which was determined by comparison to 1, 3, 5-trimethoxybenzene as an internal standard.

Authentic sample of **3c** was obtained by general procedure B.

Characterization data for 3c

^{1}H NMR (499 MHz, C_6D_6) δ 8.08 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H), 7.52 (dd, $^{3}J_{HH}$ = 8.2, $^{5}J_{HH}$ 1.4 Hz, 2H), 7.46 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H), 7.07 (dd, $^{3}J_{HH}$ = 8.3, $^{3}J_{HH}$ = 7.1 Hz, 2H), 6.98 (dd, $^{3}J_{HH}$ = 8.1, $^{5}J_{HH}$ = 1.3 Hz, 2H), 6.95 (tt, $^{3}J_{HH}$ = 7.3, $^{5}J_{HH}$ = 1.4 Hz, 1H), 6.87 (dd, $^{3}J_{HH}$ = 8.4, $^{3}J_{HH}$ = 6.9 Hz, 2H), 6.77 (tt, $^{3}J_{HH}$ = 7.4, $^{5}J_{HH}$ = 1.1 Hz, 1H), 6.65 (s, 1H), 3.42 (s, 3H), 1.91 (s, 15H), 1.83 (s, 15H).

^{13}C NMR (126 MHz, C_6D_6) δ 166.69, 157.45, 151.70, 143.46, 141.14, 131.93, 129.73, 129.22, 129.15, 128.71, 127.40, 126.52, 125.35, 121.53, 121.36, 120.17, 113.35, 84.50, 51.25, 11.38, 11.20.

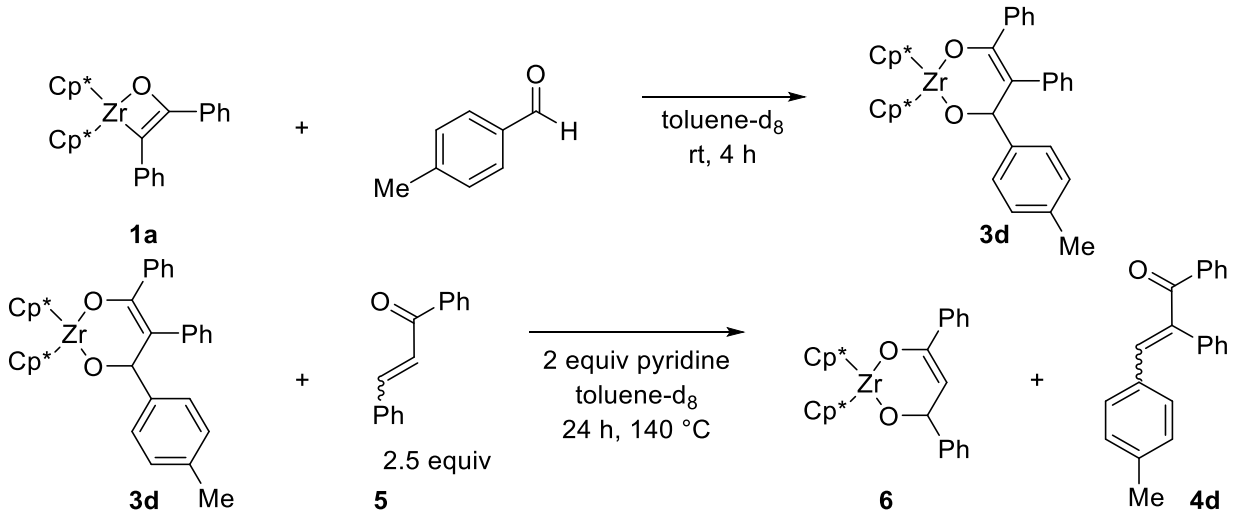
Characterization data for 4c

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, $^{3}J_{HH}$ = 8.3, $^{5}J_{HH}$ = 1.2 Hz, 2H, minor diastereomer), 7.93 (dd, $^{3}J_{HH}$ = 8.2, $^{5}J_{HH}$ = 1.4 Hz, 2H), 7.90 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H), 7.61 (tt, $^{3}J_{HH}$ = 7.5, $^{5}J_{HH}$ = 1.2 Hz, 1H), 7.51 (dd, $^{3}J_{HH}$ = 8.4, $^{3}J_{HH}$ = 7.1 Hz, 2H), 7.45 – 7.36 (m, 4H), 7.34 – 7.30 (m, 2H), 7.21 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H), 3.93 (s, 3H), 3.91 (s, 3H, minor diastereomer).

^{1}H NMR (499 MHz, toluene-*d*$_8$) δ 7.96 (dd, $^{3}J_{HH}$ = 8.3, $^{5}J_{HH}$ = 1.6 Hz, 2H, minor diastereomer), 7.86 (dd, $^{3}J_{HH}$ = 8.3, $^{5}J_{HH}$ = 1.5 Hz, 2H), 7.79 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H), 7.39 (dd, $^{3}J_{HH}$ = 8.2, $^{5}J_{HH}$ = 1.4 Hz, 2H, minor diastereomer), 7.21 (dd, $^{3}J_{HH}$ = 7.5, $^{5}J_{HH}$ = 2.0 Hz, 2H), 7.15 – 7.01 (m, 6H), 6.88 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H), 3.46 (s, 3H), 3.42 (s, 3H, minor diastereomer).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.33, 166.67, 142.89, 139.56, 137.86, 137.73, 136.00, 134.07, 132.65, 130.18, 130.00, 129.98, 129.84, 129.79, 129.63, 129.54, 129.09, 129.02, 128.98, 128.80, 128.52, 128.41, 126.55, 52.31, 52.23.

HRMS (ESI/TOF) *m/z*: [M+H$^+$] calculated for $C_{23}H_{19}O_3$, 343.1334; found, 343.1339.



Cp*$_2$Zr(O-C(Ph)=C(Ph)-CH((4-Me)C$_6$H$_4$)-O) (3d and 4d): **1a** 27.8 mg, 4-tolualdehyde 5.89 μL.

An authentic sample of **4d** was obtained by general procedure A. The NMR yield of **4d** was 82% (dr not determined due to coincidental peaks in the ^{1}H NMR) and the NMR yield of **6** was 57% which was determined by comparison to internal standard.

Characterization data for 4d:

^{1}H NMR (499 MHz, C_6D_6) δ 7.57 (dd, $^3J_{HH}$ = 8.0, $^5J_{HH}$ = 1.4 Hz, 2H), 7.41 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 7.13 – 7.06 (m, 4H), 6.99 – 6.93 (m, 3H), 6.91 (t, $^3J_{HH}$ = 7.7 Hz, 2H), 6.78 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 6.72 (s, 1H), 2.04 (s, 3H), 1.95 (s, 15H), 1.88 (s, 15H).

^{13}C NMR (126 MHz, C_6D_6) δ 156.88, 143.90, 143.43, 141.81, 135.49, 132.00, 129.89, 129.44, 128.39, 127.68, 127.36, 126.35, 125.13, 121.31, 121.19, 114.05, 85.23, 21.09, 11.42, 11.25.

^{1}H and ^{13}C NMR matched previously reported spectra.[10]

Characterization data for 4d:

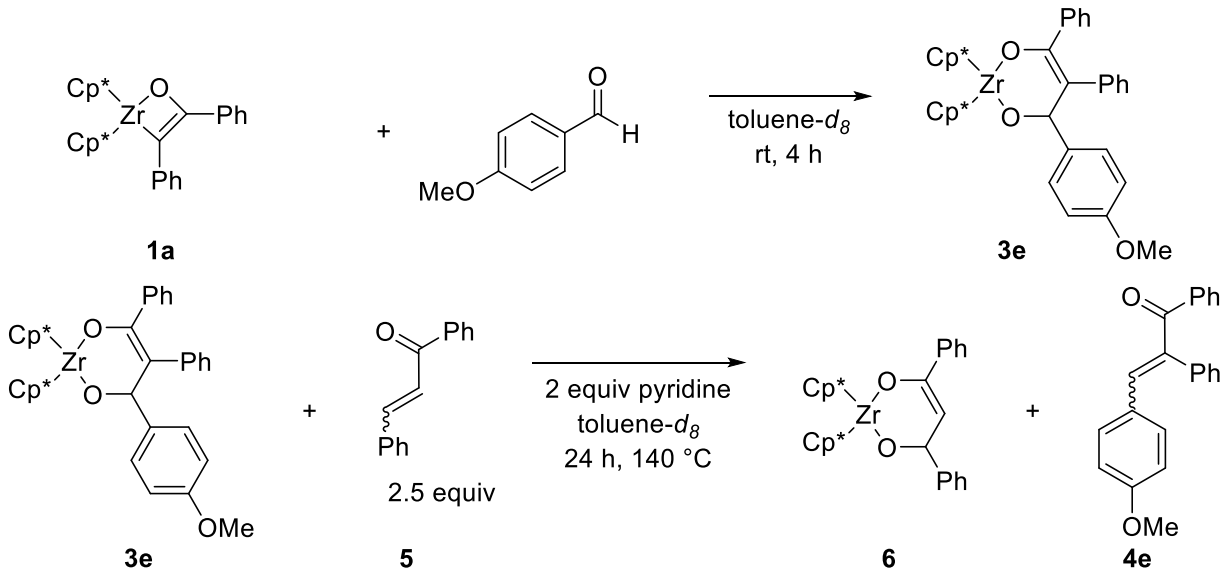
^{1}H NMR (499 MHz, $CDCl_3$) δ 7.85 (dd, $^{3}J_{HH}$ = 8.3, $^{5}J_{HH}$ = 1.4 Hz, 2H), 7.54 (tt, $^{3}J_{HH}$ = 7.3, $^{5}J_{HH}$ = 1.4 Hz, 1H), 7.45 (dd, $^{3}J_{HH}$ = 8.2, $^{3}J_{HH}$ = 6.9 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.32 – 7.28 (m, 2H), 7.25 (s, 1H), 7.03 – 6.94 (m, 4H), 2.29 (s, 3H).

^{1}H NMR (499 MHz, toluene-d_8) δ 7.86 (dd, $^{3}J_{HH}$ = 8.3, $^{5}J_{HH}$ = 1.5 Hz, 2H), 7.30 (dd, $^{3}J_{HH}$ = 8.2, $^{5}J_{HH}$ = 1.7 Hz, 2H), 7.20 (s, 1H), 7.16 – 7.11 (m, 1H), 7.10 – 7.05 (m, 4H), 6.87 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H), 6.68 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H), 1.96 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.80, 140.95, 140.04, 139.48, 138.58, 136.91, 132.09, 132.03, 130.55, 129.85, 129.83, 129.15, 128.91, 128.36, 127.95, 21.47.

HRMS (ESI/TOF) *m/z*: [M+H^{+}] calculated for $C_{22}H_{19}O$, 299.1436; found, 299.1433.

^{1}H and ^{13}C NMR matched previously reported spectra[22]



Cp*$_2$Zr(O-C(Ph)=C(Ph)-CH((4-OMe)C$_6$H$_4$)-O) (3e and 4e): **1a** 27.8 mg, 4-anisaldehyde 6.07 μL. The NMR yield of **4e** was 99% (1.4:1 dr) and the NMR yield of **6** was 52% which was determined by comparison to 1, 3, 5-trimethoxybenzene as internal standard.

An authentic sample of **4e** was obtained by general procedure A.

Characterization data for 3e:

^{1}H NMR (499 MHz, C_6D_6) δ 7.57 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H), 7.40 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H), 7.14 – 7.05 (m, 4H), 6.99 – 6.89 (m, 3H), 6.80 (td, $^{3}J_{HH}$ = 7.4, $^{5}J_{HH}$ = 1.1 Hz, 1H), 6.75 – 6.73 (m, 1H), 6.72 (d, $^{3}J_{HH}$ = 5.0 Hz, 2H), 3.22 (s, 3H), 1.95 (s, 15H), 1.88 (s, 15H).

^{1}H NMR (499 MHz, C_6D_6) δ 7.57 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H), 7.40 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H), 7.13 – 7.07 (m, 4H), 6.97 (d, $^{3}J_{HH}$ = 7.7 Hz, $^{5}J_{HH}$ = 1H), 6.92 (t, $^{3}J_{HH}$ = 7.7 Hz, 2H), 6.80 (t, $^{3}J_{HH}$ = 7.9 Hz, 1H), 6.74 (s, 1H), 6.72 (d, $^{3}J_{HH}$ = 5.0 Hz, 2H), 3.22 (s, 3H), 1.95 (s, 15H), 1.88 (s, 15H).

^{13}C NMR (126 MHz, C_6D_6) δ 158.57, 156.78, 143.93, 141.92, 138.57, 131.96, 130.47, 129.91, 127.73, 127.37, 126.36, 125.13, 121.29, 121.19, 114.13, 113.14, 85.02, 54.52, 11.42, 11.26.

Characterization data for 4e:

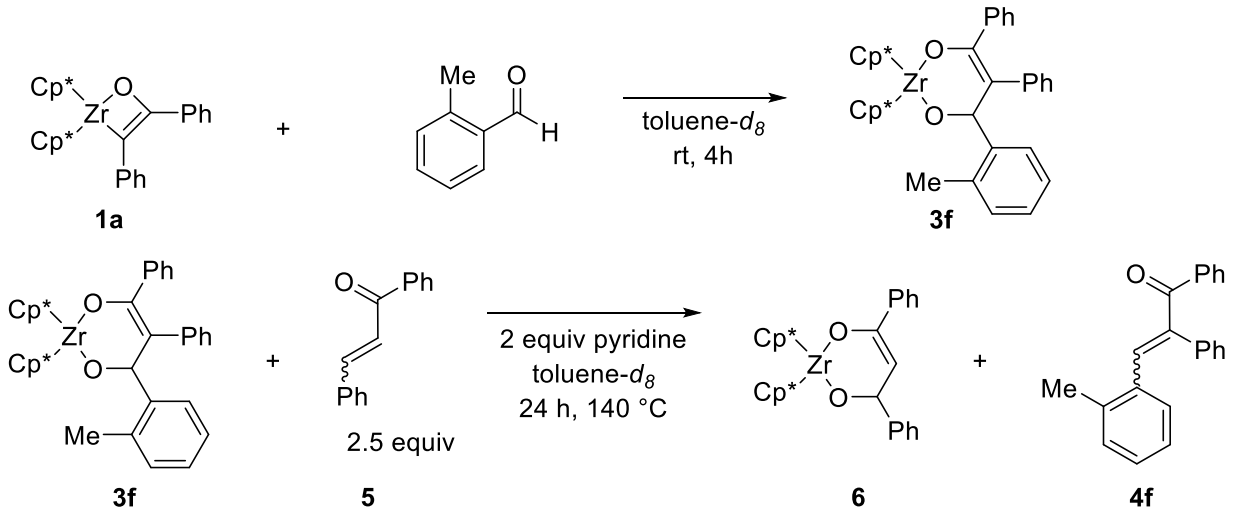
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 8.00 (m, 2H, minor diastereomer), 7.85 – 7.79 (m, 2H), 7.54 – 7.27 (m, 12H), 7.23 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H, minor diastereomer), 7.15 (s, 1H), 7.02 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.70 (m, 3H, major and minor diastereomer), 3.74 (s, 3H), 3.70 (s, 3H, minor diastereomer).

^{1}H NMR (500 MHz, toluene-d_8) δ 8.08 (dd, $^{3}J_{HH}$ = 8.1, $^{5}J_{HH}$ = 1.7 Hz, 2H, minor diastereomer), 7.85 (dd, $^{3}J_{HH}$ = 6.9, $^{5}J_{HH}$ = 1.1 Hz, 2H), 7.43 (dd, $^{3}J_{HH}$ = 7.1, $^{5}J_{HH}$ 1.6 Hz, 2H, minor diastereomer), 7.33 (dd, $^{3}J_{HH}$ = 6.9, $^{5}J_{HH}$ 1.5 Hz, 2H), 7.26 – 7.21 (m, 2H), 7.18 – 7.12 (m, 2H), 7.09 – 7.04 (m, 3H), 6.98 – 6.92 (m, 2H, minor diastereomer), 6.89 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 6.47 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H, minor diastereomer), 6.43 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 3.15 (s, 3H), 3.12 (s, 3H, minor diastereomer).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.92, 197.79, 160.39, 159.44, 141.38, 138.78, 138.74, 138.32, 137.05, 136.48, 133.72, 132.31, 131.86, 130.41, 129.84, 129.80, 129.71, 128.95, 128.90, 128.85, 128.29, 128.16, 127.97, 127.87, 127.30, 126.29, 113.98, 113.83, 55.31, 55.24.

HRMS (ESI/TOF) *m/z*: [M+H$^+$] calculated for $C_{22}H_{19}O_2$, 315.1385; found, 315.1378.

^{1}H and ^{13}C NMR matched previously reported spectra[23]



Cp*$_2$Zr(O-C(Ph)=C(Ph)-CH((2-Me)C$_6$H$_4$)-O) (3f and 4f): **1a** 27.8 mg, 2-tolualdehyde 9.3 μL (1.6 eq)

An authentic sample of **4f** was obtained by general procedure A. The NMR yield of **4f** was 91% (1.1:1 dr) and the NMR yield of **6** was 40% which was determined by comparison to 1, 3, 5-trimethoxybenzene as internal standard.

Characterization data for 3f:

^{1}H NMR (500 MHz, C_6D_6) δ 7.50 (dd, $^3J_{HH}$ = 8.0, $^5J_{HH}$ = 1.6 Hz, 2H), 7.19 – 7.07 (m, 4H), 7.05 (t, $^3J_{HH}$ = 7.7 Hz, 3H), 6.96 – 6.83 (m, 5H), 6.74 (tt, $^3J_{HH}$ = 7.5, $^5J_{HH}$ = 1.3 Hz, 1H), 2.37 (s, 3H), 1.89 (s, 15H), 1.78 (s, 15H).

^{13}C NMR (126 MHz, C_6D_6) δ 157.35, 143.91, 143.75, 141.51, 136.75, 131.70, 130.18, 129.97, 129.46, 127.69, 127.35, 126.81, 126.39, 125.20, 121.36, 121.20, 114.12, 81.88, 19.51, 11.24, 11.17. One sp^2 resonance not located

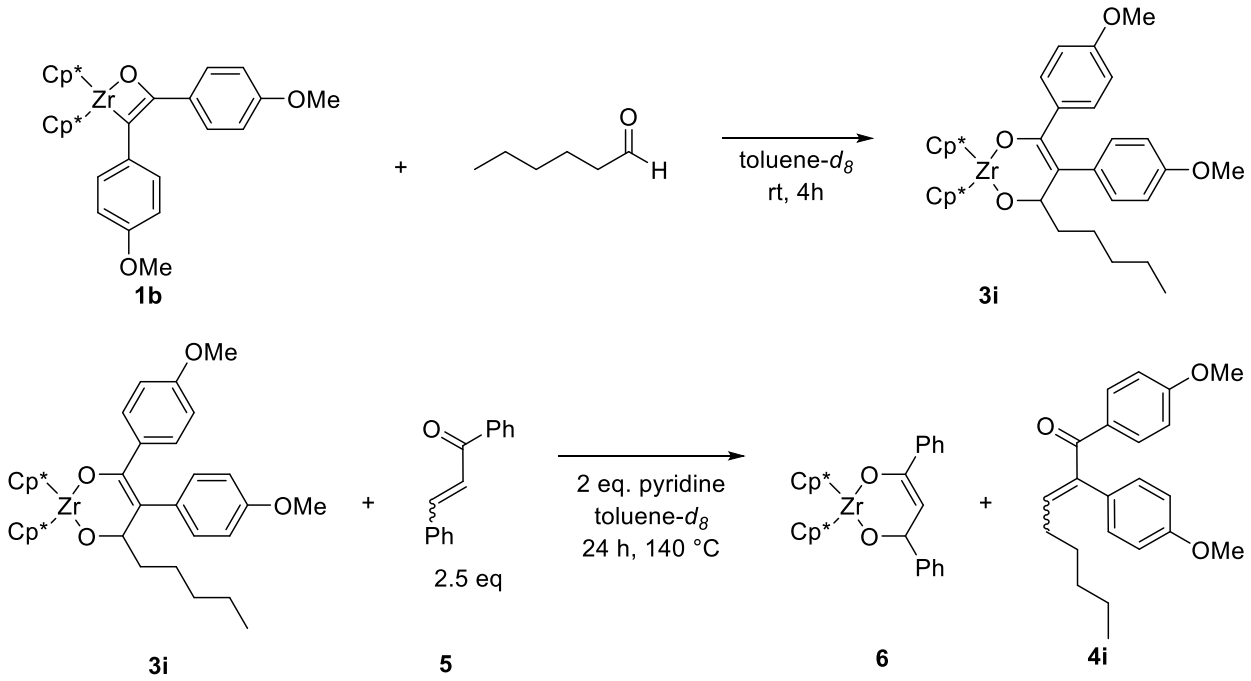
Characterization data for 4f

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.90 (dd, $^3J_{HH}$ = 8.3, $^5J_{HH}$ = 1.4 Hz, 2H), 7.53 (tt, $^3J_{HH}$ = 7.2, $^5J_{HH}$ = 1.6 Hz, 1H), 7.44 (dd, $^3J_{HH}$ = 8.4, $^3J_{HH}$ = 7.1 Hz, 2H), 7.33 (s, 1H), 7.24 (dd, $^3J_{HH}$ = 5.2, $^5J_{HH}$ = 2.1 Hz, 3H), 7.20 – 7.11 (m, 4H), 6.93 (dd, $^3J_{HH}$ = 4.5, $^5J_{HH}$ 1.4 Hz, 2H), 2.40 (s, 3H, minor diastereomer), 2.29 (s, 3H).

^{1}H NMR (499 MHz, toluene-d_8) δ 7.88 (dd, $^{3}J_{HH}$ = 8.2, $^{5}J_{HH}$ 1.5 Hz, 2H), 7.42 (dd, $^{3}J_{HH}$ = 8.1, $^{5}J_{HH}$ = 1.6 Hz, 2H, minor diastereomer), 7.35 (d, $^{3}J_{HH}$ = 7.4 Hz, 2H, minor diastereomer), 7.22 (s, 1H), 7.20 (dd, $^{3}J_{HH}$ = 7.9, $^{5}J_{HH}$ 1.7 Hz, 2H), 7.15 (s, 1H, minor diastereomer), 7.06 – 7.00 (m, 4H), 6.94 – 6.83 (m, 5H), 6.76 – 6.75 (m, 2H, minor diastereomer), 6.73 – 6.64 (m, 1H), 2.09 (s, 3H, minor diastereomer), 1.98 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.84, 141.65, 138.19, 138.12, 137.30, 136.31, 134.62, 132.52, 130.26, 130.05, 129.99, 129.80, 129.48, 128.99, 128.53, 128.42, 127.85, 126.79, 125.62, 20.25.

HRMS (ESI/TOF) *m/z*: [M+H^{+}] calculated for $C_{22}H_{19}O$, 299.1436; found, 299.1444.



Cp*$_2$Zr(O-C((4-OMe)C$_6$H$_4$)=((4-OMe)C$_6$H$_4$)-CH(*n*-C$_5$H$_{11}$)-O) (3h and 4h): **1b** 30.8 mg, *n*-hexanal 6.1 μL. The NMR yield of **4i** was 40% (1.4:1 dr) and the NMR yield of **6** was 18% which was determined by comparison to 1, 3, 5-trimethoxybenzene as internal standard.

An authentic sample of **4h** was obtained by subjecting 3h to silica chromatography eluting with 10% ethyl acetate in hexane.

Characterization data for 3h:

^{1}H NMR (499 MHz, C_6D_6) δ 7.47 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 7.13 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H), 6.73 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 6.66 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 5.50 (dd, $^{3}J_{HH}$ = 10.1, 2.7 Hz, 1H), 3.22 (s, 3H), 3.18 (s, 3H), 2.18 – 2.09 (m, 2H), 1.97 (s, 15H), 1.93 (s, 15H), 1.46 – 1.18 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, C_6D_6) δ 158.06, 157.96, 153.47, 136.88, 135.17, 132.79, 130.89, 120.70, 114.02, 113.81, 112.90, 83.39, 83.35, 54.49, 54.42, 54.39, 38.86, 32.48, 27.59, 14.43, 11.50, 11.18.

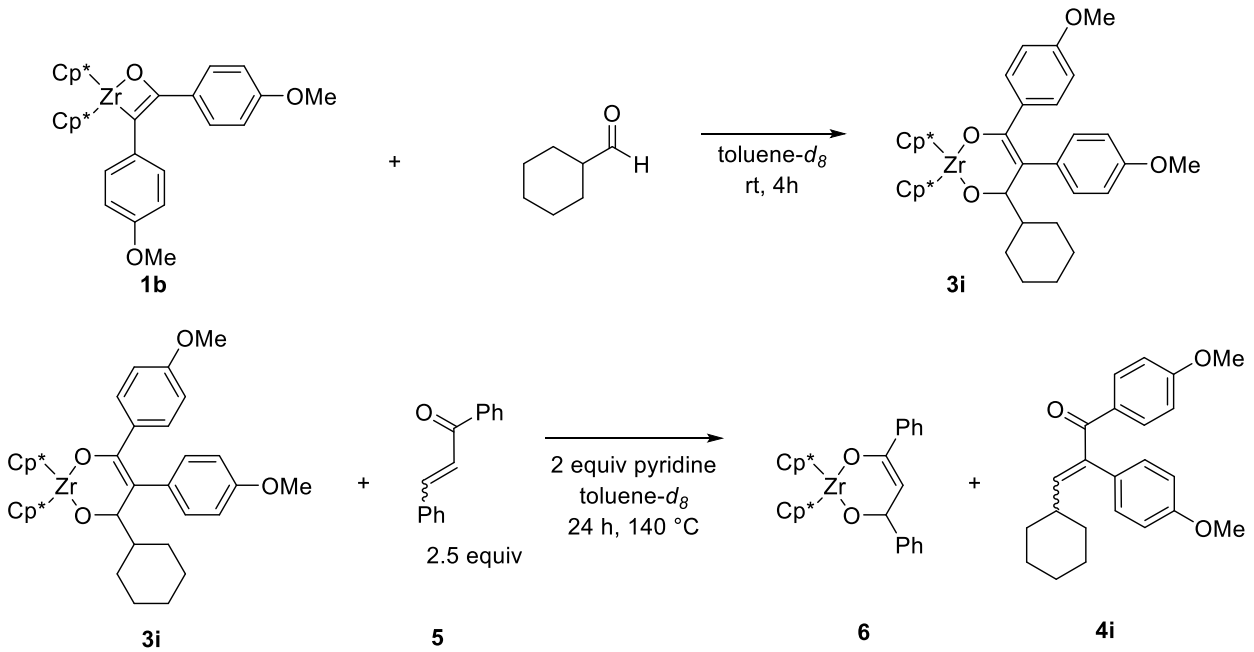
Characterization data for 4h:

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.94 (d, $^{3}J_{HH}$ = 8.9 Hz, 2H, minor diastereomer), 7.80 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 7.26 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H, minor diastereomer), 7.19 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 6.92 – 6.87 (m, 6H, overlapping major and minor diastereomer), 6.81 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H, minor diastereomer), 6.30 (t, $^{3}J_{HH}$ = 7.5 Hz, 1H), 6.11 (t, $^{3}J_{HH}$ = 7.7 Hz, 1H, minor diastereomer), 3.85 (s, 3H), 3.85 (s, 3H, minor diastereomer), 3.81 (s, 3H), 3.77 (s, 3H, minor diastereomer), 2.27 (q, $^{3}J_{HH}$ = 7.5 Hz, 2H), 2.05 (q, $^{3}J_{HH}$ = 7.5 Hz, 2H, minor diastereomer), 1.62 (m, 2H), 1.49 – 1.37 (m, 4H), 1.27 (m, 4H), 0.96 – 0.78 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.62, 163.08, 159.05, 142.03, 141.98, 141.22, 132.39, 131.11, 130.82, 129.07, 113.93, 113.64, 55.65, 55.61, 55.45, 55.40, 31.80, 29.63, 29.23, 22.68, 14.22 . One sp^2 resonance not located.

^{1}H NMR (499 MHz, toluene-d_8) δ 8.05 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H, minor diastereomer), 7.94 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 7.34 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H, minor diastereomer), 7.29 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 6.75 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 6.63 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H, minor diastereomer), 6.57 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.29 (t, $^{3}J_{HH}$ = 7.4 Hz, 1H), 6.03 (t, $^{3}J_{HH}$ = 7.7 Hz, 1H, minor diastereomer), 3.30 (s, 3H), 3.27 (s, 3H, minor diastereomer), 3.21 (s, 3H), 3.16 (s, 3H, minor diastereomer), 2.20 (q, $^{3}J_{HH}$ = 7.5 Hz, 2H), 2.13 (q, $^{3}J_{HH}$ = 7.5 Hz, 2H, minor diastereomer), 1.54 (m, 2H), 1.51 – 1.34 (m, 2H), 1.28 (m, 2H), 1.17 (m, 4H), 0.98 – 0.86 (m, 4H), 0.86 – 0.81 (m, 6H).

HRMS (ESI/TOF) *m/z*: [M+H$^+$] calculated for $C_{22}H_{27}O_3$, 339.1960; found, 339.1963.



Cp*$_2$Zr(O-C((4-OMe)C$_6$H$_4$)=((4-OMe)C$_6$H$_4$)-CH(*cy*-C$_6$H$_{11}$)-O) (3i and 4i): **7a** 30.8 mg, cyclohexanecarboxaldehyde 6.0 μL. The NMR yield of **4i** was 86% (1.3:1 dr) and the NMR yield of **6** was 59% which was determined by comparison to 1, 3, 5-trimethoxybenzene as internal standard.

An authentic sample of **4i** was obtained by subjecting **3i** to silica chromatography eluting with 10% ethyl acetate in hexane.

Characterization data for 3i:

^{1}H NMR (499 MHz, C_6D_6) δ 7.46 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 7.15 (dd, $^3J_{HH}$ = 8.7, 2H), 6.73 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 6.70 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 5.57 (d, $^3J_{HH}$ = 2.5 Hz, 2H), 3.24 (s, 3H), 3.20 (s, 3H), 2.07 (d, $^3J_{HH}$ = 2.5 Hz, 1H), 2.02 (s, 15H), 1.96 (s, 15H), 1.93 – 1.81 (m, 4H), 1.81 – 1.58 (m, 4H), 1.26 (s, 2H).

^{13}C NMR (126 MHz, C_6D_6) δ 158.03, 157.72, 156.10, 137.16, 135.04, 130.89, 120.93, 120.74, 113.44, 112.83, 112.09, 86.57, 54.46, 54.36, 43.29, 27.85, 27.54, 27.32, 27.13, 11.79, 11.43.

Characterization data for 4i:

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.95 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 7.25 (d, $^{3}J_{HH}$ = 8.9 Hz, 2H), 6.90 (d, $^{3}J_{HH}$ = 8.9 Hz, 2H), 6.81 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 5.94 (d, $^{3}J_{HH}$ = 10.3 Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 1.88 – 1.58 (m, 5H), 1.43 – 1.03 (m, 4H), 0.95 – 0.74 (m, 2H). (minor diastereomer)

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.81 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 7.20 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 6.91 (dd, $^{3}J_{HH}$ = 8.8, 4.8 Hz, 4H), 6.11 (d, $^{3}J_{HH}$ = 10.3 Hz, 1H), 3.86 (s, 4H), 3.83 (s, 4H), 2.52 – 2.30 (m, 1H), 1.79 – 1.66 (m, 7H), 1.33 – 1.12 (m, 8H), 0.92 – 0.76 (m, 3H). (major diastereomer)

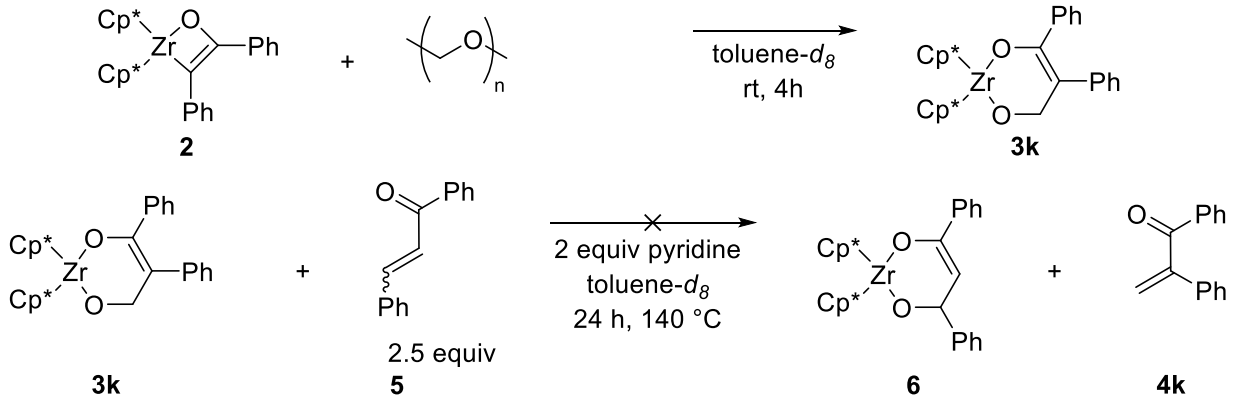
^{13}C NMR (126 MHz, $CDCl_3$) δ 197.65, 164.00, 159.34, 138.71, 135.39, 132.33, 130.35, 127.35, 114.30, 114.07, 55.71, 55.51, 39.01, 34.26, 33.15, 26.08, 25.70. (minor diastereomer)

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.87, 163.07, 159.05, 147.26, 139.13, 132.44, 131.19, 130.68, 129.35, 113.97, 113.62, 55.68, 55.49, 38.32, 32.85, 26.07, 25.56. (major diastereomer)

^{1}H NMR (499 MHz, toluene-d_8) δ 8.08 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 7.34 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.66 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.56 (d, $^{3}J_{HH}$ = 8.9 Hz, 2H), 5.94 (d, $^{3}J_{HH}$ = 10.2 Hz, 1H), 3.27 (s, 3H), 3.15 (s, 3H), 2.04 – 1.65 (m, 7H), 1.64 – 0.86 (m, 4H). (minor diastereomer)

^{1}H NMR (499 MHz, toluene-d_8) δ 7.97 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 7.33 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 6.76 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 6.66 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.15 (d, $^{3}J_{HH}$ = 10.3 Hz, 1H), 3.30 (s, 4H), 3.24 (s, 4H), 2.52 (d, $^{3}J_{HH}$ = 10.3, 1H), 1.78 – 1.44 (m, 6H), 1.15 – 0.93 (m, 4H). (major diastereomer)

HRMS (ESI/TOF) *m/z*: [M+H$^+$] calculated for $C_{23}H_{27}O_3$, 351.1960; found, 351.1962.



Cp*$_2$Zr(O-C(Ph)=C(Ph)-CH$_2$-O) (3k): **2** 27.8 mg, paraformaldehyde 1.5 mg.

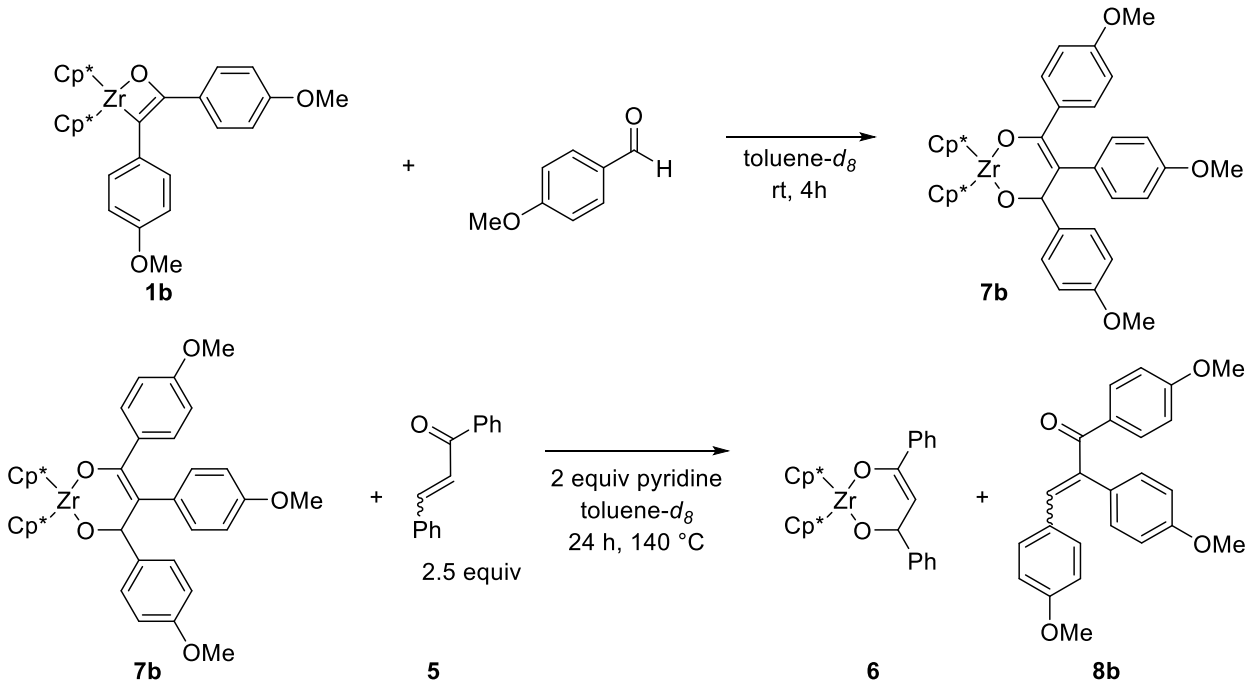
Characterization data for 3k:

^{1}H NMR (499 MHz, C_6D_6) δ 7.58 (dd, $^{3}J_{HH}$ = 8.3, $^{5}J_{HH}$ = 1.3 Hz, 2H), 7.25 (dd, $^{3}J_{HH}$ = 7.8, $^{5}J_{HH}$ = 1.5 Hz, 2H), 7.08 (dd, $^{3}J_{HH}$ = 8.2, $^{3}J_{HH}$ = 7.1 Hz, 4H), 7.00 (tt, $^{3}J_{HH}$ = 7.8, $^{5}J_{HH}$ = 1.1 Hz, 1H), 6.96 (tt, $^{3}J_{HH}$ = 7.4, $^{5}J_{HH}$ = 1.2 Hz, 1H), 5.31 (s, 2H), 1.91 (s, 30H).

^{13}C NMR (126 MHz, C_6D_6) δ 153.13, 143.09, 141.54, 131.32, 129.65, 128.45, 127.44, 126.42, 125.75, 120.89, 113.12, 76.17, 11.00.

^{1}H and ^{13}C NMR matched previously reported spectra.[10]

Subjecting **3k** to the standard retro-[4+2]-cycloaddition conditions did not lead to any product formation after heating to 140 °C for 24 h.



Cp*$_2$Zr(O-C((4-OMe)C$_6$H$_4$)=C((4-OMe)C$_6$H$_4$)-CH((4-OMe)C$_6$H$_4$)-O) (7b and 8b): **1b** 30.8 mg, 4-methoxybenzaldehyde 6.1 μL. The NMR yield of **8b** was 95% (1.7:1 dr) and the NMR yield of **6** was 55% which was determined by comparison to 1, 3, 5-trimethoxybenzene as internal standard.

An authentic sample of **8b** was obtained by subjecting 0.1 mmol of **7b** to silica gel chromatography eluting with 10 % ethyl acetate in hexane.

Characterization data for 7b

^{1}H NMR (499 MHz, C_6D_6) δ 7.55 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 7.45 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 7.07 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 6.77 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 6.72 (d, $^{3}J_{HH}$ = 8.9 Hz, 2H), 6.70 (s, 1H), 6.60 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 3.25 (s, 3H), 3.23 (s, 3H), 3.14 (s, 3H), 1.99 (s, 15H), 1.91 (s, 15H).

^{13}C NMR (126 MHz, C_6D_6) δ 158.57, 158.32, 157.50, 156.04, 138.92, 136.54, 134.27, 132.84, 130.97, 130.58, 121.19, 121.09, 113.49, 113.16, 112.91, 112.66, 85.31, 54.54, 54.49, 54.29, 11.45, 11.30.

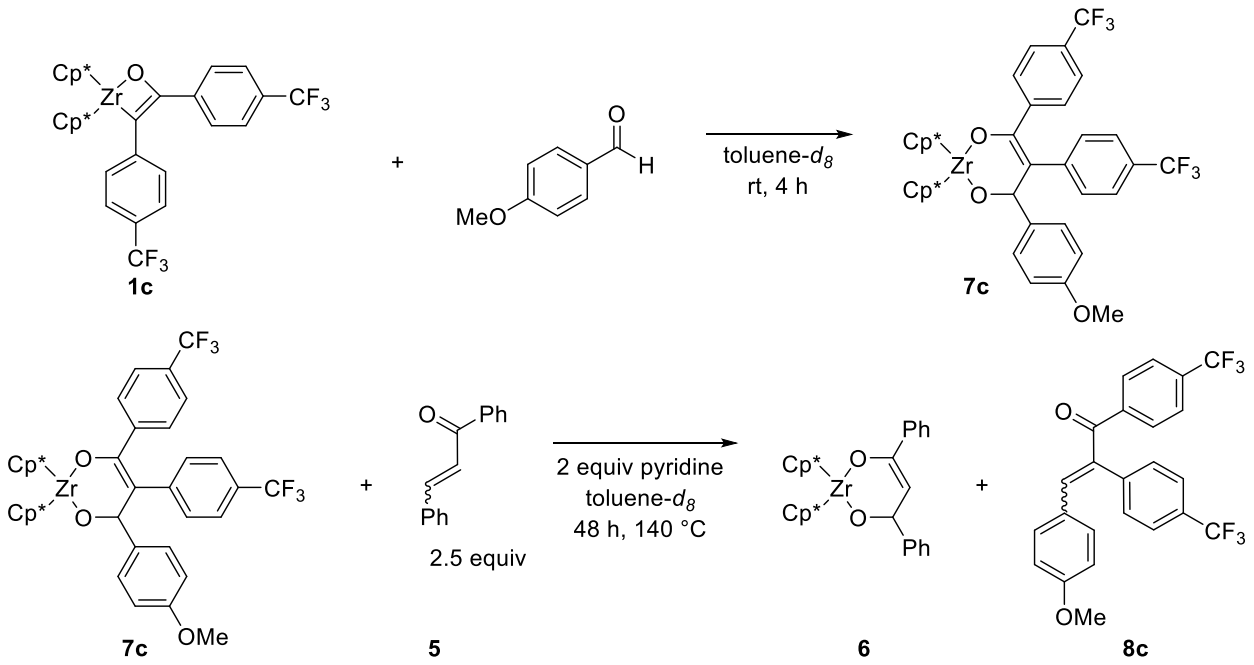
Characterization data for 8b

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.97 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 7.85 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 7.37 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 7.21 (t, $^{3}J_{HH}$ = 8.9 Hz, 4H), 7.11 (s, 1H), 7.08 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 7.01 (s, 1H), 6.94 – 6.82 (m, 8H), 6.73 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.71 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H).

^{1}H NMR (499 MHz, toluene-d_8) δ 8.11 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 7.96 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 7.44 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 7.33 (t, $^{3}J_{HH}$ = 8.6 Hz, 4H), 7.20 (s, 1H), 7.05 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.98 (s, 1H), 6.73 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 6.69 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.64 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 6.54 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 6.50 (d, $^{3}J_{HH}$ = 8.7 Hz, 4H), 3.29 (s, 6H), 3.23 (s, 3H), 3.20 (s, 3H), 3.15 (s, 3H), 3.08 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.66, 196.83, 164.04, 162.94, 160.05, 159.54, 159.27, 159.23, 138.78, 138.62, 138.34, 132.33, 132.26, 131.99, 1;31.21, 131.14, 131.05, 130.25, 129.81, 129.56, 128.63, 127.91, 127.53, 114.45, 114.35, 114.15, 114.01, 113.85, 113.61, 55.58 , 55.45, 55.37, 55.33.

HRMS (ESI/TOF) *m/z*: [M+H^{+}] calculated for $C_{24}H_{23}O_4$, 375.1596; found, 375.1591.



Cp*$_2$Zr(O-C((4-CF$_3$)C$_6$H$_4$)=C((4-OMe)C$_6$H$_4$)-CH((4-CF$_3$)C$_6$H$_4$)-O) (7c and 8c): **1c** 34.6 mg, 4-methoxybenzaldehyde 6.1 μL.

An authentic sample of **8c** was obtained by subjecting 0.05 mmol of **7c** to silica gel chromatography eluting with 10 % ethyl acetate in hexane.

Characterization data for 7c:

^{1}H NMR (499 MHz, C_6D_6) δ 7.37 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H), 7.25 (dd, $^{3}J_{HH}$ = 8.7, $^{5}J_{HH}$ = 2.1 Hz, 4H), 7.10 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H), 6.90 (dd, $^{3}J_{HH}$ = 8.5, $^{5}J_{HH}$ = 1.1 Hz, 2H), 6.72 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 6.59 (s, 1H), 3.22 (s, 3H), 1.89 (s, 15H), 1.82 (s, 15H).

^{13}C NMR (126 MHz, C_6D_6) δ 158.89, 156.54, 146.96, 145.46, 137.61, 131.90, 130.07, 129.99, 128.65 (q, $^{2}J_{CF}$ = 31.9 Hz), 127.38 (q, $^{2}J_{CF}$ = 32.5 Hz), 124.82 (q, $^{1}J_{CF}$ = 271.8 Hz), 124.67 (q, $^{3}J_{CF}$ = 3.6 Hz), 124.51 (q, $^{3}J_{CF}$ = 3.8 Hz), 121.66, 121.52, 114.65, 113.35, 84.28, 54.60, 11.35, 11.17. One CF_3 resonance not located

^{19}F NMR (470 MHz, toluene-*d*$_8$) δ -62.46, -62.56.

Characterization data for 8c:

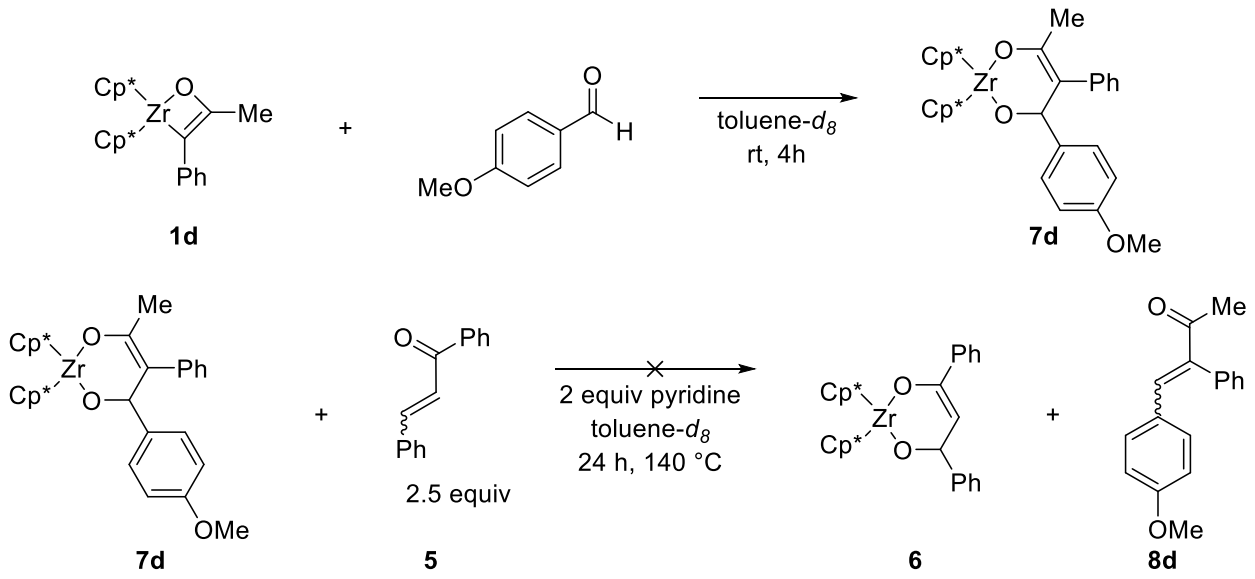
^{1}H NMR (499 MHz, $CDCl_3$) δ 8.06 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H), 7.88 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H), 7.80 – 7.71 (m, 2H), 7.68 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H), 7.63 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H), 7.60 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H), 7.52 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.33 (s, 1H), 7.28 (s, 1H), 7.21 (d, $^{3}J_{HH}$ = 8.7 Hz, 1H), 6.97 (dd, $^{3}J_{HH}$ = 9.3, $^{3}J_{HH}$ = 7.7 Hz, 3H), 6.74 (d, $^{3}J_{HH}$ = 3.3 Hz, 2H), 6.72 (d, $^{3}J_{HH}$ = 3.5 Hz, 2H), 3.78 (s, 3H), 3.74 (s, 3H).

^{1}H NMR (499 MHz, toluene-d_8) δ 7.83 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H), 7.55 (d, $^{3}J_{HH}$ = 8.0 Hz, 3H, overlapping major and minor diastereomer), 7.38 (d, $^{3}J_{HH}$ = 8.0 Hz, 3H, overlapping major and minor diastereomer), 7.29 (d, $^{3}J_{HH}$ = 8.1 Hz, 5H, overlapping major and minor diastereomer), 7.22 – 7.17 (m, 6H), 7.13 (d, $^{3}J_{HH}$ = 2.2 Hz, 2H), 7.06 (s, 1H), 6.93 (d, $^{3}J_{HH}$ = 7.3 Hz, 3H), 6.88 – 6.81 (m, 2H), 6.73 (d, $^{3}J_{HH}$ = 8.7 Hz, 3H, overlapping major and minor diastereomer), 6.47 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H, minor diastereomer), 6.38 (d, $^{3}J_{HH}$ = 8.6 Hz, 3H, overlapping major and minor diastereomer), 3.11 (s, 3H), 3.10 (s, 3H, minor diastereomer).

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.09, 161.24, 144.54, 141.93, 140.40, 136.85, 133.44 (q, $^{2}J_{CF}$ = 32.9 Hz), 132.71, 130.51, 130.08, 129.77, 128.97, 126.28, 126.06 (t, $^{3}J_{CF}$ = 4.2 Hz), 125.56 (q, $^{3}J_{CF}$ = 3.6 Hz), 124.23 (q, $^{1}J_{CF}$ =273.0 Hz), 123.81 ($^{1}J_{CF}$ = 273.0 Hz, 114.24, 55.50.

^{19}F NMR (470 MHz, toluene-d_8) δ -62.59, -62.73, -63.11, -63.45.

HRMS (ESI/TOF) *m/z*: [$M+H^+$] calculated for $C_{24}H_{17}F_6O_2$, 451.1133; found, 451.1137.



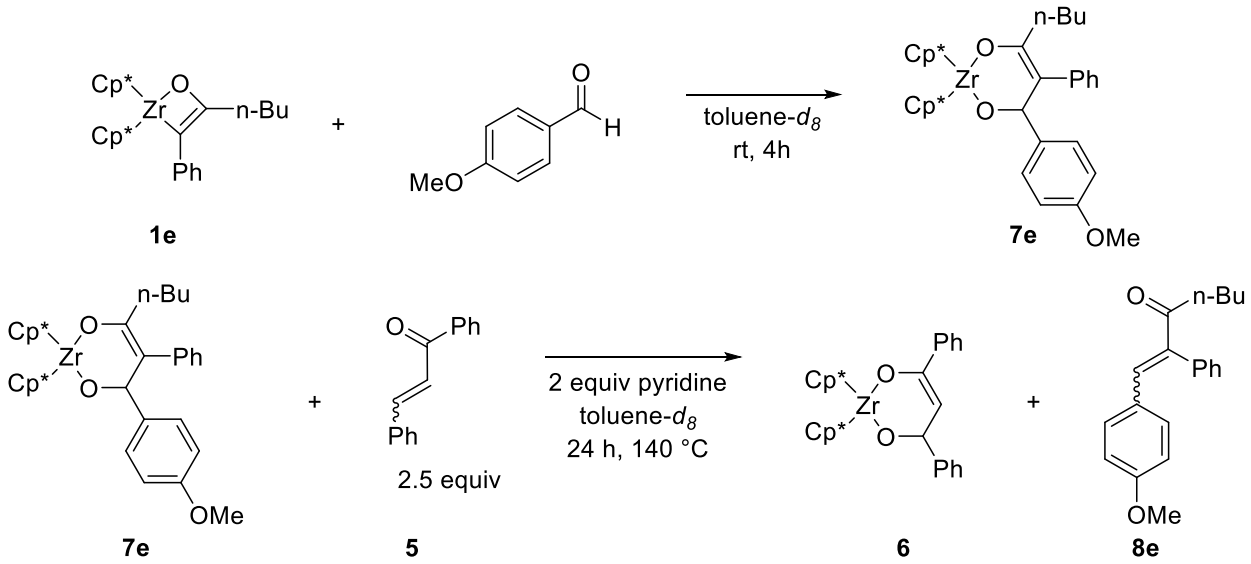
Cp*$_2$Zr(O-C(Me)=C(Ph)-CH((4-OMe)C$_6$H$_4$)-O) (7d): **1c** 24.7 mg, 4-methoxybenzaldehdye 6.1 μL.

Characterization data for 7d:

^{1}H NMR (499 MHz, C_6D_6) δ 7.38 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 7.23 (dd, $^3J_{HH}$ = 8.1, $^5J_{HH}$ = 1.4 Hz, 2H), 7.10 (t, $^3J_{HH}$ = 7.7 Hz, 2H), 6.91 (tt, $^3J_{HH}$ = 7.3, $^5J_{HH}$ = 1.3 Hz, 1H), 6.72 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 6.49 (d, $^3J_{HH}$ = 1.8 Hz, 1H), 3.21 (s, 3H), 2.08 (d, $^3J_{HH}$ = 1.7 Hz, 3H), 1.97 (s, 15H), 1.87 (s, 15H).

^{13}C NMR (126 MHz, C_6D_6) δ 158.47, 154.58, 143.40, 139.06, 131.24, 130.71, 125.04, 120.93, 120.74, 113.06, 110.26, 84.75, 54.46, 24.42, 11.39, 11.15. One sp^2 resonance not located.

After subjecting **7c** to the reaction conditions, neither **8c** nor **6** are observed while starting material although starting material is consumed. The lack of formation of **8c** and **6** is likely due to the deprotonation of **8c** by the transiently formed Zr=O.



Cp*$_2$Zr(O-C(nBu)=C(Ph)-CH((4-OMe)C$_6$H$_4$)-O) (7e and 8e): **1e** 26.8 mg, 4-methoxybenzaldehyde 6.1 μL. The NMR yield of **8e** was 53% (1.2:1 dr) and the NMR yield of **6** was 30% which was determined by comparison to 1, 3, 5-trimethoxybenzene as internal standard.

An authentic sample of **8e** was obtained by subjecting **7e** to silica gel chromatography eluting with 10 % ethyl acetate in hexane.

Characterization data for 7e:

^{1}H NMR (499 MHz, C_6D_6) δ 7.39 (dd, $^3J_{HH}$ = 8.6, $^5J_{HH}$ = 1.6 Hz, 2H), 7.24 (dd, $^3J_{HH}$ = 8.0, $^5J_{HH}$ = 1.4 Hz, 2H), 7.10 (t, $^3J_{HH}$ = 7.7 Hz, 2H), 6.90 (tt, $^3J_{HH}$ = 7.3, $^5J_{HH}$ = 1.3 Hz, 1H), 6.73 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 6.46 (s, 1H), 3.22 (s, 3H), 2.47 – 2.39 (m, 2H), 2.37 – 2.27 (m, 2H), 1.99 (d, 15H), 1.91 (s, 15H), 1.45 – 1.34 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, C_6D_6) δ 158.46, 158.37, 143.11, 139.12, 131.36, 130.48, 127.73, 125.20, 120.96, 120.79, 113.05, 110.73, 84.78, 54.48, 36.64, 31.25, 23.41, 14.34, 11.48, 11.24.

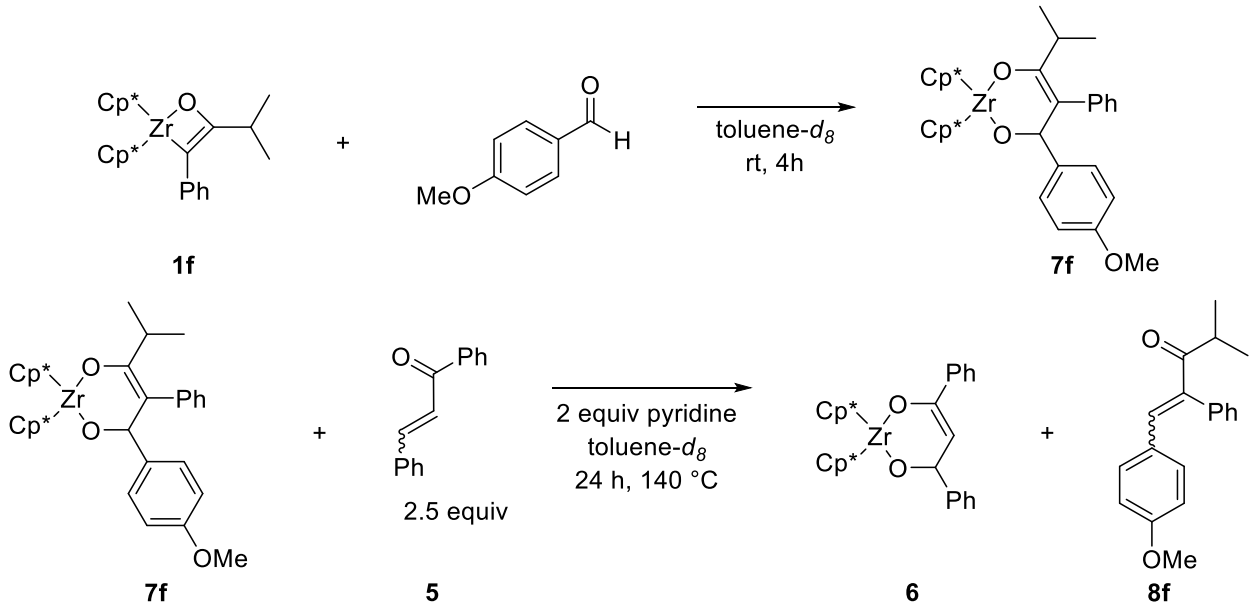
Characterization data for 8e:

^{1}H NMR (499 MHz, $CDCl_3$) δ 8.10 (s, 1H, minor diastereomer), 7.60 (s, 1H), 7.40 (m, 3H), 7.18 (dd, $^3J_{HH}$ = 7.7, $^5J_{HH}$ = 1.6 Hz, 2H), 6.96 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 6.88 (d, $^3J_{HH}$ = 8.7 Hz, 2H, minor diastereomer), 6.68 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 3.83 (s, 3H, minor diastereomer), 3.75 (s, 3H), 2.52 (t, $^3J_{HH}$ = 7.4 Hz, 2H), 1.67 – 1.57 (m, 2H), 1.34 – 1.24 (m, 4H), 0.87 (t, $^3J_{HH}$ = 7.4 Hz, 3H).

^{1}H NMR (499 MHz, toluene-d_8) δ 7.73 (s, 1H), 7.13 (dd, $^{3}J_{HH}$ = 8.1, $^{3}J_{HH}$ = 6.6 Hz, 2H), 7.09 (d, $^{3}J_{HH}$ = 1.5 Hz, 1H), 7.05 – 7.02 (m, 2H), 6.86 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.39 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 3.22 (s, 3H, minor diastereomer), 3.10 (s, 3H), 2.33 (t, $^{3}J_{HH}$ = 7.2 Hz, 2H), (tt, $^{3}J_{HH}$ = 7.1, $^{3}J_{HH}$ = 7.1 Hz, 2H), 1.19 (tq, $^{3}J_{HH}$ = 7.1, $^{3}J_{HH}$ = 7.1 Hz, 2H), 0.80 (t, $^{3}J_{HH}$ = 7.4 Hz, 3H), 0.69 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, minor diastereomer).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.73, 160.46, 138.81, 137.81, 137.78, 132.80, 129.85, 129.26, 127.87, 127.52, 113.90, 55.37, 39.71, 26.82, 22.54, 14.07.

HRMS (ESI/TOF) *m/z*: [M+H^{+}] calculated for $C_{20}H_{23}O_2$, 295.1698; found, 295.1695.



Cp*$_2$Zr(O-C(iPr)=C(Ph)-CH((4-OMe)C$_6$H$_4$)-O) (7f and 8f): **1f** 26.8 mg, 4-methoxybenzaldehyde 6.1 μL. The NMR yield of **8f** was 95% (5.2:1 dr) and the NMR yield of **6** was 65% which was determined by comparison to 1, 3, 5-trimethoxybenzene as internal standard.

An authentic sample of **8f** was obtained by subjecting **7f** to silica chromatography eluting with 10% ethyl acetate in hexane.

Characterization data for 7f:

^{1}H NMR (499 MHz, C_6D_6) δ 7.36 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H), 7.22 – 7.19 (m, 3H), 7.09 (t, $^{3}J_{HH}$ = 7.7 Hz, 2H), 6.92 – 6.85 (m, 1H), 6.72 (d, $^{3}J_{HH}$ = 8.6 Hz, 1H), 6.35 (s, 1H), 3.22 (s, 3H), 2.91 (p, $^{3}J_{HH}$

= 6.8 Hz, 1H), 1.98 (s, 15H), 1.92 (s, 15H), 1.39 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 1.15 (d, $^3J_{HH}$ = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, C_6D_6) δ 160.88, 158.41, 143.40, 139.49, 131.37, 130.43, 125.23, 121.08, 120.80, 113.05, 108.71, 85.37, 54.45, 32.20, 23.45, 21.10, 11.79, 11.40. One sp^3 resonance not found

Characterization data for 8f:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.45 – 7.34 (m, 3H), 7.20 (dd, $^3J_{HH}$ = 8.1, $^5J_{HH}$ = 1.5 Hz, 2H), 7.13 (d, $^3J_{HH}$ = 8.9 Hz, 2H, minor diastereomer), 7.00 – 6.92 (m, 2H), 6.87 (d, $^3J_{HH}$ = 8.7 Hz, 2H, minor diastereomer), 6.76 (d, $^3J_{HH}$ = 8.7 Hz, 2H, minor diastereomer), 6.68 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 3.83 (s, 3H, minor diastereomer), 3.75 (s, 3H), 3.08 (hept, $^3J_{HH}$ = 6.8 Hz, 1H), 2.66 (hept, $^3J_{HH}$ = 6.9 Hz, 1H, minor diastereomer), 1.08 (dd, $^3J_{HH}$ = 6.8, 0.7 Hz, 6H), 1.03 (d, J = 7.0 Hz, 6H, minor diastereomer).

^{1}H NMR (499 MHz, toluene-d_8) δ 7.71 (s, 1H), 7.44 (d, $^3J_{HH}$ = 7.8 Hz, 2H), 7.14 (d, $^3J_{HH}$ = 7.5 Hz, 3H), 6.88 (d, $^3J_{HH}$ = 8.7 Hzye, 2H), 6.81 (d, $^3J_{HH}$ = 9.6 Hz, 2H, minor diastereomer), 6.64 (d, $^3J_{HH}$ = 8.4 Hz, 2H, minor diastereomer), 6.42 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 3.25 (s, 3H, minor diastereomer), 3.13 (s, 3H), 2.93 (d, $^3J_{HH}$ = 6.9 Hz, 1H), 2.59 (d, $^3J_{HH}$ = 7.2 Hz, 1H, minor diastereomer), 1.05 (dd, $^3J_{HH}$ = 6.8 Hz, 6H), 0.97 (d, $^3J_{HH}$ = 6.9 Hz, 1H, minor diastereomer).

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.02, 160.38, 138.32, 138.08, 137.74, 132.74, 129.85, 129.22, 127.85, 127.58, 113.85, 55.36, 35.61, 19.30.

HRMS (ESI/TOF) *m/z*: [M+H$^+$] calculated for $C_{19}H_{21}O_2$, 281.1542; found, 281.1549.

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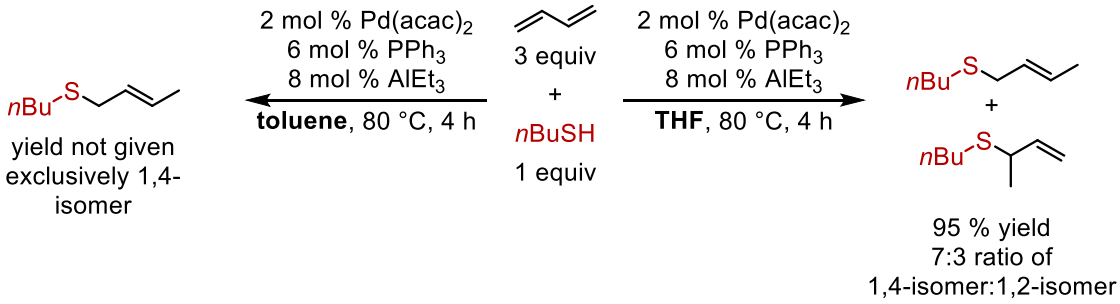
Chapter 2: Regiodivergent Rhodium-Catalyzed Allyl-Amine and Allyl-Imine Hydrothiolation[†‡]

2.1 Introduction.

The hydrothiolation reaction directly couples two abundant building blocks, a thiol and an unsaturated C–C bond. This process forms a C–S and a C–H bond with 100% atom economy.[1] This efficient strategy toward the construction of C–S bonds is highly valuable, as organosulfur compounds are common synthetic intermediates,[2] composed approximately 20% of the top-selling US pharmaceutical drugs in 2012,[3] and are a common motif in ligand structures for catalysis. Compared to other hydrofunctionalization methods, however, transition metal-catalyzed hydrothiolation is relatively underexplored, likely due to the strong coordinating ability of sulfur, and the ensuing catalyst deactivation.[4]

The first transition metal-catalyzed hydrothiolation of unsaturated C-C bonds was reported by Dzhemilev in 1981[5] (Scheme 13). It was shown that butadiene undergoes a hydrothiolation reaction utilizing a low valent palladium catalyst. Interestingly, when the reaction was conducted in toluene or benzene, the 1,4-hydrothiolation isomer is the exclusive product formed. Switching the solvent from nonpolar solvents to THF results in a modest change in regioselectivity to 7:3 still



Scheme 13: Dzhemilev's Seminal Report of a Transition-Metal-Catalyzed Olefin Hydrothiolation.

in favor of the 1,4-isomer. Since this report, organometallic chemists have been developing systems that can access both linear and branched hydrothiolation isomers selectively. Tremendous success has been had developing regioselective, regiodivergent, and asymmetric hydrothiolation

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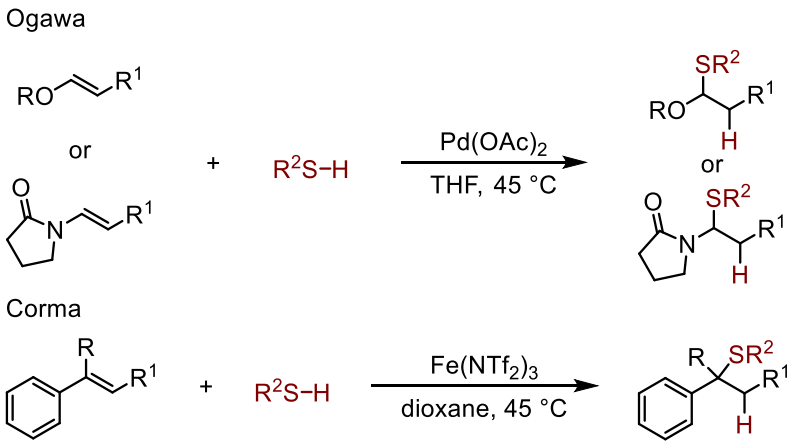
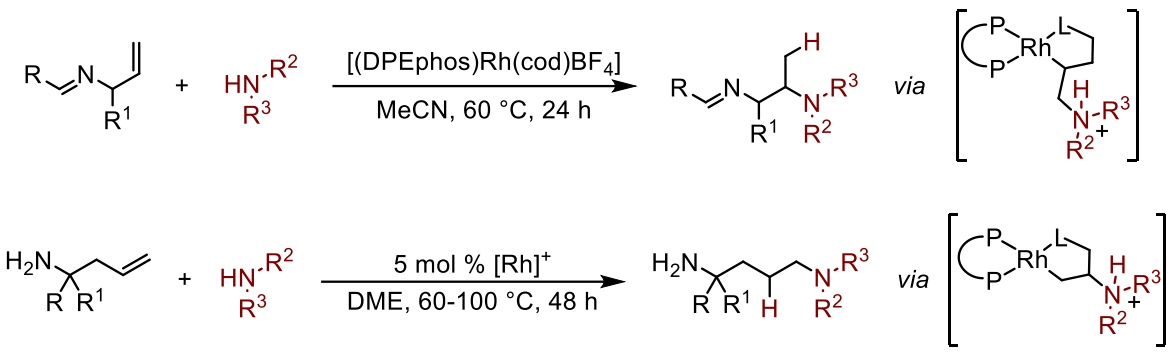
[‡] The work in this chapter was conducted in collaboration with Ms. Jennifer Kennemur.

reactions of alkynes[6] and allenes.[7] In contrast, transition metal-catalyzed hydrothiolation reactions of alkenes is relatively underdeveloped. [8] Ogawa recently demonstrated the Au-catalyzed anti-Markovnikov hydrothiolation of terminal olefins to afford linear C–S bonds.[9] However, thus far, only electronically activated alkenes give access to branched C–S bonds (Scheme 14).[10]



Scheme 14: Markovnikov Hydrothiolation of Electronically Activated Alkenes.

The development of alkene functionalization reactions is an important challenge in modern catalysis.[11] Our group is specifically interested in using transition metal-catalysis to form C–X bonds from these ubiquitous organic moieties with high degrees of regio-, chemo-, and stereoselectivity. Recently, our group has demonstrated the Rh-catalyzed hydroamination of allylimines and homoallylamines for the selective synthesis of 1,2- and 1,4-diamines, respectively (Scheme 15).[12] We propose that the Lewis basic nitrogen binds to the catalyst and promotes the functionalization of the proximal alkene.[13] The regioselectivity is dictated by the formation of the favored, five-membered metalacyclic intermediate.



Scheme 15: Hydroamination Reactions Developed in the Hull Group.

We hypothesized that a similar approach may allow for the Markovnikov-selective hydrothiolation of electronically unactivated allyl amines and imines to afford 1,2-amino- and iminothioethers, respectively (Figure 7a). The 1,2-*N*,*S*- moiety is commonly found in modern pharmaceuticals[14] (Figure 7b) and as bidentate ligands for palladium-catalyzed allylic substitution reactions[15,16] (Figure 7c). However, thus far, the incorporation of these moieties has, in many cases, depended on pre-installed functionality from ephedrine and cysteine, limiting substitution patterns for derivatization along the carbon skeleton. The development of a more general methodology for

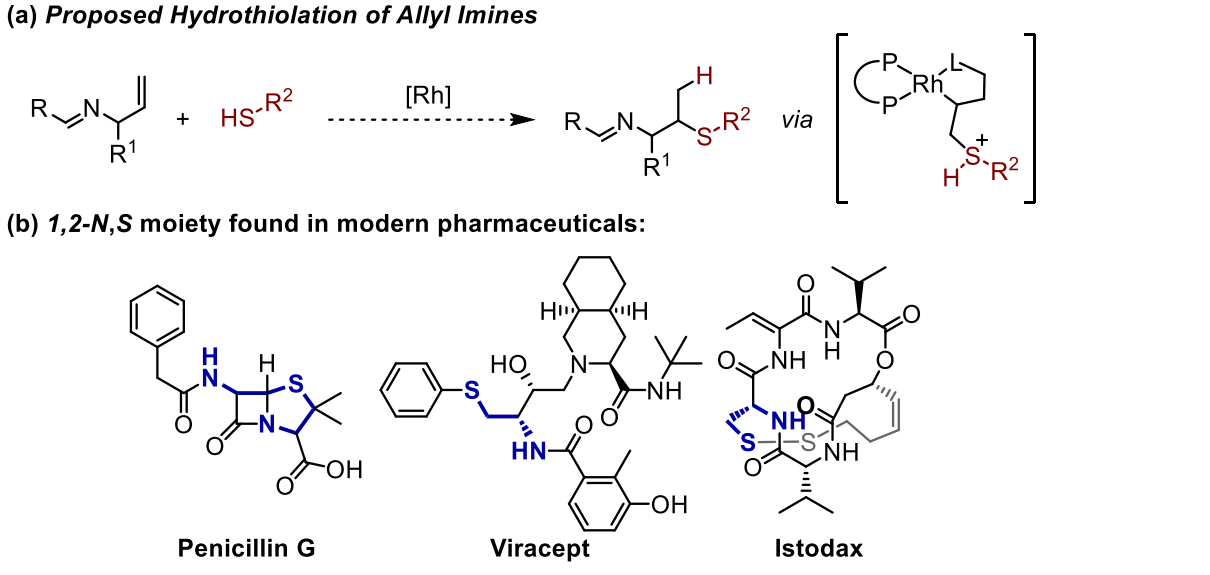


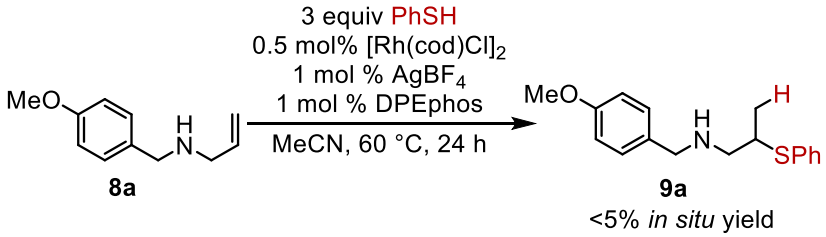
Figure 7: Proposed Transformation and 1,2-Aminothioethers in Pharmaceuticals and Ligands.

the synthesis of 1,2-aminothioethers may enable broader applicability of this moiety with increased structural diversity.

Excitingly, we discovered that 1,2-aminothioethers can be synthesized via the hydrothiolation of easily accessible allyl amine derivatives. To our surprise, the regioselectivity of the olefin functionalization is ligand-controlled, allowing us to access both the Markovnikov and anti-Markovnikov isomers.

2.2 Reaction Discovery and Optimization.

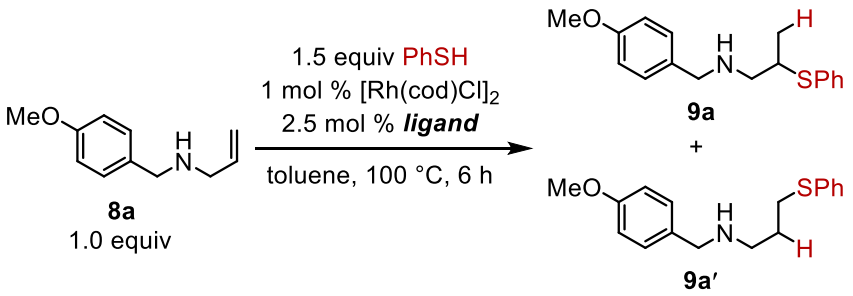
Ms. Kennemur's initial attempt at the Rh-catalyzed hydrothiolation of alkenes explored the use of thiophenol under our previously optimized conditions for the hydroamination reaction. Excitingly, it was found that allyl imine **7a** and secondary allyl amine **8a** act as directing groups, affording the Markovnikov-selective hydrothiolation product, albeit in trace quantities, as detected by GC analysis (Scheme 16).



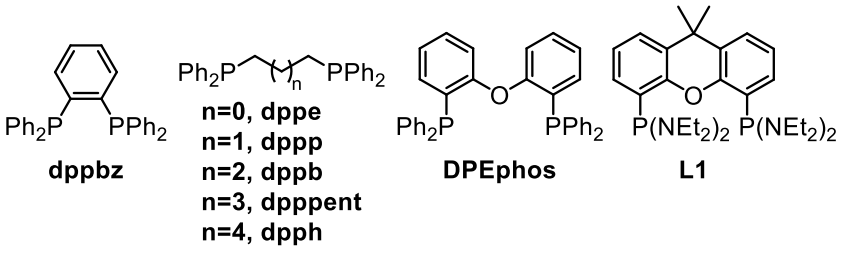
Scheme 16: Application of the Hydroamination Conditions to Hydrothiolation.

Increasing catalyst loading and temperature along with using a non-polar solvent, led to the formation of **9a** in 66% yield from amine **8a** with >20:1 selectivity for the Markovnikov isomer (Table 8, entry 7).

Table 8: Effect of Bidentate Phosphine Ligands on the Rh-Catalyzed Hydrothiolation Reaction.



Entry	ligand	β_n[a]	yield **9a**[b] (%)	yield **9a'**[b] (%)
1	dppbz	83°	<1	3
2	dppe	85°	<1	7
3	dppp	86°	<1	19
4	dppb	99°	12	<1
5	dpppent	107°	31	<1
6	dpph		32	<1
7	DPEphos	102°	66	<1
8	L1	168°	21	<1



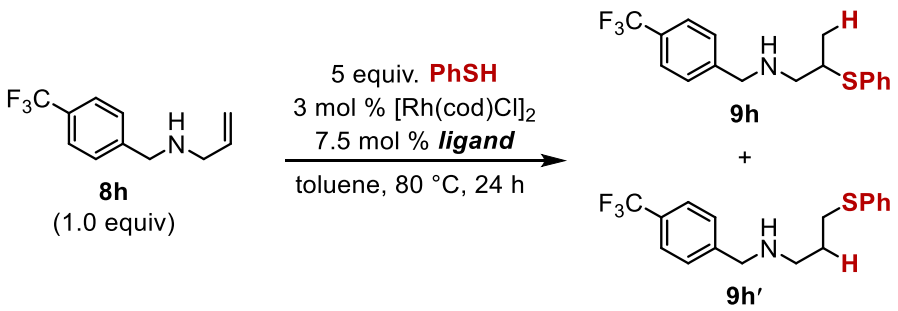
[a] Natural bite angle (β_n), as defined by the preferred chelation angle based on the ligand backbone and not on the metal valence angle.[18] [b] Yield determined by comparison to an internal standard using gas chromatography.

Intriguingly, during the optimization, it was observed that the regioselectivity of the directed hydrothiolation of allyl amines is dictated by the ligand employed. As seen in Table 8,

ligands with smaller bite angles ($83° \leq \beta_n \leq 86°$) (entries 1-3) are selective for the anti-Markovnikov hydrothiolation product. Alternatively, ligands with larger bite angles ($99° \leq \beta_n \leq 168°$) favor the Markovnikov isomer (entries 4-8). A similar trend is observed when allyl imines are employed. Control reactions, including addition of radical traps and using radical initiators instead of [Rh] indicate that the regioisomeric transformations are rhodium-catalyzed. These control reactions suggest that a change in mechanism based on the ligand employed, allows for the catalyst-controlled, regiodivergent hydrothiolation reactions. Ms. Kennemur further optimized the reaction finding that increasing catalyst loading, thiol equivalents, and time led to a more general reaction scope. The addition of 0.5 equivalents of LiBr increases the yield, potentially a consequence of suppressed product inhibition or an effect of a more active rhodium–bromide intermediate following salt metathesis.

While optimizing the anti-Markovnikov reaction, I discovered that dppbz was a superior ligand to dppe when optimizing the reaction on **8h** (Table 9, entry 1), so it was used for generality. I further found that increasing the temperature from 80 °C to 100 °C further increased the yield of **9a'** to a 76% ^{1}H NMR yield (Table 10, entry 4).

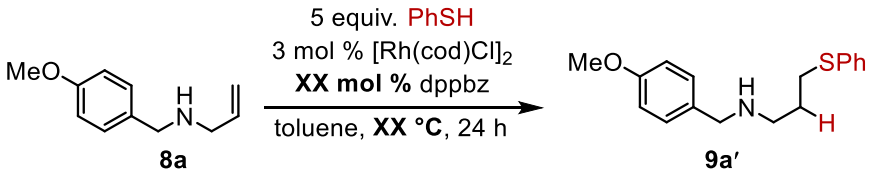
Table 9: Effect of Small Bite Angle Bidentate Phosphine Ligands on the Rh-Catalyzed Hydrothiolation Reaction of 8h.



entry	ligand	β_n[a]	Yield **9h** (%)[b]	Yield **9h'** (%)[b]
1	dppbz	83°	1	34
2	dppm	72°	4	>1
3	dppe	85°	3	10
4	dppp	91°	1	>1
5	dppb	98°	5	>1
6	dpppent	107°	54	>1

[a] Natural bite angle (β_n), as defined by the preferred chelation angle based on the ligand backbone and not on the metal valence angle.[17] [b] Yield determined by comparison to an internal standard using ^{1}H NMR.

Table 10: Effect of Temperature and Ligand Loading on the Rh-Catalyzed Anti-Markovnikov Hydrothiolation Reaction.



8a **9a′**

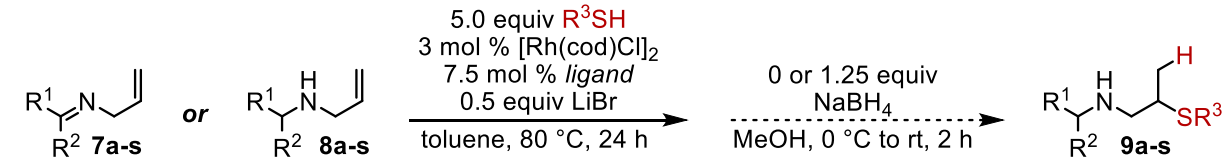
entry	mol % dppbz	temperature (°C)	yield **9a'** (%)[a]
1	6.0	80	36
2	6.0	100	58
3	7.5	80	48
4	7.5	100	76

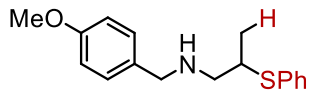
[a]yield determined by ^{1}H NMR by comparison to 1-methylnaphthalene as an internal standard.

2.3 Scope of Markovnikov Hydrothiolation.

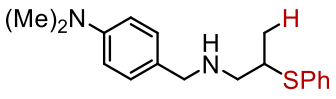
With optimized conditions for the Markovnikov-selective hydrothiolation reaction, the scope of allyl amines, imines and thiols that participate in the reaction was investigated. As demonstrated in Table 11, secondary amines and imines are excellent directing groups for hydrothiolation, affording 1,2-aminothioethers in good yields (38-82%) with excellent regioselectivity (>20:1 in all cases). Notably, the optimal ligand changes depending on the directing group utilized; i.e., with imines, higher yields are observed with **L1**; whereas DPEphos affords higher yields when starting with a secondary amine (Table 11). The imine products are not stable to column chromatography; thus, these compounds are isolated by immediate reduction to the corresponding 1,2-aminothioether. These products can also be accessed through a three-component procedure, i.e. starting with *p*-methoxybenzaldehyde and allyl amine, a one-pot imine condensation and *in-situ* hydrothiolation reaction with thiophenol yielded **3a** in 58% isolated yield following reduction with $NaBH_4$.

Table 11: Markovnikov-Selective Hydrothiolation of Allyl-Imines and Secondary Allyl-Amines.[a,b]

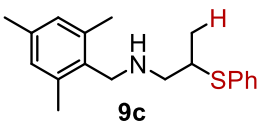




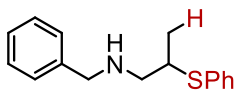
9a
82%[c], 72%[d]



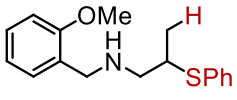
9b
48%[d]



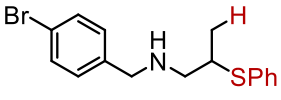
9c
66%[c,e]



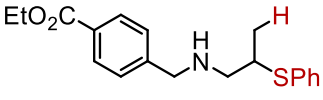
9d
72%[c], 74%[d]



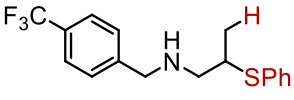
9e
73%[d]



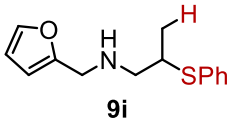
9f
72%[d]



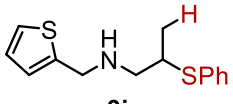
9g
54%[d]



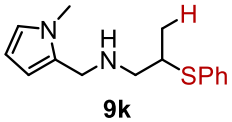
9h
41%[c,f], 41%[d]



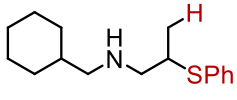
9i
70%[d]



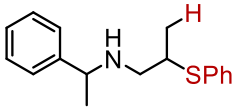
9j
73%[c], 68%[d]



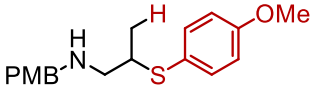
9k
38%[d]



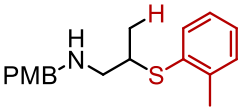
9l
65%[d]



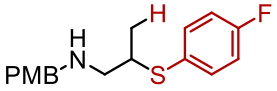
9m
58%[d]



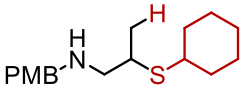
9n
65%[d]



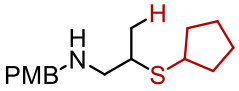
9o
59%[d]



9q
47%[d]



9r
59%[c,g]



9s
65%[c], 59%[d]

[a] Isolated yields are reported as an average of two runs. [b] >20:1 regioselectivity is observed, as determined by NMR or GC analysis of the crude reaction mixtures. [c] Reaction conditions: (i)$[Rh(cod)Cl]_2$ (0.012 mmol, 3.0 mol %), **L1** (0.03 mmol, 7.5 mol%), LiBr (0.2 mmol, 0.5 equiv), toluene (2 M), allyl imine **7** (0.4 mmol, 1 equiv), and thiol (2.0 mmol, 5.0 equiv) at 80 °C for 24 h. (ii) $NaBH_4$ (0.6 mmol, 1.5 equiv), MeOH, 0 °C to rt for 2 h. [d] Reaction conditions: $[Rh(cod)Cl]_2$ (0.012 mmol, 3.0 mol %), DPEphos (0.03 mmol, 7.5 mol%), LiBr (0.2 mmol, 0.5 equiv), toluene (2 M), allyl amine **8** (0.4 mmol, 1 equiv), and thiol (2.0 mmol, 5.0 equiv) at 80 °C for 24 h. [e] 100 °C. [f] 48 h, 7.0 equiv PhSH. [g] 48 h.

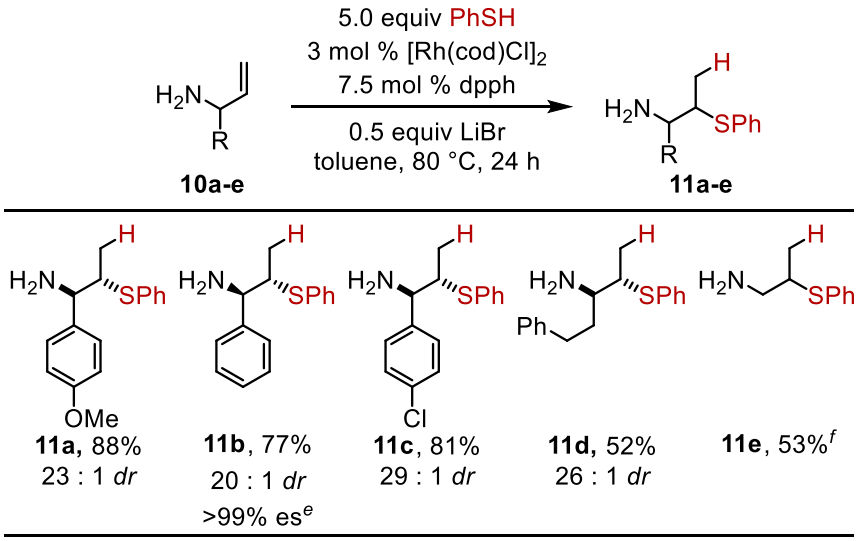
A variety of functional groups are well-tolerated, including *p*- and *o*-substituted ethers (**9a**, **9e**), a tertiary amine (**9b**), an aryl bromide (**9f**), and an ester (**9g**). Heterocycles, including

thiophene, furan, and *N*-methyl pyrrole afforded good yields of the Markovnikov hydrothiolation products **9i-9k**. Aliphatic amine **8l** also readily undergoes the hydrothiolation reaction in 65% yield. In general, decreasing the electron density on benzyl-substituted allyl amines decreases reactivity but not selectivity (**9g**, **9h**). This is likely due to reduction of Lewis basicity of the directing group and thus its ability to promote the reaction. Similarly, increasing the steric hindrance proximal to the secondary amine moderately reduces the yield of **9m** to 58%. Likewise, substitution at the α-position of the secondary allyl amine results in poor conversion to the hydrothiolation product (<5%). Unfortunately, this reaction is also limited to terminal, monosubstituted alkenes, as both 1,1- and 1,2-disubstitued alkenes afforded <5% of the desired product.

A variety of thiophenol derivatives are tolerated under the reaction conditions, including electron-rich (**9n**), sterically encumbered (**9o**), and electron-poor (**9q**) thiophenols. Additionally, this method proves general for both cyclic aryl and alkyl thiols, as cyclopentane and cyclohexane thiol are effective nucleophiles for the hydrothiolation reaction (**9r-9s**). However, linear thiols (ethane thiol, octane thiol) do not participate in the reaction, potentially due to catalyst poisoning by these less sterically hindered alkyl thiols.

To our delight, primary amines are also effective directing groups for the Rh-catalyzed hydrothiolation reaction. In addition to simple allyl amine, as seen in Table 12, both aromatic and aliphatic substituted allyl amines proceed to afford *anti*-1,2-aminothioethers in good to excellent yields as a single diastereomer (>20:1 in all cases). When enantiomerically-enriched **10b** was employed, the stereochemical information remained with >99% enantiospecificity, showing that the Rh-catalyst does not isomerize to the allylic position. The relative stereochemistry was confirmed by x-ray crystallography of tosyl-**10c** which shows an anti-relationship between the amine and thioether.

Table 12: Markovnikov-Selective Hydrothiolation of Primary Allyl-Amines.[a,b,c,d]



[a-] See Table 11. [c]Diastereoselectivities were determined by GC analysis of the crude reaction mixture. [d]Reaction conditions: $[Rh(cod)Cl]_2$ (0.009 mmol, 3.0 mol %), dpph (0.023 mmol, 7.5 mol%), LiBr (0.15 mmol, 0.5 equiv), toluene (2M), allyl amine **10** (0.3 mmol, 1 equiv), and thiol (1.5 mmol, 5.0 equiv). [e] When starting with enantiomerically enriched **10a**. [f] Isolated following boc-protection.

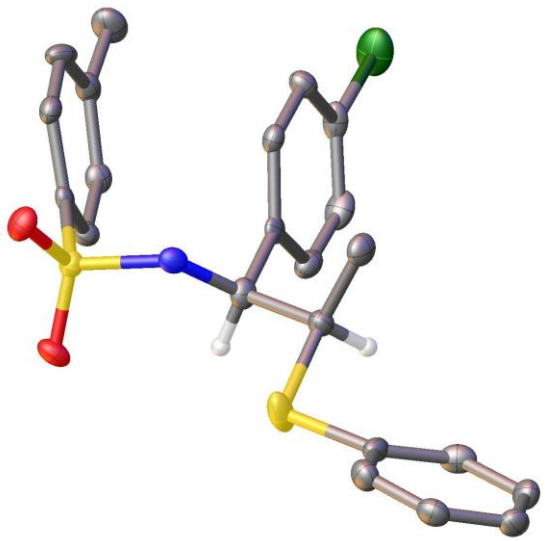
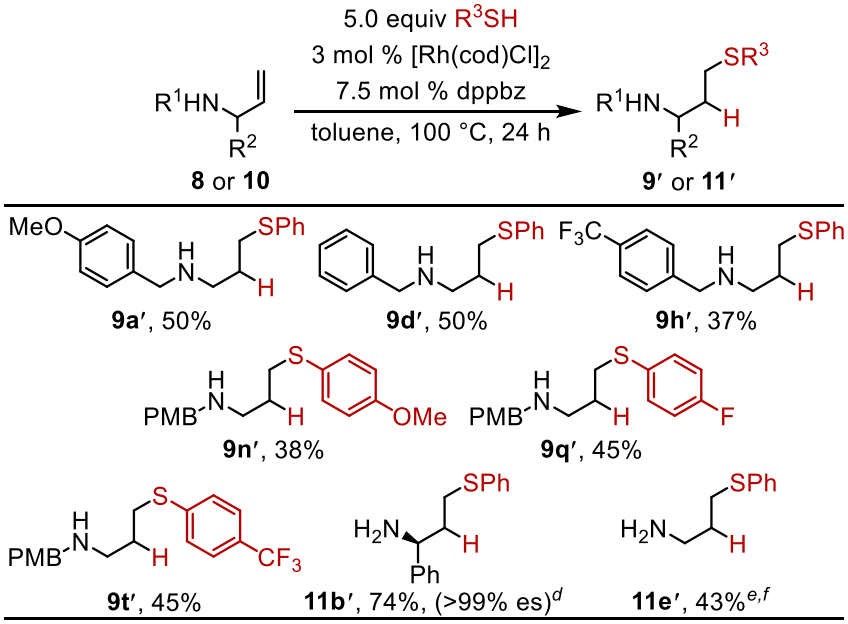


Figure 8: Crystal Structure of Tosyl-5c. Hydrogen atoms (except for Hydrogen atoms attached to C14 and C15 to unambiguously show diastereoselectivity) are omitted for clarity. Ellipsoids are drawn at 50% probability level.

2.4 Scope of Anti-Markovnikov Hydrothiolation.

I next explored the anti-Markovnikov hydrothiolation of allyl amine derivatives as a demonstration of the catalyst-controlled regiodivergent reaction. Although the regioselective synthesis of linear C–S bonds from olefins has been demonstrated for over a century with both activated and unactivated substrates *via* the thiol-ene reaction,[18] the synthetic versatility and mechanistic implications of a regiodivergent pathway is both advantageous and intriguing. Gratifyingly, both secondary and primary amines afford 1,3-aminothioethers in fair to very good yields (37-74%) when dppbz is employed as the ligand (Table 13). Secondary and substituted primary allyl amine substrates afforded the anti-Markovnikov product as a single regioisomers (>20:1 a-M:M). Notably, when allyl amine is subjected to the reaction conditions both regioisomers are observed in a 5.5:1 of **11e′**:**11e**. Unlike the Markovnikov-selective conditions, these reactions are limited to thiophenol nucleophiles.

Table 13: Anti-Markovnikov-Selective Hydrothiolation of Allyl-Amines.[a,b,c]



[a-b] See Table 11. [c] Reaction conditions: $[Rh(cod)Cl]_2$ (0.012 mmol, 3.0 mol %), dppbz (0.030 mmol, 7.5 mol, toluene (2.0 M), allyl amine **8** or **10** (0.40 mmol, 1.0 equiv), and thiol (2.0 mmol, 5.0 equiv). [d] Starting with enantiomerically enriched **4a.** [e] Isolated following boc-protection. [f] A regioselectivity of 5.5:1 **11e′**:**11e** was observed by ^{1}H NMR analysis of the crude reaction mixture.[17]

2.5 Markovnikov Selective Hydrothiolation Mechanistic Investigations and Catalytic Cycle.

I was interested in determining the role that the ligand bite angle had in the regioselectivity of the hydrothiolation reaction.[19] Several mechanisms were considered and experiments were conducted to support or refute the mechanistic hypotheses. For the Markovnikov selective conditions, which utilize a large bite angle ligand, two potential mechanisms were considered, first a mechanism which is consistent with the proposed mechanism for allyl amine hydroamination which would proceed through a thiometallation followed by proton transfer/reductive elimination or protolytic cleavage of the Rh–H bond. The second mechanism begins with oxidative addition into the S–H bond which then undergoes selective Rh–S migratory insertion and then C–H reductive elimination. Stoichiometric investigations of $[Rh(cod)Cl]_2$, DPEphos, and 4-methoxythiophenol in THF-d_8 show a Rh–H resonance at -17.2 ppm (dt, J = 19.4, 18.1) in the ^{1}H NMR at -35°C (Figure 9).

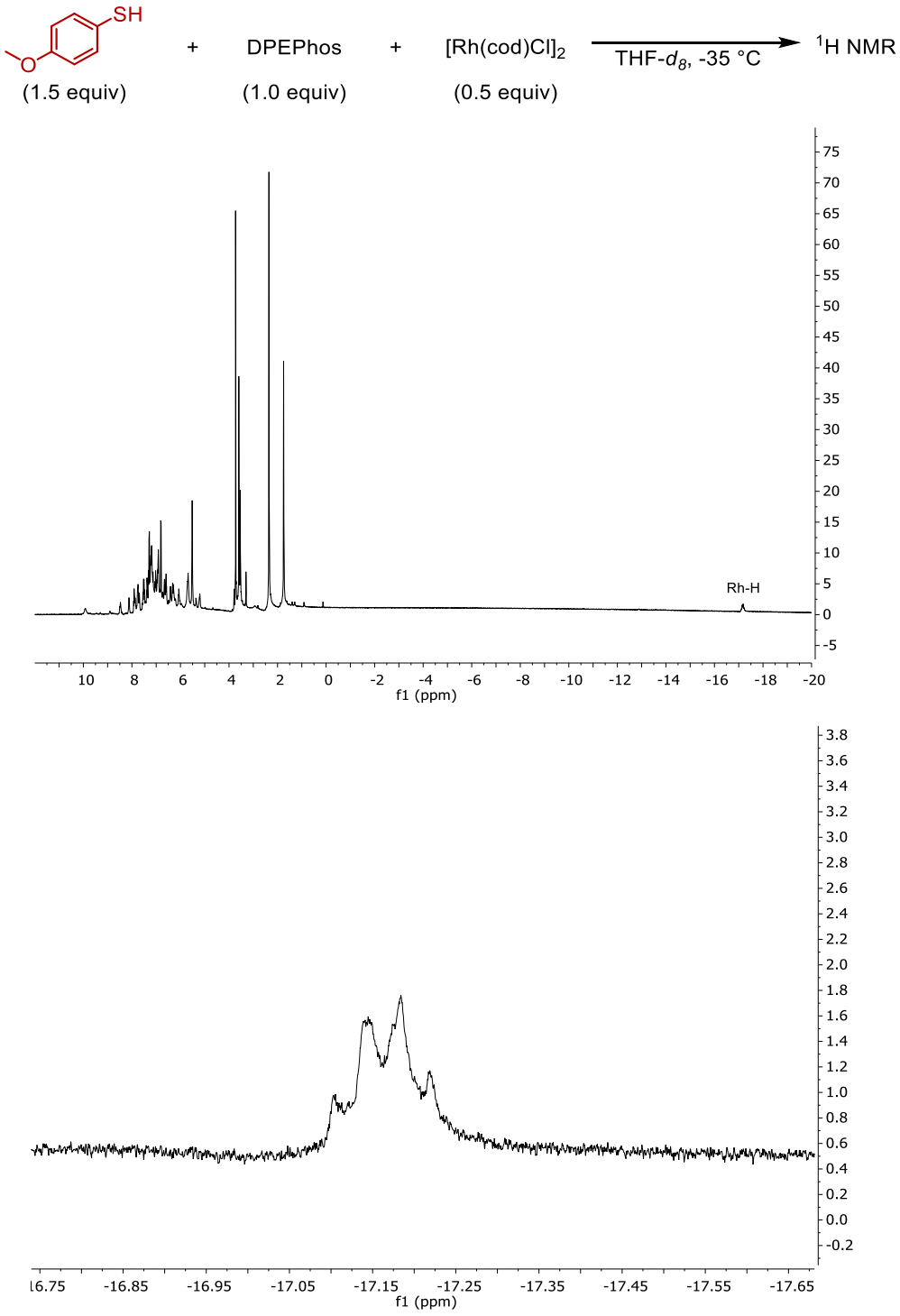
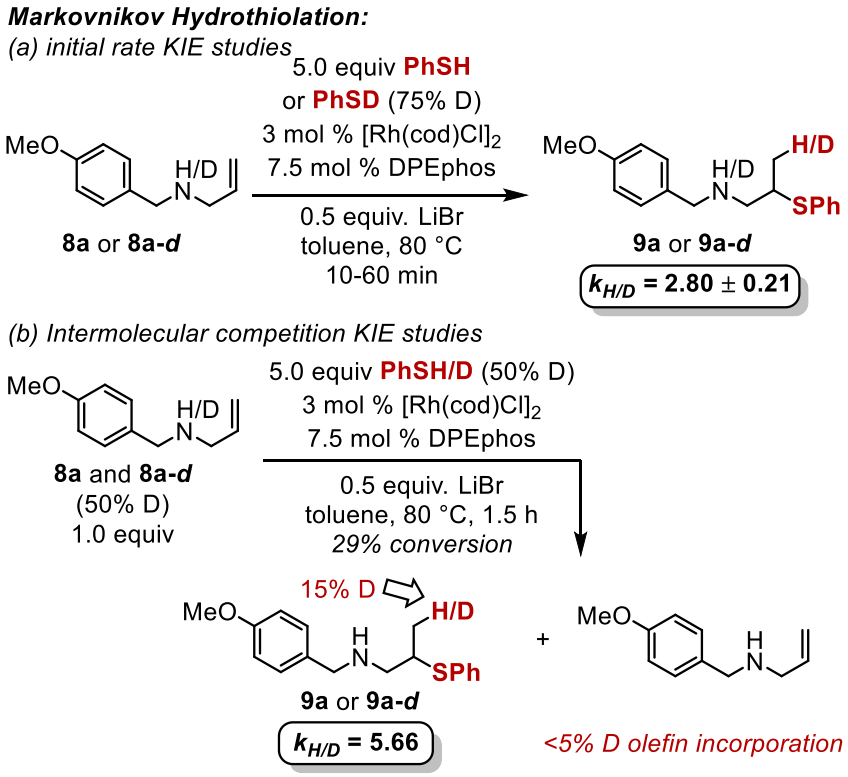


Figure 9: Full ^{1}H NMR Spectrum of $[Rh(cod)Cl]_2$ with DPEphos and 4-OMethiophenol in THF-*d*$_8$ at -35 °C (Top). Zoom of Rh-H (Bottom).

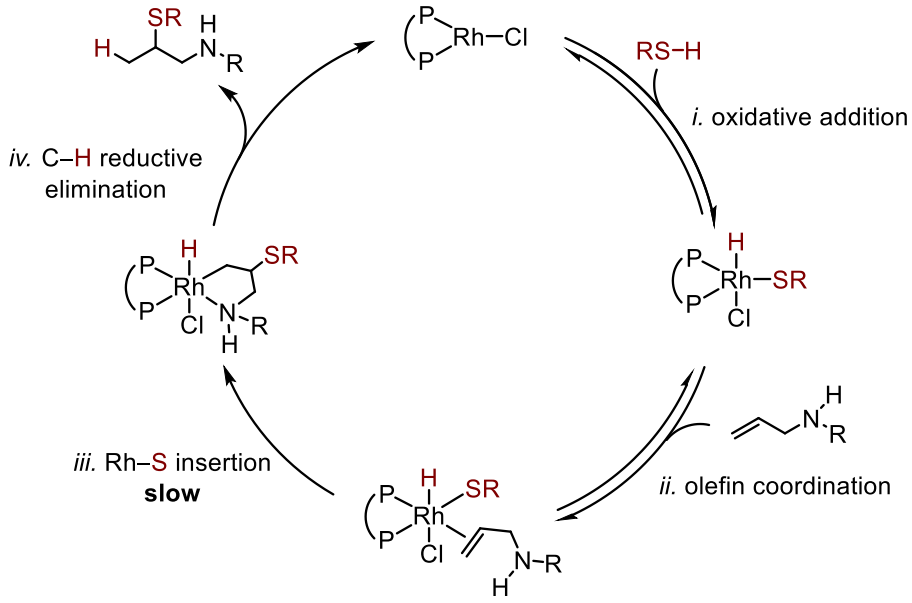
This observation indicates that the Rh complex can undergo oxidative addition into the PhS–H bond to afford a Rh(III) intermediate. Furthermore, the splitting pattern and coupling constants are consistent with the hydride being *cis* to both phosphines. We next explored kinetic isotope effects (KIEs) under the Markovnikov-selective hydrothiolation conditions. Initial rate



Scheme 17: Kinetic Isotope Effect Studies for the Markovnikov Selective Conditions.

KIE experiments performed with deuterated thiophenol (75 %-d_1) are consistent with a primary KIE (k_H/k_D = 2.8) (Scheme 17a); whereas, competition experiments afford a KIE of k_H/k_D = 5.7 (Scheme 17b). The large difference between the initial rate KIE and competition KIE likely arises from a rapid exchange of the allyl amine N-H/D with thiophenol S-H/D leading to Curtin-Hammett conditions. This exchange is supported by the coalescence of the N-H/D and S-H/D that is observed in the ^{1}H and ^{2}H NMR. The KIE experiments can be explained with X–H bond breaking/forming at or before the turnover limiting step. Furthermore, the new C–D bond is formed exclusively at the terminal carbon, indicating that β-hydride elimination is not occurring after olefin insertion as this would result in the incorporation of deuterium at the internal position. Combined, these data are consistent with (*i*) reversible oxidative addition into the PhS–H/D bond followed by (*ii*) olefin coordination and a subsequent (*iii*) slow migratory insertion of the Rh–S

bond into the olefin and (*iv*) fast reductive elimination to form the C–H/D bond (Scheme 18). Transition metal-catalyzed hydrothiolations of alkynes and allenes with group 9 metals are thought to occur through similar oxidative addition/insertion/reductive elimination steps.[6b,h,i,7b]



Scheme 18: Proposed Markovnikov-Selective Hydrothiolation Mechanism.

2.6 Anti-Markovnikov Selective Hydrothiolation Mechanistic Investigations and Catalytic Cycle.

I next performed similar investigations on the anti-Markovnikov-selective reaction. For the anti-Markovnikov reaction, an oxidative addition mechanism was the only mechanism considered as the thiometallation pathway would require the formation of a four-membered metallocycle. In this mechanistic pathway, Rh–H migratory insertion would occur over Rh–S migratory insertion and would conclude with C-S reductive elimination. When $[Rh(cod)Cl]_2$, dppp (employed for its increased solubility relative to dppbz), and 4-methoxythiophenol are combined in THF-d_8 in the presence of Bn_2NH which was added to act as a surrogate for the allylic amine substrate, a Rh–H resonance is observed at -13.63 ppm (dt, J = 16.1, 11.2 Hz, 1H) in the ^{1}H NMR spectrum (Figure 10). Again, this demonstrates that oxidative addition can occur into the PhS–H bond and that the Rh(III) hydride generated is *cis* to both phosphines.

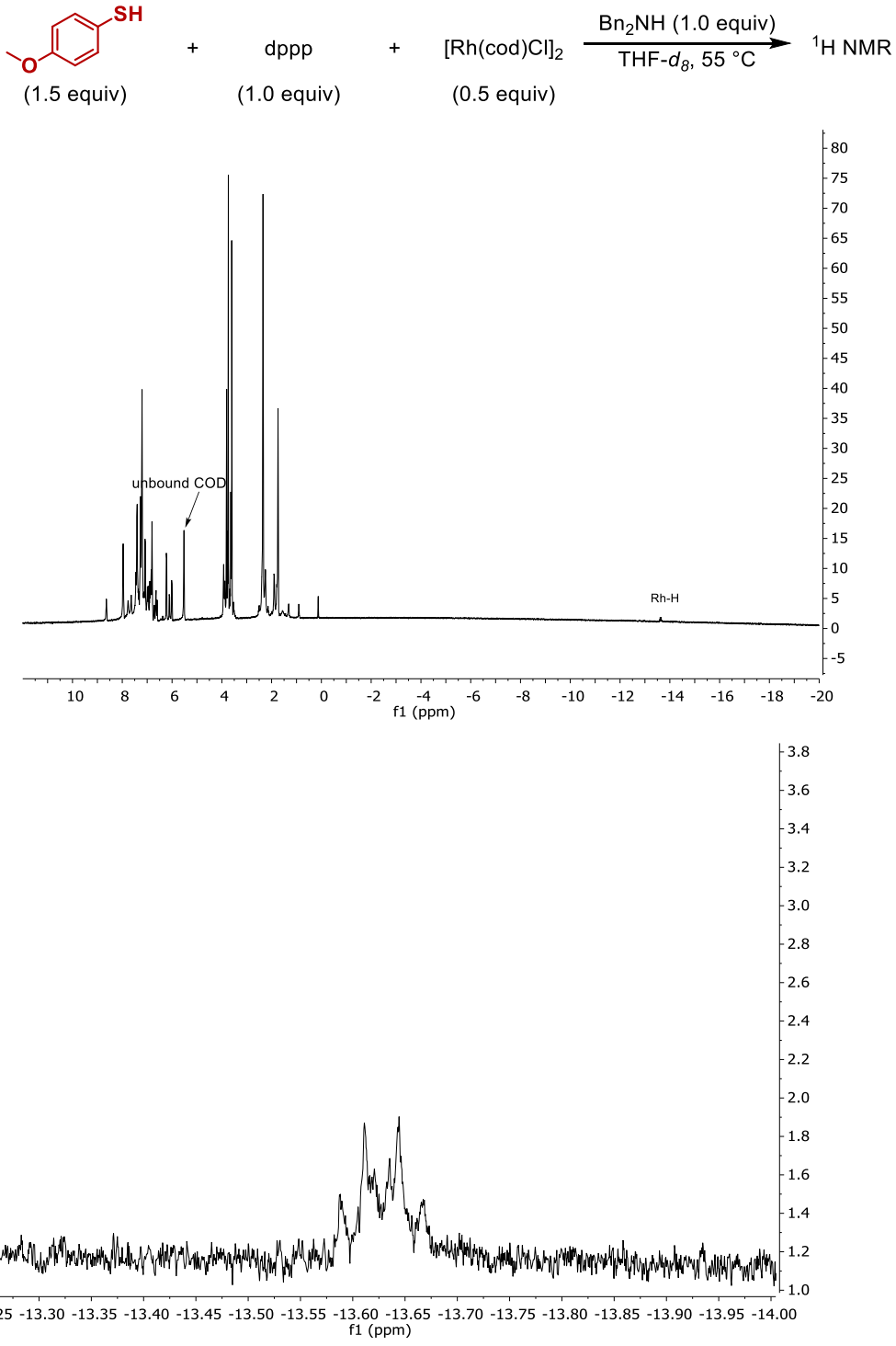
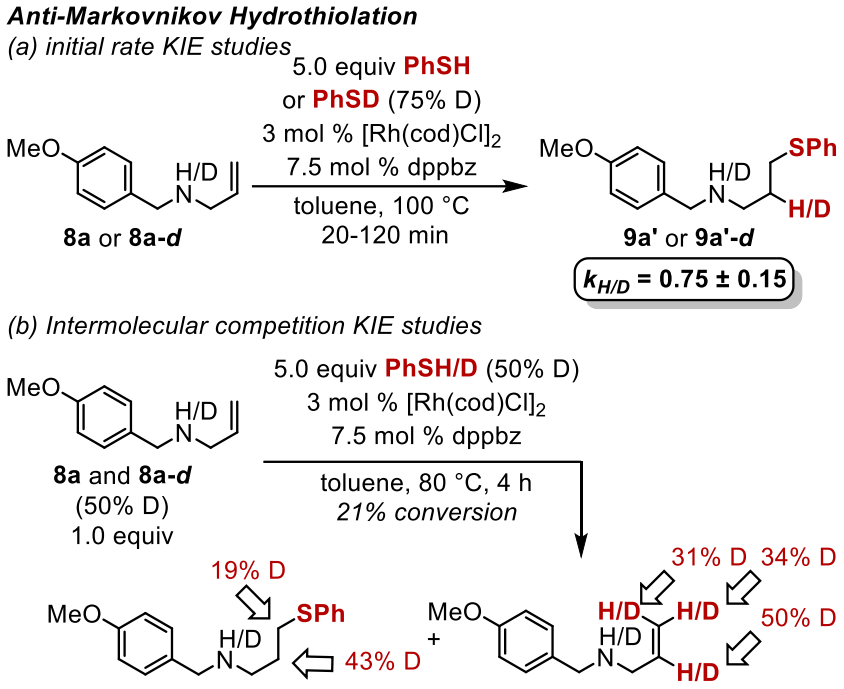


Figure 10: Full ^{1}H NMR Spectrum of [Rh(cod)Cl]$_2$, dppp, 4-OMethiophenol and Bn$_2$NH in THF-d_8 at 55 °C (Top). Zoom of Rh-H (Bottom).

When PhS–D is employed under anti-Markovnikov conditions in intermolecular competition studies, extensive deuterium incorporation into each olefinic position of the recovered starting material is observed (Scheme 19b). While this precluded us from determining a competition KIE, the extensive deuterium incorporation indicates a reversible insertion of the Rh–H/D into the olefin (Scheme 20, step *iii′*). Deuterium incorporation at the terminal position of the olefin can be rationalized by a reversible Rh–H/D migratory insertion to form **E′**, followed by β-hydride elimination to form deuterated starting material.



Scheme 19: Anti-Markovnikov-Selective Hydrothiolation KIE Studies.

To measure a KIE under anti-Markovnikov conditions, we performed initial rate KIE experiments comparing the reactivity of thiophenol to deuterated thiophenol (75 %-d_1). Under these conditions, an inverse KIE was observed ($k_H/k_D = 0.75 \pm 0.15$) (Scheme 19a), suggesting that X–H bond making or breaking does not influence the rate of the reaction. Rather, an equilibrium isotope effect explains the observed inverse KIE, an effect of the reversible olefin insertion of the Rh–H/D bond (Figure 11). Under pre-equilibrium conditions, the rate of product formation is affected by the equilibrium between the [L_nRhCl] and **C′**. The stronger C–D bond, relative to the

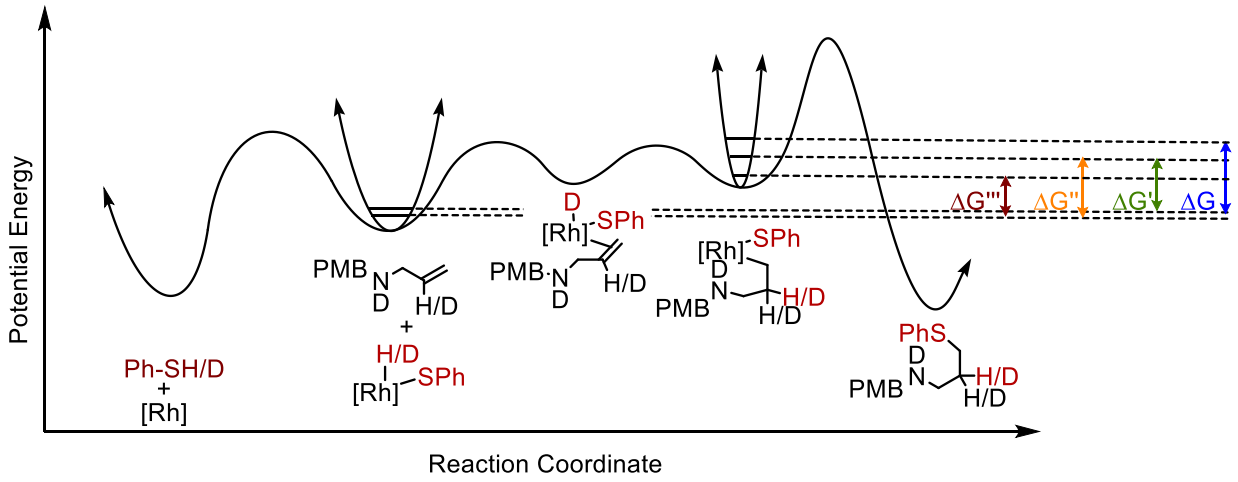
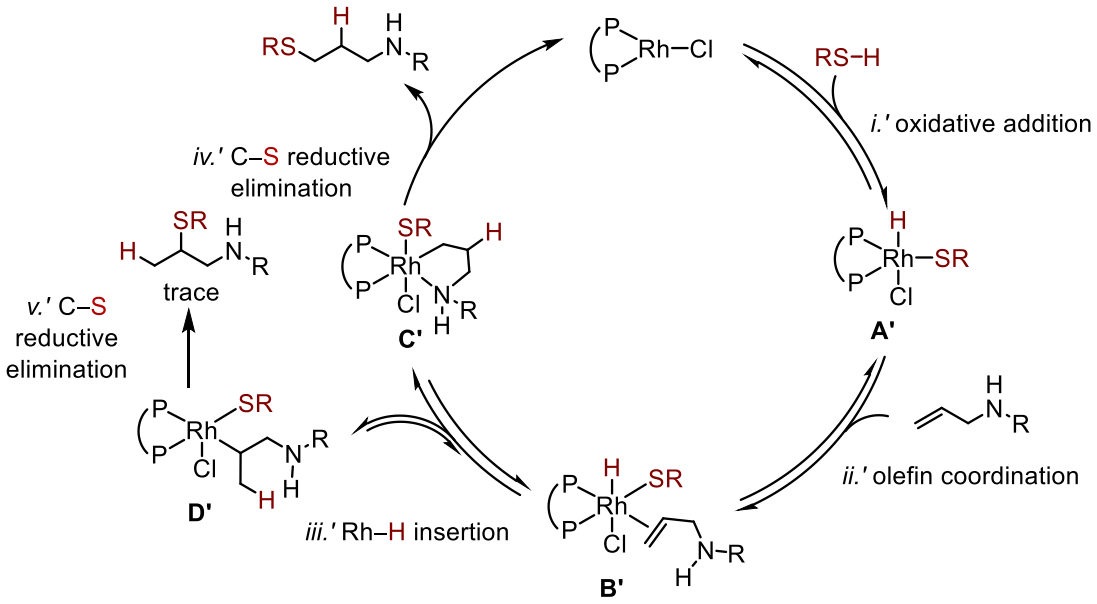


Figure 11: Equilibrium Isotope Effect of Anti-Markovnikov Hydrothiolation KIE Studies.

C–H bond, will increase the concentration of the **C′-*d*** intermediate by decreasing the ΔG, thereby increasing the rate of reductive elimination from **C′-*d*** compared to **C′**.[17] Combined, these observations are consistent with (*i*) oxidative addition into the PhS–H/D, (*ii′*) olefin coordination, and (*iii′*) rapid, reversible migratory insertion into the Rh–H/D bond, followed by (*iv′*) slow reductive elimination to form the C–S bond (Scheme 20).



Scheme 20: Proposed Mechanism of Anti-Markovnikov Hydrothiolation Reaction.

2.7 Conclusions.

We have demonstrated the first catalyst-controlled regiodivergent hydrothiolation of electronically unactivated alkenes for the selective synthesis of 1,2- and 1,3-aminothioethers. The reactions are chemo-, regio-, and stereoselective. Initial mechanistic investigations suggest that the two catalytic cycles are both occurring *via* oxidative addition into the RS–H bond, but that large bite angle ligands favor insertion into the Rh–SR bond while small bite angle ligands favor insertion into the Rh–H bond. The mechanism of both transformations and source for the observed regiodivergence is currently under investigation. Additionally, future studies will focus on expanding to alkenes lacking a directing group and rendering the Markovnikov-selective reaction asymmetric.

2.8 Experimental Procedures.

General Experimental Procedures: All reactions were carried out in flame-dried (or oven-dried at 140 °C for at least 2 h) glassware under an atmosphere of nitrogen unless otherwise indicated. Nitrogen was dried using a drying tube equipped with Drierite™ unless otherwise noted. Air and moisture sensitive reagents were handled in a nitrogen-filled glovebox (working oxygen level <0.1 ppm). Column chromatography was performed with silica gel from Silicycle (40-63 μm) mixed as a slurry with the eluent. Columns were packed, rinsed, and run under air pressure. Analytical thin-layer chromatography (TLC) was performed on pre-coated glass silica gel plates (by EMD Chemicals Inc.) with F-254 indicator. Visualization was by short wave (254 nm) ultraviolet light, or by staining with ninhydrin, potassium permanganate, or I_2 on silica followed by brief heating on a hot plate or by a heat gun. Distillations were performed using a 3 cm short-path column under reduced pressure or by using a Hickman Still at ambient pressure.

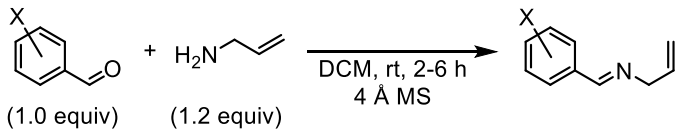
Instrumentation: ^{1}H NMR, ^{13}C NMR, and ^{19}F were recorded on a Varian Unity 400/500 MHz (100/125 MHz respectively for ^{13}C) or a VXR-500 MHz spectrometer. Spectra were referenced using either $CDCl_3$ or C_6D_6 as solvents (unless otherwise noted) with the residual solvent peak as the internal standard (^{1}H NMR: δ 7.26, ^{13}C NMR: δ 77.36 for $CDCl_3$ and ^{1}H NMR: δ 7.16, ^{13}C NMR: δ 128.62 for C_6D_6). Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet,) d (doublet,) t (triplet,) q (quartet,) p (pentet,) m (multiplet,) and br (broad). Coupling constants, *J*, are reported in Hertz and integration is provided, along with assignments, as indicated. Gas Chromatography (GC) was performed on a Shimadzu GC-2010 Plus gas chromatograph with SHRXI–MS- 15m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and

a flame ionization detector (FID). Low-resolution Mass Spectrometry and High Resolution Mass Spectrometry were performed in the Department of Chemistry at University of Illinois at Urbana-Champaign. The glove box, MBraun LABmaster sp, was maintained under nitrogen atmosphere.

Materials: Solvents used for extraction and column chromatography were reagent grade and used as received. Reaction solvents tetrahydrofuran (Fisher, unstabilized HPLC ACS grade), diethyl ether (Fisher, BHT stabilized ACS grade), methylene chloride (Fisher, unstabilized HPLC grade), dimethoxyethane (Fisher, certified ACS), toluene (Fisher, optima ACS grade), 1,4-dioxane (Fisher, certified ACS), acetonitrile (Fisher, HPLC grade), and hexanes (Fisher, ACS HPLC grade) were dried on a Pure Process Technology Glass Contour Solvent Purification System using activated stainless steel columns while following manufacture's recommendations for solvent preparation and dispensation unless otherwise noted. All amines and thiols were distilled, degassed, and stored under an atmosphere of nitrogen in glove box before use.

Synthesis of Starting Materials:

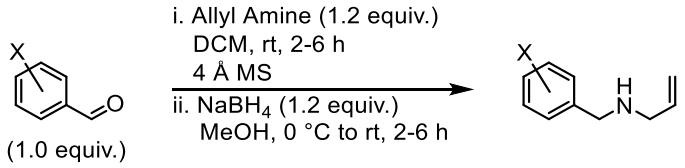
Synthesis of allyl imines



General procedure for the synthesis of imines

The corresponding benzaldehyde derivative (1.0 equiv), 4 Å MS (beads) and dry CH_2Cl_2 (1.0 M wrt benzaldehyde) were added to a round bottom flask with a stir bar. Allylamine (1.5 equiv) was added while stirring. The reaction mixture was stirred open to air at room temperature for 3-24 h. The crude mixture was filtered through Celite, washing with CH_2Cl_2. The filtrate was washed with water (200 mL × 2) and brine (200 mL × 1). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give imine. All imines were vacuum distilled using a short path distillation chamber and degassed, then stored under N_2 in the glovebox. The spectroscopic data for imines **7a**, **7c**, **7d**, **7h**, and **7j** agreed with reported literature: **7a**,[12a] **7c**,[12a] **7d**,[20] **7h**,[12a] **7j**.[21]

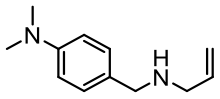
ii. Synthesis of secondary amines



General procedure for the synthesis of secondary amines

The corresponding aldehyde (1.0 equiv), 4 Å MS (beads) and dry CH_2Cl_2 (1.0 M wrt benzaldehyde) were added to a round bottom flask with a stir bar. Allylamine (1.2 equiv) was added while stirring. The reaction mixture was stirred open to air at room temperature for 3-12 h. The crude mixture was filtered through Celite, washing with CH_2Cl_2. The filtrate was concentrated under reduced pressure, dissolved in MeOH (1.0 M wrt aldehyde), then cooled to 0 °C. $NaBH_4$ (1.2 equiv) was slowly added. The solution was warmed to rt and stirred for 3-12 hours. The crude mixture was concentrated under reduced pressure and dissolved in $CHCl_3$. The solution was washed with a saturated solution of aqueous $NaHCO_3$ (200 mL x 1) and DI water (200 mL × 2). The organic layer was collected and dried with $MgSO_4$, filtered through a bed of Celite, and concentrated under reduced pressure to give amines **8a**-**8i**, **8k**. All amines were distilled under reduced pressure (0.1 torr) using a short path distillation chamber, degassed, then stored under N_2 in the glovebox. Amines **8a**, **8d**, **8f**, **8g**, **8h**, **8l**, **8m** were previously reported and consistent with literature spectra: **8a**[22], **8d**[23], **8f**[24], **8g**[25], **8h**[26], **8l**[27], **8m**[28].

Synthesis of **8b**



Amine **8b** was synthesized according to the general procedure for the synthesis of secondary amines with 4-(dimethylamino)benzaldehyde (6.96 mL, 50.00 mmol, 1.00 equiv), allyl amine (4.49 ml, 60.00 mmol, 1.20 equiv), and $NaBH_4$ (2.27 g, 60.00 mmol, 1.20 equiv). Purification by distillation under reduced pressure afforded amine 2b as a colorless liquid (6.24 g, 66%).

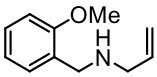
R_f (3% MeOH/CH_2Cl_2) = 0.08

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.29 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 5.89 (ddt, J = 17.2, 10.2, 5.8 Hz, 1H), 5.17 (dq, J = 17.1, 1.8 Hz, 1H), 5.02 (dq, J = 10.3, 1.5 Hz, 1H), 3.66 (s, 2H), 3.15 (dt, J = 5.9, 1.6 Hz, 2H), 2.55 (s, 6H), 0.96 (s, 1H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 150.20, 138.10, 129.38, 129.34, 115.15, 113.08, 53.32, 52.04, 40.54.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{12}H_{18}N_2$ = 190.1470; found mass = 190.1472

Synthesis of **8e**



Amine **8e** was synthesized according to the general procedure for the synthesis of secondary amines with *o*-methoxybenzaldehyde (6.09 mL, 50.0 mmol) and allyl amine (4.49 ml, 60.0 mmol). Purification by distillation under reduced pressure afforded amine 2e as a colorless liquid (7.06 g, 80%).

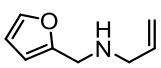
R_f (3% MeOH/CH_2Cl_2) = 0.04

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.33 (dd, J = 7.3, 1.8 Hz, 1H), 7.10 (td, J = 7.8, 1.8 Hz, 1H), 6.89 (td, J = 7.4, 1.1 Hz, 1H), 6.54 (dd, J = 8.1, 1.1 Hz, 1H), 5.91 (ddt, J = 17.3, 10.3, 5.7 Hz, 1H), 5.17 (dq, J = 17.2, 1.8 Hz, 1H), 5.01 (dq, J = 10.2, 1.6 Hz, 1H), 3.88 (s, 2H), 3.28 (s, 3H), 3.17 (dt, J = 5.7, 1.6 Hz, 2H), 1.33 (s, 1H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 157.96, 138.10, 129.84, 129.47, 128.06, 120.70, 115.17, 110.36, 54.76, 52.08, 48.59.

HRMS (EI-TOF) *m/z*: [M+H$^+$] calculated for $C_{11}H_{16}NO$ = 176.1075; found mass = 176.1072

Synthesis of **8i**



Amine **8i** was synthesized according to the general procedure for the synthesis of secondary amines with furane-2-carboxaldehyde (1.16 mL, 20.0.0 mmol) and allyl amine (2.24 ml, 30.0

mmol, 1.5 equiv). Purification by distillation under reduced pressure afforded amine 2i as a colorless liquid (979 mg, 36%).

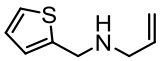
R_f (3% MeOH/CH_2Cl_2) = 0.12

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.11 (d, J = 1.6 Hz, 1H), 6.10 (dd, J = 3.1, 1.8 Hz, 1H), 6.00 (d, J = 3.2 Hz, 1H), 5.77 (ddt, J = 17.4, 10.4, 5.8 Hz, 1H), 5.09 (dq, J = 17.2, 1.8 Hz, 1H), 4.97 (dq, J = 10.4, 1.6 Hz, 1H), 3.57 (s, 2H), 3.02 (dt, J = 6.0, 1.5 Hz, 2H), 0.98 (s, 1H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 155.10, 141.65, 137.43, 115.54, 110.41, 106.78, 51.58, 45.76.

HRMS (EI-TOF) *m/z*: [M+H$^+$] calculated for $C_8H_{12}NO$ = 136.0762; found mass = 136.0759

Synthesis of **8j**



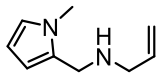
Amine **8j** was synthesized according to previously reported conditions.[29] Thiophene-2-carboxaldehyde (4.38 mL, 50.0 mmol) was dissolved in 2,2,2-trifluoroethanol in a 250 mL round bottom flask equipped with a stirbar. Allyl amine (4.49 mL, 60.0 mmol) was added and the reaction stirred for 10 minutes. The reaction was cooled to 0 °C and $NaBH_4$ (2.27 g, 60.0 mmol) was slowly added. After the reaction stirred for 10 minutes, the crude mixture was concentrated under reduced pressure and then dissolved in CH_2Cl_2. The solution was washed with an aqueous solution of NaOH (2M, 200 mL x 1) and DI water (200 mL × 2). The organic layer was collected and dried with $MgSO_4$, filtered through a bed of Celite, and concentrated under reduced pressure. The crude mixture was distilled under reduced pressure (0.1 torr) using a short path distillation chamber to afford 2j (3.75 g, 49%). *Note: the general conditions for secondary amines can also be used to synthesize **8j**.*

R_f (3% MeOH/CH_2Cl_2) = 0.16

^{1}H NMR (400 MHz, Benzene-d_6) δ 6.88 (dt, J = 5.1, 1.2 Hz, 1H), 6.79 – 6.68 (m, 2H), 5.74 (ddtd, J = 17.1, 10.2, 5.9, 1.0 Hz, 1H), 5.06 (ddt, J = 17.2, 2.8, 1.2 Hz, 1H), 4.97 (ddq, J = 10.1, 2.4, 1.3 Hz, 1H), 3.65 (s, 2H), 2.99 (d, J = 5.9 Hz, 2H).
^{13}C NMR (126 MHz, Benzene-d_6) δ 145.25, 137.35, 126.64, 124.63, 124.46, 115.59, 51.64, 47.97.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_8H_{11}NS$ = 153.0612; found mass = 153.0611

Synthesis of **8k**



Amine **8k** was synthesized according to the general procedure for the synthesis of secondary amines with 1-methyl-pyrrole-2-carboxaldehyde[30] (1.01 g, 9.209 mmol) and allyl amine (1.04 ml, 13.8 mmol, 1.5 equiv). Purification by distillation under reduced pressure afforded amine 2k as a colorless liquid (0.805 mg, 58%).

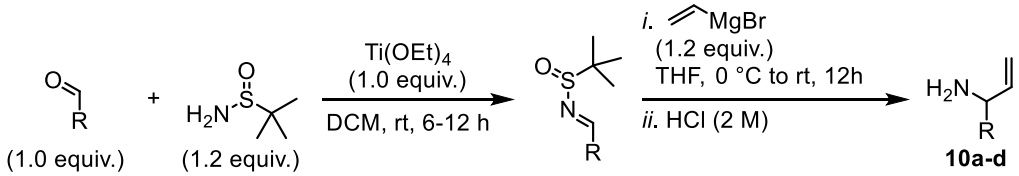
R_f (3% MeOH/CH_2Cl_2) = 0.12

^{1}H NMR (500 MHz, Benzene-d_6) δ 6.40 (t, *J* = 2.3 Hz, 1H), 6.25 (td, *J* = 3.0, 2.6, 0.9 Hz, 1H), 6.18 – 6.12 (m, 1H), 5.83 – 5.70 (m, 1H), 5.08 (dq, *J* = 17.2, 1.9 Hz, 1H), 4.98 (dq, *J* = 10.1, 1.5 Hz, 1H), 3.45 (s, 2H), 3.16 (s, 3H), 3.02 (dt, *J* = 6.0, 1.7 Hz, 2H), 0.65 (s, 1H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 137.68, 131.06, 122.42, 115.32, 108.76, 106.96, 51.91, 45.36, 33.31.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_9H_{14}N_2$ = 150.1157; found mass = 150.1161

iii. Synthesis of primary amines



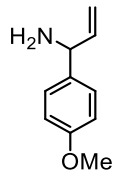
General procedure for the synthesis of primary amines

Titanium ethoxide (1.0 equiv) was added to a solution of CH_2Cl_2 (1M) and the corresponding aldehyde (1.0 equiv). Subsequently, 2-methylpropane-2-sulfinamide (1.2 equiv) was added and the solution stirred at room temperature for 6-12 hours. The reactions were monitored by crude NMR. Upon completion, water (ca. 15 mL) was added and white titanium salts precipitated from the solution. The mixture was filtered through Celite and the layers were separated in a separatory funnel. The aqueous layer was further extracted with CH_2Cl_2 (3 x 50 mL). The solution was dried

with $MgSO_4$, filtered, and concentrated *in-vacuo* to yield the corresponding imine, which was distilled under reduced pressure to purity.

In an oven-dried Schlenk flask, equipped with a stir bar, the sulfonimide intermediate (1.0 equiv) was dissolved in dry THF (1M) and the reaction was cooled to 0 °C. Vinylmagnesium bromide (1.2 equiv) was subsequently added and the solution warmed to room temperature and stirred overnight (ca. 12 hours). Reaction progress was monitored by crude NMR. To quench, the reaction was cooled to 0 °C and a saturated solution of aqueous NH_4Cl was added. The aqueous and organic layers were separated in a separatory funnel and the aqueous layer was further washed with CH_2Cl_2 (3 x 50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated *in-vacuo*. The amine was purified by column chromatography (ca. 100 mL silica, 5% NH_4OH and 0 to 5% MeOH in CH_2Cl_2) and distilled under reduced pressure to purity.

Synthesis of **10a**



Amine **10a** was synthesized according to the general procedure for the synthesis of primary amines with 4-methoxybenzaldehyde (3.04 mL, 25.0 mmol), 2-methylpropane-2-sulfinamide (3.3 g, 27.5 mmol, 1.1 equiv), and vinylmagnesium bromide (29.1 mL (1.00 M), 29.1 mmol, 1.20 equiv). The crude product was purified by column chromatography (ca. 100 mL silica, 5% NH_4OH and 0 to 5% MeOH in CH_2Cl_2), then distilled under reduced pressure (0.1 torr) to afford amine **10a** as a colorless liquid (979 mg, 25%).

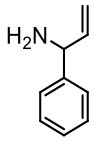
R_f (3% MeOH/CH_2Cl_2) = 0.16

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.26 – 7.20 (m, 2H), 6.84 – 6.77 (m, 2H), 5.93 (dddd, J = 16.2, 10.2, 6.1, 0.7 Hz, 1H), 5.15 (dt, J = 17.1, 1.6 Hz, 1H), 4.95 (dt, J = 10.3, 1.5 Hz, 1H), 4.27 (dd, J = 6.1, 1.5 Hz, 1H), 3.32 (s, 3H), 1.01 (s, 2H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.28, 143.71, 137.36, 128.21, 114.13, 112.80, 58.25, 54.83.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{10}H_{13}NO$ = 162.0919; found mass = 162.0920

Synthesis of **10b**



Amine **10b** was synthesized according to the general procedure for the synthesis of primary amines with benzaldehyde (2.04 mL, 20.0 mmol), 2-methylpropane-2-sulfinamide (2.91 g, 24.0 mmol, 1.20 equiv.), and vinylmagnesium bromide (24.0 mL (1.00 M), 24.0 mmol, 1.2 equiv). The crude product was purified by column chromatography (ca. 100 mL silica, 5% NH_4OH and 0 to 5% MeOH in CH_2Cl_2), then distilled under reduced pressure (0.1 torr) to afford amine **10b** as a colorless liquid (1.05 g, 40%).

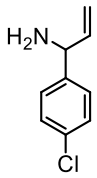
R_f (3% MeOH/CH_2Cl_2) = 0.10

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.30 – 7.20 (m, 2H), 7.15 – 7.10 (m, 2H), 7.08 – 7.00 (m, 1H), 5.86 (ddt, *J* = 11.6, 7.5, 3.8 Hz, 1H), 5.10 (dt, *J* = 17.1, 1.6 Hz, 1H), 4.91 (dt, *J* = 10.2, 1.6 Hz, 1H), 4.22 (d, *J* = 6.2 Hz, 1H), 1.32 (s (br), 2 H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 145.07, 143.10, 128.65, 127.22, 127.19, 113.26, 58.78.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_9H_{11}N$ = 132.0813; found mass = 132.0813

Synthesis of **10c**



Amine **10c** was synthesized according to the general procedure for the synthesis of primary amines with 4-chlorobenzaldehyde (3.51 g, 25.0.0 mmol) and 2-methylpropane-2-sulfinamide (3.33, 27.5 mmol, 1.1 equiv) and vinylmagnesium bromide (30.0 mL (1.00 M), 30.0 mmol, 1.2 equiv).. The crude product was purified by column chromatography (ca. 100 mL silica, 5% NH_4OH and 0 to 5% MeOH in CH_2Cl_2), then distilled under reduced pressure (0.1 torr) to afford amine 3c as a colorless liquid (708 mg, 18%).

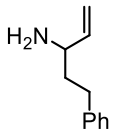
R_f (3% MeOH/CH_2Cl_2) = 0.16

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.14 – 7.09 (m, 2H), 7.01 – 6.96 (m, 2H), 5.72 (ddd, *J* = 16.7, 10.2, 6.2 Hz, 1H), 5.02 (dt, *J* = 17.0, 1.5 Hz, 1H), 4.89 (dt, *J* = 10.2, 1.4 Hz, 1H), 4.06 (d, *J* = 6.3 Hz, 1H), 0.85 (s, 2H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 143.63, 142.72, 132.87, 128.72, 128.54, 113.50, 58.03.

HRMS (EI-TOF) *m/z*: [M+H$^+$] calculated for $C_9H_{11}ClN$= 166.0423; found mass = 166.0425

Synthesis of **10d**



Amine **10d** was synthesized according to the general procedure for the synthesis of primary amines with hydrocynamylaldehyde and 2-methylpropane-2-sulfinamide and vinylmagnesium bromide (12.6 mL (1.00 M), 12.6 mmol, 1.20 equiv). The crude product was purified by column chromatography (ca. 100 mL silica, 5% NH_4OH and 0 to 5% MeOH in CH_2Cl_2), then distilled under reduced pressure (0.1 torr) to afford amine **10d** as a colorless liquid (511 mg, 25%).

R_f (5% MeOH/CH_2Cl_2) = 0.35

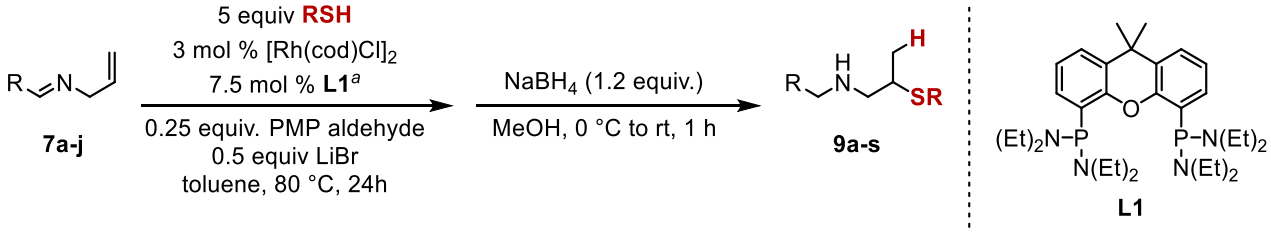
^{1}H NMR (400 MHz, Benzene-d_6) δ 7.22 – 7.13 (m, 2jH), 7.09 (d, *J* = 7.5 Hz, 3H), 5.66 (ddd, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.08 – 4.86 (m, 2H), 3.07 (q, *J* = 6.6 Hz, 1H), 2.55 (t, *J* = 7.9 Hz, 2H), 1.69 – 1.45 (m, 2H), 1.07 (s, 2H).

^{13}C NMR (101 MHz, Benzene-d_6) δ 144.07, 142.67, 128.80, 128.67, 126.06, 113.11, 54.13, 39.54, 32.68.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{11}H_{15}N$ = 161.1204; found mass = 161.1202

Markovnikov-Selective Hydrothiolation of Allyl Imines and Amines

i. Markovnikov-selective hydrothiolation of allyl imines

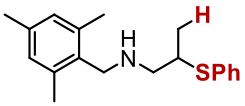


General Procedure for the Markovnikov hydrothiolation of imines

$[Rh(cod)Cl]_2$ (5.92 mg, 0.012 mmol, 3.0 mol %), L1 (16.76 mg, 0.03 mmol, 7.5 mol %), LiBr (17.37 mg, 0.2 mmol, 0.5 equiv), dry toluene (200 μL), imine (0.4 mmol, 1.0 equiv), and the corresponding aldehyde (0.1 mmol, 0.25 equiv) were added to 4 mL scintillation vial equipped with a magnetic stir bar in the glove box. The reaction stirred in the glove box for 45 minutes. Subsequently, thiol (2.0 mmol, 5.0 equiv) was added. The vial was sealed with a Teflon-lined cap, brought out of the glove box and stirred at 80 ˚C for 24 h. After 24 hours, the crude solution was cooled to room temperature, transferred to a 100 mL round bottom flask, and dissolved in MeOH. $NaBH_4$ (22.70 mg, 1.5 equiv, 0.6 mmol) was added at 0 °C and the reaction stirred for ca. 1 h. The crude mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2, and washed with $NaHCO_3$ (1 x 50 mL). The crude solution was dried with $MgSO_4$, filtered through a bed of Celite, and concentrated under reduced pressure. The resulting 1,2-aminothioether was purified by silica gel chromatography (125 mL silica loaded in 10% Et_2O in CH_2Cl_2 and eluted with 3% NH_4OH : 2 to 3% MeOH : 10 % Et_2O: 84 to 85% $CHCl_2$ v/v prepared by extracting saturated NH_4OH with CH_2Cl_2, removing aqueous layer, then adding to a solution of MeOH and Et_2O). Following *in-vacuo* concentration, the amine was dissolved in hexanes and filtered through a celite plug to remove [Rh] and afford the pure 1,2-aminothioether.

Products **9a**, **9d**, **9h**, **9j**, and **9r** were synthesized by the general procedure from imines 7**a**, **7d**, **7h**, **7j**, and **7a**, respectively. The spectroscopic data was consistent with products **9a**, **9d**, **9h**, **9j**, and **9r** obtained from the hydrothiolation of secondary amines **8a**, **8d**, **8h**, **8j**, and **8a**. See hydrothiolation of secondary amine section for full characterization data of **9a**, **9d**, **9h**, **9j**, and **9r**.

Synthesis of **9c** from imine **7c**



9c was synthesized according to the general procedure for the Markovnikov hydrothiolation of imines at 100 °C with 1c (0.4 mmol, 74.86 mg), mesitylaldehyde (0.1 mmol, 14.58 µL) and thiophenol (2.0 mmol, 205.37 µL). The reduced product was purified by silica gel chromatography to afford **9c** (78.9 mg, 66% yield) as a pale yellow oil.

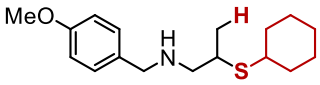
R_f (3% MeOH/CH_2Cl_2) = 0.39

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.36 – 7.32 (m, 2H), 7.02 – 6.97 (m, 2H), 6.97 – 6.92 (m, 1H), 6.78 (s, 2H), 3.60 (d, *J* = 6.2 Hz, 2H), 3.21 (h, *J* = 6.7 Hz, 1H), 2.71 (dd, *J* = 12.1, 6.7 Hz, 1H), 2.61 (dd, *J* = 12.1, 5.9 Hz, 1H), 2.32 (s, 3H), 2.16 (s, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.13 (s, 1H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 137.15 , 136.28 , 135.45 , 134.18 , 132.57 , 129.37 , 129.07 , 126.98 , 55.14 , 47.80 , 44.13 , 21.08 , 19.75, 19.73.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{19}H_{26}NS$ = 300.1786; found mass = 300.1787

Synthesis of **9r** from imine **7a**



9r was synthesized according to the general procedure for the Markovnikov hydrothiolation of imines at 100 °C with **7a** (0.4 mmol, 68.91 mg), mesitylaldehyde (0.1 mmol, 12.16 µL) and cyclohexanethiol (2.0 mmol, 244.94 µL). The reduced product was purified by silica gel chromatography to afford **9r** (69.2 mg, 59% yield) as a pale yellow oil.

R_f (3% MeOH/CH_2Cl_2) = 0.40

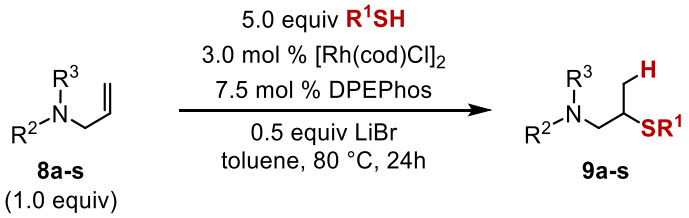
^{1}H NMR (500 MHz, Benzene-d_6) δ 7.27 – 7.23 (m, 2H), 6.85 – 6.80 (m, 2H), 3.64 (s, 2H), 3.33 (s, 3H), 2.88 (p, *J* = 6.6 Hz, 1H), 2.68 – 2.54 (m, 3H), 1.89 (dq, *J* = 12.2, 3.6 Hz, 2H), 1.65 – 1.56 (m, 2H), 1.45 – 1.28 (m, 4H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.12 – 1.07 (m, 2H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.27, 133.23, 129.55, 114.10, 55.38, 54.82, 53.49, 42.90, 39.72, 34.74 (d, J = 22.2 Hz), 26.37, 26.15, 21.06.

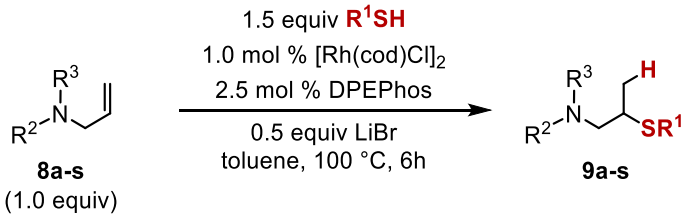
HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{28}NOS$ = 294.1892; found mass = 294.1893

ii. Markovnikov-selective hydrothiolation of secondary allyl amines

Conditions A:



Conditions B:



General procedures for the Markovnikov hydrothiolation of secondary amines

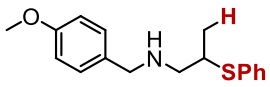
Conditions A:

$[Rh(cod)Cl]_2$ (5.92 mg, 0.012 mmol, 3.0 mol %), DPEphos (16.16 mg, 0.03 mmol, 7.5 mol %), LiBr (17.37 mg, 0.2 mmol, 0.5 equiv), dry toluene (200 μL), and amine (0.4 mmol, 1.0 equiv) were added to 4 mL scintillation vial equipped with a stir bar in the glove box. Subsequently, thiol (2.0 mmol, 5.0 equiv) was added. The vial was sealed with a Teflon-lined cap, brought out of the glove box and stirred at 80 ˚C for 24 h. The crude solution was cooled to room temperature, dissolved in CH_2Cl_2, and purified by silica gel chromatography (125 mL silica loaded in 10% Et_2O in CH_2Cl_2, 3% NH_4OH : 2 to 3% MeOH : 10 % Et_2O: 84 to 85% $CHCl_2$ v/v prepared by extracting saturated NH_4OH with CH_2Cl_2, removing aqueous layer, then adding to a solution of MeOH and Et_2O). Following *in-vacuo* concentration, the amine was dissolved in hexanes and filtered through a celite plug to remove [Rh] and afford the pure 1,2-aminothioether.

Conditions B:

$[Rh(cod)Cl]_2$ (1.97 mg, 0.004 mmol, 1.0 mol %), DPEphos (5.39 mg, 0.01 mmol, 7.5 mol %), LiBr (17.37 mg, 0.2 mmol, 0.5 equiv), dry toluene (200 µL), and amine (0.4 mmol, 1.0 equiv) were added to 4 mL scintillation vial equipped with a stir bar in the glove box. Subsequently, thiol (0.6 mmol, 1.5 equiv) was added. The vial was sealed with a Teflon-lined cap, brought out of the glove box and stirred at 80 ˚C for 24 h. The crude solution was cooled to room temperature, dissolved in CH_2Cl_2, and purified by silica gel chromatography (125 mL silica loaded in 10% Et_2O in CH_2Cl_2, and eluted with 3% NH_4OH : 2 to 3% MeOH : 10 % Et_2O: 84 to 85% $CHCl_2$ v/v prepared by extracting saturated NH_4OH with CH_2Cl_2, removing aqueous layer, then adding to a solution of MeOH and Et_2O). Following i*n-vacuo* concentration, the amine was dissolved in hexanes and filtered through a celite plug to remove [Rh] and afford the pure 1,2-aminothioether.

Synthesis of **9a**



9a was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8a** (0.4 mmol, 70.85 mg) and thiophenol (A: 2.0 mmol, 205.37 µL; B: 0.6 mmol, 61.61 µL). The crude product was purified by silica gel chromatography to afford **9a** (A: 83.3 mg, 73% yield; B: 72.3 mg, 63% yield) as a pale yellow oil.

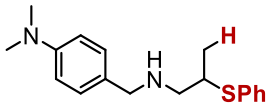
R_f (3% MeOH/CH_2Cl_2) = 0.36

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.36 (m, 2H), 7.19 (m, 2H), 7.01 (m, 2H), 6.98 – 6.93 (m, 1H), 6.84 – 6.79 (m, 2H), 3.55 (s, 2H), 3.34 (s, 3H), 3.22 (h, *J* = 6.5 Hz, 1H), 2.64 (dd, *J* = 12.2, 6.6 Hz, 1H), 2.56 (dd, *J* = 12.2, 6.2 Hz, 1H), 1.21 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.10, 135.44, 133.02, 132.32, 129.36, 128.92, 126.78, 113.92, 54.66, 54.29, 53.21, 44.04, 19.53.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{22}NOS$ = 288.1422; found mass = 288.1428

Synthesis of **9b**



9b was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8b** (0.4 mmol, 76.06 mg) and thiophenol (A: 2.0 mmol, 205.37 µL; B: 0.6 mmol, 61.61 µL). The crude product was purified by silica gel chromatography to afford **9b** (A: 57.1 mg, 48% yield; B: 53.8 mg, 45% yield) as a pale yellow oil.

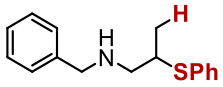
R_f (3% MeOH/CH_2Cl_2) = 0.38

^{1}H NMR (400 MHz, Benzene-d_6) δ 7.39 - 7.34 (m, 2H), 7.31 – 7.26 (m, 2H), 7.04 – 6.92 (m, 3H), 6.67 – 6.62 (m, 2H), 3.65 (s, 2H), 3.26 (h, *J* = 6.6 Hz, 1H), 2.71 (dd, *J* = 12.2, 6.6 Hz, 1H), 2.62 (dd, *J* = 12.2, 6.2 Hz, 1H), 2.54 (s, 6H), 1.22 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 150.24, 135.74, 132.51, 129.36, 129.21, 129.06, 126.86, 113.10, 54.50, 53.67, 44.27, 40.52, 19.75.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{18}H_{25}N_2S$ = 299.1582; found mass = 299.1574

Synthesis of **9d**



9d was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A) with **8d** (0.4 mmol, 58.84 mg) and thiophenol (2.0 mmol, 205.37 µL). The crude product was purified by silica gel chromatography to afford **9d** (76.4 mg, 74% yield) as a pale yellow oil.

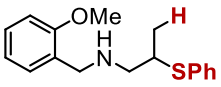
R_f (3% MeOH/CH_2Cl_2) = 0.38

^{1}H NMR (500 MHz, Benzene-d6) δ 7.37 – 7.32 (m, 2H), 7.28 – 7.24 (m, 2H), 7.20 – 7.15 (m, 2H), 7.13 – 7.08 (m, 1H), 7.03 – 6.98 (m, 2H), 6.98 – 6.93 (m, 1H), 3.54 (s, 2H), 3.23 – 3.14 (m, 1H), 2.60 (dd, J = 12.2, 6.6 Hz, 1H), 2.52 (dd, J = 12.2, 6.1 Hz, 1H), 1.38 (s, 1H), 1.18 (d, J = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 141.02, 135.38, 132.34, 128.92, 128.41, 128.21, 126.94, 126.80, 54.3, 53.71, 44.02, 19.49.

HRMS (ESI-TOF) *m/z*: [M] calculated for $C_{16}H_{19}NS$ = 257.1204; found mass = 257.1237

Synthesis of **9e**



9e was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions B) with **8e** (0.4 mmol, 70.85 mg) and thiophenol (A: 2.0 mmol, 205.37 µL; B: 0.6 mmol, 61.61 µL). The crude product was purified by silica gel chromatography to afford **9e** (A: 83.5 mg, 73% yield; 76.3 mg, 66% yield) as a pale yellow oil.

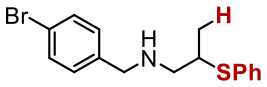
R_f (3% MeOH/CH_2Cl_2) = 0.33

^{1}H NMR (400 MHz, Benzene-d_6) δ 7.39 - 7.33 (m, 2H), 7.32 - 7.27 (m, 1H), 7.14 - 7.06 (m, 1H), 7.02 - 6.91 (m, 3H), 6.88 (td, *J* = 7.5, 1.2 Hz, 1H), 6.53 (dd, *J* = 7.9, 1.2 Hz, 1H), 3.88 (s, 2H), 3.30 (s, 3H), 3.26 (h, *J* = 6.9 Hz, 1H), 2.71 (ddt, *J* = 12.1, 6.6, 1.1 Hz, 1H), 2.62 (ddt, *J* = 12.1, 5.9, 1.0 Hz, 1H), 1.95 (s, 1H), 1.21 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 157.99, 135.46, 132.80, 129.88, 129.31, 129.02, 128.17, 126.95, 120.74, 110.41, 54.82, 54.54, 49.12, 44.38, 19.73.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{22}NOS$ = 288.1422; found mass = 288.1417

Synthesis of **9f**



9f was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and conditions B) with **8f** (0.4 mmol, 90.01 mg) and thiophenol (A: 2.0 mmol, 205.37 µL; B: 0.6 mmol, 61.61 µL). The crude product was purified by silica gel chromatography to afford **9f** (A: 94.3 mg, 70% yield; B: 52.5 mg, 39% yield) as a pale yellow oil.

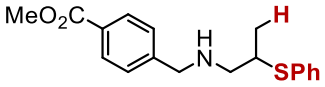
R_f (3% MeOH/CH_2Cl_2) = 0.36

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.35 – 7.30 (m, 2H), 7.27 (dd, J = 8.1, 1.3 Hz, 2H), 7.04 – 6.93 (m, 3H), 6.87 (d, J = 8.0 Hz, 2H), 3.31 (s, 2H), 3.14 (h, J = 6.9 Hz, 1H), 2.49 (dd, J = 12.3, 6.6 Hz, 1H), 2.43 (dd, J = 12.3, 6.0 Hz, 1H), 1.26 (s, 1H), 1.17 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 139.92, 135.21, 132.33, 131.45, 129.86, 128.97, 126.93, 120.72, 54.13, 52.77, 43.95, 19.45.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{16}H_{18}BrNS$ = 336.0422; found mass = 336.0417

Synthesis of **9g**



9g was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8g** (0.4 mmol, 82.04 mg) and thiophenol (A: 2.0 mmol, 205.37 µL; B: 0.6 mmol, 61.61 µL). The crude product was purified by silica gel chromatography to afford **9g** (A: 68.3 mg, 54% yield; B: 44.1 mg, 33% yield) as a pale yellow oil.

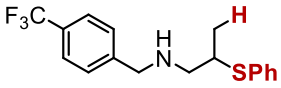
R_f (3% MeOH/CH_2Cl_2) = 0.36

^{1}H NMR (500 MHz, Benzene-d_6) δ 8.14 (d, J = 8.2 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.21 – 7.14 (m, 2H), 7.05 – 6.92 (m, 3H), 3.52 (s, 3H), 3.43 (s, 2H), 3.15 (h, J = 6.5 Hz, 1H), 2.52 (dd, J = 12.2, 6.5 Hz, 1H), 2.45 (dd, J = 12.1, 6.0 Hz, 1H), 1.33 (s, 2H), 1.18 (d, J = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 166.73, 146.42, 135.44, 132.48, 130.01, 129.52, 129.12, 128.15, 127.08, 54.50, 53.33, 51.57, 44.13, 19.60.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{16}H_{22}NO_2S$ = 316.1371; found mass = 316.1364

Synthesis of **9h**



9h was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8h** (0.4 mmol, 86.04 mg) and thiophenol (A: 2.0

mmol, 205.37 µL; B: 0.6 mmol, 61.61 µL). The crude product was purified by silica gel chromatography to afford **9h** (A: 53.9 mg, 41% yield; B: 33.5 mg, 26% yield) as a pale yellow oil.

R_f (3% MeOH/CH_2Cl_2) = 0.38

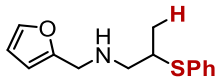
^{1}H NMR (500 MHz, Benzene-d_6) δ 7.38 – 7.31 (m, 4H), 7.07 – 6.93 (m, 5H), 3.35 (s, 2H), 3.14 (h, *J* = 6.8 Hz, 1H), 2.47 (dd, *J* = 12.2, 6.6 Hz, 1H), 2.42 (dd, *J* = 12.2, 5.9 Hz, 1H), 1.18 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 144.54, 134.17, 132.70, 129.34 (q, *J* = 32.1 Hz), 129.00, 128.37, 127.33, 125.42 (q, *J* = 3.8 Hz), 124.40 (q, *J* = 272.10 Hz), 54.15, 52.85, 43.97, 19.40.

^{19}F NMR (376 MHz, Benzene-d_6) δ -114.90.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{19}F_3NS$ = 326.1190; found mass = 326.1194

Synthesis of **9i**



9i was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8i** (0.4 mmol, 54.83 mg) and thiophenol (A: 2.0 mmol, 205.37 µL; B: 0.6 mmol, 61.61 µL). The crude product was purified by silica gel chromatography to afford **9i** (A: 68.7 mg, 70% yield; B: 45.8 mg, 46% yield) as a pale yellow oil.

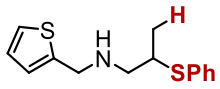
R_f (3% MeOH/CH_2Cl_2) = 0.42

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.36 – 7.32 (m, 2H), 7.09 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.04 – 6.92 (m, 3H), 6.08 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.99 – 5.94 (m, 1H), 3.55 (s, 2H), 3.13 (h, *J* = 6.7 Hz, 1H), 2.59 (dd, *J* = 12.1, 6.6 Hz, 1H), 2.49 (dd, *J* = 12.1, 6.1 Hz, 1H), 1.46 (s, 1H), 1.16 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 154.85, 141.53, 135.18, 132.54, 128.89, 126.85, 110.26, 106.65, 54.04, 46.19, 44.01, 19.42.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{18}NOS$ = 248.1109; found mass = 248.1106

Synthesis of **9j**



9j was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8j** (0.4 mmol, 61.22 mg) and thiophenol (A: 2.0 mmol, 205.37 µL; B: 0.6 mmol, 61.61 µL). The crude product was purified by silica gel chromatography to afford **9j** (A: 71.8 mg, 68% yield; B: 46.0 mg, 45% yield) as a pale yellow oil.

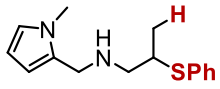
R_f (3% MeOH/CH_2Cl_2) = 0.48

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.36 – 7.31 (m, 2H), 7.03 – 6.98 (m, 2H), 6.98 – 6.93 (m, 1H), 6.89 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.74 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.71 (dq, *J* = 3.4, 1.0 Hz, 1H), 3.65 (d, *J* = 1.0 Hz, 2H), 3.19 – 3.10 (m, 1H), 2.59 (dd, *J* = 12.2, 6.6 Hz, 1H), 2.51 (dd, *J* = 12.1, 6.2 Hz, 1H), 1.41 (s, 1H), 1.17 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 145.14, 135.31, 132.33, 128.92, 126.81, 126.49, 124.49, 124.36, 54.05, 48.36, 43.91, 19.41.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{18}NS_2$ = 264.0881; found mass = 264.0885

Synthesis of **9k**



9k was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A at 60 °C instead of 80 °C) with **8k** (60.09 mg, 0.4000 mmol) and thiophenol (205.37 µL, 2.000 mmol). The crude product was purified by silica gel chromatography to afford **9k** (39.7 mg, 38% yield) as a yellow oil.

R_f (3% MeOH/CH_2Cl_2) = 0.33

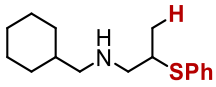
^{1}H NMR (500 MHz, Benzene- d_6) δ 7.34 (d, *J* = 7.9 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 2H), 6.96 (t, *J* = 7.3 Hz, 1H), 6.40 (t, *J* = 2.2 Hz, 1H), 6.24 (t, *J* = 3.1 Hz, 1H), 6.13 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.44

(s, 2H), 3.18 (s, 3H), 3.11 (ddt, *J* =6.0, 6.8, 6.7 Hz, 1H), 2.58 (dd, *J* = 12.4, 6.7 Hz, 1H), 2.51 (dd, *J* = 12.2, 6.0 Hz, 1H), 1.13 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 135.55, 132.48, 130.83, 129.03, 126.91, 122.45, 108.84, 106.92, 54.24, 45.72, 43.96, 33.30, 19.57

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{15}H_{20}N_2S$ = 260.1347; found mass = 260.1353.

Synthesis of **9l**



9l was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8l** (0.4 mmol, 61.26 mg) and thiophenol (A: 2.0 mmol, 205.37 µL; B: 0.6 mmol, 61.61 µL). The crude product was purified by silica gel chromatography to afford **9l** (A: 68.3 mg, 65% yield; B: 51.2 mg, 48% yield) as a pale yellow oil.

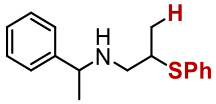
R_f (3%MeOH/CH_2Cl_2) = 0.26

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.44 – 7.39 (m, 2H), 7.04 – 7.00 (m, 2H), 6.98 – 6.93 (m, 1H), 3.26 (h, *J* = 6.7 Hz, 1H), 2.66 (dd, *J* = 12.2, 6.7 Hz, 1H), 2.56 (dd, *J* = 12.2, 6.1 Hz, 1H), 2.30 (dd, *J* = 6.6, 1.6 Hz, 2H), 1.78 – 1.71 (m, 2H), 1.71 – 1.59 (m, 3H), 1.34 – 1.26 (m, 1H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.22 – 1.07 (m, 3H), 0.85 (qd, *J* = 12.1, 3.3 Hz, 2H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 135.54, 132.32, 128.92, 126.78, 56.74, 55.49, 44.13, 38.43, 31.62, 27.01, 26.38, 19.57.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{16}H_{26}NS$ = 264.1786; found mass = 264.1783

Synthesis of **9m**



9m was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8m** (0.4 mmol, 64.45 mg) and thiophenol (A: 2.0

mmol, 205.37 µL; B: 0.6 mmol, 61.61 µL). The crude product was purified by silica gel chromatography to afford **9m** (A: 62.5 mg, 58% yield; B: 23.7 mg, 22% yield) as a pale yellow oil.

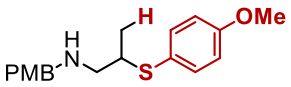
R_f (3% MeOH/CH_2Cl_2) = 0.38

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.37 – 7.33 (m, 2H), 7.33 – 7.25 (m, 3H), 7.22 – 7.17 (m, 2H), 7.10 (m, 1H), 7.03 – 6.92 (m, 3H), 3.54 (p, *J* = 6.7 Hz, 1H), 3.25 – 3.12 (m, 1H), 2.59 – 2.44 (m, 2H), 1.21 – 1.13 (m, 6H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 146.34, 146.25, 135.50, 135.47, 132.24, 132.03, 128.91, 128.54, 126.99, 126.82, 126.76, 126.65, 58.44, 58.31, 53.10, 52.71, 44.33, 43.99, 24.92, 24.85, 19.60, 19.36.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{22}NS$ = 272.1473; found mass = 272.1470

Synthesis of **9n**



9n was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8a** (0.4 mmol, 70.85 mg) and *p*-methoxythiophenol (A: 2.0 mmol, 246.84 µL; B: 0.6 mmol, 73.68 µL). The crude product was purified by silica gel chromatography to afford **9n** (A: 82.3 mg, 65% yield; B: 58.4 mg, 46% yield) as a pale yellow oil.

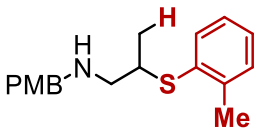
R_f (3% MeOH/CH_2Cl_2) = 0.19

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.39 – 7.32 (m, 2H), 7.25 – 7.19 (m, 2H), 6.85 – 6.78 (m, 2H), 6.68 – 6.61 (m, 2H), 3.60 (s, 2H), 3.34 (s, 3H), 3.23 (s, 3H), 3.11 (h, J = 6.8 Hz, 1H), 2.64 (dd, J = 12.1, 6.9 Hz, 1H), 2.57 (dd, J = 12.1, 5.9 Hz, 1H), 1.50 (s, 1h), 1.22 (d, J = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 160.04, 159.26, 136.38, 133.28, 129.58, 124.82, 114.75, 114.09, 54.82, 54.80, 54.26, 53.41, 45.35, 19.72.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{18}H_{24}NO_2S$ = 318.1528; found mass = 318.1526

Synthesis of **9o**



9o was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A) with **8a** (0.4 mmol, 70.85 mg) and *o*-methylthiophenol (2.0 mmol, 236.57 µL). The crude product was purified by silica gel chromatography to afford **9o** (78.6 mg, 65% yield) as a pale yellow oil.

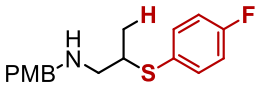
R_f (5% MeOH/CH_2Cl_2) = 0.428

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.35 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.01 – 6.93 (m, 3H), 6.81 (dt, *J* = 8.5, 2.8, 1.9 Hz, 2H), 3.55 (s, 2H), 3.34 (s, 3H), 3.23 (q, *J* = 6.6 Hz, 1H), 2.69 (dd, *J* = 12.2, 6.3 Hz, 1H), 2.58 (dd, *J* = 12.1, 6.3 Hz, 1H), 2.36 (s, 3H), 1.37 (s, 1H), 1.22 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.10, 139.46, 135.08, 132.93, 131.60, 130.45, 129.36, 126.66, 126.49, 113.91, 54.66, 54.52, 53.26, 43.30, 20.83, 19.44.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{18}H_{24}NOS$ = 302.1579; found mass = 302.1582.

Synthesis of **9q**



9q was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8a** (0.4 mmol, 70.85 mg) and *p*-fluorothiophenol (A: 2.0 mmol, 213.08 µL; B: 0.6 mmol, 64.00 µL). The crude product was purified by silica gel chromatography to afford **9q** (A: 57.7 mg, 47% yield; B: 34.2 mg, 28% yield) as a pale yellow oil.

R_f (3% MeOH/CH_2Cl_2) = 0.23

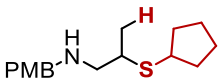
^{1}H NMR (500 MHz, Benzene-d_6) δ 7.19 (d, J = 8.5 Hz, 2H), 7.15 – 7.09 (m, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.64 (t, J = 8.7 Hz, 2H), 3.56 (s, 1H), 3.34 (s, 1H), 3.03 (h, J = 6.7 Hz, 0H), 2.56 (dd, J = 12.2, 6.7 Hz, 0H), 2.49 (dd, J = 12.2, 6.0 Hz, 0H), 1.36 (s, 1H), 1.14 (d, J = 6.8 Hz, 1H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 163.67, 161.71, 159.33, 135.54 (d, J = 8.1 Hz), 133.07, 129.54, 116.05 (d, J = 21.7 Hz), 114.11, 54.82, 54.14, 53.36, 45.01, 19.57.

^{19}F NMR (376 MHz, Benzene-d_6) δ -62.37.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{21}FNOS$ = 306.1328; found mass = 306.1323.

Synthesis of **9s**



9s was synthesized according to the general procedure for the Markovnikov hydrothiolation of secondary amines (conditions A and B) with **8a** (0.4 mmol, 70.85 mg) and cyclopentane thiol (A: 2.0 mmol, 214.03 µL; B: 0.6 mmol, 64.08 µL). The crude product was purified by silica gel chromatography to afford **9s** (A: 66.3 mg, 59% yield; B: 29.1 mg, 26% yield) as a pale yellow oil.

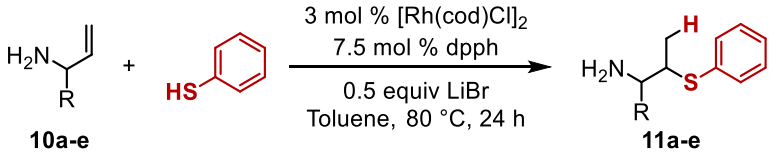
R_f (3% MeOH/CH_2Cl_2) = 0.25

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 3.64 (s, 2H), 3.33 (s, 3H), 2.95 (p, *J* = 7.2 Hz, 1H), 2.86 (h, *J* = 6.7 Hz 1H), 2.68 – 2.58 (m, 2H), 1.88 – 1.77 (m, 2H), 1.65 – 1.56 (m, 3H), 1.55 – 1.44 (m, 2H), 1.40 – 1.29 (m, 2H), 1.26 (dd, *J* = 6.9, 0.9 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.27, 133.32, 129.52, 114.10, 55.24, 54.81, 53.53, 42.98, 41.17, 34.85 (d, *J* = 12.5 Hz), 25.05 (d, *J* = 7.0 Hz), 20.70.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{23}NS$ = 280.1735; found mass = 280.1737

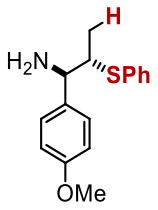
iii. Markovnikov-selective hydrothiolation of primary allyl amines



General Procedure for Markovnikov hydrothiolation of primary amines

$[Rh(cod)Cl]_2$ (4.44 mg, 0.009 mmol, 3.0 mol %), dpph (10.23 mg, 0.0225 mmol, 7.5 mol %), LiBr (13.03 mg, 0.15 mmol, 0.5 equiv) and dry toluene (150 µL) were added to 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added amine (0.3 mmol, 1.0 equiv). Subsequently, thiophenol (1.5 mmol, 5.0 equiv, 154.03) was added. The vial was brought out of the box (sealed) and stirred at 80 ˚C for 24 h. The crude solution was cooled to room temperature, dissolved in CH_2Cl_2, and purified by silica gel chromatography (125 mL silica loaded in 10% Et_2O in CH_2Cl_2, and eluted with 3% NH_4OH : 2 to 3% MeOH : 10 % Et_2O: 84 to 85% $CHCl_2$ v/v prepared by extracting saturated NH_4OH with CH_2Cl_2, removing aqueous layer, then adding to a solution of MeOH and Et_2O). Following *in-vacuo* concentration, the amine was dissolved in hexanes and filtered through a celite plug to remove [Rh] and afford the pure 1,2-aminothioether.

Synthesis of **11a**



11a was synthesized according to general procedure for Markovnikov hydrothiolation of primary amines with **10a** (0.3 mmol, 48.93 mg). The crude product was purified by silica gel chromatography to afford **11a** (72.1 mg, 88% yield) as a pale yellow oil.

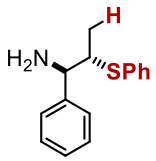
R_f (3% MeOH/CH_2Cl_2) = 0.28

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.39 (d, J = 7.1 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H), 7.04 (t, J = 7.4 Hz, 2H), 6.98 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 8.7 Hz, 2H), 4.04 (d, *J* = 3.5 Hz, 1H), 3.45 (qd, *J* = 7.0, 3.5 Hz, 1H), 3.32 (s, 3H), 1.26 (s, 2H), 1.19 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.26, 136.21, 135.79, 132.26, 129.23, 128.32, 127.03, 113.88, 56.86, 54.79, 51.56, 14.06.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{16}H_{19}NOS$ = 273.1187; found mass = 273.1182

Synthesis of **11b**



11b was synthesized according to general procedure for Markovnikov hydrothiolation of primary amines with **10b** (0.3 mmol, 39.93 mg). The crude product was purified by silica gel chromatography to afford **11b** (56.0 mg, 77% yield) as a pale yellow oil.

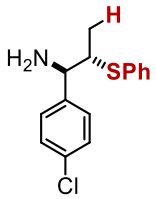
R_f (3% MeOH/CH_2Cl_2) = 0.36

^{1}H NMR (499 MHz, Benzene-d6) δ 7.37 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 7.1 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 7.10 – 7.02 (m, 3H), 6.98 (t, J = 7.3 Hz, 1H), 4.04 (d, J = 3.4 Hz, 1H), 3.44 (qd, J = 7.0, 3.4 Hz, 1H), 1.24 (s, 2H), 1.14 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 143.87, 136.07, 132.30, 129.24, 128.37, 127.31, 127.22, 127.09, 57.28, 51.41, 13.82.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{15}H_{17}NS$ = 243.1082; found mass = 243.1082

Synthesis of **11c**



11c was synthesized according to general procedure for Markovnikov hydrothiolation of primary amines with **10c** (0.3 mmol, 50.12 mg). The crude product was purified by silica gel chromatography to afford **11c** (67.7 mg, 81% yield) as a pale yellow oil.

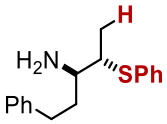
R_f (3% MeOH/CH_2Cl_2) = 0.40

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.33 (d, J = 7.2 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.03 (t, J = 7.3 Hz, 2H), 7.00 – 6.97 (m, 1H), 6.95 (d, J = 8.2 Hz, 2H), 3.84 (d, *J* = 3.6 Hz, 1H), 3.28 (qd, *J* = 7.0, 3.5 Hz, 1H), 1.12 (s, 2H), 1.04 (dd, *J* = 7.0, 1.0 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 142.30, 135.70, 132.88, 132.42, 129.28, 128.71, 128.48, 127.29, 56.63, 51.16, 13.76.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{15}H_{16}ClNS$ = 277.0692; found mass = 277.0691

Synthesis of **11d**



11d was synthesized according to general procedure for Markovnikov hydrothiolation of primary amines with **10d** (0.3 mmol, 48.34 mg). The crude product was purified by silica gel chromatography to afford **11d** (42.1 mg, 52% yield) as a pale yellow oil.

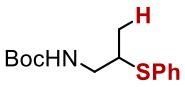
R_f (3% MeOH/CH_2Cl_2) = 0.24

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.31 (dt, *J* = 6.2, 1.3 Hz, 2H), 7.18 – 7.11 (m, 2H), 7.09 – 7.04 (m, 1H), 7.04 – 6.97 (m, 4H), 6.97 – 6.91 (m, 1H), 3.08 (qd, *J* = 7.0, 3.3 Hz, 1H), 2.76 (dt, *J* = 9.1, 3.8 Hz, 1H), 2.64 (ddd, *J* = 14.5, 9.7, 5.4 Hz, 1H), 2.42 (ddd, *J* = 13.6, 9.6, 6.7 Hz, 1H), 1.55 (dddd, *J* = 13.7, 9.4, 6.8, 4.1 Hz, 1H), 1.44 (ddt, *J* = 14.7, 9.4, 4.7 Hz, 1H), 1.07 (dd, *J* = 7.0, 3.2 Hz, 3H), 0.92 (s, 2H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 142.57, 136.23, 132.02, 129.17, 128.77, 128.66, 126.82, 126.08, 53.43, 50.71, 36.86, 33.36, 14.75.

HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{17}H_{21}NS$ = 272.1473; found mass = 272.1469

Synthesis of boc-protected-**11e**



$[Rh(cod)Cl]_2$ (4.44 mg, 0.009 mmol, 3.0 mol %), dpph (10.23 mg, 0.0225 mmol, 7.5 mol %), LiBr (13.03 mg, 0.15 mmol, 0.5 equiv) and dry toluene (150 µL) were added to 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added allyl amine (0.3 mmol, 1.0 equiv, 22.45 µL). Subsequently, thiophenol (1.5 mmol, 5.0 equiv, 154.03 µL) was added. The vial was brought out of the box (sealed) and stirred) at 100 ˚C for 48 h. After cooling to room temperature, di-*tert*-butyl carbonate (0.45 mmol, 1.5 equiv., 103.38 µL) was added and the reaction stirred for 6 hours. The crude product was purified by silica gel chromatography (10% EtAc in hexanes) to afford boc-protected-**11e** (60.6 mg, 57% yield) as a pale yellow oil.

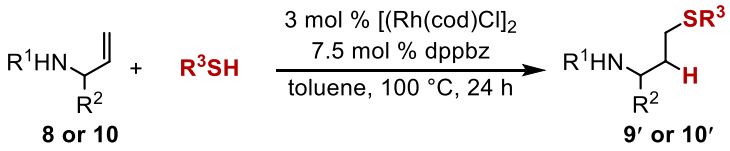
R_f (10% EtAc/Hexanes) = 0.50

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.32 (d, J = 8.1 Hz, 2H), 6.99 (t, J = 7.4 Hz, 2H), 6.93 (d, *J* = 7.4 Hz, 1H),4.63 (s, 1H), 3.15 (dt, *J* = 12.5, 6.2 Hz, 2H), 3.04 (dt, *J* = 11.9, 5.6 Hz, 1H), 1.43 (s, 9H), 1.03 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 155.85, 134.96, 132.20, 129.18, 127.03, 78.82, 45.81, 43.49, 28.50, 18.51.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{22}NO_2S$ = 268.0102; found mass = 268.0102

Anti-Markovnikov-Selective Hydrothiolation of Allyl Amines

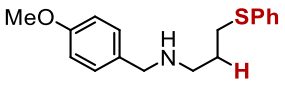


General Procedure for anti-Markovnikov hydrothiolation

$[Rh(cod)Cl]_2$ (5.92 mg, 0.012 mmol, 3.0 mol %), dppbz (13.39 mg, 0.03 mmol, 7.5 mol %), and dry toluene (200 µL) were added to 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added amine (0.4 mmol, 1.0 equiv). Subsequently, thiol (2.0 mmol, 5.0 equiv) was added. The vial was brought out of the box (sealed) and stirred (420 rpm) at 80 ˚C for 24 h. The crude solution was cooled to room temperature, dissolved in CH_2Cl_2, and purified by silica gel chromatography (125 mL silica loaded in 10% Et_2O in CH_2Cl_2, and eluted with 3% NH_4OH : 2 to 3% MeOH : 10 % Et_2O: 84 to 85% $CHCl_2$ v/v prepared by extracting saturated

NH_4OH with CH_2Cl_2, removing aqueous layer, then adding to a solution of MeOH and Et_2O). Following *in-vacuo* concentration, the amine was dissolved in hexanes and filtered through a celite plug to remove [Rh] and afford the pure 1,3-aminothioether.

Synthesis of **9a'**



9a' was synthesized according to the general procedure for anti-Markovnikov hydrothiolation with **8a** (70.90 mg, 0.4000 mmol) and thiophenol (205.37 µL, 2.000 mmol). The crude product was purified by silica gel chromatography to afford **9a'** (57.9 mg, 50% yield) as a yellow oil.

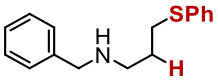
R_f (3% MeOH/CH_2Cl_2) = 0.13

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.29 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.03 (tt, *J* = 8.0, 7.5, 1.8 Hz, 2H), 6.92 (tt, *J* = 7.4, 1.3 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.51 (s, 2H), 3.34 (s, 3H), 2.78 (t, *J* = 7.1 Hz, 2H), 2.46 (t, *J* = 6.6 Hz, 2H), 1.62 (p, *J* = 7.1 Hz, 2H), 1.01 (br s, 1H).

^{13}C NMR (101 MHz, Benzene-d_6) δ 159.19, 137.71, 133.00, 129.49, 129.06, 129.03, 125.67, 113.98, 54.78, 53.50, 47.97, 31.29, 29.82.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{22}NOS$ = 288.1422; found, 288.1413.

Synthesis of **9d'**



9d' was synthesized according to the general procedure for anti-Markovnikov hydrothiolation with **8d** (58.89 mg, 0.4000 mmol) and thiophenol (205.37 µL, 2.000 mmol). The crude product was purified by silica gel chromatography to afford **9d'** (52.5 mg, 50% yield) as a yellow oil.

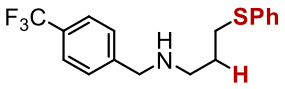
R_f (3% MeOH/CH_2Cl_2) = 0.14

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.32 – 7.23 (m, 4H), 7.19 (dd, J = 8.4, 6.7 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 7.03 (t, J = 7.7 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 3.50 (s, 2H), 2.76 (t, J = 7.3 Hz, 2H), 2.42 (t, J = 6.7 Hz, 2H), 1.59 (p, J = 6.9 Hz, 2H), 0.88 (br s, 1H).

^{13}C NMR (101 MHz, Benzene-d_6) δ 140.98, 137.58, 128.95, 128.37, 128.22, 126.93, 125.58, 53.92, 47.93, 31.14, 29.72. One C(sp^2) resonance not located.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{16}H_{20}NS$ = 258.1316; found mass = 258.1317.

Synthesis of **11h'**



9h' was synthesized according to the general procedure for anti-Markovnikov hydrothiolation with **8h** (86.08mg, 0.400 mmol) and thiophenol (205.37 µL, 2.00 mmol). The crude product was purified by silica gel chromatography to afford **9h'** (52.5mg, 37% yield) as a yellow oil.

R_f (3% MeOH/CH_2Cl_2) = 0.29

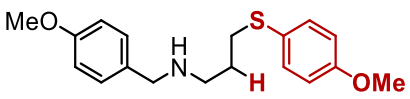
^{1}H NMR (499 MHz, Benzene-d_6) δ 7.38 (d, J = 8.0 Hz, 2H), 7.29 (dd, J = 8.3, 1.2 Hz, 2H), 7.07 – 7.01 (m, 4H), 6.94 (t, J = 7.2 Hz, 1H), 3.31 (s, 2H), 2.75 (t, J = 7.2 Hz, 2H), 2.32 (t, J = 6.7 Hz, 2H), 1.56 (p, J = 6.9 Hz, 2H), 0.56 (br s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.38, 136.61, 129.31, 129.04 (q, J = 31.1 Hz), 129.02, 128.42, 126.07, 124.38 (q, J = 3.7 Hz), 123.30 (q, J = 273.3 Hz), 53.40, 48.07, 31.61, 29.52.

^{19}F NMR (376 MHz, Benzene-d_6) δ -62.34.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{17}H_{19}NSF_3$ = 326.1190; found mass = 326.1180.

Synthesis of **9n'**



9n' was synthesized according to the general procedure for anti-Markovnikov hydrothiolation with **8a** (70.90mg, 0.400 mmol) and *p*-methoxythiophenol (2.0 mmol, 246.84 µL). The crude product was purified by silica gel chromatography to afford **9n'** (48.3 mg, 38% yield) as a yellow oil.

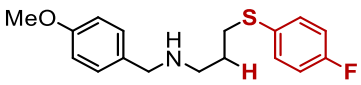
R_f (3% MeOH/CH_2Cl_2) = 0.13

^{1}H NMR (499 MHz, Benzene-d_6) δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 3.53 (s, 2H), 3.34 (s, 3H), 3.24 (s, 3H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 6.7 Hz, 2H), 1.65 (p, *J* = 6.9 Hz, 2H), 0.94 (s, 1H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.27, 159.22, 133.32, 133.22, 129.47, 127.58, 114.90, 114.01, 54.79, 53.61, 48.09, 33.80, 30.23. One C(sp^3) resonance not located.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{18}H_{24}NO_2S$ = 318.1528; found mass = 318.1520.

Synthesis of **9q'**



9q' was synthesized according to the general procedure for anti-Markovnikov hydrothiolation with **8a** (70.90mg, 0.4000 mmol) and thiophenol (205.37 µL, 2.000 mmol). The crude product was purified by silica gel chromatography to afford **9q'** (55.0 mg, 45% yield) as a yellow oil.

R_f (3% MeOH/CH_2Cl_2) = 0.17

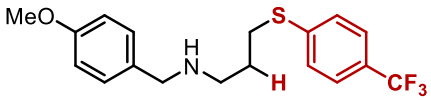
^{1}H NMR (500 MHz, Benzene-d_6) δ 7.19 (d, *J* = 8.5 Hz, 2H), 7.07 (dd, *J* = 8.8, 5.2 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.68 (t, *J* = 8.7 Hz, 2H), 3.51 (s, 2H), 3.34 (s, 3H), 2.68 (t, *J* = 7.3 Hz, 2H), 2.45 (t, *J* = 6.6 Hz, 2H), 1.56 (p, *J* = 6.9 Hz, 2H), 1.00 (br s, 1H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 161.77 (d, *J* = 245.1 Hz), 159.16, 132.88, 132.30 (d, *J* = 3.4 Hz), 131.88 (d, *J* = 7.8 Hz), 129.37, 115.97 (d, *J* = 21.9 Hz), 113.92, 54.66, 53.45, 47.78, 32.50, 29.76.

^{19}F NMR (376 MHz, Benzene-d_6) δ -116.71.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{21}NSF$ = 306.1328; found mass = 306.1318.

Synthesis of **9t'**



9t' was synthesized according to the general procedure for anti-Markovnikov hydrothiolation with **8a** (70.90mg, 0.4000 mmol) and 4-trifluoromethylthiophenol (273.84 µL, 2.000 mmol). The crude product was purified by silica gel chromatography to afford **9t'** (64.2 mg, 45 % yield) as a yellow oil.

R_f (5% MeOH/CH_2Cl_2) = 0.26

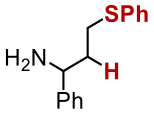
^{1}H NMR (500 MHz, Benzene-d_6) δ 7.23 – 7.17 (m, 4H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.84 (dt, *J* = 8.6, 2.8, 1.9 Hz, 2H), 3.51 (s, 2H), 3.35 (s, 3H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 1.53 (p, *J* = 7.3, 6.7, 6.7 Hz, 2H), 0.85 (s, 1H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.18, 143.26, 132.84, 129.36, 127.03, 126.72 (q, *J* = 32.5 Hz), 125.64 (q, *J* = 3.8 Hz), 123.83 (q, *J* = 271.8 Hz), 113.93, 54.66, 53.47, 47.71, 29.81, 29.33.

^{19}F NMR (470 MHz, Benzene-d_6) δ -62.37.

HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{18}H_{21}NOSF_3$ = 356.1296; found mass = 356.1290.

Synthesis of **11c'**



11c' was synthesized according to the general procedure for anti-Markovnikov hydrothiolation with **10c** (53.28mg, 0.4000 mmol) and thiophenol (205.37 µL, 2.000 mmol). The crude product was purified by silica gel chromatography to afford **11c'** (72.0 mg, 74% yield) as a yellow oil.

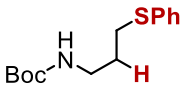
R_f (3% MeOH/CH_2Cl_2) = 0.19

^{1}H NMR (499 MHz, Benzene-d_6) δ 7.20 (dd, *J* = 7.5, 1.7 Hz, 2H), 7.12 – 7.06 (m, 4H), 7.06 – 7.01 (m, 1H), 6.97 (t, *J* = 7.7 Hz, 2H), 6.88 (t, *J* = 7.3 Hz, 1H), 3.73 (t, *J* = 6.7 Hz, 1H), 2.71 (t, *J* = 7.4 Hz, 2H), 1.77 (ddt, *J* = 17.6, 13.7, 6.7 Hz, 2H), 0.89 (br s, 2H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 146.58, 137.53, 129.09, 128.63, 127.13, 126.61, 125.75, 55.23, 39.21, 30.47.

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] calculated for $C_{15}H_{18}NS$ = 244.1160; found mass = 244.1151.

Synthesis of boc-protected-**11e'**



11e' was synthesized according to the general procedure for anti-Markovnikov hydrothiolation with allyl amine (30.00 μL, 0.4000 mmol) and thiophenol (205.37 μL, 2.000 mmol). After cooling to room temperature, di-*tert*-butyl carbonate (137.82 μL, 0.6000 mmol) was added and the reaction was stirred for 6 hours. The crude product was purified by silica gel chromatography (9:1 hexanes: ethyl acetate) to afford boc-protected **11e'** (46.0 mg, 43% yield) as a colorless oil.

R_f (10%EtAc/Hexanes) = 0.17

^{1}H NMR (499 MHz, Benzene-d_6) δ 7.17 (d, *J* = 7.7 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 2H), 6.89 (t, *J* = 7.6, 7.2 Hz, 1H), 3.97 (br s, 1H), 3.00 – 2.83 (m, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.44 (p, *J* = 6.8 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 155.73, 137.21, 129.32, 129.08, 125.90, 78.50, 39.65, 30.81, 30.18, 29.68, 28.48.

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] calculated for $C_{15}H_{21}NO_2SNa$, 290.1186; found, 290.1181.

The crude reaction mixtures of allyl amine (**11e**) could not be analyzed by GC, likely due to protonation of allyl amine under the reaction conditions. The regioselectivity of the hydrothiolation of allyl amine was therefore determined by ^{1}H NMR analysis of the crude reaction mixture.

2.9 References.

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Chapter 3: Copper-Catalyzed Hydroarylation of Internal Alkynes: Highly Diastereo- and Regioselective Synthesis of 1,1-Diaryl, Trisubstituted Alkenes[§]

3.1 Introduction.

Olefins are prominent functional groups found in organic materials and pharmaceuticals and are versatile synthetic intermediates for further functionalization. Despite well-established methods for forming disubstituted olefins,[1] the regio- and stereospecific synthesis of trisubstituted olefins remains a challenge.[2] Alkyne hydroarylation represents an attractive route for the synthesis of this important functionality in an efficient manner.[3] 1,1-diaryl olefins, specifically, represent a class of compounds for which hydroarylation would decrease synthetic overhead and promote rapid assembly of diverse products (Figure 12).[4]

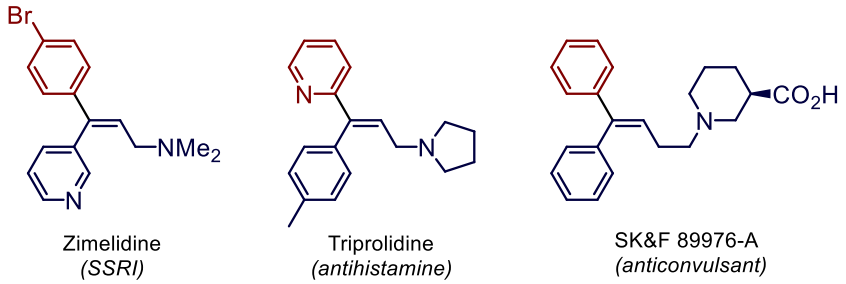

Figure 12: Biologically Active 1,1-Diaryl Olefins.

Several hydroarylation methods have been reported for the assembly of 1,1-diaryl alkenes (Scheme 21a-c); however, these methods have shortcomings which preclude them from being broadly applicable. Friedel-Crafts hydroarylation (Scheme 21a) relies on a π-acidic catalyst to activate the alkyne for an electrophilic aromatic substitution. These reactions are limited to nucleophilic electron neutral and rich arenes.[5] The use of organometallic arenes with transition metal catalysts was an important advance, providing access to broader substrate classes; however, 1,2-diaryl alkenes are formed as the major or exclusive regioisomer with aryl- or alkyl-substituted internal alkynes.[6] Directing groups on the alkyne which employ steric, electronic, or chelation

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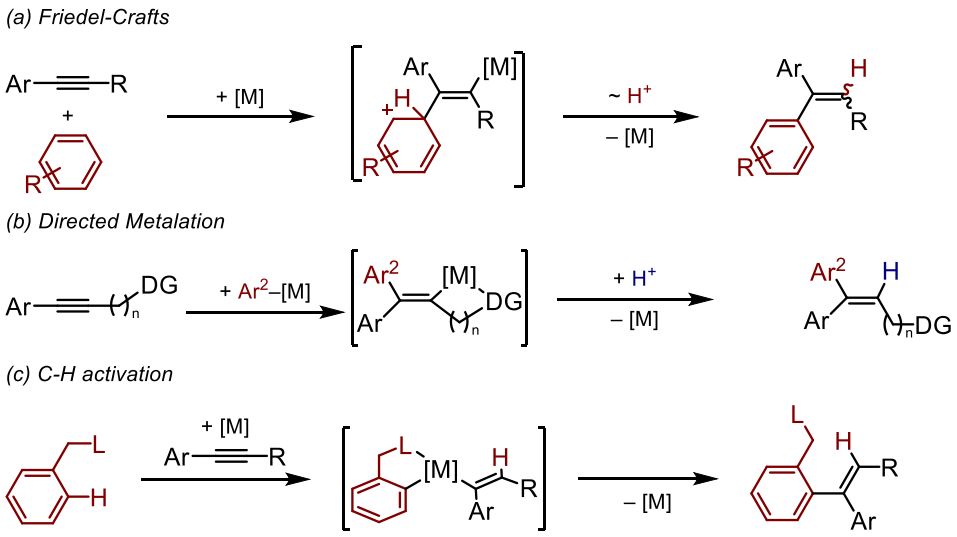
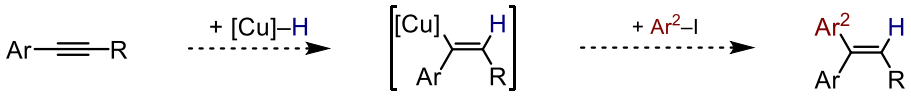
effects can control the selectivity of a metal–arene migratory insertion to afford the 1,1-diaryl alkene (Scheme 21b).[7] While the scope of arenes is vastly improved compared to Friedel-Crafts methods, the alkyne partners are limited due to the requisite directing group. Arenes bearing a ligand directing group can also select for the 1,1-diaryl alkene product if C–H migratory insertion



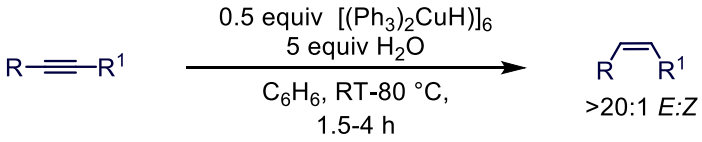
Scheme 21: Previously Reported Alkyne Hydroarylation Reactions.

occurs prior to C–C bond formation (Scheme 21c). Unfortunately, the scope of this approach is limited to 2-pyridyl[8] and 1-benzotriazole[9] directing groups, as they do not undergo further intramolecular cyclization after hydroarylation.[3b]Despite the limited scope of these C–H activation methods, we were inspired by the excellent selectivity for the 1,1-diaryl product without the need for a directing group on the alkyne. We hypothesized that an *in situ* generated metal–hydride could undergo a selective migratory insertion across an aryl alkyne. Subsequent oxidative addition into an aryl iodide and reductive elimination would furnish a 1,1-diaryl alkene (Scheme 22). We chose to pursue a Cu-catalyzed hydroarylation reaction utilizing a silane as an *in situ* hydride source given the tremendous recent advances in other Cu-catalyzed hydrofunctionalization reactions.[10]



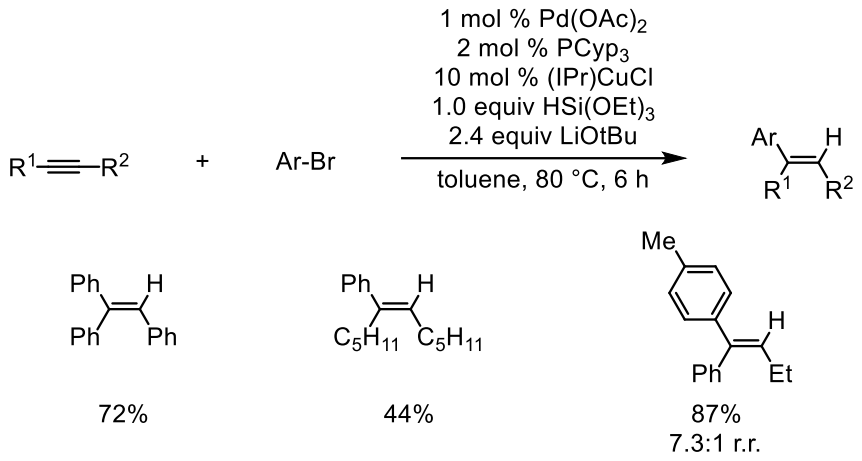
Scheme 22: Proposed Transformation.

In 1990, Stryker reported the formal *cis*-hydrogenation of alkynes via a Cu–H intermediate wherein water served as the H^+ source (Scheme 23).[11] Later, other electrophiles were utilized in



Scheme 23: Stryker's Initial Cu–H-Mediated Alkyne Semi-Reduction.

this reaction to trap the vinyl copper intermediate to form α,β-unsaturated carboxylic acids,[12] vinyl boranes,[13] enamines,[14] vinyl bromides,[15] and alkenes[16] utilizing a silane as the hydride source; however, the related Cu-catalyzed C–Aryl bond forming reaction has not been described. The hydroarylation of styrene with dual Cu/Pd catalysts (the Cu catalyst generates the Cu–benzyl intermediate which then transmetalates to Pd and undergoes C–C bond forming reductive elimination) has been reported to provide the 1,1-diaryl alkanes by Nakao and Buchwald.[17] Furthermore, Nakao demonstrated that alkynes can undergo hydroarylation with this Cu/Pd co-catalytic system; however, only three examples were shown and a moderate 7.3:1 regioselectivity was observed for 1-phenyl-1-butyne[17a] (Scheme 24). Given the recent advances in Cu-catalyzed C–C bond forming reactions by Giri[18] and carboboration by Brown,[19] we hypothesized that the Pd cocatalyst could be removed and the formed Cu(I)-vinyl intermediate, generated upon alkyne insertion into a Cu–H, could be directly oxidized with an aryl iodide to give the desired 1,1-diaryl alkene upon reductive elimination.

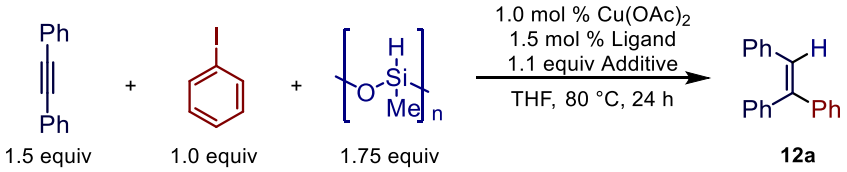


Scheme 24: Nakao's Cu/Pd Dual Catalytic Alkyne Hydroarylation.

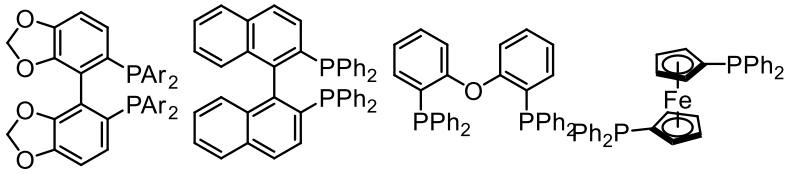
3.2 Reaction Optimization.

We began our studies on the coupling of diphenylacetylene with PhI with $Cu(OAc)_2$ as the precatalyst and polymethylhydrosiloxane (PMHS) as the hydride source (Table 14). Acetate salts were added to the reaction to transmetalate with CuI to form CuOAc thereby increasing the rate of transmetalation with PMHS.[20] Investigation of bidentate phosphines showed that dppf afforded **12a** in an excellent yield (92%) with 1.0 mol % catalyst. Reducing CsOAc to 0 or 0.5 equiv significantly reduced the yield of **12a** to 3% or 42%, respectively, indicating that added acetate is required for catalyst turnover. Cesium acetate proved to be a superior over sodium or potassium acetate (Table 14, entries 4, 7, and 8), likely due to its increased solubility in THF. Finally, alkyne equivalency was reevaluated and we found that a moderate excess of alkyne is required for excellent yields (Table 14, entries 4, 9, and 10).

Table 14: Selected Reaction Optimization.[a]



Entry	Ligand	Additive	Yield of **12a** (%)[b]
1	DTBM-segphos	CsOAc	4
2	BINAP	CsOAc	42
3	DPEphos	CsOAc	82
4	dppf	CsOAc	92
5	dppf	None	3
6	dppf	CsOAc[c]	42
7	dppf	KOAc	15
8	dppf	NaOAc	4
9[d]	dppf	CsOAc	62
10[e]	dppf	CsOAc	76

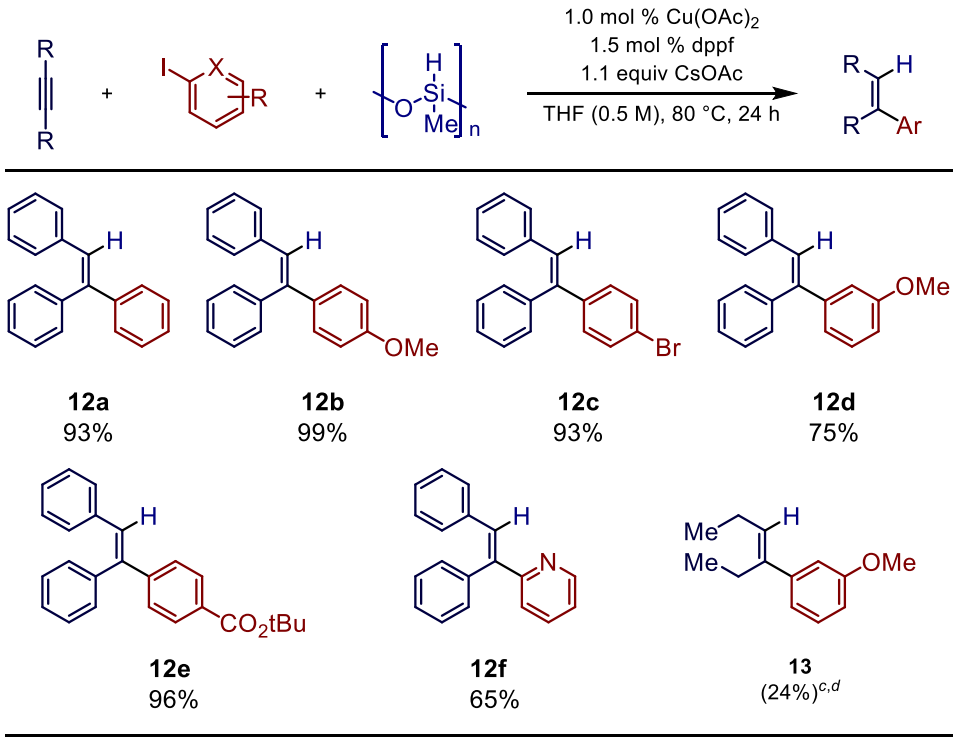


[a] Reaction conditions: $Cu(OAc)_2$ (1.0 mol %), Ligand (1.5 mol %), PMHS (1.75 equiv), Additive (1.1 equiv), diphenylacetylene (1.5 equiv), PhI (1.0 equiv), THF (0.5 M), at 80 °C for 24 h. [b] Yield determined by GC analysis of the crude reaction mixture by comparison to undecane as an internal standard. [c] 0.50 equiv of CsOAc used. [d] 1.0 equiv of diphenyl acetylene added. e 1.25 equiv of diphenyl acetylene added.

3.3 Scope of the Cu-Catalyzed Hydroarylation Reaction.

With the optimized conditions in hand, we explored aryl coupling partners (Table 15). Aryl iodides with varying electronic profiles were well tolerated resulting in the formation of the coupled products in excellent yields as single diastereomers. A 2-pyridyl group was also amenable to the reaction, although with slightly reduced yield which is due to protodeiodination of the starting material. A *t*-butyl ester group was tolerated; however, reducing the size of the alkyl group on the ester to a methyl group lead to did not afford any of the coupled product. This is likely due to reduction of the carbonyl, although products of reduction are not observed, either because after the reduction the copper is slow to turnover, or because these products would be bound to the silane polymer byproduct which would not be observed by GC. Similarly, other reducible functional groups were not tolerated; e.g. 4-iodobenzonitrile, and 4-iodoacetophenone. Finally, under these optimized conditions, 3-hexyne provided trace quantities of **13** (< 5% yield); however, increasing the equivalents of alkyne to 2.5 and temperature to 120 °C provided **13** in a moderate 24% NMR yield.

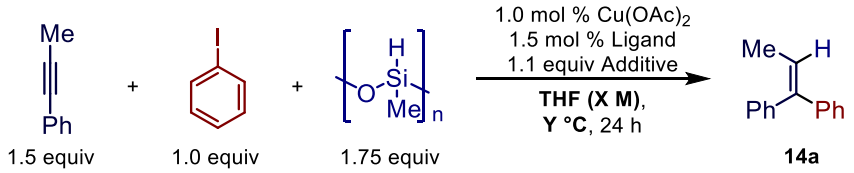
Table 15: Scope of Symmetric Alkynes.[a,b]



[a] Isolated yields reported as an average of two runs. [b] Reaction conditions: $Cu(OAc)_2$ (1.0 mol %), dppf (1.5 mol %), PMHS (1.75 equiv), CsOAc (1.1 equiv), diphenylacetylene (1.5 equiv), and ArI (1.0 equiv) in THF (0.5 M) at 80 °C for 24 h. [c] Reaction conducted at 120 °C for 60 h with 3-hexyne (2.5 equiv). [d] Yield determined by ^{1}H NMR analysis of the crude reaction mixture and comparison to 1-methylnaphthalene as an internal standard.

Next, differentially substituted internal alkynes were investigated. Using 1-phenyl-1-propyne, under the conditions utilized in Table 15, gave **14a** in 24% GC yield when coupled with PhI (Table 15, entry 7). Optimization of temperature and concentration (Table 15) revealed that increasing the concentration to 100 °C and increasing the concentration to 1.0 M afforded **14a** in a 63 % yield (Table 16, entry 5). I further evaluated the equivalents of alkyne and pyridine as an additive (Table 17). I found that increasing alkyne equivalents to 1.75 and utilizing 50 mol % pyridine provided **14a** in an 81% GC yield. The discovery of pyridine as an additive in the reaction was rather serendipitous and was selected as an additive because the crude GC for **14k** appeared to be very clean and the conversion of 2-iodopyridine was quantitative. I later learned that 2-iodopyridine undergoes protodeiodination to a significate extent, thus the yield of **14k** is much lower than expected. Nevertheless, pyridine is an effective additive in the reaction. The exact role of the pyridine is not well understood, but it is likely that it solubilizes [Cu]–H clusters or prevents

Table 16: Effect of Concentration and Temperature on the Hydroarylation of 1-Phenyl-1-Propyne.[a]

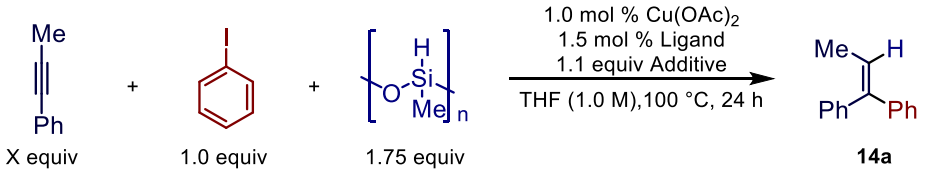


entry	concentration (M)	temperature (°C)	yield of (**14a**)[b]
1	2.0	80	5
2	2.0	100	8
3	2.0	120	18
4	1.0	80	45
5	1.0	100	63
6	1.0	120	50
7	0.5	80	24
8	0.5	100	47
9	0.5	120	68

[a] Reaction conditions: $Cu(OAc)_2$ (1.0 mol %), Ligand (1.5 mol %), PMHS (1.75 equiv), CsOAc (1.1 equiv), 1-phenyl-1-propyne (1.5 equiv), PhI (1.0 equiv), THF (X M), at Y °C for 24 h. [b] Yield determined by GC analysis of the crude reaction mixture by comparison to undecane as an internal standard.

catalyst decomposition thus increasing the catalyst life time, leading to increased turnover numbers. Varying the aryl iodide results in the formation of 1,1-diaryl propenes in good yields and excellent regioisomeric ratios (r.r.) as single diastereomers (Table 18). Gratifyingly, given their readily derivatized functionalities, 4-Br-, 4-Cl-, and 4-tosyl- substituted iodobenzenes react readily affording **14d**, **14e**, and **14f** in 68%, 60%, and 79% yields. The regio- and diastereoselectivity were unambiguously confirmed by xray crystallography of **14d**. (Figure 13). The electronic nature of

Table 17: Effect of Varying Alkyne and Pyridine Equivalents on the Hydroarylation of 1-Phenyl-1-Propyne.[a]

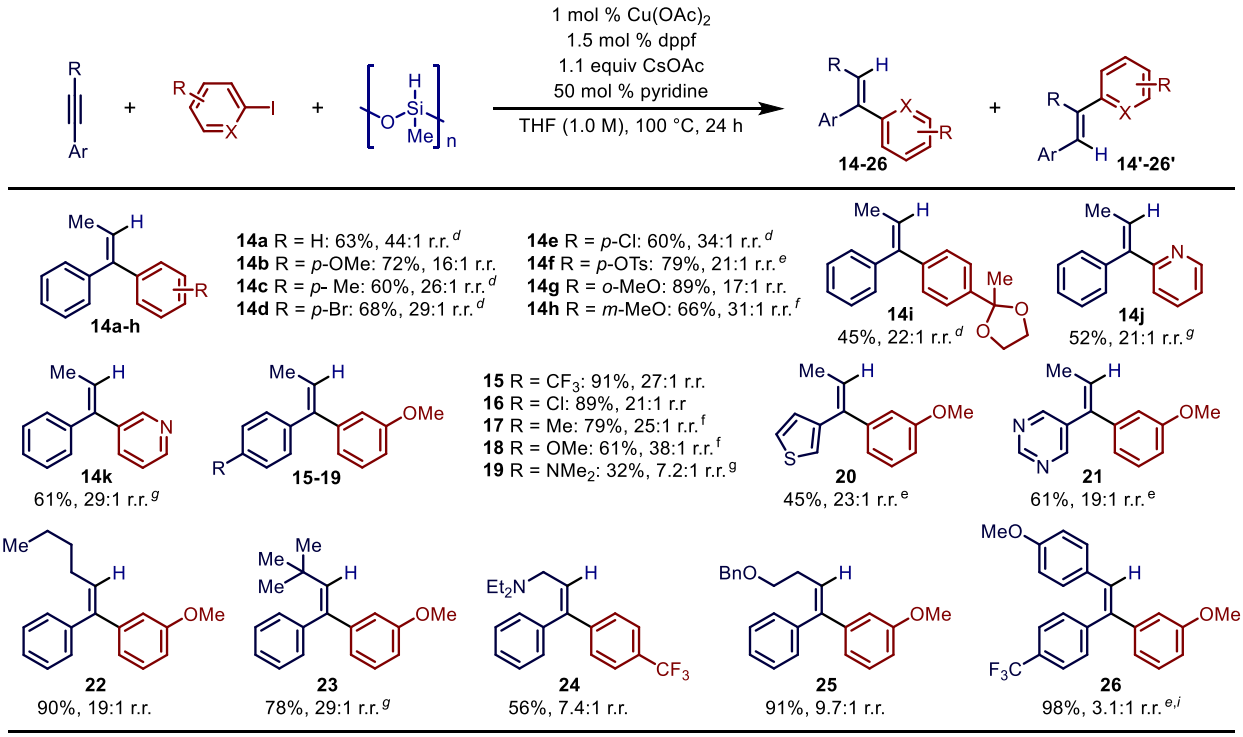


entry	equiv alkyne	equiv pyridine	yield of **14a** (%)[b]
1	1.25	0	28
2	1.50	0	63
3	1.75	0	69
4	2.0	0	78
5	1.25	0.50	37
6	1.50	0.50	65
7	1.75	0.50	81
8	2.0	0.50	72

[a] Reaction conditions: $Cu(OAc)_2$ (1.0 mol %), Ligand (1.5 mol %), PMHS (1.75 equiv), CsOAc (1.1 equiv), 1-phenyl-1-propyne (1.5 equiv), PhI (1.0 equiv), THF (X M), at Y °C for 24 h. [b] Yield determined by GC analysis of the crude reaction mixture by comparison to undecane as an internal standard.

the aryl iodide does not have a significant effect on the yield or selectivity of the reaction; both electron rich and electron poor arenes are incorporated in good to excellent yields. An ortho-substituent on the aryl iodide is tolerated; although, the rate of the reaction is slowed; 2-methoxyiodobenzene is coupled with 1-phenyl-1-propyne to supplying **14h** in an 89% yield after 48 h. Sensitive functionalities and Lewis basic groups are incorporated into the products (**14i** and **14j and 14k** respectively), albeit in somewhat reduced yields. Other hetercyclic aryl iodides; e.g. 2-iodothiophene, 1-methyl-2-iodo-indole, 2-iodobenzofuran, and 2-iodobenzothiophene, did participate in the hydroarylation. The reaction is readily scaled, as **14a**,

Table 18: Scope of Unsymmetric Alkynes.[a,b,c]



[a] Isolated yields reported as an average of two runs. [b] Regioisomeric ratio(**14-26:14'-26'**) determined by GC analysis of the crude reaction mixture. [c] Reaction conditions: $Cu(OAc)_2$ (1 mol %), dppf (1.5 mol %), PMHS (1.75 equiv) CsOAc (1.1 equiv), pyridine (0.5 equiv), alkyne (1.75 equiv), ArI (1.0 equiv) in THF (1.0 M) at 100 °C for 24 h. [d] $Cu(OAc)_2$ (2 mol %), dppf (3 mol %) [e] Regioselectivity determined by NMR analysis of the crude reaction mixture. [f]48 h. [g]Reaction conducted without pyridine. [h]120 °C. [i]Reaction conducted with conditions shown in table 14.

Figure 13: Crystal Structure of 14d. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at 50% probability level.

14c, **14d**, and **14e** were run on 2.0 mmol scale and isolated by recrystallization with no need for chromatographic purification.

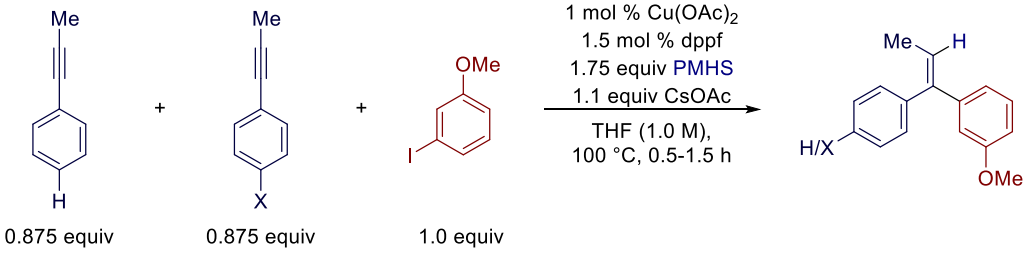
The conditions for 1-phenyl-1-propyne proved to be general for other 1-aryl-2-alkyl alkynes. Coupling alkynes of varying electronic profiles with 3-methoxyiodobenzene gave excellent yields for electron withdrawing substrates; 4-CF_3- and 4-Cl- phenyl groups provided **15** and **16** in 91% and 89% yields respectively. The less electrophilic 4-Me- and 4-OMe-phenyl propynes are sluggish and require 48 h for full conversion, giving **17** and **18** in 79% and 61% yield, respectively. The extremely electron donating 4-NMe_2-phenyl required elevated temperature to promote the reaction and afforded **19** in a 7.2:1 (**19:19'**) regioisomeric ratio in a 32% combined yield. Heteroarenes can also be incorporated into the alkyne, including thiophene and pyrimidine, affording **20** and **21** in 45% and 61% yield respectively. The yield and selectivity of the reaction is not sensitive to steric changes of the alkyl substituent of the alkyne as substrates with either a *n*-butyl or *t*-butyl are obtained in good yields and regioisomeric ratios (90% for **22** and 78% for **23**). A propargyl amine and homopropargyl benzyl ether also couple successfully; however, at slightly reduced regioselectivities. The reduction in regioselectivity for these substrates is likely due to a competing Lewis base directed hydrocupration. Finally, an electronically biased diphenyl acetylene derivative was tested, yielding **26** in a 98% yield and a 3.1:1 regioisomeric ratio, demonstrating a moderate electronic bias for the hydrocupration step.

3.4 Mechanistic Studies.

Previously reported Cu-catalyzed C–C bond forming reactions proceed through two-electron oxidative addition/reductive elimination sequences.[18] To gain insight into the mechanism, competition Hammett studies on both the alkyne and aryl iodide coupling partners were conducted. Competition Hammett studies were utilized over traditional Hammett studies because when crude classic Hammett studies were conducted there was a zero slope when plotted against σ_p which means that one of the transmetalation steps is rate determining and no information can be garnered from kinetic Hammett studies.

The results for competition Hammett studies for the alkyne coupling partner (Scheme 25) are plotted in Figures 14-17 against various σ values. As σ_p and σ_p- give the best fit, $R^2 = 0.99$ and

0.98 respectively, there is likely a negative charge build up in the transition state. This result is



Scheme 25: Alkyne Competition Hammett Study.

supported by the experimental evidence of electron donating aryl substituents on the alkyne requiring more forcing conditions. It also supports the poor selectivity of the 4-dimethylaminophenyl propyne and the slight selectivity for **26**. With these data, it is reasonable to suggest that the regioselectivity is governed by the ability of the aryl substituent to stabilize the negative charge build up.

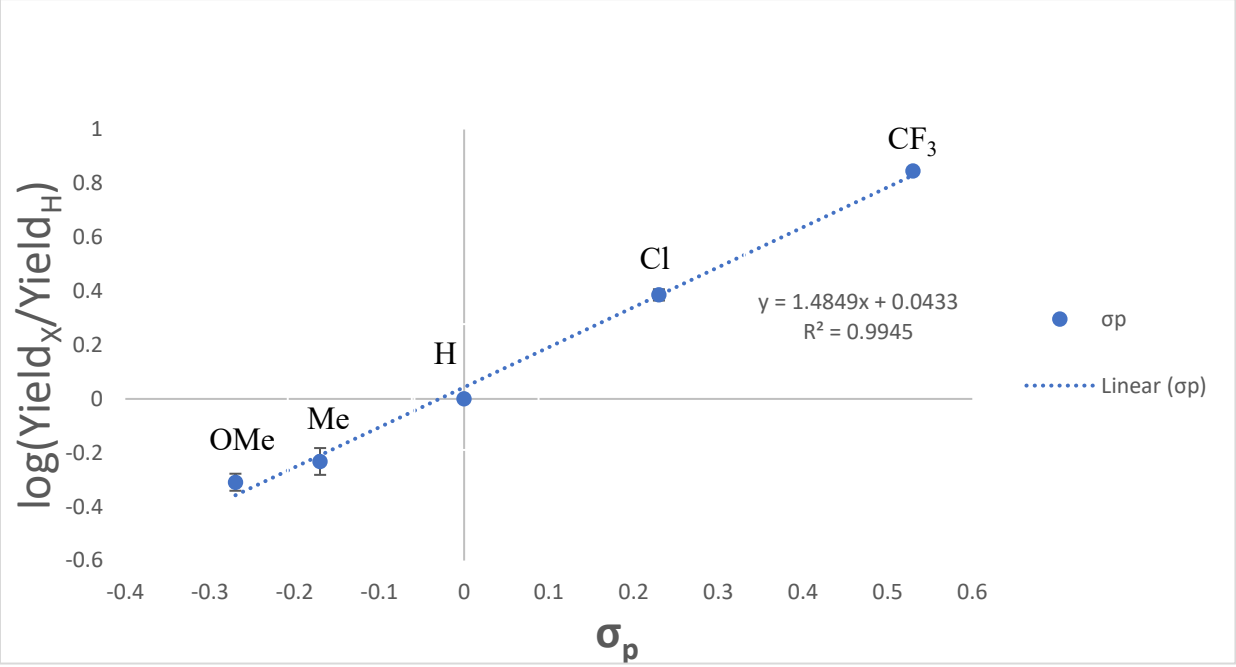


Figure 14: Competition Alkyne Hammett Study Plotted against σ_p.

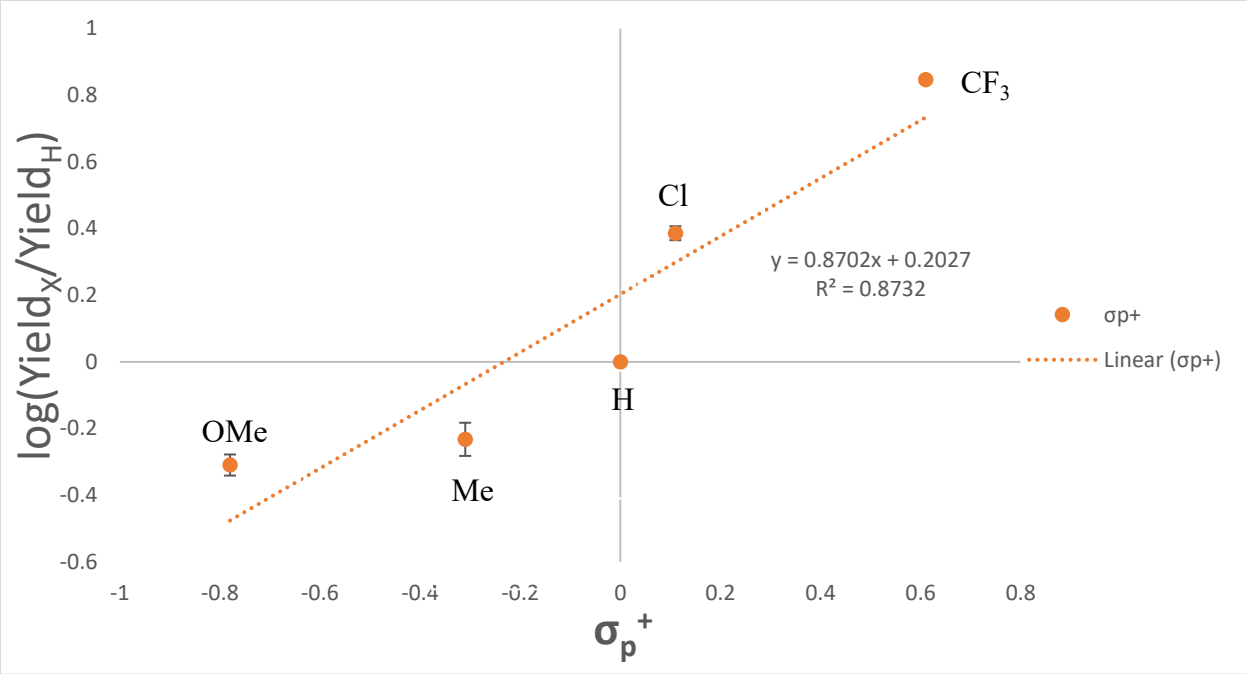


Figure 15: Competition Alkyne Hammett Study Plotted against σ_p^+.

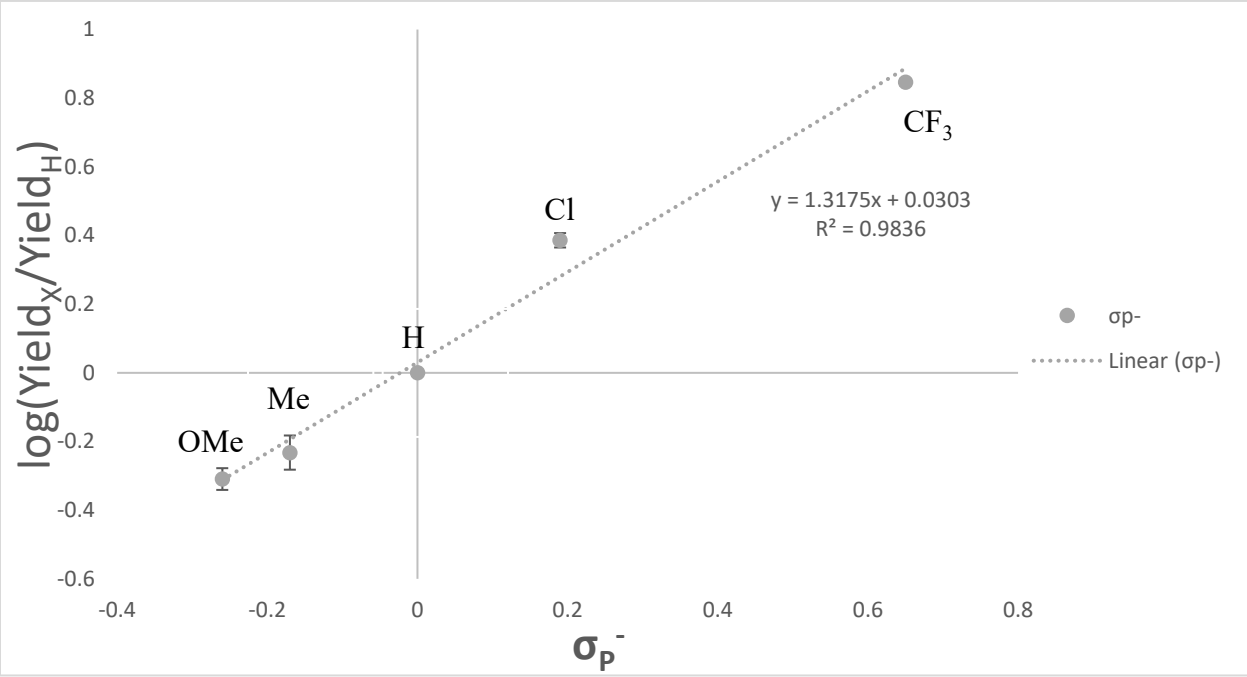


Figure 16: Competition Alkyne Hammett Study Plotted against σ_p^-.

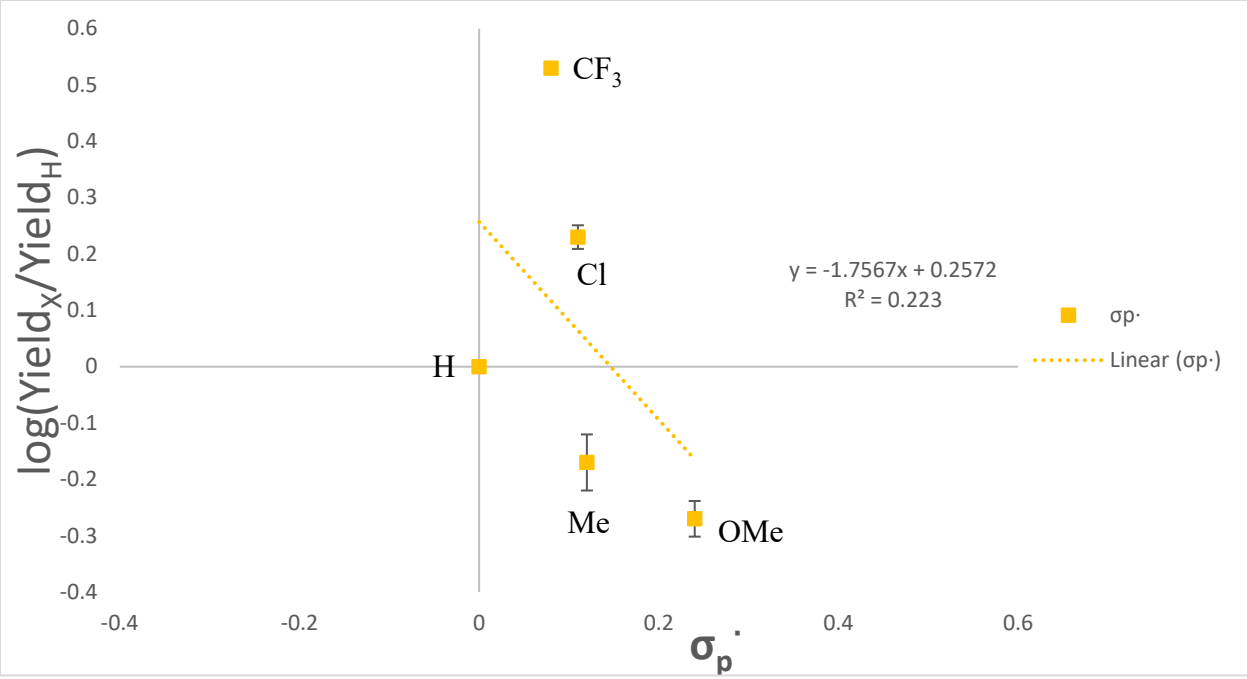
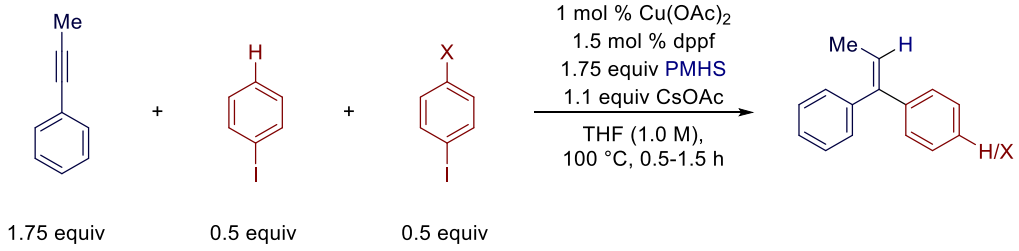


Figure 17: Competition Alkyne Hammett Study Plotted against σ_p·.

Next, the competition Hammett study was conducted on the aryl iodide coupling partner (scheme 26) which are plotted against several σ values in Figures 18-21. Again, σ_p and σ_p- resulted



Scheme 26: Aryl Iodide Competition Hammett Study.

in the best fit, R^2 = 0.93 and 0.93 respectively. These results are consistent with a two-electron oxidative addition/ reductive elimination sequence and the reductive elimination being the slower of the two steps comparatively and the reductive elimination being irreversible.[21]

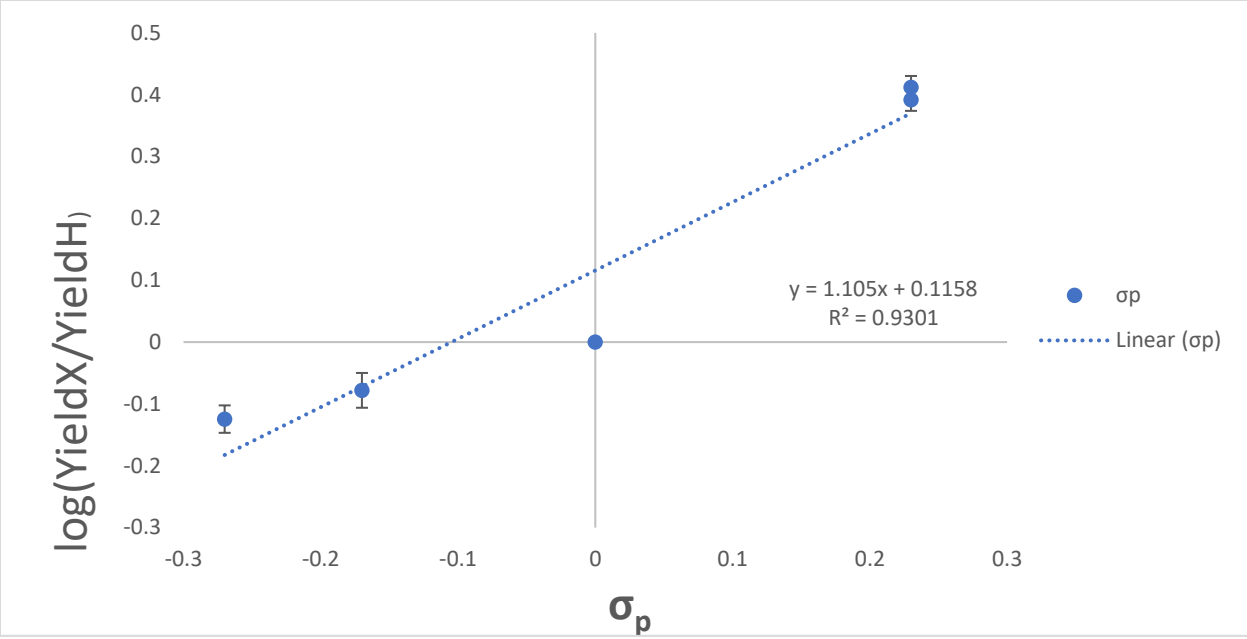


Figure 18: Competition Aryl Iodide Hammett Study Plotted against σ_p.

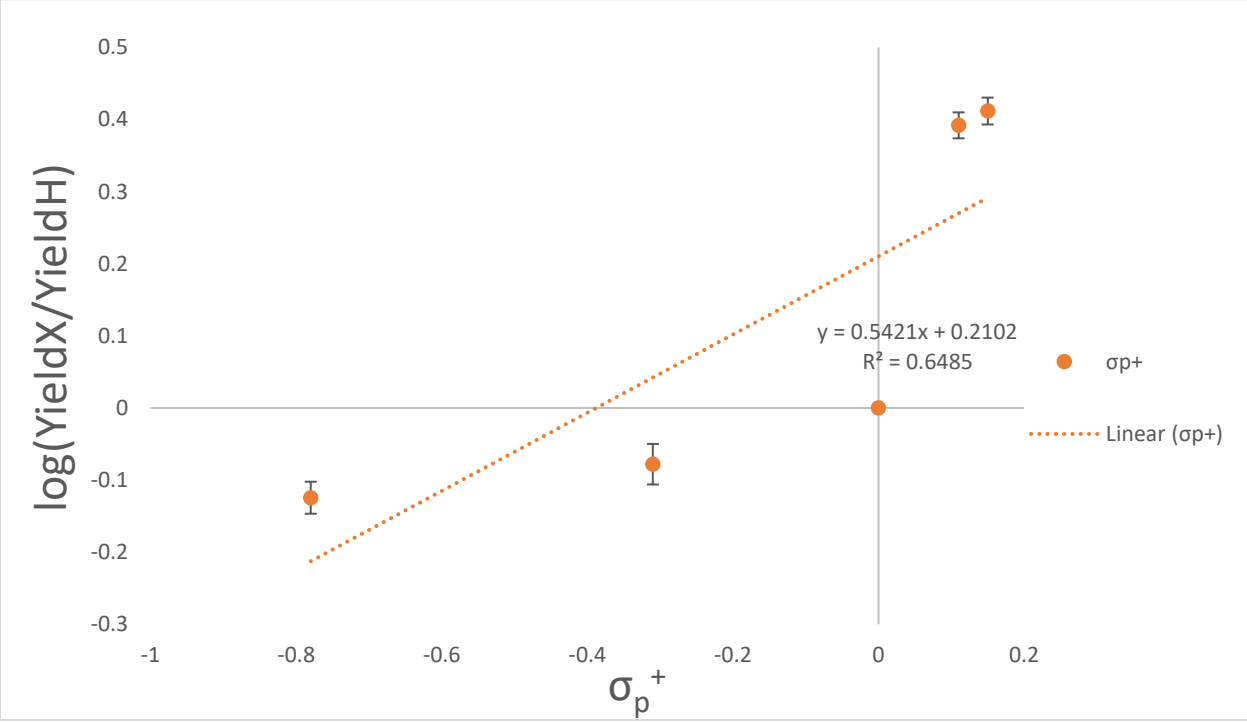


Figure 19: Competition Aryl Iodide Hammett Study Plotted against σ_p^+.

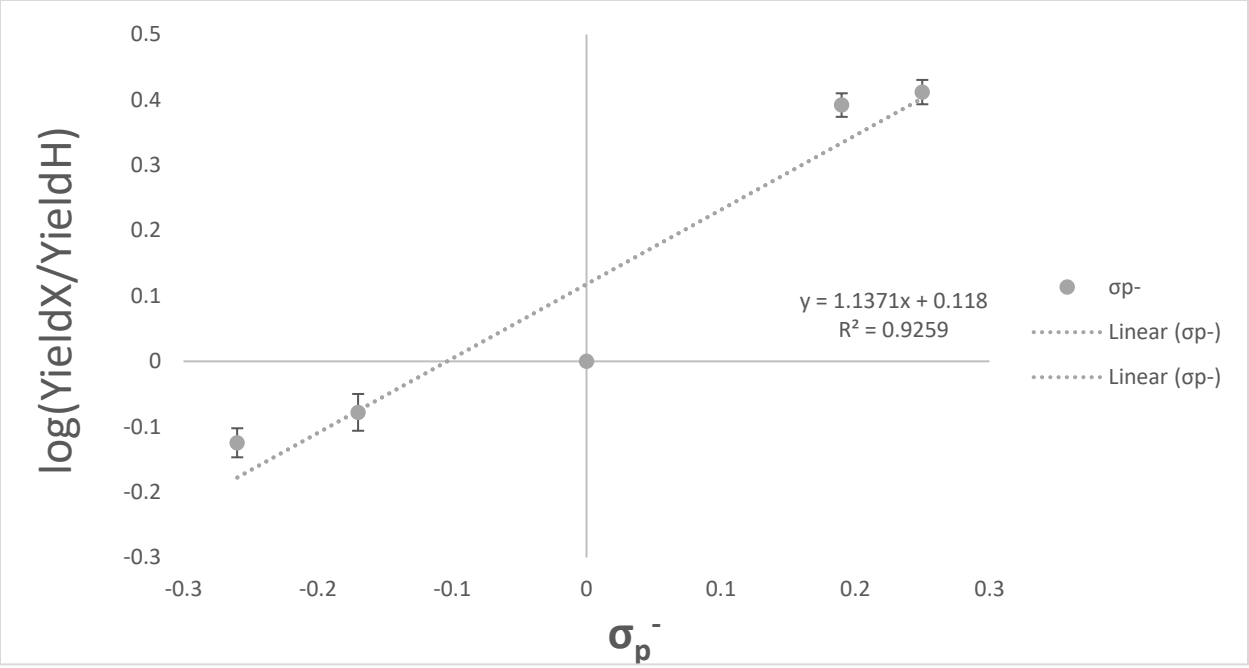


Figure 20: Competition Aryl Iodide Hammett Study Plotted against σ_p^-.

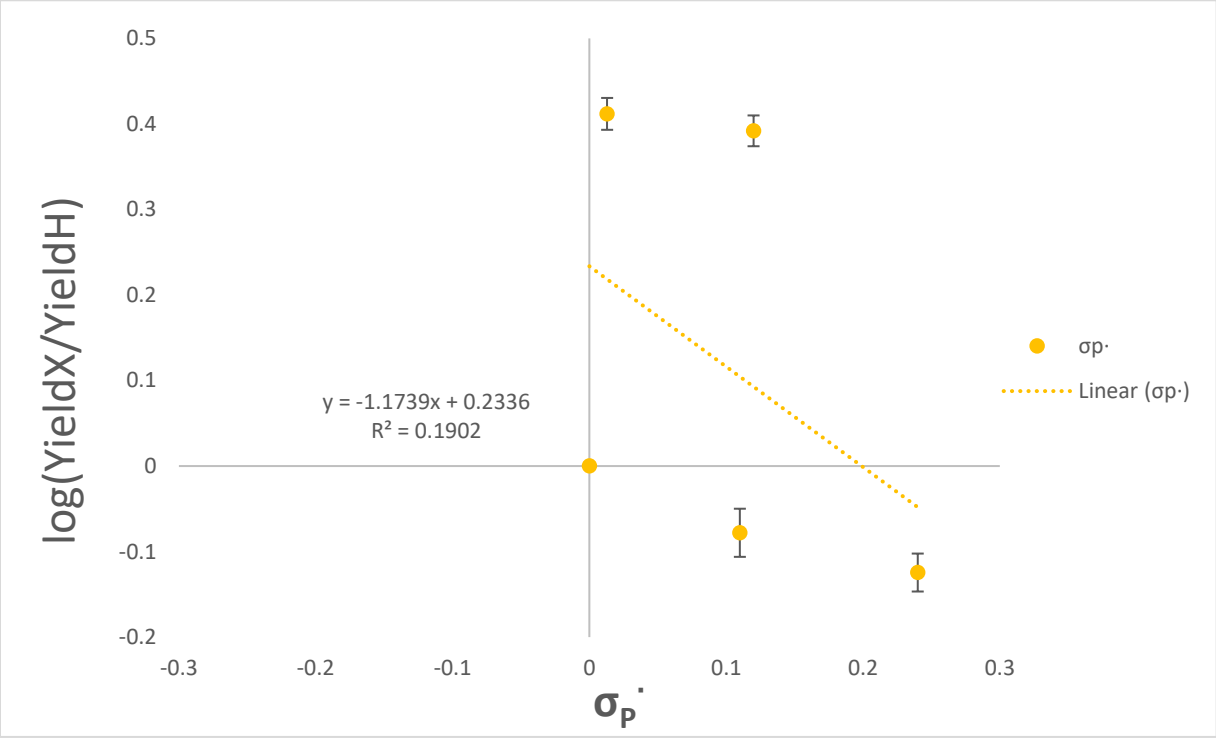
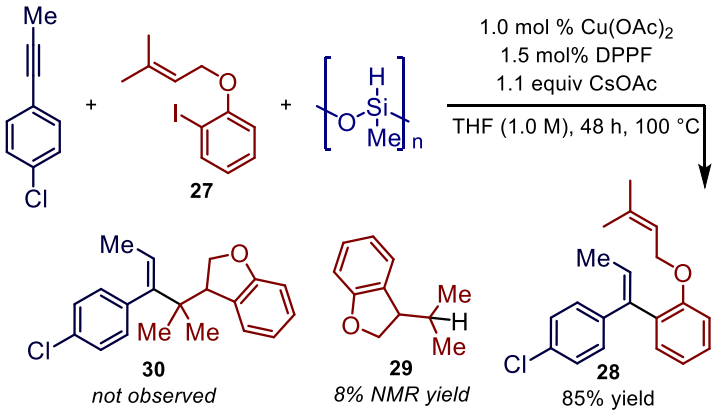


Figure 21: Competition Aryl Iodide Hammett Study Plotted against $\sigma_p^{\cdot}$.

To further support the hypothesis of a two-electron oxidative addition/reductive elimination sequence an intramolecular trap substrate (**27**) was subjected to the standard reaction

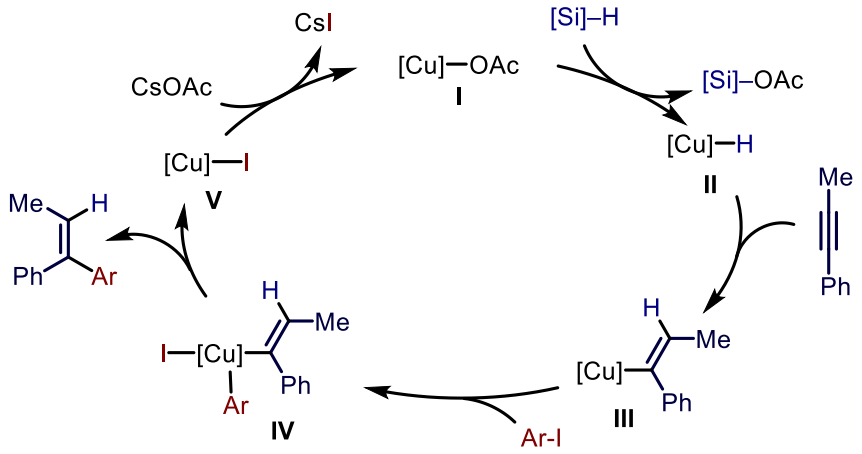
conditions (Scheme 27). The pendant prenyl group is known to undergo a rapid 5-exo-trig cyclization when the aryl radical is formed. I obtained **28** in 85% yield along with an 8% NMR yield of **29**; **30** was not observed. As **28** is the major product, it is likely that the reaction is proceeding though a two-electron oxidative addition/reductive elimination pathway and **29** is being formed either via an off-cycle reaction or by a migratory insertion after the oxidative addition step; however, a rapid one- electron oxidative addition pathway cannot be ruled out.[18,22]



Scheme 27: Intramolecular Radical Clock Experiment.

3.5 Proposed Catalytic Cycle.

A catalytic cycle consistent with the mechanistic insights is proposed in Scheme 28. [Cu]–OAc (**I**) can undergo a transmetalation with PMHS to yield **II**, subsequent hydrocupration of an alkyne yields the vinyl copper intermediate **III**. **III** can then undergo oxidative addition into the aryl iodide resulting in the formation of the Cu^{+3} intermediate **IV**[18] which undergoes rapid reductive elimination to furnish the product and **V**.[18] Finally, a transmetalation with CsOAc regenerates **I**.



Scheme 28: Proposed Copper-Catalyzed Alkyne Hydroarylation Catalytic Cycle.

3.6 Conclusions.

In conclusion, a Cu-catalyzed hydroarylation reaction has been developed. Yields ranging from 32-99% are obtained with regioisomeric ratios of 7.2-44:1 as single diastereomers in all cases. A variety of electronically and sterically differentiated alkynes and aryl iodides are competent coupling partners, and the reaction is readily scalable. Initial mechanistic studies show electronic bias of the alkyne is the source of regioselectivity in the hydrocupration step and the oxidative addition/reductive elimination sequence is likely a two-electron process.

3.7 Experimental Procedures.

General Experimental Procedures: All reactions were carried out in flame-dried (or oven-dried at 140 °C for at least 2 h) glassware under an atmosphere of nitrogen unless otherwise indicated. Nitrogen was dried using a drying tube equipped with Drierite™ unless otherwise noted. Air- and moisture-sensitive reagents were handled in a nitrogen-filled glovebox (working oxygen level <0.1 ppm). Column chromatography was performed with silica gel from Silicycle (40-63 μm) mixed as a slurry with the eluent. Columns were packed, rinsed, and run under air pressure. Analytical thin-layer chromatography (TLC) was performed on pre-coated glass silica gel plates (by EMD Chemicals Inc.) with F-254 indicator. Visualization was by short wave (254 nm) ultraviolet light. Distillations were performed using a 3 cm short-path column under reduced pressure or by using a Hickman still at ambient pressure.

Instrumentation: ^{1}H NMR, ^{13}C NMR, and ^{19}F were recorded on a Varian Unity 400/500 MHz (100/125 MHz respectively for ^{13}C), a VXR-500 MHz spectrometer, or a Bruker 500 MHz

spectrometer. Spectra were referenced using $CDCl_3$ as solvent with the residual solvent peak as the internal standard (^{1}H NMR: δ 7.26 ppm, ^{13}C NMR: δ 77.00 ppm). Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet,) d (doublet,) t (triplet,) q (quartet,) p (pentet,) m (multiplet,) and br (broad). Coupling constants, *J*, are reported in Hertz and integration is provided, along with assignments, as indicated. Gas Chromatography (GC) was performed on a Shimadzu GC-2010 Plus gas chromatograph with SHRXI–MS- 15m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and a flame ionization detector (FID). Low-resolution Mass Spectrometry and High Resolution Mass Spectrometry were performed in the Department of Chemistry at University of Illinois at Urbana-Champaign. The glove box, MBraun LABmaster sp, was maintained under nitrogen atmosphere.

Materials: Solvents used for extraction and column chromatography were reagent grade and used as received. Reaction solvents tetrahydrofuran (Fisher, unstabilized HPLC ACS grade), diethyl ether (Fisher, BHT stabilized ACS grade), methylene chloride (Fisher, unstabilized HPLC grade), dimethoxyethane (Fisher, certified ACS), toluene (Fisher, optima ACS grade), 1,4-dioxane (Fisher, certified ACS), THF (Fisher, optima ACS grade) acetonitrile (Fisher, HPLC grade), and hexanes (Fisher, ACS HPLC grade) were dried on a Pure Process Technology Glass Contour Solvent Purification System using activated stainless steel columns while following manufacture's recommendations for solvent preparation and dispensation unless otherwise noted.

Synthesis of Starting Materials

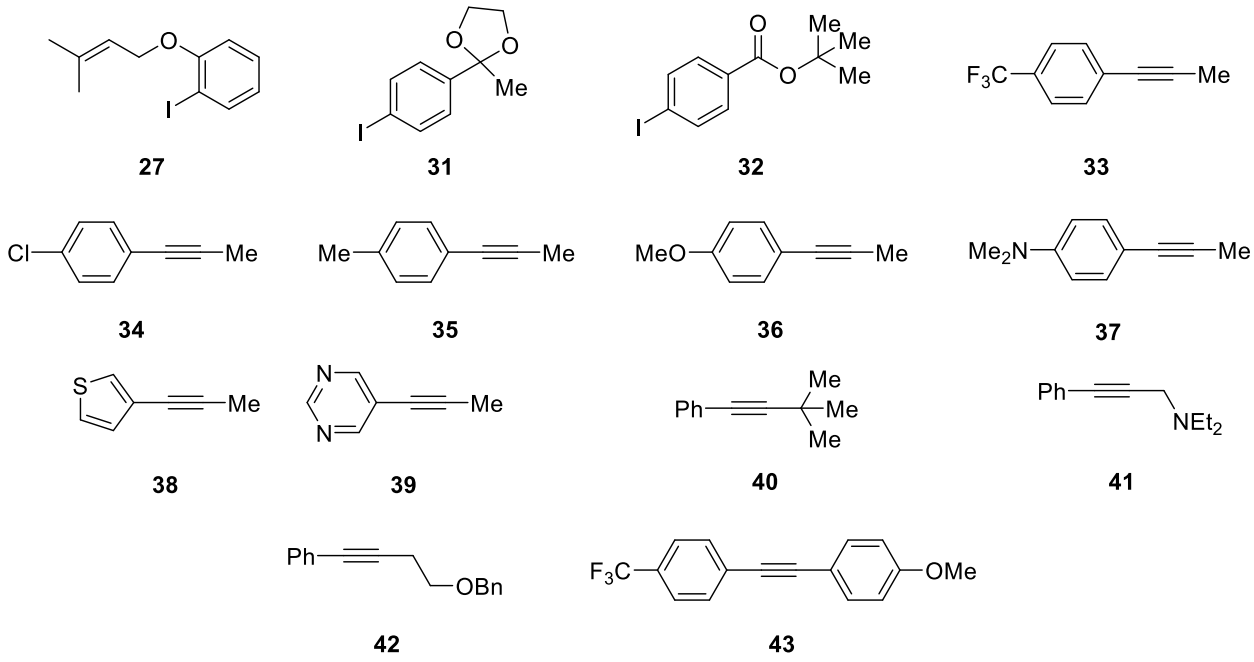
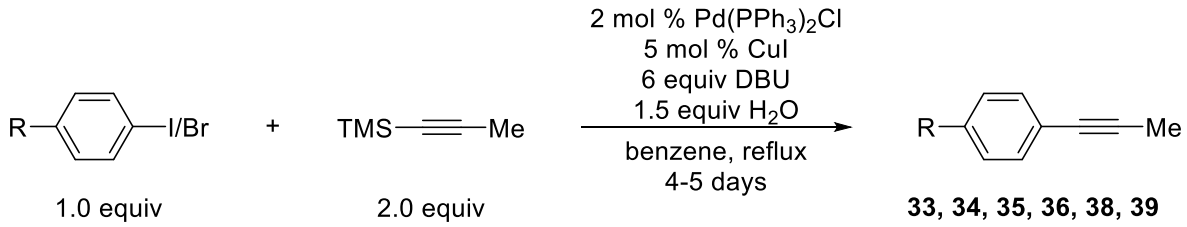


Figure 22: Starting Materials Which are not Readily Available from Commercial Sources.

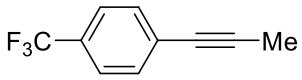
The following starting materials were synthesized following known literature procedures: **27**,[23] **31**,[24] **32**,[25] **40**,[26] **S41**,[27] **S42**,[28] **43**.[29]



General Procedure for the synthesis substituted phenyl propynes:

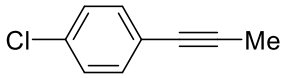
To a 250 mL round bottom was added DBU (6.0 equiv). The DBU was sparged with N_2 for 10 minutes and then dry benzene (0.125 M), $Pd(PPh_3)_2Cl$ (2.0 mol %), CuI (5.0 mol %), aryl iodide or aryl bromide (1.0 equiv), 1-(trimethylsilyl)propyne (2.0 equiv) and H_2O (1.5 equiv) were added. A reflux condenser was attached and the reaction was heated to reflux under an atmosphere of N_2 in an oil or sand bath. Reaction progress was checked by GC/MS analysis of an aliquot after 48 h and every 24 h thereafter until complete consumption of aryl halide. Typical reaction times were

4-5 d. Upon completion, the mixture was cooled to room temperature and transferred to a separatory funnel along with EtOAc (10 mL per mmol or aryl halide) and washed with 3 M HCl, (3 washes of 5 mL per mmol of aryl halide) H_2O, (2 washes of 10 mL per mmol aryl halide) and brine (1 wash of 5 mL per mmol). The organic layer was dried with $MgSO_4$, filtered through a 2 cm plug of silica, and concentrated. The resulting oil was purified by column chromatography.



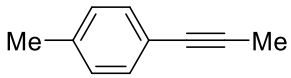
1-prop-1-yn-1-yl)-4-(trifluoromethyl)benzene (**33**)

33 was synthesized following the general procedure for the synthesis substituted phenyl propynes with 1-bromo-4-(trifluoromethyl)benzene (1.40 mL, 10.0 mmol). Purification by column chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) afforded a colorless oil (1.47 g, 80%). ^{1}H and ^{13}C NMR and matched the known literature spectra.[30]



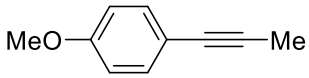
1-chloro-4-(prop-1-yn-1-yl)benzene (**34**)

34 was synthesized following the general procedure for the synthesis substituted phenyl propynes with 1-chloro-4-iodobenzene (4.77 g, 20.0 mmol). Purification by column chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) afforded a light yellow oil (2.723 g, 90%). ^{1}H and ^{13}C NMR and matched the known literature spectra.[9]



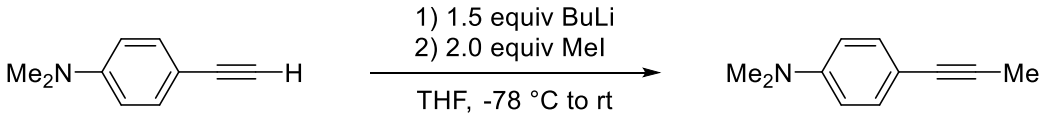
1-methyl-4-(prop-1-yn-1-yl)benzene (**35**)

35 was synthesized following the general procedure for the synthesis substituted phenyl propynes with 1-iodo-4-methylbenzene (2.18 g, 10.0 mmol). Purification by column chromatography (gradient 100% hexanes to 1% EtOAc:99% hexanes) afforded a colorless oil (1.06 g, 81%). ^{1}H and ^{13}C NMR and matched the known literature spectra.[9]

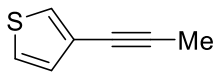


1-methoxy-4-(prop-1-yn-1-yl)benzene (**36**)

36 was synthesized following the general procedure for the synthesis substituted phenyl propynes with 1-iodo-4-methoxybenzene (2.34 g, 10.0 mmol). Purification by column chromatography (gradient 2% EtOAc: 98% hexanes to 5% EtOAc: 95% hexanes) afforded a colorless oil (1.344 g, 92%). ^{1}H and ^{13}C NMR and matched the known literature spectra.[9]



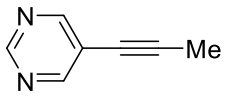
Synthesis of *N*,*N*-dimethyl-4-(prop-1-yn-1-yl)aniline (**37**): To a 50 mL Schlenk flask under N_2 atmosphere containing a stir bar was added 4-ethynyl-*N*,*N*-dimethylaniline (725 mg, 5.00 mmol, 1.00 equiv) and dry THF (10 mL). The flask was cooled to -78 °C and *n*-BuLi (1.6 M, 4.70 mL, 7.50 mmol, 1.50 equiv) was added slowly. After stirring for 30 min at -78 °C the flask was warmed to 0 °C in an ice bath and stirred for an additional 30 min. After this time had passed the flask was cooled to -78 °C and iodomethane (620 µL, 10.0 mmol, 2.00 equiv) was added slowly, after stirring for 30 min at 78 °C the reaction was warmed to room temperature and stirred for an additional 4 h. The reaction was quenched by adding H_2O (5 mL). and transferred to a separatory funnel with EtOAc (50 mL) and an additional portion of H_2O (10 mL). The layers were separated and the organic layer was washed with an additional portion of H_2O (10 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by column chromatography (5% EtOAc: 95% hexanes) affording a white solid (620 mg, 78%). ^{1}H and ^{13}C NMR and matched the known literature spectra.[9]



3-(prop-1-yn-1-yl)thiophene (**38**)

38 was synthesized following the general procedure for the synthesis substituted phenyl propynes with 3-bromothiophene (0.936 mL, 10.0 mmol). Purification by column chromatography (2%

EtOAc: 98% hexane) afforded a light brown oil (1.060 g, 87%). ^{1}H and ^{13}C NMR and matched the known literature spectra.[9]



5-(prop-1-yn-1-yl)pyrimidine (**39**)

39 was synthesized following the general procedure for the synthesis substituted phenyl propynes with 5-bromopyrimidine (1.59 g, 10.0 mmol). The separatory funnel HCl washes were replaced with additional water washes. Purification by column chromatography (20% EtOAc: 80% hexane) afforded a white solid (0.7644 g, 65%). ^{1}H and ^{13}C NMR and matched the known literature spectra.[31]

Unsuccessful Substrates

The following alkynes and aryl iodides were not successful coupling partners in the hydroarylation reaction.

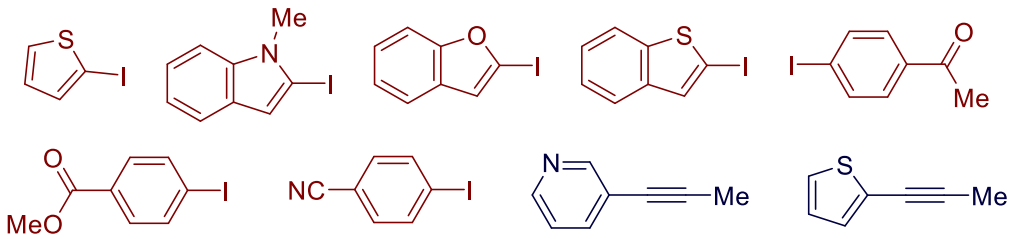
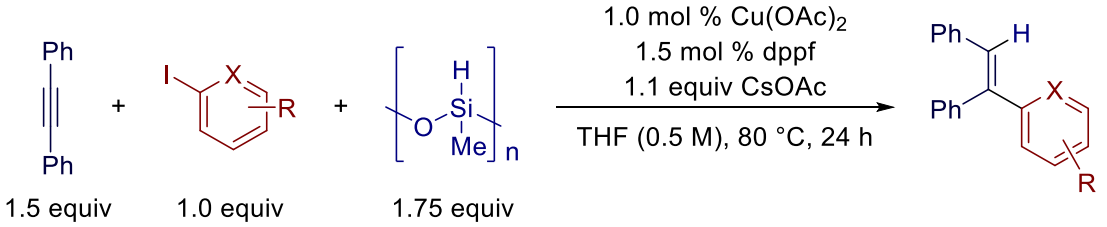


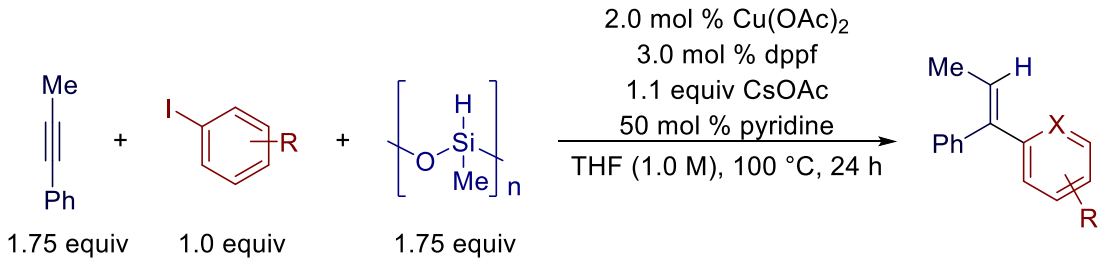
Figure 23: Unsuccessful Substrates in the Hydroarylation Reaction.

Procedures and Characterization



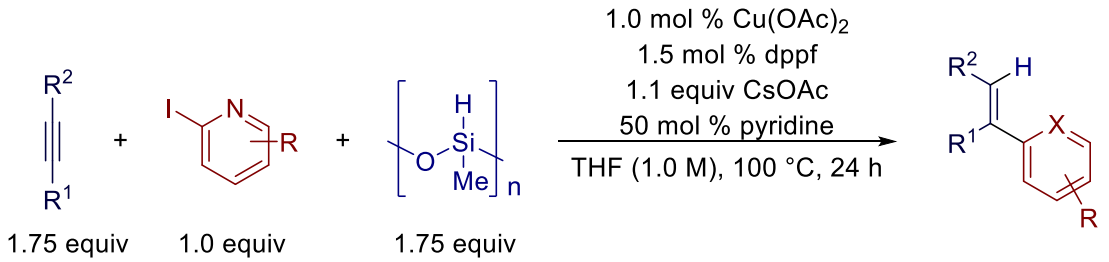
General Procedure A: general procedure for the hydroarylation of diphenylacetylene

A stock solution of $Cu(OAc)_2$ and dppf was made as follows: to a 20 mL scintillation vial was added $Cu(OAc)_2$ (10.9 mg, 0.600 mmol) and dppf (49.9 mg, 0.900 mmol) and THF (12 mL) and a magnetic stir bar. A cap was affixed and the vial was stirred in the glove box for 10 minutes or until it was a homogeneous green solution. To a separate 4 mL scintillation vial was added diphenyl acetylene (106.9 mg, 0.6000 mmol, 1.5000 equiv) and CsOAc (84.5 mg, 0.440 mmol, 1.100 equiv). Next $Cu(OAc)_2$/dppf stock solution (800. µL, 1.0 mol % $Cu(OAc)_2$ and 1.5 mol % dppf) and a magnetic stir bar were added to the vial containing alkyne and CsOAc followed by PMHS (42.0 µL, 0.700 mmol, 1.75 equiv) This solution was stirred for 10 minutes over which time the color of the solution changed from green to orange. Finally, aryl iodide (0.400 mmol, 1.00 equiv) was added, a Teflon lined cap was affixed, the vial was removed from the glovebox and heated to 80 °C in a pre-equilibrated aluminum heating block. After 24 h the reaction vial was cooled to room temperature and directly loaded on to a silica gel column (2 cm column containing 120 mL dry silica equilibrated which was slurry loaded with eluent) and purified by flash chromatography. See specific substrates below for eluent conditions.



General Procedure B: general procedure for the 2 mmol scale hydroarylation of 1-phenyl-1-propyne

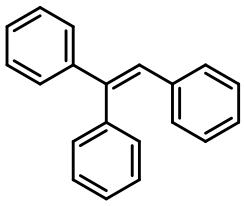
To a 20 mL scintillation vial was added $Cu(OAc)_2$ (7.3 mg, 0.040 mmol, 2.0 mol %,), dppf (33.3 mg, 0.0600 mmol, 3.0 mol %), CsOAc (422.3 mg, 2.200 mmol, 1.100 equiv.) and THF (2.0 mL) and a magnetic stir bar. The solution was stirred for 10 minutes until all the blue $Cu(OAc)_2$ was dissolved affording a green solution (CsOAc does not dissolve). Next PMHS (210. µL, 3.50 mmol, 1.75 equiv) was added and the solution was stirred an additional 10 minutes over which time the color of the solution turned orange. Finally, 1-phenyl-1-propyne (438. µL, 3.50 mmol, 1.75 equiv) followed by aryl iodide (1.00 equiv) and pyridine (80.5 µL, 1.00 mmol, 0.500 equiv) A Teflon lined cap was affixed and the vial was removed from the glovebox and heated to 100 °C in a pre-equilibrated aluminum heating block for 24 h. After 24 h the vial was cooled to room temperature and the regioisomeric ratio of the reaction was determined by GC analysis of a reaction aliquot. The volume of the scintillation vial was then diluted with THF to 12 mL. NaOH (4 mL, 5 M in H_2O) was added (slight effervescence) with stirring and was left to stir for 30 min. The contents of the vial were transferred to a separatory funnel and extracted with diethyl ether (100 mL) the aqueous layer was washed with an additional portion of diethyl ether (50 mL). The combined organic layers were washed with water (50 mL) and brine (25 mL) dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was crystallized from anhydrous ethanol (8 mL) in a test tube in a -78 °C bath. Crystallization often needed to be induced by scratching of the side walls of the test tube with a spatula. The solid was isolated by filtration and was washed with a small portion of -78 °C ethanol. The mother liquor was concentrated and crystallized two more times as described above but with 6 mL and 4 mL portions of ethanol.



General procedure C: general procedure for 0.4 mmol scale hydroarylation of differentially substituted alkynes

A stock solution of $Cu(OAc)_2$ and dppf was prepared as follows: to a 4 mL scintillation vial was added $Cu(OAc)_2$ (3.6 mg, 0.020 mmol), dppf (16.6 mg, 0.030 mmol), THF (2.0 mL) and a magnetic stir bar. A cap was affixed and the mixture was stirred for 10 minutes or until a homogeneous green solution was formed. To a separate 4 mL scintillation vial was added CsOAc (84.5 mg, 0.440 mmol, 1.10 equiv), $Cu(OAc)_2$/dppf stock solution (400. µL, 1.0 mol % $Cu(OAc)_2$ and 1.5 mol % dppf), PMHS (42.0 µL, 0.700 mmol, 1.75 equiv), and a magnetic stir bar. The mixture was stirred for 10 minutes over which time the solution turned from green to orange. Next alkyne (1.75 equiv), aryl iodide (1.00 equiv), and pyridine (16.1 µL, 0.200 mmol, 0.500 equiv) were added and a teflon lined cap was affixed. The vial was removed from the glovebox and heated to 100 °C in a pre-equilibrated aluminum block for 24 to 48 h. The reaction was then cooled to room temperature and the selectivity was determined by GC or ^{1}H NMR analysis of an aliquot. The crude reaction mixture was loaded onto a silica gel column (120 mL dry silica slurry loaded with eluent) and purified by flash chromatography. See specific substrates below for eluent conditions.

Ethene-1,1-1,2-tryltribenzene (**12a**)



12a was synthesized following general procedure A with iodobenzene (44.59 µL, 0.4000 mmol, 1.000 equiv). Purification by flash chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes afforded a colorless oil (95.2 mg, 93% yield).

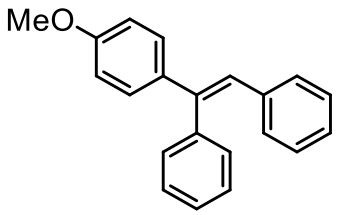
R_f (1% EtOAc: 99% Hexane) = 0.41

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 8H), 7.25 – 7.21 (m, 2H), 7.19 – 7.09 (m, 3H), 7.08 – 7.02 (m, 2H), 6.99 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.58, 142.73, 140.50, 137.52, 130.53, 129.69, 128.76, 128.34, 128.31, 128.10, 127.75, 127.65, 127.55, 126.88.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{20}H_{16}$ = 265.1252; found mass = 256.1252

(*E*)-(1-4(-methoxyphenyl)ethane-1,2-diyl)dibenzene (**12b**)



12b was synthesized following general procedure A with 1-iodo-4-methoxybenzene (95.48 mg, 0.4080 mmol, 1.000 equiv). Purification by flash chromatography (gradient 1% EtOAc: 99% hexanes to 2% EtOAc: 98%) hexanes afforded a colorless oil (115.85 mg, 99% yield).

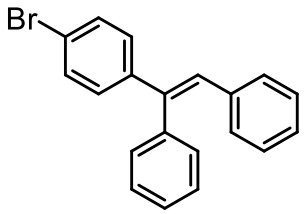
R_f (1% EtOAc: 99% Hexanes) = 0.26

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.32 (m, 3H), 7.29 (dd, *J* = 6.8, 2.1 Hz, 2H), 7.25 – 7.22 (m, 2H), 7.18 – 7.08 (m, 3H), 7.07 – 7.00 (m, 2H), 6.92 (s, 1H), 6.88 (dd, *J* = 9.0, 2.3 Hz, 2H), 3.83 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.38, 142.25, 140.69, 137.73, 136.19, 130.52, 129.57, 128.90, 128.73, 128.06, 127.48, 126.66, 126.59, 113.73, 55.44.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{21}H_{18}O$ = 286.1358; found mass = 286.1357

(*E*)-1(4-bromophenyl)ethane-1,2-diyl)dibenzene (**12c**)



12c was synthesized following general procedure A with 1-bromo-4-iodobenzene (113.06 mg, 0.39964 mmol, 1.0000 equiv). Purification by flash chromatography (gradient 1% EtOAc: 99% hexanes to 2% EtOAc: 98% hexanes) afforded a colorless oil (107.0 mg, 93%).

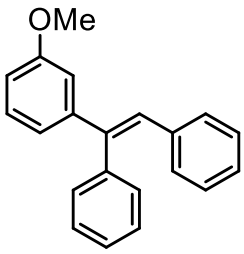
R_f (1% EtOAc: 99% hexanes) = 0.43

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dt, *J* = 6.6, 2.5, 2.1 Hz, 2H), 7.37 – 7.32 (m, 3H), 7.22 – 7.17 (m, 4H), 7.17 – 7.10 (m, 3H), 7.06 – 7.00 (m, 2H), 6.96 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.53, 141.61, 139.96, 137.19, 131.44, 130.46, 129.69, 129.33, 128.90, 128.69, 128.16, 127.79, 127.13, 121.69.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{20}H_{15}Br$ = 334.0357; found mass = 334.0356

(*E*)-(1-(3-methoxyphenyl)ethane-1,2-diyl)dibenzene (**12d**)



12d was synthesized following general procedure A with 1-iodo-3-methoxybenzene (47.64 µL, 0.4000 mmol, 1.000 equiv). Purification by flash chromatography (gradient 1% EtOAc: 99% hexanes to 2% EtOAc: 98% hexanes) afforded a colorless oil (86.2 mg, 75%).

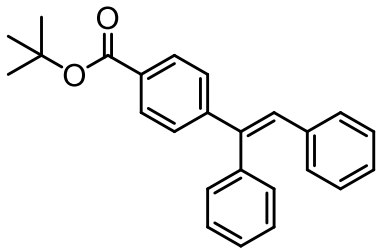
R_f (1% EtOAc: 99% hexanes) = 0.26

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 3H), 7.26 – 7.19 (m, 3H), 7.18 – 7.07 (m, 3H), 7.04 – 7.01 (m, 2H), 6.98 (s, 1H), 6.92 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 6.89 (dd, *J* = 2.5, 1.7 Hz, 1H), 6.84 (ddd, *J* = 8.1, 2.6, 0.9 Hz, 1H), 3.79 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.64, 145.11, 142.60, 140.37, 137.44, 130.49, 129.71, 129.25, 128.76, 128.46, 128.10, 127.58, 126.93, 120.43, 113.60, 112.98, 55.38.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{21}H_{18}O$ = 286.1358; found mass = 286.1361

tert-butyl (*E*)-4-(1,2-diphenylvinyl)benzoate (**12e**)



12e was synthesized following general procedure A with *tert*-butyl 4-iodobenzoate (121.65 mg, 0.39932 mmol, 1.0000 equiv). Purification by flash chromatography (gradient 20% DCM: 80% hexanes to 30% DCM: 70% hexanes) afforded a colorless oil (136.5 mg, 96%).

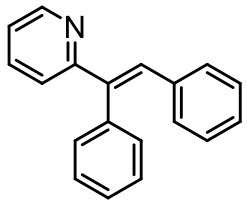
R_f (1% EtOAc: 99% hexanes) = 0.22

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dt, *J* = 8.6, 1.9 Hz, 2H), 7.41 – 7.32 (m, 5H), 7.23 – 7.16 (m, 2H), 7.16 – 7.11 (m, 3H), 7.09 – 7.01 (m, 3H), 1.60 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.76, 147.57, 141.93, 140.00, 137.10, 130.98, 130.45, 129.81, 129.80, 129.49, 128.91, 128.17, 127.79, 127.49, 127.29, 81.07, 28.36.

HRMS (EI-TOF) *m/z*: [M] calculated $C_{25}H_{24}O_2$ = 356.1776; found mass = 356.1777

(*E*)-2-(1,2-diphenylvinyl)pyridine (**12f**)



12f was synthesized following general procedure A with 2-iodopyridine (42.53 µL, 0.4000 mmol, 1.000 equiv). Purification by flash chromatography (5% EtOAc: 95% hexanes) afforded a colorless oil (67.0 mg, 65%).

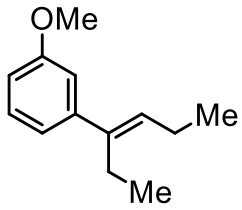
R_f (5% EtOAc: 95% Hexanes) = 0.14

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 7.85 (s, 1H), 7.55 (td, *J* = 7.7, 1.9 Hz, 1H), 7.45 – 7.34 (m, 3H), 7.31 – 7.23 (m, 2H), 7.19 – 7.10 (m, 4H), 7.10 – 7.03 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.02, 149.39, 140.59, 139.34, 136.90, 136.45, 131.03, 130.39, 130.17, 129.18, 128.06, 127.77, 127.40, 122.60, 122.10.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{19}H_{14}N$ = 256.1126; found mass = 256.1129

(*E)*-1-(hex-3-en-3-yl)-3-methoxybenzene (**13**)



13 was synthesized following general procedure C with 3-hexyne (114.08 µL, 1.0000 mmol, 2.5000 equiv) and 3-iodoanisole (47.64 µL, 0.4000 mmol, 1.000 equiv) at 120 °C for 60 h. The yield of the reaction was determined by analysis of the crude reaction mixture by comparison to an internal standard (1-methylnaphthalene, 40.0 µL). in the ^{1}H NMR spectrum.[32]

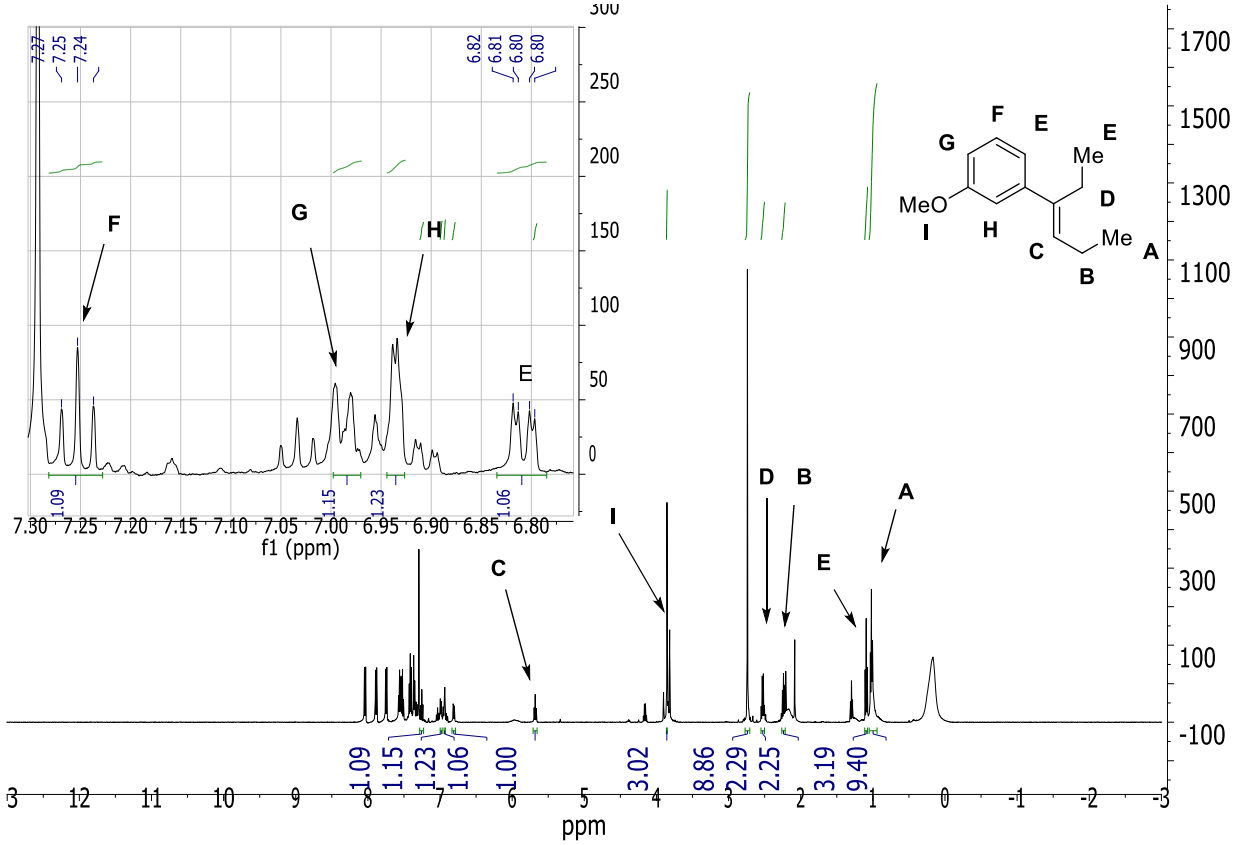
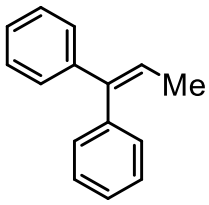


Figure 24: Crude NMR of the Reaction Between 3-hexyne and 1-Iodo-3-Methoxybenzene with 1-Methylnaphthalene (40.0 µL, Internal Standard). The Yield of 2 was Determined to be 24% by Comparison to 1-Methylnaphthalene.

Prop-1-ene-1,1-diyldibenzene (**14a**)



14a was synthesized and purified following general procedure B with iodobenzene (223.8 µl, 2.000 mmol, 1.000 equiv) affording a white powder (247.0 mg, 63%). The regioisomeric ratio was 44:1 as determined by GC analysis of the crude reaction mixture.

MP = 46.1-46.6 °C

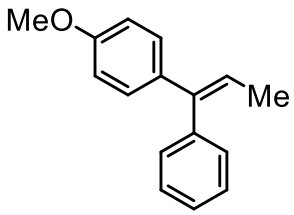
R_f (1% EtOAc: 99% Hexanes) = 0.38

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.36 (m, 2H), 7.32 (tt, *J* = 7.7, 2.1 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.25 – 7.18 (m, 5H), 6.20 (q, *J* = 7.0 Hz, 1H), 1.78 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.11, 142.58, 140.17, 130.20, 128.28, 128.20, 127.34, 126.97, 126.86, 124.29, 15.85.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{15}H_{14}$ = 194.1096; found mass = 194.1094

(*E*)-1-methoxy-4-(1-phenylprop-1-en-1-yl)benzene (**14b**)



14b was synthesized following general procedure C with 1-phenyl-1-propyne (87.62 µL, 0.7000 mmol, 1.750 equiv) and 1-iodo-4-methoxybenzene (94.18 mg, 0.4024 mmol, 1.000 equiv) for 24 h. Purification by flash chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) affording a colorless oil (65.2 mg, 72%). The regioisomeric ratio of the reaction was 16:1 as determined by GC analysis of the crude reaction mixture.

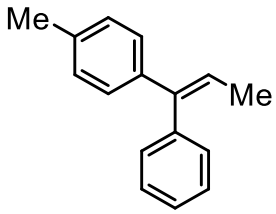
R_f (1% EtOAc: 99% Hexanes) = 0.31

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.4 Hz, 2H), 7.30 (tt, *J* = 7.7, 7.2, 2.0 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 2H), 7.14 (ddd, *J* = 8.7, 3.0, 1.8 Hz, 2H), 6.80 (ddd, *J* = 9.0, 2.9, 1.7 Hz, 2H), 6.08 (q, *J* = 6.9, Hz, 1H), 3.79 (s, 3H), 1.74 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.72, 141.98, 140.41, 135.88, 130.17, 128.39, 128.24, 126.90, 122.56, 113.58, 55.41, 15.77.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{16}H_{16}O$ = 224.1201; found mass = 224.1202

(*E*)-1-methyl-4-(1-phenylprop-1-en-1-yl)benzene (**14c**)



14c was synthesized and purified following general procedure B with 1-iodo-4-methylbenzene (438.91 mg, 2.0131 mmol, 1.0000 equiv) affording a white powder (253.0 mg, 60%). The regioisomeric ratio was 26:1 as determined by GC analysis of the crude reaction mixture.

MP = 26.9-27.3 °C

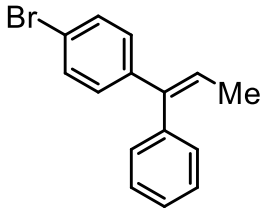
R_f (1% EtOAc: 99% Hexanes) = 0.38

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.4 Hz, 2H), 7.32 (tt, *J* = 7.3, 1.1 Hz, 1H), 7.20 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.16 (q, *J* = 7.0 Hz, 1H), 2.34 (s, 3H), 1.77 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.40, 140.34, 136.54, 130.19, 128.91, 128.24, 127.22, 126.89, 123.40, 21.18, 15.79. One sp^2 carbon could not be located due to overlap.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{16}H_{16}$ = 208.1252; found mass = 208.1250

(*E*)-1-bromo-4-(1-phenylprop-1-en-1-yl)benzene (**14d**)



14d was synthesized and purified following general procedure B with 1-bromo-4-iodobenzene (568.59 mg, 2.0099 mmol, 1.0000 equiv) as a white powder (371.6 mg, 68%). The regioisomeric ratio of the reaction was 29:1 as determined by GC analysis of the crude reaction mixture.

MP = 43.2-44.0 °C

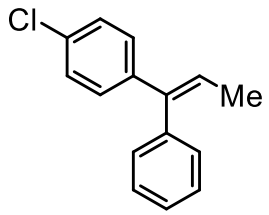
R_f (1% EtOAc: 99% hexanes) = 0.59

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 4H), 7.31 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.15 (dd, *J* = 6.9, 1.4 Hz, 2H), 7.08 (dt, *J* = 8.7, 2.2 Hz, 2H), 6.17 (q, *J* = 7.0 Hz, 1H), 1.75 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.07, 141.61, 139.59, 131.28, 130.12, 128.98, 128.42, 127.22, 124.94, 120.83, 15.89.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{15}H_{13}Br$ = 272.0201; found mass = 272.0208

(*E*)-1-chloro-4-(1-pheylprop-1-en-1-yl)benzene (**14e**)



14e was synthesized and purified following general procedure B with 1-chloro-4-iodobenzene (478.55 mg, 2.0069 mmol, 1.0000 equiv) as a white powder (276.9 mg, 60%). The regioisomeric ratio of the reaction was 34:1 as determined by GC analysis of the crude reaction mixture.

MP= 70.7-71.4 °C

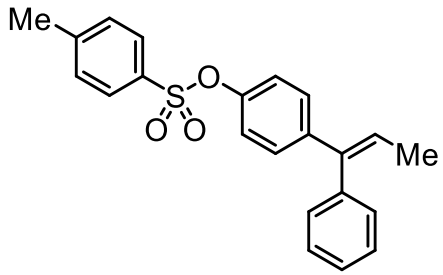
R_f (1% EtOAc: 99% hexanes) = 0.62

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (tt, *J* = 7.7, 7.0, 1.6 Hz, 2H), 7.32 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.22 (dt, *J* = 8.7, 2.1 Hz, 2H), 7.18 – 7.11 (m, 4H), 6.16 (q, *J* = 7.0 Hz, 1H), 1.76 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.60, 141.55, 139.66, 132.66, 130.11, 128.60, 128.41, 128.32, 127.19, 124.83, 15.87.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{15}H_{13}Cl$ = 228.0706; found mass = 228.0710

(*E*)-4-(1-phenylprop-1-en-1-yl)phenyl 4-methylbenzenesulfonate (**14f**)



14f was synthesized following general procedure C with 1-phenyl-1-propyne (87.62 µL, 0.7000 mmol, 1.750 equiv) and 4-iodophenyl 4-methylbenzenesulfonate (149.27 mg, 0.39890 mmol, 1.0000 equiv). Purification by flash chromatography (gradient 2% EtOAc: 98% hexanes to 5% EtOAc: 95% hexanes) affording a white powder (115.05 mg, 79%). The regioisomeric ratio of the reaction was determined to be 21:1 by ^{1}H NMR analysis of the crude reaction mixture.

MP= 88.6-89.5 °C

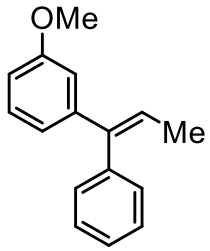
R_f (5% EtOAc: 95% hexanes) = 0.18

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 8.1, 2.1, 1.7 Hz, 2H), 7.36 (tt, *J* = 7.1, 1.6, 1.0 Hz, 2H), 7.33 – 7.28 (m, 3H), 7.16 – 7.05 (m, 4H), 6.85 (dt, *J* = 8.9, 2.8, 2.1 Hz, 2H), 6.14 (q, *J* = 7.0 Hz, 1H), 2.44 (s, 3H), 1.74 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.54, 145.39, 141.96, 141.40, 139.58, 132.73, 130.08, 129.87, 128.67, 128.41, 128.32, 127.21, 125.25, 122.05, 21.86, 15.88.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{22}H_{20}O_3S$ = 364.1133; found mass = 364.1138.

(*E*)-1-methoxy-3-(1-phenylprop-1-en-1-yl)benzene (**14g**)



14g was synthesized following general procedure C with 1-phenyl-1-propyne (87.62 µL, 0.7000 mmol, 1.750 equiv) and 1-iodo-3-methoxybenzene (47.64 µL, 0.4000 mmol, 1.000 equiv) for 24 h. Purification by flash chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) affording a colorless oil (58.9 mg, 66%). The regioisomeric ratio of the reaction was determined to be 31:1 by GC analysis of the crude reaction mixture.

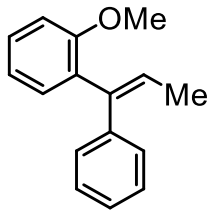
R_f (1% EtOAc: 99% Hexanes) = 0.28

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.32 (tt, *J* = 7.5, 2.1 Hz, 1H), 7.24 – 7.16 (m, 3H), 6.86 – 6.76 (m, 3H), 6.22 (q, *J* = 7.0 Hz, 1H), 3.78 (s, 3H), 1.78 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.53, 144.62, 142.44, 140.01, 130.15, 129.08, 128.26, 126.98, 124.48, 120.01, 113.25, 112.12, 55.27, 15.81.

HRMS (EI-TOF) *m/z*: [M] calculated $C_{16}H_{16}O$ = 224.1201; found mass = 224.1202.

(*E*)-1-methoxy-2-(1-phenylprop-1-en-1yl)benzene (**14h**)



14h was synthesized following general procedure C with 1-phenyl-1-propyne (87.62 µL, 0.7000 mmol, 1.750 equiv) and 1-iodo-2-methoxybenzene (52.00 µL, 0.4000 mmol, 1.000 equiv) for 48 h. Purification by flash chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) affording a white solid (79.7 mg, 89%). The regioisomeric ratio of the reaction was 17:1 as determined by GC analysis of the crude reaction mixture.

MP= 89.4-91.0 °C

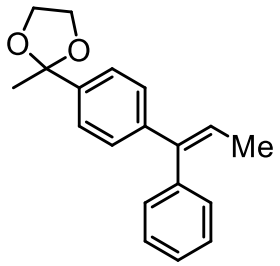
R_f (1% EtOAc: 99% hexanes) = 0.26

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (tt, *J* = 7.9, 1.7 Hz, 2H), 7.26 – 7.22 (m, 2H), 7.22 – 7.18 (m, 3H), 6.93 (td, *J* = 7.4, 1.1 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.1 Hz, 1H), 5.95 (q, *J* = 7.1 Hz, 1H), 3.58 (s, 3H), 1.85 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.23, 140.90, 140.10, 133.85, 131.16, 129.29, 128.37, 127.74, 126.42, 126.34, 120.63, 111.70, 55.75, 15.52.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{16}H_{16}O$ = 224.1201; found mass = 224.1201.

(*E*)-2-methyl-2-(4-(1phenylprop-1-in-1-yl)phenyl-1,3-dioxolane (**14i**)



14i was synthesized following general procedure C with 1-phenyl-1-propyne (87.62 µL, 0.7000 mmol, 1.750 equiv) and 2-(4-iodophenyl)-2-methyl-1,3-dioxolane (122.05 mg, 0.40129 mmol, 1.0000 equiv) for 24 h. Purification by flash chromatography (gradient 2% EtOAc: 98% hexanes to 5% EtOAc: 95% hexanes) afforded a white powder (71.7 mg, 45%). The regioisomeric ratio of the reaction was 22:1 as determined by GC analysis of the crude reaction mixture.

MP= 78.2-79.5 °C

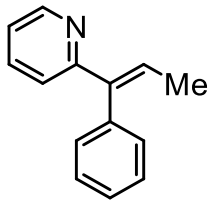
R_f (5% EtOAc: 95% hexanes) = 0.21

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 4H), 7.31 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.23 – 7.10 (m, 4H), 6.19 (q, *J* = 7.0 Hz, 1H), 4.08 – 3.97 (m, 2H), 3.81 – 3.75 (m, 2H), 1.75 (d, *J* = 7.0 Hz, 3H), 1.65 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.56, 142.21, 141.79, 140.06, 130.16, 128.31, 127.04, 127.01, 125.16, 124.42, 108.96, 64.58, 27.66, 15.84.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{19}H_{20}O_2$ = 280.1463; found mass = 280.1469.

(*E*)-2-(1-phenylprop-en-1-yl)pyridine (**14j**)



14j was synthesized following general procedure C with 1-phenyl-1-propyne (87.62 µL, 0.7000 mmol, 1.750 equiv) and 2-iodopyridine (42.53 µL, 0.4000 mmol, 1.000 equiv) for 24 h. Purification by flash chromatography (5% EtOAc: 95% hexanes) afforded a colorless oil (40.3 mg, 52%). The regioisomeric ratio of the reaction was 21:1 as determined by GC analysis of the crude reaction mixture.

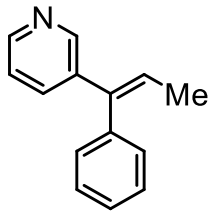
R_f (5% EtOAc: 95% hexanes) = 0.11

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 7.50 (td, *J* = 7.7, 1.9 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.34 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.09 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 6.97 (q, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 1.78 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.91, 149.26, 141.70, 138.89, 136.31, 130.19, 128.56, 128.39, 127.23, 122.08, 121.63, 15.64.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{14}H_{13}N$ = 195.1048; found mass = 195.1048.

(*E*)-3-(1-phenylprop-en-1-yl)pyridine (**14k**)



14k was synthesized following general procedure C with 1-phenyl-1-propyne (87.62 µL, 0.7000 mmol, 1.750 equiv) and 3-iodopyridine (82.00 mg, 0.4000 mmol, 1.000 equiv) for 24 h. Purification by flash chromatography (gradient 5% EtOAc: 95% hexanes to 10% EtOAc: 90%

hexanes) afforded a colorless oil (48.0 mg, 61%). The regioisomeric ratio of the reaction was 29:1 as determined by GC analysis of the crude reaction mixture.

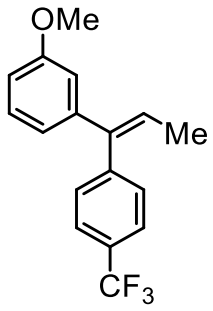
R_f (10% EtOAc: 90% hexanes) = 0.22

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 2.6 Hz, 1H), 8.48 – 8.42 (m, 1H), 7.43 (ddd, *J* = 8.0, 2.3, 1.6 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.35 – 7.29 (m, 1H), 7.21 – 7.13 (m, 3H), 6.21 (q, *J* = 7.0 Hz, 1H), 1.80 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.09, 147.58, 139.25, 138.56, 138.23, 134.15, 129.62, 128.12, 126.99, 125.78, 122.64, 15.49.

HRMS (ESI-TOF) *m/z*: [M+H] calculated for $C_{14}H_{14}N$ = 196.1126; found mass = 196.1131.

(*E*)-1-methoxy-3-(1-(4-trifluoromethyl)phenyl)prop-1-en-1-yl)benzene (**15**)



15 was synthesized following general procedure C with 1-(prop-1-yn-1-yl)-4-(trifluoromethyl)benzene (128.91 mg, 0.70000 mmol, 1.7500 equiv) and 1-iodo-3-methoxybenzene (47.63 µL, 0.4000 mmol, 1.000 equiv) for 24 h. Purification by flash chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) afforded a colorless oil (105.9 mg, 91%). The regioisomeric ratio the reaction was 27:1 as determined by GC analysis of the crude reaction mixture.

R_f (1% EtOAc: 99% hexanes) = 0.25

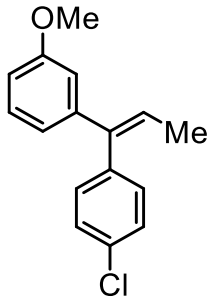
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dt, *J* = 8.4, 0.9, 0.6 Hz, 2H), 7.31 (dt, *J* = 7.8, 0.7 Hz, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.79 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.76 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 6.72 (t, *J* = 2.0 Hz, 1H), 6.25 (q, *J* = 7.1 Hz, 1H), 3.77 (s, 3H), 1.75 (d, *J* = 7.1 Hz, 3H).

^{19}F NMR (471 MHz, $CDCl_3$) δ -62.43.

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.67, 143.90, 143.79, 141.35, 130.52, 129.31, 129.24 (q, *J* = 31.8 Hz), 125.64, 125.29 (q, *J* = 3.8 Hz), 124.39 (q, *J* = 272.2 Hz), 119.94, 113.38, 112.32, 55.30, 15.76.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{17}H_{15}OF_3$ = 292.1075; found mass = 292.1075.

(*E*)-1-(1-(4-chlorophenyl)prop-1-en-1-yl)-3-methoxybenzene (**16**)



16 was synthesized following general procedure C with 1-chloro-4-(prop-1-yn-1-yl)benzene (105.43 mg, 0.70000 mmol, 1.7500 equiv) and 1-iodo-3-methoxybenzene (47.64 µL, 0.4000 mmol, 1.000 equiv) for 24 h. Purification by flash chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) afforded a colorless oil (92.5 mg, 89%). The regioisomeric ratio of the reaction was 21:1 as determined by GC analysis of the crude reaction mixture.

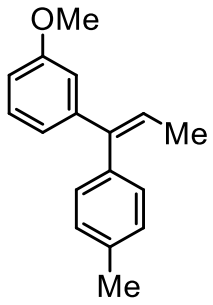
R_f (1% EtOAc: 99% hexanes) = 0.28

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 2H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.13 (dt, *J* = 8.5, 2.4, 1.9 Hz, 2H), 6.79 (dt, *J* = 8.2, 1.3 Hz, 2H), 6.75 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.21 (q, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 1.77 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.59, 144.16, 141.34, 138.44, 132.86, 131.54, 129.20, 128.52, 125.06, 119.94, 113.28, 112.28, 55.30, 15.80.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{16}H_{15}OCl$ = 258.0811; found mass = 258.0813.

(*E*)-1-methoxy-3-(1-(*p*-tolyl)prop-1-en-1-yl)benzene (**17**)



17 was synthesized following general procedure C with 1-methyl-4-(prop-1-yn-1-yl)benzene (91.13 mg, 0.7000 mmol, 1.750 equiv) and 1-iodo-3-methoxybenzene (47.64 µL, 0.4000 mmol, 1.000 equiv) for 48 h. Purification by flash chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) afforded a colorless oil (75.5 mg, 79%). The regioisomeric ratio of the reaction was 25:1 as determined by GC analysis of the crude reaction mixture.

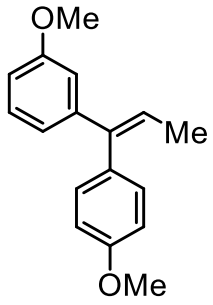
R_f (1% EtOAc: 99% hexanes) = 0.26

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (td, *J* = 7.8, 1.2 Hz, 3H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.80 (dt, *J* = 8.1, 1.5 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.15 (q, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 2.38 (s, 3H), 1.76 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.52, 144.90, 142.35, 136.98, 136.55, 130.05, 129.04, 128.96, 124.28, 120.08, 113.29, 112.08, 55.33, 21.39, 15.87.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{17}H_{18}O$ = 238.1358; found mass = 238.1360.

(*E*)-1-methoxy-3-(1-(4-methoxyphenyl)prop-1-en-1-yl)benzene (**18**)



18 was synthesized following general procedure C with 1-methoxy-4-(prop-1-yn-1-yl)benzene (102.33 mg, 0.70000 mmol, 1.7500 equiv) and 1-iodo-3-methoxybenzene (47.63 µL, 0.4000 mmol, 1.000 equiv) for 48 h. Purification by flash chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) afforded a colorless oil (62.4 mg, 61%). The regioisomeric ratio of the reaction was 38:1 as determined by GC analysis of the crude reaction mixture.

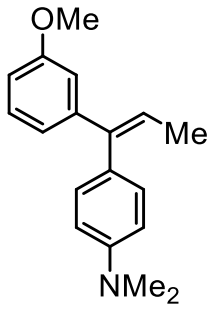
R_f (1% EtOAc: 99% hexanes) = 0.32

^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 – 7.15 (m, 1H), 7.11 (dt, *J* = 8.9, 2.8, 2.1 Hz, 2H), 6.91 (dt, *J* = 8.7, 2.8, 2.1 Hz, 2H), 6.81 (dt, *J* = 7.9, 1.2 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.13 (q, *J* = 7.0 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 1.77 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.52, 158.58, 145.05, 142.01, 132.31, 131.31, 129.04, 124.20, 120.09, 113.65, 13.31, 112.13, 55.37, 55.32, 15.89.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{17}H_{18}O_2$ = 254.1307; found mass = 254.1307.

(*E*)-4-(1-(3-methoxyphenyl)prop-1-en-1-yl)-*N*,*N*-dimethylaniline (**19**)



19 was synthesized following general procedure C with *N*,*N*-dimethyl-4-(prop-1-yn-1-yl)aniline (111.46 mg, 0.70000 mmol, 1.750 equiv) and 1-iodo-3-methoxybenzene (47.63 µL, 0.4000 mmol, 1.000 equiv) at 120 °C for 24 h. Purification by flash chromatography (5% EtOAc: 95% hexanes) afforded a colorless oil (34.6 mg, 32%). The regioisomeric ratio of the reaction was 7.2:1 as determined by GC analysis of the crude reaction mixture.

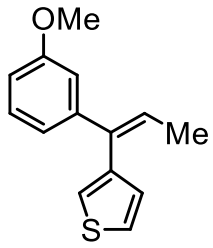
R_f (5% EtOAc: 95% hexanes) = 0.21

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.0 Hz, 1H), 7.06 (dt, *J* = 8.7, 3.0, 2.0 Hz, 2H), 6.90 – 6.79 (m, 2H), 6.79 – 6.69 (m, 3H), 6.07 (q, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 2.98 (s, 6H), 1.81 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.48, 149.49, 145.66, 142.43, 131.04, 128.93, 127.99, 123.53, 120.36, 113.40, 112.13, 112.06, 55.32, 40.71, 15.98.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{18}H_{21}NO$ = 267.1623; found mass = 267.1620.

(*Z*)-3-(1-(3-methoxyphenyl)prop-1-en-1-yl)-thiophene (**20**)



20 was synthesized following general procedure C with 3-(prop-1-yn-1-yl)thiophene (78.53 mg, 0.7000 mmol, 1.750 equiv) and 1-iodo-3-methoxybenzene (47.63 µL, 0.4000 mmol, 1.000 equiv) at 100 °C for 24 h. Purification by flash chromatography (10% DCM: 90% hexanes) afforded a colorless oil (41.1 mg, 45%). The regioisomeric ratio of the reaction was 23:1 as determined by NMR analysis of the crude reaction mixture.

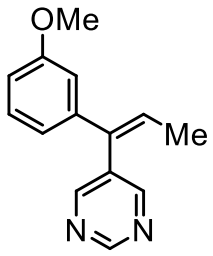
R_f (20% DCM: 80% hexanes) = 0.30

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.20 (td, *J* = 7.5, 1.3 Hz, 1H), 7.13 (dd, *J* = 3.0, 1.3 Hz, 1H), 6.93 (dd, *J* = 4.9, 1.3 Hz, 1H), 6.85 (dt, *J* = 7.8, 1.2 Hz, 1H), 6.80 (q, *J* = 1.4 Hz, 1H), 6.78 (dd, *J* = 2.6, 1.0 Hz, 1H), 6.14 (q, *J* = 7.0 Hz, 1H), 3.78 (s, 3H), 1.86 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.39, 144.40, 139.86, 137.22, 129.33, 128.94, 125.28, 124.69, 123.98, 119.76, 113.01, 112.14, 55.16, 15.82.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{14}H_{14}OS$ = 230.0765; found mass = 230.0766.

(*Z*)-5-(1-(3-methoxyphenyl)prop-1-en-1-yl)pyrimidine (**21**)



21 was synthesized following general procedure C with 5-(prop-1-yn-1-yl)pyrimidine (82.70 mg, 0.7000 mmol, 1.750 equiv) and 1-iodo-3-methoxybenzene (47.63 µL, 0.4000 mmol, 1.000 equiv) at 100 °C for 24 h. Purification by two flash chromatography columns (20% EtOAc: 80% hexanes then 10% Et_2O: 90% DCM) afforded a colorless oil (55.6 mg, 61%). The regioisomeric ratio of the reaction was 19:1 as determined by NMR analysis of the crude reaction mixture.

R_f (20% EtOAc: 80% hexanes) = 0.19

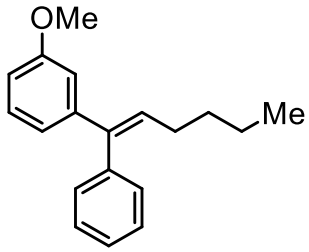
R_f (20% Et_2O: 80% DCM) = 0.42

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.59 (s, 2H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.82 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.75 – 6.68 (m, 2H), 6.36 (q, *J* = 7.1 Hz, 1H), 3.78 (s, 3H), 1.81 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.67, 157.62, 157.18, 142.63, 135.69, 133.71, 129.48, 128.08, 119.71, 113.14, 112.73, 55.22, 15.68.

HRMS (ESI-TOF) *m/z*: [M+H] calculated for $C_{14}H_{15}N_2O$ = 227.1184; found mass = 227.1188.

(*E*)-1-methoxy-3-(1-phenylhex-1-en-1-yl)benzene (**22**)



22 was synthesized following general procedure C with 1-phenyl-1-hexyne (110.76 mg, 0.70000 mmol, 1.7500 equiv) and 1-iodo-3-methoxybenzene (47.63 µL, 0.4000 mmol, 1.000 equiv) for 24 h. Purification by flash chromatography (gradient 100% hexane to 1% EtOAc: 99% hexanes) afforded a colorless oil (96.4 mg, 90%). The regioisomeric ratio of the reaction was 19:1 as determined by GC analysis of the crude reaction mixture.

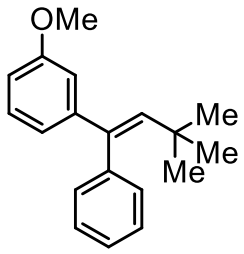
R_f (1% EtOAc: 99% hexanes) = 0.34

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (tt, *J* = 7.6, 7.1, 1.7, 1.0 Hz, 2H), 7.29 (tt, *J* = 7.6, 1.6 Hz, 1H), 7.20 – 7.14 (m, 3H), 6.81 (dt, *J* = 8.1, 1.3 Hz, 1H), 6.79 – 6.74 (m, 2H), 6.09 (t, *J* = 7.5 Hz, 1H), 3.76 (s, 3H), 2.11 (q, *J* = 7.4 Hz, 2H), 1.42 (p, *J* = 7.9, 7.6, 6.8 Hz, 2H), 1.31 (h, *J* = 7.6, 7.1 Hz, 2H), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.54, 144.60, 141.39, 140.34, 130.67, 130.05, 129.08, 128.23, 126.95, 120.03, 113.36, 112.03, 55.32, 32.28, 29.61, 22.50, 14.12.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{19}H_{22}O$ = 266.1671; found mass = 266.1671.

(*E*)-1-(3,3-dimethyl-1-phenylbut-1-en-1-yl)-3-methoxybenzene (**23**)



23 was synthesized following general procedure C with (3,3-dimethylbut-1-yn-1-yl)benzene (110.77 mg, 0.70000 mmol, 1.7500 equiv) and 1-iodo-3-methoxybenzene (47.63 µL, 0.4000 mmol, 1.000 equiv) for 24 h without pyridine. Purification by flash chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) afforded a colorless oil (83.1 mg, 78%). The regioiosmeric ratio of the reaction was 29:1 as determined by GC analysis of the crude reaction mixture.

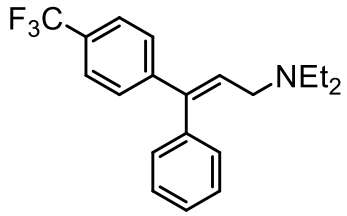
R_f (1% EtOAc: 99% hexanes) = 0.34

^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.27 (m, 3H), 7.23 – 7.13 (m, 3H), 6.80 (dt, *J* = 7.8, 1.5 Hz, 1H), 6.77 – 6.70 (m, 2H), 6.10 (s, 1H), 3.75 (s, 3H), 0.96 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.48, 145.81, 140.77, 140.39, 139.00, 130.43, 129.01, 127.88, 126.90, 119.67, 113.27, 111.66, 55.30, 34.10, 31.43.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{19}H_{22}O$ = 266.1671; found mass = 266.1671.

(*E*)-*N*,*N*-diethyl-3-phenyl-3-(4-(trifuoromethyl)phenyl)prop-2-en-1-amine (**24**)



24 was synthesized following general procedure C with *N*,*N*-diethyl-3-phenylprop-2-yn-1-amine (131.10 mg, 0.70000 mmol, 1.7500 equiv) and 1-iodo-4-(trifluoromethyl)benzene (58.78 µL, 0.4000 mmol, 1.000 equiv) for 24 h. Purification by flash chromatography (gradient 100% DCM to 3% MeOH, 3% NH_4OH, 94% DCM) afforded a yellow oil (74.2 mg, 56%). The regioisomeric ratio of the reaction was 7.4:1 as determined by GC analysis of the crude reaction mixture. The eluent for column chromatography was generated by mixing 1.0 L of DCM and 30 mL of 25% aqueous NH_4OH in a 1 L separatory funnel. After allowing the layers to separate 970 mL of the DCM layer was added to a 1.0 L graduated cylinder along with 30 mL MeOH. The resulting solution was mixed thoroughly and used immediately.

R_f (5% MeOH: 95% DCM) = 0.13

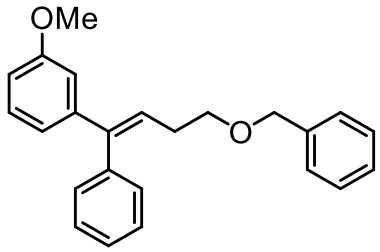
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.39 (tt, *J* = 7.0, 1.7 Hz, 2H), 7.37 – 7.33 (m, 3H), 7.14 (dt, *J* = 6.8, 2.2, 1.6 Hz, 2H), 6.35 (t, *J* = 6.7 Hz, 1H), 3.26 (d, *J* = 6.8 Hz, 2H), 2.61 (q, *J* = 7.1 Hz, 4H), 1.01 (t, *J* = 7.2 Hz, 6H).

^{19}F NMR (471 MHz, $CDCl_3$) δ -62.50.

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.49, 143.24, 138.75, 129.77, 129.34 (q, *J* = 32.4 Hz), 128.58, 128.08, 127.80, 127.62, 125.23 (q, *J* = 3.7 Hz), 124.31 (q, *J* = 272.1 Hz), 51.64, 47.10, 11.39.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{20}H_{22}NF_3$ = 333.1704; found mass = 333.1703.

(*E*)-1-(4-benzyloxy)-1-phenyl-but-1-en-1-yl)-3-methoxybenzene (**25**)



25 was synthesized following general procedure C with (4-(benzyloxy)but-1-yn-1-yl)benzene (165.42 mg, 0.70000 mmol, 1.7500 equiv) and 1-iodo-3-methoxybenzene (47.63 µL, 0.4000 mmol, 1.000 equiv) for 24 h. Purification by flash chromatography (gradient 2% EtOAc: 98% hexanes to 5% EtOAc: 95% hexanes) afforded a colorless oil (100.0 mg, 91%). The regioisomeric ratio of the reaction was 9.7:1 as determined by GC analysis of the crude reaction mixture.

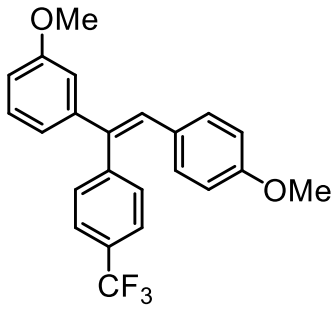
R_f (5% EtOAc: 95% hexanes) = 0.25

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 8H), 7.21 – 7.15 (m, 3H), 6.83 – 6.80 (m, 1H), 6.77 (dt, *J* = 3.3, 1.6 Hz, 2H), 6.15 (t, *J* = 7.4 Hz, 1H), 4.50 (s, 2H), 3.76 (s, 3H), 3.56 (t, *J* = 6.7 Hz, 2H), 2.44 (q, *J* = 6.9 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.55, 144.24, 143.27, 139.96, 138.61, 129.99, 129.11, 128.50, 128.33, 127.76, 127.68, 127.16, 126.18, 120.08, 113.34, 112.37, 72.96, 70.08, 55.33, 30.59.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{24}H_{24}O_2$ = 344.1776; found mass = 344.1776.

(E)-1-methoxy-3-(2-(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)vinyl)benzene (**26**)



26 was synthesized following general procedure A with 1-methoxy-4-((4-(trifluoromethyl)phenyl)ethynyl)benzene (165.76 mg, 0.60000 mmol, 1.5000 equiv) and 1-iodo-3-methoxybenzene (47.64 µL, 0.4000 mmol, 1.000 equiv). Purification by flash chromatography (gradient 100 hexanes to 1% EtOAc: 99% hexanes) affording a colorless oil (150.5 mg, 98%). The regioisomeric ratio of the reaction was 3.1:1 as determined by NMR analysis of the crude reaction mixture. The major regioisomer was determined by oxidative cleavage (See section F).

R_f (5% EtOAc: 95% hexanes) = 0.32

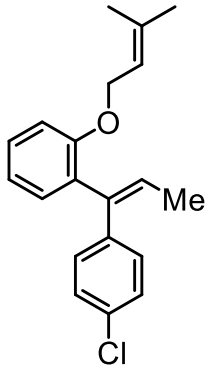
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.39 (dt, *J* = 7.7, 0.9 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 6.98 (dt, *J* = 8.5, 2.8, 1.8 Hz, 2H), 6.91 – 6.85 (m, 3H), 6.74 (dt, *J* = 8.8, 3.0, 2.2 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H).

^{19}F NMR (471 MHz, $CDCl_3$) δ -62.36.

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.73, 158.88, 144.64, 144.56, 139.24, 131.05, 131.01, 129.64 (d, *J* = 32.4 Hz), 129.43, 129.40, 129.21, 125.75 (q, *J* = 3.8 Hz), 124.38 (d, *J* = 272.3 Hz), 113.76, 113.58, 112.84, 55.38, 55.30.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{23}H_{19}O_2F_3$ = 384.1337; found mass = 384.1340.

(*E*)-1-(1-(4-chlorophenyl)prop-1-en-1-yl)-2-((3-methylbut-2-en-1-yl)oxy)benzene (**28**)



28 was synthesized following general procedure C with 1-chloro-4-(prop-1-yn-1-yl)benzene (105.42 mg, 0.70000 mmol, 1.7500 equiv) and 1-iodo-2-((3-methylbut-2-en-1-yl)oxy)benzene (115.25 mg, 0.40000 mmol, 1.0000 equiv) for 48 h. Purification by flash chromatography (gradient 100% hexanes to 1% EtOAc: 99% hexanes) afforded a colorless oil (105.9 mg, 85%, contaminated with a small amount of 3-methylbut-2-en-1-yl)oxy)benzene as a result of protodeiodination). The regioselectivity of the reaction was 23:1 as determined by GC analysis of the crude reaction mixture.

R_f (1% EtOAc: 99% hexanes) = 0.27

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 4H), 7.05 (dt, *J* = 8.5, 1.8 Hz, 2H), 6.87 (td, *J* = 7.5, 1.8 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 5.87 (q, *J* = 7.1 Hz, 1H), 4.90 (tsep, *J* = 6.6, 1.3 Hz, 1H), 4.17 (d, *J* = 6.7 Hz, 2H), 1.76 (d, *J* = 7.1 Hz, 3H), 1.62 (d, *J* = 1.3 Hz, 3H), 1.45 (d, *J* = 1.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.45, 139.60, 139.56, 137.03, 133.67, 131.87, 131.03, 130.72, 128.62, 127.77, 126.69, 120.63, 119.85, 112.90, 65.34, 25.76, 18.00, 15.42.

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