Cobalt(I)-Catalyzed [2+2] and [3+2] Cycloaddition Reactions between Alkylidenecyclopropanes and Alkynes

Undergraduate Research Thesis
Presented in Partial Fulfillment of the Requirements for graduation *with Research Distinction* in Chemistry in the undergraduate colleges of The Ohio State University

By: Haozheng Li
The Ohio State University

14 April, 2021

Project Advisor: Dr. T.V. RajanBabu, Department of Chemistry and Biochemistry

Abstract

Alkylidenecyclopropanes (ACPs) are highly-strained but thermally-stable structures that can undergo a multitude of different reactions with the assistance of transition metal catalysts, especially cycloaddition reactions toward the synthesis of carbocycles and heterocycles. However, the majority of reported reactions utilize harsh conditions such as high temperature or other high-energy compounds. ACP reactivity has seldom been explored under cationic cobalt(I)-catalyzed systems. Here, we report two novel cobalt(I)-catalyzed cycloaddition reactions between ACPs and alkynes: (i) an enantioselective [2+2] cycloaddition that yields uncommon spiro[2.3]hex-4-ene motif up to 80% yield and up to 96% ee; and (ii) a [3+2] cycloaddition that yields alkylidenecyclopent-1-ene structures between 20-60% yield. Both reactions are performed under ambient conditions.

Acknowledgements

I want to thank Professor RajanBabu for helping me discover my passion in organic chemistry. It was through his class that I gained the respect for organic synthesis and catalysis that I have today, and it was through working in his lab that crystallized my goals to research chemistry professionally. You have been tremendously kind and supportive, and I strive to follow your example in the future.

I also want to thank the graduate students and postdoctoral fellows in the RajanBabu group, Mahesh Parsutkar, James Herbort, Jon Gordon, Dipshi Singh, Sondra Lionetti, and Dr. Subhajit Bhunia, for training me and providing all the resources for this project. Thank you also for helping me fit in this lab, especially in the times when I had to depend on your advice.

Lastly, I want to thank my family for helping me instill my passion to learn since my childhood. I am truly thankful for your endless love and support.

Table of Contents

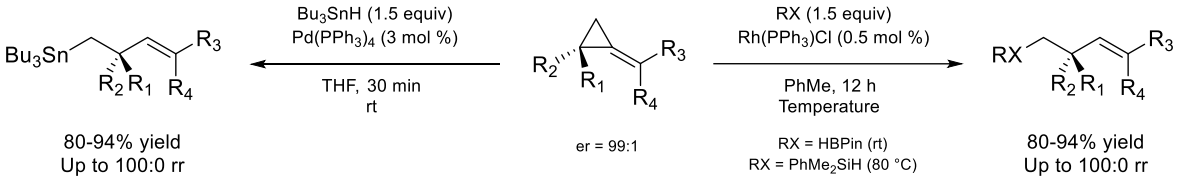
List of Tables

List of Figures

Chapter 1: Introduction and Background

Over the past several decades, methylenecyclopropane and alkylidenecyclopropane (ACP) derivatives have become valuable chemical building blocks in organic synthesis. They are highly-strained, but thermally-stable systems. With the assistance of transition-metal catalysis, many different reaction pathways have been proposed and achieved, yielding a diversity of products from the alkylidenecyclopropane motif. Figure 1 showcases some reactivities achieved by transition-metal-catalyzed reactions involving ACPs. Marek et al have developed several ring-opening reactions, including ring expansion and addition reactions such as hydrostannation, hydrosilylation, and hydroboration.[1–3] ACPs have also been extensively studied for cycloaddition reactions in the synthesis of carbocycles and heterocycles.[4,5] Shibata et al reported a Mg-catalyzed [2+2] cycloaddition reaction towards spiro[2.3]hexanes, which can be thermally decarboxylated to construct five-membered rings.[6] However, ACPs are mainly studied for [3+2] cycloaddition reactions towards five-membered rings directly. For heterocycles, a classic example of is the synthesis of furans reported by Yamamoto et al in 2001.[7] Towards the intermolecular synthesis of five-membered carbocycles, Takaya et al provided the first report in 1970 using a Ni(0) catalyst.[8] Since then, Bhargava et al have also developed their own Ni(0)-catalyzed [3+2] cycloaddition reaction in 2015.[9] However, for five-membered carbocycles, much work has been limited to intramolecular reactions, exemplified by the works of Lautens et al[10,11] and Mascareñas and López et al.[12–14]

a) Marek et al (2010): Ring-opening addition reactions



80-94% yield
Up to 100:0 rr

er = 99:1

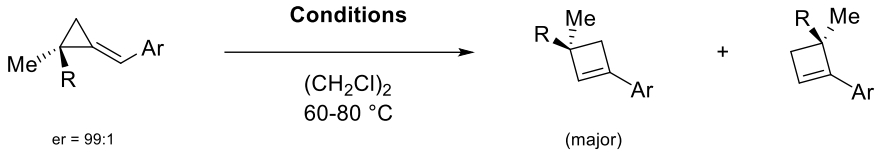
RX = HBPin (rt)
RX = $PhMe_2SiH$ (80 °C)

80-94% yield
Up to 100:0 rr

R_1 = Me, Bu
R_2 = Et, Bu, Hex, Ph
R_3 = H, Me Ph, $(CH_2)_2Ph$, 4-Br-Ph, 4-Me-Ph
R_4 = H, Me, Ph

---

b. Marek et al (2009): Ring-expansion



er = 99:1

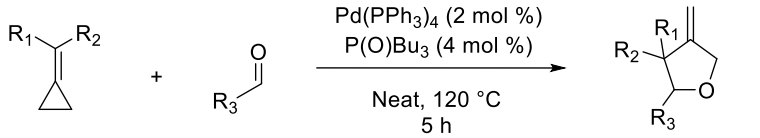
(major)

50-85% yield
Up to >99:1 rr

Condition 1: $PtCl_2$ (10 mol %)
Condition 2: $Pd(OAc)_2$ (10 mol %), CuBr (20 mol %)
R = Et, Bu
Ar = Ph, 4-Me-Ph, 4-MeO-Ph, 4-Br-Ph, 2-OBn-Ph, $(CH_2)_2Ph$

---

c) Yamamoto et al (2001): [3+2] cycloaddition towards furans



1 equiv

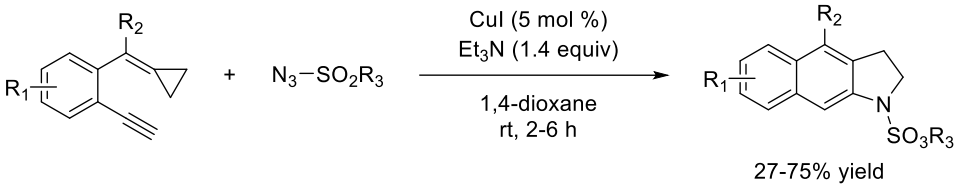
1.5 equiv

38-86% yield

R_1, R_2 = H, Me, Bu, Hex, $(CH_2)_2Ph$, $(CH_2)_5$
R_3 = 2-furyl, 3-furyl, 5-Me-2-furyl, 2-thiophenyl, 5-benzo[1,3]dioxole, 4-OMe-Ph

---

d) Wu et al(2011): Synthesis of fused indoline systems



27-75% yield

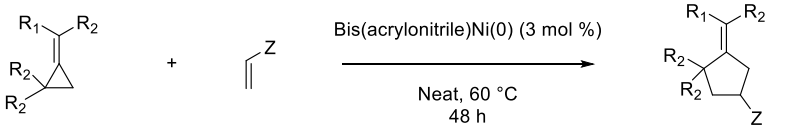
R_1 = H, 5-OMe, 4,5-$(OMe)_2$, 4-Me, 4-Cl, 5-F, 4-F
R_2 = H, Me
R_3 = Ph, 4-Me-Ph, 4-Br-Ph, 4-NO_2Ph, Me

Figure 1. Examples of transition-metal-catalyzed reactions involving ACPs.

However, a significant limitation for several of the reactions aforementioned is that harsh conditions are required. With exception to hydroboration and hydrostannation reported by Marek et al[2], the majority of reactions require prolonged exposure to high temperatures, especially to those forming new carbon-carbon bonds. This is particularly detrimental to the aforementioned intermolecular [3+2] cycloaddition reactions, which also require strongly activated alkenes as shown in Figures 2a and 2b. Wu et al,[15] shown in Figure 1d, in their Cu(I)-catalyzed synthesis towards indoline rings, were able to avoid using elevated temperatures. However, they still require highly-activated substrates, in this case sulfonyl azides. Such conditions intrinsically limit the substrate scope of many reactions. Furthermore, while robust and enantioselective *intra*molecular [3+2] cycloaddition have been achieved recently,[12,16] they leave a generalizable, *inter*molecular reaction to be desired.

In this work, intermolecular cycloaddition reactions involving simple ACPs and alkynes are explored under different cobalt(I)-catalyzed systems. Unlike its predecessors, this work studies only simple ACPs and alkynes, where the only unique condition is that such reactions are performed in an inert atmosphere. This is a precedent by the RajanBabu group, who have developed multiple enantioselective Co(I)-catalyzed reactions at room temperature, including olefin heterodimerization[17], hydroboration[18], and [2+2] cycloaddition[19]. The following reactions occur quickly at room temperature. This project began with the goal of finding an enantioselective cobalt(I)-catalyzed method to synthesize five-member carbocycles, which ultimately led to testing ACPs as a substrate. Testing the reactivity of ACPs and alkynes under a Co(I)-catalyzed system, [3+2] cycloaddition towards alkylidenecyclopent-1-enes has been achieved as well as a novel, enantioselective [2+2] cycloaddition reaction towards spiro[2.3]hex-4-enes.

a) Takaya et al (1970):

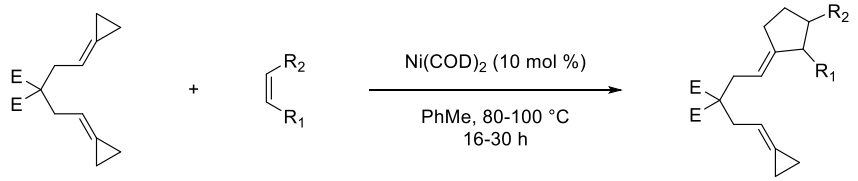


1 equiv 16 equiv 60-72% yield

R_1, R_2 = H, Me
Z = CO_2Me, COMe, CN

---

b) Bhargava et al (2015):

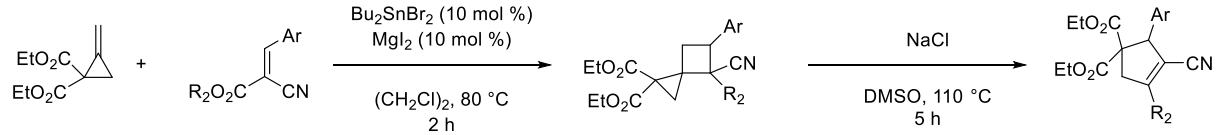


1 equiv 10 equiv 41-93% yield

E = CO_2Me, CO_2Et
R_1 = H, CO_2Me
R_2 = CO_2Me, COMe, SO_2Ph, CHO
R_1, R_2 = *N*-(4-Me-Ph)-Maleimide

---

c) Shibata et al (2019):

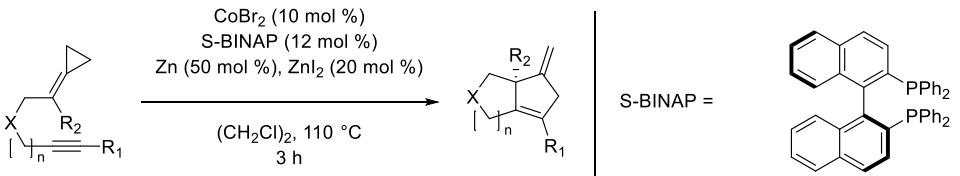


1.5 equiv 1.0 equiv 63-97% yield 63% yield

Ar = Ph, 4-R_1-Ph, 3,5-R_1-Ph, naphthyl, furyl
R_1 = OMe, Br, F, CF_3
R_2 = Me, Et, Bn

---

d) Mascareñas and López et al (2021):



54-85% yield
Up to 97:3 er

n = 1, 2
X = $C(CO_2Me)_2$, TsN, O
R = H, Me, TMS, allyl, Ph, 4-OMe-Ph, 4-CF_3-Ph, OH, OTBS, O-allyl

Figure 2. Previous cycloaddition reactions involving ACPs

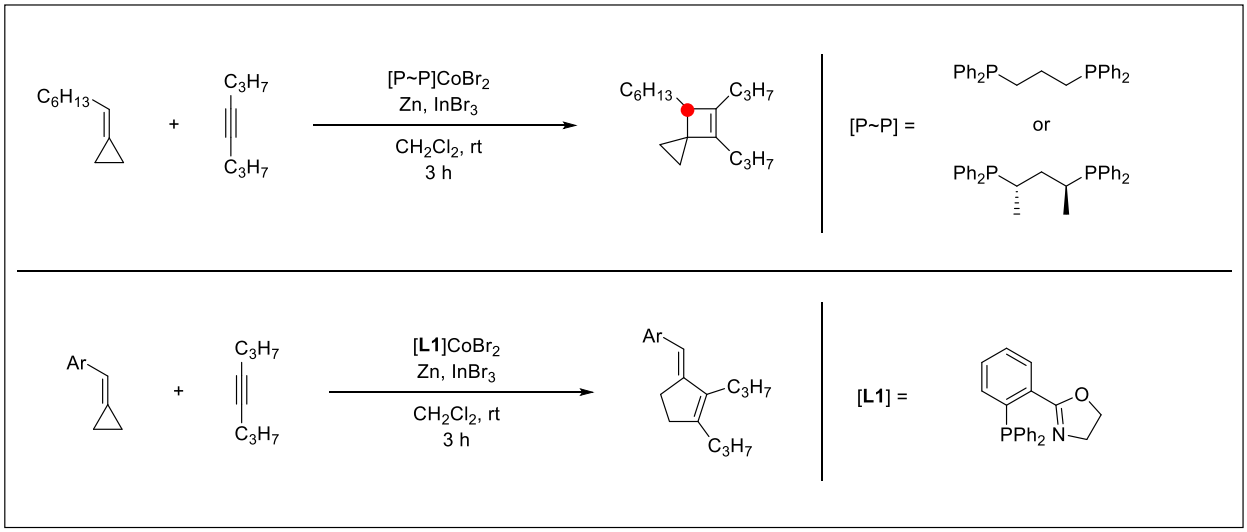


Figure 3. Reactions discovered in this work.

Chapter 2: Results and Discussions

2.1 Finding a Reactive Substrate

This project began with attempts to find a facile and stereoselective Co(I)-catalyzed [3+2] cycloaddition between alkynes and cyclopropane motifs. Several different classes of structures bearing the cyclopropane motif were tested before we found success with alkylidenecyclopropanes (ACPs). Unsuccessful substrates are summarized in Figure 4. The first substrate tested as cyclopropyl ketones. Ogoshi et al in 2011 have reported [3+2] cycloaddition between cyclopropyl ketones and alkynes in the presence of Ni(0) and Al co-catalysts.[20] Initially, we attempted to replicate some of the reactivity found by Ogoshi to see if Co(I) species can catalyze the same reaction. For this test, cyclopropyl phenyl ketone **1** was combined with 4-octyne with a 10 mol % loading of Co(I) catalyst, prepared under our standard conditions.[17] However, [3+2] cycloaddition never occurred under our Co(I)-catalyzed system. Even with different ligand systems, activated substrates like 2,2,2-trifluoroethyl acrylate instead of 4-octyne, and the use of trimethylaluminum as prescribed in the original work by Ogoshi et al, the cyclopropyl group did not open. We eventually concluded that cyclopropyl ketones are unreactive in this system. Vinylcyclopropanes were then tested, as they have been implemented to produce valuable carbocyclic structures, including five-membered rings via [3+2] cycloaddition. This includes intramolecular Rh(I)-catalyzed [3+2] cycloaddition with alkynes, as reported by Yu et al,[21] and intramolecular Co(I)-catalyzed [5+2] cycloaddition with alkynes, as reported by Yoshikai et al in 2018.[22] Vinylcyclopropane **3** was synthesized from **1** via Wittig olefination, and this was combined with 2,2,2-trifluoroacrylate for attempted [3+2] cycloaddition. Acrylate was chosen instead of 4-octyne because it was thought that the electron-deficient alkene would be more activated towards cycloaddition. Remarkably, the vinylcyclopropane did react in the presence of Co(I), but

cycloaddition did not occur. Instead, **3** underwent a ring-opening isomerization, forming diene **7**. This was a significant result, as in this system, ring-opening occurred at room temperature under mild conditions. Literature reactions reported by Yoshikai et al involving the opening of cyclopropyl species generally use high temperatures to occur.[22,23] However, the ring-opening reaction occurs very quickly even at -10 °C, and [3+2] cycloaddition was not possible. The presence of the phenyl group may have influenced the reactivity of **3**, but they were not pursued further. The main motivation for discontinuing was the possibility of **7** undergoing Diels-Alder reactions, thus making product isolation difficult even if a [3+2] or [5+2] product was achieved with **3**.

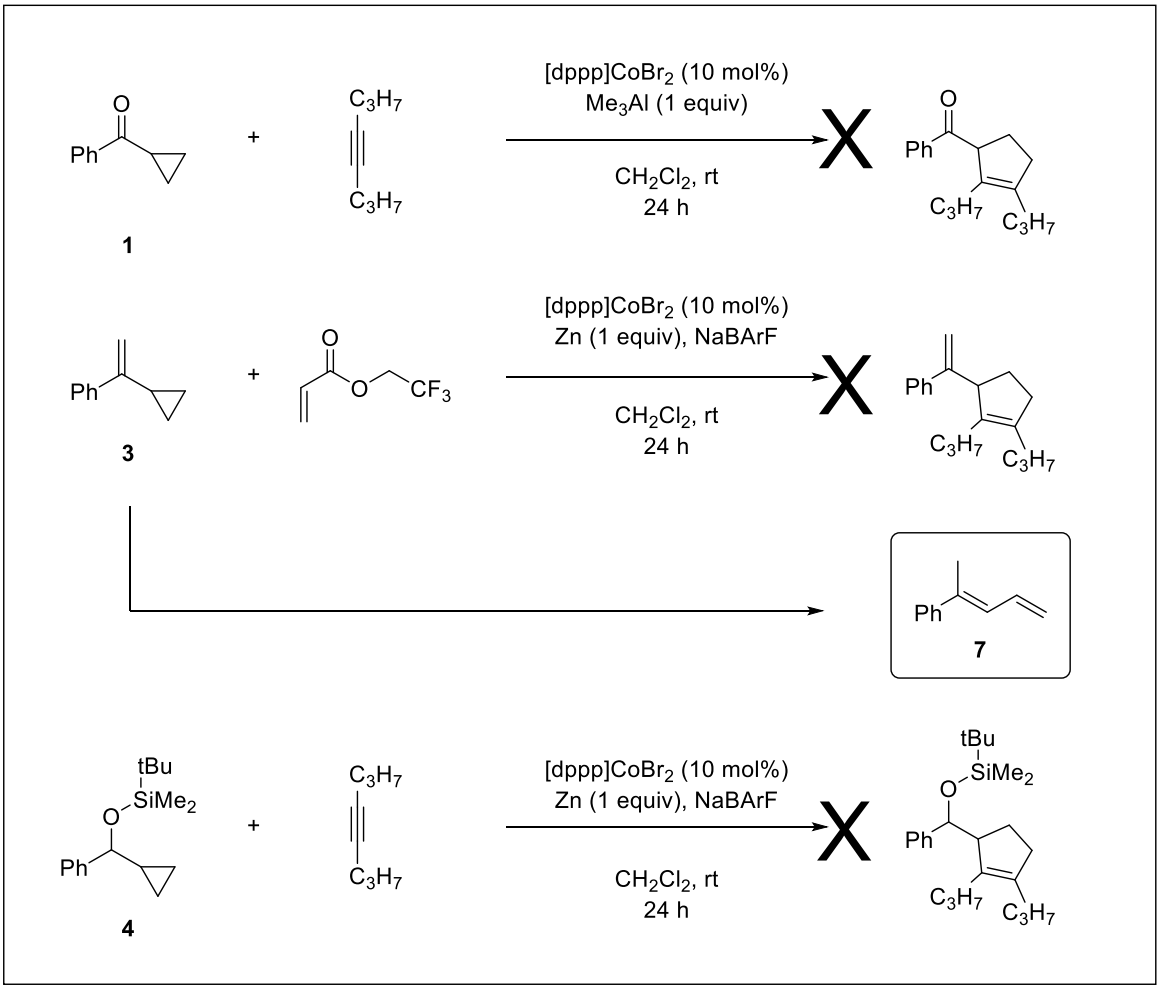


Figure 4. Unsuccessful reactions toward finding a Co(I)-catalyzed [3+2] ring-opening cycloaddition reaction.

A question that arose during previous experiments was if it was necessary for cyclopropane to be connected to a π-system, as shown in substrates **1** and **3**. To test the reactivity of a bare cyclopropyl group under our Co(I)-catalyzed conditions, we prepared cyclopropyl silyl ether **4**, prepared from reduction of **1** and protection of the alcohol with *tert*-butyldimethylsilyl chloride. While **4** was highly reactive under the Co(I)-catalyzed system, the selectivity was poor. This may be due to the weak C-O bond rupturing easily, resulting in cationic intermediates, ultimately yielding poor selectivity. This reaction was found not produce any synthetically useful addition products.

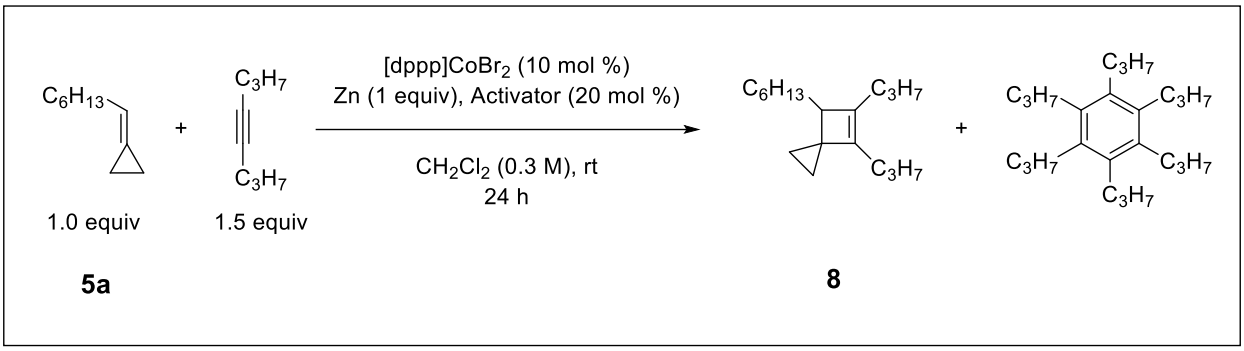
After several failed substrates, we began the pursuit of [3+2] cycloaddition to alkylidenecyclopropanes (ACPs). As highlighted in the previous chapter, ACPs have been optimized for several [3+2] cycloaddition reactions towards five-membered heterocycles and carbocycles under transition-metal catalysts. Furthermore, at the time of the beginning of this research in early 2020, there have not been any reports of Co(I)-catalyzed reactions involving ACPs. Only recently, in 2021, have ACPs been explored under Co(I) catalysts, and they are limited to intramolecular applications.[12,16] When testing ACP **5a** under standard Co(I)-catalyzed conditions, [2+2] cycloaddition was observed, giving spiro[2.3]hex-4-ene **8**, an uncommon structure that has significant biological implications.[24,25] When expanding the substrate scope for the [2+2] cycloaddition reaction, a new reaction, a [3+2] cycloaddition was observed with aromatic ACP **6a**. These two new reactions were studied further as detailed in the following sections.

2.2 Optimization of [2+2] Cycloaddition

Following the discovery of [2+2] cycloaddition, we proceeded to optimization the reaction. The first optimization was with the Co(I) activator. Table 1 summarizes this optimization, and every activator tested can be found in Chapter 3.5, Table S2. All reactions were performed with

ACP **5a** and 4-octyne as a substrate, and the values reported are based on conversion of **5a** as observed by gas chromatography (GC). Interestingly, sodium *tetrakis*(3,5-*bis*(trifluoromethyl)phenyl)borate (NaBArF), which has been used extensively by RajanBabu et al in many optimized reactions, used in Entry 1 is not the optimal activator in this reaction. Instead, the optimal conversion was with $InBr_3$, which converts **5a** quantitatively, 94% of which forms as **8**. On the other hand, $ZnBr_2$ also provided subpar conversion in Entry 2. A significant side product on Entry 2 is hexapropylbenzene, which was produced from the [2+2+2] trimerization of 4-octyne. What we observe here is that for this [2+2] cycloaddition pathway, an optimal extent of catalyst activation is required. $ZnBr_2$, the weakest activator here, do not activate the Co(II) or Co(I) precatalyst to an appropriate extent for the [2+2] pathway to compete with the cyclotrimerization pathway, especially when 1.5 equivalents of alkyne is present. However, the strongest activator here, NaBArF, may be excessively activating the Co(I) catalyst, to the extent that it is decomposing **8**. This is plausible, since it **8** is already at a highly-strained system. $InBr_3$ and $Ag[SbF_6]$ activators are stronger than $ZnBr_2$, but weaker than NaBArF, providing an optimal extent in activating the Co(II) precatalyst.

Table 1. Optimization of catalyst activator for [2+2] cycloaddition between ACP **5a** and 4-octyne.

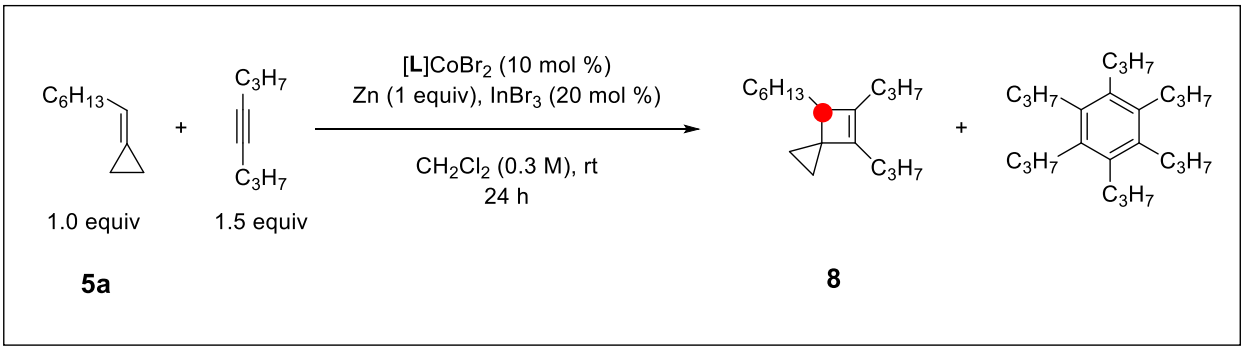


Entry	Activator	GC Conversion %	8
1	NaBArF	15	3
2	$ZnBr_2$	43	43
3	$InBr_3$	100	94
4	$Ag[SbF_6]$	94	94

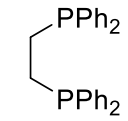
At this point, having founded optimal conversion, we proceeded to screen ligand effects. Table 2 shows GC conversion of **5a** and **2** under select ligand systems, using $InBr_3$ to activate the Co(I) catalyst. The complete data is in Chapter 3.5, Table S3. On some entries, the conversion percent is not necessarily the same as the percentage converted to **8**. The remaining material is lost due to side reactions, and the products from these reactions are difficult to identify. Remarkably, *bis*-phosphine ligands provided the best results for this reaction, with bis-diphenylphosphiopropane [dppp] providing the most complete racemic conversion, and with (*S,S*)-BDPP providing excellent enantioselectivity of 96% ee according to chiral stationary-phase gas chromatography. This finding also differentiates this work from the [2+2] cycloaddition reported by Shibata et al, as the former do not report enantioselectivity. Phosphinooxazoline ligands **L1** to **L6** (see Figure 3 for the structures of ligands used in this study) were comparatively less effective for this reaction. These results deviate significantly from reports from RajanBabu et al on Co(I)-

catalyzed [2+2] cycloadditions in 2019,[19] where chiral phosphinooxazoline ligands, specifically **L6**, provided excellent yield and enantioselectivity. For this reaction, **L6** failed to convert **5a** into any product. The main difference in the reaction reported here is that the ACP **5a** is a trisubstituted alkene, which is made electron-rich from its alkyl substituents. In this reaction, it is also interesting that neither **5a** nor the alkyne are electron-deficient. functional groups.

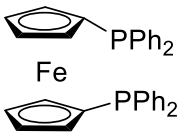
Table 2. Ligand screening for Co(I)-catalyzed [2+2] cycloaddition between ACP and 4-octyne. Red circle indicates chiral center.



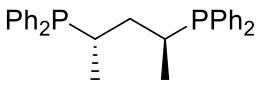
Entry	[L]	GC Conversion	8	ee%
1	dppp	100	94	--
2	dppf	71	20	--
3	(*R*)-BINAP	47	42	50
4	(*S*,*S*)-BDPP	100	52	96
5	(-)-DIOP	90	32	72
6	Josiphos-II	73	73	78
7	(*S*,*S*)-PhBPE	0	--	--
8	^{iPr}DuPhos	0	--	--
9	**L1**	45	38	--
10	(*rac*)-**L2**	80	33	--
11	**L3**	82	48	74



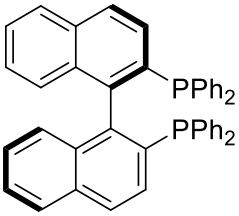
n = 1 dppe
n = 2 dppp



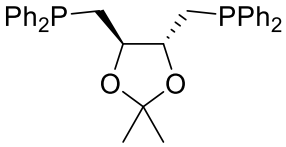
dppf



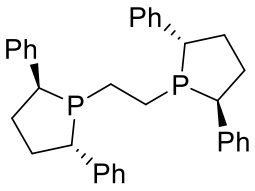
(*S,S*)-BDPP



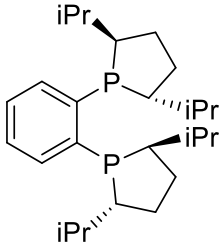
(*R*)-BINAP



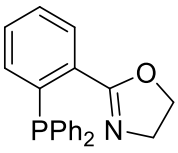
(-)-DIOP



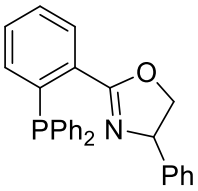
(*S,S*)-^{Ph}BPE



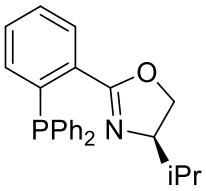
^{iPr}DuPhos



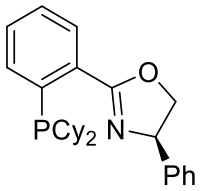
L1



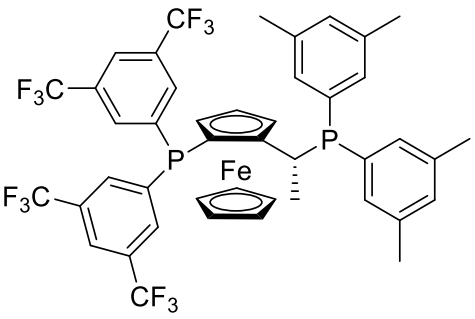
L2



L3



L6

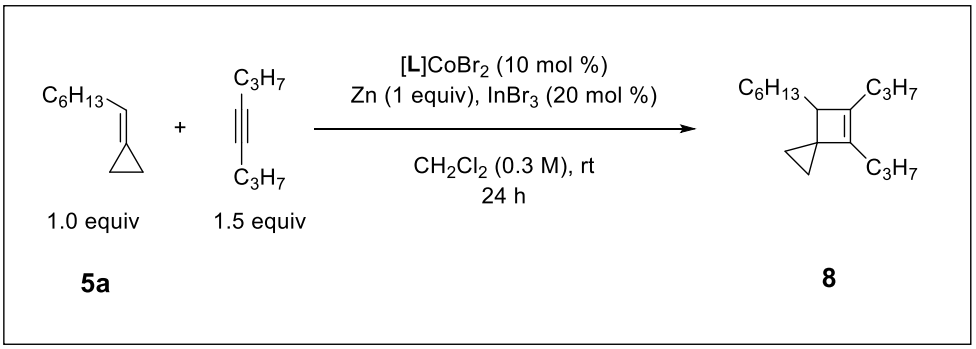


Josiphos II

Figure 5. Select ligands tested for Co(I)-catalyzed [2+2] and [3+2] cycloaddition reactions for ACP systems. See Chapter 3.4.7 for all ligands tested.

Finally, with optimal ligand systems and activator, we proceeded to modify the reaction conditions to optimize yield. As [dppp] provided the best conversion, the racemic yield was optimized for this reaction. Table 3 shows the results for optimization. Modifications to the condition are limited to changing the reaction time, catalyst loading, and concentration. The most significant finding in these experiments is that as the reaction time decreases, the recovered yield increases. Decreasing the time of reaction from 24 h to 3 h, the yield drastically increases from 44% to 76%. This is also indicating that the product **8** is decomposing in the presence of the Co(I) catalyst, initially postulated when NaBArF was tested as a catalyst activator. Furthermore, compared to previous reports, the [2+2] cycloaddition reaction proceeds very quickly, converting **5a** to **8** in only 3 h without requiring elevated temperatures. The dilution of 0.15 M with respect to **5a** was also tested, but this did not impact the yield significantly. Entry 6, where a 5 mol % of Co(I) catalyst is used, is also interesting, as though it shows nearly quantitative conversion on GC, its yield is only 63% compared to 76% achieved with a 10 mol % precatalyst loading. It is unknown what is happening to **8** under a 5 mol % catalyst loading.

Table 3. General reaction optimization for Co(I)-catalyzed [2+2] cycloaddition reaction between ACP 5a and 4-octyne.



Entry	Time	Change from Conditions Above	GC Conversion 8	Yield %
1	24	None	94	44
2	5	None	100	70
3	5	0.15 M reaction	91	65
4	3	None	91	76
5	3	5 mol% catalyst loading	91	63
6	3	0.15 M reaction	96	80
7	5	5 mol% TMS-Pyrazine instead of Zn	--	71
8	3	(*S*,*S*)-BDPP instead of dppp	85	48

When attempting to expand the substrate scope for [2+2] cycloaddition, we tested ACP **5b** under the same conditions shown on Table 2, using [dppp] and **L1** ligand systems. However, we were not able to isolate the [2+2] product. [**L1**]Co(I) was inert to **5b**, producing only the trimer of 4-octyne, while [dppp]Co(I) converted only 26% of **5b** after 24 h. This conversion resulted in multiple products that could not be separated.

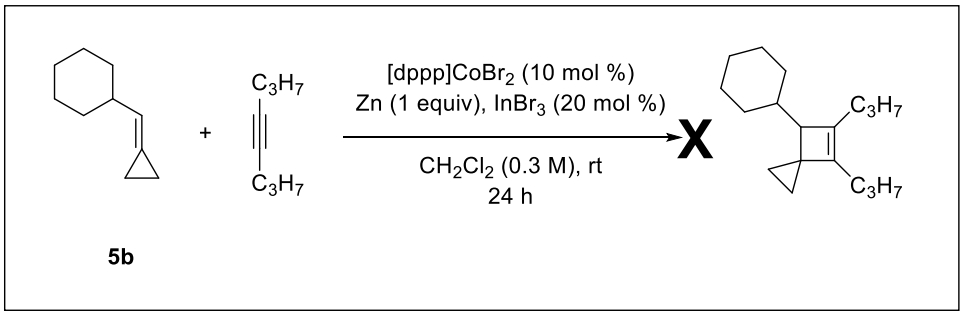
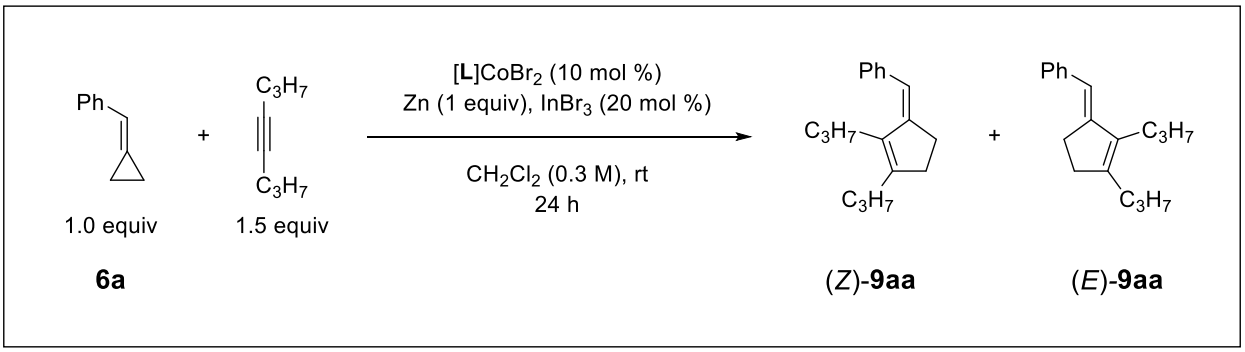


Figure 6. Unsuccessful [2+2] reaction between **5b** and **2**.

2.3 Optimization of [3+2] Cycloaddition

Initially, ACP **6a** was tested to expand the substrate scope for the [2+2] pathway, but we observed the [3+2] product **9aa** instead. The optimization for this new reaction began with finding an optimal ligand Since this is a new mechanism, we wanted to see if **6a** can undergo [2+2] cycloaddition by manipulating the ligand system. Table 4 shows the reactivity of **6a** and 4-octyne under several ligand systems. The complete table is in Chapter 3, Table S5. Unlike the [2+2] pathway, *bis*-phosphine ligands (Entries 1-4) were poor for this reaction, with [dppp] being the only *bis*-phosphine ligand that favored the conversion of **6a**. Meanwhile, phosphinooxazoline ligands worked well for this reaction. The ligand **L1** was particularly effective, providing quantitative conversion. This minimally substituted PHOX ligand **L1** specifically converted the substrates to the (*E*)-isomer, assigned with the assistance of 1D selective nOe NMR spectroscopy. Specifically, product **9ba** (see Figure 6) was characterized with selective nOe NMR. Entry 7, using the **L3** ligand system, another product was observed, selecting **9aa** as a minor product. This product is hypothesized to be the (*Z*)-isomer of **9aa**, based on later studies with product **9ba** and its (*Z*)-isomer, which was isolated. During this entire ligand screening, the [2+2] product was not observed once, even with [dppp] and (*S,S*)-BDPP ligands.

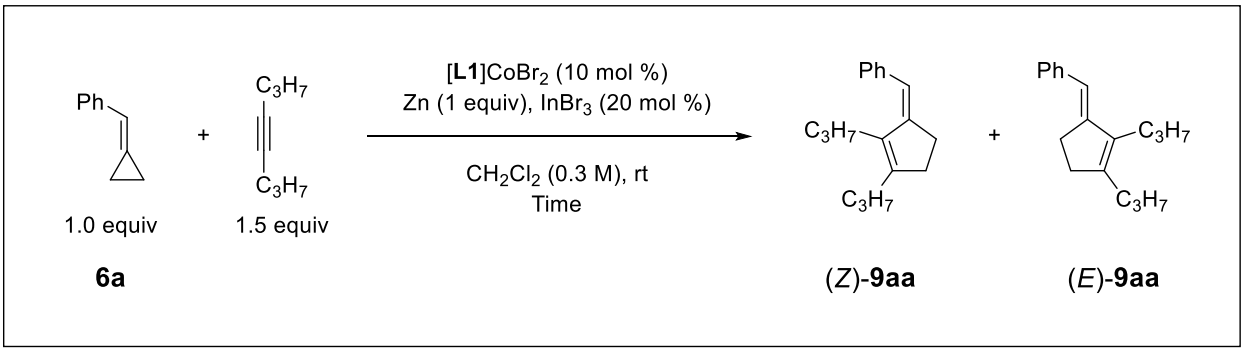
Table 4. Ligand screening for [3+2] cycloaddition between ACP 6a and 4-octyne.



Entry	[L]	GC Conversion	(*Z*)-9aa	(*E*)-9aa
1	dppp	79	0	62
2	dppf	0	--	--
3	(*S*,*S*)-BDPP	11	0	5
4	(*R*)-BINAP	8	0	4
5	L1	100	0	97
6	L2	6	0	6
7	L3	100	51	31

Having found an optimal ligand system for this procedure, we proceeded to optimize the yield by modifying the reaction conditions. Table 5 shows some changes to the reaction conditions. Entry 1 and its recovered yield is representative of the yield for this reaction. Overall, this reaction is not efficient. However, the most interesting result from Table 4 was entry 5, when a 5 mol% catalyst loading was used. Because of the low recovered yield from Entry 1, we reduced the loading of $InBr_3$ to 7.5 mol % in consideration that the Lewis acidity of $InBr_3$ may possibly be decomposing **9aa**. Regardless, Entry 5 was significant in how (*Z*)-isomer of **9aa** was the major product. This was never observed previously with the 10 mol % loading of [**L1**]Co(I).

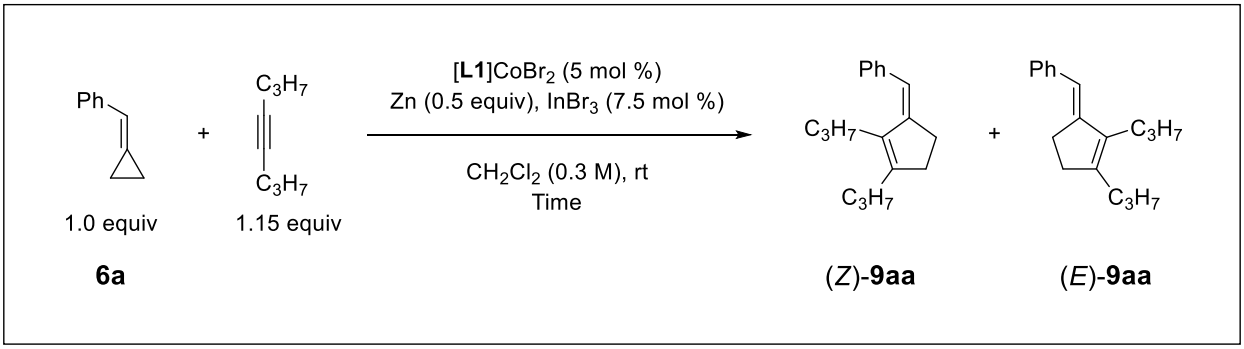
Table 5. General Reaction Optimization for [3+2] cycloaddition reaction between ACP 6a and 4-octyne. For GC conversion, only the (E)-isomer is considered.



Entry	Time (h)	Change to Conditions Above	GC Conversion	(*E*)-9aa %	Recovered Yield %
1	3	None	100	96	23%
2	1.5	None	99	51	n.d.
3	1	NaBArF instead of $InBr_3$	100	100	n.d.
4	1	$Ag[SbF_6]$ instead of $InBr_3$	91	83	n.d.
5	3	5 mol % catalyst 7.5 mol % $InBr_3$	93	15	n.d.

Not knowing how (*Z*)-**9aa** was being produced, we repeated Entry 5 on Table 5 and closely tracked the progress of the reaction on GC. The solvent was spiked with 0.5 equivalents of dodecane as an internal standard, as it was inert to the chemistry performed here. Therefore, the concentration of dodecane in this reaction is be constant, and the concentration of (*Z*)-**9aa** and (*E*)-**9aa** can be tracked by directly comparing their respective percent areas to the percent area of dodecane. The absolute concentration of each compound was not directly measured. This reaction was performed at 0.1 M with respect to the limiting reagent **6a** in an attempt to slow down the reaction and track it more precisely. Figure 5 shows the progress of the reaction, which was quenched after 150 minutes. While the percent area of dodecane increased slightly (likely due to decomposition), the concentration of **9aa** increased while the concentration of (*Z*)-**9aa** decreased as the reaction progressed. Figure 2 also shows that percent area plots for both species have similar

slopes, implying that the rate of the loss of (*Z*)-**9aa** is similar to the rate of production of **9aa**. From this, we conclude that (*Z*)-**9aa** is an intermediate product after [3+2] cycloaddition, which is then converted into the thermodynamically-stable (*E*)-isomer. This was not detectable with a 10 mol % catalyst loading because there was enough of the catalyst to fully isomerize (*Z*)-**9aa**. However, using a 5 mol % catalyst loading, the catalyst was deactivated before the all of (*Z*)-**9aa** was isomerized.



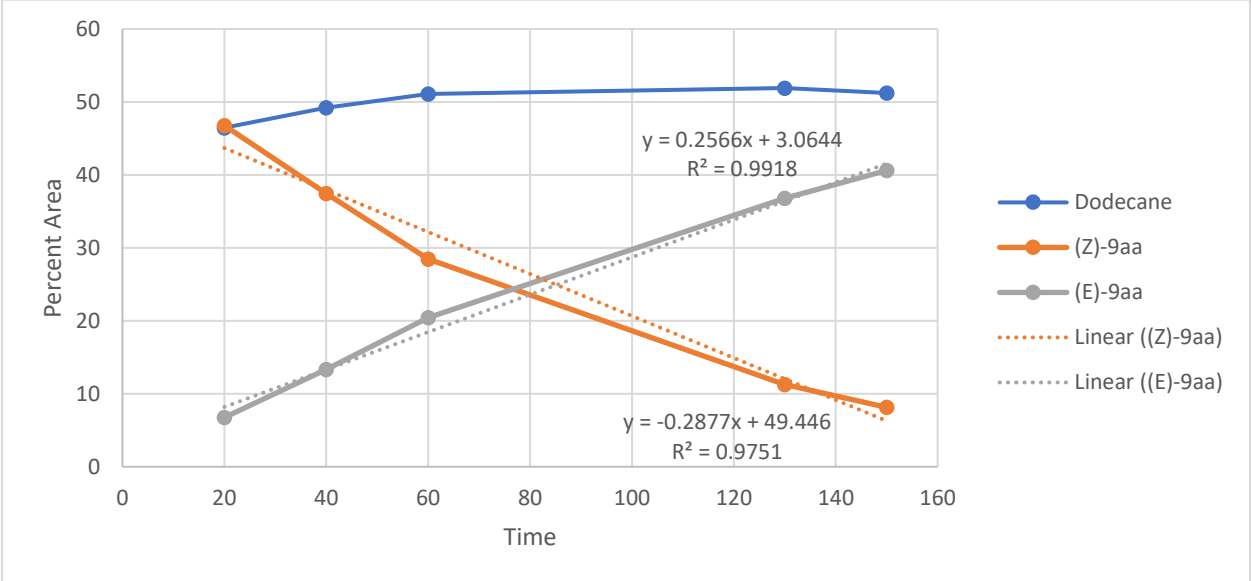


Figure 7. Isomerization progress of 9aa in Co(I)-catalyzed [3+2] reaction. See Chapter 3.5 Table S7 for raw data.

At the same time, we proceeded to examine the substrate scope for [3+2] cycloaddition. All reactions were performed using the standard conditions proposed on Table 4. Each product is

shown in Figure 6. With the exception to **9aa**, yields ranged from 40% to 60%, and the (*E*)-isomer is produced almost exclusively. The regioselectivity of products **9ab**, **9bc**, and **9bd**, where unsymmetrical alkynes were used were all likely dictated by the steric effect, where it is less favorable for the bulkier group to be adjacent to the aromatic ring. The (*Z*)-isomer of **9ba** was recovered in about 75% purity by mass after toluene was used as the solvent instead of CH_2Cl_2. Depicted in Figure 8 is an unsuccessful reaction between ACP **6d** did not undergo any reaction. What is also not shown are reactions using terminal alkynes, specifically phenylacetylene. Such products provided unselective conversion of the starting material.

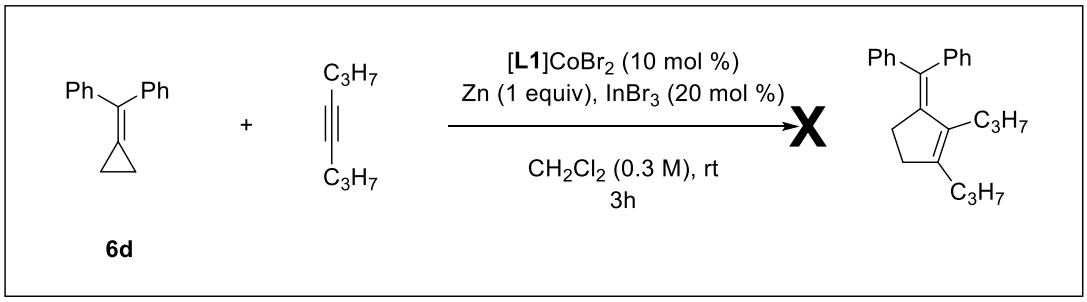


Figure 8. Unsuccessful reaction between ACP 6d and 4-octyne.

However, **9be** was a significant exception to what was normally observed. This is compared to product (*Z*)-**9ba** in Figure 9. For most substrates, the alkyne is added to the proximal position adjacent to the alkene (9a). However, diphenylacetylene is added further away from the alkene (9b). This product was not observed for any other ACP or alkyne substrates. However, another product was observed in this reaction, hypothesized as **9be'**. We hypothesize that this minor product is the result of an isomerization as shown in Figure 9c. This product would be thermodynamically favorable. However, it is only clear that there are two separate isomers isolated upon purification of **9be**. Additional research is needed to confirm the structure of **9be'**, as well as why diphenylacetylene afforded a different type of [3+2] cycloaddition.

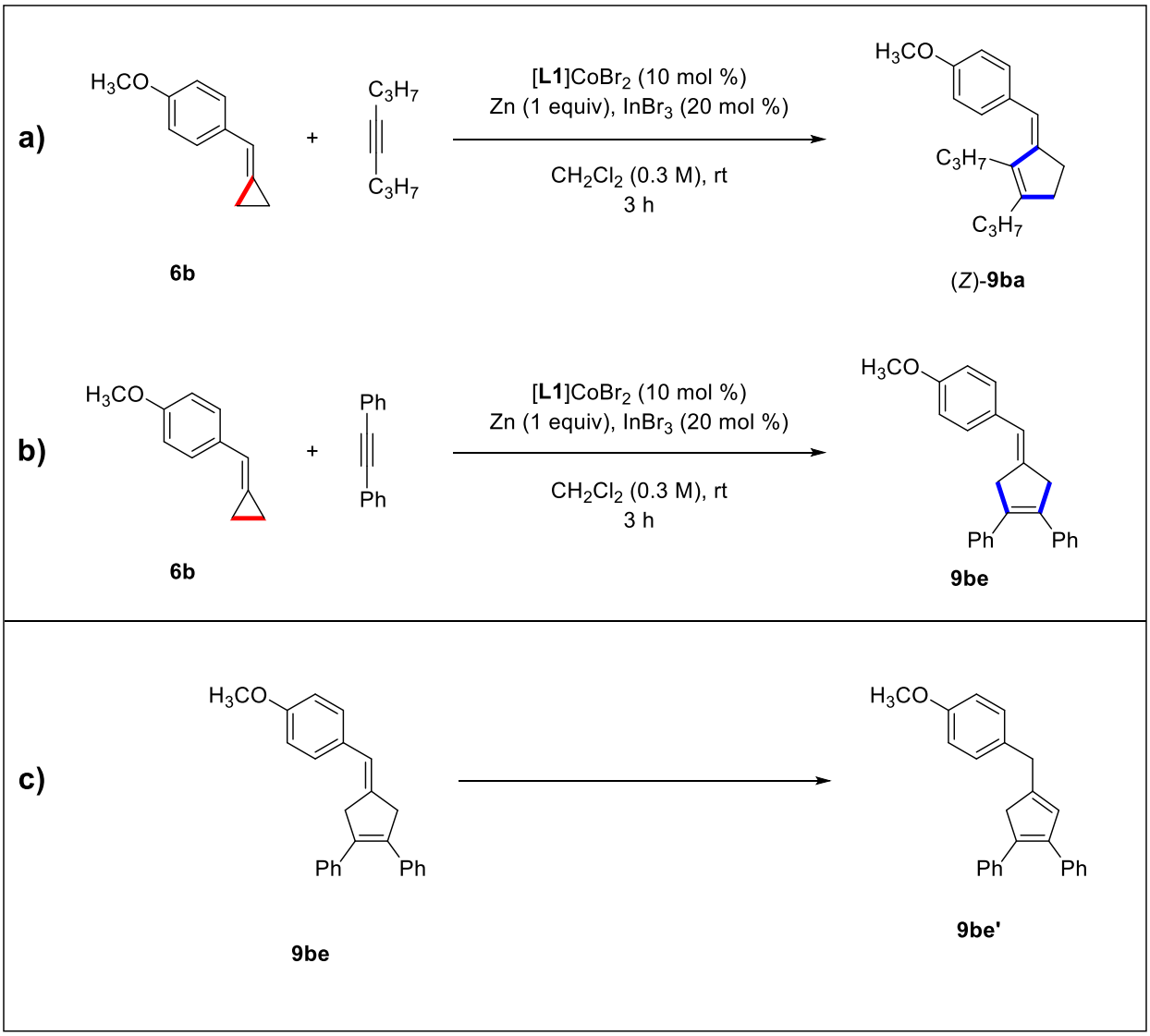
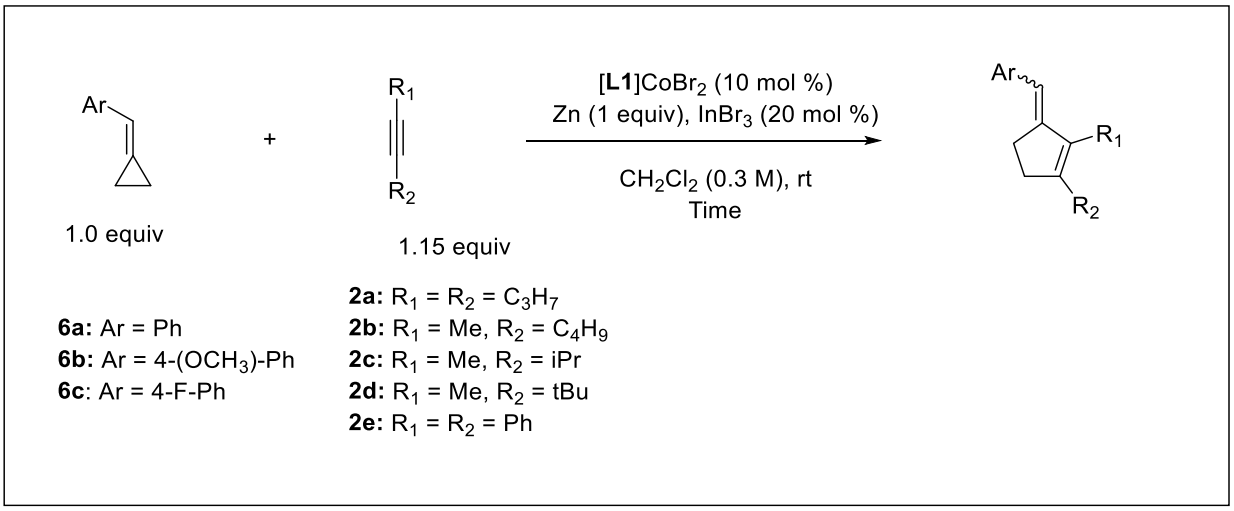
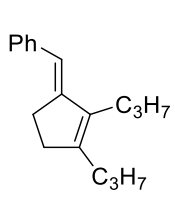
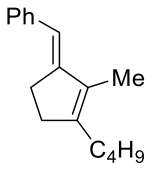
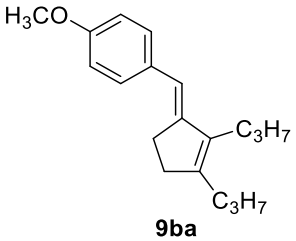


Figure 9. (a) Proximal addition of 4-octyne to form (Z)-**9ba**. (b) Distal addition of 4-octyne to form **9be**. (c) Proposed isomerization of **9be**. Red bonds are broken, blue bonds are formed.

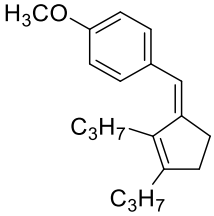


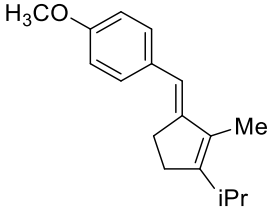


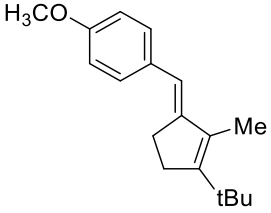




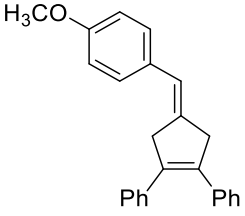
Compound: **9aa** **9ab** **9ba**
Yield: 23% 44% 52%
rr: -- 66:34 --

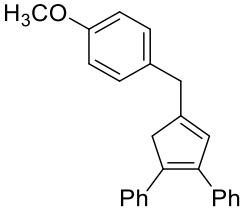


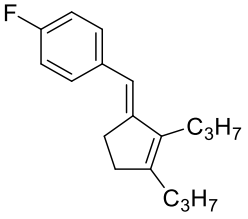




(*Z*)-**9ba** **9bc** **9bd**
39% 59% 44%
-- 81:19 --





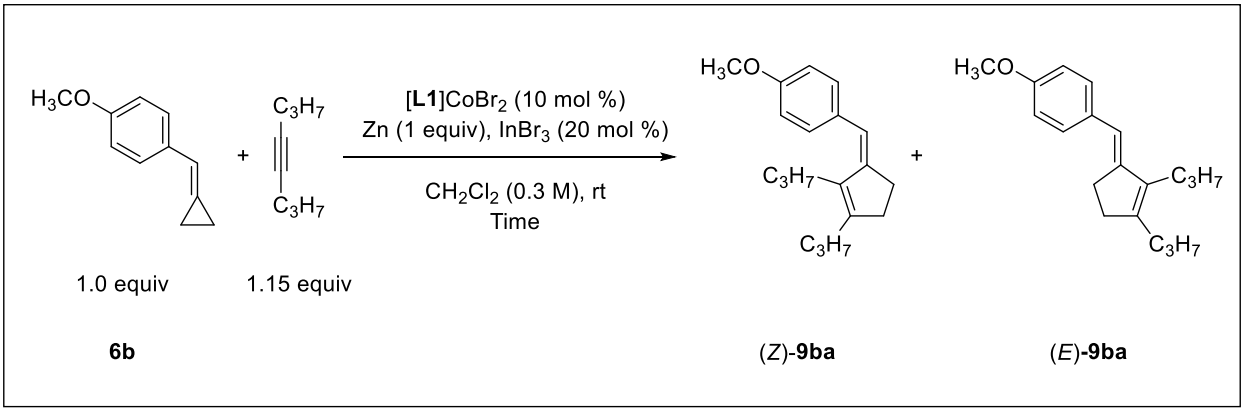


9be **9be'** **9ca**
41% 50%
-- --

Figure 10. Substrate scope of intermolecular [L1]Co(I)-catalyzed [3+2] cycloaddition reaction.

For further mechanistic studies on [3+2] cycloaddition, **6b** was used as the ACP substrate. Substrate screening has also shown that the electronic properties of the aromatic group have little effect on the yield of the reaction. Based on our previous hypothesis that the Co(I) catalyst first produces the (*Z*)-isomer, then isomerize it to the final (*E*)-isomer, we then tried to isolate the intermediate (*Z*)-isomer. This was done by using different solvents to inhibit the catalyst, and the solvent screening is summarized in Table 5. The complete table is in Chapter 3, Table S8. On Entry 1, using toluene and maintaining all other optimized conditions for [**L1**]Co(I)-catalysis, we isolated and identified (*Z*)- **9ba** as a major product for the first time in 39% yield. What is likely occurring is that $InBr_3$, being an ionic compound, does not activate the Co(II) precatalyst as effectively as it does in CH_2Cl_2. Using NaBArF in Entry 2, which should be more soluble in toluene than $InBr_3$, we observed quantitiative conversion of **6b**, 77% of of which is converted to (*E*)-**9ba** as previously observed when using CH_2Cl_2 solvent. We also attempted to directly inhibit the catalyst from isomerizing (*Z*)-**9ba** To test this, we conducted the reaction in a 1:1 CH_2Cl_2:ethyl acetate (EtOAc) (v/v) solution. EtOAc has lone electron pairs that can coordinate to the Co(I) catalyst, so it should inhibit isomerization. This was indeed observed, as shown in Entries 3 and 4. However, while this is inhibiting the isomerization of (*Z*)-**9ba**, it is also limiting the conversion of **6b**, thus reducing the yield of the reaction.

Table 6. Conversion of **6b** to **9ba** in different solvents. *NaBArF was used as an activator in Entry 2.



Entry	Solvent	Time (h)	GC Conversion	(*Z*)-9ba %	(*E*)-9ba %
1	PhMe	3	91	77	5
2*	PhMe	3	100	6	77
3	CH_2Cl_2:EtOAc (50:50 v/v)	2	52	48	4
4	CH_2Cl_2:EtOAc (50:50 v/v)	26	75	69	6

Since our solvent screening provided an enriched sample of (*Z*)-**9ba**, we proceeded to confirm that Co(I) is indeed isomerizing (*Z*)-**9ba** into the (*E*)-isomer. After stirring for 1.5 h and purifying, only (*E*)-**9ba** is recovered in 71% yield with respect to the initial mass of (*Z*)-**9ba**. Part of the loss in yield is from the decomposition of starting material **6b**, which composed 11% by weight of (*Z*)-**9ba** sample based on its ^{1}H NMR spectrum. Nonetheless, this experiment does confirm that Co(I), in addition to catalyzing [3+2] cycloaddition for aromatic ACPs, also catalyzes the isomerization of the [3+2] products into the more stable (*E*)-isomer.

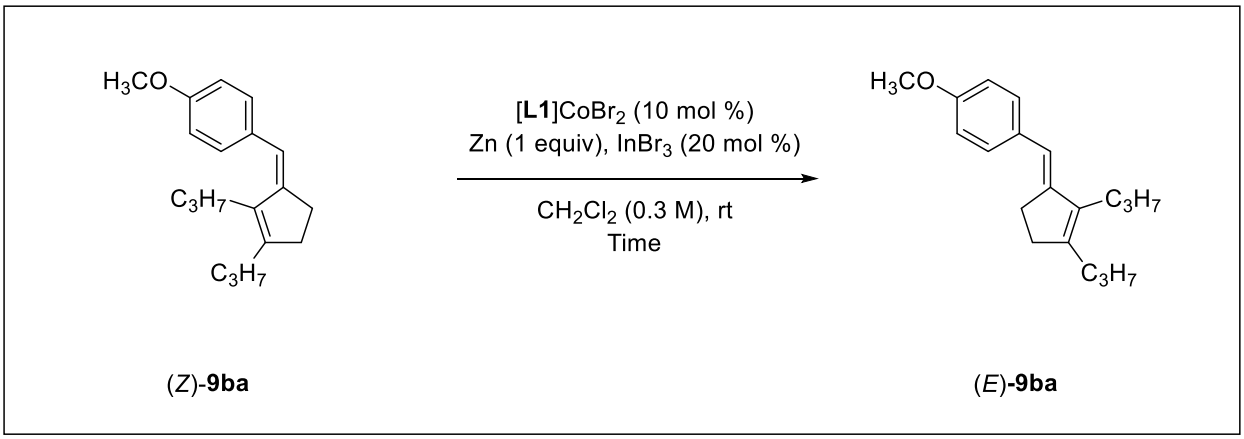


Figure 12. Co(I)-catalyzed isomerization of (*Z*)-**9ba**.

A proposed mechanism for both [2+2] and [3+2] cycloaddition is proposed in Figure 7. Not depicted is the reduction and activation of the Co(I) catalyst. The [2+2] pathway is likely occurring as proposed by RajanBabu et al.[19] When both ACP and alkyne are coordinating to the Co(I) catalyst (depicted as **a**), oxidative cyclization occurs to produce the metallocycle **b**. This intermediate produces the [2+2] product **c** upon reductive elimination of the Co(I) catalyst. The proposed mechanism is based on the proposals made by Bhargava et al.[9] The Co(I) catalyst first undergoes oxidative insertion between the $C(sp^2)$-$C(sp^3)$ bond in the ACP, producing metallocycle **d**. Then, alkyne is added, forming the larger metallocycle **e** before forming the intermediate (*Z*)-isomer **f** upon reductive elimination of Co(I). Co(I) continues to interact with the exocyclic double bond, producing the intermediate **g**. The structure of intermediate **g** is unconfirmed, but the addition of Co(I) somehow makes the exocyclic bond rotatable, allowing it to convert to the thermodynamically-favorable (*E*)-isomer **h**. An important feature of **d** is that the aromatic R_1 acts like an intramolecular tether to the Co(III) nucleus. This is hypothesized to help stabilize the metallocycle and make the [3+2] mechanism, at first, select for the thermodynamically-unfavorable product **f**. The steric bulk of the ACP plays some role in whether it undergoes the [2+2] or [3+2] pathway. Substrate **5a** readily undergoes [2+2] cycloaddition, while steric bulk in

substrates **5b** and **6a** (and all other aromatic substrates) blocks this pathway. However, **6a** is able to form some intramolecular tether, making [3+2] cycloaddition possible, unlike **5b**. Additional research is needed to confirm the validity of this hypothesis.

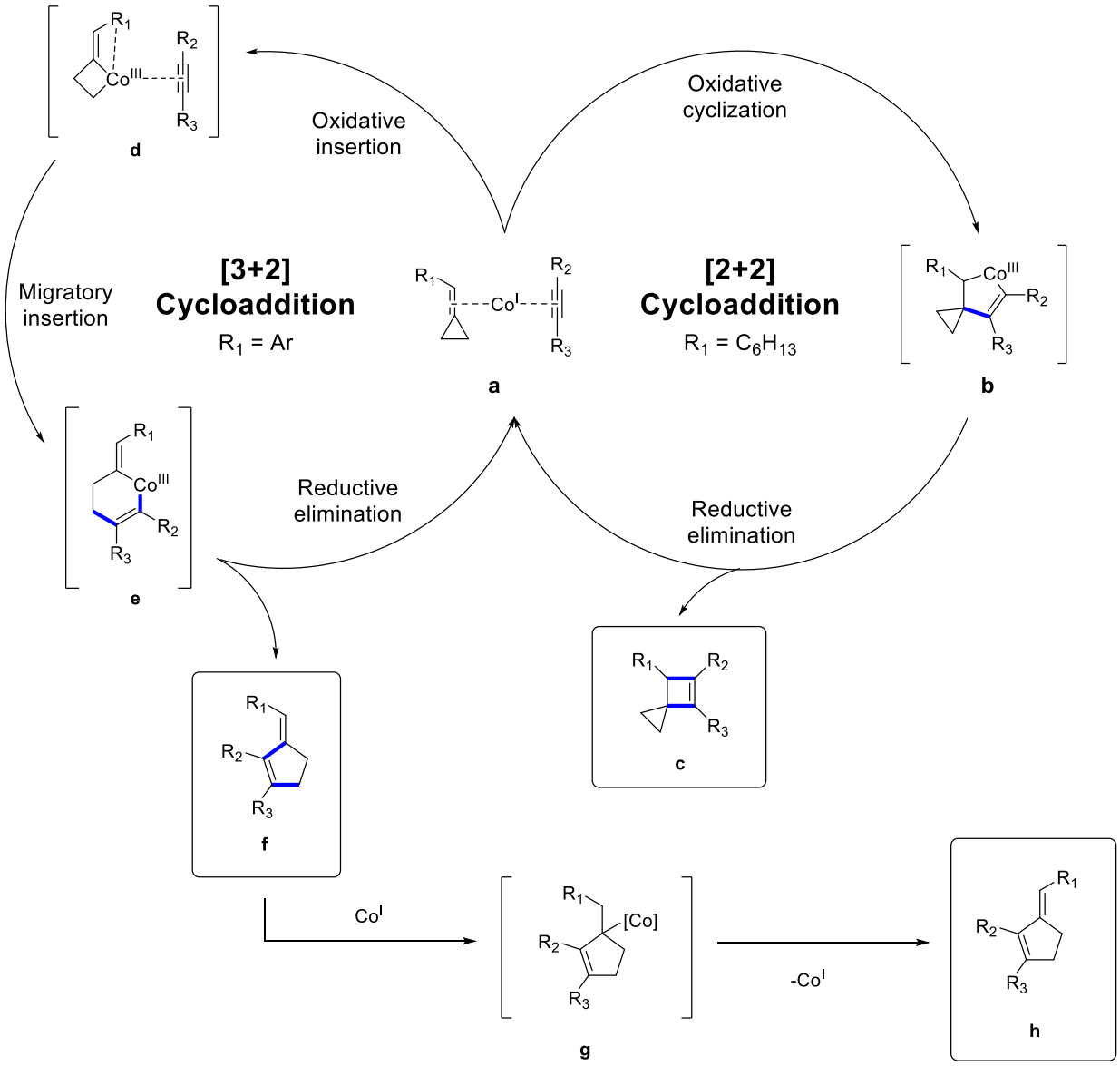


Figure 13: Proposed mechanisms for Co(I)-catalyzed [2+2] and [3+2] cycloaddition reactions and isomerization.

2.4: Conclusion

Alkylidenecyclopropanes are versatile chemical building blocks in transition-metal-catalyzed cycloaddition chemistry. We report two cobalt(I)-catalyzed cycloaddition pathways to synthesize carbocycles from ACPs and alkynes: a [2+2] pathway to synthesize chiral spiro[2.3]hex-4-enes with potentially excellent enantioselectivity and a [3+2] pathway to synthesize five-membered carbocycles. Both reactions are complete in less than 3 hours at mild conditions. Additional research is needed to determine the potential scope of these reactions and to elucidate the mechanisms of these reactions. The facile syntheses of five-member carbocycles and chiral spiro[2.3]hex-4-enes, when controlled and optimized, could be used for synthesis of potentially new scaffoldings for bioactivity screening.

2.5: References.

1. Masarwa, A.; Marek, I. Selectivity in Metal-Catalyzed Carbon□Carbon Bond Cleavage of Alkylidenecyclopropanes. *Chem. - Eur. J.* **2010**, *16* (32), 9712–9721.

2. Simaan, S.; F. G. Goldberg, A.; Rosset, S.; Marek, I. Metal-Catalyzed Ring-Opening of Alkylidenecyclopropanes: New Access to Building Blocks with an Acyclic Quaternary Stereogenic Center. *Chem. - Eur. J.* **2010**, *16* (3), 774–778.

3. Masarwa, A.; Fürstner, A.; Marek, I. Metal-Catalyzed Rearrangement of Enantiomerically Pure Alkylidenecyclopropane Derivatives as a New Access to Cyclobutenes Possessing Quaternary Stereocenters. *Chem. Commun.* **2009**, No. 38, 5760-5762.

4. Yu, L.; Liu, M.; Chen, F.; Xu, Q. Heterocycles from Methylenecyclopropanes. *Org. Biomol. Chem.* **2015**, *13* (31), 8379–8392.

5. Cao, H.; Chen, F.; Su, C.; Yu, L. Construction of Carbocycles from Methylenecyclopropanes. *Adv. Synth. Catal.* **2020**, *362* (3), 438–461.

6. Suzuki, I.; Shimazu, J.-Y.; Tsunoi, S.; Shibata, I. Diastereoselective Synthesis of Spiro[2.3]Hexanes from Methylenecyclopropane and Cyanoalkenes Catalyzed by a Tin-Ate Complex. *Eur. J. Org. Chem.* **2019**, *2019* (22), 3658–3661.

7. I. Nakamura; B.H. Oh; S. Saito; Y. Yamamoto. Novel [3+2] Cycloaddition of Alkylidenecyclopropanes with Aldehydes Catalyzed by Palladium. *Angew. Chem. Int. Ed.* **2001**, *40*, 1338–1340.

8. Noyori, R.; Odagi, T.; Takaya, H. Nickel(0)-Catalyzed Reaction of Methylenecyclopropanes with Olefins. A Novel [σ2 + π2] Cycloaddition. *J. Am. Chem. Soc.* **1970**, *92* (19), 5780–5781.

9. B. Kuila; D. Mahajan; L. Castedo; P. Singh; G. Bhargava. Nickel Catalyzed [3+2] Cycloaddition Reaction of Bis(Methylenecyclopropane) with Cyclic and Acyclic Dienophiles. *Tetrahedron Lett.* **2015**, *56*, 1307–1311.

10. Lautens, M.; Ren, Y. Palladium-Catalyzed Intramolecular [3 + 2] Cycloadditions of Methylenecyclopropanes With Alkenes: Diastereomeric Methylenecyclopropanes Exhibit Complementary Facial Selectivity. *J. Am. Chem. Soc.* **1996**, *118* (43), 10668–10669.

11. Lautens, M.; Ren, Y.; Delanghe, P. H. M. Stereochemical Control in Metal-Catalyzed [3 + 2] Cycloadditions of Methylenecyclopropanes. *J. Am. Chem. Soc.* **1994**, *116* (19), 8821–8822.

12. Da Concepción, E.; Fernández, I.; Mascareñas, J. L.; López, F. Highly Enantioselective Cobalt-Catalyzed (3+2) Cycloadditions of Alkynylidenecyclopropanes. *Angew. Chem. Int. Ed.* **2021**, 8182–8188.

13. García-Fandiño, R.; Gulías, M.; Castedo, L.; Granja, J. R.; Mascareñas, J. L.; Cárdenas, D. J. Palladium-Catalysed [3+2] Cycloaddition of Alk-5-Ynylidenecyclopropanes to Alkynes: A Mechanistic DFT Study. *Chem. - Eur. J.* **2008**, *14* (1), 272–281.

14. Saya, L.; Fernández, I.; López, F.; Mascareñas, J. L. Nickel-Catalyzed Intramolecular [3 + 2 + 2] Cycloadditions of Alkylidenecyclopropanes. A Straightforward Entry to Fused 6,7,5-Tricyclic Systems. *Org. Lett.* **2014**, *16* (19), 5008–5011.

15. Li, S.; Luo, Y.; Wu, J. An Efficient Approach to Fused Indolines via a Copper(I)-Catalyzed Reaction of Sulfonyl Azide with 2-Ethynylaryl Methylenecyclopropane. *Org. Lett.* **2011**, *13* (12), 3190–3193.

16. Xiao, X.; Yu, Z. Co-Catalyzed Asymmetric Intramolecular [3+2] Cycloaddition of Yne-Alkylidenecyclopropanes and Its Reaction Mechanism. *Chem. – Eur. J.* **2021**, *27*, 1-8.

17. Jing, S. M.; Balasanthiran, V.; Pagar, V.; Gallucci, J. C.; Rajanbabu, T. V. Catalytic Enantioselective Hetero-Dimerization of Acrylates and 1,3-Dienes. *J. Am. Chem. Soc.* **2017**, *139* (49), 18034–18043.

18. Duvvuri, K.; Dewese, K. R.; Parsutkar, M. M.; Jing, S. M.; Mehta, M. M.; Gallucci, J. C.; Rajanbabu, T. V. Cationic Co(I)-Intermediates for Hydrofunctionalization Reactions: Regio- and Enantioselective Cobalt-Catalyzed 1,2-Hydroboration of 1,3-Dienes. *J. Am. Chem. Soc.* **2019**, *141* (18), 7365–7375.

19. Parsutkar, M. M.; Pagar, V. V.; Rajanbabu, T. V. Catalytic Enantioselective Synthesis of Cyclobutenes from Alkynes and Alkenyl Derivatives. *J. Am. Chem. Soc.* **2019**, *141* (38), 15367–15377.

20. Tamaki, T.; Ohashi, M.; Ogoshi, S. [3+2] Cycloaddition Reaction of Cyclopropyl Ketones with Alkynes Catalyzed by Nickel/Dimethylaluminum Chloride. *Angew. Chem.* **2011**, *123* (50), 12273–12276.

21. Lin, M.; Kang, G.-Y.; Guo, Y.-A.; Yu, Z.-X. Asymmetric Rh(I)-Catalyzed Intramolecular [3 + 2] Cycloaddition of 1-Yne-Vinylcyclopropanes for Bicyclo[3.3.0] Compounds with a Chiral

Quaternary Carbon Stereocenter and Density Functional Theory Study of the Origins of Enantioselectivity. *J. Am. Chem. Soc.* **2012**, *134* (1), 398–405.

22. Wu, C.; Yoshikai, N. Cobalt-Catalyzed Intramolecular Reactions between a Vinylcyclopropane and an Alkyne: Switchable [5+2] Cycloaddition and Homo-Ene Pathways. *Angew. Chem. Int. Ed.* **2018**, *57* (22), 6558–6562.

23. Yang, J.; Mori, Y.; Yamanaka, M.; Yoshikai, N. Cobalt-Catalyzed Intramolecular Hydroacylation Involving Cyclopropane Cleavage. *Chem. – Eur. J.* **2020**, *26* (37), 8302–8307.

24. Carreira, E. M.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114* (16), 8257–8322.

25. Bondada, L.; Gumina, G.; Nair, R.; Ning, X. H.; Schinazi, R. F.; Chu, C. K. Synthesis of Novel Spiro[2.3]Hexane Carbocyclic Nucleosides via Enzymatic Resolution. *Org. Lett.* **2004**, *6* (15), 2531–2534.

Chapter 3: Experimental Information

3.1: General Methods

All substrate preparations were performed under an inert atmosphere either in a glove box at an O_2 concentration less than 5 ppm or using standard Schlenk line techniques. The Schlenk line was equipped with a vacuum pump maintained between 0.2 and 0.01 mmHg for all evacuation and drying of air-sensitive compounds. All glassware were cleaned by soaking in a base bath overnight, then rinsing with water and acetone, then dried overnight in an oven at 160 °C. All solvents were distilled using appropriate drying agents under nitrogen. All substrates are prepared using chemicals from Aldrich or Alfa.

Analytical thin layer chromatography (TLC) was performed on Merck pre-coated (0.25 mm) silica gel 60 F254 plates. Visualization was accomplished with UV light (254 nm) and/or an aqueous $KMnO_4$ solution. Gas chromatography of reaction mixtures was done on the HP 5890 series II GC equipped with HP-5MS (crosslinked 5% Ph Me Silicone) methyl phenyl silicone column (30 m, 0.32 mm ID, 0.25 µm) and hydrogen as carrier gas with an FID detector at 250 °C. GC-MSD analysis was performed on an Agilent 6850 GC-5975 MSD or 7820A system, both using helium carrier gas and EI-ionizers. Enantiomeric ratios of chiral compounds were determined with chiral stationary-phase (CSP) gas chromatography, which were performed on an Agilent 7850 A equipped with a cyclosil-B column, hydrogen carrier gas, using an FID detector at 250 °C. Proton and carbon nuclear magnetic resonance spectra (^{1}H and 13C NMR) were recorded on a Bruker Avance III HD Ascend 400 MHz or Avance 400 MHz Neo. Solvent resonance was used as an internal standard (^{1}H NMR, $CDCl_3$ at 7.26 ppm, ^{13}C NMR, $CDCl_3$ at 77.16 ppm). NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, sept = septet, m = multiplet, dd = doublet of doublet, dt = doublet of

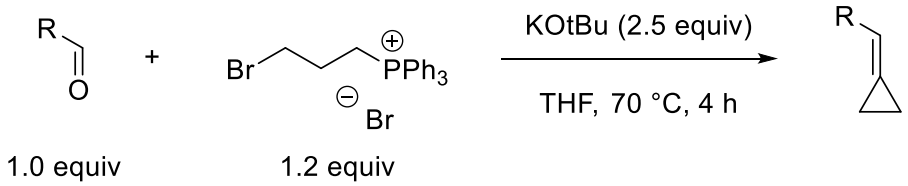
triplet, dq = doublet of quartet), coupling constants (Hz), and integration. 1D selective nOe spectra were recorded on a Bruker Avance III HD Ascend 600 MHz.

3.2: Chemicals

Methylene chloride, toluene, and ethyl acetate were distilled by following appropriate procedures and stored in the glove box over activated 4Å molecular sieves for prolonged use in the glove box. All commercially-available alkynyl derivatives were purchased from Aldrich or Alfa and used as received. Phosphinooxazolines ligands were prepared according to the literature procedure.[1,2] All other reagents have been generously provided by the RajanBabu group.

3.3: Synthesis of Reagents

3.3.1: General Procedures for the Synthesis of ACP (Alkylidenecyclopropane) Substrates (Procedure A).

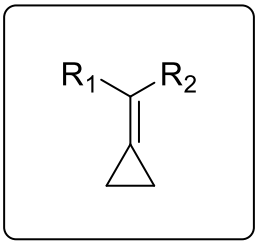


Literature procedure was used for the preparation of ACP substrates.[3,4] A 100-mL three-necked round-bottom flask equipped with a magnetic stir bar was added (3-bromopropyl)triphenylphosphonium bromide (1.2 equiv) and KO^{t}Bu (2.5 equiv), and THF (0.5 M, freshly distilled over Na) under argon. This mixture was stirred at 70 °C for 1 h. Then, a solution of the corresponding aldehyde (2.0 M in THF, 1.0 equiv) was added dropwise and the mixture was refluxed for 3 h. After cooling, the reaction mixture was quenched with water and extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure (bath temperature kept at 20 °C). After the solvent was evaporated, the crude

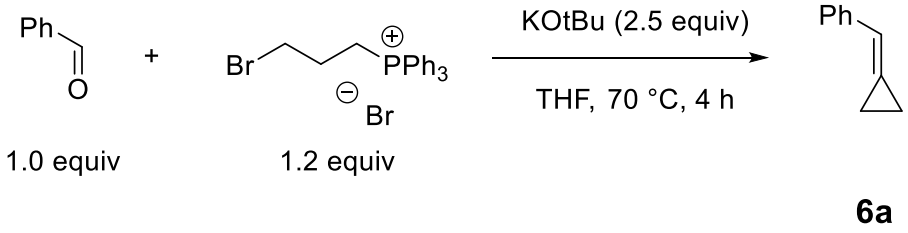
product was purified by column chromatography (hexanes: EtOAc) to afford ACP as a yellow liquid. Products were characterized by ^{1}H and ^{13}C NMR spectroscopy.

Table S1: Compounds Produced by Procedure A

Compound	R_1, R_2	Yield %	Characterization
5a	C_6H_{13}, H	38	^{1}H and ^{13}C NMR[1]
5b	Cyclohexyl, H	54	^{1}H and ^{13}C NMR[2]
6a	Ph, H	65	^{1}H and ^{13}C NMR[3]
6b	4-(OMe)-Ph, H	62	^{1}H and ^{13}C NMR[4]
6c	4-F-Ph, H	50	^{1}H and ^{13}C NMR[3]
6d	Ph, Ph	45	^{1}H and ^{13}C NMR[3]

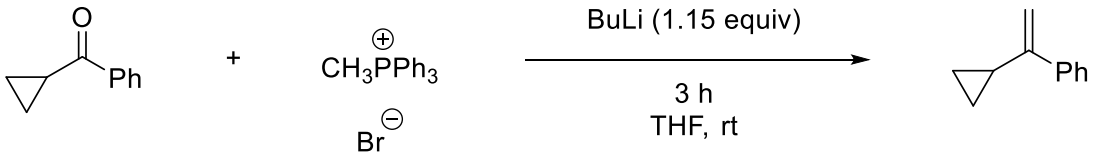


3.3.2: Procedure for Synthesis of ACP 6a



A 100-mL two-necked round-bottom flask equipped with a magnetic stir bar was added (3-bromopropyl)triphenylphosphonium bromide (1.2 equiv) and KO^{t}Bu (2.5 equiv), and THF (0.5 M, freshly distilled over Na) under argon. This mixture was stirred at 70 °C for 1 h. Then, a solution of the corresponding aldehyde (2.0 M in THF, 1.0 equiv) was added dropwise and the mixture was refluxed for 3 h. After cooling, the reaction mixture was quenched with water and extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure (bath temperature kept at 20 °C). After the solvent was evaporated, the crude product was purified by column chromatography (hexanes 100%) to afford ACP (**6a**) as a yellow liquid (yield 65%). Spectroscopic data matches literature reports.[5]

3.3.3: Procedure for Synthesis of (1-cyclopropylvinyl)benzene (3)

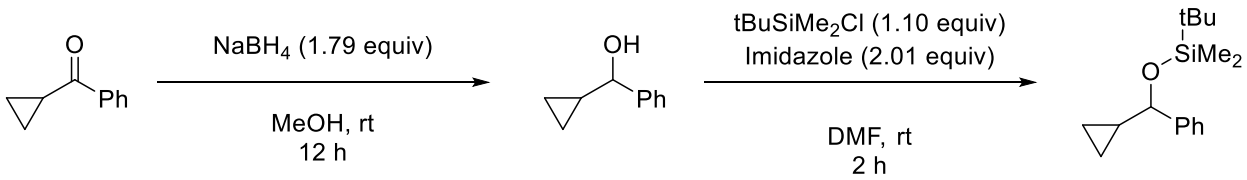


1.0 equiv 1.15 equiv

3

To a 250-mL two-necked round-bottom flask was added methyltriphenylphosphonium bromide (5.644 g, 15.7 mmol, 1.15 equiv) and a magnetic stir bar. The flask was flushed with dry argon for 15 min before dry THF (30 mL, freshly distilled over Na) was transferred to it using a syringe. The mixture was cooled to 0 °C under argon. To this mixture was added butyllithium (2.5 M in hexane, 6.3 mL, 1.15 equiv) dropwise. After stirring for 45 min at room temperature, a solution of cyclopropyl phenyl ketone (1 M in THF, 13.7 mL, 1.00 equiv) was added dropwise, and the resulting mixture was stirred for 2 h. The reaction mixture was quenched with deionized water (50 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure (bath kept at 20 °C). After the solvent was evaporated, the crude product was purified by column chromatography (hexanes 100%) to afford (1-cyclopropylvinyl)benzene **3** as a colorless liquid (1.435 g, 72%). Product was characterized by ^1H and ^{13}C NMR. Spectroscopic data matches literature reports.[6]

3.3.4: Procedure for Synthesis of Tert-Butyl(cyclopropyl(phenyl)methoxy)timethylsilane (4)

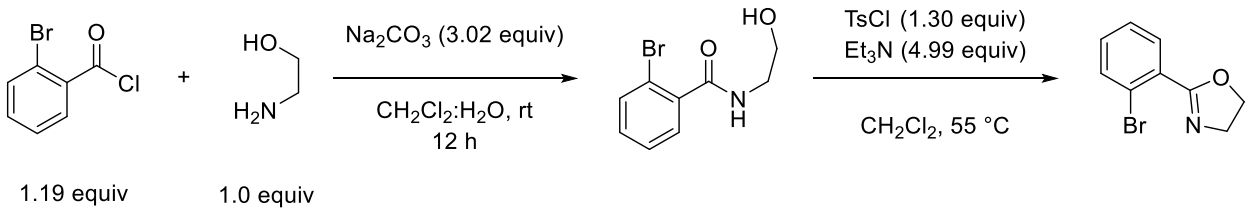


1.0 equiv

4

To a 250-mL two-necked round-bottom flask equipped with a magnetic stir bar was added cyclopropyl phenyl ketone (4.505 mL, 30.24 mmol, 1 equiv) and methanol (1 M). This solution was cooled to 0 °C under argon. To this solution was added $NaBH_4$ (2.048 g, 54.1 mmol, 1.79 equiv). The solution was stirred for 12 h, after which it is quenched with saturated NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). This solution was concentrated under reduced pressure. The crude alcohol was then dissolved in 30 mL DMF and combined with imidazole (4.142 g, 60.8 mmol, 2.01 equiv) in a 250-mL two-necked round-bottom flask. This solution was cooled to 0 °C under argon, and to this solution was added *tert*-butyldimethylsilyl chloride (5.002 g, 33.2 mmol, 1.10 equiv) and imidazole (4.142 g, 60.84 mmol, 2,01 equiv), and this solution was stirred at room temperature for 2 h. The reaction solution was quenched with deionized water (30 mL) and extracted with 1:1 Et_2O:hexanes (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure, The crude product was purified by column chromatography (hexanes 100%) to afford *tert*-butyl(cyclopropyl(phenyl)methoxy)timethylsilane **4** as a colorless liquid (5.130 g, 63%). Product was characterized by ^1H, ^{13}C NMR, and GC-MS.

3.3.5: Procedure for Synthesis of L1 Precursor 2-(2-bromophenyl)-4,5-Dihydrooxazole s-2

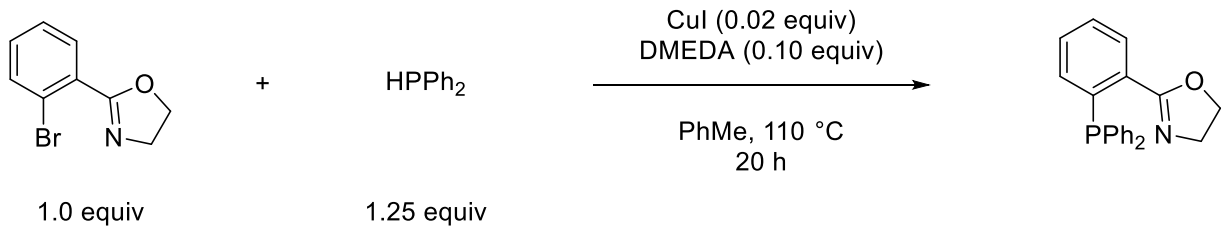


Literature procedure was used for the preparation of compound **s-1** and **s-2**.[7] To a 500-mL three-necked round-bottom flask equipped with a magnetic stir bar was added 2-aminoethanol (1.86 g, 30.5 mmol, 1 equiv), CH_2Cl_2 (100 mL), and Na_2CO_3 (9.77 g, 92.2 mmol, 3.02 equiv) in deionized water (75 mL). While the biphasic mixture was stirred vigorously, 2-bromobenzoyl

chloride (4.75 mL, 36.3 mmol, 1.19 equiv) was added dropwise. The mixture was stirred for 12 h at room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 * 50 mL). The combined organic layer were stirred with KOH (1 M in methanol, 15 mL) for 15 min, then neutralized with 3 M HCl (diluted from 12 M HCl) and diluted with water (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure (bath temperature kept at 20 °C), and purified by column chromatography (1:1 acetone:hexanes) to give 2-bromo-N-(2-hydroxyethyl)benzamide **s-1** as a white solid (5.617 g, yield 75%).

To a 500-mL three-necked round-bottom flask equipped with a reflux condenser and a magnetic stir bar was added **s-1** (5.617 g, 23.0 mmol, 1 equiv), CH_2Cl_2, 4-toluenesulfonyl chloride (5.93 g, 29.8 mmol, 1.30 equiv), and triethylamine (16 mL, 114.8 mmol, 4.99 equiv). The solution was stirred at 55 °C for 22 h. After stirring, deionized water (27 mL) was added, and the mixture was stirred at 75 °C for 2 h. The reaction mixture was then cooled, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 *x25 mL). [Be consistent use * or x, NOT both, see later] The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (1:1 ethyl acetate:hexanes) to give 2-(2-bromophenyl)-4,5-dihydrooxazole **s-2** as an orange oil (4.497 g, yield 86%). Product was characterized by ^{1}H and ^{13}C NMR as reported in the literature.[8]

3.3.6: Procedure for Synthesis of 2-(2-diphenylphosphanyl-phenyl)-4,5-dihydrooxazole L1

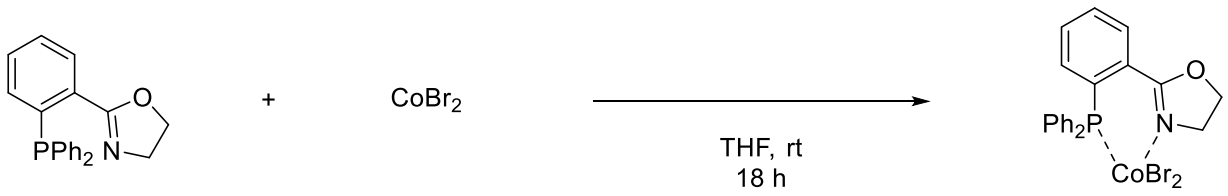


1.0 equiv 1.25 equiv

s-2 **L1**

Literature procedure was used for the preparation of compound **L1**.[8] Prior to this synthesis, **s-2** was further purified by azeotroping with toluene. To a 100-mL Schlenk flask equipped with a magnetic stir bar was added CuI (31.0 mg, 0.17 mmol, 0.02 equiv), *N,N'*-dimethylethylenediamine (70.2 mg, 0.80 mmol, 0.10 equiv), diphenylphosphine (1.931 g, 10.4 mmol, 1.25 equiv), and toluene (9 mL). The solution was stirred at room temperature for 20 min. **s-2** (1.80 g, 7.96 mmol, 1 equiv) dissolved in toluene (16 mL) was injected into the flask, followed by Cs_2CO_3 (3.952 g, 12.1 mmol, 1.52 equiv). The flask was sealed with a teflon cap, and the solution was stirred vigorously at 110 °C for 20 h. Afterwards, the solution was cooled to room temperature, filtered through celite by vacuum. The vacuum was washed with CH_2Cl_2 (2 * 25 mL), and the filtrate was concentrated under reduced pressure and purified by column chromatography (hexanes to 3:1 hexanes:ethyl acetate) to afford 2-(2-diphenylphosphanyl-phenyl)-4,5-dihydrooxazole as a viscous white oil (729 mg, yield 28%). Product was characterized by ^{1}H and ^{31}P NMR. Spectroscopic data matches literature reports.[8]

3.3.7: Procedure for Synthesis of [L1]$CoBr_2$.



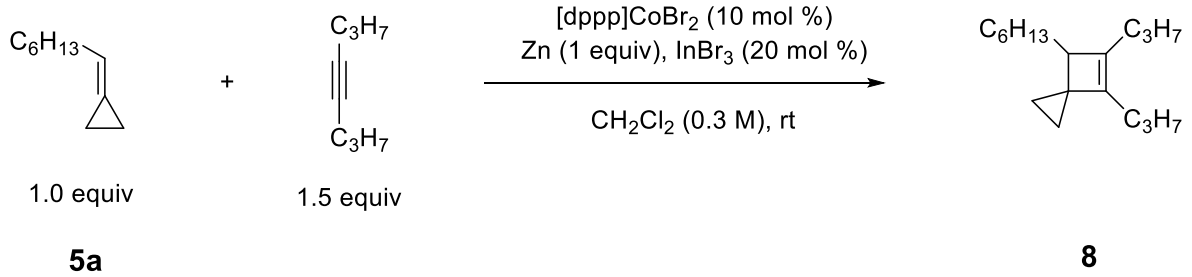
1.0 equiv 0.95 equiv

L1 [**L1**]$CoBr_2$

Literature procedure was used to prepare the [**L1**]$CoBr_2$ complex.[9] In a dry-box, a 100-mL Schlenk flask was charged with anhydrous $CoBr_2$ (457 mg, 2.09 mmol, 0.95 equiv.), THF (15 mL), and a magnetic stirrer bar. The resulting mixture was stirred until all the $CoBr_2$ dissolved to afford a homogenous solution. A 20-mL vial was charged with **L1** (729 mg, 2.20 mmol, 1.0 equiv.), a magnetic stirrer bar, and THF (10 mL). The resultant mixture was stirred until most of the **L1** dissolved, stirring was stopped and the vial allowed to sit for ca. 5 min to allow undissolved **L1** to settle. A glass pipette was used to transfer the **L1** solution to the solution of $CoBr_2$ while stirring in the Schlenk flask. More THF (ca. 5 mL) was added to the vial to dissolve the remaining solids and transferred to the Schlenk flask. The resultant mixture was stirred at rt in the dry-box overnight (ca. 18 h), stirring was stopped, and hexanes (ca. 25 mL) was added to the mixture and stirred for 5 min resulting in precipitation of the complex. The mixture was allowed to sit for ca. 5 minute and the supernatant decanted to afford a sea green mixture which was washed with ether (2 x 20 mL) and dried in vacuum (ca. 0.1 mmHg) to afford a blue-green solid which was made into a fine powder and further dried to remove any residual THF in high vacuum (0.1 mm Hg, 12 h) to afford a complex as a fine green powder (890 mg, 77% yield). This complex was used directly for catalytic synthesis.

3.4: General Procedures for Cycloaddition Reactions

3.4.1: Procedure for [dppp]$CoBr_2$-Catalyzed [2+2] Cycloaddition of ACP 5a with 4-Octyne (Procedure B)



1.0 equiv

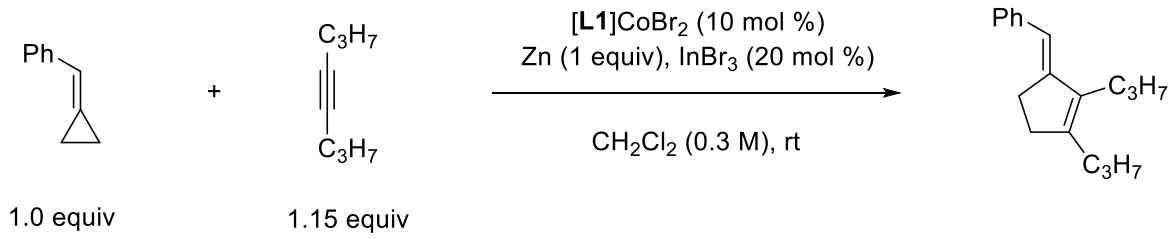
1.5 equiv

5a

8

In a N_2-filled glove box, an 8-mL vial equipped with a septum screw cap was charged with a magnetic stir bar, [dppp]$CoBr_2$ (11 mg, 0.02 mmol, 0.1 equiv.), activated zinc dust (13 mg, 0.2 mmol, 1 equiv.), $InBr_3$ (14 mg, 0.04 mmol, 0.2 equiv.) and methylene chloride (0.3 M). The vial was capped and while stirring the mixture, **5a** (28 mg, 0.2 mmol, 1 equiv.) was added neat using microliter syringe via the septum, followed by 4-octyne (33 mg, 0.3 mmol, 1.5 equiv.) Upon completion of the reaction (24 h), the vial was taken out of the box and quenched with hexanes (5 mL). The resulting mixture was filtered through a plug of silica in a glass pipette, eluted with hexanes and concentrated using rotary evaporator, then purified via column chromatography eluting with hexane/ethyl acetate to afford compound **8** as pale-yellow oil (yield 44%). Product characterized by ^{1}H and ^{13}C NMR spectroscopy and GC-MS. Enantiomeric excess was determined using CSP-GC. See Chapter 3.6 for full data of this compound.

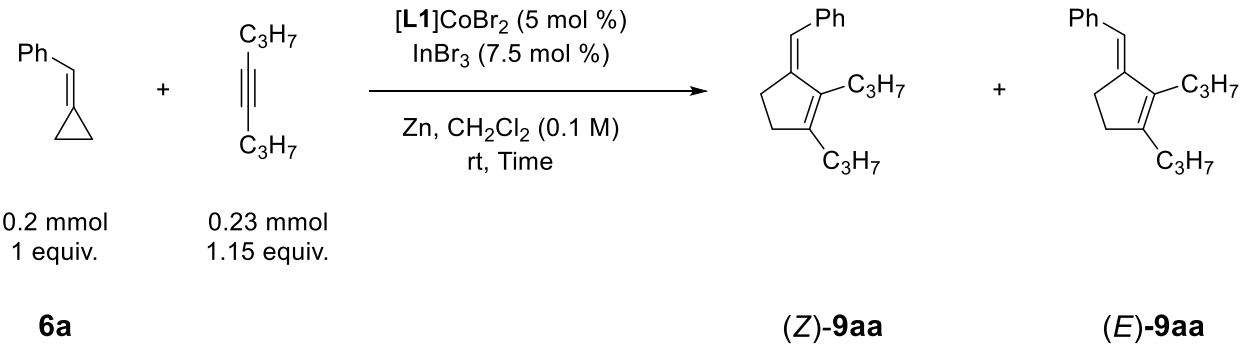
3.4.2: Procedure for [L1]$CoBr_2$-Catalyzed [3+2] Cycloaddition of 6a with 4-octyne 2a (Procedure C)



6a **9aa**

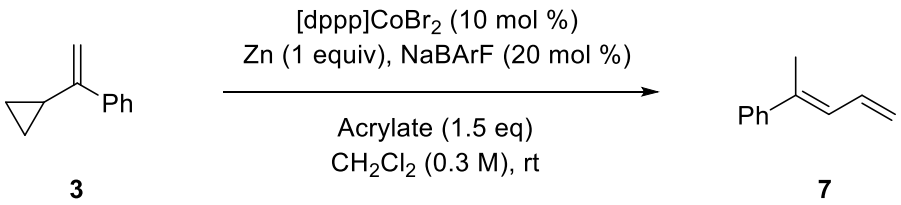
In a N_2-filled glove box, an 8-mL vial equipped with a septum screw cap was charged with a magnetic stir bar, [dppp]$CoBr_2$ (11 mg, 0.02 mmol, 0.1 equiv.), activated zinc dust (13 mg, 0.2 mmol, 1 equiv.), $InBr_3$ (14 mg, 0.04 mmol, 0.2 equiv.) and methylene chloride (0.3 M). The vial was capped and while stirring the mixture, **6a** (26 mg, 0.2 mmol, 1 equiv.) was added neat using microliter syringe via the septum, followed by 4-octyne (25 mg, 0.23 mmol, 1.15 equiv.) Upon completion of the reaction (3 h), the vial was taken out of the box and quenched with 1:1 hexane:ether (5 mL). The resulting mixture was filtered through a plug of silica in a glass pipette eluting 1:1 hexane:ether and concentrated using rotary evaporator, then purified via column chromatography eluting with hexane/ethyl acetate to afford compound **9aa** as yellow oil (yield 23%). Product characterized by ^1H and ^{13}C NMR spectroscopy and GC-MS. See Chapter 3.6 for full data of this compound.

3.4.3: Procedure for Observing Reaction Progress of [L1]$CoBr_2$-Catalyzed [3+2] Cycloaddition of ACP 6a with 4-octyne (Procedure D)



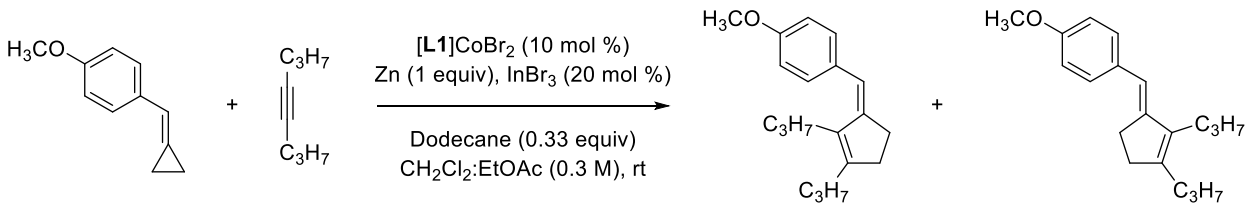
In a N_2-filled glove box, a stock solution of **6a** (0.2 M), 4-octyne (0.2 M), and internal standard dodecane (0.1 M) in methylene chloride was prepared. A separate 8-mL vial equipped with a septum screw cap was charged with a magnetic stir bar, [**L1**] $CoBr_2$ (0.01 mmol, 0.05 equiv.), activated zinc dust (0.1 mmol, 0.5 equiv.), $InBr_3$ (0.015 mmol, 0.075 equiv.), and methylene chloride (0.1 M). The vial was capped and while stirring the mixture, 1 mL of the stock solution was injected via the septum. The mixture was stirred at rt. The reaction was monitored by taking an aliquot using a glass pipette, diluting with a 1:1 mixture of hexane and ether and filtered through a plug of silica in a glass pipette eluting with ether and analyzed via GC-FID. Upon completion of the reaction (2-3h), the vial was taken out of the box and quenched with 1:1 hexane:ether (5 mL). Recovered yield was not determined.

3.4.4: Procedure for Attempted [dppp]$CoBr_2$-Catalyzed [3+2] Cycloaddition of 3 with 2,2,2-Trifluoroethyl Acrylate (Procedure E)



In a N_2-filled glove box, an 8-mL vial equipped with a septum screw cap was charged with a magnetic stir bar, [dppp]$CoBr_2$ (20 mg, 0.03 mmol, 0.1 equiv.), activated zinc dust (20 mg, 0.3 mmol, 1 equiv.), NaBArF (54 mg, 0.06 mmol, 0.2 equiv.) and methylene chloride (0.3 M). The vial was capped and while stirring the mixture, vinylcyclopropane **3** (43 mg, 0.3 mmol, 1 equiv.) was added neat using microliter syringe via the septum, followed by 2,2,2-trifluoroethyl acrylate (69 mg, 0.45 mmol, 1.5 equiv.) Upon completion of the reaction (24 h), the vial was taken out of the box and quenched with 1:1 hexane (5 mL). The resulting mixture was filtered through a plug of silica in a glass pipette eluting hexane and concentrated using rotary evaporator, then purified via column chromatography eluting with hexane to afford isomer **7** as a colorless oil (yield 62%). Product characterized by ^1H and ^{13}C NMR spectroscopy. Spectroscopic data matches literature reports.[10]

3.4.5: Procedure for [L1]$CoBr_2$-Catalyzed [3+2] Cycloaddition of ACP 6b with 4-Octyne in CH_2Cl_2 and EtOAc (Procedure F)



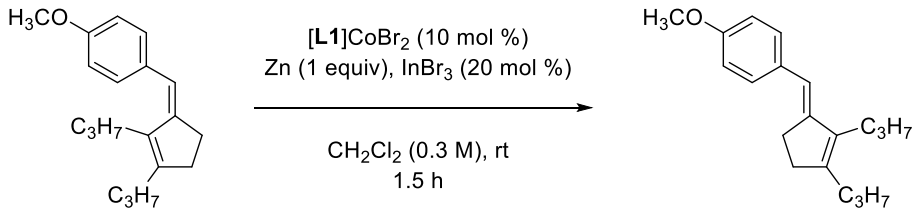
1.0 equiv 1.15 equiv

6b (*Z*)-**9ba** (*E*)-**9ba**

In a N_2-filled glove box, a stock solution of CH_2Cl_2 and EtOAc (1:1 v/v) containing dodecane (0.1 M) was prepared. A separate 8-mL vial was charged with a magnetic stir bar, [**L**]$CoBr_2$ (0.02 mmol, 0.1 equiv), activated zinc dust (0.2 mmol, 1 equiv), $InBr_3$ (0.04 mmol, 0.2 equiv) and the stock solution (0.3 M). The vial was capped and while stirring the mixture, ACP **6b** (0.2 mmol, 1 equiv) was added neat using microliter syringe via the septum, followed by 4-octyne

(0.23 mmol, 1.15 equiv) The mixture was stirred at rt. The reaction was monitored by taking an aliquot using a glass pipette, diluting with a 1:1 mixture of hexane and ether and filtered through a plug of silica in a glass pipette eluting with ether and analyzed via GC-FID. Upon completion of the reaction, the vial was taken out of the box and quenched with 1:1 hexane:ether (5 mL). The resulting mixture was filtered through a plug of silica in a glass pipette eluting 1:1 hexane:ether. Yield was not determined.

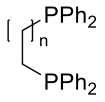
3.4.6: Procedure for PHOXCoBr$_2$-Catalyzed Isomerization of Product (*Z*)-9ba to (*Z*)-9ba (Procedure G)



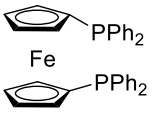
(*Z*)-**9ba** (*E*)-**9ba**

In a N_2-filled glove box, an 8-mL vial equipped with a septum screw cap was charged with a magnetic stir bar, [**L1**]$CoBr_2$ (5 mg, 0.009 mmol, 0.1 equiv.), activated zinc dust (6 mg, 0.091 mmol, 1 equiv.), $InBr_3$ (6 mg, 0.018 mmol, 0.2 equiv.) and methylene chloride (0.3 M). The vial was capped and while stirring the mixture, (*Z*)-**9ba** (24 mg, 0.091 mmol, 1 equiv.) was added neat using microliter syringe via the septum. The mixture was stirred at rt. Upon completion of the reaction (1.5 h), the vial was taken out of the box and quenched with 1:1 hexane:ether (5 mL). The resulting mixture was filtered through a plug of silica in a glass pipette eluting 1:1 hexane:ether and concentrated using rotary evaporator, then purified via column chromatography eluting with hexane/ethyl acetate (95:5) to afford compound (*E*)-**9ba** as yellow oil (24 mg, recovered 71%).

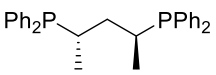
3.4.7: All Ligands Tested for Cobalt-Catalyzed Cycloadditions between ACP Derivatives and Alkynes



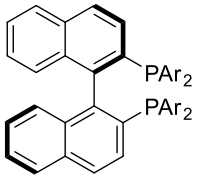
n = 1 dppe
n = 2 dppp



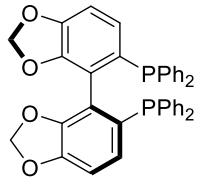
dppf



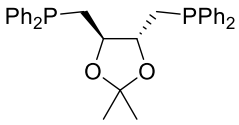
(*S*,*S*)-BDPP



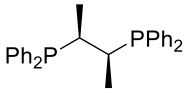
Ar = Ph (*R*)-BINAP
Ar = 4-Me-Ph (*R*)-tol-BINAP



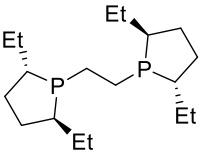
(*S*)-SEGPHOS



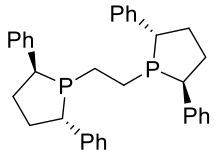
(-)-DIOP



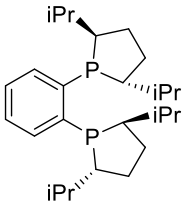
(*S*,*S*)-CHIRAPHOS



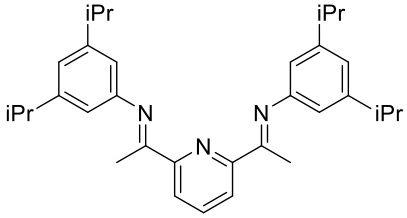
(*R*,*R*)-EtBPE



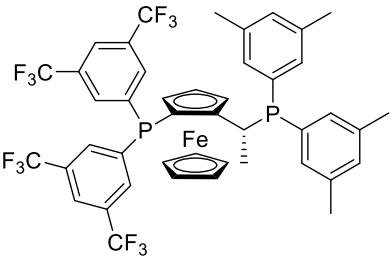
(*S*,*S*)-PhBPE



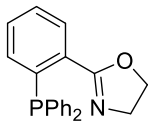
^{iPr}DuPhos



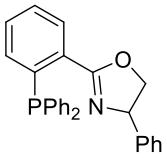
^{iPr}PDI



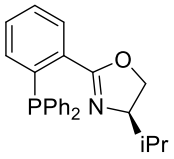
Josiphos II



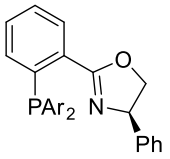
L1



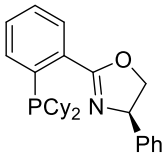
L2



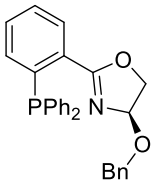
L3



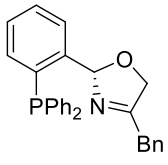
L4: Ar = (3,5)-Me-Ph
L5: Ar = (3,5)-CF_3Ph



L6



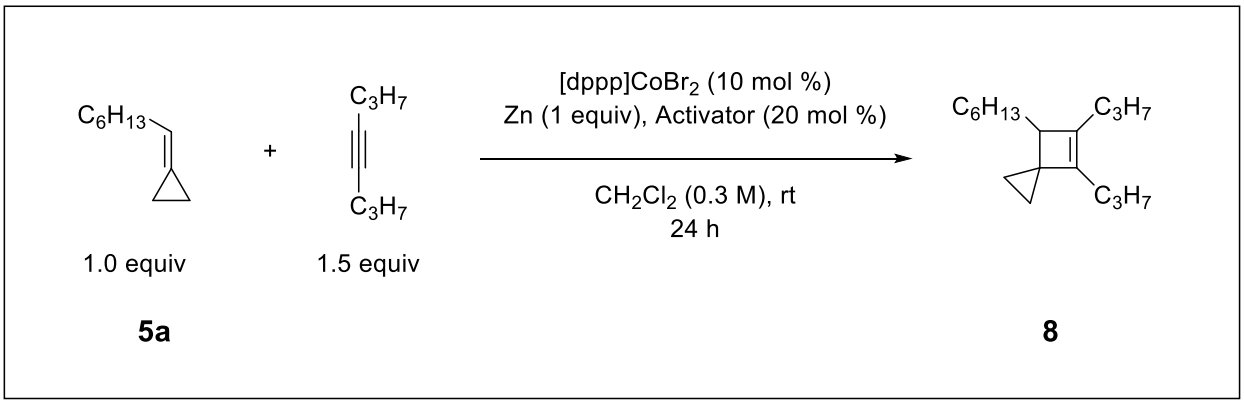
L7



L8

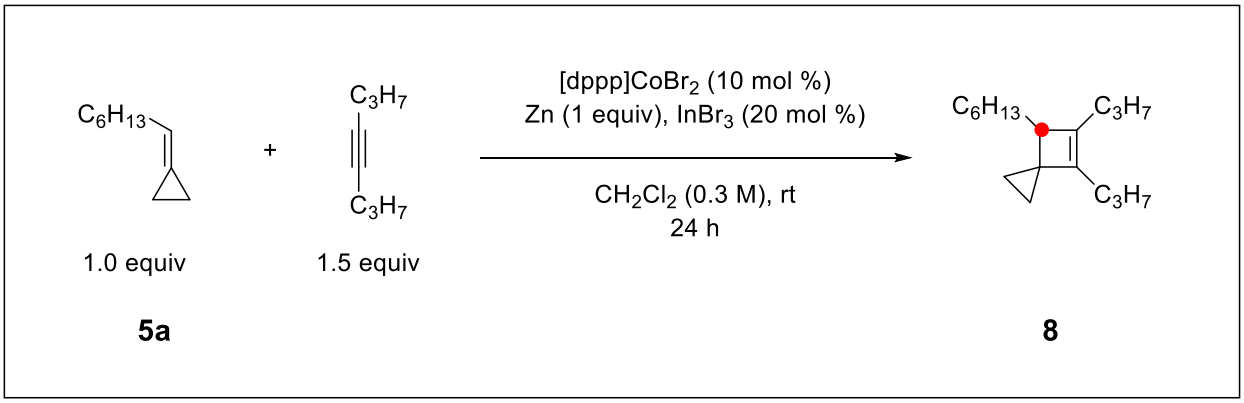
3.5: Experimental Data

Table S2: Activator Screening for Racemic Co-Catalyzed [2+2] Cycloaddition of ACP and 4-Octyne (Procedure B)



Entry	Time	Activator	GC-FID Analysis	
			Conversion %	8
1	24	NaBArF	15	3
2	2	NaBArF	26	26
3	24	$ZnBr_2$	43	43
4	24	$InBr_3$	100	94
5	24	$Ag[SbF_6]$	94	94
6	24	$Ag[BF_4]$	52	50

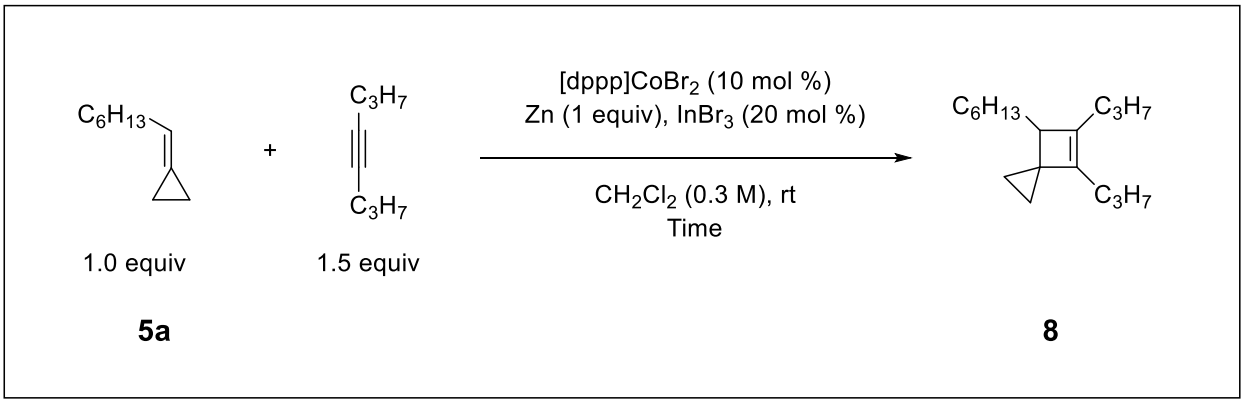
Table S3: Ligand Screening for Co-Catalyzed [2+2] Cycloaddition of ACP and 4-Octyne (Procedure B)



Entry	Ligand	GC-FID Analysis		
		Conversion	8 %	ee%
1	dppp	100	94	0
2	dppe	20	6	n.d.
3	dppf	71	20	n.d.
4	(*R*)-BINAP	47	42	50
5	(*S*,*S*)-BDPP	100	52	96
6	(-)-DIOP	90	32	72
7	(*S*,*S*)-CHIRAPHOS	2	0	n.d.
8	(*R*)-(tol)-BINAP	36	34	62
9	(*S*)-SEGPHOS	17	15	69
10	Josiphos-II	73	73	78
11	(*R*,*R*)-EtBPE	5	5	n.d.
12	(*S*,*S*)-PhBPE	0	--	--
13	^{iPr}DuPhos	0	--	--
14	L1	44	38	n.d.
15	(*rac*)-L2	80	33	--
16	L3	82	48	74
17	L4	86	39	81
18	L5	58	42	80
19	L6	0	--	--
20	L7	57	35	85
21	L8	2	2	n.d.

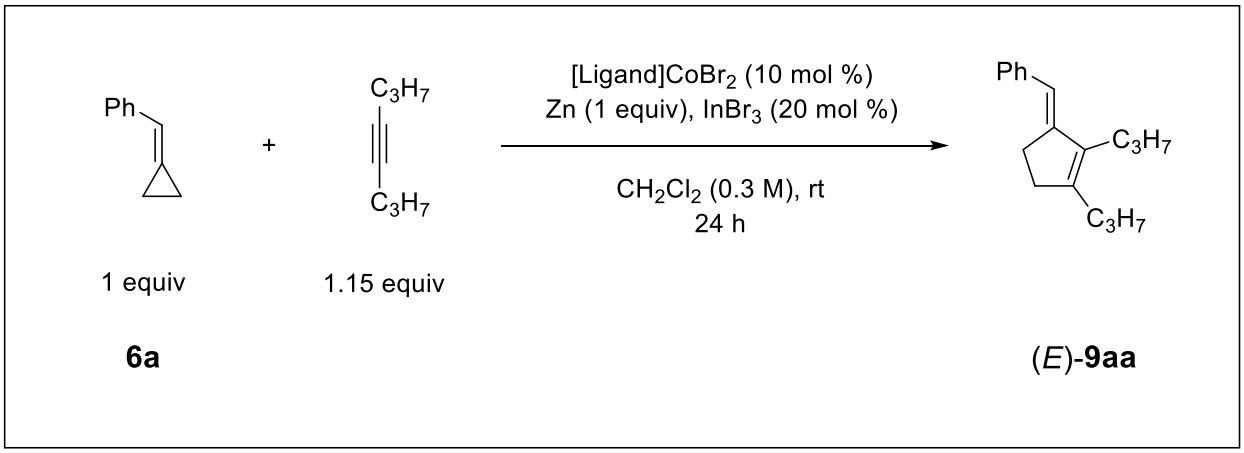
Red circle indicates chiral center

Table S4: General Reaction Optimization for Co-Catalyzed [2+2] Cycloaddition of ACP and 4-Octyne (Procedure B)



Entry	Time	Change to Conditions Above	GC Conversion %	8 %	Recovered Yield %
1	5	None	100	92	70
2	5	0.15 M reaction	100	91	65
3	3	None	100	92	76
4	3	5 mol% catalyst loading	100	91	63
5	3	0.15 M reaction	100	96	80
6	5	5 mol% TMS-Pyrazine instead of Zn	n.d.	n.d.	71
7	3	(*S*,*S*)-BDPPCoCl$_2$ instead of [dppp]CoBr$_2$	92	85	48

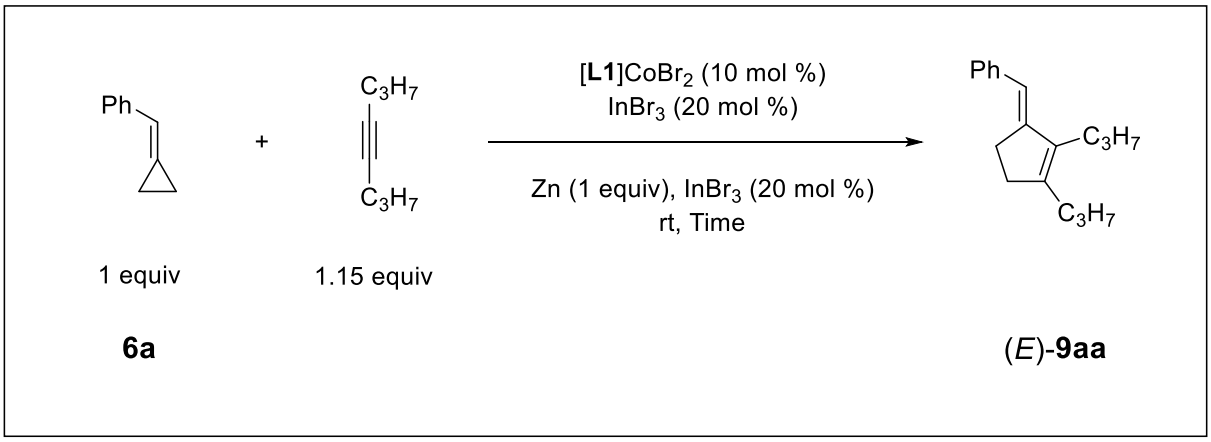
Table S5: Ligand Screening for Co-Catalyzed [3+2] Cycloaddition of Aryl ACP and Alkyne (Procedure C*)



Entry	Ligand	GC-FID Analysis	
		Conversion (%)	(*E*)-9aa (%)
1	dppp	79	62
2	dppe	6	6
3	dppf	23	0
4	(*S*,*S*)-BDPP	11	5
5	(*R*)-BINAP	8	4
6	(*S*)-SEGPHOS	2	0
7	^{iPr}PDI	23	0
8	L1	100	97
9	(*rac*)-L2	100	88
10	L3	100	31

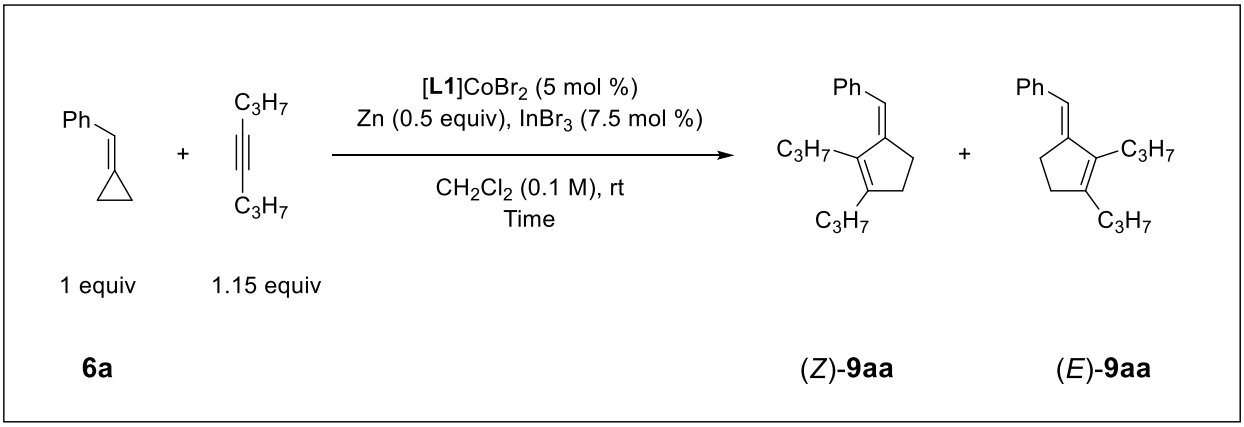
*Procedure C is followed, except each reaction lasts 24 h

Table S6: General Reaction Optimization for Co-Catalyzed [3+2] Cycloaddition of ACP and Alkyne (Procedure D)



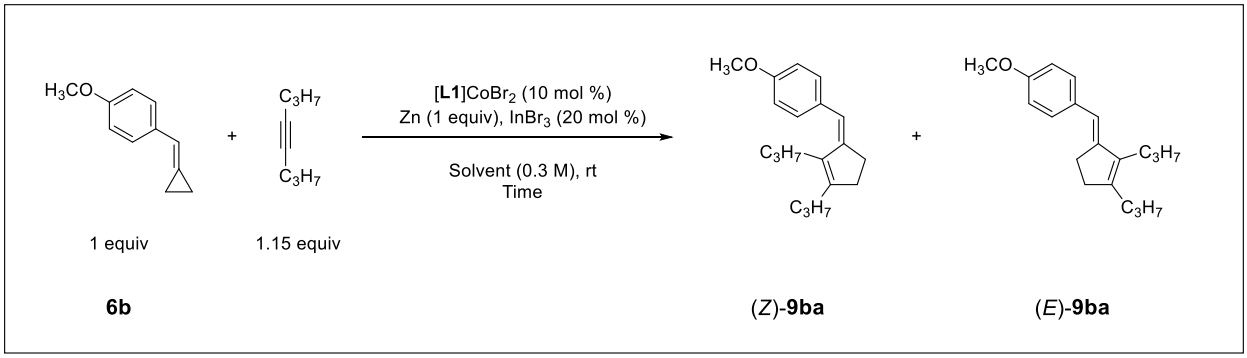
Entry	Time (h)	Change to Conditions Above	GC-FID Analysis		Recovered Yield %
			Conversion	GC 9aa %	
1	3	None	100	96	23%
2	1	None	99	51	n.d.
3	1	NaBArF instead of $InBr_3$	100	100	n.d.
4	1	$Ag[SbF_6]$ instead of $InBr_3$	92	85	n.d.
5	3	5 mol % catalyst, 7.5 mol % $InBr_3$	93	60	15

Table S7: Reaction Progress Tracking for Co-Catalyzed [3+2] Cycloaddition of ACP 6a and 4-Octyne (Procedure D)



Entry	Time (min)	GC-FID Analysis (%)		
		Dodecane	(*Z*)-9aa	(*E*)-9aa
1	20	46.47247	46.77415	6.753385
2	40	49.19442	37.46013	13.34545
3	60	51.08146	28.48002	20.43852
4	130	51.91216	11.26586	36.82198
5	150	51.24033	8.148936	40.61073

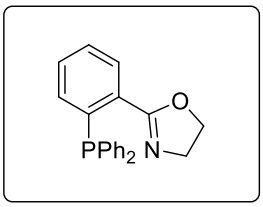
Table S8: Solvent Screening on Co-catalyzed [3+2] cycloaddition of ACP and alkyne (Procedures C and G)



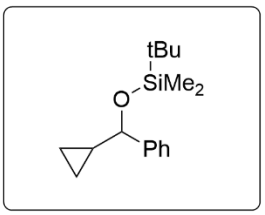
Entry	Solvent	Time	GC-FID Analysis		
			Conversion	(*Z*)-9ba %	(*E*)-9ba %
1	PhMe	3	91	77	5
2	PhMe*	3	100	6	77
3	CH_2Cl_2:EtOAc (95:5 v/v)	3	86	35	42
4	CH_2Cl_2:EtOAc (50:50 v/v)	2	52	48	4
5	CH_2Cl_2:EtOAc (50:50 v/v)	26	75	69	6

*NaBArF is used as activator instead of $InBr_3$

3.6: Analytical Data for Key Compounds



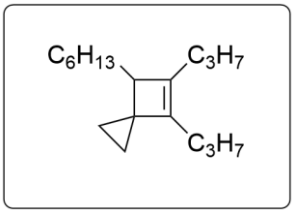
2-(2-(diphenylphosphaneyl)phenyl)-4,5-dihydrooxazole (L1): Prepared from **s-2** and commercially-available reagents (viscous white oil, yield 28%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.85 (dd, *J* = 7.7 Hz, 3.53 Hz, 1H), 7.39-7.27 (m, 12H), 6.90 (dd, *J* = 8.8 Hz, 4.3 Hz), 4.08 (t, *J* = 7.6 Hz, 3.4 Hz, 2H), 3.78 (t, *J* = 9.4 Hz, 2H). 31P: -5.05 (s). Spectroscopic data matches literature reports.[2]



Tert-butyl(cyclopropyl(phenyl)methoxy)timethylsilane (4): Prepared from commercially-available cyclopropyl phenyl ketone, sodium borohydride, and tert-butyldimethylsilyl chloride (colorless liquid, yield 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 4H), 7.23 (tt, 1H), 4.27 (d, *J* = 6.1 Hz, 1H), 1.08 (m, 1H), 0.88 (s, 9H), 0.42 (m, 4H), 0.02 (s, 3H), -0.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 128.1, 127.0, 126.1, 77.2, 26.0, 20.2, 18.4, 2.8, 2.4, -4.5, -4.6.

GC (Methyl silicone. 120 °C, 3 min, 20 °C/min to 250 °C): R_t = 5.41 min.

GC-MS: m/z [M^+] = 262, exact mass calculated for $C_{16}H_{26}OSi$: 262.18



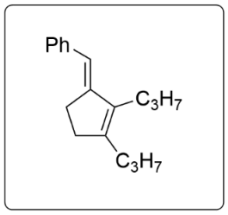
6-hexyl-4,5-dipropylspiro[2.3]hex-4-ene (8): Prepared from reaction between ACP **5a** (28 mg, 0.2 mmol) and 4-octyne (33 mg, 0.3 mmol) with optimized conditions using [dppp]$CoBr_2$, stirred for 24 h, followed by purification by column chromatography (hexanes 100%) to afford the title compound (25 mg, yield 50%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (m, 1H), 2.18-1.96 (m, 3H), 1.82 (t, *J* = 7.6 Hz, 2H), 1.56-1.19 (m, 17H), 0.95-0.83 (m, 12H), 0.66-0.59 (m, 2H), 0.58-0.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 143.3, 141.2, 47.7, 32.9, 32.1, 31.5, 30.9, 29.8, 27.7, 27.3, 22.8, 21.5, 21.4, 14.5, 14.4, 14.2, 6.1, 4.4.

GC (Methyl silicone. 120 °C, 3 min, 20 °C/min to 250 °C): R_t = 8.13 min.

CSP-GC (cyclosil-B, 90 °C, 300 min, 20 °C/min to 175 °C): R_t, from [dppp]$CoBr_2$: 276.04 (50%) and 279.62 (50%); from [(*S*,*S*)-BDPP]$CoBr_2$-derived product: 275.42 min (97%) and 279.30 min (3%); major (94% ee).

GC-MS: m/z [M^+] = 248, exact mass calculated for $C_{18}H_{32}$: 248.25.

Optical rotation of [(*S*,*S*)-BDPP]$CoBr_2$-derived product to be determined later.

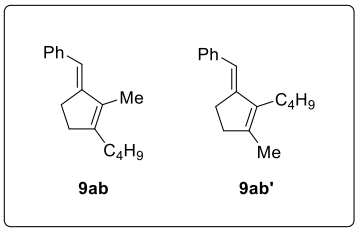


(*E*)-((2,3-dipropylcyclopent-2-en-1-ylidene)methyl)benzene (9aa): Prepared from reaction of ACP **6a** (26 mg, 0.2 mmol) and 4-octyne (25 mg, 0.23 mmol) and with optimized condition using **[L1]**$CoBr_2$, stirred for 3 h, followed by purification by column chromatography (hexanes, 100%) to afford title compound (11 mg, yield 23%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 8.5 Hz, 0.8 Hz, 2H), 7.21 (t, *J* = 7.9 Hz, 2H), 7.02 (tt, *J* = 7.3 Hz, 1.3 Hz, 1H), 6.09 (t, *J* = 2.2 Hz, 1H), 2.74 (sxt, *J* = 2.7 Hz, 2H), 2.39 (t, *J* = 5.3 Hz), 2.20-2.11 (m, 4H), 1.43-1.34 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 148.1, 139.4, 139.1, 128.4, 128.3, 128.0, 125.1, 115.1, 38.8, 31.7, 29.2, 26.9, 22.2, 21.5, 14.6, 14.4.

GC (Methyl silicone. 120 °C, 3 min, 20 °C/min to 250 °C): R_t = 7.84 min.

GC-MS: m/z [M^+] = 240.24, exact mass calculated for $C_{18}H_{24}$: 240.19.

Absolute configuration assigned as (*E*) by analogy.



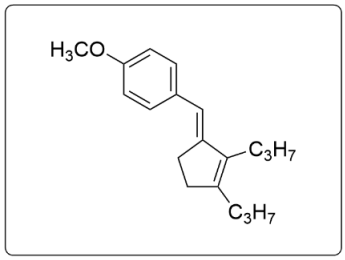
(*E*)-((3-butyl-2-methylcyclopent-2-en-1-ylidene)methyl)benzene (9ab): Prepared from reaction of ACP **6a** (26 mg, 0.2 mmol) and 2-heptyne (22 mg, 0.23 mmol) and with optimized condition using [L1]$CoBr_2$, stirred for 24 h, followed by purification by column chromatography (hexanes = 100%) afforded title compound (rr 66:34, 20 mg, yield 44%) as a yellow oil.; δ 7.40 (d, *J* = 7.7 Hz, 3.2H), 7.33 (t, 7.4 Hz, 3.2H), 7.14 (t, *J* = 7.27 Hz, 1.8H), 6.21-

6.14 (m, 1.5H), 2.86 (m, 3H), 2.51 (m, 3H), 2.29 (t, *J* = 7.2, 3H), 1.86 (s, 1.5H), 1.81 (s, 3H), 1.50-1.17 (m, 11H), 0.99-0.89 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 151.8, 150.4, 148.3, 143.9, 139.5, 139.4, 128.4, 128.1, 128.0, 125.3, 125.2, 36.6, 34.3, 30.9, 30.4, 29.9, 29.4, 29.2, 24.7, 23.1, 22.8, 15.3, 14.2, 14.1, 10.5.

GC (Methyl silicone. 120 °C, 3 min, 20 °C/min to 250 °C): R_t = 8.08 min (34% minor isomer) and 8.38 min (66% major isomer).

GC-MS: m/z [M^+] = 226.2, exact mass calculated for $C_{17}H_{22}$: 226.17.

Absolute configurations assigned as (*E*) by analogy.



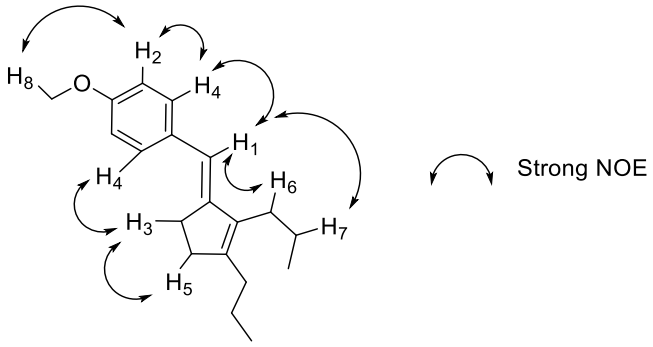
(*E*)-1-((2,3-dipropylcyclopent-2-en-1-ylidene)methyl)-4-methoxybenzene ((*E*)-9ba): Prepared from reaction of ACP **5b** (32 mg, 0.2 mmol) and 4-octyne (25 mg, 0.23 mmol) and with optimized condition using [L1]$CoBr_2$, stirred for 3 h, followed by purification by column chromatography (hexanes/ethyl acetate = 95:5) afforded title compound (28 mg, yield 52%) as a yellow oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.14 (m, 1H), 3.81 (s, 3H), 2.81 (sxt, *J* = 2.8 Hz, 2H), 2.48 (t, *J* = 5.4 Hz), 2.25 (t, *J* = 7.2 Hz, 2H), 2.23 (t, *J* = 7.4 Hz, 2H) 1.55-1.42 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 148.5, 147.0, 139.2, 132.4, 129.2, 114.6, 113.9, 55.4, 33.9, 31.8, 29.2, 27.1, 22.2, 21.6, 14.6, 14.4, 1.2.

GC (Methyl silicone. 120 °C, 3 min, 20 °C/min to 250 °C): R_t = 9.05 min.

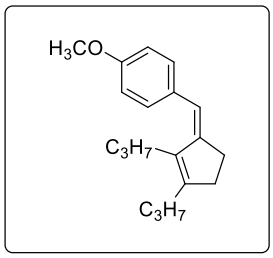
GC-MS: m/z [M^+] = 270.25, exact mass calculated for $C_{19}H_{26}O$: 270.20.

Absolute configuration assigned as (*E*) by NOE-enhanced 1D ^{1}H NMR.

^{1}H Selective NOE Data of 9ba



Irradiation	Intensity Increases
H_1	H_4 (δ 7.35, 4.33%), H_6 (δ 2.25, 6.03%), H_7 (δ 1.50, 2.19%)
H_2	H_4 (δ 7.35, 3.87%), H_8 (δ 3.81, 2.32%)
H_3	H_4 (δ 7.35, 5.95%), H_5 (δ 2.51, 4.68%)
H_4	H_1 (δ 6.16, 1.63%), H_2 (δ 6.87, 3.99%), H_3 (δ 2.81, 3.36%)

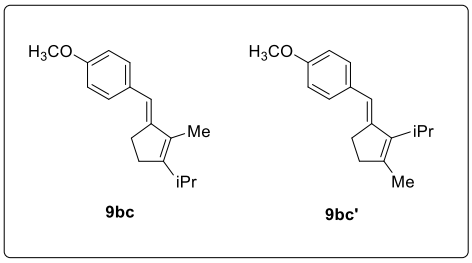


(*Z*)-1-((2,3-dipropylcyclopent-2-en-1-ylidene)methyl)-4-methoxybenzene ((*Z*)-9ba): Prepared from reaction of 1b (32 mg, 0.2 mmol) and 2a (25 mg, 0.23 mmol) and with optimized conditions using [L1]$CoBr_2$ in toluene, stirred for 3 h, followed by purification by column chromatography (hexanes/ethyl acetate = 95:5) afforded title compound (rr 94:6, 26 mg, yield 48%) as a yellow oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 0.6H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.23 (m, 1H), 3.80 (s, 3.7H), 2.62 (td, *J* = 6.2 Hz, 2.0 Hz 2H), 2.35 (m, 2.7H), 2.15 (t, *J* = 7.7 Hz, 2.5H), 1.92 (t, *J* = 7.9 Hz, 2H) 1.50-1.40 (m, 2.9H), 1.02-0.94 (m, 2.9H). 0.91 (t, *J* = 7.3 Hz, 3.5H), 0.47 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 151.3, 148.3, 137.8, 132.1, 130.3, 127.8, 115.4, 113.0, 55.4, 33.7, 32.7, 31.8, 28.2, 22.3, 21.4, 14.6, 14.4.

GC (Methyl silicone. 120 °C, 3 min, 20 °C/min to 250 °C): R_t = 8.16 (67% major isomer) and 9.06 (minor isomer).

GC-MS: m/z [M^+] = 270.3, exact mass calculated for $C_{19}H_{26}O$: 270.20.

Absolute configuration assigned as (*Z*) by analogy.

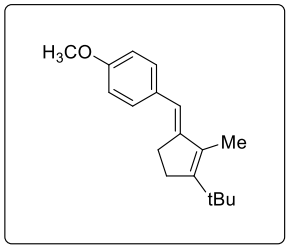


(E)-1-((3-isopropyl-2-methylcyclopent-2-en-1-ylidene)methyl)-4-methoxybenzene (9bc): Prepared from reaction of ACP **5b** (32 mg, 0.2 mmol) and 4-methyl-2-pentyne (19 mg, 0.23 mmol) and with optimized condition using [L1]$CoBr_2$, stirred for 3 h, followed by purification by column chromatography (hexanes/ethyl acetate = 95:5) afforded title compound (rr 81:19, 29 mg, yield 59%) as a yellow oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 2.53H), 6.87 (m, 2.57H), 6.69 (quin, 1H), 6.26 (m, 0.23H), 6.11 (m, 1H), 3.81 (s, 3.62H), 2.92 (m, 1.32H), 2.79 (m, 2.61H), 2.50 (m, 2H), 2.43 (m, 0.5H), 1.89 (s, 0.72H), 1.79 (t, *J* = 1.95 Hz, 3H), 1.26 (d, *J* = 7.2 Hz, 1.78H) 1.06 (d, *J* = 6.87 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 152.2, 149.9, 148.2, 143.4, 141.9, 132.9, 132.4, 132.3, 129.3, 129.1, 114.9, 114.8, 113.9, 113.8, 55.4, 37.4, 29.5, 28.8, 28.0, 25.8, 21.3, 21.1, 16.0, 10.3.

GC (Methyl silicone. 120 °C, 3 min, 20 °C/min to 250 °C): R_t = 8.08 min (17% minor isomer) and 8.38 (78% major isomer).

GC-MS: m/z [M^+] = 242.18, exact mass calculated for $C_{17}H_{22}O$: 242.17.

Absolute configuration assigned as (*E*) by analogy.



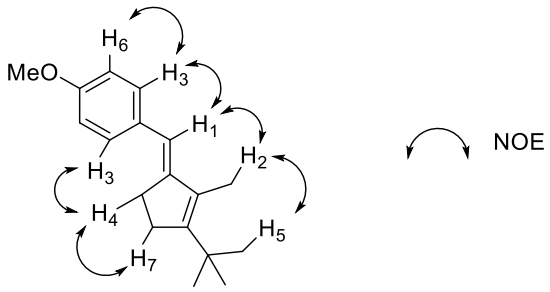
(E)-1-((2-(tert-butyl)-3-methylcyclopent-2-en-1-ylidene)methyl)-4-methoxybenzene (9bd): Prepared from reaction of ACP **5b** (32 mg, 0.2 mmol) and 4,4-dimethyl-2-pentyne (22 mg, 0.23 mmol) and with optimized condition using [L1]$CoBr_2$, stirred for 3 h, followed by purification by column chromatography (hexanes/ethyl acetate = 95:5) afforded title compound (rr

= 100:0, 26 mg, yield 51%) as a pale-yellow oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2.65H), 6.16-6.12 (m, 1H), 5.90-5.87 (m, 0.09H), 3.83-3.80 (s, 3.82H), 2.91-288 (m, 0.11H), 2.79-2.73 (m, 2H), 2.69-2.66 (m, 0.21H), 2.63-2.56 (m, 2H), 2.13 (s, 0.31H), 2.03 (s, 0.36H), 1.96 (t, *J* = 1.9 Hz, 3H), 1.26 (s, 0.91H), 1.24 (s, 9.70H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 153.9, 151.2, 133.3, 132.4, 129.2, 114.3, 113.9, 55.4, 34.0, 33.4, 30.2, 28.7, 12.6. GC (Methyl silicone. 120 °C, 3 min, 20 °C/min to 250 °C): R_t = 7.71 min (16% minor isomer) and 8.83 (75% major isomer).

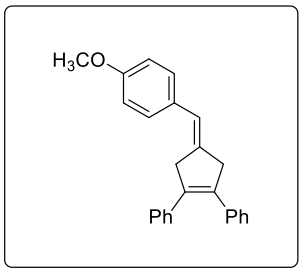
GC-MS: m/z [M^+] = 256, exact mass calculated for $C_{18}H_{24}O$: 256.18.

Absolute configuration assigned as by NOE-enhanced 1D ^{1}H NMR.

^{1}H Selective NOE Data of 9bd



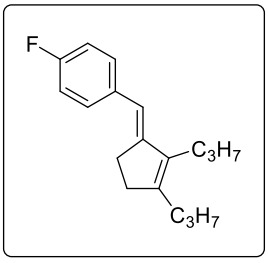
Irradiation	Intensity Increases
H_1	H_2 (δ 1.98, 6.40%), H_3 (δ 7.35, 3.81%)
H_2	H_1 (δ 6.16, 2.11%), H_5 (δ 1.26, 1.28%)
H_3	H_1 (δ 6.16, 1.92%), H_4 (δ 2.78, 3.44%), H_6 (δ 6.90, 4.23%),
H_4	H_3 (δ 7.35, 4.39%), H_7 (δ 2.62, 4.27%)



(4-(4-methoxybenzylidene)cyclopent-1-ene-1,2-diyl)dibenzene (9be): Prepared from reaction of ACP **5b** (32 mg, 0.2 mmol) and diphenylacetylene (41 mg, 0.23 mmol) and with optimized condition using [L1]$CoBr_2$, stirred for 3 h, followed by purification by column chromatography (hexanes/ethyl acetate = 95:5) afforded title compound (xx mg, yield --%) as a yellow oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.32 (m, 0.79H), 7.24-7.18 (m, 0.63H), 7.17-7.09 (m, 4.46H), 7.08-7.01 (m, 2.12H), 7.00-6.80 (m, 5.90H), 6.57 (d, *J* = 8.7H, 2H), 6.50 (s, 1H), 6.33 (d, *J* = 8.7 Hz, 2H), 6.00 (s, 0.21H), 3.81 (s, 0.75H), 3.65 (s, 3H), 3.13 (s, 0.90H), 2.97 (s, 4H), 1.45 (s, 0.11H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 146.7, 143.3, 139.9, 137.7, 137.0, 136.7, 131.6, 130.0, 129.9, 129.8, 129.6, 129.4, 128.7, 128.4, 127.9, 127.6_5, 127.6_1, 127.2, 126.9, 126.2, 120.2, 119.7, 113.8, 112.2, 55.3, 55.2, 35.0, 34.7, 33.8, 29.5.

GC (Methyl silicone. 120 °C, 3 min, 20 °C/min to 250 °C): R_t = 11.51 min (88% major isomer) and 11.86 (12% minor isomer).

GC-MS: m/z [M^+] = 338.17, exact mass calculated for $C_{25}H_{22}O$: 338.17.



(E)-1-((2,3-dipropylcyclopent-2-en-1-ylidene)methyl)-4-fluorobenzene (9ca): Prepared from reaction of 1b (30 mg, 0.2 mmol) and 2a (25 mg, 0.23 mmol) and with optimized condition using [L1]$CoBr_2$, stirred for 3 h, followed by purification by column chromatography (hexanes = 100%) afforded title compound (26 mg, 50%) as a yellow oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 2H), 7.00 (t, *J* = 8.8 Hz, 2H), 6.14 (m, 1H), 2.81 (sxt, *J* = 2.7 Hz, 2H), 2.49 (t, *J* = 5.4 Hz), 2.24 (m, 2H), 1.54-1.42 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 148.2, 139.1, 135.6_3, 135.6_0, 129.4_3, 129.3_5, 115.3, 115.1, 114.1, 33.9, 31.9, 29.3, 27.1, 22.2, 21.6, 14.6, 14.4.

GC (Methyl silicone. 120 °C, 3 min, 20 °C/min to 250 °C): 7.802 min.

GC-MS: m/z [M^+] = 258.24, exact mass calculated for $C_{18}H_{23}F$: 258.18.

Absolute configuration assigned as (*E*) by analogy.

3.7: References

1. Nordvik, T.; Mieusset, J.-L.; Brinker, U. H. Regioselective Formation of Alkylidenecyclopropanes from 2-Substituted Cyclobutylidenes Generated from Geminal Dibromocyclobutanes and Methyllithium†. *Org. Lett.* **2004**, *6* (5), 715–718.

2. Kippo, T.; Hamaoka, K.; Ryu, I. Bromine Radical-Mediated Sequential Radical Rearrangement and Addition Reaction of Alkylidenecyclopropanes. *J. Am. Chem. Soc.* **2013**, *135* (2), 632–635.

3. Leškovskis, K.; Gulbe, K.; Mishnev, A.; Turks, M. Ring Opening of Methylenecyclopropanes with Halides in Liquid Sulfur Dioxide. *Tetrahedron Lett.* **2020**, *61* (46), 152528.

4. Zhu, Z.-Z.; Chen, K.; Yu, L.-Z.; Tang, X.-Y.; Shi, M. Copper(I)-Catalyzed Intramolecular Trifluoromethylation of Methylenecyclopropanes. *Org. Lett.* **2015**, *17* (24), 5994–5997.

5. Nordvik, T.; Brinker, U. H. Thermolysis of 1-(1-Aryl-1-Bromomethyl)Cyclopropyl Bromides: A Reinvestigation. *J. Org. Chem.* **2003**, *68* (18), 7092–7093.

6. Kristensen, S. K.; Laursen, S. L. R.; Taarning, E.; Skrydstrup, T. Ex Situ Formation of Methanethiol: Application in the Gold(I)-Promoted Anti-Markovnikov Hydrothiolation of Olefins. *Angew. Chem. Int. Ed.* **2018**, *57* (42), 13887–13891.

7. Tani, K.; Behenna, D. C.; Mcfadden, R. M.; Stoltz, B. M. A Facile and Modular Synthesis of Phosphinooxazoline Ligands. *Org. Lett.* **2007**, *9* (13), 2529–2531.

8. Hong, A. Y.; Bennett, N. B.; Krout, M. R.; Jensen, T.; Harned, A. M.; Stoltz, B. M. Palladium-Catalyzed Asymmetric Alkylation in the Synthesis of Cyclopentanoid and Cycloheptanoid Core

Structures Bearing All-Carbon Quaternary Stereocenters. *Tetrahedron* **2011**, *67* (52), 10234–10248.

9. Jing, S. M.; Balasanthiran, V.; Pagar, V.; Gallucci, J. C.; Rajanbabu, T. V. Catalytic Enantioselective Hetero-Dimerization of Acrylates and 1,3-Dienes. *J. Am. Chem. Soc.* **2017**, *139* (49), 18034–18043.

10. Chen, X.-W.; Zhu, L.; Gui, Y.-Y.; Jing, K.; Jiang, Y.-X.; Bo, Z.-Y.; Lan, Y.; Li, J.; Yu, D.-G. Highly Selective and Catalytic Generation of Acyclic Quaternary Carbon Stereocenters via Functionalization of 1,3-Dienes with CO2. *J. Am. Chem. Soc.* **2019**, *141* (47), 18825–18835.