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The Ligand Effects in the Rhodium Catalyzed 1,4-Addition Reaction of Terminal Alkynes to ???-Unsaturated Ketones

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The Ligand Effects in the Rhodium Catalyzed 1,4-Addition Reaction of Terminal Alkynes to α,β-Unsaturated Ketones

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APPROVED

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Abstract:

Ligand effects play an important role in reactivity and selectivity in many transition metal catalyzed processes. The role of the phosphine ligand is critical to the product ratio in rhodium-catalyzed reaction of methyl vinyl ketone and terminal alkynes. For a ligand with a hemilabile oxygen on the phosphine, smaller ligands shift the product ratio in favor of the 1,4-addition product while with bulky oxygen ligands a dimerization/addition product manifold is dominant. Ligand screen results show that tri-*o*-tolylphosphine (TOTP) provided the best yields and highest selectivity for dimer-addition product.

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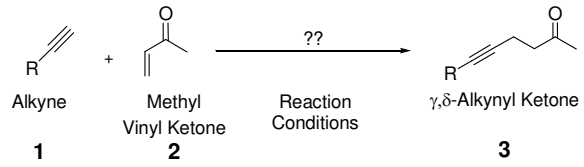
Introduction:

Carbon-carbon bond formation is an essential part of organic chemistry. While much progress has been made in this area, some types of carbon-carbon bond formation are still problematic. One such problematic area is the 1,4–addition of terminal alkynes **1** to α,β-unsaturated ketones **2** to yield γ,δ-alkynyl ketones **3** as seen in Scheme 1.

Scheme 1



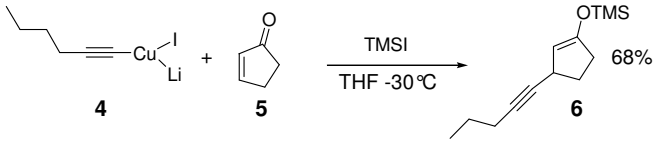
Products such as **3** are useful as intermediates in the synthesis of prescription drugs, natural products and other interesting organic molecules.

Background:

Recognizing this limitation, organic chemists have made efforts to solve this synthetic problem. Notable are the efforts of Bergdahl, who was quite successful in carrying out such a reaction (Scheme 2).[1] Although the reaction was successful in producing the desired product in moderate yield, there are many aspects to this reaction that make it less than optimal. For example, a stoichiometric amount of copper is needed to activate the alkyne in order for the addition to occur. At the completion of the reaction, the copper is not present in product **6** but remains as byproduct. As a result, appropriate measures must be taken in order to safely dispose of the copper waste. This precaution requires both time and financial resources. The reaction also requires a stoichiometric amount

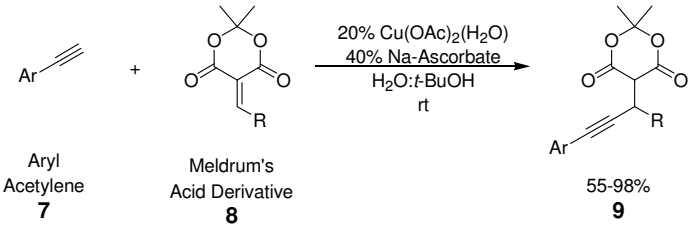
of trimethylsilyl iodide (TMSI). TMSI promotes side-reactions with starting materials that contain ethers and/or acetals. This limits the scope of the useful starting materials.

Scheme 2



Aware of the disadvantages of the use of an alkyne/copper regeant in this type of chemistry, Carreira developed a similar reaction where under specific conditions copper acetate catalyzed the addition of aryl acetylene **7** to Meldrum's acid derivatives **8** (Scheme 3).[2]

Scheme 3

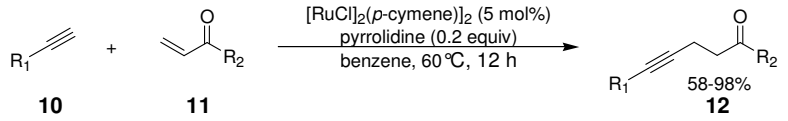


This reaction is environment friendly in the sense that it does not generate stoichiometric amounts of copper waste. In addition, it is a cost-effective reaction using a commercially available and inexpensive catalyst. The drawback of this reaction is that the selection of starting materials is somewhat limited for it requires the use of aryl acetylene **7** and Meldrum's acid derivatives **8**. However, it is not a practical method for synthesis of compounds that do not contain aryl acetylene or a Meldrum's acid derivative.

In 2001, Chang made significant progress in solving this synthetic problem by showing that the ruthenium complex [RuCl(*p*-cymene)]$_2$ in the

presence of an amine base is a useful catalyst for the addition of terminal alkyne **10** to α,β-unsaturated ketone **11** (Scheme 4).[3]

Scheme 4

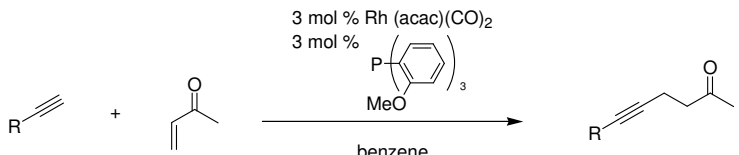


10 **11** **12**

This particular method did not use stoichiometric amounts of a metal and the reaction conditions were generally mild. In contrast to Carreira's copper acetate method, the ruthenium reaction is tolerant to a variety of functional groups, allowing the reaction to occur in the presence of silyl, cyano, halide, alkenyl, carbonyl and alcohol substituted alkynes. The reaction can be performed on methyl, ethyl, and phenyl vinyl ketones. The drawback is in the presence of an alcohol the overall yield of the γ-alkynyl ketones product decreases to moderate yield. The reaction has yet to be applied in the presence of esters.

In an effort to find an improved system, Lerum[4] searched for a method that was just as effective as the reaction carried out by Chang.[3] Building upon a rhodium-catalyzed reaction developed by Kovalev,[5] Lerum found that $Rh(acac)(CO)_2$ (acac = acetylacetonoate) and tris-*o*-methoxyphenylphosphine catalyzed the reaction with methyl vinyl ketone (Scheme 5).

Scheme 5

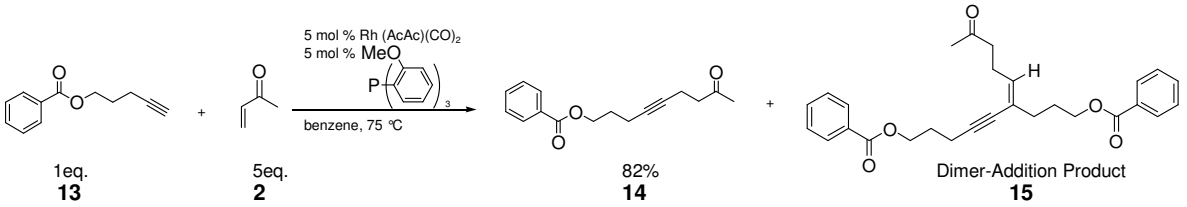


1 eq. 5 eq.
1 **2** **3**

The yields of the desired product varied greatly when various types of phosphine ligands were used in the reaction. A ligand is a compound that coordinates to a metal catalyst preventing it from decomposing. A ligand also affects reactivity of the catalyst as seen in this reaction. The rhodium complex, Rh (acac)$(CO)_2$, in the presence of the tris-*o*-methoxyphenylphosphine gave the best yield compared to other ligands.[4]

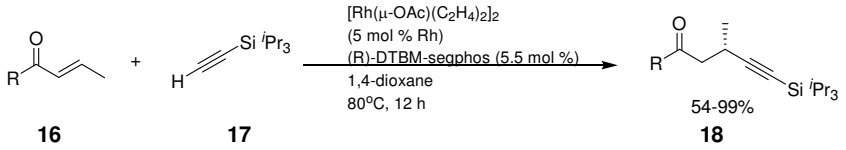
This reaction has the potential to be a very useful method for several reasons. It incorporates the use of catalytic amount of metal as opposed to the larger stoichiometric amounts. It produces less chemical waste and protects the environment because all the atoms present in the starting material are present in the product. Beneficially, this reaction works well with a variety of functional groups. Under the described conditions, it will produce good yields of product in the presence of a halide, alcohol, ester or cyano substituted alkyne, which eliminates the need of protecting groups. In addition, the reaction yields another interesting product, dimer-addition product **15**, which results from two carbon-carbon bond forming events involving two alkynes and one vinyl ketone (Scheme 6).

Scheme 6



More recently, Hayashi developed a rhodium-catalyzed method using (triisopropylsilyl)acetylene **17** with DTBM-segphos, a chiral ligand, in order to selectively synthesize 1,4-addition product **18** in high yields and high ee (Scheme 7).[6] Hayashi found that the bulky groups on the silicon and ligand hinders the acetylene from reacting to form dimer-addition products. This reaction does not use stoichiometric amounts of the rhodium-metal and the reaction conditions are mild. Hayashi's method can be applied to several types of α,β-unsaturated ketones including enones with aryl, alkenyl or alkyl groups, linear (long chain) enones and cyclic enones. Drawbacks to this reaction are that removal of the silyl requires another step and the reaction has yet to be applied in the presence of alcohols or esters.

Scheme 7



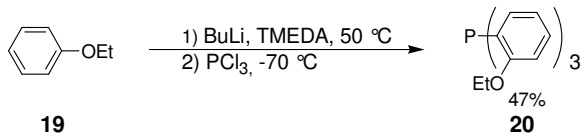
16 **17** **18**

Taking all things into consideration, it became the project goal to synthesize phosphorus, oxygen ligands with various alkoxy groups and determine if there is a trend in the yield of the 1,4-addition product as well as the dimerization-addition product. By modifying the phosphine ligand, the reactivity of the entire reaction is affected possibly increasing the selectivity for one of the products. Although the extent to which the phosphorus, oxygen ligands play a role in the reaction is still unclear, it is known that in many reactions catalyzed by transition metals, the phosphine ligands used greatly affect the yield and selectivity of the reaction. The modification of the ligand in a systematic way will

provide a better understanding of the ligand's role in the overall chemistry of the 1,4-addition reaction and the formation of the dimer-addition product.

Experimental Details:

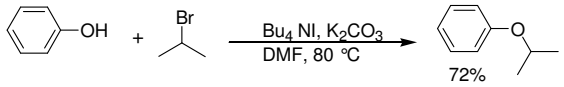
[JEM–I–1]



19 **20**

To a flame dried round-bottomed flask filled with argon, a solution of butyllithium in hexanes (5.64 mL, 1.6 M, 9 mmol) was added followed by TMEDA (1.36 mL, 9 mmol) and ethoxybenzene **19** (1.14 mL, 9 mmol). The mixture was then warmed in an oil bath (45-50 ºC) while stirring for 40 minutes. After the warming, the mixture was removed from the bath, dry THF (5.3 mL) was added and the solution was cooled to –78 ºC using a dry ice/acetone bath. To the resultant mixture, PCl_3 (0.26 mL, 3 mmol) was then added to the cold solution. After 30 minutes, the mixture was then transferred to a separatory funnel and the reaction was then quenched by the addition of 1 M HCl (25 mL). After the addition of diethyl ether to the separatory funnel, the layers were separated and the aqueous layer was extracted with Et_2O three times. The combined ether extracts were then dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude oil. This oil was then purified using silica gel column chromatography using 10% acetone/hexane as the solvent system. TLC was performed on the fractions, and the ones that contained the desired product were combined and concentrated *in vacuo*. This afforded 0.552g (47 %) of JEM–I–1 (phosphine ligand **20**). This procedure is modified from work performed by Brandsma.[7]

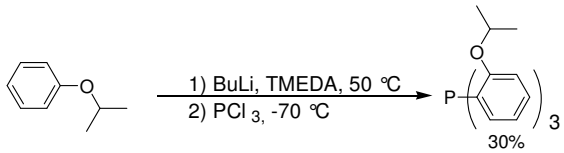
[JEM–I–3]



21 **22** **23**

To a round-bottomed flask filled with argon, 40 ml of DMF, phenol **21** (2.00 g, 21.2 mmol), Bu_4NI (0.786 g, 2.13 mmol) and K_2CO_3 (7.06 g, 51.2 mmol) was added. The mixture was then warmed in an oil bath (80ºC) while stirring. 2-Bromopropane **22** (21.2 mmol, 2 mL) was then added to the flask. The resultant mixture was warmed for 33 h. After warming, the mixture was removed from the bath, and diluted with Et_2O. The mixture was then transferred to a separatory funnel and washed with water and brine twice. The combined extracts were concentrated *in vacuo* to give a crude product. This product was purified using silica gel column chromatography using 6% ethyl acetate/hexane as the solvent system. TLCs were performed on the fractions, and the ones that contained the desired product were combined and concentrated *in vacuo*. This afforded 2.098 g (72 %) of JEM–I–3 (alkoxy benzene **23**). This procedure is modified from work performed by Pasquini.[8]

[JEM–I–4]

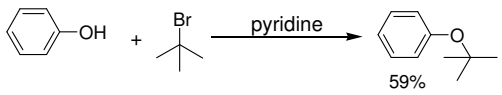


23 **24**

To a flame-dried round-bottomed flask filled with argon, a solution of butyl lithium (5.64 ml, 9 mmol) was added followed by TMEDA (1.36 mL, 9

mmol) and alkoxy benzene **23** (1.23 mL, 9 mmol). The mixture was then warmed in an oil bath (45 ºC) while stirring for 106 minutes. After the warming, the mixture was removed from the bath, dry THF (6 mL) was added and the solution was cooled to –78 ºC using a dry ice/acetone bath. To the resultant mixture, PCl_3 (0.25 mL, 3 mmol) was then added to the cold solution. After 30 minutes, to a separatory funnel and the reaction was then quenched by the addition of 1 M HCl (25 mL). After the addition of diethyl ether to the separatory funnel, the layers were separated and the aqueous layer was extracted with Et_2O thrice. The combined ether extracts were then dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give crude yellow oil. This oil was the purified using silica gel column chromatography using 10% acetone/hexane as the solvent system. TLCs were performed on the fractions, and the ones that contained the desired product were combined and concentrated *in vacuo*. This afforded 0.39 g (30 %) of JEM–I–4 (phosphine ligand **24**). TLC R_f = 0.4 (5% acetone: hexanes). IR: 3057, 2979, 2932 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.9 Hz, 3H), 6.89-6.99 (m, 3H), 6.86 (dd, *J* = 7.2, 4.0 Hz, 3H), 6.81 (t, *J* = 7.2 Hz, 3H), 4.51 (sp, *J* = 6.0 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 18H).

[JEM–I–6]

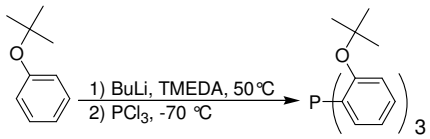


21 **25** **26**

To a round-bottomed flask filled with argon and a magnetic stirrer, phenol **21** (19.3 g, 200 mmol) was added. Then pyridine (1.58 g, 20 mmol) and t-butyl

bromide **25** (2.25 mL, 20 g) were added to the cooled solid. The mixture was then warmed in an oil bath (30 ºC) while stirring. The resultant mixture was warmed for 1h and 38 minutes. After warming, the mixture was removed from the bath, and combined with water/ethylene glycol mixture (50 mL). After the addition, the mixture was transferred to a separatory funnel and washed with pentane (40 mL), the layers were separated and the bottom aqueous layer was extracted again with pentane. The combined organic extracts were washed with 5 % NaOH (45 mL) once and distilled water (45 mL) twice. The combined ether extracts were then dried with sodium sulfate, filtered, and concentrated *in vacuo* to give a crude product liquid. This liquid was the purified using silica gel column chromatography using 3 % acetone/hexane as the solvent system. TLCs were performed on the fractions, and the fractions that contained the desired product were combined and concentrated *in vacuo*. This afforded 1.78g (59 %) of JEM–I–6 (alkoxy benzene **26**). This molecule is referenced from work performed by Masada.[9]

[JEM–I–8B]

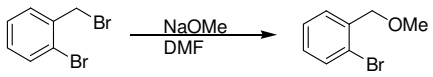


26 **27** 27%

To a flame dried round-bottomed flask filled with argon, a solution of butyl lithium in hexanes (4.1 mL, 1.6 M, 9 mmol) was added followed by TMEDA (1.36 mL, 9 mmol) and aryl ether **26** (1.35 g, 9 mmol). The mixture was

then warmed in an oil bath (45-50 ºC) while stirring for 70 minutes. After the warming, the mixture was removed from the bath, 6.0 mLof dry THF was added and the solution was cooled to –78 ºC using a dry ice/acetone bath. To the resultant mixture, PCl_3 (0.26 mL, 3 mmol) was then added to the cold solution. After 110 minutes, the mixture was then transferred to a separatory funnel and the reaction was then quenched by the addition of 1 M HCl (25 mL). After the addition of diethyl ether to the sep. funnel, the layers were separated and the aqueous layer was extracted and washed in Et_2O thrice. The combined ether extracts were then dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a crude oil. This oil was then purified using silica gel column chromatography using 3% acetone/hexane as the solvent system. TLCs were performed on the fractions, and the ones that contained the desired product was combined and concentrated *in vacuo*. This afforded 0.92 g (64 %) of JEM-1-8. This oil was then purified using silica gel column chromatography again using 5% EtOAc/hexane as the solvent system. TLC were performed on the fractions, and the one's that contained the desired product was combined, concentrated *in vacuo*. This afforded 0.39 g (27 %) of JEM-I-8B (phosphine ligand **27**). TLC R_f = 0.46 (5% ethyl acetate: hexanes). IR: 3057, 2978, 2932 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.17-7.24 (m, 3H), 6.98-7.07 (m, 3H), 6.84 (td, *J* = 7.5, 0.9 Hz, 3H), 6.66 (ddd, *J* = 7.8, 5.1, 1.8 Hz, 3H), 1.39 (s, 27H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8 (d, *J* = 17.7 Hz), 134.6, 128.7, 121.9, 119.3, 79.2, 29.3. This molecule is referenced in work performed by Sarraf.[10]

[JEM–I–15]

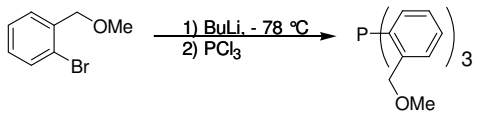


98%

28 **29**

To a flame dried round-bottomed flask filled with argon, DMF (20 ml) was added followed by sodium methoxide (3.3 g, 60 mmol) then placed in a water bath. 2-Bromobenzyl bromide **28** (3 g, 12.0 mmol) was then added and allowed to stir for 2 hours. The mixture was then transferred to a separatory funnel and the reaction was then quenched by the addition of 100 ml of ethyl acetate. After the addition of ethyl acetate to the separatory funnel, the layers were separated and the organic layer was extracted and washed in H_2O (50 mL) twice and brine once. The combined organic extracts were then dried with $NaSO_4$, filtered, and concentrated *in vacuo* to give a crude oil. This oil was then purified using silica gel column chromatography using 3% ethyl acetate/hexane then 10% ethyl acetate/hexane as the solvent system. TLCs were performed on the fractions, and the ones that contained the desired product were combined and concentrated *in vacuo*. This afforded 2.355 g (98 %) of JEM–I–15 (ether **29**). This procedure is modified from work performed by Reich.[11]

[JEM–I–16]



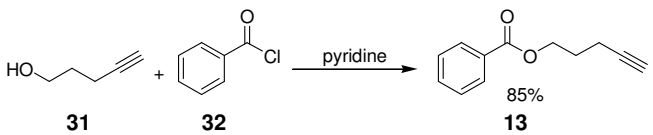
44%

29 **30**

To a flame dried round-bottomed flask filled with argon, dry diethyl ether (20 mL) was added followed by ether **29** (1.18 g, 5.86 mmol) then the solution

was cooled to –78 ºC using a dry ice/acetone bath. Then a solution of butyllithium in hexanes (2.55 mL, 2.2 M, 5.63 mmol) was added and allowed to stir for 120 minutes. To the resultant mixture, PCl_3 (0.26 mL, 3 mmol) was added to the cold solution. After the stirring, the mixture was warmed to room temperature and stirred overnight. The mixture was then placed in an ice bath and ammonium chloride (3 mL) was added. The mixture was warmed to room temperature. Afterward, the mixture was then transferred to a separatory funnel and the reaction was then quenched by the addition of water (30 mL). After the addition of diethyl ether (30 ml) to the separatory funnel, the layers were separated and the aqueous layer was extracted and washed in Et_2O thrice. The combined ether extracts were then dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude oil. This oil was then purified using silica gel column chromatography using 6% ethyl acetate/hexane then 9% ethyl acetate/hexane as the solvent system. TLC were performed on the fractions, and the ones that contained the desired product was combined and concentrated *in vacuo*. This afforded 0.33 g (44 %) of JEM–I–16 (phosphine ligand **30**). This molecule is referenced in work performed by Letsinger.[12]

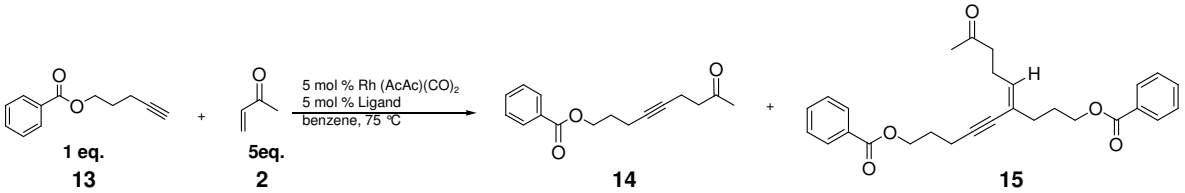
[JEM–I–17]



To a flame dried round-bottomed flask filled with argon, 4-pentyn-1-ol **31** (1.060 g, 12.60 mmol) was dissolved in pyridine (6 mL). Then benzoyl chloride

32 (1.46 mL, 12.60 mmol) was added and the mixture was allowed to stir overnight. The mixture was then transferred to a separatory funnel with ethyl acetate (200 mL). After the addition of ethyl acetate to the separatory funnel, the layers were separated and the organic layer was extracted and washed in 1 M HCl (25 mL). The combined organic extracts were then dried with $NaSO_4$, filtered, and concentrated *in vacuo* to give a crude oil. This oil was then purified using silica gel column chromatography using 10% ethyl acetate/hexane as the solvent system. TLCs were performed on the fractions, and the ones that contained the desired product was combined and concentrated *in vacuo*. This afforded 2.018 g (85 %) of JEM–I–17 (alkyne **13**). TLC R_f = 0.44 (15% ethyl acetate:hexanes). IR (neat): 3299, 2959, 2117, 1720, 1113cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.56 (tt, *J* = 7.5, 1.4 Hz, 1H), 7.44 (tt, *J* = 7.7, 1.5 Hz, 2H), 4.44 (t, *J* = 6.3 Hz, 2H), 2.39 (dt, *J* = 7.0, 2.6 Hz, 2H), 2.05-1.98 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 132.9, 130.3, 129.6, 128.4, 83.1, 69.5, 63.5, 27.7, 15.4. Anal calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.39; 6.37.

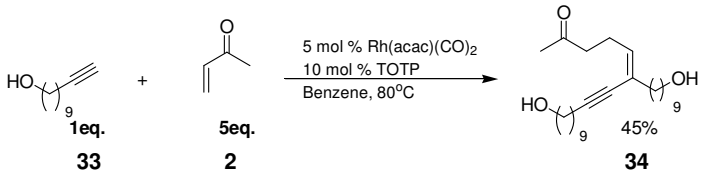
The phosphine ligands that were synthesized were applied in a ligand screen which followed this general procedure:



To reaction tube #1 $Rh(acac)(CO)_2$ (0.025mmol) and **phosphine ligand** (0.025 mmol) was added and then placed under argon and warmed to 75 ºC in an silicone

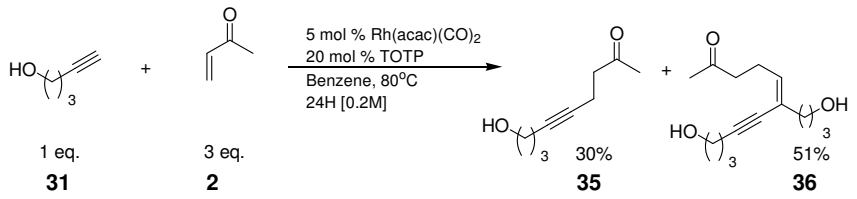
oil bath. To reaction tube #2 alkyne **13** (94.5 mg, 0.5 mmol) and methyl vinyl ketone **2** (175.23 mg, 2.5 mmol) were added and then placed under argon. To reaction tube #2 1 ml of benzene was added. The mixture was then transferred to reaction tube #1. The reaction mixture was then sealed and stirred at 75 ºC for 24 hours. The reaction mixture was then preabsorbed on silica gel and purified by silica gel column chromatography by a gradient using 20-30% ethyl acetate/hexane as the solvent system. TLCs were performed on the fractions, and the ones that contained the desired products was combined separately and concentrated *in vacuo*. This afforded products **14** and **15**. Product **14**: TLC R_f = 0.36 (20% ethyl acetate: hexanes). IR (neat): 2921, 1717, 1274, 1116 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.06-8.01 (m, 2H), 7.55 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.43 (tt, *J* = 7.2, 1.5 Hz, 2H), 4.39 (t, *J* = 6.3 Hz, 2H), 2.61 (t, *J* = 6.9 Hz, 2H), 2.42-2.29 (m, 4H), 2.15 (s, 3H), 1.93 (p, *J* = 6.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1, 166.7, 133.1, 130.5, 129.8, 128.5, 79.7, 79.4, 63.9, 43.0, 30.1, 28.3, 15.8, 13.5. HRMS (EI): *m/z* calcd for $C_{16}H_{18}O_3Na$ (M+Na) 281.1148. Found: 281.1151. Product **15**: TLC R_f = 0.32 (20% ethyl acetate: hexanes). IR (neat): 1717, 1274, 1116 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.05-8.01 (m, 4H), 7.56-7.51 (m, 2H), 7.46- 7.40 (m, 4H), 5.63 (broad, 1H), 4.42 (t, *J* = 6.2 Hz, 2H), 4.30, (t, *J* = 6.4 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.48 (d, *J* = 3.4 Hz, 4H), 2.23 (t, *J* = 7.3 Hz, 2H), 2.11 (s, 3H), 2.01 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 135.3, 133.1, 133.0, 129.7, 128.5, 123.3, 94.0, 79.2, 64.3, 63.8, 43.2, 34.0, 28.3, 27.6, 24.9, 16.6. HRMS (EI): *m/z* calcd for $C_{28}H_{30}O_5Na$ (M+Na) 469.1990. Found: 469.1988.

[JEM–I–49]



To a round-bottom flask $Rh(acac)(CO)_2$ (0.05 mmol) and TOTP (0.1 mmol) was added and then placed under argon with reflux condenser. To a reaction tube 10-undecyn-1-ol **33** (168.3 mg, 1 mmol) and methyl vinyl ketone **2** (350.5 mg, 5 mmol) were added. To the reaction tube, benzene (1 mL) was added. The mixture was then transferred from the reaction tube to the round-bottom flask. The reaction mixture stirred under argon at 75 ºC for 24 h. The reaction mixture was diluted in chloroform then preabsorbed on silica gel and purified by silica gel column chromatography using 70 and 80% ethyl acetate/hexane as the solvent system. TLCs were performed on the fractions, and the ones that contained the desired products was combined separately and concentrated *in vacuo*. This afforded 45% (91 mg) of product **34**. Product **34**: TLC R_f = 0.39 (80% ethyl acetate: hexanes). IR (neat): 3431, 2925, 2851, 1703, 1062 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (t, *J* = 6.8Hz, 1H), 3.62 (t, *J* = 6.6Hz, 4H), 2.49 (bs, 4H), 2.33 (t, *J* = 6.8Hz, 2H), 2.13 (s, 3H), 2.03 (t, *J* = 6.4Hz, 2H), 1.57-1.45 (m, 10H), 1.35-1.23 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 133.4, 125.031, 95.2, 78.8, 62.8, 62.8, 43.3, 37.5, 32.8, 29.8, 29.6, 29.5, 29.4, 29.2, 29.0, 28.9, 28.8, 28.5, 27.2, 25.8, 24.9, 19.5. Anal calc'd for $C_{26}H_{46}O_3$: C, 76.79; H, 11.40. Found: C, 76.81; H, 11.59.

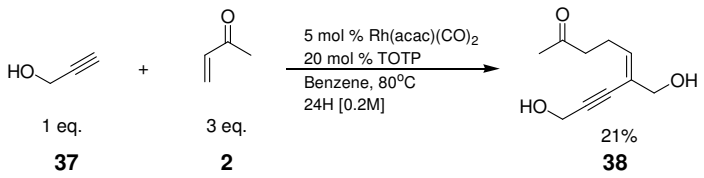
[JEM–I–50] see also [RVL-V-137]



1 eq. **31** 3 eq. **2** 30% **35** 51% **36**

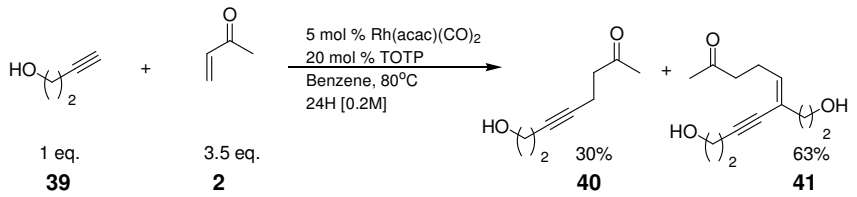
To a round-bottom flask $Rh(acac)(CO)_2$ (21.6 mg, 0.084 mmol) and TOTP (102.3 mg, 0.336 mmol) was added and then placed under argon with reflux condenser. To a reaction tube 4-pentyn-1-ol **31** (145.7 mg, 1.68 mmol) and methyl vinyl ketone **2** (413 µl, 5.04 mmol) were added. To the reaction tube, benzene (1 mL) was added. The mixture was then transferred from the reaction tube to the round-bottom flask. The reaction mixture stirred under argon at 80 ºC for 24 h. The reaction mixture was diluted in chloroform then preabsorbed on silica gel and purified by silica gel column chromatography using 40, 60 and 90% ethyl acetate/hexane and 100% ethyl acetate as the solvent system. TLCs were performed on the fractions, and the ones that contained the desired product were combined and concentrated *in vacuo*. This afforded 30% (78 mg) of product **35** and 51% (101 mg) of product **36**. Product **36**: TLC R_f = 0.26 (100% ethyl acetate). IR (neat): 3397, 2940, 1709, 1055 cm^{-1}. ^{1}H NMR (300 MHz, C_6D_6) δ 5.52 (t, *J* = 6.7Hz, 1H, 3.67 (t, *J* = 6.2Hz, 2H), 3.52 (t, *J* = 6.5Hz, 2H), 3.12 (s, 1H), 2.85 (s, 1H), 2.45-2.36 (m, 6H), 2.07 (s, 5H) 1.75-1.62 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 134.2, 124.1, 94.7, 78.9, 61.8, 61.2, 43.1, 33.6, 31.5, 31.4, 29.9, 24.8, 16.0.

[JEM–I–51d]



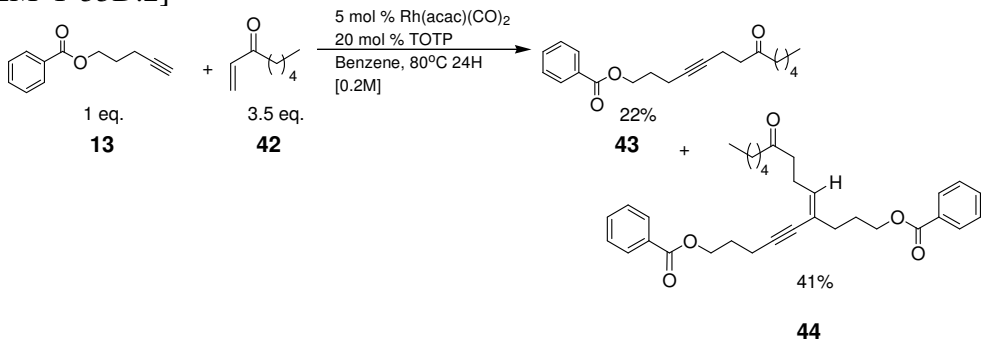
To a round-bottom flask $Rh(acac)(CO)_2$ (28.1 mg, 0.109 mmol) and TOTP (133.3 mg, 0.438 mmol) was added and then placed under argon with reflux condenser. To a reaction tube propargylic alcohol **37** (124 mg, 2.19 mmol) and methyl vinyl ketone **2** (460.5 mg, 6.57 mmol) were added. To the reaction tube, benzene (1 mL) was added. The mixture was then transferred from the reaction tube to the round-bottom flask. The reaction mixture stirred under argon at 80 ºC for 24 hours. The reaction mixture was diluted in chloroform then preabsorbed on silica gel and purified by silica gel column chromatography using 20, 40, 60 and 80% ethyl acetate/hexane and 100% ethyl acetate as the solvent system. TLC were performed on the fractions, and the ones that contained the desired products was combined separately and concentrated *in vacuo*. This afforded 21% (42 mg) of product **38**. Product **38**: TLC R_f = 0.25 (80% ethyl acetate: hexanes). IR (neat): 3445, 2922, 2863, 1707, 1362 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 5.88 (t, J = 6.7Hz, 1H), 4.38 (s, 2H), 4.05 (s, 2H), 3.47 (s, 2H), 2.56-2.47 (m, 4H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 136.6, 123.9, 93.9, 81.8, 65.9, 51.4, 42.7, 30.1, 24.6.

[JEM–I–53] see also [RVL–IV–21]



To a round-bottom flask $Rh(acac)(CO)_2$ (25 mg, 0.095 mmol) and TOTP (115.6 mg, 0.38 mmol) was added and then placed under argon with reflux condenser. To a reaction tube 3-butyn-1-ol **39** (136 mg, 1.9 mmol) and methyl vinyl ketone **2** (545 µl, 6.65 mmol) were added. To the reaction tube, 1 mL of benzene was added. The mixture was then transferred from the reaction tube to the round-bottom flask. The reaction mixture stirred under argon at 80 ºC for 24 h. The reaction mixture was diluted in chloroform then preabsorbed on silica gel and purified by silica gel column chromatography using 3, 10, 50, 80 and 90% ethyl acetate/hexane as the solvent system. TLC were performed on the fractions, and the ones that contained the desired products was combined separately, concentrated *in vacuo*. This afforded 30% (81mg) of product **40** and 63% (125.3 mg) of product **41**. Spectral data for products **40** and **41** is referenced from work performed by Lerum.[13]

[JEM–I–55D.2]

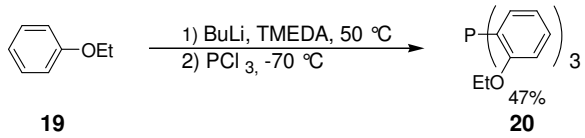


To a round-bottom flask $Rh(acac)(CO)_2$ (10.2 mg, 0.0398 mmol) and TOTP (48.4 mg, 0.159 mmol) was added and then placed under argon with reflux condenser. To a reaction tube alkyne **13** (149.6 mg, 0.795 mmol) and 1-octen-3-one **42** (360.8 mg, 2.78 mmol) were added. To the reaction tube, benzene (1 mL) was added. The mixture was then transferred from the reaction tube to the round-bottom flask. The reaction mixture stirred under argon at 80 ºC for 24 h. The reaction mixture was diluted in chloroform then preabsorbed on silica gel and purified by silica gel column chromatography by a gradient using 3, 10, 50, 70, 80% DCM/hexane, 100% DCM as the solvent system. TLCs were performed on the fractions, and the ones that contained the desired product were combined and concentrated *in vacuo*. Product **44** was purified again using silica gel column with 10 then 20% ethyl acetate/hexane. This afforded 22% (54 mg) of product **43** and 41% (81 mg) of product **44**. Product **44**: TLC R_f = 0.66 (20% ethyl acetate: hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07-8.03 (m, 4H), 7.57-7.53 (m, 2H), 7.43 (td, *J*= 9 Hz, 3 Hz, 4H), 5.65 (t, *J*= 6 Hz, 1H), 4.44 (t, *J*= 6 Hz, 2H), 4.32 (T, *J*= 7.2 Hz, 2H), 2.56 (t, *J*= 6 Hz, 2H), 2.47 (m, 4H), 2.38 (t, *J*= 6 Hz, 2H), 2.25 (t, *J*=6 Hz, 2H), 2.00 (m, 4H), 1.56 (p, *J*=6 Hz, 2H), 1.27 (m, 4H), 0.88 (t, *J*=6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 166.8, 166.7, 135.6, 133.2, 133.0, 130.6, 130.5, 129.8, 129.7, 128.6, 128.5, 123.2, 93.9, 79.3, 64.4, 63.9, 42.9, 42.2, 34.0, 31.6, 28.4, 27.6, 24.9, 23.7, 22.7, 16.7, 14.1.

Results and Discussion:

For the synthesis of JEM–I–1 (phosphine ligand **20**), ethoxybenzene was commercially available so it was not necessary to synthesize. During the reaction, ethoxy benzene was deprotonated at the ortho position by the strong base butyllithium (BuLi). When PCl_3 was added to the system, through an S_N2-like displacement, the electrons of the carbon-lithium bond attacked the phosphorus atom and displaced the one of the chlorine atoms on PCl_3. This reaction continued until ethoxybenzene groups displaced all the chlorine atoms on the phosphorus atom (Scheme 8).

Scheme 8

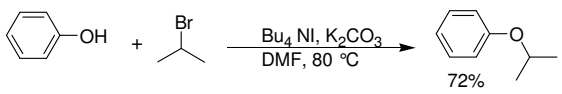


19 **20**

The yield of this reaction was 47% and was an adequate amount needed to test in the rhodium-catalyzed reaction mentioned.

In order to continue in our efforts to change the steric environment around the phosphorus atom, it was necessary to synthesize JEM–I–3 (alkoxy benzene **23**) since it was not commercially available. In order to carry out this synthesis, phenol was used as a nucleophile in the displacement of bromine from 2-bromopropane, shown in Scheme 9.

Scheme 9

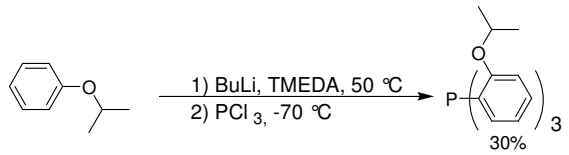


21 **22** **23**

The yield of this reaction was 72%, which was a good amount for the purpose we intend on using it. In order to produce the respective phosphine

ligand, JEM–I–3 (alkoxy benzene **23**) was used as the starting material to react with PCl_3. This second step was carried out under similar conditions as the reaction of ethoxybenzene with PCl_3 as seen below (Scheme 10).

Scheme 10

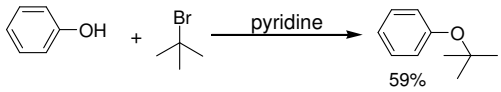


23 **24**

JEM–I–3 (alkoxy benzene **23**) was deprotonated by the strong base butyllithium, producing an ionic carbon-lithium bond. When PCl_3 was added to the system, through an S_N2-like displacement, the electrons of the carbon-lithium interaction attacked the phosphorus atom and displaced the one of the chlorine atoms on PCl_3. This reaction continued until JEM–I–3 (alkoxy benzene **23**) groups displaced all the chlorine atoms on the phosphorus atom. The yield of this reaction was 30%, which was adequate to test in the rhodium-catalyzed reaction.

The subsequent alkoxy benzene synthesized during this project was JEM–I–6 (alkoxy benzene **26**), of which the reaction equation is shown in Scheme 11.

Scheme 11



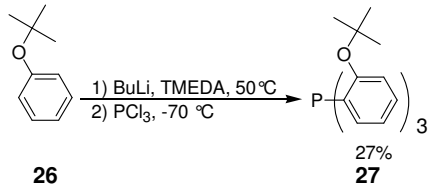
21 **25** **26**

Since alkoxy benzene **26** was not available in the laboratory it was necessary to synthesize. In order to carry out this synthesis, phenol and tert-butyl bromide were used in an S_N1 reaction. The yield of this reaction is 59%.

For the synthesis of JEM–I–8B (phosphine ligand **27**), ether **26** was deprotonated at the ortho position by the strong base BuLi. When PCl_3 was added

to the system, through an S_N2-like displacement, the electrons of the carbon-lithium bond attacked the phosphorus atom and displaced the one of the chlorine atoms on PCl_3. This reaction continued until the ether **26** groups displaced all the chlorine atoms on the phosphorus atom (Scheme 12).

Scheme 12

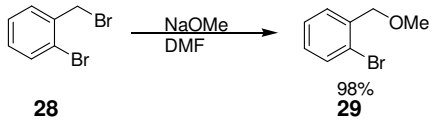


26 **27**

The yield of this reaction was 27% and provided an adequate amount needed to test it in the subsequent ligand screen.

To explore the effect of a ligand with the oxygen atom one carbon away from the aromatic ring, JEM–I–15 (ether **29**) was synthesized as a precursor to that ligand. In order to carry out this synthesis, sodium methoxide was used as a nucleophile in an S_N2 displacement of alkyl bromide **28** (Scheme 13).

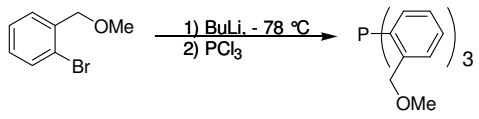
Scheme 13



28 **29**

The yield of this reaction was 98%, an excellent result. The second step of the ligand synthesis, described below, was carried out under similar conditions as the reaction of aryl ether **26** with PCl_3 (Scheme 14). In this case, the aryllithium was prepared by transmetallation of the bromine.

Scheme 14



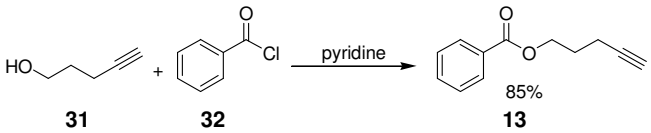
44%

29 **30**

The reaction of the aryllithium continued until JEM–I–15 (ether **29**) groups displaced all the chlorine atoms on the phosphorus atom. The yield of this reaction was 44%, which was adequate to test it in the subsequent ligand screen.

It is reasonable to speculate that there exists a pattern in the yield amongst the alkoxy benzenes, the precursor to the phosphine ligands and the actual ligands and that the trend is due to steric hindrance. The trend shows that by increasing steric hindrance due to the bulk of the functional group on the aromatic ring the yield tends to decrease subsequently as seen with alkoxy benzene **23, 26** and **29** with 72, 59 and 98% yield respectively. The reasoning behind this should be explored in future works. As for the phosphine ligands, the trend due steric hindrance was also present. Coupled with the presence of the phosphine atom and two additional alkoxy ether groups in one molecule the decrease in the yield was more drastic as seen with ligands **20, 24, 27** and **30** with 47, 30, 27 and 44% yield respectively. According to the data, it suggests that larger alkoxy group lowers the yield in the ligand synthesized. In addition to the ligands, it was necessary to synthesize the alkyne substrate previously mentioned in order to apply the ligands for our screening. The synthesis of this alkyne is shown below (Scheme 15).

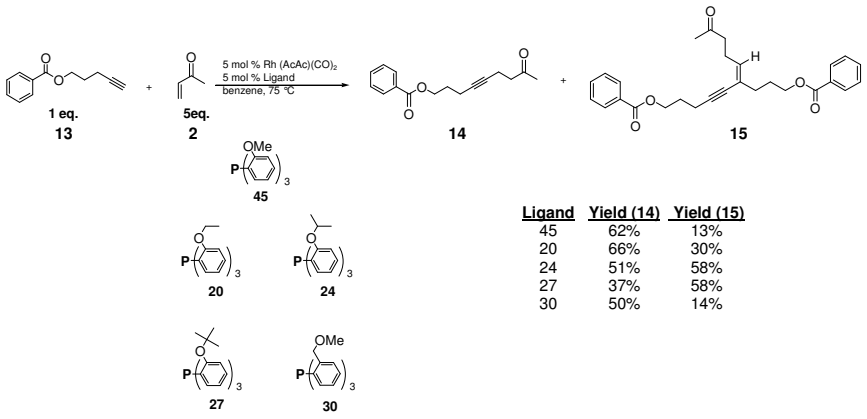
Scheme 15



It was necessary to synthesize JEM–I–17 (alkyne **13**) because it was also not available in the laboratory. In order to carry out this synthesis, alkyne **31** and benzoyl chloride **32** were used in an nucleophilic acyl substitution reaction. The yield of this reaction was 85 %. The purpose of synthesizing JEM–I–17 (alkyne **13**) is to add to methyl vinyl ketone **2** as done by Lerum[5] in the rhodium-catalyzed reaction modifying ligands.

Using the optimized conditions of Scheme 7, the original ligand was replaced with the new synthetisized ligands in order for the results to be most comparable with that of Lerum. Scheme 16 shows the results of this screen.

Scheme 16



Ligand	Yield (14)	Yield (15)
45	62%	13%
20	66%	30%
24	51%	58%
27	37%	58%
30	50%	14%

Ligand **45** represents the optimal ligand originally used in Lerum's[5] work. The noticeable trend that occurred was that as the alkoxy substituent increased in bulk there was an increase in the yield of product **15**. Another noticeable relationship was that ligand **30** and ligand **45** gave similar results since the yield of both products for ligand **30** was similar to that of **45**. Ligands **24** and **27** increased the

yield of the dimer product. The difference was that using ligand **24** resulted in a 1:1 ratio of 1,4-addition:dimer products in moderate yields while ligand **27** showed selectivity for dimer-addition product over 1,4-addition product. This may be due to the severity of the steric bulk of the ligand. This information provides evidence of the possibility that continual modification of ligand **45** might yield a reaction selective towards product **14** or **15**.

The conditions from Scheme 6 were modified slightly in Scheme 17. The mole percentage of the catalyst remained the same while the mole % of the ligand was increased to 20 mole %. Ligand **46** showed substantial selectivity for product **15** in comparison to ligand **45**. The yield for product **15** increased to 69%. This could be due to the lack of an alkoxy group on the ligand effects the reactivity of the rhodium metal as it coordinates to the starting materials. Using the optimized conditions of Scheme 6, the ligand was also substituted for the ligands that were commercially available. Scheme 18 shows the results of this screen. The commercial names of these ligands are seen in Table 1.

Scheme 17

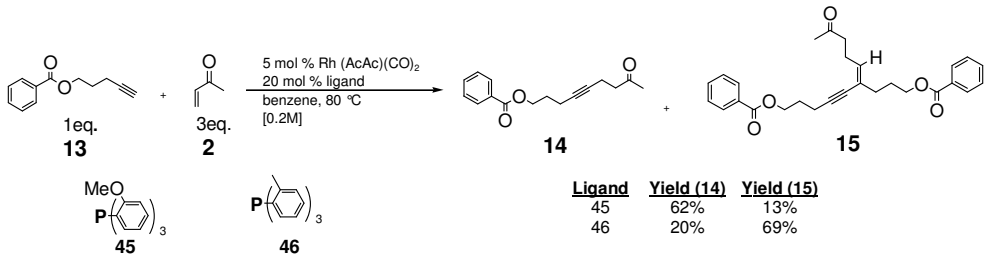
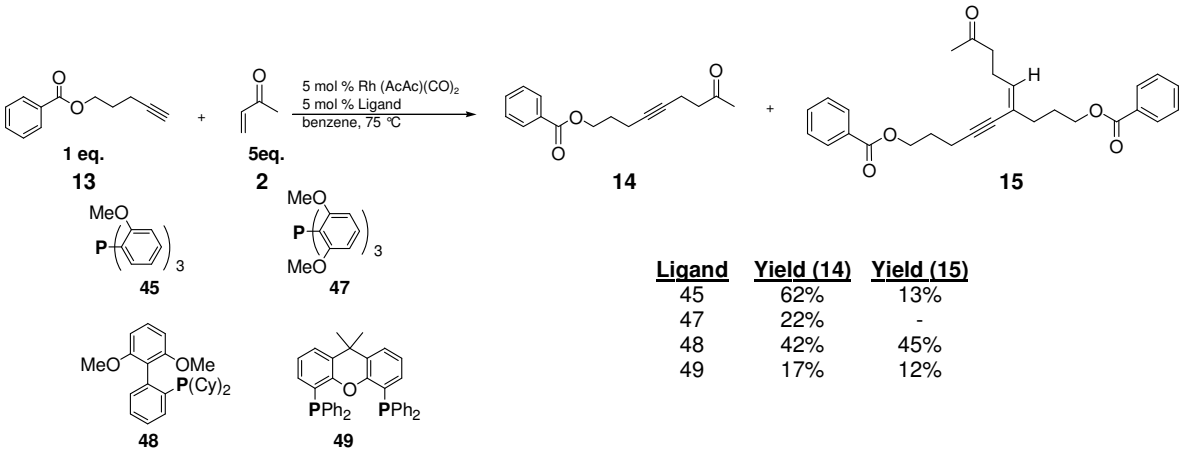


Table 1: Commercially Available Ligands Used in Ligand Screen

Commercially Available Ligands	
Ligand	**Name**
45	Tris-(*o*-methoxyphenyl)phosphine
46	Tri-*o*-toly phosphine (TOTP)
47	Tris-(2,6-dimethoxy phenyl) phosphine
48	2-dicyclohexylphosphino-2',6'-dimethoxy-1',1'-biphenyl,(S-phos)
49	9,9-dimethyl-4,5-bis(diphenylphosphino) (xantphos)
50	2-(diphenylphosphino)-2'-(N,N-dimethyl amino) biphenyl
51	2-(di-t-butylphosphino)-2'-(N,N-dimethyl amino) biphenyl
52	2-(dicyclohexylphosphino)-2'-(N,N-dimethyl amino) biphenyl

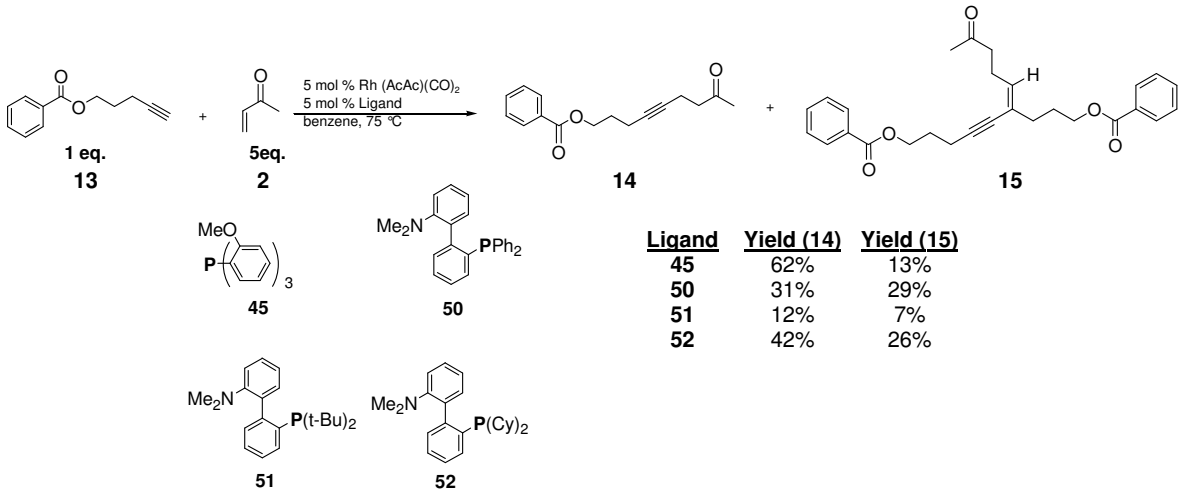
Scheme 18



Ligand	Yield (14)	Yield (15)
45	62%	13%
47	22%	-
48	42%	45%
49	17%	12%

The ligand screen was also applied to ligands with amines that are commercially available ligands. Scheme 19 shows the results of this screen.

Scheme 19



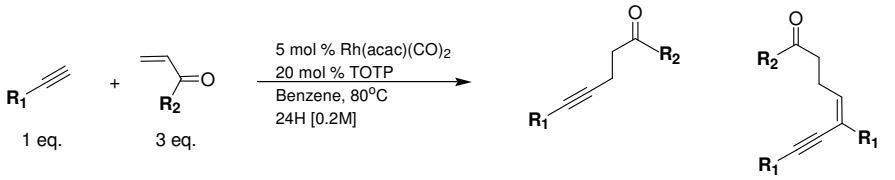
Ligand	Yield (14)	Yield (15)
45	62%	13%
50	31%	29%
51	12%	7%
52	42%	26%

The commercially available ligands that were also subjected for ligand compatibility all possessed heteroatoms oriented so they could bind to the metal. The trend that became apparent when the results were analyzed was that ligands **48** and **50** provided almost a 1:1 ratio of **14** to **15**, where ligand **48** gave them in reasonable yields. In terms of using the commercially available ligands to selectively synthesize specifically either **14** or **15**, none were effective.

The ligand screen found that ligand **45** provided the highest selectivity for product **14**. Ligand **46** (TOTP) provided highest selectivity and yield for product **15**. As a result, a variety of alkynes and enones were screened using the optimized conditions in Scheme 17 and ligand **46** to observe the trends of the yield of the corresponding dimer-addition product. The results from this alkyne and enone screen are shown in Scheme 20. In all cases, the dimer-addition molecule was the major product. The results showed that 3-butyn-1-ol **39** and 4-pentyn-1-ol **31** provided the best alcohol dimer-addition product. The propargylic alcohol **37** had very poor yields and the 1,4-addition product was not isolated. For 10-undecyn-1-ol **33**, the yield of the dimer was moderate. The results also showed that reaction

using product **13** and 1-octen-3-one **42** was successful and favored the dimer-addition product in moderate yield.

Scheme 20



molecule #	R_1	molecule #	R_2	Ref.	1,4 - Addition Yield	Dimer - Addition Yield
33	$-(CH_2)_9OH$	**2**	$-CH_3$	JEM-I-49	-	45%
31	$-(CH_2)_3OH$	**2**	$-CH_3$	JEM-I-50 & RVL-V-137	30%	51%
37	$-CH_2OH$	**2**	$-CH_3$	JEM-I-51	-	21%
39	$-(CH_2)_2OH$	**2**	$-CH_3$	JEM-I-53 & RVL-IV-21	30%	63%
13	$-(CH_2)_3OBz$	**42**	$-(CH_2)_4CH_3$	JEM-I-55	22%	41%

Conclusion:

Based on the results there seems to be a relationship between the structure of the phosphine ligand and the reactivity of the catalyst. Since the rhodium complex $Rh(acac)(CO)_2$ is in fact a precatalyst that transforms into an active catalyst by adding to the phosphine which displaces one CO molecule it is possible to modulate the reactivity of the catalyst by modifying the phosphine.

Ligand synthesis results show that there is a correlation between the steric environment of the molecule and the yield. As the ligand becomes increasingly bulky, the yield subsequently decreases. Ligand screen shows that in alkoxy ligands, an increase steric bulk increases selectivity for dimer product. However, ligand **46** provided highest selectivity and best yields for the dimer product. In the alkyne and enone screen using ligand **46**, the dimer-addition product was the major product.

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