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Rhodium-catalyzed 1,4-addition of terminal alkynes to vinyl ketones

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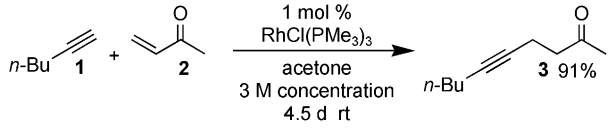
Abstract—The metal complex $Rh(acac)(CO)_2$ in the presence of an eqimolar amount of tris(*o*-methoxyphenyl)phosphine provides a useful catalyst system for the 1,4-addition of alkynes to unsubstituted vinyl ketones. Best yields are obtained when the transformation is performed in benzene at reflux with an excess of vinyl ketone. Both aryl and alkyl substituted alkynes participate in the reaction. Primary alcohols and alkyl chlorides are well tolerated under these reaction conditions. The reaction also proceeds in aqueous solvent mixtures, unlike most organometallic addition reactions.

The 1,4-addition of alkynes to enones is known to be a problematic reaction. The most common reaction conditions for the 1,4-addition of carbon anions, cuprate chemistry, fails when attempted with alkynes.[1,2] This is unfortunate because the products of the 1,4-addition of alkynes, γ, δ-alkynyl ketones, are useful intermediates for organic synthesis providing ready access to 1,4-diketones,[3] furans,[4] and pyrroles.[5]

Numerous attempts have been made to bridge this gap in synthetic methodology.[6–13] In each of these cases, acetylides must be generated by deprotonation, which requires stoichiometric quantities of at least one metal. Recently, several examples of the 1,4-addition of alkynes have emerged that are catalytic in transition metals.[4,14,15] These methods take advantage of the facile C–H insertion chemistry of alkynes to generate the acetylide, which then adds to the enone. Such reactions are advantageous because they minimize waste with all of the atoms in the stoichiometric starting materials present in the reaction product.

In 1990, Kovalev published a rhodium catalyzed addition of alkynes to methyl vinyl ketone (Scheme 1).[16] This reaction possesses many promising features, such as not needing to activate the alkyne with a stoichiometric amount of another metal and low catalyst loading.



Scheme 1.

Because the reaction is performed in acetone as the solvent, it is likely tolerant of at least small quantities of water.

Intrigued by the potential of this process, a study was undertaken to improve upon the reaction. Despite its promise, the original reaction conditions are marred by some significant disadvantages. The addition is very slow, requiring between two and five days to proceed to useful levels of completion. Heating does not provide a satisfactory solution, as it results in alkyne dimerization as the major reaction pathway. The catalyst for the 1,4-addition reaction, $RhCl(PMe_3)_3$, is not commercially available. This limits the usefulness of the reaction to laboratories, which are skilled in the synthesis of organometallic compounds. Furthermore, synthesis of the catalyst requires trimethylphosphine, a volatile, toxic, and air-sensitive compound.

The first goal of this program was to find a catalyst that did not require trimethylphosphine. The second was to find a catalyst that increased the reaction rate. Pursuant to these goals, a stable rhodium complex with ligands that may be displaced easily with exogenous phosphines

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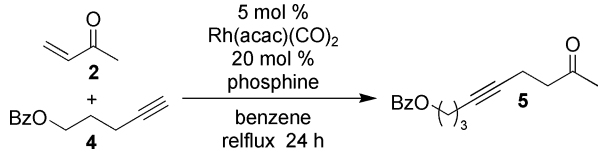
was desired. This stable rhodium complex would then be the precatalyst, with the active catalyst formed in situ.

The benzoate of 4-pentyn-1-ol and methyl vinyl ketone (3 equiv) were used as the initial coupling partners for this investigation. After examining several rhodium (I) sources, $Rh(acac)(CO)_2$ (acac = acetylacetonoate) proved to be the most effective precatalyst. The carbon monoxide ligand is readily and quantitatively displaced by better ligands, such as phosphines.[17] Other precatalysts (such as $[Rh(cod)Cl]_2$ (cod = cyclooctadiene) and $[Rh(norbornadiene)Cl]_2$) also gave small amounts of 1,4-addition product, however this was always contaminated with products resulting from dimerization or polymerization of the alkyne. These side reactions were less prevalent when $Rh(acac)(CO)_2$ was used as the precatalyst. While use of $Rh(acac)(CO)_2$ without any phosphine ligands provided only small amounts of product, addition of a phosphine ligand significantly increased the yield of the reaction in most cases (Table 1).

Changing the phosphine used in the reaction significantly changed the isolated yield of the 1,4-addition product. With the initial experiments showing some promise, a brief screen of phosphine ligands was performed in an effort to find one that gave a reasonable yield of the 1,4-addition product on a faster timescale than observed by Kovalev. From this initial screen, tris-(*o*-methoxyphenyl)phosphine **10** emerged as the best ligand. No trend as to what type of ligand (electron rich or electron poor, large cone-angle, or small cone-angle) emerged from this ligand screen. A control experiment using phosphine **10** with no rhodium complex present provided no 1,4-addition product.

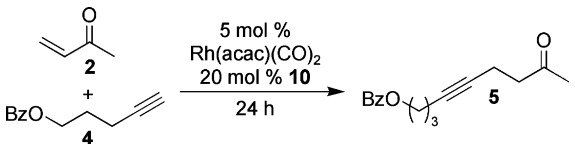
With a promising catalyst-phosphine combination, a number of experimental factors were varied in an effort to further increase the yield and rate of the 1,4-addition reaction (Table 2). Varying the temperature of the reaction showed that a relatively high temperature was required (above 50 °C). Changing the solvent showed little difference among toluene, benzene, and dioxane. The reaction demonstrated a significant water tolerance, with little decrease in yield observed when the reaction

Table 1. Screen of phosphine ligands



Entry	Phosphine	Yield (%)
1	None	6
2	Tris(pentafluorophenyl)phosphine (**6**)	21
3	Tris(*p*-trifluoromethylphenyl)phosphine (**7**)	18
4	Triphenylphosphine (**8**)	Trace
5	Tri-*o*-tolylphosphine (**9**)	20
6	Tris(*o*-methoxyphenyl)phosphine (**10**)	61
7	Tris(*p*-methoxyphenyl)phosphine (**11**)	17
8	Tris(2,4,6-trimethoxyphenyl)phosphine (**12**)	11

Table 2. Screen of reaction conditions



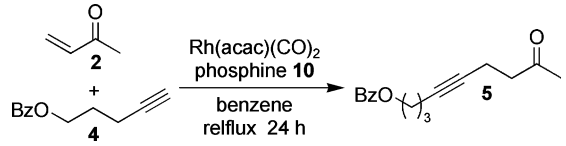
Entry	Solvent	Temperature (°C)	Yield (%)
1	Benzene	50	22
2	Benzene	80	61
3	Toluene	90	49
4	Dioxane	90	56
5	90% Dioxane/10% H_2O	90	53
6	75% Dioxane/25% H_2O	90	15

was performed in 10% water/dioxane. Greater amounts of water were not as well tolerated, likely because the rhodium–phosphine complex lacked solubility.

The stoichiometry of rhodium complex and phosphine ligand was the next reaction parameter investigated. Further examination showed that only one equivalent of the phosphine ligand with respect to the rhodium complex was required for catalytic activity (Table 3). This implies that one of the carbon monoxide ligands may still be attached to the reactive catalytic complex. Lowering the catalyst loading to 3 mol% or 1 mol% resulted in a significant reduction in the yield of the reaction. In an attempt to recoup some of the loss in yield, a greater excess of methyl vinyl ketone was used in these experiments. Using five equivalents of methyl vinyl ketone instead of three significantly improved the yield of the reaction (Table 3, entry 4).

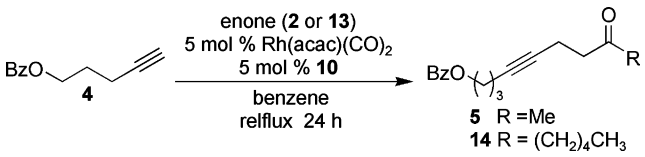
An excess of enone **2** may be required because of evaporation, as the boiling point of methyl vinyl ketone **2** is close to that of benzene. To investigate this postulate 1-octen-3-one (**13**) was explored as a reaction partner. Both methyl vinyl ketone **2** and 1-octen-3-one **13** were used in varying amounts to determine if the requirement for excess vinyl ketone applied to only to methyl vinyl ketone or to all substrates (Table 4). Use of a lesser amount of enone **13** also resulted in lowered yields. This result rules out evaporation as the reason an excess of enone is needed. Instead, the excess of ketone is likely

Table 3. Effect of catalyst and phosphine loading



Entry	Mol% Rh	Equiv **2**	Mol% **10**	Yield (%)
1	5	3	20	63
2	5	3	10	53
3	5	3	5	54
4	5	5	5	82
5	3	5	3	63
6	1	5	1	11

Table 4. Effect of decreasing the amount of enone



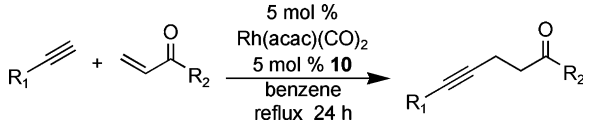
Entry	Enone	Equiv enone	Yield
1	**2**	5	82% (**5**)
2	**2**	3	54% (**5**)
3	**2**	1	16% (**5**)
4	**13**	5	71% (**14**)
5	**13**	3	48% (**14**)
6	**13**	1	28% (**14**)

required because it is a less effective ligand for the transition metal catalyst than a second equivalent of alkyne. Binding of two alkynes to the rhodium catalyst is undesirable because this could lead to dimerization and polymerization.

With good conditions for the 1,4-addition in hand, the substrate tolerance of the reaction with respect to functionality on the alkyne and the enone was explored (Table 5). Both aromatic and alkyl substituted alkynes showed good reactivity in the 1,4-addition reaction. Polar protic functionality, such as alcohols, were well tolerated. Good electrophiles, such as primary alkyl chlorides, also gave useful yields of the 1,4-addition product. No 1,2-addition of the alkyne to the carbonyl was observed in any of these rhodium-catalyzed reactions. While the rhodium catalyzed 1,4-addition of alkynes performed well with unsubstituted enones, substituted systems still provide a challenge. Only 10–20% yields of 1,4-addition product were obtained when alkynes were added to 3-octen-2-one under these reaction conditions.

A proposed reaction mechanism for the reaction is shown in Figure 1. Insertion of the rhodium catalyst

Table 5. Substrate generality of the rhodium-catalyzed 1,4-addition of alkynes[18–20]



Entry	Alkyne	Enone	Yield
1	$R_1 = (CH_2)_5CH_3$ (**15**)	**2**	63% (**22**)
2	R_1 = Ph (**16**)	**2**	61% (**23**)
3	$R_1 = (CH_2)_3Cl$ (**17**)	**2**	66% (**24**)
4	$R_1 = (CH_2)_3OBz$ (**4**)	**2**	82% (**5**)
5	$R_1 = (CH_2)_3OH$ (**18**)	**2**	74% (**25**)
6	R_1 = TIPS (**19**)	**2**	76% (**26**)
7	$R_1 = (CH_2)_3CN$ (**20**)	**2**	63% (**27**)
8	**4**	**13**	71% (**14**)
9	**18**	**13**	86% (**28**)
10	**18**	R_2 = Ph (**21**)	72% (**29**)
11	**19**	**21**	67% (**30**)

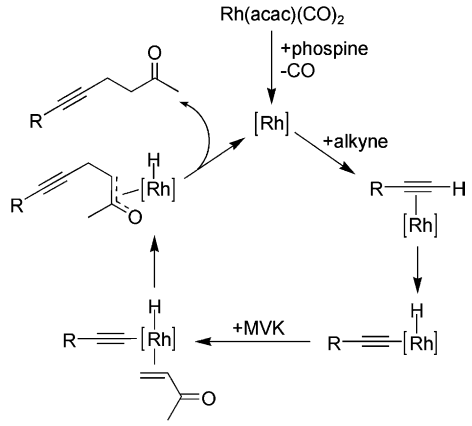


Figure 1. Proposed mechanism of the rhodium-catalyzed 1,4-addition of alkynes.

into the alkyne C–H bond is well precedented from other published studies.[21,22] After coordination of the enone, formation of the new C–C bond occurs by migratory insertion of the alkyne into the olefin. The resulting oxy-π allyl complex is then protonated by reductive elimination. This releases the 1,4-addition product and regenerates the catalyst for further reaction.

The rhodium-catalyzed 1,4-addition of alkynes represents an entry to γ,δ-alkynyl ketones, products that are not easily accessed through classical methods. Currently, the reaction functions on unsubstituted vinyl ketones with yields in the 61–86% range. Studies to elucidate the mechanistic features of the reaction and expand the substrate scope are ongoing.

Acknowledgements

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18. Representative experimental procedure: Benzene (0.5 mL) was added to $Rh(acac)(CO)_2$ (9.0 mg, 0.035 mmol, 5 mol%) and phosphine **10** (12.3 mg, 0.035 mmol, 5 mol%). A solution of the alkyne **19** (157 μL, 0.70 mmol) and methyl vinyl ketone **2** (286 μL, 3.5 mmol) in benzene (3.0 mL) was then added. The reaction vessel was then placed in a pre-heated oil bath at 85 °C and stirred for 24 h at this temperature. The reaction mixture was then pre-absorbed on silica gel and purified by silica gel chromatography (gradient elution using 6–10% ethyl acetate/hexanes) to afford 176 mg (76%) of pure 6-(triisopropylsilyl)-5-hexyn-2-one **(26)** as a clear yellow oil. TLC $R_f = 0.29$ (10% ethyl acetate/hexanes). IR (neat): 2942, 2865, 2173, 1721 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.63 (t, $J = 7.6$, 2H), 2.46 (t, $J = 7.4$, 2H), 2.13 (s, 3H), 0.92–1.04 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.6, 107.4, 81.0, 42.9, 30.0, 18.7, 14.8, 11.3. Anal. Calcd for $C_{15}H_{28}OSi$: C, 71.36; H, 11.18. Found: C, 71.19; H, 11.40.
19. Characterization data for new compounds: **5**: TLC $R_f = 0.36$ (20% ethyl acetate/hexanes). IR (neat): 2921, 1717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.06–8.01 (m, 2H), 7.55 (tt, $J = 7.3$, 1.4, 1H), 7.43 (tt, $J = 7.2$, 1.5, 2H), 4.39 (t, $J = 6.3$, 2H), 2.61 (t, $J = 6.9$, 2H), 2.42–2.29 (m, 4H), 2.15 (s, 3H), 1.93 (p, $J = 6.4$, 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. **14**: TLC $R_f = 0.39$ (10% ethyl acetate/hexanes). IR (neat): 2956, 2930, 1719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, $J = 7.5$, 2H), 7.55 (t, $J = 7.5$, 1H), 7.43 (t, $J = 7.6$, 2H), 4.39 (t, $J = 6.3$, 2H), 2.58 (t, $J = 7.6$, 2H), 2.41–2.32 (m, 6H), 1.93 (p, $J = 6.6$, 2H) 1.57 (p, $J = 7.3$, 2H), 1.33–1.21 (m, 4H), 0.88 (t, $J = 7.2$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 166.4, 132.9, 130.3, 129.5, 128.3, 79.7, 79.1, 63.7, 432.8, 41.8, 31.4, 28.1, 23.4, 22.4, 15.6, 13.9, 13.4. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.22; H, 8.22. **22**: TLC $R_f = 0.27$ (10% ethyl acetate/hexanes). IR (neat): 2956, 2930, 1720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.57 (t, $J = 7.1$, 2H), 2.35–2.29 (m, 2H), 2.08 (s, 3H), 2.05–2.00 (m, 2H), 1.42–1.16 (m, 8H), 0.80 (t, $J = 7.1$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 80.9, 78.5, 43.0, 31.4, 29.9, 29.0, 28.6, 22.6, 18.7, 14.1, 13.5. Anal. Calcd for $C_{12}H_{20}O$: C, 74.84; H, 9.96. Found: C, 74.69; 10.25. **25**: TLC $R_f = 0.20$ (50% ethyl acetate/hexanes). IR (neat): 3419, 2924, 1716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (t, $J = 6.2$, 2H), 2.59 (t, $J = 7.2$, 2H) 2.39–2.32 (m, 2H), 2.24–2.18 (m, 2H) 2.13 (s, 3H), 1.67 (p, $J = 6.2$, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 80.12, 79.3, 61.8, 43.0, 31.6, 30.0, 15.4, 13.5. HRMS (EI): *m/z* calcd for $C_9H_{14}O_2Na$ (M+Na) 177.0885. Found: 177.0883. **28**: TLC $R_f = 0.42$ (50% ethyl acetate/hexanes). IR (neat): 3326, 2920, 1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (t, $J = 6.1$, 2H), 2.60 (t, $J = 7.4$, 2H), 2.44–2.37 (m, 4H), 2.28–2.23 (m, 2H), 1.82 (s, 1H), 1.72 (p, $J = 6.1$, 2H), 1.58 (p, $J = 7.5$, 2H), 1.33–1.24 (m, 4H), 0.89 (t, $J = 6.8$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 80.1, 79.7, 62.1, 43.0, 42.1, 31.7, 31.6, 23.7, 22.6, 15.6, 14.1, 13.6. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.35; H, 10.56. **29**: TLC $R_f = 0.34$ (50% ethyl acetate/hexanes). IR (neat): 3220, 2925, 2868, 1701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, $J = 8.0$, 1.4, 2H), 7.57 (tt, $J = 8.2$, 1.3, 1H), 7.46 (t, $J = 8.0$, 2H), 3.72 (t, $J = 6.1$, 2H), 3.19 (t, $J = 7.0$, 2H), 2.61–2.55 (m, 2H), 2.29–2.23 (m, 2H), 2.03 (s, 1H), 1.71 (p, $J = 6.2$, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 136.6, 133.3, 128.7, 128.1, 80.2, 79.5, 61.7, 38.2, 31.6, 15.4, 13.8. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.61; H, 7.58. **30**: TLC $R_f = 0.39$ (6% ethyl acetate/hexanes). IR (neat): 2942, 2864, 2174, 1690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, $J = 7.4$, 2H), 7.57 (tt, $J = 7.6$, 1.4, 1H), 7.47 (tt, $J = 7.7$, 1.4, 2H), 3.24 (t, $J = 7.6$, 2H), 2.69 (t, $J = 7.7$, 2H), 1.06–1.02 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 136.9, 133.4, 128.8, 128.3, 107.7, 81.2, 38.3, 18.8, 15.2, 11.4. Anal. Calcd for $C_{20}H_{30}OSi$: C, 76.37; H, 9.61. Found: C, 76.37; H, 9.45.
20. Compound **23** (Ref. 4), compound **24** (Ref. 14) and compound **27** (Ref. 14) have been previously reported.
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