Chemo- and Regioselective Cyclohydrocarbonylation of α-Keto Alkynes Catalyzed by a Zwitterionic Rhodium Complex and Triphenyl Phosphite

Bernard G. Van den Hoven, Bassam El Ali,† and Howard Alper*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada, K1N 6N5

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α-Keto alkynes react with CO and H_2 in the presence of catalytic quantities of the zwitterionic rhodium complex (η^6-$C_6H_5BPh_3$)$^-$Rh$^+$(1,5-COD) and triphenyl phosphite affording either the 2-, 2(3*H*)-, or 2(5*H*)-furanones in 61−93% yields. The cyclohydrocarbonylation is readily accomplished using substrates containing alkyl, aryl, vinyl, and alkoxy groups at the acetylenic terminal, as well as a variety of primary, secondary, and tertiary alkyl, aryl, and heteroaryl groups connected to the ketone functionality. Structural and electronic properties present in the starting materials mediate the chemo- and regioselectivity of the reaction.

Introduction

Furanones have been of interest for many years due to their biological activity.[1] A variety of transition metal catalyzed methods have been utilized for the preparation of γ-lactones including the transition metal catalyzed cyclocarbonylation of alkenols,[2] alkynols,[3] alkynes,[4] and alkynoic acids.[5] Several of these reactions are of value for the synthesis of multifunctionalized lactones.

The cyclocarbonylation of acetylene containing substrates requires high temperatures and pressures for both palladium[3h]- (eq 1) and rhodium[5a]-catalyzed reactions (eq 2). Obstacles have been encountered in attaining high yields of these highly substituted furanones under milder temperatures and pressures.[3d,k] The ability to use milder conditions may be of importance for the preparation of chiral furanones from achiral substrates, as found for the asymmetric hydroformylation of alkenes.[6]

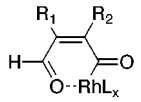
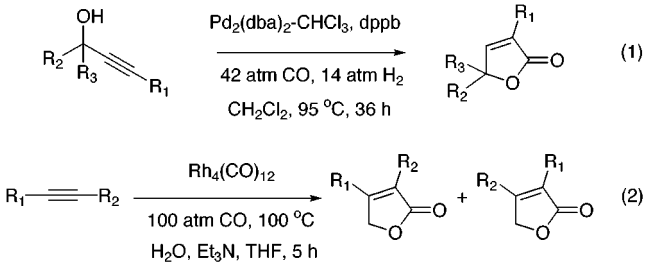


Figure 1. Proposed intermediate in $Rh_4(CO)_{12}$-catalyzed carbocyclization.



Previous work with $Rh_4(CO)_{12}$ utilizing internal alkynes[5a,c] postulated a dicarbonyl−metal complex as a reaction intermediate (Figure 1). Here, R_1 and R_2 were alkyl or aromatic groups. A conceivably similar intermediate may result from the hydroformylation of an α-keto alkyne if the carbonylation step occurred at the triple bond carbon closest to R_2.

The use of an achiral substrate, an alkynone, would create a new chiral center in the preparation of furanones. A phase transfer nickel catalyst was used for the cyclohydrocarbonylation of α-keto alkynes in 1995.[7] Although the yields were low, ring cleavage occurred to form alkenoic acids. In addition, in 1996, tetrasubstituted 3(2*H*)-furanones were readily prepared in moderate yields from 4-hydroxyalk-2-ynones and alkyl halides using tandem CO_2 addition−elimination conditions.[8]

In recent years, a better understanding of the hydroformylation of internal alkynes to form α,β-unsaturated

† Present address: Department of Chemistry, King Fahd University of Petroleum and Minerals, Dhahran, Saudi Arabia.

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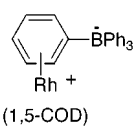
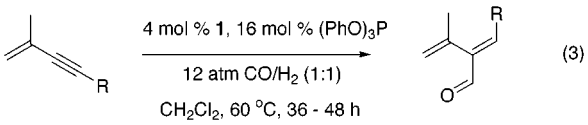
aldehydes was initiated by Buchwald and co-workers,[9] and by Hidai and co-workers.[10] In 1999, we reported the hydroformylation of both enynes[11] and acetylenic thiophenes[12] using the zwitterionic rhodium complex (η^6-$C_6H_5BPh_3$)$^-$-Rh^+(1,5-COD) (**1**) and triphenyl phosphite under moderate temperatures and low pressures affording products in good to excellent regioselectivities and yields.



(1,5-COD)

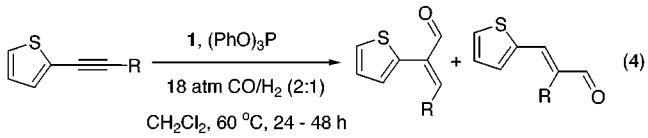
1

The hydroformylation of conjugated enynes resulted in the preparation of branched formyl dienes in 50−55% yields (eq 3).



(3)

Acetylenic thiophenes reacted to form, preferentially, α,*β*-unsaturated aldehydes branched to the thiophene. Excellent regioselectivities resulted when the acetylenic unit was a propargyl ether or ester, phenylacetylene, or an enyne in yields ranging from 65 to 99% (eq 4). This selectivity may be attributed, at least in part, to the coordination of sulfur to rhodium.

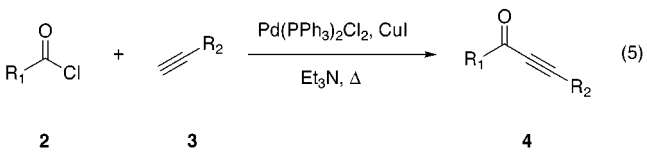


(4)

We now describe the use of catalytic quantities of **1**, in the presence of triphenyl phosphite, CO, and H_2 for the cyclohydrocarbonylation of multifunctionalized α-keto alkynes to give 2-, 2(3*H*)-, and 2(5*H*)-furanones with good to excellent chemo- and regioselectivities, conversions, and yields.

Results and Discussion

There are a number of procedures to prepare alkynones.[13−16] A facile approach is the coupling of terminal alkynes and acyl chlorides described by Hagihara and co-workers using catalytic quantities of $Pd(PPh_3)_2Cl_2$ and CuI in the presence of Et_3N (eq 5).[13] This procedure was



(5)

2 **3** **4**

applied to the coupling of secondary and tertiary alkyl, and aryl R_1 groups with alkyl, alkoxy, vinyl, and aryl terminal alkynes.

Table 1. Reaction Optimization Using 4e[a]

entry	$(PhO)_3P$ (mol %)	pressure (atm)	$CO:H_2$	*T* (°C)	t (h)	conv[b] (%)	**5**:**7**[c]
1	8	21	2:1	60	20	NR	−
2	8	21	2:1	120	20	100	1:1.8
3	8	21	2:1	100	20	100	1:1.6
4	8	21	5:1	100	20	100	1.1:1
5	8	21	5:1	90	20	75	1.7:1
6	8	42	11:1	90	20	100	1:1
7	8	42	11:1	80	20	93	1.4:1
8	16	42	11:1	80	20	85	1.7:1
9	32	42	11:1	80	20	73	1.9:1
10	32	42	11:1	90	20	100	1.8:1

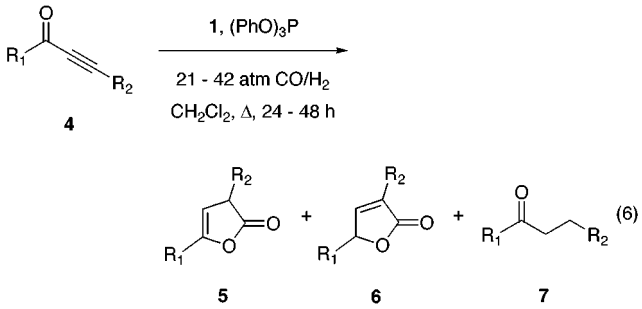
[a]Reaction conditions: **4**, 1.5 mmol; **1**, 0.03 mmol (2%); $(PhO)_3P$, 0.12−0.48 mmol (8−32%); CH_2Cl_2, 10 mL; CO, 14−38.5 atm; H_2, 3.5−7 atm; 60−120 °C, 20 h. [b] The percent conversion was determined by ^{1}H NMR. [c] The ratio of **5**:**7** was determined by ^{1}H NMR. Trace amounts of **6** were detected in these reactions.

Table 2. Catalyst and Ligand Optimization Using 4e[a]

entry	ligand	conv[b] (%)	**5**:**6**:**7**[c]	entry	ligand	conv[b] (%)	**5**:**6**:**7**[c]
1	$(PhO)_3P$	93	1.4:t:1	3	Ph_3P	100	t:t:1
2	$(EtO)_3P$	23	t:t:1	4	dppb[d]	100	t:t:1

[a] Reaction conditions: **4**, 1.5 mmol; **1**, 0.03 mmol (2%); ligand, 0.12 mmol (8%); CH_2Cl_2, 10 mL; CO, 38.5 atm; H_2, 3.5 atm; 80 °C, 20 h. [b] The percent conversion was determined by ^{1}H NMR. [c] The ratio of **5**:**6**:**7** was determined by ^{1}H NMR. [d] dppb, 0.06 mmol (4%).

α-Keto alkynes are cyclohydrocarbonylated by using the zwitterionic rhodium complex (**1**) and $(PhO)_3P$ under similar conditions to those utilized for the hydroformylation of conjugated enynes and thiophenynes (eq 6). Using 2 mol % **1**, 8−32 mol % $(PhO)_3P$, 1.5 mmol of **4**, 17.5−38.5 atm CO, and 3.5 atm H_2 at 70−120 °C for 24−48 h afforded either the 2(3*H*)-furanone (**5**) or 2(5*H*)-furanone (**6**) with the hydrogenated alkynone **7** (Tables 1−6).



(6)

4 **5** **6** **7**

The conditions for the cyclohydrocarbonylation of α-keto alkynes were optimized using 2,2-dimethylnon-4-yn-3-one (**4e**) as a model substrate. Treating the alkynone with 2 mol % **1**, 8 mol % $(PhO)_3P$, 10 mL of CH_2Cl_2, 14 atm CO, 7 atm H_2 at 60 °C for 20 h resulted in no reaction (Table 1, entry 1). Increasing the temperature from 100 to 120 °C after 20 h favored the production of ketone **7e** (Table 1, entries 2 and 3). Increasing the CO/H_2 ratio to 5:1 at 21 atm CO/H_2 gave low selectivity (Table 1, entries 4 and 5). However, increasing the pressure to 42 atm with a CO/H_2 ratio of 11:1 results

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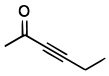
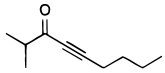
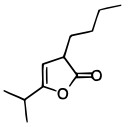
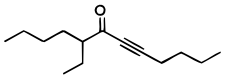
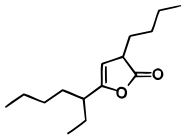
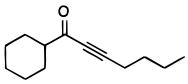
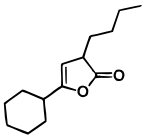
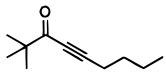
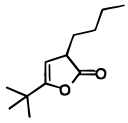
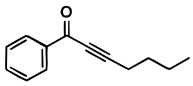
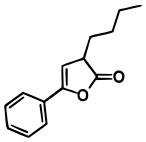
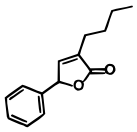
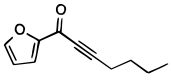
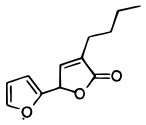
Table 3. Cyclohydrocarbonylation Where R_2 Is an Alkyl Chain[a]

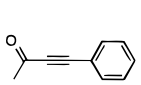
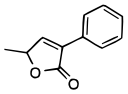
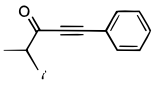
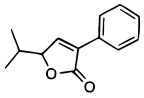
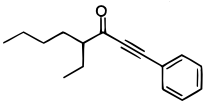
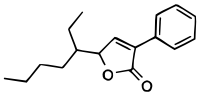
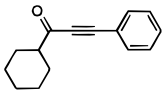
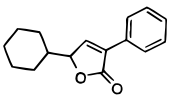
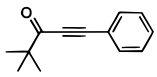
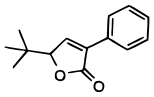
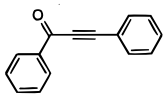
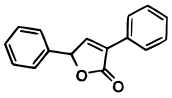
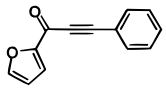
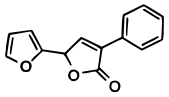
Entry	4	Conv.[b] (%)	Heterocycle	Isolated Yield[c] (%)
1	 **4a**	100	 **5a**	91
2	 **4b**	100	 **5b**	88
3	 **4c**	100	 **5c**	83
4[d]	 **4d**	90	 **5d**	63
5	 **4e**	100	 **5e**	64
6[d]	 **4f**	100	 **5f**[e]	63
7[e]		100	 **6f**[e]	61
8	 **4g**	100	 **6g**[e]	68

[a] Reaction conditions: **4**, 1.5 mmol; **1**, 0.03 mmol (2%); $(PhO)_3P$, 0.48 mmol (32%); CH_2Cl_2, 10 mL; CO, 38.5 atm; H_2, 3.5 atm; 90 °C, 24 h. [b] The percent conversion was determined by ^1H NMR. [c] The products were isolated by Kugelrohr distillation followed by flash silica gel chromatography using pentane:ether (99:1) as eluant. [d] 36 h. [e] The products were isolated by flash silica gel chromatography using pentane:ether (85:15) as eluant.

in a moderate preference for **5e** to **7e** (Table 1, entries 6 and 7). Surprisingly, the amount of $(PhO)_3P$ had a further influence on the ratio of **5** to **7**. Increasing the amount of $(PhO)_3P$ from 8 to 32% raised the preference for **5e** from 1.4:1 to 1.9:1 at 80 °C with a consequential lowering in conversion (Table 1, entries 8 and 9). At 90 °C, full conversion of the reactant occurred with a **5**/**7** product ratio of 1.8:1 (Table 1, entry 11). Applying the conditions of Table 1, entry 7 (42 atm, CO/H_2 of 11:1, 80 °C, and 20 h) to $(EtO)_3P$, and phosphine ligands $(Ph)_3P$ and dppb resulted in the predominant production of **7e** (Table 2, entries 2 to 4).

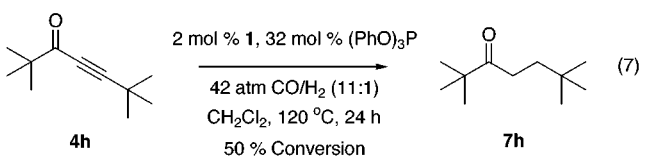
The cyclohydrocarbonylation of conjugated ynones may be readily applied to a variety of substrates using 2 mol % **1**, 32 mol % $(PhO)_3P$, 1.5 mmol of **4**, 38.5 atm CO, 3.5 atm H_2 at 90 °C for 24 h. The structure of the functional

Table 4. Cyclohydrocarbonylation Where R_2 Is a Phenyl Group[a]

Entry	4	t (h)	Conv.[b] (%)	Heterocycle	Isolated Yield[c] (%)
1	 **4i**	24	100	 **6i**	83
2	 **4j**	36	100	 **6j**	88
3	 **4k**	36	100	 **6k**	87
4	 **4l**	48	100	 **6l**	84
5	 **4m**	48	100	 **6m**	85
6	 **4n**	24	100	 **6n**	61
7	 **4o**	24	100	 **6o**	67

[a] Reaction conditions: **4**, 1.5 mmol; **1**, 0.03 mmol (2%); $(PhO)_3P$, 0.48 mmol (32%); CH_2Cl_2, 10 mL; CO, 38.5 atm; H_2, 3.5 atm; 120 °C. [b] The percent conversion was determined by ^1H NMR. [c] The products were isolated by flash silica gel chromatography using pentane:ether (90:10) as eluant followed by crystallization.

group in the R_1 position significantly influences the ratio of **5** to **7**. Placement of a primary or alkyl chain substituted secondary R_1 group increases the selectivity for **5** from 83 to 91% (Table 3, entries 1−3). Using a cyclohexyl, phenyl, or furyl group results in a decreased preference of **5** ranging from 61 to 68% (Table 3, entries 4−8). The use of a furyl substituent favors **5g** after 18 h, and **6g** after 24 h. Attempts to isolate **5g** by silica gel chromatography results in its isomerization to **6g**. In addition, the complete isomerization of **5f** to **6f** was observed utilizing a reaction time of 36 h (Table 3, entry 7). Replacing the *n*-butyl group of **4e** with *tert*-butyl, i.e., 2,2,6,6-tetramethylhept-4-yn-3-one (**4h**), results in no cyclohydrocarbonylation products. The substrate **4h** did not react at 90 °C and only gave a 50% conversion to **7h** at 120 °C (eq 7).

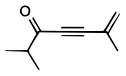
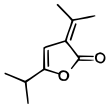
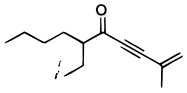
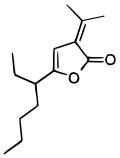
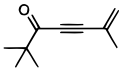
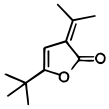
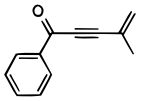
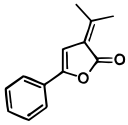


(7)

High selectivity for the 2(5*H*)-furanone (**6**) was attained when R_2 of **4** is a phenyl group. The temperature was increased from 90 °C to 120 °C to enable furanone production to be complete in 24−48 h due to decreased reactivity for the reactions of **4i**−**o** compared with **4a**−**g**. The reaction was complete in 24 h when R_1 was a primary alkyl, or aryl group. Secondary and tertiary alkyl-substituted substrates required 36−48 h for completion. The preference for furanone production was far superior when R_2 is a phenyl group rather than an alkyl chain, resulting in yields of **6** ranging from 84 to 93% when R_1 is an alkyl group (Table 4, entries 1−5), and 61 to 67% when R_1 is aryl group (Table 4, entries 6 and 7). Having an aromatic ring adjacent to the triple bond appears to favor the formation of the unsaturated γ-lactone.

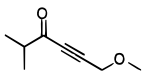
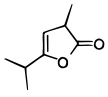
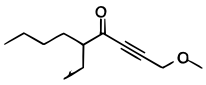
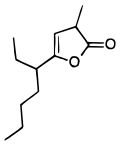
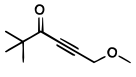
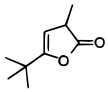
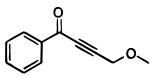
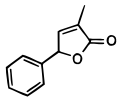
The examination of other α-keto alkynes with functionalized R_2 groups such as vinyl (Table 5) and methoxymethyl (Table 6) results in decreased production of **7**. The cyclohydrocarbonylation of α-keto alkynes with smaller functionalized groups at the acetylenic terminal may be readily accomplished under milder pressure (21

Table 5. Cyclohydrocarbonylation Where R_2 Is a Vinyl Group[a]

Entry	4	t (h)	Conv. [b] (%)	Heterocycle	Isolated Yield [c] (%)
1	 **4p**	24	100	 **8p**	71
2	 **4q**	24	100	 **8q**	76
3	 **4r**	36	100	 **8r**	69
4	 **4s**	24	100	 **8s [d]**	75

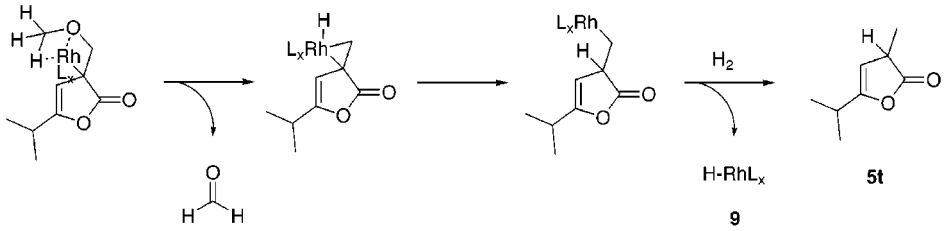
[a] Reaction conditions: **4**, 1.5 mmol; **1**, 0.03 mmol (2%); $(PhO)_3P$, 0.12 mmol (8%); CH_2Cl_2, 10 mL; CO, 17.5 atm; H_2, 3.5 atm; 70 °C. [b] The percent conversion was determined by ^1H NMR. [c] The products were isolated by Kugelrohr distillation followed by flash silica gel chromatography using pentane:ether (97.5:2.5) as eluant. [d] Flash silica gel chromatography using pentane:ether (90:10) as eluant.

Table 6. Cyclohydrocarbonylation Where R_2 Is a Methoxymethyl Group[a]

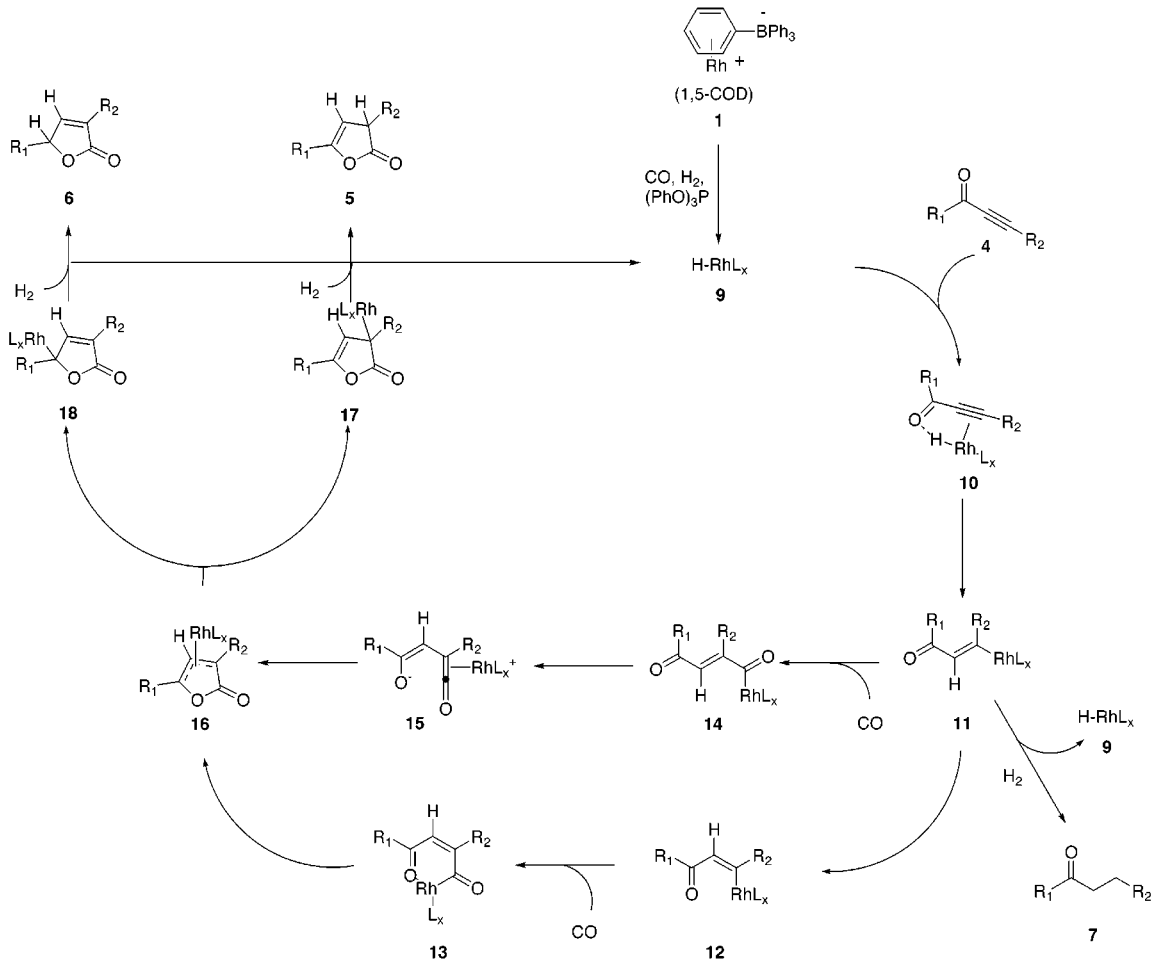
Entry	4	t (h)	Conv. [b] (%)	Heterocycle	Isolated Yield [c] (%)
1	 **4t**	24	100	 **5t**	92
2	 **4u**	24	100	 **5u**	91
3	 **4v**	36	100	 **5v**	89
4	 **4w**	24	100	 **6w [d]**	93

[a] Reaction conditions: **4**, 1.5 mmol; **1**, 0.03 mmol (2%); $(PhO)_3P$, 0.12 mmol (8%); CH_2Cl_2, 10 mL; CO, 17.5 atm; H_2, 3.5 atm; 70 °C. [b] The percent conversion was determined by ^1H NMR. [c] The products were isolated by Kugelrohr distillation followed by flash silica gel chromatography using pentane:ether (95:5) as eluant. [d] Flash silica gel chromatography using pentane:ether (85:15) as eluant.

Scheme 1. Possible Route to Demethoxylation



Scheme 2. Proposed Mechanism for the Cyclohydrocarbonylation Reaction



atm, CO/H_2 being 5/1) and lower temperature (70 °C). Interestingly, 2-furanones (**8**) were obtained from enynones and may result from a 1,5 proton shift of **6**. The 2-furanone (**8**) was obtained in 69−76% yields along with oligomeric materials (Table 5, entries 1−4). An increased preference for furanone production was observed when R_1 was either a secondary or tertiary alkyl, or aryl group. The addition of a R_2 group capable of coordinating with the rhodium prior to addition to the triple bond readily promoted the carbonylation of the triple bond at the carbon nearest R_2 as observed previously in our studies on the hydroformylation of enynes and thiophenynes.[17,18]

The cyclohydrocarbonylation of methoxymethyl-substituted acetylenes resulted in the production of the 2(3*H*)-furanones **5** in 89−93% yields (Table 6, entries 1−3). Demethoxylation occurs in the reaction, possibly in the final stages of the catalytic cycle, transforming the methoxymethyl to a methyl group (Scheme 1). It is conceivable that prior to the hydrogen addition step to form **5**, the rhodium−furanone complex is in an orientation that allows the metal to coordinate with the oxygen from the methoxymethyl group. Hydrogen abstraction and rhodium migration leads to formaldehyde production, and the methyl-substituted furanone. The phenyl-substituted alkynone (**4w**) affords the methyl-substituted 2(5*H*)-furanone **6w** (Table 6, entry 4). The 2(3*H*)-furanone appears to be the kinetic product, and the 2(5*H*)-furanone is the thermodynamic product. The placement of an electron-withdrawing group in position five promotes the isomerization of **5** to **6** when there is a small substituent in position three.

It was indicated that a number of factors influenced the preparation of the unsaturated γ-lactones from α-keto alkynes. Only a five-membered ring was formed, indicating that the acyl−rhodium intermediate always originates at the triple bond carbon closest to R_2. The nature

(17) Please see the Supporting Information for additional information on the preparation of α-keto alkynes (**4**) by the $Pd(PPh_3)_2Cl_2$/CuI-catalyzed coupling of acyl chlorides (**2**) and terminal alkynes (**3**).

(18) Schrock, P. R.; Osborn, J. A. *Inorg. Chem.* **1970**, *9*, 2339.

of R_1 and R_2 substantially influences both the formation of the unsaturated lactone and hydrogenation. Given this information, one can envisage a mechanism (Scheme 2) for the preparation of furanones from α-keto alkynes which involve the following steps:

(1) the rhodium hydride complex (**9**) binds to the triple bond of the alkynone with possible weak H-bonding interaction to the ketone functionality (**10**);

(2) intramolecular addition of the rhodium hydride to the triple bond of the α-keto alkyne can afford the *E* isomer **11**;

(3) depending upon the extent of interaction between R_1 and R_2, one of two possible paths may occur in the next stage of the process: appreciable steric interaction between R_1 and R_2 would destabilize **11** resulting in further hydrogenation of the alkenyl intermediate to the ketone **7** and regeneration of **9**; if **11** is stable, carbonylation (**14**) and reaarrangement to the zwitterionic ketene (**15**), or isomerization (**12**) and carbonylation (**13**), would generate **16** via intramolecular cyclization;

(4) either the rhodium−furanone complex **17** or **18** will form. The reaction of either rhodium complex with H_2 affords the 2(3*H*)-furanone **5** or the 2(5*H*)-furanone **6**, and regeneration of the rhodium hydride **9**.

In conclusion, the cyclohydrocarbonylation of α-keto alkynes was readily accomplished by the zwitterionic rhodium complex **1** and triphenyl phosphite in the presence of CO and H_2. The temperatures and pressures required were sometimes milder than those previously reported for other reactions (especially when functionalized α-keto alkynes were used). Good chemo- and regioselectivity were observed for a variety of multifunctionalized alkynones to produce 2-, 2(3*H*)-, or 2(5*H*)-furanone as the dominant product. This research has the potential to be used in the synthesis of chiral furanones from achiral substrates.

Experimental Section

Materials. Hex-3-yn-2-one (**4a**), 4-phenylbut-3-yn-2-one (**4i**), and all acyl chlorides and terminal alkynes were purchased from commercial sources. Other alkynones were prepared according to the procedure described by Hagihara and co-workers.[13,17] The zwitterionic rhodium complex (η^6-C_6H_5-BPh_3)$^-$Rh$^+$(1,5-COD) (**1**) was prepared according to the procedure of Schrock and Osborn.[18] All solvents were dried, and distilled under N_2, prior to use.

General Procedure for the Cyclohydrocarbonylation of α-Keto Alkynes. To a 45 mL autoclave with a glass liner and stirring bar was placed the zwitterionic rhodium complex **1** (0.03 mmol), triphenyl phosphite (0.12−0.48 mmol), the α-keto alkyne **4** (1.5 mmol), and CH_2Cl_2 (10 mL). The autoclave was flushed three times with carbon monoxide, pressurized to 17.5−38.5 atm, and then hydrogen was introduced up to a total pressure of 21−42 atm. The autoclave was placed in an oil bath at 70−120 °C for 24−48 h and then allowed to cool to room temperature. The autoclave was depressurized, the reaction mixture filtered through Celite, and the solvent removed by rotary evaporation. The resulting residue was purified by Kugelrohr distillation, flash silica gel chromatography, or crystallization to afford products **5**, **6**, and **8** (see Tables 3−6**)**.

3-Ethyl-5-methyl-2(3*H*)-furanone (5a): colorless liquid; IR ν(C=O) 1797 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.08 (d, 1H, J = 4.6 Hz), 3.12 (m, 1H), 1.93 (s, 3H), 1.68 (m, 2H), 0.89 (t, 3H, J = 7.6 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 180.1, 150.8, 104.1, 46.9, 24.5, 14.5, 11.4; EI MS (*m*/*e*) 126 [M$^+$]; HRMS calculated for $C_7H_{10}O_2$ [M$^+$] 126.06808, found 126.06610.

5-Methyl-3-phenyl-2(5*H*)-furanone (6i): colorless liquid; IR ν(C=O) 1756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85−7.80 (m, 2H), 7.52 (d, 1H, J = 1.8 Hz), 7.42−7.35 (m, 3H), 5.14 (qd, 1H, J = 6.8, 1.6 Hz), 1.49 (d, 3H, J = 6.8 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.3, 149.6, 131.9, 130.1, 129.9, 129.2, 127.6, 77.3, 19.7; EI MS (*m*/*e*) 174 [M$^+$]; HRMS calculated for $C_{11}H_{10}O_2$ [M$^+$] 174.06808, found 174.06854.

3-Dimethylmethylene-5-isopropyl-2-furanone (8p): colorless liquid; IR ν(C=O) 1760 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.72 (s, 1H), 2.62 (septet, 1H, J = 7.6 Hz), 2.30 (s, 3H), 2.01 (s, 3H), 1.15 (d, 6H, J = 7.6 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 168.5, 161.2, 151.7, 123.5, 99.6, 28.5, 24.7, 21.1, 20.1; EI MS (*m*/*e*) 166 [M$^+$]; HRMS calculated for $C_{10}H_{14}O_2$ [M$^+$] 166.09938, found 166.09952.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for support of this research.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for **4b**−**w**, **5a**−**f**, **5t**−**v**, **6f**−**o**, **6w**, and **8p**−**8s** (60 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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