Innovative Synthesis of 4-Carbaldehydepyrrolin-2-ones by Zwitterionic Rhodium Catalyzed Chemo- and Regioselective Tandem Cyclohydrocarbonylation/CO Insertion of α-Imino Alkynes

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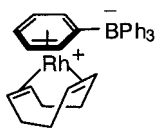
Abstract: The tandem cyclohydrocarbonylative/CO insertion of α-imino alkynes employs CO, H_2, and catalytic quantities of zwitterionic rhodium complex $(\eta^6\text{-}C_6H_5BPh_3)^-Rh^+$(1,5-COD) and triphenyl phosphite affording aldehyde substituted pyrrolinones in 67−82% yields. This unique transformation is readily applied to imino alkynes containing alkyl, alkoxyl, vinyl, and aryl substituents. The ability to prepare highly functionalized pyrrolinones makes this an attractive route to these important and versatile pharmaceuticals.

Introduction

It has been our goal in recent years to discover and develop rhodium catalyzed transformations of functionalized alkynes utilizing the zwitterionic rhodium complex $(\eta^6\text{-}C_6H_5BPh_3)^-Rh^+$-(1,5-COD (**1**) in the presence of CO and H_2. A fascinating aspect to this research concerns the chemo- and regioselectivity effects directed by functional groups adjacent to a triple bond. We have demonstrated the regioselective hydroformylation of both enynes[1] and acetylenic thiophenes[2] to their α,β-unsaturated aldehydes and the chemo- and regioselective cyclohydrocarbonylation of α-keto alkynes and acetylenic thiazoles to furanones[3] and thiazepinones.[4]



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Pyrrolinones, especially enantiomerically pure forms, are pharmacologically active materials that are important synthons in the preparation of γ-amino acids,[5] various alkaloids,[6] and natural products.[7] These five-membered rings express antitumor properties,[8] as well as inhibition of COX-2[9] and HIV-1 protease.[10] The versatility of pyrrolinones is extended upon hydrogenation to their pyrrolidinone analogues. Additional biological activities have been described, including HIV protease inhibition,[11] cognitive performance enhancement,[12] selective estrogen receptor modulation (SERM),[13] anticonvulsant activities,[14] renin inhibition,[15] and amnesia reversal activity.[16]

Pyrrolinones have been prepared from catalytic methods which include the ruthenium catalyzed Alder-ene reaction[17] and ring closing metathesis,[18] the rhodium catalyzed hydrocarbonylation of alkenamides,[19] and the iron catalyzed carbonylation of allenyl imines.[20] Though many catalytic processes result in limited chirality, racemic pyrrolinones have been efficiently resolved by enzymatic kinetic resolution to their enantiomeric counterparts.[21]

It was anticipated that the use of α-imino alkynes as functionalized alkynes for the reaction with CO/H_2 and **1** would

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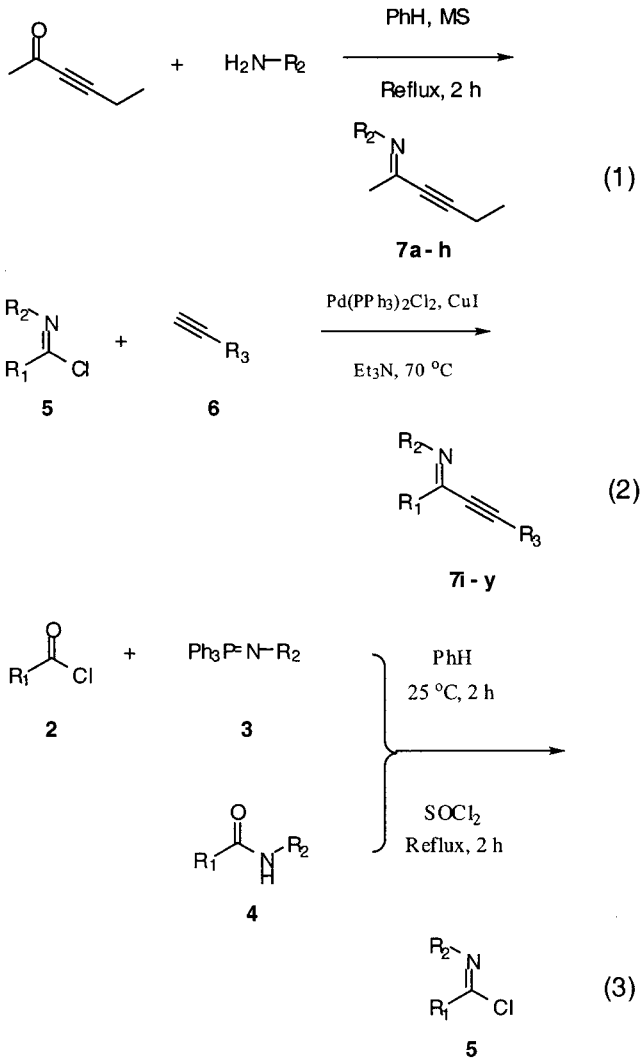
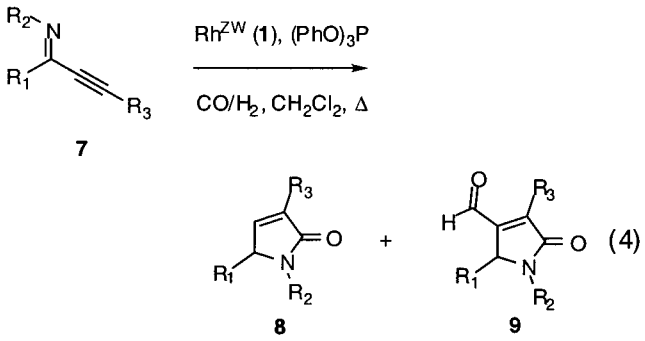
afford pyrrolinones. We now describe a novel chemo- and regioselective route to 4-carbaldehydepyrrolin-2-ones in 67−82% yields by the zwitterionic rhodium complex (**1**) and triphenyl phosphite catalyzed cyclohydrocarbonylation/CO insertion of trisubstituted acetylenic imines.

Results and Discussion

There are many approaches to the preparation of alkynyl imines. In our study, we utilized two routes: (a) the direct amination/dehydration of alkynones (eq 1 and Table S1; throughout the text, the S refers to Supporting Information)[22] and (b) the cross coupling reaction between imidoyl chlorides (**5**) and terminal alkynes (**6**) using catalytic amounts of $Pd(PPh_3)_2Cl_2$ and CuI (eq 2, Table S4).[23] Imidoyl chlorides (eq 3) were prepared by the direct reaction of secondary amides (**4**) with $SOCl_2$ (Table S2)[24] or by the reaction of acyl chlorides (**2**) with aza-Wittig reagents (**3**) (Table S3).[25] In this manner, hex-3-yn-2-one was reacted with primary amines to form Schiff bases in 66−78% yields, while imino alkynes (**7**) were formed in 65−96% yields, obtained from the terminal alkyne to imidoyl chloride (**5**) coupling reaction. These trisubstituted alkynyl imines (**7**) readily incorporate alkyl, alkoxyl, vinyl, and aryl groups in the R_1, R_2, and R_3 positions.



The reaction of an alkynyl imine (**7**) with carbon monoxide and hydrogen in the presence of catalytic quantities of the zwitterionic rhodium complex (**1**) and triphenyl phosphite affords the pyrrolin-2-one (**8**) and the 4-carbaldehydepyrrolin-2-one (**9**) (eq 4). The reaction is both temperature and pressure dependent. The use of 1.5 mmol of **7** with 2 mol % of **1**, 8 mol % of $(PhO)_3P$, 10 mL of CH_2Cl_2, and total pressures of 21 and 42 atm at optimum CO/H_2 ratios of 5:1 and 11:1 affords various mixtures of **8** and **9**. Temperatures between 70 and 100 °C favor the production of **9** over **8** with some residual polymeric material. The longer the reaction takes place at these elevated temperatures, the greater the abundance of **9**. The temperature and time dependence of **9** has lead us to reason that **9** likely arises from **8** or an intermediate closely related to **8**.



The tandem cyclohydrocarbonylation/CO insertion of imino alkynes was evaluated by determining the dependence on R_2 (Table 1), R_3 (Table 2), and R_1 (Table 3). To initiate our investigation, imino alkynes with R_1 = methyl, R_3 = ethyl, and R_2 groups containing *n*-butyl, isopropyl, cyclohexyl, and ethyl phenyl were determined to react best by treating 1.5 mmol of **7** with 2 mol % of the zwitterionic rhodium complex (**1**), 8 mol % of triphenyl phosphite, 10 mL of CH_2Cl_2, 18.5 atm of CO, and 3.5 atm of H_2 in a 45 mL autoclave for 18−36 h at 100 °C. Placement of a minimum two carbon spacer between the imino nitrogen and a substituent within R_2 removes possible steric interference and allows the reaction to **9** to be complete within 18 h (Table 1, entries 1 and 5). The addition of substituents to C1 of R_2 required an increased reaction time of 24 h when R_2 is isopropyl (Table 1, entry 2) and 36 h when R_2 is cyclohexyl (Table 1, entry 3). Utilizing 2-methyltetrahydrofuran as R_2 (**7d**) preferentially leads to **9d** at 80 °C instead of 100 °C. Higher temperatures result in a dark discoloration of the reaction mixture and inhibiton of **9d**. The placement of allyl (**7f**), benzyl (**7g**), and methylbenzyl (**7h**) groups at R_2 results in products with no CO incorporation. Aromatic R_2 groups such as phenyl (**7w**), tolyl (**7x**), and 4-chlorophenyl (**7y**) revealed a complicated reaction mixture where **8** was minor and **9** was no longer present.

The unique transformation of **7** to **9** (eq 5) may be extended to α-imino alkynes where R_1 contains an aromatic unit. These unsaturates preferentially react at 90 °C with a total pressure of 42 atm and a CO/H_2 ratio of 11/1. To determine the scope at

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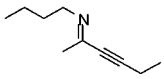
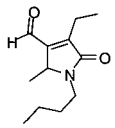
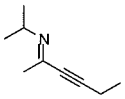
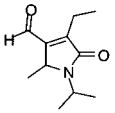
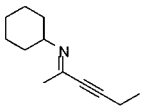
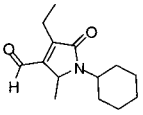
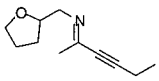
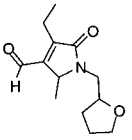
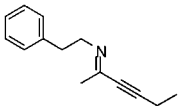
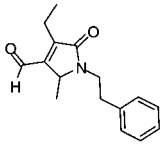
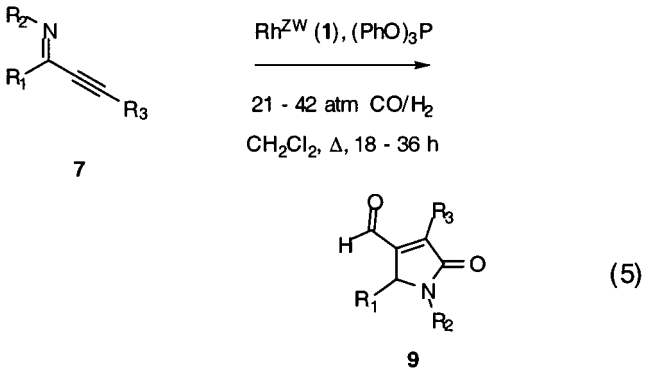
Table 1. Tandem Cyclohydrocarbonylation/CO Insertion of α-Imino Alkyne with Different R_2 Groups[a]

Entry	7	T (°C)	t (h)	9	Isolated Yield (%)[b]
1	 **7a**	100	18	 **9a**	82
2	 **7b**	100	24	 **9b**	79
3	 **7c**	100	36	 **9c**	80
4	 **7d**	80	36	 **9d**	73
5	 **7e**	100	18	 **9e**	75

[a] Reaction conditions: **7**, 1.5 mmol; **1**, 0.03 mmol (2 mol %); $(PhO)_3P$, 0.12 mmol (8 mol %); CH_2Cl_2, 10 mL; CO, 17.5 atm; H_2, 3.5 atm. [b] The reactions proceeded to full conversion (obtained by NMR), and the products were isolated by silica gel chromatography using 33:67 to 50:50 ethyl acetate/hexane as eluant.

the alkynyl unit (R_3), we evaluated imino alkynes with R_1 = phenyl and R_2 = *n*-butyl. The R_3 group employed alkyl, alkoxyl,



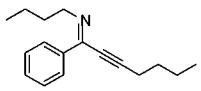
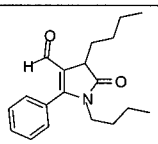
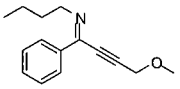
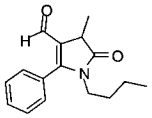
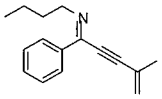
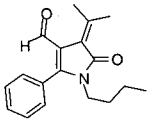
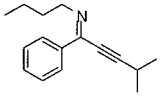
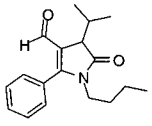
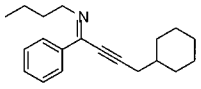
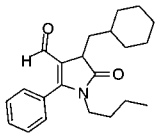
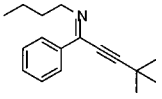
7 **9** (5)

vinyl, and aryl groups (Table 2). Interestingly, increasing the size of R_3 to *n*-butyl (**7i**), isopropyl (**7l**), and methylcyclohexyl (**7m**) has little influence on **9**, as all reactions are complete within 24 h and have comparable yields ranging from 75 to 79% (Table 2, entries 1, 4, and 5). Utilizing the *tert*-butyl substituted α-imino alkyne (**7n**) causes the reaction to take place very slowly (Table 2, entry 6), even at temperatures exceeding 110 °C, while placement of a methoxy methyl group (**7j**) and a vinyl group (**7k**) at R_3 favors a reaction temperature of 75 °C. In particular, **7j** gives the demethoxylated product **9j** in 72% yield (Table 2, entry 2), and **7k** gives the conjugated 3-isopropylidenepyrrolin-2-one **9k** in 67% yield, as expected from our recent study on alkynones (Table 2, entry 3).[4] Aromatic R_3 units consisting of phenyl (**7o**) and 4-methoxyphenyl (**7p**) favor five-membered pyrrolinones where the R_2 group (*n*-butyl) is cleaved and replaced by hydrogen.

To evaluate the effect of substitution on the aromatic R_1 unit, the R_2 and R_3 substituents used were isopropyl and *n*-butyl, respectively, while the aromatic unit varied from phenyl (**7q**) to 4-tolyl (**7r**) and 4-anisolyl (**7s**), forming **9q**−**s** with 78−81% yields (Table 3, entries 1−3). Placement of an electron withdrawing group on the ring reduces the reactivity of **7**. Utilizing a 4-chlorophenyl substituted at R_1 (**7t**) gives **9t** in 72% yield after 36 h (Table 3, entry 4), and 4-nitrophenyl (**7v**) affords **8v** (64% yield) as the major product after reacting for 18 h. If **7v** is permitted to react for additional time, the hydrogenation of the nitro group to an amine begins to compete with the production of **9**, leading to a complicated reaction mixture. Increasing the size of the aryl group from phenyl (**7q**) to naphthyl (**7u**) requires a reaction time of 36 h to obtain **9u** in 75% yield (Table 3, entry 5).

Certain criteria appear to be evident for the preparation of 4-carbaldehydepyrrolin-2-ones (**9**). The R_1 unit may be alkyl or aryl, while R_2 and R_3 preferentially give **9** when strong electron donating groups are used, as well as groups that are nonconjugating to the imino alkyne. Increasing the size of the R_1 and R_2 groups decreases the reactivity toward cyclization. Primary and secondary substituted R_3 groups have minimal

Table 2. Tandem Cyclohydrocarbonylation/CO Insertion of α-Imino Alkyne with Different R_3 Groups[a]

Entry	7	T (°C)	t (h)	9	Isolated Yield (%) [b]
1	 **7i**	90	24	 **9i**	78
2	 **7j**	75	24	 **9j**	72
3	 **7k**	75	36	 **9k**	67
4	 **7l**	90	24	 **9l**	75
5	 **7m**	90	24	 **9m**	79
6	 **7n**	90	24	No Reaction	-

[a] Reaction conditions: **7**, 1.5 mmol; **1**, 0.03 mmol (2 mol %); $(PhO)_3P$, 0.12 mmol (8 mol %); CH_2Cl_2, 10 mL; CO, 38.5 atm; H_2, 3.5 atm. [b] The reactions proceeded to full conversion (obtained by NMR), and the products were isolated by using silica gel chromatography using 33:67 to 50:50 ethyl acetate/hexane as eluant.

reactivity differences, but placement of tertiary substituted groups appreciably reduce the reactivity of the imino alkyne.

In 1995, it was observed that catalytic amounts of the zwitterionic rhodium complex (**1**) and bisdiphenylphosphinobutane readily hydrogenate imines in the presence of hydrogen and methanol.[26] In our reaction system, we have placed an imine under hydroformylation conditions. As a result, there is potential for formamides to be produced which may lead to the cyclization we have observed. To determine whether the imine functional group initiated the cyclization with the alkyne in a CO and H_2 atmosphere, we prepared *sec*-butylideneisopropylamine and isopropyl(1-phenylethylidene)amine and reacted them under our conditions. After 24 h, neither imine generated the expected formamides, and only trace amounts of the hydrogenated counterparts were observed. The lack of formamides implied that cyclization to the core pyrrolinone ring must originate from the rhodium addition to the triple bond and a consequential acyl rhodium intermediate or that the presence of a triple bond adjacent to the imine functionality alters its reactivity to allow the rhodium to initially add to the imine.

In our reaction system, the presence of both **8** and **9** leads us to speculate that **9** may originate from **8** or that an intermediate related to **8** may lead to both **8** and **9** (Scheme 1). To test whether **9** originated from **8**, we placed a number of pyrrolinones **8** (isolated prior to substrate optimization) back under a carbon monoxide/hydrogen atmosphere or a complete carbon monoxide atmosphere. Reintroduction of **8** utilizing the conditions noted for **7**,[27] under a CO/H_2 or a CO atmosphere, resulted in low conversions to **9** after 24 h. These results indicate for the conversion of α-imino alkynes to 4-carbaldehydepyrroli-2-ones that **8** is the minor and not the major route to **9**.

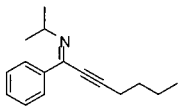
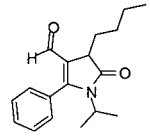
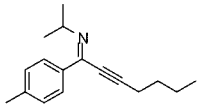
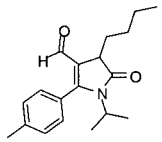
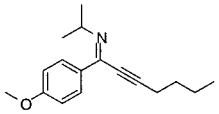
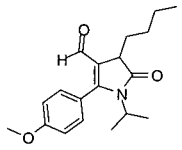
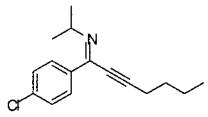
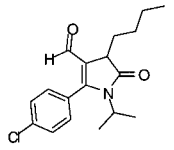
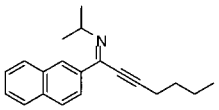
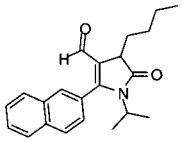
A possible mechanism is outlined in Scheme 2. The active rhodium complex (**10**), generated from **1** (Scheme 2), binds to the acetylenic imine via the triple bond and the imine (**11**) or directly to the imine (**12**). Intramolecular hydrorhodation leads to **13**, and subsequent carbonylation gives **14**. Reorientation of **14** to **15** promotes intramolecular cyclization across the triple bond to the 4-rhodiumpyrrolinone (**16**). Hydrogen addition to **15** creates the trisubstituted pyrrolinone **8** and regenerates the rhodium complex **10**. Alternatively, **16** undergoes CO insertion to generate **17**. Addition of H_2 generates the aldehyde substituted pyrrolinone ring **9** and regenerates the rhodium complex **10**.

In conclusion, we have described a unique preparation of tetrasubstituted pyrrolinones. The unexpected tandem cyclohydrocarbonylation/CO insertion catalyzed by zwitterionic rhodium

(26) Zhou, Z.; James, B. R.; Alper, H. *Organometallics* **1995**, *14*, 4209.

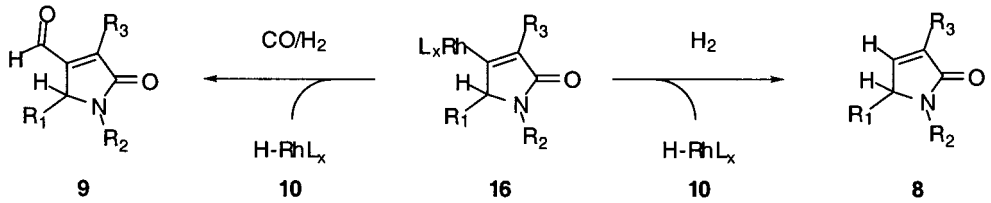
(27) Please see the Supporting Information for procedures used to reintroduce **8** to a CO or CO/H_2 atmosphere.

Table 3. Tandem Cyclohydrocarbonylation/CO Insertion of α-Imino Alkyne with Substituted Aromatic R_1 Groups[a]

Entry	7	T (°C)	t (h)	9	Isolated Yield (%) [b]
1	 **7q**	90	24	 **9q**	80
2	 **7r**	90	24	 **9r**	81
3	 **7s**	90	24	 **9s**	78
4	 **7t**	90	36	 **9t**	72
5	 **7u**	90	36	 **9u**	75

[a] Reaction conditions: **7**, 1.5 mmol; **1**, 0.03 mmol (2 mol %); $(PhO)_3P$, 0.12 mmol (8 mol %); CH_2Cl_2, 10 mL; CO, 38.5 atm; H_2, 3.5 atm. [b] The reactions proceeded to full conversion (obtained by NMR), and the products were isolated by silica gel chromatography using 33:67 to 50:50 ethyl acetate/hexane as eluant.

Scheme 1. Possible Route to **8** and **9**



complex **1** $(\eta^6\text{-}C_6H_5BPh_3)^-Rh^+(1,5\text{-COD})$ and triphenyl phosphite is both electronically and sterically controlled within the acetylenic imine. Utilizing a reasonable degree of control, these 4-carbaldehydepyrrolin-2-ones are readily prepared and have potential use as precursors toward important pharmacological applications.

Experimental Section

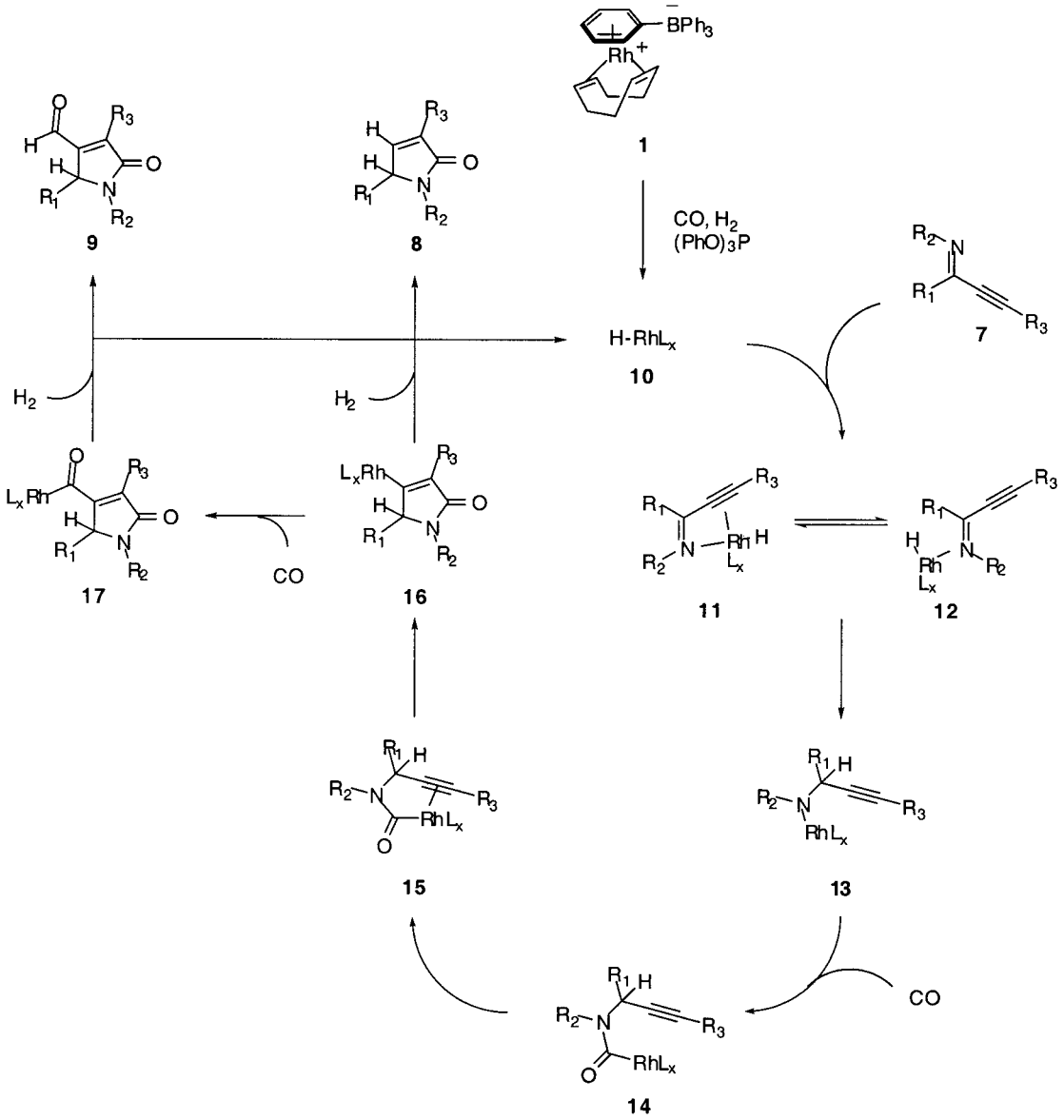
Materials. All acyl chlorides, primary amines, and terminal alkynes were purchased from commercial sources. The zwitterionic rhodium complex, $(\eta^6\text{-}C_6H_5BPh_3)^-Rh^+(1,5\text{-COD})$ (**1**), was prepared according to the procedure of Schrock and Osborn.[28] All solvents were dried and distilled under N_2 prior to use.

General Procedure for the Cyclohydrocarbonylative/CO Insertion of Acetylenic Imines. In a 45 mL autoclave containing a glass liner and stirring bar was placed zwitterionic rhodium complex **1** (0.03 mmol), triphenyl phosphite (0.12 mmol), acetylenic imine **7** (1.5 mmol), and CH_2Cl_2 (10 mL). The autoclave was flushed three times with carbon monoxide, pressurized from 17.5 to 38.5 atm followed by the introduction of hydrogen to a total pressure of 21−42 atm. The autoclave was placed in an oil bath at 75−100 °C for 18−36 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 silica gel chromatography using an ethyl acetate/hexanes gradient ranging from 33:67 to 50:50 as the eluant to afford **9** (Tables 1−3).

1-Butyl-4-carbaldehyde-3-ethyl-5-methyl-3-pyrrolin-2-one (9a). Colorless liquid; IR ν_1(C=O) 1727 cm^{-1}, ν_2(C=O) 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 3.55 (t, 1H, J = 7.7 Hz), 3.45 (t, 1H, J = 7.7 Hz), 3.30 (m, 1H), 2.38 (br, 3H), 2.01 (m, 2H), 1.52 (q, 2H, J = 7.7 Hz), 1.32 (sextet, 2H, J = 7.7 Hz), 0.92 (t, 3H, J = 7.4 Hz), 0.71 (t, 3H, J = 7.5 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 182.9, 180.1, 159.9, 118.8, 46.0, 40.5, 31.9, 22.5, 20.7, 14.3, 11.4,

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

Scheme 2. Proposed Mechanism



9.6; EI MS (*m*/*z*) 209 [M$^+$]; HRMS calculated for $C_{12}H_{19}NO_2$ [M$^+$], 209.141 58; found, 209.141 73.

4-Carbaldehyde-3-ethyl-1-isopropyl-5-methyl-3-pyrrolin-2-one (9b). Colorless liquid; IR ν_1(C=O) 1725 cm^{-1}, ν_2(C=O) 1641 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 4.05 (septet, 1H, J = 6.5 Hz), 3.17 (m, 1H), 2.32 (br, 3H), 1.92 (m, 2H), 1.35 (d, 3H, J = 6.2 Hz), 1.33 (d, 3H, J = 6.3 Hz), 0.61 (t, 3H, J = 7.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 182.3, 179.6, 159.6, 118.1, 45.4, 21.7, 20.1, 19.9, 11.1, 8.5; EI MS (*m*/*z*) 195 [M$^+$]; HRMS calculated for $C_{11}H_{17}NO_2$ [M$^+$], 195.125 93; found, 195.127 07.

4-Carbaldehyde-1-cyclohexyl-3-ethyl-5-methyl-3-pyrrolin-2-one (9c). Colorless liquid; IR ν_1(C=O) 1723 cm^{-1}, ν_2(C=O) 1642 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.67 (s, 1H), 3.59 (m, 1H), 3.23 (m, 1H), 2.36 (br, 3H), 1.57−2.22 (m, 8H), 1.18−1.30 (m, 4H), 0.65 (t, 3H, J = 7.6 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 182.5, 179.8, 159.8, 118.2, 54.1, 45.5, 29.9, 29.7, 26.0, 24.9, 21.9, 11.4, 8.6; EI MS (*m*/*z*) 235 [M$^+$]; HRMS calculated for $C_{14}H_{21}NO_2$ [M$^+$], 235.157 23; found, 235.155 58.

4-Carbaldehyde-3-ethyl-5-methyl-1-(tetrahydrofuran-2-ylmethyl)-3-pyrrolin-2-one (9d). Yellow liquid; IR ν_1(C=O) 1726 cm^{-1}, ν_2(C=O) 1642 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.67 (s, 1H), 3.95 (m, 1H), 3.59−3.82 (m, 3H), 3.26−3.46 (m, 2H), 2.39 (br, 3H), 1.75−2.09 (m, 6H), 0.68 (t, 3H, J = 7.4 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 182.6, 179.8, 160.6, 118.0, 77.1, 68.0, 45.4, 44.1, 29.0, 25.5, 21.8, 11.0, 9.1; EI MS (*m*/*z*) 237 [M$^+$]; HRMS calculated for $C_{13}H_{19}NO_3$ [M$^+$], 237.136 49; found, 237.135 25.

4-Carbaldehyde-3-ethyl-5-methyl-1-phenethyl-3-pyrrolin-2-one (9e). Yellow liquid; IR ν_1(C=O) 1725 cm^{-1}, ν_2(C=O) 1642 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.10−7.27 (m, 5H), 3.62−3.79 (m, 2H), 2.90 (m, 1H), 2.86 (t, 2H, J = 6.6 Hz), 1.99 (q, 2H, J = 7.4 Hz), 1.95 (br, 3H), 0.74 (t, 3H, J = 7.4 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 182.4, 179.5, 159.4, 137.8, 129.8, 128.9, 127.0, 118.0, 45.4, 42.1, 35.1, 21.8, 10.3, 9.3; EI MS (*m*/*z*) 257 [M$^+$]; HRMS calculated for $C_{16}H_{19}NO_2$ [M$^+$], 257.141 58; found, 257.143 01.

1,3-Dibutyl-4-carbaldehyde- -5-phenyl-4-pyrrolin-2-one (9i). Yellow liquid; IR ν_1(C=O) 1727 cm^{-1}, ν_2(C=O) 1649 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.44−7.48 (m, 3H), 7.32−7.38 (m, 2H), 3.31−3.43 (m, 3H), 1.98 (q, 2H, J = 7.2 Hz), 1.18−1.28 (m, 6H), 1.03 (sextet, 2H, J = 7.7 Hz), 0.79 (t, 3H, J = 7.1 Hz), 0.65 (t, 3H, J = 7.3 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 184.6, 179.3, 161.7, 130.3, 128.8, 128.5, 126.9, 119.9, 44.6, 40.1, 30.3, 28.3, 26.7, 22.3, 19.3, 13.5, 13.0; EI MS (*m*/*z*) 299 [M$^+$]; HRMS calculated for $C_{19}H_{25}NO_2$ [M$^+$], 299.188 53; found, 299.187 08. Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.10; H, 8.30; N, 4.46.

1-Butyl-4-carbaldehyde-3-methyl-5-phenyl-4-pyrrolin-2-one (9j). Yellow liquid; IR ν_1(C=O) 1730 cm^{-1}, ν_2(C=O) 1648 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.51−7.53 (m, 3H), 7.39−7.41 (m, 2H), 3.39−3.42 (m, 3H), 1.47 (d, 3H, J = 7.6 Hz), 1.32 (q, 2H, J =

7.4 Hz), 1.08 (sextet, 2H, $J = 7.3$ Hz), 0.72 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 185.0, 180.3, 161.7, 130.7, 129.2, 128.9, 127.2, 122.2, 40.4, 40.0, 30.7, 19.6, 14.9, 13.4; EI MS (*m*/*z*) 257 [M^+]; HRMS calculated for $C_{16}H_{19}NO_2$ [M^+], 257.141 58; found, 257.140 55.

1-Butyl-4-carbaldehyde-3-isopropylidene-5-phenyl-4-pyrrolin-2-one (9k). Yellow liquid; IR ν_1(C═O) 1730 cm^{-1}, ν_2(C═O) 1648 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.46−7.49 (m, 3H), 7.33−7.36 (m, 2H), 3.43 (t, 2H, $J = 7.5$ Hz), 2.50 (s, 3H), 2.46 (s, 3H), 1.33 (quintet, 2H, $J = 7.5$ Hz), 1.10 (sextet, 2H, $J = 7.6$ Hz), 0.70 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 184.3, 167.3, 161.3, 160.8, 130.2, 129.5, 128.6, 128.0, 127.7, 121.6, 115.3, 40.6, 30.9, 28.0, 23.7, 19.7, 13.3; EI MS (*m*/*z*) 283 [M^+]; HRMS calculated for $C_{18}H_{21}NO_2$ [M^+], 283.157 23; found, 283.155 25.

1-Butyl-4-carbaldehyde-3-isopropyl-5-phenyl-4-pyrrolin-2-one (9l). Yellow liquid; IR ν_1(C═O) 1726 cm^{-1}, ν_2(C═O) 1649 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.46−7.52 (m, 3H), 7.35−7.38 (m, 2H), 3.47 (m, 1H), 3.35 (d, 1H, $J = 3.3$ Hz), 2.63 (septet, 1H, $J = 6.9$ Hz), 1.36 (m, 1H), 1.28 (quintet, 2H, $J = 6.9$ Hz), 1.18 (d, 3H, $J = 7.0$ Hz), 1.07 (sextet, 2H, $J = 7.5$ Hz), 0.86 (d, 3H, $J = 7.0$ Hz), 0.67 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 185.0, 178.5, 162.9, 130.6, 129.1, 128.8, 127.3, 119.8, 50.5, 40.3, 30.7, 29.2, 19.7, 19.4, 17.5, 13.3; EI MS (*m*/*z*) 285 [M^+]; HRMS calculated for $C_{18}H_{23}NO_2$ [M^+], 285.172 88; found, 285.171 65. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.61; H, 8.08; N, 4.74.

1-Butyl-4-carbaldehyde-3-cyclohexylmethyl-5-phenyl-4-pyrrolin-2-one (9m). Yellow liquid; IR ν_1(C═O) 1727 cm^{-1}, ν_2(C═O) 1649 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.47−7.54 (m, 3H), 7.34−7.38 (m, 2H), 3.29−3.50 (m, 3H), 1.78−1.94 (m, 2H), 1.51−1.68 (m, 7H), 0.90−1.36 (m, 8H), 0.71 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 185.0, 179.9, 161.5, 130.6, 129.1, 128.8, 127.4, 121.3, 43.0, 40.0, 36.8, 34.7, 33.9, 32.9, 30.6, 26.4, 26.2, 26.1, 19.7, 13.4; EI MS (*m*/*z*) 339 [M^+]; HRMS calculated for $C_{22}H_{29}NO_2$ [M^+], 339.219 83; found, 339.218 33. Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.64; H, 8.75; N, 4.01.

3-Butyl-4-carbaldehyde-1-isopropyl-5-phenyl-4-pyrrolin-2-one (9q). Yellow liquid; IR ν_1(C═O) 1726 cm^{-1}, ν_2(C═O) 1648 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.46−7.51 (m, 3H), 7.31−7.36 (m, 2H), 3.69 (septet, 1H, $J = 6.9$ Hz), 3.38 (t, 1H, $J = 5.5$ Hz), 2.00 (m, 2H), 1.34 (d, 3H, $J = 6.9$ Hz), 1.28 (d, 3H, $J = 6.9$ Hz), 1.11−1.26 (m, 4H), 0.82 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 185.0, 179.9, 162.8, 130.5, 129.3, 129.0, 128.8, 127.6, 120.2, 46.8, 45.3, 28.6, 26.7, 22.5, 20.0, 19.6, 13.8; EI MS (*m*/*z*) 285 [M^+]; HRMS calculated for $C_{18}H_{23}NO_2$ [M^+], 285.172 88; found, 285.171 36. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.91; H, 7.92; N, 4.84.

3-Butyl-4-carbaldehyde-1-isopropyl-5-*p*-tolyl-4-pyrrolin-2-one (9r). Yellow liquid; IR ν_1(C═O) 1727 cm^{-1}, ν_2(C═O) 1648 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.30 (d, 2H, $J = 8.2$ Hz), 7.23−7.25 (m, 2H), 3.73 (septet, 1H, $J = 6.9$ Hz), 3.40 (t, 1H, $J = 5.2$ Hz), 2.42 (s, 3H), 1.98−2.07 (m, 2H), 1.36 (d, 3H, $J = 6.9$ Hz), 1.30 (d, 3H, $J = 6.9$ Hz), 1.10−1.26 (m, 4H), 0.84 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 185.3, 180.1, 163.2, 140.9, 129.5, 129.3, 128.9, 124.6, 120.2, 46.8, 45.3, 28.7, 26.7, 22.6, 21.4, 20.0, 19.6, 13.8; EI MS (*m*/*z*) 299 [M^+]; HRMS calculated for $C_{19}H_{25}NO_2$ [M^+], 299.188 53; found, 299.187 09.

3-Butyl-4-carbaldehyde-1-isopropyl-5-(4-methoxyphenyl)-4-pyrrolin-2-one (9s). Yellow liquid; IR ν_1(C═O) 1725 cm^{-1}, ν_2(C═O) 1646 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.25−7.27 (m, 2H), 7.00 (d, 2H, $J = 8.9$ Hz), 3.85 (s, 3H), 3.76 (septet, 1H, $J = 6.9$ Hz), 3.39 (m, 1H), 2.00 (m, 2H), 1.37 (d, 3H, $J = 6.9$ Hz), 1.31 (d, 3H, $J = 6.8$ Hz), 1.10−1.26 (m, 4H), 0.84 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 185.3, 180.1, 163.0, 161.3, 130.9, 130.5, 120.3, 119.5, 114.3, 55.4, 46.7, 45.4, 28.7, 26.8, 22.6, 20.0, 19.7, 13.9; EI MS (*m*/*z*) 315 [M^+]; HRMS calculated for $C_{17}H_{25}NO_3$ [M^+], 315.183 44; found, 315.181 92. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.17; H, 7.93; N, 4.36.

3-Butyl-4-carbaldehyde-1-isopropyl-5-(4-chlorophenyl)-4-pyrrolin-2-one (9t). Yellow oil; IR ν_1(C═O) 1726 cm^{-1}, ν_2(C═O) 1649 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.50 (d, 2H, $J = 8.7$ Hz), 7.28−7.33 (m, 2H), 3.69 (septet, 1H, $J = 6.9$ Hz), 3.41 (t, 1H, $J = 5.4$ Hz), 1.97−2.07 (m, 2H), 1.36 (d, 3H, $J = 6.9$ Hz), 1.31 (d, 3H, $J = 6.9$ Hz), 1.10−1.27 (m, 4H), 0.84 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 184.6, 179.8, 161.3, 137.0, 130.7, 130.4, 129.8, 129.3, 126.1, 120.7, 46.9, 45.4, 28.7, 26.8, 22.6, 20.1, 19.8, 13.9; EI MS (*m*/*z*) 319 [M^+]; HRMS calculated for $C_{18}H_{22}NO_2Cl$ [M^+], 319.133 91; found, 319.134 76.

3-Butyl-4-carbaldehyde-1-isopropyl-5-(2-naphthalenyl)-4-pyrrolin-2-one (9u). Yellow oil; IR ν_1(C═O) 1725 cm^{-1}, ν_2(C═O) 1647 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.88−7.99 (m, 4H), 7.53−7.63 (m, 2H), 7.36−7.42 (m, 1H), 3.77 (septet, 1H, $J = 6.8$ Hz), 3.44−3.51 (m, 1H), 2.00−2.14 (m, 2H), 1.16−1.45 (m, 10H), 0.89 (t, 1.5H, $J = 6.7$ Hz), 0.87 (t, 1.5H, $J = 6.6$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 185.3, 185.1, 180.0, 162.9, 162.8, 133.7, 132.5, 129.8, 129.6, 128.9, 128.8, 128.3, 127.9, 127.4, 125.4, 125.0, 124.9, 120.6, 47.1, 47.0, 45.5, 28.9, 28.7, 26.9, 26.8, 22.6, 20.1, 20.0, 19.8, 19.6, 13.9; EI MS (*m*/*z*) 335 [M^+]; HRMS calculated for $C_{22}H_{25}NO_2$ [M^+], 35.188 53; found, 335.189 05. Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 79.00; H, 7.15; N, 3.87.

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Supporting Information Available: Experimental procedures for the synthesis of **4**, **5**, and **7**. ^{1}H and ^{13}C NMR spectra for **5a**−**5j**, **7a**−**7y**, **8e**, **8k**, **8t**−**8v**, and **9a**−**9u** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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