$Ru_3(CO)_{12}$-Catalyzed Intermolecular Cyclocoupling of Ketones, Alkenes or Alkynes, and Carbon Monoxide. [2 + 2 + 1] Cycloaddition Strategy for the Synthesis of Functionalized γ-Butyrolactones

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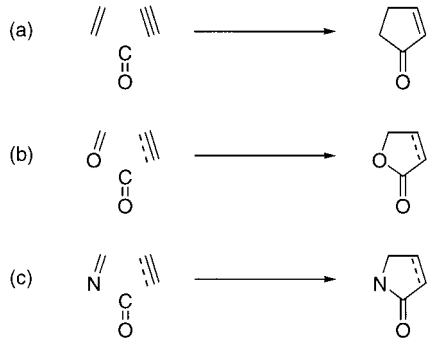
Abstract: The ruthenium-catalyzed intermolecular cyclocoupling of ketones (or aldehydes), alkenes (or alkynes), and CO, which leads to γ-butyrolactones, is described. The reaction represents the first example of the catalytic synthesis of heterocycles via an intermolecular carbonylative [2 + 2 + 1] cycloaddition. A wide variety of ketones, such as α-dicarbonyl compounds and *N*-heterocyclic ketones, can be used in this cycloaddition. The addition of phosphines is quite effective in reactions of α-dicarbonyl compounds. Of the phosphines examined, $P(4\text{-}CF_3C_6H_4)_3$ represents the additive of choice. Cyclic olefins, unpolarized terminal olefins, and internal alkynes can be successfully used in the synthesis of highly functionalized lactones. The introduction of a CF_3 group to the aromatic portion of an aromatic keto ester accelerates the reaction of the keto ester with ethylene, while the introduction of a MeO group enhances the rate of the reaction of *N*-heterocyclic ketones with ethylene. The rate of the reaction increases with increasing pressure of ethylene or a lower pressure of CO relative to the reaction of a keto ester. However, these pressure−rate relations are reversed for the reaction of an *N*-heterocyclic ketone with ethylene. Such differences can be rationalized by assuming that the rate-limiting step in the catalytic cycle is different for these reactions.

Introduction

Transition-metal-catalyzed cycloaddition reactions have clearly been demonstrated to be a powerful tool in organic synthesis.[1] Metal catalysts enable one to employ molecules that are thermally unreactive toward cycloadditions by taking advantage of their ability to be activated through complexation. An important example of this is the utilization of carbon monoxide as a one-carbon unit in cycloaddition chemistry. This approach leads to the direct formation of carbocyclic and heterocyclic carbonyl compounds from simple acyclic building blocks.[2,3] Among such carbonylative cycloaddition processes, the Pauson−Khand reaction, in which an alkyne, an alkene, and carbon monoxide are condensed in a formal [2 + 2 + 1] cycloaddition to form cyclopentenones (Scheme 1a), has attracted considerable attention. Significant progress, including the development of a catalytic variant for use in this process, has been reported recently.[3]

If the π-bond of a carbonyl or an imino moiety can be utilized in place of the alkene or alkyne π-bond in [2 + 2 + 1] cycloadditions, it would open new pathways for the construction of γ-lactones or γ-lactams, respectively (Scheme 1b,c). However, as of 1996, such an approach had not been reported. Crowe and Vu reported a titanium-mediated synthesis of γ-lactones which proceeds via the reaction sequence involving reductive coupling of an olefinic aldehyde/insertion of CO/reductive elimination.[4] This process requires the use of a stoichiometric amount of a titanium complex. Buchwald et al. independently reported a similar transformation and found that the reaction can be conducted catalytically when olefinic ketones which contain an aryl ketone moiety were used as substrates.[5]

Scheme 1. Synthesis of Five-Membered Carbonyl Compounds via [2 + 2 + 1] Cyclocoupling



(1) For general reviews on transition-metal-promoted cycloadditions, see: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523.

(2) For recent papers on the carbonylative cycloadditions, see the following. (a) [4 + 1]: Morimoto, T.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 1758. Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4130. (b) [4 + 4 + 1]: Murakami, M.; Itami, K.; Ito, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 3418.

(3) For recent reviews on the Pauson−Khand reaction, see: Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297. Brummond, K.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263.

(4) Crowe, W. E.; Vu, A. T. *J. Am. Chem. Soc.* **1996**, *118*, 1557.

(5) Kablaouni, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818. Kablaouni, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4424.

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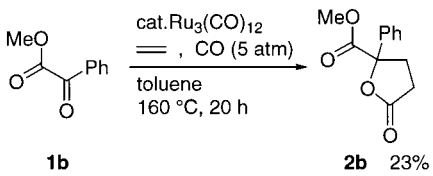
Subsequently, we reported on the $Ru_3(CO)_{12}$-catalyzed cyclocarbonyltions of yne-aldehydes[6] and yne-imines,[7] which produced bicyclic α,β-unsaturated γ-lactones and γ-lactams, respectively. With respect to the catalytic method, Buchwald's methodology and ours were the only successful systems that exemplified the strategies shown in reactions b and c of Scheme 1. These two systems fall in the class of an intramolecular cycloaddition, and there was no precedent for *intermolecular* variants of the process. Quite recently, we discovered that $Ru_3(CO)_{12}$ catalyzes the [2 + 2 + 1] cyclocoupling of ketones which contain a carbonyl group or *N*-heterocycles, ethylene, and CO.[8,9] The reaction represents the first example of the catalytic synthesis of heterocycles via *intermolecular* carbonylative [2 + 2 + 1] cycloaddition. In addition, it is interesting to note that the original meaning of the word "synthesis" is "to put together" in Greek. In this context, the intermolecular cyclocoupling described here is really a "synthesis" of cyclic carbonyl compounds. The full details of our investigation, including the scope and mechanistic aspects of this new cycloaddition, are reported herein.

Results and Discussion

In our attempts to carry out the cyclocoupling reaction shown in reaction b of Scheme 1, we began by employing a wide variety of aldehydes and ketones as substrates. However, the desired cyclocoupling did not occur. We then extended our efforts to more reactive carbonyl compounds including α-dicarbonyl compounds, and, as a result, we found that reaction b of Scheme 1 can be realized by the use of α-keto esters as the substrate in conjunction with $Ru_3(CO)_{12}$ as the catalyst. The reaction of methyl benzoylformate (**1b**) (2 mmol) with ethylene (initial pressure 3 atm at 25 °C in a 50-mL stainless steel autoclave) at 5 atm of CO (initial pressure at 25 °C) at 160 °C in toluene (6 mL) in the presence of $Ru_3(CO)_{12}$ (0.05 mmol) for 20 h gave tetrahydro-5-oxo-2-phenyl-2-furancarboxylic acid methyl ester (**2b**) in 23% isolated yield, with 75% of **1b** being recovered (eq 1). A prolonged reaction time (40 h) did not

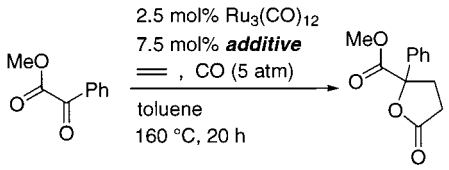


1b **2b** 23% (1)

significantly increase the product yield (40%). A variety of other transition metal complexes were examined for their ability to catalyze the coupling reaction, and none of these catalysts, which included $Fe_3(CO)_{12}$, $Co_2(CO)_8$, $Rh_4(CO)_{12}$, $Ir_4(CO)_{12}$, $Os_3(CO)_{12}$, $[RuCl_2(CO)_3]_2$, $RuCl_2(PPh_3)_3$, and $CpRuCl(PPh_3)_2$, were found to be active.

Effect of Additives. To improve catalytic efficiency, we next examined the effect of additives. The use of PPh_3 (0.15 mmol, i.e., 1 equiv to each Ru atom) in the $Ru_3(CO)_{12}$-catalyzed reaction of **1b** increased the yield of **2b** from 23% to 61%. This dramatic effect prompted us to survey an array of phosphines as additives. Some selected results are shown in Table 1. It was found that the yields are relatively parallel to the basicity of phosphines, except for the case of PCy_3. Thus, the lower the pK_a, the higher the yield. It was found that, of the phosphines investigated, $P(4\text{-}CF_3C_6H_4)_3$ gave the highest yield of **2b**. Decreasing the amount of $P(4\text{-}CF_3C_6H_4)_3$ to 0.05 mmol (i.e., 1 equiv to $Ru_3(CO)_{12}$ molecule) resulted in a lower yield of **2b** (56%), with 36% of **1b** being recovered. This indicates that one molecule of the phosphine per Ru atom is necessary in order to generate an active catalyst. We had postulated that the phosphine complex $Ru_3(CO)_9(PPh_3)_3$ might show a comparable activity. As expected, the use of $Ru_3(CO)_9(PPh_3)_3$ as a catalyst under otherwise identical conditions afforded 62% of **2b**, comparable to the yield obtained when 0.15 mmol of PPh_3 was added to 0.05 mmol of $Ru_3(CO)_{12}$. Similarly, the use of a mononuclear phosphine complex $Ru(CO)_2(PPh_3)_3$ (0.15 mmol) resulted in 51% of **2b**. Bidentate phosphines were also examined as additives. Of interest here is the fact that the yield of **2b** is dependent on the length of the carbon tether between the two phosphorus atoms. Of the bidentate phosphines examined, 1,4-bis(diphenylphosphino)butane (dppb) gave the highest yield of **2b** (56%), comparable to the yield obtained when PPh_2Me was used (50%). This observation suggests that only one phosphorus atom in dppb coordinates to the ruthenium to generate an active catalyst. In addition, non-phosphine additives, such as triethylamine (32%), 2,6-lutidine (23%), *tert*-butyl isocyanide (31%), 2,6-xylyl isocyanide (18%), and triphenylarsine (20%), were found to be less effective for this coupling.

Table 1. Effect of the Additives on $Ru_3(CO)_{12}$-Catalyzed Cyclocoupling[a]



1b **2b**

additive	pK_a[b]	yield[c]
none		23%
PCy_3	9.70	60%
PBu_3	8.43	25%
PPh_2Me	4.59	50%
$P(4\text{-}MeOC_6H_4)_3$	4.57	59%
$P(4\text{-}MeC_6H_4)_3$	3.84	54%
$P(2\text{-}MeC_6H_4)_3$	3.08	32%
PPh_3	2.73	61%
$P(4\text{-}FC_6H_4)_3$	1.97	64%
$P(4\text{-}ClC_6H_4)_3$	1.03	72%
$P(4\text{-}CF_3C_6H_4)_3$	−1.55	94%
$P(OPh)_3$	−1.20	9%
dppm[d]		3%
dppe[d]		14%
dppp[d]		25%
dppb[d]		56%

[a] Reaction conditions: ketone (2 mmol), ethylene (initial pressure 3 atm at 25 °C), CO (initial pressure 5 atm at 25 °C), $Ru_3(CO)_{12}$ (0.05 mmol), and additive (0.15 mmol) in toluene (6 mL) at 160 °C for 20 h in a 50-mL stainless autoclave, unless otherwise noted. [b] pK_a values of the corresponding conjugate acids.[10] [c] Isolated yields based on the starting ketones. [d] 0.075 mmol of the phosphine was added.

α-Dicarbonyl Compounds as a Ketone Component. Having optimized the reaction conditions and the additive of choice, we then performed cyclocoupling reactions with a range of α-dicarbonyl compounds as the ketone component. The results are shown in Table 2. In all cases, the reactions were clean, and no byproducts could be detected by GC or TLC, even in the crude reaction mixture. We first examined a set of α-keto

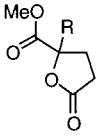
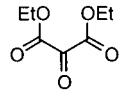
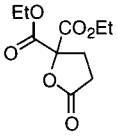
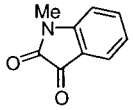
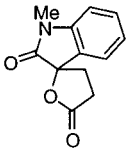
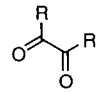
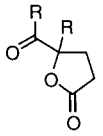
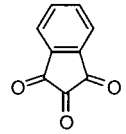
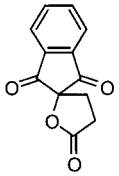
(6) Chatani, N.; Morimoto, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 5335.

(7) Chatani, N.; Morimoto, T.; Kamitani, A.; Fukumoto, Y.; Murai, S. *J. Organomet. Chem.* **1999**, *579*, 177.

(8) A preliminary result has been communicated: Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 7160.

(9) For a related [2 + 2 + 1] cycloaddition leading to γ-lactams, see: Chatani, N.; Tobisu, M.; Asaumi, T.; Murai, S. *Synthesis* **2000**, 925.

Table 2. $Ru_3(CO)_{12}$-Catalyzed [2 + 2 + 1] Cyclocoupling of α-Dicarbonyl Compounds, Ethylene, and CO[a]

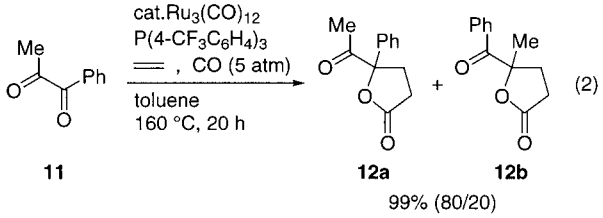
ketone	additive[b]	product[c]	
			
1a R = 4-$CF_3C_6H_4$	+	**2a**	99%
	−	**2a**	36%
1b R = Ph	+	**2b**	94%
	−	**2b**	23%
1c R = 4-$MeOC_6H_4$	+	**2c**	47%
	−	**2c**	7%
1d R = Me	+	**2d**	28%[d]
	−	**2d**	0%
1e R = CF_3	+	**2e**	48%
1f R = 	+	**2f**	32%
 **3**	+	 **4**	83%
 **5**	+	 **6**	96%
	−	**6**	95%
			
7a R = Ph	+	**8a**	98%
	−	**8a**	73%
7b R = 4-FC_6H_4	+	**8b**	98%
	−	**8b**	60%
7c R = 4-$MeOC_6H_4$	+	**8c**	97%
	−	**8c**	27%
7d R = Me	+	**8d**	70%
	−	**8d**	37%
7e R = 2-furanyl	+	**8e**	70%
	−	**8e**	86%
7f R = 2-thienyl	+	**8f**	58%
	−	**8f**	52%
 **9**	+	 **10**	48%
	−	**10**	51%

[a] Reaction conditions: ketone (2 mmol), ethylene (initial pressure 3 atm at 25 °C), CO (initial pressure 5 atm at 25 °C), and $Ru_3(CO)_{12}$ (0.05 mmol) in toluene (6 mL) at 160 °C for 20 h in a 50-mL stainless autoclave, unless otherwise noted. [b] +, $P(4\text{-}CF_3C_6H_4)_3$ (0.15 mmol) was added; −, no phosphine was added. [c] Isolated yields based on the starting ketones. [d] For a reaction run at 180 °C.

esters. The substituents on the ketone moiety have a significant effect on the efficiency of the reaction. The introduction of an electron-withdrawing group on the phenyl ring, as in **1a**, increased the yield of the lactone, while an electron-donating group, as in **1c**, retarded the reaction. A keto ester **1d** which contains an aliphatic keto moiety was less reactive in this coupling. As was the case with the aromatic keto esters, the introduction of electron-withdrawing groups, as in **1e**, enhanced the reactivity to afford the corresponding lactone **2e** (detailed discussion on the substituent effect, vide infra). Oxomalonic acid diethyl ester (**3**) also serves as a good substrate.

We next examined α-keto amides as possible substrates. The results obtained with acyclic keto amides such as *N*,*N*-dimethyl benzoylformamide (no reaction) and *N*-methyl-*N*-phenyl benzoylformamide (14%) were disappointing. However, a cyclic keto amide **5** afforded the corresponding spirolactone **6** in excellent yield. Interestingly, the addition of phosphine was not necessary for this substrate. The enhanced reactivity of **5** presumably stems from the rigid *s-cis* orientation of the dicarbonyl moiety in **5**, which permits the facile formation of a chelation complex with ruthenium, which we currently believe to be a key intermediate in this catalysis, as in **13** (vide infra).

Finally, α-diketones were investigated as a family of α-dicarbonyl compounds. In contrast to α-keto esters, both aromatic and aliphatic ketones gave the coupling products in good yields. Electron-poor as well as electron-rich diketones, such as **7b** and **7c**, efficiently afforded the corresponding lactones **8b** and **8c**, respectively. Furthermore, heteroaromatic groups, including a furan **7e** and a thiophene **7f**, can be tolerated. Indane-1,2,3-trione (**9**) was also a good substrate for this cyclocoupling reaction. The reaction took place specifically at the central carbonyl group, which would be expected to be more reactive than the terminal carbonyl groups in **9**,[11] to give a spirolactone **10**. When unsymmetrical α-diketone **11** was reacted with ethylene and CO under the same conditions as mentioned above, isomeric lactones **12a** and **12b** were formed in favor of **12a** (eq 2). The preferential incorporation of a benzoyl group over



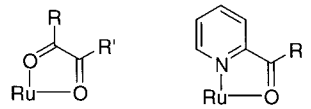
an acetyl group into the lactone ring is consistent with the fact that **7a** showed a higher reactivity than **7d** in this cyclocoupling reaction.

***N*-Heterocyclic Ketones as a Ketone Component.** All the applicable substrates discussed thus far have a carbonyl group adjacent to the reacting ketone moiety. To better understand the role of the adjacent carbonyl group, we examined some ketones bearing other electron-withdrawing groups. Reactions of benzoyl cyanide and pentafluoroacetophenone, as electronically activated ketones, were first investigated. However, no reactions occurred with these substrates. On the basis of these observations, we speculate that the adjacent carbonyl group was not able to serve as an electron-withdrawing group but, rather, functioned as a coordinating group and that the chelation

(10) Golovin, M. N.; Rhaman, Md. M.; Belmonte, J. E.; Giering, W. P. *Organometallics* **1985**, *4*, 1981. Neubrand, A.; Poë, A. J.; van Eldik, R. *Organometallics* **1995**, *14*, 3249.

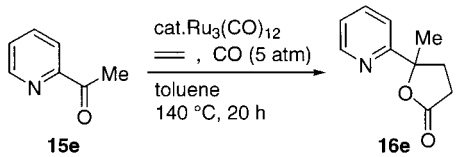
(11) Gill, R. B.; Idris, M. S. Hj.; Kirollos, K. S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2355.

Chart 1



13 **14**

complex **13** (Chart 1) would be a key intermediate in this cyclocoupling reaction. This speculation led us to employ the 2-pyridyl group as an adjacent group, since it could participate in forming a chelation ring, as in **14** (Chart 1). Indeed, the reactions proceeded well. In contrast to the reactions of α-dicarbonyl compounds, the addition of phosphines was, curiously, not required to obtain lactones in good yields (eq 3).



15e **16e** (3)

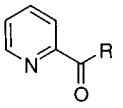
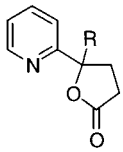
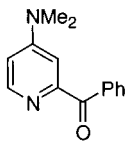
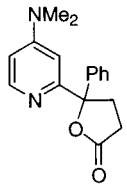
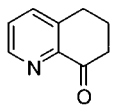
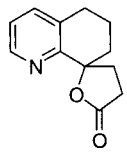
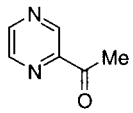
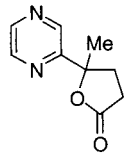
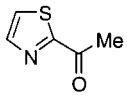
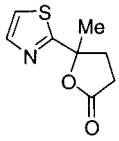
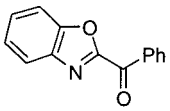
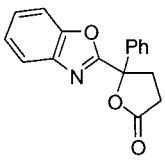
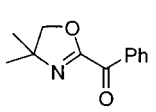
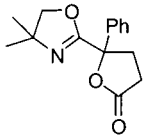
with P(4-$CF_3C_6H_4$)$_3$	92%
without P(4-$CF_3C_6H_4$)$_3$	**92%**

The reactions of a range of *N*-heterocyclic ketones and aldehydes were carried out (Table 3). Both aromatic and aliphatic ketones, even the sterically congested ketone **15g**, can be incorporated into the lactone ring efficiently in the absence of phosphines. In the case of aldehyde **15h**, the addition of PPh_3 was effective in giving a high yield of the lactone **16h**. It should be noted that a variety of functional groups, such as trifluoromethyl, methoxy, and dimethylamino groups, can be tolerated (see **15a**, **15c**, and **17**, respectively). The spirolactone **20** is also accessible from the reaction of the cyclic ketone **19**. Heteroaromatic ketones containing pyrazine, **21**, thiazole, **23**, and oxazole, **25**, rings gave the corresponding lactones in nearly quantitative yields. Furthermore, the reaction is not limited to heteroaromatic ketones. An oxazoline system, **27**, also served as a good substrate.

It is important to note that heteroaromatic ketones which do not contain an sp^2 nitrogen, such as 2-acetylpyrrole (**29**), 2-acetylfuran (**30**), and 2-acetylthiophene (**31**) (Chart 2), did not give the corresponding lactones. In addition, the cyclocoupling reaction of 3-acetylpyridine (**32)** and 2-pyridylacetone (**33)** did not take place. These results indicate that the five-membered chelation complex, formed through the coordination of sp^2-hybridized heteroatom (N or O) to the ruthenium, as in **13** and **14** (Chart 1), appears to be a key intermediate as speculated above. Interestingly, 4-acetylthiazole (**34)**, which is able to form a five-membered chelation complex similar to **14**, did not afford a cyclocoupling product, while the isomeric ketone **23** proved to be a good substrate. This observation has an important implication, in that conjugation between the adjacent C=X moiety (X = O, N) and the reacting carbonyl group is a significant factor for this coupling reaction to proceed.

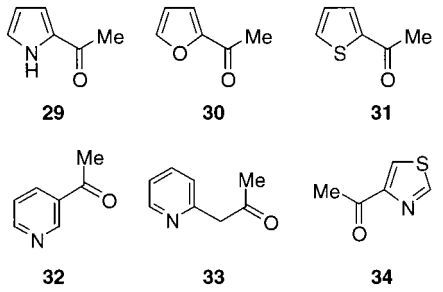
Substituted Alkenes as an Olefin Component. We next examined the scope of the reaction in the context of the olefin component. The reactions of unsymmetrical ketones with unsymmetrical olefins could, in theory, result in the formation of four isomeric lactones. To avoid complexities that might arise in these reactions, we initially investigated the reactions of symmetrical ketones with an array of symmetrical olefins (Table 4). The reaction of di-2-pyridyl ketone (**15d**) with *cis*-5-decene in the presence of $Ru_3(CO)_{12}$ and P(4-$CF_3C_6H_4$)$_3$ afforded the *cis*-substituted lactone **35** as the sole product in modest yield.

Table 3. $Ru_3(CO)_{12}$-Catalyzed [2 + 2 + 1] Cyclocoupling of *N*-Heterocyclic Ketones, Ethylene, and CO[a]

ketone	product[b]	
		
15a R = 4-$CF_3C_6H_4$	**16a**	92%
15b R = Ph	**16b**	93%
15c R = 4-$MeOC_6H_4$	**16c**	98%
15d R = 2-pyridinyl	**16d**	72%
15e R = Me	**16e**	92%
15f R = Bu	**16f**	96%
15g R = *t*-Bu	**16g**	45% (94%)[c]
15h R = H	**16h**	34% (85%)[c,d]
 **17**		**18** 93%
 **19**		**20** 29% (79%)[c]
 **21**		**22** 94%
 **23**		**24** 97%
 **25**		**26** 95%
 **27**		**28** 78%

[a] Reaction conditions: ketone (2 mmol), ethylene (initial pressure 3 atm at 25 °C), CO (initial pressure 5 atm at 25 °C), and $Ru_3(CO)_{12}$ (0.05 mmol) in toluene (6 mL) at 140 °C for 20 h in a 50-mL stainless autoclave, unless otherwise noted. [b] Isolated yields based on the starting ketones. [c] For a reaction run at 160 °C. [d] PPh_3 (0.15 mmol) was added.

Chart 2



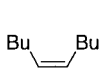
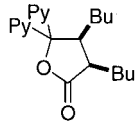
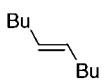
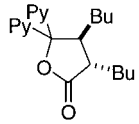
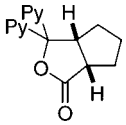
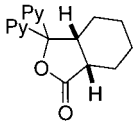
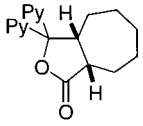
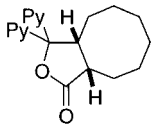
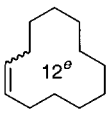
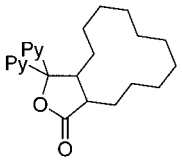
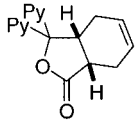
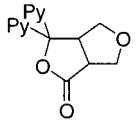
Prolongation of the reaction time (60 h) increased the yield to 85% with no loss of stereoselectivity. Likewise, the use of *trans*-5-decene as an olefin produced the *trans*-substituted lactone **36** stereospecifically, while the reaction rate was considerably slow relative to that of *cis*-isomer. Based on the observation that the *cis*-isomer showed a higher reactivity than the *trans*-isomer, cyclic olefins were assumed to serve as a good coupling partner. As expected, the reaction of **15d** with cyclopentene furnished the bicyclic lactone **37** in excellent yield, even in the absence of the phosphine ligand. The remarkable acceleration effect of $P(4\text{-}CF_3C_6H_4)_3$ was again observed in the reactions with larger membered cycloalkenes, such as cyclohexene, cycloheptene, and cyclooctene, which afforded *cis*-fused bicyclic lactones **38**−**40** quite efficiently. Furthermore, the reaction of stereoisomeric mixture of cyclododecene (*cis*/*trans* = ca. 2/1) afforded the corresponding lactone **41** as a mixture of stereoisomers. As would be expected from the higher reactivity of *cis*-olefins, the stereochemistry of the major isomer of **41** was determined to be *cis* by an NOE experiment (see Supporting Information for details). 1,4-Cyclohexadiene also serves as an olefin component to give bicyclic lactone **42**, which contains an olefin moiety, which can be amenable to further elaboration. The tetrahydrofuran-fused lactone **43** was also synthesized through this catalysis, although the reaction rate was relatively slow compared to that of cyclopentene. These results obtained for the reactions with cycloalkenes demonstrate that the present intermolecular [2 + 2 + 1] cycloaddition would provide a new convergent method for the construction of a wide range of bicyclic skeletons, which are not otherwise easily accessible.

We then turned our attention to the use of terminal olefins as the alkene component and discovered that some unpolarized olefins were applicable to this cyclocoupling, as shown in Table 5. In all cases, regioisomeric products were obtained. Both regioisomers **a** and **b** can be isolated in pure form by flash chromatography. The constitutions of the products have been determined by either deuterium exchange experiments, X-ray crystallography, or long-range C−H COSY spectra (see Supporting Information for details). Propylene can be coupled with **15d** and CO in the absence of phosphines to give the β-substituted lactone **44a** regioselectively (entry 1). A similar trend was observed in the cyclocoupling reactions using other terminal olefins such as 1-hexene and allyltrimethylsilane, which afforded β-substituted isomers preferentially (entries 3 and 5). The decrease in regioselectivities compared to the case of propylene indicates that the increased steric bulk of the olefin favors the formation of the α-substituted isomers. The cyclocoupling reactions of 1,1-disubstituted, conjugated, and electron-deficient olefins, as shown in Chart 3, did not proceed at an appreciable rate.

It is noteworthy that the addition of PPh_3 led to the converse in regioselectivity, namely, α-substituted lactones **b** predominated over β-substituted isomers **a** (entries 2, 4, and 6). This finding led us to examine a series of phosphines, as potential additives to clarify the factors which control the regioselectivity of the reaction. As a result, it was found that neither an increase in the amount of the phosphine nor the change in the electronic nature of the phosphine affected the regioselectivity significantly (see table in Supporting Information for details).

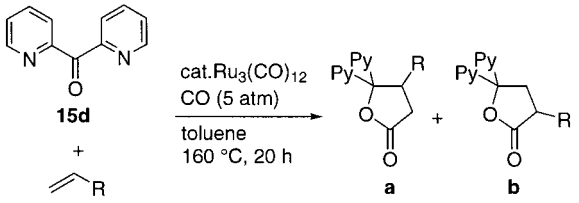
We next investigated the reactions of unsymmetrical ketones with symmetrical cyclic olefins, in which the formation of two stereoisomeric lactones is possible (Table 6). It was found that 2-benzoylthiazole (**47**) reacted with cyclopentene smoothly to furnish the bicyclic lactone **48** as the sole product (entry 1), the stereochemistry of which was determined by X-ray crystal-

Table 4. $Ru_3(CO)_{12}$-Catalyzed [2 + 2 + 1] Cyclocoupling of Di-2-pyridyl Ketone (**15d**), Symmetrical Olefins, and CO[a]

olefin	additive[b]	product[c]	
	+		**35** 53% (85%)[d]
	+		**36** 19% (30%)[d]
	−		**37** 94%
	−		**38** 14%
	+		**38** 97%
	+		**39** 97%
	−		**40** 17%
	+		**40** 94%
	+		**41** 70% (84/16)[f,g]
	+		**42** 83%
	+		**43** 51% (74%)[h]

[a] Reaction conditions: ketone (1 mmol), olefin (10 mmol), CO (initial pressure 5 atm at 25 °C), and $Ru_3(CO)_{12}$ (0.025 mmol) in toluene (3 mL) at 160 °C for 20 h in a 50-mL stainless autoclave, unless otherwise noted. [b] +, $P(4\text{-}CF_3C_6H_4)_3$ (0.075 mmol) was added; −, no phosphine was added. [c] Isolated yields based on the starting ketones. [d] For a reaction run for 60 h. [e] Ca. 2:1 *cis*/*trans* mixture. [f] The numbers in the parentheses are the ratios of isomers determined by ^1H NMR. [g] For a reaction run for 64 h. [h] For a reaction run for 80 h.

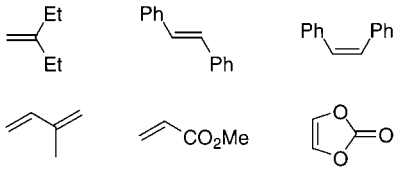
Table 5. $Ru_3(CO)_{12}$-Catalyzed [2 + 2 + 1] Cyclocoupling of Di-2-pyridyl Ketone (**15d**), Terminal Olefins, and CO[a]



entry	olefin	additive[b]	yield (**a**/**b**)[c]
1	R = Me[d]	−	**44**, 91% (94/5)
2		+	**44**, 90% (40/60)
3	R = Bu	−	**45**, 91% (78/22)
4		+	**45**, 90% (13/87)
5	R = CH_2SiMe_3	−	**46**, 85% (81/19)
6		+	**46**, 88% (14/86)

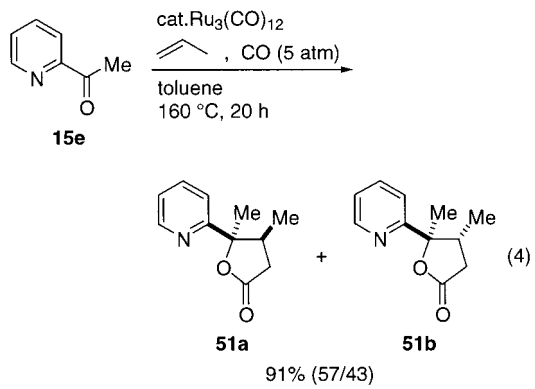
[a] Reaction conditions: ketone (2 mmol), olefin (20 mmol), CO (initial pressure 5 atm at 25 °C), and $Ru_3(CO)_{12}$ (0.05 mmol) in toluene (6 mL) at 160 °C for 20 h in a 50-mL stainless autoclave, unless otherwise noted. [b] +, PPh_3 (0.15 mmol) was added; −, no phosphine was added. [c] Isolated yields based on the starting ketones. The numbers in the parentheses are the ratios of isomers determined by GC analysis. [d] Initial pressure 3 atm at 25 °C of propylene was used.

Chart 3



lography. Similarly, the reaction of 2-benzoylpyridine (**15b**) also proceeded in a stereoselective manner to give the corresponding lactone **49** (entry 3). The stereochemistry of **49** was determined by analogy to **48**. On the other hand, a very low selectivity as well as a low reactivity was observed for 2-acetylpyridine (**15e**) (entry 5). When P(4-$CF_3C_6H_4$)$_3$ was used as an additive, **50** was formed with a high degree of stereoselectivity (entry 6), while no significant change in stereoselectivity was observed for the reactions of phenyl ketones (entries 2 and 4). The stereochemistry of the major isomer of **50** was determined by comparison with related compounds (see Supporting Information for details).

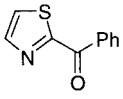
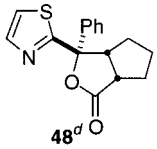
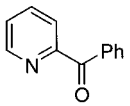
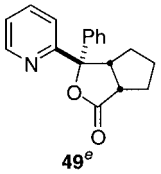
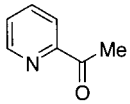
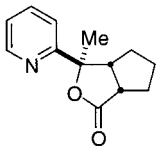
Finally, the reaction of unsymmetrical ketone **15e** with propylene, in which four stereoisomeric lactones could be formed, was performed. The reaction proceeded in a normal manner with a high degree of regioselectivity, affording β-substituted lactones **51a** and **51b** in a ratio of 57:43 (eq 4).



(4)

Cyclocoupling Using Alkynes. To further extend the scope of this new cycloaddition, we next investigated the reactivity

Table 6. $Ru_3(CO)_{12}$-Catalyzed [2 + 2 + 1] Cyclocoupling of Unsymmetrical Ketones, Cyclopentene, and CO[a]

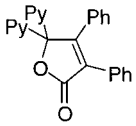
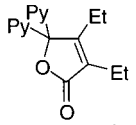
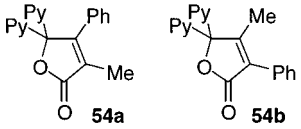
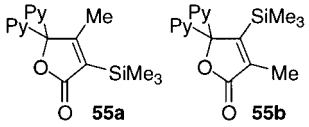
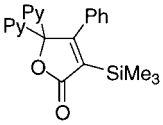
entry	ketone	additive[b]	product[c]
	 **47**		 **48**[d]
1		−	87% (>99/1)
2		+	92% (>98/2)
	 **15b**		 **49**[e]
3		−	99% (91/9)
4		+	99% (92/8)
	 **15e**		 **50**[f]
5		−	53% (42/58)[g]
6		+	96% (93/7)[g]

[a] Reaction conditions: ketone (2 mmol), olefin (20 mmol), CO (initial pressure 5 atm at 25 °C), and $Ru_3(CO)_{12}$ (0.05 mmol) in toluene (6 mL) at 160 °C for 20 h in a 50-mL stainless autoclave, unless otherwise noted. [b] +, P(4-$CF_3C_6H_4$)$_3$ (0.15 mmol) was added; −, no phosphine was added. [c] Isolated yields based on the starting ketones. The numbers in the parentheses are the ratios of isomers determined by ^{1}H NMR and GC analysis. [d] The stereochemistry was determined by X-ray crystallography. [e] The stereochemistry was determined by analogy to **48**. [f] The stereochemistry was determined by comparison with related compounds. [g] For a reaction run for 72 h.

of alkynes as a two-carbon π-system. A representative selection of internal alkynes was tested in the catalyzed cycloaddition of di-2-pyridyl ketone (**15d**). The results are summarized in Table 7. The reaction of **15d** with diphenylacetylene and CO in the presence of $Ru_3(CO)_{12}$ and PPh_3 led to the formation of the unsaturated lactone **52** in excellent yield (entry 1). Dialkyl acetylene can also be incorporated to give the corresponding lactone **53** in modest yield. (entry 2). In addition, it was found that phenyl and methyl groups on the alkyne moiety were well-differentiated in the present cyclocoupling. The use of 1-phenyl-1-propyne resulted in the formation of **54** in a regioselective manner (entry 3). Furthermore, silyl alkynes were found to be good coupling partners. The silyl group serves not only as an activating agent for the alkyne moiety toward cycloaddition but also to regulate the regiochemical course of the cycloaddition. As a result, the α-silylated lactone **55a** was produced highly regioselectively in an excellent yield (entry 4). The silylated phenyl acetylene gave **56** in a similar manner (entry 5). Since the silyl groups in **55** and **56** can be removed by treatment with tetrabutylammonium fluoride in methanol, the silyl alkynes can therefore function as the equivalent of terminal alkynes. Bis-(trimethylsilyl)acetylene and dimethyl acetylenedicarboxylate did not give the corresponding lactones.

The reactions presented in Table 7 can be regarded as the hetero Pauson−Khand type reaction, in which a carbonyl group in place of an olefin is incorporated into the five-membered

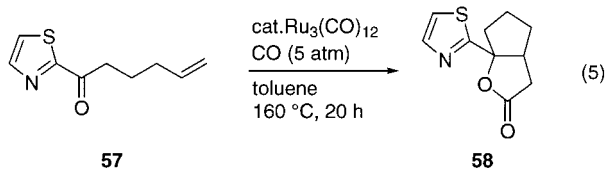
Table 7. $Ru_3(CO)_{12}$-Catalyzed [2 + 2 + 1] Cyclocoupling of Di-2-pyridyl Ketone (**15d**), Alkynes, and CO[a]

entry	alkyne	product[b]
1[c]	Ph—≡—Ph	 **52** 99%
2	Et—≡—Et	 **53** 50%[d]
3	Ph—≡—Me	 **54a** **54b** 76% (94/6)[e,f]
4	Me—≡—$SiMe_3$	 **55a** **55b** 98% (96/4)[g]
5[h]	Ph—≡—$SiMe_3$	 **56** 98%

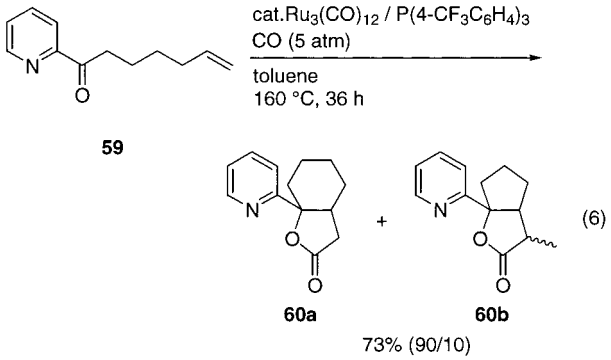
[a] Reaction conditions: **15d** (1 mmol), alkyne (10 mmol), CO (initial pressure 5 atm at 25 °C), $Ru_3(CO)_{12}$ (0.025 mmol), and $P(4\text{-}CF_3C_6H_4)_3$ (0.075 mmol) in toluene (3 mL) at 160 °C for 20 h in a 50-mL stainless autoclave, unless otherwise noted. [b] Isolated yields based on **15d**. [c] 1.1 mmol of diphenyl acetylene and PPh_3 in place of $P(4\text{-}CF_3C_6H_4)_3$ were used. [d] 6% of unidentified isomers and 22% of **15d** were also obtained. [e] For a reaction run for 70 h. [f] The ratio of the isomers was determined by ^1H NMR. [g] The ratio of the isomers was determined by GC analysis. [h] 2 mmol of trimethyl(phenylethynyl)silane was used.

ring. To our knowledge, there is no precedent for *catalytic intermolecular* variants of this process.[12]

Intramolecular Cyclocoupling. Although an *intramolecular* [2 + 2 + 1] cycloaddition of ketones, olefins, and CO has been achieved by use of titanium complexes as mentioned above,[4,5] it remains a rare phenomenon. Our successful application of *intermolecular* [2 + 2 + 1] cycloaddition to the synthesis of γ-butylolactone encouraged us to examine the *intramolecular* cyclocoupling, which leads to relatively complex bicyclic lactones in a single step. As a result, we were pleased to find that *N*-heterocyclic ketones, which contain a suitably positioned olefin, underwent the expected carbonylative cycloaddition. Olefinic ketone **57** reacted with CO in the presence of the $Ru_3(CO)_{12}$ catalyst, affording the bicyclic lactone **58** in good yield (eq 5). Lengthening the tethered chain resulted in the formation of cyclohexane-fused γ-lactone **60a**, along with cyclopentane-fused γ-lactone **60b**, while the reaction rate was relatively slow



57 **58** 86% (5)

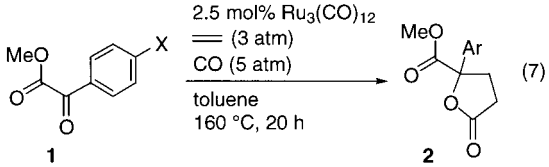


59 **60a** **60b** 73% (90/10) (6)

(eq 6). The cyclopentane-fused lactone **60b** is presumably formed via the cyclization of the isomerized starting material.[13]

Substituent Effects. In the course of our investigation on functional group compatibility of the reaction, it was observed that the electronic nature of the reacting ketone moiety has a significant effect on the reaction rate. Because of this, the substituent effects of a representative set of the reactions were examined.

First, the cyclocoupling of a set of aromatic keto esters **1** was tested. As shown in Table 2, both **1a** and **1b** gave the corresponding lactones in excellent yields when the reactions were carried out in the presence of $P(4\text{-}CF_3C_6H_4)_3$, whereas the use of **1c**, which contains an electron-donating group, led to a lowered yield. To evaluate the reactivity of each substrate, the reaction was conducted in the absence of the phosphine (eq 7). As a result, it was found that the order of the reactivity is as follows: $OCH_3 < H < CF_3$.



1 **2** (7)

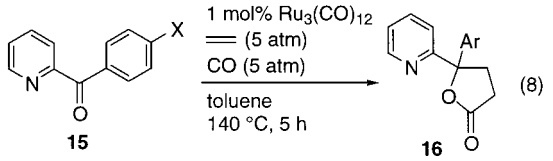
a:	X = CF_3	36 %
b:	H	23 %
c:	OMe	7 %

The reactions of a set of pyridyl aryl ketones **15** in the absence of the phosphine were next investigated. In sharp contrast to the results obtained for the keto esters shown in eq 7, the introduction of an electron-donating group enhanced the reactivity, and a dramatic decrease in rate was observed for the case of the CF_3 containing ketone **15a** (eq 8).

Last, we examined the substituent effects on the reactions of pyridyl ketones **15** with cyclohexene, in which the remarkable acceleration effect of $P(4\text{-}CF_3C_6H_4)_3$ was observed, as shown in Table 4. Interestingly and importantly, an inverse order

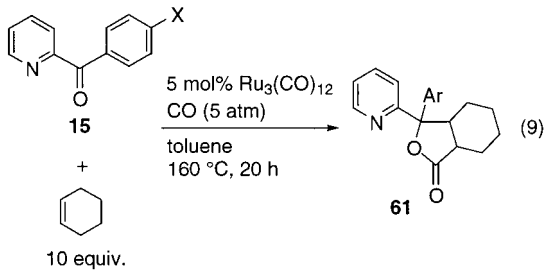
(12) For a catalytic intramolecular hetero Pauson−Khand type reaction, in which an alkyne, a C=X moiety (X = O, N), and CO are incorporated, see refs 6 and 7.

(13) Olefin isomerization occurred to some extent after 20 h of reaction.



a:	X = CF_3	7 %
b:	H	35 %
c:	OMe	49 %

compared to the reaction with ethylene was observed, namely, the reactivity order was as follows: OCH_3 < H < CF_3 (eq 9).



a:	X = CF_3	53 %
b:	H	23 %
c:	OMe	13 %

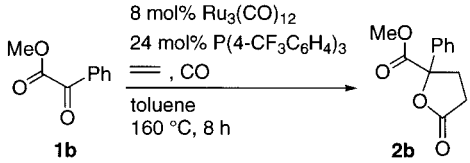
As shown in eqs 7−9, the reactions are quite sensitive to the electronic nature of the reacting keto moiety. The trends in substituent effect are closely related to the additive effect of phosphine derivatives. In the case of reactions in which the addition of phosphines accelerates the reaction rate, electron-deficient ketones are more reactive (eqs 7 and 9). On the other hand, electron-rich ketones show a higher reactivity in the reactions in which it is not necessary to use a phosphine ligand to obtain a high product yield (eq 8).

Effects of CO and Ethylene Pressures. In view of the marked difference in the substituent effect between the reactions of keto esters and those of pyridyl ketones, a comparison between these reactions with regard to other reaction parameters, such as CO and ethylene pressure, has been made. Initially, the cyclocoupling of the keto ester **1b** was conducted under various pressures of ethylene and CO, as shown in Table 8. As the pressure of ethylene increased, higher yields of **2b** were observed (entries 1−4). In contrast, the reaction rates were lowered when higher pressures of CO were used (entries 1, 5, 6, and 7).

Next, the effects of ethylene and CO pressures on the cycloaddition of **15b** were investigated (Table 9). Again, **15b** behaved in a manner distinctly different from **1b**. The higher yields of **16b** were obtained either at a lower pressure of ethylene or at a higher pressure of CO. These observations provide valuable insight into the rate-limiting step of the catalytic cycle (vide infra).

Mechanistic Aspects. A literature survey led us to discover a stoichiometric transformation which is relevant to the present results, reported by Frühauf and co-workers. They reported a series of reactions of complexes $M(CO)_3(R{-}N{=}C{-}C{=}N{-}R)$ and $M(CO)_3(R{-}N{=}C{-}C{=}O)$ (M = Fe, Ru) with electron-deficient alkenes and alkynes. For example, the ruthenium complex of 1,4-diaza-1,3-butadiene **62** reacted with dimethyl

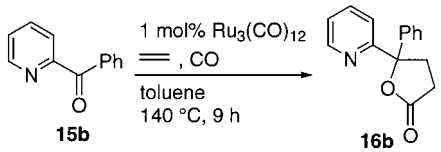
Table 8. Effects of Ethylene and CO Pressures on the Cycloaddition of **1b**, Ethylene, and CO[a]



entry	ethylene (atm)	CO (atm)	yield[b] (%)
1	5	5	59
2	10	5	64
3	15	5	71
4	20	5	79
5	5	10	27
6	5	15	15
7	5	20	11

[a] Reaction conditions: **1b** (0.5 mmol), ethylene, CO, $Ru_3(CO)_{12}$ (0.04 mmol), and $P(4\text{-}CF_3C_6H_4)_3$ (0.12 mmol) in toluene (6 mL) at 160 °C for 8 h in a 50-mL stainless autoclave. [b] GC yields based on **1b**.

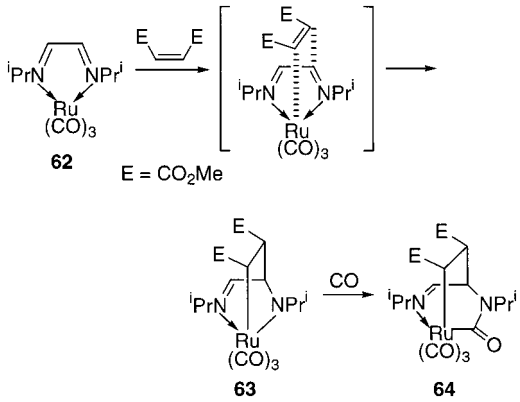
Table 9. Effects of Ethylene and CO Pressures on the Cycloaddition of **15b**, Ethylene, and CO[a]



entry	ethylene (atm)	CO (atm)	yield[b] (%)
1	5	5	54
2	10	5	49
3	15	5	45
4	20	5	30
5	5	10	74
6	5	15	78
7	5	20	100

[a] Reaction conditions: **15b** (1 mmol), ethylene, CO, and $Ru_3(CO)_{12}$ (0.01 mmol) in toluene (6 mL) at 140 °C for 9 h in a 50-mL stainless autoclave. [b] GC yields based on **15b**.

Scheme 2. A Related Stoichimetric Reaction (1)[14]



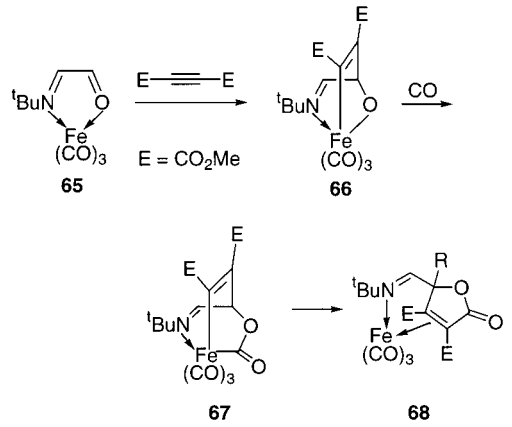
maleate and CO to afford the metallacycle **64** (Scheme 2).[14] The formation of **64** was rationalized by assuming the formation of complex **63**, which could be formed via the cycloaddition of dimethyl maleate onto the complex **62**.[15]

Another example is the reaction of the iron complex of 1-aza-4-oxo-1,3-butadiene **65** with dimethyl acetylenedicarboxylate

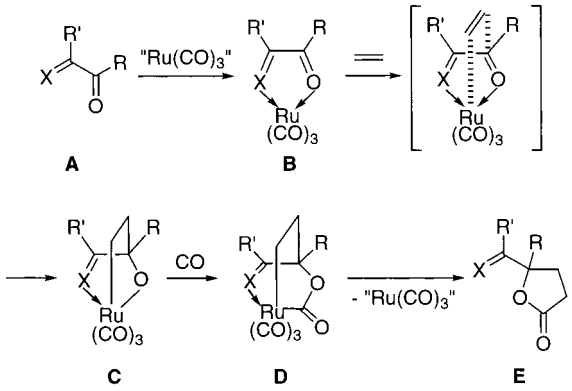
(14) van Wijnkoop, M.; de Lange, P. P. M.; Frühauf, H.-W.; Vrieze, K.; Smeets, W. J. J.; Spek, A. L. *Organometallics* **1995**, *14*, 4781.

(15) A related complex was characterized by X-ray crystallography: van Wijnkoop, M.; de Lange, P. P. M.; Frühauf, H.-W.; Vrieze, K.; Wang, Y.; Goubitz, K.; Stam, C. H. *Organometallics* **1992**, *11*, 3607.

Scheme 3. A Related Stoichiometric Reaction (2)[16a]



Scheme 4. A Possible Mechanism



and CO, which leads to the formation of butenolide complex **68**, presumably via the reductive elimination of the iron moiety from the metallacycle **67** (Scheme 3).[16a]

In light of the results of these stoichiometric reactions, we propose a reaction mechanism as shown in Scheme 4. The coordination of the substrate **A** (X = O or N) to a coordinatively unsaturated ruthenium species,[17] such as $Ru(CO)_3$ or $Ru(CO)_2(PAr_3)$,[18] forms a σ,σ-chelate ruthenium complex **B**.[19] The complex **B** reacts with an alkene (or an alkyne) to give the oxametallacycle **C**, with the coordination of X to ruthenium remaining intact. The subsequent CO insertion into a Ru−O bond[20] in **C** affords the metallacycle **D**, as for the cases of **64** and **67** in Schemes 2 and 3, respectively. The reductive elimination of **D** leads to the formation of the final product **E**.

The rate of the cycloaddition of **B** with an alkene would be expected to be accelerated by increasing the electron density in the vicinity of the ruthenium, since the ruthenium is oxidized from 0 to 2+ when **C** is formed. Indeed, Frühauf et al. reported that replacing the CO ligands with more σ-donating isonitrile ligands enhanced the reactivity of the related iron complex toward cycloaddition with electron-deficient alkenes and alkynes.[21] It therefore seems likely in our system that the phosphine derivative serves as a σ-donor ligand and thus facilitates the cycloaddition step. Although a σ-donor ligand has a positive effect on the rate of the cycloaddition step, the use of more basic phosphines could inhibit both the initial formation of coordinatively unsaturated ruthenium species and the coordination of the substrate to the ruthenium center. Accordingly, the success of the utilization of $P(4\text{-}CF_3C_6H_4)_3$ presumably stems from its less basic character that facilitates the oxametallacycle **C**-forming process without interrupting the formation of the catalytically active species.

The issue of whether the addition of phosphine ligands increases the yield largely depends on the structures of the ketones and olefins. In the reactions of α-dicarbonyl compounds with ethylene and those of *N*-heterocyclic ketones with internal alkenes, the yields are dramatically increased by using $P(4\text{-}CF_3C_6H_4)_3$. Following the rationale of the role of the phosphine ligands, it is most likely that the rate-limiting step in these reactions is the cycloaddition step of an alkene to complex **B**. Substituent effects of these reactions also support this view. The oxametallacycle **C**-forming step can be regarded as a formal oxidative cyclization, in which the valence of the ruthenium increases by 2. During this event, the ligand which participates in the oxidative cyclization (i.e., **A**) is reduced, so that an electron-deficient ketone would be expected to form oxametallacycle **C** more rapidly. Consistent with this consideration, the introduction of an electron-withdrawing group on the ketone moiety indeed led to an increased yield of the products in the phosphine-accelerated reactions, as shown in eqs 7 and 9. Furthermore, the effects of pressures of ethylene and CO, as shown in Table 8, can also be explained by the assumption that the cycloaddition of an olefin onto **B** is rate-limiting. A higher pressure of ethylene clearly would enhance the rate of the catalysis, since ethylene is involved in the rate-limiting step. In contrast, a higher pressure of CO should render it difficult both for the coordinatively unsaturated ruthenium species to be generated and for the substrate to coordinate to ruthenium, thus retarding the overall reaction.

On the other hand, the cyclocoupling occurs smoothly, even in the absence of phosphine derivatives in the reactions of *N*-heterocyclic ketones with relatively reactive alkenes, such as ethylene, cyclopentene, and terminal olefins. The observation indicates that the rate-limiting step in these reactions is not the oxidative cyclization process but a later step, most likely CO insertion or reductive elimination. The observation that the cyclocoupling of the pyridyl ketone is retarded at higher pressure of ethylene (see Table 9) is also indicative of its irrelevance to the rate-limiting step. Considering the observation on the effect of CO pressures (see Table 9), the CO insertion step (i.e., **C** → **D**) is likely to be rate-limiting. This rationale is corroborated by the finding that the opposite substituent effect relative to the phosphine-accelerated reactions was observed, as shown in eq 8. The fact that the CO insertion process is accelerated by the introduction of an electron-donating group on the migrating group[22] could account for the observed substituent effect.

(16) (a) van Wijnkoop, M.; Siebenlist, R.; de Lange, P. P. M.; Frühauf, H.-W.; Vrieze, K.; Smeets, W. J. J.; Spek, A. L. *Organometallics* **1993**, *12*, 4172. For a related stiochiometric reaction using methyl propynoate, see: (b) van Wijnkoop, M.; Siebenlist, R.; Ernsting, J. M.; de Lange, P. P. M.; Frühauf, H.-W.; Horn, E.; Spek, A. L. *J. Organomet. Chem.* **1994**, *482*, 99.

(17) The precise structure of the catalytically active species is not clear. A mononuclear species is postulated here on the basis of the related stoichiometric reactions, as shown in Schemes 2 and 3.

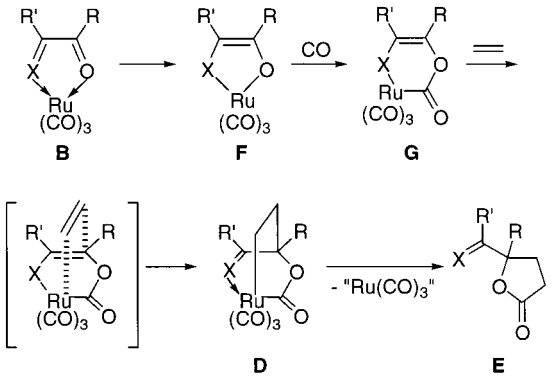
(18) In the phosphine-accelerated reactions, it is likely that the monophosphine complex is responsible for the catalysis. Both the catalyst/ligand ratio and the observed low activity on using bidentate phosphines support this view.

(19) Beers, O. C. P.; Bouman, M. M.; Elsevier, C. J.; Smeets, W. J. J.; Spek, A. L. *Inorg. Chem.* **1993**, *32*, 3015.

(20) The possibility that CO is inserted into a Ru−C bond in **C** cannot be excluded.

(21) de Lange, P. P. M.; Frühauf, H.-W.; van Wijnkoop, M.; Vrieze, K.; Wang, Y.; Heijdenrijk, D.; Stam, C. H. *Organometallics* **1990**, *9*, 1691. de Lange, P. P. M.; Frühauf, H.-W.; Kraakman, M. J. A.; van Wijnkoop, M.; Kranenburg, M.; Groot, A. H. J. P.; Vrieze, K.; Fraanje, J.; Wang, Y.; Neuman, M. *Organometallics* **1993**, *12*, 417. de Lange, P. P. M.; de Boer, R. P.; van Wijnkoop, M.; Ernsting, J. M.; Frühauf, H.-W.; Vrieze, K.; Smeets, W. J. J.; Spek, A. L.; Goubitz, K. *Organometallics* **1993**, *12*, 440.

Scheme 5. An Alternative Mechanism



The distinct difference in reactivities between α-dicarbonyl compounds and *N*-heterocyclic ketones can be attributed to differences in the coordination ability between oxygen and nitrogen atoms. Because of the strong basicity of the nitrogen atom, *N*-heterocyclic ketones themselves can serve as a good *σ*-donor ligand that renders the ruthenium center sufficiently electron-rich to undergo the cycloaddition with relatively reactive alkenes, such as ethylene, cyclopentene, and terminal olefins, in the absence of external *σ*-donor ligands. While the exact mechanism for the key oxidative cyclization step (i.e., **B** → **C**) remains unknown,[23] the conjugation between the C═X moiety (X = N, O) and C═O in **A** appears to be one of the important factors for the cycloaddtion step to proceed. It should be noted that an alternative mechanism, which consists of the initial CO insertion to **F** and the subsequent addition of an alkene (or an alkyne) onto the resulting metallacycle **G**, cannot be excluded (Scheme 5).

Although the regio- and stereoselectivities observed in the reactions of unsymmetrical substrates (Tables 5 and 6) represent quite interesting phenomena, the issue of what determines the regio- or stereochemical course of the reactions is not presently clear. With respect to the regioselectivity in reactions which involve the use of terminal alkenes, not only steric and electronic properties of the olefin employed but also steric and electronic environments provided by the ligand significantly affect the regioselectivity of the reaction. The unraveling of these entangled factors will be the subject of future studies.

Conclusion

We have demonstrated herein that $Ru_3(CO)_{12}$ catalyzes the intermolecular cyclocoupling of ketones (or aldehydes), alkenes (or alkynes), and CO. The reaction represents the first example of the catalytic synthesis of heterocycles via an intermolecular carbonylative [2 + 2 + 1] cycloaddition. A variety of ketones, such as α-dicarbonyl compounds and *N*-heterocyclic ketones, are applicable to the present reaction. In the case of the cycloaddition of α-dicarbonyl compounds, the addition of P(4-$CF_3C_6H_4)_3$ led to a dramatically enhanced reaction rate. A variety of cyclic olefins, unpolarized terminal olefins, and internal alkynes have been successfully used in the synthesis of highly functionalized *γ*-lactones. Remarkable differences in additive effects, substituent effects, and a dependence on reaction parameters, such as the pressure of ethylene and CO, were observed between the reactions of α-dicarbonyl compounds and those of *N*-heterocyclic ketones with ethylene. Such differences can be rationalized by assuming that the rate-limiting step in the catalytic cycle is different for these two types of reactions. The present catalytic reactions demonstrate the potential utility of the intermolecular [2 + 2 + 1] cycloaddition protocol for the synthesis of functionalized lactones. Further studies on this and related carbonylative cycloadditions are currently underway.

Experimental Section

Materials. Commercial grade reagents were used as received except as indicated below. Toluene was distilled over CaH_2. PBu_3 and **15h** were purified by distillation prior to use. $Ru_3(CO)_{12}$ was prepared according to the literature procedure[24] and used after recrystallization from hexane. Ketones **1b**, **1d**, **1e**, **3**, **5**, **7a**−**7f**, **9**, **11, 15b**, **15d**, **15h**, **21**, **23**, **29**, **30**, **31**, and **32** are commercially available and were used as received. **1c**,[25] **1f**,[26] **9**,[11] **15g**,[27] **19**,[28] **25**,[29] **27**,[30] **33**,[31] **34**,[32] and trimethyl(phenylethynyl)silane[33] were prepared according to the literature procedures. **1a** was prepared by the $Ti(O^iPr)_4$-catalyzed transesterification[34] of the corresponding ethyl ester.[35] **15a** and **15c** were prepared by the reactions of the corresponding arylmagnesium bromides, with **15h**, followed by PCC oxidation. **15f** was prepared from butylmagnesium bromide and 2-cyanopyridine. **47** was prepared by the reaction of 2-lithiothiazole and benzonitrile. See Supporting Information for the preparation of **17**, **57**, and **59**.

Typical Procedure for Cyclocoupling of Ketones, Ethylene, and CO. A 50-mL stainless autoclave was charged with methyl benzoylformate (**1b**) (2 mmol, 328 mg), $P(4\text{-}CF_3C_6H_4)_3$ (0.15 mmol, 70 mg), toluene (6 mL), and $Ru_3(CO)_{12}$ (0.05 mmol, 32 mg) under N_2. After the system was flushed with 10 atm of ethylene three times, it was pressurized with ethylene to 3 atm and then with carbon monoxide to an additional 5 atm. The autoclave was then immersed in an oil bath at 160 °C. After 20 h had elapsed, it was removed from the oil bath and allowed to cool for ca. 1 h, and the gases were then released. The contents were transferred to a round-bottomed flask with toluene, and the volatiles were removed by flash evaporation. The residue was subjected to column chromatography on silica gel (eluent, hexane/EtOAc = 5/1) to give tetrahydro-5-oxo-2-phenyl-2-furancarboxylic acid methyl ester (**2b**) (413 mg, 94% yield) as a colorless solid. Purification by bulb-to-bulb distillation afforded an analytically pure product.

Tetrahydro-5-oxo-2-phenyl-2-furancarboxylic acid methyl ester (2b): colorless solid; mp 54−56 °C (hexane); R_f 0.34 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 2.52−2.71 (c, 3H), 3.06−3.12 (m, 1H), 3.75 (s, 3H), 7.38−7.43 (c, 3H), 7.49−7.53 (c, 2H); ^{13}C NMR ($CDCl_3$) δ 28.00, 33.37, 53.30, 86.79, 124.92 (2C), 128.63 (2C), 128.77, 137.92,

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170.78, 174.88; IR (KBr) 1796 s, 1746 s, 1603 w; MS, *m*/*z* (relative intensity) 220 (M^+, 1), 161 (100). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.34; H, 5.49.

***cis*-3,4-Dibutyldihydro-5,5-di(2-pyridinyl)-2(3*H*)-furanone (35):** colorless oil; R_f 0.34 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.62 (t, J = 6.9 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H), 0.95−1.08 (c, 4H), 1.22−1.58 (c, 7H), 1.72−1.87 (m, 1H), 2.17−2.57 (m, 1H), 4.11−4.17 (m, 1H), 7.12−7.20 (c, 2H), 7.48 (dd, J = 7.9 Hz, J = 1.0 Hz, 1H), 7.61 (td, J = 7.9 Hz, J = 1.0 Hz, 1H), 7.69 (td, J = 7.9 Hz, J = 1.0 Hz, 1H), 7.78 (td, J = 7.9 Hz, J = 1.0 Hz, 1H), 8.58 (ddd, J = 4.6 Hz, J = 1.0 Hz, J = 0.7 Hz, 1H), 8.66 (ddd, J = 5.0 Hz, J = 1.0 Hz, J = 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.53, 13.91, 22.61, 23.03, 24.95, 25.09, 28.24, 30.05, 44.44, 44.82, 90.96, 120.01, 121.56, 122.07, 122.54, 136.39, 136.63, 148.54, 149.01, 158.82, 160.12, 178.17; IR (neat) 1784 s; MS, *m*/*z* (relative intensity) 352 (M^+, 4), 185 (100); HRMS calcd for $C_{22}H_{28}N_2O_2$ 352.2151, found 352.2158. The stereochemistry of **35** was assigned to be *cis* on the basis of the NOE enhancement exhibited between the ring junction protons (12%).

***trans*-3,4-Dibutyldihydro-5,5-di(2-pyridinyl)-2(3*H*)-furanone (36):** white solid; mp 65−67 °C (hexane/EtOAc); R_f 0.40 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.77−0.86 (c, 6H), 0.92−0.97 (m, 1H), 1.13−1.80 (c, 11H), 2.70−2.75 (m, 1H), 3.53−3.61 (m,1H), 7.13−7.18 (m, 1H), 7.22−7.29 (c, 2H), 7.51 (dd, J = 7.9 Hz, J = 0.7 Hz, 1H), 7.58−7.70 (c, 2H), 8.59 (ddd, J = 4.6 Hz, J = 1.0 Hz, J = 0.7 Hz, 1H), 8.68 (ddd, J = 4.6 Hz, J = 1.0 Hz, J = 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.87, 13.98, 22.61, 22.86, 28.91, 29.63, 29.98, 31.18, 46.48, 46.87, 90.70, 120.71, 121.84, 122.24, 122.77, 136.09, 136.63, 148.20, 148.98, 159.11, 160.81, 179.06; IR (neat) 1780 s; MS, *m*/*z* (relative intensity) 352 (M^+, 5), 185 (100). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 75.04; H, 8.10; N, 7.97.

Dihydro-4-methyl-5,5-di(2-pyridinyl)-2(3*H*)-furanone (44a): colorless oil; bp 200 °C (5 mmHg); R_f 0.26 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.9 Hz, 3H), 2.45 (dd, J = 16.5 Hz, J = 3.6 Hz, 1H), 2.80 (dd, J = 16.5 Hz, J = 7.9 Hz, 1H), 3.94−4.01 (m, 1H), 7.16−7.26 (c, 2H), 7.46 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.63−7.71 (c, 2H), 8.61 (d, J = 4.6 Hz, 1H), 8.67 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.52, 37.40, 37.63, 92.22, 120.42, 122.17, 122.37, 122.93, 136.41, 136.71, 148.45, 149.25, 158.69, 159.93, 176.28; IR (neat) 1789 s; MS, *m*/*z* (relative intensity) 254 (M^+, 20), 185 (100). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.59; H, 5.46; N, 11.02. The regiochemistry was determined by long-range ^{1}H−^{13}C COSY measurements (see Supporting Information for details).

Dihydro-3-methyl-5,5-di(2-pyridinyl)-2(3*H*)-furanone (44b): colorless oil; bp 200 °C (5 mmHg); R_f 0.20 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.29 (d, J = 7.3 Hz, 3H), 2.62 (t, J = 12.0 Hz, 1H), 2.75−2.84 (m, 1H), 3.79 (dd, J = 12.6 Hz, J = 8.2 Hz, 1H), 7.18−7.23 (c, 2H), 7.48 (d, J = 7.0 Hz, 1H), 7.57 (d, J = 6.8 Hz, 1H), 7.64−7.72 (c, 2H), 8.62 (d, J = 4.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.86, 34.90, 40.72, 87.96, 120.11, 120.86, 122.71, 122.82, 136.77 (2C), 149.06, 149.18, 159.87, 160.61, 179.01; IR (neat) 1786 s; MS, *m*/*z* (relative intensity) 254 (M^+, 11), 210 (100). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.87; H, 5.59; N, 10.95. The regiochemistry was determined by long-range ^{1}H−^{13}C COSY measurements (see Supporting Information for details).

Hexahydro-3-phenyl-3-(2-thiazolyl)-1*H*-cyclopenta[*c*]furan-1-one (48): colorless crystals; mp 119−120 °C (hexane); R_f 0.03 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 1.10−1.18 (m, 1H), 1.50−1.67 (c, 3H), 2.04−2.13 (m, 2H), 3.28 (td, J = 12.4 Hz, J = 4.1 Hz, 1H), 3.98−4.07 (m, 1H), 7.25−7.40 (c, 4H), 7.56 (dd, J = 8.0 Hz, J = 1.2 Hz, 2H), 7.76 (d, J = 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.64, 29.02, 29.51, 46.40, 50.93, 88.72, 120.88, 125.01 (2C), 128.01, 128.30 (2C), 139.30, 142.37, 174.03, 179.44; IR (KBr) 1780 s; MS, *m*/*z* (relative intensity) 285 (M^+, 13), 105 (100). Anal. Calcd for $C_{16}H_{15}NOS$: C, 67.35; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.20; H, 5.33; N, 4.83; S, 11.22. The stereochemistry of **48** was determined by X-ray crystallography.

Hexahydro-3-methyl-3-(2-pyridinyl)-1*H*-cyclopenta[*c*]furan-1-one (50). Major isomer: colorless oil; bp 180 °C (1 mmHg); R_f 0.31 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.53−1.82 (c, 6H), 1.89−2.17 (c, 3H), 2.88 (td, J = 8.9 Hz, J = 3.6 Hz, 1H), 3.34 (q, J = 7.9 Hz, 1H), 7.21 (ddd, J = 7.6 Hz, J = 5.0 Hz, J = 1.0 Hz, 1H), 7.51 (dd, J = 7.9 Hz, J = 1.0 Hz, 1H), 7.70 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.7 Hz, 1H), 8.59 (ddd, J = 5.0 Hz, J = 1.7 Hz, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.65, 26.29, 28.42, 28.82, 45.46, 49.73, 87.32, 118.34, 122.23, 136.79, 148.91, 163.78, 180.36; IR (neat) 1786 s; MS, *m*/*z* (relative intensity) 217 (M^+, 9), 122 (100). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.79; H, 7.18; N, 6.44.

Minor isomer: colorless oil; R_f 0.26 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.77−0.88 (m, 1H), 1.42−1.55 (s, 3H), 2.03 (q, J = 5.6 Hz, 2H), 3.06 (q, J = 7.9 Hz, 1H), 3.33 (td, J = 7.9 Hz, J = 5.6 Hz, 1H), 7.18 (ddd, J = 7.6 Hz, J = 4.6 Hz, J = 1.0 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.69 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.6 Hz, 1H), 8.59 (ddd, J = 4.6 Hz, J = 1.6 Hz, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.09, 29.13, 29.21, 29.86, 46.13, 51.31, 88.17, 119.01, 122.12, 136.54, 148.94, 161.32, 179.85; IR (neat) 1776 s; MS, *m*/*z* (relative intensity) 217 (M^+, 3), 146 (100); HRMS calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1107. The stereochemistry of the minor isomer was determined by comparison with **51a**. The upfield shift of 4-H (0.77−0.88 ppm) in the minor isomer relative to 4-H in the major isomer (1.53−2.17 ppm) indicates the *cis* relationship between the pyridine ring and the fused ring.[36]

***cis*-Dihydro-4,5-dimethyl-5-(2-pyridinyl)-2(3*H*)-furanone (51a):** colorless oil; bp 130 °C (2 mmHg); R_f 0.09 (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$) δ 0.67 (d, J = 6.9 Hz, 3H), 1.82 (s, 3H), 2.35 (dd, J = 17.2 Hz, J = 5.9 Hz, 1H), 2.72 (ddd, J = 8.3 Hz, J = 6.9 Hz, J = 5.9 Hz, 1H), 2.87 (dd, J = 17.2 Hz, J = 8.3 Hz, 1H), 7.20 (ddd, J = 7.6 Hz, J = 4.0 Hz, J = 1.7 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.69 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.7 Hz, 1H), 8.60 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.18, 26.00, 36.98, 40.56, 89.52, 119.64, 122.39, 136.50, 149.00, 159.84, 176.42; IR (neat) 1781 s; MS, *m*/*z* (relative intensity) 191 (M^+, 2), 122 (100). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.12; H, 6.90; N, 7.43. The regiochemistry of **51a** was determined by long-range ^{13}C−^{1}H COSY measurements (see Supporting Information for details). The stereochemistry of **51a** was determined by comparison with 4,5-dimethyl-5-phenyl-2(3*H*)-furanone.[36]

***trans*-Dihydro-4,5-dimethyl-5-(2-pyridinyl)-2(3*H*)-furanone (51b):** colorless oil; bp 130 °C (2 mmHg); R_f 0.14 (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 6.9 Hz, 3H), 1.64 (s, 1H), 2.29 (dd, J = 17.5 Hz, J = 7.3 Hz, 1H), 2.61 (dd, J = 17.5 Hz, J = 7.9 Hz, 1H), 2.92 (qdd, J = 7.9 Hz, J = 7.3 Hz, J = 6.9 Hz, 1H), 7.22 (ddd, J = 7.6 Hz, J = 4.0 Hz, J = 1.0 Hz, 1H), 7.54 (dd, J = 7.9 Hz, J = 1.0 Hz, 1H), 7.71 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.7 Hz, 1H), 8.57 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.19, 21.66, 36.73, 38.94, 89.56, 118.67, 122.48, 136.87, 148.84, 162.93, 175.99; IR (neat) 1781 s, 1692 s; MS, *m*/*z* (relative intensity) 191 (M^+, 9), 122 (100). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.15; H, 6.86; N, 7.47. The regiochemistry of **51b** was determined by long-range ^{13}C−^{1}H COSY measurements (see Supporting Information for details).

3-Methyl-4-phenyl-5,5-di(2-pyridinyl)-2(5*H*)-furanone (54a): white solid; mp 158−159 °C (hexane/EtOAc); R_f 0.34 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H), 7.00 (ddd, J = 7.1 Hz, J = 4.6 Hz, J = 1.0 Hz, 2H), 7.19−7.28 (c, 5H), 7.42 (dt, J = 7.9 Hz, J = 1.0 Hz, 2H), 7.69 (ddd, J = 7.9 Hz, J = 7.1 Hz, J = 1.0 Hz, 2H), 8.50 (ddd, J = 4.6 Hz, J = 1.6 Hz, J = 1.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 10.49, 93.23, 122.78 (2C), 123.22 (2C), 125.46, 127.69 (2C), 128.55, 129.07 (2C), 132.35, 136.63 (2C), 148.62 (2C), 157.34, 162.95, 173.64; IR (KBr) 1758 s, 1652 m; MS, *m*/*z* (relative intensity) 328 (M^+, 4), 283 (100). Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.55; H, 4.95; N, 8.41. The regiochemistry of **54a** was determined by comparison with **55**. A lower ^{1}H chemical shift of Me group in **54a** (2.01 ppm) relative to that in **54b** (2.46 ppm) indicates that the Me group in **54a** is at the 3-position.

4-Methyl-3-phenyl-5,5-di(2-pyridinyl)-2(5*H*)-furanone (54b). An analytical sample was obtained as a 35/64 regioisomeric mixture of **54b**/**54a**: R_f 0.31 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) *o*f the sample showed only two well-resolved peaks, δ 8.61 (ddd, J = 4.6 Hz, J = 1.6 Hz, J = 1.0 Hz, 2H), 2.46 (s, 3H); MS, *m*/*z* (relative

(36) Hoppe, D.; Brönneke, A. *Tetrahedron Lett.* **1983**, *24*, 1687. Fang, J.-M.; Hong, B.-C.; Liao, L.-F. *J. Org. Chem.* **1987**, *52*, 855.

intensity) 328 (M^+, 27), 78 (100); HRMS calcd for $C_{21}H_{16}N_2O_2$ 328.1211, found 328.1218.

4-Methyl-5,5-di(2-pyridinyl)-3-(trimethylsilyl)-2(5*H*)-furanone (55a): white solid; mp 100−102 °C (hexane/EtOAc); R_f 0.23 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.35 (s, 9H), 2.42 (s, 3H), 7.25−7.30 (m, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.73 (dd, J = 7.9 Hz, J = 7.6 Hz, 2H), 8.60 (d, J = 4.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −0.95 (3C), 16.28, 94.02, 122.07 (2C), 123.09 (2C), 125.46, 136.87 (2C), 148.77 (2C), 158.47 (2C), 175.78, 179.01; IR (KBr) 1739 s, 1613 m; MS, *m*/*z* (relative intensity) 324 (M^+, 8), 185 (100). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 66.63; H, 6.21; N, 8.63. Found: C, 66.86; H, 6.06; N, 8.58. The regiochemistry of **55a** was determined by its conversion to **44a** (see Supporting Information for details).

3-Methyl-5,5-di(2-pyridinyl)-4-(trimethylsilyl)-2(5*H*)-furanone (55b): colorless oil; R_f 0.51 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 9H), 2.11 (s, 3H), 7.24−7.28 (m, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.71 (t, J = 7.9 Hz, 2H), 8.54 (d, J = 4.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −0.27 (3C), 11.79, 95.76, 122.77 (2C), 123.16 (2C), 135.38, 136.53 (2C), 148.27 (2C), 158.69 (2C), 169.00, 174.34; IR (neat) 1760 s; MS, *m*/*z* (relative intensity) 324 (M^+, 0), 309 (M^+ − 15, 79), 78 (100); HRMS calcd for $C_{18}H_{20}N_2O_2Si$ 324.1293, found 324.1292. The regiochemistry was confirmed on the basis of ^{1}H NMR analysis of the desilylated lactone (see Supporting Information for details).

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Note Added in Proof: Following the submission of this manuscript, the thermal [2 + 2 + 1] cycloaddition reaction of quinones, dimethyl acetylenedicarboxylate, and isocyanide has been reported: Nair, V.; Vinod, A. U.; Nair, J. S.; Sreekanth, A. R.; Rath, N. P. *Tetrahedron. Lett.* **2000**, *41*, 6675.

Supporting Information Available: Full characterization data for all new compounds and a table concerning the effect of additives on the regioselectivity in the cycloaddition of **15d**, 1-hexene, and CO (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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