THE STUDY ON THE RUTHENIUM–CATALYZED CYCLOCOUPLING OF KETONES, OLEFINS, AND CARBON MONOXIDE

Mamoru Tobisu

Osaka University

2001

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（ルテニウム触媒によるケトンとオレフィンと一酸化炭素との環化カップリング反応に関する研究）

Mamoru Tobisu

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ACKNOWLEDGEMENT

At the conclusion of my Ph.D. study and of my life as a student, I have numerous people to thank.

I would like to express my utmost gratitude to *Professor Shinji Murai* for his guidance throughout this work. His philosophy about chemistry has deeply influenced me. He often describes his unique discovery-based way of studying as 'risky', but I feel the study in Murai research group was not only risky but also thrilling. I am now addicted to its attractiveness. For what I respect him the most is his ability to take essence from things. Any small words from him in the meetings taught me something. And I am also grateful for giving me a chance to study at MIT for five month.

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Last but not least, I would like to express my thanks to my parents for their perpetual support and to my wife *Tomomi* for her continuous encouragement.

Suita, Osaka
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Mamoru Tobisu

Preface

The study presented in this thesis has been carried out under the direction of Professor Shinji Murai at the Department of Applied Chemistry, Faculty of Engineering, Osaka University from April, 1995 to March 2001. The thesis is concerned with the ruthenium-catalyzed cyclocoupling of ketones, olefins, and carbon monoxide.

List of publication

Parts of this thesis have been adapted from the following articles co-written by the author.

(1) Ruthenium Carbonyl-Catalyzed [2 + 2 + 1]Cycloaddition of Ketones, Olefins, and Carbon Monoxide, Leading to Functionalized γ-Butyrolactones
Naoto Chatani, Mamoru Tobisu, Taku Asaumi, Yoshiya Fukumoto, Shinji Murai
J. Am. Chem. Soc. **1999**, *121*, 7160.

(2) The $Ru_3(CO)_{12}$-Catalyzed Intermolecular [2 + 2 + 1] Cyclocoupling of Imines, Alkenes or Alkynes, and Carbon Monoxide: A New Synthesis of Functionalized γ-Lactams
Naoto Chatani, Mamoru Tobisu, Taku Asaumi, Shinji Murai
Synthesis **2000**, 925.

(3) $Ru_3(CO)_{12}$-Catalyzed Intermolecular Cyclocoupling of Ketones, Alkenes or Alkynes, and Carbon Monoxide: [2 + 2 + 1] Cycloaddition Strategy for the Synthesis of Functionalized γ-Butyrolactones
Mamoru Tobisu, Naoto Chatani, Taku Asaumi, Katsuya Amako, Yutaka Ie, Yoshiya Fukumoto, Shinji Murai
J. Am. Chem. Soc. in press.

Supplementary List of Publications

(1) Enantioselective Isomerization of Allylic Alcohols Catalyzed by a Rhodium/Phosphaferrocene Complex
Ken Tanaka, Shuang Qiao, Mamoru Tobisu, Michael M.-C. Lo, Gregory C. Fu
J. Am. Chem. Soc. **2000**, *122*, 9870.

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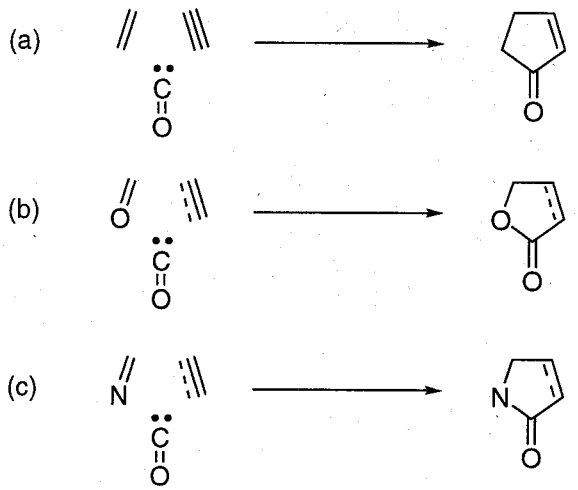
INTRODUCTION

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 1-1 (a)), has attracted considerable attention. Significant progress, including the development of a catalytic variant for use in this process, has been reported recently.[3]

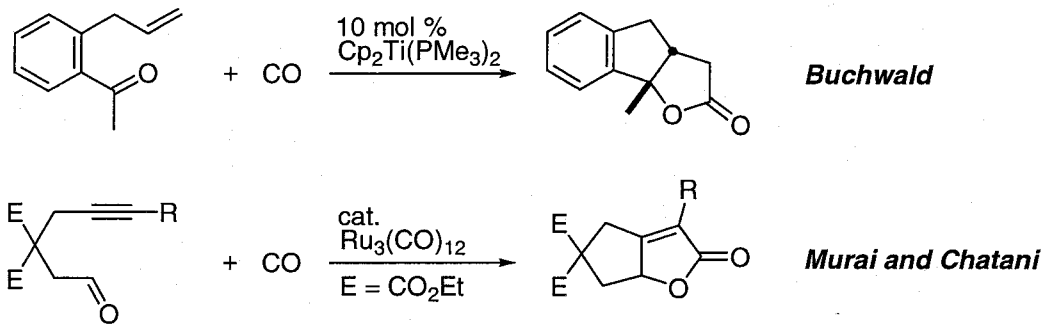
Scheme 1-1. Synthesis of Five-Membered Carbonyl Compounds *via* [2 + 2 + 1] Cyclocoupling



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 1-1 (b),(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 (see Scheme 1-2).[5] Subsequently, Murai and Chatani 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 (see Scheme 1-2). With respect to the catalytic method, Buchwald's methodology, as well as Murai and Chatani's were the only successful systems that exemplified the strategies shown in reactions b and c of Scheme 1-1. These two systems fall in the class of an intramolecular cycloaddition, and there was no precedent for *intermolecular* variants of the process.

Scheme 1-2. Catalytic Intermolecular [2 + 2 + 1] Cyclocoupling Leading to γ-Lactones



The prime objective of this research is to develop intermolecular carbonylative cycloadditions which utilize C=X bonds (X = heteroatom), especially a C=O bond. This thesis consists of the following four chapters.

Chapter 1 discusses the ruthenium-catalyzed cyclocoupling reaction of 1,2-dicarbonyl compounds, olefins, and carbon monoxide. This reaction represents the first example of catalytic synthesis of heterocycles *via* an intermolecular carbonylative [2 + 2 + 1] cycloaddition. α-Keto esters, α-keto amides, and α-diketones can be utilized in this reaction.

Chapter 2 discusses the ruthenium-catalyzed cyclocoupling reaction of *N*-heterocyclic ketones, olefins, and carbon monoxide. The presence of an adjacent C=N unit in conjugation with the reacting ketone moiety is necessary for the reaction o proceed. The details of the scope and limitation with respect to the alkene component are included.

Chapter 3 discusses the mechanistic aspects of the above-mentioned ruthenium-catalyzed reactions. On the basis of the relevant stoichiometric reactions, a possible

mechanism is proposed. The marked differences between the reaction of 1,2-dicarbonyl compounds and those of *N*-heterocyclic ketones can be rationalized.

Chapter 4 discusses the cyclocoupling reaction of imines, alkenes or alkynes, and carbon monoxide, which leads to γ-lactams.

References

(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.

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

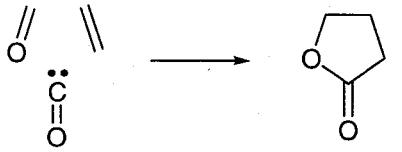
(7) Chatani, N.; Morimoto, T.; Kamitani, A.; Fukumoto, Y.; Murai, S. *J. Organomet. Chem.* **1999**, *579*, 177.

CHAPTER 1

Ruthenium-Catalyzed Cyclocoupling of 1,2-Dicarbonyl Compounds, Olefins, and Carbon Monoxide

1.1 Background

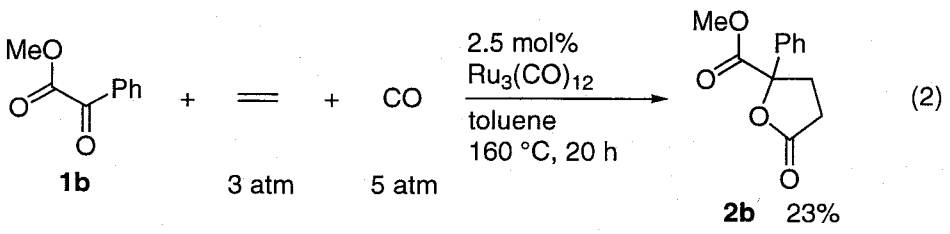
As mentioned in Introduction, there had been no precedents for catalytic intermolecular cyclocoupling of ketones, alkenes, and CO (*i.e.*, eq 1) prior to this work. In the hope of carrying out the cyclocoupling reaction shown in eq 1, the reactivities of a wide variety of aldehydes and ketones were examined, but the experiments were unsuccessful. The author then extended his efforts to more reactive carbonyl compounds including α-dicarbonyl compounds, and, as a result, it was found that eq 1 can be realized by the use of α-keto esters as the substrate in conjunction with $Ru_3(CO)_{12}$ as the catalyst.



(1)

1.2 Results and Discussion

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 (eq 2), along

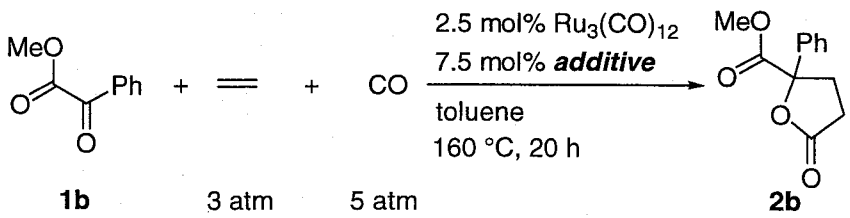


(2)

with 75% of **1b** being recovered. A prolonged reaction time (40 h) did not 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, I 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 me to survey an array of phosphines as additives. Some selected results are shown in Table1. It was found that the yields are relatively parallel to the pK_a values[1] of the conjugate acids of the phosphines, except for the case of PCy_3. Thus, the less basic the phosphine, 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. The author 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]



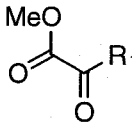
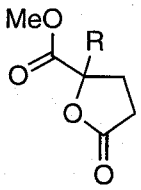
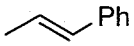
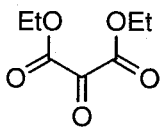
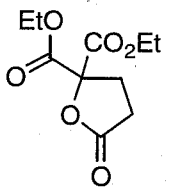
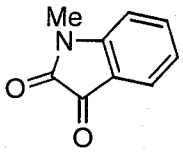
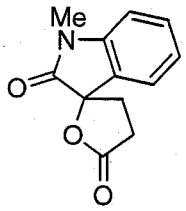
1b 3 atm 5 atm **2b**

entry	additive	pK_a[b]	yield[c]
1	none	-	23%
2	PCy_3	9.70	60%
3	PBu_3	8.43	25%
4	PPh_2Me	4.59	50%
5	$P(4\text{-}MeOC_6H_4)_3$	4.57	59%
6	$P(4\text{-}MeC_6H_4)_3$	3.84	54%
7	$P(2\text{-}MeC_6H_4)_3$	3.08	32%
8	PPh_3	2.73	61%
9	$P(4\text{-}FC_6H_4)_3$	1.97	64%
10	$P(4\text{-}ClC_6H_4)_3$	1.03	72%
11	$P(4\text{-}CF_3C_6H_4)_3$	-1.55	94%
12	$P(OPh)_3$	-1.20	9%
13	dppm[d]	-	9%
14	dppe[d]	-	14%
15	dppp[d]	-	25%
16	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), 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.[1] [c] Isolated yields based on the starting ketones. [d] 0.075 mmol of the phosphine was added.

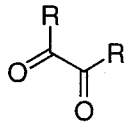
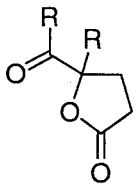
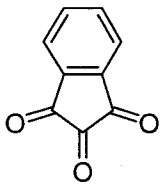
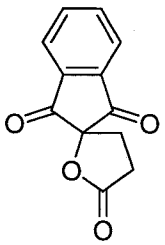
α-Dicarbonyl Compounds as a Ketone Component. Having optimized the reaction conditions and the additive of choice, the author then performed cyclocoupling reactions with a range of α-dicarbonyl compounds as the ketone component. The results are shown in Table 2. In all cases, the reactions were clean,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

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

entry	ketone	additive[b]	product[c]	
				
1	**1a** R = 4-$CF_3C_6H_4$	+	**2a**	99%
2		−	**2a**	36%
3	**1b** R = Ph	+	**2b**	94%
4		−	**2b**	23%
5	**1c** R = 4-$MeOC_6H_4$	+	**2c**	47%
6		−	**2c**	7%
7	**1d** R = Me	+	**2d**	28%[d]
8		−	**2d**	0%
9	**1e** R = CF_3	+	**2e**	48%
10	**1f** R = 	+	**2f**	32%
11	 **3**	+		**4** 83%
12	 **5**	+		**6** 96%
13		−		**6** 95%

[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) 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.

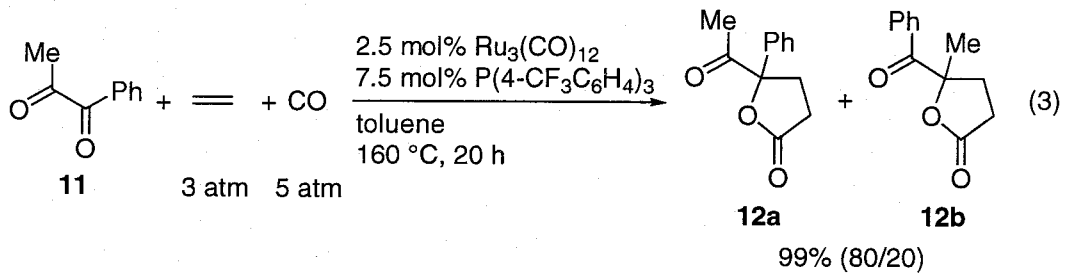
Table 2. (continued)[a]

entry	ketone	additive[b]	product[c]
			
22	**7a** R = Ph	+	**8a** 98%
23		–	**8a** 73%
24	**7b** R = 4-FC_6H_4	+	**8b** 98%
25		–	**8b** 60%
26	**7c** R = 4-$MeOC_6H_4$	+	**8c** 97%
27		–	**8c** 27%
28	**7d** R = Me	+	**8d** 70%
29		–	**8d** 37%
30	**7e** R = 2-furanyl	+	**8e** 70%
31		–	**8e** 86%
32	**7f** R = 2-thienyl	+	**8f** 58%
33		–	**8f** 52%
34		+	 **10** 48%
35		–	**10** 51%
	9		

even in the crude reaction mixture. The author first examined a set of α-keto 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, see Chapter 3). Oxomalonic acid diethyl ester (**3**) also serves as a good substrate.

The author 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 the author currently believe to be a key intermediate in this catalysis, as in **13** (see Chapter 3 for a mechanistic discussion).

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**,[2] 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 3). 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.



1.3 Conclusion

The first example of the catalytic intermolecular [2 + 2 + 1] cyclocoupling of ketones (or aldehydes), olefins, and CO has been demonstrated.[3] $Ru_3(CO)_{12}/P(4\text{-}CF_3C_6H_4)_3$ has proved to be a remarkable catalytic system for the cyclocoupling of a variety of 1,2-dicarbonyl compounds, such as α-keto esters, α-keto amide, and α-diketones. This reaction is potentially useful in the synthesis of γ-butyrolactones, which bear a carbonyl group at the γ-position and would be amenable to further elaboration.

1.4 Experimental Section

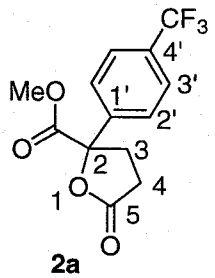
General Information. Boiling points (bp) refer to air bath temperatures for bulb-to-bulb distillation and are uncorrected. ^1H NMR and ^{13}C NMR were recorded on a JEOL JMN-270 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Data are reported as follows: chemical shifts in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, and c = complex), coupling constant (Hz), integration, and interpretation. Infrared spectra (IR) were obtained on a Hitachi 270-50 spectrometer; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained on a Shimadzu GCMS-QP 5000 instrument using ionization voltages of 70 eV. Elemental analyses were performed by the Elemental Analysis Section of Osaka University. Analytical GC was carried out on a Shimadzu GC-14A or GC-14B gas chromatograph, equipped with a flame ionization detector. Recycling preparative HPLC was performed on a Japan Analytical industry LC-908. Column chromatography was performed with SiO_2 (Wakogel or Merck SilicaGel 60 (230-400 mesh)).

Materials. Commercial grade reagents were used as received except as indicated below. Toluene was distilled over CaH_2. PBu_3 were purified by distillation prior to use. $Ru_3(CO)_{12}$ was prepared according to the literature procedure[4] and used after recrystallization from hexane. Ketones **1b**, **1d**, **1e**, **3**, **5**, **7a-7f**, **9**, and **11** are commercially available and were used as received. **1c**[5], **1f**[6], and **9**[2] were prepared according to the literature procedures. **1a** was prepared by the $Ti(O^iPr)_4$-catalyzed transesterification[7] of the corresponding ethyl ester.[8]

Typical Procedure for Cyclocoupling of Ketones, Olefins, 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 hours had elapsed, it was removed from the oil bath, 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

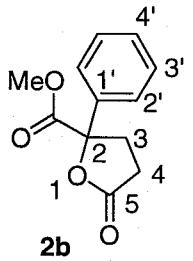
afforded an analytically pure product.

Tetrahydro-5-oxo-2-(4-trifluoromethylphenyl)-2-furancarboxylic acid methyl ester (2a). Colorless oil; bp 170 °C (1 mmHg) ; R_f 0.43 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.52-2.77 (c, 3H, 3, 4-H), 3.11-3.18 (m, 1H, 3-H or 4-H), 3.78 (s, 3H, OMe), 7.62-7.69 (c, 4H, Ar); ^{13}C NMR ($CDCl_3$) δ 27.91 (3-C or 4-C), 33.57 (3-C or 4-C), 53.58 (OMe), 86.17 (2-C), 123.59 (q, J = 271.9 Hz, CF_3), 125.39-125.60 (c, 4C, 2',3'-C), 130.80 (q, J = 33.0 Hz, 4'-C), 141.74 (1'-C), 170.02 (5-C or CO_2Me), 174.27 (5-C or CO_2Me); IR (neat) 3010 w, 2960 m, 2846 w, 1933 w, 1797 s, 1745 s, 1621 m, 1587 w, 1459 m, 1440 s, 1415 s, 1330 s, 1268 s, 1227 s, 1166 s, 1120 s, 1067 s, 1011 s, 971 m, 903 s, 844 s, 815 m; MS, *m/z* (relative intensity, %) 288 (M^+, 0.2), 230 (16), 229 (100), 201 (12), 173 (46), 145 (19). Anal. Calcd for $C_{13}H_{11}F_3O_4$: C, 54.16; H, 3.85. Found: C, 54.01; H, 3.83.



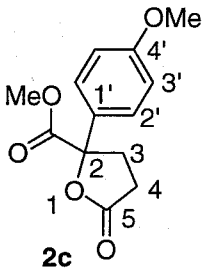
2a

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, 4-H), 3.06-3.12 (m, 1H, 3-H or 4-H), 3.75 (s, 3H, CH_3), 7.38-7.43 (c, 3H, Ph), 7.49-7.53 (c, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.00 (3-C or 4-C), 33.37 (3-C or 4-C), 53.30 (CH_3), 86.79 (2-C), 124.92 (2C, 3'-C or 4'-C), 128.63 (2C, 2'-C or 3'-C), 128.77 (4'-C), 137.92 (1'-C), 170.78 (5-C or CO_2Me), 174.88 (5-C or CO_2Me); IR (KBr) 3018 m, 2960 m, 1796 s, 1746 s, 1603 w, 1498 m, 1452 s, 1438 s, 1261 s, 1228 s, 1162 s, 1088 s, 1058 s, 1002 s, 967 m, 903 s, 811 m; MS, *m/z* (relative intensity, %) 220 (M^+, 1), 162 (11), 161 (100), 133 (14), 115 (15), 105 (55), 77 (44), 51 (20). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.34; H, 5.49.



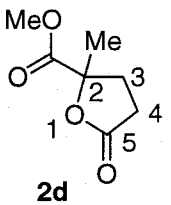
2b

Tetrahydro-5-oxo-2-(4-methoxyphenyl)-2-furancarboxylic acid methyl ester (2c). Colorless oil; bp 195 °C (1 mmHg) ; R_f 0.43 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.53-2.66 (c, 3H, 3, 4-H), 3.00-3.06 (m, 1H, 3-H or 4-H), 3.74 (s, 3H, CO_2CH_3 or $CH_3OC_6H_4$), 3.80 (s, 3H, CO_2CH_3 or $CH_3OC_6H_4$), 6.91 (d, J = 2.3 Hz, 2H, 2'-H or 3'-H), 7.42 (dd, J = 7.8 Hz, 2.3 Hz, 2H, 2'-H or 3'-H); ^{13}C NMR ($CDCl_3$) δ 28.00 (3-C or 4-C), 33.10 (3-C or 4-C), 53.12 (CO_2CH_3 or $CH_3OC_6H_4$), 55.14 (CO_2CH_3 or $CH_3OC_6H_4$), 86.46 (2-C), 113.71 (2C, 2'-C or 3'-C), 126.19 (2C, 2'-C or 3'-C), 129.53 (1'-C), 159.53 (4'-C), 170.67 (5-C or CO_2Me), 174.72 (5-C or CO_2Me); IR (neat) 3554 w, 3004 m, 2958 s, 2842 m, 1790 s, 1740 s, 1614 s, 1584 m, 1517 s, 1465 s, 1443 s, 1420 m, 1301 s, 1254 s, 1163 s, 1119 s, 1066 s, 1032 s, 999 s, 968 m, 907 s, 835 s, 810 s; MS, *m/z* (relative intensity, %) 250 (M^+, 5), 192 (16), 191 (100), 135 (30). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.38; H, 5.64. Found: C, 62.12; H, 5.60.



2c

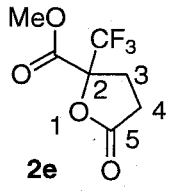
Tetrahydro-2-methyl-5-oxo-2-furancarboxylic acid methyl ester (2d). Colorless oil; bp 90 °C (5 mmHg); R_f 0.26 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3H, 2-CH_3), 2.13-2.21 (m, 1H, 3-H or 4-H), 2.53-2.69 (c, 3H, 3,4-H), 3.80 (s, 3H, CH_3O); ^{13}C NMR ($CDCl_3$) δ 23.74 (2-CH_3), 28.32 (3-C or 4-C), 32.94 (3-C or 4-C), 52.96 (CH_3O), 83.72 (2-C), 172.11 (5-C or CO_2Me), 175.76 (5-C or CO_2Me); IR (neat) 2992 m, 2960 m, 1790 s, 1744 s, 1461 m, 1382 m, 1322 s, 1297 s, 1275 s, 1246 s, 1199s, 1175 s, 1141 s, 1117 s, 1100 s, 980 m, 956 s, 914 m, 873 m, 809 m; MS, *m/z* (relative intensity, %) 158 (M^+, 0.5), 99 (100), 43 (41). Anal. Calcd for



2d

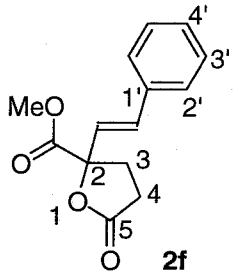
$C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.91; H, 6.32.

Tetrahydro-2-trifluoromethyl-5-oxo-2-furancarboxylic acid methyl ester (2e). - Colorless oil; bp 110 °C (2 mmHg); R_f 0.49 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.57-2.81 (c, 4H, 3, 4-H), 3.91 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$) δ 26.34 (q, J = 1.1 Hz, 3-C), 26.53 (4-C), 53.96 (OMe), 82.47 (q, J = 32.0 Hz, 2-C), 122.30 (q, J = 282.8 Hz, CF_3), 165.42 (5-C or CO_2Me), 173.14 (5-C or CO_2Me); IR (neat) 3604 w, 3020 m, 2966 m, 2856 w, 1824 s, 1769 s, 1465 s, 1443 s, 1424 m, 1320 s, 1277 s, 1235 s, 1201 s, 1095 s, 1056 s, 1002 m, 970 m, 900 s, 815 m; MS, *m/z* (relative intensity, %) 212 (M^+, 0.4), 153 (100), 125 (13), 97 (16), 75 (17), 69 (18). Anal. Calcd for $C_7H_7F_3O_4$: C, 39.64; H, 3.33. Found: C, 39.55; H, 3.40.



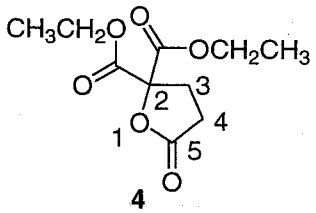
2e

Tetrahydro-5-oxo-2-(2-phenylethenyl)-2-furancarboxylic acid methyl ester (2f). Yellow oil; bp 150 °C (1 mmHg); R_f 0.54 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.35-2.45 (m, 1H, 3-H or 4-H), 2.60-2.76 (c, 3H, 3, 4-H), 3.83 (s, 3H, OMe), 6.42 (d, J = 16.2 Hz, 1H, vinyl), 6.80 (d, J = 16.2 Hz, 1H, vinyl), 7.27-7.42 (c, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.57 (4-C), 32.69 (3-C), 53.21 (OMe), 85.30 (2-C), 124.96 (vinyl), 126.79 (2C, 2'-C or 3'-C), 128.50 (4'-C), 128.66 (2C, 2'-C or 3'-C), 131.03 (vinyl), 135.20 (1'-C), 170.53 (5-C or CO_2Me), 175.08 (5-C or CO_2Me); IR (neat) 3554 w, 3028 m, 2956 m, 2846 s, 1791 s, 1755 s, 1652 m, 1602 m, 1580 m, 1499 s, 1452 s, 1438 s, 1401 m, 1321 s, 1166 s, 1064 s, 1015 m, 973 s, 949 m, 906 s, 843 m, 810 m; MS, *m/z* (relative intensity, %) 246 (M^+, 2), 188 (12), 187 (100), 159 (12), 141 (11), 131 (30), 103 (21), 77 (24), 55 (10), 51 (26). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.32; H, 5.73.



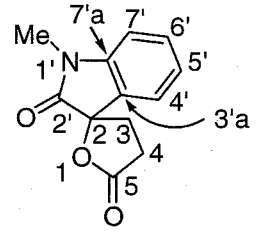
2f

Dihydro-5-oxo-2,2(3*H*)furandicarboxylic acid diethyl ester (4). Colorless oil; bp 150 °C (2 mmHg); R_f 0.43 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 6H, CH_2CH_3), 2.67-2.70 (c, 4H, 3, 4-C), 4.32 (q, J = 7.1 Hz, 4H, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 13.68 (CH_2CH_3), 27.01 (3-C or 4-C), 28.32 (3-C or 4-C), 62.73 (CH_2CH_3), 84.08 (2-C), 166.49 (5-C or CO_2Et), 174.21 (5-C or CO_2Et); IR (neat) 3586 w, 2988 s, 1801 s, 1748 s, 1470 s, 1421 m, 1394 m, 1371 s, 1307 s, 1176 s, 1080 s, 1012 s, 956 w, 910 m, 859 m, 818 w; MS, *m/z* (relative intensity, %) 230 (M^+, 0), 158 (40), 157 (52), 129 (34), 102 (16), 101 (100), 55 (11), 29 (22). Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.12; H, 5.97.



4

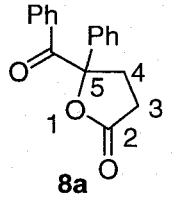
3,4-Dihydro-1'-methyl-spiro[furan-2(5*H*),3'-[3*H*]indole]-2',5(1'*H*)-dione (6). Pale red solid; mp 127-128 °C (hexane/EtOAc); R_f 0.23 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.40-2.63 (c, 2H, 3-H and/or 4-H), 2.77 (ddd, J = 17.5 Hz, 9.6 Hz, 3.3 Hz, 1H, 3-H or 4-H), 3.13-3.28 (c, 4H, 1'-Me and 3-H or 4-H), 6.87 (d, J = 7.6 Hz, 1H, 4'-H or 7'-H), 7.14 (td, J = 7.4 Hz, 0.7 Hz, 1H, 4'-H or 7'-H), 7.34-7.44 (c, 2H, 5',6'-H); ^{13}C NMR ($CDCl_3$) δ 26.26 (1'-Me), 28.21 (3-C or 4-C), 31.18 (3-C or 4-C), 82.23 (2-C), 108.82 (4'-C or 7'-C), 123.52 (4'-C or 7'-C), 124.13 (5'-C or 6'-C), 126.36 (3'a-C), 131.14 (5'-C or 6'-C), 143.86 (7'a-C), 174.14 (5-C or 2'-C), 175.94 (5-C or 2'-C); IR (KBr) 3060 w, 2998 w, 2956 w, 1783 s, 1715 s, 1619 s, 1501 s, 1475 s, 1426 m, 1414 m, 1377 s, 1356 s, 1316 s, 1275 m, 1245 s, 1222 s, 1199 m, 1171 s, 1153 s, 1125 s, 1098 s, 1051 s, 1015 w, 989 s, 941 m, 924 w, 898 s, 865 m, 844 m, 814 w; MS, *m/z*



6

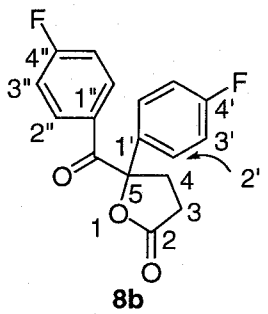
(relative intensity, %) 217 (M^+, 100), 189 (32), 175 (49), 173 (11), 162 (30), 161 (22), 160 (39), 158 (34), 146 (16), 144 (33), 134 (31), 133 (24), 132 (25), 131 (10), 130 (34), 117 (15), 116 (11), 115 (16), 105 (22), 104 (26), 103 (15), 91 (17), 90 (17), 89 (16), 80 (16), 78 (24), 77 (60), 76 (19), 75 (13), 74 (10), 66 (53), 65 (32), 64 (19), 63 (33), 62 (13), 58 (11), 57 (10), 55 (27), 52 (46), 51 (59). Anal. Calcd for $C_{12}H_{11}NO_3$; C, 66.35; H, 5.10; N, 6.45. Found: C, 66.24; H, 5.11, N; 6.44.

5-Benzoyltetrahydro-5-phenyl-2(3*H*)-furanone (8a). Colorless oil; bp 180 °C (5 mmHg); R_f 0.14 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 2.28-2.39 (m, 1H, 3-H or 4-H), 2.54-2.61 (c, 2H, 3-H and/or 4-H), 3.38-3.48 (m, 1H, 3-H or 4-H), 7.30-7.49 (c, 8H, Ph), 7.95 (d, *J*=7.3 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.77 (3-C or 4-C), 34.13 (3-C or 4-C), 91.90 (5-C), 123.56 (2C, Ph), 128.09 (2C, Ph), 128.37 (Ph), 129.09 (2C, Ph), 130.53 (2C, Ph), 133.24 (Ph), 133.39 (Ph), 139.23 (Ph), 175.35 (2-C), 195.02 (Ph(*C*=O)); IR (neat) 3060 m, 1784 s, 1679 s, 1597 m, 1579 m, 1493 m, 1448 s, 1415 w, 1305 w, 1263 s, 1211 s, 1158 s, 1081 s, 1051 s, 997 m, 945 m, 895 m, 848 m; MS, *m/z* (relative intensity, %) 266 (M^+, 0), 265 (M^+-1, 1), 162 (11), 161 (100), 133 (12), 105 (71), 77 (67), 51 (22). Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.58; H, 5.36.



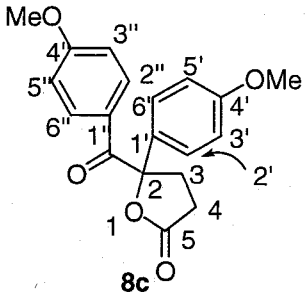
8a

5-(4-Fluorobenzoyl)-5-(4-fluorophenyl)-tetrahydro-2(3*H*)-furanone (8b). Colorless oil; bp 180 °C (5 mmHg); R_f 0.20 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 2.24-2.35 (m, 1H, 3-H or 4-H), 2.51-2.65 (c, 2H, 3-H and/or 4-H), 3.38-3.48 (m, 1H, 3-H or 4-H), 6.99-7.13 (c, 4H, 3',3"-H), 7.42-7.47 (c, 2H, 2'-H or 2"-H), 7.97-8.03 (c, 2H, 2'-H or 2"-H); ^{13}C NMR ($CDCl_3$) δ 27.84 (3-C or 4-C), 34.27 (3-C or 4-C), 91.56 (5-C), 115.56 (2C, d, *J* = 22.0 Hz, 2'-C or 2"-C), 116.35 (2C, d, *J* = 22.0 Hz, 2'-C or 2"-C), 125.63 (2C, d, *J* = 8.6 Hz, 3'-C or 3"-C), 129.65 (1'-C or 1"-C), 133.53 (2C, d, *J* = 9.8 Hz, 3'-C or 3"-C), 135.01 (1'-C or 1"-C), 162.65 (d, *J* = 247.8 Hz, 4'-C or 4"-C), 165.80 (d, *J* = 256.4 Hz, 4'-C or 4"-C), 175.08 (2-C), 193.48 (Ar*C*O); IR (neat) 3074 w, 1791 s, 1680 s, 1598 s, 1505 s, 1451 m, 1411 m, 1299 m, 1263 s, 1229 s, 1152 s, 1101 m, 1082 m, 1058 s, 1000 m, 941 m, 897 m, 861 m, 835 s; MS, *m/z* (relative intensity, %) 302 (M^+, 0), 180 (11), 179 (M^+-FC_6H_4CO, 100), 151 (14), 123 (75), 95 (44), 75 (15). Anal. Calcd for $C_{17}H_{12}F_2O_3$; C, 67.55; H, 4.00. Found: C, 67.74; H, 4.02.



8b

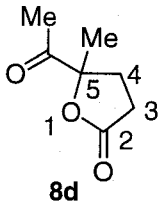
5-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)-tetrahydro-2(3*H*)-furanone (8c). Analytically pure sample was obtained by recycling preparative HPLC. Colorless oil; R_f 0.26 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.24-2.34 (m, 1H, 4-H), 2.52-2.58 (c, 2H, 3-H), 3.34-3.44 (m, 1H, 4-H), 3.78 (s, 3H, MeO), 3.81 (s, 3H, MeO), 6.81 (d, *J* = 8.9 Hz, 2H, 3'-C or 3"-C), 6.90 (d, *J* = 8.9 Hz, 2H, 3'-C or 3"-C), 7.37 (d, *J* = 8.9 Hz, 2H, 2'-C or 2"-C), 7.97 (d, *J* = 8.9 Hz, 2H, 2'-C or 2"-C); ^{13}C NMR ($CDCl_3$) δ 27.78 (3-C or 4-C), 34.05 (3-C or 4-C), 55.02 (MeO), 55.15 (MeO), 91.83 (5-C), 113.30 (2C, 3'-C or 3"-C), 114. 30 (2C, 3'-C or 3"-C), 124.96 (2C, 2'-C or 2"-C), 126.13 (1'-C or 1"-C), 131.43 (1'-C or 1"-C), 132.99 (2C, 2'-C or 2"-C), 159.39 (4'-C or 4"-C), 163.38 (4'-C or 4"-C), 175.51 (2-C), 193.46 (*C*OAr); IR (neat) 3560 w, 3010 m, 2962 m, 2842 m, 1787 s, 1674 s, 1601 s, 1575 s, 1514 s, 1464 s, 1446 m, 1422 m, 1308 s, 1257 s, 1160 s, 1117 m, 1086 m, 1061 s, 1028 s, 997 m, 939 m, 901 m, 861 m, 833 s, 811 m; MS, *m/z* (relative intensity, %) 326 (M^+, 2), 192 (15), 191 (100), 135



8c

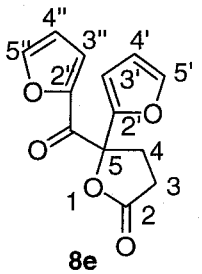
(37). HRMS Calcd for $C_{19}H_{18}O_5$: 326.1154. Found: 326.1149.

5-Acetyltetrahydro-5-methyl-2(3*H*)-furanone (8d). Colorless oil; bp 90 °C (5 mmHg); R_f 0.17 (hexane/EtOAc = 2/1); ^{1}H NMR ($CDCl_3$) δ 2.48-2.68 (c, 3H, 3,4-H), 2.30 (s, 3H, CH_3(C=O)-), 2.04-2.12 (m, 1H, 3-H or 4-H), 1.54 (s, 3H, 5-CH_3); ^{13}C NMR ($CDCl_3$) δ 23.40 (5-*C*H_3), 25.21 (*C*H_3(C=O)-), 28.29 (3-C or 4-C), 30.73 (3-C or 4-C), 89.13 (5-C), 175.58 (2-C), 208.07 (CH_3(*C*=O)-); IR (neat) 2986 m, 2942 m, 1788 s, 1723 s, 1458 m, 1423 m, 1377 m, 1361 m, 1292 m, 1237 m, 1209 s, 1166 s, 1139 s, 1107 s, 1093 s, 1003 m, 973 m, 949 m, 902 m, 859 w, 805 w; MS, *m/z* (relative intensity, %) 158 (M^+, 1), 199 (100), 43 (41). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.93; H, 6.92.



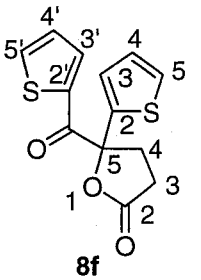
8d

5-(2-furanyl)-5-(2-furanylcarbonyl)-dihydro-2(3*H*)-furanone (8e). White solid; mp 111-113 °C (hexane); R_f 0.11 (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$) δ 2.58-3.09 (c, 4H, 3, 4-H), 6.37-6.39 (m, 1H, 4'-C), 6.43 (d, J = 3.6 Hz, 1H, 3'-C or 5'-C), 6.55-6.57 (m, 1H, 4''-C), 7.43 (s, 1H, 3-C or 5-C), 7.51 (d, J = 4.0 Hz, 1H, 3''-C or 5''-C), 7.68 (s, 1H, 3''-C or 5''-C); ^{13}C NMR ($CDCl_3$) δ 27.68 (3-C or 4-C), 29.81 (3-C or 4-C), 86.16 (5-C), 109,45 (3'-C or 5'-C), 110.78 (4'-C), 112.60 (4''-C), 123.13 (3''-C or 5''-C), 143.85 (3'-C or 5'-C), 148.19 (3''-C or 5''-C), 149.07 (2-C or 2'-C), 149.90 (2-C or 2'-C), 174.91 (2-C), 181.98 (Ar*C*=O); IR (KBr) 3346 w, 3120 w, 1774 s, 1681 s, 1562 m, 1502 m, 1470 s, 1421 m, 1394 s, 1282 s, 1260 s, 1227 m, 1191 s, 1172 s, 1084 s, 1060 m, 1022 s, 995 m, 972 s, 936 m, 911 s, 886 m, 848 s, 835 m, 809 m; MS, *m/z* (relative intensity, %) 246 (M^+, 7), 152 (11), 151 (100), 95 (45). Anal. Calcd for $C_{13}H_{10}O_5$: C, 63.42; H, 4.09. Found: C, 63.29; H, 4.11.



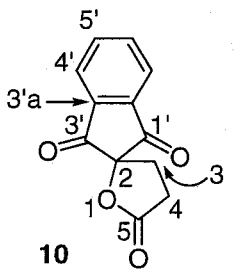
8e

Dihydro-5-(2-thienyl)-5-(2-thienylcarbonyl)-2(3*H*)-furanone (8f). Pale yellow oil; bp 180 °C (5 mmHg); R_f 0.11 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 2.57-2.72 (c, 3H, 3,4-H), 3.21-3.36 (m, 1H, 3-H or 4-H), 6.97-7.00 (m, 1H, 4-Th or 4'-Th), 7.10-7.13 (c, 2H, Th), 7.32 (d, J = 5.0 Hz, 1H, 3-Th or 5-Th or 3'-Th or 5'-Th), 7.70 (d, J = 5.0 Hz, 1H, 3-Th or 5-Th or 3'-Th or 5'-Th), 8.10 (d, J = 4.0 Hz, 1H, 3-Th or 5-Th or 3'-Th or 5'-Th); ^{13}C NMR ($CDCl_3$) δ 27.91 (3-C or 4-C), 34.34 (3-C or 4-C), 90.05 (5-C), 125.36 (4-Th or 4'-Th), 126.43 (3-Th or 5-Th or 3'-Th or 5'-Th), 127.48 (3-Th or 5-Th or 3'-Th or 5'-Th), 128.57 (4-Th or 4'-Th), 135.89 (3-Th or 5-Th or 3'-Th or 5'-Th), 136.46 (3-Th or 5-Th or 3'-Th or 5'-Th), 139.05 (2-Th or 2'-Th), 141.76 (2-Th or 2'-Th), 174.63 (2-C), 187.92 (Th(*C*=O)); IR (neat) 3106 m, 2956 w, 1793 s, 1659 s, 1515 m, 1457 m, 1411 s, 1354 s, 1263 s, 1235 s, 1165 s, 1062 s, 1039 s, 994 w, 920 m, 851 m, 818 m, 800 m; MS, *m/z* (relative intensity, %) 278 (M^+, 1), 168 (12), 167 (100), 111 (34). Anal. Calcd for $C_{13}H_{10}O_3S_2$: C, 56.10; H, 3.62; S, 23.04. Found: C, 56.14; H, 3.67; S, 22.75.



8f

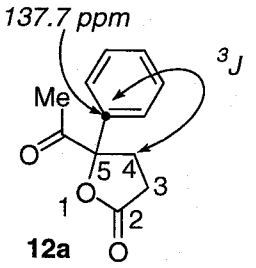
3,4-Dihydro-spiro[furan-2(5*H*),2'-[1*H*]indene]-1',3',5(2'*H*)-trione (10). White solid; mp 142-144 °C (hexane); R_f 0.29 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.41-2.47 (m, 2H, 3-H or 4-H), 2.86-2.92 (m, 2H, 3-H or 4-H), 7.98-8.10 (c, 4H, Ar); ^{13}C NMR ($CDCl_3$) δ 27.39 (3-C or 4-C), 27.94 (3-C or 4-C), 80.85 (2-C), 124.44 (2C, 4'-C or 5'-C), 137.30 (2C, 4'-C or 5'-C), 140.13 (2C, 3'a-C), 175.11 (5-C), 195.09 (2C, 1'-C); IR (KBr) 3584 w, 3452 w, 3078 w, 3026 w, 2992 w, 2946 w, 2876 w, 1803



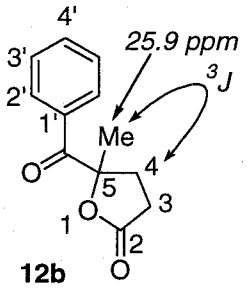
10

s, 1752 s, 1722 s, 1603 m, 1591 m, 1470 w, 1451 w, 1409 m, 1355 m, 1331 m, 1291 m, 1276 m, 1218 m, 1276 m, 1218 m, 1189 s, 1167 s, 1153 s, 1129 m, 1096 w, 1075 s, 1049 w, 994 w, 965 w, 941 s, 886 w, 877 w, 862 w, 820 m; MS, *m/z* (relative intensity, %) 216 (M^+, 57), 146 (14), 132 (39), 105 (13), 104 (100), 77 (11), 76 (50), 75 (10), 66 (14), 55 (22), 52 (12), 50 (44). Anal. Calcd for $C_{12}H_8O_4$; C, 66.67; H, 3.73. Found: C, 66.67; H, 3.83.

5-Acetyltetrahydro-5-phenyl-2(3*H*)-furanone (12a). Colorless oil; bp 145 °C (2 mmHg); R_f 0.31 (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H, Me), 2.31-2.42 (m, 1H, 4-H), 2.51-2.60 (m, 2H, 3-H), 3.07-3.18 (m, 1H, 4-H), 7.36-7.43 (c, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 25.00 (Me), 28.18 (3-C), 31.56 (4-C), 92.08 (5-C), 124.39 (2C, 2'-C or 3'-C), 128.75 (4'-C), 129.00 (2C, 2'-C or 3'-C), 137.66 (1'-C), 175.15 (2-C), 204.62 ((*C*O)CH_3); IR (neat) 3554 w, 3422 w, 3062 m, 3006 m, 2216 w, 1787 s, 1725 s, 1602 m, 1497 s, 1452 s, 1420 s, 1358 s, 1283 m, 1236 s, 1161 s, 1111 m, 1092 s, 1060 s, 1037 s, 1000 m, 980 m, 950 m, 921 m, 900 s, 871 m, 810 w; MS, *m/z* (relative intensity, %) 204 (M^+, 1), 162 (14), 161 (100), 133 (18), 115 (14), 105 (51), 77 (24). Anal. Calcd for $C_{12}H_{12}O_3$; C, 70.58; H, 5.92. Found: C, 70.43; H, 5.95. The regiochemisitry of **12a** was determined by long range ^{1}H-^{13}C cosy measurements. The long range ^{1}H-^{13}C coupling indicative of the regiochemistry and the corresponding ^{13}C chemical shifts are given here.



5-Benzoyltetrahydro-5-methyl-2(3*H*)-furanone (12b). Colorless oil; R_f 0.23 (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 3H, Me), 2.12-2.23 (m, 1H, 4-H), 2.51-2.62 (c, 2H, 3-H), 2.96-3.06 (m, 1H, 4-H), 7.44-7.62 (c, 3H, 3',4'-H), 8.12 (d, J = 7.3 Hz, 2H, 2'-H); ^{13}C NMR ($CDCl_3$) δ 25.88 (Me), 28.11 (3-C), 32.24 (4-C), 89.81 (5-C), 128.52 (2C, 2'-C or 3'-C), 130.21 (2C, 2'-C or 3'-C), 133.53 (4'-C), 133.61 (1'-C), 175.58 (2-C), 198.63 (*C*OPh); IR (neat) 2948 w, 1786 s, 1683 s, 1599 m, 1578 m, 1451 m, 1422 m, 1378 m, 1270 m, 1234 m, 1198 s, 1178 s, 1127 m, 1001 m, 948 m, 899 m, 835 w; MS, *m/z* (relative intensity, %) 204 (M^+, 0.4), 105 (47), 99 (100), 77 (21), 43(21). Anal. Calcd for $C_{12}H_{12}O_3$; C, 70.58; H, 5.92. Found: C, 70.54; H, 6.04. The regiochemisitry of **12b** was determined by long range ^{1}H-^{13}C cosy measurement. The long range ^{1}H-^{13}C coupling indicative of the regiochemistry and the corresponding ^{13}C chemical shift are given here.



References and Notes

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(8) Creary, X. *J. Org. Chem.* **1987**, *52*, 5026.

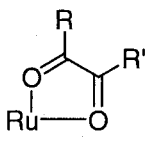
CHAPTER 2

Ruthenium-Catalyzed Cyclocoupling of *N*-Heterocyclic Ketones, Olefins, and Carbon Monoxide

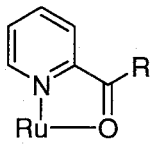
2.1 Background

All the applicable substrates discussed in Chapter 1 have a carbonyl group adjacent to the reacting ketone moiety. To better understand the role of the adjacent carbonyl group, the author 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, the author 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 complex **13** (Chart 1) would be a key intermediate in this cyclocoupling reaction. This speculation led me to employ the 2-pyridyl group as an adjacent group, since it could participate in forming a chelation ring, as in **14** (Chart 1). As expected, the reactions of 2-pyridyl ketones were found to proceed well.

Chart 1.



13

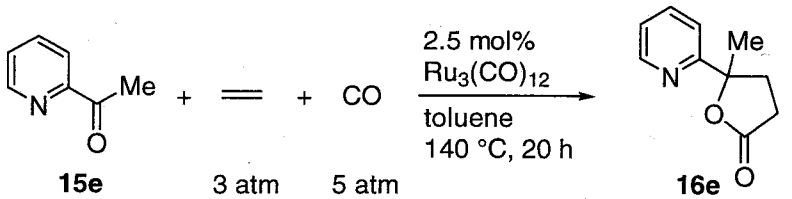


14

2.2 Results and Discussions

***N*-Heterocyclic Ketones as a Ketone Component.** Following the consideration mentioned above, 2-acetylpyridine (**15e**) was first investigated as a possible substrate. The author was pleased to find that the reaction proceeded smoothly. In contrast to the reactions

of α-dicarbonyl compounds, the addition of phosphines was, curiously, not required to obtain lactones in good yields (eq 4).



15e 3 atm 5 atm **16e** (4)

with $P(4\text{-}CF_3C_6H_4)_3$ 92%
without $P(4\text{-}CF_3C_6H_4)_3$ 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

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

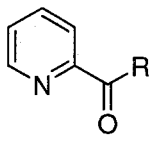
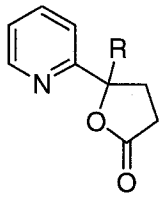
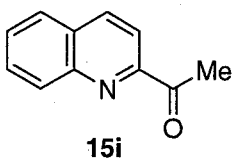
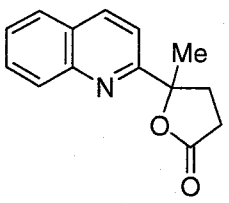
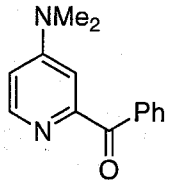
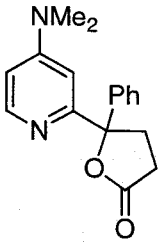
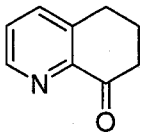
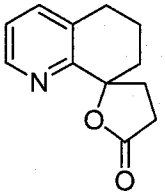
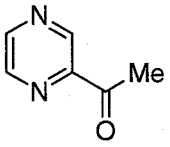
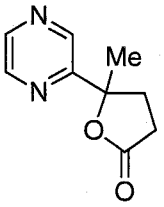
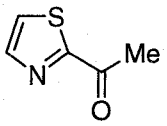
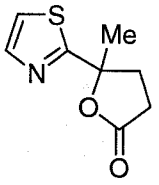
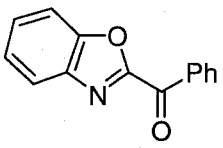
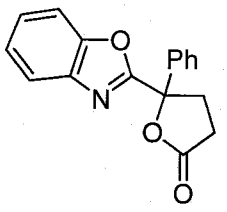
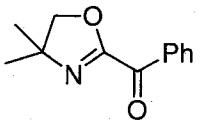
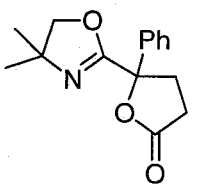
entry	ketone		product [b]	
				
1	**15a**	R = 4-$CF_3C_6H_4$	**16a**	92%
2	**15b**	R = Ph	**16b**	93%
3	**15c**	R = 4-$MeOC_6H_4$	**16c**	98%
4	**15d**	R = 2-pyridinyl	**16d**	72%
5	**15e**	R = Me	**16e**	92%
6	**15f**	R = Bu	**16f**	96%
7	**15g**	R = *t*-Bu	**16g**	45%
8				(94%)[c]
9	**15h**	R = H	**16h**	34%
10				(85%)[c,d]
11	 **15i**			**16i** 88%

Table 3. (continued) [a]

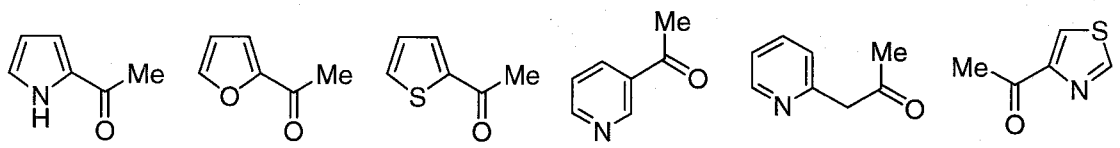
entry	ketone	product [b]
12	 **17**	 **18** 93%
13 14	 **19**	 **20** 29% (79%)[c]
15	 **21**	 **22** 94%
16	 **23**	 **24** 97%
17	 **25**	 **26** 95%
18	 **27**	 **28** 78%

[a] Reaction conditions: ketone (2 mmol), ethylene (initial pressure 3 atm at 25 °C), CO (initial pressure 5 atm at 25 °C), $Ru_3(CO)_{12}$ (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.

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.

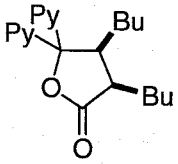
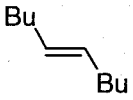
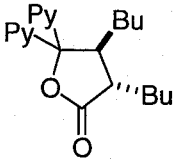
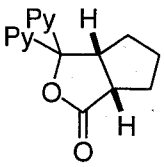
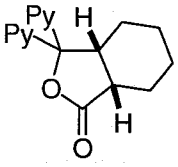
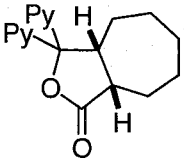
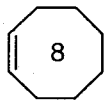
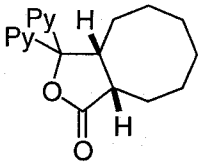
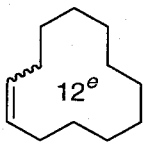
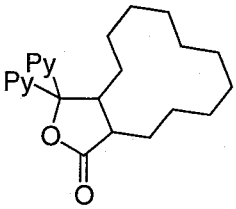
Chart 2.



29 **30** **31** **32** **33** **34**

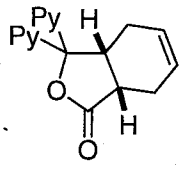
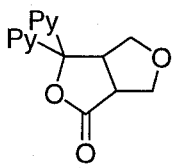
Substituted Alkenes as an Olefin Component. The author next examined the scope of the reaction in the context of the olefin component. The reactions of unsymmetrical ketones with unsymmetrical olefins could, in theory, result in the formation of four isomeric lactones. To avoid complexities that might arise in these reactions, the author 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 $P(4\text{-}CF_3C_6H_4)_3$ afforded the *cis*-substituted lactone **35** as the sole product in modest yield. 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.

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

entry	olefin	additive[b]	product[c]
1		+	 **35** 53%
2		+	(85%)[d]
3		+	 **36** 19%
4		+	(30%)[d]
5		–	 **37** 94%
6		–	 **38** 14%
7		+	**38** 97%
8		+	 **39** 97%
9		–	 **40** 17%
10		+	**40** 94%
11		+	 **41** 70% (84/16)[f,g]

[a] Reaction conditions: ketone (1 mmol), olefin (10 mmol), CO (initial pressure 5 atm at 25 °C), $Ru_3(CO)_{12}$ (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.

Table 4. (continued) [a]

entry	olefin	additive[b]	product[c]
12		+	 **42** 83%
13		+	 **43** 51%
14		+	(74%)[h]

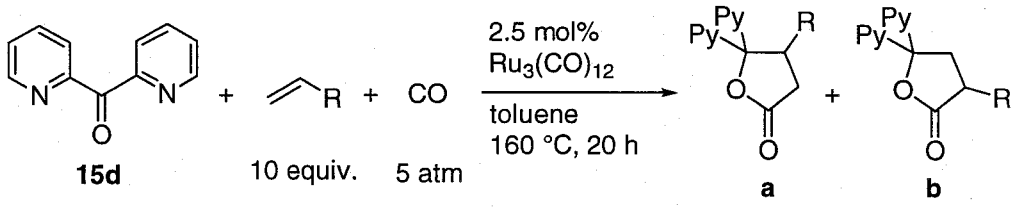
[h] For a reaction run for 80 h.

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 Experimental Section 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.

The author 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 Experimental Section 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.

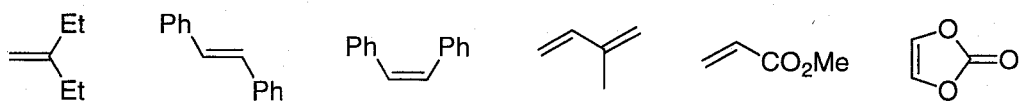
Table 5. $Ru_3(CO)_{12}$-Catalyzed [2 + 2 + 1] Cyclocoupling of Di-2-pyridyl Ketone (**15d**), Terminal Olefins, and CO [a]



entry	olefin	additive[b]	yield (**a**/**b**)[c]
1	R = Me[d]	–	**44** 91% (95/ 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)

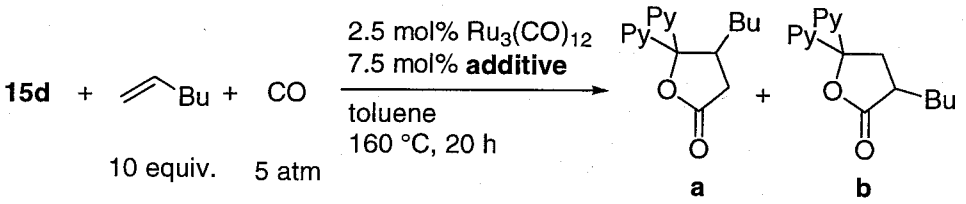
[a] Reaction conditions: ketone (2 mmol), olefin (20 mmol), CO (initial pressure 5 atm at 25 °C), $Ru_3(CO)_{12}$ (0.05 mmol) in toluene (6 mL) at 160 °C for 20 h in a 50-mL stainless autoclave, unless otherwise noted. [b] + : PPh_3 (0.15 mmol) was added. – : No phosphine was added. [c] Isolated yields 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.



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 the author to examine a series of phosphines, as potential additives to clarify the factors which control the regioselectivity of the reaction (Table 6). As a result, it was found that neither an increase in the amount of the phosphine (entries 2-5) nor the change in the electronic nature of the phosphine (entries 6-8 and 10) affected the regioselectivity significantly. Of interest is the fact that the use of phosphine ligands which posses a large cone angle[1] resulted in the formation of the α-substituted lactone **45b** preferentially over **45a** (entries 9 and 11).

Table 6. Effect of Additives on Regioselectivity in the Cycloaddition of **15d** with 1-Hexene and CO[a]

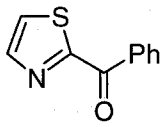
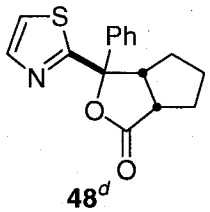
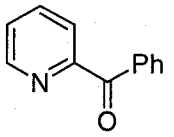
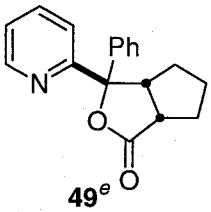
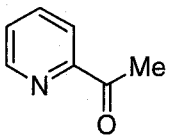
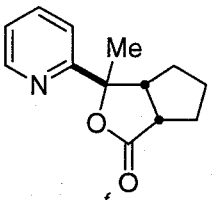


entry	additive	yield (**45a**/**45b**)[b]
1	none	91% (78/ 22)
2	PPh_3	90% (13/ 87)
3	PPh_3[c]	92% (12/ 88)
4	PPh_3[d]	90% (14/ 86)
5	PPh_3[e]	95% (14/ 86)
6	$P(4\text{-}ClC_6H_4)_3$	96% (17/ 83)
7	$P(4\text{-}CF_3C_6H_4)_3$	95% (24/ 76)
8	$P(4\text{-}MeOC_6H_4)_3$	93% (13/ 87)
9	$P(2\text{-}MeC_6H_4)_3$	92% (78/ 22)
10	PBu_3	88% (12/ 88)
11	PCy_3	75% (80/ 20)

[a] Reaction conditions: di-2-pyridyl ketone (2 mmol), 1-hexene (20 mmol), CO (initial pressure 5 atm at 25 °C), $Ru_3(CO)_{12}$ (0.05 mmol), additive (0.15 mmol) in toluene (6 mL) at 160 °C for 20 h in a 50-mL stainless autoclave, unless otherwise noted. [b] Isolated yields based on the starting ketones. The numbers in the parentheses are the ratios of isomers determined by GC analysis. [c] 0.30 mmol of PPh_3 was used. [d] 1 mmol of PPh_3 was used. [e] $Ru_3(CO)_9(PPh_3)_3$ (0.05 mmol) was used as the catalyst.

The author next investigated the reactions of unsymmetrical ketones with symmetrical cyclic olefins, in which the formation of two stereoisomeric lactones is possible (Table 7). 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 crystallography. 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 $P(4\text{-}CF_3C_6H_4)_3$ was used as an additive, **50** was formed with a high degree of

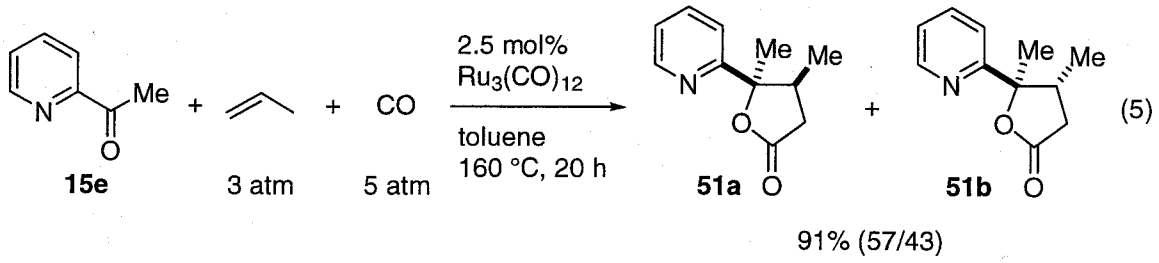
Table 7. $Ru_3(CO)_{12}$-Catalyzed [2 + 2 + 1] Cyclocoupling of Unsymmetrical Ketones, Cyclopentene, and CO [a]

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

[a] Reaction conditions: ketone (2 mmol), cyclopentene (20 mmol), CO (initial pressure 5 atm at 25 °C), $Ru_3(CO)_{12}$ (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. The numbers in the parentheses are the ratios of isomers determined by ^1H 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.

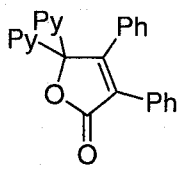
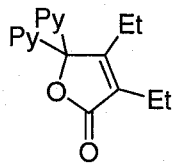
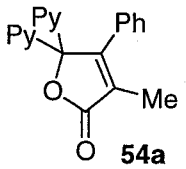
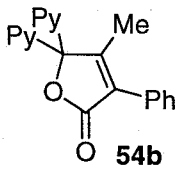
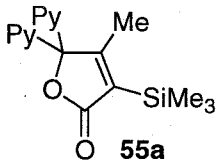
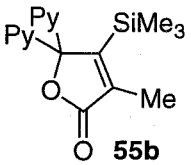
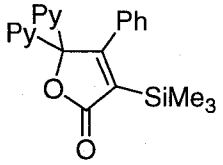
stereoselectivity (entry 6), while no significant change in stereoselectivity was observed for the reactions of phenyl ketones (entries 2 and 4). The stereochemistry of the major isomer of **50** was determined by comparison with related compounds (see Experimental Section for details).

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 5).



Cyclocoupling Using Alkynes. To further extend the scope of this new cycloaddition, the author next investigated the reactivity 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 8. 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.

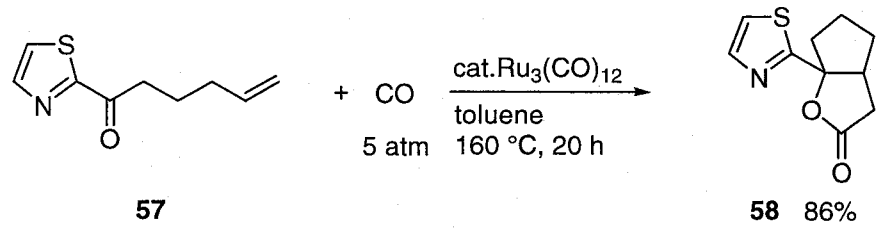
Table 8. $Ru_3(CO)_{12}$-Catalyzed [2 + 2 + 1] Cyclocoupling of Di-2-pyridyl Ketone (**15d**), Alkynes, and CO [a]

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%

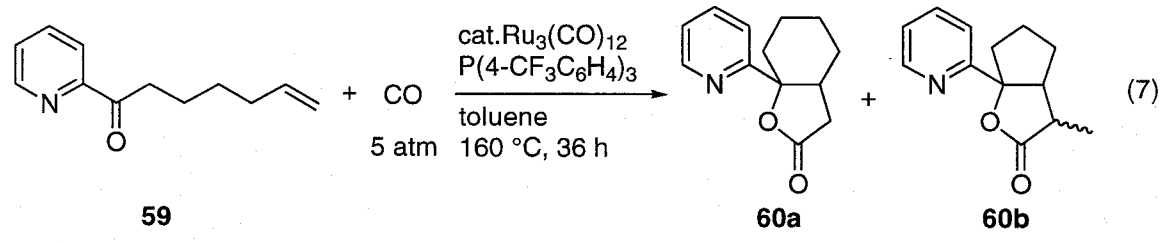
[a] Reaction conditions: **15d** (1 mmol), alkyne (10 mmol), CO (initial pressure 5 atm at 25 °C), $Ru_3(CO)_{12}$ (0.025 mmol), P(4-$CF_3C_6H_4)_3$ (0.075 mmol) in toluene (3 mL) at 160 °C for 20 h in a 50-mL stainless autoclave, unless otherwise noted. [b] Isolated yields based on **15d**. [c] 1.1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

The reactions presented in Table 8 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 ring. To the author's knowledge, there is no precedent for *catalytic intermolecular* variants of this process.[2]

Intramolecular Cyclocoupling. Although an *intramolecular* [2 + 2 + 1] cycloaddition of ketones, olefins, and CO has been achieved by use of titanium complexes as mentioned in Introduction,[3] it remains a rare phenomenon. The present successful application of *intermolecular* [2 + 2 + 1] cycloaddition to the synthesis of γ-butylolactone encouraged the author to examine the *intramolecular* cyclocoupling, which leads to relatively complex bicyclic lactones in a single step. As a result, the author was 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 6). 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 (eq 7). The cyclopentane-fused lactone **60b** is presumably formed *via* the cyclization of the isomerized starting material.[4]



57 **58** 86% (6)



59 **60a** **60b** 73% (90/10) (7)

2.3 Conclusion

In this chapter, it has been demonstrated that $Ru_3(CO)_{12}$ catalyzes the intermolecular cyclocoupling of *N*-heterocyclic ketones (or aldehydes), alkenes (or alkynes), and CO. *N*-heterocyclic ketones which contain a C=N unit in conjugation with the reacting ketone moiety, such as 2-acylpyridines, were found to be an effective substrate. A variety of cyclic olefins, unpolarized terminal olefins, and internal alkynes have been successfully used as two-carbon π-system in the synthesis of highly functionalized γ-lactones.

2.4 Experimental Section

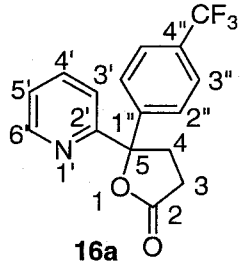
General Information. Boiling points (bp) refer to air bath temperatures for bulb-to-bulb distillation and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a JEOL JMN-270 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Data are reported as follows: chemical shifts in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, and c = complex), coupling constant (Hz), integration, and interpretation. Infrared spectra (IR) were obtained on a Hitachi 270-50 spectrometer; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained on a Shimadzu GCMS-QP 5000 instrument using ionization voltages of 70 eV. Elemental analyses were performed by the Elemental Analysis Section of Osaka University. Analytical GC was carried out on a Shimadzu GC-14A or GC-14B gas chromatograph, equipped with a flame ionization detector. Recycling preparative HPLC was performed on a Japan Analytical industry LC-908. Column chromatography was performed with SiO_2 (Wakogel or Merck SilicaGel 60 (230-400 mesh)).

Materials. Commercial grade reagents were used as received except as indicated below. Toluene was distilled over CaH_2. **15h** were purified by distillation prior to use. $Ru_3(CO)_{12}$ was prepared according to the literature procedure[5] and used, after recrystallization from hexane. Ketones **15b**, **15d**, **15h**, **15i**, **21**, **23**, **29**, **30**, **31**, and **32** are commercially available and were used as received. **15g**[6], **19**[7], **25**[8], **27**[9], **33**[10], **34**[11], and trimethyl(phenylethynyl)silane[12] were prepared according to the literature procedures. **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.

Typical Procedure for Cyclocoupling of Ketones, Olefins, and CO. A 50-mL stainless autoclave was charged with 2-acetylpyridine (**15e**) (2 mmol, 242 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 140 °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

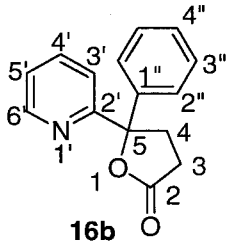
column chromatography on silica gel (eluent; hexane/EtOAc = 3/1) to give dihydro-5-methyl-5-(2-pyridinyl)-2(3*H*)-furanone (**16e**) (327 mg, 92% yield) as a colorless oil. Purification by bulb-to-bulb distillation afforded an analytically pure product.

Dihydro-5-(2-pyridinyl)-5-(4-trifluoromethylphenyl)-2(3*H*)-furanone (16a). White solid; mp 68-69 °C (hexane/EtOAc); R_f 0.23 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 2.55-2.75 (c, 3H, 3,4-H), 3.53-3.62 (m, 1H, 3-H or 4-H), 7.20-7.25 (m, 1H, 5'-H), 7.49 (d, J = 7.9 Hz, 1H, 3'-H), 7.58-7.70 (c, 5H, 4'-H and Ar), 8.60 (d, J = 4.6 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 28.74 (3-C or 4-C), 34.75 (3-C or 4-C), 89.28 (5-C), 123.77 (q, J = 271.6 Hz, CF_3), 120.82 (3'–C or 4'-C), 122.98 (5'-C), 125.20 (2C, 2"-C), 125.37 (q, J = 3.9 Hz, 2C, 3"-C), 129.89 (q, J = 32.4 Hz, 4"-C), 137.00 (3'-C or 4'-C), 146.48 (1"-C), 148.84 (6'-C), 159.97 (2'-C), 175.66 (2-C); IR (neat) 1788 s, 1676 w, 1622 w, 1590 m, 1472 m, 1438 m, 1414 m, 1328 s, 1292 m, 1222 s, 1156 s, 1116 s, 1056 s, 1018 m, 992 s, 906 s, 836 s; MS, *m/z* (relative intensity, %) 307 (M^+, 100), 262 (17), 252 (20), 251 (36), 250 (18), 229 (42), 223 (35), 201 (10), 173 (38), 145 (21), 106 (17), 79 (13), 78 (11). Anal. Calcd for $C_{16}H_{12}F_3NO_2$: C, 62.54; H, 3.94; N, 4.56. Found: C, 62.55; H, 3.92; N, 4.61.



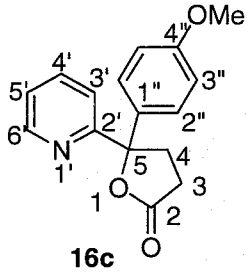
16a

Dihydro-5-phenyl-5-(2-pyridinyl)-2(3*H*)-furanone (16b). Colorless solid; mp 38-39 °C (hexane/EtOAc); R_f 0.06 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 2.55-2.62 (c, 2H, 3,4-H), 2.67-2.78 (m, 1H, 3-H or 4-H), 3.46-3.57 (m, 1H, 3-H or 4-H), 7.20 (ddd, J = 7.6 Hz, J = 5.0 Hz, J=1.0 Hz, 1H, 5'-H), 7.23-7.37 (c, 3H, 3'-H and/or Ph), 7.46-7.53 (c, 3H, 3'-H and/or Ph), 7.65 (ddd, J = 7.9 Hz, J=7.6 Hz, J=1.7 Hz, 1H, 4'-H), 8.59 (d, J = 5.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 28.88 (3-C or 4-C), 34.50 (3-C or 4-C), 89.96 (5-C), 121.13 (3'–C or 5'-C or 4"-C), 122.77 (3'–C or 5'-C or 4"-C), 124.83 (2C, 2"-C or 3"-C), 127.76 (3'–C or 5'-C or 4"-C), 128.46 (2C, 2"-C or 3"-C), 136.91 (4'-C), 142.68 (1"-C), 148.72 (6'-C), 160.90 (2'-C), 176.39 (2-C); IR (KBr) 3060 m, 3004 m, 2954 w, 1790 s, 1778 s, 1588 s, 1574 m, 1495 m, 1470 s, 1434 s, 1316 m, 1284 s, 1256 s, 1219 s, 1162 s, 1098 s, 1082 m, 1044 s, 906 s, 903 s, 849 w; MS, *m/z* (relative intensity, %) 239 (M^+, 35), 194 (14), 183 (30), 182 (21), 161 (45), 155 (34), 133 (16), 115 (17), 106 (57), 105 (78), 80 (16), 79 (41), 78 (66), 77 (100), 55 (11), 52 (24), 51(73), 50(20). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.11; H, 5.41; N, 5.83.



16b

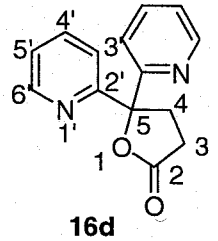
Dihydro-5-(4-methoxylphenyl)-5-(2-pyridinyl)-2(3*H*)-furanone (16c). An analytically pure sample was obtained by recycling preparative HPLC. Colorless oil; R_f 0.34 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.55-2.61 (c, 2H, 3-H or 4-H), 2.78-2.67 (m, 1H, 3-H or 4-H), 3.39-3.49 (m, 1H, 3-H or 4-H), 3.78 (s, 3H, OMe), 6.90 (d, J = 9.1 Hz, 2H, 2"-H or 3"-H), 7.18 (ddd, J = 7.6 Hz, J = 4.9 Hz, J=1.0 Hz, 1H, 5'-H), 7.41 (d, J = 9.1 Hz, 2H, 2"-H or 3"-H), 7.48 (dt, J = 7.9 Hz, J = 1.0 Hz, 1H, 3'-H), 7.64 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.6 Hz, 1H, 4'-H), 8.57 (ddd, J = 4.9 Hz, J = 1.6 Hz, J = 1.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 28.62 (3-C or 4-C), 34.29 (3-C or 4-C), 54.84 (OCH_3), 89.44 (5-C), 113.38 (2C, 2"-C or 3"-C), 120.34 (3'-C), 122.26 (5'-C), 125.88 (2C, 2"-C or 3"-C), 134.29 (1"-C or 4"-C), 136.44 (4'-C), 148.28 (6'-C), 158.61 (1"-C or 4"-C), 160.78 (2'-C), 175.84 (2-C); IR (KBr) 3060 w, 3008 w, 2960 w, 2844 w, 1782 s, 1614 m, 1590 s, 1516 s, 1470 s, 1438 m, 1420 m, 1306 m, 1252 s, 1222 s, 1164 s, 1118 m, 1098 m, 1050 s, 988 s, 908 s, 834 s; MS, *m/z* (relative intensity, %) 269



16c

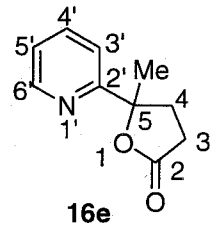
(M^+, 28), 192 (11), 191 (100), 185 (13), 135 (71), 121 (13), 107 (16), 106 (49), 92 (19), 79 (17), 78 (49), 77 (38), 64 (12), 63 (12), 55 (17), 52 (13), 51 (27). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.46; H, 5.67; N, 5.28.

Dihydro-5,5-di(2-pyridinyl)-2(3*H*)-furanone (16d). Colorless solid; mp 67-68 °C (hexane/EtOAc); R_f 0.09 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.68 (t, J = 8.1 Hz, 2H, 3-H or 4-H), 3.26 (t, J = 8.1 Hz, 2H, 3-H or 4-H), 7.17-7.30 (m, 2H, 5'-H), 7.49 (d, J = 7.9 Hz, 2H, 3'-H), 7.68 (td, J = 7.7 Hz, J = 1.7 Hz, 2H, 4'-H), 8.63 (dd, J = 4.3 Hz, J = 0.7 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 28.81 (3-C or 4-C), 32.58 (3-C or 4-C), 90.21 (5-C), 120.56 (2C, 3'-C), 122.80 (2C, 5'-C), 136.75 (2C, 4'-C), 149.15 (2C, 6'-C), 160.16 (2C, 2'-C), 176.50 (2-C); IR (KBr) 3052 w, 3010 w, 1769 s, 1589 m, 1571 m, 1480 m, 1469 m, 1439 m, 1429 m, 1221 m, 1163 m, 1101 m, 1044 m, 907 m; MS, *m/z* (relative intensity, %) 240 (M^+, 1), 196 (34), 195 (41), 134 (31), 106 (56), 80 (12), 79 (25), 78 (100), 52 (29), 51 (58), 50 (13). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.03; H, 5.09; N, 11.64.



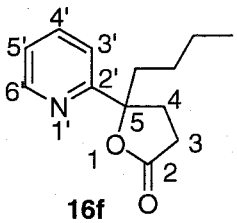
16d

Dihydro-5-methyl-5-(2-pyridinyl)-2(3*H*)-furanone (16e). Colorless oil; R_f 0.06 (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3H, CH_3), 2.27-2.65 (c, 3H, 3,4-H), 2.72-2.84 (m, 1H, 3-H or 4-H), 7.18 (dd, J = 7.3 Hz, J = 4.6 Hz, 1H, 5'-H), 7.48 (d, J = 7.9 Hz, 1H, 3'-H), 7.67 (ddd, J = 7.9 Hz, J = 7.3 Hz, J = 1.7 Hz, 1H, 4'-H), 8.53 (d, J = 4.6 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 27.51 (CH_3), 28.52 (3-C or 4-C), 34.05 (3-C or 4-C), 87.31 (5-C), 118.67 (3'-C), 122.35 (5'-C), 136.68 (4'-C), 148.84 (6'-C), 162.05 (2'-C), 176.42 (2-C); IR (neat) 3060 m, 2980 m, 2940 m, 1779 s, 1613 m, 1590 s, 1574 m, 1473 s, 1434 s, 1372 m, 1290 s, 1233 s, 1208 s, 1131 s, 1107 s, 1074 s, 1045 m, 992 m, 974 m, 943 s, 919 m, 862 m; MS, *m/z* (relative intensity, %) 177 (M^+, 7), 149 (23), 134 (28), 132 (15), 122 (72), 118 (12), 117 (17), 106 (100), 104 (13), 99 (44), 93 (16), 80 (43), 79 (60), 78 (63), 71 (17), 65 (12), 55 (16), 53 (13), 52 (41), 51 (54), 50 (19). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.69; H, 6.34; N, 8.14.



16e

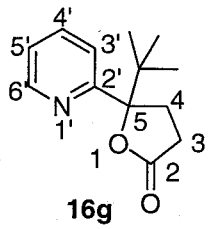
5-Butyldihydro-5-(2-pyridinyl)-2(3*H*)-furanone (16f). Colorless oil; bp 130 °C (2 mmHg); R_f 0.14 (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.3 Hz, 3H, CH_3), 0.97-1.05 (m, 1H, $CH_2CH_2CH_2CH_3$), 1.20-1.34 (c, 3H, $CH_2CH_2CH_2CH_3$), 1.89-2.01 (m, 1H, $CH_2CH_2CH_2CH_3$), 2.12-2.19 (m, 1H, $CH_2CH_2CH_2CH_3$), 2.34-2.48 (c, 2H, 3,4-H), 2.52-2.68 (m, 1H, 3-H or 4-H), 2.75-2.84 (m, 1H, 3-H or 4-H), 7.22 (ddd, J = 7.6 Hz, J = 4.9 Hz, J = 0.7 Hz, 1H, 5'-H), 7.51 (d, J = 7.9 Hz, 1H, 3'-H), 7.71 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.7 Hz, 1H, 4'-H), 8.59 (d, J = 4.9 Hz, 1H, 2'-H); ^{13}C NMR ($CDCl_3$) δ 13.23 (CH_3), 22.03 ($CH_2CH_2CH_2CH_3$), 25.18 ($CH_2CH_2CH_2CH_3$), 27.85 (3-C or 4-C), 32.54 (3-C or 4-C), 40.06 ($CH_2CH_2CH_2CH_3$), 89.36 (5-C), 119.21 (3'-C), 121.85 (5'-C), 136.01 (4'-C), 148.60 (6'-C), 161.04 (2'-C), 176.01 (2-C); IR (neat) 3058 m, 2946 s, 2872 s, 1780 s, 1590 s, 1574 s, 1532 m, 1469 s, 1435 s, 1380 m, 1328 s, 1291 s, 1267 s, 1224 s, 1181 s, 1137 s, 1122 s, 1026 s, 990 s, 950 s, 928 s, 877 m; MS, *m/z* (relative intensity, %) 219 (M^+, 1), 176 (20), 163 (57), 162 (46), 135 (35), 134 (63), 130 (11), 121 (19), 120 (16), 117 (19), 107 (40), 106 (52), 80 (17), 79 (53), 78 (100), 57 (16), 55 (19), 53 (13), 52 (29). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.84; H, 7.93; N, 6.47.



16f

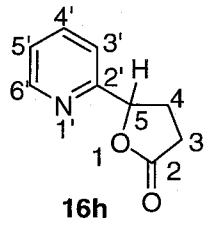
Dihydro-5-(1,1-dimethylethyl)-5-(2-pyridinyl)-2(3*H*)-furanone (16g). Colorless

solid; mp 99-100 °C (hexane/EtOAc); R_f 0.06 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 9H, $C(CH_3)_3$), 2.15-2.30 (m, 1H, 3-H or 4-H), 2.43-2.59 (c, 2H, 3,4-H), 2.97-3.07 (m, 1H, 3-H or 4-H), 7.17-7.22 (m, 1H, 5'-H), 7.57 (d, J = 7.9 Hz, 1H, 3'-H), 7.67 (td, J = 7.9 Hz, J = 1.6 Hz, 1H, 4'-H), 8.56 (d, J = 4.6 Hz, 1H, 2'-H); ^{13}C NMR ($CDCl_3$) δ 25.32 (3C, $C(CH_3)_3$) 28.02 (3-C or 4-C), 29.06 (3-C or 4-C), 37.76 ($C(CH_3)_3$), 94.50 (5-C), 122.37 (5'-C), 122.75 (3'-C), 135.76 (4'-C), 148.01 (6'-C), 160.27 (2'-C), 177.05 (2-C); IR (KBr) 2980 m, 2880 m, 1769 s, 1589 s, 1574 m, 1479 s, 1435 s, 1422 m, 1399 m, 1369 m, 1293 m, 1272 s, 1253 s, 1238 m, 1207 s, 1176 s, 1101 s, 1080 m, 1064 m, 1046 m, 1032 m, 993 s, 968 m, 915 s, 891 m, 820 m, 807 m; MS, *m/z* (relative intensity, %) 219 (M^+, 0), 204 (M^+-15, 1), 163 (78), 162 (56), 135 (47), 134 (64), 107 (51), 106 (36), 93 (51), 79 (66), 78 (100), 57 (46), 55 (21), 53 (15), 52 (32), 51 (42), 50 (11). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.23; H, 7.80; N, 6.38.



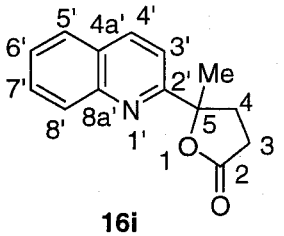
16g

Dihydro-5-(2-pyridinyl)-2(3*H*)-furanone (16h). Colorless oil; bp 100 °C (2 mmHg); R_f 0.09 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 2.46-2.64 (m, 1H, 4-H), 2.72-2.94 (c, 3H, 3,4-H), 5.69 (t, J = 6.8 Hz, 1H, 5-H), 7.34-7.39 (m, 1H, 5'-H), 7.53 (d, J = 8.1 Hz, 1H, 3'-H), 7.84 (ddd, J = 8.1 Hz, J = 7.6 Hz, J = 1.6 Hz, 1H, 4'-H), 8.70 (d, J = 4.6 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 28.09 (3-C or 4-C), 28.43 (3-C or 4-C), 80.92 (5-C), 120.07 (3'-C), 123.11 (5'-C), 136.89 (4'-C), 149.43 (6'-C), 158.43 (2'-C), 176.98 (2-C); IR (neat) 3070 m, 3002 m, 2950 m, 1782 s, 1762 s, 1649 m, 1595 s, 1575 s, 1537 m, 1477 s, 1459 s, 1440 s, 1417 s, 1327 s, 1294 s, 1270 s, 1215 s, 1177 s, 1144 s, 1094 s, 1039 s, 990 s, 946 s, 888 s, 833 m; MS, *m/z* (relative intensity, %) 163 (M^+, 8), 135 (36), 119 (35), 118 (46), 117 (12), 108 (100), 106 (35), 85 (21), 80 (38), 79 (81), 78 (60), 58 (14), 57 (12), 56 (13), 55 (16), 53 (14), 52 (65), 51 (70), 50 (25). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 65.90; H, 5.71; N, 8.71.



16h

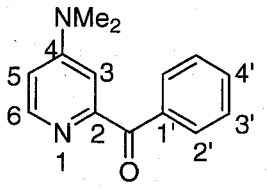
Dihydro-5-methyl-5-(2-quinolinyl)-2(3*H*)-furanone (16i). Colorless oil; bp 160 °C (5 mmHg); R_f 0.06 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3H, CH_3), 2.35-2.72 (c, 3H, 3,4-H), 3.09-3.22 (m, 1H, 3-H or 4-H), 7.53 (td, J = 8.3 Hz, J = 1.2 Hz, 1H, 6'-H), 7.66-7.74 (c, 2H, 3',7'-H), 7.81 (d, J = 8.3 Hz, 1H, 5'-H), 8.06 (d, J = 8.6 Hz, 1H, 8'-H), 8.17 (d, J = 8.6 Hz, 1H, 4'-H); ^{13}C NMR ($CDCl_3$) δ 27.84 (CH_3), 28.95 (3-C or 4-C), 33.89 (3-C or 4-C), 88.14 (5-C), 117.20 (3'-C), 126.52 (6'-C), 127.15 (4a'-C), 127.44 (5'-C), 129.16 (8'-C), 129.60 (7'-C), 137.02 (4'-C), 147.13 (2'-C or 8a'-C), 162.03 (2'-C or 8a'-C), 176.66 (2-C); IR (neat) 3052 m, 2980 m, 2938 m, 1781 s, 1684 m, 1620 s, 1600 s, 1563 s, 1538 m, 1503 s, 1451 s, 1427 s, 1374 s, 1289 s, 1267 s, 1242 s, 1207 s, 1160 s, 1134 s, 1086 s, 998 s, 974 s, 942 s, 916 s, 832 s, 805 m; MS, *m/z* (relative intensity, %) 227 (M^+, 24), 199 (12), 184 (21), 182 (15), 172 (68), 170 (12), 167 (16), 157 (12), 156 (100), 143 (23), 130 (26), 129 (67), 128 (60), 102 (22), 101 (28), 99 (42), 90 (12), 83 (16), 77 (31), 76 (16), 75 (22), 70 (28), 64 (27), 63 (16), 55 (19), 51 (33), 50 (21). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.08; H, 5.87; N, 6.30.



16i

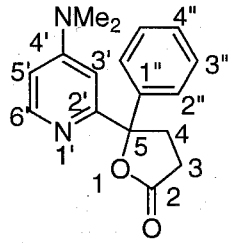
2-Benzoyl-4-*N*,*N*-dimethyl-pyridinamine (17). **17** was prepared by following the literature procedure.[13] Greenish yellow oil; bp 200 °C (1 mmHg); R_f 0.23 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) 3.04 (s, 6H, NMe_2), 6.60 (dd, J = 5.9 Hz, J = 2.8 Hz, 1H, 5-H), 7.21 (d, J = 2.8 Hz, 1H, 6-H), 7.41-7.47 (m, 2H, 3'-C), 7.51-7.57 (m, 1H, 4'-H), 8.01-8.05 (m, 2H,

2'-H), 8.24 (d, J = 5.9 Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$) δ 39.09 (2C, NMe_2), 107.05 (3-C), 108.12 (5-C), 127.76 (2C, 3'-C), 130.64 (2C, 2'-C), 132.36 (4'-C), 136.50 (1'-C or 4-C), 148.38 (6-C), 154.56 (1'-C or 4-C), 155.06 (2-C), 194.83 (C=O); IR (neat) 2932 w, 1666 s, 1600 s, 1542 m, 1512 m, 1452 m, 1436 m, 1380 m, 1314 m, 1286 s, 1226 m, 1178 w, 1148 w, 1114 w, 1068 w, 1012 m, 982 m, 938 m, 862 w, 808 m; MS, *m/z* (relative intensity, %) 226 (M^+, 100), 225 (97), 211 (24), 209 (17), 198 (47), 197 (44), 183 (57), 182 (11), 155 (27), 154 (14), 105 (34), 77 (39). Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.43; H, 6.43; N, 12.40.



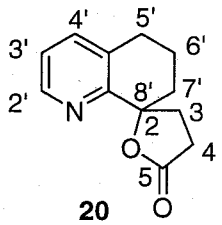
17

Dihydro-5-phenyl-5-(4-*N*,*N*-dimethylamino-2-pyridinyl)-2(3*H*)-furanone (18). White solid; mp 139-140 °C (hexane/EtOAc); R_f 0.23 (hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$) δ 2.52-2.58 (c, 2H, 3-H or 4-H), 2.65-2.76 (m, 1H, 3-H or 4-H), 2.95 (s, 6H, NMe_2), 3.42-3.52 (m, 1H, 3-H or 4-H), 6.37 (dd, J = 5.9 Hz, J = 2.5 Hz, 1H, 5'-H), 6.72 (d, J = 2.5 Hz, 1H, 3'-H), 7.21-7.35 (c, 3H, Ph), 7.53-7.56 (m, 2H, Ph), 8.20 (d, J = 5.9 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 28.89 (3-C or 4-C), 34.50 (3-C or 4-C), 39.01 (2C, NMe_2), 90.12 (5-C), 102.98 (3'-C), 105.48 (5'-C), 124.70 (2C, 2"-C or 3"-C), 127.35 (4"-C), 128.09 (2C, 2"-C or 3"-C), 142.84 (4'-C or 1"-C), 148.57 (6'-C), 154.56 (4'-C or 1"-C), 160.73 (2'-C), 176.44 (2-C); IR (neat) 2904 m, 2820 w, 2396 m, 1776 s, 1602 s, 1542 m, 1512 m, 1472 w, 1452 m, 1420 w, 1380 m, 1294 m, 1228 s, 1158 s, 1122 w, 1092 w, 1062 w, 1014 m, 986 m, 960 w, 930 w, 912 m, 854 w, 816 m; MS, *m/z* (relative intensity, %) 282 (M^+, 54), 238 (11), 237 (41), 227 (20), 198 (38), 183 (29), 155 (14), 149 (34), 123 (16), 122 (100), 121 (32), 118 (13), 113 (15), 105 (45), 80 (12), 79 (11), 78 (12), 77 (54), 55 (12), 52 (14), 51 (28). HRMS Calcd for $C_{17}H_{18}N_2O_2$: 282.1368. Found: 282.1361.



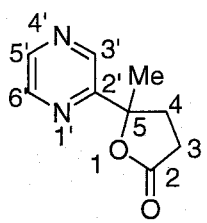
18

4,5,6',7'-Tetrahydrospiro[5-oxo-furan-2(3*H*),8'(5'*H*)-quinoline] (20). Colorless oil; bp 210 °C (5 mmHg); R_f 0.23 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.82-2.21 (c, 4H, 4,5',6'-H), 2.30-2.40 (m, 1H, 5'-H), 2.66 (ddd, J=17.1 Hz, J=9.9 Hz, J=4.3 Hz, 1H, 3-H), 2.77-2.90 (c, 3H, 4,7'-H), 3.23 (ddd, J=17.1 Hz, J=9.9 Hz, J=8.6 Hz, 1H, 3-H), 7.14 (dd, J = 7.9 Hz, J = 4.6 Hz, 1H, 3'-H), 7.42 (dd, J = 7.9 Hz, J=1.0 Hz, 1H, 4'-H), 8.44 (dd, J = 4.6 Hz, J=1.0 Hz, 1H, 2'-H); ^{13}C NMR ($CDCl_3$) δ 19.23 (6'-C), 28.59 (7'-C), 30.07 (3-C), 33.98 (4-C), 36,97 (5'-C), 84.78 (2-C), 123.22 (3'-C), 131.99 (4a'-C), 136.91 (4'-C), 147.71 (2'-C), 155.67 (8a'-C), 177.52 (5-C); IR (neat) 3054 m, 2942 s, 2872 s, 1766 s, 1670 m, 1654 m, 1574 s, 1542 m, 1522 m, 1508 m, 1454 s, 1408 s, 1362 s, 1345 s, 1314 s, 1266 s, 1240 s, 1203 s, 1158 s, 1112 s, 1082 s, 1043 s, 1024 s, 1002 s, 987 s, 954 s, 915 s, 902 s, 868 s, 851 s, 812 s; MS, *m/z* (relative intensity, %) 203 (M^+, 5), 158 (12), 148 (100), 130 (12), 118 (14), 65 (10), 58 (12), 55 (10), 51 (14). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.79; H, 6.53; N, 7.04.



20

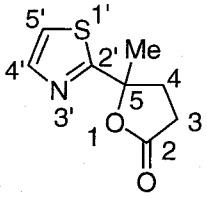
Dihydro-5-methyl-5-(2-pyradinyl)-2(3*H*)-furanone (22). Colorless solid; mp 63-64 °C (hexane/EtOAc); R_f 0.09 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 3H, CH_3), 2.30-2.90 (c, 4H, 3,4-H), 8.56-8.58 (c, 2H, 5',6'-H), 8.85 (d, J = 1.0 Hz, 1H, 3'-H); ^{13}C NMR ($CDCl_3$) δ 27.50 (CH_3), 28.43 (3-C or 4-C), 33.93 (3-C or 4-C), 86.11 (5-C), 141.15 (3'-C), 143.47 (5'-C or 6'-C), 143.92 (5'-C or 6'-C), 157.45 (2'-C), 175.92 (2-C); IR (neat)



22

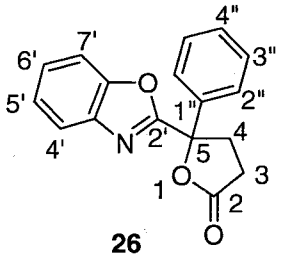
3136 w, 3086 w, 3058 w, 2982 m, 2930 w, 2880 w, 2816 w, 1769 s, 1669 s, 1609 s, 1582 s, 1530 s, 1483 m, 1452 m, 1411 s, 1376 m, 1347 s, 1322 m, 1299 m, 1254 s, 1204 s, 1138 s, 1088 s, 1049 m, 1017 s, 979 w, 948 s, 908 m, 857 s, 803 w; MS, *m/z* (relative intensity, %) 178 (M^+, 4), 150 (25), 123 (12), 107 (24), 99 (100), 80 (10), 79 (18), 71 (20), 55 (13), 53 (19), 52 (33), 51 (11). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.03; H, 5.09; N, 11.64.

Dihydro-5-methyl-5-(2-thiazolyl)-2(3*H*)-furanone (24). Colorless oil; bp 100 °C (2 mmHg); R_f 0.20 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H, CH_3), 2.36-2.48 (m, 1H, 3-H or 4-H), 2.64-2.70 (c, 2H, 3,4-H), 2.85-2.95 (m, 1H, 3-H or 4-H), 7.34 (d, J = 3.4 Hz, 1H, 5'-H), 7.78 (d, J = 3.4 Hz, 1H, 4'-H); ^{13}C NMR ($CDCl_3$) δ 27.93 (CH_3), 28.66 (3-C or 4-C), 34.76 (3-C or 4-C), 85.86 (5-C), 119.62 (5'-C), 142.82 (4'-C), 172.83 (2'-C), 175.60 (2-C); IR (neat) 3172 w, 3100 m, 3030 w, 2984 m, 2938 m, 1786 s, 1637 m, 1541 m, 1502 m, 1455 m, 1421 m, 1376 m, 1317 m, 1288 m, 1249 s, 1204 s, 1128 s, 1090 s, 1056 s, 1002 m, 977 m, 943 s, 899 s, 837 m, 801 m; MS, *m/z* (relative intensity, %) 183 (M^+, 27), 168 (70), 155 (14), 140 (40), 138 (23), 128 (100), 124 (18), 112 (75), 100 (11), 99 (90), 86 (42), 85 (11), 71 (26), 59 (29), 58 (86), 57 (34), 56 (28), 55 (21), 53 (11). Anal. Calcd for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.65; S, 17.50. Found: C, 52.40; H, 5.03; N, 7.68; S, 17.35.



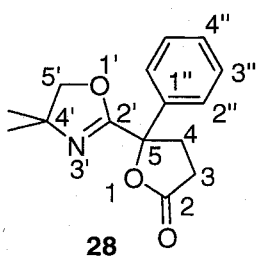
24

Dihydro-5-(2-benzoxazolyl)-5-phenyl-2(3*H*)-furanone (26). Colorless solid; mp 117-118 °C (hexane/EtOAc); R_f 0.03 (hexane/EtOAc = 10/1); ^{1}H NMR ($CDCl_3$) δ 2.64-2.98 (c, 3H, 3,4-H), 3.36 (td, J = 9.7 Hz, J = 8.0 Hz, 1H, 3-H or 4-H), 7.34-7.52 (c, 8H, Ar), 7.74-7.78 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 28.54 (3-C or 4-C), 34.56 (3-C or 4-C), 84.53 (5-C), 111.21 (4'-C or 5'-C or 6'-C or 7'-C or 4"-C), 120.61 (4'-C or 5'-C or 6'-C or 7'-C or 4"-C), 124.71 (4'-C or 5'-C or 6'-C or 7'-C or 4"-C), 124.78 (2C, 2"-C or 3"-C), 126.02 (4'-C or 5'-C or 6'-C or 7'-C or 4"-C), 128.88 (2C, 2"-C or 3"-C), 139.19 (1"-C), 140.23 (3'a-C), 151.39 (7'a-C), 163.92 (2'-C), 175.17 (2-C); IR (KBr) 3064 w, 3028 m, 2930 w, 1783 s, 1713 w, 1635 w, 1612 m, 1566 m, 1498 w, 1452 m, 1430 w, 1417 w, 1346 w, 1294 w, 1278 w, 1237 m, 1219 m, 1196 m, 1183 m, 1153 s, 1106 w, 1086 m, 1054 m, 1016 m, 1000 m, 987 w, 945 w, 920 w, 900 m, 880 m; MS, *m/z* (relative intensity, %) 279 (M^+, 10), 162 (11), 161 (100), 133 (13), 115 (15), 105 (50), 77 (40), 63 (12), 51 (19). Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.07; H, 4.81; N, 4.99.



26

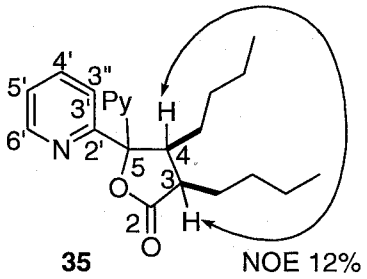
Dihydro-5-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-5-phenyl-2(3*H*)-furanone (28). Colorless solid; mp 100-102 °C (hexane/EtOAc); R_f 0.29 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 2.37-2.61 (c, 2H, 3,4-H), 2.75 (quint, J = 8.7 Hz, 1H, 3-H or 4-H), 3.22-3.32 (m, 1H, 3-H or 4-H), 3.96 (d, J = 8.2 Hz, 1H, 5'-H), 3.99 (d, J = 8.2 Hz, 1H, 5'-H), 7.34-7.47 (c, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.87 (CH_3), 27.96 (CH_3), 28.38 (3-C or 4-C), 34.13 (3-C or 4-C), 67.48 (4'-C), 80.11 (5'-C), 84.19 (5-C), 124.19 (2C, 2"-C or 3"-C), 128.52 (4"-C), 128.70 (2C, 2"-C or 3"-C), 139.23 (1"-C), 163.88 (2'-C), 175.45 (2-C); IR (neat) 3054 w, 2976 m, 2910 w, 1782 s, 1659 s, 1602 w, 1499 m, 1481 m, 1454 m, 1412 m, 1385 w, 1364 m, 1347 m, 1305 m, 1278 m, 1235 m, 1216 m, 1186 m, 1161 s, 1086 m, 1059 s, 1035 m, 991 s, 969 m, 935 m, 897 m, 845 m, 805 m; MS, *m/z* (relative



28

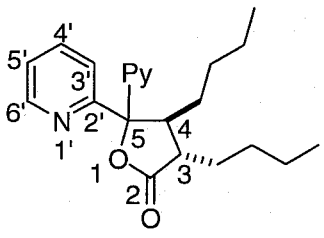
intensity, %) 259 (M^+, 19), 215 (13), 214 (14), 204 (16), 172 (10), 161 (54), 133 (12), 126 (42), 119 (14), 117 (12), 115 (24), 105 (100), 103 (12), 91 (13), 84 (11), 77 (80), 58 (23), 56 (34), 55 (43), 51 (43), 50 (13). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.12; H, 6.66; N, 5.32.

***cis*-3,4-Dibutyldihydro-5,5-di(2-pyridinyl)-2(3*H*)-furanone (35).** An analytically pure sample was obtained by recycling preparative HPLC. Colorless oil; R_f 0.34 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.62 (t, J = 6.9 Hz, 3H, $CH_2CH_2CH_2CH_3$), 0.89 (t, J = 6.9 Hz, 3H, $CH_2CH_2CH_2CH_3$), 0.95-1.08 (c, 4H, Bu), 1.22-1.58 (c, 7H, Bu), 1.72-1.87 (m, 1H, Bu), 2.17-2.57 (m, 1H, 3-H or 4-H), 4.11-4.17 (m, 1H, 3-H or 4-H), 7.12-7.20 (c, 2H, 5'-H), 7.48 (dd, J = 7.9 Hz, J = 1.0 Hz, 1H, 3'-H), 7.61 (td, J = 7.9 Hz, J = 1.0 Hz, 1H, 4'-H), 7.69 (td, J = 7.9 Hz, J = 1.0 Hz, 1H, 4'-H), 7.78 (td, J = 7.9 Hz, J = 1.0 Hz, 1H, 3'-H), 8.58 (ddd, J = 4.6 Hz, J = 1.0 Hz, J = 0.7 Hz, 1H, 2'-H), 8.66 (ddd, J = 5.0 Hz, J = 1.0 Hz, J = 0.7 Hz, 1H, 2'-H); ^{13}C NMR ($CDCl_3$) δ 13.53 ($CH_2CH_2CH_2CH_3$), 13.91 ($CH_2CH_2CH_2CH_3$), 22.61 (Bu), 23.03 (Bu), 24.95 (Bu), 25.09 (Bu), 28.24 (Bu), 30.05 (Bu), 44.44 (3-C or 4-C), 44.82 (3-C or 4-C), 90.96 (5-C), 120.01 (3'-C), 121.56 (3'-C), 122.07 (5'-C), 122.54 (5'-C), 136.39 (4'-C), 136.63 (4'-C), 148.54 (6'-C), 149.01 (6'-C), 158.82 (2'-C), 160.12 (2'-C), 178.17 (2-C); IR (neat) 3060 w, 2964 s, 2868 s, 1784 s, 1590s, 1470 s, 1434 s, 1380 m, 1324 m, 1216 m, 1164 s, 1114 m, 1094 m, 1054 m, 994 m, 842 w; MS, *m/z* (relative intensity, %) 352 (M^+, 4), 295 (14), 237 (11), 186 (31), 185 (100), 78 (12). 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%).



35 NOE 12%

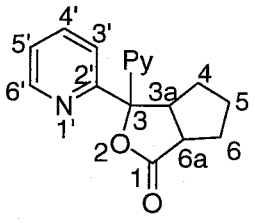
***trans*-3,4-Dibutyldihydro-5,5-di(2-pyridinyl)-2(3*H*)-furanone (36).** White solid; mp 65-67 °C (hexane/EtOAc); R_f 0.40 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.77-0.86 (c, 6H, $CH_2CH_2CH_2CH_3$), 0.92-0.97 (m, 1H, Bu), 1.13-1.80 (c, 11H, Bu), 2.70-2.75 (m, 1H, 3-H or 4-H), 3.53-3.61 (m,1H, 3-H or 4-H), 7.13-7.18 (m, 1H, 5'-H), 7.22-7.29 (c, 2H, 3',5'-H), 7.51 (dd, J = 7.9 Hz, J = 0.7 Hz, 1H, 3'-H), 7.58-7.70 (c, 2H, 4'-H), 8.59 (ddd, J = 4.6 Hz, J = 1.0 Hz, J = 0.7 Hz, 1H, 2'-H), 8.68 (ddd, J = 4.6 Hz, J = 1.0 Hz, J = 0.7 Hz, 1H, 2'-H); ^{13}C NMR ($CDCl_3$) δ 13.87 ($CH_2CH_2CH_2CH_3$), 13.98 ($CH_2CH_2CH_2CH_3$), 22.61 (Bu), 22.86 (Bu), 28.91 (Bu), 29.63 (Bu), 29.98 (Bu), 31.18 (Bu), 46.48 (3-C or 4-C), 46.87 (3-C or 4-C), 90.70 (5-C), 120.71 (3'-C), 121.84 (3'-C), 122.24 (5'-C), 122.77 (5'-C), 136.09 (4'-C), 136.63 (4'-C), 148.20 (6'-C), 148.98 (6'-C), 159.11 (2'-C), 160.81 (2'-C), 179.06 (2-C); IR (neat) 2960 m, 2868 m, 1780 s, 1590 m, 1470 m, 1436 m, 1382 m, 1322 w, 1260 w, 1186 s, 1152 w, 1094 w, 996 m, 942 w, 804 w; MS, *m/z* (relative intensity, %) 352 (M^+, 5), 295 (15), 237 (11), 186 (32), 185 (100), 135 (10), 78 (13). 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.



36

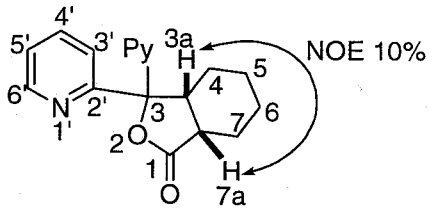
Hexahydro-3,3-di(2-pyridinyl)-1*H*-cyclopenta[c]furan-1-one (37). Colorless oil; bp 150 °C (5 mmHg); R_f 0.06 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 0.97 –1.05 (m, 1H, 4-H), 1.54-1.68 (c, 2H, 5-H), 1.71-1.79 (m, 1H, 4-H), 2.04-2.11 (c, 2H, 6-H), 4.24 (td, J = 8.1 Hz, J = 5.1 Hz, 1H, 6a-H), 4.29 (q, J = 8.1 Hz, 1H, 3a-H), 7.16-7.22 (c, 2H, 5'-H), 7.35 (dd, J = 7.0 Hz, J = 0.81 Hz, 1H, 3'-H), 7.61 (td, J = 8.1 Hz, J = 1.6 Hz, 1H, 4'-H), 7.17-7.75 (c, 2H, 3',4'-H), 8.60-8.66 (c, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 25.90 (5-C), 28.74 (6-C), 29.44

(4-C), 46.24 (6a-C), 49.22 (3a-C), 90.67 (3-C), 119.68 (3'-C), 121.62 (3'-C), 122.32 (5'-C), 122.86 (5'-C), 136.66 (4'-C), 136.71 (4'-C), 148.73 (6'-C), 149.34 (6'-C), 159.71 (2'-C), 160.52 (2'-C), 180.32 (1-C); IR (neat) 3362 w, 3058 w, 2960 m, 2870 m, 1773 s, 1587 s, 1467 s, 1432 s, 1303 m, 1250 w, 1162 s, 1095 m, 1048 w, 989 m, 968 m, 906 w, 858 w; MS, *m/z* (relative intensity, %) 280 (M^+, 5), 186 (11), 185 (72), 146 (12), 106 (21), 80 (11), 79 (15), 78 (100), 67 (12), 52 (19), 51 (39). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.83; H, 5.83; N, 10.10.



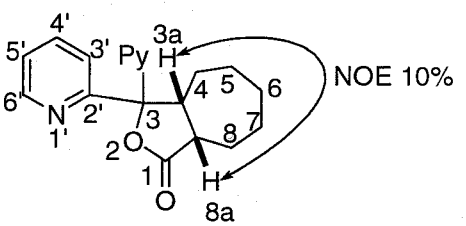
37

Hexahydro-3,3-di(2-pyridinyl)-1(3*H*)-isobenzofuranone (38). Colorless solid; mp 114-116 °C (hexane/EtOAc); R_f 0.49 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.73-0.81 (m, 1H, 4-H), 1.15-1.24 (c, 3H, 5,6-H), 1.51-1.73 (c, 3H, 4,6,7-H), 2.12-2.17 (m, 1H, 7-H), 2.69-2.78 (m, 1H, 7a-H), 3.98-4.07 (m, 1H, 3a-H), 7.10-7.20 (c, 2H, 5'-H), 7.47 (d, J = 7.9 Hz, 1H, 3'-H), 7.57-7.72 (c, 2H, 4'-H), 7.77 (d, J = 7.9 Hz, 1H, 3'-H), 8.56 (d, J = 4.6 Hz, 1H, 6'-H), 8.65 (d, J = 5.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 22.48 (5-C), 22.75 (7-C), 23.69 (6-C), 25.03 (4-C), 40.61 (7a-C), 42.09 (3a-C), 90.50 (3-C), 119.68 (3'-C), 121.98 (3'-C), 122.12 (5'-C), 122.71 (5'-C), 136.64 (2C, 4'-C), 148.63 (6'-C), 149.31 (6'-C), 158.67 (2'-C), 159.94 (2'-C), 177.30 (1-C); IR (KBr) 3060 w, 2934 m, 2858 m, 1784 s, 1587 m, 1574 m, 1468 m, 1435 m, 1363 w, 1327 m, 1186 m, 1168 s, 1133 m, 1112 m, 1038 m, 988 m, 955 m, 926 m, 912 m, 862 m; MS, *m/z* (relative intensity, %) 294 (M^+, 5), 186 (19), 185 (100), 106 (15), 80 (13), 79 (15), 78 (78), 53 (11), 52 (13), 51 (25). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.26; H, 6.29; N, 9.27. The stereochemistry of **38** was assigned to be *cis* on the basis of the NOE enhancement exhibited between the ring junction protons (10%).



38

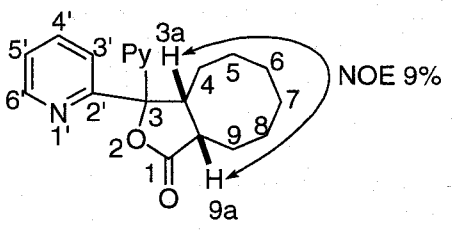
Hexahydro-3,3-di(2-pyridinyl)-1*H*-cyclohepta[c]furan-1-one (39). White solid; mp 131-132 °C (hexane/EtOAc); R_f 0.436 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.91-1.04 (m, 1H, 4-H), 1.15-1.39 (c, 4H, 4,5,6,7-H), 1.61-1.74 (c, 4H, 5,6,7,8-H), 2.03-2.13 (m, 1H, 8-H), 2.87-2.97 (m, 1H, 8a-H), 4.03-4.11 (m, 1H, 3a-H), 7.08-7.19 (c, 2H, 5'-H), 7.39 (d, J = 7.9 Hz, 1H, 3'-H), 7.53-7.66 (c, 3H, 3',4'-H), 8.53 (d, J = 4.3 Hz, 1H, 6'-H), 8.63 (d, J = 4.3 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 26.11 (5-C or 6-C or 7-C), 26.58 (4-C), 27.31 (8-C), 28.29 (5-C or 6-C or 7-C), 30.60 (5-C or 6-C or 7-C), 45.32 (8a-C), 48.11 (3a-C), 91.11 (3-C), 119.95 (3'-C), 122.10 (2C, 3',5'-C), 122.73 (5'-C), 136.42 (4'-C), 136.63 (4'-C), 148.24 (6'-C), 149.26 (6'-C), 159.31 (2'-C), 160.22 (2'-C), 178.81 (1-C); IR (KBr) 3064 w, 3008 w, 2932 m, 2860 w, 1766 s, 1590 m, 1472 m, 1436 s, 1318 w, 1284 m, 1264 m, 1220 s, 1184 m, 1150 w, 1100 w, 1072 w, 1028 s, 996 m, 946 w, 924 w, 888 w, 844 w; MS, *m/z* (relative intensity, %) 308 (M^+, 7), 186 (22), 185 (100), 80 (11), 79 (11), 78 (50), 51 (12). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.89; H, 6.64; N, 8.98. The stereochemistry of **39** was assigned to be *cis* on the basis of the NOE enhancement exhibited between the ring junction protons (10%).



39

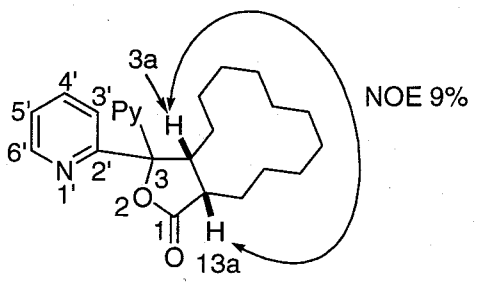
Hexahydro-3,3-di(2-pyridinyl)-1*H*-cycloocta[c]furan-1-one (40). White solid; mp

139-140 °C (hexane/EtOAc); R_f 0.60 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.09-1.22 (m, 1H, CH_2), 1.39-1.86 (c, 10H, CH_2), 2.07-2.17 (m, 1H, CH_2), 2.57-2.65 (m, 1H, 3a-H or 9a-H), 4.04 (t, J = 8.9 Hz, 1H, 3a-H or 9a-H), 7.12-7.23 (c, 2H, 5'-H), 7.49- 7.53 (c, 2H, 3'-H), 7.60-7.69 (c, 2H, 4'-H), 8.60 (d, J = 4.0 Hz, 1H, 6'-H), 8.68 (d, J = 4.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 23.91 (CH_2), 24.62 (CH_2), 25.24 (CH_2), 25.33 (CH_2), 28.14 (CH_2), 29.62 (CH_2), 45.66 (3a-C or 9a-C), 47.03 (3a-C or 9a-C), 91.94 (3-C), 120.37 (3'-C), 121.72 (3'-C), 122.14 (5'-C), 122.62 (5'-C), 136.40 (4'-C), 136.62 (4'-C), 148.56 (6'-C), 149.39 (6'-C), 159.34 (2'-C), 160.32 (2'-C), 179.13 (1-C); IR (KBr) 3072 w, 2932 s, 2860 m, 1782 s, 1590 s, 1470 s, 1434 s, 1366 w, 1316 m, 1278 m, 1260 m, 1230 m, 1166 s, 1140 m, 1116 m, 1094 m, 1050 m, 994 s, 920 w, 902 w, 868 w, 838 w; MS, *m/z* (relative intensity, %) 322 (M^+, 7), 186 (22), 185 (100), 106 (11), 80 (10), 78 (43). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.47; H, 6.93; N, 8.63. The stereochemistry of **40** was assigned to be *cis* on the basis of the NOE enhancement exhibited between the ring junction protons (9%).



40

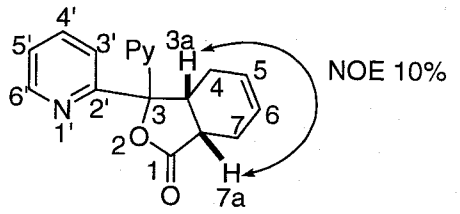
Hexahydro-3,3-di(2-pyridinyl)-1*H*-cyclododeca [c]furan-1-one (41). **41** was obtained as a 84:16 stereoisomeric mixture. Colorless oil; R_f 0.54 (major), 0.46 (minor) (EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.86-1.87 (c, 20H, cyclododecy), [2.57 (ddd, J = 10.8 Hz, J = 6.6 Hz, J = 3.5 Hz, major), 2.78-2.82 (m, minor), 1H, 3a-H or 13a-H], [3,98 (dt, J = 6.6 Hz, J = 3.5 Hz, major), 4.03-4.11 (m, minor), 1H, 3a-H or 13a-H], 7.08-7.19 (c, 2H, 5'-H), 7.40 (dd, J = 7.9 Hz, J = 1.0 Hz, major, 1H, 3'-H), 7.50-7.81 (c, 3H, 3',4'-H), 8.50-8.53 (c, 1H, 6'-H), 8.65-8.67 (c, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ [20.97 (major), 21.74 (minor), 22.56 (minor), 22.97 (overlapping peaks), 23.12 (major), 23.22 (minor), 23.29 (minor), 23.35 (minor), 23.92 (major), 24.64 (major), 24.97 (major), 25.32 (major), 25.93 (two overlapping peaks), 26.29 (minor), 26.47(major), 28.01 (minor), 28.98 (minor), cyclododecyl], [46.28 (major), 46.64 (major), 44.12 (minor), 42.44 (minor), 3a,13a-H], [91.68 (minor), 91.95 (major), 3-C], [119.88 (minor), 120.13 (major), 121.37 (minor), 122.03 (major), 122.52 (major), 122.58 (minor), 3',5'-C], [136.32 (minor), 136.44 (major), 4'-C], [136.56 (major), 136.64 (minor), 6'-C], [148.13 (minor), 148.47 (major), 6'-C], [149.03 (major), 149.12 (minor), 6'-C], [158.82 (major), 159.03 (minor), 2'-C], 159.93 (major), 160.99 (minor), 2'-C], [177.73 (major), 179.41 (minor), 1-C]; IR (KBr) 2928 m, 2860 m, 1778 s, 1588 m, 1472 m, 1442 w, 1338 w, 1276 w, 1218 w, 1186 w, 1160 w, 1094 w, 1046 w, 992 w, 918 w; MS, *m/z* (relative intensity, %) 378 (M^+, 8), 186 (22), 185 (100), 106 (10), 80 (12), 79 (10), 78 (40), 55 (14). HRMS Calcd for $C_{24}H_{30}N_2O_2$: 378.2307. Found: 378.2301. The stereochemistry of the major isomer of **41** was assigned to be *cis* on the basis of the NOE enhancement exhibited between the ring junction protons (9%).



41(major isomer)

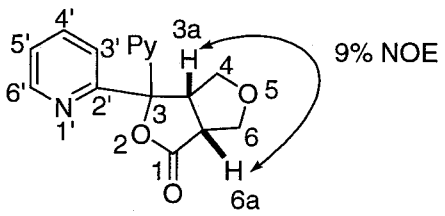
***cis*-3a,4,7,7a-Tetrahydro-3,3-di(2-pyridinyl)-1(3*H*)-isobenzofuranone (42).** Colorless plate; mp 128-130 °C (hexane/EtOAc); R_f 0.20 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.40-1.52 (m, 1H, 4-H or 7-H), 1.97 (dt, J = 17.6 Hz, J = 5.7 Hz, 1H, 4-H or 7-H), 2.30-2.41 (m, 1H, 4-H or 7-H), 2.56 (d, J = 19.8 Hz, 1H, 4-H or 7-H), 2.87 (t, J = 7.9 Hz, 1H, 3a-H or 7a-H), 4.14 (dt, J = 10.6 Hz, J = 6.9 Hz, 1H, 3a-H or 7a-H), 5.59-5.67 (c, 2H, 5,6-H),

7.12-7.21 (c, 2H, 5'-H), 7.52 (d, J = 7.9 Hz, 1H, 3'-H), 7.59-7.72 (c, 2H, 4'-H), 7.76 (d, J = 7.9 Hz, 1H, 3'-H), 8.58 (dd, J = 4.0 Hz, J = 1.0 Hz, 1H, 6'-H), 8.65 (dd, J = 4.0 Hz, J = 1.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 21.96 (4-C or 7-C), 22.47 (4-C or 7-C), 38.38 (3a-C or 7a-C), 38.60 (3a-C or 7a-C), 91.26 (3-C), 119.82 (3'-C), 121.64 (3'-C), 122.19 (5'-C), 122.70 (5'-C), 124.06 (5-C or 6-C), 124.77 (5-C or 6-C), 136.58 (4'-C), 136.63 (4'-C), 148.63 (6'-C), 149.21 (6'-C), 158.40 (2'-C), 159.10 (2'-C), 177.57 (1-C); IR (KBr) 3044 m, 2904 m, 2844 m, 1790 s, 1664 m, 1588 s, 1468 s, 1434 s, 1354 s, 1332 m, 1304 m, 1280 m, 1252 m, 1170 s, 1146 s, 1124 s, 1102 s, 1046 s, 984 s, 930 s, 906 m, 842 m; MS, *m/z* (relative intensity, %) 292 (M^+, 6), 186 (17), 185 (100), 158 (10), 132 (13), 106 (10), 80 (13), 79 (18), 78 (65), 77 (10), 52 (12), 51 (21). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.89; H, 5.58; N, 9.56. The stereochemistry of **42** was assigned to be *cis* on the basis of the NOE enhancement exhibited between the ring junction protons (10%).



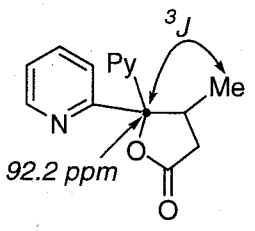
42

***cis*-Tetrahydro-3,3-di(2-pyridinyl)-1*H*,3*H*-furo[3,4-c]furan-1-one (43).** White solid; mp 127-128 °C (hexane/EtOAc); R_f 0.29 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.34 (dd, J = 10.2 Hz, J = 6.3 Hz, 1H, 4-H or 6-H), 3.54-3.59 (m, 1H, 3a-H or 6a-H), 3.92-3.99 (c, 2H, 4,6-H), 4.29 (d, J = 8.9 Hz, 1H, 4-H or 6-H), 4.56 (dd, J = 14.8 Hz, J = 8.2 Hz, 1H, 3a-H or 6a-H), 7.20-7.24 (c, 3H, 3',5'-H), 7.63 (t, J = 7.6 Hz, 1H, 4'-H), 7.76-7.71 (c, 2H, 3',4'-H), 8.61-8.66 (c, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 47.65 (3a-C or 6a-C), 48.70 (3a-C or 6a-C), 70.64 (4-C or 6-C), 71.08 (4-C or 6-C), 96.67 (3-C), 120.28 (3'-C), 121.19 (3'-C), 122.71 (5'-C), 123.01 (5'-C), 136.77 (4'-C), 136.92 (4'-C), 148.77 (6'-C), 149.23 (6'-C), 158.46 (2'-C), 159.88 (2'-C), 177.37 (C=O); IR (KBr) 3060 w, 2996 w, 2864 w, 1776 s, 1592 m, 1470 m, 1434 m, 1364 w, 1330 w, 1310 w, 1284 w, 1218 m, 1194 m, 1176 s, 1148 w, 1092 m, 1052 m, 1024 m, 992 m, 972 m, 938 w, 906 m, 870 w, 820 w; MS, *m/z* (relative intensity, %) 282 (M^+, 3), 186 (14), 185 (100), 106 (14), 79 (14), 78 (91), 52 (14), 51 (27). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.89; H, 4.98; N, 9.87. The stereochemistry of **43** was assigned to be *cis* on the basis of the NOE enhancement exhibited between the ring junction protons (10%).



43

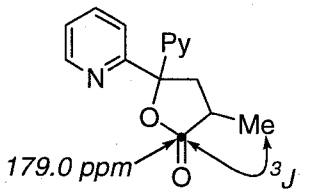
Dihydro-4-methyl-5,5-di(2-pyridinyl)-2(3*H*)-furanone (44a). Colorless oil; bp 200 °C (5 mmHg); R_f 0.26 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.9 Hz, 3H, CH_3), 2.45 (dd, J = 16.5 Hz, J = 3.6 Hz, 1H, 3-H), 2.80 (dd, J = 16.5 Hz, J = 7.9 Hz, 1H, 3-H), 3.94-4.01 (m, 1H, 4-H), 7.16-7.26 (c, 2H, 5'-H), 7.46 (d, J = 8.3 Hz, 1H, 3'-H), 7.49 (d, J = 7.9 Hz, 1H, 3'-H), 7.63-7.71 (c, 2H, 4'-H), 8.61 (d, J = 4.6 Hz, 1H, 6'-H), 8.67 (d, J = 5.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 16.52 (CH_3), 37.40 (3-C), 37.63 (4-C), 92.22 (5-C), 120.42 (3'-C), 122.17 (3'-C), 122.37 (5'-C), 122.93 (5'-C), 136.41 (4'-C), 136.71 (4'-C), 148.45 (6'-C), 149.25 (6'-C), 158.69 (2'-C), 159.93 (2'-C), 176.28 (2-C); IR (neat) 3060 w, 2978 w, 2934 w, 2878 w, 1789 s, 1589 s, 1574 m, 1470 s, 1434 s, 1378 w, 1347 w, 1269 m, 1213 s, 1166 s, 1112 m, 1050 m, 1015 m, 993 s, 934 m, 879 w; MS, *m/z* (relative intensity, %) 254 (M^+, 20), 210 (10), 195 (14), 186 (22), 185 (100), 78 (20). Anal. Calcd for



44a

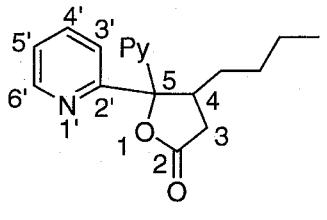
$C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.59; H, 5.46; N, 11.02. The regiochemistry was determined by long range ^1H-^{13}C cosy measurements. The long range ^1H-^{13}C coupling indicative of the regiochemistry and the corresponding ^{13}C chemical shifts are given here.

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); ^1H NMR ($CDCl_3$) δ 1.29 (d, J = 7.3 Hz, 3H, CH_3), 2.62 (t, J = 12.0 Hz, 1H, 4-H), 2.75-2.84 (m, 1H, 3-H), 3.79 (dd, J = 12.6 Hz, J = 8.2 Hz, 1H, 4-H), 7.18-7.23 (c, 2H, 5'-H), 7.48 (d, J = 7.0 Hz, 1H, 3'-H), 7.57 (d, J = 6.8 Hz, 1H, 3'-H), 7.64-7.72 (c, 2H, 4'-H), 8.62 (d, J = 4.9 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 14.86 (CH_3), 34.90 (3-C), 40.72 (4-C), 87.96 (5-C), 120.11 (3'-C), 120.86 (3'-C), 122.71 (5'-C), 122.82 (5'-C), 136.77 (2C, 4'-C), 149.06 (6'-C), 149.18 (6'-C), 159.87 (2'-C), 160.61 (2'-C), 179.01 (2-C); IR (neat) 3058 w, 2974 w, 2936 w, 2878 w, 1786 s, 1588 s, 1574 m, 1470 s, 1435 s, 1379 w, 1333 w, 1312 m, 1262 m, 1168 s, 1101 m, 1065 w, 1032 m, 991 s, 951 w, 931 m, 876 w, 823 w; MS, *m/z* (relative intensity, %) 254 (M^+, 11), 211 (19), 210 (100), 209 (42), 208 (12), 195 (59), 186 (13), 185 (81), 182 (18), 176 (28), 169 (20), 156 (20), 148 (38), 120 (50), 106 (34), 79 (11), 78 (55). 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 ^1H-^{13}C cosy measurements. The long range ^1H-^{13}C couplings indicative of the regiochemistry and the corresponding ^{13}C chemical shifts are given here.



44b

4-Butyldihydro-5,5-di(2-pyridinyl)-2(3*H*)-furanone (45a). Colorless solid; mp 99-100 °C (hexane/EtOAc); R_f 0.14 (hexane/EtOAc = 2/1); ^1H NMR ($CDCl_3$) δ 0.75-0.95 (c, 4H, $CH_2CH_2CH_2CH_3$), 1.10-1.40 (c, 4H, $CH_2CH_2CH_2CH_3$), 1.45-1.65 (m, 1H, $CH_2CH_2CH_2CH_3$), 2.60 (dd, J = 17.5 Hz, J = 5.9 Hz, 1H, 3-H), 2.73 (dd, J = 17.5 Hz, J = 7.9 Hz, 1H, 3-H), 3.72-3.75 (m, 1H, 4-H), 7.16-7.29 (c, 2H, 5'-H), 7.36 (d, J = 8.3 Hz, 1H, 3'-H), 7.45 (d, J = 7.9 Hz, 1H, 3'-H), 7.62-7.70 (c, 2H, 4'-H), 8.60 (d, J = 4.0 Hz, 1H, 6'-H), 8.66 (d, J = 4.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 13.66 ($CH_2CH_2CH_2CH_3$), 22.25 ($CH_2CH_2CH_2CH_3$), 29.51 ($CH_2CH_2CH_2CH_3$), 29.94 ($CH_2CH_2CH_2CH_3$), 34.58 (3-C), 43.13 (4-C), 91.83 (5-C), 120.59 (3'-C or 5'-C), 122.05 (3'-C or 5'-C), 122.30 (3'-C or 5'-C), 122.80 (3'-C or 5'-C), 136.17 (4'-C), 136.57 (4'-C), 148.27 (6'-C), 148.98 (6'-C), 158.63 (2'-C), 159.96 (2'-C), 176.30 (2-C); IR (KBr) 3066 m, 3016 m, 2964 m, 2936 m, 2906 m, 2862 m, 1777 s, 1763 s, 1617 m, 1590 s, 1574 m, 1511 m, 1469 m, 1444 s, 1415 m, 1382 m, 1355 m, 1317 m, 1294 m, 1270 s, 1226 s, 1208 s, 1171 s, 1155 s, 1129 m, 1095 m, 1055 m, 1021 s, 993 s, 960 m, 944 m, 913 m, 899 m, 883 m; MS, *m/z* (relative intensity, %) 296 (M^+, 1), 186 (23), 185 (100), 135 (12), 106 (20), 80 (28), 79 (14), 78 (73), 52 (12), 51 (18). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.89; H, 6.93; N, 9.56. The regiochemistry was determined by deuterium exchange experiments.

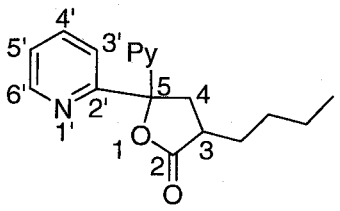


45a

α-Deuteration of 45a. A dry, 20 mL, two-neck round-bottomed flask equipped with magnetic stirring, cold bath, and a nitrogen inlet was charged with 0.5 mL of THF, 0.7 mL of diisopropylamine (5 mmol) and at -78 °C 3.4 mL (5 mmol) of 1.5 M *n*-butyllithium in hexane. The resulting solution was warmed to 25 °C, stirred for 15 min, cooled to -78 °C again, and 196 mg of **25a** (0.66 mmol) in 3 mL of THF added via syringe. The reaction mixture was then warmed to 25 °C, stirred for 30 min, quenched with 0.5 mL of D_2O, and

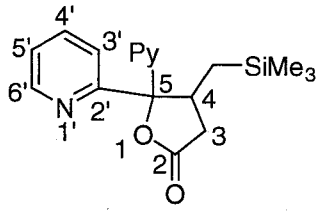
extracted with EtOAc. The organic layer was dried over magnesium sulfate, and concentrated. GC/MS analysis of the crude product indicated the incorporation of deuterium (*m/z* 273, M^+). The ^1H NMR spectra showed a diminished in the absorption at δ 2.58-2.72 derived from the methylene in the lactone ring, while the methine absorption (δ 3.71-3.74) appeared at full strength. These observations indicate that the methylene group is at the α-position of the carbonyl group in **45a**.

3-Butyldihydro-5,5-di(2-pyridinyl)-2(3*H*)-furanone (45b). Colorless oil; bp 180 °C (2 mmHg); R_f 0.04 (hexane/EtOAc = 2/1); ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.30-1.50 (c, 5H, $CH_2CH_2CH_2CH_3$), 1.80-2.00 (m, 1H, $CH_2CH_2CH_2CH_3$), 2.62-2.80 (c, 2H, 3,4-H), 3.67-3.80 (m, 1H, 4-H), 7.17-7.23 (m, 2H, 5'-H), 7.48 (dd, *J* = 6.9 Hz, *J* = 1.0 Hz, 1H, 3'-H), 7.56 (d, *J* = 6.9 Hz, 1.0 Hz, 1H, 3'-H), 7.63-7.71 (c, 2H, 4'-H), 8.62 (dd, *J* = 4.0 Hz, *J* = 1.0 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 13.66 ($CH_2CH_2CH_2CH_3$), 22.21 ($CH_2CH_2CH_2CH_3$), 29.17 ($CH_2CH_2CH_2CH_3$), 29.78 ($CH_2CH_2CH_2CH_3$), 38.74 (4-C), 39.82 (3-C), 88.09 (5-C), 120.09 (5'-C), 120.63 (5'-C), 122.62 (3'-C), 122.70 (3'-C), 136.68 (2C, 4'-C), 149.04 (6'-C), 149.07 (6'-C), 159.95 (2'-C), 160.57 (6'-C), 178.42 (2-C); IR (neat) 3006 m, 2958 m, 2932 m, 2864 m, 1780 s, 1663 m, 1635 m, 1587 s, 1574 m, 1468 s, 1433 s, 1382 m, 1294 m, 1260 m, 1221 m, 1178 s, 1157 s, 1122 m, 1100 m, 1056 m, 1044 m, 1006 m, 990 m, 963 m, 924 m, 893 m; MS, *m/z* (relative intensity, %) 296 (M^+, 1), 252 (12), 209 (30), 195 (28), 190 (10), 185 (25), 162 (20), 130 (11), 117 (11), 106 (26), 79 (19), 78 (100), 55 (11), 52 (14), 51 (28). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.83; H, 6.84; N, 9.53.



45b

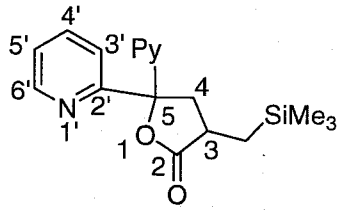
Dihydro-5,5-di(2-pyridinyl)-4-[(trimethylsilyl)methyl]-2(3*H*)-furanone (46a). Colorless solid; mp 122-123 °C (hexane/EtOAc); R_f 0.20 (hexane/EtOAc = 3/1); ^1H NMR ($CDCl_3$) δ 0.03-0.25 (c, 10H, CH_2SiMe_3), 0.99 (dd, J=14.3 Hz, *J*=1.9 Hz, 1H, CH_2SiMe_3), 2.60 (dd, *J* = 17.1 Hz, *J* = 8.1 Hz, 1H, 3-H), 2.77 (dd, *J* = 17.1 Hz, *J* = 8.1 Hz, 1H, 3-H), 3.67-3.74 (m, 1H, 4-H), 7.18-7.29 (c, 3H, 3',5'-H), 7.51 (d, *J* = 7.8 Hz, 1H, 3'-H), 7.61-7.73 (c, 2H, 4'-H), 8.63-8.69 (c, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ -0.99 (3C, CH_2SiMe_3), 18.60 (CH_2SiMe_3), 36.91 (3-C), 40.79 (4-C), 92.83 (5-C), 121.51 (3'-C or 5'-C), 122.21 (3'-C), 122.50 (3'-C or 5'-C), 122.95 (3'-C or 5'-C), 136.15 (4'-C), 136.73 (4'-C), 148.48 (6'-C), 149.18 (6'-C), 158.94 (2'-C), 160.40 (2'-C), 176.66 (2-C); IR (KBr) 3066 w, 3014 w, 2964 m, 2924 w, 2888 w, 1783 s, 1715 w, 1630 w, 1636 w, 1589 s, 1571 m, 1525 w, 1508 w, 1422 m, 1433 s, 1402 w, 1350 w, 1320 w, 1290 w, 1261 s, 1251 s, 1223 s, 1174 s, 1154 w, 1129 w, 1094 w, 1019 s, 993 m, 970 w, 942 w, 905 w, 891 w, 881 w, 857 s, 839 s; MS, *m/z* (relative intensity, %) 326 (M^+, 0), 311 (M^+-15, 3), 186 (25), 185 (100), 80 (18), 78 (30), 73 (54). Anal. Calcd for $C_{18}H_{22}N_2O_2Si$: C, 62.22; H, 6.79; N, 8.58. Found: C, 66.27; H, 6.67; N, 8.60. The regiochemistry was determined by single-crystal X-ray analysis.[14]



46a

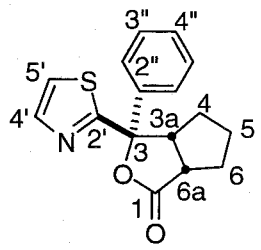
Dihydro-5,5-di(2-pyridinyl)-3-[(trimethylsilyl)methyl]-2(3*H*)-furanone (46b). Colorless solid; mp 94-95 °C (hexane/EtOAc); R_f 0.11 (hexane/EtOAc = 3/1); ^1H NMR ($CDCl_3$) δ 0.06 (s, 9H, CH_2SiMe_3), 0.69 (dd, J = 14.9 Hz, *J* = 11.1 Hz, 1H, CH_2SiMe_3), 1.30 (dd, *J* = 14.9 Hz, *J* = 3.4 Hz, 1H, CH_2SiMe_3), 2.53-2.76 (c, 2H, 3,4-H), 3.86 (dd, *J* = 11.9 Hz, *J* = 7.6 Hz, 1H, 4-H), 7.19-7.25 (c, 2H, 5'-H), 7.51 (d, *J* = 7.8 Hz, 1H, 3'-H), 7.60 (d, *J* = 8.1 Hz, 1H, 3'-H), 7.65-7.72 (c, 2H, 4'-H), 8.62-8.67 (c, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ -1.24

(3C, CH_2SiMe_3), 17.85 (CH_2SiMe_3), 36.70 (3-C), 41.06 (4-C), 87.94 (5-C), 119.95 (3'-C), 120.94 (3'-C), 122.70 (5'-C), 122.82 (5'-C), 136.82 (2C, 4'-C), 149.15 (6'-C), 149.29 (6'-C), 159.96 (2'-C), 160.86 (2'-C), 179.98 (2-C); IR (KBr) 2954 m, 2924 w, 2896 w, 1772 s, 1696 w, 1666 w, 1636 w, 1586 m, 1573 w, 1541 w, 1464 m, 1435 m, 1329 w, 1308 w, 1291 w, 1246 s, 1179 s, 1130 m, 1109 m, 1093 m, 1060 m, 1044 m, 1008 w, 993 m, 972 m, 894 w, 848 s; MS, *m/z* (relative intensity, %) 326 (M^+, 0), 311 (M^+-15, 15), 293 (24), 253 (12), 209 (62), 205 (32), 195 (14), 185 (41), 183 (14), 182 (19), 181 (56), 130 (34), 117 (12), 78 (45), 75 (24), 73 (100), 59 (16), 55 (12), 52 (14). Anal. Calcd for $C_{18}H_{22}N_2O_2Si$: C, 62.22; H, 6.79; N, 8.58. Found: C, 65.95; H, 6.70; N, 8.55.



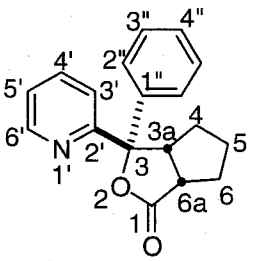
46b

Hexahydro-3-phenyl-3-(2-thiazolyl)-1*H*-cyclopenta[c]furan-1-one (48). Colorless crystal; 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, 4-H), 1.50-1.67 (c, 3H, 4,5-H), 2.04-2.13 (m, 2H, 6-H), 3.28 (td, J = 12.4 Hz, J = 4.1 Hz, 1H, 6a-H), 3.98-4.07 (m, 1H, 3a-H), 7.25-7.40 (c, 4H, Ph,5'-H), 7.56 (dd, J = 8.0 Hz, J = 1.2 Hz, 2H, Ph), 7.76 (d, J = 3.0 Hz, 1H, 4'-H); ^{13}C NMR ($CDCl_3$) δ 25.64 (5-C), 29.02 (6-C), 29.51 (4-C), 46.40 (6a-C), 50.93 (3a-C), 88.72 (3-C), 120.88 (5'-C), 125.01 (2C, 2"-C or 3"-C), 128.01 (4"-C), 128.30 (2C, 2"-C or 3"-C), 139.30 (1"-C), 142.37 (4'-C), 174.03 (2'-C), 179.44 (1-C); IR (KBr) 3330 w, 3136 w, 3088 w, 2962 m, 2868 m, 1780 s, 1615 w, 1501 m, 1470 w, 1451 s, 1429 w, 1324 m, 1303 m, 1298m, 1277 m, 1250 m, 1236 m, 1197 s, 1157 s, 1126 s, 1084 s, 1066 m, 1047 m, 1024 m, 1004 s, 980 s, 962 s, 933 s, 907 w, 881 m, 843 w, 827 m; MS, *m/z* (relative intensity, %) 285 (M^+, 13), 191 (15), 190 (93), 180 (38), 161 (11), 112 (44), 105 (100), 77 (97), 68 (48), 67 (45), 65 (11), 59 (24), 58 (58), 57 (13), 53 (16), 50 (53). 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.[15]



48

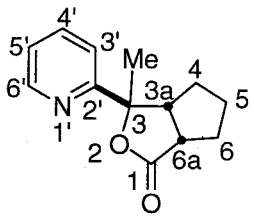
Hexahydro-3-phenyl-3-(2-pyridinyl)-1*H*-cyclopenta[c]furan-1-one (49). ***Major isomer***: White solid; mp 74-76 °C (hexane/EtOAc); R_f 0.29 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 1.10-1.23 (m, 1H, 4-H), 1.50-1.69 (c, 2H, 4,5-H), 2.00-2.09 (c, 2H, 6-H), 3.06 (td, J = 8.4 Hz, J = 4.6 Hz, 1H, 6a-H), 4.25 (q, J = 8.4 Hz, 1H, 3a-H), 7.18 (dd, J = 7.6 Hz, J =4.6 Hz, 1H, 5'-H), 7.20-7.34 (c, 3H, Ph), 7.46 (d, J = 7.8 Hz, 1H, 3'-H), 7.52-7.55 (m, 2H, Ph), 7.61 (ddd, J = 7.8 Hz, J = 7.6 Hz, J = 1.6 Hz, 1H, 4'-H), 8.59 (dd, J = 4.6 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 25.72 (5-C), 28.86 (6-C), 29.42 (4-C), 46.24 (6a-C), 49.15 (3a-C), 90.39 (3-C), 121.47 (3'-C), 122.64 (5'-C), 125.03 (2C, 2"-C or 3"-C), 127.26 (4"-C), 128.05 (2C, 2"-C or 3"-C), 136.89 (4'-C), 140.70 (1"-C), 148.30 (6'-C), 161.92 (2'-C), 180.13 (1-C); IR (KBr) 3060 w, 2964 m, 2940 m, 2870 m, 1775 s, 1589 s, 1571 m, 1493 m, 1468 s, 1448 s, 1431 s, 1326 m, 1296 m, 1281 m, 1246 s, 1208 s, 1164 s, 1098 s, 1065 m, 1050 m, 1010 s, 990 s, 970 s, 918 m, 894 m; MS, *m/z* (relative intensity, %) 279 (M^+, 15), 201 (23), 184 (14), 155 (13), 146 (10), 106 (29), 105 (100), 78 (37), 77 (62), 67 (13), 52 (11), 51 (32). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.60; H, 6.22; N, 5.00. The stereochemistry of the major isomer was determined by analogy to **48**. ***Minor isomer***: White solid; mp 114-115 °C (hexane/EtOAc); R_f



49 (major isomer)

0.26 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 0.96-1.11 (m, 1H, 4-H), 1.56-1.68 (c, 2H, 5-H), 1.84-1.98 (m, 1H, 4-H), 1.99-2.09 (c, 2H, 6-H), 3.00-3.04 (m, 1H, 6a-H), 3.62-3.71 (m, 1H, 3a-H), 7.11-7.16 (m, 1H, 5'-H), 7.24-7.36 (c, 3H, Ph and/or 3'-C and/or 4'-C), 7.64-7.75 (c, 4H, Ph and/or 3'-C and/or 4'-C), 8.57 (d, *J* = 4.6 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 25.68 (5-C), 28.07 (6-C), 29.45 (4-C), 45.70 (6a-C), 52.53 (3a-C), 89.69 (3-C), 119.53 (3'-C), 122.14 (5'-C), 125.37 (2C, 2"-C or 3"-C), 127.75 (4"-C), 128.34 (2C, 2"-C or 3"-C), 136.62 (4'-C), 143.09 (1"-C), 148.97 (6'-C), 160.70 (2'-C), 180.05 (1-C); IR (KBr) 3064 w, 3028 w, 2970 m, 2882 w, 1781 s, 1587 m, 1574 w, 1496 w, 1472 m, 1452 m, 1436 m, 1316 w, 1300 w, 1280 w, 1239 w, 1198 m, 1182 m, 1161 s, 1097 m, 1068 w, 1051 w, 1032 m, 1010 m, 1002 m, 989 m, 973 m, 908 w, 893 w, 825 w; MS, *m/z* (relative intensity, %) 279 (M^+, 40), 185 (21), 184 (64), 155 (55), 154 (13), 107 (10), 106 (99), 105 (62), 79 (19), 78 (100), 77 (74), 68 (11), 67 (27), 53 (11), 52 (15), 51 (48). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.23; H, 6.21; N, 5.06.

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, Me,5-H and 4-H or 6-H), 1.89-2.17 (c, 3H, 4,6-H), 2.88 (td, *J* = 8.9 Hz, *J* = 3.6 Hz, 1H, 3a-H or 6a-H), 3.34 (q, *J* = 7.9 Hz, 1H, 3a-H or 6a-H), 7.21 (ddd, *J* = 7.6 Hz, *J* = 5.0 Hz, *J* = 1.0 Hz, 1H, 5'-H), 7.51 (dd, *J* = 7.9 Hz, *J* = 1.0 Hz, 1H, 3'-H), 7.70 (ddd, *J* = 7.9 Hz, *J* = 7.6 Hz, *J* = 1.7 Hz, 1H, 4'-H), 8.59 (ddd, *J* = 5.0 Hz, *J* = 1.7 Hz, *J* = 1.0 Hz, 1H, 6'-H),; ^{13}C NMR ($CDCl_3$) δ 23.65 (Me), 26.29 (5-C), 28.42 (4-C or 6-C), 28.82 (4-C or 6-C), 45.46 (3a-C or 6a-C), 49.73 (3a-C or 6a-C), 87.32 (3-C), 118.34 (3'-C), 122.23 (5'-C), 136.79 (4'-C), 148.91 (6'-C), 163.78 (2'-C), 180.36 (1-C); IR (neat) 3060 w, 2968 s, 2876 m, 1786 s, 1590 s, 1472 s, 1438 s, 1376 m, 1316 m, 1226 s, 1150 s, 1128 s, 1104 s, 1078 s, 1034 s, 972 s, 912 m; MS, *m/z* (relative intensity, %) 217 (M^+, 9), 123 (18), 122 (100), 78 (20), 67 (10), 51 (10). 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.

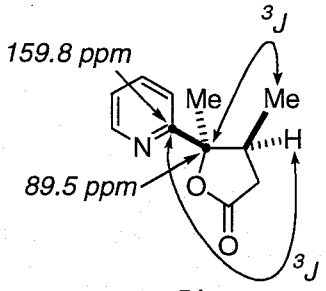


50 (major isomer)

Minor isomer: Colorless oil; R_f 0.26 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.77-0.88 (m, 1H, 4-H), 1.42-1.55 (s, 3H, Me), 2.03 (q, *J* = 5.6 Hz, 2H, 6-H), 3.06 (q, *J* = 7.9 Hz, 1H, 3a-H), 3.33 (td, *J* = 7.9 Hz, *J* = 5.6 Hz, 1H, 6a-H), 7.18 (ddd, *J* = 7.6 Hz, *J* = 4.6 Hz, *J* = 1.0 Hz, 1H, 5'-H), 7.55 (d, *J* = 7.9 Hz, 1H, 3'-H), 7.69 (ddd, *J* = 7.9 Hz, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H, 4'-H), 8.59 (ddd, *J* = 4.6 Hz, *J* = 1.6 Hz, *J* = 1.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 26.09 (5-C), 29.13 (Me or 6-C), 29.21 (Me or 6-C), 29.86 (4-C), 46.13 (6a-C), 51.31 (3a-C), 88.17 (3-C), 119.01 (3'-C), 122.12 (5'-C), 136.54 (4'-C), 148.94 (6'-C), 161.32 (2'-C), 179.85 (1-C); IR (neat) 1776 s (C=O); MS, *m/z* (relative intensity, %) 217 (M^+, 3), 174 (20), 173 (78), 172 (32), 158 (11), 149 (17), 147 (12), 146 (100), 144 (30), 139 (33), 130 (19), 122 (94), 117 (13), 106 (20), 104 (18), 93 (18), 80 (25), 79 (40), 78 (56), 77 (14), 68 (24), 67 (40), 65 (17), 53 (23), 52 (36), 51 (48), 50 (13). 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 major isomer (1.53-2.17 ppm) indicates the *cis* relationship between the pyridine ring and the fused ring.[16]

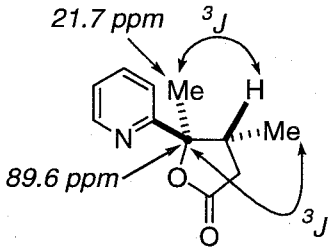
***cis*-Dihydro-4,5-dimethyl-5-(2-pyridinyl)-2(3*H*)-furanone (51a).** Colorless oil; bp 130 °C (2 mmHg); R_f 0.09 (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$) δ 0.67 (d, *J* = 6.9 Hz, 3H, 4-CH_3), 1.82 (s, 3H, 5-CH_3), 2.35 (dd, *J* = 17.2 Hz, *J* = 5.9 Hz, 1H, 3-H), 2.72 (ddd, *J* = 8.3 Hz, *J* = 6.9 Hz, *J* = 5.9 Hz, 1H, 4-H), 2.87 (dd, *J* = 17.2 Hz, *J* = 8.3 Hz, 1H, 3-H), 7.20 (ddd, *J* = 7.6 Hz, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H, 5'-H), 7.43 (d, *J* = 7.9 Hz, 1H, 3'-H), 7.69 (ddd, *J* = 7.9 Hz, *J* = 7.6 Hz, *J* = 1.7 Hz, 1H, 4'-H), 8.60 (d, *J* = 4.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 16.18 (4-CH_3), 26.00 (5-CH_3), 36.98 (3-C), 40.56 (4-C), 89.52 (5-C), 119.64 (3'-

C), 122.39 (5'-C), 136.50 (4'-C), 149.00 (6'-C), 159.84 (2'-C), 176.42 (2-C); IR (neat) 3062 m, 2980 m, 2938 m, 2882 w, 1781 s, 1591 s, 1575 s, 1475 s, 1437 s, 1382 s, 1334 m, 1233 s, 1182 s, 1157 s, 1129 s, 1073 s, 1048 s, 1025 m, 1004 s, 993 s, 956 s, 937 s, 860 m; MS, *m/z* (relative intensity, %) 191 (M^+, 2), 123 (25), 122 (100), 93 (27), 79 (15), 78 (12). 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-^1H cosy measurements. Long range ^1H-^{13}C couplings indicative of the regiochemistry and corresponding ^{13}C chemical shifts are given here. The stereochemistry of **51a** was determined by comparison with 4,5-dimethyl-5-phenyl-2(3*H*)-furanone.[16]



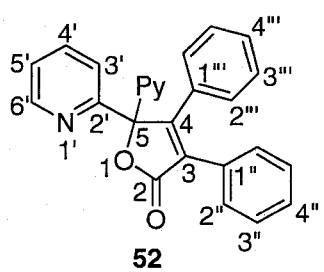
51a

***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); ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6.9 Hz, 3H, 4-CH_3), 1.64 (s, 1H, 5-CH_3), 2.29 (dd, J = 17.5 Hz, J = 7.3 Hz, 1H, 3-H), 2.61 (dd, J = 17.5 Hz, J = 7.9 Hz, 1H, 3-H), 2.92 (qdd, J = 7.9 Hz, J = 7.3 Hz, J = 6.9 Hz, 1H, 4-H), 7.22 (ddd, J = 7.6 Hz, J = 4.0 Hz, J = 1.0 Hz, 1H, 5'-H), 7.54 (dd, J = 7.9 Hz, J = 1.0 Hz, 1H, 3'-H), 7.71 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.7 Hz, 1H, 4'-H), 8.57 (d, J = 4.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 15.19 (4-CH_3), 21.66 (5-CH_3), 36.73 (3-C), 38.94 (4-C), 89.56 (5-C), 118.67 (3'-C), 122.48 (5'-C), 136.87 (4'-C), 148.84 (6'-C), 162.93 (2'-C), 175.99 (2-C); IR (neat) 3060 m, 2978 m, 2940 m, 1781 s, 1692 s, 1574 m, 1474 m, 1435 m, 1382 m, 1333 m, 1280 s, 1230 s, 1193 m, 1172 m, 1150 m, 1124 m, 1082 m, 1052 m, 1011 m, 992 m, 951 s, 934 s, 856 w; MS, *m/z* (relative intensity, %) 191 (M^+, 9), 176 (15), 148 (23), 147 (32), 146 (30), 123 (17), 122 (100), 120 (25), 113 (21), 106 (12), 93 (23), 80 (16), 79 (40), 78 (22), 43 (16). 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-^1H cosy measurements. Long range ^1H-^{13}C couplings indicative of the regiochemistry and corresponding ^{13}C chemical shifts are given here.



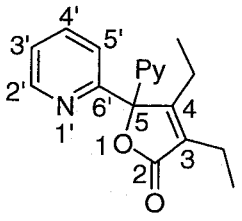
51b

3,4-Diphenyl-5,5-di(2-pyridinyl)-2(5*H*)-furanone (52). Pale yellow solid; mp 152-154 °C (hexane); R_f 0.26 (hexane/EtOAc = 1/1); ^1H NMR ($CDCl_3$) δ 6.96 (d, J = 7.4 Hz, 2H, Ph), 7.11 (t, J = 7.4 Hz, 2H, Ph), 7.18-7.28 (c, 6H, 5'-H,Ph), 7.47-7.50 (m, 2H, Ph), 7.51 (d, J = 7.9 Hz, 2H, 3'-H), 8.52 (d, J = 4.5 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 92.67 (5-C), 122.93 (2C, 3'-C), 123.31 (2C, 5'-C), 127.39 (3-C or 1"-C or 1"'-C), 127.62 (2C, 2"-C or 2"'-C or 3"-C or 3"'-C), 127.98 (2C, 2"-C or 2"'-C or 3"-C or 3"'-C), 128.34 (4"-C or 4"'-C), 128.63 (4"-C or 4"'-C), 129.45 (2"-C or 2"'-C or 3"-C or 3"'-C), 129.58 (2C, 2"-C or 2"'-C or 3"-C or 3"'-C), 129.85 (3-C or 1"-C or 1"'-C), 132.24 (3-C or 1"-C or 1"'-C), 136.66 (2C, 4'-C), 148.64 (2C, 6'-C), 157.16 (2'-C), 163.85 (4-C), 171.82 (2-C); IR (KBr) 3056 w, 1754 s, 1632 w, 1586 m, 1494 w, 1468 m, 1436 m, 1350 m, 1298 m, 1262 w, 1230 m, 1136 m, 1090 w, 1050 w, 1028 m, 990 m, 950 m, 918 w, 810 w; MS, *m/z* (relative intensity, %) 390 (M^+, 5), 346 (20), 345 (75), 254 (11), 178 (10), 173 (14), 172 (20), 106 (13), 78 (100), 52 (10), 51 (24). Anal. Calcd for $C_{26}H_{18}N_2O_2$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.01; H, 4.73; N, 7.16.



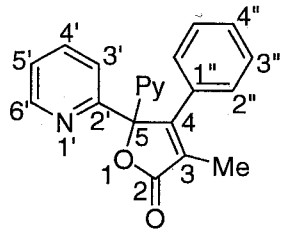
52

3,4-Dibutyl-5,5-di(2-pyridinyl)-2(5*H*)-furanone (53). White solid; mp 82-83 °C (hexane/EtOAc); R_f 0.14 (hexane/EtOAc = 10/1); ^{1}H NMR ($CDCl_3$) δ 0.75 (t, J = 7.6 Hz, 3H, CH_2CH_3), 1.20 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.43 (q, J = 7.6 Hz, 2H, CH_2CH_3), 2.82 (q, J = 7.6 Hz, 2H, CH_2CH_3), 7.28-7.31 (m, 2H, 5'-H), 7.45 (d, J = 7.9 Hz, 2H, 3'-H), 7.73 (t, J = 7.9 Hz, 2H, 4'-H), 8.60 (d, J = 4.0 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 12.56 (CH_2CH_3), 12.83 (CH_2CH_3), 17.49 (CH_2CH_3), 20.92 (CH_2CH_3), 92.09 (5-C), 122.07 (2C, 3'-C), 123.13 (2C, 5'-C), 128.75 (3-C), 136.78 (2C, 4'-C), 148.73 (2C, 6'-C), 158.56 (2'-C), 167.82 (4-C), 173.78 (2-C); IR (neat) 3058 w, 2976 m, 2938 m, 2880 w, 1757 s, 1668 m, 1588 s, 1574 m, 1468 s, 1435 s, 1378 m, 1352 m, 1299 m, 1258 w, 1190 m, 1150 w, 1121 m, 1093 m, 1052 m, 1018 s, 993 s, 954 m, 923 w, 893 w, 809 m; MS, *m/z* (relative intensity, %) 294 (M^+, 12), 250 (19), 249 (15), 235 (21), 186 (10), 185 (79), 106 (11), 79 (17), 78 (100), 52 (15), 51 (28). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.32; H, 6.11; N, 9.40. Two unidentified byproducts (M^+, 294, by GC/MS) were also obtained (17 mg, 7%), along with **53**.



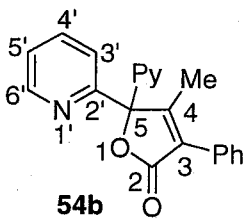
53

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, Me), 7.00 (ddd, J = 7.1 Hz, J = 4.6 Hz, J = 1.0 Hz, 2H, 5'-H), 7.19-7.28 (c, 5H, Ph), 7.42 (dt, J =7.9 Hz, J = 1.0 Hz, 2H, 3'-H), 7.69 (ddd, J = 7.9 Hz, J = 7.1 Hz, J = 1.0 Hz, 2H, 3'-H), 8.50 (ddd, J = 4.6 Hz, J = 1.6 Hz, J = 1.0 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 10.49 (Me), 93.23 (5-C), 122.78 (2C, 3'-C), 123.22 (2C, 2"-C or 3"-C), 125.46 (1"-C or 3-C), 127.69 (2C, 2"-C or 3"-C), 128.55 (4"-C), 129.07 (2C, 5'-C), 132.35 (1"-C or 3-C), 136.63 (2C, 4-C), 148.62 (2C, 6'-C), 157.34 (4-C), 162.95 (2'-C), 173.64 (2-C); IR (KBr) 3492 w, 3092 w, 3060 w, 2956 w, 1974 w, 1758 s, 1714 w, 1652 m, 1588 s, 1500 w, 1472 m, 1440 s, 1384 w, 1338 s, 1306 w, 1284 m, 1258 w, 1140 s, 1092 m, 1068 w, 1044 m, 1024 s, 994 s, 952 w, 918 w, 890 w, 850 w; MS, *m/z* (relative intensity, %) 328 (M^+, 4), 284 (31), 283 (100), 78 (12). 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) is indicative of the regiochemistry shown here.



54a

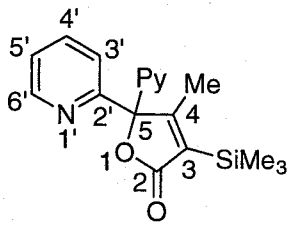
4-Methyl-3-phenyl-5,5-di(2-pyridinyl)-2(5*H*)-furanone (54b). An analytical sample was obtained as a 35/64 regioisomeric mixture of **54b/54a**. R_f 0.31 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) of the sample showed only two well-resolved peaks. 8.61 (ddd, J = 4.6 Hz, J = 1.6 Hz, J = 1.0 Hz, 2H, 6'-H), 2.46 (s, 3H, Me); MS, *m/z* (relative intensity, %) 328 (M^+, 27), 311 (10), 284 (20), 185 (53), 141 (14), 115 (17), 106 (13), 79 (14), 78 (100), 52 (14), 51 (30). HRMS Calcd for $C_{21}H_{16}N_2O_2$: 328.1211. Found: 328.1218.



54b

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, $SiMe_3$), 2.42 (s, 3H, 4-Me), 7.25-7.30 (m, 2H, 5'-H), 7.45 (d, J = 7.9 Hz, 2H, 3'-H), 7.73 (dd, J = 7.9 Hz, J = 7.6 Hz, 2H, 4'-H), 8.60 (d, J = 4.6 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ -0.95 (3C, $SiMe_3$), 16.28 (4-Me), 94.02 (5-C), 122.07 (2C, 3'-C), 123.09 (2C, 5'-C), 125.46 (3-C),

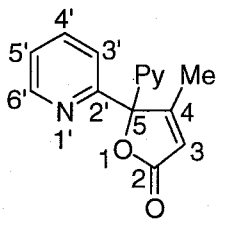
136.87 (2C, 4'-C), 148.77 (2C, 6'-C), 158.47 (2C, 2'-C), 175.78 (4-C), 179.01 (2-C); IR (KBr) 3062 w, 2958 w, 2902 w, 1739 s, 1613 m, 1587 m, 1575 m, 1468 m, 1432 m, 1372 w, 1255 s, 1246 s, 1186 m, 1156 w, 1104 w, 1072 w, 1014 m, 996 m, 927 w, 889 w, 857 s, 809 w; MS, *m/z* (relative intensity, %) 324 (M^+, 8), 307 (15), 265 (16), 218 (10), 207 (11), 186 (16), 185 (100), 132 (28), 117 (11), 78 (42), 73 (37), 51 (16). 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 convertion to **44a** as shown below.



55a

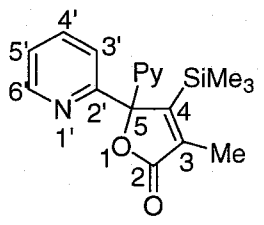
Typical Procedure for the Desilylation of Silyl Lactones. Tetrabutylammonium fluoride (1.0 M in THF, 1mL) was added to a solution of 55a (50 mg, 0.15 mmol) and MeOH (3 mL), and the resulting mixture was refluxed overnight. The reaction mixture was then concentrated, and the resulting residue was purified by flash chromatography, which afforded the desilylated lactone 55a' (31 mg, 82%).

4-Methyl-5,5-di(2-pyridinyl)-2(5*H*)-furanone (55a'). White solid; mp 82-84 °C (hexane/EtOAc); R_f 0.34 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.38 (d, J = 1.3 Hz, 3H, Me), 5.98 (q, J = 1.3 Hz, 1H, 3-H), 7.28 (ddd, J = 7.6 Hz, J = 5.0 Hz, J = 1.3 Hz, 2H, 5'-H), 7.42 (ddd, J = 7.9 Hz, J = 1.3 Hz, J = 1.0 Hz, 2H, 3'-H), 7.73 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.7 Hz, 2H, 4'-H), 8.60 (ddd, J = 5.0 Hz, J = 1.7 Hz, J = 1.0 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 15.91 (Me), 93.60 (5-C), 116.67 (3-C), 122.11 (2C, 3'-C), 123.33 (2C, 5'-C), 136.99 (2C, 4'-C), 148.79 (2C, 6'-C), 157.59 (2C, 2'-C), 172.14 (two overlapping peaks, 2C, 2,4-C); IR (KBr) 3064 w, 3008 w, 1760 s, 1646 m, 1590 s, 1470 s, 1436 s, 1378 m, 1292 m, 1254 m, 1200 s, 1152 w, 1098 m, 1054 m, 1034 m, 994 m, 946 m, 922 s, 846 m; MS, *m/z* (relative intensity, %) 252 (M^+, 10), 235 (24), 208 (31), 207 (34), 193 (14), 185 (47), 146 (24), 117 (10), 106 (13), 79 (13), 78 (100), 52 (24), 51 (50), 50 (11). Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.34; H, 4.85; N, 11.01. The regiochemistry of **55a'** was confirmed by its convertion to **44a** by treatment with $NaBH_4$ in the presence of $NiCl_2$ catalyst.[17]



55a'

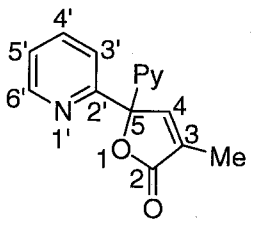
3-Methyl-5,5-di(2-pyridinyl)-4-(trimethylsilyl)-2(5*H*)-furanone (55b). Colorless oil; R_f 0.51 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 9H, $SiMe_3$), 2.11 (s, 3H, 3-Me), 7.24-7.28 (m, 2H, 5'-H), 7.39 (d, J = 7.9 Hz, 2H, 5'-H), 7.71 (t, J = 7.9 Hz, 2H, 4'-H), 8.54 (d, J = 4.6 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ -0.27 (3C, $SiMe_3$), 11.79 (3-Me), 95.76 (5-C), 122.77 (2C, 3'-C), 123.16 (2C, 5'-C), 135.38 (3-C), 136.53 (2C, 4'-C), 148.27 (2C, 6'-C), 158.69 (2C, 2'-C), 169.00 (4-C), 174.34 (2-C); IR (neat) 1760 s; MS, *m/z* (relative intensity, %) 324 (M^+, 0), 309 (M^+-15, 79), 281 (17), 280 (24), 266 (22), 265 (95), 235 (15), 232 (17), 231 (28), 207 (30), 205 (13), 203 (23), 175 (29), 174 (24), 133 (24), 132 (43), 126 (12), 117 (20), 106 (22), 97 (29), 96 (10), 81 (30), 79 (18), 78 (100), 77 (11), 75 (19), 73 (67), 69 (19), 67 (23), 55 (15), 53 (22), 52 (26), 51 (70). HRMS Calcd for $C_{18}H_{20}N_2O_2Si$: 324.1293. Found: 324.1292.



55b

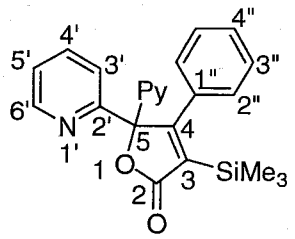
3-Methyl-5,5-di(2-pyridinyl)-2(5*H*)-furanone (55b'). Colorless oil; R_f 0.31 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.99 (d, J = 1.3 Hz, 3H, Me), 7.22 (ddd, J = 7.6 Hz, J = 4.9 Hz, J = 1.3 Hz, 2H, 5'-H), 7.56 (ddd, J = 7.9 Hz, J = 1.3 Hz, J = 1.0 Hz, 2H, 3'-H), 7.71 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.7 Hz, 2H, 4'-H), 8.07 (q, J = 1.3 Hz, 1H, 4-H), 8.60 (ddd, J = 4.9 Hz, J = 1.7

Hz, J = 1.0 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 10.76 (Me), 90.50 (5-C), 120.68 (2C, 3'-C), 123.16 (2C, 5'-C), 128.13 (3-C), 137.22 (2C, 4'-C), 149.25 (2C, 6'-C), 152.29 (4-C), 158.88 (2C, 2'-C), 173.35 (2-C); IR (neat) 3064 w, 1768 s, 1662 w, 1590 m, 1468 m, 1438 s, 1318 w, 1270 w, 1190 m, 1144 w, 1092 m, 1064 m, 994 s, 952 m, 856 w; MS, *m/z* (relative intensity, %) 252 (M^+, 12), 208 (40), 207 (38), 195 (17), 194 (15), 193 (83), 174 (21), 147 (12), 146 (100), 118 (14), 117 (10), 106 (15), 78 (41). HRMS Calcd for $C_{15}H_{12}N_2O_2$: 252.0899. Found: 252.0904. The higher chemical shift of H-4 (8.07 ppm) in **55b'** relative to that of H-3 (5.98 ppm) in **55a'** indicates the regiochemistry of **55b'** shown here.



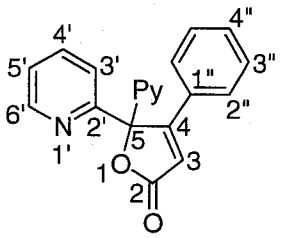
55b'

4-Phenyl-5,5-di(2-pyridinyl)-3-(trimethylsilyl)-2(5*H*)-furanone (56). White solid; mp 169-171 °C (hexane/EtOAc); R_f 0.26 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.03 ($SiMe_3$), 6.82-6.85 (m, 2H, Ph), 7.13-7.28 (c, 5H, Ph,5'-H), 7.43 (dt, J = 7.9 Hz, J = 1.0 Hz, 2H, 3'-H), 7.69 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.7 Hz, 2H, 4'-H), 8.51 (ddd, J = 4.9 Hz, J = 1.6 Hz, J = 1.0 Hz, 2H, 6'-H) ; ^{13}C NMR ($CDCl_3$) δ -1.15 ($SiMe_3$), 94.92 (5-C), 122.70 (2C, 3'-C), 123.11 (2C, 5'-C), 127.08 (2C, 2"-C or 3"-C), 128.27 (4"-C), 128.93 (2C, 2"-C or 3"-C), 129.59 (1"-C or 3-C), 134.29 (1"-C or 3-C), 136.61 (2C, 4'-C), 148.48 (2C, 6'-C), 157.26 (4-C), 175.36 (2C, 2'-C), 179.43 (2-C); IR (KBr) 3068 m, 3016 m, 2968 m, 2904 m, 1746 s, 1624 s, 1590 s, 1492 m, 1466 s, 1436 s, 1286 s, 1248 s, 1192 s, 1154 m, 1098 w, 1078 w, 1038 s, 982 s, 954 m, 926 w, 804 s; MS, *m/z* (relative intensity, %) 386 (M^+, 17), 385 (20), 357 (10), 341 (14), 327 (21), 314 (24), 313 (100), 309 (12), 308 (38), 297 (15), 269 (15), 268 (18), 163 (21), 159 (55), 156 (22), 155 (26), 148 (20), 134 (21), 129 (21), 106 (12), 79 (12), 78 (53), 73 (49), 51 (27). Anal. Calcd for $C_{23}H_{22}N_2O_2Si$: C, 71.47; H, 5.74; N, 7.25. Found: C, 71.52; H, 5.82; N, 7.14.



56

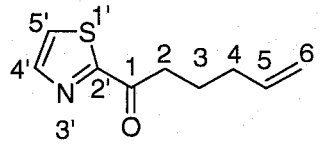
3-Phenyl-5,5-di(2-pyridinyl)-2(5*H*)-furanone (56'). White solid; mp 178-180 °C (hexan/EtOAc); R_f 0.14 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 6.60 (s, 1H, 3-H), 7.22-7.36 (c, 5H, Ph,5'-H), 7.52 (d, J = 7.9 Hz, 2H, 3'-H), 7.56-7.61 (m, 2H, Ph), 7.73 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.6 Hz, 2H, 4'-H), 8.52 (d, J = 4.6 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 114.72 (3-C), 123.23 (2C, 3'-C), 123.44 (2C, 3'-C), 127.83 (2C, 2"-C or 3"-C), 129.70 (2C, 2"-C or 3"-C), 130.06 (1"-C), 130.55 (4"-C), 136.67 (2C, 4'-C), 148.65 (2C, 6'-C), 157.29 (2C, 2'-C), 169.95 (4-C), 171.79 (2-C); IR (KBr) 3064 w, 1754 s, 1610 m, 1586 m, 1498 w, 1466 s, 1430 s, 1326 w, 1302 w, 1282 w, 1256 m, 1236 m, 1214 m, 1156 w, 1096 w, 1044 w, 992 s, 942 s, 894 w, 854 m; MS, *m/z* (relative intensity, %) 314 (M^+, 2), 297 (32), 270 (25), 269 (100), 208 (18), 180 (15), 134 (16), 102 (17), 78 (73), 57 (15), 55 (11), 52 (14), 51 (31). HRMS Calcd for $C_{20}H_{14}N_2O_2$: 314.1055. Found: 314.1057. The regiochemistry of **56'** was determined by comparison with 4,5,5-triphenyl-2(5*H*)-furanone[18] and 3,5,5-triphenyl-2(5*H*)-furanone[19].



56'

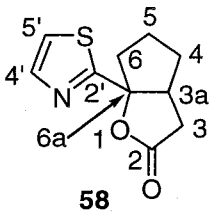
1-(2-Thiazolyl)-5-hexene-1-one (57). To a stirred solution of CH_2Cl_2 (100 mL) and 2-trimethylsilylthiazole[20] a solution of CH_2Cl_2 (100 mL) and 5-hexenoylchloride (4.08 g, 30 mmol), which was prepared from 5-hexenoic acid and thionyl chloride, was added. The resulting mixture was stirred at r.t. overnight, quenched with saturated aqueous $NaHCO_3$, and

stirred for 0.5 h. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography and subsequent bulb-to-bulb distillation, which afforded **57** (1.20 g, 44%). Pale yellow oil; bp 120 °C (5 mmHg); R_f 0.26 (hexane/EtOAc = 10/1); ^{1}H NMR ($CDCl_3$) δ 1.83-1.94 (m 2H, 3-H), 2.11-2,22 (m, 2H, 4-H), 3.18 (t, J = 7.6 Hz, 2H, 2-H), 4.97-5.10 (c, 2H, 6-H), 5.83 (ddt, J = 17.1 Hz, J = 10.2 Hz, J = 6.6 Hz, 1H, 5-H), 7.67 (d, J = 3.3 Hz, 1H, 5'-H), 8.00 (d, J = 3.3 Hz, 1H, 4'-H); ^{13}C NMR ($CDCl_3$) δ 23.14 (3-C), 33.13 (4-C), 37.80 (2-C), 115.27 (6-C), 137.63 (5-C), 144.47 (4'-C), 167.02 (2'-C), 193.59 (1-C); IR (neat) 3084 w, 2940 m, 1690 s, 1486 s, 1442 m, 1394 s, 1328 m, 1240 m, 1208 m, 1150 m, 1110 m, 1062 m, 994 m, 950 m, 914 s, 882 m, 852 m; MS, *m/z* (relative intensity, %) 181 (M^+, 2), 162 (10), 153 (17), 152 (11), 138 (14), 127 (31), 125 (20), 112 (52), 99 (100), 86 (19), 85 (29), 84 (19), 69 (10), 59 (26), 58 (38), 57 (41), 55 (29), 54 (11), 53 (11). HRMS Calcd for $C_9H_{11}NOS$: 181.0562. Found: 181.0562.



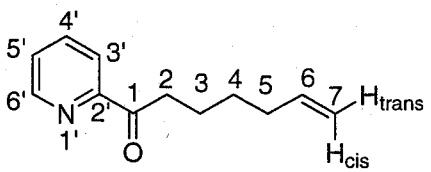
57

Hexahydro-6a-(2-thiazolyl)-2*H*-cyclopenta[b]furan-2-one (58). Colorless oil; bp 130 °C (5 mmHg); R_f 0.11 (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$) δ 1.62-1.71 (m, 1H, 4-H), 1.82-1.94 (c, 2H, 5-H), 2.14-2.30 (m, 1H, 4-H), 2.32-2.42 (c, 3H, 6-H), 2.91 (dd, J = 18.5 Hz, J = 9.9 Hz, 1H, 3-H), 3.14-3.22 (m, 1H, 3a-H), 7.29 (d, J = 3.3 Hz, 1H, 5'-H), 7.75 (d, J = 3.3 Hz, 1H, 4'-H); ^{13}C NMR ($CDCl_3$) δ 24.58 (5-C), 34.04 (4-C), 35.71 (3-C), 40.72 (6-C), 45.25 (3a-C), 96.34 (6a-C), 119.43 (5'-C), 143.18 (4'-C), 172.29 (2'-C), 176.19 (2-C); IR (neat) 3120 m, 3088 m, 2968 s, 2878 m, 1785 s, 1472 m, 1456 m, 1315 m, 1237 s, 1177 s, 1087 s, 910 m, 892 m, 867 m, 846 w, 814 w; MS, *m/z* (relative intensity, %) 209 (M^+, 100), 181 (51), 168 (70), 166 (27), 165 (24), 164 (16), 153 (44), 152 (48), 150 (18), 140 (22), 139 (28), 138 (24), 136 (14), 128 (14), 127 (29), 125 (35), 124 (11), 113 (17), 112 (49), 111 (12), 99 (41), 97 (26), 86 (21), 85 (21), 69 (16), 59 (12), 58 (23), 55 (24). Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.40; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.36; H, 5.23; N, 6.79; S, 15.20.



58

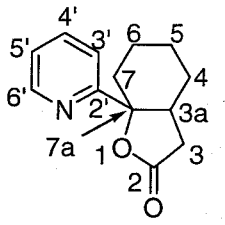
1-(2-Pyridinyl)-6-heptene-1-one (59). 2-Cyanopyridine (2.9 mL, 30 mmol) was added to a stirred THF solution of 6-hexenylmagnisium bromide, which was prepared from 6-bromo-1-hexene (5 g, 30 mmol) and magnisium (730 mg, 30 mmol). The resulting mixture was stirred at r.t. overnight, quenched with dilute aqueous HCl, and stirred for 3 h. The mixture was neutralized by the addition of Na_2CO_3, extracted with Et_2O, dried over $MgSO_4$, and concentrated. The residue was purified by bulb-to-bulb distillation, which afforded **59** (3.02 g, 53%). Colorless oil; bp 140 °C (5 mmHg); R_f 0.49 (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$) δ 1.40 (quint, J = 7.6 Hz, 2H, 4-H), 1.66 (quint, J = 7.6 Hz, 2H, 3-H), 2.01 (td, J = 7.6 Hz, J = 6.6 Hz, 2H, 5-H), 3.13 (t, J = 7.6 Hz, 2H, 2-H), 4.84 (dd, J = 10.2 Hz, J = 1.0 Hz, 1H, 7-H_{trans}), 4.91 (d, J = 17.2 Hz, 1H, 7-H_{cis}), 5.72 (ddt, J = 17.2 Hz, J = 10.2 Hz, J = 6.6 Hz, 1H, 6-H), 7.36 (ddd, J = 7.6 Hz, J = 5.0 Hz, J = 1.3 Hz, 1H, 5'-H), 7.72 (dd, J = 7.9 Hz, J = 7.6 Hz, 1H, 4'-H), 7.93 (dd, J = 7.9 Hz, J = 1.0 Hz, 1H, 3'-H), 8.58 (d, J = 5.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 23.29 (3-C), 28.41 (4-C), 33.44 (5-C), 37.31 (2-C), 114.36 (7-C), 121.55 (3'-C), 126.81 (5'-C), 136.68 (4'-C), 138.45 (6-C), 148.73 (6'-C), 153.33 (2'-C), 201.71 (1-C); IR (neat) 3076 w, 2936 m, 2862 w, 1699 s, 1642 w, 1585 m, 1572 w, 1465 w, 1439 m, 1403 w, 1360 w, 1313 w, 1285 w, 1261 w, 1224 m, 1146 w, 1089 w, 1042 w, 994 s, 911 m; MS, *m/z* (relative intensity, %) 189 (M^+, 2), 148 (14), 134 (17), 107



59

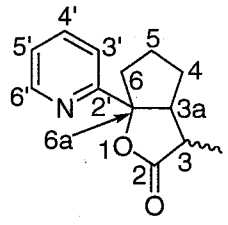
(11), 106 (38), 93 (34), 80 (16), 79 (88), 78 (100), 55 (30), 53 (13), 52 (32), 51 (45). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.00; H, 8.04; N, 7.41.

Hexahydro-7a-(2-pyridinyl)-2(3*H*)-benzofuranone (60a). White solid; mp 56-57 °C (hexane/EtOAc); R_f 0.20 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.12-2.14 (c, 5H, 3,4,5,6,7-H), 2.31 (dd, J = 17.0 Hz, J = 6.4 Hz, 1H, 3-H), 3.07-3.16 (m, 1H, 3a-H), 7.21 (ddd, J = 7.6 Hz, J = 5.0 Hz, J = 1.3 Hz, 1H, 5'-H), 7.54 (d, J = 7.9 Hz, 1H, 3'-H), 7.70 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.7 Hz, 1H, 4'-H), 8.59 (d, J = 5.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 20.86 (4-C or 5-C or 6-C or 7-C), 22.79 (4-C or 5-C or 6-C or 7-C), 28.56 (4-C or 5-C or 6-C or 7-C), 34.70 (4-C or 5-C or 6-C or 7-C), 36.95 (3-C), 37.92 (3a-C), 88.50 (7a-C), 119.70 (3'-C), 122.43 (5'-C), 136.80 (4'-C), 148.97 (6'-C), 162.59 (2'-C), 177.23 (2-C); IR (KBr) 3084 w, 3056 w, 3012 w, 2940 s, 2858 m, 1774 s, 1588 m, 1573 w, 1469 m, 1441 m, 1417 m, 1359 w, 1347 w, 1325 w, 1308 w, 1279 w, 1237 m, 1186 m, 1167 s, 1137 m, 1120 m, 1110 m, 1091 w, 1067 w, 1049 w, 1027 w, 997 m, 975 w, 947 s, 917 w, 892 w, 821 w; MS, *m/z* (relative intensity, %) 217 (M^+, 1), 173 (25), 172 (25), 158 (13), 144 (10), 139 (11), 134 (13), 130 (11), 121 (12), 106 (27), 93 (100), 80 (33), 79 (69), 67 (14), 55 (59), 53 (21), 52 (37), 51 (49), 50 (11). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.69; H, 6.34; N, 6.34.



60a

Hexahydro-3-methyl-6a-(2-pyridinyl)-2*H*-cyclopenta[b]furan-2-one (60b). **60b** was formed as a 86/14 stereoisomeric mixture by GC analysis of the crude reaction mixture. Colorless oil; bp 150 °C (5 mmHg); R_f 0.26 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J = 7.6 Hz, 3H, Me), 1.67-1.77 (m, 1H, 4-H), 1.80-1.97 (c, 2H, 6-H), 2.16-2.32 (c, 3H, 4,5-H), 2.49 (qd, J = 7.6 Hz, J = 3.3 Hz, 3-H), 2.89 (dt, J = 8.9 Hz, J = 3.3 Hz, 3a-H), 7.19 (ddd, J = 7.6 Hz, J = 4.9 Hz, J = 1.2 Hz, 1H, 5'-H), 7.53 (d, J = 8.1 Hz, 1H, 3'-H), 7.69 (ddd, J = 8.1 Hz, J = 7.6 Hz, J = 1.6 Hz, 1H, 4'-H), 8.58 (d, J = 4.9 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 17.70 (Me), 25.18 (6-C), 34.61 (4-C), 41.06 (5-C), 43.43 (3-C), 53.08 (3a-C), 96.50 (6a-C), 118.98 (3'-C), 122.32 (5'-C), 136.71 (4'-C), 149.38 (6'-C), 162.59 (2'-C), 180.48 (2-C); IR (neat) 3060 w, 2942 s, 2876 m, 1778 s, 1589 s, 1574 m, 1471 s, 1450 m, 1437 s, 1377 m, 1280 m, 1253 m, 1232 m, 1193 s, 1168 s, 1137 m, 1121 s, 1087 m, 1050 m, 1023 s, 994 s, 953 m, 921 w, 894 w, 854 w; MS, *m/z* (relative intensity, %) 217 (M^+, 13), 176 (42), 173 (18), 158 (32), 148 (30), 146 (18), 144 (38), 130 (17), 117 (13), 107 (11), 106 (35), 93 (37), 80 (17), 79 (69), 77 (100), 65 (14), 55 (89), 53 (25), 52 (45), 51 (67), 50 (14). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.58; H, 6.94; N, 6.45.



60b

References and Notes

(1) Cone angles of the phosphines are as follows: PPh_3 (145), $P(4\text{-}ClC_6H_4)_3$ (145), $P(4\text{-}CF_3C_6H_4)_3$ (145), $P(4\text{-}MeOC_6H_4)_3$ (145), $P(2\text{-}CH_3C_6H_4)_3$ (194), PBu_3 (132), PCy_3 (170).

(2) 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 in Introduction.

(3) See refs 4 and 5 in Introduction.

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

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(14) Crystal data for **46a**: $C_{18}H_{22}N_2O_2Si$, M_w = 326.47, triclinic, a = 9.993(2) Å, b = 10.516(2) Å, c = 9.102(2) Å, α = 92.40(2)°, β = 101.20(2)°, γ = 108.47(2)°, V = 884.5(3) Å^3, space group $P\bar{1}$ (#2), Z = 2, D_{calc} = 1.221 g/cm^3, $F(000)$ = 348.00, T = 23 °C, μ(MoKα) = 1.37 cm^{-1}; Diffraction data were collected in the ω-scan mode (ω-2θ); final R = 0.058 (Rw = 0.030) for 4090 unique reflections.

(15) Crystal data for **48**: $C_{16}H_{15}NO_2S$, M_w = 285.36, monoclinic, a = 10.217(2) Å, b = 9.279(2) Å, c = 15.361(2) Å, β = 106.06(1)°, V = 1399.4(3) Å^3, space group $P2_1/c$ (#14), Z = 4, D_{calc} = 1.354 g/cm^3, $F(000)$ = 600.00, T = 23 °C, μ(MoKα) = 2.21 cm^{-1}; Diffraction data were collected in the ω-scan mode (ω-2θ); final R = 0.059 (Rw = 0.031) for 3433 unique reflections.

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CHAPTER 3

Mechanistic Aspects of the Ruthenium-Catalyzed Cyclocoupling of Ketones, Olefins, and Carbon Monoxide

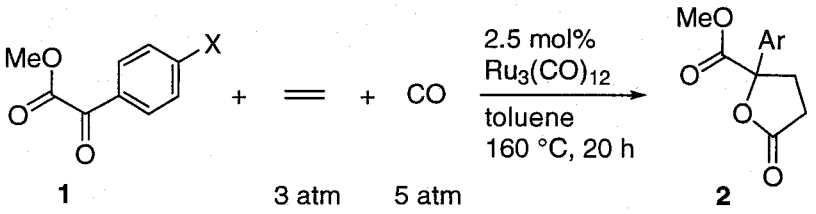
3.1 Background

In Chapters 1 and 2, the author described the ruthenium-catalyzed cyclocoupling reactions of ketones, olefins, and CO, focusing on their synthetic aspects. In addition to the potential utility of these newly discovered catalytic reactions, their mechanistic aspects are also of interest to better understand the reactions, especially to elucidate the role of the C=X group adjacent to the reacting ketone moiety and of the phosphine additives. Substituent effect as well as effects of CO and ethylene pressures on the reaction rate has been investigated to gain some insight into the mechanism of the reaction.

3.2 Results and Discussion

Substituent Effects. In the course of the 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 (see Table 2 in Chapter 2). Because of this, the substituent effects of a representative set of the reactions were examined.

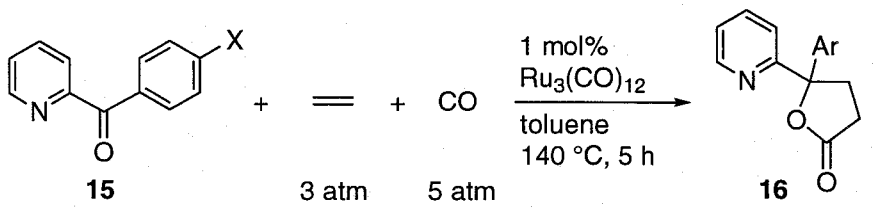
First, the cyclocoupling of a set of aromatic keto esters **1** was tested. As shown in Table 2, both **1a** and **1b** gave the corresponding lactones in excellent yields when the reactions were carried out in the presence of $P(4\text{-}CF_3C_6H_4)_3$, whereas the use of **1c**, which contains an electron-donating group, led to a lowered yield. To evaluate the reactivity of each substrate, the reaction was conducted in the absence of the phosphine (eq 8). As a result, it was found that the order of the reactivity is as follows: $OCH_3 < H < CF_3$.



(8)

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

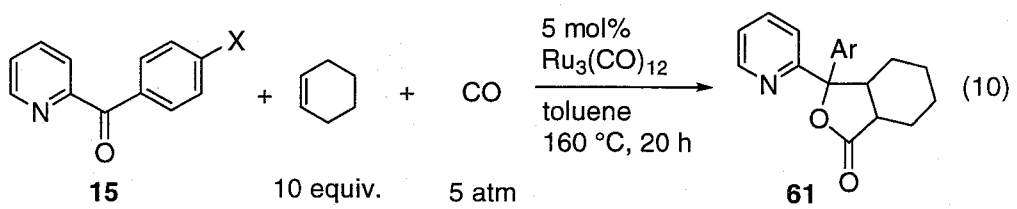
The reactions of a set of pyridyl aryl ketones **15** in the absence of the phosphine were next investigated. In sharp contrast to the results obtained for the keto esters shown in eq 7, the introduction of an electron-donating group enhanced the reactivity, and a dramatic decrease in rate was observed for the case of the CF_3 containing ketone **15a** (eq 9).



(9)

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

Last, the author 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 compared to the reaction with ethylene was observed, namely, the reactivity order was as follows: OCH_3 < H < CF_3 (eq 10).



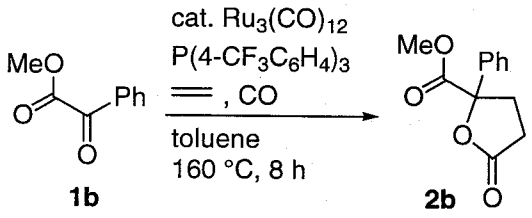
(10)

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

As shown in eqs 8-10, 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 8 and 10). 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 9).

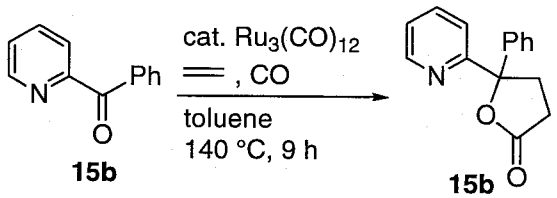
Effects of CO and Ethylene Pressures. In view of the marked difference in the substituent effect between the reactions of keto esters and those of pyridyl ketones, a comparison between these reactions with regard to other reaction parameters, such as CO and ethylene pressure, has been made. Initially, the cyclocoupling of the keto ester **1b** was conducted under various pressures of ethylene and CO, as shown in Table 9. As the pressure of ethylene increased, higher yields of **2b** were observed (entries 1-4 in Table 9). In contrast, the reaction rates were lowered when higher pressures of CO were used (entries 1,5,6 and 7 in Table 9).

Table 9. 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

Table 10. Effects of Ethylene and CO Pressures on the Cycloaddition of **11b**, Ethylene, and CO[c]



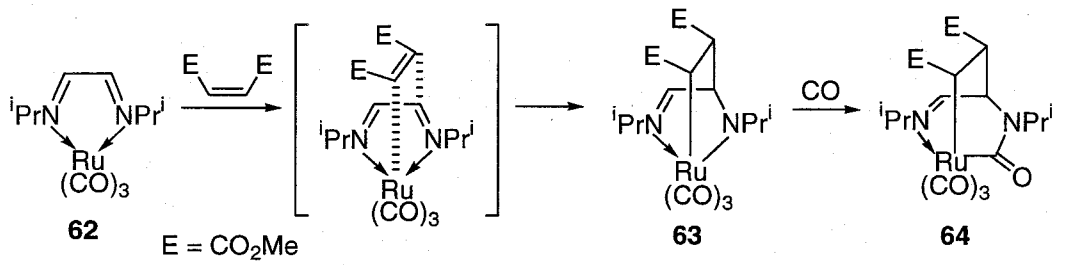
entry	ethylene (atm)	CO (atm)	yield[d] (%)
1	5	5	54
2	10	5	49
3	15	5	45
4	20	5	30
5	5	10	74
6	5	15	78
7	5	20	100

[a] Reaction conditions: **1b** (0.5 mmol), ethylene, CO , $Ru_3(CO)_{12}$ (0.04 mmol), P(4-$CF_3C_6H_4)_3$ (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**. [c] Reaction conditions: **15b** (1 mmol), ethylene, CO , $Ru_3(CO)_{12}$ (0.01 mmol) in toluene (6 mL) at 140 °C for 9 h in a 50-mL stainless autoclave. [d] GC yields based on **15b**.

Next, the effects of ethylene and CO pressures on the cycloaddition of **15b** were investigated (Table 10). 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*).

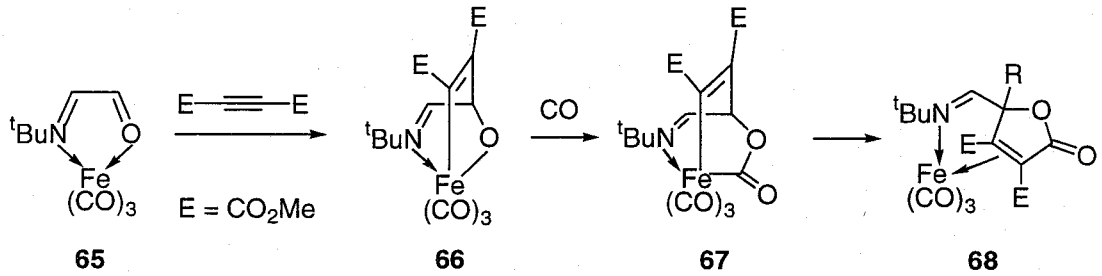
Mechanistic Aspects. A literature survey led the author to discover a stoichiometric transformation which is relevant to the present results, reported by Frühauf and co-workers. They reported a series of reactions of complexes $M(CO)_3$(R-N=C-C=N-R) and $M(CO)_3$(R-N=C-C=O) (M = Fe, Ru) with electron-deficient alkenes and alkynes. For example, the ruthenium complex of 1,4-diaza-1,3-butadiene **62** reacted with dimethyl maleate and CO to afford the metallacycle **64** (Scheme 2).[1] The formation of **64** was rationalized by assuming the formation of complex **63**,[2] which could be formed *via* the cycloaddition of dimethyl maleate onto the complex **62**.

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



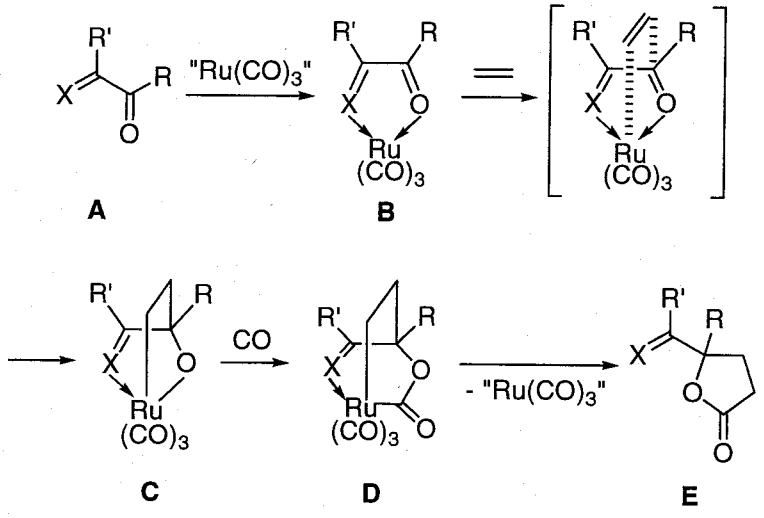
Another example is the reaction of the iron complex of 1-aza-4-oxo-1,3-butadiene **65** with dimethyl acetylenedicarboxylate and CO, which leads to the formation of butenolide complex **68**, presumably *via* the reductive elimination of the iron moiety from the metallacycle **67** (Scheme 3).[3a]

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



In light of the results of these stoichiometric reactions, the author 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,[4] such as $Ru(CO)_3$ or $Ru(CO)_2(PAr_3)$,[5] forms a σ,σ-chelate ruthenium complex **B**.[6] 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[7] 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**.

Scheme 4. A Possible Mechanism



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.[8] It therefore seems likely in the present 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 of the

oxametallacycle **C**-forming process without interrupting the formation of the catalytically active species.

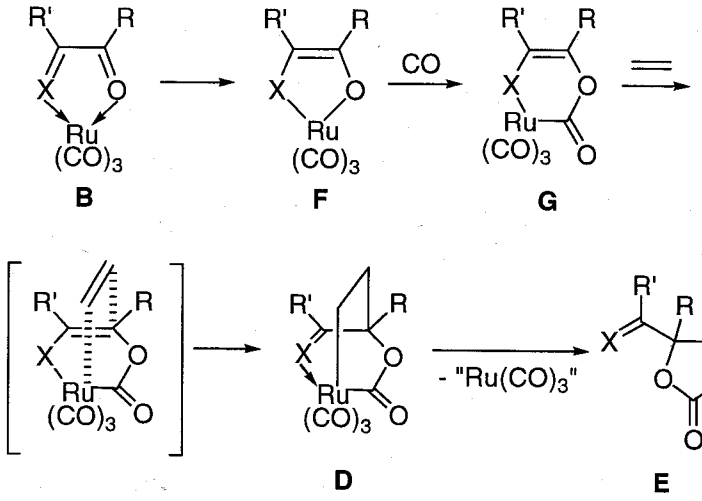
The issue of whether the addition of phosphine ligands increases the yield largely depends on the structures of the ketones and olefins. In the reactions of α-dicarbonyl compounds with ethylene and those of *N*-heterocyclic ketones with internal alkenes, the yields are dramatically increased by using $P(4\text{-}CF_3C_6H_4)_3$. 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 9, 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 10) is also indicative of its irrelevance to the rate-limiting step. Considering the observation on the effect of CO pressures (see Table 10), 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 9. The fact that

the CO insertion process is accelerated by the introduction of an electron-donating group on the migrating group[9] could account for the observed substituent effect.

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,[10] 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.[11] 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).

Scheme 5. An Alternative Mechanism



Although the regio- and stereoselectivities observed in the reactions of unsymmetrical substrates (Tables 5 and 7) 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.

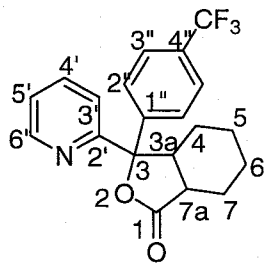
3.3 Conclusion

On the basis of the related stoichiometric reactions, a possible mechanism was proposed. The role of the phosphine ligand is most likely to facilitate the cycloaddition of alkenes onto the first formed chelation complex **B**. 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.

3.4 Experimental Section

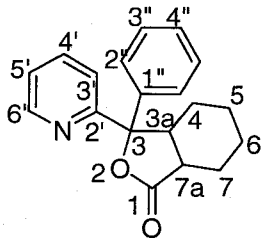
For information on analytical methods, materials used in this chapter, and typical procedures, see Experimental Sections in Chapters 1 and 2.

Hexahydro-3-(2-pyridinyl)-3-(4-trifluoromethylphenyl)-1(3*H*)-isobenzofuranone (61a). **61a** was formed as a 93/7 stereoisomeric mixture by GC analysis of the crude reaction mixture. An analytically pure sample was obtained by recrystallization. White solid; mp 55-58 °C (hexane/CH_2Cl_2); R_f 0.51 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.74-0.80 (m, 1H, 4-H or 5-H or 6-H or 7-H), 1.12-1.37 (c, 3H, 4-H or 5-H or 6-H or 7-H), 1.52-1.71 (c, 3H, 4-H or 5-H or 6-H or 7-H), 2.13-2.18 (m, 1H, 4-H or 5-H or 6-H or 7-H), 2.62-2.66 (m, 1H, 3a-H or 7a-H), 3.83-3.92 (m, 1H, 3a-H or 7a-H), 7.21 (ddd, J = 7.3 Hz, J = 4.9 Hz, J = 1.3 Hz, 1H, 5'-H), 7.50-7.57 (c, 3H, 3',3"-H), 7.63 (ddd, J = 7.9 Hz, J = 7.3 Hz, J = 1.7 Hz, 1H, 4'-H), 7.71 (d, J = 8.2 Hz, 2H, 2"-H), 8.61 (ddd, J = 4.9 Hz, J = 1.7 Hz, J = 1.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 22.54 (4-C or 5-C or 6-C or 7-C), 22.89 (4-C or 5-C or 6-C or 7-C), 23.85 (4-C or 5-C or 6-C or 7-C), 25.69 (4-C or 5-C or 6-C or 7-C), 40.86 (3a-C or 7a-C), 42.90 (3a-C or 7a-C), 89.99 (3-C), 121.79 (3'-C), 123.05 (5'-C), 124.03 (q, J = 272.1 Hz, CF_3), 125.25 (q, J = 3.9 Hz, 2C, 3"-C), 125.73 (2C, 2"-C), 129.63 (q, J = 32.5 Hz, 4"-C), 137.23 (4'-C), 143.37 (1"-C), 148.79 (6'-C), 160.45 (2'-C), 177.03 (1-C); IR (KBr) 3068 w, 2940 m, 2864 w, 1792 s, 1622 w, 1590 m, 1470 w, 1438 m, 1416 w, 1328 s, 1250 w, 1168 s, 1124 s, 1070 m, 1038 m, 1022 m, 990 m, 926 m, 884 w, 848 m, 820 w; MS, *m/z* (relative intensity, %) 361 (M^+, 8), 253 (18), 252 (94), 222 (14), 172 (100), 160 (18), 145 (40), 109 (14), 106 (19), 81 (12), 80 (13), 79 (28), 78 (47), 67 (28), 54 (25), 53 (16), 52 (14), 51 (20). HRMS Calcd for $C_{20}H_{18}N_2O_2F_3$: 361.1289. Found: 361.1297.



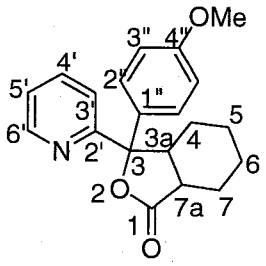
61a

Hexahydro-3-phenyl-3-(2-pyridinyl)-1(3*H*)-isobenzofuranone (61b). **61b** was formed as a 86/14 stereoisomeric mixture by ^{1}H NMR analysis of the crude reaction mixture. An analytically pure sample was obtained by recrystallization. White solid; mp 117-119 °C (hexane/CH_2Cl_2); R_f 0.54 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.72-0.87 (m, 1H, 4-H or 7-H), 1.06-1.27 (c, 2H, 5-H or 6-H), 1.31-1.37 (m, 1H, 4-H or 7-H), 1.45-1.60 (c, 3H, 5-H or 6-H), 2.11-2.17 (m, 1H, 4-H or 7-H), 2.62-2.66 (m, 1H, 3a-H or 7a-H), 3.82-3.91 (m, 1H, 3a-H or 7a-H), 7.14-7.29 (c, 4H, Ph and 3'-H or 4'-H or 5'-H), 7.48-7.62 (c, 4H, Ph and 5-H or 6-H), 8.59 (dd, J = 4.0 Hz, J = 1.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 22.61 (5-C or 6-C), 22.94 (4-C or 7-C), 23.92 (5-C or 6-C), 25.60 (4-C or 7-C), 40.99 (3a-C or 7a-C), 42.54 (3a-C or 7a-C), 90.32 (3-C), 121.86 (5'-C), 122.52 (3'-H or 4"-H), 124.97 (2C, 2"-C or 3"-C), 127.11 (3'-C or 4"-C), 128.00 (2C, 2"-C or 3"-C), 136.80 (4'-C), 139.23 (1"-C), 148.19 (6'-C), 160.95 (2'-C), 177.18 (1-C); IR (KBr) 3064 w, 3012 w, 2932 s, 2860 m, 1788 s, 1588 s, 1496 m, 1466 s, 1452 s, 1434 s, 1360 m, 1330 s, 1290 m, 1272 m, 1246 s, 1206 m, 1168 s, 1136 s, 1112 s, 1078 m, 1038 s, 988 s, 928 m, 912 m, 880 m, 856 m, 828 w, 800 w; MS, *m/z* (relative intensity, %) 293 (M^+, 10), 215 (19), 185 (16), 184 (86), 160 (11), 155 (14), 106 (31), 105 (100), 79 (12), 78 (36), 77 (45), 67 (10), 54 (11), 51 (22). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.78; H, 6.62; N, 4.77.



61b

Hexahydro-3-(4-methoxyphenyl)-3-(2-pyridinyl)-1(3*H*)-isobenzofuranone (61c). White solid; mp 77-80 °C (hexane/EtOAc); R_f 0.49 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.77-0.88 (m, 1H, 4-H or 5-H or 6-H or 7-H), 1.11-1.39 (c, 3H, 4-H or 5-H or 6-H or 7-H), 1.53-1.65 (c, 3H, 4-H or 5-H or 6-H or 7-H), 2.61-2.65 (m, 1H, 4-H or 5-H or 6-H or 7-H), 3.76-3.86 (c, 4H, OMe and 3a-H or 7a-H), 6.83 (d, *J* = 8.9 Hz, 2H, 3"-H), 7.16 (ddd, *J* = 7.3 Hz, *J* = 4.9 Hz, *J* = 1.3 Hz, 1H, 5'-H), 7.44 (d, *J* = 8.9 Hz, 2H, 2"-H), 7.51 (ddd, *J* = 7.9 Hz, *J* = 1.3 Hz, *J* = 1.0 Hz, 1H, 3'-H), 7.61 (ddd, *J* = 7.9 Hz, *J* = 7.3 Hz, *J* = 1.7 Hz, 1H, 4'-H), 8.58 (ddd, *J* = 4.9 Hz, *J* = 1.7 Hz, *J* = 1.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 22.72 (4-C or 5-C or 6-C or 7-C), 23.04 (4-C or 5-C or 6-C or 7-C), 24.02 (4-C or 5-C or 6-C or 7-C), 25.74 (4-C or 5-C or 6-C or 7-C), 41.12 (3a-C or 7a-C), 42.67 (3a-C or 7a-C), 55.20 (OMe), 90.34 (3-C), 113.48 (2C, 3"-C), 121.78 (3'-C), 122.51 (5'-C), 126.28 (2C, 2"-C), 131.50 (1"-C), 136.90 (4'-C), 148.22 (6'-C), 158.57 (2'-C or 4"-C), 161.36 (2'-C or 4"-C), 177.42 (2-C); IR (KBr) 3060 w, 2940 m, 2860 m, 1786 s, 1614 m, 1590 m, 1516 s, 1468 m, 1436 m, 1364 w, 1330 m, 1304 m, 1252 s, 1210 w, 1172 s, 1136 m, 1116 m, 1072 w, 1038 s, 984 m, 924 m, 882 w, 862 w, 840 m, 818 m, 800 m; MS, *m/z* (relative intensity, %) 323 (M^+, 6), 245 (25), 214 (32), 187 (30), 185 (12), 135 (100), 107 (12), 106 (22), 92 (11), 79 (10), 78 (29), 77 (22), 51 (10). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.05; H, 6.58; N, 4.27.



61c

References and Notes

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

(2) 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.

(3) (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.

(4) 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.

(5) 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.

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

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

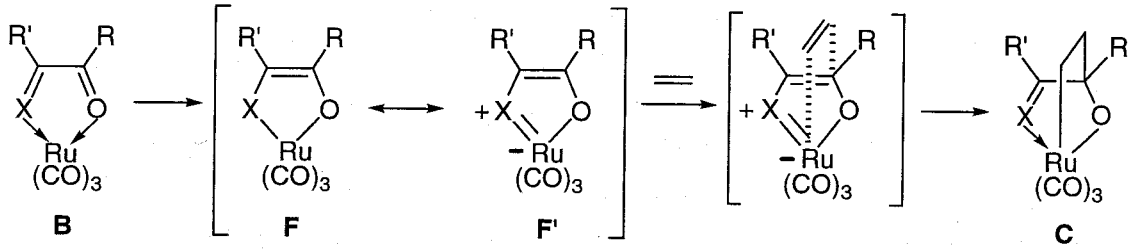
(8) de Lange, P. P. M.; Frühauf, H.-W.; van Wijnkoop, M.; Vrieze, K.; Wang, Y.; Heijdenrijk, D.; Stam, C. H. *Organometallics* **1990**, *9*, 1691. de Lange, P. P. M.; Frühauf, H.-W.; Kraakman, M. J. A.; van Wijnkoop, M.; Kranenburg, M.; Groot, A. H. J. P.; Vrieze, K.; Fraanje, J.; Wang, Y.; Neuman, 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.

(9) (a) The rates of migration of M–C onto CO are accelerated by the presence an electron-donating group: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapter 6 and references therein. (b) The rates of migratory insertion of CO into M–O bonds are thought to be accelerated by the presence of an electron-donating group, since the nucleophilicity of alkoxo ligands is an impotant factor for the process: Rees, W. M.; Churchill, M. R.; Fettinger, J. C.; Atwood, J. D. *Organometallics* **1985**, *4*, 2179.

(10) Frühauf mentioned in his reports that the addition of an activated alkene (or alkyne) toward σ-N, σ-X chelate iron and ruthenium complexes, such as **62** and **65**, can be regarded as a 1,3-dipolar cycloaddition, in view of the isolobal relationship. However,

some of the results obtained in our system, such as the low reactivity of electron-deficient olefins, are difficult to explain by the 1,3-dipolar cycloaddition mechanism.

(11) One possible mechanism for the oxidative cyclization **B→C** is the formal [4 + 2] cycloaddition of metalladiene **F'**, which is one of the resonance structures of **F**, with an olefin as shown below. This mechanism may be able to explain the necessity of the conjugation between the reacting C=O and the adjacent C=N moiety.

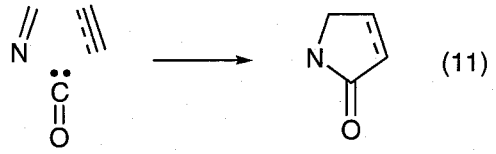


CHAPTER 4

Ruthenium-Catalyzed Cyclocoupling of Imines, Olefins, and Carbon Monoxide

4.1 Background

In the previous Chapters, the author described the first example of the *intermolecular* [2 + 2 + 1] cyclocoupling of ketones, olefins, and CO catalyzed by $Ru_3(CO)_{12}$, a reaction which leads to the formation of γ-butyrolactones bearing carbonyl or *N*-heterocyclic groups at the γ-position. This finding prompted the author to examine the possibility of using imines in place of ketones for the synthesis of γ-lactams, since they are of importance for use as pharmaceutical agents.[1] Furthermore, it should be noted that the application of the [2 + 2 + 1] cycloaddition to the synthesis of γ-lactam derivatives (eq 11), had never been successful prior to this work, except the $Ru_3(CO)_{12}$-catalyzed *intramolecular* cyclocarbonylation of yne-imines reported by Murai and Chatani.[2]



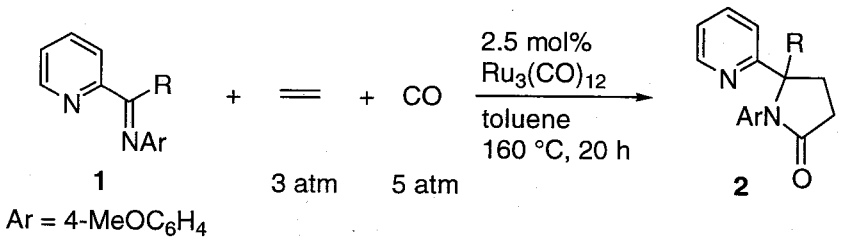
(11)

In this chapter, the author wish to report that the intermolecular [2 + 2 + 1] cyclocoupling of imines, alkene or alkynes, and CO can be achieved catalytically, using $Ru_3(CO)_{12}$ as the catalyst.

4.2 Results and Discussion

The author initially examined the reaction of an imine which contained a 2-pyridyl group as a substrate, since it has been found that such a group, when adjacent to a carbonyl group has an accelerating effect in ketone cycloaddition reactions (see Chapter 2). The author was pleased to observe that the reaction proceeded smoothly and efficiently. The

reaction of imine **1a** (1 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 (3 mL) in the presence of $Ru_3(CO)_{12}$ (0.025 mmol) for 20 h furnished the expected γ-lactam **2a** in 97% isolated yield, based on **1a** (eq 12). The yields were lower when a *tert*-butyl group (38%)[3], a benzyl group (57%)[4], or a 4-toluenesulfonyl group (0%) were used as *N*-protecting groups of the imine moiety under identical reaction conditions. It was found that the structure of the ketone significantly affects the yield of the γ-lactam, when ketimines derived from 2-pyridyl ketones were used. The introduction of an additional 2-pyridyl group at the imino carbon resulted in the formation of the corresponding γ-lactam **2b** in quantitative yield. Acetyl pyridine-derived imine **1c** (*E*-isomer only) also underwent cycloaddition to give lactam **2c** in a good yield. In contrast, the use of benzoylpyridine-derived imine **1d** (1.4:1 stereoisomeric mixture) resulted in only modest yields of lactam **2d**. Since the author has found that the addition of $P(4\text{-}CF_3C_6H_4)_3$ enhances the efficiency of the catalysis in the previously described ketone cyclocoupling (see Chapter 1), the cyclocoupling of **1d** was conducted in the presence of this phosphine. As predicted, the yield of **2d** was increased to 88%.

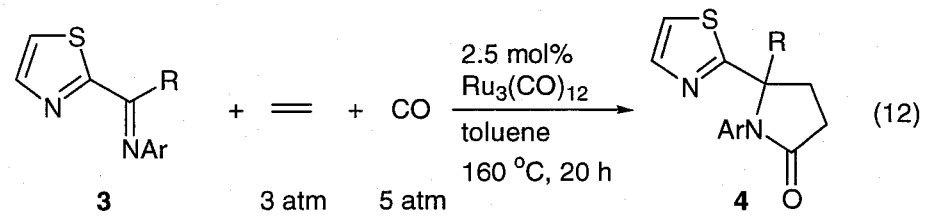


(12)

a: R = H	97 %
b: R = 2-pyridyl	99 %
c: R = CH_3	78 %
d: R = Ph	42 % (88 %)*

* In the presence of $P(4\text{-}CF_3C_6H_4)_3$ (7.5 mol%)

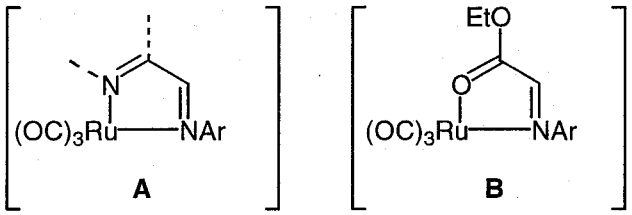
Thiazole containing imines **3** were also able to be successfully applied to the [2 + 2 + 1] cycloaddition (eq 13). Again, addition of $P(4\text{-}CF_3C_6H_4)_3$ was effective in the case of the less reactive substrate **3b**. Since a thiazole ring can be converted into a formyl group without interfering with the functionality of the lactam,[5] thiazolyl lactams **4** represent potentially useful intermediates for organic synthesis.

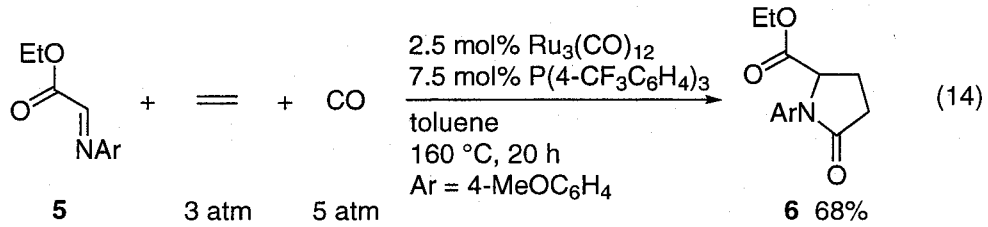


a: R = H	92 %
b: R = CH_3	54 % (78 %)*

* In the presence of $P(4\text{-}CF_3C_6H_4)_3$ (7.5 mol%)

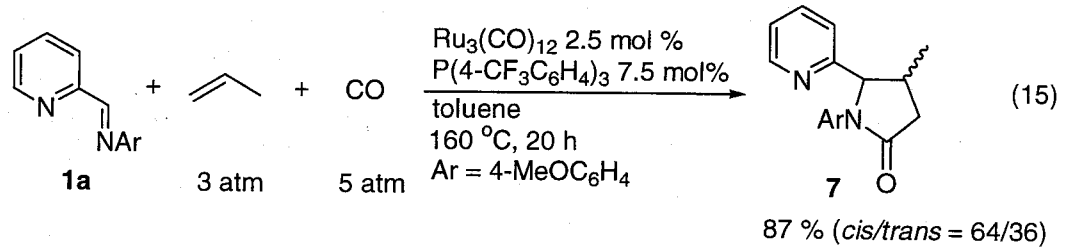
This new cycloaddition presumably proceeds *via* the initial formation of the σ-N, σ-N chelate ruthenium carbonyl complex **A** or related complexes.[6] This proposal led the author to test the reaction of the α-imino ester **5**, which would be expected to form a similar chelation complex **B**. Indeed, the reaction of the imino ester **5** with ethylene and CO in the presence of $P(4\text{-}CF_3C_6H_4)_3$ as an additive afforded the corresponding lactam **6** in good yield (eq 14).





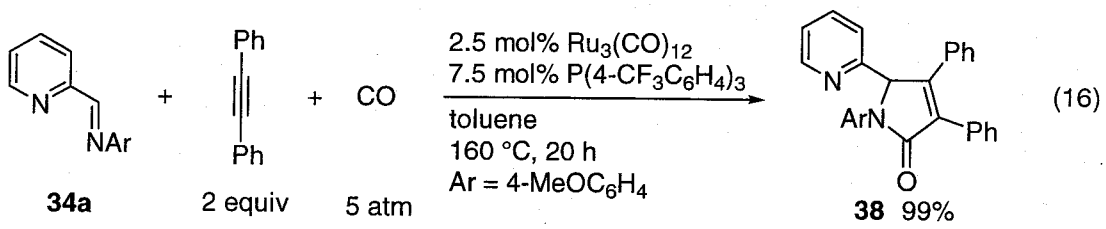
The author then turned our attention to the scope of the two-carbon π-system. The use of propylene in place of ethylene afforded the methyl-substituted lactam **7** with a high degree of regioselectivity but with low stereoselectivity (eq 15).[7] Internal alkenes, such as cyclopentene and stilbene, failed to give any cyclocoupling products, while some substituted alkenes were applicable in the ketone cyclocoupling, as mentioned in chapter 2. The lack of

reactivity may be related to the increased steric bulk resulting from the replacement of a divalent oxygen with a trivalent nitrogen.



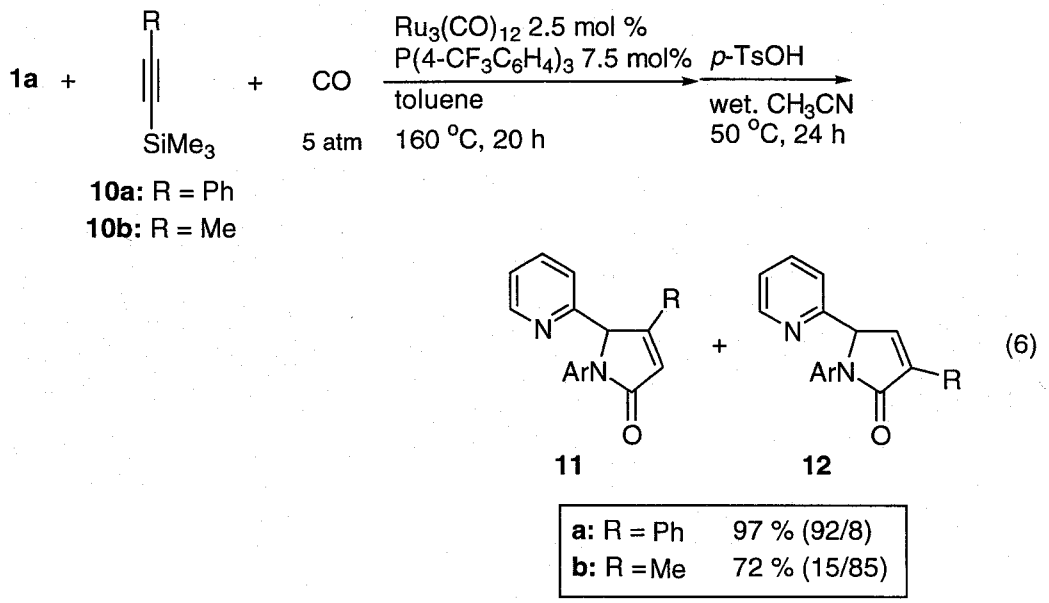
(15)

Alkynes were also examined as the two-carbon π-system. Whereas 3-hexyne, 1-phenyl-1-propyne, bis(trimethylsilyl)acetylene, and dimethyl acetylenedicarboxylate failed to react, diphenylacetylene proved to be an excellent coupling component for this reaction (eq 16).



(16)

Furthermore, mono-silylated alkynes can also serve as the two-carbon unit. Since the desilylation of the primary products occurred, to some extent, under the reaction conditions employed here, yields were determined after the complete desilylation, by treatment of the crude reaction mixture with *p*-TsOH (eq 17). This methodology allows straightforward access to highly substituted γ-lactams.



4.3 Conclusion

It was demonstrated in this chapter, the $Ru_3(CO)_{12}$-catalyzed *intermolecular* [2 + 2 + 1] cycloaddition of imines, alkenes or alkynes, and CO, which provides a highly convergent pathway to the synthesis of functionalized γ-lactam derivatives. The reaction represents the first application of *catalytic intermolecular* [2 + 2 + 1] cycloaddtion for the synthesis of γ-lactams.

4.4 Experimental Section

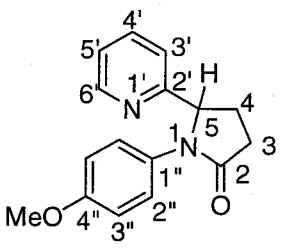
General Information. Boiling points (bp) refer to air bath temperatures for bulb-to bulb distillation and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a JEOL JMN-270 spectrometer in $CDCl_3$ using tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, quint = quintet, m = multiplet, and c = complex), coupling constant (Hz), integration, and interpretation. Infrared spectra (IR) were obtained on a Hitachi 270-50 spectrometer; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained on a Shimadzu GCMS-QP 5000 instrument with ionization voltages of 70 eV. Elemental analyses were performed by the Elemental Analysis Section of Osaka University. Analytical GC was carried out on a Shimadzu GC-14A gas chromatograph, equipped with a flame ionization detector. Column chromatography was performed using SiO_2 (Merck Silica Gel 60 (230-400 mesh)) .

Materials. Toluene was distilled over CaH_2 prior to use. $Ru_3(CO)_{12}$ was prepared according to the literature procedure[8] and used after recrystallization from hexane. Imines **1a**, **3a**, and **5** were prepared by the condensation of the corresponding aldehydes and 4-anisidine in the presence of $MgSO_4$ in EtOH at 70 °C and used after distillation. Ketimines **1b**, **1c**, **1d**,

and **3b** were prepared by the azeotropic dehydration of the corresponding ketones and 4-anisidine in toluene in the presence of a catalytic amount of 4-TsOH and used after distillation or recrystallization. $P(4\text{-}CF_3C_6H_4)_3$, diphenylacetylene (**8**), and 1-(trimethylsilyl)-1-propyne (**10b**) are commercially available and used as received. Trimethyl(phenylethynyl)silane (**10a**) was prepared according to the literature procedure.[9]

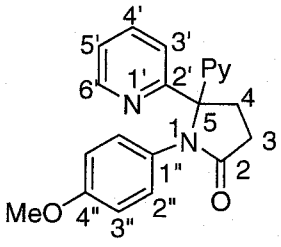
Typical Procedure for Cyclocoupling of Imines, Alkenes or Alkynes, and CO. A 50-mL stainless steel autoclave was charged with the imine **1a** (1 mmol, 212 mg), $Ru_3(CO)_{12}$ (0.025 mmol, 16 mg), and toluene (3 mL). After the system was flushed with 10 atm of ethylene three times, it was pressurized 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 hours had elapsed, it was removed from the oil bath, allowed to cool for ca. 1 h, the gases were then released. The contents were transferred with toluene to a round-bottomed flask, and the volatiles were removed in vacuo. The residue was subjected to column chromatography on silica gel (eluent; EtOAc) to give 1-(4-methoxyphenyl)-5-(2-pyridinyl)-2-pyrrolidinone (**2a**) (259 mg, 97 % yield) as a pale yellow solid. Recrystallization of the solid afforded the analytically pure product.

1-(4-Methoxyphenyl)-5-(2-pyridinyl)-2-pyrrolidinone (2a). White solid; mp 130-131 °C (hexane/EtOAc); R_f 0.06 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.09-2.17 (m, 1H, 3-H or 4-H), 2.59-2.82 (c, 3H, 3,4-H), 3.73 (s, 3H, OCH_3), 5.31 (dd, J = 7.8 Hz, J = 4.6 Hz, 1H, 5-H), 6.78 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.10-7.18 (c, 2H, 3',5'-H), 7.33 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.59 (ddd, J = 7.8 Hz, J = 7.6 Hz, J = 1.6 Hz, 1H, 4'-H), 8.58 (d, J = 3.8 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 26.88 (3-C or 4-C), 30.93 (3-C or 4-C), 55.22 (OCH_3), 65.45 (5-C), 113.91 (2C, 2"-C or 3"-C), 120.41 (3'-C), 122.59 (5'-C), 123.79 (2C, 2"-C or 3"-C), 131.12 (1"-C or 4"-C), 136.86 (4'-C), 149.78 (6'-C), 156.75 (1"-C or 4"-C), 160.50 (2'-C), 174.75 (2-C); IR (KBr) 3046 w, 2942 w, 1676 s, 1612 w, 1591 m, 1574 w, 1515 s, 1460 m, 1441 m, 1399 s, 1356 m, 1287 s, 1244 s, 1186 m, 1174 m, 1145 w, 1119 w, 1105 w, 1092 w, 1025 m, 991 w, 961 w, 893 w, 839 m; MS, *m/z* (relative intensity, %) 268 (M^+, 39), 214 (14), 213 (100), 190 (23), 118 (12), 117 (11), 92 (10), 80 (12), 79 (11), 78 (15), 77 (15), 64 (11), 52 (12), 51 (15). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.50; H, 6.08; N, 10.38.



2a

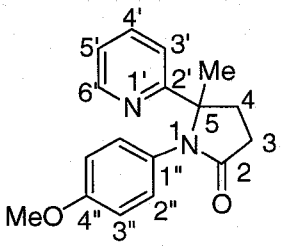
1-(4-Methoxyphenyl)-5,5-di-(2-pyridinyl)-2-pyrrolidinone (2b). White solid; mp 124-125 °C (hexane/EtOAc); R_f 0.09 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.63 (t, J = 7.6 Hz, 2H, 3-H or 4-H), 3.12 (t, J = 7.6 Hz, 2H, 3-H or 4-H), 3.65 (s, 3H, OCH_3), 6.62 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 6.89 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.11 (d, J = 7.9 Hz, 2H, 3'-H), 7.20 (dd, J = 7.6 Hz, J = 4.0 Hz, 2H, 5'-H), 7.55 (dd, J = 7.9 Hz, J = 7.6 Hz, 2H, 4'-H), 8.65 (d, J = 4.0 Hz, 2H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 29.72 (3-C or 4-C), 34.92 (3-C or 4-C), 54.97 (OCH_3), 77.68 (5-C), 113.32 (2C, 2"-C or 3"-C), 122.35 (2C, 3'-C), 123.76 (2C, 5'-C), 128.84 (2C, 2"-C or 3"-C), 129.92 (1"-C or 4"-C), 135.74 (2C, 4'-C), 148.73 (2C, 6'-C), 157.63 (1"-C or 4"-C), 160.14 (2C, 2'-C), 176.05 (2-C); IR (KBr) 3056 m, 3004 m, 2964 m, 2838 m, 1699 s, 1610 s, 1588 s, 1514 s, 1470 s, 1435 s, 1359 s, 1294 s, 1247 s, 1180 m, 1148 m, 1080 m, 1056 m, 1031 m, 992 m, 914 m; MS, *m/z* (relative intensity, %) 345 (M^+, 100), 291 (15), 290 (69), 268 (14), 267 (76), 266 (12), 239 (23), 211 (11), 195 (23), 122 (24), 117 (10). Anal. Calcd for $C_{21}H_{19}N_3O_2$: C,



2b

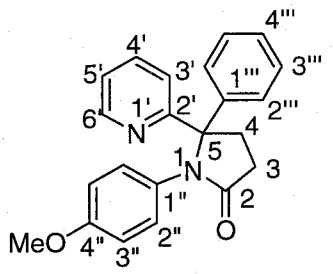
73.03; H, 5.54; N, 12.17. Found: C, 72.89; H, 6.46; N, 12.10.

1-(4-Methoxyphenyl)-5-methyl-5-(2-pyridinyl)-2-pyrrolidinone (2c). White solid; mp 118-119 °C (hexane/EtOAc); R_f 0.11 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3H, 5-CH_3), 2.16-2.28 (m, 1H, 3-H or 4-H), 2.44-2.65 (c, 2H, 3,4-H), 2.80-2.93 (m, 1H, 3-H or 4-H), 3.72 (s, 3H, OCH_3), 6.75 (d, J = 9.1 Hz, 2H, 2"-H or 3"-H), 6.84 (d, J = 9.1 Hz, 2H, 2"-H or 3"-H), 7.17-7.25 (m, 1H, 5'-H), 7.27 (d, J = 7.9 Hz, 1H, 3'-H), 7.63 (td, J = 7.9 Hz, J = 2.0 Hz, 1H, 4'-H), 8.64 (d, J = 5.6 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 24.95 (3-C or 4-C), 30.39 (3-C or 4-C), 35.71 (5-CH_3), 55.16 (OCH_3), 68.42 (5-C), 113.80 (2C, 2"-C or 3"-C), 119.64 (3'-C), 122.13 (5'-C), 128.45 (2C, 2"-C or 3"-C), 129.13 (1"-C or 4"-C), 136.19 (4'-C), 149.20 (6'-C), 157.94 (1"-C or 4"-C), 162.71 (2'-C), 175.68 (2-C); IR (KBr) 3066 m, 2974 s, 2936 m, 2844 w, 1694 s, 1608 s, 1584 s, 1571 m, 1515 s, 1476 m, 1465 s, 1447 s, 1437 s, 1383 s, 1296 s, 1243 s, 1224 s, 1170 s, 1148 s, 1123 s, 1110 m, 1093 m, 1030 s, 1003 w, 990 m, 948 w, 898 w, 850 s, 811 m; MS, *m/z* (relative intensity, %) 282 (M^+, 30), 227 (25), 205 (13), 204 (100), 148 (14), 132 (17), 122 (17), 117 (22), 92 (12), 80 (14), 78 (20), 77 (22), 64 (12), 55 (12), 52 (13), 51 (18). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.25; H, 6.46; N, 9.89.



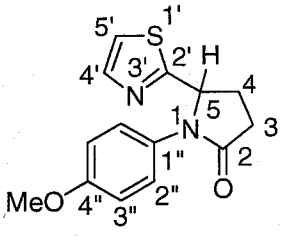
2c

1-(4-Methoxyphenyl)-5-phenyl-5-(2-pyridinyl)-2-pyrrolidinone (2d). White solid; mp 96-97 °C (hexane/EtOAc); R_f 0.31 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.50-2.67 (c, 3H, 3'4-H), 3.39-3.46 (m, 1H, 3-H or 4-H), 3.67 (s, 3H, OCH_3), 6.61 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 6.90 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.06 (d, 1H, 3'-H), , 7.16 (dd, J = 7.6 Hz, J = 5.0 Hz, 1H, 5'-H), 7.26-7.36 (c, 5H, Ph), 7.47 (dd, J = 8.3 Hz, J = 7.6 Hz, 1H, 4'-H), 8.65 (d, J = 5.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 30.05 (3-C or 4-C), 37.16 (3-C or 4-C), 55.17 (OCH_3), 76.91 (5-C), 113.48 (2C, 2"-C or 3"-C), 122.46 (5'-C), 124.64 (3'-C), 127.57 (4'''-C), 128.12 (two overlapping peaks, 2''',3'''-C), 128.36 (2C, 2"-C or 3"-C), 130.08 (1"-C or 4"-C), 135.67 (4'-C), 142.05 (6'-C), 148.75 (1'''-C), 157.54 (1"-C or 4"-C), 159.96 (2'-C), 175.87 (2-C); IR (KBr) 3010 w, 2972 w, 1694 s, 1609 m, 1585 w, 1513 s, 1469 m, 1450 m, 1430 w, 1349 m, 1320 w, 1292 m, 1249 s, 1173 m, 1100 w, 1069 w, 1030 m, 991 w, 931 w, 904 w, 879 w, 856 w, 841 w, 814 w; MS, *m/z* (relative intensity, %) 344 (M^+, 76), 289 (20), 267 (24), 266 (100), 222 (13), 195 (18), 194 (33). Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.49; H, 5.82; N, 8.14. Found: C, 76.72; H, 5.85; N, 8.13.



2d

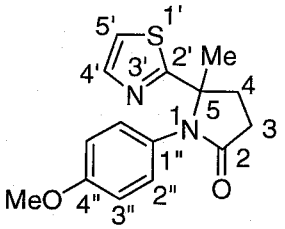
1-(4-Methoxyphenyl)-5-(2-thiazolyl)-2-pyrrolidinone (4a). Pale yellow crystal; mp 95-96 °C (hexane/EtOAc); R_f 0.14 (hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$) δ 2.24-2.32 (m, 1H, 3-H or 4-H), 2.60-2.89 (c, 2H, 3,4-H), 3.75 (s, 3H, MeO), 5.60 (dd, J = 7.8 Hz, J = 4.1 Hz, 1H, 5-H), 6.83 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.34 (d, J = 3.2 Hz, 1H, 5'-H), 7.32 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.70 (d, J = 3.2 Hz, 1H, 4'-H); ^{13}C NMR ($CDCl_3$) δ 27.17 (3-C or 4-C), 30.44 (3-C or 4-C), 55.24 (MeO), 62.01 (5-C), 114.07 (2C, 2"-C or 3"-C), 119.46 (5'-C), 124.53 (2C, 2"-C or 3"-C), 130.33 (1"-C or 4"-C), 142.61 (4'-C), 157.30 (1"-C or 4"-C), 171.28 (2'-C), 173.98 (2-C); IR (KBr) 3114 w, 2954 m, 2838 w, 1681 s, 1613 m, 1506 w, 1515 m, 1452 m, 1393 m, 1283 m, 1247 m, 1188 m, 1176 m, 1151 m, 1109 m, 1088 m, 1024 m, 874 w, 836 m; MS, *m/z* (relative intensity, %) 274 (M^+, 54), 264 (24), 226 (21), 220 (22), 219 (99), 190 (13), 189 (18), 134 (21), 125 (10), 124 (18), 92 (16), 86 (100), 78 (12), 77 (24), 64 (15), 59 (16), 58 (27), 54



4a

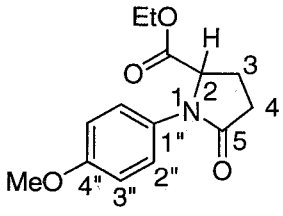
(13), 51 (11). Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.30; H, 5.14; N, 10.21; S, 11.24. Found: C, 61.19; H, 5.15; N, 10.11; S, 11.22.

1-(4-Methoxyphenyl)-5-methyl-5-(2-thiazolyl)-2-pyrrolidinone (4b). Pale yellow crystal; mp 93-94 °C (hexane/EtOAc); R_f 0.17 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H, 5-CH_3), 2.25-2.36 (m, 1H, 3-H or 4-H), 2.57-2.68 (c, 2H, 3,4-H), 2.90-3.04 (m, 1H, 3-H or 4-H), 3.73 (s, 3H, MeO), 6.78 (d, J = 9.1 Hz, 2H, 2"-H or 3"-H), 6.85 (d, J = 9.1 Hz, 2H, 2"-H or 3"-H), 7.28 (d, J = 3.3 Hz, 1H, 5'-H), , 7.76 (d, J = 3.3 Hz, 1H, 4'-H); ^{13}C NMR ($CDCl_3$) δ 26.39 (5-CH_3), 30.03 (3-C or 4-C), 35.78 (3-C or 4-C), 55.27 (MeO), 66.69 (5-C), 114.10 (2C, 2"-C or 3"-C), 119.29 (5'-C), 128.35 (1"-C or 4"-C), 129.42 (2C, 2"-C or 3"-C), 142.58 (4'-C), 158.64 (1"-C or 4"-C), 174.05 (2'-C), 175.10 (2-C); IR (KBr) 3086 w, 3068 m, 2970 m, 2842 w, 1691 s, 1610 m, 1583 w, 1515 s, 1492 m, 1464 m, 1446 m, 1414 w, 1389 s, 1298 s, 1247 s, 1179 s, 1105 w, 1057 w, 1031 s, 981 w, 948 w, 891 w, 872 w, 839 m, 816 w, 800 w; MS, *m/z* (relative intensity, %) 288 (M^+, 92), 273 (17), 245 (14), 233 (35), 204 (43), 167 (12), 166 (100), 165 (10), 160 (20), 149 (14), 148 (60), 140 (11), 139 (84), 138 (70), 134 (16), 124 (23), 123 (91), 122 (34), 111 (10), 108 (36), 107 (17), 106 (13), 99 (33), 92 (35), 86 (21), 80 (12), 78 (21), 77 (60), 65 (14), 64 (39), 63 (24), 59 (36), 58 (65), 57 (13), 55 (46), 53 (26), 52 (24), 51 (25), 50 (12). Anal. Calcd for $C_{15}H_{16}N_2O_2S$: C, 62.48; H, 5.59; N, 9.71; S, 11.12. Found: C, 62.44; H, 5.61; N, 9.67; S, 11.07.



4b

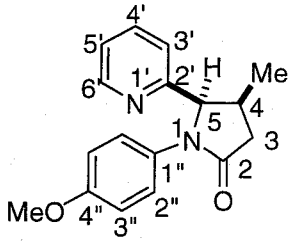
1-(4-Methoxyphenyl)-5-oxoproline ethyl ester (6). White solid; mp 83-84 °C (hexane/EtOAc); R_f 0.14 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.3 Hz, 3H, OCH_2CH_3), 2.10-2.22 (m, 1H, 3-H or 4-H), 2.41-2.59 (c, 2H, 3,4-H), 2.64-2.78 (m, 1H, 3-H or 4-H), 3.78 (s, 3H, CH_3O), 4.15 (q, J = 7.3 Hz, 2H, OCH_2CH_3), 4.63 (dd, J = 8.6 Hz, J = 3.0 Hz, 1H, 2-H), 6.88 (d, J = 8.9 Hz, 2H, 2'-H or 3'-H), 7.33 (d, J = 8.9 Hz, 2H, 2'-H or 3'-H); ^{13}C NMR ($CDCl_3$) δ 14.02 (OCH_2CH_3), 23.17 (3-C or 4-C), 30.46 (3-C or 4-C), 55.38 (CH_3O), 61.57 (OCH_2CH_3), 62.37 (2-C), 114.23 (2C, 2'-C or 3'-C), 124.39 (2C, 2'-C or 3'-C), 130.89 (1'-C or 4'-C), 157.52 (1'-C or 4'-C), 171.82 (5-C or EtO(*C*=O)), 174.32 (5-C or EtO(*C*=O)); IR (KBr) 3070 w, 2990 m, 2964 m, 2932 m, 2838 w, 1740 s, 1693 s, 1657 m, 1609 m, 1589 w, 1515 s, 1484 m, 1462 s, 1444 s, 1427 m, 1397 s, 1373 m, 1343 m, 1310 s, 1297 m, 1279 s, 1244 s, 1190 s, 1130 s, 1106 s, 1020 s, 961 w, 949 w, 882 w, 842 s, 819 m, 804 m; MS, *m/z* (relative intensity, %) 263 (M^+, 17), 191 (12), 190 (100), 134 (16), 122 (13), 92 (11), 77 (20), 64 (16). Anal. Calcd for $C_{14}H_{17}O_4N$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.74; H, 6.44; N, 5.24.



6

1-(4-Methoxyphenyl)-4-methyl-5-(2-pyridinyl)-2-pyrrolidinone (7). A typical procedure was used except that propylene (3 atm) was pressurized in place of ethlene. Trans/cis ratios were determined by GC analysis of the crude reaction mixture. Relative configurations were determined by analogy with related compounds.[10]

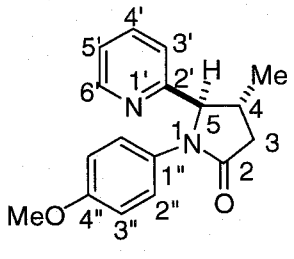
Cis isomer: White solid; mp 140-142 °C (hexane/EtOAc); R_f 0.20 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.72 (d, J = 6.9 Hz, 3H, 4-CH_3), 2.48-2.93 (c, 2H, 3-H), 2.93-3.05 (m, 1H, 4-H), 3.68 (s, 3H, OCH_3), 5.21 (d, J = 7.9 Hz, 1H, 5-H), 6.75 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.10 (d, J = 7.9 Hz, 1H, 3'-H), 7.16 (td, J = 6.3 Hz, J = 0.7 Hz, 1H, 5'-H), 7.37 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.58 (t, J = 7.7 Hz, 1H, 4'-H), 8.58-8.60 (m, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 15.57 (4-CH_3), 31.95 (4-C), 38.69 (3-C), 55.12 (OCH_3),



***cis*-7**

69.36 (5-C), 113.66 (2C, 2"-C or 3"-C), 121.52 (3'-C), 122.43 (5'-C), 123.29 (2C, 2"-C or 3"-C), 131.44 (1"-C or 4"-C), 136.21 (4'-C), 149.36 (6'-C), 156.33 (1"-C or 4"-C), 157.42 (2'-C), 174.28 (2-C); IR (KBr) 3048 w, 2968 m, 2928 m, 2844 m, 1682 s, 1614 m, 1594 s, 1518 s, 1476 s, 1456 s, 1440 s, 1400 s, 1356 s, 1290 m, 1272 s, 1250 s, 1210 s, 1194 s, 1174 m, 1144 m, 1124 m, 1096 m, 1024 s, 996 m, 964 m, 914 m, 884 m, 842 s, 816 m; MS, *m/z* (relative intensity, %) 282 (M^+, 22), 214 (15), 213 (100), 80 (12), 78 (12), 77 (12), 55 (24). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.14; H, 6.32; N, 9.88.

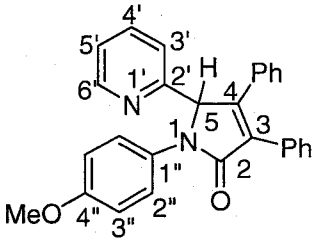
Trans isomer: White solid; mp 104-106 °C (hexane/EtOAc); R_f 0.14 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 6.6 Hz, 3H, 4-CH_3), 2.30 (dd, J = 16.5 Hz, J = 6.3 Hz, 1H, 3-H), 2.42-2.52 (m, 1H, 4-H), 2.92 (dd, J = 16.5 Hz, J = 7.9 Hz, 1H, 3-H), 3.73 (s, 3H, OCH_3), 4.85 (d, J = 5.0 Hz, 1H, 5-H), 6.77 (d, J = 9.1 Hz, 2H, 2"-H or 3"-H), 7.11-7.18 (c, 2H, 3',5'-H), 7.29 (d, J = 9.1 Hz, 2H, 2"-H or 3"-H), 7.58 (td, J = 7.6 Hz, J = 1.6 Hz, 1H, 4'-H), 8.55-8.58 (m, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 19.51 (4-CH_3), 35.58 (4-C), 39.27 (3-C), 55.30 (OCH_3), 72.80 (5-C), 113.83 (2C, 2"-C or 3"-C), 120.55 (3'-C or 5'-C), 122.56 (3'-C or 5'-C), 123.81 (2C, 2"-C or 3"-C), 131.08 (1"-C or 4"-C), 136.76 (4'-C), 149.51 (6'-C), 156.59 (1"-C or 4"-C), 159.60 (2'-C), 173.96 (2-C); IR (KBr) 3064 w, 2972 m, 2936 w, 2844 w, 1688 s, 1612 m, 1594 m, 1520 s, 1472 m, 1446 m, 1404 s, 1352 m, 1320 m, 1302 s, 1282 m, 1252 s, 1228 s, 1178 m, 1154 m, 1132 m, 1108 m, 1082 m, 1028 s, 994 m, 910 m, 836 m; MS, *m/z* (relative intensity, %) 282 (M^+, 29), 214 (15), 213 (100), 204 (14), 117 (12), 92 (11), 80 (13), 79 (11), 78 (15), 77 (15), 64 (11), 55 (24), 52 (12), 51 (13). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.29; H, 6.38; N, 9.91.



***trans*-7**

1,5-Dihydro-3,4-diphenyl-1-(4-methoxyphenyl)-5-(2-pyridinyl)-2*H*-pyrrole-2-one (9). A typical procedure was used, except diphenylacetylene (356 mg, 2 mmol) was employed in place of ethylene.

Pale yellow solid; mp 180-182 °C (hexane/EtOAc); R_f 0.17 (hexane/EtOAc = 4/3); ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H, OCH_3), 6.26 (s, 1H, 5-H), 6.80 (d, J = 9.2 Hz, 2H, 2"-H or 3"-H), 7.00-7.05 (m, 1H, 5'-H), 7.12-7.23 (c, 6H, Ar), 7.30-7.36 (c, 3H, Ar), 7.46-7.53 (c, 6H, Ar), 7.57 (d, J = 9.2 Hz, 2H, 2"-H or 3"-H), 8.38-8.40 (m, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 55.31 (OCH_3), 69.37 (5-C), 113.94 (2C, 2"-C or 3"-C), 120.98, 122.97 (5'-C,2"-C, or 3"-C), 122.99 (5'-C, 2"-C, or 3"-C), 128.17, 128.69, 128.82, 129.68, 130.67, 131.12, 131.77, 132.36, 136.92, 149.03 (6'-C), 151.47, 156.17 (2'-C,1"-C, or 4"-C), 156.38 (2'-C,1"-C, or 4"-C), 169.14 (2-C); IR (KBr) 3076 w, 3008 w, 2940 w, 2840 w, 1694 s, 1610 w, 1592 m, 1516 s, 1472 m, 1442 s, 1378 s, 1316 w, 1300 m, 1256 s, 1186 s, 1146 m, 1110 w, 1086 w, 1036 s, 996 w, 982 w, 912 m, 854 w, 834 s, 812 m; MS, *m/z* (relative intensity, %) 418 (M^+, 100), 389 (13), 340 (13), 269 (32), 268 (10), 211 (12), 134 (13). Anal. Calcd for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.27; H, 5.37; N, 6.69.

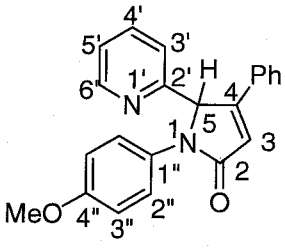


9

Procedure for the Reaction with Mono-Silylated Alkynes. A typical procedure was used except 1-(trimethylsilyl)-1-propyne (**10a**, 1.5 mL, 10 mmol) or trimethyl(phenylethynyl)silane (**10b**, 348 mg, 2 mmol) was employed in place of ethylene, and P(4-$CF_3C_6H_4)_3$ (35mg, 0.075 mmol) was also added, along with the catalyst. After 20 h, *p*-TsOH·H_2O (951mg, 5 mmol) and CH_3CN (5 mL) was added to the crude reaction mixture, which was then stirred at 50 °C for 24h. The solution was cooled to r.t. and concentrated. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and the mixture was extracted with

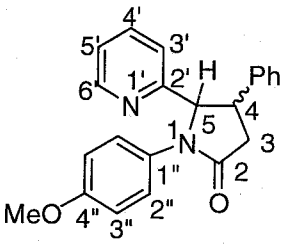
EtOAc (3 x 5 mL). The extract was dried over $MgSO_4$ and concentrated. The ratios of **11/12** were determined by ^1H NMR of the mixture. The mixture was purified by column chromatography. Regiochemistries of **11** and **12** were confirmed by converting them to the corresponding saturated lactams by treatment with $NaBH_4$ in the presence of $NiCl_2$ catalyst (*vide infra*).[11]

1,5-Dihydro-1-(4-methoxyphenyl)-4-phenyl-5-(2-pyridinyl)-2*H*-pyrrole-2-one (11a). Pale yellow solid; mp 174-176 °C (hexane/EtOAc); R_f 0.46 (EtOAc); ^1H NMR ($CDCl_3$) δ 3.72 (s, 3H, OCH_3), 6.31 (s, 1H, 5-H), 6.65 (s, 1H, 3-H), 6.79 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.04-7.09 (m, 1H, 5'-H), 7.13 (d, J = 7.9 Hz, 1H, 3'-H), 7.28-7.32 (c, 3H, Ph), 7.46-7.52 (c, 3H, 2"-H or 3"-H and 4'-H), 7.59-7.63 (m, 2H, Ph), 8.48 (d, J = 5.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 55.32 (OCH_3), 69.88 (5-C), 113.98 (2C, 2"-C or 3"-C), 120.88 (3-C or 3'-C), 120.99 (3-C or 3'-C), 123.15 (5'-C), 123.38 (2C, 2"-C, or 3"-C), 127.06 (2C, 2'''-C or 3'''-C), 128.61 (2C, 2'''-C or 3'''-C), 130.04 (4'''-C)), 130.19 (1"-C or 1'''-C), 130.64 (1"-C or 1'''-C), 137.12 (4'-C), 149.07 (6'-C), 156.15 (4-C, 2'-C, or 4"-C), 156.52 (4-C, 2'-C, or 4"-C), 157.34 (4-C, 2'-C, or 4"-C), 169.87 (2-C); IR (KBr) 3056 w, 2908 w, 2836 w, 1674 s, 1612 m, 1590 m, 1518 s, 1470 m, 1438 m, 1390 s, 1326 m, 1300 m, 1252 s, 1174 m, 1142 m, 1106 w, 1032 m, 994 w, 922 w, 902 w, 868 m, 834 m; MS, *m/z* (relative intensity, %) 342 (M^+, 43), 236 (15), 221 (20), 194 (14), 193 (100), 78 (16), 77 (17), 51 (11). HRMS Calcd for $C_{22}H_{18}N_2O_2$: 342.1368. Found: 342.1364.



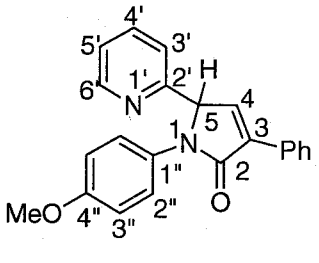
11a

The regiochmistry of **11a** was confirmed by ^1H NMR spectrum of the corresponding saturated lactam **11a'**, which was prepared as a mixture of diasteromers (2:1). The peaks assigned to 5-H were observed in *doublets* at 5.33 ppm (J = 7.8 Hz) and 5.13 ppm (J = 4.3 Hz), indicating the regiochemistry shown here.



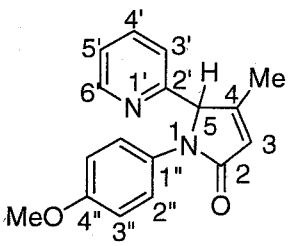
11a'

1,5-Dihydro-1-(4-methoxyphenyl)-3-phenyl-5-(2-pyridinyl)-2*H*-pyrrole-2-one (12a). Pale yellow oil; R_f 0.51 (EtOAc); ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H, OCH_3), 5.91 (d, J = 2.3 Hz, 1H, 5-H), 6.84 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.05 (d, J = 7.9 Hz, 1H, 3'-H), 7.18 (ddd, J = 7.6 Hz, J = 5.0 Hz, J = 1.0 Hz, 1H, 5'-H), 7.35 (d, J = 2.3 Hz, 1H, 4-H), 7.36-7.45 (c, 3H, Ph), 7.52-7.60 (c, 3H, 4'-H and 2"-H or 3"-H), 7.92-7.95 (m, 2H, Ph), 8.58 (dd, J = 5.0 Hz, J = 1.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 55.39 (OCH_3), 66.82 (5-C), 114.11 (2C), 120.48, 122.56 (2C), 123.03, 127.24 (2C), 128.39 (2C), 128.82, 130.74, 131.00, 135.61, 137.29, 139.32, 149.60, 156.03, 156.41, 169.01 (2-C). HRMS Calcd for $C_{22}H_{18}N_2O_2$: 342.1368. Found: 342.1367.



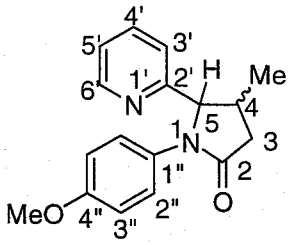
12a

1,5-Dihydro-1-(4-methoxyphenyl)-4-methyl-5-(2-pyridinyl)-2*H*-pyrrole-2-one (11b). White solid; R_f 0.17 (EtOAc); ^1H NMR ($CDCl_3$) δ 1.92 (d, J = 1.3 Hz, 3H, 4-Me), 3.72 (s, 3H, OCH_3), 5.64 (s, 1H, 5-H), 6.00-6.02 (m, 1H, 3-H), 6.78 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.06 (d, J = 7.9 Hz, 1H, 3'-H), 7.19 (ddd, J = 7.6 Hz, J = 5.0 Hz, J = 1.0 Hz, 1H, 5'-H), 7.43 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.59 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 1.7 Hz, 1H, 4'-H), 8.57 (dd, J = 5.0 Hz, J = 1.7 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 14.53 (4-Me), 55.35 (OCH_3), 72.01 (5-C), 114.01 (2C, 2"-C or 3"-C), 120.46 (3'-C), 122.38 (2C, 2"-C or 3"-C), 122.52 (3-C), 123.14 (5'-C), 130.78



11b

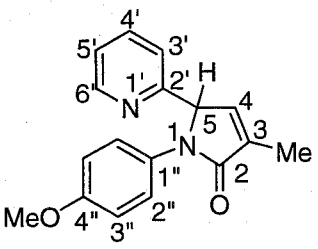
(1"-C), 137.32 (4'-C), 149.40 (6'-C), 156.08 (4-C, 2'-C, or 4"-C), 156.12 (4-C, 2'-C, or 4"-C), 158.17 (4-C, 2'-C, or 4"-C), 170.61 (2-C); MS, *m/z* (relative intensity, %) 280 (M^+, 100), 237 (12), 213 (10), 211 (10), 202 (35), 159 (33), 158 (31), 134 (10), 131 (55), 130 (45), 122 (11), 118 (11), 108 (21), 92 (21), 79 (11), 78 (29), 77 (34), 64 (20), 63 (14), 52 (15), 51 (24). HRMS Calcd for $C_{17}H_{16}N_2O_2$: 280.1211. Found: 280.1209.



11b'

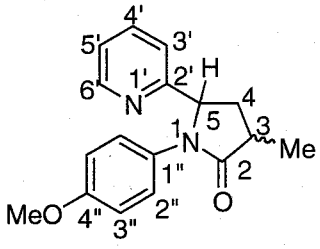
The regiochmistry of **11b** was confirmed by ^{1}H NMR spectrum of the corresponding saturated lactam **11b'**, which was prepared as a mixture of diastereomer (16:1). The ^{1}H NMR spectrum of **11b'** was consistent with that of ***trans*-7**.

1,5-Dihydro-1-(4-methoxyphenyl)-3-methyl-5-(2-pyridinyl)-2*H*-pyrrole-2-one (12b). White solid; mp 129-131 °C (hexane/EtOAc); R_f 0.29 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.00 (t, J = 1.6 Hz, 3H, 4-Me), 3.73 (s, 3H, OCH_3), 5.73 (t, J = 2.0, 1H, 5-H), 6.77-6.85 (c, 3H, 4-H and 2"-H or 3"-H), 6.96 (d, J = 8.9 Hz, 2H, 2"-H or 3"-H), 7.15 (ddd, J = 6.9 Hz, J = 5.0 Hz, J = 0.7 Hz, 1H, 5'-H), 7.47-7.57 (c, 3H, 4'-H and 2"-H or 3"-H), 8.55 (d, J = 5.0 Hz, 1H, 6'-H); ^{13}C NMR ($CDCl_3$) δ 11.33 (4-Me), 55.36 (OCH_3), 67.19 (5-C), 114.00 (2C, 2"-C or 3"-C), 120.23 (3'-C), 121.96 (2C, 2"-C or 3"-C), 122.81 (5'-C), 130.91 (3-C or 1'-C), 134.62 (3-C or 1'-C), 137.14 (4'-C), 139.46 (4-C), 149.43 (6'-C), 156.08 (2'-C, or 4"-C), 156.37 (2'-C, or 4"-C), 170.99 (2-C); IR (KBr) 3072 w, 3012 w, 2924 w, 2844 w, 1684 s, 1614 w, 1590 m, 1572 w, 1516 s, 1472 m, 1436 m, 1372 s, 1304 w, 1254 s, 1218 w, 1186 m, 1156 m, 1102 m, 1036 m, 992 w, 962 w, 894 m, 876 m, 832 m, 800 w; MS, *m/z* (relative intensity, %) 280 (M^+, 100), 251 (26), 237 (17), 202 (29), 174 (12), 159 (24), 147 (25), 134 (21), 131 (39), 130 (42), 108 (18), 92 (19), 78 (27), 77 (35), 64 (18), 63 (12), 52 (14), 51 (24). HRMS Calcd for $C_{17}H_{16}N_2O_2$: 280.1211. Found: 280.1209. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 77.84; H, 5.75; N, 9.99. Found: C, 72.68; H, 5.75; N, 9.99.



12b

The regiochmistry of **12b** was confirmed by ^{1}H NMR spectrum of the corresponding saturated lactam **12b'**, which was prepared as a mixture of diasteromers (2:1). The peaks assigned to 5-H were observed in *doublets of doublet* (J = 8.2 Hz and J = 2.6 Hz) and *triplet* (J = 7.8 Hz) at 5.24 ppm and 5.26 ppm, respectively, indicating the regiochemistry shown here.



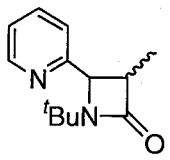
12b'

References and Notes

(1) Gamzu, E. R.; Hoover, T. M.; Gracon, S. I. *Drug. Dev. Res.* **1989**, *18*, 177 and references cited therein.

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

(3) β-Lactam derivative **13** was also obtained (7 %) as a 6.1:1 stereoisomeic mixture.



13

(4) The corresponding β-lactam derivative was also obtained (ca. 9 %).

(5) Tejero, T.; Dondoni, A.; Rojo, I.; Merchán, F. L.; Merino, P. *Tetrahedron* **1997**, *53*, 3301.

(6) Although the mechanism for this reaction is not clear, the reaction mechanism similar to the ketone cyclocoupling is likely to be operating here on the basis of stoichiometric reactions reported by Frühauf and co-workers. See Chapter 3 for detailed discussions.

(7) A trace amount of the regioisomer of **7** was detected by GC.

(8) Bruce, M. I.; Jensen, C. M.; Jones, N. L. *Inorg. Synth.* **1989**, *26*, 259.

(9) Kurita, J.; Ishii, M.; Yasuike, S.; Tsuchiya, T. *J. Chem. Soc., Chem. Commun.* **1993**, *17*, 1309.

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

(11) Jacobi, P.; Craig, T. A.; Walker, D. G.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585.

CONCLUSION

In this thesis, ruthenium-catalyzed cyclocoupling of ketones, olefins, and carbon monoxide was discussed. The results in each chapter of this thesis are summarized as follows.

In Chapter 1, the ruthenium-catalyzed [2 + 2 + 1] cycloaddition reaction of 1,2-dicarbonyl compounds, olefins, and carbon monoxide was discussed. A variety of 1,2-dicarbonyl compounds, which included α-keto esters, α-keto amides, and α-diketones, reacted with ethylene and CO smoothly in the presence of phosphine additives to give the γ-lactone derivatives. The reaction represents the first example of *catalytic intermolecular* cyclocoupling of ketones, olefins, and CO.

The results of using *N*-heterocyclic ketones as a ketone component in the ruthenium-catalyzed [2 + 2 + 1] cyclocoupling reaction were discussed in Chapter 2. A C=N unit in conjugation with the reacting ketone moiety, as in 2-acyl pyridine, is necessary for the reaction to proceed. This indicates that the five-membered chelation complex formed through the coordination of the substrate to a ruthenium center would be a key intermediate. Cyclic olefins, unpolarized terminal olefins, and some alkynes were successfully applied to the cyclocoupling reaction.

Chapter 3 gave a detailed discussion on the mechanism of the above-mentioned ruthenium-catalyzed cyclocoupling reactions. Possible mechanisms were proposed on the basis of the related stoichiometric reactions. It was observed the sharp contrast between the reactions of keto esters and *N*-heterocyclic ketones in the effects of additives, the substituents on the reacting ketone moiety, and pressure of ethylene and CO. Such differences can be rationalized by assuming that the rate-limiting step in the catalytic cycle is different for these reactions.

In Chapter 4, application of this ruthenium-catalyzed cyclocoupling to the synthesis of γ-lactams was discussed. *N*-aryl imines containing an ester group or *N*-heterocycles were applicable to the catalytic reaction.

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 in the present studies is really a "synthesis" of cyclic carbonyl compounds.

The knowledge gained through the present studies will undoubtedly contribute to the advancement of organic synthesis and homogeneous catalysis.