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A New Route to Cyclopentenones via Ruthenium-Catalyzed Carbonylative Cyclization of Allylic Carbonates with Alkenes

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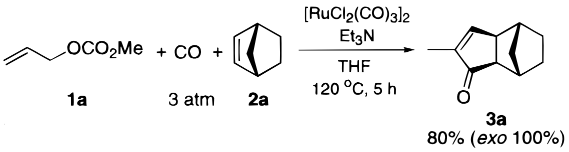
ABSTRACT



$[RuCl_2(CO)_3]_2$/Et_3N and (η^3-C_3H_5)$RuBr(CO)_3$/Et_3N are highly effective catalyst systems for carbonylative cyclization of allylic carbonates with alkenes to give the corresponding cyclopentenones in high yields. For example, treatment of allyl methyl carbonate (1a) with 2-norbornene (2a) in the presence of a catalytic amount of $[RuCl_2(CO)_3]_2$ (2.5 mol %) and Et_3N (10 mol %) at 120 °C for 5 h under 3 atm of carbon monoxide gave the corresponding cyclopentenone, *exo*-4-methyltricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3a), in 80% yield with high stereoselectivity (*exo* 100%).

The development of simple and general methods for the synthesis of cyclopentenones from readily available substrates continues to be one of the most active and challenging areas of synthetic research,[1] due to the wide abundance of this structural unit in a large number of natural products. Cocyclization of alkynes, alkenes, and carbon monoxide by transition metal complexes leading to cyclopentenones (known as the Pauson−Khand reaction[2]) has been accepted as one of the most powerful and convergent methods for the construction of cyclopentenones and has been used successfully as the key step in the synthesis of a variety of natural products.[3] Many advances relating to this method have been reported recently, including the development of catalytic versions of this reaction.[4] Another formally related process, the carbonylative cyclization of allylic halides with alkynes promoted by nickel[5] and palladium[6] complexes via η^3-allyl intermediates, has recently been reported. However, the use of alkyne substrates is essential for both the Pauson−

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(1) Ellison, R. A. *Synthesis* **1973**, 397 and pertinent references therein.

(2) For recent review on the Pauson−Khand reaction, see: (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977. (b) Pauson, P. L.; Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2. (c) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. (d) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (e) Schore, N. E. *Org. React.* **1991**, *40*, 1. (f) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911 and references therein. (g) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U.K., 1991; Vol. 5, pp 1037−1064. (h) Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, U.K., 1995; Vol. 12, pp 703−739. (I) Jeong, N. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: New York, 1998; Vol. 1, pp 560−577.

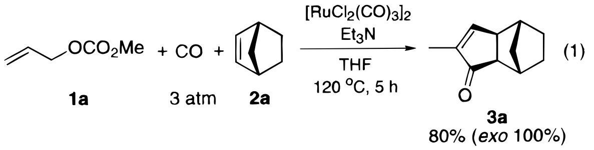
(3) Donkervoort, J. G.; Gordon, A. R.; Johnstone, C.; Kerr, W. J.; Lange, U. *Tetrahedron* **1996**, *52*, 7391 and references therein.

(4) For cobalt catalysts, see: (a) Rautenstrauch, V.; Megard, P.; Conesa, J.; Kuster, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1413. (b) Jeong, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 3159. (c) Lee, B. Y.; Chung, Y. K.; Jeong, N.; Lee, Y.; Hwang, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 8793. (d) Lee, N. Y.; Chung, Y. K. *Tetrahedron Lett.* **1996**, *37*, 3145. (e) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285. (f) Jeong, N.; Hwang, S. H.; Lee, Y. W.; Lim, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 10549. (g) Sugihara, T.; Yamaguchi, M. *J. Am. Chem. Soc.* **1998**, *120*, 10782 and references therein. For titanocene catalysts, see: (h) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450. (i) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688. (j) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5881 and references therein. For ruthenium catalyst, see: (k) Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc.* **1997**, *119*, 6187. (l) Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **1997**, *62*, 3762. For rhodium catalysts, see: (m) Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* **1998**, 249. (n) Jeong, N.; Lee, S.; Sung, B. K. *Organometallics* **1998**, *17*, 3642.

10.1021/ol0000206 CCC: $19.00

Khand reaction and the carbonylative cyclization reactions.[7] During our investigation of the η^3-allylruthenium chemistry[8] as well as the ruthenium-catalyzed Pauson−Khand reaction,[4k] we found the first example of the ruthenium-catalyzed carbonylative cyclization of allylic carbonates with *alkenes*, which offers a new route to cyclopentenones. We report here the development of this new catalyst system for the synthesis of cyclopentenones via an η^3-allylruthenium intermediate.

Treatment of allyl methyl carbonate (**1a**) with 2-norbornene (**2a**) in the presence of 2.5 mol % of $[RuCl_2(CO)_3]_2$ and 10 mol % of Et_3N in THF at 120 °C for 5 h under 3 atm of carbon monoxide gave the corresponding cyclopentenone, *exo*-4-methyltricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (**3a**), in 80% yield with high stereoselectivity (*exo* 100%) (eq 1).



(1)

The effects of the catalysts and the amine ligands were examined in the reaction of **1a** with **2a**, and the results are summarized in Table 1. An appropriate catalyst combined with an amine ligand was critically important for a successful reaction. For example, no catalytic activity of $[RuCl_2(CO)_3]_2$ was observed in the absence of Et_3N, but the concomitant use of $[RuCl_2(CO)_3]_2$ with Et_3N dramatically increased the catalytic activity to give **3a** in the best yield of 80%. A small amount of the hydrogenated cyclopentanone, *exo*-4-methyltricyclo[5.2.1.0^{2,6}]decan-3-one (**4a**), was obtained as a byproduct. $[(p\text{-Cymene})RuCl_2]_2/Et_3N$, which would give the same active species as $[RuCl_2(CO)_3]_2/Et_3N$, also showed good catalytic activity (yield of **3a**, 60%). However, other ruthenium complexes, such as Cp*RuCl(cod) [Cp* = pentamethylcyclopentadienyl; cod = 1,5-cyclooctadiene], $RuCl_2(PPh_3)_3$, $Ru_3(CO)_{12}$, and $Ru(CO)_3(PPh_3)_2$, were almost ineffective even in the presence of Et_3N. Since the catalytic activity of $[RuCl_2(CO)_3]_2$ was highly affected by the amine ligand, the effect of the several amine ligands was also examined. Tertiary alkylamines, such as quinuclidine and *N*-methylpiperidine, generally enhanced the catalytic activity (yields of **3a**, 68% and 50%, respectively), and Et_3N gave the best result. Almost no promoting effect was observed with aromatic amines, such as *N,N*-dimethylaniline and pyridine, or bidentate amines, such as *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), and 1,10-phenanthroline.

Table 1. Effects of the Catalysts and Amine Ligands on the Carbonylative Cyclization of **1a** with **2a**[a]

catalyst	amine ligand[b]	yield of **3a** (%)[c]	yield of **4a** (%)[c,d]
$[RuCl_2(CO)_3]_2$		0	0
$[RuCl_2(CO)_3]_2$	Et_3N	80	8
$[(p\text{-cymene})RuCl_2]_2$	Et_3N	60	6
Cp*RuCl(cod)		0	0
Cp*RuCl(cod)	Et_3N	13	0
$RuCl_2(PPh_3)_3$		0	0
$Ru_3(CO)_{12}$		0	0
$Ru_3(CO)_{12}$	Et_3N	0	0
$Ru(CO)_3(PPh_3)_2$	Et_3N	0	0
$[RuCl_2(CO)_3]_2$	quinuclidine	68	3
$[RuCl_2(CO)_3]_2$	*N*-methylpiperidine	50	4
$[RuCl_2(CO)_3]_2$	*N,N*-dimethylaniline	17	4
$[RuCl_2(CO)_3]_2$	pyridine	0	0
$[RuCl_2(CO)_3]_2$	TMEDA[e,f]	0	0
$[RuCl_2(CO)_3]_2$	1,10-phenanthroline[f]	0	0

[a] **1a** (1.0 mmol), **2a** (2.0 mmol), catalyst (0.050 mmol as Ru atom), and THF (8.0 mL) at 120 °C for 5 h under 3 atm of carbon monoxide. [b] 0.10 mmol. [c] Determined by GLC. [d] **4a**: *exo*-4-methyltricyclo[5.2.1.0^{2,6}]decan-3-one. [e] *N,N,N′,N′*-Tetramethylethylenediamine. [f] 0.050 mmol.

The carbon monoxide pressure also had a dramatic effect on the carbonylative cyclization of **1a** with **2a** (Figure 1). The best result was obtained under 3 atm of carbon monoxide, and either an increase or decrease in the carbon monoxide pressure caused the rapid decrease in the yield of **3a**.

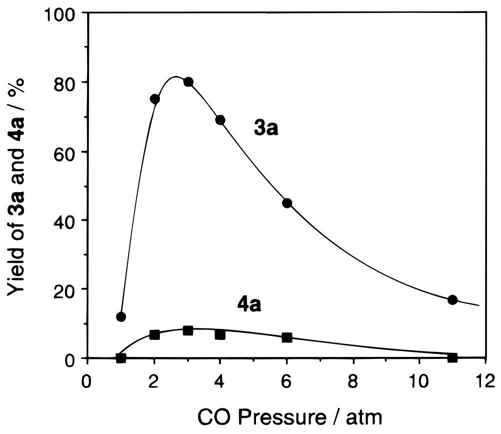


Figure 1. Effect of CO pressure on the formation of **3a** by the carbonylative cyclization of **1a** with **2a**. Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), $[RuCl_2(CO)_3]_2$ (0.025 mmol), Et_3N (0.10 mmol) at 120 °C for 5 h.

To clarify the intermediacy of an η^3-allylruthenium complex, the stoichiometric reaction of $(\eta^3\text{-}C_3H_5)RuBr(CO)_3$ (**5**) with an equimolar amount of **2a** was examined, and the

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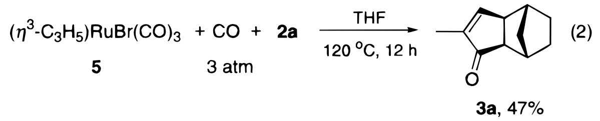
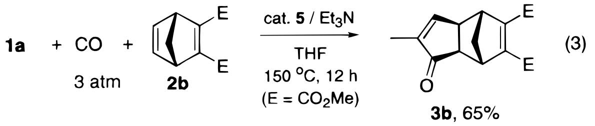
(5) (a) Chiusoli, G. P. *Acc. Chem. Res.* **1973**, *6*, 422 and references therein. (b) Camps, F.; Coll, J.; Moretó, J. M.; Torras, J. *J. Org. Chem.* **1989**, *54*, 1969. (c) Pagès, L.; Llebaria, A.; Camps, F.; Molins, E.; Miravitlles, C.; Moretó, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 10449. (d) Champs, F.; Llebaria, A.; Moretó, J. M.; Pagès, L. *Tetrahedron Lett.* **1992**, *33*, 109. (e) Camps, F.; Moretó, J. M.; Pagès, L. *Tetrahedron* **1992**, *48*, 3147. (f) Llebaria, A.; Camps, F.; Moretó, J. M. *Tetrahedron* **1993**, *49*, 1283. (g) Villar, J. M.; Delgado, A.; Llebaria, A.; Moretó, J. M. *Tetrahedron; Asymmetry* **1995**, *6*, 665. (h) Villar, J. M.; Delgado, A.; Llebaria, A.; Moretó, J. M. *Tetrahedron* **1996**, *52*, 10525. (i) García-Gómez, G.; Moretó, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 878 and references therein.

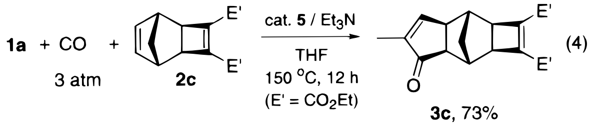
(6) (a) Negishi, E.; Wu, G.; Tour, J. M. *Tetrahedron Lett.* **1988**, *29*, 6745. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. (c) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941. (d) Oppolzer, W.; Xu, J.-Z.; Stone, C. *Helv. Chim. Acta* **1991**, *74*, 465. (e) Ihle, N. C.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 560. (f) Oppolzer, W.; Robyr, C. *Tetrahedron* **1994**, *50*, 415.

corresponding cyclopentenone (**3a**) was obtained in an isolated yield of 47% (eq 2). Complex **5** also showed the high catalytic activity in the presence of Et_3N for the carbonylative cyclization of **1a** with **2a** to give **3a** in a 65% yield. Consequently, the η^3-allylruthenium complex, an analogue of complex **5**, appears to be the key intermediate as well as an active catalyst precursor in the present reaction.[9]



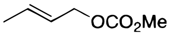
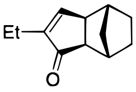
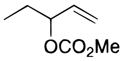
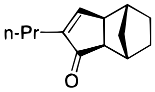
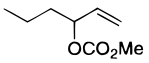
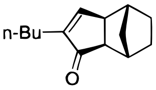
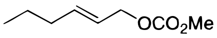
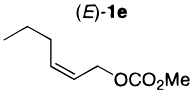
The carbonylative cyclization of **1a** with norbornene derivatives **2b** and **2c** also gave the corresponding cyclopentenones, **3b** and **3c**, in isolated yields of 65% and 73%, respectively (eqs 3 and 4). Efforts to obtain cyclopentenones with other alkenes are now in progress.[10]





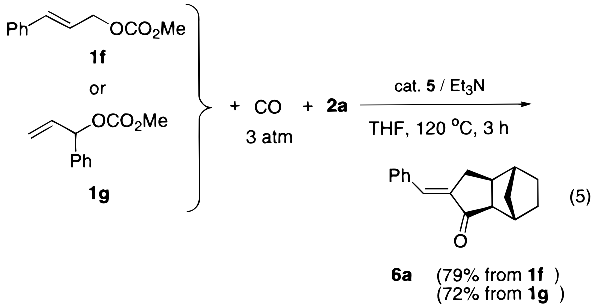
The results obtained from the reactions of several substituted allylic carbonates with 2-norbornene (**2a**) are summarized in Table 2. In all cases, allylic carbonates were completely consumed, and the corresponding cyclopentenones were obtained in high yields. The regioisomeric allylic carbonates, e.g., 1-hexene-3-yl methyl carbonate (**1d**) and (*E*)-2-hexenyl methyl carbonate ((*E*)-**1e**), gave the same product (**3f**) in high yields, respectively, which suggests that the present reaction proceeds via an η^3-allylruthenium intermediate. In addition, the result that cyclopentenone (**3f**) was also obtained from carbonylative cyclization of either (*Z*)-**1e** and (*E*)-**1e** with **2a** indicates the rapid isomerization between *anti*- and *syn*-η^3-allylruthenium intermediates.

Table 2. (η^3-C_3H_5)RuBr(CO)$_3$/Et_3N-Catalyzed Carbonylative Cyclization of Several Allylic Carbonates with **2a**[a]

Allylic Carbonate	Products (%)[b]
 **1b**	 **3d** (73)
 **1c**	 **3e** (91)
 **1d**	 **3f** (73)
 (*E*)-**1e**	**3f** (75)
 (*Z*)-**1e**	**3f** (95)

[a] Allylic carbonate **1** (1.0 mmol), **2a** (1.1 mmol), (η^3-C_3H_5)RuBr(CO)$_3$ (0.50 mmol), Et_3N (0.10 mmol), and THF (2.0 mL) at 120 °C for 3 h under 3 atm of carbon monoxide. [b] Determined by GLC based on the amount of **1** charged.

On the other hand, aryl-substituted allylic carbonates, such as cinnamyl methyl carbonate (**1f**) and 1-phenylallyl methyl carbonate (**1g**), gave 2-benzylidenecyclopentanone (**6a**) even by the use of (η^3-C_3H_5)RuBr(CO)$_3$/Et_3N catalyst,[9] probably due to the π-conjugation of an olefinic moiety with the phenyl group (eq 5). The structure of **6a** was confirmed by X-ray crystallography (Figure 2).[12]



A synthetic application of the present reaction is demonstrated in the following *intramolecular* carbonylative cy-

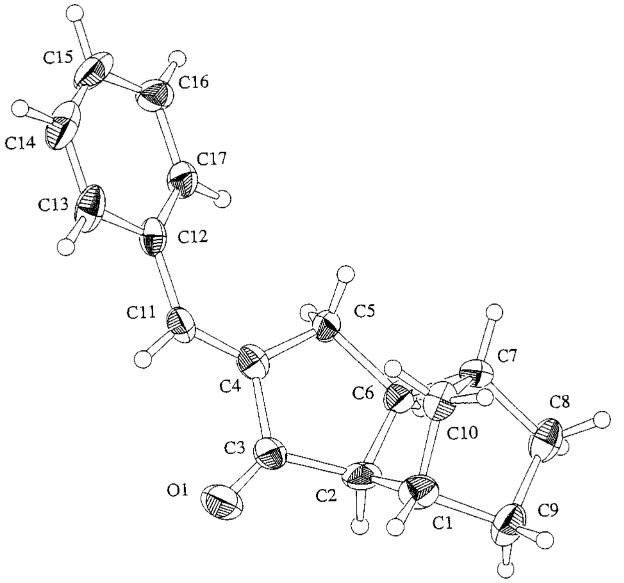
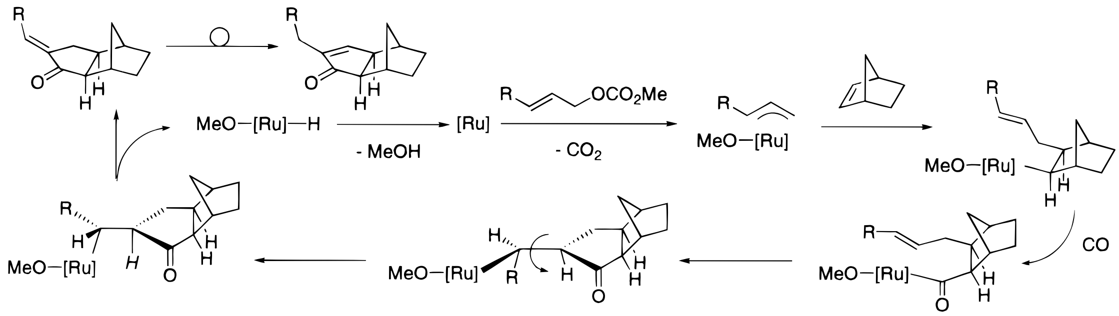
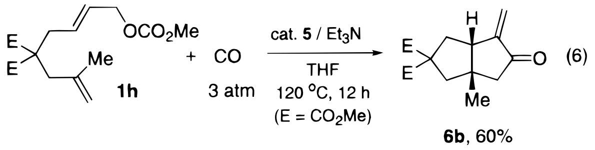


Figure 2. ORTEP drawing of **6a** with 30% thermal ellipsoids. Selected bond length [Å]: C2−C3 = 1.53(2), C3−O1 = 1.22(1), C3−C4 = 1.50(2), C4−C5 = 1.50(2), C4−C11 = 1.34(2), C5−C6 = 1.58(2). Selected bond angles [deg]: C1−C2−C3 = 109(1), C3−C4−C11 = 118(1), C4−C11−C12 = 129(1), C5−C4−C11 = 130(1), C5−C6−C7 = 114(1).

Scheme 1



clization of **1h** (eq 6). Treatment of **1h** under the present reaction conditions gave the bicyclic cyclopentanone **6b** in 60% yield.[6b,c,13]



The most plausible mechanism is illustrated in Scheme 1. Invariable *exo*-coordination of 2-norbornene derivatives to an active η^3-allylruthenium intermediate, stereoselective *cis*-carbo-ruthenation, and successive insertion of CO would give an (acyl)ruthenium intermediate. Subsequent intramolecular insertion of a C═C bond into an acyl−ruthenium bond, followed by β-hydride elimination/isomerization, would give the corresponding cyclopentenones exclusively in an *exo* form. Higher carbon monoxide pressure (over 3 atm) would suppress coordination of 2-norbornene, and lower carbon monoxide pressure (below 3 atm) would prevent insertion of CO.

In conclusion, we have found the first practically useful ruthenium catalyst for the rapid construction of cyclopentenones without the use of an alkyne substrate. This catalytic process, which is an alternative to the Pauson−Khand reaction, could become a valuable tool in the field of organic and natural product synthesis.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan. Y.M. appreciates Research Fellowships from the Japan Society for the Promotion of Science for Young Scientists.

Supporting Information Available: Complete experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Palladium-catalyzed cyclocarbonylation of allylic halides with 2-norbornene and/or 2,5-norbornadiene to 2-alkylidenecyclopentanones, not cyclopentenones, has been reported, see: Amari, E.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, *285*, 383. (b) For the stoichiometric reaction of $[(\eta^3\text{-}C_3H_5)PdX]_2$ with 2-norbornene and CO to cyclopentenones, see: Larock, R. C.; Takagi, K.; Burkhart, J. P.; Hershberger, S. S. *Tetrahedron* **1986**, *42*, 3759.

(8) (a) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587. (b) Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.; Watanabe, Y. *Organometallics* **1995**, *14*, 1945 and references therein.

(9) Since $[RuCl_2(CO)_3]_2/Et_3N$-catalyzed carbonylative cyclization of substituted allylic carbonates often gave 2-alkylidenecyclopentanones in place of the desired cyclopentenones, the catalyst system of $(\eta^3\text{-}C_3H_5)RuBr(CO)_3/Et_3N$ in place of $[RuCl_2(CO)_3]_2/Et_3N$ was used in the following reactions.

(10) For example, the reaction of cinnamyl methyl carbonate with ethylene gave the co-dimerization product, 1-phenyl-1,3-pentadiene ((1*E*,3*E*):(1*E*,4*Z*) = 79:21), in 67% yield,[11] which would be obtained by β-hydride elimination prior to CO insertion.

(11) For a similar co-dimerization reaction of allylic carbonate with electron-deficient alkenes via an η^3-allylruthenium intermediate, see: Mitsudo, T.; Zhang, S.-W.; Kondo, T.; Watanabe, Y. *Tetrahedron Lett.* **1992**, *33*, 341.

(12) Crystal data for **6a**: $C_{17}H_{18}O$; FW = 238.33, orthorhombic, space group $P2_12_12_1$ [No. 19], colorless prismatic, $a = 11.51(1)$ Å, $b = 11.42(2)$ Å, $c = 9.90(1)$ Å, $V = 1300(2)$ Å^3, $Z = 4$, $D_{calc} = 1.217$ g/cm^3, μ(Mo Kα) = 0.74 cm^{-1}, Rigaku AFC-7R diffractometer, $\lambda = 0.71069$ Å, $\omega-2\theta$ scan (16.0°/min), $2\theta_{max} = 55.1°$, 1489 reflections (unique), $R = 0.068$, $R_w = 0.070$, GOF = 1.12.

(13) Palladium- and nickel-catalyzed *intramolecular* carbonylative cyclization of 2,7-octadienyl iodide or acetate to bicyclic cyclopentenone derivatives has been reported. (a) Yamamoto, K.; Terakado, M.; Murai, K.; Miyazawa, M.; Tsuji, J.; Takahashi, K.; Mikami, K. *Chem. Lett.* **1989**, 955. (b) Oppolzer, W.; Keller, T. H.; Bedoya-Zurita, M.; Stone, C. *Tetrahedron Lett.* **1989**, *30*, 5883. (c) Keese, R.; Guidetti-Grept, R.; Herzog, B. *Tetrahedron Lett.* **1992**, *33*, 1207. (d) Terakado, M.; Murai, K.; Miyazawa, M.; Yamamoto, K. *Tetrahedron* **1994**, *50*, 5705.