

**The First Catalytic Carbonylative [4 + 1]
Cycloaddition Using a 1,3-Conjugated System. A
New Transformation of α,β -Unsaturated Imines to
Unsaturated γ -Lactams Catalyzed by $\text{Ru}_3(\text{CO})_{12}$**

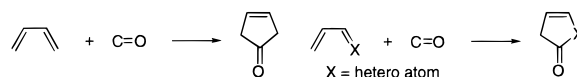
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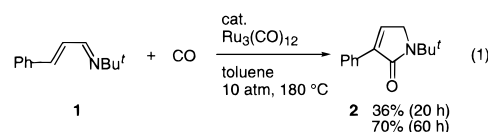
Transition-metal-catalyzed cycloaddition reactions using carbon monoxide as a one-carbon unit have been extensively studied.¹ One of the most familiar examples is the Pauson–Khand reaction,^{2,3} in which an alkyne, an alkene, and carbon monoxide are condensed in a formal [2 + 2 + 1] cycloaddition to form cyclopentenones. This transformation has been the subject of intense investigation, both stoichiometrically and catalytically³ because of its utility in the construction of five-membered cyclic systems. In terms of the construction of a five-membered ring system, the [4 + 1] mode, in which conjugated systems act as four-atom assembling units, is also attractive. In this mode, the reaction of 1,3-dienes with carbon monoxide would be expected to afford cyclopentenones, and the replacement of a terminal carbon by a heteroatom, such as oxygen and nitrogen, would give rise to unsaturated γ -lactones and γ -lactams, respectively (Scheme 1). Especially, the latter catalytic transformation using α,β -unsaturated imines would be useful in synthetic organic chemistry, because γ -lactam skeleton is one of the most important nitrogen heterocycles for pharmaceutical agents.^{4,5} To our knowledge, however, such transformations of conjugated systems are known to proceed only with the η^4 -diene iron carbonyl complex,⁶ and no precedent for a catalytic reaction in this area has been reported. As a similar transformation, Et_2AlCl -mediated [4 + 1] cycloaddition of α,β -unsaturated carbonyl compounds with isocyanides, which are isoelectronic to carbon monoxide, has been reported.⁷ Recently, a special class of catalytic [4 + 1] cycloaddition reactions using cumulene has been reported as well. The applicable substrates for these reactions are limited to particular molecules having cumulated double bonds and include vinylallenes,⁸ diallenes,⁹ allenyl aldehydes/ketones,¹⁰ and allenyl imines.¹¹ Herein

Scheme 1



we wish to report the first example of a [4 + 1] cycloaddition of structurally simple α,β -unsaturated imines with carbon monoxide.

The reaction of the α,β -unsaturated imine **1** (2 mmol), which was derived from the reaction of *trans*-cinnamaldehyde with *tert*-butylamine, with CO (10 atm) in toluene (3 mL) in the presence of a catalytic amount of $\text{Ru}_3(\text{CO})_{12}$ (0.04 mmol) at 180 °C for 20 h gave a 1,5-dihydro-1-(1,1-dimethylethyl)-3-phenyl-2H-pyrrol-2-one (**2**)¹² in 36% isolated yield (eq 1) with 47% of the imine being recovered as *trans*-cinnamaldehyde by silica gel column chromatography. Prolongation of the reaction time (60 h) increased the yield of **2** to 70%. When the reaction was carried out at 160 °C, **2** was formed only in 7% yield, and 90% of the original aldehyde was recovered. Both a lower pressure (3 atm)¹³ and a higher pressure (30 atm) decreased the yield to 26 and 12%, respectively. Among the solvents examined (dioxane 25% yield, CH_3CN 22%, cyclohexane 23%, pyridine 0%), toluene was the solvent of choice when the reaction was run at 180 °C under 10 atm of CO for 20 h. Changing the substituent on the nitrogen atom to *i*-Pr, *n*-Bu, or *p*-MeOC₆H₄ resulted in no corresponding products being produced. No reaction was observed when other complexes, such as $\text{Cp}^*\text{RuCl}(\text{cod})$, $\text{Ru}(\text{CO})_2(\text{PPh}_3)_3$, $[\text{RuCl}_2(\text{CO})_3]_2$, $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$, and $\text{Ru}(\text{acac})_3$ were used as catalysts. The standard reaction conditions established are 2 mol % of $\text{Ru}_3(\text{CO})_{12}$, 10 atm of CO, in toluene, and at 180 °C. This reaction represents the first example of catalytic carbonylative [4 + 1] cycloaddition using a structurally simple 1,3-diene system.¹⁴



Selected results are shown in Table 1. The reaction of imine **3** of 2-methylcinnamaldehyde gave the corresponding lactam **4** in 77% yield (entry 1). Replacement of the phenyl group in **1** with an alkyl group, as in **5**, led to higher yield (entry 2). β,β -Disubstituted imines also worked well (entries 3 and 4). The reactions of imines having cyclic olefin counterparts also proceeded to give bicyclic γ -lactams (entries 5–7). Changing the aldimino group to a ketimino group permitted a more efficient transformation (entries 4 and 6).¹⁵ Use of imine **15** derived from the commercially available, optically active aldehyde, (1*R*)-(–)-myrtenal, and cyclic imine **17** also gave rise to the formation of tricyclic γ -lactams (entries 7 and 8). The reaction of α -oxyimine **19**, which contains an oxygen-functionality at the α -carbon, gave the corresponding lactam **20** (entry 9), however, the β -oxyimine **21** failed to react. This catalytic system lacks the ability to carbonylate aromatic imines **22** and **23**.^{14a}

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(13) The reaction was run in *o*-xylene.

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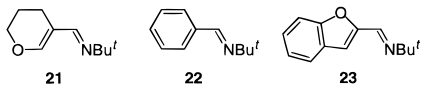
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Table 1. Ru₃(CO)₁₂-Catalyzed [4 + 1]Cycloaddition of α,β -Unsaturated Imines with CO^a

entry	α,β -unsaturated imine	lactam ^b
1		 4 51% (43%) 77% (13%) ^c
2		 6 71%
3		 8 91%
4		 10 96% (endo/exo=20/80) ^d
5		 12 81%
6		 14 94%
7		 16 60% (28%) 79% (7%) ^c
8		 18 65% ^c
9		 20 83%

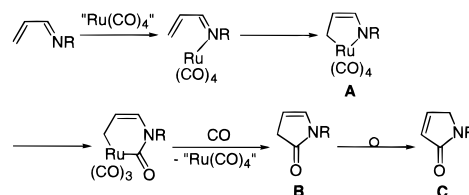
^a Reaction conditions: α,β -unsaturated imine (2 mmol), CO (10 atm), Ru₃(CO)₁₂ (0.04 mmol), toluenes (3 mL) at 180 °C for 20 h. ^b Isolated yield. Values in parentheses are the yield of enamines recovered as the original aldehydes. ^c The reaction was run for 60 h. ^d The ratio of products is determined by ¹H NMR.



We propose that the reaction proceeds via a pathway shown in Scheme 2.¹⁶ The coordination of a nitrogen to ruthenium allows the complex to be easily converted to metallacycle **A** via an oxidative cyclization of the α,β -unsaturated imine. No examples exist in which metallacycle **A** is formed by the reaction of a late transition metal complex with a α,β -unsaturated imine,^{19,20} although it is well-known that metallacyclopentenes which contain early transition metals, such as Ti and Zr, are formed by the reaction of Cp₂Ti and Cp₂Zr with α,β -unsaturated imines.²¹ The

(14) For papers on [4 + 1] cycloaddition in which an aromatic π -bond is utilized as a part of a four-atom assembling unit, see: (a) It has been reported that the *N*-phenylimine derivative of benzaldehyde reacted with carbon monoxide in the presence of a catalytic amount of Co₂(CO)₈ to yield phthalimidine. Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403. Horiie, S.; Murahashi, S. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 247. (b) We have previously observed formal [4 + 1] cycloaddition of (β -phenylvinyl)lithium and its nitrogen-containing analogues with carbon monoxide. Ryu, I.; Hayama, Y.; Hirai, A.; Sonoda, N.; Orita, A.; Ohe, K.; Murai, S. *J. Am. Chem. Soc.* **1990**, *112*, 7061. Orita, A.; Fukudome, M.; Ohe, K.; Murai, S. *J. Org. Chem.* **1994**, *59*, 477.

(15) Ketimines **9**, **13**, **19** were used as syn and anti mixture in favor of the *anti* isomer (60–70%).

Scheme 2

subsequent insertion of CO and reductive elimination of ruthenium initially produce the β,γ -unsaturated γ -lactam **B**. For the reaction of imines which contain a β -hydrogen, **B** is transferred to the thermally more stable α,β -unsaturated isomer **C**. We speculate that the significant difference between the reactivity of imines **19** and **21** is due to the different direction of the resonance effect by the oxygen atom to π -system. The nitrogen in imine **21** partially loses, by the resonance effect, its sp²-character which appears to be essential for the interaction between the α,β -unsaturated imine and ruthenium.²²

In summary, we have demonstrated a new Ru-catalyzed [4 + 1] cycloaddition of α,β -unsaturated imines with carbon monoxide. The present reaction represents the first reported [4 + 1] cycloaddition using a structurally simple 1,3-diene system. We are now expanding the scope of this transformation with special regard to the compatibility of the reaction with respect to functional group, as well as exploring more mild reaction conditions.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) The detail of the reaction mechanism, especially the molecularity of true catalyst, is unclear. It is, in general, difficult to establish with precision whether the cluster loaded or its fragment species are actually responsible for the catalytic phenomenon. Thus, the molecularity of catalyst is the long-standing unsolved subject in cluster chemistry. However, Laine demonstrated that studies of turnover frequency (TOF) as a function of total metal concentration can be a useful proof of catalysis mechanism.^{17,18} Thus, as the total catalyst concentration increases, the TOF increases are indicative of cluster catalysis, and, conversely, the TOF decreases are indicative of lower nuclearity species catalysis. We followed his criteria and constructed plots of TOF vs Ru₃(CO)₁₂ concentration (see Supporting Information), and the curve obtained shows that as the cluster concentration is increased, there is a decrease in the TOF number, indicating that the active catalytic species is not Ru₃(CO)₁₂ but a lower nuclearity species, such as Ru(CO)₅. At the present time, we cannot determine the structure of the true catalytic species; however, we speculate that monoruthenium complex, Ru(CO)_{*n*} (*n* = 4 or 5) is a key catalytic species. We still need additional experiments.

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