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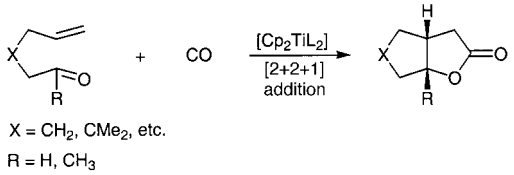
Synthesis of α-Methylene-γ-butyrolactones: Ru-Catalyzed Cyclocarbonylation of Allenyl Aldehydes and Allenyl Ketones**

Suk-Ku Kang,* Kwang-Jin Kim, and Young-Taek Hong

Recently, Buchwald and co-workers[1] as well as Crowe et al.[2] independently described new titanium-mediated and -catalyzed hetero-Pauson – Khand reactions, which involved the [2 + 2 + 1] cycloaddition of δ-unsaturated ketones and aldehydes with carbon monoxide to form fused bicyclic γ-butyrolactones (Scheme 1). Although titanium catalysis of



Scheme 1. [2 + 2 + 1] Cycloaddition of δ-unsaturated ketones and aldehydes with CO to form fused bicyclic γ-butyrolactones. Ts = toluene-4-sulfonyl.

this process has proven to be efficient, the strength of the early transition metal–oxygen bond makes the catalytic sequence difficult when titanium reagents are used. A solution to this potential problem was provided by Murai and co-workers,[3] who demonstrated that the late transition metal reagent $[Ru_3(CO)_{12}]$ smoothly catalyzes [2 + 2 + 1] cycloadditions of substituted δ-alkynyl aldehydes, with carbon monoxide to form fused α,β-unsaturated γ-butyrolactones.

To the best of our knowledge, late transition metal catalyzed hetero-Pauson – Khand reactions of simple allenyl aldehydes and ketones have not yet been reported. Furthermore, this methodology has not been applied to the synthesis of α-methylene-γ-butyrolactones, a ring system found in numerous, biologically active natural products.[4, 5] Hetero-Pauson – Khand carbonylative cyclizations of δ-allenyl aldehydes and ketones would serve as a direct entry into this family of compounds. We describe herein the preliminary results of an investigation into the latter and demonstrate that ruthenium-catalyzed [2 + 2 + 1] cycloadditions of allenyl aldehydes and ketones with carbon monoxide serve as an efficient and direct route to α-methylene-γ-butyrolactones (Scheme 2).[6–8]

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Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

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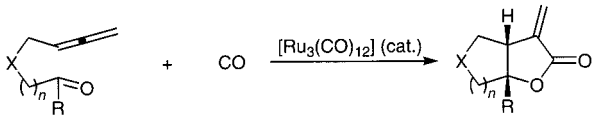
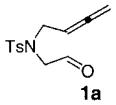
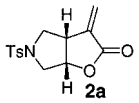
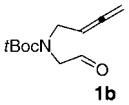
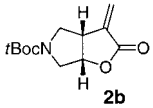
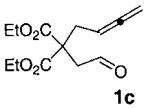
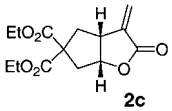
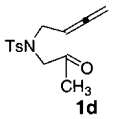
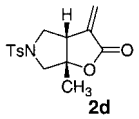
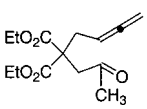
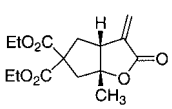


Scheme 2. Ru-catalyzed [2 + 2 + 1] cycloadditions of allenyl aldehydes and ketones with CO to form α-methylene-γ-butyrolactones.

δ-Allenyl aldehyde **1a**[9] was used to evaluate the feasibility of and to find optimal conditions for the α-methylene-γ-butyrolactone-forming cycloaddition process. Exploratory studies with this substrate showed that a variety of ruthenium reagents serve as effective catalysts for the conversion of **1a** into butyrolactone **2** (Table 1, entry 1). Among $[Ru_3(CO)_{12}]$, $[RuCl_2(CO_3)_2]$, $[RuCl_2(PPh_3)_3]$, and $[Cp_2Ru]$, the best catalyst for this process is $[Ru_3(CO)_{12}]$. Furthermore, dioxane was found to be superior to either toluene or *N*,*N*-dimethylformamide (DMF) as a solvent for this reaction. Thus, the optimum reaction conditions (75% yield) for cyclocarbonylation of **1a** involves $[Ru_3(CO)_{12}]$ (1 mol%) in dioxane under CO (20 atm) at 120°C for 12 h. The *cis* ring-fusion stereochemistry in **2a** was determined by using 2D-NOESY techniques in conjunction with molecular modeling (see Supporting Information).

The results presented in Table 1 demonstrate the generality of the α-methylene-γ-butyrolactone-forming, ruthenium-catalyzed carbonylative cycloaddition process. Importantly, under the reaction conditions described above, the δ-allenyl ketone **1d** affords the methyl-substituted *cis*-γ-butyrolactone **2d** in 82% yield (Table 1, entry 4). The *cis* ring-fusion stereochemistry in **2d** was unambiguously assigned by using NOE methods (methyl and ring-junction hydrogen atom). Likewise, the branched malonate **1e** was smoothly transformed into the *cis* lactone **2e** (Table 1, entry 5) under the ruthenium-catalyzed reaction conditions.

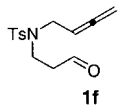
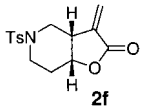
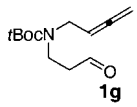
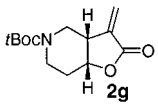
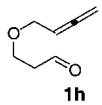
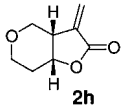
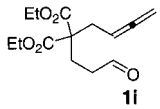
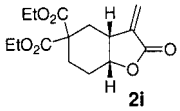
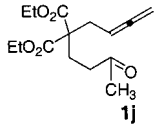
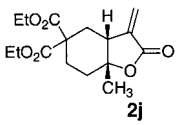
Table 1. $[Ru_3(CO)_{12}]$-catalyzed cycloaddition of allenyl aldehydes and allenyl ketones with CO.[a]

Entry	Substrate	Product	Yield [%]
1	 **1a**	 **2a**	75
2	 **1b**	 **2b**	70
3	 **1c**	 **2c**	60
4	 **1d**	 **2d**	82[b]
5	 **1e**	 **2e**	58[b]

[a] The reactions were carried out with $[Ru_3(CO)_{12}]$ (1 mol%) and allenyl aldehyde or ketone **1** (1.0 equiv) in dioxane under CO (20 atm) at 120°C for 12 h. [b] For 17 h. *t*Boc = *tert*-butoxycarbonyl.

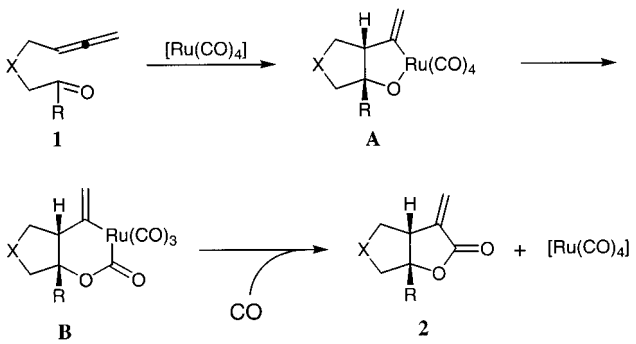
The cyclocarbonylation methodology is also applicable to the conversion of ε-allenyl aldehydes and ketones into the corresponding six-membered *cis* ring-fused α-methylene-γ-butyrolactones (Table 2). Notably, the ω-allenyl ketone **1j** afforded the methyl-substituted quaternary *cis*-γ-butyrolactone **2j** (Table 2, entry 5).

Table 2. $[Ru_3(CO)_{12}]$-catalyzed cycloaddition of allenyl aldehydes and allenyl ketones with CO.[a]

Entry	Substrate	Product	Yield [%]
1	 **1f**	 **2f**	60
2	 **1g**	 **2g**	72
3	 **1h**	 **2h**	61
4	 **1i**	 **2i**	55
5	 **1j**	 **2j**	48[b]

[a] The reactions were carried out with $[Ru_3(CO)_{12}]$ (1 mol%) and allenyl aldehyde or ketone **1** (1.0 equiv) in dioxane under CO (20 atm) at 120°C for 12 h. [b] For 17 h.

The mechanistic pathway followed in this catalytic process most likely involves the intermediacy of metallacyclopentene **A** (Scheme 3), which undergoes insertion of CO to form the carbonylated metallacycle **B**. Reductive elimination then yields the bicyclic α-methylene-γ-butyrolactone product. In further studies to test this kind of cycloaddition in the formation ruthenacycle **A** with carbon monoxide to prepare



Scheme 3. Proposed mechanistic pathway for the Ru-catalyzed [2 + 2 + 1] cycloaddition.

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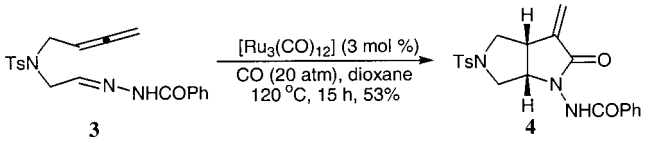
fused α-methylene-γ-butyrolactam, we explored the cyclocarbonylation of δ-allenyl imine **3** and examined the stereochemistry of the resulting products (Scheme 4). We observed only the *cis*-fused α-methylene-γ-butyrolactam **4** as the sole product, which supports a $[2+2+1]$ cycloaddition. The *cis* stereochemistry of **4** was clearly determined by NOE interactions in NOESY experiments (see Supporting Information).



3 4

Scheme 4. The cyclocarbonylation of δ-allenyl imine **3** gave *cis*-fused α-methylene-γ-butyrolactam **4** as the sole product.

In summary, the results presented above show that ruthenium-catalyzed cycloaddition reactions of allenyl aldehydes and ketones with carbon monoxide efficiently afford α-methylene-γ-butyrolactone products. This methodology should find wide applications in the synthesis of natural products that contain the *exo*-methylene-γ-butyrolactone functionality, and further investigations are underway in our laboratory.

Experimental Section

Typical procedure: A stainless-steel autoclave was charged with the allenyl aldehyde **1a** (80 mg, 0.30 mmol), 1,4-dioxane (4 mL), and $[Ru_3(CO)_{12}]$ (2 mg, 1 mol %). The system was flushed three times with CO (20 atm). The autoclave was then pressurized to 20 atm, and the mixture was stirred at 120°C for 12 h. The solution was then cooled and concentrated in vacuo to give a residue, which was subjected to silica-gel column chromatography (EtOAc/hexane 1:2) to yield the cyclized product **2a** (66 mg, 75 %) as a white solid. M.p. 115°C; $R_f = 0.48$ (EtOAc/hexanes 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.45$ (s, 3H), 3.07 (dd, 1H, $J = 5.3$, 11.7 Hz), 3.22 (dd, 1H, $J = 10.0$, 7.6 Hz), 3.37 (dd, 1H, $J = 10.0$, 2.9 Hz), 3.55 (m, 1H), 3.63 (dd, 1H, $J = 0.6$, 11.7 Hz), 4.97 (m, 1H), 5.77 (d, 1H, $J = 2.4$ Hz), 6.35 (d, 1H, $J = 2.4$ Hz), 7.36 (d, 2H, $J = 8.2$ Hz), 7.68 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.6$, 145.2, 137.4, 132.1, 130.6, 128.7, 125.8, 79.7, 55.2, 54.7, 42.6, 22.3; HR-MS: calcd for $C_{14}H_{15}NO_4S$: 293.0776, found: 293.0705.

Typical experimental procedures for the preparation of **1a**, **1c**–**j**, **2a**, and **3**, as well as spectroscopic and analytical data for **1a**–**j**, **2a**, **2c**–**f**, **2i**–**j**, and **4** can be found in the Supporting Information.

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[9] Preparation of allenyl aldehyde **1a**: a) propargyl *p*-tosylamide, $BrCH_2CH_2(OMe)_2$, K_2CO_3, DMF, 100°C, 10 h, 85 %; b) Crabbe reaction: HCHO, CuBr, iPr_2NH, dioxane, reflux, 68 % (see: F. Crabbe, B. Nassim, M-T. Robert-Lopes, *Org. Synth. Coll. Vol. 7* (Ed.: J. P. Freeman), **1990**, pp 276–277); c) trifluoroacetic acid/$CHCl_3$/H_2O (1:2:1), 0°C, 1.5 h, 78 % (see Supporting Information).

Novel Ene-Like Cycloisomerization Reaction of Nitrile Oxides with a Tethered Allyltrimethylsilyl Group**

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The nitrile oxide functional group is a well-known 1,3-dipole and highly useful owing to its high reactivity toward unsaturated C–C bonds to furnish [3+2] cycloadducts.[1] In addition to such a traditional role, we have found that it also functions as an enophile[2] in an intramolecular reaction with an allyltrimethylsilyl group.[3] 5-Methylene-6-(trimethylsilyl)-hexanal oxime (**1a**) was treated with sodium hypochlorite[4] in dichloromethane at 0°C for 2 h to give the product of an ene-like reaction (**2a**) in 82 % yield as a single diastereomer; no

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