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

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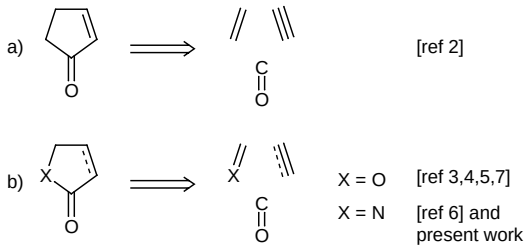
Abstract: The reaction of imines which contain *N*-heterocycles or an ester group with alkenes or alkynes and carbon monoxide in the presence of a catalytic amount of a ruthenium carbonyl results in [2+2+1] cyclocoupling to give γ-butyrolactams in good yields.

Key words: ruthenium carbonyl, [2+2+1] cyclocoupling, cycloaddition, imines, carbon monoxide

A [2+2+1] cycloaddition represents one of the most direct and convenient strategies for the construction of five-membered carbocyclic and heterocyclic carbonyl compounds from simple acyclic building blocks.[1] In particular, the Pauson−Khand reaction, in which an alkyne, an alkene, and carbon monoxide are assembled into cyclopentenones, mediated by $Co_2(CO)_8$ (Scheme 1, a), has been a subject of great interest.[2]

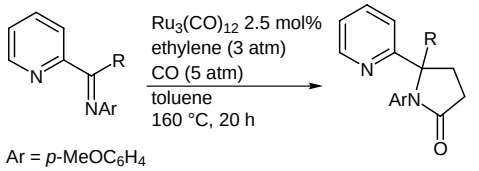


[2+2+1] Cycloaddition approaches to the construction of five-membered carbonyl compounds

Scheme 1

It should be noted, however, that the application of the [2+2+1] cycloaddition to the synthesis of heterocycles, such as γ-lactone and γ-lactam derivatives (Scheme 1, b), has met with limited success. In 1996, Crowe and Buchwald independently reported on the cyclocarbonylation of olefinic aldehydes and ketones leading to bicyclic γ-butyrolactones, mediated[3,4] or catalyzed[4] by a titanocene complex. Subsequently, we reported on the $Ru_3(CO)_{12}$-catalyzed cyclocarbonylation of yne-aldehydes[5] and yne-imines[6] to give bicyclic γ-lactones and γ-lactams, respectively. In these cases, a C=X moiety (X = O, N) and an alkene or alkyne are incorporated in an intramolecular manner. Quite recently, we reported 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.[7] This finding prompted us to examine the possibility of using imines in place of ketones for the synthesis of γ-lactams, which are of importance for use as pharmaceutical agents.[8] Herein, we 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.

We initially examined the reaction of an imine which contained a 2-pyridyl group, since it has been reported that such a group, when adjacent to a carbonyl group has an accelerating effect in the ketone cycloadditions.[7] We were pleased to observe that the reaction proceeded smoothly and efficiently. The reaction of imine **1a** (1 mmol) with ethylene (3 atmospheres) at 5 atmospheres of CO in toluene (3 mL) in the presence of $Ru_3(CO)_{12}$ (0.025 mmol) at 160 °C for 20 hours furnished the expected γ-lactam **2a** in 97% isolated yield, based on **1a** (eq 1). The yields were lower when a *tert*-butyl group (38%), or a benzyl group (57%), or a *p*-toluenesulfonyl group (0%) were used as the *N*-protecting groups of the imine moiety. The introduction of an additional 2-pyridyl group at the imino carbon (i.e. **1b**) resulted in the formation of the corresponding γ-lactam **2b** in quantitative yield. 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 we have found that the addition of $P(4\text{-}CF_3C_6H_4)_3$ enhances the efficiency of the catalysis in the previously reported ketone cyclocou-



Ar = *p*-$MeOC_6H_4$

1 **2**

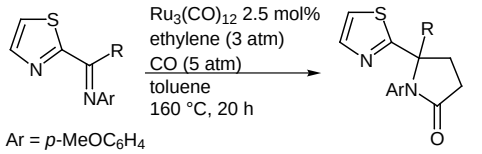
a: R =	H	97 %
b: R =	2-pyridyl	99 %
c: R =	CH_3	78 %
d: R =	Ph	42 % (88 %)*

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

Equation 1

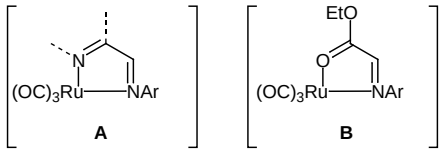
pling,[7] the cyclocoupling of **1d** was conducted in the presence of this phosphine. As predicted, the yield of **2d** was increased to 88%.

Thiazole containing imines **3** were also applicable to the [2+2+1] cycloaddition (eq 2). Since a thiazole ring can be converted into a formyl group without interfering with the functionality of lactam,[9] thiazolyl lactams **4** represent potentially useful intermediates for organic synthesis.

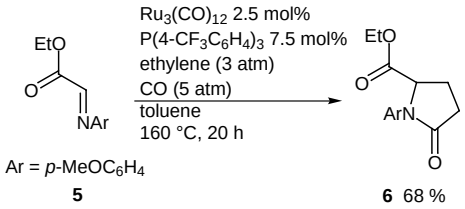


Equation 2

This new cycloaddition presumably proceeds via the initial formation of the σ-N, σ-N chelate ruthenium carbonyl complex **A** or related complexes.[10] This proposal led us 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 afforded the corresponding lactam **6** in good yield (eq 3).

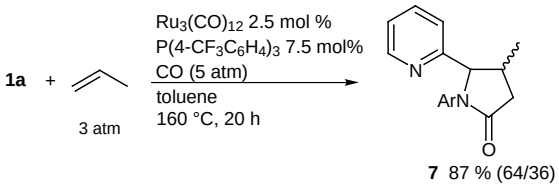


Structural Formula



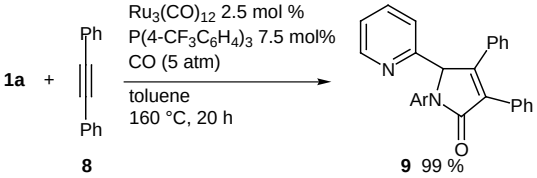
Equation 3

The use of propylene in place of ethylene afforded the methyl-substituted lactam **7** with a high degree of regioselectivity (eq 4).[11]



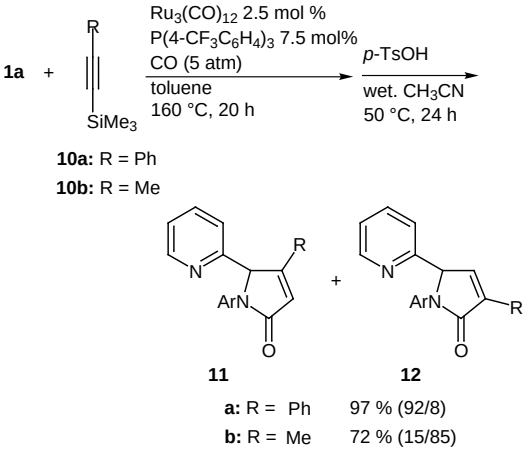
Equation 4

Alkynes were also examined as the two-carbon π-system. Diphenylacetylene is an excellent coupling component for this reaction (eq 5).



Equation 5

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, the yields were determined after the complete desilylation, by treatment of the crude reaction mixture with *p*-TsOH (eq 6). This methodology allows straightforward access to highly substituted γ-lactams.



Equation 6

In conclusion, we demonstrate herein, the $Ru_3(CO)_{12}$-catalyzed intermolecular [2+2+1] cycloaddition of imines, alkenes or alkynes, and CO, which provides a new pathway to the synthesis of functionalized γ-lactam derivatives.[12]

^{1}H NMR and ^{13}C NMR were recorded on a JEOL JMN-270 spectrometer in $CDCl_3$ using TMS as the internal standard. Infrared spectra (IR) were obtained on a Hitachi 270−50 spectrometer. Mass spectra were obtained on a Shimadzu GCMS-QP 5000 instrument with ionization voltages of 70 eV. Column chromatography was performed on Merk Silica Gel 60 (230−400 mesh). $Ru_3(CO)_{12}$ was prepared according to the literature procedure[13] and used after recrystallization from hexane. Imines were prepared by the reaction of the corresponding aldehydes or ketones with *p*-anisidine and used after distillation or recrystallization.

Typical Procedure

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 CO to an additional 5 atm. The autoclave was then immersed in an oil bath at 160 °C. After 20 h it was removed from the oil bath, allowed to cool for approx. 1 h, and 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 (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).

IR (KBr): ν = 1676 cm^{-1}.

^{1}H NMR: δ = 2.09−2.17 (m, 1H), 2.59−2.82 (c, 3H), 3.73 (s, 3H), 5.31 (dd, *J* = 7.8, 4.6 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 7.10−7.18 (c, 2H), 7.33 (d, *J* = 8.9 Hz, 2H), 7.59 (ddd, *J* = 7.8, 7.6, 1.6 Hz, 1H), 8.58 (d, *J* = 3.8 Hz, 1H).

^{13}C NMR: δ = 26.9, 30.9, 55.2, 65.5, 113.9, 120.4, 122.6, 123.8, 131.1, 136.9, 149.8, 156.8, 160.5, 174.8.

MS: *m/z* = 268 (M^+).

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.

1-(4-Methoxyphenyl)-5-phenyl-5-(2-pyridinyl)-2-pyrrolidinone (2d)

White solid; mp 96−97 °C (hexane/EtOAc); R_f 0.31 (EtOAc).

IR (KBr): ν = 1694 cm^{-1}.

^{1}H NMR: δ = 2.50−2.67 (c, 3H), 3.39−3.46 (m, 1H), 3.67 (s, 3H), 6.61 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.06 (d, 1H), 7.16 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.26−7.36 (c, 5H), 7.47 (dd, *J* = 8.3, 7.6 Hz, 1H), 8.65 (d, *J* = 5.0 Hz, 1H).

^{13}C NMR: δ = 30.1, 37.2, 55.2, 76.9, 113.5, 122.5, 124.6, 127.6, 128.1, 128.4, 130.1, 135.7, 142.1, 148.8, 157.5, 160.0, 175.9.

MS: *m/z* = 344 (M^+).

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.

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).

IR (KBr): ν = 1681 cm^{-1}.

^{1}H NMR: δ = 2.24−2.32 (m, 1H), 2.60−2.89 (c, 3H), 3.75 (s, 3H), 5.60 (dd, *J* = 7.8, 4.1 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 3.2 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.70 (d, *J* = 3.2 Hz, 1H).

^{13}C NMR: δ = 27.2, 30.4, 62.0, 114.1, 119.5, 124.5, 130.3, 142.6, 157.3, 171.3, 174.0.

MS: *m/z* = 274 (M^+).

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).

IR (KBr): ν = 1691 cm^{-1}.

^{1}H NMR: δ = 1.77 (s, 3H), 2.25−2.36 (m, 1H), 2.57−2.68 (c, 2H), 2.90−3.04 (m, 1H), 3.73 (s, 3H), 6.78 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 9.1 Hz, 2H), 7.28 (d, *J* = 3.3 Hz, 1H),, 7.76 (d, *J* = 3.3 Hz, 1H).

^{13}C NMR: δ = 26.4, 30.0, 35.8, 55.3, 66.7, 114.1, 119.3, 128.4, 129.4, 142.6, 158.6, 174.1, 175.1.

MS: *m/z* = 288 (M^+).

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.

1-(4-Methoxyphenyl)-5-oxoproline Ethyl Ester (6)

White solid; mp 83−84 °C (hexane/EtOAc); R_f 0.14 (hexane/EtOAc, 1:1).

IR (KBr): ν = 1740, 1693 cm^{-1}.

^{1}H NMR: δ = 1.19 (t, *J* = 7.3 Hz, 3H), 2.10−2.22 (m, 1H), 2.41−2.59 (c, 2H), 2.64−2.78 (m, 1H), 3.78 (s, 3H), 4.15 (q, *J* = 7.3 Hz, 2H), 4.63 (dd, *J* = 8.6, 3.0 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 7.33 (d, *J* = 8.9 Hz, 2H).

^{13}C NMR: δ = 14.0, 23.2, 30.5, 55.4, 61.6, 62.4, 114.2, 124.4, 130.9, 157.5, 171.8, 174.3.

MS: *m/z* = 263 (M^+).

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.

1-(4-methoxyphenyl)-4-methyl-5-(2-pyridinyl)-2-pyrrolidinone (7)

cis-isomer: White solid; mp 140−142 °C (hexane/EtOAc); R_f 0.20 (EtOAc).

IR (KBr): ν = 1682 cm^{-1}.

^{1}H NMR: δ = 0.72 (d, *J* = 6.9 Hz, 3H), 2.48−2.93 (c, 2H), 2.93−3.05 (m, 1H), 3.68 (s, 3H), 5.21 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 8.9 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.16 (td, *J* = 6.3, 0.7 Hz, 1H), 7.37 (d, *J* = 8.9 Hz, 2H), 7.58 (t, *J* = 7.7 Hz, 1H), 8.58−8.60 (m, 1H).

^{13}C NMR: δ = 15.6, 32.0, 38.7, 55.1, 69.4, 113.7, 121.5, 122.4, 123.3, 131.4, 136.2, 149.4, 156.3, 157.4, 174.3.

MS: *m/z* = 282 (M^+).

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).

IR (KBr): ν = 1688 cm^{-1}.

^{1}H NMR: δ = 1.32 (d, *J* = 6.6 Hz, 3H), 2.30 (dd, *J* = 16.5, 6.3 Hz, 1H), 2.42−2.52 (m, 1H), 2.92 (dd, *J* = 16.5, 7.9 Hz, 1H), 3.73 (s, 3H), 4.85 (d, *J* = 5.0 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 7.11−7.18 (c, 2H), 7.29 (d, *J* = 9.1 Hz, 2H), 7.58 (td, *J* = 7.6, 1.6 Hz, 1H), 8.55−8.58 (m, 1H).

^{13}C NMR: δ = 19.5, 35.6, 39.3, 55.3, 72.8, 113.8, 120.6, 122.6, 123.8, 131.1, 136.8, 149.5, 156.6, 159.6, 174.0.

MS: *m/z* = 282 (M^+).

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.

1,5-Dihydro-3,4-diphenyl-1-(4-methoxyphenyl)-5-(2-pyridinyl)-2*H*-pyrrole-2-one (9)
Pale yellow solid; mp 180−182 °C (hexane/EtOAc); R_f 0.17 (hexane/EtOAc, 4:3).

IR (KBr): ν = 1694 cm^{-1}.

^{1}H NMR: δ = 3.72 (s, 3H), 6.26 (s, 1H), 6.80 (d, *J* = 9.2 Hz, 2H), 7.00−7.05 (m, 1H), 7.12−7.23 (c, 6H), 7.30−7.36 (c, 3H), 7.46−7.53 (c, 3H), 7.57 (d, *J* = 9.2 Hz, 2H), 8.38−8.40 (m, 1H).

^{13}C NMR: δ = 55.3, 69.4, 113.9, 121.0, 123.0, 128.2, 128.7, 128.8, 129.7, 130.7, 131.1, 131.8, 132.4, 136.9, 149.0, 151.5, 156.2, 156.4, 169.1.

MS: *m/z* = 418 (M^+).

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.

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).

IR (KBr): ν = 1674 cm^{-1}.

^{1}H NMR: δ = 3.72 (s, 3H), 6.31 (s, 1H), 6.65 (s, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 7.04−7.09 (m, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.28−7.32 (c, 3H), 7.46−7.52 (c, 3H), 7.59−7.63 (m, 2H), 8.48 (d, *J* = 5.0 Hz, 1H).

^{13}C NMR: δ = 55.3, 69.9, 114.0, 120.9, 121.0, 123.2, 123.4, 127.2, 128.6, 130.0, 130.2, 130.6, 137.1, 149.1, 156.2, 156.5, 157.3, 169.9.

MS: *m/z* = 342 (M^+).

1,5-Dihydro-1-(4-methoxyphenyl)-3-phenyl-5-(2-pyridinyl)-2*H*-pyrrole-2-one (12a)
Pale yellow solid; R_f 0.51 (EtOAc).

^{1}H NMR: δ = 3.75 (s, 3H), 5.91 (d, *J* = 2.3 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 1H), 7.18 (ddd, *J* = 7.6, 5.0, 1.0 Hz, 1H), 7.35 (d, *J* = 2.3 Hz, 1H), 7.36−7.45 (c, 3H), 7.52−7.60 (c, 3H), 7.92−7.95 (m, 2H), 8.58 (dd, *J* = 5.0, 1.0 Hz, 1H).

^{13}C NMR: δ = 55.4, 66.8, 114.1, 120.5, 122.6, 123.0, 127.2, 128.4, 128.8, 130.7, 131.0, 135.6, 137.3, 139.3, 149.6, 156.0, 156.4, 169.0.

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