Heterocycles

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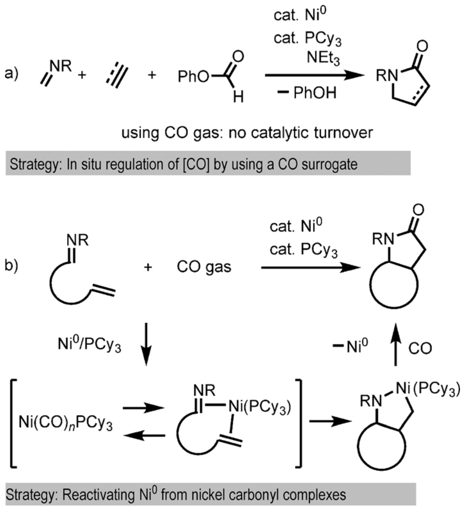
Efficient Synthesis of Polycyclic γ-Lactams by Catalytic Carbonylation of Ene-Imines via Nickelacycle Intermediates

*Yoichi Hoshimoto, Keita Ashida, Yukari Sasaoka, Ravindra Kumar, Ken Kamikawa, Xavier Verdaguer, Antoni Riera, Masato Ohashi, and Sensuke Ogoshi**

Abstract: *The nickel(0)-catalyzed carbonylative cycloaddition of 1,5- and 1,6-ene-imines with carbon monoxide (CO) is reported. Key to this reaction is the efficient regeneration of the catalytically active nickel(0) species from nickel carbonyl complexes such as [Ni(CO)$_3$L]. A variety of tri- and tetracyclic γ-lactams were thus prepared in excellent yields with 100 % atom efficiency. Preliminary results on asymmetric derivatives promise potential in the synthesis of enantioenriched polycyclic γ-lactams.*

The use of gaseous carbon monoxide (CO) in organic synthesis is ideal since it offers a straightforward, cost-economical, atom-efficient, and widely applicable synthetic pathway to a variety of carbonyl compounds.[1] The Pauson–Khand reaction is a representative carbonylation which is mediated or catalyzed by transition metals and yields cyclic ketones.[2] In contrast, the corresponding catalytic carbonylation to prepare lactones and lactams, the so-called hetero-Pauson–Khand reaction, remains limited because of difficulties associated with the repeated generation of key heterometalacycle intermediates under a CO atmosphere.[3] The judicious choice of both the transition-metal catalyst and the reaction conditions is critical for generating these heterometalacycle intermediates in high efficiency under the catalytic carbonylation conditions.

We expect the desirable reactivity from nickel(0) as a catalyst in the hetero-Pauson–Khand reaction, considering that a variety of hetero-nickelacycles were obtained by the oxidative cyclization of unsaturated compounds with nickel(0) species.[4,5] These hetero-nickelacycles afforded the corresponding lactones and lactams in the presence of an excess amount of CO gas. However, the simultaneous formation of nickel(0) carbonyl complexes such as [Ni(CO)$_3$L] was inevitable.[5,6] The formation of a nickel(0) species from nickel(0) carbonyl complexes, which promote the oxidative cyclization, is generally challenging in the presence of CO gas, and the development of a nickel(0)-catalyzed carbonylative cycloaddition with CO gas itself might thus be hampered.[1c,6,7] To overcome this limitation, we employed phenyl formate as a CO source[8] to regulate the concentration of CO, as it has to be sufficiently high for the reaction with the nickelacycle intermediates, yet also sufficiently low to ensure the formation of [Ni(CO)$_3$L]. Thus, the first nickel(0)-catalyzed [2+2+1] carbonylative cycloaddition was developed with imines and either alkynes or norbornene.[9] However, the direct use of CO gas remains unsuccessful because of the rapid formation of [Ni(CO)$_3$PCy$_3$] (Scheme 1 a).



Scheme 1. Nickel(0)-catalyzed carbonylation with a) phenyl formate and b) CO itself.

Direct utilization of gaseous CO leads to the development of an ideal nickel(0)-catalyzed carbonylation system proceeding via nickelacyles. Thus, the system should be constructed to effectively regenerate an active nickel(0) species from nickel(0) carbonyl complexes under a CO atmosphere. Herein, we demonstrate our strategy to utilize gaseous CO itself in a nickel(0)-catalyzed intramolecular [2+2+1] carbonylative cycloaddition of ene-imines, a reaction which affords polycyclic γ-lactams (Scheme 1 b).

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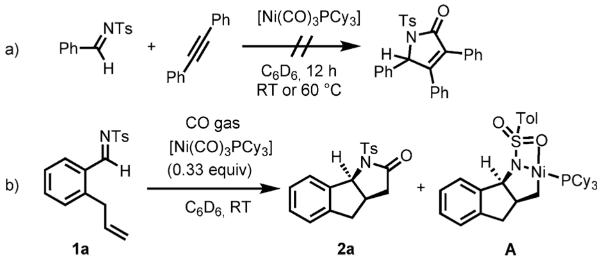
To confirm the reactivity of [Ni(CO)$_3$PCy$_3$] as a nickel(0) source in the carbonylative cycloaddition,[10] the reaction with *N*-benzylidene toluenesulfonamide and diphenylacetylene was examined. The formation of the target lactam was not observed under the reaction conditions shown in Scheme 2a (conversion of [Ni(CO)$_3$PCy$_3$] is less than 1 and 5% at room temperature and 60 °C, respectively).[11] Thus, the 1,5-ene-imine **1a** (Scheme 2b) was examined based on our previous report that 1,5-enals efficiently coordinate to nickel(0) in an η^2-alkene:η^2-aldehyde fashion.[12] Treatment of **1a** with [Ni(CO)$_3$PCy$_3$] (0.33 equiv) resulted in the formation of the tricyclic γ-lactam **2a** in 85% yield as a single diastereomer after 32 hours at room temperature. In the presence of 5.0 atm of CO, this reaction furnished **2a** in 79% yield. Notably, these reactions were conducted in a pressure-tight NMR tube (inner volume: 2.2 mL) without stirring the reaction mixture. These results show that a nickel(0)-catalyzed intramolecular carbonylative cycloaddition of an imine and an alkene with CO gas can be achieved even after the complete transformation of the nickel(0) species into [Ni(CO)$_3$PCy$_3$]. This type of tricyclic γ-lactam is part of the core structure of strigolactam, which exhibited agrochemical activity during the generation of parasitic weed seeds.[13] Strigolactam is useful as a seed germination simulator and plant growth regulator,[13a,b] but straightforward and efficient methods to synthesize strigolactam derivatives remain to be developed. The formation of the hetero-nickelacycle **A** was confirmed by NMR analyses, and indicates that **2a** was generated via **A** (Scheme 2b). The intramolecular coordination of the tosyl (Ts) group to the nickel(II) center is proposed based on our previous report[5] as well as on the results that are discussed later.



CO	*t* [h]	Yield [%] (NMR)	
none	32	85%	9%
5.0 atm	9	79%	10%

Scheme 2. Stoichiometric carbonylative cycloadditions with [Ni(CO)$_3$PCy$_3$]. Ts = 4-toluenesulfonyl.

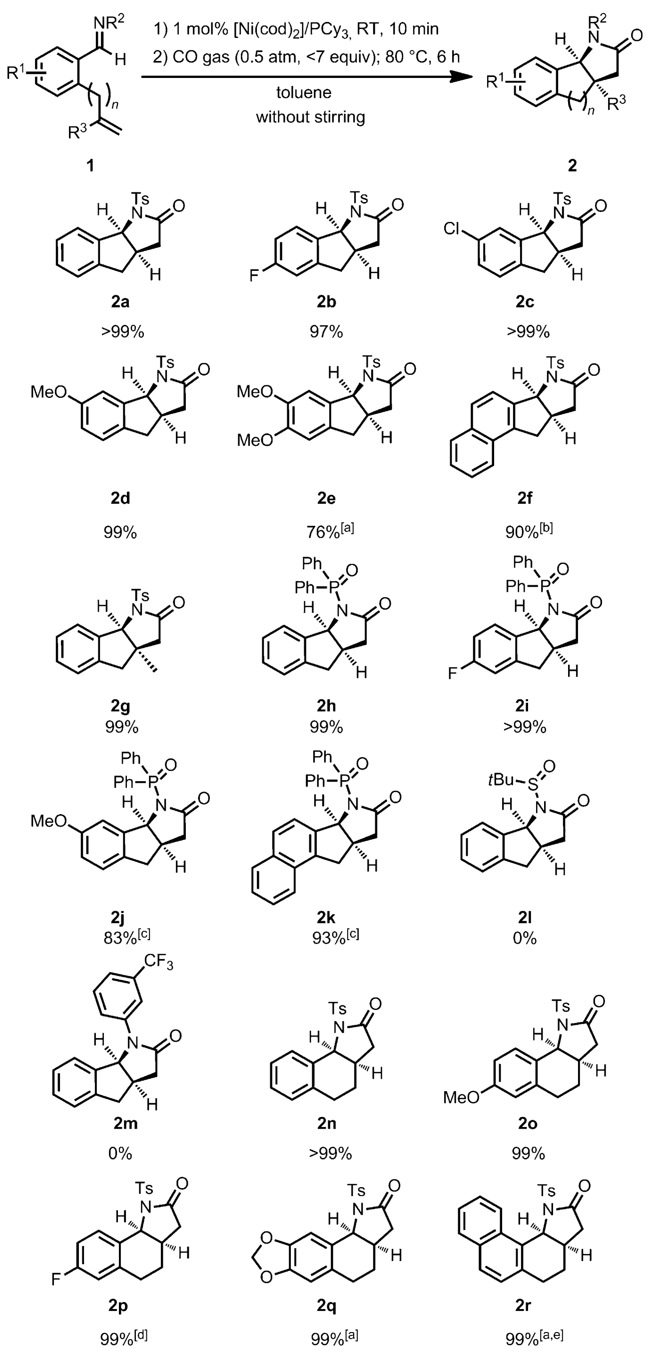
Subsequently, the nickel-catalyzed carbonylative cycloaddition of **1a** was examined under an atmosphere of CO (Scheme 3). A 25 mL autoclave reactor was filled with **1a** (0.4 mmol), [Ni(cod)$_2$/PCy$_3$] (0.04 mmol, 10 mol%), toluene (1.0 mL), and 0.5 atm of CO gas (ca. 0.5 mmol, 1.3 equiv with respect to **1a**) at room temperature to give a red solution. Then, the reaction mixture was allowed to stand for 18 hours without stirring, and furnished **2a** in greater than 99% yield upon isolation (entry 1). At the end of the reaction, the reaction mixture was colorless, thus suggesting the quantitative formation of [Ni(CO)$_3$PCy$_3$].[11] When the reaction was conducted under vigorous stirring (1350 rpm), the color of the reaction mixture changed to colorless within 15 minutes, and **2a** was obtained in only 12% yield. Continuing stirring did not increase the conversion of **1a** at room temperature. Even after stopping stirring, the yield of **2a** did not increase substantially at either room temperature or 80 °C (ca. 5% increase after 4 h). These results indicate that stirring of the reaction mixture leads to a rapid CO saturation, which hampers the progress of the catalytic carbonylation. Therefore, the following experiments were conducted without stirring. Heating at 60 °C for 4 hours gave **2a** in 94% yield (entry 2). Even in the presence of about 12.5 equivalents of CO, **2a** was obtained in greater than 99% yield at 60 °C (entry 3). Moreover, upon decreasing the catalyst loading to 1 mol%, **2a** was still formed in 99% yield after 6 hours at 80 °C (entry 4). A variety of ligands were examined to demonstrate that a combination of [Ni(cod)$_2$] with monodentate tertiary phosphine ligands such as PCy$_3$, PPh$_3$, and P*t*Bu$_3$ affords better results than with P(OPh)$_3$, bidentate phosphines (DCPE, Xantphos), and an N-heterocyclic carbene.[11] Based on these results, the optimized reaction conditions used 1 mol% [Ni(cod)$_2$/PCy$_3$] in toluene at 80 °C with 0.5 atm of CO gas.

$$\mathbf{1a}\ \xrightarrow[\text{toluene, RT, 10 min}]{\text{cat. [Ni(cod)}_2\text{], cat. PCy}_3}\ \xrightarrow{\text{CO gas}}\ \xrightarrow[\text{w/o stirring}]{T,\ t}\ \mathbf{2a}$$

Entry	cat. (mol%)	CO	*T* [°C]	*t* [h]	Yield [%]
1	10	0.5 atm (1.3 equiv)	RT	18	>99 (12)[a]
2	10	0.5 atm (1.3 equiv)	60	4	94
3	10	5.0 atm (12.5 equiv)	60	1.5	>99
4	1	0.5 atm (1.3 equiv)	80	6	>99

Scheme 3. Optimization of the catalytic conditions. Yields of isolated products are given. [a] Yield given by stirring the mixture at 1350 rpm. cod = 1,5-cyclooctadiene.

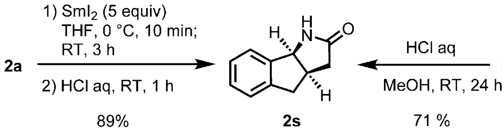
The nickel(0)/PCy$_3$-catalyzed carbonylative cycloaddition of the 1,5-ene-imines **1a**–**g** was carried out under the optimized reaction conditions, thus resulting in the generation of tricyclic the γ-lactams **2a**–**g** in excellent yields (Scheme 4). Notably, the larger-scale synthesis of **2a** (2.0 mmol) was successfully achieved in greater than 99% yield by using a 50 mL autoclave reactor. Fluorine- and chlorine-substituted substrates successfully afforded **2b** and **2c** in 97 and greater than 99% yield, respectively. Introduction of a single methoxy group furnished **2d** in 99% yield, even though the reaction of **1e** having two methoxy groups required 5 mol% catalyst to obtain **2e** in 76% yield. Because of the low solubility of **1f** in toluene, a mixed solvent of THF/toluene (3:2, v/v) was used, and gave the tetracyclic γ-lactam **2f** in 90% yield. A substrate with the methallyl group was efficiently converted into **2g** (99% yield). Replacing the N-Ts with a N-diphenylphosphinic group did not affect the reaction, thus reflecting the ability of the N-diphenylphosphinic group to stabilize the hetero-nickelacycle intermediate



Scheme 4. Nickel(0)-catalyzed [2+2+1] carbonylative cycloaddition with CO gas. General conditions: A multiple autoclave reactor (*V*: 3.7 mL × 18 reactors) was used. **1** (0.20 mmol), [Ni(cod)$_2$]/PCy$_3$ (1 mol%), and toluene (0.50 mL) were mixed in the each reactor, followed by pressurizing CO at 0.5 atm at RT, and heating at 80°C. Yields of isolated products are given. [a] 5 mol% catalyst. [b] THF/toluene (3:2, v/v). [c] THF/toluene (1:1, v/v). [d] 3 mol% catalyst. [e] 24 h.

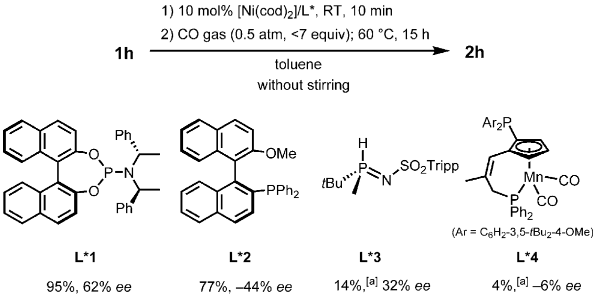
by intramolecular coordination of P=O moiety to the nickel(II) center,[5d,e] which manifested excellent yields of **2h**–**k**. Neither **1l** nor **1m** afforded the target products (**2l** or **2m**), presumably because of the limited ability of the N-substituted groups to stabilize the nickelacycle intermediates. The present catalytic system was also successfully applied to the synthesis of **2n**–**r** with a tetralin core, all of which were isolated in excellent yields. All products were obtained as a single diastereomer. These reactions represent 100% atom efficiency, and thus, generated no waste.

Derivatization of **2a** and **2h** by removal of the N-Ts and the N-diphenylphosphinic groups resulted in the formation of **2s**, which is a key component in the synthesis of strigolactam,[13a] thus demonstrating the utility of the present catalytic system (Scheme 5).



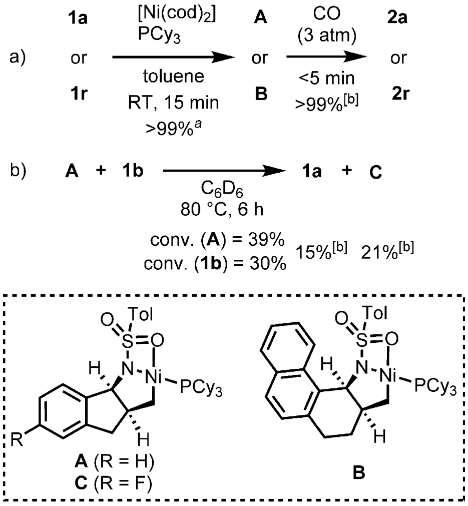
Scheme 5. Synthesis of **2s** from either **2a** or **2h**. Yields of isolated products are given. THF = tetrahydrofuran.

Given the mild reaction conditions in the present carbonylative cyclization, the expansion of the present system to an asymmetric variant was also examined, and preliminary results for the ligand screening with **1h** are shown in Scheme 6. The chiral phosphoramidite ligand[14] **L*1** worked well to give **2h** in 95% yield and 62% *ee*. The chiral MOP ligand[15] **L*2**, P-stereogenic iminophosphorane[16] **L*3**, and the planar-chiral phosphine-olefin ligand[17] **L*4** were also used, as these compounds should act as hemilabile bidentate ligands. However, any improvements on the results were not observed. Nevertheless, the result given by **L*1** shows promising reactivity of nickel(0)/chiral monodentate phosphine systems in this first example of a nickel(0)-catalyzed asymmetric carbonylative cycloaddition of ene-imines and CO. Further studies to attain higher enantioselectivity are currently ongoing.



Scheme 6. Nickel(0)-catalyzed asymmetric [2+2+1] carbonylative cycloaddition with **1h**. General conditions: A multiple autoclave reactor (*V*: 3.7 mL × 18 reactors) was used. **1h** (0.20 mmol), [Ni(cod)$_2$]/**L*1**–**L*4** (0.020 mmol), and toluene (0.50 mL) were mixed in the each reactor, followed by pressurizing CO at 0.5 atm at RT, and heating at 60°C for 15 h. Yields of isolated products are given. The *ee* values were determined by SFC, using a chiral stationary phase. [a] Yield determined by NMR spectroscopy.

As described in Scheme 2b, the nickelacycle **A** was formed by the reaction of **1a** with [Ni(CO)$_3$PCy$_3$], as well as by the reaction with [Ni(cod)$_2$] and PCy$_3$ (Scheme 7a). Similarly, the nickelacycle **B** was synthesized quantitatively



Scheme 7. a) Formation of nickelacycles, and their transformations into **2**. b) Reaction of **A** with **1b**. [a] Yield of isolated product. [b] Yield determined by NMR spectroscopy.

by the stoichiometric reaction of **1r** with [Ni(cod)$_2$] and PCy$_3$. The molecular structure of **B** was unambiguously confirmed by X-ray crystallography (see Figure S4 in the Supporting Information). A distorted square-planar structure was observed, and includes an intramolecular coordination of the Ts group to the nickel(II) center. Treatment of either **A** or **B** with CO gas (3 atm) resulted in the quantitative formation of either **2a** or **2r**. These results support the formation of a hetero-nickelacycle by the oxidative cyclization with an active in situ generated nickel(0) species as the key intermediate in the present catalytic reaction (Scheme 1b). Treatment of **A** with **1b** at 80 °C resulted in the formation of the nickelacycle **C** in 21 % yield with the concomitant production of **1a** (15 %) and an unidentified compound (Scheme 7b).[11] Thus, the retro-oxidative cyclization from **A** to [(η^2:η^2-**1a**)Ni(PCy$_3$)] is possible, even though this process would be unlikely to occur under the present catalytic conditions.

In summary, CO gas itself has been utilized in a nickel(0)-catalyzed [2+2+1] carbonylative cycloaddition reaction with 1,5- and 1,6-ene-imine substrates. A variety of tri- and tetracyclic γ-lactams were prepared in excellent yields with 100 % atom efficiency. The key to this catalytic process is a reaction environment, in which the active nickel(0) species can be reactivated from nickel(0) carbonyl complexes such as [Ni(CO)$_3$L] in the presence of CO gas. Preliminary results on the development of an asymmetric variant showed promising reactivity for a nickel(0)/chiral phosphoramidite ligand system, which yielded enantioenriched γ-lactams. Further expansion of the present approach should provide a straightforward and practical method to prepare valuable heterocyclic compounds.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbonylation · cyclization · enantioselectivity · heterocycles · nickel

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Communications

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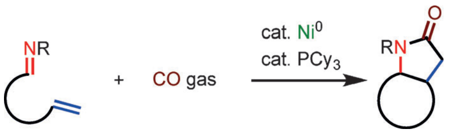
Efficient Synthesis of Polycyclic γ-Lactams by Catalytic Carbonylation of Ene-Imines via Nickelacycle Intermediates



CO gas is employed in a nickel(0)-catalyzed [2+2+1] carbonylative cycloaddition reaction with 1,5- and 1,6-ene-imine substrates. The method affords a variety of tri- and tetracyclic γ-lactams in excellent yields with 100% atom efficiency.