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

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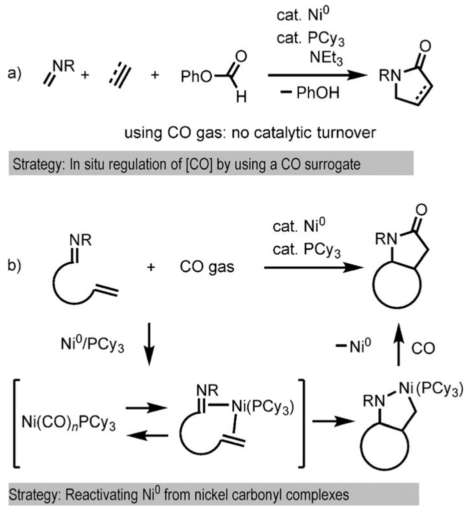
Abstract: *The nickel(0)-catalyzed carbonylative cycloaddition of 1,5- and 1,6-ene-imines with carbon monoxide (CO) is reported. Key to this reaction is the efficient regeneration of the catalytically active nickel(0) species from nickel carbonyl complexes such as* $[Ni(CO)_3L]$*. A variety of tri- and 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 hetero-metalacycle 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 $[Ni(CO)_3L]$ 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 $[Ni(CO)_3L]$. 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 $[Ni(CO)_3PCy_3]$ (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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