JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Nickel(0)-Catalyzed [2 + 2 + 1] Carbonylative Cycloaddition of Imines and Alkynes or Norbornene Leading to γ-Lactams

Yoichi Hoshimoto,[†,‡] Tomoya Ohata,[†] Yukari Sasaoka,[†] Masato Ohashi,[†] and Sensuke Ogoshi*[,†,§]

[†]Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

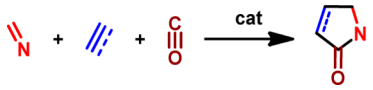
[‡]Frontier Research Base for Global Young Researchers, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

[§]JST, ACT-C, Suita, Osaka 565-0871, Japan

Supporting Information

ABSTRACT: The first nickel(0)-catalyzed [2 + 2 + 1] carbonylative cycloaddition reaction of imines and alkynes or norbornene has been achieved by employing phenyl formate as a CO source. With this method, a variety of *N*-benzenesulfonyl, -tosyl, and -phosphoryl-substituted γ-lactams can be prepared in good to high yields.

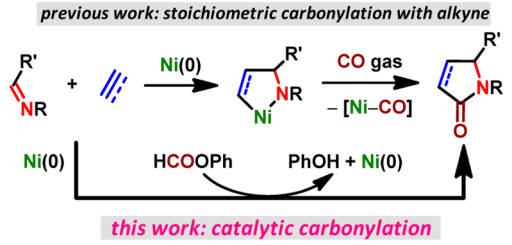
γ-Lactams are an important synthetic intermediate of a variety of natural products and biologically active compounds in drug discovery.[1] One of the straightforward approaches for the construction of the γ-lactam structure is the transition-metal-catalyzed or -mediated carbonylative cycloaddition, which has been referred to as the hetero-Pauson−Khand (or aza-Pauson−Khand) reaction, shown by eq 1:[2]



(1)

The synthesis of γ-lactams, particularly the α,β-unsaturated ones, via transition-metal-catalyzed carbonylative cycloaddition has historically been somewhat limited in the well-established Pauson−Khand reaction.[2,3] This might be due to inadequate development of the procedures needed in order to generate the heterometalacycle compounds that would be a key reaction intermediate in the hetero-Pauson−Khand reaction. For the development of an efficient and a straightforward synthetic method of γ-lactams by carbonylation, it would be critical to employ an appropriate transition metal that can efficiently form a heterometalacycle. Therefore, nickel(0) is a promising candidate since many studies on the formation of heteronickelacycles have been reported.[4,5] We reported the formation of α,β-unsaturated γ-lactams by the reaction of CO gas with heteronickelacycle compounds generated through the oxidative cyclization of an imine and an alkyne on nickel(0) (Scheme 1).[5a,b,d] Thus far, however, the expansion of this carbonylation to the catalytic process has been totally hampered under the CO atmosphere by the formation of catalytically unreactive nickel carbonyl complexes such as $Ni(CO)_3L$.[6] Herein, we report the nickel(0)-catalyzed [2 + 2 + 1] carbonylative cycloaddition of imines and alkynes to give a variety of α,β-unsaturated γ-lactams. Furthermore, norbornene was also utilized instead of alkynes under the optimized conditions, which afforded bicyclic γ-lactams. The key to the present system is the use of phenyl formate as a CO source that enables both carbonylation of the heteronickelacycle intermediate and the resultant regeneration of the nickel(0) catalyst without the formation of $Ni(CO)_3L$ (Scheme 1).

Scheme 1. Nickel(0)-Catalyzed [2 + 2 + 1] Carbonylative Cycloaddition of an Imine and an Alkyne or Alkene

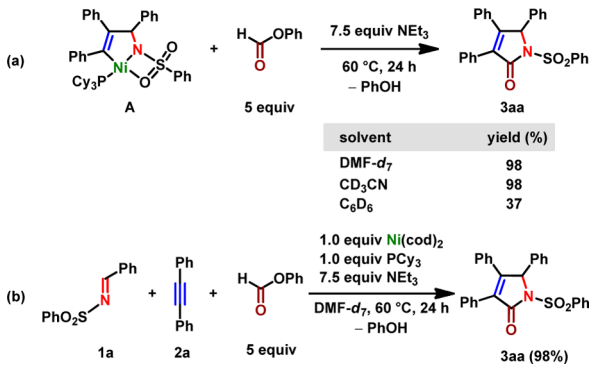


In order to achieve the nickel(0)-catalyzed carbonylative cycloaddition, the concentration of CO should be high enough to react with the heteronickelacycle intermediate, yet simultaneously low enough for the formation of a catalytically unreactive nickel tricarbonyl complex. Among the reported procedures used to generate CO *in situ* from a variety of carbonyl compounds,[7] the use of phenyl formate was interesting, because Tsuji et al.[7c] and Manabe et al.[7b] had already used it to develop a procedure whereby CO could be generated through a reaction with organic/inorganic bases such as NEt_3 or $NaHCO_3$ in the absence of transition metal reagents. First, we examined the reaction of the isolated heteronickelacycle **A**[5a] with phenyl formate (5 equiv) and NEt_3 (7.5 equiv) in DMF-d_7, CD_3CN, or C_6D_6 at 60 °C (Scheme 2a). The transformation of **A** into α,β-unsaturated γ-lactam **3aa** took place almost quantitatively in DMF-d_7 and CD_3CN, both of which were reported as suitable solvents to generate CO from phenyl formate.[7b,c] The formation of PhOH and $Ni(CO)_3(PCy_3)$ was also observed by ^1H and ^{31}P NMR analyses. On the other hand, the reaction in C_6D_6, with an efficiency of CO generation that is only moderate,[7b,c] gave a rather complicated mixture that includes **3aa** (37%), PhOH, and a trace amount of $Ni(CO)_3(PCy_3)$.[8] Next, we examined the carbonylation of **A** generated *in situ* through the oxidative cyclization of *N*-benzylidene benzenesulfonamide (**1a**) and

Received: September 5, 2014
Published: October 29, 2014

dx.doi.org/10.1021/ja509171a | J. Am. Chem. Soc. 2014, 136, 15877−15880

Scheme 2. Reaction of A with Phenyl Formate in the Presence of NEt_3[a]

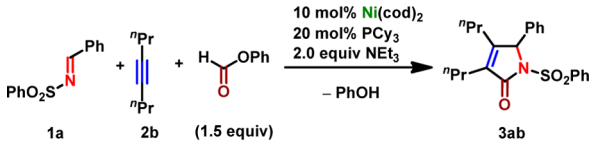


[a]NMR yields determined by using 2-methoxynaphthalene as an internal standard.

diphenylacetylene (**2a**) with $Ni(cod)_2/PCy_3$ (Scheme 2b). Although CD_3CN did not afford a positive result due to the poor solubility of $Ni(cod)_2$, **3aa** was again formed in excellent yield in DMF-d_7. These results showed the possibility that phenyl formate can be used as a CO source in the nickel(0)-catalyzed [2 + 2 + 1] carbonylative cycloaddition of alkynes and imines.

In the presence of 10 mol % $Ni(cod)_2$ and 20 mol % PCy_3, the reaction of **1a**, 4-octyne (**2b**) (1.0 equiv), phenyl formate (1.5 equiv), and NEt_3 (2.0 equiv) was examined in DMF-d_7; however, the desired γ-lactam **3ab** was not obtained at all because of the rapid and quantitative formation of $Ni(CO)_3(PCy_3)$ based on the amount of Ni(0), which was confirmed by ^{31}P NMR (entry 1, Table 1). In order to efficiently prepare **3ab** with the nickel(0) catalyst, the rate of the *in situ* generation of CO should be lowered. Thus, C_6D_6 was employed as a solvent (entry 2). As a result, **3ab** was formed in 44% yield at 60 °C over a period of 48 h.[8] It is noteworthy that PhOH did not react with the heteronickelacycle intermediate while PhOH was incorporated into the product in the reported works.[7b,c] Employing other phosphine ligands such as PPh_3, P(*o*-tol)$_3$, P^{n}Bu$_3$, P^{t}Bu$_3$, and PMe^{t}Bu$_2$, or IPr[9] dramatically lowered the yield of **3ab**.[10] In these reactions, only trace amounts of **1a** and **2b** were consumed. Employing 2 equiv of **2b** gave a better result over a period of 110 h (entry 3). Elevating the reaction temperature promoted the reaction efficiency (entries 4 and 5), and **3ab** was formed in 74% yield for 24 h at 70 °C, which was chosen as our optimal conditions. The reaction also took place to give **3ab** in 63% yield in THF-d_8 at 70 °C (entry 6). DBU, DMAP, and quinuclidine were not suitable as a base under the presented conditions.[10] In entries 3−6, the concomitant formation of hexapropylbenzene and/or 1,2-dihydropyridine was also detected by NMR, the former of which was formed by the nickel-catalyzed trimerization of **2b**[11] and the latter by the [2 + 2 + 2] cycloaddition reaction of **1a** and 2 equiv of **2b**.[5a,b,d]

Table 1. Optimization of Reaction Conditions[a]



entry	**2b** (equiv)	solv	temp (°C)	time (h)	yield (%)
1	1.0	DMF	60	48	–
2	1.0	C_6D_6	60	48	44
3	2.0	C_6D_6	60	110	83
4	2.0	C_6D_6	70	24	74
5	2.0	C_6D_6	80	32	69
6	2.0	THF-d_8	70	24	63

[a]Reaction conditions: **1a** (0.20 mmol), **2b** (0.20−0.40 mmol), phenyl formate (0.30 mmol), NEt_3 (0.40 mmol), $Ni(cod)_2$ (0.020 mmol), PCy_3 (0.040 mmol), solvent (0.50 mL). The reaction was monitored, and the yield of **3ab** was determined by ^1H NMR by using 1,3,5-trioxane or 2-methoxynaphthalene as an internal standard.

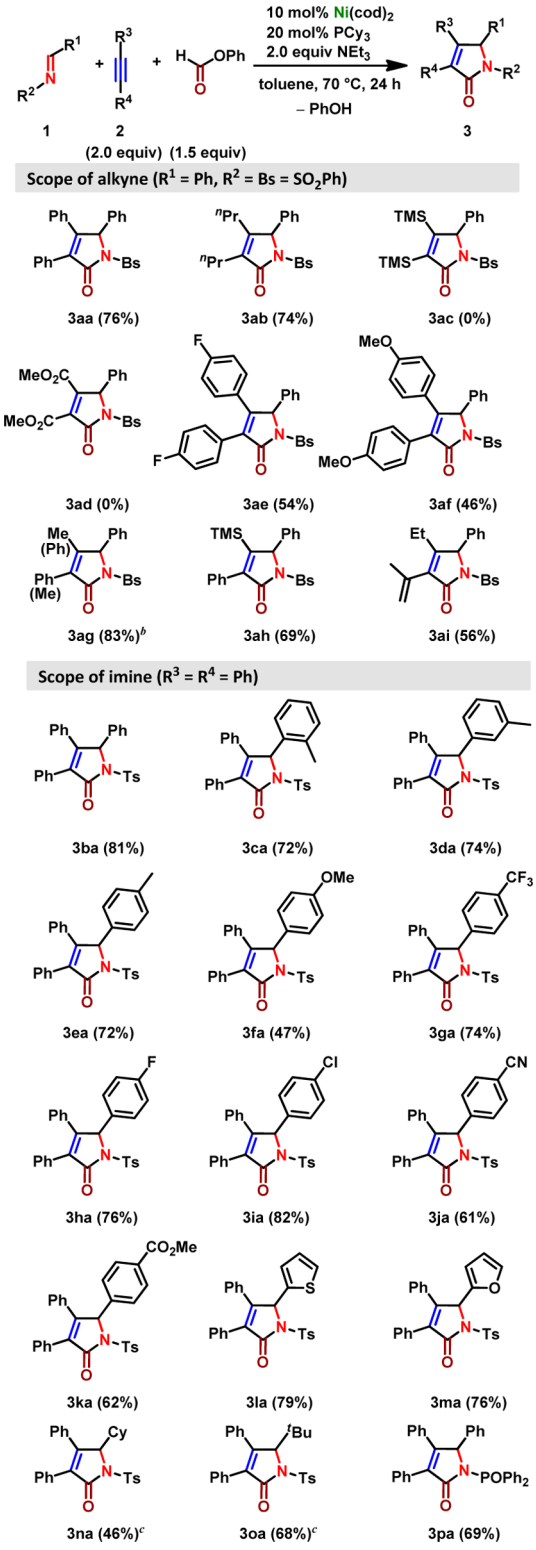
In order to gain insight into the rate of the *in situ* generation of CO, the reaction of phenyl formate with NEt_3 (1.3 equiv) was monitored in C_6D_6 or THF-d_8 by ^1H NMR at 70 °C. The rate of the generation of CO is described as $d[CO]/dt = k[HCOOPh]$ and k was estimated as $2.23(1) \times 10^{-6}$ and $5.00(1) \times 10^{-6}$ s^{-1} in C_6D_6 and THF-d_8, respectively. Thus, both the carbonylation of the heteronickelacycle intermediate and the regeneration of an active nickel(0) species could be compatible under these reaction conditions (entries 4 and 6 in Table 1).[12] In addition, this information would help in the practice and/or reproduction of the present catalytic system.

A variety of α,β-unsaturated γ-lactams (**3**) were prepared by the nickel(0)-catalyzed [2 + 2 + 1] carbonylative cycloaddition of imines (**1**) and alkynes (**2**) with phenyl formate (Table 2). The aryl- and alkyl-substituted symmetrical alkynes (**2a**, **2b**, **2e**, and **2f**) gave the corresponding γ-lactams (**3aa**, **3ab**, **3ae**, and **3af**) in moderate to good isolated yields; however, bis(trimethylsilyl)-acetylene (**2c**) and dimethyl acetylenedicarboxylate (**2d**) did not afford the targets. This is probably due to a difficulty in the simultaneous coordination of the alkyne (**2c** or **2d**) and **1a** to nickel(0).[13] Asymmetric alkyne **2g** gave **3ag** in 83% yield as a mixture of regioisomers with a ratio of 89/11, and the major isomer is shown in Table 2. On the other hand, **3ah** and **3ai** were formed as single regioisomers from **2h** and **2i**, respectively. We reported that oxidative cyclization of (*p*-$CF_3C_6H_4$)N=C(H)Ph and **2i** with a nickel(0) complex proceeded in a highly regioselective manner to give a sole heteronickelacycle with an η^3-butadienyl moiety.[5d] The scope of imines (**1b**−**1p**) was conducted with **2a** under the optimized conditions. A variety of *N*-benzylidene-toluenesulfonamide derivatives (**1b**−**1k**) including chloro-, cyano-, and ester-substituted ones were applicable to the presented catalytic system giving the γ-lactams (**3ba**−**3ka**) in good to high yields while a significant decrease in the yield was found in the case of **1f** having an electron-rich arene ring. The thienyl- and furyl-substituted imines (**1l** and **1m**) also afforded **3la** and **3ma** in 79% and 76% yields, respectively. Employing alkyl-tosylimines was more challenging under the presented conditions; in the presence of 20 mol % $Ni(cod)_2$ and 40 mol % PCy_3, *N*-Cy- and *N*-^{t}Bu-γ-lactams (**3na** and **3oa**) were obtained in 46% and 68% yields, respectively. We reported that an *N*-diphenylphosphinic group on imine can accelerate the formation of a heteronickelacycle as an electron-withdrawing group.[5d] In fact, the catalytic carbonylation proceeded to give **3pa** in good yield (69%).

Next, we employed norbornene instead of alkynes as a preliminary scope of alkene substrates (Table 3). Under the optimized conditions in Table 2, the carbonylative [2 + 2 + 1] cycloaddition of imines (**1a**, **b**, **l**, and **m**) and norbornene (1.5 equiv) occurred to furnish bicyclic γ-lactams (**4**−**7**) in good to high yields.[14] The structure of the products was unambiguously determined by NMR spectroscopy. In addition, the structure of **5** was also confirmed by X-ray analysis, and its crystal structure is

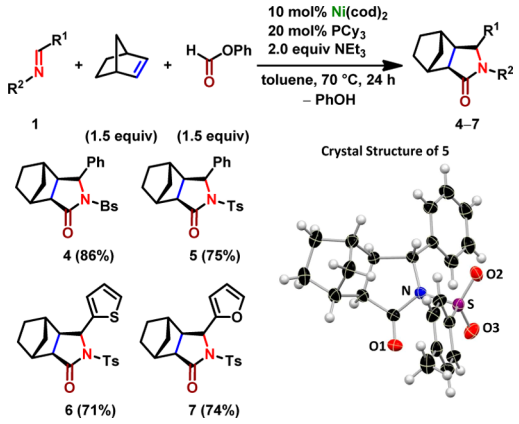
dx.doi.org/10.1021/ja509171a | J. Am. Chem. Soc. 2014, 136, 15877−15880

Table 2. Nickel(0)-Catalyzed Carbonylative [2 + 2 + 1] Cycloaddition of Imines (1) and Alkynes (2) with Phenyl Formate[a]



[a]Reaction conditions: **1** (0.4 mmol), **2** (0.8 mmol), phenyl formate (0.6 mmol), NEt_3 (0.8 mmol), $Ni(cod)_2$ (0.04 mmol), PCy_3 (0.08 mmol), toluene (1 mL). Isolated yields are given. [b]The structure of the minor regioisomer was shown in parentheses. The ratio of regioisomers is 89/11. [c]20 mol % $Ni(cod)_2$/40 mol % PCy_3 was used.

Table 3. Ni(0)-Catalyzed Carbonylative [2 + 2 + 1] Cycloaddition of Imines (1) and Norbornene with Phenyl Formate[a]

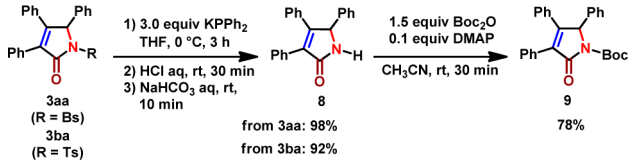


[a]Reaction conditions: **1** (0.40 mmol), norbornene (0.6 mmol), phenyl formate (0.60 mmol), NEt_3 (0.80 mmol), $Ni(cod)_2$ (0.040 mmol), PCy_3 (0.080 mmol), toluene (1.0 mL). Isolated yields are given. The crystal structure of **5** is shown with ellipsoids set at 30% probability.

shown in Table 3. This result is consistent with the result from NMR.

Removal of the *N*-SO_2Ar groups in **3aa** (Ar = Ph) or **3ba** (Ar = *p*-tolyl) via nucleophilic substitution reaction by using a phosphide anion[15] gave a synthetically valuable *N*-protonated *γ*-lactam **8** in excellent yields (Scheme 3). Treatment of **8** with

Scheme 3. Synthesis of *N*-Protonated and *N*-Boc-Substituted *γ*-Lactams 8 and 9[a]



[a]Isolated yields are given.

Boc_2O (1.5 equiv) and DMAP (0.1 equiv) afforded *N*-Boc-*γ*-lactam **9** in 78% yield, the structural motif of which is an important synthetic intermediate.[1p−s,16] Combined with these derivatizations, the present catalytic system would afford a wide range of *γ*-lactams without employing toxic CO gas and expensive transition metals under the harsh reaction conditions, which were often found in the reported works.[3]

In summary, a nickel(0)-catalyzed [2 + 2 + 1] carbonylative cycloaddition of imines and alkynes or norbornene was achieved for the first time. A variety of *γ*-lactams with *N*-benzenesulfonyl and tosyl groups were prepared in good to high yields by employing phenyl formate as a CO source. In addition, these *N*-substituent groups were easily removed, which would give diversity for an accessible *γ*-lactam. A key to the success of this method was to control the concentration of CO *in situ*; i.e., the concentration had to be high enough to react with the heteronickelacycle intermediate, yet simultaneously low enough not to quench the catalytic activity of the nickel(0) complex. The present methodology will contribute to the development of a straightforward, simple, and versatile synthetic method to give valuable heterocyclic compounds.

dx.doi.org/10.1021/ja509171a | J. Am. Chem. Soc. 2014, 136, 15877−15880

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

ogoshi@chem.eng.osaka-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Scientific Research (A) (21245028), Scientific Research on Innovative Area "Molecular Activation Directed toward Straightforward Synthesis" (23105546), Grants-in-Aid for Young Scientists (A) (25708018) from MEXT, ACT-C from JST, and the Asahi Glass Foundation. Y.H. acknowledges support from the Frontier Research Base for Global Young Researchers, Osaka University, on the program of MEXT.

■ REFERENCES

(1) Book: (a) Crawley, M. L.; Trost, B. M. *Applications of transition metal catalysis in drug discovery and development: an industrial perspective*; John Wiley & Sons: Hoboken, NJ, 2012. Review: (b) Gamzu, E. R.; Hoover, T. M.; Gracon, S. I. *Drug Dev. Res.* **1989**, *18*, 177. For selected examples, see: (c) Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1073. (d) Masse, C. E.; Morgan, A. J.; Adams, J.; Panek, J. S. *Eur. J. Org. Chem.* **2000**, 2513. (e) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355. (f) Guntern, A.; Ioset, J. R.; Queiroz, E. F.; Sándor, P.; Foggin, C. M.; Hostettmann, K. *J. Nat. Prod.* **2003**, *66*, 1550. (g) Stuk, T. L.; Assink, B. K.; Bates, R. C., Jr.; Erdman, D. T.; Fedij, V.; Jennings, S. M.; Lassig, J. A.; Smith, R. J.; Smith, T. L. *Org. Process Res. Dev.* **2003**, *7*, 851. (h) Manam, R. R.; Teisan, S.; White, D. J.; Nicholson, B.; Grodberg, J.; Neuteboom, S. T. C.; Lam, K. S.; Mosca, D. A.; Lloyd, G. K.; Potts, B. C. M. *J. Nat. Prod.* **2005**, *68*, 240. (i) Okazaki, Y.; Ishizuka, A.; Ishihara, A.; Nishioka, T.; Iwamura, H. *J. Org. Chem.* **2007**, *72*, 3830. (j) Ng, P. Y.; Tang, Y.; Knosp, W. M.; Stadler, H. S.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5352. (k) Fenical, W.; Jensen, P. R.; Palladino, M. A.; Lam, K. S.; Lloyd, G. K.; Potts, B. C. *Bioorg. Med. Chem.* **2009**, *17*, 2175. (l) Tan, D. Q.; Atherton, A. L.; Smith, A. J.; Soldi, C.; Hurley, K. A.; Fettinger, J. C.; Shaw, J. T. *ACS Comb. Sci.* **2012**, *14*, 218. For selected examples on α,β-unsaturated γ-lactams, see: (m) Uno, H.; Baldwin, J. E.; Russell, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2139. (n) Chang, T. T.; More, S. V.; Lu, I.-H.; Hsu, J.-C.; Chen, T.-J.; Jen, Y. C.; Lu, C.-K.; Li, W.-S. *Eur. J. Med. Chem.* **2011**, *46*, 3810. (o) Li, S.; Qiu, S.; Yao, P.; Sun, H.; Fong, H. H. S.; Zhang, H. *Evid. Based Complement. Alternat. Med.* **2013**, No. 432829. For examples of *N*-Boc-substituted α,β-unsaturated γ-lactams as synthetic intermediates, see: (p) Jayasundera, K. P.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1998**, *27*, 1227. (q) Farran, D.; Parrot, I.; Martinez, J.; Dewynter, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 7488. (r) Storgaard, M.; Dörwald, F. Z.; Peschke, B.; Tanner, D. *J. Org. Chem.* **2009**, *74*, 5032. (s) Chaubet, G.; Coursindel, T.; Morelli, X.; Betzi, S.; Roche, P.; Guari, Y.; Lebrun, A.; Toupet, L.; Collette, Y.; Parrot, I.; Martinez, J. *Org. Biomol. Chem.* **2013**, *11*, 4719.

(2) Book: (a) Torres, R. R. *The Pauson–Khand Reaction: Scope, Variations and Applications*; John Wiley & Sons: U.K., 2012. For recent reviews, see: (b) Park, J. H.; Chang, K.-M.; Chung, Y. K. *Coord. Chem. Rev.* **2009**, *253*, 2461. (c) Omae, I. *Cood. Chem. Rev.* **2011**, *255*, 139.

(3) For a recent review on the hetero-Pauson–Khand reaction, see: (a) Chatani, N. *Chem. Rec.* **2008**, *8*, 201. For selected recent reports on the synthesis of lactams via carbonylative cycloaddition reaction, see: (b) Wu, X.-F.; Neumann, H. *ChemCatChem* **2012**, *4*, 447. (c) Iwata, T.; Inagaki, F.; Mukai, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 11138 and references therein. (d) Fukuyama, T.; Nakashima, N.; Okada, T.; Ryu, I. *J. Am. Chem. Soc.* **2013**, *135*, 1006 and references therein.

(4) For reviews on the nickel-catalyzed reactions via (hetero) nickelacycle intermediate, see: (a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (b) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441. (c) Ng, S.-S.; Ho, C.-Y.; Schleicher, K. D.; Jamison, T. F. *Pure Appl. Chem.* **2008**, *80*, 929. (d) Tanaka, K.; Tajima, Y. *Eur. J. Org. Chem.* **2012**, 3715. (e) Montgomery, J. Organonickel Chemistry. In *Organometallics in Synthesis: Fourth Manual*; Lipshutz, B. H., Ed.; Wiley: Hoboken, N.J., 2013; pp 319–428. (f) Ogoshi, S. *Yuki Gosei Kagaku Kyokaishi* **2013**, *71*, 14. (g) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299.

(5) For our recent works on heteronickelacycle chemistry, see: (a) Ogoshi, S.; Ikeda, H.; Kurosawa, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4930. (b) Ogoshi, S.; Ikeda, H.; Kurosawa, H. *Pure Appl. Chem.* **2008**, *80*, 1115. (c) Ohashi, M.; Kishizaki, O.; Ikeda, H.; Ogoshi, S. *J. Am. Chem. Soc.* **2009**, *131*, 9160. (d) Hoshimoto, Y.; Ohata, T.; Ohashi, M.; Ogoshi, S. *Chem.—Eur. J.* **2014**, *20*, 4105.

(6) Buchwald et al. reported a nickel(0)-catalyzed hetro-Pauson–Khand type reaction of enynes and isocyanides; see: Zhang, M.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 4498.

(7) Review: (a) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580. For selected recent reports on the transition-metal-free method to generate CO from carboxylic acid derivatives, see: (b) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2012**, *14*, 3100. (c) Fujihara, T.; Hosoki, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *Chem. Commun.* **2012**, *48*, 8012. (d) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2013**, *15*, 5370. (e) Ueda, T.; Konishi, H.; Manabe, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 8611.

(8) The formation of an unidentified compound was observed by ^{31}P NMR (δ 41.8) in the stoichiometric condition in C_6D_6 (Scheme 2a). However, under the catalytic conditions shown in entry 2 of Table 1, the formation of this compound was not observed.

(9) IPr is 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene. IPr was found to react with phenyl formate as a base. Thus, rapid formation of $Ni(CO)_3(IPr)$ was observed in the presence of IPr as a ligand.

(10) See Supporting Information for experimental details and optimization of conditions.

(11) Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Justus Liebigs Ann. Chem.* **1948**, *560*, 1.

(12) The rate of the *in situ* generation of CO in DMF was reported as $k = 1.6 \times 10^{-4}$ s^{-1} at 80 °C; see ref 7d.

(13) The simultaneous coordination of two π-components to nickel(0) would be a minimum requirement to form a nickelacycle. In the case of **2c**, the coordination of **2c** to nickel was hampered under these conditions. In the case of **2d**, the facile cyclotrimerization reaction of **2d** proceeded. See ref 5a for details.

(14) The structural motif of the bicyclic γ-lactams was reported to have antipsychotic activity; see: (a) Ishizumi, K.; Kojima, A.; Antoku, F.; Saji, I.; Yoshigi, M. *Chem. Pharm. Bull.* **1995**, *43*, 2139. See also the following reports about the synthesis of bicyclic γ-lactams: (b) Matsuki, K.; Inoue, H.; Ishida, A.; Takeda, M.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull.* **1994**, *42*, 9. (c) Takebayashi, S.; John, J. M.; Bergens, S. H. *J. Am. Chem. Soc.* **2010**, *132*, 12832.

(15) Yoshida, S.; Igawa, K.; Tomooka, K. *J. Am. Chem. Soc.* **2012**, *134*, 19358.

(16) For examples, see: (a) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168. (c) Zanardi, F.; Battistini, L.; Nespi, M.; Rassu, G.; Spanu, P.; Cornia, M.; Casiraghi, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1167. (d) Rassu, G.; Pinna, L.; Spanu, P.; Zanardi, F.; Battistini, L.; Casiraghi, G. *J. Org. Chem.* **1997**, *62*, 4513. (e) Planas, L.; Pérard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087. (f) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Zanardi, F.; Casiraghi, G. *Tetrahedron Lett.* **2009**, *50*, 3428.