Nickel-Catalyzed Cycloaddition

DOI: 10.1002/ange.200700688

Formation of an Aza-nickelacycle by Reaction of an Imine and an Alkyne with Nickel(0): Oxidative Cyclization, Insertion, and Reductive Elimination**

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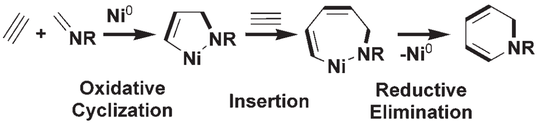
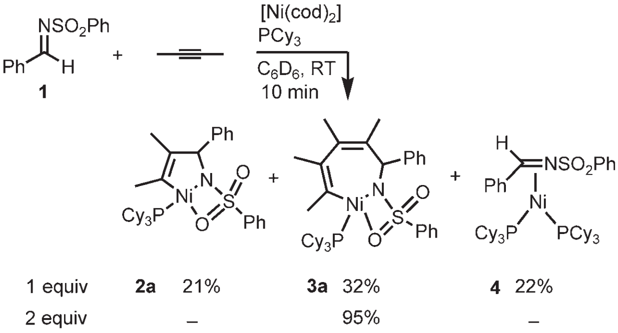
In memory Yoshihiko Ito

Oxidative cyclization with transition metals is an efficient method for the simultaneous construction of one carbon–carbon and two carbon–metal bonds, and a variety of catalytic reactions involving the oxidative cyclization of two π components with a transition metal have been reported to date. For example, a hetero-nickelacycle derived from an alkyne and an aldehyde, ketone, or imine is known to play an important role as a key intermediate in two types of catalytic reactions,[1–3] namely the formation of allyl alcohols or allyl amines by reaction of a hetero-nickelacycle with alkylmetal compounds or reducing reagents[1,2] and the formation of a pyran by reductive elimination from seven-membered oxa-nickelacycles generated by the insertion of a second alkyne into a nickeladihydrofuran.[3] A 1,2-dihydropyridine is also a possible product of the [2+2+2] cycloaddition of two alkynes and an imine (Scheme 1), although no such reaction has yet been reported. The formation of aza-nickelacycles might prove to be key to the success of this reaction, although thus far only two nickelacycles containing a nitrogen atom have been reported.[4,5] Recently we reported the formation of oxa-nickelacycles by the oxidative cyclization of aldehydes or ketones and an unsaturated carbon–carbon bond with nickel(0),[6] therefore the formation of an aza-nickelacycle from an imine and an alkyne seemed to be the next logical step. Herein we report the formation of a five-membered aza-nickelacycle—a nickelapyrroline—by the oxidative cyclization of an imine and an alkyne with nickel(0). The insertion of a second alkyne into this ring to give a seven-membered aza-nickelacycle—a nickeladihydroazepine—followed by reductive elimination to give a 1,2-dihydropyridine, as well as the catalytic application of these reactions, are also discussed.



Scheme 1. A possible reaction between an alkyne and an imine with nickel(0).

The reaction of *N*-(benzenesulfonyl)benzaldimine (**1**) with 2-butyne (1 equiv) in the presence of [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) and PCy$_3$ (Cy = cyclohexyl) at room temperature for 10 min gives an inseparable mixture of a nickelapyrroline (**2a**), a nickeladihydroazepine (**3a**), and an η^2-iminenickel complex (**4**; Scheme 2). The addition of an additional equivalent of 2-butyne (total 2 equiv) to this reaction mixture generates **3a**, the molecular structure of which was determined by X-ray crystallography (Figure 1), as the sole product in 95 % yield.[7] The coordination of oxygen



Scheme 2. Reaction of 2-butyne (1 or 2 equiv) and **1** with nickel(0).

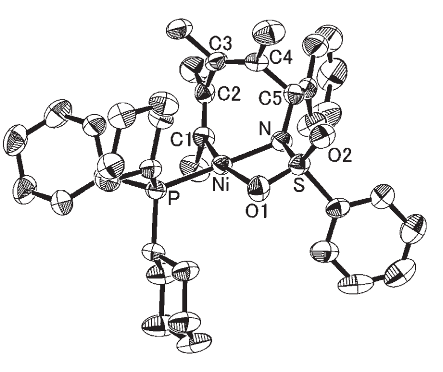


Figure 1. Molecular structure of **3a**.

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[**] Partial support of this work by the ENEOS Hydrogen Trust Fund and by a Grant-in-Aid for Scientific Research on Priority Area “Advanced Molecular Transformations of Carbon Resources” from the Ministry of Education, Culture, Sports, Science and Technology, Japan is gratefully acknowledged.

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

to nickel might play an important role in the isolation of **3a** as a stable square-planar complex.[8] The molecular structure of **4**, in which η^2-coordination of the carbon–nitrogen double bond is observed, was also confirmed by X-ray crystallography (Figure 2).[9] As mentioned above, isolation of the five-membered aza-nickelacycle **2a** was not possible due to a very rapid second insertion of 2-butyne to give **3a**, therefore a bulkier alkyne was examined as a carbon-carbon triple bond component to suppress the formation of the seven-membered aza-nickelacycle.

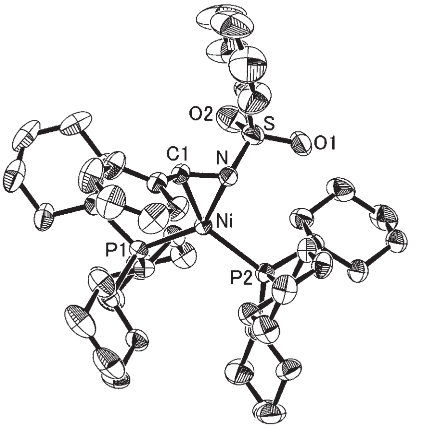
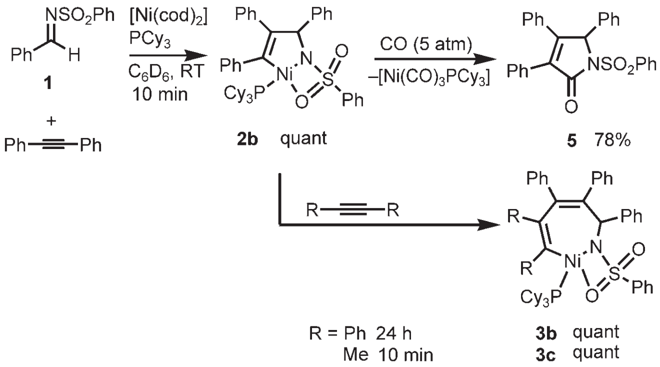
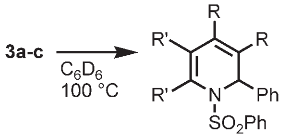


Figure 2. Molecular structure of **4**.

The reaction of **1** with diphenylacetylene in the presence of [Ni(cod)$_2$] and PCy$_3$ at room temperature proceeded to give the corresponding nickelapyrroline (**2b**) quantitatively (Scheme 3). Elemental analysis of **2b** confirmed the expected composition. The coordination of oxygen to nickel is inferred by analogy with the molecular structure of **3a**. The reaction of **4** with diphenylacetylene also gave **2b** quantitatively along with the dissociation of one equivalent of PCy$_3$. The treatment of **2b** with carbon monoxide (5 atm) led to the formation of the corresponding γ-lactam (**5**), which is also consistent with the structure of **2b** depicted in Scheme 3. The insertion of diphenylacetylene or 2-butyne into **2b** proceeded at room temperature to give the corresponding nickeladihydroazepine (**3b** or **3c**, respectively). The insertion of 2-butyne proceeded much faster than that of diphenylacetylene, which might explain why **2a** is obtained as a mixture with **3a**. Heating the nickeladihydroazepines **3a–c** at 100 °C promoted the reductive elimination to give 1,2-dihydropyridine compounds **6a–c**, respectively (Scheme 4). The formation of a 1,2-dihydropyridine by reductive elimination suggested that the development of a nickel-catalyzed [2+2+2] cycloaddition reaction of two alkynes and an imine might be possible.



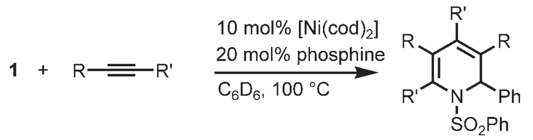
Scheme 3. Reaction of diphenylacetylene and **1** with nickel(0) followed by addition of another alkyne (same or different) or CO.



R, R' = Me	5 h	**6a**	72%
R, R' = Ph	27 h	**6b**	28%
R = Ph, R' = Me	3 h	**6c**	68%

Scheme 4. Reductive elimination from **3**.

The intermolecular [2+2+2] cycloaddition of two alkynes and **1** in the presence of 10 mol % of [Ni(cod)$_2$] and PMe*t*Bu$_2$ at 100 °C gave the expected 1,2-dihydropyridine (**6a**) in 87 % yield (Scheme 5). 3-Hexyne and trimethylsilylacetylene also gave the corresponding 1,2-dihydropyridines (**6d** and **6e**, respectively). The reaction proceeded catalytically also in the presence of PCy$_3$, although PMe*t*Bu$_2$ gave better results. The less bulkier or less basic phosphines P*n*Bu$_3$ or P(*o*-tol)$_3$ (*o*-tol = *ortho*-tolyl) were not efficient for this reaction. Although the complex Ni^0-NHC (NHC = N-heterocyclic carbene) was also found to be a good catalyst for the [2+2+2] cycloaddition of two alkynes and a ketone or an aldehyde, this reaction did not proceed in the presence of 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene. To the best of our knowledge, only one example of the catalytic formation of a 1,2-dihydropyridine from two alkynes and an imine has been reported, however, in this example the 1,2-dihydropyridine was an undesired product and was obtained as a mixture.[10] Thus, our nickel-catalyzed reaction might be very attractive as a new method for the preparation of 1,2-dihydropyridines. The reaction might proceed as follows: oxidative cyclization with nickel(0), which gives rise to a nickelapyrroline, is followed by the insertion of a second alkyne to form a nickeladihydroazepine. Reductive elimina-



R, R' = Me	PMe*t*Bu$_2$	48 h	**6a**	87%
	PCy$_3$	24 h		64%
	P*n*Bu$_3$	24 h		17%
	P(*o*-tol)$_3$	29 h		6%
R, R' = Et	PMe*t*Bu$_2$	70 h	**6d**	64%
	PCy$_3$	24 h		26%
R = TMS, R' = H	PMe*t*Bu$_2$	18 h	**6e**	58%

Scheme 5. The nickel(0)-catalyzed reaction. TMS = trimethylsilyl.

tion from this nickeladihydroazepine gives a 1,2-dihydropyridine and regenerates nickel(0). The previously reported nickel-catalyzed [2+2+2] cycloaddition of alkynes with a ketone might also proceed by a similar reaction path.[3]

In conclusion, we have demonstrated that the oxidative cyclization of an imine and an alkyne with nickel(0) gives a nickelapyrroline and that subsequent insertion of a second alkyne gives a nickeladihydroazepine. This complex then undergoes reductive elimination to give a 1,2-dihydropyridine. We have developed this sequential reaction process into a nickel-catalyzed [2+2+2] cycloaddition of two alkynes and an imine that yields 1,2-dihydropyridines. This is the first example of the selective formation of a 1,2-dihydropyridine in the presence of a transition-metal catalyst. Further studies on the oxidative cyclization of an imine and unsaturated carbon–carbon bonds with nickel(0), and on the application of this process to other catalytic reactions are in progress in our group.

Experimental Section

Synthesis of **3a**: 2-Butyne (276.4 mg, 400 μL, 5.11 mmol) was added to a solution of [Ni(cod)$_2$] (274.8 mg, 1.00 mmol), PCy$_3$ (288.4 mg, 1.00 mmol), and **1** (244.0 mg, 0.99 mmol) in 5 mL of toluene at room temperature. The reaction mixture was stirred for 1 h, whereupon the color changed from red to dark red. The reaction mixture was then concentrated in vacuo to give a red solid. This solid was washed with hexane to give 467.5 mg of complex **3a** (orange solid) in 68 % yield. ^{1}H NMR (400 MHz, C$_6$D$_6$): $\delta = 0.87$–1.96 (m, 39 H; Cy and signals for NiC(Me)=C(Me)C(*Me*)= (1.09, 3 H), NiC(*Me*)= (1.69, 3 H), and NiC(Me)=C(*Me*) (1.95, 3 H)), 2.38 (br. s, 3 H, Cy), 2.55 (br. s, 3 H, NiC(Me)=C(Me)C(Me) = C(*Me*)), 5.07 (s, 1 H, C*H*Ph), 6.97–7.02 (m, 4 H), 7.11 (t, $J_{\rm H,H} = 7.6$ Hz, 2 H), 7.31 (br. s, 2 H), 8.29 ppm (br. d, $J_{\rm H,H} = 6.5$ Hz, 2 H). ^{13}C NMR (100 MHz, C$_6$D$_6$): $\delta = 15.6$ (s), 18.2 (s), 22.2 (s), 24.8 (d, $J_{\rm C,P} = 6.1$ Hz; Cy), 27.2 (s), 28.4 (d, $J_{\rm C,P} = 9.9$ Hz; Cy), 28.5 (d, $J_{\rm C,P} = 9.9$ Hz; Cy), 30.2 (s), 31.0 (s), 33.6 (d, $J_{\rm C,P} = 17.5$ Hz; Cy), 60.2 (s, *C*HPh), 125.5 (s), 126.5 (s), 127.5 (s), 127.7 (s), 128.3 (s), 128.5 (s), 128.7 (s), 129.1(s), 131.3 (s), 135.5 (s), 135.9 (s), 146.0 ppm (s). ^{31}P NMR (109.4 MHz, C$_6$D$_6$): $\delta = 31.3$ ppm (s). Elemental analysis (%) calcd for C$_{39}$H$_{56}$NNiO$_2$PS: C 67.63, H 8.15, N 2.02; found: C 67.36, H 8.21, N 2.12.

Received: February 14, 2007
Published online: May 24, 2007

Keywords: alkynes · cycloaddition · imines · metallacycles · nickel

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[1] Alkyne with an aldehyde/ketone: a) E. Oblinger, J. Montgomery, *J. Am. Chem. Soc.* **1997**, *119*, 9065; b) W.-S. Huang, J. Chan, T. F. Jamison, *Org. Lett.* **2000**, *2*, 4221; c) Y. Ni, K. K. D. Amarasinghe, J. Montgomery, *Org. Lett.* **2002**, *4*, 1743; d) K. M. Miller, W.-S. Huang, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 3442; e) G. M. Mahandru, G. Liu, J. Montgomery, *J. Am. Chem. Soc.* **2004**, *126*, 3698; f) K. M. Miller, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 15342; g) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2005**, *127*, 6932.

[2] Alkyne with an imine: a) S. J. Patel, T. F. Jamison, *Angew. Chem.* **2003**, *115*, 1402; *Angew. Chem. Int. Ed.* **2003**, *42*, 1364; b) S. J. Patel, T. F. Jamison, *Angew. Chem.* **2004**, *116*, 4031; *Angew. Chem. Int. Ed.* **2004**, *43*, 3941.

[3] Two alkynes with an aldehyde/ketone: a) T. Tsuda, T. Kiyoi, T. Miyane, T. Saegusa, *J. Am. Chem. Soc.* **1988**, *110*, 8570; b) T. N. Tekevac, J. Louie, *Org. Lett.* **2005**, *7*, 4037; c) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2006**, *128*, 2166.

[4] Nickelalactams formed from an alkyne, an isocyanate, and nickel(0): a) H. Hoberg, B. W. Oster, *J. Organomet. Chem.* **1982**, *234*, C35; b) H. Hoberg, B. W. Oster, *J. Organomet. Chem.* **1983**, *252*, 359.

[5] A nickel-catalyzed reaction of two alkynes and a carbodiimide to give a 2-imino-1,2-dihydropyridine has been reported: H. Hoberg, G. Burkhart, *Synthesis* **1979**, 525.

[6] a) S. Ogoshi, M.-a. Oka, H. Kurosawa, *J. Am. Chem. Soc.* **2004**, *126*, 11082; b) S. Ogoshi, M. Ueta, T. Arai, H. Kurosawa, *J. Am. Chem. Soc.* **2005**, *127*, 12810; c) S. Ogoshi, K.-i. Tonomori, M.-a. Oka, H. Kurosawa, *J. Am. Chem. Soc.* **2006**, *128*, 7077; d) S. Ogoshi, M. Nagata, H. Kurosawa, *J. Am. Chem. Soc.* **2006**, *128*, 5350.

[7] Crystal data for **3a**: C$_{39}$H$_{56}$NNiO$_2$PS: $M = 692.61$, brown, monoclinic, $P2_1/n$ (no. 14), $a = 10.1244(3)$, $b = 21.5519(6)$, $c = 17.5944(5)$ Å, $\beta = 102.400(1)$°, $V = 3749.5(2)$ Å^3, $Z = 4$, $\rho_{\rm calcd} = 1.227$ g cm^{-3}, $T = 0$ °C, R ($R_{\rm w}$) = 0.054 (0.069).

[8] K.-i. Fujita, M. Yamashita, F. Puschmann, M. M. Alvarez-Falcon, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 9044.

[9] Crystal data for **4**: C$_{49}$H$_{77}$NNiO$_2$P$_2$S, $M = 864.86$, brown, monoclinic, $P2_1/n$ (no. 14), $a = 10.8288(3)$, $b = 17.5527(4)$, $c = 25.9319(8)$ Å, $\beta = 99.124(1)$°, $V = 4866.6(2)$ Å^3, $Z = 4$, $\rho_{\rm calcd} = 1.180$ g cm^{-3}, $T = 0$ °C, R ($R_{\rm w}$) = 0.060 (0.097). CCDC 637051 (**3a**) and CCDC 637052 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] The catalytic formation of a 1,2-dihydropyridine from two alkynes and an imine has been reported: P. A. Wender, T. M. Pedersen, M. J. C. Scanio, *J. Am. Chem. Soc.* **2002**, *124*, 15154.