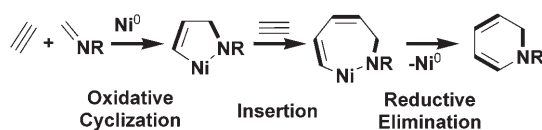


Formation of an Aza-nickelacycle by Reaction of an Imine and an Alkyne with Nickel(0): Oxidative Cyclization, Insertion, and Reductive Elimination**

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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

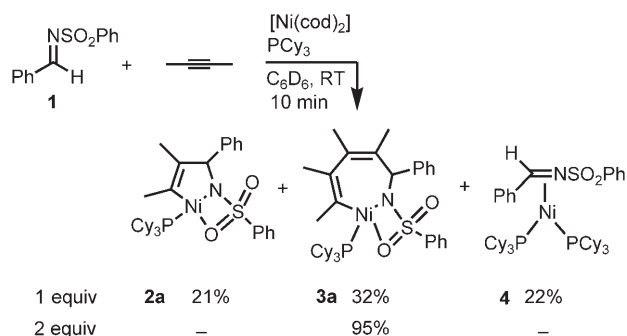


Scheme 1. A possible reaction between an alkyne and an imine with nickel(0).

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.

The reaction of *N*-(benzenesulfonyl)benzaldimine (**1**) with 2-butyne (1 equiv) in the presence of $[\text{Ni}(\text{cod})_2]$ (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



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

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

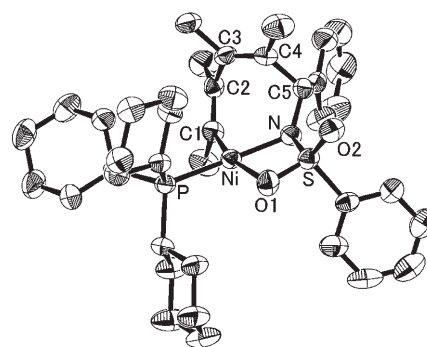


Figure 1. Molecular structure of **3a**.

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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-

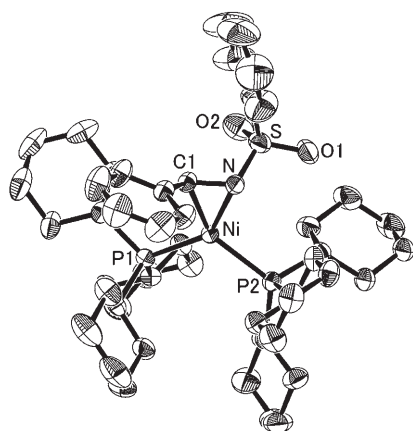
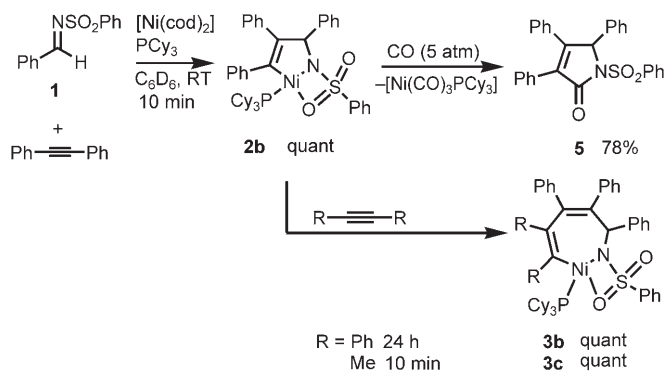


Figure 2. Molecular structure of **4**.

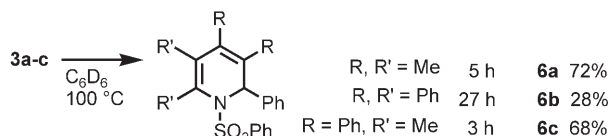
membered aza-nickelacycle **2a** was not possible due to a very rapid second insertion of 2-butyne to give **3a**, therefore a bulkier alkyne was examined as a carbon–carbon triple bond component to suppress the formation of the seven-membered aza-nickelacycle.

The reaction of **1** with diphenylacetylene in the presence of $[\text{Ni}(\text{cod})_2]$ 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



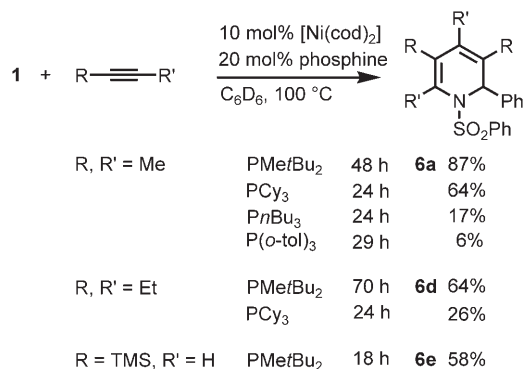
Scheme 3. Reaction of diphenylacetylene and **1** with nickel(0) followed by addition of another alkyne (same or different) or CO.

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 4. Reductive elimination from **3**.

The intermolecular [2+2+2] cycloaddition of two alkynes and **1** in the presence of 10 mol % of $[\text{Ni}(\text{cod})_2]$ and $\text{PMe}t\text{Bu}_2$ at 100 °C gave the expected 1,2-dihydropyridine (**6a**) in 87 % yield (Scheme 5). 3-Hexyne and trimethylsilylacetylene also



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

gave the corresponding 1,2-dihydropyridines (**6d** and **6e**, respectively). The reaction proceeded catalytically also in the presence of PCy_3 , although $\text{PMe}t\text{Bu}_2$ gave better results. The less bulkier or less basic phosphines PnBu_3 or $\text{P}(o\text{-tol})_3$ (*o*-tol = *ortho*-tolyl) were not efficient for this reaction. Although the complex $\text{Ni}^0\text{-NHC}$ (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-

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 μ L, 5.11 mmol) was added to a solution of [Ni(cod)₂] (274.8 mg, 1.00 mmol), PCy₃ (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. ¹H NMR (400 MHz, C₆D₆): δ = 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, CHPh), 6.97–7.02 (m, 4 H), 7.11 (t, $J_{\text{H,H}}$ = 7.6 Hz, 2 H), 7.31 (br.s, 2 H), 8.29 ppm (br.d, $J_{\text{H,H}}$ = 6.5 Hz, 2 H). ¹³C NMR (100 MHz, C₆D₆): δ = 15.6 (s), 18.2 (s), 22.2 (s), 24.8 (d, $J_{\text{C,P}}$ = 6.1 Hz; Cy), 27.2 (s), 28.4 (d, $J_{\text{C,P}}$ = 9.9 Hz; Cy), 28.5 (d, $J_{\text{C,P}}$ = 9.9 Hz; Cy), 30.2 (s), 31.0 (s), 33.6 (d, $J_{\text{C,P}}$ = 17.5 Hz; Cy), 60.2 (s, CHPh), 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). ³¹P NMR (109.4 MHz, C₆D₆): δ = 31.3 ppm (s). Elemental analysis (%) calcd for C₃₉H₅₆NNiO₂PS: C 67.63, H 8.15, N 2.02; found: C 67.36, H 8.21, N 2.12.

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