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Nickel-Catalyzed Synthesis of *N*-Aryl-1,2-dihydropyridines by [2+2+2] Cycloaddition of Imines with Alkynes through T-Shaped 14-Electron Aza-Nickelacycle Key Intermediates

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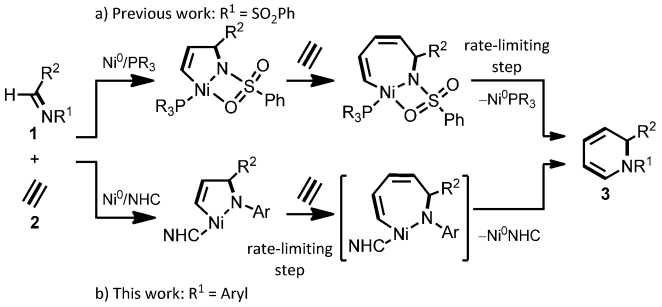
Abstract: Despite there being a straightforward approach for the synthesis of 1,2-dihydropyridines, the transition-metal-catalyzed [2+2+2] cycloaddition reaction of imines with alkynes has been achieved only with imines containing an *N*-sulfonyl or -pyridyl group. Considering the importance of 1,2-dihydropyridines as useful intermediates in the preparation of a wide range of valuable organic molecules, it would be very worthwhile to provide novel strategies to expand the scope of imines. Herein we report a successful expansion of the scope of imines in nickel-catalyzed [2+2+2] cycloaddition reactions with alkynes. In the presence of a nickel(0)/PCy_3 catalyst, a reaction with *N*-benzylidene-*P,P*-diphenylphosphinic amide was developed. Moreover, an application of *N*-aryl imines to the reaction was also achieved by adopting N-heterocyclic carbene ligands. The isolation of an (η^2-*N*-aryl imine)nickel(0) complex containing a 14-electron nickel(0) center and a T-shaped 14-electron five-membered aza-nickelacycle is shown. These would be considered as key intermediates of the reaction. The structure of these complexes was unambiguously determined by NMR spectroscopy and X-ray analyses.

Introduction

The formation of metalacycles by the reaction of unsaturated compounds with low valent transition metals is a key reaction in transition-metal-catalyzed cycloaddition reactions.[1] The development of efficient methods to generate a variety of metalacycles would provide us more opportunities to access cyclic organic compounds. Nickel is a highly promising candidate as a catalyst for cycloaddition reactions since a number of oxidative cyclization reactions of two unsaturated compounds with nickel(0) giving nickelacycles have been reported.[2] During the course of studying hetero-nickelacycles,[2b,3] we reported that the reaction of *N*-benzylidene benzenesulfonamide (*N*-BBSA) and alkynes with [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) and PCy_3 gave aza-nickelacycle compounds, which we proposed as a key intermediates in the [2+2+2] cycloaddition of an imine (**1**) with two alkynes (**2**) to yield a 1,2-dihydropyridine (**3**) (Scheme 1a).[3b,c] Similar [2+2+2] cycloaddition reactions giving dihydropyridines have been reported by Yoshikai[4a] and Gandon and Aubert;[4b] thus far, however, the substituent groups on imine nitrogen atom have been limited to sulfonyl and pyridyl groups. This result indicates that the chelate coordination of the heteroatom on the N-substituent group to the metal center is key to success in the catalytic reaction. In the nickel catalysis, electron-withdrawing substituents would be required for oxidative cyclization by promoting back donation from nickel(0) to imines. The coordination of a heteroatom to the nickel(II) center would stabilize the aza-nickelacycle intermediate through the occupation of a vacant coordination site.[2b,3,4a] Based on these points of view, we propose two strategies. Considering the importance of 1,2-dihydropyridines as useful intermediates in the preparation of a wide range of valuable organic molecules, it would be very worthwhile to provide novel strategies to expand the scope of imines. One is the development of a substituent group on nitrogen, such as sulfonyl and pyridyl groups, which can decrease the electron den-



Scheme 1. Formation of 1,2-dihydropyridines by [2+2+2] cycloaddition of imines with alkynes in the presence of nickel(0).

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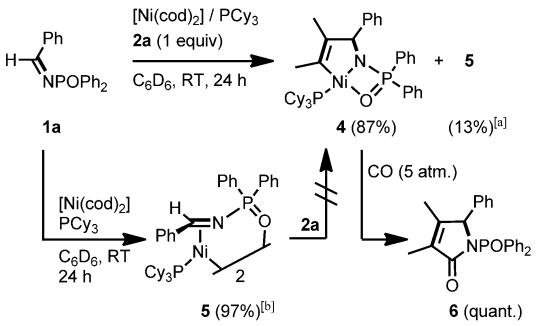
sity on the imine and act as an intramolecular coordination group. The other is employing N-heterocyclic carbenes (NHCs) instead of tertiary phosphines since a stronger electron-donating and more steric-demanding ligand might allow us to construct a catalytic reaction with *N*-aryl imines by stabilizing a T-shaped 14-electron aza-nickelacycle intermediate by covering a vacant site. In fact, we reported the preparation of T-shaped 14-electron hetero-nickelacycles with NHCs.[3d,f] Here we report the formation of a T-shaped 14-electron five-membered aza-nickelacycle by the oxidative cyclization of an *N*-aryl imine and an alkyne with nickel(0)/NHC. Moreover, a successful expansion of the imine scope to include *N*-aryl imines in transition-metal-catalyzed [2+2+2] cycloaddition with alkynes is also shown for the first time, which would proceed through the five-membered aza-nickelacycle intermediate (Scheme 1b).

Results and Discussion

First, *N*-benzylidene-*P,P*-diphenylphosphinic amide (**1a**) was employed in the reaction with 2-butyne (**2a**) (1 equiv), $[Ni(cod)_2]$ (1 equiv), and PCy_3 (1 equiv) (Scheme 2). The reaction was completed in 24 h to afford aza-nickelacycle **4** in 87% yield with the concomitant formation of complex **5** in 13% yield. An analogous aza-nickelacycle complex **4′** was prepared from **1a** and diphenylacetylene, with a molecular structure of **4′** that was unambiguously determined by X-ray crystallography (Figure 1a).[5] Complex **4′** has a planar tetracoordinate nickel(II) center with an intramolecular coordination of oxygen to nickel. In addition, the formation of γ-lactam derivative **6** by the carbonylation of **4** would support the five-membered nickelacycle skeleton of complex **4**. Complex **5** existed as a mixture of *syn*/*anti* isomers in solution. In the solid state, only an *anti* isomer was observed, as shown in Figure 1b (please see the Supporting Information for details of *syn*/*anti* isomers). No reaction took place when an excess amount of **2a** was added at room temperature to **5**, which was prepared by the reaction of **1a** with one equivalent of $[Ni(cod)_2]$ and PCy_3 in C_6D_6. These results suggest that **5** would be highly stabilized through the intramolecular coordination of oxygen to nickel, and thus the simultaneous coordination of **1a** and **2a** might be inhibited.



Scheme 2. The stoichiometric reactions with **1a**. Yields of products determined by ^1H NMR spectroscopy are given in parenthesis. [a] the ratio of *syn*/*anti* is 42:58. [b] The ratio of *syn*/*anti* is 18:82.

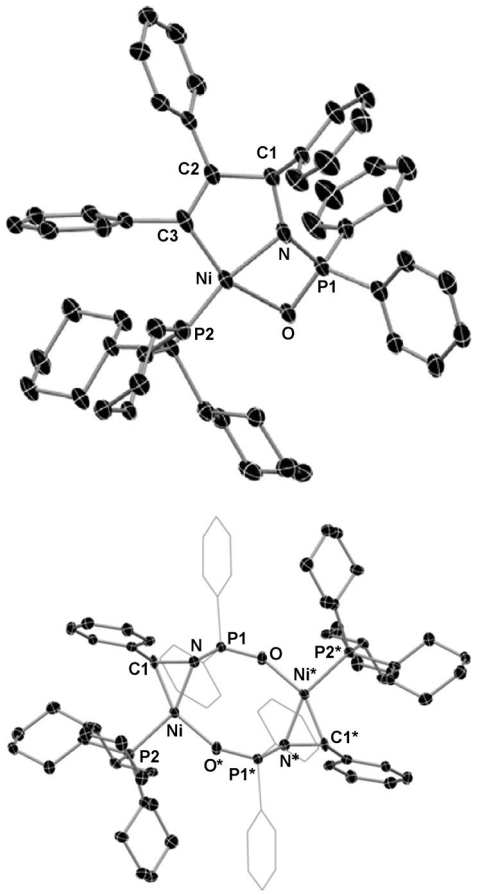
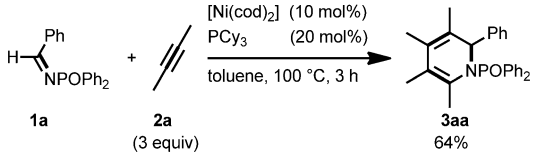


Figure 1. Molecular structures of a) **4′** and b) **5** with thermal ellipsoids at the 30% probability level. H atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: a) Ni–N 1.893(4), Ni–C3 1.894(5), Ni–P2 2.198(1), Ni–O 2.094(4); N-Ni-O 75.2(1), O-Ni-P2 100.6, P2-Ni-C3 104.3(1), C3-Ni-N 84.0(1); b) Ni–N 1.903(5), Ni–C1 1.904(5), C1–N 1.40(1).

In the presence of $[Ni(cod)_2]$ (10 mol%) and PCy_3 (20 mol%), the treatment of **1a** with **2a** (2 equiv) at 100 °C resulted in the formation of 1,2-dihydropyridine **3aa** in 64% yield (Scheme 3).



Scheme 3. Nickel(0)-catalyzed [2+2+2] cycloaddition of **1a** with **2a**. Yield of **3aa** was determined by ^1H NMR spectroscopy.

Next, we turned our attention to utilizing NHCs as a ligand to test our hypothesis that NHCs can help the formation of aza-nickelacycle compounds by the oxidative cyclization of alkynes and imines without a chelation group.

We examined the reaction of *N*-benzylidene-4-trifluoromethyl aniline (**1b**) or *N*-benzylidene-2-aminopyridine (**1c**) with a stoichiometric amount of $[Ni(cod)_2]$ and IPr (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene) (Scheme 4). Both reac-

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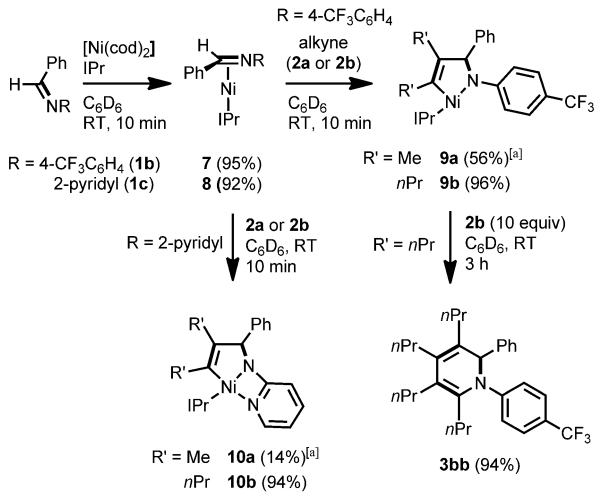

Scheme 4. The stoichiometric reactions using *N*-aryl imines and alkynes with Ni^0 and IPr. Yields were determined by ^1H NMR spectroscopy. [a] The reaction was carried out in toluene. Isolated yields after recrystallization are shown.

tions were completed within 10 min to give [Ni(IPr)(η^2-imine)] complexes in 95 (**7**) and 92% (**8**) yields, respectively. The molecular structure of **7** was confirmed by X-ray crystallography (Figure 2a). The C1–N bond length is 1.37(1) Å, which is clearly elongated compared with a typical C=N bond length (ca. 1.27–1.30 Å)[6] due to the back donation from the nickel(0) center. Moreover, **7** was found to have a 14-electron nickel(0) center while the previously reported [Ni(PCy_3)$_2$(η^2-PhCH=NSO_2Ph)] had a 16-electron center.[3b] This structural difference might be caused by the steric bulkiness of IPr, that is, a more bulky IPr would stabilize the highly reactive 14-electron nickel(0) complex by covering its vacant coordination sites. The reaction of *N*-BBSA with [Ni(cod)$_2$] and IPr did not afford the corresponding [Ni(IPr)(η^2-PhCH=NSO_2Ph)] complex at all, and unidentified white precipitates were observed.[7]

Treatment of **7** with **2a** or 4-octyne (**2b**) in C_6D_6 at room temperature gave five-membered aza-nickelacycles **9a** (56% isolated yield) or **9b** (96% NMR spectroscopic yield). The molecular structure of **9a** was determined by X-ray crystallography, showing its T-shaped 14-electron nickel(II) center (Figure 2b). The sum of the bond angles around Ni along the C3, N, and C4 is 359.0°. Thus, Ni and these three atoms are on the same plane. A space-filling model of **9a** clearly indicates that such a geometry is due mostly to the bulkiness caused by the aryl group on the imine nitrogen atom together with the bulky IPr ligand.[5] On the other hand, the structure of aza-nickelacycles **10a** and **10b**, which were prepared by the reaction of **8** with either **2a** or **2b**, would have a planar tetracoordinate nickel(II) center with an intramolecular coordination of the *N*-pyridine ring.[4a] The crystal structure of **10a** is shown in Figure 2c.

We reported that the reaction of the planar tetracoordinate five-membered aza-nickelacycle prepared from *N*-BBSA, diphenylacetylene, [Ni(cod)$_2$], and PCy_3, with another equivalent of the alkyne, afforded a seven-membered aza-nickelacycle;[3b,c] however, **9b** reacted with the second **2b** at room temperature

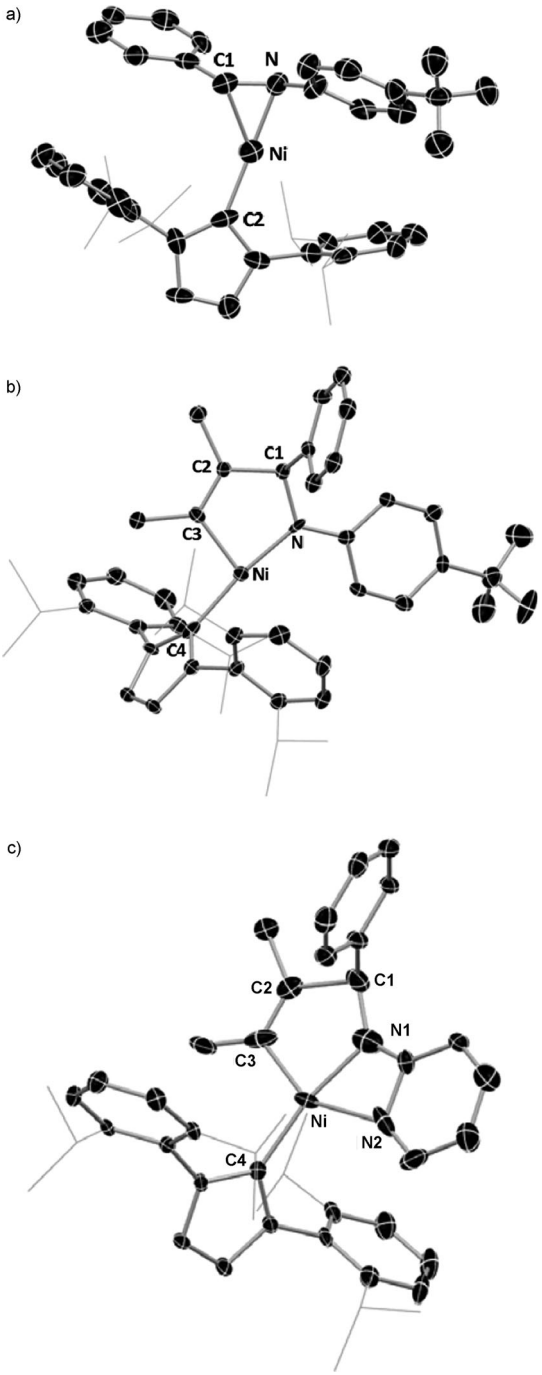

Figure 2. Molecular structures for a) **7**, b) **9a**, and c) **10a** with thermal ellipsoids at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: a) Ni–N 1.85(1), Ni–C1 1.94(1), Ni–C2 1.84(1), C1–N 1.37(1), N-Ni-C2 172.8(6); b) Ni–N 1.859(6), Ni–C3 1.861(7), Ni–C4 1.877(8), N-Ni-C3 85.7(3), C3-Ni-C4 101.3(3), N-Ni-C4 172.0(3); c) Ni–N1 1.872(9), Ni–N2 2.116(8), Ni–C3 1.906(9), Ni–C4 1.876(7), N1-Ni-N2 63.6(4), N1-Ni-C3 84.9(5), C3-Ni-C4 105.5(4), N2-Ni-C4 106.5(3).

to yield 1,2-dihydropyridines **3bb** in 94% yield. The formation of the corresponding seven-membered aza-nickelacycle was not observed at all by ^1H NMR spectroscopy. This result might indicate that the rate of reductive elimination from the seven-membered aza-nickelacycle to give 1,2-dihydropyridine is faster than that of the insertion of the second alkyne into the

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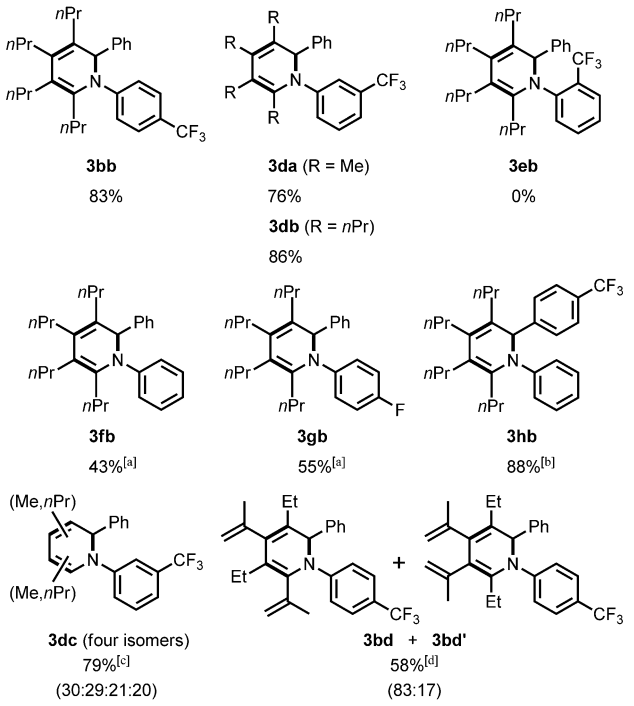
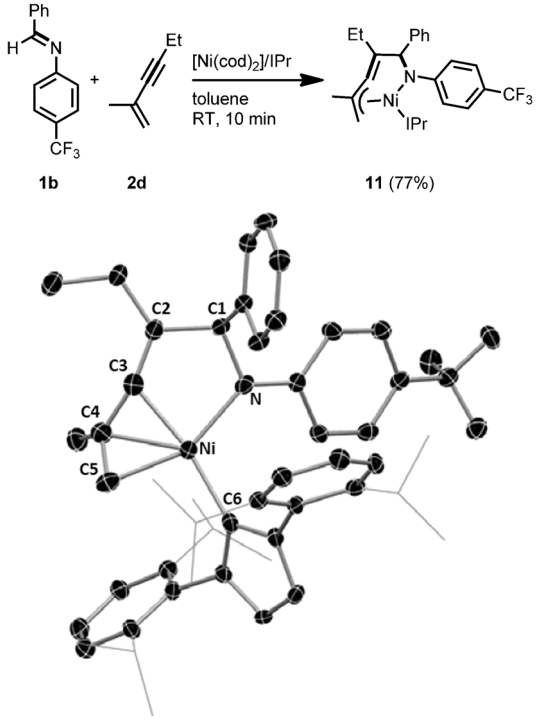


Scheme 5. Nickel(0)/NHC-catalyzed [2+2+2] cycloaddition reaction of *N*-aryl imines with alkynes. General conditions: imines (1.00 mmol), alkynes (2.00 mmol) and [Ni(cod)$_2$/IMes] (2 mol%) were reacted in THF (1.0 mL) at 40 °C for 24 h. Yields of isolated products are given. [a] 5 mol% of [Ni(cod)$_2$] and IPr was used. [b] 2 mol% of [Ni(cod)$_2$] and IPr was used (48 h). [c] Total yield of the four products after isolation. [d] 10 mol% of [Ni(cod)$_2$] and IPr was used in 1,4-dioxane at 100 °C (72 h). Total yield of **3bd** and **3bd′** is given.



Scheme 6. The stoichiometric reaction of **1b** and **2d** with [Ni(cod)$_2$] and IPr. Isolated yield of **11** is given. Molecular structure of **11** (thermal ellipsoids at the 30% probability level) is also shown. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: Ni–N 1.965(6), Ni–C3 1.932(7), Ni–C4 2.045(8), Ni–C5 2.024(8), Ni–C6 1.936(6).

five-membered complex. In sharp contrast, complex **10b** did not react with **2b** at room temperature. This might be due to the suppression of the coordination of **2b** by the intramolecular coordination of the *N*-pyridine.

Catalytic [2+2+2] cycloaddition reactions of *N*-aryl imines with alkynes were carried out (Scheme 5). The reaction of **1b** with **2b** proceeded efficiently with 5 mol% of [Ni(cod)$_2$] and IPr to give **3bb** in 91% yield. Moreover, the catalyst loading can be decreased to 2 mol% without loss of efficiency by employing 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene (IMes) as a ligand (**3bb**; 92% NMR yield, 83% isolated yield). A substrate with an *N*-3-$CF_3C_6H_4$ group (**1d**) gave the corresponding 1,2-dihydropyridines **3da** (from **2a**) or **3db** (from **2b**) in 76 and 86% yields, respectively, by using 2 mol% of [Ni(cod)$_2$] and IMes; however, an imine with an *N*-2-$CF_3C_6H_4$ (**1e**) did not afford the product at all under the same reaction conditions. It is noteworthy that the present reaction conditions were successfully applied to a simple *N*-phenyl imine **1f** and gave **3fb** in 43% yield in the presence of [Ni(cod)$_2$] and IPr (5 mol%). In addition, **1g** containing a 4-fluorophenyl group also reacted with **2b** to afford **3gb** in a moderate yield. While the reaction time had to be extended to 48 h, imine **1h** was successfully converted into **3hb** in 88% yield in the presence of 2 mol% [Ni(cod)$_2$] and IPr. Employing an unsymmetrical alkyne **2c** afforded a mixture of four 1,2-dihydropyridines with a ratio of 30:29:21:20 and a total product yield of 79%. On the other hand, the reaction of **1b** with 2-methyl-1-hexen-3-yne (**2d**) at 100 °C for 72 h gave a mixture of two products (**3bd** and **3bd′**) in a total yield of 58%. The ratio of **3bd**/**3bd′** was 83:17. This result can be rationalized by the following results shown in Scheme 6. The stoichiometric treatment of **1b** with **2d**, [Ni(cod)$_2$], and IPr at room temperature resulted in the formation of aza-nickelacycle **11** in 97% NMR spectroscopic yield, which was isolated in 77% yield. The crystal structure of **11** is also shown in Scheme 6. Because an η^3-butadienyl coordination can highly stabilize nickelacycles,[3h,8] the oxidative cyclization of **1b** with **2d**, which was found to be reversible, would take place regioselectively.[9] The transition state of the insertion of the second **2d** into **11**, which can proceed at 100 °C, might also be stabilized by the assistance of η^3-butadienyl coordination. Thus, **3bd** was formed as a major product while the regioselectivity of the insertion of the second **2d** was not perfectly controlled at 100 °C. Employing terminal alkynes such as phenyl- and trimethylsilylacetylene gave a complicated mixture, and the formation of the corresponding dihydropyridines was not observed at all by GC analysis.

Nickel(0)-catalyzed [2+2+2] cycloaddition of imines with alkynes would proceed through the steps proposed in Scheme 1: 1) oxidative cyclization of an imine and an alkyne giving a five-membered aza-nickelacycle, 2) formation of a seven-membered aza-nickelacycle by the insertion of a second alkyne, and 3) reductive elimination. In our previous report using *N*-BBSA, the formation of the seven-membered aza-nickelacycle was observed at room temperature, and re-

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ductive elimination to give 1,2-dihydropyridine took place at 100 °C, which indicates that reductive elimination significantly influenced the reaction rate. In addition, Yoshikai also proposed that, based on DFT calculations, reductive elimination would be the rate-limiting step of the reaction with *N*-pyridyl imines.[4a] On the other hand, the reaction rate of the [2+2+2] cycloaddition of *N*-aryl imines with alkynes in the presence of a nickel(0)/NHC catalyst might be determined by the insertion of the second alkyne into the five-membered aza-nickelacycle, as mentioned above.

Conclusion

In summary, an expansion of the scope of N-substituents of imines in the nickel(0)-catalyzed [2+2+2] cycloaddition with alkynes giving 1,2-dihydropyridines was successfully achieved. In the presence of a catalytic amount of nickel(0) and PCy_3, the [2+2+2] cycloaddition reaction of *N*-benzylidene-*P,P*-diphenylphosphinic amide with alkynes was developed, and the isolation of a planar tetracoordinate five-membered aza-nickelacycle complex was achieved. In addition, an application of *N*-arylimines to the reaction was demonstrated by adopting NHCs as a ligand. The isolation of an (η^2-*N*-aryl imine)nickel complex containing a 14-electron nickel(0) center and a T-shaped 14-electron five-membered aza-nickelacycle complex was presented. Based on the results of stoichiometric reactions, the insertion of a second alkyne into the five-membered aza-nickelacycle might control the rate of this catalytic reaction.

Experimental Section

Isolation of 9a

Compound **2a** (15.7 μL, 0.20 mmol) was added to a solution of complex **7** (139.3 mg, 0.20 mmol) in toluene (5 mL) at room temperature. The solution changed from dark green to dark brown. After stirring for 10 min, the reaction mixture was concentrated in vacuo. The resulting brown solid was reprecipitated from toluene/pentane to give **9a** as a brown solid in 56% yield (84.07 mg, 0.11 mmol). An analytical sample and a single crystal for X-ray diffraction analysis were prepared by recrystallization from toluene/hexane at −30 °C. ^{1}H NMR (400 MHz, C_6D_6): δ = 0.65 (s, 3H; CH_3), 0.91–0.94 (m, 12H; IPr), 1.16 (d, J = 6.6 Hz, 6H; IPr), 1.29 (s, 3H; CH_3), 1.31 (d, J = 6.6 Hz, 6H; IPr), 2.59 (sept, J = 6.6 Hz, 2H; IPr), 3.13 (sept, J = 6.6 Hz, 2H; IPr), 4.38 (s, 1H; C*H*Ph), 5.66 (d, J = 8.8 Hz, 2H; 2-(4-$C_6H_4CF_3$)), 6.53 (s, 2H; IPr), 7.00–7.24 (m, 9H), 7.36 (t, J = 7.8 Hz, 2H; Ar-*H*), 7.47 ppm (d, J = 6.4 Hz, 2H; Ar-*H*); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 12.1 (NiC(*C*H$_3$)), 22.6, 23.3, 23.7 (NiC(CH$_3$)=C(*C*H$_3$)), 25.6, 26.2, 29.4, 29.8, 75.0 (*C*HPh), 109.4 (2-(4-$C_6H_4CF_3$)), 110.4 (NiC(CH$_3$)=*C*(CH$_3$)), 111.7 (q, J_{CF} = 32.0 Hz; *C*CF$_3$), 124.9, 125.0, 125.1, 125.7, 126.2, 126.3 (q, J_{CF} = 3.0 Hz; 3-(4-$C_6H_4CF_3$)), 127.5 (q, J_{CF} = 266.3 Hz; *C*F$_3$), 129.3, 130.7, 136.0, 145.6, 145.7, 145.7, 146.8 (Ni*C*(CH$_3$)), 159.5 (*ipso*-Ph), 183.9 ppm (N*C*N); elemental analysis calcd (%)for $C_{45}H_{52}F_3N_3Ni$: C 72.01, H 6.98, N 5.60; found: C 71.89, H 6.93, N 5.57; X-ray data for **9a**: M = 750.62, brown, triclinic, $P\bar{1}$ (#2), a = 11.244(1), b = 11.9223(9), c = 16.212(2) Å, α = 73.459(2), β = 73.333(8), γ = 81.203(3)°, V = 1989.8(3) Å^3, Z = 2, ρ_{calcd} = 1.253 g cm^{-3}, T = −150 °C, R_1 (wR_2) = 0.0859 (0.2735).

General procedure for catalytic reactions (Scheme 5)

The reaction was conducted in a pyrex test tube equipped with a magnetic stirrer bar. An imine (1.0 mmol) was added to a solution of [Ni(cod)$_2$] (5.5 mg, 0.02 mmol, 2 mol%) and IMes (6.1 mg, 0.02 mmol, 2 mol%) in THF (1 mL). The solution was stirred for 5 min, and then an alkyne (2.0 mmol, 2 equiv) was added. The reaction mixture was heated at 40 °C and stirred for the indicated time. After cooling to room temperature, the resulting mixture was filtered through a silica gel short column (eluted with AcOEt). Then all volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography. Further purification was carried out by Kugelrohr distillation or recycle HPLC.

Acknowledgements

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Keywords: 1,2-dihydropyridine · cycloaddition · nickel · nickelacycle · oxidative cyclization

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