Nickel(0)-Catalyzed [2+2+2] Cycloaddition of Diynes and 3,4-Pyridynes: Novel Synthesis of Isoquinoline Derivatives

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A transition metal-catalyzed [2+2+2] cycloaddition between α,ω-diynes and 3,4-pyridynes has been realized for the first time, producing isoquinolines in good yields by using a nickel(0)
10 **catalyst.**

A transition metal-catalyzed [2+2+2] cycloaddition of alkynes is a useful and highly atom-economic way to construct various aromatic rings.[1] In recent years, arynes have been utilized as substrates in [2+2+2] cycloaddition.[2-5]
15 Pyridynes are the analogues of arynes containing a nitrogen in the ring and can be classified into 2,3-pyridyne and 3,4-pyridyne by the position of the nitrogen in the ring (Figure 1).
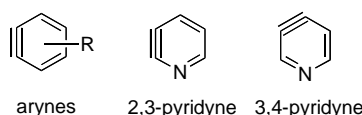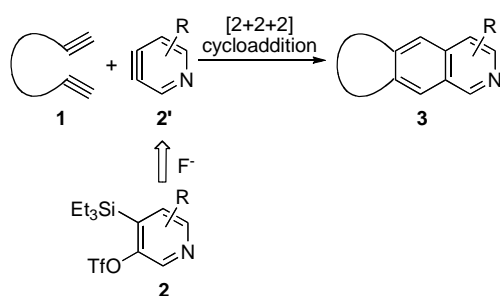

arynes   2,3-pyridyne 3,4-pyridyne

Figure 1. Arynes and Pyridynes

20 Their reactivities have been investigeted in Diels-Alder reactions and nucleophilic substitution reactions.[6] Compared with the extensive study on utilization of arynes in a [2+2+2] cycloaddition, the reactivity of pyridynes toward the [2+2+2] cycloaddition has not been studied at all. Herein we report
25 the first example for a transition metal-catalyzed [2+2+2] cycloaddition of diynes **1** and 3,4-pyridynes **2'**, generated in situ from silyl-triflate precursor **2**,[7] providing isoquinoline derivative **3** (Scheme 1).

30 **Scheme 1.** Plan for [2+2+2] Cycloaddition of Diynes and 3,4-Pyridynes

Initially, a [2+2+2] cycloaddition of diyne **1a** with the precursor **2a** was investigated using a palladium catalyst according to the optimized conditions of the above-mentioned arynes.[5] However, the desired product **3a** was not obtained,
35 and **1a** was recovered in 95% yield. After various attempts to find a good catalyst for this reaction, it was found that nickel is suitable as a catalyst in the [2+2+2] cycloaddition of 3,4-pyridynes. That is, to a mixture of Ni(cod)$_2$ (10 mol%), PPh$_3$

(40 mol%), and CsF (3 equivalents to **2a**) in CH$_3$CN was
40 added a solution of diyne **1a** (2 equivalents to **2a**) and 3,4-pyridyne precursor **2a** in CH$_3$CN via a canula at room temperature, and the mixture was stirred for 3 hours. After the usual work-up, the isoquinoline derivative **3aa** was obtained in 43% yield along with dimer **4a** in 28% yield
45 (Table 1, run 1). Increasing both the ratio of **2a** to **1a** and the amount of the catalyst loading from 10% to 20% slightly improved the yield of **3aa** to 50% (run 2). To suppress the formation of the dimer **4a**, we investigated the protocol for addition of substrates. When a solution of diyne **1a** was
50 added to a mixture of the precursor **2a**, nickel catalyst, and CsF using a syringe pump over a period of 3 hours, the yield of **3aa** was improved to 58% and the formation of the dimer **4a** was also reduced (run 3). Furthermore, when 4 equivalents of **2a** with respect to **1a** were used, the yield of the product
55 reached 62% (run 4). According to this optimal protocol, the loading of the catalyst could be reduced to 10 mol%, giving **3aa** in 63% yield (run 5).
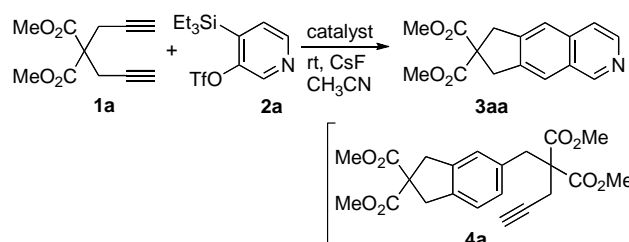

Table 1. [2+2+2] Cycloaddition of **1a** and **2a**[a]

run	catalyst (mol%)	Time (h)	**3aa** (%)	**4a** (%)[b]
1[c,d]	Ni(cod)$_2$ (10) PPh$_3$ (40)	3	43	28
2[e]	Ni(cod)$_2$ (20) PPh$_3$ (80)	3	50	13
3[e,f]	Ni(cod)$_2$ (20) PPh$_3$ (80)	—[g]	58	8
4[f,h]	Ni(cod)$_2$ (20) PPh$_3$ (80)	—[g]	62	6
5[f,h]	Ni(cod)$_2$ (10) PPh$_3$ (40)	—[g]	63	7

60 [a] 3 equiv of CsF to the precursor **2a** was used. [b] Based on **1a**. [c] The ratio of **1a/2a** was 2/1. [d] Diyne **1a** was recovered in 20%. [e] The ratio of **1a/2a** was 1/2. [f] A solution of **1a** was added over a period of 3 h to a mixture of **2a**, Ni catalyst, and CsF. [g] The reaction was quenched just after finishing addition of a solution of **1a**. [h] The ratio of **1a/2a** was 1/4.

65 Next, the scope of both diynes and 3,4-pyridynes in the [2+2+2] cycloaddition was investigated under the above-mentioned optimal conditions. The results are summarized in

Table 2.

Table 2. Scope of Diynes and Pyridynes in [2+2+2] Cycloaddition[a]

run	diyne	pyridyne precursor	product	yield (%)
1	1b	2a	3ba	65
2	1c	2a	3ca	50
3	1d	2a	3da	38
4	1a	2b	3ab	61
5	1a	2c	3ac	60
6	1a	2d	3ad	18

[a] A solution of diyne **1** was added via a syringe pump over a period of 3 h to a mixture of precursor **2** (4 equiv), Ni(cod)$_2$ (10 mol%), PPh$_3$ (40 mol%), and CsF (3 equiv to **2**) in CH$_3$CN at room temperature.

The reaction of 1,6-heptadiyne (**1b**), having no geminal substituents, with **2a** proceeded smoothly, giving isoquinoline derivative **3ba** in 65% yield (run 1). The diyne **1c** or **1d**, containing a tosyl amide or an oxygen atom in the tether, was also tolerated in the [2+2+2] cycloaddition with **2a** to produce the corresponding isoquinoline derivative **3ca** or **3da**, respectively, although the yield was modest (runs 2 and 3). The reaction of **1a** and the precursor **2b** or **2c**, having a methoxy group at the C6 or C2 position, also gave isoquinoline derivative **3ab** or **3ac**, respectively, in good yields (runs 4 and 5). On the other hand, the existence of an elecron-withdrawing substituent on the aromatic ring in the precursor clearly retarded the reaction, resulting in a decrease in the yield of the product **3ad** in the reaction of **1a** and **2d** (run 6).

We next turned our attention to an intramolecular [2+2+2] cycloaddition of diyne and pyridyne in the tether. In the intramolecular reaction, synchronous coordination of the diyne part and the pyridyne part to the nickel complex would be important. Thus, the reaction protocol was again modified. It was found that the reaction proceeded even at 0 °C and that the ratio of catalyst to ligand could be reduced from 1/4 to 1/2. When the period of addition of the substrate was prolonged from 3 hours to 8 hours, the yield of the product reached to 75% (Table 3, run 1). The existence of a protected nitrogen such as a tosyl amide in the tether did not affect the reaction, producing the polycyclic isoquinoline derivatives **6b**-**6d** in good yields (runs 2-4). On the other hand, the reactions of the substrates **5e** and **5f**, having an oxygen in the tether, under the above-mentioned optimized conditions gave the corresponding products **6e** and **6f**, respectively, in 41% and 43% yields. It was speculated that coordination of an oxygen

atom to the nickel catalyst retarded the reaction, resulting in a lower yield (runs 5 and 6).

Table 3. Intramolecular [2+2+2] Cycloaddition of Various Substrates[a,b]

run	substrate	product	yield (%)
1	5a	6a	75
2	5b	6b	69
3	5c	6c	62
4	5d	6d	59
5	5e	6e	41
6	5f	6f	43

[a] A solution of substrate **5** was added via a syringe pump over a period of 8 h to a mixture of Ni(cod)$_2$ (10 mol%), PPh$_3$ (20 mol%), and CsF (3 equiv) in CH$_3$CN at 0 °C. [b] E=CO$_2$Me

A possible mechanism of the [2+2+2] cycloaddition of diyne and 3,4-pyridyne is shown in Scheme 2. Oxidative addition of diyne **1** to nickel(0) complex would proceed to afford nickelacyclopentadiene intermediate **I**. Then insertion of pyridyne **2'**, generated in situ from precursor **2** and CsF, into the nickel-carbon bond of **I** would afford seven-membered nickelacycle intermediate **IIa** or **IIb**. Reductive elimination of nickel(0) complex from **IIa** or **IIb** would proceed to give isoquinoline **3**. An alternative pathway that involves the formation of nickelacycle **IIIa** or **IIIb** by oxidative cycloaddition of one alkyne part of diyne **1** and pyridyne **2'** would not be excluded. In this pathway, insertion of the residual alkyne part into the nickel-carbon bond of **IIIa** or **IIIb** also gave the intermediate **IIa** or **IIb**, respectively, producing isoquinoline **3**.
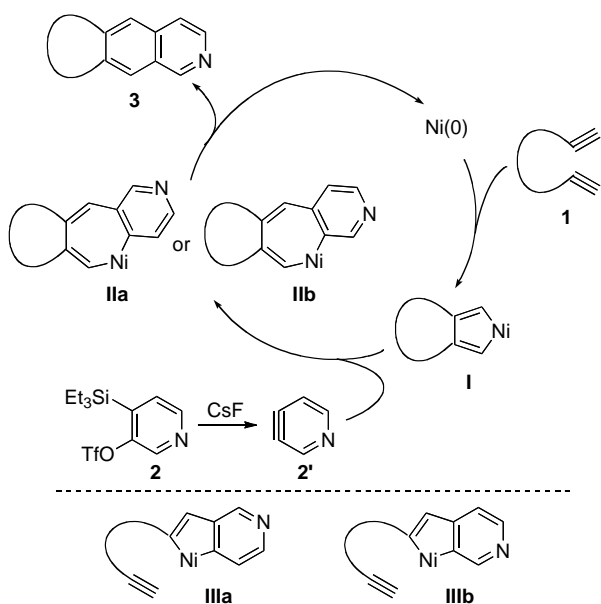
Scheme 2. Possible Mechanism for [2+2+2] Cycloaddition

In summary, we succeeded in utilizing 3,4-pyridynes in a transition metal-catalyzed [2+2+2] cycloaddition for the first time, and we obtained various isoquinolines including a polycyclic skeleton containing an isoquinoline subunit. Although the yields are still modest in some cases, the present results should pave the way for the development of a novel method for the synthesis of isoquinolines, which are an important class of compounds found in a variety of natural products and biologically active substances. Further studies along this line are in progress.

Notes and references

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† Electronic Supplementary Information (ESI) available: [typical procedures for [2+2+2] cycloaddition, spectal data and ¹H and ¹³C NMR spectra of all new compounds]. See DOI: 10.1039/b000000x/

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