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) catalyst.

The 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] cycloadditions.^{2–5} 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 (Fig. 1).

Their reactivities have been investigated in Diels–Alder and nucleophilic substitution reactions.⁶ Compared with the extensive studies on the utilization of arynes in [2 + 2 + 2] cycloadditions, the reactivity of pyridynes towards [2 + 2 + 2] cycloadditions has not been studied at all. Herein, we report 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).

Initially, the [2 + 2 + 2] cycloaddition of diyne **1a** with precursor **2a** was investigated using a palladium catalyst according to the optimized conditions of the above-mentioned



Fig. 1 Arynes and pyridynes.



Scheme 1 Plan for the [2 + 2 + 2] cycloaddition of diynes and 3,4-pyridynes.

[†] Electronic supplementary information (ESI) available: Typical procedures for [2 + 2 + 2] cycloaddition, spectral data, and ¹H and ¹³C NMR spectra of all new compounds. See DOI: 10.1039/b912022j

arvnes.⁵ However, the desired product, **3aa**, was not obtained 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%), PPh₃ (40 mol%) and CsF (3 equiv. with respect to 2a) in CH₃CN, was added a solution of divne 1a (2 equiv. with respect to 2a) and 3.4-pyridyne precursor 2a in CH₃CN via a canula at room temperature, and the mixture was stirred for 3 h. After the usual work-up, isoquinoline derivative 3aa was obtained in 43% yield along with dimer 4a in 28% yield (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 added to a mixture of precursor 2a, nickel catalyst and CsF using a syringe pump over a period of 3 h, the yield of **3aa** was improved to 58% and the formation of the dimer 4a was also reduced (run 3). Furthermore, when 4 equiv. of 2a with respect to **1a** were used, the yield of the product 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).

Next, the scope of both diynes and 3,4-pyridynes in the [2 + 2 + 2] cycloaddition was investigated under the

Table 1[2 + 2 + 2] Cycloaddition of 1a and 2a^a

MeO ₂ C	$ \begin{array}{c} $	Iyst MeO ₂ ' sF MeO2 MeO2C MeO2C	C 3aa C C C C C C C C C C C C C C C C C	$\int_{2}^{N} N$ $CO_2 Me$
Run	Catalyst (mol%)	Time/h	3aa (%)	4a (%) ^b
1^{cd}	Ni(cod) ₂ (10), PPh ₃ (40)	3	43	28
2^e	Ni(cod) ₂ (20), PPh ₃ (80)	3	50	13
3^{ef}	Ni(cod) ₂ (20), PPh ₃ (80)	g	58	8
4^{fh}	Ni(cod) ₂ (20), PPh ₃ (80)	g	62	6
5^{fh}	$Ni(cod)_2$ (10), PPh_3 (40)	g	63	7

^{*a*} 3 equiv. of CsF with respect 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.

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^{*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%), PPh₃ (40 mol%), and CsF (3 equiv. with respect to **2**) in CH₃CN at room temperature.

above-mentioned optimal conditions. The results are summarized in Table 2.

The reaction of 1,6-heptadiyne (1b), which has no geminal substituents, with 2a proceeded smoothly, giving isoquinoline derivative 3ba in 65% yield (run 1). Diynes 1c or 1d, containing a tosyl amide or an oxygen atom in the tether, were also tolerated in the [2 + 2 + 2] cycloaddition with 2a to produce the corresponding isoquinoline derivatives 3ca or 3da, respectively, although the yields were 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 electron-withdrawing substituent on the aromatic ring in the precursor clearly retarded the reaction, resulting in a decrease of the yield of product 3ad in the reaction between 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 h to 8 h, the yield of the product reached 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

Run Substrate Product Yield (%) Et₃Si 1 TfO 75 5a 6a Έ Et₃S 69 2 TfC 5b 6b N^ Ts Et₃Si Tsl TsN 3 62 TfC 60 5c F E Et₃Si Ts TsN 4 TfO 59 6d 5d // Et₃Si 5 41 5e ∭ Et₃Si 43 6 TfC 6f 5f F È F

Table 3 Intramolecular [2 + 2 + 2] cycloaddition of various substrates^{ab}

^{*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%), PPh₃ (20 mol%), and CsF (3 equiv.) in CH₃CN at 0 °C. ^{*b*} E = CO₂Me.

hand, the reactions of the substrates 5e and 5f, with 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).

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 sevenmembered 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.

In summary, we succeeded in utilizing 3,4-pyridynes in a transition metal-catalyzed [2 + 2 + 2] cycloaddition for the



Scheme 2 Possible mechanism for the [2 + 2 + 2] cycloaddition.

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.

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