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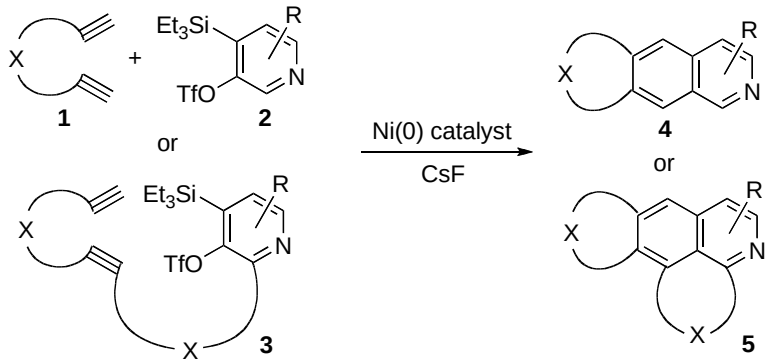
SYNTHESIS OF SUBSTITUTED ISOQUINOLINES *VIA* NICKEL-CATALYZED [2+2+2] CYCLOADDITION OF ALKYNES AND 3,4-PYRIDYNES

Toshihiko Iwayama and Yoshihiro Sato*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan
E-mail: biyo@pharm.hokudai.ac.jp

Abstract – A novel methodology for the synthesis of substituted isoquinolines via a nickel(0)-catalyzed [2+2+2] cycloaddition of 3,4-pyridynes with two molecules of alkyne has been established. In this reaction, it was found that 2-butyn-1,4-diol derivatives and 1,3-diynes are suitable as substrates and that a propargylic oxygen functionality in alkynes is essential for the reactivity and the selectivity of the products.

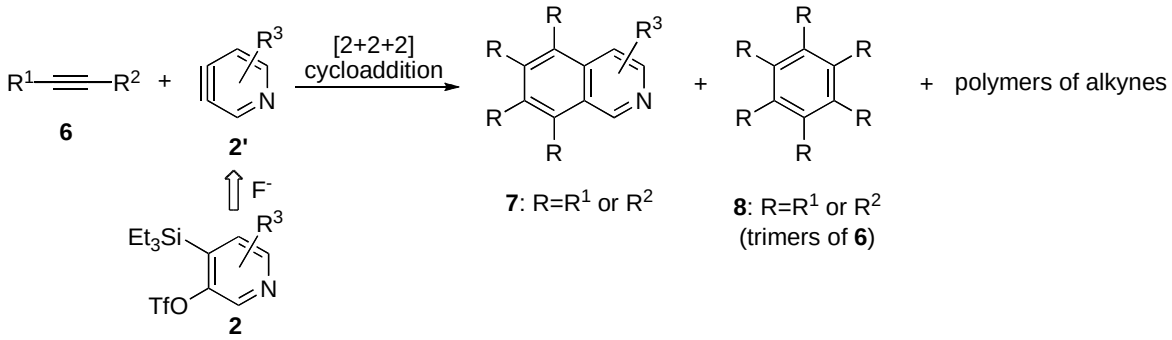
A transition metal-catalyzed [2+2+2] cycloaddition of three components of alkynes is a useful and highly atom-economic way for constructing various aromatic compounds.[1] Recently, we have succeeded in developing the first transition metal-catalyzed [2+2+2] cycloaddition of pyridynes with diynes by virtue of a nickel(0) catalyst (Scheme 1).[2,3]



Scheme 1. Previous study on Ni(0)-catalyzed [2+2+2] cycloaddition of 3,4-pyridynes

This paper is dedicated to Prof. Akira Suzuki in celebration of his 80th birthday.

The reaction of α,ω-diynes **1** and 3,4-pyridyne precursors **2** or diynes **3** having a 3,4-pyridyne precursor moiety in the chain with a zerovalent nickel catalyst in the presence of CsF gave the corresponding tricyclic isoquinolines **4** or tetracyclic isoquinolines **5**, respectively, in good yields. In the context, we planned to develop the synthesis of substituted isoquinolines via a [2+2+2] cycloaddition of 3,4-pyridynes with two molecules of alkynes, as shown in Scheme 2. If a [2+2+2] cycloaddition of two molecules of alkyne **6** and 3,4-pyridyne **2'** derived from the precursor **2** in the presence of a fluoride anion proceeds in a similar to that in the previous study shown in Scheme 1, substituted isoquinoline derivative **7** should be produced. By using alkynes as a substrate instead of diynes in the [2+2+2] cycloaddition, it would be more difficult to control the stereochemistry of the product **7** and to prevent the formation of trimers **8** and polymers of alkynes. Thus, this would be a more challenging subject than previously reported cases.

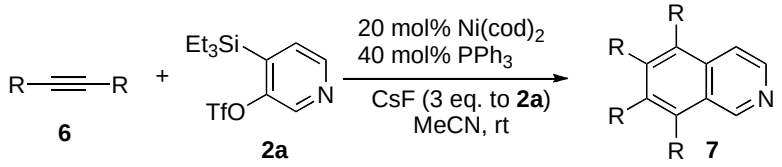


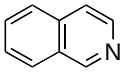
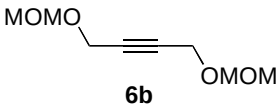
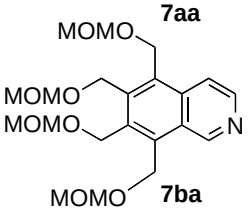
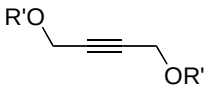
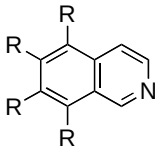
Scheme 2. Plan for synthesis of substituted isoquinolines from two molecules of alkyne and pyridynes.

First, a [2+2+2] cycloaddition of 3,4-pyridyne and two molecules of acetylene (**6a**) was examined (Table 1, run 1). Treatment of **2a** with 20 mol% $Ni(cod)_2$ and 40 mol% PPh_3 in the presence of CsF (3 equivalents to **2a**) under an atmosphere of acetylene (**6a**, 1 atm) in CH_3CN at room temperature gave isoquinoline (**7aa**) in 40% yield accompanied by the formation of unidentified polymers. Various symmetrical di-substituted alkynes were screened as a coupling partner instead of acetylene under conditions similar to those previously reported, and it was found that 2-butyn-1,4-diol derivative **6b** could be applied to the nickel-catalyzed [2+2+2] cycloaddition of 3,4-pyridyne precursor **2a**. Thus, the reaction of **6b** and **2a** (ratio of **6b**/**2a**=1/4) with 20 mol% $Ni(cod)_2$ and 40 mol% PPh_3 in the presence of CsF (3 equivalents to **2a**) in CH_3CN at room temperature gave the corresponding isoquinoline derivative **7ba** in 60% yield (run 2). When the ratio of the substrates **6b** and **2a** was changed from 1/4 to 4/1, the yield of **7ba** was improved to 72% (run 3). It was found that loading of the nickel catalyst could be reduced to 10 mol% without lowering of the yield under the conditions, producing **7ba** in 73% yield (run 4). On the other hand, the yield of **7ba** was decreased to 51% when the catalyst loading was reduced to 5 mol % (run 5). When non-protected 2-butyn-1,4-diol (**6c**) was used as an alkyne substrate, no desired

product **7ca** was obtained (run 6). On the other hand, the reaction of **6d**, having two THP groups as protecting groups, and **2a** under the same conditions gave isoquinoline **7da** in 70% yield (run 7). The existence of a carbonyl group in the protecting groups also retarded the reaction, and the reaction of **6e** or **6f** under the same conditions gave the corresponding product **7ea** or **7fa**, respectively, in a low yield (runs 8 and 9).

Table 1. [2+2+2] Cycloaddition of alkynes **6** and **2a**[a]



run	alkyne (**6**)	ratio of **6**/**2a**	product (**7**)	yield (%)
1[b]	**6a**	—	 **7aa**	40[c]
2	 **6b**	1/4	 **7ba**	60[d]
3	**6b**	4/1	**7ba**	72[c]
4[e]	**6b**	4/1	**7ba**	73[c]
5[f]	**6b**	4/1	**7ba**	51[c]
				
6	**6c**: R'=H	4/1	**7ca**: R=CH_2OH	—
7[e]	**6d**: R'=THP	4/1	**7da**: R=CH_2OTHP	70[c]
8[e]	**6e**: R'=$CONEt_2$	4/1	**7ea**: R=$CH_2OCONEt_2$	12[c]
9[e]	**6f**: R'=Ac	4/1	**7fa**: R=CH_2OAc	14[c]

[a] All reactions except for run 1 were carried out as follows: a solution of **6** was added over a period of 3 h to a mixture of **2a**, $Ni(cod)_2$, PPh_3, and CsF, and the resultant mixture was stirred for an additional 2 h. [b] The reaction was carried out under an atmosphere of acetylene (1 atm). [c] Based on **2a**. [d] Based on **6**. [e] 10 mol% $Ni(cod)_2$ and 20 mol% PPh_3 were used. [f] 5 mol% $Ni(cod)_2$ and 10 mol% PPh_3 were used.

Next, unsymmetrical alkynes having a propargylic oxygen functionality such as **6g**-**6i** (Figure 1) were screened in the [2+2+2] cycloaddition with **2a** under the similar conditions, producing none or a trace amount of desired isoquinolines as a mixture of isomers. After various attempts, it was found that 1,3-diyne **6j** showed a good reactivity and selectivity.[4] Thus, the reaction of **6j** and **2a** under the optimized conditions gave the corresponding isoquinoline derivative **7ja** as a single isomer in 60% yield along with a mixture of unidentified polymers (Table 2, run 1). The stereochemistry of **7ja** was unambiguously determined by NOE experiments after assignment of the related protons using ^{1}H NMR, ^{13}C NMR, and HMBC spectra (Figure 2). The reactions of 1,3-diynes **6k**-**6n** under the same conditions

also produced isoquinolines **7ka**-**7na** as single isomers (Table 2, runs 2-5), and those stereochemistries were determined in a manner similar to that in the case of **7ja** by NOE experiments.

Figure 1.

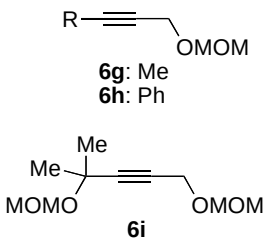


Figure 2.

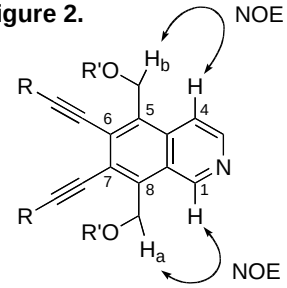
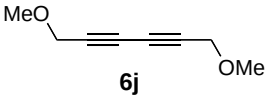
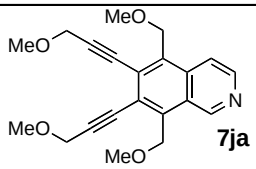
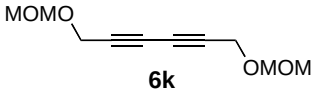
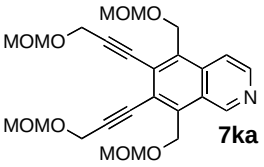
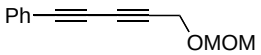
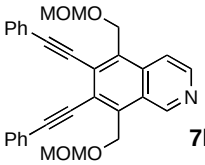
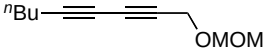
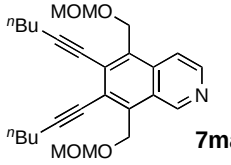
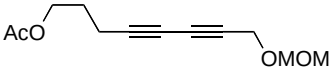
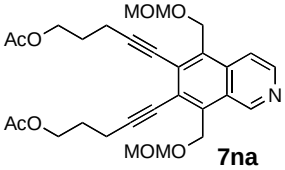


Table 2. [2+2+2] Cycloaddition of 1,3-diynes and **2a**[a]

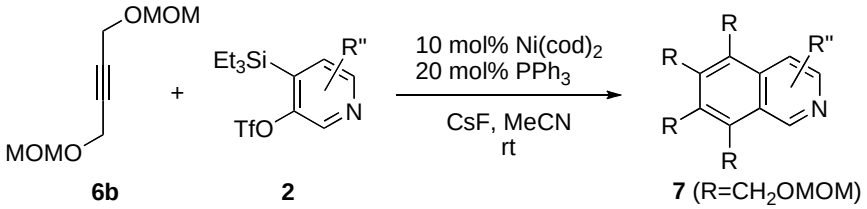
run	alkyne (**6**)	product (**7**)[b]	yield (%)
1	 **6j**	 **7ja**	60
2	 **6k**	 **7ka**	68
3	 **6l**	 **7la**	46
4	 **6m**	 **7ma**	61
5	 **6n**	 **7na**	57

[a] All reactions were carried out as follows: a solution of alkyne **6** (4 eq. to **2a**) was added via a syringe pump over a period of 3 h to a mixture of **2a**, $Ni(cod)_2$ (10 mol%), PPh_3 (20 mol%), and CsF (3 equiv. to **2a**) in MeCN at room temperature, and the resulting mixture was stirred for an additional 2 h. [b] The stereochemistries of products **7ja**-**7na** were determined by NOE experiments between H_1 and H_a, and H_4 and H_b, respectively (see, **Figure 2**).

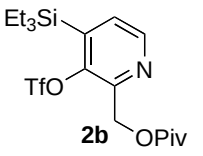
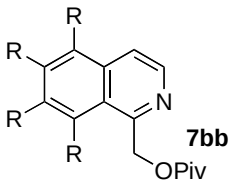
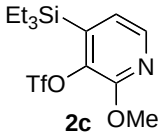
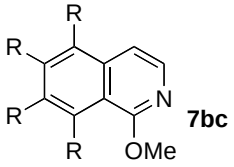
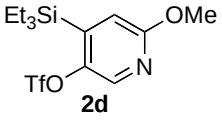
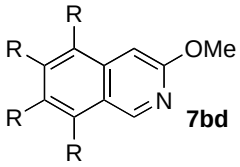
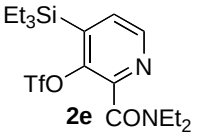
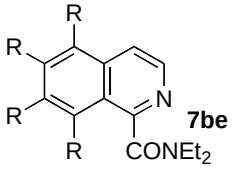
It is noteworthy that all products in these cases were always obtained as a single isomer, with unreacted alkyne parts of the starting 1,3-diynes **6j**-**6n** located at C6- and C7-positions and protected hydroxymethyl moieties located at C5- and C8-positions in the isoquinoline rings of the products **7ja**-**7na**.

We next turned our attention to the scope of 3,4-pyridynes in the [2+2+2] cycloaddition. The results of reactions of **6b** with various 3,4-pyridyne precursors **2** are summarized in Table 3.

Table 3. Scope of 3,4-pyridyne precursors in the [2+2+2] cycloaddition with **6b**



6b **2** **7** (R=CH_2OMOM)

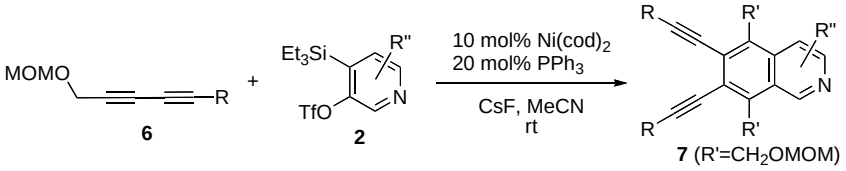
run	pyridyne precursor (**2**)	product (**7**)	yield (%)
1	 **2b**	 **7bb**	80
2	 **2c**	 **7bc**	81
3	 **2d**	 **7bd**	80
4	 **2e**	 **7be**	10

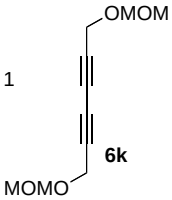
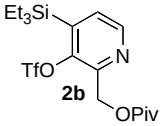
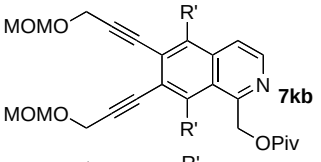
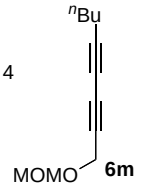
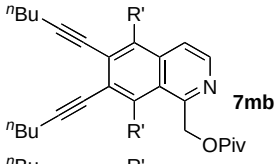
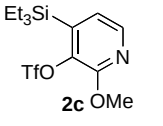
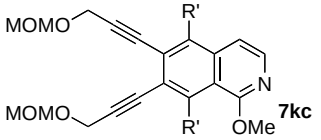
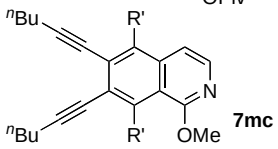
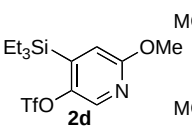
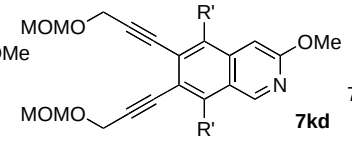
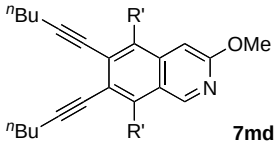
The reaction of **6b** and **2b**, which has a pivaloyloxymethyl group at the C2 position of the pyridine ring, under the above-described optimal conditions gave the corresponding isoquinoline **7bb** in 80% yield (Table 3, run 1). Electron-donating groups such as a methoxy group on the pyridyne precursor are tolerated in the [2+2+2] cycloaddition, and the reaction of **2c** or **2d** with **6b** produced the corresponding isoquinoline **7bc** or **7bd** in 81% or 80% yield, respectively. On the other hand, in the case of **2e** having an electron-withdrawing group, the yield of the product **7be** was lowered to 10%.

The scope of 3,4-pyridynes in the [2+2+2] cycloaddition of 1,3-diynes was also investigated, and the results of the reaction with **6k** and **6m** are summarized in Table 4. The reaction of 1,3-diyne **6k** and the precursor **2b**, **2c**, or **2d** under the optimized conditions produced the corresponding isoquinoline **7kb**, **7kc**, or **7kd** as a single isomer in 72%, 70%, or 74% yield, respectively (runs 1-3). In the case of the reaction

of **2b**, **2c**, and **2d** with **6m** under the same conditions, the isoquinolines **7mb**, **7mc**, and **7md** were again produced as a single isomer in good yields, respectively (runs 4-6).

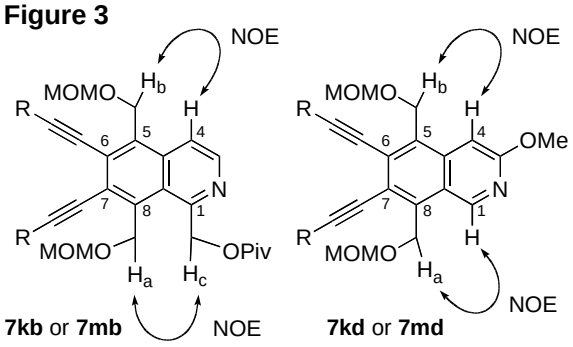
Table 4. Scope of 3,4-pyridyne precursors in the [2+2+2] cycloaddition of 1,3-diynes



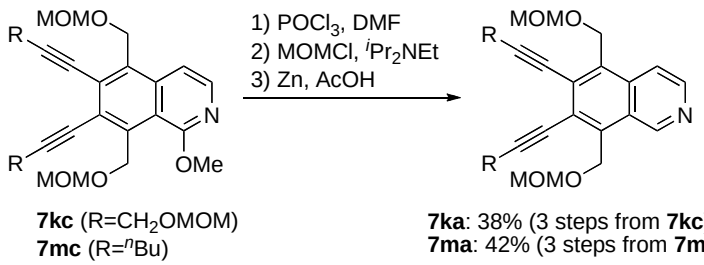
run	alkyne (**6**)	precursor (**2**)	product (**7**)	yield (%)	run	alkyne (**6**)	precursor (**2**)	product (**7**)	yield (%)
1				72	4		**2b**		79
2	**6k**			70	5	**6m**	**2c**		77
3	**6k**			74	6	**6m**	**2d**		82

The stereochemistries of **7kb**, **7kd**, **7mb**, and **7md** were determined in a similar manner by NOE experiments (Figure 3). On the other hand, **7kc** and **7mc** were successfully converted to **7ka** and **7ma** via conversion of the C1-methoxy group to a chloride[5] (Scheme 3), the spectral data of which were identical to those obtained by the experiments described in Table 2. Notably, in these cases, the same tendency as that in the above-mentioned reactions in Table 2 was observed for the stereochemistry concerned the alkyne moieties and the protected hydroxymethyl moieties in the products.

Figure 3



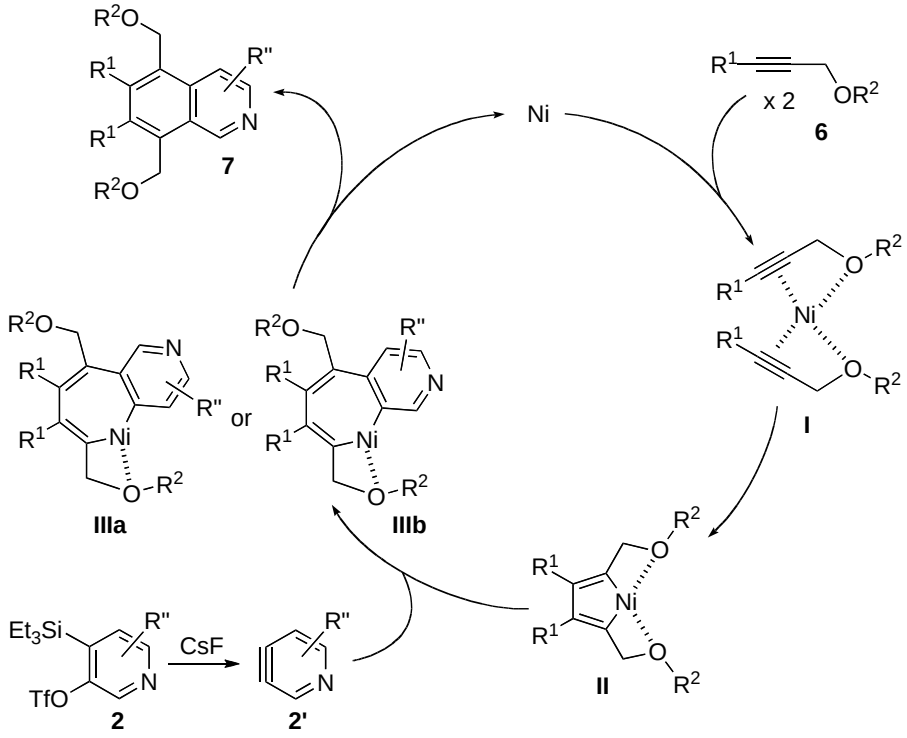
Scheme 3



A possible mechanism of the [2+2+2] cycloaddition of 3,4-pyridyne and two molecules of alkynes is shown in Scheme 4. On the basis of the results described above, it is obvious that the existence of a propargylic oxygen functionality in alkynes **6** is crucial to enhance the reactivity and to control the

selectivity of the products in this nickel(0)-catalyzed [2+2+2] cycloaddition with 3,4-pyridiynes.[6] Thus, the oxygen at a propargylic position of **6** would initially coordinate to a nickel complex and form the nickel complex **I**. Then oxidative addition would proceed to produce nickelacyclopentadiene intermediate **II** in a stereoselective manner. Insertion of 3,4-pyridyne **2'**, generated in situ from the precursor **2** and CsF, into the nickel-carbon bond of **II** would afford seven-membered nickelacycle intermediate **IIIa** or **IIIb**, from which reductive elimination would proceed to stereoselectively produce substituted isoquinoline **7**.

Scheme 4. Mechanism for [2+2+2] cycloaddition of 3,4-pyridynes and two molecules of alkyne



In summary, we succeeded in developing a novel methodology for the synthesis of substituted isoquinolines via a nickel(0)-catalyzed [2+2+2] cycloaddition of 3,4-pyridynes with two molecules of alkyne. Through screening of various alkynes, 2-butyn-1,4-diol derivatives and 1,3-diynes were found to be suitable as substrates for this [2+2+2] cycloaddition. It was also found that a propargylic oxygen functionality in these alkynes is essential for the reactivity and the selectivity of the products in the reaction. Further studies along this line are in progress.

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