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Ruthenium(II)-Catalyzed Cycloaddition of 1,6-Diynes with Isocyanates Leading to Bicyclic Pyridones

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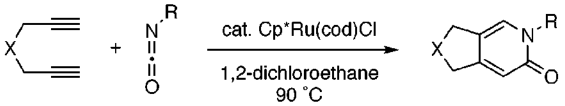
ABSTRACT



A ruthenium(II) complex possessing a planar Cp* ligand, Cp*Ru(cod)Cl, effectively catalyzed the [2 + 2 + 2] cycloaddition of 1,6-diynes with isocyanates to afford bicyclic pyridones in 58–87% yields.

Transition-metal-catalyzed cyclocotrimerization of two molecules of an alkyne and an isocyanate is an efficient method to construct substituted 2-pyridone rings.[1] Such a catalytic pyridone formation has first been accomplished independently by Yamazaki using Co catalysts[2] and by Hoberg using Ni catalysts.[3]

The cobalt catalysis has further been extended to partially intramolecular versions utilizing isocyanatopentynes or α,ω-diynes by Vollhardt and co-workers.[4] The cycloadditions of isocyanatoalkynes with several silylalkynes effectively gave 2,3-dihydro-5(1*H*)-indolizinones (Figure 1, Type I), and this strategy was elegantly applied to the total synthesis of the antitumor agent Camptothecin.[4] In contrast, the related cycloadditions of α,ω-diynes with isocyanates (Figure 1, Type II) have been less attractive, although a wide variety of readily accessible diynes and isocyanates can be directly used for this type of cycloaddition. Actually, the reactions of 1,7-octadiyne with phenyl isocyanate or 1,6-heptadiyne with β-phenethyl isocyanate were carried out in the presence of 15 mol % $CpCo(CO)_2$ by the same authors, but the expected pyridones were obtained only in 16% and 31% yields, respectively.[4] Moreover, no pyridone was formed as a result of the facile cyclotrimerization of the diyne substrate when the reaction was conducted with $Ni(cod)_2$ as the catalyst.[4]

With these facts in mind, we developed more efficient Type II cycloaddition using the ruthenium catalyst. Herein, we wish to report our preliminary results of the ruthenium-catalyzed cycloaddition of 1,6-diynes with isocyanates.

To search for a new catalytic system,[5] we first attempted the cycloaddition of a malonate-derived 1,6-diyne **1a** (X = $C(CO_2Me)_2$) and phenyl isocyanate (**2a**) in the presence of

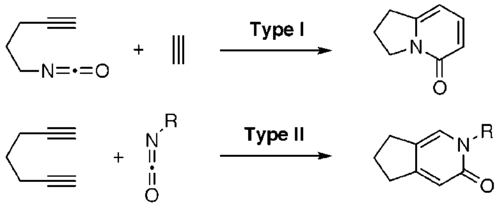


Figure 1. Partially intramolecular [2 + 2 + 2] cyclocotrimerizations of alkynes and isocyanates.

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[1] (a) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, Chapter 7.3, pp 741−770. (b) Shore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 9.4, pp 1129−1162.

[2] Hong, P.; Yamazaki, H. *Tetrahedron Lett.* **1977**, 1333−1336.

[3] Hoberg, H.; Oster, B. W. *Synthesis* **1982**, 324−325.

[4] Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786−4800.

[5] For other examples, see: (a) Flynn, S. T.; Hasso-Henderson, S. E.; Parkins, A. W. *J. Mol. Catal.* **1985**, *32*, 101−105. (b) Diversi, P.; Ingrosso, G.; Lucherini, A.; Malquori, S. *J. Mol. Catal.* **1987**, *40*, 267−280.

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a catalytic amount of Cp*Ru(cod)Cl (Cp* = pentamethylcyclopentadienyl, cod = 1,5-cyclooctadiene), which is the excellent catalyst for the related cycloaddition of 1,6-diynes with alkenes or monoalkynes.[6] A 1,2-dichloroethane (DCE) solution of **1a** was added to the solution of **2a** (2 equiv) and 10 mol % Cp*Ru(cod)Cl in DCE at room temperature, and the resultant solution was then refluxed for 2 h to afford the desired bicyclic pyridone **3aa** and the diyne dimer **4a** in 45% and 18% yields, respectively (Scheme 1 and Table 1, run 1). The competitive formation of **4a** was effectively suppressed by improving the procedure as follows: to a refluxed solution of the catalyst and 2 equiv of **2a** in DCE was added dropwise a solution of **1a** and another 2 equiv of **2a** in DCE. As a result, the yield of **3aa** was raised to 89% (run 2).[7] The yield was, however, considerably lowered in benzene (run 3), and the reaction hardly proceeded in acetonitrile even after 27 h (run 4).

Scheme 1

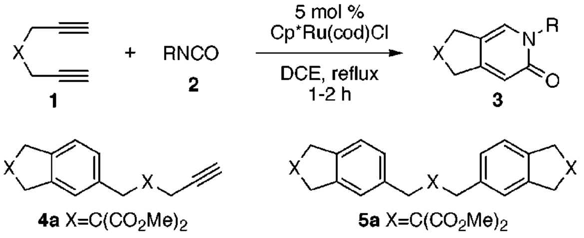


Table 1. Ru-Catalyzed Cycloaddition of 1,6-Heptadiyne **1a** with Isocyanate **2a**[a]

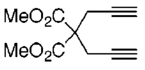
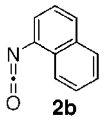
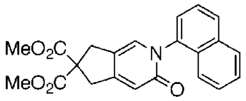
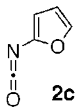
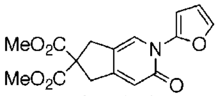
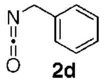
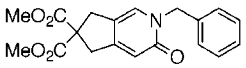
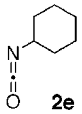
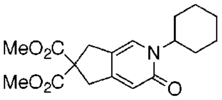
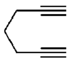
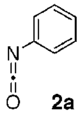
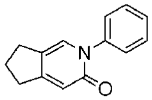
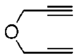
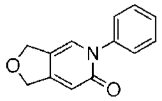
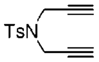
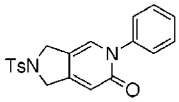
run	catalyst (mol %)	**2a** (equiv)	solvent[b]	time (h)	**3aa** yield (%)[c]
1	Cp*Ru(cod)Cl (10)	2	DCE	2	45
2	Cp*Ru(cod)Cl (10)	2 + 2[d]	DCE	1	89
3	Cp*Ru(cod)Cl (10)	2 + 2[d]	C_6H_6	20	34
4	Cp*Ru(cod)Cl (10)	2 + 2[d]	AN	27	7[e]
5	$[Cp^*RuCl_2]_2$ (10)	2 + 2[d]	DCE	1	74
6	$Ru(cod)(AN)_2Cl_2$ (10)	2 + 2[d]	DCE	3	35
7	$C_6Me_6Ru(cod)$ (10)	2 + 2[d]	DCE	18	0
8	Cp*Ru(cod)Cl (5)	2 + 2[d]	DCE	1	87
9	Cp*Ru(cod)Cl (2)	2 + 2[d]	DCE	2	65

[a] To a solution of a catalyst and **2a** (2 equiv) was added a solution of **1a**, and the solution was refluxed for the time indicated. [b] DCE = 1,2-dichloroethane; AN = acetonitrile. [c] Isolated yields. [d] To a refluxed solution of a catalyst and 2 equiv of **2a** in DCE was added dropwise a solution of **1a** and another 2 equiv of **2a** in DCE. [e] The diyne **2a** was recovered in 61% yield.

We then examined other typical organoruthenium complexes with various oxidation states and ligand fields. A dinuclear ruthenium(III) complex having a Cp* ligand, $[Cp^*RuCl_2]_2$, also gave **3aa**, albeit in slightly lower yield (run 5). The importance of the planar Cp* ligand was clearly elucidated by the fact that a ruthenium(II) complex without the Cp* ligand, $Ru(cod)(AN)_2Cl_2$, gave **3aa** only in 35% yield along with an inseparable mixture of **4a** and unknown byproducts (run 6). On the other hand, a ruthenium(0) complex having a bulky planar hexamethylbenzene ligand, $C_6Me_6Ru(cod)$, was found totally ineffective for the present cycloaddition (run 7). Finally, the catalyst amount was optimized using the best catalyst. A lower catalyst load of 5 mol % Cp*Ru(cod)Cl gave **3aa** in similar high yield (run 8), although 2 mol % of the catalyst was not enough for the completion of the reaction (run 9).

Having optimized the reaction conditions, other isocyanates were subjected to the cycloaddition with the diyne **1a** as summarized in Table 2. In the same manner with **2a**, 1-naphthyl isocyanate (**2b**) and 2-furyl isocyanate (**2c**) underwent the cycloaddition with **1a** to afford the corre-

Table 2. Cp*Ru(cod)Cl-Catalyzed Cydoaddition of 1,6-Heptadiynes **1a−d** with Isocyanates **2a−f**[a]

run	diynes	isocyanates	pyridones yield (%)[b]
1	 **1a**	 **2b**	 **3ab** (79)
2	**1a**	 **2c**	 **3ac** (87)
3	**1a**	 **2d**	 **3ad** (93)
4	**1a**	 **2e**	 **3ae** (85)
5	 **1b**	 **2a**	 **3ba** (62)
6	 **1c**	**2a**	 **3ca** (58)
7	 **1d**	**2a**	 **3da** (82)

[a] To a refluxing solution of 5 mol % Cp*Ru(cod)Cl and **2** (2 equiv) in DCE was added dropwise a solution of **1** and **2** (2 equiv) in DCE, and the solution was refluxed for 1 h (2 h for runs 6 and 7). [b] Isolated yields.

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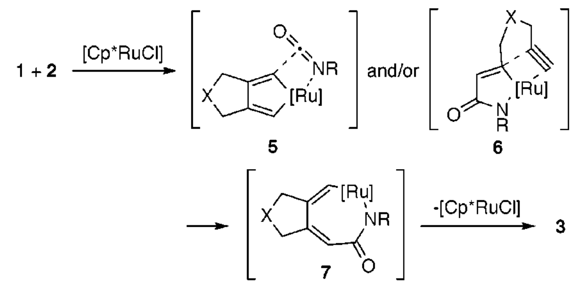
[6] (a) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549−550. (b) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Kawaguchi, H.; Tatsumi, K.; Itoh, K. *J. Am. Chem. Soc.* **2000**, *122*, 4310−4319.

[7] An excess of the isocyanate **2a** was recovered as carbanilide.

sponding products **3ab** and **3ac** in 79% and 87% yields, respectively (runs 1 and 2). In addition to the aryl isocyanates, alkyl isocyanates can be employed in the present protocol. Isocyanates **2d** and **2e**, which possess a primary or secondary alkyl group on their nitrogen atom, effectively gave the desired *N*-alkyl pyridones **3ad** and **3ae** in high yields. Exceptionally, *tert*-butyl isocyanate **2f** gave no pyridone product under the same reaction conditions. This is probably because the coordination of its C═N bond to the ruthenium center was completely hindered by the bulky *tert*-butyl group on the nitrogen atom. In this case, the diyne cyclotrimerization products **4a** and **5a** were formed in 17% and 71% yields, respectively.

The generality of the present ruthenium catalysis was further examined with respect to the diyne substrate. Parent 1,6-heptadiyne (**1b**) and dipropargyl ether (**1c**), having no tertiary center on the tether chain, also reacted with **2a** to afford the expected *N*-phenyl pyridones **3ba** and **3ca** in 62% and 58% yields, respectively (runs 5 and 6), although these diynes were anticipated to be ineffective without the kinetic Thorpe−Ingold effect.[8] *N*,*N*-Dipropargyl *p*-toluenesulfonamide (**1d**) efficiently afforded a pyrroline-fused pyridone **3da** in high yield with the aid of the proximity effect caused by the bulky *p*-tosyl group (run 7).

Scheme 2



Scheme 2 shows a plausible mechanism of the Ru(II)-catalyzed cycloaddition of 1,6-diynes **1** with isocyanates **2**. Yamazaki has proposed that a cobaltacyclopentadiene is initially formed from the oxidative cyclization of two molecules of an alkyne, and the subsequent reaction of the cobaltacycle intermediate with an isocyanate affords a pyridone. Such a metallacyclopentadiene mechanism was supported by the fact that isolated cobaltacyclopentadienes and isocyanates produced the corresponding pyridones.[9] On the other hand, an alternative mechanism, which starts with the formation of an azanickelacyclopentenone from an alkyne and an isocyanate, was proposed in Hoberg's nickel-catalyzed cyclocotrimerizations.[10] According to these claims, two mechanisms including ruthenacyclopentadiene intermediates[11,12] **5** or azaruthenacyclopentenones **6** can be assumed for our case. In either event, common intermediates **7** is consequently produced, and the reductive elimination of the [Cp*RuCl] fragment from **7** gives the bicyclic pyridones **3**. The metallacyclopentadiene mechanism is, however, preferable to the ruthenium-catalyzed cycloaddition using diynes as alkyne components. Without exception, 1,6-diynes are essential substrates for our previously reported ruthenium-catalyzed [2 + 2 + 2] cycloadditions.[6] This is also true of the present pyridone annulation. A typical monoalkyne, 1-hexyne, did not undergo [2 + 2 + 2] cyclocotrimerization with **2a** under the same reaction conditions with the diyne cycloaddition. This is probably because the ruthenacyclopentadiene formation from a 1,6-diyne is entropically more favorable than that from two molecules of a monoalkyne. These facts supports the ruthenacyclopentadiene mechanism (**1** + **2** → **5** → **7** → **3**).

Acknowledgment. We gratefully acknowledge financial support (09750947, 09305059, 10132222, 12450360, and 13875174) from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: Typical procedure for the cycloaddition of **1** and **2** and analytical data for the pyridones **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080−1106.

(9) Hong, P.; Yamazaki, H. *Synthesis* **1977**, 50−52.

(10) (a) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1982**, *234*, C35−C38. (b) Hoberg, H.; Oster, B. W. *J. Orgnomet. Chem.* **1983**, *252*, 359−364.

(11) For catalytic reactions involving ruthenacyclopentadiene intermediates, see: (a) Lidner, E.; Jansen, R.-M.; Mayer, H. A.; Hiller, W.; Fawzi, R. *Organometallics* **1989**, *8*, 2355−2360. (b) Yi, C. S.; Torres-Lubian, J. R.; Liu, N.; Rheingold, A. L.; Guzei, I. A. *Organometallics* **1998**, *17*, 1257−1259. (c) Chatani, N.; Fukumoto, Y.; Ida, T.; Murai, S. *J. Am. Chem. Soc.* **1993**, *115*, 11614−11615. Also, see ref 6.

(12) For the formation of ruthenacyclopentadiene/ruthenacyclopentatriene complexes from alkynes, see: (a) Bruce, M. I.; Matisons, J. G. *J. Organomet. Chem.* **1983**, *251*, 249−260. (b) Albers, M. O.; de Waal, D. J. A.; Liles, D. C.; Robinson, D. J.; Singleton, E.; Wiege, M. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1680−1682. (c) Campion, B. K.; Heyn, R. H.; Tilley, T. D. *Organometallics* **1990**, *9*, 1106−1112. (d) Bruce, M. I.; Koutsantonis, G. A. *Aust. J. Chem.* **1991**, *44*, 207−217. (e) Ernst, C.; Walter, O.; Dinjus, E.; Görls *J. Prakt. Chem.* **1999**, *341*, 801−804. Also see refs 10a and 10b.