J. Am. Chem. Soc. **2001,** *123,* 6189−6190 6189

Significant Chemo- and Regioselectivies in the Ru(II)-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes with Dicyanides

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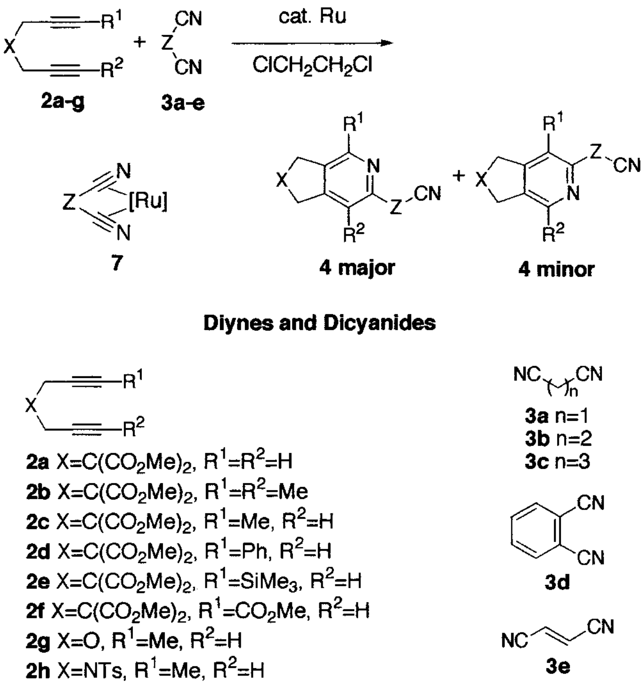
Received November 7, 2000

The transition-metal-mediated [2 + 2 + 2] cyclocotrimerization of two alkynes and a nitrile is a powerful and straightforward route to substituted pyridines.[1,2] Especially, catalytic cyclocotrimerization is undoubtedly desirable as a metal-atom economical and environmentally benign process. Having improved the chemo- and regioselectivities, catalytic methods have also been applied to the practical syntheses of biologically or functionally interesting molecules.[3] Surprisingly, such useful catalysis has completely been confined to cobalt[4] and rhodium[5] since first reported by Wakatsuki and Yamazaki,[1] although a variety of transition metals (Ti,[6] Ta,[7] Co,[1] Rh,[8] and Ni[9]) have been found to mediate the stoichiometric cyclocotrimerization. With these facts in mind, we investigated the first ruthenium(II)-catalyzed version of this useful pyridine annulation and found that the cycloaddition of 1,6-diynes with dicyanides proceeded with the significant chemo- and regioselectivities under mild conditions.[10]

Scheme 1



As an initial attempt, we first examined the reaction of a symmetrical 1,6-diyne **2a** with acetonitrile. The ruthenium(II) complex, Cp*Ru(cod)Cl (**1a**), having both a planar ligand (Cp* = pentamethylcyclopentadienyl) and a readily leaving ligand (cod = 1,5-cyclooctadiene), is a catalyst of choice, because **1a** was found to be an efficient catalyst for the cycloaddition of the 1,6-diynes with alkynes or alkenes.[11a,b] The reaction of **2a** and acetonitrile (2 equiv. of **2a**) in the presence of 1 mol % **1a** at room temperature, however, only gave a mixture of the diyne cyclotrimerization products.[12] The diyne **2a** was quantitatively recovered using acetonitrile as the solvent. In sharp contrast, **2a** reacted with malononitrile (**3a**) (1.5 equiv) in the presence of 2 mol % **1a** at room temperature for 26 h to afford the bicyclic pyridine **4a** in 72% yields along with the recovered **2a** (Scheme 1). It is noteworthy that the undesired cyclotrimerization of the diyne **2a** was completely restrained in the presence of **3a**. At 60 °C, the diyne **2a** was completely consumed for 7 h, and the yield was improved to 91% (Table 1, entry 1). An increased amount of the catalyst **1a** (5 mol %) effectively converted **2a** into **4a** with an excellent yield (95%) even at room temperature (entry 2). A Ru(III) complex, [Cp*RuCl$_2$]$_2$ (**1b**), exhibiting a similar efficiency in the cycloaddition of 1,6-diynes with alkynes or heterocycloalkenes was found less effective for the present case (entry 3). The necessity of a planar supporting ligand was demonstrated by the reaction using RuCl$_2$(cod)(CH$_3$CN)$_2$ (**1c**), which gave no cycloadduct in the same reaction conditions. A Ru(0) complex, (C$_6$Me$_6$)Ru(cod) (**1d**), also gave no cycloadduct at all, whereas it has a planar hexamethylbenzene ligand.

In addition to the above terminal diyne **2a**, an internal diyne **2b** can also be used to the present cycloaddition. In the presence of 5 mol % **1a**, **2h** reacted with **3a** at 80 °C for 20 h to chemoselectively afford a bicyclic pyridine **4b** in 70% yield (entry 4).

As already mentioned, Co catalysts have extensively been used for the [2 + 2 + 2] pyridine annulation.[2a] The most widely used,

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10.1021/ja003890r CCC: $20.00

Table 1. Cp*Ru(cod)Cl-Catalyzed Cycloaddition of 1,6-Diynes **2a**−**g** with Dicyanides **3a**−**e**

entry	diyne/ dicyanide	cat (mol %)/ temp./time	product [yield (%)/ isomer ratio[a]]
1	**2a/3a**	**1a** (2)/60 °C/7 h	**4a** [91]
2	**2a/3a**	**1a** (5)/rt/2.5 h	**4a** [95]
3	**2a/3a**	**1b** (2)/rt/22 h	**4a** [22][b]
4	**2b/3a**	1a (5)/80 °C/20 h	**4b** [70]
5	**2c/3a**	**1a** (2)/60 °C/5 h	**4c** [97/95:5]
6	**2d/3a**	**1a** (10)/60 °C/24 h	**4d** [78/100:0][c]
7	**2e/3a**	**1a** (5)/60 °C/5.5 h	**4e** [92/100:0]
8	**2f/3a**	**1a** (5)/rt/24 h	**4f** [80/100:0]
9	**2 g/3a**	**1a** (2)/60 °C/16 h	**4 g** [97/95:5]
10	**2h/3a**	**1a** (2)/60 °C/0.5 h	**4h** [95/100:0]
11	**2c/3b**	**1a** (2)/60 °C/1.5 h	**4i** [73/100:0]
12	**2c/3c**	**1a** (5)/rt/22 h	**4j** [46/100:0]
13	**2c/3d**	**1a** (2)/60 °C/2.5 h	**4k** [88/100:0]
14	**2c/3e**	**1a** (2)/60 °C/7 h	**4l** [88/100:0]

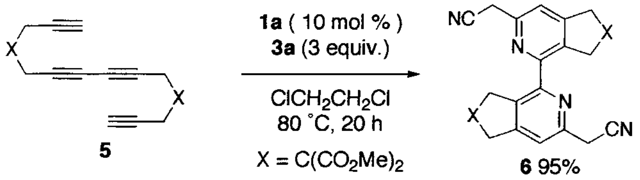
[a] The isomer ratio was determined by ^{1}H NMR. [b] The diyne **2a** was recovered in 72%. [c] The diyne **2d** was recovered in 11% yield.

readily accessible CpCo(cod) (5 mol %), however, failed to catalyze the cycloaddition of the diyne **2a** and the dicyanide **3a** at room temperature,[13] although it has a similar ligand field with the ruthenium complex **1a**. Another interesting feature of the present Ru(II)-catalyzed protocol is that only one of the two cyano groups in **3a** was involved in the pyridine-ring formation while the other remained intact after the complete conversion of the diyne **2a**. This is in striking contrast to the CpCo(cod)-catalyzed cyclocotrimerization of alkynes with dicyanides, which gave both monopyridines and bipyridines.[14a] The selective formation of the mono annulation product requires excess dicyanides for the cobalt catalysis.[14b]

The regiochemistry of the present pyridine synthesis was then investigated using unsymmetrical 1,6-diynes **2c**−**h** having a variety of terminal substituents and malononitrile (**3a**) (Scheme 1). As summarized in Table 1, all of the reactions were carried out under mild conditions (rt or 60 °C) to furnish fused pyridines in good yields with excellent regioselectivity preferable to the 2,3,4,6-substituted isomers over the 2,3,4,5-substituted isomers. In some cases, increased amounts of the catalyst **1a** were required due to the slow reaction rates (entries 6 and 7). A propiolate derivative **2f** proved to dimerize more easily than the other diynes, but the reaction employing 5 mol % **1a** at room temperature effectively gave rise to a 2-pyridinecarboxylate **4f** as the major product (entry 8). Moreover, interesting 2,5-dihydrofuran- and 3-pyrroline-fused pyridines **4g** and **4h** were effectively assembled in one step from **3a** and an ether **2g** or a tosylamide **2h** (entries 9 and 10).

To establish the generality of the observed chemo- and regioselectivities of our protocol, several other dinitriles **3b**−**e** were then subjected to the catalyzed cycloaddition with the diyne **2c**. A tether unit connecting the two cyano groups has a decisive effect upon the chemoselectivity. Succinonitrile (**3b**) and glutaronitrile (**3c**), in which the two cyano groups are separated by two or tree methylene units gave **4i** and **4j** in 73 and 46% yields, respectively, along with the concomitant formation of the dimer of **2b** (entries 11 and 12). These results clearly suggest that the longer tether favored the competitive cyclotrimerization of the diyne. On the other hand, *o*-phthalonitrile (**3d**) and fumaronitrile (**3e**), in which two cyano groups are connected by a two-sp^2-carbon tether, gave better results. The corresponding cycloadducts **4k** and **4l** were obtained as the sole product both in the higher yields of 88% than **4i** (entries 13 and 14).

Scheme 2



The synthetic potential of the present protocol was further demonstrated by the following one-step construction of a 2,2′-bipyridine framework (Scheme 2). Recently, Saá et al. have reported the co-catalyzed tandem cycloaddition of 5-hexynenitrile with 1,3-diynes to give 2,2′-bipyridines and 2,3′-bipyridines in the yields of 9−63% with variable isomer ratio.[3f] Interestingly, in our case, a 1,6,8,13-tetrayne **5**, which was readily synthesized from commercial hexa-2,4-diyne-1,6-diol, was reacted with malononitrile (**3a**) using 10 mol % **1a** at 80 °C for 20 h to afford the desired bipyridine **6** as the sole product in 95% yield.

Although the present cycloaddition was envisaged to proceed via the metallacyclopentadiene mechanism, similar to the well-established mechanism of co-catalysis,[2] the origin of the significant chemoselectivity due to the dicyanides has not yet been clarified. The IR spectra of the 1:1 solution of **1a** and **3a** in CHCl$_3$ showed a strong band at 1720 cm^{-1}, which is typical η^2-nitrile absorption.[15] The two cyano groups in **3a** might be favorable for the η^2-coordination of the cyano group in a bidentate fashion (**7** in Scheme 1). As a result, the cyclotrimerization of the diynes was suppressed, and the η^2-coordination of the cyano moiety facilitates the insertion of the C−N triple bond into ruthenacyclopentadienes. Such an assumption, however, cannot be applied to the dicyanide **3e**, because its cyano groups oriented *trans* to each other. The elucidation of the detailed reaction mechanism must wait further study.

Acknowledgment. This work was supported by the Ministry of Education, Science, Sports, and Culture, Japan (Grants No.12450360 and 12875175).

Supporting Information Available: Experimental procedures and analytical data for **4a**−**l** and **6** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] CpCo(cod) can be activated by the irradiation with a mercury high-pressure lamp to catalyze pyridine annulation even at 25 °C (Schulz, W.; Pracejus, H.; Oehme, G. *Tetrahedron Lett.* **1989**, *30*, 1229−1232). A more labile complex CpCo(C$_2$H$_4$)$_2$ and arene-solvated cobalt atoms, obtained by Co vapor and arenes, have also been reported to promote pyridine-annulation at room temperature (see refs 10d,e).

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