

Synthesis of Substituted 2,2'-Bipyridines and 2,2':6',2''-Terpyridines by Cobalt-Catalyzed Cycloaddition Reactions of Nitriles and α,ω -Diyne with Exclusive Regioselectivity

Avijit Goswami,^a Kazuhiko Ohtaki,^a Kouki Kase,^a Taichi Ito,^a and Sentaro Okamoto^{a,*}

^a Department of Material & Life Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan
Fax: (+81)-45-413-9770; e-mail: okamos10@kanagawa-u.ac.jp

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Abstract: A variety of substituted 2,2'-bipyridines were synthesized by a 1,2-bis(diphenylphosphino)ethane (dppe)/cobalt chloride hexahydrate ($\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$)/zinc-catalyzed [2+2+2] cycloaddition reaction of diynes and nitriles, with all reactions exhibiting exclusive regioselectivity. Thus, symmetrical and unsymmetrical 1,6-diynes and 2-cyanopyridine reacted in the presence of 5 mol% of dppe, 5 mol% of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ and 10 mol% of zinc powder to provide the corresponding 2,2'-bipyridines. Under identical reaction conditions, 1-(2-pyridyl)-1,6-diynes and nitriles reacted smoothly with exclusive regioselectivity to produce 2,2'-bipyridines in good yield. 2,2'-Bi-

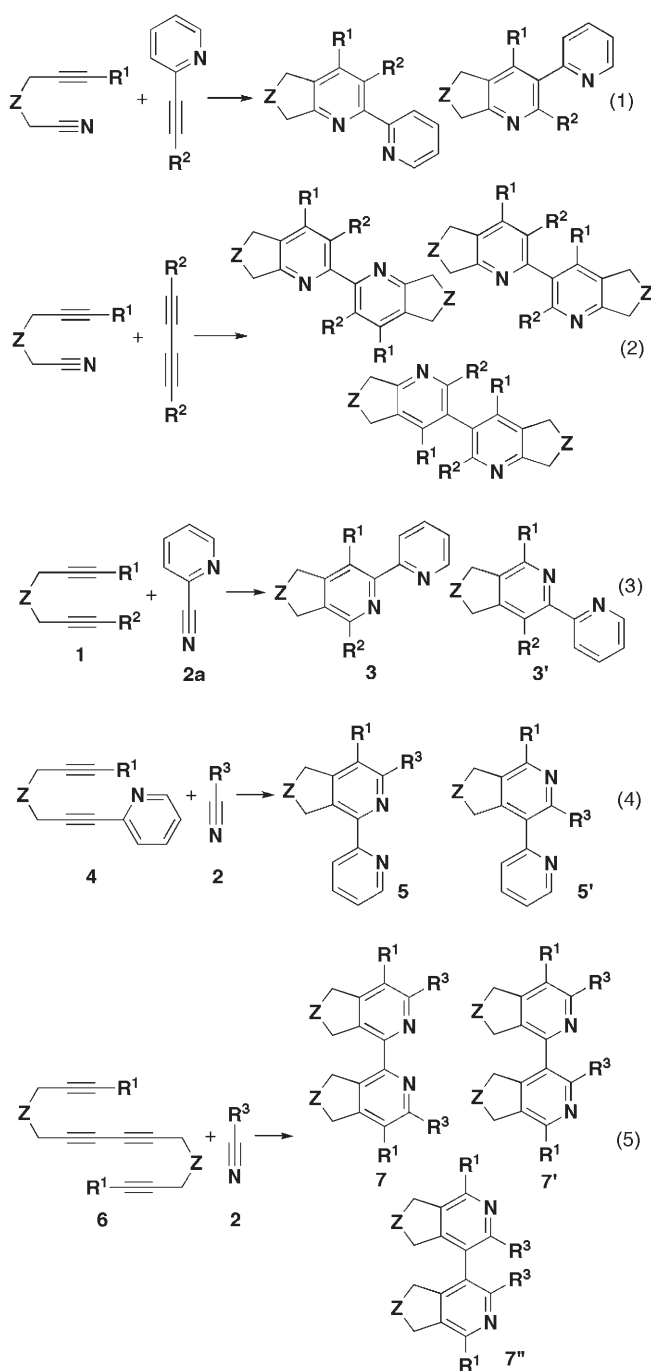
pyridines were also obtained by the double [2+2+2] cycloaddition reaction of 1,6,8,13-tetraynes with nitriles. Similarly, 2,2':6',2''-terpyridines were synthesized from 1-(2-pyridyl)-1,6-diyne and 2-cyanopyridine. The regiochemistry observed can be explained by considering the electronic nature of cobaltacyclopentadiene intermediates and nitriles. A survey of the exclusive regiochemical trend gives reasonable credence to the synthetic potential of the present method.

Keywords: 2,2'-bipyridine; cobalt catalyst; [2+2+2] cycloaddition; terpyridine

Introduction

2,2'-Bipyridines are of great importance as the substructure of biologically active compounds and particularly as a ligand capable of attachment to various metal atoms. Their metal complexes exhibit unique characteristics allowing them to fulfill a variety of synthetically useful roles such as a catalyst and its precursor, the substructure of polymer and self-assembling molecules, photosensitizer, and optical device materials.^[1] Therefore, many synthetic methods consisting of non-catalyzed heterocycle syntheses^[2] and metal-catalyzed reactions have been developed. In modern organic synthesis, the bipyridines have been prepared by transition metal-catalyzed homo-coupling (Ullmann-type reactions) of 2-halopyridine or cross-coupling between 2-halo- and 2-metalated pyridines.^[3] However, these processes are not necessarily general and are limited by the availability and reactivity of the halo- and/or metalated pyridine substrates. Recently, the metal-catalyzed [2+2+2]-type cycloaddi-

tion reaction of alkynes and nitriles has attracted much interest as a straightforward, atom-economical route to substituted pyridines^[4] and the methods have been extensively applied to bipyridine synthesis. Although several fully intra- and intermolecular reactions with alkynes and nitriles to bipyridines have been reported,^[5] from a synthetic viewpoint they suffer from lack of selectivity control, i.e., regio- and chemoselectivity for intermolecular reactions, or substrate availability and generality of the product structure for intramolecular reactions. In contrast to these reactions, the partially intramolecular reactions shown as Eq. (1) to Eq. (5) in Scheme 1 can be performed with readily available substrates and will have a reasonable generality with respect to product structure and, therefore, further development of this synthetic method is likely. In contrast to many results of bipyridine synthesis by the reactions of cyanoalkynes and alkynes shown in Eqs. (1) and (2), the regioselectivity of which was not necessarily high,^[6] the reactions of diynes and nitriles depicted in Eqs. (3) to (5) have



Scheme 1. Synthesis of bipyrindines by [2+2+2] cycloaddition reactions.

been less explored and thus lack information to evaluate their synthetic potential. To our knowledge, there is one example of the reaction of Eq. (3) where **1** consisting of two terminal alkynes ($R^1, R^2 = H$) and 2,6-dicyanopyridine instead of **2a** were used and their Ru-catalyzed reaction yielded 2-(2-pyridyl)-6-cyanopyridine.^[4b] The reactions of unsymmetrical diynes **1** ($R^1 \neq R^2$) and their regioselectivity have not been investigated at all. During our investigation, quite re-

cently, 2,2'-bipyridine synthesis by the reaction of **4** and **2** [Eq. (4)] has been reported: tetrahydro-1,1'-bisisoquinoline derivatives were synthesized by the microwave-assisted $CpCo(CO)_2$ -catalyzed reaction of nitriles with isoquinoline-attached 1,7-diyne, where a high regioselectivity to produce the 2,2'-bipyridine structure was attained.^[7] Regarding the tandem reaction of Eq. (5), it has been reported that the Ru-catalyzed reaction of a tetrayne of the type **6** with malononitrile or chloroacetonitrile gave the corresponding **7** selectively,^[8] however, there is no report of the reaction with usual unactivated alkyl and aryl nitriles.

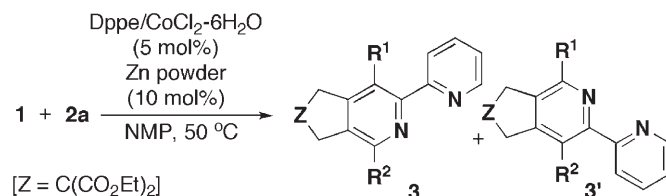
We have recently developed a facile synthesis for substituted pyridines by [2+2+2] cycloaddition reaction of α,ω -diynes and nitriles by using a 1,4-diphosphine/ $CoCl_2 \cdot 6H_2O/Zn$ catalyst, where unactivated nitriles such as acetonitrile and benzonitrile reacted smoothly under mild reaction conditions.^[9] Based on these results, we planned the preparation of 2,2'-bipyridines by the cycloadditions of the types in Eqs. (3) to (5). Thus, the cycloaddition of 1,6-diynes **1** with 2-cyanopyridine (**2a**) will give 2,2'-bipyridines **3** and their regioisomers **3'** [Eq. (3)], whereas the reaction of 1-(2-pyridyl)-1,6-diynes **4** with nitriles **2** may afford 2,2'-bipyridines **5** and their 2,3'-isomers **5'** [Eq. (4)]. In addition, 2,2'-bipyridines **7** and their isomers **7'** and **7''** may be obtained by tandem cycloaddition of tetraynes **6** and nitriles **2** [Eq. (5)]. In these reactions, it is desired that the individual regioselectivity could be controlled to produce 2,2'-isomers. Herein we disclose the successful results of these syntheses.

Results and Discussion

Reactions of 1,6-Diynes **1** with 2-Cyanopyridine (**2a**)

A preliminary investigation revealed that the reactions of Eq. (1) were not effectively catalyzed by the present reagent, a $dppe/CoCl_2 \cdot 6H_2O/Zn$, but the reactions of diynes and nitriles [Eqs. (3) to (5)] proceeded smoothly.

First, Table 1 summarizes the results of the reaction of Eq. (3) in Scheme 1. In the reaction of diynes involving a terminal alkyne group(s), a large excess amount (20 equivs.) of **2a** was employed to minimize self-cycloaddition of the diynes to a dimer. The reactions of symmetrical 1,6-diynes **1a** and **1b** with 2-cyanopyridine (**2a**) provided the corresponding 2,2'-bipyridines in good isolated yields (entries 1 and 2). Unsymmetrical diynes **1c–h** also reacted smoothly with **2a** and it is noteworthy that the reactions provided the corresponding bipyrindine with complete regioselectivity (entries 3–8). In the reactions of mono-substituted diynes **1c–e** ($R^2 = H$), the substituent R^1 is located at the 3-position of the generated pyridine ring (entries 3–5). Meanwhile, the reaction of **1f** exclusive-

Table 1. 2,2'-Bipyridine synthesis by the reaction of **1** and **2a** [Eq. (3) of Scheme 1].

Entry	1	2a (equivs.)	Time [h]	Product	Yield ^[a] (3:3') ^[b]
1	1a : R ¹ = H, R ² = H	(20)	3	3aa	65 % (–)
2	1b : R ¹ = Me, R ² = Me	(2)	12	3ba	58 % (–)
3	1c : R ¹ = Me, R ² = H	(20)	12	3ca	78 % (> 99:1)
4	1d : R ¹ = <i>n</i> -Bu, R ² = H	(20)	3	3da	67 % (> 99:1)
5	1e : R ¹ = SiMe ₃ , R ² = H	(20)	12	3ea	76 % (> 99:1)
6	1f : R ¹ = H, R ² = Ph	(20)	12	3fa	78 % (> 99:1)
7	1g : R ¹ = Me, R ² = Ph	(2)	12	3ga	47 % (> 99:1)
8	1h : R ¹ = SiMe ₃ , R ² = <i>n</i> -Bu	(2)	24	3ha	91 % (> 99:1)

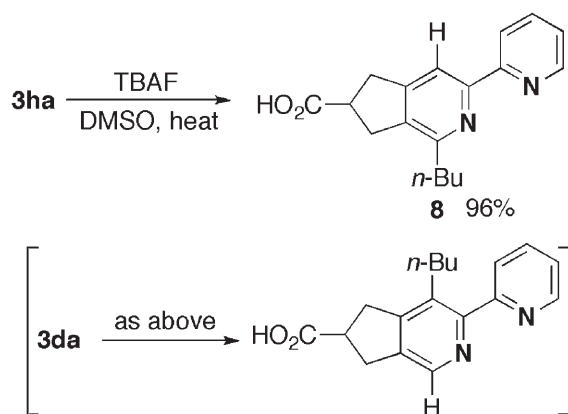
^[a] Isolated yield.^[b] Determined by ¹H NMR analysis of the crude mixture.

ly gave the product 2,2'-bipyridine **3fa** with a phenyl group at the 2-position of the resulting pyridine (entry 6). In addition, unsymmetrical diynes with two internal alkynes **1g** and **1h** also reacted with **2a** in a completely regioselective fashion. These results sug-

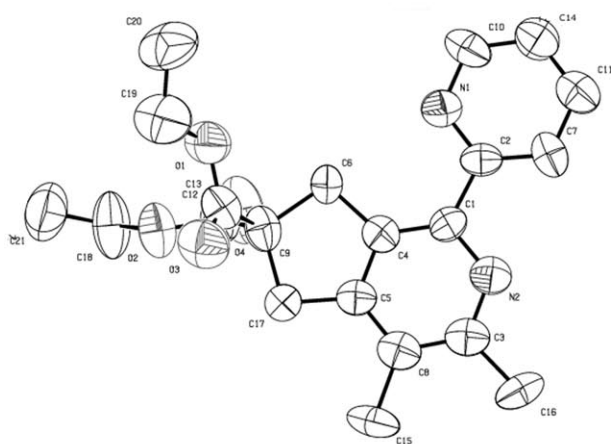
gest that the regioselectivity was controlled not sterically but electronically. It can be considered that, in all cases, the more electron-rich alkyne of the two present in diynes **1** is attached to the carbon of cyano group of **2a** (*vide infra*).

The resulting silyl-substituted pyridines such as **3ha** are synthetically useful: Protidesilylation and saponification/decarboxylation of **3ha**, by treatment with *n*-Bu₄NF in wet DMSO, provided 4,5,6-trisubstituted 2,2'-bipyridine **8** as a single regioisomer (Scheme 2), the ¹H NMR spectra of which were compared with those of the carboxylic acid derived from **3da** by saponification/decarboxylation. Regiochemically, the method is complementary to the exclusive formation of 3,4,5- or 4,5,6-trisubstituted 2,2'-bipyridines.

The formation of **8** and subsequent comparison of the aromatic peaks of its NMR spectra with those of the isomer derived from **3da** confirmed the regiochemistries of **3da** and **3ha**. Likewise, the structure was suggested for **3ca** and **3fa** as depicted in Table 1. The COLOC (correlation spectroscopy *via* long-range coupling spectrum) experiment of **3ca** and **3ga** confirmed their regiochemistry: In each case the fact that the ring methyl protons had correlations with three aromatic carbons indicated that the methyl group is present at the 3-position of the pyridine.



Scheme 2. Protidesilylation of silylated pyridine **3ha**.



Reactions of 1-(2-Pyridyl)-1,6-diynes **4** with Nitriles **2**

Next, we investigated the reaction of nitriles **2** with unsymmetrical diynes of type **4** having a 2-pyridyl moiety as a terminus [Eq. (4) in Scheme 1] and confirmed the regioselectivity between 2,2'-isomer **5** and 2,3'-isomer **5'**. Several representative results are shown in Table 2. The reaction with an appropriate amount of nitrile proceeded smoothly to give the corresponding bipyridines in good yields and, to our delight, 2,2'-bipyridines **5** were produced exclusively in all cases. Malononitrile (**2c**)^[8,9] and perfluoroalkylnitrile **2e**^[10] were highly reactive so that the reaction with 1.5 equivs. of them proceeded smoothly to provide the corresponding **5** in good yield (entries 2 and 5). The resulting cyanomethyl-substituted 2,2'-bipyridines such as **5bc** and **5ac** or their derivatives after manipulation of the cyano moiety might be expected as a tridentate ligand to metal. In addition, perfluoroalkylated bipyridines such as **5ce** might be interesting from the viewpoint of fluorine chemistry.^[11]

To confirm the regiochemistry of the products, the COLOC measurement was carried out. In the case of **5ab** and **5cb**, protons of one methyl group had two correlations with aromatic carbons, while another methyl showed three correlations. Methyl protons of **5ac**, **5ad** and **5ce**, respectively, had three correlations with aromatic carbons. In addition, the methylene protons of the nitrile α in **5bc** and **5ac** had two correlations with pyridine carbons, respectively. These facts establish that their regiochemistry is as depicted. Crystallography of **5ab** and **5ac** fully confirmed their 2,2'-bipyridine structure (Figure 1).

Reactions of 1,6,8,13-Tetraynes **6** with Nitriles **2**

Table 3 shows the results of the tandem reaction of tetraynes **6** with nitriles **2** to bis-annulated bipyridines.

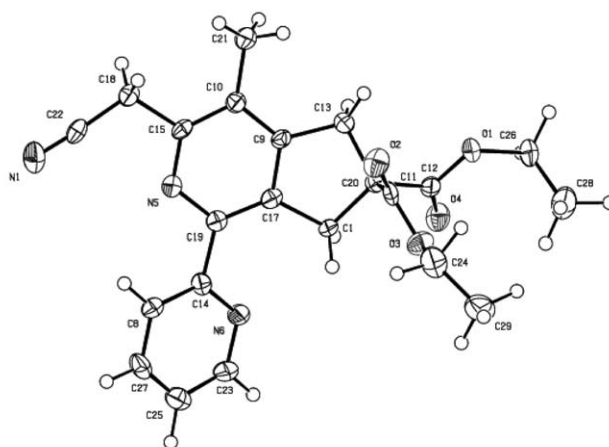


Figure 1. X-ray structures of compounds **5ab** (left) and **5ac** (right).

Table 2. Bipyridine synthesis by the reaction of **2** and **4** [Eq. (4) of Scheme 1)].

$ \begin{array}{c} \text{Dppe/CoCl}_2 \cdot 6\text{H}_2\text{O} \\ (5 \text{ mol}\%) \\ \text{Zn powder (10 mol}\%) \\ \text{NMP, 50 }^\circ\text{C} \\ \hline \mathbf{4} + \mathbf{2} \longrightarrow \begin{array}{c} \text{R}^1 \\ \text{R}^3 \\ \text{Z} \end{array} \begin{array}{c} \text{N} \\ \text{N} \end{array} \begin{array}{c} \text{5} \\ \text{5}' \end{array} \end{array} $					
Entry	4	2 (equivs.)	Time [h]	Product	Yield ^[a] (5 : 5') ^[b]
1	4a : R ¹ = Me, Z = C(CO ₂ Et) ₂	2b : R ³ = Me (20)	12	5ab	81 % (> 99:1)
2	4b : R ¹ = H, Z = C(CO ₂ Et) ₂	2c : R ³ = CH ₂ CN (1.5)	6	5bc	71 % (> 99:1)
3	4a	2c : R ³ = CH ₂ CN (1.5)	6	5ac	86 % (> 99:1)
4	4a	2d : R ³ = Ph (5)	12	5ad	54 % (> 99:1)
5	4c : R ¹ = Me, Z = O	2b (20)	12	5cb	89 % (> 99:1)
6	4c	2e : R ³ = C ₇ F ₁₅ (1.5)	6	5ce	64 % (> 99:1)

^[a] Isolated yield.^[b] Determined by ¹H NMR analysis of the crude mixture.

As revealed from the table, all reactions performed gave the corresponding bipyridine in moderate to excellent yield and, among three possible regioisomers, the 2,2'-bipyridine **7** was obtained exclusively.

Similar to the assignment of **5**, the correlations of aromatic carbons to methyl protons on the COLOC

measurement confirmed the regiochemistry as depicted for **7ab**, **7bb** and **7cb**. In addition, the structures of **7bb** and **7cd** were corroborated by X-ray crystallography (Figure 2).

Table 3. Bipyridine synthesis by the tandem reaction of **2** and **6** [Eq. (5) of Scheme 1].

$ \begin{array}{c} \text{6} + \text{2} \xrightarrow[\text{NMP, 50 } ^\circ\text{C, 12-15 h}]{\text{Dppe/CoCl}_2 \cdot 6\text{H}_2\text{O (5 mol\%)}, \text{Zn powder (10 mol\%)}} \\ \text{7 (2,2')} \quad \begin{array}{l} \text{7' (2,3')} \\ \text{7'' (3,3')} \end{array} \quad \begin{array}{l} \text{not detected} \end{array} \end{array} $				
Entry	6	2 (equivs.)	Product	Yield ^[a] (7:7' + 7'') ^[b]
1	6a : R ¹ = Ph, Z = O	2b : R ³ = Me (80) ^[c]	7ab	68 % (> 99:1)
2	6a	2d : R ³ = Ph (10)	7ad	41 % (> 99:1)
3	6b : R ¹ = H, Z = C(CO ₂ Et) ₂	2b (80) ^[c]	7bb	87 % (> 99:1)
4	6c : R ¹ = Ph, Z = C(CO ₂ Et) ₂	2b (40)	7cb	90 % (> 99:1)
5	6c	2d (10)	7cd	86 % (> 99:1)

^[a] Isolated yield.^[b] Determined by ¹H NMR analysis of the crude mixture.^[c] Acetonitrile was used as a solvent. When 40 equivs. of acetonitrile in NMP were used, a similar yield of the corresponding bipyridine was obtained.

Study for the Preparation of Terpyridines and Quarterpyridines

With the aforementioned results in hand, we next concentrated our efforts to the preparation of terpyri-

dines and quarterpyridines by the present method.^[12] These polypyridines are of interest as a ligand for metal complexes and substructure of other functionalized molecules. Thus, based on the results of the reactions of Eqs. (3) and (4), a mixture of 1-(2-pyridyl)-

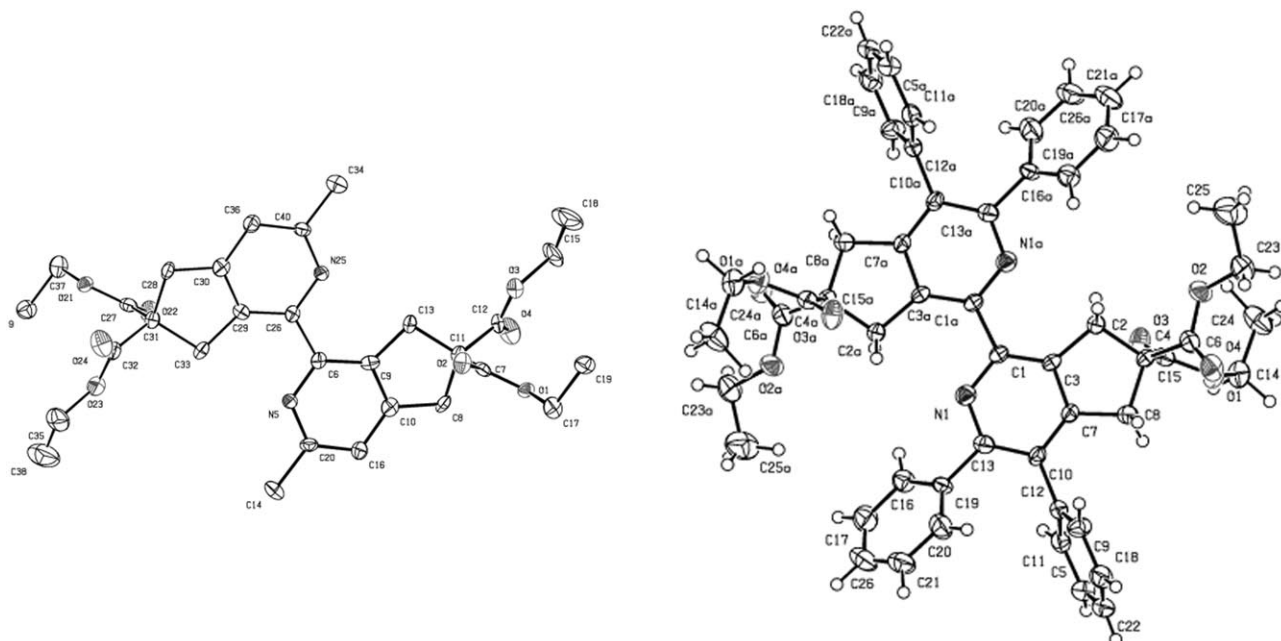
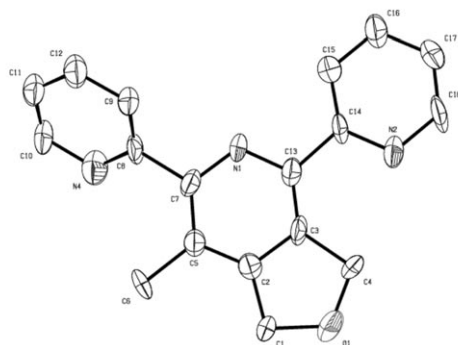
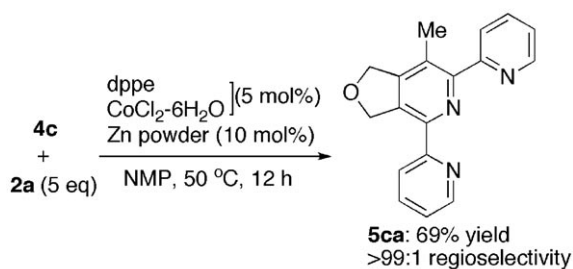


Figure 2. X-ray structures of compounds **7bb** (left) and **7cd** (right).

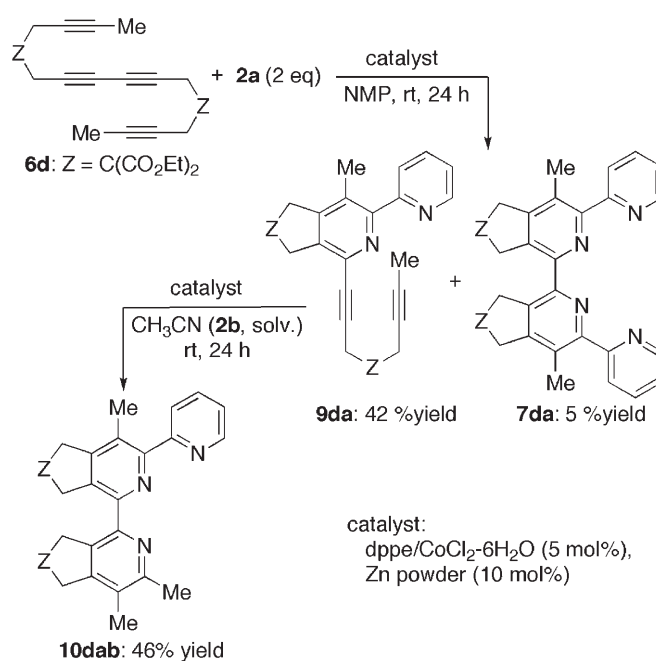
1,6-diyne **4c** and 2-cyanopyridine (**2a**) was subjected to the catalysis and the reaction provided 2,2':6',2''-terpyridine **5ca** as a sole product in 69% isolated yield (Scheme 3).

It was expected that a combination of tetraynes **6** and 2-cyanopyridine (**2a**) would provide quarterpyridines by the reaction of type Eq. (5). As illustrated in Scheme 4, the reaction of **6d** and **2a** (2 equiv.) in the

presence of a dppe/CoCl₂·6H₂O/Zn catalyst produced 2,2':6',2''-6',2''-quarterpyridine **7da** with complete regioselectivity but the yield was low (5%), due to steric hindrance. Instead, the reaction mainly produced mono-cyclized product **9da** in 42% isolated yield with >99:1 regioselectivity. Although further improvement is required to successfully form quarterpyridine, the resulting dipyridyl-diyne **9** was a good substrate for preparing terpyridines of type **10**



Scheme 3. Synthesis of 2,2':6',2''-terpyridine **5ca** and its crystallographic structure.



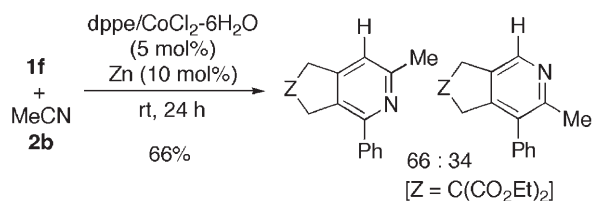
Scheme 4. Terpyridine and quarterpyridine from tetrayne **6**.

(Scheme 4). Thus, treatment of isolated **9da** with a dppe/CoCl₂·6H₂O/Zn catalyst in acetonitrile (**2b**) yielded terpyridine **10dab** as a single isomer in 46% isolated yield. Crystallographic results of the resulting **7da** and **10dab** are shown in Figure 3.

Consideration of Regioselectivity and Its Prospects

The reactions of Eqs. (3) to (5) in Scheme 1 by a dppe/CoCl₂·6H₂O/Zn catalyst gave 2,2'-bipyridines with high regioselectivity. Regarding the reaction of **1** and 2-cyanopyridine (**2a**), the selectivity may be controlled electronically: The inductive effect of the two substituents R¹ and R² of **1** affects the reactivity of the proposed cobaltacyclopentadiene intermediates in directing the regioisomeric pathway of the addition reaction with the cyano group of **2a**. It is noteworthy that the regioselectivity observed here in the reaction of 2-cyanopyridine (**2a**) is much better than that in the reaction with usual nitriles such as PhCN and MeCN as we reported (Scheme 5).^[9] This may be attributed to the more electron deficient nature of the 2-pyridyl moiety of **2a** compared to the substituent of usual nitriles.

Regarding the reaction of **4** and **2** [the type of Eq. (4)], the electronic nature of the two alkyne groups of the diyne **4** utilized here is very different compared to that of usual diynes such as **1a–h**, due to electron-de-

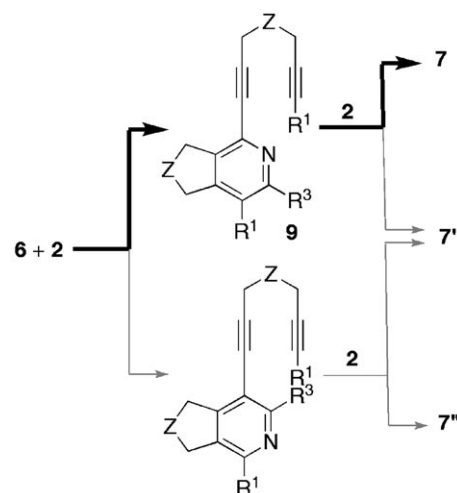


Scheme 5. Reaction of **1f** and **2b**.^[9]

ficiency of the 2-pyridyl moiety. This characteristic may be responsible for the regioselectivity of the reaction, independent of the nitriles utilized.

The reactions of **6** with **2** to **7** may seem to be of the tandem type but actually they proceeded in a domino fashion^[13] and involved two different types of regioselection as illustrated in Scheme 6. Thus, for 2,2'-bipyridine formation, it is essential that the formation of the first pyridine provides an intermediate **9** selectively. The following cycloaddition of **9** with **2** providing 2,2'-isomer **7** might also proceed selectively, similarly to the reaction of **4** and **2** to **5**.

We postulate that the dppe/CoCl₂·6H₂O/Zn-catalyzed pyridine formation may proceed through a (dppe)Co(I)Cl complex generated by the reduction of (dppe)CoCl₂ with zinc, which might react with diynes to provide cobaltacyclopentadiene intermediates **11** (Scheme 7). The exclusive regioselectivity observed throughout the three different types of reactions in



Scheme 6. Reaction pathway from **6** and **2** to **7**, **7'** or **7''**.

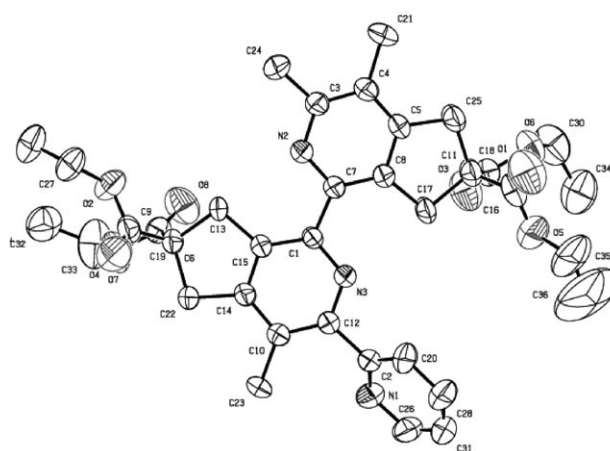
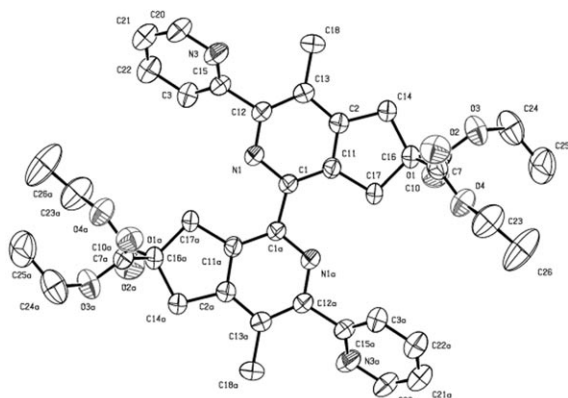
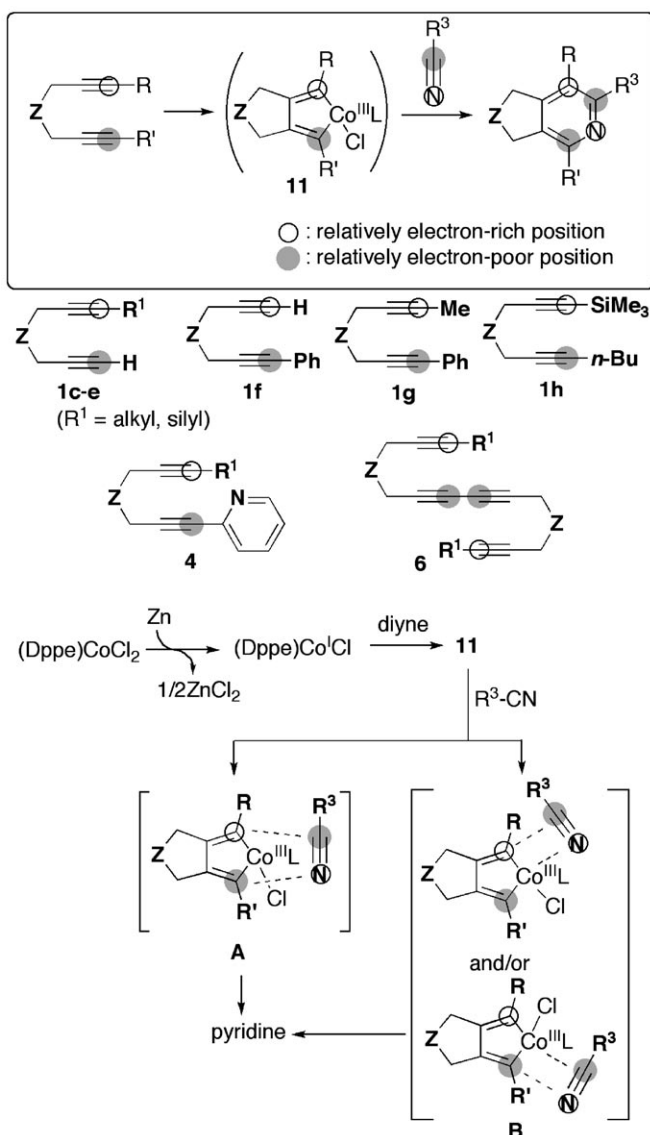


Figure 3. X-ray structures of compounds **7da** (left) and **10dab** (right). Hydrogen atoms have been excluded for clarity.



Scheme 7. Summary of regioselectivity with electronic nature of the substrates.

the present work, i.e., the reactions of Eq. (3), Eq. (4) and the transformation of **6** to **9** in the reaction of Eq. (5), can be systematically rationalized by considering the differences of the electronic natures between the two alkynes in the diynes (Scheme 7): Thus, a relatively electron-rich alkyne moiety in diynes **1**, **4** and **6** was attached to the electron-poor position (carbon atom) of the cyano group in **2** in all cases. Probably, an intermediate cobaltacycle of the type **11** derived from the corresponding **1**, **4** or **6** might have a similar electronic nature influenced by the substituents R and R' and the reaction may proceed through [4+2] cycloaddition (A) or insertion (B) pathways.^[4c,14] Although confirmation of the reaction mechanism from metallacycle intermediates **11** to pyridines, i.e., A or B, is difficult at this time and must await the results of further

studies, a survey of the exclusive regiochemical trends observed here gives reasonable credence to the synthetic potential of the present method.

Conclusions

We have demonstrated that a dppe/cobalt-catalyzed cycloaddition reaction of diynes and nitriles is an efficient means for preparation of substituted 2,2'-bipyridines and 2,2':6',2''-terpyridines with exclusive regioselectivity. A survey of the results provides reasonable credence to the synthetic potential to the method. Moreover, the reaction is practical since the catalysis uses commercially available inexpensive starting materials, and the reaction procedure is operationally simple. Because of the broad application of 2,2'-bipyridines in medicinal, synthetic, and material chemistry fields, a practical and atom-economical method for their synthesis should generate great interest.

Experimental Section

General Procedure for the Cycloaddition of Diynes **1**, **4** or **6** and Nitriles **2** to 2,2'-Bipyridine Derivatives Catalyzed by a Dppe/CoCl₂·6H₂O/Zn Reagent

To a stirred mixture of zinc powder (3.5 mg, 0.05 mmol), diyne **1**, **4** or tetrayne **6** (0.5 mmol) and nitrile **2** (1.5–80 equivs.) in NMP (1 mL) was added a solution of CoCl₂·6H₂O (6 mg, 0.025 mmol) and dppe (12 mg, 0.03 mmol) in NMP (1 mL) at room temperature. The mixture was then stirred at room temperature or at 50 °C. The reaction progress was monitored by TLC analysis. After completion of the reaction, a small portion of EtOAc or ether was added and the mixture was passed through a pad of Celite with EtOAc or ether. The filtrate was concentrated to dryness and the residue was chromatographed on silica gel using hexane/AcOEt to give the corresponding bipyridine derivative.

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