

HETEROCYCLES, Vol. 85, No. 7, 2012, pp. 1579 - 1602. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 29th February, 2012, Accepted, 30th March, 2012, Published online, 2nd April, 2012
DOI: 10.3987/REV-12-737

SYNTHESIS OF 2,2'-BIPYRIDINES BY TRANSITION METAL-CATALYZED ALKYNE/NITRILE [2+2+2] CYCLOADDITION REACTIONS

Sentaro Okamoto*

Department of Material and Life Chemistry, Kanagawa University, 3-27-1
Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan.

okamos10@kanagawa-u.ac.jp

Abstract – 2,2'-Bipyridines are of great importance in the fields of catalysis, coordination chemistry, supramolecular chemistry, macromolecular chemistry and photochemistry. Recently, the metal-catalyzed [2+2+2]-type cycloaddition reaction of alkynes and nitriles has attracted considerable interest as a straightforward, atom-economical route to substituted pyridines and methods have been extensively applied to bipyridine synthesis. Developments in the field of 2,2'-bipyridine synthesis through alkyne/nitrile [2 + 2 + 2] cycloaddition reactions catalyzed by transition metals are reviewed in this article involving two types of fully intramolecular reaction, five types of partially intramolecular reaction and fully intermolecular reactions.

CONTENTS

1. Introduction
2. Fully Intramolecular Reactions
3. Partially Intramolecular Reactions
 - 3-1. Starting from Substrates Bearing a Pyridine Unit
 - 3-1-1. 2-Cyanopyridines
 - 3-1-2. Alkynes Bearing a 2-Pyridyl Group
 - 3-2. Double Cycloaddition Reactions
 - 3-3. Terpyridine and Quarterpyridine Formation
4. Fully Intermolecular Reactions
5. Mechanism and Regioselectivity
6. Appendix

7. Conclusion

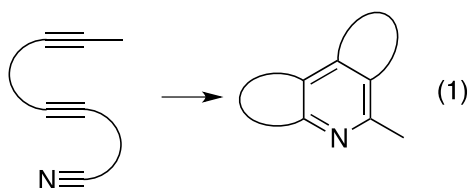
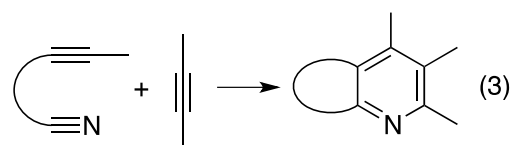
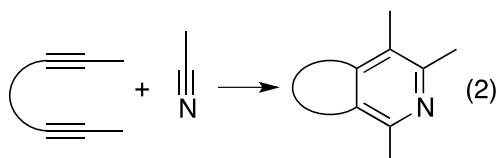
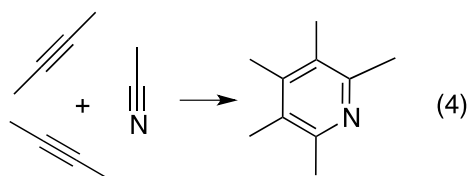
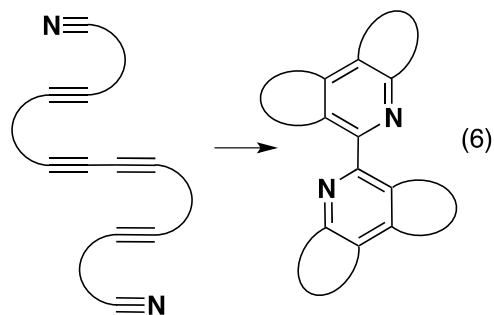
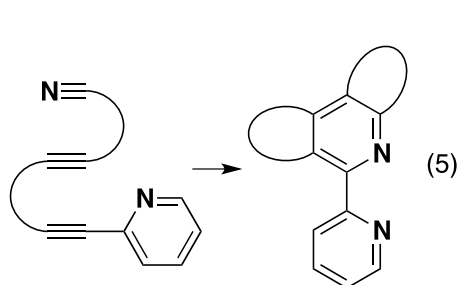
1. INTRODUCTION

2,2'-Bipyridines are of great importance in the fields of catalysis, coordination chemistry, supramolecular chemistry, macromolecular chemistry, and photochemistry. They form a part of the substructure or main component in biologically active natural and artificial compounds, and in particular are versatile as a ligand capable of attaching 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 polymers or self-assembling molecules, photosensitizer, and optical device materials.¹ Therefore, many synthetic methods consisting of non-catalyzed heterocycle syntheses² and metal-catalyzed reactions have been developed. In modern organic synthesis, bipyridines have been prepared by transition metal-catalyzed homocoupling (Ullmann-type reactions) of 2-halopyridine or cross-coupling between 2-halo and 2-metalated pyridines.³ However, in general, these processes are not necessarily applicable and are limited by the availability and reactivity of the halo- and/or metalated pyridine substrates. Recently, the metal-catalyzed [2 + 2 + 2]-type cycloaddition reaction of alkynes and nitriles has attracted considerable interest as a straightforward, atom-economical route to substituted pyridines,⁴ and the methods have been extensively applied to bipyridine synthesis. Developments in the field of 2,2'-bipyridine synthesis through alkyne/nitrile [2 + 2 + 2] cycloaddition reactions catalyzed by transition metals will be reviewed in this article.

Substituted pyridines can be synthesized from alkyne and nitrile substrates through three types of [2+2+2] cycloaddition reaction (Scheme 1); i.e., a fully intramolecular reaction (Equation 1), two partially intramolecular reactions (Equations 2 and 3), and a fully intermolecular reaction (Equation 4).

Based on these three types of pyridine formation as shown in equations 1-4, the examples of 2,2'-bipyridine synthesis reported so far can be classified into two types of fully intramolecular reaction (Scheme 2), five types of partially intramolecular reaction (Scheme 3) and fully intermolecular reactions (Scheme 4).

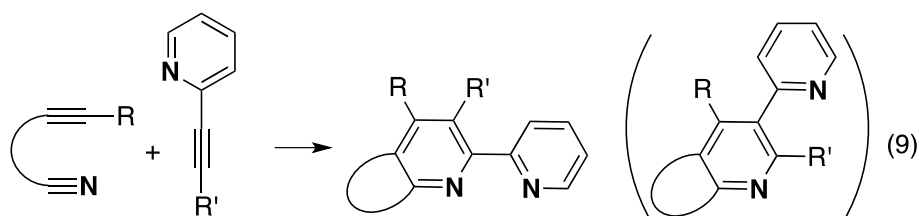
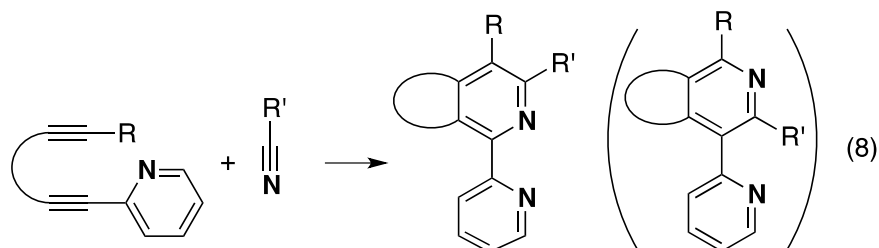
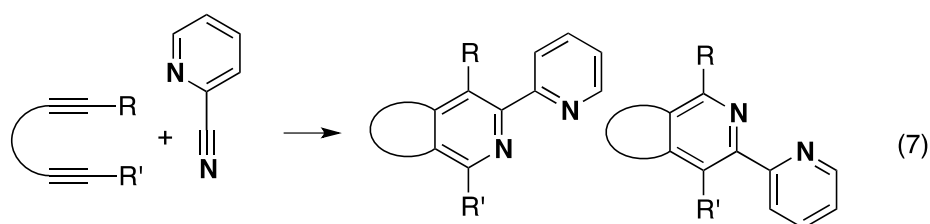
Synthesis of 2,2'-bipyridines *via* fully intramolecular reactions involves the reaction of diyne—nitrile substrates bearing 2-pyridyl moiety at the terminal position (Equation 5) and the double cycloaddition reaction of α,ω -dicyanotetraynes (Equation 6), both of which have no chemo- or regiochemical problem when having appropriate tether lengths.

Fully Intramolecular**Partially Intramolecular****Fully Intermolecular****Scheme 1.** Pyridine Synthesis *via* Alkyne—Nitrile [2 + 2 + 2] Cycloaddition**Fully Intramolecular****Scheme 2.** Bipyridine Synthesis *via* Fully Intramolecular Alkyne—Nitrile [2 + 2 + 2] Cycloaddition

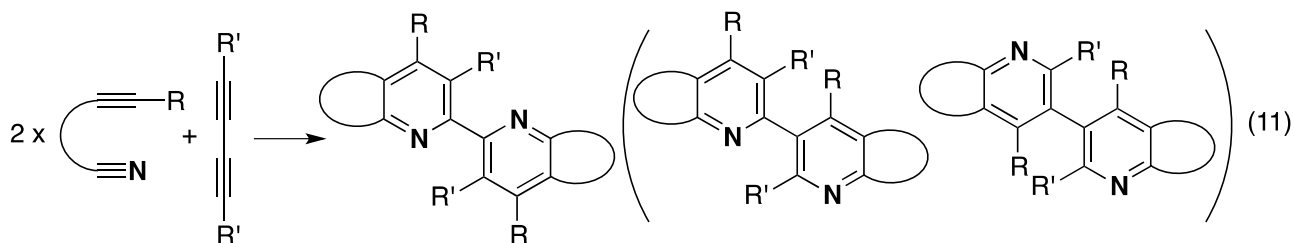
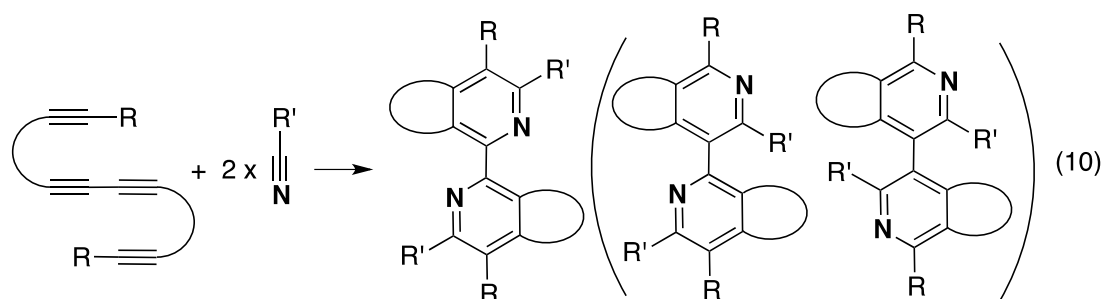
The partially intramolecular reactions illustrated in Scheme 3 consist of three types of reaction using substrates bearing a 2-pyridyl group (Equations 7-9) and two types of double cycloaddition reaction (Equations 10 and 11). The addition of α,ω -diynes with 2-cyanopyridine can infallibly provide 2,2'-pyridines, but two regioisomeric products may be formed (Equation 7). Meanwhile, in the additions of diynes bearing a terminal 2-pyridyl moiety with nitriles and of α,ω -cyanoalkynes with 2-pyridylacetylenes, 2,2'- and 2,3'-isomers can be produced competitively (Equations 8 and 9). The regiochemical control is also important for the selective formation of 2,2'-bipyridienes in the double cycloadditions of tetraynes with nitriles and of α,ω -cyanoalkynes with 1,3-diynes (Equations 10 and 11).

Partially Intramolecular

Using Substrate(s) bearing pyridine unit

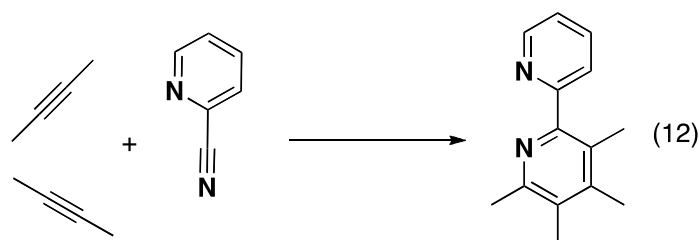


Double Cycloaddition



Scheme 3. Bipyridine Synthesis *via* Partially Intramolecular Alkyne—Nitrile [2 + 2 + 2] Cycloaddition

Selective formation of 2,2'-bipyridenes by a fully intermolecular reaction is restricted to a few examples of the reaction of two molecules of alkynes and 2-cyanopyridine because of intrinsic difficulties in the selective cross-addition of two alkynes and a nitrile over the formation of benzenes.



Scheme 4. Bipyridine Synthesis *via* Fully Intermolecular Alkyne—Nitrile [2 + 2 + 2] Cycloaddition

As an additional caution, the generated 2,2'-bipyridine can affect the catalysis by its tendency to coordinate to the metal species. In fact, a few catalysts did not work well; therefore, inactivation by trapping of the metal catalyst by the bipyridine product is rationalized.

2. FULLY INTRAMOLECULAR REACTIONS

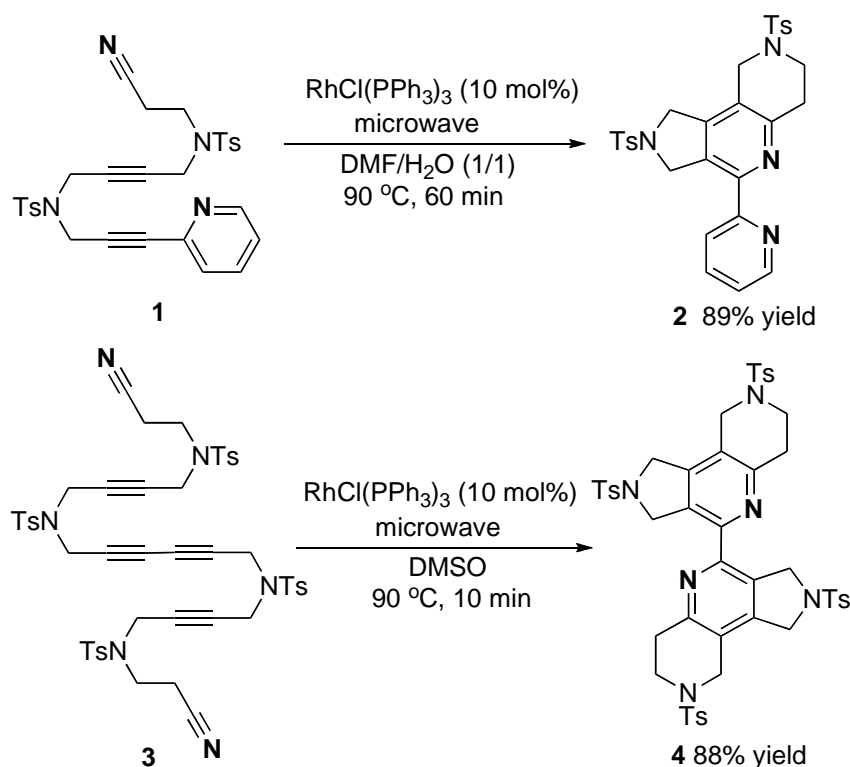
Roglans and co-workers reported the formation of bis-annulated 2,2'-bipyridine **2** from diyne—nitrile **1** with a nitrogen tether, which was effectively cycloadded intramolecularly in the presence of a Rh-catalyst (Wilkinson catalyst) under microwave irradiation conditions (a reaction of the same type as Equation 5).⁵ In the study, synthesis of bipyridine **4** by the double intramolecular cycloaddition reaction of 1,22-dicyano-5,10,12,17-tetrayne **3** under identical reaction conditions was also described (a reaction of the same type as Equation 6).

3. PARTIALLY INTRAMOLECULAR REACTIONS

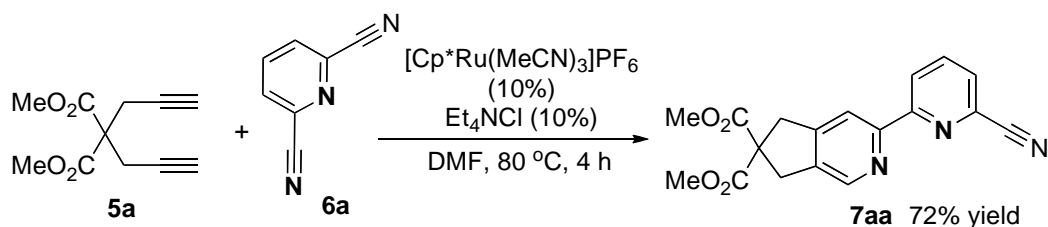
3-1. Starting from Substrates Bearing a Pyridine Unit

3-1-1. 2-Cyanopyridines

The [2 + 2 + 2] cycloaddition reactions of α,ω -diynes with 2-cyanopyridine derivatives are a reliable approach to 2,2'-bipyridines without regiochemical concerns, as first demonstrated by Saá *et al.* in 2003 (Scheme 6, a reaction of the same type as Equation 7).⁶ In the presence of 10 mol% of a cationic Ru-catalyst [$\text{Cp}^*\text{Ru}(\text{MeCN})_3$] PF_6 ($\text{Cp}^* = \eta^5$ -pentamethylcyclopentadienyl)], α,α -dipropargyl malonate **5a** reacted with 2,6-dicyanopyridine (**6a**) selectively to produce 2,2'-bipyridine **7aa** in a good yield. Note that under these conditions, neither 2-cyanopyridine nor **7aa** reacted with **5a**, and therefore, **7aa** was selectively formed from **5a** and **6a** without further reaction of the remaining cyano moiety.



Scheme 5. Bipyridine Synthesis *via* Fully Intramolecular Reactions



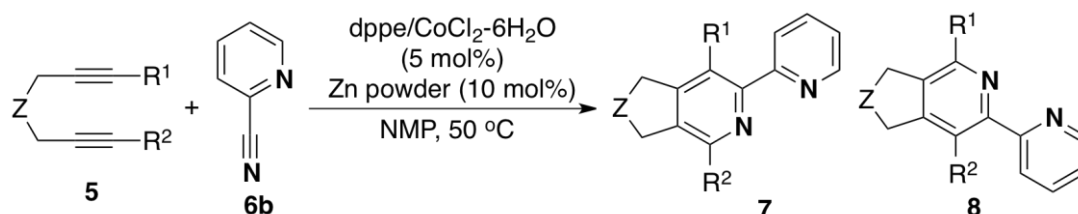
Scheme 6. Ru-Catalyzed Reaction of 1,6-Diyne and 2-Cyanopyridine Derivative

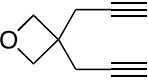
Table 1 summarizes the results of the cycloaddition of 2-cyanopyridine (**6b**) with various 1,6-diyne **5** reported by our group, in which the reaction was catalyzed by a dppe/CoCl₂·6H₂O/Zn reagent (dppe = 1,2-bis(diphenylphosphino)ethane) (a reaction of the same type as Equation 7).⁷⁻⁹ Symmetrical diynes **5b**, **5c**, and **5k** were converted to the corresponding 2,2'-bipyridines in moderate-to-good yield.

Unsymmetrical diynes **5d—j** also reacted smoothly with **6b**, and it is noteworthy that the reactions provided the corresponding 2,2'-bipyridine with complete regioselectivity (runs 3—9). In the reactions of alkyl or silyl mono-substitute diynes **5d—f** (R² = H), the substituent R¹ was located at the 3-position of the generated pyridine ring (runs 3—5). Meanwhile, the reaction of **5g** gave the product 2,2'-bipyridine **8gb** exclusively, with a phenyl group at the 2-position of the resulting pyridine ring (run 6). In addition, unsymmetrical diynes with two internal alkynes **5h—j** also reacted with **6b** in a completely regioselective

fashion. Note that silyl-substituted internal diynes such as **5i** and **5j** exclusively yielded 3-silyl-2,2'-bipyridines **7**, independent of the substituent R². It was suggested that the regiochemistry was controlled by the electronic nature of the diynes.⁸

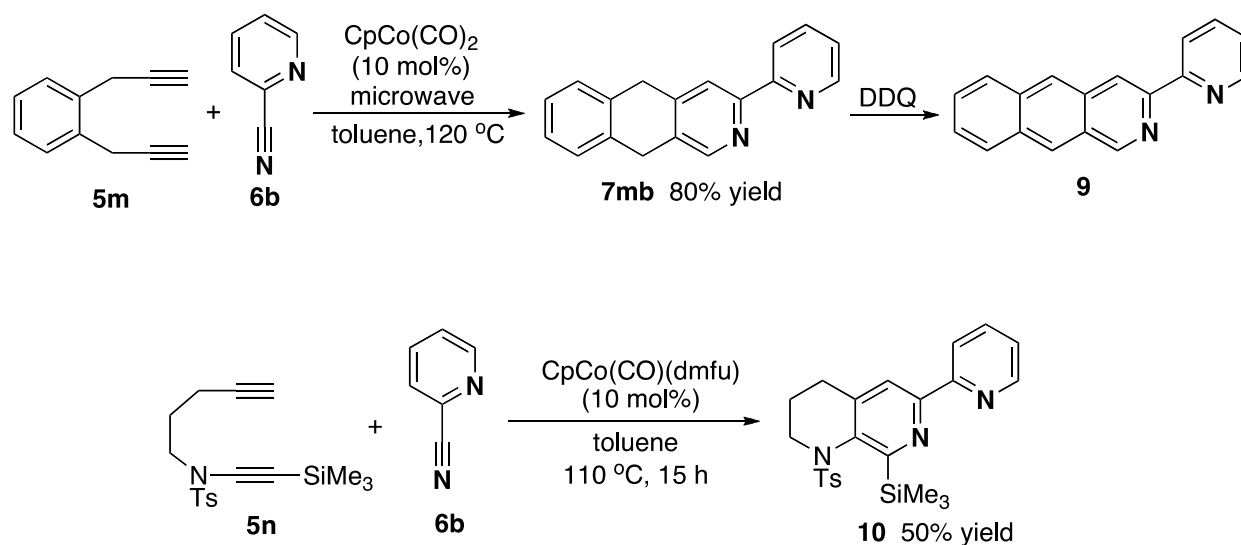
Table 1. Partially Intramolecular Cycloaddition of 1,6-Diynes **5** and 2-Cyanopyridine (**6b**)



Run	Diyne 5	Equiv of 6a	h	Product: Yield (7:8)	Ref.
1	5b : R ¹ , R ² = H, Z = C(CO ₂ Et) ₂	20	3	7bb : 65%	7
2	5c : R ¹ , R ² = Me, Z = C(CO ₂ Et) ₂	2	12	7cb : 58%	7
3	5d : R ¹ = Me, R ² = H, Z = C(CO ₂ Et) ₂	20	12	7db : 78% (>99:1)	7
4	5e : R ¹ = <i>n</i> -Bu, R ² = H, Z = C(CO ₂ Et) ₂	20	3	7eb : 67% (>99:1)	7
5	5f : R ¹ = SiMe ₃ , R ² = H, Z = C(CO ₂ Et) ₂	20	12	7fb : 76% (>99:1)	7
6	5g : R ¹ = Ph, R ² = H, Z = C(CO ₂ Et) ₂	20	12	8gb : 78% (1:>99)	7
7	5h : R ¹ = Ph, R ² = Me, Z = C(CO ₂ Et) ₂	2	12	8hb : 47% (1:>99)	7
8	5i : R ¹ = SiMe ₃ , R ² = <i>n</i> -Bu, Z = C(CO ₂ Et) ₂	2	24	7ib : 91% (>99:1)	7
9	5j : R ¹ = SiMe ₃ , R ² = Ph, Z = C(CO ₂ Et) ₂	2	24	7jb : 91% (>99:1)	8
10	5k : 	3	16	7kb : 25%	9

Deiters and co-workers have reported the synthesis of 3-(2-pyridyl)-2-aza-anthracene **9**, as a new fluorescent molecule, *via* its dihydro derivative **7mb** prepared by microwave-assisted CpCo(CO)₂-catalyzed cycloaddition of 1,2-dipropargylbenzene **5m** and 2-cyanopyridine (**6b**) (Scheme 7).¹⁰

Malacria, Aubert, Gandon, and co-workers reported synthesis of 2,2'-bipyridiene **10** having a 1,2,3,4-tetrahydroquinoline structure by a CpCo(CO)(dmfu)-catalyzed reaction of nitrogen-tethered 1,7-diyne **5n** with **6b** (Cp = η⁵-cyclopentadienyl, dmfu = dimethyl fumarate) (Scheme 7, a reaction of the same type as Equation 7).¹¹ The authors suggested that the moderate yield (50%) may be due to the chelating nature of the bipyridine scaffold that is capable of trapping the catalyst. The regioselectivity was exclusive, but the sole generation of 2-silyl substituted pyridine differed from the results of runs 8 and 9 in Table 1. The production of **10** may be rationalized by steric constraints.



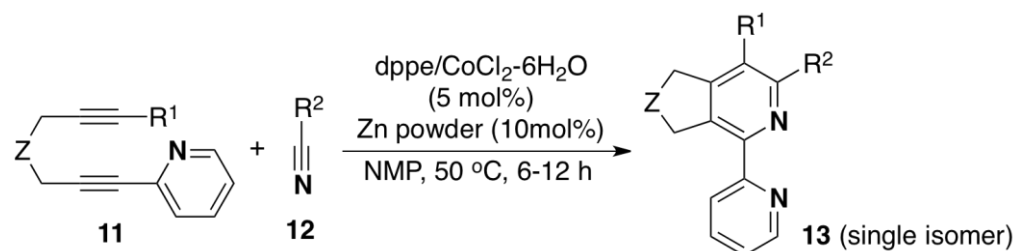
Scheme 7. Cobalt-Catalyzed Reactions of Diynes and 2-Cyanopyridine

3-1-2. Alkynes Bearing a 2-Pyridyl Group

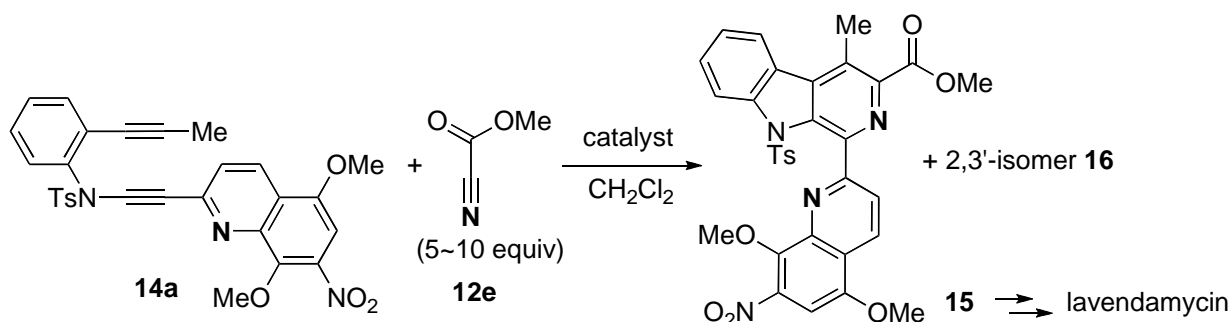
The bipyridine synthesis starting from alkynes bearing a 2-pyridyl moiety shown in Equations 8 and 9 in Scheme 3 has been most extensively explored. It is necessary to consider the regiochemical selectivity because these reactions have the potential to provide both 2,2'- and 2,3'-bipyridines.

The cycloaddition of 6-(2-pyridyl)-1,6-diynes **11** with nitriles may yield the 2,2'-bipyridides **13** and its 2,3'-isomer (Equation 8). We have demonstrated exclusive production of 2,2'-bipyridine from the pyridyl—diynes **11** and nitrile **12** with use of a dppe/CoCl₂·6H₂O/Zn catalyst (Table 2).⁷ 2-Pyridyl-diynes **11** bearing an internal or terminal alkyne moiety were converted to the 2,2'-bipyridines **13** as a single isomer in moderate-to-good yield.

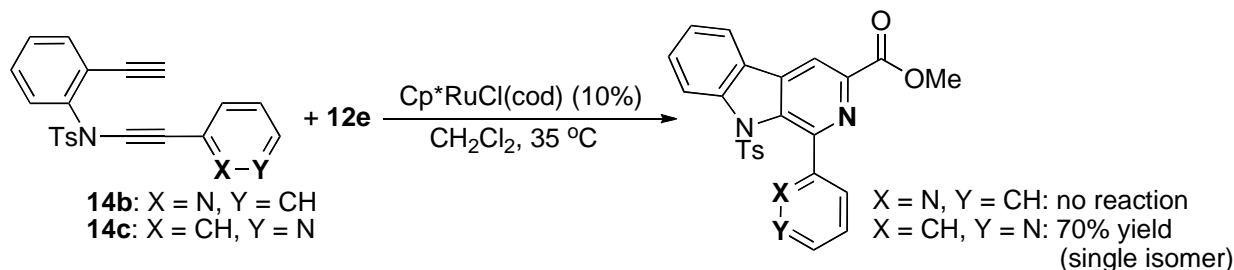
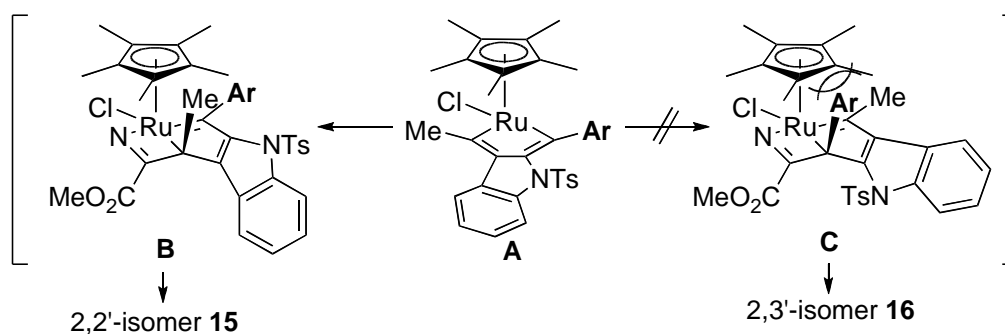
Recently, Nissen and Detert have elegantly applied a Cp**Ru*Cl(cod)-catalyzed [2+2+2] cycloaddition to the total synthesis of lavendamycin, a bacterial-derived antitumor antibiotic, as one of the key reactions (cod = 1,4-cyclooctadiene) (Scheme 8, a reaction of the same type as Equation 8).¹² Thus, the Ru-catalyzed reaction of highly functionalized 2-pyridyl-diyne **14a** with methyl cyanofornate **12e** furnished the desired 2,2'-bipyridine derivative **15** exclusively in excellent yield. The origin of the excellent regioselectivity of Ru-catalyzed reaction has been rationalized by considering the [2+2] addition of the electron-deficient nitrile to metallacyclic intermediate **A**. In the [2+2] adduct **C**, the sterically more demanding substituent Ar will come close to the bulky Cp* ligand. In contrast, the formation of **B** will avoid this steric repulsion and lead to the formation of 2,2'-isomer **15**. It was reported that the Rh-catalyzed reactions of **14a** and **12e** gave the 2,3'-isomer predominantly, the ratio of which was varied by the reaction temperature.

Table 2. Partially Intramolecular Cycloaddition of Pyridyl—diynes **11** and Nitriles **12**⁷

Run	11 : R ¹ , Z	12 : R ² (equiv)	13 : Yield
1	11a : Me, C(CO ₂ Et) ₂	12a : Me (20)	13aa : 81%
2	11b : H, C(CO ₂ Et) ₂	12b : CH ₂ CN (1.5)	13bb : 71%
3	11a	12b (1.5)	13ab : 86%
4	11a	12c : Ph (5)	13ac : 54%
5	11b : Me, O	12a (20)	13ba : 89%
6	11b	12d : C ₇ F ₁₅ (1.5)	13bd : 64%

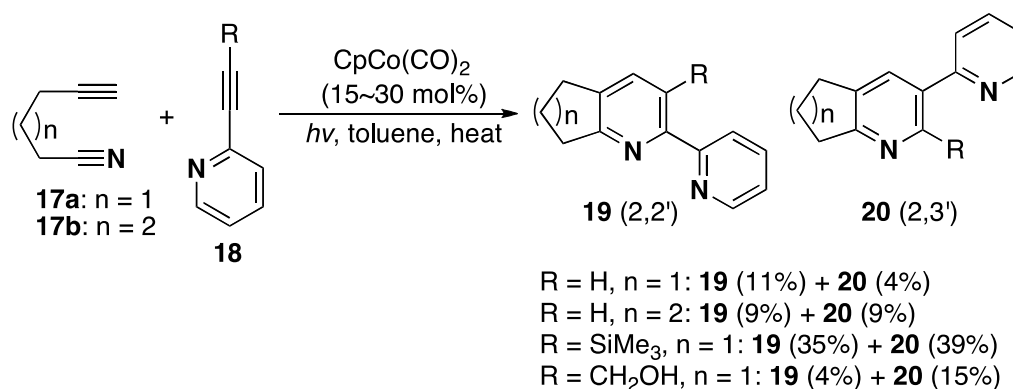


catalyst: [Rh(cod)₂BF₄/BINAP (6%): 81~92% yield (**15**:**16** = 27:73~38:62)
Cp^{*}RuCl(cod) (2%): 92% yield (**15**:**16** = 100:0)

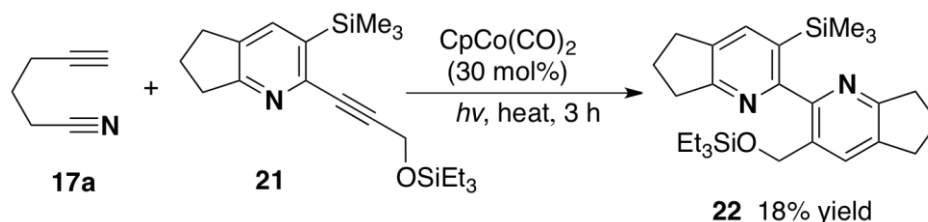
**Scheme 8.** Reactions of α -(2-Pyridyl)diynes and Cyanoformate and Its Application to Synthesis of Lavendamycin

Interestingly, Cp**RuCl(cod)*-catalyzed reactions of similar but more simple substrate **14b** did not produce the corresponding 2,2'-bipyridine derivative, which was explained by assuming that the bipyridyl moiety in the product inhibits the catalytic cycle by complexation to the catalyst (Scheme 8). On the other hand, the reaction 3-pyridyl derivative **14c** underwent cycloaddition with an exclusive regioselectivity to give the corresponding β -carboline in 70% yield.¹³

The pioneering work by Castedo and Saá in the field of bipyridine synthesis *via* [2+2+2] cycloaddition involves the reactions of 5-hexynenitrile (**17a**) or 6-heptynenitrile (**17b**) with 2-pyridylacetylene derivatives **18** providing 2,2'- and 2,3'-bipyridines (Scheme 9, a reaction of the same type as Equation 9),¹⁴ which were catalyzed by CpCo(CO)₂ under photo-irradiation conditions. Saá's group also reported the selective formation of bis-annulated 2,2'-bipyridine **22** but in a low yield with recovery of 40% of **21** (Scheme 10).¹⁵

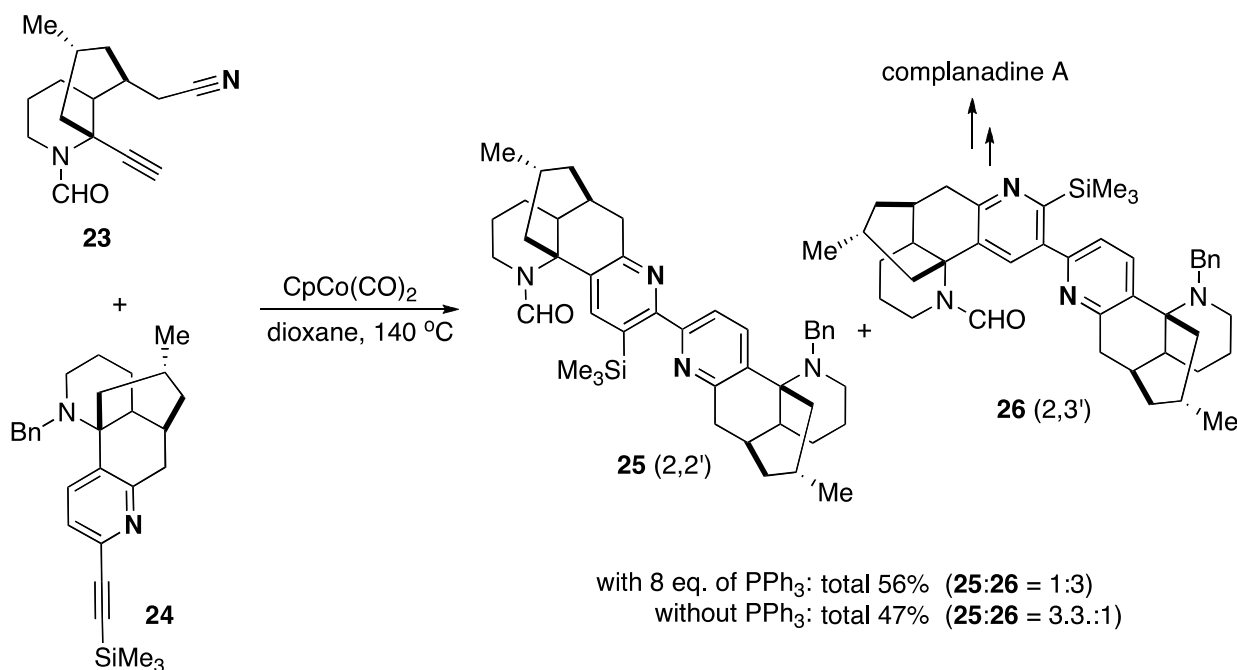


Scheme 9. Reactions of 5-Hexynenitrile or 6-Heptynenitrile with 2-Pyridylacetylene Derivatives

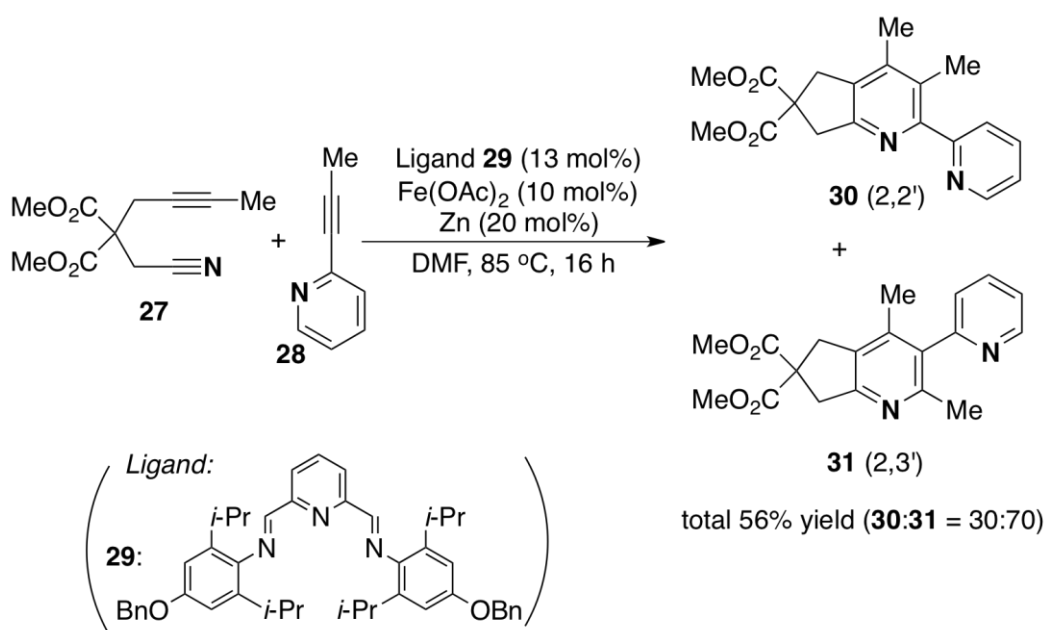


Scheme 10. Reaction of 5-Hexynenitrile with a 2-Pyridylacetylene Derivative

In 2010, Siegel and co-workers reported an elegant application of the cycloaddition of 6-heptynenitrile and 2-pyridylacetylene derivatives to the total synthesis of (+)-complanadine A,¹⁶ which was identified in a screen of compounds from the club moss *Lycopodium complanatum* and induces secretion of neurotrophic factors from 1321N1 cells, promoting the differentiation of PC-12 cells (Scheme 11, a



Scheme 11. Application of Reaction of 5-Hexynenitrile with a 2-Pyridylacetylene Derivative to Synthesis of Complanadine A



Scheme 12. Iron-Catalyzed Cycloaddition of Reaction of a 5-Hexynenitrile Derivative with 2-Pyridylalkyne

reaction of the same type as Equation 9). Under $\text{CpCo}(\text{CO})_2$ -catalyzed reaction conditions, the 6-heptynenitrile derivative **23** could undergo cycloaddition with the 2-(2-trimethylsilylethyne)pyridine derivative **24** to produce a mixture of 2,2'- and 2,3'-bipyridenes **25** and **26**, the latter of which is suitable

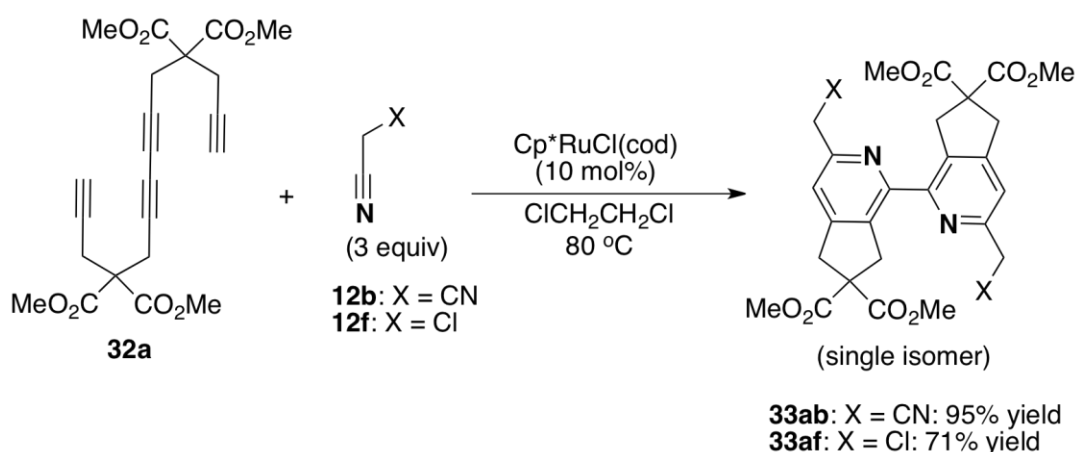
for the synthesis of complanadine A. Interestingly, the authors found that the regioselectivity could be changed by the addition of PPh_3 . The ability of PPh_3 to change the regioselectivity warrants further study.

Recently, Louie and co-workers have developed the first homogeneous iron complex-catalyzed [2+2+2] cycloaddition reaction of 5-hexynenitrile or 6-heptynenitrile derivatives with internal alkynes, in which the production of a mixture of 2,2'- and 2,3'-bipyridines from the 5-hexynenitrile derivative **27** and 2-alkynylpyridine **28** was reported (Scheme 12, a reaction of the same type as Equation 9).¹⁷ Based on the results of the reaction of **27** with other unsymmetrical alkynes, it can be assumed that the regioselectivity may be controlled electronically as well as sterically.

3-2. Double Cycloaddition Reactions

The bipyridine preparation by a double (domino) [2 + 2 + 2] cycloaddition depicted in Equations 10 and 11 in Scheme 3 involves the reaction of 1,6,8,13-tetraynes **32** with nitriles (Scheme 13 and Table 3) and that of 5-hexynenitrile (**17a**) with 1,3-diynes (**34**) (Table 4), both of which have an intrinsic regiochemical issue; i.e., the possibility of the production of three different regioisomers, 2,2'-, 2,3'-, and 3,3'-bipyridines.

In 2001, Itoh and co-workers reported the exclusive production of 2,2'-bipyridines from tetrayne **32a** and nitriles **12b** or **12f**, which was effectively catalyzed by $\text{Cp}^*\text{RuCl}(\text{cod})$. For successful cycloaddition, the nitrile substrate requires a coordinative group such as CN or Cl at the α position.^{18,19}

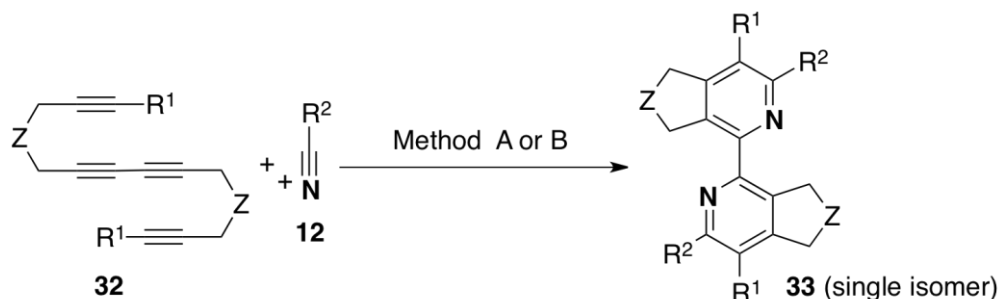


Scheme 13. Ru-Catalyzed Double Cycloaddition of Tetrayne **32a** with Nitriles

Table 3 summarizes the results of the cobalt-catalyzed reaction of various tetraynes **32** and nitriles **12**, reported by Kotora *et al.*,²⁰ and our group^{7,8} in 2008 (Table 3). Both of the catalytic systems, (i.e.,

dppe/CoCl₂·6H₂O/Zn (Method A, runs 1—5) and CpCo(CO)₂/microwave (Method B, runs 6—14)), could furnish the corresponding bipyridines **33** with exclusive 2,2'-selectivity.

Table 3. Double Cycloaddition of Tetrynes **32** with Nitriles **12**



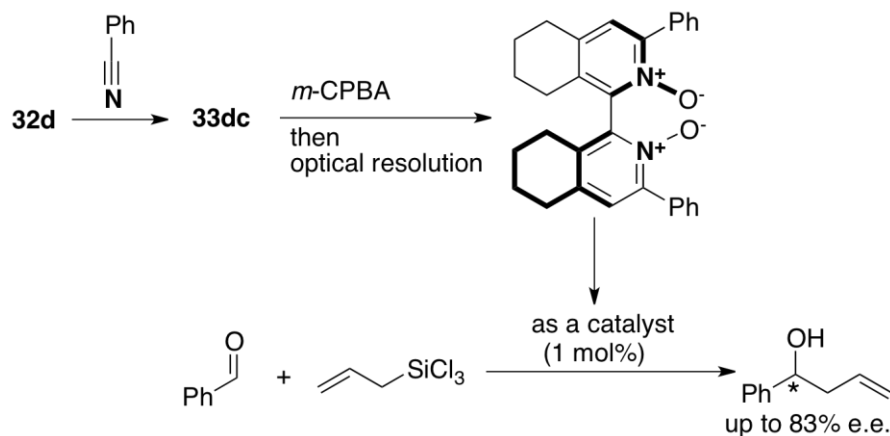
Method A: dppe/CoCl₂·6H₂O (5 mol%), Zn powder (10 mol%), NMP, 50 °C

Method B: CpCo(CO)₂ (19 mol%), neat or in THF, microwave

Run	32 : R ¹ , Z	12 : R ² (equiv)	Method	33 : Yield	Ref.
1	32b : Ph, O	12a : Me (80) [as a solvent]	A	68%	7
2	32b	12c : Ph (10)	A	41%	7
3	32a : H, C(CO ₂ Et) ₂	12a (80) [as a solvent]	A	87%	7
4	32c : Ph, C(CO ₂ Et) ₂	12a (40)	A	90%	7
5	32c	12c (10)	A	86%	7
6	32d : H, (CH ₂) ₂	12a (>21)	B	36%	20
7	32d	12c (>21)	B	51%	20
8	32d	12g : <i>p</i> -CF ₃ C ₆ H ₄ (>21)	B	47%	20
9	32d	12h : <i>p</i> -MeOC ₆ H ₄ (>21)	B	50%	20
10	32d	12i : 2,3,4-(MeO) ₃ C ₆ H ₂ (>21)	B	46%	20
11	32d	12j : tetrahydrofuran-2-yl (>21)	B	48%	20
12	32d	12k : CH ₂ Ph (>21)	B	34%	20
13	32d	12l : <i>cycl</i> -C ₆ H ₁₁ (>21)	B	21%	20
14	32d	12m : <i>cycl</i> -C ₃ H ₅ (>21)	B	9%	20

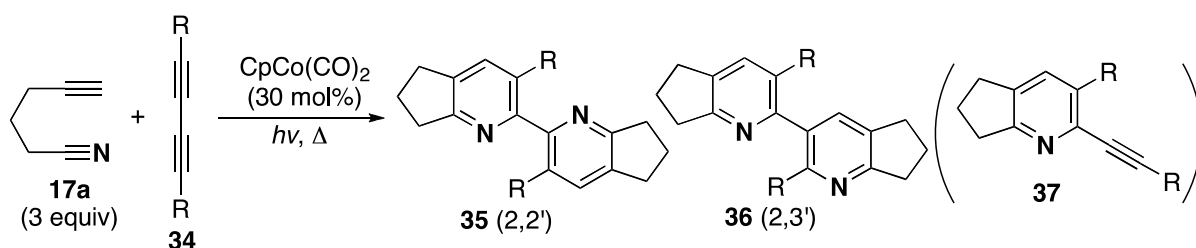
Some of the products have been oxidized to the corresponding axially chiral bis-*N*-oxide compounds, which were resolved to their optically active form, and were applied to asymmetric allylation reactions as a chiral Lewis base-catalyst (Scheme 14).²⁰

Another type of double cyclization has been reported by Saá's group in 1998,^{15,21} which cycloadded two molecules of 5-hexynenitrile (**17a**) to 1,3-diynes **34** (Table 4, a reaction of the same type as Equation 11).



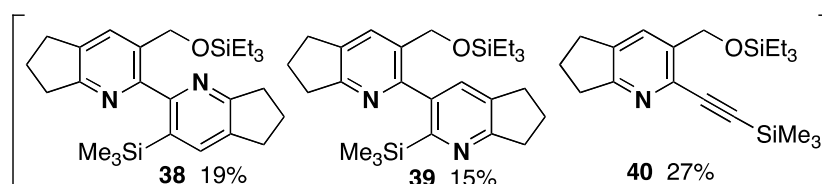
Scheme 14. Application of 2,2'-Bipyridine *N*-Oxides to Asymmetric Synthesis

Table 4. Double Cycloaddition of Hexynenitrile (**17a**) with Dienes **34**^{15,21}



Run	Diyne 34 : R	Total Yield (35:36)
1	34a : SiMe ₃	[37 : 77%]
2	34b : Me	48% (63:37)
3	34c : CH ₂ OH	9% (100:0)
4	34d : CH ₂ OMe	63% (73:27)
5	34e : CH ₂ OSiEt ₃	45% (80:20)
6	34f : CO ₂ Me	18% (58:42)
7	34g : Me ₃ Si—≡—≡—SiMe ₃	31% (32:68)
8	34h : CH ₂ NMe ₂	49% (100:0)
9	34i : Me ₃ Si—≡—≡—CH ₂ OSiEt ₃	34% (56:44)*

*For run 9,



Despite the possibility of producing three regioisomers, the reaction actually yielded only a mixture of 2,2'- and 2,3'-bipyridines **35** and **36**. It was realized that employing 1,3-diyne bearing coordinative

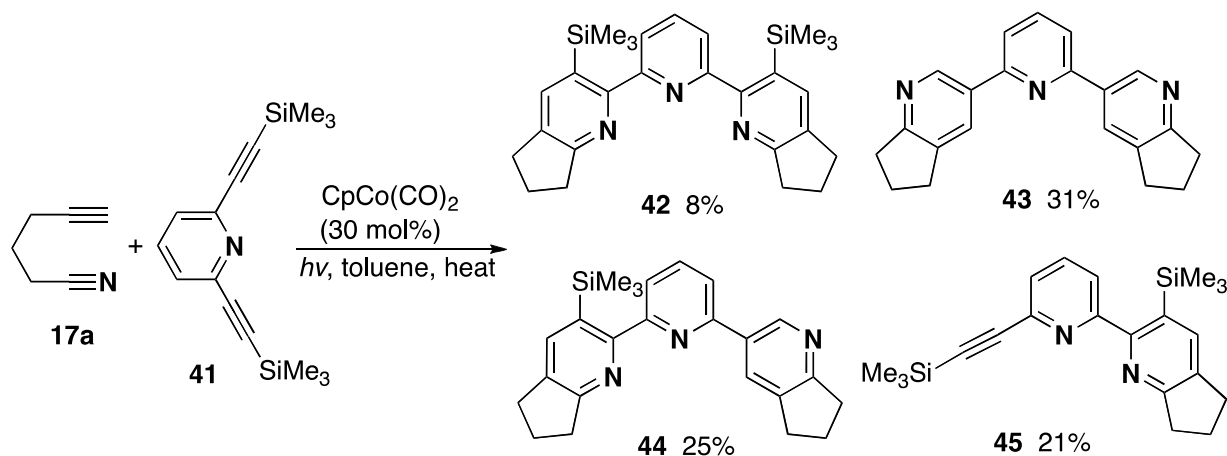
oxygen or nitrogen functionalities at the propargylic positions, such as **34c** and **34h**, resulted in a complete regiocontrol giving 2,2'-isomer (runs 3 and 8). In the reaction of the sterically demanding 1,3-diyne **34a**, one of the triple bonds of the diyne could be associated to the cycloaddition (run 1).

3-3. Terpyridine and Quarterpyridine Formation

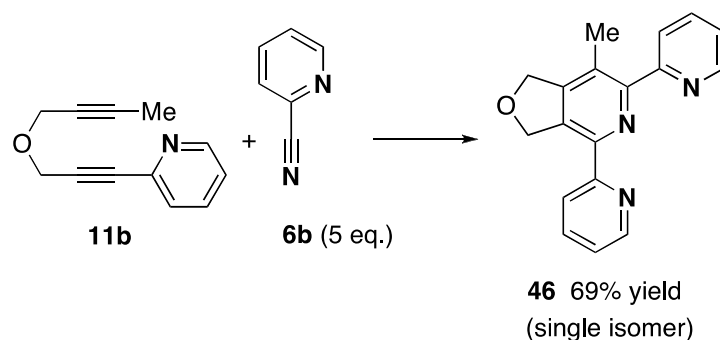
Based on the bipyridine formation processes mentioned above, several applications in the production of terpyridines and quarterpyridines have been demonstrated.

In 1997, Castedo and Saá reported pioneering work on the formation of terpyridines by $\text{CpCo}(\text{CO})_2$ -catalysis with 6-hexynenitrile (**17a**) and 2,6-dialkynylpyridine **41** *via* double cycloaddition (Scheme 15). The reaction resulted in the production of a mixture of 2,2':6',2''-, 2,2':6',3''-, and 3,2':6',3'-isomers, **42**, **43**, **44**, with the co-production of the mono-cyclized product **45**.¹⁴

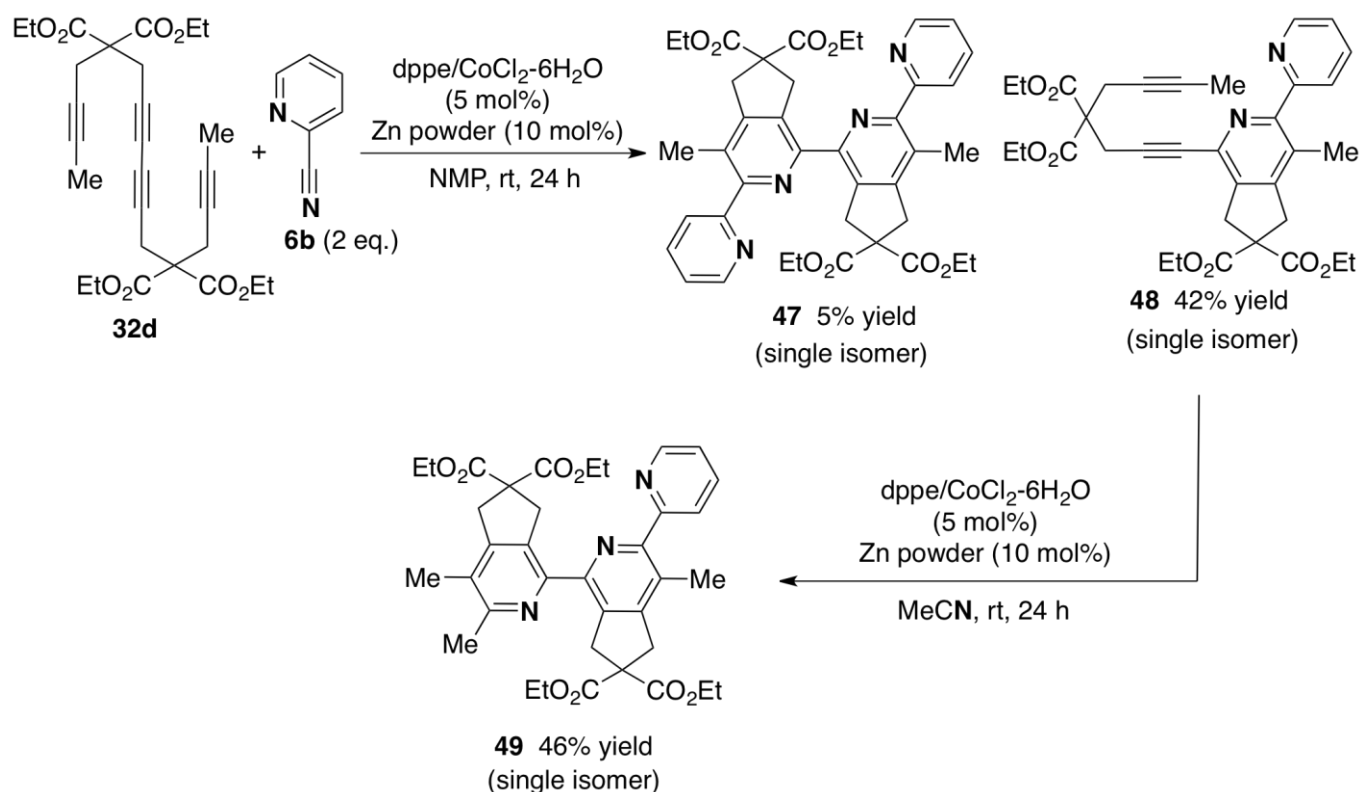
The highly selective preparation of 2,2':6',2''-terpyridine **46** has been demonstrated by us, where a diyne bearing a 2-pyridyl substituent cycloaddled with 2-cyanopyridine (**6b**) in the presence of a $\text{dppe}/\text{CoCl}_2\cdot 6\text{H}_2\text{O}/\text{Zn}$ catalyst (Scheme 16).⁷ We have also attempted the synthesis of quarterpyridine **47** by the double cycloaddition reaction of tetrayne **32d** with two molecules of 2-cyanopyridine (**6b**), but the reaction yielded only 5% of quarterpyridine **47** (a single regioisomer) with co-production of the mono-cyclized product **48** (Scheme 17). The low reaction rate of the second cycloaddition reaction is presumably because of a steric factor. The separated **48** was converted into 2,2':6',2''-terpyridine **49** by reaction with another nitrile by the same catalyst system, in which complete regioselectivity was again observed.



Scheme 15. Reaction of 5-Hexynenitrile with 2,6-Dialkynylpyridine **41**



Scheme 16. Terpyridine Synthesis from α -(2-Pyridyl)diyne and 2-Cyanopyridine



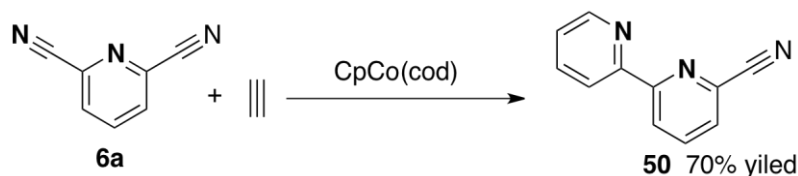
Scheme 17. Attempt to Synthesis of Quarterpyridine by Double Cycloaddition of Tetrayne **32d** and 2-Cyanopyridine

4. FULLY INTERMOLECULAR REACTIONS

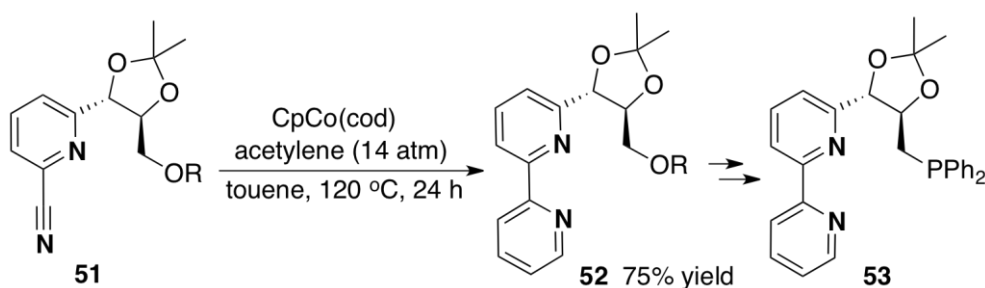
Pyridine synthesis by fully intermolecular alkyne/nitrile [2 + 2 + 2] cycloaddition is not easy because it requires high levels of chemo- and regioselectivities. To date, the reported synthesis of 2,2'-bipyridines in this method (a reaction of the same type as Equation 12) has been restricted to the reaction of two molecules of an alkyne with a nitrile.

In 1994, Chelucci *et al.* reported that CpCo(cod) catalyzed cocyclotrimerization of 2,6-dicyanopyridine (**6a**) with acetylene to give 2,2'-bipyridine-6-carbonitrile (**50**) in 70% yield (Scheme 18).²² The method

has been applied to the synthesis of optically active bipyridine-phosphine compound **53** (Scheme 19).²³ A chiral cyanopyridine **51** reacted with acetylene in the presence of CpCo(cod) to furnish optically active bipyridine **52** in 75% yield, which was converted to **53**.

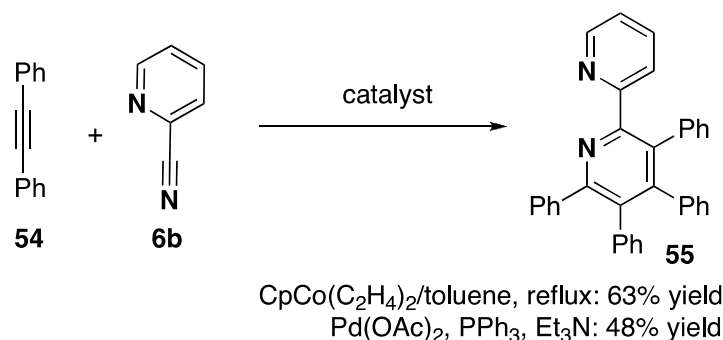


Scheme 18. Fully Intermolecular Reaction of 2,6-Dicyanopyridine with Acetylene



Scheme 19. Application of Fully Intermolecular Reaction to Synthesis of Chiral Bipyridine

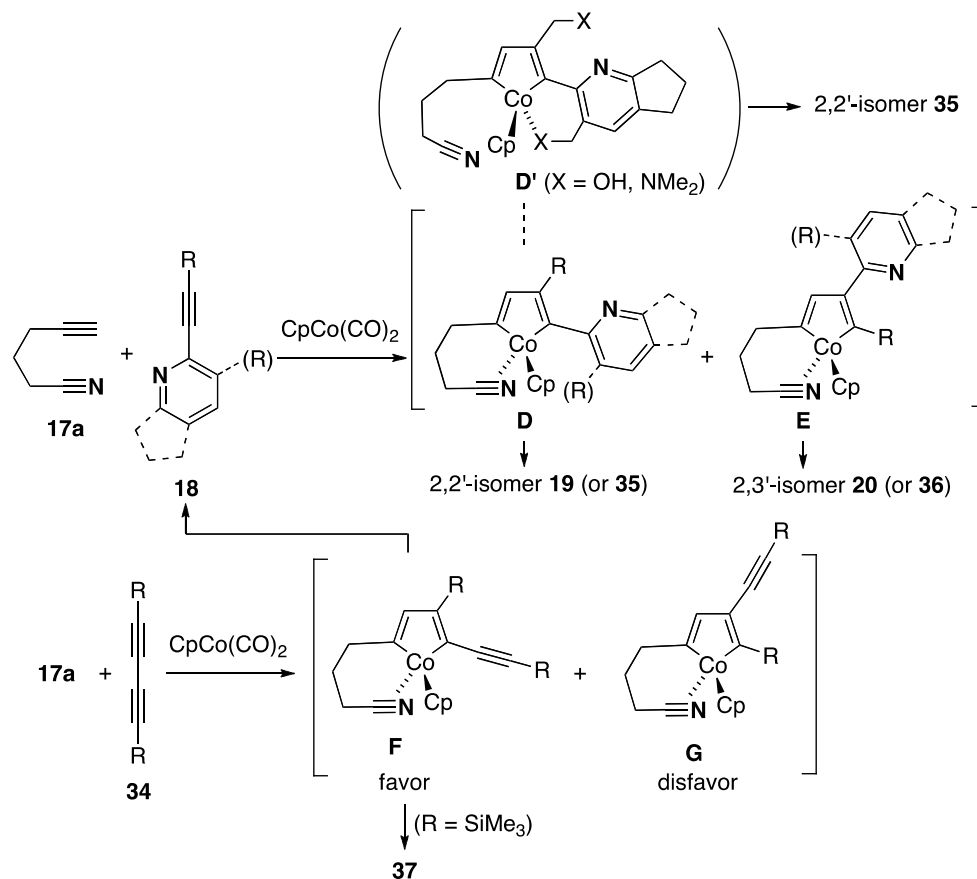
In addition, a report of the cobalt- or palladium-catalyzed synthesis of 3,4,5,6-tetraphenyl-2,2'-bipyridine (**55**) by co-cycloaddition of tolan (**54**) and 2-cyanopyridine (**6b**) by Uhm and An can be found in a journal online search (Scheme 20), although the details are unknown.²⁴



Scheme 20. Fully Intermolecular Reaction of Tolane with 2-Cyanopyridine

5. MECHANISM AND REGIOSELECTIVITY

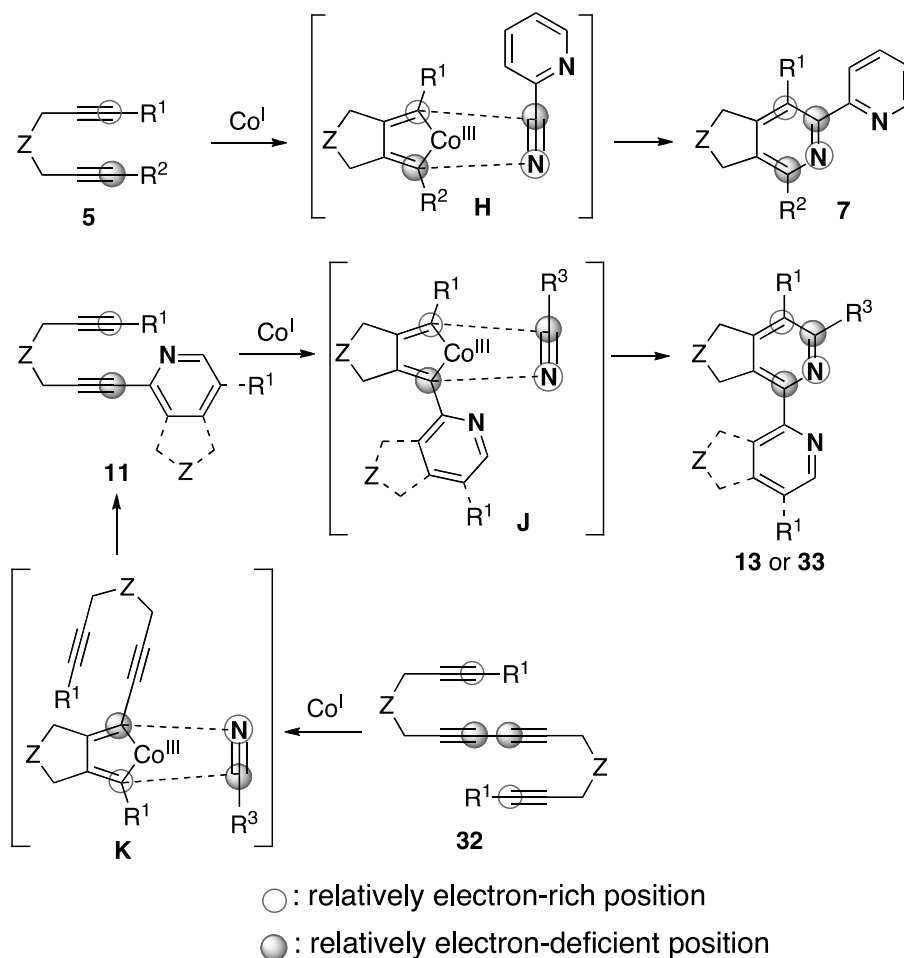
In the several reports mentioned above, the origin of the regioselectivity was discussed by consideration of the electronic and/or steric factors. As illustrated in Scheme 8, Cp^{*}RuCl(cod)-catalyzed reactions might be controlled mainly by the steric factor in the reacting intermediate(s).



Scheme 21. Mechanism and Regiochemistry of CpCo^I-Catalyzed Reactions

As shown in Scheme 21, the CpCo^I-catalyzed reactions of hexynenitrile **17a** with (2-pyridyl)alkynes **18** generally afford a mixture of 2,2'- and 2,3'-isomers (Scheme 9, 11 and 15), which may proceed *via* both intermediates **D** and **E**. For the reaction of **17a** with 1,3-diynes **34** (Table 4), based on the B3LYP/LANL2DZ *ab initio* calculations (R = SiH₃ or H), Saá *et al.* suggested that the cobaltacycle **F** is more stable than its isomer **G**. In fact, when R was a sterically demanding SiMe₃, the reaction yielded a mono-cycloadded product **37** as a sole isomer (run 1 in Table 4). The intermediate **F** gives the compound of type **18**, which is further reacted with **17a**. When diyne **34** has coordinative substituents (R) such as CH₂OH and CH₂NMe₂, the second cycloaddition proceeds predominantly through an intermediate **D'**, which can be stabilized by the coordination of a directing group at the 3-position of the first-generated pyridyl moiety to the cobalt, to yield 2,2'-isomer **35**.

Regarding a dppe/CoCl₂·6H₂O/Zn catalyst developed by us, we postulate that the pyridine formation may proceed through a (dppe)Co^ICl complex generated by the reduction of (dppe)CoCl₂ with zinc, which might react with diynes **5** or **11** to provide cobaltacyclopentadiene intermediates **H** or **J**, respectively (Scheme 22). The regioselectivity can be systematically rationalized by considering differences in the



Scheme 22. Summary of The Regiochemical Trend of Dipimp/CoCl₂-6H₂O/Zn-Catalyzed Reactions

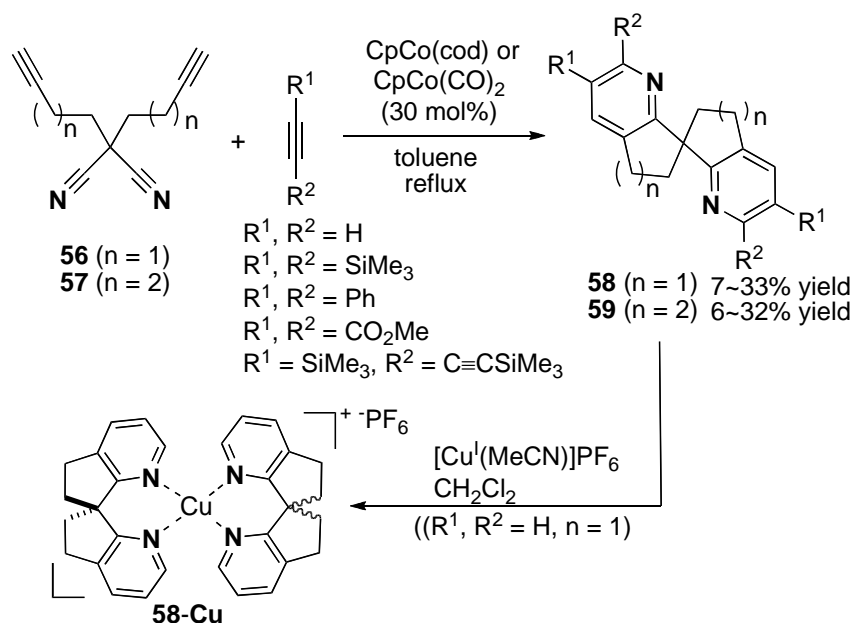
electronic nature between the diynes' two alkynes. Thus, a relatively electron-rich alkyne moiety in diynes **5** or **11** was bonded to the electron-poor position (carbon atom) of the cyano group in nitriles. It is plausible that an intermediate cobaltacycle of the type **H** or **J** derived from the corresponding **5** or **11** might have a similar electronic nature influenced by the substituents R¹ and R² in the reaction proceeding through [4 + 2] cycloaddition and/or insertion pathways. Thus, the regioselectivity can be predicted accurately by ordering the electronic nature of alkynes as Me₃Si-, alkyl-, H-, Ph-, C≡C-, and 2-pyridyl-substituted alkynes from electron rich to electron poor. The double cycloaddition reactions of tetraynes **32** with nitriles are the case: the first cycloaddition may proceed similarly to the reaction of **5** through an intermediate **K** and the resulting adduct further reacts with a nitrile like the reaction of **11**. Overall, the regioselectivity may be altered mainly by electronic effects. In conclusion, the consideration of the regiochemical trend lends credence to our method's synthetic potential, although confirmation of the reaction mechanism involving the conversion of metallacycle intermediates **H**, **J** or **K** to pyridines will require further studies.

6. APPENDIX

This section adds several interesting topics, highly related to synthesis of 2,2'-bipyridines by a cycloaddition reaction.

Although the following two examples are not for formation of 2,2'-bipyridines, Co- and Rh-catalysts could effectively convert malononitrile derivatives **56**, **57**, and **60** to the unique spiro compounds, i.e., tetrahydro-7,7'-spirobi[cyclopenta[*b*]pyridine]s and tetrahydro-8,8'-spirobi[quinoline]s, by a [2 + 2 + 2] double cycloaddition reaction of nitrile and two alkynes (Scheme 23 and Scheme 24).

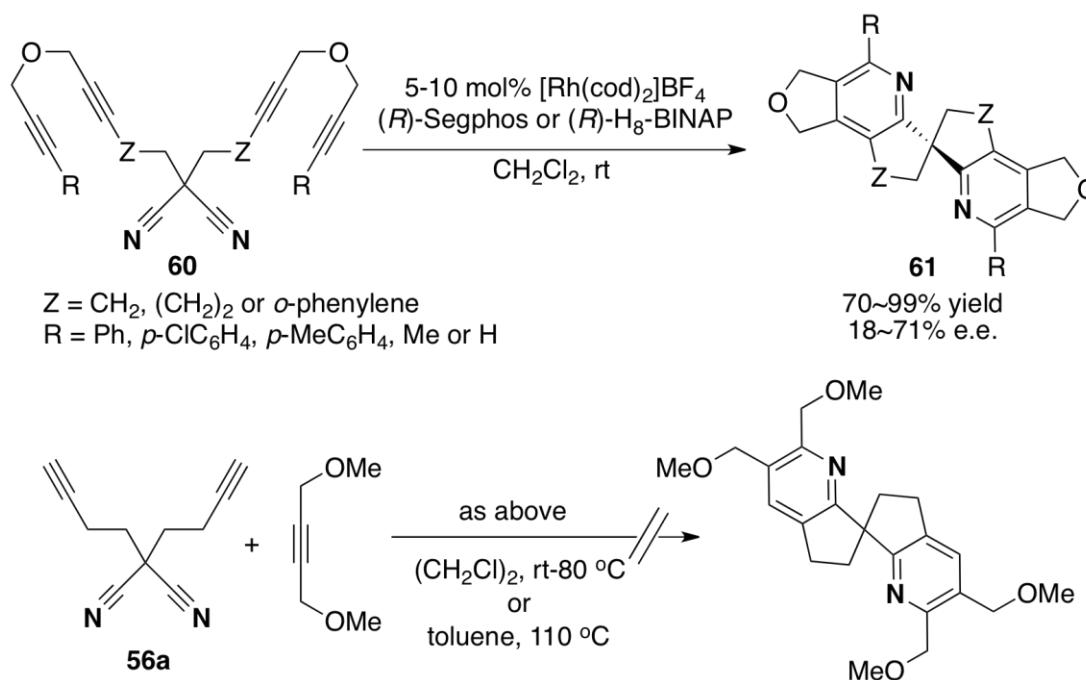
Saá *et al.* first demonstrated synthesis of 7,7'-spirobi[cyclopenta[*b*]pyridine]s **58** and 8,8'-spirobi[quinoline]s **59** from dialkylated malononitriles **56** and **57**, respectively, by treatment with a CpCo(cod) or CpCo(CO)₂ catalyst in a refluxed toluene (Scheme 23).²⁵ For the reaction with acetylene (R¹, R² = H) as an alkyne counterpart, use of CpCo(cod) gave a better yield. The moderate or low yields of these reactions were explained by assuming that the *gem*-dinitrile unit of malononitriles **56** and **57** may reduce the donor character of the nitrile, disfavoring stabilization of the cobaltacycle intermediate. They also studied formation of coordination complexes with use of the resulting racemic 7,7'-spirobipyridine **58** (R¹ = R² = H, n = 1). Thus, the tetra-coordinate complex **58-Cu** was obtained as a diastereomeric mixture when [Cu^I(CH₃CN)]PF₆ was added to solution of (±)-**58** in CH₂Cl₂ at room temperature.



Scheme 23. Synthesis of Spirobipyridines by Double Cycloaddition Catalyzed by CpCo^I

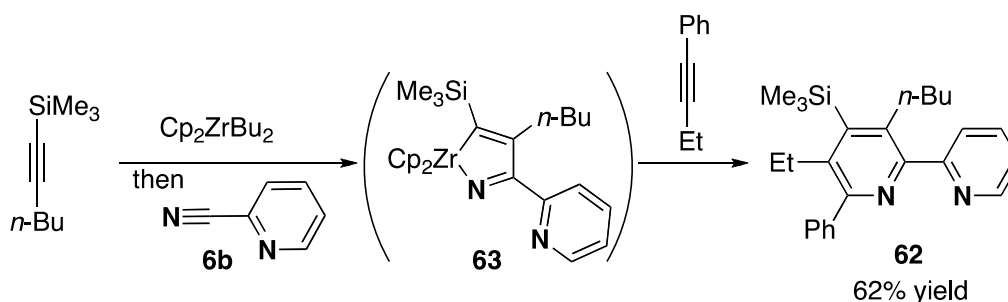
Tanaka and co-workers have reported that a fully intramolecular double cycloaddition of dicyano-tetrayne

compounds **60** catalyzed by $[\text{Rh}(\text{cod})_2]\text{BF}_4$ in the presence of a chiral diphosphine such as (*R*)-Segphos and (*R*)-H₈-BINAP proceeded smoothly in CH_2Cl_2 at ambient temperature to provide the corresponding 7,7'-spirobi[cyclopenta[*b*]pyridine]s and 8,8'-spirobi[quinoline]s **61** in good-to-excellent yields as an optically active form (up to 71% enantiomeric excess) (Scheme 24).²⁶ In contrast to the cobalt-catalyst systems mentioned in Scheme 23, the Rh-catalyst system could not cycloadd dicycano-diyne **56a** to an internal alkyne intermolecularly, and the compound **56a** was recovered even at elevated temperature.



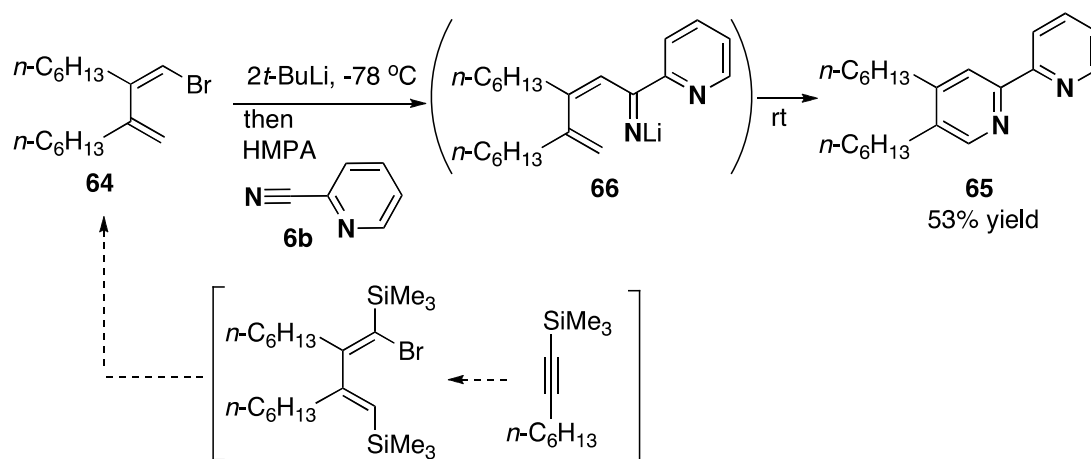
Scheme 24. Cationic Rh-Catalyzed Asymmetric Synthesis of Spirobipyridines by Double Cycloaddition

In the report of selective pyridine formation from two different unsymmetrical alkynes and a nitrile developed by Takahashi's group, an efficient chemoselective and regioselective synthesis of 2,2'-bipyridine **62** from 2-cyanopyridine (**6b**) and two different alkynes has been reported, albeit the process is not catalytic and requires a stoichiometric amount of zirconium reagent (Scheme 25).²⁷



Scheme 25. Zirconium-Mediated Synthesis of Bipyridine from Two Different Alkynes and 2-Cyanopyridine

Xi and co-workers synthesized 4,5-disubstituted 2,2'-bipyridine **65** starting from 1-halo-1,3-diene **64** by lithiation and the following addition reaction with 2-cyanopyridine (**6b**) (Scheme 26).²⁸ The 1-halo-1,3-diene **64** may be prepared from trimethylsilylalkynes by zirconium-mediated reaction, and therefore, the overall processes are a formal [2 + 2 + 2] cycloaddition of 2-cyanopyridine and alkynes, albeit it needs a stoichiometric amount of metallic reagents.



Scheme 26. Bipyridine Formation by Addition of 1-Lithiated 1,3-diene with 2-Cyanopyridine

7. CONCLUSION

In recent years, the transition metal-catalyzed *de novo* synthesis of 2,2'-bipyridines by [2 + 2 + 2] cycloaddition of alkynes and nitriles has been evolving as a versatile method in synthetic chemistry. In general, the reactions proceed through the formation of metallacyclopentadiene intermediates and subsequent insertion or [4 + 2] cycloaddition of another unsaturated bond. In several reaction types, regioisomeric bipyridine products can be generated with a selectivity determined by the regiochemistry of the metallacyclopentadiene formation and/or the following reaction of another unsaturated bond. With the advances accounted here, an efficient, straightforward, and atom-economical construction of 2,2'-bipyridines as well as several high regioselectivities have been realized in fully and partially intramolecular reactions. Meanwhile, the fully intermolecular reaction is still not much explored. In particular, the regioselective catalytic assembly of two different unsymmetrical acetylenes and a nitrile, leading to a single pyridine product, still remains a challenge.

In addition, the results of the reports reviewed here may be a prompt to investigate bipyridine synthesis by other catalytic systems active for an alkyne/nitrile [2 + 2 + 2] cycloaddition reaction, such as *N*-heterocyclic carbene/Ni(cod)₂,²⁹ Xantphos/Ni(cod)₂,³⁰ and dppp/FeI₂/Zn.³¹ The development of new catalytic reactions applicable to bipyridine synthesis in this fashion is also expected.

REFERENCES

1. J. G. Cordaro, J. K. McCusker, and R. G. Bergman, [Chem. Commun., 2002, 1496](#) and references cited therein. R. W. J. Chubb, M. R. Bryce, and B. Tarbit, [J. Chem. Soc., Perkin Trans. 1, 2001, 1853](#); J. G. Cordaro, J. K. McCusker, and R. G. Bergman, [Chem. Commun., 2002, 1496](#); C. Kaes, A. Katz, and M. W. Hosseini, [Chem. Rev., 2000, 100, 3553](#); K. T. Potts, K. A. Gheysen Raiford, and M. Keshavarz-K, [J. Am. Chem. Soc., 1993, 115, 2793](#); E. Constable, [Tetrahedron, 1992, 48, 10013](#); V. Grosshenny, A. Harriman, and R. Ziessel, [Angew. Chem., Int. Ed. Engl., 1995, 34, 2705](#); P. Belser, R. Dux, M. Baak, L. De Cola, and V. Balzani, [Angew. Chem., Int. Ed. Engl., 1995, 34, 595](#); A. Livoreil, C. O. Dietrich-Buchecker, and J.-P. Sauvage, [J. Am. Chem. Soc., 1994, 116, 9399](#); F. Barigelletti, L. Flamigni, V. Balzani, J.-P. Sauvage, A. Sour, E. C. Constable, and A. M. W. Cargill Thompson, [J. Am. Chem. Soc., 1994, 116, 7692](#); C. Dhenaut, I. Ledoux, I. D. W. Samuel, J. Zyss, M. Bourgault, and H. Le Bozec, [Nature, 1995, 374, 339](#); Y. Eichen, J.-M. Lehn, M. Scherl, D. Haarer, J. Fischer, A. DeCian, A. Corval, and H. P. Trommsdorff, [Angew. Chem., Int. Ed. Engl., 1995, 34, 2530](#); D. Gust, [Nature, 1994, 372, 133](#); J. Zyss, *Molecular Nonlinear Optics: Materials, Physics and Devices*; Academic Press: Boston, 1993.
2. S. P. Stanforth, B. Tarbit, and M. D. Watson, [Tetrahedron Lett., 2003, 44, 693](#); T. Shintou, F. Ikeuchi, H. Kuwabara, K. Umihara, and I. Itoh, [Chem. Lett., 2005, 34, 836](#) and cited therein.
3. M. Hapke, L. Brandt, and A. Lützen, [Chem. Soc. Rev., 2008, 37, 2782](#); T. D. Nelson and R. D. Crouch, *Organic Reactions*, 2004, **63**, 265; A. A. Fuller, H. R. Hester, E. V. Salo, and E. P. Stevens, [Tetrahedron Lett., 2003, 44, 2935](#) and cited therein.
4. Reviews for pyridine formation by the transition-metal-catalyzed [2 + 2 + 2] cycloaddition reactions: H. Bönnenmann, [Angew. Chem., Int. Ed. Engl., 1985, 24, 248](#); J. A. Varela and C. Saá, [Chem. Rev., 2003, 103, 3787](#); I. Nakamura and Y. Yamamoto, [Chem. Rev., 2004, 104, 2127](#); P. R. Chopade and J. Louie, [Adv. Synth. Catal., 2006, 348, 2307](#); B. Heller and M. Hapke, [Chem. Soc. Rev., 2007, 36, 1085](#); B. Heller and M. Hapke, [Chem. Soc. Rev., 2007, 36, 1085](#).
5. L. Garcia, A. Pla-Quintana, A. Rogalans, and T. Parella, [Eur. J. Org. Chem., 2010, 3407](#).
6. J. A. Varela, L. Castedo, and C. Saá, [J. Org. Chem., 2003, 68, 8595](#).
7. A. Goswami, K. Ohtaki, K. Kase, T. Ito, and S. Okamoto, [Adv. Synth. Catal., 2008, 350, 143](#).
8. Y. Sugiyama and S. Okamoto, [Synthesis, 2011, 2247](#). Errata: 2011, 3928.
9. J. Watanabe, Y. Sugiyama, A. Nomura, S. Azumatei, A. Goswami, N. Saino, and S. Okamoto, [Macromolecules, 2010, 43, 2213](#).
10. Y. Zou, D. D. Young, A. Cruz-Montanez, and A. Deiters, [Org. Lett., 2008, 10, 4661](#).
11. P. Garcia, Y. Evanno, P. George, M. Sevrin, G. Ricci, M. Malacria, C. Aubert, and V. Gandon, [Org. Lett., 2011, 13, 2030](#).

12. F. Nissen and H. Detert, [Eur. J. Org. Chem.](#), 2011, 2845.
13. F. Nissen, V. Richard, C. Alayrac, and B. Witulski, [Chem. Commun.](#), 2011, 47, 6656.
14. J. A. Varela, L. Castedo, and C. Saá, [J. Org. Chem.](#), 1997, 62, 4189.
15. J. A. Varela, L. Castedo, M. Maestro, J. Mahía, and C. Saá, [Chem. Eur. J.](#), 2001, 7, 5203.
16. C. Yuan, C.-T. Chang, A. Axelrod, and D. Siegel, [J. Am. Chem. Soc.](#), 2010, 132, 5924.
17. B. R. D'Souza, T. K. Lane, and J. Louie, [Org. Lett.](#), 2011, 13, 2936.
18. Y. Yamamoto, R. Ogawa, and K. Itoh, [J. Am. Chem. Soc.](#), 2001, 123, 6189.
19. Y. Yamamoto, K. Kinpara, R. Ogawa, H. Nishiyama, and K. Itoh, [Chem. Eur. J.](#), 2006, 12, 5618.
20. R. Hrdina, M. Dracínský, I. Valterová, J. Hodacová, I. Císarová, and M. Kotora, [Adv. Synth. Catal.](#), 2008, 350, 1449.
21. J. A. Varela, L. Castedo, and C. Saá, [J. Am. Chem. Soc.](#), 1998, 120, 12147.
22. G. Chelucci, M. A. Cabras, and A. Saba, [J. Heterocycl. Chem.](#), 1994, 31, 1289.
23. G. Chelucci, M. A. Cabras, C. Botteghi, and M. Marchetti, [Tetrahedron: Asymmetry](#), 1994, 5, 299; G. Chelucci, [Tetrahedron: Asymmetry](#), 1995, 6, 811.
24. J.-K. Uhm and H. W. An, [J. Korean Chem. Soc.](#), 2001, 45, 268.
25. J. A. Varela, L. Castedo, and C. Saá, [Org. Lett.](#), 1999, 1, 2141.
26. A. Wada, K. Noguchi, M. Hirano, and K. Tanaka, [Org. Lett.](#), 2007, 9, 1295.
27. T. Takahashi, F.-Y. Tsai, Y. Li, H. Wang, Y. Kondo, M. Yamanaka, K. Nakajima, and M. Kotora, [J. Am. Chem. Soc.](#), 2002, 124, 5059.
28. C. Wang, Z. Wang, L. Liu, C. Wang, G. Liu, and Z. Xi, [J. Org. Chem.](#), 2006, 71, 8565.
29. M. M. McComick, H. A. Duong, G. Zuo, and J. Louie, [J. Am. Chem. Soc.](#), 2005, 127, 5030; R. M. Stolley, M. T. Maczka, and J. Louie, [Eur. J. Org. Chem.](#), 2011, 3815.
30. P. Kumar, S. Prescher, and J. Louie, [Angew. Chem. Int. Ed.](#), 2011, 50, 10694.
31. C. Wang, X. Li, F. Wu, and B. Wan, [Angew. Chem.](#), 2011, 123, 7300.



Professor Sentaro Okamoto was born in 1961 in Hiroshima, Japan. He received his M. S. degree from Tokyo Institute of Technology in 1987 and became an assistant professor at the same institute in 1989. He obtained his Ph. D. in 1993 from Tokyo Institute of Technology under the supervision of Prof. Fumie Sato. He was also a visiting associate of Montana State University with Prof. T. Livinghouse for 1998-1999. He was promoted to associate professor in 2002 and then professor in 2008 at Kanagawa University. He received Toray Award in Synthetic Organic Chemistry, Japan in 1997 and Incentive Award in Synthetic Organic Chemistry, Japan in 2000. His research interest is in the area of organometallic chemistry toward synthetic organic chemistry, asymmetric synthesis, and synthesis of biologically active compounds and organic materials.