Regiocontrolled One-Step Synthesis of 3,3′-Disubstituted 2,2′-Bipyridine Ligands by Cobalt(I)-Catalyzed Cyclotrimerization

Jesús A. Varela,[a] Luis Castedo,[a] Miguel Maestro,[b] José Mahía,[b] and Carlos Saá*[a]

Abstract: A one-step, regioselective synthesis of annelated symmetric and asymmetric 3,3′-disubstituted 2,2′-bipyridines by cobalt(I)-catalyzed [2+2+2] cycloadditions between 5-hexynenitrile and 1,3-diynes is described. In the symmetric case, the total regioselectivity of the first cycloaddition is ensured electronically by the conjugation of the triple bonds, and for aminomethylated diynes that of the second is ensured by the cobalt coordinating to the aminomethyl rather than to the hexynenitrile nitrogen. In the asymmetric case, the first cycloaddition took place chemoselectively, which in the case of bis(trimethylsilyl)-1,3,5-hexatriyne (viewed as a 1,3-diyne) is explained by semiempirical calculation of LUMO coefficients. The copper(I) complex of **6b**, constituting the first reported complex of the form ML_2 (L is a symmetric 3,3′-disubstituted 2,2′-bipyridine), has been prepared. It had UV/Vis and NMR spectra reflecting the 3-substituent-induced mutual torsion of the bipyridine rings in the *cis* conformation, as was confirmed by x-ray diffractometric determination. The bipyridine **6c** forms the dinuclear complex $[Cu_2(\mathbf{6c})_2(CH_3CN)_2]^{2+}$ in the solid state.

Keywords: alkynes · cobalt · coordination chemistry · cyclotrimerization · N ligands

Introduction

The compounds 2,2′-bipyridines and other oligopyridines are particularly attractive building blocks for the preparation of supramolecular structures[1] because they easily form well-defined chelate complexes with many metals.[2] In recent years, they have been used to create exotic structures such as molecular knots,[1] catenanes,[3] well-defined helicates,[4] molecular grids,[5] rotaxanes,[6] nanocyclic architectures,[7] and liquid crystals.[8] Additionally, many of their transition metal complexes have interesting paramagnetic, optical, photophysical, and redox properties, which can be controlled by choice of the appropriate oligopyridine.

In view of these fascinating applications, there is a need to develop efficient synthetic routes to desired bipyridine units. Most of the methods commonly used to synthesize functionalized bipyridines are based on Pd- or Ni-catalyzed heteroaryl C–C coupling reactions (Stille, Negishi, or Suzuki cross-couplings)[9, 10] or on the Kröhnke[11] and Potts[12] strategies, all of which often require multiple steps and are unsuitable for the preparation of 3,3′-disubstituted bipyridines. The 3,3′-substitution pattern is very attractive because a) metal complexes of ditopic 3,3′-crown ether 2,2′-bipyridine ligands have shown promise for use as antitumor agents[13] or as molecular machines based on allosteric effects,[14] and b) this pattern can also be used in the design of efficient chiral catalysts.[15] An attractive new approach to 3,3′-disubstituted bipyridines is based on pioneer work by Wakatsuki,[16] Bönnemann,[17] and Vollhardt[18] on the synthesis of pyridines by cobalt(I)-catalyzed or mediated [2+2+2] cyclotrimerization of alkynes and nitriles.[19] We recently published a preliminary communication on the application of this method to the one-step synthesis of annelated symmetrical 3,3′-disubstituted 2,2′-bipyridines by cobalt(I)-catalyzed [2+2+2] cyclotrimerization of 5-hexynenitrile with 1,3-diynes.[20] As far as we know, this was the first one-step construction of 2,2′-bipyridines from acyclic precursors. Here we present a full account of this work and of our recent findings on the regioselectivity of the reaction with symmetrically substituted diynes, the regio- and chemoselectivities of the reaction with asymmetric diynes, and the coordination properties of the bipyridines synthesized, including the first preparation of a ML_2 complex (M = metal, L = a symmetric 3,3′-disubstituted 2,2′-bipyridine).

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Results and Discussion

[2+2+2] Cocyclizations with symmetrical 1,3-diynes: regioselectivity: At the beginning of this work, symmetrical 1,3-diynes had only been used in cobalt chemistry for dimeriza-

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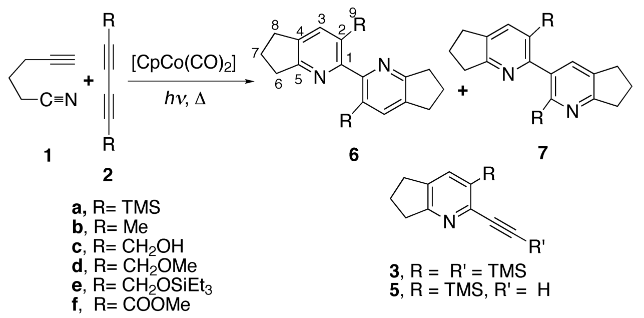
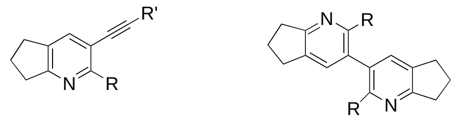
tion.[21, 22] We believed it would be interesting to evaluate their behavior in Co^I-catalyzed [2+2+2] cocyclizations because, in principle, this would allow functionalized biaryl ligands to be assembled in one step. For the sake of comparison, in all our studies of Co^I-catalyzed [2+2+2] cyclotrimerization we used 5-hexynenitrile (**1**) as one of the cocyclization partners.

[CpCo(CO)$_2$]-catalyzed cocyclization of **1** with 1,4-bis(trimethylsilyl)-1,3-butadiyne (**2a**) produced a 77% yield of pyridine **3** (Scheme 1). The structure of **3** was inferred by preparing its monodesilylated product (K_2CO_3 in MeOH)



Scheme 1. [CpCo(CO)$_2$]-catalyzed cycloaddition of **1** to symmetrical 1,3-diynes **2a**–**f**.

and observing NOEs between the protons of the remaining TMS group and the aromatic proton, and this indicated that the alkyne substituent must be in position 2, and the product was therefore pyridine **5** (Scheme 1). The cocyclization reaction needed irradiation for only 1 h, and required no high dilution techniques. Interestingly, neither the regioisomer **4** (Scheme 2, R = R′ = TMS) nor η^4-cyclobutadienecobalt complexes of the diyne[21] were observed in the reaction mixture;



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Scheme 2. Regioisomers not found.

this unprecedented regioselectivity was subsequently explained by calculations (see below).

Suspecting that steric hindrance by the TMS group at position 3 of the pyridine ring might be blocking the second cycloaddition (since unsubstituted 2-(trimethylsilyl)ethynylpyridine does undergo cycloaddition),[23] we then used the sterically less demanding 2,4-hexadiyne **2b**. The second cocyclization now occurred as expected, producing a 1.7:1 ratio of the 2,2′-bipyridine **6b** and the 2,3′-bipyridine **7b** as the main reaction products in, respectively, 30% and 18% isolated yields after chromatographic separation (Scheme 1 and Table 1).[24] Compound 2,2′-bipyridine **6b** was distinguished from 3,3′-bipyridine **8b** (Scheme 2, R = Me) by HMQC (heteronuclear multiple quantum coherence) and HMBC (heteronuclear multiple bond correlation) experiments, which showed a three-bond ^{1}H-^{13}C correlation between the aromatic proton and the methyl group. The 3,3′-bipyridine **8b** was not detected in the reaction mixture.

As far as we know, this was the first one-step construction of a 2,2′-bipyridine from acyclic precursors. Although the yield may seem modest, it compares well with those of multistep syntheses[9–12] and was unaffected by scaling up from the 0.3 to the 6.8 mmol scale.

Having thus found that bulky substituents on the diyne partner can prevent the formation of the second pyridine ring, we decided to investigate the influence of electronic factors on the course of the reaction. Cocyclization of **1** with 2,4-hexadiyn-1,6-diol (**2c**) gave a complex mixture from which the 2,2′-bipyridine **6c** could only be isolated in 9% yield, but reaction with the methyl ether **2d**[25] proceeded smoothly, giving a 73:27 mixture of the 2,2′-bipyridine **6d** (46% isolated yield) and the 2,3′-bipyridine **7d** (17% isolated yield); see Table 1. The identity of **6c** was confirmed by reciprocal NOEs between the aromatic proton and the methylene of the hydroxymethyl group, and this ruled out the regioisomeric 3,3′-structure, and that of **6d** by a combination of HMQC and HMBC experiments.

Table 1. Results of cocyclization of **1** with symmetrical diynes **2a**–**2f**.

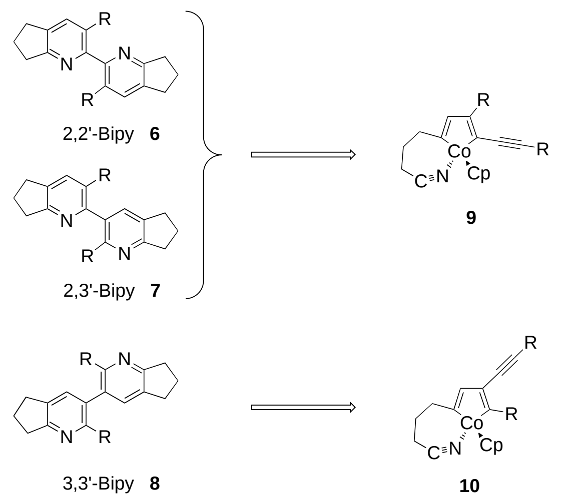
	Diyne[a]	Products	2,2′:2,3′ ratio (**6**:**7**) [%][b]	Yield [%][c]
1	**2a**	**3a**	–	77
2	**2b**	**6b**, **7b**	63:37	48
3	**2c**	**6c**	–	9
4	**2d**	**6d**, **7d**	73:27	63
5	**2e**	**6e**, **7e**	80:20	45
6	**2f**	**6f**, **7f**	58:42	18

[a] Typically, 0.1 g was employed. For **2b** and **2e**, reactions with 0.5 g (6.41 mmol) and 2.3 g (6.8 mmol), respectively, were also performed. [b] The two isomers are easily separable by column chromatography or preparative TLC (silica gel); for example, R_f: **6d** = 0.52; R_f: **7d** = 0.37. [c] Combined yields of **6** + **7** after separation by chromatography.

Abstract in Spanish: *Se describe la síntesis regioselectiva en un solo paso de 2,2′-bipiridinas 3,3′-disustituidas, tanto simétrica como asimétricamente, mediante reacciones de cicloadición [2+2+2] catalizadas por Co^I entre el 5-hexinonitrilo y 1,3-diinos. En el caso de los diinos simétricos, la regioselectividad en la primera cicloadición se debe al efecto electrónico causado por la conjugación de los triples enlaces mientras que la regioselectividad en la segunda cicloadición, en el caso del diino aminometilado, es debida a la coordinación del nitrógeno del aminometilo al cobalto en vez del resto nitrilo. Con los diinos asimétricos, se observa que la primera cicloadición es quimioselectiva y para el caso del bis(trimetilsilil)-1,3,5-hexatriino se puede explicar mediante cálculos semiempíricos de los coeficientes LUMO. Se han preparado por primera vez complejos de Cu^I con estructura ML$_2$ en los que sus datos espectrales de UV/Vis y RMN reflejan la torsión de los anillos de bipiridina causada por la presencia de sustituyentes en posiciones 3 y 3′. Se pudo confirmar en algún caso este efecto mediante el espectro de difracción de rayos X. En el caso de la bipiridina* ***6c*** *se obtuvo el complejo dinuclear [Cu_2(**6c**)$_2$(CH_3CN)$_2$]$^{2+}$ en forma cristalina.*

With a view to facilitating subsequent manipulation of the substituent, and to evaluate the influence of a bulky group separated from the diyne unit by $-CH_2O-$, the triethylsilyl ether **2e**[26] was also employed. Not unexpectedly, with **2e** the bulk of the triethylsilyl group did not impede the second cyclization, and there was in fact a slight improvement in the ratio of the 2,2′-product (**6e**, 36% yield) to the 2,3′-product (**7e**, 9% yield); see Table 1. By contrast, with **2f**,[27] in which carbonyl groups are conjugated to the diyne triple bonds, there was only an 18% combined yield of the 2,2′- and 2,3′-bipyridines **6f** and **7f** in 1.4:1 ratio (Table 1). The low yield of this latter reaction may be due to the starting diyne **2f** being unstable, both neat and in solution.

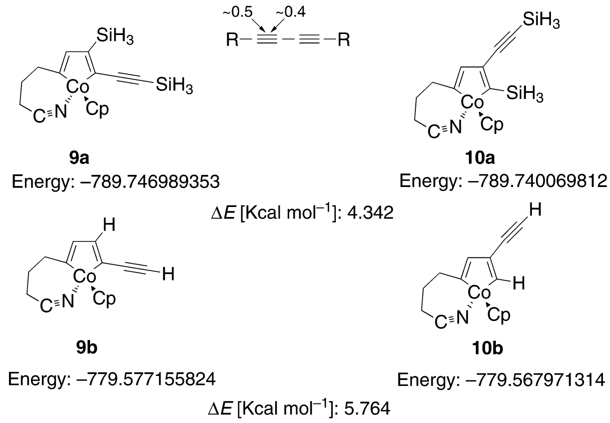
A common feature of all the above cycloadditions is their high regioselectivity in the first cocyclization; no 3,3′-bipyridines **8** were observed in any case (Scheme 3). Assuming the commonly accepted mechanism for the oxidative coupling reaction, the electronic influence of the adjacent alkyne during metallacycle formation seems in this respect completely to override the electronic and/or steric properties of the other substituent.



Scheme 3. Cobaltacycle intermediates **9** and **10**.

To gain further understanding of these experimental results, we performed calculations on the starting diyne and the metallacycles. Since Hoffmann et al. have suggested that the alkyne partner enters the intermediate metallacycle with the biggest lobe of its LUMO β to the metal,[28] we calculated LUMO coefficients for the various diynes by using semi-empirical methods.[29] All the diynes have their biggest LUMO lobes on the terminal diyne carbons (Scheme 4), which may explain why no 3,3′-bipyridines were obtained.

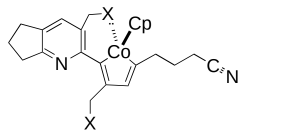
In addition, B3LYP/LANL2DZ ab initio calculations[30] of the energies of the intermediate metallacycles in the reactions of **2a**[31] and its desilylated analogue show that the cobaltacycle **9**, in which the ethyne is α to the cobalt, has in both cases, lower energy than that of **10** (Scheme 4). Assuming that both electronic and steric factors are operative in **9a**, and only



Scheme 4. Relative magnitudes of LUMO coefficients of symmetrical 1,3-diynes and energies (hartrees) of intermediate cobaltacycles (1 hartree = 627.5 Kcal mol^{-1}).

electronic factors in **9b**, and that electronic and steric factors have opposite regiodirective influence, it would appear that it is the electronic factor that is responsible for the observed regioselectivity.[32] As far as we know, this would be the first case of a [2+2+2] cycloaddition reaction in which the regiochemical outcome is completely controlled, both mechanistically and energetically, by the electronic influence of the alkyne partner (here, the diyne).[33]

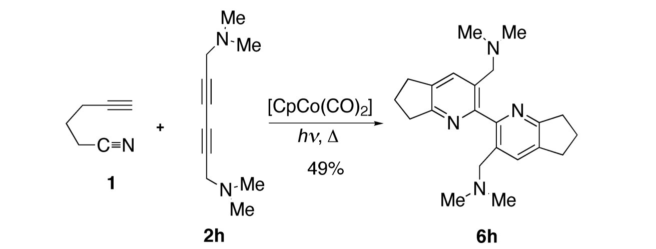
The results listed in Table 1 show that by choosing diyne substituents with a suitable combination of steric and electronic properties it is possible to achieve a 2,2′:2,3′ regioisomer ratio of 4:1. Since the best results were obtained with **2d** and **2e**, another effect we thought it would be interesting to evaluate was the presumed coordination of diyne substituent heteroatoms to the cobalt during the formation of the second cobaltacycle intermediate (Scheme 5). Specifically, we envisaged that replacing the oxygens of **2d** and **2e** with more avidly coordinating heteroatoms such as sulfur or nitrogen might improve the 2,2′:2,3′ ratio (*chelation control*).



X = OCH_3 (**2d**), SEt (**2g**), NMe_2 (**2h**)

Scheme 5. Chelation control.

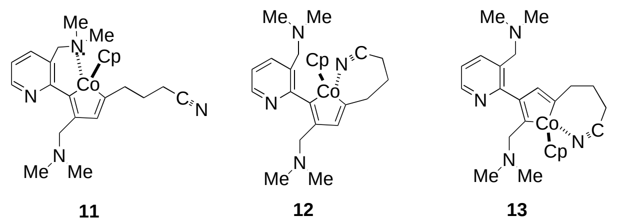
Unfortunately, the propargylic disulfide **2g** (R = CH_2SEt), prepared in 90% yield by copper-catalyzed oxidative homocoupling[34] of ethyl 2-propynyl sulfide,[35] was too unstable to be used. However, with the amine derivative **2h** (R = CH_2NMe_2)[36] both [2+2+2] cycloadditions were completely regioselective, giving the 2,2′-bipyridine **6h** in fairly good yield (49%) as the only product (Scheme 6). A combination of DEPT (distortionless enhancement by polarization transfer), HMQC, and HMBC experiments confirmed the structure of **6h** showing ^1H-^{13}C correlation between the aromatic proton and the methylene carbon group of the dimethylami-



Scheme 6. $[CpCo(CO)_2]$-catalyzed cycloaddition of **1** to diyne **2h**.

nomethyl substituent. In view of the aforementioned observation, the complete regioselectivity of the reaction with **2h** seems likely to be due to two electronic effects, that of the conjugated diyne unit on the formation and energy of the first cobaltacycle (Scheme 4) and the *chelation effect* of the nitrogen during the formation of the second cobaltacycle (Scheme 5).

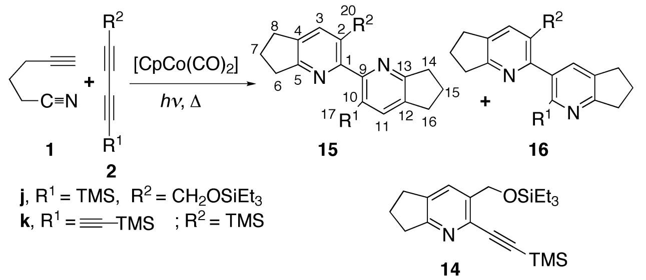
The hypothesis of *chelation control* during the formation of the second intermediate cobaltacycle is supported by the results of HF/3-21G ab initio calculations on the three possible metallacycles (Scheme 7), which showed that the 2,2′-precursor cobaltacycles **11** and **12**[37] have much lower energies than the 2,3′-precursor **13**, and that **11**, in which the amino group is coordinated to the cobalt, has lower energy than **12**, in which it is the nitrile group that coordinates.



Scheme 7. Cobaltacycle intermediates **11**–**13**.

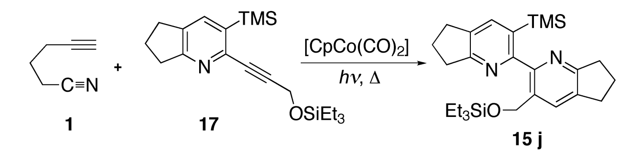
[2+2+2] Cocyclizations with asymmetric 1,3-diynes: chemoselectivity: We next examined the chemoselectivity of the reactions of the asymmetric 1,3-diyne **2j**[38] and the 1,3,5-hexatriyne **2k**, which may also be considered as an asymmetric 1,3-diyne (Scheme 8).

$[CpCo(CO)_2]$-catalyzed cocyclization of **1** and **2j** afforded a mixture of silylated products from which pyridine **14** was easily isolated in 27% yield. To facilitate the separation and identification of the remaining products, the mixture was treated with K_2CO_3 in MeOH, and this, after chromatography, allowed the isolation of the 2,2′-bipyridine **15j** and its desilylated derivative **15j′** (R^1 = TMS, $R^2 = CH_2OH$) in 2% and 17% yield, respectively, and of the 2,3′-bipyridine **16j″** (R^1 = H, $R^2 = CH_2OTES$)[39] in 15% yield (Scheme 8). The identities of these products were confirmed by NOE studies. For pyridine **14**, reciprocal NOEs between aromatic and benzylic ($ArCH_2OTES$) protons indicated the *ortho* position of one group to the other. In the case of **15j′**, NOEs between one of the aromatic protons and the TMS group, and between the other and the methylene of the hydroxymethyl group, show that **15j′** must be a 2,2′-bipyridine. In the ^1H NMR spectrum of **16j″**, a singlet at low field ($\delta = 8.43$) is attributable to a proton α to the nitrogen in the pyridine ring, and the other two aromatic protons show NOEs with the methylene, showing that this compound must be a 2,3′-bipyridine.



Scheme 8. $[CpCo(CO)_2]$-catalyzed cycloaddition of **1** to asymmetric alkynes **2j** and **2k**.

Since the reaction of the asymmetric diyne **2j** afforded no products corresponding to initial formation of the pyridine **4** (Scheme 2, $R = CH_2OTES$, R′ = TMS), regioisomer of **14**, it conserved the regioselectivity observed with symmetric diynes, at least when the initial cycloaddition involved the CH_2OTES-substituted ethyne moiety. The absence of **17** (Scheme 9) and its corresponding regioisomer **4** (Scheme 2, R = TMS, $R' = CH_2OTES$) from the reaction mixture also clearly suggested that the initial cycloaddition was strongly chemoselective, and that it took place only at the CH_2OTES-substituted ethyne moiety, since the TMS groups of these species would be likely to prevent a second cycloaddition (cf. the results obtained with **2a**). To support this latter reasoning, we prepared **17** (by treatment of pyridine **5** with BuLi and paraformaldehyde, followed by reaction of the resulting alcohol with TESCl; overall yield 80%), and then subjected a solution of **17**, **1**, and the catalyst in toluene to three hours irradiation; although an 18% yield of **15j** was obtained, the recovery of 40% of **17** strongly suggested that in the reaction of **2j** it cannot ever have been formed, and hence that the first cycloaddition in this reaction was strongly chemoselective. It is nevertheless worth noting the contrast between the 0% yield of bipyridine obtained with compound **3**, in which the ethyne substituent has a TMS group, and the 18% obtained with **17**, which has an electronically more favorable ethyne substituent that, furthermore, places the bulky $SiEt_3$ group farther from the triple bond than is the TMS group on the ethyne in **3**.



Scheme 9. $[CpCo(CO)_2]$-catalyzed cycloaddition of **1** to pyridine **17**.

Experiments were carried out with the 1,3,5-hexatriyne **2k**,[40] considered as an asymmetric 1,3-diyne, in order to investigate the effect of conjugation with another triple bond on the chemoselectivity of the reaction. Cocyclization of **1** with **2k** afforded two products that were identified, by a

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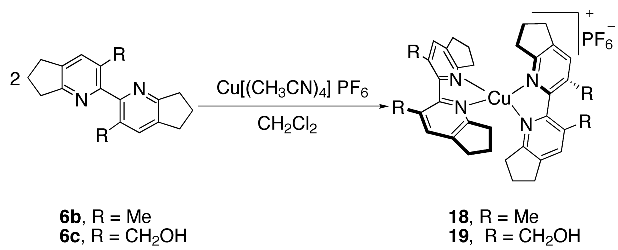
combination of HMQC, HMBC, and NOE experiments, as the 2,2′-bipyridine **15k** (10%) and the 2,3′-bipyridine **16k** (21%) (Scheme 8). The initial cycloaddition is likely to have occurred at the central triple bond;[41] if it had occurred at a terminal triple bond, the diyne substituent of the resulting pyridine would have been *ortho* to a TMS substituent that would probably have blocked further cycloaddition, at least at the proximal triple bond of the diyne, and the mixture of products in fact contained neither this intermediate pyridine nor any di(pyridyl)acetylene. Initial cycloaddition on the central triple bond must have been followed by further cycloadditions on both the ethyne *ortho* to the pyridine nitrogen (giving **15k**) and the *meta* ethyne (giving **16k**). Note that both this second set of cycloadditions created rings with the first pyridine in position 2′. A third set of cycloadditions on the remaining ethyne is presumably prevented by steric hindrance.

Semiempirical calculations[29] showed the largest LUMO lobes of diyne **2j** to be located on the terminal carbons C1 and C4, and those of **2k** on the central carbons C3 and C4 (Scheme 10). The latter finding would explain the observed chemoselectivity of the first cycloaddition in the reaction of **2k**, and the former the regioselectivity of the formation of **14**, but the apparently negligible difference between the C1 and C4 LUMO coefficients of **2j** can hardly account for the chemoselectivity of the first cycloaddition to this diyne.

Scheme 10. Relative magnitudes of LUMO coefficients for diyne **2j** and **2k**.

Coordination complexes: Compound 2,2′-bipyridine is extensively used as a neutral metal-chelating ligand as a result of its redox stability and ease of pre-functionalization.[2] However, symmetrical 3,3′-disubstituted 2,2′-bipyridines have been used relatively rarely, at least partly because of the difficulty of their preparation. Probably because of the lack of research in this area, there have been no reports of complexes of the form ML_2 with M a tetracoordinated metal and L a symmetric 3,3′-disubstituted 2,2′-bipyridine; most complexes of these ligands are of the form ML_3, with M an octahedrally hexacoordinated Fe^0,[42] Ni^{II},[42] Ru^{II},[43] Co^{III},[44] or Rh^{III}.[45] We therefore investigated whether our new symmetric 3,3′-disubstituted 2,2′-bipyridines would form complexes of the previously unknown ML_2 type.[46]

*Complex of Cu^I with **6b***: Compound **18**, a cationic complex of stoichiometry $[Cu(\mathbf{6b})_2]^+$, was obtained in 90% yield by mixing 2 equiv of **6b** and 1 equiv of $[Cu^I(CH_3CN)_4]PF_6$ in CH_2Cl_2 at RT (Scheme 11). The coordination of the ligands was reflected by downfield shifts in the NMR signals of the aromatic and methyl protons ($\Delta\delta = 0.22$ and 0.28 ppm, respectively), and by the appearance of a metal-ligand charge-transfer band at 392 nm in the UV/Vis spectrum. Since this band usually appears at around 440 nm in Cu^I



Scheme 11. Cu^I complexes of 3,3′-disubstituted 2,2′-bipyridines.

complexes of 2,2′-bipyridines, shifting to shorter wavelengths only when retrodonation is hampered,[47] its position in **18** may be taken to reflect the mutual torsion of the rings of each bipyridine due to the steric influence of the substituents at positions 3 and 3′ when the *cis* conformation necessary for chelation is adopted. This torsion was confirmed by x-ray diffractometric determination of the structure of crystals of **18** obtained by slow diffusion into ether of a solution of **18** in dichloromethane (Figure 1, Table 2), and this also showed the expected distorted tetrahedral coordination polyhedron (with Cu–N distances close to 2 Å) and that the two bipyridines are not equivalent (in particular, N–C–C–N = 41° in one and 36° in the other); see Table 3.

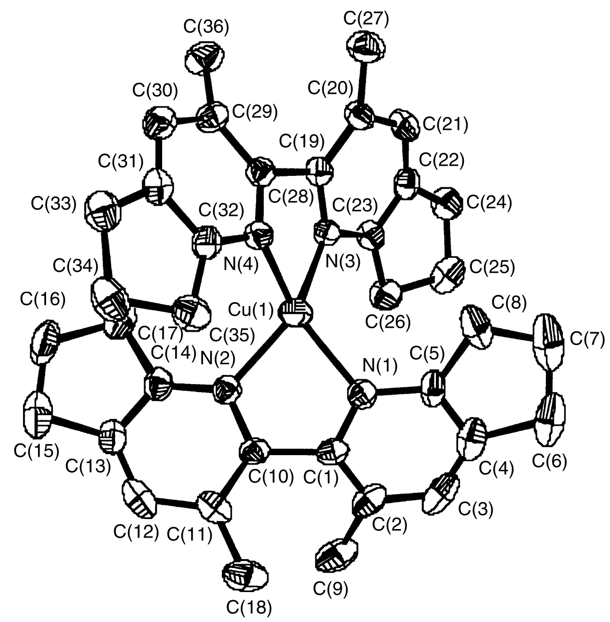


Figure 1. ORTEP representation of the cation $[Cu(\mathbf{6b})_2]^+$ (**18**). Hydrogen atoms are omitted for clarity.

*Complex of Cu^I with **6c***: In view of the above result, we investigated whether placing a substituent bulkier than Me at positions 3 and 3′, like **6c**, might lead to a nontetrahedral complex. The FAB and HRMS spectra of the yellow complex obtained by the same method as for **18** showed peaks at 655 indicative of $[Cu(\mathbf{6c})_2]^+$. The NMR signals of the aromatic and hydroxymethyl protons were shifted downfield by 0.21 and 0.05 ppm, respectively, from their positions in the free ligand (7.68 and 4.36 ppm, respectively), but the fact that the hydroxymethyl peak showed no spreading was interpreted as

Table 2. Crystal and structure refinement data for complexes **18** and **20**.

	$[Cu(\mathbf{6b})_2](PF_6)$ (**18**)	$[Cu_2(\mathbf{6c})_2(CH_3CN)_2](PF_6)_2$ (**20**)
empirical formula	C 36 H 40 Cu F 6 N 4 P	C 40 H 46 Cu 2 F 12 N 6 O 4 P 2
formula weight	737.23	1091.85
T	298(2) K	298(2) K
λ	0.71073 Å	0.71073 Å
crystal system	orthorhombic	monoclinic
space group	$Fdd2$	$P2(1)/c$
unit cell dimensions	$a = 29.333(17)$ Å, $\alpha = 90°$ $b = 30.758(17)$ Å, $\beta = 90°$ $c = 15.224(9)$ Å, $\gamma = 90°$	$a = 21.543(5)$ Å, $\alpha = 90°$ $b = 13.138(2)$ Å, $\beta = 111.82$ (14)° $c = 16.866(3)$ Å, $\gamma = 90°$
V	13736.1(14) Å^3	4431.4(15) Å^3
Z	16	4
ρ_{calcd}	1.426 mg m^{-3}	1.637 mg m^{-3}
absorption coefficient	0.747 mm^{-1}	1.131 mm^{-1}
$F(000)$	6112	2224
crystal size	$0.40 \times 0.25 \times 0.20$ mm^3	$0.30 \times 0.25 \times 0.10$ mm^3
θ range for data collection	1.65 to 25.14°	1.02 to 25.04°
index ranges	$-35 \leq h \leq 35$, $-36 \leq k \leq 31$ $-13 \leq l \leq 18$	$-25 \leq h \leq 24$, $-15 \leq k \leq 15$ $-13 \leq l \leq 20$
reflections collected	14282	18391
independent reflections	5492 [R(int) = 0.0596]	7807 [R(int) = 0.0545]
completeness to $\theta = 25.14°$	99.7 %	99.6 %
absorption correction	empirical	empirical
max. and min. transmission	0.865 and 0.754	0.895 and 0.728
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
data/restraints/parameters	5492/1/433	7807/0/674
goodness-of-fit on F^2	1.037	1.028
final R indices [$I > 2\sigma(I)$]	$R1 = 0.0597$, $wR2 = 0.1339$	$R1 = 0.0528$, $wR2 = 0.1143$
R indices (all data)	$R1 = 0.1064$, $wR2 = 0.1598$	$R1 = 0.0981$, $wR2 = 0.1352$
absolute structure parameter	0.02(2)	–
largest diff. peak and hole	0.288 and -0.246 e Å^{-3}	0.530 and -0.561 e Å^{-3}

Table 3. Metal-to-ligand bond lengths [Å], bite angles, and N–C–C–N dihedral angles in the complex $[Cu(\mathbf{6b})_2]^+$ (**18**).

Cu–N1	Cu–N2	Cu–N3	Cu–N4	N1CuN2	N3CuN4	N1C1C10N2	N3C19C28N4
2.032(5)	2.037(5)	2.021(5)	2.007(5)	82.8(2)	82.16(18)	41.5(7)	36.3(8)

possible evidence against $[Cu(\mathbf{6c})_2]^+$ having the tetrahedral structure, and the position of the metal-ligand UV/Vis band, 430 nm, indicated the absence of significant geometric impediment to retrodonation.

X-ray analysis of colorless crystals obtained by slow diffusion into MeOH/ether did not show the mononuclear complex $[Cu(\mathbf{6c})_2](PF_6)$ but the dinuclear complex $[Cu_2(\mathbf{6c})_2(CH_3CN)_2](PF_6)_2$ (**20**),[48] in which each copper atom is coordinated to an acetonitrile molecule and to one nitrogen of each of the two bipyridines (Figure 2). The Cu–N distances are still close to 2 Å, and the N(bipy)–Cu–N(acetonitrile) and N(bipy)–Cu–N(bipy) angles, close to 120 and 112° respectively (Table 4), indicate trigonal planar coordination geometry with a slight distortion toward the trigonal pyramidal form. The pyridine rings of each bipyridine ligand are almost perpendicular to each other, and they lie at an angle of 111° in one ligand and 109° in the other. We conclude that it is the fact that the 3,3′-substituents are larger in **6c** than in **6b** that prevents **6c** from acting as a chelating ligand in **20**.

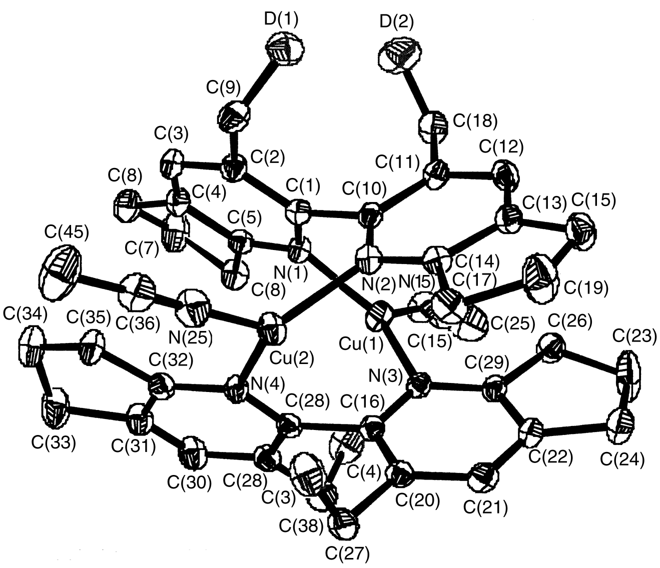


Figure 2. ORTEP representation of the dinuclear complex **20**.

Table 4. Selected bite angles and N–C–C–N dihedral angles in the complex $[Cu_2(\mathbf{6c})_2(CH_3CN)_2]^+$ (**20**).

N1Cu1N3	N1Cu1N1S	N2Cu2N4	N2Cu2N2S	N1C1C10N2	N3C19C28N4
112.46(14)	124.23(16)	111.35(13)	123.42(16)	−109.4(4)	−111.1(4)

Conclusion

We have developed a one-step, regioselective synthesis of annelated symmetric and asymmetric 3,3′-disubstituted 2,2′-bipyridines by Co^I-catalyzed [2+2+2] cycloadditions between 5-hexynenitrile and 1,3-diynes. This approach reverses the usual strategy for bipyridine synthesis, with the biaryl bond present prior to the construction of either of the two aryl rings. In the symmetric case, the total regioselectivity of the first cycloaddition is ensured electronically by the conjugation of the triple bonds, and for aminomethylated diynes that of the second set is ensured by the cobalt coordinating to the aminomethyl rather than to the hexynenitrile nitrogen. In the asymmetric case, the first cycloaddition takes place chemoselectively, which at least in the case of bis(trimethylsilyl)-1,3,5-hexatriyne (viewed as a 1,3-diyne) is again due to electronic effects. The Cu^I complex of **6b** constitutes the first reported complex of the form ML_2 with L a symmetric 3,3′-disubstituted 2,2′-bipyridine. The UV/Vis and NMR spectra of this complex reflect the 3-substituent-induced mutual torsion of the bipyridine rings in the *cis* conformation. The bipyridine **6c** forms the dinuclear complex $[Cu_2(\mathbf{6c})_2(CH_3CN)_2]^{2+}$ in the solid state.

Experimental Section

General: All commercial chemicals (ABCR, Aldrich, Fluka, Strem Chemicals) were of the best available grade and used without further purification. Bis(trimethylsilyl)-1,3,5-hexatriyne **2k** was prepared according to published procedures.[40] Irradiation was performed with a Philips PF808 300 W tungsten slide projector lamp placed approximately 5 cm from the center of the flask and operated at 225 W. NMR spectra (^{1}H, ^{13}C, DEPT, NOE, HMBC, and HMQC) were recorded either on Bruker DPX-250, AMX-300, or WM-500 instruments, with residual solvent peak as standard. Chemical shifts are reported in ppm on the δ scale. Mass spectral data were obtained on a Hewlett-Packard 59970-GCMS operating at 70 eV and on a VG-AUTOSPEC-M instrument with a FAB inlet system. UV/Vis spectra were measured by using a Hewlett-Packard HP8452A, and the results are given in λ (nm).

The numbering scheme of the ligands is given in Scheme 1 and 8.

1,6-Dimethoxy-2,4-hexadiyne 2d:[25b] A solution of diol **2c** (0.5 g, 4.54 mmol) in dry THF (4 mL) was slowly added to a suspension of NaH (0.41 g, 13.6 mmol) in dry THF (5 mL). Then the mixture was heated to reflux for 1 h. After cooling to RT, MeI (2.06 g, 14.5 mmol) was added, and the mixture was heated again under reflux for another 4 h. Once the mixture reached RT, H_2O (50 mL) was added to the mixture, and then it was extracted with ether (3 × 25 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude material was purified by column chromatography on silica by using hexane:EtOAc 8:2 as eluent, and this gave 0.395 g of **2d** (63 %) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 4.17 (s, 4H), 3.99 (s, 6H); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): δ = 75.1 (C), 70.2 (C), 59.9 (CH_2), 57.6 (CH_3).

1,6-Bis(triethylsilyloxy)-2,4-hexadiyne 2e: A solution of **2c** (0.2 g, 1.8 mmol), TESCl (0.8 mL, 4.7 mmol), and imidazole (0.79 g, 11.6 mmol) in dry DMF (4 mL) was stirred for 12 h at RT. Then H_2O (20 mL) was added to the mixture, and this was extracted with ether (2 × 20 mL). The organic layer was washed with water and brine (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was purified by column chromatography on silica by using hexane:EtOAc 9:1 as eluent giving 0.52 g of **2e** (84 %) as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 4.37 (s, 4H), 0.97 (t, ^3J = 7.7 Hz, 18H), 0.64 (q, ^3J = 7.7 Hz, 12H); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): δ = 76.4 (C), 69.1 (C), 51.7 (CH_2), 6.6 (CH_3), 4.4 (CH_2).

Dimethyl 2,4-hexadiyndioate 2f:[27b] A solution of methyl propionate (2 g, 23.8 mmol) in acetone (14 mL) was introduced into a two-necked flask provided with a cold finger. Then, the Hay catalyst, prepared by stirring at RT CuCl (0.235 g, 2.38 mmol) and TMEDA (tetramethylethylenediamine, 0.12 mL, 0.8 mmol) in acetone (5 mL) for 40 min, was added. After bubbling O_2 through the mixture for 2 h, the solvent was concentrated, and the resulting residue was dissolved in ether (20 mL) and washed with HCl (5 %, 2 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated giving crude **2f** (1.41 g, 71 %) as a clear oil that rapidly became dark. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 3.82 (s, 6H); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): δ = 152.1 (CO), 72.3 (C), 68.1 (C), 53.4 (CH_3).

1,6-Di(ethylsulfanyl)-2,4-hexadiyne 2g

Preparation of ethyl 2-propynyl sulfide:[35] Propargyl bromide (29.72 g, 18 mL, 250 mmol) was added to a cooled solution (0 °C) of NaOH (11 g, 275 mmol) and ethanethiol (17.05 g, 275 mmol) in a mixture of MeOH:H_2O 8:2 (100 mL), and the mixture was stirred for 30 min. Once it reached RT, the stirring was continued for another 30 min. After addition of H_20 to the mixture (500 mL), this was extracted with ether (6 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated at atmospheric pressure to give the propargylic sulfide as an unstable oil (24.9 g, quantitative yield) that was used without further purification.

Oxidative homocoupling of ethyl 2-propynyl sulfide: Anhydrous $Cu(OAc)_2$ (4.5 g, 25 mmol) was added to a solution of the above sulfide (0.5 g, 5 mmol) in pyridine (25 mL). After stirring at RT for 5 h, a saturated solution of $CuSO_4$ (50 mL) was added, and the resulting mixture was extracted with ether (3 × 10 mL). The organic layer was successively washed with a saturated solution of $CuSO_4$ (3 × 10mL), H_2O (2 × 10 mL), and brine (1 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated at reduced pressure. The crude residue obtained was purified by column chromatography on silica by using hexane:EtOAc 9.5:0.5 as eluent to give **2g** (0.45 g, 91 %) as an unstable oil. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 3.34 (s, 4H), 2.72 (q, ^3J = 7.4 Hz, 4H), 1.29 (t, ^3J = 7.4 Hz, 6H).

***N,N,N,N*-Tetramethyl-2,4-hexadiyn-1,6-diamine 2h**:[36] A solution of *N,N*-dimethyl-2-propyn-1-amine (1.29 mL, 12 mmol) in acetone (7 mL) was introduced into a two-necked flask provided with a cold finger. Then, the Hay catalyst prepared by stirring at RT CuCl (0.12 g, 1.2 mmol) and TMEDA (0.06 mL, 0.04 mmol) in acetone (2 mL) for 40 min was added. After bubbling O_2 through the mixture for 2 h, the solvent was concentrated, and the resulting residue was dissolved in ether (10 mL) and washed with HCl (5 %, 2 × 12 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give **2h** (0.76 g, 77 %) as yellow crystals. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 3.35 (s, 4H), 2.31 (s, 12H); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): δ = 73.5 (C), 69.6 (C), 48.3 (CH_2), 44.1 (CH_3).

1-(Triethylsilyloxy)-5-(trimethylsilyl)-2,4-pentadiyne 2j: A solution of alcohol **2i**[38b] (0.2 g, 1.3 mmol), TESCl (0.34 mL, 2 mmol), and imidazole (0.92 g, 13.5 mmol) in dry DMF (3 mL) was stirred at RT for 12 h. Then, H_2O (25 mL) was added to the mixture, and this was extracted with ether (2 × 10 mL). The organic layer was washed with water and brine (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was purified by column chromatography on silica by using hexane:EtOAc 9.5:0.5 as eluent to give 0.22 g of **2j** (60 %) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 4.36 (s, 2H), 0.97 (t, ^3J = 7.7 Hz, 9H), 0.63 (q, ^3J = 7.7 Hz, 6H), 0.19 (s, 9H); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): δ = 87.5 (C), 86.7 (C), 76.3 (C), 69.7 (C), 51.6 (CH_2), 6.5 (CH_3), 4.4 (CH_2), 0.5 (CH_3).

General procedure for the cobalt(I)-catalyzed [2+2+2] cycloaddition: A solution of **2** (1 equiv), **1** (3 equiv), and $[CpCo(CO)_2]$ (30 %) in toluene (10 mL) was irradiated for 1 h under Ar in a round-bottomed flask equipped with a reflux condenser. The reaction vessel was irradiated with a Philips PF808 300 W tungsten slide projector lamp placed approximately 5 cm from the center of the flask and operated at 225 W. The volatile components were removed under vacuum, and the residue was purified by chromatography on silica gel.

Cocyclization of 1 with diyne 2a: Compound 5-hexynenitrile **1** (0.3 g, 1.5 mmol), diyne **2a** (0.43 g, 4.6 mmol), and $[CpCo(CO)_2]$ (28.4 µL, 0.23 mmol, 15 %) in toluene (100 mL) were cocyclized under the conditions of the general procedure. Pyridine **3** (0.34 g, 77 % yield) was obtained as white crystals (from hexane). m.p. 60–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.53$ (s, 1H; ArH), 2.96 (t, $^3J = 7.5$ Hz, 2H; CH_2), 2.88 (t, $^3J = 7.5$ Hz, 2H; CH_2), 2.05 (quintet, $^3J = 7.5$ Hz, 2H; CH_2), 0.35 (s, 9H; CH_3), 0.23 (s, 9H; CH_3); ^{13}C NMR (75.44 MHz, $CDCl_3$, 25 °C): $\delta = 166.2$ (C), 145.0 (C), 137.5 (CH), 136.1 (C), 134.3 (C), 106.0 (C), 95.7 (C), 34.2 (CH_2), 30.7 (CH_2), 22.8 (CH_2), −0.5 (CH_3), −1.5 (CH_3); MS (70 eV, EI): m/z (%): 287 $[M]^+$ (22), 272 (100), 256 (6); HRMS (ESI): calcd for $C_{16}H_{25}NSi_2$ 287.15256; found: 287.15253.

Cocyclization of 1 with diyne 2b: Compound 5-hexynenitrile **1** (0.36 g, 3.84 mmol), diyne **2b** (0.1 g, 1.28 mmol), and $[CpCo(CO)_2]$ (47 µL, 0.038 mmol, 30 %) were cocyclized following the conditions of the general procedure. Two products were isolated after column chromatography on silica by using EtOAc:MeOH 9:1 as eluent: 2,2′-bipyridine **6b** (104 mg, 30 %, $R_f = 0.57$) and 2,3′-bipyridine **7b** (59 mg, 17 %, $R_f = 0.42$).

*2,2′-Bipyridine **6b***: colorless crystals (from ethyl acetate/hexane), m.p. 118–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.36$ (s, 2H; H(3), H(3′)), 2.96 (t, $^3J_{6,7} = 7.5$ Hz, 4H; H(6), H(6′)), 2.70 (t, $^3J_{8,7} = 7.5$ Hz, 4H; H(8), H(8′)), 2.14–2.06 (m, 4H; H(7), H(7′)), 2.04 (s, 6H; H(9), H(9′)); ^{13}C NMR, DEPT, HMQC, HMBC (125.76 MHz, $CDCl_3$, 25 °C): $\delta = 162.5$ (C(5)), 155.6 (C(1)), 136.1 (C(4)), 134.1 (CH, C(3)), 128.4 (C(2)), 36.3 (CH_2, C(6)), 30.4 (CH_2, C(8)), 23.3 (CH_2, C(7)), 18.3 (CH_3, C(9)); UV/Vis (CH_2Cl_2): λ_{max} (ε) = 232, 288 nm; MS (70 eV, EI): m/z (%): 264 $[M]^+$ (34), 249 (100); HRMS (ESI): calcd for $C_{18}H_{20}N_2$ 264.162649; found: 264.163216; elemental analysis calcd (%) for $C_{18}H_{20}N_2$: C 81.78, H 7.63, N 10.6; found: C 81.38, H 7.53, N 10.65.

*2,3′-Bipyridine **7b***: (EtOAc:MeOH 9:1); brown oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.38$ (s, 1H; ArH), 7.28 (s, 1H; ArH), 3.02–2.87 (m, 8H; 4 × CH_2), 2.25 (s, 3H; CH_3), 2.18–2.04 (m, 4H; 2 × CH_2), 2.04 (s, 3H; CH_3); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): $\delta = 164.3$ (C), 162.7 (C), 155.7 (C), 153.4 (C), 135.9 (C), 134.0 (CH), 133.9 (C), 133.1 (CH), 132.8 (C), 128.3 (C), 34.05 (CH_2), 33.8 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 23.2 (2 × CH_2), 22 (CH_3), 18.8 (CH_3); MS (70 eV): m/z (%): 264 $[M]^+$ (25), 249 (100); MS (70 eV, EI): m/z (%): 264 $[M]^+$ (25), 249 (100), 149 (17); 58 (37); HRMS (ESI): calcd for $C_{18}H_{20}N_2$ 264.162649; found: 264.163770.

Cocyclization of 1 with diyne 2c: Compound 5-hexynenitrile **1** (0.25 g, 2.27 mmol), diyne **2c** (0.1 g, 0.91 mmol), and $[CpCo(CO)_2]$ (33 µL, 0.27 mmol, 30 %) in THF (15 mL) were cocyclized following the conditions of the general procedure. Compound 2,2′-bipyridine **6c** (24 mg, 9 % yield) was obtained as white crystals (from ethyl acetate/hexane), m.p. 198–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.68$ (s, 2H; ArH), 6.19 (brs, 2H; OH), 4.36 (s, 4H; 2 × CH_2), 3.03 (t, $^3J = 7.44$ Hz, 4H; 2 × CH_2), 3.00 (t, $^3J = 7.44$ Hz, 4H; 2 × CH_2), 2.18 (quintet, $^3J = 7.44$ Hz, 4H; 2 × CH_2); ^{13}C NMR (75.44 MHz, $CDCl_3$, 25 °C): $\delta = 163.3$ (C), 155.4 (C), 137.6 (C), 136 (CH), 134.2 (C), 63.5 (CH_2), 33.7 (CH_2), 30.4 (CH_2), 23.2 (CH_2); MS (70 eV, EI): m/z (%): 296 $[M]^+$ (4), 278 (31), 249 (100), 150 (7); HRMS (ESI): calcd for $C_{18}H_{20}N_2O_2$ 296.152478; found: 296.153303; elemental analysis calcd (%) for $C_{18}H_{20}N_2O_2$: C 72.95, H 6.80, N 9.45; found: C 72.89, H 6.78, N 9.52.

Cocyclization of 1 with diyne 2d: Compound 5-hexynenitrile **1** (0.20 g, 2.17 mmol), diyne **2d** (0.1 g, 0.072 mmol), and $[CpCo(CO)_2]$ (27 µL, 0.022 mmol, 30 %) in toluene (10 mL) were cocyclized following the conditions of the general procedure. Two products were isolated after column chromatography on silica by using EtOAc:MeOH 9:1 as eluent: 2,2′-bipyridine **6d** (107 mg, 46 %, $R_f = 0.56$) and 2,3′-bipyridine **7d** (39 mg, 17 %, $R_f = 0.37$).

*2,2′-Bipyridine **6d***: colorless crystals (from ethyl acetate/hexane), m.p. 130–132 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.71$ (s, 2H; H(3), H(3′)), 4.30 (s, 4H; H(9), H(9′)), 3.26 (s, 6H; H(10), H(10′)), 3.01 (t, $^3J_{8,7} = 7.5$ Hz, 4H; H(8), H(8′)), 2.98 (t, $^3J_{6,7} = 7.5$ Hz, 4H; H(6), H(6′)), 2.15 (quintet, $^3J_{8,7}$ and $^3J_{6,7} = 7.5$ Hz, 4H; H(7), H(7′)); ^{13}C NMR, DEPT, HMQC, HMBC (125.76 MHz, $CDCl_3$, 25 °C): $\delta = 164.0$ (C(5)), 154.1 (C(1)), 136.6 (C(4)), 132.1 (CH, C(3)), 130.0 (C(2)), 71.1 (CH_2, C(9)), 58.3 (CH_3, C(10)), 34.0 (CH_2, C(6)), 30.6 (CH_2, C(8)), 23.3 (CH_2, C(7)); MS (70 eV, EI): m/z (%): 324 $[M]^+$ (1), 293 (43), 261 (41), 149 (100); HRMS (ESI): calcd for $C_{20}H_{24}N_2O_2$ 324.183778; found: 324.183531.

*2,3′-Bipyridine **7d***: brown oil; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.66$ (s, 1H; ArH), 7.35 (s, 1H; ArH), 4.28 (s, 2H; CH_2), 4.15 (s, 2H; CH_2), 3.26 (s, 3H; CH_3), 3.23 (s, 3H; CH_3), 3.09–2.89 (m, 8H; 4 × CH_2), 2.21–2.10 (m, 4H; 2 × CH_2); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): $\delta = 165.3$ (C), 164.4 (C), 154.3 (C), 152.7 (C), 136.3 (C), 135.9 (C), 133.2 (CH), 132.2 (CH), 129.9 (2 × C), 73.4 (CH_2), 71.3 (CH_2), 58.3 (2 × CH_3), 34.2 (CH_2), 34.0 (CH_2), 30.5 (2 × CH_2), 23.2 (CH_2), 23.1 (CH_2); MS (70 eV, EI): m/z (%): 324 $[M]^+$, (14), 309 (41), 279 (69), 249 (100); HRMS (ESI): calcd for $C_{20}H_{24}N_2O_2$ 324.183778; found: 324.183113.

Cocyclization of 1 with diyne 2e: Compound 5-hexynenitrile **1** (0.165 g, 1.77 mmol), diyne **2e** (0.2 g, 0.059 mmol), and $[CpCo(CO)_2]$ (22 µL, 0.017 mmol, 30 %) in toluene (10 mL) were cocyclized following the conditions of the general procedure. Two products were isolated after column chromatography on silica by using hexane:EtOAc 1:1 as eluent: 2,2′-bipyridine **6e** (112 mg, 36 %, $R_f = 0.56$) and 2,3′-bipyridine **7e** (29 mg, 10 %, $R_f = 0.40$).

*2,2′-Bipyridine **6e***: white crystals (from hexane), m.p. 40–42 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.76$ (s, 2H; H(3), H(3′)), 4.54 (s, 4H; H(9), H(9′)), 2.95 (t, $^3J_{6,7}$ and $^3J_{8,7} = 7.5$ Hz, 8H; H(6), H(8), H(6′), H(8′)), 2.10 (quintet, $^3J_{6,7}$ and $^3J_{8,7} = 7.5$ Hz, 4H; H(7), H(7′)), 0.87 (t, $^3J_{10,11} = 7.8$ Hz, 18H; H(11), H(11′)), 0.51 (q, $^3J_{11,10} = 7.8$ Hz, 12H; H(10), H(10′)); ^{13}C NMR, DEPT, HMQC, HMBC (125.76 MHz, $CDCl_3$, 25 °C): $\delta = 163.0$ (C(5)), 153.0 (C(1)), 136.3 (C(4)), 132.9 (C(2)), 131.2 (CH, C(3)), 61.4 (CH_2, C(9)), 33.8 (CH_2, C(6)), 30.7 (CH_2, C(8)), 23.3 (CH_2, C(7)), 6.5 (CH_3, C(11)), 4.3 (CH_2, C(10)); UV/Vis (CH_2Cl_2): λ_{max} (ε) = 244, 290 nm; MS (70 eV, EI): m/z (%): 524 $[M]^+$ (2), 392 (65), 261 (100); HRMS (ESI): calcd for $C_{30}H_{48}N_2O_2Si_2$ 524.325436; found: 524.324987.

*2,3′-Bipyridine **7e***: brown oil; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.68$ (s, 1H; ArH), 7.36 (s, 1H; ArH), 4.80–4.50 (m, 2H; CH_2), 4.39 (s, 2H; CH_2), 3.07–2.88 (m, 8H; 4 × CH_2), 2.17–2.10 (m, 4H; 2 × CH_2), 0.90 (t, $^3J = 7.8$ Hz, 9H; 3 × CH_3), 0.76 (t, $^3J = 7.8$ Hz, 9H; 3 × CH_3), 0.54 (q, $^3J =$ Hz, 6H; 3 × CH_2), 0.37 (q, $^3J = 7.8$ Hz, 6H; 3 × CH_2); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): $\delta = 164.5$ (C), 163.4 (C), 155.2 (C), 154.3 (C), 136.0 (C), 135.5 (C), 133.6 (CH), 132.7 (C), 132.4 (C), 131.5 (CH), 65.3 (CH_2), 62.0 (CH_2), 34.0 (2 × CH_2), 30.7 (CH_2), 30.4 (CH_2), 23.4 (CH_2), 23.3 (CH_2), 6.7 (CH_3), 6.6 (CH_3), 4.3 (CH_2), 4.2 (CH_2); MS (70 eV, EI): m/z (%): 524 $[M]^+$ (13), 495 (21), 393 (61), 261 (100); HRMS (ESI): calcd for $C_{30}H_{48}N_2O_2Si_2$ 524.325436; found: 524.326588.

Cocyclization of 1 with diyne 2f: Compound 5-hexynenitrile **1** (0.17 g, 1.80 mmol), diyne **2f** (0.1 g, 0.06 mmol), and $[CpCo(CO)_2]$ (22 µL, 0.018 mmol, 30 %) in toluene (10 mL) were cocyclized following the conditions of the general procedure. Two products were isolated after column chromatography on silica by using EtOAc:MeOH 9:1 as eluent: 2,2′-bipyridine **6f** (22 mg, 10 %, $R_f = 0.26$) and 2,3′-bipyridine **7f** (16 mg, 7 %, $R_f = 0.13$).

*2,2′-Bipyridine **6f***: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 8.15$ (s, 2H; H(3), H(3′)), 3.67 (s, 6H; H(10), H(10′)), 3.00 (m, 8H; H(6), H(8), H(6′), H(8′)), 2.10 (m, 4H; H(7), H(7′)).

*2,3′-Bipyridine **7f***: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 8.14$ (s, 1H; ArH), 7.48 (s, 1H; ArH), 3.78 (s, 3H; CH_3), 3.67 (s, 3H; CH_3), 3.00 (m, 8H; 4 × CH_2), 2.10 (m, 4H; 2 × CH_2).

Cocyclization of 1 with diyne 2h: Compound 5-hexynenitrile **1** (0.17 g, 1.82 mmol), diyne **2h** (0.1 g, 6.09 mmol), and $[CpCo(CO)_2]$ (22 µL, 0.018 mmol, 30 %) in toluene (10 mL) were cocyclized under the conditions of the general procedure. Purification by column chromatography on silica by using EtOAc:triethylamine 9.9:0.1 as eluent ($R_f = 0.11$) gave 2,2′-bipyridine **6h** (104 mg, 49 % yield) as white crystals (from hexane). m.p. 55–57 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.70$ (s, 2H; H(3), H(3′)), 3.17 (s, 4H; H(9), H(9′)), 2.96 (t, $^3J_{6,7} = 7.6$ Hz, 4H; H(6), H(6′)), 2.93 (t, $^3J_{8,7} = 7.6$ Hz, 4H; H(8), H(8′)), 2.15 (m, 4H; H(7), H(7′)), 2.08 (s, 6H; H(10), H(10′)); ^{13}C NMR, DEPT, HMQC, HMBC (125.76 MHz, $CDCl_3$, 25 °C): $\delta = 163.2$ (C(5)), 155.3 (C(1)), 136.1 (C(4)), 132.9 (CH, C(3)), 130.6 (C(2)), 59.9 (CH_2, C(9)), 45.6 (CH_3, C(10)), 33.9 (CH_2, C(6)), 30.5 (CH_2, C(8)), 23.3 (CH_2, C(7)); MS (FAB, *m*-nitrobenzyl alcohol): m/z (%): 351 $[M+1]^+$ (100), 305 (34), 290 (13); elemental analysis calcd (%) for $C_{22}H_{30}N_4$: C 75.39, H 8.63, N 15.98; found: C 75.30, H 8.71, N 15.61.

Cocyclization of 1 with diyne 2j: Compound 5-hexynenitrile **1** (0.104 g, 1.12 mmol), diyne **2j** (0.1 g, 3.76 mmol), and $[CpCo(CO)_2]$ (14 µL, 0.11 mmol, 30 %) in toluene (10 mL) were cocyclized under the conditions of the general procedure. The crude residue was purified by chromatography on silica by using hexane:EtOAc 8:2 as eluent and gave two bands containing pyridine **14** (36 mg, 27 %, $R_f = 0.68$) and a mixture of silylated products, respectively. This mixture was dissolved in MeOH and stirred with silica gel for 48 h. After filtration further column chromatography on silica by using a gradient from hexane:EtOAc 8:2 to hexane:EtOAc 1:1 as eluent was performed and gave three products: 2,2′-bipyridine **15j** (3 mg, 2%), 2,2′-bipyridine **15j′** (22 mg, 17%), and 2,3′-bipyridine **16j″** (22 mg, 15%).

Pyridine 14: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.66$ (s, 1H; ArH), 4.84 (s, 2H; CH_2), 2.97 (t, $^3J = 7.6$ Hz, 2H; CH_2), 2.93 (t, $^3J = 7.6$ Hz, 2H; CH_2), 2.10 (quintet, $^3J = 7.6$ Hz, 2H; CH_2), 0.98 (t, $^3J = 7.8$ Hz, 9H; CH_3), 0.66 (q, $^3J = 7.8$ Hz, 6H; CH_2), 0.25 (s, 9H; CH_3); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): $\delta = 164.4$ (C), 137.5 (C), 137.3 (C), 130.1 (CH + C), 101.9 (C), 98.7 (C), 61.8 (CH_2), 33.8 (CH_2), 30.8 (CH_2), 23.1 (CH_2), 6.65 (CH_3), 4.39 (CH_3), −0.31 (CH_3).

2,2′-Bipyridine 15j: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.77$ (s, 2H; ArH), 4.59 (s, 2H; CH_2), 2.97 (m, 8H; 4 × CH_2), 2.17–2.09 (m, 4H; 2 × CH_2), 0.90 (t, $^3J = 7.7$ Hz, 9H; CH_3), 0.56 (q, $^3J = 7.7$ Hz, 6H; CH_2); −0.01 (s, 9H; 3 × CH_3); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): $\delta = 164.6$ (C), 162.3 (C), 161.5 (C), 155.3 (C), 139.0 (CH), 136.2 (C), 134.8 (C), 132.8 (C), 131.0 (CH + C), 61.7 (CH_2), 34.2 (CH_2), 33.6 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 23.3 (CH_2), 23.0 (CH_2), 6.7 (CH_3), 4.3 (CH_2), 0.0 (CH_3).

2,2′-Bipyridine 15j′: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.87$ (s, 1H; ArH), 7.58 (s, 1H; ArH), 6.29 (brs, 1H; OH), 4.38 (s, 2H; H(10)), 3.00 (m, 8H; 4 × CH_2), 2.16 (m, 4H; 2 × CH_2), 0.05 (s, 9H; 3 × CH_3); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): $\delta = 163.7$ (C), 163.6 (C), 161.5 (C), 157.6 (C), 140.2 (CH), 138.8 (C), 135.7 (C), 134.7 (CH), 133.1 (C), 132.6 (C), 63.6 (CH_2), 33.9 (CH_2), 33.4 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 23.3 (CH_2), 23.1 (CH_2), 0.7 (CH_3); MS (70 eV, EI): m/z (%): 338 $[M]^+$ (2), 323 $[M - \text{Me}]^+$ (16), 265 $[M - \text{TMS}]^+$ (100).

2,3′-Bipyridine 16j″: brown oil; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta =$ 8.43 (s, 1H; ArH), 7.72 (s, 1H; ArH), 4.61 (s, 2H; H(10)), 3.09–2.95 (m, 8H; 4 × CH_2), 2.16 (quintet, $^3J_{7,8}$ and $^3J_{8,9} = 7.5$ Hz, 4H; H(8), H(8′)), 0.90 (t, $^3J_{10,11} = 7.7$ Hz, 9H; H(11)), 0.60 (q, $^3J_{11,10} = 7.7$ Hz, 6H; H(10)); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): $\delta = 165.2$ (C), 164.6 (C), 153.2 (C), 147.5 (CH), 136.7 (C), 136.2 (C), 133.5 (C), 132.7 (CH), 132.5 (CH), 131.7 (C), 62.2 (CH_2), 34.1 (CH_2), 34.0 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 23.3 (2 × CH_2), 6.7 (CH_3), 4.4 (CH_2).

Cocyclization of 1 with diyne 2k: Compound 5-hexynenitrile **1** (0.136 g, 1.46 mmol), diyne **2k** (0.1 g, 0.46 mmol), and $[CpCo(CO)_2]$ (17 µL, 0.137 mmol, 30%) in toluene (10 mL) were cocyclized under the conditions of the general procedure for 2 h. Two products were isolated after column chromatography on silica by using hexane:EtOAc 9:1 as eluent.

2,3′-Bipyridine 16k: $R_f = 0.53$ (hexane:EtOAc 1:1); brown oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 7.69$ (s, 1H; H(3)), 7.66 (s, 1H; H(11)), 3.00–2.91 (m, 8H; H(6), H(8), H(14), H(16)), 2.14–2.08 (m, 4H; H(7), H(15)), −0.02 (s, 9H; H(20)), −0.08 (s, 9H; H(19)); ^{13}C NMR, DEPT, HMQC, HMBC (125.76 MHz, $CDCl_3$, 25 °C): $\delta = 165.3$ (C(5)), 165.2 (C(13)), 160.4 (C(1)), 140.4 (C(9)) 140.2 (C(10)), 138.2 (CH, C(3)), 136.1 (C, C(4) or C(12)), 134.9 (C, C(4) or C(12)), 132.4 (CH, C(11)), 130.5 (C, C(2)), 103.6 (C, C(17)), 97.8 (C, C(18)), 34.2 (CH_2, C(6)), 34.0 (CH_2, C(14)), 30.7 (CH_2, C(8)), 30.5 (CH_2, C(16)), 23.1 (2 × CH_2, C(7), C(15)), 0.0 (CH_3, C(20)), −0.6 (CH_3, C(19)); MS (70 eV, EI): m/z (%): 404 $[M]^+$ (97), 389 (61), 331 (100); HRMS (ESI): calcd for $C_{24}H_{32}N_2Si_2$ 404.210406; found: 404.209736.

2,2′-Bipyridine 15k: $R_f = 0.46$ (hexane:EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.74$ (s, 1H; H(3)), 7.61 (s, 1H; H(11)), 3.02 (t, $^3J_{6,7}$ and $^3J_{14,15} = 7.5$ Hz, 4H; H(6) and H(14)), 2.95 (t, $^3J_{7,8}$ and $^3J_{15,16} = 7.5$ Hz, 4H; H(8) and H(16)), 2.20–2.06 (m, 4H; H(7) and H(15)), 0.0 (s, 9H; H(20)), −0.01 (s, 9H; H(19)); ^{13}C NMR, DEPT, HMQC, HMBC (125.76 MHz, $CDCl_3$, 25 °C): $\delta = 164.7$ (C(5)), 164.1 (C(13)), 161.2 (C(9)), 160.9 (C(1)), 138.4 (CH, C(3)), 135.6 (C(4) or C(12)), 135.3 (CH, C(11)), 135.1 (C(4) or C(12)), 130.9 (C(2)), 128.8 (C(10)), 120.9 (C(17)), 99.5 (C(18)), 34.2 (CH_2, C(6)), 34.1 (CH_2, C(14)), 30.6 (CH_2, C(8)), 30.3 (CH_2, C(16)), 23.2 (CH_2, C(7)), 23.1 (CH_2, C(23)), −0.1 (CH_3, C(19) or C(20)), −0.6 (CH_3, C(19) or C(20)); MS (70 eV, EI): m/z (%): 404 $[M]^+$ (76), 389 (100); HRMS (ESI): calcd for $C_{24}H_{32}N_2Si_2$ 404.210406; found: 404.209740.

Pyridine 17

6,7-Dihydro-2-ethynyl-3-(trimethylsilyl)-5H-cyclopenta[b]pyridine 5: K_2CO_3 (66 mg, 0.5 mmol) was added to a solution of **3** (0.2 g. 0.7 mmol) in MeOH (5 mL), and the mixture was stirred at RT overnight. After removal of the solvent, the resulting residue was dissolved in CH_2Cl_2 (10 mL), washed with NaOH (2%, 2 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude material **5** was used in the next step without further purification. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.56$ (s, 1H; ArH), 3.19 (s, 1H; ≡CH), 2.98 (t, $^3J = 7.6$ Hz, 2H; CH_2), 2.90 (t, $^3J = 7.6$ Hz, 2H; CH_2), 2.07 (quintet, $^3J = 7.6$ Hz, 2H; CH_2), 0.35 (s, 9H; CH_3); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): $\delta = 166.5$ (C), 144.3 (C), 137.5 (CH), 136.6 (C), 134.5 (C), 85.0 (C), 78.4 (C), 34.1 (CH_2), 30.7 (CH_2), 22.7 (CH_2), −0.5 (CH_3), −1.5 (CH_3).

Intermediate alcohol: A solution of BuLi in hexane (0.44 mL, 1.6 M) was slowly added to a solution of crude **5** in dry THF (2 mL) and was cooled at −78 °C, which turned the solution dark red colored. The mixture was stirred for 1 h and cannulated over a suspension of paraformaldehyde (75 mg, 0.04 mmol) in dry THF (1 mL) at −78 °C. The resulting solution was allowed to reach RT and stirred for 3 h. The reaction was quenched with H_2O (50 mL) and extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude alcohol obtained was used without further purification.

Silyl ether 17: A solution of the crude alcohol, TESCl (0.175 mL, 1.04 mmol), and imidazole (0.475 g, 6.98 mmol) in dry DMF (2 mL) was stirred at RT for 12 h. Then, H_2O (20 mL) was added to the mixture, and this was extracted with ether (2 × 15 mL). The organic layer was washed with water and brine (4 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was purified by column chromatography on silica by using a gradient from hexane to hexane:EtOAc 9:1 as eluent and gave 0.202 g of **17** (80%, overall yield) as a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.56$ (s, 1H; ArH), 4.55 (s, 2H; CH_2) 2.98 (t, $^3J = 7.7$ Hz, 2H; CH_2), 2.94 (t, $^3J = 7.7$ Hz, 2H; CH_2), 2.08 (quintet, $^3J =$ 7.7 Hz, 2H; CH_2), 0.98 (t, $^3J = 7.8$ Hz, 9H; CH_3), 0.65 (q, $^3J = 7.7$ Hz, 6H; CH_2), 0.37 (s, 9H; CH_3); ^{13}C NMR (62.83 MHz, $CDCl_3$, 25 °C): $\delta = 165.7$ (C), 144.0 (C), 136.5 (CH), 134.8 (C), 133.2 (C), 87.8 (C), 84.9 (C), 50.8 (CH_2), 33.2 (CH_2), 29.7 (CH_2), 21.8 (CH_2), 5.6 (CH_3), 3.4 (CH_2), −2.3 (CH_3).

Cocyclization of 1 with 17: Compound 5-hexynenitrile **1** (0.042 g, 0.4 mmol), **17** (0.1 g, 0.3 mmol), and $[CpCo(CO)_2]$ (11 µL, 0.09 mmol, 30%) in toluene (10 mL) were cocyclized under the conditions of the general procedure for 3 h. The crude residue was purified by chromatography on silica by using hexane:EtOAc 1:1 as eluent and gave 2,2′-bipyridine **15j** (25 mg, 18%) and recovered alkynenitrile **1** (40%).

Complex 18, $[Cu(6b)_2](PF_6)$: $[Cu(CH_3CN)_4](PF_6)$ (35 mg, 0.095 mmol) was added to a stirred solution of 2,2′-bipyridine **6b** (50 mg, 0.19 mmol) in dry, degassed CH_2Cl_2 (4 mL), and the resulting yellow-orange solution was kept at room temperature under Ar overnight. After removal of solvent under reduced pressure, the solid residue was recrystallized from CH_2Cl_2/MeOH to yield 62 mg of **18** (90%): orange powder, m.p. > 210 °C (dec); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.58$ (s, 1H; H(3)), 3.00 (t, $^3J_{6,7} = 7.2$ Hz, 2H; H(6)), 2.80–2.49 (m, 2H; H(7)), 2.32 (s, 3H; H(9)), 2.04 (t, $^3J_{8,7} = 7.2$ Hz, 2H; H(8)); ^{13}C NMR (75.44 MHz, $CDCl_3$, 25 °C): $\delta = 163$ (C), 152.4 (C), 138.4 (C), 135.5 (CH), 130.4 (C), 33.7 (CH_2), 30.6 (CH_2), 22.9 (CH_2), 19.2 (CH_3); UV/Vis (CH_2Cl_2): λ_{max} $\varepsilon = 248$, 304, 392 nm (sh); MS (FAB, *m*-NBA): m/z (%): 591, $[M - PF_6]^+$ (100); HRMS: calcd for $C_{36}H_{40}N_4Cu$ ($[M - PF_6]^+$) 591.254897; found: 591.255543; elemental analysis calcd (%) for $C_{36}H_{40}N_4F_6PCu$: C 58.65, H 5.47, N 7.60; found: C 58.38, H 5.56, N 7.59.

Complex 20, $[Cu_2(6c)_2(CH_3CN)_2](PF_6)_2$: $[Cu(CH_3CN)_4](PF_6)$ (94 mg, 0.253 mmol) was added to a stirred solution of 2,2′-bipyridine **6c** (150 mg, 0.506 mmol) in dry, degassed CH_2Cl_2 (5 mL), and the resulting yellowish solution was kept at room temperature under Ar overnight. After removal of the solvent under reduced pressure, the solid residue was recrystallized from CH_2Cl_2 to yield 197 mg of complex **20** (90%): pale yellow powder, m.p. 163–165 °C; ^{1}H NMR (250 MHz, CD_3COCD_3, 25 °C): $\delta = 7.89$ (s, 1H; H(3)), 4.41 (s, 2H; H(9)), 2.94 (t, $^3J_{6,7} = 7.4$ Hz, 2H; H(6)), 2.67 (brs, 2H; H(8)), 2.40 (brs, 2H; H(7)); UV/Vis (CH_2Cl_2): λ_{max} $\varepsilon = 230$, 300, 430 nm (b); UV/Vis (CH_3COCH_3): λ_{max} $\varepsilon = 210$, 328, 410 nm (sh); MS (FAB, *m*-NBA): m/z (%): 655, $[M - PF_6]^+$ (21), 341 (44), 281 (78), 221 (100); HRMS calcd for $C_{36}H_{40}N_4O_4Cu$ ($[M - PF_6]^+$ 655.234555; found: 655.231694; HRMS x-ray sample; found: 655.233298 (cluster at 717 corresponding to $Cu_2(\mathbf{6c})_2$).

X-ray crystallography: Crystal data and details on the data collection and refinement are summarized in Table 2. X-ray data for compounds **18** and **20** were collected by using a Bruker SMART CCD area detector single-crystal diffractometer with graphite monochromatized $Mo_{K\alpha}$ radiation ($\lambda =$ 0.71073 Å) by the phi-omega scan method operating at room temperature. A total of 1271 frames of intensity data were collected for each compound.

Absorption corrections were applied by using the SADABS program.[49] The structures were solved by direct methods by using the Bruker SHELXTL-PC[50] software and refined by full-matrix least-squares methods on F^2. Hydrogen atoms were included in calculated positions and refined in the riding mode by using SHELXTL default parameters. All non-hydrogen atoms were refined with anisotropic displacement parameters. For **20**, the F atoms of the PF_6^- anions were refined in two different positions as a result of the disorder.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-161160 ($[Cu(\mathbf{6b})_2](PF_6)$) and CCDC-161161 ($[Cu_2(\mathbf{6c})_2(CH_3CN)_2](PF_6)_2$. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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