

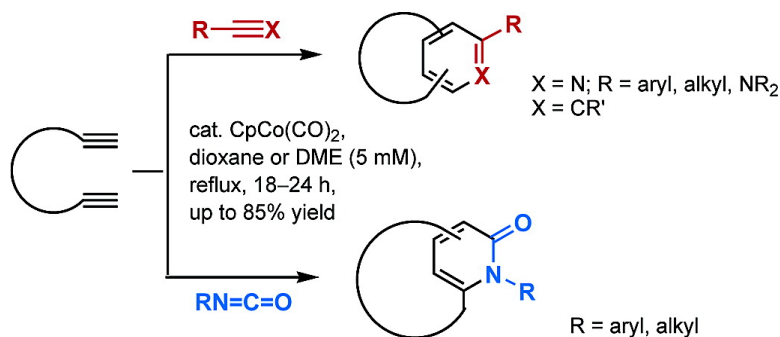
Article

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Synthesis of Macrocycles via Cobalt-Mediated [2 + 2 + 2] Cycloadditions

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Abstract: We investigated the formation of macrocycles from α,ω -diynes in cobalt-mediated co-cyclotrimerization reactions. Long-chain α,ω -diynes underwent metal-mediated [2 + 2 + 2] cycloadditions with nitriles, cyanamides, or isocyanates in the presence of $\text{CpCo}(\text{CO})_2$ (Cp = cyclopentadienide) to yield pyridine-containing macrocycles, i.e., *meta*- and *para*-pyridinophanes, such as **5m/5p**, **35m/35p**, and **41m/41p**. The regioselectivity of these reactions was affected by the length and type of linker unit between the alkyne groups, as well as by certain stereoelectronic factors. An analogous α,ω -cyano-alkyne, **28**, combined with an alkyne to yield two isomeric *meta*-pyridinophanes, such as **5m** and **29m**, and an ortho cycloadduct (benzannulation product), such as **29o**. We developed a reaction protocol for these cobalt-based [2 + 2 + 2] cycloadditions that involves markedly improved conditions such that this process offers a convenient, flexible synthetic approach to macrocyclic pyridine-containing compounds. For example, diyne **6** reacted with *p*-tolunitrile in 1,4-dioxane to give **7p** and **7m** (7:1 ratio) in 87% yield at a moderate temperature of ca. 100 °C in 24 h without photoirradiation or syringe-pump addition. Isocyanates were also effective reactants, as exemplified by the formation of **44p** almost exclusively (**44p:44m** > 50:1) in 64% yield from diyne **8** and 2-phenylethylisocyanate. By using this improved protocol we were able to co-cyclotrimerize long-chain α,ω -diynes with alkynes in certain cases to demonstrate a successful macrocyclic variant of the Vollhardt reaction. For instance, diyne **6** reacted with dipropylacetylene to give paracyclophane **57p** and benzannulene **57o** (2:1 ratio) in 29% yield.

Introduction

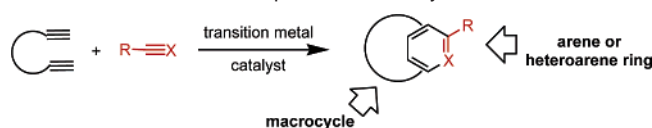
Macrocyclic compounds are important synthetic targets due to their broad applications in host–guest and supramolecular chemistry.¹ Biologically active macrocycles are also of high interest on account of their therapeutic applications, as exemplified by macrolide antibiotics,² macrocyclic protease inhibitors,³ and Taxol analogues.⁴ To achieve effective macrocyclizations it is often necessary to employ special reaction conditions, such as high dilution, template control, and/or conformational control.⁵ Since the synthesis of large rings can be problematic, most approaches involve the formation of a single ring, often

via a new carbon–carbon or carbon–heteroatom bond, with the desired functionalities already intact.^{5,6} A more challenging process is the simultaneous generation of a large ring and a smaller ring to provide considerable molecular complexity in one step.

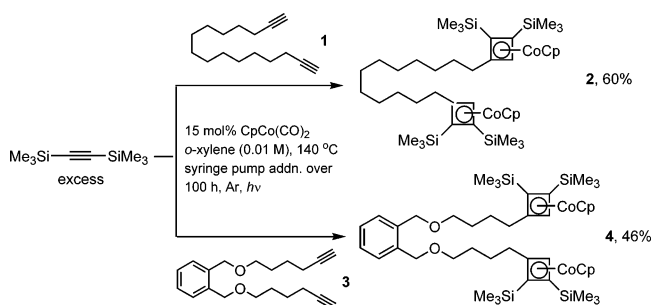
Transition-metal-based reactions are appealing for macrocyclization because the metal center can preorganize the reactive groups and lower the activation free energy of the entropically disfavored end-to-end cyclization of long-chain α,ω -bifunctionalized substrates. In addition, numerous transition-metal-mediated carbocyclizations for forming small- and medium-size rings are available.⁷ Macrocyclizations have been effected with impressively high yields for ruthenium- and molybdenum-catalyzed ring-closing metathesis (RCM) reactions of bis-alkenes and bis-alkynes.^{8,9} Relative to the mode of assembly of interest to us, some cyclizations that simultaneously generate a macrocycle and another small ring (e.g., arene or heterocycle) have

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Scheme 1. General Concept of the Macrocyclization Method

been reported, such as for the intramolecular addition of rhodium carbenes,¹⁰ the palladium-catalyzed coupling of enynes with alkynes,¹¹ and the cycloaddition of Fischer chromium carbenes with alkynes.¹² Macrocyclizations via the Heck reaction are also noteworthy.¹³ Although these various methods deliver macrocycles in a single step, with a significant increase in molecular complexity, they all are *unimolecular* in nature, which inherently limits the available product diversity. Additionally, this intramolecularity enhances the degree of success. We wondered: Could a *bimolecular* macrocyclization process¹⁴ that is conducive to a wider range of product diversity also be viable? For this purpose we envisioned the use of transition-metal-mediated [2 + 2 + 2] cycloadditions of long-chain α,ω -diynes and monoalkynes (Scheme 1), such as in the well-known “Vollhardt reaction”.^{15,16} However, it is important to keep in mind that such a bimolecular reaction poses a significant barrier to the efficient formation of macrocycles in that the high-dilution conditions

Scheme 2. Cobaltacyclobutadiene Complexes from α,ω -Diynes and BTMSA

(e.g., 0.005 M) required to optimize the macrocyclization relative to oligomerization can also serve to impede the necessary bimolecular process.¹⁷ To achieve success, these competing factors would have to be adequately balanced.

We describe herein our studies on the cobalt-catalyzed [2 + 2 + 2] cycloaddition of α,ω -diynes with a third reactive group, including nitriles, cyanamides, isocyanates, and alkynes. The scope and limitations of these reactions, in terms of substrates, conditions, regiochemistry, and mechanism, have been explored. In several cases this chemistry has provided effective syntheses of macrocycles containing pyridine, 2-aminopyridine, or 2-oxopyridine units, as *meta*- and *para*-pyridinophanes, in isolated yields greater than 50%. Additionally, we were able to co-cyclotrimerize alkynes in an *intermolecular*, macrocyclic variant of the “Vollhardt reaction”.

Results and Discussion

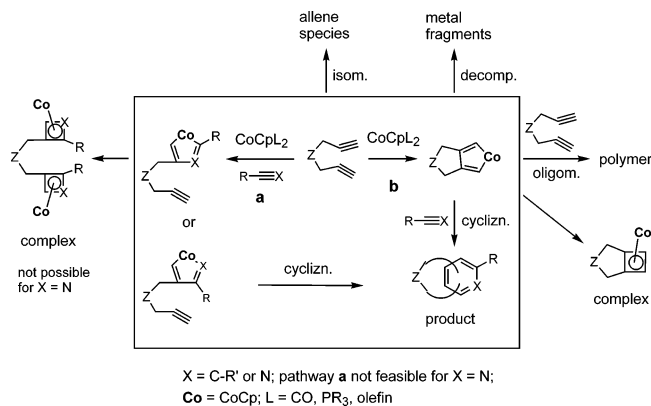
Preliminary Studies. We initially investigated the synthesis of macrocycles by co-cyclotrimerization of α,ω -diynes and an external alkyne by virtually no success. For instance, in the reactions of bis-alkynes **1** or **3** with bis(trimethylsilyl)acetylene (BTMSA),^{15a–c} which does not suffer self-trimerization, the hoped-for benzannulene or cyclophane products were not formed at all. Instead, we isolated the corresponding bis- η^4 -cyclobutadiene–cobalt complexes **2** or **4** along with unreacted diynes (Scheme 2; Cp = cyclopentadienide). Use of a stoichiometric amount of BTMSA (relative to the diyne) rather than a large excess resulted only in intractable, presumably polymeric material. In this regard, cyclobutadiene–cobalt complexes have already been identified in reactions of BTMSA with 1,*n*-diynes ($n = 6, 7$)¹⁵ and long-chain bis-alkynes.¹⁸ It is noteworthy that significant amounts of macrocyclic [2 + 2 + 2] adducts were not produced in the study by Brisbois et al.¹⁸ Reported examples of macrocycle formation via metal-mediated alkyne cyclotrimerization are uncommon, and the successful cases have been intramolecular reactions in which all three alkyne groups are tethered to the same molecular backbone.¹⁶

One can appreciate these negative results in the synthesis of macrocycles by examining the mechanism of the cobalt-mediated alkyne cyclotrimerization (Scheme 3, X = CR').¹⁹ The formation of arene adducts could be achieved via two main pathways, **a** and **b**, depending on which alkyne moieties undergo

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Scheme 3. Generalized Mechanism for “CpCo”-Mediated Cyclotrimerization of α,ω -Diynes with Alkynes ($X = CR'$) or Nitriles ($X = N$)



oxidative addition to generate the cobaltacyclopentadiene intermediates. Incorporation of the alkyne via a cycloaddition process,^{19b} with subsequent decomplexation, generates the arene. Unfortunately, there are several adverse processes, including oligomerization, polymerization, isomerization, decomposition, self-trimerization, and cyclobutadienecobalt complex formation, which militate against the desired outcome. The isolation of bis- η^4 -cyclobutadiene-cobalt complexes in our experiments indicates that when insertion of another alkyne molecule is slow or less favored, a formal [2 + 2] cycloaddition occurs preferentially (via pathway a). Consequently, the catalytically active cobalt species would be sequestered as inert η^4 -cyclobutadiene-cobalt complexes.^{15,18,20} To overcome this problem, we sought a different triply bonded species, one with $X \neq CR'$, which is unlikely to coordinate with a reactive Co(I) species. A nitrile reactant ($X = N$) seemed like a promising candidate²¹ as it is suitably reactive and can only insert into a Co(III) intermediate. In this way, we would obviate pathway a to generate macrocyclic pyridine derivatives via pathway b.²²

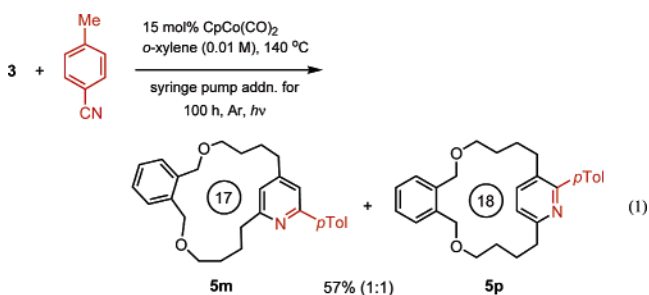
Cyclotrimerization with Nitriles.²³ We were gratified to find that reaction of bis-alkyne **3** with *p*-tolunitrile (1 mol equiv) provided a 57% yield of two pyridine-containing macrocycles, **5m** and **5p**, in a 1:1 ratio (eq 1).²⁴ Pyridinophanes **5m** and **5p** differ in their substitution pattern for the pyridine units, i.e., 2,4,6- (*meta*-) and 2,3,6- (*para*-) trisubstituted pyridines,

Table 1. Pyridinophanes from α,ω -Diynes and *p*-Tolunitrile

entry ^b	α,ω -diyne substrate	products	% yield (<i>meta</i> : <i>para</i>) ^c
1	n = 2 (6)	7m, 7p	61 (1:5)
2	n = 3 (3)	5m, 5p	57 (1:1)
3	8	9m, 9p	55 (1:5)
4	10	11m, 11p	34 (1:7)
5	1	12m, 12p	42 (1:1)
6	13	14m, 14p	49 (3:4)
7	15 , R ₁ = H, R ₂ = CO ₂ Me	16m, 16p	22 (3:1)
8	17 , R ₁ = H, R ₂ = SiMe ₃	--	--
9	18 , R ₁ , R ₂ = SiMe ₃	--	--
10	19 , R ₁ , R ₂ = CO ₂ Me	--	--

^a Conditions: molar ratio of nitrile:diyne = 1:1; 15 mol % CpCo(CO)₂, *o*-xylene (0.01 M), 140 °C, syringe-pump addition, 100 h, Ar atmosphere, *hν*. ^b Entries 1–6, R = H; entry 7, R = R₂ = CO₂Me. ^c Ratios determined from isolated isomeric products.

respectively. Since the regiochemistry obtained here is fairly similar to that observed in the analogous acyclic reaction (2,4,6:2,3,6 = ca. 2:1),^{21f} there are probably no special forces influencing the overall chemical pathway. Formation of a pyridine group as part of a new macrocycle in this way supplies substantial molecular complexity in a single step with excellent atom economy.²⁵

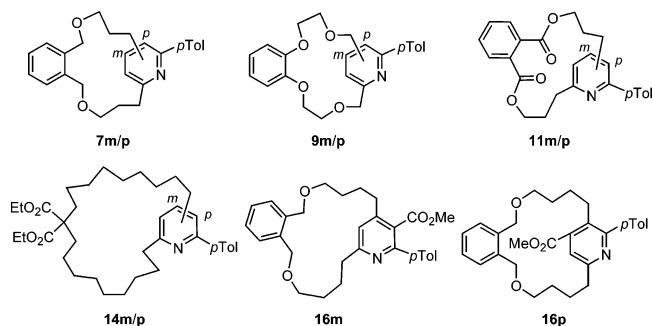


We explored the scope and limitations of this novel macrocyclization strategy, such as variation of the α,ω -diyne substrates with respect to length and substitution of the tether, and the electronic nature of the alkyne groups. As shown in Table 1, moderate to good yields of *meta*- and *para*-pyridinophanes with ring sizes ranging from 15 to 23 were obtained from the

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cyclotrimerizations of various α,ω -bis-alkynes with *p*-tolunitrile. 1,15-Bis-alkynes appended to the ortho positions of a benzene ring with ether (entry 1), bis-ether (entry 3),²⁶ or ester (entry 4) linkages provided 15-membered *meta*- and 16-membered *para*-pyridinophanes, with the latter predominating. An acyclic 1,15-diyne **1** devoid of substitution on the tether and thus lacking any Thorpe–Ingold assistance in the cyclization gave a 1:1 ratio of 15- and 16-membered pyridinophanes (entry 5). Cyclization of a 1,22-diyne **13** bearing a geminal disubstitution in the tether chain resulted in the formation of 22- and 23-membered macrocycles (entry 6).

The potential for one-step formation of a highly substituted pyridine unit led us to investigate the substitution pattern in the alkyne moieties. Macrocycles bearing tetrasubstituted pyridine units were formed from *p*-tolunitrile and diyne **15**, which bears an ester substituent (entry 7). Silyl-substituted pyridines would be attractive targets;^{15d,27} however, monosilylated bis-alkyne **17** was unreactive to cycloaddition with *p*-tolunitrile (entry 8). Alkynes substituted on both termini with TMS or ester groups, as in **18** and **19**, also did not react (entries 9 and 10).



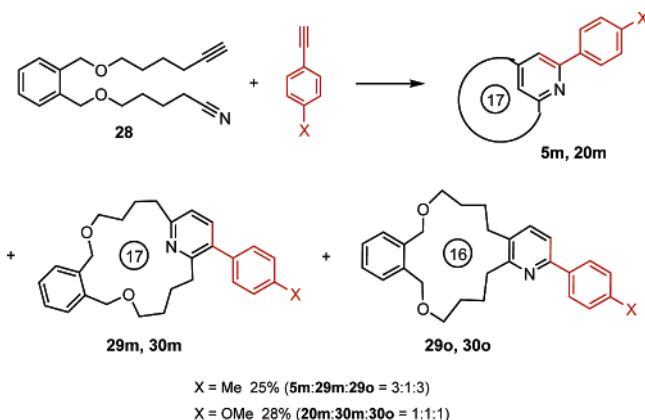
Various nitrile partners with different types of substituents were surveyed to assess reactivity as well. In general, nitriles conjugated to an arene, heteroarene, or alkene group underwent macrocyclization with diyne **3** with reasonable efficiency (Table 2). Nitriles with phenyl (entries 1–4), furyl (entry 5), and pyridyl (entry 6) substituents gave moderate to good yields of pyridinophanes. The electronic nature of substituents on the phenyl ring showed a minor influence on yield, although an electron-withdrawing substituent favored the formation of the *meta* isomer (entry 4 vs entries 1–3). Nitriles conjugated to the cyclohexenyl (entry 7) and styrene units (entry 8) furnished pyridinophanes in moderate yields with the former preferentially generating the *meta* isomer. Nitriles linked to cyclic and acyclic alkyl groups furnished trace amounts of cycloadducts (entries 10 and 11). Conversely, 1-cyanoadamantane gave a yield of 11% (entry 9) with the macrocyclic product being essentially just the *meta* isomer. A silylated nitrile did not undergo cycloaddition with **3** (entry 12).

Table 2. Pyridinophanes from α,ω -Diyne **3** and Various Nitriles

entry	nitrile	products	% yield (<i>meta</i> : <i>para</i>) ^b
1		5m, 5p	57 (1:1)
2		20m, 20p	38 (1:1)
3		21m, 21p	35 (1:1)
4		22m, 22p	46 (2:1)
5		23m, 23p	38 (1:3)
6		24m, 24p	33 (1:1)
7		25m, 25p	30 (2:1)
8		26m, 26p	43 (1:2)
9		27	11 (>50:1)
10		–	trace
11	<i>n</i> -C ₅ H ₁₁ CN	–	trace
12	<i>t</i> -BuMe ₂ SiCN	–	0

^a Conditions: molar ratio of nitrile:diyne = 1:1; 15 mol % CpCo(CO)₂, *o*-xylene (0.01 M), syringe-pump addition, 100 h, 140 °C, Ar atmosphere, *hv*. ^b Ratios determined from isolated isomeric products.

Scheme 4. Co-cyclotrimerization of ω -Alkynyl Nitrile **28** with Alkynes



A complementary cyclization strategy could also involve the reaction of ω -alkynyl nitriles with alkynes,^{21a,b} as exemplified by the cycloaddition of **28** with aromatic alkynes (Scheme 4). In contrast to the reaction of diyne **3** with 4-methylbenzonitrile (Table 2, entry 1), the reaction of **28** with *p*-tolylacetylene furnished the 2,4,6-substituted pyridine *meta* isomer **5m** along with two macrocycles bearing the 2,3,6-substituted pyridines,

- (25) For reviews on heterophanes, see: (a) Newkome, G. R.; Traynham, J. G.; Baker, G. R. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon: New York, 1984; Vol. 7, Part 5, pp 763–780. (b) Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513–597. For reviews on synthesis of pyridinophanes, see: (c) Shkil, G. P.; Sagitullin, R. S. *Chem. Heterocycl. Compds.* **1998**, *34*, 507–528. (d) Majestic, V. K.; Newkome, G. R. *Top. Curr. Chem.* **1982**, *106*, 79–118.
- (26) Addition of Na⁺ ion in the form of NaB[1.3-(CF₃)₂C₆H₃]₄ did not meaningfully influence the macrocyclization of diyne **8** and *p*-tolunitrile via a template effect.
- (27) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5245–5253.

Table 3. Optimization of Macrocyclization Conditions^a

$$6 + p\text{ToICN} \xrightarrow[\text{solvent, reflux, atm}]{\text{CpCo(CO)}_2} 7\text{m} + 7\text{p}$$

entry	solvent	conc (M)	rxn atm	% yield (7m:7p) ^b
1 ^c	toluene	0.005	N ₂	81 (1:1)
2	toluene	0.005	N ₂	5 (<1:50) ^d
3	DME	0.005	CO	73 (1:5)
4	DME	0.005	Ar	62 (1:4)
5	1,4-dioxane	0.005	CO	59 (1:5)
6	1,4-dioxane	0.005	Ar	87 (1:7)

^a Conditions: molar ratio of nitrile:diyne = ca. 5:1; 15 mol % CpCo(CO)₂; reflux; 24 h; argon, nitrogen, or carbon monoxide atmosphere. ^b Ratios determined from isolated isomeric products. ^c A 2.3 mol equiv amount of CpCo(CO)₂, reflux, 43 h. ^d Forty-nine percent recovered **6**.

29m and **29o**. It is interesting that the regioisomeric para cycloadduct **5p** was not observed. Cyclotrimerization of **28** with 1-ethynyl-4-methoxybenzene provided a 1:1:1 ratio of three isomers of similar substitution pattern: **20m**, **30m**, and **30o** (entry 2). Despite the α,ω -alkynyl nitrile/alkyne cycloaddition being nonselective compared with the α,ω -diyne/nitrile cycloaddition, it offers access to other isomeric products that are not obtainable via the original route.

Improved Reaction Conditions. The reaction conditions employed by us were adopted from the standard cobalt-catalyzed alkyne trimerization protocol.¹⁵ To generate the macrocyclic products with reasonable efficiency, we also relied on the high-dilution technique of syringe-pump addition.^{5,17} This process is inconvenient and cumbersome, especially if one were interested in producing chemical libraries. Thus, we sought to develop an improved procedure for macrocycle formation via CpCo(CO)₂-catalyzed cyclotrimerizations of diynes and nitriles.²⁸ The typical literature procedure entails slow addition of a xylene or toluene solution of the diyne, nitrile, and cobalt catalyst into a large volume of refluxing xylene or toluene (either with or without additional catalyst).¹⁵ To minimize the unproductive oligomerization of reactants,^{5,17} addition of the reagents is controlled by using a syringe pump over an extended period of time while the reaction mixture is irradiated with light.²⁹ High-intensity light (e.g., from a 300-W slide projector lamp) is commonly used in order to promote decarbonylation of the cobalt catalyst and release the reactive cobalt species.^{15,29} Although this classical protocol established the basis for our early work, we now wanted to perform the co-cyclotrimerization effectively without a syringe pump, without high-intensity light, and at a lower reaction temperature.

Initially, we examined the reaction of **6** and *p*-tolunitrile in a dilute toluene solution (0.005 M) at reflux with a large amount of CpCo(CO)₂ present (Table 3, entry 1). A remarkable result was realized in that pyridinophanes **7m** and **7p** were obtained

in 81% yield. However, when the amount of CpCo(CO)₂ was reduced to a more standard 15 mol %, we obtained only 5% yield of **7p** (**7p:7m** > 50:1) along with 49% of unreacted **6** (entry 2). We then turned our attention to ether-type solvents and the use of a CO atmosphere (Table 3). This approach was based on speculation that catalytic efficiency might be enhanced (e.g., better catalyst turnover) by providing free ligands to the cobalt catalyst and intermediates thereof.³⁰ Efficient macrocyclizations were attained in reactions conducted in either 1,2-dimethoxyethane (DME) or 1,4-dioxane (entries 3–6), with the latter delivering a yield as high as 87% (entry 6); however, the effect of a CO atmosphere was relatively insignificant.³¹

As mentioned earlier, the bimolecular macrocyclization process is associated with an intrinsic paradox. The success of the reaction simultaneously requires high dilution to favor macrocyclization and sufficient concentration to favor a bimolecular reaction. Thus, the intermolecular [2 + 2 + 2] cycloaddition differs inherently from many published metal-mediated macrocyclizations.^{8–13} Considering this aspect, one can appreciate why the Vollhardt reaction has been problematic in forming rings larger than six members.^{15,18,32} To follow up on this point, we investigated the effect of concentration on the macrocyclization to form pyridinophanes via the reaction of **6** with *p*-tolunitrile to give **7m** and **7p** (Figure 1). The yield of product was found to be highly dependent on concentration in the range of 0.0005–0.1 M,³³ and an optimal yield occurs at a concentration in the vicinity of 0.005 M. Our data indicate that there is a favorable zone of operation from 0.002 to 0.05 M. These results are consistent with the following fundamental point: While fairly high dilution can favor macrocyclization, this factor cannot be stretched to an extreme because the required bimolecular process would suffer. At a concentration of 0.005 M, the α,ω -diyne self-trimerized to a minor extent. For example, the DME reaction without any nitrile present (Table 3, entry 4) afforded just 6% yield of a dimer of **6** and 62% of unreacted **6**. Given these results, we suggest that an optimal concentration range for our macrocyclization method would be 0.002–0.05 M.

We pursued further studies with our improved reaction conditions to assess the scope and limitations (Table 4). Cycloaddition of *p*-tolunitrile with a series of diynes of different tether lengths (*n* = 1–4) indicated that cyclizations to form

(28) Bis-alkyne **6** failed to undergo cycloaddition with *p*-tolunitrile under the following catalytic systems: (a) RuCl₂(imidazolydine)(PCy₃)CHPh; (b) [RhCl(cod)]₂, dppe; (c) Ir(cod)Cl₂, dppe; and (d) Pd₃(dba)₃, PPh₃. It was recovered unreacted after prolonged heating, 14–32 h. A similar result was observed using [RhCl(CO)₂]₂, dppe, and AgOTf. For references on diyne–nitrile cycloadditions promoted by transition metals, see ref 19a. (29) (a) Vollhardt, K. P. C.; Bergman, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 4996–4998. (b) Vollhardt, K. P. C.; Bercaw, J. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 4998–5000.

(30) The solvents used in cobalt-mediated alkyne trimerization are normally aromatic and alkyl hydrocarbons, such as xylene, toluene, and octane.¹⁵ An atmosphere of CO has been shown to regenerate the active cobalt catalyst in the Pauson–Khand reaction, see: (a) Krafft, M. E.; Boñaga, L. V. R.; Hirotsawa, C. *J. Org. Chem.* **2001**, *66*, 3004–3020 and references therein. (b) Park, K. H.; Jung, I. G.; Chung, Y. K. *Org. Lett.* **2004**, *6*, 1183–1186. (31) Under these conditions macrocyclizations of **6** and *p*-tolunitrile were achieved in toluene and isooctane to furnish **11m** and **11p** in 41% (1:8) and 62% (1:4) yields, respectively. Reactions in 1,2-dichloroethane were unsatisfactory; only unreacted diyne **6** was isolated. (b) For reference purposes, we reacted 1,7-octadiyne with *p*-tolunitrile under our improved reaction conditions [15 mol % CpCo(CO)₂, 0.005 M in 1,4-dioxane, reflux, 24 h, argon atmosphere] and obtained the cycloadduct in 74% yield (69% yield with an atmosphere of CO). For the reaction of 1,7-octadiyne and benzonitrile under classical conditions [10 mol % CpCo(CO)₂, 0.17 M in xylene, reflux, syringe pump addition over 5 days, nitrogen atmosphere], Naiman and Vollhardt obtained a 70% yield of cycloadduct.^{21a} (32) From an observation of Naiman and Vollhardt the [2 + 2 + 2] reaction of bis-alkynes with nitriles appears to be intrinsically better than the [2 + 2 + 2] reaction of bis-alkynes with alkynes.^{21a} In the reaction of 1,8-nonadiyne with PhCN or C₃H₁₁CN under classical conditions, seven-membered annulated pyridines were obtained in ca. 50% yield.^{21a} (33) For an example of the effect of reaction concentration on macrocyclization, see: Yamamoto, K.; Biswas, K.; Gaul, K.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297–3299.

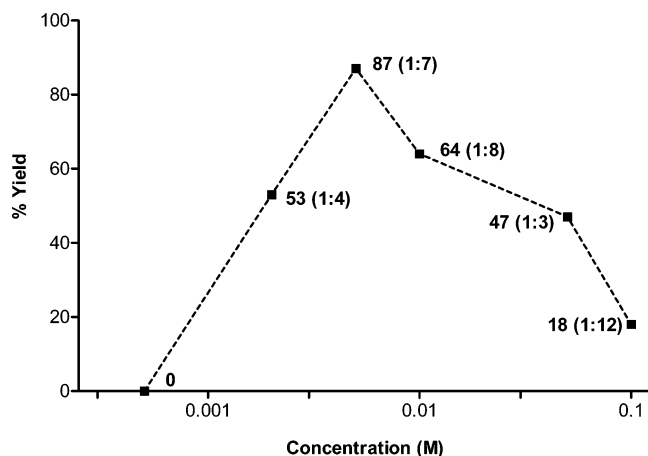


Figure 1. Reaction efficiency (% yield) vs concentration (0.0005, 0.002, 0.005, 0.01, 0.05, and 0.1 M) for the cobalt-mediated cycloaddition of diyne **6** with *p*-tolunitrile. The regioisomer ratio is **7m**:**7p**. Unreacted **6** was recovered in 17% and 23% from the reactions conducted at 0.0005 and 0.002 M, respectively. The abscissa is presented on the log 2 scale. The dashed line is provided to facilitate visualization of the results (no mathematical relationship is implied).

Table 4. Cyclotrimerization of α,ω -Diyne with Nitriles Using Improved Conditions^a

entry	α,ω -diyne substrate	nitrile	products	% yield (<i>meta:para</i>) ^b
1	$n = 4, 3$	<i>p</i> TolCN	5m , 5p	58 (1:1)
2	$n = 3, 6$	<i>p</i> TolCN	7m , 7p	87 (1:7)
3	$n = 2, 31$	<i>p</i> TolCN	32m , 32p	4 (1:1)
4	$n = 1, 33$	<i>p</i> TolCN	--	0
5	8	<i>p</i> TolCN	9m , 9p	80 (1:7)
6	10	<i>p</i> TolCN	11m , 11p	30 (1:4)
7	3	Br--CN	21m , 21p ^c	25 (1:1)
8	3	-CN	27 ^c	9 (>50:1)
9	3	-CN	--	0
10	3	Me ₃ Si-CN	--	0

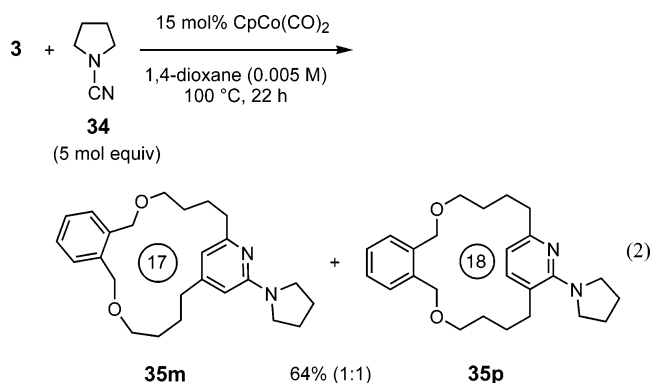
^a Conditions: molar ratio of nitrile:diyne = ca. 5:1; 15 mol % CpCo(CO)₂, 1,4-dioxane (0.005 M), reflux, ca. 24 h. ^b Ratios determined from isolated isomeric products. ^c See Table 2.

smaller medium-sized rings are not effective (entries 1–4).³⁴ For the reactions of diynes **31** and **33**, the anticipated, analogous 13/14-membered and 11/12-membered macrocycles were not forthcoming (entries 3 and 4); unreacted starting material was recovered. Cycloaddition of *p*-tolunitrile with diynes **3**, **6**, **8**, and **10** furnished the corresponding pyridinophanes in similar or better yields (entries 1, 2, 5, and 6, respectively) compared with our original method (cf. Table 1). Macrocyclization of diyne **3** with 4-bromobenzonitrile provided the pyridinophanes **21m** and **21p** in 25% yield (entry 7; cf. Table 2, entry 3). Adamantyl-substituted pyridinophane **27** was obtained in a similar yield when it was generated using the previous method (entry 8; cf. Table 2, entry 9). Diyne **3** failed to undergo cycloaddition with cyanocyclopentane (entry 9, cf. Table 2, entry 10).³⁵ A similar result was also observed in the reaction of **3** with a cyanosilane (entry 10, cf. Table 2, entry 12). At this

(34) Strain must be overcome to synthesize medium-sized rings.⁷⁸

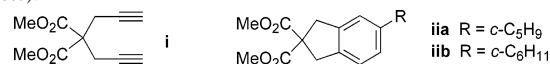
point we developed a method for the cobalt(I)-catalyzed [2 + 2 + 2] cycloaddition of α,ω -diynes and nitriles to *meta*- and *para*-pyridinophanes, which is much more convenient than our original protocol²³ and has a reasonable scope for synthetic applications.

Cyclotrimerization with Cyanamides. Given this procedural advance, we became interested in the potential utility of cyanamides as reactants as there is a scarcity of published information on this aspect.³⁶ Bönnemann and co-workers reported the reaction of acetylene with cyanamide in the presence of a η^6 -borinano cobalt catalyst;³⁷ Heller and co-workers reported photoinduced cyclotrimerizations of acetylene with *N*-cyanopyrrolidine or *N*-cyanopiperidine in the presence of CpCo(cod)₂,³⁸ and another example of this reaction is mentioned briefly in a patent.³⁹ We conducted the CpCo(CO)₂-catalyzed cyclotrimerization of α,ω -bis-alkynes with cyanamides, under moderate thermal conditions without any photo-stimulation, to produce various amino-substituted pyridinophanes (Table 5).^{36,40}



In an early test example the reaction of **3** with *N*-cyanopyrrolidine (**34**) gave regioisomeric pyrrolidine-substituted pyridinophanes **35m** and **35p** (1:1 ratio) in 64% yield (eq 2). Several other reactions of diynes and cyanamides afforded *meta*- and *para*-pyridinophanes in good-to-excellent yields under fairly mild reaction conditions,³⁶ and some representative examples are presented in Table 5. Cyclotrimerization of 1,15-bis-alkynes **6**, **8**, and **10** with cyanamides gave predominantly the corresponding 16-membered *para*-pyridinophanes (entries 2–5), whereas 1,17-bis-alkyne **3** provided a mixture (1:1) of the 17-membered *meta*- and 18-membered *para*-pyridinophanes in good yields (entry 1). Cyanamides disubstituted with alkyl

(35) For reference purposes we reacted cyanocyclopentane or cyanocyclohexane with short-tethered diyne **1** (15 mol % CpCo(CO)₂, 0.005 M in DME, reflux, ca. 18 h) to obtain low yields of benzannulated products **11a** (25%) or **11b** (10%).



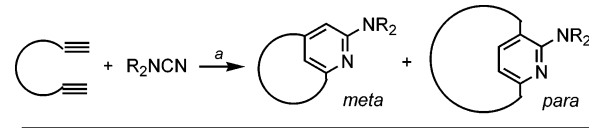
(36) For a preliminary report, see: Boñaga, L. V. R.; Zhang, H.-C.; Maryanoff, B. E. *Chem. Commun.* **2004**, 2394–2395.

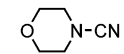
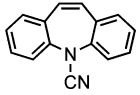
(37) (a) Bönnemann, H.; Brijoux, W. *Adv. Heterocycl. Chem.* **1990**, *48*, 177–222. (b) Bönnemann, H.; Brijoux, W. *Aspects Homogen. Catal.* **1984**, *5*, 75–196. (c) Bönnemann, H.; Brijoux, W.; Brinkmann, R.; Meurers, W. *Helv. Chim. Acta* **1984**, *67*, 1616–1624.

(38) (a) Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H.-J.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, *67*, 4414–4422. Heller, B.; Reihsig, J.; Schulz, W.; Oehme, G. *Appl. Organomet. Chem.* **1993**, *7*, 641–646. (b) cod = 1,5-cyclooctadiene.

(39) Vollhardt, K. P. C.; Naiman, A. U.S. Patent 4,328,343, 1982; *Chem. Abstr.* **1978**, *90*, 186806.

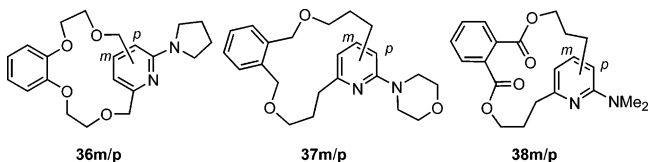
(40) A survey of cyanamide reactivity with diynes of varying tethered lengths is given in ref 36.

Table 5. Cyclotrimerization of α,ω -Diynes with Cyanamides


entry	α,ω -diyne	cyanamide	products	% yield (<i>meta</i> : <i>para</i>) ^b
1	3	34	35m, 35p	64 (1:1)
2	8	34	36p	50 (<1:50)
3	6		37p	54 (<1:50)
4	10	Me₂N-CN	38p	32 (<1:50)
5	8		39m, 39p	80 (1:6)

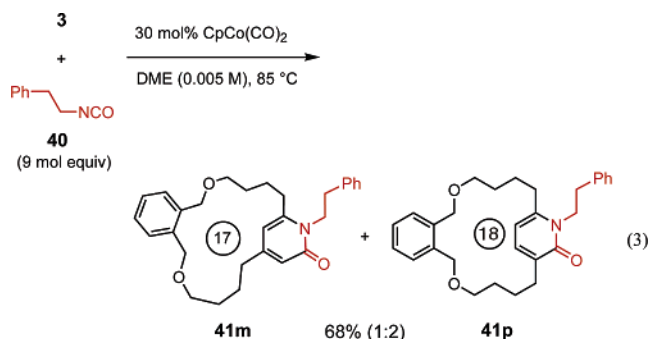
^a Conditions: molar ratio of cyanamide:diyne = ca. 5:1; 15 mol % CpCo(CO)₂, 1,4-dioxane (0.005 M), reflux, 18–24 h. ^b Ratios determined from isolated isomeric products.

(entries 1–4) or aryl groups (entry 5) were compatible cyclotrimerization partners.³⁶ The regiochemical outcome observed in the reaction of **8** with *N*-cyanopyrrolidine is noteworthy since the *para* isomer was produced exclusively (entry 2; cf. entry 5). Thus, 2-aminopyridinophanes⁴¹ can be conveniently formed in one step through this macrocyclization process.



Cyclotrimerization with Heterocumulenes. We were also interested in the [2 + 2 + 2] cycloaddition of α,ω -diynes and heterocumulenes using our improved procedure.^{42,43} Reaction of diyne **3** with 2-phenylethylisocyanate (**40**) using 30 mol % of CpCo(CO)₂ furnished a mixture of 2-oxopyridinophanes **41m** and **41p** in 68% yield (eq 3).⁴⁴ Among all possible regioisomeric products, only two cyclophanes, the 4,6- (*meta*-) and 3,6- (*para*-) substituted 2-pyridones, were obtained in a 1:2 ratio.⁴⁵ This result is remarkable considering previous reports on poor

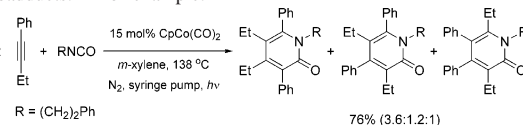
cyclization efficiency for the reaction of 1,*n*-bis-alkynes ($n = 6, 7$) with isocyanates using catalytic CpCo(CO)₂ under typical reaction conditions (*m*-xylene, 140 °C, *hν*, syringe pump, 3–5 h).^{42a} Recently, Yamamoto et al. addressed this shortcoming by introducing Cp**Ru*(cod)Cl for the cycloaddition of 1,6-diynes and isocyanates to give bicyclic pyridones (58–87% yields).⁴⁶



To explore the scope of the isocyanate [2 + 2 + 2] reaction, several symmetrical acyclic α,ω -diynes were cyclized with alkylisocyanate **40** (Table 6). 1,15-Bis-alkynes connected to the ortho positions of a benzene ring possessing ether (entry 2), bis-ether (entry 5), or ester linkages (entry 6) gave mainly 16-membered *para*-2-oxopyridinophanes in good yields. In contrast, co-cyclotrimerization of the homologous 1,13-alkyne **31** (entry 3) or 1,11-bis-alkyne **33** (entry 4) with **40** proceeded poorly or not at all. A 1,17-bis-alkyne **46**, with a biphenyl scaffold, provided 17-membered *meta*- and 18-membered *para*-2-oxopyridinophanes, **47m** and **47p**, with the latter predominating (entry 7). Bis-silyl-diyne **18** failed to cyclotrimerize with isocyanate **40** (entry 8), presumably because **18** bears two internal alkyne groups.

The reactivity of several isocyanates with bis-alkyne **8** was studied (Table 6). The scope of isocyanate reactivity in such cobalt-mediated cycloadditions involving short-chain bis-alkynes is not known because the reaction has proceeded poorly.^{42a} Reaction of **8** with unhindered alkyl isocyanates gave fair to good yields of 2-oxopyridinophanes (entries 9–11). Hindered aliphatic isocyanates also underwent co-cyclotrimerization smoothly (entries 12–14). The successful reaction of adamantyl isocyanate with **8** (entry 14) is particularly significant since *tert*-butylisocyanate failed to react with diethyl 2,2-di(prop-2-ynyl)malonate under Ru(II) catalysis.^{46a} In contrast to the cyclotrimerization of α,ω -bis-alkynes with nitriles (viz. Tables 2 and 4), aliphatic isocyanates led to better yields of cycloadducts than did aromatic isocyanates (cf. entries 1, 2, 5–7, 9–14 with entries 15–17). Similar to the cycloaddition of 1,15-bis-alkyne **6** with isocyanate **40**, only the *para*-2-oxopyridinophanes were formed in the cycloadditions of **8** and **10**. The low efficiency of

(45) Intermolecular cycloaddition of two molecules of an internal alkyne and one molecule of an isocyanate provides a mixture of regioisomeric cycloadducts.^{42a} For example:



(46) (a) Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001**, *13*, 2117–2119. (b) The analogous cyclotrimerization of isocyanatoalkynes with monoalkynes to form 2,3-dihydro-5(1*H*)-indolizinones appears to be more synthetically useful.^{42a,b} (c) cod = 1,5-cyclooctadiene; Cp* = pentamethylcyclopentadiene.

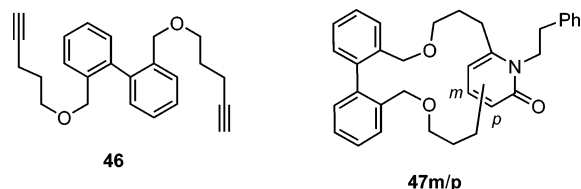
(41) Aminopyridines, which are important as pharmaceutical agents, ligands in inorganic and organometallic chemistry, and fluorescent dyes, are typically prepared by the substitution of halogenated pyridines (Thomas, S.; Roberts, S.; Pasmansky, L.; Gamsey, S.; Singaram, B. *Org. Lett.* **2003**, *5*, 3867–3870 and references therein).

(42) For cobalt-mediated cycloaddition of alkynes with isocyanates, see: (a) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786–4800. (b) Earl, R. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6991–6993. (c) Hong, P.; Yamazaki, H. *Tetrahedron Lett.* **1977**, 1333–1336. (d) Hong, P.; Yamazaki, H. *Synthesis* **1977**, 50–52. For nickel-mediated cycloaddition of alkynes with isocyanates, see: (e) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1983**, *252*, 359–364. (f) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1982**, *234*, C35–C38. (g) Hoberg, H.; Oster, B. W. *Synthesis* **1982**, 324–325. For the synthesis of pyridone-containing macrocycles without using transition metals, see: (h) Bradshaw, J. S.; Nakatsuji, Y.; Huszthy, P.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1986**, *23*, 353–360. For a recent synthesis of 2-pyridones, see: (i) Hachiya, I.; Ogura, K.; Shimizu, M. *Org. Lett.* **2002**, *4*, 2755–2757.

(43) For a preliminary communication, see: Boñaga, L. V. R.; Zhang, H.-C.; Gauthier, D. A.; Reddy, I.; Maryanoff, B. E. *Org. Lett.* **2003**, *5*, 4537–4540.

(44) The larger amount of the Co(I) catalyst was used to achieve complete reactions. DME was found to be a better solvent than 1,4-dioxane.

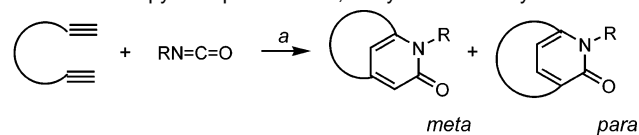
cyclotrimerization with the aromatic isocyanates (entries 15–17) may be due to some self-condensation of the isocyanate to give a symmetrical urea.⁴⁷ In the reaction of **8** with 4-methoxybenzylisocyanate, *N,N'*-bis(4-methoxybenzyl)urea (**56**) was obtained along with **44** (entry 10), but the yield of **44** could be improved by using excess isocyanate (5–10 mol equiv). Similarly, excess isocyanate (4 mol equiv) was used (added in two batches) to favor the cycloaddition in a Ru(II)-catalyzed reaction of 1,6-diynes.^{46a}



To expand on the product diversity, we attempted reactions with other heterocumulenes such as isothiocyanates and carbodiimides.^{42c,d} In the presence of a catalytic amount of CpCo(CO)₂ the reaction of diyne **6** with *p*-tolylisothiocyanate or cyclohexylisothiocyanate did not yield the desired macrocycles bearing 2-pyridinethiones. Similarly, the reactions of diyne **8** with 1,3-di(*p*-tolyl)carbodiimide or 1,3-dicyclohexylcarbodiimide did not produce the corresponding macrocycles bearing 2-imino-1,2-dihydropyridines. Negative results were also obtained in Cp₂Co-catalyzed cycloadditions of diynes **8** or dimethyl 2,2-di(prop-2-ynyl)malonate with 1,3-di(*p*-tolyl)carbodiimide.^{42d}

Cyclotrimerization of Alkynes. Our favorable results for cyclotrimerizations of α,ω -diynes with nitriles and isocyanates to yield macrocycles, under convenient reaction conditions, encouraged us to reevaluate the corresponding reaction with alkynes (“Vollhardt reaction”). In our hands and in the hands of others,^{18,23} transition-metal-mediated cyclotrimerizations of alkynes for macrocycle production have not yielded positive results.^{48,49} A study of reactions of short-chain diynes and

Table 6. 2-Oxopyridinophanes of α,ω -Diynes and Isocyanates



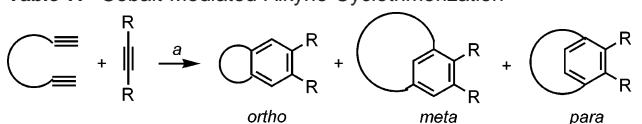
entry	α,ω -diyne	isocyanate	products	% yield (meta:para) ^b
1	3	40	41m, 41p	68 (1:2)
2	6	40	42m, 42p	41 (1:20)
3	31^c	40	43m, 43p	7 (1:1)
4	33^c	40	--	0
5	8	40	44	64 (<1:50)
6	10	40	45	40 (<1:50)
7	46	40	47m, 47p	30 (1:5)
8	18^d	40	--	0
9	8		48	48 (<1:50)
10	8		49	70 (<1:50)
11	8	C ₁₂ H ₂₅ -NCO	50	31 (<1:50)
12	8		51	60 (<1:50)
13	8		52	47 (<1:50)
14	8		53	36 (<1:50)
15	8		54	23 (<1:50)
16	8		55	19 (<1:50)
17	8		--	0

^a Conditions: molar ratio of isocyanate:diyne = 5–10:1; 30 mol % CpCo(CO)₂, DME (0.005 M), 85 °C, ca. 24 h. ^b Ratios determined from isolated isomeric products. ^c See Table 4. ^d See Table 1.

- (47) (a) Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*; Academic Press: New York, 1967. (b) *The Chemistry of Cyanates and Their Thio Derivatives*; Patai, S., Ed.; Wiley-Interscience: New York, 1977; Parts 1 and 2. (c) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457–496.
- (48) Bis-alkyne **6** failed to co-cyclotrimerize with an excess of 1-hexyne (20–65 mol equiv) under thermal conditions using various catalytic systems: (a) RuCl₂(imidazolidine)(PCy₃)₂CHPh; (b) RuCl₂(PCy₃)₂CHPh; (c) [RhCl(CO)₂]₂, dppe, AgOTf; (d) RhCl(PPh₃)₃; (e) [RhCl(cod)]₂, dppe; (f) Ni(cod)₂, dppe; (g) Ni(acac)₂, PPh₃, (*i*-Bu)₂AlH; (h) [Ir(cod)Cl]₂, dppe; (i) Pd₂(dba)₃, PPh₃. The diyne was recovered unreacted after prolonged heating (ca. 32 h) except in the last two systems, where it was consumed without yielding cyclophane products. A similar result occurred when **6** was reacted with 4-octyne using RhCl(PPh₃)₃.
- (49) References on alkyne cyclotrimerization with other transition metals. RuCl₂(PCy₃)₂CHPh: (a) Peters, J.-U.; Blechert, S. *Chem. Commun.* **1997**, 1983–1984. (b) Witulski, B.; Stengel, T.; Fernandez-Hernandez, J. M. *Chem. Commun.* **2000**, 1965–1966. RhCl(PPh₃)₃: (c) Sun, Q.; Zhou, X.; Islam, K.; Kyle, D. J. *Tetrahedron Lett.* **2001**, *42*, 6495–6497. (d) Grigg, R.; Scott, R.; Stevenson, P. J. *Chem. Soc., Perkin Trans. 1* **1988**, 1357–1363. (e) McDonald, F. E.; Zhu, H. Y. H.; Holmquist, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 6605–6606. (f) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2426–2430. (g) Grigg, R.; Sridharan, V.; Wang, J.; Xu, J. *Tetrahedron* **2000**, *56*, 8967–8976. [Ir(cod)Cl]₂/dppe: (h) Takeuchi, R.; Tanaka, S.; Nakaya, Y. *Tetrahedron Lett.* **2001**, *42*, 2991–2994. Cp^{*}Ru(cod)Cl: (i) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 269–270. Pd₂(dba)₃/PPh₃: (j) Yamamoto, Y.; Nagata, A.; Itoh, K. *Tetrahedron Lett.* **1999**, *40*, 5035–5038. (k) Yamamoto, Y.; Nagata, A.; Arikawa, Y.; Tatsumi, K.; Itoh, K. *Organometallics* **2000**, *19*, 2403–2405. Ni(acac)₂/PPh₃/*i*-Bu₂AlH: (l) Sato, Y.; Ohashi, K.; Mori, M. *Tetrahedron Lett.* **1999**, *40*, 5231–5234. (m) Sato, Y.; Nishimata, T.; Mori, M. *J. Org. Chem.* **1994**, *59*, 6133–6135. [RhCl(cod)]₂/tppts: (n) ref 16b.

alkynes under our improved reaction conditions⁵⁰ prompted us to pursue reactions of α,ω -diynes with selected alkynes (Table 7). Under the conditions shown in Table 7, bis-cobaltacyclobutadiene complex **4** was not formed on reacting 1,17-diyne **3** with 100 mol equiv of BTMSA under argon or carbon monoxide (unreacted **3** was recovered). By employing 50 mol equiv of BTMSA under argon or 5 mol equiv of BTMSA under argon or CO, **3** was consumed and a complex mixture of unidentified products was observed. A similar result was noted when 1,15-diyne **6** was reacted with 5 mol equiv of BTMSA (Ar atmosphere). Also, (trimethylsilyl)acetylene, 2-ethynylpyridine, 1-ethynylcyclohexene, but-1-ynylcyclohexane, trimethyl(phenylethynyl)silane, and trimethyl(phenylethynyl)stannane did not

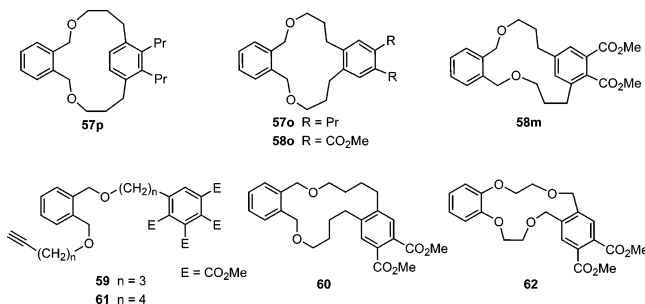
- (50) In studying the effect of solvent and reaction atmosphere on the cycloaddition of a short-tethered diyne, we found that cyclotrimerization is more efficient in DME than in 1,4-dioxane and that it is not influenced by a CO atmosphere. The observed low yields, which reflect the poor efficiency of such alkyne cyclotrimerizations, are comparable to those reported for cyclizations of analogous substrates conducted with traditional reaction conditions (3 mol % CpCo(CO)₂, 0.5 M in octane, reflux, syringe-pump addition, 36 h; 14–50% yields).¹⁵ See Supporting Information.

Table 7. Cobalt-Mediated Alkyne Cyclotrimerization

entry	α,ω -diyne substrate	R	equiv alkyne	rxn atm	products	% yield (isomer ratio) ^b
1	6	Pr	10	Ar	57p	23
2	6	Pr	5	CO	57o, 57p	29 (1:2)
3	6	CO ₂ Me	10	Ar	58o	33 ^c
4	6	CO ₂ Me	5	CO	58m, 58o	36 (1:11) ^d
5	3	CO ₂ Me	10	Ar	60	12 ^e
6	8	CO ₂ Me	5	Ar	62	31 ^f

^a Conditions: 15 mol % CpCo(CO)₂, DME (0.005 M), reflux, argon or carbon monoxide atmosphere. ^b Ratios determined from isolated isomeric products. ^c Also, 9% yield of **59**. ^d Also, 7% yield of **59**. ^e Also, 11% yield of **61**. ^f A 27% yield of **62** with 1,4-dioxane as the solvent.

cyclotrimerize with diyne **6** to give macrocycles. After many negative results in pursuit of this reaction class, we were delighted to find that 4-octyne underwent macrocyclization with diyne **6**, albeit in low yields (entry 1). Interestingly, different regiochemistry was observed in this benzannulation depending on whether we used an atmosphere of argon or carbon monoxide. The cycloaddition of diyne **6** and 4-octyne under argon provided paracyclophane **57p** almost exclusively, whereas the reaction under CO provided a mixture of ortho and para isomers, **57o** and **57p** (cf. entries 1 and 2). The cyclization of diyne **6** with dimethyl acetylenedicarboxylate (DMAD) under argon yielded benzannulene **58o** (entry 3); however, under carbon monoxide the reaction provided the meta and ortho isomers, **58m** and **58o**, in a ratio of 1:11 (entry 4). Similarly, macrocyclizations of DMAD with bis-alkynes **3** and **8** furnished only the benzannulenes **60** and **62**, respectively (entries 5 and 6). Macrocyclizations in DME and 1,4-dioxane gave similar yields and regiochemistry (entry 6). Undesired cycloadducts derived from the incorporation of two molecules of DMAD and only one of the alkyne moieties of the α,ω -diyne, such as **59** and **61**, were also isolated.⁵¹



Regiochemical and Mechanistic Considerations. Cobalt(I)-mediated [2 + 2 + 2] cycloadditions of bis-alkynes with nitriles, isocyanates, and alkynes proceed through a similar catalytic cycle (Scheme 3).¹⁹ Mechanistic studies, along with the isolation of intermediate complexes, for CpCoL₂-catalyzed (L = CO, PR₃, olefin) cyclotrimerizations of three alkyne units, to form a benzene ring, have supplied crucial information about

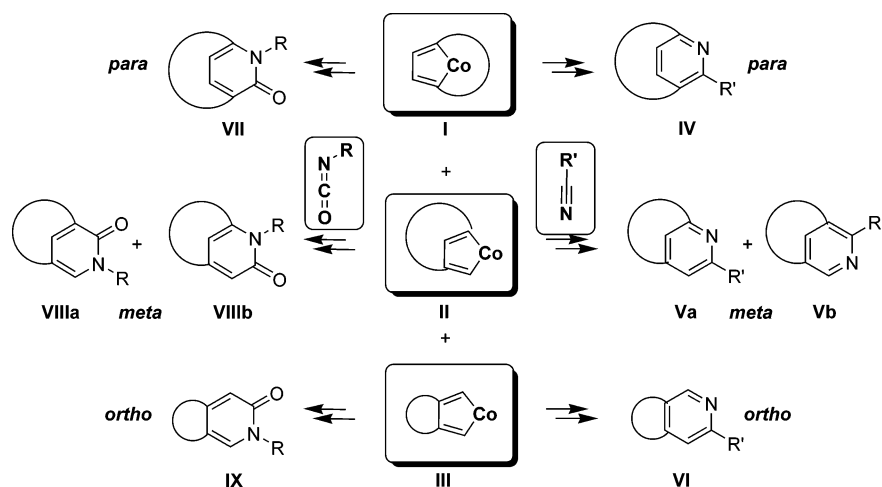
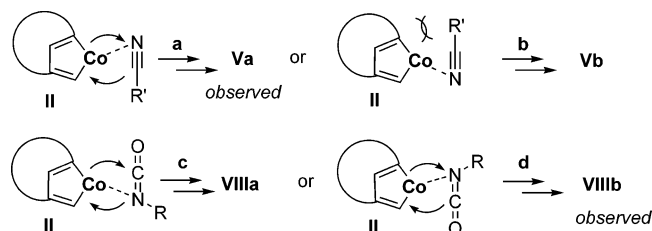
details of the process.^{19b} Presumably, these findings are also applicable to the related reactions of a bis-alkyne with a nitrile or an isocyanate.^{19a} The catalytic cycle would be initiated by sequential exchange of the ligands, L, in the cobalt catalyst for two alkyne units. Oxidative coupling of the alkynes would generate the coordinatively unsaturated cobaltacyclopentadiene intermediate, which would readily coordinate to the third reactive component, be it a nitrile or an isocyanate, or an alkyne in the classical process. In the case of an alkyne reactant direct cycloaddition would produce an η^4 -benzene complex that would undergo decomplexation to liberate the arene product and the CpCo catalyst with further cycling of the reaction. Whereas an alternative pathway involving insertion and reductive elimination steps is energetically less favorable according to density-functional theory (DFT) calculations, it may still be possible for the related reactions of a cobaltacyclopentadiene complex with a nitrile or an isocyanate to proceed via either pathway.^{42a,d}

Although we were able to effect the cobalt(I)-mediated [2 + 2 + 2] alkyne cycloaddition for the preparation of macrocycles (benzannulenes or cyclophanes), this route does not appear to be very efficient or general. The most notable previous successes with the bimolecular cyclotrimerization of α,ω -diynes and monoalkynes have been for reactions of 1,6-, 1,7-, and 1,8-diynes with BTMSA, the latter being present in a large excess.¹⁵ However, with long-chain α,ω -diynes the side reactions depicted in Scheme 3 tend to dominate, leading to an unsatisfactory macrocyclization process.

A similar trend in the regiochemical product distribution was observed in our cyclotrimerizations that furnished macrocycles containing pyridine and 2-oxypyridine moieties. On this basis we suggest that cobaltacyclopentadiene formation may be the regiochemistry-determining step with common intermediates being involved (Scheme 5). Three different regiochemical permutations are possible in the oxidative addition of the alkyne moieties in long-chain acyclic diynes, which implicates intermediates **I** (head-to-head reaction), **II** (head-to-tail reaction), and **III** (tail-to-tail reaction). To probe the reaction outcomes we performed DFT⁵² calculations (B3LYP with LACVP basis set for cobalt⁵³ and 6-31G for the other atoms⁵⁴) on key intermediates **I**, **II**, and **III** derived from a series of related bis-alkynes, **3**, **6**, **31**, and **33** as well as from bis-alkynes **1**, **8**, and **13**. In general, such DFT methodology has proven to be accurate and useful to study the energetics and reaction mechanisms for organometallic compounds.⁵⁵

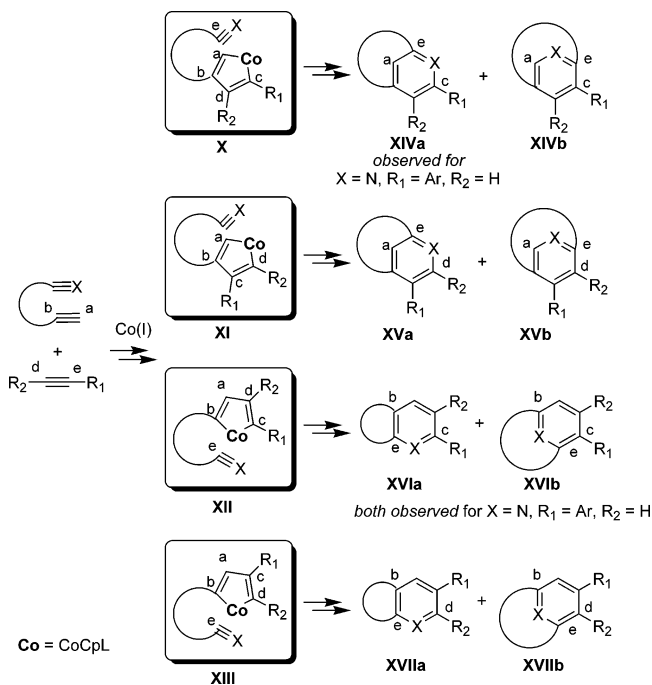
In the case of 1,17-diyne **3**, our DFT calculations indicate that α,α' -substituted cobaltacycle **I** is favored by only 0.5 kcal/mol over α,β -substituted cobaltacycle intermediate **II** but by 7.5 kcal/mol over β,β' -substituted cobaltacycle **III**. This result suggests that the cycloaddition of **3** would generally yield a mixture of regioisomeric products **IV/VII** and **V/VIII** in a ratio of approximately 1:1, as observed in the reaction of **3** with nitriles (Table 1, entry 2; Table 2, entries 1–8; Table 4, entries

- (51) Dimethyl 2,2-di(prop-2-ynyl)malonate and maleic anhydride gave no cycloadduct under these reaction conditions; mostly unreacted diyne was observed at the end of the reaction.
 (52) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, 1989.
 (53) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
 (54) *Jaguar 4.2*; Schrodinger, LLC: Portland, OR, 2002.
 (55) An issue of *Chem. Rev.* is devoted to computational transition-metal chemistry: (a) *Chem. Rev.* **2000**, *100*, 351–818. (b) Davidson, E. R. *Chem. Rev.* **2000**, *100*, 351–352. See also ref 19.

Scheme 5. Permutations for Cyclopentadiene Formation Leading to Regioisomeric Pyridinophanes and 2-Oxopyridinophanes (Co = CoCpL)**Scheme 6.** Nitrile/Isocyanate Addition to a Disubstituted Cobaltacycle (Co = CoCpL)

1 and 7; Table 5, entry 1) and an isocyanate (Table 6, entry 1). In the case of *1,15-diyne* **6**, cobaltacycle **I** is favored over cobaltacycle **II** by 1.4 kcal/mol and over cobaltacycle **III** by 3.6 kcal/mol. This result suggests that cycloaddition of **6** would generally yield a mixture of regioisomeric products **IV/VII** and **V/VIII** biased toward paracyclophanes **IV/VII**, as observed in the reactions of **6**, and its analogues **8** and **10**, with nitriles (Table 1, entries 1, 3, and 4; Table 3, entries 3–6; Table 4, entries 2, 5, and 6; Table 5, entries 2–5) and isocyanates (Table 6, entries 2, 5, 6, 9–16). This effect is evidently much more pronounced in the cycloadditions of *1,15-diyne* **8** with cyanamides (Table 5, entries 2 and 5) and isocyanates (Table 6, entries 5, 9–16) where the *para*-pyridinophane isomer (**IV/VII**) generally predominated. For *1,15-diyne* **8**, our DFT calculations indicate that cobaltacycle **I** is preferred over cobaltacycles **II** and **III** by 4.5 and 14.2 kcal/mol, respectively (cf. *1,15-diyne* **6**). With the more conformationally flexible diynes **1** and **13** (Table 1) the energy differences for intermediates **I–III** were less pronounced, as reflected in the products (Table 1, entries 5 and 6). Cobaltacycle **I** derived from *1,15-diyne* **1** was preferred over **II** by only 0.9 kcal/mol and over **III** by 6.2 kcal/mol (cf. *1,15-diyne* **6**). The shorter chain homologues **31** and **33** (Table 4) incur higher strain energies in the formation of cobaltacycles **I–III**, as evidenced from the low-to-nonexistent yields from their cyclizations (Tables 4 and 6, entries 3 and 4). In the case of *1,13-diyne* **31**, DFT calculations indicated that **I** is preferred over **II** and **III** by 0.6 and 4.4 kcal/mol; however, for *1,11-diyne* **33**, **III** was preferred over **II** and **I** by 5.8 and 8.8 kcal/mol, respectively.

In the addition of nitriles to cobaltacycle **II**, *meta*-pyridinophanes of form **Va**, rather than form **Vb**, were invariably obtained (Scheme 6). Of the two possible modes of nitrile addition, pathway **a** is strongly favored over pathway **b**,

Scheme 7. Cyclophanes from ω -Alkynyl Nitrile **28** (X = N) or α,ω -Diynes (X = CH) and External Alkynes

probably because of steric interactions that govern the direction of addition (as illustrated). In the addition of an isocyanate to cobaltacycle **II**, *meta*-pyridinophanes of form **VIIIb**, rather than form **VIIIa**, were obtained (e.g., Table 6, entries 1–3). Of the two possible modes of isocyanate insertion, pathway **d** is strongly favored over pathway **c**, perhaps because of an electronic effect associated with the isocyanate 1,3-dipole and the charge distribution at the α -carbons of the cobaltacycle. In any event, no steric aspect is apparent to explain this preference for pathway **d**.

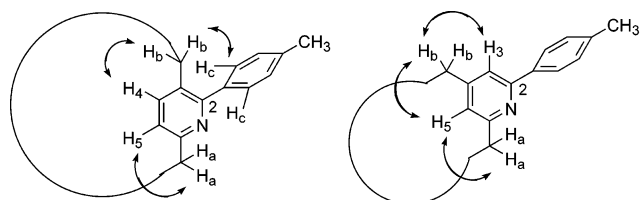
In the cyclotrimerization of a long-chain α,ω -alkynyl nitrile, such as **28**, with an alkyne there would be four possible cobaltacyclopentadiene intermediates, **X–XIII**, which would lead to eight possible products, **XIVa/b–XVIIa/b** (Scheme 7, X = N, $R_1 \neq R_2$). The cyclotrimerization of α,ω -alkynyl nitrile **28** with an aromatic alkyne (Scheme 4) provided three regioisomeric macrocycles in an even distribution: a 2,4,6-substituted *meta*-pyridinophane (**5m**, **20m**), a 2,3,6-substituted *meta*-

pyridinophane (**29m**, **30m**), and a 2,3,6-substituted pyridinophane (**29o**, **30o**). The three observed products, represented by **XIVa**, **XVIa**, and **XVIIb** ($X = N$, $R_1 = Ar$, $R_2 = H$), arise from the corresponding cobaltacycles, **X** and **XII** ($X = N$, $R_1 = Ar$, $R_2 = H$). The preference for intermediates **X** and **XII** relative to **XI** and **XIII** in this situation is presumably caused by stabilization that is imparted by the aromatic group being positioned α on the cobaltacycle. Then, the absence of **XVIIb** relates to a predilection for nitrile addition in cobaltacycle **X** head-to-head ($a-e$ bond formation) rather than head-to-tail ($c-e$ bond formation). The two products from nitrile addition in cobaltacycle **XII**, **XVIa** and **XVIIb**, arise from head-to-head ($b-e$ bond formation) and head-to-tail ($c-e$ bond formation) modes, respectively.

In the cyclotrimerization of a long-chain α,ω -bis-alkyne with an alkyne there would be up to seven possible cobaltacyclopentadiene intermediates from the pairwise oxidative addition of alkyne units: **I–III** (Scheme 5) and **X–XIII** (Scheme 7, $X = CR$, $R_1 \neq R_2$), which would lead to eight possible products, **XIVa/b–XVIIa/b** (Scheme 7, $X = CR$, $R_1 \neq R_2$). Our successful cyclotrimerization of symmetrical α,ω -diynes with an identically substituted alkyne ($R_1 = R_2$) provided three distinct types of macrocycles (Table 7). 1,15-Diyne **6** combined with dipropylacetylene under argon to give paracyclophane **57p** (Scheme 7; **XIVb/XVb**, $X = CH$, $R_1 = R_2 = Pr$) or under CO to give **57p** and benzannulene **57o** (**XVIa/XVIIa**, $X = CH$, $R_1 = R_2 = Pr$). With DMAD, 1,15-diyne **6** gave benzannulene **58o** under argon (**XVIa/XVIIa**, $X = CH$, $R_1 = R_2 = CO_2Me$) or **58o** and metacyclophane **58m** under CO (**XIVa/XVa/XVIIb/XVIIb**, $X = CH$, $R_1 = R_2 = CO_2Me$); 1,15-diyne **8** gave benzannulene **62** under argon (**XVIa/XVIIa**, $X = CH$, $R_1 = R_2 = CO_2Me$). It is also evident that the regiochemistry in the reaction of long-chain bis-alkynes with an alkyne can be influenced by the electronic nature of the monoalkyne, such as nonpolar vs polar substituents, to switch between paracyclophane, metacyclophane, and benzannulene products (Table 7, entries 1–4). The formation of side products **59** and **61** in the reactions of DMAD with **3** and **6** points to another possible mechanism other than those depicted in Scheme 5, such as a Diels–Alder-type cycloaddition. This pathway could be responsible in part for the formation of the benzannulenes. However, no cycloadducts were produced in a control experiment that probed possible Diels–Alder reactivity.⁵¹

We thought that a breakdown of the catalytic cycle (i.e., low turnover numbers) might be behind the low yields and prevalence of side products (viz. Scheme 3) in our all-alkyne cyclotrimerizations. An atmosphere of carbon monoxide, instead of argon, was explored in an attempt to enhance the catalytic cycle from this standpoint. Although the yields for the argon and carbon monoxide are not meaningfully different, the reaction products were surprisingly affected (Table 7). For example, the cyclotrimerization of **6** with 4-octyne gave **57p** under argon but **57o** and **57p** under carbon monoxide. At this time we do not have an adequate explanation for these observations.

We also wondered about the possibility of reversal of cobaltacyclobutadiene complexes as a source of active cobalt species in the cyclotrimerization and any effect that carbon monoxide might exert. In this regard, we found no evidence for the reactivity of a cobaltacyclobutadiene complex from two separate experiments. Diyne **3** failed to react with *p*-tolunitrile



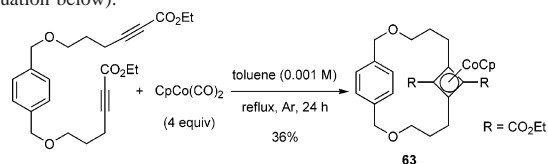
(a) 2,3,6-trisubstituted pyridinophane, *para* (b) 2,4,6-trisubstituted pyridinophane, *meta*

Figure 2. Observed NOEs for regioisomeric pyridine-containing macrocycles, e.g., **5p** (*para*) and **5m** (*meta*).

(5 mol equiv) in the presence of 15 mol % of complex **4** (viz. Scheme 2) in refluxing 1,4-dioxane over 4 days (CO atmosphere; unreacted **3** was recovered), and complex **63**^{18,56} failed to react with *p*-tolunitrile (5 mol equiv) in refluxing 1,4-dioxane over 3 days (CO or Ar atmosphere; unreacted **63** was recovered). Consistent with this point, Vollhardt found that harsh conditions, such as flash-vacuum pyrolysis ($\sim 10^{-5}$ Torr, 540–650 °C), are required for cobaltacyclobutadiene complexes to undergo retro-[2 + 2] cycloaddition.⁵⁷ Also, Gleiter demonstrated that higher temperatures, such as 140 °C (refluxing xylene) or 200 °C (without solvent), are needed for the cobaltacyclobutadiene complexes to undergo cyclotrimerization with nitriles.²⁰ Therefore, under our milder reaction protocol for cobalt-mediated alkyne cyclotrimerizations, any cobaltacyclobutadiene complexes that form should not revert into the reaction manifold.

Structural Assignments by NMR and X-ray Crystallography. Structures of the macrocycles were unambiguously assigned from one- and two-dimensional ¹H and ¹³C NMR experiments, such as COSY, NOESY, HMQC, and HMBC (see Supporting Information). The regioisomeric pyridinophanes were easily identified by ¹H NMR from the protons on the pyridine ring, which appears as a pair of singlets for the meta isomer and a pair of doublets for the para isomer ($J_{AB} \approx 8.0$ Hz) in the aromatic region (5–8 ppm). Regioisomers, such as **5m** and **5p**, were also identified from ¹H NOESY spectra, where the sets of benzylic protons, H_a and H_b , exhibited strong NOEs with the pyridine protons in a distinct pattern for each isomer (Figure 2). For **5p** an NOE was observed between the benzylic protons H_a and H_5 (doublet), while for **5m** an NOE was observed between the benzylic protons H_a and H_5 (singlet). The other set of benzylic protons, H_b , for **5p** has an NOE with H_4 (doublet) and the aromatic protons of the tolyl group, H_c . The benzylic protons H_b for **5m** have NOE's with the pyridine protons H_3 and H_5 (singlets). The HMBC experiment, optimized for ³ J_{HC} , was also used to confirm both structures. C_2 was easily identified by its chemical shift (158.8 ppm) and correlations with the H_c protons of the *p*-tolyl ring. Additional correlations for C_2 derive from a one-proton doublet integrating in the aromatic region

(56) Complex **63** was prepared by a modification of the literature method¹⁸ without the use of syringe-pump addition or high-intensity light (see equation below).



(57) This conversion presumably occurs via a retrocyclization, rotation, and ring-closure sequence. (a) Ville, G.; Vollhardt, K. P. C.; Winter, M. J. *J. Am. Chem. Soc.* **1981**, *103*, 5267–5269. (b) Fritch, J. R.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 9–11.

(58) See the Supporting Information for general experimental methods.

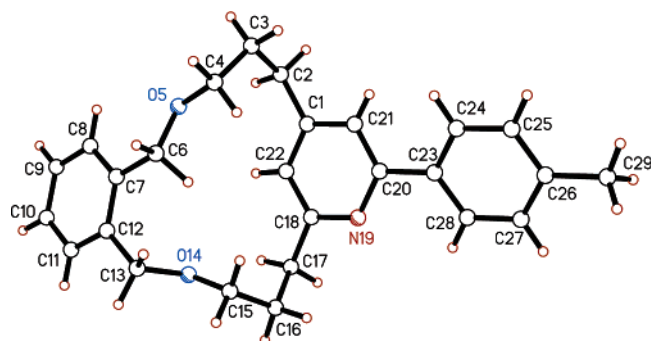
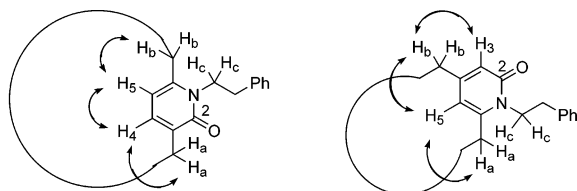


Figure 3. View of 15-membered *meta*-pyridinophane **7m** from the X-ray crystal structure showing the atom-labeling scheme.



(a) 3,6-disubstituted 2-oxopyridinophane, *para* (b) 4,6-disubstituted 2-oxopyridinophane, *meta*

Figure 4. Observed NOEs for regioisomeric 2-oxopyridine-containing macrocycles, e.g., **41p** (*para*) and **41m** (*meta*).

(H_4) and triplets integrating for two protons in the aliphatic region (H_b), which relate to three-bond J_{CH} couplings, consistent with a *para* substitution pattern. In contrast, regioisomer **5m** showed an additional two-bond J_{CH} coupling correlating a one-proton aromatic singlet (H_3) to C_2 , which is consistent with a *meta* substitution pattern. The structure of 17-membered *meta*-pyridinophane **7m** was confirmed by single-crystal X-ray diffraction (Figure 3).

Regioisomeric 2-oxopyridinophanes were identified from the 2-pyridone protons, which are observed as distinct pairs of singlet (in the *meta* isomer) and doublet resonances (for the *para* isomer, $J_{AB} = 5.5\text{--}7.0$ Hz) in the olefinic and aromatic regions in ^1H NMR spectra. NOESY data were also used to establish the structures of these regioisomers (Figure 4). The *para* isomer showed a one-proton doublet in the aromatic region (H_4 or H_5), which exhibited an NOE to a set of triplet in the aliphatic region (H_a or H_b). Another doublet aromatic proton showed an NOE with a different set of triplet aliphatic protons. On the contrary, the *meta* isomer showed a singlet aromatic proton (H_5) exhibiting an NOE with two sets of aliphatic triplet protons (H_a and H_b). Another singlet aromatic proton (H_3) indicated an NOE with only one of the two sets of aliphatic triplet protons (H_b). HMBC data were used to confirm the structures of the isomers. The C_2 carbonyl carbon was easily recognized by its chemical shift (163.5 ppm) and a three-bond J_{CH} correlation to the triplet aliphatic phenethyl protons (H_c). Three-bond J_{CH} correlations from a doublet aromatic proton (H_4) and a set of triplet aliphatic proton (H_a) to C_2 were observed in the *para* isomer. A two-bond J_{CH} correlation from the singlet aromatic proton (H_3) to C_2 was observed in the *meta* isomer. The structure of 16-membered 2-oxo-*para*-pyridinophane **44p** was confirmed by single-crystal X-ray diffraction, as previously described.⁴³

For the cyclophanes or benzannulenes the protons of the newly generated benzene rings were observed as a singlet (*ortho* and *para* isomers) or a pair of singlets (*meta* isomer) in the aromatic region in the ^1H NMR spectra. Similar trends as above

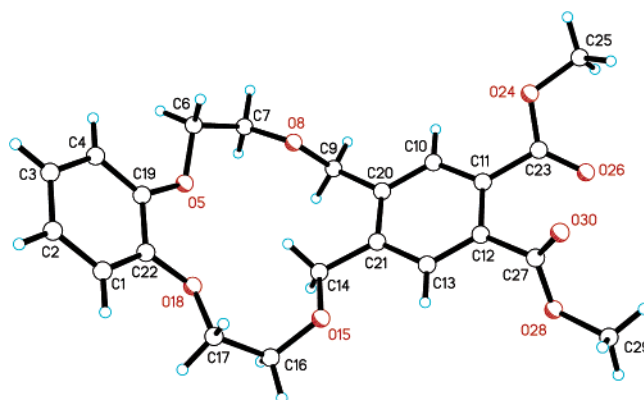


Figure 5. View of 14-membered benzannulene **62** from the X-ray crystal structure showing the atom-labeling scheme.

in the NOESY experiments were helpful in characterizing the regioisomers (see Supporting Information). The structure of a 14-membered benzannulene **62** was confirmed by single-crystal X-ray diffraction (Figure 5).

Conclusion

We developed the cobalt-mediated [2 + 2 + 2] cycloaddition of α,ω -diynes with nitriles, cyanamides, and isocyanates as a facile, flexible macrocyclization approach to *meta*- and *para*-pyridinophanes. We have also been able to effect the related co-cyclotrimerization of α,ω -diynes and alkynes, but this reaction type is much less general, with low efficiency and predictability. The regioselectivity of the pyridinophane reactions was impacted by the length and type of the tether as well as by stereoelectronic factors. The nitrile macrocyclizations could be achieved in an optimal concentration range of 2–50 mM, which is consistent with a balance of the requisite unimolecular and bimolecular processes. By producing a macrocycle and a pyridine ring simultaneously, the co-cyclotrimerization process affords substantial molecular complexity in a single step. In the area of metal-mediated [2 + 2 + 2] cycloadditions, it is particularly noteworthy to be able to incorporate an external nitrile or isocyanate in a *bimolecular process* under convenient reaction conditions.

Experimental Section⁵⁸

Procedure for the Synthesis of Pyridinophanes by Using Classical Reaction Conditions.²³ In a 50-mL round-bottom flask, equipped with a magnetic stirring bar and a condenser under argon, was added 25 mL of *o*-xylene. A 300-W slide projector lamp, connected to a Variac set at 30 V, was mounted 3 cm from the reaction flask. The solvent was purged with argon for 20 min and then heated in a 140 °C oil bath. With the aid of an automatic syringe pump, a solution of *o*-xylene (10 mL), diyne (**2** mmol), nitrile (1 mol equiv), and $\text{CpCo}(\text{CO})_2$ (0.15 mol equiv) was added into the solvent over 100 h using a gastight syringe wrapped in aluminum foil. The black mixture was then cooled to room temperature. Subsequent removal of the solvents in vacuo, followed by MPLC (0–40% ethyl acetate in hexanes), afforded the *meta* and *para* regioisomeric products. In the case of the synthesis of **7m** and **7p**, diyne **6** (500 mg, 1.85 mmol, 1 mol equiv), *p*-tolunitrile (217 mg, 1.85 mmol, 1 mol equiv), and $\text{CpCo}(\text{CO})_2$ (50 mg, 0.28 mmol, 15 mol %) in 9 mL of *o*-xylene were added into the reaction flask over 100 h. Purification by MPLC afforded 72 mg of *meta*-pyridinophane **7m** (10%) and 366 mg of the *para*-pyridinophane **7p** (51%). Note: A similar procedure was followed in the cyclotrimerization of ω -alkynyl nitriles with the aromatic alkynes.

Improved Procedure for the Synthesis of Pyridinophanes. Into a 100-mL round-bottom flask, equipped with a condenser and a three-way stopper connected to an argon-filled balloon, a mixture of diyne **6** (100 mg, 0.37 mmol) and *p*-tolunitrile (246 mg, 2.10 mmol, 5.7 mol equiv) was pumped briefly and the vessel purged three times with argon. 1,4-Dioxane (50 mL) was added, followed by 10 mL of a 1,4-dioxane solution of CpCo(CO)₂ (7.0 μL, 0.056 mmol, 15 mol %), and the remaining solvent (19 mL) to provide a final concentration of 0.005 M (relative to diyne **6**). The resulting solution was heated at reflux for ca. 24 h, and the light-brown mixture was cooled to room temperature. Subsequent removal of the solvents in vacuo, followed by flash chromatography (silica gel; ethyl acetate/hexanes, 1:10, followed by ethyl acetate/hexanes, 1:4), afforded 16 mg of *meta*-pyridinophane **7m** (11%) and 109 mg of the *para*-pyridinophane **7p** (76%). For best results, newly opened bottles of DME, 1,4-dioxane, and CpCo(CO)₂ (Strem Chemicals) were used. A similar procedure was followed in the cycloadditions of α,ω -diynes or short-tethered diynes with cyanamides,³⁶ isocyanates,⁴³ and alkynes.

The following compounds were synthesized and fully characterized in our previous reports: **1**, **3**, **4**, **5m**, **5p**, **6**, **7m**, **7p**, **10**, **11m**, **11p**, **12m**, **12p**, **15**, **16m**, **16p**, **28** (ref 23); **41m**, **41p**, **42m**, **42p**, **44**, **45**, **46**,

47m, **47p**, **48–55** (ref 43); **8**, **35m**, **35p**, **36p** (ref 36); **63** (ref 18). Additional experimental details and compound characterization data are presented in the Supporting Information.

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Supporting Information Available: Data for the cyclotrimerization of dimethyl 2,2-di(prop-2-ynyl)malonate and 4-ocytene; characterization data for the compounds described in refs 32, 35, and 50 and for **9m**, **9p**, **21m**, **21p**, **24m**, **24p**, **25m**, **25p**, **27**, **29m**, **29o**, **30o**, **31**, **32m**, **32p**, **33**, **37**, **38p**, **39m**, **39p**, **43p**, **57o**, **57p**, **58m**, **58o**, **59**, **60**, **61**, and **62**; 2-D NMR experiments on **58m** and **58o**; X-ray crystallographic details for macrocycles **7m** and **62**; ¹H NMR spectra of **ii**, **iii**, **9m**, **9p**, **21m**, **21p**, **29m**, **29o**, **30o**, **32m**, **32p**, **37p**, **38p**, **39m**, **39p**, **43p**, **57o**, **57p**, **58m**, **58o**, **59**, **60**, **61**, and **62**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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