Pyridine-containing macrocycles via cobalt-mediated [2 + 2 + 2] cycloadditions of α,ω-bis-alkynes

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Dedicated to Prof. Madeleine M. Joullié on the occasion of her 80th birthday

Abstract

We have been investigating the formation of macrocycles from α,ω-diynes in Co(I)-mediated co-cyclotrimerization reactions. In these metal-mediated [2 + 2 + 2] cycloadditions, long-chain α,ω-diynes were reacted with nitriles, cyanamides, or isocyanates in the presence of $CpCo(CO)_2$ (Cp = cyclopentadienide) to yield pyridine-containing macrocycles, in the form of *meta*- and *para*-pyridinophanes (e.g., **5m**/**5p**, **35m**/**35p**, **41m**/**41p**). The regioselectivity of these reactions was influenced by the length and type of linker unit between the alkyne groups, as well as by stereoelectronic factors. We developed an improved reaction protocol for these Co(I)-promoted [2 + 2 + 2] cycloadditions that 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 ca. 100 °C in 24 h, without photo-irradiation or syringe-pump addition. With this improved protocol, we were able to co-cyclotrimerize long-chain α,ω-diynes with alkynes in certain cases to effect a macrocyclic variant of the Vollhardt reaction (e.g., **6** + Pr-C≡C-Pr → **56p**). We used our improved [2 + 2 + 2] cycloaddition method to synthesize some macrocyclic bis-indolemaleimides as potential protein kinase inhibitors. Thus, we prepared "multiheterophanes" **63p**, **63m**, and **64p** and determined that they are potent, selective inhibitors of glycogen synthase kinase-3β (GSK-3β).

Keywords: Cycloaddition, pyridine, cobalt catalysis, Vollhardt reaction, macrocycle, protein kinase inhibitors

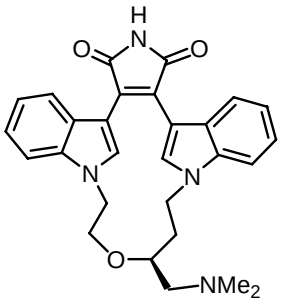
Contents

1. Introduction

Heterocycles. ♦ What are they good for? ♦ As any red-blooded medicinal chemist can tell you, a molecule that lacks a heterocyclic structure, of one kind or another, is unlikely to possess worthwhile biological activity. Indeed, heterocycles are commonly part and parcel of most medicinally important agents. Thus, it can well be appreciated why the thoughts and dreams of medicinal chemists tend to wander the alleys and byways of heterocyclic chemistry to find the next great drug candidate. ♦ We, too, share that obsession.

1.1. Macrocyclic heterocycles

Macrocyclic compounds, including a wide range of heterocyclic derivatives, have attracted much interest from synthetic and medicinal chemists. Various macrocycles are important in host–guest chemistry,[1] have noteworthy biological activities, or are integral to intriguing natural substances. Examples of biologically active macrocycles are macrolide antibiotics,[2] protease inhibitors,[3] and taxanes.[4] Also, there are certain inhibitors of protein kinases that possess a macrocyclic motif, such as bis-indolemaleimide **1** (ruboxistaurin; LY-333351), which is related to the natural product staurosporin (**2**). Ruboxistaurin is a selective inhibitor of protein kinase C-β (PKC-β) with a reported IC_{50} of 5 nM.[5] Our interest in novel inhibitors of protein kinases,[6] such as macrocycles related to **1**,[6a] led us to explore the construction of compounds of general type **3**, with aryl/heteroaryl subunits A *or* B, by using a synthetic route that could form the macrocycle and the accompanying smaller ring simultaneously. These compounds retain the critical pharmacophore for key interactions within the kinase ATP binding pocket, while allowing modification of the variable molecular components. Thus, we developed reasonably serviceable methods for the synthesis of pyridine-containing macrocycles,[7] as discussed herein.



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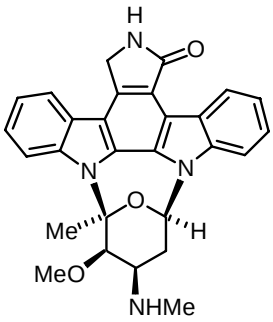

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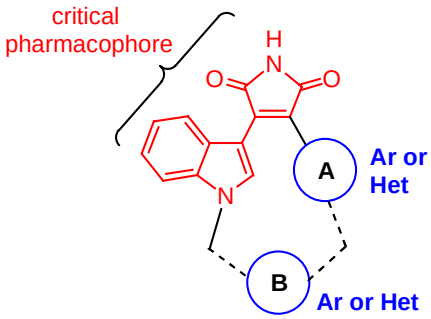
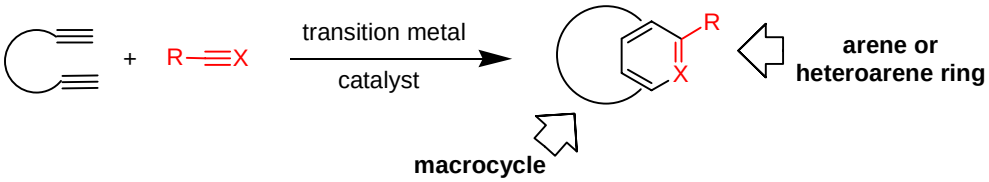


Novel Kinase Inhibitors, **3**

1.2. Macrocycle synthesis and transition metals

To conduct macrocyclizations in with good yields, it is often necessary to employ special reaction conditions, such as high dilution, template control, and/or conformational control.[8] 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.[8,9] Our desire for the simultaneous generation of a large ring and a smaller ring, thereby providing considerable molecular complexity in one step, would be more challenging.

Transition metal-based reactions are appealing for macrocyclization. The metal center can serve to organize the reactive groups and lower the activation free energy of the entropically disfavored end-to-end cyclization of long-chain α,ω-bifunctionalized substrates. Indeed, there are numerous transition metal-mediated carbocyclizations for forming small- and medium-size rings.[10] Macrocyclizations have been effected with high yields for ruthenium- and molybdenum-catalyzed ring-closing metathesis (RCM) reactions of bis-alkenes and bis-alkynes.[11,12] 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 been reported, such as intramolecular addition of rhodium carbenes,[13] palladium-catalyzed coupling of enynes with alkynes,[14] and cycloaddition of Fischer chromium carbenes with alkynes.[15] Macrocyclizations via the Heck reaction are also noteworthy.[16] Although such methods deliver macrocycles in a single step, with a significant increase in molecular complexity, they all are *unimolecular* in nature, which inherently limits product diversity. Additionally, this intramolecularity is a key source of success. We desired to perform a *bimolecular* macrocyclization process,[17] which can offer a wider range of product diversity. Our interest was directed to 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."[18,19] However, there is a paradox for successful execution. Whereas macrocyclization would require high-dilution conditions (e.g., 0.005 M) for optimal results, the concurrent bimolecular reaction would require higher concentrations.[20] These two competing factors must be adequately balanced to attain the desired objective.



Scheme 1. General Concept of the Macrocyclization Method.

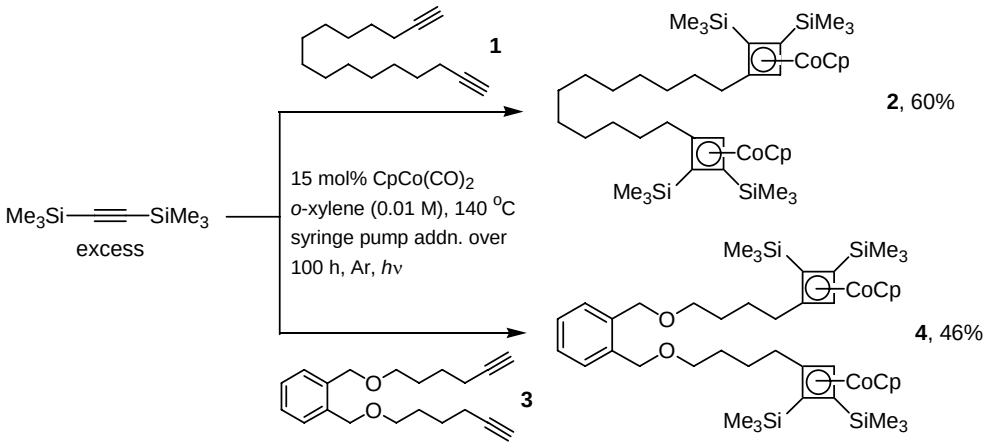
In this Account, we review our research work on the cobalt-catalyzed [2 + 2 + 2] cycloaddition of α,ω-diynes with a third reactive group, including nitriles, cyanamides, isocyanates, and alkynes. This discussion includes, to some extent, scope and limitations in terms of substrates, conditions, and regiochemistry. This chemistry can provide efficient syntheses of macrocycles containing pyridine, 2-aminopyridine, or 2-oxopyridine units, in the form of *meta*- and *para*-pyridinophanes, with the ability to achieve isolated yields of >50%.

2. Cycloaddition between diynes and alkynes: preliminary studies

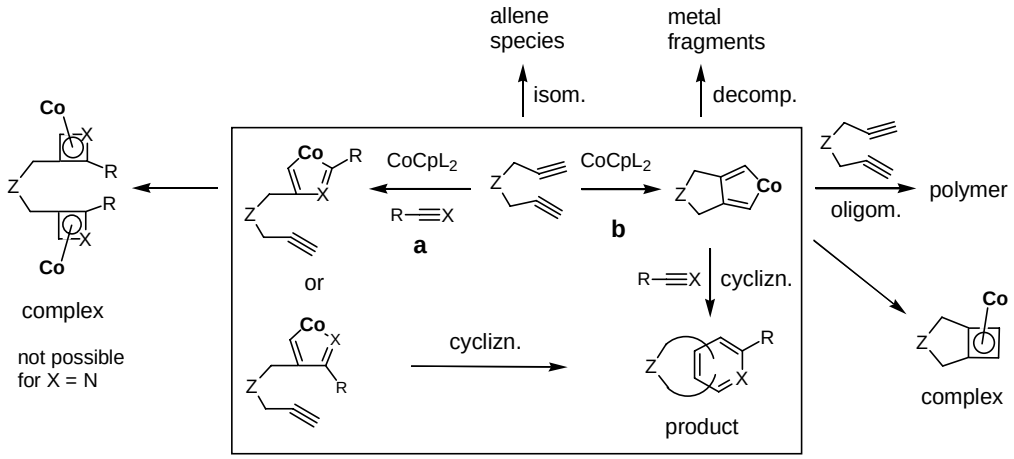
We initially investigated the synthesis of macrocycles by co-cyclotrimerization of α,ω-diynes and an external alkyne with virtually no success.[7a,d] For instance, in the reactions of bis-alkynes **1** or **3** with bis(trimethylsilyl)acetylene (BTMSA),[18a–c] which does not self-trimerize, the hoped-for 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)[18] and long-chain bis-alkynes.[21] Virtually no macrocyclic [2 + 2 + 2] adducts were obtained in the study by Brisbois et al.[21] Examples of macrocycle formation via metal-mediated alkyne cyclotrimerization are quite uncommon, and the successful cases have only been intramolecular reactions, where all three alkyne groups are tethered to the same molecular backbone.[19a–c]

One can appreciate these negative results in the synthesis of macrocycles by considering the mechanism of the cobalt-mediated alkyne cyclotrimerization (Scheme 3, X = CR').[22] The formation of arene adducts could be achieved via two main pathways, **a** and **b**, depending on which alkyne moieties undergo oxidative addition to generate the cobaltacyclopentadiene intermediates. Incorporation of the alkyne via a cycloaddition process,[22b] 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. Our isolation of bis-η^4-cyclobutadiene-cobalt complexes indicates that, when insertion of another alkyne molecule is sluggish, a formal [2 + 2] cycloaddition occurs preferentially (via pathway **a**). Consequently, the catalytically active cobalt species become bound into unreactive η^4-

cyclobutadiene-cobalt complexes.[18,21,23] To overcome this problem, we elected to use a different triply-bonded species, one with X ≠ CR', which is unlikely to coordinate with a reactive Co(I) species. A nitrile reactant (X = N) seemed like a promising candidate,[24] 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**.[25]



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



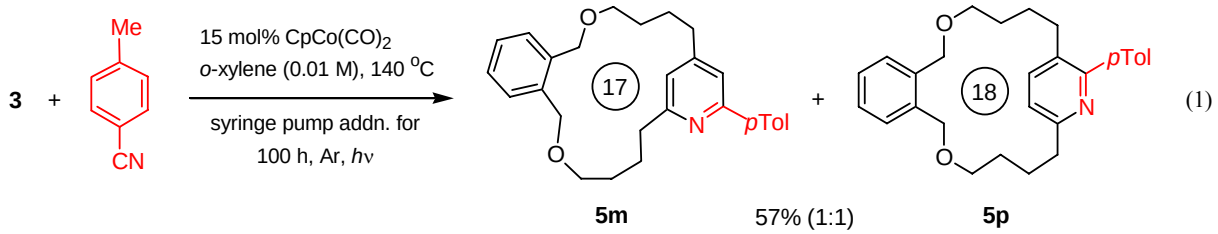
Scheme 3. Generalized Mechanism for "CpCo"–Mediated Cyclotrimerization of α,ω-Diynes with Alkynes (X = CR') or Nitriles (X = N). For X = C-R' or N; pathway **a** is not feasible for X = N; **Co** = CoCp; L = CO, PR_3, or olefin.

3. Cycloaddition between diynes and nitriles

3.1. Initial reaction conditions[7a,d]

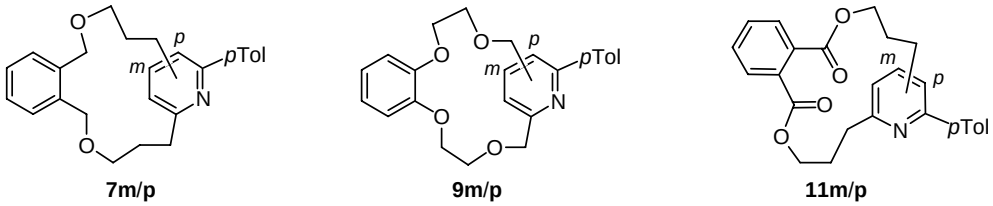
Remarkably, the reaction of bis-alkyne **3** with *p*-tolunitrile (1 mol equiv) provided a 57% isolated yield of two pyridine-containing macrocycles, **5m** and **5p**, in a 1:1 ratio (eq 1).[26]

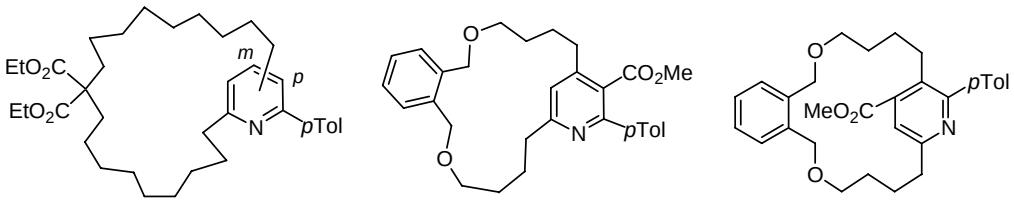
Pyridinophanes **5m** and **5p** differ in their substitution pattern for the pyridine units, i.e., 2,4,6- (*meta*-) and 2,3,6- (*para*-) trisubstituted pyridines, respectively. Since the regiochemistry obtained here is fairly similar to that observed in the analogous acyclic reaction (2,4,6:2,3,6 = ca. 2:1),[24f] there are probably no special forces influencing the overall chemical pathway. This chemistry affords substantial molecular complexity in a single step, with excellent atom-economy.[27]



(1)

We explored the scope and limitations of this macrocyclization method, such as variation of the α,ω-diyne substrates with respect to length and substitution of the tether, and the electronic nature of alkynes. Moderate to good yields of *meta*- and *para*-pyridinophanes with ring sizes ranging from 15 to 23 were obtained from the cyclotrimerization of various α,ω-bis-alkynes with *p*-tolunitrile (Table 1). 1,15-Bis-alkynes appended to the *ortho* positions of a benzene ring, with ether (entry 1), bis-ether (entry 3), 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 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 on the formation of 22- and 23-membered macrocycles (entry 6).

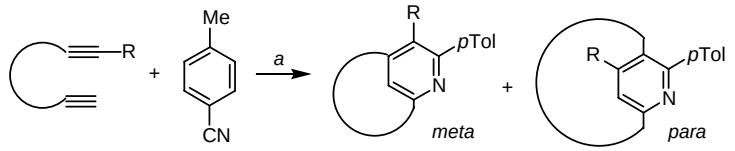


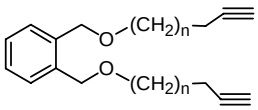
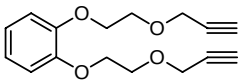
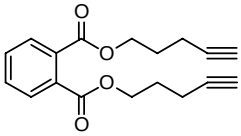
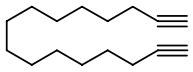
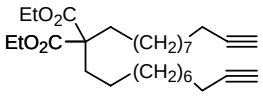
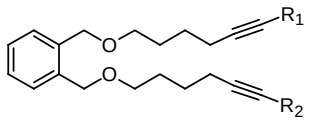


The potential for one-step formation of a highly substituted pyridine brought us to investigate alkyne substitution. Macrocycles bearing tetrasubstituted pyridine units were formed from *p*-tolunitrile and diyne **15**, which bears an ester substituent (entry 7). Silyl-substituted pyridines would be attractive targets;[18d,28] 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).

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



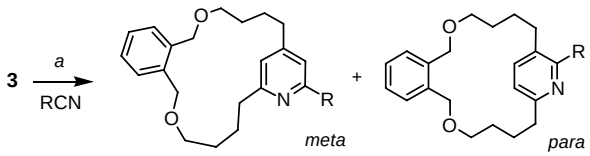
entry[b]	α,ω-diyne substrate		products	% yield (*meta*:*para*)[c]
1		n = 2 (**6**)	**7m**, **7p**	61 (1:5)
2		n = 3 (**3**)	**5m**, **5p**	57 (1:1)
3		**8**	**9m**, **9p**	55 (1:5)
4		**10**	**11m**, **11p**	34 (1:7)
5		**1**	**12m**, **12p**	42 (1:1)
6		**13**	**14m**, **14p**	49 (3:4)
				
7	**15**, R_1= H, R_2 = CO_2Me		**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_2Me		--	--

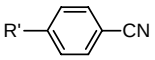
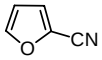
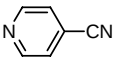
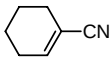
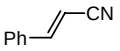
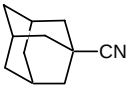
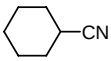
[a]Conditions molar ratio of nitrile: diyne, 1:1; 15 mol % $CpCo(CO)_2$, *o*-xylene (0.01 M), 140 °C, syringe-pump addition, 100 h, Ar atmosphere, *hv*. [b]Entries 1-6, R = H; entry 7, R = R_2 = CO_2Me. [c]Ratios determined from isolated isomeric products.

Various nitrile partners with different substituents were surveyed to assess reactivity. In general, nitriles conjugated with an arene, heteroarene, or alkene 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 exerted a minor influence on yield, although

an electron-withdrawing substituent favored 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). On the other hand, 1-cyanoadamantane gave a yield of 11% (entry 9), with the macrocylic 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 Nitriles



entry	nitrile	products	% yield (*meta*:*para*)[b]
			
1	R' = Me	**5m**, **5p**	57 (1:1)
2	R' = OMe	**20m**, **20p**	38 (1:1)
3	R' = Br	**21m**, **21p**	35 (1:1)
4	R' = CO_2Me	**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	*n*-$C_5H_{11}CN$	–	trace
12	*t*-$BuMe_2SiCN$	–	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.

Structures of the macrocycles were unambiguously assigned from one- and two-dimensional ^{1}H and ^{13}C NMR experiments, such as COSY, NOESY, HMQC, and HMBC methodology. The regioisomeric pyridinophanes were easily identified by ^{1}H NMR from the protons on the pyridine ring, which appear as a pair of singlets for the *meta* isomer and a pair of doublets for the *para* isomer (J_{AB} ~8.0 Hz) in the aromatic region (5–8 ppm). Regioisomers, such as **5m** and **5p**, were also identified by ^{1}H 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.[7d] An HMBC experiment, optimized for $^{3}J_{HC}$, was also used to confirm structures **5m** and **5p**.[7d] The structure of 17-membered *meta*-pyridinophane **7m** was confirmed by single-crystal X-ray diffraction (Figure 1).

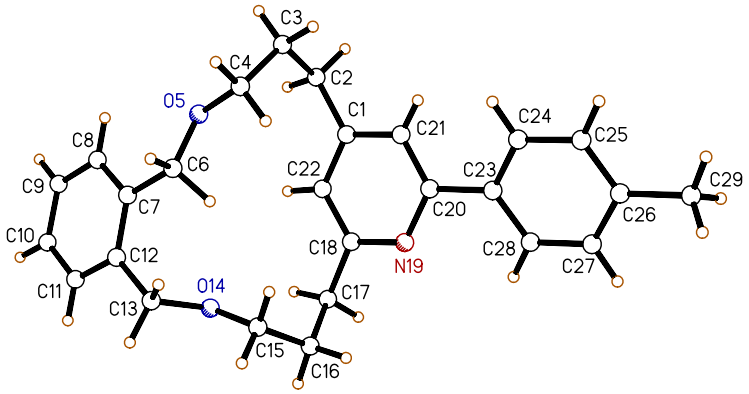
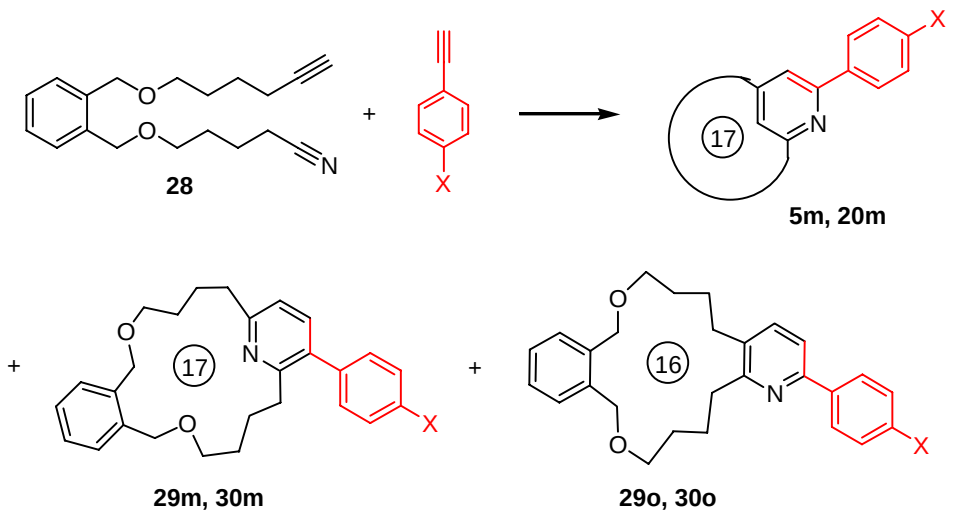


Figure 1. View of 15-membered *meta*-pyridinophane **7m** from the X-ray crystal structure.

A complementary cyclization strategy could involve the reaction of ω-alkynyl nitriles with alkynes,[24a,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, **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 rather nonselective, it offers access to other isomeric products that are not obtainable from the α,ω-diyne/nitrile cycloaddition.



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

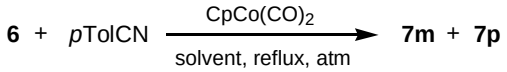
3.2. Second-generation reaction conditions

The reaction conditions that we employed were adopted from the standard cobalt-catalyzed alkyne trimerization protocol.[18] To generate the macrocyclic products with reasonable yields, we also relied on the high-dilution technique of syringe-pump addition.[8,20] However, this operation is inconvenient and cumbersome, especially if one wants to generate chemical libraries. Thus, we sought to develop an improved procedure for macrocycle formation via $CpCo(CO)_2$-catalyzed cyclotrimerizations of diynes and nitriles. 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 (with or without additional catalyst).[18] To minimize the unproductive oligomerization of reactants,[8,20] the 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 to promote decarbonylation of the cobalt catalyst and release the reactive cobalt species.[18,29] Although this classical method served as the basis for our early work, we now wanted to eliminate the syringe pump and high-intensity light, and reduce the 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 employed ether-type solvents and a CO atmosphere (Table 3). This approach emanated from our 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 achieved in reactions conducted in 1,2-dimethoxyethane (DME) or 1,4-dioxane (entries 3–6), with the latter delivering a yield as high as 87% (entry 6). The effect of a CO atmosphere was relatively minor.

Table 3. Optimization of Macrocyclization Conditions[α]



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)

[α]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]2.3 mol equiv of $CpCo(CO)_2$, reflux, 43 h. [d]49% recovered **6**.

The bimolecular macrocyclization process is associated with an intrinsic paradox in that it simultaneously requires high dilution to favor macrocyclization and sufficient concentration to favor a bimolecular reaction. In this way, the *intermolecular* [2 + 2 + 2] cycloaddition differs inherently from successful metal-mediated *intramolecular* macrocyclizations.[11–14] Thus, it is understandable why the Vollhardt reaction would be problematic for generating medium- and large-size rings.[18,21] To examine this issue, 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 2). The yield of product was found to be highly dependent on concentration in the range of 0.0005–0.1 M,[31] and an optimal yield occurred at a concentration in the vicinity of 0.005 M. Thus, there is a favorable zone of operation from 0.002–0.05 M, which is consistent with the fundamental point that while fairly high dilution can favor macrocyclization, this factor cannot be taken to an extreme without harming the required bimolecular process. 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) gave just 6% yield of a dimer of **6** and 62% of unreacted **6**. Given these results, an optimal concentration range for our macrocyclization method would be 0.002–0.05 M.

We employed our improved reaction conditions to assess scope and limitations (Table 4). Cycloaddition of *p*-tolunitrile with diynes of different tether lengths (n = 1–4) indicated that

cyclizations to form smaller medium-sized rings are not effective (entries 1–4), presumably due to an increase in strain. 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). A similar result was observed in the reaction of **3** with a cyanosilane (entry 10, cf. Table 2, entry 12). At this point, we developed a method for the Co(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 protocol[7a,d] and has a reasonable scope for synthetic applications.

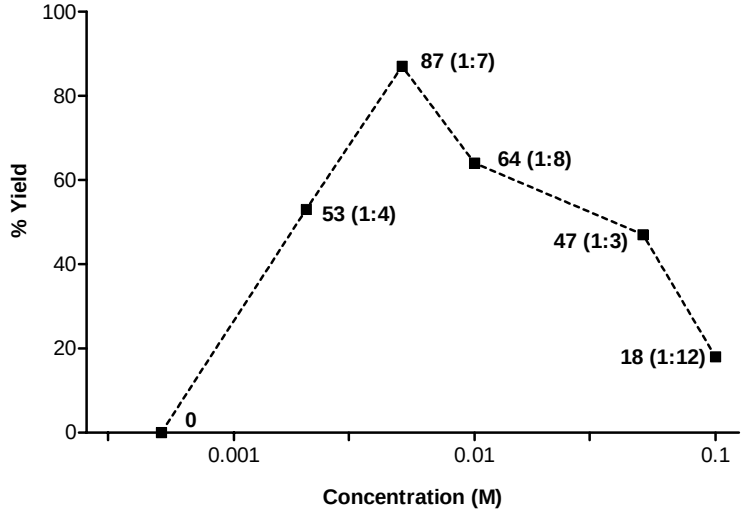


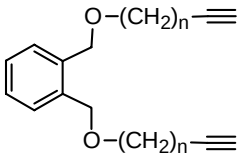
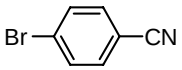
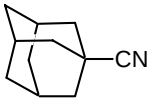
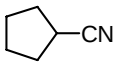
Figure 2. Reaction efficiency (% yield) vs concentration (0.0005, 0.002, 0.005, 0.01, 0.05, 0.1 M) for the cobalt-mediated cycloaddition of diyne **6** with *p*-tolunitrile. The regioisomer ratio is for **7m**:**7p**. Unreacted **6** was recovered in 17% and 23% yields from the reactions conducted at 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).

3.3. Cycloaddition involving cyanamides

Given this procedural advance, we became interested in extending the chemical scope, especially by using cyanamides as reactants to obtain aminopyridines. Our examination of the literature indicated an absence of published information on this aspect.[7c] Bönnemann and coworkers

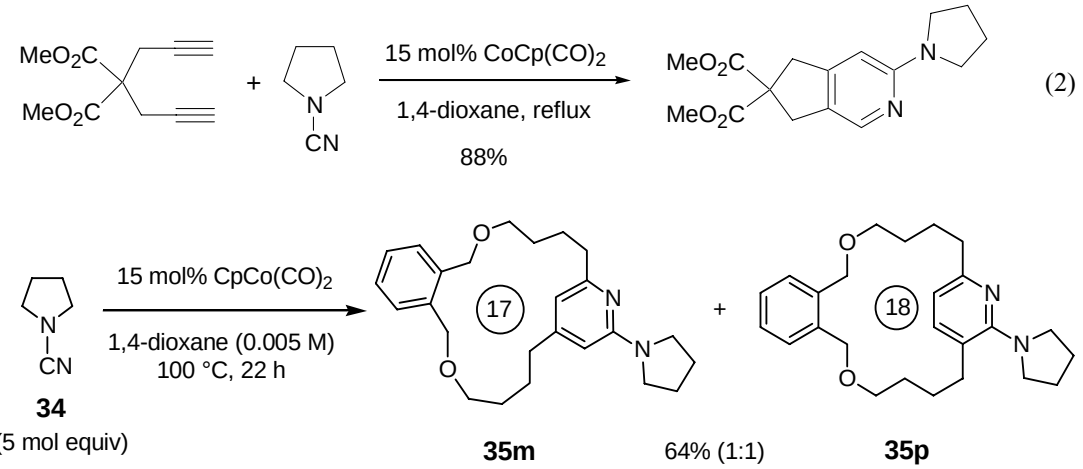
reported the reaction of acetylene with cyanamide in the presence of a η^6-borinato cobalt catalyst;[32] Heller and coworkers reported photo-induced cyclotrimerizations of acetylene with *N*-cyanopyrrolidine or *N*-cyanopiperidine the presence of $CpCo(cod)_2$ (cod = 1,5-cyclooctadiene);[33] an example of this reaction was also mentioned briefly in a patent.[34] We investigated the co-cyclotrimerization of bis-alkynes with cyanamides catalyzed by $CpCo(CO)_2$ under moderate thermal conditions (at ca. 100 °C, without photo-activation) to give annulated aminopyridines or *meta*- and *para*-aminopyridinophanes with good yields (70–90%).

Table 4. Cyclotrimerization of α,ω-Diynes with Nitriles using Improved Conditions[α]

entry	α,ω-diyne substrate	nitrile	products	% yield (*meta*:*para*)[b]
1	 n = 4, **3**	*p*TolCN	**5m**, **5p**	58 (1:1)
2	n = 3, **6**	*p*TolCN	**7m**, **7p**	87 (1:7)
3	n = 2, **31**	*p*TolCN	**32m**, **32p**	4 (1:1)
4	n = 1, **33**	*p*TolCN	--	0
5	**8**	*p*TolCN	**9m**, **9p**	80 (1:7)
6	**10**	*p*TolCN	**11m**, **11p**	30 (1:4)
7	**3**		**21m**, **21p**[c]	25 (1:1)
8	**3**		**27**[c]	9 (>50:1)
9	**3**		--	0
10	**3**	Me_3Si—CN	--	0

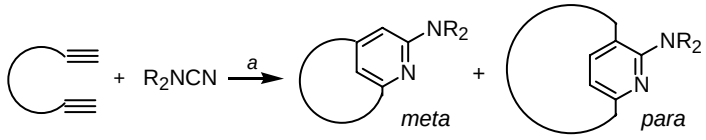
[α]Conditions: molar ratio of nitrile: diyne, ca. 5:1; 15 mol % $CpCo(CO)_2$, 1,4-dioxane (0.005 M), reflux, ca. 24 h. [b]Ratios determined from isolated isomeric products. [c]See Table 2.

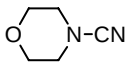
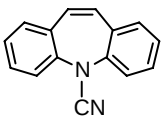
Initially, we used *N*-cyanopyrrolidine and dimethyl 1,5-pentadiyne-3,3-dicarboxylate as a test case under our improved reaction conditions, and there was smooth co-cyclotrimerization to give the annulated aminopyridine 88% yield (eq 2).[7c] We then conducted a brief survey of reactions of *N*-cyanopyrrolidine with several bis-alkynes, probing length and substitution of the tether, and substitution of the alkyne units (Table 1).[7c] The $CpCo(CO)_2$-catalyzed co-cyclotrimerization of long-chain α,ω-bis-alkynes with cyanamides produced amino-substituted pyridinophanes (Table 5; eq 3).[35] Diyne **3** and *N*-cyanopyrrolidine (**34**) gave regioisomeric pyrrolidine-substituted pyridinophanes **35m** and **35p** (1:1 ratio) in 64% yield (eq 2; Table 5).



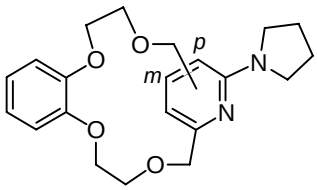
Other reactions of diynes and cyanamides afforded *meta*- and *para*-pyridinophanes in good-to-excellent yields under fairly mild reaction conditions (Table 5, entries 2–5). Cyclotrimerization of 1,15-bis-alkynes **6**, **8**, and **10** with cyanamides yielded almost exclusively the 16-membered *para*-pyridinophanes **36p**, **37p**, and **38p** (entries 2–4). 1,17-Bis-alkyne **3** gave a mixture (1:1) of the 17-membered *meta*- and 18-membered *para*-pyridinophanes **35m**/**p** in good yields (entry 1). The tricyclic cyanamide dibenz[*b*,*f*]azepine-5-carbonitrile reacted with diyne **8** to furnish a 1:6 mixture of **39m** and **39p** in a remarkable 80% yield (entry 5). Thus, 2-aminopyridinophanes can be conveniently formed in one step through this [2 + 2 + 2]-based macrocyclization process.

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

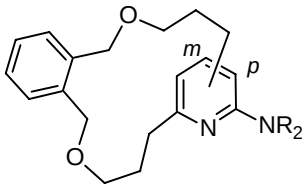


entry	α,ω-diyne	cyanamide	products	% yield (*meta*:*para*)[b]
1	**3**	**34**	**35m**, **35p**	64 (1:1)
2	**8**	**34**	**36p**	50 (<1:50)
3	**6**		**37p**	54 (<1:50)
4	**10**	Me_2N-CN	**38p**	32 (<1:50)
5	**8**		**39m**, **39p**	80 (1:6)

[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.

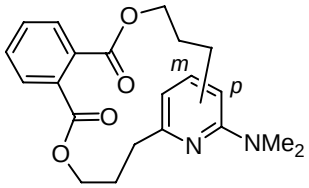


36m/p



37m/p NR_2 = 1-morpholino

39m/p NR_2 = 5-dibenzazepino



38m/p

4. Cycloaddition between diynes and isocyanates[7b,d]

We became interested in the [2 + 2 + 2] cycloaddition of α,ω-diynes and heterocumulenes using our improved procedure.[7b,36] Reaction of diyne **3** with 2-phenylethylisocyanate (**40**) using 30 mol % of $CpCo(CO)_2$ afforded a mixture of 2-oxopyridinophanes **41m** and **41p** in 68% yield (eq 4). 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. This result is remarkable considering prior 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, *hv*, syringe pump, 3–5 h).[36a,37] To explore the scope of this reaction, several symmetrical acyclic α,ω-diynes were reacted with alkyl isocyanate **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. 1,17-Diyne **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.

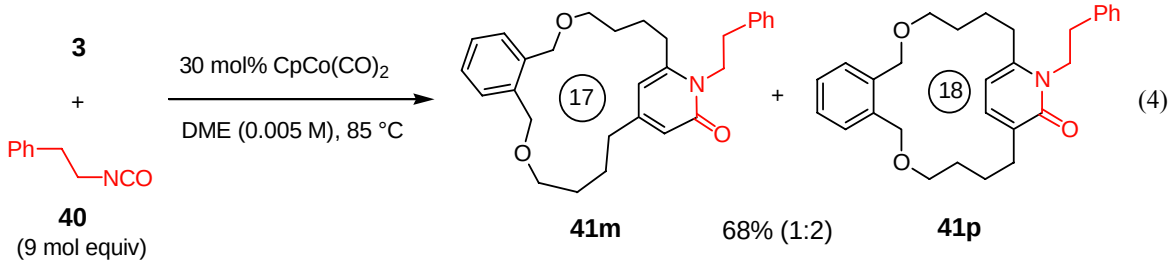
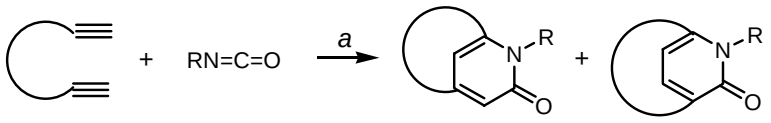
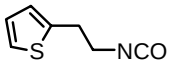
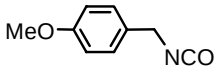
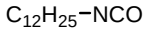
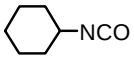
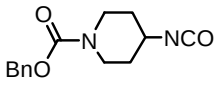
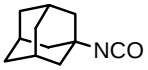
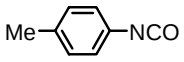
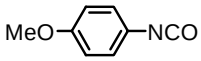
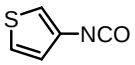


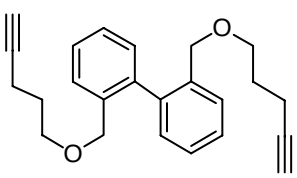
Table 6. 2-Oxopyridinophanes from α,ω-Diynes and Isocyanates



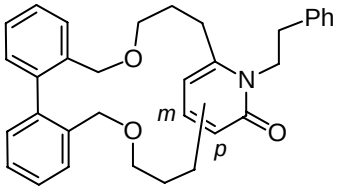
meta *para*

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**		**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.



46



47m/p

The reaction 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.[36a] 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 significant since *tert*-butylisocyanate failed to react with diethyl 2,2-di(prop-2-ynyl)malonate under Ru(II) catalysis.[37a] 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 cyclotrimerization with the aromatic isocyanates (entries 15–17) may be due to some self-condensation of the isocyanate to yield a symmetrical urea.[38] In the reaction of **8** with 4-methoxybenzylisocyanate, *N*,*N*'-bis(4-methoxybenzyl)urea was formed 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.[37a]

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} = 5.5–7.0 Hz) in the olefinic and aromatic regions in ^{1}H NMR spectra.[7b] NOESY data were also used to establish the structures of these regioisomers.[7b,d] HMBC data were also used to confirm structures of the isomers.[7b,d] The structure of 16-membered 2-oxo-*para*-pyridinophane **44p** was confirmed by single-crystal X-ray diffraction (Figure 3).[7b]

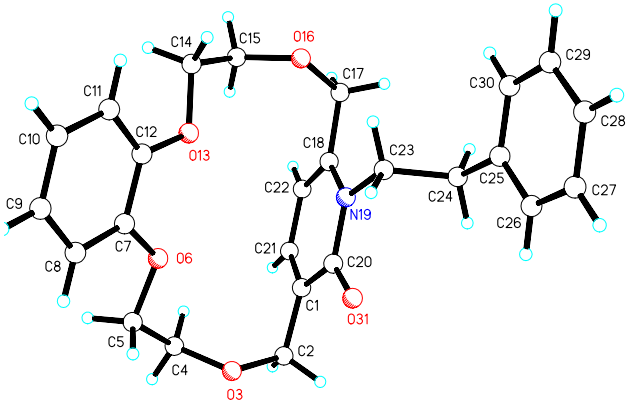


Figure 3. View of 16-membered 2-oxo-*para*-pyridinophane **44p** from the X-ray structure.

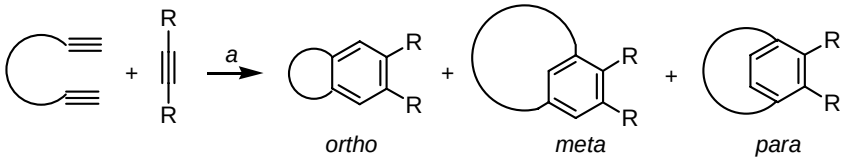
To expand on the product diversity, we attempted reactions with other heterocumulenes such as isothiocyanates and carbodiimides.[36c,d] In the presence of a catalytic amount of $CpCo(CO)_2$, the reaction of diyne **6** with *p*-tolylisothiocyanate or cyclohexylisothiocyanate did not yield the desired 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 Cp_2Co-catalyzed cycloadditions of diynes **8** or dimethyl 2,2-di(prop-2-ynyl)malonate with 1,3-di-(*p*-tolyl)carbodiimide.[36d]

5. Cycloaddition between diynes and alkynes: revisited[7d]

Given positive results for cyclotrimerizations of α,ω-diynes with nitriles and with isocyanates to yield macrocycles, under convenient conditions, we were encouraged to reevaluate the corresponding reaction with alkynes ("Vollhardt reaction"). In our hands and in the hands of others,[7a,21] transition metal-mediated cyclotrimerizations of alkynes for macrocycle production have not yielded positive results.[39] A study of reactions of short-chain diynes and alkynes under our improved reaction conditions 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 there was a complex mixture of unidentified products. A similar result was noted for the reaction of 1,15-diyne **6** and BTMSA (5 mol equiv; Ar atmosphere). Also, diyne **6** did not give any macrocyclic products in reactions with (trimethylsilyl)acetylene, 2-ethynylpyridine, 1-ethynylcyclohexene, but-1-ynylcyclohexane, trimethyl(phenylethynyl)silane, and trimethyl(phenylethynyl)stannane. After many negative results, we were able to effect the macrocyclization of 4-octyne with diyne **6**, although the yield

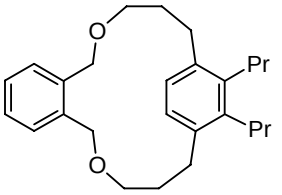
was fairly low (entry 1). Interestingly, different regiochemistry occurred in this benzannulation depending on whether we used an atmosphere of argon or carbon monoxide. The cycloaddition of diyne **6** and 4-octyne under argon provided paracyclophane **56p** almost exclusively, whereas the reaction under CO provided a mixture of *ortho*- and *para*-isomers, **56o** and **56p** (cf. entries 1 and 2). The cyclization of diyne **6** with dimethyl acetylenedicarboxylate (DMAD) under argon yielded benzannulene **57o** (entry 3); however, under carbon monoxide the reaction provided the *meta*- and *ortho*-isomers, **57m** and **57o**, in a ratio of 1:11 (entry 4). Similarly, macrocyclizations of DMAD with bis-alkynes **3** and **8** furnished only the benzannulenes, **59** and **61**, respectively (entries 5 and 6). Macrocyclizations in DME and 1,4-dioxane gave similar yields and regiochemistry (entry 6). Undesired cycloadducts from the incorporation of two molecules of DMAD and only one of the alkyne moieties of the α,ω-diyne, such as **58** and **60**, were also isolated.

Table 7. Cobalt-mediated Alkyne Cyclotrimerization

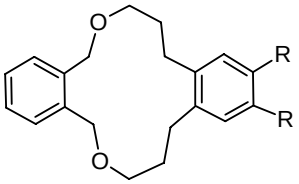


entry	α,ω-diyne substrate	R	equiv alkyne	rxn atm	products	% yield (isomer ratio)[b]
1	**6**	Pr	10	Ar	**56p**	23
2	**6**	Pr	5	CO	**56o**, **56p**	29 (1:2)
3	**6**	CO_2Me	10	Ar	**57o**	33[c]
4	**6**	CO_2Me	5	CO	**57m**, **57o**	36 (1:11)[d]
5	**3**	CO_2Me	10	Ar	**59**	12[e]
6	**8**	CO_2Me	5	Ar	**61**	31[f]

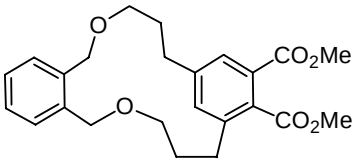
[a] Conditions: 15 mol % $CpCo(CO)_2$, DME (0.005 M), reflux; argon or carbon monoxide atmosphere. [b] Ratios determined from isolated isomeric products. [c] Also, 9% yield of **58**. [d] Also, 7% yield of **58**. [e] Also, 11% yiled of **60**. [f] 27% yield of **61** with 1,4-dioxane as the solvent.



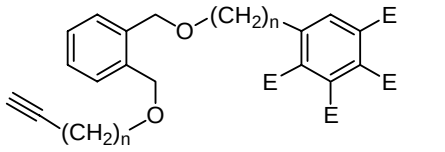
56p



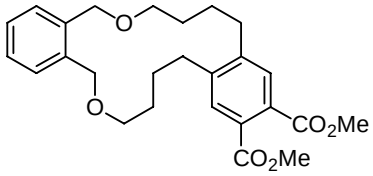
56o R = Pr
57o R = CO_2Me



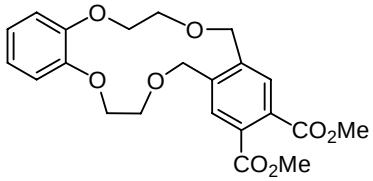
57m



58 n = 3
60 n = 4
E = CO_2Me



59



61

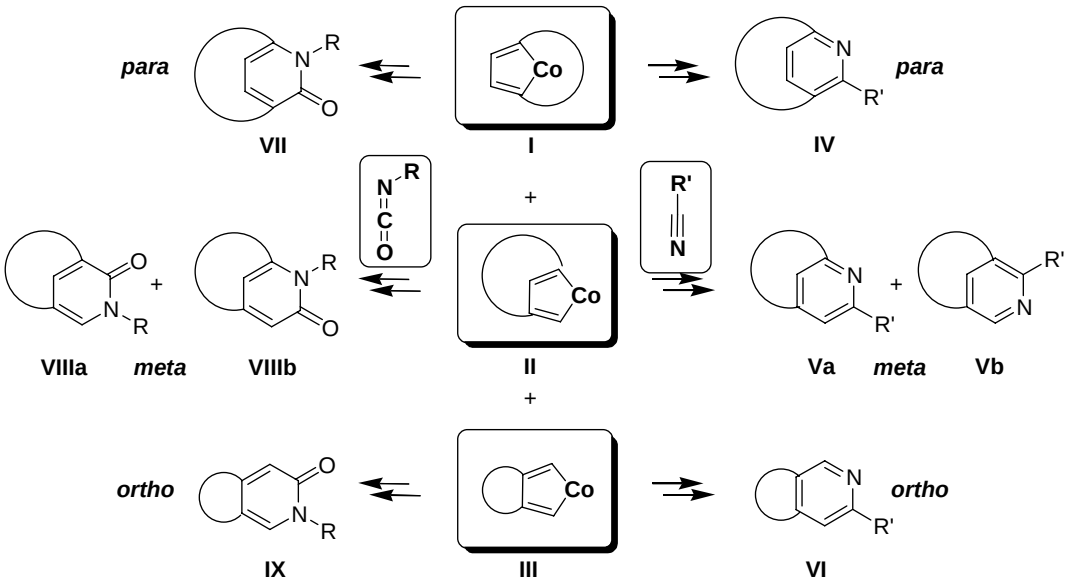
For the cyclophanes or benzannulenes, the protons of the newly generated benzene rings were observed as a singlet (*ortho* and *para* isomers) or a pair of singlets (*meta* isomer) in the aromatic region in the ^{1}H NMR spectra.[7d] Similar trends as above in NOESY experiments were helpful in characterizing the regioisomers. The structure of a 14-membered benzannulene **61** was confirmed by single-crystal X-ray diffraction.[7d]

6. Regiochemical and mechanistic aspects

Cobalt(I)-mediated [2 + 2 + 2] cycloadditions of bis-alkynes with nitriles, isocyanates, and alkynes proceed through a similar catalytic cycle (Scheme 3).[22] Mechanistic studies, along with the isolation of reaction intermediates, for $CpCoL_2$-catalyzed cyclotrimerizations of three alkynes, to form a benzene ring, have supplied crucial information about details of the process.[22b] Presumably, these findings are applicable to the related reactions of a bis-alkyne with a nitrile or with an isocyanate.[22a] 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 of it 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 is possible for the related reactions of a cobalta-cyclopentadiene complex with a nitrile or an isocyanate to proceed by either pathway.[36a,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

efficient or general. The most notable 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 large excess.[18] However, with long-chain α,ω-diynes ("Z") the side reactions in Scheme 3 tend to dominate, leading to an unsatisfactory macrocyclization.

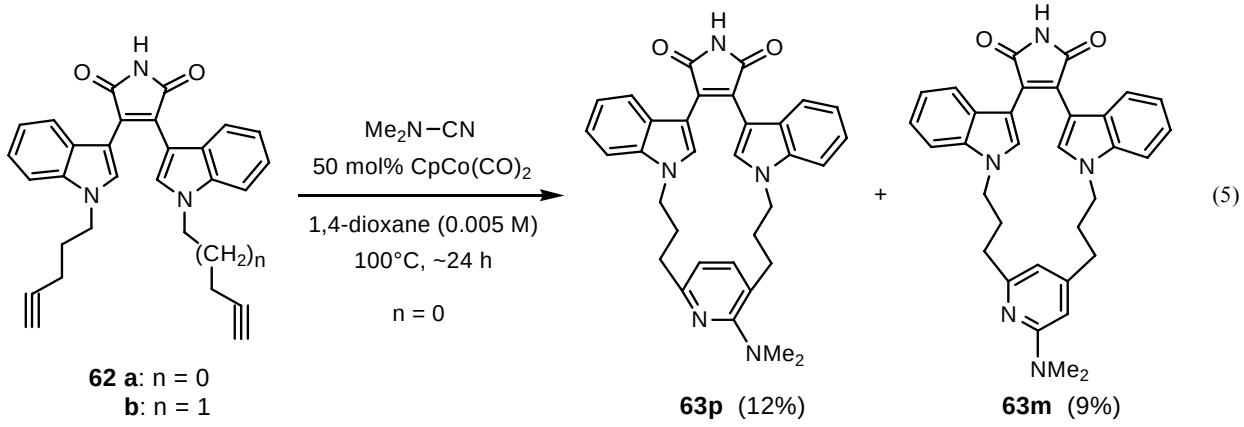


Scheme 5. Permutations for Cyclopentadiene Formation Leading to Regioisomeric Pyridinophanes and 2-Oxopyridinophanes (**Co** = CoCpL).

There was a similar trend in the regiochemistry for our cyclotrimerizations to macrocycles containing pyridine and 2-oxopyridine. 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 DFT[40] calculations (B3LYP with LACVP basis set for cobalt[41] and 6-31G for the other atoms[42]) 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, DFT methodology has proven to be accurate and useful for studying the energetics and reaction mechanisms of organometallic compounds.[43] For further details and reaction analysis, the interested reader should refer to our *JACS* article.[7d]

7. Macrocyclic "multiheterophanes" as protein kinase inhibitors

We applied our [2 + 2 + 2] macrocyclization methodology to the synthesis of novel molecules with the bis(indole)maleimide motif, so-called macrocyclic "multiheterophanes", to identify novel inhibitors of protein kinases. For example, α,ω-diyne **62a** was reacted with *N*,*N*-dimethylcyanamide to give two aminopyridinocyclophanes, **63p** and **63m**, in 21% isolated yield (eq 5). These compounds were found to be *potent* inhibitors of glycogen synthase kinase-3β (GSK-3β), and evaluation in a panel of 100 protein kinases indicated high *selectivity*.[44,45] The IC_{50} values for **63p** and **63m** were determined to be 37 and 7 nM, respectively. Similarly, we prepared homologous *para*-aminopyridinophane **64p** in 10% isolated yield from α,ω-diyne **62b**. Compound **64p** was also a very potent, highly selective inhibitor of GSK-3β (IC_{50} = 3 nM).[45] Given these exciting results, we explored ways to improve the synthetic protocol and discovered that the addition of triphenylphosphine to the reaction of **62a** produced **63p** and **63m** in an impressive 69% isolated yield (4:3 ratio).[45]



62 a: n = 0
b: n = 1

63p (12%) + **63m** (9%) (5)

We were able to obtain an X-ray structure of a co-crystal of **64p** and GSK-3β, which shows the interaction of the inhibitor ligand within the ATP binding pocket (Figure 4).[45] The maleimide portion of **64p** makes direct contact by hydrogen bonding with the enzyme residues Asp-133 (amide carbonyl oxygen) and Val-135 (Nα), as expected.[46] The other maleimide carbonyl is hydrogen bonded to a water molecule that bridges to Asp-200 (Nα). Ligand **64p** makes hydrophobic contacts with the side chains of Ile-62, Phe-67, Thr-138, Leu-188, and Cys-199. It is evident that the 2-dimethylaminopyridine unit in the macrocyclic linker is not involved in important interactions with the enzyme, and is largely solvent-exposed. Although the origin of the noteworthy selectivity for **64p** has not fully understood, we suggest that the *para*-pyridinophane unit may govern the conformation of the macrocycle, thereby conveying the high inhibitory potency for GSK-3β and influencing the selectivity over several other kinases.

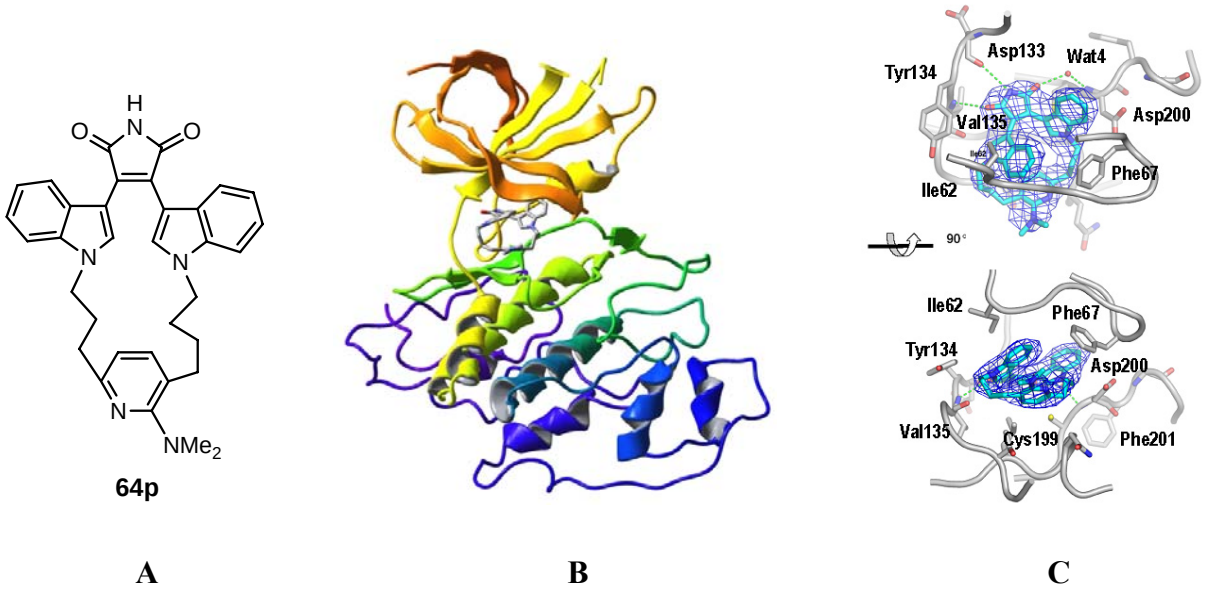


Figure 4. A: Structure of **64p**. **B:** Ribbon-and-tube diagram of the structure of GSK-3β•**64p**, as determined by X-ray crystallography (2.8 Å), showing the ligand in the ATP binding pocket. **C:** Two views of the complexed ligand, **64p**, rotated 90° relative to each other, depicting the electron density of the ligand.

8. Conclusions

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 also were able to effect the related co-cyclotrimerization of α,ω-diynes and alkynes, but this reaction type is much less practical, 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 are best performed in a concentration range of 2-50 mM, which is consistent with a balance of requisite unimolecular and bimolecular processes. By producing a macrocycle and a pyridine ring simultaneously, the co-cyclotrimerization affords substantial molecular complexity in a single step. In the area of metal-mediated [2 + 2 + 2] cycloadditions, it is noteworthy to be able to incorporate an external nitrile or isocyanate in a *bimolecular process* under convenient reaction conditions. We applied this synthetic method to obtain macrocyclic bis-indolemaleimide derivatives as potential protein kinase inhibitors. The novel "multiheterophanes" **63p**, **63m**, and **64p** turned out to be potent and selective inhibitors of GSK-3β. Thus, we were able to come full-circle in our research by achieving the original idea about using the [2 + 2 + 2] co-cyclotrimerization process to access new and unusual protein kinase inhibitors.

9. Acknowledgements

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10. References and Notes

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