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Cobalt-Mediated Macrocyclizations. Facile Synthesis of 2-Oxo Pyridinophanes via [2 + 2 + 2] Cycloaddition of α,ω-Diynes and Isocyanates†

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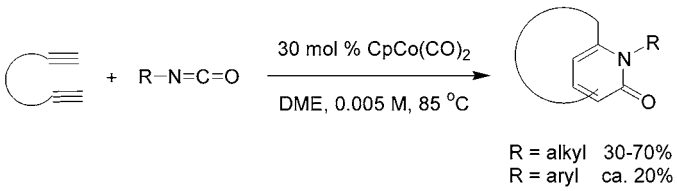
ABSTRACT



Cobalt-mediated [2 + 2 + 2] cycloaddition of α,ω-diynes and isocyanates provides a direct approach to macrocyclic 2-oxopyridinophanes. This macrocyclization process, which proceeded most efficiently with aliphatic isocyanates, was conveniently performed at a moderate temperature (85 °C) without irradiation or syringe-pump addition.

Cycloadditions mediated by transition metals constitute versatile methods for the assembly of complex polycyclic molecules.[1] Macrocycle formation is especially facilitated by such reactions because the metal center can help to preorganize the reactants and lower the activation free energy for entropically disfavored end-to-end cyclization of long acyclic substrates. For example, macrocyclizations have been achieved with impressively high yields in ruthenium- and molybdenum-catalyzed ring-closing metathesis (RCM) reactions of bis-alkenes and bis-alkynes,[2,3] and in intramolecular additions of rhodium carbenes.[4] Recently, we reported the synthesis of pyridine-containing macrocycles via cobalt-mediated cyclotrimerization of α,ω-diynes and nitriles, as part of our focus on reactions that can simultaneously generate a macrocycle and an arene/heteroarene ring (e.g., Scheme 1, eq 1).[5] This mode of assembly has been achieved by other processes, such as the intramolecular palladium-catalyzed enyne coupling with alkynes[6] and the cycloaddition of Fischer chromium carbenes with alkynes,[7] but they always

† Dedicated to Prof. Kurt Mislow on the occasion of his 80th birthday.

(1) (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, Germany, 1999; Vols. 1 and 2. (b) Beller, M.; Bolm, C. *Transition Metals in Organic Synthesis*; Wiley-VCH: Weinhem, Germany, 1998; Vols. 1 and 2. (c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. (d) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283. (e) Fruhauf, H.-W. *Chem. Rev.* **1997**, *97*, 523−596. (f) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662.

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(6) Saito, S.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 5042−5047.

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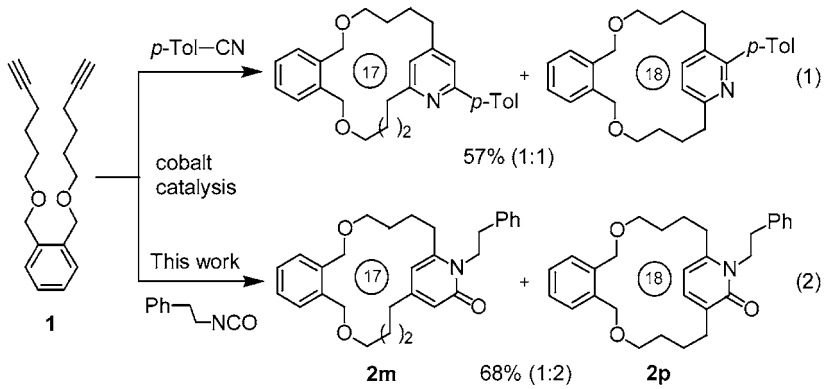
Scheme 1. Expeditious Syntheses of Pyridinophanes



involve *unimolecular* reactions. While such methods can deliver macrocycles in a single step, with a significant increase in molecular complexity, our *bimolecular* reaction is inherently conducive to a wider structural diversity in the products. However, the bimolecular reaction poses an issue for effectively achieving macrocycle formation because of an intrinsic contradiction. High-dilution conditions (e.g., 0.005 M) are needed to optimize macrocyclization, but those conditions can also impede the bimolecular process.

Our synthesis of pyridinophanes from α,ω-diynes and nitriles (e.g., Scheme 1, eq 1), which has excellent atom-economy and supplies substantial molecular complexity in a single step, is proof of the viability of such bimolecular assembly.[5] However, the method suffers from cumbersome reaction conditions that are in need of improvement: specifically, heating at ca. 140 °C, irradiation with a 300-W lamp, syringe-pump addition, and prolonged reaction times (e.g. 100 h).[5] Although irradiation with high-intensity light is meant to decarbonylate the $CpCo(CO)_2$ catalyst to generate an active cobalt species,[8] and high dilution via syringe-pump addition is meant to minimize unproductive oligomerization,[9] we have been able to eliminate both conditions.[10] Also, we have been able to reduce the temperature to 85 °C and shorten the reaction times.[10] Therefore, our original macrocyclization method[5] can now be conducted with 15−30 mol % of catalyst loading at 0.005 M in 1,2-dimethoxyethane (DME) at 85 °C over about 20 h.[11] Given this procedural advance, we became intent on applying the improved method to novel macrocycles appended to various heteroarene rings. We have been successful with the [2 + 2 + 2] cycloaddition of α,ω-diynes and isocyanates, and now report a convenient synthesis of 2-oxopyridinophanes, as exemplified in Scheme 1, eq 2.[12]

Reaction of diyne **1** with β-phenethyl isocyanate in the presence of 30 mol % of $CpCo(CO)_2$ furnished a mixture of 2-oxopyridinophanes **2m** and **2p** in 68% yield (eq 2). Among all possible regioisomeric products, we obtained only two cyclophanes, the 4,6- (*meta*) and 3,6- (*para*) 2-pyridones, with the latter product predominating. This result is remarkable considering previous reports on poor cyclization efficiency for the reaction of 1,*n*-bis-alkynes ($n = 6$ or 7) with isocyanates, using catalytic $CpCo(CO)_2$ under typical reaction conditions (*m*-xylene, 140 °C, *hν*, 3−5 h).[13,14] Recently, this shortcoming was addressed by the introduction of Cp*Ru(COD)Cl to effect the cycloaddition of 1,6-diynes and isocyanates to give bicyclic pyridones (58−87% yields).[15] The analogous co-cyclotrimerization of isocyanatoalkynes and monoalkynes to form 2,3-dihydro-5(1*H*)-indolizinones was more synthetically useful.[13a,b]

To explore the scope of this macrocyclization method, several symmetrical acyclic α,ω-diynes were reacted with β-phenethyl isocyanate (Table 1). Substrate **3**, a 1,17-bis-alkyne anchored onto a biphenyl scaffold, provided the 17-

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(11) These conditions are considerably improved over those reported for $CpCo(CO)_2$-mediated alkyne and diyne-nitrile cyclotrimerizations: For example, see: (a) Petit, M.; Chouraqui, G.; Phansavath, P.; Aubert, C.; Malacria, M. *Org. Lett.* **2002**, *4*, 1027−1029. (b) Varela, J. A.; Castedo, L.; Saa, C. *J. Org. Chem.* **1997**, *62*, 4189−4192. (c) Lofthagen, M.; Chadha, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 8795−8790. (d) Bönnemann, H.; Brijoux, W. *Adv. Heterocycl. Chem.* **1990**, *48*, 177−222. (e) See also refs 8c and 8d.

(12) For a synthesis of pyridone-containing macrocycles without using transition metals, see: (a) 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 synthetic strategy to 2-pyridones, see: (b) Hachiya, I.; Ogura, K.; Shimizu, M. *Org. Lett.* **2002**, *4*, 2755−2757.

(13) 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**, 1333−1162. (d) Hong, P.; Yamazaki, H. *Synthesis* **1977**, 50−52.

(14) For nickel-mediated cycloaddition of alkynes with isocyanates, see: (a) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1983**, *252*, 359−364. (b) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1982**, *234*, C35−C38. (c) Hoberg, H.; Oster, B. W. *Synthesis* **1982**, 324−325.

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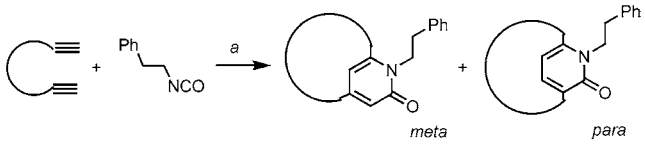
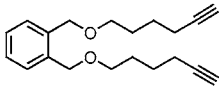
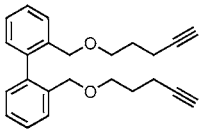
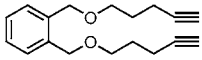
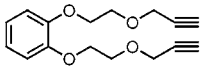
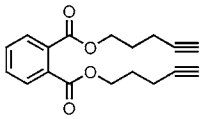
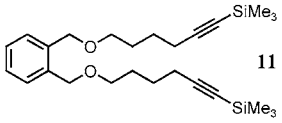
Table 1. Macrocyclic Pyridinophanes from Cyclotrimerization of α,ω-Diynes and β-Phenethyl Isocyanate



entry	α,ω-diyne substrate		products	% yield (*meta*:*para*)[b]
1		**1**	**2m**, **2p**	68 (1:2)
2		**3**	**4m**, **4p**	30 (1:5)
3		**5**	**6m**, **6p**	41 (1:20)
4		**7**	**8**	64 (<1:50)
5		**9**	**10**	40 (<1:50)
6		**11**	NR	0

[a] 30 mol % of $CpCo(CO)_2$, DME (0.005 M), 85 °C, 24 h. [b] Ratio determined from isolated isomeric products. NR = no reaction.

membered *m*-pyridone and 18-membered *p*-pyridone cyclophanes, with a predominance of the latter (entry 2). 1,15-Bis-alkynes connected to *ortho* positions on a benzene ring with ether (entries 3 and 4) or ester linkages (entry 5) gave mainly 16-membered *p*-pyridone cyclophanes in good yields. Substrate **11**, which bears internal (instead of terminal) alkyne groups, failed to cyclotrimerize with β-phenethyl isocyanate (entry 6).

The regioisomeric products were easily identified from the 2-pyridone protons, which are observed as distinct pairs of singlets (*meta* isomer) or doublets (*para* isomer; $J_{AB} = 5.5-7.0$ Hz) in the olefinic/aromatic regions in the ^{1}H NMR spectra. Structures were unambiguously assigned by two-dimensional NMR experiments, such as COSY, HETCOR, HMBC, and NOESY (see Supporting Information). The structure of **8**, a 16-membered 2-oxopyridinophane, was confirmed by single-crystal X-ray diffraction (Figure 1).

The observed regiochemical outcome[16] can be explained by considering the mechanism of cycloaddition in terms of the cobaltacyclopentadiene intermediates.[13a,17] The co-cyclotrimerization of alkynes with isocyanates, mediated by $CpCoL_2$ [$L_2 = (CO)_2$, $(PPh_3)_2$, or COD], probably proceeds by the catalytic cycle proposed for co-cyclotrimerization of alkynes with nitriles. We conducted density functional theory[18] calculations (B3LYP with an LACVP basis set for cobalt[19] and 6-31G for other atoms)[20] on the possible cobaltacyclopentadiene intermediates formed from different permutations of intermediates from irreversible oxidative coupling of the alkyne groups in diynes **1** and **5** (Scheme 2). Density functional theory has been proven to be a useful tool for studying the energetics and mechanisms of organometallic compounds.[21] In the case of 1,15-diyne **5**, calculations indicated that α,α′-substituted cobaltacycle **I** is favored over α,β-substituted cobaltacycle **II** by 1.4 kcal/mol and over

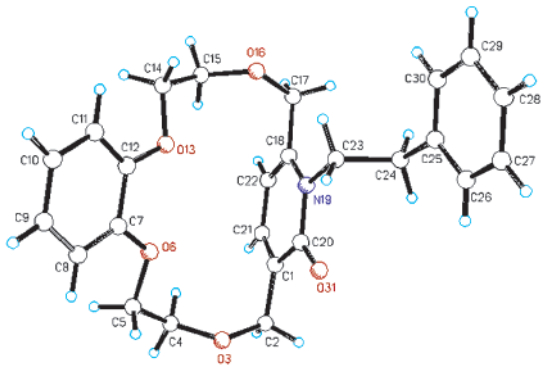
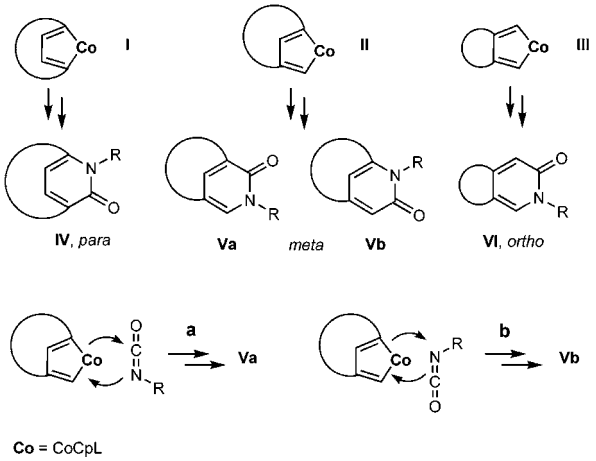


Figure 1. View of **8** from the X-ray crystal structure, showing the atom-labeling scheme.

Scheme 2. Regiochemical Permutations for Cobaltacyclopentadiene Formation and Isocyanate Insertion



(16) Nonselective cocyclizations of monoalkynes with isocyanates have been observed: refs 13a, 13c, and 13d. See also: Bönnemann, H. *Angew. Chem., Int. Ed.* **1978**, *17*, 505−514.

(17) The intermediacy of aza-cobaltacyclopentenones cannot be ruled out rigorously (see ref 13a).

(18) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, UK, 1989.

(19) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

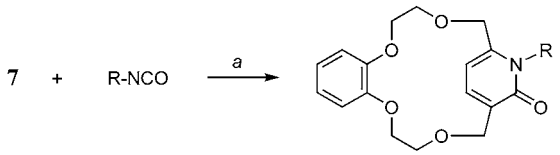
(20) *Jaguar 4.2*; Schrodinger, LLC: Portland, OR, 2002.

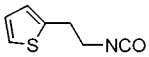
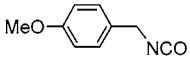
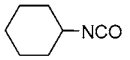
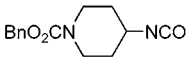
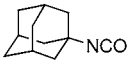
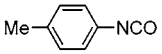
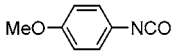
β,β'-substituted cobaltacycle **III** by 3.6 kcal/mol. Consequently, cycloaddition of a 1,15-diyne with an isocyanate should occur regioselectively to provide mainly the *p*-pyridone cyclophane **IV**, as observed. In the case of a 1,17-diyne, the α,α'-substituted cobaltacycle, **I**, is favored only by 0.5 kcal/mol over α,β-substituted cobaltacycle **II** and by 7.5 kcal/mol over β,β'-substituted cobaltacycle **III**. Thus, cycloaddition of a 1,17-bis-alkyne should yield two regioisomeric products derived from **I** and **II**, as observed. Isolation of macrocycles of the form **Va** further suggests that, of the two possible modes for isocyanate insertion, pathway **b** is favored over pathway **a** (Scheme 2).

To probe the scope of this method further, we examined cycloadditions of bis-alkyne **7** with several commercially available isocyanates (Table 2). It is noteworthy that the scope of isocyanate reactivity in the cobalt-mediated cycloaddition with short-chain bis-alkynes is not known because this reaction proceeds poorly.[13a] The reaction of **7** with unhindered alkyl isocyanates gave fair to good yields of *p*-2-oxopyridophanes (entries 1−3). Hindered aliphatic isocyanates also underwent co-cyclotrimerization smoothly (entries 4−6). The successful reaction of **7** with adamantyl isocyanate (entry 6) is particularly significant since *tert*-butyl isocyanate failed to react with diethyl 2,2-diprop-2-ynylmalonate under Ru(II) conditions.[15] Better yields of [2 + 2 + 2] cycloadducts were obtained with aliphatic substituents than with aromatic substituents (e.g., cf. entries 4 and 7), in contrast to the reaction of α,ω-bis-alkynes with nitriles.[5,10] Thiophene and carbamate groups were stable under the reaction conditions (entries 1 and 5). Only *p*-oxopyridinophanes were formed in the cycloadditions of bis-alkyne **7**, similar to the results with 1,15 bis-alkynes **5** and **9**.

In summary, macrocyclization via the cobalt-catalyzed cycloaddition of α,ω-diynes and isocyanates offers a straightforward approach to 2-oxopyridinophanes. This reaction occurs more efficiently with aliphatic isocyanates than with aromatic isocyanates. Contrary to standard protocols for $CpCo(CO)_2$ diyne cycloadditions, these macrocyclizations are conveniently carried out at reduced temperature (85 °C vs 140 °C), without irradiation or syringe-pump addition. In the [2 + 2 + 2] cycloaddition of 1,15-diynes, there was a strong predominance of the 3,6-disubstituted pyridone macrocycles (>20:1) relative to 4,6-disubstitution. In the case of 1,17-diynes, although the 3,6-disubstituted pyridone macrocycles were the major isomer, the 4,6-disubstituted pyridones had a significant presence. It is noteworthy that these positive results were achieved for a very challenging reaction involving incorporation of an external reactive species in a bimolecular macrocyclization.

Table 2. Macrocyclic 2-Oxopyridinophanes from Cyclotrimerization of Bis-alkyne **7** with Various Isocyanates



entry	isocyanate	products	% yield
1		**12**	48
2		**13**	70
3	$C_{12}H_{25}$−NCO	**14**	31
4		**15**	60
5		**16**	47
6		**17**	36
7		**18**	23
8		**19**	19

[a] 30 mol % of $CpCo(CO)_2$, DME (0.005 M), 85 °C, 22−24 h.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds and X-ray crystallographic details for 2-oxopyridinophane **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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