Cobalt-Catalyzed Cyclotrimerization of Alkynes in Aqueous Solution

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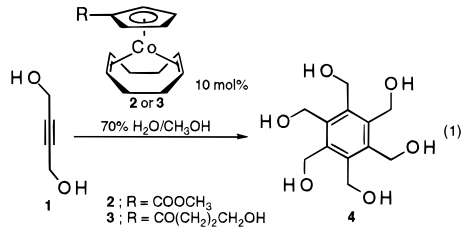
Many of the most useful methods for the assembly of cyclic organic molecules involve transition-metal-catalyzed cycloaddition. Because aromatic rings are central to many biological, pharmaceutical, and polymer molecules, alkyne cyclotrimerization is an important methodology. Vollhardt was first to realize the potential of cobalt-catalyzed cyclotrimerization in organic synthesis.[1] Recent examples that demonstrate the breadth of chemistry and concomitant diversity in structures that may be assembled by cobalt-catalyzed cyclotrimerization include steroids,[2] carbazoles,[3] stemodin,[4] illudol,[5] phenylenes,[6] γ-lycorane,[7] and the ergot alkaloids lysergic acid and lysergene.[8] From conducting oligomers to important medicinal compounds, cyclotrimerization has had an enormous impact on the synthetic strategies that can be envisaged.

Our interest in alkyne cyclotrimerization stems from a continued search for transition-metal catalysts that will perform in water. For environmental reasons water is a preferred reaction medium.[9] In addition, hydrophobic effects in organic reactions can provide substantial rate enhancements,[10] chemoselectivity,[11] and stereoselectivity.[12] Another motivation for performing organometallic catalysis in aqueous solution could entail merging biochemical[13] and organometallic techniques to reveal new horizons in combinatorial chemistry. Herein we describe a new cobalt catalyst that performs cyclotrimerization under mild conditions in water to prepare benzenes with unprotected functional groups.

(Cyclopentadienyl)cobalt dicarbonyl [$CpCo(CO)_2$] has been used in numerous cyclotrimerization reactions. However, no literature reports exist that describe CpCo catalysis in aqueous solutions,[14] despite the fact that numerous historically significant examples of transition-metal catalysis in water are known.[15] At the outset we were concerned that low-valent cobalt organometallics would be unstable and become oxidized in the presence of water. A simple first test of stability in aqueous solutions was performed on $CpCo(CO)_2$. After 65 h at 75 °C in 60% H_2O:CH_3OH[16] there was no detectable decomposition of $CpCo(CO)_2$ by ^{1}H NMR. Alkyne **1** was added and the sample heated again for 65 h at 75 °C followed by irradiation with a Kr ion laser (308 nm, 175 mJ/pulse) for 1 h. None of the desired cyclotrimerization product could be detected by ^{1}H NMR.

One problem in using $CpCo(CO)_2$ in water stems from the difficulty in substituting the CO ligands, which may be due in part to enhanced back-bonding in this high dielectric solvent. We reasoned that a CpCo-η^4-cyclooctadiene complex was desired, where the Cp had attached a substituent that aided its water solubility and a cyclooctadiene that would control access to the cobalt coordination sphere. From previous reports on the cyclotrimerization of alkynes in acetonitrile to form pyridines it was determined that electron-withdrawing groups on the Cp were desirable.[17] Ketone and ester groups appeared most attractive. The Cp^{z}Co catalyst **2** with an appended ester was prepared[18] and treated with alkyne **1**. Complex **2** was competent at cyclotrimerization of **1**, but at 85 °C the half-life was greater than 1 week, limiting the utility of this catalyst.



Encouraged by these preliminary results, the design of the Cp ligand was again evaluated. It is well-known that ketones are more electron withdrawing than esters, but it was unclear whether this subtle difference in Cp substituents would be sufficient to enhance the rate of cyclotrimerization.[19] It was of interest to appended a functional group that contained both a carbonyl and a hydrophilic group. Complex **3** (Cp$^{\$}$Co-COD) was prepared,[18] containing a ketone carbonyl to increase catalytic activity and a hydroxyl to aid in water solubility. The solubility of **3** was dramatically improved (20 mM in 80% H_2O/CH_3OH). Gratifyingly, **3** gave cyclotrimerization of **1** at an observed rate >50-fold higher than **2** under identical reaction conditions. After greater than 3 half-lives no detectable decomposition of **3** was observed by ^{1}H NMR.

Next the scope of alkyne cyclotrimerization via **3** and the degree of functional group protection required was investigated. Equation 2 shows the general reaction conditions and Table 1

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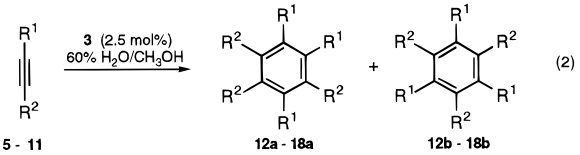
Table 1. Cyclotrimerization Products from 3 with Functionalized Alkynes

alkyne:product	R^1	R^2	yield, %	*a*/*b*
5:**12**	H	$COCH_3$	44	0[a]/44
6:**13**	H	CO_2CH_3	67	47/20
7:**14**	H	$(CH_2)_2OH$	85	62/23[b]
8:**15**	H	CH_2NHCH_3	73	47/26[b]
9:**16**	H	$C(CH_3)_2OH$	81	53/28
10:**17**	H	$CH_2N(CH_3)_2$	78	51/27
11:**18**	H	$(CH_2)_2CO_2H$	56	36/20

[a] Minor isomer not isolated. [b] Ratios determined by HPLC.

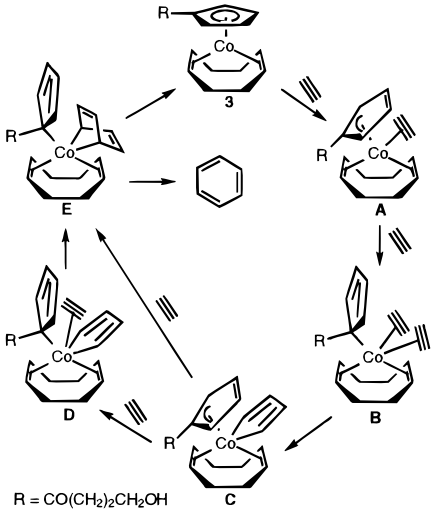


summarizes the yield data (not optimized) where all reactions were performed under identical conditions. Good yields were obtained for both **16a**, **17a**, **16b**, and **17b** isomers despite the fact that for **16** and **17** the substituents in the **a** isomers must be ortho and sterically demanding. This is surprising because the more highly strained products were favored. Table 1 shows that amine, hydroxyl, ketone, ester, and carboxylic acid groups were all tolerated in this aqueous [2 + 2 + 2] cycloaddition chemistry. However, **5** gave only the **b** isomer product.[20]

The mechanism of $CpCo(CO)_2$ alkyne cyclotrimerization in organic solvents has been studied in detail, yet several proposed steps elude verification or clarification. The accepted mechanism involves rate determining photochemical or thermal dissociation of one ligand to allow the first alkyne into the cobalt coordination sphere.[21] To begin to understand alkyne cyclotrimerizations via **3** in water the reaction kinetics were measured to determine the affect of catalyst **3** and substrate **1** concentration.[18] The observed first-order rate is unaffected by the concentration of **1**. As expected the cyclotrimerization of **1** to give **4** showed a first-order dependence on the catalyst concentration **3**. These data are consistent with the accepted dissociative mechanisms of cobalt-catalyzed alkyne cyclotrimerization.

A crucial aspect of the CpCo alkyne cyclotrimerization mechanism in organic solvents is the dissociative formation of 16 e complexes at several points in the reaction[22] to allow the alkyne access to the metal center. To test if dissociation of either the Cp or the COD was occurring during the catalytic cycle two deuterio catalyst isomers were prepared, $Cp^{\$}$Co-COD-$d_8$ (**19**) and $Cp^{\$}$-$d_4$Co-COD (**20**), and double isotopic crossover experiments were performed in triplicate with an equal mixture of **19**:**20**.[18] The cycloaddition was monitored by ^{1}H NMR and ligand exchange by mass spectrometry. At 60% conversion of **1** (^{1}H NMR, >5 catalyst cycles) to **4** the mass spectrum of the recovered catalyst was identical and unchanged in all experiments. These data rule out rate determining dissociative loss of either the COD or the Cp and instead would be consistent with alkyne coordination occurring by ligand slippage of either the COD or the Cp. Slippage of Cp ligands in associative substitution reactions has been suggested previously for isoelectronic CpRh complexes,[22] but we are unaware of any previous examples for ligand slippage in cobalt complexes. While clearly more research is needed to elucidate the mechanism of alkyne cyclotrimerization via **3** in aqueous solutions, the crossover experiments may explain why **3** shows remarkable stability in water because coordinatively

Scheme 1



unsaturated intermediates are not necessary. One possible mechanistic alternative is shown in Scheme 1.

Complex **3** could undergo slippage of the Cp ligand from η^5 to η^3 as in **A** and subsequent coordination of the first alkyne.[23] A second alkyne could enter the metal binding sphere by further Cp slippage to η^1 giving **B**. Cp ring slippage from η^5 to η^1 has been reported previously for CpRe[24] and CpPd[25] complexes. Oxidative coupling of the alkyne ligands in **B** with Cp slippage back from η^1 to η^3 as in **C** could provide a driving force for metallacycle formation and maintain a filled cobalt valence (18 e). The most direct path to the product could involve Diels−Alder addition of the cobalt bound third alkyne to the metallacycle in **D**,[26] or prior to metal coordination by direct reaction on **C** by the third alkyne to give the η^2-benzene complex **E**.[27] Reductive elimination of the η^2-benzene from the cobalt would give the product, and slippage of the Cp from η^1 to η^5 would regenerate the resting state of the catalyst.

In summary a new cobalt catalyst has been prepared that performs alkyne cyclotrimerization in water solutions under mild conditions. Protection of the alkyne functional groups is not required even for amines and carboxylic acids. The kinetic and double isotopic crossover data gave some surprising results consistent with rate determining dissociative coordination of alkyne, which implies ligand slippage to allow access of the alkyne to the metal center. Further investigations are in progress to better define the scope and mechanism of this new alkyne cyclotrimerization chemistry in water.

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Supporting Information Available: Experimental details and chemical characterization data (10 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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