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A New $Co_2(CO)_8$-Mediated Tandem [5 + 1]/[2 + 2 + 1]-Cycloaddition Reaction: A One-Pot Synthesis of Tricyclic δ-Lactones from *cis*-Epoxy Ene-ynes

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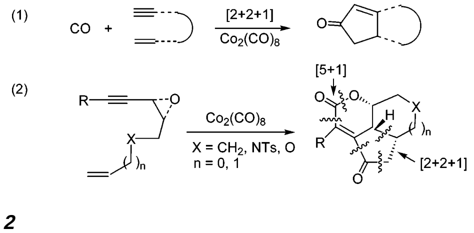
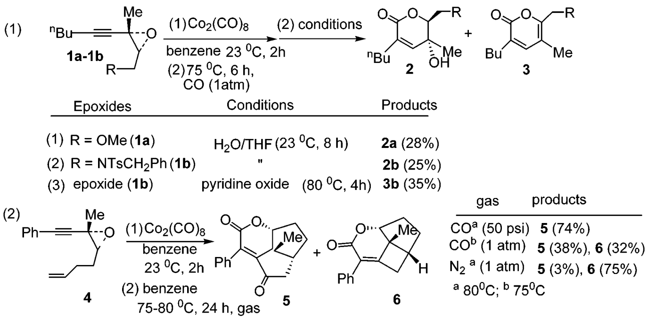
The synthesis of complex polycyclic molecules from acyclic precursors via tandem cyclizations[1] is a fascinating subject because the formation or cleavage of multiple C−X bonds (X = C, O, N) can be achieved in a one-pot operation. Many useful tandem reactions are implemented by transition-metal species to provide a short route to complex bioactive molecules.[2,3] Alkynes, olefins, and CO are the most useful components in metal-mediated organic synthesis. One of the most prominent examples is the Pauson−Khand reaction, which involves the coupling of alkyne, olefin, and CO to give cyclopentenone derivatives (Scheme 1, eq 1).[4,5] This reaction has been thoroughly studied, both stoichiometrically[4,5] and catalytically,[5] because of its widespread application. Many new metal-mediated reactions have been developed by changing one of these three components, such as by replacing the olefin or alkyne with allene,[6a] ketone,[6b] aldehyde,[6c−d] or imine[6e] or by replacing CO with aldehyde,[6f] to give an easy synthesis of five-membered carbo- or heterocyclic compounds. In this communication, we report new findings in the $Co_2(CO)_8$-mediated coupling of epoxyalkyne, CO, and olefin functionalities, leading to tandem [5 + 1]/[2 + 2 + 1] cycloadditions to give tricyclic δ-lactones efficiently (eq 2, Scheme 1).

Scheme 1



Scheme 2



As shown in Scheme 2, *cis*-epoxyalkynes **1a** and **1b** were treated with $Co_2(CO)_8$ (1.1 equiv) in benzene at 23 °C for 2 h under N_2 to afford a black organometallic species, corresponding to $Co_2(CO)_6$(alkyne) species[7] Further heating this benzene solution under CO (1 atm) at 75 °C for 6 h led to formation of new major organometallics which liberated the alcohols **2a**−**2b** (25−28%) or pyran-2-one **3b** (35%) upon treatment with H_2O/THF or pyridine oxide. The deuterium content of the olefin proton of alcohol **2a** was ca. 91% if D_2O was used for demetalation. The reaction intermediate can be trapped more efficiently by an olefin tethered with *cis*-epoxyalkyne **4**, as depicted in eq 2. Heating a $Co_2(CO)_6$(alkyne) solution of species **4** in benzene under CO (80 °C, 50 psi, 24 h) gave a single product **5** in 74% isolated yield, which was characterized by an X-ray diffraction study[8] and mass and NMR spectra. Structurally, compound **5** consists of a 5,6-dihydro-pyran-2-one core fused to cyclopentane and cyclopentanone groups, respectively; the methyl group is cis to the two adjacent protons. Notably, heating the same benzene solution (80 °C, 24 h) under a N_2 atmosphere generated compound **6** in 75% isolated yield after workup. An X-ray diffraction study[8] revealed that compound **6** contains an unusual cyclobutane ring with a central methyl group cis to two adjacent protons. We prepared various epoxyalkynes **7**−**16** to investigate the generality for the tandem [5 + 1]/[2 + 2 + 1] cyclization (Table 1). The $Co_2(CO)_6$(alkyne) species of these substrates were heated in benzene under appropriate conditions to cause liberation of an organic product with yields exceeding 65% in all cases. Similar to its phenyl analogue **4**, epoxides **7a** and **7b** (R = ⁿBu, TMS) gave good yields of tricyclic oxygenated molecules **17a** and **17b** under CO (50 psi). A similar framework can be constructed with acetate and methoxy functionalities **18a** and **18b**. The cyclization is applicable to the formation of tricyclic molecule **19** that contains a cyclohexane ring. This tandem cyclization works well for the synthesis of the oxygen- and nitrogen-containing molecules **20** and **21** (entries 3 and 4) under a N_2 or CO (1.0 atm) atomsphere. The methyl groups of compounds **19**−**21** are cis to the two adjacent protons according to an NOE experiment (see Supporting Information). The conditions for cyclizations of 1,2-disubstituted epoxides **12**−**16** (entries 6−10) are more mild than those for their tertiary epoxide analogues **7**−**11** because the former avoids generation of a quaternary central carbon. No carbon monoxide is required for formation of tricyclic molecules **22a**−**22b**, **23**, and **24**. The structure of compound **22b** was confirmed by an X-ray diffraction study.[8] Epoxyalkynes **15** and **16** undergo efficient transformation into tricyclic pyran **25** and piperidine **26** at 28 and 50 °C, respectively. The cis configuration of epoxyalkyne[9] is crucial for the cyclization. Heating a benzene solution of *trans*-epoxyalkyne **27** under N_2 or CO (50 psi) failed to give any organic product, which is in contrast with its *cis*-epoxy analogue **10**. The major species of this solution was the $Co_2(CO)_6$(alkyne) species, which led to 56% recovery yield of **27** upon Ce(IV)-oxidation (0.95 equiv).

Our preliminary investigation showed that *cis*-epoxyalkynes **7a** and **7b** gave good yields of unusual cyclobutane derivatives **28a** and **28b** under a nitrogen atmosphere (Scheme 3). Molecular structure of **28b** was confirmed by X-ray diffraction study.[8] Such a tandem [5 + 1]/[2 + 2]-cycloaddition is compatible with acetate

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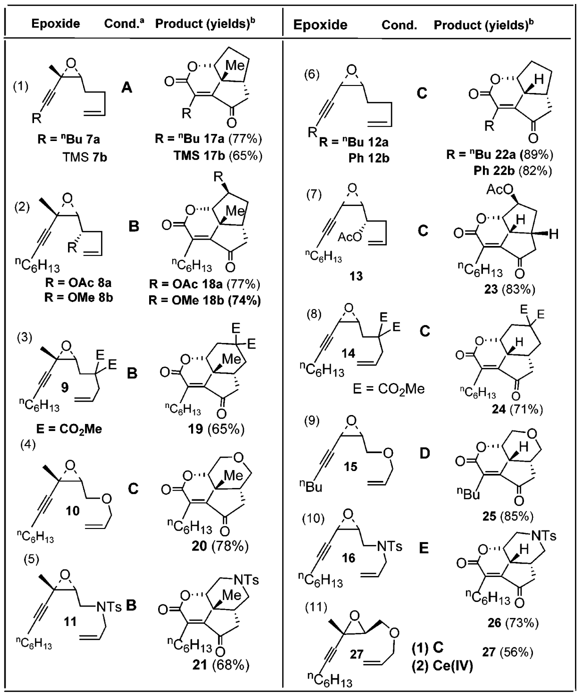
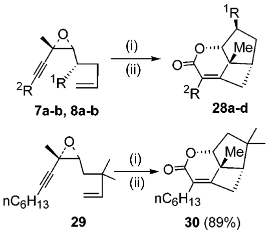
Table 1. $Co_2(CO)_8$-Mediated Tandem [5 + 1]/[2 + 2 + 1]-Cycloadditions



ᵃ Epoxyalkyne (1.0 equiv, 0.15 M) was treated with $Co_2(CO)_8$ (1.1 equiv) in benzene at 23 °C for 2 h, followed by stirring at appropriate conditions. Cond. **A**, CO (50 psi), benzene, 80 °C, 24 h; **B**, CO (1 atm), benzene, 75 °C, 12 h; **C**, N_2, benzene, 80 °C, 24 h; **D**, N_2, benzene, 28 °C, 24 h; **E**, CO (1 atm), benzene, 60 °C, 24 h. ᵇ Yields were reported after silica column.

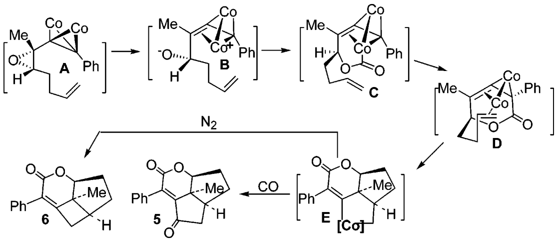
Scheme 3



	Epoxide	product (yields)
(1)	^1R=H, ^2R=ⁿBu(**7a**)	**28a** (72%) **17a** (3%)
(2)	^1R=H, ^2R=TMS(**7b**)	**28b** (75%) **17b**(2%)
(3)	^1R=OAc, ^2R=ⁿC_6H_{13} (**8a**)	**28c** (66%) **18a** (4%)
(4)	^1R=OMe, ^2R=ⁿC_6H_{13} (**8b**)	**28d** (63%) **18b** (3%)

(i) Epoxyalkyne (1.0 equiv), $Co_2(CO)_8$ (1.1 equiv) benzene, 23°C, 2 h
(ii) N_2, 80 °C, 24 h

Scheme 4



and methoxy functionalities **28c** and **28d**. Similar framework **30** was obtained in 89% yield from *cis*-epoxyalkyne **29** under the same condition.

This new process likely involves an initial coupling of $Co_2(CO)_8$ with epoxyalkyne and CO in [5 + 1] mode, to give cobalt-stabilized cyclic allene species[10] **D** (Scheme 4), which was generated by the ring-opening of epoxide **4** by S_N2-attack of the $Co_2(CO)_6$ fragment. The alcohols **2a**−**2b** or pyran-2-one **3b** are thought to derive from 1,2-addition of H_2O or intramolecular proton transfer of their corresponding intermediates **D**. Coordination of species **D** with a tethered olefin species leads to oxidative cyclization to give cobalt-containing cyclopentane species **E**. In the conversion of species **D** to **E**, the C−C bond formation proceeds from the metal face such that the methyl group is cis to the two neighboring protons. Insertion of CO or reductive elimination of intermediate **E** gives the derivative of cyclopentanone **5** or cyclobutane **6**, respectively.

In summary, we have reported a new and highly stereocontrolled coupling reaction of epoxyalkyne, CO, olefin which leads to tandem cyclocarbonylation/[2 + 2 + 1] cycloadditions. The mechanism involves an unusual cobalt-stablized cyclic allene intermediate. This new approach is successfully extended to construct various tricyclic carbo- and heterocyclic frameworks that can tolerate suitable oxygen and nitrogen functionalities. Further application of this new method to a short synthesis of complex bioactive molecules is under investigation.

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Supporting Information Available: Experimental procedures, synthetic schemes, and spectral data of new compounds **1**−**31** and X-ray data of tricyclic compounds **5**, **6**, **22b** and **28b** (PDF).

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(8) The ORTEP drawing and crystal data of tricyclic compounds **5**, **6**, **22b**, and **29b** are provided in Supporting Information.
(9) The ease in the ring-opening of *cis*-epoxyalkyne is unclear at the present stage. We believe that the vinyl or heteroatom at the cis substituent may coordinate to the cobalt metal to increase its basicity that facilitates the ring-opening of epoxide.
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