

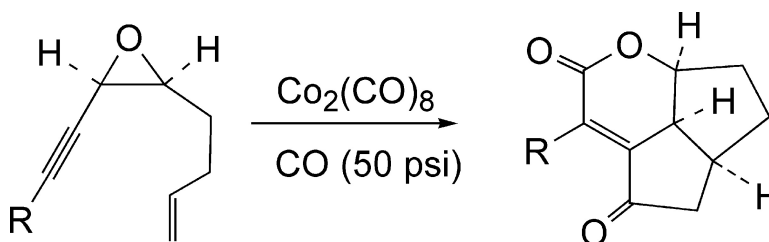
Communication

**A New Co(CO)-Mediated Tandem [5 + 1]/[2 + 2 + 1]-Cycloaddition Reaction:
 A One-Pot Synthesis of Tricyclic β -Lactones from *cis*-Epoxy Ene-yne**

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A New $\text{Co}_2(\text{CO})_8$ -Mediated Tandem $[5 + 1]/[2 + 2 + 1]$ -Cycloaddition Reaction: A One-Pot Synthesis of Tricyclic δ -Lactones from *cis*-Epoxy Ene-yne

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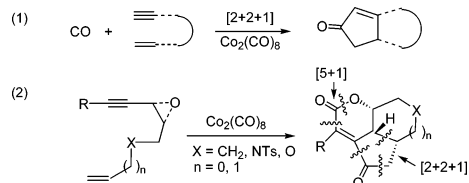
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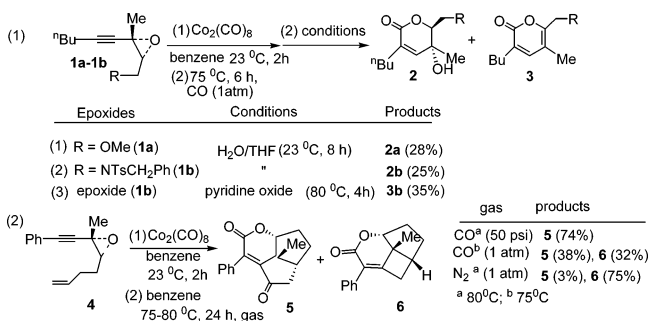
The synthesis of complex polycyclic molecules from acyclic precursors via tandem cyclizations¹ is a fascinating subject because the formation or cleavage of multiple C–X bonds (X = C, O, N) can be achieved in a one-pot operation. Many useful tandem reactions are implemented by transition-metal species 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 carbonyl or heterocyclic compounds. In this communication, we report new findings in the $\text{Co}_2(\text{CO})_8$ -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).

As shown in Scheme 2, *cis*-epoxyalkynes **1a** and **1b** were treated with $\text{Co}_2(\text{CO})_8$ (1.1 equiv) in benzene at 23 °C for 2 h under N_2 to afford a black organometallic species, corresponding to $\text{Co}_2(\text{CO})_6$ -(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 $\text{H}_2\text{O}/\text{THF}$ 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 $\text{Co}_2(\text{CO})_6$ -(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 study⁸ 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 study⁸ 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 $\text{Co}_2(\text{CO})_6$ -(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

Scheme 1



Scheme 2



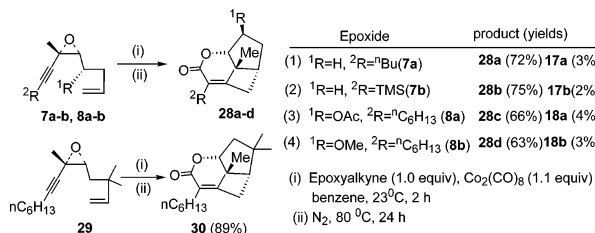
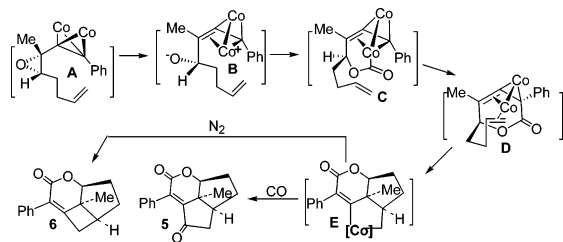
constructed with acetate and methoxy functionalities **18a** and **18b**. The cyclization is applicable to the formation of tricyclic molecule **19** that contains a cyclohexane ring. This tandem cyclization works well for the synthesis of the oxygen- and nitrogen-containing molecules **20** and **21** (entries 3 and 4) under a N_2 or CO (1.0 atm) atmosphere. 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 epoxyalkyne⁹ 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 $\text{Co}_2(\text{CO})_6$ -(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

Table 1. $\text{Co}_2(\text{CO})_8$ -Mediated Tandem $[5 + 1]/[2 + 2 + 1]$ -Cycloadditions

Epoxide	Cond. ^a	Product (yields) ^b	Epoxide	Cond.	Product (yields) ^b
(1)	A	R = ⁿ Bu 17a (77%) TMS 17b (65%)	(6)	C	R = ⁿ Bu 22a (89%) Ph 22b (82%)
(2)	B	R = OAc 18a (77%) R = OMe 18b (74%)	(7)	C	23 (83%)
(3)	B	19 (65%)	(8)	C	24 (71%)
(4)	C	20 (78%)	(9)	D	25 (85%)
(5)	B	21 (68%)	(10)	E	26 (73%)
			(11)	(1) C (2) Ce(IV)	27 (56%)

^a Epoxyalkyne (1.0 equiv, 0.15 M) was treated with $\text{Co}_2(\text{CO})_8$ (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**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 $\text{Co}_2(\text{CO})_8$ with epoxyalkyne and CO in $[5 + 1]$ mode, to give cobalt-stabilized cyclic allene species **D** (Scheme 4), which was generated by the ring-opening of epoxide **4** by $\text{S}_{\text{N}}2$ -attack of the $\text{Co}_2(\text{CO})_6$ 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-stabilized 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.

Acknowledgment. We thank National Science Council, Taiwan, for support of this work.

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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