Dicobaltoctacarbonyl-Mediated Synthesis of Tricyclic 5,6-Diydropyran-2-one Derivatives via Tandem Cycloaddition Reaction between *cis*-Epoxyalkynes, a Tethered Olefin, and Carbon Monoxide

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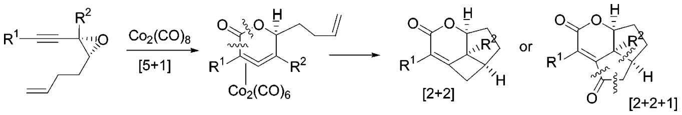
Received October 5, 2006



Cobalt carbonyl complex $Co_2(CO)_8$ implemented an intramolecular carbonylation of *cis*-epoxyalkynes to generate $Co_2(CO)_6$-stabilized γ-lactonyl allene species. For 1,1,2-trisubstituted epoxyalkynes, this $Co_2(CO)_6$-allene species reacted with a tethered olefin to give [2 + 2]-cycloadducts, and with CO and a tethered olefin to produce [2 + 2 + 1]-cycloadducts. These resulting cycloadducts have a 5,6-diydropyran-2-one core fused with a cyclobutane and a cyclopentanone ring, respectively. For 1,2-disubstituted *cis*-epoxyalkyne and 1,1,2-trisubstituted *cis*-epoxyalkynes bearing a heteroatom constituent, cyclization of the corresponding epoxyalkyne with a tethered alkene is invariably accompanied by incorporation of CO to produce a [2 + 2 + 1]-cycloadduct, even in the absence of CO. We have prepared various 1,1,2-trisubstituted and 1,2-disubstituted *cis*-epoxyalkynes to generalize such cycloaddition pathways. Attempt to use an organic promoter to perform these tandem cycloadditions was unsuccessful because of a competing Pauson−Khand reaction. Cyclization of a 1,2-disubstituted epoxyalkyne with a tethered diene was achieved successfully in one case, but the yield was low (25%).

Introduction

The synthesis of complex polycyclic molecules from metal-catalyzed multicomponent coupling reactions[1−2] is fascinating because multiple C−X bonds (X = C, O, N) can be formed simultaneously. Such coupling reactions are often accompanied by tandem cyclizations to form two or three rings sequentially. Many tandem cyclizations are implemented by transition-metal species to provide a short route for the synthesis of complex bioactive molecules.[3,4] Alkynes, olefin, and CO are the most useful components in metal-mediated organic synthesis; a prominent example is the Pauson−Khand reaction,[5] which involves the coupling of an alkyne, an olefin, and CO to give a cyclopentenone framework.[6−9] Besides the Pauson−Khand reaction, cobalt-catalyzed/-mediated tandem cycloaddition reaction between alkyne, olefin, and carbon monoxide functionalities is reported to form other polycyclic structures.[10]

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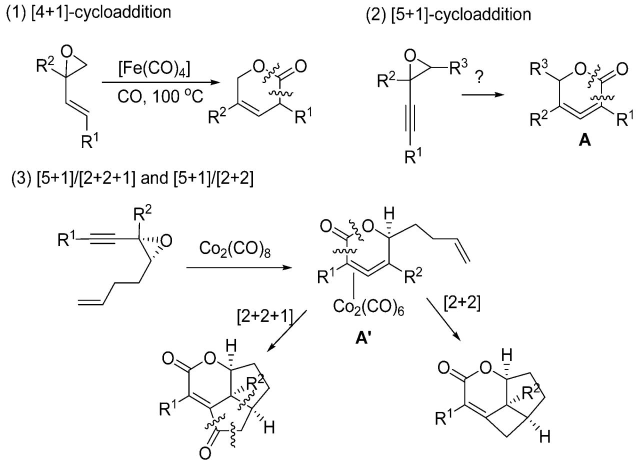
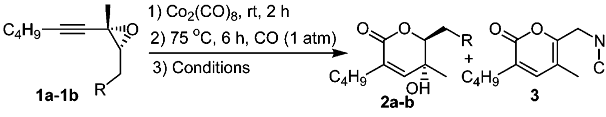
10.1021/jo0620617 CCC: $37.00

SCHEME 1



SCHEME 2



	Epoxides	Conditions[a]	Products (yield)[b]
(1)	R = OMe (**1a**)	H_2O/THF, rt, 8 h	**2a** (28%)
(2)	R = $NTsCH_2Ph$ (**1b**)	H_2O/THF, rt, 8 h	**2b** (25%)
(3)	**1b**	pyridine-*N*-oxide, 80 °C, 4 h	**3** (35%)

[a] Benzene, [epoxyalkyne] = 0.11 M, $Co_2(CO)_8$ (1.1 equiv). [b]The product yields given are after separation on a silica column.

Epoxides are a common and practical functionality, and there are only several reports on the use of epoxide as a coupling component.[11] Cobalt carbonyl complex $Co_2(CO)_8$ is known to catalyze copolymerization[12] of epoxide with CO and ring expansion of epoxide to give β-latcones.[13] Ley and co-workers reported an unusual $Fe(CO)_4$-mediated cyclocarbonylation of vinyl epoxides to yield δ-lactone products as shown in Scheme 1 (eq 1).[14] By analogy with this cyclization, we envisage that a suitable metal complex should implement a [5 + 1]-cyclization of epoxyalkynes with one CO molecule to generate δ-lactonyl allene species A as depicted in eq 2. Within our continuing interest in the metal-catalyzed coupling reaction of epoxides,[15] we report here a new and efficient $Co_2(CO)_8$-mediated tandem cycloaddition of epoxyalkyne, alkene, and CO to produce tricyclic δ-lactones via a formal [5 + 1]/[2 + 2 + 1]-cycloaddition mode (eq 3).[16] This unusual reaction is thought to arise from an intramolecular [2 + 2 + 1]-cycloaddition of the hypothetical cyclic allene intermediate **A′**. For 1,1,2-trisusbtituted epoxides ($R^2 \neq H$), the corresponding $Co_2(CO)_6$-stabilized allene species **A′** undergoes an alternative [2 + 2]-cycloaddition to form a fused cyclobutane ring. Here we report the details of such substrate-dependent cycloaddition reactions.[16]

Results and Discussion

As shown in Scheme 2, treatment of *cis*-epoxyalkynes **1a** with $Co_2(CO)_8$ in benzene at 25 °C produced its corresponding $Co_2(CO)_6(\pi\text{-alkyne})$ species as revealed by its IR absorption [ν(CO) 2050 cm^{-1}]; attempts to characterize its structure were hampered by its broad ^1H NMR spectra in $CDCl_3$ or C_6D_6. Subsequent heating of this benzene solution at 75 °C (6 h) under CO (1 atm) produced one major organometallic species that decomposed on treatment either with H_2O/THF to give alcohol **2a** in 28% yield or with pyridine-*N*-oxide to afford pyran-2-one **3** in 35% yield. The deuterium content of the olefin proton of alcohol **2a** was ca. 91% if D_2O was used for demetalation. *cis*-Epoxyalkyne **1b** gave alcohol **2b** in 25% yield under similar hydrolysis condition.

This new process likely involves an initial coupling of $Co_2(CO)_8$ with epoxyalkyne and CO in a [5 + 1]-cycloaddition mode to form cobalt-stabilized cyclic allene species[17] **A′** (Scheme 3). We envisage that ring opening of the epoxide

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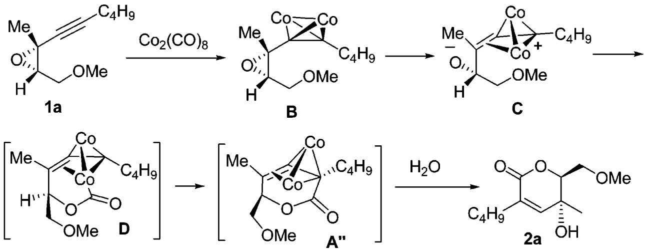
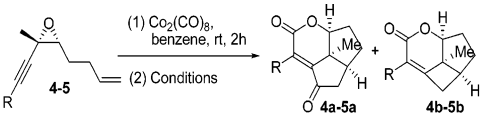
SCHEME 3



SCHEME 4



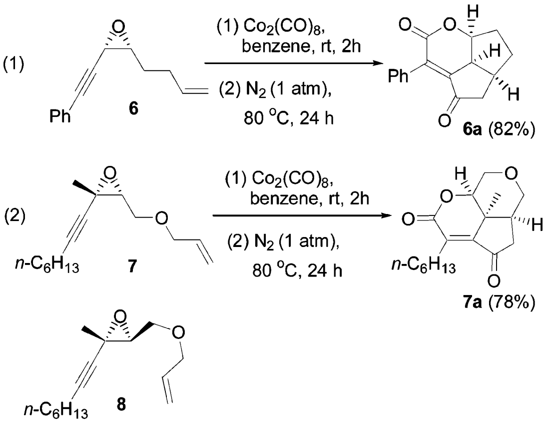
Entry	*cis*-Epoxyalkyne	Conditions	Products
1	**4**: R = Ph	CO (50 psi), 80 °C	**4a** (74%)
2	**4**	CO (1 atm), 75 °C	**4a** (38%), **4b** (32%)
3	**4**	N_2 (1 atm), 80 °C	**4a** (3%), **4b** (75%)
4	**5**: R = *n*-C_6H_{13}	CO (50 psi), 80 °C	**5a** (77%)
5	**5**	CO (1 atm), 75 °C	**5a** (34%), **5b** (39%)
6	**5**	N_2 (1 atm), 80 °C	**5a** (3%), **5b** (72%)

[a] Benzene, [epoxyalkyne] = 0.11 M, $Co_2(CO)_8$ (1.1 equiv). [b]The product yields given are after separation on a silica column.

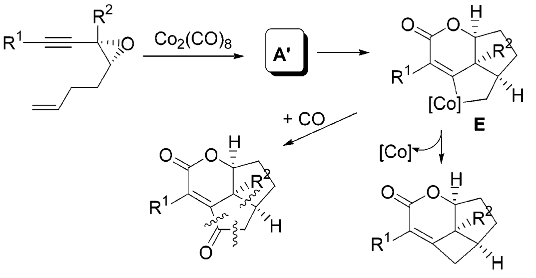
species **B** is promoted by a S_N2-attack of the $Co_2(CO)_6$ fragment to give propargyl cationic intermediate **C**, of which the hydroxyl group attacks one carbonyl group to generate acylcobalt species **D**. A subsequent reductive elimination of species **D** leads to formation of the desired cyclic allene intermediate **A″**.[17] Alcohols **2a,b** or pyran-2-one **3** are thought to derive from 1,2-addition of H_2O or intramolecular proton transfer upon demetalation of this intermediate.

Our mechanistic speculation in Scheme 3 reveals that cobalt-stabilized allene species **D** may act as a precursor for a reactive cycloallene, which is synthetically useful upon thermal decomplexation with an alkene functionality. To realize this hypothesis, we prepared *cis*-epoxyalkyne **4** having a tethered alkene to trap the hypothetic allene intermediate. As shown in Scheme 4, when *cis*-epoxyalkynes **4** was treated with $Co_2(CO)_8$ (1.1 equiv) in benzene at 23 °C for 2 h under a nitrogen atmosphere, a black organometallic species corresponding to its $Co_2(CO)_6$-π-alkyne species was formed. Heating this benzene solution at 80 °C under CO (50 psi, 24 h) gave the single product **4a** in 74% yield (entry 1). Its mass spectra reveals an increment of 56 in parent molecular weight, and the ^{13}C NMR spectra show two diagnostic carbon signals at 203.4 and 163.3 ppm, characteristic of a ketone and a lactone group, respectively. Because of its molecular complexity, the structure of this novel tricyclic compound was elucidated from an X-ray diffraction analysis.[18] Structurally, compound **4a** consists of a 5,6-dihydro-pyran-2-one core fused with cyclopentane and cyclopentanone groups; the methyl group is *cis* to the two adjacent protons. Notably, heating the same benzene solution (80 °C, 24 h) under CO (1 atm) gave a mixture of the two compounds **4a** and **4b** in 38% and 32% yields, respectively. The yield of compound **4b** was increased to 75% when the same benzene solution of $Co_2(CO)_6$-(alkyne) species was heated under a N_2 atmosphere. The structure of compound **4b** was assigned from X-ray crystallographic analysis.[18] Compound **4b** contains a 5,6-dihydropyran-2-one core fused with an unusual cyclobutane ring having a central methyl group *cis* to two adjacent protons. Relative to starting epoxyalkyne **4**, formation of compound **4a** is described as a [5 + 1]/[2 + 2 + 1]-cycloaddition adduct, whereas formation of **4b** is described as a [5 + 1]/[2 + 2]-cycloadduct. Similar to its phenyl analogue **4**, when the $Co_2(CO)_6(\pi$-alkyne) species obtained from *cis*-epoxyalkyne **5** was heated in benzene (80 °C, 24 h) under CO (50 psi), tricyclic cyclopentanone **5a** was obtained in 77% yield (entry 4). In contrast, tricyclic cyclobutane species **5b** was obtained in 72% yield when the same $Co_2(CO)_6$(alkyne) complex was decomposed under a N_2 atmosphere (entry 6). In a separate experiment, we treated species **4b** with $Co_2(CO)_8$ (1.0 equiv) in hot benzene under N_2 or CO for 24 h, and we did not obtain cyclopentanone species **4a**.

SCHEME 5



SCHEME 6



To understand the effect of epoxide substituents on the two cycloaddition reactions, as outlined in Scheme 5, we prepared also 1,2-disubstituted epoxide **6**. The conditions for carbonylative cyclization of *cis*-epoxyalkyne **6** were much milder than for the 1,1,2-trisubstituted epoxide analogue **4**, because the former avoids formation of a quaternary central carbon during the product formation. No carbon monoxide was required for the synthesis of tricyclic cyclopentanone product **6a**, which was obtained in 82% yield when $Co_2(CO)_6$(alkyne) species of epoxide **6** was heated in benzene under a N_2 atmosphere (Scheme 5, eq 1). The structure of **6a** was confirmed from an X-ray diffraction study.[18] We further examined the effect of a heteroatom in this double carbonylative cycloaddition reaction. When the benzene solution of the $Co_2(CO)_6$(alkyne) species of *cis*-epoxyalkyne **7** bearing a tethered *O*-allyl ether was heated

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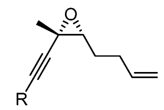
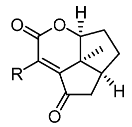
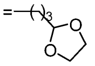
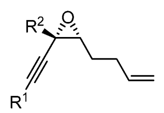
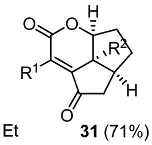
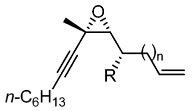
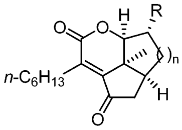
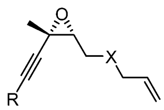
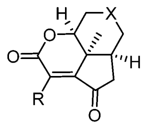
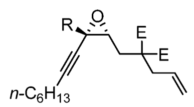
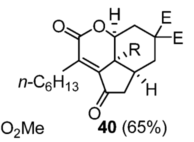
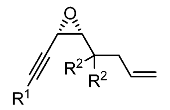
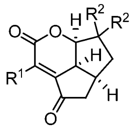
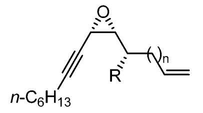
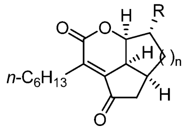
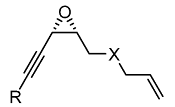
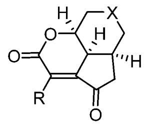
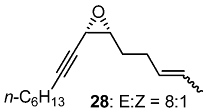
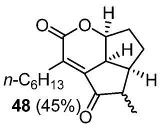
(17) For metal-stabilized cyclic allene species, see: (a) Yin, J.; Abboud, K. A.; Jones, W. M. *J. Am. Chem. Soc.* **1993**, *115*, 3810. (b) Jones, W. M.; Klosin, J. *Adv. Organomet. Chem.* **1998**, *42*, 147.

(18) The x-ray crystallographic data of compounds **4a**, **4b**, and **6a** have been reported in Supporting Information of the early communication of this work; see ref 16.

TABLE 1. Cobalt-Mediated Tandem [5 + 1]/[2 + 2 + 1]-Cycloadditions

Entry	Epoxides[a]	Products (yields)[b]
		
1[c]	**9**: R = TMS	**29** (65%)
2[c]	**10**: R = 	**30** (66%)
		
3[c]	**11**: R^1 = *n*-C_4H_9, R^2 = Et	**31** (71%)
4[c]	**12**: R^1 = R^2 = *n*-C_6H_{13}	**32** (59%)
5[c]	**13**: R^1 = Ph, R^2 = *n*-C_6H_{13}	**33** (58%)
		
6[d]	**14**: R = OAc, n = 1	**34** (77%)
7[d]	**15**: R = OMe, n = 1	**35** (74%)
8[d]	**16**: R = OAc, n = 2	**36** (65%)
		
9[e]	**17**: R = *n*-C_4H_9, X = O	**37** (75%)
10[d]	**18**: R = *n*-C_6H_{13}, X = NTs	**38** (68%)
11[d]	**19**: R = *n*-C_4H_9, X = NTs	**39** (66%)
		
12[d]	**20**: R = Me, E = CO_2Me	**40** (65%)
13[e]	**21**: R = H, E = CO_2Me	**41** (71%)
		
14[e]	**22**: R^1 = *n*-C_4H_9, R^2 = H	**42** (82%)
15[e]	**23**: R^1 = TMS, R^2 = Me	**43** (73%)
		
16[e]	**24**: R = OAc, n = 1	**44** (83%)
17[e]	**25**: R = OAc, n = 2	**45** (70%)
		
18[f]	**26**: R = *n*-C_4H_9, X = O	**46** (85%)
19[g]	**27**: R = *n*-C_6H_{13}, X = NTs	**47** (71%)
20[e]	 **28**: E:Z = 8:1	 **48** (45%)

[a] Epoxyalkyne (1.0 equiv, 0.11 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. [b] Isolated yields. [c] CO (50 psi), 80 °C, 24 h. [d] CO (1 atm), 80 °C, 24 h. [e] N_2, 80 °C, 24 h. [f] N_2, rt, 12 h. [g] CO (1 atm), 60 °C, 24 h.

under N_2, tricyclic cyclopentanone **7a** was obtained in 78% yield (eq 2). For this 1,1,2-trisubstitued epoxyalkyne, we obtained no tricyclic cyclobutane product at under a N_2 atmosphere even at short reaction periods. The enhancing effect of the heteroatom on the carbonylation reaction was well documented in the Pauson−Khand reaction.[19,20] The *cis*-configuration of the epoxyalkyne substrate is crucial for such cycloaddition reactions. Heating a benzene solution of *trans*-epoxyalkyne **8** under N_2 or CO (50 psi) failed to give any organic product, which is in sharp contrast with its *cis*-epoxy analogue **7**. The major species of this solution was the $Co_2(CO)_6$(alkyne) species, which led to a 56% recovery yield of starting epoxide **8** upon Ce(IV)-oxidation (0.95 equiv).

According to the results in Scheme 4, we envisage that tricyclic cyclopentanones **4a** and **5a** and cyclobutane products **4b** and **5b** should have the same intermediate because the presence of CO alters the chemoselectivity of trisubstituted epoxide **4** and **5**. We propose that the tethered alkene of cyclic allene species **A′** (see Scheme 1, eq 3) approached the allene functionality for cobalt-cyclobutane species **E**. In the absence of CO, this species undergoes reductive elimination to form cyclobutane products as depicted in Scheme 6. In the presence of CO, species **E** undergoes CO-insertion to form tricyclic cyclopentanones. The type of epoxide substrates is also crucial for the cyclization chemoselectivity, and as shown in Scheme 5, we did not observe cyclobutane products from epoxides **6** and **7**. We believe that disubstitued epoxide **6** and the tethered oxygen connecting atom of species **7** is prone to carbonylation, and in such cases $Co_2(CO)_8$ provided two CO molecules suffice for the reaction.

To investigate the generality of the preceding [5 + 1]/[2 + 2 + 1]-cycloaddition and its compatibility of this reaction with various functional groups, we prepared various 1,1,2-trisbustitued epoxides **9**−**20** and 1,2-disubstitued epoxides **21**−**28**, according to the information provided in Schemes 4 and 5; the results are summarized in Table 1. Epoxides **14**−**16** and **24**−**25** were prepared with *m*-CPBA-oxidation of their *cis*-allylic alcohol precursors, and such epoxidation led to a high *threo*-selectivity.[21] The $Co_2(CO)_6$(π-alkyne) species of *cis*-epoxyalkyne **9**−**28** were heated in benzene under appropriate conditions to cause liberation of the desired tricyclic cyclopentanone products **29**−**48**. Entries 1−5 show an alternation of the R^1 and R^2 substituents of trisubstituted *cis*-epoxyalkynes **9**−**13**, and

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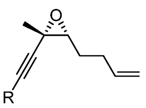
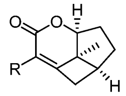
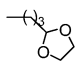
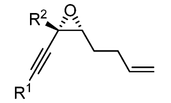
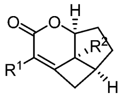
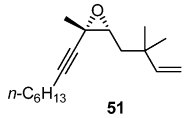
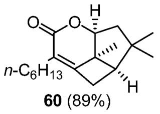
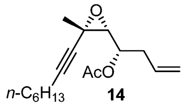
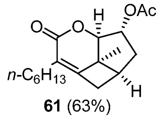
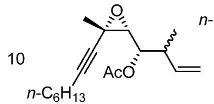
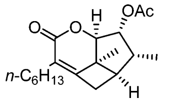
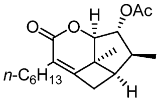
(19) Krafft, M. E.; Scott, I. L.; Romero, R. H. *Tetrahedron Lett.* **1992**, *33*, 3829.

(20) For a mechanistic discussion on the effect of the heteroatom on the Pauson−Kand reaction, see: Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S.; Van Pelt, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 7199.

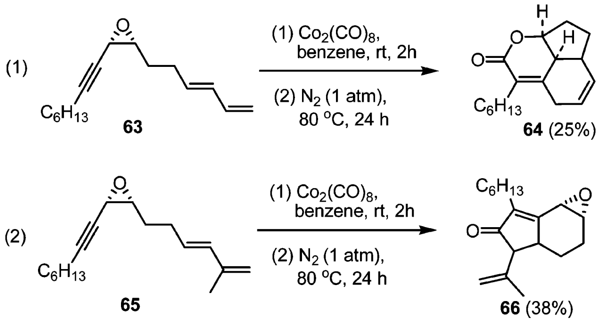
(21) The *m*-CPBA-epoxidation shows good diastereoselectivity for *cis*-allylic alcohol and gave excellent *threo*-selectivity; see: Rossiter, B. R.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *20*, 1979.

TABLE 2. Cobalt-Mediated Tandem [5 + 1]/[2 + 2]-Cycloadditions

Entry	Epoxides[a]	Products (yields)[b]
		
1	**9**: R = TMS	**53** (75%)
2	**10**: R = 	**54** (52%)
		
3	**11**: R^1 = *n*-C_4H_9, R^2 = Et	**55** (68%)
4	**12**: R^1 = R^2 = *n*-C_6H_{13}	**56** (63%)
5	**13**: R^1 = Ph, R^2 = *n*-C_6H_{13}	**57** (61%)
6	**49**: R^1 4-F-Ph, R^2 = *n*-C_6H_{13}	**58** (59%)
7	**50**: R^1 = 4-OMe-Ph, R^2 = *n*-C_6H_{13}	**59** (63%)
8	 **51**	 **60** (89%)
9	 **14**	 **61** (63%)
10	 **52** (dr = 1:1)	 **a**  **b** **62** (85%, **a**/**b** = 1)

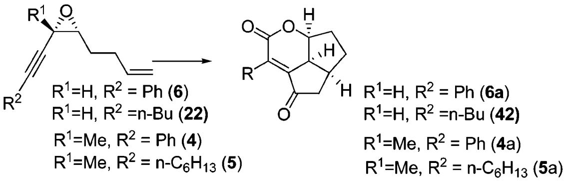
[a] Epoxyalkyne (1.0 equiv, 0.11 M) was treated with $Co_2(CO)_8$ (1.1 equiv) in benzene at 23 °C for 2 h, followed by stirring under N_2, 80 °C, 24 h. [b] Isolated yield.

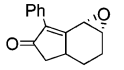
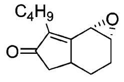
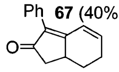
SCHEME 7



heating the benzene solution of their $Co_2(CO)_6(\pi$-alkyne) species under CO (50 psi) produced tricyclic cyclopentanones **29**−**33** in 58−71% yields (entries 1−5). Tricyclic cyclopentanone products **29** and **30** contain a TMS and 1,3-dioxolane group, respectively, which are useful for further functionalization. Entries 3−5 show that an ethyl and a hexyl chain can be incorporated at the quaternary central carbon of the tricyclic cyclopentanone structure, as evident from the reasonable yields of compounds **31**−**33**. Entries 6−8 reveal the suitability of this cycloaddition for trisubstituted epoxyalkynes **14**−**16** containing an acetate and methoxy group, and their tricyclic cyclopentanones **34**−**36** were obtained in 65−77% yield under CO (1 atm). The linkage groups[19,20] such as oxygen, tosylamide, and $C(CO_2Me)_2$ in *cis*-epoxyalkynes **17**−**21** facilitated the cycloaddition and gave cyclopentanone products **37**−**41** in 65−75% yields (entries 9−13) under nitrogen or ambient CO pressure (1 atm). The conditions for the synthesis of tricyclic pyranone derivatives **41**−**48** bearing a secondary central carbon were much milder (entries 13−20) than for their quaternary analogues. Cobalt-π-alkyne complexes generated from epoxyalkynes **21**−**28** were decomposed in benzene exclusively under N_2 to afford tricyclic cyclopentanones **41**−**48** with yields exceeding 70% except for product **48** that comprised a 1,2-disubstituted alkene. The transformation of epoxyalkyne **26** into the corresponding tricyclic lactone **46** performed under nitrogen was effective even at about 23 °C. Similar to preceding trisubstituted epoxyalkynes **9**−**20**, this cycloaddition reaction is compatible with various 1,2-disubstituted *cis*-epoxyalkynes having an acetate group and various linkage groups including oxygen, tosylamide, and $C(CO_2Me)_2$. *cis*-Epoxyalkyne substrates of such a wide scope truly reflect the reliability of this [5 + 1]/[2 + 2 + 1]-cycloaddition.

TABLE 3. Effect of Additives in the Cobalt-Catalyzed Cycloaddition Reaction

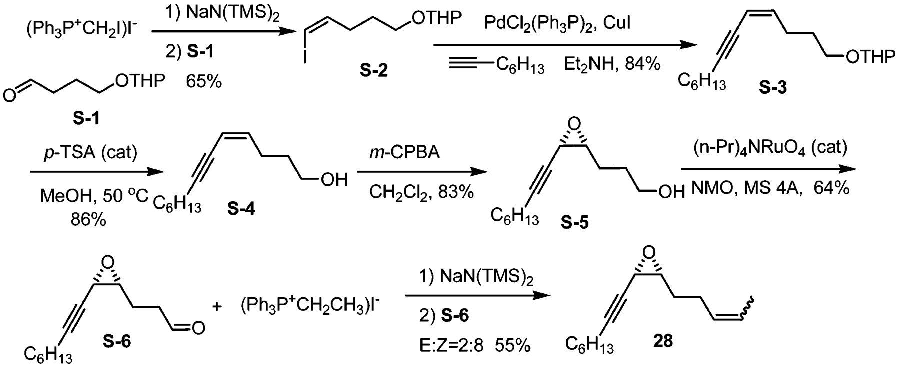


Entry	Epoxides[a]	$Co_2(CO)_8$ (mol %)	Additive (mol %)	Products(yield %)[b]
1[c]	**22**	10	None	**42** (7%)
2[d]	**22**	10	$P(OPh)_3$	**22** (55%)
3	**22**	10	Bu_3PS (60)	**42** (40%)
4	**6**	10	Bu_3PS (60)	 **67** (53%)
5	**22**	15	TMTU (50)	 **68** (60%)
6	**6**	15	TMTU (50)	**67** (40%)  **69** (10%)
7	**4**	10	Bu_3PS (60)	**4a** (13%)
8	**5**	10	Bu_3PS (60)	messy products

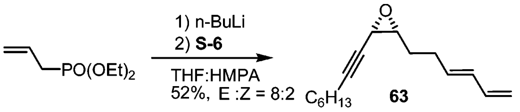
[a] Epoxyalkyne (1.0 equiv, 0.11 M), $Co_2(CO)_8$, and additive was stirred in benzene at 80 °C under CO (1 atm), 24 h. [b] Isolated yield. [c] Under CO (50 psi). [d] 120 °C, under CO (3 atm) pressure.

As shown in Scheme 4, tricyclic butane products **4b** and **5b** were formed exclusively upon heating a benzene solution of

SCHEME 8



SCHEME 9



$Co_2(CO)_6$(alkyne) species generated from 1,1,2-trisubstituted epoxides **4** and **5** lacking a linkage heteroatom. We thoroughly investigated this novel cycloaddition reaction using various 1,1,2-trisubstituted epoxyalkynes **9**−**14** and **49**−**52** as depicted in Table 2. Similar to their phenyl and hexyl analogues **4** and **5**, *cis*-epoxyalkyes **9** and **10** afforded tricyclic cyclobutane derivatives **53** and **54** in 75% and 52% yields, respectively, through heating their cobalt-π-alkyne species in benzene under N_2. Entries 3−7 show alternation of the R^1 and R^2 substituents of epoxyalkynes **11**−**13** and **49** and **50**, and their corresponding tricyclic cyclobutane products **55**−**59** were produced smoothly with yields exceeding 59% in all cases. *cis*-Epoxyalkyne **51** bearing a dimethyl group adjacent to the vinyl group gave the corresponding cyclobutane product **60** in 89% yield. This cycloaddition is compatible with an acetate group as in epoxyalkyne **14** and **52**, which delivered cyclobutane product **61** and **62** in 63% and 85%, respectively.

The relative configurations of the two diastereomers **62a** and **62b** were determined from NOE experiments (see Supporting Information). Compound **57** and **60** are active in vivo against the human corona virus of the severe acute respiratory syndrome (SARS).[22]

We turned our attention to trap the hypothetical $Co_2(CO)_6$-stabilized cyclic allene species **A** with a tethered diene group. We prepared *cis*-epoxyalkynes **63** having a pendent diene as shown in Scheme 7; heating its $Co_2(CO)_6(\pi\text{-alkyne})$ derivative in benzene under N_2 produced cycloadduct **64** in 25% yield. Compound **64** was formed *via* a tandem [5 + 1]/[4 + 2]-cycloaddition between epoxyalkyne, CO and diene functionalities. An attempt to perform a similar reaction on epoxyalkyne **65** gave, however, tricyclic cyclopentenone product **66** via the Pauson−Khand reaction with intact epoxide functionality. The reason for such a different behavior is unclear.

Table 3 shows our efforts to realize this cycloaddition using $Co_2(CO)_8$ in catalytic proportion in the presence of organic additives[23−25] including triphenylphosphite,[23] tributyl-phosphane sulfides,[24] and tetramethyl thiourea (TMTU),[25] which effectively enhanced the $Co_2(CO)_8$-catalyzed Pauson−Khand reaction. We first examined the reaction using *cis*-epoxyalkyne **22** and 10 mol % $Co_2(CO)_8$ in hot benzene (80 °C, 24 h) under CO (50 psi), but we obtained desired tricyclic cyclopentanone **42** in only 7% yield (entry 1). When epoxyalkyne **22** was heated in benzene (80 °C, 24 h) using $Co_2(CO)_8$ (10 mol %) and triphenylphosphite (60 mol %) under CO pressure (3 atm), we observed no cycloaddition reaction and epoxide **22** was recovered in 55% yield (entry 2). The desired tricyclic cyclopentanone **42** was nevertheless obtained in 40% yield from epoxyalkyne **22** and $Co_2(CO)_8$ (10 mol %, entry 3) using tributylphosphane sulfide (60 mol %) and CO (1 atm). When we attempted a similar reaction on epoxide **6** using tributylphosphane sulfide, we obtained Pauson−Khand reaction product **67** in 53% yield (entry 4). In the presence of tetramethyl thiourea (TMTU) additive,[25] epoxides **6** and **22** preferably gave Pauson−Khand reaction products **67** and **68** in 40% and 60% yields, respectively (entries 5 and 6). These organic additives seem to be more favorable for Pauson−Khand reaction rather than our desired tandem cyclocarbonylation.

Conclusion

In summary, we have developed a new and highly chemoselective coupling reaction of epoxyalkyne, CO, and olefin that effects tandem [5 + 1]/[2 + 2 + 1] or cyclocarbonylation/[2 + 2]-cycloadditions depending on substrates and conditions. This novel cycloaddition reaction constructs complex tricyclic molecules from acyclic epoxyalkyne via formation of multiple C−C and one C−O bonds along with cleavage of one C−O bond. The mechanism of this novel cycloaddition reaction involves an unusual cobalt-stabilized cyclic allene intermediate. This new approach is successfully extended to construct various tricyclic carbo- and heterocyclic frameworks, which could be useful for the formation of a library of synthetic small molecules for medicinal applications.

Experimental Section

General Sections. Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe, cannula, and septa apparatus. Benzene was dried with sodium benzophenone and distilled before use. Syntheses of representative *cis*-epoxyalkynes are given in Supporting Information.

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(22) Wu, C.-Y.; Jan, J.-T.; Ma, S.-H.; Kuo, C.-J.; Juan, H.-F.; Cheng, Y.-S. E.; Hsu, H.-H.; Huang, H.-C.; Wu, D.; Brik, A.; Liang, F.-S.; Liu, R.-S.; Fang, J.-M.; Chen, S.-T.; Liang, P.-H.; Wong, C.-H. *Proc. Nat. Acad. Sci.* **2004**, *101*, 10012.

(23) Jeong, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 3159.

(24) Hayashi, M.; Hashimoto, Y.; Yamamoto, Y.; Usuki, J.; Saigo, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 631.

(25) Tang, Y.-F.; Deng, L.-J.; Zhang, Y.-D.; Dong, G.-B.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2005**, *7*, 593.

(A) Representative Procedure for Preparation of *cis*-Epoxyalkynes. (I) Synthesis of (2*R,3*S**)-2-(1-Octynyl)-3-[(*Z*)-3-pentenyl]oxirane (28).** See Scheme 8.

(a) Synthesis of 2-(5-Iodo-pent-4-enyloxy)-tetrahydropyran (S-2). To a suspension of iodomethyltriphenylphosphonium iodide (25.22 g, 47.6 mmol) in THF (250 mL) at 23 °C was slowly added a THF solution of sodium hexamethyldisilazane (43.9 mL, 1 M), and the mixture was stirred for 1 h. To this solution was added HMPA (20 mL) at −60 °C, followed by addition of aldehyde **S-1** (6.30 g, 36.6 mmol), and the mixture was stirred for 1 h before addition of water. The organic layer was extracted with diethyl ether (50 mL × 2), dried over $MgSO_4$, and concentrated under reduced pressure. The residues were chromatographed on a silica column to afford vinyl iodide **S-2** as a colorless oil (7.04 g, 23.8 mmol, 65%)

(b) Synthesis of 2-Tridec-4-en-6-ynyloxy-tetrahydro-pyran (S-3). To a mixture of $PdCl_2(Ph_3P)_2$ (350 mg, 0.51 mmol) and CuI (40 mg, 0.25 mmol) in Et_2NH (50 mL) was added compound **S-2** (7.0 g, 23.63 mmol) at 25 °C under N_2, and the mixtures were stirred for 10 min before the addition of 1-hexyne (2.52 g, 30.66 mmol). The resulting reaction was stirred at 25 °C for 8 h and quenched by an aqueous NH_4Cl solution. The organic layer was extracted with ether, washed with H_2O, dried over $MgSO_4$, and concentrated. The residues were chromatographed through a silica column to give product **S-3** (5.53 g, 19.85 mmol, 84%) as a colorless oil.

(c) Synthesis of Tridec-4-en-6-yn-1-ol (S-4). In the presence of *p*-TSA (10 mol %), THP-protected alcohol **S-3** (5.00 g, 17.96 mmol) was heated in methanol (50 mL) at 50 °C for 5 h, and methanol was removed under reduced pressure. The residues were dissolved in ether and washed with $NaHCO_3$. The ether solution was dried over $MgSO_4$, concentrated, and chromatographed on a silica column (hexane/EtOAc, 2:1) to give pure alcohol **S-4** (3.00 g, 15.44 mmol, 86%) as a colorless oil.

(d) Synthesis of (3-[(2*S,3*R**)-3-(1-Octynyl)oxiran-2-yl]-1-propanol) (S-5).** To a CH_2Cl_2 solution (10 mL) of *cis*-diene **S-4** (3.00 g, 15.44 mmol) was added *m*-chloroperbenzoic acid (3.46 g, 20.07 mmol), and the mixture was stirred for 12 h at 25 °C under N_2. The resulting solution was quenched with an aqueous $NaHCO_3$ solution, extracted with diethyl ether, and dried over $MgSO_4$. The solution was filtered through a short basic Al_2O_3 bed, concentrated, and eluted through a Et_3N-pretreated silica column (diethyl ether/hexane, 1:1) to afford the *cis*-epoxyalkyne **S-5** as a yellow oil (2.69 g, 12.81 mmol, 83%).

(e) Synthesis of 3-[(2*S,3*R**)-3-(1-Octynyl)oxiran-2-yl]propanal (S-6).** Solid TPAP (tetra-*n*-propylammonium perruthenate) (188 mg, 0.6 mmol) was added in one portion to a mixture of the alcohol **S-5** (2.69 g, 12.79 mmol), NMO (2.25 g, 19.18 mmol), and powdered 4 Å molecular sieves (6.00 g) in CH_2Cl_2 (30 mL) at 23 °C under N_2. After stirring for 2 h, the mixture was filtered through a short silica pad with CH_2Cl_2 as the eluent. The filtrate was concentrated, and the crude residues were purified by a silica column to afford pure aldehyde **S-6** as a light yellow oil (1.70 g, 8.18 mmol, 64%).

(f) Synthesis of (2*R,3*S**)-2-(1-Octynyl)-3-[(*Z*)-3-pentenyl]oxirane (28).** To a THF (10 mL) suspension of ethyltriphenylphosphonium iodide (1.30 g, 3.1 mmol) was slowly added sodium hexamethyldisilazane (2.9 mL, 1 M in THF) at 25 °C, and the mixture was stirred for 1 min and cooled to −78 °C before addition of a HMPA solution (1 mL) of aldehyde **S-6** (0.50 g, 2.4 mmol). The cold bath was removed, and the stirring was continued for 30 min. To the reaction mixture was added water, and the organic layer was separated, dried over $MgSO_4$, concentrated, and chromatographed on a silica column to afford epoxyalkyne **28** (0.29 g, 1.3 mmol, 55%) as a colorless oil: IR (neat, cm^{-1}) 2238(w), 1641(w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54−5.40 (m, 2 H), 3.41−3.39 (m, 1 H), 3.01−2.97 (m, 1 H), 2.26−2.15 (m, 4 H), 1.78−1.67 (m, 2 H), 1.62 (d, 3 H, $J = 6.0$ Hz), 1.48 (quin, 2 H, $J = 7.2$ Hz), 1.40−1.24 (m, 6 H), 0.87 (t, 3 H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.0, 124.6, 86.3, 75.0, 57.3, 45.3, 31.2, 29.1, 28.3, 28.2, 23.2, 22.4, 18.6, 13.8, 12.5; HRMS calcd for $C_{15}H_{24}O$ 220.1827, found 220.1824.

(II) Synthesis of (2*S,3*R**)-2-[(3*E*)-3,5-hexadienyl]-3-(1-octynyl)oxirane (63).** See Scheme 9. To a solution of diethyl allylphosphonate (1.07 g, 6.0 mmol) in THF (15 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 2.4 mL, 6.0 mmol) at −78 °C. After stirring for 15 min, a solution of aldehyde **S-6** (1.04 g, 5.0 mmol) in HMPA (2.1 mL, 12 mmol) was added dropwise. The resulting solution was stirred for 2 h at −78 °C and then warmed to 25 °C. Stirring was continued for an additional 12 h before addition of a saturated NH_4Cl solution. The mixture was extracted with diethyl ether (3 × 15 mL), and the organic phase was washed with brine, dried over $MgSO_4$, and concentrated to afford the crude product. Purification by flash chromatography gave desired diene **63** (0.60 g, 2.6 mmol) in 52% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34−6.24 (m, 1 H), 6.13−6.03 (m, 1 H), 5.76−5.67 (m, 1 H), 5.09 (d, 1 H, $J = 17.6$ Hz), 4.97 (d, 1 H, $J = 10.4$ Hz), 3.41−3.39 (m, 1 H), 3.03−2.98 (m, 1 H), 2.31−2.15 (m, 4 H), 1.84−1.72 (m, 2 H), 1.52−1.43 (m, 2 H), 1.40−1.24 (m, 6 H), 0.87 (t, 3 H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 133.3, 131.6, 115.1, 86.4, 74.8, 57.1, 45.3, 31.1, 28.8, 28.7, 28.3, 28.2, 22.3, 18.6, 13.8; HRMS calcd for $C_{16}H_{24}O$: 232.1827, found 232.1824.

(B) Representative Procedure for Cobalt-Mediated Cycloaddition Reaction. To a benzene solution (5 mL) of *cis*-epoxy ene-yne **28** (100 mg, 0.45 mmol) was added $Co_2(CO)_8$ (171 mg, 0.50 mmol) under nitrogen, and the mixture was stirred for 2 h at 23 °C. The solution was transferred to a high-pressure reactor under CO (50 psi) and heated at 80 °C for 24 h. The solution was filtered over a short silica pad; the filtrate was concentrated and purified using preparative TLC (diethyl ether/hexane, 1/1) to afford tricyclic cyclopentanone *rel*-(5a*S*,7a*R*,7b*R*)-3-hexyl-5-methyl-2,4,5,5a,6,7,-7a,7b-octahydropentaleno[1,6-*bc*]pyran-2,4-dione (**48**) (56 mg, 0.20 mmol, 45%): IR (neat, cm^{-1}) 1722(w), 1710(s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (q, 1 H, $J = 8.0$ Hz), 3.36 (t, 1 H, $J = 6.8$ Hz), 2.91−2.81 (m, 1 H), 2.64−2.57 (m, 1 H), 2.03−2.97 (m, 1 H), 2.35−2.20 (m, 2 H), 2.02−1.85 (m, 2 H), 1.49−1.12 (m, 8 H), 1.14 (d, 3 H, $J = 7.6$ Hz), 1.18−0.98 (m, 1 H), 0.83 (t, 3 H, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 163.7, 141.8, 136.0, 81.3, 50.8, 43.1, 40.8, 31.4, 30.6, 29.6, 29.3, 29.2, 25.8, 22.5, 17.3, 14.0; HRMS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1722.

Spectal data for *rel*-(6a*R*,8a*R*,8b*R*)-3-Hexyl-4,6a,7,8,8a,8b-hexahydro-2*H*- cyclopenta[*ij*]isochromen-2-one (64): IR (neat, cm^{-1}) 1725 (s), 1620(w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (t, 1 H, $J = 5.0$ Hz), 5.66 (br, 1 H), 4.92 (q, 1 H, $J = 8.0$ Hz), 3.13 (dd, 1 H, $J = 21.5$, 4.5 Hz), 2.96 (t, 1 H, $J = 8.0$ Hz), 2. 79 (d, 1 H, $J = 21.5$ Hz), 2.69 (br, 1 H), 2.44−2.36 (m, 1 H), 2.34−2.27 (m, 1 H), 2.20−2.12 (m, 1 H), 1.97−1.84 (m, 2 H), 1.40−1.21 (m, 9 H), 0.85 (t, 3 H, $J = 6.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 147.0, 128.6, 126.1, 123.1, 79.1, 40.2, 39.0, 31.8, 31.7, 29.7, 29.2, 29.0, 28.3, 26.8, 22.6, 14.0; HRMS calcd for $C_{17}H_{24}O_2$ 260.1776, found 260.1760.

Acknowledgment. The authors thank the National Science Council, Taiwan for supporting this work.

Supporting Information Available: Experimental procedures, spectral data, and NMR spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0620617