Synthesis of Cyclic *cis*-Enediynes from Manganese Carbyne Complexes and α,ω-Diynes

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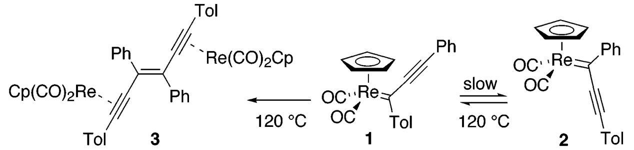
Cyclic *cis*-enediynes are readily prepared by a two-step one-pot procedure. The first step is the copper-catalyzed addition of α,ω-diynes to manganese carbyne complexes to give intermediate bis(alkynylcarbene) complexes that rearrange to enediyne complexes below room temperature. In the second step, the free enediyne is released from manganese by photolysis, copper-catalyzed air oxidation, or stoichiometric Cu(II) oxidation. These new procedures have been applied to a variety of five-, six-, and seven-membered-ring cyclic enediynes containing a range of ether, ester, and ketone functional groups.

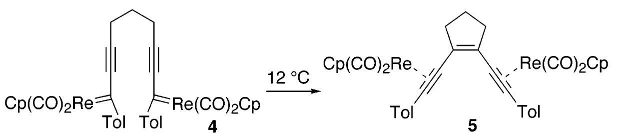
Introduction

Heteroatom-substituted alkynylcarbene complexes such as $(CO)_5M{=}C(OR)C{\equiv}CR'$ are highly reactive, easily accessible, and useful in a plethora of high-yielding transformations.[1,2] Recently, we prepared non-heteroatom-substituted alkynyl carbene complexes such as $Cp(CO)_2Re{=}C(Tol)C{\equiv}CPh$ (**1**) ($Cp = \eta^5\text{-}C_5H_5$, $Tol = 4\text{-}MeC_6H_4$) to investigate the possibility of [1,3] metal shifts. However, at 120 °C, the rearrangement of **1** to $Cp(CO)_2Re{=}C(Ph)C{\equiv}CTol$ (**2**) was much slower[3] than the unexpected formation of the dimeric *E*-enediyne complex $[Cp(CO)_2Re]_2[\eta^2,\eta^2\text{-}TolC{\equiv}C(Ph)C{=}C(Ph)C{\equiv}CTol]$ (**3**) (Scheme 1).[4] **3** is formed by the regioselective "tail-to-tail" coupling of the remote alkynyl carbons in a kinetically second-order process.[5] In contrast, Sierra recently reported the selective "head-to-head" Pd-catalyzed coupling of $(CO)_5Cr{=}C(OEt)C{\equiv}CPh$ to (*E*,*Z*)-$PhC{\equiv}C(OEt)C{=}C(OEt)C{\equiv}CPh$.[6,7]

Scheme 1



Scheme 2



We recently found that the tethered bis(alkynylcarbene) rhenium complex $Cp(CO)_2Re{=}C(Tol)C{\equiv}CCH_2CH_2CH_2C{\equiv}CC(Tol){=}Re(CO)_2Cp$ (**4**) readily rearranges to the cyclic enediyne complex $[Cp(CO)_2Re]_2[\eta^2,\eta^2\text{-}TolC{\equiv}CC(CH_2CH_2CH_2){=}CC{\equiv}CTol]$ (**5**) below room temperature by the coupling of the remote alkynyl carbons (Scheme 2).[5] This straightforward route to enediyne complexes under mild conditions has potential value in the synthesis of pharmaceutically interesting enediynes.[8]

This new rhenium route to enediyne complexes suffers from the high thermal stability of the rhenium diyne complexes and the high costs associated with stoichiometric rhenium reactions. To circumvent these problems, we recently extended this chemistry to the analogous manganese series.[9] Simple manganese alkynylcarbene complexes such as $Cp(CO)_2Mn{=}C(Ph)C{\equiv}$

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(1) For reviews of heteroatom-substituted alkynylcarbene complexes, see: (a) Aumann, R.; Nienaber, H. *Adv. Organomet. Chem.* **1997**, *41*, 163. (b) Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, Chapter 5.3. (c) Herndon, J. W. *Coord. Chem. Rev.* **1999**, *181*, 177. (d) Sierra, M. A. *Chem. Rev.* **2000**, *100*, 3591. (e) de Meijere, A.; Schriemer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964, and references therein. (f) Herndon, J. W. *Tetrahedron* **2000**, *56*, 1257.

(2) For group 7 Fischer alkynylcarbene complexes, see: (a) Weng, W.; Ramsden, J. A.; Arif, A. M.; Gladysz, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 3824. (b) Weng, W.; Arif, A. M.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 891. (c) Terry, M. R.; Kelly, C.; Lugan, N.; Geoffroy, G. L.; Haggerty, B. S.; Rheingold, A. J. *Organometallics* **1993**, *12*, 3607. (d) Weng, W.; Bartik, T.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2199. (e) Casey, C. P.; Kraft, S.; Powell, D. R.; Kavana, M. *J. Organomet. Chem.* **2001**, *617/618*, 723.

(3) Casey, C. P.; Kraft, S.; Powell, D. R. *Organometallics* **2001**, *20*, 2651.

(4) Casey, C. P.; Kraft, S.; Kavana, M. *Organometallics* **2001**, *20*, 3795.

(5) (a) Casey, C. P.; Kraft, S.; Powell, D. R. *J. Am. Chem. Soc.* **2000**, *122*, 3771. (b) Casey, C. P.; Kraft, S.; Powell, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 2584.

(6) Sierra, M. A.; del Amo, J. C.; Mancheño, M. J.; Gómez-Gallego, M. *J. Am. Chem. Soc.* **2001**, *123*, 851.

(7) For earlier work on carbene coupling of metal carbene complexes, see: (a) Casey, C. P.; Anderson, R. L. *J. Chem. Soc., Chem. Commun.* **1975**, 895. (b) Casey, C. P.; Burkhardt, T. J.; Bunnell, C. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 2127. (c) Casey, C. P.; Polichnowski, S. W. *J. Am. Chem. Soc.* **1977**, *99*, 6097. (d) Fischer, H.; Schmid, J. *J. Mol. Catal.* **1988**, *46*, 277. (e) Fischer, H.; Zeuner, S.; Ackermann, K.; Schmid, J. *Chem. Ber.* **1986**, *119*, 1546. (f) Fischer, H.; Zeuner, S.; Ackermann, K. *Chem. Commun.* **1984**, 684. (g) Hohmann, F.; Siemoneit, S.; Nieger, M.; Kotila, S.; Dötz, K. H. *Chem. Eur. J.* **1997**, *3*, 853.

(8) For reviews of enediynes, see: (a) Nicolaou, K. C.; Smith, A. L. *The Enediyne Anitbiotics in Modern Acetylene Chemistry*, Stang, P. D., Diederich, F., Eds.; VCH: Weinheim, 1995; p 203. (b) Maier, M. E. *Synlett* **1995**, 13. (c) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (d) Smith, A.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 2103. (e) Sander, W. *Acc. Chem. Res.* **1999**, *32*, 669. (g) Konig, B. *Eur. J. Org. Chem.* **2000**, 381.

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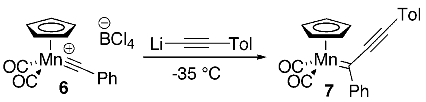
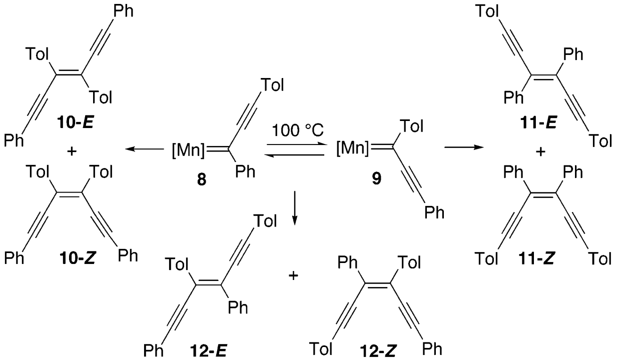
Scheme 3



Scheme 4



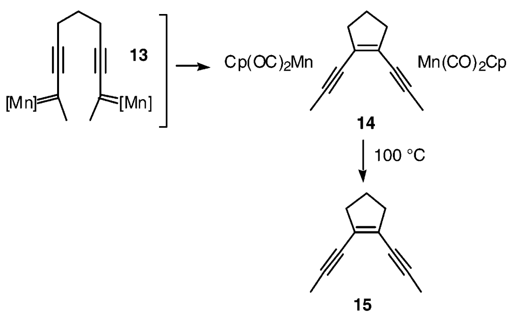
CTol (**7**) were readily prepared from $[Cp(CO)_2Mn{\equiv}CPh]BCl_4$[10] (**6**) and lithiotolylacetylene (Scheme 3).[9,11] The classic Fischer synthesis of carbyne complex **6** involves (1) addition of PhLi to $CpMn(CO)_3$ to give the isolated acyl manganese complex $Cp(CO)_2MnCOPhLi$, (2) reaction of the acyl manganese complex with Me_3SiCl to give the siloxycarbene complex $Cp(CO)_2Mn{=}C(OSiMe_3)Ph$, and (3) reaction of the siloxycarbene complex with BCl_3 to give **6**, which is very temperature sensitive ($T_{dec} < -20$ °C).[10]

While both the rhenium and manganese alkynyl carbene complexes were efficiently converted to enediyne metal complexes upon heating above 100 °C, there were two notable differences between the reactions. First, while rhenium complexes led exclusively to *trans*-enediyne complexes, the manganese analogues gave mixtures of *cis*- and *trans*-enendiyne complexes along with free enediynes formed from loss of the manganese fragment.[9] Second, while dimerization of rhenium complexes to "tail-to-tail" products was much faster than [1,3]-rhenium migration, the dimerization of manganese complex $(C_5H_4Me)(CO)_2Mn{=}C(Ph)C{\equiv}CTol$ (**8**) was competitive with a [1,3]-manganese shift to give isomer **9** and products were seen resulting from formal "head-to-head" and "head-to-tail" dimerization: (*E*/*Z*)-$PhC{\equiv}C(Tol)C{=}C(Tol)C{\equiv}CPh$ (**10**), (*E*/*Z*)-$TolC{\equiv}C(Ph)C{=}C(Ph)C{\equiv}CTol$ (**11**), and (*E*/*Z*)-$PhC{\equiv}C(Tol)C{=}C(Ph)C{\equiv}CTol$ (**12**) (Scheme 4).[9]

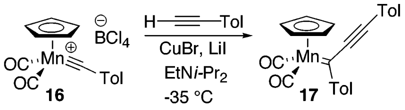
The attempted synthesis of a tethered bis(alkynylcarbene) manganese complex, $Cp(CO)_2Mn{=}C(Ph)C{\equiv}CCH_2CH_2CH_2C{\equiv}CC(Ph){=}Mn(CO)_2Cp$ (**13**), led directly to the rearranged cyclic enediyne complex $[Cp(CO)_2Mn]_2$-$[\eta^2,\eta^2$-$PhC{\equiv}CC(CH_2CH_2CH_2){=}CC{\equiv}CPh]$ (**14**) (Scheme 5). Thermolysis of the enediyne complex at 100 °C generated free bis(phenylethynyl)cyclopentene (**15**) in moderate yield.[9]

Here we report several improvements in the synthesis of cyclic enediynes by this manganese alkynylcarbene route. First, we have developed a milder procedure for synthesis of alkynylcarbene complexes from the copper(I)-catalyzed reaction of terminal alkynes with carbyne complexes; this procedure gets around the use of alkynyllithium reagents. Second, we have developed three new mild methods for conversion of manganese enediyne complexes to the free enediynes that involve photolysis or Cu-catalyzed air oxidation or stoichiometric Cu(II) oxidation. The combination of these advances has allowed us to synthesize new cyclic enediynes containing a variety of reactive functionalities.

Scheme 5



Scheme 6



Results

Copper-Catalyzed Addition of Alkynes to $[Cp(CO)_2Mn{\equiv}CAr]^+$. Previous syntheses of manganese alkynylcarbene complexes involved addition of reactive alkynyllithium reagents to cationic manganese carbyne complexes.[8,10] We have now found that alkynylcopper intermediates generated catalytically from terminal alkynes, Cu(I) salts, and amine bases react with cationic carbyne complexes to produce manganese alkynylcarbene complexes. Addition of a THF solution of 4-ethynyltoluene and EtN*i*-Pr_2 containing a catalytic amount of CuBr (10%) and LiI to a yellow CH_2Cl_2 solution of $[Cp(CO)_2Mn{\equiv}CTol]BCl_4$ (**16**)[10] formed the deep red-brown alkynylcarbene complex $Cp(CO)_2Mn{=}C(Tol)C{\equiv}CTol$ (**17**) in 73% yield (Scheme 6). IR spectroscopy showed that the reaction was complete within a minute at −35 °C. The carbyne ν_{CO} peaks at 2084 and 2042 cm^{-1} disappeared, and new peaks, assigned to the manganese alkynylcarbene complex **17**, grew in at 1972 and 1921 cm^{-1}. The alkynylcarbene complex **17** was isolated by column chromatography and characterized spectroscopically. A study of reaction variables indicated that higher yields were obtained using EtN*i*-Pr_2 rather than Et_3N as base and using either CuBr or CuI rather than CuCl as a catalyst; similar yields were obtained using either phenyl or tolyl carbyne complexes or using C_5H_5 or C_5H_4Me manganese complexes.

When the copper-catalyzed addition of tethered alkynes to manganese alkynes was studied at low temperature, color changes indicated the formation of tethered bis alkyne complexes that underwent C=C bond formation below room temperature to form manganese enediyne complexes. When a mixture of dipropargyl ether (0.4 mol

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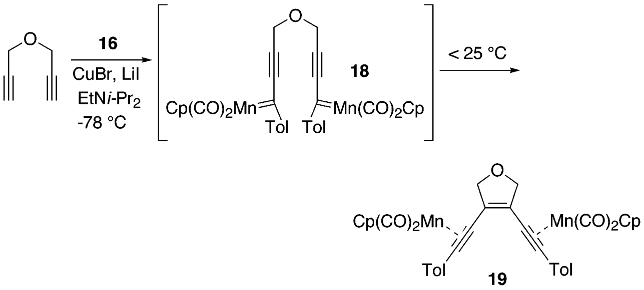
[9] (a) Casey, C. P.; Dzwiniel, T. L.; Kraft, S.; Kozee, M. A.; Powell, D. R. *Inorg. Chim. Acta* **2003**, *345*, 320. (b) Kraft. S. Ph.D. Thesis, University of Wisconsin−Madison, 2001.

[10] Fischer, E. O.; Meineke, E. W.; Kreissl, F. R. *Chem. Ber.* **1977**, *110*, 1140.

[11] Ortin, Y.; Coppel, Y.; Lugan, N.; Mathieu, R.; McGlinchey, M. J. *Chem. Commun.* **2001**, 1690.

Scheme 7

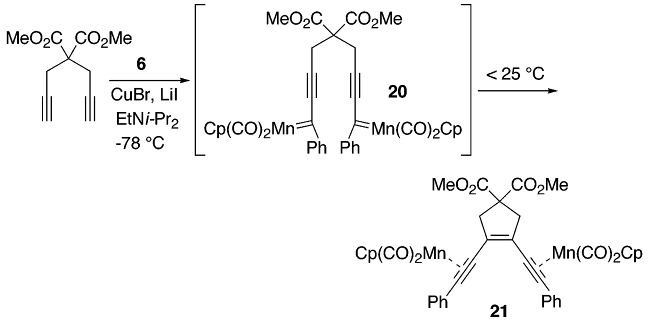


per mol Mn), EtN*i*-Pr$_2$, and catalytic amounts of CuBr and LiI was added to a yellow solution of [Cp(CO)$_2$Mn≡CTol]BCl$_4$ (**16**) in CH$_2$Cl$_2$ at −78 °C, an immediate color change to deep red-brown occurred, consistent with formation of the bis(alkynylcarbene) complex Cp(CO)$_2$Mn=C(Tol)C≡CCH$_2$OCH$_2$C≡CC(Tol)=Mn(CO)$_2$Cp (**18**) (Scheme 7). When a sample taken from the −78 °C reaction mixture was immediately analyzed by thin-layer chromatography, only the bright red coupled product [Cp(CO)$_2$Mn]$_2$[η^2,η^2-TolC≡CC(CH$_2$OCH$_2$)=CC≡CTol] (**19**) was seen. There was no evidence for a dark red-brown manganese carbene complex such as **18**. Slow warming to room temperature over several hours led to a noticeably lighter red solution, from which the bright red enediyne complex **19** was isolated in moderate (38%) yield after silica gel chromatography. Mass spectroscopic data were consistent with the dimeric manganese enediyne complex **19**. The infrared spectrum contained two peaks at 1973 and 1907 cm^{-1}, consistent with a dicarbonyl complex. The ^{1}H NMR spectrum was similar to those observed for known rhenium enediyne complexes.[5]

When the reaction of carbyne complex **16** (16 mM) with dipropargyl ether, EtN*i*-Pr$_2$, and catalytic amounts of CuBr and LiI was monitored by in situ IR spectroscopy at −70 °C using a ReactIR system, carbyne complex **16** was consumed within 30 s. However, because of the similarity of the metal carbonyl stretching frequencies of the manganese alkynylcarbene complexes (**17**, ν_{CO} = 1971, 1921 cm^{-1}) and enediyne complexes (**19**, ν_{CO} = 1973, 1907 cm^{-1}), it was not possible to follow the conversion of **18** to **19** by IR spectroscopy. Attempts to follow the low-temperature conversion of **18** to **19** by NMR spectroscopy were unsuccessful due to the formation of trace paramagnetic impurities.

The greater functional group tolerance of the copper-catalyzed addition of terminal alkynes to carbyne complexes compared with the use of alkynyllithium reagents is illustrated by the reaction of dimethyl dipropargylmalonate with [Cp(CO)$_2$Mn≡CPh]BCl$_4$ (**6**). In this reaction, the initially formed tethered bis(alkynylcarbene) complex Cp(CO)$_2$Mn=C(Ph)C≡CCH$_2$C(CO$_2$Me)$_2$CH$_2$C≡CC(Ph)=Mn(CO)$_2$Cp (**20**) rearranged below room temperature to the enediyne complex [Cp(CO)$_2$Mn]$_2$[η^2,η^2-PhC≡CC(CH$_2$C(CO$_2$Me)$_2$CH$_2$)=CC≡CPh] (**21**) (Scheme 8). The deep red complex **21** was isolated by column chromatography in 85% yield and was characterized both spectroscopically and by X-ray crystallography (Figure 1).[12,13]

Scheme 8



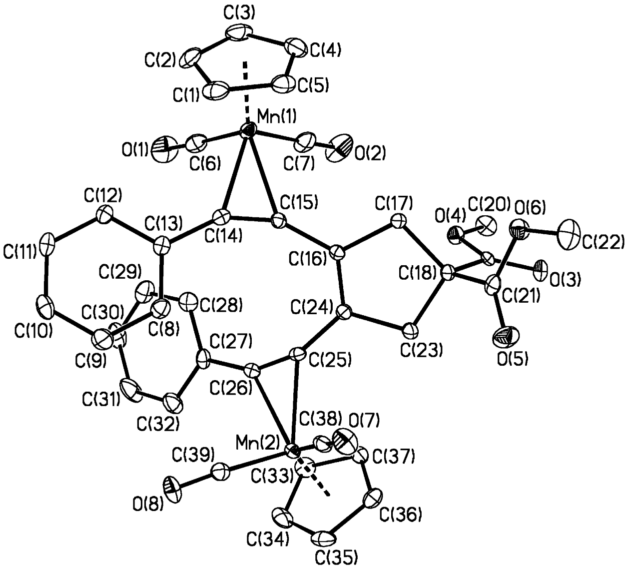


Figure 1. X-ray crystal structure of [Cp(CO)$_2$Mn]$_2$[η^2,η^2-PhC≡CC(CH$_2$C(CO$_2$Me)$_2$CH$_2$)=CC≡CPh] (**21**). Selected bond lengths (Å) and angles (deg): Mn(1)−C(6), 1.771(5); Mn(1)−C(7), 1.784(5); Mn(1)−C(14), 2.088(4); Mn(1)−C(15), 2.138(4); C(14)−C(15), 1.245(5); C(15)−C(16), 1.442(5); C(16)−C(24), 1.353(5); C(13)−C(14)−C(15), 149.8(4); C(14)−C(15)−C(16), 154.5(4); C(6)−Mn(1)−C(7), 87.3(2); C(6)−Mn(1)−C(14), 86.5(2); C(7)−Mn(1)−C(15), 81.1(2); C(14)−Mn(1)−C(15), 34.3(1).

Photochemical Release of Enediynes from Manganese Complexes. Earlier we established that release of the coordinated alkyne could be achieved by thermolysis. For example, when the manganese enediyne complex [Cp(CO)$_2$Mn]$_2$[η^2,η^2-PhC≡CC(CH$_2$CH$_2$CH$_2$)=CC≡CPh] (**14**) was heated at 90 °C, the free enediyne 1,2-bis(phenylethynyl)cyclopentene (**15**) was obtained in 70% yield.[9] We have now found three milder methods for release of the enediynes: sunlamp photolysis, copper-catalyzed air oxidation, and stoichiometric Cu(II) oxidation. Application of the new copper-catalyzed addition of alkynes to manganese carbyne complexes together with direct cleavage of the manganese enediyne complexes with these new cleavage methods has allowed the synthesis of a variety of cyclic enediynes with a range of ring sizes and with incorporation of a range of

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[12] See Supporting Information.

[13] For related manganese complexes, see: (a) Cash, G. G.; Pettersen, R. C. *J. Chem. Soc., Dalton Trans.* **1979**, 1630. (b) Löwe, C.; Hund, H.-U.; Berke, H. *J. Organomet. Chem.* **1989**, *378*, 211. (c) Akita, M.; Ishii, N.; Takabuchi, A.; Tanaka, M.; Moro-oka, Y. *Organometallics* **1994**, *13*, 258.

[14] **15** has been prepared previously. Jones, G. B.; Wright, J. M.; Plourde, G., II; Purohit, A. D.; Wyatt, J. K.; Hynd, G.; Fouad, F. *J. Am. Chem. Soc.* **2000**, *122*, 9872.

Scheme 9

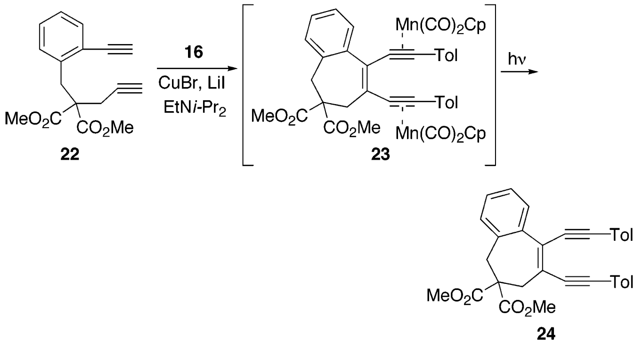
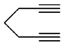
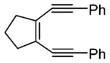
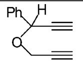
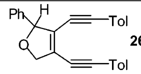
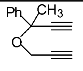
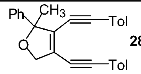
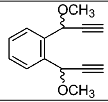
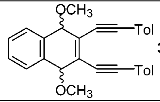
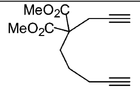
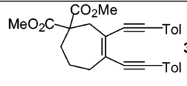
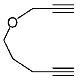
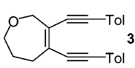
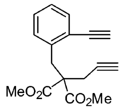
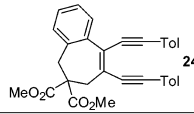


Table 1. Synthesis of Enediynes by Photolysis of Manganese Enediyne Complexes Derived from Copper-Catalyzed Addition of Diynes to Manganese Carbyne Complexes

Entry	Diyne[a]	Enediyne[b]	Yield[c]
1		 15	60 %
2	 25	 26	49%
3	 27	 28	100%[c]
4	 29	 30, 31	55%[d] 59%[d]
5	 32	 33	20%
6	 34	 35	35%
7	 22	 24	67%

[a] For preparation of diynes, see Supporting Information. [b] Conditions: 0.42 equiv of diyne per carbyne, CuBr, LiI, EtN*i*-Pr$_2$, CH$_2$Cl$_2$, −78 °C. [c] After purification by column chromatography. [d] Isomers separated as manganese enediyne complexes.

functional groups. Avoiding isolation of the manganese enediyne complexes resulted in much higher yields of enediynes.

Photolysis of solutions of manganese enediyne complexes with a sunlamp was followed by TLC. The disappearance of a bright red spot due to the manganese enediyne complex was accompanied by the appearance of a strongly fluorescent spot due to the free enediyne. At the end of photolysis, a fine brown precipitate that had formed was removed by filtration. For small-scale work involving less than 1 mmol of enediyne complex, photolysis is the preferred method, as photolysis byproducts are the easiest to separate chromatographically. However, this method suffers from scale-up difficulties since dilute (<0.01 M) solutions are required and since the buildup of suspended insoluble manganese-containing byproducts interferes with the photolysis.

Photolysis of the isolated enediyne complex **14** produced the free enediyne **15** in 70% yield. When the enediyne complex **23** generated in situ from the low-temperature reaction of [Cp(CO)$_2$Mn≡CTol]BCl$_4$ (**16**) with CuBr, LiI, diyne **22**, and EtN*i*-Pr$_2$ was photolyzed without isolation, a 67% yield of free enediyne **24** was obtained (Scheme 9). Other enediynes obtained by photolytic cleavage are reported in Table 1.

Scheme 10

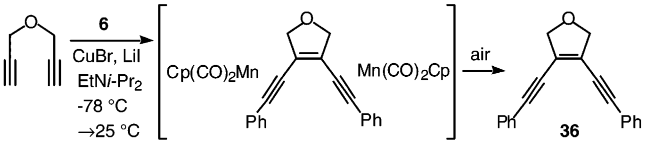
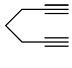
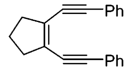
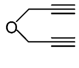
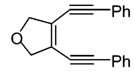
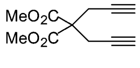
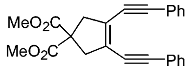
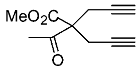
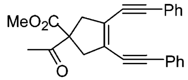
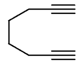
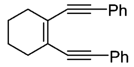
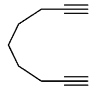
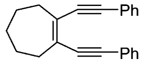


Table 2. Synthesis of Enediynes by Air Oxidation of Manganese Enediyne Complexes Derived from Copper-Catalyzed Addition of Diynes to Manganese Carbyne Complexes

Entry	Diyne[a]	Enediyne[b]	Yield[c]
1		 15	93%
2		 36	95%
3		 37	53%
4		 38	75%
5		 39	89%
6		 40	74%

[a] For preparation of diynes, see Supporting Information. [b] Conditions: 0.42 equiv of diyne per carbyne, CuBr, LiI, EtN*i*-Pr$_2$, CH$_2$Cl$_2$, −78 °C. [c] After purification by column chromatography.

Copper-Catalyzed Air Oxidation Releases Enediynes from Manganese Complexes. Isolated manganese enediyne complexes purified by column chromatography are air stable as solids and in solution in the dark. However, in the initial reaction solutions, these manganese enediyne complexes were readily oxidized by air to give free enediynes and uncharacterized brown manganese solids (Table 2).

We suggest that copper salts remaining in solution from the copper-catalyzed addition of alkynes to manganese carbyne complexes catalyze the air oxidation of the manganese enediyne complexes. Copper(I) compounds are readily oxidized to copper(II) species, and (see below) CuCl$_2$·2H$_2$O efficiently oxidizes manganese enediyne complexes to release the free enediyne in good yield. Compared with stoichiometric oxidation, the copper-catalyzed air oxidation offers the advantage that smaller amounts of copper salts need to be separated from the free enediyne product. In one example, a solution of manganese enediyne complex [Cp(CO)$_2$Mn]$_2$[η^2,η^2-PhC≡CC(CH$_2$CH$_2$CH$_2$)=CC≡CPh] (**14**) was generated in situ from reaction of [Cp(CO)$_2$Mn≡CPh]BCl$_4$ (**6**) with 1,6-heptadiyne, CuBr, LiI, and EtN*i*-Pr$_2$; air was bubbled through the crude reaction solution to give a 93% isolated yield of free enediyne **15**. Similarly, air oxidation of the crude reaction mixture from the preparation of [Cp(CO)$_2$Mn]$_2$[η^2,η^2-PhC≡CC(CH$_2$OCH$_2$)=CC≡CPh] led to isolation of 2,3-(phenylethynyl)1,4-dihydrofuran (**36**) in 95% yield (Scheme 10).

Scheme 11

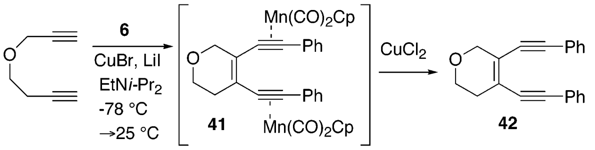
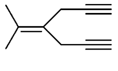
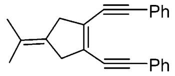
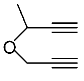
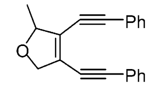
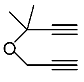
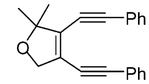
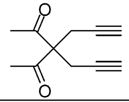
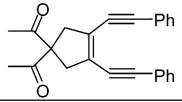
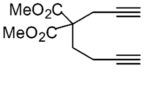
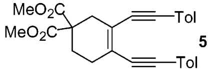
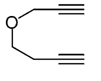
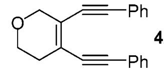
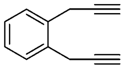
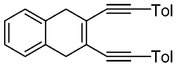


Table 3. Synthesis of Enediynes by Cu(II) Oxidation of Manganese Enediyne Complexes Derived from Copper-Catalyzed Addition of Diynes to Manganese Carbyne Complexes

Entry	Diyne[a]	Enediyne[b]	Yield[c]
1		 43	79%
2	 44	 45	93%
3	 46	 47	77%
4		 48	55%
5	 49	 50	50%
6		 42	82%
7		 51	29%

[a] For preparation of diynes, see Experimental Section. [b] Conditions: 0.42 equiv of diyne per carbyne, CuBr, LiI, EtN*i*-Pr$_2$, CH$_2$Cl$_2$, −78 °C. [c] After purification by column chromatography.

Cu(II) Oxidation Releases Enediynes from Manganese Complexes. Stoichiometric oxidation of manganese enediyne complexes with $CuCl_2\cdot 2H_2O$ occurs rapidly and releases the enediyne in good yield (Table 3). The chief advantage of this method is the speed of the oxidation; its disadvantage is the use of large quantities of copper salts that need to be removed in the purification of the free enediynes. For example, a solution of manganese enediyne complex $[Cp(CO)_2Mn]_2[\eta^2,\eta^2\text{-}PhC{\equiv}CC(CH_2CH_2OCH_2){=}CC{\equiv}CPh]$ (**41**) generated in situ from the low-temperature reaction of $[Cp(CO)_2Mn{\equiv}CPh]BCl_4$ (**6**) with $HC{\equiv}CCH_2CH_2OCH_2C{\equiv}CH$, CuBr, LiI, and EtN*i*-Pr$_2$ was oxidized with CuCl$_2$ to give an 82% yield of free enediyne **42** (Scheme 11). Similar yields of enediynes were obtained either from photolysis, copper-catalyzed air oxidation, or stoichiometric Cu(II) oxidation of enediyne complexes.

Scope of Enediyne Synthesis. This new procedure involving copper-catalyzed addition of diynes to manganese carbyne complexes followed by release of the enediyne from the intermediate manganese enediyne complexes has a broad scope. The procedure is highly tolerant of most functional groups, including alkenes, ethers, esters, and ketones (Tables 1−3). However, the amine-containing substrates, tripropargylamine and benzyl dipropargylamine, failed to undergo cyclization and instead generated intractable material. Simple substituents on the propargylic center of the starting diynes are tolerated well, and unsymmetric enediyne complexes are readily prepared by suitable choice of the diyne precursor. The yields of the enediyne products depended upon the size of the ring system formed: five-membered cyclic enediynes were formed in highest yield, six-membered cyclic enediynes were formed in good yields, and seven-membered cyclic enediynes were formed in moderate yield. Bicyclic systems (**37**−**40**) have also been formed via this process. However, all attempts to cyclize eight-membered or larger systems failed, resulting in uncharacterized decomposition products.

Summary

Compared with our initial synthesis of rhenium enediyne complexes, this new one-pot manganese-based synthesis of free enediynes offers the advantage of economical manganese starting materials and ease of release of the enediynes from their metal complex. A drawback of the current synthetic procedure is the need to use very temperature sensitive and functional group intolerant manganese carbyne complexes as starting materials. Further efforts to improve this route will focus on finding suitable substitutes for the highly electrophilic carbyne complexes.

Experimental Section

$Cp(CO)_2Mn{=}C(Tol)C{\equiv}CTol$ (17). 4-Ethynyltoluene (0.089 mL, 0.702 mmol), CuBr (10.7 mg, 0.075 mmol), LiI (7.8 mg, 0.058 mmol), and EtN*i*-Pr$_2$ (0.135 mL, 0.780 mmol) in 4 mL of tetrahydrofuran were added to a solution of $[Cp(CO)_2Mn{\equiv}CTol]BCl_4$ (**16**) (0.3372 g, 0.781 mmol) in CH$_2$Cl$_2$ (35 mL) at −78 °C. The yellow solution quickly turned a dark red. After 30 min at −78 °C, solvents were evaporated under vacuum. Column chromatography (silica, 10% ether/hexanes) gave dark red-black crystals of **17** (203 mg, 73%). ^{1}H NMR (250 MHz, CD$_2$Cl$_2$): δ 7.93 (d, $J = 8.5$ Hz, 2H, Tol), 7.48 (d, $J = 8.0$ Hz, 2H, Tol), 7.24 (d, $J = 8.5$ Hz, 2H, Tol), 7.25 (d, $J = 8.5$ Hz, 2H, Tol), 5.19 (s, 5H, Cp), 2.37 (s, Me), 2.34 (s, Me). ^{13}C{^{1}H} NMR (125 MHz, CD$_2$Cl$_2$): δ 300.6 (Mn=C), 233.8 (CO), 152.5 (C_{ipso}), 139.9 (*C*Me), 129.6 (*C*Me), 134.7 (C_{ipso}), 130.7 (HC_{Tol}), 129.3 (HC_{Tol}), 128.5 (HC_{Tol}), 125.5 (HC_{Tol}), 121.5 (C≡C), 104.7 (C≡C), 93.27 (Cp), 21.1 (Me), 20.8 (Me). IR (hexanes): 1978, 1922 cm^{-1}.

$[Cp(CO)_2Mn]_2[\eta^2,\eta^2\text{-}TolC{\equiv}CC(CH_2OCH_2){=}CC{\equiv}CTol]$ (19). A solution of dipropargyl ether (0.026 mL, 0.252 mmol), CuBr (8.8 mg, 0.061 mmol), LiI (9.0 mg, 0.067 mmol), and EtN*i*-Pr$_2$ (0.104 mL, 0.601 mmol) in 3 mL of tetrahydrofuran was added to a solution of $[Cp(CO)_2Mn{\equiv}CTol]BCl_4$ (0.2592 g, 0.600 mmol) in CH$_2$Cl$_2$ (50 mL) at −78 °C. After 30 min at −78 °C, solvents were evaporated under vacuum. Column chromatography (silica, 20−50% ether/hexanes) gave **19** (63 mg, 38%) as a bright red powder. ^{1}H NMR (500 MHz, CD$_2$Cl$_2$, −30 °C): δ 7.07 (d, $J = 7.5$ Hz, 4H, H_{Tol}), 6.93 (d, $J = 7.5$ Hz, 4H, H_{Tol}), 5.46 (d, $J = 9$ Hz, 2H, C*H*H), 5.04 (d, $J = 9$ Hz, 2H, CH*H*), 4.80 (s, Cp), 2.20 (s, Me). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, −30 °C): δ 232.2 (CO), 231.2 (CO), 137.0 (*C*Me), 133.3 (C=C), 132.3 (HC_{Tol}), 131.8 (C_{ipso}), 127.9 (HC_{Tol}), 88.3 (C≡C), 84.9 (Cp), 78.9 (CH$_2$), 63.2 (C≡C), 20.04 (Me). IR (CH$_2$Cl$_2$): 1973, 1907 cm^{-1}. MS (ESI): *m*/*z* calcd for $C_{36}H_{28}O_5{}^{55}Mn_2$ (M$^+$) 650.1, found 650.1.

$[Cp(CO)_2Mn]_2[\eta^2,\eta^2\text{-}PhC{\equiv}CC(CH_2C(CO_2Me)_2CH_2){=}CC{\equiv}CPh]$ (21). A solution of dimethyl dipropargylmalonate (183 mg, 0.88 mmol), CuBr (60 mg, 0.42 mmol), LiI (58 mg, 0.43 mmol), and EtN*i*-Pr$_2$ (365 μL, 2.11 mmol) in 10 mL of tetrahydrofuran was added to a solution of $[Cp(CO)_2Mn{\equiv}CPh]BCl_4$ (**6**) (881 mg, 2.11 mmol) in CH$_2$Cl$_2$ (170 mL) at −78 °C.

After 30 min at −78 °C, solvents were evaporated under vacuum, and the residue was extracted with CH_2Cl_2 (20 mL) and diluted with 200 mL of hexanes. The solution was filtered and evaporated under a nitrogen stream to give **21** (0.549 g, 85%) as a bright red powder. A sample for NMR experiments was further purified by column chromatography (silica, 20−50% ether/hexanes). X-ray quality crystals were grown by layering ether onto a concentrated CH_2Cl_2 solution of **21**. ^1H NMR (300 MHz, CD_2Cl_2): δ 7.21−7.17 (m, 4H, H_{Ph}), 7.10−7.05 (m, 6H, H_{Ph}), 4.83 (s, Cp), 3.86 (s, CO_2Me), 4.0−3.6 (broad, CH_2). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, −30 °C): δ 232.3 (CO), 231.3 (CO), 171.0 ($\mathit{C}O_2Me$), 134.3 ($C{=}C$), 132.5 (HC_{Ph}), 129.9 (C_{ipso}), 127.0 (HC_{Ph}), 126.2 (HC_{Ph}), 87.5 ($C{\equiv}C$), 85.1 (Cp), 67.8 ($C{\equiv}C$), 57.1 ($\mathit{C}(CO_2Me)_2$), 52.7 ($CO_2\mathit{Me}$), 44.9 (Me). IR (CH_2Cl_2): 1972, 1907, 1734 cm^{-1}. MS (ESI): m/z calcd for $C_{39}H_{30}O_8{}^{55}Mn_2$ (M^+) 736.07, found 736.0.

$\mathrm{TolC{\equiv}CC[(C_6H_4)CH_2C(CO_2Me)_2CH_2]{=}CC{\equiv}CTol}$ (24). A solution of diyne **22** (118 mg, 0.415 mmol), CuBr (12 mg, 0.084 mmol), LiI (17 mg, 0.12 mmol), and EtN*i*-Pr_2 (170 μL, 1.00 mmol) in 3 mL of tetrahydrofuran was added to a solution of $[Cp(CO)_2Mn{\equiv}CTol]BCl_4$ (**16**) (472 mg, 1.09 mmol) in CH_2Cl_2 (70 mL) at −78 °C. The solution was stirred overnight at room temperature and poured into 20% ether/hexanes (200 mL) and photolyzed with a 150 W sunlamp for several hours. One strongly fluorescent spot was observed by TLC analysis. The combined solvents were evaporated, and the residue was purified by flash chromatography (silica, 10% ethyl acetate/hexanes) to give **24** (130 mg, 67%) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, $J = 7.5$ Hz, 1H, H_{Ar}), 7.46 (d, $J = 8.0$ Hz, 4H, H_{Tol}), 7.37 (td, $J = 7.3, 2.0$ Hz, 1H, H_{Ar}), 7.32−7.26 (m, 2H, H_{Ar}), 7.17 (d, $J = 8.0$ Hz, 2H, H_{Tol}), 7.16 (d, $J = 8.0$ Hz, 2H, H_{Tol}), 3.81 (s, CO_2Me), 3.34 (s, CH_2), 2.88 (s, CH_2), 2.39 (s, Me), 2.38 (s, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8 (s, $\mathit{C}O_2Me$), 138.6 (s, C_{Ar}), 138.2 (s, C_{Ar}), 136.0 (s, C_{Ar}), 131.4 (d, $^1J_{CH} = 160$ Hz, C_{Tol}), 131.4 (d, $^1J_{CH} = 160$ Hz, C_{Tol}), 130.2 (d, $^1J_{CH} = 140$ Hz, C_{Ar}), 130.0 (s, C_{Ar}), 129.1 (d $^1J_{CH} = 153$ Hz, C_{Tol}), 129.0 (d $^1J_{CH} = 153$ Hz, C_{Tol}), 128.4 (dd, $^1J_{CH} = 158$ Hz, $^2J_{CH} = 7$ Hz, C_{Ar}), 128.2 (dd, $^1J_{CH} = 160$ Hz, $^2J_{CH} = 8$ Hz, C_{Ar}), 127.2 (dd, $^1J_{CH} = 159$ Hz, $^2J_{CH} = 8$ Hz, C_{Ar}), 126.0 (s, $C{=}C$), 120.3 (t, $^2J_{CH} = 8$ Hz, C_{ipso}), 120.1 (t, $^2J_{CH} = 8$ Hz, C_{ipso}), 97.5 (s, $C{\equiv}\mathit{C}Tol$), 97.1 (s, $C{\equiv}\mathit{C}Tol$), 90.7 (s, $\mathit{C}{\equiv}CTol$), 88.7 (s, $\mathit{C}{\equiv}CTol$), 66.8 (s, $\mathit{C}(CO_2Me)_2$), 52.8 (q, $^1J_{CH} = 147$ Hz, $CO_2\mathit{Me}$), 37.3 (t $^1J_{CH} = 131$ Hz, CH_2), 37.0 (t $^1J_{CH} = 134$ Hz, CH_2), 21.4 (q, $^1J_{CH} = 126$ Hz, Me). IR (CH_2Cl_2): 1735 cm^{-1}. HRMS(ESI): m/z calcd for $C_{33}H_{28}O_4Na$ (M^+) 511.1886; found, 511.1907.

$\mathrm{PhC{\equiv}CC(CH_2CH_2CH_2){=}CC{\equiv}CPh}$ (15).[14] Addition of 1,6-heptadiyne (55.2 mg, 0.60 mmol), CuI (57 mg, 0.30 mmol, 25 mol % per $C{\equiv}CH$), LiI (40 mg, 0.30 mmol), and 500 mg of EtN*i*-Pr_2 in 2 mL of THF to an orange solution of $[Cp(CO)_2Mn{\equiv}CPh]BCl_4$ (**6**) (687 mg, 1.64 mmol) in 5 mL of THF at −35 °C produced a dark red color immediately. The crude product was washed through a 3 cm silica pad with 2:1 hexane/diethyl ether to give $[Cp(CO)_2Mn]_2[\eta^2,\eta^2\text{-}PhC{\equiv}CC(CH_2CH_2CH_2){=}CC{\equiv}CPh]$ (**14**) as a red solid (318 mg, 0.51 mmol, 85%). Photolysis with a medium-pressure Hg lamp (254 nm maximum) in 100 mL of THF/CH_3CN under air gave **15** as a colorless solid (96.0 mg, 70% yield from **14**, yield from 1,6-heptadiyne: 60%). ^1H NMR (500 MHz, CD_2Cl_2): δ 2.03 (t, $^3J = 8$ Hz, $CH_2C\mathit{H}_2CH_2$), 2.70 (t, $^3J = 8$ Hz, $CH_2C{=}C$), 7.30−7.40 (m, aromatic CH), 7.46−7.56 (m, aromatic CH). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 23.5 (t, $^1J_{CH} = 131$ Hz, $CH_2\mathit{C}H_2CH_2$), 37.4 (t, $^1J_{CH} = 132$ Hz, $\mathit{C}H_2CH_2\mathit{C}H_2$), 86.6 (s, $\mathit{C}{\equiv}CAr$), 96.8 (t, $^3J_{CH} = 5$ Hz, $C{\equiv}\mathit{C}Ar$), 123.8 (t, $^3J_{CH} = 7$ Hz, aromatic), 128.8 (d, $^1J_{CH} = 162$ Hz, aromatic), 128.8 (dd, $^1J_{CH} = 163$ Hz, $^3J_{CH} = 7$ Hz, aromatic), 130.7 (m, $C{=}C$), 131.9 (dt, $^1J_{CH} = 160$ Hz, $^3J_{CH} = 6$ Hz, aromatic). HRMS(EI): m/z calcd for $C_{21}H_{16}$ (M^+) 268.1252, found 268.1239.

$\mathrm{PhC{\equiv}CC(CH_2CH_2CH_2){=}CC{\equiv}CPh}$ (15). A solution of 1,6-heptadiyne (64 μL, 0.56 mmol), CuBr (18 mg, 0.123 mmol), LiI (16 mg, 0.12 mmol), and EtN*i*-Pr_2 (230 μL, 1.33 mmol) in 3 mL of tetrahydrofuran was added to a solution of $[Cp(CO)_2Mn{\equiv}CPh]BCl_4$ (**6**) (558 mg, 1.33 mmol) in CH_2Cl_2 (90 mL) at −78 °C. The red solution was stirred at room temperature for several hours and poured into an equal volume of THF. Air was slowly bubbled through the solution for 90 min, resulting in a color change from deep red to brown. One strongly fluorescent spot was observed by TLC analysis. Solvents were evaporated under vacuum, and the residue was purified by flash chromatography (silica, 10% ethyl acetate/hexanes) to give **15** (139 mg, 93%) as a pale yellow solid.

$\mathrm{PhC{\equiv}CC(CH_2OCH_2){=}CC{\equiv}CPh}$ (36). A solution of dipropargyl ether (54 μL, 0.524 mmol), CuBr (30 mg, 0.209 mmol), LiI (29 mg, 0.22 mmol), and EtN*i*-Pr_2 (227 μL, 1.31 mmol) in 3 mL of THF was added to a solution of $[Cp(CO)_2Mn{\equiv}CPh]BCl_4$ (**6**) (548 mg, 1.31 mmol) in CH_2Cl_2 (100 mL) at −78 °C. The red solution was stirred at room temperature for 1 h and poured into an equal volume of THF (90 mL). Air was slowly bubbled through the solution for 1.5 h, resulting in a color change from deep red to brown. One strongly fluorescent spot was observed by TLC analysis. The combined solvents were removed by rotary evaporation. The residue was dissolved in ethyl acetate, and the solution was filtered and evaporated again. The residue was purified by flash chromatography (silica, 25% ethyl acetate/hexanes) to give **36** (135.2 mg, 95%) as an off-white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.53 (br s, 4H, Ph), 7.37 (br s, 6H, Ph), 4.85 (s, 4H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.5 (d, $^1J_{CH} = 160$ Hz, C_{Ph}), 129.6 (dt, $^1J_{CH} = 161$ Hz, $^2J_{CH} = 8$ Hz, C_{Ph}), 129.1 (d, $^1J_{CH} = 160$ Hz, C_{Ph}), 126.4 (s, $C{=}C$), 123.3 (s, C_{ipso}), 99.8 (s, $C{\equiv}\mathit{C}Ar$), 82.0 (s, $\mathit{C}{\equiv}CAr$), 78.2 (t, $^1J_{CH} = 151$ Hz, CH_2). HRMS(EI): m/z calcd for $C_{20}H_{14}O$ (M^+) 278.1045, found 270.1036.

$\mathrm{PhC{\equiv}CC(CH_2CH_2OCH_2){=}CC{\equiv}CPh}$ (42). A solution of (3-butynyl) propynyl ether (79 μL, 81% solution in toluene, 0.978 g mL^{-1}, 0.579 mmol), CuBr (23 mg, 0.161 mmol), LiI (21 mg, 0.15 mmol), and EtN*i*-Pr_2 (239 μL, 1.38 mmol) in 3 mL of THF was added to a solution of $[Cp(CO)_2Mn{\equiv}CPh]BCl_4$ (**6**) (577 mg, 1.38 mmol) in CH_2Cl_2 (110 mL) at −78 °C. The resulting red solution was stirred at room temperature for several hours. The solution was poured into an equal volume of THF (150 mL), and an ethanol solution (20 mL) of $CuCl_2\cdot 2H_2O$ (530 mg, 3.12 mmol) was added. A color change from deep red to brown occurred, and one strongly fluorescent spot was observed by TLC analysis. The combined solvents were evaporated under vacuum, and the residue was extracted into ethyl acetate. The solution was filtered and evaporated. The residue was purified by flash chromatography (silica, 25% ethyl acetate/hexanes) to give **42** (135.3 mg, 82%) as a slightly yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.55−7.45 (m, 4H, Ph), 7.35−7.30 (m, 6H, Ph), 4.34 (t, $J = 3$ Hz, $OCH_2C{=}C$), 3.87 (t, $J = 6$ Hz, $OC\mathit{H}_2CH_2$), 2.49 (tt, $J = 6, 3$ Hz, $OCH_2C\mathit{H}_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.3 (d, $^1J_{CH} = 160$ Hz, C_{Ph}), 129.1 (d, $^1J_{CH} = 162$ Hz, C_{Ph}), 126.0 (s, $C{=}C$), 124.5 (s, $C{=}C$), 123.9 (s, C_{ipso}), 123.7 (s, C_{ipso}), 97.1 (s, $C{\equiv}\mathit{C}Ph$), 95.5 (s, $C{\equiv}\mathit{C}Ph$), 89.4 (s, $\mathit{C}{\equiv}CPh$), 86.7 (s, $\mathit{C}{\equiv}CPh$), 68.5 (t, $^1J_{CH} = 146$ Hz, CH_2), 64.6 (t, $^1J_{CH} = 137$ Hz, CH_2), 30.0 (t, $^1J_{CH} = 130$ Hz, CH_2). HRMS(EI): m/z calcd for $C_{21}H_{16}O$ (M^+) 284.1201; found, 284.1200.

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Supporting Information Available: Preparation of compounds, spectroscopic data, and X-ray crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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