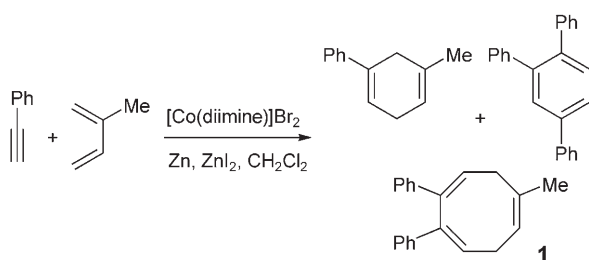


Cycloaddition Reactions

Cobalt-Catalyzed [4+2+2] Cycloaddition for the Synthesis of 1,3,6-Cyclooctatrienes**

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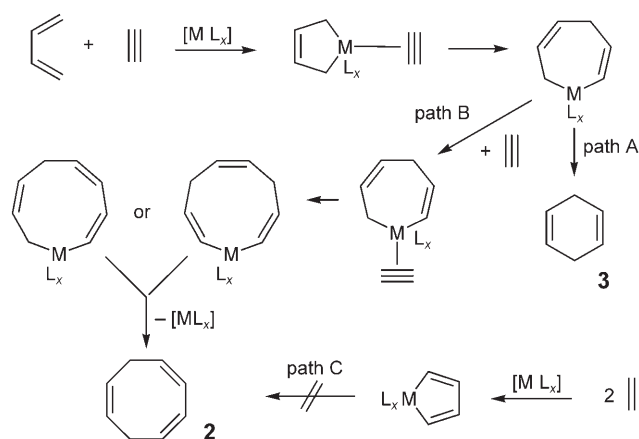
The atom-economical synthesis of carbocyclic eight-membered rings from double- and triple-bond systems is a forte of organometallic catalysis. Nickel-catalyzed cyclotetramerizations of alkynes^[1] and dimerizations of 1,3-butadienes with nickel or iron catalysis^[2] are among the most common representatives of this class of reaction. One of the limiting aspects of these intermolecular reactions is the required use of identical starting materials. To our knowledge, a mild cobalt-catalyzed method for the generation of eight-membered rings in an intermolecular reaction utilizing different building blocks has not been described previously.^[3] In contrast to the nickel-catalyzed cyclotetramerization of alkynes, cobalt-catalyzed reactions predominantly lead to [2+2+2] cyclotrimerizations forming benzene derivatives.^[4] In the presence of 1,3-dienes alkynes react in the presence of cobalt catalysts in a Diels–Alder reaction to yield 1,4-cyclohexadiene derivatives.^[5] A single report for the cobalt-catalyzed formation of an eight-membered-ring side product was contributed by us recently (Scheme 1). In this example the eight-membered



Scheme 1. Products of the cobalt-catalyzed reaction of phenylacetylene with isoprene.

cyclic product **1** was formed in 31% yield along with the Diels–Alder and the cyclotrimerization products.^[6]

A prerequisite for the formation of an eight-membered-ring system **2** is a low-valent metal complex (Scheme 2) with free sites for the coordination and activation of the substrates. If the reductive elimination to the 1,4-cyclohexadiene product (**3**) proceeds slowly (path A), further coordination and insertion of an alkyne (path B) and subsequent reductive elimination to the 1,3,6-cyclooctatriene (**2**) is possible. In



Scheme 2. Proposed pathways for the metal-catalyzed reactions leading to 1,4-cyclohexadiene (**3**) and 1,3,6-cyclooctatriene (**2**).

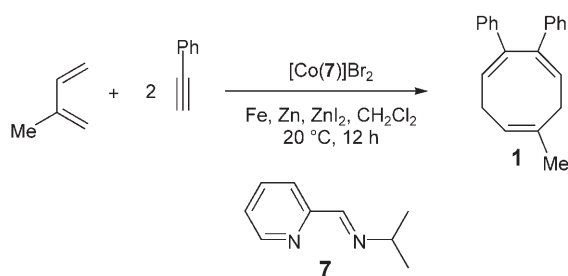
contrast the formation of eight-membered-ring products when asymmetric alkynes are used cannot be rationalized by formation of a cobaltacyclopentadiene intermediate (path C) because the corresponding 3,4-disubstituted pattern is disfavored for energetic reasons.^[4] Under optimized conditions for the formation of the eight-membered-ring products only traces of the cyclotrimerization product were detected, leading to the assumption that the pathway which proceeds via the cobaltacyclopentadienes (path C) can be excluded as a plausible alternative.

Concerning the effect of the donor ligands on the chemoselectivity of the cobalt catalysts, it was found that the use of cobalt phosphine complexes preferentially leads to cyclohexadienes **3** by reaction path A and no product of type **2** was observed.^[5] Aliphatically substituted cobalt diimine complexes in the absence of 1,3-dienes lead to a fast cyclotrimerization of the applied alkynes.^[7] In the presence of 1,3-dienes regioselective Diels–Alder reactions are facilitated when pyridine–imine ligands are utilized with aromatic substituents on the imine moiety.^[8] Only when the aromatic substituent is replaced by an aliphatic substituent in the imine subunit of the ligand (**7**, Scheme 3) is the reductive elimination to **2** slow enough to permit further alkyne coordination, insertion, and finally reductive elimination to give the eight-membered-ring product **1** by reaction path B (Scheme 2). In the context of the formation of the eight-membered-ring [4+2+2] cyclization product from alkynes with 1,3-dienes, the following points are remarkable:

1. An excess of the alkyne is not required.
2. The products are formed regioselectively with the two substituents from the alkyne (Ph, Scheme 3) in a 1,2-relation.

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Scheme 3. Intermolecular cobalt-catalyzed [4+2+2] cycloaddition.

3. The addition of iron powder reduces the amount of side products and increases the yield of the eight-membered-ring products.

In most reactions the Diels–Alder reaction products are observed as side products; they can be removed easily by column chromatography.

The role of the iron powder remains unclear; however, the addition of 10 mol % iron powder has a positive effect on the chemoselectivity of the reaction (reaction path B is preferred) and the purity of the products. The preparative results of the cobalt-catalyzed intermolecular and atom-economical synthesis of eight-membered-ring products from 1,3-dienes and terminal as well as internal alkynes are summarized in Table 1.

Table 1: Results of the cobalt-catalyzed synthesis of 1,3,6-cyclooctatrienes.

Entry	R ¹	R ²	R ³	Product	Yield
1	H	Ph	H	1	65 %
2	H	2-thienyl	H	8a	40 %
3	H	<i>n</i> Bu	H	8b	17 %
4	H	CH ₂ OBn	H	8c	50 %
5	H	CH ₂ OAc	H	8d	63 % ^[a]
6	H	CH ₂ CH(OAc)Me	H	8e	56 % ^[b]
7	H	CH ₂ SO ₂ Ph	H	8f	28 %
8	H	CO ₂ Me	H	8g	78 %
9	Me	CO ₂ Me	H	8h	88 %
10	Me	CH ₂ OAc	H	8i	43 % ^[c]
11	H	CO ₂ Et	Me	8j	29 %
12	Me	CO ₂ Me	Me	8k	49 %

[a] The product consists of a mixture of 80 % **8e** and 20 % of the regioisomer 1,3-bis(2-acetoxypropyl)-6-methylcycloocta-1,3,6-triene.

[b] The product was obtained in racemic form. [c] The product consists of a mixture of 80 % **8e** and 20 % of the regioisomer 1,3-bis(2-acetoxypropyl)-6,7-dimethylcycloocta-1,3,6-triene.

The yield of the eight-membered-ring product **1** generated from phenylacetylene and isoprene could be increased from 31 %^[6] to 65 %, whereas product **8a** generated from 2-ethynylthiophene was obtained in 40 % yield owing to the deactivating effect of sulfur.^[9] Surprisingly, the nonfunction-

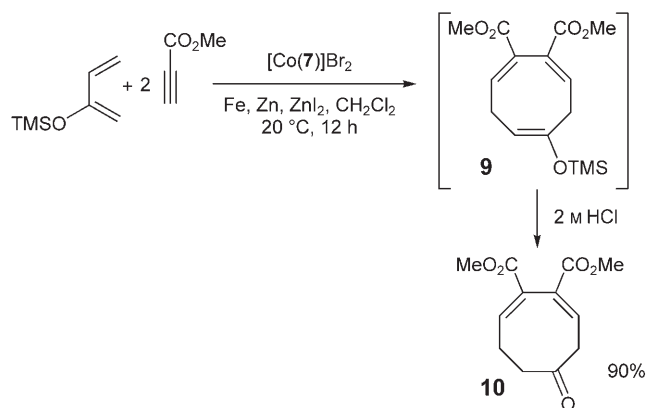
alized product **8b** prepared from 1-hexyne and isoprene was obtained in only 17 % yield. On the other hand when an oxygen-functionalised alkyne was applied up to 63 % yield could be obtained (**8d**). The reaction of phenylpropynylsulfone gave a moderate yield of 28 % (**8g**) which is consistent with the earlier findings of reduced activity of this alkyne in cobalt-catalyzed Diels–Alder reactions.^[9] When an acceptor-substituted alkyne was used (Table 1, entry 8) the yield increased considerably (**8g**, 78 %). The yield of eight-membered-ring products was also increased when isoprene was exchanged for the sterically more hindered but more electron-rich 2,3-dimethyl-1,3-butadiene (**8h**, 88 %). These results indicate that acceptor-substituted alkynes and electron-rich 1,3-dienes are required for good results in the cycloaddition process.

When internal alkynes were applied (Table 1, entries 11 and 12) the yields were somewhat diminished; however, a complex pentasubstituted product (**8j**) was generated. In this case the electronic effect of the 2,3-dimethyl-1,3-butadiene also contributes to the higher yield, so that the hexasubstituted product **8k** was isolated in 49 % yield. Acceptor-substituted internal alkynes as well as disubstituted 1,3-dienes could be used.

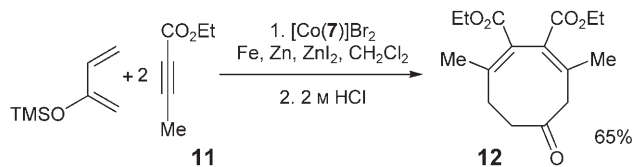
Consequently, excellent results should be obtained when acceptor-substituted terminal alkynes are reacted with an electron-rich 1,3-diene. Accordingly, methyl acetylenecarboxylic acid and 2-trimethylsilyloxy-1,3-butadiene were used in the cobalt-catalyzed cyclization reaction (Scheme 4). Instead of the direct isolation of intermediate **9**, which was detected by GCMS, hydrolysis with 2 M HCl followed by column chromatography gave the corresponding cyclooctadienone **10** in excellent 90 % yield.

Analogously, the acceptor-substituted internal alkyne **11** was reacted with 2-trimethylsilyloxy-1,3-butadiene (Scheme 5), and in one synthetic operation a highly substituted cyclooctadienone product (**12**) with a high density of functional groups was generated from two relatively simple, commercially available starting materials with a good yield of 65 %.

Utilizing a new cobalt-catalyzed reaction pathway we have successfully coupled two alkynes with a 1,3-diene to



Scheme 4. Cobalt-catalyzed synthesis of a cycloocta-3,5-dienone. TMS = trimethylsilyl.



Scheme 5. Cobalt-catalyzed synthesis of a tetrasubstituted cycloocta-3,5-dienone.

generated eight-membered-ring systems in an unprecedented fashion, thereby generating complex ring systems with a high functional-group density. The electronic parameters responsible high selectivity and yield were identified, thus opening the way to an elegant method for the generation of unsaturated medium-sized ring systems.

Experimental Section

Representative protocol for the cobalt-catalyzed [4+2+2] cycloaddition (Table 1, entry 1): A mixture of [Co(7)]Br₂ (37 mg, 0.1 mmol, 5.0 mol %), zinc iodide (64 mg, 0.2 mmol, 10.0 mol %), zinc powder (13 mg, 0.2 mmol, 10.0 mol %), and iron powder (11 mg, 0.2 mmol, 10.0 mol %) was suspended in anhydrous dichloromethane (1 mL) under a nitrogen atmosphere. Isoprene (136 mg, 2.0 mmol) and phenylacetylene (204 mg, 2.0 mmol) were added, and the resulting suspension was stirred for 16 h. (As the reaction times were longer with other substrates, stirring was continued until complete conversion was detected by GC/GCMS.) The solution was subsequently filtered through a plug of silica gel (eluent: diethyl ether), the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: pentane/dichloromethane 100:1). The product was obtained as a colorless oil (177 mg, 0.65 mmol, 65 %). The analytical data are in accordance with the literature values.^[6]

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- [1] W. Reppe, O. Schlichting, K. Klager, T. Toepel, *Justus Liebigs Ann. Chem.* **1948**, 560, 1; P. W. Jolly in *Comprehensive Organometallic Chemistry*, Vol. 8 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, London, **1982**, p. 649; H. tom Dieck, M. Svoboda, J. Kopf, *Z. Naturforsch. B* **1978**, 33, 1381; R. Diercks, L. Stamp, H. tom Dieck, *Chem. Ber.* **1984**, 117, 1913; D. Walther, D. Braun, W. Schulz, U. Rosenthal, *Z. Anorg. Allg. Chem.* **1989**, 577, 270; T. R. Boussie, A. Streitwieser, *J. Org. Chem.* **1993**, 58, 2377; G. Wilke, *Pure Appl. Chem.* **1978**, 50, 677.
- [2] H. tom Dieck, R. Diercks, *Angew. Chem.* **1983**, 95, 801; *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 778; H. W. B. Reed, *J. Chem. Soc.* **1954**, 1931; W. Brenner, P. Heimbach, H. Hey, E. W. Müller, G. Wilke, *Justus Liebigs Ann. Chem.* **1969**, 727, 161; A. Tenaglia, P. Brun, B. Waegell, *J. Organomet. Chem.* **1985**, 285, 343; P. Brun, A. Tenaglia, B. Waegell, *Tetrahedron Lett.* **1983**, 24, 385; H. tom Dieck, J. Dietrich, *Chem. Ber.* **1984**, 117, 694; M. Mallien, E. T. K. Haupt, H. tom Dieck, *Angew. Chem.* **1988**, 100, 1091; *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 1062; K.-U. Baldenius, H. tom Dieck, W. A. König, D. Icheln, T. Runge, *Angew. Chem.* **1992**, 104, 338; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 305; P. A. Wender, N. C. Ihle, *J. Am. Chem. Soc.* **1986**, 108, 4678; P. A. Wender, M. L. Snapper, *Tetrahedron Lett.* **1987**, 28, 2221; P. A. Wender, N. C. Ihle, *Tetrahedron Lett.* **1987**, 28, 2451; P. A. Wender, M. J. Tebbe, *Synthesis* **1991**, 1089.
- [3] For the construction of eight-membered-ring systems see: N. A. Petasis, M. A. Patane, *Tetrahedron* **1992**, 48, 5757; S. M. Sieburth, N. T. Cunard, *Tetrahedron* **1996**, 52, 6251; G. Mehta, V. Singh, *Chem. Rev.* **1999**, 99, 881. Reviews on [4+4] cycloadditions: S. M. Sieburth, N. T. Cunard, *Tetrahedron* **1996**, 52, 6251; J. H. Rigby in *Comprehensive Organic Synthesis*, Vol. 5 (Ed.: B. M. Trost), Pergamon, New York, **1991**, chap. 5.2, p 617; P. A. Wender, J. M. Nuss, D. B. Smith, A. Suarez-Sobrinio, J. Vagberg, D. Decosta, J. Bordner, *J. Org. Chem.* **1997**, 62, 4908; M. Murakami, K. Itami, Y. Ito, *Synlett* **1999**, 951. [6+2] Cycloadditions: J. H. Rigby, *Org. React.* **1997**, 49, 336; J. H. Rigby, *Tetrahedron* **1999**, 55, 4521; P. A. Wender, A. G. Correa, Y. Sato, R. Sun, *J. Am. Chem. Soc.* **2000**, 122, 7815; M. Achard, A. Tenaglia, G. Buono, *Org. Lett.* **2005**, 7, 2353; M. Achard, M. Mosrin, A. Tenaglia, G. Buono, *J. Org. Chem.* **2006**, 71, 2907. [4+2+2] Cycloadditions: P. A. Evans, J. E. Robinson, E. W. Baum, A. N. Fazal, *J. Am. Chem. Soc.* **2002**, 124, 8782; S. R. Gilbertson, B. DeBoef, *J. Am. Chem. Soc.* **2002**, 124, 8784; J. A. Varela, L. Castedo, C. Saa, *Org. Lett.* **2003**, 5, 2841; P. A. Evans, E. W. Baum, *J. Am. Chem. Soc.* **2004**, 126, 11150; P. A. Evans, E. W. Baum, A. N. Fazal, M. Pink, *Chem. Commun.* **2005**, 63; M.-H. Baik, E. W. Baum, M. C. Burland, P. A. Evans, J. *Am. Chem. Soc.* **2005**, 127, 1602; M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2006**, 128, 2166; S. I. Lee, S. Y. Park, Y. K. Chung, *Adv. Synth. Catal.* **2006**, 348, 2531; B. DeBoef, W. R. Counts, S. R. Gilbertson, *J. Org. Chem.* **2007**, 72, 799. For palladium-catalyzed cyclization cascade reactions see: P. H. Lee, K. Lee, *Angew. Chem.* **2005**, 117, 3317; *Angew. Chem. Int. Ed.* **2005**, 44, 3253.
- [4] Reviews on cobalt-catalyzed cycloadditions: I. Omae, *Appl. Organomet. Chem.* **2007**, 21, 318; M. Malacria, C. Aubert, J. L. Renaud in *Science of Synthesis: Methods of Molecular Transformations (Houben-Weyl) 4th ed. 1952-*, Vol. 1 (Eds.: M. Lautens, B. M. Trost), Thieme, Stuttgart, **2001**, p. 439; S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, 100, 2901; I. Ojima, M. Tzamar-ioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, 96, 635; M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, 96, 49; D. B. Grotjahn in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson, L. Hegedus), Pergamon Press, Oxford, **1995**, p. 741; N. E. Schore in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon Press, Oxford, **1991**, p. 1129; K. P. C. Vollhardt, *Angew. Chem.* **1984**, 96, 525; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 539.
- [5] Leading references: G. Hilt, K. I. Smolko, *Angew. Chem.* **2003**, 115, 2901; *Angew. Chem. Int. Ed.* **2003**, 42, 2795; G. Hilt, W. Hess, K. Harms, *Org. Lett.* **2006**, 8, 3287.
- [6] G. Hilt, W. Hess, T. Vogler, C. Hengst, *J. Organomet. Chem.* **2005**, 690, 5170.
- [7] L. Doszczak, P. Fey, R. Tacke, *Synlett* **2007**, 753; H. T. Chang, M. Jeganmohan, C. H. Cheng, *Org. Lett.* **2007**, 9, 505; N. Saino, F. Amemiya, E. Tanabe, K. Kase, S. Okamoto, *Org. Lett.* **2006**, 8, 1439; G. Hilt, T. Vogler, W. Hess, F. Galbiati, *Chem. Commun.* **2005**, 1474; M. S. Wu, M. Shanmugasundaram, C. H. Cheng, *Chem. Commun.* **2003**, 718; L. Yong, H. Butenschön, *Chem. Commun.* **2002**, 2852; T. Sugihara, A. Wakabayashi, Y. Nagai, H. Takao, H. Imagawa, M. Nishizawa, *Chem. Commun.* **2002**, 576; M. S. Sigman, A. W. Fatland, B. E. Eaton, *J. Am. Chem. Soc.* **1998**, 120, 5130.
- [8] G. Hilt, J. Janikowski, W. Hess, *Angew. Chem.* **2006**, 118, 5328; *Angew. Chem. Int. Ed.* **2006**, 45, 5204.
- [9] G. Hilt, S. Lüers, K. Harms, *J. Org. Chem.* **2004**, 69, 624.