

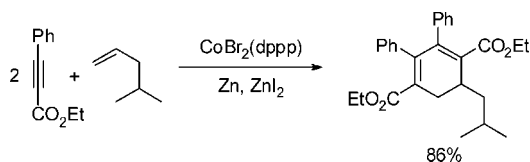
**Cobalt-Catalyzed Intermolecular [2 + 2 + 2] Cycloaddition for the Synthesis of 1,3-Cyclohexadienes**

Gerhard Hilt,\* Anna Paul, and Klaus Harms

Fachbereich Chemie, Philipps-Universität Marburg,  
Hans-Meerwein-Strasse, 35043 Marburg, Germany

hilt@chemie.uni-marburg.de

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A cobalt(I)-catalyzed [2 + 2 + 2] cycloaddition reaction between an internal acceptor-substituted alkyne and a terminal alkene leads to the formation of regiochemically enriched polysubstituted 1,3-cyclohexadiene derivatives in acceptable yields when methyl butynoate is used, whereas regiochemically pure products are formed in good yields from phenyl propynoate. The concurrent cyclotrimerization reaction of the alkyne to the corresponding benzene derivative is dependent on the sterical bulk of the alkyne and is considerably reduced with the sterically more hindered alkyne.

The atom-economic generation of complex molecules from simple building blocks in the context of diversity-oriented synthesis is of great interest. The cobalt-catalyzed transformations of alkynes, alkenes, and 1,3-dienes<sup>1</sup> in [4 + 2]

cycloaddition reactions,<sup>2</sup> 1,4-hydrovinylation reactions,<sup>3</sup> alkyne cyclotrimerizations,<sup>4</sup> Alder–ene reactions,<sup>5</sup> [4 + 2 + 2] cycloadditions,<sup>6</sup> and other cobalt-catalyzed transformations have been under investigation in our group for quite some time.<sup>7</sup> Over the course of our studies, we observed that in some cases the outcome of the cobalt-catalyzed reactions is dependent on minor changes in either the precatalyst such as the use of other ligands or the reaction conditions (solvent effect).<sup>8</sup>

While internal alkynes led to a reduced rate in the competing cyclotrimerization reaction to the corresponding benzene derivative,<sup>9</sup> the reaction with alkenes leads either to the formation of the Alder–ene reaction product **1** or an unprecedented 1,3-cyclohexadiene product **2** derived from a [2 + 2 + 2] cycloaddition process (scheme 1).<sup>10</sup> Surprisingly, the chemoselectivity was influenced by the ligand as well as by the electron demand of the alkyne. When a nonacceptor-substituted alkyne was used (R<sup>3</sup> = alkyl or aryl), the dppp ligand led predominantly to the Alder–ene product of type **1** and with the dppe ligand to the 1,3-cyclohexadiene product **2**.

On the other hand, when acceptor-substituted alkynes were utilized (R<sup>3</sup> = CO<sub>2</sub>Et), the use of the Co(dppe) complex led predominantly to the Alder–ene product **1**, while the transform-

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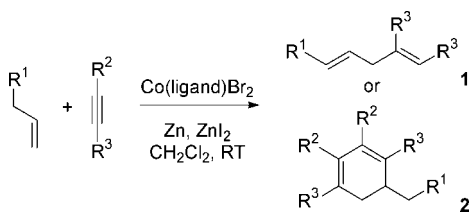
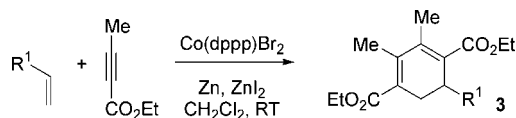
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(8) Compare results in ref 2b and ref 2f (regioselective Diels–Alder reaction, as well as the results in ref 4a and ref 4b (regioselective cyclotrimerization)).

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**SCHEME 1. Ligand-Dependent Cobalt-Catalyzed Alder–Ene vs [2 + 2 + 2] Cycloaddition Reaction**

**SCHEME 2. Cobalt-Catalyzed [2 + 2 + 2] Cycloaddition Reaction**

**TABLE 1. Cobalt-Catalyzed [2 + 2 + 2] Cycloaddition Utilizing Ethyl Butynoate as Starting Material**

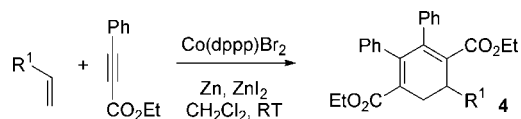
entry	alkene	product (3)	yield <sup>[a]</sup>
1			28% (80:20) <sup>[b]</sup>
			(56%) <sup>[c]</sup>
2			48% (80:20) <sup>[b]</sup>
			(43%) <sup>[c]</sup>
3			39% (n.d.) <sup>[b]</sup>
			(n.d.) <sup>[c]</sup>
4			26% (75:25) <sup>[b]</sup>
			(61%) <sup>[c]</sup>
5			31% (76:24) <sup>[b]</sup>
			(59%) <sup>[c]</sup>

<sup>a</sup> Combined yields of the regioisomers. The percentage of the other isomers (methyl groups in 1,3-relation) range from 5 to 15%. <sup>b</sup> Ratio of regioisomers. Shown is the major regioisomer. <sup>c</sup> GC yield of the cyclotrimerization side products.

mation applying the Co(dppp)Br<sub>2</sub> catalyst precursor led to the corresponding 1,3-cyclohexadiene product **2**. Therefore, we applied the Co(dppp)Br<sub>2</sub> catalyst precursor in the [2 + 2 + 2] cycloaddition reaction with terminal alkenes for the formation of polysubstituted 1,3-cyclohexadienes (Scheme 2).<sup>11</sup>

The results of the application of ethyl butynoate are summarized in Table 1.

The yields for the reactions with the butyric ester are moderate to good when taking into account that polysubstituted 1,3-

**SCHEME 3. Cobalt-Catalyzed [2 + 2 + 2] Cycloaddition Reaction**


cyclohexadienes must be generated in an intermolecular fashion. The separation from the accompanying cyclotrimerization side product can be easily accomplished by column chromatography. Nevertheless, the product consists of a mixture of regioisomers which could not be separated. In the major isomer, the two methyl groups are located next to each other in the cyclohexadiene ring system as was indicated by NMR spectroscopy and later confirmed by X-ray analysis of two crystalline compounds. It should also be noted that the oxidation of the 1,3-cyclohexadiene derivative by oxygen is a relatively slow process compared to the oxidation of 1,4-cyclohexadiene derivatives so that the dihydroaromatic products can be isolated without extra precaution or exclusion of air. However, oxidation to the corresponding aromatic products is sometimes encountered. In the case of product **3c** the second double bond does not participate in the cyclization process, thus opening a new reaction pathway to other products, nor was it incorporated in a second cycloaddition process. The steric bulk of the alkenes utilized for the formation of products **3d** and **3e** reduced the yields, but the major problem with this type of product was the concurrent cyclotrimerization reaction of the alkyne. This process becomes predominant with terminal alkynes where only 5–10% of the cyclohexadiene product is obtained, so that these starting materials can not be applied in this [2 + 2 + 2] cycloaddition reaction. The next set of experiments was conducted utilizing ethyl phenyl propynoate (Scheme 3) as the alkyne component. The sterical bulk of the cobalt catalyst, so that the cyclotrimerization reactivity of the alkyne should also be less favorable. We were delighted to find considerably increased yields of the desired cyclohexadiene derivatives as well as a reduced amount of the cyclotrimerization side product.

Therefore, we applied the Co(dppp)Br<sub>2</sub> catalyst precursor in the [2 + 2 + 2] cycloaddition reaction with several terminal alkenes utilizing ethyl phenyl propynoate. The results are summarized in Table 2.

Fortunately, in this series of experiments, the regiochemistry of the products of type **4** is uniform, placing the two phenyl substituents on the cyclohexadiene ring exclusively in a 1,2-relation. Noteworthy are the products **4c** and **4g** which provide rich opportunities for follow-up reactions.

Surprisingly, product **4h**, which was generated from 3-buten-1-ol, was obtained in a good yield of 65%, whereas the corresponding transformation, utilizing 2-propen-1-ol (scheme 4), led to lactonization to afford **6c** in 62% overall yield. The reaction with the corresponding 1-methyl-2-propen-1-ol led to product **6d** in excellent 81% yield when taking into account that three new carbon–carbon bonds were formed accompanied by a lactonization reaction to generate a new carbon–oxygen bond. Intermediates of type **5** were identified as the primary product by GCMS which subsequently cyclized to the lactone. In contrast, the transformations of the two alkenoles with ethyl butynoate led to the corresponding lactones **6a** and **6b** in moderate yields in both cases. Unfortunately, an intramolecular approach utilizing the unsaturated ester **7** did not lead to the desired lactone product. This can be rationalized by the *transoid*

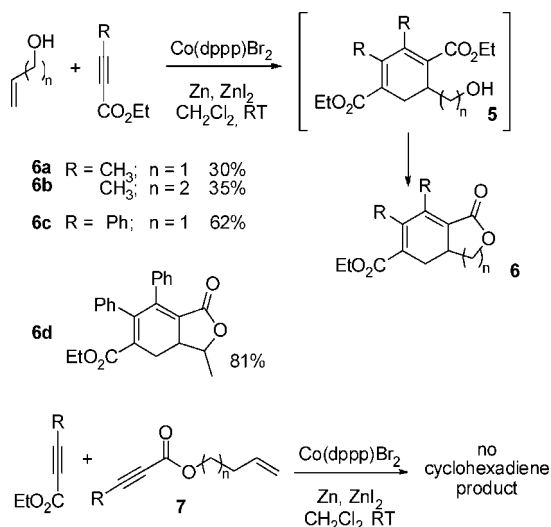
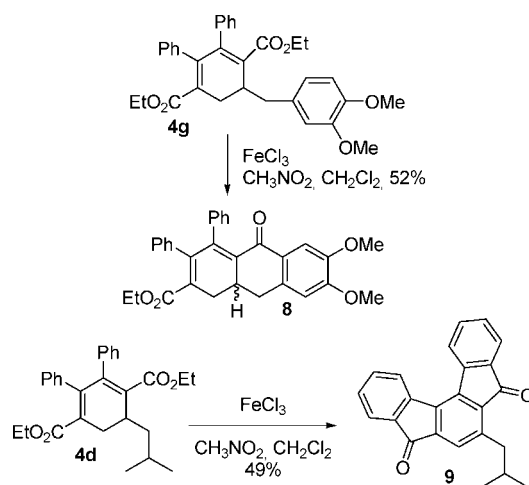
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**TABLE 2.** Cobalt-Catalyzed [2 + 2 + 2] Cycloaddition Utilizing Ethyl Phenyl Propynoate as Starting Material

entry	Alkene	product (4)	yield
1			50%
2			71%
3			60%
4			86%
5			45%
6			74%
7			48%
8			65%

conformation of the ester **7** which is much more favorable than adoption of a *cisoid* conformation. The *cisoid* conformation apparently is not adopted during the coordination of unsaturated groups to the cobalt center. This would lead to the desired cyclization process. In contrast, for compound **7** cyclotrimerization of the alkynes is found and the alkene functionality is untouched.

The identity of the products was verified using two-dimensional NMR techniques and by the X-ray analysis of two crystalline products **4h** and **6a**. Nevertheless, the high regioselectivity with which the three starting materials are incorporated is remarkable. Only very minor signals attributed to regioisomers were found by NMR analysis (see the Supporting Information). The cyclohexadiene derivative **4g** can be cyclized under mild reaction conditions utilizing an excess of FeCl<sub>3</sub> (5.2 equiv) in nitromethane/dichloromethane (1:1) (Scheme 5) at ambient temperature. Under these reaction conditions, the terphenyl diester intermediate leads to the corresponding dihydroanthrone derivative **8** which was isolated in 52% yield. A further

**SCHEME 4.** Cobalt-Catalyzed [2 + 2 + 2] Cycloaddition Reaction and Lactonization**SCHEME 5.** Iron-Initiated Cyclization Reactions

Friedel–Crafts-type cyclization of the second ester functionality with the less electron rich phenyl substituent was not observed.

However, the transformation of the 1,3-cyclohexadiene derivative **4d** led to different observations. In the presence of an excess of iron(III) chloride (5.2 equiv) and prolonged reaction times (96 h), the oxidation of the dihydroaromatic ring to yield compound **9** in an acceptable yield (49%) was observed alongside the two Friedel–Crafts-type cyclizations of the ester functionalities to the phenyl rings.

## Summary

In summary, we have developed an intermolecular, atom-economic synthetic method that allows prompt access to polysubstituted 1,3-cyclohexadiene derivatives bearing functional groups suited to interesting follow-up chemistry, such as the cyclization to anthrone-type products. The chemo- and regioselectivities of the formation of 1,3-cyclohexadienes from phenyl propynoates are good to excellent and the yields are in a preparatively useful range, allowing the exploration of further applications of these polyfunctionalized and polysubstituted compounds.

**Experimental Section**

**General Methods.** All reactions were carried out under an argon atmosphere in flame-dried glassware. Dichloromethane was distilled under nitrogen from  $P_4O_{10}$ , and  $ZnI_2$  was dried in vacuo at 150 °C prior to use. Commercially available materials were used without further purification. Structural assignments were made by NOESY NMR (mixing time = 1.5 s).

**Representative Procedure for the [2 + 2 + 2] Cycloaddition.**

**Synthesis of Diethyl 5-Isobutyl-2,3-diphenylcyclohexa-1,3-diene-1,4-dicarboxylate (4d).** Zinc iodide (64 mg, 0.2 mmol, 20 mol %), zinc dust (13 mg, 0.2 mmol, 20 mol %), and  $CoBr_2 \cdot dppp$  (63 mg, 0.1 mmol, 10 mol %) are suspended in 1.0 mL of dichloromethane. Then 4-methyl-1-pentene (0.17 mL, 1.0 mmol) and ethyl 3-phenylpropiolate (0.41 mL, 2.5 mmol) were added to the reaction mixture, which was stirred for 16 h. The reaction mixture was filtered over a short pad of silica gel, and then the solvent was removed under vacuum. Purification by flash column chromatography (pentane/methyl *tert*-butyl ether 5:1) gave the desired product **4d** (370 mg, 0.86 mmol, 86%) as a colorless oil.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  = 7.04–7.00 (m, 6H), 6.80–6.76 (m, 4H), 3.91–3.82 (m, 4H), 2.96–2.88 (m, 1H), 2.82–2.72 (m, 2H),

1.76–1.64 (m, 2H), 1.54–1.44 (m, 1H), 0.96 (dd, 6H,  $J$  = 3.3, 6.3 Hz), 0.81 (dt, 6H,  $J$  = 2.7, 7.1 Hz).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  = 168.8, 168.7, 143.1, 142.3, 138.4, 138.3, 135.6, 128.9, 128.8, 127.7, 127.0, 126.5, 60.2, 39.3, 31.9, 28.8, 25.2, 23.7, 21.5, 13.4. IR (film,  $cm^{-1}$ ): 3056, 3025, 2870, 1705, 1603, 1576, 1490, 1465, 1443, 1171, 1100, 1073, 1019, 915, 859, 759. MS (EI):  $m/z$  432 (6,  $[M^+]$ ), 417 (1,  $[M^+ - Me]$ ), 387 (14,  $[M^+ - OEt]$ ), 374 (5), 359 (16), 329 (4), 313 (85), 283 (39), 269 (5), 257 (100), 241 (9), 228 (36), 215 (12), 202 (8), 165 (5). HRMS (EI):  $m/z$  calcd for  $C_{28}H_{32}O_4$  432.2301  $[M^+]$ , found  $m/z$  432.2303.

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**Supporting Information Available:** Experimental procedures detailed X-ray structures of **4h** and **6a** and full characterization of the compounds **3a–e**, **4a–h**, **6a–d**, **8**, and **9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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