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Synthetic Methods

Cobalt-Catalyzed [2+2] Cycloaddition**

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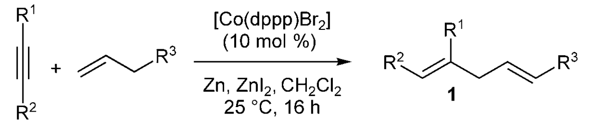
Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 75th birthday

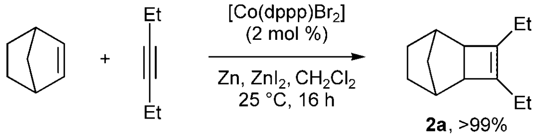
Carbocyclic four-membered rings can be synthesized by cycloaddition reactions through the photochemical conversion of alkenes into cyclobutanes or thermal [2+2] cycloaddition reactions of acceptor-substituted alkynes with alkenes to give cyclobutenes.[1] Transition-metal-catalyzed reactions of non-activated starting materials, which only undergo thermal cycloaddition under harsh conditions, are usually carried out with ruthenium[2] or rhodium[3] complexes, or alternatively with cobalt or nickel complexes.[4]

A while ago we reported the first cobalt-catalyzed Alder-ene reaction between internal alkynes and terminal alkenes to give 1,4-dienes **1** (Scheme 1).[5] It is assumed that the low-valent cobalt complex coordinates to both unsaturated starting materials, and that the reaction proceeds via a cobaltacycle to form the new C−C bond. Subsequent β-hydride elimination and reductive elimination lead to the final product **1**.[6]



Scheme 1. Cobalt-catalyzed Alder-ene reaction. dppp = 1,3-bis(diphenylphosphanyl)propane.

We report herein that the reaction of internal, strained alkenes, such as norbornene, with internal alkynes in the presence of a cobalt–diphosphine complex leads to cyclobutene derivatives in quantitative yield with high chemoselectivity (Scheme 2). The only other reported synthetically useful transition-metal-catalyzed [2+2] cycloaddition reactions with norbornene involve rhodium or ruthenium complexes.[2,3] The use of a very simple cobalt complex, [$CoI_2(PPh_3)_2$], in the presence of a further equivalent of the free ligand PPh_3 under reductive conditions (Zn powder) in [2+2] cycloaddition reactions was pioneered by Cheng and co-workers.[4] These early cobalt-catalyzed transformations are somewhat limited in that they require harsh conditions (toluene, 90°C) and a 10-fold excess of the alkyne, and seem to be restricted to 7-oxa-bicyclo[2.2.0]heptenes as substrates. Furthermore, the catalyst system presented herein does not lead to the dimerization of norbornene, as reported by Cheng and co-workers, and the addition of a further equivalent of the phosphine ligand is not necessary.



2a, >99%

Scheme 2. Cobalt-catalyzed [2+2] cycloaddition reaction between norbornene and 3-hexyne.

A further advantage of the Co(dppp) catalyst system is that, in contrast to most transition-metal-catalyzed [2+2]-cycloaddition reactions, no large excess of either starting material is required: The substrates can usually be used in a 1:1 ratio, which greatly simplifies the purification of the products.[7] Laborious column-chromatographic purification can be avoided: Simple filtration through a silica-gel plug is sufficient to remove the residual (in)organic catalyst components and provide analytically pure reaction products of type **2**. The cobalt catalyst system described herein is also considerably less expensive than alternative rhodium- or ruthenium-based compounds, and the substrate scope is significantly wider than previously reported for cobalt-based systems.

The results of the cycloaddition of norbornene derivatives in the presence of the Co(dppp) catalyst (2 or 10 mol%) are summarized in Table 1. The transformations involving symmetrical internal alkynes and norbornene (Table 1, entries 1–3) gave the desired [2+2] cycloaddition products in quantitative yield. Unsymmetrical 1-phenylalkynes also yielded the desired products (Table 1, entries 4 and 5) quantitatively, whereas the reaction of ethyl 2-butynoate with norbornene gave the desired cycloaddition product in an acceptable yield of 51% (Table 1, entry 6), along with a small quantity of a 1:2 (alkene/alkyne) adduct (18%, as determined by GC–MS). The [2+2] cycloaddition products were also formed in good to very good yields from 1-substituted bicyclo[2.2.0]hept-3-enes (Table 1, entries 7–14). These substrates were sometimes used as an *endo*/*exo* mixture, whereby the cycloaddition products were formed as an *endo*/*exo* mixture in the same ratio.[8] When terminal alkynes were used as substrates, only very little of the [2+2] cycloaddition product was detected by GC–MS. With these substrates, [2+2+2] cyclotrimerization of the alkyne appears to occur preferentially.

It seems plausible that the transformation proceeds through the coordination of the substrates to the cobalt center, followed by the formation of a cobaltacyclopentene intermediate by oxidative addition. A β-hydride elimination

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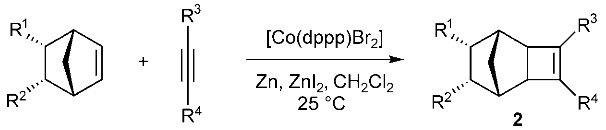
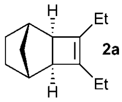
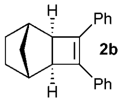
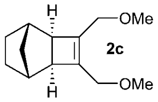
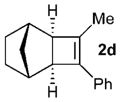
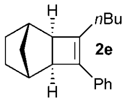
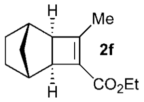
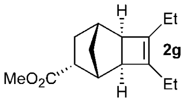
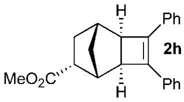
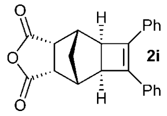
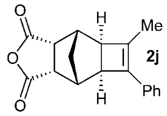
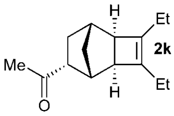
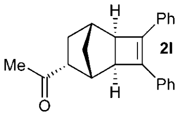
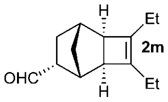
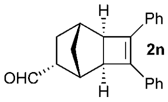
Table 1: Cobalt-catalyzed [2+2] cycloaddition.



Entry	R^1	R^2	R^3	R^4	**2**	Yield [%]
1	H	H	Et	Et	 **2a**	> 99[a]
2	H	H	Ph	Ph	 **2b**	> 99
3	H	H	CH_2OMe	CH_2OMe	 **2c**	98[b,c]
4	H	H	Me	Ph	 **2d**	> 99
5	H	H	*n*Bu	Ph	 **2e**	> 99
6	H	H	Me	CO_2Et	 **2f**	51
7	H	CO_2Me	Et	Et	 **2g**	91[b]
8	H	CO_2Me	Ph	Ph	 **2h**	99[b]
9	C_2O_3		Ph	Ph	 **2i**	95[b,d]
10	C_2O_3		Me	Ph	 **2j**	95[b,d]
11	H	Ac	Et	Et	 **2k**	84[b]
12	H	Ac	Ph	Ph	 **2l**	84[b]
13	H	CHO	Et	Et	 **2m**	90[b,e]
14	H	CHO	Ph	Ph	 **2n**	94[b]

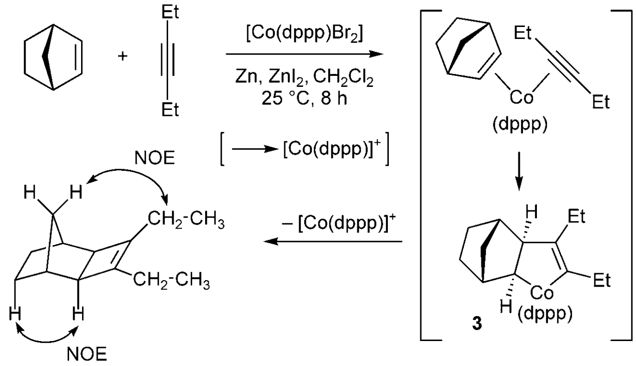
[a] The reaction was carried out with 2 mol% of [Co(dppp)Br$_2$]. [b] The reaction was carried out with 10 mol% of [Co(dppp)Br$_2$]. [c] The reaction was carried out with 2 equivalents of the alkyne. The cyclotrimerization product was also observed, but was removed readily by filtration through a short plug of silica gel (eluent: pentane/methyl *tert*-butyl ether 10:1). [d] Significant loss of material was observed upon extended column chromatography. [e] The product contained 3–4% of the aldehyde starting material, which could not be removed by column chromatography.

to give an Alder-ene product would contradict the Bredt rule. Instead, reductive elimination of the Co(dppp) moiety from the cobaltacycle **3** leads to the product and regenerates the catalytically active species (Scheme 3). A further alkyne insertion leading to a [2+2+2] cycloaddition reaction could not be detected by GC–MS analysis. The only exception was the reaction of norbornene with ethyl 2-butynoate, in which case the 2:1 adduct (the product of a formal [2+2+2] cycloaddition) was observed by GC–MS but could not be isolated in any significant amount.

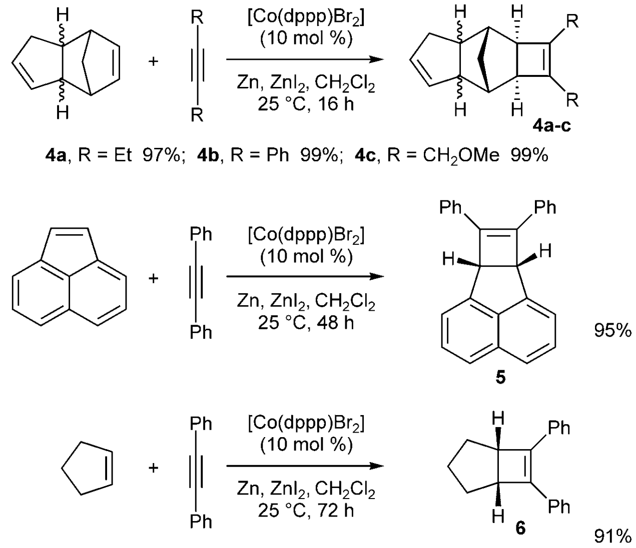
The *exo* relative configuration of the cyclobutene ring was confirmed by two-dimensional NMR spectroscopic analysis of **2a**. A clear NOE contact was observed between pseudoaxial H atoms of the norbornene moiety, as well as separate contacts between the methylene groups of the ethyl substituents and one of the bridge H atoms (Scheme 3).

The cyclopentadiene dimer can also be used as a substrate. Its reaction with internal alkynes led exclusively to products derived from the participation of the strained double bond, in excellent yields of 97–99% (Scheme 4). Against all expectations, acenaphthylene reacted with tolane to generate the cyclobutene derivative **5**, which was isolated in 95% yield. Phenanthrene does not demonstrate this remarkable reactivity, most likely as a result of the higher degree of delocalization of the π electrons and the lower ring strain.

Until now, no cobalt-catalyzed [2+2] cycloaddition reactions have been reported in which cyclopentene can be used as a substrate.[9] The previously mentioned cyclopentadiene dimer does contain a cyclopentene moiety; however, it is the other double bond which participates in the reaction with alkynes. All the greater was our surprise when control experiments revealed that cyclopentene reacts slowly but quantitatively with tolane to give the bicyclic product **6**. To the best of our knowledge, this reaction is the first reported example of an effi-



Scheme 3. Postulated mechanism of the cobalt-catalyzed [2+2] cycloaddition.



Scheme 4. Transformations of tricyclic alkenes and cyclopentene.

cient transition-metal-catalyzed, electron-neutral [2+2] cycloaddition that does not require bicyclic or highly strained alkenes. Critical to the success of this reaction is the requirement that the competing trimerization of the alkyne is slow in relation to the [2+2] cycloaddition reaction. With the $CoBr_2$(dppp) catalyst and tolane as the alkyne component, the trimerization is the slower of the two competing reactions.

In conclusion, we have presented an intermolecular atom-efficient cobalt-catalyzed [2+2] cycloaddition reaction with significantly wider scope in terms of possible substrates than previously reported cobalt-catalyzed transformations of this type. Alongside diverse norbornene derivatives, acenapthylene and even cyclopentene reacted with alkynes to give the desired cyclobutene derivatives in excellent yield with excellent *exo* selectivity.

Experimental Section

Representative procedure: [Co(dppp)Br_2] (32 mg, 0.05 mmol, 5 mol %), zinc iodide (32 mg, 0.10 mmol, 10 mol %), and zinc powder (6.5 mg, 0.10 mmol, 10 mol %) were suspended in anhydrous dichloromethane (1 mL) under a nitrogen atmosphere. Norbornene (94 mg, 1.00 mmol) and 3-hexyne (114 μL, 1.00 mmol) were added, and the resulting suspension was stirred for up to 16 h or until complete conversion (the reaction was monitored by GC). The suspension was then filtered through a short plug of silica gel (eluent: pentane), and the solvent was removed under reduced pressure to give **2a** (176 mg, 1.00 mmol, >99 %) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.23$ (s, 2 H), 2.02–1.93 (m, 6 H), 1.54–1.49 (m, 2 H), 1.41 (br s, 1 H), 1.02–0.95 (m, 8 H), 0.91–0.88 ppm (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 141.7$, 47.2, 34.3, 30.5, 28.5, 20.5, 12.4 ppm; IR: 2947, 2870, 2839, 1670, 1458, 1374, 1318, 1296, 1246, 1177, 1110, 1052, 952, 925, 910 cm^{-1}; MS (EI): *m/z* (%): 176 (M^+, 8), 161 (5), 147 (24), 135 (100), 128 (5), 119 (45), 107 (31), 91 (38), 79 (40), 67 (12), 51 (5); HRMS (EI): *m/z* calcd for $C_{13}H_{20}$: 176.1565; found: 176.1578. Stereoisomers were identified from NOE contacts between axial H atoms of the bicyclo[4.2.1.$0^{2,5}$]heptene framework.

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Keywords: alkenes · alkynes · cobalt · cycloaddition

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[1] For leading studies, see: Y. Takenaka, H. Ito, M. Hasegawa, K. Iguchi, *Tetrahedron* **2006**, *62*, 3380; N. P. Tsvetkov, A. B. Koldobskii, V. N. Kalinin, *Dokl. Chem.* **2005**, *404*, 174, and references therein.

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[7] A relatively slow cyclotrimerization of the internal alkyne was observed as an alternative reaction pathway with 1,4-dimethoxy-2-butyne. When a slight excess of the alkyne component was used, the alkene underwent complete conversion, and the desired product could be purified by simple filtration through a plug of silica gel.

[8] It seems that in the context of the cobalt-catalyzed [2+2] cycloaddition reaction, only the *exo* products with respect to the cyclobutene ring are generated, as confirmed by NMR spectroscopy and X-ray crystal-structure analysis.

[9] For an iron-catalyzed [2+2] cycloaddition with simple alkenes, see: M. Rosenblum, D. Scheck, *Organometallics* **1982**, *1*, 397.