Cobalt-Catalyzed [2+2+2] Cycloaddition of Phenylacetylene with 1,3-Dienes for the Synthesis of Vinyl-Substituted 1,4-Diphenylcyclohexa-1,3-dienes

Gerhard Hilt,* Wilfried Hess, Klaus Harms

Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Straße, 35043 Marburg, Germany
Fax +49(6421)2825677; E-mail: Hilt@chemie.uni-marburg.de

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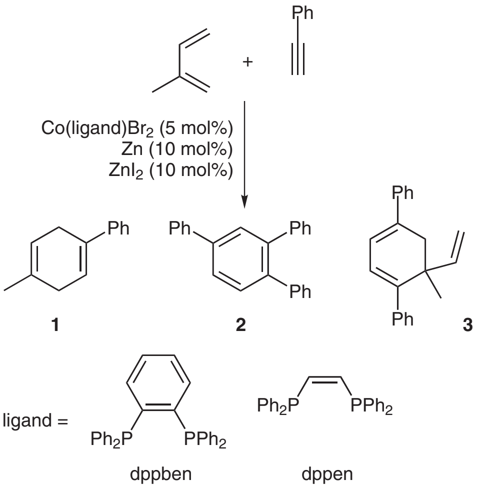
Abstract: The cobalt-catalyzed [2+2+2] cycloaddition of two alkynes and a 1,3-diene, utilizing either a dibromo[1,2-bis(diphenylphosphino)]benzene cobalt or a dibromobis(triphenylphosphino)cobalt complex, under reductive conditions gives vinyl-substituted cyclohexa-1,3-diene derivatives in acceptable yields. The oxidation of 5-methyl-1,4-diphenyl-5-vinylcyclohexa-1,3-diene by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone leads to a rearrangement resulting in a vinyl-terphenyl derivative.

Key words: cobalt, cycloaddition, cyclohexadiene, oxidation

Cobalt-catalyzed cycloaddition processes, such as the [2+2+2] cyclotrimerization of alkynes and the [4+2] cycloaddition of alkynes and 1,3-dienes, are among the most powerful methods for the construction of six-membered carbocyclic ring systems.[1] In recent years we have thoroughly investigated the cobalt-catalyzed Diels–Alder reaction of nonactivated building blocks for the generation of dihydroaromatic compounds.[2] Besides the Diels–Alder reaction, reactive cobalt catalysts have also been identified for the hydrovinylation of alkenes,[3] trimerization of alkynes,[4] [4+2+2] cycloaddition,[5] Alder–ene reaction,[6] and *meta*-selective Diels–Alder reaction.[7] In this context we also investigated 1,2-bis(diphenylphosphino)ethane (dppe) analogues, which exhibit an unsaturated backbone, as can be found in the 1,2-bis(diphenylphosphino)benzene (dppben) and the (*Z*)-1,2-bis(diphenylphosphino)ethene (dppen) ligands (Scheme 1). The corresponding cobalt(II) bromide complexes of these ligands were tested in the reaction of phenylacetylene and isoprene under reductive conditions (zinc powder) in the presence of a mild Lewis acid (zinc iodide). While other diphosphine ligands gave the Diels–Alder product **1** as the major product and small amounts of the cyclotrimerization product **2**, with these unsaturated ligands a new product was observed.



Scheme 1

The analysis of the spectral data supports the formation of the [2+2+2]-cycloaddition product where two alkynes and one double bond of a 1,3-diene reacted to give the cyclohexa-1,3-diene derivative **3**.[8] The product **3** was isolated as a single isomer where the two phenyl substituents are exclusively in a 1,4-relation with respect to each other. The higher substituted double bond of the 1,3-diene was chemoselectively used in the cycloaddition process. Different solvents were tested in order to optimize the reaction in favor of the formation of **3**. Among several polar solvents, the best result was obtained in acetone where the desired product **3** was detected in a good ratio compared to the other identified products **1** and **2** (ratio **1/2/3** 50:10:30).[9] Similar results were obtained in tetrahydrofuran (ratio **1/2/3** 60:5:30), 1,2-dichloroethane (ratio **1/2/3** 45:5:30), and dichloromethane (ratio **1/2/3** 35:15:25). Depending on the solvent, other products were also generated that were not identified. Dichloromethane gave the least amount of isomers or side products, as determined by GC and GCMS, and, as such, dichloromethane was selected as the solvent of choice for further investigation. In a previous report the addition of a further reducing agent in addition to zinc improved the product selectivity, hence iron powder, indium shots, and magnesium turnings were also tested as additives. However, in this reaction the product ratios were only marginally altered with respect to the formation of the desired product **3**. In contrast, when triphenylphosphine (10 mol%) was added to the catalyst system generated from the dppben ligand and cobalt(II) bromide the product distribution was altered in favor of **3** (ratio **1/2/3** 30:8:40), so that **3** was formed as the major product for the first time and could be isolated in 33% yield. The ratio of products did not change significantly when the amount of the triphenylphosphine additive was altered between 5–20 mol%. However, when 50 mol% of triphenylphosphine was used no conversion was observed. Because of the structural similarity between the

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additive and the dppben ligand we investigated catalyst systems where cobalt(II) bromide, zinc, and zinc iodide were stirred with different amounts of triphenylphosphine without the bidentate ligand before addition of the substrates. A reactive catalyst system was obtained when 5–20 mol% of triphenylphosphine was present (5 mol% $CoBr_2$) but the ratios of the products did not alter significantly (typical ratio **1**/**2**/**3** 32:4:53). Applying more than 40 mol% of triphenylphosphine led to an unreactive catalyst mixture and no conversion of the starting materials. Nevertheless, a cobalt/ligand mixture in the range of 1:1 up to 1:4 is capable of catalyzing the desired reaction. Analysis of a suitable crystal by X-ray spectroscopy revealed that the proposed $CoBr_2$(dppben) catalyst precursor consists of a $[CoBr(dppben)_2]\cdot[CoBr_3(thf)]\cdot CH_2Cl_2$ conglomerate (Figure 1).

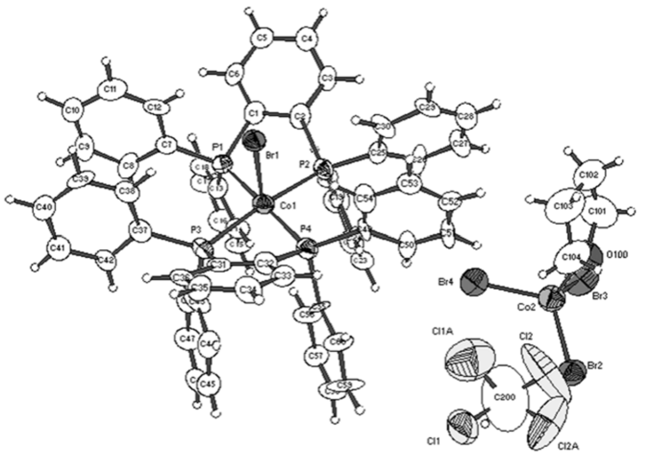


Figure 1 X-ray crystal structure analysis of $[CoBr(dppben)_2]\cdot[CoBr_3(thf)]\cdot CH_2Cl_2$[10]

Consequently, the catalytic active species in these cases might be formed from the $[CoBr_3(thf)]$ component and a small amount of free ligand (dppben) or the additive (Ph_3P) replacing the thf ligand.[11] On the other hand, when cobalt(II) bromide was mixed with lithium bromide in tetrahydrofuran, the obtained residue after the evaporation of the solvent did not catalyze the desired [2+2+2] cycloaddition to give **3** utilizing zinc and zinc iodide in dichloromethane.

These facts prompted us to investigate electronic and steric variations of the monodentate phosphine ligand (Table 1).

From Table 1, it can be seen that the product distribution is shifted towards the formation of the Diels–Alder adduct **1** if electron-deficient or electron-rich phosphines with respect to triphenylphosphine are used. On the other hand, only the diphenyl(2-pyridyl)phosphine ligand shifts the product distribution significantly to the formation of the cyclotrimerization product **2**.

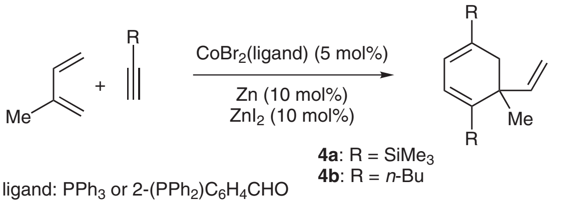
Accordingly, the best results were obtained utilizing the cobalt catalyst consisting of a 1:1 mixture of triphenylphosphine and cobalt(II) bromide, which gave up to 51% isolated yield of **3**. However, from the solution of the phosphine–cobalt(II) bromide mixture in dichloromethane, a suitable crystal for X-ray analysis was obtained, which had the composition $[CoBr_2(PPh_3)_2]\cdot CH_2Cl_2$ where the cobalt center has a tetrahedral environment.[12] Therefore, we propose an equilibrium between the $[CoBr_2(PPh_3)_2]\cdot CH_2Cl_2$ species, the corresponding monophosphine complex $[CoBr_2(PPh_3)]\cdot xCH_2Cl_2$, and solvated cobalt bromide $CoBr_2\cdot xCH_2Cl_2$. The active species could well be derived from the $[CoBr_2(PPh_3)]\cdot xCH_2Cl_2$ complex because not only must the two alkynes coordinate within the ligand sphere of the cobalt center, but the 1,3-diene must also coordinate via at least one of its double bonds. For an efficient insertion process of the double bond to give **3** over the insertion of a triple bond from a third alkyne (for the formation of **2**) the free coordination sites must be blocked, which might be achieved by the 1,3-diene. This could be the reason why corresponding [2+2+2]-cycloaddition products for simple terminal alkenes such as hex-1-ene, butyl acrylate, and styrene could not be obtained. Further modifications of the 1,3-diene revealed that the scope of the reaction is limited. While the reactivity for 2,3-dimethylbuta-1,3-diene is low giving a product distribution with only 5% of the desired [2+2+2]-cycloaddition product, the ratio was increased to 43% when 2-(diphenylphosphino)benzaldehyde was used as a ligand bearing a labile second coordination site in form of the aldehyde group. However, the [2+2+2]-cycloaddition products derived from this reaction consisted of a diverse mixture of several isomers.

Table 1 Variation of the Phosphine Ligands[a]

Entry	Ligand	Ratio **1/2/3**
1	$(4\text{-}FC_6H_4)_3P$	25:41:34
2	Ph_2MeP	63:0:35
3	Ph_2(2-pyridyl)P	5:66:19
4	Cy_3P	94:5:0
5	$(2\text{-}MeC_6H_4)_3P$	30:28:16
6	$(i\text{-}PrO)_3P$	87:0:10
7	$(C_6F_5)_3P$	95:0:0
8	$(pyrrol\text{-}1\text{-}yl)_3P$	52:13:19
9	Ph_3As	55:4:30

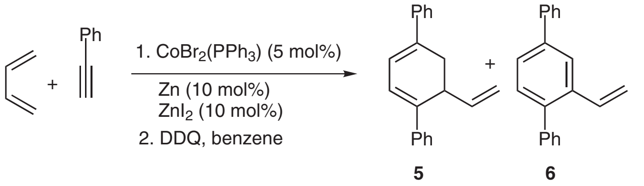
[a] $CoBr_2$ (5 mol%), ligand (10 mol%), Zn (10 mol%), ZnI_2 (10 mol%), CH_2Cl_2 (1.0 mL), r.t., 15 h.

Variation of the substituents (R in Scheme 2) on the alkyne revealed that the application of the reaction with isoprene can be expanded to (trimethylsilyl)acetylene. With the 2-(diphenylphosphino)benzaldehyde ligand 90% of the desired product **4a** (R = $SiMe_3$) and only 5% of the corresponding Diels–Alder adduct were observed. However, along with **4a** several isomers, which could not



Scheme 2

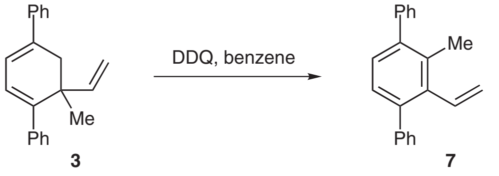
be isolated in pure form, were obtained. The application of hex-1-yne led to **4b** (R = Bu) in 46% yield, also as a mixture of isomers, accompanied by small amounts of the Diels–Alder adduct (5%) and the cyclotrimerization product (13%) when the 1:1 mixture of triphenylphosphine and cobalt(II) bromide was used as the catalyst precursor. Nevertheless, we were able to find a reaction pathway for the formation of cyclohexa-1,3-diene derivatives by a cobalt catalyst, which is theoretically described by Vollhardt, Malacria, and co-workers for a $CpCo^+$ fragment.[13] On the other hand, when internal alkynes, such as hex-3-yne, ethyl butynoate, and 1-phenylpropyne were used, only the Diels–Alder adducts (75–100% yield) accompanied by small amounts of the corresponding cyclotrimerization products were obtained.



Scheme 3

The use of buta-1,3-diene (Scheme 3) led to satisfactory results in the synthesis of the desired cyclohexa-1,3-diene product **5**. One can imagine that separation by column chromatography of the products **1**, **2**, and **3** is not a trivial task based on their high R_f values,[14] especially when one considers that the Diels–Alder and the [2+2+2]-cycloaddition product have very similar R_f values. A better separation was achieved when the dihydroaromatic Diels–Alder adduct was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone before separation by column chromatography. While products of type **3** are rather difficult to oxidize to yield an aromatic compound (*vide infra*), the cyclohexa-1,3-diene **5** can be transformed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to the corresponding aromatic product **6**. Nevertheless, the oxidation of cyclohexa-1,4-dienes by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone is more rapid than the oxidation of the hexa-1,3-diene derivative **5**, so that 14% of **5** and 37% of **6** could be obtained from this reaction.

The quaternary center in **3** should prohibit oxidation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. However, when **3** was stirred in benzene solution (Scheme 4) for two hours an oxidative rearrangement to the vinyl-terphenyl derivative **7** was observed and this product was obtained in 31% yield over two steps.



Scheme 4

This reaction is believed to proceed via electron abstraction by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to give a cyclohexadienyl cation intermediate, which allows the rearrangement to give **7**.

The cobalt-catalyzed cycloaddition of alkynes and 1,3-dienes could be expanded to the [2+2+2]-cycloaddition process to yield vinyl-substituted cyclohexa-1,3-dienes in moderate yield. The reaction conditions were optimized and it was determined that the best catalyst precursor was dibromobis(triphenylphosphine)cobalt (5 mol%) together with zinc and zinc iodide in dichloromethane. The 2,3-dichloro-5,6-dicyano-1,4-benzoquinone oxidation of the cyclohexa-1,3-diene **3** led unexpectedly to the rearrangement product **7**.

NMR spectra were recorded on a 300 MHz instrument. Electron impact mass (EI) spectra were recorded on a Varian MAT CH 7A. High resolution mass spectra were recorded on a Finnigan MAT95Q instrument. GC and GCMS were recorded on a Hewlett Packard 5890 and an Agilent 6890N gas chromatograph with a mass detector Agilent 5973. All reagents were of commercial quality, zinc iodide was dried in vacuo at 150 °C before use.

Cobalt-Catalyzed [2+2+2] Cycloaddition; General Procedure

The catalyst was prepared by stirring $CoBr_2(PPh_3)_2$, $CoBr_2$(dppen), or $CoBr_2$(dppben) (5 mol%), Zn powder (10 mol%), and ZnI_2 (10 mol%) in CH_2Cl_2 for 5 min. Then the 1,3-diene (1.0 equiv) and alkyne (2.0 equiv) were subsequently added. The mixture was stirred at r.t. for 15 h and filtered through silica gel (MTBE or Et_2O). The solvent was removed under reduced pressure and the residue purified by flash column chromatography.

5-Methyl-1,4-diphenyl-5-vinylcyclohexa-1,3-diene (3)

Eluent: pentane; colorless oil; yield: 51%; 95% pure.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.20 (m, 10 H, H_{ar}), 6.44 (dt, J = 5.9, 1.3 Hz, 1 H, H_{olef}), 6.19 (d, J = 5.9 Hz, 1 H, H_{olef}), 6.01 (dd, J = 17.4, 10.1 Hz, 1 H, H_{olef}), 5.14 (dd, J = 17.4, 1.3 Hz, 1 H, H_{olef}), 5.05 (dd, J = 10.4, 1.3 Hz, 1 H, H_{olef}), 2.71 (s, 2 H, CH_2), 1.29 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9, 143.8, 141.3, 140.7, 135.3, 128.4, 127.8, 127.8, 127.2, 126.7, 125.0, 124.8, 120.7, 112.5, 42.0, 41.1, 24.0.

MS (EI): m/z (%) = 272 (100, $[M]^+$), 257 (24 $[M - CH_3]^+$), 241 (9), 230 (17), 215 (23), 202 (10), 191 (4), 181 (23), 165 (30), 152 (27), 141 (11).

HRMS (EI): m/z calcd for $C_{21}H_{20}$: 272.1565; found: 272.1556.

1,4-Diphenyl-5-vinylcyclohexa-1,3-diene (5)

Eluent: pentane; colorless oil; yield: 14%; 100% pure.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.47 (m, 4 H, H_{ar}), 7.37–7.33 (m, 4 H, H_{ar}), 7.26–7.21 (m, 2 H, H_{ar}), 6.62 (d, J = 6.1 Hz, 1 H, H_{olef}), 6.50 (dd, J = 6.1, 2.8 Hz, 1 H, H_{olef}), 5.92 (ddd, J = 17.0, 10.2, 6.8 Hz, 1 H, H_{olef}), 5.13 (dt, $J = 17.2$, 1.5 Hz, 1 H, H_{olef}), 4.98 (dt, $J = 10.2$, 1.3 Hz, 1 H, H_{olef}), 3.55–3.50 (m, 1 H, CH), 3.00 (ddd, $J = 16.6$, 6.1, 2.6 Hz, 1 H, C*H*H), 2.82 (dd, $J = 16.6$, 2.3 Hz, 1 H, CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.7, 139.8, 138.8, 137.3, 134.4, 128.4, 127.1, 125.4, 125.1, 121.8, 121.1, 114.9, 39.6, 32.5.

MS (EI): *m*/*z* (%) = 258 (100, $[M]^+$), 241 (26), 230 (30), 217 (21), 202 (13), 289 (8), 179 (21), 165 (33), 152 (23), 141 (12), 128 (13).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{18}$: 258.1409; found: 258.1399.

1,4-Diphenyl-5-vinylbenzene (6)
Eluent: pentane; colorless oil; yield: 37%; ~85% pure.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, $J = 1.9$ Hz, 1 H, H_{ar}), 7.68–7.65 (m, 2 H, H_{ar}), 7.56 (dd, $J = 7.9$, 1.9 Hz, 2 H, H_{ar}), 7.50–7.30 (m, 8 H, H_{ar}), 6.77 (dd, $J = 17.6$, 10.9 Hz, 1 H, H_{olef}), 6.50 (dd, $J = 17.4$, 1.3 Hz, 1 H, H_{olef}), 5.92 (dd, $J = 10.9$, 1.1 Hz, 1 H, H_{olef}).

MS (EI): *m*/*z* (%) = 256 (100, $[M]^+$), 239 (38), 226 (7), 178 (19), 165 (12), 151 (7).[15]

2-Methyl-1,4-diphenyl-3-vinylbenzene (7)
Eluent: pentane–MTBE (10:1); colorless oil; yield: 31%; 95% pure.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.30 (m, 10 H, H_{ar}), 7.22 (s, 2 H, H_{ar}), 6.68 (dd, $J = 17.9$, 11.5 Hz, 1 H, H_{olef}), 5.37 (dd, $J = 11.5$, 1.9 Hz, 1 H, H_{olef}), 5.11 (dd, $J = 17.9$, 1.9 Hz, 1 H, H_{olef}), 2.30 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.4, 142.3, 141.9, 140.4, 137.3, 135.7, 133.6, 130.0, 129.4, 128.5, 128.1, 127.8, 127.5, 126.8, 126.5, 120.7, 18.8.

MS (EI): *m*/*z* = 270 (84, $[M]^+$), 255 (100, $[M - CH_3]^+$), 239 (38), 226 (8), 215 (6), 202 (5), 189 (10), 178 (16), 165 (9), 152 (6), 139 (3), 126 (20), 113 (9), 101 (5), 91 (4), 77 (6).

HRMS (EI): calcd for $C_{20}H_{18}$: 258.1409; found: 258.1414.

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(10) CCDC 659433 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(15) ^{1}H NMR data were assigned of the major component to the best of our knowledge and ^{13}C NMR and HRMS data were not obtained based on the low purity of the sample.