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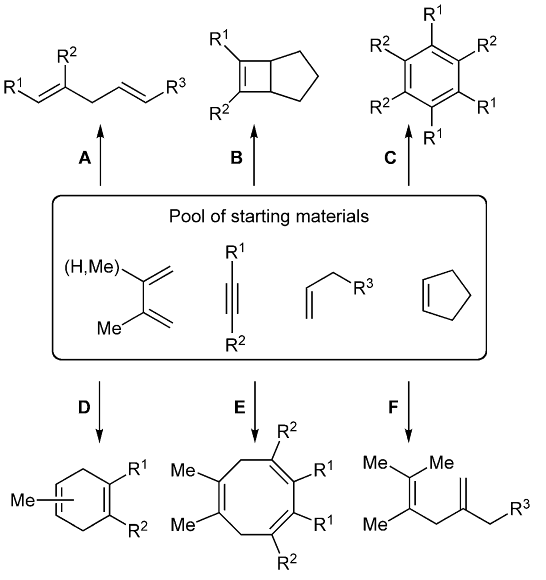
Synthetic Methods

Cobalt-Catalyzed 1,4-Hydrobutadienylation of 1-Aryl-1,3-dienes with 2,3-Dimethyl-1,3-butadiene**

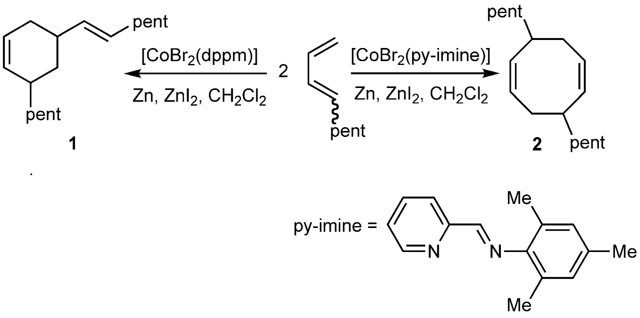
Martin A. Bohn, Anastasia Schmidt, Gerhard Hilt, Mehmet Dindaroğlu, and Hans-Günther Schmalz*

The application of cobalt-based catalysts for the construction of new carbon–carbon bonds, beyond simple cross-coupling, is of increasing interest and opens access to a wide range of products.[1] The $CoBr_2$-ligand-Zn-ZnI_2 system has been identified as a versatile precatalyst for the controlled and atom-economical transformation of unsaturated organic molecules. Two broad classes of reactions, which are promoted by this fascinating transition metal and differ by the starting materials and ligands, are discernable (Scheme 1). The first class concerns transformations of alkynes such as the Alder-ene reaction between internal alkynes and terminal olefins (**A**),[2] the [2+2] cycloaddition between internal alkynes and cyclopentene (**B**),[3] and the [2+2+2] trimerization of alkynes (**C**).[4] The second class involves reactions based upon the 1,3-butadiene motif. These reactions are the Diels–Alder reaction (a *para-* or *meta*-selective version) of alkynes and 1,3-dienes (**D**),[5] the [4+2+2] cycloaddition leading to eight-membered rings (**E**),[6] and the 1,4-hydrovinylation reaction,[7] which leads to 1,4-dienes starting from 1,3-dienes and terminal olefins (**F**). The cobalt-catalyzed 1,4-hydrovinylation reaction is complementary to an iron-based transformation which delivers the corresponding linear 1,4-hydrovinylation products.[8]



Scheme 1. Portfolio of atom-economical cobalt-catalyzed reactions utilizing unsaturated starting materials.

During our ongoing investigations into the rich chemistry of cobalt-catalyzed reactions of 1,3-dienes we recently came across a novel reaction pathway. Initial studies carried out with 1-alkyl-1,3-dienes showed the predominant formation of dimers **1** and **2**, resulting from unprecedented cobalt-catalyzed [4+2] and [4+4] cycloadditions, respectively (Scheme 2).[9,10] Actually, the product **1** corresponds to the long sought-after Diels–Alder reaction with neutral electron demand. Thus, the potential of the cobalt-catalyzed reactions of 1-substituted 1,3-dienes deserves further investigation.



Scheme 2. Cobalt-catalyzed [4+2] and [4+4] cycloaddition of 1,3-nonadiene.

Interestingly, when 1-aryl-substituted 1,3-dienes **3** (Scheme 3) were reacted under the same reaction conditions little to no dimerization products **1** and **2** were observed.[11] Instead, the cobalt-catalyzed reaction of such aryldienes with 2,3-dimethyl-1,3-butadiene afforded linear (*E*,*E*)-1,3,6-trienes **4**, which result from a 1,4-hydrobutadienylation, that is, from the addition of the 1-aryl-1,3-diene **3** to 2,3-dimethyl-1,3-butadiene (DMB).

We were intrigued by this complete change of reactivity, which led to the unexpected formation of **4**, and so sought to identify the reason for this change. While the overall reaction

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[*] Dipl.-Chem. M. A. Bohn, Dipl.-Chem. A. Schmidt, Prof. Dr. G. Hilt
Fachbereich Chemie, Philipps-Universität Marburg
Hans-Meerwein-Strasse, 35043 Marburg (Germany)
E-mail: hilt@chemie.uni-marburg.de
Dipl.-Chem. M. Dindaroğlu, Prof. Dr. H.-G. Schmalz
Department für Chemie, Universität zu Köln
Greinstrasse 4, 50939 Köln (Germany)

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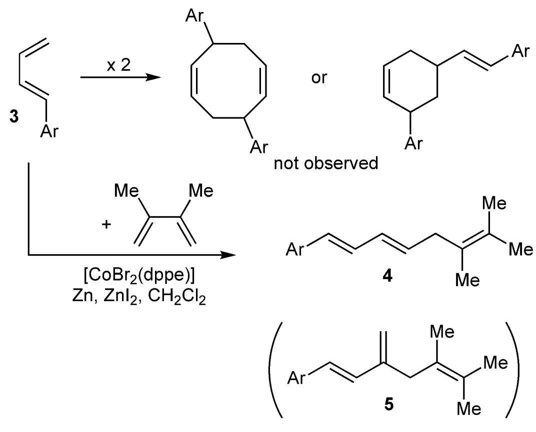


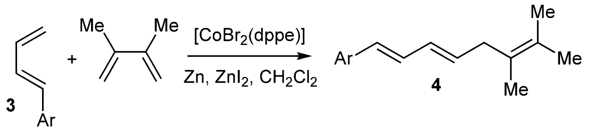
Scheme 3. Cobalt-catalyzed formation of a 1,3,6-triene **4**.

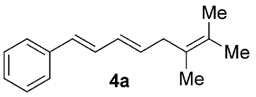
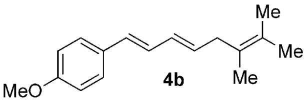
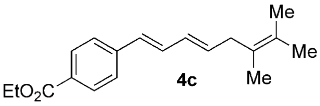
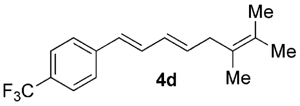
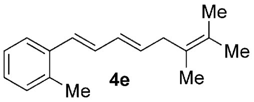
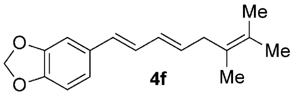
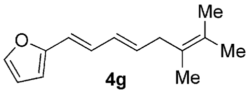
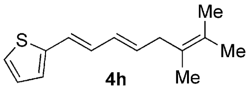
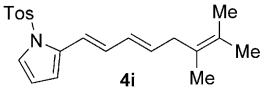
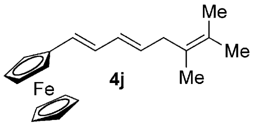
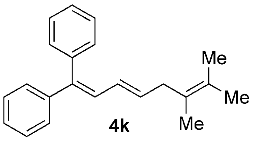
is related to the 1,4-hydrovinylation (**F**) we considered it remarkable that the 1-aryl-1,3-diene selectively acts as the alkene component in the presence of the 2,3-disubstituted 1,3-butadiene, to which it is added in a 1,4-fashion. As indicated in Scheme 3, the linear 1,3,6-triene (**4**) is the major product, whereas the branched product (**5**) is detected only as a minor component (up to ca. 10%). The separation of the two isomers **4** and **5** could not be accomplished utilizing flash column chromatography on silica gel.

Obviously, the catalyst is able to discriminate with an excellent degree of precision between the 1-mono- and the 2,3-disubstituted 1,3-diene as no products corresponding to the inverted reaction were observed. The precatalyst system applied was identical to the one used before in the 1,4-hydrovinylation reaction: cobalt (1,2-bis-(diphenylphosphino)ethane) bromide ([CoBr$_2$(dppe)]), zinc iodide, and zinc powder suspended in anhydrous dichloromethane.

To probe the scope of the method, we tested a series of 1-aryl-1,3-butadienes, which were prepared by the Wittig reaction of allyltriphenylphosphonium bromide and the respective aromatic aldehydes. The cobalt-catalyzed transformation of the aryldienes proceeded smoothly, when using 3 equivalents of 2,3-dimethyl-1,3-butadiene (DMB), to give the products **4** in moderate to excellent yields (Table 1). As shown in the case of **4b** a decrease of the amount of DMB to 1.5 equivalents resulted in lower yields. We briefly assessed the effect of the configuration and the stereochemical purity of the 1-aryl-1,3-dienes **3** on the outcome of the reaction. As the diene moiety of **3** is formally carried over into the triene product **4**, the question was whether the reaction would proceed with retention of stereochemical information or not. Therefore, we compared the outcome of the reaction of an *E*/*Z* mixture (1:2.7) of **3** (Table 1, entry 7) with the outcome of the reaction of the pure *E* isomer. As the resulting mixtures of **4g** and **5g** showed identical NMR spectra we can conclude that both the *E* and the *Z* isomer of **3** are acceptable substrates and both give *E*,*E*-**4** as the main product. However, to avoid any uncertainty the *E* isomers were used throughout, unless specified otherwise (Table 1).[12]

Table 1: Results of the cobalt-catalyzed 1,4-hydrobutadienylation reaction.[a]



Entry	Ar	Product (**4**)	Yield [%] (**4**/**5**)[b]
1	Ph	 **4a**	91 (6.0:1)
2	4-MeOC$_6$H$_4$	 **4b**	93 (8.5:1) 72[c]
3	4-EtO$_2$CC$_6$H$_4$	 **4c**	84 (8.2:1)
4	4-F$_3$CC$_6$H$_4$	 **4d**	75 (5.8:1)
5	2-MeC$_6$H$_4$	 **4e**	85 (4.0:1)
6	(3,4-OCH$_2$O) C$_6$H$_4$	 **4f**	86 (7.5:1)
7	2-furanyl	 **4g**	94 (6.9:1) 67[c,d]
8	2-thienyl	 **4h**	68[c,d] (11.7:1)
9	*N*-tosyl-2-pyrrolyl	 **4i**	36[c,d] (4.6:1)
10	ferrocenyl	 **4j**	49 (6.1:1)
11	(C$_6$H$_5$)$_2$	 **4k**	89 (3.8:1)

[a] Reaction conditions: 1-Aryl-1,3-butadiene (1.0 equiv), 2,3-dimethyl-1,3-butadiene (3.0 equiv), [CoBr$_2$(dppe)] (10 mol%), ZnI$_2$ (20 mol%), Zn (20 mol%), dichloromethane, ambient temperature, 4–18 h. [b] Ratio determined by ^{1}H NMR spectroscopy by comparison of the integrals of the newly formed methylene moiety of the 1,3,6-triene system. [c] Only 1.5 equiv of 2,3-dimethyl-1,3-butadiene were used. [d] Starting materials applied as a mixture of *E* and *Z* isomers.

The reactions of a range of 1-aryl-substituted 1,3-dienes with DMB were examined (Table 1). Electron-rich and electron-deficient phenyl derivatives were both viable reaction partners. Excellent yields were obtained when electron-rich aryls were used.

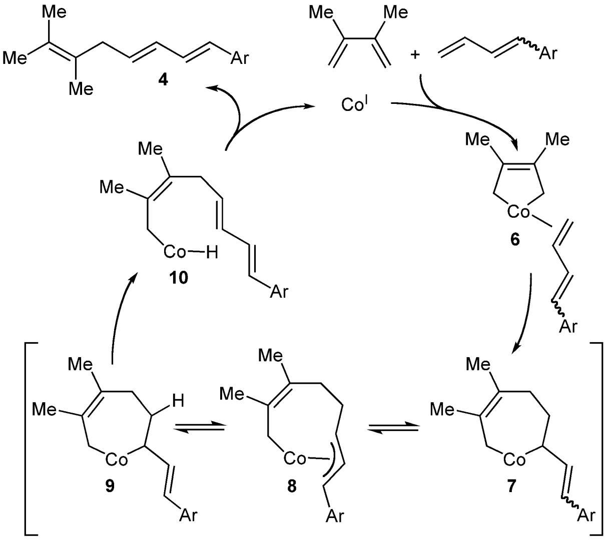
Both 1-phenyl- and 1-(4-methoxyphenyl)-1,3-butadiene lead to nearly quantitative yields of the target 1,3,6-trienes **4a** and **4b**, respectively (Table 1, entries 1 and 2). Electron-poor and sterically hindered aryl substituents proved to be slightly less reactive; nevertheless very satisfactory yields were obtained for all the reactions.

Ester- and trifluoromethyl-substituted aromatic systems led to slightly diminished yields (84% for **4c**, 75% for **4d**). When 1,1-diphenyl-1,3-butadiene reacted with DMB, **4k** was obtained in excellent yield, which is noteworthy as the diene system is sterically quite congested. In addition, in the case of **4e**, which has an *ortho*-tolyl substituent, a yield of 85% demonstrates that steric bulk adjacent to the diene moiety is acceptable. Heteroaryl-substituted dienes are equally viable starting materials as was demonstrated when the furan- and thiophene-substituted products **4g** and **4h** were obtained in good to excellent yields. However, the 2-(*N*-tosyl)-pyrrolyl derivative **4i** was isolated in only 36% yield. The yields for **4h** and **4i** are acceptable especially considering the fact that these compounds were only reacted with 1.5 equivalents of DMB. With regards to the selectivity of the reaction for the linear products **4** over the branched products **5,** a clear preference for the linear products was observed; in no case was the branched product the major component. The ratio of the two isomers for the reactions of monosubstituted 1,3-dienes **3** varied from 4.0:1 to 11.7:1 (**4**/**5**) with no simple trends presenting themselves.

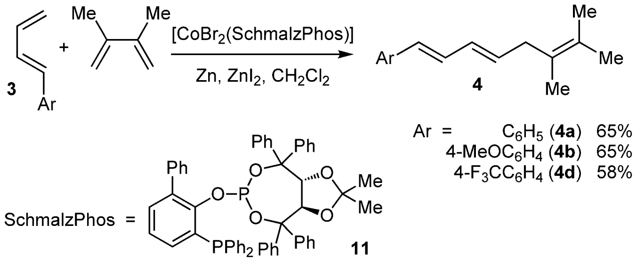
The postulated mechanism for the 1,4-hydrobutadienylation reaction is relatively straightforward (Scheme 4). In analogy to the mechanism proposed by us for the 1,4-hydrovinylation reaction,[7,8] the initial step after the formation of the catalytically active cationic cobalt(I) species (abbreviated as Co^I) is the formation of a cobaltacyclopentene (Co^{III}) intermediate **6** through oxidative cyclization. The terminal double bond of the 1-substituted 1,3-diene subsequently inserts into the cobalt–carbon σ bond of **6**, thus leading to the key intermediate **7**. At this point the regiochemistry of the subsequent product has already been decided. The alternative carbon–carbon bond formation, in which the insertion of the terminal double bond of the 1-substituted 1,3-diene occurs with the opposite regiochemistry to give the branched product **5,** is omitted from Scheme 4 for clarity.[13]

The isomerization of the double bond of the mixture of *E* and *Z* isomers of the 1-substituted 1,3-diene can be rationalized by intermediate **8**, which leads predominantly to the *E*-configured intermediate **9** by σ–π–σ equilibrium of cobaltacycles **7**–**9**. A β-hydride elimination generates **10** and a reductive elimination gives the acyclic 1,3,6-triene product **4** together with regeneration of the low-valent cobalt catalyst. A tentative explanation for the preferential formation of the linear product **4** in the 1,4-hydrobutadienylation reaction is the possibility of an attractive interaction between the second double bond of the 1-substituted 1,3-diene and the transition metal in the step from intermediate **6** to **7**. This secondary attractive interaction might be influential enough during the precoordination of the reaction partners to explain how the more-substituted carbon atom ends up in the sterically more-congested position next to the cobalt atom.

During the course of our investigation of the 1,4-hydrobutadienylation reaction, reported herein, a brief ligand screening was carried out. Use of the common bisdiphenylphosphino-type chelating ligands, dppp and dppb,[14] did not lead to any significant improvement. However, when the taddol-derived bidentate ligand **11** (SchmalzPhos), which has proven useful in several other cases,[15] was tested the linear product was produced exclusively (Scheme 5) without the formation of any other side products.

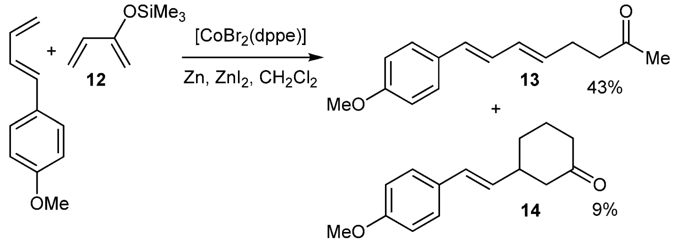


Scheme 4. Postulated mechanism for the cobalt-catalyzed 1,4-hydrobutadienylation.



Scheme 5. Cobalt-catalyzed formation of 1,3,6-trienes using the SchmalzPhos ligand.

Although the yields are somewhat diminished when utilizing 5 mol% of the [$CoBr_2$(SchmalzPhos)] catalyst, the products **4a**, **4b**, and **4d** could be isolated as single regio- and double-bond isomers, thus constituting a significant improvement. When unsymmetrical electron-rich 1,3-dienes, such as 2-trimethylsilyloxy-1,3-butadiene (**12**), were used, the [$CoBr_2$(dppe)] catalyst precursor led to a mixture of **13** and the corresponding branched 1,4-hydrobutadienylation product in 43% yield (ratio: 4.3:1), as well as a [4+2] cycloaddition product **14** in 9% yield (Scheme 6). In this case, the [CoBr$_2$(SchmalzPhos)] catalyst precursor gave the desired product **13** with a disappointing yield of 30%, the strong preference for the linear product remained unchanged.[16] Therefore, in principle the 1,4-hydrobutadienylation could be expanded to unsymmetrical starting materials, and out of the many possible 1,4-hydrobutadienylation products that could be formed **13** should be the preferred isomer.



Scheme 6. Cobalt-catalyzed formation of a 1,3-diene-7-one (**13**).

This high degree of selectivity is encouraging and our future efforts will include a detailed examination of the reactivity of unsymmetrical mono- and disubstituted 1,3-butadiene systems and an improved ligand design for regio- and chemoselective bond-formation processes for the synthesis of linear triene products.

In conclusion, we have reported herein a new carbon–carbon bond-forming process, which uses easily obtainable starting materials and exploits a well-known reactive cobalt-based system. The active catalyst exhibits exquisite discrimination of the two different 1,3-diene types applied, with only the 1-aryl-substituted 1,3-butadiene acting as the alkene component. Linear 1,3,6-trienes **4** are the predominant products when the simple, readily available [CoBr$_2$(dppe)] catalyst precursor is used, whereas the use of the somewhat more elaborate complex [CoBr$_2$(SchmalzPhos)] leads to exclusive formation of the linear product **4**, with no formation of the branched side product **5**.

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Keywords: alkenes · cobalt · homogeneous catalysis · hydrobutadienylation · polyenes

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[9] dppm = 1,1-bis(diphenylphosphino)methane, py-imine = 2,4,6-trimethyl-*N*-(pyridin-2-ylmethylene)aniline.

[10] The reaction for the formation of **1** was performed utilizing [CoBr$_2$(dppm)] (10 mol%), Zn powder (20 mol%), ZnI$_2$ (20 mol%) in dichloromethane at ambient temperature. Product **1** was obtained in 73% yield as a colorless oil. The reaction for the formation of **2** was performed utilizing [CoBr$_2$(py-imine)] (10 mol%) under otherwise identical reaction conditions. Product **2** was obtained in 27% yield as a colorless oil. The NMR data for **1** and **2** did not allow unambiguous assignments of the regiochemistry for **1** or the differentiation between the *cis* and *trans* diastereomers for both products **1** and **2**.

[11] When 1,3-nonadiene was reacted with 2,3-dimethyl-1,3-butadiene in the presence of [CoBr$_2$(dppm)] as catalyst precursor, the mixed [4+2] cycloaddition product was isolated in 43% yield. Utilizing the [CoBr$_2$(dppe)] catalyst precursor led to an inseparable mixture of 1,4-hydrobutadienylation and [4+2] cycloaddition products.

[12] A number of compounds were available as the (*E*)-3-arylpropenal, which could be converted into the (*E*)-1-aryl-1,3-dienes by the Wittig reaction. For cases where the respective propenals were not commercially available a procedure by Battistuzzi et al. lead to the desired intermediates starting from the aryl bromides and acrolein diethyl acetale: G. Battistuzzi, S. Cacchi, G. Fabrizi, *Org. Lett.* **2003**, *5*, 777.

[13] For a cobalt-catalyzed hydrovinylation of alkynes with similar postulated intermediates see: S. Mannathan, C.-H. Cheng, *Chem. Commun.* **2010**, *46*, 1923.

[14] dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane.

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[16] In the 1,4-hydrobutadienylation reaction of the unsymmetrical 1,3-diene myrcene with a 1-aryl-1,3-diene the corresponding product **13** was observed. The accompanying product **14** could not be separated by column chromatography on silica gel. The two products (ratio = 1.0:1.7) were obtained in a combined yield of 59%.