ORGANIC
LETTERS

2013
Vol. 15, No. 11
2708–2711

Scope and Limitations of 1,3,5-Hexatriene Derivatives in Regioselective Cobalt-Catalyzed Reactions

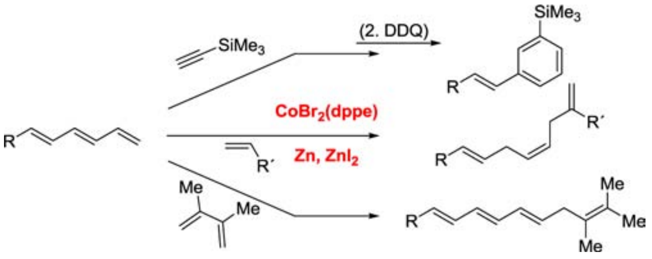
Anastasia Schmidt and Gerhard Hilt*

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

hilt@chemie.uni-marburg.de

Received April 12, 2013

ABSTRACT



Applications of 1,3,5-hexatriene derivatives in atom-economic cobalt-catalyzed transformations, such as the Diels–Alder reaction with alkynes, the 1,4-hydrovinylation reaction with terminal alkenes, and the 1,4-hydrohexatrienylation reaction, are investigated. In all cases, regioselective transformations were found to generate cyclic derivatives such as stilbenes or acyclic products with a high control of the double bond geometry in the skipped trienes derived from the 1,4-hydrovinylation process or the tetraenes generated in the so far unprecedented 1,4-hydrohexatrienylation reaction.

Low-valent cobalt complexes are excellent catalysts for the reaction of unsaturated educts, such as alkenes, 1,3-dienes, allenes, alkynes, enynes, diynes, and many other unsaturated starting materials.[1] Generally, cyclic products are generated by cobalt-catalyzed [2 + 2], [4 + 2], [6 + 2], [4 + 2 + 2], and other cycloaddition reactions via cobalt-initiated insertion reactions and reductive eliminations as key steps in the reaction mechanisms. On the other hand, acyclic products are obtained when a competing β-hydride elimination is possible, mostly outrunning the alternative reductive elimination processes of a cycloaddition. In these cases, cobalt-catalyzed 1,2- or 1,4-hydrovinylation,[2] Alder–ene reactions,[3] or alternatively the reductive codimerization reactions[4] in the presence of a proton source are encountered.

Herein, we report our investigation of 1,3,5-hexatriene derivatives as starting materials in several cobalt-catalyzed

---

(1) (a) Okamoto, S. *Heterocycles* **2012**, *85*, 1579. (b) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (c) Jeganmohan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2008**, *14*, 10876. (d) Omae, I. *Appl. Organomet. Chem.* **2007**, *21*, 318. (e) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (f) Malacria, M.; Aubert, C.; Renaud, J. L. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Lautens, M., Trost, B. M., Eds.; Thieme: Stuttgart, 2001; Vol. 1, p 439. (g) Welker, M. E. *Curr. Org. Chem.* **2001**, *5*, 785.

(2) (a) Arndt, M.; Dindaroğlu, M.; Schmalz, H.-G.; Hilt, G. *Org. Lett.* **2011**, *13*, 6236. (b) Hilt, G.; Roesner, S. *Synthesis* **2011**, 662. (c) Arndt, M.; Reinhold, A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 5203. (d) Hilt, G.; Arndt, M.; Weske, D. F. *Synthesis* **2010**, 1321. (e) Kersten, L.; Roesner, S.; Hilt, G. *Org. Lett.* **2010**, *12*, 4920. For 1,2-hydrovinylation reactions, see: (f) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 3295. (g) Saha, B.; Smith, C. R.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2008**, *130*, 9000. (h) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (i) Lassauque, N.; Franciò, G.; Leitner, W. *Adv. Synth. Catal.* **2009**, *351*, 3133. (j) Lassauque, N.; Franciò, G.; Leitner, W. *Eur. J. Org. Chem.* **2009**, 3199. (k) Grutters, M. M. P.; Müller, C.; Vogt, D. *J. Am. Chem. Soc.* **2006**, *128*, 7414. (l) RajanBabu, T. V. *Chem. Rev.* **2003**, *103*, 2845. (m) Yi, C. S.; Lee, D. W.; Chen, Y. *Organometallics* **1999**, *18*, 2043.

(3) (a) Cho, E. J.; Lee, D. *J. Am. Chem. Soc.* **2007**, *129*, 6692. (b) Trost, B. M.; Papillon, J. P. N.; Nussbaumer, T. *J. Am. Chem. Soc.* **2005**, *127*, 17921. (c) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630. (d) Neisius, N. M.; Plietker, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5752. (e) Ogoshi, S.; Haba, T.; Ohashi, M. *J. Am. Chem. Soc.* **2009**, *131*, 10350. (f) Gooßen, L. J.; Rodríguez, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 7544. (g) Tsujita, H.; Ura, Y.; Matsuki, S.; Wada, K.; Mitsudo, T.-a.; Kondo, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5160.

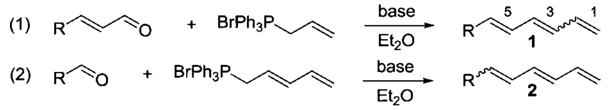
(4) (a) Mannathan, S.; Cheng, C.-H. *Chem.—Eur. J.* **2012**, *18*, 11771. (b) Wei, C.-H.; Mannathan, S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 6942. (c) Mannathan, S.; Cheng, C.-H. *Chem. Commun.* **2010**, *46*, 1923. (d) Jeganmohan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2008**, *14*, 10876. (e) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (f) Ikeda, S. *Acc. Chem. Res.* **2000**, *33*, 511. (g) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (h) Reichard, H. A.; McLaughlin, M.; Chen, M. Z.; Micalizio, G. C. *Eur. J. Org. Chem.* **2010**, 391.

10.1021/ol401015e

transformations to verify whether chemo-[5] and/or regioselective reactions of the hexatrienes can be observed. Also, we were interested if the double-bond configurations in the starting materials are preserved in the products or if double bond isomerizations can be observed as recently reported by us.[6]

For the synthesis of the 1,3,5-hexatrienes, we selected the Wittig olefination of an *E*-configured α,*β*-unsaturated aldehyde with an allyl phosphorylide (1) or a Wittig olefination of a simple aldehyde with a pentadienyl phosphorylide (2) to furnish the hexatrienes **1** and **2** (Scheme 1).[7] Thereby, the desired 1,3,5-hexatriene derivatives were obtained either as a 3-(*E*/*Z*) mixture (**1**) or as 5-(*E*/*Z*) mixture as in **2**.

Scheme 1. Synthesis of Monosubstituted 1,3,5-Hexatrienes **1** and **2**

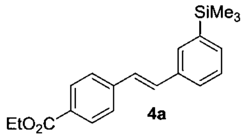
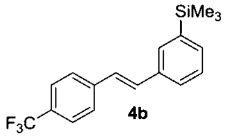
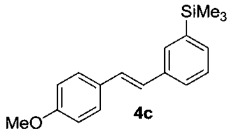
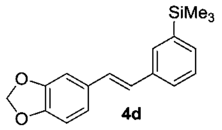
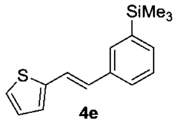
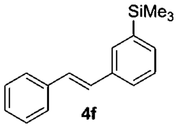
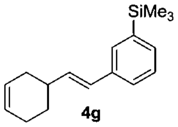


First, we applied the 1,3,5-hexatriene derivatives in cobalt-catalyzed Diels–Alder reactions (Scheme 2) with trimethylsilylacetylene as a benchmark dienophile, followed by a DDQ oxidation of the dihydroaromatic intermediate.[8]

Scheme 2. Cobalt-Catalyzed Diels–Alder Reaction of 3-(*E*/*Z*)-**1**

In principle, the Diels–Alder reaction of 3-(*E*/*Z*)-**1** with trimethylsilylacetylene can generate up to four different regio- and chemoisomers **3**–**6**. When the CoBr$_2$(dppe) catalyst precursor was used only the products of type **4** were obtained. Unfortunately, when hexatrienes of type 5-(*E*/*Z*)-**2** were applied mixtures of *E*/*Z*-isomers of type **4** were obtained in slightly changed *E*/*Z* ratios. In order to minimize the number of possible regio- and stereoisomers at this stage, only hexatrienes of type 3-(*E*/*Z*)-**1** were applied. The results of these reactions are summarized in Table 1.

Table 1. Results of the Cobalt-Catalyzed Diels–Alder Reactions of 3-(*E*/*Z*)-**1** with TMS-acetylene[a]

no.	product **4**	yield
1	 **4a**	68%[b]
2	 **4b**	82%
3	 **4c**	94%
4	 **4d**	88%
5	 **4e**	73%
6	 **4f**	88%
7	 **4g**	41%

[a] (1) CoBr$_2$(dppe) (10 mol %), zinc powder (20 mol %), zinc iodide (20 mol %), 1,3,5-hexatriene **1** (1.0 equiv) and TMS-acetylene (1.3–1.5 equiv), CH$_2$Cl$_2$, 16 h, rt. (2) DDQ (1.1 equiv), toluene, 1 h, rt. [b] Including 15% of ethyl biphenyl-4-carboxylate that could not be separated by column chromatography.

Aromatic hexatriene derivatives are well accepted as starting materials, and electron-rich hexatriene derivatives gave the best results (entries 3 and 4) whereas the yields for electron-deficient hexatrienes are slightly diminished (entries 1 and 2). The use of the aliphatic substituted 3-cyclohexenyl hexatriene (entry 7) gave only a moderate yield, which is attributed to overoxidation of the cyclohexene moiety to the corresponding 1,3-cyclohexadiene and eventually to the benzene-substituted side product with DDQ. This phenomenon was encountered earlier when the DDQ

---

(5) In this respect, a chemoselective reaction means a reaction between a reactant selectively with either one or two double bonds of the hexatriene moiety.

(6) Pünner, F.; Schmidt, A.; Hilt, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 1270.

(7) (a) Sünnemann, H. W.; Banwell, M. G.; de Meijere, A. *Eur. J. Org. Chem.* **2007**, 3879. (b) von Essen, R.; von Zezschwitz, P.; Vidović, D.; de Meijere, A. *Chem.—Eur. J.* **2004**, *10*, 4341. (c) de Meijere, A.; von Zezschwitz, P.; Nüske, H.; Stulgies, B. *J. Organomet. Chem.* **2002**, *653*, 129. (d) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (e) von Zezschwitz, P.; de Meijere, A. *Top. Organomet. Chem.* **2006**, *19*, 49. (f) Benson, C. L.; West, F. G. *Org. Lett.* **2007**, *9*, 2545.

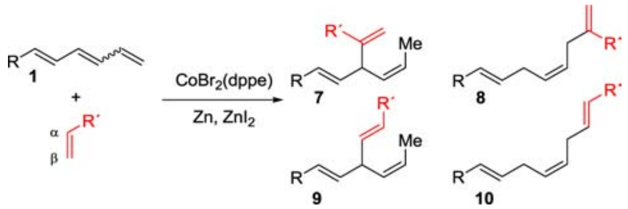
(8) In this series of experiments the focus was on the application of the CoBr$_2$(dppe) catalyst precursor. The reactions of the hexatrienes with other cobalt catalyst precursors will be performed soon. For control of the regioselectivity of the cobalt-catalyzed Diels–Alder reaction, see: (a) Danz, M.; Hilt, G. *Adv. Synth. Catal.* **2011**, *353*, 303. (b) Hilt, G.; Janikowski, J. *Org. Lett.* **2009**, *11*, 773. (c) Hilt, G.; Janikowski, J.; Hess, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 5204.

(9) Hilt, G.; Erver, F.; Harms, K. *Org. Lett.* **2011**, *13*, 304.

oxidation was performed with skipped double bonds leading to a conjugated system.[9]

In the next step, the cobalt-catalyzed hydrovinylation of the hexatriene derivatives 3-(*E*/*Z*)-**1** were investigated (Scheme 3).[2,10] In principle, in these transformations, 1,2-, 1,4-, as well as 1,6-hydrovinylation products could be formed, leading to a vast number of possible regio- and *E*/*Z*-isomers. Under the assumption that double bond between C5 and C6 is unreactive with the Co(dppe)-based catalyst, four products (**7**–**10**) of a 1,4-hydrovinylation process with a terminal alkene can be envisaged. The products **7** and **8** are regioisomers of branched-type products where the carbon–carbon bond formation took place at the higher substituted α-carbon of the alkene and either C1 or C4 of the hexatriene subunit. The other isomers (**9**/**10**) are the corresponding linear-type products.

Scheme 3. Cobalt-Catalyzed 1,4-Hydrovinylation of Hexatriene Derivatives (*E*/*Z*)-**1** with Terminal Alkenes

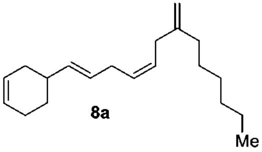
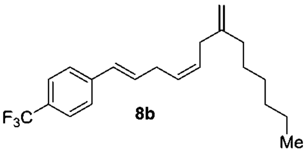
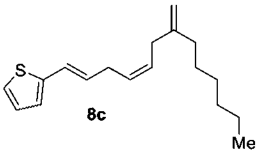
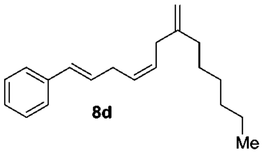
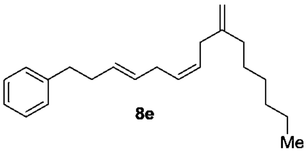
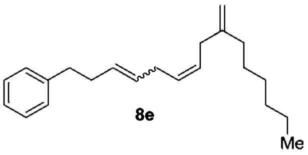
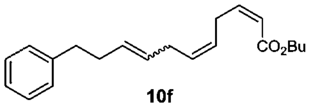


In this series of experiments, the cobalt catalyst precursor CoBr$_2$(dppe) was used which is known to generate the branched-type products **8** predominantly with nonactivated alkenes and 1,3-dienes, whereas linear products such as **10** are formed with acrylates.[2a−e] Therefore, 1-octene and butyl acrylate were selected as the terminal alkenes. The results of the cobalt-catalyzed 1,4-hydrovinylation experiments are summarized in Table 2.

The transformations led exclusively to the 1,4-hydrovinylation products, and no traces of 1,2- or 1,6-hydrovinylation reactions were observed. Also, the cobalt-catalyzed 1,4-hydrovinylation generated the branched-type products of type **8** exclusively. The reactions led to the desired skipped 1,4,7-triene derivatives with exclusive 4*Z*,7*E*-double bond configuration in moderate to good yields. Surprisingly, the cyclohexenyl-substituted hexatriene (entry 1) gave the best results. The product **8a** is a nonconjugated tetraene derivative with four different types of carbon–carbon double bonds in a single molecule. Such material could be useful for the determination of relative rates of double-bond transformation reactions.

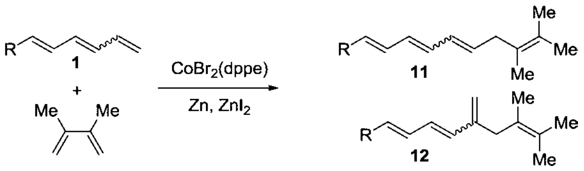
Interestingly, **8e** was generated in two different ways: first, from 3-(*E*/*Z*)-**1** (entry 5), and second, from 5-(*E*/*Z*)-**2** (entry 6). In the case of (5-*E*/*Z*)-**2**, the ratio of the *E*/*Z* mixture is translated into the product **8e** revealing a nearly unchanged *E*/*Z* ratio (1.1:1, starting material: 1.3:1). On the other hand, when 3-(*E*/*Z*)-**1** was applied **8e** was obtained in somewhat lower yield but as a single isomer.

Table 2. Results for the Cobalt-Catalyzed 1,4-Hydrovinylation Reaction with Terminal Alkenes[a]

no.	product **8**	yield (*E*/*Z*)
1	 **8a**	69% (-)
2	 **8b**	68%[b] (-)
3	 **8c**	33%[c] (-)
4	 **8d**	49%[d] (-)
5	 **8e**	46% (-)
6	 **8e**	55%[e,f] (1.1:1)
7	 **10f**	31% (1.8:1)[e,f,g]

[a] CoBr$_2$(dppe) (10–25 mol %), zinc powder (20–50 mol %), zinc iodide (20–50 mol %), 1,3,5-hexatriene **1** (1.0 equiv), and 1-alkene (1.0–3.0 equiv), CH$_2$Cl$_2$, 24–160 h, rt to 40 °C. [b] Including 37% of unreacted triene that could not be separated by column chromatography. [c] Including small amounts of an unidentified side product that could not be separated by column chromatography. [d] Including 30% of biphenyl and traces of an unidentified side product that could not be separated by column chromatography. [e] Instead of triene 3-(*E*/*Z*)-**1**, 5-(*E*/*Z*)-**2** was used. [f] Ratio determined by integration of suitable ^{1}H NMR signals. [g] The analysis of the NMR spectra does not allow to assign the main product to the *E*- or *Z*-configuration.

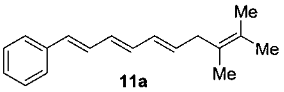
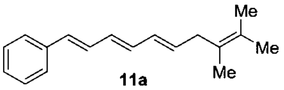
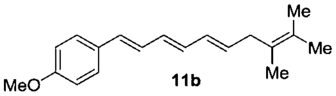
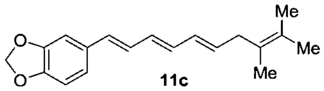
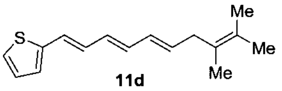
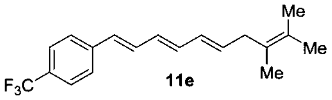
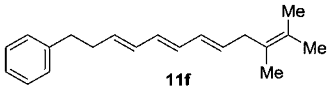
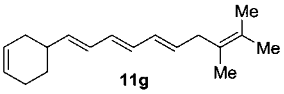
Scheme 4. Cobalt-Catalyzed 1,4-Hydrohexatrienylation Reaction



---

(10) Hilt, G. *Eur. J. Org. Chem.* **2012**, 4441.

Table 3. Cobalt-Catalyzed 1,4-Hydrohexatrienylation of 3-(*E*/*Z*)-**1** with 2,3-Dimethyl-1,3-butadiene[a]

no.	main product **11**	yield (**11**:**12**)[b] (*E*-**11**:*Z*-**11**)[b]
1	 **11a**	89%[c] (>20:1) (1:1)
2	 **11a**	64% (5.8:1) (>20:1)
3	 **11b**	73% (7.8:1) (>20:1)
4	 **11c**	78%[d] (7.7:1) (>20:1)
5	 **11d**	75% (6.4:1) (>20:1)
6	 **11e**	77% (11.0:1) (>20:1)
7	 **11f**	62% (5.2:1) (4.2:1)
8	 **11g**	74% (1.3:1) (5.5:1)

[a] $CoBr_2$(dppe) (10 mol %), zinc powder (20 mol %), zinc iodide (20 mol %), 1,3,5-hexatriene **1** (1.0 equiv), and 2,3-dimethyl-1,3-butadiene (3.0 equiv), CH_2Cl_2, 16–32 h, rt. [b] Ratio determined by integration of suitable ^{1}H NMR signals. [c] $CoBr_2$(SchmalzPhos) (5 mol %), zinc powder (10 mol %), zinc iodide (10 mol %) were used; SchmalzPhos = (3a*R*,8a*R*)-6-(3-(diphenylphosphinobiphenyl-2-yloxy)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (for the structure of SchmalzPhos, see the Supporting Information). [d] Including 8% of (3,4-methylenedioxyphenyl)benzene.

In the reaction where butyl acrylate was used (entry 7, Table 2), **10f** was obtained with a 1*Z*,4*Z*-configuration in moderate yield. As in entry 6, the ratio of the *E*/*Z* mixture of the starting material was translated into the product even though the ratio (1.8:1) was somewhat altered (starting material: 1.3:1).

Finally, we investigated the conversion of the hexatrienes 3-(*E*/*Z*)-**1** with 2,3-dimethyl-1,3-butadiene in a hitherto unprecedented cobalt-catalyzed 1,4-hexatrienylation reaction (Scheme 4). In the case of the similar $CoBr_2$-(dppe)-catalyzed 1,4-hydrobutadienylation,[11] two regioisomers were obtained, and in analogy the two isomers **11** and **12** were expected.

For these reactions, 3-(*E*/*Z*)-**1** was chosen to verify if the cobalt catalyst could lead to an isomerization of the double bond 3 to yield a single double bond isomer, such as **11**. The results of these reactions are summarized in Table 3.

The results presented in Table 3 reveal three major aspects of the cobalt-catalyzed hydrohexatrienylation reaction. First, the application of the SchmalzPhos ligand led to an excellent differentiation between products **11a** and **12a** (compare entries 1 and 2) while the *E*/*Z* ratio remained unchanged compared to the starting materials. Second, the control of the *E*/*Z* ratio of **11** is efficiently controlled with the cobalt catalyst utilizing the dppe ligand when aryl-substituted hexatrienes are used (entries 2–6). This indicates that an isomerization of the double bonds must take place during the reaction leading to the more stable *all-trans*-type isomers. Third, alkyl-substituted hexatrienes gave a mixture of regioisomers as well as *E*/*Z* isomers (entries 7 and 8) and are rather poor substrates in this transformation.

The application of 5-(*E*/*Z*)-**2** in the 1,4-hexatrienylation was successful as it led to the desired products in comparable yields. However, the *E*/*Z* ratios of the double bond 5 of the 5-(*E*/*Z*)-**2**-type starting materials were isomerized preferentially toward the *E*-isomer, but this isomerization was incomplete so that *E*/*Z*-mixtures were still obtained.

In conclusion, we were able to demonstrate that conjugated 1,3,5-hexatrienes can be applied successfully in cobalt-catalyzed reactions for the synthesis of cyclic as well as acyclic products in an atom-economic fashion. With the right choice of double-bond isomers in the starting materials, such as 3-(*E*/*Z*)-**1**, regioselective Diels–Alder, 1,4-hydrovinylation, and even 1,4-hydrohexatrienylation reactions can be realized, and in most cases, the products were obtained as single isomers in moderate to good yields.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft for financial support. We thank Dr. M. Schäfer, University of Cologne, for the HRMS spectra of some compounds.

Supporting Information Available. Experimental procedures and full characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(11) Bohn, M. A.; Schmidt, A.; Hilt, G.; Dindaroğlu, M.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2011**, *50*, 9689.

The authors declare no competing financial interest.