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Regioselective Cobalt-Catalyzed Alder-ene Reaction toward Silicon- and Boron-Functionalized Building Blocks

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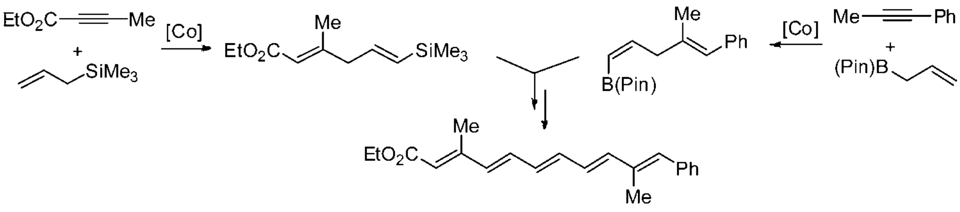
ABSTRACT



The cobalt-catalyzed formal Alder-ene reaction of functionalized alkenes and alkynes leads to bifunctionalized 1,4-dienes in high yields and excellent regio- and stereoselectivities. The silicon-functionalized building blocks are easily converted into iodo-functionalized derivatives and in combination with boron-functionalized building blocks polyenes can be generated utilizing a Suzuki cross-coupling. In addition, building blocks incorporating allylic silane functionalities can be used in Sakurai allylation or Prins-type cyclization reactions for the synthesis of heterocyclic products such as tetrahydrofuranes or tetrahydropyranes.

Cobalt-catalyzed transformations of unsaturated compounds have steadily gained importance in modern organic synthesis. Specifically atom economic carbon−carbon bond formations are of increasing interest.[1] Especially the 1,4-hydrovinylation of substituted 1,3-butadienes with terminal alkenes as well as the Alder-ene reaction of terminal alkenes with internal alkynes are relevant for the construction of linear carbon-skeletons.[2] The application of the 1,4-hydrovinylation reaction in the synthesis of 1,3-dicarbonyl derivatives[3] and the chemoselective cobalt-catalyzed Alder-ene reaction[4] versus the competing [2 + 2] cycloaddition have been explored in more detail.[5] Herein, we specifically report the generation of silicon- and boron-functionalized 1,4-dienes via the cobalt-catalyzed Alder-ene reaction.

For the synthesis of 1,4-dienes via the cobalt-catalyzed Alder-ene reaction of arene substituted alkynes, the $[CoBr_2(dppp)]$ catalyst precursor proved to be the most efficient.[6] On the other hand, when electron-deficient alkynes were applied, the $[CoBr_2(dppe)]$ complex gave the best results[7] (Scheme 1). Nevertheless, in both cases various functional groups were tolerated both in the internal alkynes **1** and in the terminal alkenes **2**.[8] In this study, we focused our attention upon the generation of silicon- and boron-functionalized 1,4-dienes, in which these functional groups are located in the vinylic or allylic

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(1) (a) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (b) Omae, I. *Appl. Organomet. Chem.* **2007**, *21*, 318. (bb) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, 2547. (c) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (d) 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. (e) Welker, M. E. *Curr. Org. Chem.* **2001**, *5*, 785. (f) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (g) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (h) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(2) Hilt, G.; Treutwein, J. *Chem. Commun.* **2009**, 1395.

(3) (a) Kersten, L.; Roesner, S.; Hilt, G. *Org. Lett.* **2010**, *12*, 4920. (b) Arndt, M.; Reinhold, A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 5203. (c) Hilt, G.; Arndt, M.; Weske, D. F. *Synthesis* **2010**, 1321.

(4) (a) Hilt, G.; Treutwein, J. *Angew. Chem.* **2007**, *119*, 8653. (b) Hilt, G.; Treutwein, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8500.

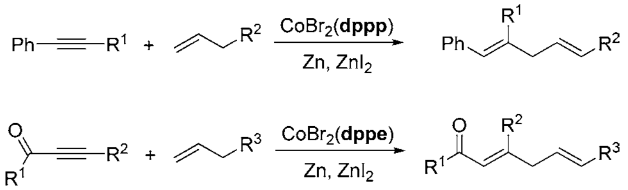
(5) Hilt, G.; Paul, A.; Treutwein, J. *Org. Lett.* **2010**, *12*, 1536.

(6) $[CoBr_2(dppp)]$ = cobalt(1,2-bis(diphenylphosphino)propane) dibromide.

(7) $[CoBr_2(dppe)]$ = cobalt(1,2-bis(diphenylphosphino)ethane) dibromide.

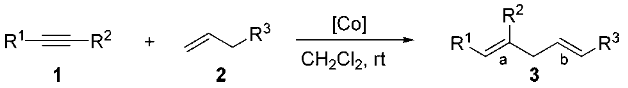
10.1021/ol102764w

Scheme 1. Cobalt-Catalyzed Alder-ene Reaction with Electron-Rich and Electron-Deficient Alkynes



position in the product **3** (Scheme 2).[9] The results of these investigation are summarized in Table 1.

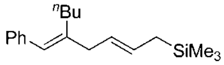
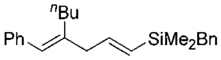
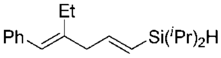
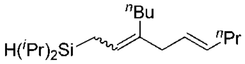
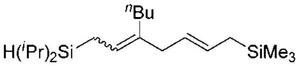
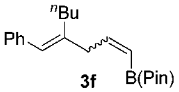
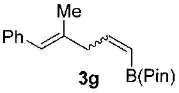
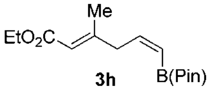
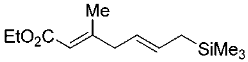
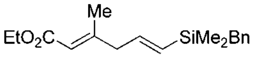
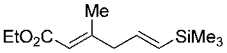
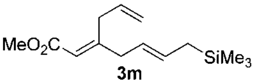
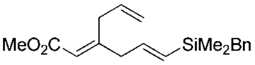
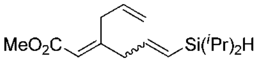
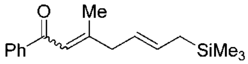
Scheme 2. Cobalt-Catalyzed Alder-ene Reaction for the Generation of Polysubstituted 1,4-Dienes



Concerning the configuration of the double bonds in the 1,4-dienes in **3**, the products are formed predominantly as the *E*,*E*-isomers concerning double bond a or b (see Scheme 2). Nevertheless, the most striking finding in this series of experiments is the fact that the configuration of double bond b is altered depending on whether a trialkylsilicon-functionalized alkene or a pinacolboronic ester alkene is applied (compare entries 8 and 11). While the *E*-configuration of double bond b is adopted when trialkylsilicon based groups are used the corresponding *Z*-configured double bond is formed predominantly with the boron-functionalized alkenes. This observation can be explained by postulating coordination of one of the pinacol oxygen lone pairs to the cobalt center. In the case of a bulky silyl-group a transoid conformation in transition state $\mathbf{B}_{\mathbf{Si}}$ leads predominantly to a β-hydride elimination via H_a toward an *E*-configured double bond. When the allyl pinacolboronic ester is used a cisoid comformation is adopted in transition state $\mathbf{B}_{\mathbf{B}}$ which favors the β-hydride elimination via the proton H_b toward the predominantly formed *Z*-isomer (Scheme 3).

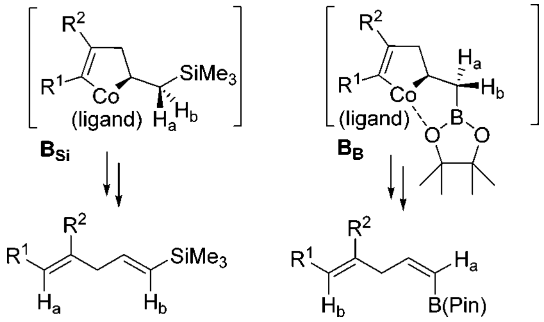
In addition, when allylpinacolboronic ester is used, the results suggest that the smaller the substituent R^2 in the alkyne is the higher the ratio for the formation of the *Z*-configured double bond becomes (Bu vs Me, entries 6,7). Moreover, this finding is hard to explain by the mechanistic sketch proposed in Scheme 3. Also, the application of the diisopropylsilane group in the alkyne (entries 4,5) and in the alkene component (entries 12, 15) resulted in unexpected findings. In these cases a rather low or in some cases an even ratio of *E*/*Z*-isomers concerning double bond a or b is obtained no matter if this functional group adopts a vinylic or an allylic position in the product of type **3**. The only option to rationalize the formation of *E*/*Z*-isomers in these cases seems to be the intermediate formation of an attractive hydrogen bridge between the cobalt center and the silicon

Table 1. Results of the Cobalt-Catalyzed Alder-ene Reaction of Silicon- And Boron-Functionalized Alkynes and Alkenes[a]

entry	1,4-diene 3[b]	method, yield (*E*:*Z*)[c]
1	 **3a**	**A**, 75% (only *E*,*E*)
2	 **3b**	**A**, 69% (only *E*,*E*)
3	 **3c**	**A**, 76% (only *E*,*E*)
4	 **3d**	**A**, 92% (50:50)
5	 **3e**	**A**, 53% (58:42)
6	 **3f**	**A**, 74% (11:89)[d]
7	 **3g**	**A**, 60% (7:93)[d]
8	 **3h**	**B**, 66% (only *E*,*Z*)
9	 **3i**	**B**, 80% (only *E*,*E*)
10	 **3j**	**B**, 80% (only *E*,*E*)
11	 **3k**	**B**, 81% (only *E*,*E*)
12	 **3l**	**B**, 65% (80:20)
13	 **3m**	**B**, 60% (only *E*,*E*)
14	 **3n**	**B**, 43% (only *E*,*E*)
15	 **3o**	**B**, 56% (58:42)
16	 **3p**	**B**, 47% (80:20)

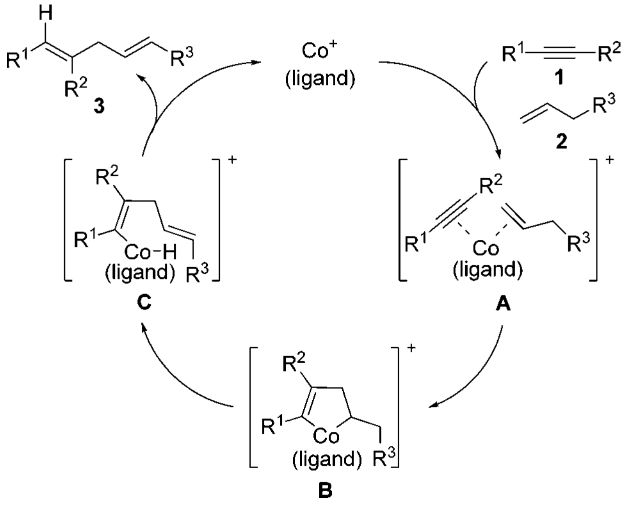
[a] Method **A**: $CoBr_2$(dppp) (10 mol %), zinc dust (20 mol %), zinc iodide (20 mol %), alkyne addition (1.5 equiv) in one portion. Method **B**: $CoBr_2$(dppe) (20 mol %), zinc dust (40 mol %), zinc iodide (40 mol %); alkyne addition (3.0 equiv) over 7 h. [b] Pin = pinacol. [c] *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy. [d] Performed according to method **A** utilizing $CoBr_2$(dppp) (20 mol %); zinc dust (40 mol %); zinc iodide (40 mol %).

Scheme 3. Rationale for the *E*-Selectivity for Silyl-Functionalized Educts and *Z*-Selectivity for Boron-Functionalized Alkenes



atom via the hydrogen atom (Co−H−Si bridge). Nevertheless, only the *E*,*E*-configured product **3c** utilizing the diisopropylsilane group (entry 3) could be observed. However, in most cases good yields, exclusive regioselectivities concerning the site of the carbon−carbon bond formation in both the alkyne and the alkene, and the exclusive formation of the desired *E*,*E*-configured isomers can be reported. Finally, for the first time an alkynone could be deployed in the cobalt-catalyzed Alder-ene reaction leading to the corresponding 1,4-diene **3p** in a moderate yield (entry 16). The proposed mechanism is initiated by the coordination of the alkyne and the alkene component to the active cationic cobalt complex leading to the generation of intermediate **A** (Scheme 4).

Scheme 4. Mechanism of the Cobalt-Catalyzed Alder-ene Reaction



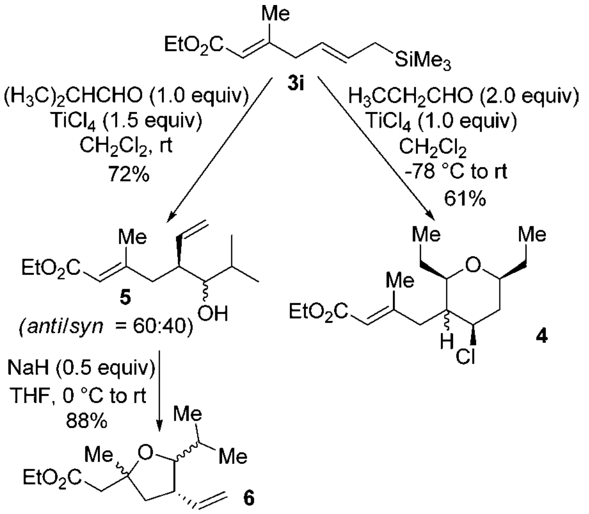
Then the regioselective carbon−carbon bond formation process leads to intermediate **B** from which a β-hydride elimination furnishes the intermediate cobalt−hydride complex **C**.

Finally, a reductive elimination under retention of double bond configuration generates the *E*-configured double bond a in the product and regenerates the active catalyst unless the coordination of functional groups interferes with this reaction pathway to induce double bond isomerizations.

If both components lack such coordinating groups, the Alder-ene reaction usually leads to *E*,*E*-configured 1,4-dienes **3**.

We envisage that many of the silicon- and boron-functionalized 1,4-dienes generated by the atom economic cobalt-catalyzed Alder-ene reaction are useful building blocks for further transformations to generate advanced products in a concise manner. In fact, the allyl silane **3i** can be reacted with propionaldehyde leading to the rapid generation of the polysubstituted tetrahydropyran **4** by Prins-type cyclization in good yields (Scheme 5). On the other hand, when isobutyraldehyde was used under slightly modified conditions, alcohol **5** was generated via a Sakurai allylation in a 72% yield. In this proof-of-principle investigation catalytic amounts of sodium hydride converted this compound smoothly into the corresponding polysubstituted tetrahydrofuran **6** in an excellent 88% yield as a mixture of diastereomers.[10]

Scheme 5. Alder-ene Product in the Generation of a Polysubstituted Tetrahydropyran and -Furan



The boron- and silicon-functionalized building blocks were then applied in a palladium-catalyzed coupling reaction. To do so, the vinyl silane **3k** was first converted into the

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(8) When terminal alkynes were used the cyclotrimerization of the alkynes to the corresponding 1,2,4-trisubstituted benzene derivatives became the predominant reaction pathway, see: (a) Hilt, G.; Hengst, C.; Hess, W. *Eur. J. Org. Chem.* **2008**, 2293. (b) Hilt, G.; Hess, W.; Harms, K. *Synthesis* **2008**, 75. (c) Hilt, G.; Hess, W.; Vogler, T.; Hengst, C. *J. Organomet. Chem.* **2005**, *690*, 5170.

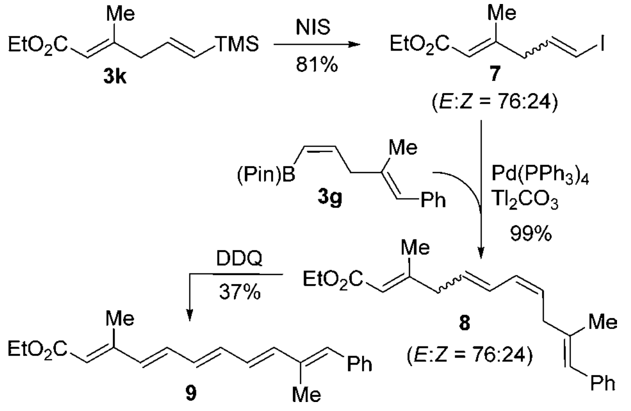
(9) For cobalt-catalyzed reactions involving borylated partners, see: (a) Geny, A.; Leboef, D.; Rouquié, G.; Vollhardt, K. P. C.; Malacria, M.; Gandon, V.; Aubert, C. *Chem.—Eur. J.* **2007**, *13*, 5408. (b) Leboef, D.; Iannazzo, L.; Geny, A.; Malacria, M.; Vollhardt, K. P. C.; Aubert, C.; Gandon, V. *Chem.—Eur. J.* **2010**, *16*, 8904.

(10) Reddipalli, G.; Venkataiah, M.; Mishra, M. K.; Fadnavis, N. W. *Tetrahedron: Asymmetry* **2009**, *20*, 1802.

corresponding vinyl iodide **7** under slightly modified Kishi conditions.[11]

Unfortunately, this conversion was always accompanied by isomerization of the affected double bond (Scheme 6). Nevertheless, the iodo-substituted 1,4-diene **7** could be obtained in good yield.

Scheme 6. Synthesis of a Pentaene via Suzuki Cross-Coupling of Alder-ene Products with Subsequent DDQ Oxidation



The Suzuki cross-coupling with the *Z*-configured enriched vinyl pinacolboronic ester **3g** proceeded smoothly at room temperature within 2 h to yield the tetraenoate **8** in a nearly quantitative yield.[12]

In previous studies concerning cobalt-catalyzed Diels−Alder reactions we utilized DDQ for the oxidation of the dihydroaromatic compounds to the corresponding aromatic products.[13] Based on these results we envisaged that the oxidation of the 1,4,6,9-tetraene derivative **8** substituted with an ester functionality and a phenyl substituent at both ends of the molecule could be used to generate a conjugated push−pull substituted pentaene **9** by DDQ dehydrogenation. To the best of our knowledge, such an interconversion has not been described in the literature. Accordingly, the ratio of retention or inversion of double bond configurations over the course of such a dehydrogenative oxidation process has not been described. We were very pleased to isolate the pentaene product **9** in a moderate yield of 37% as a solid of intense yellow color crystallizing directly from the crude reaction mixture. The all-*trans* configuration of the double bonds, as was determined by X-ray analysis (Figure 1) of the isolated solid, must be generated during the course of the DDQ oxidation which can be best explained by a radical type intermediate.[14] The generation of such polyenes via such a short reaction sequence from four simple starting materials (two alkynes and two alkenes) is very appealing, leading to either a 1,4,6,9-tetraene or a 1,3,5,7,9-pentaene product after DDQ oxidation.

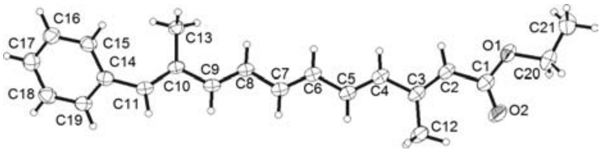


Figure 1. Crystal structure of compound **9**.

In conclusion we have demonstrated that the cobalt-catalyzed Alder-ene reaction can be used to generate *E*-configured silicon- or *Z*-configured boron-functionalized 1,4-diene building blocks. These adducts were transformed in proof-of-principle transformations into polysubstituted heterocycles. Moreover, the generation of unprecedented 1,4,6,9-tetraene and conjugated 1,3,5,7,9-pentaene derivatives, by simple DDQ oxidation, was accomplished.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie by a fellowship (FE) and the German Science Foundation. Their support is gratefully acknowledged.

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

OL102764W

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[11] Jiang, X.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 11600.

[12] Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 9657.

[13] For a recent reference, see: Auvinet, A.-L.; Harrity, J. P. A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 3893.

[14] The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 798849.