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Double- and Triple-Cobalt Catalysis in Multicomponent Reactions

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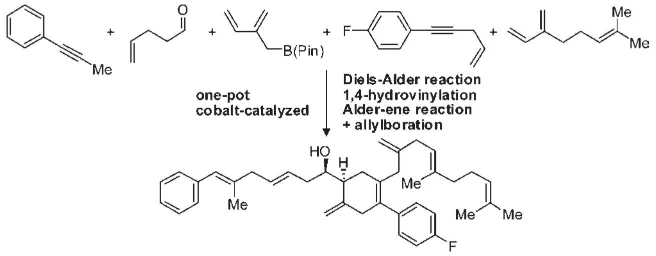
ABSTRACT



The combination of different types of cobalt-catalyzed transformations in one-pot procedures is described. One of the key building blocks, a boron-functionalized isoprene derivative (boroprene), led to the realization of four-component reaction sequences comprising the cobalt-catalyzed Diels–Alder and a 1,4-hydrovinylation reaction. Eventually, a reaction sequence including a cobalt-catalyzed Diels–Alder reaction, a cobalt-catalyzed 1,4-hydrovinylation, an allylboration, and a cobalt-catalyzed Alder-ene reaction led to a five-component one-pot reaction sequence in which five carbon–carbon bonds were formed in excellent regio- and diastereoselectivity to generate complex products in good overall yields.

The generation of increasingly complex molecules in atom- and step-economic one-pot multicomponent reactions starting from readily available starting materials is attracting many chemists. Moreover, it is of great interest when one catalyst is able to initiate two or more different types of reactions in a multicomponent transformation (double catalysis).[1,2]

The application of a wide variety of cobalt-catalyzed transformations[3] led us to consider such reactions in multicomponent sequences. In this respect, we recently described the application of the boron-functionalized isoprene derivative **1**[4] in a cobalt-catalyzed 1,4-hydrovinylation[5]/allylboration/1,4-hydrovinylation reaction sequence for the generation of **2**. This sequence represents a benchmark

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(1) For selected recent reviews, see: (a) Zhou, J. *Chem.—Asian J.* **2010**, *5*, 422. (b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. (c) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (d) Mayer, S. F.; Kroutil, W.; Faber, K. *Chem. Soc. Rev.* **2001**, *30*, 332.

(2) For recent reviews on transition-metal- and organo-catalyzed multicomponent reactions, see: (a) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *J. Organomet. Chem.* **2005**, *690*, 539. (b) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857. For an example of a multicomponent reaction initiated by cobalt catalysis, see: (c) Hilt, G.; Lüers, S.; Smolko, K. I. *Org. Lett.* **2005**, *7*, 251.

(3) For recent reviews, see: (a) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (b) Omae, I. *Appl. Organomet. Chem.* **2007**, *21*, 318. (c) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, 2547. (d) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (e) 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. (f) Welker, M. E. *Curr. Org. Chem.* **2001**, *5*, 785. (g) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (h) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96* 635. (i) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (j) Jeganmohan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2008**, *14*, 10876.

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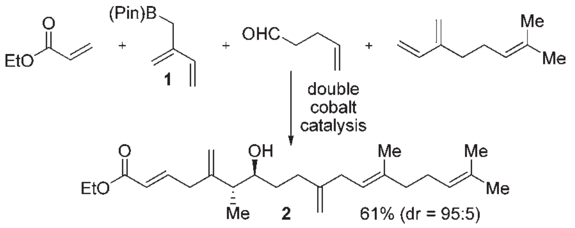
transformation of our ongoing project for efficient carbon–carbon bond formation processes (Scheme 1).

After we succeeded in the synthesis of the pinacol-boron-functionalized isoprene derivative **1** (boroprene), the generation of a complex product such as **2** was the first step to evaluate the potential embedded in the boroprene building block **1**.

Scheme 1. Multicomponent One-Pot Reaction via Two Cobalt-Catalyzed 1,4-Hydrovinylations and an Allylboration



In a first set of experiments, boroprene **1** was used as a diene component in a regioselective cobalt-catalyzed Diels–Alder reaction[6] with nonconjugated enynes **3** which were prepared adopting known procedures.[7]

As we experienced from previous investigations, cobalt catalysts with pyridyl-imine ligands[8] are highly regioselective in cobalt-catalyzed Diels–Alder reactions and are unable to perform 1,4-hydrovinylation reactions.

Accordingly, the alkyne subunit in **3** was chemo- and regioselectively transformed in a Diels–Alder reaction to the dihydroaromatic compound **4** (Scheme 2).

Scheme 2. Double-Cobalt-Catalyzed Four-Component Diels–Alder/1,4-Hydrovinylation/Allylboration Sequence

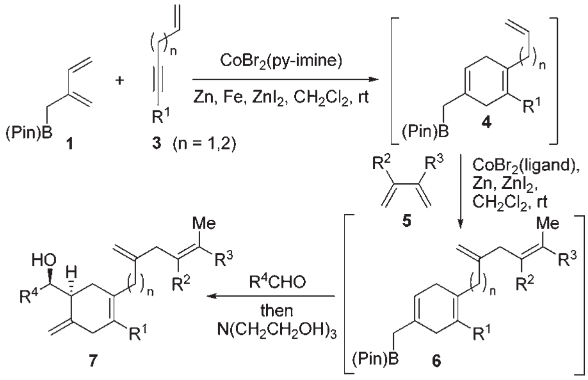
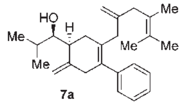
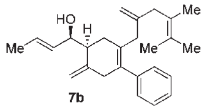
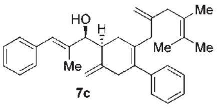
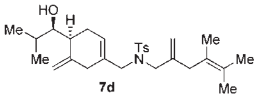
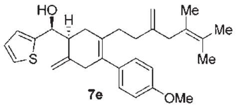
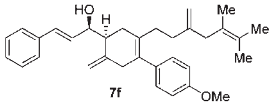
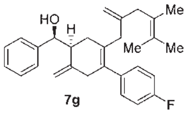
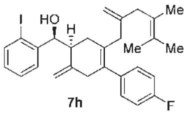
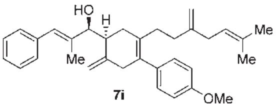
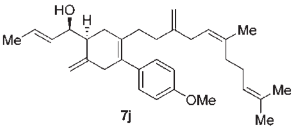
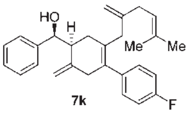
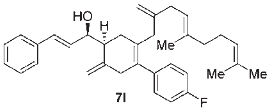
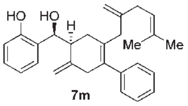
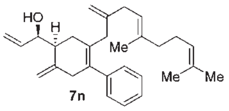


Table 1. Results for the Cobalt-Catalyzed Four-Component Reaction Sequence[a]

no.	main product 7[b]	ligand	yield
1	 **7a**	dppe	58%
2	 **7b**	dppe	74%
3	 **7c**	dppe	73%
4	 **7d**	dppe	88%
5	 **7e**	dppe	54%
6	 **7f**	dppe	61%
7	 **7g**	dppe	78%
8	 **7h**	dppe	65%
9	 **7i**	dppp	78%
10	 **7j**	dppp	67%
11	 **7k**	dppp	65%
12	 **7l**	dppp	73%
13	 **7m**	dppp	77%
14	 **7n**	dppp	75%

[a] $CoBr_2$(py-imine) (10 mol %), iron powder (20 mol %), zinc powder (20 mol %), zinc iodide (20 mol %), boroprene **1** (1.0 equiv) and enyne **3** (1.0 equiv), CH_2Cl_2, 16 h, rt, then $CoBr_2$(ligand) (10 mol %), zinc powder (20 mol %), zinc iodide (20 mol %) and 1,3-diene **5** (1.2 equiv), 16 h, rt, then 0 °C, aldehyde (1.0 equiv), 1 h, then triethanolamine (1.1 equiv), 1 h, rt. [b] Only one enantiomer is shown.

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(6) (a) Danz, M.; Hilt, G. *Adv. Synth. Catal.* **2011**, *353*, 303. (b) Auvinet, A.-L.; Harrity, J. P. A; Hilt, G. *J. Org. Chem.* **2010**, *75*, 3893. (c) Hilt, G.; Janikowski, J. *Org. Lett.* **2009**, *11*, 773. (d) Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* **2008**, *130*, 8952. (e) Hilt, G.; Danz, M. *Synthesis* **2008**, 2257. (f) Hilt, G.; Hengst, C. *J. Org. Chem.* **2007**, *72*, 7337. (g) Hilt, G.; Hengst, C. *Synlett* **2006**, 3247. (h) Hilt, G.; Janikowski, J.; Hess, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 5204. (i) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537.

(7) For the synthesis of nonconjugated enynes, see SI.

(8) py-imine = 2,4,6-trimethylphenyl-*N*-(pyridin-2-ylmethylene)aniline.

This intermediate was then treated with another 1,3-diene (**5**) applying the cobalt catalyst precursor $CoBr_2(dppe)$[9] which is able to catalyze a 1,4-hydrovinylation of the remaining terminal alkene subunit in **4** to generate intermediate **6**. Treatment of **6** with an aldehyde in an allylboration reaction and liberation of the boronic ester upon reaction with triethanolamine led to the formation of *anti*-products of type **7**.

The double-catalysis reaction sequence was performed in a one-pot protocol, and the products of type **7** were isolated after single column chromatography in good to excellent overall yields. Based on the higher C1/C4 regioselectivity in the 1,4-hydrovinylation of unsymmetrical 1,3-dienes, the cobalt catalyst precursor $CoBr_2(dppp)$[10] was applied in the sequences involving isoprene and myrcene (Table 1).

The regioselectivity of the cobalt-catalyzed Diels–Alder reaction is strongly dependent on the substituents of the alkyne subunit. The catalyst efficiently differentiates sterically demanding aryl groups from less bulky alkyl substituents. In the case where the aryl group is replaced by a hydrogen atom, the alkyl chain becomes the sterically more demanding substituent (entry 4). The excellent overall yields range between 54% and 88%, which appear to depend on neither the electronic nature of the aryl group nor the chain length of the enynes or the substituent of the aldehydes. Furthermore, this outcome indicates that the pyridyl-imine catalyst system used for the Diels–Alder reaction does not interfere with the bisphosphine catalyst used in the 1,4-hydrovinylation reaction. This sequence also demonstrates the power of the allylboration reaction, as complex intermediates could be transformed even when sterically more demanding aldehydes were used (entries 8 and 13).

After we succeded in the parent reaction sequence, we directed our attention toward a five-component triple-catalysis reaction sequence comprising a cobalt-catalyzed Diels–Alder reaction utilizing boroprene **1** as a central building block, a cobalt-catalyzed 1,4-hydrovinylation reaction, an allylboration, and another 1,4-hydrovinylation for the synthesis of increasingly complex products. The outline of this alternative five-component one-pot reaction sequence is shown in Scheme 3. Compared to the reaction sequence in Scheme 2, the parent sequence involves the introduction of an additional terminal double bond in the allylboration step. Utilizing 4-pentenal generates the intermediate **7′**, but in this sequence another cobalt-catalyzed 1,4-hydrovinylation was enabled with 1,3-diene **8** to obtain products of type **9**. As known from preliminary investigations, the cobalt catalysts suffer deactivation after a prolonged reaction time which made it beneficial to use additional cobalt catalyst in the last transformation. The results of this five-component one-pot reaction sequence with triple-cobalt catalysis are summarized in Table 2 for a selected number of combinations.

The five-component reaction sequence led to good results, and complex products could be isolated as main isomers after single column chromatography. Due to imperfect conversions of the intermediates, side reactions took place which afforded rather nonpolar and therefore separable byproducts, which explain the diminished yields. The main products were accompanied by other side products (regioisomers/diastereomers). The identification of these byproducts has been difficult, as the amounts were

Scheme 3. Triple-Cobalt-Catalyzed Five-Component Diels–Alder/1,4-Hydrovinylation/Allylboration/1,4-Hydrovinylation Sequence

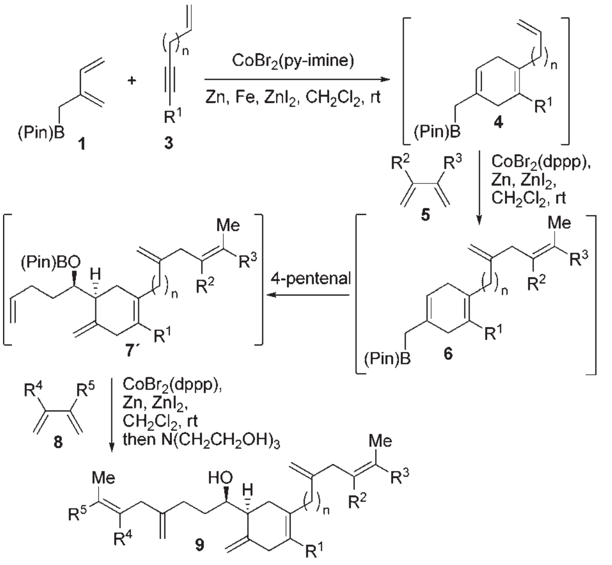
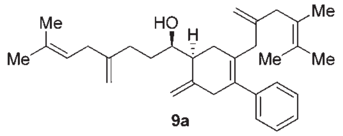
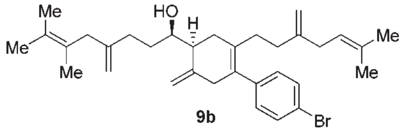
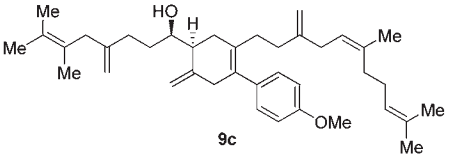


Table 2. Synthesis of Products **9** by the Triple-Cobalt-Catalyzed Five-Component Reaction Sequence[a]

no.	main product **9**[b]	yield
1	 **9a**	80%
2	 **9b**	53%
3	 **9c**	49%

[a] $CoBr_2$(py-imine) (10 mol %), iron powder (20 mol %), zinc powder (20 mol %), zinc iodide (20 mol %), boroprene **1** (1.0 equiv) and enyne **3** (1.0 equiv), CH_2Cl_2, 16 h, rt, then $CoBr_2$(dppp) (10 mol %), zinc powder (20 mol %), zinc iodide (20 mol %) and 1,3-diene **5** (1.0 equiv), 16 h, rt, then 0 °C, 4-pentenal (1.0 equiv), 1 h, then $CoBr_2$(dppp) (10 mol %), zinc powder (20 mol %), zinc iodide (20 mol %) and 1,3-diene **8** (1.2 equiv), 16 h, rt, then triethanolamine (1.1 equiv), 1 h, rt. [b] Only one enantiomer is shown.

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(9) dppe = 1,2-bis(diphenylphosphino)ethane.
(10) dppp = 1,3-bis(diphenylphosphino)propane.

Scheme 4. Triple-Cobalt-Catalyzed Five-Component Diels–Alder/1,4-Hydrovinylation/Allylboration/Alder–ene Sequence

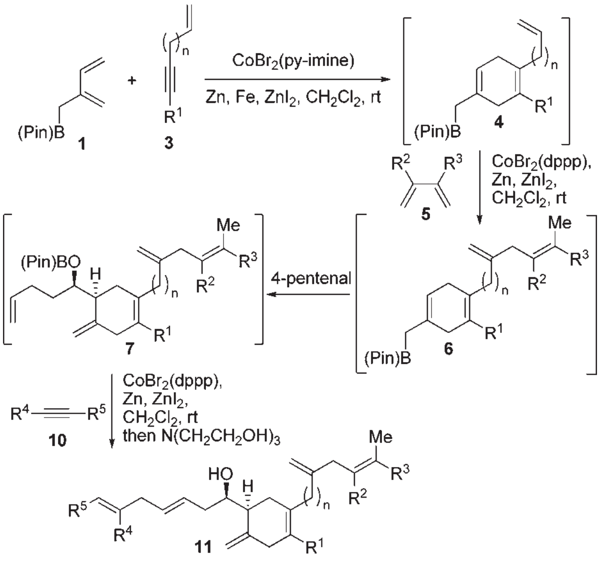
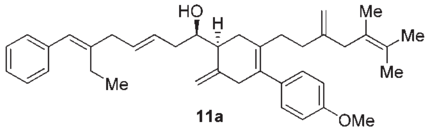
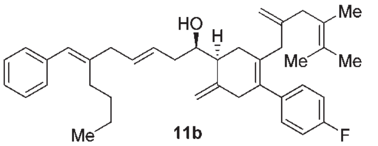
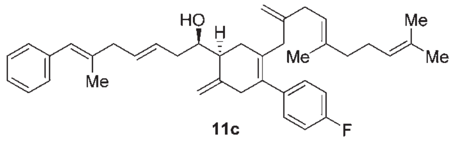


Table 3. Synthesis of Products **11** by the Triple-Cobalt-Catalyzed Five-Component Reaction Sequence[a]

no.	main product **11**[b]	yield
1	 **11a**	58%
2	 **11b**	53%
3	 **11c**	46%

[a] $CoBr_2$(py-imine) (10 mol %), iron powder (20 mol %), zinc powder (20 mol %), zinc iodide (20 mol %), boroprene **1** (1.0 equiv) and enyne **3** (1.0 equiv), CH_2Cl_2, 16 h, rt, then $CoBr_2$(dppp) (10 mol %), zinc powder (20 mol %), zinc iodide (20 mol %) and 1,3-diene **5** (1.0 equiv), 16 h, rt, then 0 °C, 4-pentenal (1.0 equiv), 1 h, then $CoBr_2$(dppp) (10 mol %), zinc powder (20 mol %), zinc iodide (20 mol %) and alkyne **10** (1.5 equiv), 16 h, rt, then triethanolamine (1.1 equiv), 1 h, rt. [b] Only one enantiomer is shown.

rather small and the polarities were very similar. Accordingly, we are not able to quantify the regio- or diastereoselectivities.

The five-component reaction sequence utilized the cobalt-catalyzed 1,4-hydrovinylation reaction twice, with one symmetrical as well as one unsymmetrical 1,3-diene. Besides the 1,3-dienes, the sequence has additional flexibility as demonstrated by the use of different functional groups on the arene substituent of the enyne. Noteworthy, arylhalides are well accepted in the cobalt-catalyzed Diels–Alder reaction allowing further modifications. Also, the chain length between alkyne and alkene in the enyne was altered, or as another possibility, the chain length within the enal component could have been modified as well.

To further evaluate the compatibility of cobalt catalysts with complex materials we decided to use the terminal double bond introduced by the allylboration step in **7** to facilitate a cobalt-catalyzed Alder–ene reaction[11] with an internal alkyne (**10**) (Scheme 4). Thereby, a triple catalysis utilizing three different cobalt-catalyzed reactions was realized and the products of type **11** were obtained in a one-pot sequence. The results of this investigation applying a selected number of combinations are summarized in Table 3.

The Alder–ene reaction worked best with unsymmetrical internal aryl-substituted alkynes **10**. Terminal alkynes as well as propiolates are primarily transformed in a cobalt-catalyzed cyclotrimerization,[12] and only small amounts of products of type **11** could be isolated. However, the tendency for the cyclotrimerization reaction decreases considerably for the internal alkynes used, so that good yields of **11a–c** could be obtained.

In conclusion we were able to demonstrate that double- and triple-cobalt catalyses utilizing different types of cobalt-catalyzed reactions with four or five components are possible to generate desired products in good yields. The cobalt-catalyzed reactions proved that they are capable of producing complex molecules from rather simple starting materials. The flexibility (e.g., additional substituents, chain length) and functional group tolerance of the cobalt-catalyzed transformations are essential to push such multicomponent reactions to the hilt.

Acknowledgment. We thank the Fonds der Chemischen Industrie for a fellowship (F.E.) and the Deutsche Forschungsgemeinschaft for financial support.

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.

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(12) (a) Hilt, G.; Hengst, C.; Hess, W. *Eur. J. Org. Chem.* **2008**, 2293. (b) Hilt, G.; Hess, W.; Vogler, T.; Hengst, C. *J. Organomet. Chem.* **2005**, *690*, 5170. (c) Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* **2005**, 1474.

The authors declare no competing financial interest.