# Asymmetric Cobalt-Catalyzed Diels−Alder Reactions of a Boron-Functionalized 1,3-Diene with Alkynes and Allylboration with Aldehydes
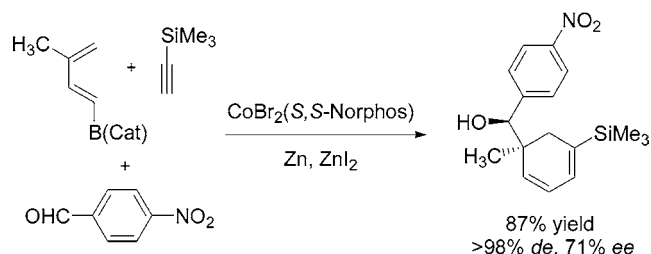
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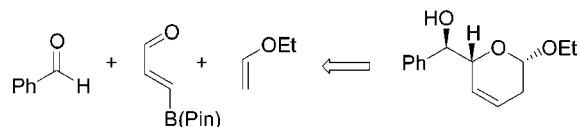
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**ABSTRACT**



**A cobalt(I)-catalyzed Diels−Alder reaction of a 1-boron-functionalized 1,3-diene is the key step in a one-pot reaction interconnecting three simple starting materials to obtain a multifunctionalized product. This product incorporates a stereogenic quaternary center next to a stereogenic secondary alcohol functionality generated with a very high degree of regio- and diastereoselectivity and good enantioselectivity in the presence of a chiral ligand such as (*S,S*)-Norphos.**

Atom-economic multicomponent reactions incorporating boron-functionalized building blocks for the fast and efficient diversity-oriented synthesis of a large number of structurally complex molecules are of great interest.[1] The chromium-catalyzed asymmetric [4 + 2]-cycloaddition/allylboration reaction sequence described by Hall, Carboni, and others is a good example for such a conversion (Figure 1), which can be used for the fast assembly of precursors in natural product synthesis.[2] Besides this hetero-Diels−Alder reaction with

inverse electron demand, no all-carbon cycloaddition of a boron-functionalized 1,3-diene with an alkyne has been described thus far.
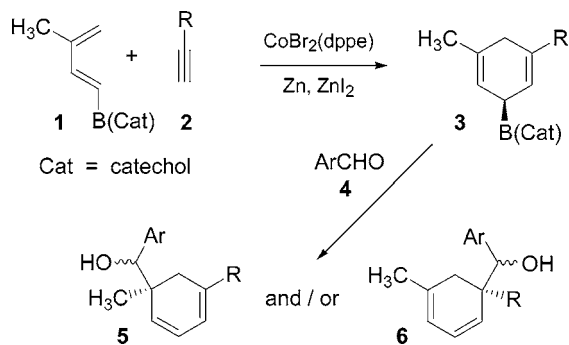


**Figure 1.** Three-component cycloaddition/allylation reaction.

In an attempt to broaden the scope of our cobalt-catalyzed Diels−Alder methodology,[3] we envisaged the use of the boron-functionalized 1,3-diene **1** for the generation of an

(1) (a) Touré, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D. G. *Chem. Eur. J.* **2003**, *9*, 466. (b) Ugi, I.; A. Dömling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647. (c) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366. For a review on boron-functionalized building blocks in cycloaddition reactions, see: (d) Hilt, G.; Bolze, P. *Synthesis* **2005**, 2091.

(2) For recent applications, see: (a) Gao, X.; Hall, D. G.; Deligny, M.; Favre, A.; Carreaux, F.; Carboni, B. *Chem. Eur. J.* **2006**, *12*, 3132. (b) Deligny, M.; Carreaux, F.; Carboni, B. *Synlett* **2005**, 1462. (c) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 1628.

**Scheme 1.** Cobalt-Catalyzed Diels−Alder/Allylboration Reaction

Cat = catechol

unique bis-allyl boron intermediate **3** (Scheme 1). The realization of this cobalt-catalyzed cycloaddition/allylboration reaction sequence with aldehydes **4** leads to four essential aspects that have to be considered:

(a) regioselectivity of the cobalt-catalyzed Diels−Alder reaction,

(b) regioselectivity of the allylboration reaction,

(c) diastereoselectivity of the allylboration,

(d) control of the absolute stereochemistry of the Diels−Alder reaction by a chiral ligand.

First, we wish to report the results for the investigation of the achiral version of the reaction sequence, and second, we will focus on an asymmetric catalysis to generate enantiomerically enriched products. Over the course of the investigation we realized that the best results were obtained when trimethylsilyl acetylene (**2**, R = SiMe$_3$) was used as dienophile in the cobalt-catalyzed Diels−Alder reaction with the boron-functionalized diene **1**. However, the diene **1** is one of the few examples of a 1-boron-functionalized 1,3-diene that can be easily accessed by hydroboration of the corresponding enyne.[1d,4] The purification of **1** is tedious, and the stability of the starting material is limited. Therefore, the reproducibility of the reactions seems to depend on the purity of **1**. Accordingly, **1** should be freshly prepared or distilled before use in the Diels−Alder reaction. The boron-functionalized diene **1** can be stored in a freezer at −20 °C for a limited period of time (several days) without decomposition. Nevertheless, one can obtain good results for the three-component one-pot reaction sequence for the synthesis of products of type **5/6**. The purification of the products **5/6** is a nontrivial task because one can observe a retro-allylboration reaction under acidic, basic, and thermal purification conditions with reformation of the aldehyde.[5]

This is most likely based on the fact that a quarternary all-carbon center is located directly next to a stereogenic secondary alcohol and that the retro-allylboration reaction combined with an oxidation of the cyclohexadiene to the aromatic derivative provides an additional driving force. Nevertheless, the regioselectivity of the cobalt-catalyzed Diels−Alder reaction provides exclusively the intermediates of type **3** with the trimethyl silyl substituent (R = SiMe$_3$) and the boron functionality in a *meta*-relationship. Therefore, the first of the four tasks in this investigation was fulfilled. The allylboration reaction of the bis-allyl boron intermediate **3** with various electron-poor aromatic aldehydes **4** gave the products of type **5** with a high degree of regioselectivity so that the new carbon−carbon bond was formed at the less hindered side bearing the methyl substituent. In these cases of a bulky substituent introduced by the Diels−Alder reaction via the alkyne, the regioselectivity of the allylboration reaction was exclusive, fulfilling the second task. In addition, the diastereoselectivity of the allylboration was also excellent so that the three-component products **5** were isolated as single regio- and diastereomers (Table 1), fulfilling also the third task. When electron-rich aromatic aldehydes such as 3,4,5-trimethoxy benzaldehyde and 4-methoxy benzaldehyde were used the corresponding three-component products were even more sensitive to acidic or basic purification conditions and the yields were dramatically lower (typically in the range of 5−15%). From these aldehydes no analytically pure samples could be obtained. The same behavior was observed when aliphatic aldehydes were used, and no formation of products was observed when ketones were applied in the allylboration reaction.[6] When other alkyne dienophiles such as phenyl acetylene or alkyl-substituted alkynes were used (Table 2), the regioselectivity of the cobalt-catalyzed Diels−Alder as well as the allylboration reaction gave exclusively the products of type **5**, whereas only in the case of 1-hexyne (entry 6) could a mixture of regioisomers **5l:6l** = 3:1 be detected. One has to keep in mind that the yields reported are based on materials that in all cases were isolated after repeated column chromatography in order to separate the desired product from the decomposition side products. The tendency for the decomposition of the desired products is enhanced if alkyl-substituted alkynes are used (entries 4 and 6). Nevertheless, one can obtain reasonable yields for propargyl phenyl sulfone (entries 5 and 7), which contains several functionalities allowing various opportunities for further functionalizations.

For the control of the absolute stereochemistry, chiral derivatives of the dppe ligand were chosen. In earlier studies we had already observed that the reactivity of the cobalt-catalyst system was considerably reduced when the chain length of the carbon backbone was altered such as in the ligands dppm, dppp, or dppb. Therefore, we decided to limit

(3) For leading references, see: (a) Hilt, G.; Lüers, S.; Smolko, K. I. *Org. Lett.* **2005**, *7*, 251. (b) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624. (c) Hilt, G.; Smolko, K. I. *Angew. Chem.* **2003**, *115*, 2901; *Angew. Chem., Int. Ed.* **2003**, *42*, 2795.

(4) For selected references, see: (a) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631. (b) Matsumoto, Y.; Naito, M.; Hayashi, T. *Organometallics* **1992**, *11*, 2732. (c) Garnier, L.; Plunian, B.; Mortier, J.; Vaultier, M. *Tetrahedron Lett.* **1996**, *37*, 6699. (d) Renard, P.-Y.; Six, Y.; Lallemand, J.-Y. *Tetrahedron Lett.* **1997**, *38*, 6589.

(5) Selected references: (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S.-i. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Shafi, S. M.; Chou, J.; Kataoka, K.; Nokami, J. *Org. Lett.* **2005**, *7*, 2957.

(6) For recent references, see: Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701. (b) Canales, E.; Prasad, K. G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572. (c) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910.

**Table 1.** Cobalt-Catalyzed Three-Component Synthesis Using Trimethylsilyl Acetylene and Boron-Functionalized Diene **1** as Starting Materials

| entry | aldehyde (4) | product (5) | yield |
|---|---|---|---|
| 1 | OHC–C6H4–Cl, **4a** | **5a** | 55% |
| 2 | OHC–C6H4–NO2, **4b** | **5b** | 84% |
| 3 | OHC–C6H4–NO2 (meta), **4c** | **5c** | 61% |
| 4 | OHC–C6H4–CF3, **4d** | **5d** | 63% |
| 5 | OHC–C6H5, **4e** | **5e** | 60% |
| 6 | OHC–(2-pyridyl), **4f** | **5f** | 78% |

**Table 2.** Cobalt-Catalyzed Three-Component Synthesis with Various Alkynes

| entry | alkyne (2) and aldehyde (4) | product (5) | yield |
|---|---|---|---|
| 1 | Ph-alkyne; **4d** | **5g** | 30% |
| 2 | Ph-alkyne; **4b** | **5h** | 36% |
| 3 | meta-CO2Me-phenyl alkyne; **4d** | **5i** | 36% |
| 4 | tBu-alkyne; **4b** | **5j** | 22% |
| 5 | SO2Ph-alkyne; **4f** | **5k** | 50% |
| 6 | nBu-alkyne; **4f** | **5l** | 43% (5l:6l = 3:1) |
| 7 | SO2Ph-alkyne; **4d** | **5m** | 50% |

the survey of chiral ligands to a rather small group of commercially available dppe analogues interconversion with the diene **1** for the synthesis of the corresponding product **6** (Scheme 2). Nevertheless, also a chiral monodentate phosphite ligand and the ubiquitous BINAP ligand were applied. As a test reaction we choose the conversion of trimethylsilyl acetylene and 4-nitro benzaldehyde as reactants in the three-component reaction.

As was illustrated by Brunner, Buono, and Lautens in similar cycloadditions including [2 + 2 + 2]-homo-Diels–Alder reactions of norbornadiene and acetylenes, the best results were obtained when the chiral Norphos ligand was used.[7]

In the asymmetric catalyzed reaction **5b** could be isolated in 87% yield and an enantioselectivity of 71% ee could be obtained at ambient temperatures.

If lower or higher temperatures were chosen either the yield or the enantioselectivities decreased, so that at 20 °C an optimimum was determined. Although the structural differences between the Norphos ligand and the Chiraphos ligand are only minor, for no obvious reason the cycloaddition with (*R,R*)-Chiraphos as chiral ligand gave a very slow conversion and a very low yield of essentially racemic product. On the other side, the ligands CatASium D(*R*)[8] and

(7) Recent contributions: (a) Achard, M.; Tenaglia, A.; Buono, G. *Org. Lett.* **2005**, *7*, 2353. (b) Pardigon, O.; Tenaglia, A.; Buono, *J. Mol. Catal. A* **2003**, *196*, 157. (c) Brunner, H.; Reimer, A. *Bull. Chem. Soc. Fr.* **1997**, *134*, 307. (d) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863.
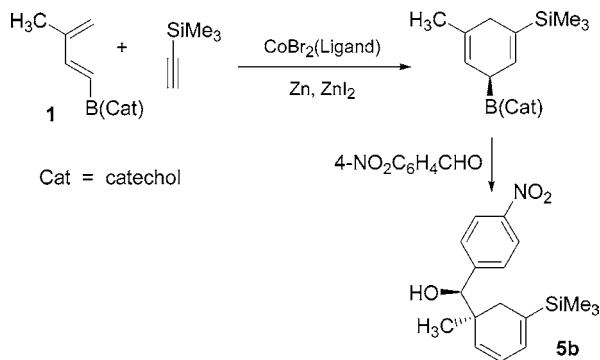
**Scheme 2.** Asymmetric Cobalt-Catalyzed Diels−Alder/Allylboration Reaction



**Table 3.** Chiral Ligands Used in the Cobalt-Catalyzed Diels−Alder/Allylboration Reaction[a]

| entry | ligand (temp) | yield of 5b (ee) |
|-------|---------------|------------------|
| 1 | (S,S)-Norphos (0 °C) | 21% (65%) |
| 2 | **(S,S)-Norphos (20 °C)** | **87% (71%)** |
| 3 | (S,S)-Norphos (40 °C) | 57% (78%) |
| 4 | (S,S)-Norphos (80 °C) | 48% (76%) |
| 5 | (R,R)-Chiraphos (20 °C) | 2% (4%) |
| 6 | CatASium D(R)[8] (20 °C) | 58% (45%)[b] |
| 7 | (R)-Monophos (20 °C) | 6% (70%) |
| 8 | (R)-Prophos (20 °C) | 39% (48%)[b] |
| 9 | (R)-BINAP (20 °C) | 2% (0%) |

[a] The product **5b** was isolated as a single regio- and diastereomer. [b] The opposite enantiomer was obtained as major product.

(R)-Prophos, which differ from (R,R)-Chiraphos not that much, gave reasonable yields of the desired product **5b** while the enantioselectivities were not as high as with the (S,S)-Norphos ligand. All attempts to verify the absolute stereochemistry of the major enantiomer derived from enantiomerically enriched product **5b** by means of an X-ray analysis and conversion into a crystalline product failed. Instead the absolute stereochemistry of the product **5m** derived from a [CoBr$_2$(S,S)-Norphos]-catalyzed Diels−Alder/allylboration reaction sequence of phenyl propargyl sulfone with the boron-functionalized diene **1** and 4-trifluoromethyl benzaldehyde **4d** could be verified by X-ray analysis.

The product **5m** was generated in 49% yield and 73% ee. The identity of the stereoisomer of the crystal was determined as the major enantiomer by means of chiral HPLC analysis. For analogy reasons we assigned the absolute stereochemistry of the major stereoisomer **5b** (Scheme 2, Table 3, entry 2).[9]

The asymmetric cobalt-catalyzed Diels−Alder reaction of a 1-boron-functionalized 1,3-butadiene derivative led to an enantiomerically enriched product in a very high regiochemical ratio concerning both the Diels−Alder as well as the allylboration reaction. In addition the diastereoselectivity of the allylboration reaction is also very high so that from three rather simple starting materials out of the various possibilities

only one regio- and stereoisomer is formed predominantly. The polyfunctionalized products could be obtained in acceptable to good yields based on their rather high tendency for a retro-allylboration reaction.



**Figure 2.** Crystal struture of **5m**.

**Supporting Information Available:** Experimental procedures and full characterization of the compounds **5a−5m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (+)-(3R,4R)-Bis(diphenylphosphino)-1-benzyl-pyrrolidine; CAS number [99135-95-2]; commercially available from STREM.
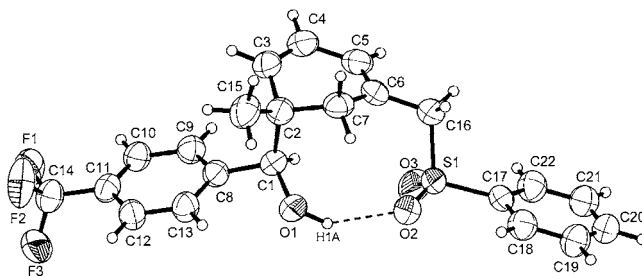
(9) Sulfur functionalities seem not to alter the diastereoselectivity of the allylboration reaction; see: Touré, B. B.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 8429.