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A Two-Step Reaction Sequence for the Syntheses of Tetrahydronaphthalenes

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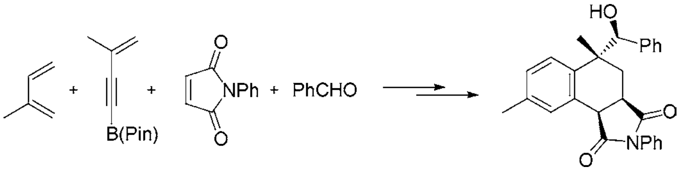
ABSTRACT

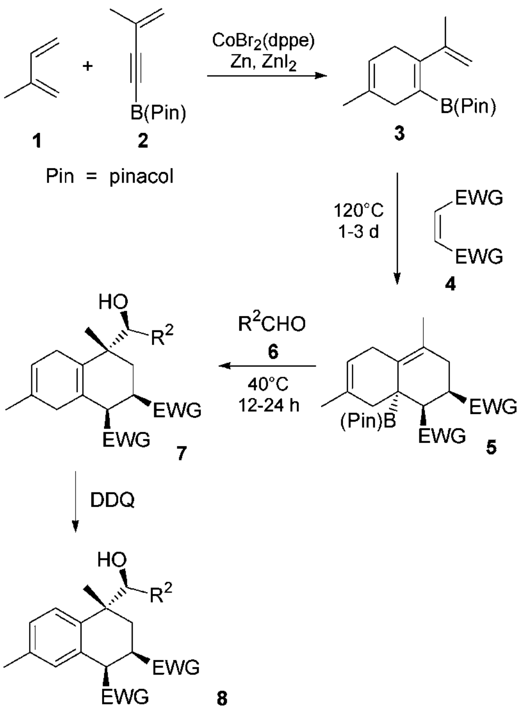


A cobalt(I)-catalyzed Diels–Alder reaction of a boron-functionalized enyne is the key step in a two-step reaction cascade interconnecting four simple starting materials to obtain polycyclic multifunctionalized products in good yields and with a very high degree of diastereoselectivity.

Atom-economic multicomponent reactions for the fast and efficient diversity-oriented synthesis of a large number of structurally complex molecules have always been of general interest. Recent progress in this field illustrates the elegance and the synthetic usefulness of such a synthetic strategy.[1]

On the basis of our cobalt(I)-catalyzed Diels−Alder reaction employing alkynyl boron derivatives and 1,3-dienes for the generation of dihydroaromatic building blocks,[2] we investigated a reaction sequence where four components are interconnected with each other. The acyclic 1,3-diene (isoprene **1**), which was mostly used in this study, could be reacted with the boron-functionalized enyne derivative (**2**) under mild reaction conditions using our cobalt(I) catalyst system to generate the boron-functionalized 1,3-diene (**3**) (Scheme 1). Then this key intermediate **3** was converted in a thermal Diels−Alder reaction with an activated dienophile (**4**) to a highly substituted boron-functionalized 1,4-diene (**5**) containing an allyl boron subunit. Consequently, the allylboration of an aldehyde (**6**) led to dihydroaromatic derivatives (**7**)[3] that could be oxidized with DDQ to the corresponding multiply substituted tetrahydronaphthalene derivatives (**8**). By this reaction sequence four mostly commercially available starting materials can be interconnected to a complex product with diverse functional groups generating five new carbon−carbon bonds with up to four new stereogenic centers (one of them quaternary).

Scheme 1



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(1) (a) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101. (b) Ugi, I.; A. Dömling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647. (c) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366.

(2) Hilt, G.; Smolko, K. I. *Angew. Chem.* **2003**, *115*, 2901; *Angew. Chem., Int. Ed.* **2003**, *42*, 2795.

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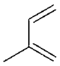
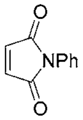
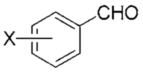
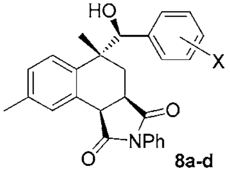
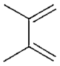
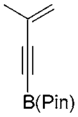
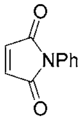
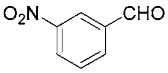
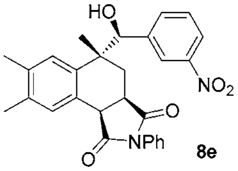
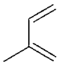
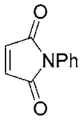
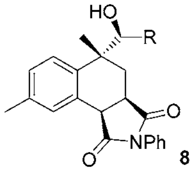
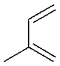
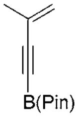
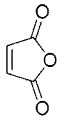
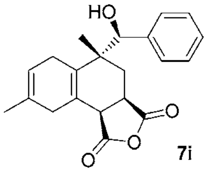
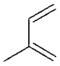
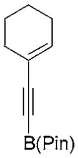
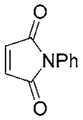
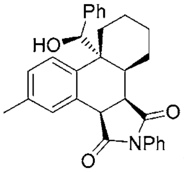
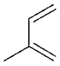
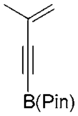
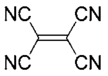
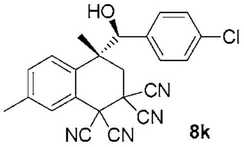
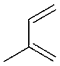
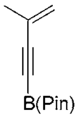
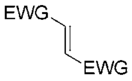
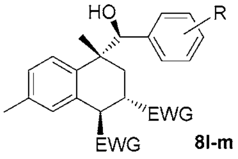
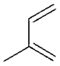
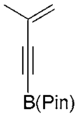
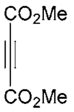
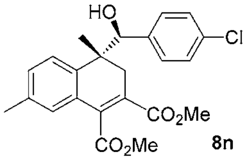
Table 1. Results for the Two-Step Synthesis of Tetrahydronaphthalenes

Entry	1,3-Diene	Boron Derivative	Dienophile	Aldehyde	Product (**8**)	Yield
1 2 3 4					 **8a-d**	X = 2-NO$_2$ 67% 3-NO$_2$ 77% 4-NO$_2$ 48% 4-Cl 56%
5					 **8e**	83%
6 7 8				RCHO	 **8f-h**	R = C$_2$H$_5$ 61% C$_2$H$_3$ 71% H 69%
9				PhCHO	 **7i**	59%[a]
10				PhCHO	 **8j**	<5%
11				4-ClPhCHO	 **8k**	<5%
12 13				3-NO$_2$PhCHO 4-ClPhCHO	 **8l-m**	EWG = CN 52% EWG = CO$_2$Et[b] 30%
14				4-ClPhCHO	 **8n**	<5%

[a] Isolated as dihydroaromatic compound of type **7i**. The DDQ oxidation procedure led to low yields of the aromatic compound and to some decomposition products. [b] Isolated as a mixture of stereoisomers of products **8m**.

Within this study we focused our attention not on the generation of the boron-functionalized dihydroaromatic building block **3**[2] but on the unusual thermal Diels–Alder reaction of the highly substituted 1,3-diene subunit in **3** with activated dienophiles and the following allylboration of the aldehyde (**6**) with the pentasubstituted allyl boron subunit in **5**.[4]

Especially interesting is the possibility to perform the reactions sequentially without tedious purifications of the intermediates. After filtration over a small amount of silica gel and remvoval of the solvent in vacuo the crude products were directly used in the next synthetic steps. The final products of type **8** were isolated by recrystallization to give acceptable to good yields. The results of these four component conversions are summarized in Table 1.

As expected the boron functionalized dihydroaromatic compounds (**3**) could only be reacted in thermal Diels–Alder reactions with quite reactive and sterically less hindered dienophiles (**4**) to give the compounds of type **5**. These reactions gave rise to allylic boron reagents (**5**) in good yields. Acrylic esters proved to be not very reactive under the chosen reaction conditions. However, stronger activated and sterically also less hindered dienophiles, such as *N*-phenylmaleimide, (*E*)-1,2-dicyanoethylene, or maleic anhydride, easily react with **3**. The desired products of type **8** from the latter dienophiles could be isolated in acceptable to good yields after performing the whole reaction sequence. Thereby the naphthalene backbone bearing functional groups prone to further functionalization could be generated selectively. Very electron poor and sterically not hindered dienophiles, such as tetracyanoethylene (TCNE) or acetylenic dicarboxylic ester (entries 11 and 14), should favor a fast thermal Diels−Alder reaction. Surprisingly, only traces of the desired intermediates of type **5** could be found in these cases. These dienophiles preferentially react in a redox reaction under electron transfer with the electron rich dihydroaromatic compound **3** to dehydrogenated aromatic products.[5]

On the other hand, a sterically more hindered boron-functionalized 1,3-diene (**3**) (entry 10) leads to a drastic decrease in reactivity. The corresponding cycloadduct of type **5** could only be detected in traces.

The reactions of the pentasubstituted allyl boron subunit in the cycloadducts of type **5** generated from *N*-phenylmaleimide, (*E*)-1,2-dicyanoethylene, fumaric ester, and maleic anhydride were much more successful. These could be reacted with a wide range of aliphatic, olefinic, and aromatic aldehydes (**6**).[6] The following DDQ oxidation under standard conditions generated the aromatic four-component reaction products (**8**). The pure products were obtained by column chromatography over a small plug of silica and subsequent recrystallization. The NMR data of the crude products showed a high level of diastereoselectivity during the Diels−Alder conversions of **3** with **4** and the allylboration reaction with the aldehyde **6**. As could be ascertained by X-ray analysis of the product of entry 4, the thermal Diels−Alder reaction to the intermediate of type **5** took place with a high *endo*-selectivity (>95:5). The boronic ester functionality and the imido group were in *trans* relation to each other.[7] The following well-described allylboration takes also place in a highly diastereoselective fashion. Therefore the products **7** and **8** are generated in a very high degree of diastereoselective purity (>95:5).

Within this study we were able to show that the dihydroaromatic boronic esters can be used as a synthetic platform not only in Suzuki coupling reactions[2] but also in Diels−Alder reaction sequences. The highly substituted and functionalized products of the reaction sequence are generated in acceptable to very good yields taking into account that four synthetic steps were involved. Five new C−C bonds from four simple components are formed in this process. Tedious workup of all of the intermediates is not necessary, and the final products are obtained by recrystallization.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Dr. Klaus Harms for the X-ray analysis and Frank Schmidt for isolating the single crystal (product of entry 4) and repeating partially the reaction sequence.

Supporting Information Available: Experimental procedures and full characterization of the compounds **8a**−**h**, **7i**, and **8l**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0477879

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(3) (a) Toure, B. B.; Hall, D. G. *Angew. Chem.* **2004**, *116*, 2035; *Angew. Chem., Int. Ed.* **2004**, *43*, 2001. (b) Deligny, M.; Carreaux, F.; Toupet, L.; Carboni, B. *Adv. Synth. Catal.* **2003**, *345*, 1215. (c) Gao, X.; Hall, D. G. *Tetrahedron Lett.* **2003**, *44*, 2231. (d) Toure, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D. G. *Chem. Eur. J.* **2003**, *9*, 466. (e) Deligny, M.; Carreaux, F.; Carboni, B.; Toupet, L.; Dujardin, G. *Chem. Commun.* **2003**, 276. (f) Lallemand, J.-Y.; Six, Y.; Ricard, L. *Eur. J. Org. Chem.* **2002**, 503. (g) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R. W.; Denne, I. *Tetrahedron Lett.* **1987**, *28*, 4169.

(4) For the Diels−Alder reactions with highly substituted 1,3-dienes see: (a) Schmittel, M.; Von Seggern, H. *J. Am. Chem. Soc.* **1993**, *115*, 2165. (b) Wehbe, M.; Lepage, L.; Lepage, Y.; Platzer, N. *Bull. Soc. Chim. Fr.* **1987**, 309. (c) Majo, V. J.; Suzuki, S.; Toyota, M.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3375. (d) Phansavath, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1998**, *39*, 1561. (e) Tjepkema, M. W.; Wilson, P. D.; Audrain, H.; Fallis, A. G. *Can. J. Chem.* **1997**, *75*, 1215. (f) Dai, W.-M.; Lau, C. W.; Chung, S. H.; Wu, Y. D. *J. Org. Chem.* **1995**, *60*, 8128. (g) Graziano, M.; Iesce, M. R.; Cermola, F. *Synthesis* **1994**, 149. (h) Nicolaou, K. C.; Hwang, C. K.; Sorensen, E. J.; Clairborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1117. (i) Bonnert, R. V.; Jenkins, P. R. *Tetrahedron Lett.* **1987**, *28*, 697. (j) Erman, W. F.; Stone, L. C. *J. Am. Chem. Soc.* **1971**, *93*, 2821.

(5) As main product of the reactions, the corresponding aromatic boronic ester (2-(2-isopropenyl-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolan was isolated.

(6) Generally the allylboration of the aldehydes was performed at 40 °C. The conversion with paraformaldehyde was performed successfully at 100 °C in a thick-walled glass tube; compare to: (a) Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem.* **2003**, *115*, 3521; *Angew. Chem., Int. Ed.* **2003**, *42*, 3399. (b) Hoffmann, R. W.; Menzel, K.; Harms, K. *Eur. J. Org. Chem.* **2002**, 2603.

(7) The X-ray data were deposited in the CCDC data bank (CCDC 246015).