Organic LETTERS

Letter

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Stereoselective Synthesis of 1,4-Diols by a Tandem Allylboration–Allenylboration Sequence

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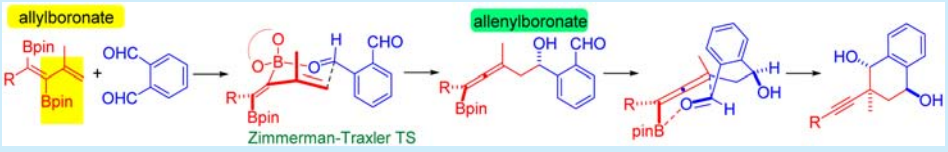
Supporting Information



ABSTRACT: The reaction of mono- and dialdehydes with bis-borodienes (incorporating an allylboronate unit) has been studied. It was found that the initial allylboration reaction results in an allenylboronate, which has two stereogenic units: one of them has axial chirality and the other one is a stereogenic carbon center. This reaction proceeds with high diastereoselectivity. The allenylboronate formed in the allylboration reacts with an additional aldehyde with fair to high stereoselectivity depending on the aldehyde substrate. Aromatic dialdehydes react with bis-boro-butadienes creating three new stereocenters with usually high diastereoselectivity.

1,4-Naphthalene-diol is an important motif in natural products. This motif occurs as an intermediate in the biosynthesis of Kinamycine derivatives,[1] and the related compounds have cytotoxic activity and antibacterial effects (Figure 1).[2]

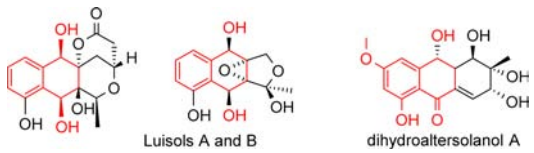


Figure 1. Examples for natural products with 1,4-naphthalene-diol motifs.

Barluenga and co-workers[3] have shown that these ring systems can be prepared by cycloaddition, while Morken and co-workers[4] reported in situ formation of bis-boronates followed by consecutive allylboration of dialdehydes. Roush and co-workers[5] published pioneering work on the synthesis of 1,5-diols by allylboration of two different aldehydes.

Synthetic methods based on application of unsaturated bis-boronates attract much attention in the synthetic community.[4,6] We hypothetized that bis-borodienes, such as **1**, can be excellent synthons for stereoselective synthesis of 1,4-diols (Figure 2). Recently, we have reported an efficient synthesis of these compounds based on catalytic diborylation of propargylic epoxides.[7] The reaction of **1** with (di)aldehydes (**2**) may be initiated by allylboration of the carbonyl group.[8] This allylation method has been widely employed for the diastereoselective synthesis of homoallylic alcohols.[9,10] Allylboration of carbonyl compounds with **1** is interesting both synthetically and mechanistically. The reaction provides allenylboronate **3** with two types of stereogenic units. One of the stereogenic units has an axial chirality (allenylboronate), and the other one has a stereogenic carbon (alcohol). Thus, the reaction of **1** and **2** may result in two diastereomeric forms of **3**. As far as we know, allylboration reactions creating both axial chirality and a stereogenic carbon center have never been studied. Therefore, it would be interesting to study both the reactivity and the stereochemical outcome in this process, as the usual allylboration reactions (creating two adjacent stereogenic carbons) proceed with very high diastereoselectivity.

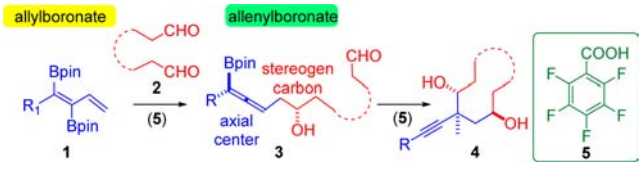


Figure 2. Reaction of (di)aldehydes with bis-boro-butadienes.

Allenylboration of carbonyl groups has been applied[11] for the highly selective synthesis of homopropargyl alcohols.[12] Since intermediate **3** incorporates an allenylboronate unit, it can react with another carbonyl group, creating a third stereocenter (e.g., **4**). The stereochemical outcome of this process is also highly interesting, as the reaction of carbonyl compounds with allenylboronates already having two stereocenters (i.e., **3**) is still a largely unexplored area.

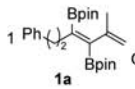
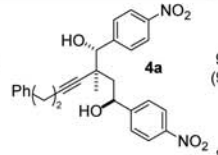
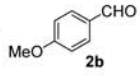
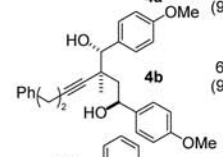
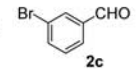
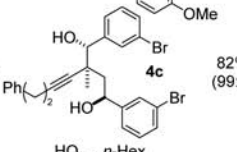
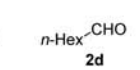
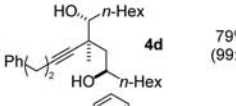
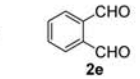
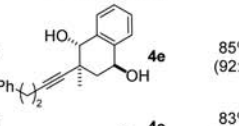
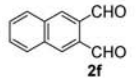
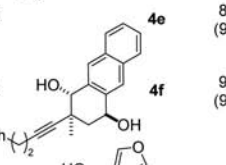
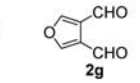
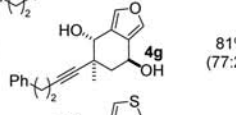
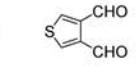
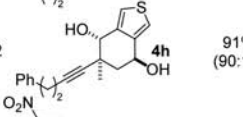
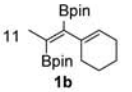
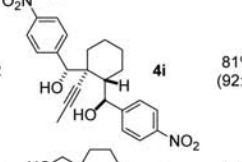
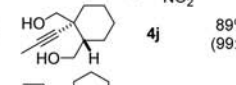
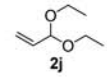
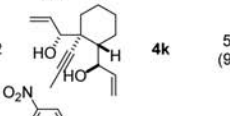
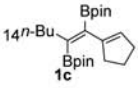
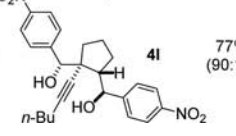
We have now found that bis-borodienes **1a–c** indeed react with aldehydes such as **2a–j** to give 1,4-diols **4a–l** (Table 1).

The reactions can be performed in toluene without any additives at 80 °C (Method A). However, the reaction temperature can be decreased to room temperature when acid **5** is added as an additive (Method B).

Received: April 11, 2015
Published: April 21, 2015

DOI: 10.1021/acs.orglett.5b01048
Org. Lett. 2015, 17, 2290–2293

Table 1. Reaction of bis-Boro-butadienes with Aldehydes

entry	substrates	method[a]	time (h)	product	yield[b]	dr[c]
1	 **1a**	A	18	 **4a**	94% (99:1)	75:25
2	**1a**	B	32	**4a**	86% (99:1)	78:22
3	**1a**  **2b**	A	18	 **4b**	65% (99:1)	81:19
4	**1a**  **2c**	A	24	 **4c**	82% (99:1)	74:26
5	**1a**  **2d**	A	24	 **4d**	79% (99:1)	70:30
6	**1a**  **2e**	A	24	 **4e**	85% (92:8)	80:20
7	**1a** **2e**	B	28	**4e**	83% (96:4)	95:5
8	**1a**  **2f**	B	24	 **4f**	95% (96:4)	95:5
9	**1a**  **2g**	B	72	 **4g**	81% (77:23)	75:25
10	**1a**  **2h**	B	72	 **4h**	91% (90:10)	84:16
11	 **1b**	A	22	 **4i**	81% (92:8)	70:30
12	**1b**  **2i**	A	22	 **4j**	89% (99:1)	99:1
13	**1b**  **2j**	A	22	 **4k**	55% (99:1)	75:25
14	 **1c**	A	22	 **4l**	77% (90:10)	80:20

[a]Method A: a mixture of **1** (0.30 mmol), **2a–d**, **2i–j** (0.62 mmol) or **2e** (0.35 mmol), in toluene (1.5 mL) was stirred at 80 °C. Method B: **1** (0.30 mmol), **2a** (0.62 mmol) or **2e–h** (0.35 mmol), **5** (0.06 mmol) in toluene (1.5 mL) stirred at 25 °C. [b]Isolated yields for both diastereomers together. The isomer purity of purified sample is given in parentheses. [c]dr of **4** in the crude product determined by ^{1}H NMR.

Decreasing the reaction temperature is usually beneficial for increasing the stereoselectivity of an allylboration reaction. Application of Brønsted acids is supposed to activate both allylboration[13] and allenylboration reactions.[12b−d] We have found that strong acids, such as *p*-toluenesulfonic acid, leads to decomposition of **1**, and therefore it cannot be used as a catalyst. However, pentafluorobenzoic acid **5** did not induce decomposition of **1**, but was still a sufficiently strong Brønsted acid to activate the Bpin group.

As mentioned above (Figure 2) the reaction of **1** with 2 equiv of aldehydes (**2**) results in three new strereocenters in product **4**; thus, a total of four diastereomers are expected to form in the reaction. Despite this, only two diastereomeric products were generated with fair to good stereoselectivity depending on the employed aldehyde **2**. Bis-borodiene **1a** reacted readily with aromatic aldehydes (2 equiv) **2a–d**, both with electron-withdrawing (**2a**, **2c**) (entries 1−2 and 4) and electron-donating (entry 3) substituents (**2b**). The ratio of the two diastereomers (out of the possible four) was varied between 3 and 4:1, as determined from the crude reaction mixture by ^{1}H NMR spectroscopy. The diastereomers were easily separated by silica gel chromatography; thus, practically pure diastereomers could be isolated. The diastereomeric purity of the main diastereomer of the final products is given in parentheses under the yields in Table 1. Using room temperature in the presence of **5** (Method B) or 80 °C (Method A) had a relatively small effect on the observed stereoselectivities of **4a** in the crude products (cf., entries 1 and 2). Aliphatic aldehyde **2d** also reacted readily to give product **4d**.

Bis-borodiene **1a** also reacted with various dialdehydes **2e–h** (entries 6−10) including even heterocyclic ones (**2g–h**), affording 1,4-naphthalene-diol derivatives **4e–h**. The reaction with **2e**, **2g**, and **2h** proceeds with a selectivity similar to that with monoaldehydes **2a–e**. Interestingly, when the reaction temperature was decreased to room temperature and **5** was employed as catalyst (Method B), the selectivity is increased for the reaction of **1a** and **2e** (cf., entries 6 and 7). Naphthyl dialdehyde **2f** was reacted with high selectivity (dr 95:5) with **1a**, affording **4f** with excellent yield and diastereomeric purity (entry 8). Heterocyclic aldehydes **2g–h** (entries 9−10) have a low thermostability, and therefore the reactions were conducted at room temperature using Method B.

Cyclic bis-borodienes **1b–c** also reacted readily with nitro benzaldehyde **2a** to give **4i** and **4l**, respectively (entries 11 and 14). In this case four new stereocenters were created in the reaction, and therefore statistically eight diastereiosmers were anticipated. Yet, we obtained only two diastereosiomers in about a 3:1 ratio. Again purification by silica gel chromatography afforded the major diastereomer of **4i** and **4l** with high purity (dr about 9:1). Dialdehyde **2e** did not react with cyclic bis-borodienes **1b–c** probably because of steric reasons (see below). However, aldehyde precursors **2i** and **2j** reacted readily with **1b**. Residual water liberated formaldehyde from **2i**, which initiated a hydroxymethylation reaction of **1b**, affording **4j** (entry 12). This process may form only two diastereomers, and it proceeds with excellent selectivity providing a single diastereomer **4j**. Acrylic aldehyde is very hygroscopic and toxic, and thus it is difficult to handle. Acetal **2j** (reacting with residual water) readily gave acrylic aldehyde, which reacts with **1b** to give two diastereomers of the eight possible in a ratio of 3:1. After silica gel chromatography the major diastereomer of **4k** could be obtained with high purity (entry 13). Compound **4k** is a useful, stereodefined, cyclohexene[14] precursor for a Grubbs metathesis reaction.[15]

We have briefly studied the mechanism of the reaction of bis-boro-butadienes **1** with aldehydes. The allenylboronate intermediate **3** could be observed in several cases, when the reaction was stopped before the reaction times indicated in

DOI: 10.1021/acs.orglett.5b01048
Org. Lett. 2015, 17, 2290−2293

Table 1 or less than 2 equiv of monoaldehyde (such as **2a**) was used. In one case, for the reaction of **1c** with only 1 equiv of **2a** (see also entry 11) we succeeded in isolating **3l** (Figure 3).

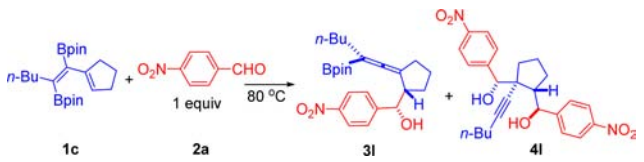


Figure 3. Isolation of allenyl boronate intermediate **3l**.

Allenylboronate **3l** could be purified by silica gel chromatography, but it proved to be rather unstable, as it decomposed in a couple of hours after the purification. Inspection of the crude reaction mixture and the purified sample indicated that **3l** was formed as a single diastereomer, suggesting that the allylboration of **2a** with **1c** is a highly streoselective process. Despite several attempts we were unable to stop the reaction of **1a** and **2a** at the formation of **3l**. Intermediate **3l** is probably more reactive than **1c**, and therefore a mixture of **3l** and **4l** was formed, even if **1c** was reacted with only 1 equiv of **2a**.

The major diastereomers of the reactions (**4a**–**l**) were oils which resisted crystallization. Likewise, our attempts to obtain crystalline derivatives of the major diastereomers of **4a**–**l** also remained fruitless.

However, we were able to determine the relative configuration of the stereocenters in the major diastereomer of **4e** (entries 6–7) using the dNOE technique.

The suggested mechanism of the stereoinduction for monoaldehydes, such as **2a**, and for dialdehydes, such as **2e**, are given in Figures 4–5. The first step is allylboration of **2a**

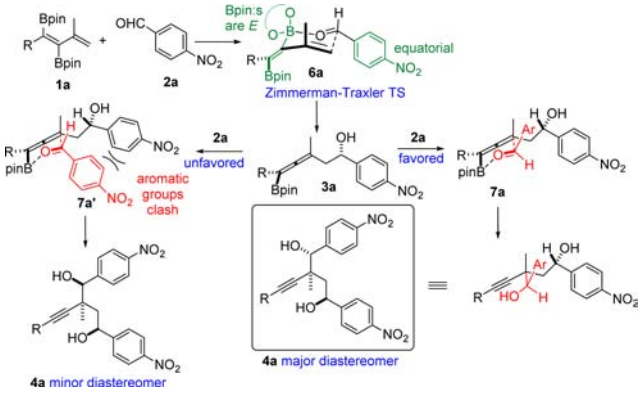


Figure 4. Mechanism and stereochemistry for the reaction of monoaldehydes (exemplified with **2a**) affording acyclic product (exemplified by **4a**). R = $-CH_2CH_2Ph$. Ar = 4-nitrophenyl.

with **1a** (Figure 4), which is supposed to proceed via a Zimmerman–Traxler TS **6a** to give **3a**. In **6a** the aryl group is supposed to be in the equatorial position and the two Bpin groups possess an *E* geometry as in **1a**. The **1a** → **3a** sequence probably proceeds with high diastereoselectivity, which is also confirmed by the finding that only a single stereoisomer was observed by ^{1}H NMR analysis of the crude reaction mixture (see above).

The next step is allenylboration of an additional aldehyde **2a**. In TS **7a** the nitro-phenyl (Ar) group avoids the steric interaction with the benzyl nitro-phenyl group (introduced in the previous reaction step). However, in **6a** there is steric

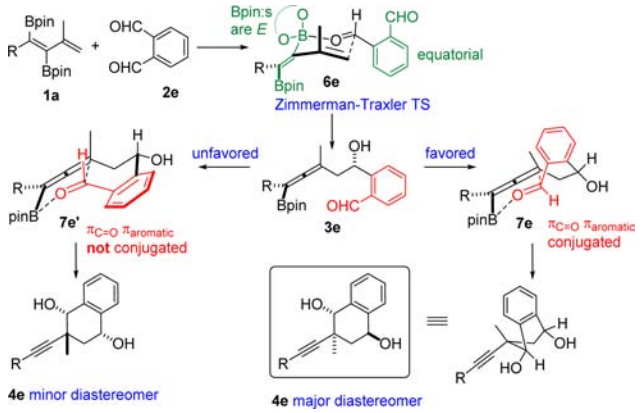


Figure 5. Plausible mechanism and streochemistry for the reaction of dialdehydes (exemplified with **2e**). R = $-CH_2CH_2Ph$.

repulsion between the nitro-phenyl (Ar) and the axial methyl groups.[12a] In **7a**′ the two large groups (nitro-phenyl and benzyl nitrophenyl) clash but the nitro-phenyl–methyl group repulsion is relieved. Probably, the clash of the two large groups is highly unfavored and, therefore, the major diasteromer of **4a** occurs via **7a**.

The initial steps and stereoselectivity is probably the same with dialdehyde **2e** (Figure 5) as with monoaldehyde **2a** (Figure 4). Thus, the allylboration results in **3e**, which has the same relative stereochemistry as **3a**. The next step is allenylboration of the second aldehyde group of **2e**. This may proceed via TS **7e**, in which the aldehyde carbonyl and the aromatic π-system are conjugated in plane. This TS leads to the favored major diastereomer of **4e**. In addition, in **7e** (even in **7a**) the formyl hydrogen may be involved in a six-membered, cyclic hydrogen bonding with the OH or OBpin group (formed in the previous allylboration step). Similarly, stabilizing, so-called "formyl C–H···O" interactions have been previously reported by Corey and co-workers.[16]

Alternatively to the formation of **7e**, the allenylboration may proceed via TS **7e**′, in which the carbonyl and the aromatic system is not able to conjugate. Therefore, we consider **7e**′ as an unfavored TS, providing the minor diastereomer for **4e**.

In summary, we have shown that bis-borodienes **1** react readily and usually selectively with mono- and dialdehydes. The reaction creates three to four stereocenters with high selectivity. However, in most of the reactions only two diastereomers were obtained with useful levels of stereoselectivity. The reaction is very interesting mechanistically, as the first allylboration step results in an allenylboronate with very high stereoselectivity. The second step is an allenylborylation to give 1,4-diols. The reaction with dialdehydes provides 1,4-naphthalene-diols, which are important motifs in natural products.[1,2]

■ ASSOCIATED CONTENT

Supporting Information

Supporting Information with experimental procedures and ^{1}H, ^{13}C NMR spectra of the products is available. This material is available free of charge via the Internet at http://pubs.acs.org.

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DOI: 10.1021/acs.orglett.5b01048
Org. Lett. 2015, 17, 2290–2293

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the financial support of the Swedish Research Council (VR) and the Knut och Alice Wallenbergs Foundation. J.-Z. acknowledges a postdoctoral position from the Wenner−Gren Foundation.

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DOI: 10.1021/acs.orglett.5b01048
Org. Lett. 2015, 17, 2290−2293