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Stereoselective construction of *trans*-1,2-benzooxadecaline frameworks by three-component cascade reactions of an α-phenethyl-β-borylallylsilane with aldehydes†

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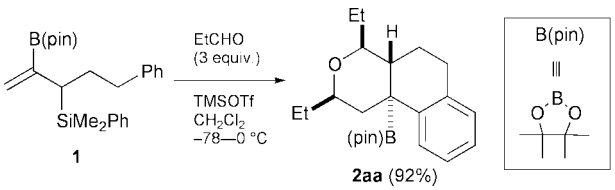
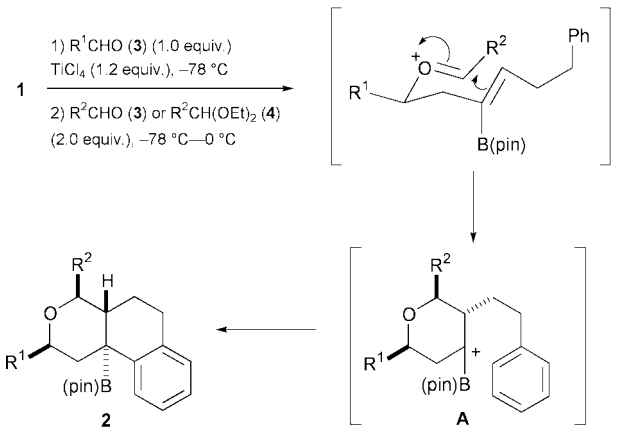
Reactions of α-phenethyl-β-borylallylsilane with aldehydes afforded tricyclic *trans*-1,2-benzooxadecaline frameworks stereoselectively in the presence of Lewis acids *via* sequential incorporation of two different aldehydes followed by cationic cascade cyclization, ending up with intramolecular Friedel–Crafts reaction.

Synthetic reactions in which multiple chemical bonds are created sequentially in a single reaction vessel are highly attractive in terms of efficiency in organic synthesis.[1] In particular, such reactions involving sequential coupling of multiple components have gained increasing attention to achieve high structural diversity which is one of the most important issues in recent synthetic organic chemistry. In our recent report that focused on the alkenylborane synthesis *via* β-borylallylsilanes, we briefly mentioned that reaction of α-phenethyl-β-borylallylsilane **1** with aldehyde afforded tricyclic **2aa** as a sole diastereomer in the presence of TMSOTf [eqn. (1)].[2,3] The reaction may proceed sequentially through allylation of the aldehyde with **1** and acetal formation with the second equiv. of the aldehyde, followed by Prins-type oxonium ion–alkene cyclization, ending up with intramolecular Friedel–Crafts reaction.[4] The remarkable increase in molecular complexity with the high stereoselection prompted us into further investigation. Herein, we report that selective formation of the *trans*-1,2-benzooxadecalines with a wide range of substituents was realized by a sequential reaction of two different aldehydes with **1**. Moreover, formation of related tricyclic frameworks on the basis of the same reaction protocol is also described.



Aiming at the selective, sequential reaction of **1** with aldehydes, we initially tried a stepwise addition of two aldehydes into a solution of **1** in the presence of TMSOTf. Thus, after propionaldehyde (**3a**, 1 equiv.) was completely consumed in the reaction mixture, acetaldehyde (**3b**, 2 equiv.) was subsequently added. Work-up of the reaction mixture, however, gave tricyclic benzooxadecaline derivative **2aa** as a major product, in which two molar equiv. of **3a** were incorporated. Selective synthesis of tricyclic benzooxadecalines, in which two different aldehydes were incorporated in a stepwise manner, was achieved by means of $TiCl_4$ instead of TMSOTf (Scheme 1).[2] In the presence of $TiCl_4$ (1.2 equiv.), aldehyde **3a** (1.0 equiv.) was reacted at −78 °C, to the consumption. Subsequent addition of **3b** (2.0 equiv.) to the reaction mixture at −78 °C, followed by warming the mixture to 0 °C, resulted in the exclusive formation of **2ab** in good yield, which had ethyl and methyl groups selectively at the right positions (Table 1; entry 1). With the optimized reaction conditions, some aliphatic and aromatic aldehydes and acetals as the second electrophile were employed in combination with the first aliphatic aldehydes for the present three component cascade cyclization. When propionaldehyde diethylacetal (**4a**) and isobutyraldehyde (**3c**) were employed as the second electrophiles, the corresponding products were obtained in good yields (entries 2 and 3). However, reaction of pivalaldehyde (**3d**) under the same reaction conditions gave **2ad** only in moderate yield, although the selectivity for the formation of **2ad** was perfect (entry 4). It was found that the yield was much improved by the additional use of TMSOTf in the second step with **3d** (entry 5).‡ A similar but more pronounced effect of the additional use of TMSOTf was found in the reaction of benzaldehyde (**3e**), which hardly



Scheme 1 Three-component cascade reaction of **1** with electrophiles.

Table 1 Stereoselective synthesis of *trans*-1,2-benzooxadecalines **2** *via* sequential reaction of aldehydes (**3**) and diethylacetals (**4**) with **1**

Entry	Aldehyde (R^1)	Aldehyde or acetal (R^2)[a]	Conditions[b]	Product (% yield)[c]
1	**3a** (Et)	**3b** (Me)	A	**2ab** (81)
2	**3a**	**4a** (Et)[d]	A	**2aa** (75)
3	**3a**	**3c** (*i*-Pr)	A	**2ac** (80)
4	**3a**	**3d** (*t*-Bu)	A	**2ad** (47)
5	**3a**	**3d**	B	**2ad** (75)
6	**3a**	**3e** (Ph)	A	**2ae** (trace)
7	**3a**	**3e**	B	**2ae** (85)
8	**3a**	**4f** ((*E*)-PrCH=CH)[d]	B	**2af** (58)
9	**3b** (Me)	**3a**	A	**2ba** (82)
10	**3c** (*i*-Pr)	**3a**	A	**2ca** (33)

[a] Aldehydes were used as the second electrophiles unless otherwise noted. [b] Condition A: (1) R^1CHO (1 equiv.), $TiCl_4$ (1.2 equiv.), −78 °C, (2) R^2CHO or $R^2CH(OEt)_2$ (2 equiv.), −78–0 °C. For condition B, TMSOTf (2 equiv.) was added with the second electrophiles. [c] Isolated yield. [d] The corresponding diethyl acetals were used as the second electrophiles.

† Electronic supplementary information (ESI) available: experimental details and spectral data. See http://www.rsc.org/suppdata/cc/b1/b102613p/

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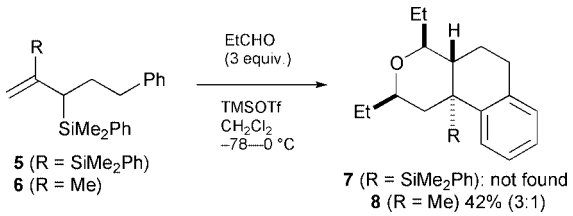
gave the desired product in the absence of TMSOTf (entries 6 and 7). Although use of (*E*)-2-hexenal as the second electrophile resulted in the formation of a complex mixture of undesired products, the corresponding acetal (**4f**) afforded the tricyclic product **2af** having alkenyl group as R^2 (entry 8). We also examined the variation of the first electrophile. Reaction using **3b** in combination with **3a** gave **2ba** with high selectivity (entry 9). Although we found that use of more sterically demanding **3c** as the first electrophile resulted in much lower yields, only **2ca** without any other tricyclic products were found in the reaction mixture (entry 10). Presumably, **3c** as well as **1** may be consumed completely in the first step by any side reaction, resulting in the highly selective formation of **2ca**.

To evaluate the role of the boryl group in the cyclization, we examined the reactions of the related allylsilanes bearing silyl (**5**) and methyl (**6**) groups at the β-positions.§ Under the same reaction conditions as for the preparation of **2aa** from the β-

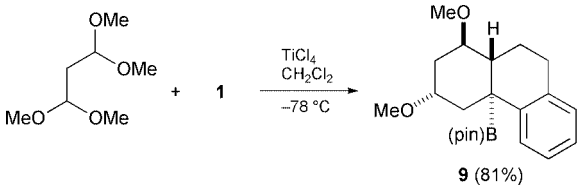


5 (R = $SiMe_2Ph$)
6 (R = Me)

7 (R = $SiMe_2Ph$): not found
8 (R = Me) 42% (3:1)

boryl counterpart **1**, 3 molar equiv. of **3a** were reacted with **5** and **6** in the presence of TMSOTf [eqn. (2)]. While the former (**5**) gave only a complex mixture of products, the methyl derivative afforded tricyclic product **8** along with its diastereomer in a ratio of 3:1 in a total yield of 42%. This result suggests that the sequential reaction with aldehydes giving the tricyclic skeleton is efficiently controlled by the boryl group with respect to yield and stereoselectivity. Presumably, the electronic nature of the β-substituent has the predominant effect on the formation and cyclization of the cationic intermediates, *e.g.*, **A** in Scheme 1.

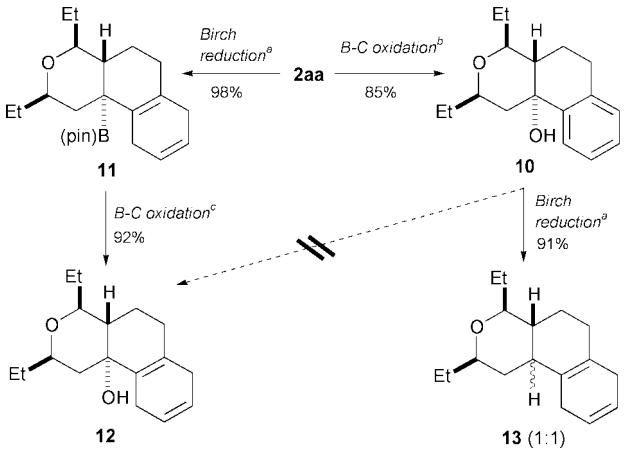
A related cascade cyclization using 1,1,3,3-tetramethoxypropane with **1** in the presence of $TiCl_4$ afforded boryl-substituted *trans*-1,2-benzodecaline derivative **9** in good yield



9 (81%)

[eqn. (3)]. Interestingly, the relative stereochemistry of the two methoxy groups was *trans*, indicating the second carbon–oxygen bond activation leading to cyclization may involve chelation of the two methoxy groups onto the titanium metal.

The tricyclic organoboron compounds served as useful synthetic precursors for the corresponding tertiary alcohols bearing the hydroxy groups at the bridgehead carbon atoms (Scheme 2). Thus, treatment of **2aa** with trimethylamine oxide at 160 °C gave the bridgehead alcohol **10** in 85% yield. Further synthetic elaboration was demonstrated by sequential treatment of **2aa** with Li–NH_3 and H_2O_2, which gave the dienyl alcohol **12** *via* isolation of **11**. An attempt at an alternative pathway to **12** *via* Birch reduction of **10** resulted in the reduction of the tertiary, benzylic hydroxy group to give **13** in high yield as a 1:1 mixture of diastereomers, indicating that the boryl group served as a masked hydroxy group in the transformation into **11**.



Scheme 2 *Reagents and conditions*: a) Li, liq. NH_3, *t*-BuOH, −33 °C; b) $Me_3NO{\bullet}2H_2O$, diglyme, 160 °C; c) H_2O_2, NaOH aq., THF, 50 °C.

In summary, we report a cascade cyclization giving *trans*-1,2-benzodecaline skeletons *via* sequential reaction of α-phenethyl-β-borylallylsilane **1** with aldehydes. The stereochemical aspects and high structural diversity may deserve further investigation of the present stereoselective cyclization. Furthermore, the boryl group incorporation at the bridgehead tertiary carbon atom as a hydroxy equivalent may open up new possibilities for the synthesis of polycyclic bridgehead alcohols *via* cationic cyclization.

Notes and references

‡ A general procedure (A) for the three component cascade reaction of **1** with electrophiles. To a mixture of **1** (50 mg, 0.12 mmol) and **3** (0.12 mmol) in CH_2Cl_2 (0.12 mL) was added a CH_2Cl_2 solution of $TiCl_4$ (2.0 M, 74 × 10^{-3} mL, 0.15 mmol) at −78 °C, and the mixture was stirred at −78 °C for 2 h. To this was added **3** or **4** (0.25 mmol) at −78 °C, and the mixture was stirred at 0 °C for 3 h. Aqueous $NaHCO_3$ (sat.) was added to the mixture. Extraction with AcOEt followed by silica gel column chromatography afforded **2**. For procedure B, the addition of the second electrophile (**3** or **4**) was followed by the addition of TMSOTf (45 × 10^{-3} mL, 0.25 mmol) at −78 °C.

§ The requisite β-silylallylsilane **5** and β-methylallylsilane **6** were prepared by palladium-catalyzed bis-silylation of 5-phenylpenta-1,2-diene[5] and Suzuki-Miyaura cross-coupling of **1** with iodomethane,[6] respectively.

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