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Boron- and Silicon-Substituted [3]-1-Heterodendralenes as Versatile Building Blocks for the Rapid Construction of Polycyclic Architectures

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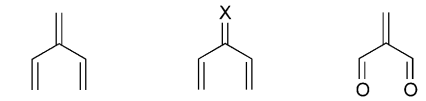
In recent years, dendralenes **1** have received increasing attention as building blocks for multiple Diels–Alder cycloadditions and rapid generation of molecular complexity.[1] These acyclic cross-conjugated polyenes are particularly well-suited to diversity-oriented synthesis (DOS), a promising strategy for lead generation in chemical genetics and drug discovery.[2] They have found numerous applications for rapid access to polycyclic frameworks,[3] and have also been engaged in targeted syntheses of natural products, such as vinigrol[4] or triptolide.[5] Since the early report of Blomquist and Verdol,[6] several routes have been developed to synthesize [*n*]dendralenes. Surprisingly, only few examples related to their heteroatom analogues are hitherto reported. Tsuge et al., Motoki et al. and Saito et al. independently described diene-transmissive hetero-Diels–Alder reactions of compounds **2**, in which the heteroatom occupies the central position of the triene skeleton.[7–9] More recently, cross-conjugated dioxatrienes **3** with two heteroatoms were synthesized and were engaged in sequential reactions to provide pyran-fused aza- and thia-heterocycles.[10,11]

In parallel, Pi and Bodwell described normal and inverse electron demand Diels–Alder reactions of dienes **4**,[12] while, more recently, Spino and Perreault have intensively investigated a very elegant intramolecular strategy to construct the quassinoid framework through tandem cycloadditions involving cyclic compounds **5** (Figure 1).[13]



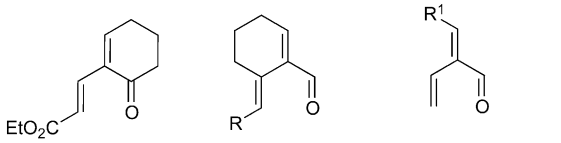
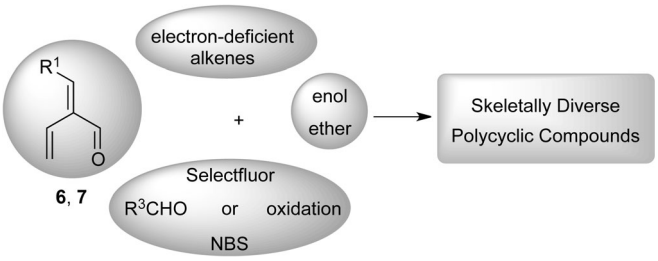


Figure 1. [3]-1-Heterotrienes **4**, **5**, **6** and **7**.

On the basis of these precedents, we initiated a research program with the aim of exploring the synthesis and reactivity of acyclic 2-vinyl α,β-unsaturated aldehydes, **6** and **7** ($R^1 = SiMe_3$ or Bpin), which we named [3]-1-heterodendralenes by analogy with the corresponding carbotrienes. These compounds were designed as potential useful starting building blocks for rapid access to a rich structural diversity with control of multiple stereocenters. Indeed, sequential Diels–Alder/hetero-Diels–Alder reactions (or vice versa) can be carried out chemoselectively, and the structures of the final polycyclic products are determined by the intrinsic reactivity of each 1,3-dienyl system or by the order of introduction of the reagents. Furthermore, the first cycloaddition step or the combination of two Diels–Alder reactions generates an allylsilane or an allylboronic ester that constitutes an additional asset for creating structural diversity.[14] Finally, most of the final products share a common motif characterized by a cyclic lactol ether system, a structural element that, as such or as precursor of the corresponding lactones or tetrahydropyrans, has been found in many bioactive compounds and drugs.[15] Herein, we report the first results to illustrate the multiple synthesis possibilities offered by the polyfunctional building blocks **6** and **7** in diene-transmissive Diels–Alder reactions (Scheme 1).



Scheme 1. DOS strategy based on boron- and silicon-substituted [3]-1-heterodendralenes **6** and **7**.

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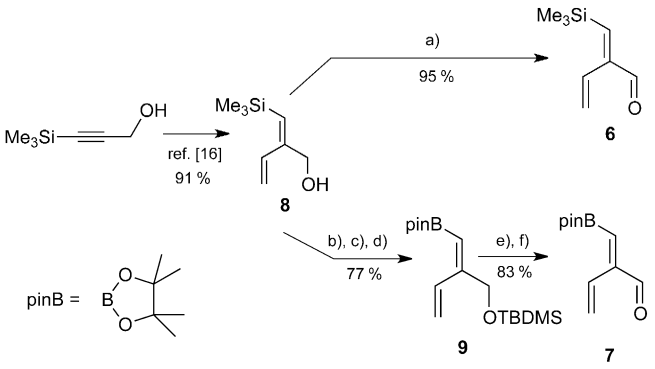
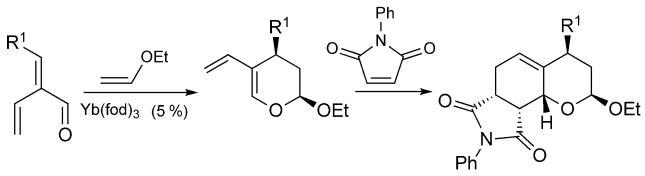
The starting dendralenes were prepared according to the following sequences (Scheme 2). Direct addition of vinylmagnesium chloride to 3-trimethylsilylpropargyl alcohol afforded the diene **8** in 91% yield according to the procedure of Fallis et al.[16] Oxidation with manganese dioxide in refluxing CH_2Cl_2 produced the aldehyde **6**. In parallel, after protection of the alcohol as a TBDMS ether, **8** was treated with *N*-iodosuccinimide; this resulted in the replacement of the trimethylsilyl group by iodine with retention of configuration. Borylation was carried out with bis(pinacolato)diboron and a catalytic amount of $PdCl_2$(dppf) in the presence of potassium acetate.[17] Deprotection of **9** with acetic acid in a mixture THF/water was followed by the oxidation of the alcohol with the Dess–Martin reagent (83%, two steps). Unlike the parent compound, 2-formyl-1,3-butadiene (R^1 = H), which shows a high propensity toward dimerization,[18] the boron- and silicon-substituted derivatives can be isolated and kept for several days, at room temperature for **6** and at −20 °C for **7**.



Scheme 2. Synthesis of boron- and silicon-substituted [3]-1-heterodendralene **6** and **7**. a) MnO_2, CH_2Cl_2, reflux, 4 h, 95%; b) TBDMSCl, imidazole, CH_2Cl_2, room temperature, 18 h, 90%; c) NIS, MeCN, 0 °C, 4 h, 98%; d) B_2pin_2, KOAc, $PdCl_2$(dppf) (3 mol%), DMSO, 50 °C, 4 h, 88% (three steps, 77%); e) AcOH, THF/H_2O (1:1), 50 °C, 5 h, 89%; f) Dess–Martin periodinane, CH_2Cl_2, room temperature, 3 h, 93% (two steps, 83%).

With the starting building blocks in hand, we first explored their reactivity as heterodienes. 3-Boronoacrolein esters are viable substrates in metal-catalyzed inverse electron demand hetero-[4+2] cycloaddition with enol ethers.[15,19] With **6** or **7** and ethylvinyl ether in the presence of Yb(fod)$_3$, the corresponding 2-alkoxy-3,4-dihydro-5-vinyl-2*H*-pyrans **10** or **11** were isolated in 81 and 63% yields, respectively. In the presence of *N*-phenylmaleimide, they underwent normal Diels–Alder reactions to afford the corresponding cycloadducts as single diastereomers (Scheme 3). The stereochemical outcome of this sequence (two consecutive *endo* cycloadditions) was assigned on the basis of X-ray crystallographic analysis of the final product **12a**.[20] These reactions can be also advantageously conducted in a one-pot process without formation of any product resulting from a first cycloaddition of the 1,3-butadienyl moiety to the electron-poor alkene. These results encouraged us to examine the reactivity of heterodendralenes **6** and **7** with respect to various other partners, and the results are presented in Table 1.



6 R^1= TMS
7 R^1= Bpin
10 R^1= TMS
11 R^1= Bpin
12a R^1= TMS
13a R^1= Bpin

Scheme 3. a) ethyl vinyl ether, Yb(fod)$_3$ (5 mol%), room temperature, overnight; **10**, 81%; **11**, 63%; b) *N*-phenylmaleimide, toluene, room temperature, 12 h; **12a**, 90%; **13a**, 88%.

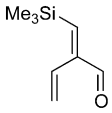
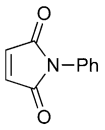
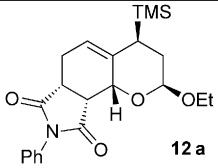
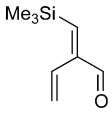
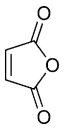
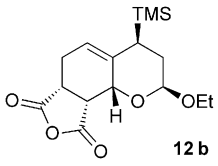
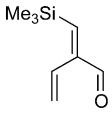
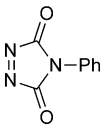
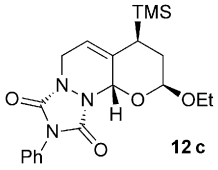
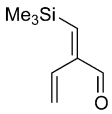
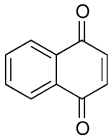
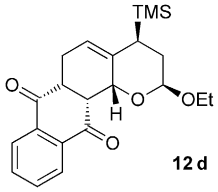
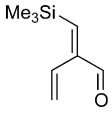
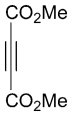
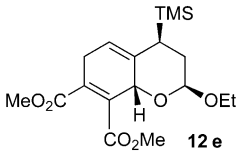
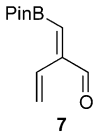
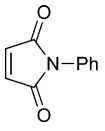
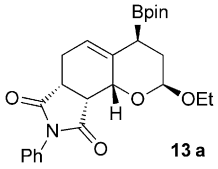
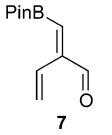
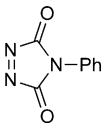
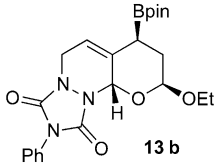
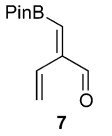
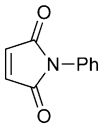
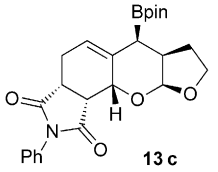
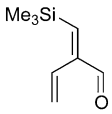
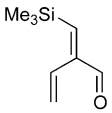
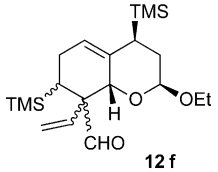
Interestingly, adducts derived from ethyl vinyl ether and α,β-unsaturated alkenes, activated azo compounds and naphtoquinone participated well in this multicomponent reaction (entries 1–4). The yield was lower with methyl acetylenedicarboxylate (entry 5), which was also the case when the silicon was replaced by boron, probably for reasons of stability rather than reactivity (entries 6–7). Other enol ether, such as 2,3-dihydrofuran, can also be engaged in this HDA/DA sequence as electron-rich dienophiles (entry 8). It is worth noting that **6** can also play the dual role of heterodiene and dienophile to give the cycloadduct **12f** when the reaction was conducted in a default of enol ether (entry 9).

Taking advantage of the presence of an allylboronate or an allylsilane moiety, we also engaged the *N*-phenylmaleimide derivatives **12a** and **13a**, chosen as examples, in various transformations (Scheme 4). The fluorination of **12a** was performed by using Selectfluor in acetonitrile to afford a single diastereomer **14** in 81% yield, while bromination with NBS afforded the corresponding allylic bromide **15**.[21] Concerning **13a**, oxidation with hydrogen peroxide gave the allylic alcohol **16**. More interesting, in terms of additional diversity, is the addition to aldehydes that provided access to the corresponding homoallylic alcohols **17a–c** in 77–86% yield (Scheme 4).[22]

Alternatively, as the cycloadduct **11** bears a boronate group in allylic position, the allylation and the cycloaddition steps can be inverted to generate a supplementary skeletal diversity from the same starting heterodendralene. Accordingly, as an illustration of this sequence, **11** and 4-nitrobenzaldehyde were allowed to react at room temperature to afford **18**, which underwent a further cycloaddition with *N*-phenylmaleimide to furnish the single tricyclic compound **19** (Scheme 5). Its stereochemistry, which was established by X-ray crystallographic analysis,[23] results first from a cyclic chair-like transition state A for the allylation reaction involving an equatorial position for the 4-nitrophenyl substituent, and then from an *endo* approach (transition state B) of the dienophile from the less hindered bottom face of the new created diene.

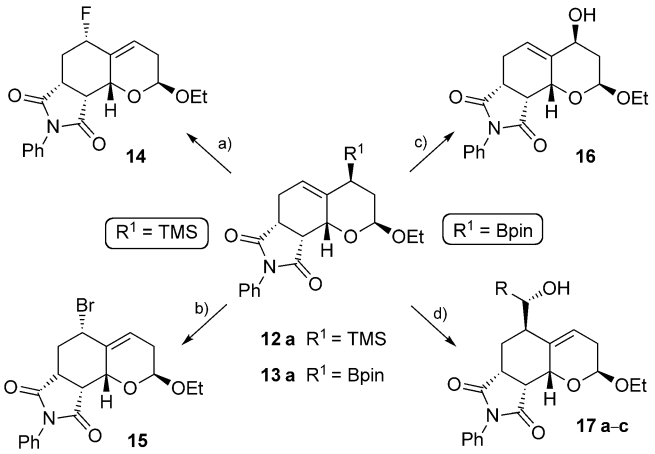
To continue the exploration of the reactivity of boron- and silicon-substituted [3]-1-heterodendralenes in diene transmissive Diels–Alder reactions, we engaged **6** and **7**

Table 1. One-pot HDA/DA sequence from heterodendralenes, **6** and **7**.

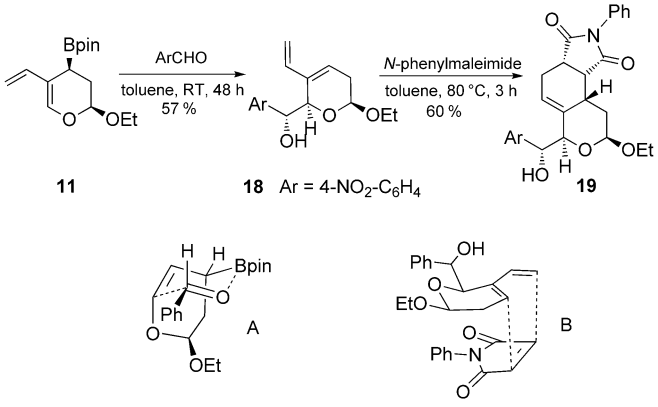
Entry	Heterodendralene	Enol ether	Electron-poor dienophile	Product	Yield [%][a]
1	 **6**			 **12a**	71
2	 **6**			 **12b**	64
3	 **6**			 **12c**	63
4	 **6**			 **12d**	68
5	 **6**			 **12e**	41
6	 **7**			 **13a**	54
7	 **7**			 **13b**	45
8	 **7**			 **13c**	43
9	 **6**		 **6**	 **12f**	63[b]

[a] Yields refer to pure products (one pot, two steps); [b] mixture of diastereomers (94:6).

through their 1,3-butadienyl moiety in normal electron-demand cycloadditions. Indeed, the cycloadducts **20a/b** and **21a/b** were obtained as single diastereomer in good yields after heating in toluene for *N*-phenylmaleimide,[24] while 4-phenyl-1,2,4,-triazoline-3,5-dione reacted at room temperature (Scheme 6).

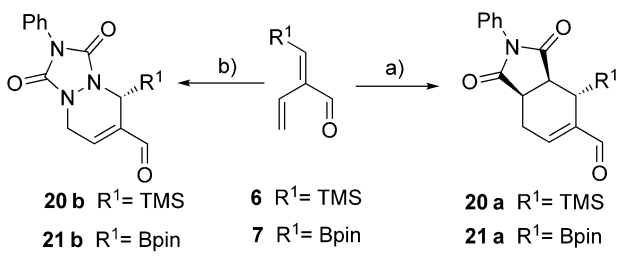


Scheme 4. Synthesis of tricyclic imides derivatives **14**–**17**. a) Selectfluor, MeCN, room temperature, 5 h, 81 %; b) NBS, MeCN, 3 h, −20 °C to 0 °C, 84 %; c) H_2O_2, NaOAc, THF, 0 °C, 6 h, 87 %; d) RCHO, toluene, 80 °C, 16 h, (R = Ph, 77 %, 4-NO_2–C_6H_4, 86 %, EtO_2C, 79 %).

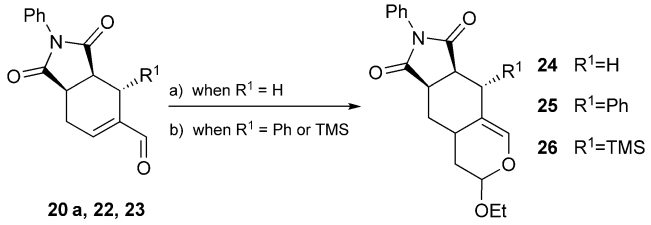


Scheme 5. Synthesis of **19** via a hetero-Diels–Alder (HDA)/allylboration/Diels–Alder (DA) sequence.

First attempts to perform the hetero-Diels–Alder cycloaddition of **20a** or **21b** with ethyl vinyl ether under standard conditions ($Eu(fod)_3$ or $Yb(fod)_3$, 1,2-dichloroethane, at room temperature or 60 °C, or by using $EtOCH{=}CH_2$ as solvent) proved to be unsuccessful, and led mainly to the starting materials or degradation. We, therefore, decided to examine the reactivity of similar cyclic enals **22** (R^1 = H) and **23** (R^1 = Ph) to determine if this unexpected low reactivity can be attributed to the presence of the TMS or Bpin substituents in the allylic position (Scheme 7). When the cycloaddition took place at 40 °C (CH_2Cl_2, $Eu(fod)_3$, 5 %) in a 74 % yield in the case of **22**, application of 16 kbar pressure at 50 °C for 4 days was necessary for **23** to afford the corresponding cycloadduct **25** as a mixture of two diastereomers in a moderate 41 % yield.[25] Under these conditions, a similar result was obtained with the trimethylsilyl derivative **20a**; this suggests that the presence of a substituent at position 6 of the 1-cyclohexene-1-carboxaldehyde fragment greatly decreases the reactivity of the heterodienes. With R^1 = Bpin we were unable to isolate any defined product, probably due to a lower stability of the starting boronated species.



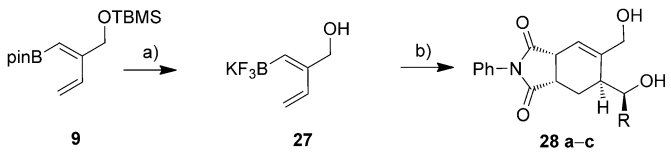
Scheme 6. Synthesis of **20**–**21**. a) *N*-phenylmaleimide, toluene, 90 °C, 15 h; **20a**, 70 %; **21a**, 64 %; b) 4-phenyl-1,2,4,-triazoline-3,5-dione, toluene, room temperature, 15 h; **20b**, 65 %; **21b**, 63 %.



Scheme 7. $Eu(fod)_3$-catalysed [4+2] cycloadditions of enals **20**–**22** to ethyl vinyl ether. Reagents and conditions: a) **22** (R^1 = H), ethyl vinyl ether (9 equiv), CH_2Cl_2, 48 h, $Eu(fod)_3$ (5 %), 40 °C, 74 %; b) ethyl vinyl ether (9 equiv), CH_2Cl_2, 16 kbar, $Eu(fod)_3$ 5 %, 50 °C, 4 days, **20a** (R^1 = TMS, 30 %) or **23** (R^1 = Ph, 41 %).

Finally, we decided to examine the behavior of **21a** as allylating reagent. When a test reaction with benzaldehyde effectively afforded the expected homoallyllic alcohols, yields were very low (≈10 %). Gratefully, this drawback can be circumvented by using a modification of the order of the reactions and by converting the initial boronic ester group in a trifluoroborate substituent that greatly increases the reactivity of the dienyl moiety.[26] This transformation was easily achieved by treatment of **9** with KHF_2 in $MeOH/H_2O$ with a concomitant deprotection of the alcohol. The resulting diene **27**, which could be isolated if necessary,[27] was directly engaged in a Diels–Alder cycloaddition with *N*-phenylmaleimide at 50 °C in acetone for 12 h in the presence of various aldehydes.[28] The diols **28a**–**c** were obtained as major diastereomers (≥95 %) in good overall yields (one pot, four steps; Scheme 8).[29]

In conclusion, we have developed efficient procedures for the rapid construction of substituted polycyclic structures from a common starting acyclic cross-conjugated diene with control of the multicreated stereogenic centers. The range of accessible scaffolds can be greatly extended by varying the nature of the different building blocks, such as the substituents of the starting heterodendralenes. Furthermore, most of the resulting products have also functional groups for easy, further diversification by classical reactions. The develop-



Scheme 8. Synthesis of **28a–c**. a) KHF_2, MeOH, water, room temperature, 18 h; b) *N*-phenylmaleimide, acetone, CH_2Cl_2, $(Bu)_4NI$, 12 h, 50 °C, **28a** PhCHO, 54%, **28b** *n*BuCHO, 66%, **28c** 4-NO_2–C_6H_4CHO, 45% (one pot, four steps).

ment of resins suitable for immobilizing boronic esters[30] would allow the transposition of these sequences to solid-supported synthesis, which would greatly improve ease of isolation, workup and purification in a context of preparation of small libraries. We have shown, through these preliminary experiments that heterodendralenes are efficient and versatile building blocks for diene transmissive cycloadditions. Further studies are in progress to determine the exact potential of these compounds in other sequential reaction processes.

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