Dendralenes

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Synthesis of Functionalized [3], [4], [5] and [6]Dendralenes through Palladium-Catalyzed Cross-Couplings of Substituted Allenoates

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Abstract: *A mild method for the synthesis of highly functionalized [3]–[6]dendralenes is reported, representing a general strategy to diversely substituted higher homologues of the dendralenes. The methodology utilizes allenoates bearing various substitution patterns, along with a wide range of boron and alkenyl nucleophiles that couple under palladium catalysis leading to sp-, sp^2-, and sp^3-substituted arrays. Regioselective transformations of the newly formed unsymmetrical dendralene derivatives are demonstrated. The use of micellar catalysis, where water is the global reaction medium, and room temperature reaction conditions, highlights the green nature of this technology.*

Dendralenes make up a fascinating class of fundamental hydrocarbons among the various types of polyenes, derived formally from ethylene (Figure 1, top).[1] No longer simply molecules of curiosity, in large measure due to the efforts of pioneers such as Hopf, and more recently Sherburn, dendralenes of both the cyclic and acyclic varieties have become useful intermediates in targeted syntheses (Figure 1, bottom).[2,3] One of many attractive features is their ready participation in cycloaddition reactions, in particular the diene-transmissive-Diels–Alder (DTDA) reaction. In this regard, they are well configured to maximize "step economy" en route to both natural and unnatural materials that contain polycyclic arrays. Notwithstanding the remarkable advances made in preparing higher homologs that now have reached [12]dendralene,[4] recent papers from the Sherburn group highlight the need for additional inroads to both the parent and especially substituted systems, as well as new chemistry that extends the repertoire of reactions of dendralenes beyond [4+2] cycloadditions. Indeed, in a recent Account,[5] Sherburn concludes: "*Regarding our deployment of the dendralenes and related unsaturated hydrocarbons in the rapid generation of structural complexity, again, we have deployed only known reactions (and in the main, just one: the venerable Diels–Alder reaction).*" Other reactions of functionalized dendralenes, especially those associated with higher homologs that are regioselective, are few in number.[2d,5] Since most published routes to dendralenes involve double cross-couplings from dihalo- and diborylated intermediates (Figure 2, top)[4,6] selective mono-functionalized and unsymmetrical patterns, which are likely to prove more

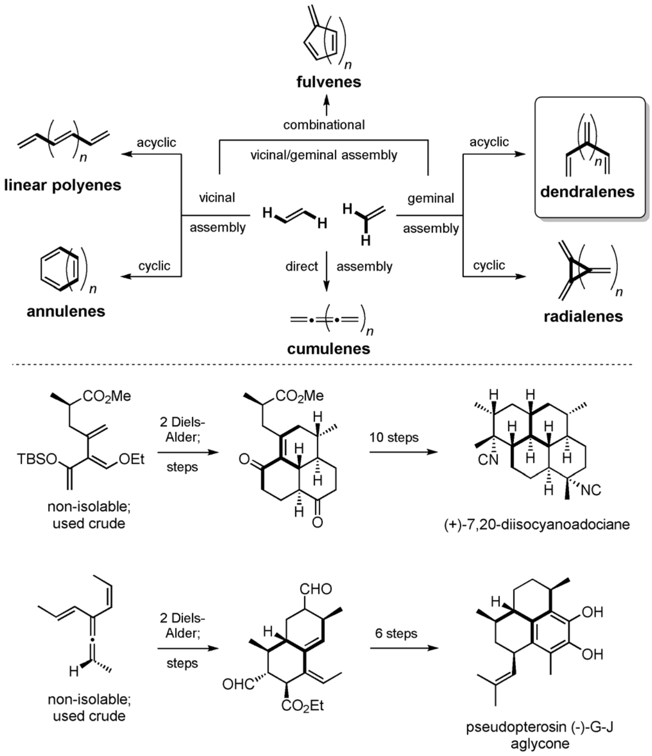

Figure 1. a) Classes of fundamental hydrocarbons assembled through connection of "ethylene units" (top). b) Use of dendralenes in natural products total synthesis (bottom).

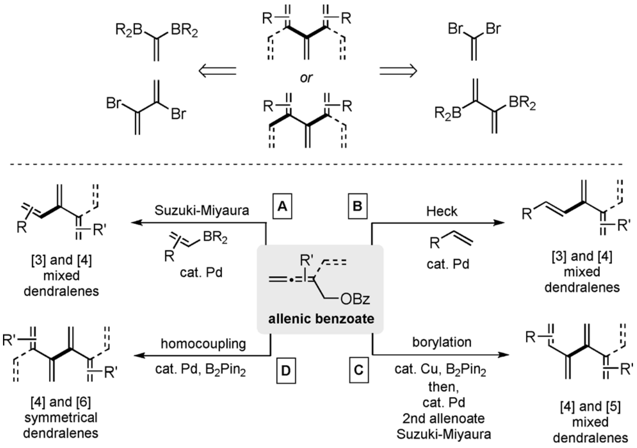

Figure 2. a) Cross-coupling disconnections to access dendralenes; prior art (top). b) General synthetic routes, **A**–**D**, utilized to prepare dendralenes; this work (bottom).

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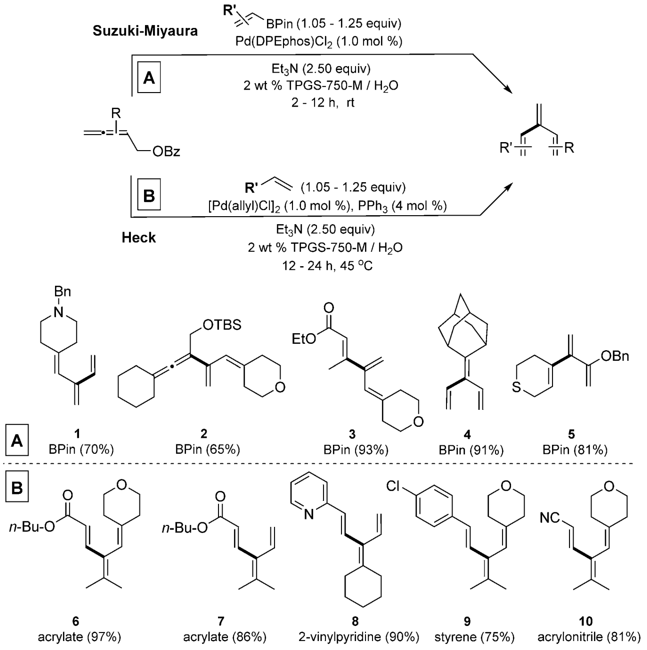
valuable in total synthesis, remain few in number. In this report, therefore, we describe rapid access to both functionalized symmetrical and unsymmetrical [3]–[6]dendralenes from a common allenic precursor, using Pd-catalyzed cross-couplings under micellar catalysis conditions; i.e., in water and typically at ambient temperature (Figure 2, bottom).[7] In addition, regioselective manipulations such as epoxidations, conjugate additions and olefin metathesis reactions, the first of their kind among dendralenes and their derivatives, are also illustrated.

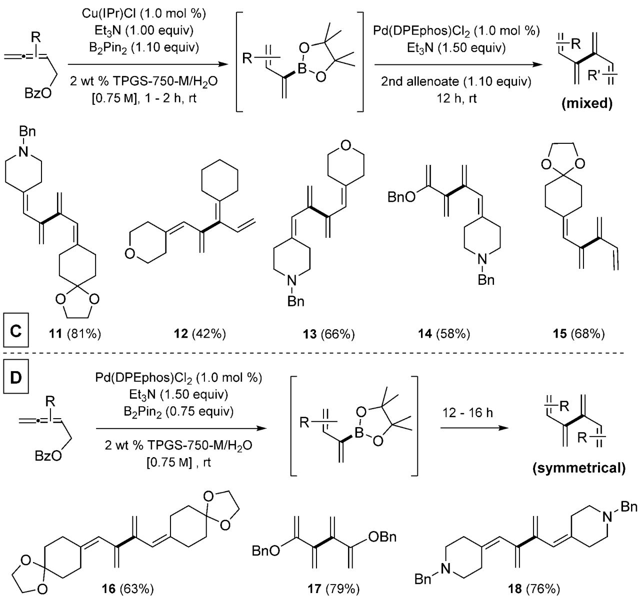
Initial studies on Pd-catalyzed couplings between an allenic benzoate and boronic acid under micellar catalysis conditions[7,8] afforded adducts (i.e., 2-substituted 1,3-butadienes) reflecting exclusive C−C bond formation at the central allenic carbon (Figure 2, path **A**). While this particular, initial transformation (to butadienes, in benzene at reflux) has been reported previously,[9] it was suggestive of the potential for a route towards only substituted [3]dendralenes. Although the full scope and utility of our modified approach to related 1,3-butadienes will be described at a later date, use of alkenylboronates as coupling partners in place of related aryl derivatives successfully provided a range of functionalized [3]dendralenes (Scheme 1, **A**). The presence of substituents on the cross-conjugated triene framework imparted sufficient stability to the products,[4] thereby leading to their facile isolation in neat form.



Scheme 1. Suzuki–Miyaura and Heck pathways to a variety of [3]dendralenes.

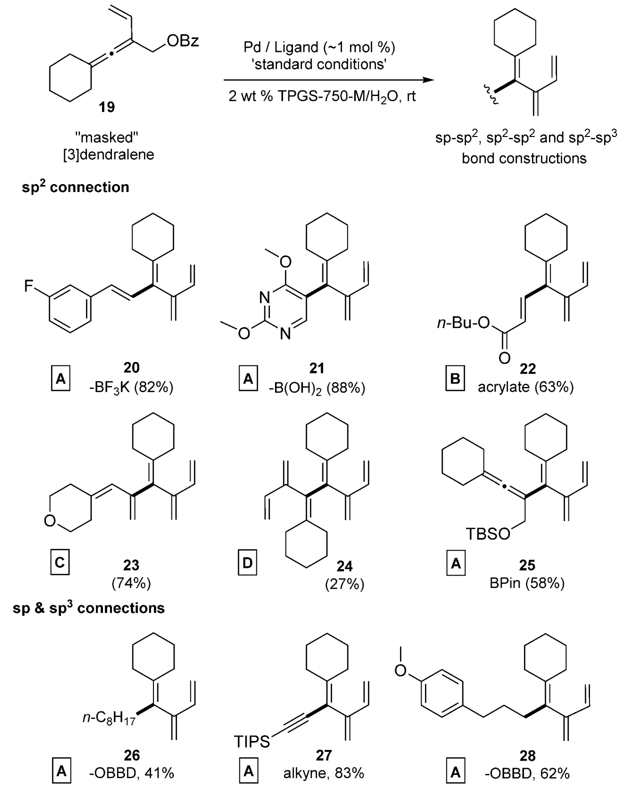
The increased electrophilicity of the in situ generated π-allenyl system relative to analogous π-allyl intermediates allows for subsequent reaction with activated olefins leading to Heck-derived [3]dendralenes (Scheme 1, **B**). Thus, acrylates, acrylamides, styrenes, and other alkenes readily participated under similar micellar conditions, providing the corresponding Heck products in good isolated yields. Noteworthy is the realization of substituted enoates at their β-positions (e.g., **3**) without observable isomerization.[10]

Given the precedent for copper-catalyzed borylations of allenic carbonates that produce 2-borylated 1,3-butadienes,[11] along with the opportunities offered by micellar catalysis for tandem reaction sequences in the same aqueous medium,[7,12] initial carbon–boron bond formation could be followed by a Pd-catalyzed cross-coupling, in 1-pot, furnishing dendralenic derivatives (Scheme 2, **C**). Borylation was initially effected employing a ligated Cu^{I} salt (1.0 mol%), B$_2$Pin$_2$ (1.1 equiv), Et$_3$N (1.0 equiv) and an allenoate, affording an intermediate alkenylboronate primed for subsequent Pd-catalyzed cross-coupling. This approach proved successful, furnishing a wide range of mixed [4]dendralenes **11**–**15**. Alternatively, borylation under palladium catalysis *alone* led to homocoupling of the intermediate borylated dienes, ultimately providing symmetrical [4]dendralenes **16**–**18**, a pathway first observed by Welker a decade ago (Scheme 2, **D**).[6h] Of note is that homocoupling does not occur under copper catalysis even after extended reaction times (i.e., from 2 to 48 h). This multi-catalytic system applied to the synthesis of functionalized dendralenes shows broad substrate compatibility, as well as functional group tolerance. Furthermore, these mild conditions compare very favorably with existing methods,[1,2,4,6] in terms of simplicity, amounts of reagents involved, and environmental concerns (such as organic waste in the form of solvents, and energy invested in the form of low temperatures).

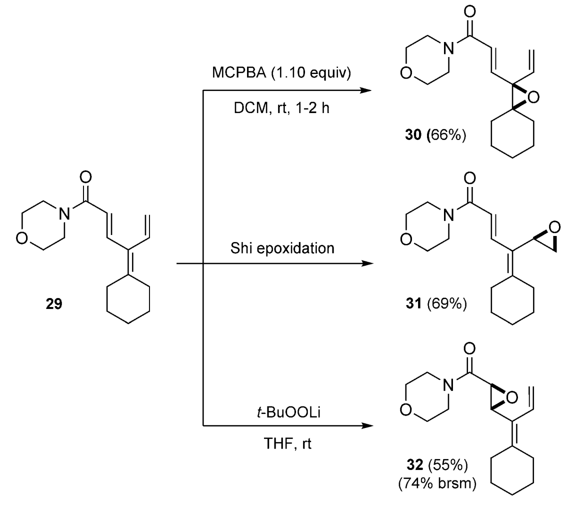


Scheme 2. Tandem borylation/Suzuki–Miyaura reactions to mixed and symmetrical [4]dendralenes.

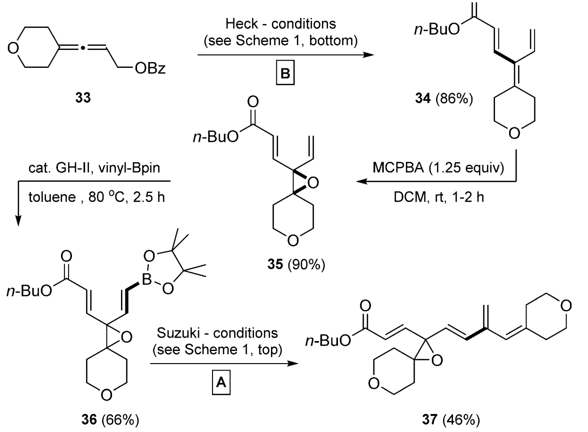
Altering the electrophilic coupling partner to a vinyl allenoate (**19**, Scheme 3) provided rapid entry to substituted [3], [4], [5] and [6]dendralenes utilizing any of the four pathways, **A**–**D** (Schemes 1 and 2). Furthermore, the Suzuki–Miyaura approach (Scheme 1, **A**) could be extended beyond



Scheme 3. Access to unsymmetrical, higher dendralenic derivatives via a vinyl allenoate.



Scheme 4. Regioselective epoxidations of unsymmetrical [3]dendralene **29**.



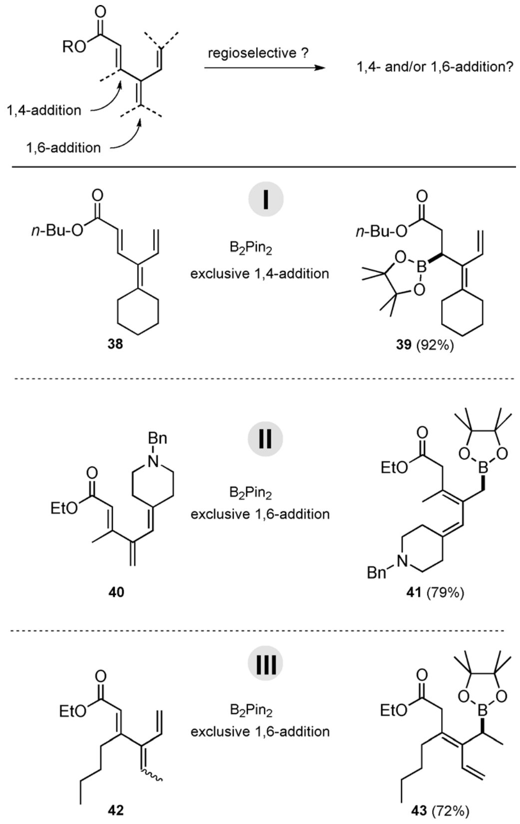
Scheme 5. Synthetic route to highly functionalized [3]dendralene **37**.

sp^2–sp^2 couplings to include sp–sp^2 and sp^2–sp^3 bond formations. Underutilized "OBBD" (9-oxa-10-borabicyclo-[3.3.2]decane) derivatives (leading to **26** and **28**),[13] as well as acetylenic partners (leading to **27**),[7,14] coupled readily with **19** to afford a range of mixed dendralenic products. Of particular note is the ability of this representative vinyl allenoate to serve as a masked [3]dendralene, providing an alternative bond disconnection relative to that found in allenoates lacking this alkenyl appendage.

Part of the incentive to develop inroads to unsymmetrical dendralenes lies in the potential for regioselective functionalization of the multiple olefinic sites within such molecules, well beyond their current utility in DTDA sequences. As illustrated in Scheme 4, site selective epoxidation furnished products **30**–**32** resulting from exclusive reaction at one of the three possible olefinic sites in representative [3]dendralene **29**.[15] In each case, differentiated dienic functionality remains in the product, thereby creating numerous opportunities for further elaboration. For example, conversion of educt **33** to [3]dendralene **34**, followed by Henbest epoxidation afforded terminal olefin **35** (Scheme 5). Grubbs–Hoveyda II-catalyzed cross-metathesis afforded the corresponding vinylboronate **36**,[16] which is well-positioned for further use via yet another cross-coupling, represented by the synthesis of new [3]dendralene **37**.

Likewise, introduction of conjugated carbonyl functionality, as present in educts **38**, **40**, and **42** (Scheme 6), sets the stage for either future 1,4- or 1,6-additions. Copper-catalyzed addition of BPin[17] to Michael [3]dendralenes, each bearing a different substitution pattern (cases **I**–**III**), led exclusively to products **39**, **41**, and **43**, respectively, suggestive of the dominance of steric effects in controlling the outcome of these conjugate additions. In case **I**, delivery of BPin occurred at the expected, sterically most favorable β-site. With β,β^1-disubstitution, however, copper adds at the unhindered δ-position (case **II**) affording the (*E*)-1,6-borylated adduct. Increasing the extent of substitution in case **III** still favors 1,6-addition over the fully substituted β-site. With both the β- and δ-positions disubstituted, little to no borylation was observed (see SI). Thus, it appears that Cu-catalyzed Michael additions to dendralenes follow similar patterns of reactivity as seen in traditional cuprate additions to unsaturated systems.

In conclusion, new technology has been developed that provides inroads to variously substituted [3]–[6]dendralenes. Key features highlighted herein include: 1) the use of a vinyl allenoate as a "masked" [3]dendralene; 2) the unified approach to a range of substituted dendritic oligomers from a common synthon; 3) first time access of the [4]allenic-



Scheme 6. Regioselective 1,4- and 1,6-additions to Michael [3]dendralenes.

dendralene framework; 4) the proclivity of these novel dendralenes towards regioselective further functionalization; 5) their ready participation as educts in several important synthetic transformations. In the composite, the processes described herein are representative of an area of fundamental research that remains, in large measure, surprisingly unexplored, especially with regard to exciting applications to various targets in synthesis, and natural products in particular.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allenes · cross-couplings · dendralenes · micellar catalysis · organometallic catalysis · regioselective reactions

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Communications

Dendralenes

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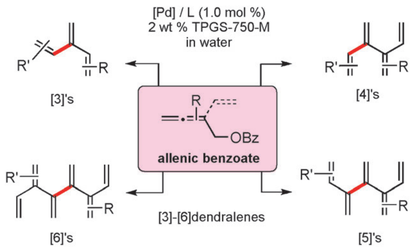
Synthesis of Functionalized [3], [4], [5] and [6]Dendralenes through Palladium-Catalyzed Cross-Couplings of Substituted Allenoates



All from allenes: New technologies for accessing functionalized, symmetrical and unsymmetrical [3] to [6]dendralenes are described. The combination of micellar reaction conditions, low catalyst loadings, and broad substrate compatibility highlights the green and robust nature of the method.