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Diene-Transmissive Diels−Alder Sequences with Benzynes

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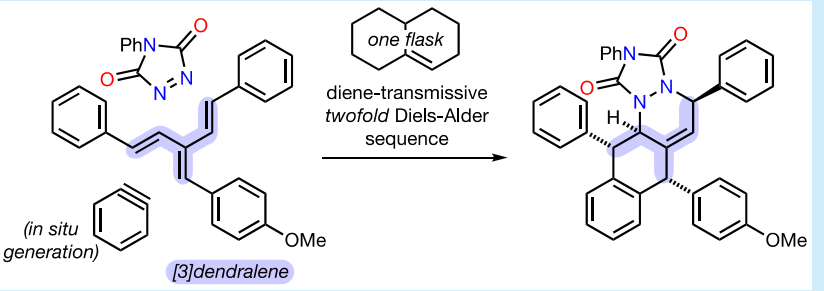
Supporting Information



ABSTRACT: Diene-transmissive Diels−Alder (DTDA) sequences are extraordinarily powerful processes for the generation of fused bicyclic systems. Nonetheless, only stable dienophiles have previously been deployed. Herein we report DTDA sequences with a variety of substituted [3]dendralenes in the first study to deploy arynes as dienophiles. We demonstrate the one-flask generation of complex, aromatic-ring-containing, multicyclic systems of relevance to medicinal chemistry. These synthetic operations provide numerous successful examples of the otherwise challenging and rarely reported intermolecular Diels−Alder reaction of acyclic 1,3-butadienes with arynes, which is made possible due to the exalted reactivity of dendralenic dienes.

Acyclic sp^2-rich hydrocarbons are excellent precursors for the step-economic generation of multicyclic systems. Dendralenes are particularly prominent in this field because they serve as multidienes in interconnected sequences of [4 + 2] cycloadditions.[1,2] The simplest cross-conjugated hydrocarbon, [3]dendralene, behaves as a double diene, reacting successively with two dienophiles in a so-called diene-transmissive Diels−Alder (DTDA) reaction sequence.[3] In DTDA sequences of [3]dendralenes, the first [4 + 2] cycloaddition is generally faster than the second, which allows the use of two different dienophiles.[4] Despite their obvious power and potential, DTDA sequences are by no means generalized processes because little in the way of dienophile variation has been investigated.[1,3,5,6] Herein we deploy dendralenes for the first time in DTDA sequences with benzynes. In addition to significantly broadening the scope of the extraordinarily powerful (four covalent bonds, two rings formed) DTDA sequence, this investigation also demonstrates the rapid construction of novel, medicinal-chemistry-relevant structures.

Specifically, this work shows that a substituted [3]-dendralene **1** undergoes an intermolecular Diels−Alder reaction with (a substituted) benzyne **2** to generate 2-vinyl-1,4-dihydronaphthalenes **3**, which, in turn, undergoes an intermolecular Diels−Alder reaction with a range of dienophiles **4** to furnish new carbo- and heteroannelated tetralins **5**. Diverse substitution of the tricyclic framework is within reach using this approach, a feature made pertinent by the privileged position of these systems in medicinal chemistry (Figure 1).[7]

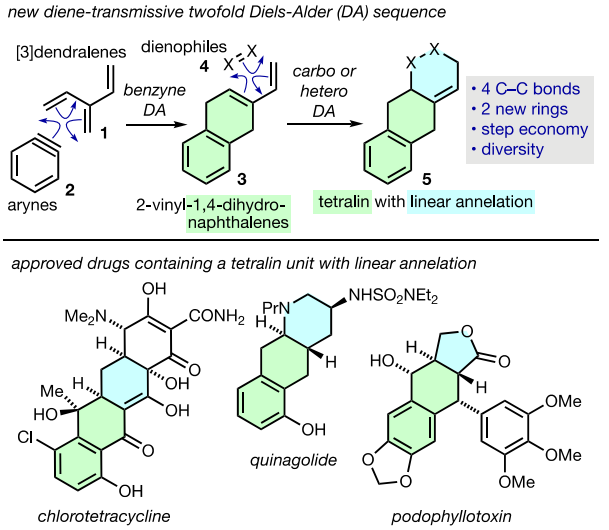


Figure 1. Proposed two-fold Diels−Alder sequence and selected clinically used substances containing a carbo-/heteroannelated tetralin core.

With diversely substituted [3]dendralenes available through a short and efficient two-step synthesis from aldehydes,[8] we set about testing the feasibility of intermolecular cycloadditions to benzynes. Our confidence was fueled by the knowledge that [3]dendralenes are reactive dienes.[1,3,4] Nonetheless, our

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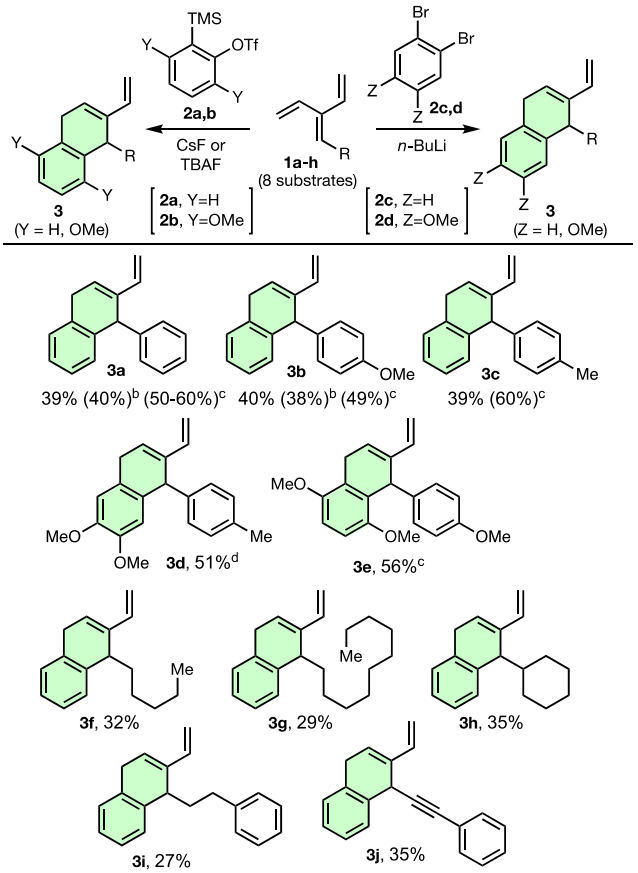
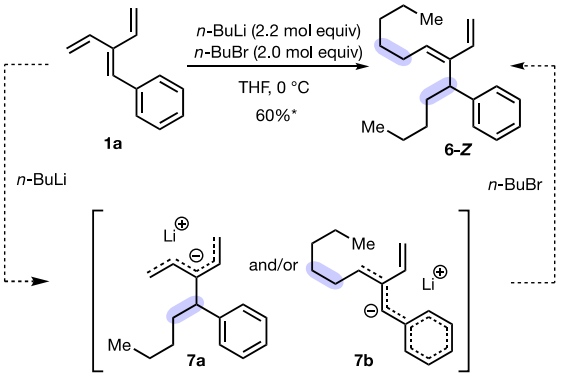
Table 1. Aryne Additions to Internally-Substituted [3]Dendralenes 1 Generate 2-Vinyl-1,4-dihydronaphthalenes 3[a]



[a]Unless otherwise specified, yields refer to isolated products from the *n*-BuLi method: To a solution of dendralene **1** and benzyne precursor **2c** (1.0 mol equiv) in PhMe at 0 °C was added *n*-BuLi (1.2 mol equiv) dropwise over 5 min. [b]To a solution of dendralene **1** and benzyne precursor **2a** or **2b** (1.5 mol equiv) in MeCN at 23 °C was added CsF (6 mol equiv). [c]To a solution of dendralene **1** and benzyne precursor **2a** or **2b** (2 to 3 mol equiv) in THF at −20 °C was added TBAF (3.5 mol equiv). [d]Procedure a was followed but with benzyne precursor **2d** (3.0 mol equiv) and *n*-BuLi (3.2 mol equiv).

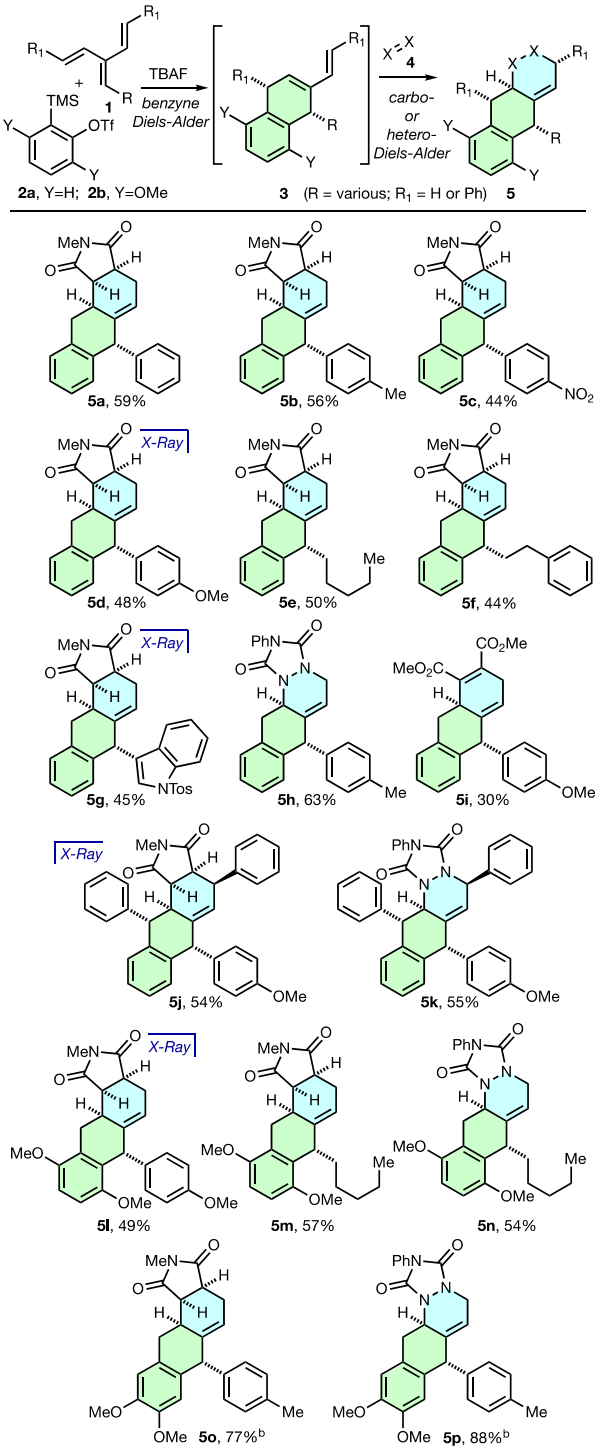
Scheme 1. Sequential 1,4-Nucleophilic Addition/Electrophilic Substitution of a 1,3-Butadiene



(* 20% yield when 1,2-dibromobenzene is used instead of *n*-BuBr)

enthusiasm was curtailed somewhat by the paucity of successful Diels–Alder reactions between benzynes and acyclic

Table 2. One-Flask, Two-Fold Cycloadditions to Substituted [3]Dendralenes Involving First an Aryne, Then an Electron-Poor Alkene, Alkyne, or Azo-Compound Dienophile[a]



[a]Unless otherwise specified, yields refer to isolated products **5** from THF solutions of dendralenes **1** through a one-pot method involving successive additions of (i) **2a** or **2b** (3 mol equiv) and TBAF (3.5 mol equiv), then (ii) MeOH, $CaCO_3$, and Dowex 50WX8-400 resin, then (iii) *N*-methylmaleimide (**4a**), *N*-phenyltriazoline-2,5-dione (**4b**), or dimethylacetylenedicarboxylate (**4c**) (6 mol equiv). [b]Isolated yield from 2-vinyl-1,4-dihydronaphthalene **3**.

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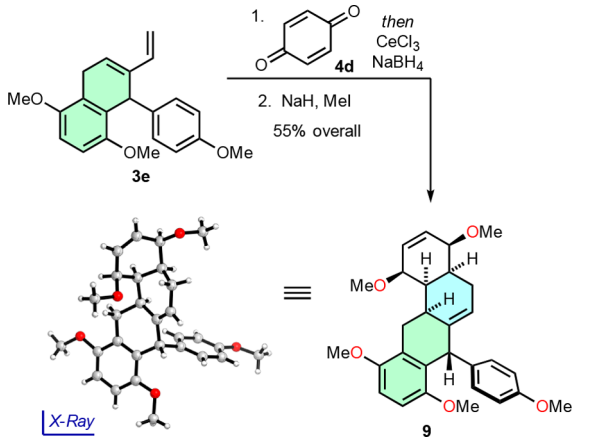
Scheme 2. Step Economic Synthesis of a 7-Arylangucycline



dienes in the literature. In fact, we could locate only eight publications reporting examples of this process, most of which describe only one or two examples.[9−16] Collectively, these reports indicate: (a) 1,4-Disubstituted-1,3-butadienes are the best performers,[8,12,13] (b) unsubstituted diene termini can be problematic, giving rise to competing [2 + 2] cycloaddition products,[9,10] (c) 2-methyl-1,3-butadienes can be challenging due to competing Alder ene reactions,[7,9] and (d) the elimination of CO_2/N_2 from *ortho*-benzendiazonium carboxylate (BDC) is the preferred method of benzyne generation.[11−13]

Table 1 reports the results of [4 + 2] cycloadditions of in-situ-generated benzyne, 3,6-dimethoxybenzyne, and 4,5-dimethoxybenzyne with [3]dendralenes **1a**−**h**, which carry a single substituent at the internal carbon. In contrast with the most recent literature findings of acyclic diene−benzyne cycloadditions, for which the BDC method is superior,[11−13] the acyclic diene units of substituted [3]dendralenes undergo the highest yielding reactions with *n*-BuLi/1,2-dibromobenzene and fluoride/2-trimethylsilyl-benzene-1-trifluoromethanesulfonate.[17] Table 1 presents successful aryne additions to [3]dendralenes carrying acyclic and cyclic alkyl, alkynyl, and diversely substituted aromatic substituents. The 2-vinyl-1,4-dihydronaphthalene products **3** are poorly represented in the literature.[18] This is surprising considering their significant potential for further elaboration into multicyclic structures.[19,20]

We selected one set of conditions for aryne generation/cycloaddition based on those developed by Coe and coworkers, who report a 89% yield for a reaction between cyclopentadiene, 1,2-dibromobenzene, and *n*-BuLi (1:1:1 stoichiometry) performed on a 100 g scale.[21] Under the same conditions, [3]dendralenes gave modest yields by comparison, and hence optimization experiments were undertaken. One attempt involved the replacement of PhMe with THF as the solvent, which led to an intriguing and unprecedented result: None of the expected benzyne addition product of dendralene **1a** was observed, but instead a product with two additional *n*-butyl units and one less C=C bond, **6**-*Z*, was isolated in ca. 20% yield. A 60% yield of this product was obtained in the absence of 1,2-dibromobenzene but with added *n*-bromobutane (Scheme 1).[22] We presume that the nucleophilic addition of *n*-BuLi to either terminus of a 1,3-butadiene moiety of **1a** generates the pentadienyl-lithium **7a** or the phenylpropenyl-lithium **7b**, which undergoes the nucleophilic substitution of bromobutane. Organolithium-initiated 1,4-addition polymerizations of dienes[23] and dendralenes[24] are known, but to our knowledge, 1,4-addition/substitution is without precedent for unsaturated hydrocarbons.[25] Attempts to generalize this three-component, two C−C bond-forming process are underway.

A significant contributing factor to the relatively low isolated yields of 2-vinyl-1,4-dihydronaphthalenes **3** (Table 1) relates to difficulties with product isolation. The separation of target product **3** from unreacted dendralene **1** and benzyne side products was nontrivial, particularly when all were hydrocarbons.[26] To circumvent this issue, we performed a second cycloaddition to semicyclic diene **3** with a nonhydrocarbon dienophile in the same reaction flask: We reasoned that the functionality in this double adduct would facilitate its isolation, hence simultaneously improving step economy and increasing isolated yields. The successful realization of this hypothesis is depicted in Table 2.[27] Thus [3]dendralenes with the substituent types listed in Table 1, along with additional substrates carrying an internal, electron-poor aromatic ring (→ **5c**) or an indole (→ **5g**) and dendralenes with phenyl groups at the terminal sites (→ **5j**, **k**), undergo one-flask DTDA sequences involving an aryne as the initial dienophile and *N*-methylmaleimide (NMM), *N*-phenyltriazoline-2,5-dione (PTAD), or dimethylacetylenedicarboxylate (DMAD[28]) as the representative second dienophile. The carbo-/heteroannelated tetralin products of these three component reactions[29] are isolated in highly respectable yields, considering that up to six new stereocenters, four new covalent bonds, and a new octalin ring system are generated in one operation.

Of the various methods of aryne generation, TBAF/2-trimethylsilyl-benzene-1-trifluoromethanesulfonate gave the best outcome in the one-flask process. For optimal yields, Kishi's method[30] of TBAF workup was deployed in situ prior to the addition of the second dienophile to the reaction mixture, and an excess of the second dienophile was used. In most cases, the second cycloaddition proceeds with (within the limits of detection) complete π-diastereofacial selectivity, with the dienophile avoiding the side of the 2-vinyl-1,4-dihydronaphthalene **3** that carries the substituents (R/R_1; Table 2). Complete endo-selectivity is also seen in cases involving NMM as the dienophile.

A final example, which extends the methodology to a more elaborate product structure, is depicted in Scheme 2.[31] Thus the reaction of 2-vinyl-1,4-dihydronaphthalene **3e** with *para*-benzoquinone **4d**, followed by the stereoselective two-fold Luche reduction and *O*-methylation, gives pentacycle **9**, containing both the tetracarbocyclic framework of angucycline antibiotics[32] and the tricyclic aryltetralin unit of antineoplastic lignans such as podophyllotoxin and its derivatives[33] (Figure 1).

In summary, the first Diels−Alder additions of arynes to dendralenes have been performed. These reactions have been sequenced with a second [4 + 2] cycloaddition in a one-flask operation to rapidly create complex multicyclic systems. This study significantly extends knowledge on aryne cycloaddition chemistry to acyclic dienes, processes that are poorly represented in the literature. Evidently, the enhanced diene reactivity of dendralenes is a contributing factor to their success in benzyne Diels−Alder additions. It is noteworthy that in contrast with 1,3-butadienes, dendralenes **1** provide reasonable yields from benzyne [4 + 2] cycloadditions irrespective of the presence or absence of terminal 1,3-butadiene substituents. The structures generated through this

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new DTDA sequence are suggestive of those found in biologically active compounds. In some cases, these new structures represent hybrids of natural products and drug molecules,[34] which have obvious potential for exploitation outside of synthetic chemistry. Extensions of these studies to unsymmetrically substituted dienophiles and applications of these concepts in target syntheses are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02807.

Experimental procedures, characterization data and nuclear magnetic resonance spectra, and crystallographic data for X-ray crystal structures (PDF)

Accession Codes

CCDC 1922951−1922955 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. J.S.W. performed the X-ray structure analyses. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(7) A small selection of the many approved and investigational drugs containing substituted tetralins includes: sertralines, steroidal estrogens and nonsteroidal estrogens such as nafoxidine and lasofoxifene, opiates, podophyllotoxin and derivatives such as etoposide and teniposide, doxorubicins and tetracyclines, tetryzoline, quinagolide, rotigotine, palonosetron, ecopipam, PF-03882845, nirogacestat, fosdagrocorat, ORG-25935, palovarotene, and dihydrexidine.

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(17) The BDC method gave mixtures of single and two-fold addition products in lower yields than the other methods, with low recoveries and no other discernible products. We attribute the poor mass balances of tractable products to polymer formation. Polymers might be generated through acid-catalyzed decomposition from traces of acid remaining from the preparation of BDC, perhaps accelerated by the higher reaction temperatures used in this procedure.

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(26) Only very small amounts of products tentatively assigned as those resulting from two-fold benzyne additions to substituted [3] dendralenes have been isolated so far. We believe that the successful monoadditions of benzynes to [3]dendralenes is a consequence of the enhanced reactivity of the latter.

(27) The benzyne monoadducts corresponding to double adducts **5g**, **5c**, **5h**, and **5k** (Table 2) could not be purified and hence were taken directly on to the double adduct stage, at which point they were readily isolated in pure form.

(28) DMAD was an insufficiently reactive dienophile to be used more widely in one-pot reactions, hence its deployment on only one occasion and its significantly lower yield (**5i**, 30%).

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