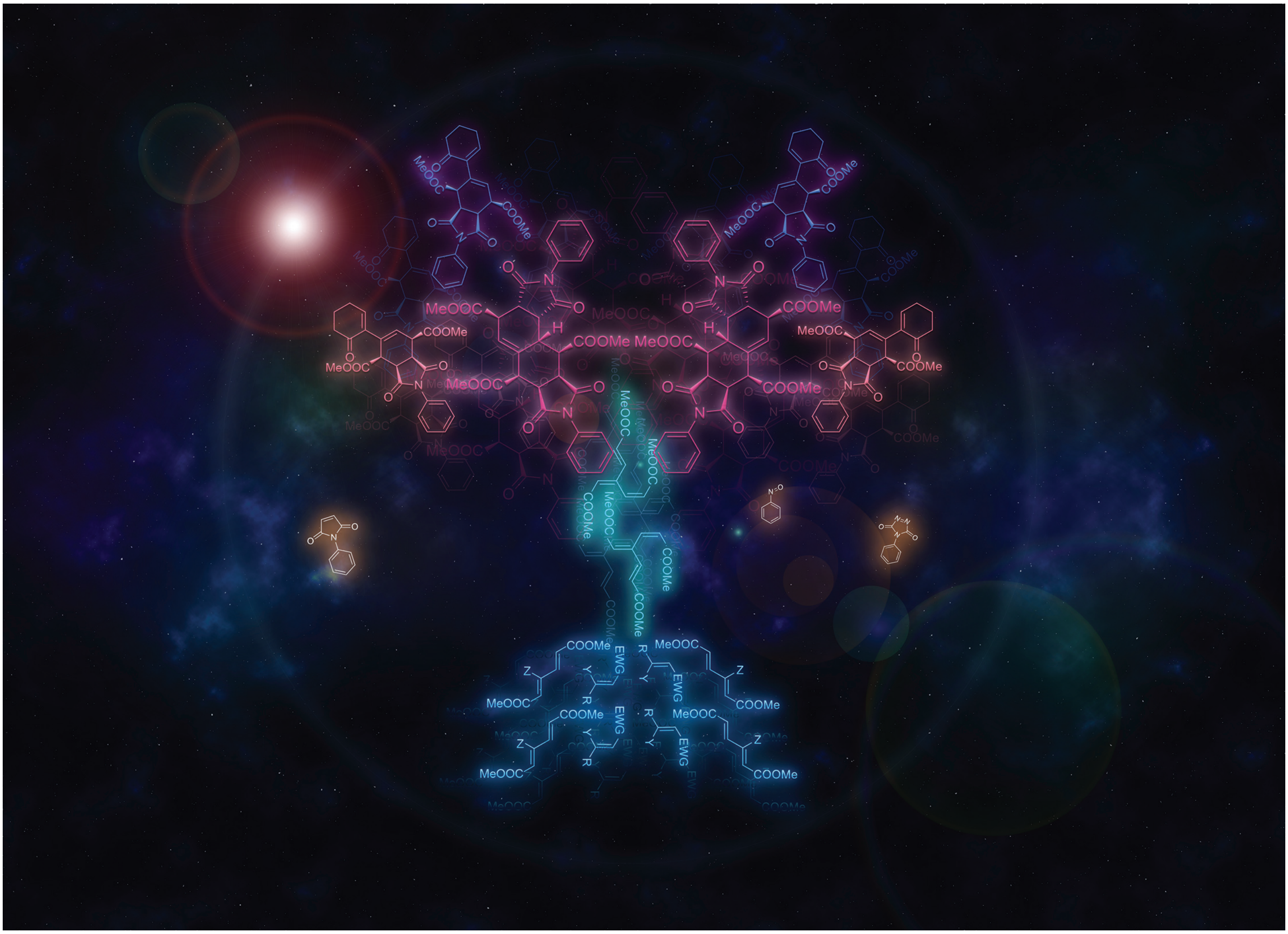

Showcasing research from Professor Milan Pour's laboratory, Faculty of Pharmacy in Hradec Králové, Charles University, Hradec Králové Region, Czech Republic.

Synthesis of highly polarized [3]dendralenes and their Diels–Alder reactions

While the Diels–Alder reactions of two electron-deficient partners are believed to be disfavored, this work shows that highly electron-deficient dendralene trienes, prepared *via* coupling chemistry from methyl propiolate in three steps, undergo selective diene-transmissive Diels–Alder reactions with highly electron-deficient dienophiles.

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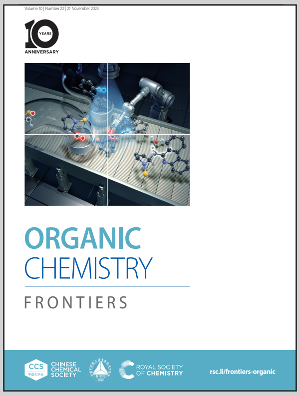
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Synthesis of highly polarized [3]dendralenes and their Diels–Alder reactions†

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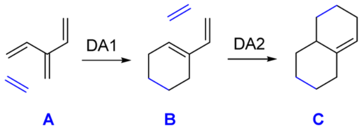
The diene-transmissive Diels–Alder (DTDA) reactions of dendralenes are emerging as a powerful synthetic tool. To date, these processes have been studied with non-polarized or mildly polarized species. We now present an expedient synthesis of strongly electron-deficient [3]dendralenes and demonstrate, for the first time, their DTDA reactions with electron-poor dienophiles. While the combination of two electron-poor partners is believed to be generally disfavored, DTDA reactions reported herein proceed at 100 °C with high yields and stereoselectivities. DFT calculations show that this electronically disfavored process is encouraged by a steric effect of the vinylic moiety within the dendralene core, driving the diene segment into the s-*cis* conformation, thereby lowering the activation energy by 2–3 kcal mol^{-1}. While the free energy barrier is typically lower for the second cycloaddition, the two barriers become similar for dendralenes with a cyclic enone fragment, which allows a controlled stepwise addition of two different dienophiles.

Introduction

Diels–Alder (DA) addition is indisputably one of the most efficient synthetic tools, as it is capable of assembling a six-membered ring with up to 4 chiral centers in a single step.[1] According to general consensus, these reactions are concerted and governed by frontier orbital interactions, where an electron-rich conjugated diene typically reacts with an electron-poor dienophile; an inverse-demand scenario, using an electron-poor diene and an electron-rich dienophile is also viable.[2] On the other hand, Diels–Alder reactions of two highly electron-deficient partners (substituted with two or more EWGs)[3] are rare and require harsh conditions to proceed. The first example was reported by Alder, who showed that the addition of (2*E*,4*E*)-dimethyl hexa-2,4-dienedioate to maleate and/or fumarate required heating at 170 °C for 10–15 h, giving rise to the corresponding adducts in 40–50% yield.[3a]

Among the potential substrates for DA reactions, dendralenes stand out as a distinct class of cross-conjugated entities.[4] The interest in these intriguing hydrocarbons[5,6] stems mainly from their ability to undergo two or more consecutive DA reactions in an interconnected manner (Diene Transmissive Diels–Alder Reactions, DTDA, Scheme 1). The archetypal DTDA reaction of [3]dendralene with ethylene (**A**) shows that the reorganization of π-electrons in a DA process results in the formation of intermediate **B** that can participate in another DA reaction. Consequently, this DTDA domino sequence represents a very attractive process, as it allows the formation of a minimum of four new bonds, two cycles, and numerous chiral centers.

As evidenced by, *e.g.*, the behavior of [3]dendralene (**1**), unsubstituted representatives suffer from enhanced reactivity and, therefore, limited stability. Thus, for example, DA dimerization of this triene affords the monocyclic tetraene **2**



Scheme 1 [3]Dendralene and its DTDA reaction with ethene.

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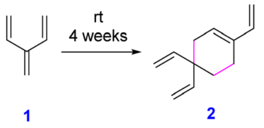
† Electronic supplementary information (ESI) available: Experimental details, spectral data, and copies of NMR spectra. CCDC 2238545. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d3qo01221b**



Scheme 2 Self-dimerization of [3]dendralene.

(Scheme 2),[4–6] in which it resembles cyclopentadiene. Notably, this DA reaction takes place at the central, most sterically demanding double bond.

It can be assumed that the reactivity of [3]dendralenes in DA reactions is controlled by charge distribution in the substrate and/or in the reaction intermediates, together with conformational factors, influencing the mutual disposition of the core double bonds. Since an absolute majority of dendralene derivatives studied to date includes compounds with non-polarized or just mildly polarized C=C bonds,[7] we set out to prepare a series of more polarized dendralenes, and address these issues by a combination of experimental and high-level theoretical approach. We expected that the attachment of polar functional groups to the dendralene scaffold would harness their reactivity both electronically and sterically. As a consequence, entirely new opportunities to achieve enhanced structural diversity of the products of DTDA sequences were likely to arise as well.

Results and discussion

The existing knowledge of dendralene behavior has been gathered mainly from the neutral or slightly polarized species. We reasoned that variation of the electron density and polarization of the core cross-conjugated triene structure by introducing electron withdrawing (EWG) and/or electron donating (EDG) groups may have a huge impact on their reactivity, decrease the propensity for dimerization (**1** → **2**), and perhaps enable other reactions to be performed.

Initial DFT calculations of the unsubstituted [3]dendralene (**1**) revealed partial negative charges at all the terminal CH_2 carbons (−0.34 to −0.37), whereas the internal carbons of the vinyl groups **CH**=CH_2 exhibit smaller charges (−0.21 and −0.22, respectively) (Fig. 1). By contrast, the central carbon of the methylene group **C**=CH_2 carries yet smaller negative charge (−0.10), which renders this double bond most polarized. This finding may rationalize the previously observed[8] preferential cyclopropanation of the central π bond in [3]dendralene (**1**) or the unusual regioselectivity of the dimerization of **1**, outlined in Scheme 2.

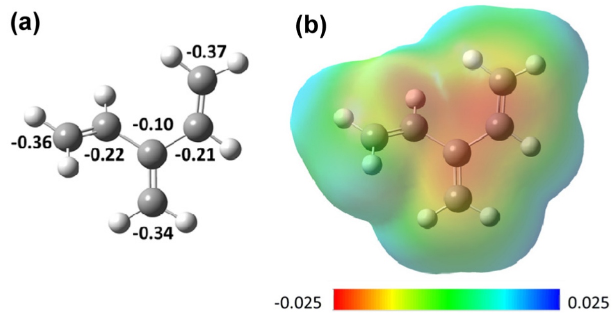


Fig. 1 (a) NBO charges and (b) electrostatic potential map of [3]dendralene (**1**).

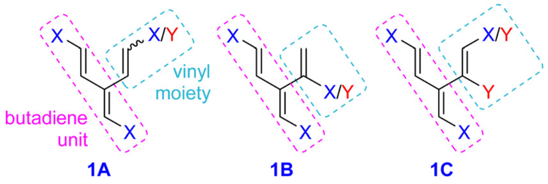


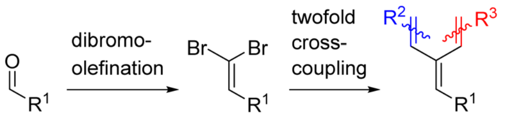
Fig. 2 X = EWG, Y = EDG, alkyl, or aryl.

To increase the polarization of the dendralene core, we set out to prepare novel [3]dendralenes, equipped with strongly electron-withdrawing groups (EWG) at the terminal sp^2 positions of the "western butadiene unit" and with EWG or EDGs at the "eastern vinyl moiety" (Fig. 2).

Synthesis of substituted [3]dendralenes

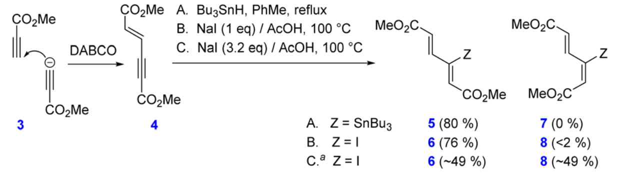
While a number of recent syntheses have opened access to limited subseries of dendralenes,[7] a general approach to substituted dendralenes was reported only in a recent paper[9] by the Sherburn group (Scheme 3). Notably, the substitution pattern, reported to date, includes alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups, *i.e.*, those, the electronic effects of which are rather small or conveyed by conjugated π-systems (Ar, HetAr). Several papers[7a,10] reported derivatives with one or two EWGs but compounds, in which all terminal sp^2 atoms of the dendralene backbone would be decorated with typical EWGs or EDGs, have not yet been described. Needless to say that, being equipped with strongly polarizing functional groups, rather than just with alkyls, the products can be expected to offer broader synthetic variability *via* subsequent functional group transformations.

Whereas efficient construction of these cross-conjugated alkenes calls for cross-coupling processes (Scheme 3), we felt that a more convergent synthesis, relying on propiolate additions would offer a truly attractive opportunity for the construction of the "western butadiene unit" bearing two $-CO_2Me$ groups at its termini (Fig. 2), which would present a versatile coupling partner for introducing a substituted vinylic moiety (the "eastern unit") *via* a selective hydrometallation or hydroiodination (Scheme 4).



R^1, R^2, R^3 = R, Ar, HetAr, alkenyl, alkynyl

Scheme 3 General synthesis of dendralenes by Sherburn.[9]



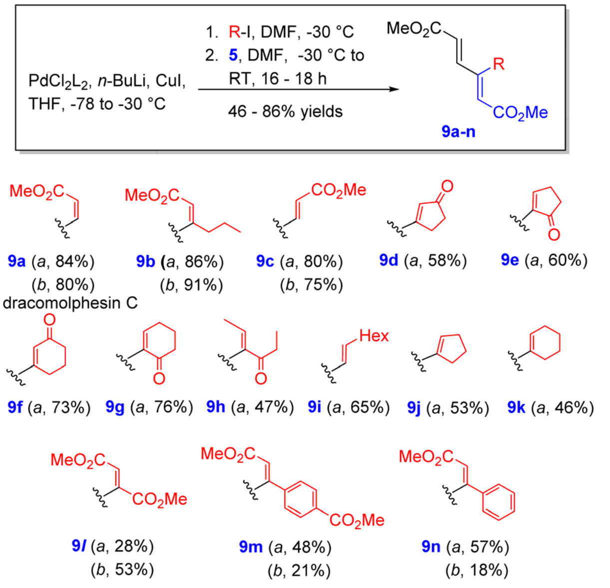
Scheme 4 Preparation of the diene coupling partners. ^{a} NMR yield.

Dimethyl (*E*)-hex-2-ene-4-ynedioate (**4**) was thus prepared in a nearly quantitative yield from methyl propiolate upon treatment with DABCO[11] (Scheme 4). Subsequent radical hydrostannation with Bu$_3$SnH afforded pure (2*Z*,4*E*)-3-tributylstannylhex-2,4-dienedioate **5** in 80% yield; no (2*E*,4*E*)-isomer **7** was detected. On the other hand, stereoselectivity of hydroiodination with NaI/AcOH turned out to be strongly dependent on the amount of NaI, giving rise to the almost pure isomer **6** with 1 equiv. of NaI (76% after crystallization). By contrast, using a three-fold excess of NaI resulted in the formation of a 1 : 1 mixture of the stereoisomers **6** and **8** in a practically quantitative yield, as revealed by the ^{1}H NMR spectrum of the crude product.

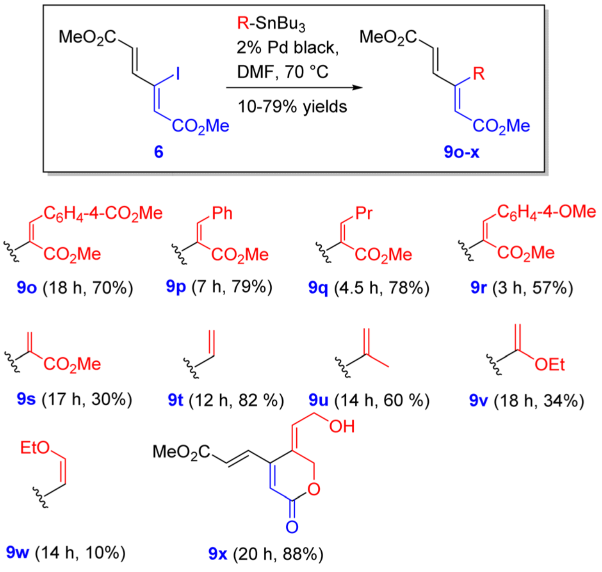
Next, following an extensive developmental experimentation, the stannyl derivative **5** was subjected to the Pd-catalyzed cross-coupling with vinylic iodides R–I (Scheme 5). The optimized protocol required *in situ* generation of the highly active 14-electron catalyst[12] Pd(TFP)$_2$ from PdCl$_2$(TFP)$_2$ (3 mol%) on reduction with *n*-BuLi (6 mol%) at −78 °C, which was followed by addition of CuI (0.9 equiv.); here, the temperature must be kept below −30 °C to avoid the formation of Pd mirror on the wall of the reaction flask. Subsequent addition of the vinyl iodide R–I (1.25 equiv.) and then addition of the vinylstannane **5** (1.0 equiv.) effected the desired coupling, presumably *via* a Pd–Sn–Cu transmetalation.[13] The resulting dendralenes **9a–n** were obtained in fair to good yields, depending on the substitution pattern (Scheme 5).

The highest yields were attained for derivatives **9a–9c**, where all three terminal atoms of the dendralene core carry EWGs (type **1A**). Notably, dendralene **9a** has recently been isolated by Ren *et al.* as a natural product[14] from plant material and named dracomolphesin C. There was negligible difference between derivatives **9d** and **9e**, in which the cyclopentenone unit is appended *via* its β- and α-position, respectively, and practically no difference in efficiency was observed in the formation of their cyclohexenone analogues **9f** and **9g**, while their acyclic counterpart **9h** was obtained in a lower yield. Simple alkenyl substituents were introduced with a good yield for the acyclic (*Z*)-oct-2-enyl (**9i**, 65%) and the cyclopentenyl (**9j**, 53%) derivatives, while a moderate yield was attained for the cyclohex-1-enyl congener (**9k**, 46%). The disubstituted alkenyl moieties were also coupled efficiently (**9*l*–9n**), with a markedly higher yield for **9n** (57%). Replacement of the TFP ligand[15] with JohnPhos[16] led to a notable yield improvement for **9*l***, while in the case of **9a–9c** the two phosphines turned out to be comparable. Apparently, the JohnPhos-Pd complex prefers the strongest π-acid (*i.e.*, the fumarate moiety, as in **9l**), whereas weaker π-acids are favored by the TFP-Pd catalyst. All in all, the yields of this reaction seem to indicate higher dependence on steric, rather than electronic demands of the vinyl halide coupling partner.

Yet another subseries was prepared from vinyl iodide **6** and the corresponding, readily available vinyl stannanes, using our protocol,[17] based on a heterogeneous Pd black catalysis (Scheme 6). Since this procedure employs **6** as the vinyl halide partner, the reaction times and yields reflect the rate of transmetalation and the stability of the vinyl stannanes R-SnBu$_3$. Using this variant, acrylate derivatives **9o** and **9p** were



Scheme 5 Preparation of substituted dendralenes **9a–9n**; (*a*) L = TFP; (*b*) L = JohnPhos.



Scheme 6 Preparation of dendralenes **9o–w**; **9x** was synthesized previously.[18]

obtained in considerably higher yields than their regio- and stereoisomers **9m** and **9n**. Triesters **9q** and **9r** were also formed in good yields (78 and 57%, respectively). Cross-coupling of **6** with tributylvinylstannane furnished **9t** in an excellent yield (82%), while an additional CH_3 group caused a decline to 60% for **9u**. The lowest yields were obtained for the vinyl ester **9s** (30%), and vinyl ethers **9v** (34%) and **9w** (10%), presumably as a result of the limited stability of the starting (ethoxyvinyl)tributylstannanes at 70 °C. Lactone **9x** was prepared previously by us[18] in the same way from **6** and (*E*)-2-tributylstannylbut-2-en-1,4-diol. While this attractive heterogeneous protocol worked well for the coupling of β-iodoacrylate **6**, all attempts to prepare the previous series **9a**–**9n** using this procedure either failed or gave inferior yields.

Natural population analysis[19] of DFT calculations shows that in triester **9a**, the β-carbon atoms of the two acrylic moieties possess, as expected, a less negative charge (−0.12, −0.11) than the α-carbons (−0.29, −0.30) and that these two double bonds are, overall, more electron deficient than those of the vinyl groups of the parent hydrocarbon **1** (Fig. 1) as a result of the electron-withdrawing effect of the ester groups (Fig. 3). Notably, their polarization, defined as a difference of the charges at neighboring carbons, in **1** and **9a** is 0.15 and 0.17, respectively. The central carbon atom in **9a** practically lost its negative charge (−0.01) and the overall polarization of the central C═C moiety remains the largest (0.25), similarly to **1** (0.24). The stereoisomer **9c** exhibited very similar characteristics.

Diels–Alder reactions of [3]dendralenes

With the dendralenes in hand, the DTDA reactions were explored, using triester **9a** as a model compound. Given the electron-deficient nature of its double bonds, inverse electron demand DA reactions with electron-rich dienophiles could be anticipated. However, **9a** failed to react with typical electron-rich dienophiles, such as 3,4-dihydro-2*H*-pyran, bis-trimethylsilylacetylene, cyclopentadiene and furan; only the starting materials were recovered even upon a prolonged heating at reflux in xylene in all these cases.

By contrast, treatment of **9a** with *N*-phenylmaleimide (**10**), one of the most reactive electron-poor, *endo*-selective dienophiles,[20] resulted in a very slow formation of the adduct at ambient temperature (Scheme 7). Upon heating in xylene with 2.5 equiv. of **10** at 100 °C for 48 h, the reaction proceeded readily to completion, giving rise to the bis-adduct **12a** as a single isomer in 78% yield (Scheme 7). Of other electron-deficient dienophiles, **9a** failed to react with 1,4-benzoquinone, 1,4-naphthoquinone or cyclopentene-1,3-dione or gave complex mixtures on treatment with dimethyl fumarate or maleate. While Lewis-acid catalysis is known to accelerate DA reactions of enone-type dienophiles, it failed to promote the reaction in this case. Attempted DA addition of acroleine and cinnamaldehyde to **9a**, carried out in the presence of MacMillan's secondary amines[21] as organocatalysts (*via* the corresponding highly reactive iminium intermediates), also failed, which is in contrast with the success reported for electron-rich dendralenes.[22] The isomeric triester **9c** exhibited similar behavior, affording the bis-adduct **12c** in high yield over a shorter period of time (using 2.5 equiv. of **10**).

The reactivity pattern was further investigated using trienes **9i** (simple alkenyl) and **9t** (unfunctionalized vinyl group) that were also treated with *N*-phenylmaleimide (**10**) (2.5 equiv.) under the same conditions as those applied for **9a**. Again, formation of the products of double DA addition, namely **12i** and **12t** was observed, both in the yields exceeding 70%; no traces of other products were detected. It is pertinent to note that when the reactions of any of the dendralenes **9a,c,i,t** were carried out in the presence of just 1.1 eq. of **10**, only the corresponding bis-adducts **12** were detected, together with *ca.* half of the unreacted starting material, showing that the second DA

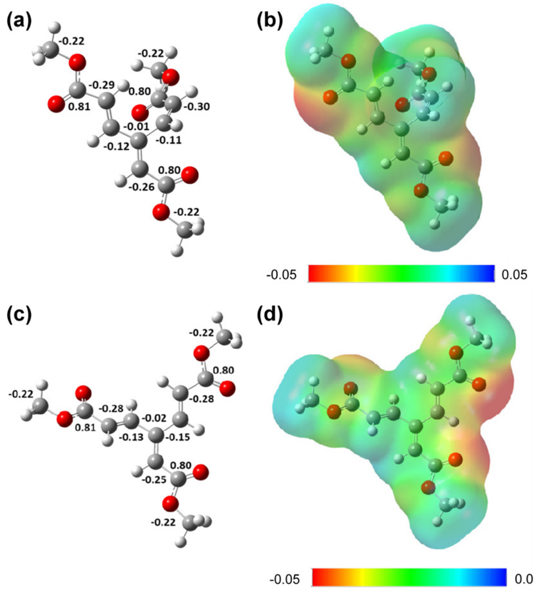
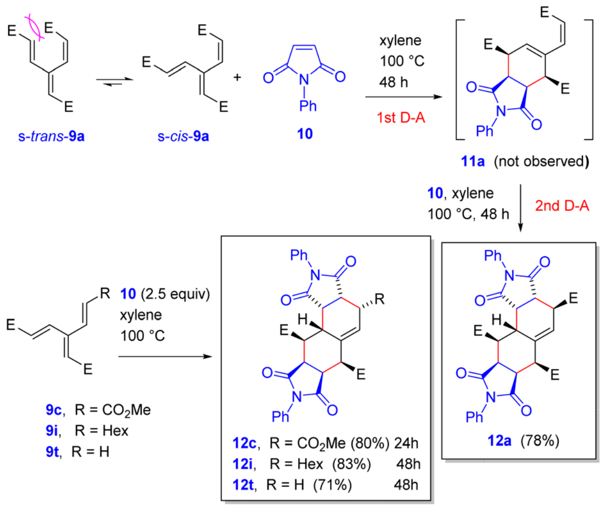


Fig. 3 NBO charges (a and c) and electrostatic potential surfaces (b and d) in [3]dendralene derivatives **9a** (a and b) and **9c** (c and d).



Scheme 7 DTDA reactions of **9a**, **9c**, **9i**, and **9t**; E = CO_2Me.

reaction proceeds faster than the first one. The structure of all products **12**, including stereochemistry, was deduced from their NOE spectra, and was corroborated by X-ray crystallography in the case of **12i** (see the ESI†).

Under the same conditions as those given in Scheme 7, the cyclopentenone derivative **9e** followed the suite, giving rise to the bis-adduct **12e** on reaction with maleimide (**10**), and so did the cyclohexenone derivative **9g**, which gave the pentacycle **12g** (Fig. 4). In addition, an interesting pentacyclic lactone (**12x**) was obtained from lactone **9x.**[18]

In sharp contrast to the reactions of **9a,c,i**, and **9t** (*vide supra*), modification of the reaction conditions for **9e** and **9g** (temperature decrease from 100 to 70 °C, dendralene : maleimide ratio 2 : 1, extended reaction time) enabled us to obtain monoadducts **11e** and **11g** in high yields (Scheme 8). Hence, the addition of another, different dienophile became a distinct possibility. Indeed, the latter diesters **11e** and **11g** readily reacted with *N*-phenyl-1,2,4-triazol-2,5-dione (**13**, *vide infra*) to afford the hetero bis-adducts **14e** and **14g**, respectively. Under similar conditions, dendralenic lactone **9x** was unreactive to both dienophiles. Interestingly, when diester **9g** was treated with triazole **13** first, only the corresponding bis-adduct **15g** was isolated.

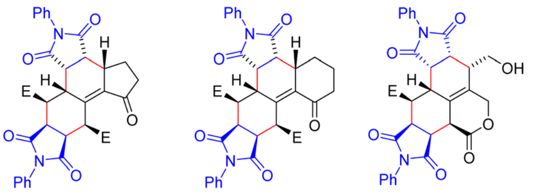
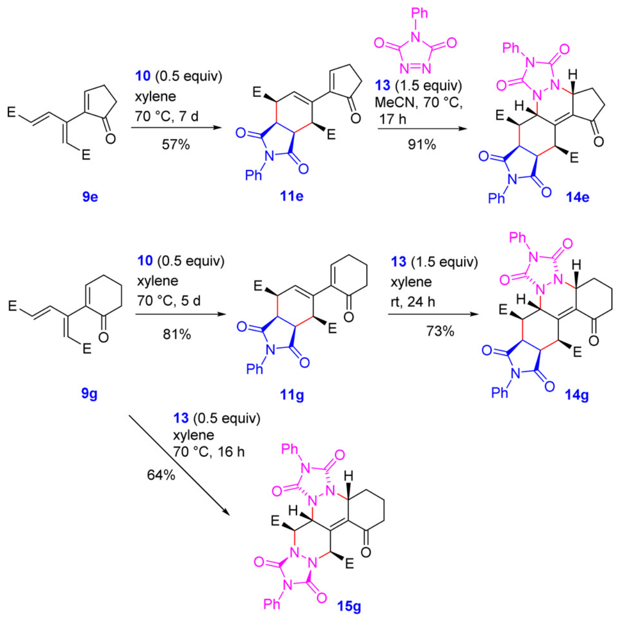
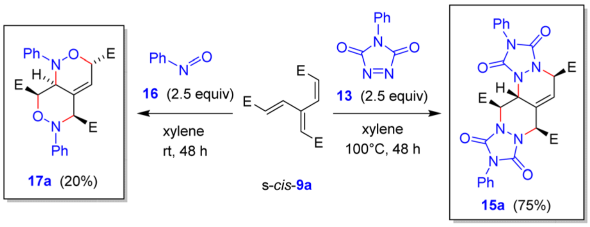

12e (86%, 48 h) **12g** (72%, 48 h) **12x** (62%, 19 h)

Fig. 4 Products of DTDA reactions of **9e**, **9g**, and **9x** with **10** (2.5 equiv., xylene, 100 °C); E = CO_2Me.



Scheme 8 Sequential reactions of **9e** and **9g** with two different dienophiles.

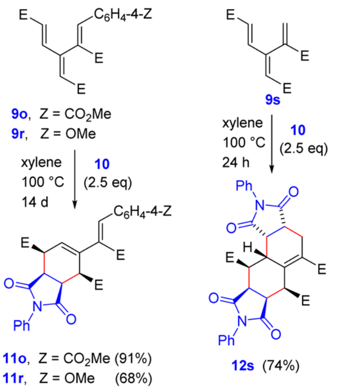


17a (20%) **15a** (75%)

Scheme 9 DTDA reactions of **9a** with nitrosobenzene (**16**) and *N*-phenyl-1,2,4-triazol-2,5-dione (**13**).

Treatment of **9a** with other highly reactive heterodienophiles, such as $(ClSO_2)N{=}C{=}O$, $(Cl_3CCO)N{=}C{=}O$, $CH_2{=}C(CN)Cl$, and singlet oxygen $^1O_2$ (generated from H_2O_2 and Na_2MoO_4[23]) were unsuccessful. On the other hand, nitrosobenzene (**16**) (2.5 equiv.) turned out to react at room temperature (Scheme 9), giving a rather intractable mixture, from which the bis-adduct **17a** was isolated in 20% yield.[24,25] More successful was the experiment with *N*-phenyl-1,2,4-triazol-2,5-dione (**13**), which afforded the bis-adduct **15a** in 75% yield.

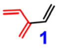
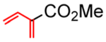
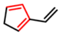
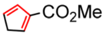
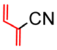
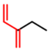
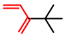
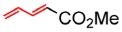
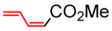
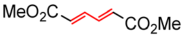
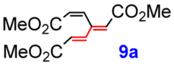
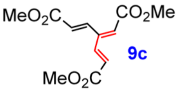
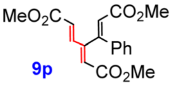
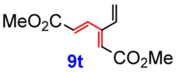
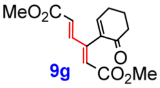
Formation of the tetracyclic products **12a**, **12c**, **12i**, **12t**, **15a**, pentacyclic compounds **12e**, **12g**, **12x**, and hetero adducts **14e** and **14g** provides evidence that it was the dienic fragment with two ester groups at the termini (Scheme 7), where the first cycloaddition must have occurred. The configuration of all adducts **12**, **14** and **15** corresponds to the *endo*/*endo* selectivity for both additions, with the second dienophile approaching the corresponding intermediate **11** from the less hindered convex face (*endo–anti–endo*). The only exception is the configuration of **17a**, whose stereochemistry indicates the direction of the second attack from the *more* hindered face of **11** (note, however, that it was only formed in 20% yield). In partial contrast, trienes **9o** and **9r** with a sterically more demanding "eastern" vinylic unit followed the same pattern, but only the monoadducts **11o** and **11r** were isolated (in 91% and 68% yields, respectively) (Scheme 10). On the other hand,



11o, Z = CO_2Me (91%)
11r, Z = OMe (68%)
12s (74%)

Scheme 10 DA reactions of **9o**, **9r** and **9s** with **10**; E = CO_2Me.

Table 1 Relative Gibbs free energies[a] for transition states ($\Delta G^{\ddagger}$) and products (ΔG) of the DA reaction in of various substituted dienes (diene functionality highlighted in red) with dienophile (DP; **10** or **13**) as well as the energy difference between s-*cis* and s-*trans* conformers ($\Delta G_{t\rightarrow c}$) for selected dienes

Entry	Diene	DP	$\Delta G_{t\rightarrow c}$	$\Delta G^{\ddagger}_{endo}$	$\Delta G^{\ddagger}_{exo}$	ΔG_{endo}	ΔG_{exo}
1		**10**	3.1	27.5	30.4	−31.3	
2	 **1**	**10**	−1.0	24.3	27.5	−35.8	
3		**10**	—	23.7	26.8	−16.1	−15.9
4		**10**	−0.3	24.0	26.7	−36.3	
5		**10**	—	23.7	25.8	−18.1	−17.9
6		**10**	—	23.7	26.6	−17.0	−16.5
7		**10**	2.5	27.9	30.1	−33.4	
8		**10**	1.8	24.6	28.8	−33.9	
9		**10**	−1.7	24.4	27.1	−36.5	
10		**10**	2.8	28.4	31.4	−26.7	−28.1
11		**10**	5.1	32.4	34.6	−30.1	−28.6
12		**10**	2.7	30.2	32.7	−22.3	−23.7
13	 **9a**	**10**	2.2	28.3	30.9	−23.1	−27.5
14	 **9c**	**10**	−3.2	27.6	29.8	−26.2	−32.0
15	 **9p**	**10**	2.4	28.3	30.1	−24.6	−30.8
16	 **9t**	**10**	−0.4	28.0	30.4	−24.8	−30.2
17	 **9g**	**10**	2.4	28.2	30.7	−23.3	−29.0
18	**9g**	**13**	2.4	23.6	33.2	−31.6	−31.7

[a] Gibbs free energies in kcal mol^{-1} at 298.15 K and 1 atm. Calculations were carried out with ωB97X-D/6-311+G(2d,p)//6-31+G(d,p) level of theory for xylene as the solvent. Reaction enthalpies can be found in Table S6.†

triene **9s** with the less encumbered "eastern" vinylic moiety afforded the bis-adduct **12s** in 74% yield.

Theoretical approach to the Diels–Alder reactions of [3] dendralenes

To shed light on the behavior of the electron-deficient dendralenes in DTDA reactions, Gibbs free energies for the individual DA additions were calculated using a series of diene substrates and *N*-phenylmaleimide as a dienophile (Table 1). In our calculations, we employed ωB97X-D[26] DFT functional, calibrated against CCSD(T)/CBS energies (for details, see ESI, section 4.2), and which has been reported to be suitable for optimization of transition state geometries.[27] On average, the ωB97X-D method gives energies 3.5 kcal mol^{-1} higher for DA TS and 1.7 kcal mol^{-1} higher for the DA products than the CCSD(T)/CBS limit.

To elucidate the effect of the electronic structure, we set out to compare the reactivity of various substituted [3]dendralenes with their 1,3-butadiene analogues (Table 1 lists Gibbs free energies; enthalpies for the reaction as orbital energies for the dienes can be found in Table S6†). In line with the Alder *endo* rule[28] and our experiments (Schemes 7–10), calculations predict the preference for the *endo* pathway (Table 1).

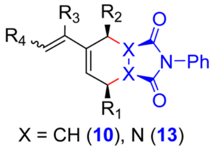
The calculated barrier for the reaction of unsubstituted 1,3-butadiene with *N*-phenylmaleimide (**10**) was found to be 27.5 kcal mol^{-1} (Table 1, entry 1); according to the literature, the reaction requires 24 h at 20 °C in benzene, to give the product in 91% yield.[20] On the other hand, the barrier for the *exo* pathway would be by ~3 kcal mol^{-1} higher (30.4 kcal mol^{-1}, entry 1). The reaction of **10** with the unsubstituted [3] dendralene **1** has a notably lower barrier of 24.3 kcal mol^{-1} (Table 1, entry 2) than that of butadiene and is known to take place at room temperature in toluene within 48 h with 83% yield.[29] Hence, according to the calculations, the addition of a vinyl group (as in **1**) reduces the energy barrier by about 3 kcal mol^{-1} compared to 1,3-butadiene. This result might, *a priori*, be attributed to the change of the electronics of the system, which would make the molecule more reactive. However, the same increase in reactivity can be observed by constraining the diene moiety in the s-*cis* conformation, as in cyclopentadiene, whose activation barrier is calculated to be 23.7 kcal mol^{-1} (Table 1, entry 3). Experimentally, the reaction between cyclopentadiene and **10** takes place at 20 °C in benzene within 15 min to afford the adduct in 98% yield.[20] Interestingly, since the energy of the s-*cis* butadiene is by 3.1 kcal mol^{-1} higher than that of its most stable s-*trans* rotamer (Table 1, entry 1), the hypothetical s-*cis* butadiene would exhibit the same reactivity with a barrier of 27.5–3.1 = 24.4 kcal mol^{-1}.

To find out whether the steric or electronic effects are responsible for the enhanced reactivity of [3]dendralenes, further calculations were performed. The presence of the vinyl group lowers the $\Delta G^{\ddagger}$ (Table 1; compare entries 1 and 2) and a similar effect was observed for an ester group appended to that position (Table 1, entry 4), which may seem to support the electronics argument. However, introduction of a vinyl or ester group to cyclopentadiene (Table 1, entries 5 and 6) was found not to affect the calculated barrier, despite significantly changing the HOMO orbital energies of the dienophiles (from −8.2 eV for cyclopentadiene to −8.0 and −8.6 eV, respectively, see Table S6†). Furthermore, the barrier for 2-cyanobuta-1,3-diene (27.9 kcal mol^{-1}; Table 1, entry 7), in which the rod-shape CN group presents much less steric influence, was found to be almost equal to the barrier of 1,3-butadiene itself (Table 1, entry 1), despite the conjugation effect and the −0.7 eV change in the HOMO orbital energy (Table S6,† entries 1 and 7). On the other hand, for ethyl and *t*-butyl group as a substituent, the barrier was found to decrease by ~3 kcal mol^{-1} (24.6 and 24.4 kcal mol^{-1}; entries 8 and 9) with respect to the 1,3-butadiene transition state (27.5 kcal mol^{-1}; Table 1, entry 1). The common factor for these two examples is the stabilization of the s-*cis* conformation (by 1.3 and 4.8 kcal mol^{-1}, respectively, compared to butadiene), which should lower the energy barrier for the DA reaction. Therefore, we can conclude that the vinylic group stabilizes the s-*cis* conformation of the diene moiety, required for the DA reaction to occur, which decreases the energy barrier for [3]dendralene.

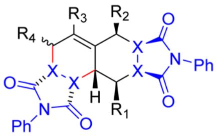
The enhancing effect of the vinyl group is mitigated by the electron-withdrawing ester groups in the butadiene segment at 1,4-positions. Their presence results in an increase of the energy barrier by 1–3 kcal mol^{-1} (compare entry 1 with 10 and 12 in Table 1). Furthermore, configuration of the "eastern" double bond has a significant impact on the activation barrier. As shown above, the transition state energy for methyl (*E*)-penta-2,4-dienoate is by ~4 kcal mol^{-1} lower than that for its (*Z*)-isomer (compare entries 10 and 11). These results take account for the way of formation of the addition products **12a, c,e,i,t**: the first DA addition occurs always at the site of the (*E*,*E*)-dienoate, since otherwise one of the ester groups would get into a steric clash. In conclusion, for substituted [3]dendralenes, the deactivating electronic effect exercised by the ester groups is partially offset by stabilizing the s-*cis* conformation owing to the steric effect of the vinyl group.

The full two-step DTDA reaction pathway, experimentally examined for **9a**, **9c**, **9p**, and **9t**, was also investigated theoretically and compared with the reactivity of unsubstituted [3]dendralene (**1**) (Table 2, entry 1). The calculated first energy barrier for these substrates is *ca.* 28 kcal mol^{-1} (Table 2, entries 2–5; the transition states corresponding to entry 2 are shown in Fig. 5). This rather high value may explain the required high temperature and long reaction time in comparison with the unsubstituted [3]dendralene **1** (24.3 kcal mol^{-1}; Table 2, entry 1). The second energy barriers for [3]dendralenes **1** and **9t** are 23.4 and 20.7 kcal mol^{-1}, respectively (entries 1 and 5). The relative energy for TS2 is lower than that associated with TS1 by 0.9 kcal mol^{-1} for **1** and 7.3 kcal mol^{-1} for **9t**, which apparently prevents the detection of the *mono*-adducts during the reaction. The larger decrease of the barrier for **9t** presumably originates from the absence of EWGs in the

Table 2 Gibbs free energies for *endo* transition states and products of the DA reaction of dendralenes **9a,c,p,t,g** with dienophiles (DP) **10** and triazole **13**[a]



first addition[b]



second addition

Entry	Diene	DP	$\Delta G^{\ddagger}_{\text{TS1}}$	$\Delta G_{\text{1st addition}}$	$\Delta G^{\ddagger}_{\text{TS2}}$ [b,c]	$\Delta G_{\text{2nd addition}}$ [c]	$\Delta\Delta G_{\text{TS2–TS1}}$
1	**1**	**10**	24.3	−35.8	23.4 (27.8)	−32.4 (−31.3)	−0.9
2	**9a**	**10**	28.3	−23.1	23.0 (31.1)	−34.7 (−28.9)	−5.3
3	**9c**	**10**	27.6	−26.2	22.2 (29.0)	−29.6 (−24.9)	−5.4
4	**9p**	**10**	28.3	−24.6	28.2 (33.8)	−24.3 (−20.6)	−0.1
5	**9t**	**10**	28.0	−24.8	20.7 (27.9)	−34.8 (−28.6)	−7.3
6	**9g**	**10**	28.2	−23.3	27.5 (30.1)	−24.5 (−26.5)	−0.7
7	**9g**	**13**	23.6	−31.6	19.8 (29.4)	−31.6 (−31.7)	−3.8

[a] Gibbs free energies in kcal mol^{-1} at 298.15 K and 1 atm. Calculations were carried out with ωB97X-D/6-311+G(2d,p)/6//6-31+G(d,p) level of theory in xylene. [b] Values are given for the preferred *endo* TS, values for *exo* TS can be found in Table 1 for the first addition, or in brackets for the second addition. [c] Free energy relative to *endo*-(**11** + dienophile) system.

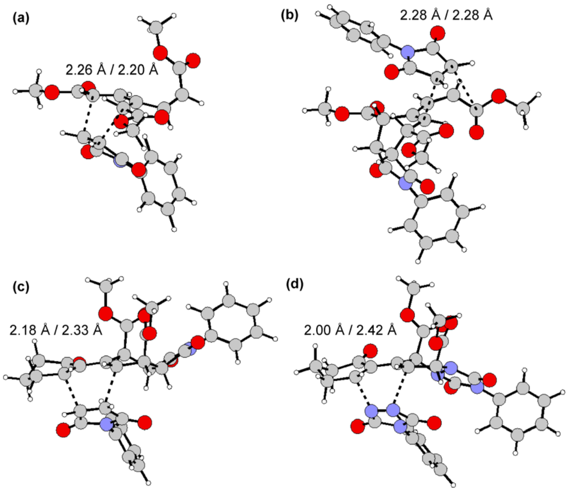


Fig. 5 *endo* transition state of the first (a) and second (b) step of the reaction of **9a** with **10** and for the second step of reaction of **9g** with **10** (c) and **13** (d).

position R^4 and stabilization of the s-*cis* conformation. On the other hand, the reaction of **9o** and **9r** stops at the stage of the *mono*-adduct. In that case, for **9p**, serving as their model, the relative energies of TS for both steps are practically identical (TS1 = 28.3 and TS2 = 28.2 kcal mol^{-1}, respectively; entry 4). The relatively high TS2 barrier here is influenced by the presence of the EWG and an impaired access to the newly formed diene system. These results also provide a rationale for the experimentally observed *endo* selectivity. For all these structures, the TS1 energy barrier is lower for the *endo* form. In the second step, the dienophile approaches the diene from a less sterically hindered convex side and formation of the *endo* isomer is favored again.

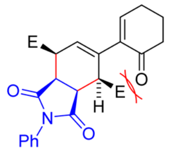


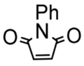
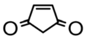
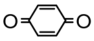
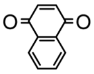
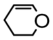
Fig. 6 Steric clash between carbonyl oxygen and hydrogen in the s-*cis* conformation of **11g**, which is present in the TS of the second DA reaction step.

We also investigated the reactions of **9g** with maleimide **10**, where the product of the first addition can be isolated (*vide supra*) and then can undergo a second addition in a controlled manner with the same (**10**) or different (**13**) dienophile.

For comparison, we studied the reaction of **9g** with triazole **13**, which could not be stopped at the first step. Comparison of the reaction barriers of the first step and the barriers in the second step (Table 2, entries 6 and 7) shows that the first barrier is lower for **13** compared to **10** by 4.6 kcal mol^{-1}. However, while the second barrier for **10** is only marginally lower than that for the first addition (by 0.7 kcal mol^{-1}), in the case of **13** it is considerably lower (by 3.8 kcal mol^{-1}). The reason for the barrier of the second step in reaction with **10** not being substantially lower (unlike for **9a**, **9c**, and **9t**), is probably the steric clash between the keto group of the cyclohexenone ring with one of the ester groups (Fig. 6), which drives the diene system out of planarity. The substantial difference in barriers for both steps found for dienophiles **10** and **13** might originate from the nature of the corresponding transition states, which are more symmetrical in the case of **10** than in **13**, as revealed by the distance of the reacting atoms (dotted lines) (Fig. 5): the more symmetric TS imposes larger constraints on both the bonds being formed, which in turn leads to stronger ketone/ester steric clash. Furthermore, the adducts with **13** seem to be less sterically congested than their counterparts arising from **10**.

Finally, we also theoretically studied the reactions between **9a** with various dienophiles (Table 3 and Table S7†). Unlike maleimide, other dienophiles, namely cyclopentadiene, furan, cyclopent-4-ene-1,3-dione, 1,4-benzoquinone, 1,4-naphthoqui-

Table 3 Gibbs free energies for transition states and products of the DA reaction of dendralene **9a** with various dienophiles[a]

Entry	Dienophile	$\Delta G^{\ddagger}_{endo}$	$\Delta G^{\ddagger}_{exo}$	ΔG_{endo}	ΔG_{exo}	Reaction yield
1	 **10**	28.3	30.9	−23.1	−27.5	78%[b]
2	PhN=O **14**	27.8	36.0	−6.7	−5.3	20%[c]
3		30.5	33.7	−16.5	−18.7	No reaction
4		38.0	40.0	−4.7	−6.4	No reaction
5		32.6	32.8	−14.4	−19.1	No reaction
6		30.3	32.0	−17.9	−21.9	No reaction
7		29.7	32.3	−17.8	−21.0	No reaction
8		37.7	37.5	−17.4	−21.8	No reaction

[a] Gibbs free energies in kcal mol^{-1} at 298.15 K and 1 atm. Calculations were carried out with ωB97X-D/6-311+G(2d,p)/6//6-31+G(d,p) level of theory in xylene. [b] 100 °C, 48 h, bis-adduct (**12a**). [c] rt, 48 h, bis-adduct (**17a**). Reaction enthalpies can be found in Table S7.†

none, and 3,4-dihydro-2*H*-pyran, exhibit calculated barriers of about or more than *ca*. 30 kcal mol^{-1} or higher respectively (Table 3, entries 3–8). Therefore, it is not surprising that these reactions do not proceed.

Conclusions

In summary, a representative set of [3]dendralenes **9a–x**, decorated with substituents at each terminal sp^2 carbon of the butadiene moiety, was prepared in two steps from the readily available enyne dicarboxylate **4**. Two complementary cross-coupling protocols were employed, including homogeneous catalysis by a PdP_2 (**5** → **9a–n**) and heterogeneous catalysis by Pd black (**6** → **9o–x**), respectively.

The electron-deficient [3]dendralenes **9a–x** thus prepared were subjected to a Diels–Alder reaction with the heterocyclic dienophiles **10** and **13**. Contrary to the general belief that the combination of two electron-poor partners is disfavored, these reactions did proceed (at 100 °C), giving rise to the bis-adducts **12** and **15** as a result of the highly *endo*/*endo* stereoselective diene transmissive Diels–Alder reactions (DTDA), occurring in two consecutive steps (**9** → **11** → **12** or **15**). The second step was found to be faster than the first one, both experimentally and computationally. However, this scenario became reversed in dendralenes **9e** and **9g** with an appended enone fragment: here, the reaction could be stopped after the first DA addition for the first time, affording mono-adducts **11e** and **11g**. This finding opened the pathway towards sequential additions of two different dienophiles, giving rise to the corresponding adducts **14e** and **14g**.

Calculations revealed that this electronically disfavored process is encouraged by a steric effect of the vinylic appendix (as part of the dendralene core), which drives the diene moiety into the s-*cis* conformation, thus lowering the activation energy by 2–3 kcal mol^{-1}. The same effect is also operating in the second step, which is actually faster, so that the intermediate **11** cannot be isolated in most cases. On the other hand, when the substitution pattern does not allow the molecule to assume the s-*cis* conformation required for the second step, as in the case of **9o,r**, the reaction stops at the stage of the mono-adduct **11o,r**. According to our calculations, carried out for **9a**, **9c**, **9p**, and **9t**, the first addition requires the highest activation energy of the whole DTDA sequence (~28 kcal mol^{-1}), which is only by less than 4 kcal mol^{-1} higher than that for the bare [3]dendralene **1**. By contrast, dendralenes decorated with simple, sterically non-demanding alkyls (methyl) but lacking electron-withdrawing substituents, react in DA processes at lower temperatures.[4–6]

From the synthetic standpoint, this approach employing functionalized starting [3]dendralenes, which generates DTDA products with up to five cycles (as in **12e,g,x**, **14e,g**, and **15g**) and up to eight chiral centers (**12**) in one pot, offers entirely new opportunities for manipulation of the structures, thereby broadening the synthetic potential of this methodology in a highly atom-economic way.

Author contributions

R.A., S.M.P., M.Š., Z.B. and J.Kr. designed and synthesized the compounds, M.S., L.R. and E.A. designed and performed computational experiments, A.R. and J.K. conducted structural analysis, P.M. and P.K. prepared the manuscript, M.P. supervised the project and prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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