

Synthetic Methods

Domino Cycloaddition Organocascades of Dendralenes**

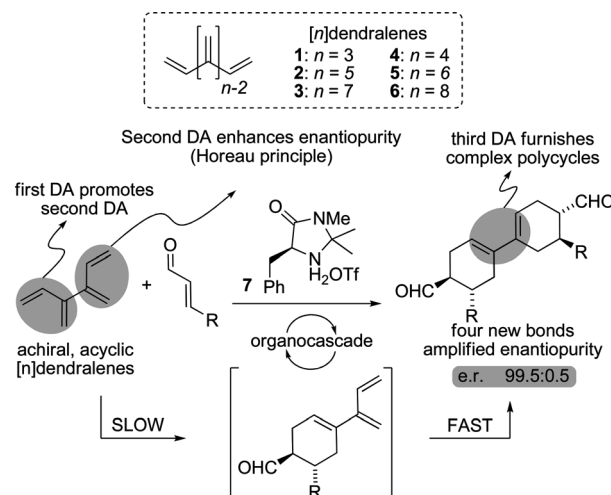
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In the past decade, organocascade reactions^[1–3] have been the subject of intense interest, primarily because of their capacity to combine two or more bond-forming events into a single synthetic operation. Considering the topical nature of organocascades and the complexity-generating power of the Diels–Alder (DA) reaction, it is surprising that there have been no reports of organocascades featuring more than one DA event.

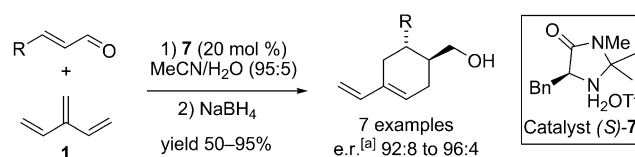
Branched acyclic polyenes ([*n*]dendralenes **1–6**; Scheme 1), have only recently become synthetically accessible^[4] and are excellent starting materials for domino reactions.^[5] The potential of these structures in enantioselective catalysis has, until now, remained untapped.^[6] Herein we disclose the first organocatalyzed cascades involving two DA reactions (Scheme 1).^[7,8] This unique combination of organocascade catalysis and π -bond-rich hydrocarbons provides exquisite examples of the amplification of enantiopurity which is predicted by the Horeau principle,^[9,10] thus transforming simple starting materials into complex products with superb enantioselectivity (e.r. > 99.5:0.5).

We initially set about performing enantioselective single cycloadditions with [3]dendralene^[11] and β -substituted acrolein dienophiles, catalyzed by MacMillan's imidazolidinones^[12,13] (Scheme 2). Optimized reaction conditions^[14,15] resulted in high yields and good enantioselectivities (e.r. 92:8–96:4) for the conversion of [3]dendralene (**1**) into a range of monocycloadducts.^[16]

We next turned our attention to the organocatalyzed reaction between [4]dendralene and acrolein. Although initially apprehensive ([4]dendralene has shown variable levels of regio- and chemoselectivity as a diene in DA reactions),^[17] we were delighted to find that terminal double



Scheme 1. Summary of the present work. Tf = trifluoromethanesulfonyl.



Scheme 2. Single cycloadditions with [3]dendralene. See the Supporting Information for full details. [a] The e.r. values were determined by HPLC analysis using a chiral stationary phase.

cycloaddition was favored under organocatalytic conditions, thus furnishing a bicycle with four new C–C bonds (Scheme 1, R = H). The second cycloaddition was so fast that the intermediate of this domino sequence^[18] was not detected. Indeed, in a separate experiment employing one molar equivalent of both acrolein and [4]dendralene, a 1:1 mixture of [4]dendralene and the bis(adduct) was formed, thus indicating a very short-lived monoadduct intermediate. Similar reactivity was exhibited by [6]- and [8]dendralene (Table 1, entries 2 and 3) and, in accordance with the Horeau principle, very high enantioselectivity was observed for each double cycloaddition (e.r. > 99.5:0.5). The double cycloaddition organocascade also tolerated substitution at the β position of the dienophile, thus leading to a range of highly enantioenriched products (Table 1, entries 1–6).

Are the very high enantiomeric ratios observed in this organocascade truly the result of two catalyst-controlled cycloadditions? We reflected that the first-formed stereogenic center(s) (i.e., from the first cycloaddition step) might be influencing the stereochemical outcome of the second cyclo-

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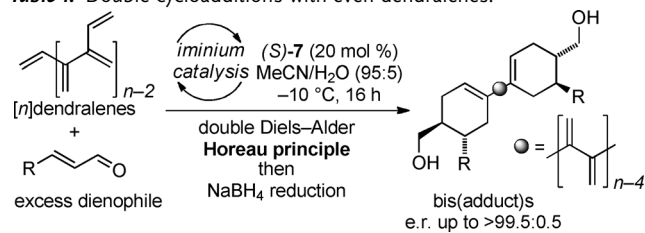
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[**] This work was supported by the Australian Research Council. M.N.P.-R. acknowledges that the computational component of this research was undertaken with the assistance of resources provided at the NCI National Facility through the National Computational Merit Allocation Scheme supported by the Australian Government. The authors thank Tony Herlt (ANU) for assistance with HPLC separations.

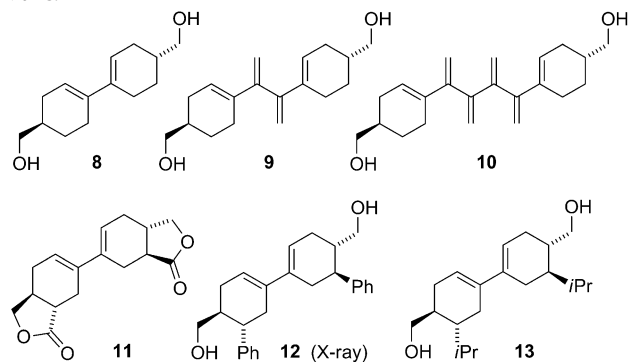
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201302185>.

Table 1: Double cycloadditions with even dendralenes.



Entry	n	R	Product	e.r. ^[a]	d.r. ^[b]	Yield [%] ^[c]
1	4	H	8	> 99.5:0.5	89:11	70
2	6	H	9	> 99.5:0.5	95:5	72
3	8	H	10	> 99.5:0.5	90:10	62 ^[d]
4 ^[e]	4	CO ₂ Me	11	> 99.5:0.5	91:9	71
5 ^[f]	4	Ph	12	99:1	82:18	50
6 ^[g]	4	iPr	13	99:1	74:26	45

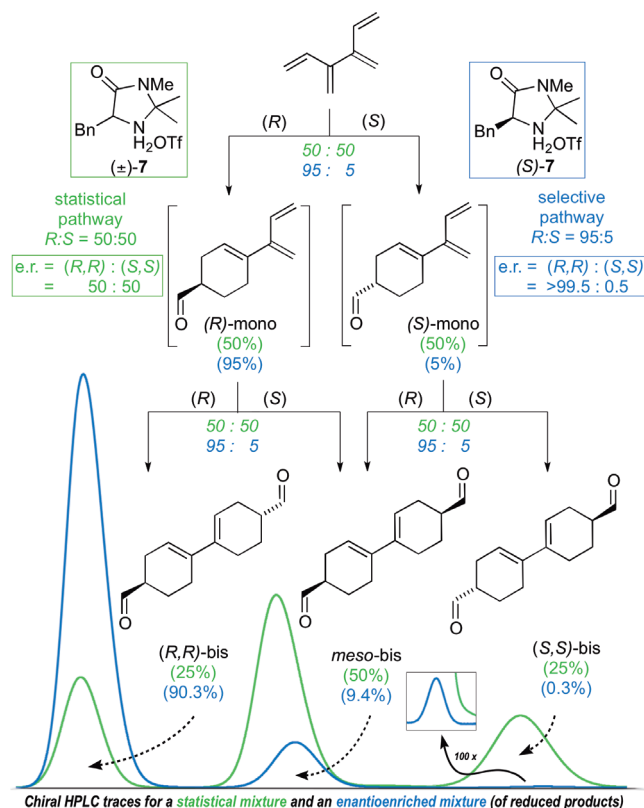
[a] Determined by HPLC analysis using a chiral stationary phase. See the Supporting Information for full details. [b] Determined by either HPLC analysis using a chiral stationary phase, or ¹H NMR spectroscopic analysis. See the Supporting Information. [c] Yield of the isolated product after reduction with sodium borohydride. See the Supporting Information. [d] Yield estimated by ¹H NMR spectroscopic analysis with an internal standard. [e] Isolated and characterized as the bis(lactone). See the Supporting Information. [f] Performed at 55 °C. [g] Performed at 70 °C.



addition.^[19] To test for the presence of this potential double stereodifferentiative effect, the racemic imidazolidinone organocatalyst (±)-**7** was synthesized. A double cycloaddition sequence between acrolein and [4]dendralene (**4**) catalyzed by the racemate furnished a statistical mixture of products composed of two diastereomers: an achiral *meso* compound and a racemic mixture of C₂-symmetric enantiomers (e.r. = 50:50, d.r. = 1:1).^[20] This result indicates that the high enantiopurity of the bis(adduct)s produced by the homochiral catalytic system stems purely from catalyst control and hence, the Horeau principle. Identical results were obtained for the range of dienophiles employed in double cycloaddition reactions (Table 1).^[21] Remarkably, even when increasingly vigorous reaction conditions were used, resulting in lower observed diastereoselectivity (Table 1, entries 5 and 6), satisfactorily high product e.r. values of 99:1 were still observed.

The symmetrical, bifunctional^[22] nature of the even parity dendralenes determines that two different reaction pathways, each featuring a single catalytic system error (formation of an *S*-configured stereocenter), lead to the *meso* bis(adduct).

These examples can be combined with the data from HPLC traces to provide the basis for a clear and straightforward demonstration of the Horeau principle in the context of double enantioselective catalysis (Scheme 3). Using the final e.r. (*R,R/S,S*) and d.r. (C₂/*meso*) values, catalyst stereoselec-

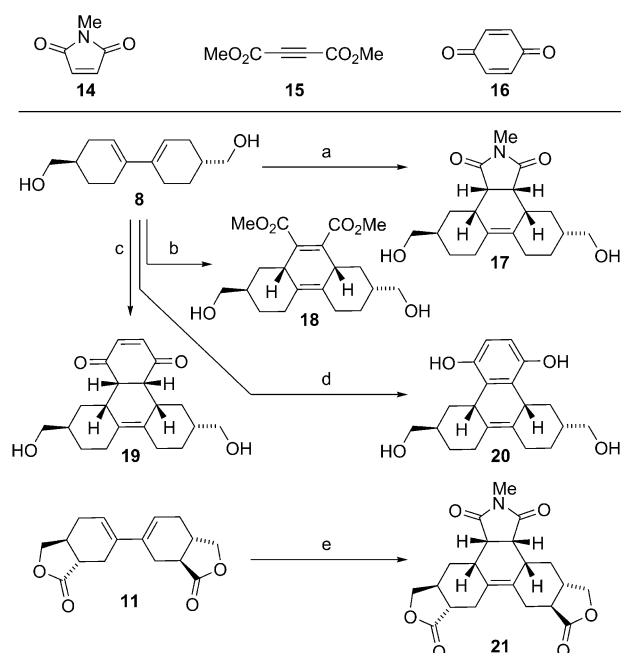


Scheme 3. Stereochemical pathways for cycloaddition leading to observed amplification of enantiopurity.

tivity for each step of about 95:5 is determined, which matches the stereoselectivity observed for single cycloadditions.

Products of this enantioselective double cycloaddition (Table 1, entries 1 and 4) react readily and in high yield with dienophiles such as *N*-methylmaleimide (NMM; **14**), dimethylacetylenedicarboxylate (**15**), and benzoquinone (**16**) to generate enantioenriched triple cycloadducts: multicyclic systems containing aliphatic and aromatic rings (Scheme 4). These highly enantiomerically enriched, functionalized polycyclic frameworks are generated in only two steps from achiral and acyclic [4]dendralene, a hydrocarbon which is prepared in only one step from the commodity chemical chloroprene.

Mechanistic insight into the enantioselectivity of the organocatalyzed DA reactions was provided by B3LYP/6-31G(d) calculations on the reaction between [3]dendralene (**1**) and acrolein, catalyzed by the imidazolidinone **7**. Twenty-one gas-phase transition structures (TSs) were located, comprising different conformations associated with the four basic modes of addition, namely, *endo*(N)/*exo*(X) modes leading to *R*- and *S*-configured adducts. The lowest energy



TSs for each mode of addition are shown in Figure 1, together with their M06-2X/6-311 + G(2df,p)//B3LYP/6-31G(d) relative enthalpies and free energies (25°C), for both gas phase and acetonitrile as a solvent. The *R* adduct is predicted to be the major one, in agreement with previous experimental findings with **7**.^[12] Furthermore, the calculated e.r. values of 96:4 (gas) and 97:3 (CH_3CN) are in agreement with the experimental value of 92:8. The origin of the enantioselectivity is largely the consequence of the benzyl group lying directly over the iminium cation—a result of both stabilizing phenyl- π /iminium- π and phenyl- π / CH_3 interactions^[23] (Figure 1)—thereby blocking approach to that face by the dendralene.

All four TSs, although concerted, display an extremely high degree of bond-forming asynchronicity, with the bond between the central methylene carbon atom of [3]dendralene and the β -carbon atom of the dienophile being well advanced (2.1–2.2 Å) and that between the terminal methylene carbon atom of the dendralene and the α -carbon atom of the dienophile barely progressed at all (3.3–3.9 Å). This high degree of asynchronicity, which is significantly higher than that found in earlier studies,^[23,24] also occurs in the TSs for DA dimerizations of dendralenes and was attributed in the latter case to the presence of strong pentadienyl radical character in the TSs.^[25] In the present case, however, the asynchronicity is attributed to the TSs acquiring quasipentadienyl cation character, thereby facilitating delocalization of the positive charge. Indeed, Mulliken population analysis reveals that

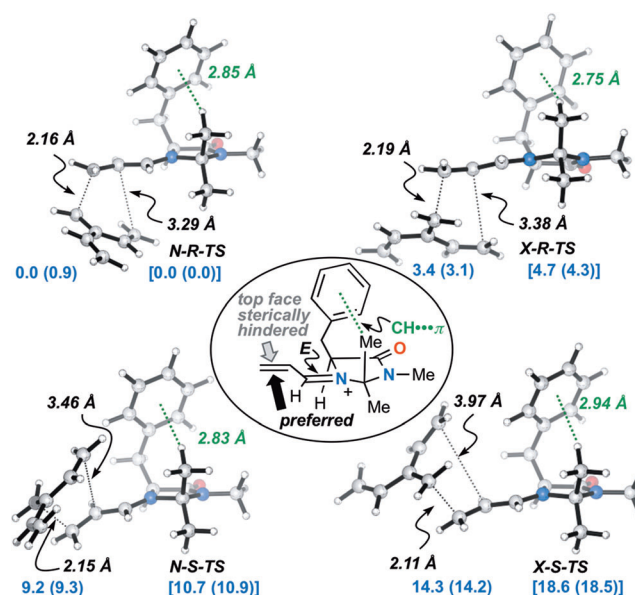


Figure 1. B3LYP/6-31G(d) transition structures (and schematic diagram) for the reaction between [3]dendralene and acrolein catalyzed by imidazolidinone **7**. Calculated M06-2X/6-311 + G(2df,p)//B3LYP/6-31G(d) gas phase relative enthalpies (free energies, kJ mol^{-1}) [CH_3CN solvent values in square brackets] are listed in blue. Developing bond lengths are shown in black and the phenyl centroid to closest H distances are shown in green.

0.33–0.44 electrons are transferred from diene to dienophile in these TSs.

In summary, dendralenes have been used to execute the first organocatalyzed double enantioselective cycloaddition cascades. Since the stereoselectivity of each cycloaddition is controlled solely by the catalyst—and in accordance with the Horeau principle—the enantiopurity of the organocascade products is extremely high. The C_2 -symmetric, chiral double cycloadducts undergo a third DA cycloaddition to generate highly functionalized hydrophenanthrenes. In terms of product enantiopurity and number of C–C bonds formed, these double cycloaddition organocascades transcend all previous efforts in organocascade catalysis.^[1–3] Furthermore, the ease of downstream manipulation of the products, coupled with simple preparation of the π -bond-rich hydrocarbon precursors, makes this new approach a convenient and powerful method for polycycle construction.

Received: March 15, 2013

Published online: June 26, 2013

Keywords: cycloaddition · hydrocarbons · polycycles · polyenes · synthetic methods

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