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Cycloaddition

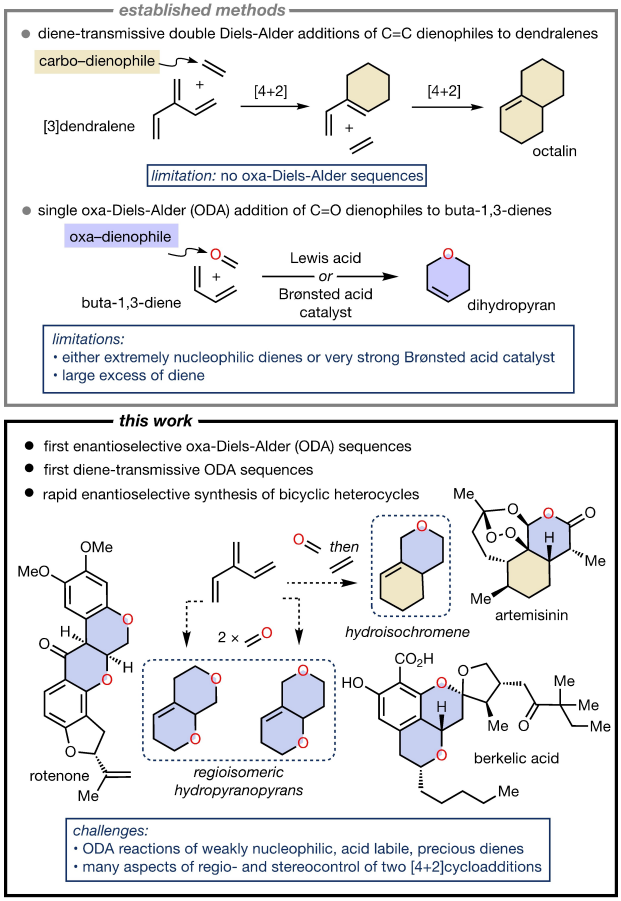
Enantioselective oxa-Diels–Alder Sequences of Dendralenes

Yi-Min Fan, Li-Juan Yu, Michael G. Gardiner, Michelle L. Coote, and Michael S. Sherburn**

Abstract: Diene-transmissive hetero-Diels–Alder sequences involving carbonyl dienophiles are reported for the first time. High enantioselectivities are achieved in the reaction of phenylglyoxal with a broad range of dendralene structures, through the optimization of a Pd^{2+} catalyst system. The initial catalyst-controlled enantioselective oxa-Diels–Alder (ODA) cycloaddition to a [3]dendralene generates a dihydropyran carrying a semicyclic diene. This participates in a subsequent catalyst or substrate-controlled Diels–Alder reaction to generate sp^3-rich fused polycyclic systems containing both heterocycles and carbocycles. Computational investigations reveal a concerted asynchronous mechanism. π-Complexation of a diene C=C bond to Pd^{2+} occurs in both the pre-transition state (TS) complex and in cycloaddition TSs, controlling stereoselectivity. A formal enantioselective [4+2]cycloaddition of a CO_2 dienophile is demonstrated.

The invention of simple, broad scope and powerful methods for rapid complex molecule synthesis goes hand-in-hand with the development of more efficient chemical synthesis.[1] One such approach for sp^3-rich poly-carbocycle construction utilizes sequences of Diels–Alder reactions of dendralenes.[2] Dendralenes are a family of cross-conjugated hydrocarbons that are garnering significant interest[3] due to their improved accessibility and recently-demonstrated kinetic stability.[4] A Diels–Alder reaction of a dendralenic diene with a separate alkenic dienophile molecule generates a new ring. It also shifts C=C bond character to a new site, creating a second, semicyclic diene that undergoes another Diels–Alder reaction with a second alkenic dienophile (Scheme 1). In this diene-transmissive[5] manner, a $\Delta^{1,9}$-octalin ring system is created from three separate building blocks through a process that can often be deployed in a one-flask operation. The robustness of this sequence with carbon-based dienes and dienophiles has been exploited in the synthesis of large libraries of racemic multi-carbocyclic systems.[6] More recently, the first applications of diene-transmissive carbo-Diels–Alder sequences in target synthesis have been reported.[7] Shortened step counts to natural products have been achieved, despite the use of smaller building blocks of considerably lower structural similarity to the target, and more covalent bonds and rings being constructed during the synthesis.[8]

The oxa-Diels–Alder (ODA) reaction, in which a carbonyl dienophile reacts with a buta-1,3-diene, is the most atom economical way to assemble a dihydropyran.[9,10] Important contributions in catalyst-controlled enantioselective ODA reactions[11] have been reported by the groups of Danishefsky,[12] Mikami,[13] Jørgensen,[14] Jacobsen,[15] Oi,[16]



Scheme 1. Carbo-Diels–Alder sequences of dendralenes and single oxa-Diels–Alder processes are established (top). Oxa-dienophile Diels–Alder sequences are unprecedented (bottom).

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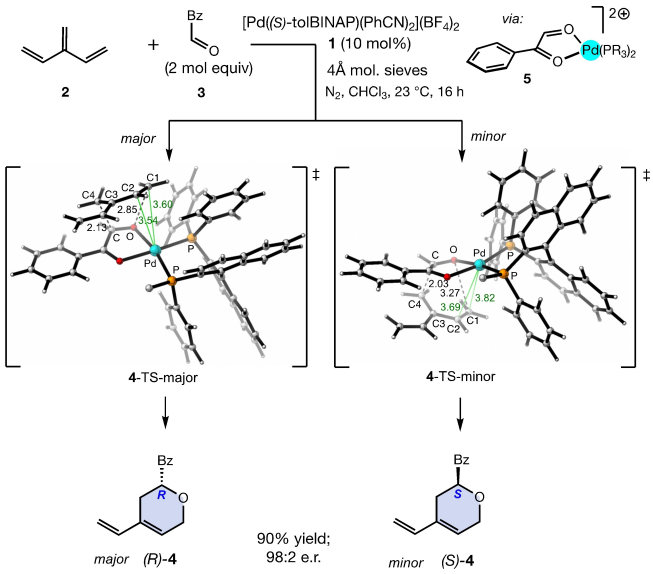
Evans,[17] Rawal,[18] Matsubara,[19] Loh[20] and List.[21] In light of the burgeoning success of diene-transmissive Diels–Alder (DTDA) sequences for poly-carbocycle construction, it is surprising that ODA reactions have not been performed on dendralenes.[22] Such processes have the potential for the one or two step generation of fused bicyclic heterocycles such as hydroisochromenes and hydropyranopyrans, scaffolds which feature in a number of important natural products, such as rotenone, berkelic acid and artemisinin.

Herein we report the successful incorporation of enantioselective ODA reactions into DTDA sequences with associated computational analysis. The method permits the rapid construction of target-relevant, fused heterocyclic ring systems in which two rings, four covalent bonds and up to five stereocenters are created from a substituted [3]dendralene precursor (Scheme 1).

Initial attempts to achieve an ODA reaction between a dendralene and a carbonyl dienophile using established methods[23] were disappointing. Ultimately, three problems were identified: firstly, the majority of reported catalyst-controlled ODA methods are effective only with extremely nucleophilic dienes such as Danishefsky and Rawal-type systems.[24] Secondly, ODA methods using less electron-rich buta-1,3-dienes deploy strong acid catalysts, which decompose dendralenes. Finally, the majority of published reports use large excesses of buta-1,3-diene reactants.[25]

After significant experimentation, we finally obtained successful Diels–Alder reactions between [3]dendralenes and the oxadienophile phenylglyoxal using Oi and co-workers' Lewis acidic [Pd((*S*)-BINAP)(PhCN)$_2$](BF$_4$)$_2$ precatalyst.[16] Whereas initial experiments gave low conversions, a ligand screening process[23] identified [Pd((*S*)-tolBINAP)(PhCN)$_2$](BF$_4$)$_2$ (**1**) with improved enantioselectivity and significantly enhanced catalytic activity.[26] Scheme 2 depicts the catalytic enantioselective Diels–Alder addition of phenylglyoxal to the parent [3]dendralene **2** (90 % yield, e.r. = 98:2 by SFC analysis)[27] using this optimized dicationic chiral Pd^{II} precatalyst **1**, along with the most important findings from the first computational modelling of the process. These computational findings reveal an asynchronous concerted mechanism[28] for the oxa-Diels–Alder reaction i.e., distinct from the stepwise ionic pathway suggested in Oi's ground-breaking work.[29]

As depicted in Scheme 2, the reaction between [3]dendralene **2** and phenylglyoxal **3** proceeds at ambient temperature with [Pd((*S*)-BINAP)(PhCN)$_2$](BF$_4$)$_2$ **1** to give the *(R)*-configured adduct **4** in high chemo-, regio- and enantioselectivity. The species [Pd((*S*)-tolBINAP)-(BzCHO)]$^{2+}$ (generalized as **5**) is assumed to be the reactive dienophile. The complex **5**, formed upon reaction between phenylglyoxal **3** and Pd precatalyst **1**, exhibits square planar geometry at the metal center. The diene, [3]dendralene **2**, may approach this complex from either above or below in an *endo*- or *exo*-mode of addition. Preferential approach from the top face as shown (Scheme 2, **4**-TS-major) minimizes destabilizing diene-phosphine ligand interactions. The *endo*-pathways shown in Scheme 2 are preferred since they benefit from a stabilizing π-complexation to the Pd (shown in green), which is not possible in *exo*-transition states (TSs).



Scheme 2. Enantioselective ODA reaction between phenylglyoxal **3** and [3]dendralene **2** instigated by chiral dicationic Pd^{II} precatalyst **1** along with the two most favored pathways. The forming C–C and C–O bonds are dashed and the Pd/C=C distances is depicted green. Interatomic distances in transition states (TSs) are in Ångstroms. The *ortho*-tolyl groups of the catalyst were truncated to phenyl groups for computational manageability. The front P-phenyl group in each TSs is hidden for clarity. Density functional theory calculations were performed in chloroform at the ωB97XD/Def2-TZVP//ωB97XD/SDD-6-31G(d,p) level of theory using the SDD ECP for Pd, and the CPCM solvation model. See the Supporting Information for details.

Non-covalent interaction analyses of the reactant **5**, the TS and also pre-TS complexes[23] also show the presence of this Pd/C=C π complexation. This *endo*-stabilizing interaction functions akin to a hybrid of the original Woodward–Hoffmann[30] and later Singleton [4+3][31] SOI modes (Figure 1) yet operates in both the ground state (GS) and the TSs. SOIs have not been demonstrated in GS species: they operate only in and around the DA TS.

The majority of substituted [3]dendralenes react in the same way as the parent [3]dendralene **2**, exhibiting the same orientational regioselectivity and high enantioselectivity

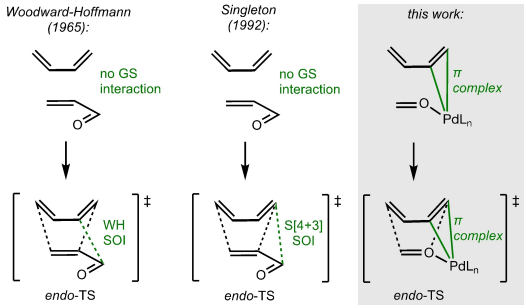


Figure 1. Secondary orbital interactions proposed by Woodward–Hoffmann and Singleton explain the kinetic *endo*-selectivity of DA reactions through a stabilizing TS interaction. This study shows a related stabilizing interaction operating in both the ground state (GS) and the TS.

(Table 1a). Thus, alkyl and aryl groups at a terminal alkene of the [3]dendralene precursor **6** are tolerated, as shown by the synthesis of the ODA adducts **7/8** (Table 1a, **9**–**13**).[23] The substituent resides on the non-participating alkene in all cases, presumably to minimize destabilizing steric interactions with the bulky ligands on Pd. 1,1,5,5-Tetramethyl [3]dendralene, with its two terminal carbons fully substituted, also participates in an enantioselective ODA reaction and yields adduct **14**, as shown in Table 1a. The outcome of these reactions, involving all possible terminal C=C bond substitutions, can be understood using the computational model shown in Scheme 2, which is summarized in docking model **A** (Table 1a).

Dendralenes substituted at the internal methylene group (**15**) also exhibit high selectivity with modified catalyst **1** to construct ODA adducts **16**, as demonstrated by the five examples **17**–**21** in Table 1b (nine more examples are provided in the Supporting Information). Intriguingly, a reversal in orientational regioselection of phenylglyoxal addition is witnessed in this series. Furthermore, within detection limits, a single *trans*-2,6-disubstituted dihydropyran product is formed, which reveals a switch to *exo*-addition. Docking model **B** (Table 1b) accounts for this switch: the reversal in orientational regioselectivity is presumably due to the aromatic substituent providing a superior stabilization of developing cationic character in the TSs of the reaction. Evidently, this reversed regioselectivity incurs a significant steric penalty, since diene substituents must now be close to the catalyst, particularly in *endo*-additions. A switch to the *exo*-orientation presumably alleviates this strain. Oi reported poor *endo/exo*-selectivities with substituted dienes and phenylglyoxal.[16] The combination of dendralenes and modified catalyst **1** permit synthetically useful versions of these reactions for the first time.

Irrespective of the orientational regioselectivity of the first C=O addition, mono-adducts depicted in Table 1 react on in a second ODA reaction to furnish fused bicyclic heterocyclic systems in spectacularly high enantioselectivity (Table 2). This unprecedented twofold ODA-ODA sequence is performed most conveniently in a one pot operation from the dendralene. The enhancement in complexity from simple, readily accessible[3i,32] achiral dendra-

Table 1: Catalytic enantioselective ODA additions of phenylglyoxal to [3]dendralenes carrying substituents at (a) end and (b) middle C=C bonds.

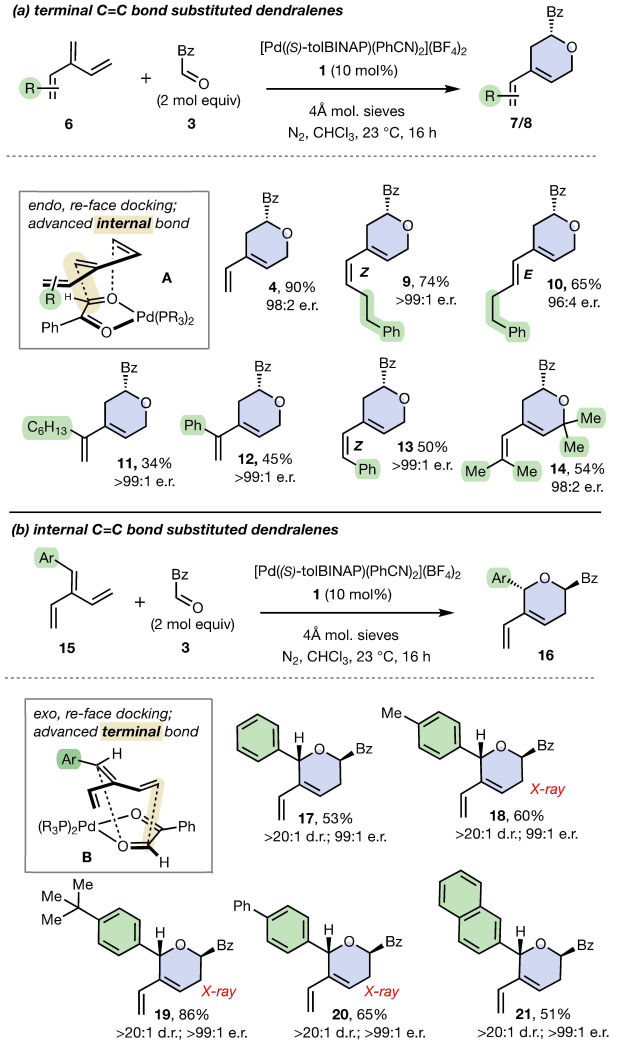
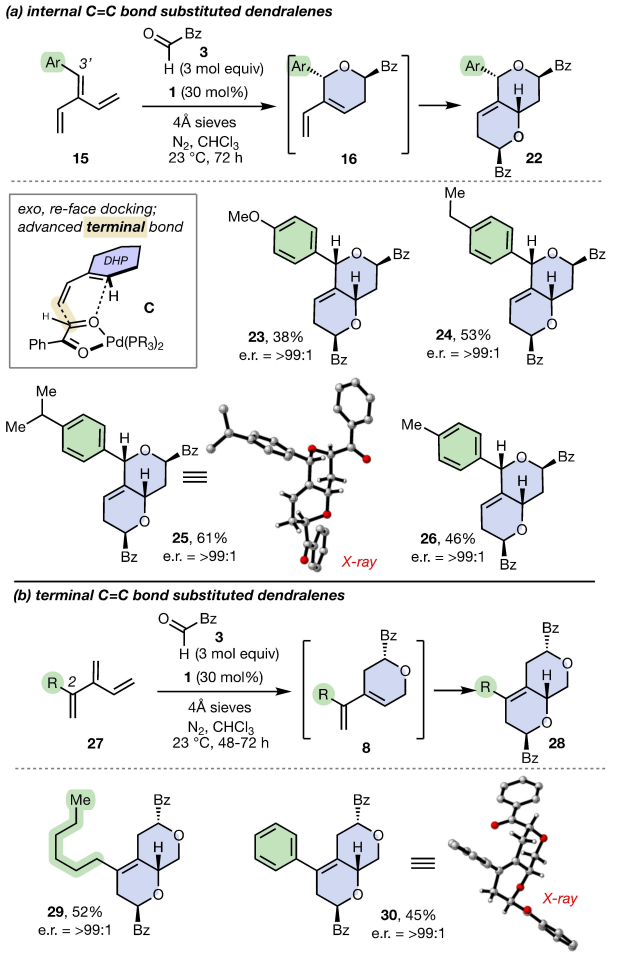


Table 2: Catalytic enantioselective diene-transmissive twofold ODA sequences of dendralenes.



lenes **15**/**27** to highly enantioenriched pyranopyrans **22**/**28** is significant, with four new covalent bonds, two new rings, and four new stereocenters created in high selectivity. The second ODA addition (Table 2; **16**→**22** and **8**→**28**) proceeds with the same orientational regioselectivity, irrespective of the intermediate regioisomeric dihydropyran (DHP), **16** (Table 2a, **23**–**26**) or **8** (Table 2b, **29** and **30**). Docking model **C** (Table 2) interprets the experimental outcome, wherein advanced bond formation at the less substituted end of the vinyldihydropyran monoadduct (**16** or **8**) gives an outcome akin to the one seen with internally-substituted dendralenes (Table 1b).

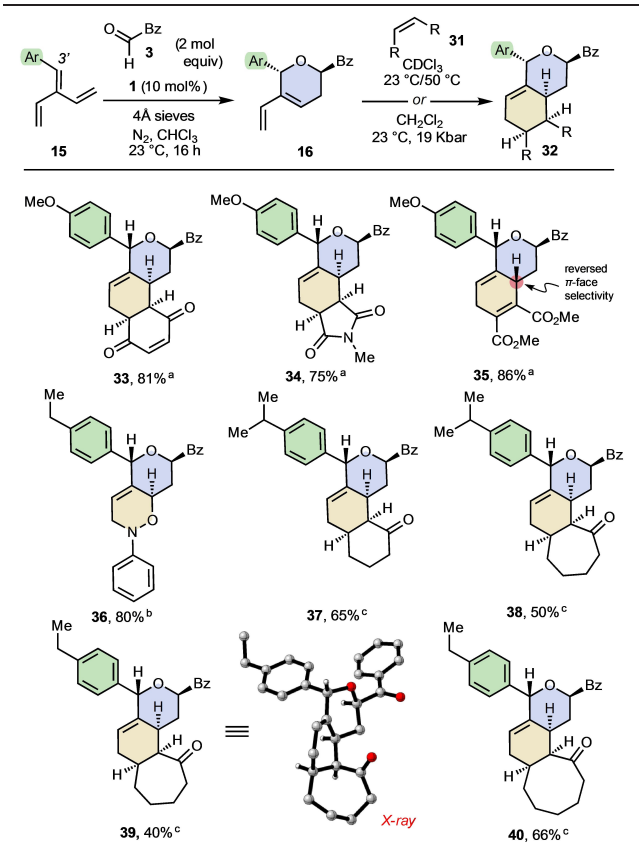
When the second cycloaddition involves dienophiles other than phenylgloxal **2**, the diene-transmissive sequence is best carried out in two separate steps. In these cases, the second, catalyst-free cycloaddition proceeds with high levels of substrate-based regio- and diastereocontrol (Table 3).

Table 3 shows cycloadditions with acyclic and cyclic C=C, C≡C and N=O dienophiles (**31**) to generate fused bicyclic and tricyclic sp^3-rich heterocycles (**32**). Where possible (**33**, **34**, **36**, **37**, **38**, **39**, **40**) the *endo*-pathway is followed exclusively, within the limits of detection. The π-diastereofacial selectivity of these additions is also very high, in all but one case with dienophile addition controlled by the steric demands imposed by the aryl substituent in monoadduct **3** (i.e. the 3′-substituent from the original [3]dendralene). The intriguing exception is the addition of the alkyne dienophile, which gives adduct **35** with reversed π-diastereofacial selectivity. To explain this unusual phenomenon, we located TSs for concerted DA cycloadditions leading to the formation of **34** and **35** and their stereoisomers at the ωB97XD/6-31G(d,p)level of theory.[23] The dienophile *N*-methylmaleimide (which forms adduct **34**) prefers *endo*- mode cycloadditions due to stabilizing SOIs in their TSs (Figure 1), thus steric strain brought to bear by the R group dominates, hence dienophile approach from above is favored. In contrast, the alkyne dienophile dimethylacetylenedicarboxylate (which forms adduct **35**) cannot participate in SOI interactions. Furthermore, its linear geometry causes destabilizing steric clashes with the Bz substituent when approaching from above.

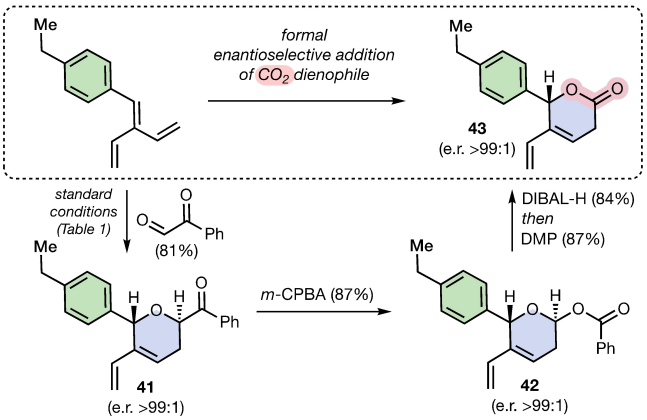
The synthetic versatility of [4+2]cycloadducts derived from phenylglyoxal is demonstrated in Scheme 3, which achieves the deletion of the phenylglyoxal-derived benzoyl group from ODA adduct **41** through oxidative C–C bond cleavage.[33] Thus, a simple Baeyer–Villiger oxidation to ester **42**, deprotection and lactol oxidation gives lactone **43**. This straightforward protocol, which should see wider application, represents a method to achieve an enantioselective formal [4+2]cycloaddition of CO_2 to a buta-1,3-diene.[34] Further novel manipulations of phenylglyoxal-derived ODA adducts are provided in the Supporting Information.[23]

In summary, the first oxa-Diels–Alder reactions of dendralenes have been achieved, and highly enantioselective processes have been incorporated into diene-transmissive, double cycloadditions. This chemistry takes one of the most powerful complexity-generating processes for poly-carbocycle construction into the heterocyclic domain. This work sets the scene for target synthesis applications, invites extensions to other heterocyclic systems, and creates precedent for stepwise, formal multi-cycloaddition sequences. In addressing the challenges presented by dendralenic dienes, we have optimized Oi's system to deliver a catalyst with improved enantioselectivity and turnover, functioning effectively with the diene as the limiting reagent. This catalyst

Table 3: Enantioselective diene-transmissive Diels–Alder sequences of dendralenes with two different dienophiles.



Reaction conditions: vinyldihydropyran **3**, dienophile **18** (2 mol equiv), [a] $CDCl_3$, 50 °C; [b] $CDCl_3$, 23 °C; [c] CH_2Cl_2, 23 °C, 19 kbar.



Scheme 3. Phenylglyoxal as a synthetic equivalent of a CO_2 dienophile in an enantioselective ODA reaction.

should enjoy broader use, particularly in ODA reactions involving more precious dienes.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetric Catalysis · Cycloadditions · Dendralenes · Domino Reactions · Hydrocarbons

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[23] See the Supporting Information for details.
[24] As is the case with other hydrocarbon buta-1,3-dienes, dendralenes were unreactive towards these catalysts.
[25] Excess diene reactant is presumably used to offset material lost due to acid-catalyzed polymerization. This approach is obvi-

ously not viable with a precursor that must react as a multiple diene.
[26] This catalyst, which was characterized through single crystal X-ray analysis (see Supporting Information for details), is bench stable as a solid but in solution its catalytic activity is attenuated by air and moisture. The results of screening experiments with six chiral ligands and three dendralene substrates are provided in the Supporting Information.
[27] The absolute configurations of major enantiomers of six of the cycloadducts were assigned through single crystal X-ray analyses, with the remainder assigned by analogy (see the Supporting Information for details).
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[35] Deposition numbers 2092161, 2092162, 2092163, 2092164, 2092165, 2092166, 2092167, 2092168 and 2092169 contain the supplementary crystallographic data for this paper (8 structures). These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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