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Multicomponent Diene-Transmissive Diels–Alder Sequences Featuring Aminodendralenes

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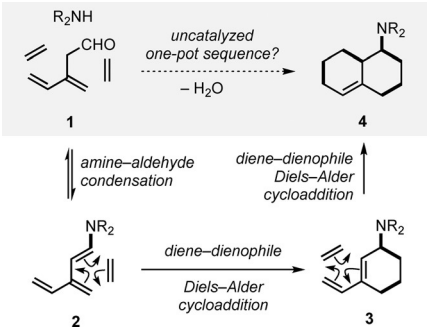
Abstract: *1-Aminodecalins were prepared from acyclic precursors by combining the powerful twofold diene-transmissive Diels–Alder chemistry of [3]dendralenes with the simplicity of enamine formation. On mixing at ambient temperature, a simple dienal condenses with a primary or secondary amine to generate the enamine, a 1-amino-[3]dendralene in situ, and this participates as a double diene in a sequence of two Diels–Alder events with separate dienophiles. Overall, four C–C bonds and one C–N bond are formed. Mechanistic insights into these reactions are provided by means of density functional theory calculations.*

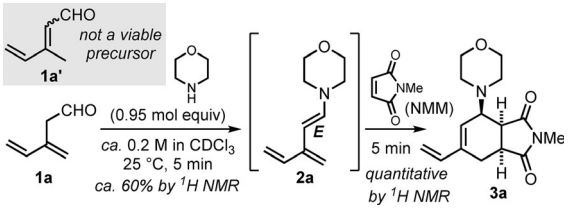
Step-economic synthesis necessitates the invention of new methods for converting simple and readily accessible precursors into more complex products.[1,2] The rapid generation of structural complexity is inexorably linked with processes that form several new covalent bonds. Such multiple single-bond-forming transformations[1] have several subclassifications, with those involving successive reactions at sequentially generated functional groups featuring strongly in current research endeavors.[3] In addition to maximizing useful structural complexity gains, a new synthetic method should ideally be atom-economic,[4] operationally simple, and robust.[5]

Dendralenes[6] are cross-conjugated olefins of significant value in the step-economic synthesis of complex molecules owing to their multiple-1,3-butadiene character, which permits their participation in diene-transmissive[7] Diels–Alder (DA) cycloaddition sequences.[8] Such sequences, which are amongst the most powerful of all multiple single-bond-forming processes,[9] are now finding application in step-economic total synthesis.[10] The dendralenes are invariably made first and then used separately in a cycloaddition sequence.[6] If it were possible to unite the preparation of dendralenes with their cycloaddition sequences in a single, simple synthetic operation, we reasoned that significant efficiency dividends would result. Herein, we report the successful realization of this proposition. The conceptualized sequence is depicted in stripped-back form in Scheme 1, and shows that skipped dienal **1** would condense reversibly with an amine to generate 1-amino-[3]dendralene **2**.[11] Steric effects notwithstanding, this species would be expected to react with an electron-poor dienophile at the more strongly activated 1,3-disubstituted 1,3-butadiene unit[12] to produce "transmitted" semicyclic diene **3**, which would in turn react with a second dienophile to deliver aminodecalin[13] system **4**. Significant structural complexity would thus be generated from four simple precursors through three consecutive reactions.



Scheme 1. Schematic representation of the four-component sequence.

E-Configured trienamine **2a** was generated in $CDCl_3$ solution at ambient temperature within 5 minutes, simply by mixing methylene-skipped dienal **1a** with morpholine (Scheme 2).[14] The new dendralene **2a** readily decomposed upon attempted isolation or standing in solution, thereby resulting in complex mixtures of products including the two geometrical isomers of isomeric conjugated dienal **1a′**. Addition of the electron-poor dienophile *N*-methylmaleimide (NMM) to a preformed solution of trienamine **2a** delivered *endo*-cycloadduct **3a** very cleanly.[12] Conjugated dienal **1a′** was not converted into trienamine **2a**, instead yielding the products of aza-Michael additions upon exposure to morpholine and NMM.[14,15]



Scheme 2. Generation and Diels–Alder reaction of trienamine **2a**.

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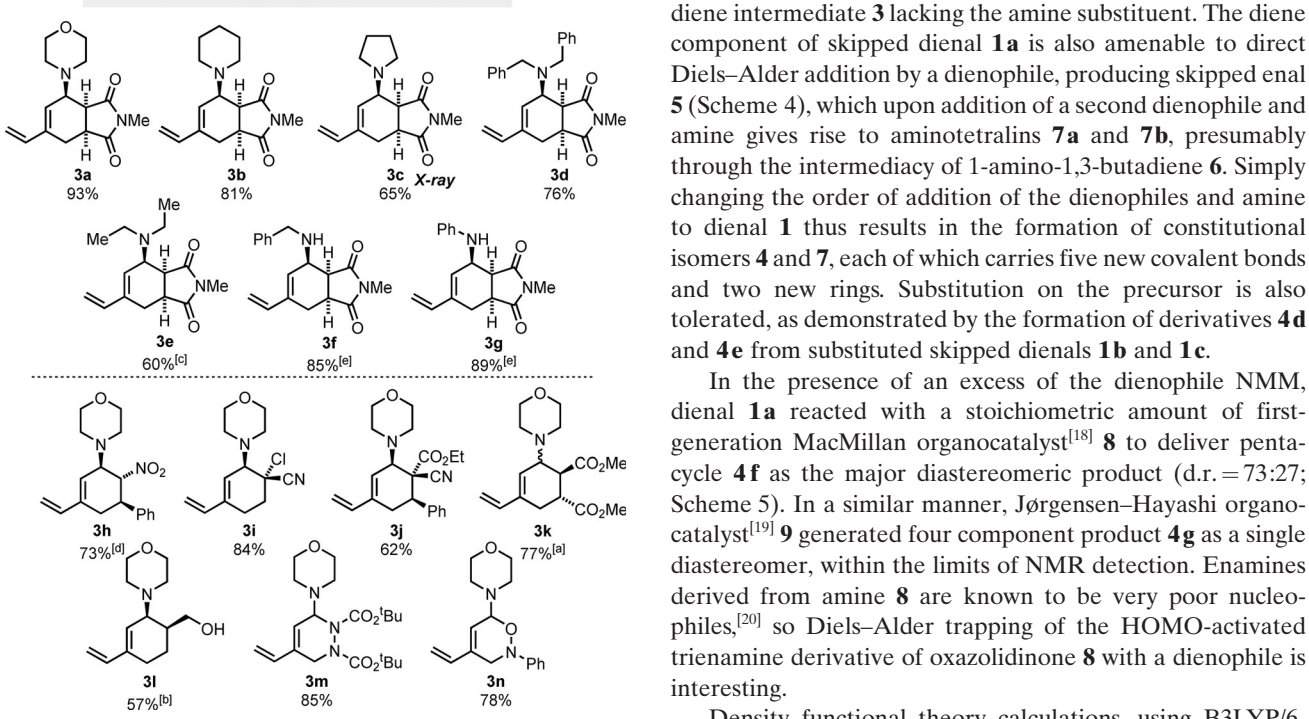
The formation of cycloadduct **3a** confirmed our expectation that 1-amino-[3]dendralene **2a** would undergo a highly site-selective addition of a dienophile to the more substituted 1,3-butadiene residue. The sequential addition of the dienophile to the preformed trienamine was not necessary, since optimal yields of products **3a**–**n** were obtained by premixing skipped dienal **1a** and the dienophile, then adding the amine last. Presumably, it is better to generate the reactive trienamine in low concentration and trap it quickly with a dienophile, rather than allow it to increase in concentration. This one-pot, three-component sequence has a broad scope with respect to both the amine and dienophile, as demonstrated by the fourteen examples depicted in Scheme 3. Primary and secondary, cyclic and acyclic, and alkyl- and aryl- amines are tolerated, as are carbo- and hetero-dienophiles with a variety of activating groups and other substituents. As might be anticipated,[16] the products of *endo*-cycloadditions were generally formed. This broad substrate tolerance is consistent with both a very favorable condensation and a trienamine that is highly reactive towards dienophiles, presumably due to its Rawal-type diene[17] character.

This sequence was extended to a one-pot, four-component reaction through the implementation of an in situ Diels–Alder addition of a dienophile to the semicyclic diene segment of mono-adduct **3** (Scheme 4). Compounds **4a**–**c** were produced through a highly diastereoselective *endo* addition of the dienophile to the face of the semicyclic diene intermediate **3** lacking the amine substituent. The diene component of skipped dienal **1a** is also amenable to direct Diels–Alder addition by a dienophile, producing skipped enal **5** (Scheme 4), which upon addition of a second dienophile and amine gives rise to aminotetralins **7a** and **7b**, presumably through the intermediacy of 1-amino-1,3-butadiene **6**. Simply changing the order of addition of the dienophiles and amine to dienal **1** thus results in the formation of constitutional isomers **4** and **7**, each of which carries five new covalent bonds and two new rings. Substitution on the precursor is also tolerated, as demonstrated by the formation of derivatives **4d** and **4e** from substituted skipped dienals **1b** and **1c**.

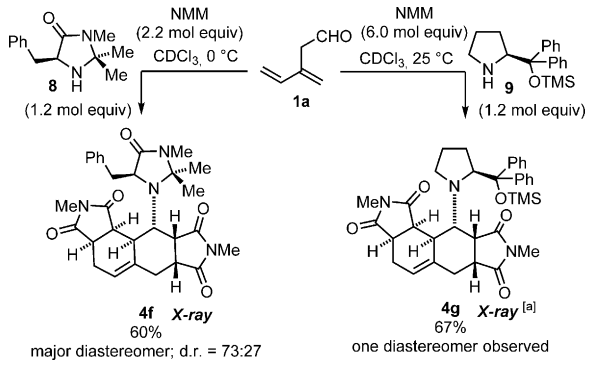
In the presence of an excess of the dienophile NMM, dienal **1a** reacted with a stoichiometric amount of first-generation MacMillan organocatalyst[18] **8** to deliver pentacycle **4f** as the major diastereomeric product (d.r. = 73:27; Scheme 5). In a similar manner, Jørgensen–Hayashi organocatalyst[19] **9** generated four component product **4g** as a single diastereomer, within the limits of NMR detection. Enamines derived from amine **8** are known to be very poor nucleophiles,[20] so Diels–Alder trapping of the HOMO-activated trienamine derivative of oxazolidinone **8** with a dienophile is interesting.

Density functional theory calculations, using B3LYP/6-31G(d) model chemistry,[14] were carried out in order to gain mechanistic insights into the origin of the observed π-diastereofacial selectivity of the first cycloadditions depicted in Scheme 5.[21] It is instructive, in the first place, to analyze the two conformations associated with rotation about the



Scheme 4. One-pot, four-component sequences with dienal **1**. Major stereoisomer depicted, d.r. > 95:5 unless indicated otherwise. [a] d.r. = 91:9. [b] d.r. = 71:29. [c] C_6D_6 solvent used. [d] 6.0 mol equiv NMM used.

Scheme 3. Scope of the condensation–cycloaddition sequence with dienal **1a**. Major stereoisomer depicted, d.r. > 95:5 unless indicated otherwise. [a] isolated as a 1:1 diastereomeric mixture. [b] 2.5 mol equiv of amine and dienophile used, acrolein as dienophile, yield of isolated product after $NaBH_4$ reduction. [c] 0.83 mol equiv amine used. [d] d.r. = 89:11. [e] 30 minute reaction time.



Scheme 5. Trapping trienamines of chiral amines as double DA adducts. [a] X-ray crystal structure of the tertiary alcohol product of silyl ether hydrolysis.

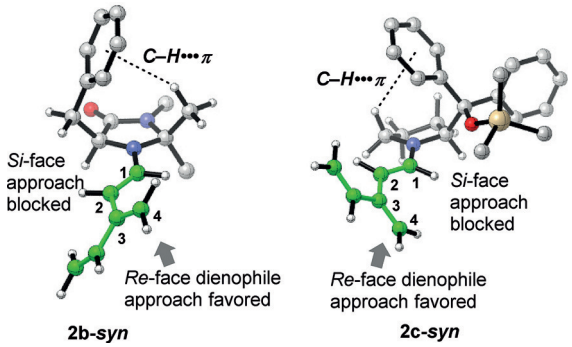


Figure 2. B3LYP/6-31G(d)-optimized structures **2b-*syn*** and **2c-*syn***, with the favored trajectories of dienophile approach indicated. H atoms are omitted from phenyl and some methyl groups and the dendralene is colored green for clarity.

bond connecting the dendralene and the heterocycle in the two reactant aminodendralenes **2b** and **2c**. As shown in Figure 1, the two conformations are distinguished according to whether the N–C2′ or N–C5′ bond partially eclipses the dendralene C1–C2 bond. The *syn/anti* notation refers to the disposition of the N–C5′ bond, that is, the bond involving the less substituted C5′ atom, with respect to the C1=C2 bond. As might be expected from the small dihedral angles between C1=C2 and the partially eclipsing N–C bond in both the *syn* and *anti* conformations of **2b** and **2c** (Figure 1), the *syn* conformer should be more stable than the *anti* conformer because of diminished adverse steric interactions between the dendralene C2–H group and the less substituted C5′ center of the heterocycle.[22] Indeed, the B3LYP calculations predict the *syn* form to be more stable than the *anti* form in both **2b** and **2c**, by 9.4 and 12.2 kJ mol^{-1}, respectively.

In both *syn* and *anti* conformers of **2c**, one of the OTMS methyl groups lies substantially over the *Si* face of the dendralene C1C2C3C4 diene component of the former and over the *Re* face of this diene component in the latter

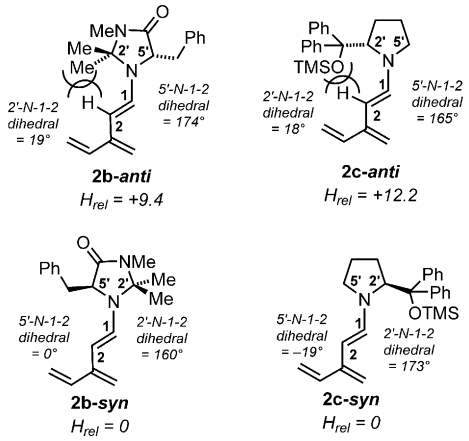


Figure 1. Schematic of the two trienamine conformations for **2b** and **2c** with respect to rotation about the C1–N bond, together with the B3LYP/6-31G(d) dihedral angles between the dendralene and N–C bonds of the heterocycle, and their relative enthalpies, H_{rel} (298 K, kJ mol^{-1}). Note the similar steric clash in the higher-energy *anti* conformations.

(Figure 2). Stabilizing CH···π interactions between a phenyl ring and the proximal methyl group in both **2b**[9,23] and **2c**[22] results in the aromatic ring partially obscuring the *Si* and *Re* faces of the diene component in the *syn* and *anti* forms, respectively (Figure 2).

The above analysis leads to a reactant-based explanation of the observed π-diastereofacial selectivity of the DA reactions of **2b** and **2c**, namely that the dienophile preferentially approaches the more exposed *Re* faces of the *syn* conformers of **2b** and **2c** and the more exposed *Si* faces of the *anti* conformers of these molecules. Because the *syn* conformer is more stable than the *anti* form in both **2b** and **2c**, which is greater for **2c**, it is concluded that *Re* facial selectivity prevails in these reactions and that it should be more pronounced when using **2c** as the diene reagent than with **2b**. A more rigorous approach is to compare the relative energies of the transition structures (TSs) for *Re* and *Si* addition modes. The results with B3LYP optimized TSs for *endo* addition of NMM to **2b** and **2c** are presented in Table 1.

Table 1: Energies of B3LYP-optimized TSs for *endo* addition of NMM to **2b** and **2c**.

Cycloaddition mode[a]	**2c** $H^{\ddagger}_{rel}$ $G^{\ddagger}_{rel}$	**2b** $H^{\ddagger}_{rel}$ $G^{\ddagger}_{rel}$
Re/syn	0 0	0 0
Si/syn	25.2 24.3	6.2 4.7
Re/anti	19.9 21.2	16.5 14.7
Si/anti	10.8 11.0	5.6 5.1

[a] See Figures 1 and 2 for definitions.

The results of these calculations clearly predict a strong preference for *Re*-face addition to the *syn* conformations of the two aminodendralenes and indicate that *Re* addition on the *anti* conformations is an unimportant pathway to *Re*-based product formation. The *Si*/*anti* channel is the near exclusive source of *Si*-based product from **2c**, whereas both *Si*/*anti* and *Si*/*syn* channels are contributors to the *Si*-based product in the case of **2b**. The relative free energy data in Table 1 indicate that π-diastereofacial selectivity in the DA reaction with NMM is stronger for aminodendralene **2c** than

for **2b**. In fact, a Boltzmann distribution calculation gives a total *Re*-based product/*Si*-based product ratio of 99:1 and 76:24 for **2c** and **2b**, respectively. These ratios are in reasonable accord with the experimental values of >95:5 and 73:27, respectively (Scheme 5).

The main structural features of the reactant aminodendralenes, as discussed above, are essentially retained in the respective Diels–Alder transition structures (TSs), as exemplified by **2c-*endo-Re-syn*-TS** and **2c-*endo-Si-anti*-TS** (Figure 3). A noteworthy feature of these TSs (and of those

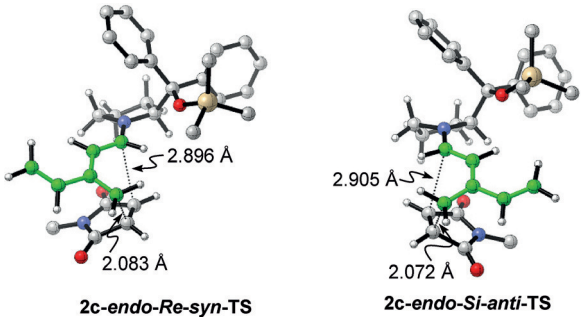
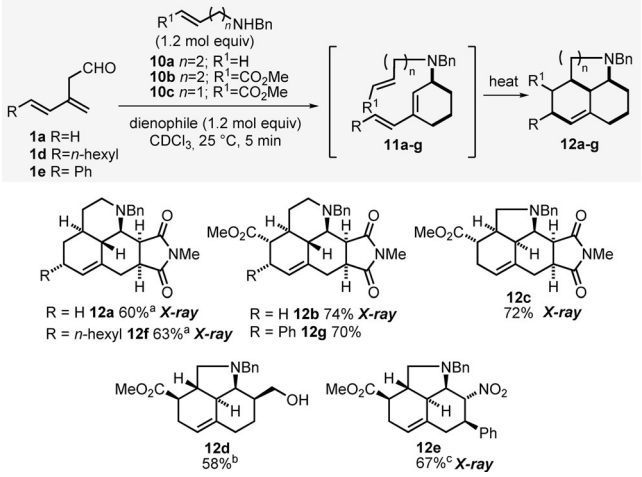


Figure 3. B3LYP/6-31G(d)-optimized TSs for the Diels–Alder cycloaddition of the NMM dienophile to aminodendralene **2c**. H atoms are omitted from phenyl and methyl groups and the dendralene is colored green for clarity.

not shown in the Figure) is the high degree of bond-forming asynchronicity between the two developing bonds between NMM and the dendralene diene component. Thus, the forming bond lengths in **2c-*endo-Re-syn*-TS** are 2.896 and 2.083 Å ($\Delta r = 0.81$ Å) and for **2c-*endo-Si-anti*-TS** they are 2.905 and 2.072 Å ($\Delta r = 0.83$ Å). The shorter forming bond involves C6 of the central double bond of the aminodendralene and this has the effect of conferring stabilizing pentadienyl radicaloid character on the dendralene component. This large degree of bond-forming asynchronicity is a general characteristic of dendralenes in their DA addition reactions.[24]

Tethering the dienophile to the amine (as in **10a–c**) permits the second cycloaddition (**11**→**12**) to be realized in an intramolecular[25] fashion (Scheme 6). The benefits of employing this tactic include: 1) the generation of additional structural complexity with complete orientational regioselectivity, 2) attainment of products with complementary stereoselectivity to the intermolecular process,[26] and 3) the ability to deploy nonactivated dienophiles (**10a**). Substituted dienals **1d** and **1e** also participate in the tricyclization sequence, thus confirming the robust character of this new method.

In summary, the first multicomponent reaction sequences involving dendralenic intermediates have been devised. These reactions are extraordinarily easy to perform in the laboratory, in most cases involving the mixing of simple precursors. The incorporation of a 1-amino-substituent on the [3]dendralene backbone simultaneously augments both its reactivity and selectivity in diene-transmissive Diels–Alder sequences,[24] at the same time delivering highly functionalized multicyclic products akin to alkaloids and medicinal



Scheme 6. Tricycle synthesis through one-pot, three-component sequences featuring an intramolecular Diels–Alder (IMDA) reaction. Major stereoisomer depicted, d.r. >95:5 unless indicated otherwise. [a] mono-adducts **11a** and **11f** were isolated before being subjected to intramolecular cycloaddition. [b] 2.5 mol equiv of amine and dienophile used, acrolein as dienophile, yield of isolated product after $NaBH_4$ reduction. [c] d.r. = 93:7.

agents. This study demonstrates the diversity of multicomponent transformations with only one amine group at a specific position of the simplest possible dendralene structure. Evidently, the possibilities for step-economic synthesis with aminodendralenes are vast.

Acknowledgements

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Keywords: density functional calculations · Diels–Alder reactions · domino reactions · multicomponent reactions · polycycles

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[1] P. A. Wender, B. L. Miller, in *Organic Synthesis: Theory and Applications* (Ed.: T. Hudlicky), JAI Press, Greenwich, **1993**, pp. 27–66.
[2] a) P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind. (London, U.K.)* **1997**, *765*, 767–769; b) P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197–201; c) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010–3021.
[3] N. J. Green, M. S. Sherburn, *Aust. J. Chem.* **2013**, *66*, 267–283.
[4] B. M. Trost, *Science* **1991**, *254*, 1471–1477.
[5] K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597–601.
[6] a) M. S. Sherburn, *Acc. Chem. Res.* **2015**, *48*, 1961–1970; b) H. Hopf, M. S. Sherburn, *Angew. Chem. Int. Ed.* **2012**, *51*, 2298–2338; *Angew. Chem.* **2012**, *124*, 2346–2389.

[7] First mention of diene-transmissive: O. Tsuge, E. Wada, S. Kanemasa, *Chem. Lett.* **1983**, 239 – 242.
[8] Reviews of diene-transmissive Diels–Alder sequences: a) J. D. Winkler, *Chem. Rev.* **1996**, *96*, 167 – 176; b) see Refs [6a] and [6b].
[9] N. J. Green, A. L. Lawrence, G. Bojase, A. C. Willis, M. N. Paddon-Row, M. S. Sherburn, *Angew. Chem. Int. Ed.* **2013**, *52*, 8333 – 8336; *Angew. Chem.* **2013**, *125*, 8491 – 8494.
[10] a) C. G. Newton, S. L. Drew, A. L. Lawrence, A. C. Willis, M. N. Paddon-Row, M. S. Sherburn, *Nat. Chem.* **2015**, *7*, 82 – 86; b) S. V. Pronin, R. A. Shenvi, *J. Am. Chem. Soc.* **2012**, *134*, 19604 – 19606; c) N. A. Miller, A. C. Willis, M. S. Sherburn, *Chem. Commun.* **2008**, 1226 – 1228.
[11] To our knowledge, only one report of such a system has been reported. Cyclic analogues of **2** participated in a [4+2] annulation with a strongly activated dienophile at the diene site remote to the amine substituent: a) K. S. Halskov, T. K. Johansen, R. L. Davis, M. Steurer, F. Jensen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 12943 – 12946. This outcome was subsequently traced to an inter-/intramolecular Michael addition sequence featuring a zwitterionic intermediate: b) A. Dieckmann, M. Breugst, K. N. Houk, *J. Am. Chem. Soc.* **2013**, *135*, 3237 – 3242.
[12] Many examples of condensations to form 1-amino-1,3-butadienes and subsequent Diels–Alder reactions have been reported. The earliest publication: a) H. R. Snyder, R. B. Hasbrouck, J. F. Richardson, *J. Am. Chem. Soc.* **1939**, *61*, 3558 – 3560; Recent reviews: b) H. Jiang, L. Albrecht, K. A. Jorgensen, *Chem. Sci.* **2013**, *4*, 2287 – 2300; c) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869 – 4883; d) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865 – 887; A review on enamine catalysis: S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471 – 5569.
[13] Notable compounds with this structure include the selective serotonin reuptake inhibitor sertraline, one of the most prescribed drugs in the USA, and members of the kalihinane diterpenoids, which exhibit potent antimalarial activity: a) W. M. Welch, *Adv. Med. Chem.* **1995**, *3*, 113 – 148; b) M. E. Daub, J. Prudhomme, K. Le Roch, C. D. Vanderwal, *J. Am. Chem. Soc.* **2015**, *137*, 4912 – 4915, and references therein.
[14] See the Supporting Information for full details.
[15] A related observation with an unbranched, skipped dienal during trienamine catalysis: L. Prieto, G. Talavera, U. Uria, E. Reyes, J. L. Vicario, L. Carrillo, *Chem. Eur. J.* **2014**, *20*, 2145 – 2148.
[16] K. Alder, G. Stein, *Angew. Chem.* **1937**, *50*, 510 – 519.
[17] The more substituted 1,3-butadiene group of 1-amino-[3]dendralene **2** contains a 1-amino substituent and a 3-vinyl group. Rawal-type dienes carry a 1-amino group and a 3-silyloxy group: S. A. Kozmin, J. M. Janey, V. H. Rawal, *J. Org. Chem.* **1999**, *64*, 3039 – 3052. Akin to Danishefsky dienes, Rawal dienes are highly reactive partners in normal-electron-demand cycloaddition reactions.
[18] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243 – 4244.
[19] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jorgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794 – 797; *Angew. Chem.* **2005**, *117*, 804 – 807; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212 – 4215; *Angew. Chem.* **2005**, *117*, 4284 – 4287.
[20] S. Lakhdar, B. Maji, H. Mayr, *Angew. Chem. Int. Ed.* **2012**, *51*, 5739 – 5742; *Angew. Chem.* **2012**, *124*, 5837 – 5840.
[21] The Gaussian 09 program was used for all calculations: M. J. Frisch, et al., Gaussian 09, revision E.1, Gaussian Inc., Wallingford CT, **2009**. See the Supporting Information for the full list of authors. All calculations refer to the gas phase and unless stated otherwise, activation parameters were calculated at 298.15 K.
[22] These findings are consistent with computational and experimental findings with related systems: a) U. Grošelj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi, T. Uchimaru, *Helv. Chim. Acta* **2009**, *92*, 1225 – 1259; b) M. B. Schmid, K. Zeitler, R. M. Gschwind, *Chem. Sci.* **2011**, *2*, 1793 – 1803; c) reference [11b].
[23] a) R. Gordillo, K. N. Houk, *J. Am. Chem. Soc.* **2006**, *128*, 3543 – 3553; b) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558 – 569.
[24] a) M. N. Paddon-Row, M. S. Sherburn, *Chem. Commun.* **2012**, *48*, 832 – 834; b) H. Toombs-Ruane, E. L. Pearson, M. N. Paddon-Row, M. S. Sherburn, *Chem. Commun.* **2012**, *48*, 6639 – 6641.
[25] Reviews of the intramolecular Diels–Alder reaction: a) A. G. Fallis, *Can. J. Chem.* **1984**, *62*, 183 – 234; b) D. Craig, *Chem. Soc. Rev.* **1987**, *16*, 187 – 238; c) B. R. Bear, S. M. Sparks, K. J. Shea, *Angew. Chem. Int. Ed.* **2001**, *40*, 820 – 849; *Angew. Chem.* **2001**, *113*, 864 – 894; d) K.-i. Takao, R. Munakata, K.-i. Tadano, *Chem. Rev.* **2005**, *105*, 4779 – 4807; e) W. R. Roush, in *Advances in Cycloaddition*, *Vol. 2* (Ed.: D. P. Curran), JAI Press, Greenwich, **1990**, pp. 91 – 146.
[26] The dienophile is constrained to approach the semicyclic diene from the same face as the amine with the shorter tether, as seen in the products **12c**, **d**, and **e**. Cycloadducts **12d** and **12e** are the result of an *endo*-selective IMDA reaction; we presume that the NMM-derived succinimide ring blocks *endo* approach of the -CO_2Me group, thereby resulting in the formation of *exo*-adduct **12c**. We suspect that similar steric influences cause an approach of the dienophile to the convex face of the semicyclic diene during the IMDA reaction of the longer tethered substrates, giving rise to adducts **12a**, **12b**, **12f**, and **12g**.
[27] CCDC nos. 1429160 – 1429173 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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