

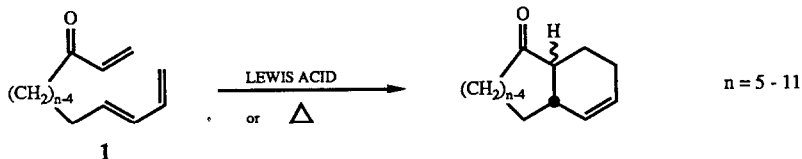
STERESELECTIVITIES OF THERMAL AND LEWIS ACID CATALYZED INTRAMOLECULAR DIELS-ALDER REACTIONS
OF INTERNALLY ACTIVATED DIENOPHILES TO FORM 5-11 MEMBERED RINGS¹

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Abstract: The thermal and Lewis acid catalyzed intramolecular Diels-Alder reactions of **1** ($n = 5-11$) have been studied. The catalyzed reactions efficiently form 7-11 membered rings and produce mainly cis adducts. Lewis acids prevent the five-membered ring forming reaction.

In 1983, Sakan showed that the Lewis acid catalyzed Diels-Alder reaction can be useful for the assembly of the fused eight-membered ring present in the taxane ring system.⁴ Sakan and Smith subsequently explored more generally the influence of methyl substituents and catalysis upon the rates and stereoselectivities of intramolecular Diels-Alder reactions which generate an eight-membered ring.^{5,6} In this paper, we report the stereochemistries and, indeed, feasibilities of the intramolecular Diels-Alder reactions of the general diene, **1**, which forms 5-11 membered rings in thermal or catalyzed processes.



The Table shows the results from our studies or from related literature studies.^{7,8} The results from the intermolecular Diels-Alder reaction of trans-piperylene with methyl vinyl ketone are also shown for comparison.

Table. Results of Thermal and Acid-Catalyzed Cycloadditions of **1** (n = 5-11).^a

n	Thermal Reactions ^b			Catalyzed Reactions ^c	
	time (h) / temp (°C)	isolated yield (%)	cis:trans ratio ^d	isolated yield (%)	cis:trans ratio ^d
5	1.5 / 180 ^e	51	87:13	0	-
6	4 / 22 ^f	100	95:5	g	-
	120 / 22 ^f	-	10:90		
	1 / 0 ^h	78	only <u>cis</u>		
7	5 / 155	90	62:38	88	only <u>cis</u>
8	68 / 140	53	64:36	69	only <u>cis</u>
9	96 / 155	14-19	46:54	23-37	90:10
10	200 / 155	0	-	6-30	80:20
11	100 / 155	0	-	11-24	86:14
0 ⁱ	252 / 140	54 ^j	78:22	25 ^k	95:5

^aAll compounds were characterized by ¹H and ¹³C NMR, IR, and high resolution MS. Cycloadducts were shown to be configurationally stable under both thermal and catalyzed conditions. For references to nmr data on such systems, see reference 1.

^b-0.01M **1** benzene or toluene, sealed tube.

^c0.02M **1** in benzene added to 0.1M Me₂AlCl in benzene over 2-3 hours at room temperature.

^dDetermined by ¹H NMR at 600 MHz or by capillary GC.

^e0.2M **1** in refluxing *o*-dichlorobenzene under argon.

^fRef. 7.

^gNot attempted, since thermal reaction is so fast.

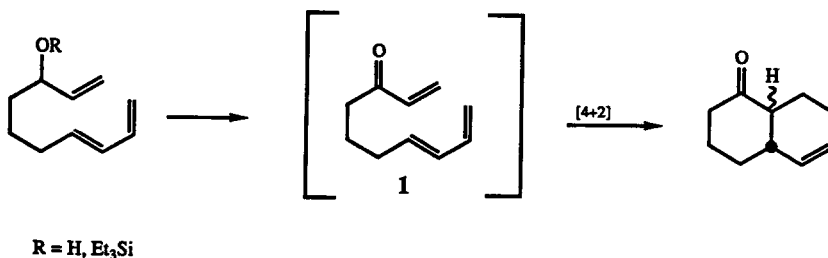
^hRef. 8

ⁱ0.1M trans-piperylene and 0.1M methyl vinyl ketone in benzene, sealed tube.

^j13% of 1.75:1 mixture of the meta cycloadducts was also observed.

^k<1% of a single meta cycloadduct was observed.

The intermolecular reactions and the intramolecular reactions leading to 5 and 7-9 membered rings all occur readily only at temperatures above 140°. The reactions which would form 10 and 11 membered rings did not occur under the conditions tried. By contrast, the reaction in which the six-membered ring is formed occurs very rapidly even at room temperature.^{7,8} Although it is possible that the oxidant used to form **1** ($n = 6$) catalyzes the reaction,⁹ it is more likely that the reactant can achieve the ideal transition state conformation without distortion of the side-chain.¹⁰ Enthalpic, rather than entropic, effects must be crucial here, since reactions with $n = 5$ or 7, which must have entropies of cyclization very similar to that in which $n = 6$, react at normal, unaccelerated, rates.



Under Lewis acid catalyzed conditions all the cycloadditions occurred at or below room temperature even when $n = 10$ or 11. The sole exception is when $n = 5$, where adduct formation is completely suppressed. The preference of Lewis acid-enone complexes to exist in a planar, s-trans enone conformation is known.¹¹ Models show that these constraints make it virtually impossible for the diene and dienophile connected by a three atom chain to adopt a conformation which is suitable for the intramolecular cycloaddition to form a hydrindenone.

The thermal reactions show high stereoselectivities only for the cases where $n = 5$ or 6. Here the cisoid enone must be involved, and the stereoselectivity is somewhat higher than for the intermolecular case. As the length of the connecting chain increases, however, the steric interactions between the connecting chain and the hydrogen on C3 of the diene (which is pyramidalized downward¹²) increases. This disfavors the endo transition state and therefore decreases the stereoselectivity of the cycloaddition.¹⁰ Similar arguments have recently been advanced to explain the stereoselectivities observed in the intramolecular Diels-Alder reaction of terminally activated trienes leading to hydrindane and decalin derivatives.¹³

The catalyzed reactions all give high cis-stereoselectivity. This is related to the transoid conformation of the Lewis acid coordinated enone. This prevents $n = 5$ (and probably $n = 6$) from reacting. The lower stereoselectivity in larger cases is most likely due to steric effects involving the side-chains.

The feasibility and stereoselectivity of the intramolecular Diels-Alder reaction for the synthesis of medium ring systems which are otherwise not readily obtainable is of major importance for natural products synthesis. Our efforts in this area will be reported in due course.

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