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Lewis Acid Catalyzed Intramolecular Diels–Alder Reactions of Acyclic (*Z*)-Substituted 1,3-Dienes

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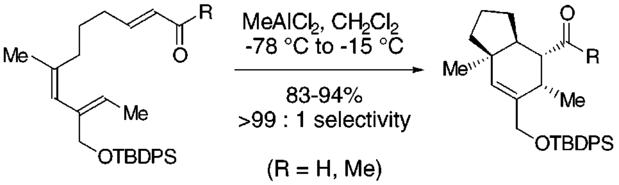
ABSTRACT



7a,b **8a,b**

Lewis acid catalyzed intramolecular Diels–Alder reactions of trienes (*E,E,Z*)-1a–d, (*E,E,Z*)-4a–d, and (*E,Z,Z*)-7a,b are described. Trienes containing enal or enone dienophiles cyclize in excellent yield under mild conditions using substoichiometric amounts of MeAlCl$_2$, in most cases with high levels of diastereoselectivity. The thermal IMDA reactions of 1a, 4a, and 7a require forcing conditions and proceed in low yield with reversed stereoselectivity in the cases of 1a and 4a.

The intramolecular Diels−Alder (IMDA) reactions of (*E*,*E*,*E*)- and (*Z*,*E*,*E*)-1,6,8-nonatrienes and -1,7,9-decatrienes are now regarded as classic methods for the synthesis of the hexahydro-1*H*-indene and octahydronaphthalene substructures that occur in a wide range of natural products.[1−3] However, use of acyclic (*Z*)-1,3-dienes or dienes with (*Z*)-substituents as substrates for intramolecular Diels−Alder has been limited owing to their substantially diminished reactivity[4,5] and propensity for olefin isomerization under thermal reaction conditions.[6−10] Apart from (*Z*)-1,3-dienes (or dienes with (*Z*)-substituents) constrained in macrocyclic ring systems,[11] the available accounts of IMDA reactions of acyclic alkyl-substituted (*Z*)-dienes have not adequately addressed the scope or utility of such systems.[12−28] In particular, use of Lewis acid catalysts to circumvent the harsh conditions

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(1) Ciganek, B. *Org. React.* **1984**, *32*, 1.
(2) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.
(3) Roush, W. R. In *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 513−550.
(4) Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*; Wiley: New York, 1990.
(5) Oppolzer, W. In *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 315−398.
(6) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061.
(7) Borch, R. F.; Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.* **1975**, *97*, 6282.
(8) Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48.
(9) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170.
(10) Matikainen, J.; Kaltia, S.; Hämäläinen, M.; Hase, T. *Tetrahedron* **1997**, *53*, 4531.
(11) Deslongchamps, P. *Tetrahedron* **2001**, in press.
(12) Pyne, S. G.; Hensel, M. J.; Byrn, S. R.; McKenzie, A. T.; Fuchs, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 5960.
(13) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719.
(14) Boeckman, R. K., Jr.; Alessi, T. R. *J. Am. Chem. Soc.* **1982**, *104*, 3216.
(15) Koreeda, M.; Luengo, J. I. *J. Org. Chem.* **1984**, *49*, 2079.
(16) Yoshioka, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133.
(17) Wattanasin, S.; Kathawala, F. G.; Boeckman, R. K., Jr. *J. Org. Chem.* **1985**, *50*, 3810.
(18) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *Tetrahedron Lett.* **1985**, *36*, 3307.
(19) Burke, S. D.; Armistead, D. M.; Shankaran, K. *Tetrahedron Lett.* **1986**, *27*, 6295.
(20) Magnus, P.; Walker, C.; Jenkins, P. R.; Menear, K. *Tetrahedron Lett.* **1986**, *27*, 651.
(21) Koreeda, M.; Ricca, D. J.; Luengo, J. I. *J. Org. Chem.* **1988**, *53*, 5586.
(22) Corey, E. J.; Jardine, P. S.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672.
(23) Kozikowski, A. P.; Tückmantel, W. *J. Org. Chem.* **1991**, *56*, 2826.
(24) Jackson, R. W.; Shea, K. J. *Tetrahedron Lett.* **1994**, *35*, 1317.
(25) Tatsuta, K.; Itoh, M.; Hirama, R.; Araki, N.; Kitagawa, M. *Tetrahedron Lett.* **1997**, *38*, 583.

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required for thermal IMDA reactions of acyclic dienes with (*Z*)-substituents has largely been restricted[21] to Type II IMDA cyclizations in the taxanoid series.[29−34] Recent work in our laboratory has established that *inter*molecular Diels−Alder reactions of (*Z*)-substituted dienes can proceed in high yields with excellent regio- and *endo*-selectivity at low temperatures in the presence of Lewis acid catalysts.[35] This prompted us to explore the Lewis acid catalyzed Type I IMDA reactions of trienes containing acyclic (*Z*)-substituted diene units, with hope that this tactic would lead to efficient cycloaddition in these cases.

We targeted trienes (*E*,*E*,*Z*)-**1**, (*E*,*E*,*Z*)-**4**, and (*E*,*Z*,*Z*)-**7** to assess the applicability of Lewis acid catalyzed IMDA reactions of (*Z*)-substituted 1,3-dienes leading to angularly methylated hexahydroindene and octahydronaphthalene ring systems (Figure 1). Substrates **1** and **4**, with terminally activated (*E*)-dienophiles, potentially can give rise to two products: the *trans*-fused cycloadducts **2** and **5** via *endo* transition states, and the *cis*-fused products **3** and **6** via *exo* transition states. Substrates with (6*Z*)-diene geometry as in **7** are known to react thermally via *cis*-fused transition states, which are the only transition structures that are geometrically feasible in such cases.[3] The effect of Lewis acid catalysis on trienes such as **1**, **4**, and **7** has not been documented previously.

The Lewis acid catalyzed IMDA reactions of trienes **1**, **4**, and **7** were initiated by addition of the Lewis acid to a 0.08 M solution of the substrate at −78 °C, typically in CH_2Cl_2 (see Table 1).[36] Warming the reaction mixtures over a several-hour period to the final temperatures indicated in the table led to smooth Diels−Alder reaction in the cases of aldehyde (**a**, **c**) and methyl ketone (**b**) activated substrates. However, the less reactive methoxycarbonyl (**d**) activated substrates did not cyclize under a variety of conditions (entries 5 and 10).[37] Monitoring of the reaction progress by TLC indicated that product formation began to occur in the $MeAlCl_2$-promoted cyclizations of **1a**, **1b**, **4a**, and **4b** at approximately −40 °C, while products began to appear in the cyclizations of **1c**, **4c**, **7a**, and **7b** at −25 to −15 °C. Competing acid-promoted pathways were observed in several instances, in particular cleavage of TBDPS ethers (for reactions above 0 °C) and acid-catalyzed diene isomerization/oligomerization depending upon reactions conditions. Use of strong Lewis acids ($AlCl_3$, $TiCl_4$, $SnCl_4$) and longer reaction times (especially with sluggish substrates) promoted substrate decomposition. While results obtained using Me_2AlCl as the Lewis acid catalyst were similar to those obtained with $MeAlCl_2$, Me_3Al (the weakest Lewis acid in the series) failed to promote IMDA reactions of the most reactive substrate, aldehyde **1a**. Comparative thermal IMDA reactions of **1a** (entry 2) and **7a** (entry 12) proceeded slowly at 180 °C. The homolog **4a** (entry 8) did not react at 180 or 250 °C, even after 96 h. Heating **4a** in a sand bath at 355 °C for 24 h finally gave a low yield of the IMDA products **5a** and **6a**, plus a complex mixture of isomerized diene.

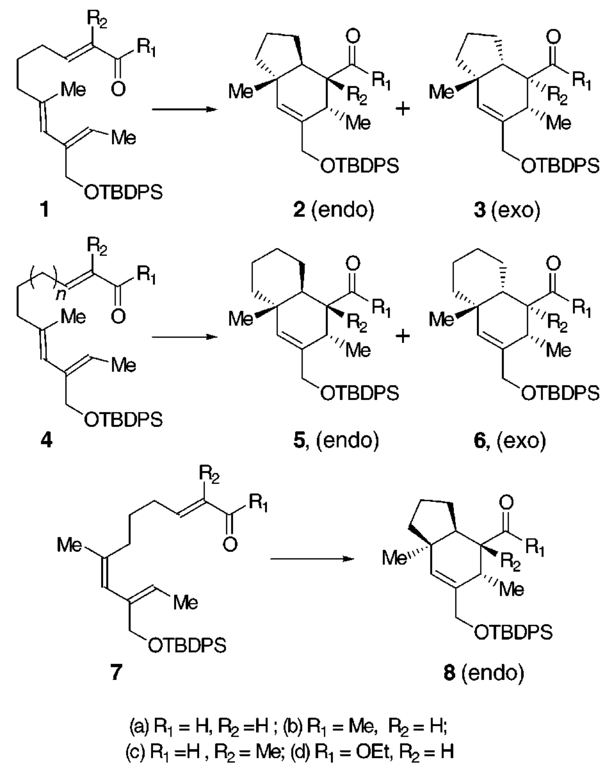

Figure 1.

The $MeAlCl_2$-catalyzed cyclizations of aldehydes **1a** (entry 1) and **4a** (entry 6) and methyl ketones **1b** (entry 2) and **4b** (entry 8) were highly selective for the *trans*-fused products **2a**, **2b**, **5a**, and **5b**, paralleling the behavior of corresponding (*E*,*E*)-diene substrates.[3,38] The selectivity in these cases can be explained by invoking transition states **A** and **E**, respectively. Since **1** and **4** have externally activated dienophiles, these reactions are thought to proceed via concerted but asynchronous pathways with advanced bonding between the internal carbons due to the high LUMO coefficient on the dienophile β-carbon.[3] *Endo* orientation of the *s-trans*, Lewis acid complexed dienophile is believed to be favored as a

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[26] Grimaud, L.; Férézou, J.-P.; Prunet, J.; Lallemand, J.-Y. *Tetrahedron* **1997**, *27*, 9253.

[27] Back, T. G.; Payne, J. E. *Org. Lett.* **1999**, *1*, 663.

[28] Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866.

[29] Brown, P. A.; Jenkins., P. R. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1303.

[30] Bonnert, R. V.; Jenkins, P. R. *Tetrahedron Lett.* **1987**, *28*, 697.

[31] Rubenstein, S. M.; Williams, R. M. *J. Org. Chem.* **1995**, *60*, 7215.

[32] Winkler, J. D.; Kim, H. S.; Kim, S. *Tetrahedron Lett.* **1995**, *36*, 687.

[33] Jenkins, P. R. *Pure Appl. Chem.* **1996**, *68*, 771.

[34] Forgione, P.; Wilson, P. D.; Yap, G. P. A.; Fallis, A. G. *Synthesis* **2000**, 921.

[35] Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402.

[36] Syntheses of trienes **1**, **4**, and **7** are described in the Supporting Information.

[37] We also synthesized an acyl oxazolidine activated triene in series **1**. Attempts to promote the Lewis acid catalyzed cyclization of this substrate were also unsuccessful under a variety of conditions.

[38] Roush, W. R.; Essenfeld, A. P.; Warmus, J. S.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7305.

[39] Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297.

[40] Raimondi, L.; Brown, F. K.; Gonzalez, J.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 4796.

[41] Roush, W. R.; Essenfeld, A. P.; Warmus, J. S. *Tetrahedron Lett.* **1987**, *28*, 2447.

Table 1. Thermal and Lewis Acid Catalyzed Intramolecular Diels−Alder Reactions of Trienes **1**, **4**, and **7**

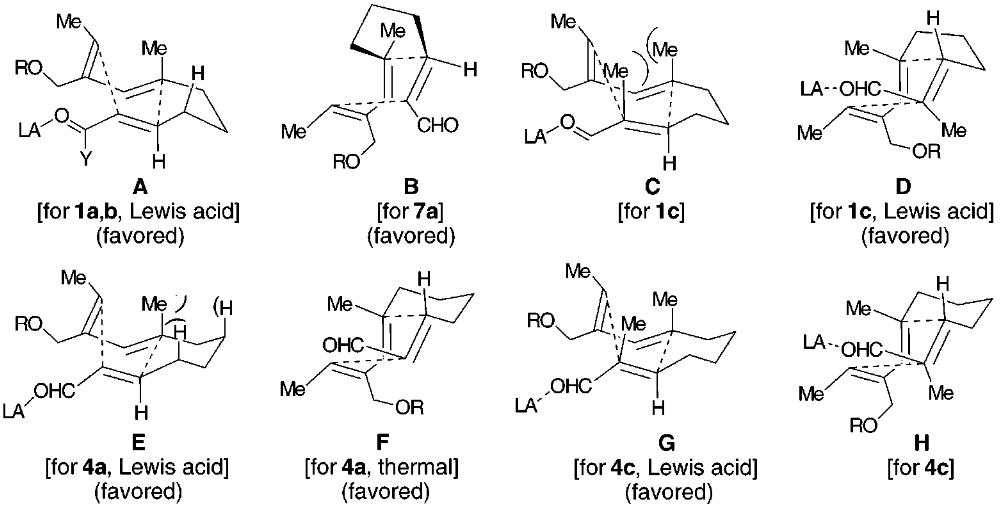
entry	substrate	conditions[a]	product yield (%)[b]	products	ratio[c]
1	**1a**	0.4 equiv $MeAlCl_2$, −78 → 23 °C, 2 h	62	**2a**:**3a**	>99:1
2	**1a**	184 °C, toluene, sealed tube, 45 h	23	**2a**:**3a**	37:63
3	**1b**	0.8 equiv $MeAlCl_2$, −78 → 23 °C, 45 min	86	**2b**:**3b**	>99:1
4	**1c**	0.8 equiv $MeAlCl_2$, −78 → 0 °C, 1.5 h	77	**2c**:**3c**	37:63
5	**1d**	1.3 equiv $MeAlCl_2$, toluene, −78 → 110 °C, 7 h	0		
6	**4a**	0.9 equiv $MeAlCl_2$, −78 → −30 °C, 4 h	66	**5a**:**6a**	89:11
7	**4a**	355 °C, toluene, sealed tube, 22 h	39	**5a**:**6a**	20:80
8	**4b**	0.4 equiv $MeAlCl_2$, −78 → −10 °C, 2 h	78	**5b**:**6b**	>99:1
9	**4c**	0.7 equiv $MeAlCl_2$, −78 → −10 °C, 4.5 h	87	**5c**:**6c**	94:6
10	**4d**	1.0 equiv $SnCl_4$, −78 → −10 °C, 3 h	0		
11	**7a**	0.6 equiv $MeAlCl_2$, −78 → −15 °C, 2 h	83	**8a**	1:>99
12	**7a**	180 °C, toluene, sealed tube, 23 h	50	**8a**	1:>99
13	**7b**	0.4 equiv $MeAlCl_2$, −78 → −20 °C, 2 h	94	**8b**	1:>99

[a] Reactions performed in CH2Cl$_2$ unless otherwise noted. $MeAlCl_2$ was added as a 1.0 M solution in hexane. [b] Combined yield of products after purification by silica gel chromatography. [c] Product ratios determined by ^1H NMR analysis of crude reaction mixtures. Stereostructures were assigned by using ^1H NOE and *J* data.

result of the steric constraints of the methylene tether and enhanced diene HOMO/dienophile LUMO orbital interactions.[39,40]

The switch in selectivity for the thermal IMDA reactions of trienes **1a** (entry 2) and **4a** (entry 7) compared to the Lewis acid catalyzed reactions (entries 1 and 6, respectively) is especially noteworthy. The thermal reactions of these trienes led to a predominance of the *cis*-fused cycloadducts in both cases. Trienes containing disubstituted (*E*,*E*)-dienes generally display good to excellent *trans* ring fusion selectivity in thermal IMDA reactions, and the preference for the *trans*-fused product is always enhanced in the presence of Lewis acids.[3,41] To reconcile this striking difference in selectivity in the thermal vs Lewis acid promoted cyclizations of **1a** and **4a**, we suggest that the thermal reaction is dominated by an overriding steric effect induced by the diene (*Z*)-methyl group (see interactions highlighted in t.s. **E**). Assuming that the four-carbon tether of **4a** adopts a chairlike conformation, 1,3-diaxial interactions involving the dienyl (*Z*)-methyl group destabilize the *trans* transition state **E** compared to the *cis*-fused t.s. **F** by up to 1.8 kcal/mol in the thermal reaction (Figure 2). The less pronounced selectivity for the *cis*-fused product **3a** in the thermal reaction of **1a** possibly can be attributed to the easing of these steric interactions, since the shorter three-carbon tether adopts an envelope conformation in which the pseudoaxial vinyl methyl group experiences less severe 1,3-interactions in transition state **C**. Evidently, Lewis acid activation of **1a** and **4a** must decrease the HOMO/LUMO gap by such a degree so as to overcome the steric demands of the *trans* transition states, such that transition states **A** and **E** are favored in the Lewis acid promoted reactions.

The results for the Lewis acid promoted cyclizations of the α-methyl enal substrates **1c** (entry 4) and **4c** (entry 9)



A [for **1a**,**b**, Lewis acid] (favored)

B [for **7a**] (favored)

C [for **1c**]

D [for **1c**, Lewis acid] (favored)

E [for **4a**, Lewis acid] (favored)

F [for **4a**, thermal] (favored)

G [for **4c**, Lewis acid] (favored)

H [for **4c**]

Figure 2. Transition States for the IMDA Reactions.

also warrant brief comment. The cyclization of **4c** gave high *trans* selectivity via t.s. **G**, similar to the selectivity pattern observed with the aldehyde (**4a**) and methyl ketone (**4b**) activated substrates. Surprisingly, however, the Lewis acid promoted cyclization of **1c** preferentially led to the *cis*-fused product **3c**, a result that deviates from the highly *trans* selectivity realized with **1a** and **1b**. Analysis of the possible transition states for **1c** reveals that the *trans* transition state **C** is destabilized by an interaction between the dienophile α-methyl group and the (*Z*)-methyl group of the diene. Application of the precepts of twist asynchronicity[39,40] in t.s. **C** for the Lewis acid promoted reaction of **1c** suggests that these methyl groups will be pushed toward one another, thereby magnifying this destabilizing interaction. Accordingly, the sterically less demanding *exo* transition state **D** is favored in this case. However, the steric requirements must be relaxed in the analogous *trans* transition state **G** for **4c** (as compared to t.s. **C** for **1c**) as a result of the extra methylene of the tether and the corresponding decreased contribution of twist asynchronicity in the IMDA reactions of 1,8,10-undecatrienes.[39] Thus, frontier orbital interactions predominate to impart the observed high *trans*-fused, *endo* selectivity in the IMDA reaction of **4c**.

The thermal and Lewis acid catalyzed cyclizations of trienes **7a,b** proceed with excellent selectivity via t.s. **B**. The corresponding *exo*- (or *trans*-fused) transition state is geometrically inaccessible with (*E*,*Z*,*Z*)-trienes of this type.[3]

In summary, we have demonstrated that carboxaldehyde or methyl ketone activated trienes **1a**–**c**, **4a**–**c**, and **7a,b**, with 1,1,4-trisubstitution patterns in the diene units, undergo efficient and usually highly stereoselective Lewis acid catalyzed intramolecular Diels–Alder reactions in the presence of substoichiometric amounts of $MeAlCl_2$ or Me_2AlCl at subambient temperatures. Accordingly, (*Z*)-alkyl-substituted 1,3-dienes may now be considered to be synthetically viable IMDA substrates. Applications of this technology in natural products synthesis will be reported in due course.

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Note Added after ASAP: The substituent key for R groups in Figure 1 was omitted in the version posted ASAP on 2/22/01. This error was corrected in the version posted 2/27/01.

Supporting Information Available: Summaries of the syntheses of trienes **1a**–**c**, **4a**–**c**, and **7a,b**; representative procedure for the Lewis acid catalyzed intramolecular Diels–Alder reactions of **1a**–**c**, **4a**–**c**, and **7a,b**; tabulated spectroscopic data for cycloadducts **2a**–**c**, **3a**, **3c**, **5a**–**c**, **6a**, **6c**, and **8a,b**; and summaries of cycloadduct stereochemical assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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