

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

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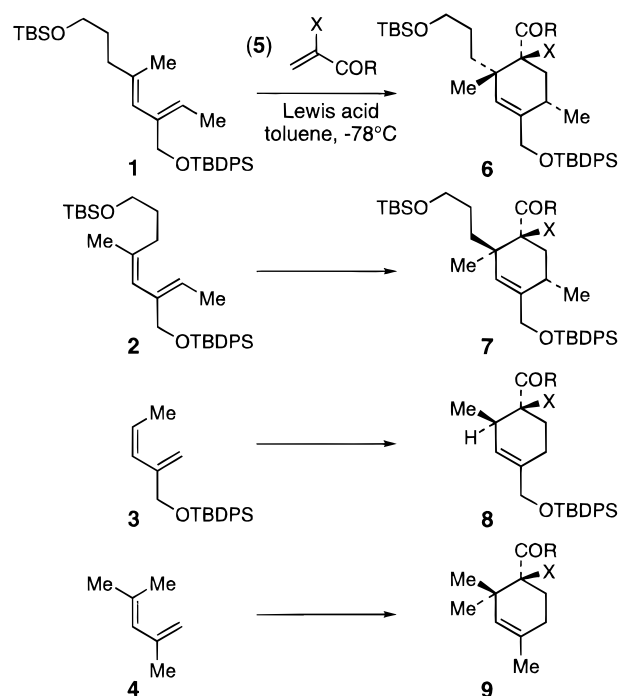
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Acyclic (*Z*)-1,3-dienes are widely regarded as exceptionally poor substrates for Diels–Alder reactions.^{1,2} Exceptions to this generalization are oxygenated and other heteroatom-substituted (*Z*)-1,3-dienes, which undergo cycloaddition reactions with a range of conventional and hetero dienophiles.^{1–5} (*Z*)-1,3-Dienes have also been successfully employed in intramolecular Diels–Alder reactions,^{6–13} especially recently in the taxane series.^{14–18} However, scattered reports of successful thermal^{19–21} and Lewis acid catalyzed^{22–29} Diels–Alder reactions of (*Z*)-1,3-dienes suggested to us that the prospects of using these compounds as intermediates in organic synthesis might not be as bleak as has been widely assumed. We are most pleased, therefore, to report herein the first extensive study of Lewis acid catalyzed Diels–Alder reactions of (*Z*)-1,3-dienes **1–4**, which in most cases proceed with excellent regio- and high *endo*-selectivity (Scheme 1).

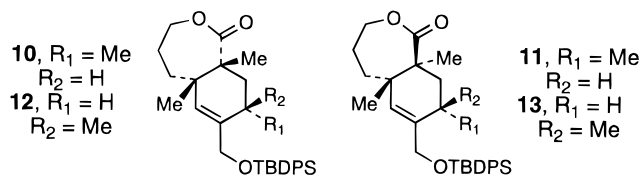
We began by exploring the Diels–Alder reactions of diene **1** with α -acetoxyacrolein (**5a**).^{28,30} Thus, treatment of **1** with 3.8 equiv of **5a** and 1.2 equiv of SnCl₄ in a 3:1 mixture of toluene and CH₂Cl₂ at –78 °C for 1 h provided *endo*-cycloadduct **6a** in 90% yield with 96:4 selectivity (Table 1, entry 1). Encouraged by this exciting result, we explored the reactions

Scheme 1



(a) X = OAc, R = H; (b) X = Br, R = H; (c) X = Me, R = H;
(d) X = R = H; (e) X = Me, R = Cl; (f) X = H, R = Cl; (g), X = Me,
R = OMe; (h) X = H, R = OMe; (i) X = H, R = NHBzl

of **1** with a range of other dienophiles, including α -bromoacrolein (**5b**), methacrolein (**5c**), acrolein (**5d**), methacryloyl chloride (**5e**), and acryloyl chloride (**5f**) (Table 1, entries 2–6). These reactions were performed in toluene using MeAlCl₂ as the Lewis acid catalyst (typically 1.1 equiv, although recently we have found that substoichiometric amounts of the Lewis acid may be employed (cf., entries 10, 17, 18, 19)). The reactions with **5b**, **5d**, and **5f** were complete within 1 h at –78 °C and provided cycloadducts **6b**, **6d**, and **6h**, respectively, in excellent yield and generally with excellent *endo*-selectivity (entries 2, 4, and 6). It should be noted that the reaction with acryloyl chloride (**5f**) was quenched with MeOH and Et₃N, thereby providing methyl ester **6h** as the major product. The reactions with methacrolein (**5c**; entry 3) and methacryloyl chloride (**5e**; entry 5) were more sluggish and required longer reaction times or higher temperatures for complete reaction. The reaction with methacryloyl chloride (entry 5) provided a 4:1 mixture of the *endo*- and *exo*-lactones **10** and **11**.



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- (30) Syntheses of dienes **1–3** and details of the stereochemical assignments for cycloadducts **6–8** are provided in the Supporting Information.

Table 1. Lewis Acid Catalyzed Diels–Alder Reactions of (*Z*)-Dienes 1–4

entry	diene	dienophile (equiv)	Lewis acid (equiv)	conditions ^a	product(s)	yield (%) ^b	endo:exo
1	1	5a (3.8)	SnCl ₄ (1.2)	A	6a (R = H, X = OAc)	90	96:4
2	1	5b (2.1)	MeAlCl ₂ (1.1)	B	6b (R = H, X = Br)	96	96:4
3	1	5c (2.5)	MeAlCl ₂ (1.1)	C	6c (R = H, X = Me)	87	90:10
4	1	5d (3.0)	MeAlCl ₂ (1.1)	B	6d (R = X = H)	88	90:10
5	1	5e (2.5)	MeAlCl ₂ (1.1)	D, E	10, 11	80 ^c	80:20 ^c
6	1	5f (3.0)	MeAlCl ₂ (1.1)	B, E	6h (R = OMe, X = H)	95	84:16
7	2	5a (2.4)	SnCl ₄ (1.2)	A	7a (R = H, X = OAc)	88	>98:<2
8	2	5b (5.0)	MeAlCl ₂ (1.1)	B	7b (R = H, X = Br)	84	97:3
9	2	5c (2.5)	MeAlCl ₂ (1.1)	F	7c (R = H, X = Me)	97	93:7
10	2	5d (2.5)	MeAlCl ₂ (0.5)	B	7d (R = X = H)	90	95:5
11	2	5e (2.5)	MeAlCl ₂ (1.1)	B, E	12, 13	86	7:93
12	2	5f (2.5)	MeAlCl ₂ (1.1)	B, G	7h (R = OMe, X = H)	98	46:54
13	3	5a (1.3)	MeAlCl ₂ (1.1)	B	8a (R = H, X = OAc)	75	96:4
14	3	5c (3.0)	MeAlCl ₂ (1.1)	H	8c (R = H, X = Me)	98	>98:<2
15	3	5d (3.0)	MeAlCl ₂ (1.1)	H	8d (R = X = H)	91	96:4
16	3	5e (3.0)	MeAlCl ₂ (1.1)	B, E	8g (R = OMe, X = Me)	77	93:7
17	4	5a (1.5)	MeAlCl ₂ (0.2)	B	9a (R = H, X = OAc)	60	
18	4	5c (2.0)	MeAlCl ₂ (0.2)	B	9c (R = H, X = Me)	64	
19	4	5d (2.0)	MeAlCl ₂ (0.2)	B	9d (R = X = H)	97	
20	4	5f (3.0)	MeAlCl ₂ (1.2)	B, I	9i (R = NHBzl, X = H)	54	

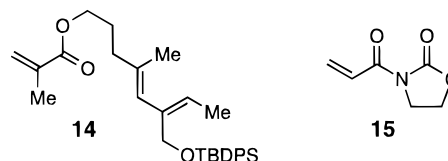
^a Conditions: A, 3:1 toluene–CH₂Cl₂, –78 °C, 1 h; B, toluene, –78 °C, 1 h; C, toluene, –60 to –65 °C, 20 h; D, toluene, –78 °C, 2 h, then –20 °C, 0.5 h; E, excess MeOH and Et₃N were added prior to workup; F, toluene, –78 to –30 °C, 90 min; G, excess MeOH and pyridine were added prior to workup; H, toluene, –78 °C, 1–3 h, then –20 °C, 30 min; I, 20 equiv of PhCH₂NH₂ was added prior to workup. ^b Combined isolated yield of *endo* and *exo* products. ^c In addition, 13% of a 4:1 mixture of methyl ketones was obtained.

93–>98% *endo*-selectivity (entries 7–10). As was also the case with the reactions of **1**, other regioisomers were not detected. The reaction of **2** and methacryloyl chloride (entry 11) provided a 93:7 mixture of lactones **13** and **12**, with the *exo*-adduct **13** predominating, while the reaction of **2** and acryloyl chloride (entry 12) provide a ca. 1:1.2 mixture of **7h** and the corresponding *exo*-cycloadduct.

Additional examples of Lewis acid catalyzed Diels–Alder reactions of acyclic (*Z*)-dienes **3** and **4** are provided in entries 13–20. The efficiency of these reactions, especially those of **4**, was lower than that obtained with **1** and **2** either due to the lower reactivity of these dienes^{31,32} and/or their increased susceptibility toward Lewis acid promoted oligomerization.³³ Nevertheless, the reactions of **3** still displayed exceptional regio- and *endo*-selectivity (93–>98%), even that with methacryloyl chloride (entry 16). However, our attempts thus far to achieve Lewis acid catalyzed Diels–Alder reactions with (*Z*)-2,4-pentadiene have been unsuccessful, even though Lewis acid catalyzed reactions of this diene with quinone and maleic anhydride dienophiles have been reported previously.^{22,29} (*Z*)-2,4-Pentadiene is an exceptionally unreactive diene,^{31,32} and we suspect that this compound simply oligomerizes under the conditions we have explored to date.^{22,33}

The reactions summarized in entries 5, 6, 11, 12, 16, and 20 are examples of relatively rare Lewis acid catalyzed Diels–Alder reactions of α,β -unsaturated acid chlorides.³⁴ It is interesting to speculate that acylium ions could be involved in

these reactions.³⁵ Careful monitoring of the reactions in entries 5 and 11 indicated that lactones **10–13** are formed post-cycloaddition. In addition, control experiments established that acrylate ester **14** failed to undergo an intramolecular Diels–Alder reaction in the presence of MeAlCl₂, even at 23 °C for 24 h. Attempts to use acrylate esters or imide **15** as the dienophile in reactions with **1** were unsuccessful.



In summary, we have demonstrated that the Lewis acid catalyzed Diels–Alder reactions of acyclic (*Z*)-dienes **1–3** proceed with exceptional regioselectivity, and in most cases, excellent stereoselectivity. The ability to generate vicinal quaternary centers in cycloadducts such as **6a–c** and **7a–c** with exceptional stereocontrol ($\geq 90:10$) is both striking and virtually unprecedented. Additional studies designed to extend the potential of these reactions in organic synthesis are in progress.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (29 pages). See any current masthead page for ordering and Internet access instructions.

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