Intramolecular Diels–Alder Reaction by Self-Assembly of the Components on a Lewis Acid Template

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ABSTRACT



Diels-Alder reactions of 2,4-hexadienol or its *O*-methyl ether with acrylate derivatives at 120 °C give mixtures of the four possible adducts with low selectivity. At ambient temperature and in the presence of Mg(II) or Al(III) Lewis acids, reactions of the dienol (but not the ether) are highly selective. Control experiments suggest that the Lewis acid serves both to tether the diene and dienophile and to induce an "intramolecular" reaction of the resulting "self-assembled" intermediate.

The Diels–Alder (DA) reaction is perhaps the most powerful and versatile reaction in the synthetic chemist's arsenal, in part because of the continuous evolution of strategies to improve reactivity and selectivity. In this regard, the use of Lewis acid mediators has been particularly successful in expanding the scope of the DA reaction.¹ Similarly, the many advantages of the intramolecular Diels–Alder (IMDA)² reaction have been extended to the intermolecular counterpart by covalently linking the diene to the dienophile via a "temporary" tether.^{3,4} In this paper we report a combination

10.1021/ol0067235 CCC: \$19.00 © 2000 American Chemical Society Published on Web 11/03/2000 of these approaches whereby a Lewis acid serves both to tether the diene and dienophile and to induce an "IMDA" reaction of the resulting "self-assembled" intermediate.

The DA reaction is often limited by the poor reactivity associated with *cis*-substituted dienes.⁵ We have investigated the potential of 2*H*-thiopyrans to act as surrogates for *cis*dienes in a strategy to overcome this limitation.^{6,7} The facility of these DA reactions is increased by using Lewis acids^{8a} and in intramolecular applications;^{8b} however, our attempts to further extend the scope of the process using a sulfurbased temporary tether to attach the dienophile were unsuccessful.^{8b} Subsequently, we considered the feasibility of using a multivalent Lewis acid to coordinate simultaneously to the diene and dienophile and promote an IMDA reaction of the resulting complex (Figure 1). A search of

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⁽²⁾ Reviews: (a) Roush, W. R. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 513– 550. (b) Oppolzer, W. Angew. Chem., Int. Ed. Engl. 1977, 16, 10–23. (c) Brieger, G.; Bennett, J. N. Chem. Rev. 1980, 80, 63–97. (d) Fallis, A. G. Can. J. Chem. 1983, 62, 183–234. (e) Taber, D. F. In Intramolecular Diels– Alder and Alder Ene Reactions; Springer-Verlag: New York, 1984. (f) Craig, D. Chem. Soc. Rev. 1987, 16, 187–238.

⁽³⁾ Reviews: (a) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289–2338. (b) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253–1277. (c) Fensterbank, L.; Malacria, M.; Sieburth, S. M. Synthesis **1997**, 813–854.

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⁽⁷⁾ Adducts from reactions of 2*H*-thiopyrans with dienophiles are, after desulfurization, synthetically equivalent to adducts from *cis*-dienes.

^{(8) (}a) Ward, D. E.; Gai, Y. *Can. J. Chem* **1992**, *70*, 2627–2633. (b) Ward, D. E.; Nixey, T. E.; Gai, Y.; Hrapchak, M. J.; Abaee, M. S. *Can. J. Chem.* **1996**, 1418–1436.



Figure 1. Diels—Alder reaction where a Lewis acid (LA) coordinates simultaneously to the diene and dienophile and induces an "intramolecular" reaction of the resulting complex.

the literature revealed several scattered examples where the reactivity and/or selectivity observed in Diels–Alder reactions was (or could have been) rationalized by proposing a favorable noncovalent association of the diene with the dienophile (e.g., hydrogen bonding⁹ or coordination to a Lewis acid¹⁰) in the transition state. In particular, two examples that closely resemble the mechanistic scenario in Figure 1 were identified: Snider's "quasi-intramolecular" hetero-DA reaction (**A**)¹¹ and Bienayme's "internally" Lewis acid-catalyzed DA reaction (**B**).¹² Nonetheless, few if any of these proposals contemplate an "intramolecular" reaction



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(11) (a) Snider, B. B.; Phillips, G. B. J. Am. Chem. Soc. **1982**, 104, 1113–1114. (b) Snider, B. B.; Phillips, G. B.; Cordova, R. J. Org. Chem. **1983**, 48, 3003–3010.

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and, to the best of our knowledge, none provides evidence for a discrete preorganized intermediate. Thus, we initiated a study to determine the feasibility of the mechanistic hypothesis outlined in Figure 1 and, if possible, to develop conditions to promote such a reaction pathway.

DA reactions of 1a or 1b with 2a or 2b at 120 °C are unselective, giving nearly equimolar mixtures of the four possible products 3 (or 7) and 4-6 (Table 1). As a



entry	diene/ dienophile	conditions ^a	adduct series	selectivity 7(or 3):4:5:6 ^b	yield ^c (%)
1	1a/2a	120 °C	а	1.3:1:1.3:1.2	90
2	1a/2a	TiCl₄		d	
3	1a/2a	TiCl ₂ (O ⁷ Pr) ₂		d	
4	1a/2a	SnCl ₄		d	
5	1a/2a	EtAlCl ₂		d	
6	1a/2a	Et ₂ AlCl	а	7 only	75
7	1a/2a	MgBr ₂ •OEt ₂	а	7 only	70
8	1a/2a	MgBr ₂ •OEt ₂ ,	а	7 only	75
		Et ₃ N ^e		-	
9	1a/2a	MeMgBr ^f	а	7 only	35
10	1a/2a	MeMgBr ^{f,g}	а	7 only	75
11	1a/2a	MeMgBr,	а	7 only	95
		pentanol ^{f,h}		Ū	
12	1b/2a	120 °C	b	1:1:1.8:1.4	90
13	1b/2a	Et ₂ AlCl	b	1:-:2:-	20
14	1b/2a	MgBr ₂ •OEt ₂		d	
15	1b/2a	MgBr ₂ •OEt ₂ ,		d	
		Et ₃ N ^e			
16	1b/2a	MeMgBr,		d	
		pentanol ^{f,h}			
17	1a/2b	120 °C	с	1.4:1:2:1	60
18	1a/2b	MgBr ₂ •OEt ₂	с	3.1:1:6.3:1	65
19	1a/2b	MeMgBr ^{f,g}	с	7.3:1.4:4.3:1	25

^{*a*} Thermal reactions: a solution of the diene (0.5-2 M) and **2a** (2 equiv) or **2b** (1 equiv) in C₆D₆ was heated for 20–36 h.LA-mediated reactions: LA (1 equiv) and **2a** (2 equiv) or **2b** (1 equiv) were sequentially added to a solution of diene (0.1-0.3 M) in CH₂Cl₂ at 0 °C and then stirred at ambient temperature for 10–48 h. ^{*b*} Ratios measured by ¹H NMR of the crude reaction mixture (relative error estimated as ±10%). ^{*c*} Isolated. ^{*d*} DA adducts not detected. ^{*e*} 2 equiv of Et₃N. ^{*f*} MeMgBr (3 M in ether) was used; reaction in toluene. ^{*g*} 0.5 equiv of MeMgBr, reaction for 7 days. ^{*h*} 1 equiv of pentanol added (cf. note 15); reaction for 2 days.

consequence, these reactions are useful probes to test the ability of Lewis acids both to preorganize the components and to catalyze Diels-Alder cycloaddition according to Figure 1. High selectivity will occur only if both attributes act in concert. A variety of Lewis acids were screened for their ability to promote the reaction between 1a and methyl acrylate (2a) (Table 1). In most cases, no DA adducts were detected;¹³ however, in the presence of Et₂AlCl or MgBr₂. OEt₂ a good yield of 7^{4a} was obtained as the only DA product from 1a and 2a. Similarly, reaction of 2a with the bromomagnesium alkoxide formed by reaction of 1a either with MgBr₂•OEt₂ in the presence of Et₃N¹⁴ or with MeMgBr gave 7 exclusively and in near quantitative yield under optimized conditions (entry 11).15 In contrast, reaction of 1b with 2a in the presence of MgBr₂·OEt₂, MgBr₂·OEt₂/ Et₃N, or MeMgBr/pentanol failed to give DA adducts (Table 1, entries 14–16), and with Et_2AlCl , a 2:1 mixture of **5b** and 3b was obtained in poor yield (entry 13). The 2:1 regioselectivity¹⁶ of the latter reaction is similar to that observed on heating in the absence of a Lewis acid (1.6:1; cf. entry 12) and is inconsistent with simultaneous coordination of diene and dienophile with the Lewis acid in the transition state (TS).¹⁷ Although the results of the DA reaction of 1a and 2a mediated by Et₂AlCl, MgBr₂•OEt₂, and MeMgBr are consistent with the mechanistic scenario outlined in Figure 1, a number of alternative pathways can be considered (Scheme 1).



The possible formation of 7 by IMDA reaction of ester 9^{18} was easily ruled out because adducts were not detected

when 9 was subjected to the same conditions (i.e., $MgBr_2$ ·OEt₂, $MgBr_2$ ·OEt₂/Et₃N, MeMgBr/pentanol, or Et₂AlCl) that gave 7 from 1a and 2a (Scheme 1).

Comparison of the DA reactions of 2a with 1a and with **1b** strongly suggest that a *covalent* interaction between the diene oxygen and the Lewis acid is an important factor in the selective formation of 7 from 1a and 2a. Because there is no background reaction between 1a and 2a at room temperature, the formation of 7 implies LA activation of 2a; assuming that MeMgBr is quantitatively converted into 8 in the presence of excess 1a, one can conclude that the "complex" 10 is involved (Scheme 1). The possibility that 3a (and thus 7) was formed by a "bimolecular" DA reaction of 1a with 10 (or other ROMgBr·2a complex, e.g., 12) was inconsistent with a number of observations (Scheme 1). Despite the similar reactivity of **1a** and **1b** in uncatalyzed reactions,¹⁹ MeMgBr-mediated reaction of **1a** with **2a** in the presence of a 10-fold excess of 1b gave 7 as the only DA product. Similarly, the bromomagnesium alkoxide formed from pentanol and MeMgBr failed to promote a DA reaction between 1b and 2a via 12 (Table 1, entry 16). In an effort to promote a "bimolecular" pathway, we examined dienophiles where an "intramolecular" DA reaction upon coordination with 8 was disfavored. DA adducts were not obtained from Mg(II)-mediated reactions of **1a** with acrylonitrile. As with 2a, the thermal DA reaction of N-acryloyloxazolidinone $(2b)^{20}$ with 1a is slightly regioselective¹⁶ in favor of adducts 5c and 6c (Table 1, entry 17). By comparison, in the presence of MgBr₂·OEt₂ a much higher endo stereoselectivity with only a marginal increase in regioselectivity results (Table 1, entry 18), as observed in the Et₂AlCl-mediated reaction of 1b with 2a (Table 1, entry 13) and consistent with reaction via 15a. Modest regioselectivity in favor of adducts 7 and 4c was observed in the MeMgBr-mediated reaction of 1a with **2b** (Table 1, entry 19), suggesting reaction via both 15b and 14. The striking contrasts between the LA-mediated reactions of 2a with 1a and 1b and of 1a with 2a and 2b militate against a "bimolecular" mechanistic hypothesis for selective formation of 7.

The above results strongly indicate that the diene and dienophile are simultaneously associated with the LA in the TS leading to 7 (i.e., TS C in Scheme 1). In an effort to provide evidence for a discrete intermediate (i.e. 10) along the reaction pathway, we examined the concentration de-

⁽¹³⁾ The dienes are acid sensitive and are consumed by dimerization and/or polymerization in these cases.

⁽¹⁴⁾ Vedejs, E.; Daugulis, O. J. Org. Chem. 1996, 61, 5702-5703.

⁽¹⁵⁾ Addition of MeMgBr (1 equiv) to a toluene solution of **1a** gave a clear solution only with a MeMgBr/**1a** ratio near 0.5; with greater or lesser amounts of MeMgBr, the mixture was cloudy. With a total ROH:MeMgBr ratio of 2, the use of pentanol (1 equiv) as a "dummy" alcohol gave a faster and more efficient reaction. Presumably, the ROH:ROMgBr ratio affects the speciation of ROMgBr. For an example of a dimeric structure, see: Moseley, P. T.; Shearer, H. M. M. J. Chem. Soc., Chem. Commun. **1968**, 279–280. Reaction is much slower with MeMgCl and faster but less efficient with MeMgI.

⁽¹⁶⁾ The regioselectivity is the ratio of ([5] + [6]):([3] + [4] + [7]).

⁽¹⁷⁾ A predominance of 5/6 regioisomers is expected on the basis of greater electron-donating properties of a methyl group vs a hydroxymethyl or methoxymethyl group. Only 3/4/7 regioisomers can form if diene and dienophile are tethered by association with a Lewis acid in the TS.

⁽¹⁸⁾ Toyota, M.; Wada, Y.; Fukumoto, K. Heterocycles 1993, 35, 111.

⁽¹⁹⁾ For example, **1a** was 1.2 times more reactive than **1b** toward **2a** in toluene solution at $120 \,^{\circ}$ C as determined in a competition experiment.

⁽²⁰⁾ Chelation of 8 by 2b (i.e. 15b) prevents IMDA reaction; IMDA reaction is feasible with monodentate coordination (e.g., 14).

pendence of the DA chemoselectivity between 1a and cyclopentadiene competing for a deficient amount of 2a (Scheme 2). In the absence of Mg(II), only adducts from



cyclopentadiene were detected (16;²¹ 3:1, endo:exo)²² In reactions mediated by MeMgBr, the reactivity of 1a was dramatically enhanced and 7 was produced competitively with 16. In these cases, adduct 16 was formed with increased diastereoselectivity (9:1, endo:exo),²² suggesting a Lewis acid-mediated reaction (e.g., cyclopentadiene and 10). Significantly, otherwise identical experiments conducted with a 10-fold difference in concentration (0.3 vs 0.03 M in 1a) showed a >8-fold difference in chemoselectivity (3.5:1 vs $1:2.5)^{22}$ but with little change in the amount of 7 formed (% yield based on 2a).²³ These results are most easily rationalized by assuming that 16 is formed by intermolecular reaction of cyclopentadiene with 10, that 7 results from an "intramolecular" reaction of 10, and that the equilibrium favors the formation of 10 from 8 and 2a (Scheme 1). By contrast, the relative reactivity of 1a is ca. 6 times greater than that of 1b toward N-phenylmaleimde (17) at room temperature. Although the higher reactivity of **1a** might be attributable to a favorable H-bond in the TS leading to 18a,²⁴ the hypothetical "intramolecular" reaction of a H-bonded complex is inconsistent with the observed concentration independence of the chemoselectivity.

Comparable increases in reactivity and selectivity were also observed on using MeMgBr and/or Et_2AlCl to mediate

(21) Kobuke, Y.; Fueno, T.; Furukawa, Y. J. Am. Chem. Soc. **1970**, *92*, 6548–6553.

reactions of **1a** with methyl methacrylate and with dimethyl fumarate, but attempted reactions with methyl crotonate failed.^{13,25} Analogous reactions with the chiral diene **19**²⁶ resulted in marked increases in diastereoselectivity compared to that of uncatalyzed reactions (Scheme 3). For example,



^{*a*} Conditions: (a) i. MeMgBr (1 equiv) **17** (1 equiv), toluene (0.1 M), rt, 3 h; (b) **17** (1 equiv), CDCl₃ (0.1 M), rt, 6 h; (c) **17** (1 equiv), C_6D_6 (0.1 M), 120 °C, 2 h.

the MeMgBr-mediated reaction of **19** with **17** gave the endo adduct **20**²⁶ with excellent diene diastereotopic face selectivity (>19:1; cf. 1.7:1 for the uncatalyzed reaction). The adduct **22**²⁷ was obtained with similar stereoselectivity from the 2*H*thiopyran diene **21**.²⁸

In summary, we have demonstrated the feasibility of a strategy to control Diels–Alder reactions based on a Lewis acid-catalyzed reaction of a "self-assembled" complex (LACASA–DA).^{29,30} Thus, the benefits of intramolecularity and Lewis acid catalysis are exploited to enhance reactivity, regioselectivity, and stereoselectivity of Diels–Alder reactions. In principle, enantioselective reactions should also be possible by providing an appropriate chiral ligand sphere for the Lewis acidic metal center.

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⁽²²⁾ Ratios were determined by $^1\mathrm{H}$ NMR of the crude reaction mixture; yields were determined using an internal standard.

⁽²³⁾ Qualitatively similar results were obtained in Et₂AlCl-mediated competition reactions which were faster though less reproducible.

⁽²⁴⁾ Khandelwal, G. D.; Wedzicha, B. L. Food Chem. 1997, 60, 237–244.

⁽²⁵⁾ Diene 1b did not react under these conditions.

⁽²⁶⁾ Tripathy, R.; Franck, R. W.; Onan, K. D. J. Am. Chem. Soc. 1988, 110, 3257–3262.

⁽²⁷⁾ The C-Me configuration of **22** was not rigorously determined.

⁽²⁸⁾ The preparation and reactions of thiopyran dienes will be described separately.

⁽²⁹⁾ For similar Mg(II)-mediated [3 + 2] cycloadditions of nitrile oxides with allylic alcohols, see: (a) Kanemasa, S.; Hidetoshi, Y.; Shinsuke, K. *Tetrahedron Lett.* **1997**, *38*, 4095–4098. (b) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324–2339.

⁽³⁰⁾ For other examples of "self-assembled" templates for DA reactions, see: (a) Walter, C. J.; Anderson, H. L.; Sanders, J. K. M. J. Chem. Soc., Chem. Commun. **1993**, 458–460. (b) Walter, C. J.; Sanders, J. K. M. Angew. Chem., Int. Ed. Engl. **1995**, 34, 217–219. (c) Wang, B.; Sutherland, I. O. J. Chem. Soc., Chem. Commun. **1997**, 1495–1496.