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

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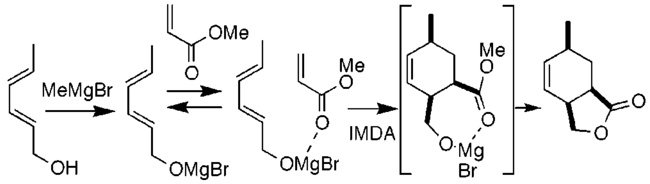
ABSTRACT



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 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 sulfur-based 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.

(4) Recent examples of Mg, Zn, B, and Al based tethers: (a) Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595−6596. (b) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450−451. (c) Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* **2000**, *2*, 1283−1286.

(5) (a) Martin, J. C.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537−562. (b) Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402−7403.

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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.

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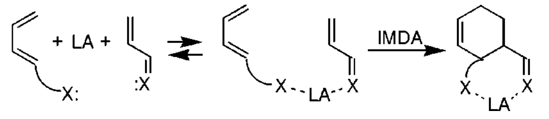


Figure 1. Diels−Alder reaction where a Lewis acid (LA) coordinates simultaneously to the diene and dienophile and induces an "intramolecular" reaction of the resulting complex.

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 bonding[9] or coordination to a Lewis acid[10]) 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 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

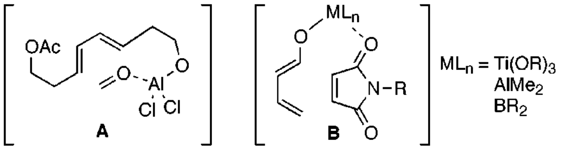
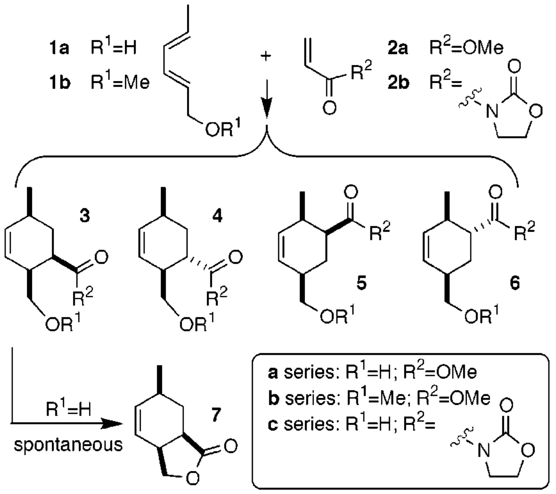


Table 1. Diels−Alder Reactions of **1** with **2**



entry	diene/ dienophile	conditions[a]	adduct series	selectivity **7**(or **3**):**4**:**5**:**6**[b]	yield[c] (%)
1	**1a**/**2a**	120 °C	**a**	1.3:1:1.3:1.2	90
2	**1a**/**2a**	$TiCl_4$		*d*	
3	**1a**/**2a**	$TiCl_2(O^iPr)_2$		*d*	
4	**1a**/**2a**	$SnCl_4$		*d*	
5	**1a**/**2a**	$EtAlCl_2$		*d*	
6	**1a**/**2a**	Et_2AlCl	**a**	**7** only	75
7	**1a**/**2a**	$MgBr_2{\cdot}OEt_2$	**a**	**7** only	70
8	**1a**/**2a**	$MgBr_2{\cdot}OEt_2$, Et_3N[e]	**a**	**7** only	75
9	**1a**/**2a**	MeMgBr[f]	**a**	**7** only	35
10	**1a**/**2a**	MeMgBr[f,g]	**a**	**7** only	75
11	**1a**/**2a**	MeMgBr, pentanol[f,h]	**a**	**7** only	95
12	**1b**/**2a**	120 °C	**b**	1:1:1.8:1.4	90
13	**1b**/**2a**	Et_2AlCl	**b**	1:-:2:-	20
14	**1b**/**2a**	$MgBr_2{\cdot}OEt_2$		*d*	
15	**1b**/**2a**	$MgBr_2{\cdot}OEt_2$, Et_3N[e]		*d*	
16	**1b**/**2a**	MeMgBr, pentanol[f,h]		*d*	
17	**1a**/**2b**	120 °C	**c**	1.4:1:2:1	60
18	**1a**/**2b**	$MgBr_2{\cdot}OEt_2$	**c**	3.1:1:6.3:1	65
19	**1a**/**2b**	MeMgBr[f,g]	**c**	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 C_6D_6 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 CH_2Cl_2 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 Et_3N. [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.

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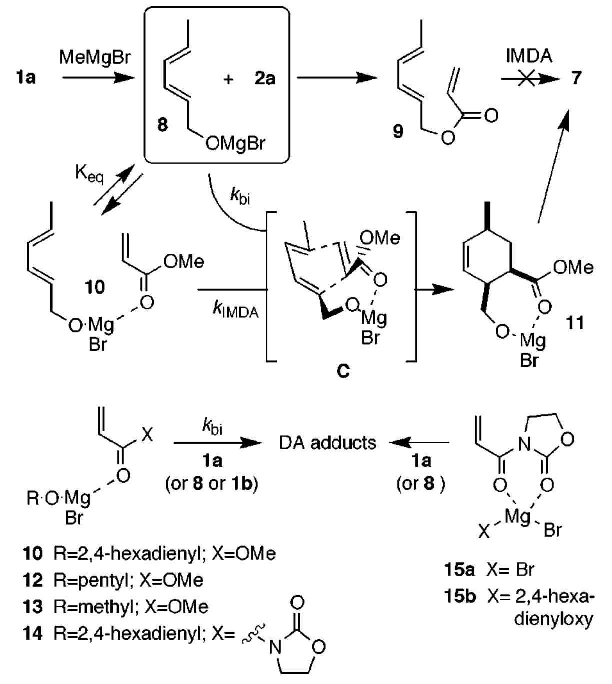
consequence, these reactions are useful probes to test the ability of Lewis acids both to preorganize the components and to catalyze Diels−Alder cycloaddition according to Figure 1. High selectivity will occur only if both attributes act in concert. A variety of Lewis acids were screened for their ability 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 Et_2AlCl or $MgBr_2{\cdot}OEt_2$ 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 $MgBr_2{\cdot}OEt_2$ in the presence of Et_3N[14] 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 $MgBr_2{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2/Et_3N$, 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 regioselectivity[16] 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 Et_2AlCl, $MgBr_2{\cdot}OEt_2$, and MeMgBr are consistent with the mechanistic scenario outlined in Figure 1, a number of alternative pathways can be considered (Scheme 1).

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., $MgBr_2{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2/Et_3N$, MeMgBr/pentanol, or Et_2AlCl) 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 regioselective[16] in favor of adducts **5c** and **6c** (Table 1, entry 17). By comparison, in the presence of $MgBr_2{\cdot}OEt_2$ a much higher endo stereoselectivity with only a marginal increase in regioselectivity results (Table 1, entry 18), as observed in the Et_2AlCl-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-

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[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.

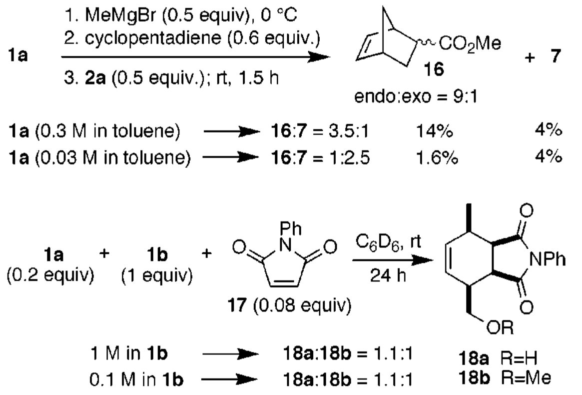
[18] Toyota, M.; Wada, Y.; Fukumoto, K. *Heterocycles* **1993**, *35*, 111.

[19] For example, **1a** was 1.2 times more reactive than **1b** toward **2a** in toluene solution at 120 °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**).

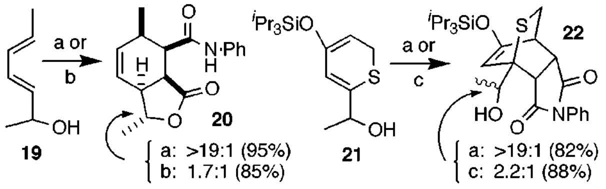
pendence of the DA chemoselectivity between **1a** and cyclopentadiene competing for a deficient amount of **2a** (Scheme 2). In the absence of Mg(II), only adducts from cyclopentadiene were detected (**16**;[21] 3:1, endo:exo)[22] In reactions mediated by MeMgBr, the reactivity of **1a** was dramatically 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.

Scheme 2



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

Scheme 3[a]



[a] Conditions: (a) i. MeMgBr (1 equiv) **17** (1 equiv), toluene (0.1 M), rt, 3 h; (b) **17** (1 equiv), $CDCl_3$ (0.1 M), rt, 6 h; (c) **17** (1 equiv), C_6D_6 (0.1 M), 120 °C, 2 h.

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

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

(23) Qualitatively similar results were obtained in Et_2AlCl-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.