Lewis Acid Catalyzed Diels−Alder Reactions of Highly Hindered Dienophiles

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In the course of examining oligomeric cyclopentanoid compounds as potential peptidomimetics, we required synthetic access to structures such as **1**. We envisioned **1** as being derived from the substituted norbornene **2**, which in turn could result from the Diels−Alder reaction of dienophile **3** and cyclopentadiene **4** (Scheme 1). However, despite the status of the Diels−Alder (DA) reaction as one of the most widely utilized and thoroughly examined strategy-level reactions in organic chemistry,[1] we were surprised to discover that intermolecular DA reactions employing a γ,γ-disubstituted, nonaromatic dienophile such as **3** were relatively rare. In the few literature examples that we were able to uncover in which this type of substitution was present, cyclic dienophiles,[2] or autoclave temperatures and high pressure,[3] were required to promote the reaction. For numerous substrates, of course, the use of a Lewis acid catalyst provides both an increase in reaction rate and enhanced diastereoselectivity. However, we found in a series of preliminary experiments (vide infra) that a variety of standard Lewis acid catalysts were ineffective at promoting DA cycloadditions between **3** (where R = OCH₃, R′ = H) and **4**. We describe herein the development of an effective means of performing DA reactions with sterically hindered dienophiles such as **3**.

A series of γ,γ-disubstituted dienophiles was synthesized by Arbuzov coupling of triisopropyl phosphite with an α-bromo ester (**5a−d**)[4] (Scheme 2) followed by Horner−Wadsworth−Emmons olefination with cyclohexanecarboxaldehyde or cyclopentanecarboxaldehyde.[5] Use of the diisopropyl phosphonate reagents provided excellent *E:Z* selectivity, in accord with the results observed by Kishi and co-workers in their synthesis of Rifamycin S.[6]

With a series of dienophiles in hand, we were ready to probe what conditions and additives might allow the DA reaction to occur. As shown in Table 1, **8b** and **9** were

subjected to a variety of Lewis acids and reaction conditions in the presence of cyclopentadiene. Surprisingly, the majority of catalysts examined were ineffective at promoting the DA reaction, and recovery of starting dienophile coupled with decomposition of the diene was the typical result. Concerned that residual water in the solution might be interfering with the cycloaddition, we decided to pretreat the dienophile solution with a chemical desiccant. Indeed, treatment of a solution of the dienophile with 0.05 equiv of Al(CH₃)₃ at 0 °C for 15 min,[7] followed by addition of AlCl₃ and cyclopentadiene at 4 °C, provided a 50% conversion of **9** to **10** after 48 h (entry 9). These same conditions afforded the DA adduct **11b** from **8b** in 89% yield with 2:1 *endo:exo* selectivity after 24 h (entry 10).[8] Since one potential mechanistic role for Al(CH₃)₃ in this process is as a chemical desiccant, we tested the effect of substituting other known desiccants for Al(CH₃)₃. Bis(cylopentadienyl)dimethylzirconocene (Cp₂Zr(CH₃)₂) has been used for this purpose by Bergman[9] and others; however, we found Cp₂Zr(CH₃)₂ to be significantly less efficient than Al(CH₃)₃, providing only 20% conversion of **8b** to **11b** after 24 h (entry 12).

Although the DA reaction had proceeded cleanly at room temperature, we were curious as to the effects of temperature on product selectivity and reaction rate. To explore this, a 0.5 M solution of dienophile **8c** in toluene was treated at 0 °C with 0.05 equiv of Al(CH₃)₃ for 15 min, and then with AlCl₃ for 10 min. The solution was then brought to the appropriate reaction temperature, and cyclopentadiene was added as a 5 M solution in toluene. As expected, as the temperature is decreased from room temperature to −20 °C the diastereoselectivity increases significantly, from 3:1 to 7:1 in favor of the *endo* diastereomer (Table 2). At temperatures lower than −20 °C, the reaction rate becomes too slow to be synthetically useful; for example, only 20% conversion was observed after 48 h at −30 °C.

Once reaction conditions were optimized, we were ready to probe how changing the ester moiety would influence the diastereoselectivity of the cycloaddition. We found that changing the ester from propyl (**8b**) or phenethyl (**8c**) to methyl (**8a**) or 3-phenylpropyl (**8d**) had little effect on the diastereomeric excess, which remains consistently around 88%, or 7:1 *endo:exo*. Because of their higher reactivity in the DA reaction, it is likely that the use of a γ,γ-disubstituted α,β-unsaturated *ketone* would allow the DA reaction to proceed at lower temperatures, potentially enhancing the diastereoselectivity. We are currently exploring whether this is indeed the case.

The significantly lower reactivity observed for cyclohexane-substituted dienophile **9** relative to the cyclopentane substituted dienophiles **8a−d** deserves comment. Conformational searches using molecular mechanics[10] of **8b** and **9** provide the minimum-energy conformers shown

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(1) For recent reviews of the Diels−Alder reaction, including Lewis acid catalysis, see: (a) Kobayashi, S. *Synlett* **1994**, 689−701. (b) Kagan, H. B.; Riaut, O. *Chem. Rev.* **1992**, *92*, 1007−1019. (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876−889.

(2) . (a) Miesch, M.; Cotté, A.; Franck-Neumann, M. *Tetrahedron Lett.* **1993**, *34*, 8085−8086. (b) Dauben, W. G.; Kowalczyk, B. A.; Lichtenthaler, F. W. *J. Org. Chem.* **1990**, *55*, 2391−2398. (c) Williams, R. V.; Sung, C.-L.; Kurtz, H. A.; Harris, T. M. *Tetrahedron Lett.* **1988**, *29*, 19−20.

(3) (a) Kitano, K.; Katagiri, N.; Kaneko, C. *Chem. Lett.* **1994**, 1285−1288. (b) Netherlands Patent 86-1541 860613.

(4) Methyl bromoacetate and propyl bromoacetate are commercially available and were used without further purification. Compounds **5a** and **5d** were made according to the procedure of Bradley, J. C.; Büchi, G. *J. Org. Chem.* **1976**, *41*, 699−700, and used without purificaiton.

(5) Cyclohexanecarboxaldehyde (**7b**) was purchased from Aldrich Chemical Co. and used without further purification. Cyclopentanecarboxaldehyde (**7a**) was prepared according to the procedure of Olah, G.; Prakash, S.; Arvanaghi, M. *Synthesis* **1984**, 228−230.

(6) Nagoaka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873−3888.

(7) Al(CH₃)₃ is well−known to react with acidic hydrogens with loss of methane; for example, see: Davidson, N.; Brown, H. C. *J. Am. Chem. Soc.* **1942**, *64*, 316−324.

(8) The major product was assigned as the *endo* diastereomer by analysis of a DQF−COSY spectrum.

(9) Proulx, G.; Bergman, R. G. *Organometallics* **1996**, *15*, 684−692.

(10) Monte Carlo multiple minimum searchers were conducted on **8b** and **9** using the MM2* force field and GB/SA model for CHCl₃ as implemented in Macromodel 6.0 (Still, W. C., et al., Columbia University, 1997).
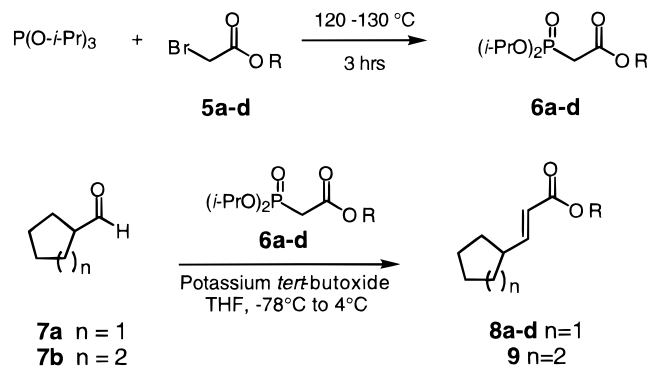
Scheme 1
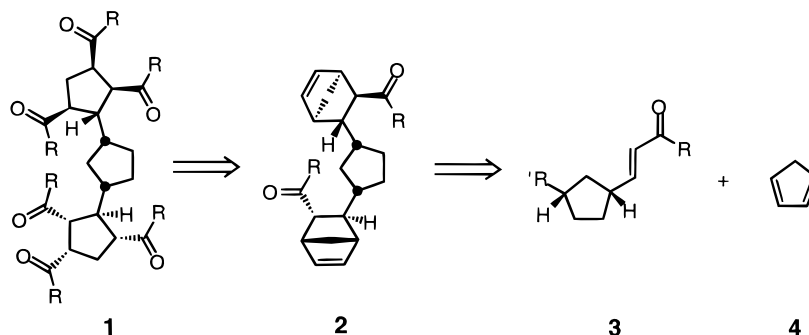
Table 1. Diels−Alder Conditions for the Reaction of Dienophiles 8b and 9 with Cyclopentadiene[12]

8b n = 1
9 n = 2

11b n = 1
10 n = 2
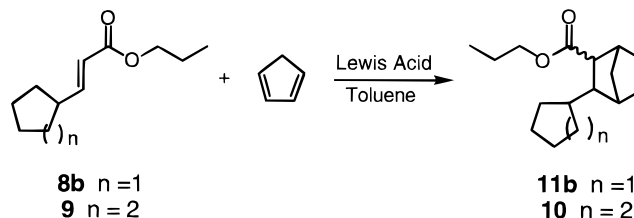
entry	dienophile	Lewis acid (equiv)	temp (°C)	yield (%)
1	**9**	TiCl$_4$ (1.0)[13a]	rt[a]	NR[b]
2	**9**	BF$_3$·O(Et)$_2$ (1.0)[13e]	rt	NR
3	**9**	5.0 M LiOCl$_4$ in Et$_2$O (5.0)[13g]	rt	NR
4	**9**	ZnCl$_2$ (0.5)[13d]	rt	NR
5	**9**	Sc(OTf)$_3$ (0.1)[13f]	rt	NR
6	**9**	AlCl$_3$ (0.5)[13c]	rt	NR
7	**8b**	(Et)$_2$AlCl (1.0)[13b]	rt	NR
8	**8b**	Al(CH$_3$)$_3$ (0.05)/B(Br)$_3$ (1.0)	rt	NR
9	**9**	Al(CH$_3$)$_3$ (0.05)/AlCl$_3$ (1.0)	rt	**10** (50% conversion after 48 h)
10	**8b**	Al(CH$_3$)$_3$ (0.05)/AlCl$_3$ (1.0)	rt	**11b** (89% yield, 2:1 *endo:exo*)
11	**8b**	Al(CH$_3$)$_3$ (0.05)/AlCl$_3$ (0.5)	−20	**11b** (91% yield, 7:1 *endo:exo*)
12	**8b**	Cp$_2$Zr(CH$_3$)$_2$ (0.05)/AlCl$_3$ (0.5)	−20	20% conversion after 24 h
13	**8b**	Al(CH$_3$)$_3$ (0.55)	−20	NR
14	**8b**	Al(CH$_3$)$_3$ (0.05)/(Et)$_2$AlCl (0.5)	−20	NR

[a] rt = room temperature. [b] NR = no reaction.

Scheme 2

5a-d

6a-d

7a n = 1
7b n = 2

6a-d

Potassium *tert*-butoxide
THF, −78°C to 4°C

8a-d n=1
9 n=2

in Figure 1. To the extent that these are representative of the reactive conformations of these dienophiles, it is immediately apparent that either an *endo* or *exo* approach by a diene to either dienophile would be severely hindered by methylene units attached to the γ-carbon.[11] However, when the α-, β-, and γ-carbon atoms of these conformers are superimposed, it becomes readily apparent that the hydrogen atoms δ to the carbonyl are slightly more oriented toward the Cα−Cβ double bond for **9** than for **8b** due to subtle differences in torsional angles between the five- and six-membered rings (Figure 2).

In conclusion, we have demonstrated methodology for the DA cycloaddition of cyclopentadiene with a range of sterically hindered dienophiles. This method relies on the use of Al(CH$_3$)$_3$ in conjunction with AlCl$_3$ as a Lewis acid catalyst. Further mechanistic studies, development of asymmetric variants, and efforts to incorporate this methodology into the synthesis of oligocyclopentanoid peptidomimetics are underway.

(11) Transition states for the Lewis acid-catalyzed cycloaddition of relatively unsubstituted dienes and dienophiles have been modeled extensively; for representative examples, see: (a) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094−4096. (b) Guner, O. F.; Ottenbrite, R. M.; Shillady, D. D.; Alston, P. V. *J. Org. Chem.* **1987**, *52*, 391−394. (c) Yamabe, S.; Dai, T.; Minato, T. *J. Am. Chem. Soc.* **1995**, *117*, 10994−10997. (d) Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1996**, *118*, 11680−11681. (e) Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Tetrahedron* **1997**, *53*, 6057−6064.

(12) Reactions were performed at a concentration of 0.5 M using toluene as the solvent. Al(CH$_3$)$_3$ and AlCl$_3$ were used as supplied by Aldrich. Further details are supplied in the experimental methods section.

(13) (a) Musselman, R. A., Ph.D. Dissertation. University of Rochester; Rochester, New York, 1994. (b) Tomioka, K.; Hamada, N.; Suengaga, T.; Koga, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 426−428. (c) Angell, E. C.; Fringuelli, F.; Guo, M.; Minuti, L.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 4325−4328. (d) Masamune, S.; Reed III, L. A.; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441−4444. (e) Drian, C. L.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473−5483. (f) Kobayashi, S.; Haciya, I.; Akari, M.; Isnitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755−3758. (g) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595−4596.

(14) The *endo:exo* selectivity was determined by integration of the diastereomeric vinyl resonances in the crude 400 MHz proton spectrum.
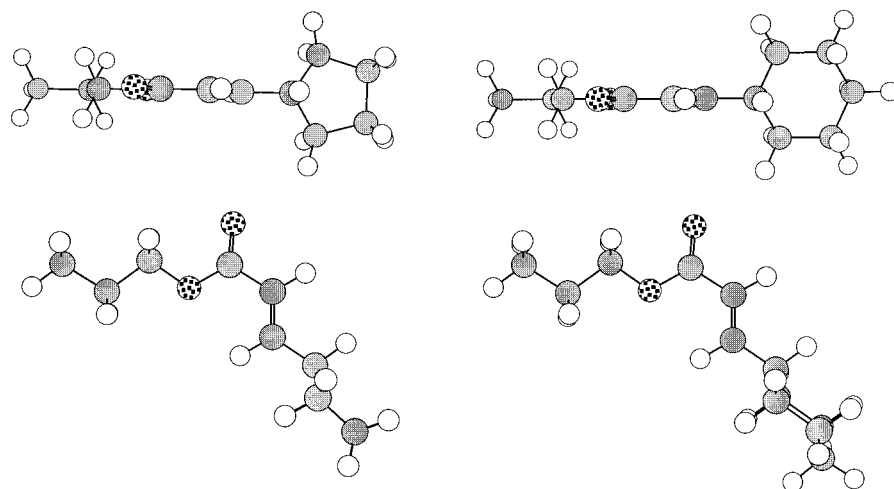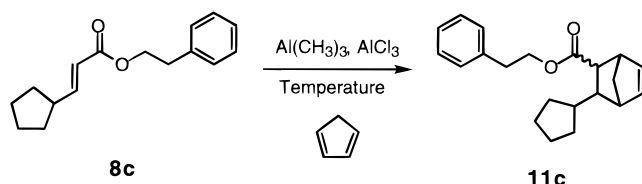
Figure 1. Minimum energy conformers for **8b** (left) and **9** (right) found using molecular mechanics.
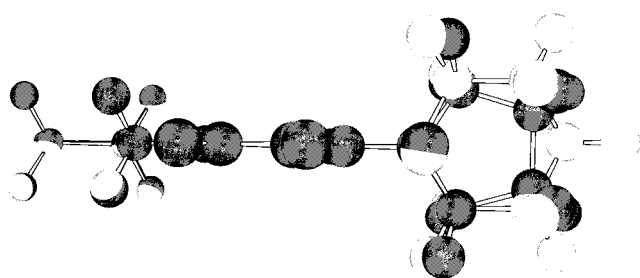
Figure 2. Superimposition of **8b** (black) and **9** (white).

Table 2: Dependence of the Diastereoselectivity of the Diels−Alder Reaction of 8c with Cyclopentadiene in the Presence of Al(CH₃)₃ and AlCl₃

entry	temp (°C)	yield (%)	*endo:exo* (% *de*)
1	RT	92	3:1 (75)
2	4	86	4:1 (80)
3	−15	89	7:1 (88)
4	−20	85	7:1 (88)

Experimental Methods

General Procedures. Unless otherwise indicated, all reactions were performed with glassware that had been flame-dried under an atmosphere of N_2. THF was distilled from sodium−benzophenone ketyl prior to usage. Methylene chloride and toluene were distilled from calcium hydride prior to usage. All commercially available reagents were purchased from Aldrich Chemical Co. and used without further purification. Flash chromatography was performed by using silica gel 60 purchased from EM Science. Radial chromatography was performed by using a Chromatotron from Harrison Research.

Preparation of Cyloadduct 11b. A 0.5 M solution of ester **8b** (41.3 mg, 0.23 mmol) was prepared in toluene and cooled to 0 °C. Al(CH₃)₃ (5.6 uL, 0.011 mmol, 2.0 M in hexanes) was added to the solution and stirred for 15 min at 0 °C. To this clear solution was added AlCl₃ (0.113 mL, 0.113 mmol, 1.0 M in nitrobenzene). The resulting solution was stirred at 0 °C for 15 min and then cooled to −20 °C. After 10 min at −20 °C, cyclopentadiene (0.45 mmol, 5.0 M in toluene) was added to the dienophile. The reaction was allowed to stir for 18 h at −20 °C.

The reaction was warmed to room temperature and quenched with 0.5 mL of pyridine. The contents of the reaction were filtered through silica and concentrated in vacuo to give a tan oil. The residue was chromatographed via radial chromatography (hexanes:ether 95:5) to give a pale yellow oil (**11b**, 51.4 mg, 91%, 88% de). IR (thin film) 1731, 1186, 716 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 6.27 (1H, dd, *J* = 3, 6 Hz), 5.96 (1H, dd, *J* = 3, 6 Hz) 3.96−4.02 (2H, m), 3.13 (1H, m), 2.67−2.68 (1H, m), 2.54−2.56 (1H, m), 1.76−1.88 (2H, m), 1.65−1.67 (2H, m), 1.59−1.65 (4H, m), 1.50−1.56 (2H, m), 1.40−1.42 (1H, m), 1.23−1.28 (3H, m), 0.95 (3H, t, *J* = 8 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 175.0, 138.7, 133.2, 65.6, 50.4, 49.3, 49.3, 46.5, 46.4, 46.3, 45.9, 44.5, 32.1, 32.0, 25.1, 22.1. HRMS calcd for C₁₆H₂₄O₂ (M⁺) 248.1776 found 248.1776. A minor diastereomer was also observed in crude NMR spectra, but could not be isolated cleanly.

Cycloadducts **11a**, **11c**, and **11d** were prepared in an analogous fashion to **11b**:

Cycloadduct 11a. From cyclopentadiene and **8a**: 71%, 85% de, pale yellow oil. IR (thin film) 3026, 1735, 1196 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 6.27 (1H, dd, *J* = 3, 6 Hz), 5.95 (1H, dd, *J* = 3, 6 Hz), 3.63 (3H, s), 3.12−3.13 (1H, m), 2.67−2.68 (1H, m), 2.54−2.56 (1H, m), 1.85−1.89 (1H, m), 1.74−1.78 (1H, m), 1.61−1.69 (3H, m), 1.51−1.59 (3H, m), 1.40−1.42 (1H, m), 1.21−1.28 (3H, m); ¹³C NMR (75 MHz, CDCl₃): δ 177.0, 138.8, 133.1, 51.5, 50.1, 49.4, 46.5, 46.4, 46.3, 32.1, 32.0, 25.2, 25.1, 10.5. HRMS calcd for C₁₄H₂₀O₂ (M⁺) 220.1463 found 220.1463.

Cycloadduct 11c. From cyclopentadiene and **8c**: 85%, 88% de, clear oil. IR (thin film) 3053, 1726, 1264, 737 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.22−7.33 (5H, m), 6.23 (1H, dd, *J* = 3, 5 Hz), 5.79 (1H, dd, *J* = 3, 5 Hz), 4.22−4.30 (2H, m), 3.06 (1H, m), 2.93 (2H, t, *J* = 7 Hz), 2.65 (1H, m), 2.51 (1H, m), 1.60−1.65 (2H, m), 1.49−1.59 (7H, m), 1.37−1.39 (1H, m), 1.17−1.26 (2H, m); ¹³C NMR (75 MHz, CDCl₃): δ 174.8, 138.7, 138.0, 133.1, 128.9, 128.4, 126.5, 64.6, 50.2, 49.3, 46.5, 46.4, 46.2, 45.8, 35.1, 32.1, 32.0, 25.1, 25.1. HRMS calcd for C₂₁H₂₇O₂ (M + H)⁺ 311.1933 found 311.2011.

Cycloadduct 11d. From cyclopentadiene and **8d**: 75%, 85% de, clear oil. IR (thin film) 1730, 1263, 716 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.19−7.32 (5H, m), 6.28 (1H, dd, *J* = 3, 6 Hz), 5.97 (1H, dd, *J* = 2, 6 Hz), 4.00−4.10 (2H, m), 3.12 (1H, m), 2.68−2.71 (3H, m), 2.56−2.58 (1H, m), 1.85−1.97 (4H, m), 1.75−1.79 (1H, m), 1.60−1.70 (3H, m), 1.51−1.57 (2H, m), 1.42−1.43 (1H, m), 1.23−1.30 (3H, m); ¹³C NMR (75 MHz, CDCl₃): δ 174.9, 141.3, 138.8, 128.4, 128.3, 126.0, 63.4, 50.4, 49.4, 46.5, 46.4, 46.3, 45.9, 44.6, 32.2, 32.1, 32.0, 30.4, 25.1, 25.1. HRMS calcd for C₂₂H₂₈O₂ (M⁺) 324.2089 found 324.2089.

Supporting Information Available: Proceedures for the preparation of compounds **6a**−**d**, **8a**−**d**, **9**, and **11a**−**d**; ^{1}H and ^{13}C spectra for all compounds, as well as the 500 MHz [1]H−^{1}H DQCOSY spectrum of **11b** (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.