Influence of Alkyl Substituent on the Asynchronous Transition Structure of Boron-Catalyzed Diels–Alder Cycloaddition of α,β-Unsaturated Aldehydes with 1,1-Dimethyl-1,3-butadiene Derivatives

W.-M. Dai,* C. W. Lau, S. H. Chung, and Y.-D. Wu

Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong

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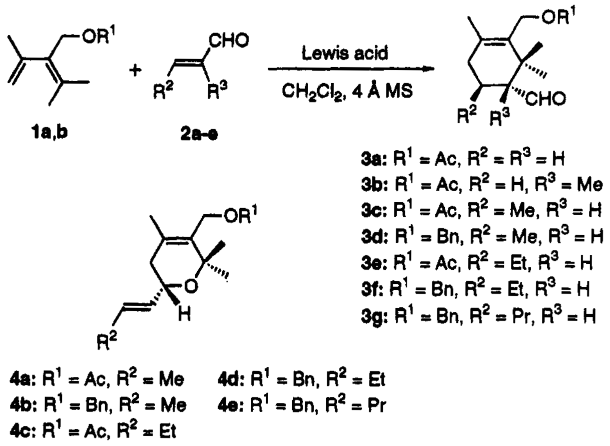
The Diels–Alder cycloaddition (DACA) has been demonstrated to be a powerful synthetic method for multiple carbon–carbon bond formation in a regio- and stereoselective manner.[1] Under Lewis acid catalysis, the DACA features additional merits in the aspects of improved regio- and stereoselectivity,[2] low-temperature reaction conditions, and enantioselective synthesis.[3] Recently, with *ab initio* calculations, Houk and co-worker[4] have located the asynchronous transition structures (TS') for the BH_3-catalyzed cycloaddition of butadiene with acrolein. In this paper, we report on the steric effects of alkyl substituents in the diene and the dienophile on the transition structure (TS) of the DACA supported by both experimental and *ab initio* calculation results.[5]

DACA has been known to be sensitive to steric interaction. It decreases the reaction rate remarkably when 1,1-dialkyl-1,3-butadienes are used.[6] Reaction of 1,1-dimethyl-1,3-butadienes has been performed only with activated dienophiles[6,7] at room temperature. For acrylic acid and 2-chloroacrylonitrile, drastic reaction conditions should be applied.[8] However, the $BF_3{\cdot}OEt_2$-catalyzed cycloaddition of **1a**[9] with acrolein can be carried out at −78 °C.[10] The regioselectivity of cycloaddition of 1,1-dimethyl-1,3-butadienes with unsymmetrical dienophiles remains very high under both thermal[8] and catalyzed[10] conditions to produce the "*ortho*" adducts exclusively. We investigated the boron-mediated DACA of **1a**,**b** with a number of α,β-unsaturated aldehydes **2a**–**e** and noted a significant influence of the β substituents in the dienophiles **2c**–**e** on the mode of the cycloaddition (Scheme 1 and Table 1).

Scheme 1



3a: R^1 = Ac, R^2 = R^3 = H
3b: R^1 = Ac, R^2 = H, R^3 = Me
3c: R^1 = Ac, R^2 = Me, R^3 = H
3d: R^1 = Bn, R^2 = Me, R^3 = H
3e: R^1 = Ac, R^2 = Et, R^3 = H
3f: R^1 = Bn, R^2 = Et, R^3 = H
3g: R^1 = Bn, R^2 = Pr, R^3 = H

4a: R^1 = Ac, R^2 = Me
4b: R^1 = Bn, R^2 = Me
4c: R^1 = Ac, R^2 = Et
4d: R^1 = Bn, R^2 = Et
4e: R^1 = Bn, R^2 = Pr

Reaction of **1a** with **2a**[10] and **2b** was carried out in dry CH_2Cl_2 under the catalysis of $BF_3{\cdot}OEt_2$ (0.5 mol equiv) at −80 °C to provide **3a**,**b** in good yield (Table 1, entries 1 and 2). The regiochemistry of the cycloaddition of **2b** remained the same as that for **2a** to give only the "*ortho*" adduct **3b**. *However, the β methyl group in* **2c** *behaved remarkably differently in the reaction with* **1**. The 3,6-dihydro-6,6-dimethyl-2*H*-pyran derivative **4a** was formed (37%) in addition to **3c** (16%) from **1a** and **2c** (Scheme 1 and Table 1, entry 3). The competition between the normal and hetero DACAs of **1a** with **2c** was confirmed to be a general phenomenon for β alkyl-substituted α,β-unsaturated aldehydes. It was found that with a bulkier β alkyl group in **2** the overall reaction rate decreased accordingly. This can be shown by the reduction in the conversion of **1a** from 66% to 27% in the reaction with **2c** and **2d**, respectively, in the presence of 0.5 mol equiv of $BF_3{\cdot}OEt_2$ (Table 1, entries 3 and 6). An increased amount of $BF_3{\cdot}OEt_2$ favored the formation of the normal Diels–Alder adduct; the product ratio **3**:**4** increased from 30–40:70–60 for 0.5 mol equiv of $BF_3{\cdot}OEt_2$ (Table 1, entries 3 and 6) to *ca.* 60:40 for 1.0 mol equiv of $BF_3{\cdot}OEt_2$ (Table 1, entries 4, 7, and 9). BBr_3 was found to be a more efficient catalyst for the reaction of **1** with **2c**–**e** (Table 1, entries 5, 8, and 10). In general, the cycloadditions catalyzed by BBr_3 completed within 5 h at −85 °C with 100% conversion of the diene. But, both adducts **3** and **4** were isolated in favor of **4** (**3**:**4** = *ca.* 35:65). The relative stereochemistry of **3c**–**g** was assigned as *trans* (R^2 and CHO) based on the vicinal proton coupling constants of 11.7 Hz between R^3 (= H) and its adjacent proton (in *gem* position with R^2 in **3c**–**g**). The latter proton (2.1–2.3 ppm) is significantly deshielded by the nearby carbonyl group. These results might suggest that the cycloaddition proceeds with a concerted mechanism.

The questions to the above-described observations are as follows: (a) influence of the *gem* dimethyl groups in the diene on the TS and regioselectivity of the cycloaddition; (b) origin of the different profiles of the alkyl group in the α or β position of the dienophiles; and (c) factor promoting the hetero DACA. According to Houk's asynchronous TS model,[4] the *gem* dimethyl groups in **1** can better stabilize the positive charge developed on the diene part in TS. This should favor one of the two possible approaches between the asymmetrical reactants. Steric interaction also prevents the σ bond formation in TS involving the *gem* dimethyl carbon center and determines the regiochemistry of the adduct. Both electronic and steric effects of the *gem* dimethyl groups in **1** should distort the TS further from that of butadiene. We performed the *ab initio* calculations at the RHF/3-21G level for the reaction of 1,1-dimethyl-1,3-butadiene with **2a** and **2c** catalyzed by BF_3. The most stable TS′ found for the normal DACA with **2a** (**A**) and **2c** (**C**) are shown in Chart 1.[11] A highly asymmetrical TS **A** with one forming bond longer than 3.4 Å (2.96 Å for butadiene[4])

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* To whom correspondence should be addressed. Phone: (852) 2358-7365. Fax: (852) 2358-1594. E-mail: chdai@usthk.ust.hk.

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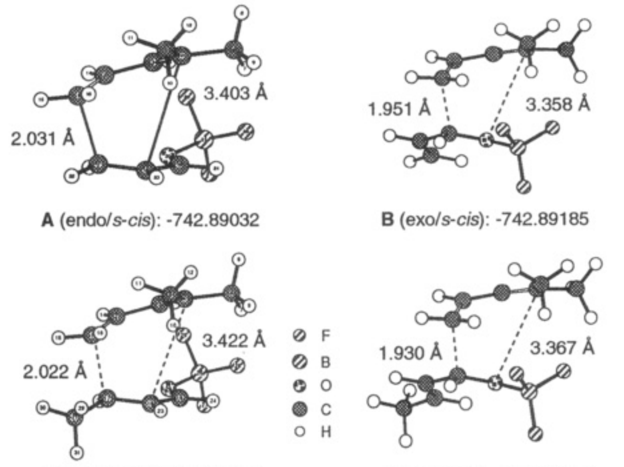
Table 1. Boron-Mediated Diels–Alder Cycloadditions of Dienes 1 with α,β-Unsaturated Aldehydes 2[a]

entry	diene (**1**)	dienophile (**2**)	Lewis acid (equiv)	T (°C), time (h)	conversn[b] (%)	products[c] (%)
1	**1a**: $R^1 = Ac$	**2a**: $R^2 = R^3 = H$	$BF_3 \cdot OEt_2$ (0.5)	−80, 12	100	**3a** (67)
2	**1a**	**2b**: $R^2 = H, R^3 = Me$	$BF_3 \cdot OEt_2$ (0.5)	−80, 16	100	**3b** (52)
3	**1a**	**2c**: $R^2 = Me, R^3 = H$	$BF_3 \cdot OEt_2$ (0.5)	−80, 34; −50, 69	66	**3c** (16); **4a** (37)
4	**1b**: $R^1 = Bn$	**2c**	$BF_3 \cdot OEt_2$ (1.0)	−60, 112	67	**3d** (50); **4b** (37)
5	**1b**	**2c**	BBr_3 (1.0)	−85, 4	100	**3d** (28); **4b** (39)
6	**1a**	**2d**: $R^2 = Et, R^3 = H$	$BF_3 \cdot OEt_2$ (0.5)	−40, 72	27	**3e** (12); **4c** (18)
7	**1a**	**2d**	$BF_3 \cdot OEt_2$ (1.0)	−40, 62	62	**3e** (26); **4c** (15)
8	**1b**	**2d**	BBr_3 (0.5)	−85, 5	100	**3f** (22); **4d** (45)
9	**1b**	**2e**: $R^2 = {}^nPr, R^3 = H$	$BF_3 \cdot OEt_2$ (1.0)	−40, 72	83	**3g** (54); **4e** (32)
10	**1b**	**2e**	BBr_3 (0.5)	−85, 5	100	**3g** (24); **4e** (43)

[a] See the supporting information for detailed reaction conditions. [b] Calculated based on the recovered amount of **1**. [c] Yields refer to the isolated homogenous materials and calculated on the consumed diene **1**.

Chart 1



A (endo/*s-cis*): -742.89032

B (exo/*s-cis*): -742.89185

C (endo/*s-cis*): -781.71226

D (exo/*s-cis*): -781.71657

is impressive. Thereby, an α substituent in **2** should not disturb the TS to a visible extent due to the longer contact distance. This explains the observed regioselectivity of **2b**. Introduction of a β methyl group into the dienophile has little effect on the geometry of TS **C** compared with **A**. However, the calculated activation energy E_a increases from 10.9 kcal/mol for **A** up to 15.0 kcal/mol for **C**, in accord with the diminished reactivity of **2c**–**e**. The main contribution to the ΔE_a of 4.1 kcal/mol is the steric interaction between the β methyl group in **2c** and the diene terminal hydrogen atoms as indicated by the close H/H contact distances of 2.32 and 2.51 Å. It was known that, under the catalysis of $BF_3 \cdot OEt_2$, alkoxy-containing electron-rich dienes undergo hetero DACA with **2c** and *trans*-cinnamaldehyde to form γ-pyrones.[12] However, the hetero DACA is seldom seen for alkyl-substituted dienes. The unusual results for **2c**–**e** may be associated with the particular diene **1** having *gem* dimethyl groups. TS′ **B** and **D** in Chart 1 correspond to BF_3-catalyzed hetero DACA of 1,1-dimethyl-1,3-butadiene with **2a** and **2c**, respectively.[13] Calculations on the hetero DACA of **2c** revealed that the exo/*s*-trans TS **E** (see the supporting information) has an E_a value of 15.0 kcal/mol which is higher than the exo/*s-cis* TS **D** (E_a = 12.3 kcal/mol). The corresponding exo/*s-cis* TS **B** for **2a** possesses an E_a value of 9.9 kcal/mol. Thus, a β methyl group in the dienophile raises the activation energy for the hetero DACA TS′ **B** and **D** by 2.4 kcal/mol, which is visibly lower than the energy gap between **A** and **C**. These calculation results indicate that the β alkyl group in **2c**–**e** reduces the reactivity of both the normal and hetero DACAs with less extent to the latter reaction so that both possible reaction pathways for α,β-unsaturated aldehydes become real in the reaction with **1a,b**. Due to the greater asynchronicity in the calculated TS′, large dipole moments were observed (11.05, 8.60, 11.27, and 8.75 D for TS′ **A**–**D**, respectively). The effect of solvation on TS has been discussed for the hetero DACA between formaldehyde and 1,3-butadiene.[13] Solvation effect on TS′ has not been performed in our study and may deserve further attention.

In summary, we have been successful in performing the cycloaddition of **1a,b** with a series of α,β-unsaturated aldehydes catalyzed by $BF_3 \cdot OEt_2$ or BBr_3 at low temperature. The phenomenal influence of the β alkyl group in **2c**–**e** on the mode of the cycloaddition could be interpreted by the steric interaction in the asynchronous TS. The current studies on both experiments and molecular orbital calculations provide further evidence, using a steric probe, to support the asynchronous TS for the Lewis acid-catalyzed normal and hetero DACAs. The adducts **3a**–**g** possess the structure of the *A*-ring fragment of Taxol.[14] They could be used for the synthesis of taxiods with modified taxane skeleton.

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Supporting Information Available: Representative experimental procedure for the reaction of **1b** with **2c**, ^1H and ^{13}C NMR spectra for **3a**–**g** and **4a**–**e**, *Z*-matrices and total energies for TS′ **A**–**E**, 1,1-dimethyl-1,3-butadiene (**F**), BF_3-complexed **2a** (**G**), and BF_3-complexed **2c** (**H**) (33 pages).

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(11) Five TS′ **A**–**D** (Chart 1) and **E** (see the supporting information) were located using the GAUSSIAN 94 program. Frequency calculations indicated that each TS has one imaginary frequency which corresponds to the motion of the C–C bond formation.

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