

# Complete $\pi$ -Facial Diastereoselectivity in Diels–Alder Reactions of Dissymmetric 2,4-Cyclohexadienones

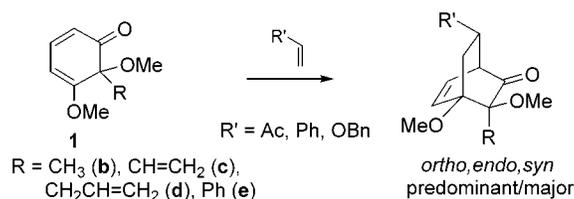
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## ABSTRACT



The studies in the Diels–Alder reactions of 5-methoxy-masked *o*-benzoquinone (1a, R = OMe) and simple dissymmetric 2,4-cyclohexadienones 1b–e with methyl vinyl ketone, styrene, and benzyl vinyl ether are described. The dienones 1b–e reacted with dienophiles to form *syn* adducts (dienophile approach is *syn* to allylic methoxy group) exclusively.

The Diels–Alder reaction is one of the most versatile and synthetically useful reactions in which four new contiguous stereogenic centers can be generated in a one-step operation.<sup>1</sup> The most recent stereochemical issue of this reaction is the  $\pi$ -facial control that arises when two faces of the diene or the dienophile are nonequivalent (dissymmetric).<sup>2</sup> Both steric and electronic factors contribute significantly toward  $\pi$ -face selection. In recent years, several readily accessible plane-nonsymmetric cyclopentadienes have been extensively probed for the diastereoselection. Considerable attention has also been focused on unsymmetrical cage-annulated 1,3-cyclohexadienes in which conformational ambiguities are minimized.<sup>3</sup> However, the potential of simple dissymmetric conjugated cyclohexadienones has not been explored presumably due to their high propensity toward dimerization

and conformational flexibility.<sup>4–7</sup> In this paper, we report our preliminary results on  $\pi$ -facial selectivity in the Diels–Alder reactions of simple dissymmetric 2,4-cyclohexadienones.

Masked *o*-benzoquinones (MOBs) and their orthoquinol variants belong to a class of conjugated cyclohexadienones and have been used to synthesize various structurally diverse organic compounds via the Diels–Alder protocol<sup>8</sup> (Figure 1). However, the synthetic utility of these building blocks is

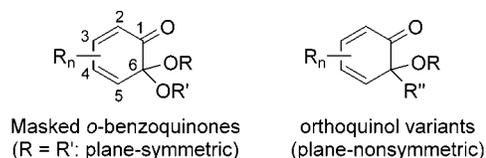


Figure 1. Masked *o*-benzoquinones and orthoquinol variants.

limited due to their high propensity toward dimerization. Recently, we have deduced a general trend for the stability and dimerization of MOBs.<sup>9</sup> Now it is clearly established

(1) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990. (b) Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*; Wiley: New York, 1990.

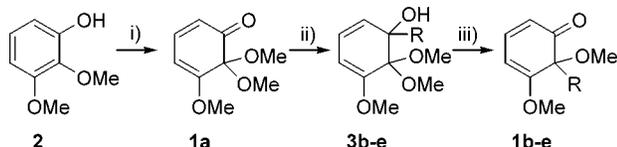
(2) (a) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199. (b) Fallis, A. G.; Lu, Y.-F. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 3, Chapter 1. (c) Ohwada, T. *Chem. Rev.* **1999**, *99*, 1337–1375.

(3) (a) Coxon, J. M.; Froese, R. D. J.; Ganguly, B.; Marchand, A. P.; Morokuma, K. *Synlett* **1999**, 1681–1703. (b) Mehta, G.; Uma, R. *Acc. Chem. Res.* **2000**, *33*, 278–286. (c) Marchand, A. P.; Chong, H. S.; Ganguly, B.; Coxon, J. M. *Croat. Chem. Acta* **2000**, *73*, 1027–1038.

that the 5-substituted MOB are nondimerizing 2,4-cyclohexadienones.<sup>10</sup> Thus, an opportunity has arisen to identify the stable MOB, and it was soon realized that these MOB could be precursors for orthoquinol variants. To study the effect of perturbation arising from the dissymmetrization of MOB on the chemical reactivities, in particular the facial selectivities, we have synthesized several 2,4-cyclohexadienones **1b–e** from 5-methoxy-MOB (**1a**) and studied their Diels–Alder reactions with different dienophiles.

The commercially available 2,3-dimethoxyphenol (**2**), when subjected to diacetoxyiodobenzene (DAIB) oxidation<sup>9b,10b</sup> in methanol, furnished the corresponding MOB **1a** in nearly quantitative yield. 1,2-Addition on the dienone **1a** with several Grignard reagents provided tertiary alcohols **3b–e**, which were transformed into the requisite cyclohexadienones **1b–e** by Lewis acid mediated rearrangement<sup>11</sup> (Scheme 1).

Scheme 1<sup>a</sup>

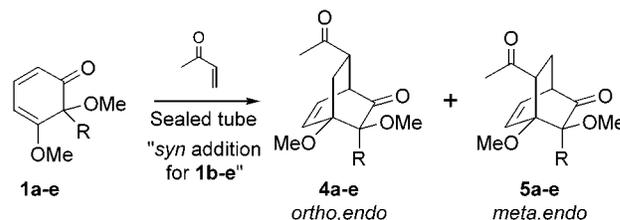


<sup>a</sup> Key: (i) DAIB, MeOH; (ii) RMgBr, THF, 0 °C, 77–98%; (iii) EtAlCl<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 40–98%; R = Me (**b**), CH=CH<sub>2</sub> (**c**), CH<sub>2</sub>CH=CH<sub>2</sub> (**d**), Ph (**e**).

At the outset of our study, we examined the Diels–Alder reaction of MOB **1a** with electron-deficient dienophile methyl vinyl ketone (MVK). As expected, the cycloaddition of this 5-substituted MOB is very slow at room temperature. However, when the reaction was performed under neat conditions with 20 equiv of MVK in a sealed tube at 100 °C, a 2:1 mixture of two regioisomers **4a** and **5a** was produced in which the *ortho* adduct (with respect to carbonyl

group of the dienone) is major.<sup>12,13</sup> Then the reaction conditions were extended to dissymmetric cyclohexadienones **1b–e**. Two regioisomers **4** and **5** were formed in each case, and the combined yields were good in almost all cases. Remarkably, all the dienones displayed complete *syn* preference (MVK approaches toward methoxy face). The results are summarized in Table 1. In the case of allyl-substituted

Table 1. Diels–Alder Reactions of Cyclohexadienones **1a–e** with Methyl Vinyl Ketone<sup>a</sup>



dienone	R	T (°C)	time (days)	yield <sup>b</sup> (%)	
				<b>4</b>	<b>5</b>
<b>1a</b>	OMe	100	1	<b>4a/60</b>	<b>5a/29</b>
<b>1b</b>	Me	100	1	<b>4b/30</b>	<b>5b/17<sup>c</sup></b>
<b>1c</b>	CH=CH <sub>2</sub>	100	1	<b>4c/39</b>	<b>5c/25</b>
<b>1d</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	100	3	<b>4d/14</b>	<b>5d/14</b>
<b>1e</b>	Ph	100	3	<b>4e/57</b>	<b>5e/16</b>

<sup>a</sup> All the reactions were carried out with 0.5 mmol of dienone and 10 mmol of MVK. <sup>b</sup> Pure and isolated products. <sup>c</sup> *meta,endo,syn-5b* and its *exo*-isomer could not be separated by chromatography and 15% of unreacted **1b** was recovered.

dienone **1d**, phenols **6** (20%) and **7** (20%) formed via [3,3] sigmatropic rearrangement were also isolated (Figure 2).

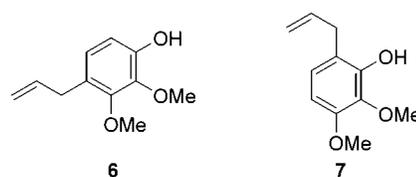


Figure 2.

To assess the influence of the dienophile on the  $\pi$ -facial selectivity, we have also employed styrene and benzyl vinyl ether (BVE) as conjugative and electron-rich dienophiles, respectively. The cycloaddition of **1a** with styrene furnished 57% of *ortho* adduct **8a** in addition to 15% of *meta* adduct.

(12) **General Procedure for Diels–Alder Reactions of 1.** A mixture of 2,3-cyclohexadienone **1** (0.5 mmol) and a dienophile (10 mmol, 20 equiv) was kept in a sealed tube at 100 or 150 °C for a period of time (see Tables 1–3). The reaction mixture was then cooled to room temperature and subjected to column chromatography (silica gel, ethyl acetate/hexanes) to afford pure cycloadducts.

(13) All the new compounds were satisfactorily characterized by IR, <sup>1</sup>H (600 MHz) and <sup>13</sup>C NMR (100 or 150 MHz), DEPT, and low- and high-resolution MS analyses.

(4) For the Diels–Alder reactions with orthoquinol acetates, see: (a) Metlesics, W.; Wessely, F.; Budzikiewicz, H. *Monatsch. Chem.* **1958**, *89*, 102–109. (b) Holmberg, K.; Kirudd, H.; Westin, G. *Acta Chim. Scand. B* **1974**, *28*, 913–921. (c) Auksi, H.; Yates, P. *Can. J. Chem.* **1981**, *59*, 2510–2517. (d) Carman, R. M.; Owsia, S.; Dongen, J. M. A. M. V. *Aust. J. Chem.* **1987**, *40*, 333–340. (e) Snider, B. B.; Chen, Z. *Org. Prep. Proc. Int.* **1999**, *31*, 537–541.

(5) For the Diels–Alder reactions with spiroepoxycyclohexadienones, see: (a) Singh, V. K.; Deota, P. T.; Bedekar, A. V. *J. Chem. Soc., Perkin Trans. 1* **1992**, 903–912. (b) Bonnarme, V.; Bachmann, C.; Cousson, A.; Mondon, M.; Gesson, J.-P. *Tetrahedron* **1999**, *55*, 433–448.

(6) For the Diels–Alder reactions with a spiroactone–cyclohexadienone, see: Drutu, I.; Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2002**, *4*, 493–496.

(7) For the Diels–Alder reactions with 2,6-dimethoxy-6-methylthio-methylcyclohexadienone, see: Katayama, S.; Hiramatsu, H.; Aoe, K.; Yamauchi, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 561–576.

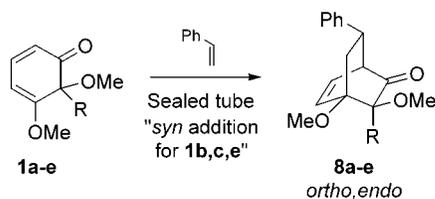
(8) (a) Liao, C.-C. In *Modern Methodology in Organic Synthesis*, Kyoto; Sheno, T., Ed.; Kodansha: Tokyo, 1992; pp 409–424. (b) Quideau, S.; Pouysegou, L. *Org. Prep. Proc. Int.* **1999**, *31*, 617–680. (c) Singh, V. *Acc. Chem. Res.* **1999**, *32*, 324–333. (d) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.*, in press.

(9) (a) Liao, C.-C.; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Ko, S.; Song, L.-D.; Shiao, H.-C. *J. Org. Chem.* **1999**, *64*, 4102–4110. (b) Yen, C.-F.; Peddinti, R. K.; Liao, C.-C. Manuscript in preparation.

(10) (a) Andersson, G. *Acta Chem. Scand. B* **1976**, *30*, 403–406. (b) Yen, C.-F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2909–2912.

(11) Bach, T.; Eilers, F. *J. Org. Chem.* **1999**, *64*, 8041–8044.

**Table 2.** The Diels–Alder Reactions of Cyclohexadienones **1a–e** with Styrene<sup>a</sup>



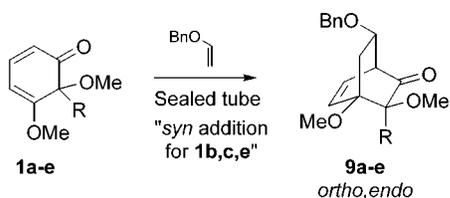
dienone	R	T (°C)	time (days)	yield <sup>b</sup> (%)
<b>1a</b>	OMe	100	3	<b>8a</b> /57 <sup>c</sup>
<b>1b</b>	Me	100	3	<b>8b</b> /6 <sup>d</sup>
<b>1c</b>	CH=CH <sub>2</sub>	100	3	<b>8c</b> /49
<b>1d</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	100	3	<b>8d</b> /0 <sup>e</sup>
<b>1e</b>	Ph	100	3	<b>8e</b> /11 <sup>f</sup>
<b>1e</b>	Ph	150	1	<b>8e</b> /32 <sup>g</sup>

<sup>a</sup> All the reactions were carried out with 0.5 mmol of dienone and 10 mmol of styrene. <sup>b</sup> Pure and isolated products. <sup>c</sup> 15% of *meta* adduct was also isolated. <sup>d</sup> 60% of **1b** was recovered. <sup>e</sup> **1d** rearranged to phenols **6** and **7**. <sup>f</sup> 74% of **1e** was recovered. <sup>g</sup> 24% of **1e** was recovered.

The dienones **1c,e** produced the single isomers **8c,e**, albeit in moderate yields (Table 2). The Diels–Alder adducts **8c,e** were formed with the dienophilic attack exclusively from the methoxy (*syn*) face. The dienone **1b** showed poor reactivity toward styrene and provided 6% of *syn* adduct **8b**. The reaction of allyl-substituted dienone **1d** with styrene could not yield any cycloadduct; instead, the rearranged phenols **6** and **7** were obtained in 10% yield each.

BVE exhibited better reactivity than styrene in the Diels–Alder reactions with dienones **1a–c,e**, and the results are shown in Table 3. A single adduct was obtained in each successful case, and the adducts **9b,c,e** were formed via exclusive *syn* addition with BVE. When the temperature was

**Table 3.** Diels–Alder Reactions of Cyclohexadienones **1a–e** with Benzyl Vinyl Ether<sup>a</sup>

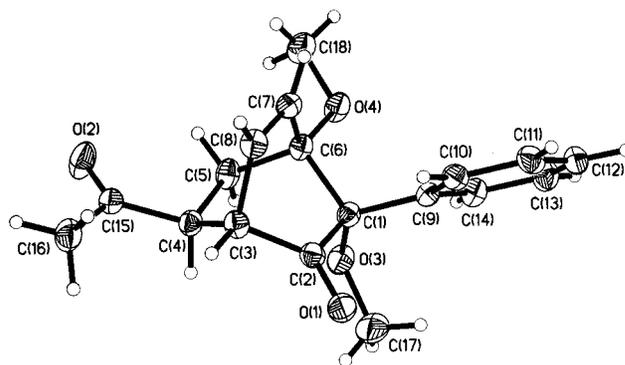


dienone	R	T (°C)	time (days)	yield <sup>b</sup> (%)
<b>1a</b>	OMe	100	3	<b>9a</b> /95
<b>1b</b>	Me	100	3	<b>9b</b> /42 <sup>c</sup>
<b>1c</b>	CH=CH <sub>2</sub>	100	3	<b>9c</b> /35 <sup>d</sup>
<b>1d</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	100	2	<b>9d</b> /0 <sup>e</sup>
<b>1e</b>	Ph	100	3	<b>9e</b> /20 <sup>f</sup>
<b>1e</b>	Ph	150	3	<b>9e</b> /76

<sup>a</sup> All the reactions were carried out with 0.5 mmol of dienone and 10 mmol of BVE. <sup>b</sup> Pure and isolated products. <sup>c</sup> 39% of **1b** was recovered. <sup>d</sup> 57% of **1c** was recovered. <sup>e</sup> **1d** rearranged to phenols **6** and **7**. <sup>f</sup> 61% of **1e** was recovered.

raised from 100 to 150 °C in the case of **1e**, the yield was increased dramatically from 20% to 76%.

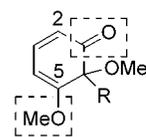
The stereochemical assignments given to the adducts were deduced from <sup>1</sup>H–<sup>1</sup>H decoupling experiments and NOE studies and by correlating chemical shifts and coupling constants of their <sup>1</sup>H NMR spectral data. Furthermore, the structure of *ortho,endo, syn*-**4e** was confirmed by its single-crystal X-ray structure (Figure 3).



**Figure 3.** ORTEP plot for X-ray crystal structure of compound **4e** (numbering is arbitrary).

It is clear, by comparison of the reaction conditions and yields of these cycloadditions, that the Diels–Alder reactivity of MOB **1a** is better than the corresponding MOB variants **1b–e** with a given dienophile. It is quite remarkable that these cyclohexadienones participated in the Diels–Alder cycloadditions with three types of dienophiles, viz. electron-deficient, conjugative, and electron-rich dienophiles. It may be noted that **1a**, being 5-substituted MOB, is less reactive than the MOB's lacking 5-substitution, where the latter smoothly undergo cycloadditions usually at 0 °C/room temperature.<sup>8d,9a</sup>

The formation of regioisomers in the above-described cycloaddition reactions may be attributed mainly to electronic effects. By virtue of the structure of the 2,4-cyclohexadienone **1**, the carbonyl and methoxy groups are present on its C-2 and C-5 positions, respectively, which exert opposite electronic effects on the incoming electron-deficient (MVK) and conjugative (styrene) dienophiles during the cycloaddition (Figure 4). As a result, the formation of both *ortho* and *meta* adducts is expected.<sup>14</sup> Nevertheless, due to the dominant regioselective directing influence of the carbonyl group of



**Figure 4.** The two electronically differed groups at the termini of the diene moiety of 2,4-cyclohexadienones.

dienone **1**, *ortho* adducts **4** were formed predominantly in the case of MVK. The regioselective outcome is much better in the reactions of **1** with styrene. In contrary to MVK and styrene, the electron-donating dienophile BVE is expected to produce *ortho* adducts based on *ortho* (C-2) directionality of carbonyl group and *meta* (C-2) directionality of methoxy group, which is in line with the experimental results.

The Diels–Alder cycloadditions proceeded in a highly stereoselective and facial selective manner under the reaction conditions. The overwhelming diastereofacial selectivity observed in these reactions is in consonance with that observed in the Diels–Alder reactions of allylic oxygen atom (OH/OAc/OMe/OCH<sub>2</sub>–) bearing cyclopentadienes<sup>2,15</sup> and cyclohexa-2,4-dienones.<sup>4–7</sup> The results can be rationalized in terms of (i) the Cieplak model,<sup>16</sup> i.e., hyperconjugative stabilization by  $\sigma$  bonds antiperiplanar to the incipient bond<sup>15</sup>—using the Baker–Nathan ordering of  $\sigma$ -donor ability<sup>17</sup> ( $\sigma_{C-O} < \sigma_{C-C}$ )—wherein a preference should exist for addition on the OMe face that is opposite to the better donating  $\sigma_{C-C}$  bond or (ii) by invoking orbital mixing rule,<sup>18</sup> i.e., a nonequivalent extension of the  $\pi$  HOMO by mixing on the  $\sigma$ -orbitals of the carbon framework through interaction with the n orbitals of oxygen atom of the C-6 methoxy group. However, the importance of steric effects on the  $\pi$ -facial selectivity cannot be ruled out in the present reactions.

(14) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1975.

(15) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136–1144.

(16) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540–4552.

In summary, in all cases shown in this work, the approach of the dienophile was strictly *syn* to allylic methoxy group (6-OMe) of the MOB variant. Only *endo* adducts were obtained for stereoelectronic effects. The regiochemistry of the cycloaddition was also well controlled in most cases, since the *ortho* adduct was always the major Diels–Alder product over the *meta* adduct, the carbonyl attached to C-2 having more influence than that of the methoxy group attached to C-5. The overwhelming *syn* control experienced in these reactions should be helpful to the organic chemists as the bicyclo[2.2.2]octenones are valuable synthons. Theoretical calculations are underway to understand the experimentally observed selectivities.

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**Supporting Information Available:** <sup>1</sup>H NMR spectra and tables of selected <sup>1</sup>H NMR chemical shifts and coupling constants. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) Epiotis, N. D.; Cherry, W. R.; Shaik, S.; Yates, R. L.; Bernardi, F. *Top. Curr. Chem.* **1977**, *70*, 1.

(18) (a) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054–4061. (b) Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, S. *J. Am. Chem. Soc.* **1990**, *112*, 8980–8982. (c) Ishida, M.; Aoyama, T.; Beniya, Y.; Yamabe, S.; Kato, S.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3430–3439.