Diastereofacial Selectivity in Diels–Alder Reactions of Buta-1,3-dienes having Stereogenic Allylic Heteroatom Substituents at the C-2 Position

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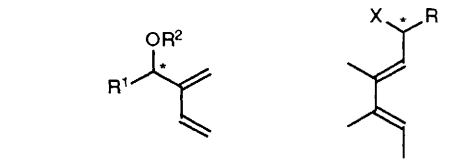
Diels–Alder reactions of ten 2-substituted buta-1,3-dienes **1a–j** with *N*-phenylmaleimide were examined under various conditions, demonstrating that an allylic heteroatom substituent at the C-2 position exerts significant directing effect on diastereofacial selection and also that the diastereofacial selectivity can be enhanced by use of 5 mol dm^{-3} $LiClO_4$–Et_2O as a reaction medium.

We have recently developed an efficient method for the preparation of chiral dienol derivatives **1**.[1] In an effort[2,3] to explore the synthetic utility of these compounds as chiral building blocks, we have focused our attention on face-selective Diels–Alder reactions. A number of reports[4] demonstrate that dienes of general structure **2** exhibit marked diastereofacial selectivity directed by the chirality of their allylic heteroatom substituents in intermolecular Diels–Alder reactions. However, surprisingly, few investigations[5] on diastereofacial selectivity of dienes **1** containing allylic heteroatom substitution at the C-2 position have been reported so far. We were, therefore, interested in probing whether a stereogenic allylic heteroatom substituent can control diastereofacial selectivity in cycloadditions of dienes of type **1**.

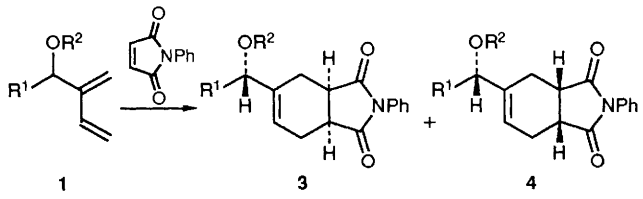
Ten dienol derivatives **1a–j**† were synthesized as follows. Dienols **1a**, **g**, **i** and methyl ethers **1b**, **h**, **j** were prepared by tin(IV) chloride mediated addition[1,6a] of 1-trimethylsilylbuta-2,3-diene[6] to the corresponding aldehydes and dimethyl acetals, respectively. Compounds **1c–f** were prepared from **1a** by silylation, acetylation, tritylation, or pivaloylation. The facial selectivity of these substances in Diels–Alder reactions was examined using *N*-phenylmaleimide (NPM) as a dienophile. The structures of the cycloadducts were determined based on those of **3b** and **4b** which were unambiguously established by single-crystal X-ray analysis of **3b**.‡ Thus, dienols **3a** and **4a** were correlated with **3b** and **4b** by methylation (MeI, Ag_2O, Et_2O, reflux). The structures of **3c–f** and **4c–f** were determined by simple correlation of these

† All new compounds reported herein exhibited satisfactory spectra (^1H NMR, IR) and high-resolution mass spectral or combustion analytical data.

‡ *Crystal data*: Compound **3b**, $C_{24}H_{25}O_3N_3$ M_r = 375.50, orthorhombic, space group $P2_12_12_1$, a = 11.135(1), b = 22.122(4), c = 8.089(1) Å, U = 1992.4(5) $Å^3$, Z = 4, D_m = 1.25, D_c = 1.25 g cm^{-3}; $F(000)$ = 800; Cu-Kα radiation (λ = 1.54178 Å), μ(Cu-Kα) = 5.74 cm^{-1}; 2016 reflections measured, 1931 unique, 1925 used in refinement; R = 0.035, R_w = 0.059. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

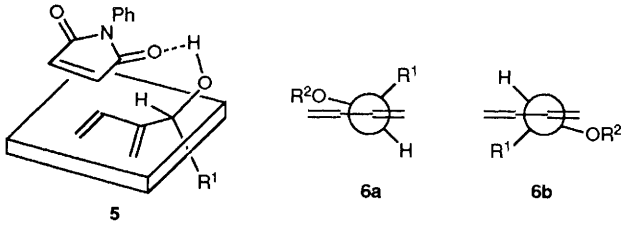


1 2 (X = OR′ or NHCOOR′)



1 3 4

a; R^1 = $PhCH_2CH_2$, R^2 = H
b; R^1 = $PhCH_2CH_2$, R^2 = Me
c; R^1 = $PhCH_2CH_2$, R^2 = Bu^tMe_2Si
d; R^1 = $PhCH_2CH_2$, R^2 = Ph_3C
e; R^1 = $PhCh_2CH_2$, R^2 = Ac
f; R^1 = $PhCH_2CH_2$, R^2 = Bu^tCO
g; R^1 = $PhCH_2$, R^2 = H
h; R^1 = $PhCH_2$, R^1 = Me
i; R^1 = cyclo-C_6H_{11}, R^2 = H
j; R^1 = cyclo-C_6H_{11}, R^2 = Me

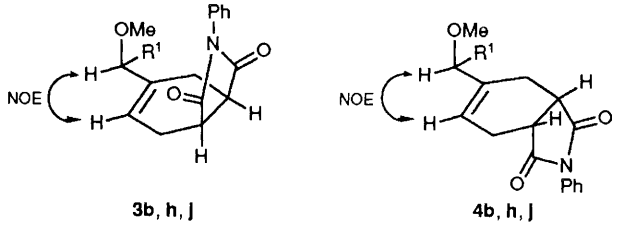


5 6a 6b

compounds with **3a** and **4a** through silylation, tritylation, acetylation, or pivaloylation. Concerning **3h, j** and **4h, j**, their stereostructures were proved by the close similarity of their ^1H NMR spectra to those of **3b** and **4b**.§ Methylation (MeI, Ag_2O, Et_2O, reflux) of **3g, i** and **4g, i** also led to a structure determination of these cycloadducts.

The results summarized in Table 1 suggest that the cycloaddition of the dienol **1a** with NPM in toluene occurred at room temperature to give the adduct **3a** as the major product and the facial selectivity was markedly solvent dependent (entries 1–4). When HMPA was employed, the sense of facial selectivity completely changed. In contrast to the dienol **1a**, the cycloaddition of the methyl ether **1b** with

§ All adducts **3b, h, j** and **4b, h, j** exhibited the same degree of NOE between their alkenic protons and methine CH bearing the methoxy group as shown below. It is, therefore, reasonable that methyl signals of **3b, h, j** consistently appeared in higher field compared with those of **4b, h, j** and also that the methylene protons of their cyclohexane rings showed a similar splitting pattern in each series of adducts regardless of the R^1 substituent.



3b, h, j **4b, h, j**

Table 1 [4 + 2] Cycloadditions at room temperature[a]

Entry	Diene	Conditions: Solvent	Conditions: *t*/h	**3** + **4**, Yield[b] (%)	Ratio[c] **3**:**4**
1	**1a**	Toluene	12	82	2.5:1
2	**1a**	Et_2O	48	92	1:1.4
3	**1a**	DMF	38	93	1:1.9
4	**1a**	HMPA	24	88	1:2.3
5	**1b**	Toluene	12	89	1:3.0
6	**1b**	HMPA	72	95	1:1.9
7	**1c**	Toluene	48	57[d]	1:1.9
8	**1d**	Toluene	48	<5[d]	1:1.3
9	**1e**	Toluene	48	83	1:1.1
10	**1f**	Toluene	48	82	1:1.1
11	**1g**	Toluene	12	82	2.5:1
12	**1h**	Toluene	12	72	1:3.2
13	**1i**	Toluene	12	83	2.0:1
14	**1j**	Toluene	72	85	1:2.7

[a] All reactions were performed by adding 1.2 equiv. of NPM to a 0.3 mol dm^{-3} solution of the diene in the indicated solvent (DMF = dimethylformamide; HMPA = hexamethylphosphoric triamide). [b] Isolated yield, unless noted otherwise. [c] Determined by HPLC of the reaction mixture. [d] The reaction was not completed.

Table 2 [4 + 2] Cycloadditions in 5 mol dm^{-3} $LiClO_4$–Et_2O[a]

Entry	Diene	Conditions: *T*/°C	Conditions: *t*/h	**3** + **4**, Yield[b] (%)	Ratio[c] **3**:**4**
1	**1a**	Room temp.	0.5	82	3.8:1
2	**1a**	0	12	86	4.0:1
3	**1a**	−30	12	74	7.5:1
4	**1b**	−30	12	88	1:4.3
5	**1g**	−30	12	67	5.7:1
6	**1h**	−30	12	72	1:4.6
7	**1i**	−30	14	84	5.3:1
8	**1j**	−30	48	83	1:8.1

[a] All reactions were performed by adding a 0.05 mol dm^{-3} solution of NPM (1.2) equiv.) in 5 mol dm^{-3} $LiClO_4$–Et_2O to a 0.2 mol dm^{-3} solution of diene in 5 mol $LiClO_4$–Et_2O at the indicated temperature. [b] Isolated yield. [c] Determined by HPLC after extractive work-up.

NPM in toluene proceeded with opposite facial selectivity to produce the adduct **4b** preferentially and showed little solvent dependence (entries 5 and 6). Similarly, the methyl ethers **1h, j** exhibited inverse facial selectivity compared with that observed in cycloadditions of the corresponding dienols **1g, i**. It can be seen that as the allylic alkoxy group (R^2O) increased in size, the reaction became more sluggish and resulted in poorer diastereofacial selection (entries 5, 7 and 8). It also turns out that an allylic acyloxy group exerted no directing influence on the facial selection (entries 9 and 10).

We would suggest that in the case of dienols, the preference for forming adducts **3** in toluene can be explained by assuming a transition state **5** which involves intermolecular hydrogen bonding between the diene OH group and the dienophile C=O group.[7] Solvent effects provide good evidence for this assumption. For protected dienols, two diene conformers **6a** and **6b** would be regarded as the most preferred conformers on the basis of arguments[8,9] put forward for acyclic dienes of general structure **2**. Now the observed preference for forming adducts **4** allows us to postulate that a protected dienol would undergo cycloaddition with NPM preferentially *via* the conformer **6a** from the bottom face where steric repulsion between diene and dienophile can be minimized.

Next, we found that the use of the 5 mol dm^{-3} $LiClO_4$–Et_2O solvent system[10–12] amplified the facial selectivity for both dienols and methyl ethers. Table 2 shows that the cycloaddi-

tions were markedly accelerated and proceeded rather smoothly even at −30 °C in this reaction medium. It is important to note that the sense of facial selectivity did not change showing the same tendency as observed in Table 1. Although we have no satisfactory rationale yet, we assume that the increased facial selectivity might be attributed to enhancement[10,11] of the *endo* selectivity in this reaction medium.

In conclusion, two new observations of potential value¶ in organic synthesis have been illustrated. First, a stereogenic allylic heteroatom substituent at the C-2 position of the buta-1,3-diene can control diastereofacial selectivity in intermolecular Diels–Alder reactions. Secondly, the diastereofacial selectivity can be amplified by the utilization of the 5 mol dm^{-3} $LiClO_4$–Et_2O solvent system.

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¶ Cycloadditions of dienes of type **1** to maleic anhydride, 1,4-benzoquinone, and ethyl acrylate were also found to proceed in moderate to excellent yields.

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