Diastereoselectivity in Diels–Alder Cycloadditions of Erythrose Benzylidene-acetal 1,3-Butadienes with Maleimides

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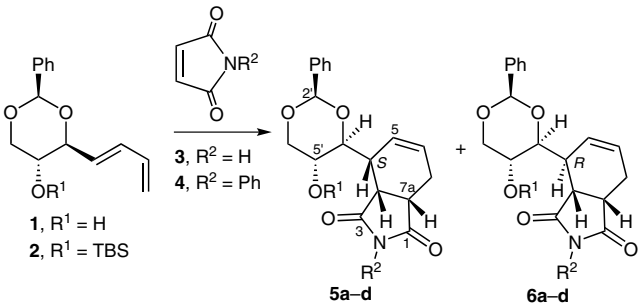
Abstract: Maleimides were combined with D-erythrose benzylidene-acetal 1,3-butadienes to study the facial selectivity of the Diels–Alder cycloadditions. The selectivity was found to range from moderate to good. The reaction diastereotopicity can be reversed with the temperature. Simultaneous coordination of the diene, having a free hydroxy group, and maleimide to a chiral bimetallic Lewis acid catalyst (LACASA–DA reaction) occurs with complete diastereocontrol to give a single adduct, using an extra chiral inductor either (*R*)- or (*S*)-BINOL.

Key words: maleimides, D-erythrose benzylidene-acetal 1,3-butadiene, Diels–Alder cycloaddition, selectivity

Small chiral synthons are becoming more and more appealing to synthetic chemists to build up target molecules possessing multistereogenic centers. We have been investigating the utility of D-erythrose 1,3-butadienes, such as **1** and **2**,[1] as chiral counterparts in diastereoselective Diels–Alder cycloadditions. In the past a high diastereotopicity was demonstrated in Diels–Alder reactions of these dienes with 2-methoxycarbonyl-*p*-benzoquinones.[1] In a previous study in our laboratory a complete chiral induction was also found in [4π+2π] cycloadditions of certain D-erythrose benzylidene-acetal 1,3-butadienes, having ether protection at C-5, with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD),[2] Maleimide (**3**), and *N*-phenylmaleimide (**4**). The facial selectivities were moderate to good under elevated temperatures, and interestingly the topicity was reversed when the cycloadditions were carried out at 5 °C. Self-assembly of the reaction components on a Lewis acid template made the selectivity complete in two cases.

D-Erythrose benzylidene-acetal 1,3-butadienes possessing the alcohol function protected (e.g., **2**) reacted with PTAD to give solely the adduct with the *endo*, *S*-configuration at the new stereogenic center.[2] The reaction turned out to be less selective when the diene bore an unprotected hydroxy group at C-5 (**1**). However, when reacting diene **2** with *N*-phenylmaleimide in dichloromethane (the solvent used in reactions with PTAD) the selectivity was reduced to a 2:1 ratio of *endo* diastereomers; the major being the *S* isomer (**5**) and the minor, its *R* diastereomer (**6**). The selectivity dropped to zero when diene **1** reacted with *N*-phenylmaleimide (**4**). The best selectivity with maleimides occurs when at least one of the reagents has the possibility of acting as a proton donor in a hydrogen bond. Thus combination of diene **2** and maleimide (**3**) affords a 3:1 (*S*/*R*) ratio of isomers; while reaction of diene **1** with maleimide (**3**) also yields the same ratio of isomers. Scheme 1 depicts the four possible combinations of the reagents and reaction conditions, and the yields of products are collected in Table 1.



Scheme 1 Four possible combinations of dienes **1** and **2** to maleimides **3** and **4** giving compounds **5** and **6**

Considering the unexpected behavior of maleimides in relation to PTAD, Figure 1 shows a possible explanation for the observation. Reagent superimposition in situations **A**, **B**, and **C** show the dienophiles approach to the *re* face of the diene, leading to the *R* configuration of products. In case **A** the proximity in space between the two electronegative atoms of the diene and dienophile may result in repulsion between reagents and render such an approach unlikely. Approach **B** does not indicate repulsion due to the nature of maleimides, which may favor such an approach. Finally, as shown in approach **C**, attack on the *si* face would result in the least hindered interaction between reagents, which may explain the *S*-configured compounds as the major isomers in most reactions.

Table 1 displays some relevant reaction conditions employed in Diels–Alder reactions between erythrose dienes **1** and **2** and maleimides **3** and **4**. In the majority of the cases a higher yield of the *S*-configured product is observed. The reactions usually require several days, but in one case reaction was shortened from 5 days to 15 hours by increasing the temperature to 40 °C with some loss of selectivity (Table 1, compare entries 3 and 4). Diene **1** and maleimide (**3**) were also combined at 5 °C (Table 1, entry 2) when the *R*-diastereomer became the major product, showing that the manner of approach of reagents is highly dependent on temperature. A possible interpretation for this fact may be the development of a hydrogen bond in

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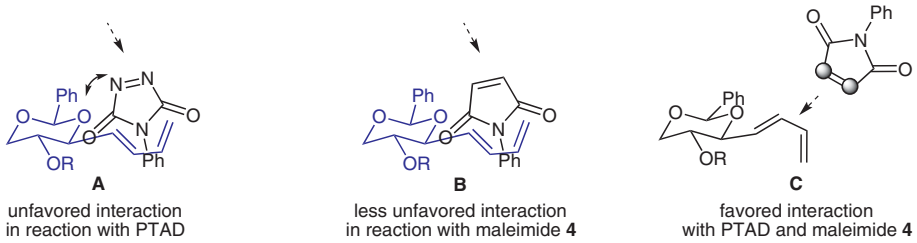


Figure 1 Different interaction at the rear double bond in maleimides and PTAD with the erythrose dienes (**A**, **B**, and **C**)

the approach of maleimide by the *re* face of the diene as shown in Figure 2 which is influential at lower temperatures. There is a good deal of information in the literature that relates the outcome of Diels–Alder cycloadditions with possible hydrogen-bonding effects between reactants.[3a–g] This is reinforced by the result of the experiment carried out at 5 °C between diene **2** and *N*-phenylmaleimide (**4**), which has no possibility of forming a hydrogen bond. The major isomer has the *S* configuration at both temperatures (Table 1, entries 5 and 6), with some selectivity improvement at the lower temperature, showing a different trend from the one in entries 2 and 3 (Table 1).

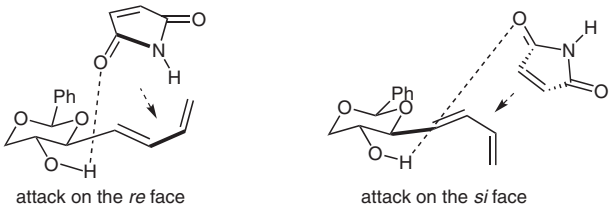


Figure 2 Approach of maleimide (**3**) to diene **1** in the *re*/*si* face showing the formation of a hydrogen bond between reagents

The *R*/*S* configurations of the products were found by comparison of ^{1}H NMR spectra of both isomers in each case to compounds **5a**/**6a**.[4] The identity of **5a** was unequivocally confirmed by X-ray crystallography (Figure 3). The chemical shifts of H-5/H-2′ differ between isomers, and the difference is reproducible in every case.[5]

Product **6a** is an *endo* product as **5a**, according to NOE experiments; irradiation of H-5′ and H-7a leading to an increase in intensity of H-4 signals by 6.27% and 10.4%, respectively.

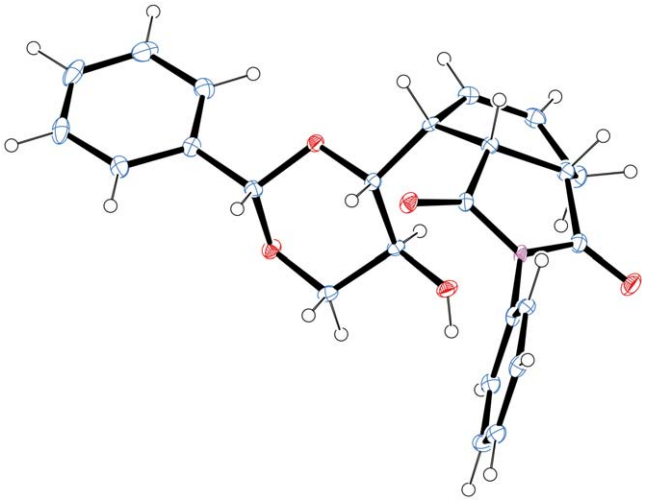


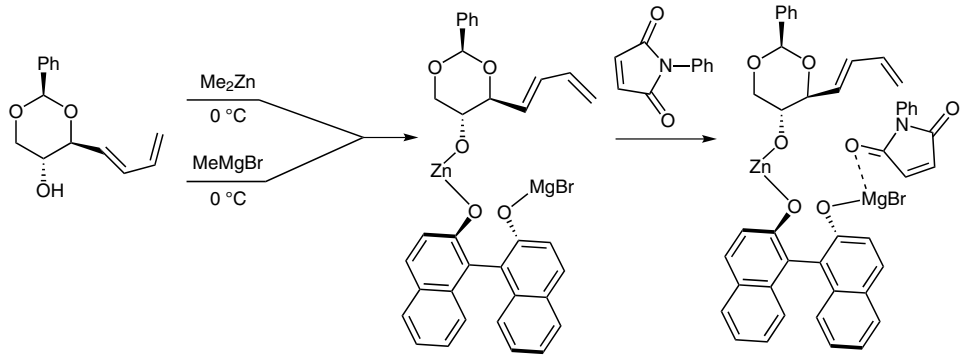
Figure 3 ORTEP view of diastereomer **5a**

To improve the facial selectivity of these cycloadditions it was decided to self-assemble the reagents by tethering erythrose diene **1** and maleimides **3** and **4** in a LACASA–Diels–Alder cycloaddition using bimetallic complexes of Mg(II) and Zn(II) in which (*R*)- and (*S*)-BINOL were chiral inducers. This brings an important advantage over sim-

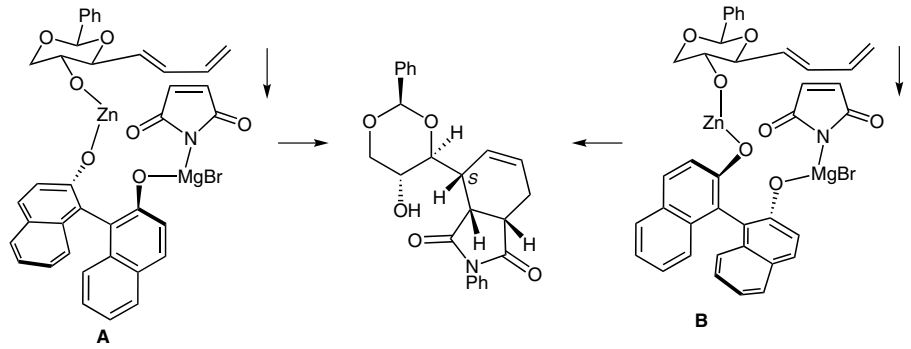
Table 1 Diels–Alder Cycloadditions of Dienes **1** and **2** with Maleimide (**3**) and *N*-Phenylmaleimide (**4**)

Entry	Diene	Dienophile (2 equiv)	Product	Solvent	Temp (°C)	Time	dr (*S*/*R*)	η (%) 5*S*/6*R*
1	**1**	**4**	**5a**/**6a**	toluene	r.t.	3 d	1[a]:1	22–23
2	**1**	**3**	**5b**/**6b**	CH_2Cl_2	5	18 d	1:2	30–19
3	**1**	**3**	**5b**/**6b**	CH_2Cl_2	r.t.	5 d	3:1	[b]
4	**1**	**3**	**5b**/**6b**	CH_2Cl_2	40	15 h	2:1	33–21
5	**2**	**4**	**5c**/**6c**	CH_2Cl_2	r.t.	9 d	2:1	43–20
6	**2**	**4**	**5c**/**6c**	CH_2Cl_2	5	18 d	3:1	22–4[c]
7	**2**	**3**	**5d**/**6d**	CH_2Cl_2	r.t.	5 d	3:1	41–39[d]

[a] Submitted to X-ray crystal structure analysis.
[b] Not isolated; dr obtained by ^{1}H NMR spectroscopy.
[c] An additional 11% of a 1:1 mixture of *R* and *S* isomers was isolated. The ratio was based up on ^{1}H NMR spectroscopic analysis of the sample.
[d] 39% is not pure *R* isomer; it is formed by a 1:2.9 (*S*/*R*) mixture of isomers based on ^{1}H NMR spectroscopic analysis of the sample.



Scheme 2 Bimetalic complex of Mg(II) and Zn(II) assembling together diene **1**, *N*-phenylmaleimide (**4**), and (*R*)-BINOL



Scheme 3 Coordination of the erythrose diene **1** with maleimide (**3**) using bimetalic complex of Mg(II) and Zn(II) with (*S*)-BINOL (**A**) and (*R*)-BINOL (**B**)

ple Lewis acid catalysts because covalent bonds to the metals are established, and the reaction occurs effectively by an intramolecular cycloaddition as shown in Scheme 2. This method has been first developed by Inomata[6a,b] using a tartaric acid–zinc complex in reaction of nitroso dienophiles with a dienol, and later by Ward.[7a,b]

The reaction combining (*S*)-BINOL (**A**), maleimide, and diene **1** was completely selective, forming exclusively the *S* product in 33% yield.[8] Scheme 3 represents the assembly of the reagents, and the direction of attack of maleimide to the front face of the diene leading to the *S*-configured product. The high selectivity observed is probably due to the covalent bond between the Mg and the nitrogen atom that forces the antarofacial interaction. The assembly of (*R*)-BINOL (**B**), *NH*-maleimide, and diene **1** give also a single *S*-configured product (29%). This means that although the flexibility of the complex is higher in the case of **B**, a similar approach takes place.

When *N*-phenylmaleimide (**4**) was used in place of maleimide (**3**) with (*R*)-BINOL and diene **1** a 2.5:1 ratio of isomers was obtained, in 50% yield, favoring the *R* compound. These products were isolated in 35% (*R*) and 15% (*S*) yields. In this case no covalent bond could have been established, and the reaction attack of the dienophile could now occur by the less bulky rear face of the diene.

In conclusion maleimides **3** and **4** reacted with erythrose dienes **1** and **2** showing at its best a 1:3 ratio of product isomers. It was found possible to reverse the selectivity on lowering the reaction temperature. Pure *S* isomers were isolated in moderate yields in the case of maleimide (**3**) and diene **1** by using bimetallic complex templates of Zn(II) and Mg(II) and (*R*)- or (*S*)-BINOL. Combination of diene **1**, *N*-phenylmaleimide (**4**), and (*R*)-BINOL under the same conditions led to the *R*-isomer (35% yield) together the *S*-isomer (15% yield).

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(4) **Analytical Data for Some Typical Compounds**
Compound **5a**: $[\alpha]_D^{20}$ –92.4 (*c* 0.45, EtOAc). IR (Nujol): ν_{max} = 3441, 1690, 1457 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.22–2.32 (1 H, m, H-7), 2.75–2.90 (2 H, m, H-7 and H-3a),

3.35 (1 H, tdd, *J* = 11.6, 5.8, 3.5 Hz, H-4), 3.60 (1 H, td, *J* = 11.2, 0.8 Hz, H-6′), 3.83 (1 H, br s, H-5′), 3.96 (1 H, dt, *J* = 15.0, 7.5 Hz, H-7a), 4.28 (1 H, t, *J* = 9.0 Hz, H-4′), 4.36 (1 H, ddd, *J* = 11.0, 5.1, 2.3 Hz, H-6′), 5.52 (1 H, s, H-2′), 6.02–6.13 (1 H, m, H-6), 6.17 (1 H, dt, *J* = 9.4, 3.2 Hz, H-5), 7.11–7.18 (2 H, m, Ph), 7.32–7.54 (8 H, m, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.27 (C-7), 39.23 (C-3a), 40.41 (C-4), 41.43 (C-7a), 66.44 (C-5′), 71.89 (C-6′), 80.46 (C-4′), 101.10 (C-2′), 126.06 (C-H, Ph), 126.42 (C-H, Ph), 128.13 (C-6), 128.23 (C-H, Ph), 128.83 (C-H, Ph), 128.94 (C-H, Ph), 129.12 (C-H, Ph), 130.14 (C-5), 131.56 (Cq, Ph), 137.49 (Cq, Ph), 178.53 (C=O), 179.81 (C=O) ppm. ESI-HRMS: *m/z* calcd for $C_{24}H_{23}NNaO_5$: 428.1467; found: 428.1468.

Compound **6a**: $[\alpha]_D^{20}$ –118.2 (*c* 0.45, EtOAc), IR (Nujol): ν_{max} = 3442, 1690, 1411, 1072 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17–2.31 (1 H, m, H-7), 2.64–2.76 (1 H, m, H-4), 2.83 (1 H, ddd, *J* = 15.4, 7.0, 1.6 Hz, H-7), 3.27 (1 H, td, *J* = 8.0, 1.6 Hz, H-3a), 3.65 (1 H, t, *J* = 10.4 Hz, H-6′), 3.81 (2 H, dd, *J* = 9.0, 5.5 Hz, H-7a and H-5′), 4.27 (1 H, dd, *J* = 10.8, 5.1 Hz, H-6′), 4.44 (1 H, t, *J* = 9.6 Hz, H-4′), 5.64 (1 H, s, H-2′), 6.02 (1 H, ddt, *J* = 12.9, 6.5, 3.3 Hz, H-6), 6.41 (1 H, dt, *J* = 9.4, 3.5 Hz, H-5), 7.19–7.22 (2 H, m, Ph), 7.35–7.40 (4 H, m, Ph), 7.43–7.47 (2 H, m, Ph), 7.50–7.52 (2 H, m, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.00 (C-7), 39.50 (C-3a), 40.09 (C-7a), 41.32 (C-4), 68.05 (C-5′), 71.24 (C-6′), 79.47 (C-4′), 100.79 (C-2′), 126.08 (C-H, Ph), 126.54 (C-H, Ph), 127.54 (C-6), 128.19 (C-H, Ph), 128.60 (C-H, Ph), 128.85 (C-H, Ph), 129.08 (Cq, Ph), 130.62 (C-5), 131.89 (Cq, Ph), 137.70 (Cq, Ph), 177.21 (C=O), 179.05 (C=O) ppm. ESI-HRMS: *m/z* calcd for $C_{24}H_{23}NNaO_5$: 428.1473; found: 428.1468.

(5) Compound **5a**: H-5: 6.40 (dt, *J* = 3.2, 9.2 Hz); H-2′: 5.64 (s).
Compound **5b**: H-5: 6.38 (dt, *J* = 3.6, 9.2 Hz); H-2′: 5.66 (s).
Compound **5c**: H-5: 6.34 (dt, *J* = 3.6, 9.2 Hz); H-2′: 5.67 (s).
Compound **5d**: H-5: 6.28 (dt, *J* = 3.6, 9.2 Hz); H-2′: 5.67 (s).
Compound **6a**: H-5: 6.17 (dt, *J* = 3.2, 9.2 Hz); H-2′: 5.51 (s).
Compound **6b**: H-5: 6.12 (dt, *J* = 3.6, 9.6 Hz); H-2′: 5.54 (s).
Compound **6c**: H-5: 6.16 (br s),* H-2′: 5.42 (s).
Compound **6d**: H-5: 6.08 (br t, 2.0 Hz),* H-2′: 5.42 (s).
* These signals coincide with H-6.

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(8) **Preparation of Solution A**
A solution of diene **1** (0.05 g, 0.22 mmol) in dry toluene (1.0 mL) was added to a solution of Me_2Zn (1.2 M) in toluene (178 μL, 0.22 mmol) at 0 °C and stirred for 5 min.
Preparation of Solution B
A solution of (*S*)-BINOL (0.061 g; 0.22 mmol) in dry toluene (1.0 mL) was added to a solution of MeMgBr (1.4 M in toluene–THF; 152 μL, 0.22 mmol) at 0 °C and stirred for 5 min. Solution **A** was added to solution **B**, the mixture diluted with dry toluene (1.8 mL) and stirred for 5 min. This mixture was refrigerated at –78 °C and a solution of maleimide (**3**; 0.02 g, 0.22 mmol) in dry toluene (1.5 mL) was then added. The temperature was allowed to rise gradually to r.t. The reaction was complete after 17 d and was quenched with an aq sat. solution of $NaHCO_3$ (1 mL), filtered through a pad of Celite, and the Celite was washed with EtOAc (4 × 10 mL). The filtrates were combined and concentrated under reduced pressure to give a yellow oil that was submitted to ‘dry-flash’ chromatography using a mixture of PE (40–60)–Et_2O. (*S*)-BINOL was recovered (0.035 g, 57%) from PE–Et_2O (1:1), and the product was eluted with PE–Et_2O (1:2.3; 0.024 g, 33%).

