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DIELS-ALDER REACTION OF CHIRAL DIENES. REMARKABLE EFFECT OF DIENOPHILE POLARITY UPON DIASTEREO FACE SELECTIVITY

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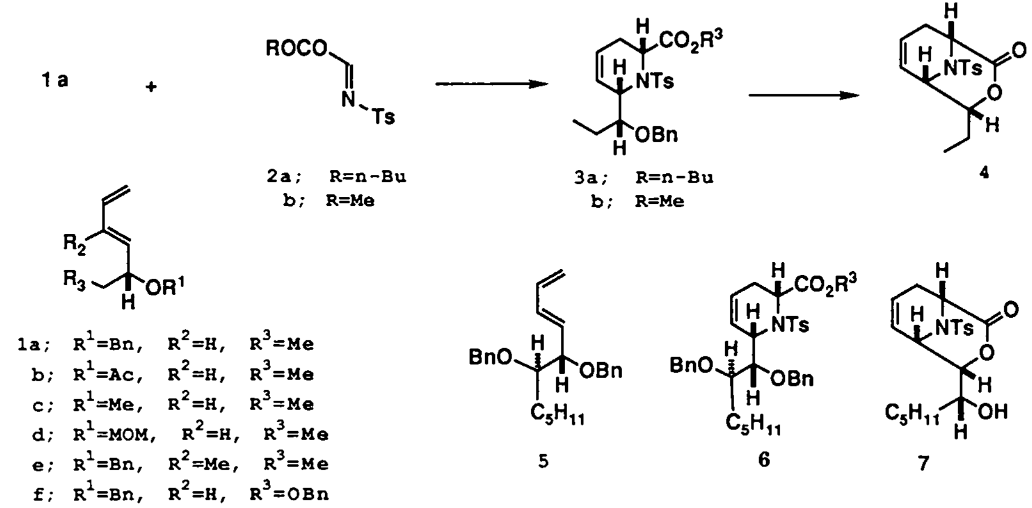
Summary: Face selectivity of Diels-Alder reaction of diene having the stereogenic center at allylic position depends on dienophile polarity, and hetero Diels-Alder reaction with dienophile such as N-tosylimine and N-tosylsulfinylimine was found to give exclusively ul product. The reaction mechanism and empirical rule of the face selectivity of these reactions are discussed.

Recently, diastereoselective reactions to chiral allylic alcohols or ethers are under active investigation to develop new methodologies for the total syntheses of complex natural products containing many chiral centers[1]. However, there has been little study so far of diene syntheses of chiral diene in spite of their synthetic importance[2]. During the course of our study aimed at the natural product synthesis, we have found that the intermolecular hetero Diels-Alder reaction of **1a** and **2a** gave the only isolable diastereomer **3a** in 83% yield (Scheme 1). The cis configuration of **3a** was proven by conversion to lactone **4**[3], whose structure was determined by X-ray crystallography (Fig 1).

Scheme 1



1a +

2a; R=n-Bu
b; R=Me

3a; R=n-Bu
b; R=Me

4

1a; R^1=Bn, R^2=H, R^3=Me
b; R^1=Ac, R^2=H, R^3=Me
c; R^1=Me, R^2=H, R^3=Me
d; R^1=MOM, R^2=H, R^3=Me
e; R^1=Bn, R^2=Me, R^3=Me
f; R^1=Bn, R^2=H, R^3=OBn

5

6

7

We were interested in the high diastereoselectivity of this intermolecular hetero Dields Alder reaction, therefore, we decided to clarify the effect of the dienophile polarity upon the diastereoface selectivity of the chiral diene having an asymmetric center such as **1** to establish a general rule to control diastereoface selectivity[4]. First, in order to show the generality of the high selectivity, several diene and dienophile **2** and **8**[5] were subjected to the hetero-Diels-Alder reaction, and the results are shown in Table I. All of the reactions listed in Table I gave single diastereomer showing that regio-, endo/exo-, and diastereoface selectivity was completely controlled[6]. The structure of the adduct **9** could not be determined directly, therefore, **9a** and **9c** were converted to **12**and **13** via several steps of the known reaction[6]: SN2 attack by phenyl Grignard reagent accompanied by inversion of sulfinate configuration to afford **10a** and **10c**, followed by 2,3-sigmatropic rearrangement to give **11a** and **11c** ; debenzylation of **11a** and ketalization to afford **12a** and debenzylation of **11c** to give triol and pivaloylation of primary alcohol and ketalization to give **13**. The structure of **12a** and **13** were shown to have twist-boat conformation of 1,3-anti-diol acetonide from 1D-difference NOE and vicinal coupling constant (Fig.2). Finally, the structure of **10a** was determined by X-ray crystallography as shown in Fig.1. Therefore, the structure of the adducts **3a**, **3b**, **6**, **9a**, **9b**, and **9c** could be the one described in Scheme 1 and 2 (exclusively ul[6]).

Scheme 2

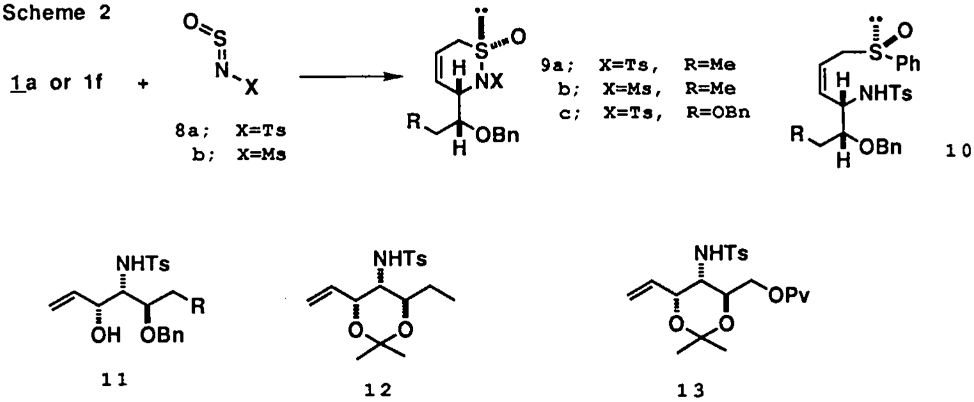


Table I Hetero Diels-Alder reaction of Dienes with Dienophile 10 and 18

Entry	Diene	Dienophile	Condition	Adduct	Total Yield(%)	Diastereoface selectivity(lk/ul)
1	1a	2a	40°C, 48h[a)]	3	83	exclusively ul
2	1a	2b	"	3b	74	"
3	5	2b	40°C, 2days[a)]	6	67	"
4	1a	8a	0°C, 2days[b)]	9a	68	"
5	1a	8b	"	9b	60	"
6	1f	8a	0°C, 40hr[a)]	9c	70	"

a) no solvent b) in benzene.

The cycloaddition of N-tosylimine **2** and N-tosylsulfinylimine **8** is known to proceed stepwise via dipolar intermediate[5]. On the other hand, maleic anhydride (MA) and N-phenylmaleinimide (NPM) are a representative dienophile to react with diene by concerted manner. In order to compare two extreme cases, diene **1a-d** were subjected to the reaction with MA or NPM. The results are shown in Table II. The structure of **14a-f** could not determined directly, therefore, they were converted to lactone **15** treating with TMSCl and NaI to give free alcohol, followed by lactonization with MeOH-HCl. The relative stereochemistry of **18** was determined from vicinal coupling constant between H_a and H_b (α-H_a; J_{ab}=0–1.5Hz, β-H_a; Jab=8.0–8.5Hz). In contrast to the results of above hetero Diels-Alder (exclusively ul), the major diasteromer is lk product though the ratio is not so high except in the case of the reaction of diene **1e**[7]. Benzyloxydiene (**1a**) did not show any specific effect in this case to control diastereoface selectivity like π to π stacking. Recently, Franck et al. reported results of Diels-Alder reaction of the dienes similar to ours and various dienophile, and discussed the effect of dienophile polarity on diastereoface selectivity. They did not arrive at a clear conclusion, but suggested the possibility of the effect of dienophile polarity for more polar (reactive) dienophile to give ul-product preferentially, although the selectivity was not so high. From our present result, we can now describe an empirical rule on the effect of dienophile polarity upon diastereo face selectivity of the diene as follows: diastereoface selectivity depends upon dienophile polarity; less polar dienophile has a tendency to give lk product ; polar dienophile, ul product. This rule could be interpreted as follows: with less polar dienophile, diastereo-face selectivity depends on the diene structure mainly governed by allylic interaction[10]; on the other hand, with polar dienophile, diastereo-face selectivity depend on a transition state structure, mainly stabilization of allyl cation by a-substituted oxygen through homoallylic interaction between cation and oxygen lone pair[11]. Considering complete end-control, there may be equilibrium between starting materials and zwitter ionic intermediate stabilized by inside alcoxy group and the intermediate cyclize to give only ul adduct (Scheme 3). In order to prove this proposed reaction mechanism, we are now conducting intensive investigation.

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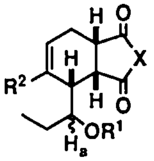
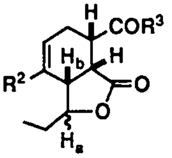


14a; R^1=Bn, R^2=H, X=O
b; R^1=Ac, R^2=H, X=O
c; R^1=Me, R^2=H, X=O
d; R^1=MOM, R^2=H, X=O
e; R^1=Bn, R^2=H, X=NHPh
f; R^1=Bn, R^2=Me, X=NHPh



15a; R^2=H, R^3=OMe
b; R^2=H, R^3=NHPh
c; R^2=Me, R^3=NHPh

Table II Diels-Alder reaction with maleic anhydride (MA) and N-phenylmaleinimide (NPMI)

Entry	Diene	Dienophile	Condition[a]	Adduct	Total Yield(%)	Lactone (18)	ratio (lk/ul)[c]
1	**1a**	MA[a]	70°C, 3day	**17a**	23[b]	**18a**	2.4 : 1
2	**1b**	MA	70°C, 20h	**17b**	68[b]	"	1.8 : 1
3	**1c**	MA	70°C, 15h	**17c**	44[b]	"	1.7 : 1
4	**1d**	MA	70°C, 38h	**17d**	66[b]	"	2.3 : 1
5	**1a**	NPMI	40°C, 35h	**17e**	56	**18b**	1.8 : 1[d]
6	**1e**	NPMI	r.t., 3day	**17f**	69	**18c**	28 : 1[d]

a) in benzene b) overall yields after conversion to lactone **18** c) lk; Ha-β ul; Ha-α d) ratio of **17**

Scheme 3

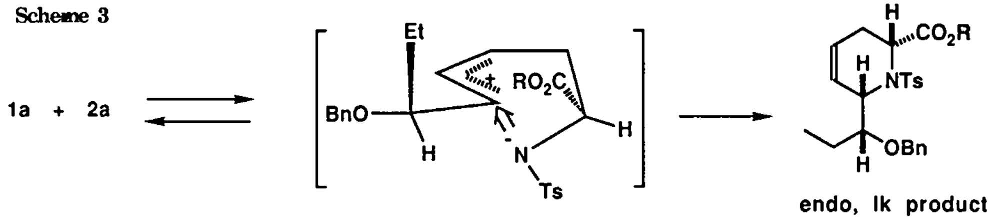
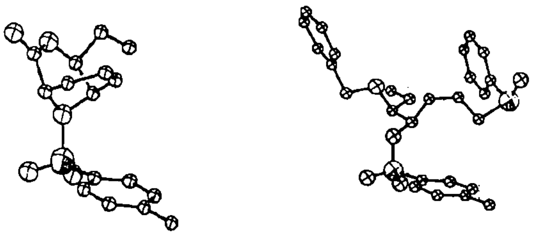
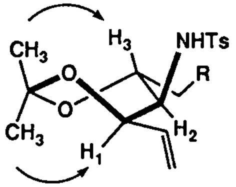


Fig.1 Oltep drawing of the X-ray structure of 4 and 10a



4 10a

Fig2 The conformation and NOE of 12a and 13



12a: $J_{1,2} = 4.0$ Hz, $J_{2,3} = 6.0$ Hz
13 : $J_{1,2} = 4.0$ Hz, $J_{2,3} = 6.2$ Hz

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3) The adducts **3b** and **6** were also converted to lactone **4** and **7**, and the relative stereochemistry of Ha and Hb of **7** was assigned to be the same as **4** from Jab(**4**; Jab= 4.0, **7**; Jab= 4.0).
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