Stereodivergent Diels-Alder Reactions Employing Cyclitols as Chiral Auxiliaries

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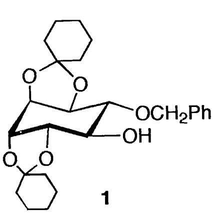
The $TiCl_4$ or $SnCl_4$ mediated Diels-Alder reaction of cyclopentadiene and chiral acryloyl ester derived from chiral cyclitols proceeded with excellent diastereoselectivity in Et_2O via re-face attack of the acrylates. In contrast, interesting changeover of the diastereofacial selectivity was observed by use of toluene or hexane as a solvent to afford the cycloadducts derived from si-face attack of the acrylates.

Asymmetric Diels-Alder reaction is an excellent method for the preparation of optically active compounds. High diastereo- and enantioselectivity have been achieved.[1] From the synthetic point of view, it is extremely significant to synthesize both enantiomers from the same starting material, only by changing the reaction conditions without use of both enantiomeric chiral auxiliaries. Although many stereodivergent reactions that fall into this category have been developed in the fields of Lewis acid promoted addition of organometallics to carbonyl compounds,[2] there are scattered examples of Diels-Alder reactions, wherein reversal of the diastereofacial selection was observed by changing the Lewis acid.[3]

In the course of investigating the utility of L-quebrachitol (1L-(–)-2-*O*-methyl-*chiro*-inositol), which is a naturally occurring optically active cyclitol obtained from an exudate of the rubber tree,[4,5] we demonstrated that chiral cyclitols derived from L-quebrachitol were efficient chiral auxiliaries.[6] In this paper, we report a diastereoselective Diels-Alder reactions employing chiral cyclitols **1** and **2** as chiral auxiliaries,[7] in which changing the solvent resulted in dramatic changeover of the diastereofacial selectivity. As far as we know, this is the first example wherein both enantiomers of Diels-Alder adduct were obtained in good enantiomeric purity only by changing the solvent.



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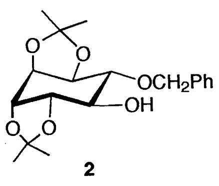

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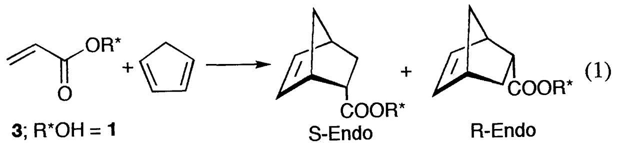

3; R*OH = **1**
4; R*OH = **2**

S-Endo
5; R*OH = **1**
7; R*OH = **2**
9; R* = H

R-Endo
6; R*OH = **1**
8; R*OH = **2**
10; R* = H

The chiral auxiliaries **1** and **2** were readily prepared starting from L-quebrachitol.[6e, 8]

Lewis acid promoted Diels-Alder reaction of an acrylate **3** with cyclopentadiene took place smoothly to afford cycloadducts and the results are shown in Table 1. Endo-exo selectivity in the range of >99: <1 to 13: 1 was found. For the endo isomers **5** and **6**, high level of diastereoselectivity was achieved. $AlCl_3$ and Et_2AlCl uniformly afforded *S*-endo isomer **5** preferentially in all solvents examined (Entries 1-5). When titanium(IV) chloride was employed as a Lewis acid in Et_2O, **5** was obtained predominantly and *R*-endo isomer **6** was negligible (Entry 6). In striking contrast, use of toluene as a solvent dramatically changed the diastereofacial selectivity to afford **6** preferentially (Entry 8). Tin(IV) chloride also exerted prominent changeover of the facial selectivity in non-coordinating solvents such as toluene, xylene, and hexane to afford **6** as a major product (Entries 11-13). The diastereoselectivity was determined by 270 MHz ^1H NMR as well as HPLC analysis.

Table 1. Diels-Alder reaction of **3** with cyclopentadiene[a]

Entry	Lewis Acid	Solvent	Reaction Conditions	Yield /%	Endo / Exo	**5** : **6**
1	$AlCl_3$	Et_2O	-78 °C, 1h	68	98 : 2	94 : 6
2	$AlCl_3$	CH_2Cl_2	r.t. 1.5 h	84	95 : 5	79 : 21
3	$AlCl_3$	Toluene	-50 °C, 1 h	84	>99:<1	85 : 15
4	Et_2AlCl	Et_2O	r.t. 2 h	46	96 : 4	88 : 12
5	Et_2AlCl	CH_2Cl_2	0 °C, 5 h	36	93 : 7	76 : 24
6	$TiCl_4$	Et_2O	-78 °C, 2 h	90	94 : 6	**>99:<1**
7	$TiCl_4$	CH_2Cl_2	0 °C, 6 h	90	93 : 7	82 : 18
8	$TiCl_4$	Toluene	0 °C, 3 h	32	97 : 3	25 : 75
9	$SnCl_4$	Et_2O	0 °C, 6 h	90	93 : 7	82 : 18
10	$SnCl_4$	CH_2Cl_2	-78 °C - r.t.	0	-	-
11	$SnCl_4$	Toluene	-78°C,1.5 h	97	98 : 2	**12 : 88**
12	$SnCl_4$	Xylene	-78°C,1.5 h	92	98 : 2	13 : 87
13	$SnCl_4$	Hexane	-78°C,2.5 h	80	97 : 3	15 : 85

[a] The reactions were carried out by using 800 mol% of cyclopentadiene and 150 mol% of Lewis acid.

Next, Diels-Alder reaction of an acrylate **4**, possessing isopropylidene groups, with cyclopentadiene was examined and the results are shown in Table 2. In this case, high endo selectivity (>40 : <1) was also observed. For the endo isomers **7** and **8**, high level of diastereoselectivity as well as dramatic changeover of the diastereofacial selectivity were observed.

The chiral auxiliary could be removed readily to afford chiral carboxylic acids **9** and **10**. Using the same chiral auxiliary, both enantiomers of the cycloadducts **9**, **10** were obtained with high enantiomeric excess just by changing the solvent.[9]

The present Diels-Alder reaction showed following selectivity; 1) Lewis acids with only a single coordination site ($AlCl_3$ and Et_2AlCl) showed *S*-endo selectivity in all solvents, 2) chelating Lewis acids ($SnCl_4$ and $TiCl_4$) showed *S*-endo selectivity both in Et_2O and CH_2Cl_2, and exhibited *R*-endo selectivity in toluene, xylene, or hexane.

Table 2. Diels-Alder reaction of **4** with cyclopentadiene[a,b]

Entry	Lewis Acid	Solvent	Reaction Conditions	Yield/ %	**7 : 8**
1	$AlCl_3$	Et_2O	-78°C, 2 h	62	98 : 2
2	$AlCl_3$	CH_2Cl_2	-78°C, 2 h	72	83 : 17
3	$AlCl_3$	Toluene	-78°C, 1.5h	41	89 : 11
4	$EtAlCl_2$	Et_2O	-78°C, 9 h	85	91 : 9
5	$EtAlCl_2$	CH_2Cl_2	-78°C, 4 h	30	83 : 17
6	$TiCl_4$	Et_2O	-78°C, 2 h	80	**>99 : <1**
7	$SnCl_4$	Et_2O	r.t. , 5 h	49	82 : 18
8	$SnCl_4$	CH_2Cl_2	-78°C, 2 h	85	85 : 15
9	$SnCl_4$	Toluene	-78°C, 5 h	81	**13 : 87**
10	$SnCl_4$	Hexane	-78°C, 3.5 h	83	26 : 74

[a]The reactions were carried out by using 800 mol% of cyclopentadiene and 120-150 mol% of Lewis acid. [b]High endo/exo selectivity was observed.

Ab initio calculations showed that methyl acrylate has small preference for s-cis conformation but the Lewis acid complexed acrylates prefer the s-trans conformation.[10,11] Thus, present stereochemical outcome might be explained by the model as shown in Figure 1. *s*-Trans conformation of the acrylate such as **A** would be favored in complexes with $AlCl_3$ and Et_2AlCl.[12] In the complex **A**, the *si* face of the dienophile is shielded by the benzyloxy group and the attack of the diene from the *re* face is favored, resulting in the selective formation of the *S*-endo adduct. When tin(IV) chloride or titanium(IV) chloride, which have two coordination sites, were employed, the same chelate complex (**A**) would be formed in Et_2O and CH_2Cl_2, resulting in the preferential formation of the *S*-endo adduct. In contrast, cyclic intermediate such as **B** may be formed[13] with chelating Lewis acids in non-coordinating solvents such as toluene and hexane. Thus *si*-face attack of the diene to the dienophile would be favored since *re*-face is hindered by the cyclohexylidene moiety, leading to the preferential formation of *R*-endo-adduct.

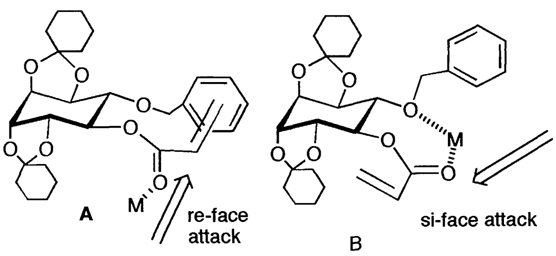

Figure 1.

Although present chiral auxiliaries still have a disadvantage such as sluggish reaction with butadiene and with isoprene, our findings could provide a guide in understanding the mechanism of Lewis acid promoted stereoselective reactions, in which solvent effect must be taken into consideration.

In summary, present Diels-Alder reaction has two intriguing features: 1) first example of the use of cyclitol as a chiral auxiliary, 2) remarkable changeover of the diastereofacial selectivity only by changing the solvent.

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