Hetero Diels–Alder Reaction of Benzenesulfonyl Cyanide with Cyclopentadiene Using Chiral Lewis Acids[1)]

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Received October 19, 1995; accepted December 5, 1995

Asymmetric induction was observed in the hetero Diels–Alder reaction of benzenesulfonyl cyanide with cyclopentadiene using chiral Lewis acids. This is the first instance of asymmetric Diels–Alder reaction involving a sulfonyl group in the presence of a chiral Lewis acid.

Key words asymmetric induction; hetero Diels–Alder reaction; benzenesulfonyl cyanide; cyclopentadiene; chiral Lewis acid; 2-azabicyclo[2.2.1]hept-5-en-3-one

2-Azabicyclo[2.2.1]hept-5-en-3-one (C=**2**),[2)] practically synthesized by the hetero Diels–Alder reaction of arylsulfonyl cyanide (A) with cyclopentadiene followed by hydrolysis, has become an important reagent in the field of nucleoside chemistry, because **2** can be readily converted to a carbocyclic sugar moiety of carbocyclic nucleosides (D).[3)] Recently, carbovir (E), regarded as a highly modified carbocyclic nucleoside, has been found to show significant anti-human immunodeficiency virus (HIV) activity[4)] and its derivative (F) is under clinical trial for treatment of AIDS patients.[5)] Most synthetic methods for E and F involve a cyclopentenylamine derivative as a key intermediate derived from **2**.[3)] Since only 1*R* isomers in both compounds have anti-HIV activity, EPC (enantiomerically pure compound) synthesis of (−)-**2** is required for the preparation of 1*R* isomers. We report here the first enantioselective synthesis of **2** using the Diels–Alder reaction with chiral Lewis acids for asymmetric induction.

Recently, asymmetric syntheses using chiral Lewis acids have been extensively studied.[6)] In particular, the chiral Lewis acid-mediated Diels–Alder reaction has become a powerful tool for the synthesis of optically active substances, because of the great improvement in its enantioselectivity. Therefore, we set out to apply this methodology to the direct synthesis of optically active **2**.

First, we chose the chiral Lewis acids (**3**—**5**) prepared from the corresponding diols and dichlorodiisopropoxy titanium because the analogues of these Lewis acids produce very high enantioselectivity in common Diels–Alder reactions.[7)] When benzenesulfonyl cyanide (**1**)[8)] (1 eq) was allowed to react with cyclopentadiene (5 eq) in the presence of a chiral Lewis acid (**3**) (0.2 eq for **1**) in toluene at −78 °C, compound **2** was obtained in 48% yield after treatment of the reaction mixture with water. Since the reaction did not proceed at this temperature without the chiral Lewis acid (**3**), the Lewis acid definitely facilitated the reaction. However, the optical rotation of the product and its HPLC analysis revealed that the enantioselectivity was low (2.8% ee). Though chiral Lewis acids (**4**, **5**[9)]) also accelerated the reaction to give **2**, enantioselectivity was hardly observed (Table 1). We considered that the low selectivity could be attributed to a weak interaction between the chiral Lewis acid and the sulfonyl group of the dienophile (**1**).

Next, we examined the Diels–Alder reaction using chiral Lewis acids (**6**—**9**) in the form of aluminum complexes, which were prepared by the reaction of the corresponding alcohols with ethylaluminum dichloride. Koga and his coworkers first examined the Diels–Alder reaction using the chiral Lewis acid (**6**).[10)] However, use of **6** did not cause asymmetric induction in the reaction of **1** with cyclopentadiene (Table 2). Kagan and his coworkers first reported the asymmetric Diels–Alder reaction of methacrolein with cyclopentadiene using chiral Lewis acids (**7**—**9**), and they obtained an enantiomeric excess of up

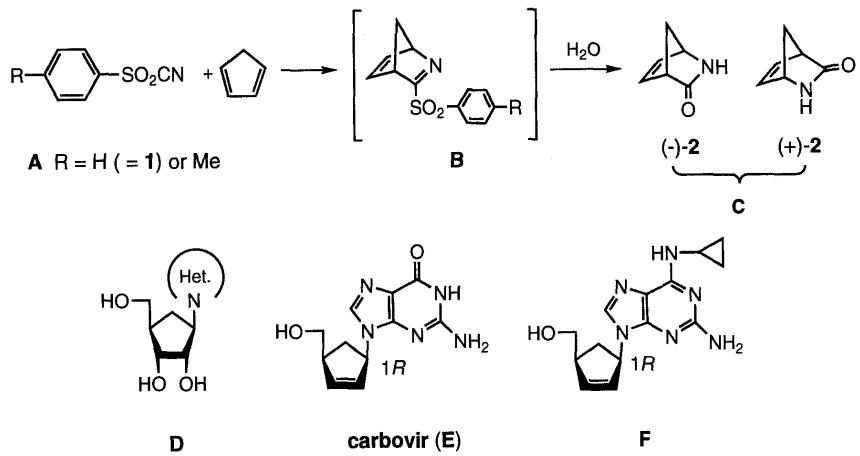

Chart 1

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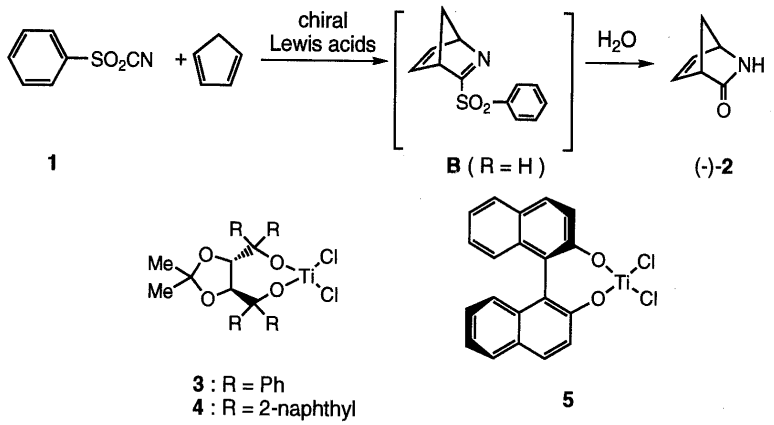

Chart 2

Table 1. Reaction of Benzenesulfonyl Cyanide (**1**) with Cyclopentadiene in the Presence of Chiral Lewis Acids (**3**—**5**)

Chiral Lewis acid	Yield of **2** (%)	$[\alpha]_D$ (c=1, MeOH)
3	48	−16.2° (2.9%)[a]
4	53	−3.8°
5	43	−0.4°

a) Enantiomeric excess (ee).

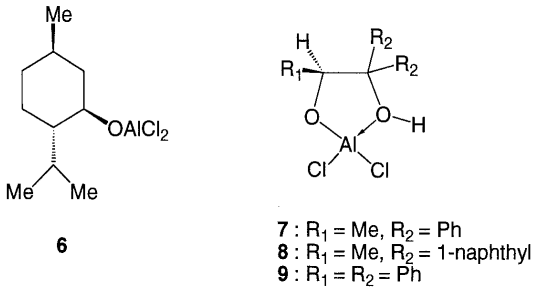

Fig. 1

to 86%.[11] Using these chiral Lewis acids, we investigated the Diels–Alder reaction of **1** with cyclopentadiene under various conditions. The results are shown in Table 2. The reaction was carried out using 0.2 eq of chiral Lewis acids and 5 eq of cyclopentadiene with respect to **1**. In the case of the chiral Lewis acid (**7**), the enantioselectivity increased with lowering of the reaction temperature. It reached a maximum at −40 °C (run 5: ee 20.0%), and then decreased at below −50 °C. This phenomenon is attributable to the fact the reaction does not proceed at this temperature and the product (**2**) would be formed during handling after the reaction (at room temperature). Neither the prolonged reaction time nor the use of 0.5 eq of chiral Lewis acid affected the enantioselectivity. The best selectivity (25.6%) was obtained at −60 °C for 24 h and then at −25 °C for 24 h (run 10). The asymmetric Diels–Alder reaction using chiral Lewis acids (**8**, **9**) was also examined under similar conditions. However, the selectivity was low. All reactions using chiral Lewis acids (**7**—**9**) gave predominantly (+)-**2**.

In conclusion, we have observed the first asymmetric induction in a chiral Lewis acid-mediated hetero Diels–Alder reaction involving a sulfonyl group, though the enantioselectivity was low. The mechanism for the asymmetric induction may be as follows. If organoaluminum complexes prefer tetracoordination,[12] the chiral Lewis acid (**7**) would form the complex (G) through a hydrogen bond between the hydroxyl group of **7** and the oxygen of **1**. Cyclopentadiene would approach from the opposite side to the aluminum atom in the complex (G) to give predominantly (+)-**2**.

Table 2. Reaction of Benzenesulfonyl Cyanide (**1**) with Cyclopentadiene in the Presence of Chiral Lewis Acids (**6**—**9**)

Run	Chiral Lewis acid[a]	Temp. (°C)	Time (h)	Yield of **2** (%)	ee (%) of (+)-**2**
1	**6**	−25	24	48	0
2	**7**	−13	4.5	42	11.1
3	**7**	−25	24	35	14.1
4	**7**	−25	48	43	14.0
5	**7**	−40	24	41	20.0
6[b]	**7**	−40	24	20	20.6
7[c]	**7**	−40	24	50	17.0
8	**7**	−50	24	45	15.4
9	**7**	−60	24	53	7.6
10[d]	**7**	−60, −25	48	45	25.6
11	**8**	−15	24	18	2.5
12	**9**	−15	24	48	7.5
13	**9**	−40	24	44	1.2

a) Chiral Lewis acid (0.2 eq) was used in each reaction except for run 6. *b*) Chiral Lewis acid (**7**) was used in the amount of 0.5 eq. *c*) The mixture of **1** and **7** in toluene was kept in a refrigerator for 4 d, and then cyclopentadiene was added. *d*) The reaction mixture was kept at −60 °C for 24 h and then at −25 °C for 24 h.

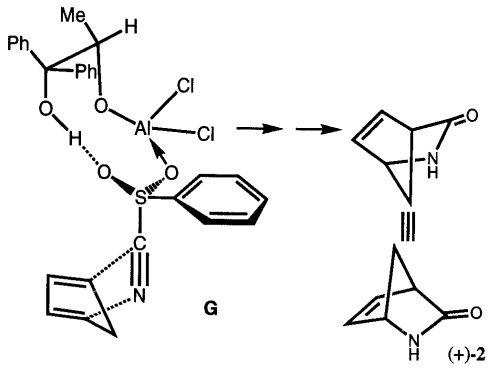

Fig. 2

Experimental

Optical rotations were measured with a JASCO DIP-340 digital

polarimeter. Enantiomeric excess (ee) was determined by HPLC analysis using a chiral column (Chiral pak AS, EtOH : hexane = 1 : 2). HPLC was carried out on a Waters Associates instrument (M 6000 pump; U6K injector) using a 254 nm UV or RI detector. Wakogel (C-200) was employed for silica gel column chromatography. The ratios of solvent mixtures for chromatography are shown as volume/volume.

General Procedure for the Synthesis of 2-Azabicyclo[2.2.1]hept-5-en-3-one (2) Using Chiral Lewis Acids (3—5) Dichlorodiisopropoxy titanium (IV) (133 mg, 0.5 mmol) and the corresponding diol (0.5 mmol) were added to a suspension of powdered molecular sieves (625 mg) in dry toluene (10 ml) at −78 °C. Then **1** (835 mg, 5 mmol) and cyclopentadiene (1.65 g, 25 mmol) were added. The mixture was stirred for 6 h, then water (1 ml) was added to hydrolyze the initially formed bicyclic compound (B). After removal of molecular sieves by filtration, the filtrate was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (80 g). Elution with ethyl acetate gave compound **2**. The results are shown in Table 1.

General Procedure for the Synthesis of 2-Azabicyclo[2.2.1]hept-5-en-3-one (2) Using Chiral Lewis Acids (6—9) Ethylaluminum dichloride (2 mmol) was added to a solution of *l*-menthol (2 mmol) or an appropriate chiral diol (2 mmol) in dry dichloromethane (18 ml) under an argon atmosphere with stirring at −78 °C. The mixture was stirred for 3 h at room temperature, then a solution of **1** (1.67 g, 10 mmol) in dichloromethane (5 ml) and cyclopentadiene (3.3 g, 50 mmol) were added successively at −78 °C. The mixture was stirred at an appropriate temperature for 24 h or 48 h. Water (1 ml) was added, and the whole was neutralized with $NaHCO_3$ (1 g). It was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (80 g). Elution with ethyl acetate gave compound **2**. The results are shown in Table 2.

Acknowledgment This work was supported in part by a Grant-in-Aid for Scientific Research (No. 06672230, to N. K.) from the Ministry of Education, Science, Sports, and Culture, Japan. The authors thank Kuraray Co., Ltd. for providing benzenesulfonyl cyanide.

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