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New chiral sulfoxide ligands in catalytic asymmetric Diels–Alder reactions: double acceleration by the chiralities of the sulfoxides and oxazolines

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Abstract—New chiral sulfoxide ligands which are useful for catalytic asymmetric Diels–Alder reactions have been developed. The new ligands involve a chiral sulfinyl function and a 1,3-oxazoline ring with an asymmetric carbon center, in which the chiral sulfinyl group has been revealed to play a crucial role in achieving high enantioselectivity in asymmetric Diels–Alder reactions. Among the Lewis acid catalysts employed, magnesium iodide provided the highest chemical and stereochemical efficiency in the cycloaddition reactions. A mechanistic pathway for the asymmetric synthesis is proposed on the basis of the stereochemical outcomes obtained.

Catalytic asymmetric cycloaddition reactions have recently attracted much attention for stereoselective and efficient preparation of optically active carbocyclic and heterocyclic compounds, especially with multifunctionalized groups.[1] A number of asymmetric synthetic methods with chiral ligands have been developed so far,[2] and are being applied to the total synthesis of natural products and biologically active compounds with high efficiency.[3]

We wish to communicate herein a novel catalytic asymmetric Diels–Alder reaction with new chiral sulfoxide ligands. Hitherto we have developed a number of chiral sulfoxide ligands and demonstrated the usefulness of the ligands in transition metal-catalyzed asymmetric reactions, indicating the mode of the coordination of the chiral sulfinyl function to the transition metals and the mechanistic pathways for the asymmetric syntheses.[4] Few chiral sulfoxide ligands have previously been

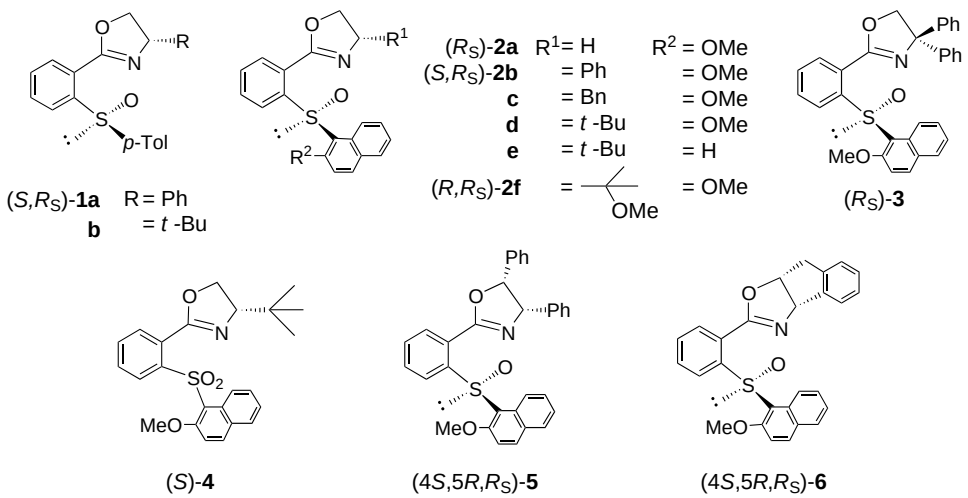

Figure 1.

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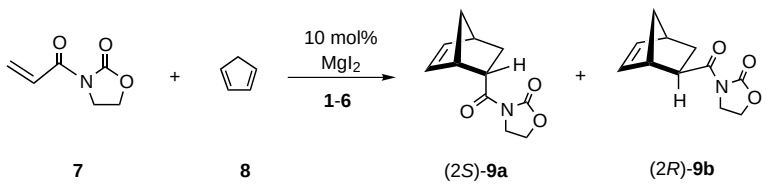
reported in asymmetric cycloaddition reactions.[5,6] We describe in this report a doubly accelerated asymmetric Diels–Alder reaction with the chirality on oxazolines and that of sulfoxides, providing the highest (>90% e.e.) enantioselectivity over those from the previous chiral sulfoxide ligands.

New chiral oxazoline-sulfoxide ligands (*R*s)-**1a**,**b**, **2a**–**f**, **3**, **5**, and **6** were prepared in the usual way by lithiation of 2-(2-bromophenyl)-1,3-oxazolines[7] (derived from the corresponding amino alcohols and 2-bromobenzoyl chloride) with *n*-butyllithium followed by the sulfinylation with (−)-menthyl (*S*s)-*p*-toluene-, 1-naphthalene-, or 2-methoxy-1-naphthalenesulfinate.[8] The oxazoline-sulfone ligand (*S*)-**4** was obtainable from (*S*,*R*s)-**2d** by oxidation with *m*-chloroperbenzoic acid (Fig. 1).

The Diels–Alder reactions of **7** with cyclopentadiene (**8**) using chiral oxazoline-sulfoxide ligands obtained above were studied under catalysis with Lewis acids. Marked effects of the Lewis acid catalysts on the asymmetric induction in the reaction of **7** with **8** were observed; among the Lewis acids examined, MgI_2 was revealed to be the most effective for giving (2*S*)-**9a** (81% e.e.; on the use of (*S*,*R*s)-**2d** in CH_2Cl_2 at −78°C for 24 h). Use of other Lewis acids ($Cu(OTf)_2$, CuI_2, FeI_3, $MgCl_2$, $MgBr_2$, $MgBr_2{\cdot}OEt_2$, and $Mg(OTf)_2$) under the same reaction conditions provided (2*S*)-**9a** with 1, 1, 41, 6, 8, 45, and 1% e.e., respectively (Scheme 1).

The reactions were carried out under the following two reaction conditions for confirming the complete formation of the Lewis acid complex with the ligands used: reacted with a ligand in CH_2Cl_2 at room temperature for 30 min (method A) or in THF at 40°C for 1.5 h (method B) prior to the addition of the substrates. The latter reaction condition was preferred, since it provided the Diels–Alder adduct **9** with higher enantioselectivity, as shown in Table 1 (entries 4 and 5).

The 2-methoxy-1-naphthyl sulfoxides (*S*,*R*s)-**2a**–**d** and (*R*,*R*s)-**2f** provided higher enantioselectivity than the other aryl sulfoxides, *p*-tolyl sulfoxides (*S*,*R*s)-**1a**,**b** and 1-naphthyl sulfoxide (*S*,*R*s)-**2e**. The effects of substituents on the oxazoline rings were studied using bulky substituents such as phenyl, benzyl, *t*-butyl or



Scheme 1.

Table 1. Studies on the MgI_2-catalyzed asymmetric Diels–Alder reactions of **7** with **8** using chiral ligands **1**–**6**[a]

Entry	Ligand (mol%)	Method[b]	Solvent	Temp. (°C)	Time (h)	Yield of **9** (%)	*endo* (**9a**)/*exo* (**9b**)[c]	e.e. (%) of the *endo* product **9a**[d]
1	**1a** (10)	B	CH_2Cl_2	−78	24	82	93/7	30 (2*S*)
2	**1b** (10)	B	CH_2Cl_2	−78	24	86	94/6	46 (2*S*)
3	**2a** (10)	B	CH_2Cl_2	−78	24	82	94/6	17 (2*S*)
4	**2b** (10)	A	CH_2Cl_2	−78	24	45	93/7	24 (2*S*)
5	**2b** (10)	B	CH_2Cl_2	−78	24	83	94/6	50 (2*S*)
6	**2c** (10)	B	CH_2Cl_2	−78	24	99	93/7	21 (2*S*)
7	**2d** (10)	B	THF	−78	24	30	88/12	3 (2*R*)
8	**2d** (10)	B	CH_3CN	−78	48	10	88/12	15 (2*S*)
9	**2d** (10)	B	Toluene	−78	24	47	98/2	21 (2*S*)
10	**2d** (10)	B	$EtNO_2$	−78	24	43	95/5	54 (2*S*)
11	**2d** (5)	B	CH_2Cl_2	−78	36	28	>99/1	70 (2*S*)
12	**2d** (10)	B	CH_2Cl_2	−78	24	90	97/3	81 (2*S*)
13	**2d** (20)	B	CH_2Cl_2	−78	12	88	97/3	75 (2*S*)
14	**2d** (30)	B	CH_2Cl_2	−78	12	89	98/2	71 (2*S*)
15	**2e** (10)	B	CH_2Cl_2	−78	24	81	93/7	36 (2*S*)
16	**2f** (10)	B	CH_2Cl_2	−20	12	98	90/10	71 (2*S*)
17	**2f** (10)	B	CH_2Cl_2	−78	24	90	94/6	92 (2*S*)
18	**3** (10)	B	CH_2Cl_2	−78	24	96	84/16	36 (2*S*)
19	**4** (10)	B	CH_2Cl_2	−78	36	62	92/8	6 (2*S*)
20	**5** (10)	B	CH_2Cl_2	−78	36	90	94/6	42 (2*S*)
21	**6** (10)	B	CH_2Cl_2	−78	24	52	96/4	37 (2*S*)

[a] The reactions of **7** with **8** (5.0 equiv.) were carried out in the presence of Lewis acid catalysts and chiral ligands **1**–**6**.

[b] The Lewis acid catalyst was reacted with a ligand in CH_2Cl_2 at room temperature for 30 min (method A) or reacted in THF at 40°C for 1.5 h (method B) prior to the addition of the substrates **7** and **8**.

[c] Determined by ^1H NMR at 270 MHz.

[d] Enantiomeric excess of the *endo* adduct **9a** was determined by HPLC analysis using a chiral column (Daicel, Chiralcel OD).

2-methoxyisopropyl groups (**2b–f**) in the magnesium iodide-catalyzed asymmetric reaction of **7** with **8**, and the results obtained are listed in Table 1. Table 1 indicates that the chiral oxazoline ligand ((*R*,*R*s)-**2f**) bearing a 2-methoxyisopropyl substituent provided (2*S*)-**9a** with the highest enantioselectivity (92%). This high asymmetric induction was clearly concluded to arise from the double acceleration with the two chiral centers, that on the oxazoline and of the sulfoxide, respectively, since the loss of chirality on the oxazoline ((*R*s)-**2a** and **3**) or of the sulfoxide ((*S*)-**4**) provided much lower enantioselectivity, as shown in Table 1.

Solvent effects were studied using THF, MeCN, toluene, nitroethane, or dichloromethane in the magnesium iodide-catalyzed Diels–Alder reaction of **7** with **8**. As listed in Table 1 (entries 7–10 and 12), use of CH_2Cl_2 as the solvent provided (2*S*)-**9a** with the highest enantioselectivity (81%) in the above reaction with MgI_2 (0.1 equiv.). Effects of the amount of catalyst (MgI_2) were examined changing the amount with a range of 0.05 to 0.3 equivalents in CH_2Cl_2: use of 0.1 equivalent of MgI_2 and a chiral ligand **2d** was the most efficient (81%) for the asymmetric cycloaddition reaction.

Thus, as summarized in Table 1, the best reaction condition for the asymmetric Diels–Alder reactions is as follows: the reaction of **7** with **8** (5.0 equiv.) was carried out at −78°C for 24 h in CH_2Cl_2 in the presence of the chiral magnesium catalyst (prepared from MgI_2[9] (0.1 equiv.) and (*R*,*R*s)-**2f** (0.1 equiv.) in THF at 40°C for 1.5 h prior to the cycloaddition reaction), providing (2*S*)-**9** in 90% yield (the ratio of the *endo* (2*S*)-**9a** (92%e.e.) to the *exo* (2*S*)-**9b** isomer, 95:5).

A possible mechanistic pathway for the above catalytic asymmetric synthesis is rationalized as follows. Intermediary tetrahedral magnesium complexes **10a**,**b** coordinated by the nitrogen atom of the oxazoline ring, the sulfinyl oxygen, and the two carbonyl oxygens of the substrate would be formed. The attack of **8** from the *Re* face side opposite the bulky 2-methoxyisopropyl group in **10a** or from the *Re* face side opposite the 2-methoxy-1-naphthyl group in **10b** gives (2*S*)-**9a**. The substantial effect of the 2-methoxy group in **2a–d**, **f** would be ascribed presumably to the fixation of the conformation of the naphthyl group by the dipole–dipole repulsion between the sulfinyl and the methoxy groups.

This paper reports one of the few precedents of chiral sulfoxide ligands in asymmetric cycloaddition reactions, and the first example of the catalytic asymmetric Diels–Alder reaction with novel chiral sulfoxide-oxazoline ligands, via seven-membered chelates of sulfoxide-magnesium complexes (normally six-membered chelates were formed in previous oxazoline ligands) indicating particularly the potential advantage of the chirality of the sulfoxide functionality for achieving high enantioselectivity, because of the synthetically ready availability of the chiral sulfoxide ligands and the chemical stability of the intermediary magnesium complex (Fig. 2).

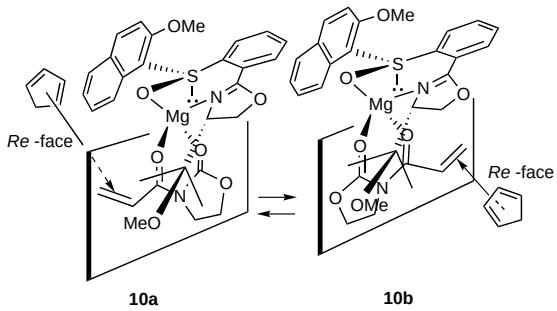


Figure 2.

Thus, chiral sulfoxide functionality was revealed to play a crucial role as a chiral ligand in catalytic asymmetric synthesis, stereocontrolled by the coordination of sulfur or oxygen atoms in the chiral sulfoxides depending on metal catalysts used.

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