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NOVEL SULFONAMIDE CATALYZED ASYMMETRIC HETERO-DIELS–ALDER REACTION OF ETHYL GLYOXYLATE WITH DANISHEFSKY'S DIENE

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Abstract – Novel sulfonamide organocatalysts were prepared from chiral Betti base and various sulfonyl chlorides, and applied to the asymmetric hetero-Diels–Alder reaction of ethyl glyoxylate with Danishefsky's diene. The sulfonamides exhibited catalytic activity as hydrogen bond donor. In particular, sulfonamide **3g** showed highest catalytic performance for the reaction. Sulfonamide **3g** catalyzed asymmetric reaction followed by treatment with TFA obtained corresponding 6-substituted 2,3-dihydropyran-4-ones in moderate yield and enantioselectivity.

INTRODUCTION

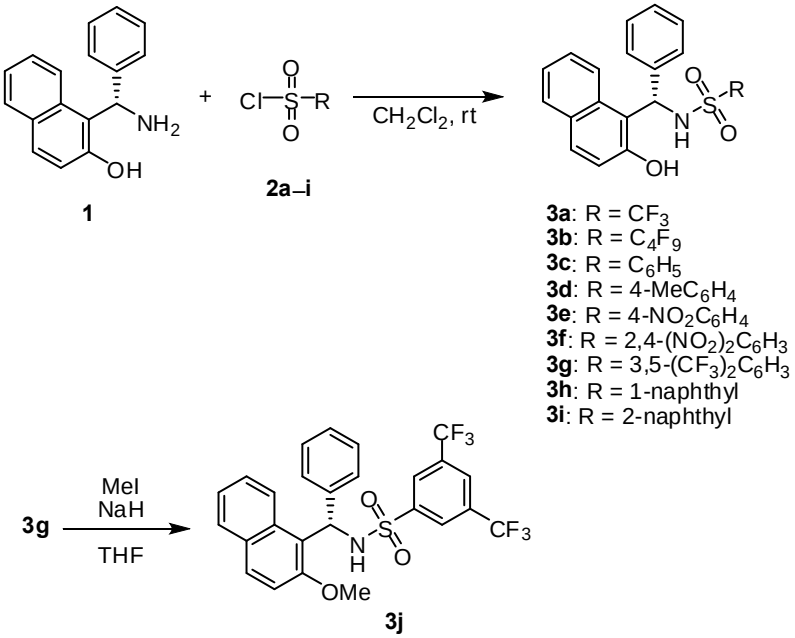
Chiral Brønsted acids have been investigated as organocatalysts in asymmetric reactions by considerable organic chemists.[1] There are several classes of Brønsted acids as metal free organocatalyst such as thiourea, TADDOL, and phosphoric acid. Thiourea catalyzed asymmetric reaction was first reported by Jacobsen and co-workers, by which asymmetric Strecker reactions were carried out with excellent yields and enantioselectivities.[2] In the Strecker reaction, Jacobsen elucidated the basis of detailed mechanism and structure for thiourea catalysis.[2(d)] Inspired by this work, several groups have developed the new thiourea organocatalysts.[3] On the other hand, Rawal and co-workers reported TADDOL catalyzed Diels-Alder reaction of aminosiloxydiene and Mukaiyama aldol reaction of *O*-silyl-*N*,*O*-ketene acetals.[4] Since the pioneering studies on chiral phosphoric acid catalysis were reported by Akiyama[5] and Terada,[6] independently, much attention has been paid to the phosphoric acid catalysis for enantioselective reaction.[7] Furthermore, Jørgensen and co-workers reported a chiral bis-sulfonamide catalyzed Mukaiyama aldol, hetero-Diels–Alder (HDA) and Friedel–Crafts reactions.[8] Mikami also reported bis-sulfonamide works effectively for HDA reaction through double hydrogen bonding.[9]

In the course of our research for the asymmetric synthesis of isoquinoline alkaloids, we have reported an

asymmetric reaction using Jacobsen's catalyst and our own thiourea catalyst.[10] Based on this work, we have been interested in the sulfonamide catalyst working as Brønsted acid for asymmetric reaction. In addition, mono-sulfonamide catalyzed asymmetric reaction is very rare, thus we have challenged to develop a catalyst which has a sulfonamide functional group. In order to evaluate the potential of the mono-sulfonamide as a hydrogen-bonding Brønsted acid catalyst, we decided to focus on the HDA reaction. The HDA reaction is one of the most important synthetic method for six membered heterocycles, which are versatile synthons for natural product and pharmaceutical compounds.[11] In this context, the development of catalytic asymmetric HDA reaction of glyoxylate with Danishefsky's diene has been important achievement.[12] However, only a few examples of asymmetric HDA reactions of glyoxylate using organocatalyst have been reported.[9,13] In addition, ethyl glyoxylate is an useful electrophile[14] and commercially available in toluene solution. Thus, the organocatalytic asymmetric reaction of ethyl glyoxylate has been quite challenging. Herein, we report the chiral mono-sulfonamide catalyzed HDA reaction of ethyl glyoxylate with Danishefsky's diene, leading to an optically active product.

RESULTS AND DISCUSSION

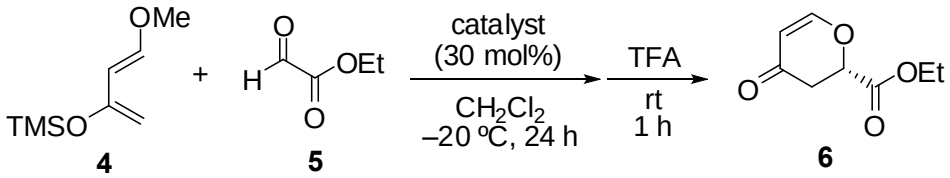
Initially, we prepared a variety of mono-sulfonamide organocatalysts **3**, whose synthetic procedure is shown in Scheme 1. The catalysts were readily prepared by coupling of a chiral amine with various sulfonyl chlorides. We chose Betti base as a chiral amine because it has been used as a potent chiral auxiliary or a ligand in asymmetric reaction.[15] Betti base was readily prepared from 2-naphthol, benzaldehyde and ammonia. Thus, (*S*)-Betti base (**1**) was converted into sufonamide organocatalysts **3a-i** by treatment with corresponding sulfonyl chlorides. In addition, to confirm the role of the phenolic hydroxyl group, we prepared sulfonamide **3j** derived from **3g**.



Scheme 1. Preparation of chiral sulfonamide catalysts

Next, we examined the reactivity of these sulfonamide catalysts **3a**–**j** for a HDA reaction of ethyl glyoxylate with Danishefsky's diene. As summarized in Table 1, the reactions proceeded in a catalytic manner using the chiral sulfonamide in CH_2Cl_2 at –20 ºC, followed by treatment with TFA to obtain corresponding 2-substituted 2,3-dihydropyran-4-ones **6**. Among these catalysts, alkyl sulfonamide catalyst **3a** and **3b** showed poor reactivity and enantioselectivity (Table 1, entries 1 and 2). In the case of aryl sulfonamide catalysts, with the exception of catalysts **3f** and **3h**, they afforded good reaction yields (Table 1, entries 3-5, 7, and 9). Catalyst **3g** bearing two electron-withdrawing CF_3 groups on the aromatic ring of sulfonamide was found to be the most effective catalyst (Table 1, entry 7). In addition, methylation of the phenolic hydroxyl group resulted in the disappearance of enantioselectivity, but reaction activity remained (Table 1, entry 10). This result suggested that the phenolic hydroxyl group of the catalyst **3g** took part in the stereoselection in this reaction. These results implied that the catalyst was capable of forming double hydrogen bonding for enantioselective HDA reaction of ethyl glyxoylate with Danishefsky's diene.

Table 1. Chiral sulfonamide catalyzed asymmetric hetero-Diels–Alder reaction



4 **5** **6**

entry[a]	catalyst	yield (%)[b]	ee (%)[c]
1	**3a**	27	0
2	**3b**	45	0
3	**3c**	70	0
4	**3d**	73	0
5	**3e**	69	12
6	**3f**	20	–11
7	**3g**	86	19
8	**3h**	31	–4
9	**3i**	72	0
10	**3j**	70	0

[a] The reaction was carried out with Danishefsky's diene **4** (1 equiv) and ethyl glyoxylate **5** (2 equiv) in the presence of catalyst **3** (30 mol%) for 24 h.

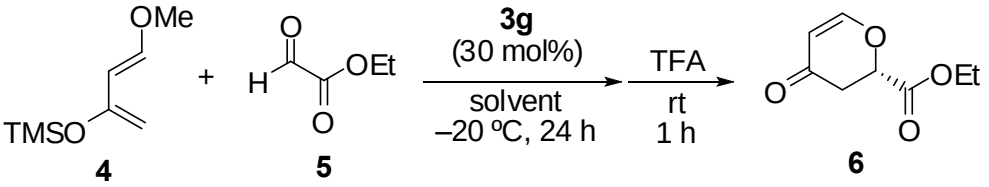
[b] Yield of isolated product.

[c] Determined by HPLC analysis with a chiral column.

Encouraged by the results, we next investigated the solvent effect of the reaction in the presence of 30 mol% of catalyst **3g** in various solvents at –20 ºC. As shown in Table 2, in CH_2Cl_2, the reaction gave the product **6** in high yield, whereas the enantioselectivity was low (Table 2, entry 1). MeCN and dioxane

showed moderate yields with poor enantioselectivities (Table 2, entry 2 and 6). Toluene, Et_2O, *n*-Bu_2O, and anisole showed moderate yield and enantioselectivity (Table 2, entry 3-5 and 9). Among them, Et_2O exhibited highest ee. Thus, we decided to use Et_2O as the solvent. This prompted us to further investigate the reaction conditions.

Table 2. Effect of solvent on the chiral sulfonamide **3g** catalyzed asymmetric hetero-Diels–Alder reaction



entry[a]	solvent	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	86	19
2	MeCN	51	13
3	toluene	71	49
4	Et_2O	50	58
5	*n*-Bu_2O	48	57
6	1,4-dioxane	52	14
7	THF	21	22
8	*t*-BuOMe	30	56
9	anisole	64	47
10	MeOH	5	nd

[a] The reaction was carried out with Danishefsky's diene **4** (1 equiv) and ethyl glyoxylate **5** (2 equiv) in the presence of catalyst **3g** (30 mol%) for 24 h.

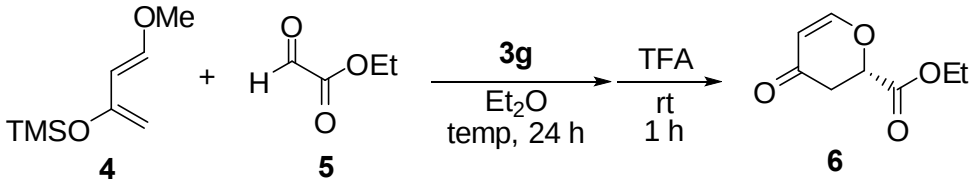
[b] Yield of isolated product.

[c] Determined by HPLC analysis with a chiral column.

In order to improve the reactivity and the enantioselectivity, the reaction conditions were screened further, and the results were summarized in Table 3. The ratio of ethyl glyoxylate **5** to diene **4** was evaluated (Table 3, entries 1-6). The higher ratio of **5** was used, the higher yield of **6** was obtained. The reaction of 2.0 equiv of **5** and 1.0 equiv of **4** gave 65% yield and 57% ee (Table 3, entry 5). Increasing the ratio of **5** resulted in the decreased enantioselectivity (Table 3, entry 6). A significant effect of MS 4A was observed on the chemical yield and enantioselectivity (Table 3, entry 5 vs entry 7). The effect of the catalyst loading was also investigated, and it was found that the amount of the catalyst did not affect the enantioselectivities (Table 3, entries 7-9). 30 mol% of catalyst loading afforded the highest yield (Table 3, entry 7). The influence of the temperature was also examined (Table 3, entries 7, 10 and 11), and lower reaction temperature was found to be beneficial to the selectivity. Although the selectivity was enhanced up to 74% ee at –60 ºC, the yield decreased drastically (Table 3, entry 11). The reaction of 1.0 equiv of **4** with 2.0 equiv of **5** in Et_2O using 30 mol% catalyst **3g** at –40 ºC afforded the product **6** in 72% yield and

70% ee (Table 3, entry 10).

Table 3. Chiral sulfonamide **3g** catalyzed asymmetric hetero-Diels–Alder reaction



entry[a]	**4** (equiv)	**5** (equiv)	**3g** (mol%)	MS 4A	temp (ºC)	yield (%)[b]	ee (%)[c]
1	1.0	1.0	30	–	–20	40	58
2	1.5	1.0	30	–	–20	50	58
3	2.0	1.0	30	–	–20	37	54
4	1.0	1.5	30	–	–20	57	58
5	1.0	2.0	30	–	–20	65	57
6	1.0	3.0	30	–	–20	70	53
7	1.0	2.0	30	+	–20	74	59
8	1.0	2.0	20	+	–20	60	57
9	1.0	2.0	40	+	–20	50	61
10	1.0	2.0	30	+	–40	72	70
11	1.0	2.0	30	+	–60	38	74

[a] The reaction was carried out with Danishefsky's diene **4** and ethyl glyoxylate **5** in the presence of catalyst **3g** for 24 h.

[b] Yield of isolated product.

[c] Determined by HPLC analysis with a chiral column.

In summary, we have developed novel mono-sulfonamide organocatalysts, which were readily accessible from chiral Betti base and various sulfonyl chlorides. The effectiveness of the sulfonamide organocatalyst was demonstrated as a catalyst for the asymmetric HDA reaction, which gives access to optically active compounds in moderate yield and enantioselectivity. This is the first example of mono-sulfonamide catalyzed asymmetric HDA reaction of ethyl glyoxylate with Danishefsky's diene. Further investigations to improve the enantioselectivity using other sulfonamide catalysts and to study the scope of this reaction are under way in our laboratory.

EXPERIMENTAL

All material were purchased from commercial suppliers and used without further purification. Column chromatography was performed using forced flow of the indicated solvent on Sigma H-type silica Gel 60N (100-210 mm). ^{1}H- and ^{13}C-NMR spectra were recorded with JEOL JNM AL-400 instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C) in deuterated solvent, using tetramethylsilane (δ = 0.0 ppm in ^{1}H-NMR spectra) and $CDCl_3$ (δ = 77.0 ppm in ^{13}C-NMR spectra) as internal standards. Optical rotations were

measured on a JASCO P1020 polarimeter operating at the sodium D line at room temperature. Concentration is given in g/100 mL. The HPLC analyses were performed with Shimadzu equipment (254 λ absorbance Detector) using Daicel Chemical Industries, LTD. CHIRALPAK AD-H column with hexane/2-propanol mixtures. HPLC method was calibrated with the corresponding racemic mixture. High-resolution mass spectra (HR-FAB MS) were measured with JEOL JMS-MS700V using *p*-nitrobenzyl alcohol as a matrix. The absolute configuration of the optically active compound **6** was determined on the basis of the measured optical rotation compared with literature values.[13(d)]

Typical procedure for the synthesis of catalysts 3a-i

To a solution of chiral amine (1.0 mmol) in CH_2Cl_2 (5 mL) was added sulfonyl chloride (1.2 mmol) and pyridine (1.0 mmol) at rt under an argon atmosphere. After stirring the reaction mixture for 24 h at rt, the solvent was removed under reduced pressure and the resulting residue was recrystallized from CH_2Cl_2/hexane to provide **3a-i**.

Catalyst 3a: 12% yield; white crystals; mp 142 ºC; $[\alpha]^{18}_D$ +28.6 (*c* 0.97, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 6.67(1H, s), 7.04 (1H, d, *J* = 8.8 Hz), 7.23 (5H, m), 7.40 (1H, t, *J* = 7.4 Hz), 7.53 (1H, t, *J* = 7.2 Hz), 7.77 (1H, d, *J* = 8.8 Hz), 7.82 (1H, d, *J* = 8.0 Hz), 7.96 (1H, d, *J* = 8.3 Hz); ^{13}C-NMR ($CDCl_3$) δ: 55.7, 117.9, 117.9, 121.7, 124.0, 126.4, 127.7, 127.9, 128.5, 128.9, 129.2, 130.7, 131.8, 139.5, 151.0; HR-FAB MAS: Calcd for $C_{18}H_{14}F_3NO_3S$ $[M]^+$: 381.0646, Found: 381.0639.

Catalyst 3b: 34% yield; white crystals; mp 157 ºC; $[\alpha]^{16}_D$ +42.5 (*c* 0.51, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 5.55 (1H, s), 6.72 (1H, d, *J* = 9.7 Hz), 7.01 (1H, d, *J* = 8.6 Hz), 7.24-7.33 (5H, m), 7.40 (1H, bs), 7.42 (1H, t, *J* = 7.4 Hz), 7.55 (1H, t, *J* = 7.7 Hz), 7.78 (1H, d, *J* = 8.6 Hz), 7.84 (1H, d, *J* = 7.4 Hz), 7.97 (1H, d, *J* = 8.6 Hz); ^{13}C-NMR ($CDCl_3$) δ: 55.9, 105.7-118.4 (m), 117.7, 118.1, 121.7, 124.2, 126.4, 127.8, 128.0, 128.6, 128.9, 129.3, 130.8, 131.7, 139.4, 150.5; HR-FAB MAS: Calcd for $C_{21}H_{14}F_9NO_3S$ $[M]^+$: 531.0551, Found: 531.0550.

Catalyst 3c: 42% yield; white crystals; mp 170 ºC; $[\alpha]^{16}_D$ +54.8 (*c* 0.70, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 6.26 (1H, s), 6.48 (1H, d, *J* = 9.8 Hz), 6.64 (1H, d, *J* = 9.5 Hz), 6.79 (1H, d, *J* = 8.8 Hz), 6.91 (2H, td, *J* = 7.9, 1.7 Hz), 7.10 (1H, tt, *J* = 7.4, 1.2 Hz), 7.20-7.33 (6H, m), 7.42 (1H, td, *J* = 7.7, 1.5 Hz), 7.44-7.50 (3H, m), 7.65 (1H, dd, *J* = 7.8, 0.7 Hz), 7.78 (1H, d, *J* = 8.5 Hz); ^{13}C-NMR ($CDCl_3$) δ: 54.4, 117.5, 118.0, 121.9, 123.5, 126.5, 126.7, 127.3, 127.4, 128.1, 128.4, 128.5, 129.0, 130.0, 132.0, 132.3, 139.5, 139.9, 150.9; HR-FAB MAS: Calcd for $C_{23}H_{19}NO_3S$ $[M]^+$: 389.1086, Found: 389.1074; Anal. Calcd for $C_{23}H_{19}NO_3S$: C, 70.93; H, 4.92; N, 3.60. Found: C, 70.66; H, 4.79; N, 3.55.

Catalyst 3d: 56% yield; white crystals; mp 180 ºC; $[\alpha]^{20}_D$ +58.8 (*c* 0.72, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, s), 6.20 (1H, s), 6.41 (1H, d, *J* = 9.5 Hz,), 6.53 (1H, d, *J* = 9.5 Hz), 6.67 (2H, d, *J* = 8.1 Hz), 6.81 (1H, d, *J* = 8.8 Hz), 7.20-7.34 (9H, m), 7.40 (1H, td, *J* = 7.8, 1.4 Hz), 7.51 (1H, d, *J* = 8.8 Hz), 7.65

(1H, d, *J* = 8.3 Hz), 7.74 (1H, d, *J* = 8.5 Hz); ^{13}C-NMR ($CDCl_3$) δ: 21.2, 54.4, 117.7, 118.1, 123.5, 126.6, 126.7,127.2, 127.4, 128.40, 128.41, 128.7, 129.0, 129.7, 132.3, 136.3, 139.9, 142.8, 150.9; Anal. Calcd for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47. Found: C, 71.23; H, 5.15; N, 3.40.

Catalyst 3e: 29% yield; yellow crystals; mp 180 ºC; $[\alpha]^{20}_D$ +6.7 (*c* 0.71, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ: 5.16 (1H, s), 6.49 (1H, d, *J* = 10.5 Hz), 6.64 (1H, d, *J* = 10.0 Hz), 6.74 (1H, d, *J* = 8.8 Hz), 7.23-7.37 (6H, m), 7.46-7.55 (4H, m), 7.60 (2H, dd, *J* = 7.0, 1.8 Hz), 7.64 (1H, d, *J* = 8.0 Hz), 7.79 (1H, d, *J* = 8.8 Hz); ^{13}C-NMR (CD_3OD) δ: 54.9, 117.7, 118.6, 123.5, 123.8, 124.0, 127.7, 127.8, 128.0, 128.7, 129.2, 129.5, 130.0, 130.9, 133.6, 141.6, 147.1, 150.3, 154.1; Anal. Calcd for $C_{23}H_{18}N_2O_5S$: C, 63.58; H, 4.18; N, 6.45. Found: C, 63.29; H, 3.95; N, 6.32.

Catalyst 3f: 13% yield; yellow syrup; ^{1}H-NMR ($CDCl_3$) δ: 6.04 (1H, bs), 6.93 (1H, d, *J* = 7.4 Hz), 7.09 (2H, d, *J* = 9.2 Hz), 7.28-7.40 (6H, m), 7.51 (1H, t, *J* = 8.2 Hz), 7.79 (1H, d, *J* = 8.8 Hz), 7.83 (1H, d, *J* = 8.0 Hz), 7.99 (1H, d, *J* = 7.4 Hz), 8.18 (1H, dd, *J* = 9.5, 2.6 Hz), 9.15 (1H, d, *J* = 2.9 Hz), 9.95 (1H, d, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$) δ: 53.9, 114.7, 117.2, 118.1, 122.2, 123.9, 124.3, 126.4, 127.81, 127.87, 129.0, 129.4, 129.8, 130.5, 130.8, 131.0, 131.9, 136.2, 139.1, 147.9, 151.5; HR-FAB MAS: Calcd for $C_{23}H_{17}N_3O_7S$ $[M]^+$: 479.0787, Found: 479.0797.

Catalyst 3g: 32% yield; white crystals; mp 193 ºC; $[\alpha]^{17}_D$ +49.5 (*c* 0.53, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 5.54 (1H, s), 6.51 (1H, d, *J* = 10.2 Hz), 6.73 (1H, d, *J* = 8.8 Hz), 6.83 (1H, d, *J* = 10.2 Hz), 7.24-7.34 (6H, m), 7.44 (1H, t, *J* = 7.7 Hz), 7.50 (1H, s), 7.51 (1H, d, *J* = 9.0 Hz), 7.64 (1H, d, *J* = 8.0 Hz), 7.73 (1H, d, *J* = 8.5 Hz), 7.84 (1H, s); ^{13}C-NMR ($CDCl_3$) δ: 54.2, 117.4, 121.2, 122.0 (q, J_{CF} = 273.1 Hz), 124.2, 125.4, 126.5, 126.7(m), 127.7, 128.1, 128.5, 128.7, 128.9, 130.6, 131.5, 131.86, 131.87, 138.9, 142.4, 150.2; HR-FAB MAS: Calcd for $C_{25}H_{17}F_6NO_3S$ $[M]^+$: 525.0833, Found: 525.0855; Anal. Calcd for $C_{25}H_{17}F_6NO_3S$: C, 57.14; H, 3.26; N, 2.67. Found: C, 57.04; H, 3.01; N, 2.67.

Catalyst 3h: 55% yield; white crystals; mp 177 ºC; $[\alpha]^{14}_D$ –217.1 (*c* 0.41, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ: 6.23 (1H, d, *J* = 8.8 Hz), 6.30 (1H, s), 6.73 (1H, t, *J* = 7.7 Hz), 7.08 (1H, d, *J* = 8.8 Hz), 7.17-7.61 (13H, m), 7.94 (1H, d, *J* = 7.3 Hz), 8.43 (1H, d, *J* = 8.3 Hz); ^{13}C-NMR ($CDCl_3$) δ: 54.2, 117.1, 117.7, 121.8, 122.7, 123.4, 123.5, 123.9, 126.1, 126.7, 127.0, 127.4, 127.6, 128.0, 128.10, 128.16, 128.5, 129.0, 129.5, 133.2, 133.3, 135.2, 140.5, 143.4, 144.8, 147.0, 151.5; Anal. Calcd for $C_{27}H_{21}NO_3S$: C, 73.78; H, 4.82; N, 3.19. Found: C, 73.63; H, 4.65; N, 3.11.

Catalyst 3i: 37% yield; white crystals; mp 223 ºC; $[\alpha]^{18}_D$ –18.3 (*c* 0.45, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ: 6.45 (1H, s), 6.61 (1H, d, *J* = 8.8 Hz), 7.06 (1H, t, *J* = 14.4 Hz), 7.13-7.34 (13H, m), 7.45 (1H, t, *J* = 8.0 Hz), 7.57 (1H, d, *J* = 8.0 Hz), 7.73 (1H, d, *J* = 8.8 Hz), 7.90 (1H, s); ^{13}C-NMR ($CDCl_3$) δ: 54.4, 117.4, 117.6, 121.3, 121.4, 122.8, 126.5, 126.7, 126.8, 126.9, 127.1, 128.0, 128.0, 128.0, 128.1, 128.9, 129.2, 131.3, 132.4, 134.1, 136.2, 140.3, 151.6; HR-FAB MS: Calcd for $C_{27}H_{21}NO_3S$ $[M]^+$: 439.1242, Found: 439.1223.

Synthesis of catalyst 3j.

To a solution of **3g** (100 mg, 0.19 mmol) in THF (5 mL) was added NaH (60% oil dispersion, 14 mg, 0.58 mmol) at –20 ºC. After stirring the mixture at –2 ºC for 1 h, the mixture was allowed to room temperature and MeI (18 μL, 0.285 mmol) was added. The mixture was stirred at room temperature for 24 h. After being diluted with H_2O, the solution was extracted with CH_2Cl_2 (x3). The combined organic layer was washed with brine and dried over $MgSO_4$. After the solvent was removed by evaporation, the residue was chromatographed on silica gel (AcOEt/hexane = 20/80) to give **3j** (66 mg) in 65% yield as a white crystals; mp 158 ºC; $[\alpha]^{18}_D$ +21.6 (*c* 0.57, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 3.71 (3H, s), 6.53 (1H, d, *J* = 10.4 Hz), 6.71 (1H, br. s), 6.98 (1H, d, *J* = 8.8 Hz), 7.21-7.25 (7H, m), 7.33 (1H, t, *J* = 7.2 Hz), 7.45 (1H, d, *J* = 7.2 Hz), 7.48 (1H, s), 7.63 (1H, d, *J* = 9.2 Hz), 7.66 (1H, d, *J* = 8.4 Hz), 7.76 (2H, s); ^{13}C-NMR ($CDCl_3$) δ: 54.3, 56.3, 112.9, 119.4, 120.9, 121.3, 123.1, 124.3, 125.3, 126.3, 126.5, 127.4, 128.1, 128.4, 128.6, 130.6, 131.5, 131.7; HR-FAB MAS: Calcd for $C_{26}H_{19}F_6NO_3S$ $[M]^+$: 539.0990, Found: 540.1046.

Typical procedure for the asymmetric hetero Diels-Alder reaction

To a suspension of ethyl glyoxylate **5** (50% toluene solution, 33μL, 0.17 mmol), catalyst **3g** (13.4 mg, 0.025 mmol), and molecular sieves (140 mg) in Et_2O (1 mL) was added Danishefsky's diene **4** (90% purity, 18 μL, 0.083 mmol) at –40 ºC. After stirring the mixture at –40 ºC for 24 h, 5% TFA in CH_2Cl_2 (4 mL) was added and the mixture was allowed to room temperature. The mixture was stirred at room temperature for 1 h. After filtration through a pad of celite, the solvent was removed by evaporation, the residue was chromatographed on silica gel (AcOEt/hexane = 50/50) to give **6** (9.9 mg) in 72% yield as a yellow oil; $[\alpha]^{18}_D$ +63.9 (*c* 0.28, CH_2Cl_2, 70% ee); ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, *J* = 7.2 Hz), 2.86 (2H, d, *J* = 7.8 Hz), 4.29 (2H, q, *J* = 7.2 Hz), 5.03 (1H, t, *J* = 7.8 Hz), 5.48 (1H, d, *J* = 6.1 Hz), 7.41 (1H, d, *J* = 6.1 Hz); ^{13}C-NMR ($CDCl_3$) δ: 14.1, 38.3, 62.3, 76.1, 107.9, 162.0, 168.0, 189.7; HPLC (Daicel Chiralpak AD-H, hexane/2-propanol 9:1, flow rate 1.0 mL/min, λ = 254 nm): major isomer: t_R = 26.9 min; minor isomer: t_R = 10.5 min; HR-FAB MS: Calcd for $C_8H_{11}O_4$ $[M+H]^+$: 171.0658, Found: 171.0653.

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