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A New Chiral Disulfonamide Ligand Derived from α-Amino Acid for Catalytic Enantioselective Cyclopropanation

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Abstract: A new disulfonamide prepared from α-amino acid in five steps catalyzed cyclopropanation of allylic alcohols with Et_2Zn and CH_2I_2 to afford the corresponding cyclopropylmethanols in moderate to good enantioselectivites. In particular, the reaction of cinnamyl alcohol in the presence of a chiral disulfonamide **1k** afforded an excellent enantioselectivity (85% ee).
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Development of a catalytic enantioselective cyclopropanation is one of the most important process because of the activities of cycloprapane-containing compounds.[1] The first and unique enantioselective Simmons-Smith cyclopropanation catalyzed by a C_2-symmetrical disulfonamide-zinc or aluminum complex has been reported by Kobayashi and the reaction of cinnamyl alcohol with Et_2Zn and CH_2I_2 in the presence of (1*R*,2*R*)-1,2-*N*,*N*'-bis(4-nitrobenzenesulfonylamino)cyclohexane afforded 76% ee.[2] Denmark optimized the conditions of the Simmons-Smith cyclopropanation (~ 80% ee) using the ligands reported by Kobayashi, and he examined several sulfonamides as chiral ligands (~ 79% ee) in the reaction of cinnamyl alcohol.[3] Furthermore, Charette reported a catalytic cyclopropanation using the *C2*-symmetrical titanium catalyst and the reaction of cinnamyl alcohol gave the corresponding product with 90% ee.[4] Methods using stoichiometric amount of a chiral auxiliary were developed by Charette and Katsuki although they gave excellent enantioselectivites (~ 94% ee).[5] Improvement of enantioselectivity in catalytic Simmons-Smith cyclopropanation is still expected. We now describe preparation of a new type of disulfonamides (**1**) derived from α-amino acids and enantioselective cyclopropanation of an allylic alcohol (**2**) in the presence of a catalytic amount of the disulfonamide **1**.

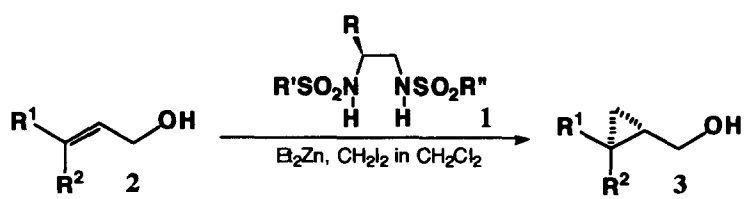
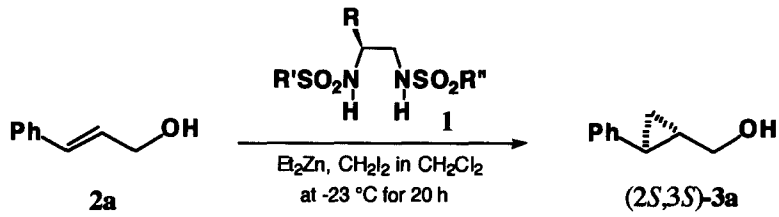


Table 1. Cyclopropanation of **2a** in the Presence of Various Chiral Disulfonamides[a]



2a (2*S*,3*S*)-**3a**

Entry	1	R	R'	R"	Yield (%)	ee (%)[b]
1	**1a**	Me	Ph	Me	quant.	58
2	**1b**	Me	Me	Ph	quant.	61
3	**1c**	Me_2CH	Ph	Me	quant.	59
4	**1d**	Me_2CH	Me	Ph	quant.	59
5	**1e**	Me_3C	Ph	Me	quant.	42
6	**1f**	Me_3C	Me	Ph	quant.	46
7	**1g**	Ph	Me	Me	quant.	6[c]
8	**1h**	$PhCH_2$	Me	Me	quant.	74
9	**1i**	$PhCH_2$	Me	CF_3	quant.	34
10	**1j**	$PhCH_2$	Me	*p*-MeC_6H_4	93	82
11	**1k**	$PhCH_2$	Me	*p*-$NO_2C_6H_4$	quant.	85
12	**1*l***	$PhCH_2$	Me	2,4,6-$Me_3C_6H_2$	quant.	75

a) The reactions were carried out with 1 mmol of **2a**, 0.1 mmol of a chiral sulfonamide **1**, 2 mmol of Et_2Zn, and 3 mmol of CH_2I_2 in 14 mL of anhydrous CH_2Cl_2. b) Determined by HPLC analysis (CHIRALCEL OD, 5% *i*-PrOH in hexane as an eluent). c) The enantiomeric isomer (2*R*,3*R*)-**3** was obtained.

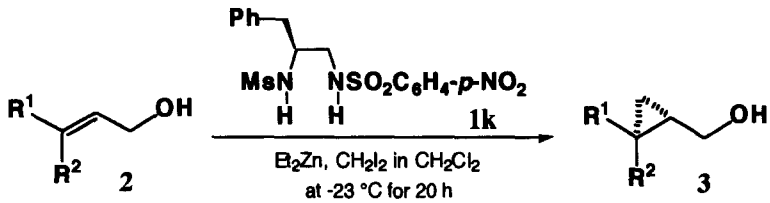
As a preliminary study, several disulfonamides (**1a~1h**) were chosen to examine effect of aromatic ring for enantioselectivity in Simmons-Smith cyclopropanation and easily synthesized in five steps from the corresponding α-amino acids in good to excellent yields.[6] The reaction of cinnamyl alcohol (**2a**) with Et_2Zn and CH_2I_2 was carried out in the presence of a catalytic amount of the disulfonamide **1** as the Kobayashi's procedures to afford (2*S*,3*S*)-2,3-methano-3-phenylpropanol ((2*S*,3*S*)-**3a**).[2, 7] The results are summarized in Table 1.

Enantioselectivities of in the reaction with **1a**, **1b** and **1c**, **1d** derived from *L*-valine and *L*-alanine, respectively, were slightly better than those with **1e**, **1f** derived from *L-tert*-leucine as shown in entries 1~6. Position of the benzene ring on the sulfonamide parts doesn't seem to be important for enantioselectivity among the disulfonamides prepared from *L*-alanine, *L*-valine, and *L-tert*-leucine (entry 1 *vs*. 2, entry 3 *vs*. 4, entry 5 *vs*. 6). The reaction of **2a** in the presence of **1g** prepared from *L*-glycine afforded the enantiomeric isomer (2*R*,3*R*)-**3** with a low enantioselectivity (6% ee, see entry 7). On the other hand, the reaction of **2a**

with **1h** prepared from *L*-phenylalanine gave (2*S*,3*S*)-**3a** with a high enatioselectivity (74% ee, see entry 8). Next, another four disulfonamides (**1i~1l**) derived from *L*-phenylalanine were synthesized and the results of the reactions of **2a** in the presence of **1i~1l** are indicated in Table 1 (entries 9~12). In this series, trifluoromethanesulfonyl group is not effective for enantioselectivity (34% ee, entry 9). Interestingly, the disulfonamides possessed a substituted benzenesulfonyl group worked effectively to give higher enantioselectivities (see entries 10~12). In particular, *p*-nitrobenzenesulfonyl and *p*-toluenesulfonyl substituted disulfonamides gave excellent enantioselectivities (85% ee and 82% ee, respectively).

The results of reactions of various allylic alcohols **2** in the presence of **1k** are indicated in Table 2. The *trans*-oriented allylic alcohols (**2b~2e**) were converted to the corresponding derivatives in execellent yields with moderate to good enantioselectivites (54~71% ee). A low enantioselectivity (39% ee) was obtained in the reaction of the *cis*-oriented allylic alcohol (**2f**). The enantiomeric excesses and absolute configurations of **3a**, **3c**, **3d**, and **3f** were determined by HPLC analysis using a Diecel OD column with 5% *i*-PrOH (2% *i*-PrOH for **3f**) in hexane as an eluent.[2] Those of **3b** ($[\alpha]^{25}D$ + 9.6° (*c* 1.88, $CHCl_3$)) and **3e** ($[\alpha]^{25}_D$ + 10.2° (*c* 2.10, $CHCl_3$)) were determined to be 2*S*, 3*S* with 54% ee and 2*R*, 3*S* with 60% ee by comparison of the specific rotations ($[\alpha]^{20}D$ - 20.3° (*c* 1.14, $CHCl_3$) for (2*R*,3*R*)-**3b** with 82%ee[2a] and ($[\alpha]^{20}_D$ - 14.6° (*c* 1.80, $CHCl_3$) for (2*S*,3*R*)-**3e** with 86% ee[2b]).

Table 2. Cyclopropanation of Various Allylic Alcohols **2a~2f** in the Presence of **1k**[a]



Entry	2	R^1	R^2	Yield (%)	ee (%)[b]
1	**2a**	Ph	H	quant.	85
2	**2b**	$PhCH_2CH_2$	H	97	54[c]
3	**2c**	$TrOCH_2$	H	89	65
4	**2d**	Me_2PhSi	H	85	71
5	**2e**	Bu_3Sn	H	93	60[c]
6	**2f**	H	$TrOCH_2$	88	39

a) All reactions were carried out with 0.5 mmol of an allylic alcohol **2**, 0.05 mmol of the chiral sulfonamide **1k**, 1 mmol of Et_2Zn, and 1.5 mmol of CH_2I_2 except entry 1 (see Table 1). b) Determined by HPLC analysis (CHIRALCEL OD). c) Determined by comparison of the specific rotation.[2a, b]

A typical procedure of the cyclopropanation using **1k** and **2a** is as follows: To a colorless clear solution of 41 mg (0.1 mmol, 0.1 equiv.) of a disulfonamide **1k** and 1.0 mL (1 mmol, 1 equiv.) of a 1.0M

solution of **2a** in CH_2Cl_2 in 14 mL of anhydrous CH_2Cl_2 were added dropwise at -50 °C 2.0 mL (2 mmol, 2 equiv.) of a 1.0M solution of Et_2Zn in hexane and 242 μL (3 mmol, 3 equiv.) of CH_2I_2. After stirring for 20 h at -23 °C, the colorless suspension was quenched at the temparature with 0.5 mL of Et_3N, diluted with 50 mL of Et_2O, washed with 5 mL of brine, and dried over $MgSO_4$. The crude product was chromatographed on silica gel with a 1 : 1 mixture of EtOAc and hexane to afford 148 mg (quantitative yield, 85% ee) of (2*S*,3*S*)-**3a**.

These results show that R, R', and R" groups of the disulfonamide could be changed to various groups for controlling enantioselectivity in the Simmons-Smith cyclopropanation. It is noted that a new type of disulfonamides derived from α-amino acids are effective as chiral controller ligands in the cyclopropanation. This kind of disulfonamides possess unlimited possibility because excellent synthetic methodology of α-amino acids has been reported.

We still optimize the chiral disulfonamide derived from *L*-phenylalanine for the cyclopropanation of various allylic alcohols. We also examine further investigations about this type of chiral controller ligands prepared from various α-amino acids for catalytic enantioselective reactions such as Diels-Alder reaction, alkylation, and so on.

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6. The disulfonamide **1k** was prepared as follows: *L*-(-)-Phenylalanine was reduced ($NaBH_4$, I_2 in THF; quantitative yield), dimesylated ($MeSO_2Cl$, Et_3N in CH_2Cl_2; 69% yield), and converted to the azide (NaN_3 in DMF; 79% yield). The azide was then hydrogenated (H_2/Pd on carbon in MeOH; quantitative yield) and treated with *p*-$NO_2C_6H_4SO_2Cl$ and Et_3N in CH_2Cl_2 to afford **1k** in 74% yield. **1k**: $[\alpha]^{24}_D$ - 38.5° (*c* 1.42, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.32 (3H, s, CH_3SO_2), 2.68 (1H, dd, *J* = 9.8, 14.2 Hz, PhC$\underline{H}_A$), 2.96 (1H, dd, *J* = 5.0, 14.2 Hz, PhC$\underline{H}_B$), 3.00-3.12 (1H, m, C$\underline{H}_A$NHSO$_2$C$_6$H$_4$-*p*-NO$_2$), 3.22-3.29 (1H, m, C$\underline{H}_B$NHSO$_2$C$_6$H$_4$-*p*-NO$_2$), 3.57-3.68 (1H, m, MsNHC$\underline{H}$CH$_2$NHSO$_2$C$_6$H$_4$-*p*-NO$_2$), 4.67 (1H, d, *J* = 8.4 Hz, MsN$\underline{H}$CHCH$_2$NHSO$_2$C$_6$H$_4$-*p*-NO$_2$), 5.70 (1H, t, *J* = 6.0 Hz, MsNHCHCH$_2$N$\underline{H}$SO$_2$C$_6$H$_4$-*p*-NO$_2$), 7.13-7.40 (5H, m, C$_6$H$_5$), 8.05, 8.35 (2H, 2H, d, d, *J* = 7.0, 7.0 Hz, C$_6$H$_4$-*p*-NO$_2$).
7. Remarkable difference of enantioselectivities between the zinc complexes (**1**-Zn) and the aluminum complexes (**1**-Al-Bu-*i*) was not observed. For example, cyclopropanation of **2a** in the presence of the disulfonamide-aluminum complex **1h**-Al-Bu-*i*, which was prepared from 0.1 mmol of **1h** and 0.08 mmol of *i*-Bu_2AlH in 1,2-dichloromethane at 80 °C for 2 h, proceeded to afford (2*S*,3*S*)-**3a** with 68% ee.[2c]

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