

## Convenient Preparation of Various Chiral Disulfonamides from $\alpha$ -Amino Acid and Alkylation of Cinnamaldehyde in the Presence of the Chiral Disulfonamides

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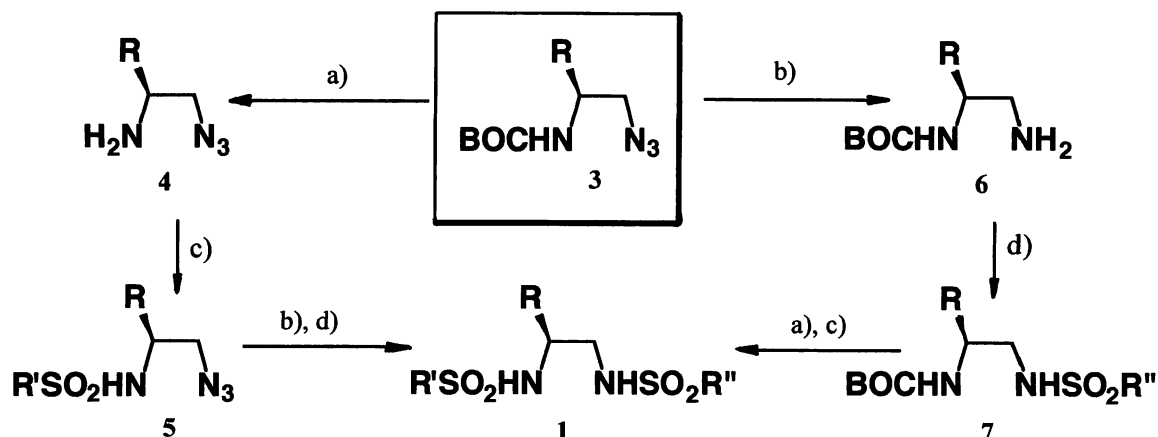
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**Abstract:** Various chiral disulfonamides (1) and diprotected diamines (2) were synthesized from the corresponding 2-(butoxycarbonyl)aminoethylazide (3) in three to four steps. The yields were good to excellent in all steps. The key intermediate 3 was easily prepared from the corresponding  $\alpha$ -amino acid in four steps. A chiral disulfonamide 1 was attempted as a chiral source for catalytic enantioselective alkylation. Interestingly, the position of the CF<sub>3</sub> group on a chiral disulfonamide gives important effect on configuration of product in the reaction of cinnamaldehyde (8) with Et<sub>2</sub>Zn in the presence of Ti(Oi-Pr)<sub>4</sub>.

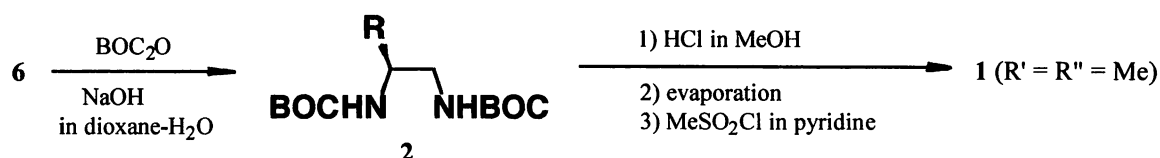
Chiral diamines were developed as important building blocks for natural products and medicines.<sup>1)</sup> Chiral sulfonamides were reported as effective catalytic ligands for cyclopropanation,<sup>2)</sup> alkylation,<sup>3)</sup> Diels-Alder reaction,<sup>4)</sup> and Aldol reaction.<sup>5)</sup> Recently, Enders and Wiedemann reported method for preparation of (*S*)-diamines from nitroalkenes and (-)-(2*S*,3*R*,4*R*,5*S*)-1-amino-3,4-dimethoxy-2,5-bis(methoxymethyl)pyrrolidine (ADMP) in two steps.<sup>6)</sup> In this communication, we describe a convenient route for synthesis of chiral disulfonamide (1) and chiral diprotected diamine (2) from the corresponding 2-(butoxycarbonyl)aminoethylazide (3)<sup>7)</sup> in three to four steps. The outline for preparation of (*S*)-1 and (*S*)-2 is summarized in Schemes 1, 2 and Table 1.



R = Bn, Ph, *i*-Pr, Me ; R', R'' = CF<sub>3</sub>, *p*-Tol, Ph, Me

Reaction conditions: a) CF<sub>3</sub>CO<sub>2</sub>H (or HCl in MeOH); b) H<sub>2</sub>/Pd-C in MeOH; c) R'SO<sub>2</sub>Cl (or Tf<sub>2</sub>O), Et<sub>3</sub>N in THF; d) R''SO<sub>2</sub>Cl (or Tf<sub>2</sub>O) in pyridine.

Scheme 1.



Scheme 2.

The BOC group of **3** was cleaved under acidic conditions to give the amine derivative (**4**), and the azide group of **3** was hydrogenated under a hydrogen atmosphere in the presence of Pd on carbon to give the other amine derivative (**6**). The amine derivatives (**4** and **6**) were converted to the monosulfonyl derivatives (**5** and **7**), respectively. The sulfonamide **5** was hydrogenated and sulfonylated to lead the disulfonamide **1**. The other one **7** was deprotected and sulfonylated to lead **1**. Furthermore, diprotected diamine **2** was prepared from **6** and converted to **1** by deprotection and sulfonylation. In this way, the azide **3** is a key intermediate for preparation of chiral disulfonamide **1** and chiral diprotected diamine **2**.

Typical procedures for preparation of (*S*)-**1a** via (*S*)-**4a** and (*S*)-**5a** are described as follows. A solution of 800 mg (2.90 mmol) of (*S*)-**3a** in 4.5 mL of CF<sub>3</sub>CO<sub>2</sub>H was stirred for 4 h and evaporated. The residue was dissolved in EtOAc, washed with sat. aq. NaHCO<sub>3</sub> and brine, and dried over MgSO<sub>4</sub>. The crude product was chromatographed on silica gel to afford 507 mg (99% yield) of (*S*)-**4a**. To a solution of 507 mg (2.88 mmol) of (*S*)-**4a** and 1.60 mL (11.5 mmol) of Et<sub>3</sub>N in 5 mL of anhydrous THF was added at -78 °C 1.37 g (7.20 mmol) of TsCl. After stirring for 2 h at -78 °C, the reaction mixture was diluted with EtOAc, washed with water and brine, and dried over MgSO<sub>4</sub>. The crude

product was chromatographed on silica gel to give 771 mg (81% yield) of (*S*)-**5a**. A suspension of 771 mg (2.34 mmol) of (*S*)-**5a** and 39 mg of 5% Pd on carbon in 5 mL of MeOH was stirred for 6 h under a hydrogen atmosphere and filtered. The filtrate was concentrated to afford 680 mg (96% yield) of a crude amine, which was used for the next step without purification. To a solution of 300 mg (0.99 mmol) of the crude amine and 345  $\mu$ L (2.48 mmol) of Et<sub>3</sub>N in 4 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> was added at -78 °C 166  $\mu$ L (0.99 mmol) of Tf<sub>2</sub>O. After stirring for 2 h at -78 °C, the reaction solution was diluted with EtOAc, washed with water, and dried over MgSO<sub>4</sub>. The crude product was purified by silica gel column chromatography to obtain 364 mg (85% yield) of (*S*)-**1a**.<sup>9)</sup>

Table 1. Preparation of (*S*)-Disulfonamides **1** and (*S*)-Diprotected Diamines **2**.

Entry	<b>3</b>	Disulfonamide <b>1</b>			Yield (%)					
		R	R'	R''	<b>3 to 4</b>	<b>4 to 5</b>	<b>3 to 6</b>	<b>6 to 7</b>	<b>6 to 2</b>	<b>5,7, or 2 to 1</b>
1	<b>3a</b>	Bn	<i>p</i> -Tol	CF <sub>3</sub>	99	81	—	—	—	82
2	<b>3a</b>	Bn	<i>p</i> -Tol	CF <sub>3</sub>	—	—	quant.	61	—	58
3	<b>3a</b>	Bn	Ph	CF <sub>3</sub>	72	86	—	—	—	65
4	<b>3a</b>	Bn	CF <sub>3</sub>	<i>p</i> -Tol	—	—	quant.	78	—	74
5	<b>3a</b>	Bn	CF <sub>3</sub>	Ph	—	—	quant.	93	—	94
6	<b>3a</b>	Bn	CF <sub>3</sub>	Me	—	—	quant.	84	—	60
7	<b>3a</b>	Bn	Me	Me	—	—	quant.	—	quant.	82
8	<b>3b</b>	Ph	CF <sub>3</sub>	<i>p</i> -Tol	—	—	93	68	—	87
9	<b>3c</b>	<i>i</i> -Pr	<i>p</i> -Tol	CF <sub>3</sub>	quant.	44	—	—	—	84
10	<b>3c</b>	<i>i</i> -Pr	CF <sub>3</sub>	<i>p</i> -Tol	—	—	quant.	68	—	55
11	<b>3c</b>	<i>i</i> -Pr	Me	Me	—	—	93	—	81	91
12	<b>3d</b>	Me	Me	Me	—	—	quant.	—	87	91

A chiral disulfonamide **1** was attempted as a chiral source for catalytic enantioselective alkylation. The alkylation of cinnamaldehyde (**8**) with Et<sub>2</sub>Zn and Ti(O*i*-Pr)<sub>4</sub> in the presence of 5 mol% of (*S*)-**1a** (R = Bn, R' = *p*-Tol, R'' = CF<sub>3</sub> in entry 1) at -20 °C for 2.5 h in toluene gave the corresponding secondary alcohol ((*R*)-**9**) in 94% yield with 23% ee. On the other hand, the reaction of **8** in the presence of (*S*)-**1b** (R = Bn, R' = CF<sub>3</sub>, R'' = *p*-Tol in entry 6) gave the enantiomer (*S*)-**9** in 80% yield with 11% ee. In the case of using (*S*)-**1c** (R = *i*-Pr, R' = *p*-Tol, R'' = CF<sub>3</sub> in entry 10) and (*S*)-**1d** (R = *i*-Pr, R' = CF<sub>3</sub>, R'' = *p*-Tol in entry 11) as a chiral ligand, the reaction of **8** afforded (*R*)-**9** in 75% yield with 20% ee and (*S*)-**9** in 82% yield with 21% ee, respectively. In the presence of (*S*)-**1e** (R = Bn, R' = Me, R'' = *p*-Tol in entry 12), which gives good enantioselectivities (82–89% ee) for Simmons-Smith cyclopropanation of allylic alcohols,<sup>2a, 8)</sup> the reaction of **8** at -20 °C for 21 h afforded 9% ee with *R* configuration in 78% yield. Interestingly,

these results show that position of the CF<sub>3</sub> group on a chiral disulfonamide gives important effect on configuration of product in the reaction of **8** with Et<sub>2</sub>Zn in the presence of Ti(O*i*-Pr)<sub>4</sub>. The results of reactions of cinnamaldehyde **8** in the presence of various chiral ligands **1** are indicated in Table 2.

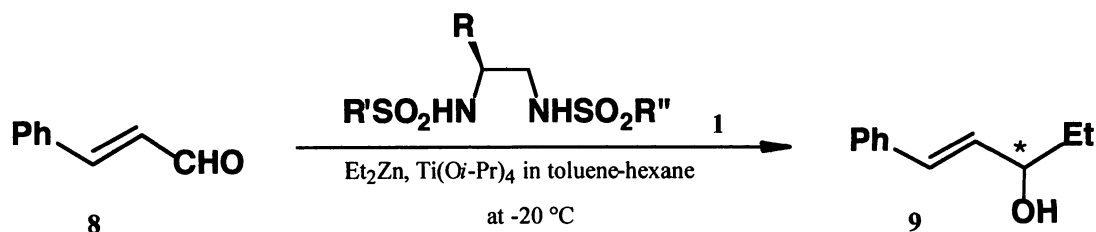


Table 2. Alkylation of **8** in the Presence of Various Chiral Disulfonamides **1**<sup>a)</sup>

Entry	Disulfonamide <b>1</b>			Time (h)	Yield (%)	ee (%) <sup>b)</sup>	Configuration
	R	R'	R''				
1	Bn	<i>p</i> -Tol	CF <sub>3</sub>	2.5	94	23	<i>R</i>
2	Bn	<i>p</i> -Tol	CF <sub>3</sub>	17	73 <sup>c)</sup>	21	<i>R</i>
3	Bn	Ph	CF <sub>3</sub>	3.5	83	21	<i>R</i>
4	Bn	Me	CF <sub>3</sub>	18	94	27	<i>R</i>
5	Bn	Me	CF <sub>3</sub>	17	64 <sup>c)</sup>	24	<i>R</i>
6	Bn	CF <sub>3</sub>	<i>p</i> -Tol	3	80	11	<i>S</i>
7	Bn	CF <sub>3</sub>	Ph	3	80	18	<i>S</i>
8	Bn	CF <sub>3</sub>	Me	3	88	19	<i>S</i>
9	Ph	CF <sub>3</sub>	<i>p</i> -Tol	17	50 <sup>c)</sup>	0.2	
10	<i>i</i> -Pr	<i>p</i> -Tol	CF <sub>3</sub>	3.5	75	20	<i>R</i>
11	<i>i</i> -Pr	CF <sub>3</sub>	<i>p</i> -Tol	2.5	82	21	<i>S</i>
12	Bn	Me	<i>p</i> -Tol	21	78	9	<i>R</i>
13	Bn	Me	Me	4	71	3	<i>R</i>
14	<i>i</i> -Pr	Ph	Me	4	48	5	<i>R</i>

a) The reactions were carried out with 1 mmol of **8**, 0.02 mmol of a chiral disulfonamide **1**, 2.2 mmol of Et<sub>2</sub>Zn, 0.6 mmol of Ti(O*i*-Pr)<sub>4</sub> in 4 mL of anhydrous toluene. b) Determined by HPLC analysis (CHIRALCEL OD, 5% *i*-PrOH in hexane as an eluent). c) The reaction was carried out at -40 °C.

It is noted that various kinds of chiral disulfonamides **1** and chiral diprotected diamines **2** are easily prepared from  $\alpha$ -amino acid *via* 2-substituted-2-(butoxycarbonyl)aminoethylazides **3** and that the CF<sub>3</sub> group on a chiral

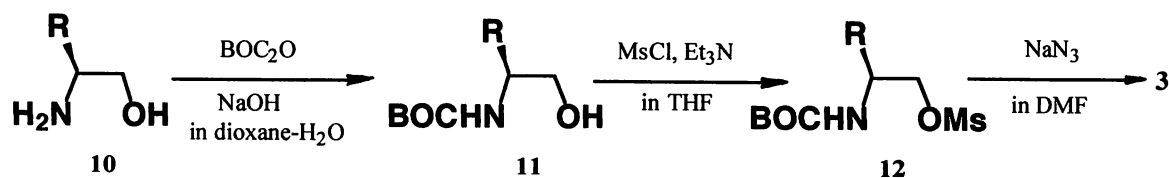
disulfonamide effects on configuration of product in catalytic enantioselective ethylation of **8** with  $\text{Et}_2\text{Zn}$  and  $\text{Ti}(\text{O}i\text{-Pr})_4$  as preliminary results. Further investigations using the sulfonamides are still under way.

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- The key intermediate **3** was prepared as follows. In the case of **3a** ( $\text{R} = \text{Bn}$ ), the starting aminoalcohol **10** was protected with BOC group ( $\text{BOC}_2\text{O}$ ,  $\text{NaOH}$  in dioxane-water) to afford the BOC-protected aminoalcohol **11**. Then, in the case of **3b** ( $\text{R} = i\text{-Pr}$ ) and **3c** ( $\text{R} = \text{Me}$ ), **11** was obtained by protection of the corresponding  $\alpha$ -amino acid with BOC group ( $\text{BOC}_2\text{O}$ ,  $\text{NaOH}$  in dioxane-water; quantitative yield), activation ( $\text{ClCO}_2\text{Et}$ ,  $\text{Et}_3\text{N}$  in THF), and reduction ( $\text{NaBH}_4$  in water). The aminoalcohol **11** was converted to the corresponding mesylate **12** ( $\text{MsCl}$ ,  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$ ) followed by azidation to give the azide **3** ( $\text{NaN}_3$  in DMF).



- 8) Reaction of 5-phenyl-2-penten-1-ol and *O*-trityl-2-butene-1,4-diol with Et<sub>2</sub>Zn and CH<sub>2</sub>I<sub>2</sub> in the presence of (*S*)-**1e** afforded the corresponding cyclopropane derivatives in quantitative yield with 89% ee and in 98% yield with 89% ee, respectively.
- 9) (*S*)-**1a**: [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 50.7 ° (*c* 1.02, CHCl<sub>3</sub>); <sup>1</sup>H NMR δ (400MHz, CDCl<sub>3</sub>) 2.43 (3H, s, CH<sub>3</sub>), 2.59 (1H, dd, *J* = 8.6, 14.0 Hz, PhCH<sub>A</sub>), 2.76 (1H, dd, *J* = 5.8, 14.0 Hz, PhCH<sub>B</sub>), 3.28-3.33 (1H, m, CH<sub>A</sub>NHTf), 3.38-3.49 (1H, m, PhCH<sub>2</sub>CH), 3.53-3.58 (1H, m, CH<sub>B</sub>NHTf), 4.70 (1H, d, *J* = 6.4 Hz, NHTs), 6.08 (1H, bs, NHTf), 6.86, 7.46 (4H, d, *J* = 7.4, 7.4 Hz, C<sub>6</sub>H<sub>4</sub>), 7.14-7.21 (5H, m, C<sub>6</sub>H<sub>5</sub>).