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Convenient Preparation of Various Chiral Disulfonamides from α-Amino Acid and Alkylation of Cinnamaldehyde in the Presence of the Chiral Disulfonamides

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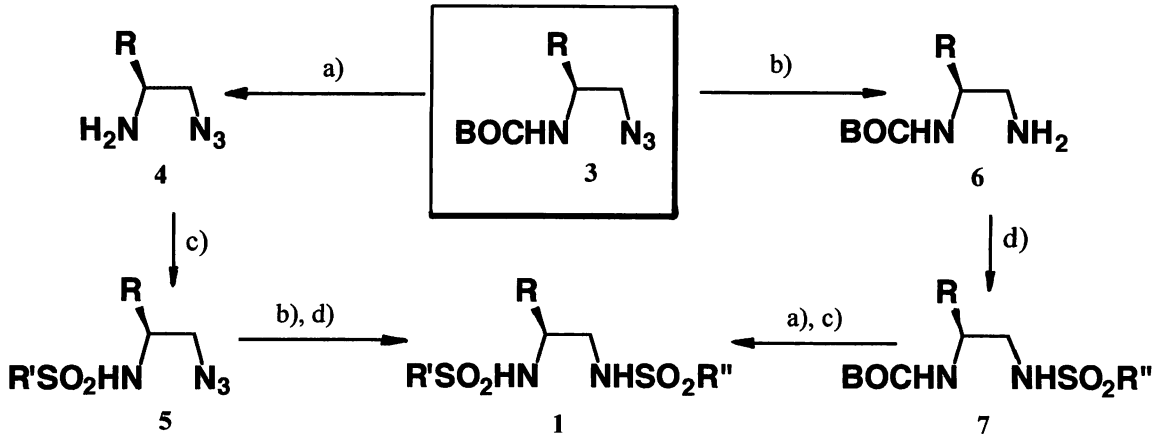
Abstract: **Various chiral disulfonamides (1) and diprotected diamines (2) were synthesized from the corresponding 2-(butoxycarbonyl)aminoethylazide (3) in three to four steps. The yields were good to excellent in all steps. The key imtermediate 3 was easily prepared from the corresponding α-amino acid in four steps. A chiral disulfonamide 1 was attempted as a chiral source for catalytic enantioselective alkylation. Interestingly, the position of the CF_3 group on a chiral disulfonamide gives important effect on configuration of product in the reaction of cinnamaldehyde (8) with Et_2Zn in the presence of $Ti(O\textit{i}\text{-}Pr)_4$.**

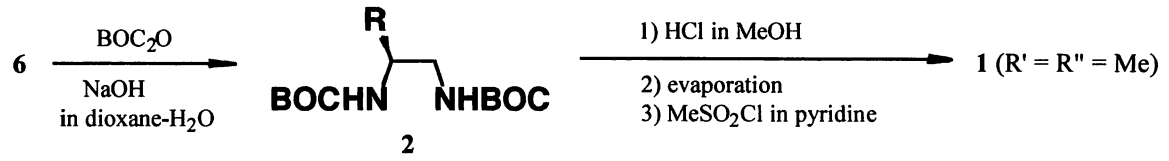
Chiral diamines were developed as important building blocks for natural products and medicines.[1] Chiral sulfonamides were reported as effective catalytic ligands for cyclopropanation,[2] alkylation,[3] Diels-Alder reaction,[4] and Aldol reaction.[5] Recently, Enders and Wiedemann reported method for 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.[6] 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**)[7] 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_3, *p*-Tol, Ph, Me

Reaction conditions: a) CF_3CO_2H (or HCl in MeOH); b) H_2/Pd-C in MeOH; c) $R'SO_2Cl$ (or Tf_2O), Et_3N in THF; d) $R''SO_2Cl$ (or Tf_2O) 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_3CO_2H was stirred for 4 h and evaporated. The residue was dissolved in EtOAc, washed with sat. aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. 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_3N 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 mixure was diluted with EtOAc, washed with water and brine, and dried over $MgSO_4$. 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 μL (2.48 mmol) of Et_3N in 4 mL of anhydrous CH_2Cl_2 was added at -78 °C 166 μL (0.99 mmol) of Tf_2O. After stirring for 2 h at -78 °C, the reaction solution was diluted with EtOAc, washed with water, and dried over $MgSO_4$. The crude product was purified by silica gel column chromatography to obtain 364 mg (85% yield) of (*S*)-**1a**.[9]

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

Entry	**3**	Disulfonamide **1**			Yield (%)					
		R	R'	R"	**3** to **4**	**4** to **5**	**3** to **6**	**6** to **7**	**6** to **2**	**5**,**7**, or **2** to **1**
1	**3a**	Bn	*p*-Tol	CF_3	99	81	—	—	—	82
2	**3a**	Bn	*p*-Tol	CF_3	—	—	quant.	61	—	58
3	**3a**	Bn	Ph	CF_3	72	86	—	—	—	65
4	**3a**	Bn	CF_3	*p*-Tol	—	—	quant.	78	—	74
5	**3a**	Bn	CF_3	Ph	—	—	quant.	93	—	94
6	**3a**	Bn	CF_3	Me	—	—	quant.	84	—	60
7	**3a**	Bn	Me	Me	—	—	quant.	—	quant.	82
8	**3b**	Ph	CF_3	*p*-Tol	—	—	93	68	—	87
9	**3c**	*i*-Pr	*p*-Tol	CF_3	quant.	44	—	—	—	84
10	**3c**	*i*-Pr	CF_3	*p*-Tol	—	—	quant.	68	—	55
11	**3c**	*i*-Pr	Me	Me	—	—	93	—	81	91
12	**3d**	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_2Zn and $Ti(O\textit{i}\text{-}Pr)_4$ in the presence of 5 mol% of (*S*)-**1a** (R = Bn, R' = *p*-Tol, R" = CF_3 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_3, 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_3 in entry 10) and (*S*)-**1d** (R = *i*-Pr, R' = CF_3, 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,[2a, 8] 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_3 group on a chiral disulfonamide gives important effect on configuration of product in the reaction of **8** with Et_2Zn in the presence of $Ti(O\textit{i}\text{-}Pr)_4$. The results of reactions of cinnamaldehyde **8** in the presence of various chiral ligands **1** are indicated in Table 2.

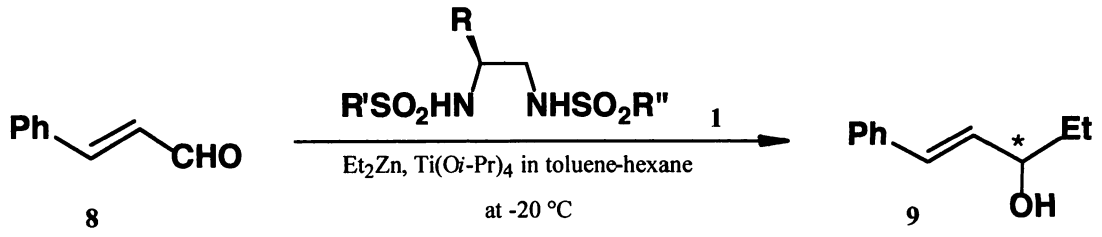


Table 2. Alkylation of **8** in the Presence of Various Chiral Disulfonamides **1**[a)]

Entry	Disulfonamide **1**						
	R	R'	R"	Time (h)	Yield (%)	ee (%)[b)]	Configration
1	Bn	*p*-Tol	CF_3	2.5	94	23	*R*
2	Bn	*p*-Tol	CF_3	17	73[c)]	21	*R*
3	Bn	Ph	CF_3	3.5	83	21	*R*
4	Bn	Me	CF_3	18	94	27	*R*
5	Bn	Me	CF_3	17	64[c)]	24	*R*
6	Bn	CF_3	*p*-Tol	3	80	11	*S*
7	Bn	CF_3	Ph	3	80	18	*S*
8	Bn	CF_3	Me	3	88	19	*S*
9	Ph	CF_3	*p*-Tol	17	50[c)]	0.2	
10	*i*-Pr	*p*-Tol	CF_3	3.5	75	20	*R*
11	*i*-Pr	CF_3	*p*-Tol	2.5	82	21	*S*
12	Bn	Me	*p*-Tol	21	78	9	*R*
13	Bn	Me	Me	4	71	3	*R*
14	*i*-Pr	Ph	Me	4	48	5	*R*

a) The reactions were carried out with 1 mmol of **8**, 0.02 mmol of a chiral disulfonamide **1**, 2.2 mmol of Et_2Zn, 0.6 mmol of $Ti(O\textit{i}\text{-}Pr)_4$ 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 carrried out at -40 °C.

It is noted that various kinds of chiral disulfonamides **1** and chiral diprotected diamines **2** are easily prepared from α-amino acid *via* 2-substituted-2-(butoxycarbonyl)aminoethylazides **3** and that the CF_3 group on a chiral

disulfonamide effects on configuration of product in catalytic enantioselective ethylation of **8** with Et_2Zn and $Ti(O\textit{i}\text{-}Pr)_4$ as preliminary results. Further investigations using the sulfonamides are still under way.

Acknowlegements

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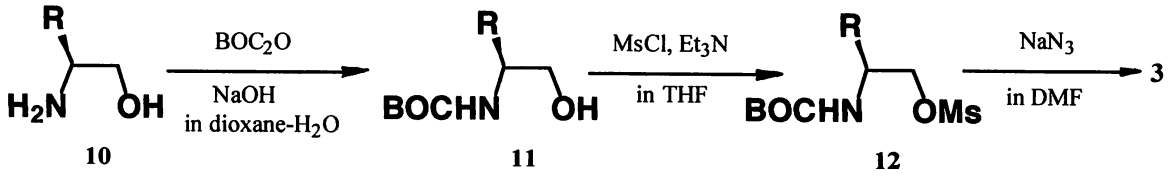
6) It takes six steps to prepare ADMP from *D*-mannitol. Enders, D.; Wiedemann, J. *Synthesis*, **1996**, 1443.

7) The key intermediate **3** was prepared as follows. In the case of **3a** (R = Bn), the starting aminoalcohol **10** was protected with BOC group (BOC_2O, NaOH in dioxane-water) to afford the BOC-protected aminoalcohol **11**. Then, in the case of **3b** (R = *i*-Pr) and **3c** (R = Me), **11** was obtained by protection of the corresponding α-amino acid with BOC group (BOC_2O, NaOH in dioxane-water; quantitative yield), activation ($ClCO_2Et$, Et_3N in THF), and reduction ($NaBH_4$ in water). The aminoalcohol **11** was converted to the corresponding mesylate **12** (MsCl, Et_3N in CH_2Cl_2) followed by azidation to give the azide **3** (NaN_3 in DMF).



8) Reaction of 5-phenyl-2-penten-1-ol and *O*-trityl-2-butene-1,4-diol with Et_2Zn and CH_2I_2 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**: $[\alpha]^{20}_D$ - 50.7 ° (*c* 1.02, $CHCl_3$); ^{1}H NMR δ (400MHz, $CDCl_3$) 2.43 (3H, s, CH_3), 2.59 (1H, dd, *J* = 8.6, 14.0 Hz, PhC$\underline{H}_A$), 2.76 (1H, dd, *J* = 5.8, 14.0 Hz, PhC$\underline{H}_B$), 3.28-3.33 (1H, m, C$\underline{H}_A$NHTf), 3.38-3.49 (1H, m, $PhCH_2C\underline{H}$), 3.53-3.58 (1H, m, C$\underline{H}_B$NHTf), 4.70 (1H, d, *J* = 6.4 Hz, N$\underline{H}$Ts), 6.08 (1H, bs, NHTf), 6.86, 7.46 (4H, d, d, *J* = 7.4, 7.4 Hz, C_6H_4), 7.14-7.21 (5H, m, C_6H_5).