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A Catalytic Enantioselective Reaction Using a C_2-Symmetric Disulfonamide as a Chiral Ligand: Alkylation of Aldehydes Catalyzed by Disulfonamide-Ti(O-*i*-Pr)4-Dialkyl Zinc System

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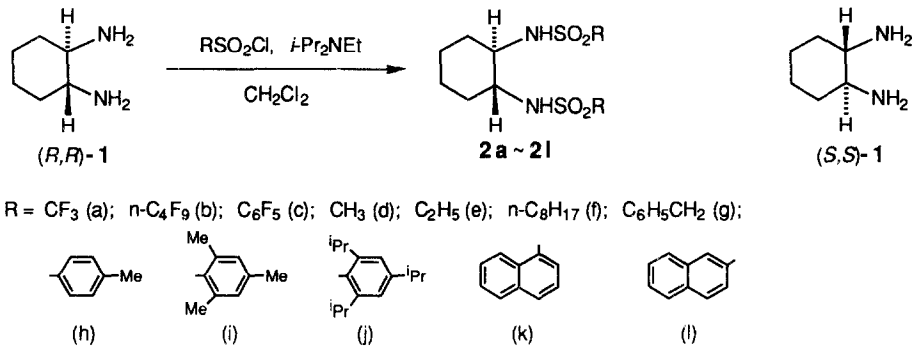
Abstract: *Excellent enantioselective alkylation of aldehydes with dialkylzinc has been developed. This methodology is based on the concept of modifying the Lewis acid with a C_2-symmetric, electron-withdrawing disulfonamide. The chiral Lewis acid catalysts used in the present study are the titanium complex, prepared in-situ from disulfonamide and Ti(O-i-Pr)4.*

An enantioselective reaction through a catalytic process is now recognized as one of the most important and challenging problems in organic synthesis.[3] There have been reported a number of chiral Lewis acids modified by a variety of chiral ligands such as chiral alcohols or amines. However, such an electron-donating ligand decreases the acidity of the Lewis acid. In order to realize an efficient catalytic process, we reasoned that the rate accelerating effect or attractive effect of the catalyst seemed to be important in addition to the stereocontrol and the facile exchange of the product with the substrate on the catalyst. Based on this consideration we became interested in modifying a Lewis acid by electron-withdrawing chiral ligands rather than chiral alcohols or amines. In such a modified Lewis acid, the chiral ligand will not only provide a chiral environment, but also increase the acidity of the Lewis acid. We describe in this paper the potential usefulness of the C_2-symmetric chiral disulfonamides as a ligand in a catalytic enantioselective alkylation of aldehydes[4] by the disulfonamide-Ti(O-*i*-Pr)4-dialkylzinc system. Independent of our work, Corey also developed a highly enantioselective Diels-Alder reaction utilizing a disulfonamide-modified aluminum catalyst.[5]

Among various acidic compounds we were interested in a chiral sulfonamide as a ligand based on the following reasons: (1) The pK_a values of *N*-methyltrifluoromethanesulfonamide[6] and methanesulfonamide are 7.56 and 10.8, respectively. Therefore, the acidity of sulfonamides are much higher than that of alcohol (pK_a; 16~18). (2) Various sulfonamides can be easily prepared from a variety of chiral amines and readily available sulfonyl chlorides. (3) Furthermore, the rotation about S-N bond might be restricted in the chiral metal complex, and which would result in the formation of a rigid and effective chiral environment around the metal ion. We selected *trans*-1,2-diaminocyclohexane (**1**) as a chiral source[7] because the racemate is commercially available. According to the known procedure,[8] the racemic diamine **1** was resolved with tartaric acids to obtain both enantiomers, (*R,R*)-**1** and (*S,S*)-**1** with >99% enantiomeric excess, respectively. Sulfonamide derivatives,

2a~2l, were prepared in good yields from the (-)-diamine, (*R,R*)-**1**, and the corresponding sulfonyl chlorides in the presence of diisopropylethylamine in CH_2Cl_2. (Scheme 1)

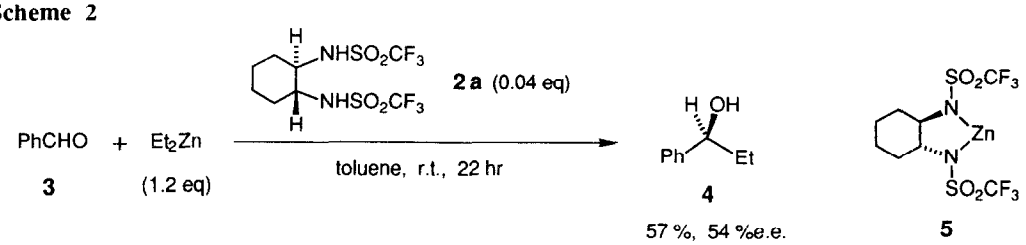
Scheme 1



In order to evaluate the electronic effect of a disulfonamide as a ligand, we examined the nucleophilic addition of a dialkylzinc to an aldehyde. Since the first report by Oguni[9] in 1984, the reaction has attracted a great deal of attention as one of the representative catalytic enantioselective reactions.[3] Most of the chiral catalysts developed are aminoalcohol derivatives, and the alkylation proceeds through the activation of dialkylzinc by an amino alcohol.

We initially carried out the reaction of benzaldehyde (**3**) and Et_2Zn in the presence of 0.04 equiv of disulfonamide **2a**. We expected that the alkylation proceeds through the activation of benzaldehyde by zinc complex **5** rather than the activation of Et_2Zn as an amino alcohol does. The alkylation was found to proceed, however, rather slowly even at room temperature to afford **4** in 57% yield with 54% e.e. (Scheme 2) The absolute configuration was established by comparison of the specific rotation value with that in the literature[1h] [lit. $[\alpha]_D^{22}$ -47.6° (*c* 6.11, $CHCl_3$) as 98% e.e.]. Enantiomeric excess was determined directly by HPLC analysis (Daicel column OB. Eluent systems: 2% *i*-PrOH in hexane; flow rate 0.5mL/min; detection 254nm; the *S*-isomer, t_R=19.5min, the *R*-isomer, t_R=23.0min). Upon use of the given enantiomer, (*R,R*)-**2**, the alkylation proceeded with the same enantioface differentiation affording 1*S*-1-phenylpropanol **4** as the major enantiomer. Although moderate enantioselections (36~83% e.e.) was achieved in all cases, the acceleration effect was not remarkable even by using **2a**. (Scheme 2)

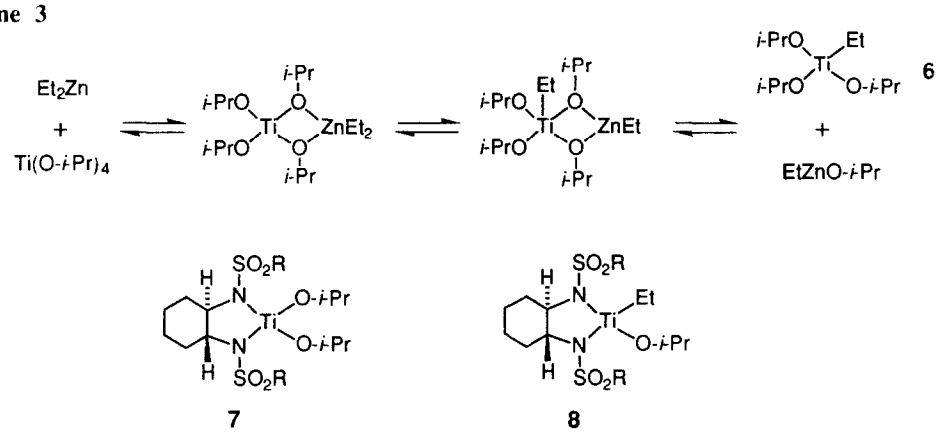
Scheme 2



The results might indicate that the Lewis acidity of the zinc complex **5**[10] is not efficient enough to activate an aldehyde for alkylation even by introducing the electron-withdrawing disulfonamides, and we therefore turned

our attention to find other Lewis acids. Thus, the reaction of benzaldehyde and Et_2Zn was carried out in the presence of various metal alkoxides (2 mol%), such as $B(O\text{-}i\text{-}Pr)_3$, $Al(O\text{-}i\text{-}Pr)_3$, $Sn(O\text{-}i\text{-}Pr)_4$, $Ti(O\text{-}i\text{-}Pr)_4$, and $Zr(O\text{-}i\text{-}Pr)_4$. Among them, only $Ti(O\text{-}i\text{-}Pr)_4$ was found to catalyze the reaction affording (±)-**4** in about 80% yield after stirring at room temperature for 12hr. The ^{1}H-NMR spectrum of the 1:1 mixture of Et_2Zn and $Ti(O\text{-}i\text{-}Pr)_4$ in toluene-d_8 indicated that monomeric Et_2Zn does not exist in the solution. Two peaks, δ 0.19 (q) and δ 1.19 (t), which correspond to $-CH_2-$ and $-CH_3$ of monomeric Et_2Zn completely disappeared, and instead, at least two ethyl signals were observed: δ 0.59 (q) and δ 1.57 (t) (due to Et-Zn-O-*i*-Pr); δ 0.67 (q) and δ 1.65 (t). In addition, at least five peaks assigned to *i*-PrO- including the signal due to Et-Zn-O-*i*-Pr were also observed. Furthermore, the ^{1}H-NMR spectra was found to be rather complicated depending on the concentration and the temperature. These facts suggested that the treatment of Et_2Zn with $Ti(O\text{-}i\text{-}Pr)_4$ generates various kinds of species including ethyltitanium species[11] in the equilibrium mixture. (Scheme 3) Although the ethyltitanium species are drawn as a monomeric structure, they are considered to exist in a rather complicated polymeric form.

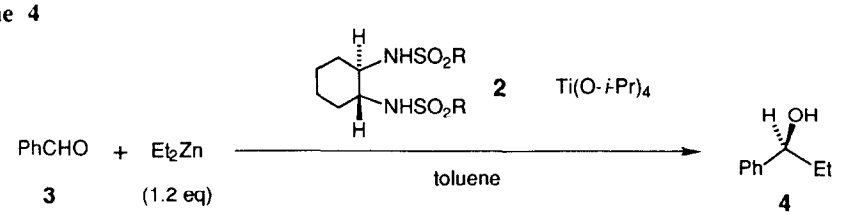
Scheme 3



We expected that the chiral ethyltitanium species **8** might also be generated from Et_2Zn and chiral titanium complex **7**, and thus the generated **8** might be more reactive than other ethylmetal species such as Et_2Zn, EtZnO-*i*-Pr and achiral ethyltitanium species **6** due to the substitution by an electron-withdrawing sulfonamide.

Thus, the chiral titanium complex **7** was prepared *in situ* by the reaction of $Ti(O\text{-}i\text{-}Pr)_4$ (0.048 equiv) and disulfonamide (0.04 equiv) in toluene at 40°C for 20 min. The mixture was cooled to -78°C, then Et_2Zn (1.2 equiv, 1.0*M* hexane solution) and benzaldehyde was added to the above solution. (Scheme 4) The results are summarized in Table 1.

Scheme 4



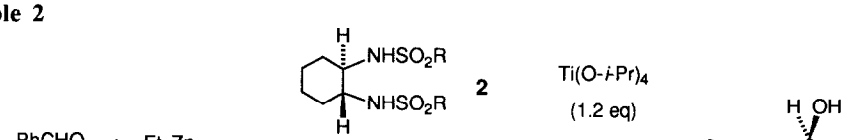
The rate acceleration as well as enantioselectivity was most significant when fluorinated disulfonamides such as **2a** and **2b** were employed (entry 1 and 6). It is also important to find that the enantioselectivities were still high in spite of an excess use of Ti(O-*i*-Pr)$_4$. (entry 2 and 3) These results shows that the addition of an excess amount of Ti(O-*i*-Pr)$_4$ does not lower the enantiomeric excess of the product, and we became interested in examining the reaction in the presence of 1.2 equiv of Ti(O-*i*-Pr)$_4$. (Table 2)

Table 1

entry	2	sulfonamide R	equiv	Ti(O-*i*-Pr)$_4$ equiv	temp. ℃	time hr	yield %	e.e. %	confign
1	**2a**	CF_3	0.04	0.048	0	2	99	98	*S*
2			0.02	0.2	0	2	99	99	*S*
3			0.005	0.02	0	16	93	99	*S*
4			0.002	0.008	0	222	93	45	*S*
5	(*S,S*)-**2a**	CF_3	0.04	0.048	0	2	95	98	*R*
6	**2b**	n-C_4F_9	0.04	0.048	0	4	79	96	*S*
7	**2c**	C_6F_5	0.04	0.048	r.t.	22	64	51	*S*
8	**2d**	CH_3	0.04	0.048	r.t.	22	90	89	*S*
9	**2f**	n-C_8H_{17}	0.04	0.048	r.t.	22	85	64	*S*
10	**2g**	$C_6H_5CH_2$	0.04	0.048	r.t.	22	86	30	*S*
11	**2h**	p-CH_3-C_6H_4	0.04	0.048	r.t.	22	45	50	*S*
12	**2k**	α-$C_{10}H_7$	0.04	0.048	r.t.	22	87	94	*S*

As shown in Table 2, the alkylation was found to proceed much faster even at a lower temperature upon use of 1.2 equiv of Ti(O-*i*-Pr)$_4$. Particular noteworthy is the exceptionally high level of catalytic efficiency. For example, the addition of only 0.0005 equivalent of **2a** was enough to achieve excellent enantioselectivity (98% e.e.) as well as chemical yield. (entry 3) The accelerating effect observed by the addition of an excess Ti(O-*i*-Pr)$_4$ might be explained by assuming that ethyltitanium species **6** reacts extremely fast with **7** (or related dialkoxytitanium species) regenerating the chiral ethyltitanium species **8**.

Table 2

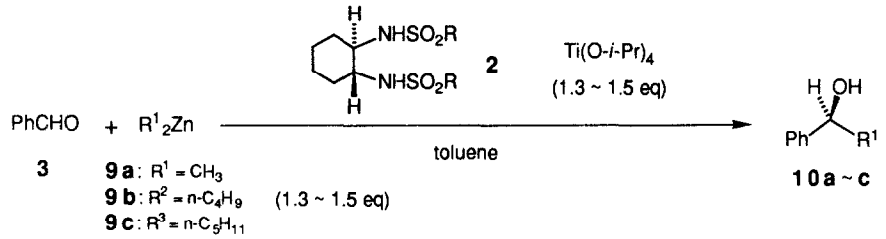


3 **4**

entry	2	sulfonamide R	equiv	temp. ℃	time hr	yield %	e.e. %	confign
1	**2a**	CF_3	0.02	-20	1.5	98	98	*S*
2			0.005	-30	2.5	98	99	*S*
3			0.0005	-20	2	97	98	*S*
4			0.0001	-20	11	99	68	*S*
5	**2b**	C_4F_9	0.02	-20	4	98	93	*S*
6	**2d**	CH_3	0.04	0	9	97	66	*S*
7	**2f**	n-C_8H_{17}	0.04	0	20	98	99	*S*
8	**2k**	α-$C_{10}H_7$	0.04	0	20	97	72	*S*

The alkylation of benzaldehyde with other dialkylzinc (**9a~9c**) was also examined. As summarized in Table 3, the alkylation proceeded smoothly affording the corresponding alcohols (**10a~10c**) with excellent enantiomeric excess except in the case of less reactive Me_2Zn.

Table 3

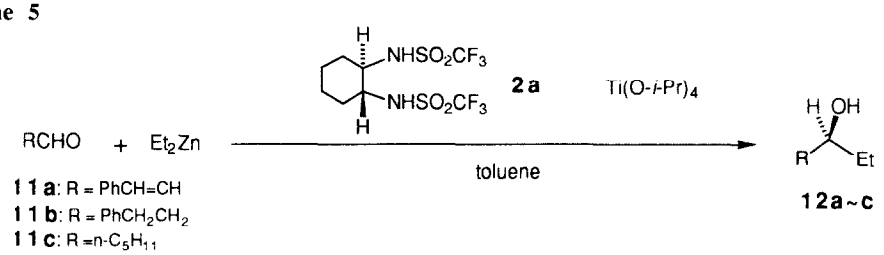


entry	dialkylzinc 9	R^1	sulfonamide 2	R	equiv	temp. ℃	time hr	yield %	e.e. %	confign
1	**9a**	CH_3	**2a**	CF_3	0.04	0	48	99	73	*S*
2					0.02	0	10	80	72	*S*
3	**9b**	n-C_4H_9	**2a**	CF_3	0.02	-20	3	98	97	*S*
4					0.005	-20	3	97	94	*S*
5			**2b**	n-C_4F_9	0.02	-30	2.5	99	98	*S*
6	**9c**	n-C_5H_{11}	**2a**	CF_3	0.02	-50	9	99	99	#

Not determined.

In order to further demonstrate the generality of the present catalytic enantioselective alkylation, we then carried out the reaction of other aldehydes including aliphatic ones. When cinnamaldehyde (**11a**) was reacted with 1.2 equiv of Ti(O-*i*-Pr)$_4$ and 1.2 equiv of Et_2Zn at -50°C in the presence of 0.02 equiv of **2a**, the corresponding (*S*)-alcohol **12a**[12] was obtained in 98% yield with 85% e.e. It was also found that cinnamaldehyde underwent alkylation with Et_2Zn-Ti(O-*i*-Pr)$_4$ at -40~ -30°C even in the absence of sulfonamide. Accordingly, the relatively low enantiomeric excess was considered to be due to the competitive path involving an achiral ethyltitanium species such as **6**. Enantiomeric excess might be improved if the amount of the achiral ethyltitanium species in the reaction mixture is decreased. Based on this assumption, we have examined the reaction in detail changing the ratio of Ti(O-*i*-Pr)$_4$ and Et_2Zn. (Scheme 5)

Scheme 5



As shown in Table 4, the slight increase in enantiomeric excess was observed by using 0.6 equiv of Ti(O-*i*-Pr)$_4$, while the reaction proceeded rather slowly (entry 2). However, the increase in both enantiomeric excess

and the reaction rate was achieved when 2.2 equiv of Et_2Zn was used (entry 4). Comparison of the data (entry 1 *vs* 3, entry 2 *vs* 4, and entry 5 *vs* 6) also indicates that an excess use of Et_2Zn results in a higher enantiomeric excess. These results might be in accordance with the assumption that ethyltitanium species exist in a rather complicated polymeric form with Et_2Zn, $Ti(O\text{-}i\text{-}Pr)_4$ and/or $EtZn(O\text{-}i\text{-}Pr)$ depending on the ratio of Et_2Zn and $Ti(O\text{-}i\text{-}Pr)_4$. From a synthetic point of view, excellent enantiomeric excess, 99% e.e., was achieved when 0.3 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ and 2.2 equiv of Et_2Zn were employed (entry 5). The use of less than 0.3 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ was found not to be practical because prolonged reaction time was necessary for completion of the reaction.

The results of 3-phenylpropanal (**11b**) and 1-hexanal (**11c**) are also summarized in Table 4. It should be emphasized that excellent enantioselectivity was achieved in the case of 1-hexanal.

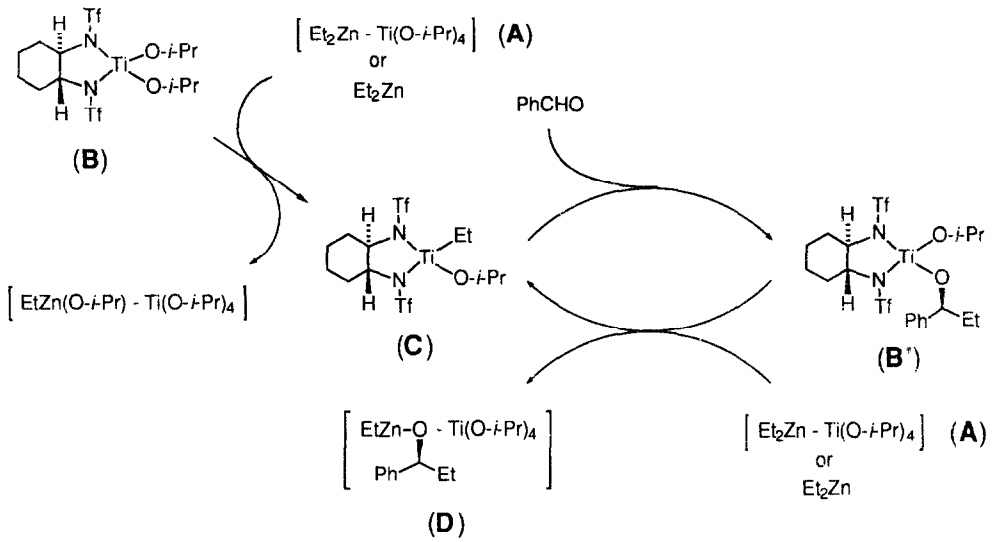
Table 4

entry	aldehyde **11** R	**2a** equiv	$Ti(O\text{-}i\text{-}Pr)_4$ equiv	Et_2Zn equiv	temp. ℃	time hr	yield %	e.e. %	confign
1	PhCH=CH	0.02	1.2	1.2	-50	1.5	98	85	*S*
2		0.02	0.6	1.2	-50	4	78	89	*S*
3		0.02	1.2	2.2	-50	2	96	88	*S*
4		0.02	0.6	2.2	-50	3	99	92	*S*
5		0.02	0.3	2.2	-50	6.5	85	99	*S*
6		0.02	0.3	1.1	-50	6.5	49	83	*S*
7		0.005	0.3	2.2	-50	3.5	67	88	*S*
8	$PhCH_2CH_2$	0.04	1.2	2.2	0	6	quant	90	*S*
9		0.04	0.6	2.2	0	6	quant	92	*S*
10		0.01	0.6	2.2	0	4.5	95	92	*S*
11		0.0005	0.6	2.2	0	4.5	93	71	*S*
12	$n\text{-}C_5H_{11}$	0.04	1.2	2.2	-20	6	62	99	*S*
13		0.04	0.6	2.2	-20	5	78	99	*S*
14		0.02	0.6	2.2	-20	7	64	98	*S*
15		0.005	0.6	2.2	-20	6.5	74	93	*S*

Although the exact structures of the active species are not clear, a probable catalytic cycle is shown in Scheme 6. We assume that chiral ethyltitanium reagent (C) is a key species in the present system. Chiral ethyltitanium species C might initially be generated by the reaction of chiral titanate B and achiral ethyltitanium species A (and/or Et_2Zn). Ethyltitanium species C reacts with an aldehyde to form dialkoxytitanium B'. Dialkoxytitanium B' then reacts with achiral ethyltitanium species A (or Et_2Zn) to regenerate the key species C establishing the catalytic cycle. A remarkable catalytic efficiency observed in the present system might be due to the high reactivity of ethyltitanium species C and extremely facile regeneration of C from B'. These potential features are, of course, derived through the substitution with electron-withdrawing sulfonamide.

In conclusion, disulfonamide-$Ti(O\text{-}i\text{-}Pr)_4$-dialkylzinc is an excellent system for a catalytic and enantioselective alkylation of aldehydes including aliphatic ones.[13] The concept of modifying a Lewis acid with chiral sulfonamide ligand is promising in developing other types of catalytic enantioselective reactions.[10] Since our original disclosure[4] the concept of using a chiral ligand in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ to catalyze the addition of R_2Zn to aldehydes enantioselectively has been used by others employing different ligands.[14]

Scheme 6



Acknowledgements

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Experimental Section

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP 140 instrument. ^{1}H-NMR (400 MHz) spectra were recorded on a JEOL GX-400 spectrometer. Abbreviations are as follows; s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). IR spectra were recorded on a PERKIN-ELMER 1600 Series FTIR spectrometer. Reagents and solvents were purified by standard procedures.

(1*R*,2*R*)-1,2-*N*,*N*'-bis(*p*-Toluenesulfonylamino)cyclohexane (2h): To a cooled (0°C) solution of (1*R*,2*R*)-1,2-diaminocyclohexane (4.57g, 40 mmol) in CH_2Cl_2 (120 mL) was added diisopropylethylamine (31.1 mL, 180 mmol), and the mixture was stirred for 10 min. *p*-Toluenesulfonylchloride (15.3 g, 80 mmol) was added at -40°C. The mixture was allowed to warm to room temperature. After being stirred for 30 min, the mixture was poured into 1*N* HCl (300 mL), and the product was extracted with Et_2O. The organic phase was washed with sat. NaCl, dried over anhydrous Na_2SO_4, and concentrated. The residue was recrystallized from CH_2Cl_2-hexane to afford **2h** (12.47g, 74%) as colorless needles. m.p. 168~170°C: Anal. calcd for $C_{20}H_{26}N_2O_4$, C 56.85, H 6.20, N 6.63, found C 56.59, H 6.18, N 6.76: $[\alpha]_D^{20}$ +2.6° (*c* 2.33, pyridine): IR

(KBr) 3439 (br), 3287, 2928, 1421, 1326, 1162, 1093, 1056, 814 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.01~1.18 (m, 4H), 1.56 (d, *J*=6.7 Hz, 2H), 1.86 (d, *J*=10.2Hz, 2H), 2.44 (s, 6H), 2.67~2.78 (m, 2H), 4.77 (d, *J*=5.6Hz, 2H), 7.32 (d, *J*=8.6Hz, 4H), 7.76 (d, *J*=8.4Hz, 4H).

In a similar manner, sulfonamides, **2a~2g** and **2i~2l**, were prepared. Spectral data are as follows: **2a**: m.p. 186~189°C (Et_2O-hexane): Anal. calcd for $C_8H_{12}N_2O_4$, C 25.40, H 3.20, N 7.40, found C 25.65, H 3.24, N 7.61: $[\alpha]_D^{20}$ -5.7° (*c* 5.01, EtOH): IR (KBr) 3450 (br), 3310, 1384, 1239, 1196, 1141, 1092, 992, cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.33 (m, 2H), 1.43 (m, 2H), 1.74~1.91 (m, 2H), 2.22 (d, *J*=11.6Hz, 2H), 3.26 (d, *J*=10.0Hz,2H), 5.21 (s, 2H). **2b**: nonafluoro-1-butanesulfonylfluoride was used. m.p. 64~76°C (colorless amorphous solid): Anal. calcd for $C_{14}H_{12}N_2O_4$, C 24.79, H 1.78, N 4.13, found C 24.98, H 1.68, N 4.12: $[\alpha]_D^{20}$ -17.1° (*c* 3.01, pyridine): IR (KBr) 3448 (br), 3311, 1458, 1377, 1238, 1196, 1142, cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.32 (m, 2H), 1.36~1.50 (m, 2H), 1.83 (d, *J*=8.1Hz, 2H), 2.21 (d, *J*=13.2Hz, 2H), 3.31 (dd, *J*=5.8, 9.6Hz, 2H), 5.55 (br, 2H). **2c**: m.p. 174~181°C (AcOEt-hexane): Anal. calcd for $C_{18}H_{12}N_2O_4$, C 37.64, H 2.11, N 4.88, found C 37.48, H 2.05, N 4.92: $[\alpha]_D^{20}$ +26.4° (*c* 1.53, pyridine): IR (KBr) 3425 (br), 3272, 1522, 1365, 1353, 1176, 1100, 992 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.25 (m, 2H), 1.29~1.45 (m, 2H), 1.73 (d, *J*=8.4Hz, 2H), 1.93 (d, *J*=12.8Hz,2H), 3.30 (br, 2H), 5.41 (br, 2H).

2d: m.p. 157~159°C (AcOEt-hexane): Anal. calcd for $C_8H_{18}N_2O_4$, C 35.54, H 6.71, N 10.36, found C 34.05, H 6.50, N 9.49; $[\alpha]_D^{20}$ -20.1° (*c* 3.07, pyridine): IR (KBr) 3425 (br), 3305, 2949, 1451, 1318, 1156, 1141, cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.24~1.43 (m, 4H), 1.75~1.82 (m, 2H), 2.18 (d, *J*=12.5Hz, 2H), 3.04 (s, 6H), 3.08 (br, 2H), 4.70 (d, *J*=6.2Hz, 2H). **2e**: m.p. 145~147°C (CH_2Cl_2-hexane): Anal. calcd for $C_{10}H_{22}N_2O_4$, C 40.25, H 7.43, N 9.39, found C 39.97, H 7.62, N 9.13: $[\alpha]_D^{20}$ -22.4° (*c* 1.98, pyridine): IR (KBr) 3420 (br), 3273, 2939, 1451, 1317, 1143, 1095, 906 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.24~1.40 (m, 4H), 1.40 (t, *J*=7.7Hz, 6H), 1.75 (d, *J*=5.7Hz, 2H), 2.15 (d, *J*=12.8Hz, 2H), 3.10 (q, *J*=7.7Hz, 4H), 3.04~3.16 (m, 2H), 4.90(d, *J*=7.0Hz, 2H). **2f**: m.p.117~119°C (CH_2Cl_2-hexane): Anal. calcd for $C_{22}H_{46}N_2O_4$, C 56.61, H 9.93, N 6.00, found C 56.48, H 10.18, N 5.90: $[\alpha]_D^{20}$ -10.5° (*c* 3.19, pyridine): IR (KBr) 3425 (br), 3278, 2922, 1456, 1316, 1277, 1132, 1121, 1091, 915cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, *J*=7.0Hz, 6H), 1.19~1.38 (m, 20H), 1.35~1.46 (m, 4H), 1.70~1.81 (m, 2H), 1.76~1.92 (m, 4H), 2.14 (d, *J*=11.7Hz, 2H), 2.98~3.13(m, 6H) 4.72 (d, *J*=7.3Hz,2H). **2g**: m.p. 164~167°C (CH_2Cl_2-hexane): Anal calcd for $C_{20}H_{26}N_2O_4$, C 56.85, H 6.20, N 6.63, found C 56.64, H 6.29, N 6.44: $[\alpha]_D^{20}$ +4.05° (*c* 2.58, pyridine): IR (KBr) 3432 (br), 3264, 2925, 1456, 1316, 1277, 1152, 1124, 1096 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.12 (br, 2H), 1.60 (d, *J*=5.6Hz, 2H), 1.96 (d, *J*=5.3Hz, 2H), 2.89 (br, 2H), 4.30 (q, *J*=13.9, 24.7Hz, 4H), 4.55 (d, *J*=3.5Hz, 2H), 7.37(t, *J*=3.3Hz, 6H) 7.40~7.46 (m, 4H). **2i**: m.p. 204~206°C (CH_2Cl_2-hexane): Anal. calcd for $C_{24}H_{34}N_2O_4$, C 60.22, H 7.16, N 5.85, found C 60.59, H 7.31, N 5.59: $[\alpha]_D^{20}$ +5.8° (*c* 1.68, pyridine): IR (KBr) 3439 (br), 3319, 2935, 1605, 1456, 1426, 1320, 1172, 1149, 1056, 862 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 0.98~1.17 (m, 4H), 1.55 (s, 2H), 1.85 (d, *J*=8.0Hz, 2H), 2.30 (s, 6H), 2.61 (s, 12H), 2.79 (br, 2H), 4.87 (d *J*=4.8Hz, 2H), 6.96 (s, 6H). **2j**: m.p. 236~240°C (AcOEt-hexane): Anal. calcd for $C_{36}H_{58}N_2O_4$, C 66.83, H 9.03, N 4.33, found C 66.60, H 9.12, N 4.47: $[\alpha]_D^{20}$ +51.3° (*c* 2.91, pyridine): IR (KBr) 3434 (br), 3279, 2964, 1599, 1459, 1328, 1152, 1039, 881 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 0.95~1,16 (m, 4H), 1.25 (d, *J*=7.0Hz, 12H), 1.27 (d, *J*=6.6Hz, 24H), 1.56 (d, *J*=6.0,.2H), 1.85 (d *J*=10.6Hz, 2H), 2.85~2.95 (m, 2H), 3.09~3.16(m, 2H) 4.11~4.21 (m, 4H), 5.09 (d, *J*=5.1Hz, 2H), 7.16 (s, 4H). **2k**: m.p. 207~209°C (AcOEt-hexane): Anal. calcd for $C_{26}H_{26}N_2O_4$, C 63.14, H 5.30, N 5.66, found C 63.30, H 5.39, N 5.55: $[\alpha]_D^{20}$ +72.6° (*c* 3.03, pyridine): IR (KBr) 3444 (br), 3306, 2940, 1440, 1333, 1306, 1278, 1163, 1132, 804, 772cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ

0.91 (d, *J*=7.7Hz, 4H), 1.38 (br, 2H), 1.57 (s, 2H), 2.76 (d, *J*=5.20,.2H), 5.03 (d *J*=5.9Hz, 2H), 7.55 (t, *J*=7.9Hz, 2H), 7.62(dt, *J*=6.8, 1.1Hz, 2H) 7.69 (dt, *J*=7.0Hz, 2H), 7.96 (d, *J*=7.3Hz, 2H), 8.09 (d, *J*=8.1Hz, 2H), 8.26 (dd, *J*=7.3, 1.5Hz, 2H),8.50 (d, *J*=7.7Hz, 2H).

2l: m.p.96~99°C (AcOEt-hexane) Anal. calcd for $C_{26}H_{26}N_2O_4$, C 63.14, H 5.30, N 5.66, found C 62.88, H 5.37, N 5.57; $[\alpha]_D^{20}$ +13.9° (*c* 1.07, pyridine): IR (KBr) 3418 (br), 3054, 2939, 1504, 1451, 1328, 1158cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 0.97~1.18 (m, 4H), 1.52 (d, *J*=9.2Hz, 2H), 1.85 (d, *J*=12.8Hz, 2H), 2.74~2.84 (m, 2H), 4.91 (d *J*=5.9Hz, 2H), 7.61~7.69 (m 4H), 7.84 (dd, *J*=9.0, 1.6Hz, 2H) 7.93 (d, *J*=8.1Hz, 2H), 7.96~8.02 (m, 4H), 8.46 (d, *J*=1.5Hz, 2H).

Typical Procedure for the Alkylation of an Aldehyde (Table 2, entry 1): In a flame-dried round-bottom flask was placed **2a** (189 mg, 0.5 mmol) under argon atmosphere. To this were added degassed toluene (10 mL) and Ti(O-*i*-Pr)$_4$ (8.53g, 30 mmol), and the mixture was stirred at 40°C for 20 min. After being cooled to -78°C, Et_2Zn (1.0*M* hexane solution, 30mL, 30 mmol) was added to the solution. In a moment, the solution turned orange. To the resulting solution was added benzaldehyde (2.12g, 25 mmol) in toluene (2mL) and the mixture was warmed to -20°C, and was stirred at that temperature for 2hr. The reaction was quenched by adding 2*N* HCl, and the product was extracted with Et_2O. The organic phase was washed with sat. NaCl, dried over anhydrous Na_2SO_4, and concentrated. The residue was chromatographed on a silica gel column chromatography (eluent; 2% AcOEt in hexane) to obtain crude 1-phenylpropanol **4**. Distillation gave pure **4** (3.27g, 98%). b.p. ~103°C/15mmHg: $[\alpha]_D^{22}$ -48.6° (*c* 5.13, $CHCl_3$).

Determination of the Absolute Configuration: $[\alpha]_D$ values of each alcohols are as follows: **4** (Table 2, entry 1); $[\alpha]_D^{22}$ -48.6° (*c* 5.13, $CHCl_3$) as 98% e.e. Lit[1h]; $[\alpha]_D^{22}$ -47.6° (*c* 6.11, $CHCl_3$) as 98% e.e. **10a** (Table 3, entry 1); $[\alpha]_D^{24}$ -30.6° (*c* 7.10, c-C_5H_{10}) as 73% e.e. Lit[15]; $[\alpha]_D^{20}$ +43.1° (*c* 7.19, c-C_5H_{10}) for *R*-enantiomer. **10b** (Table 3, entry 5); $[\alpha]_D^{25}$ -37.9° (*c* 3.13, C_6H_6) as 98% e.e. Lit[16]; $[\alpha]_D^{22}$ +35.7° (*c* 3.00, C_6D_6) for *R*-enantiomer. **10c** (Table 3, entry 6); $[\alpha]_D^{24}$ -34.2° (*c* 1.24, $CHCl_3$). **12a** (Table 4, entry 4); $[\alpha]_D^{24}$ -5.4° (*c* 2.46, $CHCl_3$) as 92% e.e. Lit[17]; $[\alpha]_D^{22}$ -5.7° (*c* 100, $CHCl_3$) as 96% e.e. **12b** (Table 4, entry 9); $[\alpha]_D^{25}$ +23.3° (*c* 3.99, EtOH) as 92% e.e. Lit[17]; $[\alpha]_D^{22}$ +23.9° (*c* 1.44, EtOH) as 90% e.e. **12c** (Table 4, entry 13); $[\alpha]_D^{24}$ +12.3° (*c* 1.24, Et_2O) as 99% e.e. Lit[18]; $[\alpha]_D^{24}$ +12.9° (*c* 6, Et_2O) as 100% e.e.

Determination of the Enantiomeric Excess: Enantiomeric excess of the alcohols were determined by HPLC analysis using chiral columns. Chiral columns; eluent; flow rate; retention times for each compounds are as follows: **4**; Daicel column OB; 2% *i*-PrOH in hexane; 0.5mL/min; t_R=19.5min, t_S=23.0min. **10a**; Daicel column OB; 10% *i*-PrOH in hexane; 0.5mL/min; t_S=11.3min, t_R=15.6min. **10b**; Daicel column OB; 1% *i*-PrOH in hexane; 1.0mL/min; t_S=25.5min, t_R=37.4min. **10c**; Daicel column OB; 1% *i*-PrOH in hexane; 1.0mL/min; t_{major}=14.2min, t_{minor}=26.0min. **12a**; Daicel column OK; 1% *i*-PrOH in hexane; 0.5mL/min; t_S=52.7min, t_R=59.3min. **12b**; Daicel column OK; 2% *i*-PrOH in hexane; 0.5mL/min; t_S=33.1min, t_R=36.6min. Benzoate of **12c**; Daicel column OT(+); MeOH; 0.2mL/min; t_S=29min, t_R=41min.

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