Stereoselective Radical Addition of an Acetal to Sterically Tuned Enantiomerically Pure *N*-Sulfinyl Imines

Tito Akindele, Ken-ichi Yamada, Takumi Sejima, Masaru Maekawa, Yasutomo Yamamoto, Mayu Nakano, and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University; Yoshida, Sakyo-ku, Kyoto 606–8501, Japan.
Received October 17, 2009; accepted November 27, 2009; published online November 27, 2009

Enantiomerically enriched sulfonamides were synthesized by the radical addition of an acetal to enantiomerically pure *N*-sulfinyl imines using dimethylzinc–air and boron trifluoride diethyl etherate. Higher levels of stereocontrol were observed by using a mesitylenesulfinyl group. Furthermore, an amine and an amino alcohol with high enantiomeric purity were obtainable from the sulfonamide product.

Key words asymmetric synthesis; radical reaction; dimethylzinc; sulfonamide

Given the ubiquitous nature of the C–N stereogenic center, efficient synthetic methods continue to be developed for its installation in both simple and complex chemical structures.[1—3] These methods could be broadly classified into reactions mediated by ionic or radical species. Majority of these methods are mediated by ionic species, requiring highly basic reagents which limit the substrate scope of these approaches, albeit the products are obtained in high yield and enantioselectivity. On the other hand, methods involving radical species[4,5] are relatively under explored despite the potential of this approach to deliver much more structurally varied products using milder reagents.

To date, the lack of a catalytic asymmetric radical addition method to *N*-sulfonyl imines[6,7] has made the use of chiral *N*-sulfinyl imines as radical acceptors, for creating predictable stereodefined C–N stereogenic centers in sulfonamides, an appealing alternative synthetic strategy. Indeed, the pioneering works of Davis and Ellman on the synthesis and reactivity of *N*-sulfinyl imines have given the synthetic community a readily available and robust precursor of optically active amine compounds.[8—16]

Due to this rarity of radical species-mediated methods as well as our ongoing interest in radical reactions,[17—19] we sought to improve the efficiency and substrate scope of our initial report on radical addition of ethers and acetals to enantiopure *N*-*p*-toluenesulfinyl aldimines.[20] In this previous report, an in-house dimethylzinc–air radical initiator was used to generate carbon-centered α-alkoxyalkyl radicals from ethers and acetals. Subsequent nucleophilic addition of the radicals to the enantiopure *N*-sulfinyl imines followed by oxidation afforded the sulfonamide adducts in enantiomerically enriched forms. It is noteworthy that boron trifluoride diethyl etherate was essential for faster reaction rate while a sterically hindered acetal was crucial to good stereocontrol (Chart 1).

Subsequent investigations have led to improved levels of stereocontrol. Herein, we detail our new findings along with a computational rationale for the improved levels of stereocontrol.

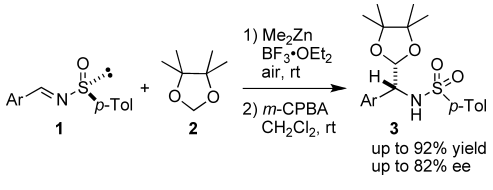


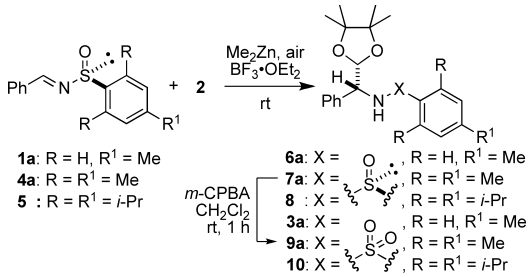
Chart 1. Asymmetric Radical Addition of Acetal **2** to *N*-Sulfinyl Imines **1**

Results and Discussion

As we previously reported,[20] the reaction of (*S*)-*N*-benzylidene-4-toluenesulfinamide (**1a**) with acetal **2**[21] proceeded smoothly in the presence of trifluoroborane diethyl etherate using dimethylzinc–air to give a crude mixture including sulfinamide products **6a** with a 9 : 1 diastereomeric ratio along with a trace amount of sulfonamide product **3a** (*ca.* 1%). Subsequent oxidation of the crude products with *m*-chloroperbenzoic acid (*m*-CPBA) provided **3a** with 80% ee in 92% yield (Table 1, entry 1). The enantiomeric ratio of **3a** was the same as the diastereomeric ratio of **6a** in the crude mixture, showing that no racemization took place during the *m*-CPBA oxidation.

We reasoned that by substituting a bulkier group for the *p*-tolyl group on the sulfur stereogenic center would presumably lead to higher levels of stereocontrol. In fact, Davis and coworkers have reported improved levels of diastereoselectivity in the synthesis of *N*-sulfinylaziridine 2-phosphonates

Table 1. Asymmetric Radical Addition of Acetal **2** to *N*-Sulfinyl Imines **1a**, **4a**, and **5**[a]



Entry	Imine	Me_2Zn (eq)	BF_3OEt_2 (eq)	Time (h)	Product	Yield (%)	ee[b] (%)
1[d]	**1a**	3	1	2	**3a**	92	80
2	**4a**	9	1	51	**9a**	73	92 (98)[c]
3	**4a**	6	2	21	**9a**	73	95
4	**5**	6	2	23	**10**	77	87

a) Acetal **2** (125 eq) was used as solvent.[22] Air was introduced into the reaction mixture at a rate of 0.5 l/(h·mol). *b*) Determined by HPLC analysis. *c*) After recrystallization from ethyl acetate/hexane. *d*) Data from ref. 20.

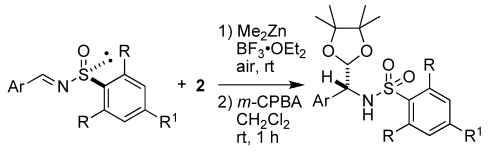
* To whom correspondence should be addressed. e-mail: tomioka@pharm.kyoto-u.ac.jp

from *N*-sulfinyl imines and lithium diethyl iodomethylphosphonates by increasing the size of the sulfinyl group.[23] They also observed increased level of stereoselectivity when bulky *N*-sulfinyl imines were reacted with prochiral lithium enolates of Weinreb amides to give syn-α-substituted β-amino Weinreb amides.[24] Also, Senanayake and coworkers have reported a highly diastereoselective addition of phenylmagnesium bromide to *N*-sulfinyl imines by tuning the size of the sulfinyl moiety.[25] Indeed, utilizing (*S*)-*N*-2,4,6-trimethylbenzenesulfinyl benzaldehyde imine (**4a**)[23] and **2** in the presence of excess reagents and air afforded a crude 1 : 1 mixture of sulfinamide **7a** and sulfonamide **9a**, which was subjected to the oxidation to give **9a** with 92% ee in moderate yield (Table 1, entry 2). The *N*-sulfonyl analog of **4a** was not detected by TLC monitoring during the radical addition step. In addition, high level of stereoselectivity was observed in spite of much oxidized product **9a** in the crude mixture. These observations suggested that non-stereoselective addition of dioxolanyl radical to the *N*-sulfonyl analog of **4a**, which is possibly formed by oxidation of **4a** during the reaction, should be negligible. Thus, **9a** in the crude mixture was probably produced by oxidation of **7a** during the longer reaction time of the radical addition step. An increased amount of trifluoroborane diethyl etherate accelerated the reaction, which was complete within 21 h to give **9a** with 95% ee after the oxidation (entry 3). With comparison to (*S*)-*N*-*p*-toluenesulfinyl benzaldehyde imine (**1a**) (entry 1), this result represents an improvement in levels of enantiocontrol. Crystallizability of the product sulfonamide is advantageous; thus, single recrystallization of **9a** with 92% ee from ethyl acetate/hexane gave enantiomerically enriched **9a** with 98% ee in 78% recovery yield (entry 2).

Further steric tuning of the sulfinyl group in the form (*S*)-*N*-2,4,6-triisopropylbenzenesulfinyl benzaldehyde imine (**5**) led to a decrease in product ee; thus the oxidation of the resulting crude 2 : 1 mixture of sulfinamide **8** and sulfonamide **10** gave **10** with 87% ee in comparable yield (entry 4). A similar observation was reported by Davis and coworkers during their investigations on the reaction of prochiral lithium enolates of Weinreb amides with *N*-sulfinyl imines.[24] As in the reaction of **4a**, oxidation of **5** to the corresponding achiral *N*-sulfonyl imine was not observed by TLC monitoring. Besides, the amount of sulfonamide product **10** (*ca.* 33%) in the crude mixture of the radical addition step with **5** was less than that with **4a** to give **9a** (*ca.* 50—66%), probably due to a steric hindrance of the triisopropylphenyl group toward the *S*-oxidation. Based on these facts, the possibility of oxidation of **5** before the addition of the dioxolanyl radical should be unlikely.

Having the newly optimized substrate and conditions in hand, we set out to define the scope of the reaction. Gratifyingly, *p*-tolualdehyde derived *N*-(2,4,6-trimethylbenzenesulfinyl)imine **4b** and 2-naphthaldehyde derived *N*-(2,4,6-trimethylbenzenesulfinyl)imine **4c** both gave the desired adducts in significantly higher enantiomeric excesses than their previously reported corresponding less bulky *N*-(*p*-toluenesulfinyl)imine derivatives **1b** and **1c**,[20] respectively (Table 2, entries 1 and 3 *vs.* entries 2 and 4, respectively). The greater resonance stabilization provided by the 2-naphthyl group relative to the *p*-tolyl group was presumably responsible for the significantly lesser reactivity of the 2-naphthaldehyde derived *N*-sulfinyl imines relative to that of the *p*-tolualdehyde derived *N*-sulfinyl imines (entry 1 *vs.* 3 and entry 2 *vs.* 4).

Table 2. Comparison of Asymmetric Radical Addition of Acetal **2** to *N*-Sulfinyl Imines **1** and **4**[a]



1b: Ar = 4-MeC_6H_4, R = H, R^1 = Me
4b: Ar = 4-MeC_6H_4, R = R^1 = Me
1c: Ar = 2-naphthyl, R = H, R^1 = Me
4c: Ar = 2-naphthyl, R = R^1 = Me

3b: Ar = 4-MeC_6H_4, R = H, R^1 = Me
9b: Ar = 4-MeC_6H_4, R = R^1 = Me
3c: Ar = 2-naphthyl, R = H, R^1 = Me
9c: Ar = 2-naphthyl, R = R^1 = Me

Entry	Imine	Me_2Zn (eq)	BF_3OEt_2 (eq)	Time (h)	Product	Yield (%)	ee[b] (%)
1[c]	**1b**	3	1	5	**3b**	77	81
2	**4b**	6	2	20	**9b**	83	91
3[c]	**1c**	12	4	49	**3c**	71	79
4	**4c**	36	12	118	**9c**	66	92

a) Acetal **2** (125 eq) was used as solvent.[22] Air was introduced into the reaction mixture at a rate of 0.5 l/(h·mol). *b*) Determined by HPLC analysis. *c*) Data from ref. 20.

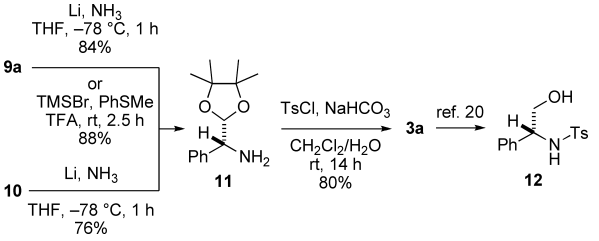


Chart 2. Determination of Absolute Configurations of Adducts **3a**, **9a**, and **10**

The sense of stereoinduction with **4a** and **5** was consistent with that observed for **1a** (Chart 2). Indeed, reductive cleavage of the sulfonyl groups of adducts **9a** and **10** under basic[26,27] or acidic[28] conditions produced amine **11**. Tosylation of **11** gave (*R*)-**3a**,[20] whose absolute configuration was previously confirmed by subsequent conversion into known alcohol **12**.[29] No racemization was observed through all these transformations. Unfortunately, reduction of the acetal moiety of **9a** with $TiCl_4$–Et_3SiH[20] resulted in partial racemization of the product, a mesitylenesulfonamide analog of **12** (from 92% ee to 87% ee) in 55% yield.

To rationalize the observed stereochemical outcome, the ground state geometries of the three imines were calculated by the B3LYP/6-31G* level density functional theory (DFT) method (Fig. 1).[30] The obtained structures were in good agreement with an X-ray structure of **1a**[31] and those calculated for simpler *N*-sulfinyl imines.[32—34] Thus, in all of these *N*-sulfinyl imines, the azomethine substituents are *trans* to the N–S bond while the S–O bond and the C=N bond are eclipsed. Accordingly, the *re*-faces of the imines are blocked from radical attack by the benzene rings of the sulfinyl groups resulting in the *si*-face selective attack of the acetal radical to the imines. The S–O bond and the *p*-tolyl plane of imine **1a** are almost eclipsed (the C=C–S–O dihedral angle=9°), while the *o*-methyl group on the benzene ring of

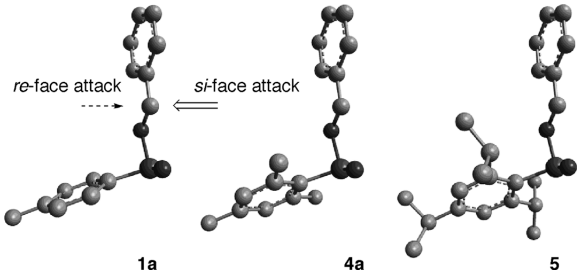


Fig. 1. The Ground State Geometries of Imines **1a**, **4a**, and **5**
The H atoms are omitted for clarity.

imine **4a** is pointed toward the azomethine carbon (the C=C–S–O dihedral angle=27°), probably to avoid steric repulsion with the oxygen atom.[35] This presumably accounts in part for the higher stereoselectivity (95% ee) observed in the reaction of **4a**. The isopropyl group of imine **5**, which exhibited a higher stereo-control (87% ee) than imine **1a** (80% ee), is also pointed toward the azomethine carbon (the C=C–S–O dihedral angle=38°). In the presence of $BF_3 \cdot OEt_2$, the imines **1** probably form imine–BF_3 complexes. Based on DFT calculations and NMR analysis, Dobrowolski and Kawęcki suggested that a sulfinyl imine coordinates to the boron of BF_3 at the oxygen atom.[32] Thus, it could be speculated that in the BF_3 complexes, the more bulky the aromatic ring of the sulfinyl group of the imine is, the more favorably the BF_3 moiety is placed on the *si*-face. This would make the *si*-face attack of the acetal radical less favorable, and may partly be the reason for the lower enantioselectivity observed in the reaction of **5** relative to that of **4a**.[36]

Conclusion

We have demonstrated the preparation of synthetically useful (>90% ee) sulfonamide compounds from enantiomerically pure *N*-sulfinyl imines in good yield using the dimethylzinc–air radical method. The reaction was facilitated by the use of boron trifluoride diethyl etherate. Equally important, the sulfonamide products served as precursors to enantiomerically enriched amine and amino alcohol building blocks.

Experimental

General All melting points are uncorrected. IR spectra were expressed in cm^{-1}. ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra were measured in $CDCl_3$. Chemical shifts and coupling constants are presented in ppm δ and Hz respectively. ^{13}C peak multiplicity assignments were made based on DEPT data. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; sep, septet; m, multiplet; br, broad. The wavenumbers of maximum absorption peaks of IR spectroscopy were presented in cm^{-1}. Column chromatography was carried out with silica gel. 4,4,5,5-Tetramethyl-1,3-dioxolane (**2**)[21] and dry *m*-CPBA[37] are prepared according to reported procedures.

Preparation of Chiral Imines The chiral *N*-sulfinyl imines **1**, **4**, and **5** were prepared by condensing the corresponding aldehyde and sulfinamide[23,38,39] according to known procedures.[40]

(*S*,*E*)-2,4,6-Triisopropyl-*N*-(benzylidene)benzenesulfinamide (5)[24] Recrystallization from hexane gave **5** as colorless prisms of mp 112—113 °C: *Rf* 0.49 (hexane/Et_2O 1/1). $[\alpha]_D^{22}$ +56.6 (c=1.00, $CHCl_3$), 98% ee (HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH 9/1, 0.5 ml/min, 254 nm, major 15.4 min and minor 16.6 min). ^{1}H-NMR δ: 1.14 (d, J=7.0, 6H), 1.25 (d, J=7.0, 6H), 1.29 (d, J=7.0, 6H), 2.89 (sep, J=7.0, 1H), 3.85 (m, 2H), 7.08 (s, 2H), 7.45 (m, 2H), 7.50 (m, 1H), 7.85 (d, J=7.0, 2H), 8.85 (s, 1H). ^{13}C-NMR δ: 23.59 (CH_3), 23.61 (CH_3), 23.9 (CH_3), 24.2 (CH_3), 27.8 (CH), 34.2 (CH), 122.9 (CH), 128.8 (CH), 129.3 (CH), 132.3 (CH), 134.3 (C), 149.7 (C), 152.7 (C), 161.2 (CH). IR (KBr): 2964, 2926, 2870, 1597, 1570, 1560, 1460, 1448, 1425, 1387, 1364, 1306, 1211, 1099, 1078, 1057, 876, 762, 692, 716, 692, 716, 637, 581. EI-MS (*m*/*z*): 355 (M^+), 250, 235, 233, 191, 163, 149, 106, 103, 91, 77 (Ph). *Anal.* Calcd for $C_{22}H_{29}NOS$: C, 74.32; H, 8.22; N, 3.94. Found: C, 74.44; H, 8.09, N, 3.85.

(*S*,*E*)-2,4,6-Trimethyl-*N*-(4-methylbenzylidene)benzenesulfinamide (4b) Recrystallization from hexane gave **4b** as colorless prisms of mp 111—112 °C: *Rf* 0.49 (hexane/Et_2O 1/1). $[\alpha]_D^{22}$ +110 (c=1.02, $CHCl_3$), >99% ee (HPLC: Daicel Chiralpak AS-H, hexane/*i*-PrOH 9/1, 0.5 ml/min, 254 nm, major 15.5 min and minor 18.1 min). ^{1}H-NMR δ: 2.28 (s, 3H), 2.41 (s, 3H), 2.50 (s, 6H), 6.86 (s, 2H), 7.26 (d, J=7.7, 2H), 7.74 (d, J=7.7, 2H), 8.79 (s, 1H). ^{13}C-NMR δ: 18.7 (CH_3), 21.0 (CH_3), 21.6 (CH_3), 129.5 (CH), 129.6 (CH), 130.8 (CH), 131.4 (C), 135.6 (C), 138.5 (C), 141.6 (C), 143.2 (C), 161.5 (CH). IR (KBr): 2914, 1595, 1562, 1508, 1458, 1173, 1090, 853, 818, 704, 621, 579, 505. EI-MS (*m*/*z*): 285 (M^+), 269 (M^+-O), 237, 167 ($M^+-SOMes$), 149, 139, 120, 105, 91 (tolyl), 65. *Anal.* Calcd for $C_{17}H_{19}NOS$: C, 71.54; H, 6.71; N, 4.91. Found: C, 71.33; H, 6.58, N, 4.94.

(*S*,*E*)-2,4,6-Trimethyl-*N*-(naphth-2-yl)benzenesulfinamide (4c) Recrystallization from EtOAc–hexane gave **4c** as colorless prisms of mp 139—140 °C: *Rf* 0.43 (hexane/Et_2O 1/1). $[\alpha]_D^{22}$ +267 (c=0.540, $CHCl_3$), 98% ee (HPLC: Daicel Chiralcel OD-H, hexane/*i*-PrOH 9/1, 0.5 ml/min, 254 nm, major 15.8 min and minor 20.4 min). ^{1}H-NMR δ: 2.29 (s, 3H), 2.53 (s, 6H), 6.88 (s, 2H), 7.57 (m, 2H), 7.87 (d, J=8.3, 1H), 7.88 (d, J=8.3, 1H), 7.94 (d, J=7.6, 1H), 8.02 (dd, J=8.4, 1.4, 1H), 8.24 (s, 1H), 8.99 (s, 1H). ^{13}C-NMR δ: 18.8 (CH_3), 21.0 (CH_3), 124.2 (CH), 126.9 (CH), 128.0 (CH), 128.3 (CH), 128.9 (CH), 129.2 (CH), 130.9 (CH), 131.7 (C), 132.4 (CH), 133 (C), 135.4 (C), 135.6 (C), 138.6 (C), 141.8 (C) 161.7 (CH). IR (KBr): 2918, 2363, 2345, 1600, 1570, 1560, 1541, 1508, 1456, 1090, 824, 743, 700, 618, 575. EI-MS (*m*/*z*): 321 (M^+), 305 (M^+-O), 273, 168, 153, 139, 127, 126, 106, 105, 91, 77, 63. *Anal.* Calcd for $C_{20}H_{19}NOS$: C, 74.73; H, 5.96; N, 4.36. Found: C, 74.61; H, 5.85, N, 4.37.

General Procedure for the Radical Addition of 2 to Imines 4 and 5. (*R*)-2,4,6-Trimethyl-*N*-[(phenyl)(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methyl]benzenesulfonamide (9a) (Table 1, Entry 3) In a dry 50 ml three-necked round-bottomed flask were placed a magnetic stirrer bar and **4a** (271 mg, 1.0 mmol). The flask was filled with argon after evacuation and refill with argon (3 times). 4,4,5,5-Tetramethyldioxolane (**2**) (18.3 ml, 125 mmol) was added at room temperature. To the stirred solution were sequentially added $BF_3 \cdot OEt_2$ (0.25 ml, 2.0 mmol) and a 1.0 M solution of Me_2Zn (6.0 ml, 6.0 mmol) in hexane. The argon source was replaced with a NaOH drying tube and air was injected into the reaction mixture *via* an air bubbler at a rate of 0.5 ml/h. The reaction mixture was stirred for 21 h at room temperature and quenched with saturated aqueous $NaHCO_3$ (30 ml) followed by extraction with EtOAc (3×30 ml). The combined organic extracts were washed with brine (30 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product as pale yellow oil. Dry CH_2Cl_2 (5 ml) and dry *m*-CPBA (173 mg, 1.0 mmol) were sequentially added to the crude product. The reaction mixture was stirred for 1 h and diluted with $CHCl_3$ (10 ml) followed by washing with saturated aqueous $NaHCO_3$ (3×15 ml). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product as pale yellow slurry-like mixture, which was purified by flash column chromatography (hexane/Et_2O 3/1) to give **9a** (306 mg, 73%) with 95% ee as white solid of mp 107—108 °C: *Rf* 0.46 (hexane/Et_2O 1/1). $[\alpha]_D^{25}$ −18.0 (c=1.02, $CHCl_3$). The ee was determined by HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH 9/1, 0.5 ml/min, 254 nm, major 27.5 min and minor 32.3 min). ^{1}H-NMR δ: 1.00 (s, 3H), 1.04 (s, 3H), 1.11 (s, 3H), 1.13 (s, 3H), 2.22 (s, 3H), 2.47 (s, 6H), 4.22 (dd, J=4.9, 4.6, 1H), 5.00 (d, J=4.9, 1H), 5.25 (d, J=4.6, 1H), 6.77 (s, 2H), 7.07—7.14 (m, 5H). ^{13}C-NMR δ: 20.5 (CH_3), 21.8 (CH_3), 22.0 (CH_3), 22.5 (CH_3), 23.5 (CH_3), 61.4 (CH), 82.6 (C), 82.8 (C), 100.7 (CH), 127.6 (CH), 128.1 (CH), 131.4 (CH), 134.0 (C), 135.9 (C), 138.9 (C), 141.8 (C). IR (KBr): 3279, 2978, 2924, 2368, 1597, 1458, 1435, 1396, 1319, 1157, 1057, 934, 880, 849, 702, 656. EI-MS (*m*/*z*): 288 ($M^+-C_7H_{13}O_2$), 234 (M^+-SO_2Mes), 167, 130, 129 ($C_7H_{13}O_2$), 119 (Mes), 101, 91, 83, 77 (Ph). *Anal.* Calcd for $C_{23}H_{31}NO_4S$: C, 66.16; H, 7.48; N, 3.35. Found: C, 66.07; H, 7.37. N, 3.52.

(*R*)-2,4,6-Triisopropyl-*N*-[(phenyl)(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methyl]benzenesulfonamide (10) (Table 1, Entry 4) Carried out according to the general procedure using **5** (356 mg, 1.0 mmol), **2** (18.3 ml, 125 mmol), $BF_3 \cdot OEt_2$ (0.25 ml, 2.0 mmol), and Me_2Zn (1.0 M in hexane; 6.0 ml, 6.0 mmol). The reaction mixture was stirred for 22.5 h. Work-up gave the crude product as colorless oil. Dry CH_2Cl_2 (5 ml) and dry *m*-CPBA (173 mg, 1.0 mmol) were sequentially added to the crude product. The reaction mixture was stirred for 1 h. Work-up gave the crude product as pale yel-

low oil, which was purified by flash column chromatography (hexane/Et_2O 3/1) to give **7** (385 mg, 77%) with 87% ee as white oily solid: *Rf* 0.71 (hexane/Et_2O 1/1). $[\alpha]_D^{22}$ −9.8 (*c*=0.885, $CHCl_3$). The ee was determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH 200/1, 0.5 ml/min, 254 nm, minor 27.7 and major 30.8 min). ^{1}H-NMR δ: 0.93 (s, 3H), 1.03 (s, 3H), 1.10 (s, 3H), 1.11 (s, 3H), 1.13 (d, *J*=6.7, 6H), 1.22 (d, *J*=6.7, 12H), 2.85 (sep, *J*=6.7, 1H), 3.99 (sep, *J*=6.7, 2H), 4.43 (dd, *J*=5.2, 4.3, 1H), 5.02 (d, *J*=4.3, 1H), 5.18 (d, *J*=5.2, 1H), 7.03 (br s, 2H), 7.10—7.15 (m, 5H). ^{13}C-NMR δ: 22.1 (CH_3), 22.2 (CH_3), 23.5 (CH_3), 23.6 (CH_3), 23.7 (CH_3), 23.8 (CH_3), 24.6 (CH_3), 24.9 (CH_3), 29.7 (CH), 34.1 (CH), 61.0 (CH), 82.8 (C), 83.0 (C), 100.9 (CH), 123.4 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 133.8 (C), 136.5 (C), 149.9 (C), 152.5 (C). IR (KBr): 3333, 2964, 2870, 1601, 1560, 1541, 1456, 1423, 1364, 1329, 1296, 1256, 1196, 1153, 1138, 1103, 1090, 1061, 1040, 1024, 961, 941, 928, 897, 881, 835, 820, 758, 721, 700, 669, 625, 581, 559. EI-MS (*m*/*z*): 267 ($SO_2(iPr)_3C_6H_2$), 129 ($C_7H_{13}O_2$), 101, 91, 83, 77 (Ph). *Anal.* Calcd for $C_{29}H_{43}NO_4S$: C, 69.42; H, 8.64; N, 2.79. Found: C, 69.43; H, 8.88; N, 2.60.

(*R*)-2,4,6-Trimethyl-*N*-[(4-methylphenyl)(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methyl]benzenesulfonamide (9b) (Table 2, Entry 2) Carried out according to the general procedure using **4b** (285 mg, 1.0 mmol), **2** (18.3 ml, 125 mmol), $BF_3\cdot OEt_2$ (0.25 ml, 2.0 mmol), and Me_2Zn (1.0 M in hexane; 6.0 ml, 6.0 mmol). The reaction mixture stirred for 20 h. Work-up gave the crude product as pale yellow oil. Dry CH_2Cl_2 (5 ml) and dry *m*-CPBA (173 mg, 1.0 mmol) were sequentially added to the crude product. The reaction mixture was stirred for 1 h. Work-up gave the crude product as pale yellow oil, which was purified by flash column chromatography (hexane/Et_2O 4/1) to give **9b** (360 mg, 83%) with 91% ee as colorless oil: *Rf* 0.49 (hexane/Et_2O 1/1). $[\alpha]_D^{22}$ −27.9 (*c*=0.855, $CHCl_3$). The ee was determined by HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH=9/1, 1.0 ml/min, 254 nm, major 10.6 and minor 17.9 min). ^{1}H-NMR δ: 1.02 (s, 3H), 1.04 (s, 3H), 1.10 (s, 3H), 1.13 (s, 3H), 2.236 (s, 3H), 2.242 (s, 3H), 2.47 (s, 6H), 4.14 (dd, *J*=5.2, 4.3, 1H), 4.97 (d, *J*=5.2, 1H), 5.21 (d, *J*=4.3, 1H), 6.78 (s, 2H), 6.91 (d, *J*=8.0, 2H), 6.98 (d, *J*=8.0, 2H). ^{13}C-NMR δ: 20.6 (CH_3), 20.9 (CH_3), 21.9 (CH_3), 22.0 (CH_3), 22.6 (CH_3), 23.6 (CH_3), 61.4 (CH), 82.7 (C), 82.8 (C), 100.8 (CH), 127.9 (CH), 128.4 (CH), 131.4 (CH), 133.0 (C), 134.0 (C), 137.3 (C), 139.0 (C), 141.8 (C). IR (KBr): 3331, 2978, 2926, 2870, 1604, 1516, 1445, 1391, 1379, 1369, 1335, 1217, 1186, 1155, 1123, 1057, 1020, 964, 903, 851, 814, 756, 658, 584. EI-MS (*m*/*z*): 432 (M^+), 129 ($C_7H_{13}O_2$), 119 (Mes), 101, 91, (tolyl), 83, 77. *Anal.* Calcd for $C_{24}H_{33}NO_4S$: C, 66.79; H, 7.71; N, 3.25. Found: C, 67.06; H, 7.82; N, 3.20.

(*R*)-2,4,6-Trimethyl-*N*-[(naphth-2-yl)(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methyl]benzenesulfonamide (9c) (Table 2, Entry 4) Carried out according to the general procedure using **4c** (321 mg, 1.0 mmol), **2** (18.3 ml, 125 mmol), $BF_3\cdot OEt_2$ (0.25 ml+0.25 ml+1.0 ml+1.0 ml, 12.0 mmol), and Me_2Zn (1.0 M in hexane; 6.0 ml+6.0 ml+12 ml+12 ml, 36 mmol). The reaction mixture stirred for 118 h. Work-up gave the crude product as pale yellow oil. Dry CH_2Cl_2 (5 ml) and dry *m*-CPBA (173 mg, 1.0 mmol) were sequentially added to the crude product. The reaction mixture was stirred for 1 h. Work-up gave the crude product as pale yellow oil, which was purified by flash column chromatography (hexane/Et_2O 3/1) to give **9c** with 92% ee (360 mg, 66%) as cream solid: *Rf* 0.40 (hexane/Et_2O 1/1). $[\alpha]_D^{22}$ −32.5 (*c*=1.01, $CHCl_3$). The ee was determined by HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH 9/1, 1.0 ml/min, 254 nm, major 14.0 and minor 20.6 min). ^{1}H-NMR δ: 1.05 (s, 3H), 1.08 (s, 3H), 1.12 (s, 3H), 1.15 (s, 3H), 2.05 (s, 3H), 2.43 (s, 6H), 4.40 (dd, *J*=4.9, 4.3, 1H), 5.11 (d, *J*=4.9, 1H), 5.33 (d, *J*=4.3, 1H), 6.60 (s, 2H), 7.24 (dd, *J*=8.9, 1.3, 1H), 7.38—7.41 (m, 2H), 7.44 (s, 1H), 7.56 (d, *J*=8.9, 1H), 7.59 (dd, *J*=6.0, 3.4, 1H), 7.71 (dd, *J*=6.0, 3.4, 1H). ^{13}C-NMR δ: 20.5 (CH_3), 22.0 (CH_3), 22.2 (CH_3), 22.7 (CH_3), 23.7 (CH_3), 23.8 (CH_3), 61.8 (CH), 82.9 (C), 83.0 (C), 100.9 (CH), 125.7 (CH), 125.8 (CH), 125.9 (CH), 127.4 (CH), 127.6 (CH), 127.9 (CH), 131.4 (CH), 132.8 (C), 133.0 (C), 133.2 (C), 134.2 (C), 138.9 (C), 141.9 (C). IR (KBr): 3314, 2974, 2934, 2860, 1605, 1560, 1508, 1458, 1393, 1383, 1367, 1331, 1151, 1120, 1076, 1057, 1022, 953, 897, 858, 812, 787, 748, 729, 660, 583. EI-MS (*m*/*z*): 338 ($M^+-C_7H_{13}O_2$), 284 (M^+-SO_2Mes), 240, 183 (SO_2Mes), 168, 155, 154, 141, 130, 129 ($C_7H_{13}O_2$), 127 ($C_{10}H_7$), 119, 115, 101, 91, 83, 77. FAB-MS (*m*/*z*): 466 ($M-H^+$). HR-MS-FAB (*m*/*z*): $[M-H]^-$ Calcd for $C_{27}H_{32}NO_4S$, 466.2052; Found, 466.2047.

Removal of the Sulfonyl Group of Adduct 9a: (*R*)-Phenyl(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methanamine (11). Method 1 NH_3 (15 ml) was condensed into a dry three-necked round-bottomed flask which was equipped with a magnetic stirrer bar under argon atmosphere, at −78 °C. To the colorless stirred solution was added Li metal (42.9 mg, 6.2 mmol) portionwise to give a blue solution. A solution of **9a** with 95% ee (83.4 mg, 0.20 mmol) in dry THF was added to the blue solution and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with NH_4Cl (0.128 mg, 2.4 mmol) and allowed to warm to room temperature. To the quenched mixture was added Et_2O followed by acidification with aqueous 10% HCl to give pH 1. Aqueous 2 N NaOH was added to the aqueous layer to give pH 10 and the mixture was extracted with Et_2O. The combined organic extracts were dried over K_2CO_3, filtered, and concentrated under reduced pressure to give the crude product as pale yellow oil, which was purified by flash column chromatography (hexane/EtOAc 3/2) to give **11** (39.5 mg, 84%,) with 94% ee as pale yellow oil: *Rf* 0.46 (hexane/EtOAc 1/1). $[\alpha]_D^{24}$ +15.3 (*c*=1.02, $CHCl_3$). The ee was determined by HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH=9/1, 1.0 ml/min, 254 nm, minor 5.0 min and major 6.4 min). ^{1}H-NMR δ: 1.16 (s, 6H), 1.18 (s, 3H), 1.20 (s, 3H), 1.64 (s, 2H), 3.89 (d, *J*=5.2, 1H), 5.03 (d, *J*=5.2, 1H), 7.26 (tt, *J*=1.3, 7.3, 1H), 7.33 (m, 2H), 7.40 (m, 2H). ^{13}C-NMR δ: 22.0 (CH_3), 22.1 (CH_3), 23.9 (CH_3), 24.0 (CH_3), 59.6 (CH), 82.0 (C), 82.1 (C), 103.1 (C), 127.3 (CH), 127.7 (CH), 128.1 (CH), 141.0 (C). IR (neat): 3387, 2978, 2932, 2870, 1604, 1450, 1373, 1157, 1118, 1011, 964, 880, 764, 702. EI-MS (*m*/*z*): 129 ($C_7H_{13}O_2$), 106 ($M^+-C_7H_{13}O_2$), 101, 85, 83, 77. *Anal.* Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.17; H, 8.81.; N, 5.87.

Method 2 In a 50 ml round-bottom flask, **9a** with 82% ee (108.4 mg, 0.26 mmol) and PhSMe (0.61 ml, 5.2 mmol) were dissolved in trifluoroacetic acid (TFA) (5.2 ml). To the solution cooled in an ice-water bath, was added Me_3SiBr (0.69 ml, 5.2 mmol). The cooling bath was removed and the resulting mixture was allowed to warm up to room temperature while being stirred. After 2.5 h TFA was removed *in vacuo* and aqueous saturated $NaHCO_3$ was added. The whole was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over K_2CO_3, and concentrated to give orange oil. Purification by column chromatography (hexane/EtOAc 2/1 then EtOAc) gave **11** (55.0 mg, 88%) with 82% ee as pale yellow oil.

Conversion of Adduct 10 into Amine 11 Carried out according to Method 1, using NH_3 (15 ml), Li metal (44.0 mg, 6.3 mmol), and **10** with 87% ee (100 mg, 0.20 mmol). The reaction mixture was stirred for 1 h. Work-up gave the crude product as pale yellow oil, which was purified by flash column chromatography (hexane/EtOAc 3/2) to give **11** (35.4 mg, 76%) with 87% ee as pale yellow oil.

Conversion of Amine 11 into Sulfonamide 3a To amine **11** with 92% ee (57.0 mg, 0.24 mmol), prepared from **9a** with 92% ee, in $CHCl_3$ (1 ml) were added aqueous saturated $NaHCO_3$ (1 ml) and TsCl (55.5 mg, 0.29 mmol) at room temperature. The mixture was stirred for 14 h at the same temperature, and then extracted with $CHCl_3$ (3×5 ml). Combined organic layers were dried over Na_2SO_4. Concentration followed by column chromatography (hexane/EtOAc 5/1) gave sulfonamide **3a** (74.4 mg, 80%) with 92% ee as white solid of mp 103—106 °C. The spectroscopic data, ^{1}H- and ^{13}C-NMR, IR, and MS, were identical to those reported.[41] The ee was determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH=9/1, 0.5 ml/min, 254 nm, major 21.3 min and minor 25.8 min). $[\alpha]_D^{25}$ −33.8 (*c*=1.03, $CHCl_3$). lit.[20]: $[\alpha]_D^{25}$ −32.6 (*c*=1.01, $CHCl_3$) for (*R*)-**3a** with 83% ee.

Reduction of the Acetal Moiety of 6a: (*R*)-*N*-(2-Hydroxy-1-phenylethyl)-2,4,6-trimethylbenzenesulfonamide $TiCl_4$ (0.18 ml, 1.6 mmol) was added dropwise to a stirred solution of **9a** with 92% ee (108 mg, 0.26 mmol) and Et_3SiH (0.64 ml, 4.0 mmol) in dry CH_2Cl_2 (0.4 ml) at 0 °C. The resulting mixture was stirred at the same temperature for 48 h and then at room temperature for 23 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (6 ml) followed by extraction with $CHCl_3$ (3×10 ml). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product as pale yellow oil, which was purified by flash column chromatography (hexane/EtOAc 7/3) to give the titled compound (46.0 mg, 55%) with 87% ee as white solid of mp 128—130 °C (lit.[42,43]: mp 131 °C, EtOAc–hexane): *Rf* 0.55 (hexane/EtOAc 1/1). $[\alpha]_D^{20}$ −67.2 (*c*=1.00, $CHCl_3$) (lit.[42]: $[\alpha]_D^{20}$ +77.6 (*c*=1.00, $CHCl_3$) for enantiomer). The ee was determined by HPLC (Daicel Chiralcel OG, hexane/*i*-PrOH 3/1, 0.5 ml/min, 254 nm, major 14.8 min and minor 18.6 min). ^{1}H-NMR spectrum agreed with that reported.[43] ^{13}C-NMR δ: 20.8 (CH_3), 22.7 (CH_3), 59.5 (CH), 66.0 (CH_2), 126.8 (CH), 127.9 (CH), 128.4 (CH), 131.8 (CH), 133.8 (C), 137.4 (C), 139.1 (C), 142.2 (C). IR (KBr): 3410, 3186, 2939, 1736, 1605, 1566, 1458, 1319, 1265, 1234, 1150, 1072, 1034, 956, 756, 702, 664. EI-MS (*m*/*z*): 288 (M^+-CH_2OH), 183 (SO_2Mes), 119 (Mes), 104, 91, 77 (Ph), 51. FAB-MS (*m*/*z*): 342 ($M+Na^+$). HR-MS-FAB (*m*/*z*): $[M+Na]^+$ Calcd for $C_{17}H_{21}NNaO_3S$, 342.1140; Found, 342.1143.

Acknowledgements This research was partially supported by a Grant-in-Aid for Young Scientist (B) and a Grant-in-Aid for Scientific Research (A) from the Japan Society for the Promotion of Science (JSPS); a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations" from the Ministry of Education, Culture, Sports, Science and Technology, Japan; and Targeted Protein Research Program from Japan Science and Technology Agency. T.A. and M.M. thank JSPS for fellowships.

References and Notes

1) Braese S., Baumann T., Dahmen S., Vogt H., *Chem. Commun.*, 1881—1890 (2007).
2) Hili R., Baktharaman S., Yudin A. K., *Eur. J. Org. Chem.*, 5201—5213 (2008).
3) Xu L.-W., Luo J., Lu Y., *Chem. Commun.*, 1807—1821 (2009).
4) "Radicals in Organic Synthesis," ed. by Renaud P., Sibi M. P., Wiley-VCH, Weinhem, 2001.
5) "Radicals in Synthesis I & II," ed. by Gansäuer A., Springer-Verlag, Berlin, Heidelberg, 2006.
6) Friestad G. K., *Tetrahedron*, **57**, 5461—5496 (2001).
7) Friestad G. K., Mathies A. K., *Tetrahedron*, **63**, 2541—2569 (2007).
8) Ellman J. A., Owens T. D., Tang T. P., *Acc. Chem. Res.*, **35**, 984—995 (2002).
9) Zhou P., Chen B.-C., Davis F. A., *Tetrahedron*, **60**, 8003—8030 (2004).
10) Senanayake C. H., Krishnamurthy D., Lu Z.-H., Han Z., Gallou I., *Aldrichim. Acta*, **38**, 93—104 (2005).
11) Davis F. A., Yang B., Deng J., Wu Y., Zhang Y., Rao A., Fang T., Goswami R., Prasad K. R., Nolt M. B., Anilkumar G., *Phosphorus, Sulfur Silicon, Relat. Elem.*, **180**, 1109—1117 (2005).
12) Davis F. A., Yang B., Deng J., Zhang J., *ARKIVOC*, **2006**, 120—128 (2006).
13) Morton D., Stockman R. A., *Tetrahedron*, **62**, 8869—8905 (2006).
14) Davis F. A., *J. Org. Chem.*, **71**, 8993—9003 (2006).
15) Lin G.-Q., Xu M.-H., Zhong Y.-U., Sun X.-W., *Acc. Chem. Res.*, **41**, 831—840 (2008).
16) Ferreira F., Botuha C., Chemla F., Pérez-Luma A., *Chem. Soc. Rev.*, **38**, 1162—1186 (2009).
17) Yamada K., Maekawa M., Akindele T., Yamamoto Y., Nakano M., Tomioka K., *Tetrahedron*, **65**, 903—908 (2008) and references cited therein.
18) Yamada K., Yamamoto Y., Tomioka K., *J. Synth. Org. Chem. Jpn.*, **62**, 1158—1165 (2004).
19) Akindele T., Yamada K., Tomioka K., *Acc. Chem. Res.*, **42**, 345—355 (2009).
20) Akindele T., Yamamoto Y., Maekawa M., Umeki H., Yamada K., Tomioka K., *Org. Lett.*, **8**, 5729—5732 (2006).
21) Acetal **2** was prepared according to reported procedure, see: Willy W. E., Binsch G., Eliel E. L., *J. Am. Chem. Soc.*, **92**, 5394—5402 (1970).
22) For reducing the amount of the acetal, see: Yamada K., Maekawa M., Yamamoto Y., Nakano M., Akindele T., Tomioka K., *Tetrahedron Lett.*, **50**, 6040—6043 (2009).
23) Davis F. A., Ramachandar T., Wu Y., *J. Org. Chem.*, **68**, 6894—6898 (2003).
24) Davis F. A., Song M., *Org. Lett.*, **9**, 2413—2416 (2007).
25) Han Z., Krisnamurthy D., Grover P., Fang Q. K., Pflum D. A., Senanayake C. H., *Tetrahedron Lett.*, **44**, 4195—4197 (2003).
26) Hayashi T., Kawai T., Tokunaga N., *Angew. Chem., Int. Ed.*, **43**, 6125—6128 (2004).
27) A mild and robust method for cleaving sulfonamides was reported during the preparation of this manuscript: Ankner T., Hilmersson G., *Org. Lett.*, **11**, 503—506 (2009).
28) Yajima H., Fujii N., Funakoshi S., Watanabe T., Murayama E., Otaka A., *Tetrahedron*, **44**, 805—819 (1988).
29) Pelter A., Ward R. S., Sirit A., *Tetrahedron: Asymmetry*, **5**, 1745—1762 (1994).
30) The final geometry optimization was performed using *Gaussian 03W*: Gaussian, Inc., Wallingford CT, 2004, for initial geometries generated by the conformational search using *Spartan '06*: Wavefunction, Inc. Irvine, CA. All the ground states were verified by vibrational frequency analysis.
31) Davis F. A., Reddy R. E., Szewczyk J. M., Reddy G. V., Portonovo P. S., Zhang H., Fanelli D., Reddy R. T., Zhou P., Carroll P. J., *J. Org. Chem.*, **62**, 2555—2563 (1997).
32) Dobrowolski J. Cz., Kawęcki R., *J. Mol. Struct.*, **734**, 235—239 (2005).
33) Bharatam P. V., Uppal P., Kaur A., Kaur D., *J. Chem. Soc., Perkin Trans. 2*, 43—50 (2000).
34) Tietze L. F., Schuffenhauer A., *Eur. J. Org. Chem.*, 1629—1637 (1998).
35) Tomioka K., Shioya Y., Nagaoka Y., Yamada K., *J. Org. Chem.*, **66**, 7051—7054 (2001).
36) Another possibility might be a reverse reaction due to lesser stability or a slower reaction with dimethylzinc of the sterically hindered intermediate aminyl radical derived from **5**.
37) Traylor T. G., Miksztal A. R., *J. Am. Chem. Soc.*, **109**, 2770—2774 (1987).
38) Han Z., Krishnamurthy D., Grover P., Fang Q. K., Senanayake C. H., *J. Am. Chem. Soc.*, **124**, 7880—7881 (2002).
39) Ramachandar T., Wu Y., Zhang J., Davis F. A., *Org. Synth.*, **83**, 131—140 (2006).
40) Davis F. A., Zhang Y., Andemichael Y., Fang T., Fanelli D. L., Zhang H., *J. Org. Chem.*, **64**, 1403—1406 (1999).
41) Yamada K., Yamamoto Y., Maekawa M., Tomioka K., *J. Org. Chem.*, **69**, 1531—1534 (2004).
42) Hope I., Hoffmann H., Gärtner I., Krettek T., Hoppe D., *Synthesis*, 1157—1162 (1991).
43) Gaul C., Schärer K., Seebach D., *J. Org. Chem.*, **66**, 3059—3073 (2001).