1,4-Asymmetric reduction of γ-keto sulfoxides bearing the 2,4,6-triisopropylphenyl group

Shuichi Nakamura, Masayuki Kuroyanagi, Yoshihiko Watanabe and Takeshi Toru

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

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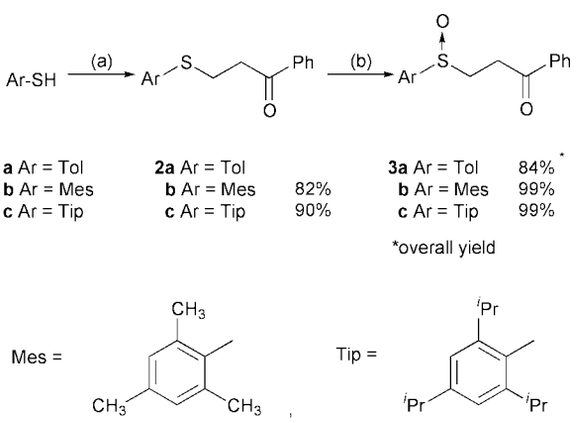
Reduction of γ-keto sulfoxides bearing the 2,4,6-triisopropylphenyl group with DIBAL gives γ-hydroxy sulfoxides with high stereoselectivity in the ratio 95:5. In comparison with the lower stereoselectivities obtained in the reaction of γ-keto sulfoxides bearing *p*-tolyl or 2,4,6-trimethylphenyl groups, the sterically bulky (2,4,6-triisopropylphenyl)-sulfinyl group is extremely efficient in effecting high 1,4-remote asymmetric induction.

Introduction

Asymmetric induction at a site remote from a chiral auxiliary or a chiral center is one of the most challenging problems in synthetic chemistry to be solved.[1] The carbonyl-face-selective reactions of β-keto sulfoxides have been intensively studied.[2,3] In particular, the reduction of β-keto sulfoxides with diisobutylaluminium hydride (DIBAL) shows an interesting aspect, giving β-hydroxy sulfoxides with high diastereoselectivity.[2] The diastereoselective outcome in the reduction with DIBAL is derived from intramolecular hydride transfer through a six-membered cyclic transition state, whereas the DIBAL reduction in the presence of a Lewis acid gives the product with reversed stereochemistry, which is rationalized by a conformationally rigid six-membered cyclic intermediate involving chelation of a Lewis acid with the sulfinyl and carbonyl oxygens. It would be interesting to establish the highly stereoselective asymmetric reduction of ketones remote by one more carbon from the sulfinyl group, *i.e.* γ-keto sulfoxides,[4,5] because the conformationally flexible and unstable seven-membered cyclic structure would make it difficult to obtain high stereoselectivity. Indeed, Solladié *et al.* have reported that the reduction of γ-keto sulfoxides with DIBAL proceeds with moderate diastereoselectivity without Lewis acids and gives the product with the reversed diastereoselectivity when carried out in the presence of $Yb(OTf)_3$.[5] These results encouraged us to examine the stereochemical effect of a sterically bulky substituent on the sulfur in the reduction of γ-keto sulfoxides. Recently, we reported the high efficiency of the bulky (2,4,6-triisopropylphenyl)sulfinyl group as a chiral auxiliary in the radical β-addition to 2-sulfinylcyclopent-2-enones[6,7] and in the Grignard reaction to 1-sulfinyl-2-naphthaldehydes.[8] These reactions proceed with high stereoselectivity by complete blocking of the side opposite to the reaction site by the bulky 2,4,6-triisopropylphenyl group. These successful asymmetric inductions rely on our newly developed and efficient method for the preparation of the optically active diacetone-D-glucosyl 2,4,6-triisopropylbenzenesulfinate, from which the chiral (2,4,6-triisopropylphenyl) sulfoxides can be easily prepared.[7,9] We now report highly diastereoselective reduction of γ-keto sulfoxides having a sterically bulky aryl group.

Results and discussion

We first examined the selectivity in the reduction of racemic 3-(*p*-tolylsulfinyl)-, 3-[(2,4,6-trimethylphenyl)sulfinyl]- and 3-[(2,4,6-triisopropylphenyl)sulfinyl]-propiophenone **3a–c** (Scheme 1). The sulfides **2a–c** were prepared by treatment of the corresponding thiols **1a–c** with 3-chloro-1-phenylpropan-1-one in the presence of 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU) at room temperature. The sulfides **2a–c** were oxidized with MCPBA to give the 3-(arylsulfinyl)propiophenones **3a–c** in high yields.

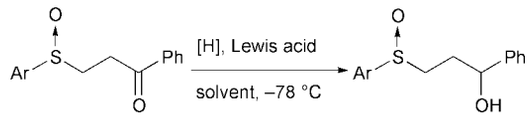


Scheme 1 *Reagents and conditions*: (a) 3-chloro-1-phenylpropan-1-one, DBU, benzene, rt; (b) MCPBA, CH_2Cl_2, −78 to −30 °C.

The carbonyl reduction of the 3-(arylsulfinyl)propiophenones **3a–c** with various reducing reagents without or in the presence of Lewis acids was next examined. The results are summarized in Table 1.

The reduction of **3a** (Ar = *p*-Tol) and **3b** (Ar = 2,4,6-trimethylphenyl) with DIBAL proceeded with moderate diastereoselectivity at −78 °C in THF to afford the alcohols **4a** and **4b** (entries 1 and 2). The DIBAL reduction of 3-[(2,4,6-triisopropylphenyl)sulfinyl]propiophenone **3c** proceeded with high stereoselectivity to give the γ-hydroxy sulfoxide **4c** in the ratio 97:3 at −78 °C and 93:7 at −105 °C, favoring the (S_S*,*S**)-isomer (entries 3 and 4). The reduction of **4c** with other reducing agents such as $LiAlH_4$, L-Selectride® and $NaBH_4$ gave the product **4c** with lower stereoselectivity (entries 5–8). The stereoselectivity in the DIBAL reduction of **3c** in the presence of $ZnCl_2$ or $Yb(OTf)_3$ in either THF or CH_2Cl_2 was reduced, but not reversed (entries 9–12), although Solladié *et al.* have shown that the reduction of the *p*-tolyl γ-keto sulfoxide with $Yb(OTf)_3$ affords the product having the opposite configuration as a major product.[5] The weak effect of Lewis acids on the stereoselectivity in the reduction of **3c** would be ascribed

Table 1 Stereoselective reduction of 3-(arylsulfinyl)propiophenones **3a**–**c**[a]



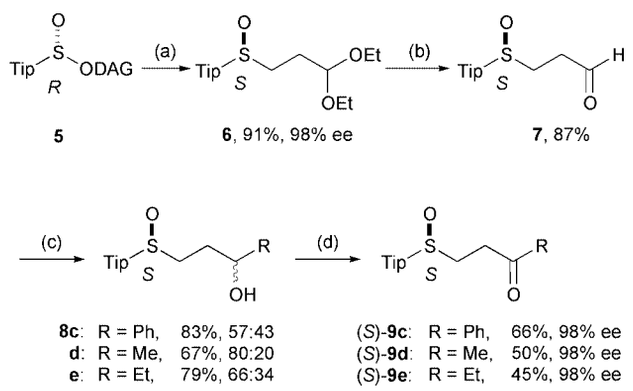
rac-**3**
3a Ar = Tol
b Ar = Mes
c Ar = Tip

rac-**4**
4a Ar = Tol
b Ar = Mes
c Ar = Tip

Entry	Substrate **3**	Solvent	Reducing agent	Lewis acid	Yield of product **4** (%)	Diastereomer ratio (S_S*,*S**):(S_S*,*R**)
1	**3a**	THF	DIBAL		98	86:14[b]
2	**3b**	THF	DIBAL		99	92:8
3	**3c**	THF	DIBAL		90	97:3
4	**3c**	THF	DIBAL[c]		31	93:7
5	**3c**	THF	$LiAlH_4$		88	74:26
6	**3c**	THF	L-Selectride®		89	70:30
7	**3c**	THF	$NaBH_4$		52	50:50
8	**3c**	EtOH	$NaBH_4$		80	51:49
9	**3c**	THF	DIBAL	$ZnCl_2$	30	80:20
10	**3c**	THF	DIBAL	$Yb(OTf)_3$[d]	31	55:45
11	**3c**	CH_2Cl_2	DIBAL		96	74:26
12	**3c**	CH_2Cl_2	DIBAL	$Yb(OTf)_3$	90	74:26

[a] Reaction was carried out at −78 °C unless otherwise noted. [b] Reduction of 4-(*p*-tolyl)butan-2-one with DIBAL has been reported to give the butan-2-ol product in the ratio 80:20.[4c] [c] Reaction was carried out at −105 °C. [d] $Yb(OTf)_3$ (2.0 equiv.) was used.

to an incompletely chelated intermediate bearing the bulky (2,4,6-triisopropylphenyl)sulfinyl group. Having established a high diastereoselection in the reaction of **3c**, we examined the chiral sulfoxides. In order to prepare the chiral sulfoxides, we first tried the Sharpless oxidation[10] of the sulfide **2c**, resulting in low yield and low enantioselectivity. The chiral sulfoxides were successfully prepared *via* the chiral sulfinates (Scheme 2).

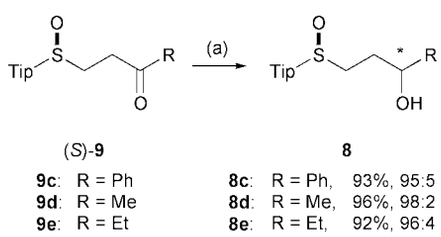


Scheme 2 *Reagents and conditions*: (a) $(EtO)_2CHCH_2CH_2MgBr$, THF, −78 °C, 1 h; (b) 50% TFA, $CHCl_3$, 0 °C, 12 h; (c) RMgX, THF, −78 °C; (d) PCC, CH_2Cl_2, rt.

Treatment of (R_S)-diacetone-D-glucosyl 2,4,6-triisopropylbenzenesulfinate[7,9] **5** with 3,3-diethoxypropylmagnesium bromide furnished the sulfinyl acetal **6**, which was converted to the aldehyde **7** on treatment with 50% TFA. Aldehyde **7** was then allowed to react with PhMgBr, MeMgI and EtMgBr to give the alcohols **8c**–**e**, respectively, as a diastereomeric mixture. Finally, **8c**–**e** were oxidized by pyridinium chlorochromate (PCC) to give ketones (*S*)-**9c**–**e** with 98% ees, completing the synthesis of the substrates required for the stereoselective reduction study.

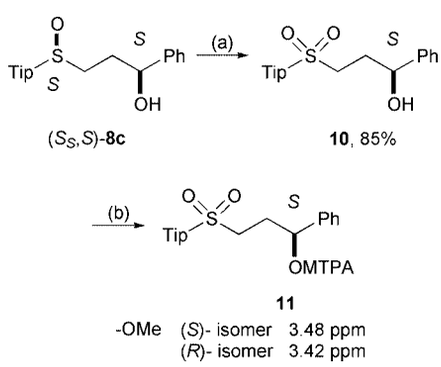
Reduction of (*S*)-**9c**–**e** with DIBAL at −78 °C in THF gave the γ-hydroxy sulfoxides **8c**–**e** in 92–96% yield with high stereoselectivity (Scheme 3).

High stereoselectivity was obtained in the reaction of all γ-keto sulfoxides **9c**–**e** irrespective of the substituent (R)



Scheme 3 *Reagents and conditions*: (a) DIBAL, THF, −78 °C.

attached to the carbonyl group, showing very weak steric or electronic effects of these substituents on the stereoselectivity. The absolute configuration of **8c** was determined by the ^1H NMR spectral behavior of the (*R*)-MTPA ester[11] of the sulfone **10** prepared on treatment of the sulfoxide (S_S,*S*)-**8c** with MCPBA, followed by acylation (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) MCPBA, CH_2Cl_2, rt; (b) DCC, (*R*)-MTPA, DMAP, CH_2Cl_2, rt.

The correlation between the configuration of the carbonyloxy methine carbon and the upfield shift of the methylene protons in the ^1H NMR spectra of the MTPA esters has been established. We, however, failed to assign the configuration of our products owing to the complicated methylene proton signals of the minor isomer in the ^1H NMR spectrum ($CDCl_3$) of **11**. Instead, we observed that the signal due to the methoxy protons appeared at δ 3.48 in the major isomer and at δ 3.42 in

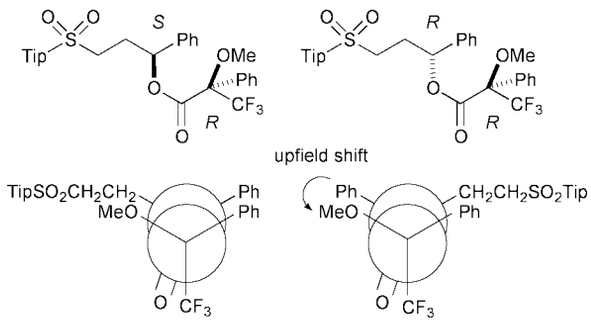
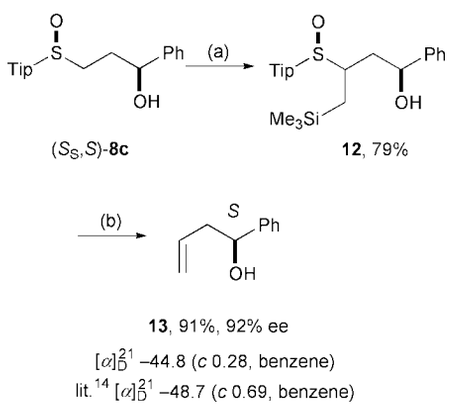


Fig. 1 ^{1}H NMR spectral behavior of the (*R*)-MTPA ester **11**.

the minor isomer. According to the established configuration–correlation model shown in Fig. 1, we assigned the configuration of the minor isomer to be *R* due to the upfield shift of the methoxy proton signal relative to the signal in the major isomer caused by the anisotropic effect of the phenyl group.

The stereochemistry of **8c** was further confirmed by its conversion to the known homoallyl alcohol **13**[12] (Scheme 5).



Scheme 5 *Reagents and conditions*: (a) i, LDA, THF, −78 °C; ii, $ICH_2Si(CH_3)_3$, −78 °C to rt; (b) TBAF, THF, rt.

Treatment of a diastereomeric mixture of **8c** with LDA (2.2 equiv.) and (iodomethyl)trimethylsilane gave the β-silyl sulfoxide **12**.[13] The sulfoxide **12** was allowed to react with a THF solution of tetrabutylammonium fluoride (TBAF) to afford a 91% yield of the homoallyl alcohol **13**, the (*S*)-configuration and the optical purity (92% ee) of which were determined by comparison of the $[\alpha]_D$-value with that reported in the literature.[14]

The high stereoselectivity, which is not much affected by the substituents attached to the carbonyl group, in the reduction of the γ-keto sulfoxide (*S*)-**9** with DIBAL, would be ascribed to a cyclic transition state as depicted in Fig. 2.

Since a chair-like 7-membered transition state, giving the (*R*)-isomer, would be less stable than a twisted-chair transition state, we assumed the presence of a twisted-chair transition state involving a trigonal bipyramidal structure.[15] The bulky triisopropylphenyl group is placed at the pseudoequatorial position and it may fix the cyclic transition state more efficiently than the *p*-tolyl and mesityl groups. The reduction would preferably occur from the *re* face of the carbonyl.

In summary, the bulky (2,4,6-triisopropylphenyl)sulfinyl group has been demonstrated to be a powerful chiral inducer in the stereoselective reduction of γ-keto sulfoxides. This efficient 1,4-remote asymmetric reduction is based on the availability of the chiral γ-keto sulfoxides.

Experimental

General

All reactions were performed in oven- and flame-dried glassware under a positive pressure of argon. Air- and moisture-sensitive reagents and solvents were transferred *via* syringe or

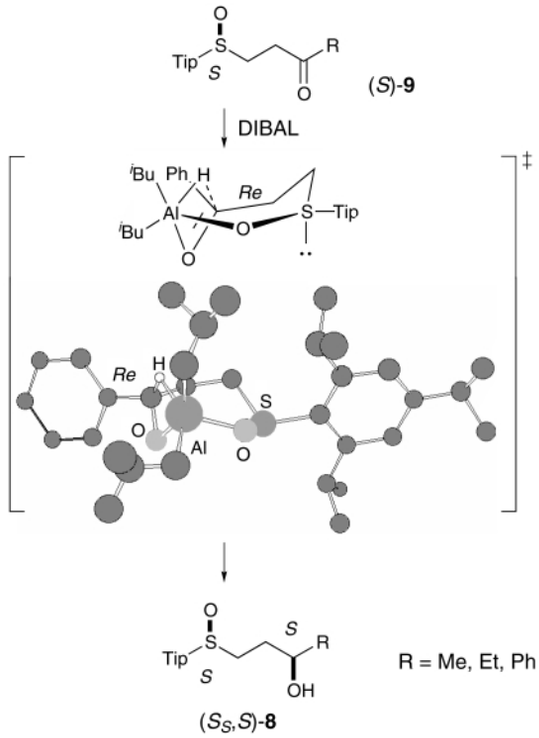


Fig. 2 Assumed transition state in reduction of sulfinyl ketones (*S*)-**9** with DIBAL.

cannula, and were introduced into the reaction vessels through a rubber septum. Diethyl ether and THF were distilled from sodium–benzophenone under a nitrogen atmosphere before use (deep blue solution: ketyl from benzophenone and sodium). CH_2Cl_2 was distilled from calcium hydride. All reactions were monitored by TLC carried out on 0.25 mm Merck silica gel plates (60f-254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid or *p*-anisaldehyde in ethanol, followed by heating. Column chromatography was carried out on a column packed with Fuji Silysia silica gel BW-200. ^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra for solutions in $CDCl_3$ were recorded on a Varian Gemini-200. Chemical shifts (δ) are expressed in ppm downfield from internal tetramethylsilane or $CHCl_3$, and *J*-values are given in Hz. IR spectra were recorded on a JASCO A-102 or a JASCO FT/IR-200 spectrometer. Mass spectra (eV) were recorded on a Hitachi M-2000 spectrometer. Microanalyses were performed with a Perkin-Elmer 240. Optical rotations were measured on a JASCO DIP-4 polarimeter operating at $\lambda = 589$ nm corresponding to the sodium D-line, in the indicated solvent and concentration in grams of solute per 100 mL. $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}. HPLC analyses were performed on a JASCO TRI ROTOR IV using 4.6 × 250 mm COSMOSIL, CHIRALCEL OD-H and CHIRALPAC AD packed columns.

Preparation of 3-(arylsulfinyl)propiophenones

1-Phenyl-3-(*p*-tolylsulfanyl)propan-1-one 2a. To a solution of toluene-*p*-thiol **1a** (203.5 mg, 1.64 mmol) in benzene (5.0 mL) was added DBU (0.27 mL, 1.80 mmol) at room temperature and the mixture was stirred for 10 min. A solution of 3-chloro-1-phenylpropan-1-one (304 mg, 1.80 mmol) in benzene (1.8 mL) was then added. After stirring for 5 h, the reaction mixture was concentrated under reduced pressure to give the crude product. Since product **2a** could not be separated from 3-chloro-1-phenylpropan-1-one by column chromatography (silica gel 10 g; hexane–ethyl acetate 90 : 10), the crude product was used without further purification for the next oxidation.

1-Phenyl-3-[(2,4,6-trimethylphenyl)sulfanylpropan-1-one 2b. The reaction was carried out as described above except using 2,4,6-trimethylbenzenethiol **1b** (1.15 g, 7.54 mmol), DBU (1.25 mL, 8.34 mmol) and 3-chloro-1-phenylpropan-1-one (1.41 g, 8.34 mmol). Usual work-up gave the crude product, which was purified by column chromatography (silica gel 30 g; hexane–ethyl acetate 90:10) to afford **2b** (1.74 g, 82%) (Found: C, 76.01; H, 7.09. $C_{18}H_{20}OS$ requires C, 76.22; H, 6.99%); R_f 0.24 (hexane–ethyl acetate 90:10); ν_{max}(neat) 2980, 1710, 1070, 950 cm^{-1}; δ_H 2.26 (s, 3H, ArCH_3), 2.51 (s, 6H, ArCH_3), 3.02 (ddd, 2H, *J* 6.3, 6.5 and 9.5, SCH_2), 3.17 (ddd, 2H, *J* 6.3, 6.5 and 9.5, $COCH_2$), 6.93 (s, 2H, ArH), 7.40–7.60 (m, 3H, ArH) 7.85–7.95 (m, 2H, ArH); *m*/*z* (EI) 284 (M^+, 100%), 207 (60), 179 (40), 133 (52).

1-Phenyl-3-[(2,4,6-triisopropylphenyl)sulfanyl]propan-1-one 2c. The reaction was carried out as described above except using 2,4,6-triisopropylbenzenethiol **1c** (1.10 g, 4.65 mmol), DBU (0.70 mL, 4.65 mmol) and 3-chloro-1-phenylpropan-1-one (713 mg, 4.22 mmol). Usual work-up gave the crude product, which was purified by column chromatography (silica gel 50 g; hexane–ethyl acetate 97:3) to afford **2c** (1.40 g, 90%) (Found: C, 78.21; H, 8.75. $C_{24}H_{32}OS$ requires C, 78.07; H, 8.89%); R_f 0.45 (hexane–ethyl acetate 90:10); ν_{max}(neat) 2970, 1710, 1300, 1070, 940 cm^{-1}; δ_H 1.25 [d, 18H, *J* 6.9, CH(CH_3)$_2$], 2.90 [hep, 1H, *J* 6.9, CH(CH$_3$)$_2$], 3.00 (t, 2H, *J* 7.1, SCH_2), 3.20 (t, 2H, *J* 7.1, $COCH_2$), 3.90 [hep, 2H, *J* 6.9, CH(CH$_3$)$_2$], 7.10 (s, 2H, ArH), 7.40–7.65 (m, 3H, ArH), 7.85–7.95 (m, 2H, ArH); *m*/*z* (EI) 368 (M^+, 42%), 236 (54), 203 (100).

1-Phenyl-3-(*p*-tolylsulfinyl)propan-1-one 3a. To a solution of the contaminated **2a** (419 mg) in CH_2Cl_2 (8.2 mL) was added MCPBA (421 mg, 2.44 mmol) at −78 °C. The mixture was warmed to −30 °C and stirred for 4 h. Saturated aq. Na_2SO_3 (10 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed successively with saturated aq. Na_2CO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave a solid, which was purified by column chromatography (silica gel 20 g; hexane–ethyl acetate 60:40) to afford **3a** (346 mg, 84% on the basis of toluene-*p*-thiol) (Found: C, 70.56; H, 5.92. $C_{16}H_{16}O_2S$ requires C, 70.54; H, 5.91%); mp 102–103 °C; R_f 0.28 (hexane–ethyl acetate 50:50); ν_{max}(KBr) 3050, 2930, 1680, 1590, 1410, 1350, 1050, 970, 740 cm^{-1}; δ_H 2.42 (s, 3H, ArCH_3), 3.00–3.60 (m, 4H, SCH_2 and $COCH_2$), 7.30–7.60 (m, 7H, ArH), 7.90–7.95 (m, 2H, ArH); δ_C 21.3, 30.3, 50.7, 123.9, 128.0, 128.6, 129.9, 133.5, 136.1, 140.0, 141.5, 196.9; *m*/*z* (EI) 272 (M^+, 0.2%), 132 (50), 105 (100).

1-Phenyl-3-[(2,4,6-trimethylphenyl)sulfinyl]propan-1-one 3b. The reaction was carried out as described above except using **2b** (735 mg, 2.59 mmol) and MCPBA (672 mg, 3.88 mmol). Usual work-up gave a solid, which was purified by column chromatography (silica gel 30 g; hexane–ethyl acetate 60:40) to afford **3b** (729 mg, 99%) (Found: C, 71.97; H, 6.71. $C_{18}H_{20}O_2S$ requires C, 71.91; H, 6.76%); R_f 0.32 (hexane–ethyl acetate 50:50); ν_{max}(KBr) 2930, 1680, 1450, 1380, 1230, 1060, 970, 850, 770 cm^{-1}; δ_H 2.29 (s, 3H, ArCH_3), 2.58 (s, 6H, ArCH_3), 3.20–3.40 (m 1H, SCH), 3.50–3.65 (m, 3H, SCH and $COCH_2$), 6.87 (s, 2H, ArH), 7.40–7.60 (m, 3H, ArH), 7.95–8.00 (m, 2H, ArH); δ_C 19.1, 21.0, 32.6, 46.5, 127.8, 128.1, 128.8, 131.0, 133.6, 136.2, 138.2, 141.2, 197.0; *m*/*z* (EI) 300 (M^+, 10%), 168 (70), 105 (100).

1-Phenyl-3-[(2,4,6-triisopropylphenyl)sulfinyl]propan-1-one 3c. The reaction was carried out as described above except using **2c** (156 mg, 0.423 mmol) and MCPBA (116 mg, 0.635 mmol). Usual work-up gave the crude product, which was purified by column chromatography (silica gel 10 g; hexane–ethyl acetate 80:20) to afford **3c** (161.5 mg, 99%) (Found: C, 74.96; H, 8.39. $C_{24}H_{32}O_2S$ requires C, 74.82; H, 8.53%); R_f 0.35 (hexane–ethyl acetate 70:30); ν_{max}(neat) 2970, 2920, 1685, 1460, 1360, 1050 cm^{-1}; δ_H 1.25 [d, 18H, *J* 6.9, CH(CH_3)$_2$], 2.90 [hep, 1H, *J* 6.9, CH(CH$_3$)$_2$], 3.20–3.30 (m, 1H, SCH), 3.50–3.75 (m, 3H, SCH and $COCH_2$), 3.80–4.10 [br, 2H, CH(CH$_3$)$_2$], 7.10 (s, 2H, ArH), 7.40–7.65 (m, 3H, ArH), 7.95–8.05 (m, 2H, ArH); δ_C 23.8, 24.3, 24.7, 28.1, 33.1, 34.3, 48.3, 123.1, 128.1, 128.7, 133.6, 134.0, 136.2, 152.2, 196.9; *m*/*z* (EI) 384 (M^+, 1%), 252 (90), 149 (80), 105 (100%).

Stereoselective reduction of 3-(arylsulfinyl)propiophenones 3a–c

For the detailed experimental procedures, see the stereoselective reduction of **9c–e** described below.

Preparation of chiral γ-keto sulfoxides

(*S*)-1,1-Diethoxy-3-[(2,4,6-triisopropylphenyl)sulfinyl]propane 6. A THF (5 mL) solution of 3,3-diethoxypropylmagnesium bromide, prepared from 3-bromo-1,1-diethoxypropane (1.04 g, 4.93 mmol) and magnesium (144 mg, 5.92 mg-atom), was slowly added to a THF (20 mL) solution of (*R*)-(−)-diacetone-D-glucosyl 2,4,6-triisopropylbenzenesulfinate[6,8] **5** (2.09 g, 4.09 mmol) at −78 °C, and the mixture was stirred for 1 h, quenched with saturated aq. NH_4Cl (10 mL), and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave an oil, which was purified by column chromatography (silica gel 50 g; hexane–ethyl acetate 85:15) to afford **6** (1.42 g, 91%, 98% ee) (Found: C, 69.06; H, 10.01. $C_{22}H_{38}O_3S$ requires C, 69.01; H, 10.10%); $[\alpha]_D^{19}$ −80.4 (*c* 0.60, $CHCl_3$); HPLC (CHIRALPAC AD, hexane–Pr^{i}OH 97:3, flow rate 0.5 mL min^{-1}) t_R 36.0 (*S*) and 47.8 min (*R*); R_f 0.37 (hexane–ethyl acetate 70:30); ν_{max}(neat) 2950, 1460, 1360, 1250, 1020 cm^{-1}; δ_H 1.25 [d, 18H, *J* 6.9, CH(CH_3)$_2$], 1.27 (t, 6H, *J* 7.0, CH_2CH_3), 1.90–2.30 (m, 4H, CH_2), 2.80–3.00 [m, 2H, CH(CH$_3$)$_2$ and SOCH], 3.35–3.70 (m, 3H, OCH_2 and SOCH), 3.70–4.10 [br, 2H, CH(CH$_3$)$_2$], 4.66 (t, 1H, *J* 5.3, OCH), 7.07 (s, 2H, ArH); δ_C 15.3, 23.7, 24.3, 24.6, 28.0, 28.6, 34.3, 49.5, 61.7, 61.9, 101.3, 134.2, 152.2; *m*/*z* (EI) 382 (M^+, 12%), 234 (100).

(*S*)-3-[(2,4,6-Triisopropylphenyl)sulfinyl]propanal 7. To a solution of **6** (140 mg, 0.366 mmol) in $CHCl_3$ (0.5 mL) was added 50% trifluoroacetic acid (0.5 mL) at 0 °C. The mixture was stirred for 12 h. Saturated aq. Na_2CO_3 was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave an oil, which was purified by column chromatography (silica gel 5 g, hexane–ethyl acetate 70:30) to afford **7** (98 mg, 87%) (Found: C, 70.09; H, 9.15. $C_{18}H_{28}O_2S$ requires C, 70.10; H, 9.10%); $[\alpha]_D^{20}$ −122.6 (*c* 0.70, $CHCl_3$); R_f 0.16 (hexane–ethyl acetate 70:30); ν_{max}(KBr) 2950, 1650, 1080, 990 cm^{-1}; δ_H 1.25 [d, 18H, *J* 6.9, CH(CH_3)$_2$], 2.90 [hep, 1H, *J* 6.9, CH(CH$_3$)$_2$], 3.00–3.20 (m, 3H, CH(CH$_3$)$_2$ and SOCH), 3.50–3.60 (m, 1H, SOCH), 3.80–4.10 [br, 2H, CH(CH$_3$)$_2$], 7.10 (s, 2H, ArH), 9.90 (s, 1H, CHO); δ_C 23.7, 24.1, 24.2, 24.5, 28.0, 34.2, 38.2, 46.2, 123.1, 133.6, 152.6, 198.4; *m*/*z* (EI) 308 (M^+, 0.2%), 235 (100), 151 (50).

(S_S,*S*)- and (S_S,*R*)-1-Phenyl-3-[(2,4,6-triisopropylphenyl)-sulfinyl]propan-1-ols 8c. To a solution of **7** (293 mg, 0.950 mmol) in THF (3.0 mL) was added PhMgBr (1.48 mol L^{-1} solution in THF, 1.0 mL, 1.48 mmol) at −78 °C. The reaction mixture was then slowly warmed to −20 °C over a period of 1 h. Usual work-up gave the crude product, which was purified by column chromatography (silica gel 30 g; hexane–ethyl acetate 60:40) to give **8c** (304 mg, 83%). The (S_S*,*S**):(S_S*,*R**) diastereomer ratio was determined to be 57:43 by HPLC analysis.

(*S*)-4-[(2,4,6-Triisopropylphenyl)sulfinyl]butan-2-ol 8d. The reaction was carried out as described above except using **7** (104

mg, 0.336 mmol) and MeMgI (0.96 mol L^{-1} solution in Et_2O; 0.55 mL, 0.528 mmol). Usual work-up gave the crude product, which was purified by column chromatography (hexane–ethyl acetate 50:50) to afford **8d** (73 mg, 67%). The (S_S*,S*):(S_S*,R*) diastereomer ratio was determined to be 80:20 by HPLC analysis.

(*S*)-1-[(2,4,6-Triisopropylphenyl)sulfinyl]pentan-3-ol 8e. The reaction was carried out as described above except using **7** (98 mg, 0.318 mmol) and EtMgBr (0.88 mol L^{-1} solution in Et_2O, 0.60 mL, 0.528 mmol). Usual work-up gave the crude product, which was purified by column chromatography (hexane–ethyl acetate 70:30) to afford **8e** (85 mg, 79%). The (S_S*,S*):(S_S*,R*) diastereomer ratio was determined to be 66:34 by HPLC analysis.

(*S*)-1-Phenyl-3-[(2,4,6-triisopropylphenyl)sulfinyl]propan-1-one 9c. To a CH_2Cl_2 (1.0 mL) solution of PCC (254 mg, 1.18 mmol) was added a solution of **8c** (304 mg, 0.787 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. After stirring of the mixture for 2 h, Et_2O was added and the supernatant decanted from the black gum. The insoluble residue was washed thoroughly with Et_2O. The ethereal solution was concentrated under reduced pressure to leave a residue, which was purified by column chromatography (silica gel 30 g; hexane–ethyl acetate 80:20) to afford **9c** (200 mg, 66%, 98% ee). HPLC (CHIRALPAC AD hexane–^{i}PrOH 95:5, flow rate 0.5 mL min^{-1}) t_R 30.9 (*R*) and 33.3 min (*S*); $[\alpha]_D^{20}$ −107.4 (*c* 0.486, $CHCl_3$).

(*S*)-4-[(2,4,6-Triisopropylphenyl)sulfinyl]butan-2-one 9d. The reaction was carried out as described above except using PCC (72 mg, 0.336 mmol) and **8d** (73 mg, 0.224 mmol). Usual work-up gave the crude product, which was purified by column chromatography (hexane–ethyl acetate 70:30) to afford **8d** (36 mg, 50%, 98% ee) (Found: C, 70.76; H, 9.38. $C_{19}H_{30}O_2S$ requires C, 70.73; H, 9.40%); mp 104–105 °C; $[\alpha]_D^{20}$ −97.6 (*c* 0.117, $CHCl_3$); HPLC (CHIRALCEL OD-H, hexane–Pr^{i}OH 95:5, flow rate 0.5 mL min^{-1}) t_R 14.4 (*S*) and 16.7 min (*R*); R_f 0.43 (hexane–ethyl acetate 50:50); ν_{max}(neat) 2960, 2860, 1710, 1600, 1460, 1360, 1180, 1050, 1030 cm^{-1}; δ_H 1.25 [d, 18H, *J* 6.9, CH(CH_3)$_2$], 2.24 (s, 3H, $COCH_3$), 2.90 [hep, 1H, *J* 6.9, C*H*(CH_3)$_2$], 3.00–3.20 (m, 3H, $COCH_2$ and SOCH), 3.40–3.60 (m, 1H, SOCH), 3.80–4.10 [br, 2H, C*H*(CH_3)$_2$], 7.08 (s, 2H, ArH); δ_C 23.7, 24.2, 24.5, 24.6, 28.0, 30.0, 34.3, 37.6, 47.8, 123.1, 123.2, 133.9, 152.5, 205.3; *m*/*z* (EI) 322 (M^+, 2%), 255 (100), 149 (90).

(*S*)-1-[(2,4,6-Triisopropylphenyl)sulfinyl]pentan-3-one 9e. The reaction was carried out as described above except using PCC (40 mg, 0.167 mmol) and **8e** (38 mg, 0.111 mmol). Usual work-up gave the crude product, which was purified by column chromatography (hexane–Et_2O 90:10) to afford **9e** (17 mg, 45%, 98% ee); $[\alpha]_D^{20}$ −100.4 (*c* 0.120, $CHCl_3$); HPLC (CHIRALPAC AD, hexane–^{i}PrOH 95:5, flow rate 0.5 mL min^{-1}) t_R 20.9 (*S*) and 24.1 min (*R*) (Found: C, 71.38; H, 9.58. $C_{20}H_{32}O_2S$ requires C, 71.45; H, 9.50%); R_f 0.27 (hexane–ethyl acetate 70:30); ν_{max}(neat) 2960, 1710, 1460, 1360, 1080, 970 cm^{-1}; δ_H 1.10 (t, 3H, *J* 7.4, CH_3), 1.25 [d, 18H, *J* 6.9, CH(CH_3)$_2$], 2.50 (q, 2H, *J* 7.4, CH_2), 2.90 [hep, 1H, *J* 6.9, C*H*(CH_3)$_2$], 2.95–3.10 (m, 3H, $COCH_2$ and SOCH), 3.45–3.60 (m, 1H, SOCH), 3.80–4.10 [br, 2H, C*H*(CH_3)$_2$], 7.08 (s, 2H, ArH); *m*/*z* (EI) 336 (M^+, 0.2%), 252 (100), 233 (48), 149 (45).

Stereoselective reduction of chiral γ-keto sulfoxides 9c–e with DIBAL

(*S*)-1-Phenyl-3-[(2,4,6-triisopropylphenyl)sulfinyl]propan-1-ol 8c. To a solution of **9c** (12.5 mg, 0.032 mmol) in THF (0.16 mL) was added DIBAL (0.95 mol L^{-1} solution in hexane, 0.05 mL, 0.049 mmol) at −78 °C. After stirring of the mixture for 1 h, MeOH (1.0 mL) was added. Usual work-up gave the crude product which was purified by column chromatography (silica gel 1 g; hexane–ethyl acetate 70:30) to afford **8c** (12 mg, 93%). The (S_S,S):(S_S,R) diastereomer ratio was determined to be 95:5 by HPLC analysis (Found: C, 74.57; H, 8.86. $C_{24}H_{34}O_2S$ requires C, 74.47; H, 8.96%); HPLC (COSMOSIL, hexane–^{i}PrOH 93:7, flow rate 1.0 mL min^{-1}) t_R 15.1 (S_S,S) and 18.7 min (S_S,R); R_f 0.13 (hexane–ethyl acetate 70:30); ν_{max}(neat) 3450, 3000, 1680, 1080 cm^{-1}; δ_H 1.25 [d, 18H, *J* 6.9, CH(CH_3)$_2$], 2.20–2.50 (m, 2H, CH_2), 2.80 [hep, 1H, *J* 6.9, C*H*(CH_3)$_2$], 2.70–3.00 (m, 1H, SCH), 3.06 (s, 1H, OH), 3.40–3.60 (m, 1H, SCH), 3.70–4.00 [br, 2H, C*H*(CH_3)$_2$], 4.90–5.00 (m 1H, C*H*OH), 7.06 (s, 2H, ArH), 7.20–7.40 (m, 5H, ArH); δ_C 23.7, 24.2, 24.6, 28.0, 34.3, 50.8, 72.9, 122.9, 123.3, 125.8, 127.8, 128.6, 133.8, 143.6, 152.4; *m*/*z* (EI) 386 (M^+, 45%), 351 (50), 279 (100), 233 (55).

(*S*)-4-[(2,4,6-Triisopropylphenyl)sulfinyl]butan-2-ol 8d. The reaction was carried out as described above except using **9d** (36 mg, 0.112 mmol) and DIBAL (0.95 mol L^{-1} solution in hexane, 0.18 mL, 0.17 mmol). Usual work-up gave the crude product, which was purified by column chromatography (hexane–ethyl acetate 60:40) to afford **8d** (35 mg, 96%). The (S_S*,S*):(S_S*,R*) diastereomer ratio was determined to be 98:2 by HPLC analysis (Found: C, 70.32; H, 9.94. $C_{19}H_{32}O_2S$ requires C, 70.30; H, 9.99%); HPLC (COSMOSIL, hexane–^{i}PrOH 94:6, flow rate 1.0 mL min^{-1}) t_R 117.9 (S_S,R) and 129.5 min (S_S,S); R_f 0.15 (hexane–ethyl acetate 70:30); ν_{max}(neat) 3500, 2980, 1660, 1500, 1280, 1060 cm^{-1}; δ_H 1.25 [d, 18H, *J* 6.9, CH(CH_3)$_2$], 1.26 (d, 3H, *J* 6.9, CH_3), 2.03 (dt, 2H, *J* 6.0, 6.9, CH_2CH_2CH), 2.68 (s, 1H, OH), 2.80–3.00 [m, 2H, C*H*(CH_3)$_2$ and SCH], 3.45–3.60 (m, 1H, SCH), 3.80–4.10 [m, 3H, C*H*(CH_3)$_2$ and C*H*OH], 7.04 (s, 1H, ArH), 7.08 (s, 1H, ArH); *m*/*z* (EI) 324 (M^+, 64%), 307 (80), 252 (60), 233 (98), 149 (100).

(*S*)-1-[(2,4,6-Triisopropylphenyl)sulfinyl]pentan-3-ol 8e. The reaction was carried out as described above except using **9e** (30 mg, 0.089 mmol) and DIBAL (0.95 mol L^{-1} solution in hexane, 0.14 mL, 0.133 mmol). Usual work-up gave the crude product, which was purified by column chromatography (hexane–ethyl acetate 60:40) to afford **8e** (28 mg, 92%). The (S_S*,S*):(S_S*,R*) diastereomer ratio was determined to be 96:4 by HPLC analysis (Found: C, 70.96; H, 10.12. $C_{20}H_{34}O_2S$ requires C, 71.01; H, 10.05%); HPLC (COSMOSIL, hexane–^{i}PrOH 94:6, flow rate 1.0 mL min^{-1}) t_R 42.9 (S_S,R) and 45.4 min (S_S,S); R_f 0.39 (hexane–ethyl acetate 50:50); ν_{max}(neat) 3480, 2970, 1660, 1250, 1080 cm^{-1}; δ_H 0.98 (t, 3H, *J* 7.4, CH_3), 1.25 [d, 18H, *J* 6.9, CH(CH_3)$_2$], 1.55 (dq, 2H, *J* 6.3, 7.4, CH_2CH$_3$), 1.95–2.10 (m, 2H, CH_2CH_2CH), 2.50–2.70 (br, 1H, OH), 2.80–3.00 [m, 2H, C*H*(CH_3)$_2$ and SOCH], 3.45–3.60 (m, 1H, SOCH), 3.60–3.85 (m, 1H, C*H*OH), 3.80–4.10 [m, 2H, CH(CH_3)$_2$], 7.08 (s, 2H, ArH); *m*/*z* (EI) 338 (M^+, 60%), 321 (78), 252 (76), 233 (100), 149 (94).

Preparation of the chiral homoallyl alcohol 13

1-Phenyl-3-[(2,4,6-triisopropylphenyl)sulfinyl]-4-(trimethylsilyl)butan-1-ol 12. To a THF (1.0 mL) solution of diisopropylamine (0.160 mL, 1.14 mmol) was added *n*-butyllithium (1.52 mol L^{-1} solution in hexane; 0.72 mL, 0.109 mmol) at 0 °C and the mixture was stirred for 10 min. The reaction mixture was then cooled to −78 °C and a THF (1.0 mL) solution of **8c** (190 mg, 0.491 mmol) was added. After stirring of the mixture for 30 min, a THF (1.0 mL) solution of (iodomethyl)trimethylsilane (1.10 mL, 0.741 mmol) was added and the mixture was warmed to room temperature and stirred for 2 h. Usual work-up gave the crude product, which was purified by column chromatography (silica gel 12 g; hexane–ethyl acetate 70:30) to give **12** (184 mg, 79%) (Found: C, 71.13; H, 9.38. $C_{28}H_{44}O_2SSi$

requires C, 71.12; H, 9.36%); R_f 0.66 (hexane–ethyl acetate 50:50); ν_{max}(neat) 3300, 2950, 1600, 1460, 1250, 1010, 840 cm^{-1}; δ_H −0.09 [s, 9H, $Si(CH)_3$], 0.35 (dd, 1H, *J* 1.9, 12.8, CHSi), 0.70 (d, 1H, *J* 12.8, CHSi), 1.10–1.40 [m, 18H, $CH(CH_3)_2$], 2.20–2.60 (m, 2H, CH_2), 2.91 [hep, 1H, *J* 6.7, $CH(CH_3)_2$], 3.60–3.90 [m, 2H, $CH(CH_3)_2$], 4.20–4.40 (m, 1H, SOCH), 4.85–5.00 (m, 1H, OCH), 5.75 (d, 1H, *J* 2.0, OH), 7.00–7.50 (m, 7H, ArH); δ_C −0.9, 18.2, 22.6, 23.8, 25.7, 28.2, 29.6, 34.4, 45.4, 59.2, 73.6, 121.4, 125.0, 125.8, 127.2, 127.9, 128.4, 131.7, 145.3, 153.1.

(*S*)-1-Phenylbut-3-en-1-ol 13. To a solution of **12** (152 mg, 0.321 mmol) in THF (1.0 mL) was added a THF solution of TBAF (1.0 mol L^{-1}; 0.64 mL, 0.64 mmol) at room temperature and the mixture was stirred for 1 h. THF was then evaporated off under reduced pressure and the residue was purified by column chromatography (silica gel 5 g; hexane–CH_2Cl_2–Et_2O 50:45:5) to afford **13** (43 mg, 91%) $[a]_D^{21}$ −44.8 (*c* 0.28, benzene) {lit.,[14] $[a]_D^{21}$ −48.7 (*c* 0.692, benzene)}.

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