Efficient 1,2-Asymmetric Induction in Radical Reactions: Stereoselective Radical Addition to 3-Hydroxy-1-(methylthio)-1-(*p*-tolylsulfonyl)-1-alkenes

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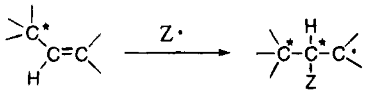
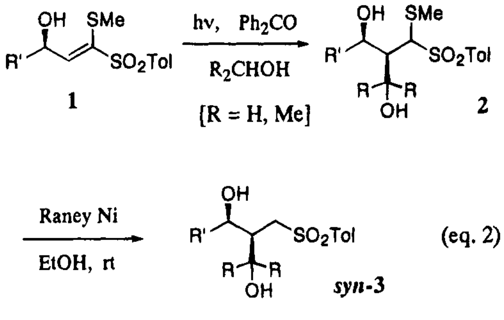
Free radical reactions have been developed into powerful carbon–carbon bond formation methodologies for organic synthesis.[1,2] Many synthetic studies have focused on radical reactions that are accompanied by asymmetric induction,[3] but there have been few reports of intermolecular radical 1,2-asymmetric induction, in which a stereogenic π-face is selected by an achiral radical (eq 1).



(eq. 1)

This paper reports very high 1,2-asymmetric induction in a radical addition to 3-hydroxy-1-(methylthio)-1-(*p*-tolylsulfonyl)-1-alkenes **1** (eq 2). The radical is 1-hydroxyalkyl (R_2COH), generated from an alcohol (R_2CHOH) by α-hydrogen abstraction with excited triplet benzophenone.[4]



(eq. 2)

[**a** R' = Me; **b** R'= Et; **c** R'= *i*-Pr]

Upon irradiation[5] of (*E*)-**1a**[6] and benzophenone in 2-propanol, an adduct (**2a**, R = Me) was formed as a mixture of four (mainly two) diastereomers. Desulfurization of the adduct with Raney-Ni (W2) afforded **3a** (R = Me) which consisted of two diastereomers (*syn*:*anti* = 95:5).[8,9] This *syn*:*anti* ratio is indicative of very high 1,2-asymmetric induction in this acyclic system.[3] Similar irradiation of (*Z*)-**1a** gave **2a** (R = Me) with a comparably high *syn*-selectivity (*syn*:*anti* = 95:5). Monitoring of the latter reaction by HPLC showed that isomerization of (*Z*)-**1a** to (*E*)-**1a** occurred concurrently.[10] Analogously, **1b** and **1c** produced the corresponding **2** in a ratio of 96:4. Hydroxymethyl radical also added to **1a** with high *syn* selectivity (Table 1).[11]

The combination of methylthio and p-tolylsulfonyl groups at the 1-position not only controls the regioselectivity of the reaction, but also amplifies the C_3 chirality through the double bond to provide high syn selectivity. Since the synergistic effect of an electron-donating methylthio group and an electron-withdrawing *p*-tolylsulfonyl group makes the carbon radical very stable,[12] addition of a radical to **1** is so exothermic[13] that its transition state is reactant-like (the Hammond postulate). The preferred conformation of **1a** was suggested by X-ray crystallography result: the crystal structure (Figure 1) of **1a** possesses the hydroxyl group outside the double bond and

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[1] Giese, B. *Radicals in Organic Synthesis*: *Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986.

[2] For a review, see: (a) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (b) Curran, D. P. *Synthesis* **1988**, 417 and 489. (c) Hart, D. J. *Science* **1984**, *223*, 883. (d) Jasperse, C. D.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

[3] For a review, see: (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (b) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969. (c) RajanBabu, R. V. *Acc. Chem. Res.* **1991**, *24*, 139. (d) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (e) Smadja, W. *Synlett* **1994**, 1.

[4] Ogura, K.; Yanagisawa, A.; Fujino, T.; Takahashi, K. *Tetrahedron Lett.* **1988**, *29*, 5387.

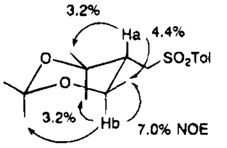
[5] A solution of **1a** (272 mg, 1.00 mmol) and benzophenone (182 mg, 1.0 mmol) in isopropyl alcohol (70 mL) was irradiated with a 100-W high-pressure Hg arc lamp (Sigemi Standard) with a water-cooled Pyrex jacket under bubbling nitrogen for 2 h. Evaporation of the solvent followed by chromatography on silica gel (eluent: hexane–ethyl acetate) gave **2a** (R = Me) (323 mg, 97% yield).

[6] Preparation of **1**. Typical procedure: Bromination of 1-(methylthio)-1-(*p*-tolylsulfonyl)-1-butene[7] with NBS (1.0 mol equiv) and benzoyl peroxide (0.1 mol equiv) in CCl_4 gave 3-bromo-1-(methylthio)-1-(*p*-tolylsulfonyl)-1-butene in 88% yield. Subsequent hydrolysis in the presence or absence of Ag_2O (1.2 mol equiv) in acetone–H_2O (2:3) at rt afforded **1a** as a mixture of (*E*)- and (*Z*)-geometric isomers in good yield. Further photoisomerization in the presence of benzophenone gave (*E*)-**1a**.[10]

[7] Ogura, K.; Iihama, T.; Kiuchi, S.; Kajiki, T.; Koshikawa, O.; Takahashi, K.; Iida, H. *J. Org. Chem.* **1986**, *51*, 709.

[8] The diastereomeric ratio was determined by ^1H NMR (270 MHz, $CDCl_3$) of **3** after purification by chromatography and preparative HPLC (GPC, $CHCl_3$ eluent).

[9] The major diastereomer was determined to have a *syn* relationship between the C_2 and C_3 chiral centers: Treatment of **3a** (R = Me) with 2,2-dimethoxypropane and 10-camphorsulfonic acid (a catalytic amount) in acetone at rt gave an acetonide (**4**), which showed H_a–H_b coupling of 9.60 Hz (^1H NMR spectrum) and satisfactory NOE. The *syn* structure of **3b** (R = Me) was determined by X-ray diffraction analysis.



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[10] Irradiation of (*Z*)-**1a** in acetonitrile (or benzene) containing benzophenone caused *Z*–*E* isomerization that reached a photostationary state (*E*:*Z* = 95:5 and 89:11, respectively).

[11] Similar irradiation of **1a** and benzophenone in ethanol gave an adduct, 3-(methylthio)-3-((*p*-tolylsulfonyl)methyl)-2,4-pentanediol, which, on reductive desulfurization with Raney Ni, afforded 3-((*p*-tolylsulfonyl)methyl)-2,4-pentanediol as a mixture of three diastereomers (*dl*:*meso*(1):*meso*(2) = 55.5:4.4:40.1). Supposing that 1,3-asymmetric induction between the 2- and 4-positions of the adduct occurs with the same efficiency, the 1,2-asymmetric efficiency was calculated from this ratio to be 90:10 (*syn*:*anti*). Further details are given in the supplementary material.

[12] Ogura, K.; Sumitani, N.; Kayano, A.; Iguchi, H.; Fujita, M. *Chem. Lett.* **1992**, 1487.

[13] Indeed, addition of a methyl radical to the energy-minimized X-ray structure of **1a** is calculated by the MNDO/PM3 method[14] to be exothermic by 34.2 kcal mol^{-1}. The transition state was estimated by the use of the appropriate reaction coordinate analysis and the SADDLE routine. Further refinement of the transition state geometries was carried out by the use of the NLLSQ algorithm. The distance between the carbon of the methyl radical and the β-carbon of **1a** is 2.20 Å.

[14] With MOPAC (ver. 6) molecular orbital package packed in Materia (ver. 2.1; Teijin System Technology, Ltd.): Stewart, J. J. P. *QCPE Bull.* **1989**, *9*, 10.

0022-3263/95/1960-1106$09.00/0

Table 1. Photochemical Additions to 1

1			yield/%	
R′	(*E*:*Z*)	R_2CHOH	**2**	**3** (*syn*:*anti*)
Me	(100:0)	*i*-PrOH	97	84 (95:5)
Me	(0:100)	*i*-PrOH	98	89 (95:5)
Me	(25:75)	*i*-PrOH	79	100 (95:5)
Me	(100:0)	MeOH	86	72 (86:14)
Et	(100:0)	*i*-PrOH	79	94 (96:4)
Et	(100:0)	MeOH	83	100 (94:6)
i-Pr	(100:0)	*i*-PrOH	69	96 (96:4)
i-Pr	(100:0)	MeOH	81	96 (94:6)

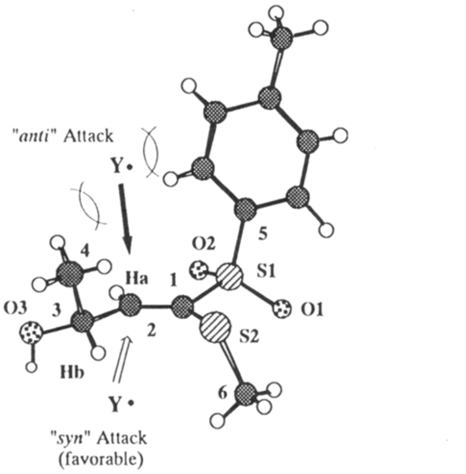
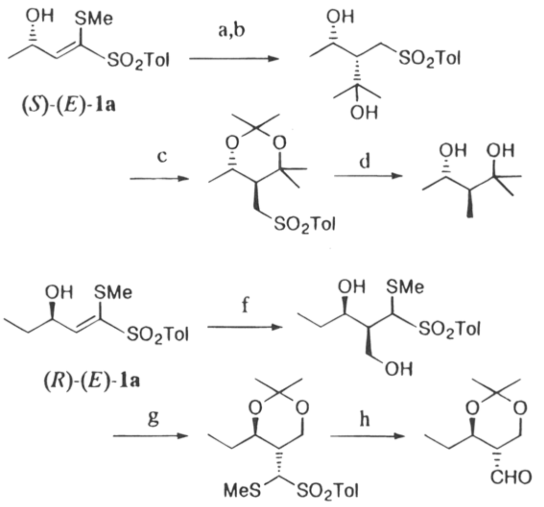


Figure 1. Chem 3D representation of the X-ray structure of **1a**.

the methine proton (H_b) inside.[15,21] The ^{1}H NMR spectra of **1a-c** in $CDCl_3$ and CD_3OD exhibited large coupling constants (7.60−9.20 Hz)[16] and no NOE between H_a and H_b. Therefore, the most favorable conformations of **1** about the C2−C3 bond in solution resemble the crystal structure of **1a**, in which allylic 1,3-strain[17] may play an important role in dictating conformation. If a radical approaches from the less crowded side, opposite the methyl and *p*-tolyl groups, the adduct would have the *syn* configuration as shown in Figure 1.

Scheme 1[19]



The present 1,2-asymmetric induction is applicable to the synthesis of various optically active organic compounds. Starting **1** was easily obtained in optically-active form by transesterification with lipase PS and vinyl acetate in benzene.[18] Optically active **1** was transformed into various synthetic precursors. Some examples are shown in Scheme 1.

It is noteworthy that 1,3-dioxolane and 2-methyl-1,3-dioxolane can be employed instead of the alcohols to achieve high 1,2-asymmetric induction (*syn*:*anti* = 78:22 and 84:16, respectively, for **1a**). Other applications are in progress in our laboratory.

Supplementary Material Available: General experimental procedures, characterization data for all new compounds, and crystal data of **1a** and **3b** (11 pages).

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[15] Important torsional angles: Ha−C2−C3−Hb = 145.3°, Ha−C2−C3−C4 = −96.1°, Ha−C2−C3−O3 = 21.9°, C5−S1−C1−C2 = 101.9°, O2−S1−C1−C2 = −13.4°, C6−S2−C1−C2 = 98.8°.

[16] (a) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870. (b) Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5561. (c) Gung, B. N.; Wolf, M. A.; Zhu, Z. *J. Org. Chem.* **1993**, *58*, 3350.

[17] Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

[18] (a) Amano PS (from *Pseudomonas cepacia*) was provided by Amano Pharm. Co., Ltd. (b) Carretero, J. C.; Dominguez, E. *J. Org. Chem.* **1992**, *57*, 3867.

[19] (a) Ph_2CO, 2-propanol, *hν* (>290 nm), 97%. (b) Raney-Ni (W2), EtOH, 77%. (c) $Me_2C(OMe)_2$, *p*-TsOH, acetone, rt, 96%. (d) Na (10 equiv), EtOH (15 mol equiv), Na_2HPO_4 (5 equiv), THF, −20 °C; *p*-TsOH, MeOH, 0 °C, 15 min, 99%. (f) *hν*, Ph_2CO (>290 nm), MeOH, rt, 98%. (g) *p*-TsOH, acetone, rt, 77%. (h) *hν* (254 nm),[20] $NaHCO_3$ (3 equiv), ether−H_2O (19:1), 44%.

[20] Ogura, K.; Ohtsuki, K.; Nakamura, M.; Yahata, N.; Takahashi, K.; Iida, H. *Tetrahedron Lett.* **1985**, *26*, 2455.

[21] The author has deposited atomic coordinates for **1a** and **3b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.