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Efficient 1,2-Asymmetric Induction in Radical Reactions: Addition of Acyl Radicals to 3-Hydroxy-1-(methylthio)-1-(*p*-tolylsulfonyl)-1-alkenes and Their Acetates

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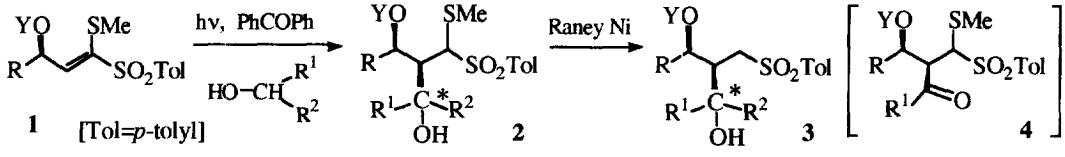
Abstract: Irradiation of aliphatic and aromatic aldehydes in the presence of benzophenone produces the corresponding acyl radicals which add to 3-hydroxy-1-(methylthio)-1-(*p*-tolylsulfonyl)-1-alkenes and their acetates with high *syn* selectivity.

Keywords: aldehydes; asymmetric induction; radicals and radical reactions; sulfur compounds

In organic synthesis, radical reactions accompanied by asymmetric induction have proven to be useful for the formation of a C-C bond.[1] However, there are only a few reports on 1,2-asymmetric induction in radical addition to chiral acyclic alkenes to select its stereogenic π-face.[2,3] Recently, we reported a novel 1,2-asymmetric induction in the addition of 1-hydroxyalkyl radicals $R^1\dot{C}H$-OH to 3-hydroxy-1-(methylthio)-1-(*p*-tolylsulfonyl)-1-alkenes (**1**), which is useful for synthesizing various optically active compounds.[4] The efficiency of this reaction is extremely high as to 1,2-asymmetric induction in a simple acyclic system.



Here we wish to report the addition of the acyl radicals to **1** which proceeds with high efficiency and high selectivity. The resulting acylated product (**4**) promises to be a useful synthetic precursor of the alcohol (**2**; R^2=H) which can be given by stereoselective reduction. These results overcome some disadvantageous points observed in the 1-hydroxyalkyl radical addition to **1**: In the case of $R^1 \neq R^2$, a new asymmetric center (*C of **2** and **3**) of the introducing 1-hydroxyalkyl group is created with very low stereoselectivity.[4a] In order to attain high chemical yield, an alcohol that is the source of the 1-hydroxyalkyl radical must be used as a solvent.[4,5] Benzyl alcohols did not give the corresponding adducts (**2**; R^1=aryl, R^2=H) because the intermediary radicals ($R^1\dot{C}H$-OH) are too stable to add to **1**.

When a solution of **1** (R=Me, Y=H) (1.0 mmol) and propionaldehyde (**5**; R'=Et) (3.0 mmol) in benzene (25 ml) was irradiated with a high-pressure Hg arc lamp (100W) through a Pyrex

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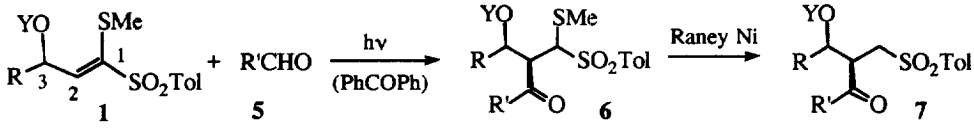


filter (>290 nm) under N_2 atmosphere for more than 2 h, the expected adduct (**6**; R=Me, R'=Et, Y=H) was not formed at all.[6] However, the presence of benzophenone (0.5 mol-equiv.) was found to initiate the reaction and, on irradiation for 2 h, gave **6** (R=Me, R'=Et, Y=H) in 92% yield (diastereomeric ratio=50:33:11:6). Treatment of the adduct with Raney Ni (WII) gave the corresponding sulfone (**7**; R=Me, R'=Et, Y=H) as a 83:17 mixture of two diastereomers. This ratio reflects the stereoselectivity for the addition of a propionyl radical to **1** (R=Me, Y=H). Irradiation of **1** (R=Me, Y=Ac) and **5** (R'=Et) in the presence of benzophenone also produced **6** (R=Me, R'=Et, Y=Ac) in 77% yield with higher selectivity (91:9). Fortunately, single crystals suitable for X-ray crystallography were obtained for the main isomer of **6** (R=Me, R'=Et, Y=H)[8] and the minor isomer of **7** (R=Me, R'=Et, Y=H), allowing us to conclude that the propionoyl radical adds to **1** with *syn* selectivity between the 2- and 3-positions.

Table 1 summarizes the results using **1** (R=Me or *i*-Pr, Y=H or Ac) and other aldehydes. In all cases, high asymmetric induction was attained. When **5** is an aromatic aldehyde, the reaction also takes place in the absence of benzophenone although a somewhat larger amount (5 mol-equiv. to **1**) of **5** is required for the reaction to proceed smoothly. It should be noted that **1** (R=Me, Y=H) and benzaldehyde (**5**; R'=Ph) gave rise to low yield (64%) of **6** (R=Me, R'=Ph, Y=H). This was thought to be due to its further photochemical decomposition via a Norrish-type II reaction, because 2-(methylthio)-2-(*p*-tolylsulfonyl)ethyl phenyl ketone was obtained as a by-product (32% yield). Therefore, **1** (Y=H) seems not to be suitable for the present addition reaction using aromatic aldehydes such as **5**. The stereochemical course of the reaction using aromatic aldehydes such as **5** was the same as in the case of aliphatic aldehydes (**5**), which was evident from single-crystal X-ray crystallographic analysis of **7** (R=Me, R'=Ph, Y=Ac; a major component).

It is apparent from Table 1 (Entries 1 and 2; 9 and 10) that **1** (Y=Ac) is better in stereoselectivity than **1** (Y=H). This tendency is contrary to the addition of 1-hydroxyalkyl radicals to **1**, in which it is compelled to use the alcohol as the solvent. In the present case, the radical addition was performed in nonpolar, aprotic benzene. As reported in our previous paper,[4] the radical addition to **1** is so exothermic that, according to the Hammond postulate, its transition state is reactant-like. The most favorable conformation about the C_2-C_3 bond of **1** in a solution is similar to that in a crystalline state (Fig. 1) and the radical approaches from the less crowded side, opposite to the alkyl (R) group, to realize *syn* selectivity. In the ^1H NMR spectra in $CDCl_3$, **1** (Y=Ac) exhibits a larger coupling constant (J) between H_a and H_b [R=Me, 7.91 Hz (140°); R=*i*-Pr, 8.57 Hz (145°)] in comparison with **1** (Y=H) [R=Me, 7.58 Hz (138°); R=*i*-Pr, 8.24 Hz (142°)].

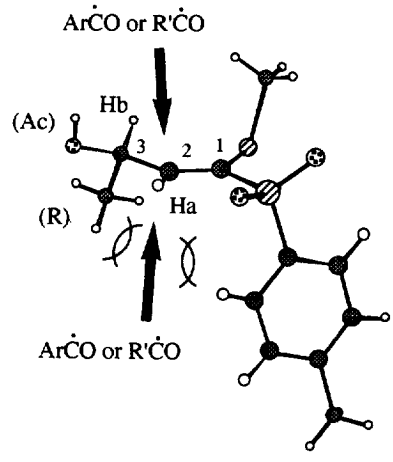


Fig. 1 X-Ray Structure of **1** (R=Me, Y=H) and Favorable Direction for Radical Approach.

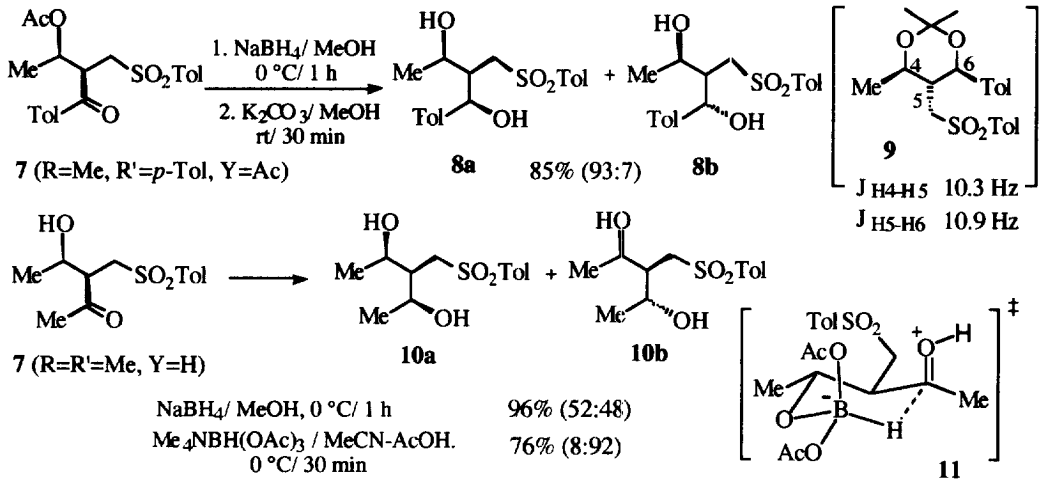
Table 1. Photochemical Addition of Aldehydes (**5**) to **1**

Entry	**1**		**5**		PhCOPh	**6**		**7**
	R	Y	R'	mol-equiv.	/mol-equiv.	time /h	yield/% [a]	syn:anti
1	Me	H	Et	3.0	0.5	2.0	92	83:17
2	Me	Ac	Et	3.0	0.5	2.0	77	91: 9
3	*i*-Pr	Ac	Et	3.0+3.0	0.5+0.5	2.0+2.0	89	96: 4
4	Me	Ac	Me	3.0	0.5	1.0	96	89:11
5	Me	H	*n*-Pr	3.0	0.5	2.5	84	84:16
6	Me	H	*i*-Bu	3.0	0.5	2.5	68	82:18
7	Me	Ac	*n*-$C_{10}H_{21}$	3.0	0.5	2.0	90	86:14
8	Me	Ac	*i*-Pr	3.0+3.0	0.5+0.5	2.0+2.0	60 (73)	90:10
9	Me	H	Ph	5.0	—	2.0	64	83:17
10	Me	Ac	Ph	5.0	—	2.0	86	93: 7
11	Me	Ac	Ph	3.0	0.5	2.0	86	92: 8
12	*i*-Pr	Ac	Ph	5.0+5.0	0+0.5	3.5+2.0	80	95: 5
13	Me	Ac	*p*-MeC_6H_4	5.0	—	2.0	54 (84)	87:13
14	Me	Ac	*p*-MeC_6H_4	3.0	2.0	2.0	81 (100)	88:12
15	Me	Ac	*m*-MeC_6H_4	5.0	—	2.0	62 (89)	87:13
16	Me	Ac	*m*-MeC_6H_4	3.0	2.0	2.0	81 (99)	86:14
17	Me	Ac	*p*-$(AcO)C_6H_4$	3.0	2.0	2.0	82 (100)	87:13
18	Me	Ac	*m*-$(AcO)C_6H_4$	3.0	2.0	2.0	75 (92)	86:14
19	Me	Ac	*o*-$(AcO)C_6H_4$	3.0	2.0	2.0	75 (100)	86:14

[a] The value in parenthesis means the yield based on the unrecovered **1**.

The values in parenthesis are the corresponding dihedral angles (H_a-C_2-C_3-H_b) which were calculated from the coupling constant according to the equation proposed by Garbisch, Jr.[10] These values suggest that, in a nonpolar, aprotic solvent, **1** (Y=Ac) has the alkyl (R) group more perpendicular to the C_1-C_2 π-plane to adopt a more favorable conformation for the *syn* attack of the radical. In the calculated dihedral angles ($\phi_{Ha\text{-}C2\text{-}C3\text{-}Hb}$), **1** (R=*i*-Pr) shows a larger value than (R=Me) in both cases of Y=H and Ac. This means that the isopropyl group stands more perpendicularly to attain higher *syn* selectivity.

Finally, we would like to describe a preliminary result on the reduction of **7**. When the major isomer of **7** (R=Me, R'=*p*-tolyl, Y=Ac) was subjected to the reduction with sodium borohydride in methanol at 0 °C, stereoselective reduction occurred to give the corresponding alcohol. Since the acetoxy group was partially hydrolyzed, we isolated a dihydroxy compound (**8**) after complete hydrolysis of the reaction mixture (see the following equation). The structure of the major isomer (**8a**) was determined from ^{1}H NMR of its acetonide derivative (**9**): large coupling constants ($J_{H4\text{-}H5}$=10.3 Hz and $J_{H5\text{-}H6}$=10.9 Hz) between the protons of the 1,3-dioxane ring were observed to show that the protons of the 4, 5, and 6 positions are located at axial positions. In the case of **7** (R=R'=Me, Y=H), reduction with sodium borohydride did not occur selectively, but highly stereoselective reduction was attained with $Me_4NBH(OAc)_3$ which gave the corresponding dihydroxy compound (**10**) with high selectivity, probably via a cyclic transition state (**11**).[11]



In conclusion, it was shown that aliphatic and aromatic aldehydes (**5**) add to **1** (Y=H or Ac) with high *syn* selectivity via the corresponding acyl radicals. Now we are investigating the application of the present radical 1,2-asymmetric induction to the synthesis of various optically active compounds.

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References

[1] (a) Beckwith AL. Tetrahedron 1981;37: 3073. (b) Giese B. Angew. Chem., Int. Ed. Engl. 1989; 28: 969. (c) RajanBabu RV. Acc. Chem. Res. 1991; 24: 139. (d) Porter NA, Giese B, Curran DP. Acc. Chem. Res. 1991; 24: 296. (e) Smadja W. Synlett 1994: 1. (d) Curran DP, Porter NA, Giese B. Stereochemistry of Radical Reactions. VCH, Winheim, 1995.

[2] (a) Giese B, Witzel T. Tetrahedron Lett. 1987; 23: 2571. (b) Yamamoto Y, Nishii S, Ibuka T. J. Am. Chem. Soc. 1988; 110: 617. (c) Smadja W, Zahouily M, Journet M, Malacria M. Tetrahedron Lett. 1991; 32: 3683. (d) Smadja W, Zahouily M, Malacria M. Tetrahedron Lett. 1992; 33: 5511. (e) Morikawa T, Washio Y, Shiro M, Taguchi T. Chem. Lett. 1993: 249.

[3] Efficient 1,3-asymmetric induction was reported in radical additions to α,β-unsaturated carbonyl compounds bearing a chiral sulfinyl group at the α position: Mase N, Watanabe Y, Toru T. J. Org. Chem. 1998; 63: 3899 and the references cited therein.

[4] (a) Ogura K, Kayano A, Sumitani N, Akazome M, Fujita M. J. Org. Chem. 1995; 60: 1106. (b) Kayano A, Sumitani N, Akazome M, Fujita M, Ogura. K. Tetrahedron. 1997; 53: 12101.

[5] (a) Ogura K, Yanagisawa A, Fujino T, Takahashi K. Tetrahedron Lett. 1988; 29: 5387. (b) Kayano A, Yajima Y, Akazome M, Fujita M, Ogura K. Bull. Chem. Soc. Jpn. 1995; 68: 3599.

[6] Recently we found that aromatic aldehydes were irradiated with 1-(methylthio)-1-(*p*-tolylsulfonyl)-1-alkenes in the absence or presence of benzophenone to give a 1:1 adduct via the corresponding aroyl radicals.[7] This reaction was applied to **1**.

[7] Ogura K, Arai T, Kayano A, Akazome M. Tetrahedron Lett. in press.

[8] Single crystal X-ray crystallographic analysis of the major component of **6** (R=Me, R'=Et, Y=H). The data were collected with CuKα (λ=1.54178 Å) radiation on Mac Science MXC18 diffractometer. The structure was solved and refined by direct methods (SIR92[9] on a computer program package: Crystan GM ver. 6.2.1 from MAC Science Co. Ltd.): Triclinic, P$\bar{1}$ (#2), a=7.977(3) Å, b=10.278(3) Å, c=10.420(4) Å, α=99.76(3)°, β=97.74(3)°, γ=101.27(3)°, V=813.1(5) Å^3, Z=2, *R*=0.068, *Rw*=0.059, T=298 K.

[9] Altomare A, Casacarano G, Giacovazzo C, Guagalaiardi A, Burla MC, Polidor G, Camalli M. J. Appl. Cryst. 1994; 27: 435.

[10] Garbisch, Jr. EW. J. Am. Chem. Soc. 1964; 86: 5561.

[11] Evans DA, Chapman KT, Carreira EM. J. Am. Chem. Soc. 1988; 110: 3560.