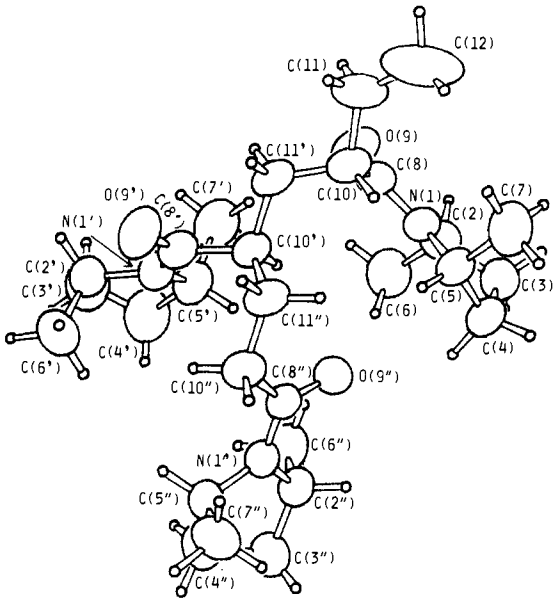
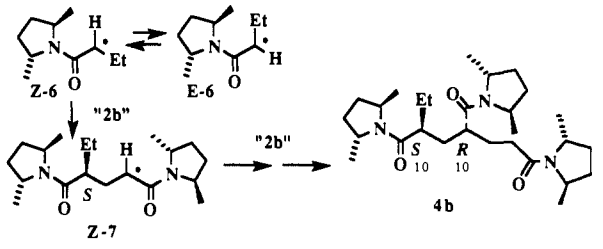


Figure 1. ORTEP diagram showing the atom numbering scheme and solid-state conformation of the major stereoisomer of **4b**; small circles represent hydrogen atoms.

Scheme I



$1/T$ suggests that the selectivity observed is enthalpy derived since there is an apparent $\Delta\Delta H^{\ddagger}$ of 1.7 kcal/mol and a $\Delta\Delta S^{\ddagger}$ of ~0 eu.

Reaction of the bromo amide precursor **1a** with **2b**, the acrylamide derived from *R,R* pyrrolidine, gives products **3** and **4** analogous to those formed from ethyl acrylate. From the reaction at 80 °C, under the same conditions as those used for ethyl acrylate additions, two **3b** stereoisomers were formed in a ratio of 25:1. The major diastereomer was prepared independently from (*S*)-2-ethylglutaric acid and the *R,R* pyrrolidine. Combined HPLC-MS (20% isopropyl alcohol) in hexane; chemical ionization NH_3/CH_4)[11] of the reaction mixture indicated the presence of one major stereoisomer of the $n = 2$ oligomer **4b** and one major stereoisomer of the $n = 3$ oligomer. Trace amounts of minor stereoisomers of these higher oligomers could be detected by selective ion monitoring of the HPLC-MS output. Crystals of **4b** were produced by slow recrystallization from hexane–ether and the stereochemistry was assigned by X-ray crystallography,[12] Figure 1.

We suggest that the radical **6** has a low-energy *Z* conformation that undergoes addition from the face opposite the proximate pyrrolidine methyl substituent, and that subsequent radicals derived from alkene **2b**, such as (*Z*)-**7**, have an analogous preferred *Z* conformer with an addition face bias originating in a proximate pyrrolidine methyl group. Although the stereocontrolling elements are the same for radicals **6** and **7**, changes in group priorities for the two centers result in C-10 (see Scheme I) having the *S* configuration, while the C-10′ center is *R*. In support of the radical conformational preference suggested here, we note that EPR studies suggest[13,14] a preferred *Z* conformation for α-amide radicals with a *Z-E* conformational barrier exceeding 11 kcal/mol.

The selectivities reported here for addition of α-amide radicals to alkenes may find use in the controlled construction of new C–C bonds in synthetic applications and in the preparation of oligomeric and polymeric acrylate structures. While the auxiliary used here is removed with difficulty, analogous pyrrolidine structures that are subject to subsequent removal without epimerization of the α-amide center should make a wide variety of compounds available by this approach.[15,16] We are currently exploring selectivity of higher oligomers as a function of auxiliary and alkene structure and will report results of these studies in due course.

Acknowledgment. This research was supported by grants from NSF and HIH (HL 17921). We also acknowledge assistance with HPLC-MS from Drs. Robert Breyer and George Dubay.

Supplementary Material Available: Tables of crystallographic data, atomic positional and thermal parameters, bond lengths, and bond angles for **4b**, and a table of chromatography conditions and retention times for products **3a,b** and **4a,b** (11 pages); table of observed and calculated structure amplitudes for the major stereoisomer of **4b** (14 pages). Ordering information is given on any current masthead page.

(11) Hewlett-Packard 5990 quadrapole mass spectrometer with a Hewlett-Packard particle beam interface.

(12) Crystal data: $C_{28}H_{49}N_3O_3$, $M = 475.72$, orthorhombic, space group $P2_12_12_1$, $a = 17.911$ (2) Å, $b = 20.189$ (2) Å, $c = 7.869$ (1) Å, $V = 2846$ (1) Å^3, $Z = 4$, $d_{calcd} = 1.110$ g cm^{-3}. Data collection parameters and a summary of the crystal structure analysis are provided in the supplementary material. Refinement of atomic positional and thermal parameters (anisotropic C, N, O; fixed H contributions) converged at $R = 0.049$ ($R_w = 0.069$) over 2058 reflections with $I > 3.0\sigma(I)$.

(13) Strub, W.; Roduner, E.; Fischer, H. *J. Phys. Chem.* **1987**, *91*, 4379, and references cited therein.

(14) One expects less stereochemical control in radicals α to ester functional groups, since there is only a small *Z-E* conformational bias in these systems; see, for example: Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, *28*, 2205.

(15) Kawanami, Y.; Fujita, I.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Chem. Lett.* **1987**, *10*, 2021.

(16) We thank Drs. D. Curran and B. Giese for informing us of parallel, but independent, studies of α-amide radicals, accompanying communications in this issue.

1,2- and 1,4-Stereoinduction in Reactions of Chiral Radicals

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Received May 23, 1990

Radical chain reactions have been proved to be very effective in organic synthesis.[1] Recently, work by Porter[2a,b] and ourselves[2a,c] has demonstrated that α,β-unsaturated amides containing the C_2-symmetrical 2,5-dimethylpyrrolidine[3] as a chiral auxiliary react stereoselectively with alkyl radicals. Using the "mercury method",[4] addition of *tert*-butyl radical to fumaramide **1** yields products **2a** and **2b** in a 40:1 ratio at 25 °C.[2a] Thus *tert*-butyl radicals attack the alkene bond of the chiral fumaramide **1** preferentially from one side, forming chiral radical **3**. We now show that the next step of the chain reaction, atom abstraction by chiral radical **3**,

(1) (a) Regitz, M.; Giese, B. *C*-Radikale, *Houben-Weyl*; Thieme: Stuttgart, 1989; Vol. E19a. (b) Curran, D. P. *Synthesis* **1988**, 417, 489. (c) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbons Bonds*, Pergamon: Oxford, 1986.

(2) (a) Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H. G.; Lindner, H. T. *J. Am. Chem. Soc.* **1989**, *111*, 8311. (b) Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1679. (c) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969.

(3) (a) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083. (b) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755.

(4) (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. (b) Giese, B.; Meister, J. *Chem. Ber.* **1977**, *110*, 2588.

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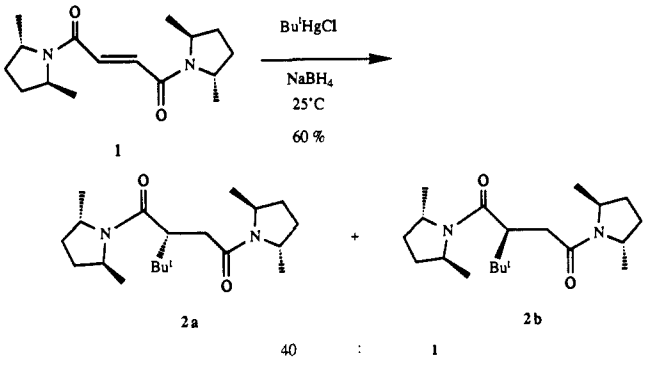
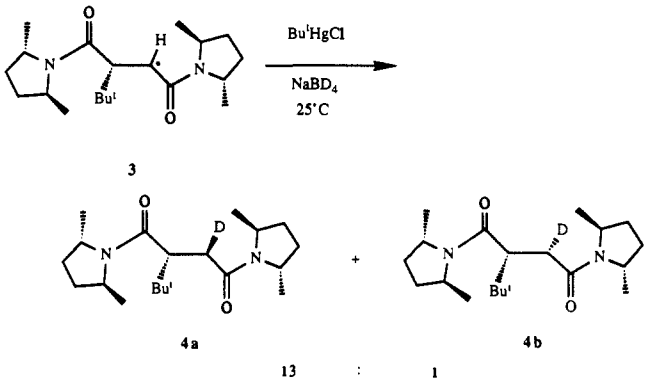
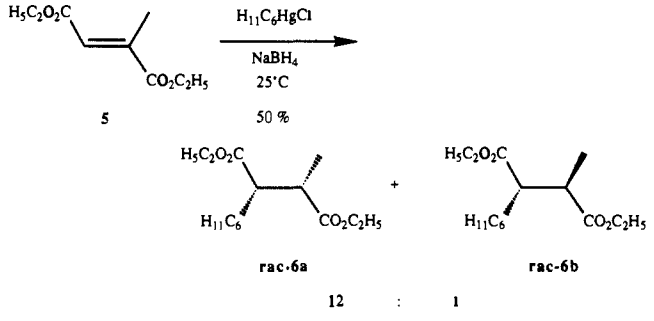


also occurs stereoselectively. With *tert*-butylmercuric deuteride, generated in situ from *tert*-butylmercuric chloride and sodium borodeuteride, products **4a** and **4b** are formed in a 13:1 ratio at 25 °C.[5]



The configuration of the main product **4a** was determined by trans addition of *tert*-butylmercuric chloride and sodium borodeuteride to maleic anhydride,[2c,6] and subsequent transformation into the diastereomeric succinic diamides with (*S*,*S*)-2,5-dimethylpyrrolidine.[7] Isomer **4a** is formed via deuterium abstraction anti to the *tert*-butyl substituent adjacent to the prochiral radical center of **3**. This selectivity is in accord with the preferred formation of *rac*-**6a** in the reaction of achiral methyl furmarate (**5**) with cyclohexylmercuric chloride and sodium borohydride.[8]



In radical **3**, 1,2-induction by the adjacent *tert*-butyl group as well as 1,4-induction by the methyl substituents of the amide shields the two faces of the radical to different extents. To establish the influence of 1,4-induction, we carried out the addition of *tert*-butyl radical from radical precursor **8** to acrylamide **7** using the Barton method.[9] At −35 °C products **9a** and **9b** are formed in a 14:1 ratio.[10]

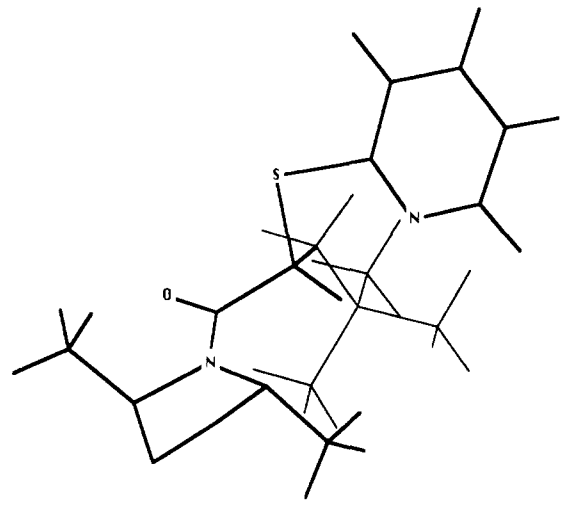
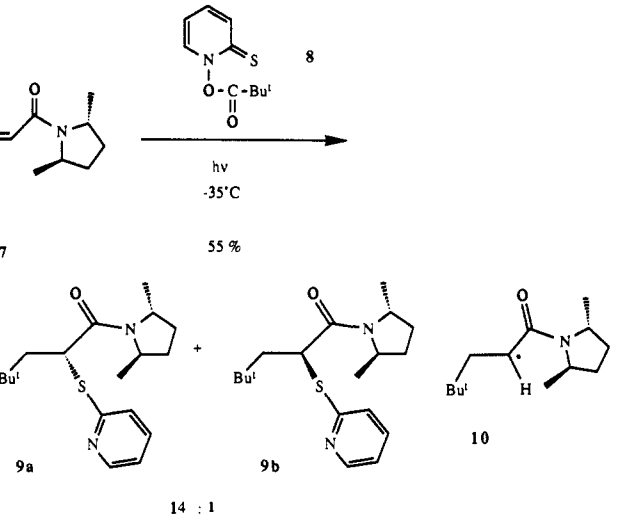


Figure 1. 1,2- and 1,4-Stereoinduction in Reactions of Chiral Radicals.



This stereochemical assignment has been proven by X-ray structure of the major isomer **9a** (Figure 1). In accord with the experiments of Porter,[11] the intermediate radical **10** should adopt a *Z* conformation. The thiocarbonyl group of **8** attacks the radical center of **10** anti to the proximate methyl group of the chiral auxiliary. This 1,4-induction is in accord with the stereochemistry of CC bond formation observed by Porter in a related system.[11]

Acknowledgment. We thank N. Porter and D. Curran for sharing their results prior to publication. This research was supported by the Swiss National Science Foundation.

Supplementary Material Available: Tables of full details of crystal data and parameters for **9a** (19 pages); table of observed and calculated structure factors (15 pages). Ordering information is given on any current masthead page.

(5) The stereoselectivity was determined by ^{2}H NMR spectroscopy of the crude reaction mixture. The main isomer **4a** was isolated in 60% yield by flash chromatography on silica (pentane–acetone–methylene chloride 30:5:1).

(6) (a) Giese, B.; Meixner, J. *Tetrahedron Lett.* **1977**, 2783. (b) Giese, B.; Kretzschmar, G. *Chem. Ber.* **1984**, *117*, 3175.

(7) The reaction leads to two diastereomers, which were separated by flash chromatography on silica (pentane–acetone–methylene chloride 30:5:1) in 20% and 14% yields, respectively. Comparison of the ^{1}H NMR spectra leads to assignment of **4a** as the main product in the deuterium abstraction reaction of radical **3**.

(8) Threo and erythro isomers *rac*-**6a** and *rac*-**6b** were independently synthesized via addition of cyclohexylmercuric chloride and sodium borohydride to methyl maleic anhydride and subsequent esterification.

(9) (a) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675. (b) Trapping of radicals with an ester group instead of an amide group as chiral auxiliary gives lower stereoselectivity; see: Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, *28*, 4205.

(10) A reversibility of the addition of radical **10** to the thio group of **8** should lower the stereoselectivity; see: Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I.; Zard, Z. *Tetrahedron* **1987**, *43*, 2733. In our experiments a linear correlation between the selectivity and the reciprocal temperature (80 to −35 °C) was observed. This makes a reversibility of the radical step unlikely.

(11) (a) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.*, companion paper in this issue. (b) See also: Strub, W.; Roduner, E.; Fischer, H. *J. Phys. Chem.* **1987**, *91*, 4379.