in a ratio of 27/3/1. The major product was **12**, and the minor product was the stereoisomer of **12**. The intermediate product (not shown) resulted from 6-endo radical cyclization. An identical mixture of cyclized products was obtained by atom-transfer cyclization of the terminal alkyne **10b**.

A transition-state model for the cyclization reaction is presented in Figure 1. We propose (1) that the α-amide radical is planar (or nearly planar) in the early transition state,[17] (2) that the radical has E/Z geometry just like an enol (even though most of the radical density is on carbon and the rotational barrier is relatively low[17]), and (3) that the isomer with the larger group in the Z orientation is strongly favored because the E substituent is quite close to the sultam O^1.[5,18] With respect to the sultam, we propose that O^1 and the amide oxygen are opposed to avoid dipole repulsion,[5] and that the alkene approaches the radical from the top face.[18] We suspect that the facial selectivity originates because there is a significant repulsive 1,4-interaction that develops between O^2 and a radical acceptor approaching the bottom face.[18]

Asymmetric radical additions, cyclizations, and annulations based on Oppolzer's chiral sultam are especially attractive because both enantiomers of the starting sultam are commercially available, because reactions conducted at room temperature and above give levels of induction that are sufficiently high for most purposes, and because there are many examples where the sultam has been cleaved from final products by either reduction or hydrolysis.[5,8]

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Supplementary Material Available: An ORTEP drawing and tables of crystal structure details, positional parameters, bond distances, and bond angles for **12** (7 pages). Ordering information is given on any current masthead page.

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Addition Reactions of Amide-Substituted Radicals: Control of Stereochemistry in Acrylamide Free-Radical Additions

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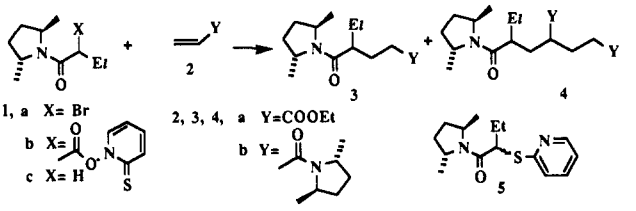
The stereochemistry of acrylate reactions has been of interest for nearly 50 years since radicals derived from acrylates are prochiral and the orientation during addition of such radicals is important in establishing polymer tacticity.[1] It can be said that significant control of stereochemistry in the addition reactions of acrylate derivatives has not been achieved to date, and vinyl polymers formed from acrylate monomers by free-radical methods are generally atactic.[2] In the course of our studies on radical addition to prochiral alkenes, we explored the use of a pyrrolidine amide as chiral auxiliary and we have reported unprecedented stereoselectivities for radical addition in those systems.[3-6] We report here high selectivities for addition reactions of acyclic radicals bearing the same auxiliary group. The high selectivities observed in these radical additions have important implications in the control of oligomer and polymer tacticity.

The radical precursors reported here are the bromo amide **1a**, used as a mixture of diastereomers at the α center, and the malonate derivative **1b**, also used as a mixture of diastereomers. Malonate **1b** was prepared from the pyrrolidine[7,8] and methyl malonyl chloride (62%), followed by alkylation of the amide ester (KH, EtI, 75%), and then hydrolysis of the ester and conversion of the amide acid to the Barton ester[9] via the acid chloride.



In a typical tin hydride reaction, a solution of Bu_3SnH and AIBN was added by syringe pump over a 30-45-min period to refluxing bromo amide **1a** (0.016 M) in benzene and the olefin **2a** or **2b** (0.16 M) in such a way that 1 equiv of tin hydride (cf. bromo amide) was added to the reaction mixture. Chromatography of the products from the reaction of **1a** and **2a** on silica (petroleum ether-ether 10% gradient elution) gave the simple reduction product **1c**, a fraction containing addition product **3a**, and another more polar fraction containing product **4a** resulting from incorporation of two units of ethyl acrylate. Other higher oligomers were formed but have not yet been characterized. Product **3a** is formed as a mixture of two stereoisomers in a 12:1 ratio at 80 °C. Conditions chosen for additions were such that significant amounts of higher oligomers were formed. Yields for the monoaddition compounds were typically 35-50%, while the diaddition compounds were formed in 15-25% yields. Independent synthesis of both **3a** stereoisomers from racemic as well as (*S*)-2-ethylglutaric acid[10] identified the major isomeric product formed in the free-radical addition as having the *S* configuration when the starting pyrrolidine used in **1a** was *R*,*R*. Product **4a** was formed as a 1:1 mixture of two major stereoisomers, presumably possessing the *S* configuration at C-2, but with *R* and *S* configurations at C-4.

Reaction of the Barton ester **1b** with ethyl acrylate was carried out at 80, 23, and -24 °C. We find that radical addition can be performed by combining the olefin **2a** (25 mM) with 1.5 molar equiv each of the Barton ester and tributyltin hydride in dichloromethane (benzene for the 80 °C reaction). Ethyl acrylate proved to be an inefficient scavenger of the radical derived from **1b**, and significant amounts of reduction product were formed. At temperatures below -30 °C, the major product from **1b** was the Barton rearrangement pyridine derivative **5**, formed in a 4:1 ratio of diastereomers at -78 °C. The room-temperature and -24 °C reactions were photoinitiated. Addition products (*S*)-**3a** and (*R*)-**3a** are formed in ratios of 12:1 (80 °C), 25:1 (23 °C), and 36:1 (-24 °C). A plot of the log of the isomeric ratio k_S/k_R vs

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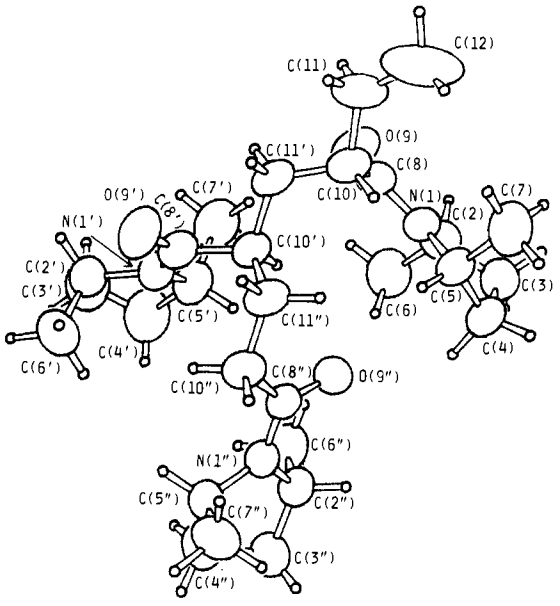
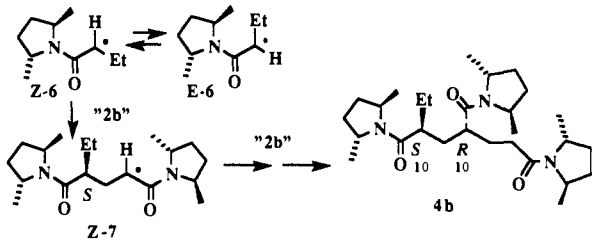


Figure 1. ORTEP diagram showing the atom numbering scheme and solid-state conformation of the major stereoisomer of **4b**; small circles represent hydrogen atoms.

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 $I > 3.0\sigma(I)$.

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(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.

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(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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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**,

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