Origins of Stereoselectivity in Radical Additions: Reactions of Alkenes and Radicals Bearing Oxazolidine and Thiazolidine Amide Groups

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Abstract: Single-crystal X-ray analysis of four alkenes that undergo stereoselective radical addition reactions are reported. The facial selectivity of radical additions to these alkenes is understood based upon their solid-state conformations. Alkenes which have a conformation placing a group at a position in space sterically protecting one of the faces from addition undergo radical addition with diastereofacial selectivity. The structures of the alkenes are analyzed by the polar coordinates of groups relative to the alkene center undergoing addition. The analysis of conformations of alkenes also provides a rationale for stereoselectivity in the reactions of radicals derived from the alkenes. Factors which influence the conformation of the alkene also apparently influence the conformation of analogous radicals. Several products of addition were also subjected to X-ray crystallographic analysis, and the steric factors which influence the conformation of the reactant alkene are also observed to affect the conformation of the radical addition products.

There has been an increase in interest in the use of free radicals in organic synthesis in recent years.[1-6] Methods for the construction of new C–C bonds via free radicals are extremely versatile and several new propagation sequences have been developed that allow for the efficient synthesis of complex structures. One problem that remains, however, has been the control of stereochemistry of new stereogenic centers that are formed in the addition reaction, whether they derive from a prostereogenic center of the alkene undergoing addition or from a prostereogenic radical center. Giese's laboratory has outlined the importance of steric effects in the addition reactions of cyclic radicals and cyclic alkenes undergoing addition,[7] and recent reports have provided an understanding of acyclic stereoselectivity based upon conformational control and steric hindrance in radical addition.[8] One can categorize stereoselective radical additions based upon whether the prostereogenic center resides on the alkene (α or β control, ref 8) or on the radical (ρ control) and also based on whether the resident stereogenic center is to become a part of the final product (substrate control) or is to be subsequently removed (auxiliary control).[8]

Hart,[9] Guindon,[10] Giese,[11] and Curran[12] have examined substrate-controlled ρ acyclic selectivity in systems where 1,3 allylic strain is thought to orient the facial bias of the radical reaction, Figure 1. Reaction of the radical on the face bearing the small (S) substituent is preferred to reaction on the radical face bearing the large (L) group. Selectivities of hydrogen atom transfer as high as 70:1 were observed in some cases.

Recent examples of acyclic auxiliary imposed stereocontrol have also been reported. The first example of auxiliary control of stereochemistry in radical addition was in a macrocyclization leading to a diastereomerically enriched muscone precursor.[13] The auxiliary, an amide derived from 2,5-dimethylpyrrolidine, was attached to the position of the alkene undergoing addition (α stereoselectivity), and alkene diastereofacial selectivity of 14:1 at 80 °C was achieved (Figure 2). This same auxiliary proved to be useful in intermolecular addition reactions, with selectivities in excess of 60:1 being obtained for the addition of tertiary radicals to alkenes bearing this group, and radicals with the same auxiliary add to alkenes with selectivities in excess of 12:1.[14-16]

The dimethylpyrrolidine substructure is not only difficult to prepare but is also difficult to remove subsequent to reaction, and alternative auxiliaries have been successfully employed. Curran has used a camphorsultam auxiliary in radical addition and cyclization reactions[17] to achieve high ρ selectivities. This auxiliary is commercially available in both enantiomeric forms, and it can be removed by hydrolysis or reduction. We have recently explored the use of heterocyclic compounds with structure **1** formed from reaction of 2-amino alcohols or 2-amino thiols with ketones (Figure 3). Our examination of these auxiliaries was based on the report of the use of the nitrogen derivative **1a** as a stereocontrol element in reductions of α keto amides[18] and also on the success of oxazolidines as auxiliaries in the reactions of metal carbenes.[19] Auxiliaries **1a–c** are similar to oxazolidinones which have been used successfully as auxiliaries in enolate chemistry, but there is no apparent requirement for chelation control of their confor-

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(1) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: New York, 1986.
(2) (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (b) Curran, D. P. *Synthesis* **1988**, 489.
(3) Hart, D. J. *Science* **1984**, *223*, 883.
(4) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
(5) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759.
(6) (a) Crich, D. *Aldrichimica Acta* **1987**, *20*, 35. (b) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.
(7) (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28(8)*, 969. See also: (b) Barton, D. H. R.; Gateau-Olesker, A.; Gero, S. D.; Lacher, B.; Tachdjian, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1987**, 1790.
(8) (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. See also: (b) Beckwith, A. L. J.; Chai, C. L. L. *J. Chem. Soc., Chem. Commun.* **1990**, 1087. (c) Beckwith, A. L. J.; Hersperger, R.; White, J. *J. Chem. Soc., Chem. Commun.* **1991**, 1151. (d) Renaud, P.; Schubert, S. *Synlett* **1990**, 624. (e) Renaud, P.; Ribezzo, M. *J. Am. Chem. Soc.* **1991**, *113(20)*, 7803. (f) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 722. (g) Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, *28*, 4205.
(9) Hart, D. J.; Krishnamurthy, R. *Synlett* **1991**, 412.
(10) Guindon, Y.; Lavallee, J.-P.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27.
(11) Bulliard, M.; Zeitz, H.; Giese, B. *Synlett* **1991**, 423.
(12) Curran, D. P.; Thoma, G. *Tetrahedron Lett.* **1991**, *32*, 6307.
(13) Porter, N. A.; Lacher, B.; Chang, V. H.-C.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309.
(14) Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H. G.; Lindner, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 8311.
(15) Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Giese, B.; Veit, Z.; Zeitz, H. G. *J. Am. Chem. Soc.* **1991**, *113*, 1791.
(16) Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1679.
(17) Curran, D.; Shen, W.; Zhang, J.; Heffner, T. *J. Am. Chem. Soc.* **1990**, *112*, 6738.
(18) Solodin, I.; Goldberg, Y.; Zelcans, G.; Lukevics, E. *J. Chem. Soc., Chem. Commun.* **1990**, 1321.
(19) (a) Imwinkelried, R.; Hegedus, L. S. *Organometallics* **1988**, *7*, 702. (b) Hegedus, L. S.; Montgomer, J.; Narukawa, Yukitoshi; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784.

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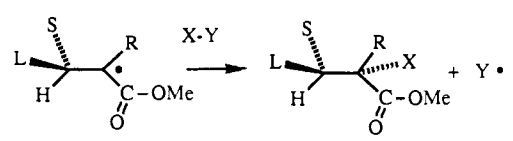


Figure 1. Substrate-controlled ρ selectivity with a 1,3 allylic strain control element.

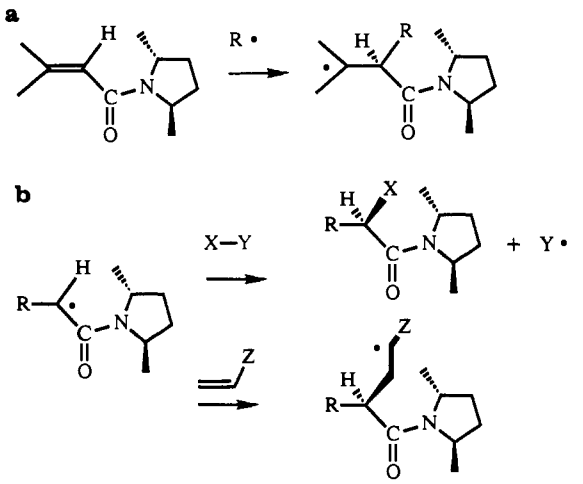


Figure 2. Dimethylpyrrolidine auxiliary control in radical additions. (a) Amide substitution on the alkene center undergoing addition (α selectivity). (b) Amide substitution on the radical center undergoing reaction (ρ selectivity).

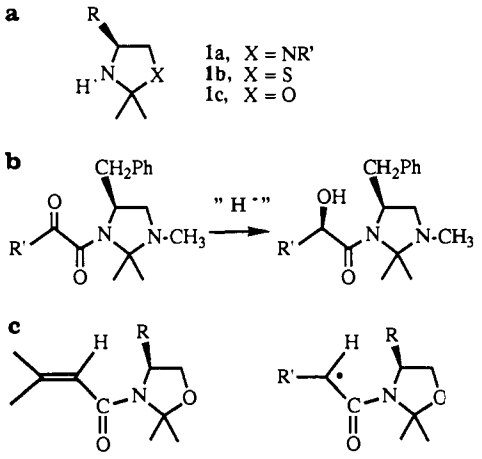


Figure 3. (a) Non-chelate auxiliaries based on heterocycles derived from acetone and diamines, amino thiols and amino alcohols. (b) Stereocontrolled reduction of α-keto amides with **1a** as an auxiliary. (c) Oxazolidine-substituted alkenes and radicals studied in α and ρ selectivity.

mations for them to serve as effective auxiliaries.[18] Oxazolidines **1c** prepared easily in one step from inexpensive commercially available aminols,[19] prove to be excellent auxiliaries in free radical reactions and give, in some cases, high α and ρ selectivities.[20] These auxiliaries can be removed by acid hydrolysis.

Selectivities observed from auxiliaries like **1** are dramatically dependent on the nature of the R group as well as on the type of free radical reaction. For example, reaction of a radical substituted with an amide bearing an oxazolidine amide auxiliary where R = Ph (Figure 3c) gives excellent ρ selectivity (33:1 at 0 °C) in addition reactions to thiohydroxamic esters, whereas addition to alkenes having the same auxiliary gives no facial α selectivity in the addition reaction (1.1:1 at 0 °C).[20] In contrast, if R = *t*-Bu, both reactions proceed with high selectivity. In order to understand better the relationship between auxiliary structure, free radical reaction type, and selectivity, we have examined a number of auxiliaries in several types of free radical reactions.

(20) Porter, N. A.; Bruhnke, J. D.; Wu, W.; Rosenstein, I. J.; Breyer, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 7788.

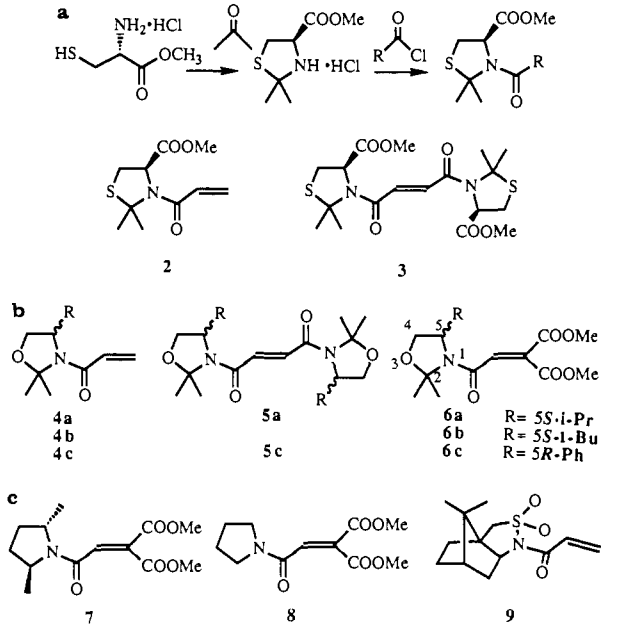


Figure 4. (a) Thiazolidine alkenes and preparative scheme. (b) Oxazolidine alkenes. (c) Pyrrolidine and camphorsultam alkenes.

We have also attempted, whenever possible, to acquire structural information about reactants and products pertinent to the issue of acyclic stereoselectivity. We report herein the results of these studies.

Results and Discussion

Synthesis and Analysis of Alkenes. Synthesis of alkenes with amide auxiliary groups attached thereto is straightforward. The synthesis of all dimethylpyrrolidine-containing alkenes discussed here has been described elsewhere,[14-16,21-23] and alkenes containing thiazolidine and oxazolidine substructures were prepared by in situ methods. Thus, reaction of acetone with β-amino alcohols or β-amino thiols gave the corresponding oxazolidine or thiazolidine intermediate. In the case of the thiazolidine derived from methylcysteine, the intermediate was isolated as the hydrochloride which was acylated with acryloyl chloride or fumaroyl chloride, Figure 4a. Oxazolidines were not isolated but were acylated with acid chlorides or mixed anhydrides to give the product alkenes **4–6**, Figure 4b.

A critical issue in determining the stereoselectivity of radical addition to auxiliary-substituted alkenes is the orientation of the resident chiral center relative to the carbon undergoing addition. Two single bonds, the C(α)–C(O) and C(O)–N bonds, link the alkene α center with the auxiliary for the alkenes **4–9**. The conformational orientation about these bonds is important in determining not only the selectivity but also the configuration of the newly formed stereogenic center in radical addition reactions which are thought to have early transition states[1,8a] and one can argue that conformations of the alkene starting material are translated to the transition state for addition. Thus, substituents which differentially hinder the alkene faces would be expected to lead to facial selectivity in addition reactions. Analysis of the preferred alkene conformation may therefore provide information about the potential selectivity of radical addition reactions.

Single-crystal X-ray analyses were performed on **2**, **4b**, **4c**, and **5c**. The solid-state conformations of these compounds are illustrated in Figures 5–8, while selected distances and angles are presented in Table I. Corresponding bond lengths and angles agree well. Torsion angles about the C—C bond in the O=C—C=C moiety of the alkenes in the solid state [**2**, 18.0 (5)°;

(21) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740.

(22) Porter, N. A.; Wu, W.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 707.

(23) Porter, N. A.; Breyer, R.; Swann, E.; Nally, J.; Pradhan, J.; Allen, T.; McPhail, A. T. *J. Am. Chem. Soc.* **1991**, *113*, 7002.

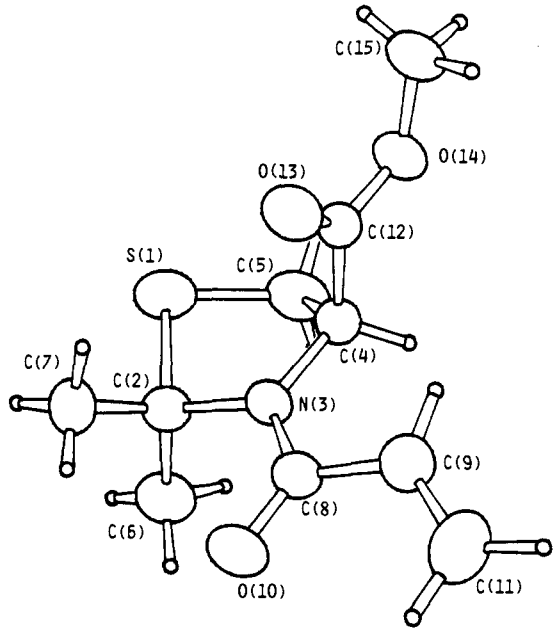


Figure 5. Solid-state conformation of **2**. ORTEP diagram (50% probability ellipsoids) showing the atom numbering scheme and solid-state conformation of **2**; small circles represent hydrogen atoms.

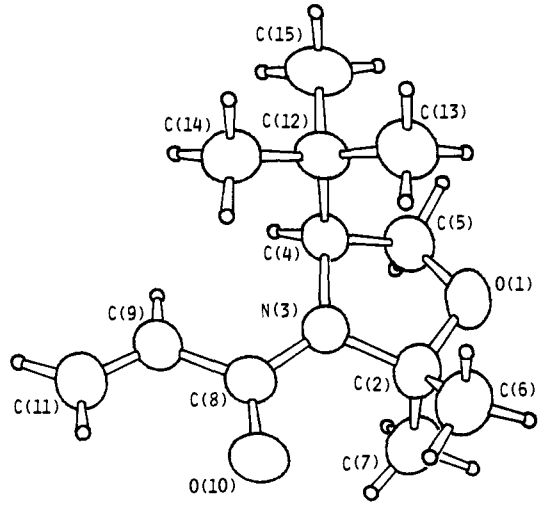


Figure 6. Solid-state conformation of **4b**. ORTEP diagram (50% probability ellipsoids) showing the atom numbering scheme and solid-state conformation of **4b**; small circles represent hydrogen atoms.

4b, 18.1 (3)°; **4c**, −7.6 (5)°; **5c**, 7.6 (4)° and 22.3 (5)°] indicate that each compound has a *Z* conformation of the carbonyl–alkene conjugated system, C(α)–C(O), Figure 9a. The alkenes **7**, **8**, and **9** also have similar solid-state conformations characterized by corresponding torsion angles of 9.4°,[22] −15.3°,[22] and −5.0°,[24] respectively. This *Z* conformation of C(α)–C(O) is expected on the basis of the facts that the carbonyl oxygen atom is smaller than the tertiary amide nitrogen atom and steric interaction of the vicinal alkene hydrogen atom attached to the β alkene center is smaller for oxygen than for the disubstituted nitrogen group.[25] The *Z* orientation of the carbonyl–alkene bond places the amide group antiperiplanar, or nearly so, to the alkene undergoing addition.

The location of the chiral groups on the amide relative to the alkene α center is also dependent on the orientation of the C(O)–N bond. For alkene **7** and other alkenes having the C_2-symmetric pyrrolidine auxiliary, the conformation about this bond is unimportant since both rotational isomers are equivalent due to symmetry. For the other auxiliary groups, however, rotamer population is presumably critical in determining the selectivity of addition and the configuration of the newly formed stereogenic center. Both NMR spectroscopy and X-ray crystallographic

(24) Curran, D. P.; Jeong, K.; Heffner, T. A.; Rebek, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 9238.

(25) The pseudotorsion angles, Me—C_q—C═O, for the two methyl substituents are 46° and 68°.

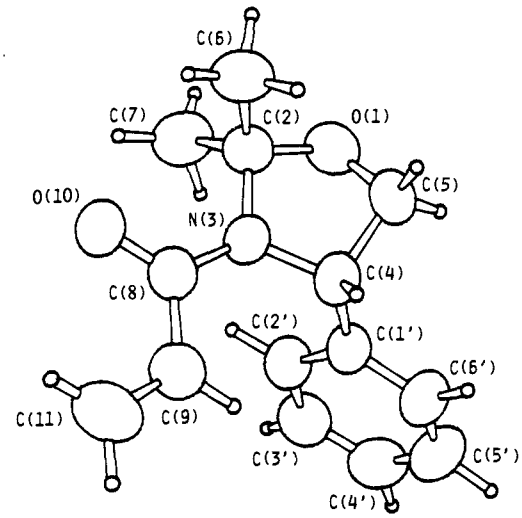


Figure 7. Solid-state conformation of **4c**. ORTEP diagram (50% probability ellipsoids) showing the atom numbering scheme and solid-state conformation of **4c**; small circles represent hydrogen atoms.

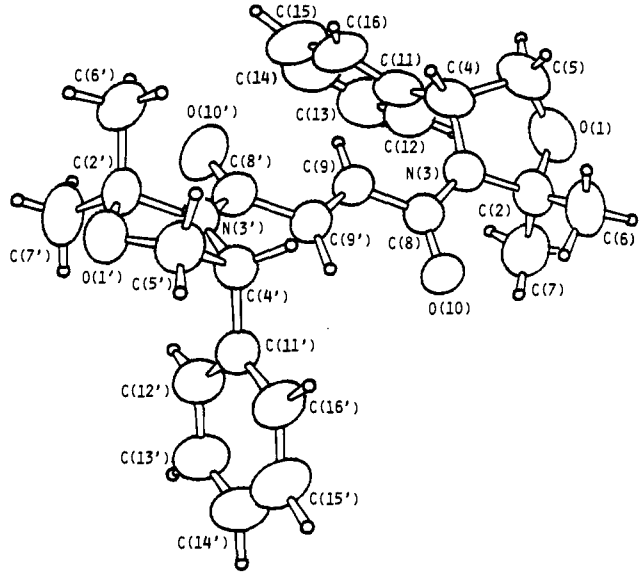


Figure 8. Solid-state conformation of **5c**. ORTEP digram (50% probability ellipsoids) showing the atom numbering scheme and solid-state conformation of **5c**; small circles represent hydrogen atoms.

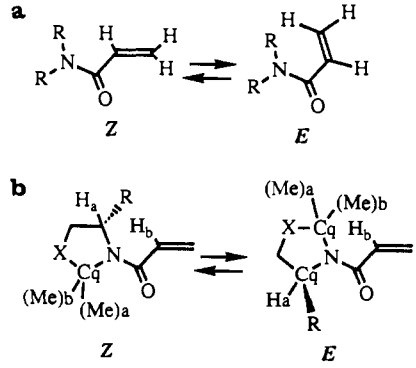
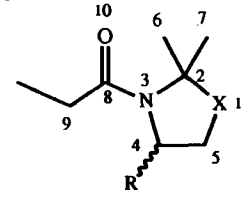


Figure 9. (a) O═C—C═C conformers of α,β-unsaturated amides. (b) O═C—N—C conformers of oxazolidine- and thiazolidine-substituted alkenes.

Table I. Selected Distances (Å) and Angles (deg) for **2**, **4b**, **4c**, **5c**, **12c**, and **15c**, with Estimated Standard Deviations in Parentheses



	2 X = S R = β-CO_2Me	**4b** X = O R = α-t-Bu	**4c** X = O R = α-Ph	**5c** X = O R = β-Ph		**12b** X = O R = α-t-Bu	**15c** X = O R = α-t-Bu		
				Bond Lengths					
X(1)–C(2)	1.828 (2)	1.422 (2)	1.423 (4)	1.425 (4)	1.427 (3)	1.430 (3)	1.430 (6)	1.420 (6)	1.426 (7)
X(1)–C(5)	1.792 (4)	1.425 (2)	1.411 (4)	1.415 (4)	1.417 (4)	1.420 (3)	1.426 (6)	1.411 (7)	1.422 (7)
C(2)–N(3)	1.488 (3)	1.494 (2)	1.487 (4)	1.487 (4)	1.494 (3)	1.496 (3)	1.492 (5)	1.504 (6)	1.488 (7)
N(3)–C(4)	1.465 (3)	1.484 (2)	1.455 (3)	1.474 (4)	1.466 (3)	1.477 (3)	1.475 (5)	1.484 (5)	1.481 (5)
C(4)–C(5)	1.518 (4)	1.525 (2)	1.537 (4)	1.528 (5)	1.521 (4)	1.517 (4)	1.527 (6)	1.531 (6)	1.525 (6)
N(3)–C(8)	1.362 (3)	1.350 (2)	1.363 (3)	1.349 (3)	1.349 (3)	1.360 (3)	1.342 (5)	1.355 (5)	1.353 (5)
C(8)–O(10)	1.225 (3)	1.241 (2)	1.237 (3)	1.224 (3)	1.227 (3)	1.223 (3)	1.217 (5)	1.214 (4)	1.232 (5)
				Bond Angles					
C(2)–X(1)–C(5)	90.9 (1)	107.8 (1)	106.6 (2)	108.9 (3)	106.9 (2)	107.2 (2)	107.0 (3)	108.5 (4)	107.3 (4)
X(1)–C(2)–N(3)	103.3 (1)	102.6 (2)	101.4 (2)	101.0 (2)	102.2 (2)	102.2 (2)	101.5 (3)	102.3 (4)	102.2 (4)
C(2)–N(3)–C(4)	115.9 (2)	111.1 (1)	111.3 (2)	112.0 (2)	111.0 (2)	110.9 (2)	111.1 (3)	110.6 (3)	111.1 (3)
N(3)–C(4)–C(5)	105.9 (2)	99.1 (1)	99.6 (2)	99.2 (3)	99.5 (2)	99.0 (2)	100.3 (3)	99.2 (4)	99.3 (3)
X(1)–C(5)–C(4)	103.5 (2)	105.0 (1)	103.8 (2)	103.9 (3)	103.4 (2)	105.0 (2)	104.6 (4)	104.9 (4)	104.6 (4)
C(2)–N(3)–C(8)	120.8 (2)	120.9 (1)	122.2 (2)	121.0 (2)	122.3 (2)	119.2 (2)	121.2 (3)	120.7 (3)	121.7 (4)
C(4)–N(3)–C(8)	123.3 (2)	126.3 (1)	125.3 (2)	126.5 (2)	126.0 (2)	126.8 (2)	126.7 (3)	127.7 (3)	126.6 (4)
N(3)–C(8)–C(9)	117.4 (2)	119.2 (2)	117.0 (2)	116.8 (2)	116.3 (2)	118.5 (2)	117.2 (3)	117.6 (3)	118.5 (4)
N(3)–C(8)–O(10)	122.2 (2)	120.5 (2)	121.6 (2)	122.8 (2)	122.6 (3)	122.0 (2)	123.7 (4)	122.1 (4)	121.4 (4)
C(9)–C(8)–O(10)	120.4 (3)	120.3 (2)	121.3 (2)	120.4 (2)	121.0 (2)	119.5 (2)	119.2 (4)	120.1 (4)	120.0 (4)
				Torsion Angles					
C(5)–X(1)–C(2)–N(3)	30.5 (2)	−28.1 (2)	−35.2 (3)	29.8 (3)	33.4 (3)	−28.5 (3)	37.4 (4)	28.1 (5)	30.9 (5)
X(1)–C(2)–N(3)–C(4)	−10.5 (2)	6.0 (2)	13.8 (3)	−7.4 (3)	−9.9 (3)	5.6 (3)	−15.7 (4)	−5.8 (4)	−9.1 (5)
C(2)–N(3)–C(4)–C(5)	−20.0 (3)	16.1 (2)	10.6 (3)	−15.1 (3)	−14.9 (3)	17.3 (2)	−7.6 (4)	−16.0 (5)	−14.1 (5)
N(3)–C(4)–C(5)–X(1)	41.5 (3)	−32.8 (2)	−31.7 (3)	32.3 (3)	34.8 (3)	−34.4 (2)	28.5 (5)	32.7 (5)	32.5 (5)
C(2)–X(1)–C(5)–C(4)	−42.4 (2)	39.9 (2)	43.4 (3)	−40.9 (3)	−44.5 (3)	41.2 (3)	−41.2 (5)	−39.9 (5)	−41.4 (6)
C(2)–N(3)–C(8)–O(10)	3.1 (4)	19.1 (2)	1.2 (4)	−1.8 (4)	−4.9 (5)	21.6 (4)	−3.6 (6)	−10.0 (6)	−4.6 (6)
C(4)–N(3)–C(8)–C(9)	3.9 (4)	4.8 (2)	−14.2 (3)	7.4 (4)	7.0 (4)	1.4 (4)	9.9 (6)	−2.1 (6)	2.6 (6)
C(2)–N(3)–C(8)–C(9)	−178.4 (2)	−159.0 (2)	−179.0 (3)	178.9 (3)	176.0 (3)	−157.0 (2)	177.3 (3)	165.5 (3)	172.5 (4)
C(4)–N(3)–C(8)–O(10)	−174.6 (3)	−177.2 (2)	168.0 (2)	−173.3 (3)	−173.9 (3)	180.0 (4)	−171.0 (4)	−177.7 (4)	−174.5 (4)
ΔN^a	0.016	0.108	0.088	0.056	0.073	0.145	0.083	0.082	0.067
ΔC^b	0.010	0.013	0.015	0.005	0.006	0.010	0.006	−0.031	0.020

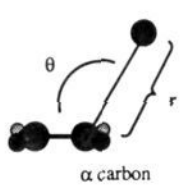
[a] ΔN is the displacement (Å) of N(3) from the C(2)–C(4)–C(8) plane. [b] ΔC is the displacement (Å) of C(8) from the N(3)–C(9)–O(10) plane.

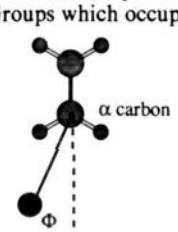
analysis provide information that is useful in a discussion of the conformational preference of the amide group in alkenes **2–6**. Evidence for two conformational isomers is observed in the NMR spectra for all of the alkenes, and our interpretation of the data is that the conformations differ by rotation about the amide C(O)–N bond, Figure 9b. Thus, two signals are observed for H_a and H_b, and four methyl singlets are present, two each for Me_a and Me_b, for each of the alkenes examined. Coalescence of the NMR signals due to the rapid interconversion of the rotamers on the NMR time scale occurs at temperatures of 50–80 °C for most of the alkenes.

Integration of characteristic signals for each rotamer gives a rotamer population distribution. Phenyl substitution on the oxazolidine ring tends to cause the largest bias of the rotamer population, 10:1 for **4c**, **5c**, and **6c**, while a *tert*-butyl substituent leads to a much smaller equilibrium distribution, 2:1 for **4b** and **6b**. The isopropyl-substituted oxazolidines **4a–6a** and the thiazolidine **2** with a carbomethoxy substituent all have rotamer distributions of ca. 5–9:1. NMR nuclear Overhauser experiments for alkenes **6a** and **5c** suggest that the major rotamer present for these alkenes is the *Z* compound, Figure 9b. Thus, irradiation of H_a leads to enhancement of the signal due to H_b for the major rotamer of each of these alkenes, whereas no enhancement of H_b is observed when H_a of the minor rotamer is irradiated.

The solid-state conformation for each of the alkenes subjected to X-ray crystallographic analysis has the thiazolidine and oxazolidine C(*O*)–N orientation in the *Z* arrangement, consistent with the solution-phase NMR studies. Torsion angles from the X-ray analyses for O=C—N—C_q, where C_q is the quaternary carbon atom of the oxazolidine or thiazolidine bearing the two methyl substituents, are as follows: **2**, 3.1 (4)°; **4b**, 19.1 (2)°; **4c**, 1.2 (4)°; **5c**, −1.8 (4)°, and −4.9 (5)°. For each of these alkenes except **4b**, the oxazolidine with the *tert*-butyl substituent, the C=O bond vector approximately bisects the Me_a–C_q–Me_b bond angle, and the O(carbonyl)–C(methyl) distance is within 0.1 Å in all cases. Hydrogen atoms on the geminal methyl groups lie 2.30 (6)–2.59 (2) Å from the carbonyl oxygen atom, and rotation away from the bisected arrangement would bring these atoms even closer together. The conformation about the amide linkage of **4b** is similar to that of the other alkenes, but cross-ring crowding of the *tert*-butyl group and the cis geminal methyl substituent results in deformation of the ring such that the C=O bond vector no longer bisects the Me_a–C_q–Me_b bond angle.[25] The amide nitrogen atom is displaced by 0.108 and 0.145 Å in **4b** and **12b**, respectively, from the plane defined by the carbonyl carbon and the ring atoms bonded to nitrogen. This deviation from a trigonal planar geometry is greater than in the phenyl-substituted compounds, where the out-of-plane displacements range from only 0.016 Å in thiazolidine **2** to 0.056–0.088 Å in oxazolidines **4c** and **5c**. The nitrogen atom displacement is consistently toward the side of the ring bearing the *tert*-butyl or phenyl substituent. This pyramidalization is also, apparently, the result of cross-ring steric strain involving the *tert*-butyl group and the cis geminal methyl attached to C_q. Hydrogens attached to these groups have a close contact of 2.25 Å.

We have suggested[22] that polar coordinates of resident groups relative to the alkene carbon center can be used to provide information about access of an attacking radical to the diastereotopic faces of a carbon–carbon bond. The distance of groups from the α carbon, *r*, and the angles Φ and θ shown below, are important parameters for evaluation of selectivity. Groups which occupy





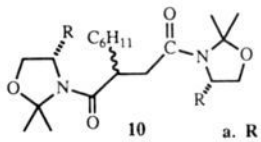
a volume of space with coordinates $\Phi \sim 0°$, $\theta \sim 110°$ and with small *r* value (2.5–4.0 Å) protect electrophilic alkenes from addition of nucleophilic radicals.[26–29] Polar coordinate analysis of resident auxiliary groups for alkenes **2**, **4**, and **5** was carried out on the basis of the solid-state conformations; the results are presented in Table II. For comparison, the alkene **7** has a pyrrolidine methyl substituent that protects one face from addition with coordinates of $r = 3.34$, $\Phi = 10.8°$, and $\theta = 141°$, while the other diastereotopic face is relatively accessible, $r = 4.35$, $\Phi = 60°$, and $\theta = 157°$.[22] Of the alkenes analyzed, on the basis of the solid-state conformations, alkene **4b** would appear to have an auxiliary group best placed in a volume of space for diastereoface protection. Thus, one of the primary carbons of the *tert*-butyl group in **4b** is only 3.18 Å from the α carbon, and it is located nearly perfectly in the preferred vector of approach of a nucleophilic group to the carbon–carbon bond. The coordinates of auxiliary groups for the alkenes **2**, **4c**, and **5c** indicate that the group attached to the heterocycle α carbon, i.e., carbomethoxy or phenyl, is oriented poorly for alkene facial shielding. While *r* for these groups is comparable to that for **4b** or **7**, the values of Φ and θ differ substantially from the ideal. Indeed, one of the phenyl groups in **5c** is virtually orthogonal to the alkene π bond with $\Phi = 90°$ and $\theta = 180°$ for the phenyl-substituted carbon.

Table II. Polar Coordinate Analysis of Solid State Conformations of Alkenes

alkene	auxiliary atom	*r* (Å)	Φ (°S)	θ (°S)
2	ester carbonyl C	3.29	66	176
4b	*tert*-butyl primary C	3.18	8	120
4c	phenyl-substituted C	3.32	60	170
5c	phenyl-substituted C_a[a]	3.37	60	166
5c	phenyl-substituted C_b[b]	3.36	90	180

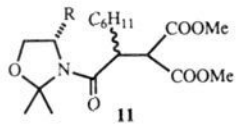
[a] C_a is the phenyl carbon attached to one of the oxazolidines. [b] C_b is the phenyl carbon of the other oxazolidine.

Addition Reactions of Alkenes and Radicals with Thiazolidine and Oxazolidine Auxiliaries. α Selectivity. Addition reactions of cyclohexyl radical to the alkenes **3**, **5**, and **6** were carried out using the "mercury" method.[1,8a] Thiazolidine fumaramide **3** gave complex product mixtures under all of the conditions surveyed, and selectivity for that reaction is not reported. For **5c**, the diastereomeric products of addition, **10c**, are formed in a ratio of 1.1:1 at 0 °C as are the products **11c** formed from addition to **6c**. Even at −78 °C utilizing Barton ester precursors and



10

a. R = i-Pr
b. R = t-Bu
c. R = Ph



11

photochemical initiation, selectivity for the formation of **11c** was only 1.3:1. Addition to the alkene derived from an isopropyl-substituted oxazolidine, **6a**, gives a diastereomer product mixture of 7:1 at 0 °C, while the *tert*-butyl-substituted analog **6b** gives essentially one product of addition, with a product diastereomer ratio in excess of 80:1. For comparison, a product ratio of 40:1 was obtained for the addition of cyclohexyl radical, under similar conditions, to the dimethylpyrrolidine-substituted alkene **7**.

Based upon the solid-state conformations of the alkenes, one can speculate on the reasons for the observed α selectivity of the addition reactions described above. For the alkyl-substituted oxazolidines **6a** and **6b**, the local conformation around the amide linkage is relatively rigid since there is a close contact of the groups attached to the oxazolidine stereogenic center α to nitrogen and the alkene carbon bearing the amide. The H_a–H_b distance for **4b** is only 2.04 Å and the *t*-Bu substituent is staggered about the C_{ring}–$C_{t\text{-}Bu}$ bond with one of its methyl groups situated over the alkene α center such that there is a "gearlike" arrangement of

(26) Houk, K. N.; Paddon-Row, M. N.; Spellmeyer, D. C.; Rondan, N. G.; Nagase, S. *J. Org. Chem.* **1986**, *51*, 2874.
(27) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
(28) Fueno, T.; Kamachi, M. *Macromolecules* **1988**, *21*, 908.
(29) For a comparison of nucleophilic and electrophilic radical addition reactions, see: Zipse, H.; He, J.; Houk, K. N.; Giese, B. *J. Am. Chem. Soc.* **1991**, *113*, 4324.

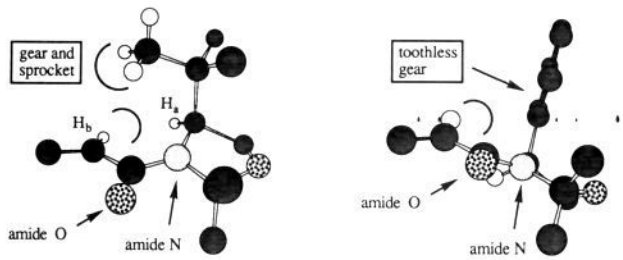


Figure 10. Gearlike arrangement of alkyl-substituted oxazolidines. (a) Portion of solid-state structure of **4b**. (b) Portion of solid-state structure of **5c**.

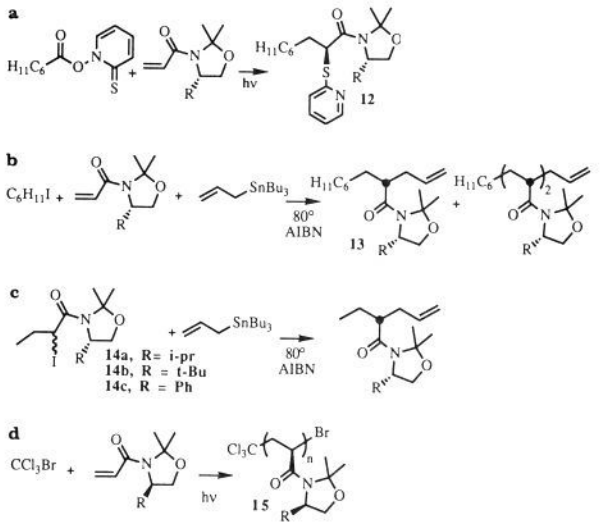


Figure 11. Reactions used to assess ρ selectivity of oxazolidines and thiazolidines. (a) Barton ester addition. (b) Allylstannane transfer. (c) Allylstannane transfer to iodoamides. (d) Bromotrichloromethane chain-transfer telomerization.

H_b and the *t*-Bu group, Figure 10. Movement about the rotatable C(O)—C=C and C(O)—N bonds cannot occur without crowding the *t*-Bu group into the alkene α center or eclipsing the amide carbonyl oxygen with one of the methyls on C_q. For the oxazolidine with R = *t*-Bu, this gearlike arrangement exists, and one expects a maximum interaction of this type for this oxazolidine. For oxazolidines substituted at the stereogenic center via an sp^2 hybridized atom, no such interaction exists, giving the molecule a greater degree of flexibility. Thus, for the alkenes **4c** and **5c**, as well as for the thiazolidine **2**, the solid-state conformation places the planar substituent (phenyl or carbomethoxy) orthogonal to the alkene α carbon. This is illustrated in Figure 10 for one of the amide linkages of the fumaramide **5c**. Partial rotation about the C(O)—C=C and C(O)—N single bonds is possible, and the amide substructure of the molecule is presumably mobile because the phenyl group acts like a toothless gear and does not fix the auxiliary with respect to the alkene α center.

The arguments made for the solid-state conformation of the alkenes discussed above also presumably apply to the transition state for addition of the cyclohexyl radical. Thus, in the transition state for addition, the phenyl group of the substrates **5c** and **6c** can slip away from a radical attacking either face of the alkene by rotation about the C(O)—C=C and C(O)—N single bonds, and this auxiliary therefore does not provide facial selectivity. The geometry of the *tert*-butyloxazolidine, on the other hand, is fixed in the transition state in an arrangement analogous to the solid-state conformation, resulting in high facial selectivity.

ρ Selectivity. Four reaction types, shown in Figure 11, were examined to assess the efficacy of thiazolidine and oxazolidine auxiliaries as stereocontrol elements when attached directly to a prostereogenic radical center. In each of these reactions, an intermediate prostereogenic radical is generated by addition of a radical to the acrylamides **2** and **4a–c**. In the Barton ester approach, reaction of the intermediate radical with the thiohydroxamate ester defines the new stereogenic center, while in the allylstannane and telomerization schemes, the new center is formed in an addition of the prostereogenic radical to a carbon–carbon double bond.

Table III. Selectivity for Cyclohexyl Thiohydroxamate Ester Addition and Allyl Transfer Reactions to Acrylamides 2 and 4a–c, Figure 11a and 11b

reaction type	alkene	*t*, (°C)	selectivity[a]
Barton ester	**2**	23	20:1
Barton ester	**4a**	23	7:1
Barton ester	**4a**	80	5:1
allyl transfer	**4a**	80	4:1
Barton ester	**4b**	23	60:1
allyl transfer	**4b**	80	25:1
Barton ester	**4c**	23	33:1
Barton ester	**4c**	−78	73:1
Barton ester	**4c**	80	23:1
allyl transfer	**14a**	80	5:1
allyl transfer	**14c**	80	3:1

[a] Analysis by GC. At least triplicate analysis of duplicate experiments; error is less than 5%.

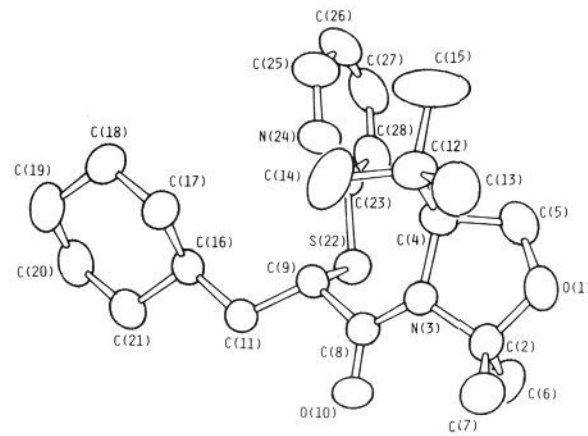


Figure 12. Solid-state conformation of **12b**. ORTEP diagram (50% probability ellipsoids) showing the atom numbering scheme and solid-state conformation of **12b**; small circles represent hydrogen atoms.

Selectivities for the reactions shown in Figure 11a, the Barton ester approach, are presented in Table III. Yields of products isolated from these addition reactions were usually in excess of 75%, and the major stereoisomer was fully characterized in every case. NMR and mass spectral data were also obtained for the minor stereoisomers formed. Presented in Table III also are the selectivities for the allylstannane transfer reaction, Figure 11b. This reaction propagates well only at temperatures of 80 °C or above.[30] The allyl transfer reaction was also carried out on the isopropyl- and phenyloxazolidine amides of 2-iodopropionic acid, **14a** and **14c**. In this reaction, a prostereogenic radical is generated directly from the iodide precursor, and this radical is trapped by allyltributylstannane.

The stereochemistry of the products formed in the thiohydroxamate ester photolysis and the allyl transfer reaction was established for products **12b** and **13b** (R = *t*-Bu). A single-crystal X-ray analysis of **12b**, Figure 12, shows that starting from **4b** having the *S* configuration, the configuration of the new stereogenic center formed in **12b** is *S*. An independent synthesis was used to provide information about the stereochemistry of the major diastereomer of **13b** formed. This synthesis is outlined in Scheme I. Allylation of the enolate of the (*S*)-prolinol amide of 3-cyclohexyl propionic acid gave an 8:1 mixture of diastereomers (the major product is shown in the scheme), and subsequent conversion of this amide, via the free acid and its acid chloride, to **13b** and to an analogous sultam product previously reported[30]

(30) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738.

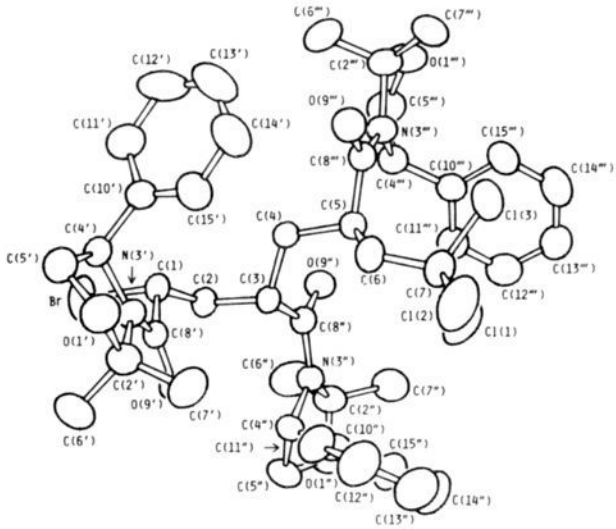
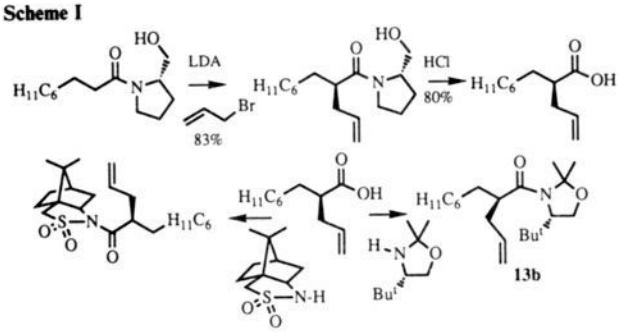


Figure 13. Solid-state conformation of **15c**. ORTEP diagram (40% probability ellipsoids) showing the atom numbering scheme and solid-state conformation of **15c**; small circles represent hydrogen atoms.

Scheme I



established the stereochemistry of the free radical allylation product.

Photolysis of the acrylamides **4a–c** and bromotrichloromethane in methylene chloride at room temperature gave a mixture of telomers of structure **15**. Analysis of the phenylglycinol-derived telomers from **4c** by normal-phase HPLC gave two $n = 1$ diastereomers with a major:minor product ratio of 10:1. Likewise, for $n = 2$ and $n = 3$, one major product dominated the diastereomer mixture. This distribution is analogous to that reported earlier[23] for telomers formed from the acrylamide of 2,5-dimethylpyrrolidine. The major $n = 3$ diastereomer was isolated by preparative HPLC, and X-ray crystallographic analysis established the stereochemistry of the three stereogenic centers formed in the telomerization, Figure 13.

Analysis of the conformational arrangement of the intermediate radicals that undergo stereoselective additions leads to the conclusion that those factors which influence selectivity in the addition of radicals to diastereotopic alkene faces (α selectivity) will also influence selectivity in the addition of alkenes to diastereotopic radical faces (ρ selectivity). It has been suggested that radicals substituted α to esters or amides are stabilized by 10–12 kcal/mol.[31] One expects that for amide or imide groups substituted on radicals, the orientation of the C–C(O) bond is fixed in the *Z* orientation since the NR_2 group is large relative to the carbonyl oxygen. In fact, Strub, Roduner, and Fischer have studied α amide radicals by EPR spectroscopy,[31] and they have suggested that the preferred conformer of such radicals has the *Z* orientation, while analogous α ester radicals exist with *Z* and *E* geometric isomers present at equilibrium. Chiral groups attached to an amide-substituted radical would therefore be fixed relative to the radical, while those attached to an ester radical would have more than one conformer contributing to the overall stereoselectivity. Fischer also suggests that the barrier separating the *Z* and *E* conformers of both α amide and α ester radicals is in excess of 11 kcal/mol.

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

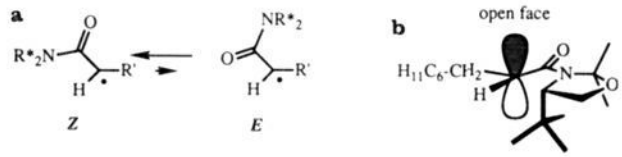


Figure 14. (a) Conformers of amide-substituted radicals. (b) Radical intermediate for reactions shown in Figures A and B with R = *t*-Bu.

Control of the orientation about the amide N–C(O) is also essential to fix the position of a resident chiral group relative to the ρ center, and we presume that factors that are important in orienting the auxiliary with respect to alkene α carbons are also important in orienting the auxiliary relative to the radical ρ center. The configuration of the new stereogenic centers formed in the addition reactions described in Figure 11 is consistent with this analysis. That is, one can understand the ρ stereoselectivity observed by assuming a preferred orientation of the auxiliary with respect to the radical center as shown in Figure 14b.

The analysis presented above ignores the Curtin–Hammett principle. The selectivity observed in such reactions, α or ρ, depends on the population of conformers and the selectivity that results from reaction of any conformer present, as well as on the rates of conformer formation, interconversion, and reaction. We have little information about any of these rates and selectivities that would allow us to provide a rational kinetic analysis of such a complex system. Nevertheless, the simple analysis based upon preferred radical conformation and access to diastereotopic alkene and radical faces apparently translates to preferred transition states for these reactions.

We note that the barriers to rotation about the radical C–C(O) and N–C(O) bonds may be different from the barriers to rotation about the same bonds in analogous alkenes. For example, one might expect that the barrier to rotation about the radical carbon–carbonyl bond would be greater than that to rotation about the analogous bond in alkenes since there is apparently significant delocalization of the radical into the adjacent carbonyl. The selectivity that results obviously depends on these factors, and significant differences are observed for different auxiliaries in the different reaction types. The phenyloxazolidine auxiliary, for example, gives essentially no α selectivity, but ρ selectivity with this same auxiliary in the thiopyridyl transfer reaction is excellent. Indeed, selectivity for the addition to thiohydroxamate esters is good to excellent for all of the auxiliaries examined, as is addition to alkenes in the telomerization reactions, while the allyl transfer occurs with much lower selectivity for all of the oxazolidines. As is the case in α selectivity, *tert*-butyloxazolidine gives the best ρ selectivity of any of the auxiliaries studied.

Single-Crystal X-ray Analysis of Reaction Products. Several single-crystal X-ray analyses have been carried out on reaction products in order to provide stereochemical information about the reactions described with oxazolidine and pyrrolidine auxiliaries, and the results derived therefrom proved to be invaluable in the assignment of stereochemistry, vide supra. Detailed analysis of the solid-state conformations of these reaction products results in interesting comparisons of local molecular conformations near the stereogenic center formed in the addition reactions. In particular, there is a common arrangement of the torsion angle H–C_s–C(O)–N (C_s is the stereogenic center formed in the addition reaction) for all of the compounds examined that places the H and N in a conformation between an eclipsed and gauche arrangement. A typical example of this local conformation is illustrated in Figure 15, where a portion of the solid-state conformation of the thiopyridyl compound **12b** is reproduced. The torsion angle H–C_s–C(O)–N is −37° for this solid-state conformation. H–C_s–C(O)–N torsion angles for product **15c**, $n = 3$ (Figure 13) are $\tau_1 = 24°$, $\tau_2 = 23°$, and $\tau_3 = 32°$. Corresponding torsion angles for compounds with a dimethylpyrrolidine attached to a stereogenic center are closer to 0°; thus, torsion angles for

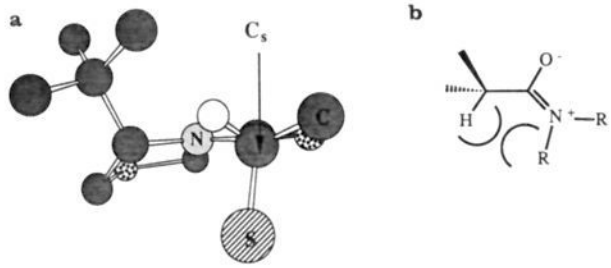


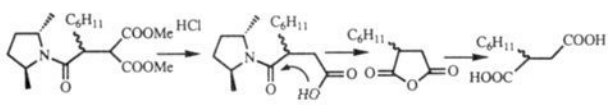
Figure 15. (a) Portion of the solid-state conformation of the compound **12b**, showing the local conformation about the stereogenic carbon, C_s. (b) Allylic strain in disubstituted amides (amide ionic resonance structure shown).

a bromo and an iodo compound reported earlier,[21] as well as an $n = 3$ telomer bearing a dimethylpyrrolidine auxiliary,[20] have magnitudes ranging from 0° to 6°.

One can understand these local conformational preferences based upon allylic strain effects in tertiary amides as shown in Figure 15b. This is essentially the same steric interaction that causes the *Z* radical to be of lower energy than the corresponding *E* radical (Figure 14). It is reasonable to suggest that this steric effect, present in the reactant radical and in the addition product, is also experienced in the transition state connecting the radical precursor and the product.

Hydrolysis of Oxazolidine and Pyrrolidine Amides. Hydrolysis of oxazolidines is possible under acidic conditions, and the compounds **10** and **11**, for example, can be converted to cyclohexylsuccinic acid in this way. Overnight heating of the major diastereomer of **11a** gives cyclohexylsuccinic acid in 90% yield with $[\alpha]^{22}_D = -21.5 \pm 0.7°$ ($c = 0.89$ in ethanol). This identifies the stereogenic center of this major diastereomer as being *R* and also indicates that the hydrolysis has occured with little racemization [optically pure (*S*)-cyclohexylsuccinic acid is reported to have $[\alpha]^{30}_D = +26.3°$ ($c = 1.937$ in ethanol),[32] but samples that we have resolved and purified according to the literature gave $[\alpha]^{22}_D = +22.0 \pm 0.6°$ ($c = 0.64$ in ethanol)].

It is interesting to note that the compound **16** also undergoes acid-catalyzed hydrolysis without racemization to give cyclohexylsuccinic acid under conditions similar to those described above for the oxazolidine. Pyrrolidine amides like that present



16

in **16** normally hydrolyze with difficulty unless there is some functional group available to assist in the hydrolysis, and we suggest that the assisting group in this case is the carboxylic acid formed from initial methyl ester hydrolysis and decarboxylation.

Hydrolysis of the Barton ester adduct is possible under acidic conditions, but reconversion of the product acid back to **12c** showed that significant racemization attended the sequence.

Experimental Section

Tetrahydrofuran was freshly distilled from sodium benzophenone. Dichloromethane was distilled from calcium hydride and stored over molecular sieves. Benzene was distilled from sodium and stored over molecular sieves. Gas chromatography was performed on a Hewlett-Packard 5890A gas chromatograph with one of two columns (column A; 30 m SPB-5, 0.20 mm i.d.; column B, 15 m SPB-1, 0.32 mm i.d.) and a flame ionization detector coupled to a Hewlett-Packard 3393A integrator. NMR spectra were run on either a Varian XL-300 or a General Electric QE-300 spectrometer set at 300 MHz for ^1H and 75 MHz for ^{13}C. Chemical shifts are reported in ppm downfield from TMS with residual solvent as an internal standard. When multiple rotational isomers are present, the data for the major one only are reported. Mass spectra were acquired on a Hewlett-Packard 5990 spectrometer. Preparative HPLC was done using an ISCO Model 2350 pump with a Dynamax 60A Si 83-121-C column and a refractive index detector. Analytical HPLC was performed using a Waters Model 590 pump with two Beckman Si columns (5 μm, 4.6 mm × 25 cm) in series and a Waters Lambda Max 481 UV detector at λ = 254 nm. Melting points are uncorrected.

Preparation of Alkenes. 4(*R*)-(Methoxycarbonyl)-2,2-dimethylthiazolidine Hydrochloride. Cysteine hydrochloride monohydrate (5.0 g, 29 mmol) was suspended in a mixture of acetone (250 mL) and 2,2-dimethoxypropane (50 mL). The mixture was heated at reflux for 1.5 h and cooled via ice bath. Collection onto a sintered glass funnel afforded 5.6 g (91%) of product: mp 160–161 °C; ^1H NMR (D_2O) δ 5.02 (dd, $J = 8.2$ Hz, 1 H), 4.80 (s, 2 H), 3.86 (s, 3 H), 3.68 (dd, $J = 8.2$ Hz, 1 H), 3.55 (dd, $J = 8.2$ Hz, 1 H), 1.82 (s, 3 H), 1.80 (s, 3 H); ^{13}C NMR (D_2O) δ 170.84, 75.45, 64.22, 56.76, 33.87, 30.48, 29.26.

***N*-Acryloyl-4(*R*)-(methoxycarbonyl)-2,2-dimethylthiazolidine (2).** To a stirring solution of acryloyl chloride (0.25 mL, 1.1 equiv, 3.1 mmol) and diisopropylethylamine (0.54 mL, 1.1 equiv, 3.1 mmol) in dry CH_2Cl_2 (15 mL) at room temperature under argon was added a solution of the thiazolidine (600 mg, 2.83 mmol) and diisopropylethylamine (0.56 mL, 1 equiv, 2.83 mmol) in 5 mL of CH_2Cl_2. An additional 5 mL of CH_2Cl_2 was used to rinse out the flask. The reaction was stirred for 2 h, and then it was poured into water. The organic phase was separated, washed with water, dried over $MgSO_4$, and concentrated in vacuo. Isolation of product by flash column chromatography (25% EtOAc in hexane, silica) yielded 0.50 g (77%) of product: mp 86–88 °C; ^1H NMR ($CDCl_3$, at −20 °C the ^1H NMR spectrum indicates a rotational isomer ratio of 5.2:1) δ 6.24 (m, 2 H), 5.61 (m, 1 H), 4.91 (m, 1 H), 3.75 (s, 3 H), 3.28 (m, 2 H), 1.90 (s, 3 H), 1.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.65, 164.19, 130.05, 128.16, 73.81, 65.56, 53.01, 31.45, 29.50, 27.22; $R_f = 0.38$ (50% EtOAc in hexane). Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11. Found: C, 52.40; H, 6.60; N, 6.04.

Acrylic 2,2-Dimethyl-5-alkyl-1,3-oxazolidinides 4a–c. The following procedure for **4a** is typical and is presented below. To a 50-mL round bottom flask containing 3.1 g of (*S*)-valinol was added 18 mL (8 equiv) of acetone. After being stirred at room temperature for 40 min, the solution was mixed with 100 mL of dichloromethane and 10 g of $MgSO_4$ and was stirred overnight. After the $MgSO_4$ was filtered off, the solvent was removed under reduced pressure to leave 3.5 g (85%) of residue: ^1H NMR ($CDCl_3$) δ 3.90 (t, $J = 7.4$ Hz, 1 H), 3.29 (t, $J = 8.0$ Hz, 1 H), 3.07 (m, 1 H), 1.55 (m, 2 H), 1.41 (s, 3 H), 1.28 (s, 3 H), 1.01 (d, $J = 6.6$ Hz, 3 H), 0.87 (d, $J = 6.6$ Hz, 3 H); ^{13}C NMR δ 95.25, 69.60, 64.90, 32.36, 27.70, 26.33, 20.62, 19.81. Without further purification, the residue was dissolved in 40 mL of CH_2Cl_2 and cooled to 0 °C, and 3.42 mL (1 equiv) of Et_3N was added dropwise followed by dropwise addition of 2 mL (1 equiv) of acryloyl chloride. The mixture was stirred at 0 °C for 30 min and then at room temperature for 3.5 h.

Acrylic 2,2-Dimethyl-5(*S*)-isopropyl-1,3-oxazolidinide (4a). The product was purified by flash column chromatography (20% EtOAc in hexane, silica), yielding 81% of a yellow oil: ^1H NMR ($CDCl_3$, rotamer ratio of ~13:1) δ 6.39 (d, $J = 5.4$ Hz, 2 H), 5.66 (m, 1 H), 3.93 (m, 2 H), 3.77 (m, 1 H), 2.00 (m, 1 H), 1.70 (s, 3 H), 1.54 (s, 3 H), 0.93 (m, 6 H); ^{13}C NMR δ 162.96, 129.64, 127.80, 95.48, 64.31, 62.13, 31.96, 25.87, 22.86, 19.76, 17.14. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.79; H, 9.74; N, 7.01.

Acrylic 2,2-Dimethyl-5(*S*)-*tert*-butyl-1,3-oxazolidinide (4b). The product was isolated by flash column chromatography (30% EtOAc in hexane, silica), giving an 80% yield of the product: mp 56–58 °C; ^1H NMR ($CDCl_3$, rotamer ratio 2:1) δ 6.51 (dd, $J = 10.07$, 16.55 Hz, 1 H), 6.34 (dd, $J = 16.55$, 2.06 Hz, 1 H), 5.62 (dd, $J = 10.07$, 2.06 Hz, 1 H), 4.01 (m, 1 H), 3.92 (m, 1 H), 3.76 (m, 1 H), 2.00 (m, 1 H), 1.74 (s, 3 H), 1.52 (s, 3 H), 0.92 (s, 9 H); ^{13}C NMR δ 166.18, 130.6, 127.2, 96.3, 65.0, 64.9, 35.7, 27.6, 26.4, 22.9; $R_f = 0.46$ (50% EtOAc in hexane). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.27; H, 10.05; N, 6.63.

Acrylic 2,2-Dimethyl-5(*R*)-phenyl-1,3-oxazolidinide (4c). The product was isolated by Kugelröhr distillation (120 °C at 0.06 mmHg), giving a 74% yield of the product. Crystals suitable for an X-ray crystal analysis were grown by slow evaporation of ether: mp 81.0–82.0 °C; ^1H NMR ($CDCl_3$, there was no evidence of a minor rotational isomer) δ 7.40–7.25 (m, 5 H), 6.28 (dd, $J = 2.02$, 16.63 Hz, 1 H), 6.08 (dd, $J = 10.14$, 16.65 Hz, 1 H), 5.45 (dd, $J = 2.01$, 10.15, Hz, 1 H), 5.00 (dd, $J = 2.26$, 6.46 Hz, 1 H), 4.38 (dd, $J = 6.53$, 8.91 Hz, 1 H), 3.92 (dd, $J = 2.38$, 8.92 Hz, 1 H), 1.87 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.3, 141.4, 129.7, 128.9, 127.8, 127.8, 125.8, 96.2, 71.3, 61.1, 25.2, 23.2; $[\alpha]^{23}_D = -85.8°$ (c 1.02, $CHCl_3$); MS (CI, isobutane) $MH^+ = 232$. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.50; H, 7.34; N, 6.01.

Fumaric Bis[2,2-dimethyl-5-alkyl-1,3-oxazolidinides] 5a,c. The following procedure for the preparation of **5c** is typical. The oxazolidine [prepared as for **4a** from 1.0 g (7.3 mmol) of (*R*)-phenylglycinol] was dissolved in 25 mL of dry CH_2Cl_2 and cooled to 0 °C under argon.

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Triethylamine (1.2 mL, 1.2 equiv) in 5 mL of dry CH_2Cl_2 was added dropwise followed by dropwise addition of fumaryl chloride (0.48 mL, 0.6 equiv). The solution was stirred at 0 °C for 30 min and then at room temperature for 3 h, and the solvent was removed. The residue was taken up in 50 mL of EtOAc and was washed with 25 mL of water, 25 mL of saturated $NaHCO_3$, and 25 mL of saturated NaCl. The organic layer was dried over $MgSO_4$, and the solvent was removed.

Fumaric Bis[2,2-dimethyl-5(*S*)-isopropyl-1,3-oxazolidinide] (5a). The product was isolated by flash column chromatography (50% EtOAc in hexane, silica), giving a 36% yield of the product: ^1H NMR ($CDCl_3$, rotamer ratio ~8:1) δ 7.22 (s, 2 H), 3.94 (m, 6 H), 2.00 (m, 2 H), 1.71 (s, 6 H), 1.53 (s, 6 H), 0.95 (d, J = 6.9 Hz, 6 H), 0.94 (d, J = 7.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 161.87, 133.04, 95.70, 64.54, 62.46, 32.23, 25.86, 22.78, 19.72, 17.31. Anal. Calcd for $C_{20}H_{34}N_2O_4$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.29; H, 9.41; N, 7.61.

Fumaric Bis[2,2-dimethyl-5(*R*)-phenyl-1,3-oxazolidinide] (5c). The product was purified by flash column chromatography (silica, gradient elution, 25–50% EtOAc in hexane) to give 46% yield of white solid. Crystals suitable for X-ray analysis were grown by slow evaporation of ether/hexane: mp 140.0–141.5 °C; ^1H NMR ($CDCl_3$, rotamer ratio 10:1) δ 7.40–7.15 (m, 10 H), 6.83 (s, 2 H), 5.03 (br d, J = 5.91 Hz, 2 H), 4.32 (dd, J = 6.42, 8.88 Hz, 2 H), 3.91 (dd, J = 2.16, 8.92 Hz, 2 H), 1.76 (s, 6 H), 1.60 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 161.9, 140.8, 133.0, 129.0, 127.9, 125.9, 96.2, 71.4, 61.1, 25.2, 23.1; $[\alpha]^{23}_D$ = −123.6° (c 1.00, $CHCl_3$); MS (CI, CH_4/NH_3) MH^+ = 435. Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.77; H, 7.00; N, 6.41.

Ethenetricarboxylic Acid, 1,1-Dimethyl Ester, 2-[2,2-Dimethyl-5-alkyl-1,3-oxazolidinides] 6a,c. The following procedure for the preparation of **6c** is representative. Ethenetricarboxylic acid (1.36 g, 1 equiv) and *N*-methylmorpholine (1.6 mL, 2 equiv) were combined in 75 mL of dry THF, the solution was cooled to −10 °C under argon, and isobutyl chloroformate (0.94 mL, 1 equiv) was added dropwise. The solution was stirred for 0.5 h at −10 °C, and the salts were filtered off. The solution was cooled back down to −10 °C, and the oxazolidine [prepared as for **4a** from 0.99 g (7.2 mmol) of (*R*)-phenylglycinol] dissolved in 8 mL of dry CH_2Cl_2 was added dropwise over a 0.5-h period. The reaction was stirred an additional 0.5 h at −10 °C and then 3 h at room temperature.

Ethenetricarboxylic Acid, 1,1-Dimethyl Ester, 2-[2,2-Dimethyl-5-(*S*)-isopropyl-1,3-oxazolidinide] (6a). The product was purified by flash column chromatography (50% EtOAc in hexane, silica) giving a 50% yield of the product. After careful recrystallization from EtOAc/hexane, a white solid was obtained: mp 60–62 °C; ^1H NMR ($CDCl_3$, rotamer ratio ~6.5–9:1) δ 7.21 (s, 1 H), 3.94 (d, J = 3.6 Hz, 2 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.75 (m, 1 H), 1.95 (m, 1 H), 1.67 (s, 3 H), 1.53 (s, 3 H), 0.95 (d, J = 6.0 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.11, 163.42, 160.61, 135.36, 133.87, 95.90, 64.59, 62.99, 53.09, 52.82, 31.99, 25.47, 22.65, 19.72, 17.28. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.37; H, 7.36; N, 4.46.

Ethenetricarboxylic Acid, 1,1-Dimethyl Ester, 2-[2,2-Dimethyl-5-(*R*)-phenyl-1,3-oxazolidinide] (6c). The product was purified by flash column chromatography (silica gel, gradient elution, 25–35% ethyl acetate in hexane), giving 52% yield of a clear, colorless oil: ^1H NMR ($CDCl_3$, rotamer ratio 10:1) δ 7.45–7.20 (m, 5 H), 6.78 (s, 1 H), 4.92 (dd, J = 2.99, 6.47 Hz, 1 H), 4.38 (dd, J = 6.62, 9.02 Hz, 1 H), 3.94 (dd, J = 3.06, 9.05 Hz, 1 H), 3.82 (s, 3 H), 3.69 (s, 3 H), 1.83 (s, 3 H), 1.65 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.8, 163.0, 161.2, 140.1, 135.8, 133.0, 129.0, 128.3, 126.3, 96.6, 71.5, 61.6, 52.8, 52.7, 24.9, 23.0; MS (CI, CH_4/NH_3) MH^+ = 348. Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.00; H, 6.13; N, 4.03.

Ethenetricarboxylic Acid, 1,1-Dimethyl Ester, 2-[2,2-Dimethyl-5-(*S*)-*tert*-butyl-1,3-oxazolidinide] (6b). When the above procedure was used to prepare this alkene, a complicated mixture of products was obtained. Low yields (~20%) of the alkene were obtained after normal-phase HPLC (30% EtOAc in hexane). The following procedure was found to be superior for preparation of this alkene. The acrylamide **4b** (740 mg) was dissolved in CH_2Cl_2 (1 mL) and MeOH (5 mL), and the solution was cooled to −78 °C. Ozone was bubbled through the mixture until the blue color persisted. At this point, excess ozone was removed by bubbling argon through the solution. A large excess of Me_2S (15 mL) was added at −78 °C, and the mixture was stirred overnight, allowing the temperature to rise from −78 °C to room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between water and ether. The water layer was separated and extracted with ether twice. The combined ether layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure, leaving a colorless liquid (786 mg). This material showed only one peak by GC (CIMS MH^+ = 214), but spectroscopic evidence suggested the presence of a hydrate as well. The infrared spectrum showed absorptions at 3399, 1726 (reduced intensity), and 1646 cm^{-1}. The NMR spectra showed aldehyde peaks, but the spectra were otherwise complicated by the presence of multiple rotamers and the hydrate. Flash column chromatography failed to remove the hydrate [R_f = 0.5 (50% EtOAc in hexane)]. Elemental analysis indicated that the molecular formula was $C_{11}H_{19}NO_3 \cdot 0.4H_2O$. Taking the hydrate into account, the yield of the ozonolysis was quantitative. The aldehyde/hydrate was generally used without further purification. The aldehyde/hydrate (100 mg) and 64 μL of dimethyl malonate (1.2 equiv) were dissolved in 10 mL of THF and cooled to −45 °C. Titanium tetrachloride (1 M, 0.47 mL, 1 equiv) was added dropwise followed by 1 mL of pyridine. This was stirred overnight, allowing the mixture to warm to room temperature. One more equivalent of malonate, $TiCl_4$, and pyridine were then added at room temperature. The suspension was refluxed for 30 min, and GC analysis showed complete consumption of the aldehyde. The only new peak formed was that of the coupling product. The solution was cooled to room temperature and diluted with EtOAc and water. The organic layer was separated and washed with saturated $NaHCO_3$ twice. The combined aqueous layers were extracted with ether twice, and the combined organic layers were dried over $MgSO_4$. After filtration and removal of solvent, the residue was purified by flash column chromatography (30% EtOAc in hexane, silica), yielding 111 mg (60%) of a pale yellow solid: ^1H NMR ($CDCl_3$, rotamer ratio 3:1) δ 7.28 (s, 1 H), 4.03 (m, 1 H), 3.93 (m, 1 H), 3.84 (s, 3 H), 3.81 (s, 1 H), 3.71 (m, 1 H), 1.70 (s, 3 H), 1.51 (s, 3 H), 0.93 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 165.27, 163.54, 162.38, 136.24, 132.60, 96.76, 66.25, 65.14, 53.15, 53.07, 35.51, 27.47, 25.83, 22.61; R_f = 0.48 (50% EtOAc in hexane). Anal. Calcd for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.72; H, 7.70; N, 4.22.

Preparation of Amides of 2-Iodobutyric Acid, 14a and 14c. 2-Iodobutyric 2,2-Dimethyl-5(*S*)-isopropyl-1,3-oxazolidinide (14a). α-Bromobutyric acid (8 mL, 75 mmol) was added dropwise to thionyl chloride (8 mL, 110 mmol) at 0 °C. After addition, the mixture was refluxed for 2 h, and excess thionyl chloride was distilled off at atmospheric pressure. The residue was then vacuum distilled (53–55 °C at 20 mmHg), giving 11.0 g (79%) of the acid chloride as a clear liquid. To a CH_2Cl_2 solution (30 mL) of Et_3N (1.35 mL, 9.7 mmol) and the oxazolidine [prepared as before from (*S*)-valinol (9.7 mmol)] was added dropwise the acid chloride (1.88 g, 10 mmol) in 10 mL of CH_2Cl_2 at −10 °C. The mixture was stirred at −10 °C for 30 min and then at room temperature overnight. Following removal of the solvent at reduced pressure, the residue was purified by flash column chromatography (10% EtOAc in hexane), giving the bromide (2.31 g, diastereomers separable by flash column chromatography) as a pale yellow oil: ^1H NMR ($CDCl_3$, major diastereomer) δ 4.17 (t, J = 7.2 Hz, 1 H), 3.92 (m, 2 H), 3.70 (m, 1 H), 2.16 (m, 1 H), 2.06 (m, 1 H), 1.89 (m, 1 H), 1.67 (s, 3 H), 1.51 (s, 3 H), 1.00 (m, 9 H). The bromide was refluxed with sodium iodide (6 g, 40 mmol) in 50 mL of acetone for 1.5 h. Acetone was removed under reduced pressure, and ether and water were added to the residue. This solution was extracted three times with ether, and the ether layers were combined and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography (15% EtOAc in hexane). The iodide (2.32 g, 70% yield from valinol, diastereomer ratio 4.2:1) was obtained as a colorless oil. For **14a**, major isomer: ^1H NMR ($CDCl_3$) δ 4.21 (t, J = 7.4 Hz, 1 H), 3.90 (m, 2 H), 3.50 (m, 1 H), 2.05 (m, 2 H), 1.88 (m, 1 H), 1.67 (s, 3 H), 1.46 (s, 3 H), 0.96 (m, 9 H); ^{13}C NMR ($CDCl_3$) 167.66, 95.68, 64.50, 63.23, 32.41, 29.06, 28.12, 26.55, 20.13, 19.75, 18.16, 14.17. Anal. Calcd for $C_{12}H_{22}NO_2I$: C, 42.49; H, 6.54; N, 4.13; I, 37.41. Found: C, 42.41; H, 6.55; N, 4.08; I, 37.31. For **14a**, minor isomer: ^1H NMR ($CDCl_3$) δ 4.30 (dd, J = 6.6, 8.5 Hz, 1 H), 3.93 (m, 2 H), 3.72 (m, 1 H), 2.32 (m, 1 H), 2.08 (m, 2 H), 1.68 (s, 3 H), 1.51 (s, 3 H), 0.95 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 168.41, 96.06, 63.57, 63.10, 31.36, 29.45, 26.06, 24.79, 22.85, 19.92, 16.06, 14.04.

2-Iodobutyric 2′,2′-Dimethyl-5′(*R*)-phenyl-1′,3′-oxazolidinide (14c). Racemic 2-bromobutyric acid (4.7 mL, 43.7 mmol) was added dropwise to freshly distilled thionyl chloride (6.4 mL, 2 equiv) at 0 °C. After the addition was complete, the mixture was refluxed for 2.5 h, and the excess thionyl chloride was removed. The oxazolidine [prepared as before from phenylglycinol (1.0 g, 18.2 mmol)] was dissolved in 65 mL of dry CH_2Cl_2 and cooled to 0 °C. Triethylamine (3.0 mL, 1.2 equiv) in 5 mL of dry CH_2Cl_2 was added dropwise, followed by dropwise addition of the acid chloride in 5 mL of dry CH_2Cl_2. The mixture was stirred for 30 min at 0 °C and then 3 h at room temperature. The solvent was removed, and the residue was taken up in 150 mL of Et_2O. The ether was washed with 50 mL of water and 50 mL of saturated $NaHCO_3$ and dried over $MgSO_4$, and the solvent was removed. The products were separated by flash column chromatography (silica gel, gradient elution, 5–15% EtOAc in hexane), providing 1.1 g (18%) of the less-polar isomer and 2.6 g (43%) of the more-polar isomer. Less polar isomer: R_f = 0.26 (15% EtOAc in hexane); ^1H NMR ($CDCl_3$) δ 7.45–7.25 (m, 5 H), 5.04 (dd, J = 2.34, 6.58 Hz, 1 H), 4.39 (dd, J = 6.63, 8.95 Hz, 1 H), 3.91 (dd,

J = 2.43, 8.95 Hz, 1 H), 3.78 (dd, J = 6.52, 8.03 Hz, 1 H), 1.99 (m, 1 H), 1.86 (s, 3 H), 1.75 (m, 1 H), 1.62 (s, 3 H), 0.59 (t, J = 7.32 Hz, 3 H). The less polar bromobutyramide (1.0 g, 3.1 mmol) was dissolved in 35 mL of acetone. Sodium iodide (2.8 g, 6 equiv) was added, and the mixture was refluxed for 3 h. The solid was filtered, and the solvent was removed. The residue was dissolved in 150 mL of Et_2O and washed with 100 mL of water, 100 mL of 5% $Na_2S_2O_3$, and 100 mL of saturated NaCl. The organic layer was dried over $MgSO_4$, and the solvent was removed. The products were separated by flash column chromatography (silica gel, gradient elution, 5–10% EtOAc in hexane), giving 0.80 g (69%) of the less polar isomer and 0.13 g (12%) of the more polar isomer. For **14c**, less polar isomer: R_f = 0.25 (10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$) δ 7.45–7.25 (m, 5 H), 4.87 (dd, J = 2.25, 6.51 Hz, 1 H), 4.38 (dd, J = 6.71, 8.90 Hz, 1 H), 3.91 (dd, J = 2.55, 8.98 Hz, 1 H), 3.82 (dd, J = 6.37, 8.34 Hz, 1 H), 1.93 (m, 1 H), 1.86 (s, 3 H), 1.78 (m, 1 H), 1.58 (s, 3 H), 0.52 (t, J = 7.35 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.8, 141.3, 129.2, 128.2, 125.6, 96.6, 71.2, 61.5, 29.2, 26.5, 25.7, 21.1, 13.7; MS (CI, CH_4/NH_3) MH^+ = 374. For **14c**, more polar isomer: R_f = 0.07 (10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$) 7.50–7.25 (m, 5 H), 4.84 (dd, J = 2.17, 6.46 Hz, 1 H), 4.36 (dd, J = 6.71, 8.93 Hz, 1 H), 4.06 (dd, J = 6.92, 8.07 Hz, 1 H), 3.89 (dd, J = 2.41, 9.02 Hz, 1 H), 2.03 (m, 1 H), 1.94 (m, 1 H), 1.85 (s, 3 H), 1.64 (s, 3 H), 0.90 (t, J = 7.35 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.6, 139.2, 129.1, 128.3, 126.5, 96.7, 71.5, 62.0, 31.2, 26.3, 24.6, 23.3, 14.1; MS (CI, CH_4/NH_3) MH^+ = 374.

Addition of Cyclohexyl Radical to 5 and 6. In a typical reaction, the olefin (~0.2 mmol) was dissolved in 7.5 mL of dry CH_2Cl_2 (25 mM in olefin). The mixture was cooled to 0 °C and degassed with argon for 10 min. Cyclohexylmercuric chloride (4 equiv) was added, and the mixture was degassed an additional 10 min. Sodium borohydride (10 equiv) was dissolved in 1 mL of water, cooled to 0 °C, and added to the olefin solution, causing immediate bubbling and precipitation of elemental mercury. After being stirred at 0 °C for 30 min, 8 mL of saturated sodium bicarbonate was added, and the solution was stirred for 15 min. The mercury was removed, and the CH_2Cl_2 layer was separated and dried over Na_2SO_4. The solvent was removed, and the residue was filtered through a short pad of silica, while being rinsed well with EtOAc. Products from addition to **5** and **6** give the following data.

From **5a**. The ratio of adducts was determined by GC (column B), and the products were isolated by preparative HPLC (20% EtOAc in hexane), giving a 39% combined yield. For **10a**, major isomer: ^{1}H NMR ($CDCl_3$) δ 3.87 (m, 4 H), 3.80 (m, 1 H), 3.72 (m, 1 H), 3.05 (m, 1 H), 2.47 (d, J = 6 Hz, 2 H), 2.20 (m, 2 H), 1.62 (s, 3 H), 1.61 (s, 3 H), 1.48 (s, 3 H), 1.45 (s, 3 H), 0.91 (m, 12 H), 1.80–0.8 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 172.75, 169.04, 95.31, 95.26, 63.95, 63.76, 62.67, 62.63, 46.00, 42.00, 36.21, 30.86, 30.74, 30.71, 30.62, 26.52, 26.47, 26.21, 25.93, 25.75, 22.79, 22.52, 19.81, 17.12, 16.72. Anal. Calcd for $C_{26}H_{46}N_2O_4$: C, 69.30; H, 10.29; N, 6.22. Found: C, 69.15; H, 10.32; N, 6.23. For **10a**, minor isomer: ^{1}H NMR ($CDCl_3$) δ 4.30 (m, 1 H), 3.86 (m, 5 H), 2.76 (m, 2 H), 2.40 (d, J = 12 Hz, 1 H), 2.10 (m, 2 H), 1.63 (s, 3 H), 1.61 (s, 3 H), 1.60 (s, 3 H), 1.44 (s, 3 H), 0.95 (m, 12 H), 2.00–0.70 (m, 11 H).

From **5c**. The ratio of adducts was determined by GC (column B), and the products were isolated by preparative HPLC (40% EtOAc in hexane), giving 16 mg (17%) of the minor adduct and 15 mg (16%) of the major adduct. For **10c**, major isomer: ^{1}H NMR ($CDCl_3$) δ 7.45–7.20 (m, 10 H), 5.33, (br d, J = 5.91 Hz, 1 H), 5.02 (dd, J = 2.38, 6.55 Hz, 1 H), 4.36 (dd, J = 6.65, 8.90 Hz, 1 H), 4.31 (dd, J = 6.60, 8.95 Hz, 1 H), 3.87 (dd, J = 2.39, 8.99 Hz, 1 H), 3.87 (dd, J = 1.20, 8.91 Hz, 1 H), 2.62 (m, 1 H), 2.50 (dd, J = 11.22, 15.20 Hz, 1 H), 1.84 (s, 6 H), 1.74 (dd, J = 2.87, 15.23 Hz, 1 H), 1.59 (s, 6 H), 1.45–1.15 (m, 4 H), 0.80–0.49 (m, 5 H), 0.37–0.21 (m, 1 H), –0.18 to –0.34 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.0, 170.7, 143.6, 141.6, 128.9, 128.6, 127.8, 127.7, 127.2, 126.2, 95.9, 95.9, 71.3, 71.1, 61.7, 61.5, 46.1, 39.4, 36.2, 30.5, 28.6, 26.3, 25.7, 25.5, 23.3, 22.3; MS (CI, CH_4/NH_3) MH^+ = 519. For **10c**, minor adduct: ^{1}H NMR ($CDCl_3$) δ 7.45–7.00 (m, 10 H), 4.98 (dd, J = 2.11, 6.45 Hz, 1 H), 4.72 (br d, J = 4.88 Hz, 1 H), 4.29 (dd, J = 6.55, 8.88 Hz, 1 H), 4.24 (dd, J = 6.39, 8.79 Hz, 1 H), 3.83 (dd, J = 2.09, 8.99 Hz, 1 H), 3.78 (dd, J = 2.46, 9.16 Hz, 1 H), 2.71 (td, J = 2.47, 8.08 Hz, 1 H), 2.05 (dd, J = 8.26, 17.24 Hz, 1 H), 1.68 (s, 3 H), 1.58 (s, 3 H), 1.57 (s, 3 H), 1.45 (s, 3 H), 1.70–1.40 (m, 6 H), 1.20–0.85 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 173.4, 167.6, 141.4, 140.9, 128.7, 127.6, 127.4, 126.2, 96.0, 95.9, 71.3, 71.1, 61.7, 61.0, 45.2, 41.3, 35.8, 31.1, 30.2, 26.6, 26.4, 26.3, 25.4, 25.2, 23.3, 23.0; MS (CI, CH_4/NH_3) MH^+ = 519.

From **6a**. The ratio of adducts was determined by GC (column A), and the products were isolated by preparative HPLC (20% EtOAc in hexane). The major adduct was isolated as a colorless oil. For **11a**, major isomer: ^{1}H NMR ($CDCl_3$) δ 3.78–3.98 (m, 3 H), 3.88 (d, J = 9.9 Hz, 1 H), 3.73 (s, 3 H), 3.65 (s, 3 H), 3.19 (dd, J = 4.8, 9.9 Hz, 1 H), 2.52 (d sep, J = 3.3, 6.9 Hz, 1 H), 1.0–1.8 (m, 11 H), 1.63 (s, 3 H), 1.44 (s, 3 H), 0.99 (d, J = 7.2 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.98, 169.44, 168.84, 95.49, 63.21, 62.23, 52.75, 52.72, 52.63, 49.12, 41.28, 30.53, 30.44, 30.27, 26.84, 26.74, 26.11, 25.51, 22.72, 20.34, 16.43. Anal. Calcd for $C_{21}H_{35}NO_6$: C, 63.45; H, 8.87; N, 3.52. Found: C, 63.37; H, 8.87; N, 3.57. For **11a**, minor adduct: ^{1}H NMR ($CDCl_3$) δ 4.20 (m, 1 H), 3.94 (m, 2 H), 3.82 (d, J = 9.0 Hz, 1 H), 3.74 (s, 3 H), 3.66 (s, 3 H), 3.03 (dd, J = 6.5, 9.2 Hz, 1 H), 2.12 (m, 1 H), 1.0–1.8 (m, 11 H), 1.63 (s, 3 H), 1.44 (s, 3 H), 0.98 (d, J = 7.2 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H).

From **6b**. The ratio of adducts was determined by GC (column B), and the products were isolated by preparative HPLC (15% EtOAc in hexane). NMR spectra are difficult to interpretate due to a 1:1 rotamer ratio, although the peaks did coalesce at 115 °C in toluene-d_8. For **11b**, mixture of isomers: GC/CIMS MH^+ = 412. Anal. Calcd for $C_{22}H_{37}NO_6$: C, 64.21; H, 9.06; N, 3.40. Found: C, 64.26; H, 9.07; N, 3.41.

From **6c**. The ratio of adducts was analyzed by GC (column B). The mixture of adducts was isolated by preparative HPLC (25% EtOAc in hexane), but the two adducts were inseparable from each other. The yield of the mixture of adducts was 33 mg (41%). For **11c**, mixture of isomers: ^{1}H NMR ($CDCl_3$) δ 7.50–7.20 (m, 5 H), 5.26 and 4.93 (br d and dd, J = 6.20 and 2.37, 6.34 Hz, 1 H), 4.38 and 4.32 (dd, J = 6.66, 8.89 and 6.39, 8.95 Hz, 1 H), 3.92 and 3.88 (dd, J = 2.46, 8.48 and 1.07, 8.89 Hz, 1 H), 3.76 and 3.61 (d, J = 9.77 and 9.30 Hz, 1 H), 3.70 and 3.67 (s, 3 H), 3.58 and 3.41 (s, 3 H), 3.04 and 3.03 (dd, J = 4.35, 9.21 and 5.62, 9.73 Hz, 1 H), 1.82 and 1.80 (s, 3 H), 1.60 and 1.54 (s, 3 H), 1.85 to –0.02 (m, 11 H); MS (CI, CH_4/NH_3) MH^+ = 432 (for each isomer).

Hydrolysis of Cyclohexyl Adducts 10a, 11a, 11b, and 16. The procedure for the hydrolysis of **11a** is typical. The adduct (34 mg) was heated with 1 N HCl (5 mL) at 100 °C for 15 h. The solution was cooled to room temperature and extracted four times with ether. The combined ether layers were then extracted three times with saturated $NaHCO_3$. The combined aqueous layers were acidified with 6 N HCl to pH ~ 2 and reextracted four times with ether. The ether layers were combined and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was placed on a high vacuum over P_2O_5 at 0.2 mmHg. The product (15.2 mg, 89% yield) showed ^{1}H and ^{13}C NMR spectra that were identical to commercially available racemic cyclohexylsuccinic acid. The product showed $[\alpha]^{22}_D$ = –21.5 ± 0.7° (c = 0.89, EtOH). While $[\alpha]^{30}_D$ = 26.3° (c = 1.937, EtOH) was reported in the literature, a sample of (*S*)-cyclohexylsuccinic acid prepared and purified according to the literature gave $[\alpha]^{22}_D$ +22.0 ± 0.6° (c = 0.64, EtOH). The pyrrolidine analog **16** was hydrolyzed similarly (yield 84%).

Barton Ester Trapping of the Acrylamides 4a–c. In a typical procedure, the acrylamide (25 mM) was dissolved in dry CH_2Cl_2 (benzene for the 80 °C reactions) and degassed with argon for 15 min. The solution was equilibrated to the proper reaction temperature (–78, 0, 25, or 80 °C), and cyclohexyl Barton ester (2 equiv) was added. The solution was irradiated with a 100-W clear tungsten bulb placed a distance of 30 cm from the reaction vessel until the bright yellow color disappeared (2–6 h). The crude reaction mixture was flushed through a plug of silica and the solvent was removed.

From **4a**. The ratio of adducts was analyzed by GC (column B). The mixture of adducts was isolated by preparative HPLC (10% EtOAc in hexane), but they were inseparable from one another. For **12a**, mixture of isomers: ^{1}H NMR ($CDCl_3$) δ 8.33 (m, 1 H), 7.47 (m, 1 H), 7.18 (m, 1 H), 6.98 (m, 1 H), 4.95 (dd, J = 6.0, 8.7 Hz, 1 H), 4.16 (t, J = 4.8 Hz, 1 H), 3.83 (m, 2 H), 2.08 (m, 1 H), 1.66 (s, 3 H), 1.43 (s, 3 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 1.95–0.75 (m, 13 H); ^{13}C ($CDCl_3$) δ 170.04, 157.52, 148.90, 136.13, 122.46, 119.88, 95.37, 64.08, 61.54, 43.53, 40.43, 35.20, 33.93, 32.80, 32.12, 26.39, 26.19, 26.00, 25.95, 21.87, 19.61, 17.11; CIMS MH^+ = 391. Anal. Calcd for $C_{22}H_{34}N_2O_2S$: C, 67.65; H, 8.77; N, 7.17; S, 8.21. Found: C, 67.69; H, 8.82; N, 7.22; S, 8.28.

From **4b**. The ratio of adducts was determined by GC (column B), and the adducts were isolated by preparative HPLC (10% EtOAc in hexane). For **12b**, major isomer: ^{1}H NMR ($CDCl_3$) δ 8.35 (m, 1 H), 7.19 (m, 1 H), 6.98 (m, 1 H), 5.27 (dd, J = 4.69, 10.2 Hz, 1 H), 4.10 (d, J = 5.78 Hz, 1 H), 3.86 (d, J = 9.29 Hz, 1 H), 3.67 (dd, J = 5.78, 9.29 Hz, 1 H), 1.72 (s, 3 H), 1.43 (s, 3 H), 1.01 (s, 9 H), 2.00–0.70 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 172.14, 157.3, 148.86, 136.28, 122.5, 120.7, 96.1, 64.9, 63.68, 44.2, 39.9, 35.1, 34.4, 34.2, 32.9, 27.4, 26.5, 26.4, 26.2, 25.9, 21.9; IR (neat) 3049, 2985, 2910, 1650 cm^{-1}.

From **4c**. The mixture of adducts was separated from the rest of the reaction mixture by preparative HPLC (15% EtOAc in hexane) and analyzed by analytical HPLC (10% EtOAc in hexane). The adducts were then separated from each other by preparative HPLC (12.5% Et-

OAc in hexane). For **12c**, major isomer: ^{1}H NMR ($CDCl_3$) δ 8.38 (m, 1 H), 7.47 (m, 1 H), 7.41–7.25 (m, 5 H), 7.17 (m, 1 H), 7.00 (m, 1 H), 5.42 (dd, J = 1.84, 6.66 Hz, 1 H), 4.50 (t, J = 7.42 Hz, 1 H), 4.31 (dd, J = 6.70, 8.85 Hz, 1 H), 3.83 (dd, J = 1.93, 8.87 Hz, 1 H), 1.89 (s, 3 H), 1.58 (m, 1 H), 1.54 (s, 3 H), 1.47–1.31 (m, 4 H), 1.26–1.15 (m, 2 H), 1.07–0.78 (m, 4 H), 0.52–0.37 (m, 1 H), 0.26–0.10 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 170.1, 157.7, 148.9, 142.4, 136.1, 128.7, 127.7, 126.4, 122.4, 119.9, 96.2, 71.2, 61.0, 44.3, 39.9, 35.1, 32.8, 32.3, 26.3, 26.2, 25.9, 25.6, 22.2; IR (neat) 3049, 2985, 2910, 1650 cm^{-1}; MS (CI, CH_4/NH_3) MH^+ = 425; $[\alpha]^{20}_D$ = −75.2° (c 1.24, $CHCl_3$). Anal. Calcd for $C_{25}H_{32}N_2O_2S$: C, 70.72; H, 7.60; N, 6.60. Found: 70.63; H, 7.62; N, 6.57. For **12c**, minor isomer: ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 1 H), 7.30–7.13 (m, 5 H), 7.18 (m, 1 H), 7.05 (m, 1 H), 6.74 (m, 1 H), 4.98 (dd, J = 2.15, 6.34 Hz, 1 H), 4.53 (t, J = 7.39 Hz, 1 H), 4.37 (dd, J = 6.54, 8.85 Hz, 1 H), 3.88 (dd, J = 2.40, 8.89 Hz, 1 H), 1.86 (s, 3 H), 1.64 (s, 3 H), 2.00–0.75 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 170.3, 157.5, 148.6, 140.3, 135.2, 128.2, 127.6, 126.1, 121.4, 118.8, 96.5, 71.1, 61.7, 45.3, 42.1, 35.6, 33.7, 33.2, 26.4, 26.2, 26.0, 25.3, 23.1; MS (CI, CH_4/NH_3) MH^+ = 425.

Hydrolysis of the Barton Ester Adduct 12c. The major Barton ester adduct (as a single diastereomer, 195 mg, 0.46 mmol) was dissolved in 6 mL of dioxane and 6 mL of 1 M H_2SO_4. The mixture was heated to 50 °C and stirred for 20 h. The dioxane was removed, and the aqueous residue was extracted with 3 × 25 mL of ether. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed, leaving 111 mg (90%) of clear oil: ^{1}H NMR ($CDCl_3$) δ 11.80 (br, 1 H), 8.40 (d, J = 5.06 Hz, 1 H), 7.66 (td, J = 1.66, 7.76 Hz, 1 H), 7.38 (d, J = 8.08 Hz, 1 H), 7.19 (dd, J = 5.22, 7.18 Hz, 1 H), 3.96 (t, J = 7.58 Hz, 1 H), 2.01 (m, 1 H), 1.45–1.76 (m, 7 H), 1.00–1.30 (m, 3 H), 0.78–1.00 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.8, 158.3, 147.7, 138.1, 124.1, 121.1, 45.2, 37.1, 34.8, 33.1, 32.7, 26.3, 26.0, 25.9.

Recoupling of the Oxazolidine to the Hydrolysis Product. The Barton ester hydrolysis product (111 mg, 0.42 mmol) was dissolved in 5 mL of freshly distilled THF and cooled to −10 °C under argon. N-Methylmorpholine (55 μL, 1.2 equiv) was added followed by dropwise addition of isobutyl chloroformate (54 μL, 1.0 equiv). The mixture was stirred at −10 °C for 30 min, and the solution was filtered and recooled to −10 °C. A solution of the oxazolidine [prepared as before from 115 mg (0.84 mmol, 2 equiv) of (R)-phenylglycinol] in 3 mL of dry CH_2Cl_2 was added dropwise. The mixture was stirred at −10 °C for 30 min and then at room temperature for 3 h. The solvent was evaporated, and the products were isolated by flash column chromatography (silica, 10% EtOAc in hexane). This gave 90 mg (90%) of clear oil which was a 4:1 mixture of diastereomers as indicated by NMR.

Barton Ester Trapping of the Thiazolidine Acrylamide 2. The reaction was carried out as described for the acrylamides **4a–c**. The ratio of adducts was determined by GC (column B), and the products were isolated by preparative HPLC (15% EtOAc in hexane) to yield 381 mg (81%) of the major adduct and 9 mg (2%) of the minor adduct. The following data are for the major adduct: ^{1}H NMR ($CDCl_3$) δ 8.31 (m, 1 H), 7.47 (m, 1 H), 7.17 (m, 1 H), 6.98 (m, 1 H), 5.70 (dd, J = 5.5, 1.4 Hz, 1 H), 4.58 (dd, J = 17.5, 5.7 Hz, 1 H), 3.81 (s, 3 H), 3.26 (dd, J = 1.4, 12.0 Hz, 1 H), 3.19 (dd, J = 5.5, 12.0 Hz, 1 H), 1.9 (s, 3 H), 1.78 (s, 3 H), 2.0–0.7 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 171.28, 170.45, 157.32, 149.01, 136.33, 122.58, 120.01, 73.91, 65.60, 52.86, 44.32, 40.16, 34.90, 33.60, 32.69, 31.38, 28.92, 27.35, 26.45, 26.19, 26.02. Anal. Calcd for $C_{21}H_{30}N_2O_3S_2$: C, 59.68; H, 7.16; N, 6.63. Found: C, 59.47; H, 7.10; N, 6.56.

Allylstannane Trapping of the Acrylamides 4a and 4b. The procedure for the acrylamide **4a** is typical. A stirring solution of the oxazolidine acrylamide, cyclohexyl iodide (5 equiv), and tributylallylstannane (2 equiv) in 10 mL of degassed benzene was heated to 80 °C under argon. AIBN (0.2 equiv) was then added, and the reaction was stirred at 80 °C for 9 h. The solvent was then removed in vacuo, and the residue was taken up in 10 mL ether and stirred with 2 mL 10% KF solution overnight to remove any Bu_3SnI.

From **4a**. The ratio of adducts was determined by GC (column B). The products were isolated by preparative HPLC (7% EtOAc in hexane). For **13a**, major isomer: ^{1}H NMR ($CDCl_3$) δ 5.74 (m, 1 H), 5.07 (dd, J = 17.1, 1.5 Hz, 1 H), 4.99 (dd, J = 9.9, 1.8 Hz, 1 H), 3.87 (m, 2 H), 3.71 (t, J = 4.4 Hz, 1 H), 2.56 (m, 1 H), 2.23 (m, 2 H), 1.99 (m, 1 H), 1.66 (s, 3 H), 1.47 (s, 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.8–1.8 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 173.57, 135.48, 116.99, 95.41, 63.59, 62.03, 41.63, 39.74, 37.62, 35.44, 34.45, 32.92, 31.70, 26.48, 26.32, 26.26, 25.94, 22.73, 19.88, 16.68. For **13a**, minor isomer: ^{1}H NMR ($CDCl_3$) δ 5.75 (m, 1 H), 5.00 (m, 2 H), 3.90 (m, 2 H), 3.65 (m, 1 H), 2.52 (m, 1 H), 2.38 (m, 1 H), 2.15 (m, 1 H), 2.05 (m, 1 H), 1.67 (s, 3 H), 1.49 (s, 3 H), 0.93 (d, J = 5.5 Hz, 3 H), 0.91 (d, J = 5.2 Hz, 3 H), 0.8–1.8 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 173.77, 136.25, 116.37, 95.40, 63.57, 62.08, 41.44, 40.85, 36.82, 35.44, 34.20, 33.43, 31.69, 26.47, 26.37, 26.29, 25.90, 22.50, 19.96, 16.5. Anal. Calcd for $C_{20}H_{35}NO_2$: C, 74.72; H, 10.97; N, 4.36. Found: C, 74.46; H, 10.93; N, 4.31.

From **4b**. The ratio of adducts was determined by GC (column B). The products were isolated by preparative HPLC (10% EtOAc in hexane), giving a 33% yield of the products. For **13b**, major isomer: ^{1}H NMR ($CDCl_3$) δ 5.76 (m, 1 H), 5.01 (m, 2 H), 4.0–3.6 (m, 3 H), 2.8 (m, 1 H), 2.20 (m, 2 H), 1.68 (s, 3 H), 1.47 (s, 3 H), 0.95 (s, 9 H), 1.75–0.7 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 176.60, 135.23, 117.13, 96.16, 64.95, 64.88, 40.94, 38.19, 36.90, 34.66, 34.52, 32.75, 27.84, 26.64, 26.51, 26.36, 26.28, 23.10; R_f = 0.43 (50% EtOAc in hexane); GC/MS, MH^+ = 336.

Independent Synthesis of 13b. 3-Cyclohexylpropionic Acid. To a stirring solution of 3-cyclohexylpropanol (16.5 mmol, 2.35 g) in acetone (150 mL) at 0 °C under argon was carefully added 2.7 M Jones reagent (2 equiv, 33 mmol, 12.2 mL). Upon addition the ice bath was removed, and the reaction was allowed to stir at room temperature overnight. The solution was then cooled via ice bath and carefully quenched by addition of 3 mL of 2-propanol. The ice bath was removed, saturated NaCl solution was added, and the mixture was stirred for 30 min. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with saturated NH_4Cl solution, dried over $MgSO_4$, and concentrated in vacuo to afford 2.55 g (99%) of the acid: ^{1}H NMR ($CDCl_3$) δ 2.34 (t, J = 7.8 Hz, 2 H), 1.66 (m, 4 H), 1.52 (q, J = 7.8 Hz, 2 H), 1.18 (m, 4 H), 0.89 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.70, 37.10, 32.92, 32.03, 31.67, 26.50, 26.18.

(S)-Prolinol Amide of 3-Cyclohexylpropionic Acid. Oxalyl chloride (15 mL) and 3-cyclohexylpropionic acid (2.53 g, 16.17 mmol) were stirred together under argon at reflux for 2 h. The solution was cooled to room temperature, and excess oxalyl chloride was removed in vacuo. The residual 3-cyclohexylpropionyl chloride was dissolved in dry THF (10 mL) at room temperature under argon and added dropwise to a stirring solution of (S)-prolinol (1.6 mL, 16.2 mmol, 1 equiv) and N-methylmorpholine (1.2 equiv, 19.4 mmol, 2.2 mL) in dry THF (40 mL) under argon at 0 °C. The reaction was allowed to stir at 0 °C for 1 h and then at room temperature overnight. The N-methylmorpholine hydrochloride salts were removed via filtering through a sintered glass funnel. The filtrate was concentrated in vacuo, and the residue was flash column chromatographed on silica gel, eluting with ethyl acetate to afford 2.98 g (77%) of the prolinol amide: ^{1}H NMR ($CDCl_3$) δ 5.20 (dd, J = 2.45, 7.74 Hz, 1 H), 4.18 (dddd, J = 2.45, 7.74, 7.74, 7.74 Hz, 1 H), 3.67–3.38 (m, 4 H), 2.27 (m, 2 H), 2.08–0.8 (m, 17 H); ^{13}C NMR ($CDCl_3$) δ 175.01, 67.69, 61.16, 48.10, 37.38, 33.10, 32.63, 32.15, 28.31, 26.51, 26.21, 24.41; R_f = 0.35 (100% EtOAc). Anal. Calcd for $C_{14}H_{25}NO_2$; C, 70.25; H, 10.53; N, 5.85. Found: C, 69.15; H, 10.38; N, 5.77.

(S)-Prolinol Amide of 2(S)-Allyl-3-cyclohexylpropionic Acid. A flame-dried 50-mL round bottomed flask equipped with stir bar and septum was charged with diisopropylamine (1.3 mL 9.00 mmol) and 10 mL of dry THF. The solution was cooled via ice bath and n-BuLi (3.6 mL of 2.5 M) was added dropwise with stirring under argon. The reaction was allowed to stir for 15 min, and then a solution of the prolinol amide (1.00 g, 4.18 mmol) in 3 mL of THF was added dropwise via a syringe. Upon addition, the reaction was stirred at 0 °C for 2 h. The reaction was cooled to −78 °C via an acetone–dry ice bath, and to this was added allyl bromide (1.1 equiv, 4.60 mmol, 398 μL) in 3 mL of THF (containing a catalytic amount of tetrabutylammonium iodide) dropwise via syringe. Upon addition, the reaction was warmed to room temperature via water bath and then heated at reflux overnight. The reaction was cooled to room temperature and quenched by addition of 4 mL of saturated NH_4Cl solution. H_2O (4 mL) was added, and the solution was extracted with ether (2 × 100 mL). The ether phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was flash column chromatographed on silica gel, eluting with 50% EtOAc in hexane to yield 0.83 g (71%) of solid product. GC (column B) showed a ratio of diastereomers of 8:1: ^{1}H NMR ($CDCl_3$) δ 5.70 (dddd, J = 7, 7, 10, 17 Hz, 1 H), 5.24 (dd, J = 1.7, 7.8 Hz, 1 H), 5.00 (d, J = 17 Hz, 1 H), 4.95 (d, J = 10 Hz, 1 H), 4.18 (dddd, J = 2.4, 7, 7, 7 Hz, 1 H), 3.65–3.35 (m, 4 H), 2.65 (m, 1 H), 2.4–0.8 (m, 19 H); ^{13}C NMR ($CDCl_3$) δ 177.17, 135.72, 116.70, 67.84, 61.24, 48.08, 41.17, 40.43, 37.01, 35.53, 33.56, 33.43, 28.40, 26.47, 25.23, 26.15, 24.44; R_f = 0.45 (100% EtOAc).

2(S)-Allyl-3-cyclohexylpropionic Acid. The prolinol amide (1.45 g, 5.19 mmol) was dissolved in 90 mL of dioxane. H_2O (90 mL) followed by 18 mL of concentrated HCl was added, and the reaction was refluxed overnight. The reaction was cooled to room temperature and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo (cyclohexane was used to azeotrope the dioxane). The residue was flash column chromatographed

on silica gel, eluting with 20% EtOAc in hexane to afford 0.84 g (83%) of product: ^{1}H NMR ($CDCl_3$) δ 5.74 (dddd, J = 6.9, 6.9, 10.1, 17.1 Hz, 1 H), 5.05 (dd, J = 1.65, 17 Hz, 1 H), 5.01 (dd, J = 1.65, 10 Hz, 1 H), 2.52 (m, 1 H), 2.32 (ddd, J = 7, 7, 13.8 Hz, 1 H), 2.21 (ddd, J = 7, 7, 13.8 Hz, 1 H), 1.8–0.8 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 182.22, 135.34, 116.89, 42.64, 39.30, 36.74, 35.44, 33.53, 32.93, 26.53, 26.21, 26.19; R_f = 0.39 (30% EtOAc in hexane).

2(*S*)-Allyl-3-cyclohexylpropionic 5′(*S*)-*tert*-Butyl-2′,2′-dimethyloxazolidinide (13b). The acid (139 mg, 0.708 mmol) was dissolved in 1 mL of oxalyl chloride under argon and heated at reflux for 1.5 h, and then excess oxalyl chloride was removed in vacuo. The residue was dissolved in 2 mL of dry THF and cooled to 0 °C under argon. To this was added a solution of *N*-methylmorpholine (1.2 equiv, 94 μL) and the *tert*-butyl oxazolidine (1.2 equiv, 134 mg) in 2 mL of THF. Upon addition, the reaction was stirred at room temperature for 20 h and then at reflux for 4 h. The reaction was filtered through a plug of silica gel on a sintered glass funnel. This product, which should be *S*,*S*, was co-injected on GC (column B) with the same product formed from the radical reaction described earlier. Co-injection supports the assignment of *S*,*S* to the major isomer of the radical reaction.

Correlation of Structure 13b with Curran's Adduct.[33] D-Camphorsultam (160 mg, 0.742 mmol) was dissolved in 8 mL of dry THF under argon and cooled via an ice bath. NaH (1 equiv, 17.8 mg of a 60% dispersion in oil) was added with stirring, and when H_2 ceased to evolve, the acid chloride (prepared as described above) as a solution in 2 mL of THF was added. Upon addition, the ice bath was removed, and the reaction was stirred at room temperature. GC co-injection (column B) with a mixture of authentic products[33] (predicted to be (*S*)-L as major and (*R*)-L as minor) proved that the major isomer of the radical addition (predicted to be (*S*)-D) coincided with the enantiomer of the (*R*)-L compound reported previously.[33]

Allylstannane Trapping of the Iodides 14a and 14c. The iodobutyramide was dissolved in dry benzene (0.2 mM in iodide). The solution was degassed with argon for 10 min, allyltributyltin (1.5 equiv) was added, and the mixture was degassed for an additional 5 min. The solution was placed in an 80 °C constant temperature bath and allowed to equilibrate. AIBN (0.1 equiv) was added, and the mixture was stirred at 80 °C under argon for 4.5 h. GC of an aliquot showed some starting iodide to remain, so an additional 0.1 equiv of AIBN was added, and the reaction was refluxed for 1 h. The solvent was removed, and the residue was taken up in 15 mL of Et_2O and 15 mL of 10% aqueous KF and stirred at room temperature overnight. The solids were filtered off, and the organic layer was dried over $MgSO_4$.

From **14a.** The product ratio was analyzed by analytical HPLC (10% EtOAc in hexane). The products (90 mg total, 60% yield) were separated by preparative HPLC (10% EtOAc in hexane). From **14a**, major isomer: ^{1}H NMR ($CDCl_3$) δ 5.72 (m, 1 H), 5.02 (m, 2 H), 3.86 (m, 2 H), 3.68 (t, J = 4.9 Hz, 1 H), 2.3 (m, 3 H), 2.0 (m, 1 H), 1.7 (m, 1 H), 1.65 (s, 3 H), 1.5 (m, 1 H), 1.46 (s, 3 H), 0.89 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.24, 135.38, 116.95, 95.39, 63.57, 61.90, 45.78, 37.87, 31.70, 25.88, 25.58, 22.68, 19.82, 16.62, 12.00; HRMS calcd for $C_{15}H_{27}NO_2$ 253.2042, found 253.2032 (−3.9 ppm). From **14a**, minor isomer: ^{1}H NMR ($CDCl_3$) δ 5.74 (m, 1 H), 5.01 (m, 2 H), 3.90 (m, 2 H), 3.71 (m, 1 H), 2.40 (m, 2 H), 2.20 (m, 1 H), 2.00 (m, 1 H), 1.67 (s, 3 H), 1.60 (m, 2 H), 1.51 (s, 3 H), 0.91 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.35, 136.11, 116.48, 95.43, 63.66, 62.13, 45.65, 36.98, 31.52, 26.32, 25.88, 22.69, 19.84, 16.65, 11.66.

From **14c**. The ratio of adducts was determined by GC (column A). The adducts were separated from the tin byproducts by flash column chromatography (silica gel, hexane to flush off the tin compounds followed by EtOAc to flush off the adducts), and the adducts were separated from each other by preparative HPLC (10% EtOAc in hexane, 10 mL/min), giving a combined total of 20 mg (34%). From **14c**, major product: ^{1}H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5 H), 5.80 (m, 1 H), 5.15–5.00 (m, 2 H), 4.89 (dd, J = 1.88, 6.53 Hz, 1 H), 4.30 (dd, J = 6.58, 8.92 Hz, 1 H), 3.86 (dd, J = 1.98, 8.92 Hz, 1 H), 2.32–2.07 (m, 3 H), 1.87 (s, 3 H), 1.61 (s, 3 H), 1.39 (m, 1 H), 1.13 (m, 1 H), 0.29 (t, J = 7.41 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 142.4, 135.6, 128.8, 127.8, 126.4, 117.0, 96.2, 71.0, 61.4, 46.1, 37.8, 25.7, 25.4, 23.0, 11.5; MS (CI, CH_4/NH_3) MH^+ = 288. From **14c**, minor product: ^{1}H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5 H), 5.05 (m, 1 H), 4.91 (dd, J = 2.11, 6.53 Hz, 1 H), 4.70–4.55 (m, 2 H), 4.35 (dd, J = 6.64, 8.92 Hz, 1 H), 3.88 (dd, J = 2.29, 8.95 Hz, 1 H), 2.18 (m, 1 H), 1.98–1.76 (m, 1 H), 1.85 (s, 3 H), 1.64 (s, 3 H), 1.62–1.40 (m, 2 H), 1.23 (m, 1 H), 0.92 (t, J = 7.42 Hz, 3 H); MS (CI, CH_4/NH_3) MH^+ = 288.

Telomerization of 4c with $BrCCl_3$. The acrylamide **4c** (0.938 g, 4.06 mmol) and $BrCCl_3$ (4.02 g, 20.3 mmol) were dissolved in 5 mL of CH_2Cl_2 in a flask that was suspended in a jacketed photoreaction vessel. The sample was irradiated at 0 °C for a total of 14 h [samples were removed periodically to monitor by GC (column B) the rate of decrease of the monomer versus an internal standard, dodecane]. About $^1/_3$ of the reaction mixture was purified by removing the solvent and placing it on the high vacuum for an extended period of time to remove the $BrCCl_3$. The mixture of telomers was isolated by solid-phase extraction (silica), starting with 8 mL of hexane followed by 100 mL of 20% ethyl acetate/hexane. This mixture was examined by GC and gradient HPLC (linear gradient 1–10% 2-propanol in hexane for 50 min, followed by a linear gradient 10–50% over the next 30 min).

n = 1, major isomer: ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 5 H), 5.52 (dd, J = 6.72, 2.47 Hz, 1 H), 4.45 (dd, J = 9.07, 6.72 Hz, 1 H), 4.35 (dd, J = 8.10, 2.51 Hz, 1 H), 4.00 (dd, J = 15.32, 8.1 Hz, 1 H), 3.98 (dd, J = 9.07, 2.47 Hz, 1 H), 3.07 (dd, J = 15.32, 2.51 Hz, 1 H), 1.95, 1.83 (s, 6 H); CIMS MH^+ = 430.

n = 2, major isomer: HPLC t_R = 35.68 min; ^{1}H NMR ($CDCl_3$) δ 7.60–7.20 (m, 10 H), 5.45 (d, J = 6.01 Hz, 1 H), 5.13 (dd, J = 6.64, 2.14 Hz, 1 H), 4.40 (m, 2 H), 3.97–3.89 (m, 2 H), 3.87 (dd, J = 9.04, 0.86 Hz, 1 H), 3.08 (dd, J = 14.55, 10.13 Hz, 1 H), 2.68 (tt, J = 10.13, 1.24 Hz, 1 H), 2.58 (tt, J = 11.69, 1.37 Hz, 1 H), 1.85 (m, 1 H), 1.38 (dd, J = 14.55, 1.24 Hz, 1 H), 1.94 (s, 3 H), 1.82 (s, 3 H), 1.70 (s, 3 H), 1.57 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.91, 165.08, 141.89, 140.43, 129.87, 128.92, 128.35, 127.70, 127.48, 125.94, 97.08, 96.86, 95.85, 71.41, 71.34, 61.12, 60.22, 52.09, 41.52, 40.78, 37.06, 25.78, 25.11, 22.34, 21.64; CIMS MH^+ = 661. Anal. Calcd for $C_{29}H_{34}BrCl_3N_2O_4$: C, 52.70; H, 5.19; N, 4.24. Found: C, 52.52; H, 5.24; N, 4.19.

n = 2, minor isomer: HPLC t_R = 33.60 min; ^{1}H NMR ($CDCl_3$) δ 7.40–7.20 (m, 10 H), 5.05 (d, J = 5.87 Hz, 1 H), 4.85 (dd, J = 6.80, 3.24 Hz, 1 H), 4.35 (dd, J = 9.06, 6.81 Hz, 1 H), 4.23 (dd, J = 8.93, 6.57 Hz, 1 H), 3.87 (dd, J = 9.08, 3.26 Hz, 1 H), 3.77 (dd, J = 8.89, 1.36 Hz, 1 H), 3.53 (dd, J = 10.24, 3.46 Hz, 1 H), 2.82 (dd, J = 14.84, 9.89 Hz, 1 H), 2.70 (dt, J = 10.19, 2.64 Hz, 1 H), 1.65 (m, 2 H), 1.40 (d, J = 14.8 Hz, 1 H), 1.81 (s, 3 H), 1.79 (s, 3 H), 1.54 (s, 3 H), 1.50 (s, 3 H).

n = 3, major isomer: HPLC t_R = 41.00 min; ^{1}H NMR δ 7.25–7.05 (m, 15 H), 5.48 (d, J = 6.05 Hz, 1 H), 5.38 (d, J = 6.01 Hz, 1 H), 5.10 (dd, J = 6.73, 2.66 Hz, 1 H), 4.42 (m, 2 H), 4.28 (dd, J = 8.90, 6.37 Hz, 1 H), 3.95 (dd, J = 9.10, 1.71 Hz, 1 H), 3.92 (dd, J = 8.92, 2.66 Hz, 1 H), 3.85 (m, 2 H), 2.85 (dt, J = 11.95, 1.31 Hz, 1 H), 2.52 (dt, J = 13.80, 1.13 Hz, 1 H), 2.45 (dd, J = 11.38, 10.38 Hz, 1 H), 1.90 (m, 1 H) 1.83 (m, 1 H), 1.39 (m, 1 H), 0.95 (dd, J = 13.80 Hz, 1 H), 0.32 (m, 1 H), 1.86 (s, 3 H), 1.80 (s, 3 H), 1.67 (s, 3 H), 1.64 (s, 3 H), 1.55 (s, 3 H), 1.52 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.54, 170.32, 165.62, 142.07, 141.94, 140.29, 130.04, 129.70, 129.19, 128.34, 128.19, 127.49, 126.72, 125.20, 97.52, 97.03, 96.02, 95.55, 71.48, 71.43, 71.36, 61.08, 59.90, 59.48, 52.18, 41.52, 39.50, 39.45, 39.03, 32.49, 26.23, 25.91, 25.36, 22.62, 22.33, 21.65; CIMS MH^+ = 894.

X-ray Crystal Structure Analysis of 2, 4b, 4c, 5c, 12b, and 15c. Crystal data: **2**, $C_{10}H_{15}NO_3S$, M = 229.30, monoclinic, space group $P2_1$, a = 8.137 (1) Å, b = 9.635 (1) Å, c = 7.826 (1) Å, β = 105.07 (1)°, V = 592.5 (2) Å^3, Z = 2, D_{calcd} = 1.285 g cm^{-3}, μ(Cu Kα) = 23.0 cm^{-1}; **4b**, $C_{12}H_{21}NO_2$, M = 211.31, orthorhombic, space group $P2_12_12_1$, a = 11.137 (1) Å, b = 15.598 (1) Å, c = 7.221 (1) Å, v = 1254.4 (4) Å^3, Z = 4, D_{calcd} = 1.119 g cm^{-1}, μ(Cu Kα) = 5.7 cm^{-1}; **4c**, $C_{14}H_{17}NO_2$, orthorhombic, space group $P2_12_12_1$, a = 10.867 (1) Å, b = 19.153 (2) Å, c = 6.277 (1) Å, V = 1306.5 (5) Å^3, Z = 4, D_{calc} = 1.176 g cm^{-3}, μ(Cu Kα) = 5.9 cm^{-1}; **5c**, $C_{26}H_{30}N_2O_4$, M = 434.54, orthorhombic, space group $P2_12_12_1$, a = 11.461 (1) Å, b = 35.216 (3) Å, c = 6.070 (1) Å, V = 2449.9 (8) Å^3, Z = 4, D_{calcd} = 1.176 g cm^{-3}, μ(Cu Kα) = 6.1 cm^{-1}; **12b**, $C_{23}H_{36}N_2O_2S$, M = 406.62, monoclinic, space group $P2_1$, a = 9.548 (1) Å, b = 13.731 (1) Å, c = 9.472 (1) Å, β = 110.47 (1)°, V = 1163.4 (4) Å^3, Z = 2, D_{calcd} = 1.155 g cm^{-3}, μ(Cu Kα) = 13.4 cm^{-1}; **15c**, $C_{43}H_{51}BrCl_3N_3O_6$, M = 892.17, monoclinic, space group $P2_1$, a = 11.527 (1) Å, b = 19.657 (2) Å, c = 9.894 (1) Å, β = 96.19 (1)°, V = 2228.8 (7) Å^3, Z = 2, D_{calcd} = 1.329 g cm^{-3}, μ(Cu Kα) = 33.4 cm^{-1}.

Intensity data were recorded on an Enraf-Nonius CAD-4 diffractometer [Cu Kα radiation, λ = 1.5418 Å; graphite monochromator; ω–2θ scans, scanwidth (0.80 + 0.14 tan θ)°]. Refined unit cell parameters were derived in each case from the diffractometer setting angles for 25 high-order reflections (θ = 36–46°) widely separated in reciprocal space. The crystal structures were all solved by direct methods (MULTAN11/82). Atomic positional and thermal parameters (anisotropic non-hydrogen atoms; isotropic H for **2**, **4b**, **4c**, **5c**, **12b**; calculated H for **15c**) were refined by full-matrix least-squares calculations to R = 0.033 (R_w = 0.046) for **2**, R = 0.033 (R_w = 0.047) for **4b**, R = 0.048 (R_w = 0.064) for **4c**, R = 0.036 (R_w = 0.048) for **5c**, R = 0.047 (R_w = 0.057) for **12b** and R = 0.038 (R_w = 0.055) for **15c** over 1197, 1320, 1322, 1938, 2313, and 3970 reflections, respectively, with $I > 3.0\sigma(I)$. Further details of the crystallographic analyses are summarized in the supplementary ma-

(33) We thank Professor Dennis Curran of the University of Pittsburgh for a sample of the allylsultam reported in ref 17, see Scheme 1.

terial.[34] Crystallographic calculations were performed on PDP11/44 and MicroVAX computers using the Enraf-Nonius Structure Determination Package (SDP 3.0). For all structure-factor calculations, neutral atom scattering factors and their anomalous dispersion corrections were taken from ref 35.

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Supplementary Material Available: ORTEP diagrams showing the atom numbering schemes and tables of crystallographic data, atomic positional and thermal parameters, and bond lengths and angles for **2**, **4b**, **4c**, **5c**, **12b**, and **15c** (56 pages); tables of observed and calculated structure amplitudes (82 pages). Ordering information is given on any current masthead page.

(34) See paragraph at the end of the paper regarding supplementary material.

(35) *International Tables for X-Ray Crystallography*; Kynoch: Birmingham, U.K., 1974; Vol. IV.

Chiral Auxiliary Control of Tacticity in Free Radical Polymerization

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Abstract: Chiral oxazolidine acrylamides undergo stereocontrolled free radical polymerization. Remarkably high degrees of tacticity have been demonstrated in the polymerization of acrylamides with these chiral auxiliaries that are derived from valine, phenylglycine, and *tert*-leucine. The polyacrylamides formed in these polymerizations can be converted to poly(acrylic acid), P(AA), and poly(methyl acrylate), P(MA), by hydrolysis and esterification. Tacticities as high as 92% have been measured for P(AA) and P(MA) resulting from these reactions. NMR studies of the microstructure of the polymers formed using chiral auxiliaries to control the stereochemistry of the reaction showed that the distribution of stereochemical sequences could be predicted by a statistical analysis based upon the mechanism of stereoselection. Specifically, these studies confirm that the stereocontrol is the result of facial selectivity in the addition of the monomer to the growing polymer radical. This face selectivity is thought to be the result of steric hindrance to approach of the monomer to one face of the radical caused by the chiral auxiliary. Further NMR studies were used to propose an analysis of the stereochemistry of P(MA) at the hexad level. Using HETCOR techniques, eight of the twenty hexads were conclusively identified, and a further six were narrowed to two possible choices.

Free radical polymerization of alkenes is an important method of making polymers. Control of the stereochemistry (i.e., the tacticity) in free radical polymerization reactions has been of interest since 1929 when Staudinger[1] pointed out that the tertiary carbons formed in vinyl polymerization reactions could have two different stereochemical arrangements. Significant stereocontrol of free radical polymerization reactions of vinyl monomers has never been achieved, with atactic polymers generally resulting from free radical polymerization. Important polymer bulk properties such as tensile strength, melting point, and solubility all have been shown to depend on the stereochemistry of the polymer,[2] and since free radical polymerization methods are convenient, the control of stereochemistry in free radical polymerization is a significant goal.

The degree of stereocontrol in a polymerization reaction is measured by the tacticity of the resulting polymer, where tacticity is defined by the relationship that adjacent stereocenters have to one another. In vinyl free radical polymerization, the difference between the activation barriers for the addition to the diastereotopic faces of the radical determines the selectivity of the polymerization, Figure 1. In a typical free radical polymerization, the stereoregulating effect results from a steric interaction between the incoming alkene and nearest stereocenter, but due to the conformational mobility of the chain, this effect is minimal. For example, the ratio of k_s/k_i for methyl acrylate is 1.1 at 0 °C.[3]

No systematic approach for controlling stereochemistry in acyclic radical reactions like those involved in polymerization had been undertaken prior to 1988. Since that time, work by several groups has employed chiral auxiliaries to control the stereochemistry of acyclic free radical addition reactions including telomerizations.[4-9] The use of groups such as pyrrolidine and

(1) Staudinger, H.; Ashdown, A.; Brunner, M.; Bruson, H. A.; Wehrli, S. *Helv. Chim. Acta* **1929**, *12*, 934.

(2) (a) Lenz, R. W. *Organic Chemistry of Synthetic High Polymers*; Wiley Interscience: New York, 1967. (b) Seymour, R. B. *Polymer Chemistry: An Introduction*; M. Dekker: New York, 1988. (c) Stevens, M. P. *Polymer Chemistry: An Introduction*; Oxford University Press: New York, 1990. (d) Nicholson, J. W. *The Chemistry of Polymers*; Royal Society of Chemistry: Cambridge, 1991.

(3) Pino, P.; Suter, U. W. *Polymer* **1976**, *17*, 977.

(4) For a review, see: Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.

(5) (a) Porter, N. A.; Lacher, B.; Chang, V.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8311. (b) Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1679. (c) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740. (d) Porter, N. A.; Breyer, B.; Swann, E.; Nally, J.; Pradhan, J.; Allen, T. R.; McPhail, A. T. *J. Am. Chem. Soc.* **1991**, *113*, 7002. (e) Porter, N. A.; Wu, W.-X.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 707.

(6) (a) Crich, D. *Aldrichimica Acta* **1987**, *20*, 35. (b) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.

(7) (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28(8)*, 969. See also: (b) Barton, D. H. R.; Gateau-Olesker, A.; Gero, S. D.; Lacher, B.; Tachdjian, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1987**, 1790.

(8) (a) Curran, D.; Shen, W.; Zhang, J.; Heffner, T. *J. Am. Chem. Soc.* **1990**, *112*, 6738. (b) Beckwith, A. L. J.; Chai, C. L. L. *J. Chem. Soc., Chem. Commun.* **1990**, *16*, 1087. (c) Beckwith, A. L. J.; Hersperger, R.; White, J. *J. Chem. Soc., Chem. Commun.* **1991**, *17*, 1151. (d) Renaud, P.; Schubert, S. *Synlett* **1990**, 624. (e) Renaud, P.; Ribezzo, M. *J. Am. Chem. Soc.* **1991**, *113(20)*, 7803. (f) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *J. Chem. Soc., Chem. Commun.* **1991**, *722*. (g) Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, *28*, 4205.

(9) (a) Hart, D. J.; Krishnamurthy, R. *Synlett* **1991**, 412. (b) Guindon, Y.; Lavallee, J.-P.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27. (c) Bulliard, M.; Zeitz, H.; Giese, B. *Synlett* **1991**, 423. (d) Curran, D. P.; Thoma, G. *Tetrahedron Lett.* **1991**, *32*, 6307.

0002-7863/92/1514-7676$03.00/0