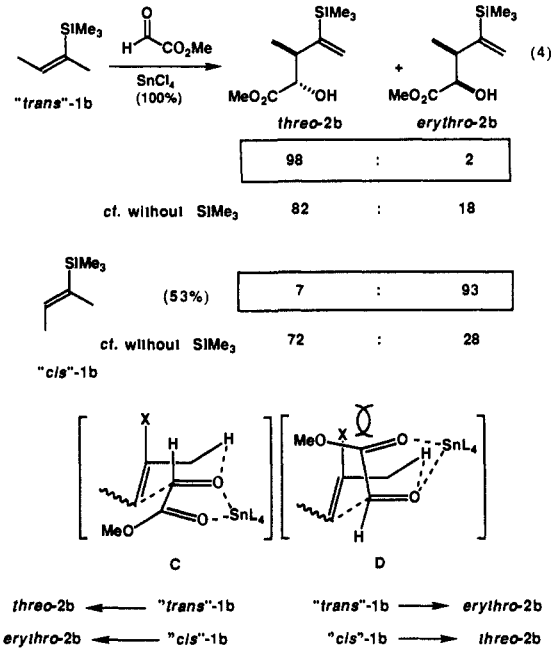
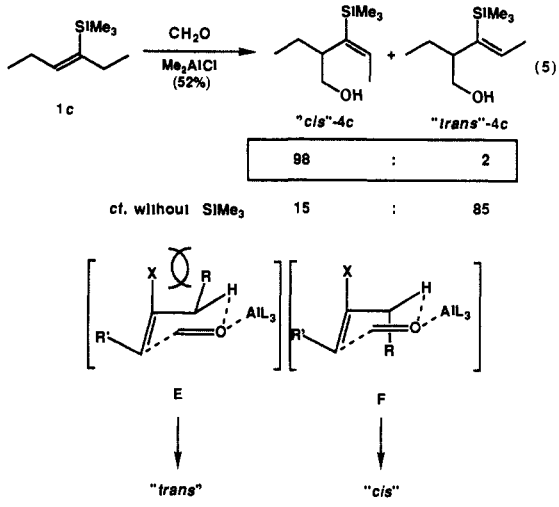
The introduction of a silyl group into the ene component is also effective for the enhancement and/or the changeover in diastereoselectivity (eq 4). The reaction with "*trans*"-vinylsilane **1b**



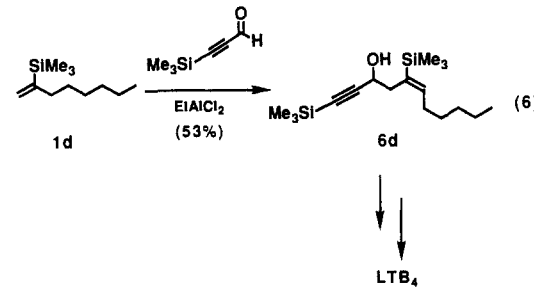
is found to give the threo product with remarkably enhanced selectivity (98%) as compared with *trans*-2-butene[8] (82%). In sharp contrast, the dramatic changeover in diastereoselectivity from threo[8] to erythro is observed for the ene reaction with "*cis*"-vinylsilane **1b**. Both the enhancement and changeover in diastereoselectivity are explicable in view of the greatly increased 1,3-repulsion of $SiMe_3$ and CO_2Me in the transition state D.

The controlling effect of the silyl group on the stereochemistry is highlighted by the changeover of the olefinic stereoselectivity from trans to "cis" (eq 5). Trans selectivity (ca. 90%) is widely



recognized for the ene reaction with alkenes without silyl group.[1,9] In direct contrast, the reaction of formaldehyde with vinylsilane **1c** provides "*cis*"-homoallyl alcohol **4c** with high (98%) selectivity.[10] Dramatic changeover into "cis" selectivity is explained in terms of the large 1,2 steric repulsion between $SiMe_3$ and R in E leading to the "trans" product.

The unprecedented "cis" selectivity should find its application to the synthesis of leukotriene B_4 (LTB_4) featuring a "*cis*"-homoallyl alcohol unit.[11] Thus, the ene reaction of silylpropynal with vinylsilane **1d** affords the disilylated enynol **6d** with a high level of "cis" selectivity (>99%),[12,13] which serves as a key intermediate of LTB_4.[14]



In conclusion, we have described here the Lewis acid promoted carbonyl–ene reaction with vinylsilanes, which allows the highly regio- and stereocontrolled introduction of vinylsilane functionality. These results clearly show the dramatic effect of silicon as a controlling element for not only the regio- but also the stereochemistry.

Acknowledgment. This research was partially supported by the Asahi-Kasei Award in Synthetic Organic Chemistry, Japan.

Supplementary Material Available: Experimental details of the glyoxylate–ene reaction with vinylsilanes (**1a,b**), the formaldehyde–ene reaction with **1c**, the propynal–ene reaction with **1d**, and the protodesilylation of **4c** and **6d** (6 pages). Ordering information is given on any current masthead page.

(9) The ene reaction of formaldehyde with 4- or 1-octene has been reported to give the *trans*-homoallyl alcohol (ca. 90% selectivity): Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555.

(10) The stereoisomeric ratio was determined by a combination of HPLC and IR analyses after protodesilylation via the reported procedure.[5]

(11) Review on the synthesis of leukotrienes: Rokach, J.; Guindon, Y.; Young, R. N.; Adams, J.; Atkinson, J. G. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1988; Vol. 7. Corey, E. J.; Cheng, X.-E. *The Logic of Chemical Synthesis*; Wiley: New York, 1989; Chapter 12. Kobayashi, Y.; Shimazaki, T.; Sato, F. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 627.

(12) The "cis" configuration of the known product **6d** was confirmed by ^{13}C NMR, IR, and HPLC analyses prior to and/or after protodesilylation according to the literature.[14]

(13) We have also found that the ene reaction of formaldehyde with vinylsilane **1d** shows >99% "cis" selectivity.

(14) Kaye, A. D.; Pattenden, G.; Roberts, S. M. *Tetrahedron Lett.* **1986**, *27*, 2033.

Asymmetric Radical Addition, Cyclization, and Annulation Reactions with Oppolzer's Camphor Sultam

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Although an understanding of the factors that control relative stereochemistry in radical cyclization reactions has matured rapidly,[2] it remains to be shown that radical reactions are generally useful for dictating acyclic stereochemistry—either relative or absolute.[3,4] We now demonstrate that chiral radicals derived from

(1) Dreyfus Teacher-Scholar, 1986–1991. NIH Research Career Development Awardee, 1987–1992. ICI Pharmaceuticals Awardee, 1990.

(2) (a) Curran, D. P. *Synthesis* **1988**, 417, 489. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. (c) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, Vol. 4, in press.

(3) For a timely review on stereoselectivity in intermolecular radical reactions, see: Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969. With few exceptions, most stereoselective intermolecular additions involve cyclic radicals bearing adjacent stereocenters.

(4) Additions of achiral radicals to chiral alkenes: (a) Porter, N. A.; Lacher, B.; Chang, V. H.-T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309. (b) Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H. G.; Lindner, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 8311. (c) Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1679.

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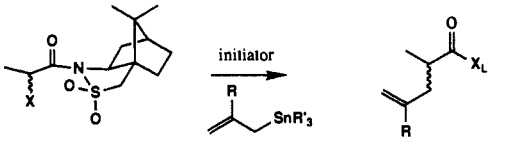
Table I. Asymmetric Allylations of Iodide **2**



1 X = H
2 X = I

3a R = H, R' = Bu
3b R = Me, R' = Bu
3c R = COOMe, R' = Ph

4a-c β-allyl
5a-c α-allyl
X_L = L-(+)-2,10-camphor sultam

entry	allyltin	solvent	initiation[a]	temp, °C	ratio **4**/**5**[b]
1	**3a**	C_6D_6	AIBN	80	12/1
2	**3a**	CH_2Cl_2	AIBN	80	12/1
3	**3a**	CH_2Cl_2	Et_3B	80	12/1
4	**3a**	C_6D_6	Et_3B	25	14/1
5	**3a**	CH_2Cl_2	Et_3B	25	14/1
6	**3b**	C_6D_6	Et_3B	25	14/1
7	**3c**	C_6D_6	Et_3B	25	15/1
8	**3a**	CH_2Cl_2	Et_3B	0	22/1
9	**3a**	CH_2Cl_2	Et_3B	−20	25/1
10	**3a**	CH_2Cl_2	Et_3B	−78	>30/1[c,d]

[a] AIBN: iodide **2** (0.2–0.5 M), allylstannane (1.5 equiv), and AIBN (0.1 equiv) were heated at 80 °C for 5 h. Et_3B: iodide **2** (0.2 M), stannane (1.5 equiv), and Et_3B (0.1 equiv) were stirred for 3–6 h under a very slow stream of air. [b] The indicated ratios were determined by capillary GC. Isolated yields of inseparable **4**,**5** exceeded 90%. [c] After 24 h (during which three additional portions of Et_3B were added), only 20% of **2** was consumed. [d] The minor product was not detected by GC.

Opplozer's camphor sultam[5,6] give high levels of asymmetric induction in radical addition, cyclization, and annulation reactions with achiral alkenes and alkynes.

Deprotonation of propionoyl camphor sultam **1** with LDA, followed by iodination with I_2, gave iodosultam **2** in 80% yield. Heating of **2**, allyltributylstannane (**3a**), and 10% AIBN at 80 °C (C_6D_6, 5 h)[7] gave a mixture of the allylated derivatives **4a** and **5a** in a ratio of 12/1 in virtually quantitative yield after flash chromatography (Table I, entry 1). This level of selectivity (85% de) is remarkable for a reaction conducted at 80 °C in the absence of Lewis acid. The configurations of **4** and **5** were assigned by the asymmetric alkylation method of Oppolzer.[8] Deprotonation of **1** with LDA, followed by addition of allyl bromide, gave **4a** and **5a** in ratios of 50/1 at −78 °C and 14/1 at −20 °C.

Table I summarizes the results of a study of temperature and substituent effects on the allylation of **1**. Reactions at 25 °C or below were initiated with triethylboron in methylene chloride.[9] Neither the chemical initiator[10] nor the solvent altered the diastereomer ratios (compare entries 2 with 3, and 4 with 5). A decrease in temperature from +80 to −78 °C gave a slow but steady increase in the ratio of **4a**/**5a**.[11] From a practical standpoint, the best results were obtained at −20 °C: after 6 h, **4a**/**5a** formed in 95% yield in a ratio of 25/1 (entry 9). At −78 °C, we could not detect the minor diastereomer **5a**, but chain propagation was too slow (20% conversion after 24 h) to be useful (entry 10). At −20 °C (and possibly also at −78 °C), the radical

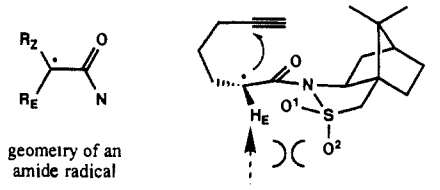
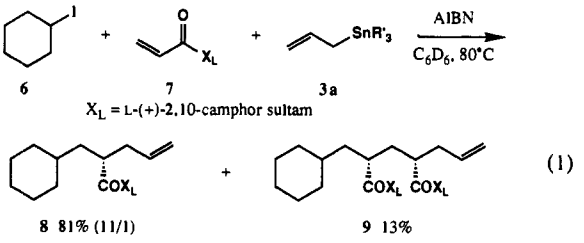


Figure 1. Transition-state model.

allylation of **2** is marginally more diastereoselective than the anion allylation of **1**.[8] Substituents on the 2-position of the allylstannane had no detectable effect on the diastereoselectivity. At 25 °C, methallylstannane **3b** and (carbomethoxy)allylstannane **3c** both gave about the same ratio of allylated products (14/1) as **3a** (compare entries 4, 6, and 7).

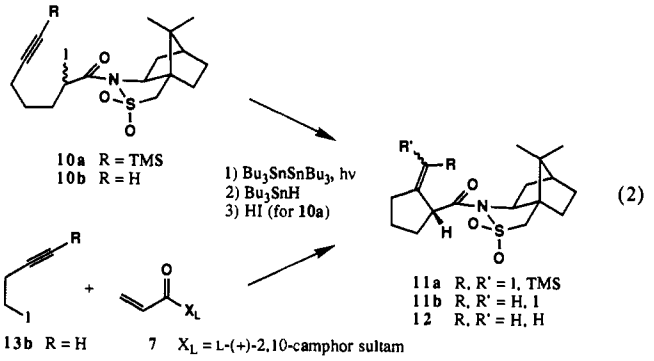
The asymmetric allylation can be placed in sequence with an addition reaction,[12] as indicated in eq 1. Heating of cyclohexyl



(1)

iodide (**6**), acryloylsultam **7**, and allyltributylstannane (**3a**) at 80 °C gave 1/1/1 adduct **8** as an 11/1 mixture of diastereomers in 81% yield, and 1/2/1 adduct **9** as largely a single product in 13% yield.[13] Thus, the chiral auxiliary controls the absolute stereochemistry of **8** and both the relative and absolute stereochemistry of **9**. It is important that good diastereoselectivity is achieved at 80 °C because these chain sequences do not propagate well at lower temperatures.

This method of asymmetric induction is not limited to additions, and several asymmetric cyclization and annulation reactions are outlined in eq 2. Atom-transfer cyclization of iodosultam **10a**[7]



(2)

by our standard ditin procedure (10% $Bu_3SnSnBu_3$, C_6H_6, 80 °C, *hν*)[14] gave an *E*/*Z* mixture of vinyl iodides **11a** (82% yield). Reductive deiodination with tributyltin hydride, followed by desilylation (HI), gave **12** and its diastereomer (not shown) in a ratio of 9/1. Compound **12** was isolated in 71% yield after purification by flash chromatography, and its structure was determined by X-ray crystallography (see supplementary material).[15] Atom-transfer annulations provide a shorter, more efficient route to **12**.[16] Standard irradiation of butynyl iodide (**13b**) and acryloyl sultam **7** (10% $Bu_3SnSnBu_3$, C_6H_6, 80 °C)[16] gave an *E*/*Z* mixture of isomers **11b**, which was deiodinated in situ with Bu_3SnH. The resulting mixture (53% isolated yield) contained three products

(5) (a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. See also, Errata: *Tetrahedron* **1987**, *43*(18). (b) Oppolzer, W. *Pure Appl. Chem.* **1988**, *60*, 39.

(6) For asymmetric sulfenylation (low to moderate selectivity) or reduction (high selectivity) of some α-carbonyl-substituted radicals, see: Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, *28*, 4205. Hart, D. J.; Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.

(7) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.

(8) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603.

(9) Miura, K.; Ichinose, I.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143.

(10) We also used photolytic initiation by irradiation of the reaction mixture with a sunlamp. For reasons that we do not understand, this method consistently gave marginally lower ratios of **4**/**5** compared to either chemical method (25 °C, 10/1; −20 °C, 13/1; −78 °C, 31/1).

(11) For some examples of the effect of temperature on the stereoselectivity of radical reactions, see: references 4 and 5. Nakamura, E.; Machii, D.; Inubushi, T. *J. Am. Chem. Soc.* **1989**, *111*, 6849.

(12) (a) Minisci, F. *Synthesis* **1973**, 1. (b) Mizuno, K.; Ikeda, M.; Toda, S.; Otsuji, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1288.

(13) The small amount of **9** formed precluded careful analysis of the isomer ratio, and the stereostructure is assigned only by analogy.

(14) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

(15) We thank Drs. K. Paris and J. Abola for solving the crystal structure of **12**.

(16) Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558.

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

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

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

Acknowledgment. We thank the National Institutes of Health for Funding (GM33378). We also thank Professors N. Porter and B. Giese for preprints of their manuscripts and for agreeing to joint publication.

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

(17) Leading reference: Strub, W.; Roduner, E.; Fischer, H. *J. Phys. Chem.* **1987**, *91*, 4379.
(18) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555. Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585.

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

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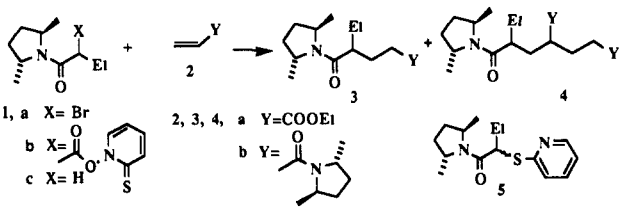
The stereochemistry of acrylate reactions has been of interest for nearly 50 years since radicals derived from acrylates are prochiral and the orientation during addition of such radicals is important in establishing polymer tacticity.[1] It can be said that significant control of stereochemistry in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

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



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

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

(1) (a) Kharasch, M. S.; Eugelmann, H.; Mayo, F. R. *J. Org. Chem.* **1937**, *2*, 288. (b) Hey, D. H.; Waters, W. A. *Chem. Rev.* **1937**, *21*, 169. (c) Flory, P. *J. Am. Chem. Soc.* **1937**, *59*, 241.
(2) Pino, P.; Suter, U. W. *Polymer* **1976**, *17*, 977.
(3) (a) Porter, N. A. Stereochemical and Regiochemical Aspects of Free Radical Macrocyclization. In *Organic Free Radicals (Proceedings of the Fifth International Symposium)*; Fischer, H., Heimgartner, H., Eds.; Springer-Verlag: Berlin, 1988; pp 157–158. (b) Porter, N. A.; Lacher, B.; Chang, V. H.-T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309.
(4) Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H. G.; Lindner, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 8311.
(5) Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1679.
(6) Giese, B. *Angew Chem., Int. Ed. Engl.* **1989**, *28*, 969.
(7) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083.
(8) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 21581.
(9) The thiohydroxamic ester was characterized by ^1H NMR; other new compounds were characterized by ^1H and ^{13}C NMR, mass spectrometry, and elemental analysis.
(10) Jacques, J.; Gros, C.; Bourcier, S.; Brienne, M. J.; Toullec, J. In *Absolute Configurations of 6000 Selected Compounds With One Asymmetric Carbon Atom Stereochemistry*; Kagan, H., Ed.; Georg Thieme Publishers: Stuttgart, 1977, Vol. 4.

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