column chromatography (20 g of silica gel, 2:3 ethyl acetate/hexane) gave 0.21 g (60%) of **20b** as a pale yellow oil, pure by GC (2% Carbowax 20M at 200 °C): bp 155-160 °C (3 mm); ^{1}H NMR ($CDCl_3$) δ 1.47 (d, 3 H, CH_3), 3.08 (s, 3 H, NCH_3), 3.48 (q, 1 H, CH), 4.43 (dd, 2 H, $ArCH_2N$), 7.00-7.43 (m, 4 H, aromatic); IR (5% solution in $CHCl_3$) 1710 cm^{-1} (C=O); *m/e* (relative intensity) 175 (M^+, 42), 118 (100), 117 (65).

4-Ethyl-2-methyl-1,3-dihydro-3(2*H*)-isoquinolinone (20c). From 0.45 g of **19c**, 0.24 g of crude product was obtained as an orange oil. Short column chromatography (30 g of silica gel, 1:9 acetone/hexane) gave 0.20 g (54%) of **20c** as a yellow oil, pure by GC (2% Carbowax 20M at 200 °C): ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3 H, CH_3), 1.87 (m, 2 H, CH_2), 3.12 (s, 3 H, NCH_3), 3.48 (t, 1 H, CH), 4.50 (dd, 2 H, $ArCH_2N$), 7.07-7.53 (m, 4 H, aromatic); IR (5% solution in $CHCl_3$) 1710 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.19; H, 7.93; N, 7.40. Found: C, 75.91; H, 8.08; N, 7.16.

***N*-(*o*-Chlorobenzyl)-*N*-(trimethylsilyl)acetamide (19e) and Its Cyclization to 20d.** To a solution of 2.57 g (15 mmol) of *N*-(*o*-chlorobenzyl)acetamide in 30 mL of anhydrous THF, was added over 10 min with stirring, 9.5 mL of 1.6 M *n*-BuLi solution. The reaction was strictly maintained at -50 °C, during addition, while keeping a positive argon atmosphere. A solution of 1.65 g (15 mmol) of chlorotrimethylsilane in 5 mL of THF was added (20 min) at the same temperature. The reaction was further stirred for 0.5 h and was brought to room temperature. The resulting oil, after removing the THF, was distilled under reduced pressure to give 3.14 g (82%) of **19e**: bp 90-93 °C (3 mm); ^{1}H NMR ($CDCl_3$ containing no Me_4Si) δ 1.60 (s, 3 H, CH_3), 4.21 (s, 2 H, CH_2), 6.86-7.19 (m, 4 H aromatic); IR (neat) 1650 cm^{-1} (C=O).

From 2.0 g (5 mmol) of **19e**, following procedure A, was obtained 0.5 g (62%) of 1,4-dihydro-3(2*H*)-isoquinolinone (**20d**) as a dark brown solid, which was sublimed as yellow needles (43%): mp 149-151 °C (lit.[32] mp 149-150 °C). Spectral data were identical with those reported by Lyle.[32]

2-Methyl-4-ethyl-4-benzyl-3(2*H*)-isoquinolinone (21). After the anion of **20b** (prepared from 0.45 g of **19b**) was irradiated for 1 h, a solution of 0.28 g of (2.2 mmol) of benzyl chloride in 10 mL of ether was added and stirred for 1 h. Quenching with solid NH_4Cl and the usual workup gave 0.48 g of crude product as a yellow oil. Short column chromatography (20 g of silica gel, 1:4 ether/hexane) gave 0.18 g (32%) of **21** as a pale yellow solid. Recrystallization from hexane gave an analytical sample as the white cubes: mp 92-93 °C; ^{1}H NMR ($CDCl_3$) δ 0.65 (t, 3 H, CH_3), 2.30 (m, 2 H, CH_2), 2.90 (s, 3 H, NCH_3), 3.03 (dd, 2 H, $ArCH_2$), 3.47 (dd, 2 H $ArCH_2N$), 6.47-7.47 (m, 9 H, aromatic); IR (5% solution in $CHCl_3$) 1705 cm^{-1} (C=O). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.72; H, 7.53; N, 5.02. Found: C, 81.69; H, 7.27; N, 5.02.

Supplementary Material Available: Tables of physical and spectral characteristics of starting materials **4**, **13**, and **20** and spectral data for certain products **5**, **14**, and **20** (10 pages). Ordering information is given on any current masthead page.

(32) Lyle, R. E.; Walsh, D. A. *Org. Prep. Proc. Int.* **1973**, *5*, 299.

Asymmetric Induction in the Claisen Rearrangement of *N*-Allylketene *N,O*-Acetals

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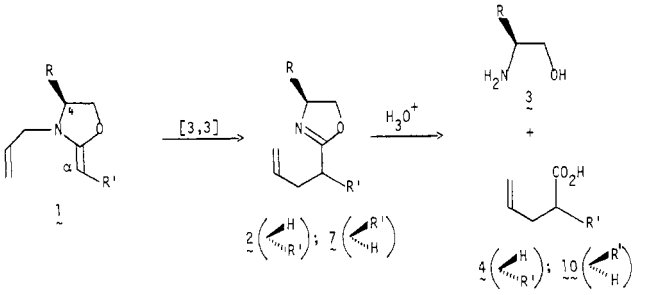
Abstract: Asymmetric C-C bond formation via the diastereoselective aza-Claisen rearrangement of *N*-allylketene *N,O*-acetal **1** is described. Diastereoselection noted for rearrangement **1** → **2** ranges from 84% to 96% and is a consequence of complete (*Z*)-*N,O*-acetal olefin selectivity in **1**, high C_α-*si*-face selectivity in the rearrangement of **1** to **2**, and the absence of C_α epimerization in oxazoline **2**. Experiments which establish the steric bulk of the C_4 appendage as a particularly important variable are also reported. Acid-catalyzed hydrolysis of rearranged oxazoline **2** completes an efficient, enantioselective synthesis of 2-substituted pent-4-enoic acid **4** and regenerates for recycling the chiral auxiliary reagent **3**, initially prepared from inexpensive α-amino acids.

The achievement of absolute stereochemical control continues to be a major goal in organic synthesis. While various methods of asymmetric induction have been recorded, remote and acyclic stereocontrol remain particularly challenging. In this regard, the regio- and stereochemically reliable Claisen rearrangement has been gainfully employed in a variety of self-immolative[1] enantioselective studies.[2] In contrast, the chiral auxiliary-mediated variant, in which auxiliary chirality is preserved, has been reported only once[3] prior to our work.[4] We were intrigued by the notion of auxiliary-reagent-mediated asymmetric Claisen rearrangements and have undertaken a study directed at the development of *N*-allylketene, *N,O*-acetal **1** as a useful chiral aza-Claisen substrate.

Substrate **1** is suitably disposed for an auxiliary-mediated Claisen rearrangement to oxazoline **2** (Scheme I). Subsequent acid-catalyzed hydrolysis of **2** would regenerate the chiral auxiliary amino alcohol **3** for recycling and provide optically active pent-4-enoic acid **4**, a versatile precursor in the enantioselective synthesis of biologically interesting compounds.[5] Inspection of the aza-

Scheme I



(1) Mislow, K. "Introduction to Stereochemistry"; Benjamin: New York, 1965; p 131.

(2) (a) For example, this reaction was elegantly applied to a synthesis of (+)-15(*S*)-PGA_2 from L-erythrose.[2b] (b) Stork, G.; Raucher, S. *J. Am. Chem. Soc.* **1976**, *98*, 1583.

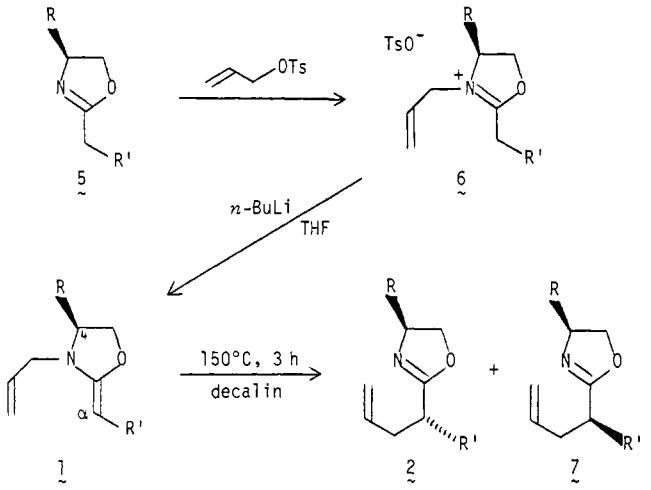
(3) Oda, J.; Igarashi, T.; Inouye, Y. *Bull. Inst. Chem. Res., Kyoto Univ.* **1976**, *54*, 180; *Chem. Abstr.* **1977**, *86*, 88836*m*.

(4) Kurth, M. J.; Decker, O. H. W. *Tetrahedron Lett.* **1983**, *24*, 4535.

(5) (a) For example optically acgtive pent-4-enoic acid derivatives have been used in convergent syntheses of ()-lasalocid A[5b] and (+)-monensin.[5c] (b) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933. (c) Colum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117, 2118, 2120.

0002-7863/85/1507-0443$01.50/0

Scheme II



Claisen rearrangement **1** → **2** reveals three parameters which collectively determine the diastereoselectivity of this reaction. They are (i) the C_α *re*/*si*-face selectivity of rearrangement **1** → **2**, (ii) the *N*,*O*-acetal olefin geometry of substrate **1**, and (iii) C_α epimerization in oxazoline **2**. We have resolved these parameters and developed a general procedure which consistently provides rearranged oxazolines **2** with high diastereoselectivity. The synthesis proceeds from inexpensive amino acids, our source of auxiliary reagent, and in the latter stages, relies on established chemistry of oxazolines[6] to liberate the desired pent-4-enoic acids.

Results and Discussion

Preparation and Aza-Claisen Rearrangement of *N*-Allylketene *N*,*O*-Acetals. The starting oxazolines were prepared by condensation of the appropriate imidate hydrochloride[7] or free carboxylic acid[8] with the requisite amino alcohols, available by diborane and reduction[7] of the corresponding α-amino acids. Others have demonstrated that while N-methylation of C_4-substituted oxazolines is trivial,[9] N-allylation is problematic.[10,11] However, when we employed allyl *p*-toluenesulfonate as the allylating agent, oxazoline **5** gave oxazolinium salt **6** in 72–98% yield (Scheme II). The success of this N-allylation step can be attributed to the nonnucleophilicity of the *p*-toluenesulfonate anion. Further, in contrast to previous methodology which required a large excess of allyl iodide at elevated temperatures for oxazoline allylation,[11] the present method proceeds in the absence of solvent at 25–85 °C with only 120 mol % allyl *p*-toluenesulfonate.

As demonstrated by Meyers and Collington,[12] oxazolinium salts undergo proton abstraction when treated with HMPA-complexed aliphatic Grignard reagents. This led us to speculate that carbon bases might convert oxazolinium **6** to neutral aza-Claisen substrate **1** without nucleophilic addition at C_2. Indeed, neutralization of **6** with *n*-butyllithium in THF proved to be a straightforward operation, giving exclusive deprotonation. In general, a total of 130 mol % *n*-butyllithium added over a period of 45 min to a THF solution of the salt at −78 °C gave the best results. This neutralization step and the subsequent sigmatropic rearrangement were conveniently performed as a one-pot operation.

Separation of the **2**/**7** mixture from decalin was accomplished by one of two procedures. For small scale rearrangements, the oxazolines could be isolated by standard silica gel chromatography. In a simpler procedure, acid extraction, neutralization, and ether extraction produced a decalin-free mixture of the rearranged oxazolines. HPLC analysis of the **2**/**7** diastereomer ratio before and after isolation established that neither procedure caused detectable (<1%) isomerization. For pragmatic reasons, the extraction procedure is preferred, even for small scale rearrangements.

Table I. Diastereoselective Aza-Claisen Rearrangements[a]

1a–h → 2a–h + 7a–h

exptl	substrate	R	R′	**2**/**7** ratio[b]	% yield from **5**[c]
1	**1a**	CH_2CH_3	CH_2Ph	92/8	67
2	**1b**	CH_2Ph	CH_2Ph	94/6	53
3	**1c**[e]	$CH(CH_3)_2$	CH_2Ph	97/3	81
4	**1d**	$C(CH_3)_3$	CH_2Ph	98/2	58
5	**1e**	Ph	CH_2Ph	78/22[d]	34
6	**1f**	$C(CH_3)_3$	CH_3	97/3	79
7	**1g**	$C(CH_3)_3$	$C(CH_3)_2Ph$	98/2	81
8	**1h**[e]	$CH(CH_3)_2$	CH_3	97/3	80

[a] Neutralization of oxazolinium salt **6** with 130 mol % *n*-butyllithium in THF at −78 °C and subsequent 3-h thermolysis in decalin at 150 °C was performed as a one-pot operation. [b] Ratios were determined by HPLC analysis of the crude reaction mixture as described in the Experimental Section. [c] Overall yield of chromatographed **2**/**7** from starting oxazoline **5** (Scheme II). [d] Ratio of crude oxazolines after 5.5-h thermolysis. [e] Chiral nonracemic.

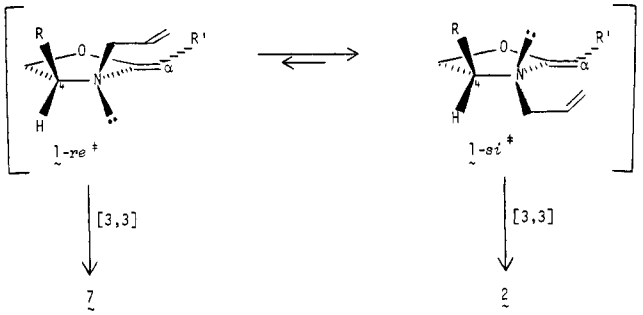


Figure 1.

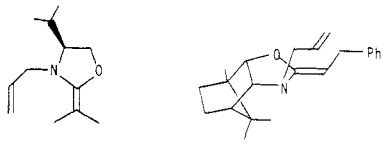
C_α-*re*/*si*-Face Selectivity. We have examined the effects of *N*-allylketene *N*,*O*-acetal substituents on diastereoselectivity in the aza-Claisen rearrangement. The results are shown in Table I. Experiments 1–4 demonstrate that the C_4 substituent in **1** is an important determinant in that as the size of this substituent increases, the diastereoselectivity of the rearrangement improves. Thus, the diastereomeric excess (de) ranges from de 84% with an ethyl substituent at C_4 to de 96% with a *tert*-butyl substituent at C_4 (experiment 1 vs. 4). Diastereoselectivity in experiment 5, where C_4 is phenyl substituted, is anomalous. This appears to be a consequence of the benzylic nature of the auxiliary chiral center which apparently accesses a mechanism for C_4 epimerization. Our results indicate that with a C_4 phenyl substituent, that observed diastereoselectivity is a function of thermolysis time. Thus, while de 56% was observed in experiment 5 after a 5-h thermolysis, a 3-h thermolysis in another experiment gave de 72% for oxazoline **2**.

Our analysis of this relationship between rearrangement diastereoselectivity and the C_4 substituent is depicted in Figure 1. Two diastereomeric transition states are available to **1**, which differ energetically by $\Delta\Delta G^\ddagger$ with the C_α-*si* transition state more stable than the congested C_α-*re* transition state. Rapid nitrogen inversion (**1**-*re*‡ ⇄ **1**-*si*‡) prior to the rate determining rearrangement step results in a C_α-*si*-face selectivity which reflects the magnitude of $\Delta\Delta G^\ddagger$. Consequently, increasing the steric bulk in the C_4 appendage enhances diastereoselectivity in the rearrangement. This analysis implies significant sp^3 hybridization at nitrogen in the transition state. Although the auxiliary chiral center and the C_α-prochiral center are remote in **1**, the face-determining interaction between the *N*-allyl and C_4 appendage is in fact vicinal.

***N*,*O*-Acetal Olefin Geometry.** As experiments 4, 6, and 7 illustrate, variation of the C_α appendage in **1** (R′) has essentially

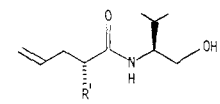
(6) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.
(7) Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2785.
(8) Dubois, J. E.; Lion, C. *C. R. Hebd. Seances Acad. Sci.* **1972**, *274*, 303.
(9) Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1865 and references cited therein.
(10) Ireland, R. E.; Willard, A. K. *J. Org. Chem.* **1974** *39*, 421.
(11) Maguet, M.; Poirier, Y.; Guglielmetti, R. *Bull. Soc. Chim. Fr.* **1978**, 550.
(12) Meyers, A. I.; Collington, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6676.

no effect on the rearrangement diastereoselectivity. Even in **1f** where C_α is methyl substituted, the (*Z*)-*N,O*-acetal configuration is preferred due to a significant nonbonding interaction in the *E* configuration.[13,14] Comparable stereoselectivities with substrates **1f** and **1g** (experiment 6 vs. 7), where steric requirements for the C_α appendages are vastly dissimilar, suggest that formation of diastereomer **7** is a consequence of incomplete *re/si*-face selectivity, not (*Z*)- vs. (*E*)-*N,O*-acetal selectivity. The following two experiments corroborate this conclusion. First, ^{1}H NMR analysis of **1h**, isolated by THF evaporation and trituration, revealed only one vinylic methyl resonance in chloroform-*d* or benzene-d_6 [($CDCl_3$) δ 1.87 (d, 3 H, J = 7 Hz); (C_6D_6) δ 2.02 (d, 3 H, J = 7 Hz)].[15] On the other hand, ^{1}H NMR of **8** revealed baseline-resolved vinylic methyl resonances [(C_6D_6) δ 1.78 (s, 3 H), 1.92 (s, 3 H)], suggesting that to the limits of detection, (*Z*)-**1h** is formed exclusively. Second, bornane-derived[16] *N*-allylketene *N,O*-acetal **9** gives exclusively one rearranged oxazoline, suggesting that with this substrate, *both re/si*-face and *N,O*-acetal selectivities are >99:1.[17,18]



8

9



11r; R' = CH_3

12s; R' = CH_2Ph

C_α Equilibration of Oxazolines. With the exception of experiment 5, the **2**/**7** oxazoline ratios were independent of thermolysis time. For example, **1c** gave oxazoline **2c** in de 94% after both 3 and 17 h at 150 °C. That is, *no equilibration occurs under the reaction conditions, even after prolonged thermolysis.* Interestingly, a 97/3 mixture of **2c** and **7c** equilibrates to a 1:1 mixture in only 15 min at 150 °C in the presence of mild Lewis acids.[19] These results indicate that high diastereoselectivity for the rearrangement **1** → **2** requires (i) that an excess of *n*-butyllithium be used in the neutralization step,[20] (ii) that the neutralization and rearrangement steps be performed as a one-pot operation, and (iii) that elevated temperatures (>50 °C) be avoided in the isolation and analysis of oxazolines **2** and **7**.

Enantioselective Synthesis of Pent-4-enoic Acids. Enantiomerically pure oxazolines **5c** and **5h** were prepared from L-valine and employed in experiments 3 and 8. Thus, preparative scale (42 mmol) allylation, neutralization, and rearrangement gave oxazoline **2h** in de 94% and in 80% overall chemical yield from **5h**. Acid-catalyzed hydrolysis of this **2h**/**7h** mixture gave (*R*)-(−)-2-methylpent-4-enoic acid[21] in 87% yield and regenerated the auxiliary reagent for recycling (85% distilled yield). This recovered L-valinol was, to the limits of detection, optically pure as determined by a chiral shift study on its corresponding 2-methyloxazoline.[22] The acid was obtained in 93% enantiomeric excess (ee) as determined by HPLC analysis of its L-valinol-derived amide (**11**).[23]

Similarly, **5c** gave **2c** which upon hydrolysis gave (*S*)-(+)-2-(phenylmethyl)pent-4-enoic acid in 80% chromatographed yield. The corresponding L-valinol-derived amide (**12**) was obtained in ee 94% and 97% yield. The major diastereomer was submitted to single-crystal X-ray diffraction analysis, confirming the absolute stereochemistry of the aza-Claisen-generated chiral center as that pictured in **12s**. Experiments 3 and 8 corroborate the stereochemical assignments for oxazolines **2a–h** (Table I) and establish this aza-Claisen rearrangement as a versatile and predictable enantioselective method.

Conclusions

We have confirmed the feasibility of auxiliary-reagent-mediated asymmetric aza-Claisen rearrangements. These are practical examples of remote stereocontrol in an acyclic system. As the results indicate, the method should be generally applicable to C_α-chiral induction in a wide variety of pent-4-enoic acids. The critical reaction parameters have been delineated and include strictly anhydrous conditions, neutralization with excess *n*-butyllithium, and employment of a one-pot neutralization/rearrangement procedure.

Experimental Section

General. Elemental analyses were performed by the University of California, Berkeley, Analytical Laboratories. MPLC refers to chromatography done at 10–50 psi through EM Lobar columns packed with LiChroprep Si60 (40–63 μm) with hexane/EtOAc eluent and monotored by refractive index detection. Chromatotron refers to preparative, centrifugally accelerated, radial, thin-layer chromatography with Silica Gel 60 PF as the stationary phase and with hexane/EtOAc as the eluent. HPLC were run on a 5-μm silica column using 95:5 *n*-hexane/EtOAc as eluent at 2 mL/min and monitored by refractive index or ultraviolet (254) detection.

General Procedure for the Preparation of Oxazolines 5a–g. An equimolar mixture of the appropriate amino alcohol and carboxylic acid was refluxed in xylene (0.5 M) under nitrogen with azeotropic removal of water for 12–36 h. After cooling, the reaction mixture was extracted with cold 10% HCl and the resulting aqueous layer neutralized with cold 40% NaOH. The mixture was extracted with Et_2O, dried (Na_2SO_4), and evaporated. Distillation gave the desired oxazoline (44–86%) as a colorless oil.

4,5-Dihydro-4-ethyl-2-(2-phenylethyl)oxazole (5a). The reaction was refluxed for 16 h and upon workup and distillation (114–116 °C/1.0 torr) gave **5a**: 65% yield; ^{1}H NMR δ 0.90 (t, J = 7 Hz, 3 H), 1.33–1.74 (m, 2 H), 2.42–2.70 (m, 2 H), 2.81–3.09 (m, 2 H), 3.71–4.38 (m, 3 H), 7.07–7.45 (m, 5 H); IR (CCl_4) 3100, 3080, 3045, 2990, 2950, 1670, 1605, 1495, 1450, 1370, 1225, 1170, 985, 910, 700 cm^{-1}; EI mass spectrum, *m/e* (rel intensity) 204 (11), 203 (79, M^+), 202 (100), 201 (32), 174 (19), 173 (9), 126 (10), 125 (14), 104 (8), 103 (12), 91 (20), 90 (33). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.47; H, 8.46; N, 6.87.

4,5-Dihydro-2-(2-phenylethyl)-4-(phenylmethyl)oxazole (5b). The reaction was refluxed for 16 h and upon workup and distillation (185–190 °C/.05 torr) gave **5b**: 49% yield; ^{1}H NMR δ 2.45–2.75 (m, 3 H), 2.86–3.21 (m, 3 H), 3.82–4.56 (m, 3 H), 7.10–7.45 (m, 10 H); IR (CCl_4) 3100, 3080, 3050, 2950, 1668, 1605, 1495, 1455, 1370, 1230, 1170, 985, 917, 705 cm^{-1}; EI mass spectrum, *m/e* (relative intensity) 266 (10), 265 (70, M^+), 175 (13), 174 (100), 104 (9), 92 (9), 91 (92), 78 (10), 77 (19), 65 (35). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.29. Found: C, 81.33; H, 7.24; N, 5.18.

(*S*)-(−)-4,5-Dihydro-4-(1-methylethyl)-2-(2-phenylethyl)oxazole (5c). The reaction was refluxed for 16 h and upon workup and distillation

(13) Sucrow, W.; Richter, W. *Chem. Ber.* **1971**, *104*, 3679.
(14) Bartlett, P. A.; Hahne, W. F. *J. Org. Chem.* **1979**, *44*, 882.
(15) For the isolation of oxazine *N,O*-acetals, see: (a) Meyers, A. I.; Nazarenko, N. *J. Am. Chem. Soc.* **1972**, *94*, 3243. (b) Meyers, A. I.; Nazarenko, N. *J. Org. Chem.* **1973**, *38*, 175.
(16) For recent examples employing bornane-derived chiral auxiliary reagents, see: (a) Oppolzer, W.; Chapuis, C.; Dao, G. M.; Reichlin, D.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4781. (b) Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935.
(17) This exciting result is complicated only by endo/exo cross-contamination in the starting amino alcohols.[18] The endo isomer of **9** gives almost no selectivity in its aza-Claisen rearrangement. A detailed investigation of borane-derived substrates will be reported in due course.
(18) Chittenden, R. A.; Cooper, G. H. *J. Chem. Soc. C* **1970**, *49*.
(19) While the oxazolines can be stored at room temperature with no equilibration, simplyt heating a decalin solution in a Pyrex vessel which has not been pretreated with *n*-butyllithium causes rapid **2**/**7** equilibration. Likewise, GC analysis causes rapid C_α isomerization.
(20) Apparently excess *n*-butyllithium is necessary to neutralize adventitious acids. While up to 150 mol % *n*-butyllithium gives no reduction in diastereoselectivity or chemical yield, 100 mol % *n*-butyllithium gives significantly poorer results.
(21) Klyne, W.; Buckingham, J. "Atlas of Stereochemistry", 2nd Ed.; Chapmen and Hall, Ltd.: London, 1978, Vol. 1, p 38.
(22) In a chiral shift study of racemic 4,5-dihydro-2-methyl-4-(1-methylethyl)oxazole (0.22 M in $CDCl_3$) with Eu(hfc)$_3$ (24 mol %), 90 MHz ^{1}H NMR revealed four methyl doublets [δ 0.73 (d, J = 7 Hz, CH(CH_3)CH_3, 3 H), 0.80 (d, J = 7 Hz, CH(CH_3)CH_3, 3 H), 1.07 (d, J = 7 Hz, CH(CH_3)CH_3, 3 H), 1.30 nd, J = 7 Hz, CH(nCH_3)CH_3, 3 H)]. Condensing this recovered L-valinol with ethyl acetimidate hydrochloride gave, to the limits of ^{1}H NMR detection, only the (*S*)-(−)-antipode [$[\alpha]^{25}_D$ −99.3 (neat); ^{1}H NMR ($CDCl_3$ with 24 mol % Eu(hfc)$_3$) δ 1.07 (d, J = 7 Hz, CH(CH_3)CH_3, 3 H), 1.30 (d, J = 7 Hz, CH(CH_3)CH_3, 3 H)].
(23) Oppolzer, W.; Löher, H. J. *Helv. Chim. Acta* **1981**, *64*, 2808.

(106–108 °C/0.05 torr) gave **5c**; 82% yield; $[\alpha]^{25}_D$ −65.6 (neat); ^{1}H NMR δ 0.85 (d, J = 7 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H), 1.40–1.90 (m, 1 H), 2.45–2.72 (m, 2 H), 2.83–3.09 (m, 2 H), 3.68–4.38 (m, 3 H), 7.12–7.45 (m, 5 H); IR (CCl_4), 3100, 3080, 3050, 2990, 2950, 1670, 1605, 1495, 1460, 1385, 1365, 1230, 1165, 1020, 990, 915, 700 cm^{-1}; EI mass spectrum, m/e (rel intensity) 218 (15), 217 (97, M$^+$), 216 (42), 175 (9), 174 (68), 140 (12), 117 (7), 104 (11), 92 (8), 91 (97), 77 (22), 65 (50), 42 (100). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.44. Found: C, 77.13; H, 8.56; N, 6.36.

4,5-Dihydro-4-(1,1-dimethylethyl)-2-(2-phenylethyl)oxazole (5d). The reaction was refluxed 12 h and upon workup and distillation (130–135 °C/0.05 torr) gave **5d**: 46% yield; ^{1}H NMR δ 0.85 (s, 9 H), 2.46–2.70 (m, 2 H), 2.85–3.10 (m, 2 H), 3.67–4.30 (m, 3 H), 7.09–7.40 (m, 5 H); IR (CCl_4) 3100, 3080, 3050, 2980, 2920, 2890, 1670, 1605, 1495, 1480, 1450, 1360, 1230, 1165, 985, 915, 700 cm^{-1}; EI mass spectrum, m/e (rel intensity) 232 (18), 231 (100, M$^+$), 230 (22), 216 (8), 175 (10), 174 (72), 173 (12), 91 (32), 77 (7), 65 (10), 57 (18). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.91; H, 9.01; N, 6.00.

4,5-Dihydro-4-phenyl-2-(2-phenylethyl)oxazole (5e). The reaction was refluxed for 27 h and upon workup and distillation (195–205 °C/0.05 torr) gave **5e**: 75% yield; ^{1}H NMR δ 2.40–3.15 (m, 4 H), 4.02 (dd, J = 8, 8 Hz, 1 H), 4.56 (dd, J = 8, 10 Hz, 1 H), 5.13 (dd, J = 8, 10 Hz, 1 H), 6.98–7.40 (m, 10 H); IR (CCl_4) 3100, 3080, 3045, 2980, 2930, 1945, 1870, 1795, 1715, 1665, 1600, 1495, 1450, 1380, 1360, 1230, 1160, 1075, 1025, 985, 905, 700 cm^{-1}; EI mass spectrum, m/e (rel intensity) 252 (17), 251 (100, M$^+$), 221 (10), 220 (16), 174 (12), 131 (8), 120 (10), 117 (17), 104 (35), 103 (30), 91 (52), 89 (13), 78 (10), 77 (23), 65 (18), 63 (8), 51 (12). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.36; H, 6.70; N, 5.46.

4,5-Dihydro-4-(1,1-dimethylethyl)-2-ethyloxazole (5f). The reaction was refluxed for 22 h and upon workup and distillation (65–73 °C/23 torr) gave **5f**: 77% yield; ^{1}H NMR δ 0.90 (s, 9 H), 1.17 (t, J = 8 Hz, 3 H), 2.29 (q, J = 8 Hz, 2 H), 3.67–4.28 (m, 3 H); IR (CCl_4) 2980, 2920, 2890, 1670, 1475, 1460, 1390, 1375, 1355, 1285, 1260, 1210, 1180, 990, 910 cm^{-1}; EI mass spectrum, m/e (rel intensity) 155 (3), 140 (3), 110 (5), 99 (22), 98 (75), 97 (25), 71 (15), 70 (88), 57 (93), 56 (35), 55 (20), 43 (95), 42 (58), 41 (100). Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.44; H, 10.90; N, 8.89.

4,5-Dihydro-4-(1,1-dimethylethyl)-2-(2-methyl-2-phenylpropyl)oxazole (5g). The reaction was refluxed for 36 h and upon workup and distillation (145–150 °C/0.05 torr) gave **5g**: 44% yield; ^{1}H NMR δ 0.80 (s, 9 H), 1.45 (s, 6 H), 2.52 (d, J = 14 Hz, 1 H), 2.73 (d, J = 14 Hz, 1 H), 3.59–4.20 (m, 3 H), 7.03–7.50 (m, 5 H); IR (CCl_4) 3100, 3075, 3020, 2980, 2920, 2880, 1665, 1600, 1495, 1480, 1445, 1390, 1360, 1240, 1205, 1130, 1030, 990, 930, 700 cm^{-1}; EI mass spectrum, m/e (relative intensity) 260 (15), 259 (100, M$^+$), 258 (24), 245 (14), 244 (95), 202 (36), 141 (20), 119 (75), 91 (56), 84 (21), 77 (16), 57 (31), 55 (23), 43 (35), 41 (95). Anal. Calcd for $C_{17}H_{25}NO$: C, 79.02; H, 9.36; N, 5.42. Found: C, 78.86; H, 9.52; N, 5.36.

(*S*)-(−)-4,5-Dihydro-2-ethyl-4-(1-methylethyl)oxazole (5h). Meyers' procedure for the preparation of oxazolines[7] was used to condense ethyl propionimidate hydrochloride with L-valinol. Distillation (113–114 °C/120 torr) gave **5h**: 87% yield; $[\alpha]^{24}_D$ −88.8 (neat); ^{1}H NMR δ 0.87 (d, J = 7 Hz, 3 H), 0.95 (d, J = 7 Hz, 3 H), 1.17 (t, J = 8 Hz, 3 H), 1.48–1.97 (m, 1 H), 2.28 (q, J = 8 Hz, 2 H), 3.42–4.38 (m, 3 H); IR (CCl_4) 2990, 2910, 1670, 1465, 1380, 1365, 1270, 1215, 1180, 1015, 995, 965, 915 cm^{-1}; EI mass spectrum, m/e (rel intensity) 141 (5, M$^+$), 131 (9), 124 (12), 119 (9), 98 (100), 97 (21), 96 (17), 70 (28), 56 (12); calcd for $C_8H_{15}NO$, 141.1154, found 141.1127.

General Procedure for the Preparation of Oxazolinium Salts 6. Oxazoline **5** and 120 mol % allyl *p*-toluenesulfonate were stirred together in an oven-dried flask under nitrogen for the indicated time and temperature. The resulting viscous oil was triturated 3 times with 10 volumes of dry Et_2O and evaporated at 1 mmHg to provide oxazolinium salt **6** which was used without further purification. An accurate elemental analysis of **6h** demonstrates the purity of these salts.

4,5-Dihydro-4-ethyl-2-(2-phenylethyl)-3-(2-propenyl)oxazolinium 4-Methylbenzenesulfonate (6a). The mixture was stirred for 16 h at 50 °C and gave **6a**: 91% yield; ^{1}H NMR δ 0.78 (t, 3 H), 1.4–2.0 (m, 2 H), 2.32 (s, 3 H), 2.84–3.34 (m, 4 H), 4.27 (d, 2 H), 4.39–4.83 (m, 2 H), 5.03–5.40 (m, 3 H), 5.48–5.97 (m, 1 H), 7.0–7.4 (m, 7 H), 7.76 (d, 2 H); IR ($CHCl_3$) 3010, 2970, 1640, 1480, 1450, 1280, 1230, 1170, 1120, 1035, 1010, 940, 815, 675 cm^{-1}.

4,5-Dihydro-2-(2-phenylethyl)-4-(phenylmethyl)-3-(2-propenyl)oxazolinium 4-Methylbenzenesulfonate (6b). The mixture was stirred for 24 h at 50 °C and gave **6b**: 92% yield; ^{1}H NMR δ 2.30 (s, 3 H), 2.6–3.33 (m, 6 H), 4.20–4.43 (m, 2 H), 4.5–5.3 (m, 5 H), 5.5–6.0 (m, 1 H), 6.9–7.35 (m, 12 H), 7.79 (d, 2 H); IR ($CHCl_3$) 3010, 1637, 1480, 1445, 1290, 1220, 1170, 1120, 1030, 1010, 940, 810, 675 cm^{-1}.

4,5-Dihydro-4-(1-methylethyl)-2-(2-phenylethyl)-3-(2-propenyl)oxazolinium 4-Methylbenzenesulfonate (6c). The mixture was stirred for 137 h at 25 °C and gave **6c**: 79% yield; ^{1}H NMR δ 0.60 (d, 3 H), 0.87 (d, 3 H), 1.85–2.30 (m, 1 H), 2.33 (s, 3 H), 2.84–3.60 (m, 4 H), 4.38 (d, 2 H), 4.45–4.95 (m, 2 H), 5.20–5.50 (m, 3 H), 5.55–6.0 (m, 1 H), 7.0–7.45 (m, 7 H), 7.80 (d, 2 H); IR ($CHCl_3$) 3050, 3010, 2990, 2890, 1650, 1635, 1480, 1450, 1390, 1375, 1230, 1170, 1120, 1035, 1010, 940, 820, 670 cm^{-1}.

4,5-Dihydro-4-(1,1-dimethylethyl)-2-(2-phenylethyl)-3-(2-propenyl)-oxazolinium 4-Methylbenzenesulfonate (6d). The mixture was stirred 72 h at 50 °C and gave **6d**: 72% yield; ^{1}H NMR δ 0.89 (s, 9 H), 2.3 (s, 3 H), 2.8–3.5 (m, 4 H), 4.1–4.9 (m, 4 H), 5.1–5.5 (m, 3 H), 5.6–6.0 (m, 1 H), 7.0–7.4 (m, 7 H), 7.80 (d, 2 H); IR ($CHCl_3$) 3050, 3010, 2990, 2890, 1650, 1625, 1480, 1450, 1400, 1370, 1230, 1170, 1120, 1030, 1010, 940, 815, 670 cm^{-1}.

4,5-Dihydro-4-phenyl-2-(2-phenylethyl)-3-(2-propenyl)oxazolinium 4-Methylbenzenesulfonate (6e). The mixture was stirred for 5 h at 70 °C and gave **6e**: 76% yield; ^{1}H NMR δ 2.30 (s, 3 H), 2.9–3.35 (m, 4 H), 3.86 (dd, J = 7, 16 Hz, 1 H), 4.20 (dd, J = 5, 16 Hz, 1 H), 4.60 (dd, J = 6, 7 Hz, 1 H), 4.75–5.14 (m, 2 H), 5.15–6.85 (m, 3 H), 6.9–7.5 (m, 12 H), 7.81 (d, 8 Hz, 2 H); IR ($CHCl_3$) 3070, 3010, 2970, 1950, 1885, 1800, 1730, 1640, 1598, 1490, 1475, 1445, 1230, 1170, 1115, 1030, 1005, 935, 810, 675 cm^{-1}.

4,5-Dihydro-4-(1,1-dimethylethyl)-2-ethyl-3-(2-propenyl)oxazolinium 4-Methylbenzenesulfonate (6f). The mixture was stirred for 16 h at 70 °C and gave **6f**: 83% yield;[1] H NMR δ 1.0 (s, 9 H), 1.23 (t, J = 7 Hz, 3 H), 2.33 (s, 3 H), 2.5–3.3 (m, 2 H), 4.25–4.85 (m, 4 H), 5.20–5.55 (m, 3 H), 5.80–6.25 (m, 1 H), 7.16 (d, J = 8 Hz, 2 H), 7.78 (d, J = 8 Hz, 2 H); IR (neat) 2970, 1625, 1480, 1450, 1400, 1365, 1200, 1115, 1030, 1005, 925, 810, 680 cm^{-1}.

4,5-Dihydro-4-(1,1-dimethylethyl)-2-(2-methyl-2-phenylpropyl)-3-(2-propenyl)oxazolinium 4-Methylbenzenesulfonate (6g). The mixture was stirred for 48 h at 85 °C and gave **6g**: 78% yield; ^{1}H NMR δ 0.75 (s, 9 H), 1.45 (s, 3 H), 1.51 (s, 3 H), 2.33 (s, 3 H), 3.28 (s, 2 H), 4.10–4.60 (m, 4 H), 5.10–5.50 (m, 3 H), 5.70–6.20 (m, 1 H), 7.13 (d, J = 8 Hz, 2 H), 7.32 (br s, 5 H), 7.80 (d, J = 8 Hz, 2 H); IR ($CHCl_3$) 3010, 2990, 2890, 1645, 1620, 1480, 1445, 1375, 1270, 1180, 1125, 1035, 1010, 940, 815, 730, 680 cm^{-1}.

(*S*)-(−)-4,5-Dihydro-2-ethyl-4-(1-methylethyl)-3-(2-propenyl)oxazolinium 4-Methylbenzenesulfonate (6h). The mixture was stirred for 48 h at 50 °C and gave **6h**: 98% yield; $[\alpha]^{25}_D$ −34.1° (*c* 6.4, $CHCl_3$); ^{1}H NMR δ 0.80 (d, J = 4 Hz, 3 H), 0.90 (d, J = 5 Hz, 3 H), 1.24 (t, J = 7 Hz, 3 H), 2.95–2.30 (m, 1 H), 2.31 (s, 3 H), 2.83 (q, J = 7 Hz, 2 H), 4.02–4.80 (m, 4 H), 5.0–5.57 (m, 3 H), 5.78–6.25 (m, 1 H), 7.14 (d, J = 8 Hz, 2 H), 7.78 (d, J = 8 Hz, 2 H); IR ($CHCl_3$) 3050, 3010, 2990, 2895, 1640, 1485, 1450, 1395, 1375, 1230, 1170, 1120, 1035, 1010, 940, 815, 675 cm^{-1}. Anal. Calcd for $C_{18}H_{27}NO_4S$: C, 61.16; H, 7.70; N, 3.96; S, 9.07. Found: C, 60.89; H, 7.59; N, 3.77; S, 8.89.

General Procedure for the Preparation of Oxazolines 2. In a typical experiment *n*-butyllithium (130 mol %, 1.5 M in hexanes) was added dropwise over 45 min to a −78 °C THF solution (0.125 M) of oxazolinium salt **6** (0.6–42 mmol) under nitrogen. After the solution was stirred an additional 15 min at −78 °C, it was allowed to warm to room temperature over 15–30 min. Dry decalin was added, and the low boiling solvents were removed by rotary evaporation at reduced pressure (5 torr). The resulting decalin mixture (0.14 M) was heated under nitrogen at 150 °C for 3 h, cooled to 0 °C, and extracted with cold 10% HCl. This aqueous layer was neutralized with cold 40% NaOH and extracted with Et_2O (3 times). Combined Et_2O extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated to give mixtures of oxazolines **2** and **7** as yellow oils which were purified by MPLC or chromatotron chromatography. Diastereomer ratios were determined by HPLC analysis.

(4*RS*,1′*RS*)- and (4*RS*,1′*SR*)-4-Ethyl-4,5-dihydro-2-(1-phenylmethyl-3-butenyl)oxazole (2a and 7a). Chromatography afforded a 92:8 mixture of diastereomers **2a** and **7a**: 67% yield; ^{1}H NMR δ 0.80 (t, J = 7.5 Hz, 3 H), 1.0–1.75 (m, 2 H), 2.2–2.4 (m, 2 H), 2.6–3.0 (m, 3 H), 3.6–4.3 (m, 3 H), 4.9–5.2 (m, 2 H), 5.5–6.05 (m, 1 H), 7.0–7.45 (m, 5 H); IR (CCl_4) 3090, 3040, 2990, 2930, 1665, 1600, 1495, 1445, 1175, 985, 915, 695 cm^{-1}; EI mass spectrum, m/e (rel intensity) 243 (16, M$^+$), 242 (12), 228 (5), 214 (6), 203 (15), 202 (100), 189 (6), 152 (15), 131 (13), 91 (66), 77 (12), 65 (29), 55 (22), 41 (37). Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.18; H, 8.56; N, 5.60.

(4*RS*,1′*RS*)- and (4*RS*,1′*SR*)-4,5-Dihydro-2-(1-phenylmethyl-3-butenyl)-4-(phenylmethyl)oxazole (2b and 7b). Chromatography afforded a 94:6 mixture of diastereomers **2b** and **7b**: 53% yield; ^{1}H NMR δ 2.1–1.6 (m, 3 H), 2.6–3.1 (m, 4 H), 3.78–4.45 (m, 3 H), 4.9–5.2 (m, 2 H), 5.5–6.05 (m, 1 H), 7.0–7.45 (m, 10 H); IR (CCl_4) 3090, 3040, 2940, 2860, 1660, 1600, 1590, 1490, 1445, 1170, 1030, 980, 915, 700 cm^{-1}; EI mass spectrum, m/e (rel intensity) 305 (25, M$^+$), 283 (59), 264 (80), 214

(100), 160 (18), 138 (22), 136 (42), 91 (85), 81 (30), 67 (50), 55 (40), 41 (79). Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.57; H, 7.66; N, 4.39.

(4*S*,1′*S*)- and (4*S*,1′*R*)-4,5-Dihydro-2-(1-phenylmethyl-3-butenyl)-4-(1-methylethyl)oxazole (2c and 7c). Chromatography afforded a 97:3 mixture of diastereomers **2c** and **7c**: 81% yield; ^{1}H NMR δ 0.78 (d, J = 7 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H), 1.40–1.90 (m, 1 H), 2.18–2.42 (m, 2 H), 2.63–3.03 (m, 3 H), 3.64–4.27 (m, 3 H), 4.90–5.20 (m, 2 H), 5.55–6.05 (m, 1 H), 7.02–7.45 (m, 5 H); IR (CCl_4) 3090, 304/, 2880, 2840, 1665, 1600, 1495, 1450, 1385, 1360, 1265, 1240, 1175, 1110, 1030, 985, 915, 700 cm^{-1}; EI mass spectrum, m/e (rel intensity) 257 (10, M$^+$), 256 (12), 242 (5), 217 (15), 216 (100), 214 (16), 166 (10), 91 (12), 43 (7), 41 (8). Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.18; H, 8.77; N, 5.16.

(4*RS*,1′*RS*)- and (4*RS*,1′*SR*)-4,5-Dihydro-2-(1-phenylmethyl-3-butenyl)-4-(1,1-dimethylethyl)oxazole (2d and 7d). Chromatography afforded a 98:2 mixture of diastereomers **2d** and **7d**: 58% yield; ^{1}H NMR δ 0.85 (s, 9 H), 2.0–2.45 (m, 2 H), 2.65–3.0 (m, 3 H), 3.67–4.20 (m, 3 H), 4.9–5.21 (m, 2 H), 5.59–6.07 (m, 1 H), 7.03–7.45 (m, 5 H); IR (CCl_4) 3090, 3040, 2980, 2920, 2895, 1670, 1605, 1495, 1480, 1450, 1395, 1365, 12458 1190, 1025, 985, 915, 700 cm^{-1}; EI mass spectrum, m/e (rel intensity) 271 (18, M$^+$), 270 (16), 231 (18), 230 (100), 215 (18), 214 (40), 180 (8), 131 (5), 91 (29), 57 (13), 41 (18). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.61; H, 9.25; N, 5.21.

(4*RS*,1′*RS*)- and (4*RS*,1′*SR*)-4,5-Dihydro-2-(1-phenylmethyl-3-butenyl)-4-phenyloxazole (2e and 7e). Chromatography afforded a 78:22 mixture of diastereomers **2e** and **7e**: 34% yield; ^{1}H NMR δ 2.3–2.55 (m, 2 H), 2.8–3.15 (m, 3 H), 3.80–4.10 (m, 1 H), 4.51 (br t, J = 8 Hz, 1 H), 4.95–5.25 (m, 3 H), 5.65–6.25 (m, 1 H), 7.00–7.50 (m, 10 H); IR (Cl_4) 3090, 3040, 2850, 1663, 1600, 1495, 1450, 1200, 1020, 985, 915, 700 cm^{-1}; EI mass spectrum, m/e (rel intensity) 291 (20, M$^+$), 290 (17), 251 (22), 250 (100), 237 (8), 200 (14), 174 (5), 131 (15), 104 (7), 91 (20), 65 (7), 41 (7). Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.72; H, 7.41; N, 4.88.

(4*RS*,1′*SR*)-, (4*RS*,1′*SR*)-, and (4*RS*,1′*RS*)-4,5-Dihydro-2-(1-methyl-3-butenyl)-4-(1,1-dimethylethyl)oxazole (2f and 7f). Chromatography afforded a 97:3 mixture of diastereomers **2f** and **7f**: 79% yield; ^{1}H NMR δ 0.89 (s, 9 H), 1.16 (d, J = 7 Hz, 3 H), 2.0–2.83 (m, 3 H), 3.67–4.25 (m, 3 H), 4.90–5.20 (m, 2 H), 5.55–6.10 (m, 1 H); IR (CCl_4) 3100, 2980, 2895, 1670, 1645, 1480, 1460, 1395, 1365, 1290, 1240, 1185, 985, 920 cm^{-1}; EI mass spectrum, m/e (rel intensity) 196 (5), 195 (14, M$^+$), 194 (8), 180 (52), 179 (14), 154 (7), 139 (56), 138 (100), 137 (51), 124 (15), 110 (13), 96 (20), 81 (10), 69 (42), 68 (45), 55 (25). Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.98; H, 10.59; N, 6.95.

(4*RS*,1′*RS*)- and (4*RS*,1′-*SR*)-4,5-Dihydro-2-[1-(1-methyl-1-phenylethyl)-3-butenyl]-4-(1,1-dimethylethyl)oxazole (2g and 7g). Chromatography afforded a 98:2 mixture of diastereomers **2g** and **7g**: 81% yield; ^{1}H NMR δ 0.83 (s, 9 H), 1.38 (s, 3 H), 1.40 (s, 3 H), 1.70–2.03 (m, 1 H), 2.14–2.50 (m, 1 H), 2.89 (dd, J_1 = 12, J_2 = 4 Hz, 1 H), 3.60–4.15 (m, 3 H), 4.86–5.07 (m, 2 H), 5.38–5.89 (m, 1 H), 7.05–7.51 (m, 5 H); IR (CCl_4) 3090, 3040, 2980, 2895, 1660, 1595, 1495, 1475, 1440, 1390, 1360, 1270, 1240, 1180, 1020, 985, 915, 700 cm^{-1}; EI mass spectrum, m/e (rel intensity) 299 (5, M$^+$), 595 (27), 258 (100), 181 (38), 187 (14), 119 (50), 91 (32), 57 (15), 41 (30). Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.44; H, 9.52; N, 4.24.

(4*S*,1′*R*)- and (4*S*,1′*S*)-4,5-Dihydro-2-(1-methyl-3-butenyl)-4-(1-methylethyl)oxazole (2h and 7h). Chromatography afforded a 97:3 mixture of diastereomers **2h** and **7h**: 80% yield; ^{1}H NMr δ 0.88 (d, J = 7 Hz, 3 H) 0.95 (d, J = 7 Hz, 3 H), 1.49–1.95 (m, 1 H), 2.00–2.71 (m, 3 H), 3.71–4.35 (m, 3 H), 4.90–5.20 (m, 2 H), 5.54–6.07 (m, 1 H); IR (CCl_4) 3100, 2990, 2920, 1665, 1480, 1460, 1385, 1370, 1270, 1240, 1180, 985, 915 cm^{-1}; EI mass spectrum, m/e (rel intensity) 181 (26, M$^+$), 180 (16), 166 (71), 139 (68), 138 (100), 124 (39), 115 (28), 112 (33), 96 (17), 81 (11.6), 69 (58), 55 (22), 41 (22). Anal. Calcd for $C_{11}H_{19}NO$: 181.1467. Found: 181.1450.

(4*S*,*Z*)-2-Ethylidene-4-(1-methylethyl)-3-(2-propenyl)oxazolidine (1h). To a −78 C THF (2 mL) solution of **6h** (193 mg, 0.55 mmol) was added n-butyllithium (400 μL of a 1.55 M solution in hexanes, 0.62 mmol). After the solution was stirred for 15 min at −78 °C, it was warmed to room temperature and the solvents were evaporated under vacuum (5 torr). The residue, consisting of **1h** and lithium p-toluenesulfonate, was triturated with either benzene-d_6 or chloroform-d. While the chloroform solution yellowed rapidly, the benzene solution was stable several days when refrigerated. ^{1}H NMR (Nicolet NTCFT-1180 360 MHz) (C_6D_6) δ 0.557 (d, J = 6.95 Hz, 3 H), 0.716 (d, J = 6.78 Hz, 3 H), 1.57–1.61 (m, C*H*(CH$_3$)$_2$, 1 H), 2.017 (d, J = 6.5 Hz, C=CHCC*H*$_3$, 3 H), 2.951–2.988 (m, N—C*H*—CO, 1 H), 3.293 (dd, J = 6.73, 16.22 Hz, NC*H*$_2$, 1 H), 3.402 (q, J = 6.5 Hz, C=C*H*CH$_3$, 1 H), 3.439–3.490 (m, NC*H*$_2$, 1 H), 3.663–3.706 (m, C*H*$_2$O, 1 H), 3.726–3.757 (m, C*H*$_2$O, 1 H), 4.978–5.156 (m, 2 H), 5.754–5.789 (m, 1 H); ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.57 (d, J = 7 Hz, C=CHC*H*$_3$, 3 H).

(4*S*)-4-(1-Methylethyl)-2-(1-methylethylidene)-3-(2-propenyl)oxazolidine (8). Condensation of L-valinol and isobutyric acid as described above for the preparation of **5** gave (*S*)-(−)-4,5-dihydro-2,4-bis(1-methylethyl)oxazole: bp 72–75 °C/20 torr; $[\alpha]^{25}_D$ −74.8° (c 9.43, $CHCl_3$); ^{1}H NMR δ 0.85 (d, J = 7 Hz, 3 H), 0.93 (d, J = 7 Hz, 3 H), 1.21 (d, J = 7 Hz, 6 H), 1.52–1.95 (m, 1 H), 2.20–2.73 (m, 1 H), 3.68–4.50 (m, 3 H); IR (CCl_4) 2990, 2895, 1665, 1465, 1385, 1360, 1320, 1270, 1240, 1195, 1145, 1095, 1020, 980, 925 cm^{-1}; EI mass spectrum, m/e (rel intensity) 155 (6, M$^+$), 140 (3), 113 (9), 112 (100), 111 (12), 110 (11), 96 (5), 84 (43), 70 (16), 55 (13), 43 (29), 42 (20), 41 (40). Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.97; H, 11.09; N, 9.23. Treatment of this dihydrooxazole with allyl p-toluenesulfonate for 48 h at 50 °C as in **5** → **6** above gave (*S*)-(−)-4,5-dihydro-2,4-bis(1-methylethyl)-3-(2-propenyl)oxazolinium 4-methylbenzenesulfonate: 96% yield; $[\alpha]^{25}_D$ −31.2° (c 17.08, $CHCl_3$); ^{1}H NMR δ 0.80 (d, J = 7 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H), 1.23 (d, J = 6 Hz, 3 H), 1.30 (d, J = 6 Hz, 3 H), 2.00–2.45 (m, 1 H), 2.37 (s, 3 H), 3.0–3.55 (m, 1 H), 4.10–4.85 (m, 5 H), 5.00–5.65 (m, 2 H), 5.80–6.20 (m, 1 H), 7.15 (d, J = 8 Hz, 2 H), 7.79 (d, J = 8 Hz, 2 H); IR ($CHCl_3$) 3040, 3010, 2990, 1635, 1480, 1445, 1390, 1370, 1230, 1175, 1120, 1090, 1030, 1010, 940, 910, 670 cm^{-1}. This salt was neutralized as described above for **1h**. Trituration with benzene-d_6 gave a colorless solution of **8**: ^{1}H NMR δ 0.60 (d, J = 7 Hz, 3 H), 0.75 (d, J = 7 Hz, 3 H), 1.30–1.70 (m, 1 H), 1.78 (s, C=C(CH$_3$)C*H*$_3$, 3 H), 1.92 (s, C=C(C*H*$_3$)CH$_3$, 3 H), 2.81–3.19 (m, 1 H), 3.21–3.43 (br d, 2 H), 3.46–3.79 (m, 2 H), 4.80–5.19 (m, 2 H), 5.60–6.20 (m, 1 H).

(*R*)- and (*S*)-2-Methylpent-4-enoic Acid (4h and 10h). A 97:3 mixture of oxazolines **2h** and **7h** (4.0 g, 22.1 mmol) was heated for 3 h at 100 °C in 10% HCl (100 mL). Upon cooling and extraction with CH_2Cl_2 (2 times), a yellow oil was obtained (2.18 g, 87% yield). Distillation (100–102 °C/5 torr) gave a colorless oil (which was a 96.5:3.5 enantiomeric mixture of **4h** and **10h**): 73% yield; $[\alpha]^{25}_D$ −7.00 (c 8.37, $CHCl_3$); ^{1}H NMR δ 1.18 (d, J = 6 Hz, 3 H), 1.95–2.75 (m, 3 H), 4.90–5.25 (m, 2 H), 5.40–6.03 (m, 1 H), 11.8 (br s, 1 H); IR (CCl_4) 350–2400 (COOH), 3100, 2995, 1705, 1640, 1560, 1515, 1290, 1245, 1215, 990, 920 cm^{-1}.

The auxiliary chiral reagent was isolated from the aqueous layer of the above extraction. Distillation (81–83 °C/8 torr) gave L-valinol (1.93 g, 85% yield) which was >99% optically pure.[22]

(2*R*,1′*S*)- and (2*S*,1′*S*)-*N*-(1-(Hydroxymethyl)-2-methylpropyl)-2-methyl-4-pentenamide (11r and 11s). Using THF as the solvent, a procedure reported by Oppolzer[22] was used to couple a mixture of enantiomers **4h** and **10h** and L-valinol to give amides **11r** and **11s**. HPLC analysis (IBM 5 μm Cyano column; 95:5 n-hexane/EtOAc; isocratic; 2 mL/min) of this crude mixture indicated a 96.5:3.5 **11r**/**11s** mixture. MPLC (60:40 n-hexane/EtOAc) gave pure **11r**: 92% yield; mp 53–55 °C from hexane/EtOAc; $[\alpha]^{25}_D$ −47.2 (c 2.37, $CHCl_3$); ^{1}H NMR δ 0.92 (d, J = 7 Hz, 3 H), 0.95 (d, J = 7 Hz, 3 H), 1.24 (d, J = 6 Hz, 3 H), 1.67–2.05 (m, 1 H), 2.05–2.65 (m, 3 H), 3.15 (br s, OH, 1 H), 3.4–4.95 (m, 3 H), 4.90–5.25 (m, 2 H), 5.55–6.25 (m, H$_2$C=C*H*, NH, 2 H); IR (CCl_4) 3450, 3350, 3100, 2990, 2950, 2895, 1645, 1525, 1460, 1385, 1370, 1225, 1070, 990, 915 cm^{-1}; EI mass spectrum, m/e (rel intensity) 199 (4, M$^+$), 181 (2), 168 (29), 114 (7), 97 (8), 72 (100), 69 (84), 60 (79), 55 (36).

(*S*)- and (*R*)-2-Phenylmethylpent-4-enoic Acid (4c and 10c). A 97:3 mixture of oxazolines **2c** and **7c** (4.57 g, 17.8 mmol) was heated 6 h at 95 °C in 10% HCl (80 mL). Upon cooling and extraction with CH_2Cl_2 (2 times) a yellow oil was obtained which was purified by MPLC (8:20:2 n-hexane/EtOAc/HOAc eluent). Azeotropic removal of HOAc with toluene gave a colorless oil (which was a 97:3 enantiomeric mixture of **4c** and **10c**): 80% yield; $[\alpha]^{25}_D$ + 19.2 (c 12.24, $CHCl_3$); ^{1}H NMR δ 2.19–2.41 (m, 2 H), 2.47–3.11 (m, 3 H), 4.88–5.20 (m, 2 H), 5.50–6.00 (m, 1 H), 7.00–7.43 (m, 5 H), 11.15 (br s, 1 H); IR (CCl_4) 3400–2400 (COOH), 1705, 1635, 1490, 1420, 1280, 1240, 1205, 985, 915, 700 cm^{-1}.

(2*S*,1′*S*)- and (2*R*,1′*S*)-*N*-(1-(Hydroxymethyl)-2-methylpropyl)-2-phenylmethyl-4-pentenamide (12s and 12r). Using THF as a solvent, a procedure reported by Oppolzer[22] was used to couple a mixture of enantiomeric acids **4c** and **10c** with L-valinol to give amides **12s** and **12r**. HPLC analysis (IBM 5-μm cyano column; 95:5 n-hexane/EtOAc; isocratic; 2 mL/min) of this crude mixture indicated a 97:3 **12s**/**12r** mixture. MPLC (60:40 n-hexane/EtOAc) gave, in order of elution, **12s** [94% yield; mp 82–84 °C from n-hexane/EtOAc; $[\alpha]^{25}_D$ +2.52 (c 5.15, $CHCl_3$); ^{1}H NMR δ 0.78 (d, J = 7 Hz, 3 H), 0.85 (d, J = 7 Hz, 3 H), 1.46–1.92 (m, 1 H), 1.83 (br s, OH, 1 H), 2.10–2.62 (m, 3 H), 2.65–2.99 (m, 2 H), 3.20–3.42 (m, 2 H), 3.3–3.75 (m, 1 H), 4.95–5.45 (m, C=CH$_2$ and NH, 3 H), 5.5–6.1 (m, 1 H), 7.0–7.5 (m, 5 H); IR (CCl_4) 3600,

3460, 3340, 3090, 3040, 2980, 1650, 1510, 1450, 1385, 1365, 1215, 1070, 985, 915, 700 cm^{-1}; EI mass spectrum, *m/e* (rel intensity) 275 (11, M$^+$), 244 (22), 234 (48), 216 (30), 190 (8), 145 (21), 131 (38), 91 (100), 72 (89), 60 (29), 41 (35). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.42; H, 8.99; N, 5.18] and **12r** [3.2% yield; mp 94.5-95.5 °C from *n*-hexane/EtOAc; $[\alpha]^{25}_D$ -7.02 (*c* 5.34, $CHCl_3$); ^{1}H NMR δ 0.63 (d, *J* = 7 Hz, 3 H), 0.70 (d, *J* = 7 Hz, 3 H), 1.43-1.80 (m, 1 H), 2.10-2.45 (m, 3 H), 2.61 (br s, OH, 1 H), 2.70-3.14 (m, 2 H), 3.40-3.73 (m, 3 H), 4.90-5.25 (m, 2 H), 5.25-5.50 (m, NH, 1 H), 5.54-6.07 (m, 1 H), 7.0-7.5 (m, 5 H); IR (CCl_4) 3450, 3090, 3040, 3010, 2980, 1650, 1595, 1500, 1450, 1375, 1355, 1240, 1070, 985, 910, 800, 695 cm^{-1}; EI mass spectrum *m/e* (rel intensity) 275 (7, M$^+$), 244 (20), 234 (46), 216 (11), 190 (8), 145 (18), 131 (38), 91 (97), 72 (100), 60 (36), 43 (30), 41 (45). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.19; H, 9.06; N, 4.97]. A recrystallized sample of **12s** was subjected to single-crystal X-ray diffraction analysis. Compound **12s** crystallizes from *n*-hexane/EtOAc in the orthorhombic space group, $P2_12_12_1$. The crystal data at 140 K are as follows: a = 5.054 (2) Å, b = 20.342 (8) Å, c = 16.170 (6) Å; ρ(calcd) = 1.10 g cm^{-3} for Z = 4; 2θ(max) = 50°; 2466 reflections with $F > 6\sigma(|F|)$ used, Mo Kα (graphite (λ = 0.71069 Å), and ω scan, 20° min^{-1}; R = 0.045. SHELXTL programs were used on a DGC Eclipse S/230 computer.

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Registry No. 1a, 93684-28-7; **1b**, 93684-29-8; **1c**, 93684-30-1; **1d**, 93684-31-2; **1e**, 93684-32-3; **1f**, 93684-33-4; **1g**, 93714-43-3; **1h**, 93684-34-5; **2a**, 93684-35-6; **2b**, 93684-36-7; **2c**, 93684-37-8; **2d**, 93684-38-9; **2e**, 93684-39-0; **2f**, 93684-40-3; **2g**, 93684-41-4; **2h**, 88362-53-2; **4c**, 93780-03-1; **4h**, 63527-49-1; **5a**, 93684-42-5; **5b**, 93684-43-6; **5c**, 93684-44-7; **5d**, 93684-45-8; **5e**, 93684-46-9; **5f**, 93684-47-0; **5g**, 93684-48-1; **5h**, 88362-45-2; **6a**, 93684-50-5; **6b**, 93684-52-7; **6c**, 93684-54-9; **6d**, 93684-56-1; **6e**, 93684-58-3; **6f**, 93684-60-7; **6g**, 93684-62-9; **6h**, 88362-48-5; **7a**, 93684-63-0; **7b**, 93684-64-1; **7c**, 93684-65-2; **7d**, 93684-66-3; **7e**, 93684-67-4; **7f**, 93684-68-5; **7g**, 93684-69-6; **7h**, 88362-54-3; **8**, 93684-70-9; **10c**, 93780-04-2; **10h**, 20626-61-3; **11r**, 93714-44-4; **11s**, 93714-45-5; **12s**, 93684-71-0; **12r**, 93780-05-3; 2-amino-1-butanol, 13054-87-0; β-aminobenzenepropanol, 1795-98-8; L-valinol, 2026-48-4; (*S*)-2-amino-3,3-dimethyl-1-butanol, 93684-72-1; β-aminobenzeneethanol, 71006-16-1; benzenepropionic acid, 501-52-0; propionic acid, 79-09-4; β,β-dimethylbenzenepropionic acid, 1010-48-6; ethyl propanimidate hydrochloride, 40546-35-8; isobutyric acid, 79-31-2; (*S*)-(-)-4,5-dihydro-2,4-bis(1-methylethyl)oxazole, 93684-73-2; (*S*)-(-)-4,5-dihydro-2,4-bis(1-methylethyl)-3-(2-propenyl)-oxazolinium 4-methylbenzenesulfonate, 93684-75-4.

Supplementary Material Available: A stereoplot of **12s**, listings of bond distances, bond angles, hydrogen atom coordinates, isotropic, and anisotropic temperature factors, and observed and calculated structure factors (18 pages). Ordering information is given on any current masthead page.

Host-Guest Complexation. 34. Bridged Hemispherands[1,2]

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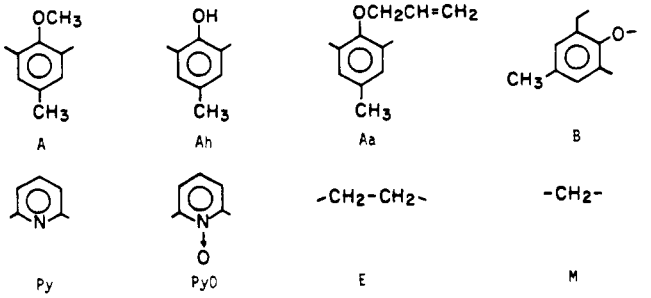
Abstract: The synthesis and binding properties of 11 new hemispherands (**2-12**) are reported, 7 of which contain extra bridges that help preorganize the systems for complexation. These hosts are composed of the following units bonded to one another in 18-membered ring systems: 2,6-disubstituted 4-methylanisyl; 2,6-disubstituted 4-methylphenol; 2,6-disubstituted 4-methyl-1-(allyloxy)benzene; 6-aryl-substituted 4-methyl-1-methoxybenzene; 2,6-disubstituted pyridine; and pyridine oxide, ethylene, methylene, and oxygen. Association constants (K_a) between host and guest to give complexes were determined by extracting picrate salts (guests) from D_2O into $CDCl_3$ in the absence and presence of hosts at 25 °C. The rates of extraction were essentially instantaneous. The free energies of complexation for the 11 new hosts with picrate salts of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ were determined. These $-\Delta G°$ values ranged from a high of 14.6 kcal mol^{-1} to a low of ~2.8 kcal mol^{-1}. Interesting structural recognition factors ($K_a^G/K_a^{G'}$) for a host distinguishing between two similar guests (G and G') are Na^+/Li^+ = 9500 (**8**), Na^+/K^+ = 14 (**9**), K^+/Na^+ = 9 (**7**), K^+/Rb^+ = 54 (**11**), Rb^+/Cs^+ = 55 (**6**), $NH_4^+/CH_3NH_3^+$ = 31 (**10**), and $CH_3NH_3^+/t$-$BuNH_3^+$ = 40 (**10**). The strongest binding host for all ions is **12**, which gave a $-\Delta G°_{av}$ for the eight ions of 12.5 kcal mol^{-1}. It is also the most rigid and least discriminating of the hosts. Correlations between the structures of the complexes and their free energies of binding are interpreted in terms of the principles of complementarity and preorganization.

Hemispherands are host compounds, at least half of whose binding sites are conformationally organized for binding during their synthesis, rather than during their complexation. In other words, hemispherands are at least half preorganized for binding. The synthesis and complexing properties have been previously reported for several members of this class of hosts for which compound **1** is prototypical.[3] This compound is composed of three self-organizing anisyl units combined with three additional

Chart I



CH_2OCH_2 binding sites. Other hemispherands have been reported that contain four anisyl units[4] or anisyl and cyclic urea units.[5,6]

(1) We warmly thank the Division of Basic Energy Sciences, Department of Energy (DOE EY 76-S-03-0034, P.A. 218), for a contract that supported this research.

(2) The binding free energies of compounds **1**, **4**, and **8** have appeared in a communication: Cram, D. J.; Dicker, I. B.; Lein, G. M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 6827-6828.

(3) Koenig, K.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553-3566.

0002-7863/85/1507-0448$01.50/0