Asymmetric Addition to Chiral Aromatic and Unsaturated Oxazolines Using a Novel Chiral Auxiliary

A. I. Meyers,* Wolfgang Schmidt, Marc J. McKennon

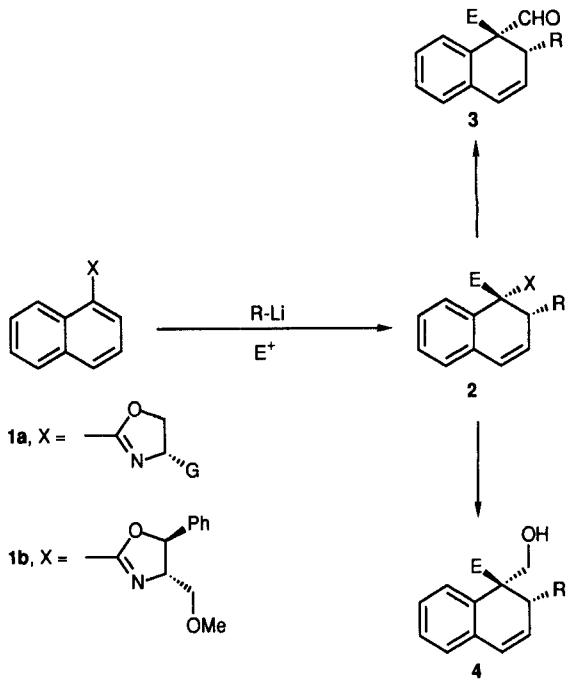
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA

Received 26 November 1992

By utilizing S-serine, both enantiomers of the reduced methoxyamino alcohol (**12**) were efficiently prepared. The corresponding oxazolines, prepared from these auxiliaries, showed favorable properties toward additions to naphthalenes **22** and cyclohexene, **27**.

The field of asymmetric synthesis has exploded in the last twenty years from a mechanistic curiosity to serious synthetic routes to chiral non-racemic (aracemic) compounds. To survey even a few of the monumental discoveries would be too much for a single article. Suffice it to say that there are excellent treatises on the subject.[1] A recent monograph[1d] nicely outlines many of the major achievements in synthetic asymmetric processes.

In this report, we wish to describe further advances in the use of chiral oxazolines, a family of chiral auxiliaries first introduced in 1974.[2] Since their introduction, many related chiral heterocycles have been reported from many diffferent laboratories[1a-e] and the successes enjoyed by these auxiliaries in promoting efficient asymmetric C-C bonds is now a well known body of knowledge.

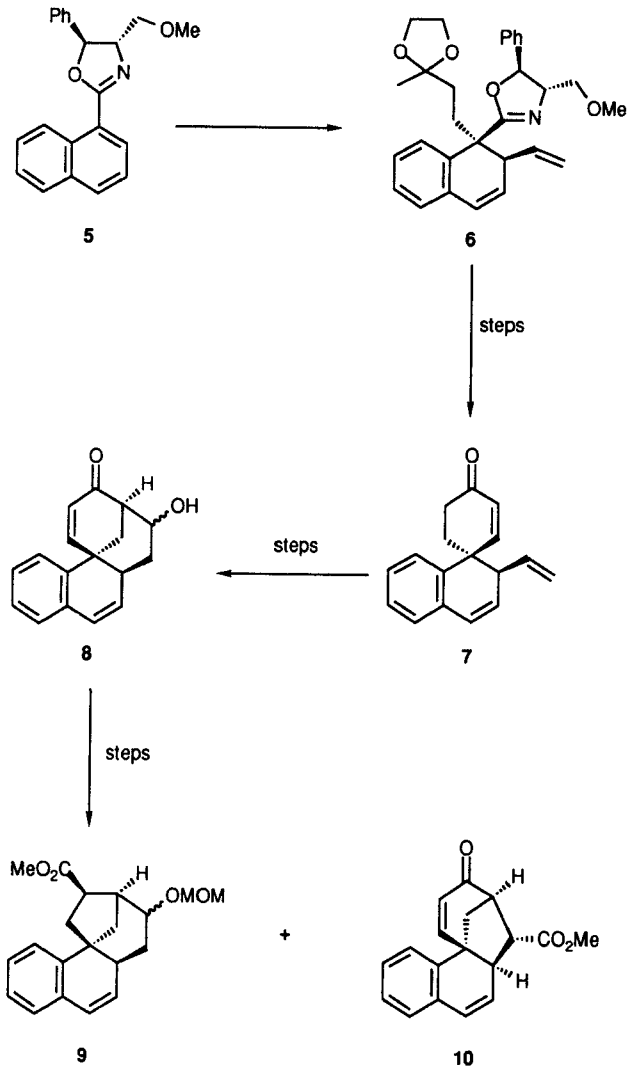


Scheme 1

In the area of aromatic substitution, the oxazoline moiety has shown considerable synthetic potential allowing a variety of substitution patterns both in chiral and achiral environments.[3] Besides substituted aromatic systems, the chiral oxazoline has shown that it can mediate asymmetric coupling furnishing biaryls containing unsymmetrical and enantiomeric features[4] as well as biaryl natural products such as (-)steganone[5] and (-)-schizandrin.[6] More recently,[7] we have described a highly diastereoselective addition of organometallics to naphthalene systems, **1** containing chiral oxazolines (Scheme 1). Using either the chiral oxazoline **1a** or the chelating system **1b**, the steric congestion imparted by the entering organolithium reagent gave the tandem addition products **2** with greater than 95:5 diastereoselectivity in most cases. Removal of the oxazoline moiety by reductive hydrolytic means led either to the aldehydes **3** or the carbinols **4** in good yields and high enantiomeric excess.

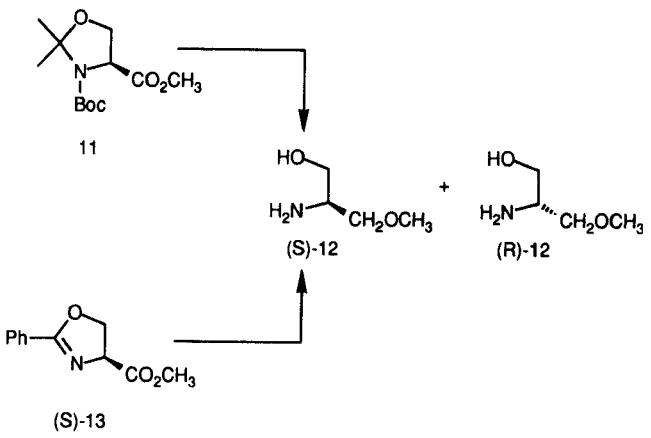
The high degree of versatility of this tandem asymmetric addition was recently demonstrated[7b] with an efficient entry into various tetracyclic terpene systems related to aphidocolin, **10** and the scopadulcic acids, **9**. This was accomplished by addition of vinyl lithium and trapping with the iodo dioxolane to afford the adduct **6**. Usual hydrolytic removal of the oxazoline provided the keto-aldehyde which was cyclized to the spiroenone, **7**. Hydroboration-oxidation gave the key tetracyclic ketone **8**, a pivotal intermediate to either **9** or **10** by virtue of ring contractions. It is important to state that both **9** and **10** were obtained enantiomerically pure due to the efficient diastereoselective additions to the chiral naphthalene systems. In recent years there have been several other other tandem additions to chiral naphthalene systems wherein related chiral auxiliaries have been used.[8,9,10] Furthermore, Kundig[11] has recently shown that highly diastereoselective additions to oxazoline-chromium complexes gave cyclohexadienes in high enantiomeric purity, whereas a Spanish group recently described tandem additions to o-(vinyl) phenyloxazolines.[12] Thus, the oxazoline and related systems continue to attract significant attention toward the goal of novel and important synthetic methods.

Since many of the most useful chiral auxiliaries have come from amino acids,[1c,13] efforts are heavily focused on these materials as sources of new and versatile stereodirecting groups. Our own efforts have depended heavily on valine, phenyl glycine, and *tert*-leucine, as their reduced amino alcohols, to provide the necessary stereocontrol in formamidines,[14] bicyclic lactams,[15] as well as oxazolines.[7c] In spite of the successes achieved with



Scheme 2

tert-leucinol and valinol as chiral starting materials, certain limitations were observed (*vide infra*) and the availability of only one enantiomer of the former led us to continue a search for other sources. The requirements we have set for a new chiral oxazoline included a) large scale availability, b) both enantiomers to be accessible, and c) the stereocontrol required for useful synthetic manipulations. We therefore turned our attention to L-serine since it has been previously shown to be an important building block[16] in the synthesis of natural products.[17] If we can transform the known oxazolidine **11**[16] or the oxazoline **13**,[18] both derived from S-serine into the desired methoxyamino alcohols R and S-**12**, this would indeed represent an efficient route to the desired chiral auxiliary. Herein, we provide the details of the multi-gram synthesis of both S-**12** and R-**12** from a *single serine enantiomer* and their use in asymmetric additions.



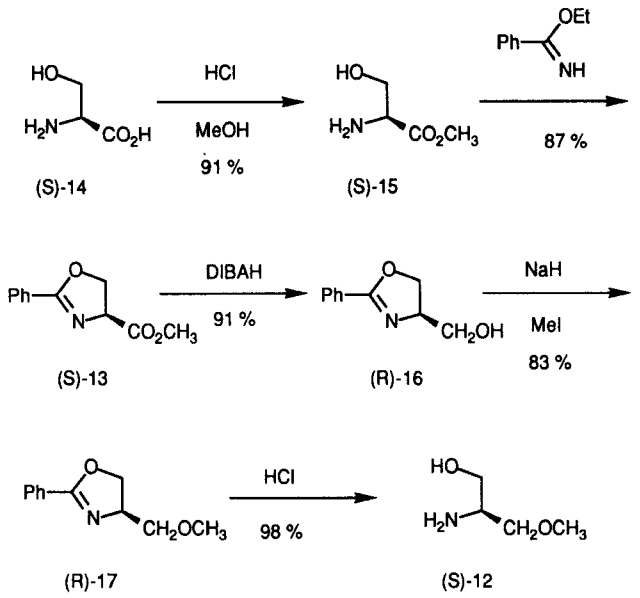
The sequence leading to (S)-**12** is shown in Scheme 3. The oxazoline ester **13** was prepared as described[18] from S-serine **14**, esterification to **15**, and reaction with ethyl benzimidate. The Fischer esterification could be done on large scale without any detectable racemization.[19,20] It was found that crude oxazoline **13** was quite suitable for studying the reduction to the carbinol **16**. Reduction using diisobutylaluminum hydride at 0°C consistently gave carbinol **16** in good chemical yields (91-93%) whereas $LiBH_4$, $LiAlH_4$, and other hydrides were inconsistent in both chemical and enantiomeric yields. The enantiomeric purity of the oxazoline carbinol **16** was assessed using ^{19}F-nmr on the Mosher ester[21] and HPLC analysis (Fig. 1) which amounted to a 99.2:0.8 ratio of enantiomers (R-enantiomer), when compared to the racemate. The S-enantiomer of **16**, also prepared in high purity (98:2) will be described later. The ^{19}F-nmr analysis (Fig. 2) was also quite convincing and was in good agreement with the HPLC technique.

Biographical Details

Professor A. I. Meyers (left) is a University Distinguished Professor who has been at Colorado State University since 1972. Before that he was on the faculty at Louisiana State University (1958-1970), and Wayne State University (1970-1972). His research interests are in synthetic chemistry, asymmetric synthesis, and use of heterocycles as vehicles in synthesis.

Dr. Wolfgang Schmidt (center) received his Ph.D. degree from the University of Münster and is a postdoctoral fellow in the Meyers' group.

Mr. Marc McKennon (right) received a B.S. degree from the University of California at Santa Barbara and is currently a graduate student in the Meyers' group.



Scheme 3

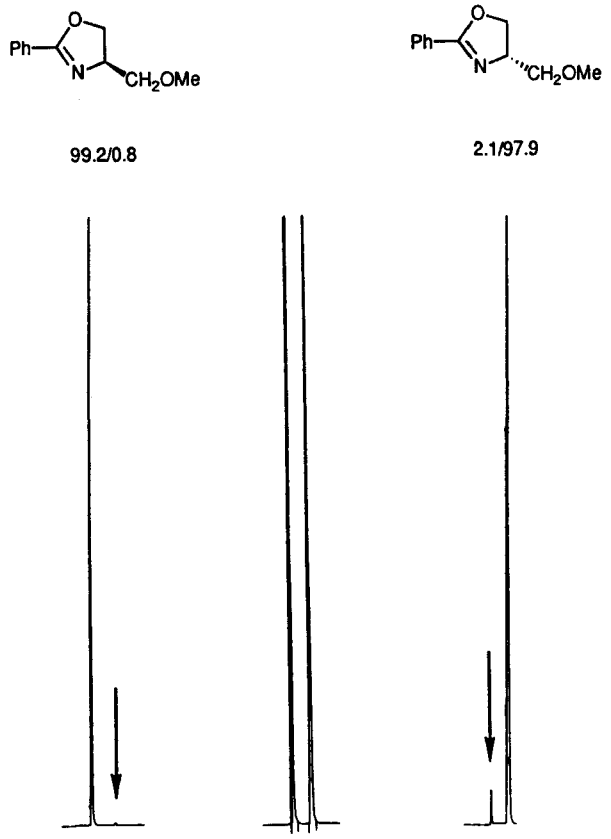


Figure 1. Chiral HPLC analysis of (R)-**16** and (S)-**16** using a Chiracel OD column, Hexane/Isopropanol 75/25, Flow of 1.0 mL min^{-1}, 264 nm.

Alkylation of carbinol **16** with sodium hydride-methyl iodides followed by flash chromatography afforded the methoxy derivative (R)-**17** in high yield and it is noteworthy that this stage

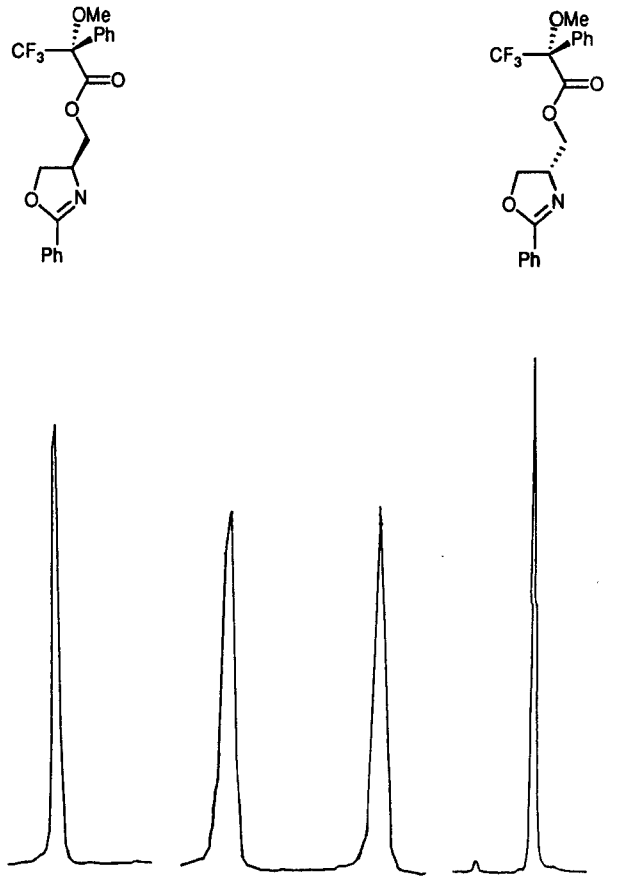
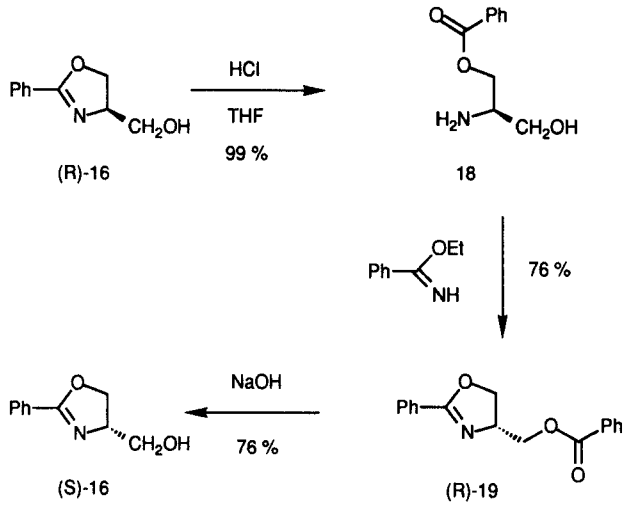


Figure 2. ^{19}F-NMR analysis of the Mosher ester derived from (R)-**16** and (S)-**16**.

of the synthetic route required the only purification step in the entire sequence. The methoxy oxazoline **17** was cleaved by heating in 4 M hydrochloric acid and produced the crude methoxyamino alcohol **12** which was isolated as its hydrochloride salt. The only by-product, benzoic acid, was removed readily by filtration. Further purification was performed by Kugelrohr distillation of the free amino alcohol. The unlikely occurrence of racemization taking place during the hydrolysis of the oxazoline **17** was quickly dispelled when (S)-**12** was transformed back to the oxazoline **17** (76%) and the same ratios were observed as portrayed in Fig. 1 and 2. Thus, the methoxyamino alcohol (S)-**12** was prepared in five steps from (S)-serine, **14**, in 59% overall yield and with an enantiomeric purity >96%.

The optical antipode of (S)-**12** was also reached using a modification of a procedure initially reported by Rapaport[22] who converted inexpensive L-serine into a variety of D-amino acids with retention of stereochemistry. We, therefore, found it plausible to transform (R)-**16** into (S)-**16** and ultimately to (R)-**12** (Scheme 4). By utilizing the hydroxymethyl oxazoline (R)- **16** obtained above from inexpensive L-serine, we could selectively cleave the oxazoline ring to the amino ester hydrochloride **18**, a

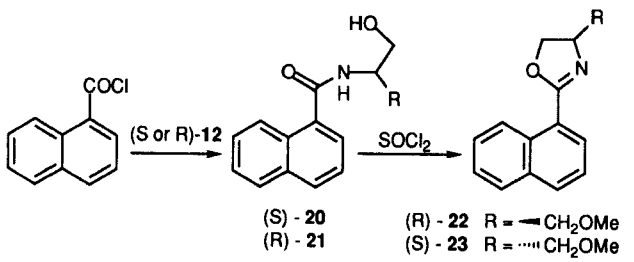
technique we first utilized in 1976.[23] The latter was condensed with ethyl benzimidate and furnished the oxazoline ester (R)-**19**, which had the opposite configuration at C-4. Subsequent alkaline hydrolysis produced the enantiomeric hydroxymethyl oxazoline (S)-**16**. This three step procedure from the (R)-oxazoline to its (S)-antipode was achieved in 63% overall yield with complete conservation of enantiomeric purity (Fig. 1, 2). The relatively high enantiomeric purity of both



Scheme 4

oxazolines confirms that our route was free of any major stereochemical problems. As before, hydrolysis of the (S)-enantiomer of **16** gave the (R) enantiomer of **12** in 96% yield as the hydrochloride salt and now fulfills our first two requirements of a chiral auxiliary-multigram synthesis and accessibility of both enantiomers from an inexpensive source (*vide supra*).

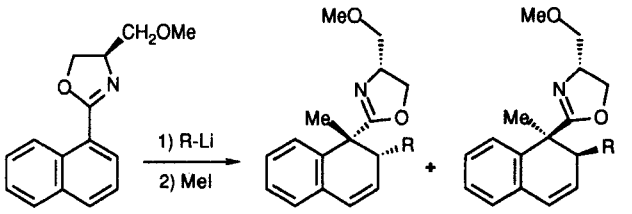
The ability of (S) and (R)-**12** to efficiently control absolute stereochemistry was next explored using an earlier reaction[7a-7c] we had successfully implemented. The antipodal naphthyloxazolines (R)-**22**, (S)-**23** were both prepared and subjected to additions with various organolithiums and trapping the initial adducts with methyl iodide. The requisite naphthyl oxazolines **22**, **23** were prepared by transforming (S or R)-**12** into the corresponding naphthamides **20**, **21** and thencyclized with thionyl chloride. This sequence furnished the R



and S naphthyloxazolines in 89% and 85% overall yields respectively.

Tandem additions with organolithium reagents followed by electrophilic trapping with iodomethane are shown in Table 1.

Table 1. Additions to Serine-Derived Naphthyloxazolines.[a]



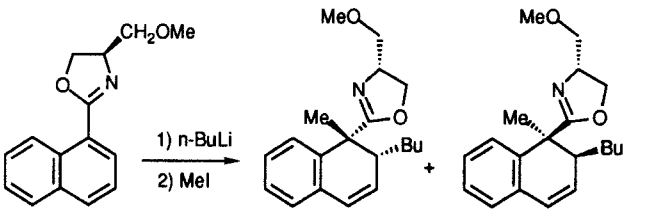
R	% yield	24a:24b
Et	66	96:4
n-Bu	94	95:5
s-Bu	72	77:23
t-Bu	79	64:36
Ph	78	91:9
Vinyl	73	97:3

a) The enantiomer of **24a** starting from S-naphthyloxazoline **23** was reached in comparable yields and ee's.

Both chemical yields and diastereoselectivity were found to be in a range comparable to that reported for the *tert*-leucinol derived oxazolines.[7c] With the exception of the *sec*-butyl - and *tert*-butyllithium addition, where poor diastereoselectivities were previously observed, all other cases gave useful levels of stereocontrol. The diastereoisomers **24a**, **b** or **25a**, **b** were readily separated by chromatography affording access to the major diastereoisomers in high purity.

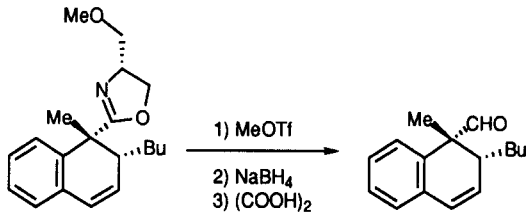
The effect of temperature on this addition process was relatively small as seen by the diastereomeric ratios of **25a** and **b** shown in Table 2.

Table 2. Effect of Addition Temperature on Stereoselectivity.



Addition T° of RLi	% yield	25a:25b
-78° C	94	95:5
-40° C	85	96:4
0° C	91	87:13

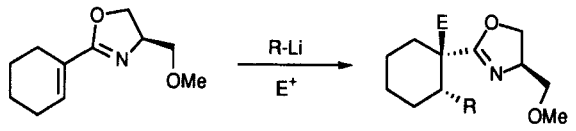
The absolute stereochemistry of the observed diastereoisomers was established by hydrolysis of the oxazoline **25a** to the aldehyde **26** and comparison with the aldehyde previously



25a **26**

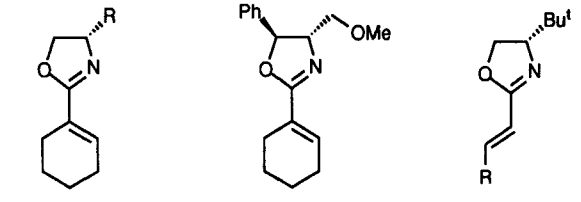
obtained from the *tert*-leucinol derivative.[7c] Furthermore, the stereochemical assignment of the substituents can be readily explained by the previously proposed transition states.[7]

To further evaluate the value of the chiral amino alcohols, we considered additions to the cyclohexenyl system **27** in the hope of achieving diastereoselective additions to the doubly



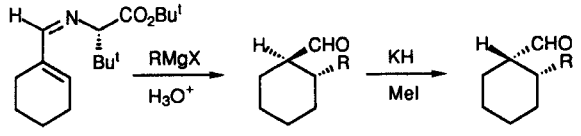
27 **28**

alkylated systems, **28**. This would provide a route to cyclohexanes containing two stereocenters and ultimately to more complex systems. We had already examined cyclohexenes in this regard in earlier efforts,[24] and were disappointed to find that the selectivity was poor to moderate when **29** and **30** were employed. In the case of **30**, selectivities were in the range of 4-5:1 for the analogous productrelated to **28** whereas employing **29** as a substrate, the yields and the selectivity were very poor. In fact, very little addition to **29** was observed. This latter result is somewhat surprising



29 R = *i*-Pr, *t*-Bu **30** **31**

since efficient diastereoselective additions were observed for the α,β-unsaturated oxazoline **31**.[25] Tomioka and Koga reported in 1980[26] that α,β-unsaturated imines derived from *tert*-leucine ester **32** were readily attacked by various Grignard

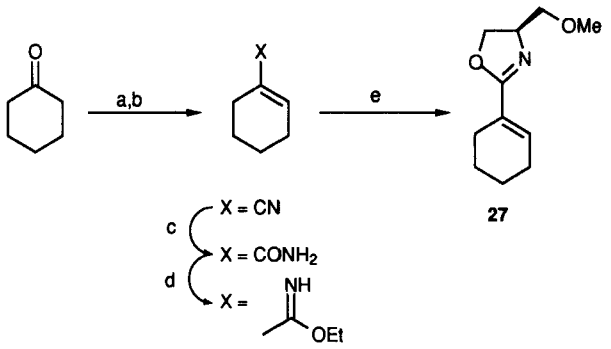


32 **33** R = Ph, vinyl **34**

reagents affording, after hydrolysis, good yields and high ee's of the aldehydes **33**. Enolization-methylation of the latter gave the dialkylated cyclohexanes in chemical yields of 52-63% and ee's of 91-93%.

In view of the lackluster performance of oxazolines **29** and **30**, we felt that another look at this tandem addition using the serine-derived methoxyamino alcohols **12** would be worthwhile.

The requisite cyclohexenyl oxazoline **27** was prepared by the sequence outlined in Scheme 5. Starting from cyclohexanone, the cyanohydrin was prepared which was dehydrated to the unsaturated nitrile. Transformation to the amide and then to the

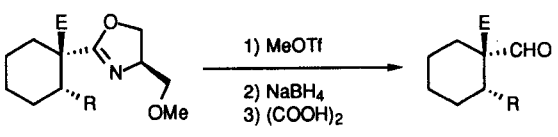


a: NaCN, $NaHSO_3$, H_2O **b**: $POCl_3$, pyridine, benzene **c**: nBu_4NHSO_4, 30% H_2O_2, 20% NaOH, CH_2Cl_2 **d**: Et_3OBF_4, $Cl(CH_2)_2Cl$ **e**: $HCl \cdot H_2N$  , $Cl(CH_2)_2Cl$.

Scheme 5

imidate gave the proper precursor for the oxazoline. Thus, treatment of the cyclohexenyl imidate with the hydrochloride of (S)-**12** formed the oxazoline **27** in 49% yield over five steps from cyclohexanone.

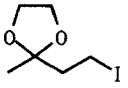
When **27** was treated with several organolithium reagents (THF, -78°C) followed by electrophilic trapping, the tandem addition products **28a-d** were formed in generally good yields (Table 3). The diastereoselectivity was also satisfactory giving ratios containing 85-97% of the major diastereomer. In the case



28 **35a,b**

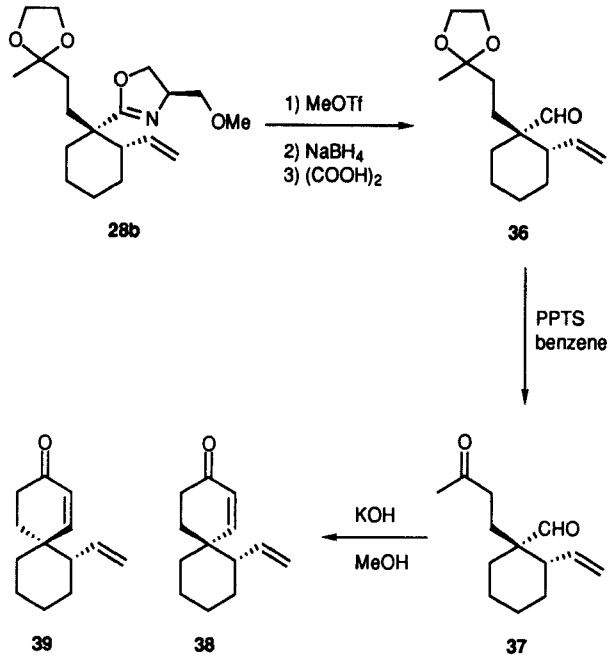
involving trapping with the 2-iodo ethyl dioxolane, the product, **28b**, gave a ratio of products 85:15 which were not

Table 3. Addition of RLi-Electrophile to **27**.

		28	
RLi	E	% yield	diastereomeric ratio[b]
a) Vinyl[a]	MeI	70	97:3
b) Vinyl[a]		82	85:15[c]
c) Phenyl	Me	63	89:11
d) Butyl	Me	99	99:1

a) Prepared by metal exchange of tributylvinyl stannane and MeLi. b) Determined by GLC or NMR. c) Calculated from product **38**, see Fig. 3.

discernible until the spiroketone **38** was prepared and evaluated for enantiomeric purity.



Since **28b** did not show the presence of any other product by usual analytical methods, we proceeded on to demonstrate that chiral, non-racemic, highly functional systems such as **38** could be readily accessed. This is related to an earlier report from our laboratory that complex systems analogous to **9** and **10** can be reached. The NMR spectrum of **38** now clearly showed the presence of an 85:15 ratio of two isomers **38**, **39** in the vinyl region which exhibited highly distinct chemical shifts (Fig. 3). The surprisingly high percentage of another isomer contrasts with the example wherein methyl iodide was used as the quenching electrophile (**28a** Table 3).

Since both examples **28a**, **28b** begin with identical initial steps - i.e. addition of vinyl lithium - they must be considered to possess the same level of diastereoselectivity at the stage of the azaenolates **40a**, **40b**.

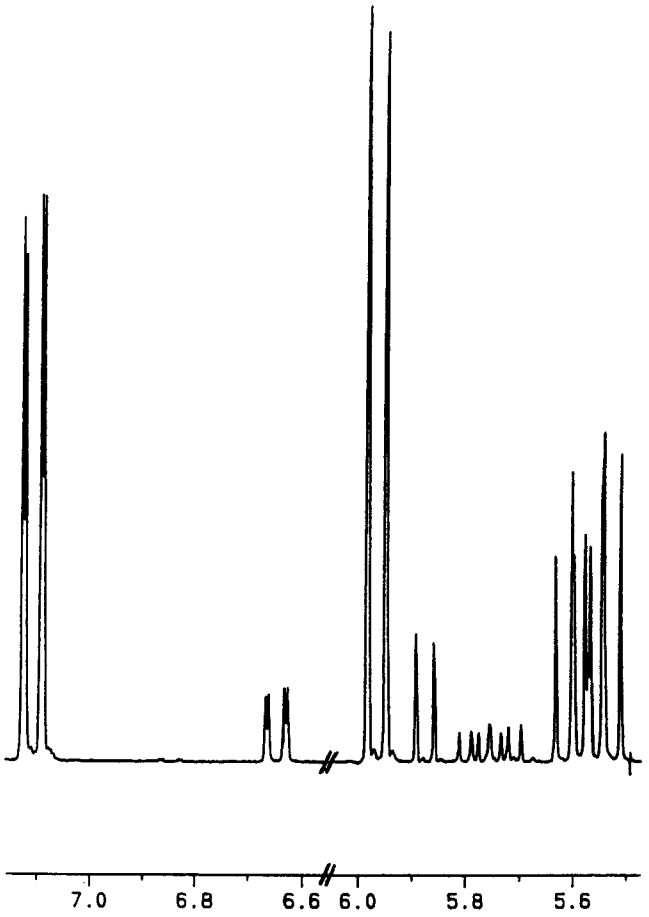
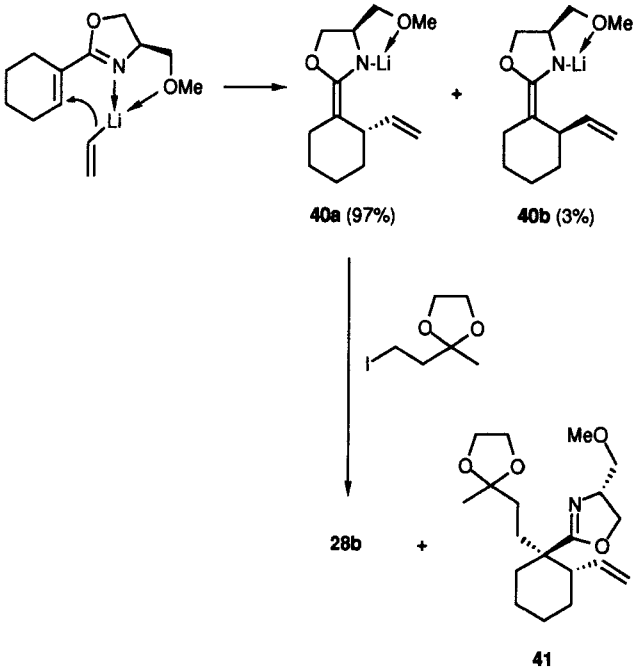


Figure 3. Vinyl region for spiroenones and the ratios of *trans* (**38**) to *cis* (**39**) isomers.



Whereas, methyl iodide addition to **40a**, **40b** gave the adducts as pure *trans* products **28a** (97:3), the alkylation with the iodoacetal gives, in addition to the *trans* adduct **28a**, 15% of the *cis*-alkylated adduct, **41**. Earlier studies in these systems, e.g.

the naphthalene additions - never gave any detectable levels of *cis*-alkylated products,[7] thus this is the first instance where we have observed this event. At this time it is not clear why *cis*-alkylation took place on **40** and this aspect is under further study.

In summary, we have shown that oxazolines continue to exhibit favorable stereocontrolling properties in asymmetric carbon-carbon bond forming reactions and the new auxiliary (R) and (S)-**12** will add to this repertoire.

Experimental section

General. All reactions were performed in flame-dried glassware under an inert atmosphere. Tetrahydrofuran (THF) was distilled under an atmosphere of argon from sodium-benzophenone ketyl. Methylene chloride was distilled under argon from calcium hydride. All other solvents and reagents were purified by standard techniques. All organic extracts were dried over sodium sulfate. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AC-300 instrument at 300 MHz and 75 MHz, respectively. Carbon multiplicities were established by DEPT experiments. Only the analytical data for the compounds derived from L-serine are given. For compounds derived from D-serine all values were in good agreement with the data given.

Benzimido ethylether Hydrochloride[18]:
Through a solution of benzonitrile (20.2 g, 20.0 ml, 0.196 mol) and ethanol (9.90 g, 12.6 ml, 0.215 mol) in dry benzene (200 ml) was bubbled HCl gas for 3 h. The solution was stirred at room temperature for 18 h. The hydrochloride formed upon standing in the freezer. Filtration and drying in vacuo yield the imidate as a white solid (33.1 g, 0.179 mol, 92 %).
^{1}H NMR δ ($CDCl_3$) 7.73 (d, J = 6.9 Hz, 2 H), 7.40 (m, 3H), 4.30 (q, J = 7.1 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H).
^{13}C NMR δ ($CDCl_3$)136,0 , 130.7, 128.3, 126.6, 62.0, 14.1; IR (neat) 2360, 1637; Mass spec. M$^+$ 148, 132, 104, 91, 77, 51.

L-Serine Methyl Ester Hydrochloride (15):
Into a solution of L-serine (Aldrich) (58.6 g, 0.558 mol) in dry methanol (300 ml) was bubbled HCl gas for 4 h. Then the solution was stirred at room temperature for 24 h. Removal of the methanol in vacuo gave a white residue. Recrystallization by refluxing in methanol (80 ml) and precipitating with hexane (200 ml) gave the pure ester hydrochloride **15** (78.4 g, 91 %) which was identical in all respects with the commercially available material (Aldrich).

In a similar fashion **D-Serine methyl ester** (4.84 g, 91 %) was prepared.

(S)-4-Carbomethoxy-2-phenyl-oxazoline[18] (13):
A solution of L-serine methyl ester hydrochloride (10.3 g, 65.9 mmol) and benzimido ethyl ether (8.87 g, 59.9 mmol) in 120 ml 1,2 dichloroethane was heated under reflux for 20 h. After filtration the solvent was removed by rotary evaporation. The residue was dried in vacuo to yield the crude oxazoline **13** (11.4 g, 93 %), which could be used without further purification.
^{1}H NMR δ ($CDCl_3$) 8.00 (d, J = 7.2 Hz, 2 H), 7.56-7.38 (m, 3H), 4.93 (dd, J = 10.5 and 8.0 Hz, 1 H), 4.70 (dd, J = 8.7 and 8.0 Hz, 1 H), 4.60 (dd, J = 10.7 and 8.7 Hz, 1 H).
^{13}C NMR δ ($CDCl_3$) 171.5, 167.0, 131.5, 129.6, 129.3, 127.3, 69.8, 68.3, 53.0; IR (neat) 1747, 1644; Mass spec. M$^+$ 205, 173, 146, 105, 77, 51.

(R)-4-Carbomethoxy-2-phenyl-oxazoline was produced in a similar manner (4.84 g, 23.6 mmol, 91.4 %).

(R)-4-Hydroxymethyl-2-phenyl-oxazoline (16):
To a solution of the oxazoline **13** (9.70 g, 47.3 mmol) in THF (200 ml) was added at 0°C a solution of diisobutyl aluminium hydride (142 ml, 1.0 M, 142 mmol) in THF over a period of 1.6 h. The mixture was stirred at 0°C for 2 h. The solution was then added to a saturated sodium tartrate solution (300 ml) and stirring was continued for 4 h at room temperature. After extraction with ethyl acetate the organic layer was dried over sodium sulfate. Removal of the solvent and purification of the residue by flash chromatography (ethyl acetate) gave the product **16** (7.65 g, 91 %) as a white solid, m.p. 86°C.
^{1}H NMR δ ($CDCl_3$) 7.95 (m, 2 H), 7.55-7.35 (m, 3 H), 4.68 (dd, J = 11.4, J = 4.2, 1 H), 4.53-4.40 (m, 2 H), 4.36 (m, 1 H), 3.95 (dd, J = 11.3 and 3.6 Hz, 1 H), 3.68 (dd, J = 11.4 and 4.2 Hz).
^{13}C NMR δ ($CDCl_3$) 165.5, 131.3, 128.2, 128.1, 127.2, 69.2, 68.1, 63.8; IR (neat) 3278, 1645; Mass spec M$^+$ 177, 159, 146, 118, 105, 91, 77, 51; $[\alpha]_D$ = +54.0° (c 1.3, EtOH).

Anal. Calc'd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90.
Found: C, 67.73; H, 6.28; N, 7.83.

In a similar fashion **(S)-4-hydroxymethyl-2-phenyl-oxazoline (16)** (5.14 g, 96 %) was prepared.

(R)-4-Methoxymethyl-2-phenyl-oxazoline (17):
A mixture of sodium hydride (759 mg, 31.6 mmol) and iodomethane (5.61 g, 2.46 ml, 39.6 mmol) in THF (80 ml) was cooled to 0°C. A solution of the crude alcohol **16** (2.80 g, 15.8 mmol) in THF (40 ml) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. After slow addition of water (20 ml) the mixture was extracted with ethyl acetate. Drying of the organic layer and removal of the solvent by rotary evaporation gave a yellow oil, which was purified by flash chromatography (ethyl acetate/hexane 2/1) to yield the methyl ether **17** (2.60 g, 82.6 %) as a yellow oil.
^{1}H NMR δ ($CDCl_3$) 7.95 (m, 2 H), 7.58-7.35 (m, 3 H), 4.50 (m, 2 H), 4.29 (m, 1 H), 3.65 (dd, J = 9.5 and 3.7 Hz, 1 H), 3.50 (dd, J = 9.5 and 5.3 Hz, 1 H), 3.40 (s, 3 H).
^{13}C NMR δ ($CDCl_3$) 164.8, 127.9, 127.8, 74.3, 69.9, 66.0, 58.8; IR (neat) 1650; Mass spec. M$^+$ 191, 161, 146, 130, 118, 105, 91, 77; $[\alpha]_D$ = +64.2° (c 2, EtOH);

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32.
Found: C, 69.17; H, 6.90; N, 7.23.

(S)-4-methoxymethyl-2-phenyl-oxazoline 17 (4.80 g, 94.0 %) was produced in a similar fashion.

(S)-2-Amino-3-methoxy-propan-1-ol Hydrochloride (12):
The oxazoline **17** *(3.00 g, 15.7 mmol) was heated to reflux in* HCl (90 ml, 4 M) for 20 h. After cooling to room temperature the solution was filtered to remove the benzoic acid. The water layer was extracted with ether (3x25 ml) and the etheral washings discarded. Removal of the water by rotary evaporation gave the *crude amino alcohol hydrochloride* **12** *(2.16 g, 98 %) as a light* yellow oil, which could be used without further purification. Upon standing the hydrochloride crystallized. An analytical sample for combustion analysis was obtained by Kugelrohr distillation of the free amino alcohol **12** (0.01 mm, 100°C).
^{1}H NMR δ ($CDCl_3$) 3.80-3.46 (m, 5 H), 3.40 (s, 3 H).
^{13}C NMR δ ($CDCl_3$) 70.4, 60.1, 59.5, 54.1; IR (neat) 3358; Mass spec. M+ 105, 74, 60, 45; $[\alpha]_D$ = -1.9° (c 1.8, EtOH).
Anal. Calcd. for $C_4H_{11}NO_2$: *C, 45.70H, 10.55; N, 13.32.* Found: C, 45.49; H, 10.62; N, 13.26.

In a similar fashion **(R)-2-amino-3-methoxy-propan-1-ol hydrochloride (12)** (3.40 g, 96 %) was prepared.

(R)-2-Amino-3-benzoyloxy-propan-1-ol (18):
To a solution of the alcohol **(R)-16** (466 mg, 2.36 mmol) in THF (20 ml) was added HCl (2.6 ml, 2 M, 5.26 mmol). The solution was stirred for 24 h at room temperature. Evaporation of the *solvent and drying in vacuo left the ester hydrochloride* **18** *(605* mg, 99.3 %) as a white solid, which was used crude in the next step.
^{1}H NMR δ ($CDCl_3$) 8.10 (dd, J = 8.25 and 1.20 Hz, 2 H), 7.65 (m, 1 H), 7.50 (m, 2H), 4.60-4.47 (m, 2 H), 3.93-3.80 (m, 2 H), 3.80-3.60 (m, 1 H).
^{13}C NMR δ ($CDCl_3$) 170.0, 137.2, 133.5, 132.2, 65.9, 62.7, 55.9; IR (neat) 3354, 1726; Mass spec. M+ 195.

(R)-4-(Benzoyloxymethyl)-2-phenyl-oxazoline (19):
A *mixture of ester hydrochloride* **18** *(196 mg, 0.85 mmol) and* benzimido ethyl ether (138 mg, 0.93 mmol) in 1,2 dichloroethane (10 ml) was heated at reflux for 18 h. After *filtration and evaporation of the solvent the residue was purified* by flash chromatography (ethylacetate/hexane 1/2) to yield the oxazoline **19** (200 mg, 0.71 mmol, 84 %) as a white solid. The material was used without further characterization for the next step.

^{1}H NMR δ ($CDCl_3$) 8.00-7.90 (m, 4 H), 7.58-7.32 (m, 6 H), 4.70-4.60 (m, 1 H), 4.60-4.50 (m, 2 H), 4.45-4.35 (m, 2 H).
^{13}C NMR δ ($CDCl_3$) 166.7, 165.8, 133.4, 131.9, 129.9, 128.7, 127.7, 126.9, 70.4, 66.6, 65.9.
IR (neat) 1720, 1648.
Mass spec. M+ 281, 159, 146, 130, 118, 105, 91, 77, 51.

(S)-4-Hydroxymethyl-2-phenyl-oxazoline (16):
The ester **19** (360 mg, 1.28 mmol) was stirred in 15 ml sodium hydroxide solution (2 M) for 20 h at room temperature. The solution was extracted with *dichloromethane and the organic* layer was dried over sodium sulfate. After evaporation of the solvent the remaining residue was purified by flash chromatography (ethyl acetate) to yield the alcohol **16** (172 mg, 0.97 mmol, 76 %) as a white solid, m.p. 86° C. The material was *identical in all respects with the R - enantiomer except for the* sign of optical rotation.

(S)-2-Amino-3-methoxy-N-naphthoyl-propan-1-ol (20):
To an ice cold solution of the aminoalcohol **12** (2.40 g, 22.9 mmol) and triethylamine (6.9 g, 9.5 ml, 68.6 mmol) in dichloromethane (60 ml) was slowly added 1-naphthoyl chloride (4.14 g, 3.3 ml, 21.7 mmol) in dichloromethane (45 ml). The *mixture was stirred at room temperature for 20 h, washed with* HCl (2 M) and saturated sodium bicarbonate solution. After drying over sodium sulfate the solvent was removed in vacuo. The resulting solid was purified by flash chromatography (ethylacetate/hexane 4/1) to yield the amide, **20**, mp 135° C *(5.19 g, 21.3 mmol, 93 %).*
^{1}H NMR δ ($CDCl_3$) 8.25 (dd, J = 9.0 and 1.8 Hz, 1 H), 7.86-7.78 (m, 2 H), 7.56-7.41 (m, 3 H), 7.39-7.31 (m, 1 H), 6.75 (d, J = 7.8 Hz,1 H), 4.33-4.24 (m, 1 H), 3.88-3.79 (m, 1 H), 3.76-3.67 (m, 1H), 3.63-3.55 (m, 2 H), 3.50 (m, 1 H), 3.35 (s, 3 H).
^{13}C NMR δ ($CDCl_3$) 170.3, 134.4, 133.9, 131.0, 130.4, 128.6, 127.4, 126.7, 125.6, 125.5, 124.9, 72.9, 63.6, 59.5, 51.4.
IR (neat) 3293, 1640.
Mass spec. M+ 259, 226, 212, 184, 155, 127, 101, 77, 63, 42.

(R)-2-Amino-3-methoxy-N-naphthoyl-propan-1-ol (21):
(3.26 g, 13.2 mmol, 93 %) was obtained in a similar fashion as above.

(R)-4-Methoxymethyl-2-naphthyl-oxazoline (22):
The amide **20** (5.19 g, 20.0 mmol) in dichloromethane (120 ml) *was cooled to 0°C. At this temperature a solution of thionyl* chloride (7.15 g, 4.4 ml, 60.1 mmol) in the same solvent (50 ml) was added slowly. The solution was stirred for 20 h at room temperature and then washed with an ice cold sodium hydroxide solution (1 M) and saturated sodium bicarbonate solution. After drying over sodium sulfate the solvent was removed in vacuo to yield the crude oxazoline **22**, which was further purified by radial chromatography (ethylacetate/hexane 1/3) to give **22** as a white *solid, mp 87° C (4.25 g, 17.6 mmol, 88 %).*
$[\alpha]_D$ = +44.5° (c 1.5, EtOH);
^{1}H NMR δ ($CDCl_3$) 9.10 (d, J = 8.31 Hz, 1 H), 8.10 (dd, J = 7.3 and 1.2 Hz, 1 H), 7.95 (d, J = 8.2 Hz, 1 H), 7.85 (dd, J = 8.0 and 0.5 Hz, 1 H), 7.60-7.40 (m, 3 H), 4.69-4.58 (m, 1 H), 4.55-4.46 (dd, J = 9.6 and 8.2 Hz, 1 H), 4.38-4.29 (dd, J = 7.9 and 7.4 Hz, 1 H), 3.80-3.73 (dd, J = 9.5 and 4.3 Hz, 1 H), 3.58-3.48 (dd, J = 9.5 and 6.7 Hz, 1 H), 3.40 (s, 3 H).

^{13}C NMR δ ($CDCl_3$) 165.2, 134.0, 132.3, 131.5, 129.4, 128.7, 127.6, 126.8, 126.4, 124.9, 75.2, 69.9, 67.4, 59.7.
IR (neat) 1641.
Mass spec. M^+ 241, 210, 196, 168, 141, 127, 115, 77.
Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80.
Found: C, 74.65; H, 6.30; N, 5.74.

(R)-4-Methoxymethyl-2-naphthyl-oxazoline (23):
(2.76 g, 91 % was obtained in a similar fashion as above.

Typical Procedure for the Addition of Alkyl or Aryl lithiums to Naphthyloxazoline, 22 and 23:
To a solution of 1-naphthyloxazoline **22** (102 mg, 0.423 mmol) at -78°C under argon was added *n*-butyllithium (0.51 ml, 2.5 M in hexane, 1.27 mmol). After 2 h excess methyl iodide (0.36 g, 0.16 ml, 2.5 mmol) was added and the solution stirred for additional 2 h at -78°C. Then the solution was quenched with saturated aq. NH_4Cl (10 ml) and extracted with ethyl acetate. The combined organic fractions were dried over sodium sulfate and concentrated in vacuo. Purification of the product by flash chromatography (ethyl acetate/hexane 1/3) gave a mixture of diastereoisomers, **24** (125 mg, 0.399 mmol, 94.4 %) as a light yellow oil. Only the analytical data for the major isomer is given (Table 4).

Vinyllithium Addition to Naphthyloxazoline, 22:
To a solution of the 1-naphthyloxazoline **22** (72.1 mg, 0.299 mmol) and tri-n-butylvinylstannane (379 mg, 1.19 mmol) in dry THF at -40°C under argon was added methyl lithium (0.81 ml,

Table 4: Physical Data for Additions to **(R)-22**

Product	Molecular Formula[a]	IR (neat) ν (cm^{-1})	MS m/z	^1H NMR δ, J (Hz)	^{13}C NMR δ
24a	$C_{18}H_{23}NO_2$	1665	295 (M+), 270, 254, 240, 230, 141, 115, 45	7.35 (m, 1 H), 7.16 (m, 3 H), 7.00 (m, 1 H), 6.43 (dd, J = 9.8 and 1.2 Hz, 1 H), 5.97 (dd, J = 9.8 and 4.6 Hz, 1 H), 4.25 (m, 2 H), 4.12 (m, 1 H), 3.60 (m, 1H), 3.38 (s, 3 H), 3.29 (m, 1 H), 2.31 (m, 1 H), 1.60 (s, 3 H), 1.60-1.26 (m, 2 H), 0.95 (m, 3 H)	
24b	$C_{20}H_{27}NO_2$	1648	313 (M+), 298, 284, 268, 256, 230, 183, 166, 155, 142, 127, 115, 71, 45	7.40-7.33 (m, 1 H), 7.19-7.10 (m, 2 H), 7.07-6.98 (m, 1 H), 6.40 (d, J = 9.8 Hz, 1 H), 6.00-5.91 (dd, J = 9.7 and 4.6 Hz , 1 H), 4.30-4.16 (m, 2 H), 4.14-4.06 (m, 1 H), 3.59-3.53 (dd, J = 9.6 and 3.9 Hz, 1 H), 3.35 (s, 3 H), 2.35 (m, 1 H), 1.60 (s, 3 H), 1.60-1.20 (m, 6 H), 0.90 (m, 3 H)	171.9, 138.2, 132.9, 130.7, 127.7, 127.4, 127.3, 127.1, 126.2, 75.0, 70.3, 65.9, 59.5, 45.6, 31.5, 29.9, 28.2, 23.1, 16.2
24c	$C_{20}H_{27}NO_2$	1648	313 (M+), 298, 284, 256, 230, 183, 169, 141, 115, 45	7.35 (m, 1 H), 7.16-7.08 (m, 3 H), 7.02-6.97 (m, 1 H), 6.50 (dd, J = 9.9 Hz, 1 H), 5.81-5.73 (dd, J = 9.9 and 5.6 Hz, 1 H), 4.40-4.12 (m, 3 H), 3.60 (m, 1 H), 3.38 (s, 3 H), 3.35 (m, 1 H), 2.55 (m, 1 H), 1.52 (s, 3 H), 1.40-0.80 (m, 6 H), 0.55 (m, 3 H)	171.9, 139.4, 132.7, 128.4, 127.7, 127.1, 126.8, 126.2, 75.0, 70.1, 66.2, 59.6, 52.1, 49.3, 38.5, 29.8, 28.8, 14.3, 12.8
24d	$C_{20}H_{27}NO_2$	1648	313 (M+), 256, 242, 230, 168, 141, 115, 45	7.91 (dd, J = 8.8 and 1.9 Hz, 1 H), 7.18-7.09 (m, 2 H), 7.00 (m, 1 H), 6.49-6.40 (d, J = 10.0 Hz, 1 H), 6.00-5.93 (dd, J = 10.0 and 6.2 Hz, 1 H), 4.40-4.23 (m, 2 H), 4.18-4.10 (m, 1 H), 3.75 (dd, J = 9.3 and 4.0 Hz, 1 H), 3.47 (m, 1 H). 3.40 (s, 3 H), 2.40 (d, J = 6.4 Hz, 1 H), 1.50 (s, 3 H), 0.85 (s, 9 H)	172.0, 140.0, 133.2, 130.0, 127.6, 127.2, 126.9, 126.6, 75.2, 69.4, 66.7, 59.8, 54.4, 44.6, 37.3, 31.7, 28.1
24e	$C_{22}H_{23}NO_2$	1646	333 (M+), 318, 288, 256, 230, 202, 169, 142, 119, 91, 45	7.30-7.08 (m, 9 H), 6.60 (d, J = 9.7 Hz, 1 H), 6.03- 5.96 (dd, J = 9.6 and 5.4 Hz, 1 H), 4.12-3.99 (m, 1 H), 3.82-3.33 (m, 4 H), 3.28 (s, 3 H), 2.92-2.84 (m, 1 H), 1.75 (s, 3 H)	171.2, 140.6, 137.5, 132.3, 129.3, 129.2, 128.5, 128.4, 128.3, 127.4, 127.1, 126.2, 75.3, 71.2, 60.1, 53.4, 47.1, 30.5
24f	$C_{18}H_{21}NO_2$	1650	283 (M+), 268, 253, 230, 195, 167, 153, 142, 127, 115, 89, 71, 45	7.35-6.98 (m, 5 H), 6.42 (d, J = 9.5 Hz, 1 H), 5.83-5.19 (m, 1 H), 5.10-4.86 (m, 2 H), 4.32-4.16 (m, 3 H), 3.60-3.50 (dd, J = 9.5 and 4.1 Hz, 1 H), 3.38 (s, 3 H), 3.35-3.20 (m, 1 H), 3.00 (m, 1 H), 1.60 (s, 3 H)	171.6, 132.4, 128.8, 128.6, 128.0, 127.6, 127.4, 127.3, 126.5, 126.4, 115.6, 75.0, 70.3, 65.9, 59.5, 51.3, 31.2, 26.6

a: Satisfactory microanalyses were obtained on several representative compounds.

1.40 M in ether, 1.14 mmol). The resulting dark brown solution was stirred at -40°C for 24 h, whereupon, excess methyliodide was added. The mixture was stirred 2 h at -40°C and then quenched with saturated aq. NH_4Cl (10 ml). After extraction with ethyl acetate the combined organic fractions were dried with sodium sulfate and concentrated in vacuo. The remaining residue was purified by flash chromatography (ethyl acetate/hexane 1/3) to yield the dihydronaphthalene **24f** (62.0 mg, 0.219 mmol, 73.2 %) as a light yellow oil (Table 4).

Hydrolysis Reduction of Oxazoline 24a to Aldehyde 26:
The dihydronaphthalene **24** (893 mg, 2.85 mmol) in dichloromethane (20 ml) under argon at room temperature was treated with methyl trifluoromethyl sulfonate (1.40 g, 8.56 mmol, 3 eq.). After 3 h, tlc examination showed only a baseline spot indicating complete quarternization of the oxazoline. The mixture was cooled to 0°C and a solution of $NaBH_4$ (540 mg, 14.26 mmol, 5 eq.) in 4:1 MeOH/THF (15 ml) was added dropwise at 0°C. The solution was warmed to room temperature and then water was added. Extraction with dichloromethane, drying over sodium sulfate and concentration *in vacuo* gave the crude oxazolidine as an oil. This was dissolved in THF-H_2O (4:1, 50 mL) and oxalic acid (1.80 g, 4.3 mmol) was added. The mixture was heated for 12 h at 35° C. After addition of aqueous sodium bicarbonate solution the layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Radial chromatography (ethyl acetate/hexane 1/9) gave the aldehyde **26**[7a] (394 mg, 1.73 mmol, 64 %) as a colorless oil.
^1H NMR δ ($CDCl_3$) 9.80 (s, 1H), 7.25-7.10 (m, 4 H), 6.47 (dd, J = 9.8 Hz, J = 2.1 Hz, 1 H), 5.96 (dd, J = 9.7 Hz, J = 3.8 Hz, 1 H), 2.48 (m, 1 H), 1.65-1.20 (m, 9 H), 0.90 (m, 3 H).
IR (neat) 1722.
Mass spec M^+ 228, 199, 155, 143, 128, 115, 102, 77, 57.

1-Cyanocyclohexene was prepared as reported previously.[27]

1-Cyclohexenecarboxamide was prepared using a variation of a known procedure.[28] A 500 mL round bottom flask was charged with 1-cyanocyclohexene (85 mmol, 9.1 g) and 50 mL of CH_2Cl_2. nBu_4NHSO_4 (17 mmol, 5.77g) was added as a solid in one portion. The flask was cooled to 0 °C with an ice bath and a solution of 30% H_2O_2 (60 mL) was added in one portion. A solution of 20% NaOH (72 mL) was added slowly. The contents were stirred at 0° C for 4 h. The layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*, yielding a white solid. The solid was dissolved in the minimum amount of $CHCl_3$ and loaded onto a plug of silica. The plug was then "eluted" with EtOAc, effectively removing the phase transfer catalyst. The filtrate was concentrated *in vacuo*, yielding a white solid which was recrystallized from EtOAc/hexanes to yield 1-cyclohexenecarboxamide as white needles (8.0g, 75%, mp 130-2 °C).
^1H NMR (300 MHz, $CDCl_3$) δ 6.68-6.65 (m, 1H) 5.70 (broad s, 2H) 2.23-2.12 (m, 4H) 1.69-1.55 (m, 4H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.73, 135.12, 132.29, 25.42, 24.28, 22.05, 21.36.

2-(1-Cyclohexenyl)-4-methoxymethyl-2-oxazoline, 27. A 50 mL round bottom was charged with 1-cyclohexenecarboxamide (485 mg, 3.88 mmol) and 10 mL of dry dichloroethane. Triethyloxonium tetrafluoroborate (770 mg, 4.06 mmol) was added as a solid at room temperature. The suspended solid slowly dissolved. After stirring for 18 h at room temperature, the solution was saturated with gaseous NH_3. The solid NH_4Cl is filtered and (S)-2-amino-1-methoxy-3-propanol hydrochloride (500 mg, 3.53 mmol) was added as a solid to the filtrate. The flask was fitted with a reflux condensor and oil bath, and heated at reflux for 18 h. The reaction was quenched with addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate. The organic layers were dried and concentrated, yielding an orange oil which was subjected to column chromatography (5 g silica, 20%-50% EtOAc/hexanes eluant) to yield a pale oil (683 mg, 99%). Chiral stationary phase HPLC analysis shows a 99:1 mixture of enantiomers (Chiracel OJ, 98:2 hexane/EtOH eluant, 0.5 mL/min flow rate).
$[\alpha]_D$ = +92.9° (c = 1.44, MeOH).
^1H NMR (300 MHz, $CDCl_3$) δ 1.58 (m, 4H) 2.15 (m, 2H) 2.32 (m, 2H) 3.35 (m, 4H) 3.56 (m, 1H) 4.0-4.4 (m, 3H) 6.66 (m, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) 165.9, 135.9, 126.5, 74.7, 69.9, 65.8, 59.3, 25.6, 24.9, 22.1, 21.6; IR (neat) 2932, 1659, 1611, 1447, 1398, 1229, 1131, 1109, 1028, 979, 919 cm^{-1}.

$C_{11}H_{17}NO_2$	calc.	C 67.77	H 8.78	N 7.17
(195.26)	found	67.15	8.85	7.10

Vinyl oxazoline adduct, 28a:
A 10 mL round bottom flask was charged with unsaturated oxazoline **27** (93 mg, 0.476 mmol), tributylvinylstannane (535 mg, 1.69 mmol) and 3 mL of THF. The solution was cooled to -78° C. A solution of MeLi (1.13 mL of 1.4 M solution in Et_2O, 1.57 mmol) is added dropwise via syringe. The flask was held at -78° C for 18 h, after which time MeI (400 mg, 2.815 mmol) was added via syringe. The flask was allowed to warm and kept at room temperature for 18 h. The reaction was quenched by the addition of saturated NH_4Cl solution and the contents were extracted with ethyl acetate (3 x 10 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude yellow oil was subjected to column chromatography (5 g silica gel, 10% EtOAc/hexanes eluant) to yield 78 mg (70%) of **28a** as a colorless oil (Table 5).

Vinyl oxazoline adduct, 28b:
A 10 mL round bottom flask was charged with unsaturated oxazoline **27** (90 mg, 0.461 mmol), tributylvinylstannane (365 mg, 1.152 mmol) and 3 mL of THF. The solution was cooled to -78° C. A solution of MeLi (658 µL of 1.4 M solution in ether, 0.922 mmol) was added dropwise via syringe. The flask was held at -78° C for 18 h, after which 2-methyl-2-(2-iodoethyl)-1,3-

Table 5: Physical Data for Additions to **27**

Product	Molecular Formula[a]	$[\alpha]_D$ (°)[b] c	IR (neat) υ (cm^{-1})	^1H NMR[c] δ, J (Hz)	^{13}C NMR δ
28a	$C_{14}H_{22}NO_2$	+90.7 1.3, MeOH	3071, 2928, 2861, 1651, 1449, 1200, 1113, 976, 612	6.1-5.9 (m, 1H) 5.0-4.8 (m, 2H) 4.3-4.1 (m, 2H) 4.0-3.9 (m, 1H) 3.3 (s, 3H) 3.2-3.1 (m, 1H) 2.1-1.9 (m, 2H) 1.8-1.4 (m, 5H) 1.4-1.2 (m, 3H) 1.2 (s, 3H)	172.70, 140.54, 114.79, 75.16, 69.67, 65.44, 59.17, 50.52, 39.73, 35.88, 28.58, 35.73, 24.28, 22.29
28b	$C_{19}H_{31}NO_4$	+51.8 0.77, MeOH	3060, 2934, 2881, 1652, 1452, 1373, 1198, 1112, 1058, 989, 910, 858	6.09-5.98 (m, 1H) 4.99-4.90 (m, 2H) 4.20-4.05 (m, 2H) 4.00-3.90 (m, 1H) 3.90-3.83 (m, 3H) 3.54-3.49 (m, 1H) 3.32 (s, 3H) 3.20-3.15 (m, 1H) 2.20-2.15 (m, 1H) 2.00-1.80 (m, 1H) 1.75-1.25 (m, 12H) 1.26 (s, 3H)	171.73, 140.05, 114.97, 110.04, 75.16, 69.81, 65.40, 64.55, 64.51, 59.13, 49.08, 42.76, 33.10, 30.58, 29.70, 28.29, 23.68, 23.01, 21.54
28c	$C_{18}H_{25}NO_2$	+121.7 2.18, MeOH	2926, 1645, 1494, 1449, 1381, 1195, 1128, 1111, 976, 934, 756, 702	3.35 (s, 0.84 H) 3.30 (s, 0.16 H)	172.18, 143.32, 129.10, 127.45, 126.20, 74.87, 69.37, 65.02, 59.13, 53.44, 40.84, 38.72, 28.97, 27.45, 26.14, 22.57
28d	$C_{16}H_{29}NO_2$	+41.1 0.73, MeOH	2930, 2860, 1651, 1468, 1447, 1197, 1139, 1113, 977	4.21-4.06 (m, 2H) 4.04-4.01 (m, 1H) 3.57-3.53 (m, 1H) 3.34 (s, 3H) 3.27-3.19 (m, 1H) 1.92-0.83 (m, 21H)	173.87, 75.05, 69.63, 65.40, 59.20, 43.80, 40.25, 34.69, 30.61, 29.19, 25.45, 25.19, 23.35, 22.85, 22.08, 14.11
35	$C_{13}H_{18}O$	+58.1 2.1, MeOH	3063, 3030, 2921, 2856, 1676, 1442, 1420, 1387, 990, 908	7.10 (dd, J = 1.7, 10.5 Hz, 0.85 H) 6.65 (dd, J = 1.7, 10.5 Hz, 0.15 H) 5.97, (d, J = 10.5 Hz, 0.85 H) 5.88 (d, J = 10.5 Hz, 0.15 H) 5.80-5.69 (m, 0.15 H) 5.63-5.50 (m, 0.85 H)	199.50, 154.70, 139.98, 129.31, 116.38, 51.02, 38.21, 37.35, 35.00, 33.97, 28.89, 25.41, 22.19

a: Satisfactory microanalyses were obtained on several representative compounds.
b: Values of $[\alpha]_D$ for **28b,c** and **35** are of the mixtures reported in Table 3.
c: The ^1H NMR data for **28c** and **35** are selected signals representative of the mixtures reported in Table 3.

dioxolane (558 mg, 2.305 mmol) was added via syringe. The flask was allowed to warm and was kept at room temperature for 18 h. The mixture was quenched by the addition of saturated NH_4Cl solution and the contents were extracted with ethyl acetate (3 x 10 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude yellow oil was subjected to column chromatography (5 g silica gel, 10% EtOAc/hexanes eluant) to yield 75 mg (48%) of **28b** as a colorless oil (Table 5).

Phenyl oxazoline adduct, 28c:
A 10 mL round bottom flask was charged with unsaturated oxazoline **27** (53 mg, 0.271 mmol) and 3 mL of THF. The solution was cooled to -40° C and a solution of phenyl lithium (300 µL of 1.8 M solution in hexanes, 0.543 mmol) was added dropwise via syringe. The flask was held at -40° C for 18 h, after which iodomethane (154 mg, 1.086 mmol) was added via syringe. The flask was allowed to warm and was kept at room temperature for 18 h. The mixture was quenched by the addition of saturated NH_4Cl solution. The contents were extracted with ethyl acetate (3 x 10 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude yellow oil was subjected to column chromatography (5 g silica gel, 10% EtOAc/hexanes eluant) to yield 61 mg (78%) of **28c** as a colorless oil, an 84:16 ratio of diastereomers as evidenced by ^1H NMR (Table 5).

Butyl oxazoline adduct, 28d:
A 10 mL round bottom flask was charged with unsaturated oxazoline **27** (63 mg, 0.323 mmol) and 3 mL of THF. The solution was cooled to -78° C. A solution of n-BuLi (325 µL of 1.49 M solution in hexanes, 0.484 mmol) was added dropwise via syringe. The flask was held at -78° C for 1 h, after which time iodomethane (229 mg, 1.613 mmol) was added via syringe. The flask was allowed to warm and was kept at room temperature for 12 h. The reaction was quenched by the addition of saturated NH_4Cl solution and the contents were extracted with ethyl acetate (3 x 10 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude yellow oil was subjected to column chromatography (5 g silica gel, 10% EtOAc/hexanes eluant) to yield 82 mg (99%) of **28d** as a colorless oil (Table 5).

Cleavage of Oxazolines to Aldehydes: General Procedure:
To a 0.1 M solution of the oxazoline (1.0 equiv) in CH_2Cl_2 was added methyl trifluoromethanesulfonate (2.0 equiv) via syringe.

The solution was stirred at room temperature for 4 h, after which time it was cooled to 0° C. A 0.1 M solution of $NaBH_4$ (2.0 equiv) in 4:1 THF/MeOH was added via syringe with vigorous sitrring and hydrogen evolution. The solution was allowed to warm to room temperature and was held there for 30 min. The reaction was quenched with the addition of 5 mL of saturated NH_4Cl solution. The mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4. Concentration *in vacuo* yields a pale yellow oil which was taken up in 1:1 H_2O/THF (0.5 M). Oxalic acid dihydrate (5.0 equiv) was added and the solution was stirred at room temperature for 18 h. The solution was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resultant yellow oil was chromatographed on silica gel to yield the aldehydes below as a colorless oil:

2-Vinyl-1-methyl-1-carboxaldehyde 35a:[26]

The product, obtained from **28a**, was afforded in 60% yield.
$[\alpha]_D$ = +9.7° (c = 1.38, acetone).
^1H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H) 6.05-5.93 (m, 1H) 5.06-5.00 (m, 2H) 1.99-1.92 (m, 1H) 1.77-1.18 (m, 8H) 1.04 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 207.11, 139.26, 116.45, 50.02, 48.96, 34.60, 29.31, 35.55, 23.04, 22.93.[26]

2-Phenyl-1-methyl-1-carboxaldehyde 35c:[26]

The product, obtained from **28c**, was afforded in 82% yield as an 84:16 ratio of enantiomers.
$[\alpha]_D$ = +28.7° (c = 1.1, MeOH).
^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H) 7.29-717 (m, 5H) 2.59-2.54 (dd, J = 3.3 Hz, J = 13.0 Hz, 1H) 2.11-1.63 (m, 5H) 1.44-1.21 (m, 3H) 0.96 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 207.06, 141.65, 129.18, 128.00, 126.60, 52.97, 48.94, 35.96, 29.80, 26.77, 23.69, 22.89; IR (neat) 3028, 2930, 2864, 2720, 1719, 1492, 1450, 909, 766, 703 cm^{-1}.[26]

1-Vinylspiro[5,5]undec-8-en-9-one, 38:

The general procedure for cleavage of the oxazoline to the aldehyde was followed utilizing 70 mg (0.207 mmol) of oxazoline **28b**. The crude material was dissolved in 5 mL of 99:1 acetone/H_2O. Pyridinium *p*-toluenesulfonate (5 mg) was added and the solution was heated to reflux for 48 h. The solution was concentrated *in vacuo*, yielding a white paste. This paste was treated directly with 5 mL of 2.5 w/w% KOH in MeOH, giving a white suspension which was stirred at room temperature for 24 h. The suspension was again concentrated *in vacuo*, yielding a white paste which was partitioned between ethyl acetate (5 mL) and saturated NH_4Cl solution (5 mL). The mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was subjected to column chromatography on silica gel (5 g silica, 5% EtOAC/hexanes eluant) to yield 26 mg (67%) of **38** as a colorless oil, an 85:15 mixture of diastereomers, as evidenced by ^1H NMR (Table 5).

The authors are grateful to the National Institutes of Health for financial support of this work and to the Deutches Forschungsgemeinshaft for a postdoctoral fellowship (to W. S.).

(1) For a detailed survey of the various asymmetric synthetic methods the reader should consult:
a) "Asymmetric Synthesis" Morrison, J. D. ed Vol. 1-5 Academic, 1985.
b) "Asymmetric Reactions and Processes", Eliel, E. L.; Otsuka, S. ed; ACS Symposium Series No. 185, 1981.
c) "Asymmetric Synthesis", Coppola, G. M.; Schuster, H. F. Wiley-Interscience, NY 1987.
d) "Stereoselective Synthesis", Nogradi, M., VCH Publishers, NY 1987.
e) "Asymmetric Synthesis", Aitken, R. A.; Kilenyi, S. N. ed, Blackie Academic and Professional (Chapman and Hall), London, 1992.

(2) Meyers, A. I.; Knaus, G.; Kamata, K. *J. Am. Chem. Soc.* **1974**, *96*, 268. For a review of this early chiral oxazoline behavior, see Meyers, A. I. *Accounts of Chem. Res.* **1978**, *11*, 375.

(3) a) For a review on oxazolines in aromatic substitution see Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.
b) For more recent work see: Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178.
c) Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854.

(4) a) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879.
b) Wilson, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881.
c) Meyers, A. I.; Meier, A.; Rawson D. J. *Tetrahedron Lett.* **1992**, *33*, 853.

(5) Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446.

(6) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090.

(7) a) Meyers, A. I.; Roth, G. P., Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.
b) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607.
c) Rawson, D. J.; Meyers, A. I.; *J. Org. Chem.* **1991**, *56*, 2292.

(8) Lejuene, J.; Lallemand, J. Y.; Prange, T.; Ricard, L. *Tetrahedron Lett.* **1991**, *32*, 2621.

(9) Pridgen, L. N.; Mokhallalati, M. K.; Wu, M-J. *J. Org. Chem.* **1992**, *57*, 1237.

(10) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681 and earlier papers cited therein.

(11) Kundig, E. P.; Ripa, A.; Bernardinelli, G. *Angew Chem. Int. Ed. Engl.* **1992**, *31*, 1071.

(12) Seijas, J. A.; Vazquez-Tato, M. P.; Castedo, L.; Estevez, R. J.; Ruiz, M. *J. Org. Chem.* **1992**, *57*, 5283.

(13) Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165.

(14) Meyers, A. I.; Highsmith, T. K. "The Asymmetric Synthesis of Alkaloids" in Adv. in Heterocyclic Nat. Product Synthesis W. H. Pearson, ed. JAI Press, 1990.

(15) Romo, D.; Meyers, A. I. *Tetrahedron* (Report) **1991**, *47*, 9503.

(16) a) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855.
b) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
c) Arnold, L. D.; Kalanter, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105.

(17) a) Dondoni, A.; Fontin, G.; Fogagnolo, M.; Medici, A. *J. Chem. Soc. Chem. Comm.* **1988**, *10*.
b) Herold, P. *Helv. Chim. Acta.* **1988**, *71*, 354.
c) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395.
d) Radunz, H. E.; Devant, R. M.; Eiermann, V. *Liebigs Ann. Chem.* **1988**, 1103.
e) Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 4151.

(18) Tkaczuk, P.; Thorton, E. R. *J. Org. Chem.* **1981**, *46*, 4393.

(19) Elliot, D. F. *J. Chem. Soc.* **1949**, 589.

(20 Garner[16b] has reported that commercially available D and L-serine contain ~1% of the respective optical antipode.

(21) The Mosher esters were prepared according to the procedure described by Gao, Y.; Hanson, R. M.; Klunder, M.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(22) Maurer, P. J.; Takata, H.; Rapaport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

(23) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 576. See also ref. 2 above.

(24) A. Warshawsky and A. Robichaud in these laboratories - unpublished results.

(25) Meyers, A. I.; Shipman, M. *J. Org. Chem.* **1991**, *56*, 7098.

(26) Kogen, H.; Tomioka, K.; Hashimoto, S.; Koga, K. *Tetrahedron*, **1981**, *27*, 3951.

(27) Wheeler, O. H.; Lerner, I. *J. Am. Chem. Soc.* **1956**, *78*, 64.

(28) Cacchi, S.; Misiti, D.; LaTorre, F. *Synthesis*, **1980**, 243.