is virtually coupled to the 4-methylene group.[26]

Dimethyl *erythro*-2,3-Dimethylpentanedioate (70c). To 108 mg (0.62 mmol) of **6a** were added 0.5 mL (0.7 mmol) of 1.5 M NaOMe in MeOH and 0.5 mL of MeOH. This was stirred at 25 °C for 2 days, hydrogen chloride was bubbled in, and 0.25 mL of water was added. The solution was stirred overnight and poured into 30 mL of water, and the mixture was extracted with Et_2O (3 × 25 mL). The Et_2O layer was washed with water and brine, dried ($MgSO_4$), and evaporated, giving 64 mg (55%) of pure **70c**: NMR (CCl_4) δ 3.63 (s, 6), 2.0–2.4 (m, 3), 1.10 (d, 3, J = 6 Hz), 0.90 (m, 3); GC t_R 17.2 min (5-ft, 20% DEGS column, 120 °C). The NMR absorption at δ 0.90 is a multiplet since the 3-methyl group is virtually coupled to the 4-methylene group.[26]

Acknowledgment. We thank the NIH, the Petroleum Research Corp. (funds administered by the American Chemical Society), and the Research Corp. for generous financial support.

Registry No. **1**, 922-67-8; **2**, 70230-16-9; **3**, 70230-17-0; **4**, 70230-18-1; **5a**, 73587-75-4; **5b**, 73587-76-5; **6a**, 70230-19-2; **6b**, 73587-77-6; **7**, 73587-78-7; **8a**, 70230-20-5; **8b**, 73587-79-8; **9**, 72163-30-5; **10**, 70230-21-6; **11** (isomer 1), 73587-80-1; **11** (isomer 2), 73587-81-2; **12**, 73610-86-3; **13**, 70230-24-9; **14**, 73587-82-3; **15**, 70230-26-1; **16**, 73587-83-4; **17**, 70230-28-3; **18**, 73587-84-5; **19**, 70230-30-7; **20**, 70230-31-8; **21a**, 73610-87-4; *anti*-**21a**, 73610-88-5; **21b**, 73587-85-6; **22**, 70230-33-0; **23**, 70230-34-1; **24**, 70230-35-2; **25a**, 73587-86-7; **25b**, 73587-87-8; **26a**, 73587-88-9; **26b**, 73587-89-0; **27**, 70230-38-5; **28**, 73587-90-3; **29**, 73610-89-6; **30**, 73587-91-4; **31**, 73587-92-5; **32**, 73587-93-6; **33**, 73587-94-7; **34**, 73587-95-8; **35**, 73587-96-9; **36**, 73587-97-0; **37**, 73587-98-1; **38**, 73587-99-2; **39**, 73610-90-9; **40a**, 73588-00-8; **40b**, 73588-01-9; **40c**, 73588-02-0; **41a**, 73588-03-1; **41c**, 73650-08-5; **42c**, 73588-04-2; **43**, 73588-05-3; **44**, 73650-09-6; **45**, 73597-07-6; **46**, 73588-06-4; **47**, 73588-07-5; **48**, 73588-08-6; **49**, 73588-09-7; **50**, 73588-10-0; **51**, 73588-11-1; **52**, 73588-12-2; **53**, 89-71-4; **54b**, 73588-13-3; **55a**, 73597-08-7; **55b**, 73597-09-8; **56**, 73588-14-4; **57**, 73588-15-5; **58**, 73588-16-6; **59**, 73588-17-7; **60**, 69218-01-5; **61**, 73588-18-8; **62**, 73588-19-9; **63**, 73588-20-2; *anti*-**63**, 73610-91-0; **64**, 73588-21-3; *anti*-**64**, 73588-22-4; **67**, 73588-23-5; **68a**, 73588-24-6; **68b**, 73588-25-7; **69a**, 73588-26-8; **69b**, 73588-27-9; **70a**, 73588-28-0; **70b**, 73588-29-1; **70c**, 73588-30-4; *trans*-1,2-dichloroethene, 156-60-5; methyl chloroformate, 79-22-1; propene, 115-07-1; *trans*-2-butene, 590-18-1; dimethyl acetylenedicarboxylate, 762-42-5; dimethyl (*Z*,*Z*)-2,4-hexadiene-3,4-dicarboxylate, 51667-97-1; *cis*-2-butene, 590-18-1; cyclohexene, 110-83-8; 2-ethyl-1-butene, 760-21-4; *trans*-2,6-dimethylmethylenecyclohexane, 20348-74-7; 2-methyl-2-butene, 513-35-9; 1-methylcyclohexene, 591-49-1; 2,3-dimethyl-2-butene, 563-79-1; norbornene, 498-66-8; norbornadiene, 121-46-0; (*E*)-3-methyl-2-pentene, 616-12-6; (*Z*)-3-methyl-2-pentene, 922-62-3; 1,6-dimethylcyclohexene, 1759-64-4; 1,2-dimethylcyclohexene, 1674-10-8; isoprene, 78-79-5; 4-isopropyl-1-methylcyclohexene, 5502-88-5; 1,3-dimethylcyclohexene, 2808-76-6; 2-cholestene, 15910-23-3; 5-cholestene, 570-74-1; limonene, 138-86-3; 6-methyl-1,5-heptadiene, 7270-50-0; 2-methyl-1,5-hexadiene, 4049-81-4; 1-methyl-1,4-cyclohexadiene, 4313-57-9; 2,5-dimethyl-2,4-hexadiene, 764-13-6; 1-octyn-1-yltrimethylsilane, 15719-55-8; (4-methylenecyclohexyl)-methanol, 1004-24-6; 3-methyl-3-buten-1-ol, 763-32-6; methyl geranoate, 1189-09-9; *l*-carvone, 2244-16-8; methylenecyclohexane, 1192-37-6; methyl bromopropiolate, 23680-40-2; anthracene, 120-12-7; methyl 12-chloro-9,10-dihydro-9,10-ethenoanthracene-11-carboxylate, 73588-31-5.

(26) Anet, F. A. L. *Can. J. Chem.* **1961**, *39*, 2262.

Asymmetric Addition of Organometallics to Chiral Ketooxazolines. Preparation of Enantiomerically Enriched α-Hydroxy Acids

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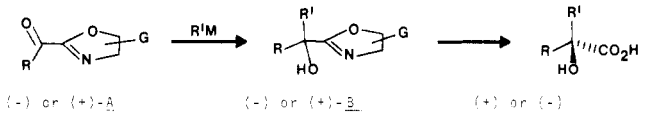
Addition of Grignard and organolithium reagents to chiral α-ketooxazolines results in α-substituted α-hydroxyoxazoline derivatives which on hydrolytic removal of the chiral auxiliary groups give rise to α-substituted α-hydroxy acids in 30–87% enantiomeric excess (ee). Studies on the various parameters (solvents, temperature, substituents) were undertaken to reach optimum asymmetric induction.

In 1904, McKenzie[1] applied the newly discovered Grignard reaction to the first asymmetric addition to chiral α-keto esters, forming the basis for extensive studies later performed by Prelog.[2] The results of these studies by Prelog and others are now well-known as the "Prelog rule"[3] and are widely used for the correlation of absolute configuration of chiral alcohols and acids. Furthermore, Grignard addition to chiral α-keto esters has been employed as a route to chiral α-hydroxy acids. However, in spite of the many studies[4] in this area, all but the single example by Berson and Greenbaum[5] have generally met with disappointing results. The enantiomeric purity of various α-hydroxy acids derived from chiral α-keto esters ranged from 0 to 30% except in the Berson report which utilized a chiral biaryl system to achieve atrolactic acid in 93% ee. Recently, several studies have appeared using novel variations of the above method which have shown greater potential in reaching chiral α-hydroxy acids in greater enantioselectivity (50–99%).[6]

This report is concerned with the further use of chiral oxazolines as auxiliary groups in asymmetric synthesis[7] and their application to chiral α-substituted α-hydroxy acids. By addition of organolithium or Grignard reagents to various optically active α-ketooxazolines ((+)-A), excellent



(1) A. McKenzie, *J. Chem. Soc.*, **85**, 1249 (1904).
(2) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).
(3) J. C. Fiaud, "Fundamentals and Methods of Stereochemistry", Vol. 3, H. B. Kagan, Ed., Georg Thieme Verlag, Stuttgart, 1977.
(4) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, NJ 1971.
(5) J. A. Berson and M. A. Greenbaum, *J. Am. Chem. Soc.*, **80**, 445, 653 (1958).
(6) E. L. Eliel and W. J. Frazee, *J. Org. Chem.*, **44**, 3599 (1979); T. Mukaiyama, Y. Saito, and M. Asani, *Chem. Lett.*, 1253 (1978); M. Newcomb and D. E. Bergbreiter, *Tetrahedron Lett.*, 103 (1979); S. Terashima and S. Jew, *ibid.*, 1005 (1977).
(7) A. I. Meyers, *Acc. Chem. Res.*, **11**, 375 (1978); A. I. Meyers, R. K. Smith, and C. E. Whitten, *J. Org. Chem.*, **44**, 2250 (1979); A. I. Meyers and R. K. Smith, *Tetrahedron Lett.*, 2749 (1979).

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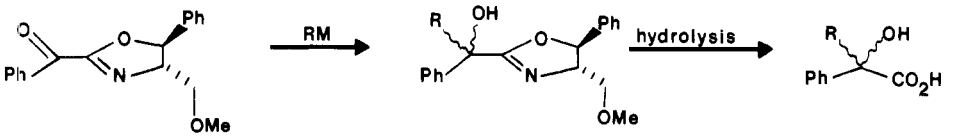
Table I. Addition of Organometallics to Benzoyloxazoline 3



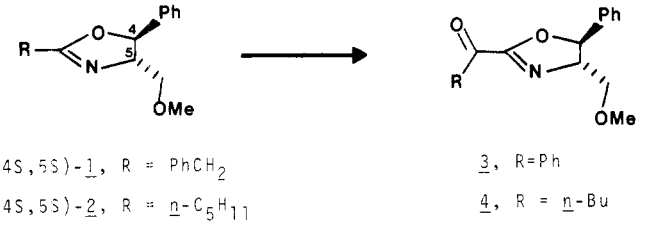
12 13

expt no.	RM (solvent)[a]	yield of 12, %	diastereomeric[b] ratio of 12	yield of 13, %	$[\alpha]_D$[c] of 13, deg	% ee of 13	config
1	MeMgBr (THF)	95	55:45	70	+3.17	9.0[d]	S
2	MeMgBr·4TMEDA (THF)	99	66:33	72	−11.2	31.7	R
3	MeMgBr·Et_3N (toluene)	94	61:39	76	+7.78	22.0	S
4	MeLi (THF)	93	50:50	70	~0.0	0	
5	MeLi (THF), $LiClO_4$[e]	99	74:26	73	+16.8	47.6	S
6	EtMgBr·Et_3N (toluene)	>99	65:35	65	+11.0	33.0[f]	S
7	*n*-PrMgBr·Et_3N (toluene)	>99	71:29	62	+8.4	39.0[g]	S
8	*i*-PrMgBr·Et_3N (toluene)	95	70:30	57	+13.2	41.0[g]	S[k]
9	*i*-BuMgBr·Et_3N (toluene)	>99	76:24	55	+10.0	50.0[g]	S[j]
10	*p*-tolyllithium	93	*h*	60	−1.83[l]	76.0[g]	S[i]
11	*p*-anisyllithium	92	*h*	55	−2.60	62.0[g]	S
12	1-naphthyllithium	>99	*h*	62	−2.60	65.0[g]	S[j]
13	2-thienyllithium	90	*h*	73	−17.4	87.0[g]	S

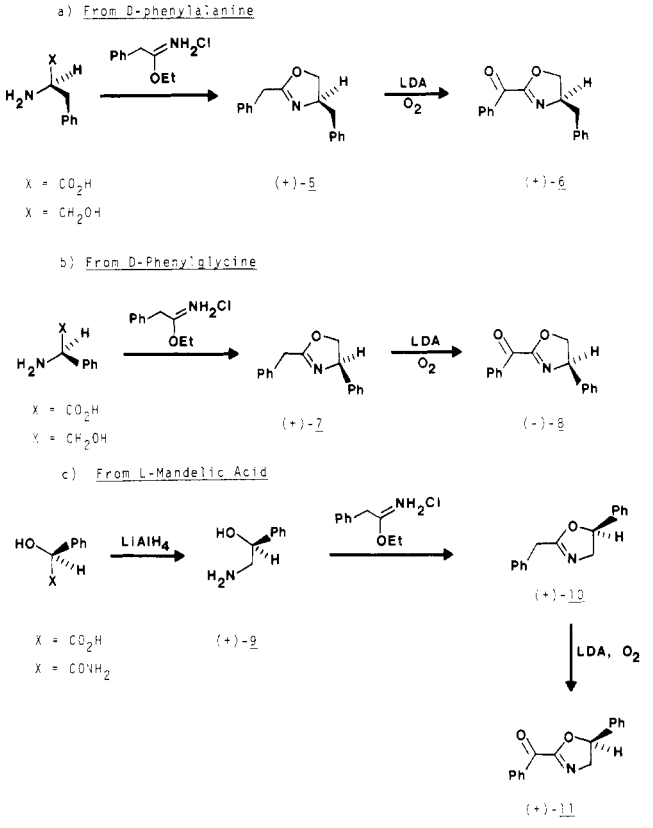
[a] Oxazolines added to organometallic at −78 °C in the appropriat solvent unless otherwise indicated. See general conditions in the Experimental Section. [b] ^1H NMR determination of C-5 H and OMe group. [c] Taken in absolute ethanol. [d] Based on $[\alpha]_D$ +35.3° (ethanol) for (*S*)-(+)-atrolactic acid: R. Barnes and B. Juliano, *J. Am. Chem. Soc.*, **81**, 6462 (1959). [e] One equivalent of $LiClO_4$ added to oxazoline prior to MeLi addition. [f] Based on $[\alpha]_D$ +33.7° reported for the (*S*)-(+) derivative: S. Mitsui et al., *Chem. Ind. (London)*, 223 (1954). [g] Meyers and Slade[22] report maximum $[\alpha]_D$ for pure enantiomer. [h] Not discernible by ^1H NMR. [i] Absolute configuration reported by A. McKenzie and E. W. Christie, *Biochem. Z.*, 277, 426 (1935). [j] Absolute configurations reported by V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953). [k] Absolute configurations reported by K. Shingu et al., *Tetrahedron Lett.*, 4371 (1967). [l] Rotation at 546 nm.

yields of the adducts B containing a new chiral center are achieved which are hydrolyzed to the desired chiral α-hydroxy acids in 30–87% enantiomeric excess. Various ring substituents (G), solvents, temperature, and the nature of the organometallic were examined in order to reach optimum conditions.

Chiral α-Ketooxazolines. The α-ketooxazolines **3** and **4** utilized in this study were obtained from the 2-alkyl oxazolines **1** and **2** previously reported from this laboratory.[8] Metalation of **1** using lithium diisopropylamide at −78 °C, followed by introduction of oxygen, gave **3** directly in 70% yield.[9] In the case of the 2-(*n*-pentyl)oxazoline, these conditions led to a mixture of the α-keto- and the α-hydroxyoxazoline. Similar results have been obtained by others[10] when enolates of carboxylic acids were reacted with oxygen. However, the problem was circumvented by quenching the initial peroxy anion with acetyl chloride. In this fashion **4** was the only product isolated in 57% yield. Chiral oxazolines **6**, **8**, and **11** containing other ring substituents were prepared from readily available natural materials by using the sequences outlined in Scheme I.



Scheme I



Asymmetric Addition of Organometallics. With the chiral ketooxazolines **3**, **4**, **6**, **8**, and **11** in hand, a series of organolithium reagents and Grignards were added in an effort to generate the new chiral center with a high degree of stereoselectivity. The oxazoline **3**, which is easiest to acquire in quantity, was studied most extensively, and

(8) A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Am. Chem. Soc.*, **98**, 567 (1976); A. I. Meyers, E. S. Snyder, and J. J. Ackerman, *ibid.*, **100**, 8186 (1978).

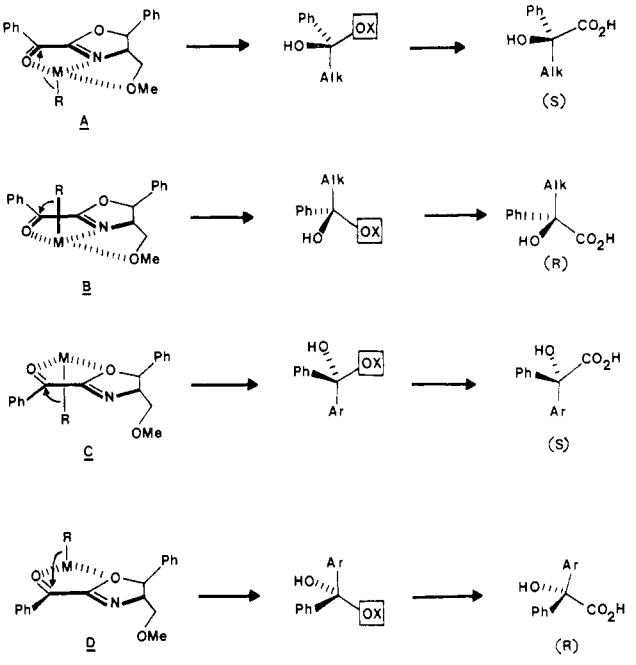
(9) For oxidation of 2-benzyl-4,4-dimethyl-2-oxazoline with these reagents, see J. F. Hansen and S. Wang, *J. Org. Chem.*, **41**, 3635 (1976).

(10) D. Konen and L. Silbert, *J. Org. Chem.*, **40**, 3253 (1975).

results are presented in Table I. The degree of asymmetric alkylation was monitored by first examining the diasteriomers present in **12** with NMR techniques. The ring proton at C-5 and the methoxy protons showed a pair of doublets (~5.2 ppm) and a pair of singlets (~3.2 ppm), respectively, as a measure of the diastereomeric ratios present. Hydrolysis to the α-hydroxy acids **13** was accomplished by using triethyloxonium fluoroborate or methyl iodide and base. Direct acid hydrolysis of the oxazolines resulted in varying degrees of dehydration and thus achiral products. The percent enantiomeric excess (ee) of the chiral hydroxy acids was determined by comparison with literature values for specific rotation, and in cases where these were unknown, chiral lanthanide shift reagents (CLSR) were employed on the methyl ether–methyl esters of **13**. Good agreement between the diastereomeric ratios in **12** (except for expt 10–13, Table I, where they were not discernible by NMR) and the percent enantiomeric excess in **13** was obtained, attesting to the absence of significant racemization during the hydrolysis. Futhermore, the dependence on specific rotation from older literature values was avoided when all the oxazolines **12** were used as resolving agents to reach pure α-hydroxy acids. This technique is described more fully in the accompanying paper.[22] Due to this resolution effort, there is considerable confidence in the maximum specific rotations of all the α-hydroxy acids reported in this study.

From Table I, addition of methylmagnesium bromide or methyllithium to **3** without added reagents gave very poor asymmetric induction (expt 1, 4). The result was unchanged when ether or THF at all temperatures from −98 to 0 °C was utilized. The reactions were very rapid, and in an attempt to slow up the addition to **3** and render the process more selective, TMEDA was employed as a coreactant (expt 2). The latter gave atrolatic acid (**13**, R = Me) in 31.7% ee as the *R* enantiomer. This significant enhancement in the percent enantiomeric excess lends some credence to the increased selectivity of Grignard reagents when complexed to TMEDA.[11] When other Grignard reagents (ethyl, isopropyl, *tert*-butyl) were precomplexed with TMEDA, the reaction with **3** was very slow, with considerable amounts of starting material (**3**) being recovered and with products derived from the destruction of the oxazoline ring being obtained. Further modifications were sought on the basis of Ashby's observation[12] that lithium salts complexed to the carbonyl group in 4-*tert*-butylcyclohexanone gave a 94:6 axial to equatorial alcohol when treated with methyllithium. From Table I it is seen that introduction of $LiClO_4$ to **3** prior to addition of methyllithium gave **12** in a 74:26 ratio and atrolactic acid (**13**, R = Me) in 47.6% ee. However, application of this technique to other organolithium reagents and Grignard reagents proved that the "Li^+ effect" was not general. Although the MeLi–$LiClO_4$ system gave the highest asymmetric alkylation to atrolactic acid, another reagent based on Ashby's report[13] of Grignard–triethylamine complexes was examined. Ashby showed some years ago that it was practical to prepare monomeric Grignard reagents in toluene if 1 equiv of triethylamine was present. The species $RMgX{\cdot}Et_3N$ was completely soluble in this solvent, and when various Grignard reagents (Me, Et, *n*-Pr, *i*-Pr, *i*-Bu) were treated at −78 °C with the benzoyloxazoline, there were obtained moderate levels of asymmetric alkylation (Table I, expt 3, 6–9). This represents,

Scheme II

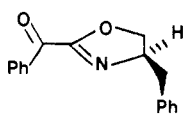


to date, the highest degree of asymmetric induction yet achieved for α-alkyl-α-hydroxy acids **13**. The use of arylmetallics as their lithium reagents was examined, and when **3** was added at −78 °C in THF, α-aryl-α-hydroxy acids **13** in 62–87% ee were produced. The corresponding Grignard reagents with or without triethylamine in ether, THF, or toluene were slower to add to **3** and gave comparable results to the more conveniently prepared aryllithium reagents. Thus, optimum results were achieved for chiral acids (expt 10–13) by simple addition of **3** to the lithium reagent.

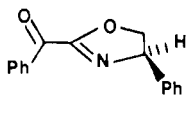
In order to rationalize the absolute configuration of the α-hydroxy acids produced by this method, we present the four possible modes of entry by the organometallic to the ketooxazoline in Scheme II (A–D). A and B are the (*S*)-cis conformers of the oxazoline, while C and D represent the (*S*)-trans conformers. Since the acids derived from alkyl Grignard addition possessed the *S* configuration, entries depicted by A or D are the only plausible routes. Previous studies[8] have shown that the phenyl group at C-5 on the oxazoline adequately shields the top of the ring, rendering entry from the top a slower process than entry from the bottom. Thus, A may be considered the prime mode of entry. However, since the α-alkyl acids are only formed in 30–40% ee, topside entry (as in B) on the (*S*)-cis conformer may also be taking place, albeit to a lesser extent than that depicted by A. The aryllithium additions to **3** (expt 10–13), furnishing the α-aryl acids in 62–87% ee, represent a marked improvement in asymmetric routes to these compounds. The absolute configurations of the acids are assigned on previous determinations (expt 10, 12), whereas the other two examples (expt 11 and 13) are assumed to be *S* on the basis of similarity factors (sign of rotations for expt 10–13 are all negative) for this process. Since the priority changes for α-aryl-α-phenyl acids in **13** (R = aryl), the transition-state alignment given in A cannot be correct. That is, for A when R = alkyl, the *S* acid is produced, while for R = aryl, the *R* acid would form. This suggests another mode of organometallic entry into the ketooxazoline. Assuming once again that topside entry (B and D) is repressed by the presence of the C-5 phenyl group and A, when R = aryl, furnishes the *R* acid, the only reasonable entry mode is given by C. This requires a prior

(11) H. O. House and J. E. Oliver, *J. Org. Chem.*, **33**, 929 (1968).
(12) E. C. Ashby, J. J. Lin, and J. J. Watkins, *Tetrahedron Lett.*, 1709 (1977); E. C. Ashby and S. A. Noding, *J. Org. Chem.*, **44**, 4371 (1979).
(13) E. C. Ashby and R. Reed, *J. Org. Chem.*, **31**, 971 (1966).

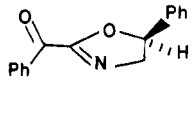
Table II. Reaction of Various Chiral Oxazolines with Organometallics



R-(+)-6



R-(-)-8



S-(+)-11

RM[a]	(R)-(+)-6 yield of adduct, %	(R)-(+)-6 yield of 13, %	(R)-(+)-6 % ee of 13[d]	(R)-(-)-8 yield of adduct, %	(R)-(-)-8 yield of 13, %	(R)-(-)-8 % ee of 13[d]	(S)-(+)-11 yield of adduct, %	(S)-(+)-11 yield of 13, %	(S)-(+)-11 % ee of 13[d]
MeMgBr	90	64	~0	99	54	8 (S)	99	34	~0
EtMgBr	77	50	5 (R)	73	40	4 (S)	99	51	6 (S)
p-TolLi	91	34	30 (R)	97	53	40 (S)	91	37	62 (S)
MeLi·LiClO$_4$	86	64	4 (R)	90	45	14 (S)	50[c]	28	9 (S)
EtLi[b]				99	53	12 (R)	99	39	21 (R)

[a] Oxazoline added to organometallic at −78 °C in THF. Reverse order of addition showed little effect on the percent enantiomeric excess of 13. A 10–20% excess of organometallic was used. [b] Ether used as solvent. [c] Starting material (25%) was recovered. [d] For isomer indicated in parentheses.

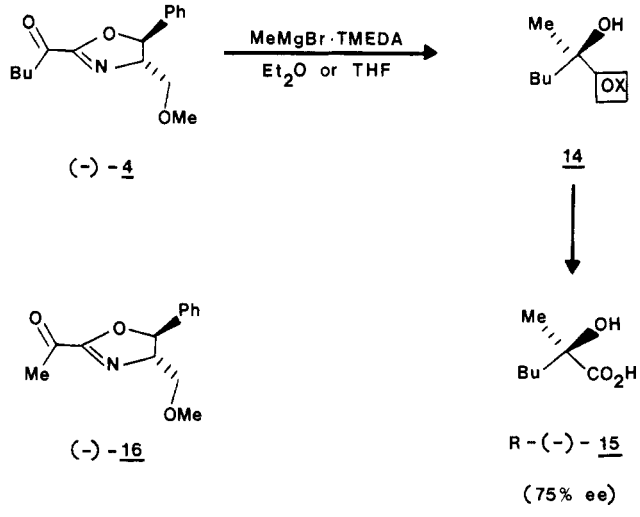
complexation of the aryllithium to the two oxygen atoms, with the aryl carbanion entering from the bottom side of the oxazoline ring. Since lithium cations are known to complex strongly with oxygen ligands,[7] it is perhaps not unexpected that C would represent the favored mode of approach by the aryl groups. A further example of this effect is seen in Table I (expt 5) where $LiClO_4$, present during the addition of MeLi, gives (S)-atrolactic acid in 47.6% ee. This would involve D as the entry mode, with $LiClO_4$ initially complexing the two oxygen atoms, followed by top-side entry of the small MeLi group. When this procedure ($LiClO_4$–RLi) was attempted with larger alkyllithiums, the addition was slow, incomplete, and gave poor enantiomeric purity (15–20%) of the products.

In summary, organometallic additions to **3** under a variety of conditions must contend with four possible modes of entry, and the extent of the asymmetric alkylations appears to be rather sensitive to subtle conformational and chelating phenomena.

In an effort to assess the scope of this process and the importance of substituents on the oxazoline ring, additional examples were investigated. The 2-pentanoyloxazoline **4** was added to methylmagnesium bromide complexed with 1 or 2 equiv of TMEDA in ether to furnish the hydroxy adduct **14** (Scheme III). The diastereomeric ratios (~86:14) were clearly discernible from the two methyl singlets in the region 1.3–1.4 ppm. Hydrolysis gave (R)-(−)-2-hydroxy-2-methylhexanoic acid (**15**) in 75% ee. The enantiomeric purity could be increased to >95% by simple recrystallization from ether–hexane. When the above sequence was carried out in toluene with MeMgBr·Et$_3$N, no addition occurred. With the acetyl oxazoline (−)-**16**, addition to *n*-BuMgBr·TMEDA gave **14** as essentially a racemic mixture rather than the anticipated (+) enantiomer. Similar results were obtained when (−)-**16** was added to phenyllithium or PhMgBr (with or without TMEDA) in an effort to reach atrolactic acid. The reaction of *n*-pentanoyl- or acetyloxazoline (**4** or **16**) was also accompanied by varying degrees of recovered keto oxazolines (20–60%), presumably due to competing proton abstraction by the organometallic reagents.

The three additional benzoyloxazolines **6**, **8**, and **11** prepared for this study and lacking the methoxyl ligand were also subjected to a representative sample of organometallic additions (Table II). The α-phenyl-α-hydroxy acids **13** were all formed in satisfactory yields but exhibited generally poor enantiomeric purity. Only the *p*-tolyllithium addition to the three oxazolines showed any signs of efficient asymmetric addition (30–62% ee). For oxazoline **6** in Table II, asymmetric additions were very poor, attesting to the importance of the nature of the C-5 substituent. Because the large phenyl group is now one carbon removed from the ring (i.e., benzyl), it appears that substantial loss in steric hindrance has occurred. As already stated, the presence of a directly attached phenyl group (as in **8** and **11**) is not the only major effect involved since **8** and **11** both exhibit very poor alkylation selectivity, except for *p*-tolyllithium. The relatively high percent enantiomeric excess for the acid in the latter case and the absolute configuration obtained are consistent with the mechanism put forth earlier (complex C) for organolithium additions. Since **6**, **8**, and **11** do not possess the methoxymethyl substituent at C-4, one can only surmise that, in addition to the C-5 phenyl group, the presence of this ligand is necessary for optimum enantioselective alkylations.

Scheme III



Experimental Section

General Methods. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Boiling points are uncorrected. Elemental analyses were performed by Midwest Microlabs, Ltd. Infrared spectra were determined either on a Perkin-Elmer 267 grating infrared spectrophotometer or on a Beckman Acculab 3 spectrometer. Nuclear magnetic resonance spectra were recorded on either a Varian T-60, EM 360A, or A-60D spectrometer using tetramethylsilane (Me_4Si) as internal standard. Optical rotations were taken on either a JASCO DIP-180 or a Perkin-Elmer 241 polarimeter using either a 1- or 0.1-dm cell. Preparative liquid chromatography at 90 psi (medium-pressure

LC) was performed on a unit previously described.[14]

***trans*-(4*S*,5*S*)-2-Benzoyl-4-(methoxymethyl)-5-phenyl-2-oxazoline (3).** Two three-necked flasks were connected with a cannula and purged with nitrogen. Flask A was fitted with a nitrogen inlet adapter and an addition funnel. Flask B contained a gas inlet tube and a nitrogen outlet adapter. Flask A was cooled to 0 °C and 11.6 g (0.12 mmol) of diisopropylamine in 150 mL of dry THF was added followed by dropwise addition of 44 mL (0.11 mmol) of 2.5 M *n*-butyllithium. The clear, slightly yellow solution was stirred for 15 min and cooled to −78 °C. Then, 28.1 g (0.1 mmol) of 1 [bp 145–148 °C (0.06 torr), $[\alpha]^{25}_D$ −35.7° (*c* 9.3, ethanol)][8] in 90 mL of THF was added dropwise through the addition funnel, and the anion solution was stirred at −78 °C for 2 h. During this period, flask B was charged with 90 mL of ether, and dry oxygen was passed into the ether at a rapid rate. The ether–O_2 solution was cooled to −78 °C, and the solution of the benzyloxazoline anion was added to it dropwise via the cannula. Total time of addition was 1 h. The reaction mixture in flask B was stirred for an additional hour at −78 °C (with O_2 bubbling in) and then quenched with saturated sodium sulfate solution (or methanol) and 40 mL of water before being warmed to room temperature. After separation of the organic phase, the aqueous phase was washed with ether (3 × 100 mL), and the organic phases were combined and dried ($MgSO_4$) prior to removal of the ether–THF in vacuo. The yellow solid obtained was recrystallized twice from 70 mL of ether to give 22.5 g (76.4%) of **3**: mp 75–76 °C; NMR (CCl_4) δ 8.35 (m, 2), 7.20–7.80 (m, 8), 5.50 (d, 1), 4.15–4.60 (m, 1), 3.50–3.90 (m, 2), 3.42 (s, 3); IR (CCl_4) 1680, 1635 cm^{-1}; $[\alpha]_D^{25}$ −37.3° (*c* 9.7, $CHCl_3$).

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.76; N, 4.75. Found: C, 73.48; H, 5.70; N, 4.79.

***trans*-(4*S*,5*S*)-2-(*n*-Pentanoyl)-4-(methoxymethyl)-5-phenyl-2-oxazoline (4).** Into a 200-mL, three-necked flask fitted with a nitrogen inlet adapter, constant addition funnel, and serum stopper was added 6.1 g (60.0 mmol) of diisopropylamine in 30 mL of THF. The solution was cooled to 0 °C and 23.0 mL (57.5 mmol) of 2.5 M *n*-butyllithium in hexane added. After the mixture was stirred 15 min, the LDA was cooled to −78 °C, and 13.1 g (50.0 mmol) of *n*-pentyloxazoline **2** [bp 162–164 °C (1.0 torr); $[\alpha]^{25}_D$ −65.6° (*c* 10.2, $CHCl_3$)][8] in 25 mL of THF was added dropwise over a 30-min period. Stirring was continued an additional 5 h and the orange solution was added via cannula to 90 mL of THF at −78 °C through which O_2 was being bubbled. Stirring was continued overnight at −78 °C (oxygen was bubbled into the solution the entire time). The reaction was quenched with 5 mL of acetyl chloride and stirred an additional 30 min, and the entire contents of the flask was poured into a mixture of 125 mL of water and 75 mL of saturated sodium bicarbonate and warmed to 25 °C. The aqueous phase was separated and extracted with ether (3 × 100 mL), and the ether extracts were combined and dried (K_2CO_3). Removal of the ether in vacuo gave 14.5 of an orange oil which was purified in two portions by medium-pressure LC (20% acetone/hexane), giving 7.8 g (56.5%) of the desired product: $[\alpha]^{24}_D$ −41.5° (*c* 11.0, $CHCl_3$); IR (neat) 1660, 1628 cm^{-1}, no OH; NMR (CCl_4) δ 7.35 (s, 5), 5.48 (d, 1), 4.20 (m, 1), 3.30–3.80 (m, 2), 3.40 (s, 3), 2.90 (br t, 2), 0.65–1.90 (m, 9). Due to the inherent instability of this compound, elemental analysis was not performed. The sample was stable if stored at −20 °C under nitrogen.

***trans*-(4*S*,5*S*)-2-Acetyl-4-(methoxymethyl)-5-phenyl-2-oxazoline (16).** A solution containing 11.0 mmol of lithium diisopropylamide in THF was cooled to −78 °C, 2.2 g (10.0 mmol) of the 2-ethyl oxazoline [bp 86–90 °C (0.15 torr), $[\alpha]^{25}_D$ −88.1° (*c* 9.8 $CHCl_3$)][8] in 10 mL of THF was added, and the mixture was stirred for 1.5 h. The resulting orange solution was added through a cannula to 85 mL of THF (−78 °C) which had dry oxygen bubbling through it. Stirring was continued for 3 h, and the reaction was quenched with 1 mL of acetyl chloride. The entire contents of the flask was then poured into a mixture of 50 mL of water and 25 mL of saturated sodium bicarbonate and allowed to warm to room temperature. The aqueous phase was separated and extracted with ether (3 × 50 mL), and all organic phases were combined and washed with 50 mL of brine prior to drying (K_2CO_3). Removal of the ether in vacuo gave 1.8 g of orange oil which was purified by medium-pressure LC (20% acetone/hexane) to give 0.7 g (28.6%) of *trans*-(4*S*,5*S*)-2-acetyl-4-(methoxymethyl)-5-phenyl-2-oxazoline: NMR (CCl_4) δ 7.25 (s, 5), 5.42 (d, 1), 4.10–4.40 (m, 1), 3.25–3.80 (m, 5), 2.46 (s, 3); IR (neat) 1715, 1630 cm^{-1}; $[\alpha]^{24}_D$ −7.45° (*c* 10.2, $CHCl_3$). Due to the inherent instability of this component, an analysis was not performed. The sample was stable at −20 °C under nitrogen.

(4*R*)-2,4-Dibenzyl-2-oxazoline (5). (a) D(+)-2-Amino-3-phenyl-1-propanol. Into a 2-L Morton flask fitted with a long reflux condenser, nitrogen inlet, constant addition funnel, heating mantle, and mechanical stirrer was placed 165.0 g (1.0 mol) of D-phenylalanine in 600 mL of THF. Then, boron trifluoride etherate (138.0 mL, 1.2 mol) was added rapidly, and the mixture was heated to gentle reflux. After 20 min, the solution became clear and homogeneous, and BH_3–Me_2S (120.0 ml, 1.2 mol) was added slowly over 3.5 h with vigorous stirring under reflux. The solution was refluxed an additional 2.5 h after all the BH_3–Me_2S had been added. Then, 100 mL of a 1:1 THF–H_2O solution was added cautiously, followed by 580 mL of 6 N sodium hydroxide which was added slowly at first and then more rapidly, all the while maintaining reflux. The reaction mixture was stirred at reflux an additional 4 h after addition of the sodium hydroxide. After the mixture cooled, the organic layer was removed and the aqueous layer extracted with ethyl acetate (5 × 250 mL). The combined organic layers were washed with water (2 × 250 mL) and brine (1 × 250 mL) and dried (K_2CO_3). Solvent removal gave a white solid which was recrystallized from a mixture of 250 mL of ethyl acetate and 150 mL of hexanes to give 119.5 g (79.1%) of the desired product: mp 88–90 °C (lit.[15] mp 90–92 °C); NMR ($CDCl_3$) δ 7.25 (s, 5), 2.20–3.80 (m, 8); IR (mineral oil) 3380, 3320, 1580 cm^{-1}; $[\alpha]^{24}_D$ +22.0° (*c* 1.5, EtOH).

(b) The above amino alcohol (15 g, 100 mmol) was stirred (15 h) with 20 g (100 mmol) of ethyl iminophenylacetate hydrochloride[8] in 150 mL of chloroform in an anhydrous atmosphere. The resulting solution was poured into 200 mL of brine and 150 mL of chloroform. The aqueous layer was separated and washed (2 × 150 mL) with chloroform, and the organic portions were combined and washed with water. After the organic phase was dried and the solvent removed in vacuo, the remaining viscous oil was distilled [bp 131–135 °C (0.05 torr)] to give 19.0 g (77%) of **5**: NMR (CCl_4) δ 7.20 (s, 5), 7.15 (s, 5), 3.70–4.60 (m, 3), 3.47 (s, 2), 2.8–3.2 (dd, *J* = 4 Hz) and 2.30–2.70 (dd, *J* = 8 Hz) (2); IR (neat) 1670 cm^{-1}; $[\alpha]_D$ +36.5° (*c* 7.7, $CHCl_3$).

(4*R*)-2-Benzoyl-4-benzyl-2-oxazoline (6). The procedure was identical with that utilized for **3**. The following amounts of reagents were employed: 2.3 g (23.0 mmol) of diisopropylamine, 9.6 mL (22.0 mmol) of 2.3 M *n*-butyllithium, 5.0 g (20.0 mmol) of oxazoline **5**. This afforded 3.3 g (62.6%) of **6** after medium-pressure LC (14% acetone/hexane): NMR (CCl_4) δ 8.10–8.40 (m, 2), 7.00–7.70 (m, 3), 7.20 (s, 5), 4.00–4.90 (m, 3), 2.50–3.40 (qd, 2); IR (neat) 1680, 1640 cm^{-1}; $[\alpha]^{25}_D$ +15.0° (*c* 12.0, $CHCl_3$).

(4*R*)-2-Benzyl-4-phenyl-2-oxazoline (7). (a) D-(−)-2-Amino-2-phenyl-1-ethanol. The procedure was identical with that used for phenylalanine and employed the following amounts of reagents: 100 g (663 mmol) of D-(−)-phenylglycine, 104 g (91 mL, 730 mmol) of boron trifluoride etherate, 55 g (73 mL, 730 mmol) of BH_3–Me_2S, 72 mL of 1:1 THF/water, 380 mL of 6 N sodium hydroxide. This afforded 58 g (64%) of the desired product: mp 71–74 °C; NMR ($CDCl_3$) δ 7.28 (s, 5), 3.60–4.20 (m, 3), 2.63 (br s, 3); IR (mineral oil) 3360, 3100, 1620 cm^{-1}; $[\alpha]^{24}_D$ −35.4° (*c* 5.0, EtOH).

(b) The procedure was identical with the preparation of **5** and employed 6.86 g (0.05 mol) of D-(−)-2-amino-2-phenyl-1-ethanol and 9.98 g (0.05 mol) of ethyl iminophenylacetate hydrochloride[8] in 75 mL of chloroform. This afforded 8.50 g (71.6%) of **7**: bp 130–135 °C/(0.08 torr); NMR (CCl_4) δ 6.90–7.50 (m, 10), 5.10 (t, 1), 4.35–4.70, 4.00 (dd and d, 2), 3.65 (s, 2); IR (neat) 1670 cm^{-1}; $[\alpha]^{24}_D$ +95.4° (*c* 9.6, $CHCl_3$).

(4*R*)-2-Benzoyl-4-phenyl-2-oxazoline (8). The procedure was identical with that used to prepare **3**. The following amounts of reagents were employed: 2.3 g (23.0 mmol) of diisopropylamine, 10.0 mL (22.0 mmol) of 2.2 M *n*-butyllithium, and 4.7 g (20.0 mmol) of oxazoline **7**. This afforded 2.9 g (56.7%) of **8** after

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(15) C. F. Lane, U.S. Patent 3 935 280.

medium-pressure LC (10% acetone/hexane: NMR (CCl_4) δ 8.10–8.50 (m, 1), 7.10–7.70 (m, 8), 5.40 (t, 1), 4.00–4.90 (quartet of overlapping doublets, J = 8 Hz, 2); IR (neat) 1680, 1635 cm^{-1}; $[\alpha]^{24}_D$ −12.8° (*c* 9.3, $CHCl_3$).

(*S*)-2-Amino-1-phenylethanol (9). (a) L(+)-Mandelamide. Into a 250-mL flask was placed 16.7 g (0.1 mol) of L(+)-mandelic acid in 440 mL of methanol. The flask was cooled to 0 °C, 6 mL of acetyl chloride was added, and the mixture was stirred overnight at room temperature. Removal of the solvent in vacuo gave a solid which was taken up in 75 mL of methanol and 185 mL of 28% aqueous ammonium hydroxide and stored in the refrigerator overnight. After removal of the solvent in vacuo, the residue was recrystallized from absolute ethanol to give 11.0 g (66.3%) of the amide: mp 121 °C (lit.[16] mp 121 °C); NMR (acetone-d_6) δ 6.30–8.33 (m, 7), 4.67–5.68 (s, 2); IR (mineral oil) 3100–3600, 1680, 1610 cm^{-1}; $[\alpha]^{24}_D$ +76.4° (*c* 1.7, acetone).

(b) Reduction of (+)-Mandelamide. Into a three-necked flask fitted with a reflux condenser and addition funnel was placed 8.0 g (211.0 mmol) of lithium aluminum hydride in 150 mL of THF. Then, 9.8 g (64.9 mmol) of mandelamide, from above, in 15 mL of THF was added slowly. After being refluxed for 4 h, the mixture was allowed to stir at room temperature overnight. The reaction was quenched by adding 8 mL of water, 3.5 mL of 40% sodium hydroxide, and 31 mL of water. After 1 h, the mixture was filtered through Celite and the residue washed with 100 mL of ether. The filtrate was dried (K_2CO_3), and the residue remaining after solvent removal (in vacuo) was recrystallized from ether to give 4.8 g (54.0%) of **9**: mp 55–57 °C (lit.[16] mp 61–62 °C); NMR ($CDCl_3$) δ 7.30 (s, 5), 4.60 (t, 1), 2.00–3.80 (m, 5); IR (mineral oil) 3000–3500, 1630 cm^{-1}; $[\alpha]^{23}_D$ +47.9° (*c* 2.4, EtOH) [lit[16] $[\alpha]^{18}_D$ +44.6 ± 2.2° (*c* 2.06, EtOH)].

(5*S*)-2-Benzyl-5-phenyl-2-oxazoline (10). The procedure was identical with the preparation of **5** and **7**, using 4.8 g (35.0 mmol) of (*S*)-(+)-2-amino-1-phenylethanol (**9**) and 7.0 g (35.0 mmol) of ethyl iminophenylacetate hydrochloride in 50 mL of chloroform. This afforded 4.9 g (59.0%) of **10**: bp 134 °C (0.09 torr); NMR (CCl_4) δ 6.80–7.67 (m, 10), 5.28 (br t, 1), 3.60 (s, 2), 3.30–3.40; IR (neat) 1675 cm^{-1}; $[\alpha]^{23}_D$ +63.1° (*c* 10.8, $CHCl_3$).

(5*S*)-2-Benzoyl-5-phenyl-2-oxazoline (11). The procedure was identical with the preparation of **3**. The following reagents and amounts were employed: 2.3 g (23.0 mmol) of diisopropylamine, 10.0 mL (22.0 mmol) of 2.2 M *n*-butyllithium, and 4.8 g (20.0 mmol) of **10**. This afforded 2.7 g (53.0%) of **11** after medium-pressure LC (15% acetone/hexane): NMR (CCl_4) δ 8.28 (m, 2), 7.05–7.90 (m, 8), 5.55 (dd, 1), 3.40–4.80 (qd, 2); IR (neat) 1670, 1630 cm^{-1}; $[\alpha]^{24}_D$ +31.10° (*c* 6.3, $CHCl_3$).

Preparation of Grignard Reagents in Toluene. The general procedure of Ashby[13] was followed. The appropriate alkyl halide (5 mmol) dissolved in 4 mL of dry toluene was added to triply sublimed magnesium shavings (6 mmol) suspended in 1 mL of toluene and 5 mmol of triethylamine. Approximately 10% of the alkyl halide–toluene solution was added initially, and the reaction was started by warming to 40–50 °C. The remainder of the alkyl halide–toluene solution was then added slowly and stirring continued at 40–50 °C for 2 h. The resulting clear, colorless solutions were used without removal of excess magnesium.

General Procedure for the Reaction of Alkyl Grignard Reagents–Triethylamine with 3 in Toluene. The Grignards prepared above (20–50% excess, 0.5 M solutions) were cooled to −78 °C in a dry ice–acetone bath and treated with 0.5–1.0 M solutions of **3** in toluene. The entire reaction was carried out under a dry nitrogen atmosphere in a three-necked flask fitted with a serum cap, addition funnel, and nitrogen inlet adapter. After **3** was added, the mixture was stirred overnight at −78 °C and then quenched with 1–2 mL of methanol. The mixture was poured into saturated ammonium chloride solution, the layers were separated, and the aqueous phase was washed twice with ether. The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo to leave an oil or solid **12** which was analyzed by H^1 NMR to determine the diastereomeric ratios (Table I). Analytically pure diastereomers of **12** were obtained by medium-pressure separations (see accompanying paper[22]).

Hydrolysis of 12 to α-Hydroxy Acids 13. (a) MeI-Me_2SO Method. A mixture of 8 mmol of **12**, 25 mmol of methyl iodide, and 3 mL of Me_2SO was stirred for 18–30 h at room temperature and monitored by TLC (30% acetone–hexane, silica gel) until the absence of starting material was indicated. The excess methyl iodide was removed in vacuo, the residual viscous red oil was treated with 25 mL of 2 N KOH and the mixture heated to reflux for 8 h. The resulting solution was extracted twice with 15-mL portions of ether to remove (1*S*,2*S*)-*N*-(methylamino)-3-methoxy-1-phenyl-1-propanol and the remaining aqueous phase acidified with 12 N HCl (0 °C) until it was acidic to pH paper. The hydroxy acid was extracted by three washings with 15-mL portions of methylene chloride and the organic phase washed with brine before drying ($MgSO_4$). Concentration of the solution gave the acidic product as a colorless solid.

(b) Triethyloxonium Fluoroborate Method. A 1–2 M solution of Et_3OBF_4[17] was prepared by drying the solid reagent in vacuo and then dissolving the material in methylene chloride in the absence of air and moisture. A volume of this solution containing 1 equiv of Et_3OBF_4 was introduced via syringe to a 1 M solution (containing 1 equiv) of **12** in methylene chloride. The mixture was stirred at room temperature overnight and the solvent removed in vacuo. After addition of 0.5–1.0 mL of Me_2SO and 25 mL of 2 N KOH, the solution was heated to reflux for 8 h and worked up as described in a part above.

Preparation of Ethyllithium. The procedure of Bryce-Smith[18] was followed. Thus, 6.00 g (0.90 mol) of lithium was cut into small pieces, washed with dry hexanes, and placed in a flask containing 120 mL of acid-washed pentane under argon. Ethyl bromide (39.20 g, 0.36 mol) in 120 mL of pentane was added over a 5-h period, maintaining a gentle reflux. After the mixture was stirred an additional hour, the pentane was removed by sweeping the flask with argon, and 100 mL of dry benzene added. The yellow solution was filtered through Celite in the absence of air and titrated by the method of Watson and Eastham.[19]

Preparation of Aryllithium Reagents by Metal–Halogen Exchange.[20] A 0.3–0.5 M solution of aryl bromide in THF was cooled to −78 °C under nitrogen and treated with an equivalent amount of *n*-butyllithium. In this manner, *p*-tolyllithium and α-naphthyllithium were prepared. *p*-Anisyllithium was generated by treating a 0.5 M solution of *p*-bromoanisole in ether with 1 equiv of *n*-butyllithium at room temperature for 30 min.

Preparation of 2-Thienyllithium. A 0.3–0.5 M solution of thiophene in THF was cooled to −78 °C and treated with 1 equiv of *n*-butyllithium. After the mixture was stirred 1–2 h at −78 °C, the organolithium reagents were ready for use.

General Procedure for the Reaction of Organolithium Reagents with 2-Benzoyloxazoline 3. The organolithium reagents prepared above (0.5 M solutions, 10–20% excess) were cooled to −78 °C in a dry ice–acetone bath and treated with 0.5–1 M solutions of 2-benzoyloxazoline **3** in THF. The reactions were stirred overnight at −78 °C and worked up as described in the procedure for alkyl Grignard reagents.

Reaction of Methyllithium with 3–Lithium Perchlorate Complex. Into a 50 mL, three-necked flask fitted with a nitrogen inlet, a serum cap, and an addition funnel was placed 0.6 g (5.5 mmol) of lithium perchlorate and 1.5 g (5.0 mmol) of 2-benzoyloxazoline **3** in 15 mL of ether. This was cooled to −78 °C, and 4.1 mL (5.5 mmol) of 1.35 M MeLi in 10 mL of ether was added over a 1-h period. After 18 h, the reaction was quenched with 1 mL of methanol and poured into 15 mL of saturated ammonium chloride. The aqueous layer was separated and extracted with ether (3 × 25 mL), and the organic layers were combined and dried (K_2CO_3). This material was then directly hydrolyzed under basic conditions to atrolactic acid by using MeI–Me_2SO.

Reaction of Methylmagnesium Bromide–TMEDA with 4. A solution of 4.1 mL (11.0 mmol) of 2.7 M MeMgBr in 95 mL of ether containing 1.3 g (11.0 mmol) of TMEDA was cooled, under nitrogen, to −78 °C. A solution of 2.8 g (10.0 mmol) of **4** in 100

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(17) Solid, stored under ether, purchased from Alfa Ventron.
(18) D. Bryce-Smith, *J. Chem. Soc.*, 861 (1953).
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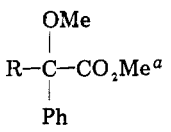
(20) B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, New York, 1974, Chapter 4.

Table III



R	$[\alpha]^{24}_D$ (c, EtOH)	amt $Eu(hfc)_3$, mg	% ee
n-Pr	+0.6 (6.3)	40	43 ± 5
i-Pr	−6.5 (3.4)	59	43 ± 5
i-Bu	+1.3 (3.1)	46	57 ± 5
α-naphthyl	−29.2 (1.3)	8	58 ± 5
p-anisyl	−2.2 (3.2)	18	55 ± 5
2-thienyl	−16.0 (2.0)	67	65 ± 5

[a] In $CDCl_3$ (30 mg of compound/0.5 mL of $CDCl_3$).

mL of ether was added dropwise over a 4-h period, and the reaction mixture was stirred for 33 h at −78 °C, at which time it was quenched with 2 mL of methanol and poured into 100 mL of saturated ammonium chloride. After the mixture reached room temperature, the aqueous phase was separated and extracted with ether (3 × 50 mL), and the organic phases were combined and dried over $MgSO_4$. Concentration in vacuo afforded 2.6 g of an oil which was purified by medium-pressure LC (20% acetone–hexane on silica) to yield 1.7 g (59%) of the α-methyl-α-hydroxy derivative **14** along with 0.8 g of starting material **4**: NMR of **14** (CCl_4) δ 7.25 (s, 5), 5.40 (d, 1), 3.20–4.30 (m, 7), 0.60–2.00 (m, 12); IR (neat) 3300–3500, 1660 cm^{-1}; $[\alpha]^{24}_D$ −37.6° (*c* 4.5, $CHCl_3$).

2-Hydroxy-2-methylhexanoic Acid (15). The α-hydroxyoxazoline from above (1.7 g) was stirred with 10 mL of MeI and 3 mL of Me_2SO for 20 h and the excess MeI removed in vacuo, leaving a red oil. The residue was treated with 25 mL of 2 N KOH and heated to reflux for 1 h. The mixture was extracted with ether (2 × 15 mL) and the ethereal layer discarded. The aqueous phase was acidified to pH ~7 with 4.2 mL of 12 N HCl, saturated with solid sodium chloride, and extracted with methylene chloride (3 × 25 mL). The organic layer was washed with 25 mL of brine and the aqueous salt solution back-extracted with 25 mL of methylene chloride. All the organic layers were combined and dried over $MgSO_4$. Filtration and concentration of the methylene chloride solution left a brown oil which was passed through a short (10 cm) column of silica gel with 20% acetone–hexane. Concentration of the eluent gave a colorless solid: 0.6 g (71%); mp 68–71 °C; NMR (CCl_4) δ 7.78 (br s, 2), 1.60–2.20 (m, 9), 1.45 (s, 3); IR (mineral oil) 3420, 1710 cm^{-1}; $[\alpha]^{24}_D$ 6.1° (*c* 1.0, H_2O) [lit.[21] $[\alpha]_D$ −8.2° (*c* 1.0, H_2O)]. Recrystallization from hexane–ether (10:1) gave a colorless solid: mp 68–70 °C; $[\alpha]^{24}_D$ −7.75° (*c* 0.85, H_2O), 95% optical purity.

Determination of Enantiomeric Excess of 13 (Methyl ester, Methyl Ether). A solution of 0.28 g of acid **13** in 3 mL of ether, cooled to 0 °C, was treated with an ethereal solution of diazomethane (from *N*-nitrosomethylurea) until the yellow color persisted. The solvent was removed by a stream of nitrogen, and the residue was redissolved in ether, filtered, and concentrated to give the methyl ester in 97% yield. The hydroxy esters in THF were treated with 1.5 equiv of sodium hydride by stirring, under nitrogen, overnight. Methyl iodide (1.5 equiv) was added, and the solution was stirred for 2 days, quenched with several drops of water, and poured into ether. The ethereal solution was washed with saturated ammonium chloride, dried (K_2CO_3), and concentrated to give the α-methoxy esters which were subjected to NMR studies using [tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]]europium(III) (Aldrich, OP-II). Listed in Table III are the specific rotations of the esters examined, the milligrams of OP-II used to achieve maximum methyl peak separation, and the percent enantiomeric excess as determined by both electronic integration of the NMR signal and triangulation. The percent enantiomeric excesses for compounds **13** in Table I are calculated on specific rotations for optically pure **13** obtained by resolution (medium-pressure LC) of **12**.[22]

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Registry No. **1**, 58635-82-8; **2**, 73713-17-4; **3**, 63007-15-8; **4**, 73713-18-5; **5**, 73713-19-6; **6**, 73713-20-9; **7**, 73713-21-0; **8**, 73713-22-1; **9**, 56613-81-1; **10**, 73713-23-2; **11**, 73713-24-3; **12** (R = Me) isomer 1, 63007-16-9; **12** (R = Me) isomer 2, 63007-17-0; **12** (R = Et) isomer 1, 69766-02-5; **12** (R = Et) isomer 2, 69766-03-6; **12** (R = *n*-Pr), 73697-92-4; **12** (R = *n*-Pr) isomer 2, 73697-93-5; **12** (R = *i*-Pr) isomer 1, 73712-27-3; **12** (R = *i*-Pr) isomer 2, 73697-94-6; **12** (R = *i*-Bu) isomer 1, 73697-95-7; **12** (R = *i*-Bu) isomer 2, 73697-96-8; (*S*)-**13** (R = Me), 13113-71-8; (*R*)-**13** (R = Me), 3966-30-1; (*S*)-**13** (R = Et), 24256-91-5; (*R*)-**13** (R = Et), 3966-31-2; (*S*)-**13** (R = *n*-Pr), 73698-05-2; (*S*)-**13** (R = *i*-Pr), 73746-01-7; (*S*)-**13** (R = *i*-Bu), 73698-06-3; (*S*)-**13** (R = *p*-tolyl), 52166-05-9; (*R*)-**13** (R = *p*-tolyl), 51999-09-8; (*S*)-**13** (R = *p*-anisyl), 73698-07-4; (*S*)-**13** (R = 1-naphthyl), 73698-08-5; (*S*)-**13** (R = 2-thienyl), 64471-38-1; **14**, 73713-25-4; **15**, 70954-68-6; **16**, 73713-26-5; methyl (*S*)-α-methoxy-α-phenylpentanoate, 73713-27-6; methyl (*S*)-2-methoxy-3-methyl-2-phenylbutanoate, 73713-28-7; methyl (*S*)-2-methoxy-4-methyl-2-phenylpentanoate, 73713-29-8; methyl (*S*)-α-methoxy-α-phenyl-1-naphthaleneacetate, 73713-30-1; methyl (*S*)-α,*p*-dimethoxy-α-phenylbenzeneacetate, 73713-31-2; methyl (*S*)-α-methoxy-α-phenyl-2-thiopheneacetate, 73713-32-3; *trans*-(4*S*,5*S*)-2-ethyl-4-(methoxymethyl)-5-phenyl-2-oxazoline, 51594-37-7; D-phenylalanine, 673-06-3; D-(+)-2-amino-3-phenyl-1-propanol, 5267-64-1; ethyl iminophenylacetate hydrochloride, 5442-34-2; D-(−)-phenylglycine, 875-74-1; D-(−)-2-amino-2-phenyl-1-ethanol, 56613-80-0; L-(+)-mandelic acid, 17199-29-0; L-(+)-mandelamide, 24008-63-7; bromomethylmagnesium, 75-16-1; methyllithium, 917-54-4; bromoethylmagnesium, 925-90-6; bromopropylmagnesium, 927-77-5; bromoisopropylmagnesium, 920-39-8; bromoisobutylmagnesium, 926-62-5; *p*-tolyllithium, 2417-95-0; *p*-anisyllithium, 14774-77-7; 1-naphthyllithium, 14474-59-0; 2-thienyllithium, 2786-07-4.

(21) Dr. R. Pappo and G. D. Searle, Skokie, IL, private communication.

(22) A. I. Meyers and J. Slade, *J. Org. Chem.*, accompanying note in this issue.