Asymmetric Carbon–Carbon Bond Formation from Chiral Oxazolines

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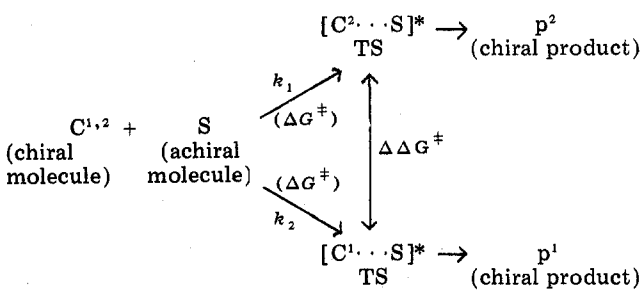
Asymmetric synthesis has long been a coveted goal for organic chemists. Unfortunately, the extensive efforts attempting to design efficient asymmetric syntheses have not borne fruit in proportion to the efforts expended. An excellent monograph by Morrison and Mosher[1] has summarized the attempts at achieving what only enzymes have done best—preparation of compounds of high enantiomeric purity. They have traced the history dealing with this subject through 1970, and the reader will find but a handful of useful synthetic techniques. In 1974, Scott and Valentine[2] discussed this subject in *Science* and covered the progress made since Morrison and Mosher's monograph. Two additional reviews, Kagan and Fiaud[3a] and Valentine and Scott,[3b] bring the subject through 1977. As the reader proceeds from the reviews of Morrison and Mosher (1971), to Scott and Valentine (1974), to the two reviews in 1978, he is struck by the tremendous increase in the efficiency of asymmetric synthetic methodology. The last 7 to 8 years have seen a number of investigations which have lent some credence to the notion that modern synthetic methodology may have reached the level of sophistication to properly meet this challenge. Although organic chemists have made tremendous strides in introduction and transposition of functional groups, stereoselective synthesis, and construction of molecules with highly complex architecture, viable asymmetric synthesis still remains a seriously underdeveloped area.

The reasons for this are many, but the single most important reason lies in the lack of understanding and control of transition-state geometry. It is this phenomenon which solely dictates which reaction profile (p^1 or p^2) will predominate. The ratio p^1/p^2 is a function of the relative rate constants, k_1, k_2 leading to the respective diastereomeric transition states (see Scheme I). Thus, identical or comparable reaction rates for each process will result in racemic or only slightly enriched enantiomeric excess of the desired product, neither of which is of any value to the desired goals. Since the competing processes are dependent on the free energy of activation ($\Delta G^{\ddagger}$) for each of them, the magnitude of the differences in this term ($\Delta\Delta G^{\ddagger}$) will be solely responsible for the ratio of enantiomeric products (p^1, p^2). A $\Delta\Delta G^{\ddagger}$ value of approximately 2 kcal at 0 °C is considered necessary to provide one of the enantiomeric products (p^1 or p^2) in at least an 80% excess (90:10 mixture of enantiomers), and this ratio

Scheme I



may be construed as synthetically useful. Herein lies the crux of the problem—how can an asymmetric synthesis be designed such that the two competing transition states, extremely similar in electronic and steric factors, exhibit a $\Delta\Delta G^{\ddagger}$ of approximately 2–3 kcal?

Although several attempts[4,5] using mathematical treatments have been made to predict the efficiency of an asymmetric synthesis (including absolute configuration of the products) without any experimental details pertaining to the geometric factors in the transition state, most of the efforts to date have been empirical experimental studies utilizing steric effects. This Account will focus on studies initiated in the author's laboratory in 1974 which have, in the main, borne fruit with regard to useful asymmetric carbon–carbon formation. It should be said at the outset that highly successful asymmetric carbon–hydrogen bond formations have been reported by the Monsanto group,[6] Kagan,[7] and Bosnich,[8] in transforming certain prochiral unsaturated amino acids to virtually enantiomerically pure α-amino acids. However, at the time these studies were initiated, there were virtually no C–C bond reactions with simultaneous enantiomeric selectivity that were considered useful.[1] It would be pleasant to relate that these studies began with an air of hope involving a totally new concept for asymmetric synthesis, but this was not the case. The program was undertaken with the usual level of curiosity that dictates most chemical studies. However, as happens in so many cases, these

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(1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971.
(2) J. W. Scott and D. Valentine, Jr., *Science*, **184**, 943 (1974).
(3) (a) H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, **10**, in press; (b) D. Valentine, Jr., and J. W. Scott, *Synthesis*, in press.
(4) E. Anders, E. Ruch, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **12**, 25 (1973).
(5) L. Salem, *J. Am. Chem. Soc.*, **95**, 94 (1973).
(6) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. Weinkauf, *J. Am. Chem. Soc.*, **97**, 2569 (1975).
(7) H. B. Kagan and T. P. Dang, *J. Am. Chem. Soc.*, **94**, 6429 (1972); G. Gelbard, H. B. Kagan, and R. Stern, *Tetrahedron*, **32**, 233 (1976).
(8) M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.*, **99**, 6262 (1977).

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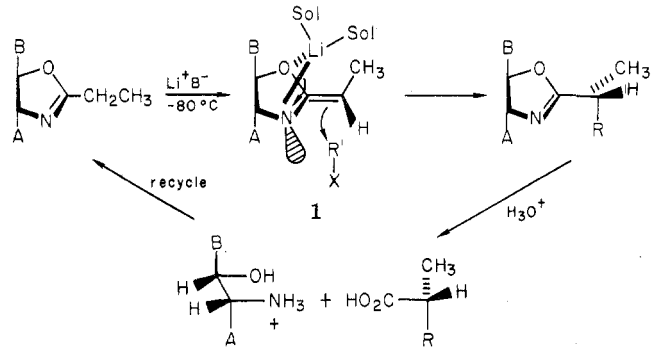
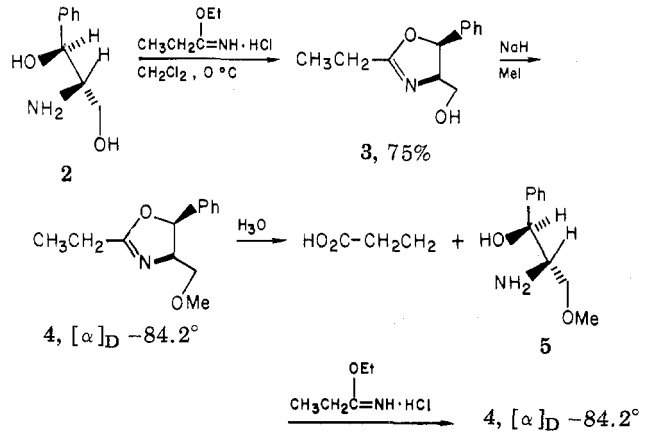
Scheme II



Scheme III



Scheme IV

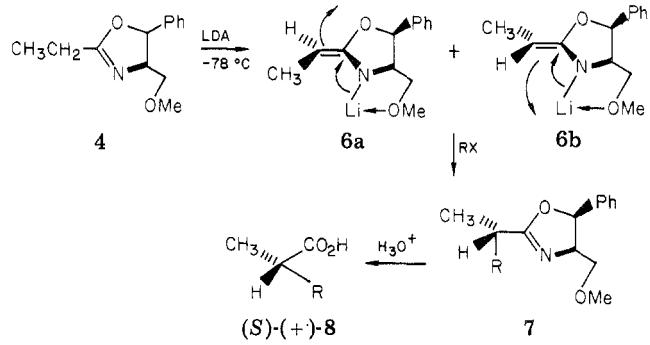
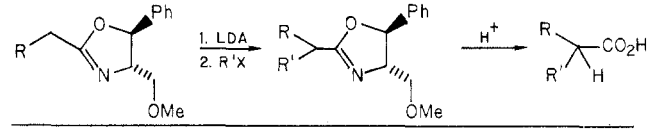


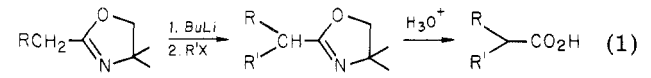
Table I
Alkylation of Oxazolines to Produce (*R*)- or (*S*)-Dialkylacetic Acids 8



		α,α-dialkylacetic acids		
R	R′X	% yield	% ee	conf'n
Me	EtI	84	78	*S*
Et	Me_2SO_4	83	79	*R*
Me	*n*-PrI	79	72	*S*
n-Pr	Me_2SO_4	75	72	*R*
Et	$PhCH_2Cl$	30	85	*S*
$PhCH_2$	EtI	37	73	*R*
n-Bu	$PhCH_2Cl$	41	82	*S*
$PhCH_2$	*n*-BuI	39	86	*R*

studies shed light on an aspect of asymmetric synthesis that has been responsible for a number of successes in laboratories in addition to the author's.

The potential asymmetric synthesis which initiated this effort was based upon earlier work[9] from this group involving metalation and alkylation of 2-alkyl-2-oxazolines, followed by hydrolysis, to furnish α,α-dialkylacetic acids (eq 1). This process was performed



(1)

in aprotic media (Et_2O, THF, DME) and was highly efficient at low temperatures (e.g., −80 to −98 °C). As seen from the scheme, the net result was α-alkylation to give a carboxylic acid which possessed an asymmetric center when R ≠ R′. This reaction appeared to have all the qualities needed for an asymmetric synthesis if a *chiral* oxazoline could be readily obtained. Thus, a chiral oxazoline could be utilized to transfer chirality to the exocyclic α position involved in the new C–C bond (Scheme II). This sequence would provide a chiral α-substituted acetic acid and, as known from the earlier work,[9] allows ready recovery of the chiral amino alcohol which may be recycled to starting material, provided no racemization occurred during the process. Another aspect of this rationale was the strong coordination ability of lithium ions to electron-rich atoms, and it was anticipated that the lithiooxazoline **1** would preferentially exist in some rigid chelate providing certain topological features which would influence the direction of approach by the alkyl halide.[10] In this case, the solvated lithium ion would present itself as a temporary bulky substituent directing entry of the alkyl halide from the opposite side.

The simplest and most direct route to a chiral oxazoline was found to arise out of the chiral, inexpensive, amino diol **2** manufactured in large quantity by Parke-Davis (Scheme III). Reaction of this diol with the imino ether of propionitrile gave the chiral oxazoline **3** (75%). However, the hydroxymethyl group in **3** appeared to be an unnecessary nuisance and was transformed into the methyl ether **4** so as not to interfere with the metalation step to follow later. Furthermore, it was found that **4** could be hydrolyzed to release the carboxylic acid and the recovered methoxy amino alcohol **5**. The latter was transformed into **4** by re-use of the imino ether. The samples of **4** had identical specific rotations, assuring us that no racemization of **5** had occurred during the hydrolysis. Thus, it was possible to recycle the chiral amino alcohol for further use.

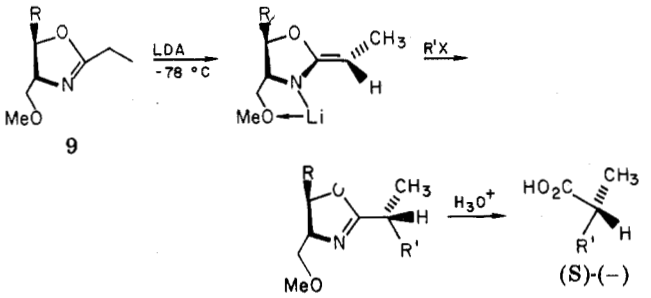
(*R*)- and (*S*)-Dialkylacetic Acids

The chiral oxazoline **4** was metalated with various bases (*n*-BuLi, *t*-BuLi, LDA, LiTMP), but the most efficient and convenient turned out to be LDA (lithium diisopropylamide). The resulting lithio salts (**6a,b**) were treated with various alkyl halides and furnished the alkylated oxazoline **7** in 80–98% yields. Without any purification, principally to avoid inadvertent resolution of the diastereomers present in **7**, hydrolysis in aqueous acid was carried out to produce a series of 2-methylalkanoic acids **8** in 70–85% enantiomeric excess

(9) A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2778 (1974).

(10) Lithium chelation has since been noted to provide certain steric features to alkylation reactions; cf. K. Kitani and H. Nozaki, *J. Am. Chem. Soc.*, **97**, 949 (1975).

Scheme V



R	R'X	% ee	R	R'X	% ee
Ph	$PhCH_2Cl$	77	Ph	BuI	78
Me	$PhCH_2Cl$	47	Me	BuI	7.2
H	$PhCH_2Cl$	24	H	BuI	3.5

(Scheme IV). Each of the chiral acids thus formed possessed the *S* configuration.[11] Furthermore, when the alkyl group introduction was reversed, the acids were formed in comparable enantiomeric purity with the opposite configuration (Table I). The significant features of this reaction are twofold: (a) *It is possible to prepare either enantiomer of chiral α-substituted acids from a single enantiomeric oxazoline*, and (b) *the chiral acids are prepared with predictable absolute configuration.* Thus, one of the bonuses for achieving an efficient asymmetric synthesis is the fact that, along with the acquisition of chiral compounds, the absolute configuration of the products is made known simultaneously. In the above cases, if the group of lower priority (Cahn–Ingold–Prelog rule) is introduced first, the acids will have the *S* configuration, while if the group of higher priority is introduced first, the acids will have the *R* configuration.

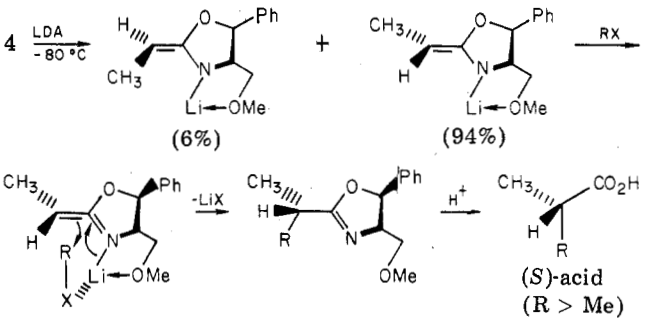
A number of studies were carried out to assess the mechanism for this process, and some are still in progress. However, some factors important in this reaction may be mentioned at this time.

The enantiomeric purity of the acids was unaffected by metalation temperatures, but was drastically dependent upon the alkylation temperatures. This indicates that an overwhelming ratio favoring one of the lithio salts (**6a** or **6b**) may be formed at all temperatures of deprotonation (kinetic control) and the entry of the alkyl halide is distributed between topside and bottomside to various extents at different temperatures. Studies to determine whether the alkyl halide approaches from the *topside* or *bottomside* of **6a** or **6b** were made since only these modes of entry could account for the configuration of the acid isolated.

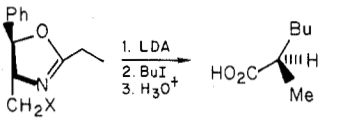
A series of chiral oxazolines **9** was prepared and subjected to the metalation–alkylation–hydrolysis sequence in Scheme V.[12] These oxazolines differed only in the nature of the "topside" substituent (Ph, Me, H) and were alkylated using either benzyl chloride or *n*-butyl iodide. As seen in Scheme V, the % ee of the chiral acid dropped off drastically when the topside substituent was decreased in bulk from Ph to Me to H. This indicates that the entry of the alkyl halide is predominantly from the bottomside so long as there is a large (phenyl) group protecting the topside of the lithiooxazoline. Another experiment was performed to assess whether the methoxy group in the oxazolines

(11) A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Am. Chem. Soc.*, **98**, 567 (1976).
(12) A. I. Meyers, A. Mazzu, C. E. Whitten, *Heterocycles*, **6**, 971 (1977).

Scheme VI



(originally thought to be superfluous) played any significant role. The oxazoline **10** was prepared from (+)-norephedrine and the synthesis of 2-methylhexanoic acid compared with that obtained with **4** (eq 2). The



(2)

10 (X = H), % ee = 12
4 (X = OMe), % ee = 74

% ee of the acid derived from **10** was only 12%. This means that the methoxyl group, considered to be a "nuisance" at the outset of these studies, was indeed critical to its success.

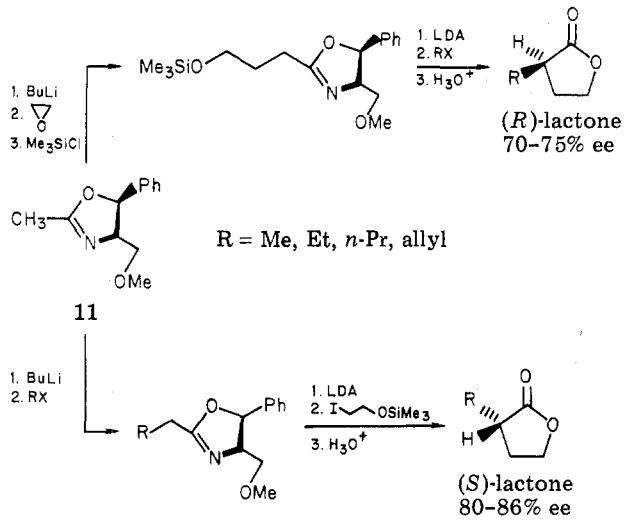
In order to assess the relative amounts of the lithio salts **6a** and **6b** present prior to alkylation, ^{13}C NMR spectra were recently taken in THF solution under preparative conditions (LDA, −80 °C) using 50% enriched methyl-^{13}C in **4**. The ratio of **6a** to **6b** as seen by the signals of the syn and anti enriched methyl were found to be 94:6. At −30 °C the ratio **6a**/**6b** varied only slightly to 88:12.[13] Although the low-temperature ^{13}C spectra do not indicate whether **6a** or **6b** is present in 94%, the probability of **6a** being in excess is supported by the absolute configuration of the chiral acids. This information, coupled with the substituent effects mentioned above, allows a sequence to be written (Scheme VI) to account for the experimental observations involving metalation and alkylation. The fact that one of the lithio salts is favored on metalation by approximately 9:1 and the presence of the phenyl group on the topside of the lithiooxazoline hinders topside entry indicate that the alkyl halide enters from the bottom. The degree to which topside entry occurs is dependent upon the temperature of alkylation since lower temperatures are likely to slow the rate and increase the selectivity of approach. It must also be stated at this time that the original choice of the amino diol **2** was indeed a fortunate one since it possessed all the features necessary for success.

(*R*)- or (*S*)-2-Alkylbutyrolactones and -valerolactones

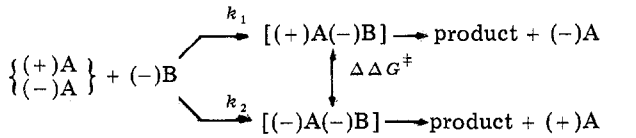
The extension of this asymmetric synthesis to chiral lactones was investigated and found to proceed as expected (Scheme VII). Utilizing the now commercially available[14] chiral oxazoline **11** as a starting material, the choice of introduction of alkyl groups leads to either the (*R*)- or the (*S*)-2-substituted butyrolactones.[15] In the sequence leading to the (*S*)-lactones,

(13) A. I. Meyers, E. Snyder, and J. J. Ackerman, unpublished results.
(14) Aldrich Chemical Co., Milwaukee, Wis.

Scheme VII

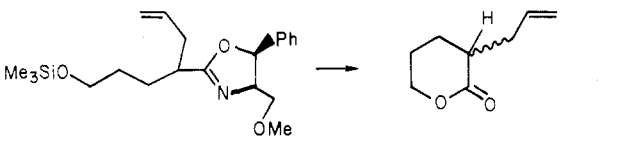


Scheme VIII



ethylene oxide could not be used due to its poor reactivity at temperatures below −60 °C. This problem was readily circumvented by employing an ethylene oxide equivalent [2-(trimethylsiloxy)ethyl iodide].

In a similar fashion, chiral valerolactones **13** were prepared using the homologue **12**. Thus, employing



12 **13**, (*R*)-(−) or (*S*)-(+)

the three-carbon electrophile [$Me_3SiO(CH_2)_3I$] in either order of addition led to either enantiomer of valerolactones.[16] The enantiomeric excess of the lactones is as yet undetermined although a number of attempts have been made using chiral shift reagents and several recent techniques involving diastereomeric separations.[17] However, based upon the previous results, the absolute configurations of the (−) and (+) enantiomers may be reliably assigned *R* and *S*, respectively.

Kinetic Resolution of (±)-Alkyl Halides

The preferential reaction of a chiral reagent (e.g., (−)-B) with a racemic substrate (±)-A such that one of the enantiomers of A is affected is termed a kinetic resolution[1] (Scheme VIII). The success of the resolution depends upon the degree of chiral recognition exhibited by (−)-B. Kinetically this means that the relative rate constants k_1 or k_2 are sufficiently different that the diastereomeric transition states (Scheme VIII, in brackets) are reached at different rates, which results in an unequal proportion of the respective products. This also means that one of the enantiomers of A is recovered in excess at the end of the reaction. Based upon the unusual steric features of the chiral lithiooxazolines, it was of interest to determine whether they would possess chiral recognition with respect to racemic alkyl halides. The experiment was designed such that 1.0 equiv of the lithiooxazoline **14** (Scheme IX) would be allowed to react with 2.0 equiv of racemic halide. If the competing rates (k_S and k_R) were sufficiently different, then the products should contain, after workup and hydrolysis of the alkylated oxazoline, β,β-dialkylpropionic acid and recovered excess halide both enantiomerically enriched. However, if k_R and k_S are very similar, then both the recovered halide and the chiral acid would be essentially racemic. As it turned out, the lithiooxazoline **14** did exhibit a significant degree of chiral recognition and $k_S > k_R$ leading to the (*R*)-carboxylic acid (**16b**) and recovery of the (*R*)-halide.[18] Some examples using different racemic halides are presented in Table II. The acquisition of the (*R*)-acid and recovered (*R*)-halide simply means that the (*S*)-halide reacts faster (k_S) with the chiral lithiooxazoline, resulting in inversion which ultimately produces the (*R*)-acid. Molecular models of **15a** and

Scheme IX

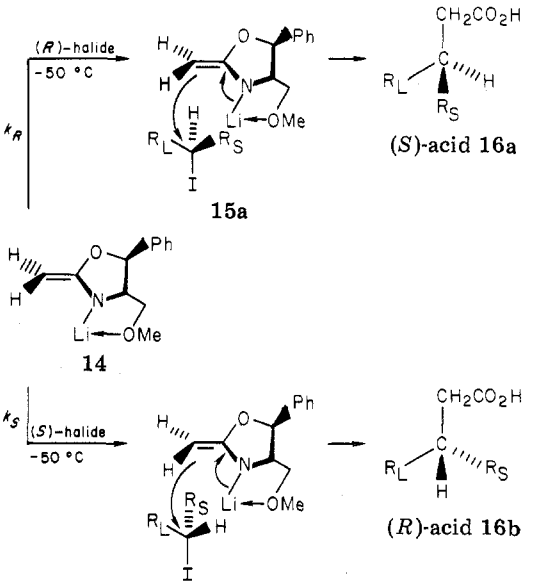


Table II
Kinetic Resolution of Racemic Halides with Lithiooxazoline 14

(±)-alkyl iodide[a]		T, °C	recovered iodide		carboxylic acid 16b	
R_L	R_S	(alkyn)	% ee	conf'n	% ee	conf'n
Et	Me	−65	34	*R*	34	*R*
n-Pr	Me	−65	30	*R*	39	*R*
n-Bu	Me	−65	49	*R*	47	*R*
n-Hex	Me	−70	31	*R*	39	*R*
n-Pr	Et	−50	[31][b]	*R*	31	*R*
n-Bu	Et	−50	(46)[c]	*R*	(20)[c]	*R*
n-Amyl	Et	−50	[58][b]	*R*	58	*R*

[a] Two equivalents of alkyl iodide used for every equivalent of lithiooxazoline 14. [b] Not reported in the literature; estimated % ee based on recovered acid. [c] Based on $[\alpha]_D$ observed divided by $[\alpha]_D$ reported. The huge discrepancy in % ee implies that the reported $[\alpha]_D$ values for the optically pure compounds are incorrect.

(15) A. I. Meyers and E. D. Mihelich, [*J. Org. Chem.*, **40**, 1186 (1975)] report the synthesis of the (*R*)-lactones. The (*S*)-lactones will be published in due course.

(16) A. I. Meyers and R. A. Bell, unpublished results.

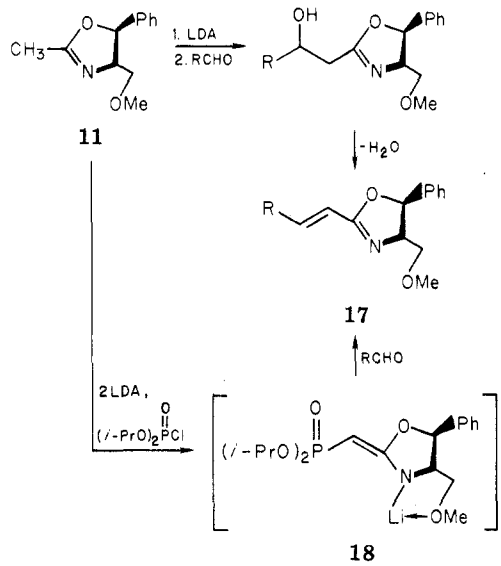
(17) W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, **42**, 384 (1977); G. Saucy, R. Borer, D. P. Trullinger, J. B. Jones, and K. P. Lok, *ibid.*, **42**, 3207 (1977).

(18) A. I. Meyers and K. Kamata, *J. Am. Chem. Soc.*, **98**, 2290 (1976).

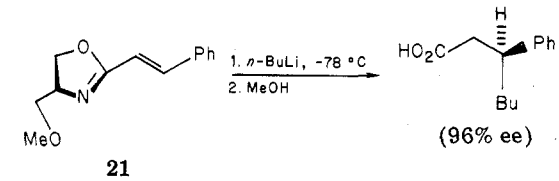
15b support the contention that the (*S*)-halide may approach the transition state with less crowding than the *R* enantiomer. Furthermore, the kinetic resolution failed completely in the absence of the "topside" phenyl substituent.[12] Although the percent asymmetric synthesis (% ee) is not high enough to make this process a synthetically useful one for alkyl halides and β,β-dialkylpropionic acids, it does provide a simple method to correlate absolute configuration of two unrelated classes of compounds—alkyl iodides (chlorides and bromides alkylate poorly in this sequence) and the β,β-dialkylpropionic acids. The method gives both products of the *R* configuration, allowing ready assignment without the need for any optically active materials except the commercially available oxazoline **11**. Two additional bonuses that arise from this method are: (a) relating configurations of alkyl halides to alcohols and vice versa since the Horeau method[19] has proven very useful for determining alcohol configurations; by employing both methods, the danger of misassignment of enantiomers in the halide-to-alcohol interconversion is essentially eliminated; (b) allowing the prediction of $[\alpha]_D$ for optically pure iodides or the acids provided one of them is reliably known. An example is given in Table II (footnote *b*) which states that the % ee of the iodide must be the same (or within 5%) of the acid (31% ee). This information, coupled with the specific rotation of the recovered iodide, will simply lead to the $[\alpha]_D$ for the pure iodide.

(*R*)- or (*S*)-β,β-Dialkylpropionic Acids

Throughout this discussion chiral oxazolines have been employed as chiral nucleophilic reagents. A study was also initiated to assess the oxazolines in a reversed role—chiral electrophiles.[20] Toward this end, vinyloxazolines (**17**) were prepared from the 2-methyl de-



rivative **11** using two routes. The route involving the intermediacy of the phosphonate **18** is distinctly superior and provides high yields of the pure *E* isomer of **17**.[21] Addition of a series of alkyl- and aryllithium reagents to **17** gave, after quenching, the alkylated oxazoline, **20**. Hydrolysis of the latter led to β,β-disubstituted propionic acids **16** in good chemical yield, but more significantly in very high enantiomeric purity (Scheme X and Table III). The proposed mechanism involved prior coordination of the organolithium reagent to the methoxyl and lone pair on nitrogen such that the alkyl group is situated at the underside of the oxazoline ring. Addition then takes place as shown in **19** to furnish the new chiral C–C bond. Once again, reversing the order of the alkyl (or aryl) group produces the enantiomeric product (Table III, examples in braces). In order to substantiate the claim that the alkyllithium approaches from the underside due to methoxyl chelation, the oxazoline **21**, derived from



(*S*)-serine, was treated in a similar manner and gave 3-phenylheptanoic acid in 96% ee.[22] This lends considerable credence to the underside approach of alkyllithium reagents to the alkenyloxazolines since removal of the large phenyl group from the topside had no effect on the efficiency of the asymmetric alkylation. Furthermore, replacement of the methoxyl group by hydrogen resulted in a drastic drop in the asymmetric alkylation (<15% ee), adding more evidence that

Scheme X

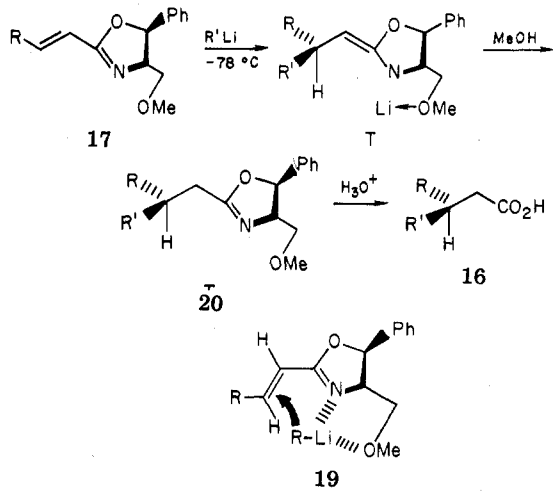


Table III
β,β-Disubstituted Propionic Acids 16 from Alkenyloxazolines 17

R (in 17)	R'Li	% yield of 16	% ee of 16	Conf'n[a]
Me	EtLi	38	92	*R*
Me	PhLi	34	98	*S*[a]
Et	*n*-BuLi	50	97	*R*
{Et[a]	{PhLi[a]	31	92	{*S*[a]
{Ph[a]	{EtLi[a]	66	97	{*R*[a]
cyclohexyl	EtLi	75	99	*R*
cyclohexyl	*n*-BuLi	76	>99	*R*

[a] All acids are configurationally related; the *S,R* notations change due to priority of phenyl over alkyl.

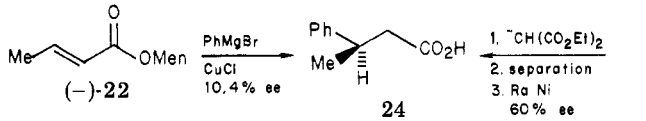
(19) A. Horeau, *Tetrahedron Lett.*, 506 (1962); A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964); A. Horeau and A. Nouaille, *Tetrahedron Lett.*, 3953 (1966); A. Horeau, A. Nouaille, and K. Mislow, *J. Am. Chem. Soc.*, **87**, 4957 (1965); R. Weidman and A. Horeau, *Bull. Soc. Chim. Fr.*, 117 (1967).

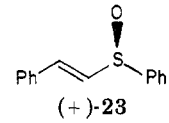
(20) A. I. Meyers and C. E. Whitten, *J. Am. Chem. Soc.*, **97**, 6266 (1975).

(21) A. I. Meyers and R. K. Smith, unpublished results.

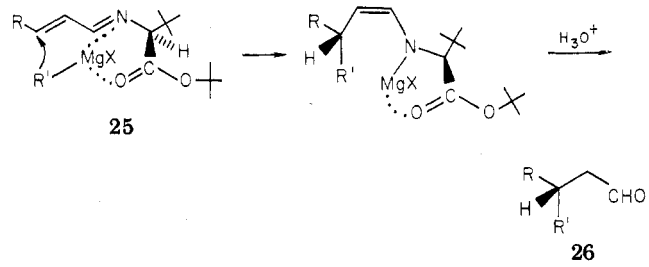
(22) A. I. Meyers and C. E. Whitten, *Heterocycles*, **4**, 1687 (1976).

lithium ion–alkoxyl interaction plays an important role in the success of these asymmetric reactions. The success of these conjugate addition reactions to chiral electrophilic olefins must be contrasted to the previous attempts to implement asymmetric syntheses of this type. The use of menthyl crotonates **22** gave, upon





addition of PhMgBr, the acid **24** in only 10% ee.[23] In a related example[24] the chiral sulfoxide **23** produced a 4:1 mixture of diastereomers (60% ee) which were first separated by crystallization and then the purified material subjected to desulfurization and decarboxylation to provide **24** in "95% ee". This, of course, is the result of a resolution rather than a true asymmetric synthesis. Note that neither of the above cases possessed any chelating groups to assist the directed entry of the nucleophilic reagent. Recently, the concept of chelation to provide rigid intermediates in asymmetric synthesis was reported by Koga[25] and represents further support for the need to invoke this phenomenon. Chelation of the Grignard to the unshared pairs on N and O (as in **25**) provided the necessary rigidity for

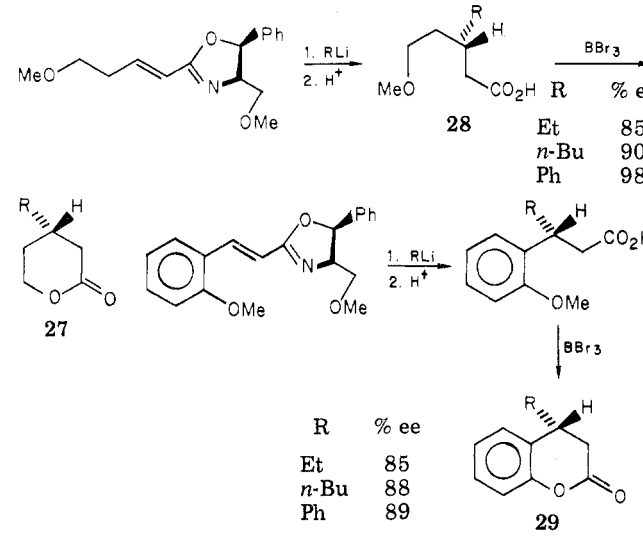


highly stereoselective alkyl addition. Hydrolysis produced the aldehydes **26** which were reduced to the alcohols previously known in the literature. Except for one example (63% ee), there were five different alcohols that were isolated in 91–98% ee. It is important to note that the main difference between the success of this work and the poor results obtained with **22** was the presence of suitably disposed ligands to complex the magnesium in the entering Grignard reagent.

β-Substituted Valerolactones

Extending the studies given in Scheme X has led to valerolactones **27** with chirality centered at the β carbon as well as 5-methoxy-3-alkylcarboxylic acids **28**.[26] The sequence is similar to that already described except that another functional group is present in the reactants. The lactones **27** were obtained in good yields (40–60%) and in quite high enantiomeric purity (determined by chiral shift reagents) (see Scheme XI). In a variation of this method, benzo derivatives **29** were prepared as

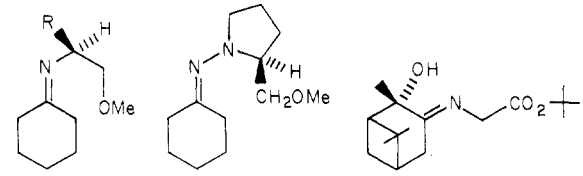
Scheme XI



shown and also were isolated in chemical yields of 70–87% and enantiomeric purity in the vicinity of 90%.

Conclusion

The previous discussion was a survey of the efforts made in these laboratories since 1974 dealing with asymmetric synthesis. The results show clearly that certain factors are indeed critical for success in this area. The ancient belief that bulky substituents in chiral reagents are necessary must be tempered somewhat due to the wholesale lack of success over the past 60 years. On the other hand, the need for in situ generation of sterically endowed groups through chelation has indeed proved to be a vital parameter in these processes. It is gratifying to see this concept continue to bear fruit. In the last several years, additional successes have been announced using internal chelation to effect efficient asymmetric synthesis. The use of chiral lithio salts derived from **30**,[27] **31**,[28] and **32**[29] have yielded alkylated



ketones and amino acids in useable enantiomeric purities for further synthesis. If the methoxyl group is absent (e.g., in **30**), the alkylation of these substances drops to 20–35%.[30] Current work in the author's laboratory and others, based upon the premise that steric effects generated via chelation, along with other bulky substituents or symmetry elements,[31] have continued to show considerable promise and will be reported in the future.

It is somewhat ironic that, in order to develop useful asymmetric methodology, organic chemists will have to

(23) H. M. Walborsky and Y. Inouye, *J. Org. Chem.*, **27**, 2707 (1962).
(24) G. Tsuchihashi, S. Mitamura, S. Inoue, and K. Ogura, *Tetrahedron Lett.*, 323 (1973).
(25) S. Hashimota, S. Yamada, and K. Koga, *J. Am. Chem. Soc.*, **98**, 7451 (1976).
(26) A. I. Meyers and C. E. Whitten, *Tetrahedron Lett.*, 1947 (1976).
(27) A. I. Meyers, D. R. Williams, and M. Druelinger, *J. Am. Chem. Soc.*, **98**, 3032 (1976); J. K. Whitesell and M. A. Whitesell, *J. Org. Chem.*, **42**, 378 (1977); S. Hashimoto and K. Koga, *Tetrahedron Lett.*, 573 (1978).
(28) D. Enders and H. Eichenauer, *Angew. Chem., Int. Ed. Engl.*, **15**, 549 (1976).
(29) S. Yamada, T. Oguri, and T. Shioiri, *J. Chem. Soc., Chem. Commun.*, 136 (1976).
(30) M. Kitomoto, K. Horoi, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.*, **22**, 459 (1974).
(31) J. K. Whitesell and S. W. Felman, *J. Org. Chem.*, **42**, 1663 (1977).

relearn how to prepare all the simple functionalized molecules that are considered trivial by current standards. However, progress in the past few years has indeed been impressive, and methodology is hopefully now firmly footed on the path to this goal. The words of Winston Churchill[32] seem particularly appropriate at this time:

"This is not the end···it is not even the beginning of the end···but, it is, perhaps, the end of the beginning."

(32) W. L. S. Churchill (Nov 10, 1942) in a speech at Mansion House after the first major British victory at El Alamein.

I wish to express my sincere gratitude to my able co-workers whose names appear in the footnotes and to the National Science Foundation, the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for providing us with generous financial assistance during the course of this work.

Ground-State and Excited-State Chemistry of Succinimidoyl Radical and Its Congeners

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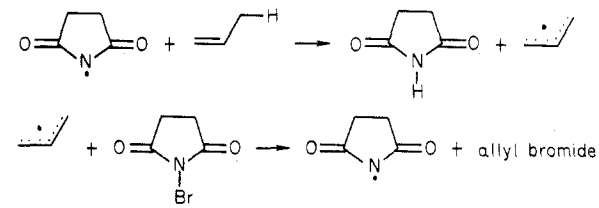
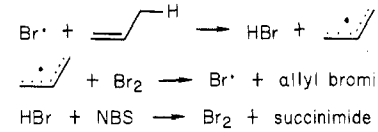
Prior to recent work, succinimidoyl radical chemistry was virtually unknown, despite a number of serious efforts. This once elusive radical system is now accessible, and the study of its reactions has yielded a number of surprises. The radical is unexpectedly reactive (early thinking suggested the opposite) in hydrogen abstractions and additions to double bonds and arenes. Further surprises resulted from the recognition that two succinimidoyl radicals were being produced, radicals with quite distinctive properties. Also, some interesting features along the way produced such questions as (1) when does a reaction take the less exothermic of two pathways and (2) are all structures contributors to a resonance hybrid structure?

Interest in the succinimidoyl radical can be traced to the recognition by Karl Ziegler and co-workers that *N*-bromosuccinimide (NBS) is a highly specific reagent for bromination of olefins at allylic positions. One feature of this surprising reaction was the requirement that carbon tetrachloride be used as the solvent, a feature which was accepted by the scientific community. Indeed this is a necessary part of the procedure, but we could not find anywhere in the abundant literature a reason for this extraordinary requirement.

Succinimidoyl radical began to receive attention when the radical-chain characteristics of the Ziegler bromination reaction[1] became apparent.[2] In the form of the Bloomfield mechanism,[2a] with succinimidoyl radical as the hydrogen-abstracting component of the chain sequence, it enjoyed only a short popularity. It yielded



to the Goldfinger hypothesis,[3] with bromine atom as



hydrogen abstractor and the *N*-bromosuccinimide serving as a scavenger of hydrogen bromide and source of further bromine.

Massive evidence can be cited for the intermediacy of bromine atoms in NBS-containing systems.[4] The chemical properties of succinimidoyl radical went almost without recognition for nearly three decades; the nearly simultaneous observations from Traynham's[5] and our laboratories[6] were the opening wedges which led to the present understanding.

While the properties of imidoyl radicals are novel in a number of respects, the most unexpected feature which came to light was that *two imidoyl radicals were being generated in thermal chain reactions*, ground state (π) and a metastable excited state (σ_N and/or σ_O).

(1) K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, *Justus Liebigs Ann. Chem.*, **551**, 80 (1942).

(2) (a) G. F. Bloomfield, *J. Chem. Soc.*, 114 (1944); (b) D. H. Hey, *Annu. Rep. Chem. Soc.*, **41**, 184 (1944); (c) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

(3) (a) J. Adam, P. A. Gosselain, and P. Goldfinger, *Nature (London)*, **171**, 704 (1953); (b) P. A. Gosselain, J. Adam, and P. Goldfinger, *Bull. Soc., Chim. Belg.*, **65**, 533 (1956).

(4) (a) F. L. J. Sixma and R. H. Riem, *K. Ned. Akad. Wet., Ser. B*, **61**, 183 (1958); (b) B. P. McGrath and J. M. Tedder, *Proc. Chem. Soc., London*, **80**, (1961); (c) R. E. Pearson, and J. C. Martin, *J. Am. Chem. Soc.*, **85**, 354, 3142 (1963); (d) C. Walling, A. L. Rieger, and D. D. Tanner, *ibid.*, **85**, 3129 (1963); (e) G. A. Russell, C. DeBoer, and K. M. Desmond, *ibid.*, **85**, 365, 3139 (1963); (f) J. H. Incremona and J. C. Martin, *ibid.*, **92**, 627 (1970).

(5) J. G. Traynham, and Y. S. Lee, *J. Am. Chem. Soc.*, **96**, 3590 (1974).

(6) J. C. Day, M. J. Lindstrom, and P. S. Skell, *J. Am. Chem. Soc.*, **96**, 5616 (1974).

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