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ASYMMETRIC CARBON-CARBON BOND FORMING REACTIONS

A. I. Meyers

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

Abstract - Enantioselective alkylations using chiral nucleophiles and electrophiles have been shown to be approaching useful levels of efficiency. Lithio oxazolines and lithio enamines containing chiral centers have been alkylated to give α-substituted carboxylic acids, ketones, and aldehydes. Chiral electrophilic oxazolines react with organolithium reagents to produce very high enantiomeric excesses of β-substituted carboxylic acids and α-hydroxy acids. Studies of the important parameters have been made and some understanding of the mechanistic aspects are in hand.

Although asymmetric syntheses have long been a coveted goal for organic chemists (1), it has only been in the last few years that viable methods have become available (2-4). There are currently several phenomenal successes in asymmetric methodology (3) which allow the practicing organic chemist to prepare chiral compounds in greater than 90% enantiomeric excess (ee). Prominent among these are the chiral phosphine-rhodium catalysts which promote asymmetric hydrogenation of α-aminoacrylic acids to α-amino acids in greater than 95% ee. However, it has been only since 1975 that efficient methods of forming chiral compounds via carbon-carbon bonds have been realized. This lecture will concern itself with the latter process and will focus on the efforts in our laboratory in Colorado since 1974 which appear to possess considerable promise. There are still many things to be done, but it is our feeling that the progress made since 1975 clearly indicates that a new and exciting period awaits us in asymmetric synthesis.

Organic chemistry has witnessed tremendous strides in introduction and transposition of functional groups, stereoselective syntheses, and construction of molecules with very intricate architecture, however, asymmetric synthesis still remains a seriously underdeveloped area. The reasons for this lie mainly in our lack of understanding and control of transition state geometry. It is this aspect of an asymmetric synthesis which plays a central role in the process and dictates which reaction profile (Pr or Ps) will predominate (Fig. 1). The ratio

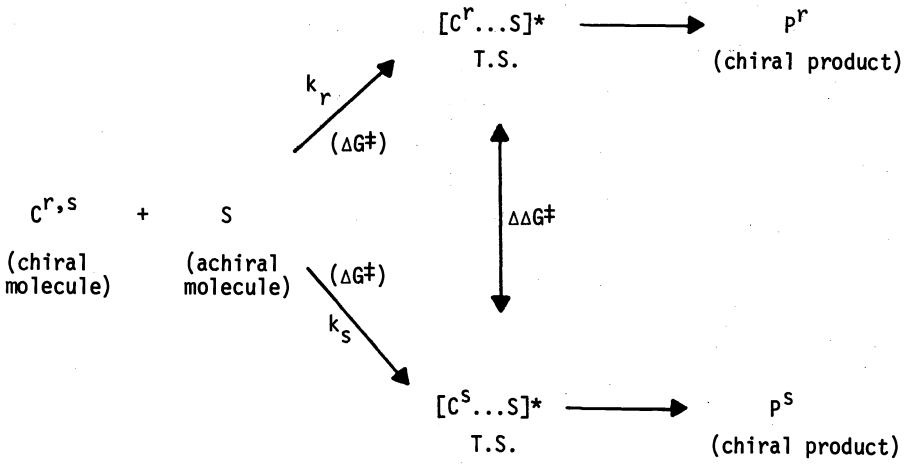


Fig. 1

P^r/P^s is dependent upon the relative rate constants k^r, k^s leading to the respective diastereomeric transition states. Since the competing processes are a function of the respective free energy of activation ($\Delta G^{\ddagger}$), the magnitude of the difference in this term ($\Delta\Delta G^{\ddagger}$) will be solely responsible for the ratio of enantiomeric products (P^r,P^s). A $\Delta\Delta G^{\ddagger}$ of approximately 2 kcal at 0° is considered essential to provide one of the enantiomers in at least 80% excess (90:10 mixture) and this ratio may be deemed as synthetically useful. Thus, the question that must be answered is - how does one design an asymmetric synthesis such that the two competing transition states, very similar in steric and electronic factors, exhibit a $\Delta\Delta G^{\ddagger}$ of ~2-3 kcal? Anyone who has studied molecular models will agree that it is very difficult to see this small energy difference in any models in use today. This leaves the chemist with the only other rational approach to this problem, namely an intuitive one. That this approach may be fruitful will be seen during the course of the discussion.

Our initial efforts began by using a reaction developed in our laboratories for preparing α,α-disubstituted alkanoic acids (5) (Fig. 2). This sequence proceeded in THF solution at -78° and as shown gives acids which possess an asymmetric center if R≠R'. If a chiral oxazoline was employed as starting material, it should be possible to transfer the chirality of the oxazoline to the newly formed C-C bond on addition of alkyl halides (Fig. 3). This process appeared to have all the necessary qualities for asymmetric synthesis. The intermediate

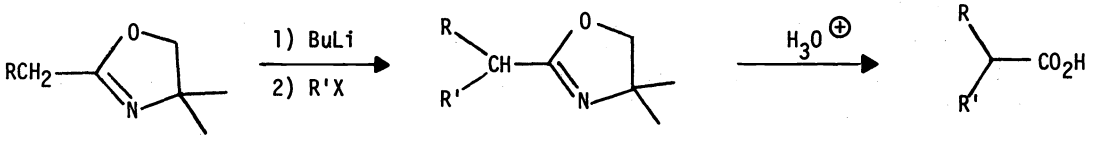


Fig. 2

lithio salt would be highly rigid and possess significantly different (?) topological faces toward an incoming electrophile and, coupled with the efficient alkylation at low temperatures, it may be possible to increase the selectivity of approach by lowering the temperature of the reaction. Furthermore, the amino alcohol released from the product could be recycled and used to prepare the chiral oxazoline for further use.

The chiral oxazoline (6) was prepared as shown in Fig. 4 using a commercially available chiral aminodiol derived from the commercial production of the anti-biotic, chloramphenicol.

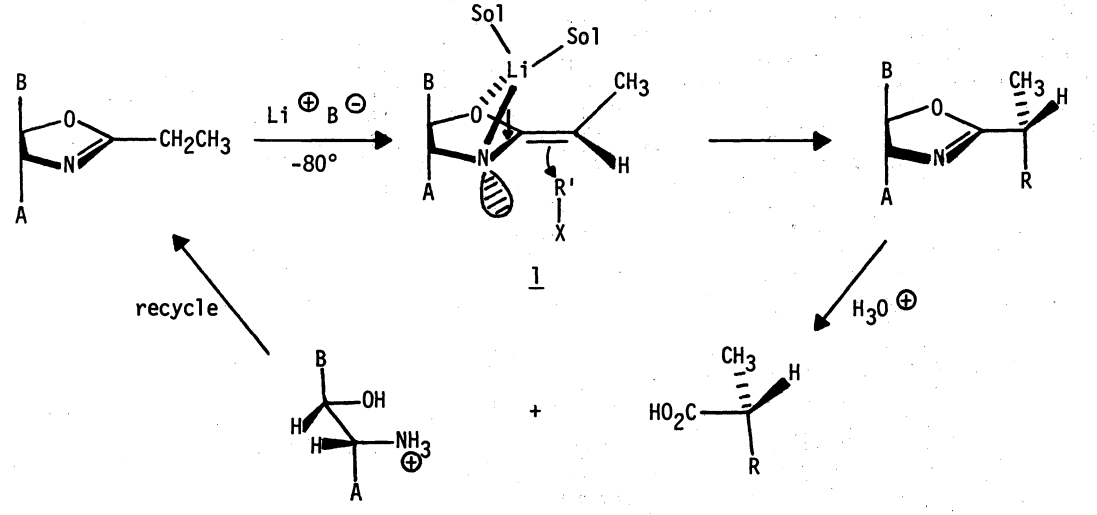


Fig. 3

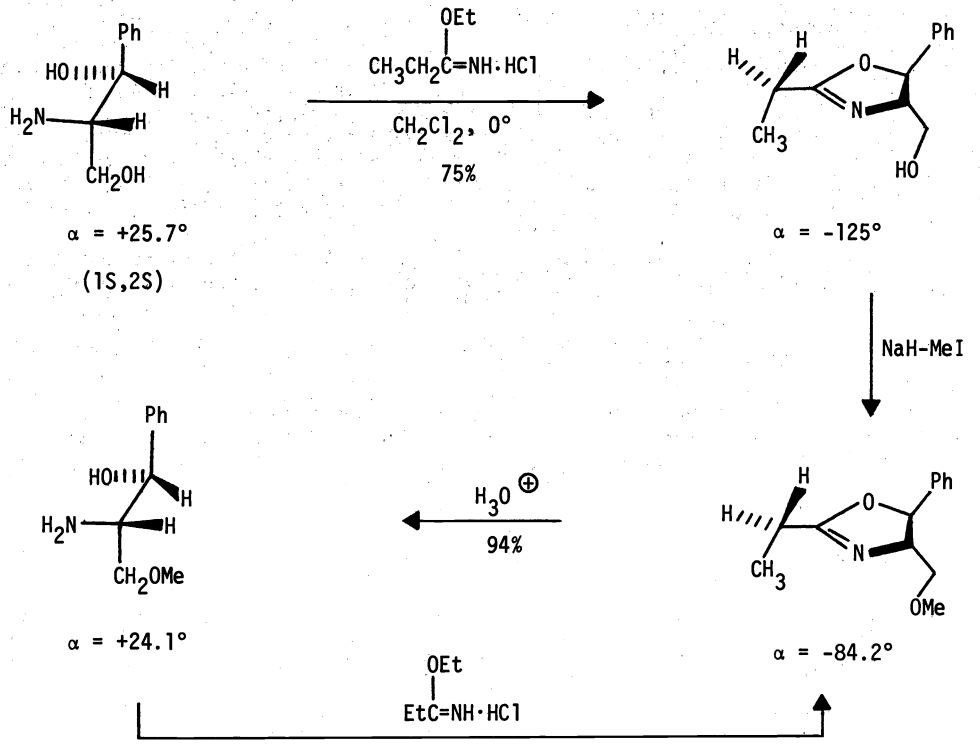


Fig. 4

The hydroxyl group was transformed into the methyl ether so as not to interfere with the metalation step to follow. In order to assess the chiral integrity of the aminoalcohol which will be recovered and recycled, the oxazoline was hydrolyzed to propionic acid and the amino methoxyalcohol. Reforming the oxazoline gave material whose specific rotation had not changed during the cycle. The stage was now set to test the asymmetric alkylation of the chiral oxazoline.

Metalation (LDA) at -78° gave a lithio oxazoline depicted as two possible but seemingly interconvertible E,Z-isomers. Treatment with a variety of alkyl halides led to the alkylated oxazolines which were hydrolyzed in aqueous acid to the α-alkylalkanoic acids (Fig. 5) (6). The acids prepared in this manner all possessed the S-configuration and were obtained in 72-82% ee with chemical yields ranging from 50-84%. The methoxyamino alcohol, as expected, was isolable in 80-85% yield and was used to reform the chiral oxazoline. A number of bases were examined, as well as solvents, temperatures of metalation and temperatures of alkylation. Optimum conditions were found to be LDA, -78°, THF for metalation, -78 - 98° for alkylation. Furthermore, it was possible to prepare either enantiomer of the α-alkyl acids from a single oxazoline by merely reversing the order of introduction of the alkyl groups (Fig. 6). In this fashion, starting with the 2-methyloxazoline and carrying out the sequence with two successive alkylations, each in reverse order of the other, it was possible to obtain in high ee either R or S-2-benzylhexanoic acid. A number of examples were investigated and proved to be consistent with these results (6). Studies were initiated to elucidate the mechanism of this synthesis. It was found that:

a) the methoxyl group in the oxazoline was needed, for in its absence, the % ee of the acid product dropped to 20-25%.
b) the phenyl group was needed, for in its absence, the % ee of the acid product dropped to 3%.
c) lithium diisopropylamide was superior to n-butyllithium in achieving high ee's of the acid (82% ee vs. 40-45% ee).
d) metalation temperatures had no effect (-90 to -30°)
e) alkylation temperatures were very important (highest ee at -78° to -95° vs. 20-25% ee at -30°)
f) ^{13}C-nmr of the lithiooxazolines using enriched ^{13}C in the methyl group gave a ratio of lithio salts of 95:5 at -78° and this ratio remained constant up to -30° for 200 h (7).

Thus, the lithiooxazolines in Fig. 7 are kinetically formed with a high degree of selectivity and do not equilibrate under the conditions used for the alkylation. If the phenyl group is

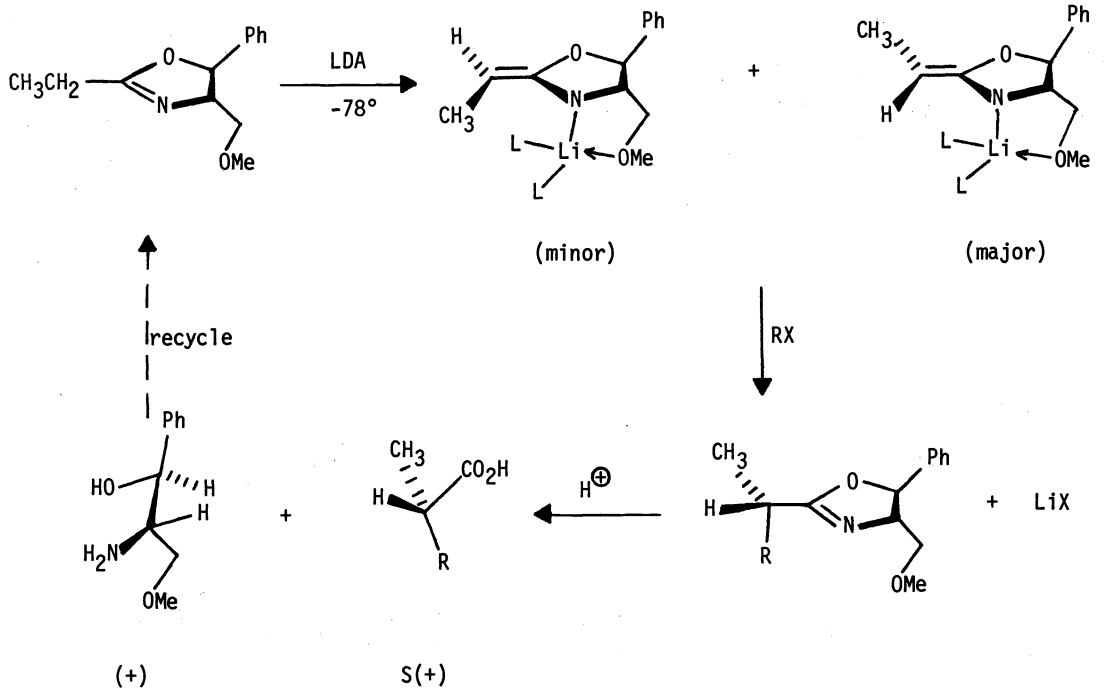


Fig. 5

also required, as mentioned previously, then the alkyl halide enters from the bottom to give the configuration of the acids observed. Although not yet confirmed, the presence of the methoxyl group is also critical in providing a high E,Z ratio of the lithiooxazolines on metalation by virtue of a rigid complex.

Additional studies led to chiral lactones as shown in Fig. 8 and Fig. 9 (9). Once again, reversing the introduction of the groups on the oxazolines gave, in a predictable manner, either R or S-lactones of comparable enantiomeric purity.

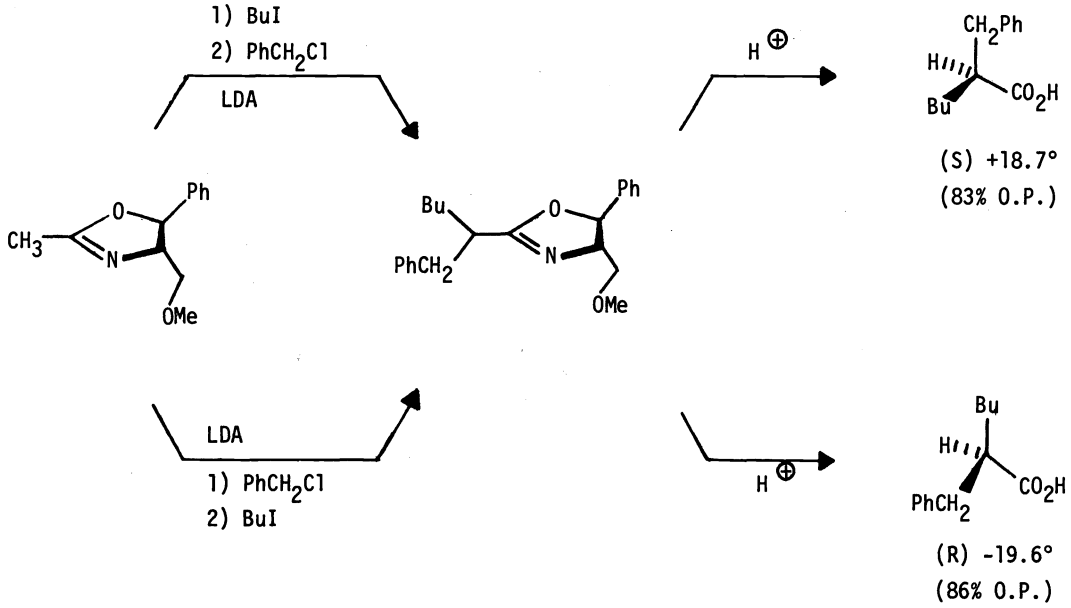


Fig. 6

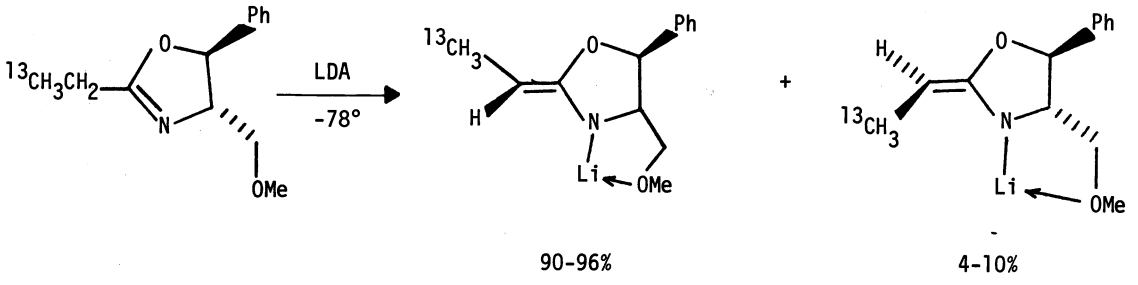


Fig. 7

The foregoing has described chiral lithio oxazolines as nucleophiles and carbon-carbon bond forming alkylations with alkyl halides. It is also feasible to prepare chiral electrophiles,

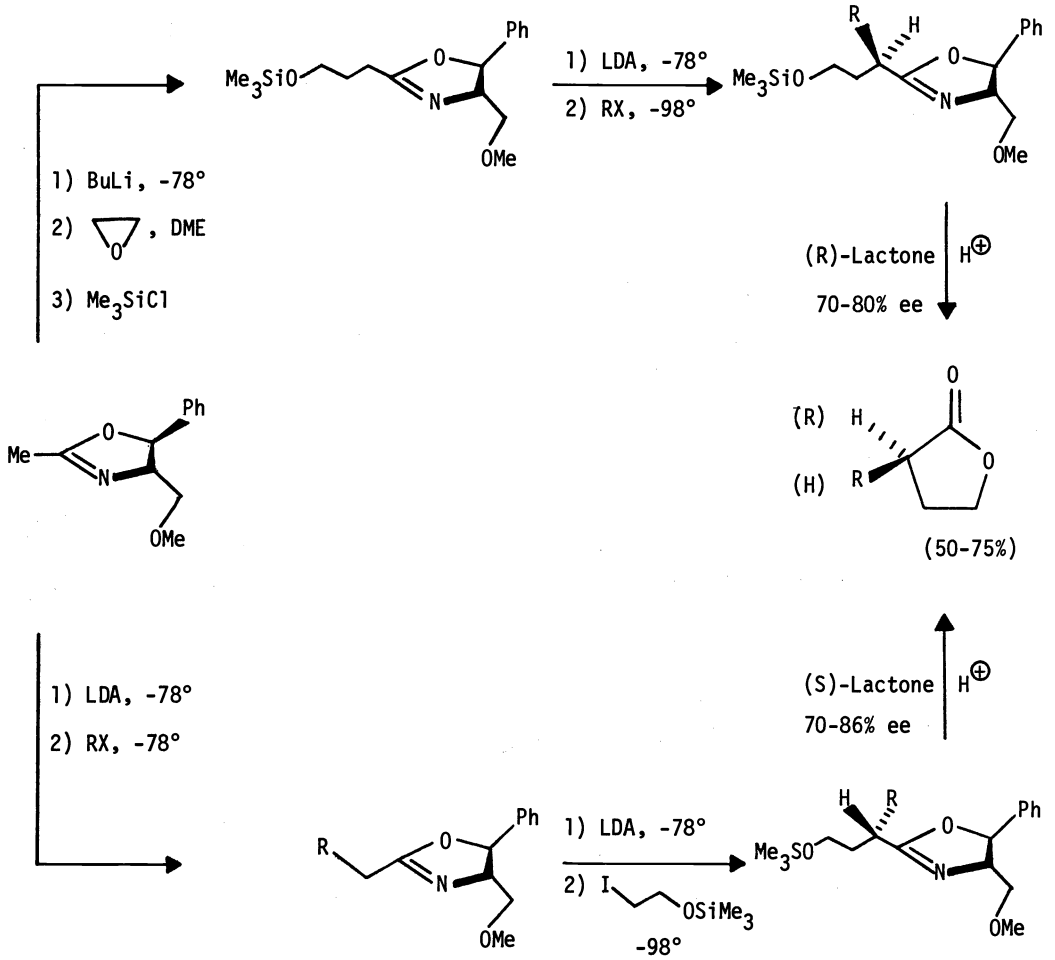


Fig. 8

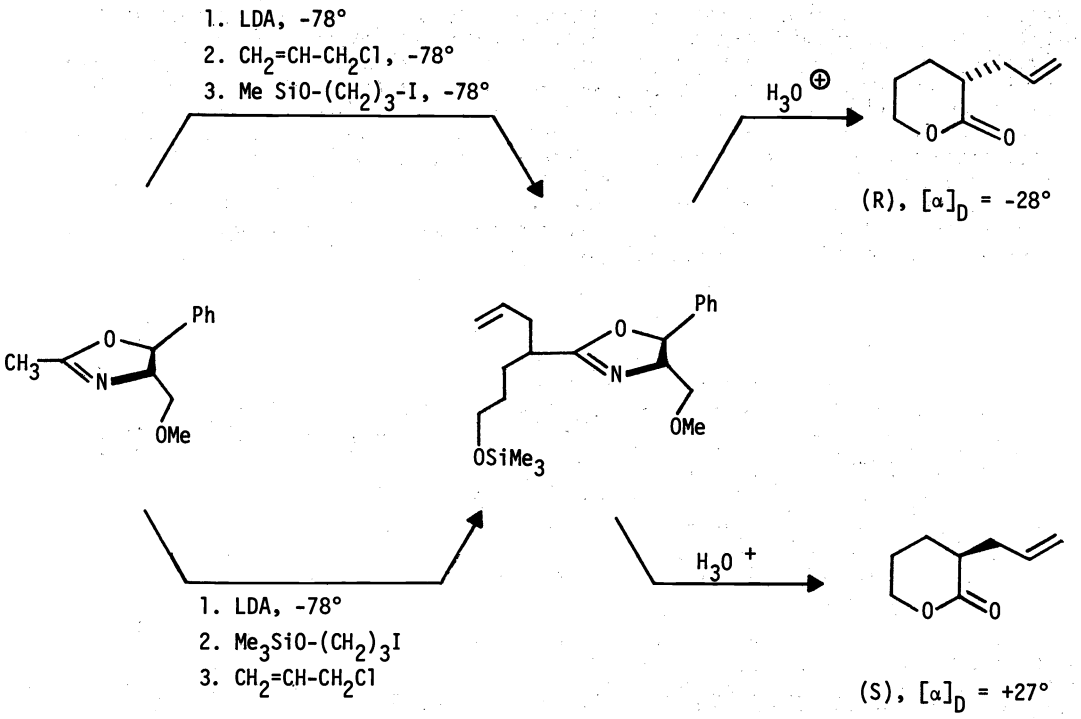


Fig. 9

namely α,β-unsaturated oxazolines, and carry out nucleophilic additions with organolithium reagents (10). In this regard, the readily available 2-methyloxazoline in Fig. 10 was

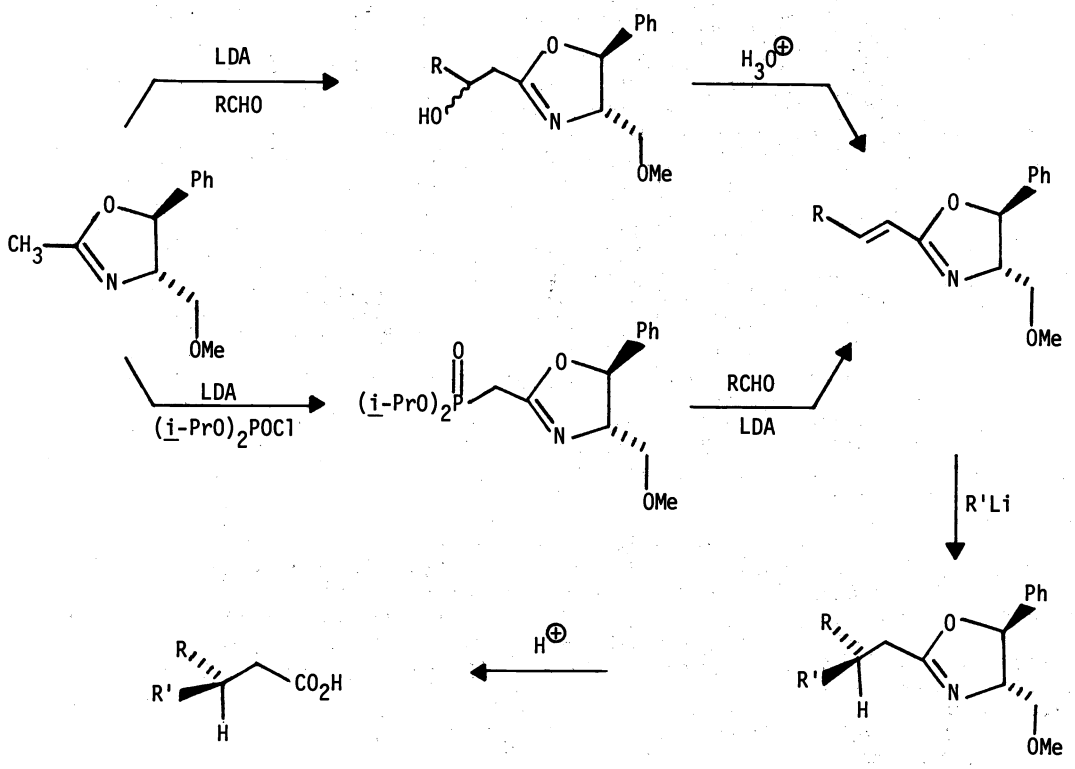


Fig. 10

transformed into the unsaturated derivative by the two routes shown. The route involving the phosphonate intermediate gave superior results and very high stereoselectivity with regard to E:Z ratios (11). Addition of various organolithium reagents to the chiral electrophilic-olefins gave conjugate adducts, which after acidic removal of the oxazoline moiety, led to β-alkyl or β-arylalkanoic acids in 95±5% ee (10,11). A wide variety of organolithium reagents and alkenyl oxazolines were examined and without exception led to virtually pure enantiomers. Either enantiomer could be reached by reversing the order of the alkyl groups in the reaction. The only exceptions found were failure of methyllithium, lithiodithiane and stabilized or delocalized ions (e.g., lithio enolates) to add stereoselectivity to the alkenyl oxazolines. Although detailed mechanistic data are still lacking, it was learned that the chiral oxazoline derived from S-serine and lacking the phenyl group gave on addition of organolithium reagents and hydrolysis, carboxylic acids of comparable ee (~90-95%) and, of course, opposite configuration (12). This behavior supports the notion

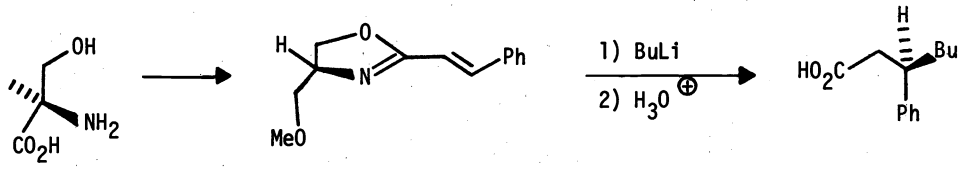


Fig. 11

that only the methoxyl group with its strong complexation to lithium cation is responsible for the high stereoselectivity in the conjugate addition and, if the absolute configurations of the products are considered, entry must be as shown in Fig. 12. Further extension of this

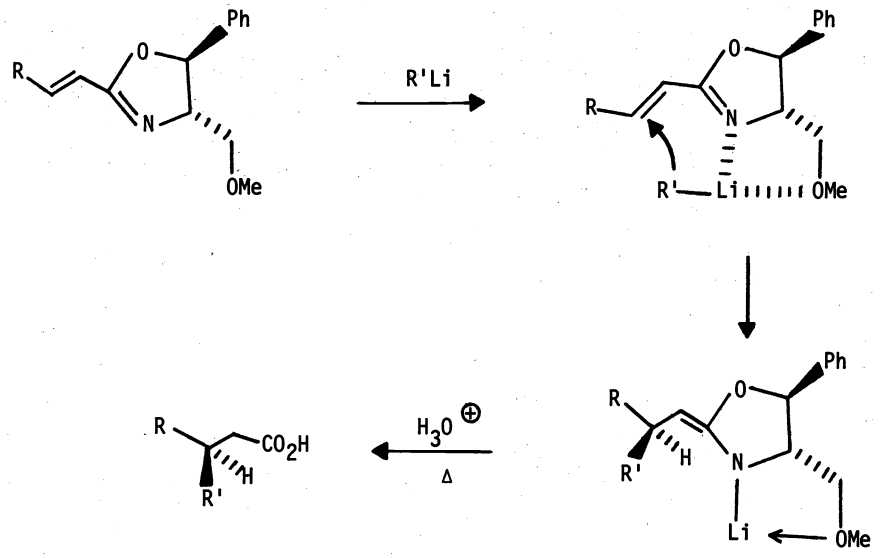


Fig. 12

method using alkoxy substituents led to 4-methoxy-3-alkyl pentanoic acids and 3-(2-methoxyphenyl)-3-alkyl propionic acids in equally high enantiomeric excess (Fig. 13). These products were not previously reported in the literature and their enantiomeric purity was determined using resolution (pressure chromatography) coupled with chiral shift reagents (11,13). Recently, another study appeared which described the conjugate addition of Grignard reagents to α,β-unsaturated imines containing a chiral amino ester (14) providing β-substituted aldehydes. Reduction to the primary alcohol led to chiral products in 95-98% ee (Fig. 14). The success of this process also appears to lie in the complexing ability of the oxygen groups as the Grignard approaches.

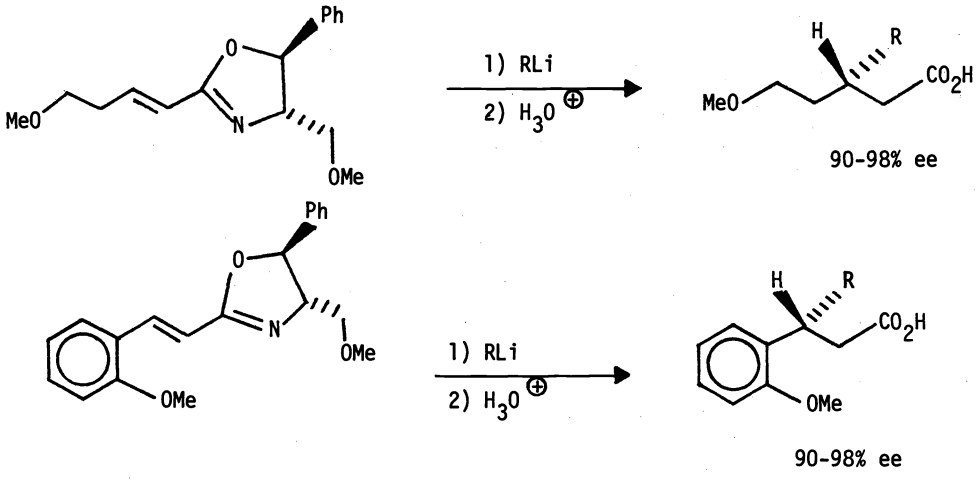


Fig. 13

To further extend the scope of this highly efficient asymmetric alkylation, the methoxy acids in Fig. 13 were transformed into chiral lactones (Fig. 15). The enantiomeric purity

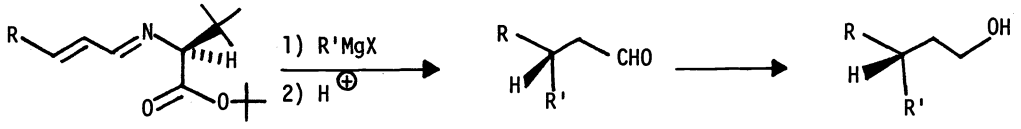


Fig. 14

of these products was also found to be very high (>95% ee) by comparison with known lactones prepared from enzymic methods.

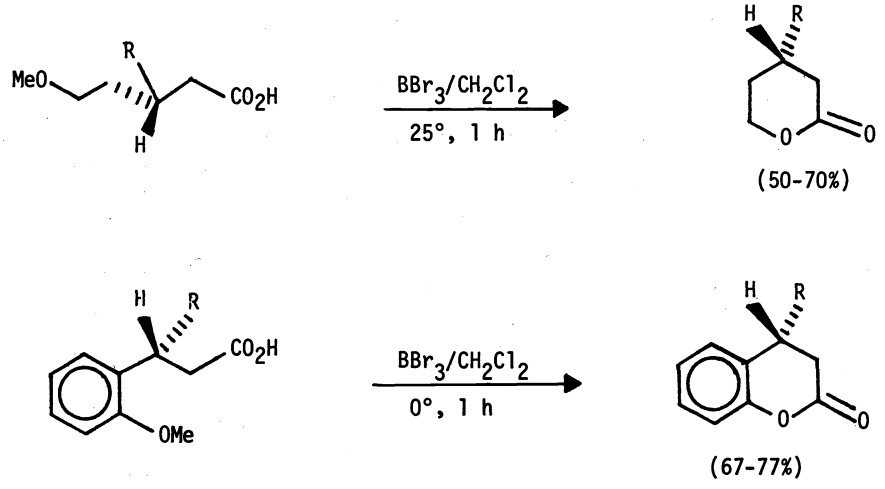


Fig. 15

In another series of experiments involving electrophilic oxazolines, organometallic reagents were added to the chiral benzoyl derivatives to provide the tertiary alcohols which furnished, after hydrolysis, α-hydroxy acids in 60-70% ee (Fig. 16). It is also possible to separate, on a preparative scale, the intermediate diastereomers using crystallization or pressure chromatography (16).

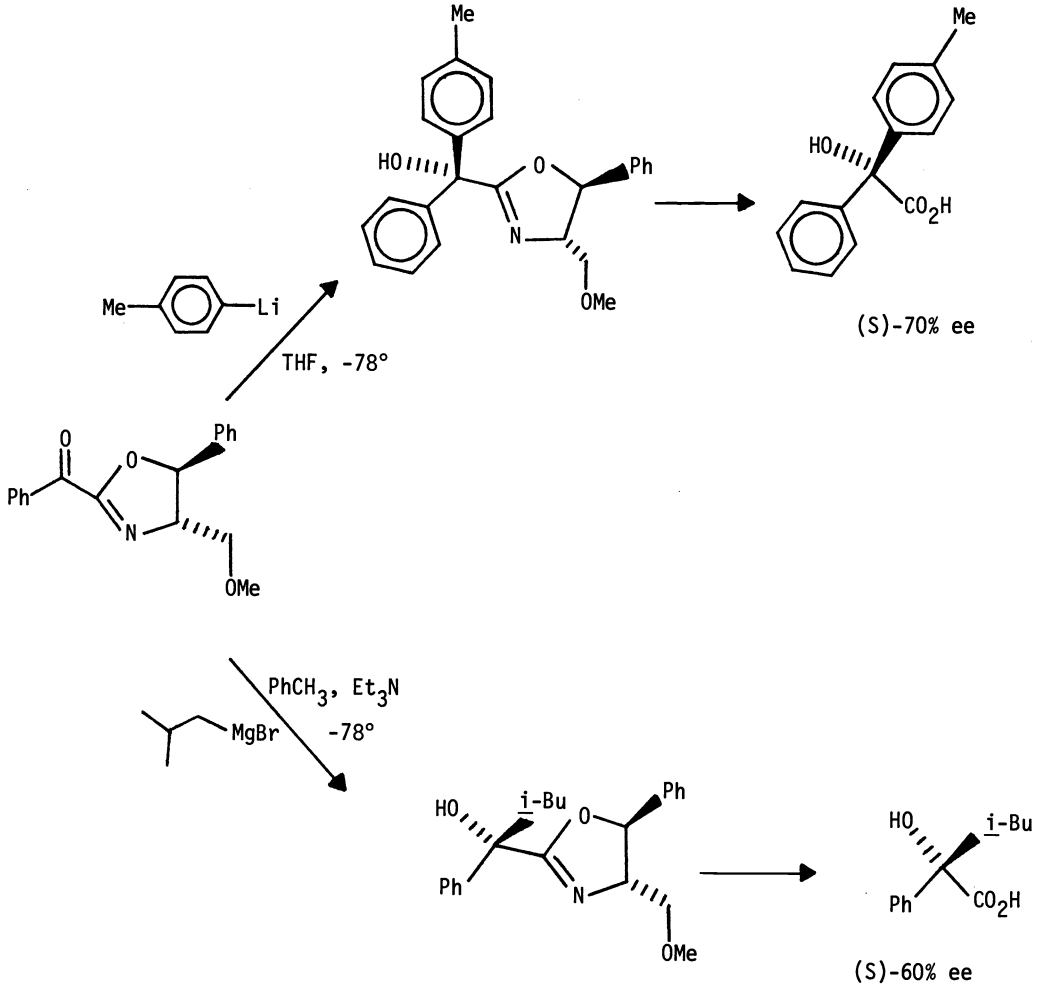
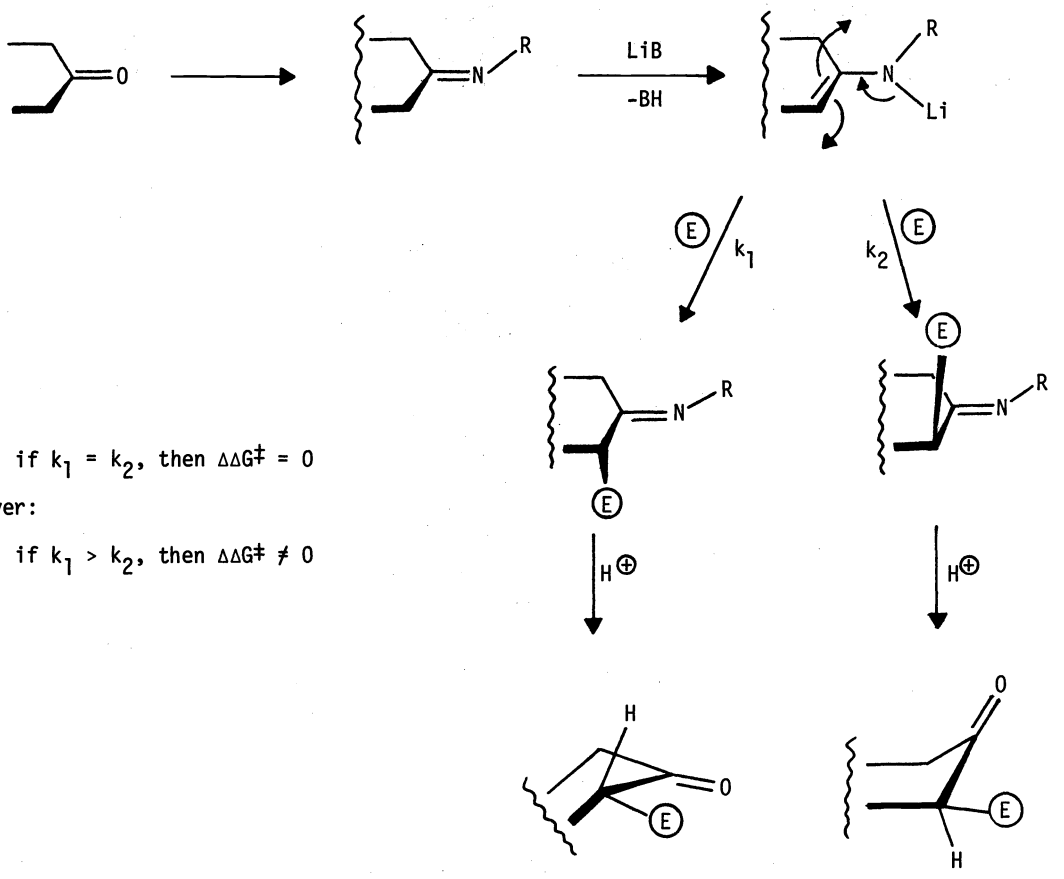


Fig. 16

Studies were also performed on chiral imines of carbonyl compounds in an effort to assess the efficiency of α-alkylation leading to chiral α-substituted ketones and aldehydes (Fig. 17). If the nature of the R-substituent on the imine was such that it provided significantly different topological features, then $k_1 >> k_2$ affording an enantiomeric excess of one of the alkylated imines. This is not a new concept since earlier workers have attempted to carry out enantioselective alkylation using hindered chiral amines; isobornyl (17), and phenethyl (18) derivatives. However, the results were only partially successful producing α-alkylated cyclohexanones in 20-60% ee. It was our feeling that the incorporation of a suitable ligand to complex the lithio enamine in Fig. 17 would provide rigidity and decrease the number of conformers present during alkylation.



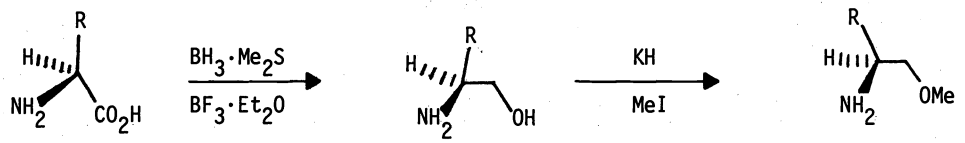
if $k_1 = k_2$, then $\Delta\Delta G^{\ddagger} = 0$

however:

if $k_1 > k_2$, then $\Delta\Delta G^{\ddagger} \neq 0$

Fig. 17

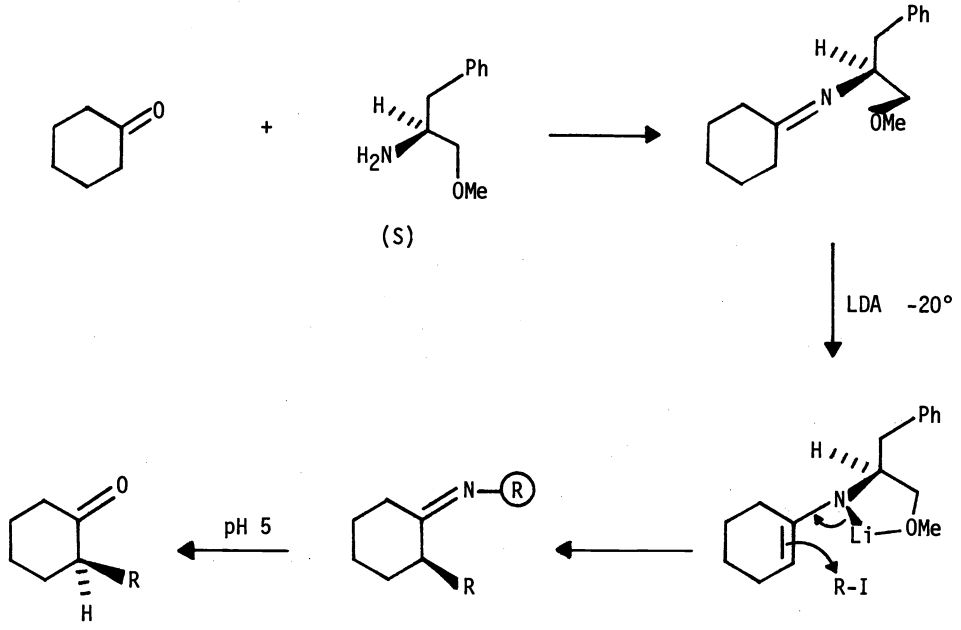
The requisite chiral amine was prepared as described in Fig. 18 and the method proved general for a number of examples. Thus, reduction using borane-dimethyl sulfide on various S-amino acids gave the amino alcohols in 80-90% yield followed by methylation with potassium hydride-methyl iodide. The enantiomeric purity of the amino alcohols was determined using Mosher's reagent and ^{19}F-nmr and found to be at least 95% ee (19,20).



R = (R)-$PhCH_2$; (S)-$PhCH_2$; (R)-Ph; (S)-i-Pr; (S)-i-Bu

Fig. 18

Using the chiral methoxyamine, the corresponding imine of cyclohexanone was prepared and subjected to metalation with LDA. Addition of a variety of alkyl halides gave the imines which were hydrolyzed in a buffer solution (pH 5) to the monoalkylated cyclohexanones. The enantiomeric excess of these compounds were all 90-100% (21) thus supporting the need for a rigid chiral metalloenamine in this reaction (Fig. 19). The configurations of the ketones



R	Me	Et	n-Pr	CH_2=CH-CH_2
% ee	91	94	∿100	∿100

Fig. 19

produced were S, except for those examples (allyl) whose priority change relative to the cyclohexyl group. Although detailed mechanistic data is lacking, an operational model for alkylation as seen in Fig. 19 may be used to account for the observed configuration. This model will also correctly predict the configurations observed in open chain ketones and aldehydes (vide infra). There have been three additional studies reported which describe the alkylation of chiral cyclohexylimines possessing an alkoxy group and in all cases the products were obtained in 80-90% ee (22,23,24) and may be formulated in the manner of Fig. 19.

Extending this enantioselective alkylation of carbonyl derivatives to open chain ketones provides an added complication to the method. Unlike the cyclohexanone imines, the metalated imines of acyclic ketones can give rise to E and Z isomers which may possess significant energy barriers to rotation to affect the outcome of the chiral product (Fig. 20). When the imine of 3-pentanone (R=Me, R'=Et) was metalated and alkylated under conditions which were so successful for cyclohexanone derivatives, the product 3-methyl-4-hexanone was obtained in 3% ee. However, if the lithio enamone (Fig. 20) was heated in the THF solution to 60° for ca. 1 hour, and then alkylated with ethyl iodide, the ketone was formed in 76% ee (25) (Fig. 21).

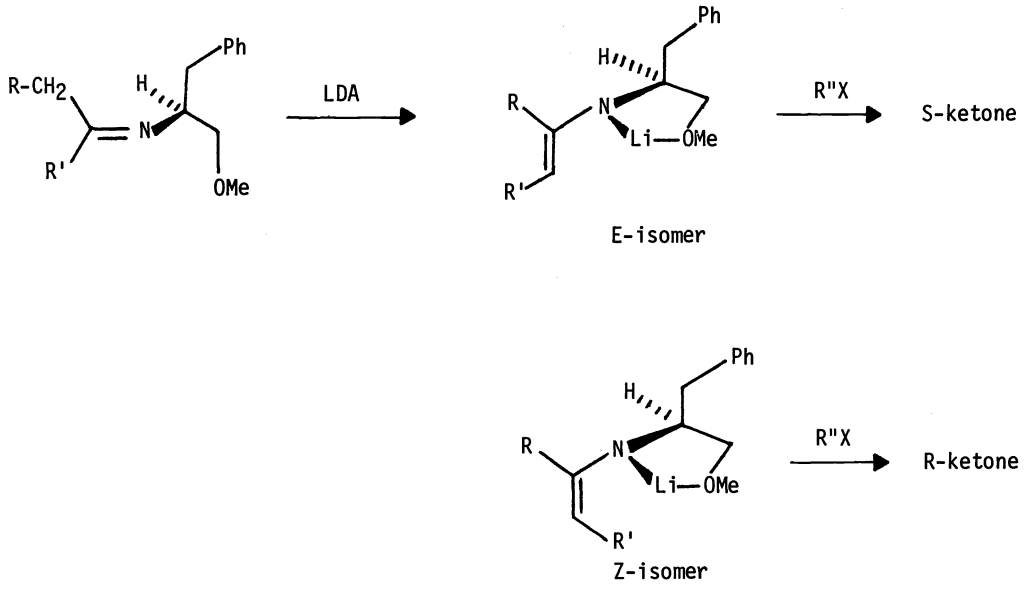


Fig. 20

Several additional examples behaved similarly in that after heating the metalloenamines, alkylations gave α-substituted ketones in 80-90% ee. This appears to indicate that the lithio enamines are formed kinetically in an unfavorable ratio and by heating it is possible to overcome the rotational barrier forming a more favorable thermodynamic ratio. At this time, this work will require additional study which hopefully will provide a route to chiral acyclic ketones of wide structural variety (26).

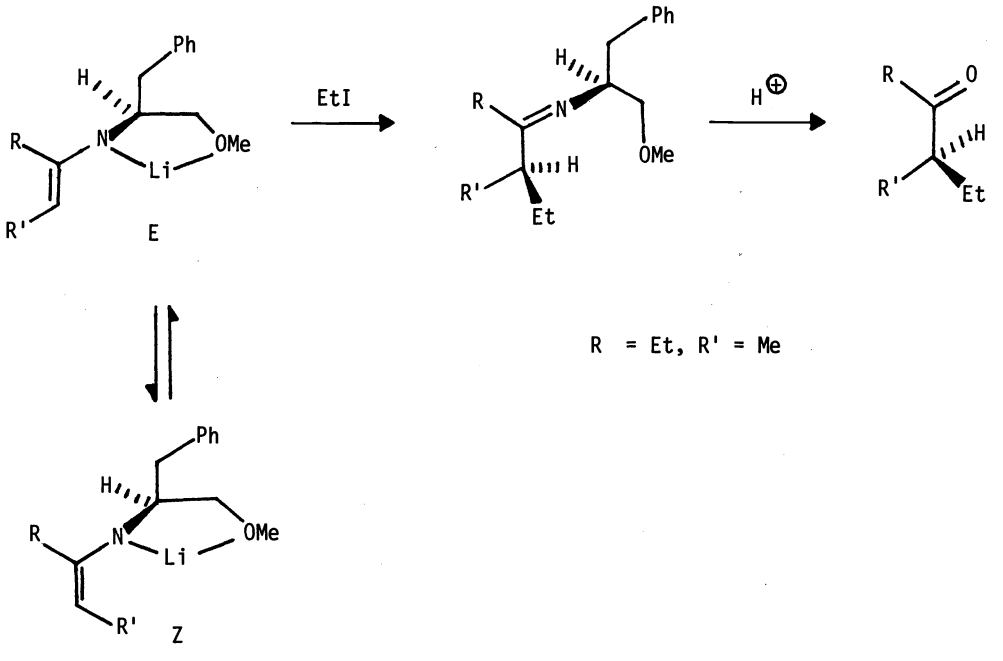
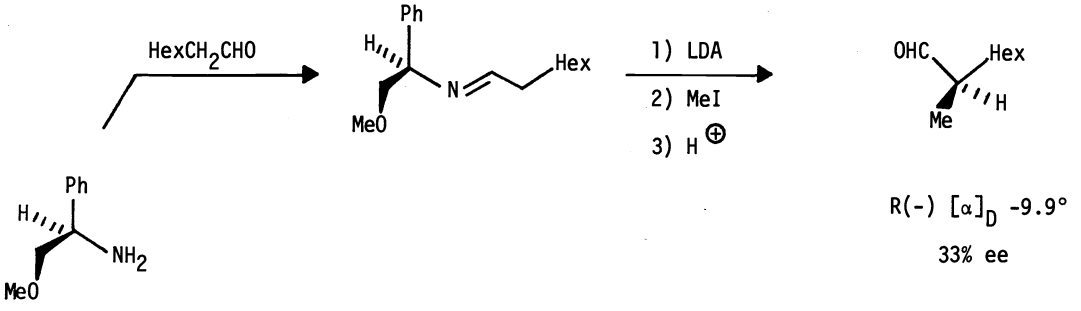


Fig. 21

The final study to be covered in this lecture relates to the preparation of α-alkyl aldehydes. Although this study is still under active investigation, some results may be mentioned. By condensing octanal with the chiral methoxyamine, the corresponding amine was prepared and subjected to metalation (LDA, -20°, THF) and alkylation. Hydrolytic work-up produced the 2-alkyloctanal in only 37% ee (Fig. 22). Reversal of the groups in the sequence produced the optical antipode in 33% ee (20). Note that the chiral imine in Fig. 22 is derived from R-phenylglycine, however, a variety of alkoxyl amines were investigated with little effect



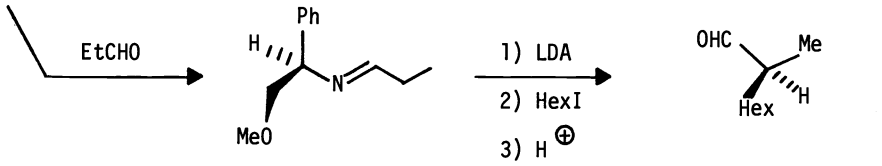


Fig. 22

upon the enantiomeric purity of the aldehydes. Further studies revealed that the use of lithium tetramethylpiperidide(LiTMP) gave a higher ee for the aldehydes (50-55% ee) than LDA and this may be a function of the kinetic deprotonation and its sensitivity toward more hindered bases. As mentioned earlier, with regard to the lithio enamines of ketones, heating the anion prior to metalation gave much higher enantiomeric purities of ketones. However, heating the anions of lithio aldimines were without effect in increasing the ee of the chiral aldehyde. It is clear that the factors responsible for ketone alkylations are not the same in the case of aldehydes and further work is in progress to assess these differences.

In summary, methodology has advanced considerably in the chemist's quest for chiral molecular synthesis, but there is still much to be done. It would appear that in order to develop useful asymmetric syntheses, we will have to relearn how to prepare all the simple functionalized molecules that are considered to be trivial by today's standards. Nevertheless, it will be exciting as we inch toward this goal and eventually the ultimate goal - catalytic methods - which today are the sole domain of enzymes.

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