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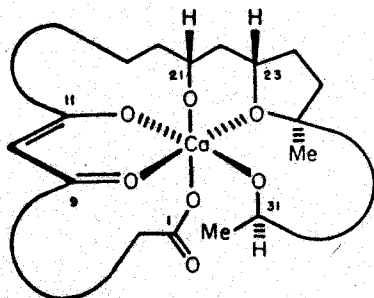
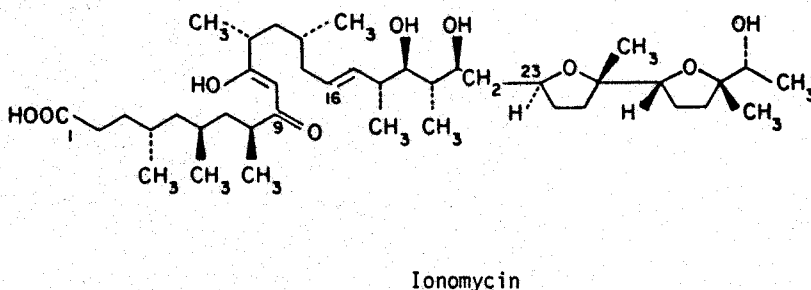
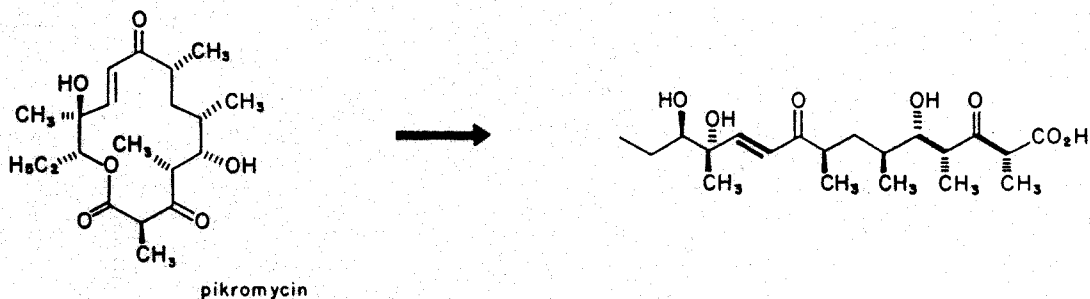
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CHIRAL ENOLATE DESIGN

**D. A. EVANS, J. M. TAKACS, L. R. MCGEE, M. D. ENNIS, D. J. MATHRE
and J. BARTROLI**

Contribution No. 6289 from the Laboratories of Chemistry, California Institute of Technology,
Pasadena, California 91125, U.S.A.

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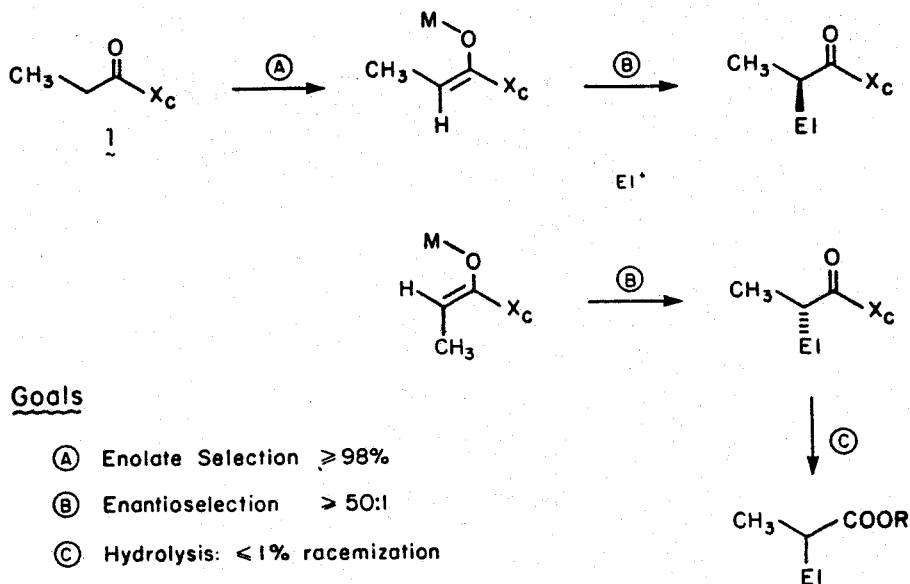


ENANTIOSELECTIVE ENOLATE ALKYLATIONS

In a general sense, if one wishes to develop enantioselective chemical operations which are to be employed in an iterative sense, one must achieve a minimum level of enantioselection of 95% to avoid the problems associated with generating gross diastereoisomer mixtures after several iterations. With regard to chiral carboxylic acid enolate design, the general problems which must be addressed to achieve minimum chirality transfer of the type indicated are illustrated in Scheme I. Given the carbonyl derivative 1, wherein X_C is the chiral auxiliary, one must address three individual chemical transformations in order to convert 1 to a chiral carboxylic acid derivative. In order to effect enantioselection at the 95% level, one must achieve at least 98% stereoselection in reaction A, the enolization step; at least 98% enantioface discrimination and the reaction of this enolate mixture with electrophiles; and finally, no more than 1% racemization must accompany the removal of the chiral auxiliary. It is clear that the chiral auxiliary employed must impart to the system both high levels of enolization stereoselection and subsequently provide a well-defined enantiotopic bias for the two faces of the given enolate. Some of the most fundamental observations in the evolution of this field have been provided from the laboratory of Professor A. I. Meyers (2).

At the present time the chemical community is just beginning to understand some of the control elements associated with the enolization process of carbonyl substrates and those architectural and reaction variables which

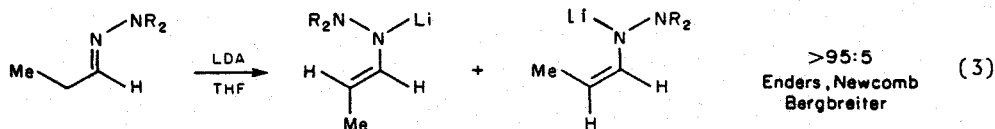
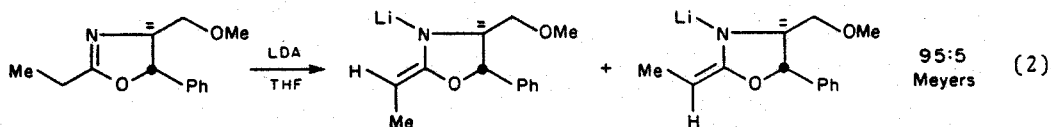
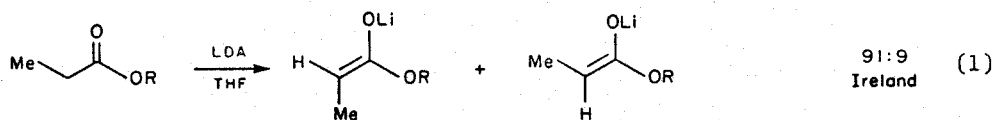
Scheme I

Goals

- (A) Enolate Selection $\geq 98\%$
- (B) Enantioselection $> 50:1$
- (C) Hydrolysis: $< 1\%$ racemization

Minimum Chirality Transfer: 95:5

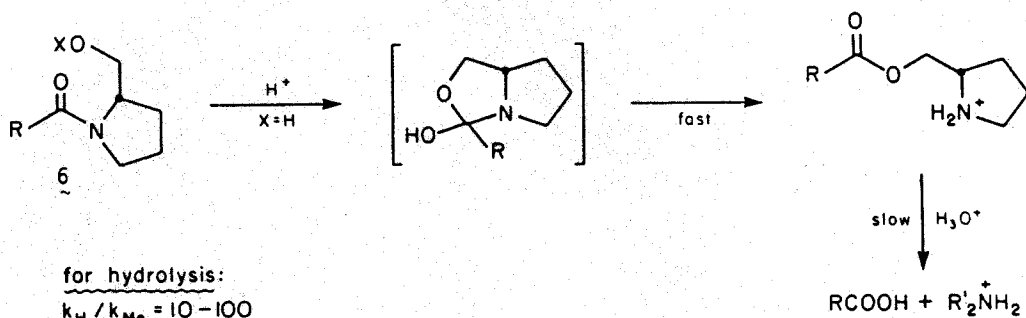
control kinetic enolate stereoselection. Equations 1-3 provide a useful background for the kinetic enolate ratios observed in the enolization of various substrates with lithium amide bases.



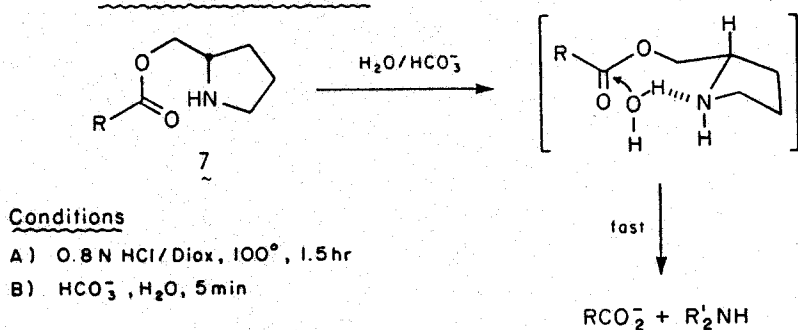
For reasons that will be more fully elaborated, we felt that carboxylic acid amides, upon deprotonation with amide bases would lead to the highly stereoselective formation of *cis*-enolates (Scheme II). This projection was based on allylic strain considerations (3) which could be expressed in the competitive enolization of dialkylamides from either conformation A or con-

Scheme V

AMIDE HYDROLYSIS

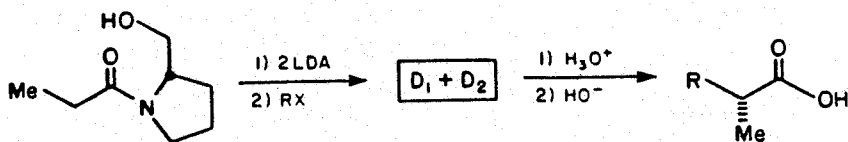


General Base Catalysis



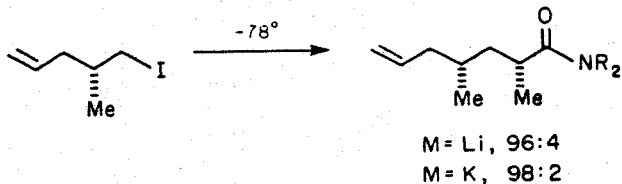
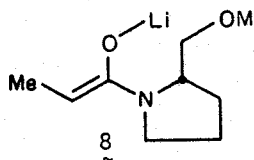
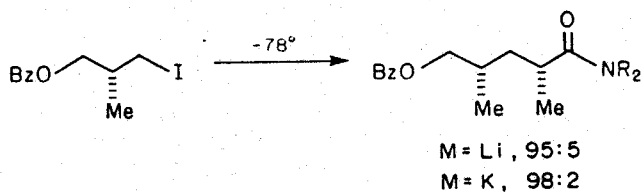
ammonium salts. Overall, acyl transfer has been observed to be virtually complete prior to the hydrolysis step. In order to minimize the contact time between the chiral substrates and the acidic medium, we have investigated the base-catalyzed hydrolysis of the resultant amino ester 7 and were pleased to find that these esters hydrolyzed with extreme facility in aqueous bicarbonate at room temperature. We surmise that the extreme lability of these β -amino esters has its origin in the catalytic role which the proximal nitrogen function plays in the base-catalyzed hydrolysis step. Overall, the hydrolysis of prolinol amides is best accomplished by brief acid treatment to promote acyl transfer and then aqueous bicarbonate hydrolysis at room temperature to affect rapid ester hydrolysis. Under these conditions we can detect no apparent racemization ($\leq 1\%$) when these types of hydrolyses are carried out on α -substituted carboxamides. In subsequent alkylation studies we have found that these amide substrates exhibit excellent levels of chirality transfer with a range of alkyl halides (Scheme VI). The illustrated diastereoisomer ratios were determined by capillary gas chromatography in all instances. In addition, detailed control experiments indicated that the hydrolyses discussed previously resulted in essentially no racemization. Consequently, we have employed the reported diastereoisomer ratios as a reflection of the optical purity of the resultant carboxylic acids. In the cases illustrated (Scheme VI), the conditions for optimal chirality transfer had to be determined for each alkyl halide (4). One obvious trend which has been noted in this and related studies, pertains to the relationship between electrophile structure and degree of enantioselection in the alkylation process. The anomalous results noted with benzyl bromide are mechanistically interesting and could implicate more than one mechanism for this alkylation reaction. For example, with this substrate, competing electron transfer-mediated alkylation cannot be discounted. After a careful survey of reaction conditions and cation studies, we have found that the mixed lithium-potassium enolate substrate 8 appears to be optimal. The comparative cation studies are illustrated in Scheme VII. At the present time no information is in hand pertaining to the structure of this enolate. It is clear however, that the nature of the pendant ligand has a profound effect on the degree and nature of chirality transfer in amide enolates derived from 5. The results summarized in Scheme VIII strikingly illustrate

Scheme VI



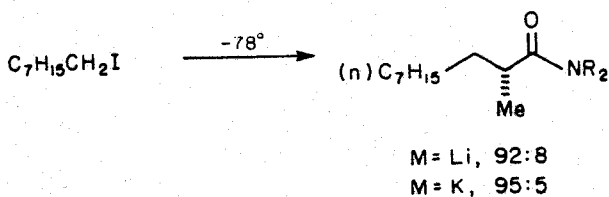
<u>Electrophile</u>	<u>D₁:D₂</u>	<u>Carboxylic Acid</u>	
$n\text{-C}_4\text{H}_9\text{-I}$	94 : 6		82%
	97 : 3		85%
	97 : 3		54%
	96 : 4		81%
PhCH_2Br	88 : 12		69%

Scheme VII

Enolization Conditions

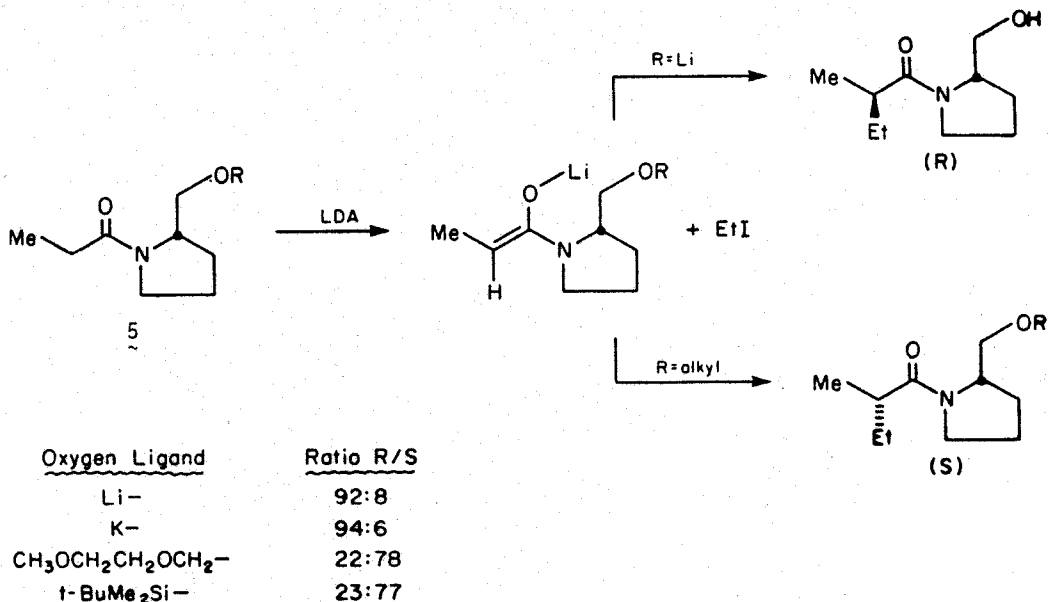
A) 2equiv $\text{LiN}(\text{i-prop})_2$
THF, HMPA

B) $\text{KH}; \text{LiN}(\text{i-prop})_2$
THF, HMPA



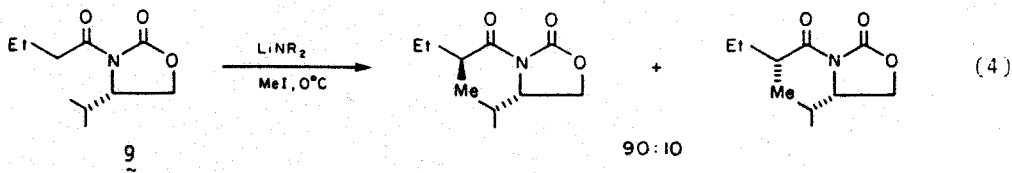
Scheme VIII

LIGAND DEPENDANT CHIRALITY TRANSFER

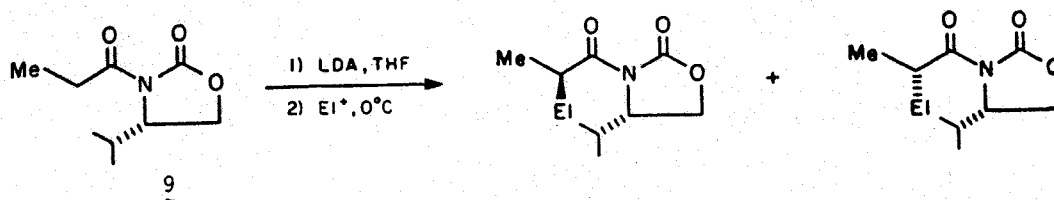


this point. These experiments indicate that the prolinol amides are: a) highly stereoselective in the enolization process; b) exhibit an excellent enantiotopic facial discrimination in the alkylation process; and c) hydrolyze with facility without racemization of the newly constructed asymmetric center. It should be noted in passing that the enolate system described above is totally ineffective in aldol condensation processes (*vide infra*).

One highly promising chiral enolate system currently under investigation in our laboratory is the valinol-derived oxazolidone imide typified by structure 9 (Scheme IX). The rationale behind the design of this system was predicated upon two points: We felt that the U-type enolates (*cf.* Scheme IV) might be intrinsically better than the W-type systems under previous investigation; and, that the analogous substrates would be ideally designed for both enolate chelation and resultant amide hydrolysis to the desired carboxylic acid derivative. The enolate derived from these systems were conveniently prepared under standard conditions (LDA -78°C THF). Initial alkylation studies with these enolates indicated that they were considerably less reactive than their amide counterparts and temperatures of *ca.* 0° were optimal for effective monoalkylations. The results in Scheme IX indicate that, in preliminary studies, the alkylations were highly enantioselective in nature. Nonetheless, there are apparently some intrinsic reactivity constraints inherent in this family of enolates which are not found with the prolinol-derived amides. As in our earlier studies, we have found methyl iodide to be the least selective alkyl halide investigated (eq. 4). Recently, we have carried out complimentary studies on the norephedrine derived oxazolidone 10 (eq. 5) in order to gain further insight into the importance of related steric effects

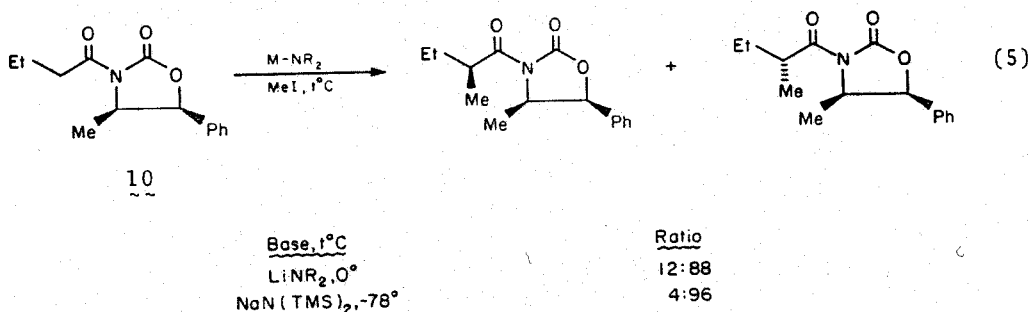


Scheme IX



<u>Electrophile</u>	<u>Ratio (GLC)</u>
PhCH ₂ Br	120:1
	98:2
	97:3
Et-I	95:5
	N.R.

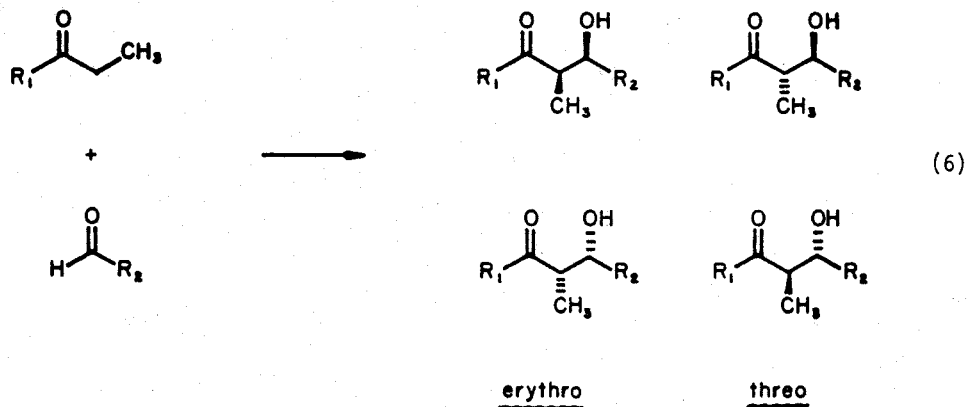
and their relationship to chirality transfer. In comparative studies on the complementary enolates 9 and 10 we have found that the norephedrine derived system is only slightly less enantioselective (cf. eq. 5). Using this system we have recently deduced what appear to be the optimal conditions for enolate alkylation in these systems. The sodium enolates (THF -78°) appear to provide significant improvements in both reactivity and enantioselectivity.



The comparative enantioselections observed with the above illustrated β -amino alcohol derived oxazolidone imides seem to indicate that a large family of β -amino alcohols may well function with comparable facility in related alkylation reactions. Preliminary studies have been carried out with phenyl-glycinol-derived oxazolidones and the results obtained from this study seem to indicate that this conclusion is valid. A routine survey of the lithium enolate-derived aldol condensations in these systems were extremely disappointing from the standpoint of both aldol diastereoselection and chirality transfer. The ensuing discussion provides a solution to this problem.

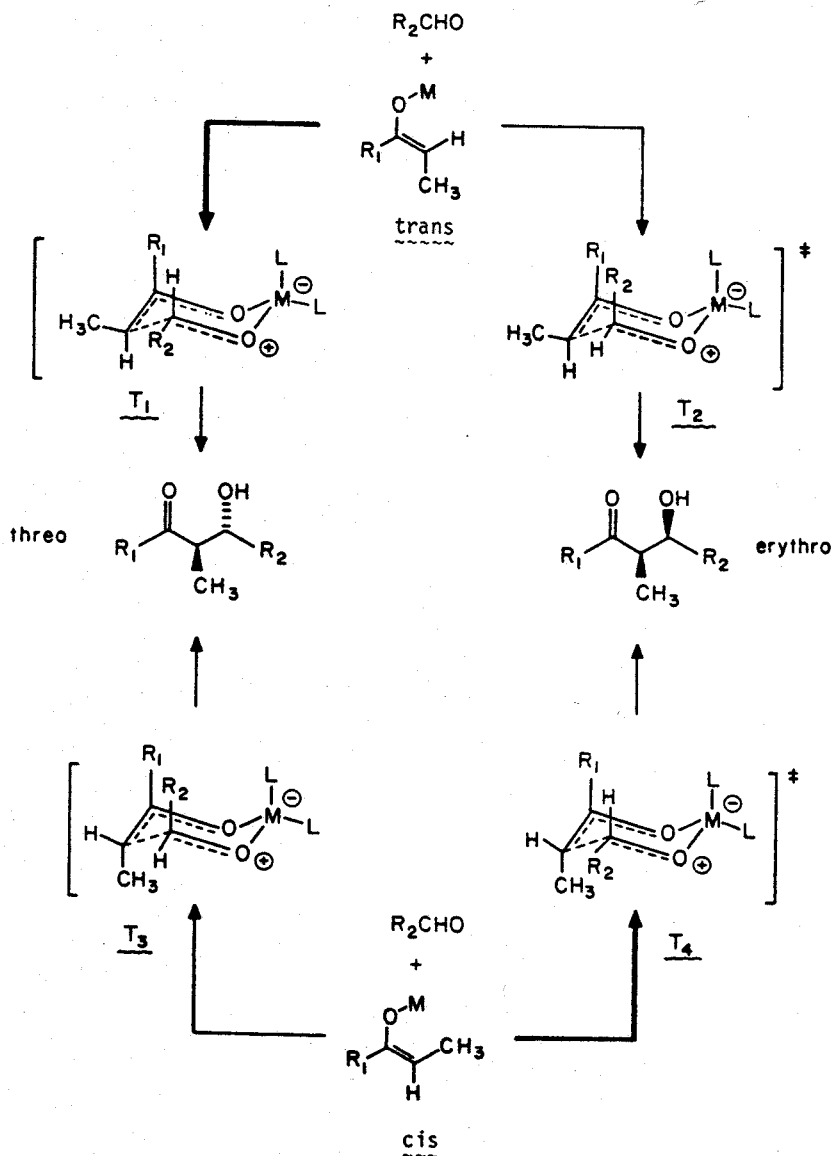
ENANTIOSELECTIVE ALDOL CONDENSATIONS

For some of the projected synthetic applications noted earlier in the lecture, we have attempted to develop a general protocol for rendering the aldol process highly stereoselective in nature. This has been indeed a challenging exercise which has required the sequential solution of two major problems (eq. 6). In the aldol condensation illustrated below, one would like to design for the synthesis of any one of the four possible aldol stereoisomers illustrated. The first task has been to devise a general protocol for



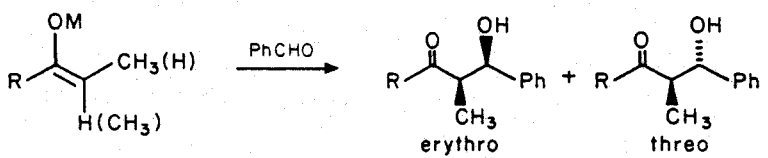
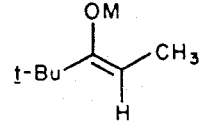
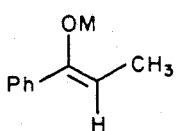
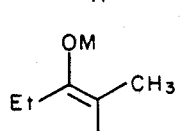
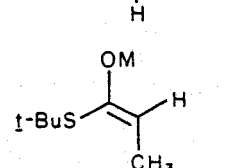
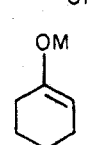
achieving high levels of reaction diastereoselection (erythro product set versus threo product set). This problem has received a great deal of recent attention (5). The working hypothesis that we have followed to control aldol diastereoselection is illustrated in Scheme X (6). Given the assumption

Scheme X



that the aldol condensation with metal enolates proceeds via a pericyclic process (7), the influence of variable steric parameters may be analyzed to determine their effect on the relative heats of formation of diastereomeric transition states from an enolate of defined geometry. For example, for trans-enolates, one might anticipate that transition state T_2 might be destabilized relative to T_1 by maximizing both $R_2 \leftrightarrow R_1$ and $R_2 \leftrightarrow L$ steric parameters. Both Dubois (8) and Heathcock (5) have demonstrated that, in part, enolate geometry correlates with product stereochemistry as predicted by this model. For lithium enolates, however, the correlation between enolate geometry and product stereochemistry is only high when the enolate ligand R_1 approximates that of a tertiary butyl group. This can be understood in terms of the major control element in the reaction being the $R_1 \leftrightarrow R_2$ transition state steric effect which destabilizes respectively, from trans-enolates, transition state T_2 , and from cis-enolates, transition state T_3 . At the outset of our current studies (6), the decision was made to explore the role of "metal-centered steric effects" in the kinetic aldol process. Accordingly, large pseudo-1,3-diaxial $R_2 \leftrightarrow L$ interactions in transition state T_2 and T_3 might render the aldol process, from either enolate geometry, both highly stereoselective and independent of the steric requirements of the enolate ligand R_1 . For the reasons outlined in our earlier communication, dialkylboryl enolates have been demonstrated to be excellent candidates for highly diastereoselective aldol condensations. In these systems, enolate geometry translates to product stereochemistry in a highly diastereoselective process. The data in Table 1 summarizes the two important reaction variables, R_1 and the metal center, in the kinetic aldol process. As is illustrated, when the R_1 -enolate ligand is sterically demanding (t-butyl) aldol diastereo-

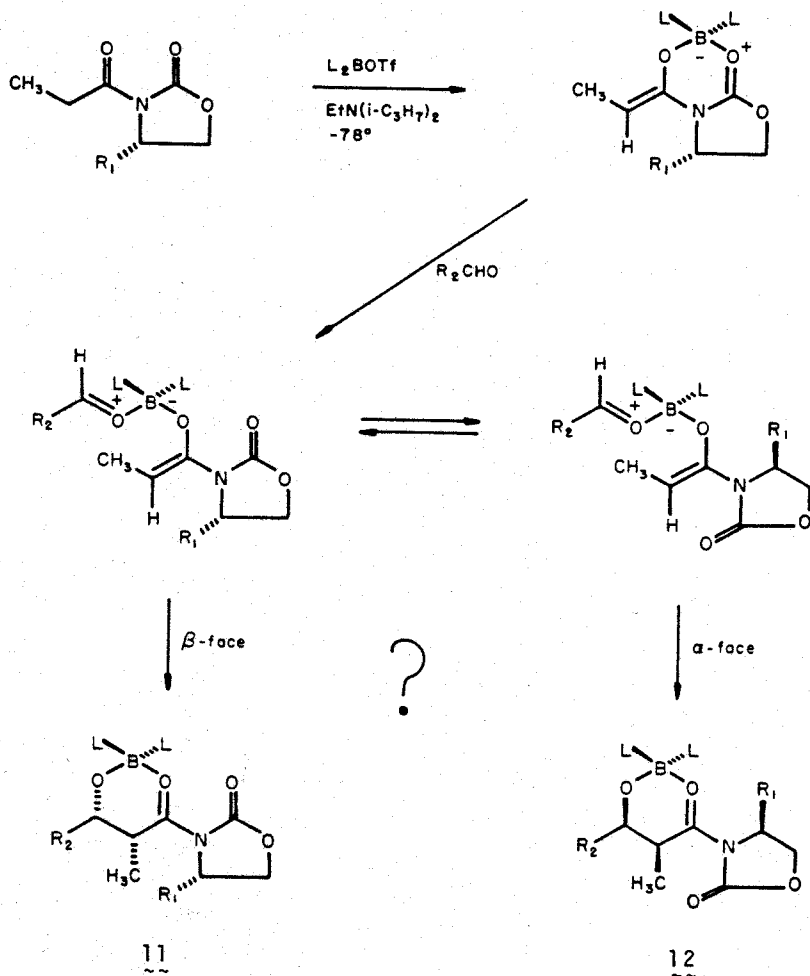
Table 1. Kinetic Aldol Diastereoselection. Metal Center and Enolate Ligand Variables.

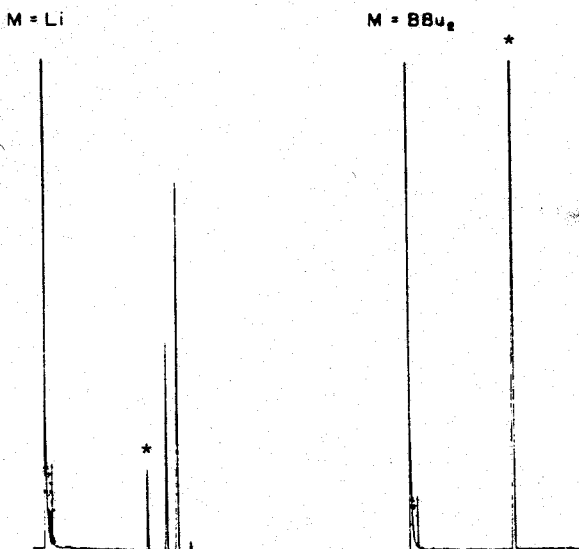
			
	Metal Li MgBr BBU ₂	E:T >98:2 >95:5 >98:2	Heathcock (1977) Dubois (1972)
	Li BBU ₂	80:20 >98:2	
	Li BBU ₂	≈80:20 >98:2	
	Li BBU ₂	60:40 5:95	
	Li AlEt ₂ B(C ₅ H ₉)C ₆ H ₁₃	48:52 50:50 3:97	House (1971) H. YAMAMOTO (1977)

selection is high and independent of metal center structure for the reasons elaborated above. As the enolate ligand R_1 becomes less sterically demanding, the importance of metal center structure becomes readily apparent.

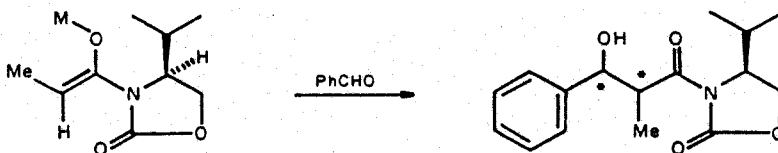
With this background information in hand the second phase of the problem, that of designing enantioselective aldol processes, has been addressed. Some of the more recent experiments undertaken in this laboratory have addressed the use of chiral oxazolidone imides in conjunction with their boron enolates for the aldol process. We have observed that these imides are readily transformed into their respective dibutylboryl enolates with dibutylboryl triflate (Hunig's base, -78° , methylene chloride) (Scheme XI). Of major concern to us at the time was that these particular enolates, upon aldehyde ligation, appeared to have no strongly preferred transition state chirality disposition with regard to the chiral auxiliary. Our preliminary projections on the sense of chirality transfer in this system were based upon transition state carbonyl-carbonyl dipole effects. Since it has been well established for imides that the preferred conformation aligns the carbonyl functions in the *E,Z*-conformation (9), we anticipated that this effect, expressed in the aldol transition state, would favor aldol diastereoisomer 12 in preference to 11. The striking results of the comparative aldol condensations of the lithium and dibutylboryl enolates are illustrated in Figure 1. The effect of metal center structure on both aldol diastereoselection and resultant enantioselection is both striking and somewhat difficult

Scheme XI





Column: 20M x 0.32 mm. Carbowax 20M at 160°C

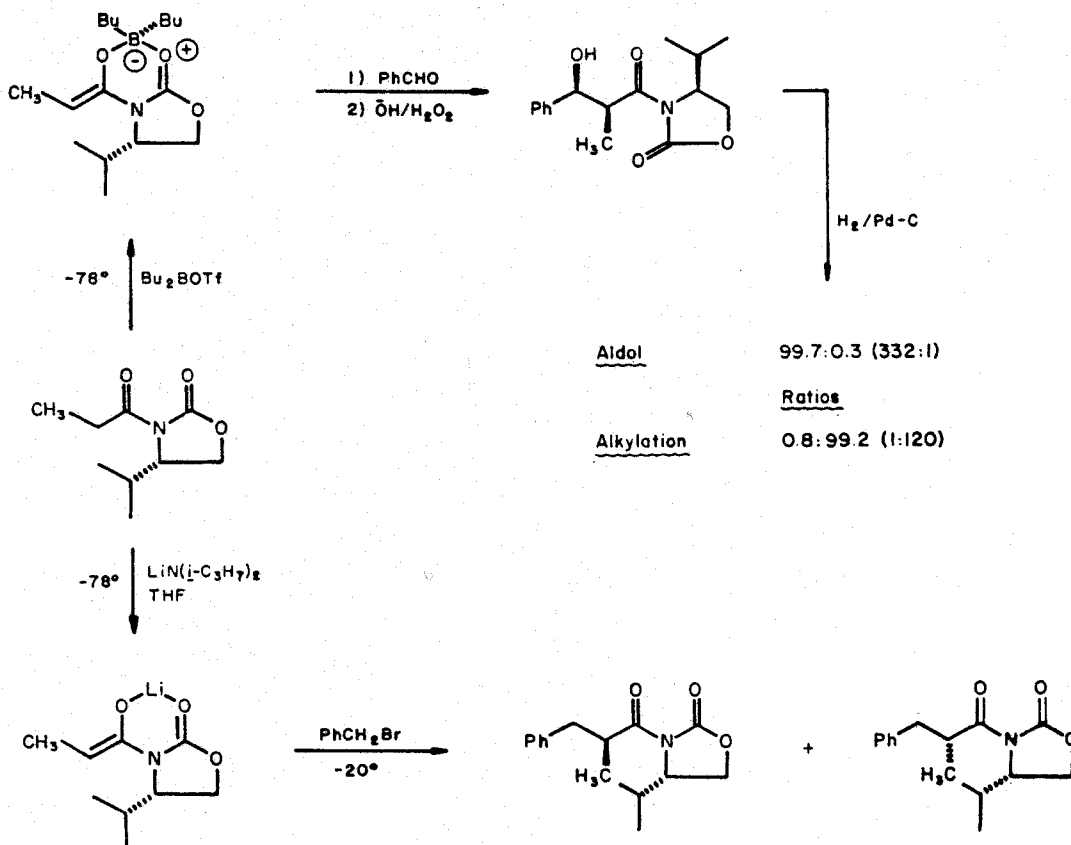


Metal	E_1	E_2	T_1	T_2
Li	9.8	29.5	59.0	1.7
BBu ₂	99.8	0.04	0.14	0.04

Figure 1

to rationalize based on the dipole arguments elaborated earlier. The absolute configuration obtained in the above-mentioned aldol process and the comparative benzyl bromide alkylation, is illustrated in Scheme XII. As can be seen, the sense of chirality transfer in the lithium enolate alkylation is opposite to that observed in the aldol condensation. The resultant (2R) and (2S)-3-phenylpropionic acid derivatives obtained from the hydrolysis of the illustrated oxazolidones indicated the compounds to be operationally optically pure substances. To date, a general survey of aldehyde structure on the generality of these observations has been gratifying, and enantioselective erythro-aldol condensations with these propionate-derived auxiliaries appears to proceed with erythro-enantioselection at the 99% level. In conjunction with our general explorations into the scope of these types of aldol condensations, we have investigated the possible applications of this technology to the creation of chiral acetate enolate equivalents. We were quite unprepared for the observation that, in contrast to our earlier observations, the derived chiral acetate enolates exhibited no chirality transfer in the aldol process (Scheme XIII). The operational solution to the creation of chiral acetate equivalents has been to employ the oxazolidone imide 13 (R = S-Me). The aldol condensation and subsequent desulfurization of this substrate leads to good levels of the chiral 3-hydroxyamide 14S whose absolute configuration has been unambiguously determined by hydrolysis to the corresponding hydroxyacid whose absolute configuration is secure (Scheme XIII). These sets of experiments raise several interesting questions pertaining to the con-

Scheme XII



control elements in the condensation process which regulate the sense and degree of chirality transfer. In conjunction with the acetate versus propionate results, we have observed (cf. Table 2) that chiral acetates are always less enantioselective than chiral cis-methyl substituted enolates (Table 2).

Although the dipole arguments elaborated earlier fortuitously predicted the stereochemical outcome of the propionate aldol condensations (Scheme XI), the lack of chirality transfer with the analogous acetate enolates (Scheme XIII) renders this stereochemical control element questionable. An alternative explanation of the importance of enolate methyl substitution in effective chirality transfer may well be associated with transition state allylic strain effects. Relative to the aldol adducts **11** and **12** (Scheme XI), the transition state leading to **11** could be destabilized by $R_1 \leftrightarrow \text{CH}_3$ allylic strain interactions which are absent in the acetate enolate counterparts. Scheme XIV illustrates the four diastereoisomeric chair transition states which lead to the two erythro-aldol isomers. The disposition of the chiral auxiliary in all four transition states has been aligned so that developing amide resonance can be accommodated. In transition states A and D the chiral ligand, R_C , is oriented exo to the pericyclic transition state while in transition states B and C the chiral auxiliary is disposed in the more sterically demanding endo-arrangement. In assessing the relative importance of transition states A and D, we presume that the aforementioned allylic strain considerations disfavor transition state D over transition state A. It is clear from the above discussion that it will be a difficult task at best to sort out all the important control elements in these chirality transfer processes. Nonetheless, we are providing an operational model for those who wish to project these results into their own applications.

For many carbonyl substrates the dialkylboron triflate reagents are simply not reactive enough to promote enolization. This is particularly true with simple ester and amide substrates. In parallel investigations we have been exploring the capabilities of other sterically demanding metal centers

Scheme XIII

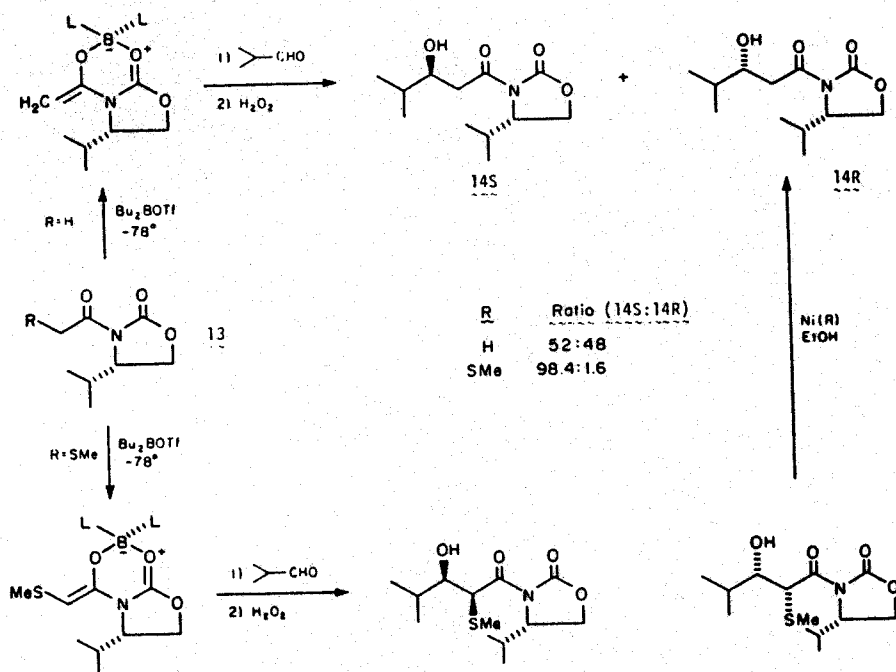
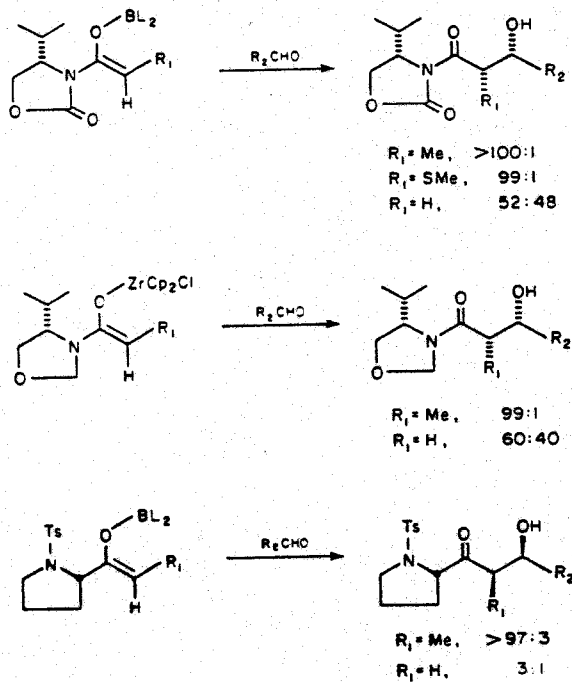
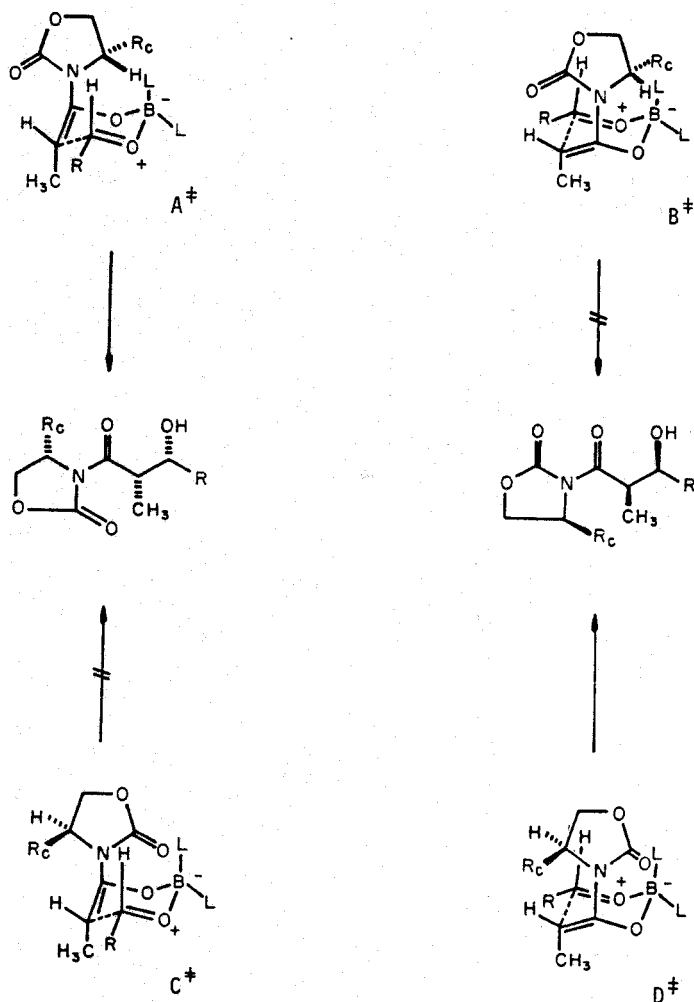


Table 2. Importance of Enolate Substitution.

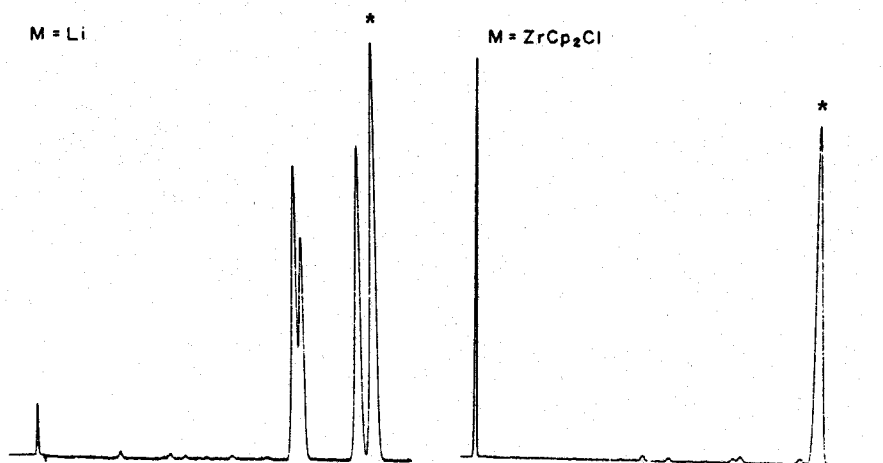


Scheme XIV

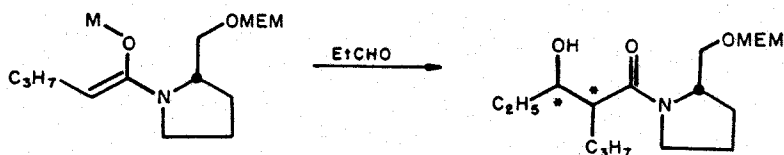


in the regulation of the aldol process. One particularly attractive amide enolate system that has been investigated in some detail in these laboratories, involves the use of zirconium sandwich complexes to which we have ligated amide enolates (10). These zirconium enolates are readily prepared from the corresponding lithium enolates and Cp_2ZrCl_2 without perceptible loss in enolate geometry. The importance of metal-center effects has been further demonstrated in the condensations of the prolinol-derived amide enolates (Figure 2). As illustrated, the lithium enolate shows little if any diastereoselection or enantioselection in the illustrated aldol process. In contrast, the zirconium-based condensation exhibits an excellent level of stereoregulation of both types. We have extensively explored the generality of these zirconium enolate condensations and find them to be completely general with regard to the aldehyde and enolate ligands. Scheme XV illustrates two types of amino acid-derived propionamides which have enjoyed considerable success in our laboratory. The overall yields of β -hydroxy esters from the precursor propionamides 15 and 16 are excellent and no racemization has been detected in the resultant amide hydrolyses. As described earlier, both substrates 15 and 16 possess latent β -hydroxy amide functionality which, under acidic conditions, reveals the crucial hydroxyl group which aids in the amide hydrolysis *via* acyl transfer.

Given the importance of transition state allylic strain factors, we have assumed that the chiral auxiliary in the enolates derived from both 15 and 16 will orient the chiral center toward the metal center. Those transition states in the zirconium aldol condensations which correlate enolate and aldol product chirality for amide substrate 15 and 16 are illustrated in



column: 20 M x 0.32 mm Carbowax 20 M at 200°

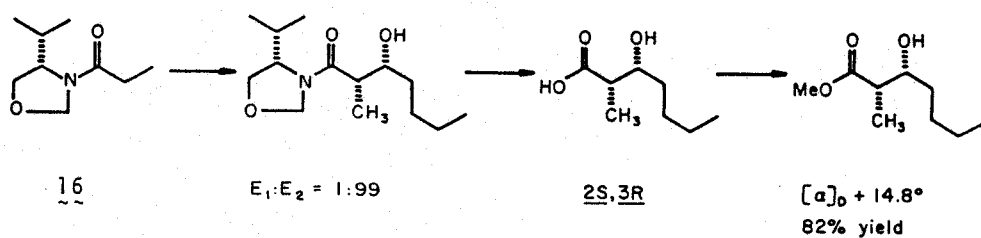
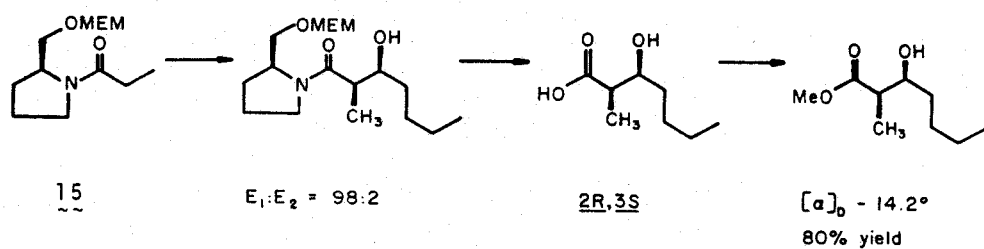


Metal	T_1	T_2	E_1	E_2
Li	21	16	26	37
Cp_2ZrCl	0.7	1.6	2.1	96

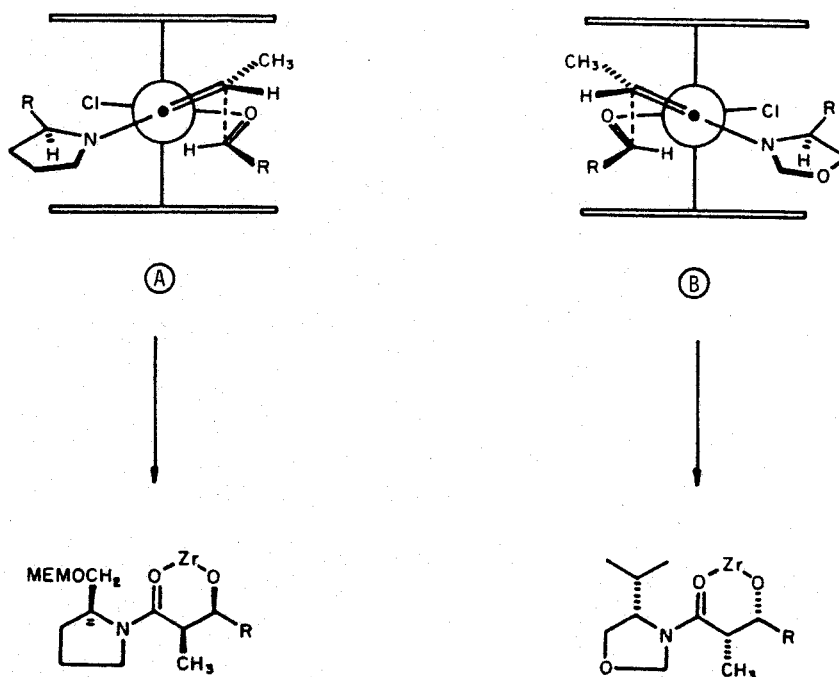
Figure 2

Scheme XVI. Theory predicts that the 16-electron zirconocenes possess a vacant orbital which lies in the X-Zr-X plane (X = Cl, OR) (11). Hence, aldehyde ligation at the metal center should result in aldol transition state conformations of the type illustrated (Scheme XVI). We feel that non-bonded interactions between the cyclopentadienyl ligands and the Z-methyl on the enolate exclude alternate transition state conformations in this system. In conjunction with these studies, we have made parallel observations on the lower enantioselection observed with the chiral acetate enolates in this series; and again, we feel that allylic strain considerations must be invoked to explain these observations (cf. Table 2). In all cases, the absolute configuration at the newly generated aldol centers has been unequivocally determined. We feel that these observations will be of fundamental importance in helping us to understand the subtle control elements that are being exerted in these highly selective condensation processes. Applications of the aforementioned chiral enolate methodology to natural Product syntheses are in progress.

Scheme XV



Scheme XVI



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REFERENCES AND NOTES

1. J. W. Scott and D. Valentine, Synthesis, 329 (1978) and references cited therein.
2. A. I. Meyers, Pure & Appl. Chem., 51, 1255 (1979).
3. For a general review see: F. Johnson, Chem. Rev., 68, 375 (1968).
4. D. A. Evans and J. M. Takacs, Tetrahedron Lett., in press.
5. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, J. Org. Chem., 45, 1066 (1980).
6. D. A. Evans, E. Vogel, and J. V. Nelson, J. Am. Chem. Soc., 101, 6120 (1979).
7. H. E. Zimmerman and M. D. Traxler, J. Am. Chem. Soc., 79, 1920 (1957).
8. J. E. Dubois and P. Fellman, Tetrahedron Lett., 1225 (1975).
9. E. A. Noe and M. Raban, J. Am. Chem. Soc., 97, 5811 (1975).
10. D. A. Evans and L. R. McGee, Tetrahedron Lett., in press.
11. J. W. Lauher and R. Hoffman, J. Am. Chem. Soc., 98, 1729 (1976).