# Chapter 1: Enolate Alkylations

## 1.1 Introduction

The alkylation of metal enolates ranks among the most powerful asymmetric C-C bond forming reactions in the arsenal of organic transformations. Their pivotal utility in the synthesis of stereochemically complex molecules stems from the predictability, reliability, and importantly, the ease of execution of these processes in the laboratory. Contributions to the field by Enders, Evans, Meyers, Myers, and Seebach clearly demonstrate that research in this area continues to provide handsome dividends in the form of new, powerful tools for asymmetric C-C bond construction.

There are numerous examples of diastereoselective alkylations of substrates wherein the extant asymmetry of the substrate provides possess suitable stereochemical control elements for efficient asymmetric alkylation.[1] Numerous useful guiding principles have been determined for each class to aid in predicting the stereochemical outcome of an alkylation. The methods discussed in this section are limited to those that are of historical importance and those that provide a general, modern approach to the preparation of optically active building blocks. The first section deals with the class of alkylations that have been typically included under the rubric of chiral-auxiliary controlled processes. As suggested by the term, the auxiliary is only transiently utilized and, following alkylation, subsequently excised. The last section of this chapter considers the alkylation of hetero-stubstituted enolates. The ready availability of optically active α-, β-, and γ- hetero-substituted carboxylic acid derivatives from the chiral pool and, more recently from catalytic, asymmetric synthesis renders this class of alkylations quite versatile for the construction of stereochemically complex systems, particularly those with quaternary stereogenic centers.[2]

Often the elaborate stereochemistry found in large target structures may be derived from the chiral pool utilizing starting materials such as carbohydrates, amino acids, and terpenes. However, the stereogenic centers that can be constructed by diastereoselective auxiliary-based alkylations are infinately more diverse and structurally unique, providing adducts that are otherwise difficult to directly access from the readily accessible set of naturally occurring and commercially available starting materials. While the auxiliaries themselves are themselves derived from the chiral pool, the advent of asymmetric enolate alkylation has reached a level of sophistication that allows the synthetic chemist greater versatility in the innovative design of synthetic strategies towards compounds of interest. Additionally, in all the modern asymmetric alkylation procedures either optical antipode is accessible with equal ease, a feat not always trivial when starting from the chiral pool. As a testimony to the remarkable progress that has been accomplished in this area, a relatively small set of auxiliaries for diastereoselective alkylations meet the requirements for a multitude of asymmetric alkylations. Moreover, the auxiliaries can serve as convenient handles leading to other functionality and even as protecting or blocking groups in subsequent synthetic transformations.[3]

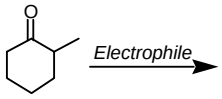
Although other processes utilizing substoichiometric quantities of chiral amide bases and metal complexing agents have been reported,[4] the diastereoselective alkylation of substrates bearing a chiral controlling group

$RCl + I^- \rightarrow RI + Cl^-$

Relative rates of substitution[a]

| Substituent | Relative Rate |
|---|---|
| *i*-propyl | 1 |
| *n*-butyl | 16 |
| *n*-propyl | 16 |
| ethyl | 40 |
| methyl | 1200 |
| allyl | 1600 |
| benzyl | 4800 |

[a] From Streitwieser, A. *Solvolytic Displacement Reactions*; McGraw: New York, 1962.




| Electrophile | Relative Rate |
|---|---|
| *n*-PrBr | 1 |
| EtBr | 1.5 |
| MeBr | 30 |
| Allyl Br | 250 |
| $PhCH_2Br$ | 600 |
| EtBr | 1 |
| EtI | 2.5 |
| EtOTs | 5 |
| $(EtO)_2SO_2$ | 48 |

Conia, J.M. *Bull Soc. Chem. Fr.* **1950**, *17*, 533. Conia, J.M. *Rec. Chem. Progr.* **1963**, *24*, 43.

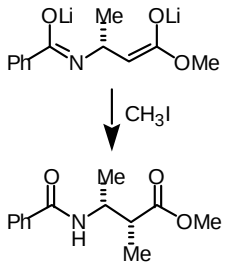
offer a higher degree of generality in the generation of stereogenic centers. In this chapter several asymmetric methods for diastereoselective enolate alkylations will be described. Importantly, for each of these methods, a number of useful procedures have been developed for scission of the auxiliary carbon bond with simultaneous carbon oxidation, reduction or homologation for conversion into various functional groups while avoiding stereochemical degradation of the recently formed chiral center. The weakly nucleophilic enolates of some of the early auxiliary-based asymmetric alkylation processes provided access to a limited set of alkylation products because only reactive electrophiles such as methyl, benzyl, and allyl iodides could be employed. Nevertheless, it is interesting to note that despite the continuous evolution of this field, some of these traditional methods remain in use in many laboratories for the preparation of specific product classes.

$N_3^- + BuBr \rightarrow BuN_3 + Br^-$

| *Solvent* | $\log\left(\frac{K_{solvent}}{k_{MeOH}}\right)$ |
|---|---|
| MeSOMe | 3.1 |
| $HCONMe_2$ | 3.4 |
| MeCN | 3.7 |
| $MeCONMe_2$ | 3.9 |
| $Me_2N_3PO$ | 5.3 |

The early reports of Meyers on the diastereoselective alkylation of oxazoline derived carbanions were followed by the oxazolidinone derived chiral carboxamides of Evans. Both of these groundbreaking classics underscore the importance of counterion effects in the effective asymmetric induction by the chiral auxiliary. Physical studies of related alkylation reactions have revealed the structural complexities of metal enolates and the dynamic intricacies of the their reactions in solution. The elegant, meticulous studies of Arnett,[5] Boche,[6] Collum,[7] Jackman,[8] Seebach,[9] Streiweiser,[10] and Willard[11] reveal the mechanism of enolate alkylation to be a multi-variable problem that is far from simple. It is clear that at the present level of understanding it is difficult to extrapolate the observations of any one enolate system into a widely applicable generalized mechanistic scheme.

Although the effect of solvents on the rate of alkylations has long been recognized and investigated,[12] the pronounced effects of adjuncts on reaction rates and stereoselectivities, such as added lithium chloride to a reaction mixture, have only been recently appreciated.[13] In a series of elegant studies on the structure and reactivity of metal enolates Seebach noted the beneficial consequences of added metal salts on the rate of enolate alkylations, possibly because new sets of enolate aggregates are kinetically accessed in solution.[9] A dramatic application of this phenomenum is found in the powerful pseduephedrine-based alkylations reported by Myers. As will be discussed below, the practical advantages of this system are that a wide range of electrophiles can be utilized: branched and unbranched alkyl halides as well as epoxides. Moreover, the unique reactivity profile of the alkylated amide products allow their conversion to a wide range of derivatives including primary alcohols, aldehydes, acids, and ketones.



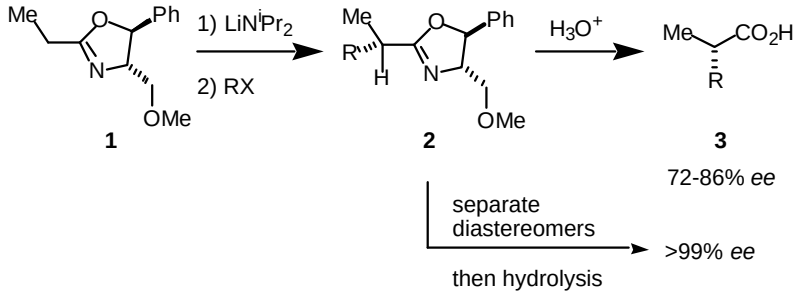

| | | |
|---|---|---|
| No LiCl | 0 °C | 4 : 1 dr |
| Added LiCl | –75 °C | 99 : 1 dr |

In contrast to the alkylation of carboxyl-derived enolates, few general highly stereoselective methods are available for the asymmetric alkylation of aldehyde and ketone enolates. In the early 1980's, Enders reported an elegant solution to ketone and aldehyde alkylation difficulties by the use of the aza metallo enolates. As will be described below, treatment of aldehydes or ketones with *N*–amino, *O*-methyl (*R*)- or (*S*)-prolinol (RAMP or SAMP) furnishes chiral hydrazones that undergo highly selective alkylation reactions.

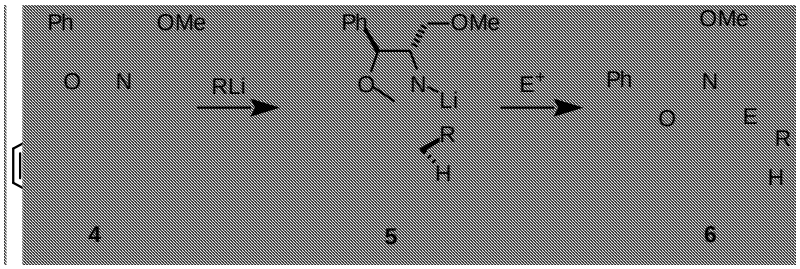
### 1.2 Auxiliary Based Alkylations

**Chiral Oxazolines as Carboxylic Acid Surrogates.** The alkylation reaction of optically active amino-acid derived oxazolines provided the first

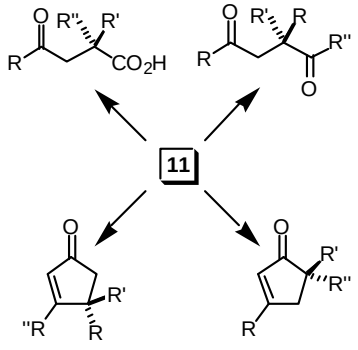
practical solution to the diastereoselective alkylation of carboxylic acid derived enolates. Alkylation of the oxazoline **1** with primary aliphatic or allylic iodide affords adducts **2** in 72-86% stereoinduction. A significant advantage to the auliliary alkylation strategy is that the alkylation products can be separated by chromatography to give diastereomerically pure compounds. Subsequent hydrolytic opening of oxazoline furnishes optically active α-substituted carboxylic acids **3**.



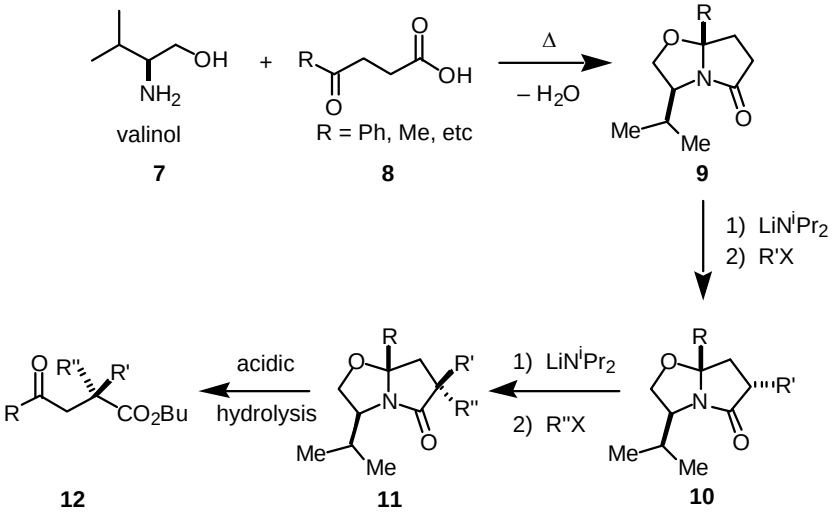

Meyers has reported a powerful application of the chiral oxazoline methodology in the asymmetric addition reactions of 1-substituted naphthalenes. Lacking sufficient acidity, the substituted naphthalenes **4** undergo conjugate addition reactions instead of enolization to furnish a stabilized carbanionic intermediate **5** that may be trapped with a variety of electrophiles to provide **5** in > 20 to 1 diastereomeric ratio.[14] The reaction chemistry developed by Meyers provides an elegant and expeditious approach to stereochemically complex ring systems that may be elaborated in synthetically useful ways.




Meyers has also developed the related stereoselective alkylation chemistry of fused, bicyclic oxazolidines (i.e., **9**), methodology that is particularly useful for the construction of a large array of molecules possessing quaternary stereogenic centers. The starting bicyclic lactams are readily prepared by condensation of amino alcohols, such as valinol with γ-keto or aldehydo acids **8** to furnish **9.** These undergo highly diastereoselective monoalkylation reactions with benzylic or allylic bromides and primary or even secondary aliphatic iodides; at the current level of development, hydrolysis of the isolated monoalkylated lactams **10** results in extensive epimerization. However, a second alkylation reaction proves equally diastereoselective, rendering this sequence of alkylations highly desirable for the synthesis of quaternary centers. The crude α,α-disubstituted acid acids are obtained in > 20 to 1 dr and in optically pure form by separation of the minor diastereomer prior to hydrolysis. Simply altering the order in which the electrophilic alkylating agents are introduced, provides ready access to either class of enantiomeric

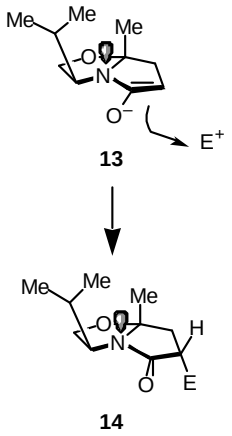


compounds **12** after acidic hydrolysis. Optically active keto acids **12** have been utilized in clever ways as powerful building blocks for the preparation of optically active cyclopropanes, cyclopentenones, cyclohexenones, and other useful compounds.[15]

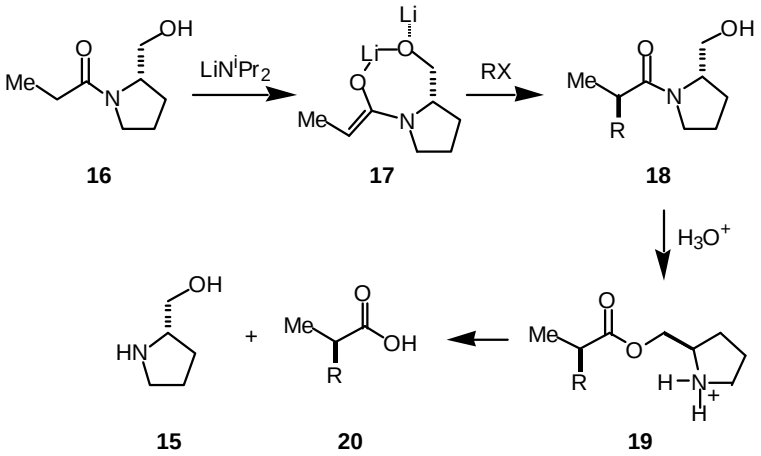



A discussion on the meticulous studies concerning the origins of the stereoseleectivity in these alkylation reactions has been documented by Meyers.[16] These studies suggest that a combination of remote steric and stereoelectronic effects operate in synergy to give the observed sense of induction in products **11**. Thus in addition to the primary steric influences at the two stereogenic centers in the starting bicyclic lactam, a nitrogen-based stereoelectronic effect, as illustrated by the lone pair nitrogen in **13**, provides further bias towards attack by the electrophilic species from the concave enolate face.

The bridgehead group and nitrogen lone pair cooperatively direct *endo*-alkylation.

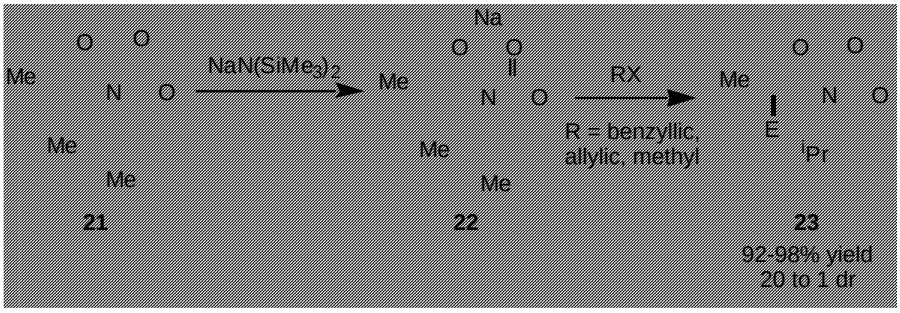



**Carboxamide Alkylations: Prolinol Amides**. One of the early successful auxiliary-based systems for carboxamide enolate alkylation reactions were the tertiary amides prepared from prolinol **15**.[17,18] The corresponding amide enolates exhibit sufficient nucleophilicity to undergo alkylation by activated or non-activated alkyl halides and other readily accessible electrophiles. The diastereoselectivity of the alkylation reaction is only marginally affected by variations in the parent carboxylate moiety; additionally, alkylations of α,β-unsaturated amides are also possible, providing α-substituted β,γ-unsaturated carboxamides.[19] Access to the enantiomeric alkylation products may be accomplished utilizing the unnatural (*R*)-prolinol derivatives. The structural and stereoelectronic characteristics that render amide-derived enolates more nucleophilic, in turn impart greater stability to the amide functional group towards hydrolysis. Thus, the identification of hydrolytic processes for the removal of this and related chiral auxiliaries is critical. In this regard, the presence of a β-alcohol in the prolinol auxiliary allows an acid-catalyzed amide to ester conversion that subsequently facilitates hydrolytic removal of the auxiliary.

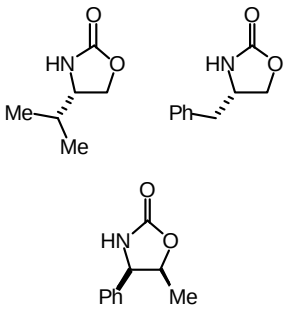



In subsequent studies Evans pioneered the use of the less nucleophilic carboximide-derived enolates in diastereoselective enolate alkylation reactions.[20] As will be discussed in subsequent chapters, the *N*-acyl oxazolidinones (e.g., **21**) enjoy a unique position in asymmetric methodology, as a chiral controlling group with wide applications in numerous mechanistically unrelated asymmetric transformations such as aldol addition, Diels Alder, enolate amination, and conjugate addition reactions.

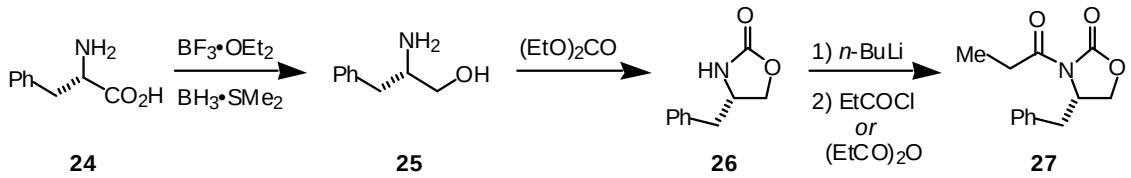
As carboxylic acid derivatives, *N*-acyl oxazolidinones approximate the reactivity patterns of thioesters: the derived alkali-metal enolates display moderate nucleophilicity. It is interesting that the difference in alkylation rates between the various alkali metal enolates is pronounced. Thus, although the reactivity of the lithium enolates is limited (0 °C), the corresponding sodium enolates undergo alkylation at lower temperatures (–20 °C). This feature results in higher observed diastereoselectivities (20:1) for the sodium enolates in the alkylation reactions with activated electrophiles.




An attractive feature of the oxazolidinone as an auxiliary stems from the fact that they are easily synthesized from inexpensive, commercially available starting materials. Moreover, their derivatives are typically crystalline, allowing for ease of purification and handling. The naturally occurring L-amino acids, typically valine and phenylalinine, provide access to oxazolidinones that lead to one enantiomeric class of C-α substituted carboxylic acids. The enantiomeric alkylation adducts can be accessed through the use of oxazolidinones derived from norephedrine, which is itself inexpensive and commercially available. The general procedure for the preparation of the chiral oxazolidinones is illustrated by the preparation of the phenyl alanine (**24**)

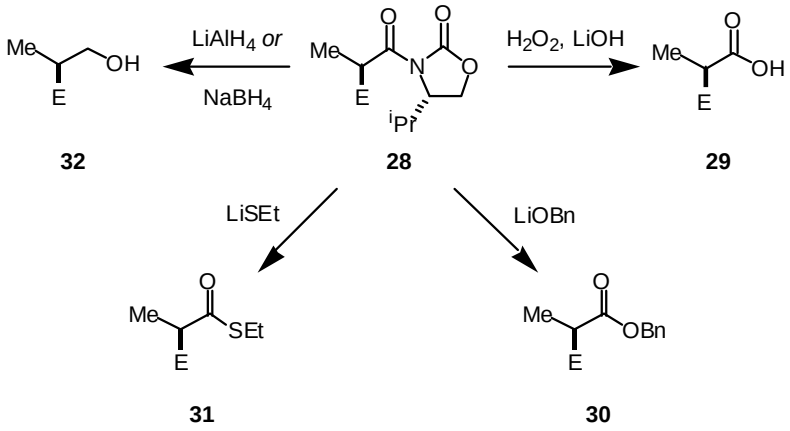


derived *N*-propionyl oxazolidinone **27**. Reduction of the amino acid furnishes amino alcohol **25** which upon heating in diethylcarbonate with azeotropic removal of the released ethanol yields **26**.[21] Deprotonation of the oxazolidinone and acylation with acid chloride or anhydride delivers **27**.




**24** **25** **26** **27**

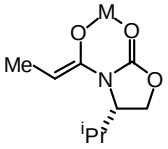
One of the advantages of the oxazolidinone auxiliaries is their ease of removal under a variety of conditions.[20] Treatment with $LiOH/H_2O_2$ or lithium alkoxides affords the free carboxylic acid and ester derivative, respectively. Additionally, treatment with LiSEt furnishes the corresponding synthetically versatile thioester **31**, itself a precursor to aldehydes ($Bu_3SnH$, $Pd^0$).[22] Treatment of *N*-acyl oxazolidinones with a variety of metal hydrides reduces to the corresponding primary alcohol **32**.




**32** **28** **29**

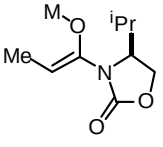
**31** **30**

There are several unique structural aspects of acyl oxazolidinones that have resulted in their central role as auxiliaries for a large array of asymmetric transformation. Although the enolization reaction of esters and ketones can lead to *E*/*Z* mixtures of diastereomeric enolates, amides and imides typically lead to the exclusive formation of *Z*-enolates.[23] This observation has been attributed to the minimization of non-bonding ($A_{1,3}$) steric interactions (present in **32**) during proton removal. A second feature of the oxazolidinone enolates is related to the ability of the carbonyl functionality of the auxiliary to coordinate to an appropriate coordinatively unsaturated metal (c.f., **33**, **17**, or **22**). This organizing feature provides rigidity to the enolate structure leading to a high degree of facial differentiation. For metals that preclude a second contact via the oxazoline C=O, it has been suggested that structure **34** is preferred as a consequence of a favorable alignment of dipoles.



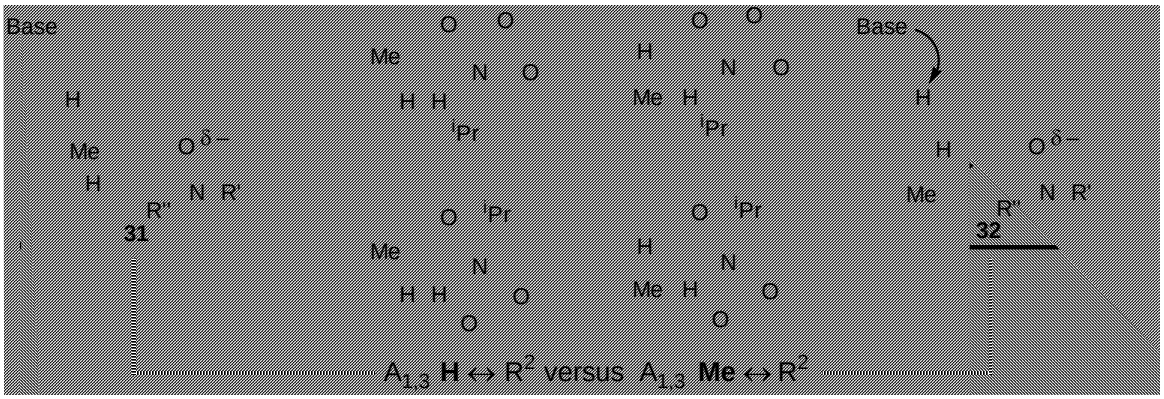

**33**

M: Chelating Metal

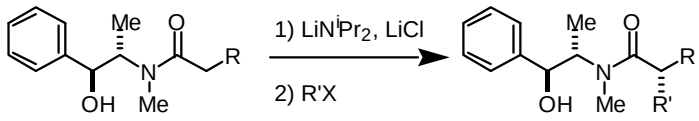



**34**

M: Coordinately Saturated Metal

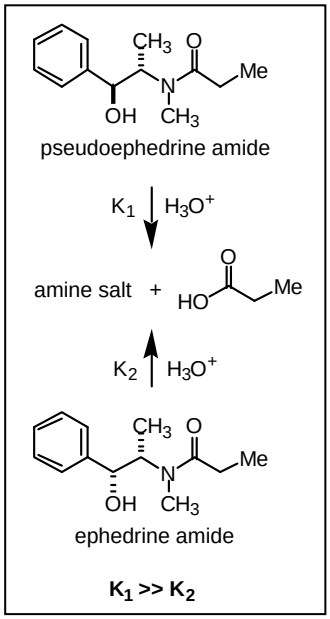



**Alkylations of Pseudoephedrine Derived Amides.** Myers has recently documented a highly selective, comprehensive method for the alkylation of pseudoephedrine derived *N*-acyl amides which offers several unique advantages.[24] Importantly, both enantiomers of pseudoephedrine are readily available as inexpensive commodity chemicals. *N*-Acylation of the optically pure pseudoephedrine with acid chlorides or anhydrides provides the corresponding tertiary amides in high yield. These amides **35** and their alkylation products often display a propensity to form crystalline materials, potentially simplifying their isolation and purification.

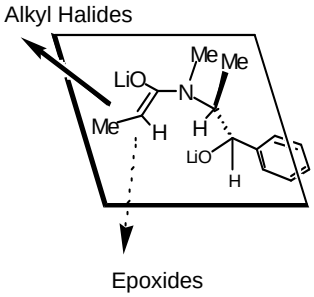



**35** **36**

85-95% Yields
> 40 to 1 dr

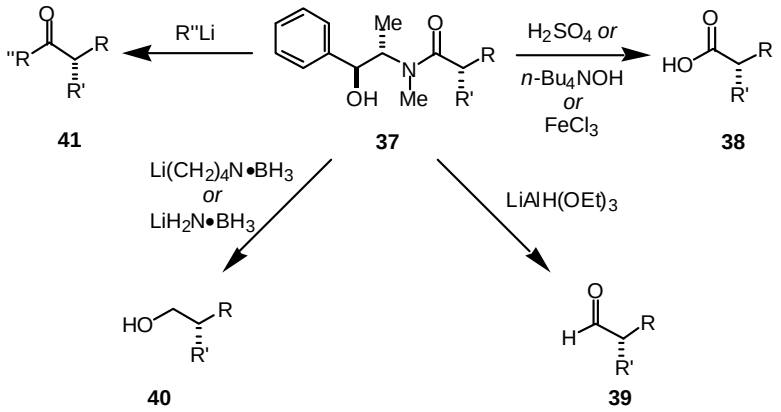



The alkylation procedure prescribes the use of sufficient base to lead to the generation of a dianionic species. The alkoxy enolate, in the presence of added excess LiCl, undergoes rapid, diastereoselective alkylation in THF with an impressively large range of electrophiles. Thus, in addition to methyl and benzylic halides that were utilized with the oxazoline and oxzolidinone auxiliaries, Myers has demonstrated that these amide enolate are sufficiently nucleophilic to react with aliphatic and β-branched alkyl halides may be employed. Moreover, epoxides[25] and α-fluorocarboxylates[26] also serve well in the alkylation reaction to afford α-substituted γ-alkoxy amides or α-substituted α-fluoro amides.



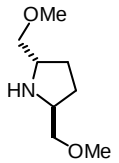

The presence of the secondary alcohol functionality in the auxiliary leads to enhanced rates of hydrolysis as was observed with the prolinol derived carboxamides. Additionally, in contrast to the ephedrine amides that had been previously investigated by Lavercheque,[27] pseudoephedrine amides hydrolyze 40 times faster than the diastereomeric ephedrine amides; it has been suggested that the 1,2-anti substitution pattern in pseudoephedrine leads to a more facile anchimeric assistance in the subsequent hydrolysis step.[28] Of great significance to the practical application of pseudoephedrine amide alkylation methodology is the fact that Myers has developed and optimized an assortment of high-yielding methods for transformation of the product amides into useful products, such as

acids, aldehydes, ketones, and alcohols, with little or no racemization.[29] These methods include: alkaline and acidic hydrolysis, hydride reduction, and carbanion addition.[30,31,32]



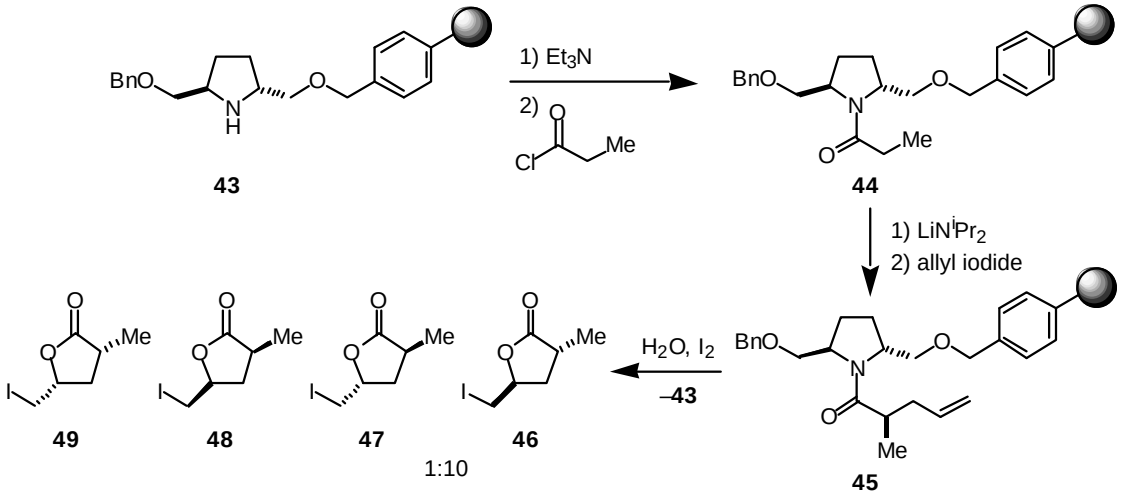

**the following sentence is out of place now**

The works of Ender, Evans and others demonstrate the versatility of auxiliaries based on the proline skeleton.[33] Katsuki and Yamaguchi have designed and utilized the $C_2$-symmetric 2,5-disubstituted pyrrolidine auxiliary **42** in a variety of asymmetric transformations. The enolates prepared from the derived carboxamides undergo alkylation reactions with superb diastereoselectivity, > 95 to 1.[34] However, in contrast to the proline-derived systems, access to the auxiliary hinges upon a multi-step synthetic preparation and the hydrolytic removal of the auxiliary necessitates considerably harsher reaction conditions.



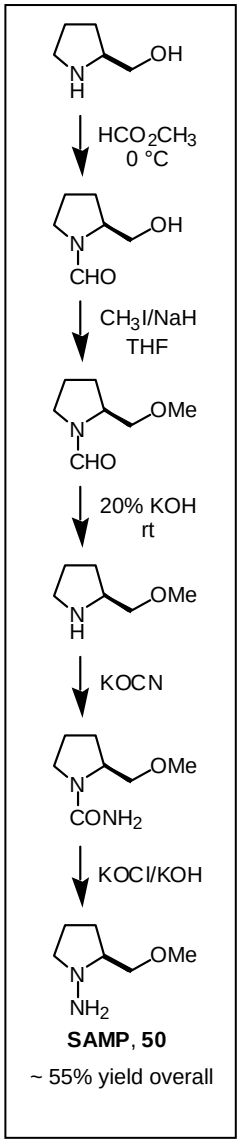
**42**

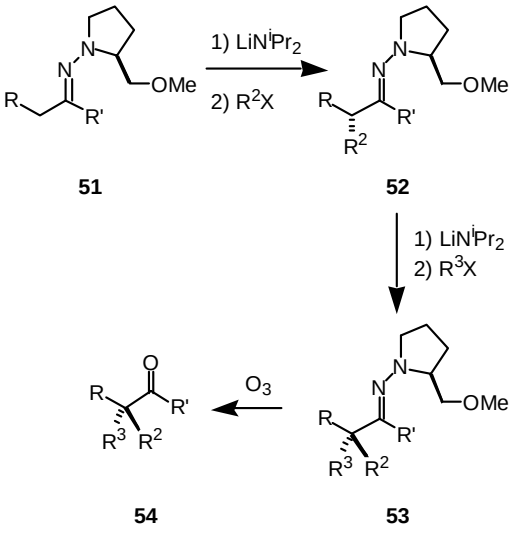
An important synthetic transformation is available to γ,δ-unsaturated amides, such as **45**, that circumvents the more rigorous hydrolysis conditions. Treatment of the unsaturated alkylation products **45** with electrophiles susceptible to attack by the alkene can lead to cyclization, and subsequent hydrolysis can provide optically active γ-lactones. This reaction has been elegantly employed by Kurth and Shore in the preparation of libraries of pharmacologically relevant stereochemically complex lactones.[35] Thus, treating amide **45** with aqueous iodine provided anti-lacones **46** and **47** in an 11:1 diastereomeric ratio in >87% ee and 35% yield from **43**. No trace of the syn-lactones **48** and **49** was detected. Additionally, this technique allows for the convenient recycling and reuse of the polymer-bound chiral auxilary **43**.

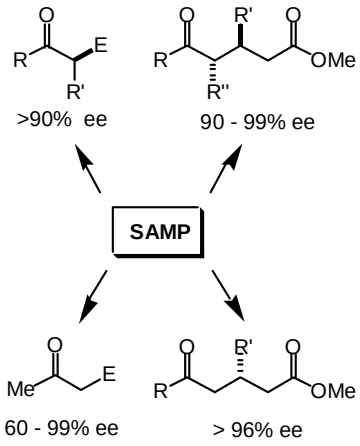



**Ketone alkylations: Proline-derived Hydrazones.** Some of the key problems associated with alkylation of ketone or aldehyde enolates have been appreciated for some time.[36] In comparison to carboxamide derived enolates the aldehyde and ketone derived counterparts are poor nucleophiles; in addition, the ease with which the alkylation products undergo epimerization under relatively mild acidic or alkaline conditions can provide a practical limit to the isolation of stereochemmcially pure alkylation adducts.

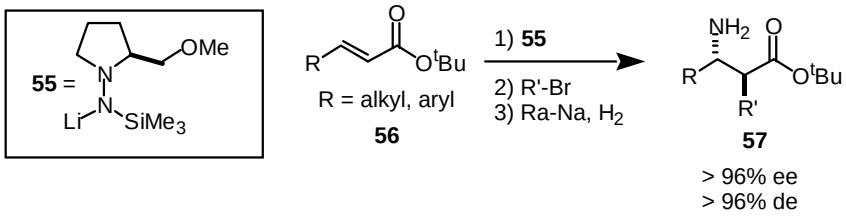
Enders has studied extensively the (*S*)-1-amino-2-methoxymethylpyrrolidine[37] auxiliary (SAMP, **50**) and its enantiomer, RAMP, in the alkylation reaction of the hydrazone derived azametallo enolates.[38] The RAMP and SAMP auxilaries circumvent most of the complications associated with ketone and aldehyde alkylations. In a typical reaction sequence, the RAMP/SAMP hydrazines are condensed with aldehydes or ketones to form the corresonding hydrazones **35**. These can be subsequently deprotonated with $LiN^iPr_2$ and the resulting enolate trapped with a variety of electrophilic reagents including alkyl halides, aldehydes, Michael acceptors, silyl triflates and disulfides. The RAMP/SAMP hydrazine auxiliary can be removed by acidic hydrolysis or oxidative cleavage to conveniently reveal the parent carbonyl without racemization






The SAMP scaffold also funtions well as nucleophilic chiral reagent. For example, the lithiated trimethylsilyl hydrazine **55** adds in a 1,4-fashion to traditional Michael acceptors such as cyclohexenones and α,β-unsaturated esters.[39] The intermetdiate ester enolate can be trapped with electrophiles to create two new chiral centers, typically with a >20 to 1 preference for the anti configuration. For this class of reactions, reduction of the N-N bond with Raney nickel affords the primary amine **57**.

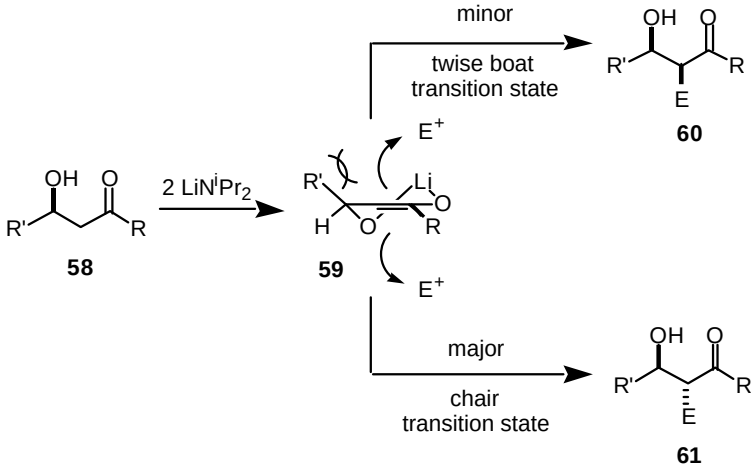


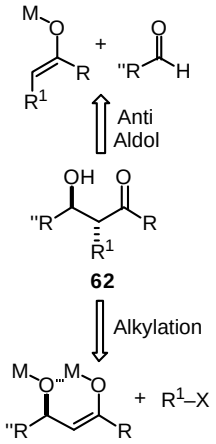

### 1.3 Hetero-Substituted Enolates

A number of optically active hetero-substituted carboxylic acids are excellent substrates for directing asymmetric alkylation reactions. Several of the classic methods are discussed below, with the exception of the alkylation of the dianion of α-hydroxy esters.[40,41] Many useful β-amino and β-hydroxyl carboxylates are inexpensive commodity chemicals or are readily accessible by facile synthesis or resolution. This has lead to the development of preparatively useful diastereoselective alkylation chemistry. For example, when **58** is treated with two equivalents of strong base, such as lithium diisopropyl amine, an alkoxy carbanion is generated. Treatment of the dianion with electrophilic alkylation agents results in highly diastereoselective C-α-alkylation products.

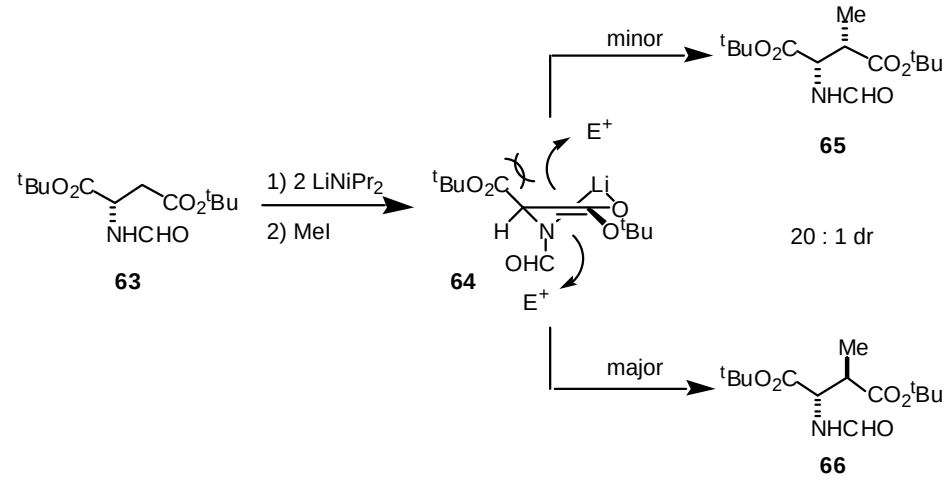
The fact that the products obtained from this alkylation reaction are anti-substituted α-substituted β-hydroxy carbonyl compounds (**61** and **62)** is noteworthy. This stereochemical pattern can in principle be accessed through an anti selective aldol addition reaction; however, this class of stereoselective aldol addition reactions has until recently remained a difficult challenge. Thus, the diastereoselective alkylation of β-hydroxy ketones and esters provides ready

access to this otherwise difficult stereochemical, functional group pattern.

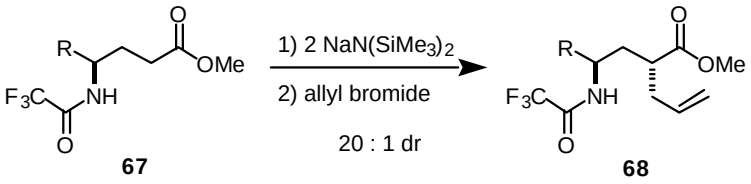



A simple chelating model allows for the systematic interpretation of the observed stereochemistry with β-hydroxy **58** or β-amino **63** carboxylates. Thus, double deprotonation leads to the formation of rigidified cyclic six-membered ring chelate **59** or **64**, wherein the enolate diastereofaces are differentiated by the allylic hetero-stereogenic center. Attack from the less hindered face accounts for the observed stereochemical outcome.[42]




Asymmetric induction from alkylation reactions of heteroatom substituted systems has been observed with more remotely substituted systems.[43,44] In this regard, γ-amino carboxylates **67** can be reliably alkylated with > 20 to 1 diastereomeric ratios.[45] Although β-oxygenated systems (**58**) necessitate that the corresponding alkoxide be utilized to prevent β-elimination, the β-amino substituted enolates need not be dianionic.[42] Indeed, numerous examples of enolate alkylations with uncharged and charged amino substituents have been reported




## 1.4 Applications of Asymmetric Alkylations to Natural Product Synthesis

The asymmetric alkylation methodologies described here constitute a powerful set of tools for the construction of complex molecules. The hallmark of the methods that have been discussed is their successful deployment in synthesis of natural products, a few examples of which are listed below. These molecules clearly illustrate the power of asymmetric alkylation methodology and should be consulted for further details. The bonds that were constructed through the use of asymmetric enolate alkylation have been highlighted in red. A survey of the methods described in this chapter highlight the high degree of sophistication to which the field of enolate alkylation has evolved. While it is tempting to state that the field has reached its apogee, such a statement would be foolhardy. Without doubt, the ingenuity and creativity of synthetic chemists in the future will produce unimagined advances in practicality and efficiency.

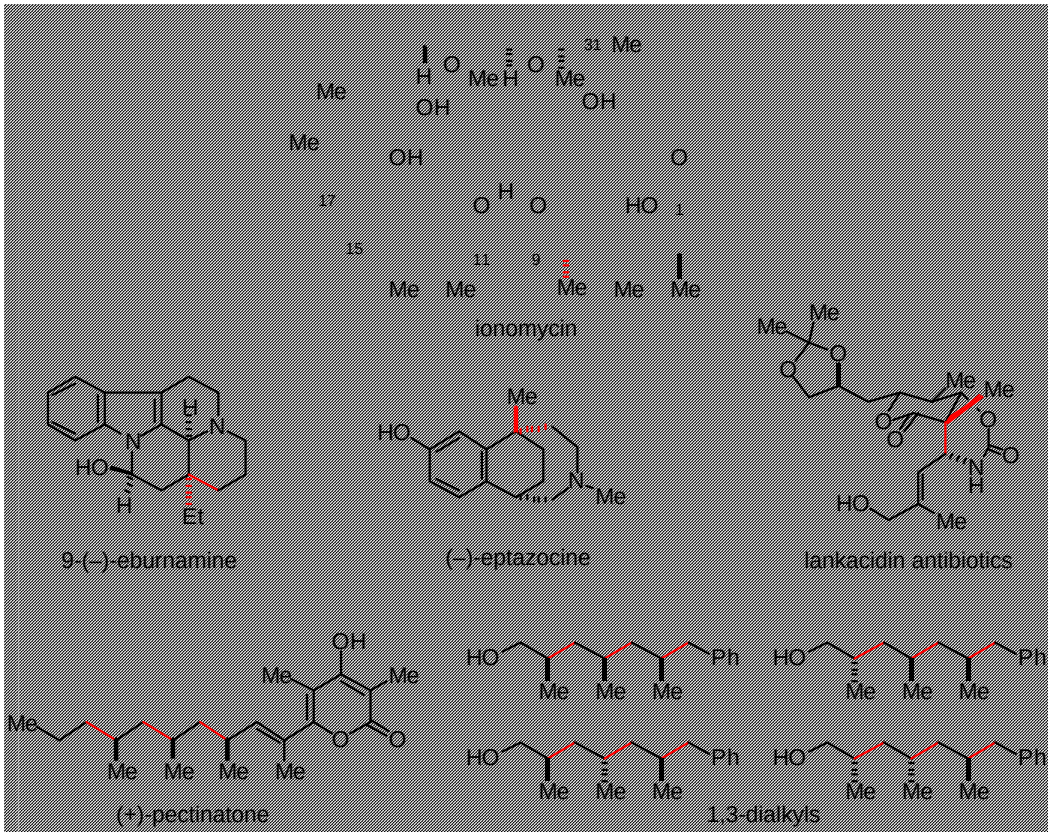



**Figure 1**. 9-(–)-eburnamine (bicyclic lactams - Meyers),[15] ionomycin (oxazolidinones - Evans, prolinol amides - Evans),[46] (–)-eptazocine (oxazoles - Meyers),[47] lankacidin antibiotics (hetero-substituted enolates – Williams),[48] (+)-

pectinatone (RAMP/SAMP - Enders),[49] 1,3-dialkyls (pseudoephedrine amides - Myers)[50].

**References**


[1] Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984, Vol 3 B, 1-110.
[2] Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. **1993**, *93*, 1307-1370.
[3] Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc*. **1995**, *117*, 3448.
[4] Beak, P; Basu, A.; Gallagher, D.J.; Park, Y.S.; Thayumanavan, S. *Accounts Chem. Res*. **1996**, *29*, 552-560.
[5] Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7288-7293.
[6] Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277-297
[7] Thompson, A.; Corley, E. G.; Huntington, M.F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028-2038.
[8] Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737-2769.
[9] Seebach, D. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 1624-1654.
[10] (a) Leung, S.S.W.; Streitwieser, A. *J. Am. Chem. Soc.* **1998**, *120*, 10557-10558. (b) Abbotto, A.; Leung, S. S-W.; Streitwieser, A,; Kilway, K. V. *J. Am. Chem. Soc.* **1998**, *120*, 10807-10813.
[11] Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602-8604
[12] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1990; Chapter 5.
[13] Yamashita, Y.; Odashima, K.; Koga, K. *Tetrahedron Lett*. **1999**, *40*, 2803-2806.
[14] (a) Meyers, A. I.; Hoyer, D. *Tetrahedron Lett.* **1984**, *25*, 3667-3670. (b) Barner, B. A.; Meyers, A. I *J. Am. Chem. Soc.* **1984**, *106*, 1865-1866. (c) Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010-1015.
[15] Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503-9569.
[16] Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7429-7438.
[17] Evans, D. A.; Takacs, J. M. *Tetrahedron Lett*. **1980**, *21*, 4233.
[18] Sonnet, P. E.; Heath, R. R. *J. Org. Chem*. **1980**, *45*, 3139-3141.
[19] Pagenkopf, B. L.; Lund, E. C.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 4421-4438.
[20] Evans, D. A.; Ennis, M. D.; Mathre, D. *J. Am. Chem. Soc*. **1982**, *104*, 1737-1739.
[21] Gage, J. R.; Evans, D. A. In *Organic Syntheses, Col. Vol. 8*; Freeman, J. P., Ed.; Wiley: New York, 1993; p 528.
[22] Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497-4513.
[23] Heathcock, C. H. In *Asymmetric Synth*., Ed. Morrison, J. D., Academic Press, New York, **1984**, *3*, 111. (b) Evans, D. A. In *Asymmetric Synth*., Ed. Morrison, J. D., Academic Press, New York, **1984**, *3*, xxx.
[24] Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361-9362.
[25] Myers, A.G.; McKinstry, L. *J. Org. Chem*. **1996**, *61*, 2428-2440.
[26] Myers, A. G.; McKinstry, L.; Barbay, J. K.; Gleason, J. L. *Tetrahedron Lett*. **1998**, *39*, 1335-1338.
[27] Larcheveque, M.; Ignatova, E.; Cuvigny, T. *Tetrahedron Lett*. **1978**, *48*, 3961-3964.

[28] Welsh, L. H. *J. Chem. Soc*. **1947**, *69*, 128-136.
[29] Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.
[30] Hutchins, R. O.; Learn, K.; El-Tebany, F.; Stercho, Y. P. *J. Org. Chem*. **1984**, *49*, 2438.
[31] Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singram, B. J. *J. Org. Chem*. **1994**, *49*, 6379.
[32] Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett*. **1996**, *37*, 3623-3626.
[33] Enders, D.; Klatt, M. *Synthesis* **1996**, 1403-1418.
[34] Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857-860.
[35] Moon, H. –s.; Schore, N. E.; Kurth, M. J. *Tetrahedron Lett*. **1994**, *35*, 8915-8918.
[36] House, H.O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin/Cummings: Menlo Park, CA, 1972; Chapter 9, pp 492-623.
[37] Enders, D.; Fey, P.; Kipphardt, H. In *Organic Syntheses, Col. Vol. 8*; Freeman, J. P., Ed.; Wiley: New York, 1993; p 26.
[38] Enders, D.; Klatt, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L.A., Ed.; Wiley: New York, 1995; p 178.
[39] Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 455-457.
[40] Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2708-2748.
[41] Seebach, D.; Sting, A. R.; Hoffmann, M. Angew. Chem., Int. Ed. Engl. 1996, 35, 2708-2748.
[42] Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824-1939.
[43] Seebach, D.; Wasmuth, D. Angew. Chem. 1981, 93, 1007.
[44] (a) Magnus, N.; Magnus, P. *Tetrahedron Lett*. **1997**, *38*, 3491-3494. (b) Linnane, P.; Magnus, N.; Magnus, P. Nature **1997**, *385*, 799.
[45] Hanessian, S.; Schaum, R. *Tetrahedron Lett*. **1997**, *38*, 163-166.
[46] Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc*. **1990**, *112*, 5290-5313.
[47] Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem*. 1995, *60*, 1265-1270.
[48] Williams, D. R.; Rojas, C. M.; Bogen, S. L. *J. Org. Chem*. **1999**, *64*, 736-746.
[49] Birkbeck, A. B.; Enders, D. *Tetrahedron Lett*. **1998**, *39*, 7823-7826.
[50] Myers, A. G.; Yang, B. H.; Chen, C.; Kopecky, D. J. *Synlett* **1997**, 457-459.