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Advances in Asymmetric Enolate Methodology☆

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1. Introduction

The driving force for the development of new methodologies in organic synthesis has been the need for simple and efficient strategies to obtain complex natural products and their analogs. Tremendous progress has been made in the area of asymmetric synthesis (i.e. formation of new bonds in a stereo- and enantiocontrolled manner) during the past few decades. Enolate chemistry has proven a powerful tool for obtaining carbon–carbon, carbon–oxygen, carbon–nitrogen, carbon–halogen bonds in organic synthesis. Aldol reaction is one of the most common reactions that utilize enolate chemistry. Two recent, excellent review articles on various aspects of aldol reaction were published by Cowden and Paterson[1] and by Nelson.[2] Cowden and Paterson summarized auxiliary-, substrate- and ligand-mediated stereo- and enantioselective aldol reactions.[1] Nelson reviewed the catalytic, enantioselective aldol reaction using chiral Lewis acids and bases.[2] The aim of the present review article is to focus upon (i) the recent developments in stereo- and enantiocontrolled synthesis

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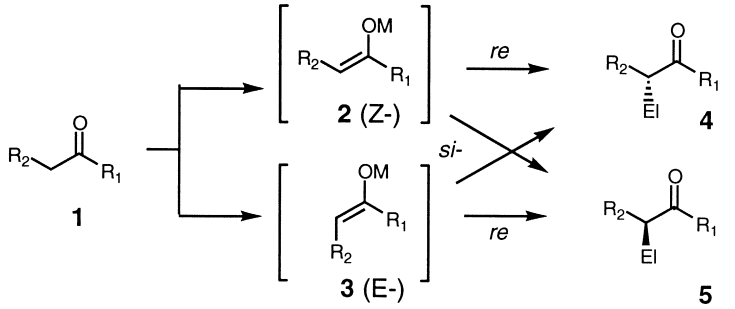
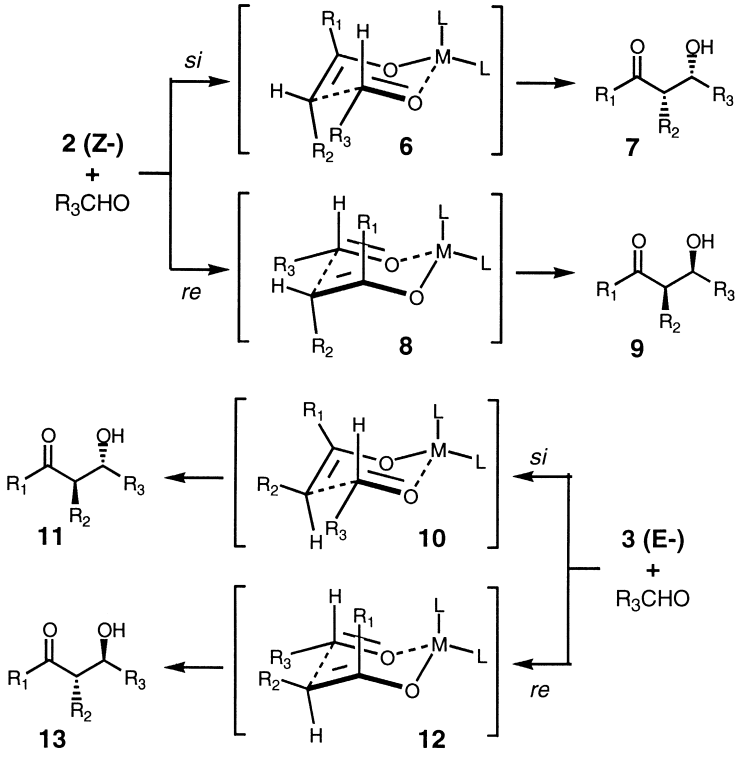


R_1, R_2: alkyl groups; M: metal; El: electrophile

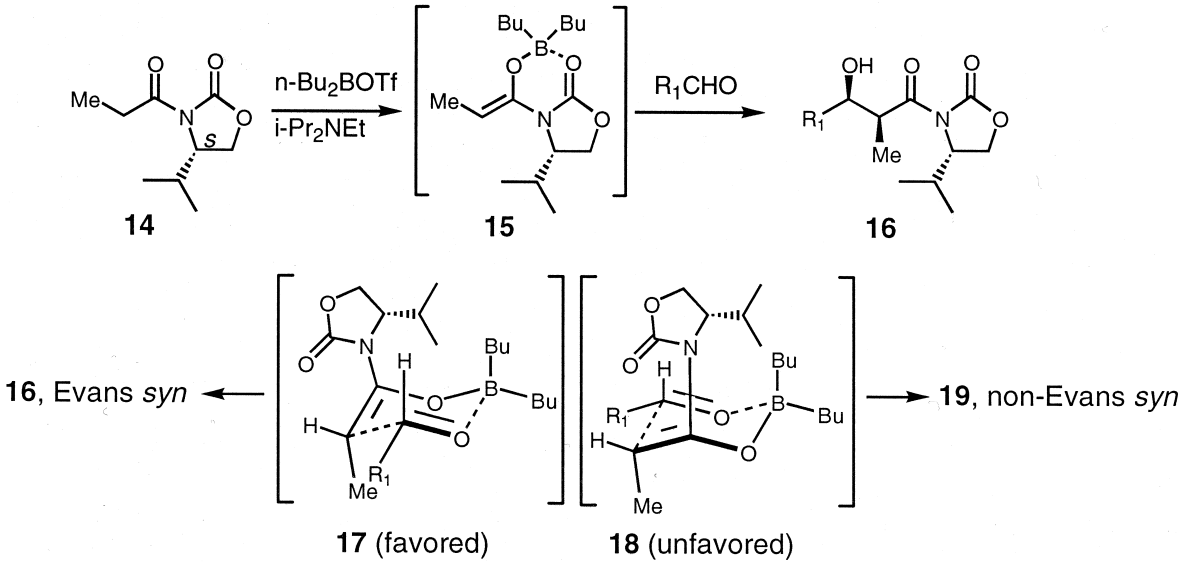


Scheme 1.

related to aldol reaction, (ii) non-aldol stereo- and enantioselective formation of C–C and C–X (X=O, N, Br, F, etc.) bonds, and (iii) stereoselective enolate reaction on solid phase synthesis. Due to the extensive body of work carried out in the area of asymmetric enolates, emphasis here is focused on topics that were not reviewed in the past, and selected examples are discussed in each category.

1.1. Stereodefined enolates and aldol reactions (Scheme 1)

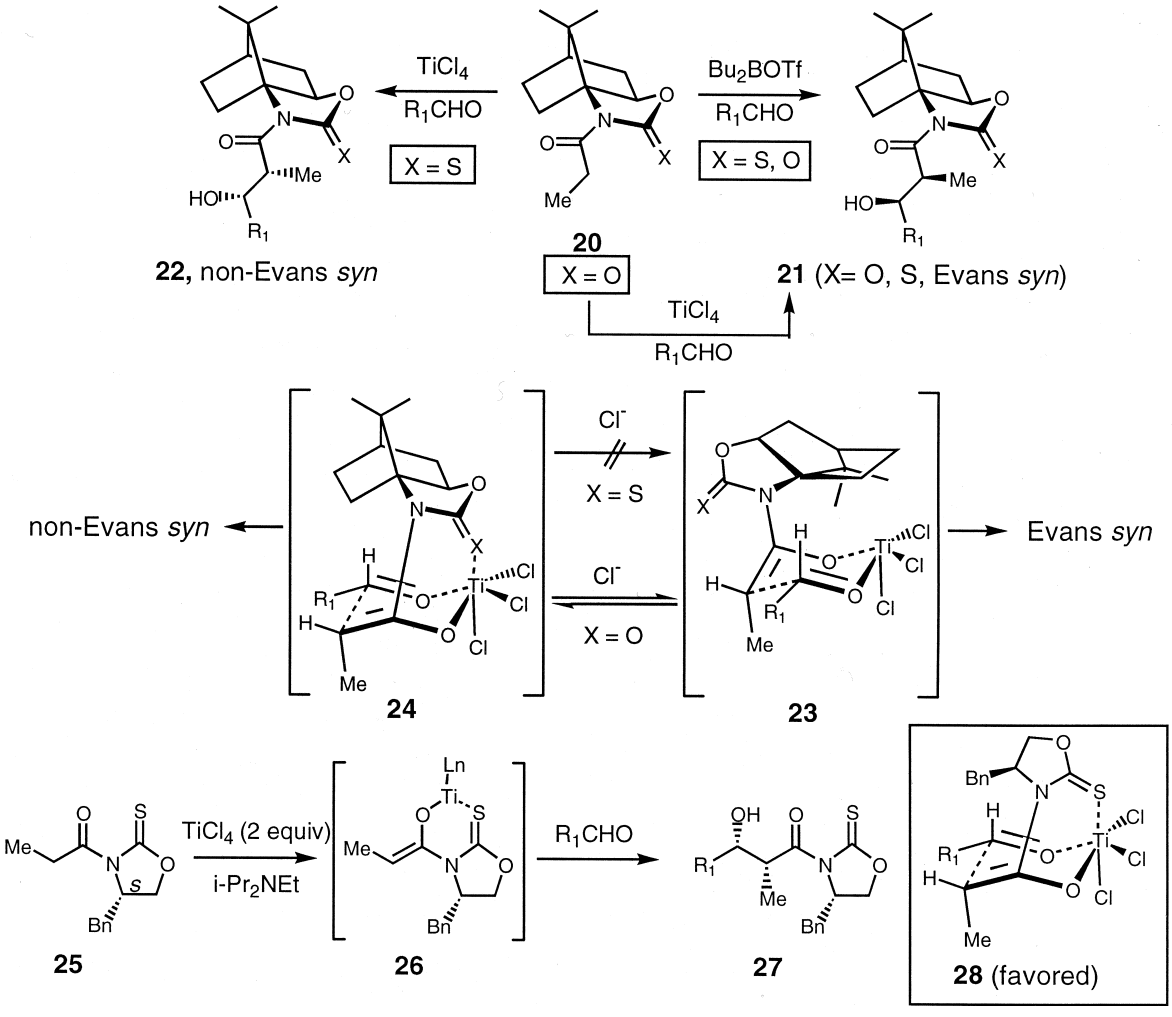
Over the years, chemists have developed methodologies to generate regioselective (kinetic vs. thermodynamic) as well as stereoselective enolates. Factors that govern these controls are summarized in several review articles.[1,3–5] Under kinetic conditions, two stereoisomers, commonly known as *Z*-(**2**) or *E*-enolates (**3**) are produced via the enol ether generated from keto derivative **1**. Each isomer then reacts with the electrophile (*re*- or *si*-face attack) to give two different products (**4** and **5**). There are several factors that control the stereoselective formation of the enol ether, subsequently followed by the π-face selective reaction with the electrophile. In general, enolate geometry plays an important role in determining the stereochemical outcome of aldol reaction which proceeds via a cyclic transition state. *Z*-enolate, **2** reacts with an aldehyde to produce 1,2-*syn* products (**7** or **9**), whereas 1,2-*anti* products (**11** or **13**) arise from an *E*-enolate. The reaction is believed to proceed via a six-membered cyclic, Zimmerman–Traxler-type transition state (only favored transition states are shown, see: **6**, **8**, **10** and **12**) in which the alkyl group of the aldehyde derivative adopts a pseudoequatorial position. Within 1,2-*syn* (**7** and **9**), or 1,2-*anti* (**11** and **13**) aldol products, enantioselection can be obtained via a chiral auxiliary or a chiral ligand based enolate.



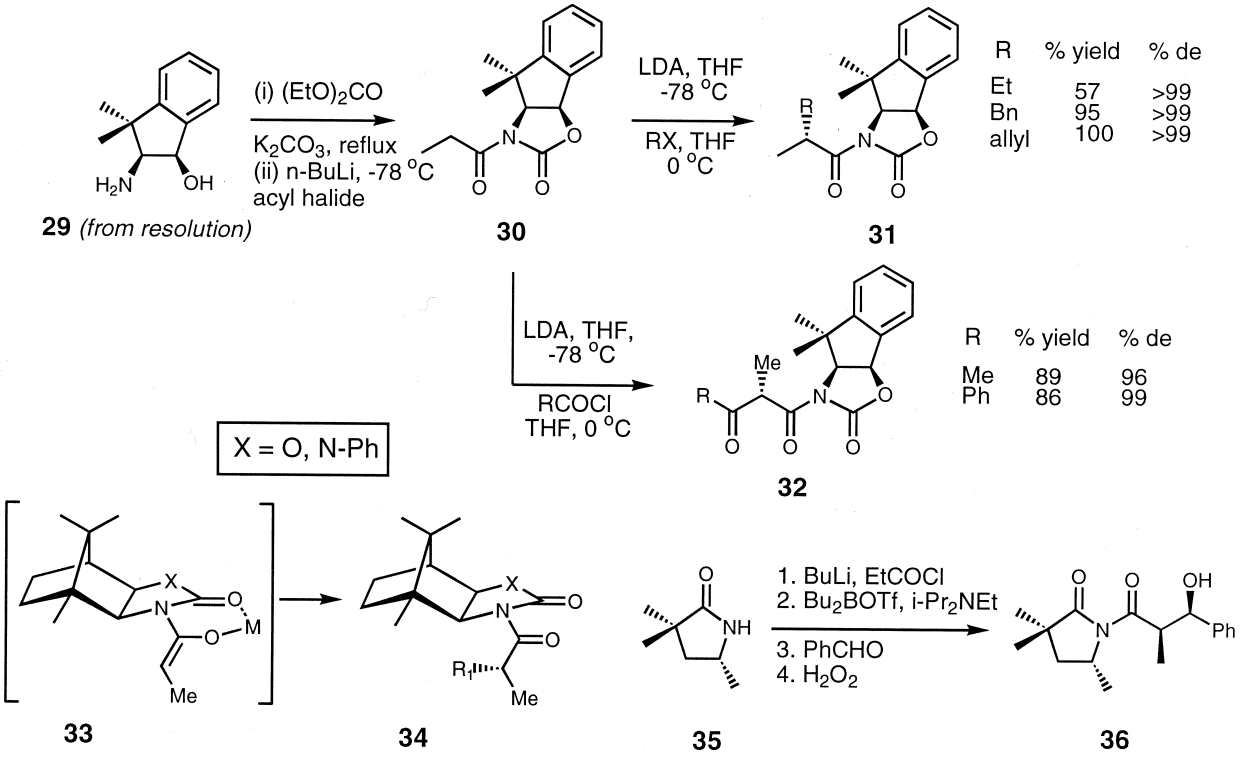
Scheme 2.

2. Chiral Auxiliary Mediated Enolate Reactions (Schemes 2–12)

The development of efficient chiral auxiliaries and reagents has fast-tracked the progress of asymmetric synthesis. A good chiral auxiliary should have the following properties: (a) easily introduced with high yield and high optical purity; (b) stable under enolate reaction conditions, (c) induces high

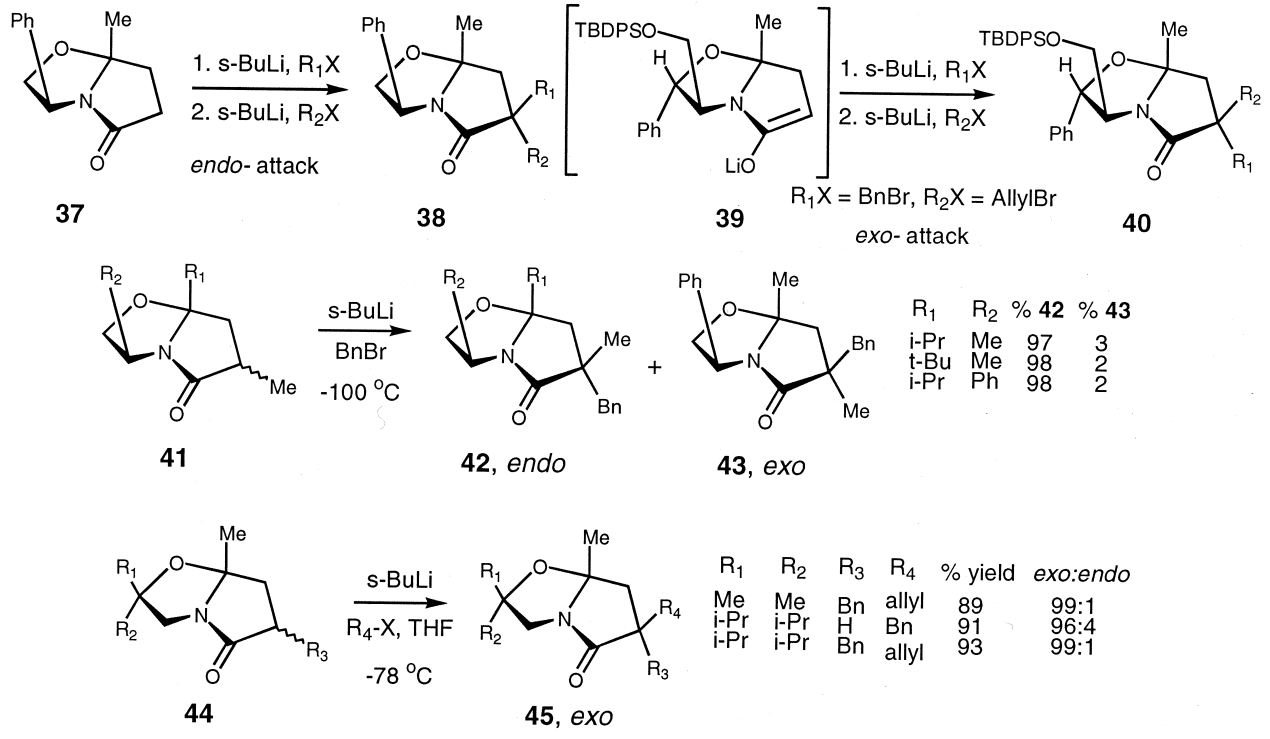


Scheme 3.



Scheme 4.

diastereofacial selectivity, and (d) easily removed and recovered. Most chiral auxiliaries are derived from natural sources such as amino acids, carbohydrates, terpenes, etc. and are used in stoichiometric quantities. A very common chiral auxiliary utilized in numerous, efficient syntheses is the amino alcohol derived from α-amino acids. Since the early 1990s, many new chiral auxiliaries have been developed for enolate chemistry, which include new derivatives of oxazolidinone, imidazolidinone, oxazoline, ephedrine, camphor, sugar derivatives, etc.



Scheme 5.

2.1. C–C: Oxazolidinone and pyrrolidinone derivatives (Schemes 2–4)

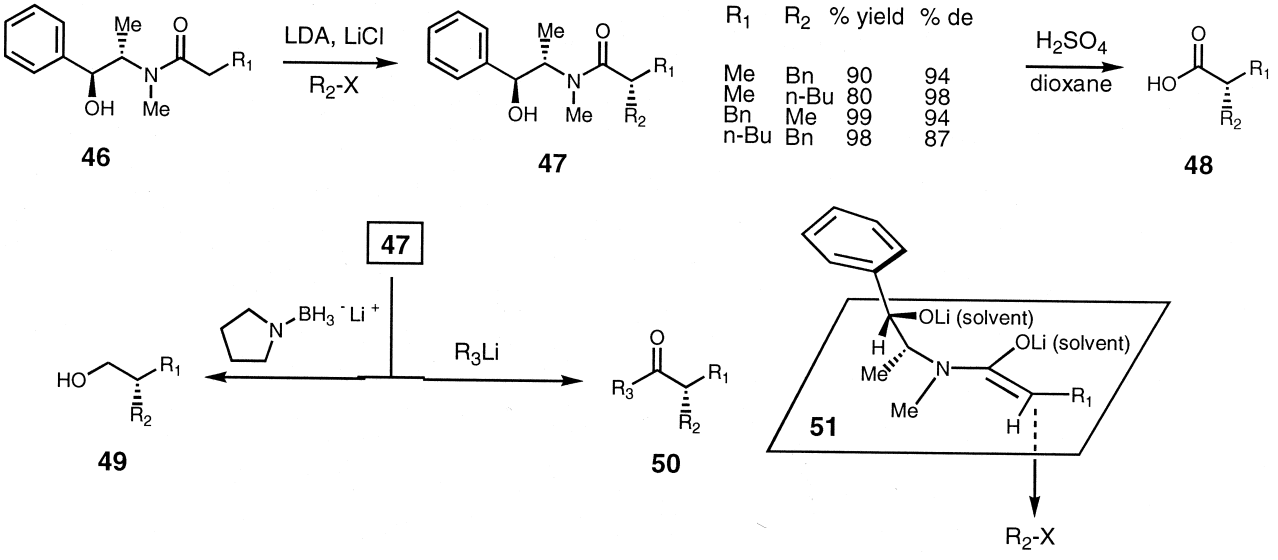
Derived from an α-amino acid, Evans' 2-oxazolidinone is the most popular auxiliary for developing efficient asymmetric strategies for C–C and C–X (X=O, N, Br, F, etc.) bond formation. Several review articles have nicely summarized the scope of Evans' oxazolidinone systems for the formation of C–C bonds.[1,6,7] As an extension to the original oxazolidinones, several modified derivatives have been developed over the years and utilized in asymmetric syntheses. A collection of successfully applied oxazolidinone based chiral auxiliaries has been presented in a review article by Cowden and Paterson.[1] The basic principles that govern stereocontrol with the chiral auxiliary are essentially the same as with the original Evans' auxiliary. Some convey better selectivity in specific reactions, producing highly diastereoselective products after crystallization.

For a typical aldol, reaction of the starting ketone derivative **14** (Scheme 2) leads to the *Z*-enolate **15** under kinetic conditions (*n*-Bu_2BOTf, *i*-Pr_2NEt, −78°C). Further reaction with an aldehyde gives the *syn*-aldol **16** (commonly known as Evans' *syn*) with a high diastereofacial (>250:1, >99% de) selectivity. The reaction is believed to proceed via a Zimmerman–Traxler-type cyclic transition state **17**, in which the *si*-face of the enol ether is hindered by the chiral auxiliary leading to attack from the *re*-face of the enol ether giving Evans' *syn* product **16**. Recently, this methodology was applied to aglycones of Vancomycin and Eremomycin antibiotics.[8] Obtaining non-Evans *syn*-aldol products has been more challenging in the past. Yan described a new model to switch between chelation and non-chelation controlled aldol reaction using camphor derived oxazolidinonethione **20** (Scheme 3).[9] The enolate (*n*-Bu_2BOTf, *i*-Pr_2NEt) of propionyloxazolidine derivative **20** (X=O, S) reacts with an aldehyde to give the expected Evans *syn* product **21** (X=O, S), however a similar reaction of **20** (X=S) using $TiCl_4$ gave the non-Evans *syn* **22**. It was proposed that the thio-oxazolidinone derivative may proceed via a chelated system, **24** (i.e. coordination of thioketone with Ti) leading to the non-Evans-type *syn*-product. Further, in the event of chelation, the small dipole moment of thioketones could override the dipole–dipole repulsions that account for Evans *syn* selectivity **23**. This observation was further confirmed by Crimmins, when non-Evans *syn* **27** was obtained from **25** using 2.0 equiv. of $TiCl_4$.[10] As suggested by Yan, a cyclic chelated model **28** was proposed to support the formation of the non-Evans *syn* product. This approach was further utilized in the total synthesis of Callystatin.[11]

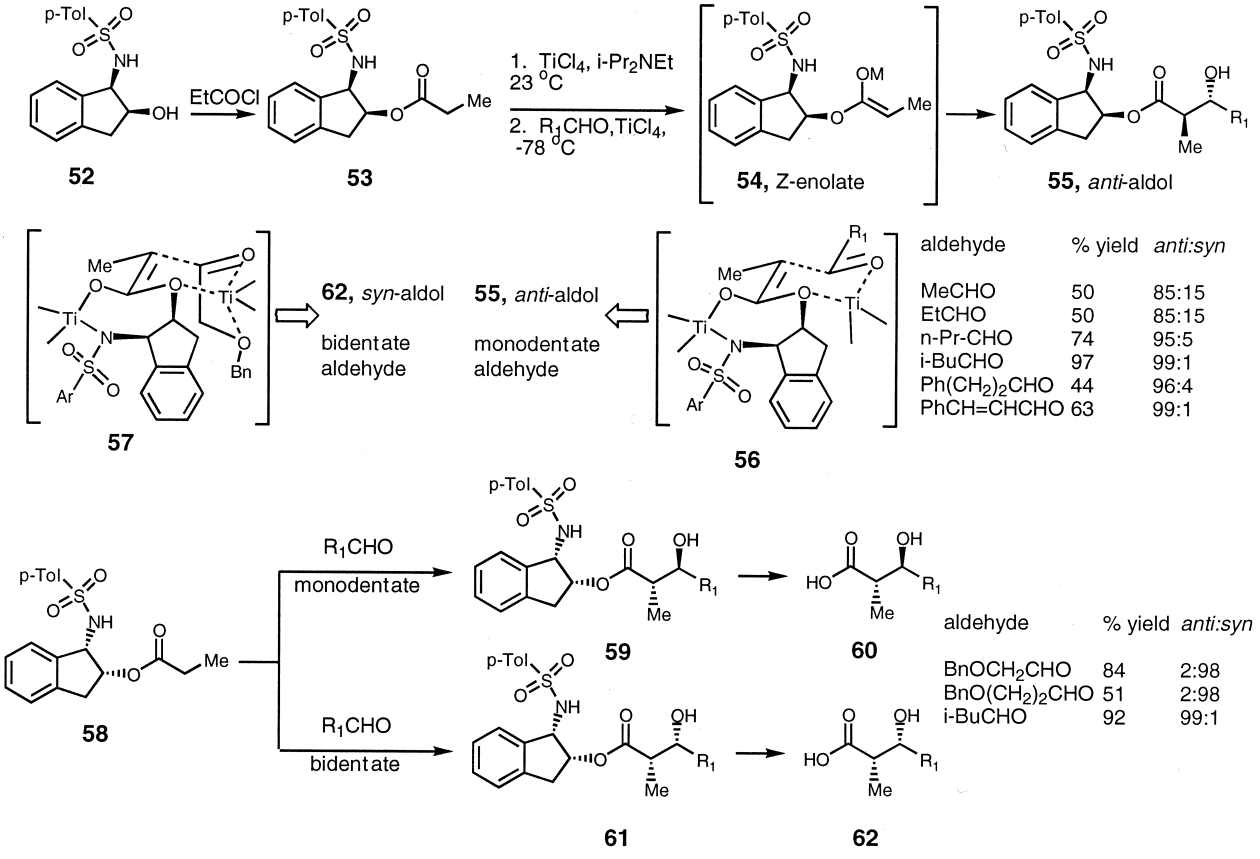
Amino indanol is another example of an oxazolidinone derived chiral auxiliary used in the formation of a C–C bond. Enantiomerically pure amino indanol was obtained via resolution and utilized by Saigo.[12,13] There are two important features in amino indanol based auxiliary methodology: (a) a fixed orientation of the amino and the hydroxyl groups, and (b) the geminal dimethyl group adjacent to the amino group. By simple modification, chiral oxazolidinone **30** was obtained from **29** (Scheme 4) and then reacted with several alkyl and acyl halides to give the alkylated and acylated products **31** (>99% de) and **32** (96–99% de). Another modification by Polomo, involved the use of *exo*, *exo*-amino borneol in developing an oxazolidinone derived auxiliary.[14–17] High selectivities with the *tert*-leucine derived oxazolidinone auxiliary prompted use of this system. Similar results from the alkylation of enolate **33** with several alkyl halides gave high selectivities.[18–20] In another approach, Davis[21–23] reported the use of 3,3-dimethyl-2-pyrrolidinone **35** as a chiral auxiliary for the stereoselective aldol reaction. Evans *syn*-aldol product **36** (>97% de) was obtained using a well-established dibutylboron methodology from **35**.

2.2. C–C: Oxazoline derivatives (Scheme 5)

Chiral oxazoline derivatives have been utilized by Meyers for several years.[24] Recently, Meyers has reported the use of chiral bicyclic lactams for controlling the stereochemistry of quaternary carbon centers.[25–31] It is known that the enol



Scheme 6.



Scheme 7.

ether from chiral lactam **37** (Scheme 5) gives *endo*-selectivity for alkylation, resulting in **38**. This approach is useful to obtain chiral cyclopentenone derivatives. A slight modification of the lactam derivatives (i.e. phenyl group at the α-position related to oxygen, see: **39**) led to *exo*-attack, **40**. The phenyl group in **39** hinders the concave site favoring attack from the *exo*-position. It is interesting to note that by a slight change in the lactam derivative, it was possible to modulate the stereochemical outcome of the alkylation reaction (**41** to **42**, *endo*-product and **44** to **45**, *exo*-product).

2.3. C–C: Pseudoephedrine derivatives (Scheme 6)

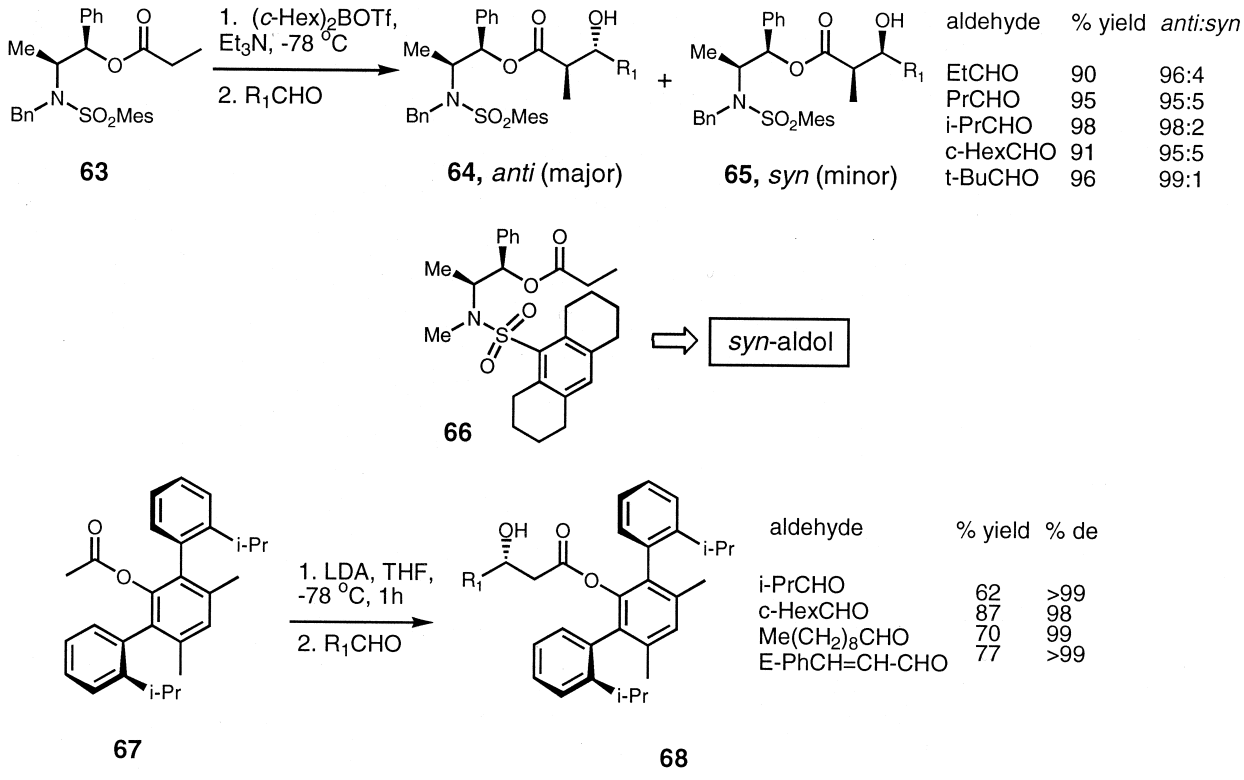
Following the leading work by Meyers for the stereoselective alkylation of the α-carbon of carboxylic acid derivatives, Myers reported the use of pseudoephedrine for a similar reaction.[32,33] Pseudoephedrine is inexpensive and readily available. The enol ether of pseudoephedrine amides, **46** (Scheme 6) on reaction with several alkyl halides gave high selectivity for attack (80–99% yields, 87–94% de). The auxiliary is cleaved by H_2SO_4 in dioxane providing **48** without any racemization. Further, the reaction of **47** with borane–lithium pyrrolidide gave pure alcohol **49**, whereas ketone derivative **50** was obtained on reaction with an alkyllithium. Although the origin of the selectivity is not clear at this stage, it is anticipated that the *Z*-enolate is preferred, followed by the *si*-face attack; it seems that the *re*-face is blocked by the solvated lithium alkoxide **51**.

2.4. C–C: *cis*-Arylsulfonamido indanol derivatives (Scheme 7)

Examples of *anti*-aldol selective reactions, using a chiral auxiliary approach, are rare. In 1996, Ghosh reported the use of *cis*-1-arylsulfonamido-2-indanol **52**[34] to obtain *anti*-aldol products from chiral ester enolate derivatives.[35] Chiral sulfonamide ester derivative **53** produces *Z*-enolate **54** using $TiCl_4$/*i*-Pr_2NEt at 23°C. This reaction with several monodentate aldehydes gave the *anti*-aldol **55** (44–97% yields, 85:15 to 99:1 for *anti*:*syn*). The formation of *anti*-aldol product was explained on the basis of a cyclic transition state model for *re*-face attack on the aldehyde. It was proposed that the titanium enolate is part of a seven-membered metallocycle which may exist in a chair-like conformation. The second titanium is complexed to the aldehyde and to the indanyloxy oxygen in a six-membered ring orientation. It was interesting to note that by using bidentate aldehydes, *syn*-aldol **62** was obtained.[36] The reaction of **58** with the monodentate aldehyde gave *anti*-aldol **59** leading to *anti*-acid **60** after hydrolysis, whereas bidentate aldehydes gave *syn*-aldol **61** (for the transition state model, see, **57**). The synthesis of the transition state mimics of HIV protease inhibitors was achieved using this methodology.[37]

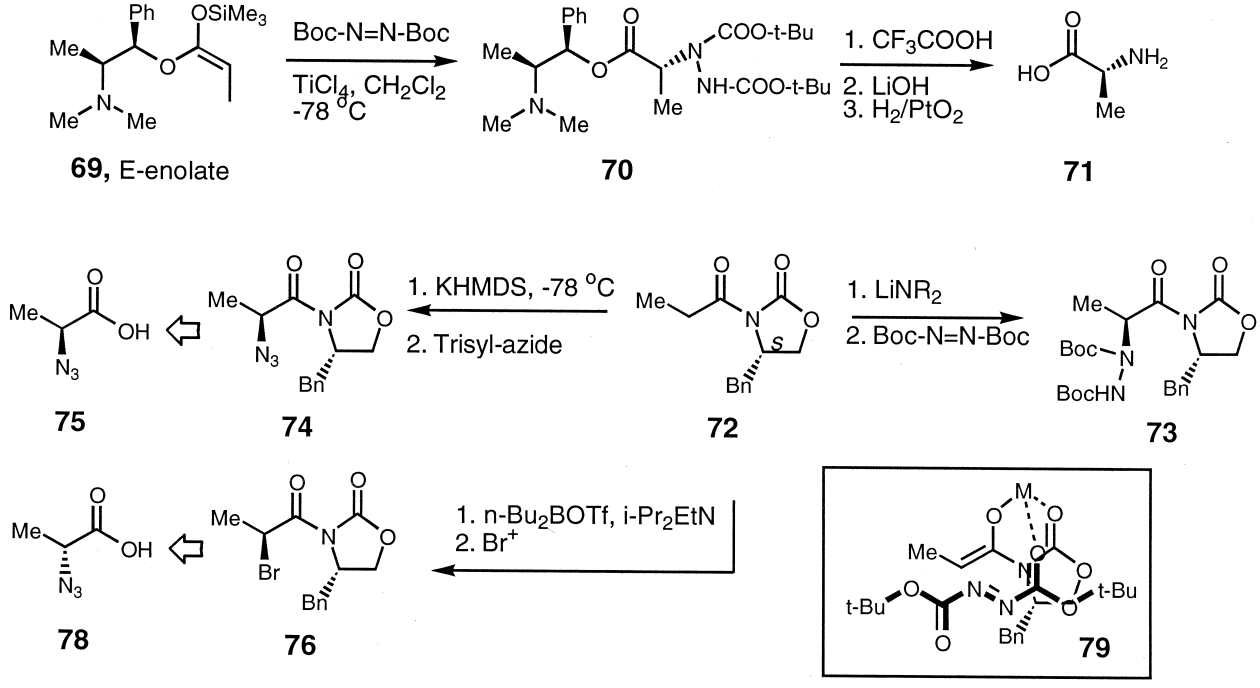
2.5. C–C: Norephedrine and bis(isopropylphenyl)-3,5-dimethylphenol derivatives (Scheme 8)

The formation of *anti*-aldol from norephedrine carboxyl



Scheme 8.

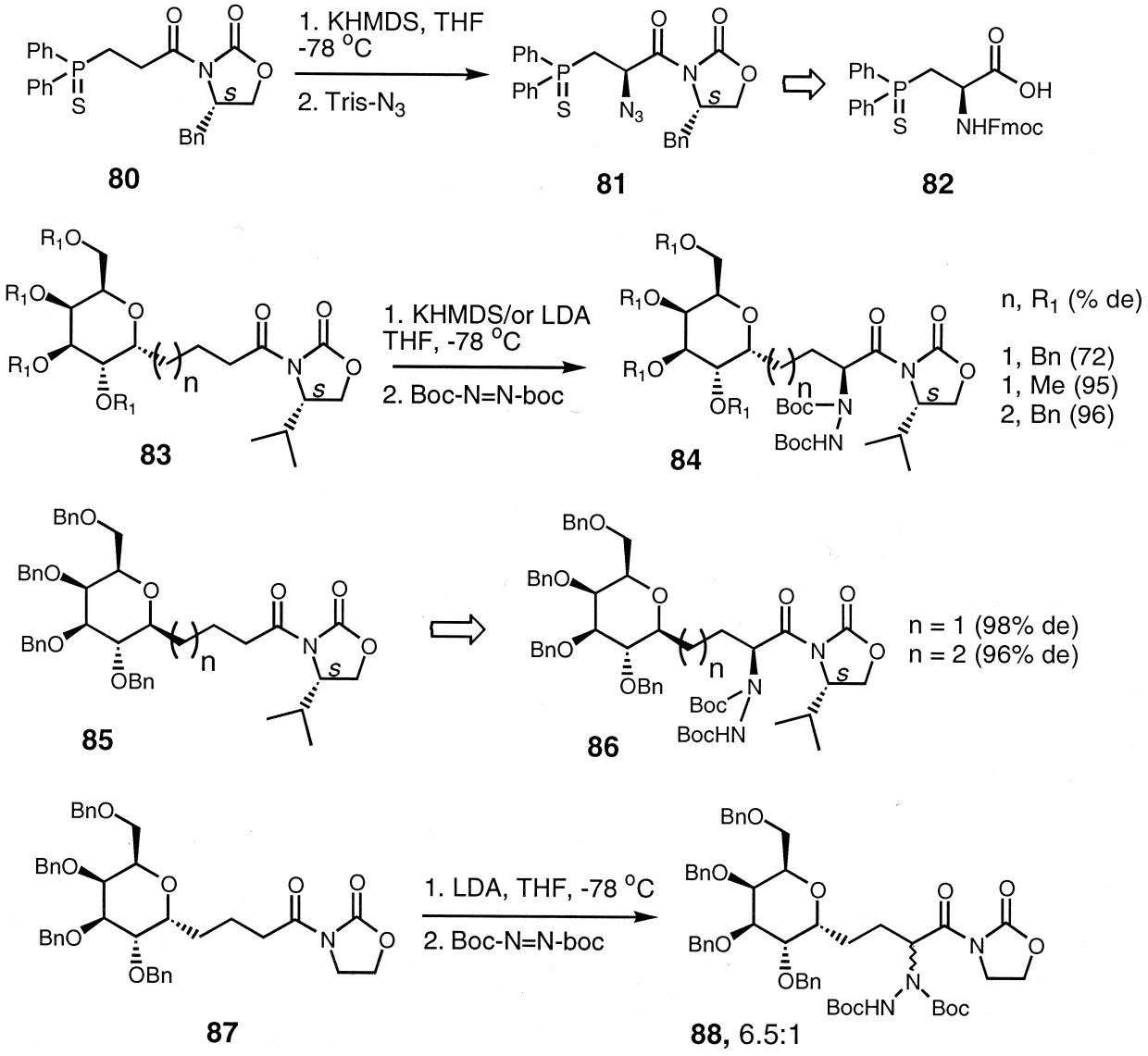
ester derivatives was reported by Abiko and Masamune.[38,39] Reaction of an ester having a chiral bulky alcohol group **63** under *E*-enolization conditions (*c*-Hex_2BOTf, Et_3N, −78°C) gave the *anti*-aldol as a major product (**64**:**65**, 90–98% yield, 95:5 to 99:1 for *anti*:*syn*). Using conditions known for the *Z*-enolate (nBu_2BOTf, *i*-Pr_2NEt), it was possible to obtain the *syn*-aldol from **66** with high selectivity.



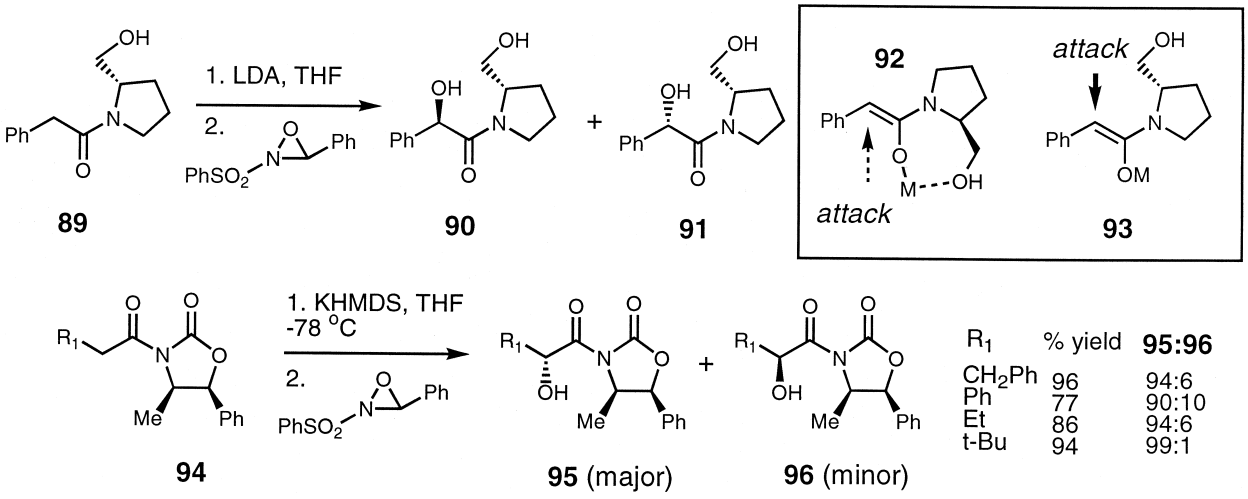
Scheme 9.

2.6. C–N: *N*-Methylephedrine and oxazolidinone derivatives (Schemes 9 and 10)

We have summarized some of the recent developments related to C–C bond formation that used a chiral auxiliary approach. Herein, approaches toward the stereoselective formation of C–N bond are discussed. This is an important area of research because it has led to the stereoselective synthesis of several unnatural amino acids. The first reports were independently published by Gennari,[40] Evans[41] and Vederas.[42] Gennari used an *N*-methylephedrine based chiral auxiliary approach to obtain a stereoselective electrophilic amination, whereas an oxazolidinone strategy was utilized by Evans and Vederas. *E*-Enolsilyl ether (>95:5, *E*:*Z*) **69** (Scheme 9), was reacted with a 1:1 complex of $TiCl_4$:Boc–N=N–Boc at −80°C to give the hydrazide derivative **70** in excellent yield and diastereoselectivity. It was further converted into the corresponding acid **71** by a simple sequence of steps.[40] In the Evans and Vederas approach, *N*-acyloxazolidinone **72** was reacted with LDA, −78°C to produce the *Z*-enolate which was then reacted with Boc–N=N–Boc to give the corresponding hydrazide **73** (>99% de).[41–43] In a similar reaction, Evans also reported the use of trisyl azide as a source of electrophilic nitrogen leading to the stereoselective C–N_3 bond formation (**72→75**).[44,45] In another attempt, NBS (as a source of electrophilic bromine) was reacted with the *Z*-enolate of **72** to obtain a stereoselective α-bromo derivative **76**.[43] Followed by a well known transformation of the bromo to the azide derivative, the synthesis of enantiomeric pure azide acid **78** was achieved. The first example of the stereoselective synthesis of a phosphine-containing amino acid, **82** (Scheme 10) was developed by Gilbertson using an α-azido methodology.[46] An oxazolidinone derivative of the protected phosphine **80** reacted with KHMDS/−78°C to generate the *Z*-enolate, which was followed by reaction with trisyl azide to give the α-azido product **81**. In another example, Arya[47] utilized this methodology to obtain carbon-linked analogs of glycosyl serine derivatives. Surprisingly, the enolate of per-*O*-benzyl-α-galactosyl derivative, **83** (*n*=1, R_1=Bn) did not react with the trisyl azide as an electrophile, and low selectivity upon reaction

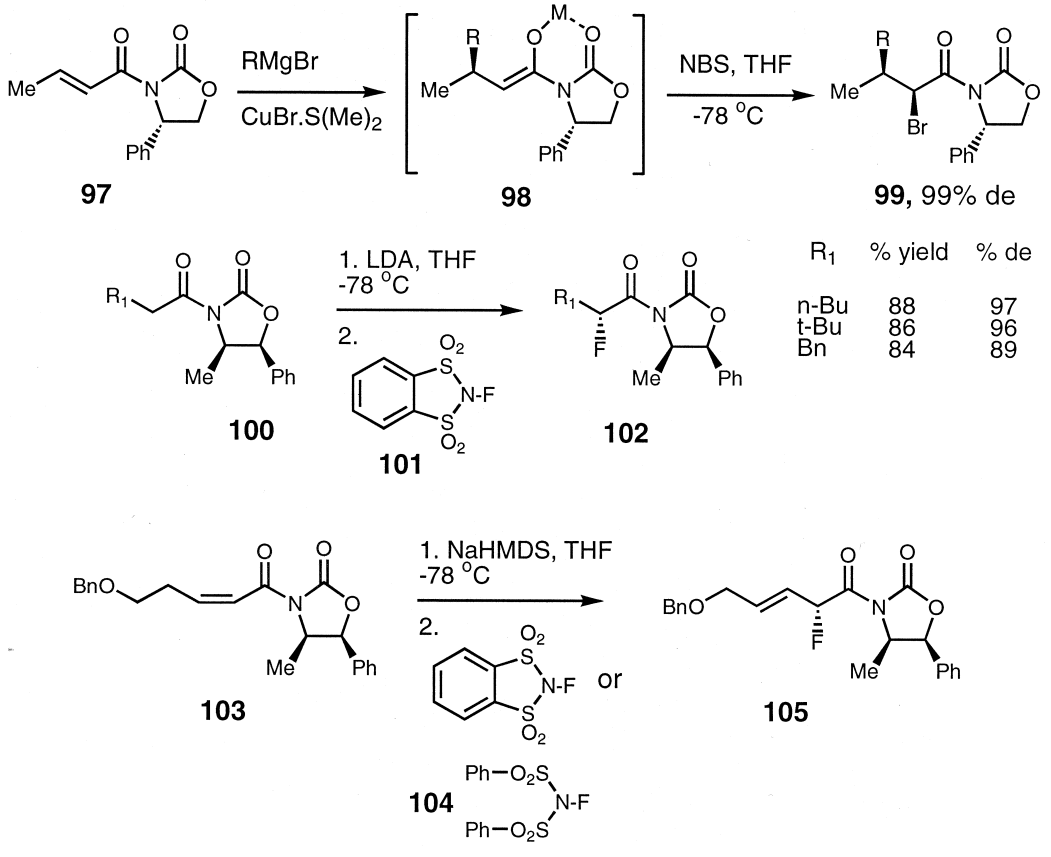


Scheme 10.



Scheme 11.

with Boc–N=N–Boc was observed. With simple substrates, this reaction usually gives high diastereoselectivity. It was proposed that the benzyl group at the C-2 position of an α-D-galactosyl moiety in **83** (n=1) hindered the approach of the electrophile. This effect was not seen with the substrate **83** (n=2, R_1=Bn). Several experiments were carried out to confirm this effect. Reaction with the per-*O*-methyl derivative **83** (n=1, R_1=Me) gave the expected high distereoselectivity (95% de). Further, β-D-galactosyl derivative **85** was subjected to investigation. Reaction with the β-galactosyl derivative (**85**, n=1, 2) gave **86** with high diastereoselectivity for the electrophilic attack which supported the hypothesis. Finally to confirm the role of the α-galactoside as a remote chiral auxiliary, electrophilic amination with the achiral oxazolidinone **86** was attempted.[48] This is the first example of electrophilic amination in which a remote chiral auxiliary has influenced the stereoselective outcome (**87→88**) with 6.5:1 selectivity. The absolute stereochemistry was not determined.



Scheme 12.

2.7. C–OH: Pyrrolidine and oxazolidinone derivatives (Scheme 11)

The first methodology that utilized electrophilic hydroxylation for stereoselective α-hydroxylation was reported by Davis.[49] 2-Phenylsulfonyl-3-phenyl oxaziridine was used as a source of the electrophilic hydroxyl group. Reaction of the phenylacetamide derivative **89** with LDA/THF/−78°C produced the enol ether. This was further reacted with the oxaziridine to give the α-hydroxyl product **91** as a major diastereomer. An intramolecular chelation based transition state was proposed to explain the high selectivity. Surprisingly, the enol ether derived from NaHMDS/THF gave the other isomer, **90**, as a major product. It was speculated that due to the poor coordination nature of Na, the reaction proceeds via a non-chelated system, **93**. A method to obtain enantiomerically pure α-hydroxy carboxyl derivatives was also reported by Evans.[50] The *Z*-enolate of chiral oxazolidine derivative **94** reacted with the oxaziridine to give the α-hydroxylated product **95** as a major diastereomer (**95**:**96**; 77–94% yield, 90:10 to 99:1).

2.8. C–Br, C–F: Oxazolidinone derivatives (Scheme 12)

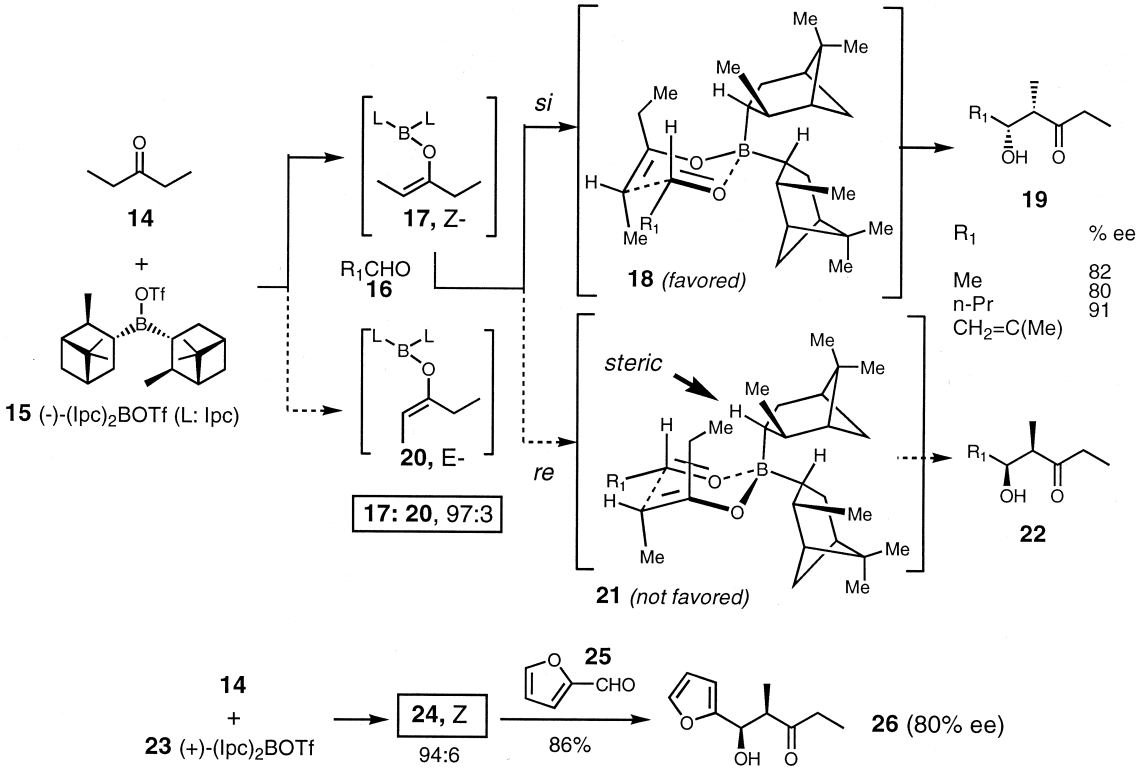
In 1993, Hruby reported application of the chiral oxazolidinone system in tandem asymmetric 1,4-conjugate addition followed by electrophilic bromination in one pot.[51,52] The conjugated derivative of oxazolidine, **97** on reaction with alkylmagnesium bromide, resulted in in situ formation of the enol ether, **98**, that reacted with NBS to give **99** (99% de) with stereoselective formation of the C–Br bond. *N*-Fluoro-*O*-benzenedisulfonamide **101** as an electrophilic fluorinating agent was utilized by Davis for the stereoselective fluorination of the oxazolidinone derived enol ether.[53–57] High selectivities with several examples were obtained. The analog of *N*-fluoro-*O*-benzenedisulfonamide, **104**, was also utilized as a fluorinating agent for the stereoselective formation of C–F bond.[58]

3. Chiral Ligand Mediated Enolate Reactions (Schemes 13–19)

For several years, a chiral auxiliary approach has proven a powerful strategy to form C–C, C–X (X=O, N, Br, F, etc) from π-face selective attack of the stereodefined (*Z*- or *E*-) enolate of the aldehyde group with other electrophiles. A similar type of control is also possible from a chiral ligand attached to the enol ether. As with the chiral auxiliary based stereo- and enantioselective reactions, there are two major challenges to overcome. The first challenge is to generate a stereoselective enolate (*Z*- or *E*-isomer), followed by the challenge of achieving a π-face selectivity during the attack of the enolate with the electrophile. Paterson and several other groups have developed methodologies that use chiral enol borinates.[1] Most of the developments in this area concern C–C bond formation, and are summarized below.

3.1. Isopinocampheyl (Ipc) as chiral ligands (Schemes 13 and 14)

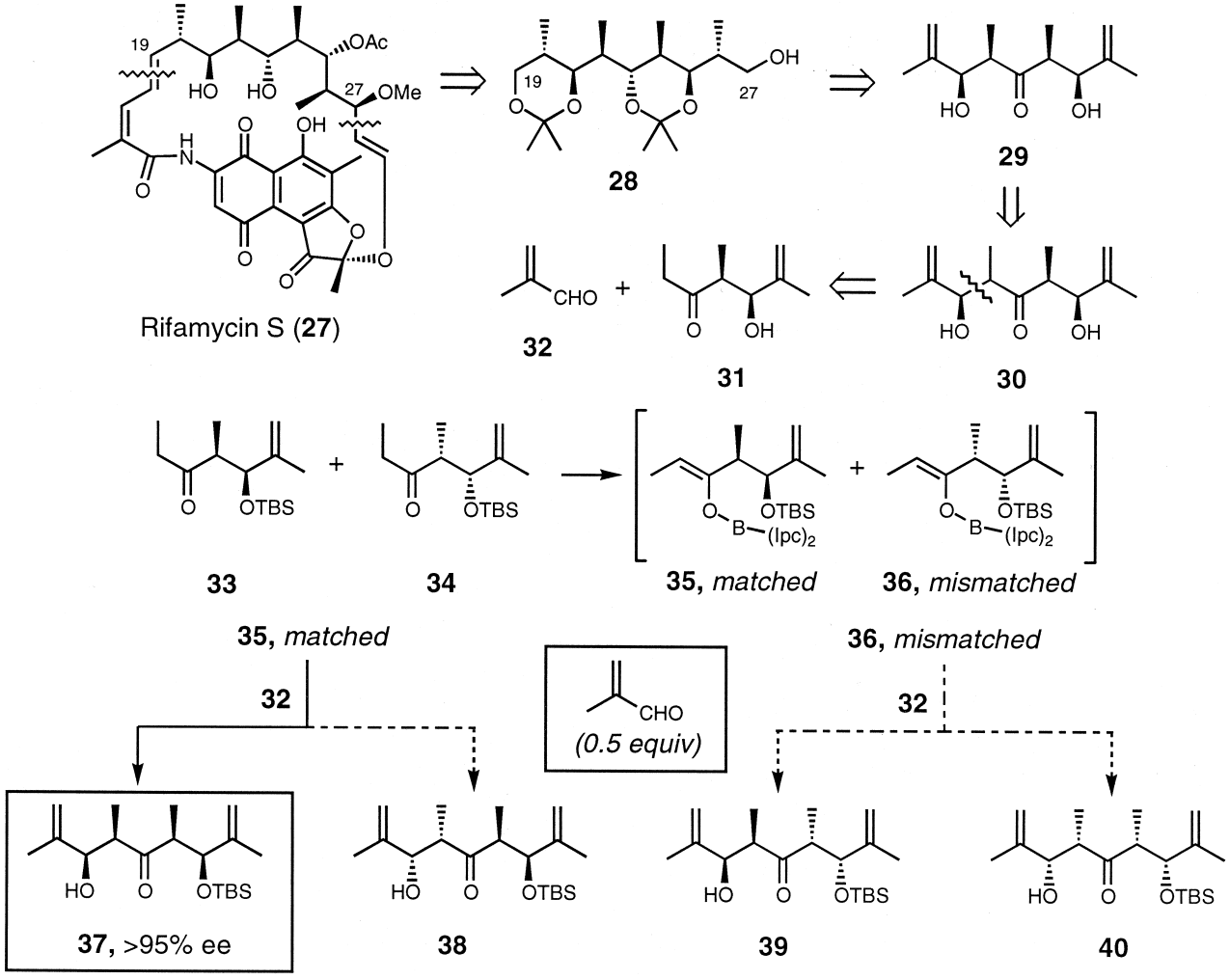
1,2-*syn*- and 1,2-*anti*-Hydroxy methyl carbonyl functionality is commonly found in macrolide antibiotics. Aldol reaction is utilized to obtain such building blocks in a stereo- and enantioselective manner. Over the years, Paterson[1,6] has pioneered the use of chiral boron ligands



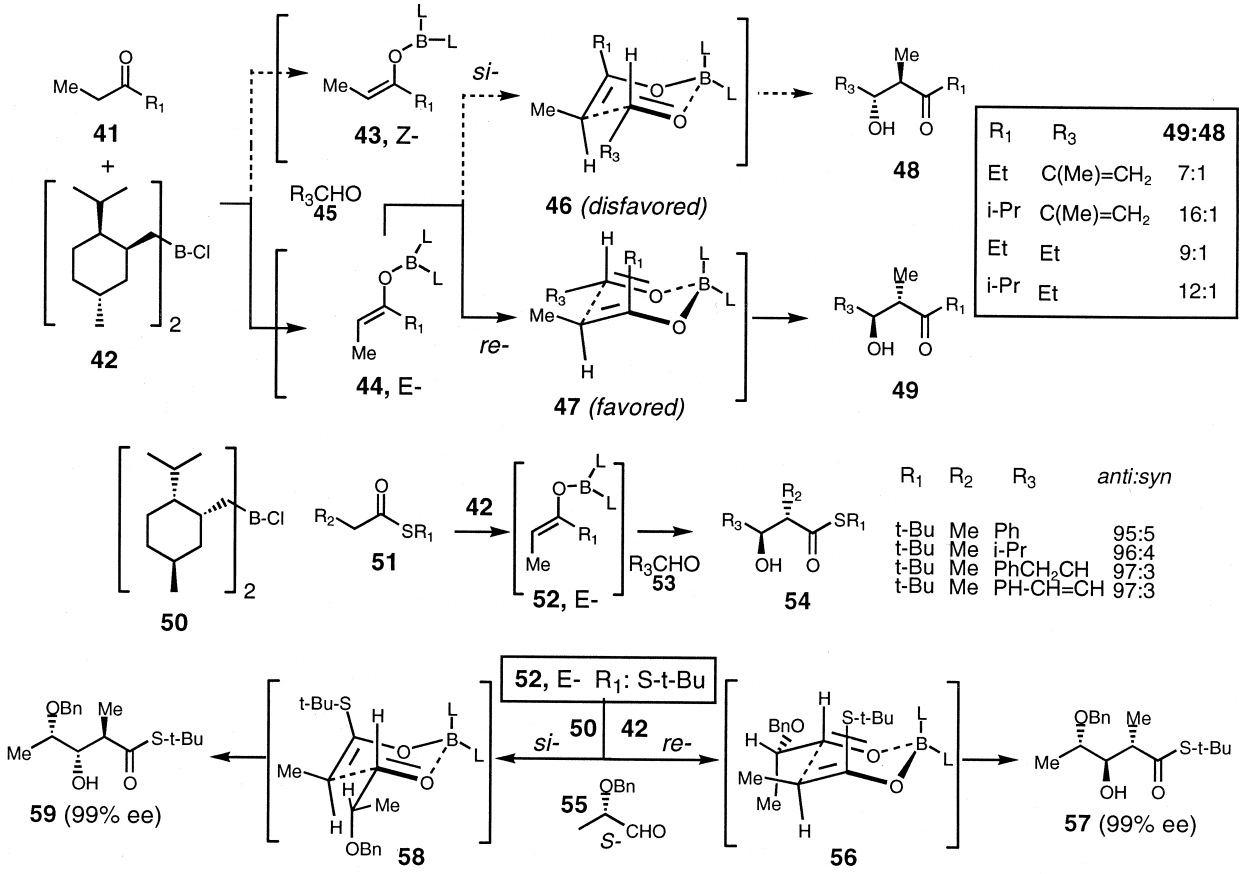
Scheme 13.

in developing enantioselective aldol reaction, and has successfully applied this to the syntheses of several complex natural products. Paterson[59,60] reported the enolization (**17**, *Z*: **20**, *E*; 97:3) of diethylketone **14** using (−)-diisopinocampheylboron triflate **15**, (−)-$(Ipc)_2BOTf$ and diisopropylethyl amine at −78°C. The enolate was further reacted with several aldehydes **16** to obtain enantiomerically pure *syn*-aldol products **19** with high enantiomeric excess (80–91% ee) in good yields. Several other boron based chiral ligands were synthesized and utilized for similar types of aldol reaction.[60] Although high selectivity for the *Z*-enolate was observed with most of them, π-face selectivity on reaction with the aldehydes was not impressive. In another attempt to obtain the *re*-face selective attack of the *Z*-enolate **24** with several aldehydes, the enolate was generated using (+)-$(Ipc)_2BOTf$, **23**. *Z*-enolate **24** was produced with high selectivity (94:6) but only reaction with furyldehyde **25** gave the enantiomerically pure *syn*-aldol **26** with high π-face discrimination (80% ee). To understand the origin of the stereoselectivity using (−)-Ipc derived chiral boron reagents, MM2 calculations were performed. These indicated a preference for *si*-face attack (see **18**) of the enolate with the aldehyde leading to **19** with high enantioselectivities.[61]

Using chiral borinate enol methodology, Paterson's group has synthesized several complex natural products. For example, this methodology was applied to develop a short asymmetric synthesis of a C19–C27 segment of Rifamycin-S, **27** (Scheme 14).[62] A key step was the generation of the *Z*-enolate from a racemic ethyl ketone derivative (mixture of **33** and **34**) using **23**, and π-face selective attack with methacrolein **32**. As a result of the matched isomer, *Z*-enolate **35** was preferentially formed over the mismatched isomer **36**. It is interesting to note that from all the expected isomers **37**–**40**, the *syn*-aldol product **37** was obtained with >95% ee. At this stage, there was still a need for a chiral boron reagent that could selectively produce *E*-enolate and provide a π-face selectivity for the attack at the aldehyde group. Until this time, there were no general methods available that could give the *anti* aldol product effectively. Reagents like (−)-Ipc_2BCl with Et_3N gave *E*-enolates but π-face selectivity for the aldehyde attack was not respectable.



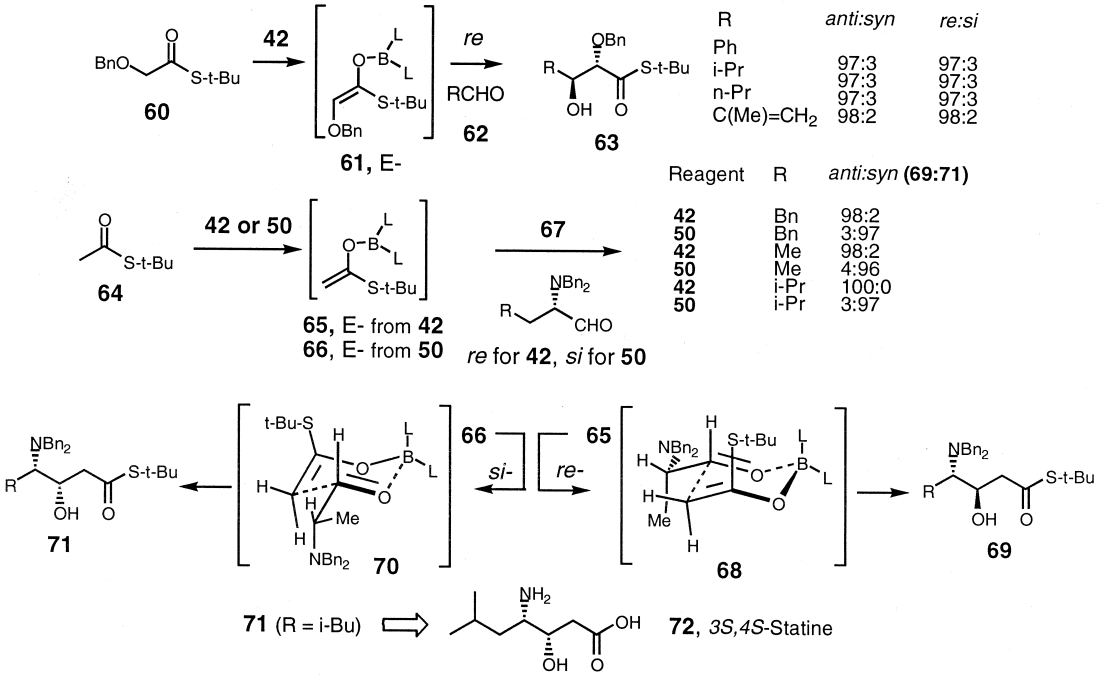
Scheme 14.



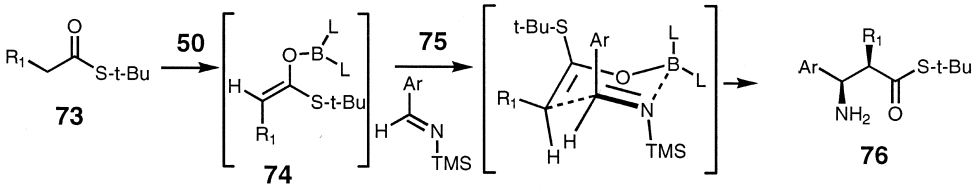
Scheme 15.

3.2. Menthol derived chiral ligands (Schemes 15–17)

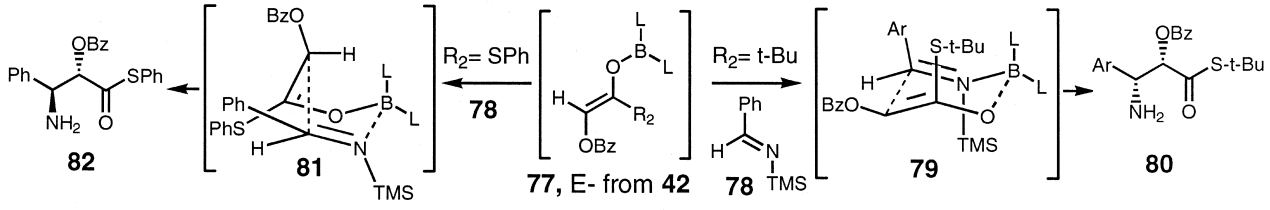
Using MM2 calculations on cyclic transition states for the aldol reaction, Gennari and Paterson developed ligand **42** (Scheme 15).[63] Several keto derivatives **41** were reacted with ligand **42** in the presence of Et_3N at −78°C. A high selectivity for the *E*-enolate **44** was observed, which upon reaction with several aldehydes **45** gave enantioselective

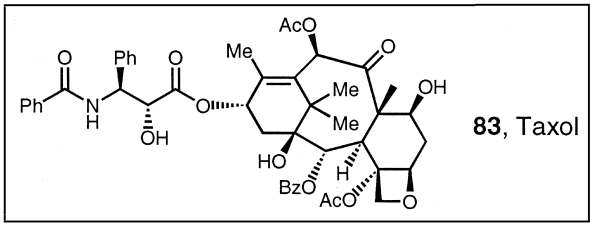


Scheme 16.



R_1, Ar	*syn:anti*	*re:si*
Br, Ph	99:1	98.5:1.5
Br, p-MeS-C_6H_4	99:1	99:1
Cl, Ph	92:8	97:3
Cl, p-MeS-C_6H_4	94:6	98:2



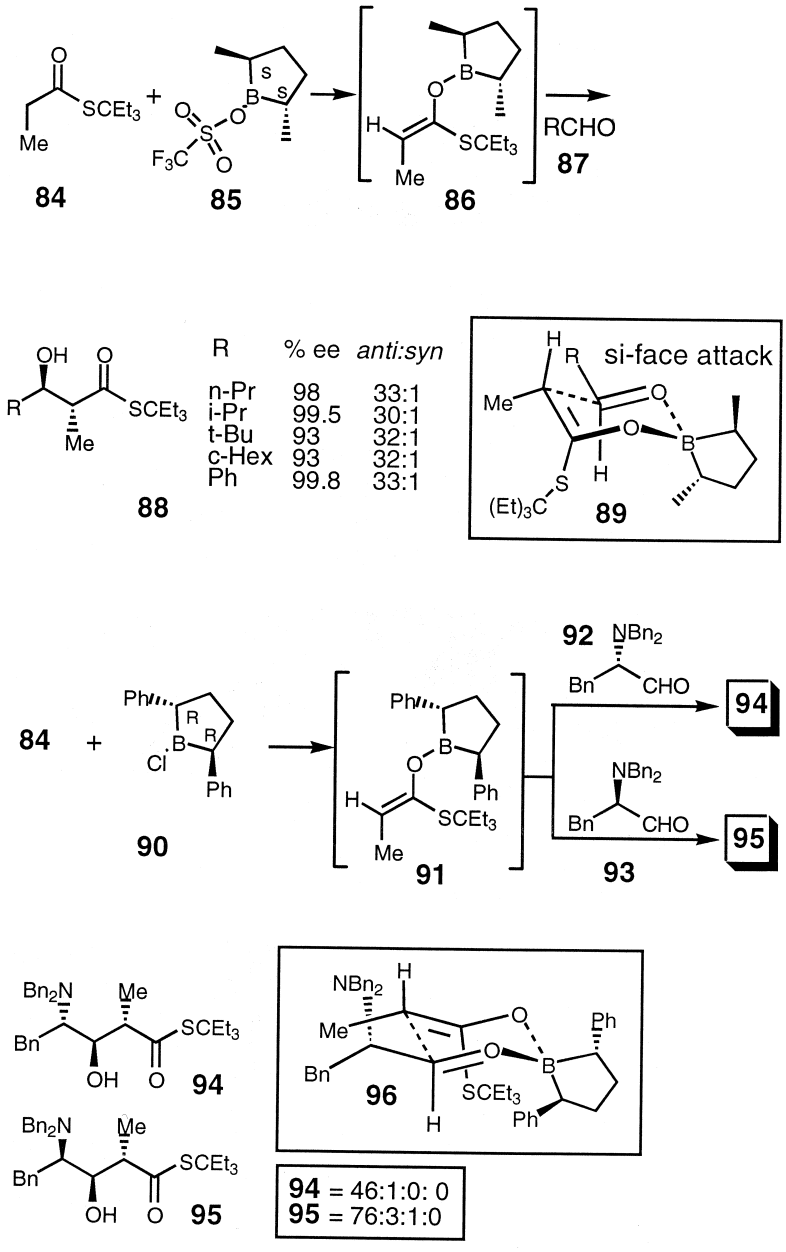


Scheme 17.

pure *anti*-aldol **49** (see, **46** and **47** for disfavored and favored transition states). This was a major accomplishment in the area of aldol chemistry, since obtaining *anti*-aldol had been a challenging task in the past. Gennari[64] further demonstrated that, depending upon the choice of ligand (**42** or **50**, derived from (−)- or (+)-menthone), it was possible to obtain either of the *anti*-aldols with high ee. Enolate **52** derived from thio ester **51** reacted with aldehyde **53** in a similar manner to give enantioselective, *anti*-aldol product **54**. *E*-Enolate **52** (R=*t*-Bu) derived from ligand **42** preferred *re*-face attack (see **56**) to *S*-aldehyde **55** to give *anti*-aldol **57** (99% ee), whereas *si*-face (see **58**) selectivity could be obtained with the enolate generated from reagent **50** to give enantioselective *anti*-aldol **59** (99% ee). Encouraged by the success of achieving π-face selectivity, *E*-enolates of α-hetero substituted thioesters were further studied with several chiral α-amino aldehydes.

Using chiral reagent **42**, *E*-enolate **61** (Scheme 16) derived from α-alkoxy thioacetate **60**, was reacted with different aldehydes **62** to give *anti*-aldol product **63** with high enantioselectivities (97–98:3–2 for *re*-face attack).[65] High selectivity for the *E*-enolate, followed by π-face selectivity was found to be independent of the nature of the alkoxy (e.g. –OTBS, –OBn) and of the thioacetate group (e.g. S–Ph, S–*t*-Bu). In most cases, the yields were moderate (40–80% range). The absolute configuration of the aldol product arising from *re*-face attack of the *E*-enolate was expected (as suggested by computer modeling of the cyclic transition state discussed earlier). Similar results were obtained from the reaction of α-halo thioacetates with various aldehydes. α-Halo-β-hydroxy derivatives were obtained with high diastereo- and enantioselectivity (structures not shown).[65]

The idea of switching π-face selectivity by simply changing the chiral boron reagents was utilized to obtain enantiomerically pure *syn*- or *anti*-amino alcohol derivatives **69** and **71**. In 1995, Gennari[66,67] reported the reaction of *E*-enolates (**65** and **66**) from two chiral boron reagents **42** and **50** with α-amino aldehyde **67**. As expected, reaction of *E*-enolate **65** with α-amino aldehyde **67** proceeded with high π-face selectivity to give *anti*-product **69**, whereas **71** *syn*-isomer was obtained from *E*-enolate **66**. Both isomers **69** and **71** were believed to originate from cyclic transition states **68** and **70**. *re*-Face selectivity with **68** was



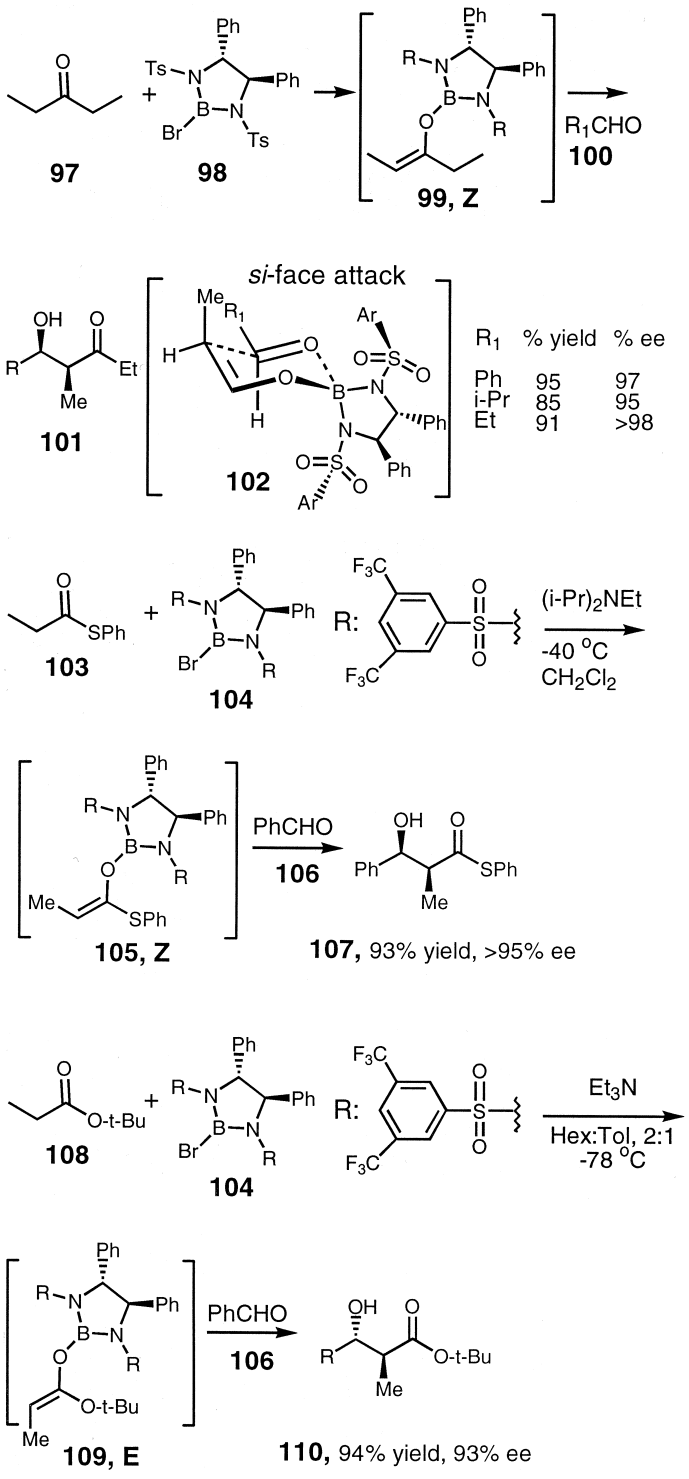
Scheme 18.

supported by Felkin-type attack, while *anti*-Felkin-type *si*-face attack was proposed for transition state **70**. This methodology was used in the synthesis of 3*S*,4*S*-statine (**72**).

Chiral boron reagents **42** and **50** were then utilized to study the stereo- and enantioselective aldol reaction of α-hetero substituted thioacetates with *trans*-silyl imines.[68–71] *E*-Enolate, **74** (Scheme 17) was obtained from thio-*t*-butyl-acetate **73** using chiral boron reagent **50**. Reaction with *trans*-silyl imine **75** gave enantioselective *syn*-halo amines **76** with the expected *re*-face selective attack. Similar π-face selectivity for the *re*-face was observed for reaction of enolate **77** (R_2=*t*-Bu) with imine **78** to give *syn*-amino alcohol **80**. The results were explained on the basis of the expected, cyclic chair-like transition state **79**. This method provided an efficient approach to the enantiomerically pure side chain of Taxol (**83**). Surprisingly, a similar type of reaction with the *E*-enolate of thiophenylacetate derivative **77** (R_2=Ph) resulted in an enantiomerically pure *anti*-amino alcohol product **82**. Although, the exact explanation of this behavior is not clearly understood, a boat-like cyclic transition state **81** was proposed.

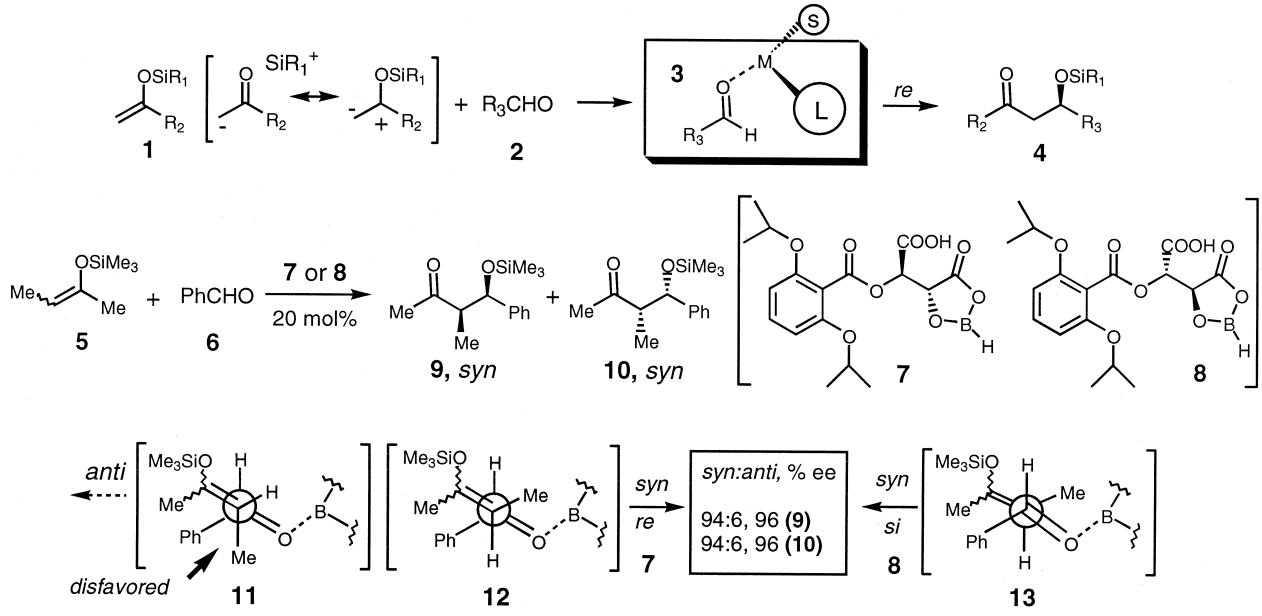
3.3. C_2-Symmetry derived chiral ligands (Schemes 18 and 19)

Several approaches are available for obtaining *syn*-aldol products either using chiral auxiliary or ligands.[72] Methodologies for preparation of 1,2-*anti*-aldol are quite limited.[73] In 1986, Masamune[74] reported the use of a chiral borolane reagent to obtain *E*-enolates that give π-face selectivity on reaction with different aldehydes producing enantioselective 1,2-*anti*-aldol products. *E*-Boron enol ether **86** (Scheme 18) was generated from the thioate ester **84** and



Scheme 19.

S,*S*-2,5-dimethylborolane trifluoromethanesulfonate (**85**) (−78°C, pentane) and reacted with several aldehydes **87**. The enantioselective *anti*-aldol **88** formation was explained by a cyclic transition state and a preference for the *si*-face attack at the aldehyde. In all cases, a high preference for the *anti* product was observed (*anti*:*syn*, 30–33:1, 93–99.9% ee). This methodology was further utilized by Reetz to study the reaction of chiral aldehydes with *S*,*S*- or *R*,*R*-diphenylborolane derived *E*-enolates.[75] Enantiomerically pure α-amino aldehyde derivatives **92** and **93** were used as electrophiles. The chiral nature of the aldehyde did not interfere with the reaction. In both cases, out of four diastereomers, a single isomer **94** or **95** was obtained as a major product. This was an interesting observation because Li-enol ether, Grignard reagents, and alkyllithium react with *N*,*N*-dibenzyl aldehydes in a stereoselective manner via non-chelation control. To confirm this result, achiral boron *E*-enolate (structure not shown) was reacted with chiral



Scheme 20.

aldehydes **92** and **93**. No stereocontrol for the new stereogenic centers was observed, whereas similar reaction with Li-enol ether gave a modest 9:1 selectivity. The present methodology is a good example of complete reagent control for obtaining 1,2-*anti*-aldol product with little or no effect of the nature of the chiral aldehyde group on the outcome of the product.

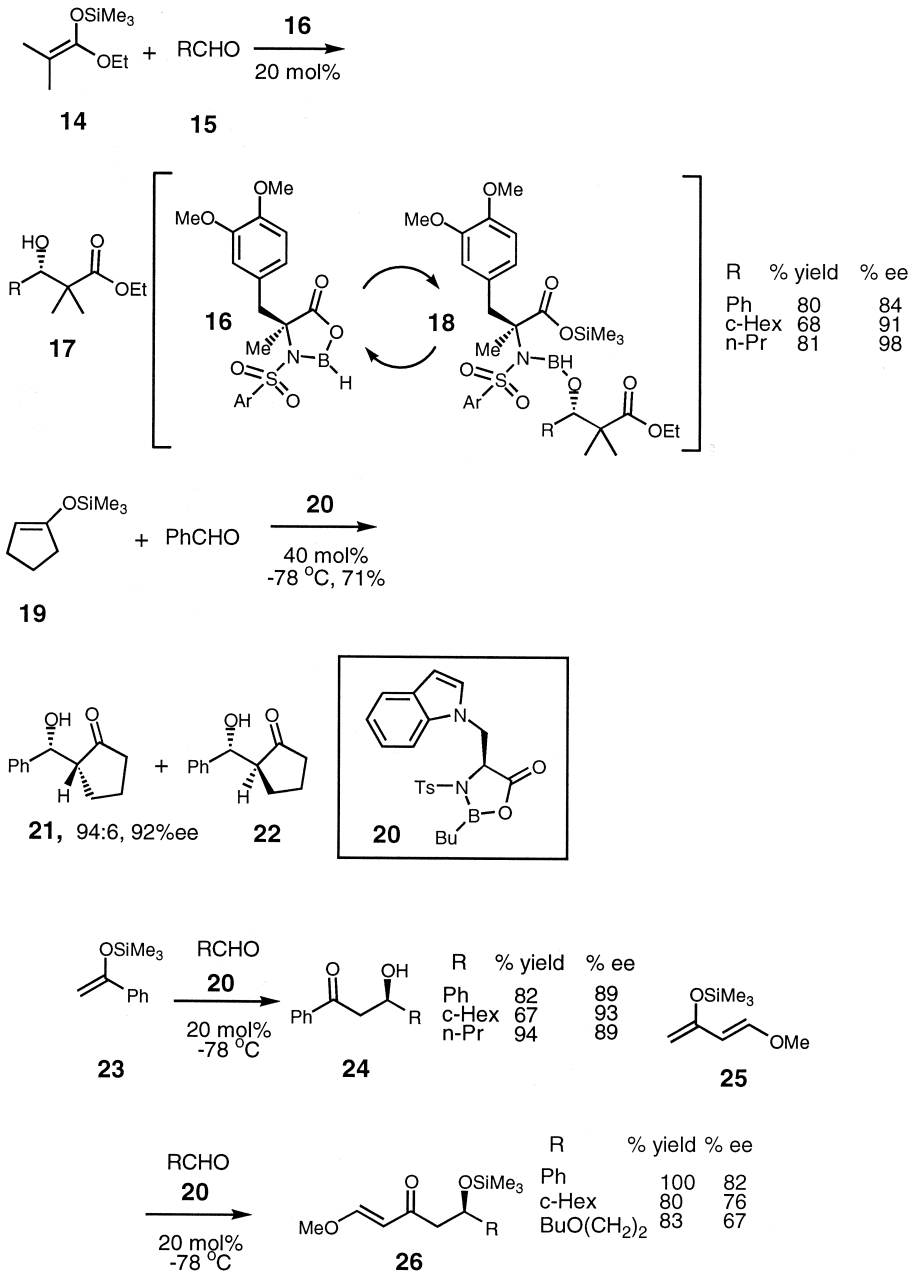
Corey reported the use of a C_2-symmetric, chiral diazaborolidine to generate stereoselective *E*- or *Z*-enolates that react with aldehydes with high π-face selectivity to give *syn*- or *anti*-aldol products.[76–79] The reaction of diethyl ketone **97** (Scheme 19) with *R,R*-diazaborolidine bromide in the presence of diisopropylethyl amine at −78°C gave *Z*-chiral boron enolate **99**. A high facial selectivity with aldehyde **100** was observed to give 1,2-*syn* aldol **101** in high yields (85–91% yields, 95–98% ee). A six-membered cyclic transition state **102** was proposed to explain the 1,2-*syn*-aldol product from the *Z*-enolate. Reaction of enol ether obtained from thiophenyl- and *O-t*-butyl ester derivatives **103** and **108** were studied further.[77] In the presence of diisopropylethyl amine at −40°C, *Z*-enolate **105** was produced from thiophenyl ester **103** and **104** which upon reaction with benzaldehyde gave the enantiomerically pure 1,2-*syn*-aldol product **107** in 93% yield (>95% ee). A similar reaction using *O-t*-butyl ester **108** (Et_3N, −78°C) gave 1,2-*anti*-aldol product **110** (94% yield, 93% ee) which was produced from *E*-enolate **109**. By simply changing the nature of the ester derivatives, it was possible to obtain selective *E*- or *Z*-chiral enolates which underwent reaction with the aldehyde with a high degree of π-face selectivity.

4. Chiral Catalysis Mediated Enolate Reactions (Schemes 20–32)

The use of chiral catalysts in stereo- and enantiocontrolled reactions in the formation of C–C and C–X (X=hetero atom) bonds has become a major area of study in asymmetric synthesis. A prime reason for this is *economics*. Efficient, economical processes are required to synthesize complex molecules and their analogs with relative ease and with low cost. In this category, reactions such as the Lewis acid catalyzed aldol reaction developed by Mukaiyama have received serious attention by several groups. In general, Mukaiyama aldol reaction involving a silyl enol ether, and a latent enolate, reacts with aldehyde in the presence of a Lewis acid catalyst.[80–83] The highly nucleophilic enol silyl ether (**1**, Scheme 20) is resonance stabilized due to the β-silicon effect. Reaction with aldehyde **2** is triggered via activation by the Lewis acid to give the silylated aldol product **4**. With use of chiral Lewis acid **3** as catalyst, one can obtain π-face selectivity for attack of the enol ether to the aldehyde group (see **4**). In this approach, it is important that the enol ether does not react with the aldehyde prior to activation. The use of a chiral Lewis acid is an alternative approach to chiral auxiliary or ligand based enol ethers, and offers an advantage in that only catalytic amounts are required. Catalytic, enantioselective aldol reactions of latent enolates have been summarized recently by Nelson.[2] Most of the work in this area involves C–C and C–N bond formation, and selected examples in each category of chiral Lewis acids are discussed below.

4.1. Tartaric acid derived chiral catalysts (Scheme 20)

Yamamoto reported the use of chiral (acyloxy)borane (CAB) complexes **7** and **8** as Lewis acid catalysts for Mukaiyama-type aldol reaction of silyl enol ether **5** with various aldehydes.[84,85] Chiral borane complexes **7** and **8** were easily prepared from *R,R*- and *S,S*-tartaric acid derivatives. Reaction of silyl enol ether **5** with benzaldehyde **6** in the presence of 20 mol% **7** gave silylated aldol **9** (*syn*:*anti*, 94:6) with 96% ee. A significant loss in reactivity was observed when 10 mol% chiral Lewis acid as a catalyst was used. Similar diastereo- and enantioselectivity was noted for aldol product **10** by using the other enantiomer of CAB **8**. Interestingly, regardless of the stereochemistry of

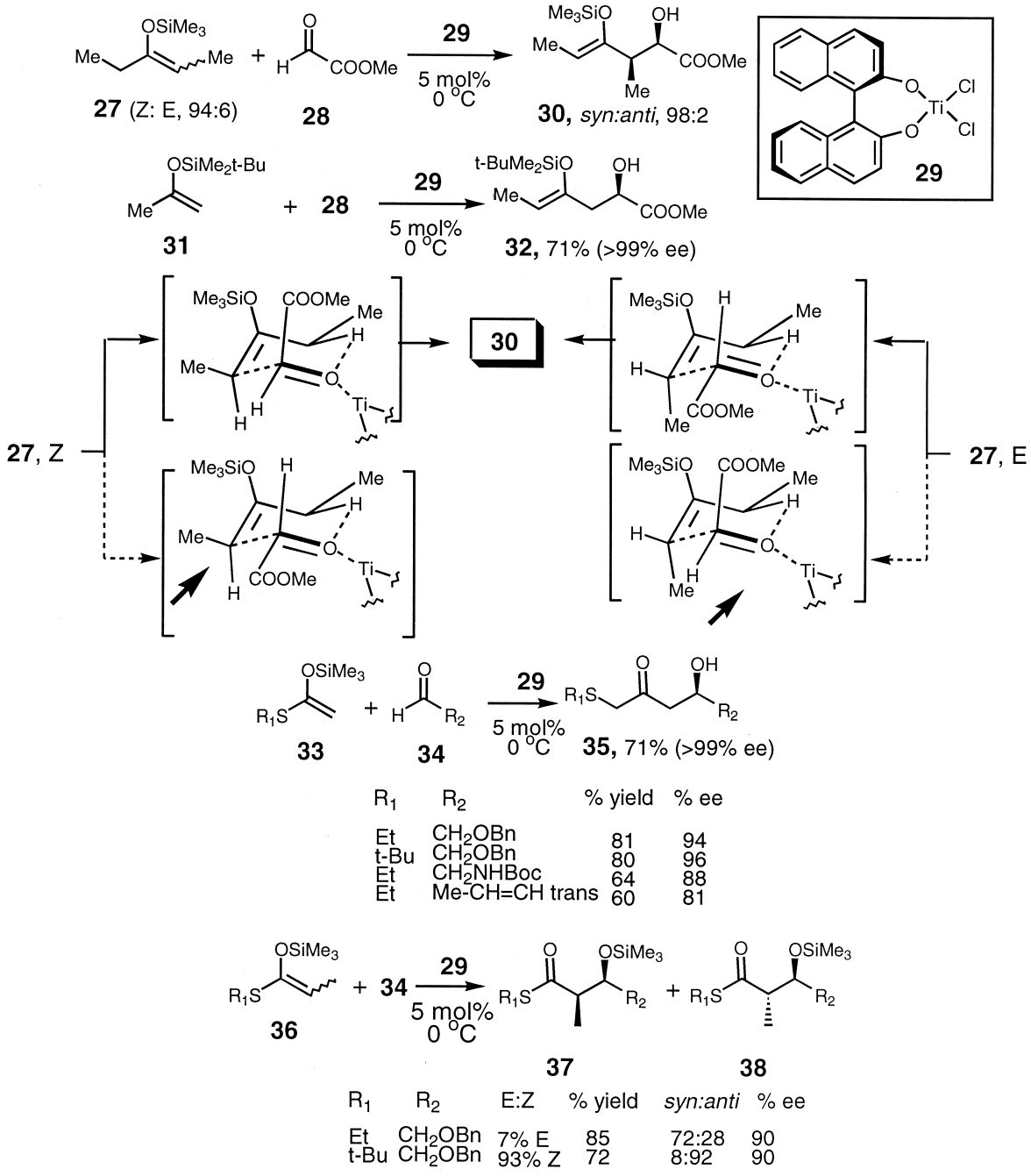


Scheme 21.

the enol ether (*Z*- or *E*-), a *syn*-product was obtained in both cases. Acylic transition state models **12** and **13** have been proposed for the Mukaiyama-type aldol reaction and are independent of the geometry of the enol ether. The 1,2-*anti*-product is disfavored due to steric, *gauche* interactions between the methyl group of the enol ether and the phenyl group of the aldehyde (see, **11**). The *si*-face of the keto group is blocked by the chiral Lewis catalyst **7** and results in *re*-face approach for the enol ether.[84] As discussed earlier, the geometry of the enolate plays a role when the reaction proceeds via a cyclic transition state.

4.2. Amino acid derived chiral catalysts (Scheme 21)

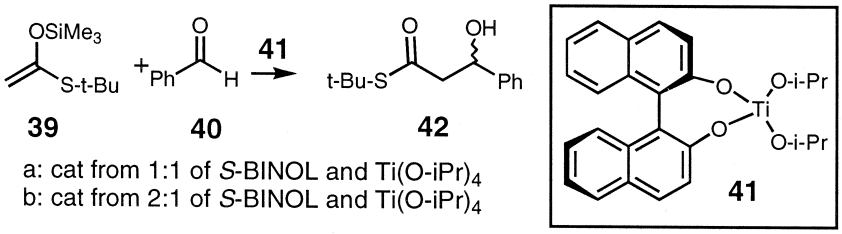
Masamune[86] developed a new chiral Lewis acid catalyst derived from α,α-disubstituted glycine, to study the asymmetric aldol reaction. In his design, he utilized α,α-disubstituted glycine arenesulfonamide **16**. The α,α-disubstitution facilitates the ring closure step (see **18**) to regenerate the catalyst. Reaction of silyl enol ether **14** with keto derivative **15** in the presence of 20 mol% catalyst gave high selectivity for the silyl ether of β-hydroxylated product **17** (84–97% ee). A similar type of catalyst from tryptophan was reported by Corey.[87] Reaction of silyl enol ether **19** with benzaldehyde in the presence of 40 mol% catalyst **20** gave major product **21** (94:6, 92% ee). High enantioselectivity for β-hydroxylated products **24** and **26** was obtained for similar reactions of silyl enol ethers **23** and **25** with various aldehydes in the presence of 20 mol% catalyst.



Scheme 22.

4.3. Binaphthol derived chiral catalysts (Schemes 22–26)

In 1993, Mikami[88] reported the aldol reaction of trimethylsilyl enol ether **27** (*Z*, major isomer, *Z*:*E*, 94:6) with methyl glyoxylate, **28**, in the presence of chiral titanium dichloride **29** prepared from *R*-binaphthol. The reaction, carried out at 0°C for 30 min in the presence of 5 mol% of the catalyst, provided aldol product **30** in high yields with high enantioselectivity for the *syn* isomer (*syn*:*anti*, 98:2). Similar selectivity with silyl enol ether **31** was obtained giving product **32** (>99% ee). Major *syn*-aldol product is formed from both isomers of the silyl enol ethers. An ene-type, cyclic transition state (see Scheme 22) was proposed to explain this effect. A decrease in *syn*-selectivity was observed with the bulky silyl enol derivatives. The bulky silyl group was expected to introduce 1,3-diaxial interactions that would result in low diastereoselectivity. Using the same chiral Lewis acid **29**, aldol-type reactions were tried with thiosilyl enol derivatives **33** and **36**.[89] With thiosilyl enol ether **36**, formation of the *syn*- or *anti*-products **37** and **38** was dependent upon the enolate geometry. In general, enolates of thioesters give *syn* products that are independent of enolate geometry, and the reactions proceed via an acyclic antiperiplanar transition state. To explain the role of geometry of the enolate towards the *syn* or the *anti* product, cyclic transition states were proposed. The effect of solvent and of the concentration of *S*-binaphthol derived chiral Lewis acid **41** was further studied by Keck.[90] Using



Method	Solvent	% catalyst	Time	% yield	% ee
a	dichloromethane	10 mol%	16h	25	36
b	toluene	10 mol%	16h	54	89
b	ether	20 mol%	10min	93	89
b	ether	20 mol%	16h	82	67
a	ether	20 mol%	4h	90	97

Scheme 23.

10 mol% catalyst **41** (Scheme 23), in dicholoromethane as a solvent (16 h), thiosilyl enol ether **39** on reaction with benzaldehyde **40** gave the aldol product **42** with low yield (27%) in only 36% ee. Under similar reaction conditions but in ether with 20 mol% catalyst at −20°C (4 h), the yield (90% yield, 97% ee) was greatly improved.

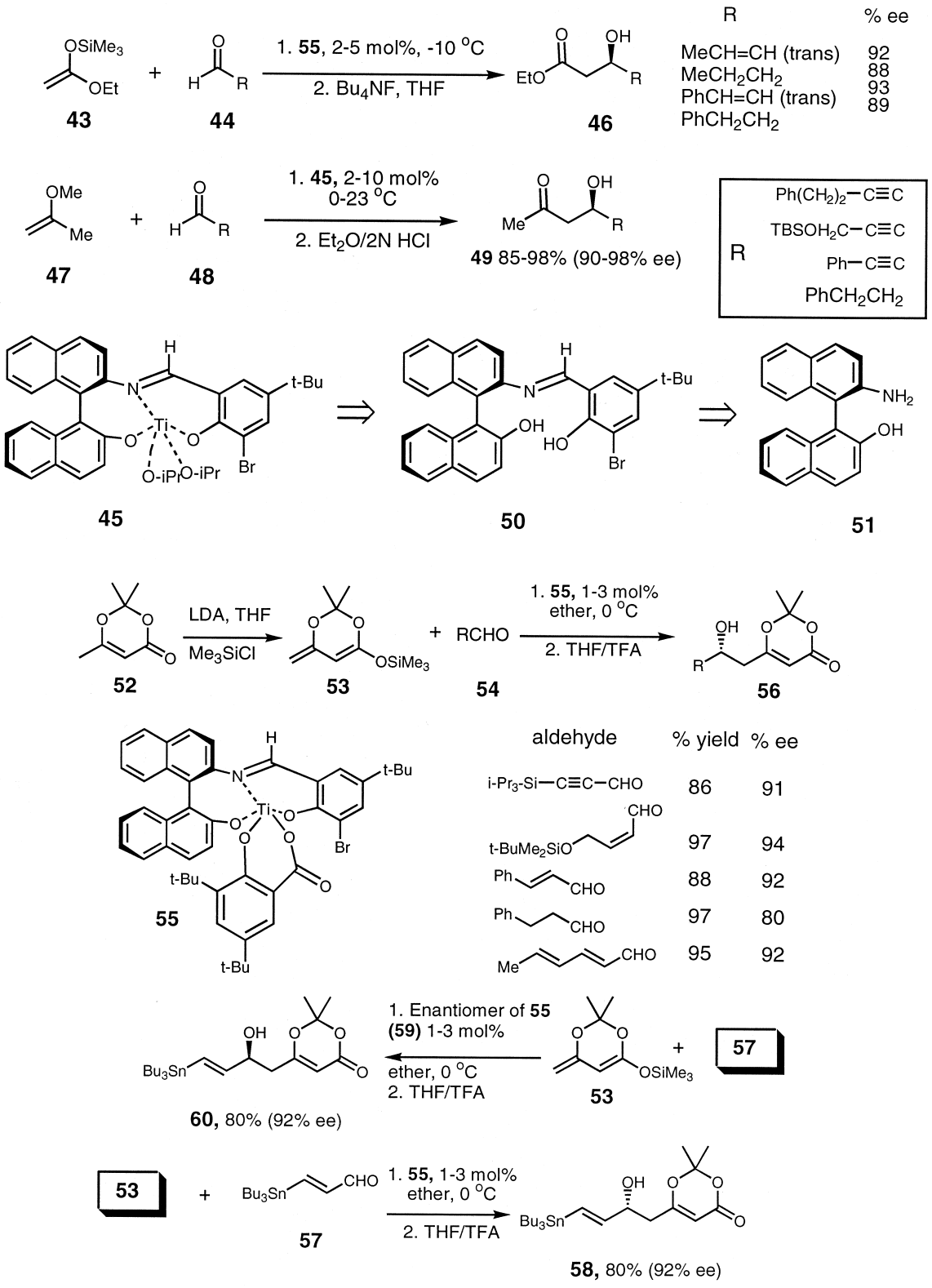
In chiral Lewis acid catalysis of the Mukaiyama aldol reaction, only bidentate based chelating groups have been used. Carreira[91–93] reported a tridentate chelating agent in the development of a new chiral Lewis acid catalyst. The mono-amine derivative of a chiral binaphthol **51** (Scheme 24) was utilized to prepare tridentate chelating ligand **50**, and Lewis acid catalysts **45** and **55** were obtained. Catalyst **45** was prepared from reaction of a titanium reagent with imino derivative **50**. Catalyst **45**, on reaction with 3,5-di-*t*-butylsalicylic acid, gave catalyst **55**. Reaction of silyl enol ether **43** with different aldehydes **44**, in the presence of 2–5 mol% **55**, gave β-hydroxyl product **46** in high yields 88–93% (94–97% ee) after desilylation.[91] The catalytic reaction generally gave high yields and high selectivities with a wide range of aliphatic and aromatic aldehydes. This reaction was further extended to commercially available 2-methoxy propene **47** as an enol derivative.[92] As with the silyl enol ethers, reaction of **47** with several aldehydes **48** in the presence of 2–10 mol% catalyst **45** (0°C to room temperature) gave aldol product **49** (85–98% yields, 90–98% ee).

As an extension of this work, Carreira reported reaction of the dienolate **53** with different aldehydes **54**.[93] The dienolate **53** is easily prepared from conjugated keto derivative **52** and is stable at the room temperature. Using 1–3 mol% chiral Lewis acid, reaction of dienolate **53** with aldehydes **54** gave aldol product **56** (86–97% yields, 80–94% ee) after desilylation. The protected, acetoacetate adducts **56** were easily utilized to obtain δ-hydroxy-β-keto esters, amides and lactones. This methodology was further applied to the synthesis of Macrolactin A, a polyene macrolide antibiotic.[94] Intermediates **58** and **60** were also independently synthesized from reaction of dienolate **53** with aldehyde **57** in the presence of Lewis acid **55** or the enantiomeric derivative **59**. Lewis acid catalyst **59** was obtained from *S*-binaphthol as discussed before.

Enantioselective aldol reaction of tin enolates with aldehydes in the presence of a chiral binaphthol silver triflate complex was reported by Yamamoto in 1997.[95] This is the first example in which tin enol ethers were utilized for Mukaiyama aldol reaction. *O*- or *C*-Tin enol ethers were prepared from the enol acetate on reaction with tributyltin methoxide in the absence of solvent. Tin enol ether could react with aldehydes in the absence or in the presence of Lewis acid. In the presence of *R*-binaphthol–AgOTf complex, **62** (Scheme 25), the reaction proceeded at low temperature (−20°C). In the presence of **62**, aldol product **63** (57–83% yields, 53–95% ee) was obtained from tin enol ether **60** and aldehyde **61**. Cyclic tin enol ether **64**, on reaction with benzaldehyde, gave *anti*-product **65** (92–94% ee). In general, in contrast to silyl enol ethers, *E*-tin enol ether gives the *anti*-product as a major isomer, whereas *syn*-selectivity can be achieved from *Z*-tin enolates. Reaction of *Z*-enolate **66** with benzaldehyde in the presence of **62** gave *syn*-aldol product **67** (*anti*:*syn*, 1:99, 95% ee). The fact that the geometry of the tin enol ether governs the *syn*- or *anti*-formation of the aldol, led to the proposal that cyclic transition states **68** and **69** lead to *syn*- or *anti*-products. Tin enol ether **73** (Scheme 26) was generated from enol acetate **71** on reaction with trialkyltin methoxide **76**. Reaction with aldehyde **70** gave *O*-Sn aldol **74**, that further reacts with enol acetate **71** to regenerate tin enol ether **73**. An alternative route used trichloro enol acetate **77**.[96] In this case, tin enol ether **73**, from tricholoro enol acetate **77** was generated on reaction with trialkyltin methoxide, followed by reaction with the aldehyde to give *O*-Sn aldol product **74**. β-Hydroxy aldol product **79** was formed from compound **74** in MeOH, and trialkyltin methoxide was regenerated. This cycle required only a catalytic amount of trialkyltin methoxide to initiate the reaction. Using 5–10 mol% of the catalyst and trialkyltin methoxide, *anti*-aldol product **82** was obtained in high yields (62–94%) with 93–95% ee.

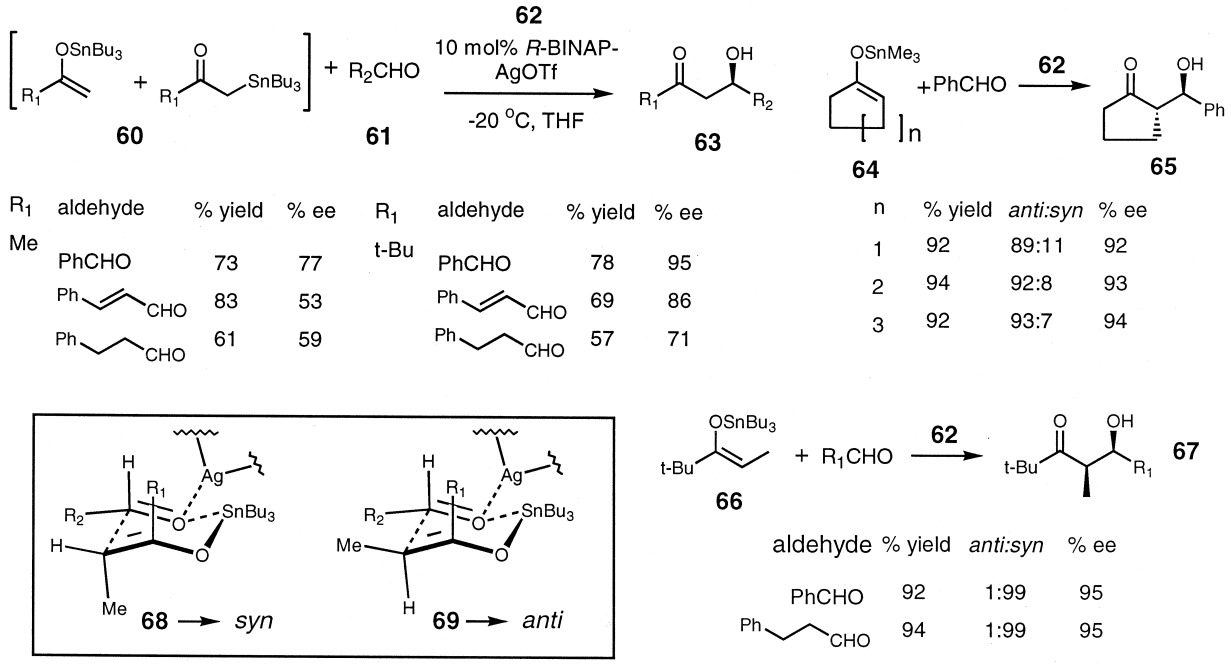
4.4. C_2-Symmetry bis(oxazolinyl) derived chiral catalysts (Schemes 27–29)

Use of chiral Lewis acid catalysts with C_2-symmetry copper (II) complexes **85** and **86** (Scheme 27) for enantioselective Mukaiyama aldol reaction was reported by Evans.[97,98] Activation of aldehydes proceeds via bidentate coordination as shown in transition states **100** and **101**. Activation of



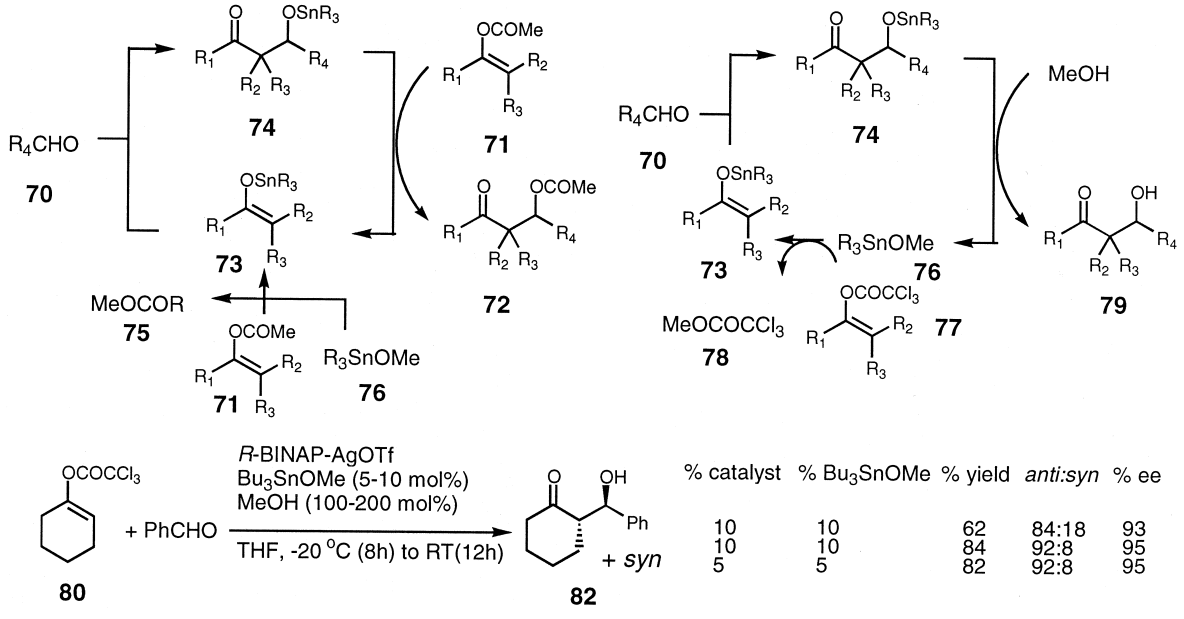
Scheme 24.

aldehydes by this type of chiral Ligand–Cu(II) complex was not utilized in the past. It was shown earlier by Evans, that bidentate coordinating bis(oxazolinyl) Cu(II) complexes **85** and **86** function as effective, enantioselective chiral Lewis acid catalysts in Diels–Alder reactions. In the presence of 0.5 mol% **86**, the reaction of the silyl ketene acetal **83** with aldehyde **84** at −78°C proceeds with high enantioselectivity (99–100% yields, 98–99% ee) to give β-hydroxy aldol product, **87** after the removal of the silyl group. Similar reaction using 5 mol% catalyst **86** with silyl enol ether **88** gave **89** in 94% yield with 92% ee. Further, it was shown that the reaction of enol ether **90** (95:5, *Z*:*E*) or **91** (1:99)

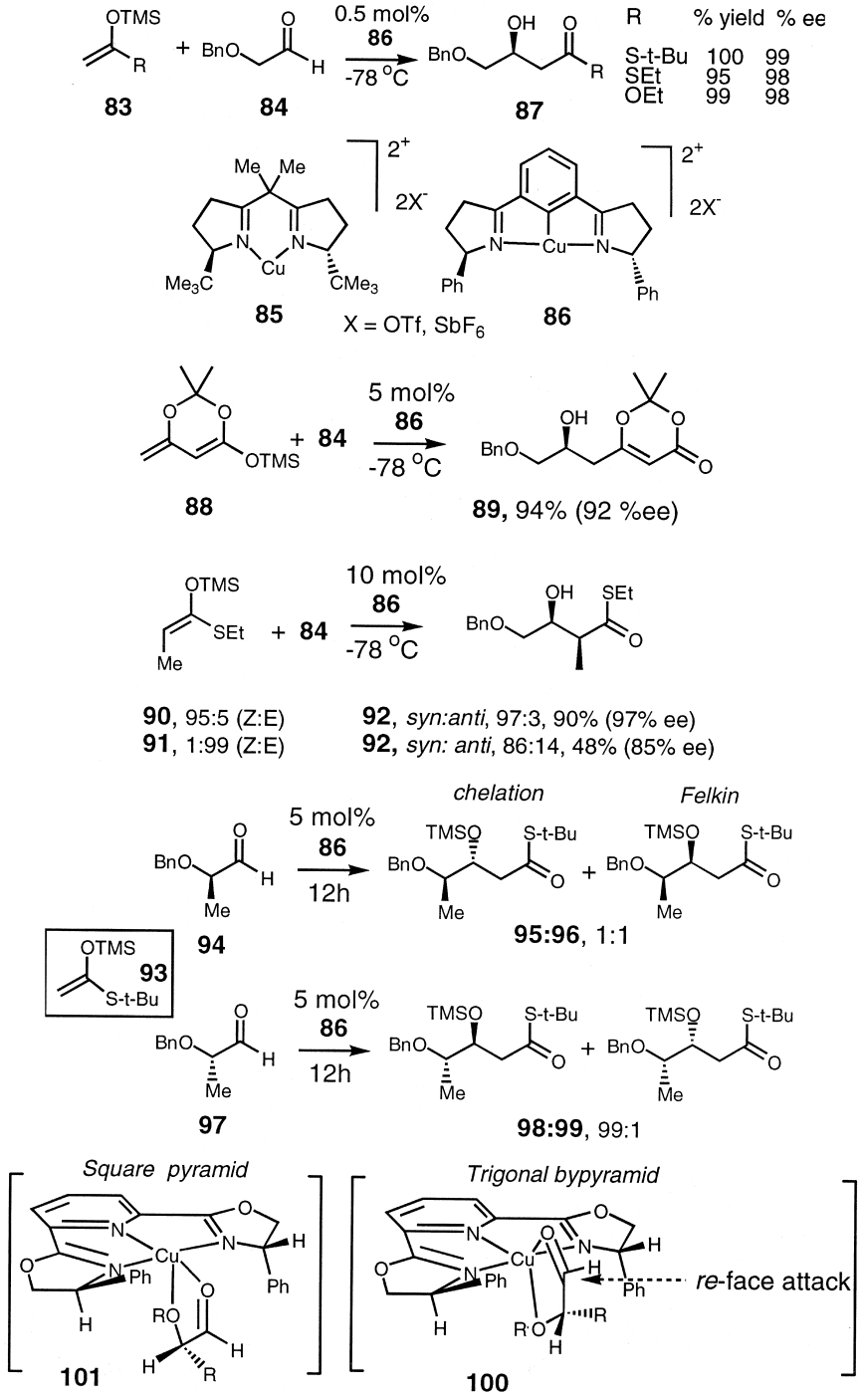


Scheme 25.

with aldehyde **84** gave the *syn* isomer, **92** (*syn*:*anti*, 97:3, 97% ee from **90**; *syn*:*anti*, 86:14, 85% ee from **91**). Low selectivity for the *syn*-product and poor yields were obtained from the *E*-enolate. No selectivity was observed with aldehydes having only one coordinating group. Five-membered chelation effect from the aldehyde seems to be crucial for facial selectivity of the attack on the enol ether. Based upon the pentacoordination geometries at Cu, two models were proposed to explain the outcome of the reaction. Model **100** is based upon the trigonal bypyramidal geometry at Cu that allows the enol ether to approach from the *re*-face. Using model **101**, that has a square pyramid orientation, one can obtain *si*-face selectivity. Based upon the results that indicate *si*-face attack to the aldehyde, the reaction was proposed to proceed via model **101**. Further support came from the reaction of chiral aldehydes **94** and **97** in the presence of catalyst **86**. From the literature, it is known that reaction with bidendate aldehydes proceeds via an *anti*-Felkin path (chelation control). The reaction of enol ether **93** with aldehyde **94** in the presence of Lewis acid **86** gave poor yields and no selectivity (**95**:**96**, 1:1). However, a similar reaction with aldehyde **97** gave the expected *anti*-Felkin product with high selectivity (**98**:**99**, 99:1). These results further supported the square bipyramid geometry for the coordination, because the other geometry is expected to give the opposite results.



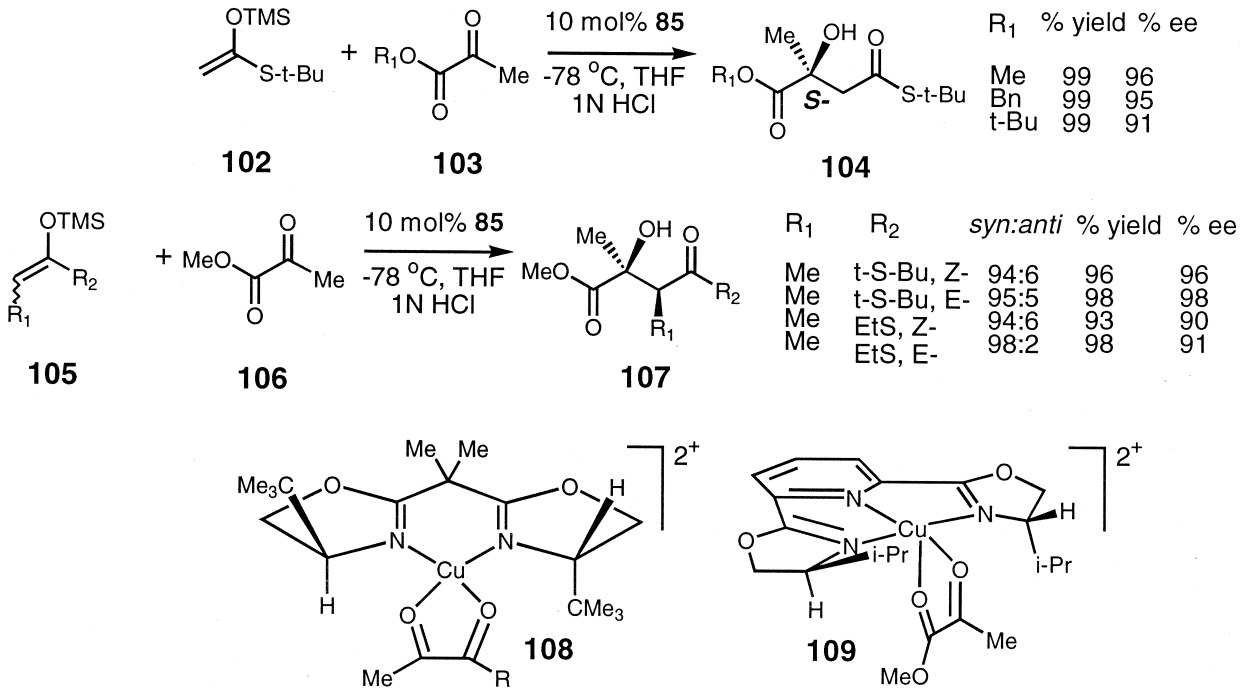
Scheme 26.



Scheme 27.

Based upon the success of C_2-symmetric copper(II) complexes for the Mukaiyama aldol reaction, reaction of silyl enol ether **102** (Scheme 28) with diketo derivatives **103** was studied.[99,100] *S*-Hydroxy-derivatives **104** (99% yields, 91–96% ee) were obtained from reaction of enol ether **102** with pyruvate esters **103** in the presence of C_2-symmetric Cu(II) Lewis acid catalysts. A change in enantioselectivity and yields was observed by varying both solvent and temperature. Reaction in THF, at −78°C, gave optimum selectivity (99% ee). The stereochemical outcome of aldol product formation was found to be independent of the stereochemistry of the enol ether. This was demonstrated by reaction of different silyl enol ethers (**105**, *E* or *Z* isomers) with methyl pyruvate **106**. In all cases, *syn*-aldol **107** was dominant (93–98% yields, 98:2 to 94:6 *syn*:*anti*, 90–98% ee). Using compounds **85** or **86** as catalysts, a square planar geometry (**108** from **85**) and a square pyramid (**109** from **86**) for complexation with the pyruvate ester was proposed on the basis of EPR studies. Both models, **108** and **109** allow enantioselective attack of the enol ether from the *si*-face leading to aldol product **107**.

In 1997, Evans used the C_2-symmetric bidendate and tridendate ligands complexed with Sn(II) based chiral Lewis

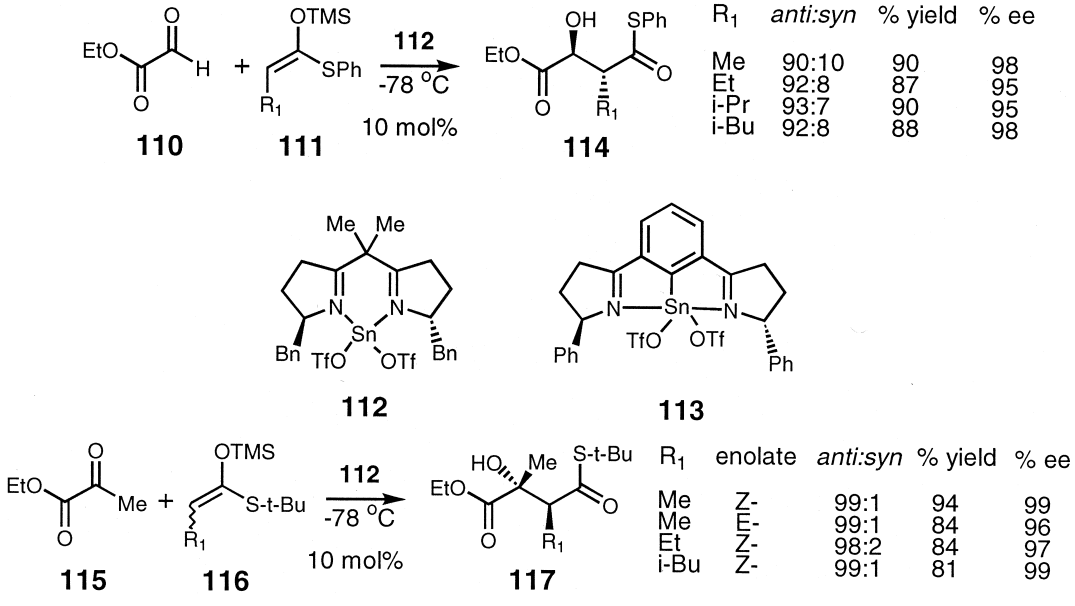


Scheme 28.

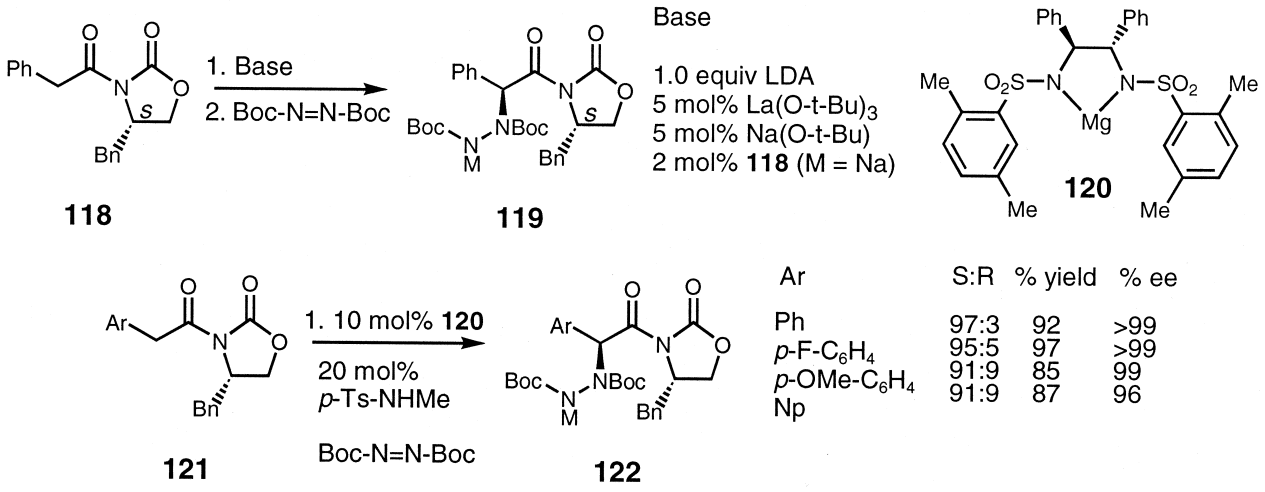
acids **112** or **113** (Scheme 29) as catalysts for the reaction of silyl enol ether with pyruvate esters.[101] Various *E*-silyl enol ethers **111** were reacted with ethyl glyoxylate **110** (−78°C with 10 mol% catalyst), and *anti*-aldol **114** was obtained in all cases. Formation of *anti*-aldol products seems to be independent of the geometry of the enol ether. Reaction of *E*- or *Z*-silyl enol ether **116** with methyl glyoxylate gave *anti*-aldol **117** with high *anti* to *syn* selectivity (*anti*:*syn*, 99:1, yields 81–94%, 96–99% ee). It is interesting to note that similar reactions using Cu(II) complexes gave the *syn*-aldol as a major product.

4.5. C_2-Symmetry derived bis(sulfonamide) chiral catalysts (Scheme 30)

Over the years, significant progress has been made in the area of chiral Lewis acid catalysts, and its application to enantioselective formation of C–C bonds (e.g. Mukaiyama aldol, Diels–Alder, etc.). Chiral catalysts that could promote formation of C–X (X=hetero atom) were not reported until 1997. Oxazolidinone chiral auxiliary based enol ethers generated under stoichiometric conditions have been effective for stereoselective amination reactions using azodicarboxylate or azide as a source of electrophilic



Scheme 29.



Scheme 30.

nitrogen. Use of a chiral catalyst in enantioselective electrophilic amination was demonstrated by Evans.[102] Reaction of the enol ether of compound **118** with di-*tert*-butyl azodicarboxylate gave the corresponding hydrazide **119** with a selectivity of 97:3 for the *S*-isomer. Using 5 mol% base, similar selectivities were achieved for product **119**. It was also found that 5 mol% of the sodium anion of **119** gave similar selectivity when NaO–*t*-Bu was used as a catalyst. Based upon these results, a similar reaction was carried out in the presence of 10 mol% C_2-symmetric magnesium bis(sulfonamide) **120** and 20 mol% *N*-methyl-*p*-toluenesulfonamide. The reaction afforded a diastereomeric preference for *S*-isomer **122** from compound **121** with a selectivity of 97:3. Further studies involved different aromatic groups. In all cases, high selectivity for *S*-isomer **122** was obtained. This was the first example of stereoselective C–N bond formation in which only 10 mol% of the chiral catalyst was utilized.

4.6. Chiral Lewis base catalysis (Scheme 31)

During 1996–1998, Denmark proposed a new class of catalytic chiral Lewis base reagents (e.g. phosphoramides **126**–**128**) that could complex with both enol ether and with aldehyde.[103–106]

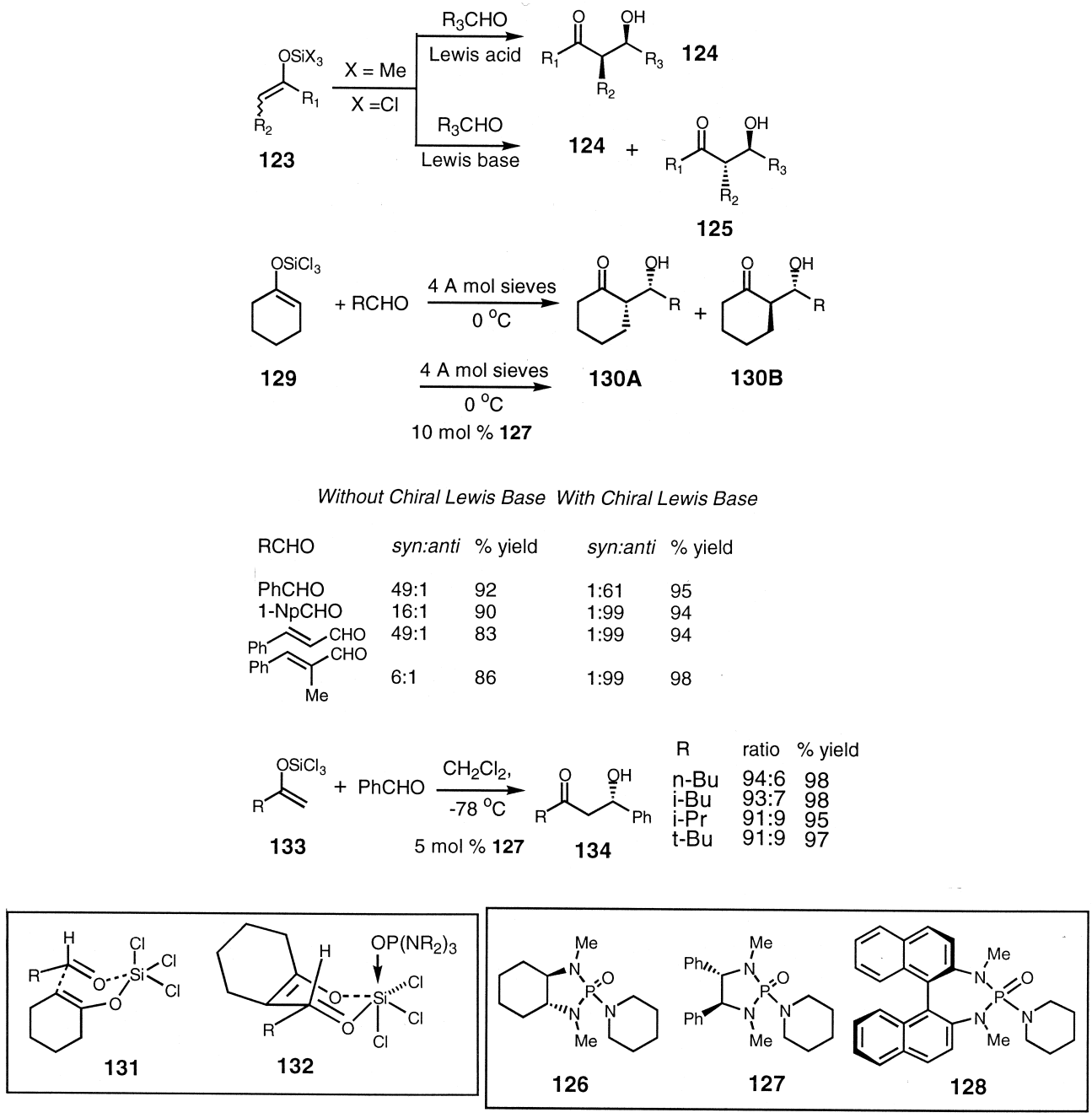
In the past, chiral Lewis acid catalysts have been used for activation of an aldehyde group in the Mukaiyama aldol reaction that proceeds via the open transition state and is independent of the geometry of the enol ether. Reaction in the presence of a catalytic chiral Lewis base differs from the standard Mukaiyama aldol reaction because the enol ether geometry can influence the stereochemical outcome of the product. Instead of the silyl enol ether, more reactive trichlorosilyl enol ethers were utilized. The reaction of the trichlorosilyl enol ether **123** was expected to give a mixture of *syn* **124** and *anti* **125**. In the absence of a chiral Lewis base the trichlorosilyl enol ether **129** upon reaction with different aldehydes, gave *syn* aldol **130A**, whereas *anti*-aldol **130B** was produced from a similar reaction in the presence of 10 mol% Lewis base catalyst. A cyclic boat transition state was proposed to explain the *syn* selectivity from *E*-enolate. A six-membered chair-like transition state with hexacoordinated geometry at silicon was proposed. Although evidence for the hexacoordinated silicon was not provided, it has been shown that in the absence of the catalyst, the reaction proceeds via pentacoordinated silicon that prefers a boat-like orientation. Further, reaction of silyl enol ether **133** with benzaldehyde in the presence of 5 mol% **127** gave enantiomerically pure β-hydroxy aldol product **134**.

4.7. Catalytic chiral metal enolate reactions (Scheme 32)

In addition to direct activation of the aldehyde and the use of chiral Lewis base (that is believed to coordinate with both the aldehyde and the enol ether), attempts were also made to generate chiral metal enol ether. This area of research is relatively unexplored. In 1998, Carreira[107] reported the use of *S*-binaphthol–copper fluoride complex to obtain chiral metal enol ether and used it in a Mukaiyama type aldol reaction.[108] It was expected that in the presence of binaphthol-copper fluoride **135**, silyl enol ether **136** would furnish a chiral copper enol ether **137**, which upon reaction with aldehyde gave aldol product **138**. Aldol **138** would undergo an exchange with the silyl enol ether **136** to give the product **139**. A labile fluoride ion in a soft metal fluoride complex was expected to result in desilylation leading to the chiral copper enol ether **137**. Reaction of the dienolate **140** with different aldehydes **141** in the presence of 2 mol% **135** gave product **142** after desilylation in good yields with high enantioselectivities (83–92% yields, 85–94% ee).

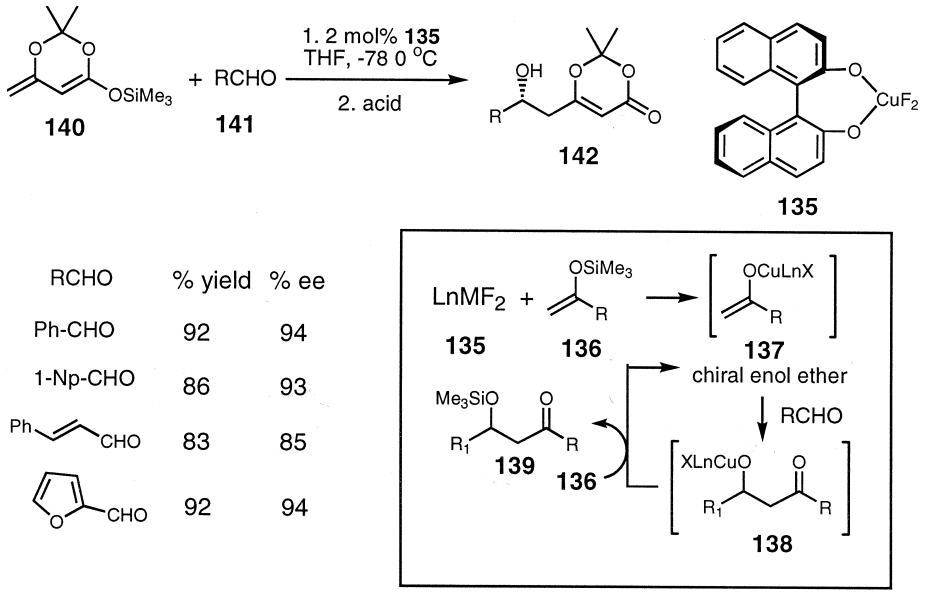
5. Asymmetric Enolate Reactions on Solid Phase (Schemes 33–36)

Due to the importance of solid phase synthesis in combinatorial chemistry, interest in this area is growing steadily.[109–114] Development of asymmetric methodologies on solid phase is a relatively young field. A major effort in this area is to anchor the chiral auxiliary onto the solid support and generate the chiral enol ether. This is then followed by reaction with different electrophiles leading to stereoselective alkylation, aldol, acylation, amination



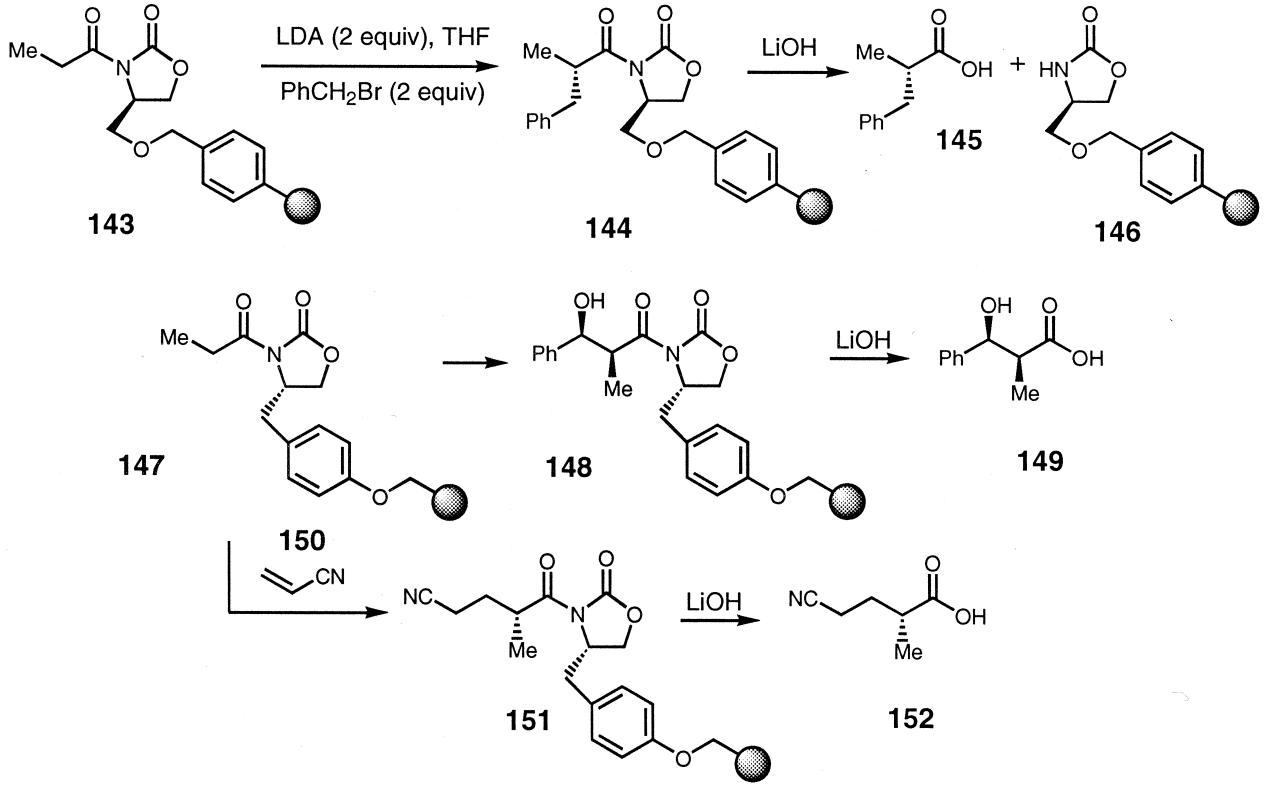
Scheme 31.

etc. In 1996, Allin reported a polymer supported oxazolidinone auxiliary **143** (Scheme 33) for development of an asymmetric enolate methodology on solid phase.[115] The enol ether was generated at 0°C using 2.0 equiv. of LDA/THF, followed by reaction with 2.0 equiv. of benzyl bromide. Alkylated resin **144** was treated with LiOH (THF/Water, 3:1, 12 h) and *S*-alkylated acid **145** was obtained (42% yield on the basis of the loading of the polymer). The chiral auxiliary anchored onto support **146** was obtained by filtration. Based upon the high % ee of product **145**, it was proposed that the reaction proceeds via a *Z*-enolate, as in solution chiral auxiliary based enol ether reaction. The application of Evans oxazolidinone chiral auxiliary on solid support **147** for aldol reaction and the conjugate addition reactions was also reported by Abell.[116] Using 13.0 equiv. of *n*-Bu_2BOTf, Et_3N (15.0 equiv.) in CH_2Cl_2 at 0°C, the stereoselective *syn*-aldol **148** was produced from benzaldehyde. Finally, product **149** was obtained from the support after treatment with LiOH. Compound **147**, in the presence of 5.0 equiv. of $TiCl_3$(*O*-*i*-Pr) and DIPEA (6.0 equiv.) at 0°C, reacted with acrylonitrile (**150**, 10.0 equiv.) to give a stereoselective conjugated product **151**. Following LiOH (5.0 equiv.) hydrolysis, acid **152** was obtained. Similar attempts were also tried by Burgess.[117] It was observed that the amount of base and the reaction time have a significant influence on the enantiomeric excess of the product. A fast reaction was noticed with the TentaGel resin.

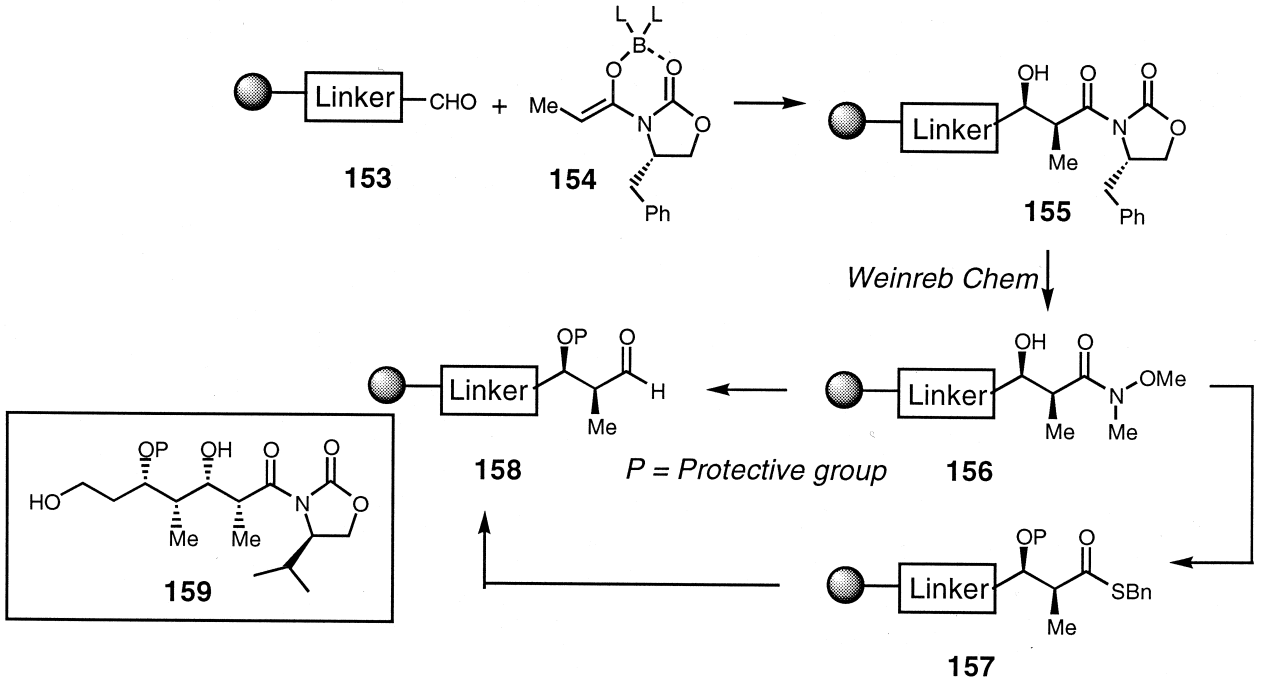


Scheme 32.

An iterative asymmetric aldol reaction on solid support for obtaining polyketide libraries was reported by Reggelin.[118,119] In a typical reaction, the aldehyde group anchored onto a solid support **153** (Scheme 34) was reacted with Evans chiral auxiliary based stereoselective, *Z*-enol ether **154**[118] to give *syn*-aldol product **155**. The aldehyde moiety was obtained on Wang resin by standard oxidation conditions (SO_3×Py). The Evans auxiliary was cleaved using Weinreb chemistry (10 equiv. Me_3Al, N,O-dimethylhydroxylamine) to give the *syn*-aldol amide **156**. After protection of the hydroxyl group, it was possible to reduce the amide group to the aldehyde **158**. Regeneration of aldehyde **158** makes it possible to carry out aldol reaction in an iterative manner to obtain polyketide derivatives. In another attempt, *syn*-aldol amide **156** was converted to the thioester derivative, followed by protection of the hydroxyl



Scheme 33.

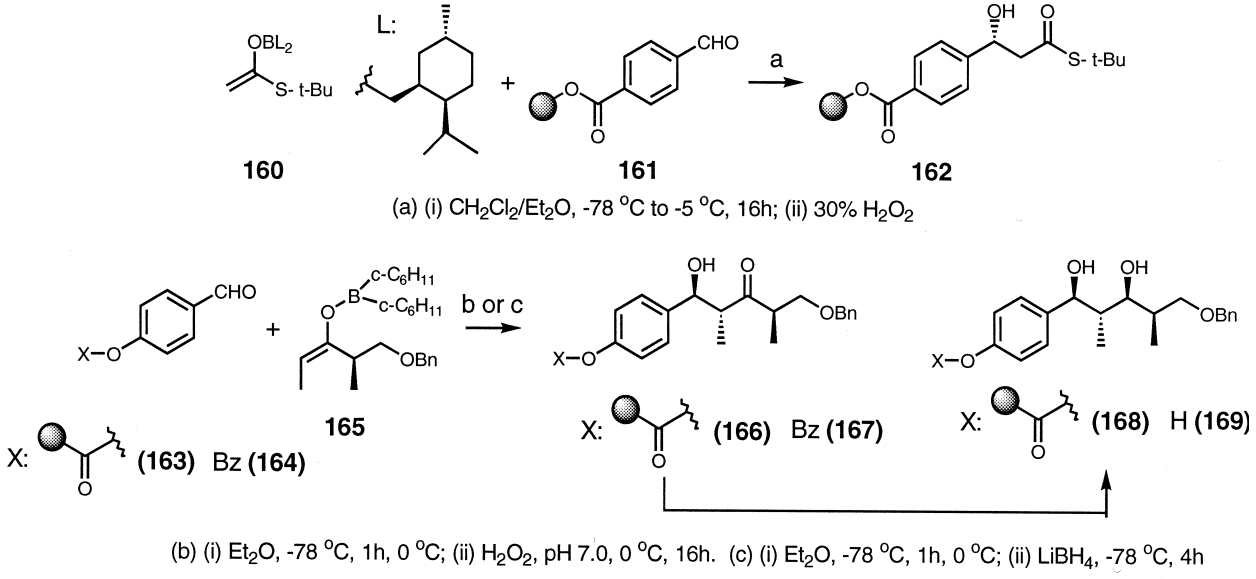


Scheme 34.

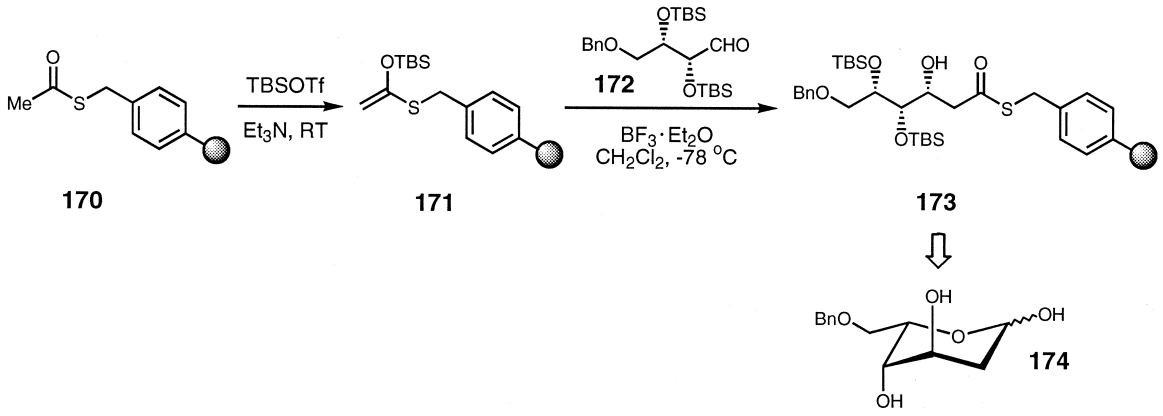
group to give compound **157**. Aldehyde derived *syn*-aldol **158** was obtained from compound **157** on reduction using $LiBH_4$ followed by Dess–Martin periodinate oxidation (10 equiv.). Thus, the synthesis of triketide **159** was achieved by iterative, asymmetric aldol methodology on solid support.[119]

Gennari and Paterson reported their results on stereoselective boron-mediated aldol reactions with aldehydes anchored onto solid support.[120] In their study, menthanone-derived thioester chiral enol ether **160** (Scheme 35) was reacted with the aldehyde on solid support **161** at −78°C to produce aldol **162**. Product stereochemistry was assigned after cleavage, and the final derivative was obtained in 18% yield. Similar yields were observed in solution chemistry. It was attributed to low aldehyde reactivity. The expected *anti*-aldol **166** was produced from reaction of aldehyde **163** with the dicyclohexyl-derived boron enol ether **165**. Aldol product **166** was reacted with $LiBH_4$ at −78°C followed by alkaline hydrolysis to give compound **169**, which was used to assign the stereochemistry. To compare the results from solution chemistry, enol ether **165** was reacted with aldehyde **164** to give aldol product **167** with >95% diastereoselectivity.

Application of aldol reaction on solid phase was utilized by Kobayashi to synthesize monosaccharide derivatives.[121] Enol ether on solid support **171** was produced from thioester



Scheme 35.



Scheme 36.

170 (Scheme 36) and reacted with aldehyde **172** in the presence of a Lewis acid at −78°C. Product **173**, upon treatment with TBAF and AcOH at 40°C followed by reaction with DIBAL, gave monosaccharide derivative **174**.

6. Conclusion

Over the years, significant advances in enolate chemistry have been made for stereoselective C–C and C–X (X=hetero atom) bond formation. New chiral auxiliaries have been developed and utilized. Several new methodologies for obtaining *anti*-aldol products have been reported. Chiral reagent based control has been studied for obtaining stereo- and enantioselective aldol and related reactions. Chiral catalysis based stereo- and enantio-selective reactions for C–C and C–X (X=hetero atom) bond formation has been a major thrust in the 1990s. At present, understanding the mechanism for catalytic reactions is still at an early stage. Efforts in this area will allow design of new and improved catalytic based reactions. In addition, applications of asymmetric enolate reactions using solid phase synthesis are beginning to appear in the literature. This is an area with tremendous potential in combinatorial chemistry and is expected to grow over the years.

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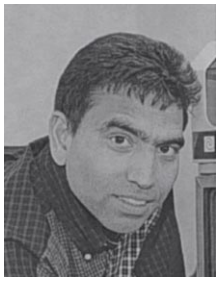
Biographical Sketch



Prabhat Arya was born in Jammu (Jammu and Kashmir, India), grew up in the premises of Delhi University where he received his education [B.Sc. (Hons), M.Sc., M.Phil. and Ph.D.]. After a short stay at the National Chemical Laboratory, Pune, India (Dr A.V. Rama Rao) and at the Université de Montpellier, France (Prof. Robert Corriu) he worked as a postdoctoral fellow with Dr. Ian Paterson (Cambridge University) and Prof. Bill Chan (McGill University). In 1989, he joined the National Research Council of Canada in Ottawa. Since 1996, he has been leading the Organic & Bioorganic Synthesis Group in the Chemical Biology Program. His current interests include the development of chemical probes using stereoselective, solid phase and automated parallel synthesis and their application towards understanding the biological function of carbohydrate conjugates (i.e. glycolipids and glycoproteins). Prabhat Arya is a Senior Research Officer in the Chemical Biology Program, Steacie Institute for Molecular Sciences, National Research Council of Canada, an Adjunct Professor at the Department of Chemistry, University of Ottawa and at the Ottawa–Carleton Chemistry Institute (OCCI), Ottawa.