Advances in Asymmetric Enolate Methodology

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Received 26 May 1999

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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 Paterson1 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...
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. 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 stereochonical 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.
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 2.

Scheme 3.
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 \( \alpha \)-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.
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. 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. 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 (Scheme 2) leads to the Z-enolate under kinetic conditions (n-Bu₂BOTf, i-Pr₂NEt, −78°C). Further reaction with an aldehyde gives the syn-aldol (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, 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. Recently, this methodology was applied to aglycones of Vancomycin and Eremomycin antibiotics. 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 (Scheme 3). The enolate (n-Bu₂BOTf, i-Pr₂NEt) of propionyloxazolidine derivative reacts with an aldehyde to give the expected Evans syn product, however a similar reaction of using TiCl₄ gave the non-Evans syn product. It was proposed that the thio-oxazolidinone derivative may proceed via a chelated system, (i.e. coordination of thio-ketone 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. This observation was further confirmed by Crimmins, when non-Evans syn was obtained from using 2.0 equiv. of TiCl₄. As suggested by Yan, a cyclic chelated model was proposed to support the formation of the non-Evans syn product. This approach was further utilized in the total synthesis of Callystatin.

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. 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 was obtained from (Scheme 4) and then reacted with several alkyl and acyl halides to give the alkylated and acylated products (96–99% de). Another modification by Polomo, involved the use of exo, exo-amino borneol in developing an oxazolidinone derived auxiliary. High selectivities with the tert-leucine derived oxazolidinone auxiliary prompted use of this system. Similar results from the alkylation of enolate with several alkyl halides gave high selectivities. In another approach, Davis reported the use of 3,3-dimethyl-2-pyrrolidinone as a chiral auxiliary for the stereoselective aldol reaction. Evans syn-aldol product (>97% de) was obtained using a well-established dibutylboron methodology from.

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

Chiral oxazoline derivatives have been utilized by Meyers for several years. Recently, Meyers has reported the use of chiral bicyclic lactams for controlling the stereochemistry of quaternary carbon centers. It is known that the enol
ether from chiral lactam \( \text{Scheme 5} \) gives \textit{endo}-selectivity for alkylation, resulting in \( \text{38} \). This approach is useful to obtain chiral cyclopentenone derivatives. A slight modification of the lactam derivatives (i.e. phenyl group at the \( \alpha \)-position related to oxygen, see: \( \text{39} \)) led to \textit{exo}-attack, \( \text{40} \).

The phenyl group in \( \text{39} \) hinders the concave site favoring attack from the \textit{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 (\( \text{41 to 42, endo-product and 44 to 45, exo-product} \)).

\subsection{2.3. C–C: Pseudoephedrine derivatives (Scheme 6)}

Following the leading work by Meyers for the stereo-selective alkylation of the \( \alpha \)-carbon of carboxylic acid derivatives, Myers reported the use of pseudoephedrine for a similar reaction. Pseudoephedrine is inexpensive and readily available. The enol ether of pseudoephedrine amides, \( \text{46} \) (Scheme 6) on reaction with several alkyl halides gave high selectivity for attack (80–99% yields, 87–94% de). The auxiliary is cleaved by \( \text{H}_2\text{SO}_4 \) in dioxane providing \( \text{48} \) without any racemization. Further, the reaction of \( \text{47} \) with borane–lithium pyrrolidide gave pure alcohol \( \text{49} \), whereas ketone derivative \( \text{50} \) was obtained on reaction with an alkyl lithium. Although the origin of the selectivity is not clear at this stage, it is anticipated that the \( Z \)-enolate is preferred, followed by the \textit{si}-face attack; it seems that the \textit{re}-face is blocked by the solvated lithium alkoxide \( \text{51} \).

\subsection{2.4. C–C: cis-Arylsulfonamido indanol derivatives (Scheme 7)}

Examples of \textit{anti}-aldol selective reactions, using a chiral auxiliary approach, are rare. In 1996, Ghosh reported the use of \textit{cis}-1-arylsulfonamido-2-indanol \( \text{52} \) to obtain \textit{anti}-aldol products from chiral ester enolate derivatives. Chiral sulfonamide ester derivative \( \text{53} \) produces \( Z \)-enolate \( \text{54} \) using \( \text{TiCl}_4/\text{i-Pr}_2\text{NEt} \) at 23\(^\circ\)C. This reaction with several monodentate aldehydes gave the \textit{anti}-aldol \( \text{55} \) (44–97% yields, 85:15 to 99:1 for \textit{anti:syn}). The formation of \textit{anti}-aldol product was explained on the basis of a cyclic transition state model for \textit{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, \textit{syn}-aldol \( \text{62} \) was obtained. The reaction of \( \text{58} \) with the monodentate aldehyde gave \textit{anti}-aldol \( \text{59} \) leading to \textit{anti-acid} \( \text{60} \) after hydrolysis, whereas bidentate aldehydes gave \textit{syn}-aldol \( \text{61} \) (for the transition state model, see, \( \text{57} \)). The synthesis of the transition state mimics of HIV protease inhibitors was achieved using this methodology.

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

The formation of \textit{anti}-aldol from norephedrine carboxyl
ester derivatives was reported by Abiko and Masamune.\textsuperscript{38,39} Reaction of an ester having a chiral bulky alcohol group 63 under $E$-enolization conditions ($c$-Hex\textsubscript{2}BOTf, Et\textsubscript{3}N, \(-78^\circ\text{C}\)) 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 ($n$Bu\textsubscript{2}BOTf, i-Pr\textsubscript{2}NEt), it was possible to obtain the syn-aldol from 66 with high selectivity.
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, Evans and Vederas. 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, was reacted with a 1:1 complex of TiCl₄:Boc–N=N–Boc at −80°C to give the hydrazide derivative in excellent yield and diastereoselectivity. It was further converted into the corresponding acid by a simple sequence of steps. In the Evans and Vederas approach, N-acyloxazolidinone 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. In a similar reaction, Evans also reported the use of trisyl azide as a source of electrophilic nitrogen leading to the stereoselective C–N bond formation. Followed by a well known transformation of the bromo to the azide derivative, the synthesis of enantiomeric pure azide acid was achieved. The first example of the stereoselective synthesis of a phosphine-containing amino acid, (Scheme 10) was developed by Gilbertson using an α-azido methodology. An oxazolidinone derivative of the protected phosphine reacted with KHMDS/−78°C to generate the Z-enolate, which was followed by reaction with trisyl azide to give the α-azido product. In another example, Arya utilized this methodology to obtain carbon-linked analogs of glycosyl serine derivatives. Surprisingly, the enolate of per-O-benzyl-α-galactosyl derivative, did not react with the trisyl azide as an electrophile, and low selectivity upon reaction.
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-L-galactosyl moiety in 83 (n=1) hindered the approach of the electrophile. This effect was not seen with the substrate 83 (n=2, R1=Bn). Several experiments were carried out to confirm this effect. Reaction with the per-O-methyl derivative 83 (n=1, R1=Me) gave the expected high diastereoselectivity (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. 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 11.

Scheme 12.
The first methodology that utilized electrophilic hydroxylation for stereoselective α-hydroxylation was reported by Davis. The 2-phenylsulfonyl-3-phenyl oxaziridine was used as a source of the electrophilic hydroxyl group. Reaction of the phenylacetamide derivative with LDA/THF/\(\text{C}_2\) produced the enol ether. This was further reacted with the oxaziridine to give the α-hydroxyl product 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, as a major product. It was speculated that due to the poor coordination nature of Na, the reaction proceeds via a non-chelated system. A method to obtain enantiomerically pure α-hydroxy carboxyl derivatives was also reported by Evans. The \(Z\)-enolate of chiral oxazolidinone derivative reacted with the oxaziridine to give the α-hydroxylated product as a major diastereomer (95:96; 77–94% yield, 90:10 to 99:1).

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

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 \(\pi\)-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 \(\pi\)-face selectivity during the attack of the enolate with the electrophile. Paterson and several other groups have developed methodologies that use chiral enol borinates. Most of the developments in this area concern C–C bond formation, and are summarized below.

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 has pioneered the use of chiral boron ligands.
in developing enantioselective aldol reaction, and has successfully applied this to the syntheses of several complex natural products. Paterson\textsuperscript{59,60} reported the enolization (17, Z; 20, E; 97:3) of diethylketone 14 using (−)-diisopinocampherylboron triflate 15, (−)-(Ipc)\textsubscript{2}BOTf and diisopropyl-ethyl 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.\textsuperscript{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)\textsubscript{2}BOTf, 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.\textsuperscript{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).\textsuperscript{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\textsubscript{2}BC1 with Et\textsubscript{3}N gave E-enolates but π-face selectivity for the aldehyde attack was not respectable.

Scheme 14.
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). Several keto derivatives 41 were reacted with ligand 42 in the presence of Et₃N at −78°C. A high selectivity for the E-enolate 44 was observed, which upon reaction with several aldehydes 45 gave enantioselective...
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 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=−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). 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−−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).

The idea of switching π-face selectivity by simply changing the chiral boron reagents was utilized to obtain enantio-merically pure syn- or anti- amino alcohol derivatives 69 and 71. In 1995, Gennari 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 17.
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 3S,4S-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. E-Enolate, 74 (Scheme 17) was obtained from thio-t-butylacetate 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 (R2=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 (R2=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. C2-Symmetry derived chiral ligands (Schemes 18 and 19)

Several approaches are available for obtaining syn-aldol products either using chiral auxiliary or ligands. Methodologies for preparation of 1,2-anti-aldol are quite limited. In 1986, Masamune 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...
The enantioselective anti-aldol 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. 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
aldehydes 92 and 93. No stereocontrol for the new stereo-
genic 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 C₂-symmetric, chiral diazaborolidine to generate stereo-selective 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 disopropylethyl 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 dioxopropylethyl 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 (Et₃N, −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. 7 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
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. 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 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. Reaction of silyl enol ether 19 with benzaldehyde in the presence of 40 mol% catalyst 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.
4.3. Binaphthol derived chiral catalysts (Schemes 22–26)

In 1993, Mikami\(^8\) 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 (\(\text{syn:anti}, 98:2\)). 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. 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.\(^9\) Using

*Scheme 22.*
10 mol% catalyst 41 (Scheme 23), in dichloromethane 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\textsuperscript{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 2–5 mol% catalyst and Lewis acid catalysts in high yields (62–94%) with 93–95% ee.\textsuperscript{91}

As an extension of this work, Carreira reported reaction of tin enolates with different aldehydes 54.\textsuperscript{92} 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, acetacetate adducts 55 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 polycene macrolide antibiotic.\textsuperscript{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.\textsuperscript{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 tributylin 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. In this case, tin enol ether 73, from trichloro enol acetate 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.\textsuperscript{97,98} Activation of aldehydes proceeds via bidentate coordination as shown in transition states 100 and 101. Activation of
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)
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 bipyramidal 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.
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. $S$-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 $-78^\circ\text{C}$, 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...
Acids 112 or 113 (Scheme 29) as catalysts for the reaction of silyl enol ether with pyruvate esters. 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
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% C₆-symmetric magnesium bis(sulfonamide) 120 and 20 mol% N-methyl-p-toluene-sulfonamide. 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
etc. In 1996, Allin reported a polymer supported oxazolidinone auxiliary \(\text{143}\) (Scheme 33) for development of an asymmetric enolate methodology on solid phase.\(^{115}\) The enol ether was generated at \(0^\circ\text{C}\) using 2.0 equiv. of LDA/THF, followed by reaction with 2.0 equiv. of benzyl bromide. Alkylated resin \(\text{144}\) was treated with LiOH (THF/Water, 3:1, 12 h) and \(S\)-alkylated acid \(\text{145}\) was obtained (42% yield on the basis of the loading of the polymer). The chiral auxiliary anchored onto support \(\text{146}\) was obtained by filtration. Based upon the high % ee of product \(\text{145}\), 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 \(\text{147}\) for aldol reaction and the conjugate addition reactions was also reported by Abell.\(^{116}\) Using 13.0 equiv. of \(n\)-Bu\(_2\)BOTf, Et\(_3\)N (15.0 equiv.) in \(\text{CH}_2\text{Cl}_2\) at \(0^\circ\text{C}\), the stereoselective \(syn\)-aldol \(\text{148}\) was produced from benzaldehyde. Finally, product \(\text{149}\) was obtained from the support after treatment with LiOH. Compound \(\text{147}\), in the presence of 5.0 equiv. of TiCl\(_3\)(\(O\)-i-Pr) and DIPEA (6.0 equiv.) at \(0^\circ\text{C}\), reacted with acrylonitrile (\(\text{150}\), 10.0 equiv.) to give a stereoselective conjugated product \(\text{151}\). Following LiOH (5.0 equiv.) hydrolysis, acid \(\text{152}\) 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.
An iterative asymmetric aldol reaction on solid support for obtaining polyketide libraries was reported by Reggelin. In a typical reaction, the aldehyde group anchored onto a solid support was reacted with Evans chiral auxiliary based stereoselective, Z-enol ether to give syn-aldol product. The aldehyde moiety was obtained on Wang resin by standard oxidation conditions. The Evans auxiliary was cleaved using Weinreb chemistry to give the syn-aldol amide. After protection of the hydroxyl group, it was possible to reduce the amide group to the aldehyde. Regeneration of aldehyde makes it possible to carry out aldol reaction in an iterative manner to obtain polyketide derivatives. In another attempt, syn-aldol amide was converted to the thioester derivative, followed by protection of the hydroxyl group.

Scheme 32.

Scheme 33.
group to give compound 157. Aldehyde derived syn-aldol 158 was obtained from compound 157 on reduction using LiBH₄ followed by Dess–Martin periodinate oxidation (10 equiv.). Thus, the synthesis of triketide 159 was achieved by iterative, asymmetric aldol methodology on solid support. Gennari and Paterson reported their results on stereo-selective boron-mediated aldol reactions with aldehydes anchored onto solid support. In their study, menthanone-derived thioester chiral enol ether 160 (Scheme 35) was reacted with the aldehyde on solid support 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 LiBH₄ 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. Enol ether on solid support 171 was produced from thioester...
170 (Scheme 36) and reacted with aldehyde 172 in the presence of a Lewis acid at \( \sim 78^\circ C \). 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.

Acknowledgements

We thank Dr Ian Paterson (University Chemical Laboratory, Cambridge University) and Prof. Scott Nelson (Department of Chemistry, University of Pittsburgh) for several useful suggestions. Michael Barnes, Najma Alibhai and Dr Brady Clark are thanked for editing the manuscript.

References

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.