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Mastering Chirality: Unlocking Bioactive Natural Products with Oxazaborolidines and Oxazaborolidinones

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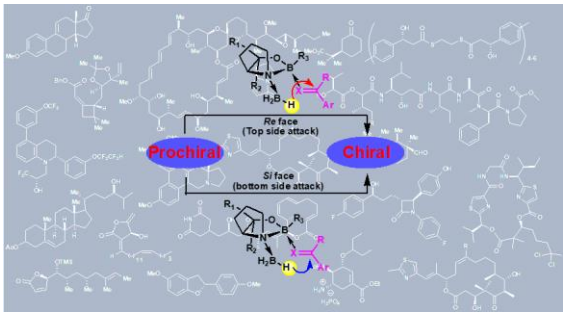
Abstract: Catalytic asymmetric synthesis has appeared as the preferred method for producing enantiomerically pure compounds, marking significant advancements in recent years. In biological processes, asymmetric catalysis governs the synthesis of chiral compounds, facilitated through the chirality transfer following reactant binding at enzyme active sites. A revolutionary milestone in this area was the discovery of oxazaborolidine chiral catalysts by Corey, Bakshi, and Shibata (CBS catalysts), empowering the enantioselective reduction of achiral ketones. This discovery has had profound implications across industry and academia, establishing oxazaborolidines as pivotal tools for achieving chirality in chemical systems. The application of oxazaborolidines and their derivatives have been extensively explored for enantioselective reductions of various functional groups. While previous review articles focused on specialized functional groups, this review provides an overview (last fifteen years) of practical advancements in the use of borane-oxazaborolidine catalysts for the enantioselective reduction of challenging functional groups such as ketones, ketimines, and oximes. These advancements have facilitated the synthesis of various building blocks for natural products. We also highlighted the potential of oxazaborolidinones as it was remains largely underutilized, presenting an exciting opportunity for future investigations.



Keywords: *enantioselective, oxazaborolidine, oxazaborolidinone, hydride transfer, reduction.*

Contents

1. Introduction

Chirality is crucial in biological, chemical, pharmaceuticals and material science. In recent years, remarkable advancement has been attained in catalytic asymmetric processes. Catalytic asymmetric synthesis has emerged the most desired technique to make enantiomerically pure compounds. Asymmetric catalysis enables the production of asymmetric compounds in biological processes. Natural processes drive reactants bind enzyme active sites by chirality transfer. Most commonly inchemical systems, one of the reactants binds to the chiral catalyst which then influences the other reactant by transferring the chirality.[1]

In the mid-20thcentury, the discovery of $NaBH_4$ (1942)[2] and $LiAlH_4$ (1945)[3], known for their typical reducing properties, transformed synthetic organic chemistry. Chemist began exploring complex metal hydrides, including $LiAlH_4$ and $LiBH_4$, for use in synthetic organic chemistry. Over the next thirty years, numerous studies investigated "mixture reagents," like $LiAlH_4$ combined with chiral 1,2-diols, 1,2-aminoalcohols, 1,2-diamines, hy-droxymethyl oxazolines, BF_3, and chiral amino acid esters.[4] These systems demonstrated good enantioselectivity but were rarely used in organic synthesis due to issues like catalyst solubility, unknown reactive species, and a lack of mechanistic understanding of enantioselectivity. While Mosher and Yamaguchi achieved promising results with Darvon alcohol and $LiAlH_4$, these problems persisted.[5]

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Dr. Prasun Kanti Pradhan earned his Ph.D. in 2006 from the CSIR-IICB (Jadavpur University), Kolkata, West Bengal, India focused on synthetic studies of β-aryl ethyl amine derivatives. He did postdoctoral research in asymmetric catalysis in the laboratory of Professors Masato Kitamura and Riyoji Noyori in Noyori's Organic Synthesis Group, under RCMS fellowship at Nagoya University, Japan. In 2010, he joined TCG Life Sciences Pvt. Ltd. in Kolkata, where he currently serves as a Senior Lead Scientist.

Although applicable to certain substrates, the high costs limited the practicality of this reducing system. After thirty years of attempting to combine these reducing agents with different chiral ligands for efficient asymmetric synthesis, results persisted disappointing. Finally, in the 1980s, Itsuno and his coworkers achieved encouraging outcomes with mixtures of chiral 1,2-amino alcohols and borane (Figure 1).[6] They used borane and chiral amino alcohols (1-4) (obtained from α-amino acids) to reduce aromatic ketones into the corresponding secondary alcohols with up to 60% stereoselectivity. The amino alcohols (1-4) formed complexes with borane (alkoxy-amine-borane complexes), releasing one

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This article is dedicated to Professor Marek Zaidlewicz on the occasion of his 86thbirthday

equivalent of hydrogen gas at -70 to 0°C. However, they could not afford a mechanistic clarification for the detected enantioselectivity.[7] It was Noyori who first provided a clear mechanistic explanation for high enantioselectivity using a mixture of (*S*)- or (*R*)-BINOL, LiAlH4, and ethanol, known as the Noyori reagent.[8]

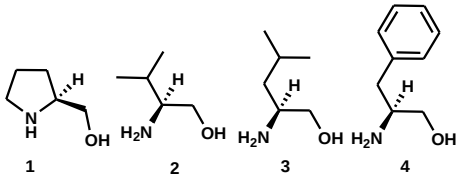
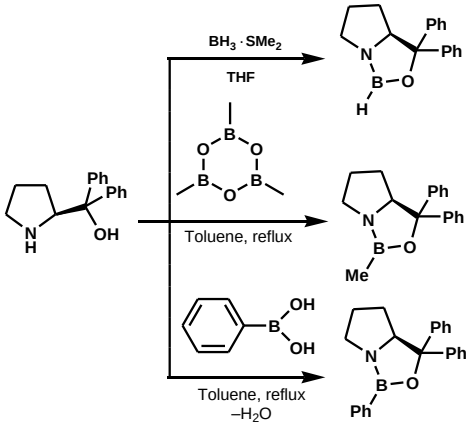


Figure 1. *Amino alcohols used by* Itsuno *and co-workers.*

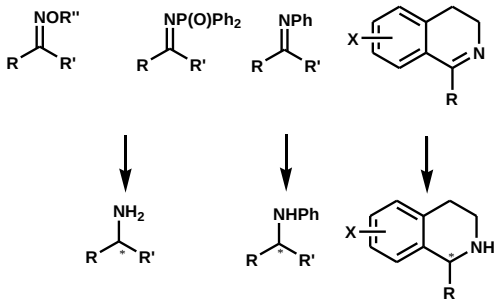
2. Oxazaborolidine synthesis and its use in asymmetric borane reduction

These critical annotations resulted in the discovery of chiral oxazaborolidine catalysts by Corey, Bakshi, and Shibata (CBS catalysts)[9] for the enantioselective reduction of various achiral ketones, known as CBS reduction. The CBS catalysts were prepared by reacting amino alcohol with two equivalents of BH_3 in THF or BMS at 30°C for 6 hours. Different borane sources and reaction conditions were also explored for making oxazaborolidine catalysts (Scheme **1**).[10]

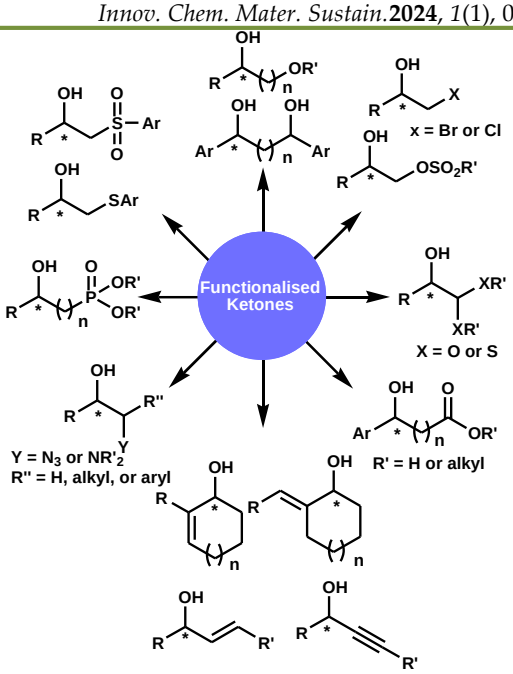
There are more reports on the enantioselective reduction of prochiral ketones than on the reduction of oximes or ketimines.[11] For prochiral ketones, these reductions are highly effective for most aryl alkyl ketones including various functionalized ketones such as heterocyclic ketones, *α*-hydroxy ketones, diketones, *α*-halo- and sulfonyloxy ketones, *α*-keto acetals or thioketals, *α*, *β*-enones and ynones, keto esters, keto phosphates, *α*-azido ketones, meso-imides, *β*-keto sulfides and sulfones, and biaryl ketones and lactones. The use of even 2 mol% of oxazaborolidine catalyst achieves high enantioselectivity with predictable configurations (Schemes **2** and **3**).



Scheme 1.*Synthesis of oxazaborolidine (*Corey-Bakshi-Shibata *Reagent).*

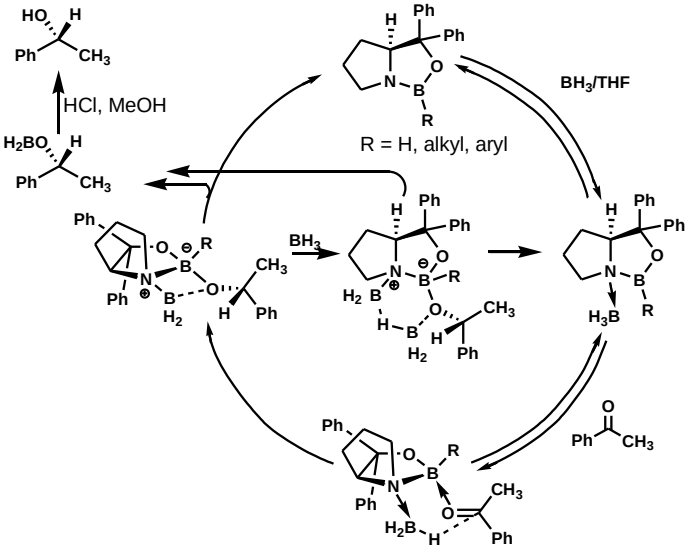


Scheme 2. *Asymmetric reduction of ketimines by borane-oxazaborolidine.*



Scheme 3. *Asymmetric reduction of functionalized ketones by borane-oxazaborolidine.*

They established the reaction of amino alcohols with two equivalents of BH_3 in THF at 35 °C formed two equivalents of H_2 gas and the oxazaborolidine, which was achieved in pure form upon subsequent elimination of the solvent and excess BH_3 under reduced pressure and sublimation (Scheme **4**).



Scheme 4. *Enantioselective reduction of ketones by oxazaborolidine proposed by* Corey.

The pioneering discovery of oxazaborolidine marked a milestone, leading to the rapid expansion of CBS reduction, which is now considered a major synthetic method for the asymmetric reduction of prochiral ketones. This reduction technique has broad applications, including the synthesis of (1) chiral ligands, (2) intermediates, (3) bioactive compounds, and (4) natural products.

The use of the above-mentioned stoichiometric reagents achieved remarkable success, but it required at least one equivalent of the reagents. This drawback, due to the low availability and high cost of the reagents, accentuated the need to develop catalytic methods for these sorts of reductions. Later, Itsuno and Corey observed high enantioselectivity with predictable configurations in the reduction of prochiral ketones, even with just 2 mol% of oxazaborolidine (Figure **2**).[12]

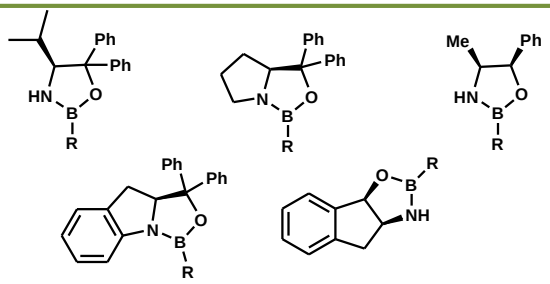


Figure 2. *Selected oxazaborolidines.*

However, these borane exporters have certain limitations for large-scale implementations, including high sensitivity to air and moisture, low concentration and stability of BH_3-THF, and the high volatility, flammability, and nasty scent of BMS.

The oxazaborolidine-catalyzed borane reductions have been extensively studied by Itsuno[13] and Corey[14]. Given the numerous reviews till date, this review attention on the fresh applications of chiral borane-oxazaborolidines in synthetic organic chemistry.[15] Baranowska-Łaczkowska and colleagues theoretically investigated B-substituted oxazaborolidine–borane complexes using MP2 and DFT/B3LYP methods. They observed that in closed structure complexes, the oxazaborolidine ring with a B–H–B bond is more planar compared to open complexes, due to a rigid hydrogen bridge between the boron atoms.[16a] The interaction energies in the closed complexes are 1.5 to 2.5 times greater than those in the open complexes, with the highest values found in B-trifluoromethyl substituted complexes. This increase is likely due to the strong electron-withdrawing trifluoromethyl (CF_3) group, which reduces electron density on the B1 atom and leads to the formation of a B–H–B bond (Figure **3**). The enhanced interactions in B-trifluoromethyl complexes suggest they may be more stable and easier to isolate, despite the computational model not considering factors like solvent effects.

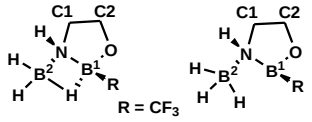


Figure 3. *Close vs open ring in B-H-B bond.*

Kettouche *et al.* explored the origin of selectivity in the [2+2] cycloaddition step of the enantioselective reduction of ketone mechanism by a *B*-methoxy oxazaborolidine catalyst resulted from (–)-*β*-pinene.[16b] They provided a clear clarification of the construction of O–B and N–B bonds through a two-stage, one-step mechanism using electron localization function topological analysis. They proposed that the stability difference between these bonds primarily arises from the methanediyl group alignment within the pinene skeleton.

In connecetion with the enantioselctive reduction of ketamine, Nacereddine *et al*. studied theoretically to undedrstand the origin of enantioselectivity by using transition state theory and DFT methods at the B3LYP/6-31G(d,p) level by oxazaborolidine catalyst.[19c] Their findings show that hydride transfer to the *Si* face is more favorable than to the *Re* face. Analysis of non-covalent interactions and molecular electrostatic potential reveals that several favorable interactions during the *Si* face hydride transfer contribute to the observed enantioselectivity (Figure **4**). Additionally, Electron Localization Function topological analysis directs that the hydride transfer mechanism occurs through a non-concerted three-stage.

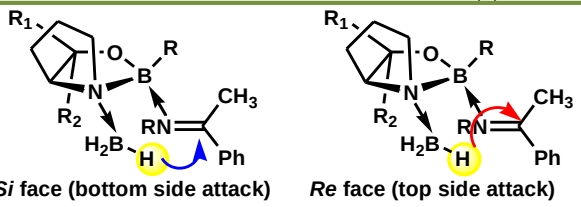


Figure 4. *Interactions during the hydride transfer (Re & Si face).*

Bach and Daniel provided an outstanding overview on the diversity and intricacy of chiral 1,3,2-oxazaborolidine catalysts used in asymmrtic photochemical reactions. They emphasized the significance of the B-H-B bridging interaction in B-substituted oxazaborolidine-BH_3 complexes. In these reductions, oxazaborolidines serve both as catalysts and stoichiometric reagents for asymmetric induction. Amongthese, the well-known, commercially available CBS reagents and their analogues are widely recognized as some of the utmost effective asymmetric catalysts for such reductions.[14,17] Typically, oxazaborolidine-mediated borane reductions are conducted by adding prochiral ketones, imines, or oximes to a mixture of oxazaborolidine and borane transporters in an suitable solvent at ambient temperature. Although, Corey and his team introduced fluorine substituents into the chiral ligand, resulting in a new, second-generation of chiral oxazaborolidinium cationic class which is effective even at loadings of 1–2 mol %.[18] These species, when combined with various Lewis acids, are highly effective for Diels–Alder reactions, achieving good yields and high enantioselectivities (>95%ee) and these new catalysts particularly appealing for large-scale production. They found that using the strong acid triflimide (Tf_2NH) in a CH_2Cl_2 solution enhances the catalytic activity of these oxazaborolidines. The combination of Tf_2NH with biscoordinating Lewis acids $TiCl_4$ or $SnCl_4$ as coactivators significantly boosts catalytic efficiency. This increase in acidity with Tf_2NH is notably greater when paired with biscoordinating agents like $TiCl_4$ and $SnCl_4$ compared to monocoordinating salts, even strong Lewis acids including $AlBr_3$ and BBr_3 in CH_2Cl_2 or CH_2Cl_2/toluene. The enhanced acidity of Tf_2NH is attributed to the formation of a stabilized cyclic anionic complex with $TiCl_4$, suggesting broader applicability. The activation of fluorinated oxazaborolidines using Tf_2NH–$TiCl_4$ has been demonstrated its effectiveness while use in the enantioselective (4 + 2) cycloaddition reaction to afford α,β-unsaturated acid chlorides (Figure **5**).

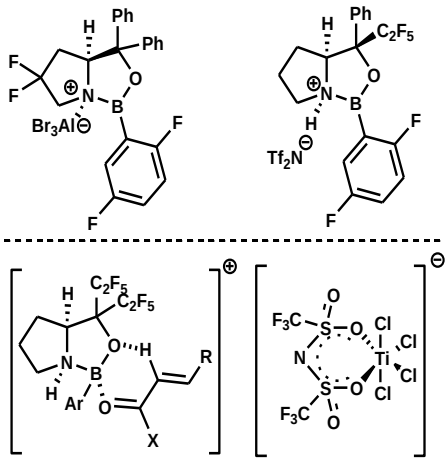
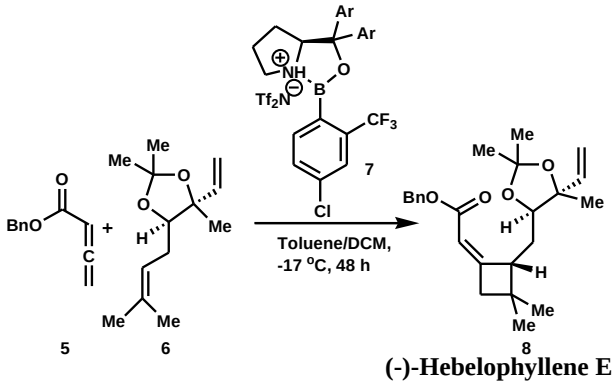


Figure 5. Corey's *Second Generation Catalysts (Top); reactive complex for [4+2]-cycloaddition reactions (Bottom)*

First, Brown *et al*. achieved the synthesis of hebelophyllene E (**8**) and established its previously strange relative configuration by synthesizing *epi*-ent-hebelophyllene E. The key of the methodology was the catalytic enantioselective [2+2]

cycloaddition step using a novel oxazaborolidine catalyst **7**, which facilitated the reaction of alkenes **6** and allenoates **5** to produce chiral geminal dimethylcyclobutanes adduct with high functional-group tolerance. This tactic permitted a late-stage cycloaddition with a completely functionalized alkene, trailed by a diastereoselective reduction, leading to the hebelophyllene natural product (Scheme **5**).[19]



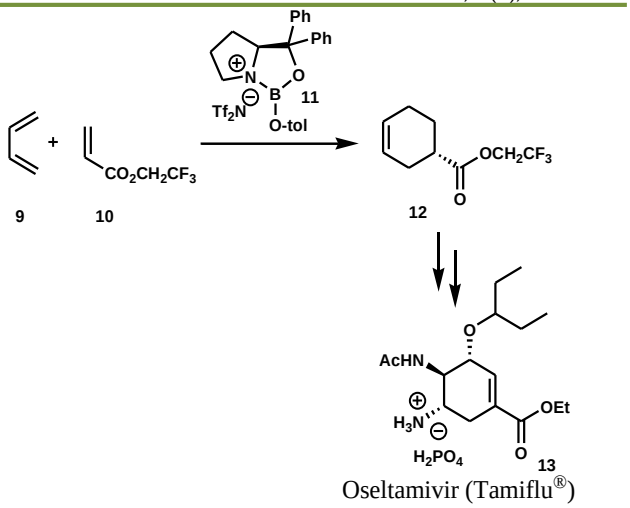
Scheme 5. *Enantioselective [2+2] cycloaddition by oxazaborolidine catalyst.*

3. Synthesis of natural products congeners

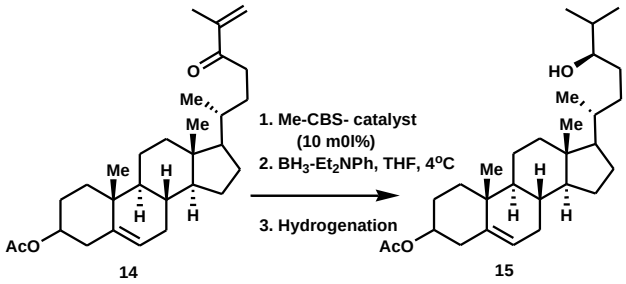
Oxazaborolidines have demonstrated to be extremely beneficial and versatile catalysts in the synthesis of various biologically significant complex molecules, such as estrone, desogestrel, laurenditerpenol, and dolabellane-type marine natural products, including the oral antiflu drug oseltamivir (Tamiflu®). The development of the avian virus N1H5 raises the opportunity of a pandemic wave of deadly flu, demanding prompt action.[20] Therefore, the total synthesis of oseltamivir offers several advantages over existing procedures and has the potential to rise the production rate.

A short, scalable, and straightforward enantioselective Diels–Alder reaction route was reported by Corey *et al*.[21] for synthesizing the anti-influenza neuraminidase inhibitor oseltamivir (Tamiflu® **13**) from 1,3-butadiene (**9**) and acrylate **10**. The reaction of butadiene **9** with trifluoroethyl acrylate (**10**), in the presence of *S*-prolinol-derived oxazaborolidine cation catalyst **11**, formed the adduct **12**. This adduct was then further elaborated through multiple steps to synthesize oseltamivir (**13**) (Scheme **6**).

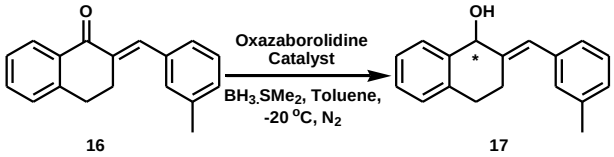
Enantioselective reduction of α-methylene ketones using oxazaborolidine-catalyst have reported Ishibashi *et al*.[22a] efficiently and conducted the rection using borane−diethylaniline (BH_3-Et_2NPh) as a stoichiometric reducing agent. Combining this method with the successive hydrogenation of the allylic alcohol produced enhanced stereoselectivity during the reduction of 24-oxocholesteryl ester to 24-(*R*)-hydroxycholesteryl ester. Under optimized conditions, the oxazaborolidine (Me-CBS)-catalyzed reduction of **14** afforded the allylic alcoholintermediate with 87% yield and high enantioselectivity (*R*/*S* 97.5:2.5). The hydrogenation *of exo*-methylene group regioselectively was achieved the intermediate using H_2 and Wilkinson's catalyst, resulting in (R)-hydroxycholesteryl acetate **15** with 84% yield (Scheme **7**). Tülay Yıldız developed a synthetic approach to produce new chiral allylic alcohols **17** through the enantioselective reduction of (E)-*α,β*-unsaturated ketones **16**. This method employs oxazaborolidine catalysts, which are derived from amino alcohol and trimethylboroxine, and achieves high enantioselectivity and chemoselectivity. The reduction is carried out in toluene at −20 °C and typically completes within 0.5–2 hours (Scheme **8**). [22b]



Scheme 6. *Enantioselective Diels-Alder reaction using chiral oxazaborolidine catalyst.*



Scheme 7. *Enantioselective reduction of α-methylene ketone.*



Scheme 8. *Enantioselective reduction of α-methylene ketone.*

Epothilones represent an encouraging new class of anticancer drugs (Figure **6**). Preclinical studies have exposed that epothilones effectively bind to and alleviate microtubules, similar to paclitaxel but with some differences, and they are effective in tumor representations resistant to paclitaxel.
Clinical data from phase I and phase II trials are accessible for BMS-247550, BMS-310705, EPO906, and KOS-862. Like taxanes, epothilones prevent cancer cell division by intrusive with tubulin. However, early trials suggest that epothilones deal better effectiveness and milder adversarial effects compared to taxanes.[23]

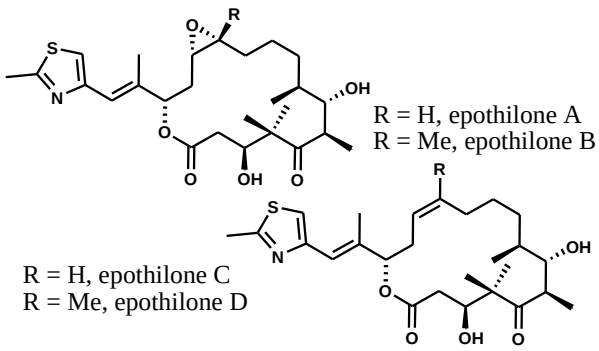
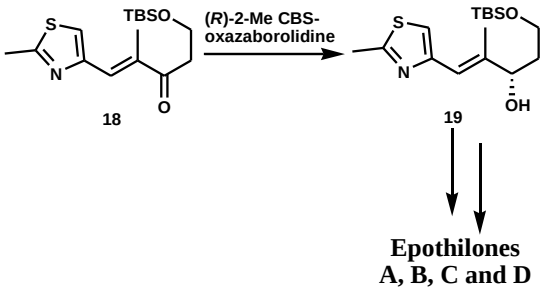


Figure 6. *Structure of Epothilones A, B, C and D.*

Reiff *et al*.[24] successfully accomplished the total synthesis of epothilones A, B, C, and D using novel and efficient asymmetric synthetic methods to prepare two key building

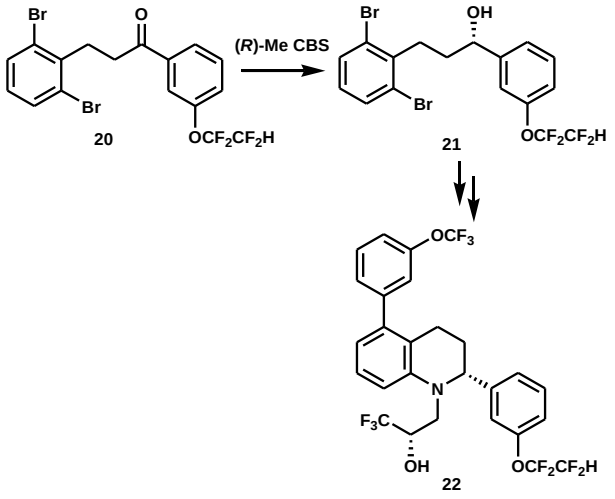
blocks (Scheme **9**). A decisive step in this synthesis was the asymmetric reduction of (*E*)-5-(tert-butyldimethylsilyloxy)-2-methyl-1-(2-methylthiazol-4-yl)pent-1-en-3-one **18**, achieved using (*R*)-Me-CBS-oxazaborolidine to yield (*S*)-alcohol **19**. The final epothilone products were achieved through a well-established total synthetic strategy.[25]



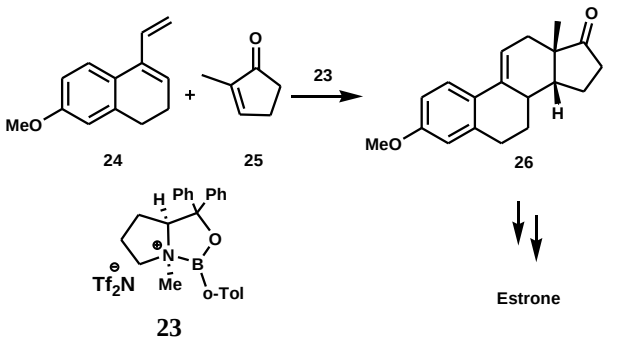
Scheme 9. *Total synthesis of Epothilones A, B, C and D.*

Rano *et al*.[26] reported the asymmetric synthesis of 3,4-dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3(trifluoromethoxy) -phenyl]-α-(trifluoromethyl)-1(2*H*)-quinoline ethanol **22**, a cholesteryl ester transfer protein (CEPT) inhibitor. The asymmetric alcohol intermediate **21** was achieved through the chiral reduction of a ketone using Corey's (*R*)-Me CBS oxazaborolidine reagent and a tetrahydroquinoline core was formed *via* a Cu-mediated intramolecular amination reaction. Additionally, the synthesis of the prochiral ketone **20** was enhanced by eradicating the use of a harmful aryltin reagent (Scheme **10**).

First, Canales et al.[27] reported the synthesis of hitherto mysterious N-methyl oxazaborolidine cations **23**, specifically a cationic proline derivative that functions as a stronger chiral Lewis acid than the typical oxazaborolidine catalyst. They presented a new method for synthesizing oxazaborolidines by reacting lithium aryl borohydrides with amino alcohol salts. This cationic oxazaborolidine reagent is highly effective in [4+2] cycloaddition reactions. For instance, the diene 7-methoxy-4-vinyl-1,2-dihydro-naphthalene **24** reacted with the 2-methyl-cyclopent-2-enone dienophile **25** to produce the adduct **26** in noble yield and with extraordinary enantioselectivity (Scheme **11**). Several diverse examples, including estrone, demonstrate the broad applicability of this catalytic methodology.



Scheme 10. *Total synthesis of 3, 4-dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-5-[3-(trifluoromethoxy) phenyl]-α-(trifluoromethyl)-1(2H)-quinoline ethanol.*

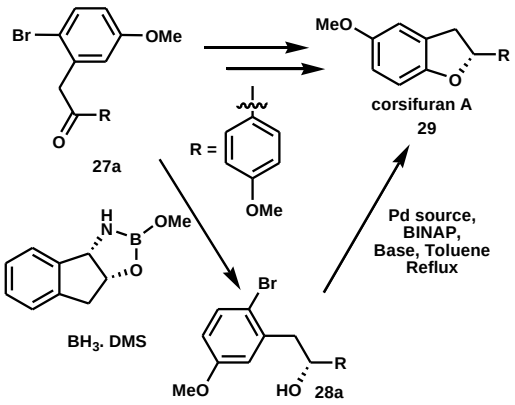


Scheme 11. *Asymmetric [4+2] cycloaddition reaction by N-methyl oxazaborolidine cations.*

Corsifuran A (**29**) is one of three corsifurans, featuring a 4',5-dioxygenated-2-arylbenzofuran skeleton. This compound was isolated from the Mediterranean liverwort *Corsinia coriandrina*.[28] The skeleton of corsifuran is believed to be biogenetically derived from a stilbenoid precursor, and the biogenic material has been validated to possess high enantiomeric purity.[29]

The asymmetric reduction of ketones using borane-oxazaborolidine could potentially enable the synthesis of various natural products.[30a] Adams *et al*. successfully synthesized enantiomerically pure corsifuran A for first time through an enantioselective reduction procedure, enabling the validation of the absolute stereochemistry of the natural product. The asymmetric reduction of ketone **27a** with the B-OMe oxazaborolidine derived from either (1*R*,2*S*)- or (1*S*,2*R*)-*cis*-1-amino-indan-2-ol afforded the *S* and *R* enantiomers of the alcohol **28a** with 76% and 78% enantiomeric excess, respectively. Further, recrystallization of the alcohol lead to in >99% enantiomeric purity. Corsifuran A (**29**) was then obtained *via* cycloetherification using numerous palladium catalysts along with widespread ligands and bases (Scheme **12**).[30b]

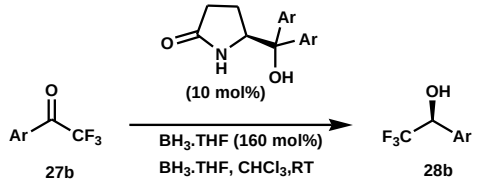
Kawanami *et al*.[30c] reported the enantioselective reduction of the highly reactive prochiral trifluoromethyl ketone **27b** to its corresponding alcohol **28b** using an oxazaborolidine catalyst produced *in situ* from BH_3–THF with chiral lactam alcohol. This catalyst assisted the enantioselective reduction of trifluoromethyl ketones **27b** in $CHCl_3$ at room temperature, achieving up to 86% enantiomeric excess (*ee*) (Scheme **13**).



Scheme 12. *Asymmetricsynthesis of corsifuran A through an enantioselective oxazaborolidine reduction.*

They also found that $CHCl_3$, a polar halogenated organic solvent, was optimal for attaining high enantioselectivities with reactive trifluoromethyl ketones, as CH_2Cl_2 generally provides

lower *ee* compared to THF and toluene in the asymmetric reduction of typical ketones. This practical method offers several advantages, including stability towards air and moisture and milder reaction conditions compared to previously reported methods.[31] They also investigated the influence of BF_3 on the enantioselective reduction of trifluoromethyl ketones **27b** with a chiral lactam alcohol and borane. They found that BF_3·THF improved the enantioselectivity of the reduction of reactive trifluoromethyl ketones at room temperature. The BF_3·THF addition to an in situ generated oxazaborolidine catalyst, derived from the chiral lactam alcohol and borane, boosted both the enantioselectivity (up to 90% ee) and yield (up to 91%).[30d]

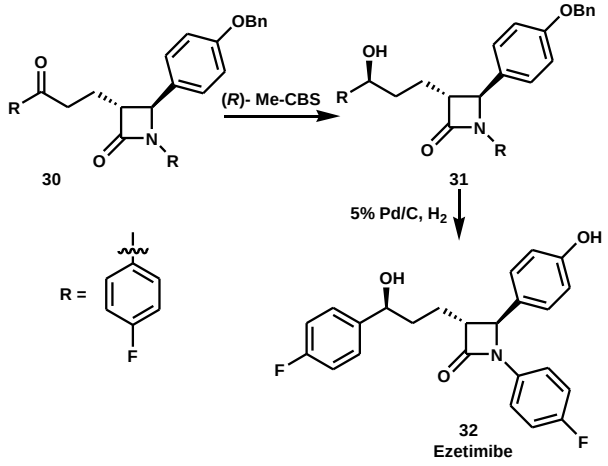


Scheme 13. *Enantioselective reduction of trifluoromethyl ketones by borane-oxazaborolidine derived from a chiral lactam alcohol.*

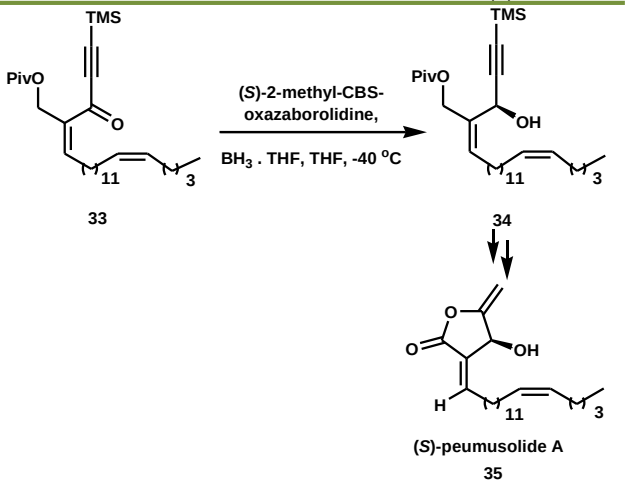
Sasikala *et al*.[32] developed an efficient, cost-effective, and scalable synthesis of ezetimibe (**32**), an antihypercholesterolemia drug. Chiral oxazolidinone chemistry was engaged to establish the necessary stereochemistry of the *β*-lactam ring **30**, while chiral oxazaborolidine was used to determine the stereochemistry of the hydroxyl group. This synthesis significantly reduces costs and facilitates large-scale production of ezetimibe (Scheme **14**).

Tamura *et al*.[33] reported the total synthesis of peumusolide A (**35**), an inhibitor of MAPK/ERK kinase (MEK) with a non-antagonistic nuclear export signal (NES)[34] mode, derived from the South American medicinal plant *Peumus boldus Molina*. Peumusolide A has been established to be a encouraging anti-tumor skeleton, showing selective growth inhibition in MEK-activated tumor cells.[35] In addition to peumusolide A, numerous related polyketides with extraordinary biological activities have also been identified.[36]

Peumusolide A had been synthesised *via* an enantioselective reduction of 4-en-1-yn-3-one **33** to form corresponding alcohol **34** with the use of chiral oxazaborolidine as the vital reaction step (Scheme **15**).

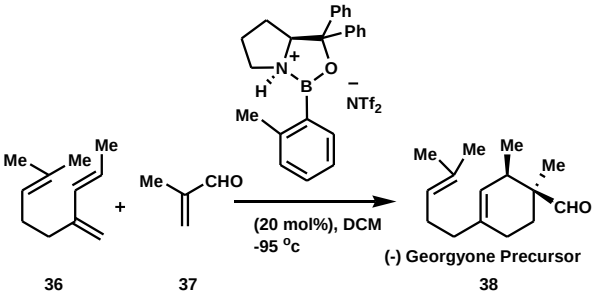


Scheme 14. *Synthesis of ezetimibe.*



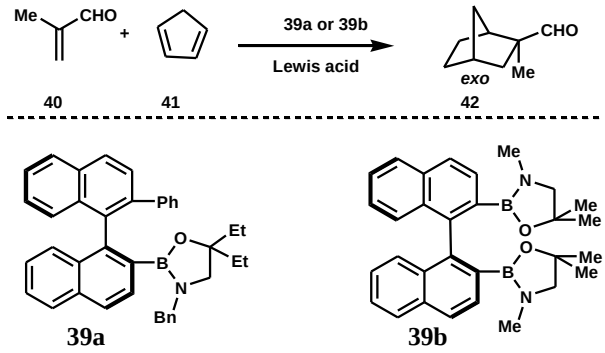
Scheme 15. *Total synthesis of (S)-peumusolide A.*

The total syntheses of the odorants georgyone, arborone, and associated structural congeners was reported by Corey and Hong[37]. A decisive step in each synthesis was the intermolecular Diels–Alder reaction between diene **36** and 2-methylacrolein **37**, catalyzed by (*S*)-oxazaborolidinium salt. This reaction was extremely enantioselective, producing the adduct **38** through an *exo* [2+4] pathway with 96% enantiomeric excess and a 76% yield. For instance, in the synthesis of (–)-georgyone, the intermediate was achieved with 96% enantiomeric excess and a diastereomeric ratio of 6:1 (Scheme **16**).



Scheme 16. *Oxazaborolidinium salt catalysed intermolecular Diels-Alder reaction.*

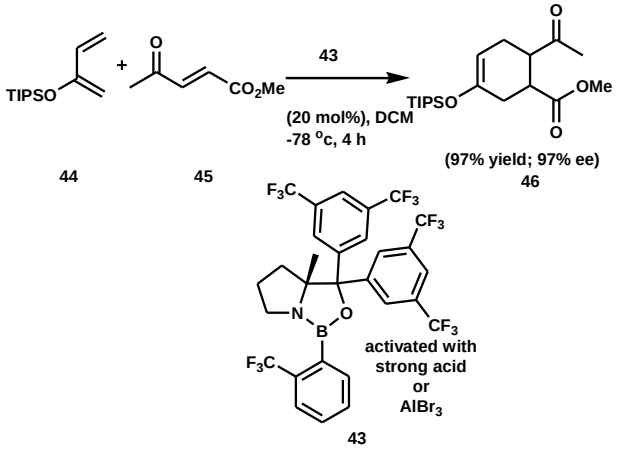
Shimoda and Yamamoto developed a novel axially chiral oxazaborolidine catalyst (**39a**), which combines a chiral boronic acid with a readily modifiable achiral amino alcohol.[38a] This catalyst demonstrated effective in a Diels–Alder reaction between diene **41** and dinophile **40**, yielding the desired adduct with notable enantioselectivity. Furthermore, the bis(oxazaborolidine) catalyst (**39b**), featuring two Lewis acidic centers, achieved even greater enantioselectivity in the Diels–Alder reaction (Scheme **17**).



Scheme 17. *Axially chiral oxazaborolidine catalysts for effective Diels-Alder [4+2] reaction.*

Chen *et al*.[38b] described a catalytic, highly regio- and enantioselective Diels–Alder reaction involving (*E*)-4-oxopent-

2-enoates (**45**) as dienophiles and diene **44** to afford the adduct **46**. This reaction was facilitated by oxazaborolidines **43**, which were activated into cationic chiral catalysts using either the strong acid triflimide or $AlBr_3$ (Scheme **18**).



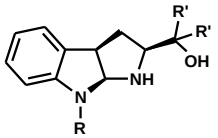
Scheme 18. *Catalytic regio- and enantioselective [4+2] Diels-Alder reaction.*

4. Synthesis of Chiral Intermediates, Ligands and Building Blocks

The synthesis of several therapeutic agents and complex natural products depends on the accessibility of chiral intermediates, which serve as essential building blocks for further structural and stereochemical variations. Asymmetric catalysis has turn into one of the most resourceful methods for preparing a diverse range of small molecules in highly enantiomerically-enriched forms.

Cho[39] reviewed the use of chiral oxazaborolidine-mediated borane reductions for prochiral ketones and ketimines. This approach has been extensively engaged for the greatly effective asymmetric synthesis of a wide array of chiral natural products, building blocks, bioactive compounds, intermediates, and ligands, all of which feature chiral alcohol or amine functionalities in their structures.

Xiao *et al*.[40] employed natural product skeletons as novel chiral synthons for asymmetric catalytic transformations and presented a new class of structurally stiff tricyclic chiral ligands for asymmetric catalysis. They described the design and synthesis of these fresh chiral ligands and their effectiveness in the asymmetric reduction of ketones, achieving good yields and enantioselectivities. They exploited a tryptophan-based hexahydropyrrolo [2,3-*b*]indole skeleton as a rigid chiral backbone to achieve enantiocontrol, benefiting from its tricyclic and structurally rigid nature (Figure **7**). This chiral oxazaborolidine ligand was synthesized *in situ* for the reduction of functionalized ketones.



R = CO_2Et, $COCH_3$, $CO_2CH(CH_3)_2$, CO_2Ph
R' = H, Ph

Figure 7. *Natural product skeletons used for oxazaborolidine catalyst.*

Yune *et al*.[41] reported the enantioselective reduction of prochiral ketones using mesoporous silica-supported oxazaborolidines in a heterogeneous phase (Figure **8**). They estimated how immobilization of oxazaborolidines on silica, with different substituents on the boron and nitrogen atoms, affected the enantioselective reduction of acetophenone. The performance of the silica-supported oxazaborolidines was compared to their homogeneous analogs by changing several parameters.

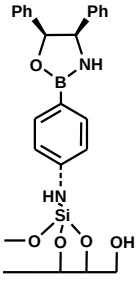
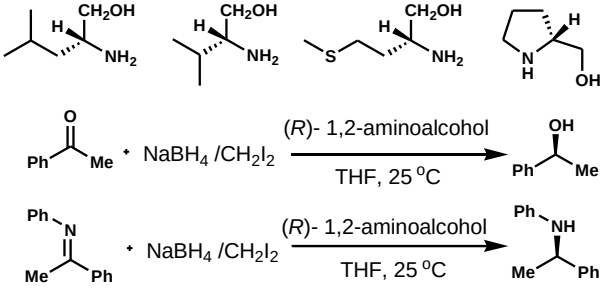


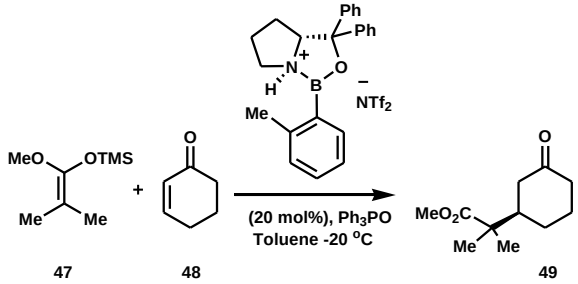
Figure 8. *Silica supported oxazaborolidine catalyst.*

Kettouche *et al*.[42] introduced a fresh method for preparing oxazaborolidine catalysts *in situ*, employing 1,2-aminoalcohol, $NaBH_4$, and CH_2I_2 for the asymmetric reduction of prochiral ketones and imines (Scheme **19**). The oxazaborolidine catalyst is handily synthesized at room temperature in THF using 1,2-aminoalcohols and BH_3 generated from the sodium borohydride/CH_2I_2 reagent system. This *in situ* prepared oxazaborolidine/BH_3 reagent system is effective for reducing prochiral ketones and N-substituted imines to their corresponding alcohols and amines with reasonable to good enantiomeric excesses. This method delivers a relatively humble and inexpensive methodology for this broadly used transformation in synthesis.

Corey and his colleagues[43] accompanied a catalytic, enantioselective Michael addition reaction using 20 mol% of catalyst. The reaction among a silyl ketene acetal **47** and cyclohexenone **48** formed the 1,4-addition product **49** with a yield of 91% and an enantiomeric excess of 90% (Scheme **20**).



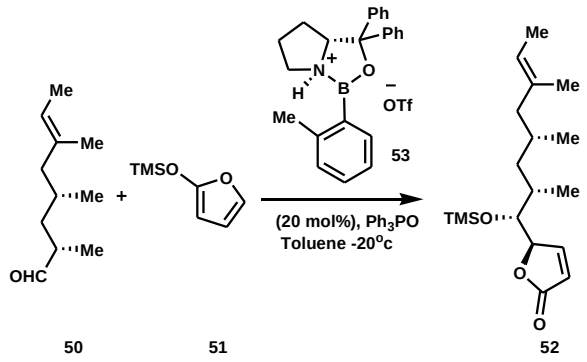
Scheme 19. *Asymmetric reduction of prochiral ketones and N-substituted imines.*



Scheme 20. *Enantioselective Michael addition reaction by oxazaborolidinum salt.*

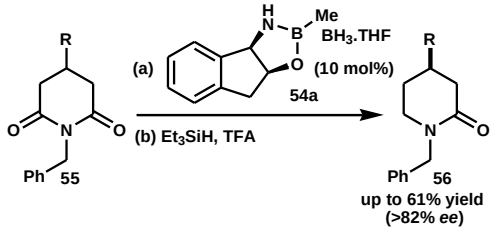
Application of chiral oxazaborolidinium salts in asymmetric vinylogous Mukaiyama Aldol reaction, was reported first by Boeckman *et al*. [44] The synthesis of butenolide **52** was achieved with good diastereoselectivity by adding trimethylsiloxyfuran **51** to aldehyde **50** in the presence of oxazaborolidine catalyst **53**. Incorporating additional methyl substituents on the diphenyl group of the oxazaborolidinium

salt enhanced the diastereoselectivity to over 90% with an 80% yield (Scheme **21**).



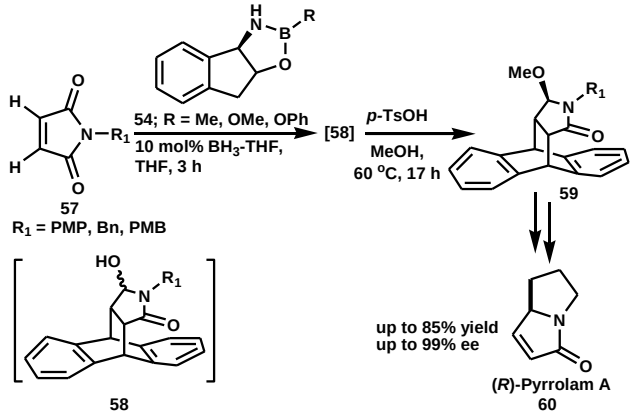
Scheme 21. *Asymmetric vinylogous Mukaiyama Aldol reaction by Oxazaborolidinium salts.*

Jones *et al*.[45a] described an enantioselective reductive desymmetrization of glutarimides **55** using an oxazaborolidine catalyst **54a** derived from *cis*-1-amino-indan-2-ol. The reaction was shown to proceed *via* a stereoablative mechanism, which boosted the enantioselectivity of the intermediate hydroxy-lactam. The process accommodated various substituents at the 4-position **56**, achieving with 61% enantiomeric excesses exceeding 82% (Scheme **22**).



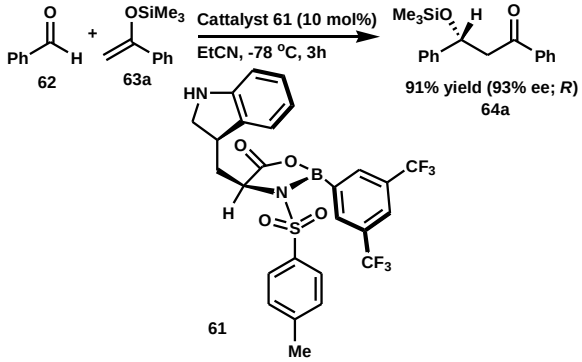
Scheme 22. *Enantioselective reductive desymmetrization of glutarimides by borane-oxazaborolidine.*

The same group also accomplished enantioselective catalytic desymmetrization of maleimides by temporarily removing an internal mirror plane and using stereoablative over-reduction. This approach led to the synthesis of (*R*)-pyrrolam A (**60**).[45b] In this over reduction course is critical for attaining product with yield 85% and up to 99% *ee* (Scheme **23**)



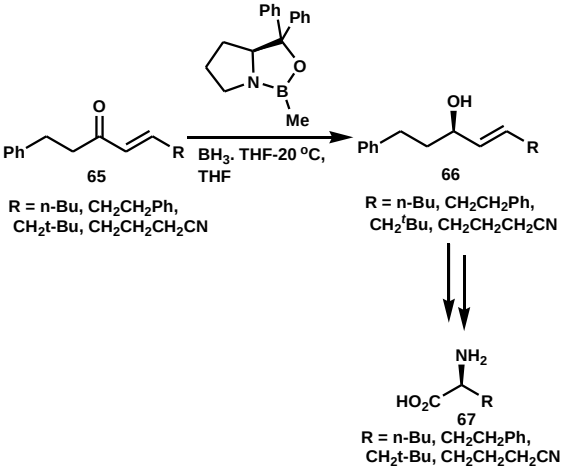
Scheme 23. *Asymmetric desymmetrization of maleimides leading to synthesis of (R)-pyrrolam A.*

Grayson and Farrar reported that their computational analyses have introduced a new reaction model with benzaldehyde **62** and alkene **63a** for the noncovalent interactions in the oxazaborolidine **61** catalyzed Mukaiyama aldol reaction, which aligns with experimental selectivity and has been validated for systems with less polarized and nonaromatic boron substituents.[46] The observed selectivity is explained by π–π interactions present in the major transition states, which are geometrically infeasible in the minor transition states due to the orientation of nucleophilic binding (Scheme **24**).



Scheme 24. *Model reaction for computational analysis.*

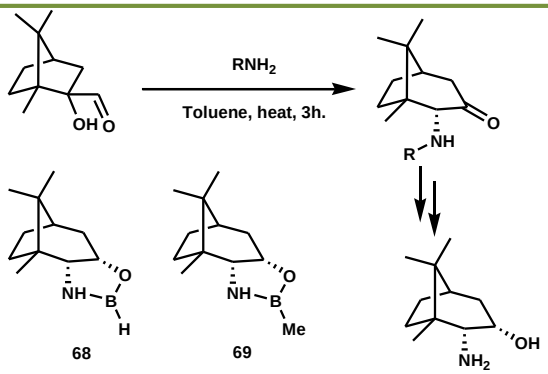
Drummond *et al*.[47] developed a new general method for preparing optically active α-amino acids. The process comprises a key ruthenium-catalyzed cross-coupling reaction to produce a range of *α,β*-unsaturated ketones **65**, which are then reduced to allylic secondary alcohols **66** using a chiral Me-CBS oxazaborolidine. The resulting alcohol endures a thermal Overman rearrangement to form a series of allylic trichloroacetimidates, which are subsequently transformed to the target *α*-amino acids **67** under standard conditions, yielding good overall results (Scheme **25**).



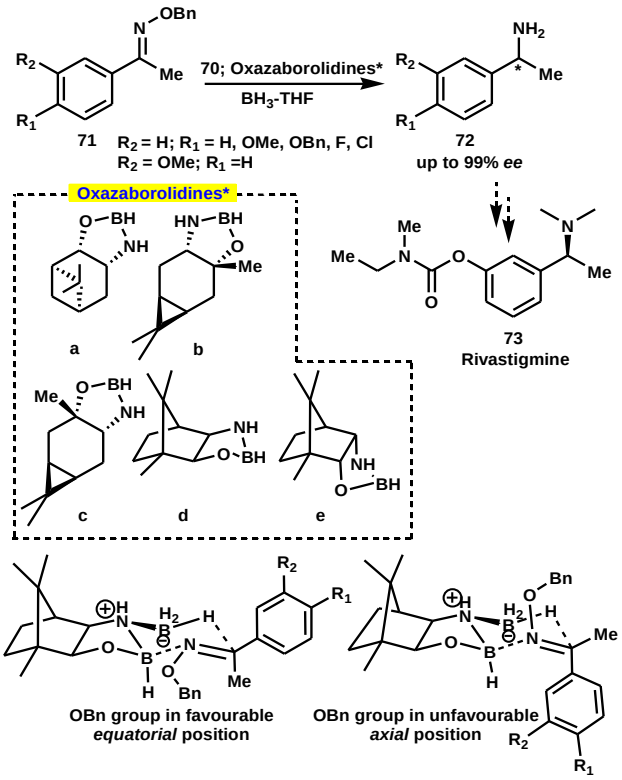
Scheme 25. *Synthesis of optically active α-amino acid.*

Yang *et al*.[48] established a novel camphor-based chiral amino alcohol and described its use in the asymmetric reduction of prochiral aryl ketones by borane at room temperature, utilizing oxazaborolidines derived from chiral amino alcohols. The oxazaborolidine **69** demonstrated greater selectivity compared to **68** (Scheme **26**).

Zaidlewicz *et. al* were introduced of some new class of oxazaborolidine derived from terpene and used for enantioselective reduction of prochiral ketones and oximeethers.[49] They found that the reduction of (*E*)-ketoxime *O*-benzyl ethers **71** using borane catalyzed by terpene-derived oxazaborolidines **70** specifically those derived from (1*R*)-nopinone and (1*R*)-camphor produced the corresponding amines up to 99% enantiomeric excess. In contrast, oxazaborolidines derived from (1*S*)-2-carene and (1*S*)-3-carene exhibited lower selectivity. Additionally, (*S*)-1-(3-methoxyphenyl)ethanamine (**72**), a key intermediate for synthesizing (*S*)-rivastigmine (**73**), was obtained with 94% ee by reducing (*E*)-1-(3-methoxyphenyl)ethanone *O*-benzyl oxime using borane and oxazaborolidine generated from (*S*)-valinol (Scheme **27**).[49e]



Scheme 26. *Synthesis of a novel camphor based chiral amino alcohol for preparing oxazaborolidine catalyst.*

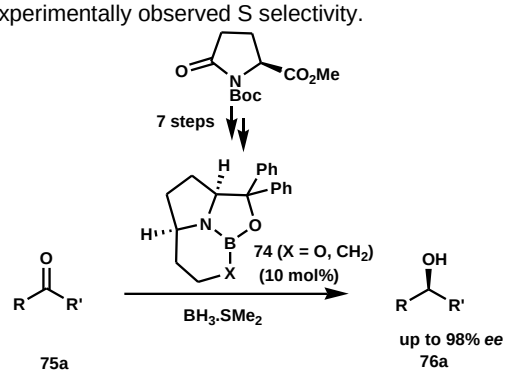


Scheme 27. *Enantioselective reduction of ketoxime ethers by terpene-derived oxazaborolidines.*

Breuning's group presented two novel tricyclic 1,3,2-oxazaborolidines **74**, synthesized in seven steps from methyl Boc-l-pyroglutamate. These compounds feature an ortho- and peri-fused 5/5/6-ring system with a B–N bond forming one of the ring junctions.[50] Asymmetric borane reduction of ketones **75a**, the B-alkoxy bridged derivative succeeds superb enantioselectivities (up to 98% ee), with activity akin to that of the standard CBS catalyst. In contrast, the closely related B-alkyl bridged derivative shows lower enantioselectivity and reduced activity, as confirmed by competition experiments (Scheme **28**).

Kettouche conducted an in-depth DFT study using wB97XD/6-31G(d,p) to explore the mechanism of enantioselective ketone reduction catalyzed by a B-methoxy-oxazaborolidine derived from (-)-β-pinene.[51] The study revealed that the reaction occurs in six steps: (a) formation of the active catalyst-borane adduct (Figure **9a**), (b) coordination of the aromatic ketone to the catalyst-borane adduct (Figure **9b**), (c) transfer of a hydrogen atom from the boron atom to the prochiral carbon center (Figure **9c**), (d) creation of a four-membered ring (B-O-B-N) through a [2 + 2] cycloaddition (Figure **9d**), (e) opening of the four-membered ring (B1-O2-B3-N4) (Figure **9e**), and (f) regeneration of the catalyst (Figure **9f**).

Kettouche concluded that the stereoselectivity of the reaction is determined by the intramolecular hydride transfer from the BH_3 moiety to the Si or Re face of the carbonyl substrate. The S-type chirality of the reduced products aligns with experimental results (Figure-**9**). Additionally, non-covalent interaction analysis of the most favorable transition state advocates a dispersive interaction between the hydrogen atom of the methanediyl group within the pinene skeleton. The stabilization provided by the two-atom [O-B] unit helps explain the experimentally observed S selectivity.



Scheme 28. *Enantioselective reduction of reactive ketones by oxazaborolidine catalyst.*

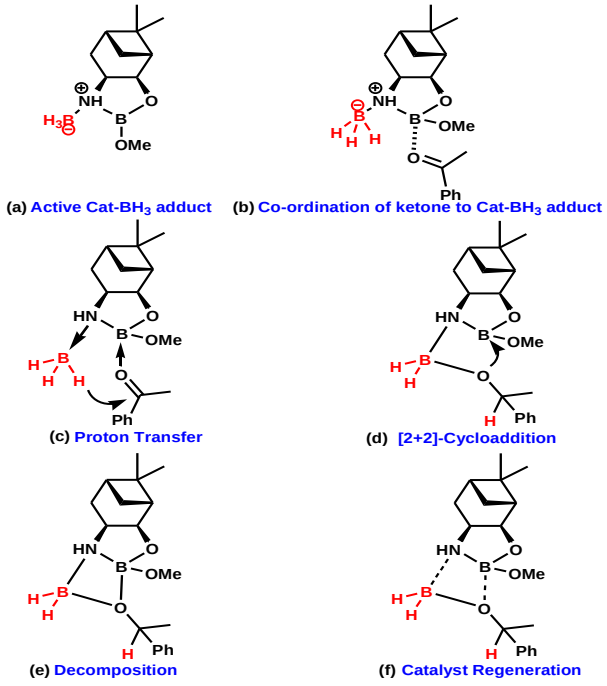
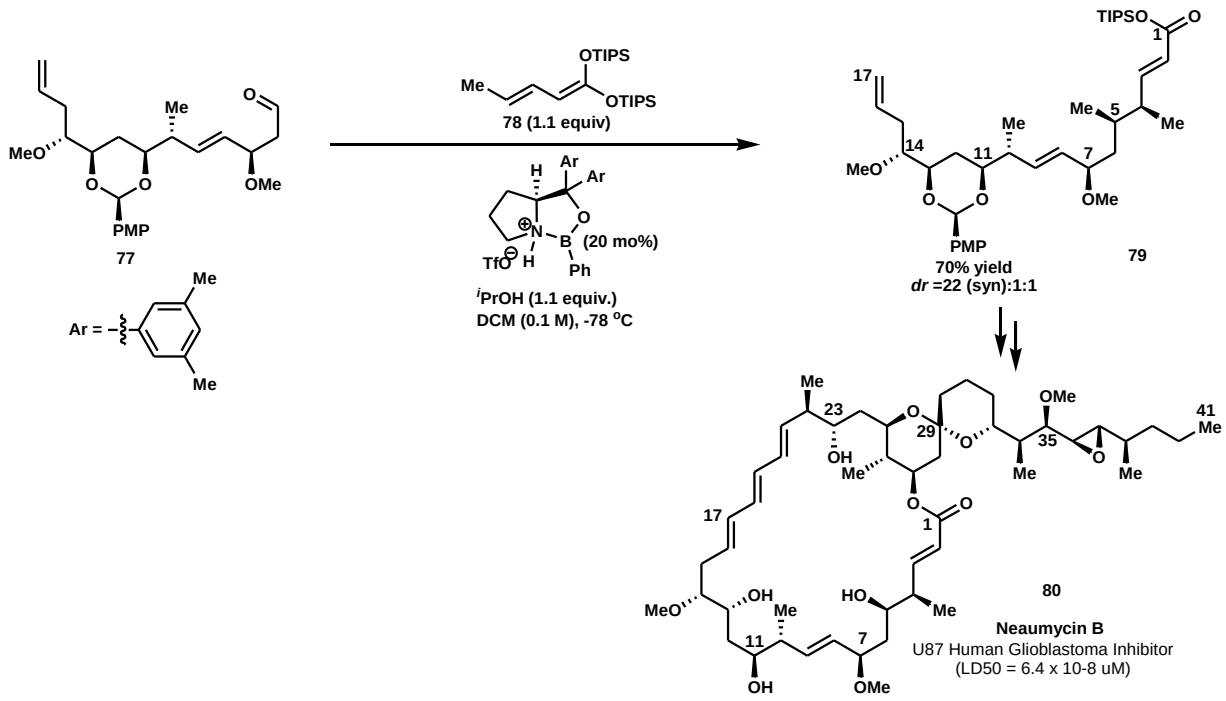


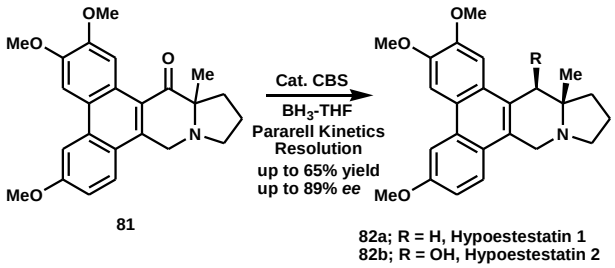
Figure 9. *Proposed catalytic steps based on DFT analyses*

Krische *et al.*[52] fruitfully synthesized neaumycin B (**80**), a femtomolar inhibitor of U87 human glioblastoma, utilizing Ru-JOSIPHOS-catalyzed C–C bond-forming reactions. The key intermediate **79** to accessing neaumycin B (**80**) was the development of an asymmetric vinylogous Mukaiyama aldol (VMA) reaction specifically designed for linear aliphatic aldehydes **77**, a novel route for terminally methylated dienyl ketene acetals (Scheme **29**).

Disadee and Ruchirawat described an enantioselective synthesis of both natural and unnatural hypoestestatin **82a** and **82b** analogues with high yields (~91%) and significant enantioselectivity (up to 89% *ee*).[53] This was achieved through the parallel kinetic resolution of racemic ketones **81** using CBS-oxazaborolidine-catalyzed reduction, which produced two separable diastereomeric alcohols. Notably, this was the first

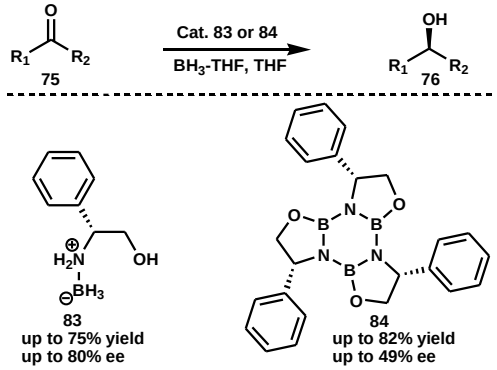


Scheme 29: *Oxazaborolidine-catalyzed Vinylogous Mukaiyama Aldol reaction leading to Neaumycin B (***80***)*

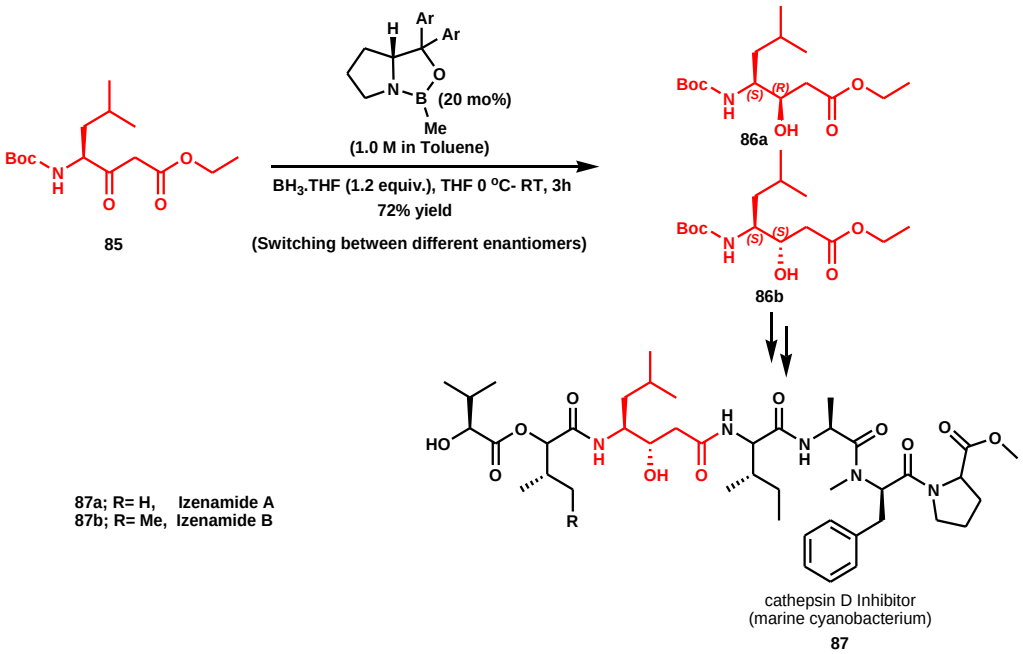


Scheme 30. *Oxazaborolidine-catalyzed asymmetric reduction for seco-hypoestestatin* ***1*** *and* ***2****.*

time demonstrated the catalytic asymmetric reduction for seco-hypoestestatin 1 and 2.



Scheme 31. *Enantioselective ketone reduction by N-boranes (noncyclic) and tris(oxazaborolidine)borazines (cyclic) derived from chiral β-amino alcohol.*



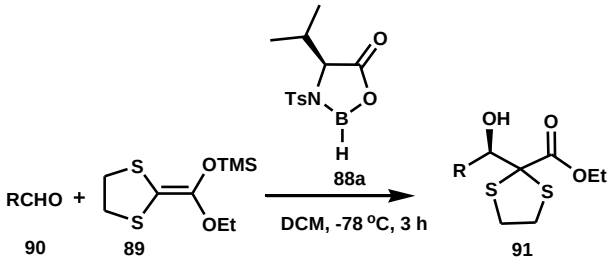
Scheme 32: *Enantioselective synthesis of Izenamide A and B by oxazaborolidine catalysts.*

This approach embraces potential for adapting racemic mixtures into enantioenriched forms, which could be useful for numerous biological assays in the future (Scheme **30**). Vougioukalakis *et al.*[54] thoroughly examined the influence of chiral *β*-amino alcohol *N*-boranes (noncyclic, **83**) and their corresponding tris(oxazaborolidine)borazines (cyclic; **84**) on the catalytic asymmetric reduction of prochiral ketones **75**. Both cyclic and noncyclic catalysts commendably twisted secondary alcohols **76** with an ~82% yield. Interestingly, polycyclic borazine catalyst proved stability merely in nonprotic dry organic solvents, whereas the noncyclic catalyst persisted stable in both aqueous and organic solvents (Scheme **31**).

Sharma and colleagues described an efficient, concise, and scalable alternative method for synthesizing Izenamide A (**87a**) and B (**87b**) with high stereoselectivity.[55] Their tactic involves the enantioselective reduction of *N*-Boc *γ*-amino *β*-keto esters **85** to the corresponding alcohols **86** using 2-methyl-CBS-oxazaborolidine catalysts. They also demonstrated that by switching between different enantiomers of the 2-methyl-CBS-oxazaborolidine catalyst, they could synthesize both diastereomers of the alcohol. This methodology could be of excessive significance, as *γ*-amino *β*-ketoesters exemplify a key motif in drug discovery (Scheme **32**).

5. Oxazaborolidinone

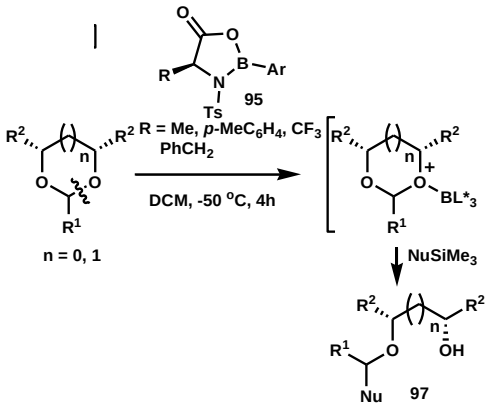
The enantioselective reduction of prochiral carbonyls and ketimines has been widely studied with oxazaborolidine catalysts compared to oxazaborolidinones. Kiyooka *et al*.[56] were the first to report an aldol reaction encouraged by a chiral oxazaborolidinone **88a**. This reaction involved a silyl ketene acetal **89** derived from ethyl 1,3-dithiolane-2-carboxylate and aldehyde **90**, resulting in the synthesis of acetate aldols **91** with high enantiomeric purity (Scheme **33**).



Scheme 33. *Chiral oxazaborolidinone catalysed aldol reaction.*

Komura *et al*.[57] discovered that the asymmetric repetitive Mukaiyama Aldol reaction among bis(trimethylsilylketene thioacetal) **92** and dialdehydes **93**, when executed in the presence of chiral oxazaborolidinone **88a**, yielded optically active poly(*β*-hydroxy thioester) **94**. The extent of asymmetric induction during polymerization was measured through a model reaction and by chiral HPLC analysis of the degradation products of the chiral polymers (Scheme **34**). Simple Mukaiyama Aldol reaction also responded under this conditions.

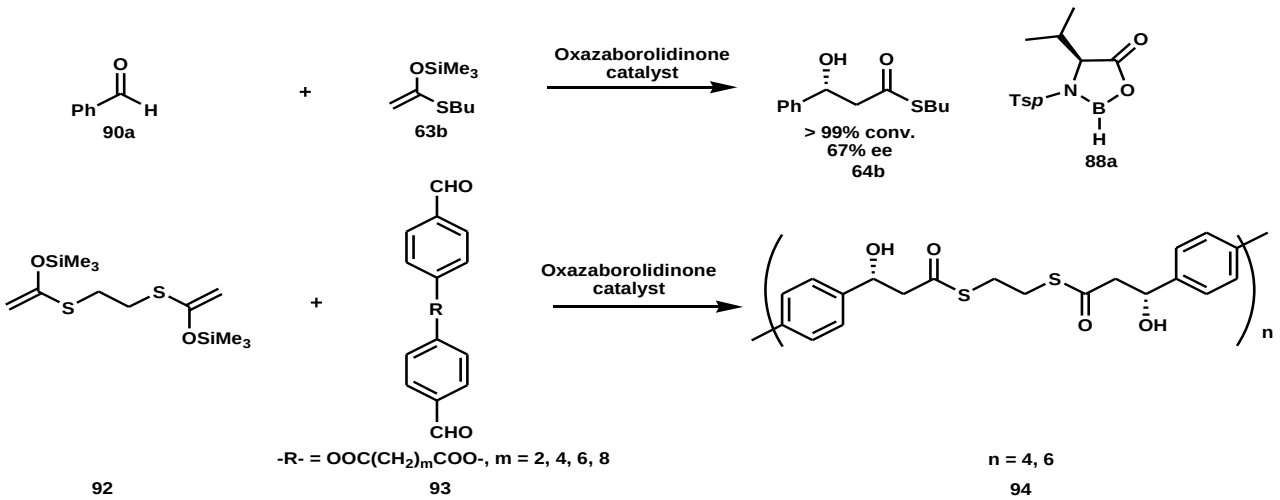
Harada *et al*.[58] reported the inter- and intra-molecular differentiation of enantiotopic dioxane acetals **96** using an oxazaborolidinone **95** mediated enantioselective ring-cleavage reaction. They also perceived the kinetic resolution of racemic 1,3-alkanediols and the asymmetric desymmetrization of *meso*-1,3-polyols (Scheme **35**).



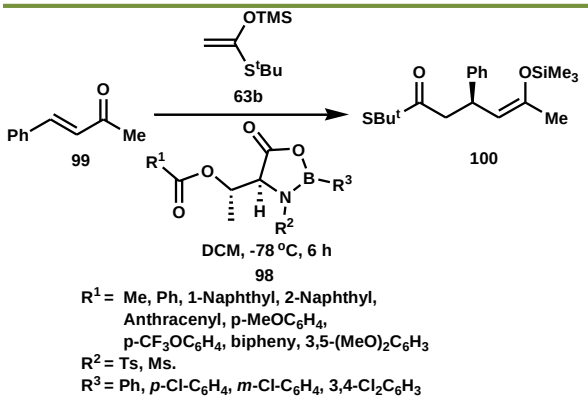
Scheme 35. *Oxazaborolidinone catalysed enantioselective ring-cleavage reaction.*

Wang *et al*.[59] reported enantioselective Lewis acid-catalyzed Mukaiyama-Michael reactions of acyclic enones **99** with trimethylsilyl ketene *S*,*O*-acetal **63b**, using allo-threonine-derived *O*-aroyl-*B*-phenyl-*N*-tosyl-1,3,2-oxazaborolidin-5-ones **98** as catalysts to produce **100** (Scheme **36**). This model for asymmetric induction was recommended based on the correlation among catalyst structures and their enantioselectivities.

This new class of oxazaborolidinone catalysts **98** compromises a convenient method for producing enantioenriched *γ*-ketoacid thiol esters. Various alkenyl methyl ketones were effectively used as Michael acceptors, accomplishing enantiomeric excess values of 85-90% with the use of 10 mol% of the catalyst.



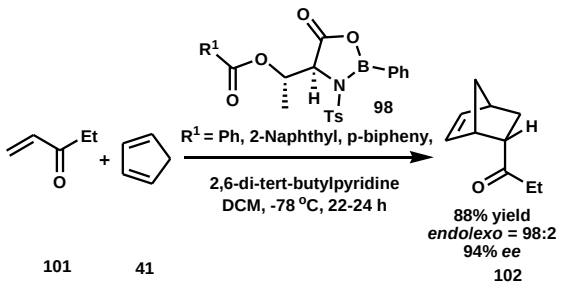
Scheme 34: *Asymmetric Mukaiyama aldol reaction by oxazaborolidinone catalyst.*



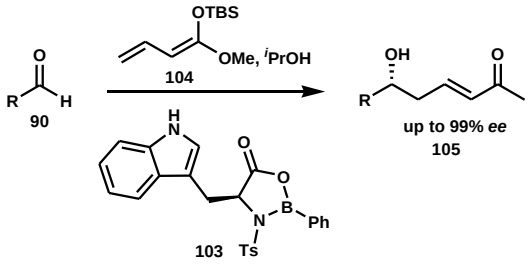
Scheme 36. *Oxazaborolidinone catalysed enantioselective Mukaiyama-Michael reactions.*

Harada and Singh [60] reported an enantioselective Diels–Alder reaction between acyclic enone dienophile **101** and diene **41**, catalyzed by allo-threonine-derived chiral oxazaborolidinone (10-20 mol%). This reaction produced the Diels-Alder adduct **102** with high yield, excellent endo selectivity, and 94% enantiomeric excess (Scheme **37**).

Simsek *et al*.[61] developed oxazaborolidinone-promoted vinylogous Mukaiyama aldol reactions. They used tryptophan-derived B-phenyl oxazaborolidinone **103** for the enantioselective vinylogous Mukaiyama aldol reaction between *O*,*O*-silyl ketene acetal **104** and aldehyde **90**, facilitating efficient entrees to chiral building blocks **105** for polyketide synthesis (Scheme **38**). Their studies also emphasized that isopropyl alcohol is compulsory as an additive to overturn the racemic TBS-catalyzed pathway and enhance enantioselectivity. For *α*-chiral aldehydes, they demonstrated that selecting proper protecting groups is crucial for achieving high selectivities. In the context of total syntheses, *R*-chiral aldehydes were utilized as substrates, revealing that TBS ethers afforded useful selectivities compared to PMB-protected substrates when the right protecting groups were chosen.

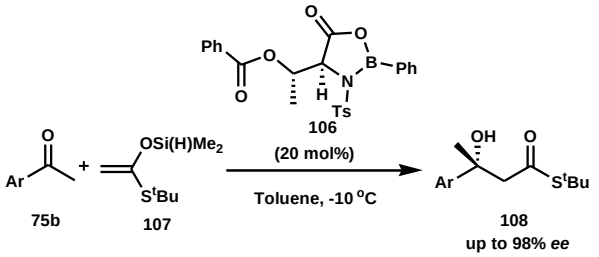


Scheme 37. *Allo-threonine-derived chiral oxazaborolidinone catalysed Diels-Alder reaction.*



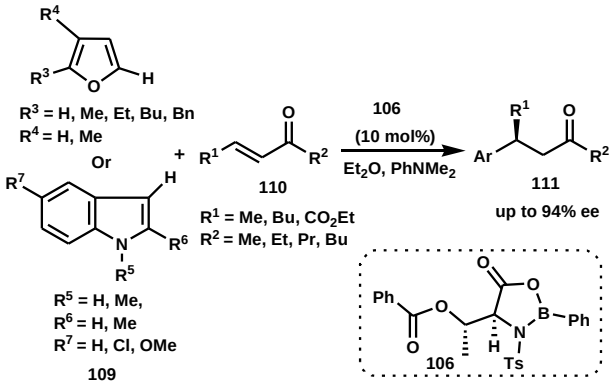
Scheme 38. *B-phenyloxazaborolidinone derived from tryptophane catalysed Mukaiyama aldol reaction.*

Adachi *et al*.[62a] established an asymmetric aldol reaction catalyzed by allo-threonine-derived oxazaborolidinone **106**. This reaction comprises nonactivated aromatic ketones **75b** and silyl ketene *S*,*O*-acetals **107**, yielding tertiary hydroxy carbonyl compounds **108** with high enantioselectivity (Scheme **39**). They found that using dimethylsilyl ketene *S*,*O*-acetals instead of the conventional trimethylsilyl derivatives are crucial for achieving both effective catalytic activity and high selectivity.



Scheme 39. *Asymmetric Aldol reaction of nonactivated aromatic ketones by oxazaborolidinone.*

They also confirmed the enantioselective Friedel-Crafts alkylation of electron-rich heteroaromatics **109**, such as furans and indoles, with *α*,*β*-unsaturated ketones **110** using same oxazaborolidinone catalyst **106**. This work marked the first successful enantioselective Friedel-Crafts alkylation of furans with a monodentate *α*,*β*-unsaturated ketone using oxazaborolidinone catalysis (Scheme **40**). Additionally, the catalyst system was effectively applied to the alkylation of indoles, widening the range of substrates. The presence of *N*,*N*-dimethylaniline as an additive was found to be essential for achieving high enantioselectivity.[62b]



Scheme 40. *Enantioselective Friedel-Crafts alkylation reaction by oxazaborolidinone.*

Micoine *et al*.[63] have reported an efficient total synthesis of the antiproliferative macrolide and cell migration inhibitor lactimidomycin **113** (Scheme **41**). The synthesis involved the key intermediate, the strained 12-membered 1,3-enyne **112**, which was elaborated to the final target through a highly diastereoselective Mukaiyama aldol reaction. This reaction was controlled using tryptophan-derived *B*-phenyloxazaborolidinone **103** as a strategic component.

Costantino *et al*.[64] introduced the first example of chiral oxazaborolidinones attached to α-layered zirconium phosphonates, demonstrating the versatility of these zirconium-based materials. They established heterogeneous catalysts that executed effectively in Mukaiyama aldol reactions, yielding good enantiomeric excess. The catalysts were derived from a mixed zirconium sulfophenylphosphonate methanphosphonate chiral borane **114** (Figure **10**).

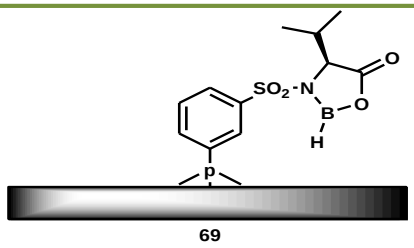


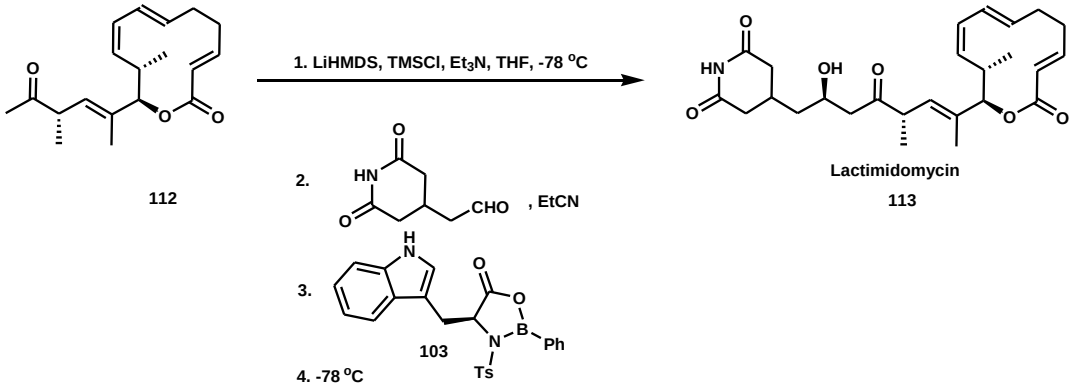
Figure 10. *Oxazaborolidinone on the surface of lamella of α-Zr[$O_3PC_6H_4SO_2NHCH(CH(CH_3)_2COOH)](O_3PCH_3).nH_2O$.*

While these heterogeneous catalysts exhibited somewhat lower performance compared to their homogeneous counterparts, the results are encouraging. This suggests substantial potential for similar systems utilizing insoluble zirconium phosphonates. The layered compounds were characterized using various techniques and subsequently reacted with BH_3-THF to obtain the heterogeneous chiral oxazaborolidinone.

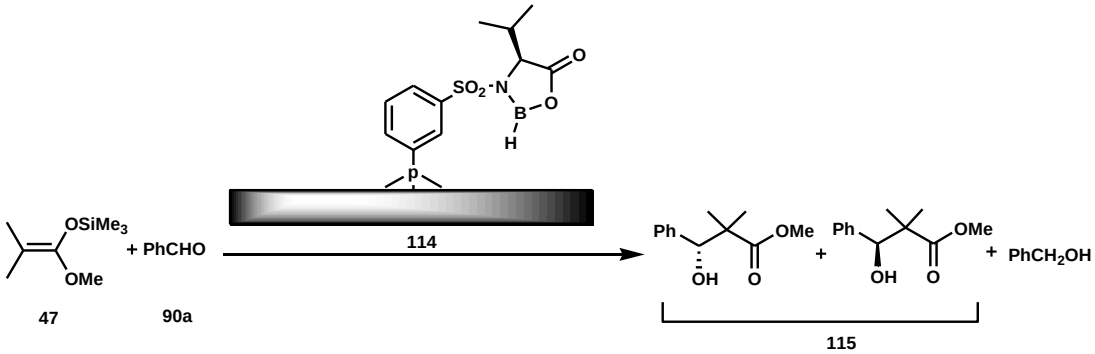
In this process, aldehyde **90a** and silyl ketene acetal **47** were reacted with the oxazaborolidinone immobilized on the surface of lamellar *α*-$ZrO_3PC_6H_4SO_2NHCH(CH(CH_3)_2COOH).nH_2O$ **114**, resulting in the formation of the corresponding secondary alcohol **115** with up to 50% enantiomeric excess and traces of benzyl alcohol (Scheme **42**).

Gieseler *et al.*[65] have recently presented an asymmetric vinylogous Mukaiyama aldol reaction using aldehyde-derived silyl dienol ethers with an oxazaborolidinone catalyst. Unsaturated aldehydes assist as valuable building blocks for further conversions in polyketide synthesis. This approach, which comprises standard transformations and the conjugate addition of hydrides followed by internal protonation, enables the synthesis of *α*-chiral aldehydes. The methodology affords an efficient route to *R*-substituted *δ*-hydroxy-*α*,*β*-unsaturated aldehydes **119** by reacting alkyl or aryl aldehydes **117** with silyl dienol ethers **118** using catalyst **116** (Scheme **43**). These *δ*-hydroxy-*α*,*β*-unsaturated aldehydes **119** are precursors for asymmetric protonation in the total synthesis of angiolam.[66] Kalesse et al.[67] described an oxazaborolidinone-mediated asymmetric bisvinylogous Mukaiyama Aldol reaction with alkene **120** and aldehyde **90** that supports the rapid formation of conjugated dienols **121**. This approach extends the vinylogy principle by adding two additional carbons and could be performed with a readily available Lewis acid within reasonable reaction times. It accommodates a wide variety of aromatic and aliphatic aldehydes, facilitating the synthesis of complex building blocks for polyketide construction (Scheme **44**).

Du *et al.*[68] reported the total synthesis of 27-Deoxylyngbyabellin A (**124**), a secondary metabolite from marine cyanobacteria, achieved in 10 linear steps with an overall yield of approximately 10%. A crucial intermediate, (*S*)-*β*-hydroxy ester **123**, was obtained through a chiral oxazaborolidinone-mediated asymmetric aldol reaction between silyl ketene acetal **47** and aldehyde **122** to afford 56% yield. This (*S*)-*β*-hydroxy ester **123**, together with two essential

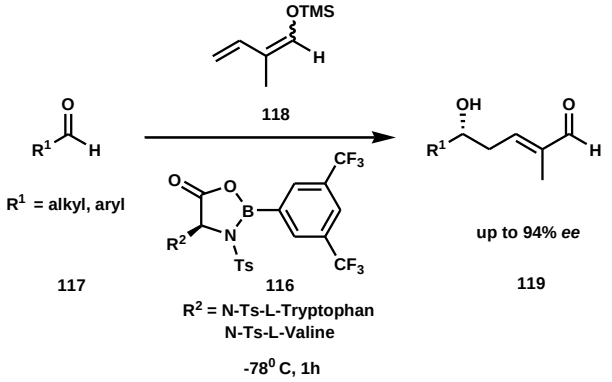


Scheme 41. *Total synthesis of lactimidomycin.*

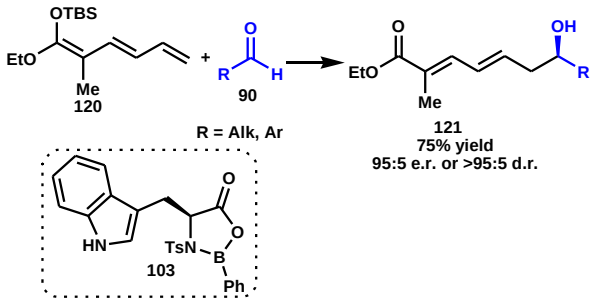


Scheme 42. *Chiral oxazaborolidinone anchored ?-layered Zr-phosphonate catalyst for Mukaiyama aldol reaction.*

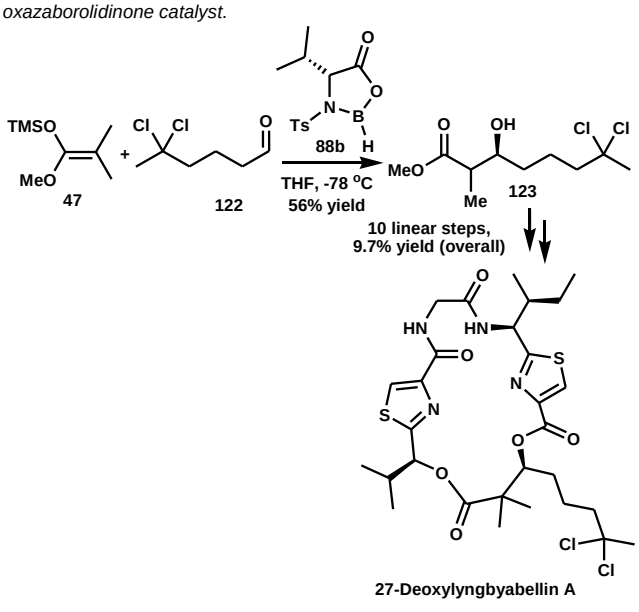
thiazole units, was subsequently assembled to produce the 27-Deoxylyngbyabellin A natural product (Scheme **45**).



Scheme 43. *Asymmetric vinylogous Mukaiyama aldol reaction by oxazaborolidinone catalyst.*



Scheme 44. *Asymmetric vinylogous Mukaiyama aldol reaction by oxazaborolidinone catalyst.*



Scheme 45. *Total synthesis of 27-Deoxylyngbyabellin A.*

6. Conclusion

Over the years, the use of oxazaborolidine and borolidinone catalysts (or stoichiometric reagent) for reducing various functionalities has been broadly validated by researchers, particularly for their key applications in synthesizing bioactive natural products and building blocks. It is clear from this comprehensive review that the oxazaborolidine catalysed enantioselective reductions play significant roles both industrial and academic settings. In contrast, the use of oxazaborolidinone catalysts remains relatively unexplored, so there is a substantial opportunity to take up further investigation in this. Although, its numerous application in various chemical reactions, especially asymmetric catalysis but there are few drabacks such as limited stability as its highly air and moisture sensitive nature; sometime difficult to control reactivity for its stoichiometric uses leads to undesired side product; highly expensive fluorinated oxazaborolidine catalyst, The study of reactions catalyzed by oxazaborolidines and oxazaborolidinones holds huge potential, innovative developments, and more fascinating aspects are expected to originate from this area by enhancing stability using more robust functional groups or protective groups, adjusting reactivity to minimize side products, and lowering catalyst costs through more economical synthetic routes.

Author Contribution Declaration

YKW: designing, drafting manuscript, literature collections, and editing; **SS**: literature collections and updating recent work; **SDP**: drafting manuscript, and editing; **PKP**: drafting, editing and finalizing the manuscript.

Data Availability Declaration

There are no new data were created hence data sharing is not applicable.

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